Lewis Acid Mediated Alkylation and Diels-Alder Reactions of 2*H*-Azirines

Licenciate thesis by Erik Risberg

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Abstract

This thesis describes the use of 2*H*-azirines as reactive substrates in Lewis acid catalysed nucleophilic additions and in the Diels-Alder reaction.

A number of carbon nucleophiles have been added to a series of 2*H*-azirines in the presence and absence of $BF_3 \cdot Et_2O$. 3-(2-Naphthyl)-2*H*-azirine has been used as a model substrate in the enantioselective addition of organolithium reagents to an 2*H*-azirine.

A selection of Lewis acids has been screened for their possible use in the normal electron demand Diels-Alder reaction between 3-alkyl-, 3-aryl-, and 3-carboxyl-2*H*-azirines and a variety of dienes. Lewis acid activation was found to shorten reaction times and facilitate lower reaction temperatures. These cycloadditions proceeded with *endo* selectivity providing a single diastereoisomeric product.

DFT calculations of Lewis acid activated 2*H*-azirines have been carried out.

Keywords: 2*H*-azirines, Lewis acid activation, chiral ligands, organolithium reagents, Diels-Alder reactions, DFT-calculations

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List of Publications

This thesis is based on the following papers, referred to in the text by their roman numerals.

I. **Enantioselective addition of organolithium reagents to a 2*H*-azirine**
Risberg, E. and Somfai, P.
Tetrahedron Asymmetry **2002**, accepted for publication

II. **Lewis acid-catalyzed hetero Diels-Alder cycloadditions of 3-alkyl, 3-phenyl and 3-carboxylated 2*H*-azirines**
Ray, C. A., Risberg, E. and Somfai, P.
Tetrahedron Letters **2001**, *42*, 9289-9291

III. **Diastereoselective Lewis acid catalysed [4+2] cycloadditions of 3-alkyl-, 3-aryl- and 3-carboxyl-2*H*-azirines: a route to aziridine containing azabicyclo[4.1.0]heptanes and azatricyclo[2.2.1.0]nonanes.**
Ray, C. A., Risberg, E. and Somfai, P.
Tetrahedron **2002**, *58*, 5983-5987

Abbreviations

aq.	aqueous
B3LYP	a hybrid density functional method
BINOL	1,1´-bi(2-naphtol)
COSY	correlation spectroscopy
DFT	density functional theory
DIPEA	*N*, *N´*diisopropylethylamine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
ee	enantiomeric excess
EWG	electron withdrawing group
HOMO	highest occupied molecular orbital
LACVP	a basis set used in DFT calculations
LAH	lithium aluminium hydride
LG	leaving group
LUMO	lowest unoccupied molecular orbital
M	metal
min.	minutes
MO	molecular orbital
Ms	SO_2CH_3, mesylate
Nap	naphthyl
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
on.	over night
Tf	SO_2CF_3, triflate
rt	room temperature
satd.	saturated
TBDMS	*tert*-butyl dimethylsilyl
temp.	temperature
TMS	trimethylsilyl

1. Introduction

1.1 General introduction

The preparation of complex natural products is an area under constant development. Since the pioneering work by Wöhler,[1] who accomplished the first total synthesis of urea, preparation of complex natural products and their slightly modified analogues has progressed spectacularly. The first examples of catalytic asymmetric synthesis were performed on racemic mixtures (kinetic resolution) in enzymatic reactions in the middle 1800´s. In early 1900´s procedures to add nucleophiles enantioselectively through employment of chiral ligands, were revealed. Interest in asymmetric synthesis has grown dramatically since the importance of enantiomeric purity was discovered. To further shorten synthetic routes and allow the preparation of even more complex structures, new strategies need to be developed, and new reactive intermediates explored. This thesis describes the use of such an intermediate, the 2*H*-azirine, for the development of interesting amino functionalities.

1.2 Properties of the azirine

Azirine is the term used to describe the smallest unsaturated nitrogen containing heterocyclic system, with two carbon atoms and one double bond in a three-membered ring. The first synthesis of a 2*H*-azirine ever reported was described by Neber *et al*. in 1932.[3] They found 2*H*-azirines as intermediates in the synthesis of aminoketones by treatment of oxime *p*-toluenesulfonates with base. Extensive investigations during the 1960s and the 1970s revealed valuable information concerning their physical properties, biological applications, and synthetic use. A number of general reviews have appeared since then.[4-9]

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1 Wöhler, F., *Ann. Phys. Chem.* 1828, 12, 253

2 Nikolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 44-122.

3 [a] Neber, P. W.; Huh, G. *Justus Liebigs Ann. Chem.* **1935**, 283-296; [b] Neber, P. W.; Burgard, A. *Justus Liebigs Ann. Chem*. **1932**, 281-294.

4 Pearson, W. H.; Lian, B. W. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 1a, pp 1-60.

5 Nair, V. In Small Ring Heterocycles; Hassner, A., Ed.; Interscience: New york, 1983; Vol. 42, pp 215-332.

6 Backes, J. In Organische Stickstoff-Verbindungen III; Klamann, D., Ed.: Stuttgart, 1992; Vol. E16c, pp 317-369.

7 [a] Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401-2414; [b] Padwa, A.; Woolhouse, A. D. In Comprehensive Heterocyclic Chemistry; Lwowski, W., Ed.; Pergamon Press: Oxford, 1984; Vol. 7, part 5, pp 47-93; [c] Rai, K. L. M.; Hassner, A. In Advances in Strained and interesting Organic Molecules; Halton, B., Ed.; JAI press, 2000; Vol. 8, pp 187-257; [d] Nair, V.; Kim, K. H. *Heterocycles* **1977**, *7*, 353-390.

8 Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51-55.

9 Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219-269.

The big interest in azirines exists due to their high reactivity and potential use in synthesis, their role as precursors for more complex heterocycles and their use in the preparation of various amines and aziridines. Azirines are divided into 1*H*-azirines **1** with a C=C bond, and 2*H*-azirines **2** with a C=N bond (Figure 1). The ring strain energy of unsubstituted 2*H*-azirines has been estimated to be 48 kcal/mol, while 1*H*-azirines were found to be 33-37 kcal/mol higher in energy. Comparable values for the aziridine **3** are 26-27 kcal/mol which leads to a decrease of around 20 kcal/mol upon reduction of the C=N bond in the 2*H*-azirine into the corresponding aziridine.[4] 2*H*-Azirines are reactive and versatile substrates because of certain inherent features within their structure. These include ring strain, an electron-rich π bond, a lone pair of electrons on nitrogen and the ability to undergo ring cleavage on thermal or photochemical excitation to give such reactive fugitive species as vinyl nitrenes, iminocarbenes, and nitrile ylides.[5]

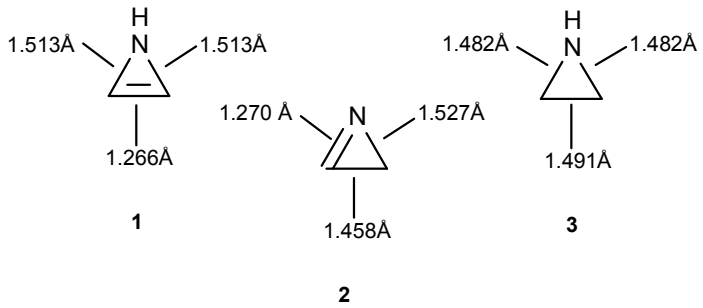


Figure 1. *Structure of the 1H-azirine **1**, the 2H-azirine **2**, and the aziridine **3***

2*H*-Azirines can be looked upon as strained imines, with an increased reactivity compared to acyclic imines. The structures have been determined with various methods such as MO calculations, X-ray crystallographic experiments and NMR studies.[4,6]

1.3 2*H*-azirines in natural products

The 2*H*-azirine ring has been found in several natural products (Figure 2). Azirinomycin (**4**),[10] isolated from *Streptomyces aureus* and its methyl ester were found to exhibit a broad spectrum of antibiotic activity, *in vitro*, against both Gram-positive and Gram-negative bacteria.[11] More recently, the azirine-containing natural products (*R*)-(-)-[12] and (*S*)-(+)-dysidazirine[13] (**5**) and (*S*)-(+)-antazirine[13] (**6**) were isolated from *Dysidea fragilis*.

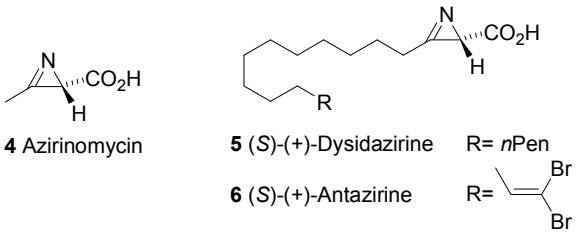
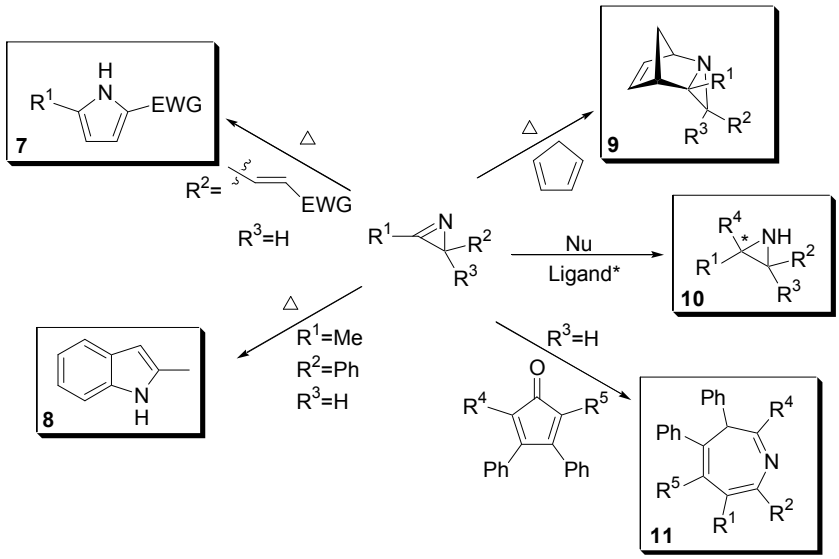


Figure 2. *Azirines found in natural products*

1.4 Azirines as synthetic intermediates

Over the years 2*H*-azirines have been found to undergo a wide variety of transformations, of which a few examples are shown in Scheme 1.



Scheme 1. *The 2H-azirine as a synthetic intermediate*

10 Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiotics* **1971**, *24*, 48-50.
11 Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. J. *J. Antibiotics* **1971**, *24*, 42-47.
12 Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103-2105.
13 Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463-1466.

Heating of 2*H*-azirines bearing vinylic functionalities in the 2-position led to rearrangements forming 2,5-disubstituted pyrroles **7** in high yields.[14] When photolysis was applied to the same substrates 2,3-disubstituted pyrroles were achieved instead. Another rearrangement is the formation of an indole **8** by heating the 2*H*-azirine, believed to take place via the breaking of the 2*H*-azirines C-N bond generating a vinyl nitrene.[15] The generation of vinylnitrenes usually achieved by thermolysis, photolysis, or Lewis acid activation will be covered in the last chapter of this thesis. Bi- and tri-cyclic ring systems have been obtained by the Diels-Alder reaction using azirines as dienophiles together with various dienes,[8] here demonstrated by the formation of **9**.[16,17] Another application is the nucleophilic addition of organometallic reagents to azirines forming aziridines **10**.[18] Another example is the ring expansion of various 2*H*-azirines with cyclopentadienones to give 3*H*-azepines **11** in good yields.[19]

1.5 Aim of the study

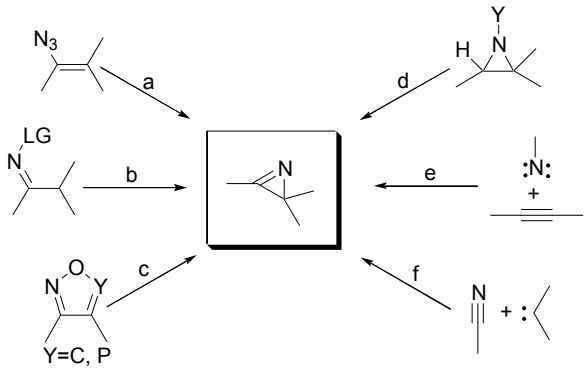
There is a growing interest concerning preparation of chiral amines, amino acids, and nitrogen containing heterocycles. Imines undergo a wide selection of transformations, and usually require an activating group attached to the nitrogen atom. We were interested in the use of 2*H*-azirines as synthetic intermediates, due to their increased reactivity (described above), for various transformations. We were also interested in how application of chiral Lewis acids affect asymmetric induction in chemistry involving 2*H*-azirines. Herein are presented our results concerning enantioselective addition of carbon nucleophiles to 2*H*-azirines, Lewis acid catalysed Diels-Alder reactions using 2*H*-azirines, and a study of complexation of Lewis acids to 2*H*-azirines.

14 Padwa, A.; Smolanoff, J.; Tremper, A. *Tetrahedron Lett.* **1974**, 29-32.
15 Isomura, K.; Kobayashi, S.; Taniguchi, H. *Tetrahedron Lett.* **1968**, 3499-3502.
16 Bhullar, P.; Gilchrist, T. L.; Maddocks, P. *Synthesis* **1997**, 271-272.
17 Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1998**, *39*, 7579-7582.
18 [a] Fowler, F. W.; Hassner, A. *J. Am. Chem. Soc.* **1968**, *90*, 2875-2881; [b] Carlson, R. M.; Yen Lee, S. *Tetrahedron Lett.* **1969**, 4001-4004.
19 Anderson, D. J.; Hassner, A. *J. Am. Chem. Soc.* **1971**, *93*, 4339-4340.

2. Preparation of 2*H*-azirines

2.1 Various methods for preparation of azirines

Various synthetic routes (a-f in Scheme 2) have been utilised in the preparation of 2*H*-azirines and these can be grouped into: internal ring closure of vinyl azides (a) and *N*-functionalised imines (b); ring-contraction of isoxazoles and oxazaphospholes (c); elimination and oxidation reactions on aziridines (d) and intermolecular cycloaddition reactions between nitrenes and acetylenes (e) or carbenes and nitriles (f).



Scheme 2. *Various routes for the preparation of 2H-azirines*

2.1.1 Intramolecular reactions

Vinyl azides can easily be prepared from the corresponding olefins, which will be illustrated later in this chapter. The cyclization of vinyl azides,[20] can be achieved by heating,[21,22] or photolysis.[23,24] (route a).

Another route (b) goes via the Neber reaction and modified versions thereof, believed to proceed either through an internal concerted nucleophilic displacement or via a vinylnitrene, a reactive species formed by base-promoted loss of the leaving group on nitrogen. A variety of leaving groups have been used such as sulfonates,[25], Grignard salt (OMgBr),[26] and quarternary amines ($^{+}NR_4$)[27].

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20 Hassner, A. In Azides and Nitrenes; Scriven, E. F. V., Ed.; Academic Press: Orlando, Florida, 1984; pp 35-94.
21 Smolinsky, G. *J. Org. Chem.* **1962**, *27*, 3557-3559.
22 Hortmann, A. G.; Robertson, D. A.; Gillard, B. K. *J. Org. Chem.* **1972**, *37*, 322-324.
23 Hassner, A.; Fowler, F. W. *J. Am. Chem. Soc.* **1968**, *90*, 2869-2875.
24 Woerner, F. P.; Reimlinger, H.; Arnold, D. R. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 130-131.
25 [a] Cram, D. J.; Hatch, M. J. *J. Am. Chem. Soc*. 1953, *75*, 33-38; [b] LaMattina, J. L. *J. Heterocyclic Chem.* **1983**, *20*, 533-538.
26 Eguchi, S.; Ishii, Y. *Bull. Chem. Soc. Japan* **1963**, *36*, 1434-1437.
27 [a] Sato, S. *Bull. Chem. Soc. Japan* **1968**, *41*, 1440 1444; [b] Chaabouni, R.; Laurent, A. *Synthesis* **1975**, 464-467.

Thermal or photochemical treatment of isoxazoles and oxazaphospholes as in route (c) leads to ring contraction to 2-carbonyl-2*H*-azirines,[28] and these transformations have also been achieved in the presence of $FeCl_2$ at room temperature.[29]

Elimination and oxidation reactions of aziridines as shown in route (d) are other approaches to 2*H*-azirines. *N*-Sulfonyl,[30] *N*-sulfinyl,[31] and *N*-chloro[32] aziridines are prone to undergo elimination when treated with base providing 2*H*-azirines. Oxidation of an aziridine using Swern conditions to furnish an 2*H*-azirine has also been accomplished.[33] Elimination and oxidation of chiral aziridines are frequently used as routes for the preparation of chiral 2*H*-azirines.[30,33]

2.1.2 Intermolecular reactions

Intermolecular cycloaddition reactions have provided 2*H*-azirines through combining nitrenes with alkynes (route e),[34] or carbenes with nitriles (route f),[35] but have so far not given yields high enough for preparative applications.

2.2 Preparation of 2*H*-azirines from the corresponding olefins

The preparation of various 2*H*-azirines played a central role in this project. After unsuccessful attempts with Neber-type reactions, preparation of 2*H*-azirines via vinyl azides were evaluated and found to work nicely with minor changes of published routes (Scheme 3). The olefins **12** and **13** were brominated to give **14** and **15**, while **16** was treated with NaN_3 and ICl yielding **17** with high regioselectivity favouring azide addition to the secondary position. **14**, **17** and **15** were then converted into their corresponding vinyl azides **18**[22], **19**[36] and **20**[37] in high yields. These vinyl azides underwent ring closure upon heating to give 2H-azirines **21**, **22** and **23**. The convenience of this reaction step was highly depending on the choice of solvent. Ring closure of **18** into **21** had been performed in refluxing toluene, but losses of the rather volatile **21** upon concentration made us evaluate other solvents. High temperatures seem to increase the reaction rate and favour clean conversion of 2*H*-azirines. To circumvent the requirement of solvents with high boiling points we carried out reactions in closed vessels at 125 ºC. Pentane worked well for ring closure of **18** and **19**, but the solubility of **20** was poor in pentane and instead Et_2O was used. Other solvents have been used and good solubility seems to be a general necessity. One way to avoid side reactions such as decomposition and polymerisation is photolytic ring closure of vinyl azides at

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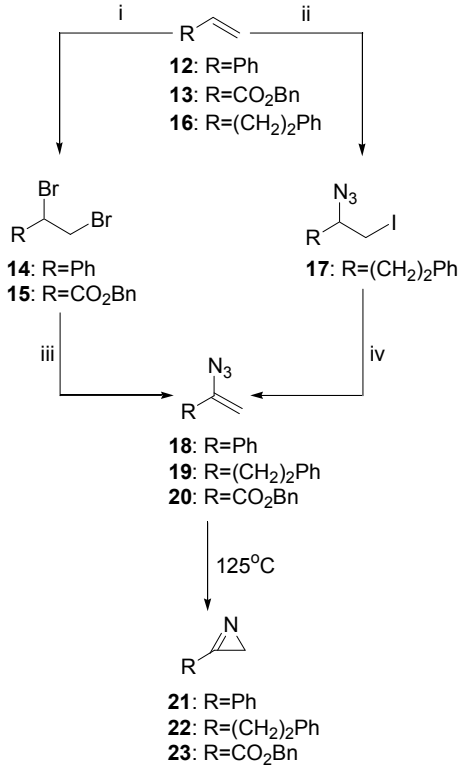
28 [a] Sauers, R. R.; Hadel, L. M.; Scimone, A. A.; Stevenson, T. A. *J. Org. Chem.* **1990**, *55*, 4011-4019; [b] Wentrup, C.; Fisher, S.; Berstermann, H.-M.; Kuzaj, M.; Lüerssen, H.; Burger, K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 85-86; [c] Lipshutz, B. H.; Reuter, D. C. Tetrahedron Lett. **1988**, *29*, 6067-6070.
29 Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*, 10911-10920.
30 Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796-3797.
31 Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651-3652.
32 Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim.* **1992**, *111*, 75-78.
33 Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665-4668.
34 Andersson, D. J.; Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans 1* **1973**, 550-555.
35 Alcaraz, G.; Wecker, U.; Baceiredo, A.; Dahan, F.; Bertrand, G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1246-1248.
36 Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077-2082.
37 Gilchrist, T. L.; Mendonca, R. *Synlett* **2000**, 1843-1845.

room temperature.[23] By decreasing the concentration of the vinyl azide solution to 0.1M, formation of such by products were avoided. Additional investigations performed in our laboratory have shown that other solvents, temperatures, and times can further improve this cyclization.[38] Addition of tertiary amines has been found to catalyze the cyclization,[39] but was not found necessary in this case. Preparation of the 3-(2-naphthyl)-2*H*-azirine was performed in the same manner as for **21** but the cyclisation was performed in Et_2O.



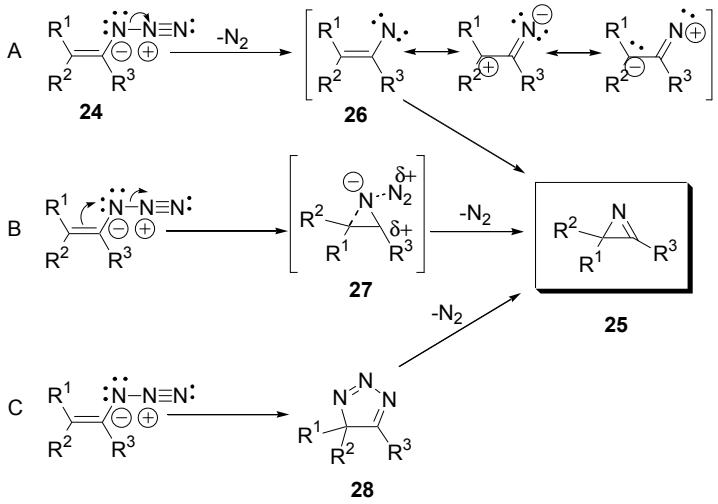
Scheme 3. *Preparation of azirines **21**, **22** and **23**. Reagents and conditions: (i) Br_2, CH_2Cl_2. 0 °C→rt (ii) NaN_3, ICl, CH_3CN, -25→rt, 24 h. (iii) **14**, 1) NaN_3, DMSO, 15 °C→rt, 15 h. 2) NaOH, DMSO, 15 °C→rt, 24 h. **15**, NaN_3, DMF, 65 °C 8 min. (iv) KO^{t}Bu, Et_2O, -30 °C, 24 h.*

2.3 Mechanism for ring closure of vinyl azides

There has been a debate concerning the mechanism of the ring closure of vinyl azides **24** to 2*H*-azirines **25** (Scheme 4). The suggested paths (A-C) are shown in Scheme 4. The three pathways proposed are: elimination of N_2 generating the vinyl nitrene **26** (presumably a singlet); which can undergo symmetry-allowed electrocyclic ring closure (A); concerted loss of N_2 and ring formation via **27** (B)

38 Sjöholm Timén, Å, unpublished results.
39 Kumatsu, M.; Ichijima, S.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1973**, *38*, 4341-4342.

and intramolecular [3+2] cycloaddition of the azido group to the double bond followed by loss of N_2 from a triazole intermediate **28** (route C),[40-42] all forming the corresponding 2*H*-azirine **25**.



Scheme 4. *Mechanism suggestions for ring closure of a vinyl azide into the corresponding 2H-azirine.*

Various substituents have been found to influence the propensity for 2*H*-azirine formation from vinyl azides.[40,42] R^3-Substituents (Scheme 4) such as aryl groups, alkyl groups, heteroatoms and often also carboxylic groups are found to yield 2*H*-azirine, while a substituent destabilizing an adjacent positive charge such as a proton rarely yield azirine. Also substituents R^1 and R^2 are found to effect product formation, with vinyl- or aryl- groups exclusively forming indoles and other cyclic products.[9,40] It has been suggested that with substituents favouring 2*H*-azirine formation as described above the reaction goes via route B,[40,43] while other products appear via route (A and C). The formation of indoles results from pyrolysis of 2*H*-azirines, and suggests that the azirine might be in thermal equilibrium with the vinyl nitrene.[44] A thermal equilibrium between vinyl azide and azirine could explain the observed increase in decomposition/polymerisation when higher reaction concentrations were applied. It has been observed that photolysis at low temperatures decreases polymerisation.[23]

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40 Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176-3180.

41 [a] Woerner, F. P.; Reimlinger, H. *Chem. Ber.* **1970**, *103*, 1908-1917; [b] L'Abbé, G.; Mathys, G. *J. Org. Chem.* **1974**, *39*, 1778-1780; [c] Henriet, M.; Houtekie, M.; Techy, B.; Touillaux, R.; Ghosez, L. *Tetrahedron Lett.* **1980**, *21*, 223-226.

42 Saalfrank, R. W.; Ackermann, E.; Fisher, M.; Wirth, U.; Zimmermann, H. *Chem. Ber.* **1990**, *123*, 115-120.

43 Suárez, D.; Sordo, T. L. *J. Am. Chem. Soc.* **1997**, *119*, 10291-10301.

44 [a] Fowler, F. W. In Advances in Heterocyclic Chemistry; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1971; Vol. 13, pp 45-76; [b] Knittel, D. *Synthesis* **1985**, 186-188.

3. Alkylation of 2*H*-Azirines[I]

3.1 Screening of various carbon nucleophiles

Preparation of optically active amines is a field of growing interest. One useful synthetic route for the preparation of those target molecules is the enantioselective additions of carbon nucleophiles to imines.[45-47] For reactions with imines to take place, an activating group attached to the C=N nitrogen is usually required to increase the reactivity and can be achieved with various electron withdrawing/donating groups.[48] By using 2*H*-azirines as reactive imine equivalents further substitution of the imine moiety can be avoided thus shortening synthetic routes and preventing troublesome deprotections at a later stage. A variety of methods have been used to promote asymmetric additions to imines including the use of chiral Lewis acids,[45,46] and imines bearing stereogenic *N*-substituents or chiral auxiliaries attached to the imine carbon.[47,49]

Organometallic reagents have only been used in azirine alkylations on rare occasions,[18] and addition of organolithium reagents to 2*H*-azirines has not been reported to our knowledge. Therefore we started screening possible carbon nucleophiles as shown in Table 1. Several 2*H*-azirines have previously been reduced by LAH in good yields.[23] Reduction of **21** gave **29a** in moderate yields of 50 % after purification by SiO_2 chromatography (entry 1, Table 1), The reaction was clean as judged by TLC, but **29a** decomposed partly upon purification. The ene reaction has successfully been applied to imines.[50] The ene reaction of **21** using α-methylstyrene as the ene component was performed in the presence of as well as without $BF_3{\cdot}Et_2O$. Azirine **21** was unreactive in the absence of Lewis acid (entry 2), while addition of $BF_3{\cdot}Et_2O$ resulted in decomposition. The next group of nucleophiles tried were Grignard reagents. Methylation of **21** with MeMgBr resulted in a clean product formation according to TLC, but some minor by-products could be detected after work-up.

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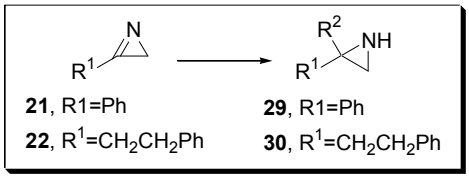
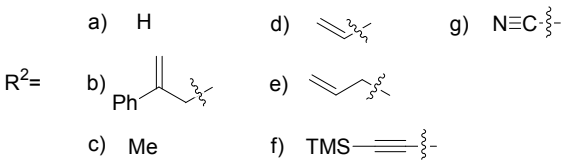
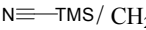
45 Denmark, S. E.; Nicaise, O. J.-C. In Comprehensive Organic Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin Heidelberg, 1999; Vol. 2, pp 923-961.
46 Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069-1094.
47 Bloch, R. *Chem. Rev*. **1998**, *98*, 1407-1438.
48 Volkmann, R. A. In Comprehensive Organic Chemistry; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 355-396.
49 Alvaro, G.; Savoia, D. *Synlett* **2002**, 651-673.
50 [a] Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347-360; [b] Weinreb, S. M. *J. Heterocyclic Chem.* **1996**, *33*, 1429-1436; [c] Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159-161.

Table 1. *Addition of various carbon nucleophiles to 2H-azirines*





Entry	Azirine	Nucleophile/Solvent	Temp. (°C)	Time (h)	Product, Yield (%)
1	**21**	LAH/ Et_2O	±0	5	**29a**, 50[a]
2	**21**	 / CH_2Cl_2	-78 → rt	24	**29b**, no reaction
3	**21**	MeMgBr/ Et_2O	-78 → rt	2.5	**29c**, >45[b]
4	**22**	MeMgBr/ Et_2O	-78 →0	2	**30c**, 35[a]
5	**21**	 / Et_2O	-78	0.5	**29d**, no isolated
6	**22**	 / Et_2O	-78	0.4	**30d**, >25[b]
7	**21**	 / CH_2Cl_2	-78 → rt	48	**29e**, no reaction
8	**22**	 / Et_2O	-78 → 5	3.25	**30f**, not expected product
9	**21**	 / CH_2Cl_2	-78 → rt	8	**29g**, no reaction

[a] Isolated yield after purification by chromatography. [b] Decomposes during purification. Yield calculated on a purity >60%

Compound **29c** decomposed almost completely upon SiO_2 chromatography, while use of Al_2O_3 chromatography gave **29c** in 45% yield (entry 3). Methylation of **22** with MeMgBr under similar conditions gave **30c** in 35% yield (entry 4). Alkylation of **21** with vinylMgBr gave no isolated **29d** (entry 5) due to decomposition. The addition of vinylMgBr to **22** gave the expected **30d** in 25% yield (entry 6). Attempts to allylate[51] **21** with allyltrimethylsilane to afford **29e** were

51 [a] Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493-9499; [b] Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614-2615; [c] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115-3121.

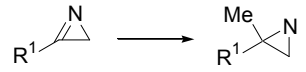
unsuccessful (entry 7), while addition of $BF_3 \cdot Et_2O$ to the same reaction mixture resulted in decomposition. Similar results were obtained with allyltributyltin. Addition of lithium-(trimethylsilyl)-acetylene to **22** did not give the expected product (entry 8). The use of $BF_3 \cdot Et_2O$ as a Lewis acid in the Strecker reaction[52] with **21** only resulted in decomposition of **21**, while no reaction occurred in the absence of $BF_3 \cdot Et_2O$ (entry 9).

This screening led us to the conclusion that 2*H*-azirines in spite of inherent ring strain need further activation to undergo addition to the C=N bond, especially when heating is not appropriate, and that Lewis acids other than $BF_3 \cdot Et_2O$ might be more suitable. During this screening we also found that the addition of organolithium reagents to 2*H*-azirines was promising. This will be described in the next section.

3.2 Addition of organolithium reagents to 2*H*-azirines

Initially various 2*H*-azirines were alkylated with MeLi to find a good model substrate for further investigations with chiral ligands (Table 2). The novel azirines **32-34** were prepared, using the same route as previously described for the preparation of **21,** and screened for their performance in the addition reaction.

Table 2. *Addition of methyl lithium to various 2H-azirines*



21, R^1=Ph
31, R^1=2-Nap
32, R^1=2-OMe-5-Br-C_6H_3
33, R^1=*p*-OMe-C_6H_4
34, R^1=2-Pyridine

35, R^1=C_6H_5
36, R^1=2-Nap
37, R^1=2-OMe-5-Br-C_6H_3
38, R^1=*p*-OMe-C_6H_4
39, R^1=2-Pyridine

Entry[a]	Azirine	Time (h)	Product	Yield[b] (%)
1	**21**	0.7	**35**	>80
2	**31**	1.25	**36**	>80
3	**32**	1	**37**	>50
4	**33**	2.5	**38**	>30
5	**34**	2.75	**39**	Only traces

[a] MeLi (1.2eq.) was added to azirine dissolved in Et_2O at –78 °C, followed by quenching at times given in table by addition of NH_4Cl (aq. satd.).[b] Yields determined by ^1H NMR spectrum of crude reaction mixture

52 [a] Chavarot, M.; Bryne, J. J.; Chavant, P. Y.; Vallée, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1147-1150; [b] Ishitani, H.; Komiyama, S.; Hasegawa, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762-766.

Addition of MeLi to **21** and **31** gave aziridines **35** and **36** in yields above 80% (entries 1 and 2), while methylation of **32** and **33** provided **37** and **38** in 50% and 30% yield, respectively (entries 3 and 4). Attempts to methylate **34** resulted only in traces of **39** (entry 5). All our attempts to purify 2,2-disubstituted aziridines by SiO_2 chromatography were unsuccessful. Attempts to determine the retention times of the racemates by Chiralcel OD-H and OJ columns for **35** and **36** resulted in decomposition as well. Purification by Al_2O_3 chromatography with and without deactivation with H_2O presented no improvement. A possible explanation for the decomposition found upon purification can be protonation of the aziridines, and this might be avoided by attachment of an activating group such as a mesylate or a tosylate to the aziridine nitrogen. Attempts to tosylate **35**,[53] using tosyl chloride and various bases resulted in no product formation. Acylation of **35** with acetyl chloride and pyridine did not work either.[54] Mesylations of **35** and **36** were achieved with mesyl chloride and DIPEA after 15 minutes and gave **40** and **41** in >80% yields, respectively (Figure 3).[55] Purification of **40** was possible with both SiO_2- and Al_2O_3-chromatography, but Al_2O_3 was found to eliminate UV-active impurities more efficiently, which otherwise disturbed ee determination by chiral HPLC.

***Figure 3**. Mesylation of aziridines **35** and **36**. Reagents and conditions: MsCl (1 eq), DIPEA (2 eq), CH_2Cl_2, -78 ºC, 15 min, >80%.*

3.3 Enantioselective additions of organolithium reagents

3.3.1 Screening of various chiral ligands

We were interested in studying the enantioselective alkylation of 2*H*-azirines using organolithium reagents in the presence of a chiral ligand. The first report concerning asymmetric alkylation of an imine using organometallic reagents appeared in 1990, when it was observed that organolithium compounds in the presence of chiral β-amino ethers add to *N*-arylimines to give the corresponding amines in up to 77% ee,[56] and since then other examples have appeared in the literature.[45]

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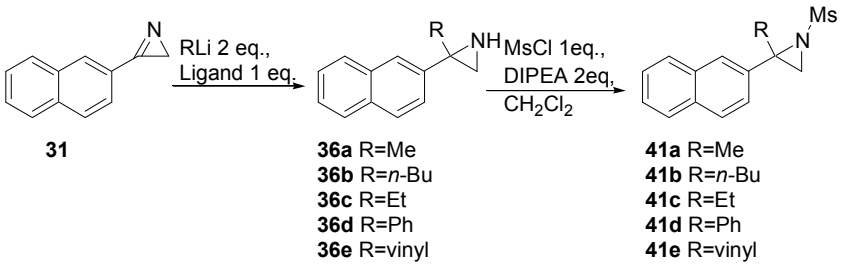
53 [a] Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619-624; [b] Löfström, C. M. G.; Bäckvall, J.-E. *Tetrahedron Lett.* **1996**, *37*, 3371-3374.

54 [a] Cardillo, D.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 563-569; [b] Toshimitsu, A.; Aoai, T.; Owada, H.; Uemura, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 4727-4733.

55 [a] Huh, N.; Kogan, T. P.; Kohn, H. *Synthesis* **1997**, 921-924; [b] Dumic, M.; Filic, D.; Vinkovic, M.; Jamnicky, B.; Kamenar, B. *Tetrahedron Lett.* **1993**, *34*, 3639-3642.

56 Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681-6684.

We have investigated the 2*H*-azirine **31** as a substrate in the asymmetric addition of organolithium reagents to the C=N double bond to afford the corresponding aziridines (Scheme 5). Azirine **31** was treated with equimolar amounts of chiral ligands and excess of organolithium reagents to give aziridines **36a-e**.[57,58]



Scheme 5. *Alkylation of azirine **31** followed by protection of aziridine **36***

For initial screening we chose five ligands, previously used for enantioselective alkylation of imines (shown in Figure 4): (-)-sparteine (**42**)[58-60], a proline derivative **43**,[59] an aminoalcohol **44**,[61] bisoxazoline **45**,[58] and quinine (**46**).[62]

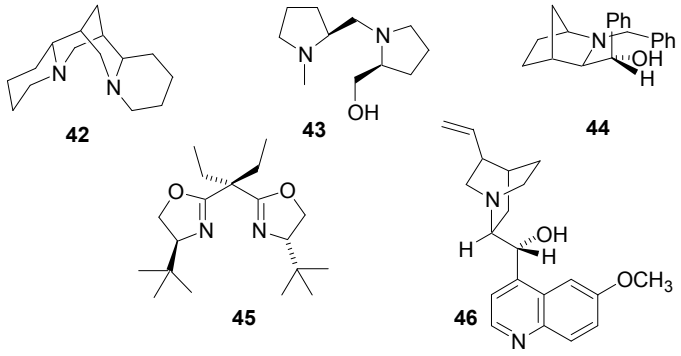


Figure 4. *Chiral ligands used together with organolithium reagents.*

Azirine **31** was chosen as the model substrate due to the good separation of the enantiomers of the corresponding mesylated aziridine **41** on a Chiralcel OD-H HPLC column. The methylation of **31** to afford **36** was found to proceed readily, and was completed in less then 10 minutes at –78 ºC. Methylations in the presence of chiral ligands **42**-**46** were therefore performed at -100±5 ºC with a reaction time of 1 hour (Table 3). Toluene was chosen as solvent due to its non coordinating characteristics and low freezing point, but temperatures under –105 ºC

57 [a] Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527-2533; [b] Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095-3098.
58 Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797-8798.
59 Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1507-1510.
60 Gittins née Jones, C. A.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3789-3799.
61 [a] Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692-1699; [b] Pinho, P.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 1615-1618.
62 Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590-1594.

resulted in freezing. Comparable reactions run in Et_2O at the same temperature for one hour resulted only in decomposition of **31**, and no product formation was noted in the presence of (-)-sparteine (**42**).

Table 3. *Addition of MeLi to azirine **31** with ligands **42-46***

Entry	Method[a]	Ligand	Product[d]	Yield (%)[e]	Ee (%)[f]
1	B	**42**	**41a**	28	9
2	A	**42**	**41a**	42	6
3	A	**43**	**41a**	30	12
4	B	**43**	**41a**	40	11
5	A	**44**		-	
6	B	**45**		-	
7	A	**45**		-	
8	B	**46**		-	
9[c]	A	**46**		-	
10[b]	R	**-**	**41a**	44	0

[a] Reactions were run using two methods: Method A where a mixture of azirine (1eq.) and ligand (1eq.) dissolved in PhMe was added to a precooled solution (-100±5 °C) of MeLi (2eq.) in PhMe and Method B where azirine (1eq.) dissolved in PhMe was added to a precooled (-100±5 °C) solution of MeLi (2eq.) and ligand (1eq.) in PhMe. [b] A reference reaction (R) was run where MeLi (2eq.) was added to azirine (1eq.) dissolved in PhMe at –78 °C in absence of ligand. [c] Reaction run in Et_2O. [d] Aziridine **36a** was mesylated giving **41a** prior to purification and analysis. [e] Purity >85 % according to ^{1}H NMR spectroscopy. [f] Determined on a Chiralcel OD-H column.

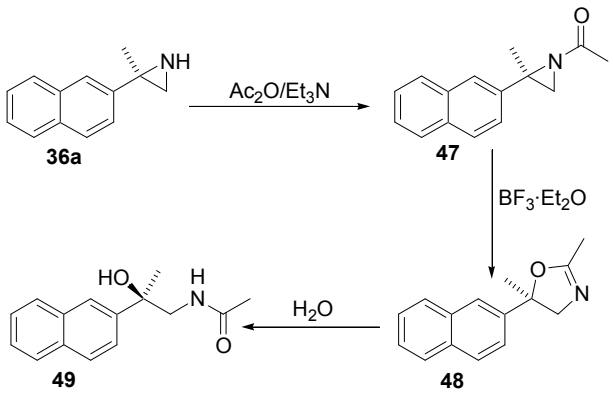
The alkylations were performed using two different procedures: in method A the organolithium reagent was added to a stirred, precooled mixture of **31** and the chiral ligand (entries 2, 3, 5, 7 and 9, Table 3),[58] while in method B a mixture of the organolithium reagent and the ligand was added to **31** (entries 1, 4, 6 and 8).[63] An alternative method was needed for reactions with MeLi-toluene solutions due to clogging of needles when the solution was transferred. Of the ligands tried, only **42** and **43** promoted formation of aziridine **36a**, albeit in modest yields and low ee (entries 1-4), while the use of ligands **44-46** resulted in decomposition of **31** and no detectable formation of **36a** (entries 5-9). The highest ee was obtained using ligand **43** together with **31** and gave aziridine **41a**, in 30 % yield and 12 % ee using method A (entry 3). A comparable result was obtained when using method B, affording **41a** in 40 % yield and 11 % ee (entry 4).

3.3.2 Determination of absolute configuration

The absolute configuration of the major enantiomer of **36a** was determined to be (*R*) by conversion of the aziridine into the previously known *N*-acylaminoalcohol **49** (scheme 6).[64] Aziridine **36a** was acetylated, the resulting

63 Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603-1606.
64 Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522-5527.

amide **47** rearranged into the corresponding oxazoline **48** in the presence of $BF_3{\cdot}Et_2O$, with retention of stereochemistry, followed by hydrolysis to give **49**.[65] Both ligands **42** and **43** were found to favour formation of (*R*)-**49**.



Scheme 6. *Determination of absolute configuration of* ***36a***

3.3.3 Screening of organolithium reagents

Next, various organolithium reagents were evaluated (Table 4). (-)-Sparteine (**42**) was chosen as chiral ligand due to its performance above. The highest enantioselectivities were exhibited for the addition of vinyllithium to **31** giving **41e** in 7% yield and 17% ee (entry 12), *n*-BuLi yielding **41b** in 15% yield and 16% ee and PhLi that gave **41d** in 30% yield and 15% ee (entry 6). Addition of EtLi afforded **41c** in low ee (entries 8 and 9). The mass balance of these additions indicated losses of approximately 30% of the crude product upon purification, as shown by reference reactions lacking ligand (entries 1,4 and 7). Most reference reactions gave clean conversion without formation of side products according to TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The crude yield of **41b** (88%) decreased to 56% after Al_2O_3 chromatography (entry 1) and similar results were found for **41c** (80% to 55% yield, entry 7) and **41d** (95% to 29% yield, entry 4). Reference reactions with MeLi (entry 10, Table 3) and vinylLi (entry 10, Table 4) were not as clean and yields could not be determined based on crude reaction mixtures.

65 Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087-4089.

Table 4. Addition of various organolithium reagents to azirine **31**

Entry	Method[a]	Nucleophile	Product[c]	Yield (%)	Ee (%)[g]
1[b]	R	*n*-BuLi	**41b**	56[e], 88[f]	0
2	A	*n*-BuLi	**41b**	15[d]	16
3	B	*n*-BuLi	**41b**	38[d]	0
4[b]	R	PhLi	**41d**	29[e], 95[f]	0
5	A	PhLi	**41d**	20[d]	5
6	B	PhLi	**41d**	30[d]	15
7[b]	R	EtLi	**41c**	55[e], 80[f]	0
8	A	EtLi	**41c**	47[d]	2
9	B	EtLi	**41c**	7[d]	5
10[b]	R	vinylLi	**41e**	18[d]	0
11	A	vinylLi	**41e**	9[d]	7
12	B	vinylLi	**41e**	7[d]	17

[a]Reactions were run using two methods: Method A where a RLi (2eq.) solution in PhMe was added to a precooled mixture of azirine (1eq.) and (-)-sparteine (1eq.) dissolved in PhMe and Method B where a solution of RLi (2eq.) and (-)-sparteine (1eq.) in PhMe was added to a precooled solution of azirine (1eq.) dissolved in PhMe. [b] Reference reaction (R) where RLi (2eq.) was added to azirine (1eq.) dissolved in PhMe at −78 °C in absence of ligand. [c] Aziridine **36** was mesylated giving **41** prior to purification and analysis. [d] Purity >85 % according to ^{1}H NMR spectroscopy. [e] Pure aziridines after chromatography. [f] Crude yield with a purity >85 % according to ^{1}H NMR spectroscopy. [g] Determined on a Chiralcel OD-H column.

3.4 Addition of diethylzinc to azirines

A possible explanation for the low ee achieved upon treatment of azirine **31** with organolithium reagents could be the competing non-selective background reaction. A possible solution to this problem might be to employ a less reactive nucleophile. Organozinc reagents have previously been added to imines with good results.[61,66] Attempts to add Et_2Zn to azirine **31** are shown in Figure 4 and were surprisingly unsuccessful.

66 Soai, K.; Hatanaka, T.; Miyazawa, T. *Chem. Comm.* **1992**, 1097-1098.

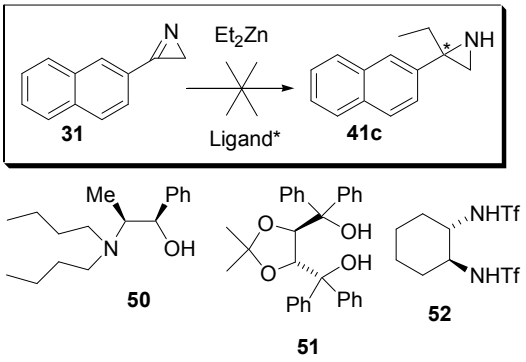


Figure 4. *Attempts to add diethyl zinc to azirine **31** with chiral ligands. Reagents and conditions: 1) Et_2Zn (2 eq), **50** (1 eq), PhMe, -78 °C→rt, 6 h; 2) Et_2Zn (1.2 eq), **51** or **52** (0.1 eq), $Ti(O^iPr)_4$ (1.2 eq), PhMe, -78 °C→-20 °C on.→ rt, 24 h.*

When Et_2Zn was added to **31** in the presence of **50**[66,67] no product formation could be detected. Attempts to increase the reactivity via addition of $Ti(O^iPr)_4$ in the presence of ligand **51**[68] and **52**[69] did not improve the outcome.

3.5 Conclusion

Organolithium reagents, R-Li, are known to form various oligomeres depending on factors such as solvent and R group. A possible explanation for the results obtained is that ligand-RLi forms other "clusters" than RLi, affecting the reactivity/Lewis acid activity in the alkylations. This could explain the much better yields attained for EtLi, PhLi and *n*-BuLi upon additions in the absence of chiral ligands. By using a coordinating solvent, such as DMPU, oligomer formation is likely to be avoided, which might help prevent formation of unfavourable clusters. Applying less reactive azirines might decrease the background reaction and favour the formation of a major enantiomer.

67 Hayase, T.; Inoue, Y.; Shibata, T.; Soai, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2509-2510.
68 [a] Seebach, D.; Beck, A. K.; Schmidt, B.; Ming Wang, Y. *Tetrahedron* **1994**, *50*, 4363-4384; [b] Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473-7484.
69 Knochel, P.; Almena Perera, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275-8319.

4. Diels-Alder Reactions with 2*H*-Azirines[II, III]

4.1 Azirines used as dienophiles

A useful method for the synthesis of six-membered rings is the Diels-Alder reaction (Figure 5). In this reaction a 2π moiety, the dienophile (shown as the 3-phenyl-2*H*-azirine in example a), reacts with a 4π moiety, the diene (shown as Danishefsky´s diene in example a). Symmetry allowed reactions can take place in two manners, either by a normal electron-demand $HOMO_{diene}$-controlled process (shown in b), or through an inverse electron-demand $LUMO_{diene}$-controlled Diels-Alder reaction (shown in c).[70,71] Hetero Diels-Alder reactions forming nitrogen containing cycloadducts, which have potential as synthetic intermediates in alkaloid synthesis, is a valuable manoeuvre.[72] While the use of aza-dienes is well established,[73] 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.[70,74] The strained, electron-rich C=N bond in the 2*H*-azirine is more reactive than the corresponding double bond in an imine.[9] 2*H*-Azirines are mainly found to participate in inverse electron-demand Diels-Alder reactions, and only a few publications describe normal electron demand reactions taking place with 2*H*-azirines.[16,17,75,76] A structural requirement to facilitate these reactions has been the presence of an electron-withdrawing group, such as an ester in the 3-position of the three membered ring, to promote its participation in the normal electron-demand reaction. We have circumvented this structural requirement through the application of Lewis acids, which presumably coordinate to the nitrogen lone pair in the 2*H*-azirine.

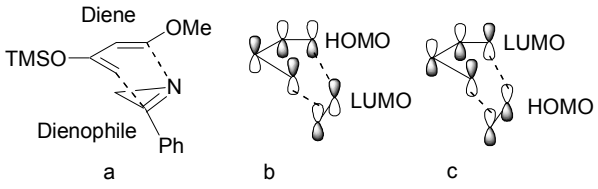


Figure 5. *Basic concepts of the Diels-Alder reaction*

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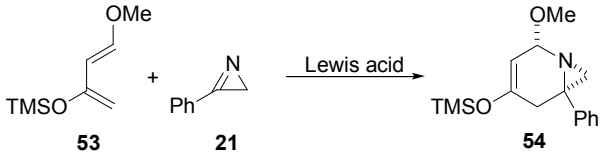
70 Buonora, P.; J.-C., O.; Oh, T. *Tetrahedron* **2001**, *57*, 6099-6138.
71 Flemming, I. Frontier Orbitals and Organic Chemical Reactions; Wiley: New York, 1976.
72 Carruthers, W. Cycloaddition reactions in organic synthesis; Pergamon press: Exeter, 1990.
73 Boger, D. L.; Weinreb, S. M. Hetero Diels-Alder methodology in organic synthesis; Academic Press: San Diego, 1987.
74 Weinreb, S. M. In Comprehensive Organic Chemistry; Paquette, L. A., Ed.; Pergamon press: Oxford, 1991; Vol. 5, pp 401-449.
75 Alves, M. J.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans 1* **1999**, 1399-1401.
76 Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans 1* **1998**, 299-303.

4.2 Screening of various Lewis acids

The reaction of **21** with Danishefsky´s diene **53** to produce 1-azabicyclo[4.1.0]-heptene **54** was adopted as the model reaction for investigation of the suitability of various Lewis acids as catalysts for these cycloadditions (Table 5).

Table 5. *Cycloaddition of azirine **21** with diene **53** catalyzed by various Lewis acids*



53 **21** **54**

Entry[a]	Lewis acid	Temp. (ºC)	Time (h)	Yield 54 (%)[d]
1	$ZnCl_2$	75	12	40
2	$YbCl_3$	75	12	55
3	$CuCl_2$	75	12	35
4	$ScCl_3$	75	12	30
5[e]	$BF_3{\cdot}Et_2O$	-78 → -60	0.3-0.4	45
6	$FeCl_3$[c]	-78 → rt	16	-[f]
7	$InCl_3$[b]	-70	48	-[f]
8	$Cu(OTf)_2$[b]	-70	12	-[f]
9	-	75	72	0[g]

[a] Reactions were performed in PhMe at 75 °C using an equimolar mixture of diene **53** and azirine **21**, using 0.2 eq. Lewis acid unless otherwise stated. [b] 0.2 eq. of Lewis acid were used. [c] Conducted in Et_2O with 0.5 eq. Lewis acid. [d] Isolated yield. [e] Conducted in CH_2Cl_2 at –78 to –60 °C. [f] Reaction conducted until decomposition of **21** was evident. [g] The starting material was recovered.

A series of azaphilic Lewis acids were selected for initial screening (entries 1-4 and 6-7).[77] In all cases elevated reaction temperatures were required to effect the cycloaddition and after varying times adduct **54** was obtained as a single isomer in moderate yields (30-50%). Addition of $BF_3{\cdot}Et_2O$ promoted the formation of **54** at – 70 ºC (entry 5), and this compound proved to be the most potent Lewis acid tried. Attempts with other boron-Lewis acids showed that BBr_3, and BCl_3 gave no reactions at low temperature, while ambient temperature resulted in decomposition of **21**. Use of $FeCl_3$ gave no reaction at low temperatures while **21** decomposed at room temperature (entry 6). Reaction mixtures with $InCl_3$ (entry 7) and $Cu(OTf)_2$ (entry 8) maintained at –70 ºC showed decomposed azirine when quenched after 48 hours and 12 hours, respectively. A reaction performed in the absence of Lewis acid activation at elevated temperatures provided only starting materials after 72 hours (entry 9).

77 Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491-3494.

The reaction of azirine **21** and diene **53** was found to give the *endo* isomer **54** as the sole cycloadduct. This structure of bicycle **54** was assigned by NMR experiments in analogy with similar compounds in the literature (Figure 6).[76] The COSY spectrum showed couplings between H-2 and H-3, H-2 and H-5$_\alpha$, and H-5$_\beta$ and H-7$_{exo}$, while an interaction between H-5$_\alpha$ and H-7$_{endo}$ was evident in the NOESY spectrum.

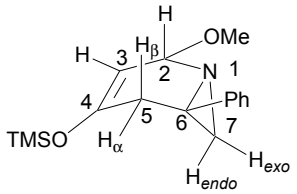


Figure 6. *Structure of adduct **54**.*

4.3 Investigation of scope and limitations

It would be beneficial if the Lewis acid mediated Diels-Alder methodology could be applied to various 2*H*-azirines. We therefore tried similar reaction conditions for the 3-(2-phenyl)ethyl-2*H*-azirine (**22)** and the benzyl 2*H*-azirine-3-carboxylate (**23)**. Cycloaddition of **22** with **53**, catalyzed by $YbCl_3$, looked promising according to TLC and NMR spectra of the crude reaction mixture, but the product decomposed upon purification (entry 1, Table 6). 2*H*-Azirines harbouring an ester substituent in the 3-position undergo thermal Diels-Alder cycloadditions with a variety of dienes.[8]

There is a potential for utilising the ester carbonyl as a second site of coordination for a Lewis acid to further facilitate the [4+2] process. Use of **23**, together with **53** and $YbCl_3$ at –20 ºC gave **61** (Figure 8) in 65% yield (entry 2, Table 2). Cycloaddition of **23** and **53** in the absence of Lewis acid gave **61** in nearly as high yield, 61%, but room temperature for 18 hours was necessary for the reaction to proceed (entry 3).

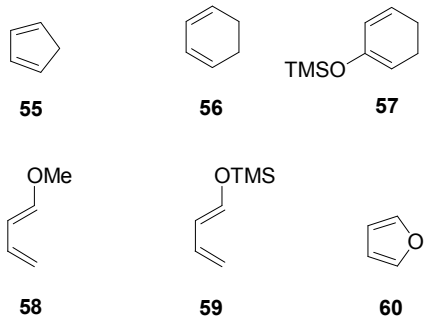


Figure 7. *Dienes used in the Diels-Alder reaction with 2H-azirines*

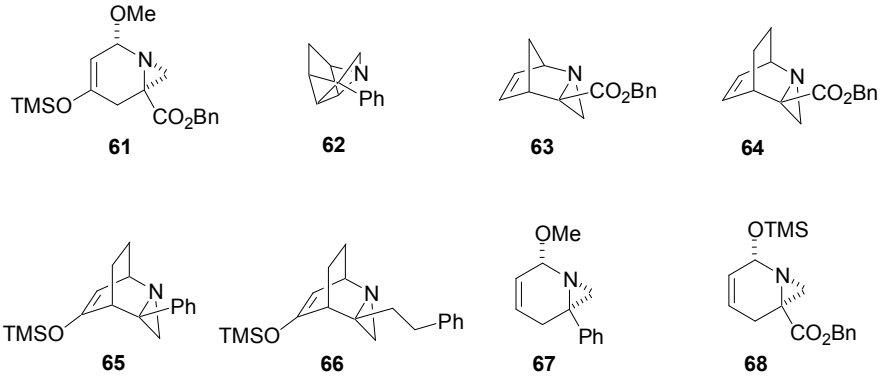


Figure 8. *Cycloadducts obtained in Diels-Alder reactions*

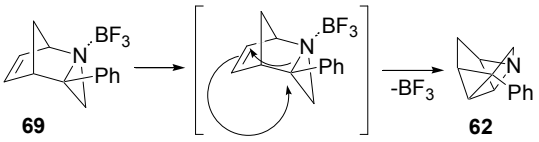
Table 6. *Diels-Alder reactions of azirines **21**, **22** and **23** with various dienes.*

Entry	Diene/Azirine	Lewis acid (eq.)	Temp. (ºC)	Time (h)	Product (%)
1[b]	**53**/**22**	$YbCl_3$ (0.2)	rt	48	-[d]
2[a]	**53**/**23**	$YbCl_3$ (0.3)	-20	3	**61** (65)
3[a]	**53**/**23**	-	rt	18	**61** (61)
4[b]	**55**/**21**	-	50	48	-
5[b]	**55**/**21**	$BF_3{\cdot}Et_2O$ (0.6)	-78	2	**62** (25)
6[a]	**55**/**23**	$ZnCl_2$ (0.1)	-20	12	**63** (32)
7[a]	**55**/**23**	-	rt	24	**63** (31)
8[c]	**56**/**23**	-	rt	1	**64** (48)
9[c]	**57**/**21**	$YbCl_3$ (0.3)	90	6	**65** (50)
10[c]	**57**/**21**	-	90	12	**65** (48)
11[c]	**57**/**22**	$YbCl_3$ (0.3)	90	12	**66** (36)
12[c]	**57**/**22**	-	90	72	**66** (32)
13[c]	**58**/**21**	$ZnCl_2$ (0.3)	75	8	**67** (50)
14[a]	**59**/**23**	$YbCl_3$ (0.3)	-20	4	**68** (52)
15[a]	**59**/**23**	-	rt	18	**68** (30)

[a] Conducted in Et_2O [b] Conducted in CH_2Cl_2 [c] Conducted in PhMe. [d] Decomposed upon work-up.

4.3.1 Screening of various dienes

Next various dienes (Figure 7) were screened together with azirines **21**, **22** and **23** to form new cycloadducts (Figure 8). The cycloaddition of **21** with **55** was unsuccessful at elevated temperature (entry 4, Table 6) and was attempted using $BF_3{\cdot}Et_2O$ at –78 ºC (entry 5) After 2-3 hours a compound assigned with the structure **62** was isolated in 25 % yield. All spectroscopic data obtained were consistent with the proposed structure of **62**, which can be formed via a Lewis acid-mediated rearrangement of the Diels-Alder product **69**, while still complexed to BF_3 (Scheme 7). Attempts to isolate **69** before rearrangement were unsuccessful.



Scheme 7. *Rearrangement of cycloadduct* ***69***

Reacting diene **55** with **23,** in the presence of $ZnCl_2$, gave **63** in 32% yield (entry 6). Compound **63** was also afforded in similar yields after 24 hours at room temperature (entry 7). No Lewis acid was found that catalyzed the formation of **64**, which instead was formed in 48% yield after one hour at room temperature in the absence of Lewis acid (entry 8). Diene **57** was found to be reactive, probably due to its activating –OTMS group and the fact that it is locked in an s-*cis* conformation. $YbCl_3$ was found to catalyze the formation of cycloadduct **65** from **57** and **21** in 50% yield (entry 9), while similar yields were achieved in the absence of Lewis acid but then requiring longer reaction times (entry 10). More surprisingly **57** reacted with **22** in the presence of $YbCl_3$, and gave **66** after in 36% yield after 12 hours (entry 11), while the uncatalyzed reaction needed 72 hours, at the same temperature, to afford **66** in similar yields (entry 12). The cycloaddition of **21** with **22** catalysed by $ZnCl_2$ gave **67** in 50% yield (entry 13). Azirine **23** was reacted with **59** in the presence of $YbCl_3$, and gave **68** in 52% yield after 4 hours at –20 ºC (entry 14), while 18 hours at room temperature was needed to accomplish the reaction in 30% yield in the absence of Lewis acid.

4.3.2 Stereo- and regioselectivity

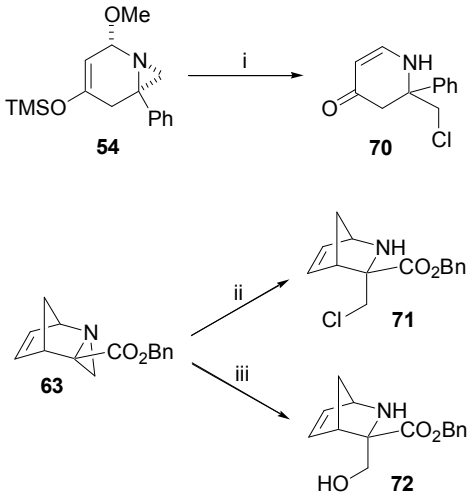
All the cycloadditions in Table 5 and 6 were found to be highly stereoselective and, with unsymmetrical dienes, completely regioselective in accordance with the literature.[8] Structures were consistent with *endo* additions of the 2*H*-azirines and with the regiochemistry expected from bonding of the more nucleophilic terminus of the diene to the electrophilic carbon of the azirine. Reaction with furan (**60**) as the diene has been found to give the *exo* selective cycloadduct,[76] but all our attempts to achieve cycloadducts with **60**, catalyzed by Lewis acids, have so far been unsuccessful.

4.4 Ring opening of cycloadducts

The regiochemistry associated with the ring-opening of bicyclic aziridines appears to be a complex issue.[78] Aziridine **54** could conceivably experience attack of a nucleophile at either C6 or C7 (labelled in Figure 6). It has previously been shown that when systems related to **54** are subjected to an acidic medium the corresponding dihydroazepinone was isolated, in which all stereochemical infor

78 [a] Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599-619; [b] McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347-1365.

mation created during the preceding cycloaddition was destroyed.[17] In the present case, treatment of **54** with 2M HCl resulted in selective cleavage of the aziridine ring providing **70** via protonation of the aziridine nitrogen and selective attack of chloride, seemingly favoured over hydroxyl, as the only product (Scheme 8). Under identical conditions, **63** provided the bicyclic compound **71**. When subjected to dilute perchloric acid in water **63** experienced selective nucleophilic attack of the hydroxyl group to provide amino alcohol **72** in 90% yield. These results suggest that the observed selective aziridine ring-cleavage may occur with a range of nucleophilic species.



Scheme 8. *Ring openings of cycloadducts **54** and **63**. Reagents and conditions*: *(i)2M HCl, THF, rt, 80%; (ii) 2M HCl THF, rt, 85%; (iii) $HClO_4$, THF, rt, 90%.*

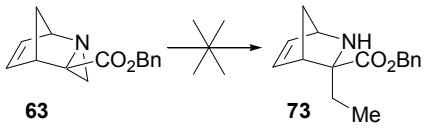
4.4.1 Attempts with carbon nucleophiles

We were also interested in trying to find suitable carbon nucleophiles, allowing selective opening of the aziridine moiety in the cycloadducts. Due to the electrophilicity of the ester functionality of **63**, we decided to investigate reactions with organocuprates, which tend not to react with esters.[79] Addition of organocuprates,[80] and copper-catalyzed Grignard reagents,[81] to activated aziridines has been shown to work. Unfortunately all our attempts to ring open **63** and achieve the bicyclic compound **73** were unsuccessful (Scheme 9). Various cuprates, copper-catalyzed Grignard reagents, and reaction conditions were screened, but non of them gave **73**.

79 Carey, F. A.; Sundberg, R. J. Advanced Organic Chemistry Part B: Reactions and Synthesis; 3:rd ed.; Plenum Press: New York, 1990.

80 [a] Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151-154; [b] Baldwin, J. E.; Spivey, A. C.; Schofield, J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309-6330.

81 [a] Gajda, T.; Napieraj, A.; Osowska-Pacewicka, K.; Zawadzki, S.; Zwierzak, A. *Tetrahedron* **1997**, *53*, 4935-4946; [b] Müller, P.; Nury, P. *Org. Lett.* **1999**, *1*, 439-442.



63 **73**

***Scheme 9**. Attempted ringopening of **63.** Examples of reagents and condition tried: 1) Me_2LiCu, $BF_3{\cdot}Et_2O$, THF/Et_2O, -78 °C, 1.25 h; 2) Me_2LiCu, Et_2O, -78°C→rt, 14 h; 3) $Me_2CNCuLi_2$, THF, -78 °C→rt, 14 h and 4) MeMgBr, CuI, THF, -35→10 °C 4 h.*

4.5 Conclusion

We have shown that various 2*H*-azirines undergo cycloaddition reactions catalyzed by Lewis acids with a number of dienes. The reactivity of Lewis acids is strongly influenced by atoms/ligands and so far halides have been favoured to more electronegative ligands such as –OTf. The choice of Lewis acid seems to be a subtle question; some favouring formation of product, while others are more prone to catalyze the decomposition of azirine, an issue dealt with in the next chapter.

5. Lewis Acid Activation of 2*H*-Azirines

5.1 Lewis acid catalysed rearrangements

Lewis acid promoted carbon-carbon bond formation is one of the most important processes in modern organic chemistry.[82] We were therefore interested in whether Lewis acids could further increase the reactivity of 2*H*-azirines and catalyze various transformations. We were also interested in broadening the knowledge about how Lewis acid activation of 2*H*-azirines will effect their behaviour.

It has been proposed that 2*H*-azirines, upon thermolysis, are likely to be in a thermal equilibrium with vinyl nitrenes.[44] This vinyl nitrene moiety, isolated by trapping,[83] has been suggested to undergo various transformations in the presence, as well as absence, of other reactive intermediates. Since the mid 1970´s different research groups have investigated the ability of forming these reactive vinyl nitrenes by activation methods other than heating. Metal activation of 2*H*-azirines has been thoroughly investigated. Metal complexes used in the literature include Pd, Pt, Rh, Mo, Cr, W, Co, Ni, Ag, Fe, Zn, and Ti, some of which are frequently used as Lewis acids.[84,85] $BF_3{\cdot}Et_2O$ has also been utilised as an activator for similar rearrangements.[86]

5.2 Proposed reactive intermediates

The yields both in the addition of organometallic reagents to, and in the Diels-Alder reactions with, 2*H*-azirines have been less than satisfactory. A possible explanation to this could be that the use of various Lewis acids will not only increase the reactivity of the 2*H*-azirines towards the desired product formation, but is also likely to catalyze numerous side reactions. As mentioned above, a number of rearrangements with 2*H*-azirines have been shown in the literature and among them dimerization products such as pyrazines, imidazoles and pyrrolines are frequently found. Different suggestions for the decomposition of 2*H*-azirine **74**, in the presence of Lewis Acids, have been proposed since the late 1970´s and some of them are shown in Scheme 10.

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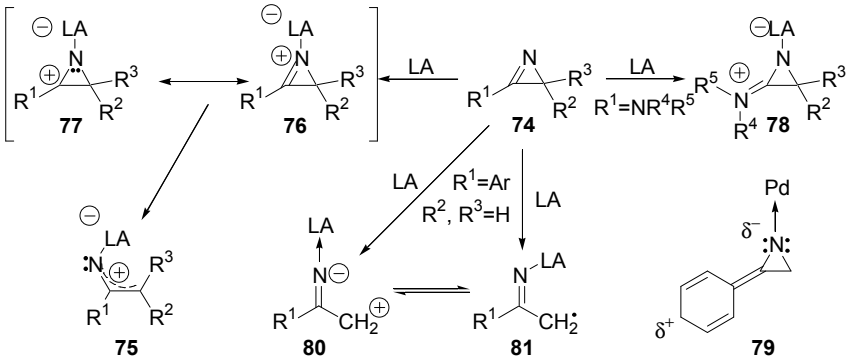
82 Yamamoto, H. In Lewis Acids in Organic Synthesis; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 1-7.

83 [a] Nishiwaki, T. *Chem. Comm.* 1972, 565-566; [b] Kanomata, N.; Nakata, T. *Heterocycles* **1998**, *48*, 2551-2558.

84 [a] Alper, H.; Perera, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 1289-1291; [b] Dietliker, K.; Schmid, U.; Mukherjee-Müller, G.; Heimgartner, H. *Chimia* 1978, 32, 164-166; [c] Faria dos Santos Filho, P.; Schuchardt, U. *J. Organomet. Chem.* **1984**, *263*, 385-393.

85 Hassner, A.; Bunnell, C. A.; Haltiwanger, K. *J. Org. Chem.* **1978**, *43*, 57-61.

86 [a] Arnhold, F.; Chaloupka, S.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 899-909; [b] Hugener, M.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 1490-1498.



Scheme 10. *Suggested reactive intermediates for Lewis activated azirines*

It has been suggested that oxazoles and imidazoles are formed by a reaction between the Lewis acid activated vinyl nitrene **75** and a C=O-, or a C≡N-moiety.[87] Varying the R^2 and R^3 substituents to groups that could stabilize a carbocation was found to increase the yields in the imidazole formation, while the R^1 substituent was found to be less important. The precursors to **75** were believed to be the resonance structures **76** and **77**. Extensive studies of $BF_3{\cdot}Et_2O$ activated 3-amino-2*H*-azirines suggest the formation of **78**.[86] In this case the free electron pair of the tertiary amine moiety will contribute with an electron pair to stabilize **78**. A similar contribution from an aryl group, see structure **79**, has been proposed for 2*H*-azirines complexed to palladium. The observed upfield shift in ^{13}C NMR, of the C4 in the phenyl ring support this suggestion.[85] Recently an equilibrium between **80** and **81** was proposed following the formation of a radical intermediate **81** or a zwitterionic structure **80,** upon complexation of $FeCl_2$ to the 2*H*-azirine.[88] Structure **81** is another possible intermediate for the generation of dimerization products.

5.3 Calculations on 2*H*-azirines

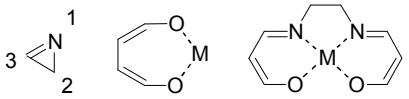
5.3.1 The unsubstituted 2H-azirine

To further broaden our knowledge about Lewis acid activation of 2*H*-azirines we decided to investigate what information DFT calculations could reveal. So far only a few studies dealing with calculations on Lewis acid activated azirines have been published,[89,90] of which only one deals with 2*H*-azirines.[89] We decided to focus on atom charge differences and the variation in the LUMO energy, localised mainly over atoms N1 and C3, of the 2*H*-azirine compared to its Lewis acid-

87 Bader, H.; Hansen, H.-J. *Helv. Chim. Acta* **1978**, *61*, 286-304.
88 Auricchio, S.; Grassi, S.; Malpezzi, L.; Sarzi Sartori, A.; Truscello, A. M. *Eur. J. Org. Chem.* **2001**, 1183-1187.
89 Alcamí, M.; Mó, O.; Yánez, M. *J. Am. Chem. Soc.* **1993**, *115*, 11074-11083.
90 Mó, O.; de Paz, J. L. G.; Yánez, M. *J. Phys. Chem.* **1987**, *91*, 6484-6490.

complex. All energies were obtained at the B3LYP/LACVP+* level, using B3LYP/LACVP to optimise structures. Many of the Lewis acids chosen were reported to activate imines, while H^+ was chosen due to its simplicity. As ligands we decided to use simplified structures of BINOL-type, **82,** and salen-type, **83**, with a matching metal M. Table 7 shows the results of the calculations with various Lewis acids and unsubstituted 2*H*-azirines.

Table 7. *Calculations of **2** activated with a variety of Lewis acids*



2 **82** **83**

Entry	Lewis acid	Ligand	Charge changes of atoms, when complexed to LA			LUMO	
			1	**2**	**3**	**kcal/mol**	**eV**
1[a]	-	-	0	0	0	0	0
2	Zn(II)	**82**	*+0.05*	*+0.04*	*+0.03*	*-51*	*-2.2*
3	Al(III)OMe	**82**	*-0.05*	*±0.00*	*+0.02*	*-40*	*-1.7*
4	Cr(III)	**83**	*-0.02*	*+0.13*	*±0.00*	*-104*	*-4.5*
5	H^+	-	*+0.19*	*+0.25*	*-0.02*	*-173*	*-7.5*
6	Mn(III)	**83**	*+0.07*	*+0.08*	*-0.04*	*-91*	*-3.9*
7	Pd(II)	**82**	*±0.00*	*+0.06*	*-0.04*	*-17*	*-0.7*
8	BF_3	-	*+0.25*	*+0.08*	*-0.08*	*-45*	*-2.0*

Method used for calculations: B3LYP/LACVP+*//B3LYP/LACVP [a] Absolute values calculated for uncomplexed **BA** was: N1=-0.32; C2= -0.39; C3=0.24; LUMO= –51 kcal/mol, -1.0 eV.

The results found upon Lewis acid complexation were somewhat surprising with only a slight increase of the δ^+ charge at C3 when Zn(II) and Al(III)OMe were bonded to N1 in **2** (entries 2 and 3). Cr(III) showed no variation upon complexation (entry 4), while H^+, Mn(III), Pd(II) and BF_3 gave a decreased δ^+ charge when complexed (entries 5-8), compared to the calculated values of the free azirine **2** (entry 1). The δ charge at C2 was increased to varying extents upon complexation, and the same was evident for N1, one exception being the Zn(II) case (entry 2) where a decrease was found. The LUMO-energy was lowered in all examples, and to a larger extent when the Lewis acid complex had a positive charge (entries 3-5). The bond strength between the Lewis acids and azirine **2** was varying between 22.8 and 32.5 kcal/mol.

5.3.2 The 3-phenyl-2H-azirine

Next we decided to study whether the trends observed for azirine **2** were also repeated for azirine **21** (Table 8). With **21** complexed to Lewis acids a more pronounced decrease of the δ^+-charge at C3 was evident in all cases (entries 2-6) with a trend among the Lewis acids similar to that observed for **2**. Charges at C2 varied randomly without a clear trend. The charges at N1 again showed increased values except for the azirine complexed to Zn(II), once more showing a clear decrease (entry 2). With **21** as well as **2** the largest LUMO-energy decrease was observed for the positively charged complexes with Cr(III) and H^+ (entries 3 and 4), but significant decreases were also observed for the other complexes.

Table 8.*Calculations on Lewis acid activation of azirine **21***

Azirine	Entry	Lewis acid	Ligand	Charge changes of atoms, when complexed to LA			LUMO	
				1	**2**	**3**	**kcal/mol**	**eV**
21	1[a]	-	-	0	0	0	0	0
	2	Zn(II)	Binol	*-0.08*	*+0.02*	*-0.22*	*-28*	*-1.2*
	3	Cr(III)	Salen	*+0.09*	*-0.04*	*-0.17*	*-81*	*-3.5*
	4	H^+	-	*+0.20*	*+0.04*	*-0.25*	*-123*	*-5.3*
	5	BF_3	-	*+0.31*	*-0.05*	*-0.25*	*-42*	*-1.2*
	6	BBr_3	-	*+0.26*	*+0.03*	*-0.26*	*-38*	*-1.6*

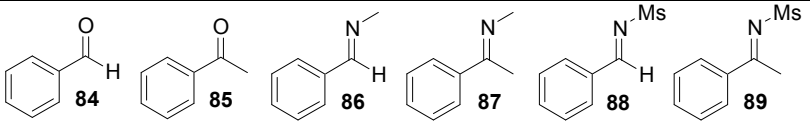
Method used for calculations: B3LYP/LACVP+*//B3LYP/LACVP [a] Absolute values calculated for uncomplexed **21** was: N1=-0.44; C2= -0.14; C3=0.41; LUMO= -44 kcal/mol, -1.9 eV.

^{13}C NMR spectroscopic studies at –80 ºC in $CD_2Cl_2/CDCl_3$ 1:1 were supporting the observation of charge-decreases at C3, with this carbon shifting upfield 6.1 ppm. Also the increased charge at C2 was supported by a downfield shift by 3.8 ppm upon complexation to BF_3.

5.4 Verification with carbonyls and imines

We were also interested in using our calculation method for other substrates to further substantiate our findings and decided to investigate the BF_3-activation of an aldehyde **84**, a ketone **85**, an *N*-methylaldimine **86**, an *N*-methylketoimine **87**, an *N*-mesylaldimine **88**, and an *N*-mesylketoimine **89**, all of them carrying a phenyl substituent at the unsaturated carbon (Table 9).

Table 9. *Calculations on Lewis acid activation of carbonyls and imines*



Entry	Compound	Lewis acid/ complexed to	Charge of atom and *change when complexed to a LA*[c]		LUMO	
			carbon	hetero atom	kcal/mol	eV
1[a]	**84**	-	0.35	-0.46	-52	-2.2
2[b]	**84**	BF_3/ O	*-0.06*	*+0.08*	*-34*	*-1.5*
3[a]	**85**	-	0.54	-0.51	-46	-2.0
4[b]	**85**	BF_3/ O	*+0.04*	*+0.41*	*-34*	*-1.5*
5[a]	**86**	-	0.31	-0.45	-36	-1.6
6[b]	**86**	BF_3/ N	*-0.25*	*+0.39*	*-29*	*-1.2*
7[a]	**87**	-	0.42	-0.46	-32	-1.4
8[b]	**87**	BF_3/ N	*-0.18*	*+0.37*	*-25*	*-1.1*
9[a]	**88**	-	0.27	-0.45	-58	-2.5
10[b]	**88**	BF_3/ O	*-0.02*	*+0.02*	*-18*	*-0.8*
11[a]	**89**	-	0.49	-0.49	-55	-2.4
12[b]	**89**	BF_3/ O	*-0.06*	*+0.04*	*-18*	*-0.8*

Method used for calculations: B3LYP/LACVP+*//B3LYP/LACVP [a] Value of calculated atom charges and energies. [b] Difference in atom charges and energies compared to the non complexed molecule. [c] See description of [a] and [b].

Activation of **84** and **85** both gave an expected LUMO energy lowering with minor changes of the charge of the carbonyl carbon (entries 1-4). Lewis acid activation of imines **86** and **87** gave significant decreases of charges of the imine carbons (entries 5-8), comparable to the situation in azirine **21** (entry 5, Table 8). Also the LUMO lowering in **86** and **87** was similar to that in **21**, but the uncomplexed azirine **21** had a value approximate 0.4 eV lower than uncomplexed imines **86** and **87**. Atom charges of **88** and **89** were not differing much upon Lewis acid complexation, even though the LUMO orbitals were lowered with approximately 1 eV (entries 9-12). These results suggest that *N*-substitution with a mesyl group make imines more carbonyl like. Mesylation of imines was also observed to lower LUMO with approximately 1 eV, a lowering similar to that effected by Lewis acid activation. Altogether this can explain why *N*-unsubstituted imines are rarely used in synthetic applications, while the chemistry of *N*-activated imines are widely used.

Contrary to experimental results, activation of **84** with BF_3 gave a slight decrease in the δ^+-charge of the carbonyl carbon (compare entries 1 and 2).[91] Activation of an aromatic aldehyde by $SnCl_4$ was shown to result in a downfield shift of the C=O by 7.1 ppm (^{13}C NMR).[92] Activation of **85** with BF_3 gave a smaller increase of the δ^+ charge of the carbonyl carbon than expected (entry 3 compared to 4). Still the NMR experiment with $BF_3 \cdot Et_2O$ activation of **21**, described earlier in this chapter, support our findings and trends observed.

5.5 Conclusion

We have confirmed that the matching of Lewis acids with azirines is a delicate matter. Lewis acid complexation of 3-phenyl-2*H*-azirines lowers the δ^+-charge at C3 in **21** (see Table 8), and also lowers the LUMO energy. This might be part of the explanation to why Diels-Alder reactions, usually considered as orbital-controlled reactions, work well under Lewis acid catalysis (chapter 4), while Lewis acid promoted nucleophilic additions to azirines (chapter 3), generally considered to be charge-controlled reactions, have not been successfully applied so far.

91 Shambayati, S.; Schreiber, S. L. In Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon Press: Exeter, 1991; Vol. 1, pp 283-324.
92 Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133-3139.

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Appendix

This appendix contains experimental details, and/or spectroscopic data of compounds **32**-**34**, **36a**-**e**, **37**, **38**, **40**, **41a**-**e** and **70**-**72**

General. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300/400 MHz, JEOL 270 MHz or Bruker dpx 400/500 MHz spectrometers in $CDCl_3$, using the residual peak of $CHCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0), or added TMS (δ 0.00), as internal standard. Chemical shifts are reported in the δ-scale with multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), integration and coupling constants (Hz). High resolution mass spectra were recorded on a JEOL SX-102 spectrometer. Analytical thin layer chromatography was performed on Merck silica gel 60 F_{254} glass plates, the plates were visualized with UV light, phosphomolybdic acid/cerium sulfate staining reagent (purchased from Aldrich as a 20 wt% solution in ethanol but diluted to ca 5 wt% before use) and a permanganate staining reagent ($KMnO_4$ (3g) + K_2CO_3 (20g) + 5% aqueous NaOH (5ml) + H_2O (300ml)). Flash chromatography employed Grace Amicon silica gel 60 (35-70 μm). Air- and moisture sensitive reactions were carried out in flame-dried, septum-capped flasks under an atmospheric pressure of nitrogen. All liquid reagents were transferred via vaccum-dried syringes. THF, Et_2O and PhMe were distilled from sodium-benzophenone ketyl before use; CH_2Cl_2 was distilled from CaH_2.

Azirine **32**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 1H, J=2.6), 7.55 (dd, 1H, J=8.9, 2.6), 6.85 (d, 1H, J=8.9), 3.91 (s, 3H), 1.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 161.1, 157.4, 135.8, 134.1, 115.3, 112.0, 111.6, 55.2, 16.6; Rf 0.83 Pentane/EtOAc 1:2

Azirine **33**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, 2H, J=8.9), 6.97 (d, 2H, J=8.9), 3.83 (s, 3H), 1.65 (s, 2H); Rf 0.83 Pentane/EtOAc 1:2

Azirine **34**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (ddd, 1H, J=4.8, 1.7, 1.1), 7.95 (dt, 1H, J=7.7, 1.1), 7.84 (td, 1H, J=7.7, 1.7) 7.42 (ddd, 1H, 7.7, 4.8, 1.1) 1.92 (s, 2H); Rf 0.42, Pentane/EtOAc 1:2

Typical procedure for the enantioselective alkylation of azirines:
Ligand **43** (56 μL, 0.28 mmol) was dissolved in toluene (3 mL) at rt under N_2. The reaction was cooled to –105 °C, whereupon MeLi (1.6M in Et_2O, 353 μL, 0.56 mmol) was added slowly via a syringe. The reaction mixture was stirred for 20 min. before a solution of **31** (47.2 mg, 0.28 mmol) dissolved in toluene (2 mL), cooled to –78 °C under N_2, was added via a double-ended cannula, over a period of five minutes. After 1 h at –100 ± 5 °C the reaction was quenched by

pouring into a separation funnel containing NH_4Cl aq. satd. (5 mL). The aqueous phase was extracted 3xEt_2O, followed by washing of the combined organic phase 2xH_2O and 1xNaCl aq. satd. and drying with $MgSO_4$. This gave a crude yield of 46.3 mg (containing byproducts) of **36a**, used in the next step.
Crude **36a** (46.3 mg, 0.25 mmol), dissolved in CH_2Cl_2 (3 mL) was stirred under N_2 at –78 °C. Diisopropylethylamine (98 μL, 0.56 mmol) was added to the reaction mixture dropwise with a syringe followed by addition of MsCl (22 μL, 0.28 mmol) after five minutes. After 15 minutes at –78 °C, the reaction was quenched by transferring it into a separation funnel containing $NaHCO_3$ aq. satd.. The aqueous phase was extracted 1xCH_2Cl_2 followed by washing of the combined organic phase with 1M H_2SO_4 (10 mL). The acidic aqueous phase was extracted 1xCH_2Cl_2 and the combined organic layer was washed 1xH_2O. This aqueous phase was extracted 1xCH_2Cl_2 and the combined organic phase was washed with 1xNaCl aq. satd. The aqueous phase was extracted 2xCH_2Cl_2 and the combined organic phase was dried with $MgSO_4$ to give the crude product. Purification was performed on an Al_2O_3 column packed in pentane. The crude was dissolved in CH_2Cl_2/pentane 1:1 and column was eluted with pentane/EtOAc 100:0→24:1→9:1→4:1 to give **41a** as a yellow oil (29 mg, 0.11 mmol, 40 %).

Alternative route for the first step
The 3-(2-naphthyl)-2*H*-azirine **31** (41.3 mg, 0.25 mmol) was dissolved in toluene (2 mL) whereupon the reaction was cooled to –78 °C under N_2 atmosphere. Ligand **43** (49 μL, 0.25 mmol) was added to the reaction mixture and after 5 minutes this solution was transferred via a double ended cannula to another flask containing MeLi (1.6M in Et_2O, 309 μL, 0.49 mmol), dissolved in toluene (3 mL) cooled to –105 °C under N_2. After 1 h at –100 ± 5 °C the reaction was quenched by pouring it into a separation funnel containing NH_4Cl aq. satd. (5 mL).Work-up and mesylation was performed as above to give **41a** as a yellow oil (19.5 mg, 0.08 mmol, 30 %).

Aziridine **36a**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77-7.83 (m, 4H), 7.43-7.47 (m, 3H), 2.06 (s, 1H), 2.03 (s, 1H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 141.0, 133.2, 132.3, 128.1, 127.7, 127.5, 126.1, 125.7, 124.8, 124.3, 37.1, 35.0, 25.1; Rf 0.17 Pentane/EtOAc 1:2

Aziridine **36b**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76-7.83 (m, 4H), 7.41-7.53 (m, 3H), 1.96 (m, 3H, J=), 1.77 (br s, 1H), 1.29 (m, 4H), 0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.9, 133.2, 132.4, 127.9, 127.8, 127.5, 126.1, 125.8, 125.7, 41.9, 39.1, 33.1, 28.3, 22.7, 14.0 Rf 0.24 Pentane/EtOAc 1:2

Aziridine **36c**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.74 (m, 4H), 7.31-7.43 (m, 3H), 1.89 (m, 3H), 1.72 (m, 1H), 0.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.6, 133.2, 132.5, 127.9, 127.8, 127.6, 126.2, 126.1, 125.8, 125.7, 42.6, 32.8, 31.9, 10.1; Rf 0.21 Pentane/EtOAc 1:2

Aziridine **36d**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12-7.81 (m, 12H), 2.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.5, 139.9, 133.2, 132.5, 128.7, 128.4, 128.1, 127.9, 127.8, 127.5, 127.2, 127.1, 126.5, 126.2, 125.9, 125.9, 44.2, 35.4; Rf 0.19 Pentane/EtOAc 4:1

Aziridine **36e**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78-7.87 (m, 4H), 7.43-7.52 (m, 3H), 5.87 (dd, 1H, J=17.1, 10.4), 5.18 (d, 1H, J=10.4), 4.97 (d, 1H, J=17.1) 2.23 (s, 1H), 2.18 (br s, 1H); Rf 0.31 Pentane/EtOAc 1:2

Aziridine **37**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, 1H, J=2.6), 7.24 (dd, 1H, J=8.7, 2.6), 6.65 (d, 1H, J=8.7), 3.78 (s, 3H), 1.83 (s, 1H), 1.77 (s, 1H), 1.44 (s, 3H) Rf 0.30 Pentane/EtOAc 1:2

Aziridine **38**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, 2H, J=8.8), 6.77 (d, 2H, J=8.8), 3.72 (s, 3H), 1.92 (br s, 1H), 1.87 (s, 1H), 1.52 (s, 3H); Rf 0.1 Pentane/EtOAc 1:2

Mesylate **40**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.43 (m, 5H), 3.16 (s, 3H), 2.96 (s, 1H), 2.61 (s, 1H), 2.00 (s, 3H); Rf 0.87 Pentane/EtOAc 1:2

Mesylate **41a**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78-7,85 (m, 4H), 7.45-7.53 (m, 3H), 3.16 (s, 3H), 3.03 (s, 1H), 2.71 (s, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 133.0, 132.8, 128.4, 128.0, 127.7, 126.5, 126.3, 125.4, 124.3, 51.3, 42.4, 42.1, 20.9; Rf 0.31 Pentane/EtOAc 4:1

Mesylate **41b**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.77 (m, 4H), 7.37-7.48 (m, 3H), 3.00 (s, 3H), 2.84 (s, 1H), 2.78 (s, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 1.14-1.32 (m, 4H), 0.72 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.1, 132.8, 132.8, 128.2, 127.9, 127.7, 126.7, 126.4, 126.3 125.7 56.3, 42.2, 40.4, 34.7, 29.0, 22.5, 13.7; Rf 0.39 Pentane/EtOAc 4:1

Mesylate **41c**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.77 (m, 4H), 7.35-7.47 (m, 3H), 3.11 (s, 3H), 2.90 (s, 1H), 2.81 (s, 1H), 2.45 (m, 1H), 2.28 (m, 1H), 0.98 (t, 3H, J=7.4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7, 132.9, 132.9 128.3, 127.9, 127.7, 126.9, 126.4, 126.3, 126.3, 125.8 57.2, 42.4, 40.2, 28.3, 11.1 Rf 0.29 Pentane/EtOAc 4:1

Mesylate **41d**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 1H), 7.76-7.85 (m, 3H), 7.45-7.52 (m, 5H), 7.31-7.36 (m, 3H), 3.24 (s, 2H), 3.07 (s, 3H)^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.4 135.2, 132.9, 132.7, 128.8, 128.6, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.2, 127.0, 126.4, 126.3, 126.3 56.6, 41.4, 40.7; Rf 0.21 Pentane/EtOAc 4:1

Mesylate **41e**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.89 (m, 4H), 7.49-7.53 (m, 3H), 6.39 (dd, 1H, J=17.1, 10.5), 5.49 (d, 1H, J=10.5), 5.09 (d, 1H, J=17.1) 3.26 (s, 1H), 3.18 (s, 3H), 2.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.9, 134.4, 133.0, 132.9, 128.3, 128.1, 128.0 127.7, 127.6, 126.6, 126.5, 126.2, 123.0, 55.5, 41.9, 22.1; Rf 0.22 Pentane/EtOAc 1:2

Cycloadduct **70**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.40 (m, 5H), 7.27 (m, 1H), 5.34 (br s, 1H), 4.94 (dd, 1H, J=7.6, 1.0), 3.94 (d, 1H, J=11.5), 3.74 (d, 1H, J=11.5), 2.77 (d, 1H, J=16.2), 2.68 (d, 1H, J=16.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.9, 129.0, 128.3, 125.4, 100.3, 65.9, 48.8, 47.1, 15.3

Cykloadduct **71**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.36 (m, 5H) 6.27 (dd, 1H, J=5.6, 2.8), 6.03 (dd, 1H, J=5.6, 2.8) 5.19 (A-part of ABq, 1H, J=12.1), 5.18 (B-part of ABq, 1H, J=12.1), 3.73 (m, 1H), 3.13 (d, 1H, J=13.8), 2.91 (d, 1H, J=13.8) 2.73 (m, 1H), 2.77 (m, 1H), 1.58 (d, 1H, J=11.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 135.3, 135.2, 133.2, 128.7, 128.5, 128.1, 67.7, 67.1, 56.1, 49.5, 48.2, 44.6

Cycloadduct **72**
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.34 (m, 5H), 6.31 (dd, 1H, J=5.8, 2.8), 6.06 (dd, 1H, J=5.8, 2.8), 5.21 (A-part of ABq, 1H, J=12.3), 5.20 (B-part of ABq, 1H, J=12.1), 3.70 (m, 1H), 3.54 (d, 1H, J=13.8), 3.22 (m, 1H), 3.15 (d, 1H, J=13.8), 1.91 (m, 1H), 1.31 (d, 1H, 11.5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 137.3, 135.1, 131.7, 128.8, 128.7, 128.6, 73.1, 67.6, 56.5, 47.7, 46.9, 40.6