A Novel Asymmetric Azaspirocyclisation Using a Morita–Baylis–Hillman-Type Reaction

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This paper is dedicated with deep respect to Gerry Pattenden on the occasion of his 70th birthday

Abstract: A Morita–Baylis–Hillman-type reaction has been applied to the asymmetric preparation of azaspirocycles in high yield and diastereoselectivity. The optimisation of the reaction is discussed and a model for the origin of diastereoselectivity is proposed.

Key Words: Morita–Baylis–Hillman-type reaction, azaspirocyclisation, spiro compounds, asymmetric synthesis, diastereoselectivity

The azaspirocyclic motif is found in a large number of natural products, including the cylindricine[1] and histronicotoxin[2] families, halichlorine and the pinnaic acids (Figure 1).[3]

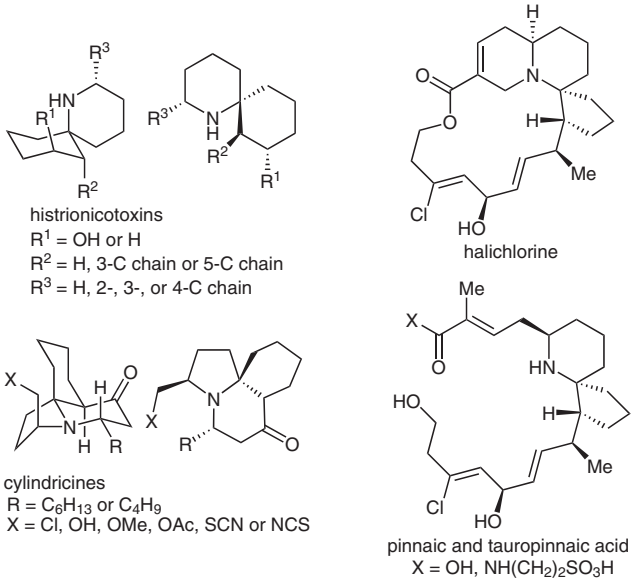
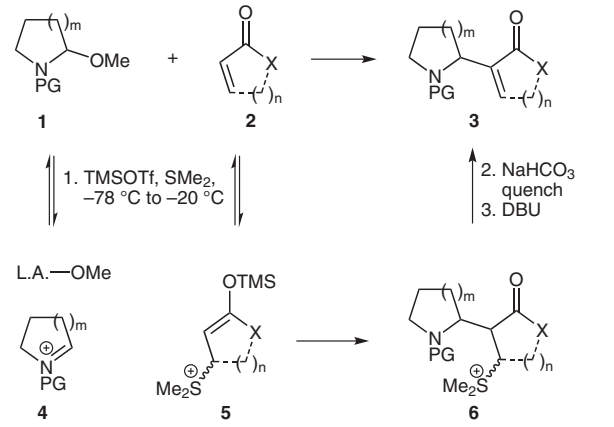


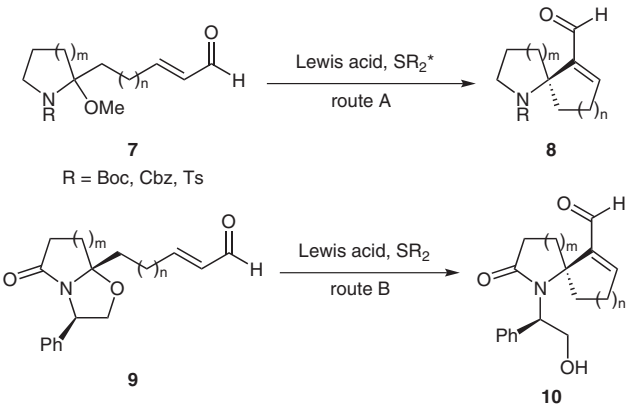
Figure 1 Azaspirocycles in natural products

Ever since their discovery, formation of the asymmetric spirocentre in these molecules has presented an inspiring challenge to synthetic chemists. Herein we report a method for high yielding, highly diastereoselective preparation of azaspirocycles amenable to a range of further functionalisation as required. We were able to obtain these azaspirocycles by development of methodology previously published from our group, in which enones **2**, activated by Michael addition of a sulfide (**5**), were able to react with in situ generated iminium ions **4** (Scheme 1).[4] Morita–Baylis–Hillman-type (MBH-type) adducts **3** were obtained after elimination of sulfide in a second step.



Scheme 1 Morita–Baylis–Hillman-type reaction

An intramolecular version of the reaction employing a combination of TMSOTf and $BF_3{\cdot}OEt_2$, forming the Lewis acid BF_2OTf in situ,[5] was used to prepare the bicyclic pyrrolizidine alkaloid (+)-heliotridine.[4] The choice of Lewis acid was critical, since a weaker Lewis acid would not form a stable sulfide adduct at room temperature[6] as required for ring closure.



Scheme 2 Strategy for asymmetric azaspirocyclisation

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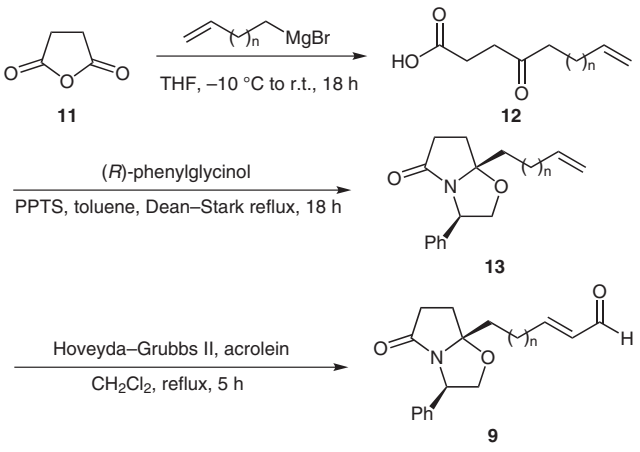
Table 1 Preparation of Azaspirocycle Precursors



n	Yield (%) of **13** (over 2 steps)	Yield (%) of **9**
1	30	61
2	24	66
3	27	56

We have investigated two approaches to asymmetric azaspirocycle formation (Scheme 2). Route A employs a racemic acyclic aminal together with a chiral sulfide. A chiral sulfide has been used previously in an MBH-type reaction to generate adducts of the form of **3** (Scheme 1) with good stereocontrol.[4] Unfortunately no methods are known for preparation of the acyclic aminals required for our study and our efforts to synthesise them proved unsuccessful.

We were successful in preparing the cyclic aminal **9** of route B. Since the aminal also functions as a chiral auxiliary, the need for a chiral sulfide is obviated. Furthermore, there was precedence for the reaction of related aminals with nucleophiles showing good levels of stereocontrol.[7]

The preparation of **9** is shown below (Table 1). The first two steps are adapted from a known preparation of aminal **13**.[8] The adaptation (reversing the order of the first two steps)[9] not only made purification of **13** much easier on the scale required, but also led to a more reproducible and less capricious process in our hands. Cross metathesis with acrolein gave the azaspirocycle precursors **9**.

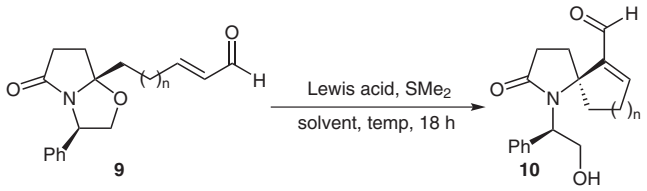
Our investigations of the key azaspirocyclisation step began by replicating the conditions previously used for intramolecular MBH-type reaction (Table 2, entry 1).[4] The reaction was successful, although low yielding. However, through variation of the Lewis acid employed we discovered that simply using $BF_3{\cdot}OEt_2$ (entry 3) gave good yields and good levels of stereocontrol. The reaction could be extended to the 5,6-spirocycle (entry 4) but not to the 5,7-spirocycle (entry 5).

It is noteworthy that in all of these cases the sulfide was eliminated on $NaHCO_3$ workup and separate treatment with DBU was not required (see Scheme 1).

Variation in the sulfide structure led to further improvements (Table 3). Anisyl methyl sulfide was found to be optimal (Table 3, entries 5 and 6), providing high levels of stereocontrol and moderate to good yields. Unfortunately we were unable to extend this protocol to the 5,7-spirocycles, 6,5- or 6,6-azaspirocycles. In fact the six-membered-ring cyclic aminals appeared to be very stable to a range of Lewis acid and nucleophile combinations.[10] In all cases we either recovered starting material or decomposition occurred.

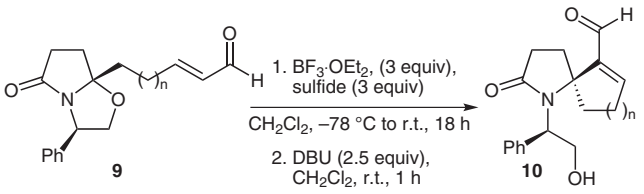
The two diastereomers could be readily separated by column chromatography. The stereochemistry of the major diastereomer was proved by X-ray diffraction analysis (Figure 2).[11] Reduction and deprotection of **10** gave the enantiopure azaspirocycle **15** (Scheme 3).[12]

Table 2 Lewis Acid and Solvent Optimisation



Entry	n	Lewis acid	Solvent	Temperature	Yield (%)	dr
1	1	TMSOTf + $BF_3{\cdot}OEt_2$ (3 equiv) each	MeCN	–15 °C	41	83:17
2	1	TMSOTf (3 equiv)	MeCN	–15 °C	trace	n/a
3	1	$BF_3{\cdot}OEt_2$ (3 equiv)	CH_2Cl_2	–78 °C to r.t.	78	82:18
4	2	$BF_3{\cdot}OEt_2$ (3 equiv)	CH_2Cl_2	–78 °C to r.t.	81	79:21
5	3	$BF_3{\cdot}OEt_2$ (3 equiv)	CH_2Cl_2	–78 °C to r.t.	trace	n/a

Table 3 Lewis Acid and Solvent Optimisation



Entry	n	Sulfide	Step 2 required?	Yield (%)	dr
1	1	SMe_2	no	78	82:18
2	2	SMe_2	no	81	79:21
3	1	PhSMe	no	53	93:7
4	2	PhSMe	no	35	88:12
5	1	$MeOC_6H_4SMe$	yes	73	89:11
6	2	$MeOC_6H_4SMe$	yes	63	92:8
7	3	$MeOC_6H_4SMe$	yes	trace	n/a

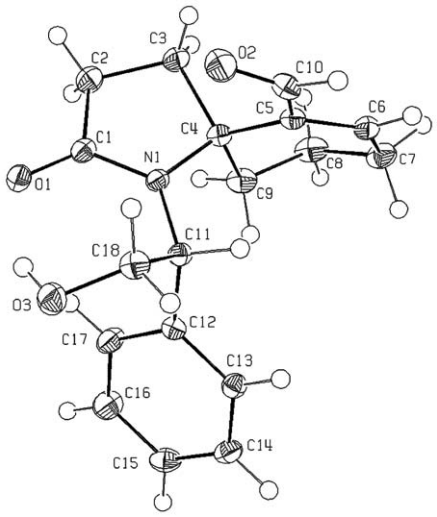
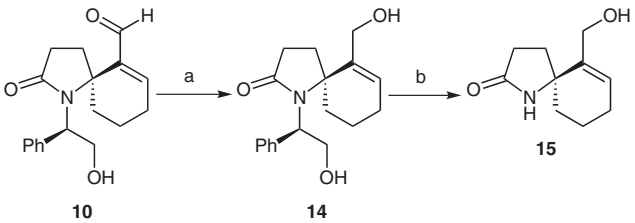


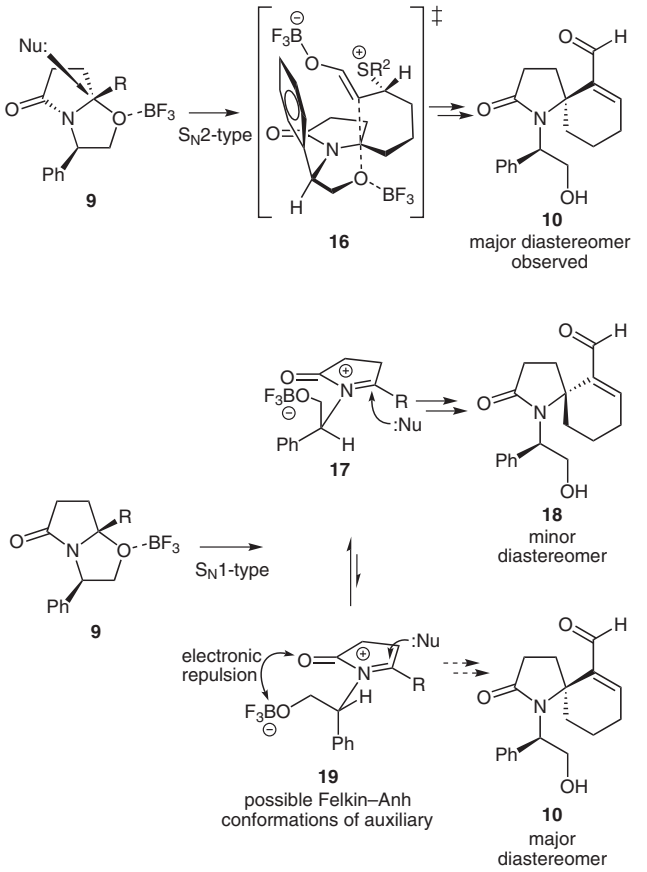
Figure 2 Single crystal structure of **10**



Scheme 3 Auxiliary cleavage. *Reagents and conditions*: (a) $NaBH_4$, MeOH, –30 °C, 1 h, 56%; (b) Na, $NH_{3(l)}$, THF, –78 °C, 90 s, 61%

The stereochemical outcome of the reaction can be rationalised by consideration of the pathways available to the activated aminal (Scheme 4).

A direct S_N2 approach of the trifluoroborate enol ether nucleophile would occur from behind the C–O bond, which coincidentally is also from the less sterically hindered



Scheme 4 Model for diastereoselectivity

convex face of the bicyclic aminal. This leads to the major diastereomer observed.

An alternative S_N1 pathway may also be operational. Applying the Felkin–Anh requirement that the nucleophile approaches over the smallest substituent (H),[13] two conformers are possible. Of these, **19** is likely to suffer electronic repulsion between the carbonyl group and the trifluoroborate ether as shown.[14] Reaction via **17** would lead to the minor diastereomer.

Meyers first proposed this competition between S_N1 and S_N2 pathways in nucleophilic addition to bicyclic aminals.[7a] His findings support the application of the Felkin–Anh model to explain diastereoselectivity in such systems. It is reasonable that the S_N2 pathway dominates over the S_N1 pathway since the reaction is intramolecular and would therefore benefit from a degree of bond formation in the transition state. In addition, the transition state on the S_N2 pathway can be stabilised by the π-stacking of the boron enolate with the phenyl ring of the auxiliary (**16**, Scheme 4).[15]

In summary, a Morita–Baylis–Hillman-type reaction has been developed and optimised for the asymmetric preparation of azaspirocycles. The auxiliary used can be cleaved using a two-step sequence. The azaspirocycles formed are potentially highly versatile synthetic intermediates with the capacity for a range of further functionalisation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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