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Synthetic and Mechanistic Investigation of an Oxime Ether Electrocyclization Approach to Heteroaromatic Boronic Acid Derivatives**

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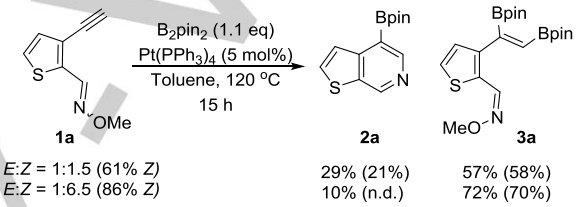
Abstract: A range of functionalized heteroaromatic boronic acid derivatives are readily accessed by a diboration/6π-electrocyclization sequence. This study revealed the surprising observation that there is a direct relationship between oxime ether stereochemistry and reactivity towards electrocyclization. Specifically, *E*-oxime ethers are found to be significantly more reactive than their *Z*-counterparts (stereochemistry relative to azatriene scaffold). In contrast, the configuration at the azatriene alkene terminus has little impact on reaction rates. Computational analysis offers a rationale for this observation; a $N_{lone\ pair} \rightarrow C{=}C\ \pi^*$ orbital interaction lowers the energy of the transition state in the electrocyclization of *E*-oxime ethers. Finally, unreactive *Z*-oxime ethers can be converted to the corresponding heterocyclic products by a photolytically promoted *E* → *Z* isomerization and electrocyclization sequence.

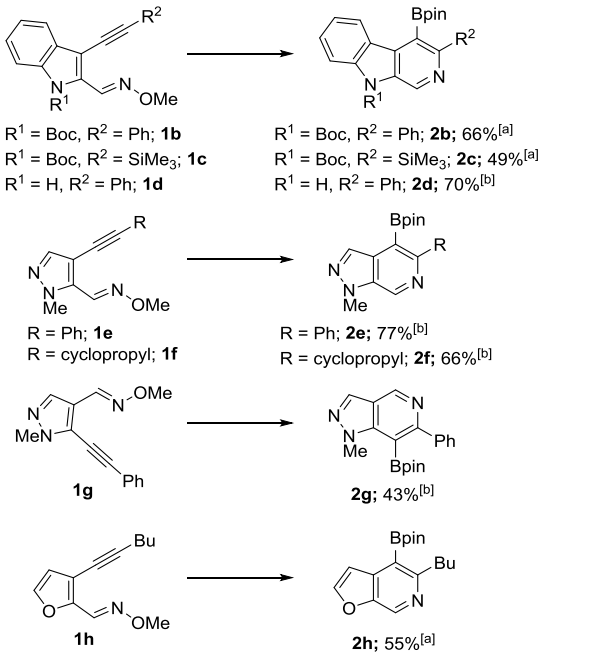
Heterocycle fused pyridines are common fragments in biologically active compounds and azole-containing analogs are particularly prominent, featuring in compounds such as nucleosides and carbolenes.[1] These compounds are often prepared via ring synthesis strategies and a number of catalytic methods have recently emerged.[2] However, suitably functionalized variants of these compounds could allow them to be introduced directly via cross-coupling reactions. In this regard, the availability of borylated azole-fused pyridine derivatives is very limited.

Recent studies in our lab have demonstrated that aromatic oxime ethers bearing an *ortho*-alkyne group can be transformed into isoquinoline boronic esters via a diboration/6π-electrocyclization sequence.[3] We therefore began our studies by investigating the applicability of this transformation for the synthesis of borylated thienopyridines as this would deliver a novel class of heteroaromatic boronic ester scaffolds.[4,5] As shown in Scheme 1, subjection of thiophene **1a** to B_2pin_2 in the presence of a Pt-catalyst led to a diboration-electrocyclization cascade that delivered thienopyridine boronic ester **2a** in poor yield. Interestingly however, the remaining mass balance consisted of diborylated alkene **3a** *which was found to contain exclusively the Z-configuration at the oxime*. This result was reproduced at higher *Z*/*E*-**1a** ratios. The correlation between initial oxime ether isomer ratio and the product ratios indicated that the *Z*-minor oxime isomer of **1a** could undergo diboration, but was inert to electrocyclization.[6]



Scheme 1. Synthesis of borylated thienopyridines. Estimated yields obtained by ^{1}H NMR spectroscopy with isolated yields in parentheses. n.d.: Not determined.

In continuing our scoping studies, we found that the majority of heterocycles examined provided very high selectivity for *E*-oxime stereoisomers and so we were able to demonstrate that



Scheme 2. Diboration-electrocyclization approach to heteroaromatic boronates. [a] B_2pin_2, 10 mol% $Pt(PPh_3)_4$, toluene, 120 °C, 16 h. [b] (i) B_2pin_2, 10 mol% $Pt(PPh_3)_4$, toluene, 120 °C, 16 h; (ii) 1,2-C_6H_4, 200 °C, 16 h.

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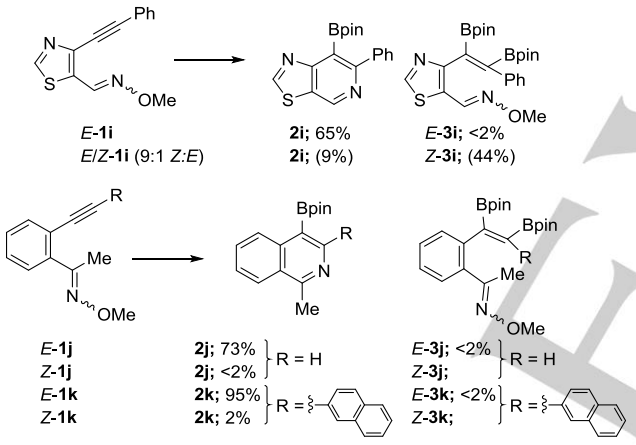
this method offers a rapid and convenient means for generating novel heteroaromatic boronic esters from readily available starting materials. As shown in Scheme 2, Boc-protected carbolenes were readily assembled by diboration of **1b-c**, although the free indole **1d** required further heating to promote cyclization. The method also allows a convenient means for accessing constitutional isomers, as exemplified by the synthesis of azaindazoles **2e,g**. Overall, this approach allows a range of functionalized scaffolds to be generated in good yield over a one or two step sequence.

Returning to the issue of the dependence of the electrocyclization step on the oxime stereochemistry we explored the generality of this observation, targeting substrates that could deliver significant yields of *Z*-oxime ethers. We were able to prepare and isolate individual isomers of thiazole **1i** and ketoximes **1j**-**k**. The diboration-electrocyclization of these compounds reinforces the observation that the cyclization was critically dependent on oxime ether stereochemistry with *Z*-substrates inert to pyridine ring formation (Scheme 3). ***E*-1i** cleanly provided 65% of pyridine **2i**, whilst a sample containing ~90% ***Z*-1i** gave <10% of the pyridine and 44% of ***Z*-3i**, which proved unstable with respect to protodeboronation. Similar observations were found in the synthesis of isoquinolines **2j** and **2k**.



Scheme 3. Diboration-electrocyclization efficiency in relation to oxime ether stereochemistry. (i) B_2pin_2, 10 mol% $Pt(PPh_3)_4$, toluene, 120 °C, 16 h; (ii) 1,2-C_6H_4, 200 °C, 16 h. Estimated yields obtained by ^1H NMR spectroscopy in parentheses.

The thermally promoted disrotatory 6π-electrocyclization of conjugated trienes to form cyclohexa-1,3-dienes is an established transformation that has attracted many theoretical and experimental studies over the years. The influence of substituent and geometrical effects in electrocyclization reactions of trienes has been studied in some detail, and it appears that the incorporation of groups in a 'cis' configuration at the termini of the triene chain significantly retard the cyclization rate.[7,8] This has been attributed to a reduced propensity for the substrate to adopt the reactive s-cis, s-cis conformation. In order to establish sensitivity of the reaction to the stereochemistry at the oxime ether, the alkenyl terminus, and the effect of congested borylated substrates, we computed the free activation energy of the cyclization of *Z* and *E* oxime ether isomers of a non-borylated substrate **4**, and compared this to **3k** (Figure 1).

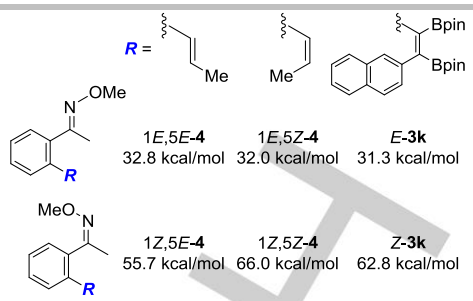


Figure 1. Calculated Free activation energies for cyclizations of *E* and *Z* oxime ethers, computed at M06-2X/6-311+G(d,p)(IEFPCM, toluene). Values in kcal/mol.

The *Z*- and *E*-isomeric forms of all initial oxime substrates show very similar relative stabilities, with differences between them of only 0-0.6 kcal/mol (see SI for details). Surprisingly however, the activation energies for the cyclization of the *Z*-oxime isomers were between 20 and 30 kcal/mol higher than those of their *E*-counterparts, which corresponds to *ten or more orders* of magnitude lower reaction rate. The reaction barriers for the *E*-isomers range from 31 - 33 kcal/mol, and these barriers are easily surmountable at the experimental temperatures typically used for the cyclization reaction. In contrast, *Z*-oximes afford activation energies over 40 kcal/mol (even as high as 63 kcal/mol), meaning that this general kind of substrate will probably never react, whatever experimental conditions are employed. In contrast to the oxime ether moiety, the computational data predict that the structural features on the alkene terminus *do not exert any significant effect on the cyclizations*. For example, 1*E*,5*Z*-**4** presents slightly *lower* activation energy than 1*E*,5*E*-**4**, suggesting that *cis*-alkenes can be as good substrates (or even better) as *trans*-alkenes in this specific reaction.[9] Furthermore, increased substitution on the alkene seems to be well tolerated, and tetrasubstituted derivative **3i** shows comparable, slightly lower activation barrier than the simplest *E*-alkene **4**. Thus, the incorporation of boronic esters, and the substitution degree and pattern of the alkene, appear to have no significant impact on reactivity towards electrocyclization.

To find an explanation for the above findings, we analyzed the structures of the four different transition states of compound **4** (Figure 2). As expected, all the cyclizations are disrotatory, and present very homogeneous C-N bond forming distances (1.90-1.94 Å). The transition states of the two *E*-oxime isomers (**TS-**1*E*,5*E*-**4** and **TS-**1*E*,5*Z*-**4**) are structurally very similar, and differ only in the relative cis/trans disposition of the methyl group at the terminal alkene which does not have any effect on their relative activation barriers (32.8 and 32.0 kcal/mol). Indeed, the terminal olefinic carbon undergoes partial pyramidalization during the transition state, releasing part of the steric repulsion between the eclipsed aryl and methyl substituents in the *Z*-olefin containing substrates, providing an explanation for the good performance of hindered *Z*-alkenes in this process. Meanwhile, the geometry of the oxime moiety during the reaction is also very instructive. We hypothesize that the lone pair of the oxime-nitrogen actively participates in the electrocyclization, and its orientation is thus crucial for the reactivity. In **TS-**1*E*,5*E*-**4**, the iminic nitrogen lone pair is pointing towards the terminal carbon of the double bond (see tentative disposition, Figure 2 in red), whereas in **TS-**1*Z*,5*E*-**4**, the lone pair is orthogonal to the forming C-N bond.

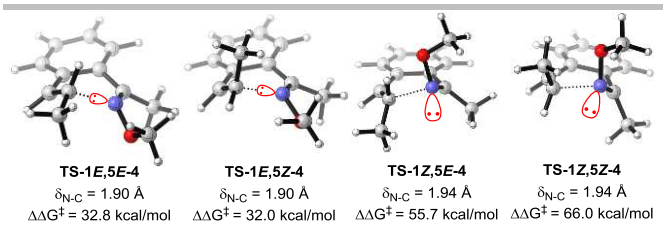


Figure 2. Structural features of the isomeric transition structures of compound **4**.

Evidence for donation of the nitrogen lone pair into the alkene antibonding π* orbital at the transition state is revealed in the plotted orbital interaction diagram for **TS-**1*E*,5*E*-**4** (**B**, Figure 3). This interaction is lacking in **TS-**1*Z*,5*E*-**4**, where the lone pair is not participating in the transition state (**C**). Also, the electronegative region (red in the ESP diagrams) of reacting oxime *Z* is large around the lone pairs of nitrogen and oxygen (**D**, Figure 3), showing that the electron density at nitrogen lies away from the forming C-N bond forming region. Meanwhile, there is an absence of negative charge around nitrogen in the *E*-oxime (**A**), since its lone pair is involved in bonding.

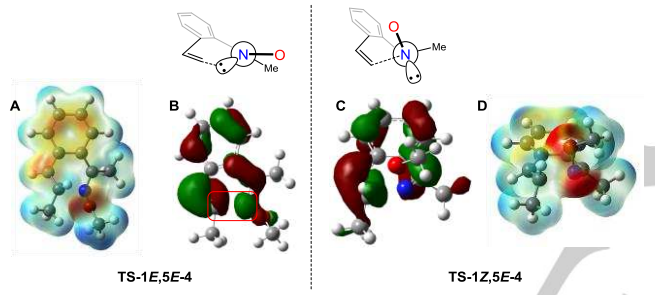
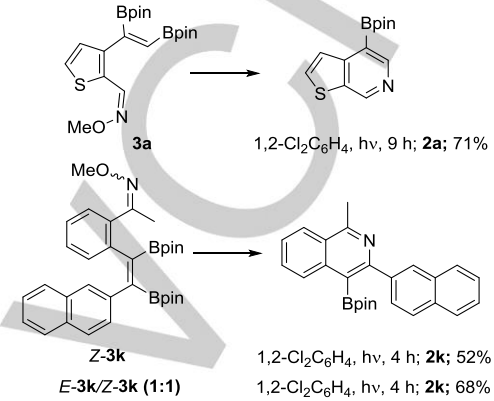


Figure 3. Orbital interaction diagrams (**B** and **C**) and Electrostatic Potential maps (**A** and **D**) for the cyclization transition states of the isomeric *E*- and *Z*-oxime ethers.

The fact that ketoxime ethers are commonly formed with significant proportions of *Z*-isomer present constitutes a limitation of this chemistry given that calculations suggest that *Z*-oximes are essentially inert to cyclization. This prompted us to consider the possibility of using photochemically promoted cyclization methods as a means to processing these unreactive azatrienes towards pyridine products. In principle, two pathways could be envisaged: (1) a photochemically promoted conrotatory cyclization reaction; (2) a photochemically promoted oxime ether isomerization followed by thermally promoted disrotatory cyclization. Regarding the latter pathway, photochemically promoted stereochemical isomerization of oximes has been established (Scheme 4).[10] Moreover, Pratt and co-workers have reported that such processes can operate during electrocyclization reactions, although they did not identify a relationship between cyclization efficiency and oxime ether stereochemistry.[11] This approach is especially attractive in the case of oxime ethers where the rate of thermal interconversion is extremely slow.

In order to establish the potential of the photochemically promoted cyclization, we subjected substrates 1*Z*,5*E*-**3a** and 1*Z*-**3i** to UV irradiation in *o*-DCB. Pleasingly, these conditions successfully furnished the desired heterocyclic substrates, albeit in modest yield (Scheme 4). In the case of the reaction of 1*Z*-**3i**, monitoring the reaction progress via LC-MS and ^{1}H NMR spectroscopic analysis showed the rapid formation of the *E*-oxime ether together with product formation. Moreover, a ~1:1 mixture of oxime ether isomers was maintained until complete consumption of starting materials (See supporting information). We therefore believe that, in this case, the reaction operates via a photolytically promoted oxime ether isomerization followed by a thermally promoted electrocyclization step.



Scheme 4. Photochemically promoted electrocyclization reaction of oxime ethers.

In conclusion, the 6π-electrocyclization of conjugated azatrienes offers a useful method for the synthesis of heterocyclic boronic acid derivatives. Our experimental studies show that, in the case of oxime ethers, there is a direct relationship between oxime stereochemistry and reactivity towards electrocyclization. Specifically, while the configuration of the alkene at the azatriene terminus has little impact on reaction rates, *E*-oxime ethers are significantly more reactive than their *Z*-counterparts (stereochemistry relative to azatriene scaffold). Computational analysis has identified a $N_{\text{lone pair}}\rightarrow$C=C π* orbital interaction that promoted the cyclization in the case of *E*-oxime isomer by lowering the energy of the transition state in the electrocyclization process. Finally, unreactive *Z*-oxime ethers can be converted to the corresponding heterocyclic products by a photolytically promoted *E*→*Z* isomerization and electrocyclization sequence.

Experimental Section

Typical diboration-electrocyclization procedure as exemplified by the formation of 2e: A mixture of oxime **1e** (1.45 g, 6.10 mmol), B_2pin_2 (1.70 g, 6.70 mmol) and $Pt(PPh_3)_4$ (759 mg, 0.61 mmol) were heated in toluene (60 mL) at reflux for 30 min in a Schlenk tube. Flash chromatography over florisil provided the diborylalkene as a yellow oil (2.50 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.14-7.05 (m, 3H), 7.00-6.96 (m, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 1.31 (s, 12H), 1.30 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.7, 138.8, 130.2 (2C), 128.8, 127.8 (2C), 126.3, 123.8, 84.3 (2C), 84.1 (2C), 62.0, 40.0, 24.9 (8C), two quaternary missing due to quadrupolar relaxation; ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.2 (br); FTIR: υ = 2978, 1459,

1308, 1140, 1052 cm^{-1}; HRMS m/z $[M+H]^+$ $C_{26}H_{38}{}^{11}B_2N_3O_5$ calcd. 494.2998, found 494.3021.

Diborylalkene (2.50 g, 5.0 mmol) in *o*-DCB (50 mL) was stirred at 200 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was filtered through silica gel. The residue was purified by flash column chromatography on silica gel to give **2e** as a yellow foam (1.60 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.23 (s, 1H), 7.68-7.63 (m, 2H), 7.45-7.36 (m, 3H), 4.21 (s, 3H), 1.32 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 142.2, 134.6, 134.0, 133.9, 133.1, 129.7 (2C), 127.9 (2C), 127.8, 84.4 (2C), 36.1, 24.8 (4C), one quaternary missing due to quadrupolar relaxation; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.6 (br); FTIR: υ = 2971, 1725, 1562, 1451, 1319, 1195, 1070 cm^{-1}; HRMS m/z $[M+H]^+$ $C_{19}H_{22}{}^{11}BN_3O_2$ calcd. 336.1878, found 336.1888;

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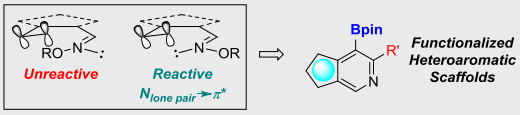

It's not all E/Z! E-oxime ethers are found to be significantly more reactive in electrocyclizations than their Z-counterparts because of an available transition state stabilizing orbital interaction in the former case. The scope of this chemistry to deliver useful heterocyclic products is also described.

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