

## Stereoselective aza-Diels–Alder reactions with 2*H*-azirines as dienophiles furnishing highly functionalized tetrahydropyridines

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Highly diastereoselective Lewis acid mediated aza-Diels–Alder reactions of chiral auxiliary derivatized 2*H*-azirines have been accomplished for the first time, yielding bi and tri-cyclic heterocyclic compounds, comprising aziridine and tetrahydropyridine substructures, in up to 97% de; with the absolute stereochemistry of the major product confirmed by X-ray crystallography.

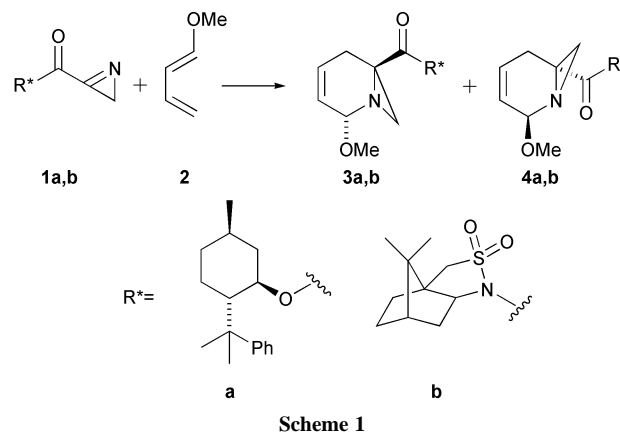
The hetero Diels–Alder reaction is an exceptionally powerful synthetic method for construction of six membered heterocycles.<sup>1</sup> In one single transformation up to four new stereo centres with defined stereochemistry can be formed. By applying 2*H*-azirines as dienophiles it is possible to form highly functionalized products with a fused [4.1.0] ring system as well as polycyclic structures incorporating the same fused subunit. Further transformations of these Diels–Alder products would lead to a great number of compounds with potential use as chiral ligands, unnatural amino acids or as part of biologically active compounds.<sup>2,3</sup> As such the stereochemical purity is of great importance. The aza-Diels–Alder reactions between azirines and many dienes are known to give products with complete regio- and endo-selectivity.<sup>4</sup> It would therefore be desirable to find a way to control the absolute stereochemistry of the formed stereo centres. A few attempts to achieve this have previously been published by others.<sup>5–7</sup> In one case the chiral information was part of the azirine ring itself giving excellent selectivity but the need for an aromatic substituent in the 2-position of the ring is a limiting factor.<sup>5</sup> Two other attempts, with chiral auxiliaries (Oppolzer's *N,N*-dialkyl-(1*R*)-isobornyl-10-sufonamide and (*S*)-phenylethylamide) attached to the azirine ring, gave low or no selectivity.<sup>6,7</sup> The 2*H*-azirines are, despite their ringstrain, generally poor dienophiles in normal electron demand Diels–Alder reactions unless substituted by an activating group such as an ester-, amide- or phosphonate group.<sup>4,5</sup> However, previous studies in our laboratory have shown that it is possible to increase the reactivity without the need for such substituents by coordination of a Lewis acid to the azirine.<sup>8,9</sup> With this in mind it seemed interesting to study the effect of a Lewis acid in combination with a chiral auxiliary on the stereoselectivity.

In order to investigate this, two enantiomerically pure 2*H*-azirines **1a** and **1b**, substituted in 3-position with a chiral auxiliary, (–)-8-phenylmenthol and Oppolzer's sultam ((+)-10,2-camphorsultam), respectively, were chosen as substrates and allowed to react with 1-methoxy-1,3-butadiene (**2**, Scheme 1). A few Lewis acids, with the ability of bidentate coordination were needed. Due to the inherent acid sensitivity of the azirines and of some commonly used dienes, mild reagents were essential. Both magnesium and zinc halides as well as lanthanide complexes fulfil these requirements and MgBr<sub>2</sub>·OEt<sub>2</sub>, ZnCl<sub>2</sub>·OEt<sub>2</sub> and YbCl<sub>3</sub> were therefore selected.<sup>†10,11</sup> Without Lewis acid, no de was obtained at room temperature with substrate **1a**, while a low selectivity was detected with **1b** (Table 1, entries 1 and 2). The reaction of **1a** with **2** was affected by both MgBr<sub>2</sub>·OEt<sub>2</sub> and ZnCl<sub>2</sub>·OEt<sub>2</sub> both favouring the formation of **3a**. Not only was the diastereoselectivity increased to 87% with MgBr<sub>2</sub>·OEt<sub>2</sub> and to 80% with ZnCl<sub>2</sub>·OEt<sub>2</sub> (entries 3 and 5) but also the reaction rate was

substantially increased. For example, the reaction time was reduced from more than 24 hours to less than 10 minutes using ZnCl<sub>2</sub>·OEt<sub>2</sub>.

The effect of the Lewis acids on the reaction was not as clear for the sultam derivatized azirine. Only a slightly larger de of 40% was obtained when applying MgBr<sub>2</sub>·OEt<sub>2</sub> to **1b** (entry 4) compared to the result without Lewis acid. Interestingly, when utilizing ZnCl<sub>2</sub>·OEt<sub>2</sub> the selectivity of the product was of the same magnitude as without any Lewis acid but with the opposite isomer as the major product (entry 6). None of the substrates gave products with appreciable selectivity in the presence of YbCl<sub>3</sub> (entries 7 and 8).

The dramatic effect observed on the reaction outcome upon addition of a Lewis acid to azirine **1a** could be explained by a bidentate coordination of the Lewis acid to the azirine nitrogen and the carbonyl group. This chelation would lead to hindered rotation around the azirine-carbonyl single bond and thus greater stereoselectivity. The increased reaction rate also indicates coordination of the Lewis acids to the azirine which leads to a lowering of the LUMO energy level and thus an increased reactivity towards the electron rich diene. The results obtained with azirine **1b** might be due to coordination of the Lewis acid to the carbonyl group and sulfone oxygen instead of to the



**Table 1** Lewis acid catalyzed Diels–Alder reactions of **1a** and **1b** with 1-methoxy-1,3-butadiene

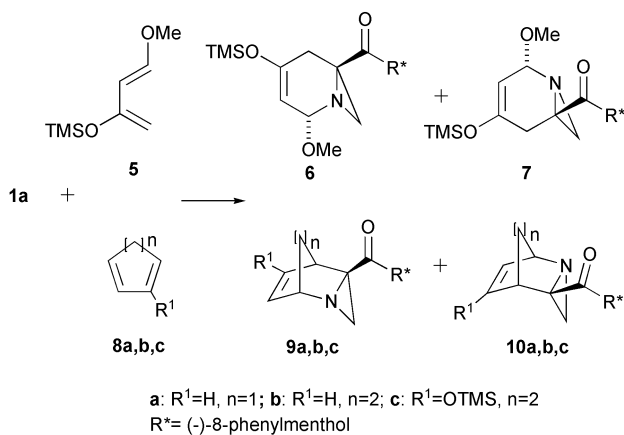
Entry	Azirine	LA	T (°C)	Yield (%)	de <sup>a</sup> (%)
1	1a	—	RT	100 <sup>b</sup>	0
2	1b	—	RT	95 <sup>b</sup>	21
3	1a	MgBr <sub>2</sub> ·OEt <sub>2</sub>	–100 to –75	82 <sup>c,d</sup>	87
4	1b	MgBr <sub>2</sub> ·OEt <sub>2</sub>	–78	38 <sup>d</sup>	40
5	1a	ZnCl <sub>2</sub> ·OEt <sub>2</sub>	–100	62 <sup>d</sup>	80
6	1b	ZnCl <sub>2</sub> ·OEt <sub>2</sub>	–78	69 <sup>d</sup>	27 <sup>e</sup>
7	1a	YbCl <sub>3</sub>	–78 to –20	43 <sup>d</sup>	27
8	1b	YbCl <sub>3</sub>	–78 to –60	100 <sup>b</sup>	25

<sup>a</sup> Selectivity determined by <sup>1</sup>H NMR. <sup>b</sup> Crude product. <sup>c</sup> Based on unreacted azirine. <sup>d</sup> After chromatography. <sup>e</sup> Opposite major diastereomer compared to entries 2, 4 and 8.

azirine. This comparative study between the two chiral auxiliaries clearly showed the 8-phenylmenthol derivatized azirine **1a** to be the most promising substrate. To confirm the usefulness of the reaction an additional set of dienes were reacted with azirine **1a**. The dienes chosen were Danishefsky's diene (**5**), cyclopentadiene (**8a**), cyclohexadiene (**8b**), and 2-(trimethylsilyloxy)-1,3-cyclohexadiene (**8c**) (Scheme 2).

All the dienes gave together with **1a** in the presence of  $\text{MgBr}_2 \cdot \text{OEt}_2$  or  $\text{ZnCl}_2 \cdot \text{OEt}_2$  products with good to excellent diastereoselectivity and in useful yields (Table 2). Both Lewis acids proved to function well together with Danishefsky's diene giving **6** in high to excellent selectivities (entries 2 and 3) albeit the obtained yield after chromatography was unsatisfactory. Hydrolysis of the TMSO-group before purification might improve the overall yield.  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted higher selectivity than  $\text{ZnCl}_2 \cdot \text{OEt}_2$  for the addition of **8a** to give **9a:10a**, although high yields were obtained in both cases (entries 5 and 6). The reaction between **1a** and diene **8b** in the presence of  $\text{MgBr}_2 \cdot \text{OEt}_2$  gave no expected product despite complete consumption of the azirine (entry 8). For this diene  $\text{ZnCl}_2 \cdot \text{OEt}_2$  was a valuable complement affording **9b:10b** in 99% yield and 80% de (entry 9). On the other hand, the TMSO substituted cyclohexadiene **8c** afforded a 98.5:1.5 mixture of **9c:10c** in 99% yield using  $\text{MgBr}_2 \cdot \text{OEt}_2$  (entry 11). The result obtained with  $\text{ZnCl}_2 \cdot \text{OEt}_2$  was similar to that without any Lewis acid (compare entries 12 and 10). It can be concluded that for all dienes a substantial increase in diastereoselectivity was obtained when performing the reactions in the presence of a Lewis acid (compare entries 1 with 2 and 3, 4 with 5 and 6, 7 with 9, 10 with 11). It is also clear that  $\text{MgBr}_2 \cdot \text{OEt}_2$  was more efficient than  $\text{ZnCl}_2 \cdot \text{OEt}_2$ , with diene **8b** being the only exception.

The aziridine moiety in **9a:10a** was easily ring opened by  $\text{MgBr}_2 \cdot \text{OEt}_2$  to form compounds **11** and **12** (Scheme 3). The major product **11** was recrystallized and the absolute configura-

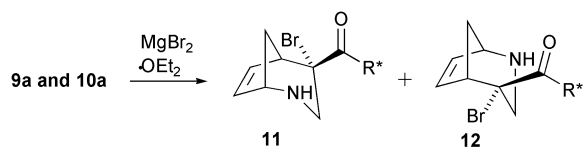


Scheme 2

Table 2 Lewis acid catalyzed D–A reactions of **1a** with dienes **4**, **7c**, **d** and **e**

Entry	Diene	LA	T (°C)	Yield (%)	de <sup>a</sup> (%)
1	5	—	–75 to –40	90 <sup>b</sup>	30
2	5	$\text{MgBr}_2 \cdot \text{OEt}_2$	–100	56 <sup>c</sup>	96
3	5	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–100 to –90	31 <sup>c</sup>	87
4	8a	—	–78 to –40	99 <sup>b</sup>	8
5	8a	$\text{MgBr}_2 \cdot \text{OEt}_2$	–100	88 <sup>c</sup>	85
6	8a	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–100	99 <sup>b</sup>	58
7	8b	—	RT	100 <sup>b,d</sup>	20
8	8b	$\text{MgBr}_2 \cdot \text{OEt}_2$	–77	—	—
9	8b	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–78	99 <sup>c</sup>	80
10	8c	—	–75 to –40	80 <sup>c</sup>	30
11	8c	$\text{MgBr}_2 \cdot \text{OEt}_2$	–75	99 <sup>b</sup>	97
12	8c	$\text{ZnCl}_2 \cdot \text{OEt}_2$	–77	99 <sup>b</sup>	34

<sup>a</sup> Selectivity determined by <sup>1</sup>H NMR. <sup>b</sup> Crude product. <sup>c</sup> After chromatography. <sup>d</sup> Based on unreacted azirine.



Scheme 3

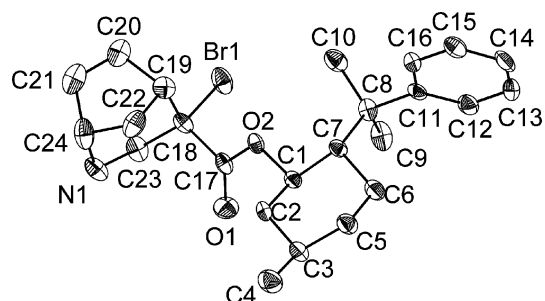


Fig. 1 X-Ray structure of compound **11**.

tion then confirmed by X-ray crystallography. The major isomers **3a**, **6**, **9b** and **9c** were assigned in analogy (Fig. 1).<sup>‡</sup> The result was in agreement with previously suggested stereochemical models of the transition state of 8-phenylmenthol derivatives.<sup>12</sup> It is assumed that the carbonyl group is aligned with the axial hydrogen on C1 in the 8-phenylmenthol group and the phenyl ring oriented parallel to the azirine ring. Chelation of the nitrogen and the carbonyl group by a Lewis acid then rigidifies the structure with the *Re*-face of the azirine being shielded by the phenyl group.

We are pleased to report herein the first successful stereoselective Diels–Alder reactions of enantiomerically pure 2*H*-azirines and a variety of dienes in the presence of a Lewis acid. Further investigations in this area are in progress and will be reported in due course. The authors are grateful for the financial support provided by the Swedish Research Council. We also thank Mr Daniel Strand for helpful discussions.

## Notes and references

† A typical procedure: the azirine **1a** (67  $\mu\text{mol}$ ) and  $\text{ZnCl}_2 \cdot \text{OEt}_2$  (134  $\mu\text{mol}$ ) were stirred for 20 min at  $-100^\circ\text{C}$  in 1.3 ml  $\text{CH}_2\text{Cl}_2$  (freshly distilled over  $\text{CaH}_2$ ) under nitrogen atmosphere before 1-methoxybutadiene (134  $\mu\text{mol}$ ) was added. The reaction was followed by TLC and quenched by addition of 1 ml  $\text{NaHCO}_3$  (aq). The biphasic mixture was after vigorous stirring filtered through an Extrelute® NT3 tube and then concentrated to give yellow oil. Purification by chromatography on  $\text{SiO}_2$  with pentane–EtOAc gave **3a:4a** as pale yellow oil.

‡ Crystal data:  $\text{C}_{24}\text{H}_{32}\text{BrNO}_2$ ,  $M = 446.43$ , orthorhombic,  $a = 6.557(1)$ ,  $b = 10.915(2)$ ,  $c = 30.422(5)$  Å,  $V = 2177.1(7)$  Å<sup>3</sup>,  $T = 100$  K, space group  $P2_12_12_1$  (No. 19),  $Z = 4$ ,  $\mu(\text{Mo–K}\alpha) = 1.9$  mm<sup>–1</sup>, 17434 reflections measured, 4969 unique reflections ( $R_{\text{int}} = 0.073$ ) used in all calculations. Friedel pairs were not merged before refinement. Hydrogen atoms were placed at calculated positions and refined using a riding model. The final  $wR(F^2)$  was 0.093 (all data). Flack parameter  $x = -0.007(10)$ . CCDC 201523. See <http://www.rsc.org/suppdata/cc/b3/b300849e/> for crystallographic data in .cif or other electronic format.

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