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Article

Transition-Metal-Free Thioboration of Terminal Alkynes

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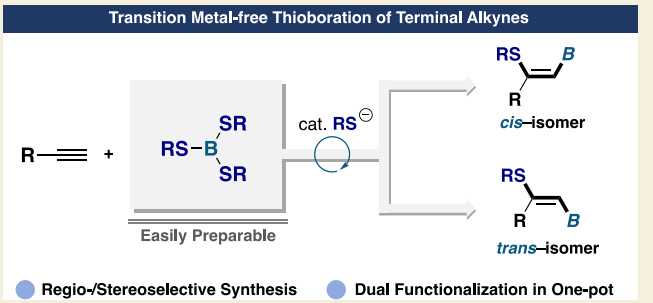
ABSTRACT: We present a new type of elementoboration reaction, the thioboration of terminal alkynes. This method enables highly controllable regio-/stereo-/chemoselective *cis*- and *trans*-thioboration on demand, affording synthetically versatile and densely functionalized vinyl boron/vinyl sulfide derivatives in a straightforward manner without the need for a transition-metal catalyst.



KEYWORDS: *thioboration, elementoboration, vinyl sulfide, vinyl boron, dual functionalization, alkyne*

Elementoboration of terminal alkynes,[1] the addition of B−X bonds across carbon−carbon π-bonds, is one of the most powerful methods for regio- and stereospecific synthesis of vinyl boron compounds, which have been widely employed as building blocks in the design and synthesis of medicines, agrochemicals, and functional materials (Figure 1A). Hydroboration (X = H) of alkynes is currently the most widely used direct elementoboration,[2,3] and synthetic applications of alkyne haloborations (X = Cl and Br) have also been well studied.[4−6] Recently, some elementoborations that are difficult by traditional methods, such as carboboration (X = C),[7] diboration (X = B),[8,9] silaboration (X = Si),[10,11] phosphinoboration (X = P),[12] selenoboration (X = Se),[13] and stanylboration (X = Sn),[14] have been accomplished by the use of transition metal (TM) catalysis, radical reaction, and so on. In contrast, thioboration (X = S) is far less developed despite the development of various thioelementations, such as thiole-yne reaction, disulfide-yne reaction, thiohalogenation, and thiosilylation.[15] The *B*,*S*-substituted olefins obtained by thioboration of terminal alkynes are attractive candidates for biologically active molecules[16] and building blocks[17] but generally require multistep synthesis.[18] In 1993, Suzuki and Miyaura reported an elegant palladium(0)-catalyzed thioboration of terminal alkynes with 9-(alkylthio)-9-borabicyclo[3.3.1]nonane derivatives (Figure 1B1);[19] however, some challenges remain. First, *B*,*S*-substituted olefins were not isolable under their reaction conditions. Second, the products (vinyl sulfide derivatives) were limited to the *cis*-isomer because the addition (thio-palladation) reaction proceeds under rigorous *syn*-addition control. Herein, we wish to report a transition-metal-free chemo-/regio-/stereoselective thiobora-

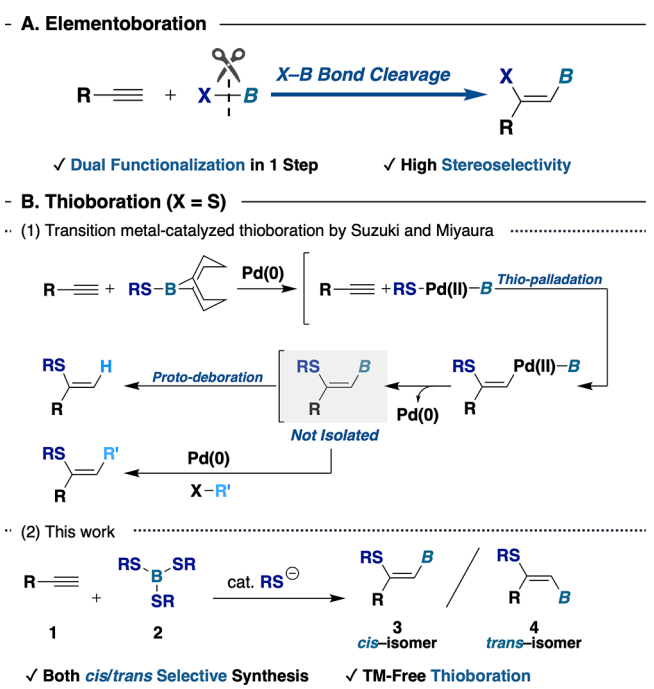


Figure 1. Background of elementoboration chemistry.

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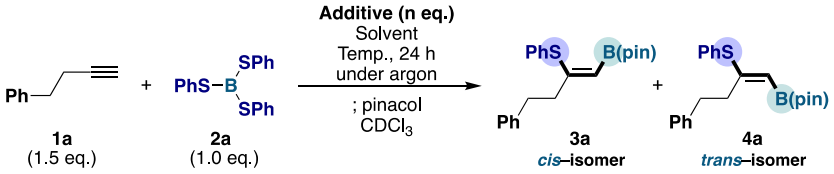
Table 1. Optimization of the Thioboration Reaction



1a (1.5 eq.) + 2a (1.0 eq.) → 3a *cis*–isomer + 4a *trans*–isomer

entry	additive	n	temp. (°C)	solvent (33 mM)	yield (%)[a]	*cis*	/	*trans*
1	none	–	120	MeCN, DMF DMSO, toluene	0		–	
2	none	–	120	neat	28	10	/	90
3	NaSPh	0.1	120	neat	80	91	/	9
4	NaSPh	0.1	100	neat	32	84	/	16
5	NaSPh	0.1	80	neat	12	75	/	25
6	pyridine	0.1	120	neat	39	56	/	44
7	NEt_3	0.1	120	neat	25	56	/	44
8	NaSPh	1.0	120	neat	68	88	/	12

[a]Yields and *cis*/*trans* ratios were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

tion of various terminal alkynes **1** by triaryl thioborates **2** leading to *cis*- and *trans*-(*β*-(arylthio)vinyl)boranes (**3** and **4**) as required, depending on the reaction conditions (Figure 1B2).

Triaryl thioborates **2** can be easily prepared by the reaction of trichloroborane (BCl_3) with arylthiolate (ArS^-).[20] Our theoretical calculations predicted that triphenyl thioborate (**2a**) exhibits potent Lewis acidity due to the poor overlap of the PhS lone pair (3p orbital) with the empty 2p orbital of the B atom, which is considered to be more acidic than BF_3 (the affinity for hydride was calculated; see Supporting Information). Hence, we commenced our study by investigating the model reaction of 4-phenyl-1-butyne (**1a**) with **2a** in the absence of TM catalysts/additives (Table 1). Preliminary investigations in a variety of (polar and nonpolar) solvents were not fruitful (entry 1), which is consistent with the findings of Suzuki and Miyaura.[19] However, we were encouraged to find that when the reaction was carried out without solvent, the desired thioboronates (**3a** and **4a**) were formed, albeit in low yields (entry 2). After a brief investigation of the neat reaction conditions, we were pleased to find that the yield was greatly improved, and the *cis*-adduct (**3a**) was selectively obtained when small excess amounts of sodium thiophenolate (NaSPh) were used (entry 3). As the reaction temperature was lowered to 100 or 80 °C, the yield dropped significantly (entries 4 and 5). The screening of Lewis basic additives revealed that pyridine slightly accelerated the reaction, but triethylamine had little effect (entries 6 and 7). Increasing the amount of NaSPh to 1.0 equiv did not improve the yield (entry 8). Finally, the set of conditions shown in entry 3 was found to be optimal.

With the optimized conditions in hand, we investigated the substrate scope of the *cis*-thioboration reaction (Table 2). A wide range of terminal alkynes such as **1a**–**1j** could be employed for this protocol. In all cases, the reactions were regiospecific, that is, boron and sulfur were added to the terminal side and internal side of the resulting alkene, respectively. The chemical structure and regio-/stereochemistry of **3** were unambiguously determined by single-crystal X-ray crystallographic analysis of **3a_DAN**, which was obtained by using 1,8-diaminonaphthalene instead of pinacol during quenching. Alkynes with primary and secondary alkyl substituents (R) were efficiently converted to the corresponding *cis*-thioboration products in moderate to good yields (**3a**–**3j**). A base/nucleophile-sensitive moiety such as the trimethylsilyl (TMS) group in **1e** remained intact, and **3e** was obtained in a good yield. In contrast, an alkyne with adjacent sterically very hindered substituents (**3k**), an internal alkyne (**3l**), and an alkene (**3m**) did not undergo the present thioboration reaction at all. On the other hand, this reaction is not limited to aliphatic alkynes. Aryl alkynes were also applicable (**3n**–**3p**), although modification of the reaction/workup conditions will be needed to improve the *cis*/*trans* selectivity. Electronic effects on the benzene ring appear to have some influence on the reactivity/stereoselectivity. The electron-neutral parent phenyl group gave the thioboration products in a 46% yield as a mixture of stereoisomers (**3n**/**4n** = 56/44). An electron-donating substituent (*p*-MeO) on the phenyl ring gave a higher chemical yield with comparable *cis*/*trans* selectivity (**3o**/**4o** = 59/41), whereas the use of an electron-withdrawing group (*p*-CF_3) decreased the yield to 29% with a higher *cis*/*trans* selectivity (**3p**/**4p** = 81/19).

During optimization of the reaction conditions, we occasionally found that the addition of water to the crude mixture led to geometrical isomerization, exclusively affording trans-thioboration products (Table 3). The structure was determined by single-crystal X-ray diffraction analysis of compound **4a**. On the other hand, **4c**, which has a bulky cyclopentyl group, hardly underwent isomerization and remained in the *cis* form (**3c**) presumably because of its inherent thermodynamic stability. The distal cyclopropyl group was untouched in the case of **1q**, affording product **4q** chemoselectively in a good yield.

Under the optimized reaction conditions, we examined the substituents on sulfur (Table 4). Triaryl or trialkyl thioborates [$B(SR)_3$ (**2b**–**2e**)] were synthesized by using the corresponding thiolates and BCl_3. The steric and electronic effects of substituents on sulfur had little influence on the regioselectivity/reactivity, and various thiols could be used for the present thioboration of terminal alkyne. In particular, the chemoselective thioboration of **1a** with **2d** afforded the desired products (**3t** and **4t**) in moderate yields, even in the presence of the aromatic C–Br bond, presumably because the reaction was transition-metal-free. In addition, an alkyl (sp^3) thiol was also applicable (**3u**).

Next, we examined the potential applications of the multifunctionalized (*β*-(arylthio)vinyl)borane compounds produced in this work (Scheme 1). The *cis*- and *trans*-thioboration

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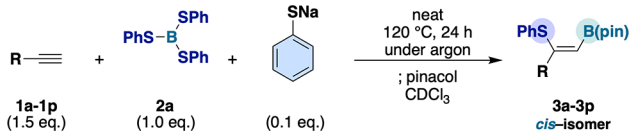
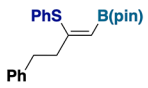
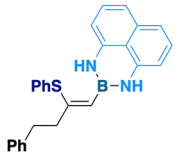
Table 2. Thioboration Reaction of Alkynes Leading to *cis*-Alkene Adducts[a]



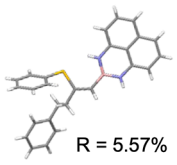
Aliphatic Alkynes



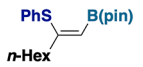
3a: 76% (*cis*/*trans* = 92/8)



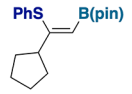
3a_DAN: 57% (*cis*/*trans* = 97/3)



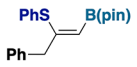
X-ray structure of **3a_DAN**



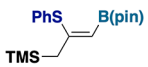
3b: 67% (*cis*/*trans* = 92/8)



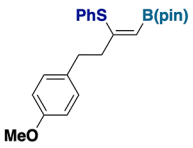
3c: 35% (64%) (*cis*/*trans* = 97/3)



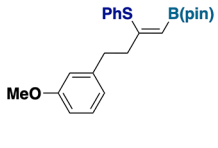
3d: 43% (*cis*/*trans* = 96/4)



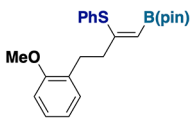
3e: 60% (86%) (*cis*/*trans* = 87/13)



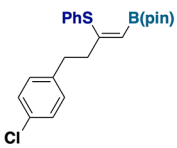
3f: 81% (*cis*/*trans* = 93/7)



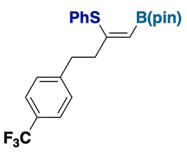
3g: 72% (*cis*/*trans* = 94/6)



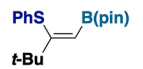
3h: 63% (*cis*/*trans* = 90/10)



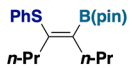
3i: 58% (*cis*/*trans* = 96/4)



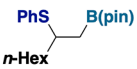
3j: 65% (*cis*/*trans* = 94/6)



3k: (0%)

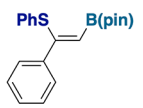


3l: (0%)

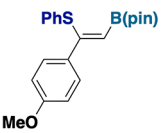


3m: (0%)

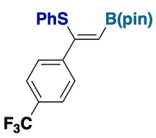
Aryl Alkynes



3n: 46% (*cis*/*trans* = 56/44)



3o: 68% (*cis*/*trans* = 59/41)



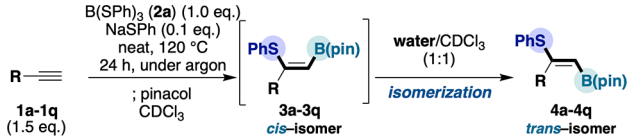
3p: 29% (*cis*/*trans* = 81/19)

[a]Isolated yields. ^{1}H NMR yields are shown in parentheses. *Cis*/*trans* ratios were determined by ^{1}H NMR. Starting materials were totally consumed, and in cases where product yields were lower than expected, this might be explained by polymerization of alkynes.

products (**3a** and **4a**) could be utilized as vinylating agents in the Suzuki–Miyaura coupling reaction with good chemo-/stereoselectivity (**5** and **6**). The vinyl borons also react with $CuBr_2$ to give the corresponding bromination products (**7** and **8**) in moderate yields (Scheme 1A).

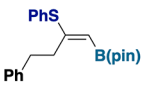
The carbonylation of vinyl sulfide **6** proceeded in a 66% yield upon treatment with hydrochloric acid in a mixed solvent with water (Scheme 1B). Further applications of this

Table 3. Thioboration Reaction of Alkynes Followed by *cis*/*trans* Isomerization of Alkene Adducts[a]

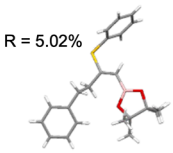


Aliphatic Alkynes

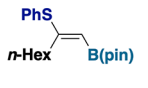
cis/*trans* < 1/99



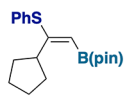
4a: 44% (77%)



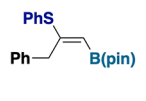
X-ray structure of **4a**



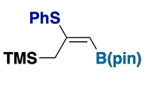
4b: 58% (70%)



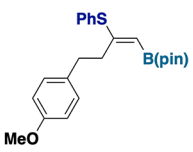
4c: 0%[b]



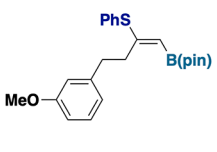
4d: 41% (46%)



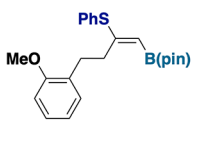
4e: 68% (80%) 83%[c]



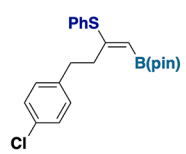
4f: 65% (64%)



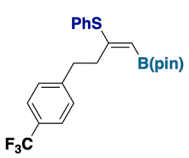
4g: 42% (71%)



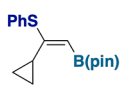
4h: 56% (75%)



4i: 36% (50%)



4j: 36% (50%)



4q: 47% (76%)

[a]Isolated yields. ^{1}H NMR yields are shown in parentheses. All *cis*/*trans* ratios were <1/99, as determined by ^{1}H NMR. [b]The *cis* isomer was obtained exclusively in a 64% yield as determined by ^{1}H NMR. [c]Scaled at 1.5 mmol instead of the usual 0.3 mmol. Starting materials were totally consumed, and in cases where product yields were lower than expected, this might be explained by polymerization of alkynes.

methodology are illustrated in Scheme 1C. Vinyl boron compound **4e** synthesized via the present *trans*-thioboration of **1e** is an intriguing chemical scaffold. **4e** underwent smooth Suzuki–Miyaura coupling with 4-iodoanisole to afford the desired styrene derivative **10**, which could be further transformed into a styryl sulfoxide (**11**) by an oxidation with *m*CPBA. Treatment of **10** with benzaldehyde dimethyl acetal in the presence of $BF_3{\cdot}OEt_2$ gave **12** in a 48% yield.

We next set out to acquire mechanistic insights into the present *cis*-thioboration and geometric isomerization. Control experiments showed that the isomerization reaction was completed within 1 h under an oxygen atmosphere but hardly proceeded under an argon atmosphere even for 24 h (Figure 2A). When the thiolate was removed by precipitation of silver thiolate,[21] it was found that the isomerization did not proceed at all. Therefore, we consider that the isomerization proceeds through addition to the C=C double bond of thiyl radicals[22] generated by the autoxidation of thiolate dissolved in water.[23] We subsequently performed density functional theory (DFT) calculations to investigate the energy diagram of the proposed

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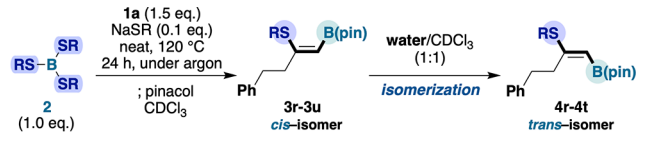
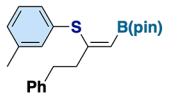
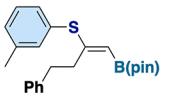
Table 4. Scope of the Substituent on Sulfur[a]



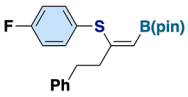
Aryl Substituents



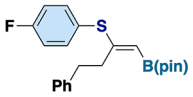
3r: 62% (*cis*/*trans* > 99/1)



4r: 52% (62%) (*cis*/*trans* < 1/99)

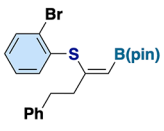


3s: 36% (*cis*/*trans* = 93/7)

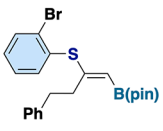


4s: 47% (72%) (*cis*/*trans* < 1/99)

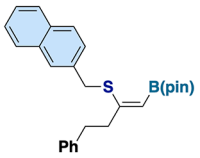
Aliphatic Substituent



3t: 61% (*cis*/*trans* > 99/1)



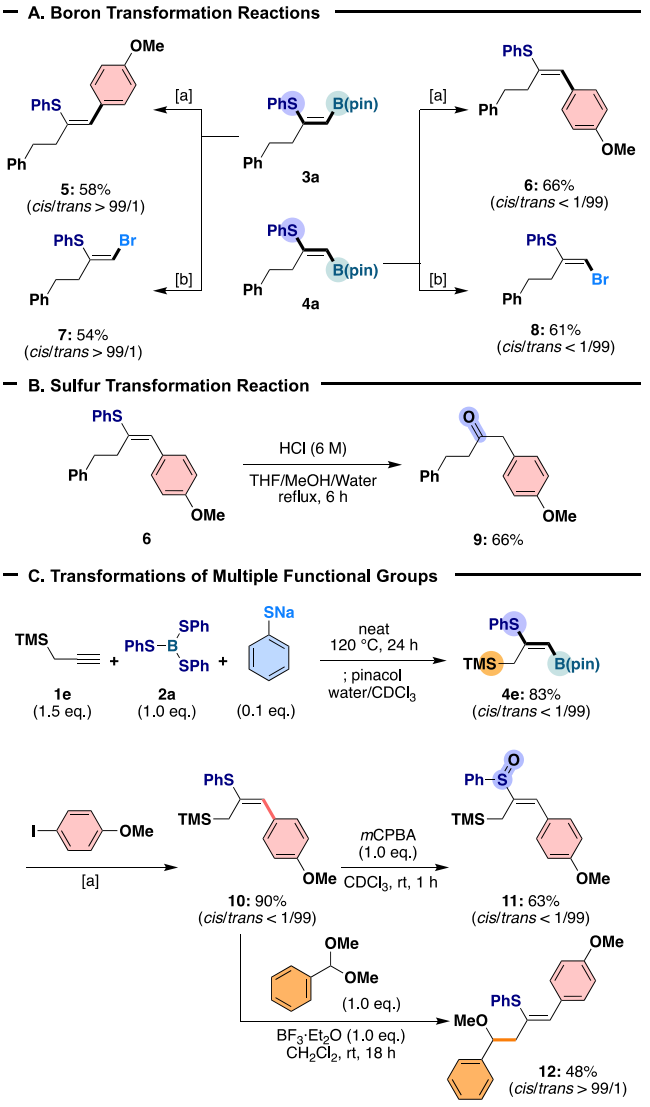
4t: 38% (46%) (*cis*/*trans* < 1/99)



3u: 34% (*cis*/*trans* > 99/1)

[a]Isolated yields based on **2**. ^{1}H NMR yields are shown in parentheses. *Cis*/*trans* ratios were determined by ^{1}H NMR. As for the synthesis of **4**, **3** was not isolated (tandem reactions). Starting materials were totally consumed, and in cases where product yields were lower than expected, this might be explained by polymerization of alkynes.

Scheme 1. Transformations of *cis*- and *trans*-Thioboration Products[a]



[a](a) 4-Iodoanisole (2.0 equiv), $Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), $CsOH{\cdot}H_2O$ (3.0 equiv), THF, rt, 48 h, under argon. (b) $CuBr_2$ (3.0 equiv), $MeOH/H_2O$, 80 °C, 30 min. Starting materials were totally consumed, and in cases where product yields were lower than expected, this might be explained by protodeboration of the starting materials or an intermolecular aldol reaction or proto-desilylation.

reaction pathway (Figure 2B): all the activation energies are sufficiently low (<11 kcal mol^{-1} in all steps) and the *trans* isomer is thermodynamically more stable (−2.5 kcal mol^{-1}).

We next focused on the mechanism of the present thioboration reaction. Initially, NaSPh was thought to react rapidly with highly Lewis-acidic $(PhS)_3B$ to form a borate complex $(PhS)_4B^-{\cdot}Na^+$. Theoretical calculations indicated that the ate complexation proceeds smoothly with a large exothermicity [−14.7 kcal mol^{-1}; M06-2X/6-31+G(d,p)] (Figures 2C and S9). This was also confirmed by the ^{1}H and ^{11}B NMR spectra, which showed only one set of signals assigned to $(PhS)_4B^-{\cdot}Na^+$ at different chemical shifts from those of the starting $(PhS)_3B$ and NaSPh (Figures S3 and S4). Notably, signal splitting was not observed, even when the temperature was lowered to −100 °C (Figure S5). Having confirmed that the ate complexation of $(PhS)_4B^-{\cdot}Na^+$ is likely to be experimentally and theoretically relevant, we then conducted control experiments and found that the thioboration reaction was shut down in the presence of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) or galvinoxyl free (stable) radical (Figure 2C and Section 3−6 in the Supporting Information). Notably, when galvinoxyl was added, peaks with molecular weights corresponding to **G1** and **G2** were observed in APCI-MS. Thus, we speculated that the thioboration reaction proceeds via the mechanism illustrated in Figure 2D. First, the highly Lewis acidic **2** and the thiolate anion (**RS**$^-$) form an ate complex (**i**). Subsequently, thermal homolysis of the B−S bond in **i** generates a boryl radical anion (**ii**) by releasing the thiyl radical (**RS**$^\bullet$). Then, **ii** adds to the alkyne π-bond at the terminal carbon, yielding a vinyl radical (**iii**), followed by the migration of the SPh group to give another boryl radical anion (**iv**). Finally, single electron transfer between **iv** and **2** produces the desired product **3**, and it regenerates the radical anion (**ii**), completing the catalytic cycle. DFT calculations were then employed to evaluate this putative mechanism (Figure 2E). The addition of the boryl radical anion (**ii**) to the alkyne was found to proceed with a low activation barrier (+12.3 kcal mol^{-1}) and a large thermodynamic stabilization (−19.8 kcal mol^{-1}). The subsequent rearrangement reaction of the SPh

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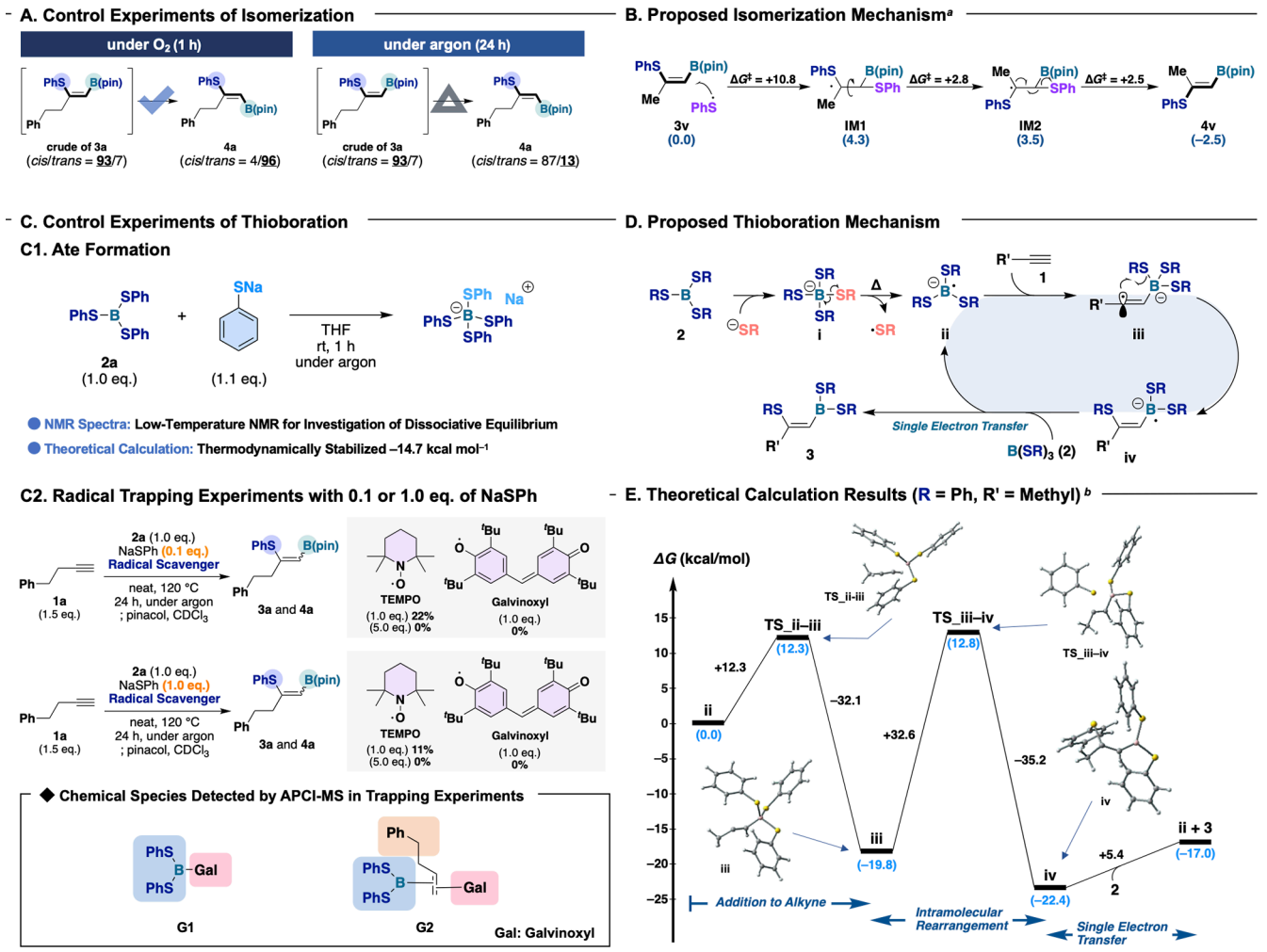

Figure 2. Mechanistic studies and proposed mechanisms. [a]Calculation was performed at the M06-2X/6-31+G(d,p) level. Gibbs free energies relative to **3v** are shown in parentheses (kcal mol^{-1}). [b]Calculation was performed at the M06-2X/6-31+G(d,p) level. Gibbs free energies relative to **ii** are shown in parentheses (kcal mol^{-1}).

group required a relatively large activation energy (+32.6 kcal mol^{-1}), which is consistent with the experimental finding that the reaction requires harsh conditions (120 °C, neat). Although the single electron transfer between **iv** and **2** proceeds with a slight endothermicity (+5.4 kcal mol^{-1}), the overall reaction stabilization of −17.0 kcal mol^{-1} shows that the thioboration reaction is greatly favored thermodynamically. We also examined the feasibility of other thioboration pathways/mechanisms by performing DFT calculations, but no other plausible thioboration pathways, including ionic mechanisms, with reasonable activation energies were found. On the basis of these results, we propose that the present thioboration reaction proceeds through a radical mechanism rather than an ionic mechanism, triggered by the formation of $(PhS)_4B^-{\cdot}Na^+$. We are currently conducting further detailed analyses of the reaction mechanism from both experimental and theoretical perspectives.

In conclusion, we present the first transition-metal-free thioboration reaction of terminal alkynes. This reaction provides access to both *cis*- and *trans*-[*β*-(arylthio)vinyl]-boranes, depending upon the reaction conditions and provides facile access to synthetically versatile unsymmetrical vinyl borons and vinyl sulfides. The method enables simple and direct regiocontrolled synthesis of trisubstituted olefins from various functionalized terminal alkyne precursors. Further work to expand the scope of the reaction and to develop applications of the products, multiple substituted olefins/vinyl borons/vinyl sulfides, for the synthesis of biologically active and functional molecules is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00907.

Synthetic experiments, data for compound characterization, and theoretical calculations (PDF)

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Notes

The authors declare no competing financial interest.

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