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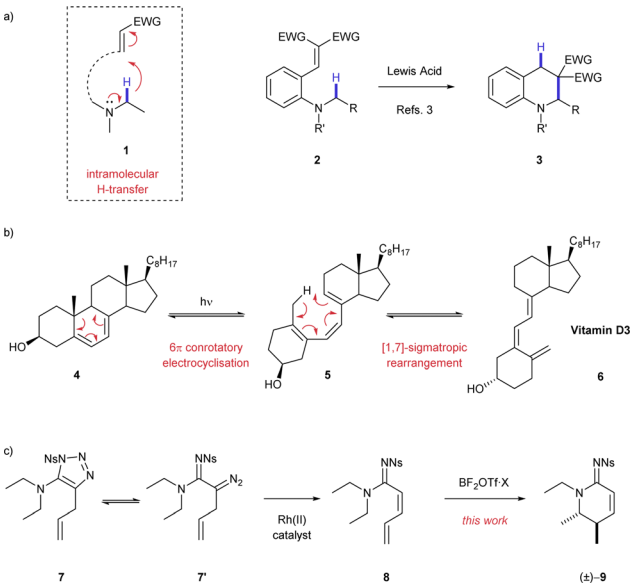
Stereodefined synthesis of cyclic amidines by domino 1,7-H shift and 6π electrocyclisation†

Matthew L. Martin, Claire Wilson and Alistair Boyer *

Unsaturated N^2-sulfonyl amidines are transformed into valuable N-heterocyclic products when heated with BF_2OTf. Mechanism studies suggest a domino 1,7-H shift, activating a C–H bond, followed by electrocylisation that results in stereodefined cyclic amidines.

The controlled transformation of simple molecules to complex products is a standing goal in the development of novel synthetic chemical methodology. Methods have been developed that activate the C–H bond[1] adjacent to a nitrogen atom for functionalisation through intramolecular transfer and cyclisation (**1**, Scheme 1a).[2,3] This approach to C–H activation is particularly useful because it allows access to complex valuable nitrogen-containing heterocycles[4] (*e.g.* **3**) from simple building blocks (*e.g.* **2**). The majority of these reactions proceed through 1,5–H transfer, exploiting a favourable 6-membered transition state. In contrast, there are few examples of any reaction that exploit a 1,7-H transfer. The most notable 1,7-process is the biosynthesis of vitamin D **6** from dehydrosterols **4** (Scheme 1b).[5] This synthesis comprises a light promoted 6π-conrotatory electrocyclisation followed by a pericyclic 1,7-H rearrangement. Although there have been extensive vitamin D synthesis studies and mechanistic studies of the 1,7-H shift, to the best of our knowledge, there are little or no applications of this reaction for chemical synthesis.[6,7]

Here, we describe a reaction that proceeds through 1,7-H shift activation of a C–H bond adjacent to a nitrogen atom and cyclisation to deliver value-added products. As part of a study into using 1-sulfonyl-1,2,3-triazoles as carbene precursors through Dimroth equilibration,[8] we developed a rhodium(II) catalysed 1,2–H shift reaction that created highly unsaturated amidine products (**8**, Scheme 1c).[9] Using a boron Lewis acid, we were able to transform these unsaturated acyclic compounds **8** into valuable stereodefined cyclic amidine products **9**.



Scheme 1 (a) General scheme for C–H activation by H-transfer adjacent to nitrogen atoms and overview of products accessed using this method; (b) Biosynthesis of vitamin D3. (c) Rhodium(II) catalysed 1,2–H shift to form unsaturated amidines **8** and their conversion to valuable nitrogen heterocycles **9** [this work]. Ns = 4-nitrobenzenesulfonyl.

The highly unsaturated amidine **8a** was treated with a series of reagents, under a range of conditions to explore its reactivity (Fig. 1).[10] In general, when treated with acids or Lewis acids the outcome was decomposition of the substrate or isomerisation of the *Z*-alkene into its *E*-geometry.

However, when treated with boron trifluoride in toluene at elevated temperature (150 °C, sealed vial), a new product was formed **9a** that was determined to be the unsaturated cyclic amidine **9a**.[10] Interestingly, a rearrangement had occurred in which one of the *N*-ethyl groups was incorporated into the newly formed ring. The high sp^2 content of the hexacycle **9a**

School of Chemistry, University of Glasgow, G12 8QQ, UK.
E-mail: alistair@boyer-research.com

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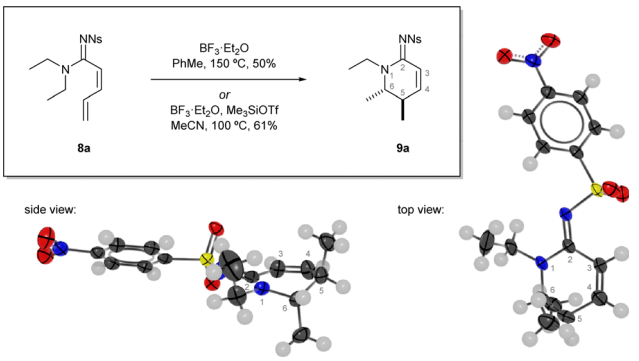


Fig. 1 Discovery of the reaction and optimisation highlight. Reactions performed in sealed a vial, isolated yields reported. Single crystal x-ray diffraction structure of **9a** from two views, atomic displacement ellipsoids at 50% probability, H atoms at 0.30 Å.[11]

resulted in the two methyl groups being axially disposed with respect to a relatively flat ring evidenced by a near-zero coupling constant between their respective methine protons in ^{1}H NMR spectrum. The structure was also confirmed by a single crystal x-ray diffraction structure.[11]

The cyclic amidine product was formed in a reasonable yield but decomposition during the reaction was still a major outcome and significantly lower yields (< 30%) were achieved when the conditions were applied to substrates with anything other than N^1,N^1-diethyl substituents. The key piece of the optimisation puzzle came by switching to a different boron-based Lewis acid accessed by mixing Me_3SiOTf and $BF_3{\cdot}OEt_2$. The synergistic combination of Me_3SiOTf and $BF_3{\cdot}OEt_2$ in acetonitrile has been shown to be beneficial due to formation of $BF_2OTf{\cdot}MeCN$.[12] The use of acetonitrile as solvent was also important because of limited substrate solubility in other solvents. Overall, these optimum conditions allowed the reaction to proceed at a reduced temperature (100 °C, sealed vial) and were able to deliver the cyclic amidine product **9a** in 61% yield. Furthermore, these conditions were found to be more generally applicable.

The scope of the reaction was explored with respect to the N^1-substituents and the sulfonyl group (Fig. 2). Under optimised reaction conditions (*in situ* generated BF_2OTf, 100 °C, 18 h), the N^1,N^1 diethyl substrate with a N^2-tosyl group gave a significantly reduced yield (18%) of its corresponding product **9aTs** compared with the N^2-nosyl group **9a** (61%). This result demonstrated the importance of the electron-poor nitro-substituted sulfonyl group in this transformation. This fortuitously matches the requirements for a nosyl group in the synthesis of these substrates.[9]

The temperature could be lowered to 80 °C for substrates that did not contain only N^1-ethyl or N^1-methyl groups and complete consumption of the starting material occurred in the same time frame (18 h). Despite proceeding at a lower temperature, the larger *n*-butyl and dibenzyl substrates gave a drop in yield, giving 38% and 14% of the amidine products **9b**, **9c** respectively. The best yield in this study was obtained for the pyrrolidine-containing precursor which gave the bicyclic

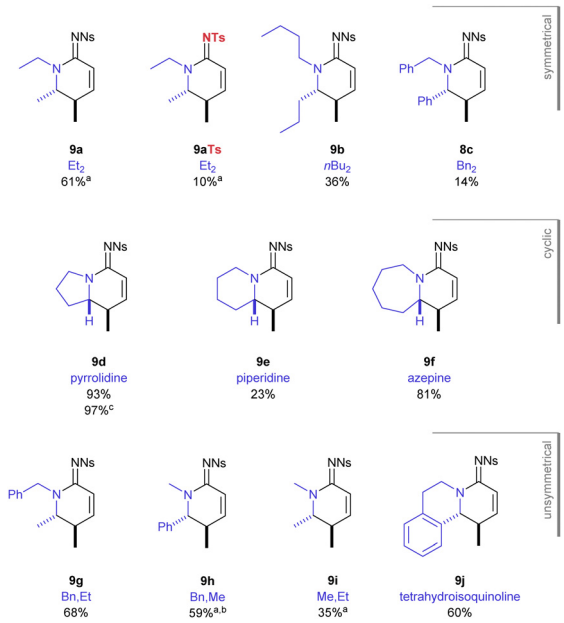
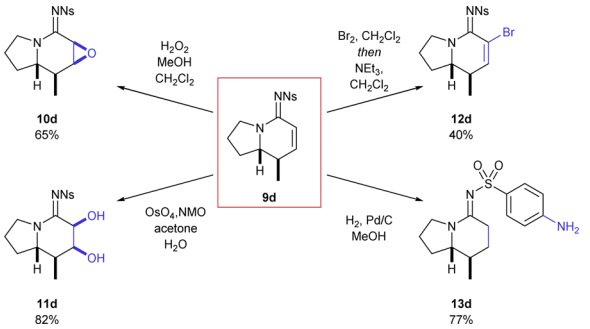


Fig. 2 Cyclic amidine products. Labels refer to N^1,N^1-substitution in the substrate 5. Reagents and conditions: Diene substrate (1.0 equiv.), $BF_3{\cdot}Et_2O$ (3.0 equiv.), Me_3SiOTf (6.0 equiv.), MeCN, 80 °C, 18 h; reactions were performed on 0.060 to 0.500 mmol scale. (a) Reaction performed at 100 °C; (b) reaction performed for 24 h; (c) reaction performed on 1.9 mmol scale.

product **9d** (93%). Increasing the heterocyclic ring size by one atom to the piperidine gave a dramatic drop in yield (23%, **9e**); but when adding a further atom, in form of an azepane ring, the excellent yield was restored (81%, **9f**).

Using non-symmetric substituents gave an opportunity to study the behaviour of this process through intramolecular competition. With N^1,N^1-benzyl,ethyl substituents, the reaction occurred entirely at the ethyl C–H to give the N^2-benzyl product **9g**. In stark contrast, given a choice between benzyl and methyl the reaction occurred entirely at the benzylic C–H (**9h**). When a N^1,N^1-ethyl,methyl substrate was studied it was consistent that it was only the ethyl group that was functionalised in the reaction sequence (**9i**). Finally, the cyclic non-symmetric tetrahydroisoquinoline substrate gave reaction at the benzylic position entirely (**9j**). Importantly, in each of the cases studied, only the product described was observed during analysis of the crude reaction mixture and there was no trace of products resulting from alternative diastereoselectivity or chemoselectivity. When the N^1,N^1-substituents were very large (*i.e.* *i*Pr or $CH_2CH_2OSiPh_2tBu$) the reaction did not occur and decomposition of the highly unsaturated substrate occurred instead.[13]

The indolizidine product **9d**, derived from pyrrolidine, is a particularly good example of the value of this transformation owing to its prevalence as a natural product core across several natural product families.[14] The reaction worked just as well on a larger scale (97%, 1.9 mmol), which both demonstrates the versatility of the transformation and allowed investigation into how the unsaturated functional group could be further elaborated (Scheme 2).



Scheme 2 Selected reactivity of cyclic amidine **9d**.

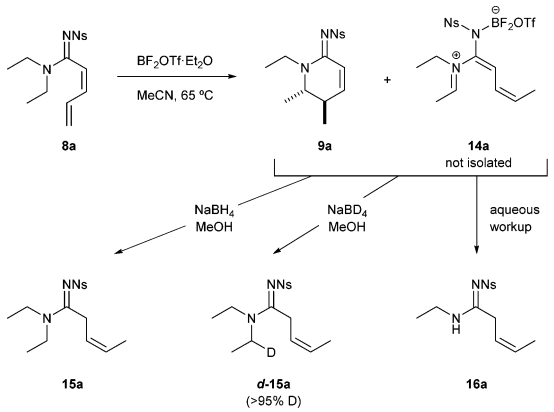
Treatment of the bicyclic azaheterocycle **9d** with hydrogen peroxide gave the epoxide **10d** as only one detectable stereoisomer.[15] Dihydroxylation also efficiently delivered a single diol product **11d** in excellent yield. Dibromination with molecular bromine followed by elimination with base (NEt_3) resulted in efficient bromine incorporation at the α-position (**12d**). Finally, hydrogenation with palladium on carbon efficiently resulted in reduction of the alkene as well as the nitro group (**13d**).

The behaviour of substrates at lower temperatures provided key insight into this mechanism (Scheme 3).

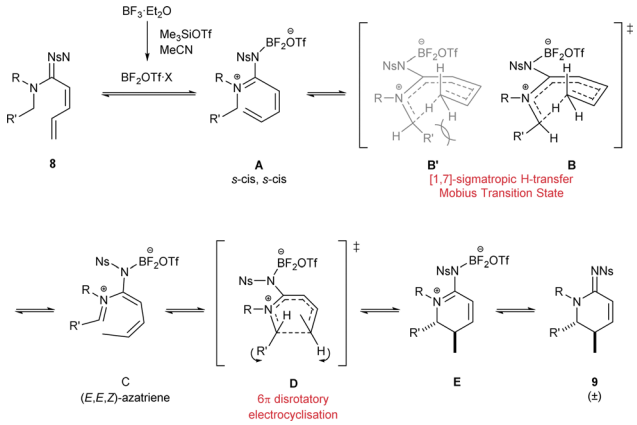
^{1}H NMR analysis of the reaction mixture following 18 h at 65 °C (instead of the optimum 100 °C) revealed a mixture of unreacted starting material **8a**, cyclic amidine **9a** and other intermediates that was believed to be related to an azatriene **14a**. This compound **14a** could neither be isolated nor observed directly but upon hydrolysis the secondary amide **16a**, resulting from iminium hydrolysis, was observed. Further evidence for the existence of azatriene **14a** came upon adding sodium borohydride to the crude mixture to give the reduced alkene product **15a**. Simple conjugate reduction of the diene starting material was ruled out because only the *Z*-geometry ($^3J_{H-H}$ = 10.6 Hz) of the alkene was observed; and using sodium borodeuteride resulted in deuterium incorporation in the *N*-substituent (**d-15a**).[16]

The mechanism for this transformation can be explained by a suggested sequence of two pericyclic reactions (Scheme 4).

First, *in situ* generated BF_2OTf Lewis acid would interact with the imine nitrogen atom (in **8**) to populate the zwitterionic



Scheme 3 Experimental evidence of an azatriene intermediate **14a**.



Scheme 4 Proposed reaction mechanism.

form **A** of the amidine resonance. Next, a 1,7-H shift would activate the position adjacent to the amidine N^2-atom. The high unsaturation in the system **A** suggests a pericyclic process with twisted or Möbius-type[17] transition state **B** to satisfy the Woodward-Hoffman rules.[18] Both geometries of the iminium portion could be possible but in order to form *Z*-iminium geometry the N^1-substituent would reach in towards the 8-membered ring (**B′**), presumably resulting in increased steric clash. The geometric requirements of the transition state are such only one geometry of the diene portion is attainable so the (*E*,*E*,*Z*)-azatriene **C** would be the favoured product of the first pericyclic process. Then, thermally allowed 6π-electrocyclisation **D** would translate of the (*E*,*E*,*Z*) geometry to a product that contains substituents on opposite sides of the closing ring **E**.[18a,19] This would also be the expected thermodynamically favoured product due to minimisation of 1,2 strain. Finally, loss of the Lewis acid would release the cyclic amidine product **9**. This mechanism explains both the product and stereocontrol observed in the reaction. Interestingly, the order of the two pericyclic processes are reversed in this mechanism compared with vitamin D biosynthesis.

However, alternative mechanistic pathways can not be ruled out. The requirement of a strong boron Lewis Acid suggests that the mechanism may have polar character. There has also been an example of a reaction where a bisborane Lewis acid played a critical role in a C–H transfer.[20]

In summary, this process represents the transformation of simple unsaturated building blocks into valuable stereodefined cyclic amidine products. A selection of valuable scaffolds was formed and the reaction was amenable to scale-up, which is a testament to the importance of BF_2OTf as a Lewis acid. Characterisation of reaction intermediates suggested a mechanism including 1,7-H shift and electrocyclisation that represents a rare example of 1,7-H shift applied to synthetic methodology. Overall, this method represents a valuable approach to azaheterocycle synthesis.

Conflicts of interest

There are no conflicts to declare.

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