Pergamon

Tetrahedron Letters 42 (2001) 9289–9291

TETRAHEDRON LETTERS

Lewis acid-catalyzed hetero Diels–Alder cycloadditions of 3-alkyl, 3-phenyl and 3-carboxylated 2*H*-azirines

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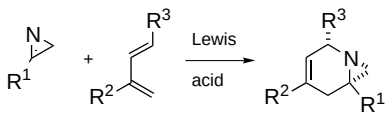
Received 7 September 2001; revised 25 October 2001; accepted 30 October 2001

Abstract—Activation by Lewis acids of 3-alkyl and 3-phenyl 2*H*-azirines promotes their participation in hetero Diels–Alder reactions with a variety of dienes. This methodology circumvents the previous requirement of an electron-withdrawing carboxyl moiety at the 3-position of the 2*H*-azirine.

The furnishing via hetero Diels–Alder chemistry of nitrogen containing cycloadducts, which have potential as synthetic intermediates in alkaloid synthesis, is a valuable manoeuvre.[1] While the use of aza-dienes is well established,[2] incorporation of the nitrogen heteroatom as part of the 2π moiety of the [4+2] process is limited for the most part to imines bearing electron-withdrawing groups.[3] The strained, electron-rich carbon–nitrogen double bond in the 2*H*-azirine is more reactive than the corresponding double bond in an imine[4] and, while 2*H*-azirines participate in reversed electron-demand Diels–Alder reactions,[5] there are only a few publications describing the normal electron-demand Diels–Alder reaction of 2*H*-azirines,[6] the requirement being an activation of the three-membered ring by an electron-withdrawing substituent. An obvious strategy to circumvent this structural limitation, and thus broadening the scope of the process, would be to use Lewis acids for activation of the C=N moiety in the three-membered ring. However, care has to be exercised since it is known that azirines are prone to acid-catalyzed decomposition.

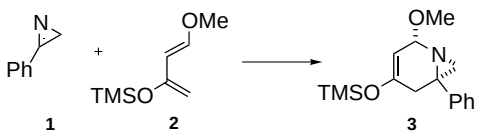
Herein is described the results of our preliminary investigation of the Lewis acid-catalyzed hetero Diels–Alder reactions of 3-alkyl, 3-phenyl and 3-carboxylated 2*H*-azirines with some model dienes (Scheme 1).

To identify suitable catalysts, 2*H*-azirine **1**[7] and Danishefsky's diene **2** were chosen as a model [4+2] system, while the Lewis acid candidates were selected for their azaphilicity, as highlighted by Kobayashi.[8] Heating an equimolar mixture of azirine **1** with **2** at 75°C in toluene in the absence of a Lewis acid after 72 h provided only starting materials (Table 1, entry 1). This failure to



Scheme 1. Lewis acid-catalyzed Diels–Alder cycloaddition of a 3-substituted 2*H*-azirine.

Table 1. Diels–Alder reactions between **1** and **2** to give **3** in the presence of Lewis acids[a]



Entry	Lewis acid	Temp. (°C)	Time (h)	Yield (%)[b]
1	–	75	72	0
2	$ZnCl_2$	75	8	40
3	$YbCl_3$	75	6	55
4	$ScCl_3$	75	12	30
5	$CuCl_2$	75	12	35
6	$BF_3{\cdot}Et_2O$[c]	−70	0.3	42
7	$InCl_3$	−70	48	–[d]
8	$Cu(OTf)_2$	−70	12	–[d]

[a] Reactions were conducted in PhMe using 0.3 equiv. Lewis acid, unless otherwise stated.
[b] Isolated product. No starting material was recovered.
[c] Conducted in CH_2Cl_2 with 0.2 equiv. $BF_3{\cdot}Et_2O$.
[d] The reaction was conducted until decomposition of **1** was evident.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)02042-1

effect a cycloaddition indicated the expected lack of reactivity exhibited by **1** in the normal electron-demand [4+2] cycloaddition. However, treatment of a mixture of azirine **1** and diene **2** with 0.3 equiv. of $ZnCl_2$, $YbCl_3$, $ScCl_3$ or $CuCl_2$ at 75°C provided *endo* cycloadduct **3**[9] exclusively and in moderate yield (Table 1, entries 2–5). The boron trifluoride-catalyzed cycloaddition was a notable exception (Table 1, entry 6). In this case treatment of a mixture of **1** and **2** with 0.2 equiv. of the Lewis acid provided after typically 0.3 h at −70°C, aziridine **3** in 42% yield. Other Lewis acids, such as $InCl_3$ and $Cu(OTf)_2$, failed to promote the cycloaddition (Table 1, entries 7 and 8).

To investigate further the scope of this Lewis acid-catalyzed process the cycloaddition of a series of azirines **1**, **4** and **5** with dienes **6**–**8** was studied (Table 2 and Fig. 1). Reaction of **1** with **6** and **4** with **7** gave exclusively *endo* isomers **9** and **10**,[9] respectively, in moderate yields (Table 2, entries 1 and 2). Interestingly, each individual transformation requires careful optimization of the reaction temperature and catalyst. Both $ZnCl_2$ and $Rh_2(OAc)_4$ promote the cycloaddition of ester derivative **5** and cyclopentadiene **8** at reduced temperatures to afford *endo* bicycle **11** (Table 2, entries 3 and 4).[9] The corresponding thermal process, in comparison, only proceeds at room temperature, indicating the beneficial influence of the Lewis acids on the reaction rate (Table 2, entry 5).

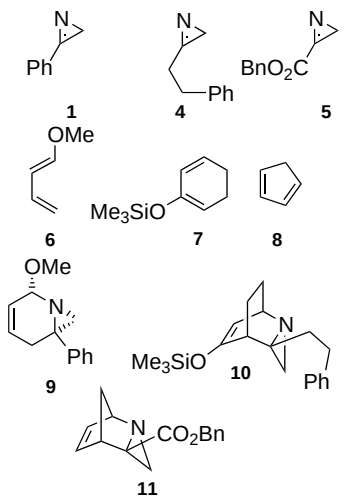
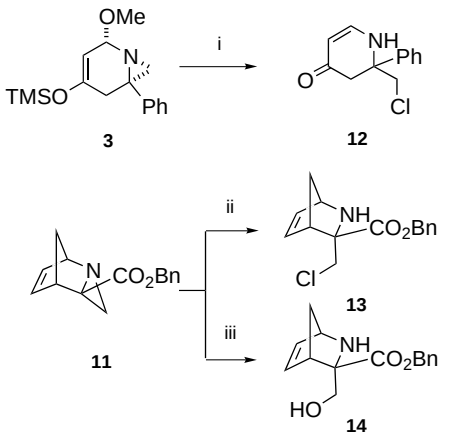


Figure 1. Azirines, dienes and products in Table 2.

The regiochemistry associated with ring-opening bicyclic aziridines appears to be a complex phenomenon.[10] Aziridine **3** could conceivably experience attack of a nucleophile at either C6 or C7. It has previously been shown that when systems related to **3** are subjected to an acidic medium the corresponding dihydroazepinone was isolated, in which all stereochemical information created during the preceding cycloaddition was destroyed.[6] In the present case, treatment of **3** with 2 M HCl resulted in selective cleavage of the aziridine providing **12** via protonation of the aziridine nitrogen and selective attack of chloride, seemingly favored over hydroxyl, as the only product (Scheme 2).[9] Under identical conditions **11** provided the bicyclic compound **13**.[9] When subjected to dilute perchloric acid in water **11** experienced selective nucleophilic attack of hydroxyl to provide amino alcohol **14** in 90% yield.[9] These results suggest that the observed selective aziridine ring-cleavage may occur with a range of nucleophilic species.

The Lewis acid-mediated activation of the carbon–nitrogen double bond in 2*H*-azirines described herein is a novel procedure illustrating that the previous requirement of an activating 3-subtituent to promote participation of the 2*H*-azirine in normal electron-demand Diels–Alder chemistry can, if so required, be avoided. It has also been shown that 3-carboxylated azirines, previously believed to be unstable to such conditions, can be activated by Lewis acids, promoting a Diels–Alder reaction at sub-zero temperature. The



Scheme 2. *Reagents and conditions*: (i) 2 M HCl, THF, rt, 80%; (ii) 2 M HCl, THF, rt, 85%; (iii) $HClO_4$, THF, rt, 90%.

Table 2. Lewis acid-catalyzed hetero Diels–Alder reactions[a]

Entry	Diene/Azirine	Lewis acid	Temp. (°C)	Time (h)	Product, yield (%)[b]
1	6/1	$ZnCl_2$	75	6	**9**, 50
2	7/4	$YbCl_3$	90	72	**10**, 36
3	8/5	$ZnCl_2$[c]	−20	12	**11**, 35
4	8/5	$Rh_2(OAc)_4$[d]	−45	24	**11**, 35
5	8/5	–[c]	Rt	24	**11**, 45

[a] Reactions were conducted in PhMe using 0.3 equiv. Lewis acid, unless otherwise stated.
[b] Isolated product.
[c] Conducted in Et_2O.
[d] Conducted in CH_2Cl_2.

yields reported are moderate and we are endeavoring to improve this element of the methodology. However, the possibility now exists to conduct Diels–Alder chemistry using a greater variety of 3-substituted 2*H*-azirines via Lewis acid-mediated catalysis. Work is in progress to investigate the scope of this process.

General procedure: synthesis of 3 catalyzed by $YbCl_3$: To a solution of azirine **1** (23 mg, 0.19 mmol) in toluene (3 mL) under a nitrogen atmosphere at ambient temperature, was added $YbCl_3$ (16 mg, 0.06 mmol, 0.3 equiv.). After 5 min a solution of diene **2** (33 mg, 0.2 mmol) in toluene (1 mL) was added and the reaction mixture was heated to 75°C. The reaction temperature was maintained until TLC indicated the absence of **1** (6 h). Once cool, the reaction mixture was washed with sat. aq. $NaHCO_3$ (2×4 mL) and the aqueous phases were extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Filtration of the residue through basic alumina (pentane:ethyl acetate 7:1) gave **3** (31 mg, 55%) as a yellow oil. $R_f=0.70$ (7:1 pentane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.47–7.23 (m, 5 H), 5.07 (br. s, 1 H), 4.66 (d, $J=1.5$, 1 H), 3.68 (s, 3 H), 2.56 (d, $J=17.3$ Hz, 1 H), 2.52 (d, $J=17.5$ Hz, 1 H), 2.24 (s, 1 H), 1.69 (s, 1 H), 0.00 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 147.5, 128.8, 128.3, 126.7, 125.9, 99.9, 88.1, 56.1, 40.0, 32.1, 31.3, 0.00; IR (neat): $\nu_{max}=2100$, 1696, 1395, 1265, 1073, 913; MS (CI, NH_3): m/z (%) 290 $[M+H]^+$; HRMS calcd for $C_{16}H_{23}NO_2Si$ $[M+H]^+$: 290.1576; found: 290.1581.

Acknowledgements

The authors thank the Swedish Foundation for Strategic Research (Selchem) for financial support and Dr. U. Jacobsson for assistance with NMR measurements.

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9. All new compounds showed spectroscopic data in complete agreement with the assigned structures (^{1}H, ^{13}C NMR, HRMS). The *endo* stereochemistry of **3**, **9**–**11** were shown by COSY experiments and analyzing the relevant coupling constants. For analogous assignments, see Ref. 6.
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