Repurposing π Electrophilic Cyclization/Dealkylation for Group Transfer

Joseph A. Kaplan‡, Adena Issaian‡, Martin Stang, David Gorial, and Suzanne A. Blum*

Abstract: A metal-free regio- and stereocontrolled group-transfer route toward the synthesis of trisubstituted alkenes is described. In this route, an electrophilic heterocyclization is followed by ring-opening group transfer. Specifically, a thioboration reaction transforms readily available alkynyl sulfide precursors into alkenyl boronates and alkenyl sulfides with defined regio- and stereochemistry in one synthetic step using commercially available *B*-chlorocatecholborane (ClBcat). Mechanistic studies identified the likely pathway as proceeding through zwitterionic rather than haloborated intermediates. The regio- and stereochemistry set in the initial cyclization step is preserved in the final acyclic alkene product, producing alkenes with up to four modifiable substituents with predictable regio- and stereochemistry. Downstream functionalization reactions showcase the versatility of the substitutions of the resulting alkenes. The mechanistic concept maps onto future reaction designs, given the abundance of known electrophiles and nucleophiles for electrophilic heterocyclization/dealkylation sequences.

Electrophilic cyclization reactions onto π bonds are a common route for the synthesis of heterocycles.[1–11] These reactions use simple acyclic precursors and employ readily available external electrophiles ranging from dihalides,[1–4] to boron[5–9] and selenium electrophiles,[1,3,4] to transition metal catalysts,[10–17] producing a range of corresponding heterocyclic products. Yet for decades since their initial popularization, including substantial work by Larock on sequences of π electrophilic cyclization followed by nucleophilic dealkylation,[3,4,18–20] the focus on forming heterocycles has left the potential of these sequences toward other pathways largely untapped. In this report, we take advantage of the initial mechanistic steps of the classic "Larock-type" catalyst-free electrophilic cyclization reaction—cyclization onto a C–C π bond followed by dealkylation—and alter the mechanistic pathway by repurposing a key cationic intermediate toward a new class of group-transfer processes that result in tri- and tetrasubstituted alkenes. Figure 1 shows this synthetic and mechanistic concept in its broadest form. The regio- and stereochemistry of the resulting alkenes are completely set by the mechanism of the electrophilic cyclization reaction, providing predictability and control. The mechanism involves two steps: (i) activation of the alkyne by the electrophile with nucleophilic attack of the heteroatom on the C–C π bond to form the key cationic intermediate; and (ii) an S_N2 ring-opening attack with transfer of the XR^1 group to reveal the acyclic alkene with set regio- and stereochemistry.

The central mechanistic concept underpinning this repurposing is the swap of position of sp^2 vs sp^3 hybridized carbons adjacent to the heteroatom, effectively blocking the established pathway and leading instead to ring opening. This diversion generates three new bonds (shown in bold) in one synthetic step (Figure 1b). The term "group-transfer" here refers to the overall transfer of heteroatom group (XR^1) from the left side of the C–C π bond to the right side (to C* in Figure 1b). Here, we initially develop this concept with a series of thioboration reactions that produce alkenyl boronates (Table 1).

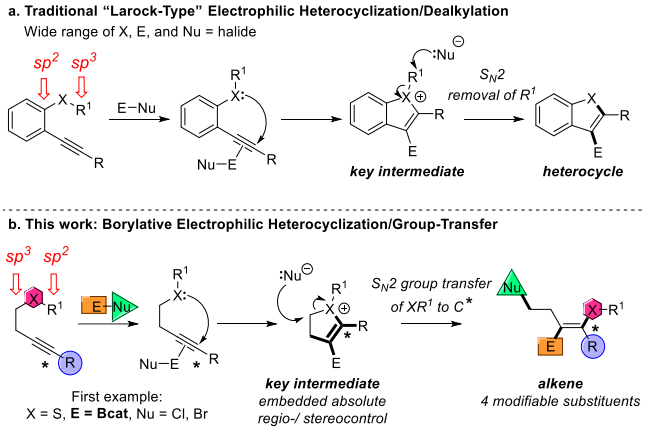

Figure 1. a) Heterocycles from traditional electrophilic cyclization/dealkylation. b) This work demonstrating electrophilic cyclization/group-transfer transformation.

In addition to the mechanistic interest, the reaction forms alkenyl boronates and alkenyl sulfides together in one synthetic step as valuable building blocks.[21–24] Alkenyl sulfides have shown antibacterial activity,[23,24] or alternatively participate in cross-coupling reactions through C–S cleavage.[25,26] Achieving high regio- and stereoselectivity in previous synthetic approaches, however, remains challenging.[27–31] Alternative pinacolboration of thioacetylene precursors to make these compounds, for example, generally provides a mixture of regioisomers and requires a metal catalyst.[31] Electrophilic cyclization/group-transfer provides a potential solution to these challenges.

Starting material **1** was obtained in one step from an S_N2 displacement reaction of 4-bromobutyne with the corresponding thiol nucleophile in good yields (see SI for details). Reaction optimization studies showed that *B*-chlorocatecholborane (ClBcat) at 120 °C in toluene yielded the best results. For ease of isolation, product **3** was then transesterified to the bench-stable pinacol boronate (Bpin) derivative **4** using known methods (Table 1).[8,9] ^{1}H NMR spectroscopy was effective for monitoring the formation of **3** and the characterization of isolated **4** owing to the distinctive downfield chemical shift (~3.6 ppm) of the methylene protons α to the chloride in the product (substantially shifted from α to the sulfur in the starting material (~2.9 ppm)). In some cases, isolation of **4** was not productive due to sensitivity of this initial product scaffold to transesterification and chromatography; in these cases, the ^{1}H NMR spectroscopy yields of **3** are given in Table 1. (This sensitivity was later solved upon substrate modification, vide infra.) Synthesis of tetrasubstituted alkenes was also viable, albeit requiring additional equivalents of ClBcat (Table 1, 3g, 66% ^{1}H NMR spectroscopy yield).

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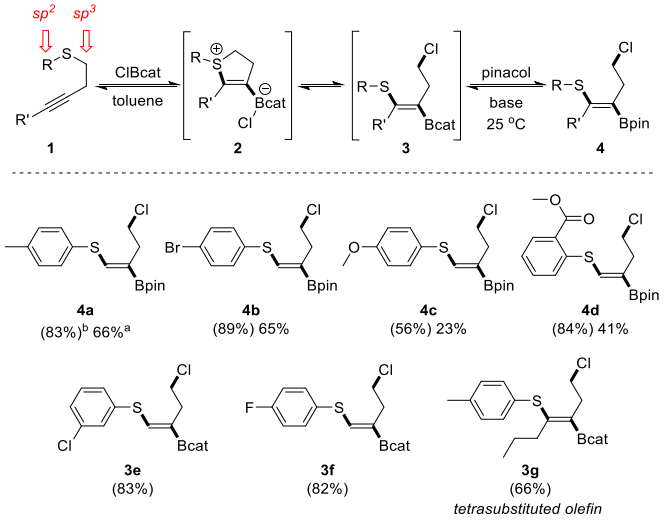
Table 1. Synthesis of borylated alkenyl sulfides via the thioboration/group-transfer reaction.



[a] Isolated yield of **4**. [b] ^{1}H NMR spectroscopy yield of **3** relative to an internal standard.

No intermediates were visible during reaction progress by ^{1}H NMR spectroscopy. However, the regio- and stereochemistry of product **4a** was unambiguously confirmed by X-ray crystallography and was consistent with that arising mechanistically from ring opening of intermediate **2** (Figure 2a).

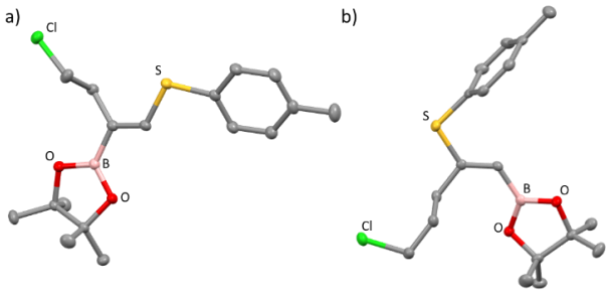
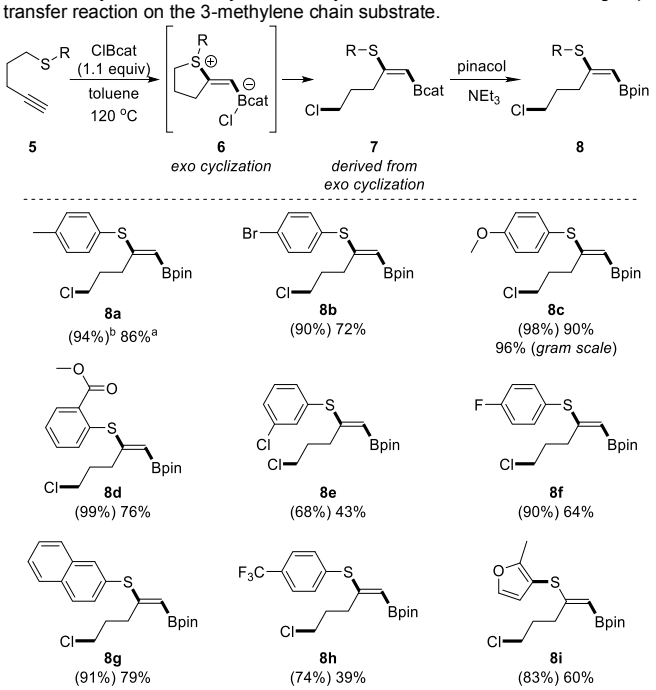


Figure 2. a) X-ray crystal structure of **4a** establishing group-transfer product regio- and stereochemistry and b) X-ray crystal structure of **8a** confirming product from *exo* cyclization. Thermal ellipsoids are shown at 50% probability (B, pink; C, gray; O, red; S, yellow; Cl, green).

Having established that cyclization sets the regio- and stereoselectivity of the reaction, it was plausible that different chain lengths may dictate other regio- or chemoselectivity patterns (e.g., *exo*, *endo*, or slow cyclization which could allow competing haloboration).[32,33] This concept was explored next.

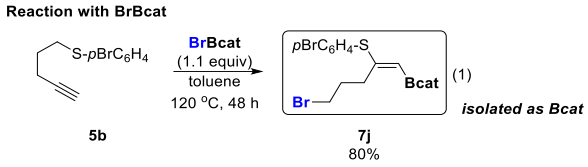
Elongation of the alkyl chain by one methylene provided enhanced product stability, facilitating isolation and enabling higher isolated yields (Table 2, **8**). The additional methylene also swapped the resulting alkene regiochemistry, producing the alkene from *5-exo-dig* cyclization/group-transfer (**7**) instead of the *endo* cyclization observed previously (Table 1). The crude ^{1}H NMR spectra in toluene-d_8 showed that Bcat products **7** generally had higher NMR spectroscopy yields compared to their 2-methylene counterparts **3**. The regio- and stereochemistry of transesterified product **8a** were confirmed by X-ray crystallography (Figure 2b), leading to assignment of the regio- and stereochemistry of **7** and derivatives of **8**.

Table 2. Synthesis of borylated alkenyl sulfides via the thioboration/group-transfer reaction on the 3-methylene chain substrate.

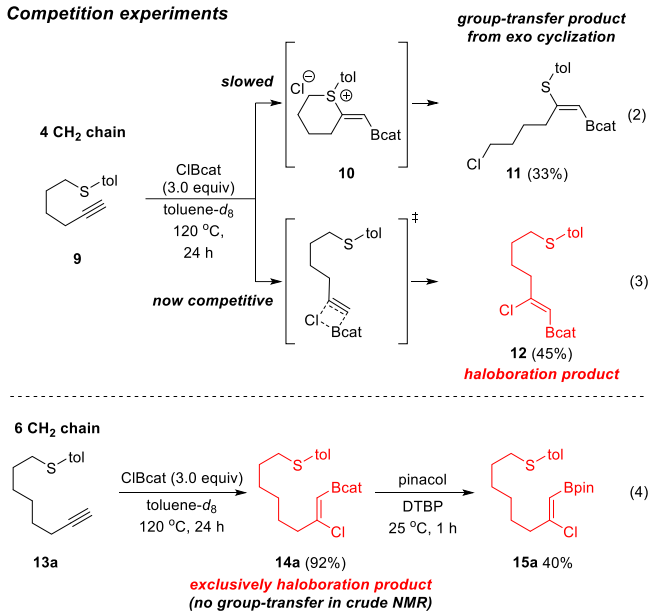


[a] Isolated yield of **8**. [b] ^{1}H NMR spectroscopy yield of **7** relative to an internal standard.

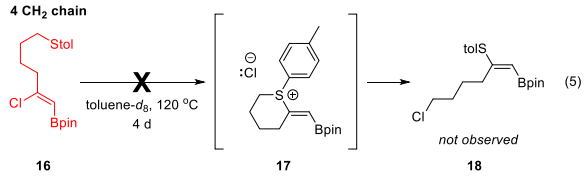
Reaction with *B*-bromocatecholborane (BrBcat) as an alternative electrophile–nucleophile pair resulted in the group transfer product **7j**. The resulting alkenyl boronate was isolable as the Bcat product via crystallization, highlighting the ability to isolate these compounds directly (i.e., without transesterification), despite the moisture sensitivity of the Bcat group[34] (eq 1).



Further elongation (4 methylene chain) apparently slowed the heterocyclization reaction by distancing the sulfur from the alkyne, giving chloride the chance to compete with sulfur for attack onto the activated alkyne resulting in chloroboration. Thioboration (**11**) was now disfavored over chloroboration (**12**) indicated by a 1:1.4 ratio of **11**:**12** by ^{1}H NMR spectroscopy at 24 h (eq 2 and eq 3; haloboration products shown in red for clarity). Consistent with this elongation trend, octynylthioether **13a** (6 methylene chain) under the same reaction conditions generated the haloboration product **14a** exclusively. The regiochemistry of isolable derivative **15a** was unambiguously determined using ^{1}H/^{13}C HMQC NMR spectroscopy (eq 4). The stereochemistry of **15a**, which is consistent with haloboration via a syn addition pathway, was determined by ^{1}H NOE NMR spectroscopy. This stereochemistry matches other known haloboration reactions with alkynes.[35] The stereo- and regiochemistry of **12**, **14**, and **16** were assigned by extrapolation of the determined features for **15a**.



The results in eq 3 and eq 4 established that chloroboration was competitive with long-chain substrates. This consideration led us to evaluate if haloboration might be part of the mechanistic pathway for *all* group-transfer reactions via an unobserved haloboration intermediate. The formation of both group-transfer and haloboration products, **11** and **12**, from the same substrate **9** (eq 2 and 3) presented an opportunity to test if an isolated chloroborated product could be transformed into the corresponding group-transfer product through an S_N2-type mechanism at an sp^2 carbon[36,37]. Starting material **16** is structurally analogous to haloborated product **12**, with the caveat that it has a less-electron-withdrawing Bpin substituent instead of Bcat,[38] which may hinder substitution reactions at the sp^2 carbon. Compound **16** was subjected to 120 °C for 4 d, the same conditions which previously produced the group-transfer product **11** (eq 5). During periodic monitoring of the reaction by ^{1}H NMR spectroscopy, only starting material **16** was observed with no detection of product **18**, the Bpin analogue of **11**. The absence of reactivity suggests that haloboration is less likely to be the operative pathway for cyclization/group-transfer.



Experiments provided evidence supporting proposed cyclic zwitterionic intermediate **2**. During most of the reactions, a precipitate formed that subsequently disappeared after longer reaction times. Hypothesizing that this may be a zwitterion intermediate, we isolated this precipitate as a crystalline solid in the case of substrate **1b**, and characterized this precipitate (Figure 3a, **20**) by X-ray crystallography. The cyclic zwitterion closely resembled expected **2b**, but with all-chloride ligands on boron. The reaction conditions could plausibly form BCl_3 from ClBcat, because nucleophiles can facilitate boron ligand redistribution;[39,40] however, a control experiment with thioanisole as a surrogate similar nucleophile and ClBcat in toluene at 120° C resulted in no observable formation of BCl_3 (Figure 3b), despite formation of BCl_3 being plausibly thermodynamically favorable.[39] Thus, ClBcat (and not BCl_3) remains the likely electrophilic cyclization agent. Generation of zwitterion **20** could instead be explained by an equilibrium with proposed **2b** via mechanisms that have been described previously.[41,42] Product **3b** was the only observed solution species in this sequence by ^{1}H and ^{11}B NMR spectroscopy. The absence of **22** can be plausibly explained by the tighter binding of chloride ions on **20** compared to **2b**,[7] which prevents subsequent ring opening. These data provide indirect evidence for the formation of intermediate **2b** during this reaction, and more generally support the formation of zwitterionic intermediates en route to products **3**, **7**, and **11**.

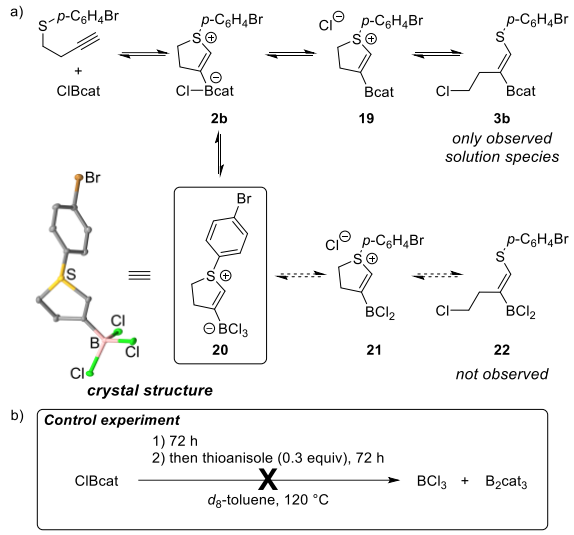
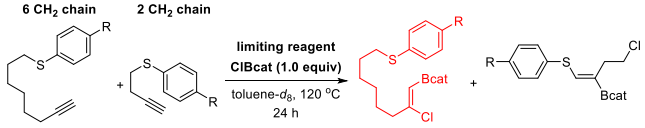


Figure 3. a) Proposed equilibrium that leads to formation of **20** and X-ray crystal structure of **20** with the thermal ellipsoids shown at 50% probability (B, pink; C, gray; S, yellow; Cl, green; Br, orange); and b) control experiments for possible formation of BCl_3.

A relative rate study established the rate-determining step with 2-methylene alkyne substrates. Heterocyclization/group-transfer involves nucleophilic attack by sulfur, whereas chloroboration does not involve sulfur. Thus, the degree of chloroboration serves as an internal control measurement that is independent of electronics at sulfur, allowing the rate of reactions involving sulfur to be measured *relative* to it. If alkyne-activation/cyclization is rate-determining, then more electron-rich sulfur would cyclize faster due to its higher nucleophilicity. If, instead, S_N2 ring opening

Table 3. Intermolecular competition experiments show cyclization is rate-determining.



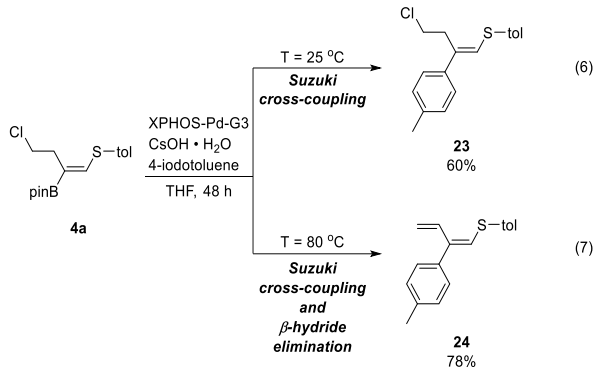
Entry	R	Ratio of **14**:**3**[a]
1	F	1:5.2
2	CH_3	1:9.3
3	OCH_3	1:27

[a] Obtained by ^{1}H NMR spectroscopic analysis of the reactions in toluene-d_8.

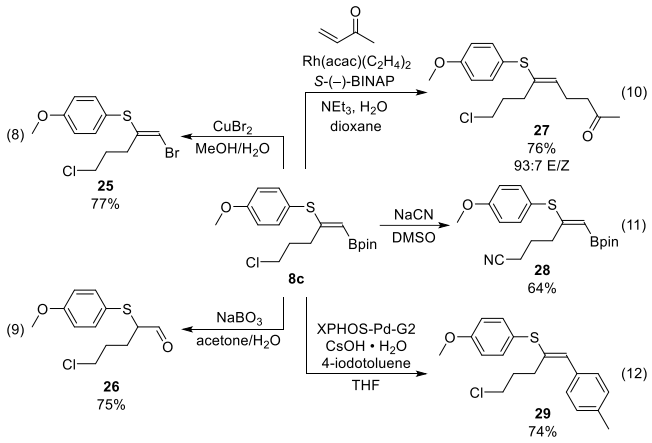
is rate-determining, then less-electron-rich sulfur would leave faster due to its better leaving-group ability. More electron rich sulfur substrates produced a higher ratio of group-transfer relative

to chloroboration (Table 3), which is consistent with rate-determining alkyne-activation/cyclization. This observation is consistent with alkyne-activation/cyclization as the rate-determining step in previous borylative cyclizations,[9] despite the increased difficulty of dealkylating the current primary alkyl sulfonium compared to the previously reported methyl sulfonium.

The synthetic utility of these group transfer products was next established. A Suzuki cross-coupling reaction of compound **4a** at 25 °C afforded the trisubstituted alkene **23** in 60% yield in 48 h (eq 6).[41] Interestingly, subjecting **4a** to otherwise identical reaction conditions but at an elevated temperature (80 °C) resulted in elimination at the alkyl chloride in addition to cross-coupling at the alkenyl boronate to yield diene **24** in 78% yield (eq 7).



To further demonstrate the synthetic utility of group transfer products, additional example functionalizations were performed. Bromination of the C–B bond occurred upon heating **8c** with a stoichiometric amount of $CuBr_2$ in 77% yield (**25**, eq 8). Oxidative workup of **8c** selectively generated aldehyde **26** in 75% yield in the presence of the sulfide (eq 9). Rhodium-catalyzed conjugate addition of **8c** with butenone gave alkene **27** in 76% yield (93:7 E/Z; eq 10). Substitution of the chloride in **8c** by cyanide generated **28** in 64% yield (eq 11). Suzuki cross-coupling of alkenyl boronate **8c** with 4-iodotoluene produced **29** in a 74% yield (eq 12).



In conclusion, a new class of group-transfer reactions diverts an intermediate during borylative electrophilic cyclization, generating borylated alkenes with predictable stereo- and regiochemistry. These group-transfer reactions proceed without the need for metal mediation or catalysis. The resulting trisubstituted alkenes have three handles for potential downstream functionalization: an alkenyl boronate,[21,22] an alkenyl sulfide,[25,26] and an alkyl halide. We envision that this group-transfer mechanism maps broadly onto the wide range of established "Larock-type" electrophilic cyclization/dealkylation sequences, therefore enabling future development of series of analogous transformations. This mechanism thus serves as a springboard toward complementary ways to access synthetically useful regio- and stereodefined alkenes.

Crystallographic Data: Deposition numbers at the CCDC – 2112411 for **4a**, 2112412 for **8a**, and 2112410 for **20**.

Acknowledgements

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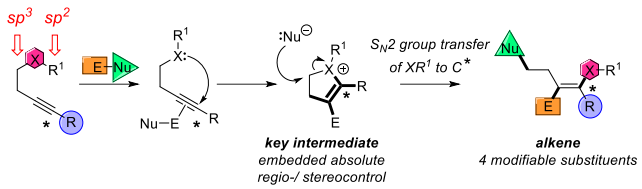

Hijacking electrophilic cyclization intermediates allows for a pathway to acyclic tri- and tetrasubstituted alkenes with predictable regio- and stereochemistry. Mechanistic studies indicate concerted thioboration of the alkyne precedes rate-determining ring opening and investigate the effects of ring-size and functional groups on reaction selectivity.

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