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Organic Chemistry

Stereodivergent Zweifel Olefination and its Mechanistic Dichotomy

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Dedicated to Professor George Zweifel

Abstract: Stereoselective Zweifel olefination using boronate complexes carrying two different reactive π-systems was achieved to synthesize vinyl heteroarenes and conjugated 1,3-dienes in good yield and up to 100% stereoselectivity, which remains unexplored until now. Most importantly, we report the unprecedented formation of *E* vs. *Z*-vinyl heteroarenes for different heteroarenes under identical conditions. Density functional theory (DFT) investigations unveil the mechanistic dichotomy between olefin and heteroarene activation followed by 1,2-migration, leading to *E* or *Z*-vinyl heteroarenes respectively. We also report a previously unknown reversal of stereoselectivity by using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an electrophile. The Zweifel olefination using a boronate complex that carries two different olefins was previously unexplored due to significant challenges associated with the site-selective activation of olefins. We have solved this problem and reported the site-selective activation of olefins for the stereoselective synthesis of 1,3-dienes.

Introduction

Alkenes are essential building blocks in organic synthesis, pharmaceuticals, material chemistry, and more as they can serve as precursors for many important C–C bond-forming reactions. As a result, the stereoselective synthesis of alkenes is a topic of wide interest in the synthetic community.[1a–c] Despite several developments in this area, no single method is ideal for achieving optimal stereoselectivity for diverse olefins due to their electronic and steric differences. The development of a uniform strategy to access both *E*- and *Z*-isomer of a different class of olefins is limited.[2a–c] Standard olefination methods like Wittig, HWE protocol, Julia olefinations suffer from poor regioselectivity due to steric effect in the transition state.[2d–e] Despite several developments in the field, stereoselective synthesis of a diverse range of tri- and tetra-substituted olefins carrying heteroaryl groups using a uniform strategy is still challenging. Although palladium-catalyzed Suzuki coupling reactions worked well for di-substituted olefins, the reaction of tetra-substituted vinyl boronic ester and aryl/heteroaryl/vinyl halides suffer from low yield.[2f–i]

Zweifel olefination is an attractive transition metal-free method for the stereoselective synthesis of olefins, which was first reported in 1967 (Scheme 1a).[3a] In the original method, *E*-vinyl boranes (derived from alkynes via hydroboration) are converted into *Z*-alkenes by the addition of iodine and sodium hydroxide in THF. The reaction is thought to proceed via the formation of iodonium species upon activation of boronate complexes with iodine, which triggers subsequent 1,2-migration to produce β-iodoborinic acid. Finally, base-induced *anti*-elimination leads to *Z*-olefins.[3b] The Zweifel group also introduced an elegant method for the synthesis of *E*-olefins via *syn*-elimination of intermediate β-bromo-boranecarbonitrile, which originated from the reaction of boronate complexes with cyanogen bromide.[2c] Following the initial demonstration by the Zweifel group, several improvements have been suggested by Matteson,[4] Evans,[5] Brown,[6] and others for the synthesis of alkenes and alkynes.[7]

The Aggarwal research group also made a major contribution to the extension of the Zweifel olefination methodology.[8] For the first time, they introduced unsubstituted vinyl lithium and vinyl Grignard reagents for Zweifel olefination.[9] Using this strategy, a large number of natural products were synthesized by various research groups.[10–16] The Aggarwal group also introduced an alternative method to access *E*-olefins using phenyl selenium chloride as an electrophile,[8e] which avoids the use of toxic cyanogen bromide as an electrophile. The concept of 1,2-migration upon electrophilic activation of a π-system was further extended to heteroaromatics and aromatic systems by Levy,[17] Suzuki,[18] and Ishikura[19] to access substituted heteroaryls and aryls respectively (Scheme 1b). Aggarwal group applied this concept for the enantioselective synthesis of chiral heteroaryls and aryls (Scheme 1b).[20] Our group also recently contributed to the development of heterobiaryls synthesis using aryl boronic esters following a similar strategy.[21]

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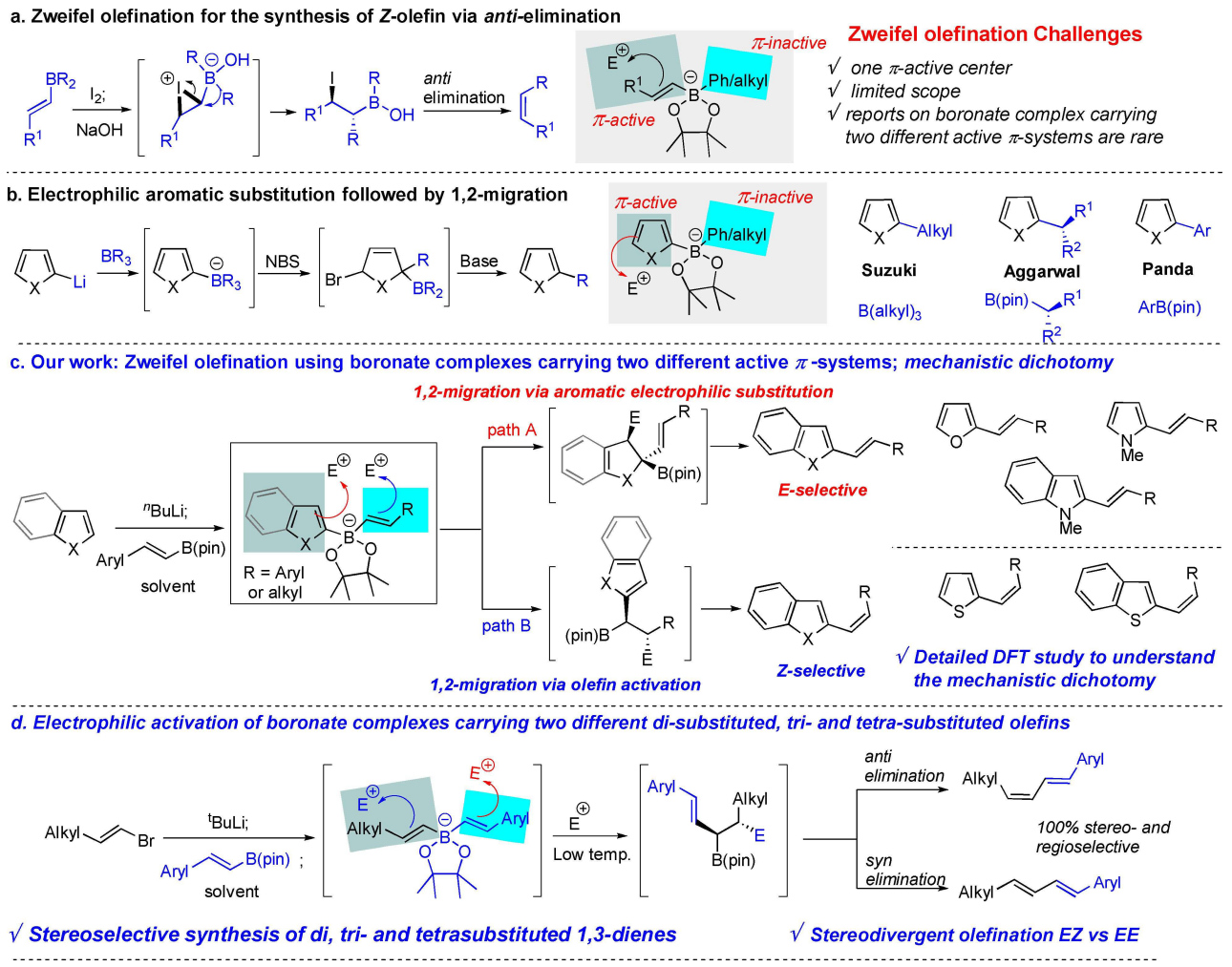

Scheme 1. Zweifel olefination, state-of-the-art and our work.

Although several developments have been made in the Zweifel olefination and its extension to heterocyclic synthesis, the chemistry has remained mostly applicable to systems bearing a combination of a π-inactive and a π-active group (alkyl/phenyl lithium with vinyl boron compounds or alkyl/phenyl boron compound with alkenyl lithium), which limits the scope of this reaction in organic synthesis (Scheme 2a).[22] The reactivity of boronate complex carrying two different reactive π-systems (vinyl vs heteroaryl or two different vinyl) challenging and remains unexplored; the stereochemical outcome from the following boronate complexes remained unexplored until now (Scheme 1c): (a) vinyl vs. heteroaryl, (b) di-substituted vs. di-substituted olefin, (c) di-substituted vs. tri-substituted olefin, (d) di-substituted vs. tetra-substituted olefin. Surprisingly, stereodivergent olefination (*E* vs *Z*-selectivity for different heteroaryls under identical conditions) was observed using different heteroaryls under identical conditions (Scheme 1c). We have performed thorough DFT calculations to understand this outcome, which will be discussed later in Scheme 5 and Figures 1, 2 & 3. Also, the stereoselectivity can be switched by using DDQ as an electrophile, which might drive the reaction via electrophilic aromatic substitution (S_EAr) over olefin activation. A detailed computational study using density functional theory (DFT) and a variety of mechanistic experiments were conducted to understand the origins of reactivity differences between the two reactive π-systems, which is the key to the stereoselective synthesis of olefins. We have not found any previous literature addressing this type of reactivity.

We have also demonstrated the stereoselective olefination using a boronate complex carrying two different olefin groups in Scheme 1d (can be di, tri-, or tetra-substituted). The reaction using a boronate complex that carries two different olefins remains unexplored due to the significant challenges associated with the site-selective activation of olefins. Herein, we report site-selective activation of olefins for the stereoselective synthesis of 1,3-dienes. Moreover, the stereodivergent synthesis *EE* vs. *EZ* –1,3-dienes was achieved using a reagent-controlled strategy. Traditionally, the stereoselective synthesis of heteroaryl substituted alkenes and 1,3-dienes using standard olefination methods such as the Wittig reaction suffers from poor *E/Z* selectivity (See SI, S2–S3 for a list of selected examples).[23] Consider-

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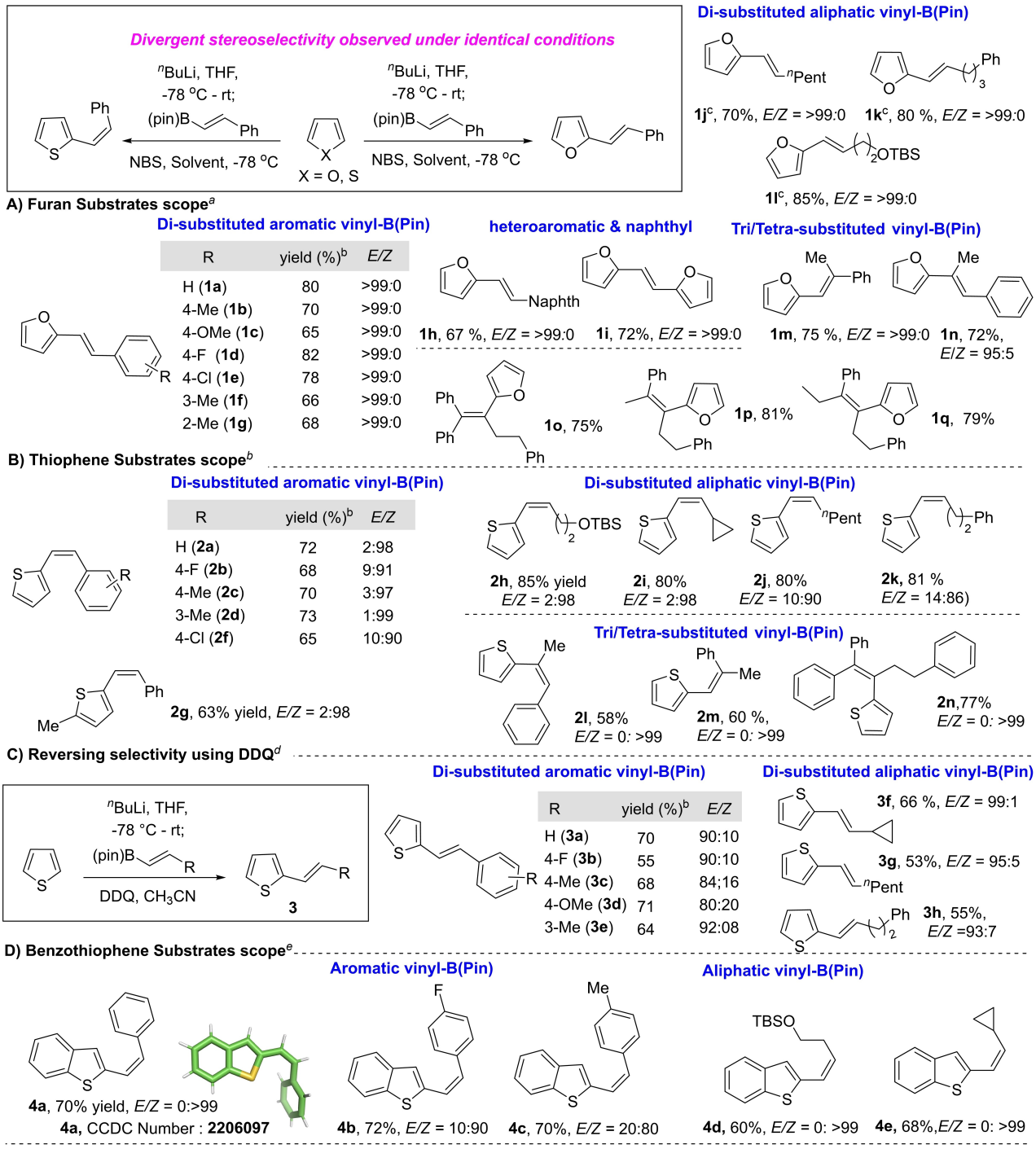

Scheme 2. Substrate scope for Heterobiaryls[f]. n-BuLi(1.2 M in hexane, 1.5 equiv) was added to furan/thiophene (1.5 equiv) in THF at −78 °C, stirred for 30 min then warmed to rt for 30 min, after that vinyl boronic ester (1 equiv) in THF was added at −78 °C and stirred for 0.5 h, then warmed to 0 °C for 1 h. a) after the boronate complex formation, NBS was added in DMF to keep THF : DMF = 1 : 1, at −78 °C and left stirring for 2 h; b) after the boronate complex formation, NBS in THF was added at −78 °C and left stirring for 2 h. c) DDQ as an electrophile in THF solvent; d) After the boronate complex formation, solvent was removed in vacuum and acetonitrile was added. The reaction was further cooled at −40 °C, DDQ was added and the mixture stirred for 2 h at −40 °C; e) NBS, THF : DMF = 1 : 1, −78 °C, 1 h then 0 °C, 1 h; f) isolated yields, diastereomeric ratio was confirmed by crude reaction mixture 1H NMR.

ing the importance of vinyl heteroarenes and 1,3-dienes in organic synthesis (See SI, S4–S6 for a list of bioactive vinyl heteroaryls and their diversification)[24] and challenges in stereodivergent synthesis in the absence of transition metals, we have developed a transition metal-free strategy to access these valuable compounds with high stereoselectivity.

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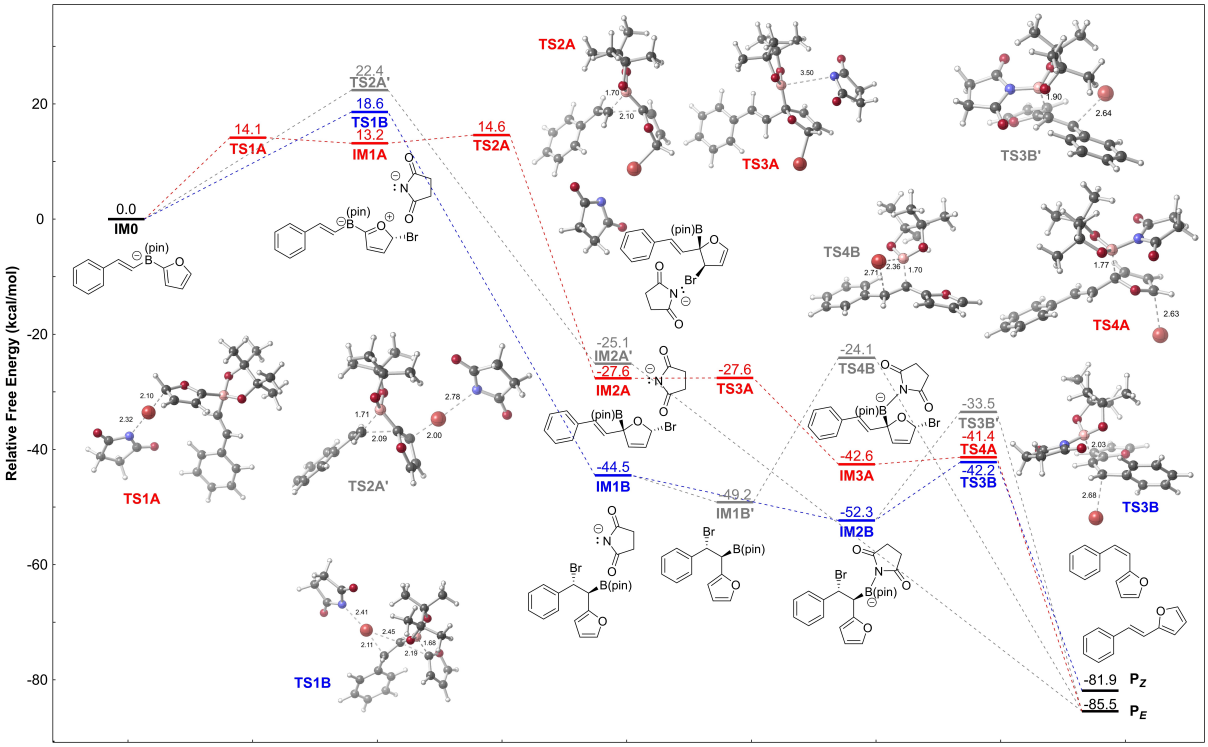

Figure 1. Computed (revDSD-PBEP86-D4/def2-TZVPPD//SMD(THF)-M06-2X/def2-SVP) reaction profiles for competing processes in the reaction of a furyl styrenyl boronic ester anion (IM0). Relative free energies are shown in kcal/mol. Selected distances are shown in Å.

Results and Discussion

We initiated our study of stereoselective synthesis of vinyl furans and thiophenes by using lithiated furan/thiophene, *E*-2-phenylvinylboronic acid pinacol ester, and various electrophilic halogen sources (detailed optimization table can be found in SI, page S18–S20). We decided to use *N*-Bromosuccinamide (NBS) as an electrophile based on our previous optimized condition.[22] Surprisingly, we observed the stereodivergent formation of *E*-vinyl furan (52 % yield, *E/Z* = 100:0) and *Z*-vinyl thiophene (56 % yield, *E/Z* = 02:98) respectively with high stereoselectivity under identical reaction conditions (Table 1, entry 1 & 2). The major by-products in all those reactions are *ipso*-substitution products, phenyl vinyl bromide/iodide, or heteroaryl-bromide/iodide. Increasing the amount of NBS up to 2 equivalents had a beneficial effect in yield (Table 1, entry 3). Solvent plays an important role in these reactions. Considering the reports on electrophilic bromination using polar nonprotic solvents like DMF, and acetonitrile, we decided to screen polar aprotic solvents available in our lab.[25] Gratifyingly, we observed 100 % conversion of the starting vinyl boronic ester and formation of the desired product in 80 % yield by using a 1:1 mixture of THF: DMF as a solvent for the electrophilic substitution step, avoiding the formation of undesired *ipso*-product (Table 1, entry 4). Further screening of electrophilic halogen sources did not lead to any improvement. Next, we optimized the reaction using thiophene. Following the optimized condition of furan, we can isolate the desired vinyl thiophene in 72 % yield (Table 1, entry 6). Next, we were interested in reversing the stereoselectivity for furans and thiophenes. We began by following Aggarwal's *E*-selective Zweifel olefination conditions using phenylselenyl chloride (PhSeCl) as an electrophile, which resulted from the formation of (*E*)-phenyl(styryl)selane with no trace of desired products (Table 1, entry 8, 9). We hypothesized that an electrophile that will selectively participate in S_EAr reaction over activation of vinyl boronate species might afford *E*-vinyl thiophenes. Among various electrophiles screened, DDQ was effective, providing the *E*-vinyl thiophene with 67 % yield and 83:17 *E/Z* ratio (Table 1, entry 10). Computations were conducted to shed light on the details of this process (vide infra). Further screening of solvent systems and reaction conditions revealed that acetonitrile at −40 °C is optimal for achieving good yields and 90 % *E*-selectivity (Table 1, Entry 11). We also observed the formation of *E*-vinyl furan under the DDQ conditions. Optimization was carried out for other heteroaryl to improve the yield and minimize the formation of undesired *ipso*-substitution products. The substrate scope for furans, thiophenes, and benzothiophenes are listed in Scheme 3, and indole and pyrrole in Scheme 4. The stereoselective synthesis of *Z*-vinyl heteroaryls is indeed challenging.[26]

Having optimized reaction conditions for synthesizing *E* vs. *Z*-olefins, we explored substrate scope by varying different aryl, heteroaryl, and alkyl vinyl boronic esters (Scheme 2). The reactions with furans proceeded efficiently with various aryl vinyl boronic esters, to generate vinyl furans in good yields and high levels of stereoselectivity (Scheme 2A). Importantly, vinyl boronic esters carrying

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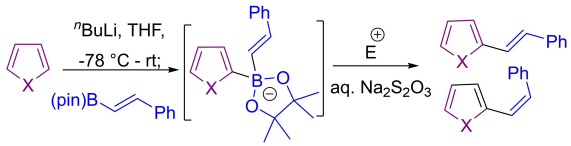
Table 1: Optimization table for vinyl furan/thiophene.[a]



Entry	X (O or S)	Electrophile (equiv)	Yield [b](%)	E : Z
1	O	NBS (1.5)	52	100:0
2	S	NBS (1.5)	56	1:99
3	O	NBS (2)	68	100:0
4[c]	O	NBS (2)	80	100:0
5[d]	O	I_2 (2)	42	100:0
6	S	NBS (2)	72	2:98
7[d]	S	I_2 (3)	45	16:84
8[e]	S	PhSeCl (1.5)	<5	ND
9[e]	O	PhSeCl (1.5)	<5	ND
10	S	DDQ (3)	67	83:17
11[f]	S	DDQ (3)	70	90:10
12	O	DDQ (3)	70	100:0

[a] nBuLi(1.2 M in hexane, 1.5 equiv) was added to furan or thiophene (1.5 equiv) in THF at −78 °C, stirred for 30 min then warmed to rt for 30 min, vinyl boronic ester (1 equiv) in THF was added at −78 °C and left stirring for 0.5 h, then warmed to 0 °C for 1 h. THF solution of the electrophile was added at −78 °C and left stirring for 2 h; b) isolated yields provided; c) electrophile was added in DMF keeping THF: DMF = 1:1; d) original Zweifel conditions (electrophile was added in MeOH (THF:MeOH = 1:1) and stirred at −78 °C for 2 h then NaOMe (5 equiv) in MeOH was added and stirred at rt for 30 min; e) solution stirred at −78 °C for 0.5 h, then warmed to rt and stirred for 15 min. Then SiO2 filtration and a THF solution of m-CPBA (2.0 equiv) was added at −78 °C and stirred at −45 °C for 30 min. (E)-phenyl-(styryl)selane was obtained in quantitative yield; f) after the boronate complex formation step, solvent was removed in vacuum and acetonitrile was added. The reaction was cooled at −40 °C, DDQ was added and the resulting solution stirred for 2 h at −40 °C.

electron-donating or withdrawing groups underwent efficient coupling to afford the vinyl furans **1a**–**1f** with 100 % stereoselectivity and good yields. We observed a slightly lower yield in the case of reactions using vinyl boronic esters carrying EDGs, which appears to be due to the formation of vinyl bromide as a result of competing *ipso*-substitution. In addition to simple aryl vinyl boronic esters, the reaction proceeded well with naphthyl and heteroaryl vinyl boronic esters to achieve 100 % stereoselectivity. Further, the reaction was carried out using tri- and tetrasubstituted vinyl boronic esters. In every case, we obtained the desired product in high stereoselectivity and good yield, which cannot be readily accomplished by known methods in the absence of transition metals to the best of our knowledge.[27]

The scope of *Z*-vinyl thiophenes was also evaluated by using several aryl vinyl boronic esters carrying electron-donating or withdrawing groups on the phenyl ring (Scheme 2B). We observed good yields and high stereoselectivity by using various aryl vinyl boronic esters (**2a**–**2f**). Even the 2-methyl thiophene was sufficiently reactive, providing a good yield of the desired product **2g**. We were also pleased to obtain good yields and high stereoselectivity using alkyl vinyl boronic esters as coupling partners (**2h**–**2k**). The scope of *E*-vinyl thiophenes using DDQ as an electrophile was further evaluated (Scheme 2C). A range of aromatic, heteroaromatic, and aliphatic vinyl boronic esters was accommodated under the optimized conditions, affording the desired *E*-vinyl thiophenes **3a**–**3h** in good yield and stereoselectivity.

We further extended the substrate scope to benzothiophenes (Scheme 2D). Interestingly, *Z*-products were formed selectively in the presence of various electrophiles (please see SI, page S21). For example, under optimized conditions using NBS as an electrophile in THF/DMF (1:1), *Z*-phenylvinyl benzothiophene was obtained in 72 % yield. The reaction worked well with various aryl and alkyl-substituted vinyl boronic esters to generate vinyl benzothiophenes (**4a**–**4e**) in good yield and high stereoselectivity.[28] In contrast, the reaction of benzofuran under similar conditions generated the vinyl benzofuran with poor stereoselectivity (*E*/*Z* = 55:45), which was also investigated in detail computationally (see below). We next turned our attention to the development of a protocol for the stereoselective synthesis of vinyl indoles and pyrroles (Scheme 3). Vinyl indoles and pyrroles are present in several bioactive com-pounds with anticancer activity, antimalarial, and more (see SI, page S4); they can also participate in Diels–Alder cycloadditions to access diverse chiral/achiral tetrahydrobenzo[c]carbazoles,[29a] carbazolespirooxindoles,[29b] indolo[2,3-a]carbazole alkaloids,[30] spiro[tetrahydrocarbazole-3,3′- oxindole][31] and more (see SI, page S5–S6), which are important structural motif present in many biologically active compounds.[24e]

Under optimized conditions, aryl vinyl boronic esters carrying electron-donating or withdrawing groups underwent efficient coupling to afford the vinyl indoles (**5a**–**5f**) with up to 100 % stereoselectivity and good yield. Most importantly, the reaction worked well with N-Boc-vinyl indole, affording the vinyl N-Boc vinyl-indole **5g** with 100 % stereoselectivity and good yield. The product **5a**, **5g**, and **5g′** can be directly converted to the bioactive compounds for cancer chemotherapy after a simple Diels–Alder reaction with maleimide (see SI, page S4 for details).[24e] Interestingly, the previous reports of 1,2-migration using indole boronate species are mostly limited to N-methylindoles.[20,21] The reaction was efficient with 3-methylindole and various substituted indoles (**5h**–**5k**). In addition to simple aryl vinyl boronic esters, the reaction proceeded well with naphthyl and heteroaryl boronic esters to produce the corresponding vinyl indoles **5n**, **5l**, and **5m** in good yield and up to 100 % stereoselectivity. We were also pleased to observe good yields and high stereoselectivity for vinyl indoles **5o**, **5p** using alkyl vinyl boronic esters as coupling partners. Moreover, the reaction with tri- and tetra-substituted vinyl boronic esters generated tri- and tetra-substituted indoles (**5s**–**5v**) in good yield and 100 % stereoselectivity, despite potential steric congestion. X-ray crystal structures for selected tri-and tetra-substituted indoles were conducted to confirm their structural integrity.[32] Thus demonstrating the potential of our strategy for the synthesis of diverse vinyl heteroarenes in great yield and high stereoselectivity.

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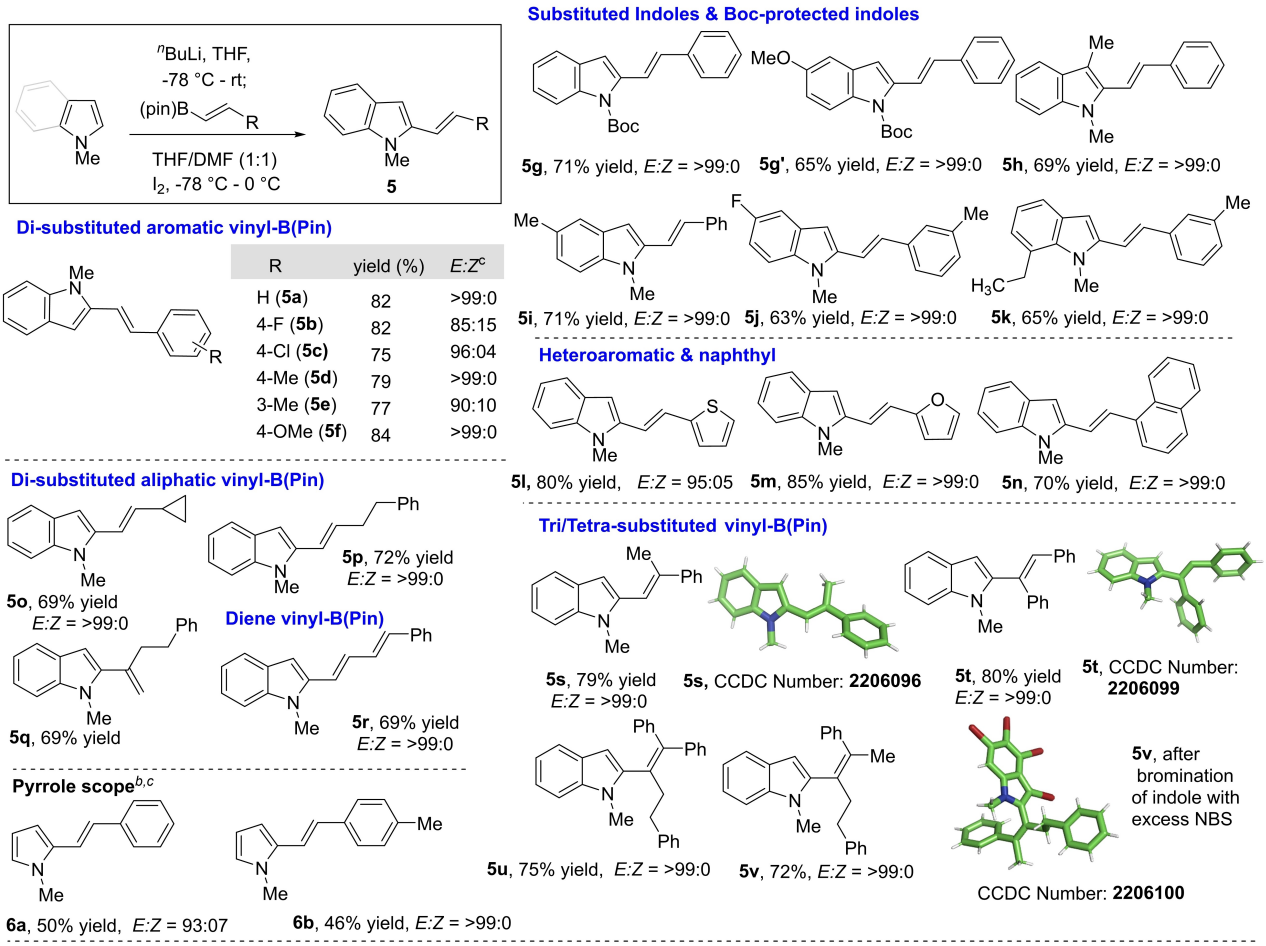

Scheme 3. Substrate scope for Indole[a,c] a) To a stirred solution of N-methylindole (1.6 equiv) in dry THF at 0 °C was added n-BuLi (1.2 M in pentane) (1.6 equiv) dropwise under argon atmosphere. The reaction was stirred at rt for 45 min. The reaction was then cooled to −78 °C and a solution of boronate ester (1 equiv) in dry THF (1 mL) was added dropwise with constant stirring. The reactions was stirred at −78 °C for 1.5 h then taken out to room temperature and stirred for 2–5 minutes to get a clear solution. After that reaction tube was transferred to the −78 °C and dropwise added I2 (2 equiv) in DMF to keep THF:DMF = 1:1, and stirred for 15 min then warm up to 0 °C for 1.5 h. b) NBS was used as an electrophile instead of iodine. c) isolated yields provided, diastereomeric ratio was confirmed by the 1H NMR of crude reaction mixture.

Stereoselective synthesis of dienes is important considering their presence in a large number of natural products and bioactive compounds.[33] However, the synthesis of conjugated dienes using Zweifel olefination remains mostly unexplored. Only one example was found in the recently published paper by Aggarwal's group,[8e] where the same vinyl B(pin) and vinyl lithium were used for the stereoselective synthesis of 1,3-dienes. However, the reaction using a boronate complex that carries two different olefins remains unexplored due to the significant challenge associated with the site-selective activation of olefins. To expand our methodology to the synthesis of conjugated dienes, we initiated a study using an aryl vinyl B(pin) and alkyl vinyl lithium, which can be generated from the corresponding vinyl bromide. Three different dienes **7**, **8**, **9** (Scheme 4a) can be formed depending on the reaction conditions. We observed the formation of compound **8** with 80 % selectivity using THF as a solvent and NaOMe as an additive following reported methods for Zweifel olefination. Conducting the reaction at −40 °C using a THF/MeOH (3:1) solvent system, led to the exclusive formation of diene **8** (please see Supporting Information page S25 for details on optimization). To explore the substrate scope of this reaction, optimized conditions were employed to structurally different vinyl boronic esters. Gratifyingly, we observed the formation of desired 1,3-dienes (Scheme 4, **8a**–**8g**) with up to 100 % selectivity and 75 % yield. Also, stereodivergent synthesis of the *EE*-isomers was achieved (**9a**–**9g**), through *syn*-elimination using PhSeCl as an electrophile.[8e]

The reactivity of boronate complexes carrying di-substituted vs tri-substituted and di-substituted vs tetra-substituted olefins was next investigated, revealing excellent stereocontrol, affording the conjugated dienes with up to 100 % stereo- and regioselectivity (Scheme 4b and 4c, **10a**–**11d**). In each cases, the reaction appears to proceed via activation of the di-substituted olefin by iodine, followed by ring opening of an iodonium intermediate via 1,2-migration of a tri- or tetra-substituted olefin. Finally, base-induced *anti*-elimination produces the *E, Z*-1,3-diene in good yield. Theoretical studies are ongoing to further understand these

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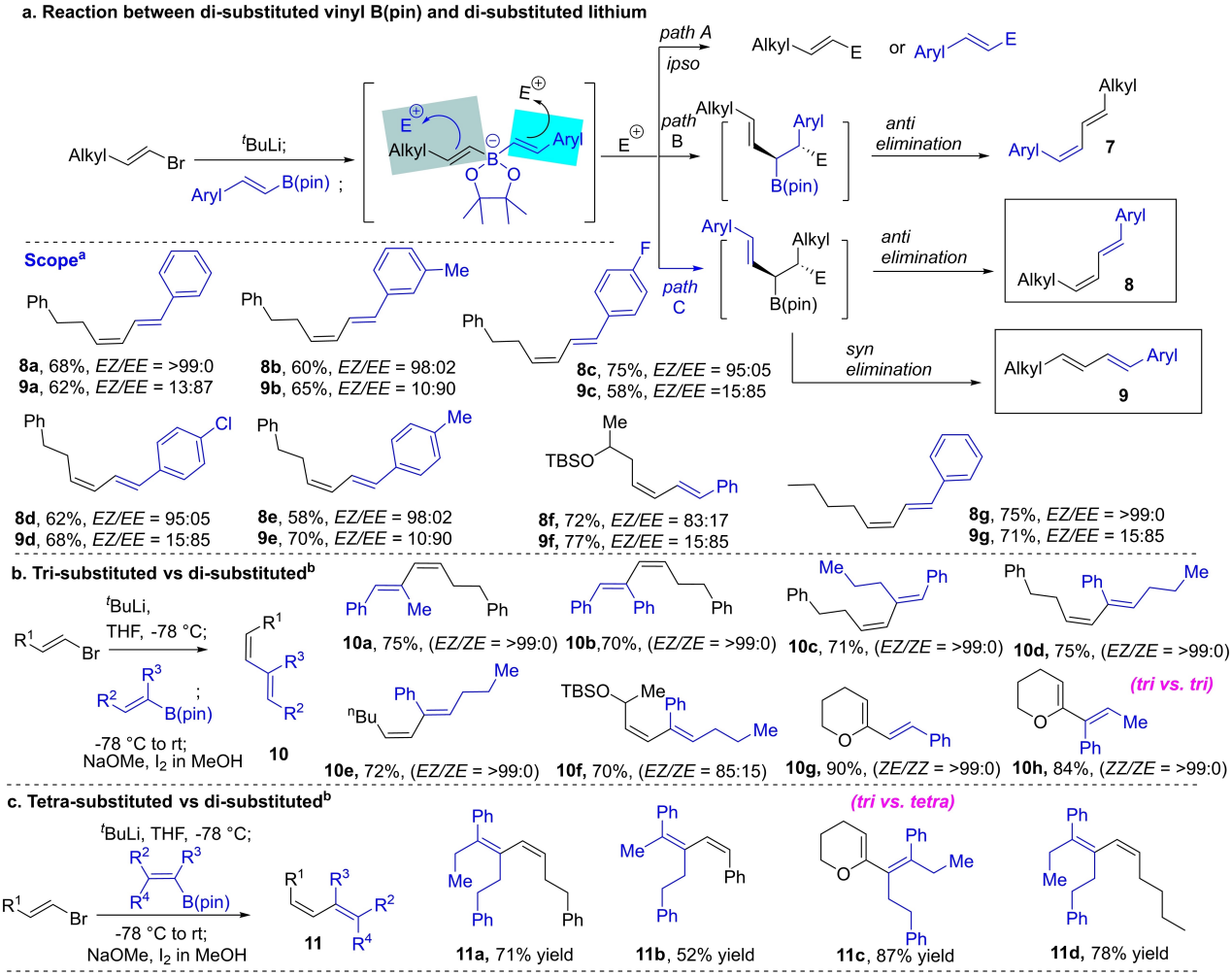

Scheme 4. Zweifel olefination between vinyl lithium and vinyl boronic ester.

results. The *E, Z*-configured 1,3-diene unit is a common motif in numerous bioactive natural products,[37] so this method may have significant applications in organic synthesis. We observed exceptions to the above results when using lithiated dihydropyran with di- and tri-substituted vinyl boronic esters (Scheme 4, **10g**, **10h**, **11c**). In the case of reaction using lithiated dihydropyran, olefin activation of dihydropyran took place, leading to the formation of an *E*-product, retaining the stereochemistry of the vinyl boronic ester. Overall, these preliminary data indicate the potential of Zweifel olefination for the stereoselective synthesis of 1,3-dienes.

Computational Investigation

To further elucidate the origins of the different stereochemical out-comes observed for different heteroaryl systems and reaction conditions, we performed DFT calculations using the revDSD-PBEP86-D4/def2-TZVPPD//SMD(THF)-M06-2X/def2-SVP level of theory with the *Gaussian 16A.03* and *ORCA 5.0.3* suites of programs; quasi-harmonic thermochemical corrections were calculated using the *GoodVibes* package, and three-dimensional renderings of molecular structures were created using *Cylview 1.0b* (see Supporting Information page S53 for further computational details). [34] Condensed Fukui Function analysis based on the Hirschfeld population was performed using Multiwfn software at SMD(THF)-M06-2X/def2-SVP level of theory.

We began by modeling aryl styrenyl boronate ester anion (**IM0**; Scheme 5). We examined both aryl = furyl and aryl = thiophenyl systems utilizing NBS as an electrophile. Two mechanistically distinct scenarios were modeled: (A) activation of the heteroaryl π-system and (B) activation of the vinyl π-bond. Results for the furan system are shown in Figure 1 and those for the thiophene system are shown in Figure 2. In path A, bromine transfers from NBS to 5-position of the heteroaryl ring (TS1 A) is followed by 1,2-migration of the vinyl group. Based on the results of our computations, this reaction"can proceed in a stepwise or a concerted but highly asynchronous manner, depending on the identity of the heteroaryl group. In the stepwise case, the vinyl transfer step (**TS2A**) is predicted to be rate-determining (but just barely). In concerted cases, the

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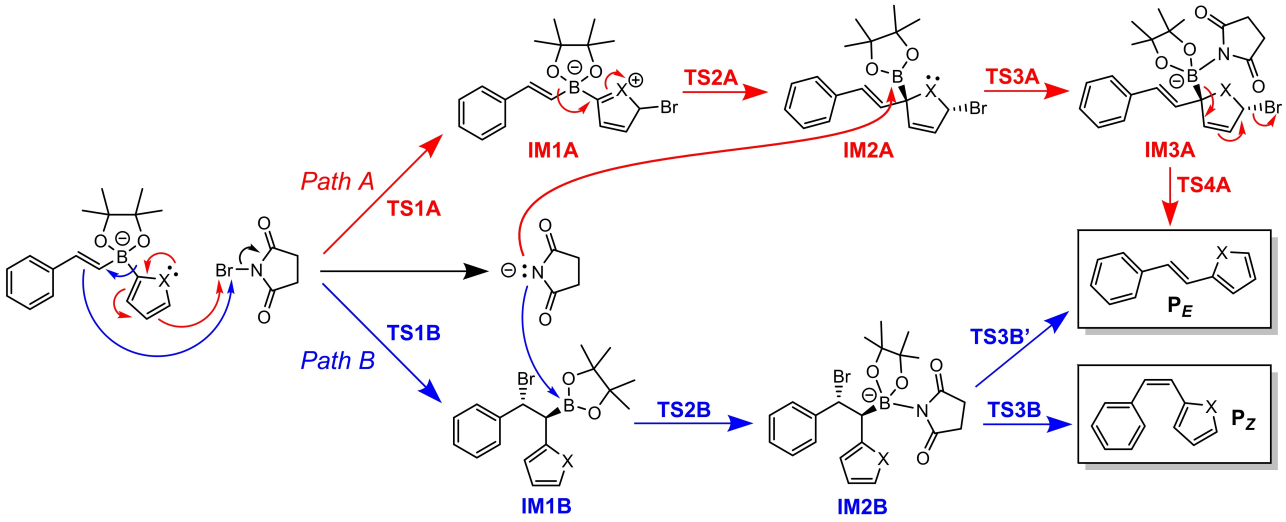

Scheme 5. Proposed mechanism.

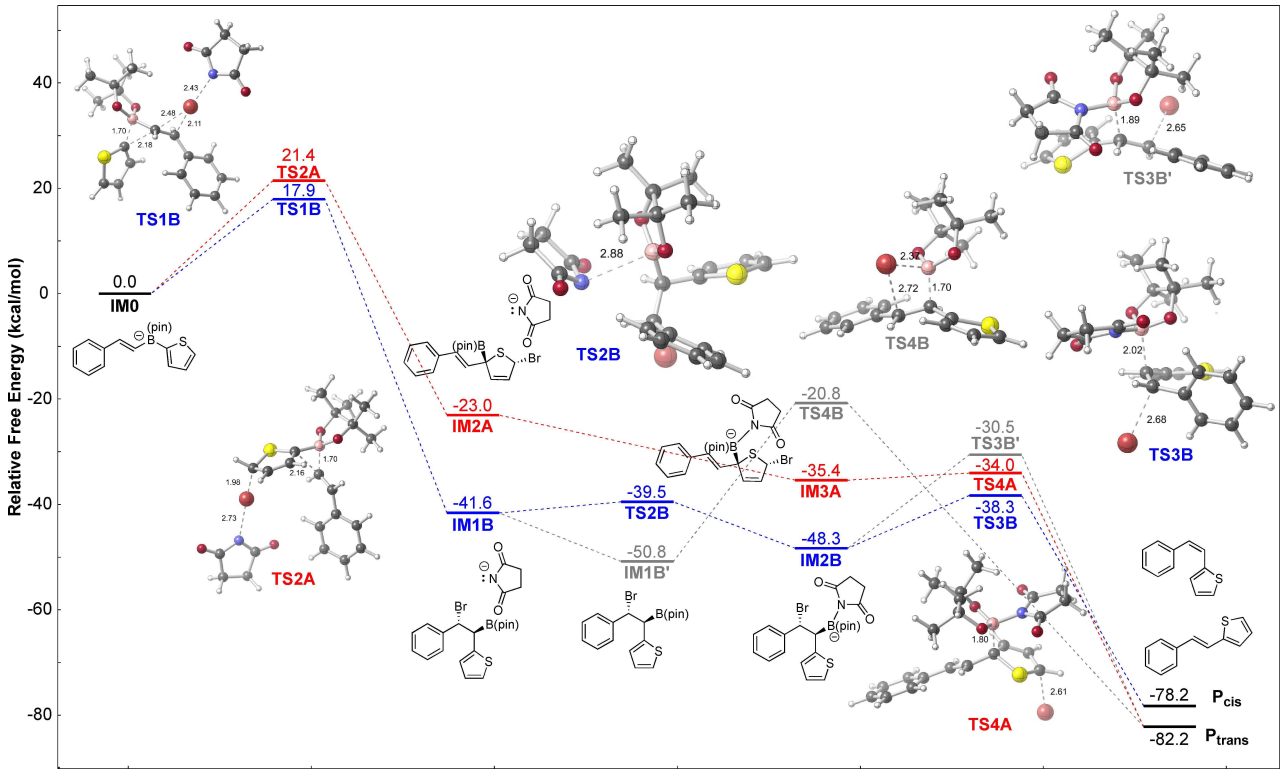

Figure 2. Computed (revDSD-PBEP86-D4/def2-TZVPPD//SMD(THF)-M06-2X/def2-SVP) reaction profiles for competing processes in the reaction of a thiophenyl styrenyl boronic ester anion (**IM0**). Relative free energies are shown in kcal/mol. Selected distances are shown in Å.

transition structure also resembles that of the vinyl group transfer (hence, we also label it **TS2A**). In either case, the vinyl group stereochemistry is conserved. Coordination by the succinimide anion to the boron center (**TS3A**)[35] followed by elimination of the bromide anion and the boronic ester (**TS4A**) affords the final *E*-product.

In path B, bromine transfer from NBS followed by aryl migration to the vinyl group (**TS1B**) occurs in a concerted but asynchronous fashion (i.e., the bromonium ion is not a distinct intermediate on the potential energy surface). After a conformational change and coordination of the succinimide anion to form a boronate complex (**TS2B**),[36] *anti*-elimination to afford the *Z*-product ensues (**TS3B**). The boronate complex, in principle, can also lead to the formation of the thermodynamically more stable *E*-product via *syn*-elimination (**TS3B′**), but we predicted that such a

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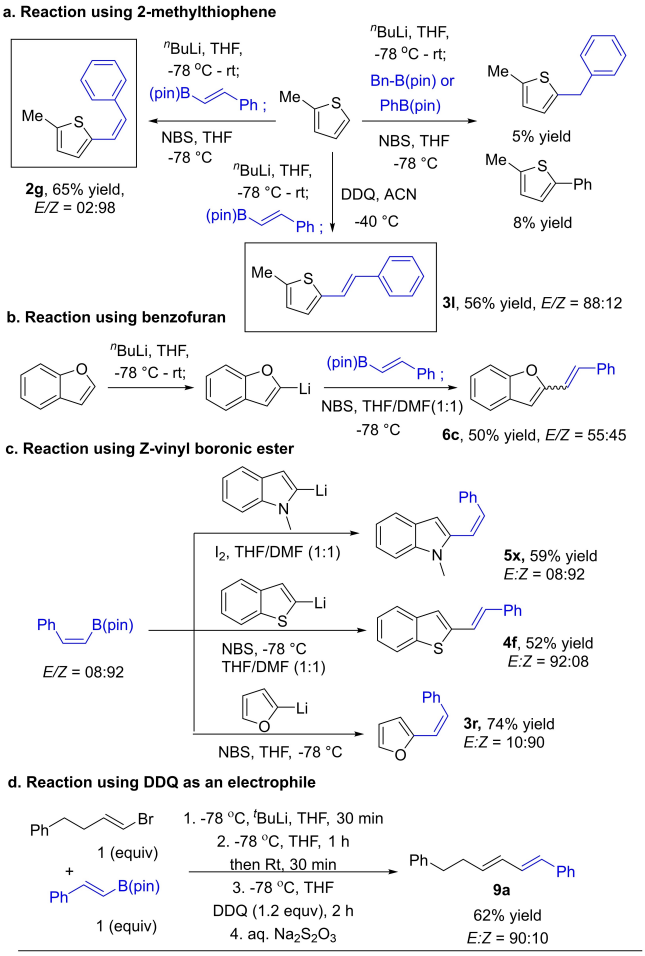
process has a higher barrier (by 8 kcal/mol with furan and 3.5 kcal/mol with thiophene). We also considered direct *syn*-elimination without involving the succinimide anion (**TS4B**) to form the *E*-product and a brominated boron species, but that pathway was predicted to have a $\Delta G^{\ddagger}$ of 25 kcal/mol with furan. Thus, we predict that activation of the vinyl π-bond should lead to the *Z*-product with high selectivity.

Our results are in good agreement with the experimental observations: For the furan system (Figure 1), activation of the heteroaryl substructure was predicted to be preferred (red) and hence the *E*- product is formed. In contrast, activation of the vinyl group is preferred for the thiophene system (Figure 2, blue), followed by *anti*-elimination leading ultimately to the *Z*-product. We also predicted that bromine transfer to the 3-position (**TS2A′**) of furan is less energetically favorable than bromination at the 5-position by 8 kcal/mol. This is further supported by condensed Fukui Function calculations, which revealed highly diminished nucleophilicity of the thiophene motif in aryl styrenyl boronate ester anions compared to other aryl groups; hence vinyl activation is preferred. (See Supporting Information S76 to S85 for further discussion on Fukui Function and Distortion-Interaction Analysis)

Inspired by the computational results, we decided to try 2-methyl thiophene as a substrate (Scheme 6), considering that the blockage of the C5-position might hamper the S_EAr activation of the thiophene ring. Indeed, the reaction of alkyl or aryl boronic esters with lithiated 2-methyl thiophene afforded less than 10 % yield of the corresponding alkyl or aryl thiophene following the literature procedure.[20,21] However, we were pleased to observe the formation of (*Z*)-2-methyl-5-styrylthiophene **2g** (65 % yield and 98 % *Z*-selectivity) using our NBS conditions, supporting our mechanistic hypothesis that these reactions occur via olefin activation (Scheme 6a). Further mechanistic support was obtained by conducting the reactions using *Z*-phenyl vinyl boronic esters under the previously optimized reaction condition (Scheme 6c). We observed reversing of stereoselectivity in comparison to the reaction using *E*-phenyl vinyl boronic esters, supporting the proposed mechanism.

Knowing that bromination and 1,2-migration should be the stereoselectivity determining steps, we considered only those steps when modeling other systems. For the Ar = pyrrolyl system, we predicted a result ($\Delta\Delta G^{\ddagger}$ = 6 kcal/mol in favor of path A) similar to that for the furan system, except that the bromine ion dissociates from the pyrrole motif after vinyl migration. Pyrrole-based systems behave similarly to furan-based systems experimentally. For the Ar = benzofuranyl system, bromination occurs in the 3-position of benzofuran such that the aromaticity of the fused benzene ring will not be disrupted. We predicted that both pathways A and B have similar free energies of activation ($\Delta\Delta G^{\ddagger}$ = 0.5 kcal/mol in favor of *E*-product), consistent with the comparatively poor stereoselectivity observed experimentally (Scheme 6b, please see Supporting Information page S24 for other optimization data). For the Ar = indolyl system, we modeled both the NBS and I_2-mediated Zweifel olefination. For the iodine-mediated mechanism, both I_2 and $(I_2)_2$ mediated processes were modeled (SI page S62 for more details). With I_2, the iodonium ion is an intermediate on the potential energy surface, but it was predicted to undergo aryl migration with ease. In all cases, indole activation was predicted to have lower activation energy ($\Delta\Delta G^{\ddagger}$ = 7 kcal/mol for NBS), and hence the *E*-product was predicted to predominate, again consistent with the experiment.



Scheme 6. Experimental evidence.

We also have experimental evidence (Scheme 6d) that *syn*-elimination occurs when using DDQ as an electrophile. To understand how DDQ reversed the stereoselectivity compared to the NBS-mediated reaction, we modeled the reaction of the thiophene boronate ester mediated by DDQ at the revDSD-PBEP86-D4/def2-TZVPPD//SMD(MeCN)-M06-2X/def2-SVP level of theory (see Supporting Information page S61 for further computational details).[34] We first modeled an S_EAr mechanism where the thiophene first undergoes electrophilic addition by the DDQ at the 5-position (**TS5A**), followed by vinyl group transfer (**TS6A**) (Figure 3).[20b,37] Both steps were predicted to have reasonably low barriers and the *trans* stereochemistry was retained from the vinyl migration. We then modeled an electrophilic attack on the vinyl group by DDQ. We observed a concerted but asynchronous reaction where aryl group transfer was followed by an electrophilic attack on the vinyl

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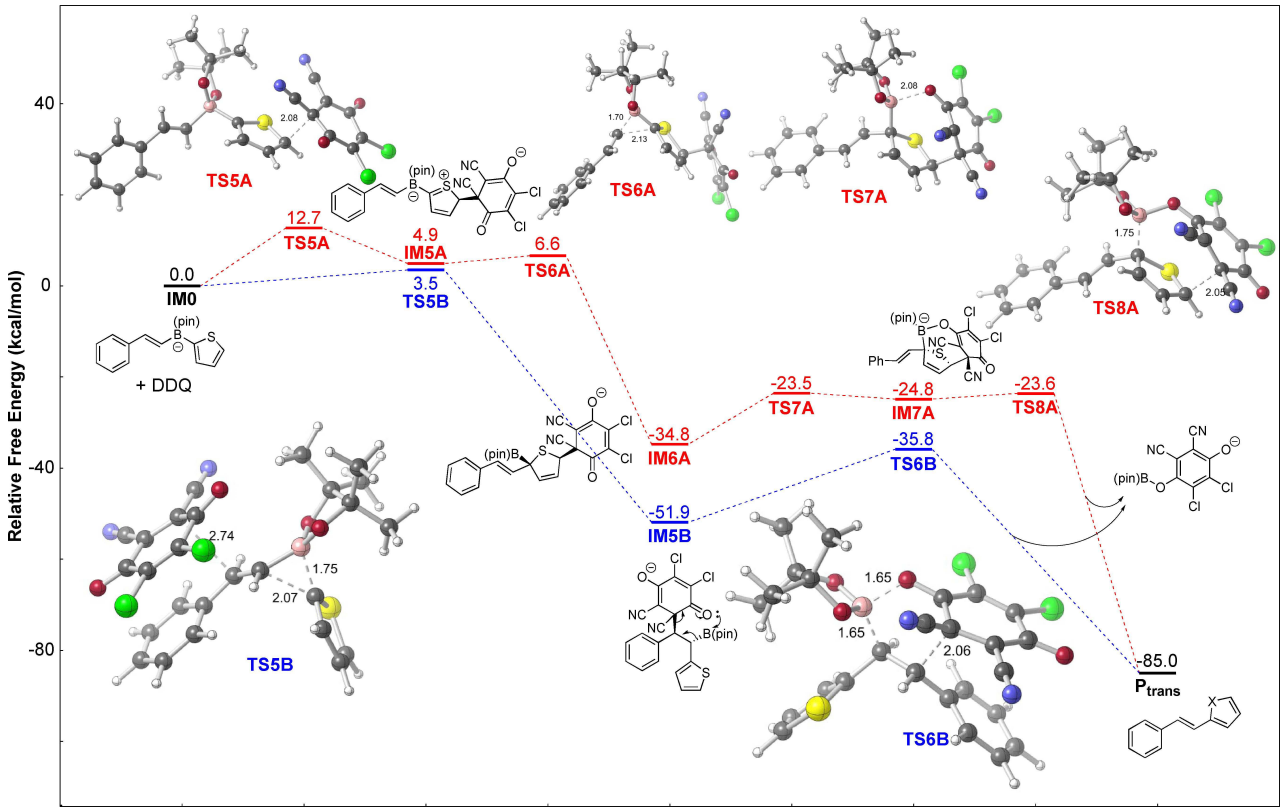

Figure 3. Computed (revDSD-PBEP86-D4/def2-TZVPPD//SMD(MeCN)-M06-2X/def2-SVP) reaction profiles the DDQ mediated reaction of a thiophenyl styrenyl boronic ester anion. Relative free energies are shown in kcal/mol. Selected distances are shown in Å.

group by DDQ, all in a single step (**TS5B**). This process was predicted to proceed with a lower barrier ($\Delta\Delta G^{\ddagger}=9$ kcal/mol) than that of the S_EAr mechanism and lead to a thermodynamically more stable intermediate ($\Delta\Delta G^{\ddagger}=$ 17 kcal/mol comparing **IM6A** and **IM5B**). At first glance, this seems to lead to the experimentally minor *Z*-product should an *anti*-elimination occur due to the presence of a freely rotating single bond in the intermediate. However, in this case, a *syn*- elimination, resulting in the *E*-product, is favorable and feasible ($\Delta G^{\ddagger}=16$ kcal/mol), as the oxygen atom on the DDQ substructure of the intermediate, following aryl migration, can attack the boron and dissociate in a concerted but asynchronous manner (**TS6B**); such a process is not possible in an *anti*-fashion. Conducting the reaction using 2-methylthiophene under DDQ conditions resulted in the formation of (*E*)-2-methyl-5-styrylthiophene **3l**, consistent with reaction via olefin activation followed by *syn*-elimination (Scheme 6a). A similar, but stepwise, elimination process (**TS7A**: attack by DDQ oxygen, **TS8A**: dissociation of the complex) was also computed for the aryl activation. Nonetheless, the manner of final product formation should have no consequence on the final stereoselectivity in this path as the vinyl configuration remains intact.

Conclusion

In summary, we have showcased the stereodivergent synthesis of vinyl heteroarenes and 1,3-dienes in good yield. Significant findings include: (1) A mechanistic dichotomy was observed in the stereoselective formation of *E* vs. *Z*-vinyl heteroarenes using different heteroarenes. The activation of the vinyl π-bond leads to the *Z*-product while activation of the heteroaryl π-system leads to the *E*-product. A competition between transition states for these two processes ultimately leads to the dichotomy of stereoselectivity observed with different heteroaryl systems. (2) Our computational studies also demonstrated the nature of the different chemical reactivity unlocked by using DDQ as an electrophile, which ultimately leads to *E*-products in a stereoconvergent fashion. (3) Stereodivergent Zweifel olefination using a boronate complex carrying two different disubstituted olefins was achieved to afford 1,3-dienes with good yield and 100 % stereoselectivity. Future research will extend the reactivity of boronate complexes carrying two different olefins to various other systems and their application to the total synthesis of bioactive compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 1,3-Diene · Furan · Indole · Stereoselectivity · Thiophene · Zweifel Olefination

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[35] Although the transition structure for coordination of the succinimide anion was not always successfully located, in those cases where it was located it often had a $\Delta G^{\ddagger}$ of <2 kcal/mol. Also, we shown succinimide attacking with its N as O attack is unlikely due to higher energy associated with the O-bound boronate complexes (See Supporting Information for more details).

[36] We predict that the iodine mediated mechanism has lower activation free energies compared to the NBS mediated reaction ($\Delta G^{\ddagger}=2.1$ and 2.7 kcal/mol for iodine and iodine dimer respectively for path A) and hence a better yield is observed experimentally. However, only small differences in the activation energies of the selectivity-determining TSs between paths A and B are predicted: ($\Delta\Delta G^{\ddagger}=0.1$ kcal/mol for iodine and $\Delta\Delta G^{\ddagger}=0.3$ kcal/mol for iodine dimer).

[37] The SET mechanism is not considered in detail here. DDQ compared to the boronate ester radical - DDQ radical anion couple is predicted to be $+40$ kcal/mol, which is much higher than the barrier for the first step of the S_EAr or vinyl activation mechanism.

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