OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

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

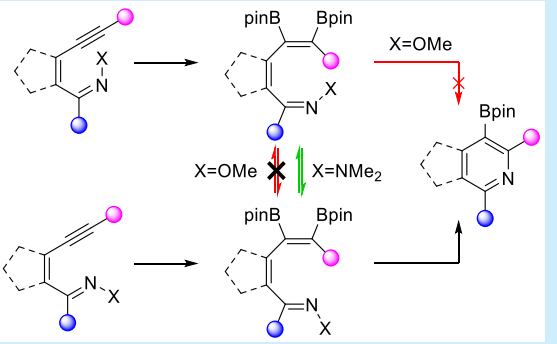
Matthew P. Ball-Jones,[†] Jasper Tyler,[†] Helena Mora-Radó,[†,‡] Werngard Czechtizky,[‡,§] María Méndez,[‡] and Joseph P. A. Harrity*[,†]

[†]Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, U.K.

[‡]Sanofi-Aventis Deutschland GmbH, R&D, Industriepark Höchst, G838, D-65926 Frankfurt Am Main, Germany

Supporting Information

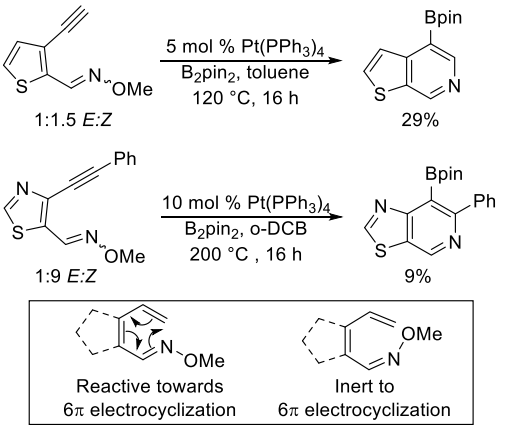
ABSTRACT: The greater geometric lability of hydrazones compared to that of oxime ethers is used as a basis to overcome the reluctance of *Z*-oxime ether azatrienes to undergo electrocyclization toward the synthesis of borylated (heteroaromatic) pyridines and ring-fused analogues. Such hydrazones now 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]

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 borylpyridine 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 to be critical to the electrocyclization efficiency. Specifically, *E*-oximes underwent efficient cyclization to the desired product, whereas *Z*-oximes were inert to cyclization. This effect therefore led to very low yields of the product in cases in which substrates contained significant proportions of the *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-yield 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.

Scheme 1. Dependence of Electrocyclization Efficiency on Oxime Ether Stereochemistry

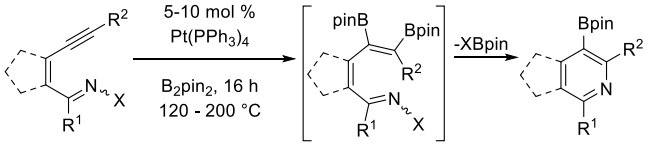


As shown in Scheme 2, we prepared a range of 2-alkynyl aryl oxime ethers and hydrazones and subjected them to the

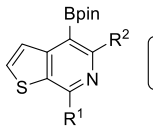
Received: July 15, 2019

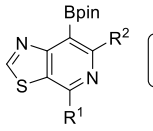
DOI: 10.1021/acs.orglett.9b02455
Org. Lett. XXXX, XXX, XXX−XXX

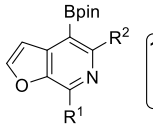
Scheme 2. One-Pot Diboration–Electrocyclization of Oximes and Hydrazones[a]



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*)	Product	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*)	Product	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*)	Product	Yield
Me		**1p**; OMe (90:10)		**12**; 64%[b]
Me		**1q**; NMe_2 (>98:2)		**12**; 84%[b]

[a]Reaction conditions: 1.1 equiv of 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; 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 to be upfield relative to their *trans* isomers.

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** and **1e** were found to undergo the transformation to products **2** and **5** in a yield significantly lower than those of the corresponding hydrazones **1b** and **1f**, respectively. We were able to extend this chemistry to heteroaromatic fused pyridines and once again found a significantly improved yield of product to be delivered from hydrazone substrates as compared to that of oxime ethers.

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 in which the *E*/*Z* ratios are poor (e.g., **1j** and **1m** in Scheme 2) or when ketoxime ethers are employed (**1a** and **1e** 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.

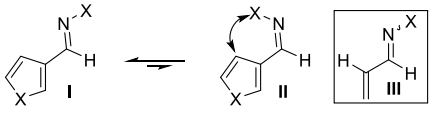
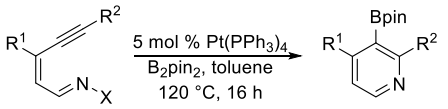
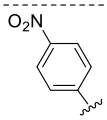
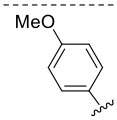


Figure 1. C=N configurational stabilities.

As shown in Scheme 3, thiophene-derived aldoxime ethers **1r** and **1t** 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** and **1u** 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** and **16** as well as in the synthesis of pyridines bearing cycloalkyl (**17**) and isopropenyl (**18**) motifs at position 2.

Scheme 3. Diboration–Electrocyclization Sequence toward Pyridines[a]



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 equiv of B_2pin_2, 5 mol % $Pt(PPh_3)_4$, toluene, 120 °C, 16 h.

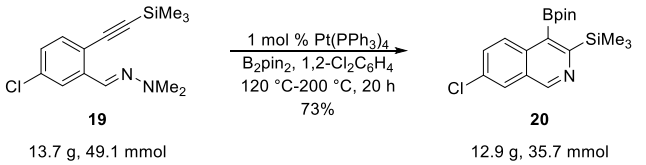
However, we sought to establish the geometric lability of these substrates. A sample of pure *E*-**1h** was obtained, and its equilibration to the *Z*-isomer was confirmed by 400 MHz ^1H NMR spectroscopy. Specifically, allowing a solution of this compound to stand in $CDCl_3$ for 14 days at room temperature 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

DOI: 10.1021/acs.orglett.9b02455
Org. Lett. XXXX, XXX, XXX–XXX

the possibility that *Z*-hydrazones are inherently more reactive toward electrocyclization than the corresponding oxime ethers.

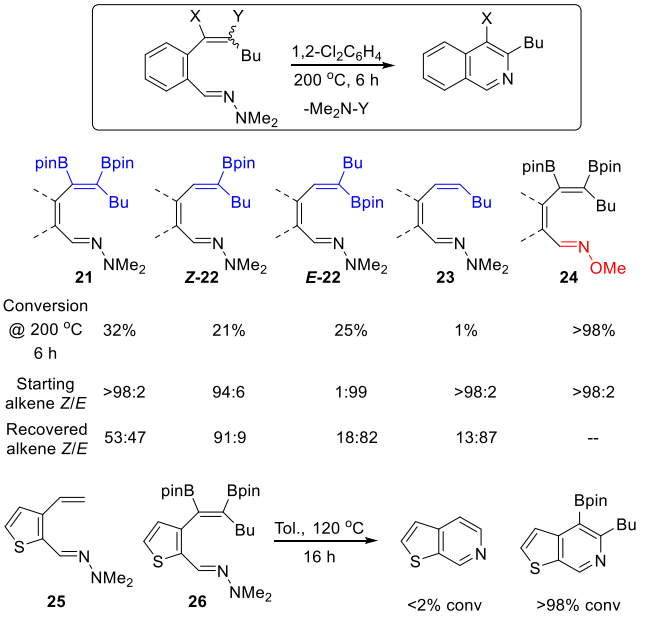
Finally, we demonstrated the amenability of this process to larger scale reactions, forming isoquinoline **20** with three orthogonal coupling sites at multigram scale, with a reduced catalyst loading (Scheme 4).

Scheme 4. Multigram Scale Synthesis of 20



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 *o*-*Z*-1-hexene groups and heated these at 200 °C for 6 h to compare their relative reactivities (Scheme 5). Borylated alkenes **21** and

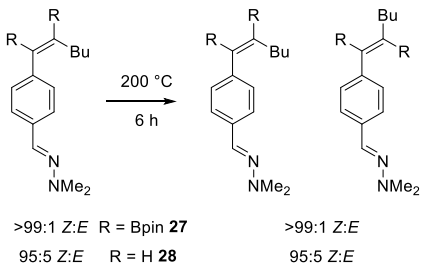
Scheme 5. Relative Reactivities in Cyclization Reactions



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 in the cases of **21** and **23**. Interestingly, 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 that showed that **26** underwent significantly faster cyclization compared to that of **25**.

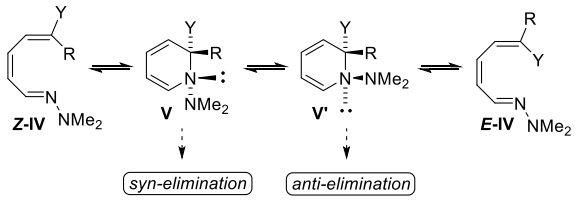
The reactions shown in Scheme 5 raise some intriguing discussion points. (1) The stereochemistry of the C1 position of the olefin does not seem to significantly impact the rate of formation of the product. (2) The incorporation of a boronic ester at C1 improves reaction conversion. (3) Measurable olefin scrambling can be observed in all cases in which 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



We have formulated a mechanism for explaining these observations. As shown in Scheme 7 (Y = H or Bpin),

Scheme 7. Proposed Mechanism



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 outward according to Houk's torquoselectivity rules,[13] thereby generating *E*-**IV**. The difference in the reactivity of borylated and nonborylated 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.

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 have 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 of this reaction mechanism are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02455.

DOI: 10.1021/acs.orglett.9b02455
Org. Lett. XXXX, XXX, XXX−XXX

Experimental procedures and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: j.harrity@sheffield.ac.uk.

ORCID

María Méndez: 0000-0002-6832-2714

Joseph P. A. Harrity: 0000-0001-5038-5699

Present Address

§W.C.: Respiratory, Inflammation, Autoimmunity IMED Biotech Unit, AstraZeneca, 431 86 Gothenburg, Sweden.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the EPSRC (EP/P025226/1) and Sanofi for financial support. This work was funded in part by the FP7Marie Curie Actions of the European Commission via the ITN COSSHNET network.

REFERENCES

(1) (a) *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; Vol. 2. (b) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611. (c) Stępień, M.; Gońka, E.; Żyła, M.; Sprutta, N. *Chem. Rev.* **2017**, *117*, 3479.

(2) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (c) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2102.

(3) (a) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (b) Yamamoto, Y.; Hattori, K.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *Chem. Commun.* **2005**, *41*, 4438. (c) Auvinet, A. L.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2769. (d) Brown, A. W.; Comas-Barceló; Harrity, J. P. A. *Chem. - Eur. J.* **2017**, *23*, 5228. (e) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592.

(4) (a) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2009**, *46*, 8770. (b) Chong, E.; Blum, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 10144. (c) Warner, A. J.; Lawson, J. R.; Fasano, V.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 11245. (d) Fricero, P.; Bialy, L.; Brown, A. W.; Czechtizky, W.; Méndez, M.; Harrity, J. P. A. *J. Org. Chem.* **2017**, *82*, 1688. (e) Fricero, P.; Bialy, L.; Czechtizky, W.; Méndez, M.; Harrity, J. P. A. *Org. Lett.* **2018**, *20*, 198.

(5) (a) Mora-Radó, H.; Bialy, L.; Czechtizky, W.; Méndez, M.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 5834. (b) Mora-Radó, H.; Sotorríos, L.; Ball-Jones, M. P.; Bialy, L.; Czechtizky, W.; Méndez, M.; Gómez-Bengoa, E.; Harrity, J. P. A. *Chem. - Eur. J.* **2018**, *24*, 9530.

(6) (a) Evanseck, J. D.; Thomas, B. E., IV; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 7134. (b) Schiess, P.; Monnier, C.; Ringele, P.; Sendi, E. *Helv. Chim. Acta* **1974**, *57*, 1676.

(7) Curtin, D. Y.; Grubbs, E. J.; McCarty, C. G. *J. Am. Chem. Soc.* **1966**, *88*, 2775.

(8) Johnson, J. E.; Silk, N. M.; Nalley, E. A.; Arfan, M. *J. Org. Chem.* **1981**, *46*, 546.

(9) (a) Padwa, A.; Albrecht, F. *J. Am. Chem. Soc.* **1972**, *94*, 1000. (b) Padwa, A.; Albrecht, F. *J. Am. Chem. Soc.* **1974**, *96*, 4849. (c) Takeda, Y.; Misawa, H.; Sakuragi, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2213.

(10) Landge, S. M.; Tkatchouk, E.; Benítez, D.; Lanfranchi, D. A.; Elhabiri, M.; Goddard, W. A., III; Aprahamian, I. *J. Am. Chem. Soc.* **2011**, *133*, 9812.

(11) (a) Fraser, R. R.; Capoor, R.; Bovenkamp, J. W.; Lacroix, B. V.; Pagotto, J. *Can. J. Chem.* **1983**, *61*, 2616. (b) Casanova, J.; Zahra, J.-P. *Tetrahedron Lett.* **1977**, *18*, 1773.

(12) Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079.

(13) (a) Patel, P.; Vella, J. R.; Ma, Z.-X.; Hsung, R. P.; Houk, K. N. *J. Org. Chem.* **2015**, *80*, 11888. (b) Evanseck, J. D.; Thomas, B. E., IV; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 7134. (c) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

DOI: 10.1021/acs.orglett.9b02455
Org. Lett. XXXX, XXX, XXX−XXX