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Exploiting Hydrazones to Improve the Efficiency of 6π-Electrocyclization Reactions of 1-Azatrienes

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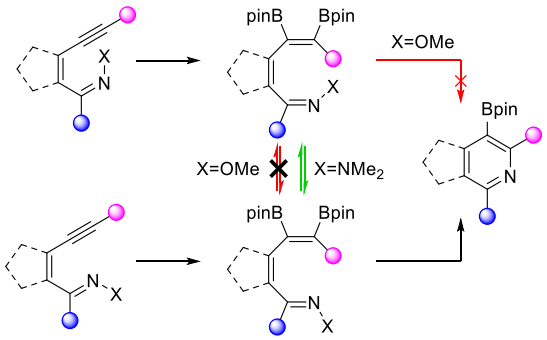
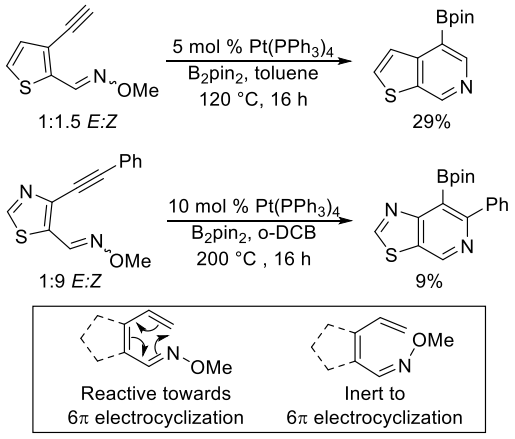
Supporting Information Placeholder



ABSTRACT: The greater geometric lability of hydrazones over oxime ethers is used as a basis to overcome the reluctance of Z-oxime ether azatrienes to undergo electrocyclization towards the synthesis of borylated (heteroaromatic) pyridines and ring-fused analogs. Such hydrazones now allow access to previously inaccessible tri- and tetrasubstituted 3-borylpyridines in high yields.

The prominence of heteroaromatic motifs in pharmaceutical agents, agrochemicals and functional materials has motivated synthetic chemists to devise new strategies for the efficient and selective incorporation of these fragments into a broad range of molecular scaffolds. In this regard, boronic acid chemistry provides one of the most widely used approaches for the coupling of heteroaromatic systems because of the synthetic versatility of these compounds.[1]

Scheme 1. Dependence of electrocyclization efficiency on oxime ether stereochemistry

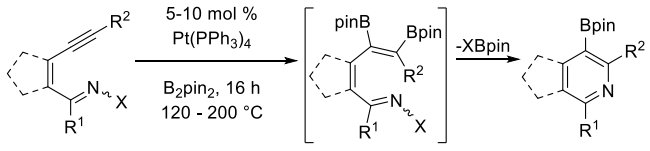


Several complementary strategies for accessing heterocyclic boronic acid derivatives now exist, including borylation of C-X/C-H bonds,[2] cycloadditions[3] and cyclization[4] processes. In this regard, we have recently reported that 2-alkynyl aryloxime ethers undergo a diboration-electrocyclization sequence to generate a range of arene and heteroarene fused pyridine boronic acid derivatives.[5,6] Such boryl pyridine species are readily converted into a range of diverse heterocyclic structures through C-C, C-O and C-N bond forming processes.[5] During these studies, we made the unexpected observation that the stereochemistry of the oxime ether substrates proved critical to the electrocyclization efficiency. Specifically, E-oximes underwent efficient cyclisation to the desired product, whereas Z-oximes were inert to cyclisation. This effect therefore led to very low yields of product in cases where substrates contained significant proportions of Z-oxime ether isomer (Scheme 1). Oxime ethers are known to be resistant to thermal equilibration,[7] and require acid catalysis[8] or UV irradiation[9] to promote isomerization. Indeed, we were able to promote low yielding transformations, such as those shown in Scheme 1, under UV irradiation that led to significant improvements in yield.[5] However, we envisaged that a potentially more practical solution to this problem would be to change the oxime ether moiety to a more geometrically labile

congener. In this regard, hydrazones are known to be stereochemically labile[10] and appeared to offer the opportunity to convert both E and Z-N-substituted azatrienes to desired products. Therefore, we set out to survey the scope of 2-alkynyl arylhydrazones in the diboration-electrocyclization process, and to assess the generality of this reaction as compared to oxime ethers.

As shown in Scheme 2, we prepared a range of 2-alkynyl aryl oxime ethers and hydrazones and subjected them to the diboration-electrocyclization sequence, as a one-pot procedure. The substrates derived from ortho-alkynylated acetophenones **1a-h** were all formed as a mixture of E/Z-isomers, however, oxime ethers **1a**,**e** were found to undergo the transformation to products **2** and **5** in significantly lower yield than the corresponding hydrazones **1b**,**f**. We were able to extend this chemistry to heteroaromatic fused pyridines and once again found significantly improved yield of product to be delivered from hydrazone substrates as compared to oxime ethers.

Scheme 2. One-pot diboration-electrocyclization of oximes and hydrazones[a]



R^1	R^2	X (*E*:*Z*)	Product	Yield
Me	Me_3Si	**1a;** OMe (75:25)		**2;** 44%
Me	Me_3Si	**1b;** NMe_2 (80:20)		**2; 75%**
Me	^nBu	**1c;** NMe_2 (85:15)		**3;** 86%
Me	$^cC_3H_5$	**1d;** NMe_2 (80:20)		**4;** 71%
Et	Me_3Si	**1e;** OMe (70:30)		**5;** 49%
Et	Me_3Si	**1f;** NMe_2 (60:40)		**5; 61%**
Et	^nBu	**1g;** NMe_2 (55:45)		**6;** 76%
Me		**1h**; NMe_2 (85:15)		**7**; 61%
R^1	R^2	X (*E*:*Z*)		Yield
H	Ph	**1j;** OMe (40:60)		**8;** 16%[a]
H	Ph	**1k;** NMe_2 (>98:2)		**8; 82%**[a]
H	Me_3Si	**1l;** NMe_2 (>98:2)		**9;** 76%
R^1	R^2	X (*E*:*Z*)		Yield
H	Ph	**1m;** OMe (20:80)		**10;** 12%
H	Ph	**1n;** NMe_2 (>98:2)		**10; 58%**
H		**1o;** NMe_2 (>98:2)		**11;** 50%
R^1	R^2	X (*E*:*Z*)		Yield
Me		**1p;** OMe (90:10)		**12;** 64%[b]
Me		**1q;** NMe_2 (>98:2)		**12;** 84%[b]

Reaction conditions: 1.1 eq B_2pin_2, 5-10 mol % $Pt(PPh_3)_4$, 1,2-$Cl_2C_6H_4$, 120 °C, 30 min, then 200 °C, 16 h; [a]120 °C, 16 h, then 200 °C, 3 h; [b]Toluene, 120 °C, 16 h. Hydrazone stereochemical assignments were made on the basis of ^{13}C-NMR spectroscopy, in line with established trends for oximes and hydrazones.[11] Specifically, resonances attributed to alkyl groups cis-to the N-heteroatom group appear upfield relative to their trans-isomers.

Arene-substituted aldoximes are typically formed with very high levels of E-stereochemistry because of the steric strain that arises in the corresponding Z-isomers (Figure 1).[12] Accordingly, the diboration-electrocyclization process generally works well on aldoxime ethers, and is only problematic in cases where the E/Z ratios are poor (eg **1j**,**m** in Scheme 2) or when ketoxime ethers are employed (**1a**,**e** in Scheme 2). However, we envisaged that enal derived oxime ethers (**III**, Figure 1) would be more likely to deliver higher proportions of unreactive Z-imine-type isomers, suggesting that these would be interesting substrates in which to compare the electrocyclization efficiencies of oxime ethers and hydrazones. Furthermore, such enal motifs (readily derived from ketones in two steps) would allow swift access to 2,3,4-trisubstituted borylpyridines that are otherwise difficult to access.

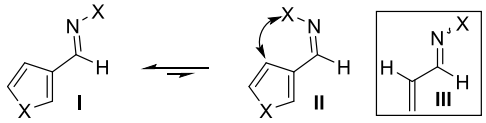
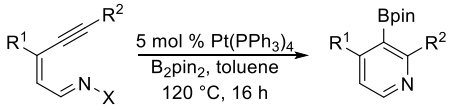


Figure 1. C=N configurational stabilities.

As shown in Scheme 3, thiophene derived aldoxime ethers **1r**,**t** were formed as 1:1 mixtures of E:Z isomers, and this is manifested in the poor yield of the isolated pyridines generated after diboration-electrocyclization. Pleasingly, however, the respective hydrazones **1s**,**u** were isolated as single geometric isomers, providing excellent isolated yields of both alkyl and aryl substituted pyridines **13** and **14**. A similar pattern was observed in the synthesis of electron deficient aryl substituted pyridines **15**,**16** as well as in the synthesis of pyridines bearing cycloalkyl (**17**) and isopropenyl (**18**) motifs at the 2-position.

Scheme 3. Diboration-electrocyclization sequence towards pyridines



R^1	R^2	X (*E*:*Z*)	Yield
	^nBu	**1r;** OMe (50:50)	**13;** 40%
	^nBu	**1s;** NMe_2 (>98:2)	**13; 90%**
	Ph	**1t;** OMe (50:50)	**14;** 52%
	Ph	**1u;** NMe_2 (>98:2)	**14; 86%**
	^nBu	**1v;** OMe (60:40)	**15;** 49%
	^nBu	**1w;** NMe_2 (>98:2)	**15; 87%**
	Ph	**1x;** OMe (70:30)	**16;** 50%
	Ph	**1y;** NMe_2 (>98:2)	**16; 68%**
Ph	$^cC_3H_5$	**1z;** NMe_2 (>98:2)	**17;** 82%
		1ba; NMe_2 (>98:2)	**18;** 55%

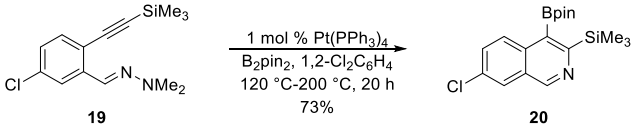
[a] Reaction conditions: 1.1 eq B_2pin_2, 5 mol % $Pt(PPh_3)_4$, toluene, 120 °C 16 h.

With the superiority of N,N-dimethylhydrazones confirmed, we sought to establish the geometric lability of these substrates. A sample of pure E-**1h** was obtained and its equilibration to the Z-isomer was confirmed by 400 MHz ^{1}H NMR spectroscopy. Specifically, allowing a solution of this compound to stand in $CDCl_3$ for 14 days at room temperature resulted in a gradual isomerization to a 90:10 E/Z ratio. Furthermore, **1g** provides a

higher yield of **6** (76%) than would be expected from the initial E/Z ratio of 55:45, suggesting that hydrazone isomerization occurs readily at the reaction temperature, and precedes electrocyclization. While this assertion builds on the assumption that the Z-hydrazone isomer is inert to cyclization, at this stage we cannot rule out the possibility that Z-hydrazones are inherently more reactive towards electrocyclization than the corresponding oxime ethers.

Finally, we demonstrated the amenability of this process to larger scale reactions, forming isoquinoline **20** with three orthogonal coupling sites at multigram-scale, with reduced catalyst loading (Scheme 4).

Scheme 4. Multi-gram scale synthesis of **20**

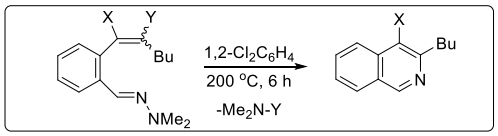


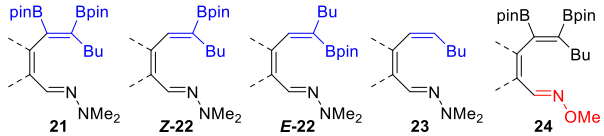
19 13.7 g, 49.1 mmol

20 12.9 g, 35.7 mmol

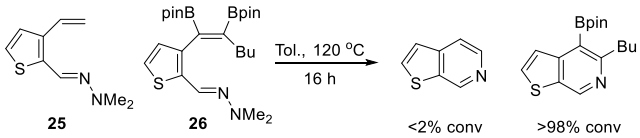
Having explored the relationship between oxime ether/hydrazone stereochemistry and the rate of electrocyclization, we next wanted to ascertain the impact that the degree of substitution and stereochemistry at the olefin moiety exerted. Accordingly, we prepared a series of hydrazones with ortho-Z-1-hexene groups and heated these at 200 °C for 6 hours in order to compare their relative reactivities (Scheme 5). Borylated alkenes **21**-**22** underwent cyclization with comparable conversions, whereas **23** proved to be significantly less reactive. In addition, E/Z isomerization was observed in the recovered starting material in all instances, with substantial stereochemical scrambling occurring the cases of **21** and **23**. Interestingly, the oxime ether **24** was found to be significantly more reactive than the corresponding hydrazones when both were employed as E-stereoisomers. Finally, the surprising rate enhancements observed by borylated alkene containing substrates were further exemplified by a competition experiment which showed that **26** underwent significantly faster cyclization as compared to **25**.

Scheme 5. Relative reactivities in cyclization reactions





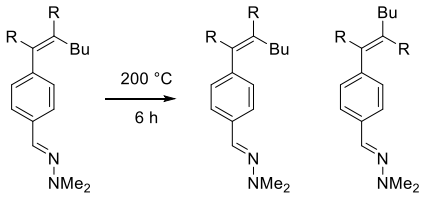
	21	***Z*-22**	***E*-22**	**23**	**24**
Conversion @ 200 °C 6 h	32%	21%	25%	1%	>98%
Starting alkene *Z*/*E*	>98:2	94:6	1:99	>98:2	>98:2
Recovered alkene *Z*/*E*	53:47	91:9	18:82	13:87	--



25 **26** <2% conv >98% conv

The reactions shown in Scheme 5 raise some intriguing discussion points: (1) the stereochemistry of the C1 position of the olefin does not seem to significantly impact the rate of formation of product; (2) The incorporation of a boronic ester at C1 improves reaction conversion; (3) Measurable olefin scrambling can be observed in all cases where starting material is recovered. With regard to this last point, we do not believe that alkene isomerization is the result of rotation around a C=C bond weakened through conjugation to the appended hydrazone (Scheme 6). Indeed, hydrazones **27** and **28** do not undergo any detectable isomerization under the same conditions.

Scheme 6. Isomerization control experiments

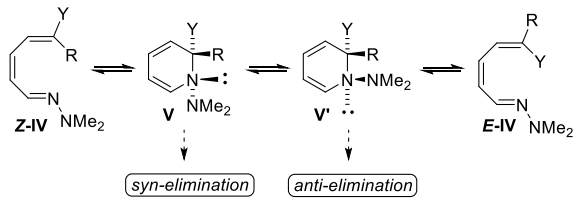


>99:1 *Z*:*E* R = Bpin **27** >99:1 *Z*:*E*

95:5 *Z*:*E* R = H **28** 95:5 *Z*:*E*

We have formulated a mechanism to explain these observations. As shown in Scheme 7 (Y=H or Bpin), reversible disrotatory electrocyclization of Z-**IV** provides **V** that can undergo syn-elimination to the product, or epimerization at nitrogen to generate **V'**. Anti-elimination of **V'** would also provide the product, however, electrocyclic ring opening should proceed such that the electron donating NMe_2 group rotates outwards according to Houk's torquoselectivity rules,[13] thereby generating E-**IV**. The difference in reactivity of borylated and non-borylated alkenes may therefore originate from the ease of aromatization by elimination of pinB-NMe_2 versus H-NMe_2, rather than their relative electrocyclization efficiency.

Scheme 7. Proposed mechanism



In conclusion, we have developed a simple and efficient route to a range of borylated pyridines through a diboration-electrocyclization strategy. Limitations associated with the poor reactivity of Z-oxime ether isomers has been overcome by the use of the corresponding hydrazones, significantly enhancing the generality of the technique. Finally, we also report that borylated alkenes lead to more reactive substrates, and we propose that this may be due to a faster elimination reaction that leads to aromatization. Further studies on this reaction mechanism are underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. The Supporting Information is available free of charge on the ACS Publications website.

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