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Institute of Organic Chemistry

Polish Academy of Sciences


Anna Kozioł

# Enantioselective synthesis of oxacephams from 4-vinyloxyazetidinone

Ph.D. thesis presented to Scientific Council of Institute of Organic Chemistry of Polish Academy of Sciences in order to receive degree of Doctor of Philosophy in Chemistry.

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## ABBREVIATIONS USED IN THIS WORK

### Reagents and chemical compounds:

AIBN - azobisisobutyronitrile
CSA – camphorosulphonic acid
CSI - chlorosulfonylisocyaniate
cod – cyclooctadien
DABCO – 1,4-diazabicyclo(2.2.2)octane
DBU – 1,8-Diazabicyclo[5.4.0]undec-7-en
$(DHQD)_2PHAL$ - Hydroquinidine 1,4-phthalazinediyl diether
DIOP - 4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMF – *N,N*-dimethylformamide
dppb – 1,4-bis(difenylofosfino)butan
LDA –lithium diisopropylamide
TBME - tert.-butyl methyl ether
nbd - n-butyraldehyde
NBS – *N*-bromosuccinimide
NMI – 1-methylimidazole
PPA – polyphosphoric acid
PPE - polyphosphate ester
Red – Al - sodium bis(2-methoxyethoxy)-aluminumhydride
TBABr – tetrabutylamonium bromide
TBAF –tetrabutyl ammonium fluoride
TBSCl – *tert*-butyldimethylsilyl chloride
TFA – trifluoroacetic acid
THF – tetrahydrofurane
TsOH – 4-methyl benzenesulfonic acid

### Protective groups:

Ac – acetyl
Ar – aryl
Boc - 1,1-dimethylethoxycarbonyl
Bn – benzyl
Bu – butyl
*t*-Bu – *tert*-butyl
Bn – benzyl
Cp - cyclopentadienyl
Et – ethy
Me – methyl
Ms – metanasulphonyl (mesyl)
Ph – phenyl
PMB – 4-methoxybenzyl
*i*-Pr – *iso*-propyl
TBS – *tert*-butyldimethylsilyl
TIPS - triisopropylsilyl
Tf – trifluoromethanesulfonic
TMS – trimethylsilyl
Ts – *p*-toluenosulfonyl (tosyl)

### Other abbreviations:

CD – circular dichroism
*de* – diastereomeric excess
*dr* – diastereomeric ratio
*ee* – enantiomeric excess
EI – electron impact ionization
ESI – electrospray ionization
HPLC –high pressure liquid chromatography
HR MS – high resolution mass spectrometry
LA – Lewis acid
LA* – chiral Lewis acid
LB – Lewis base
LB* – chiral Lewis base
IR – Infra red
MS – mass spectrometry
4Å MS – 4Å molecular severs
Nu – nucleophile
MALDI – matrix assisted laser desorption/ ionization
NMR – nuclear magnetic resonance
NOE – nuclear Overhauser effect
rt – room temperature
TOF – time of flight
TLC – thin layer chromatography



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## 1. INTRODUCTION

The Merck group synthesis of oxacephalotin (**1**)[1] and oxacephamandol (**2**)[2] which are more active than natural, sulfur-containing congeners and the isolation in 1976 by Beecham [3] of clavulanic acid (**3**), a potent β-lactamase inhibitor, demonstrated that the presence of sulfur atom is not necessary for the high antibacterial activity. The search for new oxygen analogs of penicillins and cephalosporins has led to the discovery of many natural and unnatural antibiotics.[4]

Antibacterial activity of β-lactam antibiotics depends on (*R*) configuration of the bridgehead carbon atom - C-5 of clavams (4-oxapenams) and C-6 of oxacephams. In the case of clavams, however, only **3** and its simple derivatives with the (*R*) configuration of the bridgehead carbon atom display the relatively weak antibacterial activity and the strong β-lactamase inhibition. Other natural clavams **4** which possess (*S*) configuration show activity against number species of fungi.[5] The 5-oxacephalosporins could not been introduced to the clinical use since they are relatively unstable. The broad investigations undertaken by Shionogi Co.[4,6] yielded, however, in two 5-oxacephamycins representing the third and the fourth generation of β-lactam antibiotics: latamoxef (**5**) and flomoxef (**6**). In 1988, the Merck and Meiji groups[7] reported the synthesis of a new, interesting 4-β-methyl substituted 5-oxacephem OCP-9-176 (**7**), which has been found to be stable to β-lactamases and displayed high antibacterial activity.

---

[1] Cama, L.D.; Christensen, B.G. *J. Am. Chem. Soc.*, **1974**, *96*, 7582

[2] Firestone, R.A.; Fahey, J.L.; Maciejewicz, N.S.; Patel, G.S.; Christensen, B.G. *J. Med. Chem.*, **1977**, *20*, 551

[3] a) Brown, A.G.; Butlerworth, D.; Cole, M.; Hanscomb, G.; Hood, J.D.; Reading, C.; Rolinson, G.N. *J. Antibiot.*, **1976**, *29*, 668; b) Brown, A.G.; Corbett, D.F. ; Goodacre, J.; Harbridge, J.B.; Howarth, T.T.; Ponsford, R.J.; Stirling, I.; King, T.I. *J. Chem. Soc., Perkin Trans 1*, **1984**, 635

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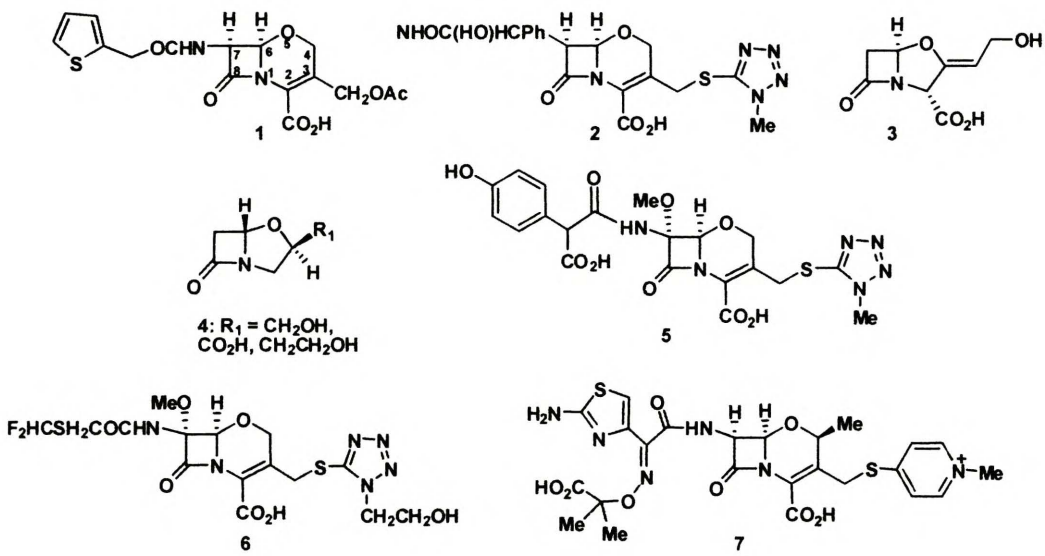

**Scheme 1**

For 25 years our laboratory has been interested in elaboration of new methodologies leading to basic skeletons of clavams and 5-oxacephams. Since the configuration at the bridgehead carbon atom of β-lactam antibiotics is essential for the biological activity of antibiotics, our special attention has been focused on the problem of stereocontrol in the formation of a desired configuration of the bridgehead carbon atom in these compounds.

This configurational problem can be solved by either the nucleophilic substitution at C-4 of the azetidin-2-one ring, or *via* the cycloaddition reaction in which simultaneously the four-membered ring and the crucial stereogenic centres are formed. Our group has elaborated two routes leading to oxygen analogues of penicillins and cephalosporins. The first one involves [2+2] cycloaddition of active isocyanates to vinyl ethers and the second one utilizes 4-vinyloxy-azetidinone (**9**) as a readily available β-lactam synthon.

It has been shown that the [2+2] cycloaddition methodology provided 4-alkoxy-azetidinones from chiral vinyl ethers in excellent yield and with high diastereoselectivity. Subsequently, five oxazolidine, or six 1,3-oxazine rings have been formed by intramolecular alkylation of the β-lactam nitrogen atom.

On the other hand, reactions between commercially available 4-acetoxy-azetidin-2-one (**8**) and chiral alcohols proceeded with low asymmetric induction. We could assume that in order to improve stereoselectivity of the nucleophilic substitution at C-4 of azetidin-2-one, the reaction should be performed as an intramolecular process. This, however, requires alkylation of the β-lactam nitrogen atom prior formation of the bicyclic skeleton *via* the nucleophilic substitution. Due to the low stability in the presence of bases, compound **8** could not be alkylated at the nitrogen atom. This prompted Dr Z. Kałuża from our group to utilize for that purpose, readily available from divinyl ether and chlorosulfonyl isocyanate, 4-vinyloxy-azetidinone (**9**) which can be easily alkylated at the nitrogen atom, whereas 4-vinyloxy group could be subsequently transformed into the formyloxy, or acetoxy



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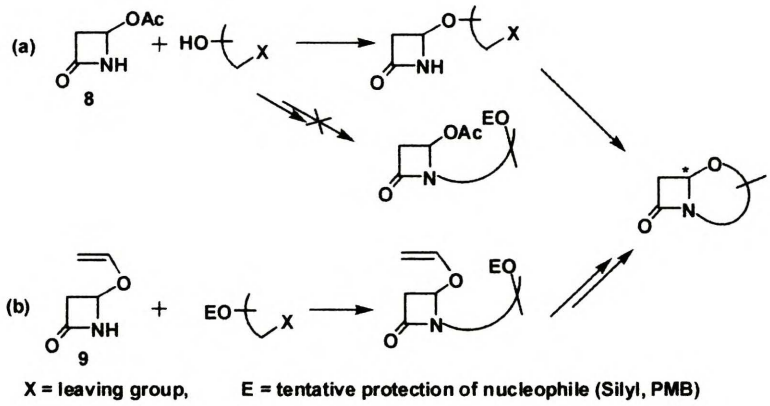
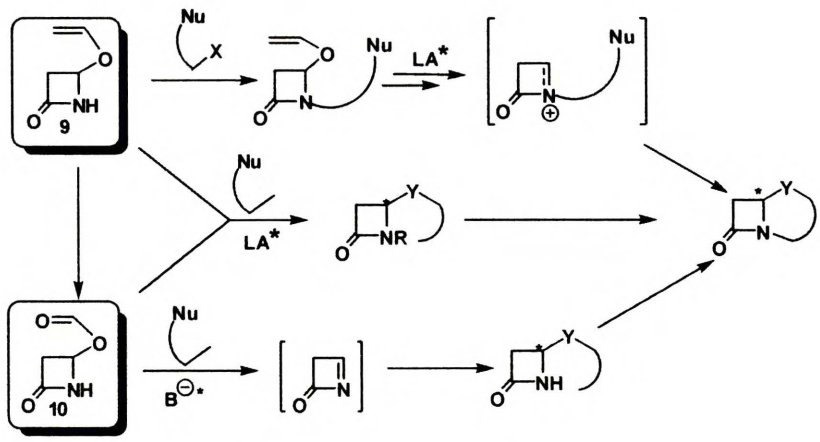
substituent. It has been shown that expected in this methodology high asymmetric induction was really achieved, if chiral *N*-fused side chains have been used (Scheme 2, route b).




**Scheme 2**

Route (b) offers also an enantioselective way of formation of desired configuration at the bridgehead carbon atom if non chiral alkylating agent is used in the presence of chiral Lewis acid (Scheme 2). We have expected that an intramolecular process which proceeded *via* a flat *N*-acyliminium cation should offer high asymmetric induction. It should be stressed that the same enantioselective reaction could be also done as an intermolecular process. This, obviously, can use azetidinone **10**, as well (Scheme 3).




**Scheme 3**

Optically enhanced 4-alkoxy-azetidinones can be also achieved *via* a chiral based catalyzed nucleophilic substitution at C-4 of azetidinone. Such reaction uses 4-acyloxy-azetidinone and involves flat 1,4-dehydro-azetidinone intermediate and proceeds *via* elimination/addition mechanism (Scheme 3).



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Reactions depicted in Scheme 3 constitute the program of my PhD thesis. I have investigated both intramolecular and intermolecular chiral Lewis acids catalyzed processes, as well as intermolecular, base catalyzed reactions. In order to facilitate experiments (to avoid formation of high volatile compounds) but to stay within biologically active β-lactam compounds, I have concentrated my program mainly on reactions which involve phenolic and thiophenolic nucleophiles. I have shown that proposed in Scheme 3 reactions can be performed effectively and in some cases high enantioselectivity can be achieved. The absolute configurations of synthesized β-lactams were proved by CD spectroscopy in collaboration with the group of Prof. J. Frelek. The mechanisms of investigated reactions were discussed.



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## 2. *LITERATURE REVIEW*

Iminium ions are important, reactive species in organic synthesis especially in the context of the preparation of various nitrogen-containing natural products.[8] They are analogues of oxonium ions as well as activated carbonyl group. Such reactive intermediates can act as carbocations toward weak nucleophiles enabling useful methodologies for both inter- and intramolecular carbon–carbon and carbon–heteroatom bond formation.[9] They were found to be reactive towards a wide range of π-nucleophiles including alkenes, allenes, alkynes and aromatic or heteroaromatic systems. Diversity of approaches to their precursors, as well as, diversity of easily available reaction partners open access to wide range of natural and synthetic biologically active and structurally interesting compounds.[10] Other favorable feature is a good stereocontrol of additions.[11]

### 2.1. Structure towards reactivity of iminium ions

As it was mentioned above, the electron-withdrawing iminium ion is the nitrogen analogue of the α-alkoxycarbenium ion (oxonium ion) or activated carbonyl group. Therefore, it is an important electrophilic component used for the C-C bond formation. Its reactivity can be changed by introduction of electron-deficient or electron-donating groups (Figure 1).

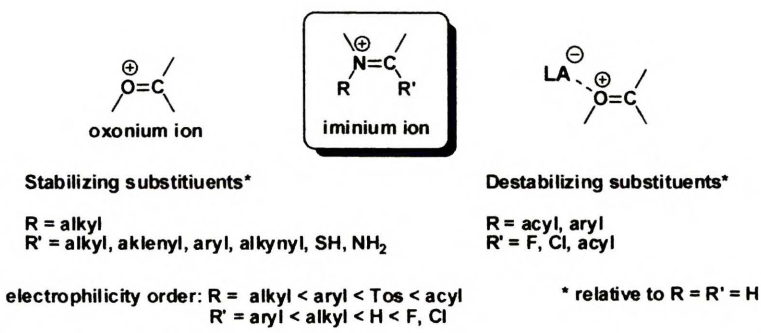


**Figure 1**

One of the most important types of iminium ions are *N*-acyliminium ions. They can be generated in stoichiometric quantities only under acidic conditions, since their conjugate bases (enamides) are only weakly basic. In contrast, conjugated bases of iminium ions are moderately strong, so iminium ions can be generated in stoichiometric amounts under essentially neutral conditions. It is important to note that low electrophilic reactivity of the iminium moiety causes a Grob fragmentation (Scheme 4).[12] It is a reverse reaction to the addition which is often the most important process. However, if the iminium fragment bears a carbonyl group on the nitrogen atom, its

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[8] Maryanoff, B. E.; Zhang, H. C;. Cohen, J. H.; Turchi, I. J; . Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431
[9] Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311
[10] Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I. Pergamon: Oxford **1992**, Vol. 2, 1007
[11] Deslongchamps, P. *Stereoelectronic Effects In Organic Chemistry* Pergamon: Oxford **1993**, 211
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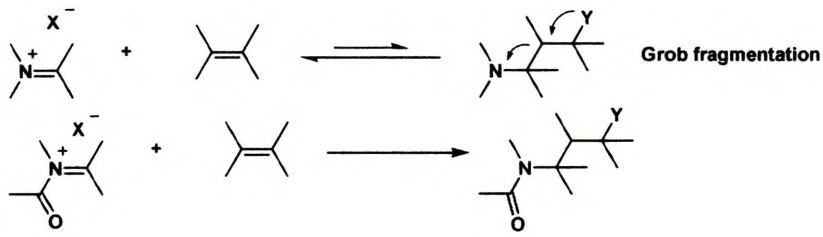
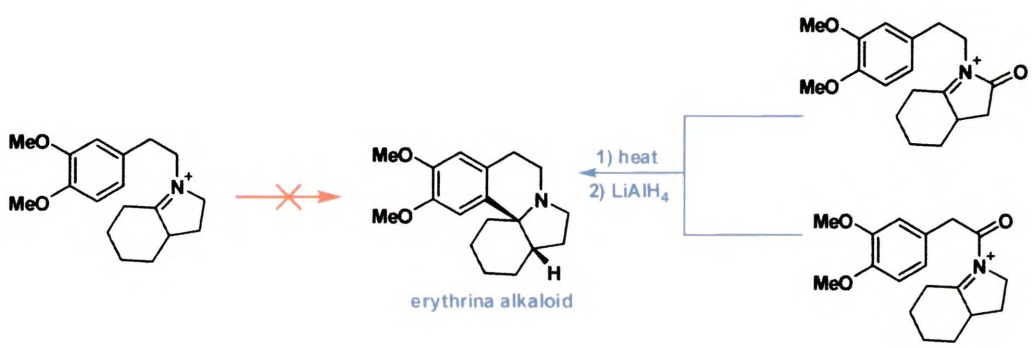
electrophilicity is strongly enhanced, and reactions with C=C bonds are irreversible and synthetically useful (Scheme 4).[13]




**Scheme 4**

The *N*-acyliminium ion is much more electrophilic in comparison with ordinary imium ion. It was nicely illustrated in total synthesis of erythrina type alkaloids when iminium path (red arrow) failed in contrast to *N*-acyliminium one (blue arrow, Scheme 5).[14]




**Scheme 5**

*N*-Acyliminium ions, as a carbocationic species can form the enamide by the proton elimination process which strongly depends on the acid used, solvent and the substrate structure (Scheme 6).[15] Nevertheless, under protic acid conditions, this side reaction can be reversed and the enamides can be, in many cases, *N*-acyliminium ion precursors. Acid mediated cyclization of enamide **11** to cyclic product **12** can serve as an example (Scheme 6).[16]

[13] Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367

[14] a) Belleau, B. *Can. J. Chem.* **1957**, *35*, 651; b) Mondon, A. *Chem. Ber.* **1959**, *92* , 1461

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[16] Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207



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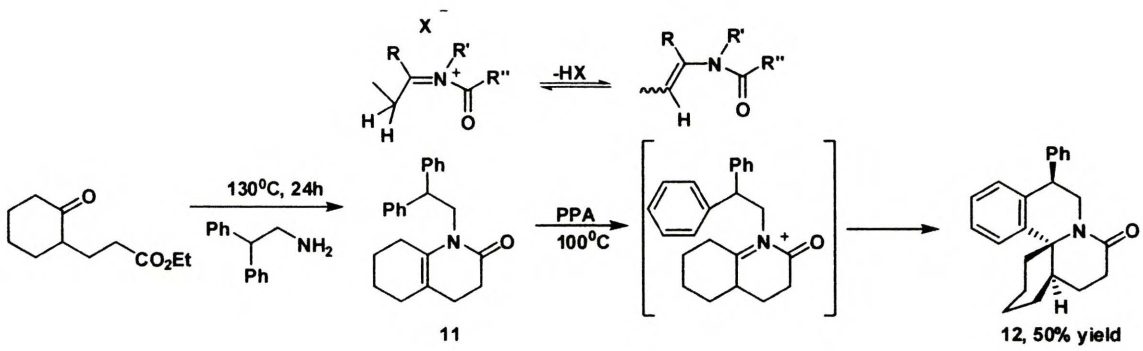
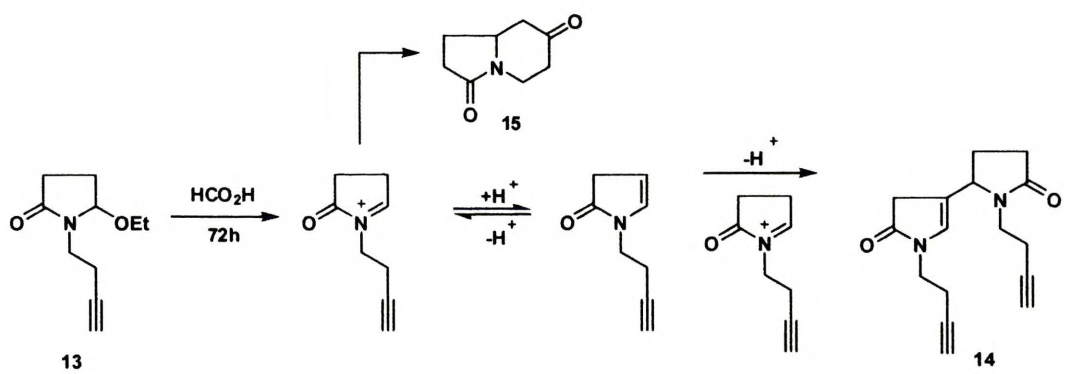



**Scheme 6**

The effective reprotonation of the enamide might not occur, therefore side reactions can be observed. It can be a problem especially when the nucleophile is not sufficiently reactive or unfavorable stereoelectronic factors exist, such as formation of medium sized rings.[13,17] As an example reaction of **13** with formic acid may serve (Scheme 7).[16,18] In this case, the substrate **13** affords dimer **14** and expected indolizidine **15** in a 1:5 molar ratio at concentration of ca. 0.15 M. In the case of more diluted reaction mixture, only expected product **15** is formed (Scheme 7).




**Scheme 7**

The ability of the carbonium ion stabilization by the carbamate group and by the oxygen atom was compared (Scheme 8).[19] The *N*-acyliminium ion appears to be *ca.* 11 kcal·mol$^{-1}$ more stable than the oxonium one. Theoretical calculations of the relative stability were confirmed by experiments performed on oxazoline **16**. The higher charge-donation ability of the carbamate nitrogen than the ether oxygen atom is demonstrated by both Vilsmeier formylation and acid-promoted reaction with acetyl chloride (Scheme 8).

---

[17] a) Hiemstra, H.; Speckamp, W, N. *The Alkaloids*, **1988**, *32*, 271; b) Hiemstra, H.; Speckamp, W, N. *Comprehensive Organic Synthesis* Trost, B. M.; Fleming, I. Pergamon: Oxford **1992**, Vol. 2, 1047; c) Hart, D. J. *Alkaloids: Chem. Biol. Perspect.* **1988**, *6*, 227; d) de Koning, H.; Speckamp, W. N. *Stereoselective Synthesis* Helmchen, G.; Hoffman, R. W.; Mulzer, J.; Schaumann, E. Verlag: Stuttgart **1995**, Vol. E 21b, 1953

[18] Schoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *Tetrahedron*, **1980**, *36*, 143

[19] Seebach, D.; Stucki, C. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1351



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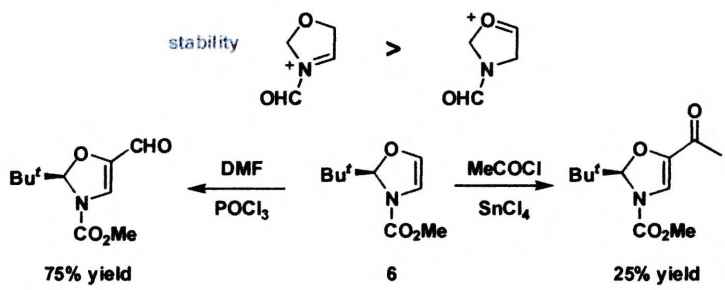
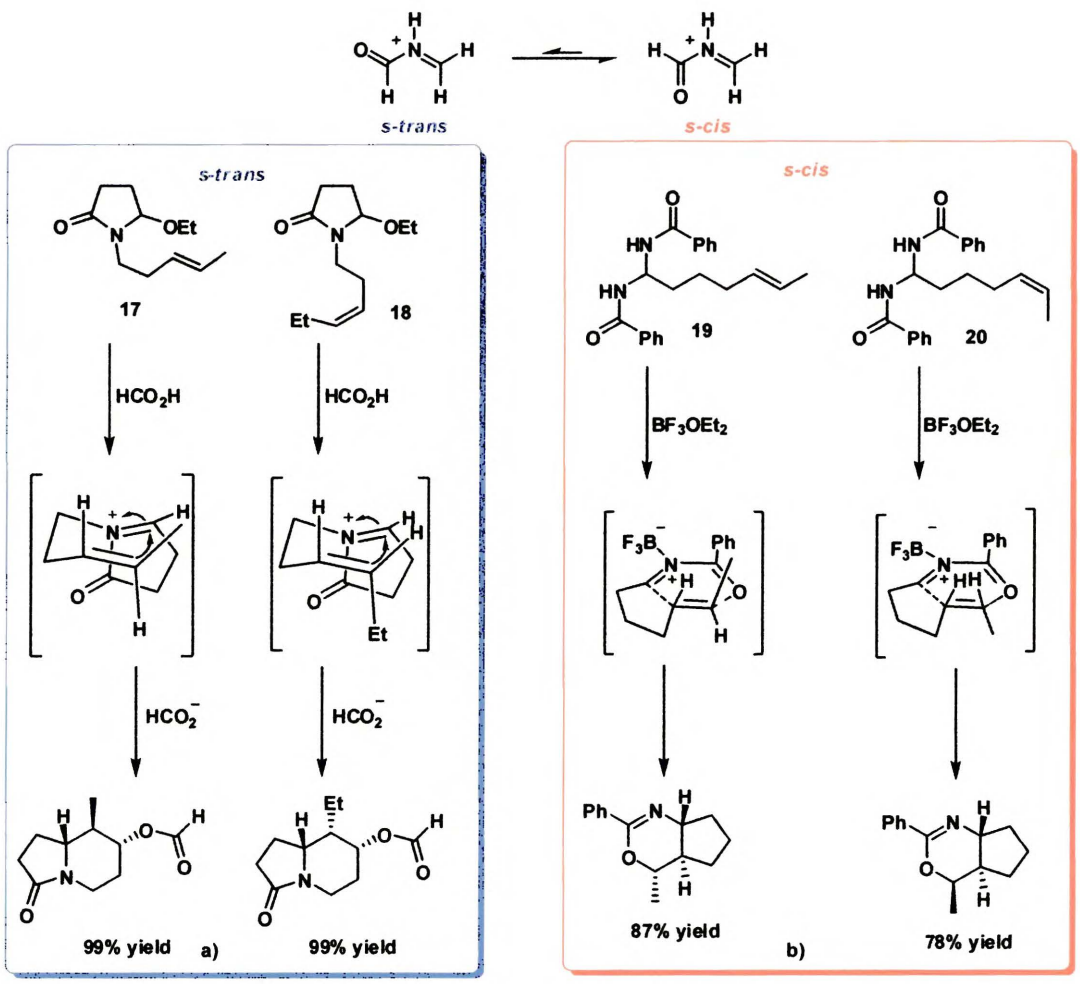



**Scheme 8**

*N*-Acyliminium ions can adapt *s-cis* or *s-trans* conformation. The *ab initio* calculation on the simplest *N*-acyliminium ion indicated that *s-cis* conformer is *ca.* 3 kcal·mol$^{-1}$ more stable than *s-trans* one (Scheme 9).[20] It can be explain by the better compensation of the dipole moment vectors of the iminium fragment and the carbonyl group in *s-cis* form. However, in highly substituted systems, steric factors may hinder such preference (Scheme 9). [21]




**Scheme 9**

[20] Kupfer, R.; Wurthwein, E.-U.; Nagel, M.; Allmann, R. *Chem. Ber.*, **1985**, *118*, 643

[21] Wanner, K. T.; Kartner, A.; Wadenstrofer, E. *Heterocycles* **1988**, *27*, 2549



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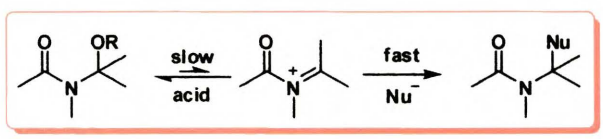
Cyclic species like **17** and **18** have fixed *s-trans* conformation (blue frame).[22] They react as nitrogen-stabilized carbocations with π-nucleophiles and the mechanistic pathway can be explained by the π-complex theory. *N*-Acylimium ions in equilibrium process form π-complex, with a quasi chair-like six-membered transition state. Reactions proceed with retention of the double-bond configuration. According to Baldwin rules it is allowed 6-endo-trig process (Scheme 9). For *N*-acylimium ions that can adopt the *s-cis* conformation like **19** and **20** (red frame), the stereochemical pathway of reaction is different. The acyl iminium cation behaves as 4π-electron component with reversed electron demand and undergoes Diels-Alder reaction. In most cases this process is highly regio- and stereoselective (Scheme 9). [23]

Usually *N*-acyliminium ions are generated under mild conditions and a low concentration of the reactive intermediate is presented. Probably the rate-determining step is *N*-acyliminium ion formation. Reaction with nucleophile is fast and therefore the reaction rate depends on stability of the iminium intermediate (Scheme 10).[17a,24]




**Scheme 10**

Relative reactivity data of different *N*-acyliminium ions can be illustrated by $AlCl_3$ promoted reaction with 1,3,5-trimethoxybenzene (Figure 2).[25] There is inverse correlation between stability (red arrow) of the *N*-acyliminium ion and its reactivity (blue arrow). This implies that the greater stability of iminium ion precursor leads to its higher reaction rate. Though there is no data, it may be expected that 4-methoxy-azetidin-2-one is less reactive than its five-membered congener due to a strain of the iminium double bond located within the four-membered ring.[17b] The carbamate is expected to be more reactive than formamide, owing to the higher availability of the carbamate nitrogen lone pair for the carbonium ion stabilization.[17b] This reaction pattern has been confirmed by addition of allyltrimethylsilane in the gas phase.[24] The relative reactivity versus carbocation stabilization is shown in Figure 2.

---

[22] Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163

[23] A) Schmidt, R. R. *Synthesis*, **1972**, 333; b) Schmidt, R. R. *Angew. Chem., Int. Ed. Endl.* **1973**, *12*, 212; c) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525; d) Seelinger, W.; Diepers, W. *Justus Liebigs Ann. Chem.* **1966**, *697*, 171, e) Scola, P. M.; Weinreb, S. M. *J. Org. Chem.* **1986**, *51*, 3248

[24] D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854

[25] Malmberg, M.; Nyberg, K. *Acta Chem. Scand. Ser. B* **1981**, *35*, 411



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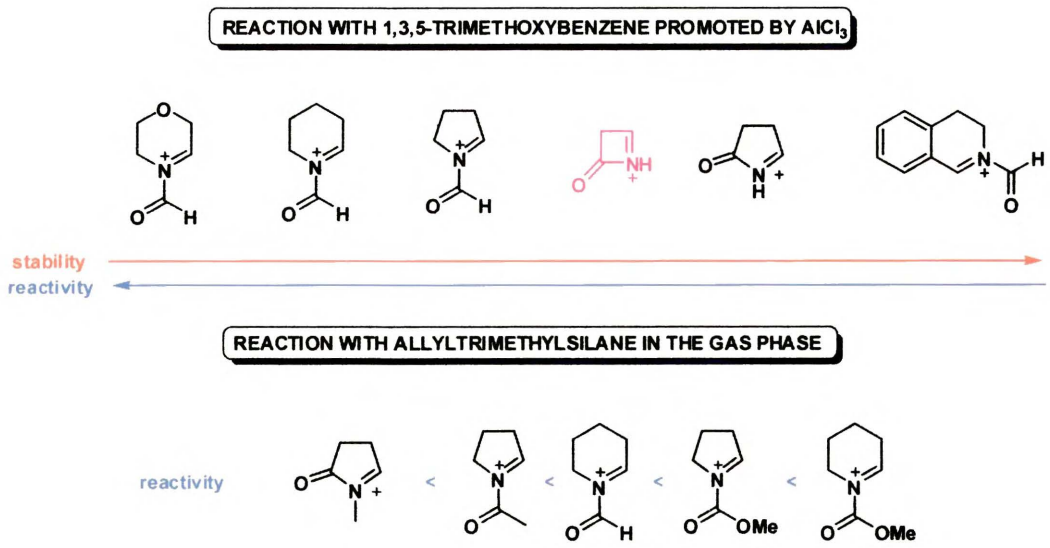


**Figure 2**



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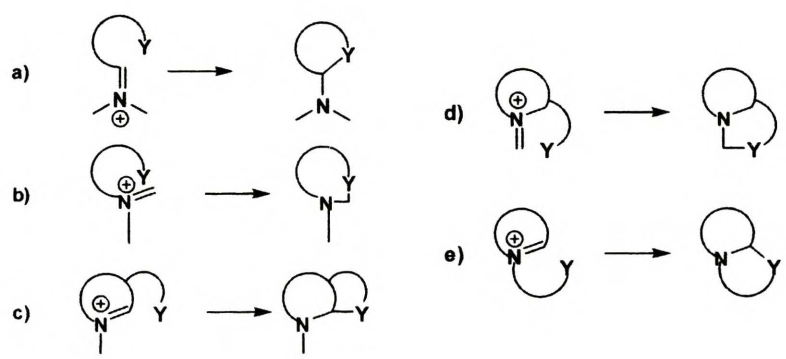
### 2.2. Mechanism and stereochemistry

Iminium cations undergoes variety of reactions with different nucleophiles. The outcome of the process depends on their structure. Reaction conditions like, type of an acid used for ionization, structure of a nucleophile, solvent, temperature and concentration of reagents affect the result, as well. It is important to note that iminium ions used for the synthesis of chiral nitrogen containing compounds offer usually the most convenient and promising route. Such compounds are widely distributed in nature and their relative and absolute configuration is known to play important role for biological activity.

Iminium ions undergo an intramolecular Mannich reaction leading to variety of azacycles (Scheme 11). Examples **a)** and **b)** represent the formation of monocyclic compounds through exocyclic-trigonal and endocyclic-trigonal processes, respectively.[26] Cases **c)**, **d)** and **e)** show formation of bicyclic compounds.




**Scheme 11**

The stereoelectronic effects determinate the success and the stereochemical pathway of the nucleophilic addition to iminium ions.[11] The addition of a nucleophile to the upper face of **A** proceeds *via* the skew-boat intermediate **B** whereas that to the lower face proceeds via the chair-like intermediate **C**. Consequently, the transition state leading to **C** should be preferred (Figure 3).

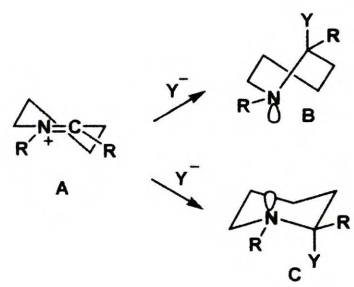



**Figure 3**

[26] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734



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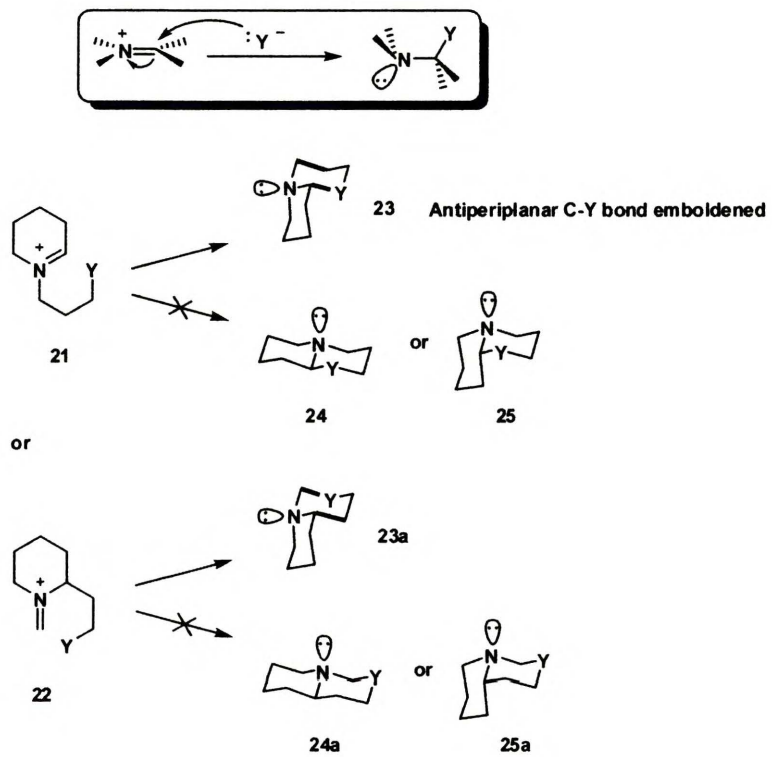
Usually an antiperiplanar orientation of an unshared electron pair of the nitrogen atom and the entering nucleophile is favored (Scheme 12). This relationship is particularly visible in the case of intramolecular reactions.[27] A consequence of the preference of the *anti* addition is formation of a single conformer of the azacyclic product. Cyclization of *N*-alkyliminium salts **21** and **22** leads to exclusive formation of *cis*-quinolizidine conformers **23** and **23a** which have the favored antiperiplanar orientation of unshared electron pair and the entering nucleophile, even though trans-quinolizidine is more stable than the alternative *cis*-quinolizidine conformer.[27]




**Scheme 12**

### 2.2.1. Diastereoselective approach

The diastereoselective approach in the synthesis of various nitrogen containing compounds plays highly important role. It can employ of chiral iminium cation, chiral nucleophile, or both chiral components. Usually intramolecular processes starting from non racemic substrates proceed with excellent diastereoselectivities and good yields. However, this approach may have some disadvantages. Particularly, in the case of introduction of chiral, expensive auxiliary to the substrate since its subsequent recovery after reaction can be often a tedious process. More attractive is a chiral pool approach which uses readily available natural products, such as carbohydrates or amnio acids of defined stereochemistry as starting material, and incorporate existing there stereogenic centers into the target molecule.

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[27] Overman, L. E.; Robichand, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300



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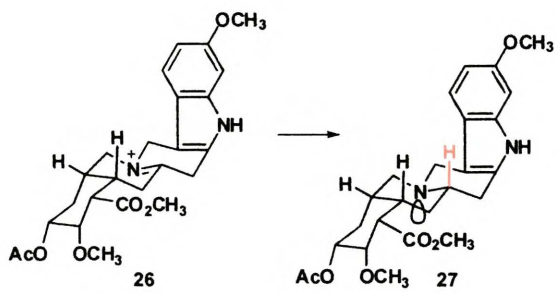
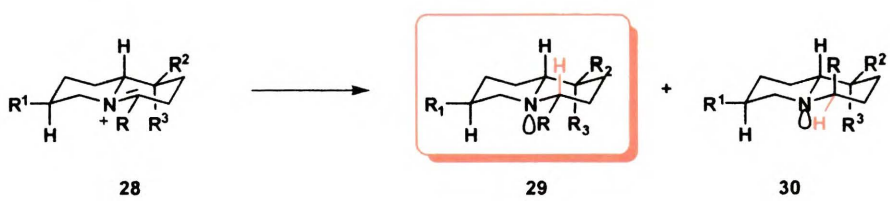
The high diastereoselectivity in inter- and intramolecular reactions of iminium ions with nucleophiles is particularly well visible in cases of conformationally rigid systems.[11] In the total synthesis of reserpine (antipsychotic and antihypertensive drug that has been used for the control of high blood pressure and for the relief of psychotic behavior), Woodward and co-workers[28] have reported reduction of quaternary iminium salt **26** with aqueous methanolic sodium borohydride to methyl *O*-acetyl isoresperate **27** (Scheme 13). As pointed out by Woodward,[28] product **27** was anticipated if the stereochemical pathway of the reaction was subjected to steric or thermodynamic control. It was also the expected one on the basis of the setreoelectronic control.




**Scheme 13**

Bohlmann and co-workers[29] have shown that the borohydride reduction of iminium salt **28** provided the isomer **29** as the main product (Scheme 14). The result indicates that in these reductions a stereoelectronic control operates, which is the antiperiplanar interaction between entering hydride ion and the unshared electron pair of the nitrogen atom. This phenomenon was discussed in details by Toromanoff.[30]




**Scheme 14**

This stereochemical preference was confirmed by Wenkert and collaborators[31] who showed that the borohydride reduction of compound **31** afforded **32** (Scheme 15). Similarly, Stork and Guthikonda[32] observed that the reduction of **33** provided (±)-yohimbine (**34**) (Scheme 15).

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[28] Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstad, R. W. *Tetraherdon*, **1985**, *2*, 1

[29] a) Bohlmann, F.; Winterfeldt, E.; Studt, P.; Laurent, H.; Boroschewski, G.; Kleine, K. M.; *Chem. Ber.* **1961**, *94*, 3151; b) Bohlmann, F.; Winterfeldt, E.; Boroschewski, G.; Mayer-Mader, R.; Gatscheff, B. *Chem. Ber.* **1963**, *96*, 1792

[30] Toromanoff, E. *Bull. Soc. Chim. Fr.* **1966**, 3357

[31] Wenkert, E.; Dave, K. G.; Lewis, R. G.; Sprague, P. W. *J. Am. Chem. Soc.* **1967**, *89*, 6741

[32] Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109



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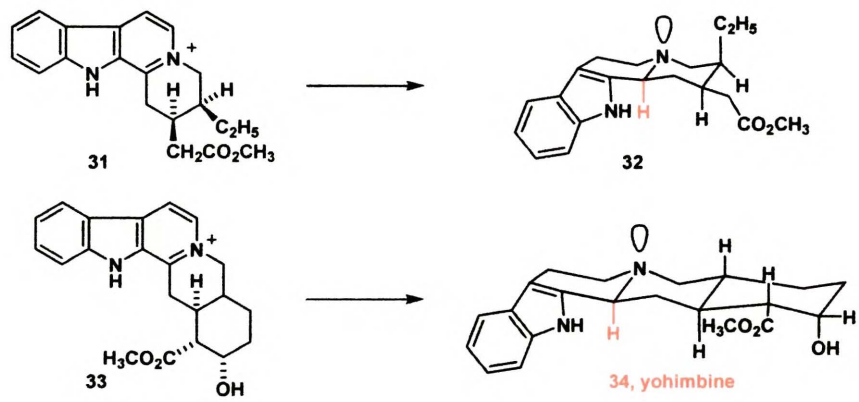
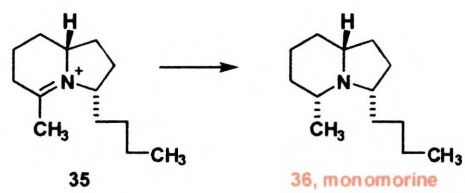



**Scheme 15**

Stevens and Lee[33] have reported a highly stereoselective synthesis of indolizidine alkaloid (±)-monomorine (**36**). In the last step of this synthesis, the piperidinium ion **35** was reduced with sodium cyanoborohydride to give only (±)-monomorine, as a sole product (Scheme 16).




**Scheme 16**

There are four possible transition states in the reduction of **35** wherein maximum orbital overlap can be maintained with the respect to the approaching hydride reagent and the electron pair on the nitrogen atom (Scheme 17). Two of them (red arrows, **37**, **38**) require boat-like transition state in order to satisfy the stereoelectronic requirements and therefore are unfavorable kinetically. Of the two possible chair-like transition states (Scheme 17, blue arrows **37**, **38**) the latter suffers from strong steric interaction between the entering nucleophile and C8 pseudo-axial hydrogen. The process leading to **39** is thus disfavored in comparison with the process **37**→**36**.[33]

[33] Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102



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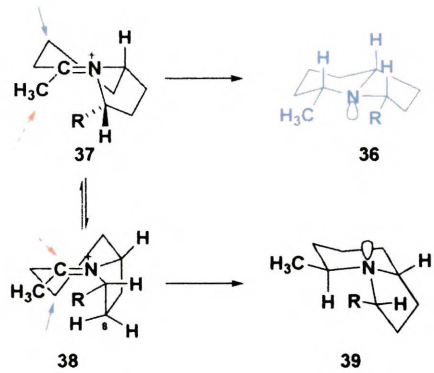
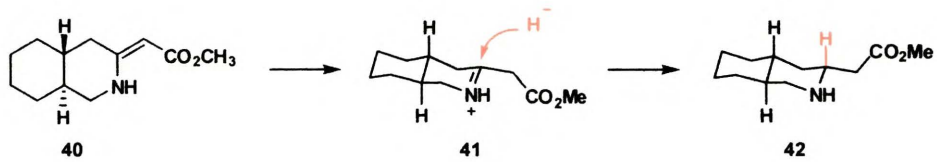


**Scheme 17**

Reduction of enaminoester **40** with sodium cyanoborohydride in acidic methanol provided exclusively the equatorial amionester **42** (Scheme 18). Eschenmoser and co-workers[34] have explained this result by invoking a streoelectronically controlled, antiperiplanar addition of the hydride ion to the lone pair of the nitrogen atom of the iminium ion **41**.



**Scheme 18**

Petrzilka, Felix and Eschenmoser[35] have shown that reaction of a cyanide ion with **43** gave mainly the product **44** (Scheme 19). Similarly, Riediker and Graf[36] observed that the addition of cyanide ion to **45** gave preferentially **46** which was the result of stereoelectronically controlled approach to the most hindered face of the iminium ion. Stereospecific addition of the cyanide ion to the rigid enamine **47**, which proceeded *via* the iminium salt **48** yielding compound **49**, has also been reported (Scheme 19).[37]

[34] Kümin, A.; Maverick, E.; Seiler, P.; Vanier, N.; Damm, L.; Hobi, R.; Dunitz, J. D.; Eschenmoser, A. *Helv. Chim. Acta* **1980**, *63*, 1158
[35] Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950
[36] Riediker, M.; Graf, W. *Helv. Chim. Acta* **1979**, *62*, 2053
[37] Mueller, R. H.; Diparo, R. M. *J. Chem. Soc. Chem. Commun.* **1975**, 565



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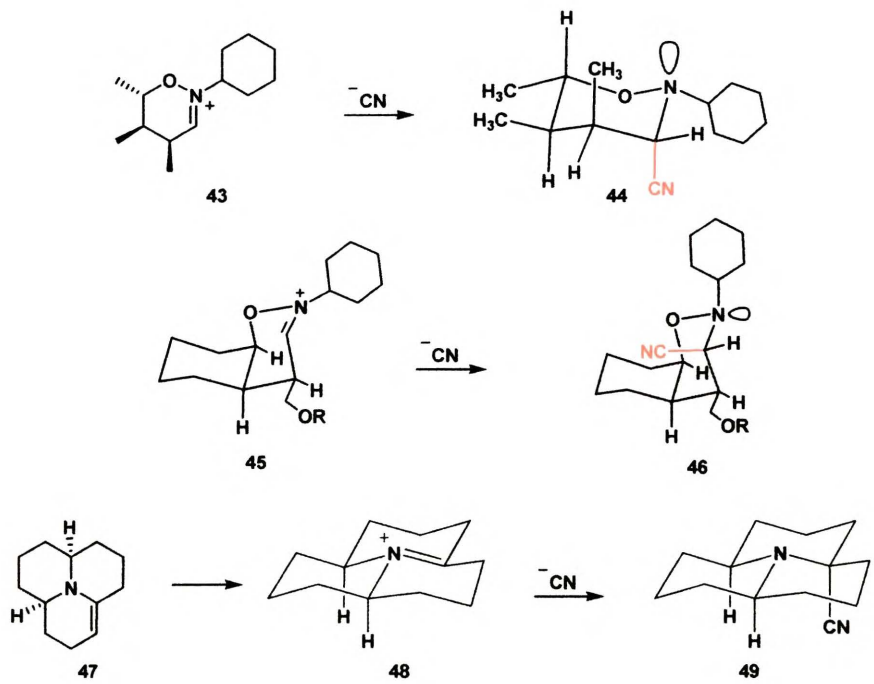

**Scheme 19**

Overman and Fukaya[38] have observed the unexpected preference of addition of organolithium and Grignard reagents to iminium ion **50**, which proceed from the more sterically hindered face yielding **51** (Scheme 20). The authors explained this result by a strong stereoelectronic control during addition of the alkyl group (**52**→**51A**→**51**). The other possible conformation **53** was eliminated because of a strong steric interaction[39] between the *N*-alkyl group and ring **A**. Similarly, lithium aluminium hydride reduction of **54** afforded **55** as the major isomer (Scheme 20). [40]

[38] Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454
[39] Johnson, F. *Chem. Rev.* **1968**, *68*, 375
[40] Overman, L. E.; Freekrs, R. L. *J. Org. Chem.* **1981**, *46*, 2833



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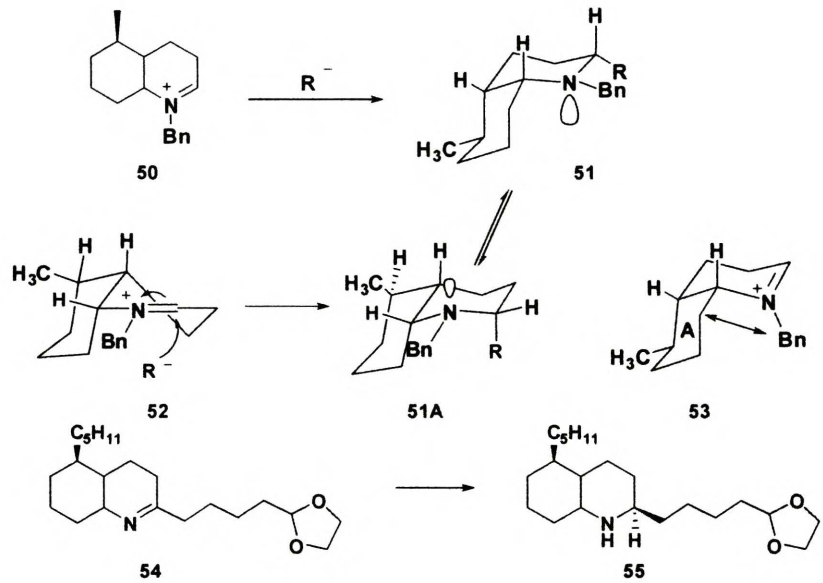
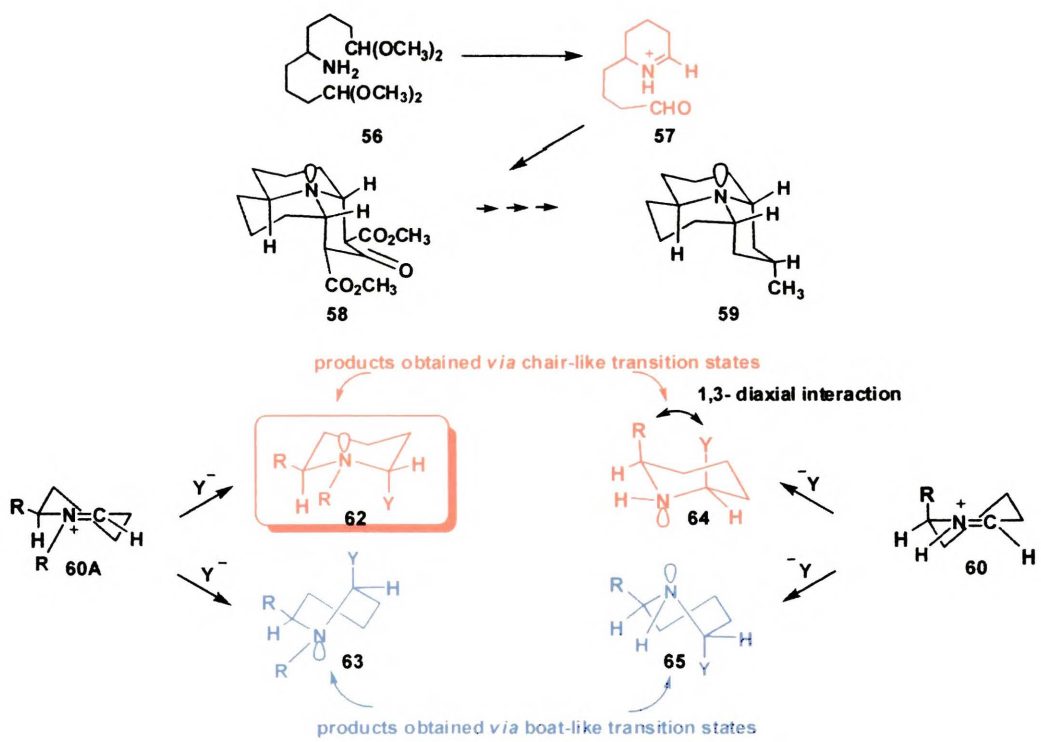


Scheme 20

Stevens and Lee[41] have reported an elegant synthesis of coccinelline (**59**) (Scheme 21). Compound **56** at pH=1 afforded intermediate **57** which was then treated with dimethoxycarbonyl acetone at pH=5.5 to afford a single tricyclic ketodiester **57** in 75% yield. Compound **57** was then converted into coccinelline **59**. This result shows that the Robinson-Schopf reaction[42] can take place with a remarkable control of stereochemistry.




Scheme 21

[41] Stevens, R. V.; Lee, A. W.M. *J. Am. Chem. Soc.* **1979**, *101*, 7032
[42] a) Robinson, R. *J. Chem. Soc.* **1917**, 762, 876; b) Schopf, C. *Angew. Chem.* **1937**, *50*, 779, 876



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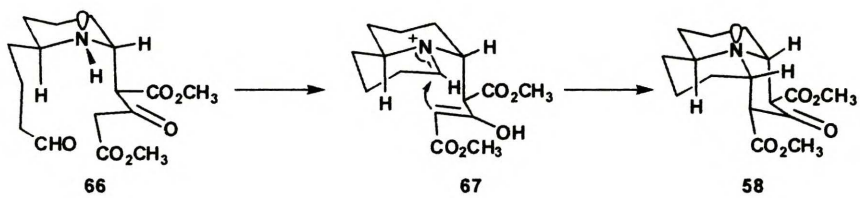
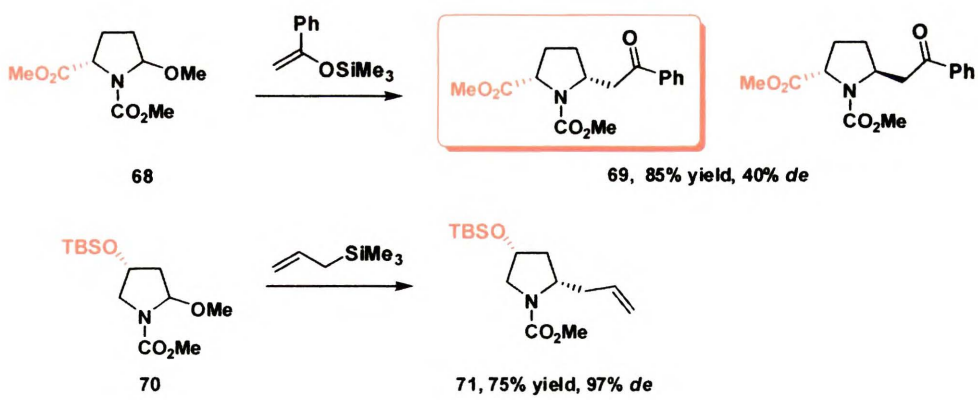
In principle, there are four possible transition states for attack of a nucleophile on a cyclic iminium ion **60** (Scheme 21). Two of them, leading to **63** and **65**, are boat-like transition states and therefore are kinetically disfavored. Of the two possible chair-like transition states, leading to **62** and **64**, the latter suffers from an unfavorable 1,3-diaxal interaction between the R group and the entering nucleophile. Therefore transition state leading to **62** is preferred.[41] Consequently, the condensation of **57** with dimethoxycarbonyl acetone must yield the *trans* intermediate **66** which after transformation into **67** should provide the *cis- trans* tricyclic ketodiester **58**, with stereoelectronic control of the ring closure (Scheme 22).[41]




**Scheme 22**

It is important to note that high stereoselectivity is also observed for simple pyrrolidines (Scheme 23). The presence of methoxycarbonyl substituent at C-2 of the pyrrolidine **68** leads to a 7:3 mixture of two diastereomers **69** with predominance of the *cis* isomer (in red frame).[43] Remarkably, a silyloxy substituent at C-4 in **70**, gives rise to a highly stereoselective reaction with allylsilane, producing the *cis* isomer **71**.[44]




**Scheme 23**

In contrast, a presence of the acetoxy function at C-3 in diastereomeric mixtures (at carbon atom bearing OMe) **72** and **73,** gave a surprisingly low selectivity of corresponding **74** and **75** which did not depend on the composition of starting mixture.[45] This was explained by a reversible loss of the OMe ion caused by participation of the acetoxy group and irreversible nature of the allylation reaction. In the case of similar allylation reaction of **76**, *trans* isomer **77** is formed exclusively (Scheme 24).[46,47]

---

[43] Asada, S.; Kato, M.; Asai, K.; Ineyama, T.; Nishi, S.; Izawa, K.; Shono, T. *J. Chem. Soc., Chem. Commun.*, **1989**, 486.
[44] Renaud P.; Seebach, D. *Helv. Chim. Acta*, **1986**, *69*, 1704.
[45] Thaning M.; Wistrand, L.-G. *Helv. Chim. Acta*, **1986**, *69*, 1711
[46] Thaning M.; Wistrand, L.-G. *Helv. Chim. Acta*, **1986**, *69*, 1711



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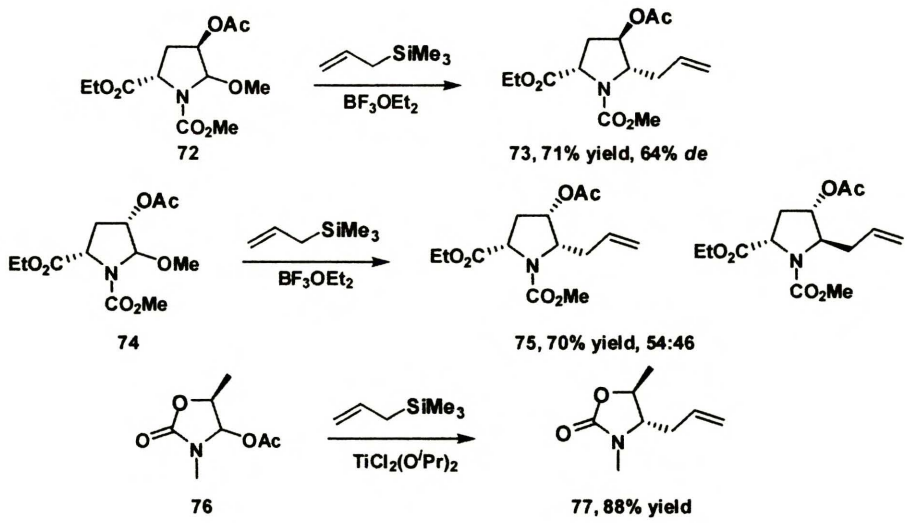
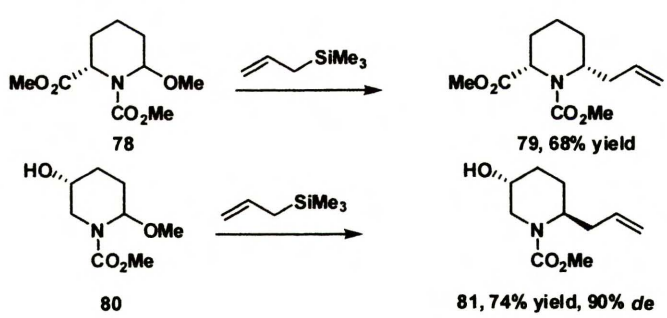



**Scheme 24**

The similar reaction on piperidine system proceeds with high selectivity (Scheme 25).[48,49] Thus, the ester substituent at C-2 in **78** induces high preference of *cis* attack at C-6 providing **79**.[48] This is in agreement with the expectation that the C-2 methoxycarbonyl function is axially disposed and addition at C-6 takes place from the axial direction. Less readily understood is the observation that the C-5 hydroxy function in **80** directs allylation at C-2 to a *trans* fashion providing **81** (Scheme 25).[49] The possible explanation can be based on intramolecular hydrogen bond which shifts hydroxyl to the axial position.




**Scheme 25**

Good stereoselectivity is observed in the case of chiral acyclic *N*-acyliminium ions obtained from urethane **82** (Scheme 26). The reaction with allylsilane leads to *syn* isomer **83** as a major product.[50]

---

[47] Liao Z.-K.; Kohn, H. *J. Org. Chem.*, **1984**, *49*, 4745.

[48] a) Irie, K.; Aoe, K.; Tanaka T.; Saito, S . *J. Chem. Soc., Chem. Commun*, **1985**, 633; b) Ciufolini, M. A.; Hermann, C. W.; Whitmire K. H.; Byme, N. E. *J. Am. Chem. Soc.*, **1989**, *111*, 3473

[49] Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.*, **1988**, *53*, 4118.

[50] Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 843



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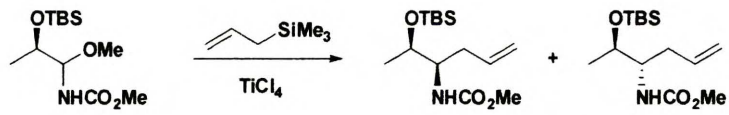
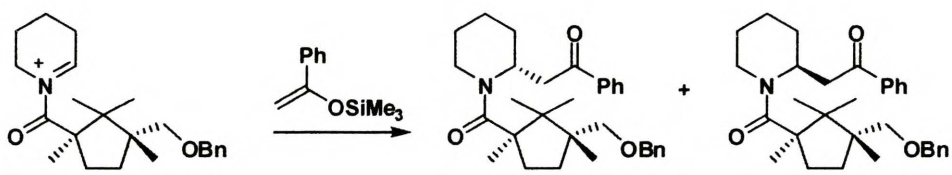



82 83, 85% yield, 80:20

**Scheme 26**

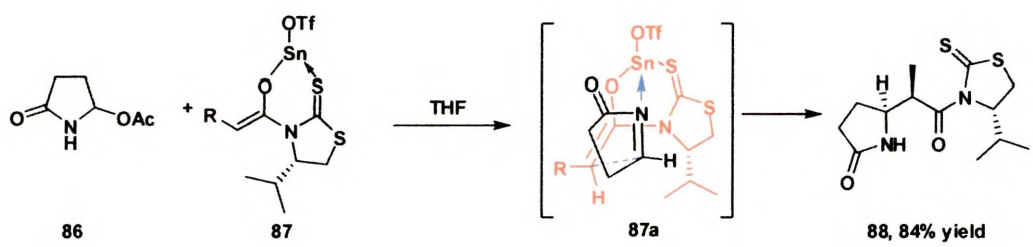
Stereogenic center located in the *N*-acyl substituent can also induce stereoselectivity of the addition to iminium ion. The chiral auxiliary in **84** is responsible for high diastereoselectivity in the reaction with the silyl enol ether of acetophenone which provide **85** (Scheme 27). In this process the *N*-acyliminium intermediate adopts *s-trans* conformation.[21]




84 85, 66% yield, 95:5

**Scheme 27**

Interesting interaction between imine nitrogen and $Sn^{II}$ atoms, which affects the stereochemical pathway of the addition, is observed in the reaction of **86** with the tin complex enolate **87** (Scheme 28).[51] The only *anti* isomer of **88** is formed *via* low energy transition state **87a**.




86 87 87a 88, 84% yield

**Scheme 28**

*N*-Acyliminium cyclizations have been also widely applied to heteroaromatic and aromatic nucleophiles.[8] Stork and Guthikonda[32] have shown that the cyclization of iminium ion **89** gave (±)-β-yohimbine **90** whereas Wenkert and co-workers[52] have observed that the acid catalyzed cyclization of enamine **91** yielded exclusively product **93** *via* cyclization of the iminium ion **92** (Scheme 29). In both cases, formation of C-C bond is the result of the *trans*-addition of the indole ring to the lone pair of the nitrogen, which is in agreement with discussed above stereoelectronic control.[51]

---

[51] a) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.*, **1988**, *110*, 289; b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; *Tetrahedron Lett.*, **1988**, *29*, 6133

[52] Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagamann, E. W.; King, J. C.; Ortio, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645



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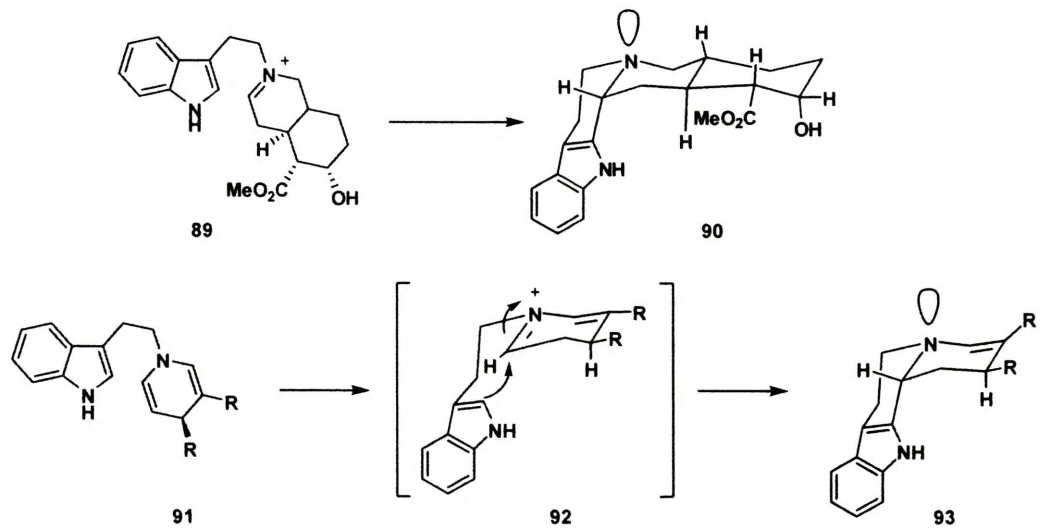
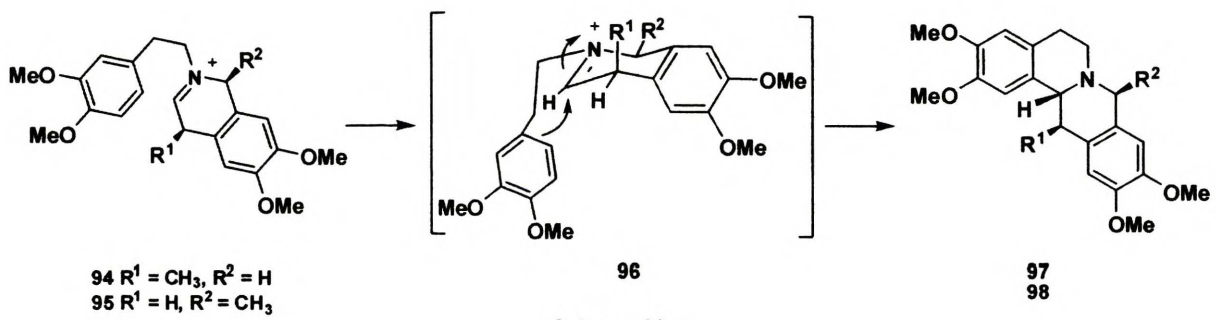


Scheme 29

Dean and Rapoport[53] have reported the stereoselective cyclization of iminium ion **94** to afford only *cis* isomer **97**. Similarly, cyclization of the imnium ion **95** gave exclusively **98**. Cyclization must proceed *via* transition state **96** (Scheme 30).



Scheme 30

Cook and collaborators[54] have shown that the Pictet-Spengler condensation of iminium salts of **99** gave in high yield only the *trans* isomer **102** (Scheme 31). This result can be explained if the geometry of the transition state corresponds to **100** → **101** where stereoelectronic effects are obeyed whereas steric interactions are reduced to the minimum.

[53] Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183

[54] Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M *J. Org. Chem.* **1981**, *46*, 164



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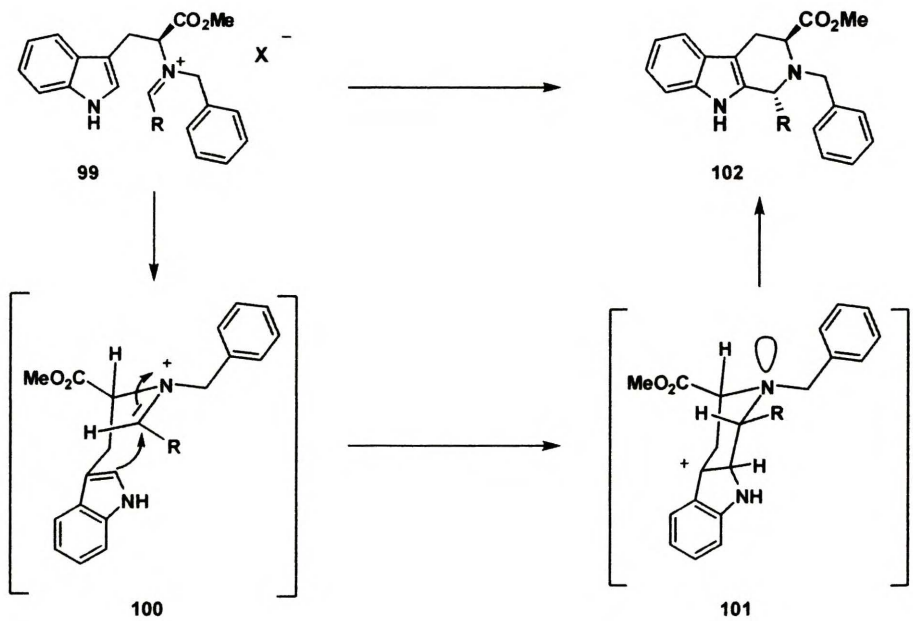
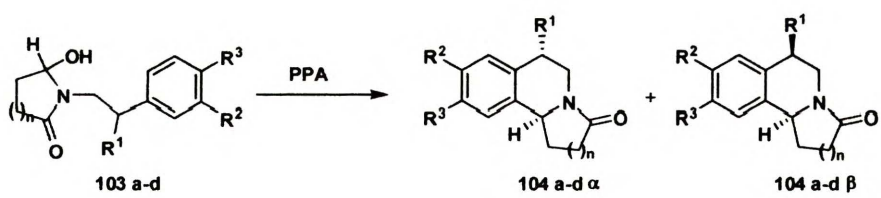



**Scheme 31**

Maryanoff's group[55] has shown that lactams **104a-d** are formed in the presence of polyphosphoric acid in moderate chemical yield and good diastereoisomer ratio (Table 1). It is important to note, that Brønsted acid does not affect the $\alpha$ to $\beta$ ratio. Empirical force field calculations (EFF) shown that both diasteromeric lactams differed only by about 0.5 kcal/mol, therefore it is scarcely believe that thermodynamics causes high stereoselectivity.[54]




| Entry | Lactam 103 | n | $R^1$ | $R^2$ | $R^3$ | Product 104 | α:β | Yield % |
|---|---|---|---|---|---|---|---|---|
| 1 | **103a** | 1 | Ph | OMe | OMe | **104a** | 90:10 | 50 |
| 2 | **103b** | 1 | DMP | OMe | OMe | **104b** | 90:10 | 60 |
| 3 | **103c** | 1 | Ph | H | H | **104c** | 93:7 | 60 |
| 4 | **103d** | 2 | Ph | H | H | **104d** | 96:4 | 74 |

**Table 1**

The cyclization shown above is a two-steps process (Scheme 32).[54] The generation of the intermediate arenium ion by ring-closing attack of the carbonium ion on the aromatic ring is probably rate-determining step. Aromatization *via* the 10a-proton abstraction from **107** is presumably very fast. The formation of two types of arenium ions, **106** and **107** is possible. Cyclization pathway (**b**) proceeds *via* a boat-like transition state that leads to a highly strained intermediate ion **106** (Dreiding molecular models, require a planar nitrogen). While pathway (**a**) involves a chair-like transition state that affords ion **107** being in a stable chair conformation. It is why

[55] Maryanoff, B. E.; McComsey, D. E.; Duhl-Emswtler, B. A. *J. Org. Chem.* **1983**, *48*, 5062



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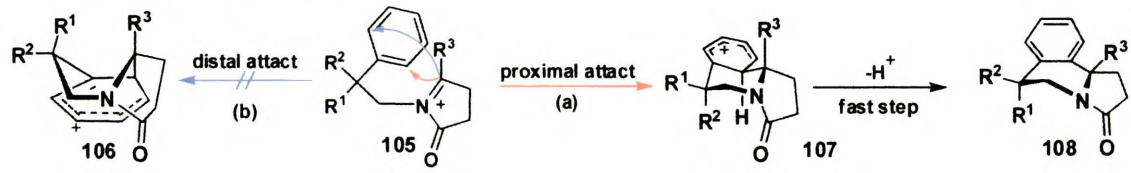
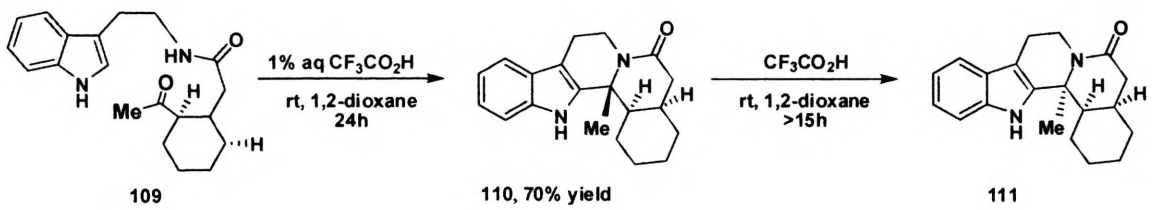
geometry of the product, **108**, must be determined by the conformational preferences of the substituents $R^1$ and $R^2$ in arenium ion transition state **107**.



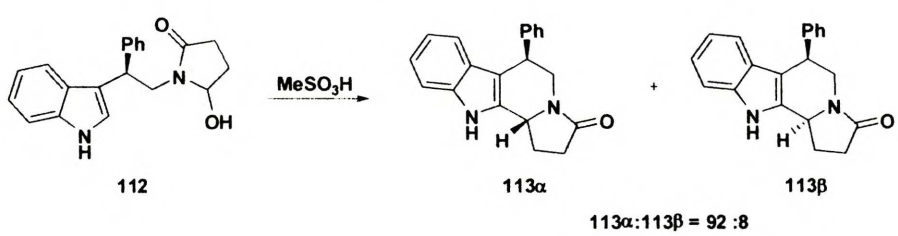

**Scheme 32**

However, isomerization of lactams can take place under special circumstances such as use of 3-indenyl nucleophile.[54, 56] During the cyclization of **109** with 1% aqueous $CF_3COOH$ only lactam **110** is formed.[55] In the case of applying of a molar amount of concentrated $CF_3COOH$ compound **110** is converted into its epimer **111** (Scheme 33).[55]




**Scheme 33**

The mechanism of lactam epimerization appears to be an $S_N1$-like heterolytic cleavage of the carbon-nitrogen bond rather than a reverse *N*-acyliminium ion cyclization.[55, 57] Fortunately, *N*-acyliminium ion cyclizations with nucleophilic heterocycles usually are performed under mild acidic conditions. Moreover, the ring closure is rapid and therefore no equilibration is observed. Cyclization of **112** to **113** with ethanolic methanesulfonic acid at room temperature may serve as an example (Scheme 34).[54]




**Scheme 34**

It is worth to mention, that in the Institute of Organic Chemistry PAS a five steps synthesis of enantiopure *cis* and *trans*-1,2-dihydroxyhexahydropyrroloisoquinolines (**116**) has been developed.[58] The synthesis started from lactones (**114**), derived from D-ribose or L-tartaric acid, respectively (Scheme 35). The key step of this methodology is Lewis acid mediated cyclization involving *N*-acyliminium ions (**115**)

---

[56] Lounasmaa, M.; Brener, M.; Brunner, M; Soumalainem, H. *Tetrahedron* **1998**, *54*, 10205

[57] Lounasmaa, M.; Brener, M.; Soumalainem, H. *Heterocycle* **1998**, *48*, 1275

[58] Kałuża, Z.; Mostowicz, D., *Tetrahedron Asymmetry*, **2003**, *14*, 225



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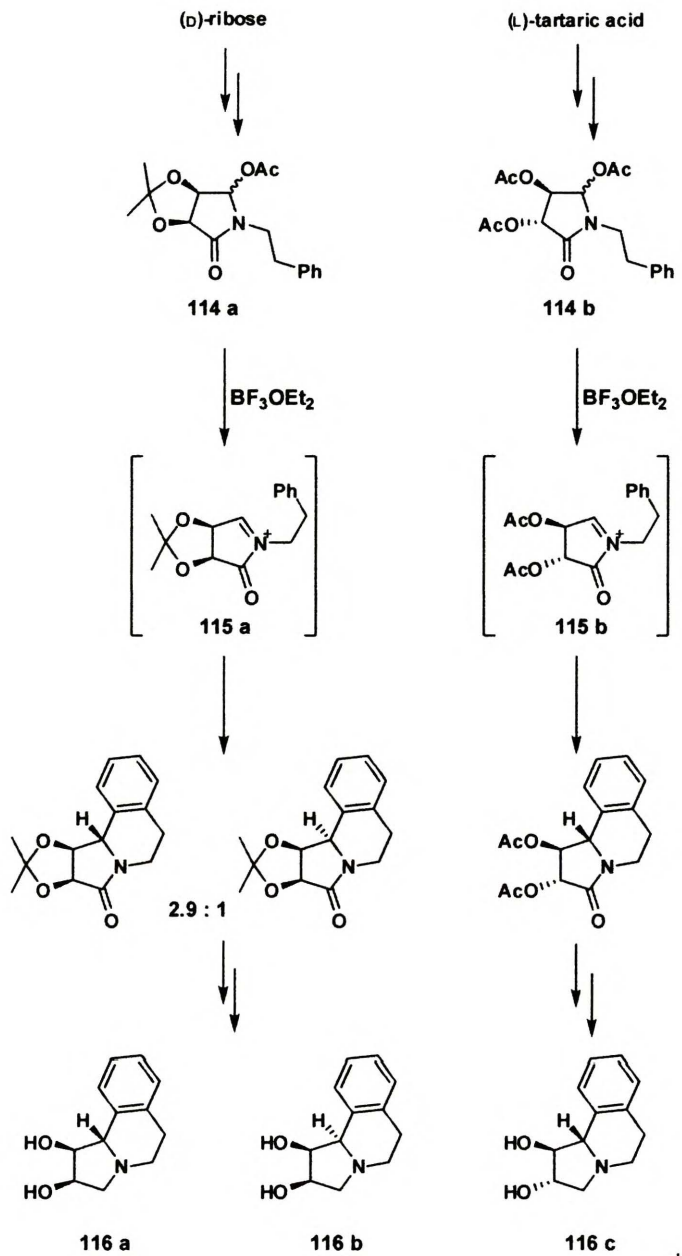


**Scheme 35**

This methodology has been successfully extended on 10b-substitiuted hexahydropyrolo-isoquinolines **118**. Suitable precursors for cyclization involving *N*-acyliminium ion have been obtained from L-tartaric acid. This methodology employs addition of a Grignard reagent to the imide carbonyl group of **117**, followed by one-pot acetylation-cyclization sequence (Scheme 36).[59] The degree of stereoselectivity strongly depended on the size of R substituent and, less so, on reaction conditions e.g temperature, concentration, or type of a Lewis acid.[59b]

[59] a) Mostowicz, D.; Wójcik, R.; Dołęga, D.; Kałuża, Z., *Tetrahedron Lett.*, **2004**, 45, 6011; b) Kałuża, Z.; Mostowicz, D.; Dołęga, D.; Mroczko, K.; Wójcik, R., *Tetrahedron*, **2006**, *62*, 943



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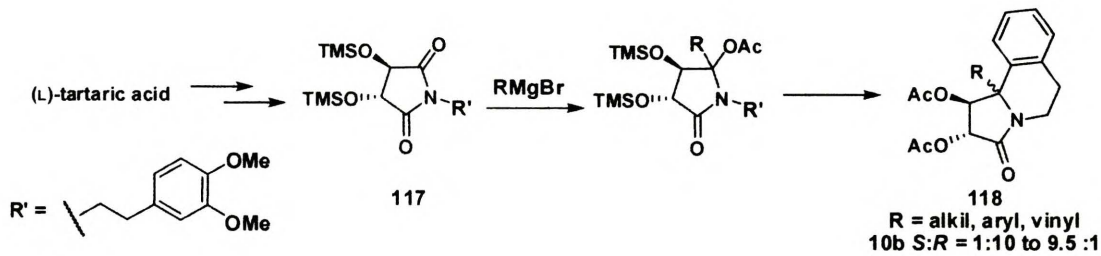


**Scheme 36**

The reaction of *N*-acyliminium ions with alkenes as nucleophiles has a broad utility in the synthesis of cyclic systems. Such ions are locked in the *s-trans* conformation and simply react as nitrogen-stabilized carbocations. Cyclization of a nitrogen-tethered, proximal alkene can occur by two different modes of attack to furnish products with two different ring size, *via* exocyclic **119** [*n-exo*-trig ring closure] or endocyclic **120** [(*n*+1)-*endo*-trig ring closure] carbocation intermediates (Figure 4).[26]

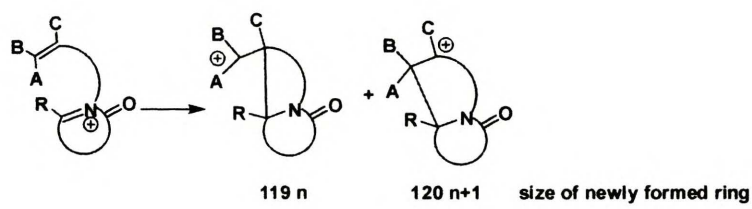


**Figure 4**

Subsequently, such carbocations could undergo standard transformation, such as addition of nucleophiles, elimination, or rearrangement, to yield the final reaction products.[8] In Figure 4 alkene is linked to the nitrogen atom, although it could be connected to another position. The stereochemistry is determinated by kinetic control which is result of conformational and stereoelectronic factors in the transition state. Mechanistically, an attack of nucleophilic alkene can be viewed in terms of antiperiplanar addition with respect to the nitrogen lone pair.

Although, the first *N*-acyliminium cyclization with an alkene was described in 1957,[60] two decades passed before this reaction has been seriously explored. Pioneering studies in the 1970s set the stage for wide application to the stereoselective synthesis of alkaloids.[13,17]

Cyclizations showed in Scheme 37 are 6-*endo*-trig process and involve chair-like transition state.[22,61] The geometry of the double bond is retained. Also, an influence of the configuration of stereogenic center in the side chain bearing π-nucleophile have been studied. In the case of a substituent adjacent to the nitrogen atom **121**, pseudoaxial orientation is preferred leading to **123**. On the other hand, the equatorial orientation of substituent is preferred when it is in the α-position to the double bond like in **122** leading to **124** (Scheme 37).

[60] Belleau, B., *J. Can. Chem.* **1957**, *35*, 673
[61] a) Nossin P,. M. M.; Speckamp, W. N. *Tetrahedron Lett.*, **1980**, *21*, 1991; b) Hart, D. J.; Hong, W.-P. *J. Org. Chem.*, **1985**, *50*, 3670



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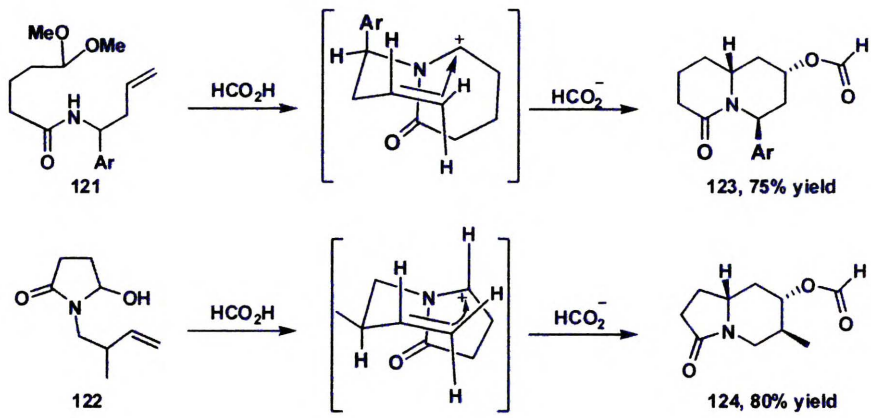
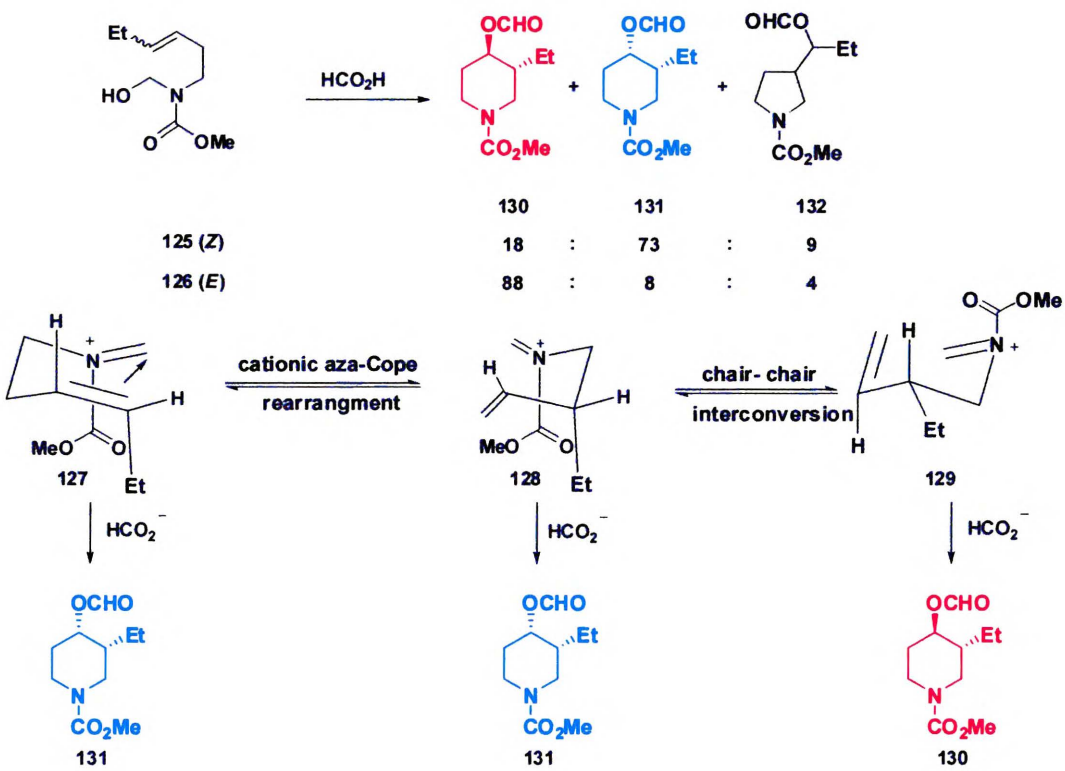



**Scheme 37**

Cyclization of isomeric, acyclic, unsaturated carbamates **125** and **126** does not show significant regio- and stereoselectivity (Scheme 38).[62] The lost of stereocontrol might be explained by occurrence of the cationic aza-Cope rearrangement in combination with chair-chair interconversion. As a rule, cyclization of **125** should occur *via* conformation **127** providing **131**. If sigmatropic rearrangement competes with the standard cyclization, **128** arises, but it should not affect the stereochemical outcome. Only after chair-chair inversion to **129** and subsequent cyclization, **130** is formed. The same mechanism is responsible for occurrence of product **131** in the cyclization of **126** (Scheme 38).[12]




**Scheme 38**

[62] Esch, P. M. PhD Thesis, University of Amsterdam, **1991**



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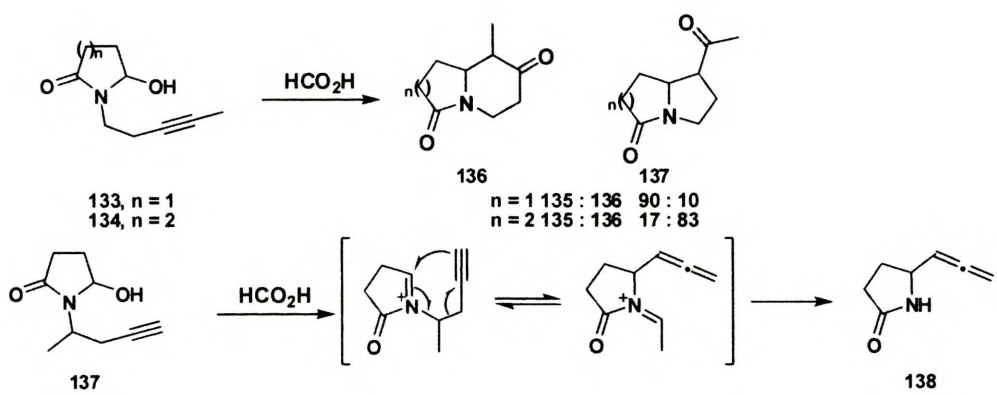
The regiochemistry of intramolecular reaction with *N*-acyliminium ions depends on more subtle factors e.g. size of the lactam ring. In general, *endo* cyclization is favored for terminal acetylenes, regardless of the influence of ring strain, whereas *exo* cyclization is favored with internal acetylenes, but only in the absence of a ring strain.[8, 11] The presence of stereogenic center in the lactam ring of cyclic *N*-acyliminium ion may, or may not create high stereoselectivity. In the case of five-membered lactam ring **133** preferentially two condensed systems having five- and six-membered (**136**) rings are formed (Scheme 39).[18] In contrast, when 6-membered lactam **134** undergoes the same process, annulations leads mainly to the five-membered ring **135**.[18] The important factor is the greater stability of linear *versus* bent vinyl cation character. In the case of six-membered lactam the less strain bicyclic system is [4.3.0] than [3.3.0]. The second one dominates in the case of five-membered lactams.[18] It should be noted that alkynes can undergo rearrangement leading to allenyl product like in the reaction **137**→**138** (Scheme 39).[63]




**Scheme 39**

Activated alkenes, wherein the nucleophilicity is enhanced by silyl, thioether, silylmethyl, or stannylmethyl substituent, cyclize with some interesting stereochemical aspects.[15] For reactions involving allylsilanes, the regiochemistry is controlled by the β-effect;[64] thus new bonds are formed at the vinyl carbon distal from silicone (at the γ-position). Treatment of **139** with formic acid provides vinylpyrrolizidine **141** as a single isomer with good yield (Scheme 40).[64] The configuration of the double bond does not influence stereochemical pathway of the reaction. The high stereoselectivity of this reaction can be explained by the chair-like geometry of the π-complex **140**[64] and is consistent with an electrophilic addition mechanism, in which the double bond approaches anti to the unshared pair of the nitrogen atom providing *syn* hydrogen atoms at C-1 and C-8. Thus, stereochemical preference for the new carbon-carbon bond formation is determinated by stereoelectronic factors in the cyclizaton step.

[63] Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.*, **1984**, *106*, 1877

[64] Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N., *Tetrahedron Lett.*, **1985**, *26*, 3155



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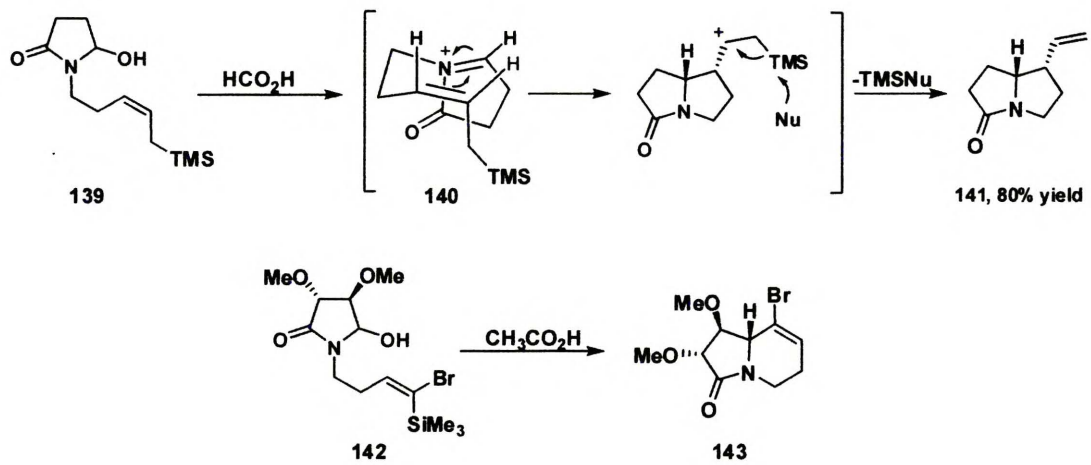
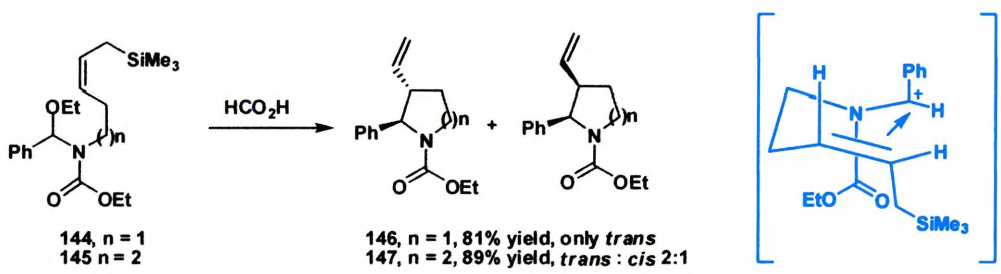



**Scheme 40**

Vinylsilane cyclization is governed also by generation of a carbocation β to silicon (β-silyl effect). Such cyclization was applied as the key step in the (+)-streptazoline synthesis **142**→**143** (Scheme 40).[65]

For acyclic *N*-acyliminium ion intermediates, intramolecular reactions usually proceed with good stereoselectivity.[64] Pyrrolidine **146** is obtained from **144** as pure *trans* isomer. It is the result of the favorable chair-like transition state with the (*E*)-iminium geometry. Under the intramolecular reaction condition, piperidine **147** was obtained from **145** in lower stereoselectively (2:1 mixture), with the *trans* isomer as the major product (Scheme 41).




**Scheme 41**

### 2.2.2. Enantioselective transformation of imines and iminium ions.

The scope of this chapter is to put more light on the most important enantioselective processes with the use of imines and iminium ions. Bearing in mind the large extent of the topic, only crucial problems will be presented.

Progress in enantioselective catalytic reactions of imines is rather slow in comparison to oxygen analogs. Mainly due to geometric isomers of the C-N double which are often under equilibrium state.[66] Therefore a possibility of

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[65] a) Flann, C.; Overman, L. E., *J. Am. Chem. Soc.*, **1987**, *109*, 6115; b) Heitz, M.-P.; Overman, L. E. *J. Org.Chem.* **1989,** *54*, 259

[66] (a) McCarty, C. G. *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; John Wiley & Sons: New York, 1970; Chapter 9; (b) Biørgo, J.; Boyd D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 757



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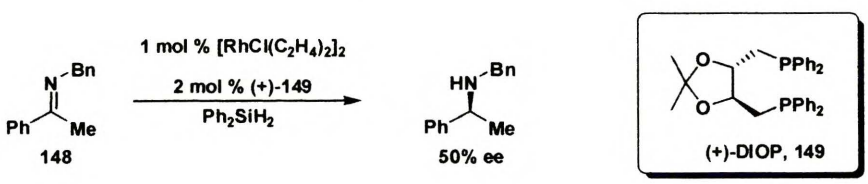
two transition states corresponding to both Lewis acid – imine complexes exists, which decreases selectivity. Moreover, due to the basic nitrogen atom, many Lewis acids form strong complexes with the starting material or product. Formation of such complexes causes usually a failure of the catalytic variant of reaction. Nevertheless, in the past decade, interesting catalytic reactions using imines as electrophiles have been reported.

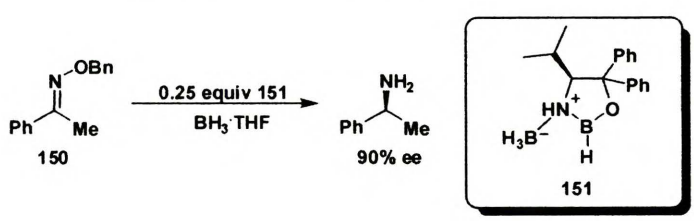
Asymmetric transformations of imine can be devided into two categories: reduction of imines and C-C bond formation. In comparison with the latter, the number of catalytic, enantioselective reductions of imines is high. In the case of C-C bond formation different strategies may by applied since the nucleophile can be activated by the external chiral ligand (Lewis base approach), or the imine can be activated with the chiral Lewis acid. Nevertheless, electrophilic activation of chiral H-donors by small molecule has emerged as an important method for enantioselective catalysis, with new applications and developments.

In 1973, Kagan and co-workers[67] reported the first example of catalytic enantioselective reduction of imines. The 50% enantiomeric excess was obtained in the reduction of *N*-(*α*-methylbenzylidene)benzylimine (**148**) using combination of rhodium complex with DIOP (**149**) (Scheme 42).




**Scheme 42**

The catalytic asymmetric hydroboration of imines were investigated in the 1980s. Itsuno and collaborators[68] developed the catalytic enantioselective reduction of oxime ether **150** using borane **151**. The good chemical and optical yield were obtained in the presence of 25 mol % of the chiral source (Scheme 43).




**Scheme 43**

In 1975, Scorrano[69] reported the asymmetric hydrogenation of a simple imine **148** using a chiral rhodium complex with diphosphine lingand like (-)-**149**. However, reaction did not proceed with good enantioselectivity (Scheme 44).

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[67] Langlois, N.; Dang, T.-P.; Kagan, H. B. *Tetrahedron Lett.* **1973**, 4865
[68] Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395
[69] Levi, A.; Modena, G.; Scorrano, G. *J. Chem. Soc., Chem. Commun.* **1975**, 6



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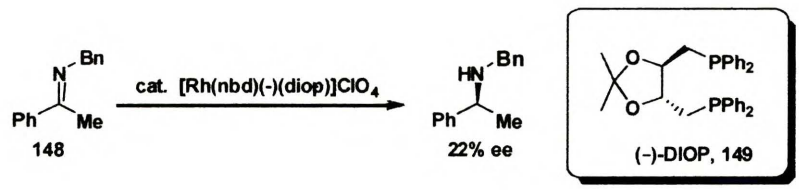
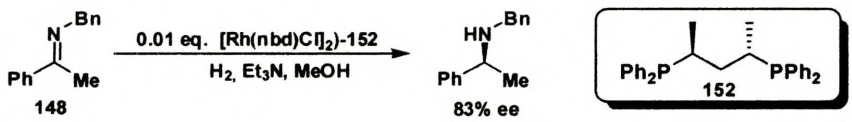


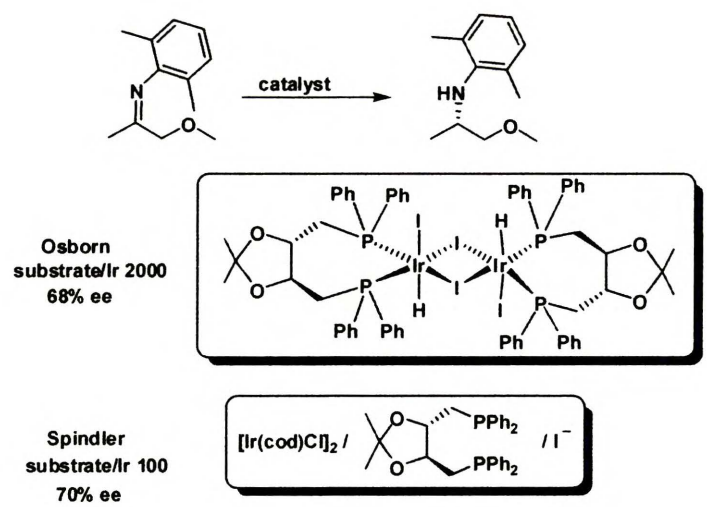

**Scheme 44**

The improvement on enantioselectivity was achived in the middle of the 1980s by Marko[70] and Bakos.[71] They investigated the asymmetric hydrogenation of imines using Rh-chiral diphosphine systems and founded out that the best result was obtained in the case of a use of ligand **152** in the presence of triethylamine (Scheme 45).[70]




**Scheme 45**

In 1990, Osborn[72] and Spindler[73] groups reported independently the enantioselective hydrogenation of imines with chiral iridium complexes (Scheme 46). Osborn[72] used $[Ir(III)(P–P)HI_2]_2$ prepared from $[Ir(I)(P–P)(cod)]BF_4$ and LiI. On the other hand, Spindler[73] used the *in situ* prepared catalyst. Both systems provided good chemical yields and moderate enantiomeric excesses. However, Spindler improved the method and scale it up to the industrial process of synthesis of potent herbicide (*S*)-Metolachor.[74]




**Scheme 46**

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[70] (a) Vastag, S.; Bakos, J.; Toros, S.; Takach, N. S. E.; King, R. B.; Heil, B.; Marko, L. *J. Mol. Catal.* **1984**, *22*, 283. (b) Bakos, J.; Toth, I.; Heil, B.; Marko, L. *J. Organomet. Chem.* **1985**, *279*, 23.

[71] Bakos, J.; Toth, I.; Heil, B.; Szalontai, G.; Parkanyi, L.; Fulop, V. *J. Organomet. Chem.* **1989**, *370*, 263

[72] (a) Chan, Y. N. C.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400. (b) Chan, Y. N. C.; Meyer, D.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 869

[73] Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558

[74] (a) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475. See also: Spindler, F.; Pugin, B.; Jalett, H.-P.; Buser, H.-P.; Pittelkow, U.; Blaser, H.-U. *Proceedings of the Conference on Catalysis of Organic Reactions, Atlanta 1996; Catal. Org. React., Chem. Ind. (Dekker).* **1996**, *68*, 153



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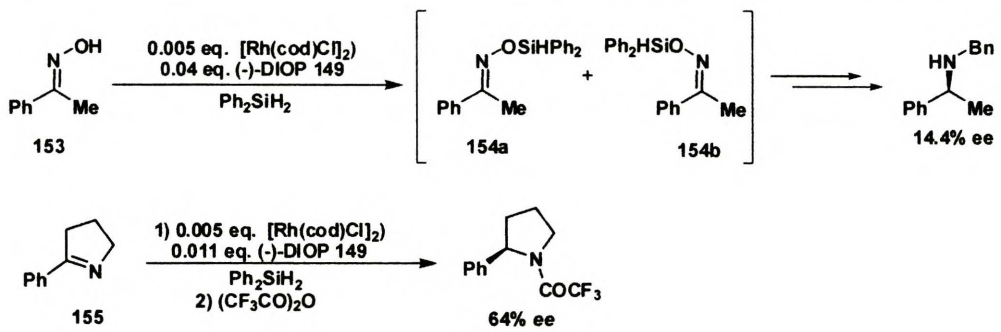
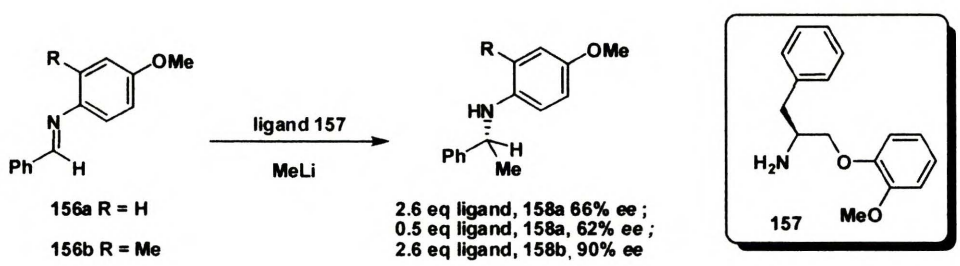
As it was mentioned above, Kagan[67] has developed the first enantioselective hydrosililation of imines in 1973. Almost 10 years later, Brunner[75] showed the second example (Scheme 47) . Reduction of **153** with diphenylsilane was performed in the presence of 0.5 mol % of $[Rh(cod)Cl]_2$ and 4 mol % of (–)-DIOP (**149**). The NMR studies showed occurrence of *E–Z* isomerization of an *O*-silylated oxime **154**, which is responsible for decreasing the enantioselectivity. The *ee* value was slightly improved in the case of cyclic imine **155** (Scheme 47).[76]




**Scheme 47**

The first report of the addition of organometallic nucleophiles to imines controlled by the chiral ligand appeared in 1990 by Tomioka's group[77] that developed stoichiometric additions of organolithium reagents (Scheme 48). Imines **156** derived from aryl aldehydes were successfully transformed into optically active amines **158** with high enantioselectivities in the presence of chiral tridentate amino ether **157**. The catalytic version of the reaction was also performed (Scheme 48). [78]




**Scheme 48**

More promising route has been proposed by Denmark's group[79] that used the chiral bis-oxazolidine ligand **160** (Scheme 49). Even in the case of a use of enolizable imine **159b**, catalytic version of the reaction proceeded with very good optical and chemical yield (Scheme 49).

---

[75] Brunner, H.; Becker, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 222
[76] Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 995
[77] Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681
[78] Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095
[79] Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797



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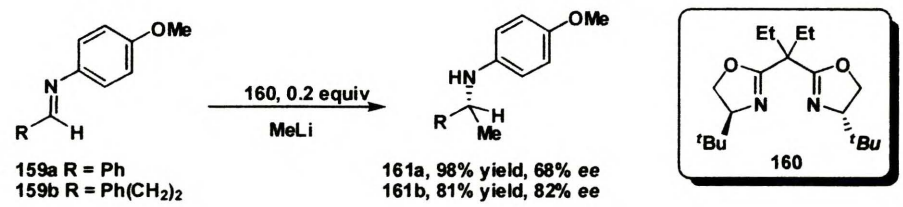
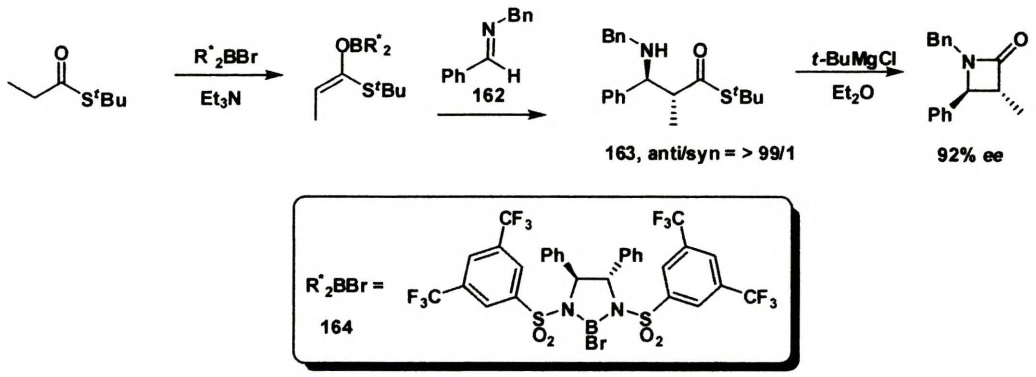


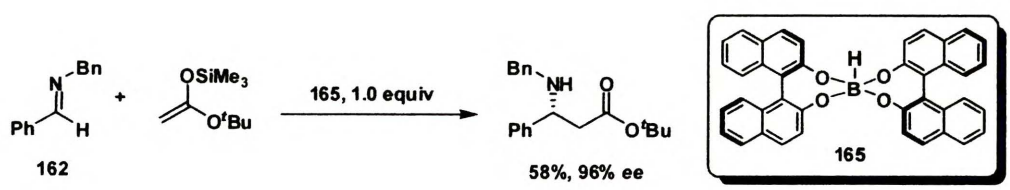

**Scheme 49**

One of the most important reaction of imines is Mannich-type process. In 1991 Corey's group[80] showed first example of enantioselective synthesis of β-amino acid thio-esters **163** followed by β-lactam formation using chiral boron enolates **164** (Scheme 50).




**Scheme 50**

In 1994, Yamamoto and co-workers[81] developed enantioselective reaction of imine **162** with ketene silyl acetal promoted by a stoichiometric amount of **165** - Brønsted acid assisted chiral Lewis acid (Scheme 51).




**Scheme 51**

The first example of catalytic, enantioselective Mannich-type reaction was reported in 1997 by Kobayashi's group.[82] They applied a novel chiral zirconium catalyst **166** (Scheme 52). Imines derived from aromatic and heterocyclic aldehydes reacted with silyl enolates with good optical and chemical yield. In the case of aliphatic aldehydes lower selectivities were noticed. [82]

---

[80] Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *39*, 5287
[81] Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520
[82] Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153



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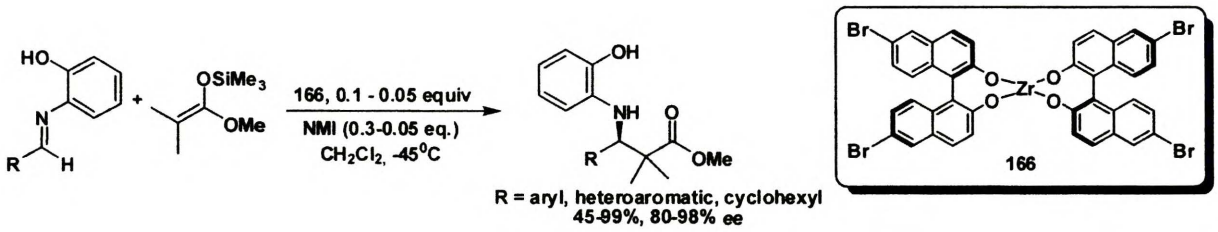
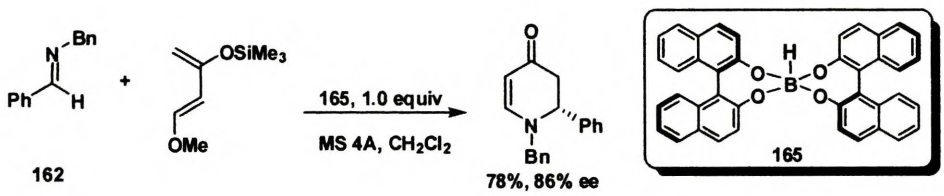


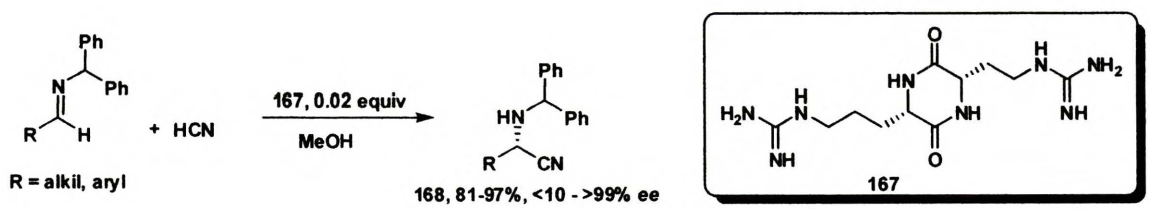

**Scheme 52**

Enantioselective Diels-Adler reaction of imines and activated dienes have also been reported. In 1992, Yamamoto[81,83] described a chiral boron catalyst **165** which was used in stoichiometric amount to promote [4+2] cycloaddition of imine **162** and Danishefsky's diene (Scheme 53).




**Scheme 53**

The asymmetric version of Strecker-type reaction has been also reported. In 1996 Lipton[84] showed that only 0.2 mol % of ligand **167** is necessary to obtain desired amino nitriles **168** (Scheme 54).




**Scheme 54**

*N*-Acyliminium ions are the most reactive imine derivatives. As it was mentioned above, the formation of a chiral Brønsted acid capable to catalyze transformation of *N*-acyliminium ions is a significant challenge. The organocatalytic acyl-Pictet-Spengler reaction promoted by thiourea **168** is first example of asymmetric catalysis with the *N*-acyliminium ions activated by chiral proton donor (Scheme 55).[85]

---

[83] (a) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749

[84] Iyer, M. S.; Gigstad, K. M.; Namdev N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910

[85] Taylor, M. S.; Jacobsen, E. N, *J. Am. Chem. Soc.* **2004**, *126*, 10558



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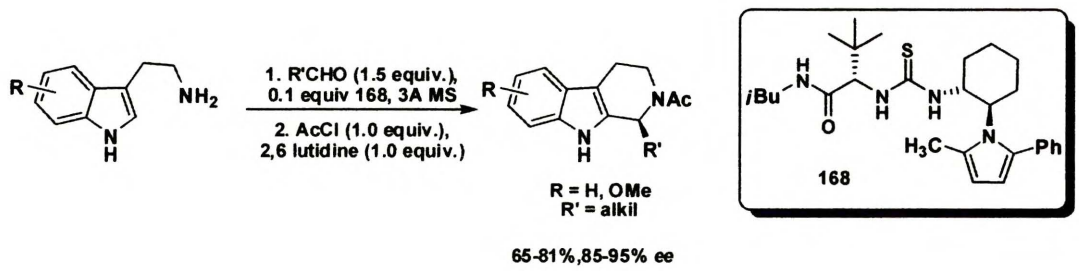
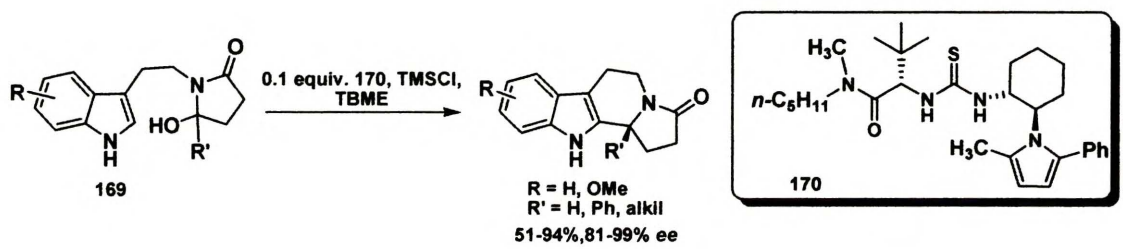



**Scheme 55**

In order to put more light on this reaction, a mechanism of the acid catalyzed cyclization of β-indolyl ethyl hydroxylactams **169** have been investigated.[86] The results of these investigation extended the scope of the reaction. The thiourea catalyst **170** in combination with TMSCl at low concentration appeared to be effective (Scheme 56).




**Scheme 56**

On the basis of spectroscopic studies of the reaction mixture, it was ascertained that formal dehydration of corresponding chlorolactam is rapid and irreversible. The enantioselectivity determinating step is probably, either the addition of indole to the *N*-acyliminium ion (path A, **B**→**C**, or path B, **B**→**D**), or alkyl migration of the spiroindoline intermediate (path A, **C**→**D**). However, in both cases the effective binding of the catalyst to the substrate is limited (lack of appropriate Lewis basic site). Authors proposed that thiourea catalyst **170** promotes cyclization by initiating dissociation of the chloride anion in the $S_N1$-type rate determining process leading to formation of a chiral *N*-acyliminium chloride-thiourea complex (Scheme 57).[86]

[86] Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2007**, *129*, 13404



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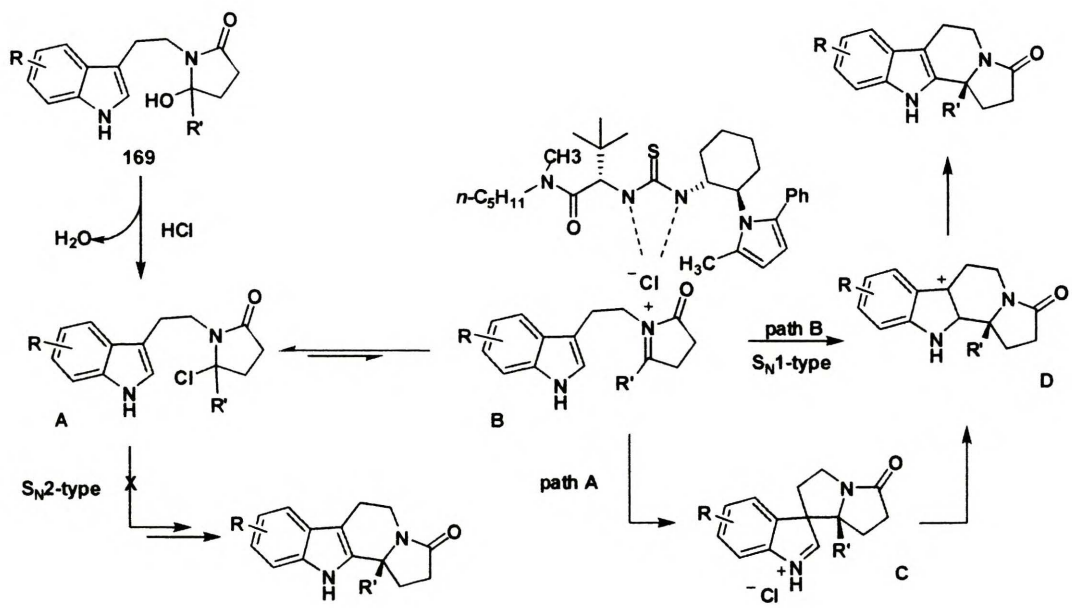
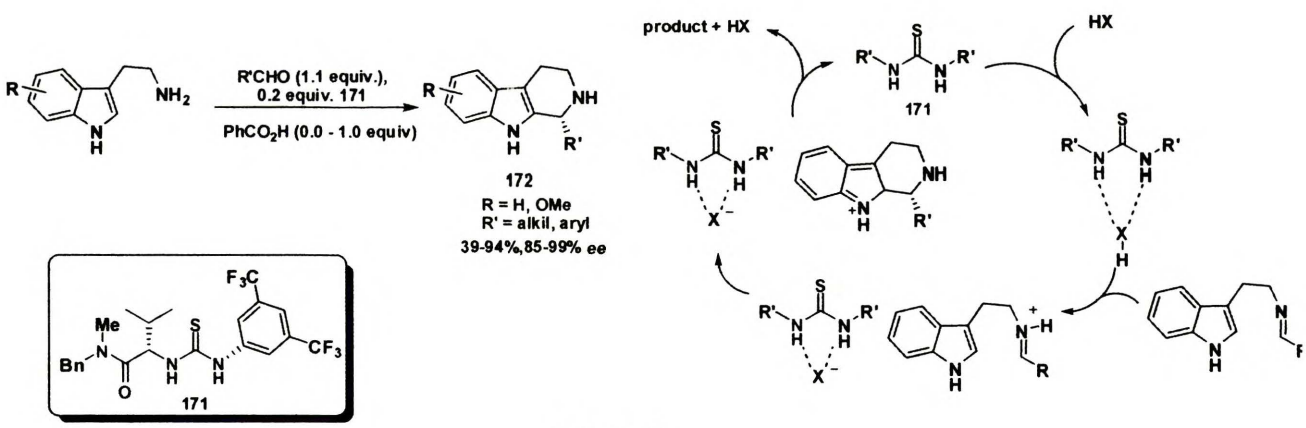



**Scheme 57**

Jacobsen's group[87] have shown that thiourea catalyst **171** with benzoic acid promotes catalytic asymmetric Pictet-Spengler reaction of sterically and electronically diverse imines, providing unprotected tetrahydro-β-carbolines **172** in high yield and excellent enantiomeric excess (Scheme 58).




**Scheme 58**

In order to extend the scope of this reaction, Jacobsen and co-workers[88] have applied pyrrole nucleophiles **173** and **174** (Scheme 59). Both enantiomeric excesses and reaction yields of the products have been high. However, when other aromatic nucleophiles like activated benzene, thiophen, or benzothiophene were used, the enantioselectivity of the process dropped to 0% *ee*.[88]

[87] Klausen, R. S.; Jacobsen, E. N., *Org. Lett.* **2009**, *11*, 887
[88] Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N., *Org. Lett.* **2008**, *10*, 1577



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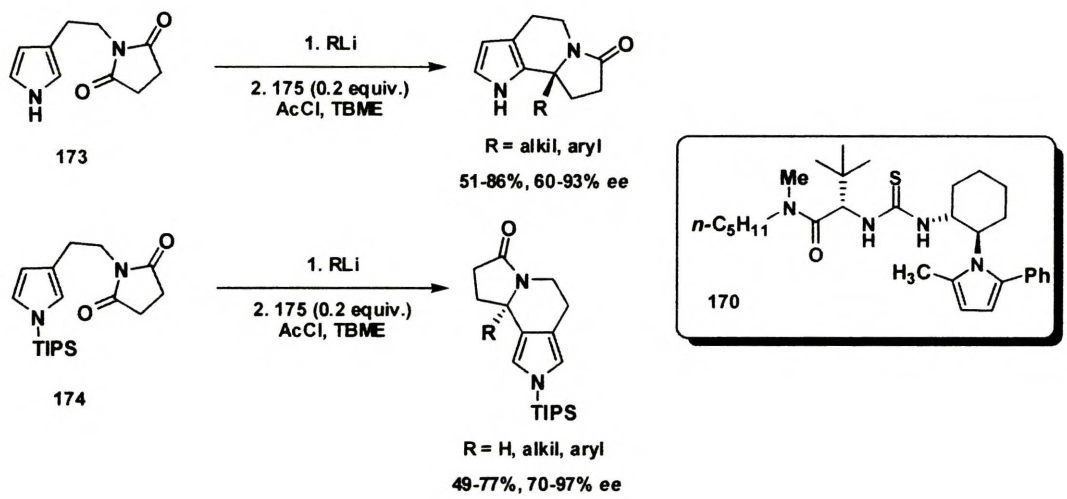
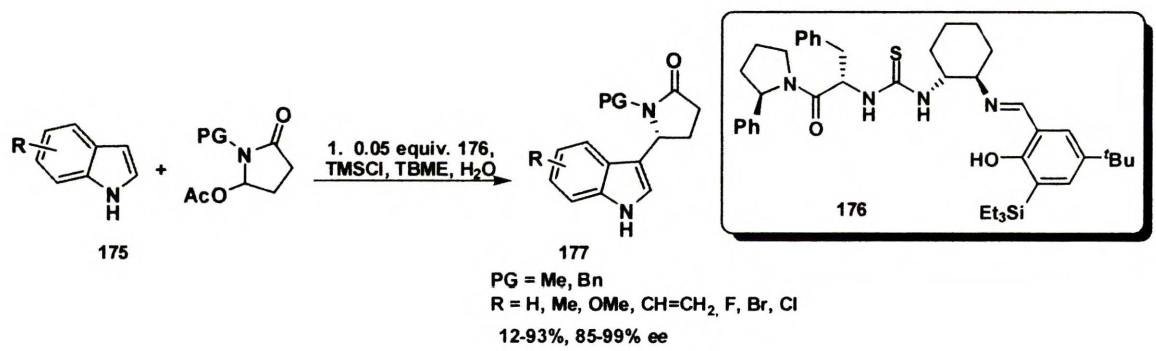



**Scheme 59**

The same group[89] have shown that intermolecular addition of activated indoles **175** to cyclic *N*-acyliminium ions promoted by chiral thiourea **176** which proceeds with excellent *ee* and yield. In the case of electron-deficient indoles **177**, enantioselectivities were similar, but yields decreased (Scheme 60).




**Scheme 60**

List and co-workers[90] showed the asymmetric Pictet-Spengler cyclization of an iminium diester derivate from **178** provided tetrahydro-*β*-carbolines **180** in 40-96% yield and with 62-96% *ee* (Scheme 61). As a catalyst triisopropylphenyl-substituted (*S*)-BINOL phosphoric acid **179** was used. Both aromatic and aliphatic aldehydes were accepted, though the method required the presence of two geminal ester functionalities. This serious drawback limited usefulness of the mentioned above approach.

[89] Peterson, E. A.; Jacobsen, E. N., *Angew. Chem., Int. Ed.* **2009**, *121*, 6446
[90] Seayad, J.; Seayad, A. M.; List, B., *J. Am. Chem. Soc.* **2006**, *128*, 1086



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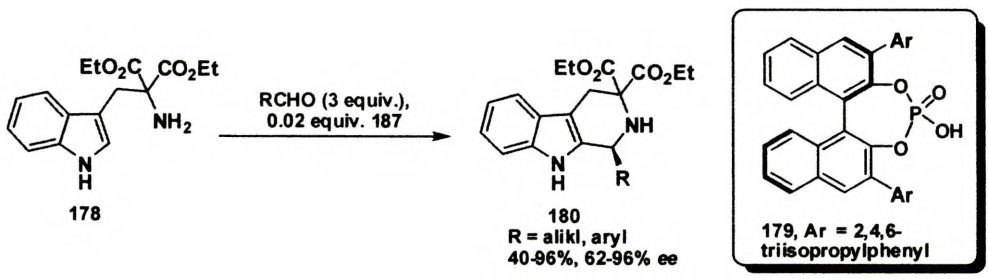
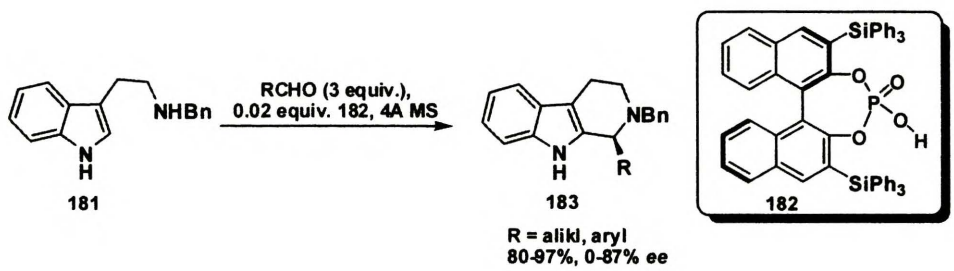


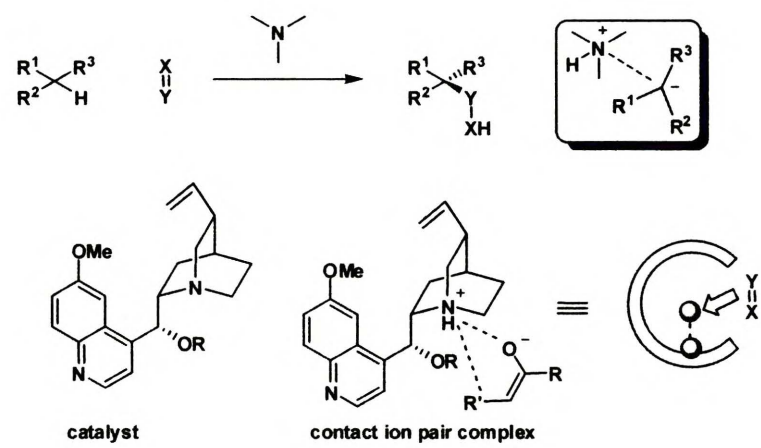

**Scheme 61**

In 2008 Hiemstra and co-workers[91] have shown promoted by the chiral phosphoric acid **182** Pictet-Spengler reaction of *N*-bezyltryptamine **181** with variety of aldehydes, both aromatic and aliphatic. The corresponding adducts **183** were obtained in good to high yields and with moderate to good *ee* (Scheme 62).




**Scheme 62**

Cinchona alkaloids also have also been applied in enantioselective processes involving *N*-iminium ion intermediates. In addition to amine function, several of these alkaloids bear acidic hydroxy group which is essential for high stereoselectivity. In most cases Cinchona alkaloids are used as bases to deprotonate substrates to form a contact ion pair between the resulting anion and protonated amine. This interaction leads to a chiral environment around the anion and permits enantioselective reaction with electrophile (Scheme 63). [92]




**Scheme 63**

[91] Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H., *J. Org. Chem.* **2008**, *73*, 6405
[92] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T., *Drug Discovery Today* **2007**, *12*, 8



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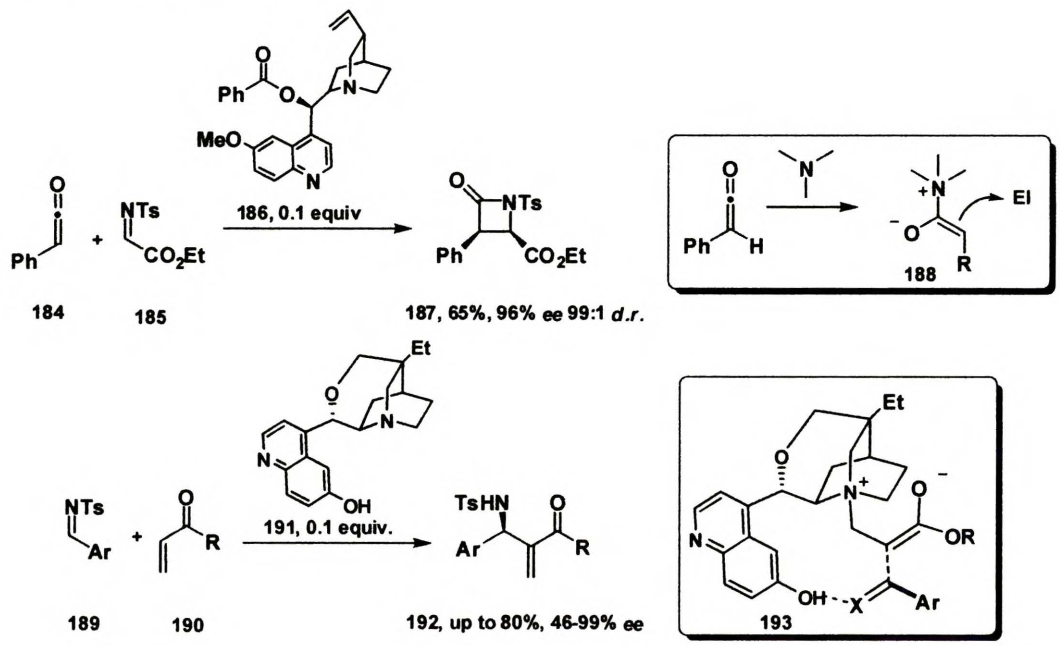
Cinchona alkaloids, however, may act as nucleophilic catalyst trough different mechanism (ammonium enolate catalysis). In that case, a ketene **184** interacts with a nucleophilic amine catalyst **186** to form 1-ammonium enolate intermediate **188** which subsequently reacts with electrophiles *e.g.* imine **186** providing the corresponding lactam **187** with 65% yield and 99% *ee* (Scheme 64).[93] Shi and co-workers[94] reported enantioselective aza-Baylis-Hillman reaction of *N*-tosylated aromatic imines **189** with acrylates **190** using catalyst **191** proceeding through the formation of a 3-ammonium enolate species **193**. Expected products **192** were formed with yield up to 80% yield and 46-99% *ee* (Scheme 64).




**Scheme 64**

[93] *a*) Taggi, A. E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III W. J.; Lectka, T., *J. Am. Chem. Soc.* **2000**, *124*, 7831; (*b*) Shah, M. H.; France S.; Lectka, T., *Synlett* **2003**, 1937; (*c*) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T., *Acc. Chem. Res.* **2004**, *37*, 592

[94] Shi, M.; Xu, Y.-M., *Angew. Chem.Int. Ed.* **2002**, *41*, 4507



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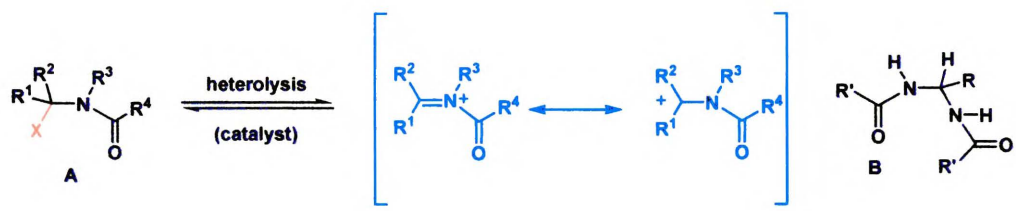
### 2.3. Sources of *N*-acyliminium ions

Due to the high reactivity, *N*-acyliminium ions are often generated *in situ* in acidic media. The most popular and effective method of generation is heterolytic cleavage of acetal-like structures of type **A** (Scheme 65). It is also possible to prepare *N*-acyliminium ions *in situ*, from two reactants. The group X can be hydroxy, alkoxy or acyloxy function. The acidic conditions generate mesomeric *N*-acyliminium ion by abstraction of the group X. However, when X is methanesulfonyloxy no catalyst is required, as thermal conditions are sufficient to produce the intermediate.[95] In the case of X = methoxyl or ethoxyl, precursor **A** is a stable molecule. This enables modification of the molecule under basic, or neutral conditions before generation of the *N*-acyliminium ion.




**Scheme 65**

Scarcely, X is chloride atom, sulfur, or nitrogen substituents. Chloride is usually used in the case of particularly reactive *N*-acyliminium species, especially when $R^1$ and $R^2$ are hydrogen atoms, or one of them is a carboxyl function. The latter species are supposed to be glycine cation equivalents and are useful for the synthesis of *α*-amino acids.[96] For ionization of chloride precursor, standard Lewis acids like $BF_3OEt_2$ and $SnCl_4$ are used. In the case of alkyl- or aryl-thio function, different ways of activations are possible. Therefore, mercury (II) acetate,[97] chloramines-T[98] and zinc reagents[99] have been employed for this purpose. Moreover α-diazocarbonyl compounds can be used in so-called carbenoid displacement reaction.[100] Moreover, precursors of *N*-acyliminium ions can bear nitrogen substitiuent like in case of bisamides, biscarbamates and bisureas **B** (Scheme 66). They are easily prepared from aldehydes and usually activated by treatment with Brønsted acid or $BF_3OEt_2$.[95]

There is several methods available for the construction of the foregoing precursors to *N*-acyliminium ions. The most direct synthesis of *N*-(1-hydroxyalkyl)-amides or carbamates engages an equilibrium process of the addition of primary or secondary amides to aldehydes or ketones (Scheme 66). In the case of intermolecular reaction, the fairly stable compounds are formed when formaldehyde (**194**), chloral (**195**) and glyoxylic acid or its ester (**196**) are used as electrophilic components.[95,101] The five or six-membered ring adducts (**197**, **198**) are formed only when very reactive aldehydes are used. In those cases the process has synthetic value.[13,17a,c,88]

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[95] Chamberlin, A. R.; Nguyen, D. H.; Chung, J.Y. L. *J. Org. Chem.* **1984**, *49*, 1682
[96] Zaugg, H. E. *Synthesis* **1984**, *85*, 181
[97] Stoodley, R. J.; Whitehouse, N. R. *J. Chem. Soc.,. Perkin Trans. I*, **1973**, 32
[98] Campbell, M. M.; Johnson, G.; Cameron, A. F.; Cameron, I. R. *J. Chem. Soc. Perkin Trans. I* **1975**, 1208
[99] Mori, S.; Iwakura, H.; Takechi, S. *Tetrahedron Lett.* **1988**, *29*, 5391
[100] Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc. Perkin Trans. I* **1988**, 833
[101] Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285



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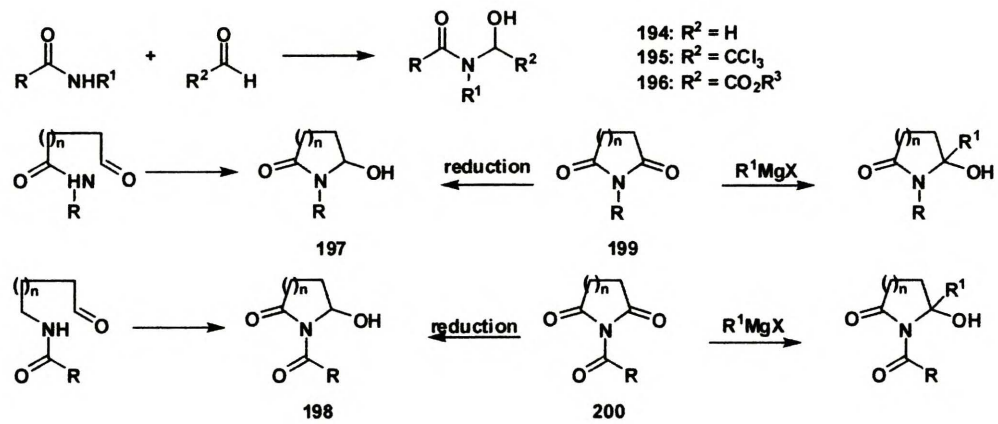


**Scheme 66**

A partial reduction of cyclic imides **199**, **200** with $NaBH_4$ or DIBAL-H is an alternative method for the preparation of **197** and **198** (Scheme 66).[102] An addition of Grignard reagents to **199** and **200** lead also to proper precursors of hemiacetals. However, obtained tertiary alcohols may undergo ring opening, as well as dehydratation (Scheme 66). Thus, their isolation may caused experimental problems. Nevertheless, this methodology has proven high synthetic usefulness.[103]

A one step protocol for the synthesis of alkoxy precursors **203** is based on addition of diethyl dicarbonate **202** to imines **201** (Scheme 67).[65,104] Acylation of **201** with acid chlorides **204** followed by treatment with ethanol in the presence of base leads to alkoxy amides **203**, as well (Scheme 67).[104a,b,105] Another methodology make use of simple acid catalyzed solvolysis of hydroxy compounds **199** or **200**, leading to corresponding alkoxy derivatives (Scheme 67).[104a] The same type of precursors can be obtained *via* a silicon assisted, TMSOTf catalyzed reaction,[106] or *via* $NaBH_4$ reduction of imidates **205**. (Scheme 67)[107]

---

[102] a) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437; b) Nagasaka, T.; Tamano, H.; Hamaguchi, F. *Heterocycles* **1986**, *24*, 1231; c) Thomas, E. W.; Rynbrandt, R. H.; Zimmermann, D. C.; Bell, L. T.; Muchmore, C. R.; Yankee, E. W. *J. Org. Chem.* **1989**, *54*, 4535

[103] a) Schoemaker H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951; b). Evans, D. A; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem.* Soc. **1982**, *104*, 3695

[104] a) Hiemstra, H.; Fortgens, H. P.; Stegenga, S.; Speckamp, W. N. *Tetrahedron Lett.*, **1985**, *26*, 3151; b) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron*, **1988**, *44*, 3919

[105] Biihme, H.; Hartke, K. *Chem. Ber*, **1963**, *96*, 600

[106] Johnson, A. P.; Luke, R. W. A.; Steele, R. W. J. *Chem. Soc., Chem. Commun.*, **1986**, 1658.

[107] a ) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron*, **1988**, *44*, 7063; b) Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J., *J. Org. Chem.*, **1989**, *54*, 4335



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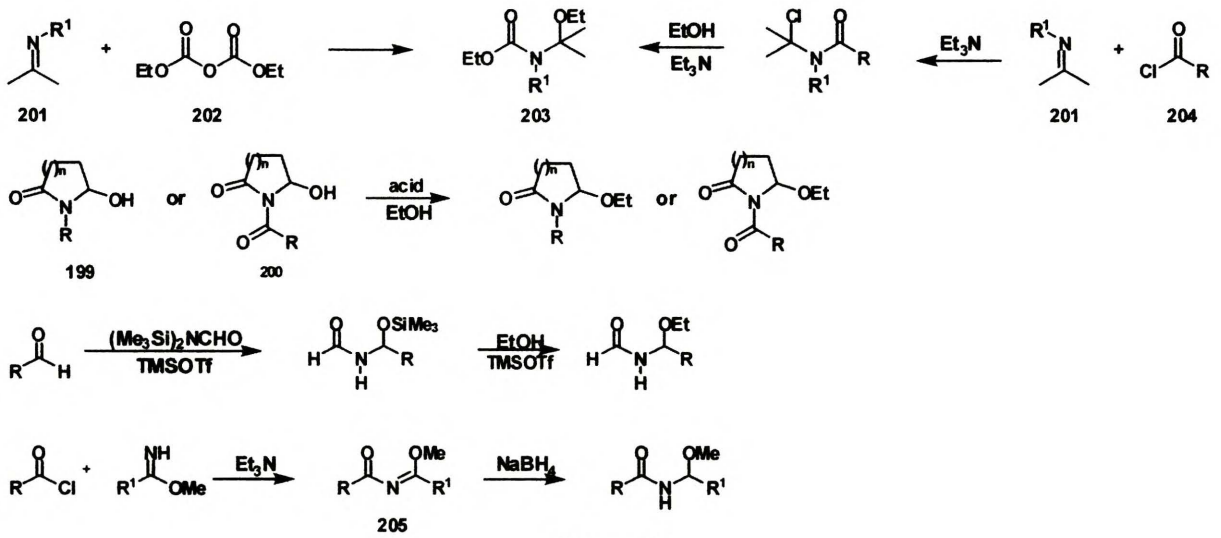
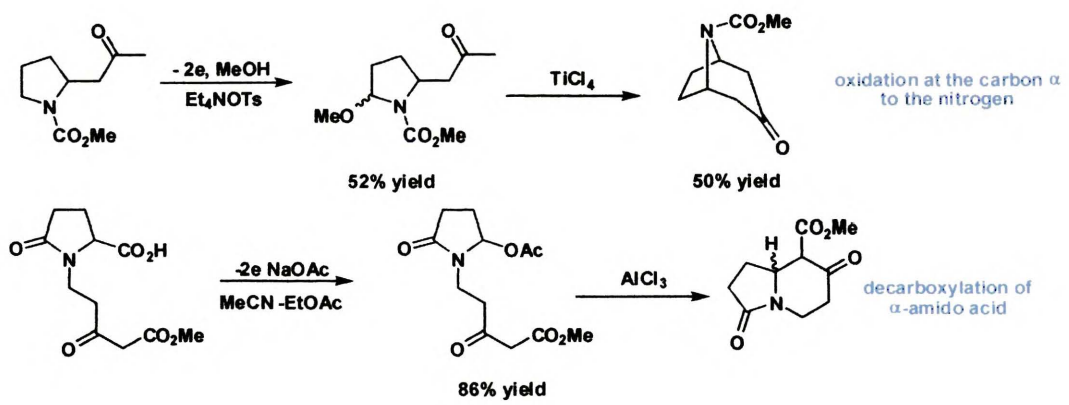


Scheme 67

Electrochemical oxidation of the carbon α to the amide's nitrogen is the versatile method for the synthesis *N*-acyliminium ion precursors.[108] A representative example is shown in Scheme 68. Electrochemical oxidative decarboxylation is also a useful method (Scheme 68).[109] Acyliminium ions are subsequently trapped with nucleophiles to form desired adducts for subsequent use.



Scheme 68

Precursors of *N*-acylimium ions can be obtained *in situ* from two reactants. Preparatively attractive method is the acid-mediated coupling of an aldehyde (ketone) with primary (or secondary) amide. This approach has been applied to the synthesis of five- and six-membered lactams *e. g.* **206a** and **206b** (Scheme 69).[110] One of the most

[108] a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172, b) Shono, T. *Tetrahedron*, **1984**, *40*, 811

[109] Moeller, K. D.; Tarazi, S.; Marzabadi, M. R. *Tetrahedron Lett.* **1994**, *35*, 1213

[110] a) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1991**, *56*, 2603; b) Marson, C. M.; Grabowska, U.; Walsgrove, T. *J. Org. Chem.* **1992**, *57*, 5045; c) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.;Baures, P. W. *J. Org. Chem.* **1994**, *59*, 284; d) Marson, C. M.; Grabowska, U.; Fallah, A.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1994**, *59*, 291.



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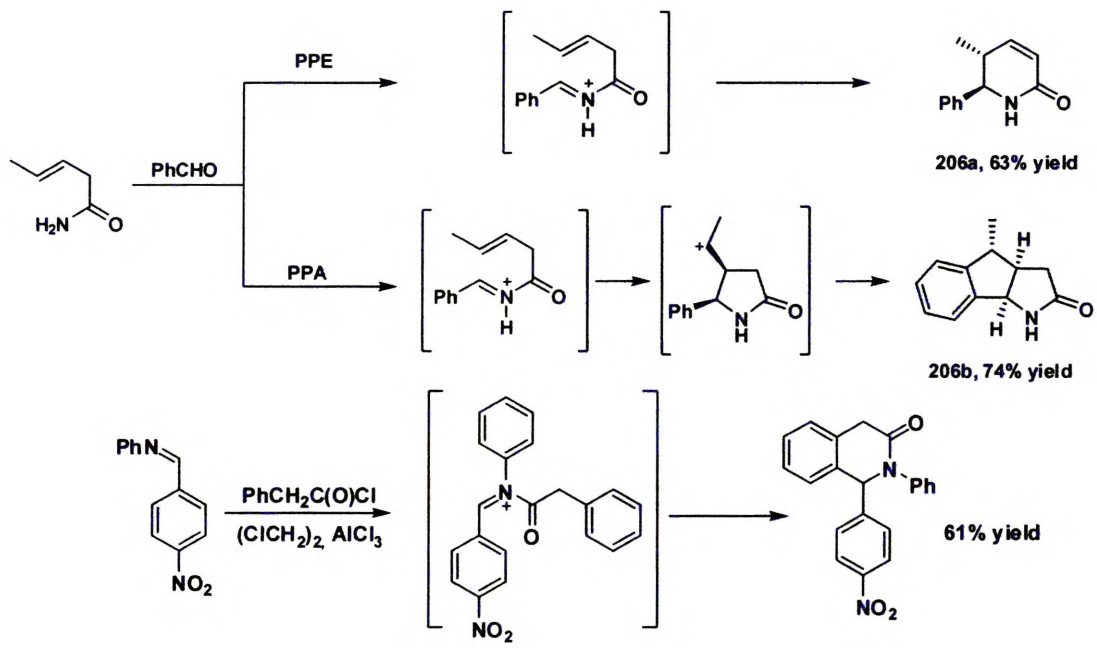
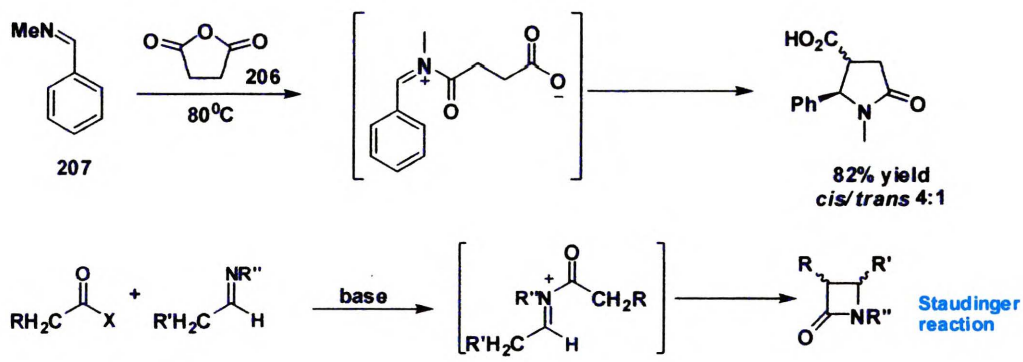
direct route to *N*-acyliminium ion species is thermal[96] or acid catalyzed acylation of *N*-alkyl or *N*-aryl imines[111] (Scheme 69).




**Scheme 69**

Among acylation processes, reaction between cyclic anhydrides **207** and imines **206**[112] and Staudinger reaction[113] are especially interesting (Scheme 70).




**Scheme 70**

[111] Venkov, A. P.; Mollov, N. M. *Synthesis* **1982**, 216

[112] Castagnioli, N. Jr,. *J. Org. Chem.* **1969**, *34*, 3187

[113] Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I. VCH: New York, **1993**; Chapter 6, 295



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## 2.4. Azetidin-2-ones as building blocks in a synthesis of biologically active compounds

The discovery and a clinical use of penicylin started world-wide career of β-lactam antibiotics. Presently, they represent the most powerful tool against bacterial infections. Recently, β-lactams also have been observed to dispay interesting activity against non-bacterial diseases. Representative antibacterial β-lactam antibiotics are shown in Figure 5. These broad class of compounds include penicillin derivatives, cephalosporin, monobactams and carbapenemes. The synthesis of antibacterial β-lactams can be achieved in two ways: transformation of reacily available by fermentation processes natural antibiotics, or a total synthesis. In the latter case the method of formation of the β-lactam ring together with stereogenic centers at C-3 and C-4 of the azetidin-2-one ring is crucal for success of the synthesis (Figure 5).

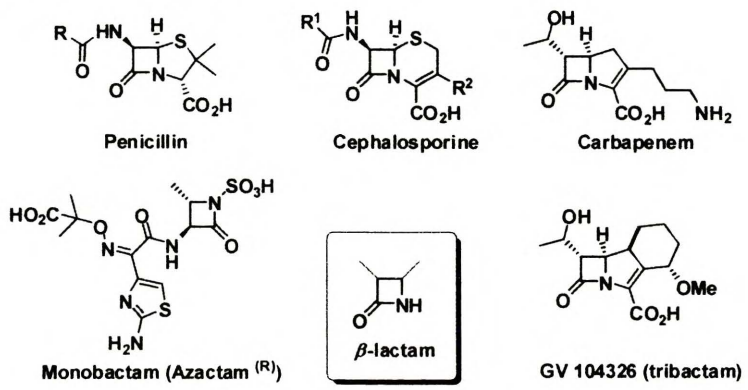


**Figure 5**

### 2.4.1. Biological activity of compound containing β-lactam core

During 50 years from introduction of penicillin to a clinical use, the exploration of β-lactam antibiotics was mainly focused on the improvement of their antibacterial properties. The intensity and success of this approach was establish by the discovery of many related, highly effective antibacterial drugs.

In the 1960s and 1970s novel, active and selective cephalosporin and penicillin remained in the center of interest of many research groups. The main strategies of the synthesis of cephalosporin and penicillin congeners make use of 6-aminopenicilanic acid (6-APA, **208a**) and 7-aminocephalosporinic acid (7-ACA, **208b**) as readily available starting materials (Figure 6). Next milestone was the discovery of carbapenams and carbacephams, as well as other compounds having C-3 and C-4 protons *trans* to each other while active penicillins and cephalosporins have *cis* orientation, respectively.



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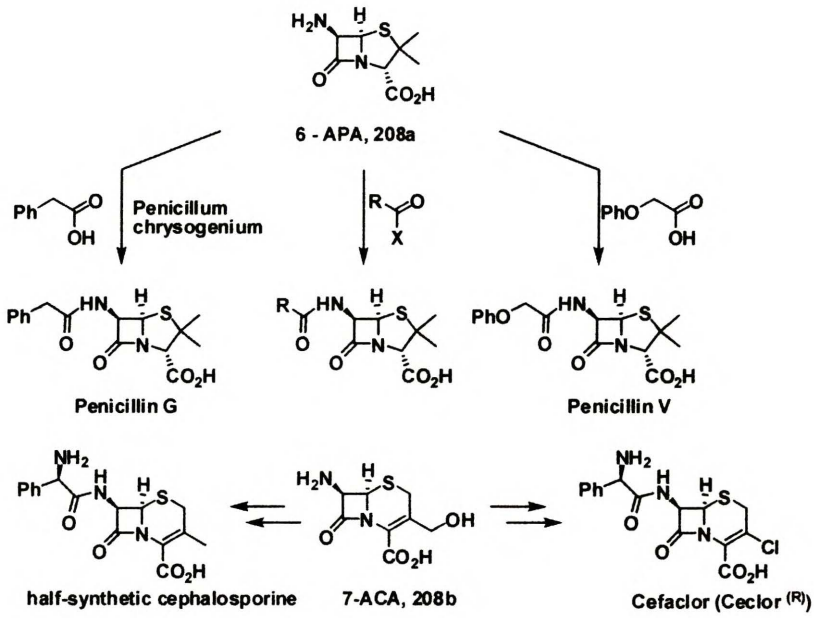


**Figure 6**

During 70's, oxygen analogs of cephalosporin (oxacephamycins) possessing methoxy group at C-7 were found to be also useful in treatment of bacterial infections. These synthetic antibiotics are more efficient in treatment of infections causes by various Gramm-positive (Flomoxef **6**) and Gramm-negative (Moxalactam **7**) organisms. In contrast to cephalosporin they are resistant against $\beta$-lactamase, enzymes responsible for opening of the $\beta$-lactam ring and deactivation of antibiotic (Figure 7).

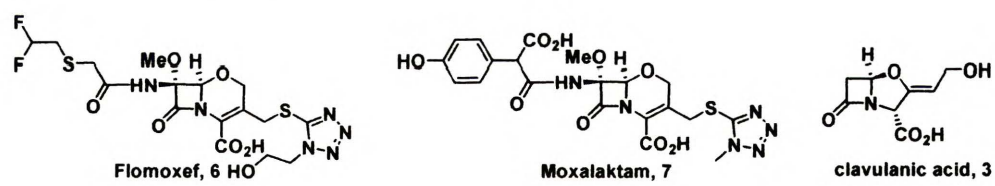


**Figure 7**

The oxygen analog of penicillin – clavulanic acid **3** is also interesting and clinically useful compound (Figure 7). It possesses only weak bacterial activity, but due to structural features is competitive inhibitor of $\beta$-lactamases. In combination with penicillins it helps to overcome antibiotic resistance and makes the drug more efficient.

In 1986 Merck specialists[114] have discovered new type of activity of structurally modified cephalosporin antibiotic presented in Figure 8. It appears to be potent elastase inhibitor. This enzyme belongs to the family of serine proteases functioning in mammalian organism. The inhibition of such enzymes activity is used in the treatment of cancer as well as respiratory, immunological, endocrinal and cardiovascular disorders. It has opened new pharmacologic perspectives for compounds with a $\beta$-lactam core.

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[114] Doherty, J.B., Ashe, B.M., Argenbright, L.W., Barker, P.L., Bonney, R.J., Chandler, G.O., Dahlgren, M.E., Dorn, Jr C.P., Finke, P.E., Firestone, R.A., Fletcher, D., Hagmann, W.K., Mumford, R., O'Grady, L., Maycock, A.L., Pisano, J.M., Shah, S.K., Thompson, K.R., Zimmerman, M. *Nature*, **1986**, *322*, 192-194.



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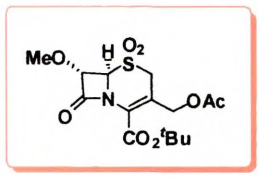

Figure 8

As it was mentioned above the family of serine proteases includes the most important mammal enzymes which regulate wide range of fundamental physiological processes like digestion, fertilization, growth, differentiation, cell signaling, immunological protection or wound healing.

Among β-lactams, monocyclic compounds proved to be very promising source of inhibitors (Figure 9).[115] As an excellent example may serve monobactam **209** actives against target HLE (human leukocyte elastase). Monobactams of type **210** appeared also to be effective as thrombin inhibitors (Figure 9).[114c,116] It's a final product of the coagulation cascade. As a consequence, its inhibitors could be used to prevent and treat both venous and arterial thrombosis (formation of the blood clot). Moreover, monocyclic *β*-lactams of type **211** and **212** appeared to be active antiviral agents (inhibited human cytomegalovirus protease (HCMV)) (Figure 9).[117]

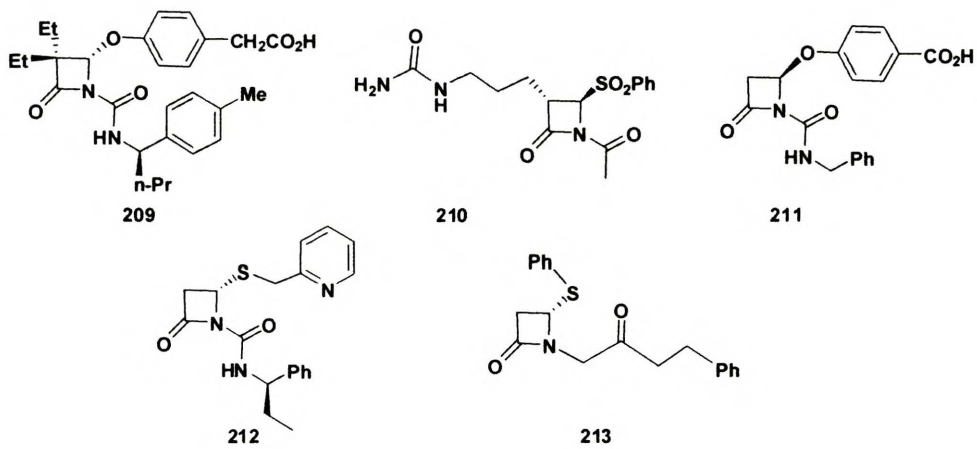

Figure 9

[115] a) Shah, S.K., Dorn, C.P., Finke, P.E., Hale, J.J., Hagmann, W.K., Brause, K.A., Chandler, G.O., Kissinger, A.L., Ashe, B.M., Weston, H., Knight, W.B., Maycock, A.L., Dellea, P.S., Fletcher, D.S., Hand, K.M., Mumford, R.A., Underwood, D.J., Doherty, J.B. *J. Med. Chem.*, **1992**, *35*, 3745; b) Doherty, J. B., Shah, S.K., Finke, P. E., Dorn, C.P., Hagmann, W.K., Hale, J.J., Kissinger, A.L., Thompson, K.R., Brause, K., Chandler, G.O., Knight, W.B., Maycock, A.L., Ashe, B.M., Weston, H., Gale, P., Mumford, R. A., Andersen, O.F., Williams, H. R., Nolan, T.E., Frankenfield, D.L., Underwood, D., Vyas, K.P., Kari, P.H., Dahlgren, M.E., Mao, J., Fletcher, D.S., Dellea, P.S., Hand, K.M., Osinga, D.G., Peterson, L.B., Williams, D.T., Metzger, J.M., Bonney, R.J., Humes, J.L., Pacholok, S.P., Hanlon, W.A., Opas, E., Stolk, J., Davies, P. *Proc. Natl. Acad. Sci. USA*, **1993**, *93*, 8727; c) Knight, W.B., Green, B.G., Chabin, R.M., Gale, P., Maycock, A.L.,Weston, H., Kuo, D.W., Westler, W.M., Dorn, C.P., Finke, P.E., Hagmann, W.K., Hale, J.J., Liesch J., MacCoss, M., Navia, M.A., Shah, S.K., Underwood, D., Doherty, J.B. *Biochemistry*, **1992**, *31*, 8160

[116] Han, W.T., Trehan, A.K., Wright, J.J.K., Federici, M.E., Seiler, S.M., Meanwell, N.A. *Bioorg. Med. Chem.*, **1995**, *3*, 1123

[117] a) Borthwick, A., D., Weingarten, G., Haley, T., M., Tomaszewski, M., Wang, W., Hu, Z., Bedard, J., Jin, H., Yuen, L., Mansour, T.S. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 365; b) Deziel, R., Malenfant, B. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 143; c) Yoakim, C., Ogilvie, W.W., Cameron, D.R., Chabot, C., Guse, I., Hache, B., Naud, J., O'Meara, J.A., Plante, R., Deziel, R. *J. Med. Chem.*, **1998**, *41*, 2882; d) Ogilvie, W.W., Yoakim, C., Do, F., Hache, B., Lagace, L., Naud, J., O'Meara, J.A., Deziel, R. *Bioorg. Med. Chem.*, **1999**, *7*, 1521; e) Bonneau, P.R., Hasani, F., Plouffe, C., Malenfant, E., LaPlane, S.R., Guse, I., Ogilvie, W.W., Plante, R., Dvidson, W.C., Hopkins, J.L., Morelock, M.M., Cordingley, M.G., Deziel, R. *J. Am. Chem. Soc.*, **1999**, *121*, 2965



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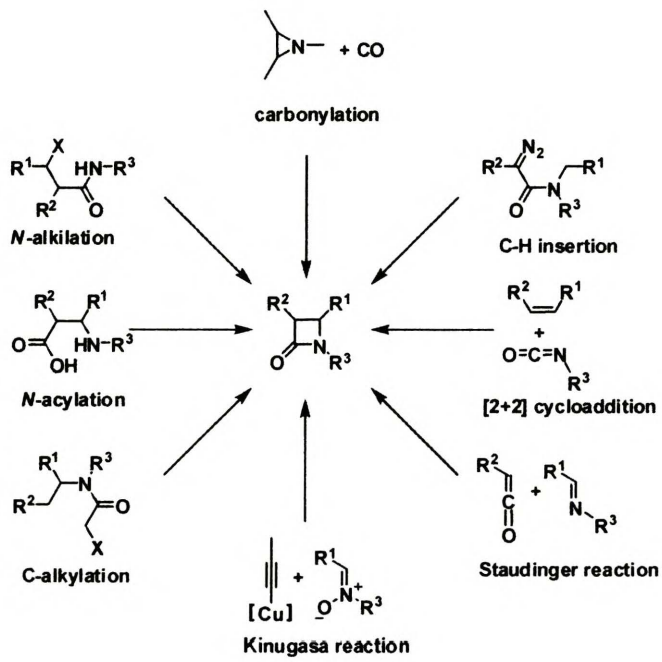
Monocyclic β-lactams **213** appers to be highly specific $LpPLA_2$ inhibitor (Figure 9).[118] Low density protein (LDL) phospholipase $A_2$ is responsible for the hydrolysys of oxidised phosphatidyl choline ester. The accumulation of cells with cholesterol ester leads to atherosclerosis. It is why such inhibitor may be useful in treatment of one of the most serious diseases in modern society responsible for sclerosis, strokes and heart attacks.

### 2.4.2. Main strategies of the synthesis of β-lactams

Owning to these attractive biological properties of β-lactams and limitation of biosynthetic approach, synthesis of mono- and polycyclic systems containing β-lactam ring have been extensively investigated (Scheme 71). [115]




**Scheme 71**

Generally β-lactam antibiotics are polycyclic systems. The bioactivity is strongly related to the configuration at C-3 and C-4 of the azetidin-2-one ring. It is why over the past years, the field of diastereo- and enantio-selective synthesis has developed into practical synthetic paradigm. The most common synthetic approaches to constructions of five or six-membered ring fused to the four-membered one are presented on Scheme 72.

[118] Tew, D.G., Boyd, H.F., Ashman, S., Theobald, C., Leach,C.A. *Biochemistry*, **1998**, *37*, 10087



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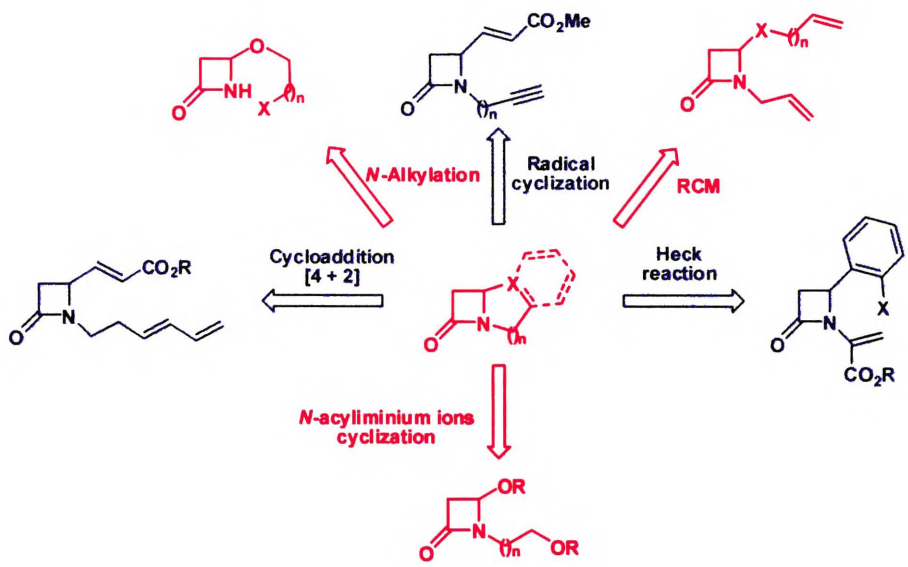
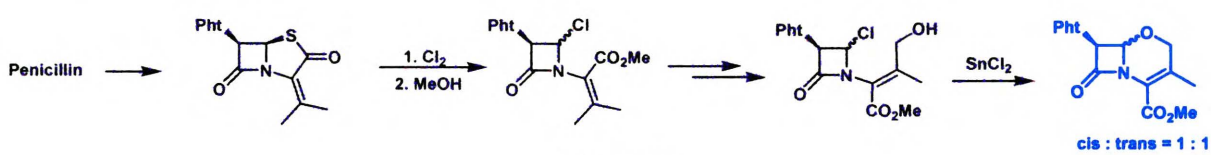



**Scheme 72**

One of the most common strategies for the synthesis of such compounds calls for a nucleophilic substitution at C-4 of the azetidin-2-one, which can either constitute the ring closure step, or can be followed by the closure of five- or six-membered ring by the intramolecular alkylation of the nitrogen atom.[115] The weak point of such a strategy relates to the low asymmetric induction in cases where the C-3 of azetidin-2-one ring is unsubstituted and the stereogenic center is located in the nucleophile, or in an exclusive formation of the *trans*-functionalized ring if the C-3 bears a substituent.[8] This chapter covers only these methodologies.

In 1974 Wolfe and co-workers[119] have reported the first example of total synthesis of 5-oxacephem starting from penicillin (Scheme 73). The idea of this synthesis was simple replacement of sulfur atom at C-4 of azetidin-2-one ring by oxygen one. This aim was achieved by chlorination of anhydropenicillin which was followed by transformation of *N*-substituent into appropriate alcohol and Lewis acid catalyzed intramolecular nucleophilic substitution of the chlorine atom.




**Scheme 73**

Furthermore, chlorine atom at C-4 of azetidin-2-one ring can be substituted by suitable nucleophiles in Lewis acids catalyzed intermolecular reactions (Scheme 74).[120] This methodology was used in the synthesis of Moxalactam **5**. However in this case 6-*epi*-aminopenicillanic acid *epi*-**208a** was used as a substrate.

---

[119] Wolfe, S.; Ducep, J. B.; Tin, K. C.; Lee, S. L. *Can. J. Chem.*, **1974**, *52*, 3996

[120] a) Narisada, M.; Onoue, H.; Nagata, W. *Heterocycle*, **1977**, *7*, 839; b) Narisada, M.; Yoshida, T.; Onoue, H.; Ohtani, M.; Okada, T.; Tsuji, T.; Kikkawa, I.; Haga, N.; Satoh, H.; Itani, H.; Nagata, W., *J. Med. Chem.*, **1979**, 22, 757



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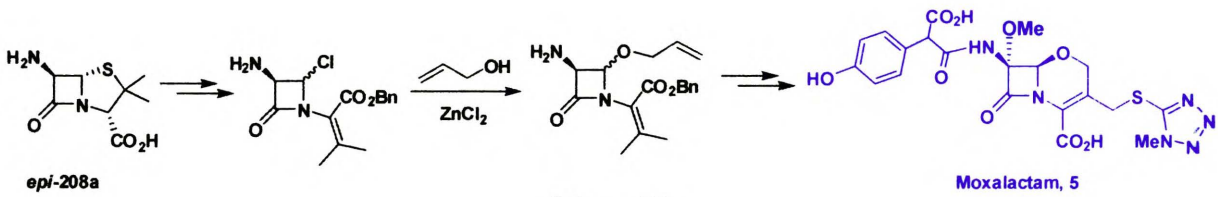
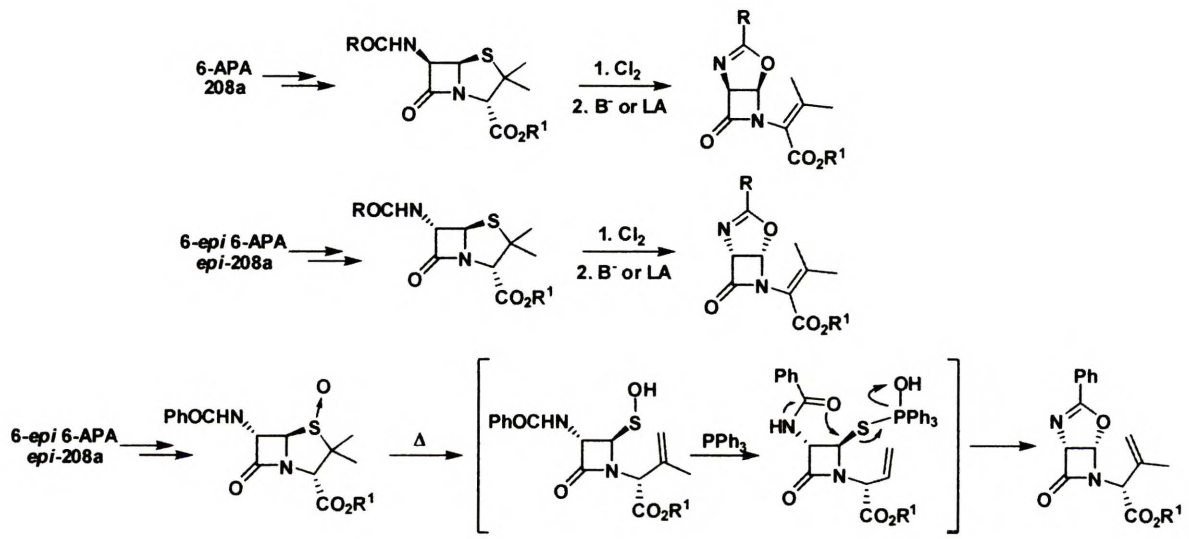



**Scheme 74**

Another useful precursors in the synthesis of oxacephams are oxazolidines (Scheme 75, 76). They are obtained through chlorination of appropriate precursor and subsequent acid catalyzed intramolecular substitution by nucleophile located at C-3 of β-lactam ring.[120b, 121] Both 6-APA (**208a**) and epimerized at C-6 6- *epi* 6-APA (*epi*-**208a**) may be used to leading to different stereoizomers of final oxazolidine. Competitive method is based on thermolysis of 6-epi-penicillin sulfur oxide in the presence of triphenylphosphine (Scheme 75).[122]




**Scheme 75**

Formation of the oxazolidine ring allows introduction of suitable substitution and configuration at C-3 and C-4 of oxazolidine ring, as well as proper *N*-substituents. The opening of oxazolidine can be performed in two ways, either by a reductive cleavage of the five-membered ring, which does not change configuration at C-4, or by a direct acid catalyzed nucleophilic inter-[121b] or intramolecular[120,121a,122b] substitution at C-4 with inversion of the configuration (Scheme 76).

[121] a) Kamata, S.; Yamamoto, S.; Haga, N.; Nagata, W. *J. Chem. Soc. Chem. Commun.*, **1979**, 1106; b) Vlietinck, A.; Roets, E.; Claes, P.; Janssen, G.; Vanderhaeghe, H. *J. Chem. Soc. Perkin Trans, I*, **1973**, 937

[122] a) Kim, C. U.; McGregor, D.N. *Tetrahedron Lett.*, **1978**, 19, 409; b) Yoshioka, M.; Tsuji, T.; Ueyo, S.; Yamamoto, S.; Aoki, T.; Nishitani, Y.; Mori, S.; Satoh, H.; Hamada, Y.; Ishitobi, H.; Nagata, W. *Tetraherdon Lett.*, **1980**, *21*, 351; c) Hamashima, Y.; Yamamoto, S.; Uyeo, S.; Yoshioka, M.; Ona, M.; Nishitani, Y.; Nagata, W. *Tetrahedron Lett.*, **1979**, *20*, 2595; d) Cooper, R. D. G. *Tetrahedron Lett.*, **1980**, *20*, 781; e) Yamamoto, S.; Kamata, S.; Haga, N.; Hamashima, Y.; Nagata, W. *Tetrahedron Lett.*, **1981**, *22*, 3089



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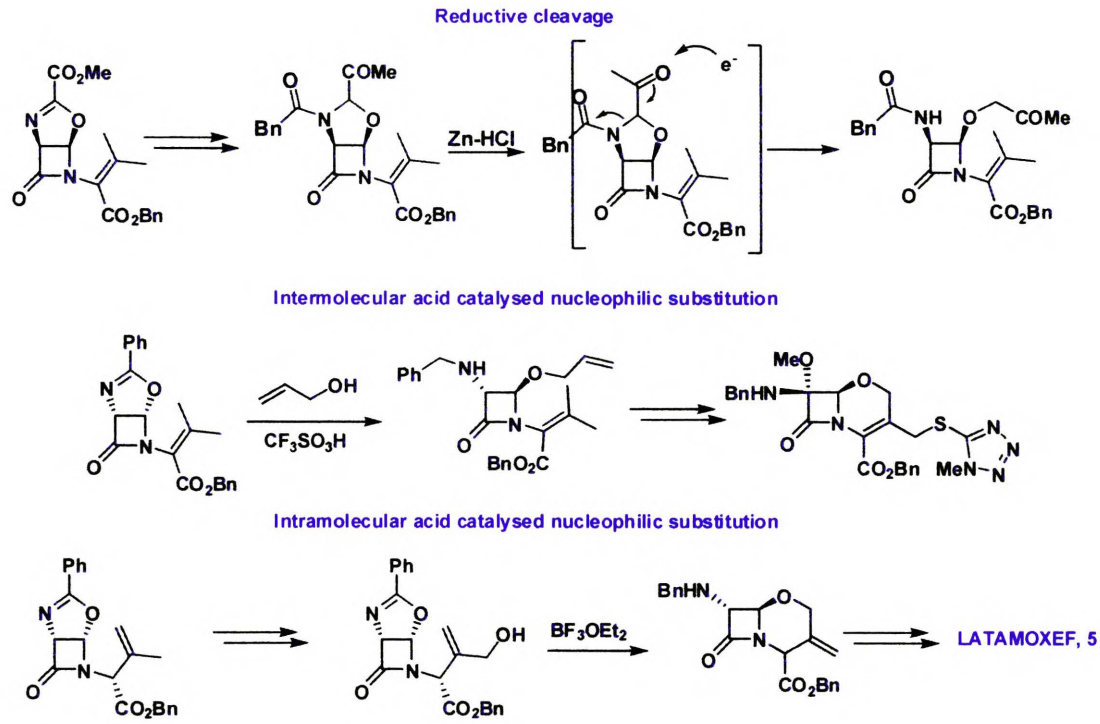


**Scheme 76**

In 1974 Clauss, Grimm and Prossel[123] reported that an 4-acetoxy-azetidin-2-one (**8**) underwent a nucleophilic displacement of an acetoxy group with variety of nucleophiles. This observation prompted many laboratories to use 4-acyloxy-azetidinones as substrates for the synthesis of variety of β-lactam antibiotics (Scheme 77).[124] However, the most serious drawbacks of this compound is low yield of its synthesis and no possibility of direct *N*-alkylation.[124]

[123] Clauss, K.; Grimm, D.; Prossel, G., *Liebigs Ann. Chem.* **1974,** 539
[124] Singh, G. S., *Tetrahedron*, **2003**, *59*, 7631



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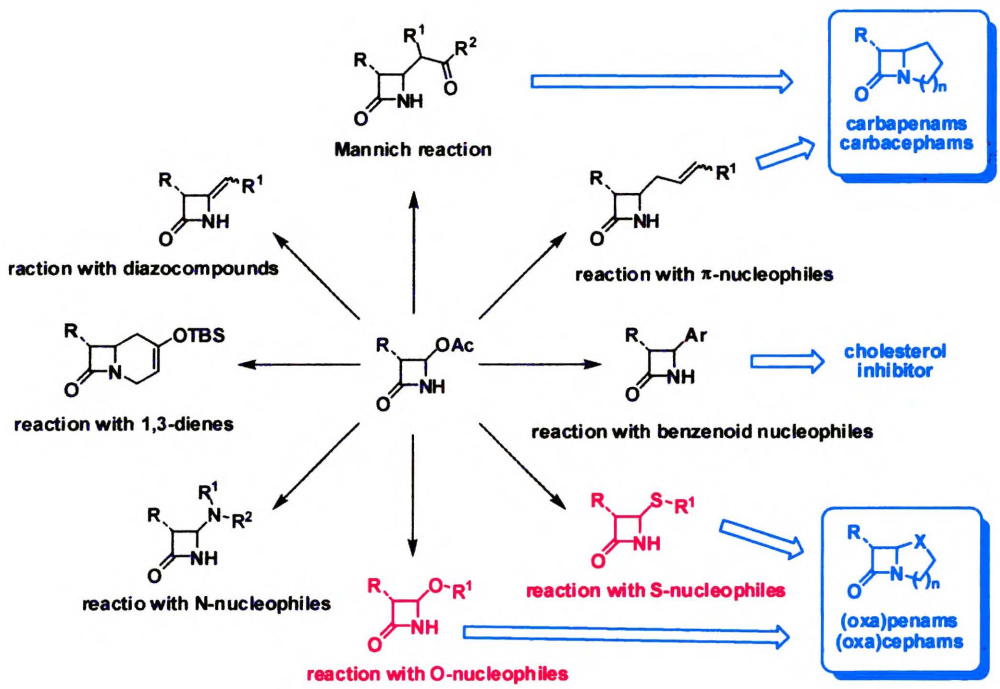


**Scheme 77**

The chiral C-3 substituted 4-acetoxyazetidin-2-one **214**[125,126] and its derivative **215**[126,127] produced by Kaneka Corporation from Osaka are the most useful building blocks in the synthesis of penems and carbapenems (Scheme 78). The key step of their synthesis is four-membered ring formation *via* [2+2] cycloaddition of chlorosulfonyl isocyanate to suitable vinyl acetate **216** (Scheme 78). [126]

[125] Berks, A. H. *Tetrahedron*, **1996**, *52*, 331

[126] a) Oida, S. *Recent Advances in β- Lactam Antibiotics*,Royal Society of Chemistry: London, **1981**, 330, b) Ohki, E.; Oida, S.; Yoshida, A.; Hayashi, T.; Sugawara, S. U.S. Patent US 4395418, Jul. 26, 1983 (Derwent WPI 81-95037D)

[127] Shih, D. H.; Baker, F.; Cama, B. G. *Heterocycles*, **1984**, *21*, 29



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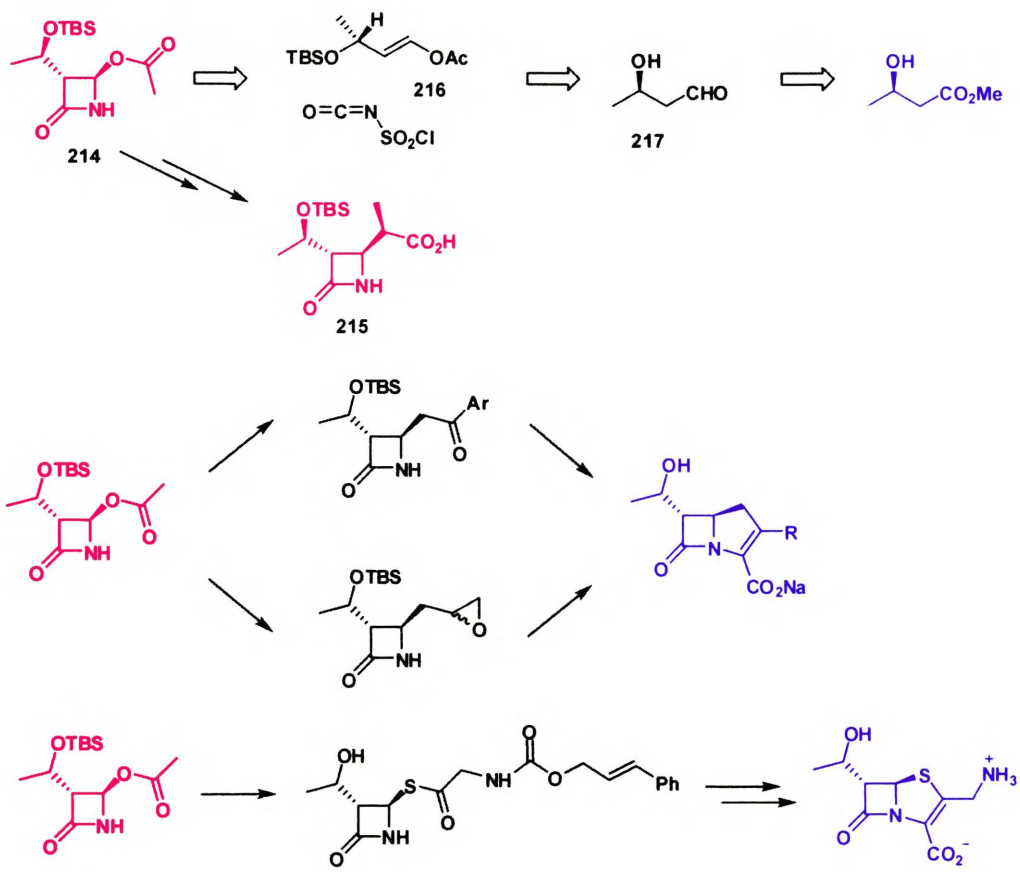
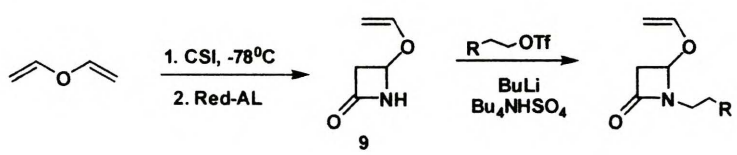



**Scheme 78**

In the middle of 90s, in Institute of Organic Chemistry PAS in our laboratory 4-vinyloxyazetidin-2-one (**9**) was discovered (Scheme 79).[128] This novel synthon is extremely useful in the synthesis of *β*-lactam antibiotics. In contrast to 4-acetoxyazetidin-2-one (**8**) it is stable in a basic media and can be effectively *N*-functionalized. The vinyloxy group can be transformed into acyl or formyl group which are potent leaving groups in acids promoted nucleophilic substitution.[129] It should be stressed that vinyloxyl itself, in the presence of acid catalysts, is also a leaving group. Therefore it plays a double role, being stable in the presence of basis whereas being a leaving group in the presence of acids.[128, 129]




**Scheme 79**

[128] Kałuża, Z.; Park, S.–H. *Synlett*, **1996**, 895

[129] a) Kałuża, Z.; Łysek, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2553; b) Kałuża, Z. *Tetrahedron Lett.* **1998**, *39*, 8349; c) Kałuża, Z. *Tetrahedron Lett.* **1999**, *40*, 1025 d) Furman, B.; Thürmer, R.; Kałuża, Z.; Łysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121



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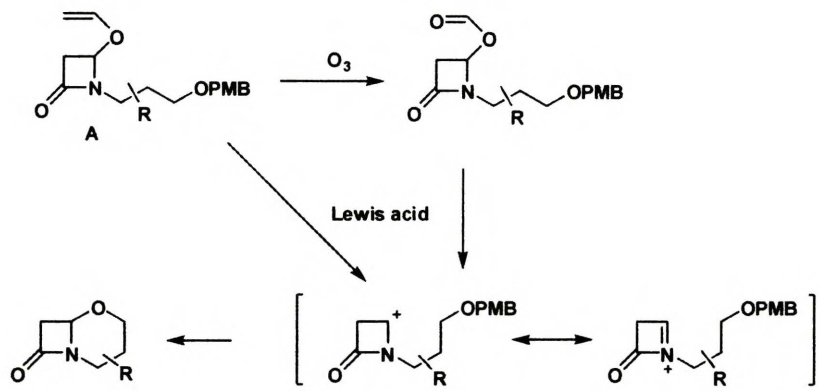
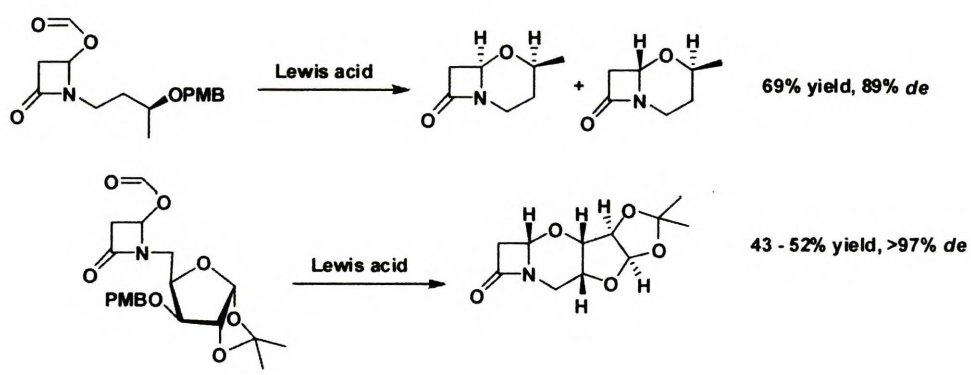
Kałuża[129] has shown that *N*-alkylated 4-vinyloxyazetidin-2-ones of type **A** were suitable substrates for the synthesis of simple oxacephams (Scheme 80).




**Scheme 80**

As have been shown in the Scheme 80, such displacement has proceeded *via* presumed planar intermediate having an *N*-acyliminium cation structure and yield of process strongly depends on type of the acid catalyst.

What is more, a diastereoselective approach have been also developed (Scheme 81). In the case of stereogenic center located in the nucleophile portion good or excellent diastereoselectivity has been observed.[129d]




**Scheme 81**

Recently it was also showed, that 4-vinyloxyazetidin-2-one (**9**) underwent in the presence of Lewis acids inter- and intramolecular Friedl-Crafts alkylation (Scheme 82).[130] The intramolecular alkylation of nucleophilic arenes by *in situ* generated *N*-acyliminium ions has proceeded successfully with variety of aryl-methyl ethers. In contrast, the intermolecular process has limited applicability to allow introduction to azetidin-2-one only the 1,4-dimethoxybenzene fragment. In all cases the equimolar amount of Lewis acid has been required.[130] This methodology provides a new access to 4-arylazetidin-2-ones related to Ezetimibe, a potent cholesterol absorption inhibitor.[115]

[130] Zambroń, B.; Masnyk, M.; Furman, B.; Chmielewski, M. *Tetrahedron*, **2009**, *65*, 4440



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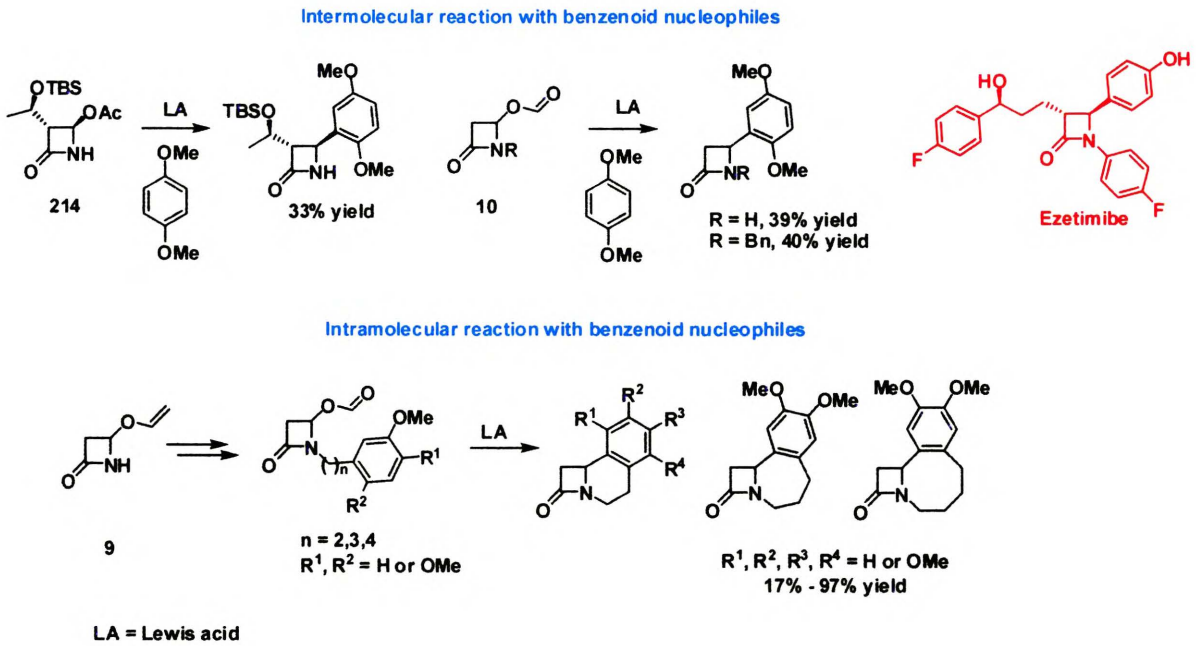
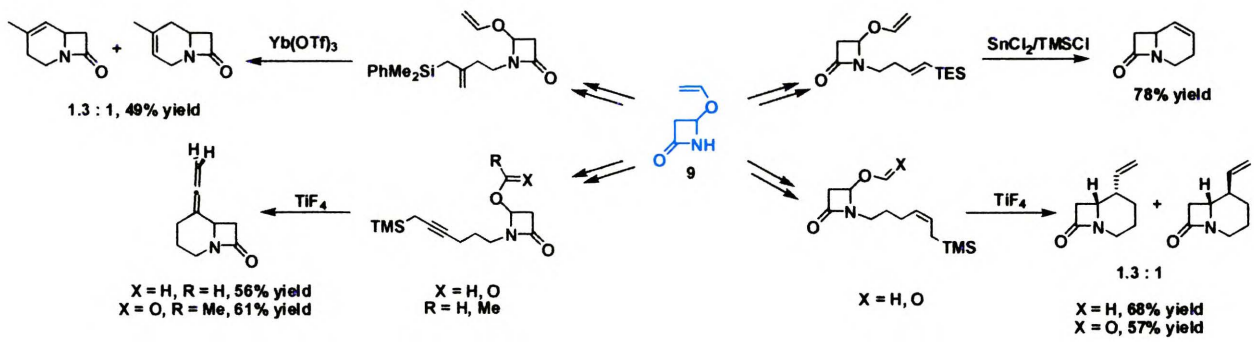



**Scheme 82**

Furthermore, reactions with different π-nucleophiles in the presence of Lewis acids have also been studied.[131] As shown in the Scheme 83, cyclization reactions involving *N*-acyliminium ions generated from the azetidin-2-one fragment with vinyl-, allyl- and propargylsilanes proceeded smoothly only if 6-membered ring can be formed.




**Scheme 83**

It is well established that nucleophilic substitution at C-4 of 4-acetoxyazetidin-2-one (**8**) undergoes in the basic media (Scheme 84). This displacement proceeds *via* flat, neutral intermediate which supposed to have 1,4-dehydroazetidin-2-one structure.[132] In 1984, Fedor[133] proposed the reversible $E_{1CB}$ mechanism for reaction of 4-acetoxy and 4-aryloxyazetidin-2-ones in basic media (Scheme 84).

[131] Grzeszczyk, B.; Szechner, B.; Furman, B.; Chmielewski, M. *Tetrahedron*, **2010**, *66*, 3904
[132] Nagaraja Rao, S.; More O'Ferral R. A.; *J. Am. Chem. Soc.* **1990**, *112*, 2729
[133] Fedor, L. R. *J. Org. Chem.*, **1984**, *49*, 5094



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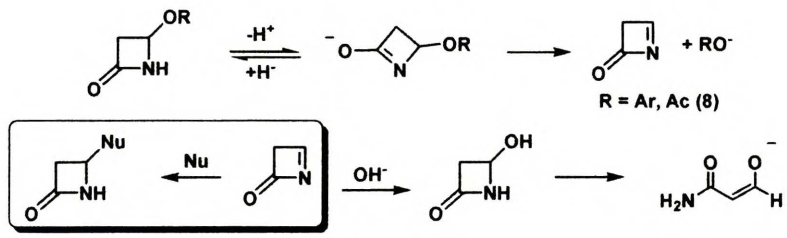
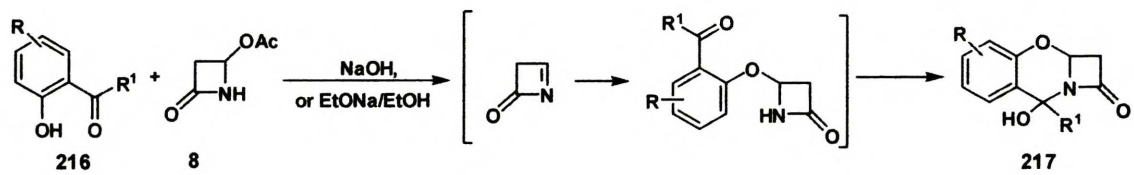



**Scheme 84**

As an interesting example may serve the synthesis of racemic 3,4-benzo-2-hydroxy-5-oxacephams **217** (Scheme 85). The condensation of salicylic aldehydes **216** with 4-acetoxyazetidin-2-one **8** is catalyzed by bases like NaOH or EtONa/EtOH.[134] It is likely a two-step process, which occurs *via* the nucleophilic substitution of the acetoxy group followed by the addition of the β-lactam NH group to the carbonyl group of the phenone. In the case of the salicylaldehyde, although two new stereogenic centers are formed (C-2 and C-6), and the hydroxy group is always *syn* located to the bridgehead proton.




**Scheme 85**

[134] Campbell, M. M.; Nelson, K. H.; Cameron, A. F. *J. Chem. Soc., Chem. Commun.* **1979**, 532; b) Arnoldi, A.; Merlini, L.; Scaglioni, L. *J. Heterocyclic Chem.* **1987**, 75



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## 2.5. Summary

Iminium ion cyclizations have been employed as key strategic steps in the stereoselective synthesis of numerous heterocyclic compounds owing to several attractive factors. This transformation enables creation of a large variety of structures, with both *endo* and *exo*-mode cyclizations, and in most of the cases with a good control of regio- and stereoselectivity. Another reason for successful applications derives from the possibility of a use of large range of nucleophiles (σ-nucleophiles, activated double and triple bonds, aromatic, heteroaromatic) in the ring closure, leading to a huge variety of compounds. Not only chemical, but also stereochemical, diversity can be achieved using iminium ion ring closures, since in some cases the stereochemical outcome of the cyclization can be tuned with changes of reaction conditions (kinetic or thermodynamic control). Moreover, all chemical arsenal developed for the generation of iminium ions from easily available precursors enables to perform these transformations in the presence of many other functional groups, in reproducible and scalable manner.

The present survey includes also catalytic enantioselective reactions of imines.

Several methodologies based on iminium cations seems to be promising; however, there are a number of problems which must be overcome. It is important to note that, in the case of *N*-acyliminium ions, only few examples of enantioselective reactions have been reported.

Among *N*-acyliminium ions, cyclizations leading to β-lactam antibiotics are the most important. Owing to discovery of many other attractive biological properties of this group of compounds, the synthesis of mono- and poly-cyclic systems containing the β-lactam ring has been continuously investigated.



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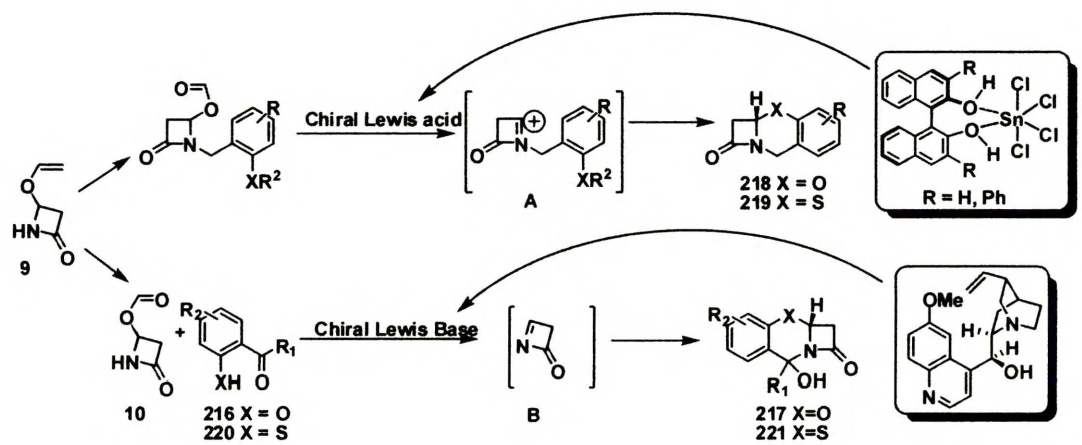
## 3. *RESULT AND DISSCUSSION*

### 3.1. Introduction

For 25 years our laboratory has been interested in the synthesis of oxygen analogs of penicillin and cephalosporin. During that time several attractive diastereoselective approaches to calvams and oxacephams from carbohydrate precursors have been reported. Contrary to previous methodologies, the aim of my work has been directed to catalytic enantioselective formation of analogues of 5-oxacephams and cephams based on nucleophilic substitution at C-4 of the azetidin-2-one ring. I concentrated mainly on two reactions involving phenolic and thiophenolic nucleophiles. The key steps of both methodologies were based either on the chiral Lewis acid or chiral Lewis base mediated, alkylation of phenol and thiophenol. The former proceeds *via* $S_N1$ mechanism involving *N*-acyliminium ion intermediate **A** whereas the latter proceeds *via* elimination/addition mechanism involving neutral 1,4-dehydro-azetidin-2-one **B** species (Scheme 86).




**Scheme 86**



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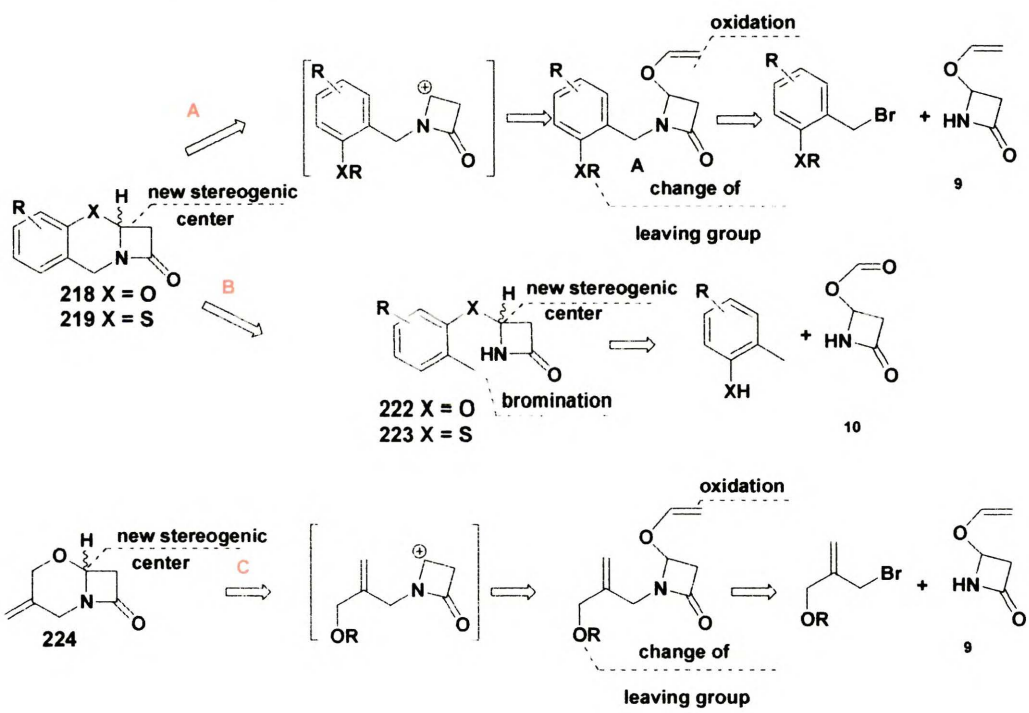
### 3.2. Chiral Lewis acid mediated nucleophilic substitution at C-4 of 4-formyloxyazetidin-2-ones

The first part of my work was concentrated on asymmetric synthesis of cephams' derivatives **218** and **219** *via* chiral Lewis acid promoted nucleophilic substitution at C-4 of azetidin-2-one ring by both oxygen and sulphur atom. I considered three synthetic pathways presented in Scheme 87. Key steps of the first approach (pathway A and C) consisted in *N*-alkylation of 4-vinyloxyazetidin-2-one (**9**) by suitable bromide and subsequent transformation of the vinyloxy group into the formyloxy one. Chiral Lewis acid promoted formation of *N*-acyliminium ion followed by an intramolecular attack of the nucleophilie constituted the final step of the reaction sequence. The crucial step for the second route (pathway B) involved a chiral Lewis acid mediated intermolecular substitution of 4-formyloxy group of azetidin-2-one **10** by the oxygen or sulfur atom of appropriate *o*-cresol or *o*-thiocresol. Subsequent steps involved bromination of the benzyl position in **222** and **223** and intramolecular *N*-benzylation leading to the ring closure.




**Scheme 87**

The most important part of my work considered development of appropriate chiral catalytic system. As a test compound, *N*-benzylated azetidin-2-one of type **A** derived from *o*-cresol was chosen in terms of its low volatility, presence of two chromophores (amide and phenyl one) and moderate toxicity of substrates. Analysis of scope and limitations of the chiral Lewis acid promoted intramolecular process was the next step of my thesis. In particular, different types of nucleophiles from aromatic to aliphatic ones and from oxygen to sulfur were investigated, since they represent biologically active structures of β-lactams. To get full scope of developed catalytic system, its application to the intermolecular nucleophilic substitution was tested, since it is a



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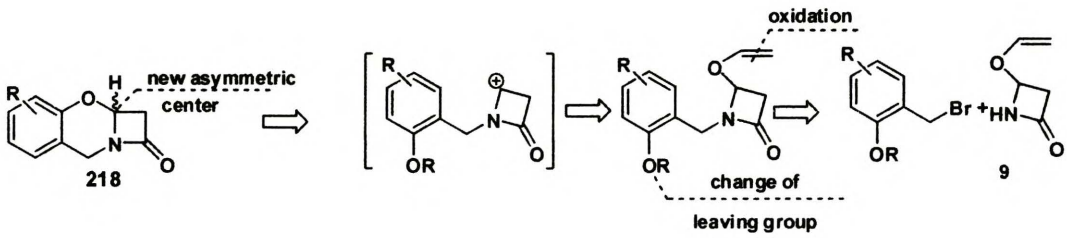
complementary methodology which may be also applied in the synthesis of cephams **218** and **219** (Scheme 87, pathway B).

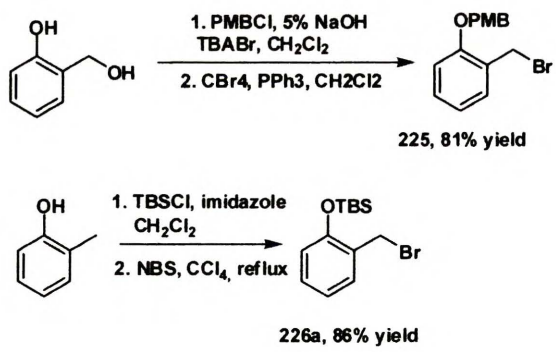
### 3.2.1. Intramolecular chiral Lewis acid mediated synthesis of 3,4-benzo-5-oxacephams 218

Presented in Scheme 88 retro-synthesis of 5-oxacephams **218** assumed *N*-alkylation of 4-vinyloxyazetidin-2-one **9** by suitable benzyl bromide and subsequent transformation of the vinyloxy group into the formyloxy one which is followed by a chiral Lewis acid promoted intramolecular nucleophilic substitution at C-4 of azetidin-2-one ring.




**Scheme 88**

Starting materials for the synthesis of 5-oxacepham **218**, compounds **225** and **226a**, were obtained from 2-hydroxymethylphenol and *o*-cresol respectively *via* standard reaction sequences (Scheme 89).[135]




**Scheme 89**

The alkylation of 4-vinyloxyazetidin-2-one (**9**) with **225** and **226a** proceeded smoothly under PTC condition ($K_2CO_3$, TEBABr, acetonitrile, reflux)[136] to afford corresponding *N*-substituted *β*-lactams **227** and **228a** in 60% and 70% yield, respectively. Other alkylation methods were not so efficient (Table 2).

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[135] a). Baughmanm, T. W; Sworen, J. C.; Wagener, K. B., *Tetrahedron*, **2004**, *60*, 10943; b) Yoshida, Y.; Okamoto, S.; Sato, F., *J. Org. Chem.*, **1996**, *22*, 7826

[136] Kałuża, Z.; Kazimierski, A.; Lewandowski, K.; Suwińska, K.; Szczęsna, B.; Chmielewski, M., *Tetrahedron*, **2003**, *59*, 5893



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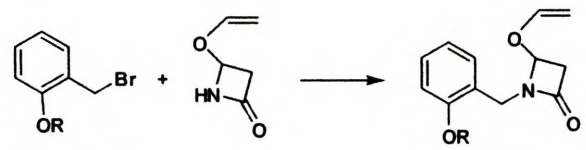


225. R = PMB
226a, R = TBS

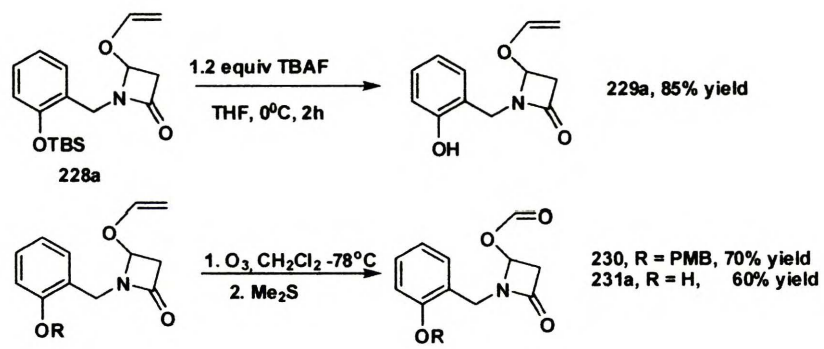
227. R = PMB
228a, R = TBS

| Entry | Substrate | R | Product | Conditions | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | **225** | PMB | **227** | 1 equiv. NaH, DMF, -78°C to rt, 12h | 40 |
| 2 | **225** | PMB | **227** | 2.2 equiv. BuLi, 1.1 equiv. $Bu_4NHSO_4$, THF, -78°C to rt, 1h | 30 |
| 3 | **225** | PMB | **227** | 5 equiv. $K_2CO_3$, 0.1 equiv. TBABr, MeCN, reflux, 1h | 60 |
| 4 | **226a** | TBS | **228a** | 5 equiv. $K_2CO_3$, 0.1 equiv. TBABr, MeCN, reflux, 1h | 70 |
| 5 | **226a** | TBS | **228a** | 1 equiv. LDA, THF, -78°C to rt, 12h | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$.

**Table 2**

Deprotection of the hydroxyl group in compound **228a** was performed in the presence of TBAF to provide **229a** in 85% yield. Vinyl ethers (**227**, **229a**) were subjected to treatment with ozone at -78°C following by reductive workup with dimethyl sulphide to give formates **230** and **231a** in 70% and 60% yield, respectively (Scheme 90).



228a

229a, 85% yield

230, R = PMB, 70% yield
231a, R = H, 60% yield

**Scheme 90**

Intramolecular alkylation reactions showed that both azetidinones **230** and **231a** underwent cyclization in the presence of variety of Lewis acid. In the case of **230**, however, expected cyclization product (±)-**218a** was accompanied by compopund **232** which was the result of the subsequent Friedl-Crafts alkylation of **218a** with *p*-methoxybenzyl cation $PMB^+$ (Table 3).



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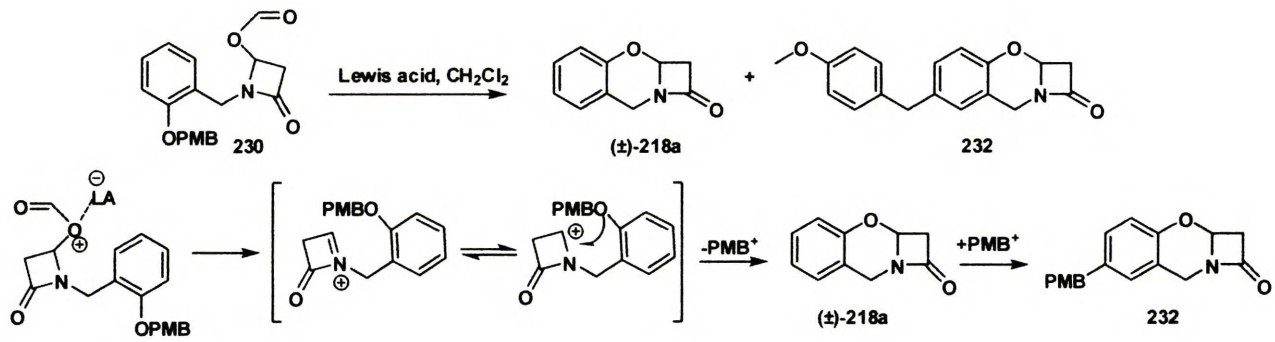
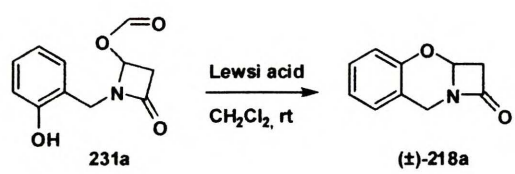



| Entry | Lewis acid | Temperature | Time [h] | Yield [%][a] **218a, 232** | (±)-**218a** : **232** |
|---|---|---|---|---|---|
| 1 | 1 equiv. $BF_3OEt_2$ | rt | 5 | 22, 26 | 1 : 1.1 |
| 2 | 1 equiv. $SnCl_2$/4 equiv. TMSCl | rt | 12 | 26, 14 | 2 : 1 |
| 3 | 0.5 equiv. $SnCl_4$ | -78°C | 0.5 | 48, 32 | 1.5 : 1 |
| 4 | 1 equiv. TMSOTf | rt | 5 | 12, 20 | 1 : 1.6 |

[a] Isolated yield determined after flash chromatography on $SiO_2$.

**Table 3**

Compound **231a** appeared to be a better substrate for the cyclization. Reactions were carried out in dichloromethane at room temperature. The reaction of **231a** with $BF_3{\cdot}OEt_2$ gave (±)-**218a** in a good yield. However, **231a** was less prone to undergo the desired ring closure when other acids such as or TMSOTf, $SnCl_4$, $SnCl_2$/TMSCl, $Yb(OTf)_3$, or $In(OTf)_3$ were used (Table 4). No reaction was observed with TFA, TsOH, $(PhO)_3B$, or $Et_3Al$.




| Entry | Lewis acid | Amount of catalyst | Time [h] | Yield [%][a] |
|---|---|---|---|---|
| 1 | $BF_3OEt_2$ | 1.1 equiv. | 2 | 84 |
| 2 | $SnCl_2$/TMSCl | 1.1 equiv. | 2 | 48 |
| 3 | $SnCl_4$ | 0.5 equiv. | 1 | 40 |
| 4 | TMSOTf | 1.1 equiv. | 1 | 45 |
| 5 | $Yb(OTf)_3$ | 1.1 equiv. | 3 | 40 |
| 6 | $Yb(OTf)_3$ | 0.5 equiv. | 5 | 0 |
| 7 | $In(OTf)_3$ | 1.1 equiv. | 1 | 40 |
| 8 | $In(OTf)_3$ | 0.5 equiv. | 5 | 0 |

[a] Isolated yield determined after flash chromatography on $SiO_2$.

**Table 4**



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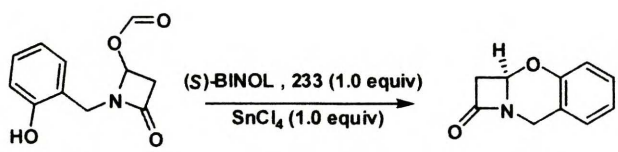
These results prompted me to check whether the azetidinone **231a** could be a substrate for the chiral Lε catalyzed enantioselective cyclization. The initial studies indicated that azetidinone **231a** did not undergo a ring closure in the presence of chiral phosphoric acids and a variety of metal-ligand combinations ($TiCl_4$, $Br_2Ti(OiPr)_4$, $ZnCl_2$, and various ligands box-type, salen ligands). In all cases expected 3,4-benzo-5-oxacephams (±)-**218a** were formed in very low yields, as racemic mixtures. However, when **231a** was stirred in $CH_2Cl_2$ in the presence of a stoichiometric mixture of (*S*)-BINOL (**233**) and $SnCl_4$ at 0°C for 3 h, the cyclization proceeded smoothly to give (+)-**218a** in 35% yield after a silica gel column chromatography (Table 5, entry 3) with 85% *ee*.[137] Reaction was carried out until disappearance of the substrate (TLC monitored).




231a 218a

| Entry | Solvent | Temperature | Time [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | -40 °C | 10 | 0 | - |
| 2 | $CH_2Cl_2$ | -20 °C | 6 | 30 | 78 |
| 3 | $CH_2Cl_2$ | 0 °C | 3 | 35 | 85 |
| 4 | Toluene | 0 °C | 3 | 34 | 80 |
| 5 | $Et_2O$ | 0 °C | 3 | 32 | 72 |
| 6 | THF | 0 °C | 10 | 0 | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **231a** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 5**

It is important to note that when the reaction temperature was decreased to -20°C, a lower enantioselectivity was observed (Table 5, entry 2). If toluene or diethyl ether were used as a solvent, the yield was practically unchanged but the enantioselectivity was reduced to 80% and 72%, respectively. There was no reaction when THF was used as a solvent.

All attempts to reduce the ratio of the substrate **231a** to the chiral ligand were unsuccessful. The use of 0.5 equiv. of chiral acid reduced the yield to 50% of that found for the primary experiment. Reduction of BINOL ratio to $SnCl_4$

[137] a) Ishibashi, H.; Ishihara, K.; Yamamoto, H., *Chem. Rec.* **2002**, *2*, 177; b) Ishihara, K.; Kaneeda, M.; Yamamoto, H., *J. Am. Chem. Soc.* **1994**, *116*, 11179; c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H., *J. Am. Chem. Soc.* **1996**, *118*, 12854; d) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H., *J. Am. Chem. Soc.* **2000**, *122*, 8120; e) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H., *J. Am. Chem. Soc.* **2003**, *125*, 24; f) Ishihara, K.; Nakamura, S.; Nakamura, H.; Yamamoto, H., *J. Org. Chem.* **1998**, *63*, 6444; g) Ishihara, K.; Ishibashi, H.; Yamamoto, H., *J. Am. Chem. Soc.* **2002**, *124*, 36475; h) Ishihara, K.; Ishibashi, H.; Yamamoto, H., *J. Am. Chem. Soc.* **2001**, *123*, 1505



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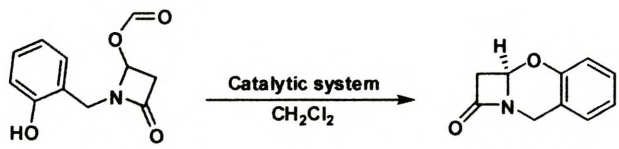
affected the enantioselectivity (Table 6). However, it is important to note, that in all cases BINOL was recovered by column chromatography in 90% yield without loss of optical purity.




**231a** **218a**

| Entry | Catalytic system | Amount of catalyst | Temperature | Time [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| 1 | $SnCl_4$/(*S*)-BINOL (**233**) 4/1 | 0.5 equiv. | 0 °C | 3 | 40 | 50 |
| 2 | $SnCl_4$/(*S*)-BINOL (**233**) 1/1 | 0.2 equiv. | 0 °C – rt | 96 | 0 | - |
| 3 | $SnCl_4$/(*R*)-BINOL (**ent-233**) 1/1 | 0.5 equiv. | 0 °C | 3 | 19 | 85 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **231a** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 6**

Having the first positive result, I investigated enantioselective cyclization under the same conditions using various chiral ligands. Suitable binaphthols were synthesised according to the literature procedures.[138] The 6,6'-dibromo-BINOL was obtained in one step by simple bromination of (*S*)-BINOL **233**.[138] Protected 3,3'-Dibromo-BINOL was transformed into desire derivatives through simple Heck or Suzuki coupling and subsequent deprotection of hydroxyl group with $PBr_3$ (Scheme 91).[138] The mono- and dimethoxy BINOLs were obtained in the presence of MeI and $K_2CO_3$ in acetone (Scheme 91).[138]

[138] Wipf, P.; Jung, J.-K., *J. Org. Chem.*, **2000**, *65*, 6319



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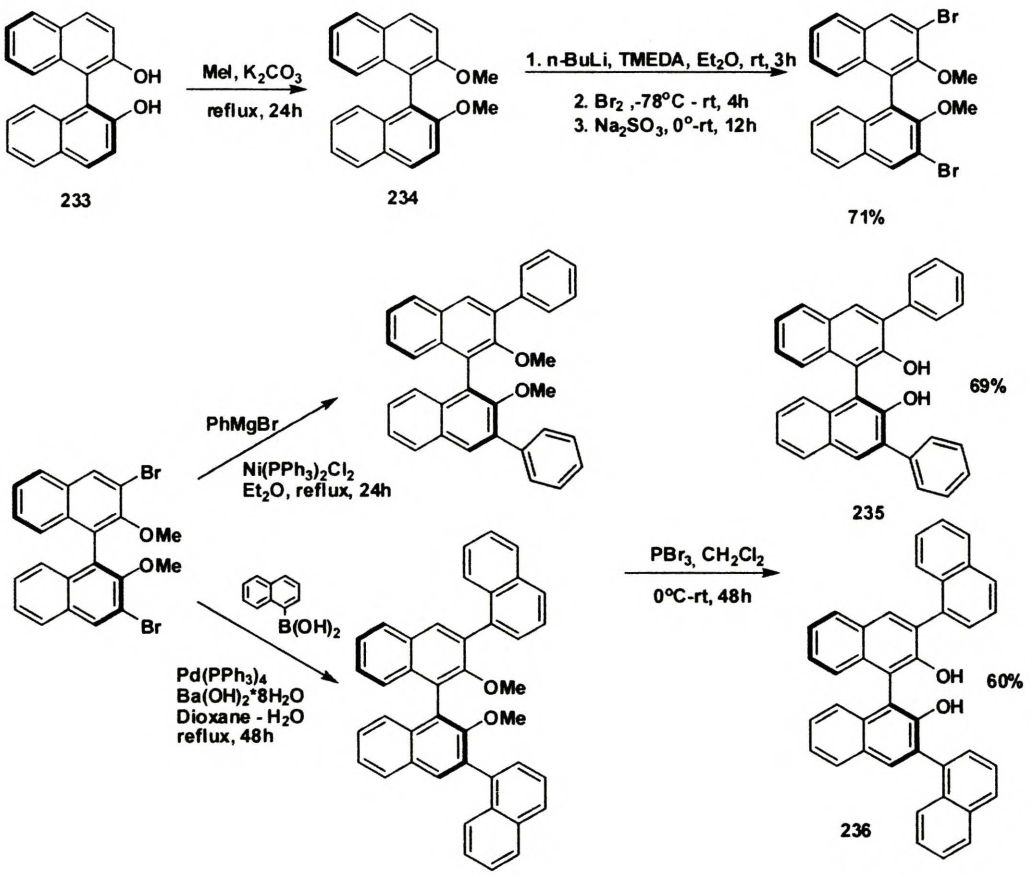


**Scheme 91**

Ligand evaluation studies for the enantioselective formation of **218a** were performed in the presence of 1 equiv. of Ligand/$SnCl_4$ complex as a catalyst ($CH_2Cl_2$, 0 °C, 3h) (Table 7). When either (*S*)-3,3'-bisphenyl-BINOL (**235**) or (*S*)-3,3'-bis-*α*-naphthyl-BINOL (**236**) were employed, **218a** was obtained in a moderate yield (35% and 39%) and excellent enantioselectivity (98% and 99% *ee*), respectively. The presence of bromide atoms at the 6- and 6'-positions of the binaphthol molecule (**237**) showed a little effect on the chemical yield, but the enantioselectivity was considerably decreased. Application of (*S,S*)-TADDOL (**239**) instead of BINOL ligands **233-238** gave a similar conversion providing ***ent*-218a,** but affected the enantioselectivity (Table 7). It is important to note that in the presence of dimethoxy BINOL (entry 3), no reaction was observed since ligand **238** does not provide any acidic proton. It may suggest that acidic protons in the optically active BINOL are important to bind the intermediate complex. This type of chirality transfer was described by Yamamoto in 2002.[137] The activation of chiral alcohol's proton by coordination of $SnCl_4$ leads to formation of Lewis acid assisted chiral Brønsted acid. Again, it should be note that in all reactions, ligands were recovered by column chromatography in 80-90% yield without lost of enantiomeric purity.



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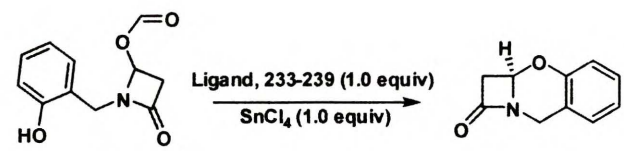
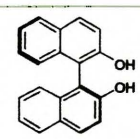
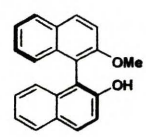
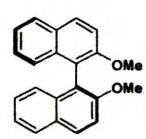
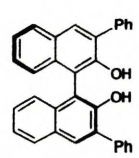
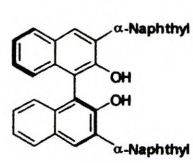
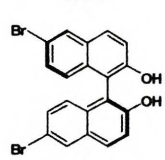
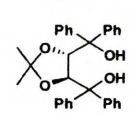



231a 218a

| Entry | Ligand | Yield [%][a] | *ee* [%][b] | Enantiomer |
|---|---|---|---|---|
| 1 |  **233** | 35 | 85 | *R* |
| 2 |  **238** | 41 | 96 | *R* |
| 3 |  **234** | 0 | - | - |
| 4 |  **235** | 38 | 98 | *R* |
| 5 |  **236** | 39 | 99 | *R* |
| 6 |  **237** | 30 | 64 | *R* |
| 7 |  **239** | 34 | 80 | *S* |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **231a** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 7**



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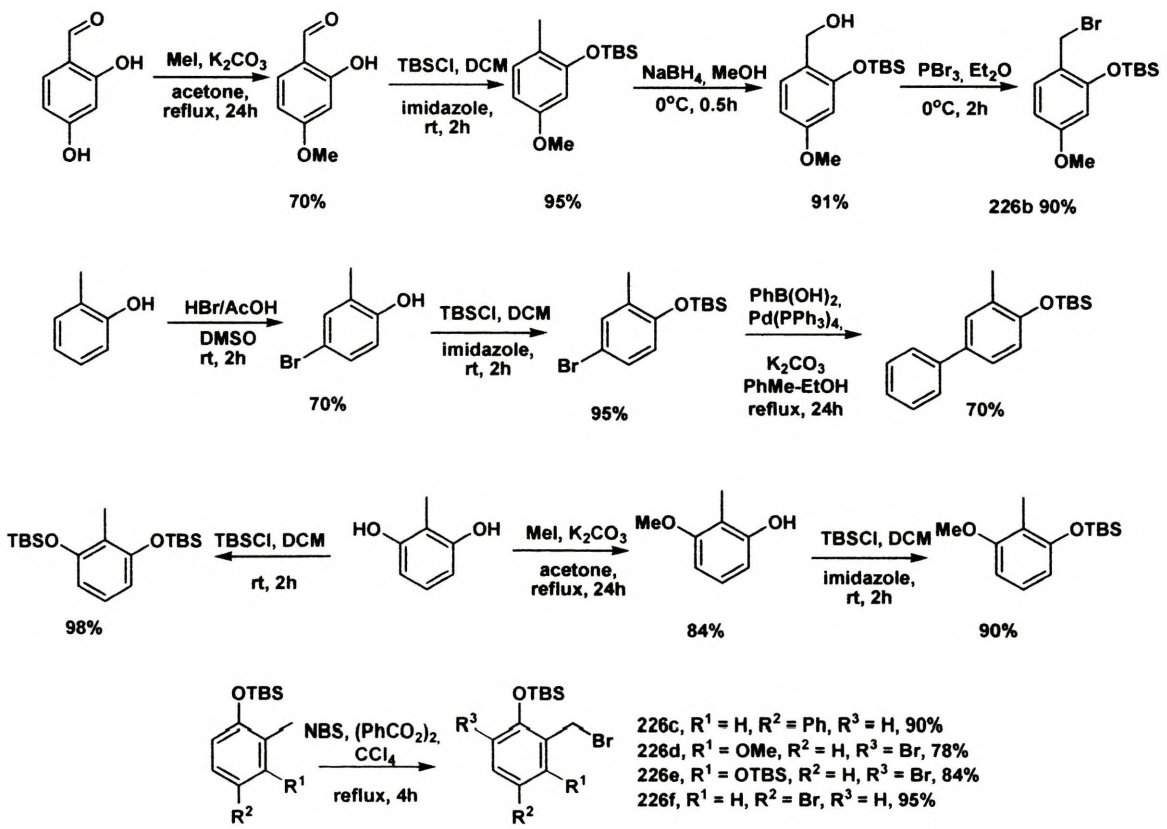
Subsequently, I decided to analyze the scope of this asymmetric reaction using variety of *N*-benzylated azetidinones, related to **231a**. The benzyl bromides were obtained form commercially available *o*-cresol or derivaties of salicylic aldehyde (Scheme 92).[135,139] The protection of hydroxyl group with *t*-butyldimethylsilane was performed in the presence of imidazole in dichloromethane at room temperature. The final step – bromination, was performed, depending of the substrate type. In the case of benzyl alcohols by treatment with $PBr_3$ in ether, whereas in the case of cresols by NBS in the presence of benzoil peroxide.




**Scheme 92**

The three step procedure, which was applied in the synthesis of **231a** (Table 2, entry 4 and Scheme 90), provided desired cyclization precursors, *N*-benzylated 4-formyloxyazetidin-2-ones **231b-f**, in moderated overall yields (Table 8 and 9). The *N*-benzylation of 4-vinyloxyazetidin-2-one (**9**) with benzyl bromides **226a-f** was performed under PTC conditions ($K_2CO_3$, $Bu_4NBr$, MeCN, reflux). The yield of this process strongly depended on substituent in the phenol ring (Table 8). However, when benzyl bromide **226f** was used, compound with deprotected phenol group **229b** (blue one) was directly formed in 40% yield (Table 8 entry 6).

[139] a) Mann, A.; Muller, C.; Tyrrell, E., *J. Chem. Soc. Perkin Trans. 1*, **1998**, 1427; b) Kölbel, M.; Beyersdorff, T.; Tschierske, C.; Diele, S.; Kain, J., *Chem. Eur. J.* **2000**, *6*, 3821



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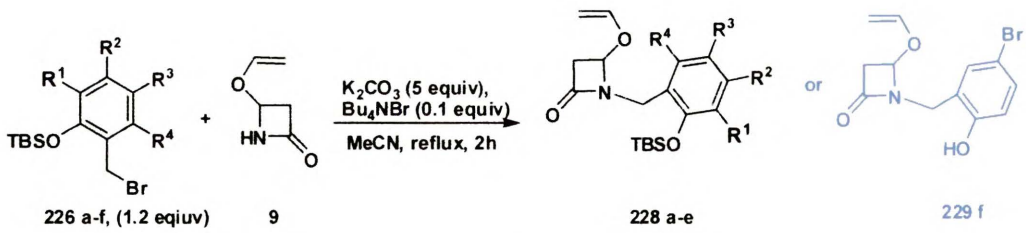


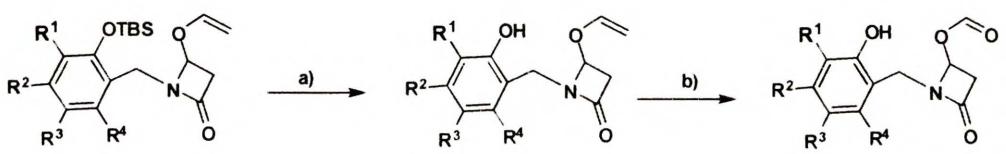

226 a-f, (1.2 eqiuv) 9 228 a-e 229 f

| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product | Yield [%][a] |
|---|---|---|---|---|---|---|---|
| 1 | **226a** | H | H | H | H | **228a** | 70 |
| 2 | **226b** | H | OMe | H | H | **228b** | 20 |
| 3 | **226c** | H | H | Ph | H | **228c** | 25 |
| 4 | **226d** | Br | H | H | OMe | **228d** | 28 |
| 5 | **226e** | Br | H | H | OTBS | **228e** | 35 |
| 6 | **226f** | H | H | Br | H | **229f** | 40 |

[a] Isolated yield determined after flash chromatography on $SiO_2$

**Table 8**

Subsequently, *t*-butyl-dimethylsilyl protection was removed in **228a-e** by treatment with TBAF to afford **229a-e**. The final ozonolysis provided the corresponding cyclization precursors **231a-f** in satisfactory yields (Table 9).




228 a-e 229 a-f 231 a-f

**a) 1M TBAF (1.2 equiv or 228e 2.2 equiv), THF, rt, 2h**
**b) $O_3$, $CH_2Cl_2$, -78 °C than $Me_2S$**

| Entry | Compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Product | Yield [%][a] | Product | Yield [%][a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **228a** | H | H | H | H | **229a** | 85 | **231a** | 60 |
| 2 | **228b** | H | OMe | H | H | **229b** | 80 | **231b** | 70 |
| 3 | **228c** | H | H | Ph | H | **229c** | 79 | **231c** | 70 |
| 4 | **228d** | Br | H | H | OMe | **229d** | 81 | **231d** | 77 |
| 5 | **228e** | Br | H | H | OTBS (OH) | **229e** | 86 | **231e** | 88 |
| 6 | **229f** | H | H | Br | H | **229f** | - | **231f** | 80 |

[a] Isolated yield determined after flash chromatography on $SiO_2$

**Table 9**

Cyclizations of **231** were performed in the presence of 1 equiv of (S)-3,3'-bis-α-naphthyl-BINOL (**236**)/$SnCl_4$ as a promoter ($CH_2Cl_2$, 0°C, 3h). As shown in Table 10, the enantiomeric excess, as well as, the yield of products depended on the nature of substituents in the phenol ring.



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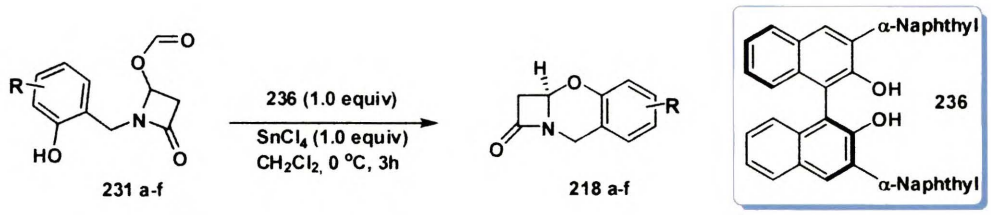
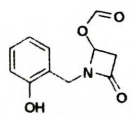
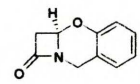
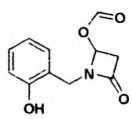
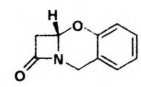
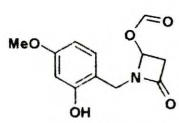
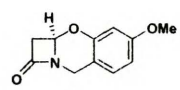
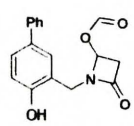
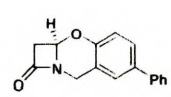
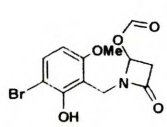
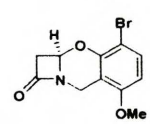
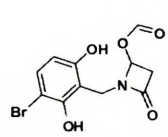
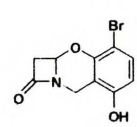
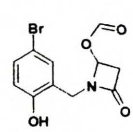
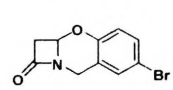



| Entry | Substrate, **231** | Product, **218** | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 |  **231a** |  **218a** | 39 | 99 |
| 2[c] |  **231a** |  **ent-218a** | 42 | 99 |
| 3 |  **231b** |  **218b** | 49 | 82 |
| 4 |  **231c** |  **218c** | 45 | 92 |
| 5 |  **231d** |  **218d** | 50 | 95 |
| 6 |  **231e** |  **218e** | 52 | 0 |
| 7 |  **231f** |  **218f** | 0 | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **231** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 10**



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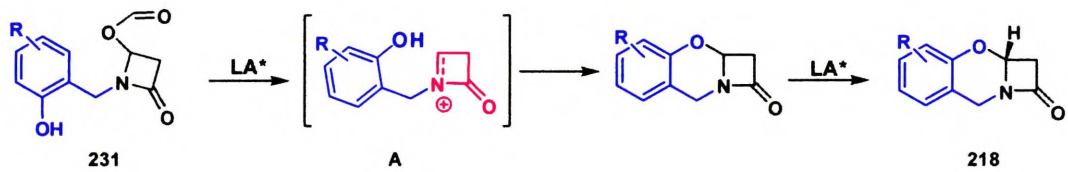
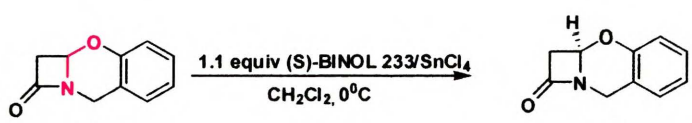
Low yield of the reaction in the presence of chiral catalysts, which never exceeds 50%, whereas high enantiomeric excess may suggest that the final result is a kinetic resolution of the initially formed racemic oxacepham (Scheme 93). Asymmetric destruction of initially formed oxacepham by a chiral acid catalyst may be caused by the opening of *N,O*-acetal in the stronger bound enantiomer, which is followed by further decomposition of the unstable acylimminium cation. Second enantiomer withstand the acid complexation and can be isolated from the post-reaction mixture. Such enantiomer differentiating processes are known in the literature.[140]




231 A 218

**Scheme 93**

This mechanistic proposition is strongly supported by the partial asymmetric destruction of the racemic **218a** in the presence of the chiral catalyst. Cepham (+)-**218a** in $CH_2Cl_2$ solution in the presence of a stoichiometric mixture of (*S*)-BINOL **233** and $SnCl_4$ at 0°C provided the enantiomerically enhanced compound (+)-**218a** - after 1.5 h in 25% yield and *ee* 56%, whereas after 3 h in 15% yield and *ee* 85% (Table 11). The same direction of asymmetric induction was noticed as in the case of the direct cyclization reaction. Equimolar amount of the Lewis acid, which is necessary to perform effectively the reaction, proves also the proposed mechsnism, since it assumes that the catalyst is not liberated.




(±) 218 (+)218

| Entry | Time [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|
| 1 | 1.5 | 25 | 56 |
| 2 | 3 | 15 | 85 |
| 3 | 6 | - | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$.. [b] The enantiomeric excess was determined by chiral HPLC.

**Table 11**

[140] Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S., *J. Am. Chem. Soc.* **2001,** *123,* 12510



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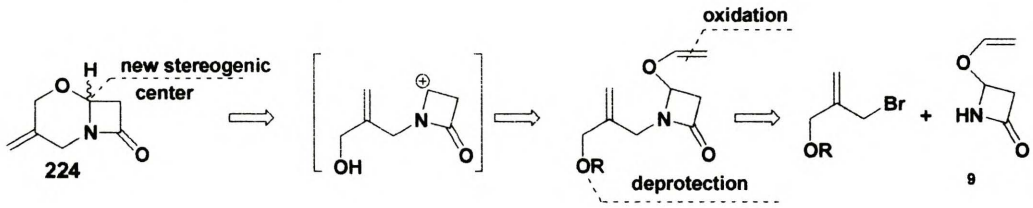
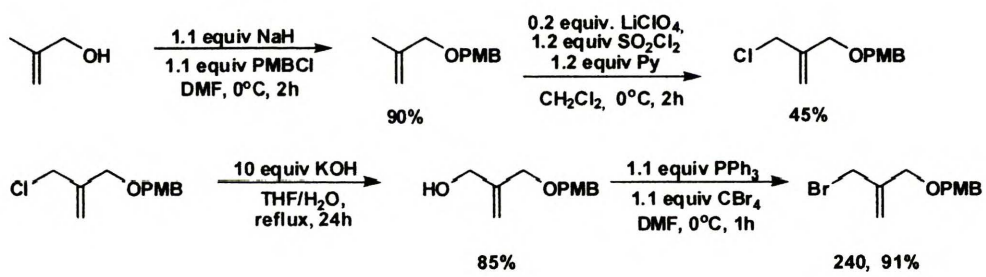
### 3.2.2. Chiral Lewis acid mediated synthesis of 5-oxacephams 224

The proposed above methodology (chapter 3.2.1) gave a unique possibility to obtain azetidin-2-ones with strictly required configuration at C-4. It is extremely important from the pharmacological point of view. To put more light on the substrate nature and universality of the chiral Lewis acid mediated nucleophilic substitution, I decided to check whether aliphatic alcohol would be suitable substrate, as well. As shown on Scheme 94, key steps of this process consists of *N*-alkylation of 4-vinyloxyazetidin-2-one (**9**) and chiral Lewis acid promoted cyclization.




**Scheme 94**

Desired bromide **240**, I prepared from *β*-methylallyl alcohol following literature methods (Scheme 95).[136] As protective group I choose PMB protection since it earlier proved utility in the *N*-acyliminium ion cyclization, as both protecting and activating group.[136] As it was shown previously only bromine derivative **240** of *β*-methylallyl alcohol was active enough to perform alkylation of 4-vinyloxyazetidin-2-one (**9**).[136]




**Scheme 95**

According to the literature procedure,[136] treatment of an equimloar mixture of *β*-lactam **9** and tetrabutylammonium hydrogen sulphate with two equivalents of n-butyllithium in THF at -78°C, followed by the addition of **240** in one portion, resulted in formation of the *N*-alkylated product **241** in 85% yield. As it was previously reported,[136] compound **241** underwent cyclization in the presence of $BF_3OEt_2$ to provide (±)-**224** in 50% yield (Scheme 96).



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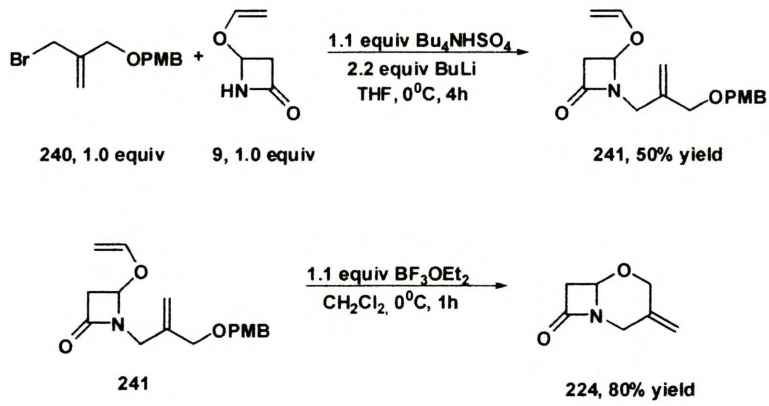
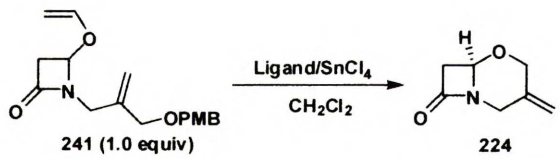



**Scheme 96**

Compound **241** treated with the equimolar amount of (*S*)-BINOL (**233**) / $SnCl_4$ complex under standard cyclization conditions gave **224** in 89% yield but only with 8% *ee* (Table 12, entry 1). The reaction was carried out until disappearance of the substrate **241**. Decrease of the temperature of the reaction and prolongation of the reaction time only slightly raised the enantiomeric excess (entry 2). Attempts to apply a catalytic version of the process was unsuccessful. Interesting result was obtained in the presence of ligand (*S*)-3,3'-bis-α-naphthyl-BINOL (**236**). 5-Oxacepham **224** was formed in 68% yield and 12% *ee,* but temperature had to be raised to room temperature (entry 4). It should be recalled that the cyclization of azetidin-2-ones **231** in the presence of equimolar amount of (*S*)-3,3'-bis-α-naphthyl-BINOL (**236**) / $SnCl_4$ yielded compounds **218** with the highest *ee* value at 0° (Table 10).




| Entry | Ligand | Conditions | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | (*S*)-BINOL (**233**) | 1.1 equiv, 0°C, 30 min | 89 | 8 |
| 2 | (*S*)-BINOL(**233**) | 1.1 equiv, -78°C, 3h | 85 | 11 |
| 3 | (*S*)-BINOL(**233**) | 0.1 equiv, rt, 24h | - | - |
| 4 | (*S*)-3,3'-bis-α-naphthyl-BINOL (**236**) | 1.1 equiv, rt, 3h | 68 | 12 |

[a] Isolated yield determined after flash chromatography on $SiO_2$ Reaction was carried out until disappearance of substrate **241** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 12**

To check whether the enantiomeric enrichment of oxacepham (±)-**224** is also induced by the asymmetric destruction of the racemic compound, I investigated reaction of (±)-**224** with equimolar amount of $SnCl_4$/BINOL (**233**). In all cases, I observed formation of enantiomerically enriched (+)-**224** (Table 13). The best result, *ee* 22% was obtained at -78°C after 36h with ligand **236** (Table 13, entry 3).



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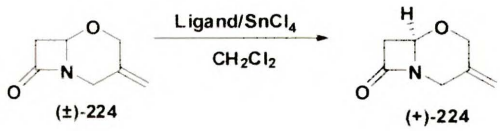



| Entry | Ligand | Conditions | Yiled [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | (*S*)-BINOL **233** | 1.0 equiv, -78°C, 3h | 87 | 6 |
| 2 | (*S*)-BINOL **233** | 1.0 equiv, -78°C, 36h | 44 | 10 |
| 3 | (*S*)-3,3'-bis-α-naphthyl-BINOL **236** | 1.0 equiv, -78°C, 36h | 48 | 22 |

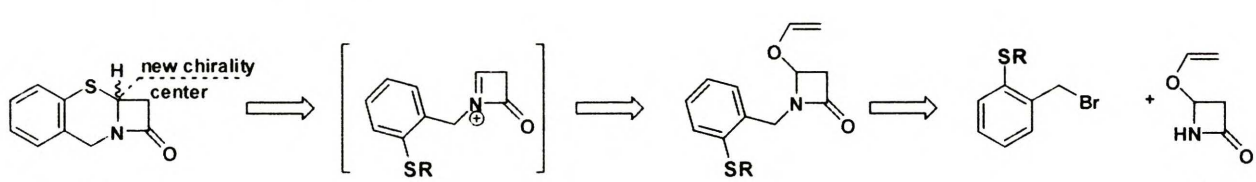
[a] Isolated yield determined after flash chromatography on $SiO_2$ [b] The enantiomeric excess was determined by chiral HPLC.

**Table 13**

In contrast to enantioselective formation of 3,4-benzo-5-oksacephams **218**, the recorded enantiomeric excess in the case of compound **224**, was much lower. However, the kinetic resolution of (±)-**224** took place in -78°C. It may suggest that both enantiomers of (±)-**224** underwent faster a chiral acid promoted opening of *N,O*-acetal than enantiomers of (±)-**218**. Moreover, the chiral promoter is probably only slightly stronger bounded to one enantiomer than to another one, so the decomposition rates of both enantiomeric complexes of (±)-**224** are comparable providing low enantioselectivity.

### 3.2.3. Chiral Lewis acid mediated synthesis of 3,4-benzocepham 219

The next step of my investigations was an application of tiophenol in the chiral Lewis acid meditated cephams formation. On the one hand, cepham structure is leading one in the synthetic β-lactam antibiotics. On the other hand, to get full scope of investigated reaction change of nucleophile type is strongly requested. Presented on Scheme 97 process leading to enatiomerically enriched 3,4-benzocepham **219** consists of *N*-benzylation of 4-vinyloxyazetidin-2-one (**9**) with benzyl bromide followed by a chiral Lewis acid promoted intramolecular substitution of the 4-vinyloxy group.




**219** **9**

**Scheme 97**

I prepared bromide **242** derived from *o*-thio-cresol following literature procedures (Scheme 98).[141] As a protective group I choose Boc since it is stable under basic conditions what enables *N*-alkylation of azetidin-2-one **9** and may be easily removed from the sulfur atom in acidic media.

[141] a) Houlihen, F.; Bouchard, J.; Frechet, J. M.; Willson, C. G., *Can. J. Chem.* **1985**, *63*, 153; b) Hartman, G. D.; Halenczko, W.; Smith, R. L.; Sugrue, F.; Mellarge P. J., *J. Med. Chem.* **1992**, *35*, 3822



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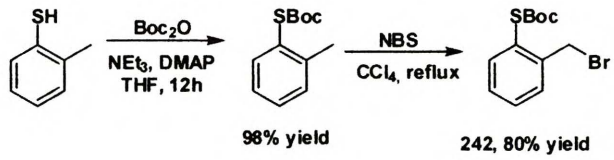
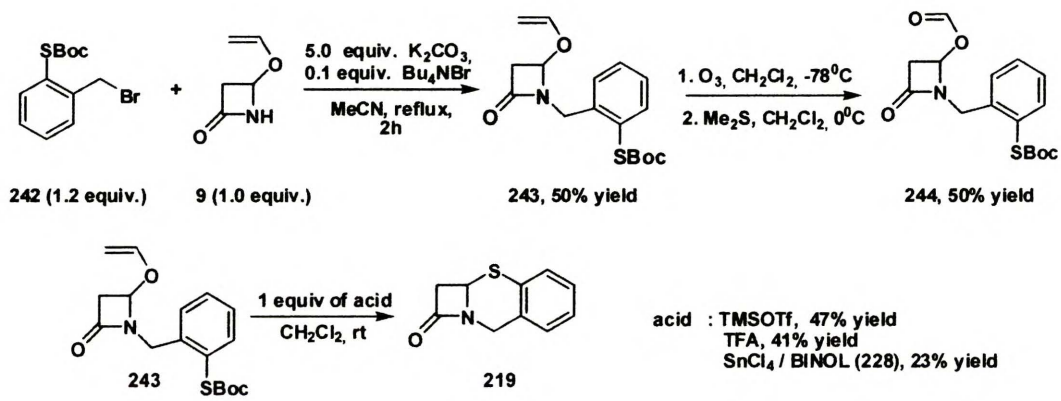



**Scheme 98**

*N*-Alkylation of azetidinone **9** with **242** was performed under PTC condition ($K_2CO_3$, TEBABr, acetonitrile, reflux) to afford compound **243** in 50% yield (Scheme 99). Compound **243** was transformed into 4-formyloxy one **244** upon treatment with ozone. It is important to note, however, that the 4-vinyloxy group in **243** can undergo acid promoted nucleophilic substitution without prior deprotection of the thiol. Cyclizations were performed in dichloromethane at room temperature with equimolar amount TMSOTf or TFA to give **219** in moderated yield (Scheme 99).




**Scheme 99**

All attempts to obtain enantiomericaly enrich cepham **219** in the presence of (*S*)-BINOL (**233**) failed as show in Table 14. Under standard cyclization conditions[142] (Table 14, entry 6) only racemic **219** was formed in low yield. Any change of the temperature of experiment did not affect the enantioselectivity, as well. As was expected, reduction of a ligand – substrate ratio did not give successful result either (entries 4, 5). However, when reaction time was extended to 7.5h and the ligand **236** was employed, cepham **219** was formed in 12% yield after silica gel column chromatography and 48% *ee*.

[142] See page 77, Table 10



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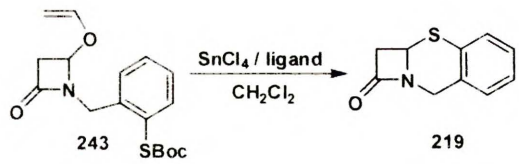
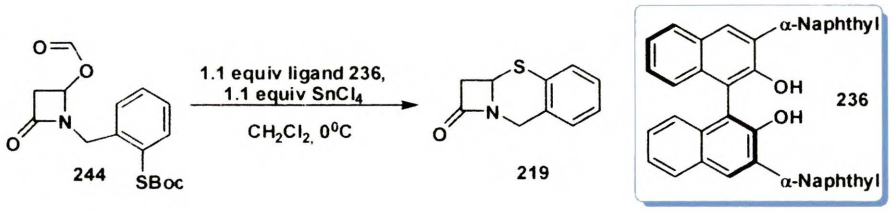



| Entry | Ligand | Conditions | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | (*S*)-BINOL **233** | 1.1 equiv 0°C, 1.5h | 23 | 0 |
| 2 | (*S*)-BINOL **233** | 1.1 equiv -78°C, 24h | - | - |
| 3 | (*S*)-BINOL **233** | 1.1 equiv, rt, 0.5h | 25 | 0 |
| 4 | (*S*)-BINOL **233** | 0.1 equiv, rt, 24h | 0 | - |
| 5 | (*S*)-BINOL **233** | 0.5 equiv, rt, 24h | 0 | - |
| 6 | (*S*)-3,3'-bis-α-naphthyl-BINOL **236** | 1.1 equiv 0°C, 1.5h | 25 | 0 |
| 7 | (*S*)-3,3'-bis-α-naphthyl-BINOL **236** | 2.2 equiv 0°C, 1.0h | 23 | 0 |
| 8 | (*S*)-3,3'-bis-α-naphthyl-BINOL **236** | 2.2 equiv 0°C, 7.5h | 12[c] | 48 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **243** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC. [c] Reaction was carried out until disappearance of substrate **243** and additional 6h.

**Table 14**

Similar result was observed when cyclization of **244** was performed following reaction conditions used for compound derivative from *o*-cresol **231** (moderate yield and a lack of enantioselectivity was noticed) (Scheme 100).




**Scheme 100**

The cyclization of **243** in the presence of chiral Lewis acid suggests that enantiomeric enrichment is induced by asymmetric destruction of initially formed cepham (Table 15, entry 8). To find the best conditions of asymmetric kinetic resolution, cepham (±)-**219** was subjected to the chiral catalyst treatment. The best result was obtained in the presence of equimolar amount of the ligand **236** and $SnCl_4$ in dichloromethane at 0°C; after 6h (+)-**219** was obtained in 48% yield and 46% *ee* (Table 15).



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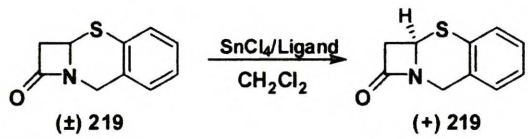



| Entry | Ligand | Conditions | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | (*S*)-BINOL **233** | 1.0 equiv, 0°C, 6h | 45 | 0 |
| 2 | (*S*)-BINOL **233** | 0.5 equiv, 0°C, 6h | 43 | 0 |
| 3 | (*S*)-3,3'-bis-*α*-naphthyl-BINOL **236** | 1.0 equiv, 0°C, 6h | 48 | 46 |

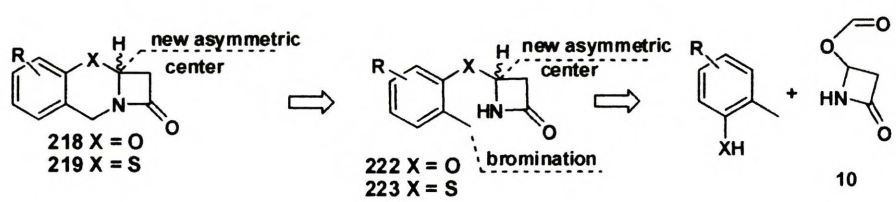
[a] Isolated yield determined after flash chromatography on $SiO_2$. [b] The enantiomeric excess was determined by chiral HPLC.

**Table 15**

The kinetic resolution of initially formed cepham *rac*-**219** is much slower than in case of 5-oxacephams: *rac*-**218** and *rac*-**224**. It remains in agreement with the fact that *N,S*-acetals are usually more stable under acidic conditions than *N,O*-acetals. The lower enantioselectivity of enantiomer-differention of cepham *rac*-**219** than *rac*-**218** may be caused also by worse matching of the sulphur atom than the oxygen one to the chiral promoter. It is why the further decomposition via the unstable acylimminium cations provides lower enantioselectivity.

### 3.2.4. Intermolecular Chiral Lewis acid mediated synthesis of azetidin-2-ones 222 and 223

As a complementary methodology for enantioselective synthesis of cephmas **218** and **219**, the intermolecular process can be applied (Scheme 101). The key step for this route involved a chiral Lewis acid mediated intermolecular substitution of 4-formyloxy group of azetidin-2-one **10** by the oxygen or sulfur atom of appropriate *o*-cresol or *o*-thiocresol. Subsequent steps assumed bromination of the benzyl position in **222** and **223** and intramolecular *N*-benzylation leading to the ring closure.




**Scheme 101**

At the beginning, due to relatively low toxicity of *o*-cresol **245a**, the scope of chiral Lewis acid promoted nucleophllic substitution at C-4 of azetidin-2-ones was extended to intermolecular reactions leading to 4-aryloxy azetidinones **222** (Table 16). In the case of Lewis acids, formation of product was not observed. Only Brønsted acids allowed to obtain the racemic compound **222a** in relatively good yield (Table 16).



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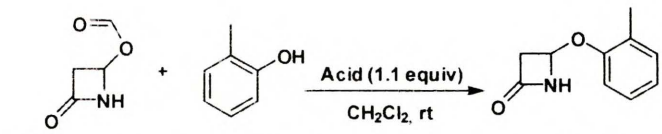


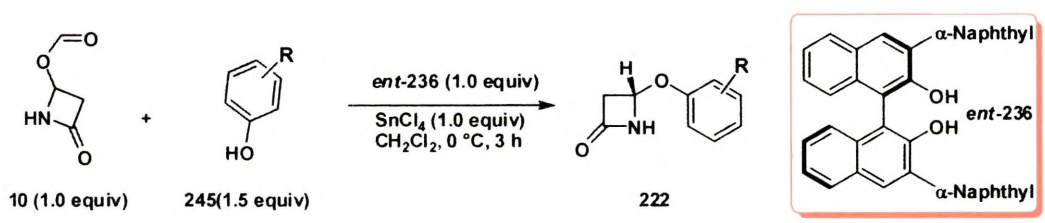

10 (1.0 equiv) 245a (1.5 equiv) 222a

| Entry | Acid | Time [h] | Yield [%][a] |
|---|---|---|---|
| 1 | $SnCl_4$ | 3 | 0 |
| 2 | $BF_3OEt_2$ | 3 | 0 |
| 3 | CSA | 24 | 23 |
| 4 | *p*-TsOH | 24 | 75 |
| 5 | TFA | 24 | 20 |
| 6 | $H_2SO_4$ | 10 | 70 |

[a] Isolated yield determined after flash chromatography on $SiO_2$

**Table 16**

It is important to note, that a combination of $SnCl_4$ / (*S*)-BINOL (**233**) works as Brønsted acid to provide expected product **222**.[135] In all cases under the standard cyclization conditions (1 equiv of (*R*)-3,3'-bis-α-naphthyl-BINOL ***ent*-236**/$SnCl_4$, $CH_2Cl_2$, 0°C, 3h), a moderate chemical yield and enantioselectivity, much lower than that observed for the intramolecular process, were noticed (Table 17). It should be stressed that in this case the enantiomeric form of ligand **236** was used (***ent*-236**), so observed direction of asymmetric induction was also opposite. Similarly as for compound **231f** (Table 10, entry 7),[143] due to bromine atom in the aromatic ring, compound **245d** did not provide expected product (Table 17, entry 4).




10 (1.0 equiv) 245(1.5 equiv) 222

| Entry | Compound | R | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **245a** | 2-Me | **222a** | 25 | 12 |
| 2 | **245b** | 2-Me, 3-OMe | **222b** | 26 | 31 |
| 3 | **245c** | 2-Me, 5-Ph | **222c** | 20 | 24 |
| 4 | **245d** | 2-Me, 5-Br | **222d** | 0 | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$ Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 17**

[143] See page 77, Table 10



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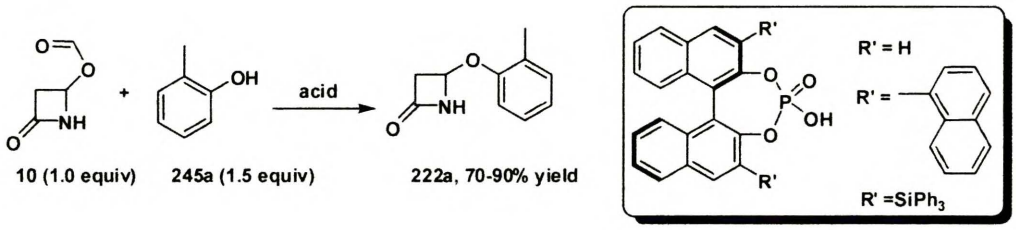
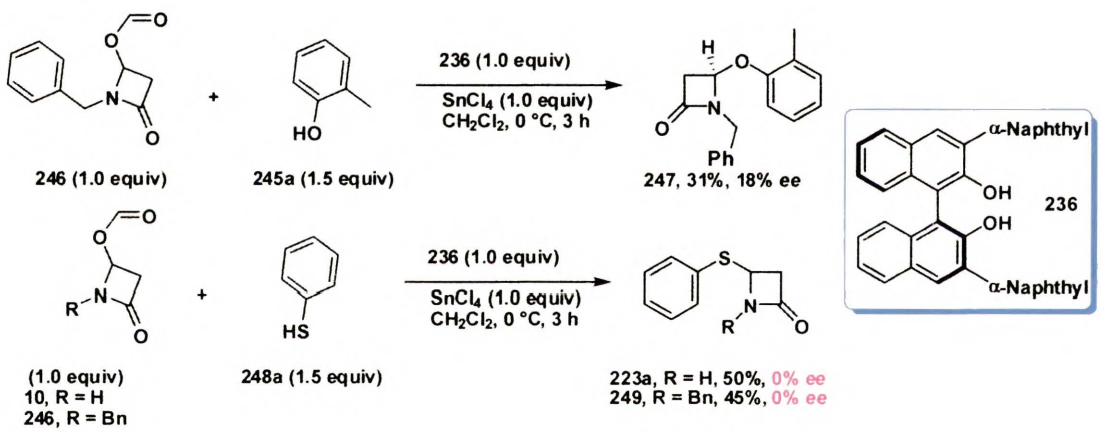
Since the phenol **245a** reacts with azetidinone **10** in the presence Brønsted acids, I decided to check whether chiral Brønsted acids would provide better results. The initial studies indicated that azetidinone **10** did not undergo nucleophlic substitution in the presence of different Brønsted acids like (*S*)-BINOL (**233**) or thiourea catalyst of type **170** (Chapter 2.2.2). Only in the presence of chiral phosphoric acids derived from BINOL, expected 4-phenoxy-azetidin-2-one **222** was formed in good yield (70-90%) but as a racemate (Scheme 102).




**Scheme 102**

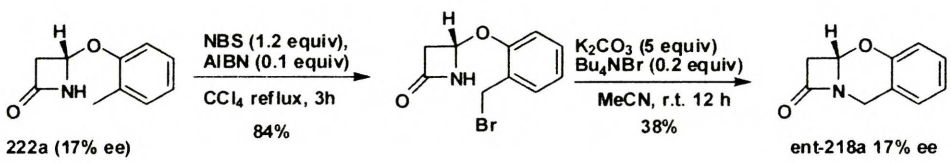
A use of *N*-benzylated azetidin-2-one **246** for alkylation of phenol **245a** did not improved enantioselectivity (Scheme 103).




**Scheme 103**

In the case of intermolecular process, involving thiophenol **248a**, expected products **223a** and **249** were obtained as a racemic mixtures (Scheme 103).

In order to make correlation of absolute configuration with compounds obtained in intramolecular process, compound ***ent*-222a** (17% ee) was transformed into ***ent*-218a** (17% ee) *via* NBS bromination of the methyl group followed by the intramolecular alkylation of the nitrogen atom (Scheme 104).




**Scheme 104**



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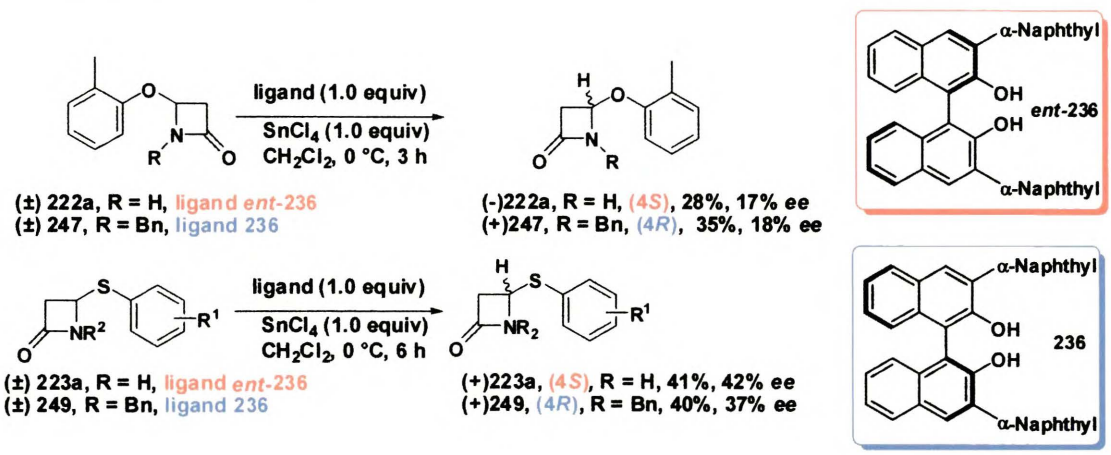
To check whether the process of asymmetric degradation is also responsible for enantiomeric enrichment of azetidin-2-ones ***ent*-222**, and **247**, compounds (±)-**222a** and (±)-**247** were subject to (*R*)-3,3'-bis-α-naphthyl-BINOL ***ent*-236**/$SnCl_4$ and (*S*)-3,3'-bis-α-naphthyl-BINOL (**236**)/$SnCl_4$ treatment, respectively. Enantiomerically enhanced 4-aryloxyazetidin-2-ones (-)-**222a** and (+)-**247** were formed with 17% and 18% *ee*, respectively to prove the same mechanism for all processes (Scheme 105).




**Scheme 105**

Asymmetric degradation of 4-phenylthio-azetidin-2-ones ((±)-**223a**, (±)-**249**), in contrast to the cyclization process, gave better results than that found for oxygen congeners. After 6h both (+)-**223a** and (+)-**249** underwent destruction in 59% and 60% with 42% and 37% *ee*, respectively (Scheme 105).

The low asymmetric induction for the intermolecular process is worth to mention since it implies that the generation of the defined absolute configuration at C-4 of azetidinone *via* that way cannot be achieved. It is know that aryloxy group at C-4 of azetidin-2-ones may be substituted by other nucleophiles in both acidic and basic conditions.[132,133,134] Therefore, the low asymmetric induction can be assigned to a reversible process abstraction-addition of the aryloxy group.

### 3.2.5. Conclusions

In conclusion, for the first time the enantioselective approach to the synthesis of oxygen analogues of cephalosporins is described. At the beginning of my investigations, we were aware that enantioselective process would be difficult to be to observed since the Lewis acid should attack acyloxy or vinyloxy substituent and depart with it leaving acyliminium cation without the face differentiating catalyst. It means that the active intermediate is not bound to the chiral ligand and consequently the chiral Lewis acid would not be able to induce enantioselectivity. The high asymmetric induction which surprised us, could be perfectly explained by a kinetic resolution of the primary formed racemic oxacepham. This mechanistic proposition is also in agreement with yield of the reaction below 50% and equimolar amount of the catalyst necessary to complete the reaction. It is important to note that while the chiral complex has to be used in a stoichiometric amount, the chiral ligand could



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be easily recovered from the post-reaction mixture and reused without any appreciable loss of enantiomeric purity.



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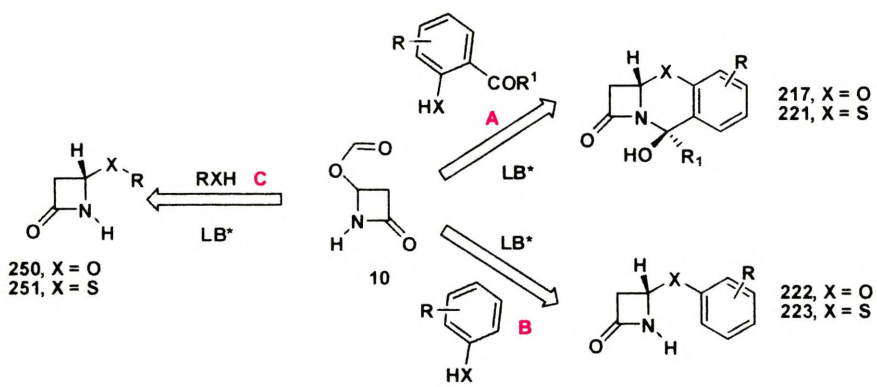
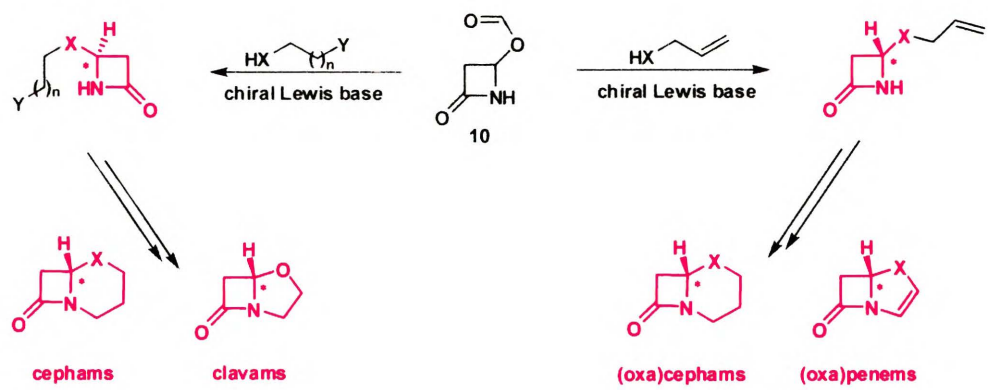
### 3.3. Chiral Lewis base mediated nucleophilic substitution at C-4 of 4-formyloxyazetidin-2-one (10)

Second part of my work was concentrated on the asymmetric synthesis of cephams **217** and **221** *via* chiral Lewis base catalyzed nucleophilic substitution at C-4 of 4-formyloxyazetidin-2-one (Scheme 106, pathway A). The reaction pathway is based on the base-promoted condensation of *o*-hydroxy-phenones. The same methodology may be applied in the synthesis of 4-substitiuted azetidin-2-ones **222** and **223** (Scheme 106, pathway B), as well as azetidin-2-ones of type **250** and **251** (Scheme 106 pathway C). Both processes proceed *via* flat 1,4-dehydroazetidin-2-one according to the elimination-addition mechanism. Therefore the corresponding intramolecular process catalysed by a chiral Lewis base cannot proceed.




**Scheme 106**

The use of both aliphatic and aromatic alcohols and thiols in substitution reactions at C-4 of acyloxy-azetidinones may lead to biologically active compounds inhibiting various enzymes (elastases, proteases).[115] Moreover, some of those products may serve as a substrates in the synthesis of enantiomerically enhanced cephams, penems, or clavams (Scheme 107).[113]




**Scheme 107**



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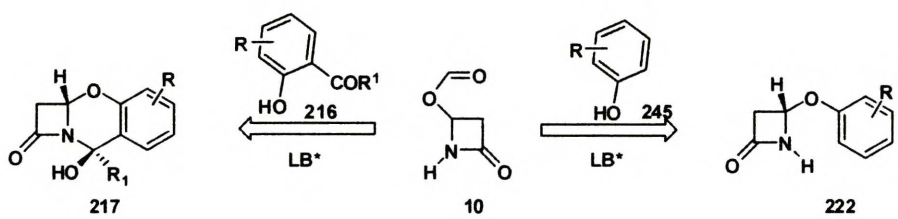
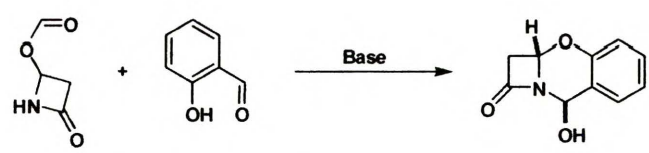
### 3.3.1. Chiral Lewis base mediated synthesis of 5-oxacephams 217 and 4-aryloxyazetidin-2-ones 222

A retro-synthesis of enantiomerically enriched oxacephams **217** and 4-aryloxyazetidinones **222** have been presented in the Scheme 108. The key step of this approach is a Lewis base catalyzed nucleophilic substitution at C-4 of the azetidin-2-on ring. The reaction pathway is based on the base-promoted condensation of *o*-hydroxy-phenones, or phenols with the 4-formyloxy-azetidin-2-on (**10**). The choice of these compounds to tests was dictated by presence of two chromophore systems, low volatility and toxicity.




**Scheme 108**

It is known, that 4-formyloxyazetidinone (**10**) undergoes condensation with the salicylaldehyde (**216a**) in the presence of different bases: inorganic, alcoxides or amines.[134] However, the most promising result was found for catalytic amount of DBU or DABCO. Both bases provide the product *rac*-**217a** in 80 and 84% yield, respectively (Table 18).




| Entry | Base | Condition | Yield [%][a] |
|---|---|---|---|
| 1 | 1M NaOH | 1 equiv, DMF/$H_2O$ 1/1, rt, 1h | 38 |
| 2 | *t*-BuONa | 1 equiv, THF, rt, 0.5h | 76 |
| 3 | MeONa | 1 equiv, MeOH, rt, 12h | 50 |
| 4 | DBU | 1 equiv, THF, rt, 24h | 84 |
| 5 | DBU | 0.1 equiv, THF, rt, 48h | 80 |
| 6 | DABCO | 1 equiv, THF, rt, 48h | 87 |
| **7** | **DABCO** | **0.1 equiv, THF, rt, 72h** | **84** |
| 8 | $Et_3N$ | 1 equiv, THF, 0°C, 3h | 55 |

[a] Isolated yield determined after flash chromatography on $SiO_2$.

**Table 18**



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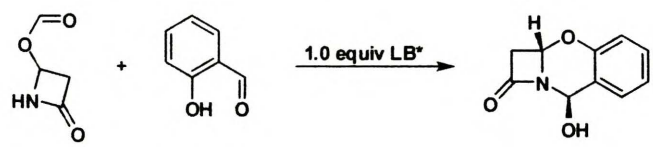
The use of catalytic amount of tertiary amines prompted me to check whether chiral amines could be use to promote the same reaction but in an enantioselective way. The initial studies indicated that in the presence of (-)-sparteine, (*S*)-*N*-bezylprolinol or non-racemic 2-dimethylamino-1,2-diphenylethanol, the expected cepham **217a** was formed in good yield but as a racemic mixture. However, when quinidine (**253**) was used, the condensation proceeded smoothly to give (+)-**217a** in 77% yield with 31% *ee* (Table 19, entry 2).




**10, 1 equiv** **216a, 1.5 equiv** **217a**

| Entry | Lewis Base | Conditions | Yield [%][a] | *ee*[%][b] |
|---|---|---|---|---|
| 1 | (-)-Sparteine **252** | THF, -78 °C, 1h | 82 | 0 |
| **2** | **Quinidine 253** | **THF, rt, 48h** | **77** | **31** |
| 3 | *(S)*-*N*-bezylprolinol **254** | toluene, reflux, 12h | 80 | 0 |
| 4 | (1*R*,2*S*)- 2-dimethylamino-1,2-diphenylethanol **255** | THF,-78 °C, 2h | 50 | 0 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 19**

This first positive results prompted me to check whether the use of quinidine (**253b**) as a promoter would provide the product with better enantioselectivity. When the reaction temperature was decreased to 0°C, the same enantioselectivity was observed (Table 20, entry 2). If dichloromethane or diethyl ether were used as solvents, the reaction yield was practically unchanged but the enantioselectivity was reduced to 24% and 6%, respectively. There was no enantioselecivity when DMF was used as a solvent. In the case of toluene enantiomeric excess raised to 51%. It should be stressed that 0.1 equiv. of the quinidine (**253**) in toluene gave product in the same yield and almost the same enantioselectivity. As a general trend, it was found that the reaction rate can be increased upon addition of $CaCO_3$ (5 equiv., entry 10). The enantiomeric excess was unchanged but the yield was reduced to 65%. A control experiment showed that $CaCO_3$ itself has not been responsible for the activation of **10**, but it trapped formic acid liberated during the substitution reaction. A combination of catalytic amount of quinidine **253** and different inorganic and organic bases ($K_2CO_3$, $NaHCO_3$, DBU, DABCO) were also tested. In all cases expected 3,4-benzo-2-hydroxy-5-oxacepham (+)-**217** was formed in good yield but enantioselectivity was considerably reduced.



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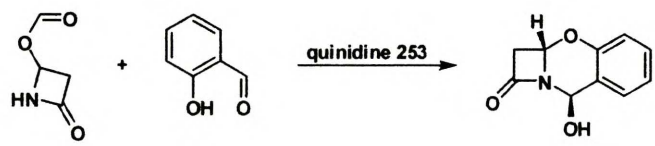


10, 1 equiv 216a, 1.5 equiv 217a

| Entry | Solvent | Amount of catalyst | Temperature | Time [h][a] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | THF | 1.0 equiv | rt | 48 | 77 | 31 |
| 2 | THF | 1.0 equiv | 0°C | 96 | 70 | 33 |
| 3 | $CH_2Cl_2$ | 1.0 equiv | rt | 24 | 83 | 24 |
| 4 | DME | 1.0 equiv | rt | 24 | 65 | 6 |
| **5** | **Toluen** | **1.0 equiv** | **rt** | **48** | **78** | **51** |
| 6 | DMF | 1.0 equiv | rt | 48 | 40 | 0 |
| 7 | DMF/MS4Å | 1.0 equiv | rt | 48 | 78 | 0 |
| 8 | Toluen | 0.5 equiv | rt | 48 | 76 | 48 |
| **9** | **Toluen** | **0.1 equiv** | **rt** | **48** | **77** | **49** |
| 10[d] | Toluen/$CaCO_3$ | 0.1 equiv | rt | 12 | 65 | 49 |

[a] Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] Isolated yield determined after flash chromatography on $SiO_2$. [c] The enantiomeric excess was determined by chiral HPLC. [d] 5 equiv. of $CaCO_3$ was added.

**Table 20**

This first attractive result prompted me to investigate enantioselective condensation under the same condition by varying the chiral amines (Table 21). In all cases 0.1 equiv of chiral Lewis base was used. Reactions were carried out in toluene at room temperature during 48h. Owing to the use of pseudoenantiomer pairs of cinchoina alkaloids the enantiomeric excess was comparable, providing enantiomers with opposite configuration. When $(DHQD)_2PHAL$ (**259**) was used, **217a** was obtained in 52% yield with 46% *ee* (entry 5). Introduction of *N*-Boc protected amine in the place of the hydroxyl group diminished both chemical yield and the enantioselectivity (entry 6). No condensation occurred when the catalyst contained acyl or silyl protected hydroxy group, or in the case of a free amino function in the place of hydroxyl (entries 7-10).



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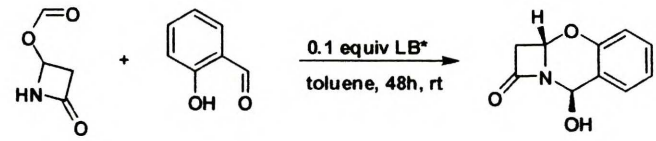
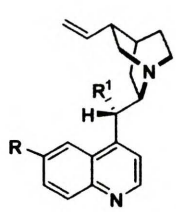


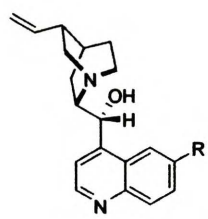

10, 1 equiv  216, 1.5 equiv  217

| Entry | Lewis base | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|
| 1 | **253** | 78 | 48 (**217a**) |
| 2[c] | **256** | 46 | 14 (***ent*-217a**) |
| 3[c] | **257** | 69 | 14 (**217a**) |
| 4[c] | **258** | 63 | 6 (***ent*-217a**) |
| 5 | **259** | 52 | 46 (**217a**) |
| 6 | **260** | 36 | 16 (**217a**) |
| 7 | **261** | 0 | - |
| 8 | **262** | 0 | - |
| 9 | **263** | 0 | - |
| 10 | **264** | 0 | - |

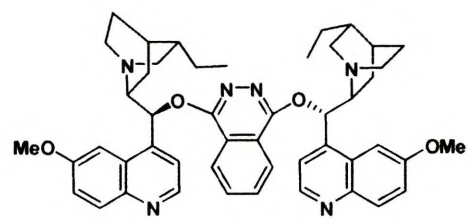
[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPL. [c] Reaction performed in THF.



**253** R = OMe, R' = OH quinidine
**257** R = H, R' = OH cinchonine
**260** R = OMe, R' = NHBoc
**261** R = OMe, R' = $NH_2$
**262** R = OMe, R' = OAc
**263** R = OMe, R' = OTBS
**264** R = OH, R' = OH



**256** R = OMe quinine
**258** R = H cinchonidine



**259**

**Table 21**



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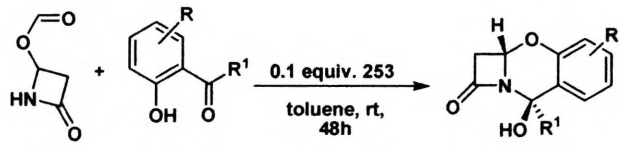
Subsequently, I analyzed the scope of this asymmetric reaction with various *o*-hydroxy-benzaldehydes and ketones. As shown in Table 22, the enantiomeric excess, as well as the yield of products, depended on the nature of the substituent in the phenol ring. In all cases only one diastereomer having *syn* hydroxyl group and the bridgehead proton was formed in good yield and moderate enantioselectivity.




1 equiv. 10 | 1.5 equiv. 216a-f | 217a-f

**216a, 217a** R = H, $R^1$ = H
**216b, 217b** R = 5-Br, $R^1$ = H
**216c, 217c** R = 4-OH, $R^1$ = H
**216d, 217d** R = H, $R^1$ = $CH_3$
**216e, 217e** R = H, $R^1$ = Ph
**216f, 217f** R = 5-F, $R^1$ = $CH_3$

| Entry | Phenone | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | **216a** | **217a** | 77 | 49 |
| 2 | **216b** | **217b** | 76 | 40 |
| 3 | **216c** | **217c** | 89 | 32 |
| 4 | **216d** | **217d** | 75 | 16 |
| 5 | **216e** | **217e** | 92 | 43 |
| 6 | **216f** | **217f** | 79 | 24 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 22**



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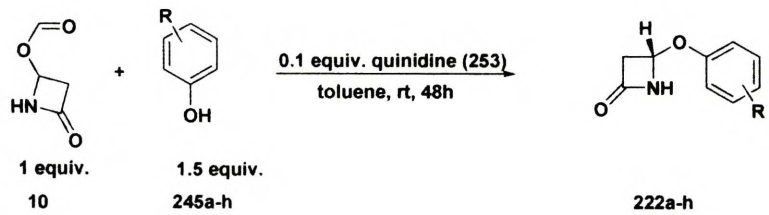
The scope of this transformation was further extended to the intermolecular reactions leading to compounds **222** (Table 23). In all cases, under the same conditions, a good chemical yield was noticed and enantioselectivity in the range of that found for reactions with hydroxy-phenones.

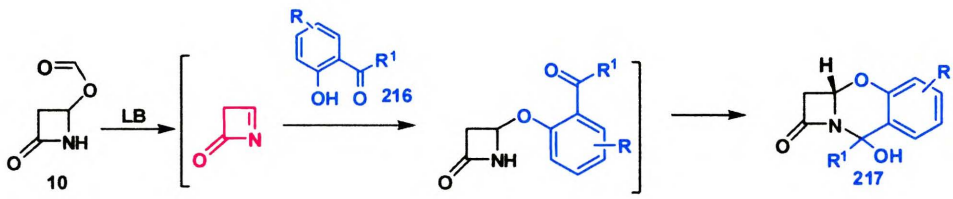



| Entry | Phenol | R | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **245a** | 2-Me | **222a** | 77 | 48 |
| 2 | **245b** | 2-Me, 3-OMe | **222b** | 69 | 46 |
| 3 | **245c** | 2-Me, 5-Ph | **222c** | 77 | 50 |
| 4 | **245d** | 2-Me, 5-Br | **222d** | 74 | 24 |
| 6 | **245e** | 2-$CO_2Me$ | **222e** | 0 | - |
| 7 | **245f** | 2-*t*-Bu | **222f** | 54 | 46 |
| 8 | **245g** | 3-$NO_2$ | **222g** | 82 | 43 |
| 9 | **245h** | 2-$CH_2CO_2Me$ | **222h** | 65 | 11 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 23**

All results suggest that in the case of hydroxy-phenones the first step of the reaction involves nucleophilic substitution *via* elimination/addition mechanism, not the acetal formation. Consequently enantioselectivity is created in an inter- not intramolecular process. The second step leading to the ring closure is controlled by thermodynamics providing always *exo* location of the hydroxy group (Scheme 109).




**Scheme 109**

Recently, it has been shown,[100] that cinchona alkaloids can act both as chiral Brønsted acid (OH-group) and chiral Lewis base (tertiary amine). However, in such a case reaction should proceed via *N*-acyliminium ion as a



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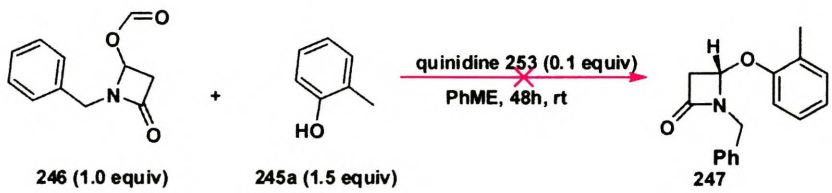
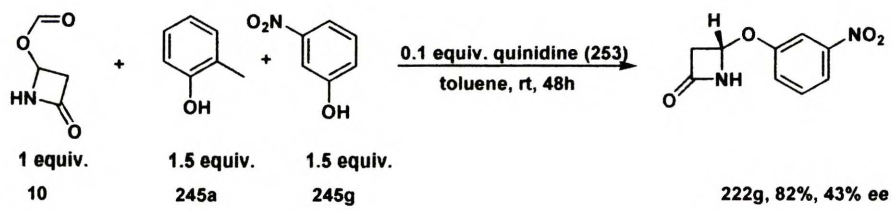
reactive species. To eliminate this hypothesis, I applied standard reaction condition for nucleophilic substitution of 4-formyloxy group in *N*-benzylated 4-fromyloxyazetidin-2-one **246** (Scheme 110). As it was expected, no reaction occured. This experiment unequivocally proved that reaction between phenols and 4-formyloxy-azetidinone (**10**) has to proceed *via* flat 1,4-dehydroazetidin-2-one.




**Scheme 110**

In order to put more light on the reaction mechanism, I decided to perform a competitive experiment using for 1 equiv. of **10**, 1.5 equiv. of **245a** and 1.5 equiv. of **245g**. As result, only compound **222g** was obtained in 82% yield and 43% *ee* (Scheme 111). This testified that deprotonated phenol is an active reagent that approaches the neutral intermediate 1,4-dehydroazetidin-2-one since *m*-nitro-phenol is more acidic then *o*-cresol. Enantioselectivity is induced by the counter ion, the protonated chiral base, which accompanied the phenol anion, although a hydrogen bond between the base hydroxyl group and the dehydroazetidinone intermediate should also be taken into account.




**Scheme 111**

These results remain in contrast to the chiral Lewis acid catalyzed intermolecular process, which was less effective. 4-Aryloxyazetidin-2-ones **222**, with the use of chiral Lewis acid, were obtained with 12-24% enantiomeric excess and up to 26% yield only, whereas the application of chiral Lewis base allowed to obtained 4-aryloxyazetidin-2-ones **222** with both higher *ee* (up to 51%) and yield (up to 82%).

### 3.3.2. Lewis base mediated synthesis of 4-aryltioazetidin-2-ones 223 and cepham 218

As a continuation of my studies, I decided to check whether a change of the nucleophile atom from oxygen in **245** to sulfur in **248** would affect the enantioselectivity of substitution process (Scheme 112). In the case of a chiral Lewis acid mediated reaction, such a change resulted in decrease of *ee*.



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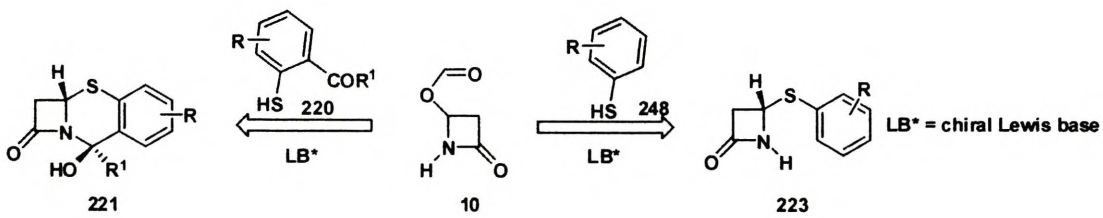
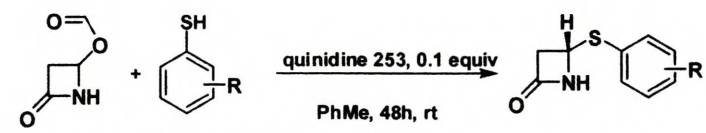



**Scheme 112**

In the case of aromatic thiols **248a-e**, quinidine **253**, as before, provided the best results. Reaction of 4-formyloxyazetidin-2-one (**10**) with thiophenols **248a-e**, in the presence of catalytic amount of quinidine **253**, in toluene at room temperature gave 4-arylthioazetidin-2-ones **223a-e** in a very good yields and moderate enantiomeric excesses (Table 24).




| Entry | Thiol | R | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **248a** | H | **223a** | 84 | 42 |
| 2 | **248b** | 2-Me | **223b** | 89 | 49 |
| 3 | **248c** | 4-OH | **223c** | 95 | 11 |
| 4 | **248d** | 2-OMe | **223d** | 75 | 34 |
| 5 | **248e** | 4-Br | **223e** | 95 | 34 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 24**

Regarding enantioselectivity the results presented in Table 24 are comparable to those obtained in reactions of **10** with phenols **245** in the presence of quinidine **253** (Table 23). Therefore, I decided to perform reaction of **10** with thiosalicyl aldehyde (**220**) only. Consequently, I did not synthesized any substituted in the aromatic ring thiosalicyl aldehydes.

Thiosalicylaldehyde (**220**) was synthesized according to literature procedure in 3 steps form commercially available *o*-thiosalicylic acid (**220**) (Scheme 103).[144] Under the same conditions of nucleophilic substitution,

[144] Sorag, P. B.; Holmgren, S. K.; Gellman,` S. H., *J. Am. Chem. Soc.*, **1993**, *115*, 7900



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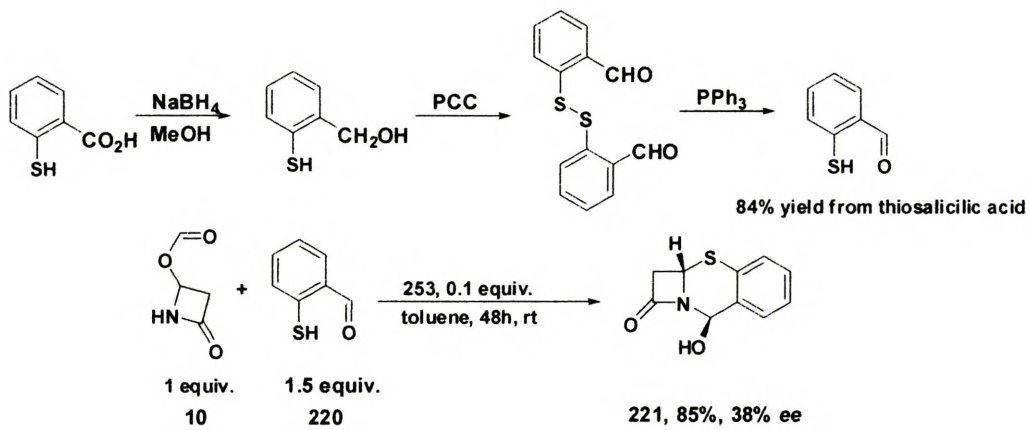
azetidinone **10** underwent condensation with the aldehyde **220** to provide 3,4-benzo-2-hydroxycepham **221** in 85% yield and with 38% *ee* (Scheme 113).

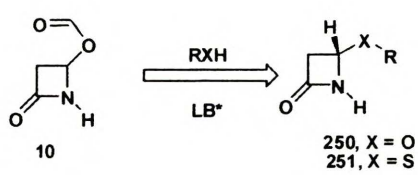



**Scheme 113**

The cepham **221** was obtained only with slightly lower yield than its oxygen analogue and comparable *ee* to those found for compound **223a**. The change from the oxygen nucleophile into the sulfur one did not affect the enantioselectivity of the process. This results is in agreement with proposed reaction mechanism.

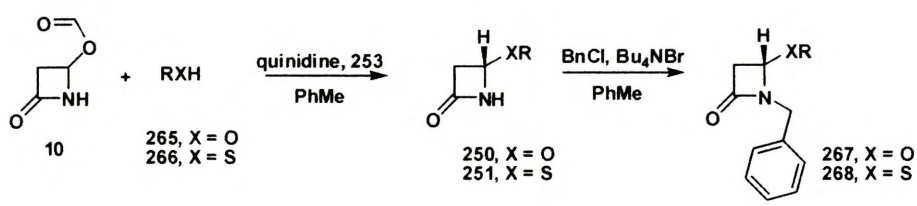
### 3.3.3. Lewis base mediated nucleophilic substitution at C-4 of azetidin-2-one by thiols and alcohols

The next stage of my work was directed to application of aliphatic alcohols and thiols as nucleophiles in the chiral Lewis base mediated substitution at C-4 of 4-formyloxyazetidin-2-one (**10**) (Scheme 114).




**Scheme 114**

First experiments showed that obtained products were volatile and hard to be detected on HPLC. In most cases only after benzylation of the nitrogen atom in **250/251** leading to corresponding **267/268**, both yields and enantiomeric excesses could be assigned (Scheme 115).




**Scheme 115**



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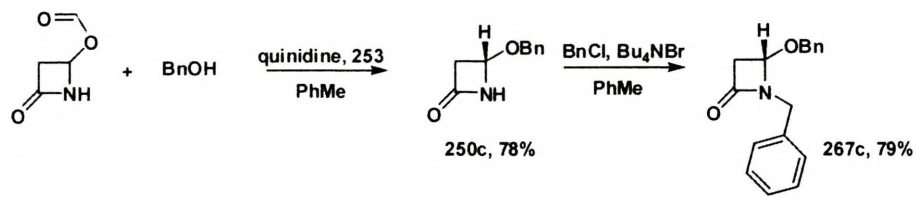
The experiment performed on 4-benzyloxy-azetidin-2-one **250c** showed that *N*-benzylation was almost a quantitive process (Scheme 116). Reaction was performed in such a way that after quinidine promoted process, the mixture was filtrated through silica gel. Subsequently the filtrate was slowly added to a solution of 50% aqueous NaOH, equimolar amount of $Bu_4NBr$ and benzyl chloride dissolved in a small amount of toluene. *N*-Benzylation performed in such a way provided expected product **267c** in quantitive yield. Moreover, the experiment performed on compound ***ent*-222a** (Scheme 104) showed that *N*-alkylation does not affect the *ee*.[145]




**Scheme 116**

In the case of phenols and thiophenols, reactions with 4-formyloxyazetidin-2-one (**10**) in the presence of catalytic amount of quinidine (**253**) provided comparable yields and enantioselectivities. Different results were obtained when alcohols and mercaptans were applied (Table 25). In the case of aliphatic alcohols at room temperature the equimolar amount of quinidine (**253**) was required to obtain 100% conversion of 4-formyloxyazetidin-2-one (**10**). An excess of the nucleophile should also been raised from 1.5 to 3 equivalents. In case of aliphatic thiols there were no necessary to change reaction conditions – only 0.1 equivalent of quinidine (**253**) was required and 1.5 equivalent of thiol.

[145] See page 86; Scheme 104



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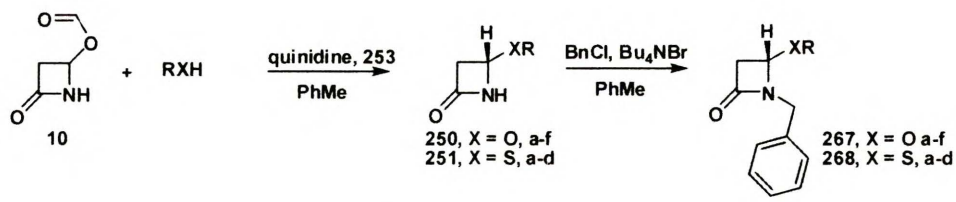


| Entry | X | R | Product | Yield[%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | O | $CH_2CHCH_2$ | **267a** | 15 | 10 |
| 3 | S | $CH_2CHCH_2$ | **268a** | 40 | 38 |
| 5 | O | $CH_2CCH$ | **267b** | 30 | 12 |
| 7 | O | $PhCH_2$ | **267c** | 77 | 4 |
| 8 | S | $PhCH_2$ | **268b** | 86 | 34 |
| 9 | O | Et | **267d** | 12 | nd |
| 10 | O | iPr | **268e** | 15 | 11 |
| 12 | S | tBu | **268c** | 65 | 12 |
| 13 | O | tBu | **267f** | 0 | - |
| 15 | S | Trytyl | **251d** | 89 | 51 |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 25**

As shown in Table 25 the aliphatic thiols gave better results than alcohols. Both yields and enantioselectivities were higher. When *t*-butyl alcohol was used no reaction was observed (Table 25, entry 13), but its thio- congener gave expected product in 65% yield and 12% *ee*. The best result was obtained for triphenylmethyl thiol. It gave an excellent yield of **251d** and 51% *ee* (entry 15). Moreover, in this case further benzylation of nitrogen atom in order to assign enantioselectivity was not necessary.

It is known from literature[146] that in some cases the nucleophilic substitution at C-4 of the azetidinone ring may proceed with amines. Therefore, I performed a nucleophilic substitution of the formyloxyl in **10** by aniline derivatives. In all cases, however, the amine did not enter nucleophilic substitution in the presence of quinidine **253** (Scheme 117).

[146] a) Abdula, R. F.; Fuhr, K. H., *J. Med. Chem.* **1975**, *18*, 625; b) Perelluen, M. *J. Am. Chem. Soc.* **1962**, *84*, 4988



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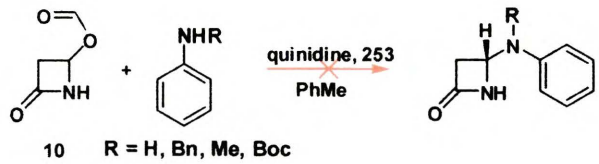
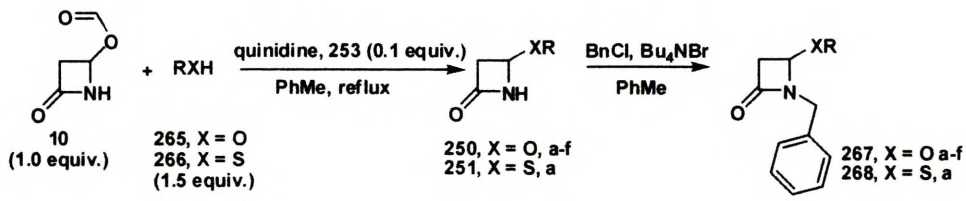



**Scheme 117**

To improved yield of reaction of **10** with aliphatic alcohols and thiols the temperature was raised. It appeared that when reaction was performed at reflux only catalytic amount of quinidine (**253**) was required and the reaction time was shorten to 12h. This provided products in satisfactory yield, but in all cases racemates were formed (Table 26).

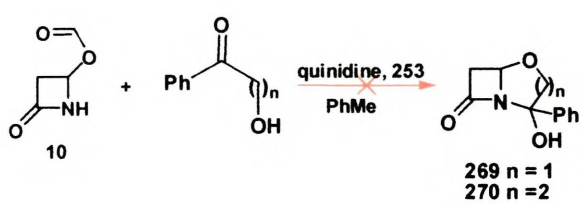



| Entry | X | R | Product | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 2 | O | $CH_2CHCH_2$ | **267a** | 70 | 0 |
| 4 | S | $CH_2CHCH_2$ | **268a** | 85 | 0 |
| 6 | O | $CH_2CCH$ | **267b** | 75 | 0 |
| 11 | O | *i*-Pr | **267e** | 70 | 0 |
| 14 | O | *t*-Bu | **267f** | 0 | - |

[a] Isolated yield determined after flash chromatography on $SiO_2$. Reaction was carried out until disappearance of substrate **10** (TLC monitored). [b] The enantiomeric excess was determined by chiral HPLC.

**Table 26**

I decided to check, if hydroxy-ketones undergo similar to salycilic aldehyde reactions with **10** to provide corresponding penams **269** and cephams **270**. In all cases no reaction was observed. Changes of the reaction conditions (amount of quinidine (**253**) and temperature) did not affect the result (Scheme 118).




**Scheme 118**



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### 3.3.4. Conclusions

In conclusion, the enantioselective approach to the synthesis of 3,4-benzo-2-hydroxy-5-oxacephams, 4-aryloxyazetidin-2-ones and its thio congeners was described. The key step of this method is based on the chiral Lewis base mediated, enantioselective, intermolecular alkylation of the phenol hydroxy or mercapto group by intermediately formed dehydro-azetidinone, which proceeds *via* the elimination/addition mechanism. It is important to note that the chiral Lewis base is used in the catalytic amount without effecting both yield and enantioselectivity. It stays in contrast with previously described the chiral Lewis acid mediated enantioselective alkylation of the phenol hydroxy group by the *N*-acyliminium ion generated from the 4-formyloxy-azetidinone (**10**), which requires always equimolar amount of the promoter and proceeds in low yield but high asymmetric induction as the intramolecular process, or in good yield but low asymmetric induction as the intermolecular process. Moreover, it should be stressed, that the method presently reported can be use in the synthesis of various phenoxy substituted azetidinones having potential biological activity.



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### 3.4. Assignment of absolute configuration of new formed sterogenic centers.

The synthesis of enantiomerically defined β-lactams remains in center of interest of many research groups, since biological properties of β-lactams depend on their structure, absolute configuration and physicochemical and chemical properties. For example, clavams with a (5*R*) configuration at the ring junction exhibit strong β-lactamase inhibition and weak antibacterial activity while clavams with an (*S*)-configuration at C-5 exhibit antifungal activity. It is why the absolute configuration of the newly formed stereogenic center is so important. In most cases the configuration of chiral azetidinones has been assigned by chemical correlation, NMR and X-ray analysis, as well as combination of these methods. It is important to note that one of the most convenient, sensitive and fast technique appears to be circular dichroism (CD) spectroscopy.

The assignment of the absolute configuration at the C-6 carbon atom in cephams **218**, **219**, **222** and **223** was performed in cooperation with Prof. J. Frelek and her group. The circular dichroism spectroscopy (CD) was applied. Additional argument for choosing this method was the fact that most of synthezised compounds were liquids. It exluded application of X-ray diffraction methods to assign the absolute configuration of synthesized compounds. Prof. Frelek developed the helicity rule for assignment of the absolute configuration of oxacephams.[147] According to this rule, the positive sign of Cotton effect (CE) arising at around 220 nm corresponds to the (*R*) absolute configuration at the ring junction while it is negative for the (*S*) configuration at the same carbon atom. The helicity rule has a general meaning and can be applied to variety of bicyclic β-lactams. It is important to note, however, that if other chromophores, are located in the molecule CD spectra should be carefully studied.

The theoretical calculations of CD spectra were done for the selected 5-oxacephams by Magdalena Woźnica from Prof. J. Frelek group. At the begining the lowest-energy conformations for each investigated compound was determined. These conformations were found by the MM3 force field and CONFLEX[148] software and were subsequently reoptimized at B3LYP/6-31 G(d,p) level.[149] All the DFT-optimized structures converged to only one stable conformer in each case. To confirm the stability of calculated structures, the frequency calculations were performed at B3LYP/6-31 G(d,p) level. For the stable structures, the rotational strengths were calculated at the B3LYP/6-31 G(d,p) level. CD and UV spectra were simulated by overlapping Gaussian functions for each transition according to the procedure described by Diedrich and Grimme.[150] No correlation for the medium

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[147] a) R. Łysek, K. Borsuk, M. Chmielewski, Z. Kałuża, Z. Urbańczyk-Lipkowska, A. Klimek, J. Frelek, *J. Org. Chem*, **2002**, *67*, 1472-1479; b) J. Frelek, P. Kowalska, M. Masnyk, A. Kazimierski, A. Korda, M. Woźnica, M. Chmielewski, F. Furche, *Chemistry – Eur. J.* **2007**, *13*, 6732-6744

[148] CaChe. Ws Pro 5.0, Fujitsu Ltd.

[149] Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JAJ, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Salvador P, Dannenberg JJ, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople. Gaussian 03. Pittsburgh, PA: Gaussian; 2003.

[150] C. Diedrich; S. Grimme, *J. Phys. Chem. A*, **2003**,*107*, 2524



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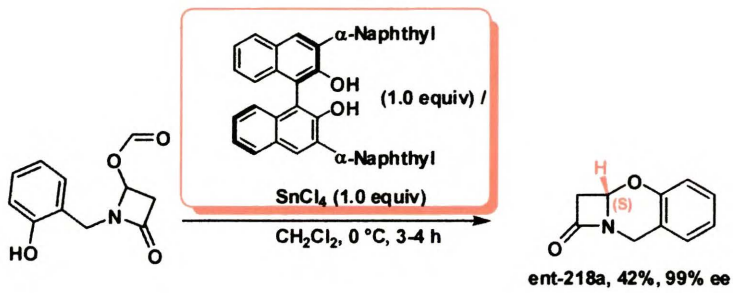
dielectric constant was implemented. The conformational analysis has been performed with the use of CaChe program package.[148]

Assignment of the C-6 configuration of oxacephams **218** began CD studies. In the case of **218,** the simple helicity rule cannot be applied. Due to the presence in compounds **218** two chromophores, namely, an amide and a phenyl/phenoxy one, the exciton chirality method (ECCD) was used.[151] The CD spectra of both enantiomerically enriched compounds **218** were measured in acetonitrile.

For compound ***ent*-218a** (6*S*) configuration was established on the basis of ECCD theory. This compound was obtained with 99% *ee*, based on HPLC analysis (OJ-H, 9:1, hexane : isopropanole), when as s ligand (*R*)-3,3'-di-α-naphthyl-BINOL (***ent*-236**) was used (Figure 10).



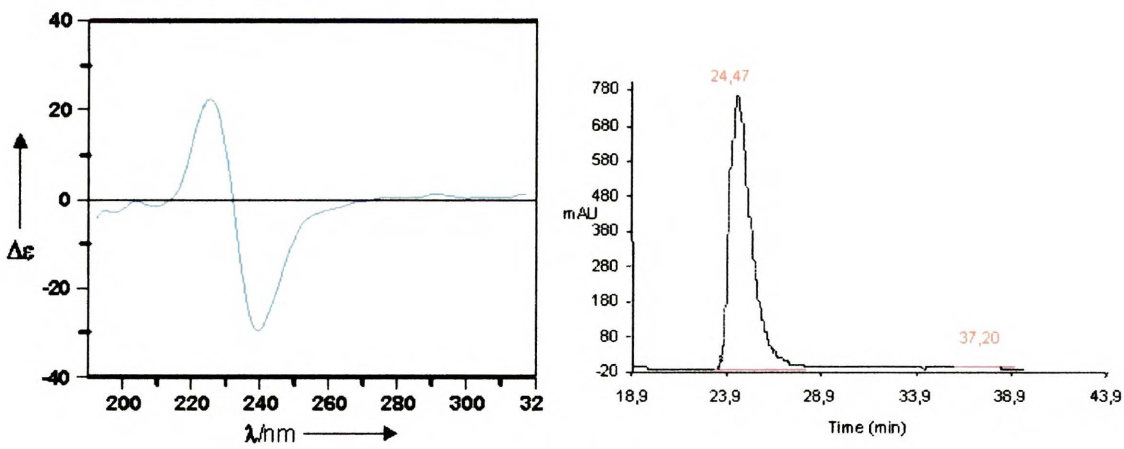




**Figure 10**

The investigated compound exhibits, in general, two intensive CD bands round 240 and 220 nm (Figure 10). The negative CD couplet [240 nm (negative sign of the CD band), 220 (positive sign of the CD band)] was observed. Upon looking through the centers of the two dipoles, a negative sign is defined when an anticlockwise rotation by an acute angle (γ-angel) brings the dipole in the front onto that in the back. It is possible only when compound ***ent*-218a** has (6*S*) configuration.

[151] N. Berova, L. Di Bari, L. G. Pescitelli, *Chem. Soc. Rev.* **2007**, *36*, 914



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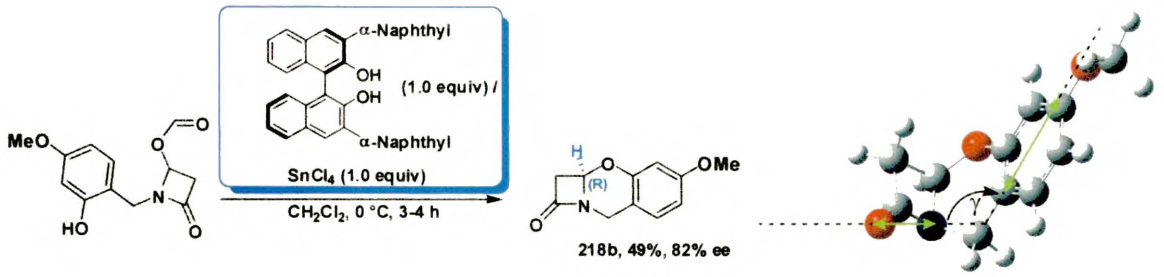
Subsequnetly, the CD spectrum was measured for the opposite enantiomer. Compound **218b** was obtained using (*S*)-3,3'-di-α-naphthyl-BINOL (**236**). On the basis of HPLC analysis **218b** was obtained with 82% *ee* (OD-H, 9:1, hexane : isopropanole). The (6*R*) configuration was established as was expected (Figure 11).



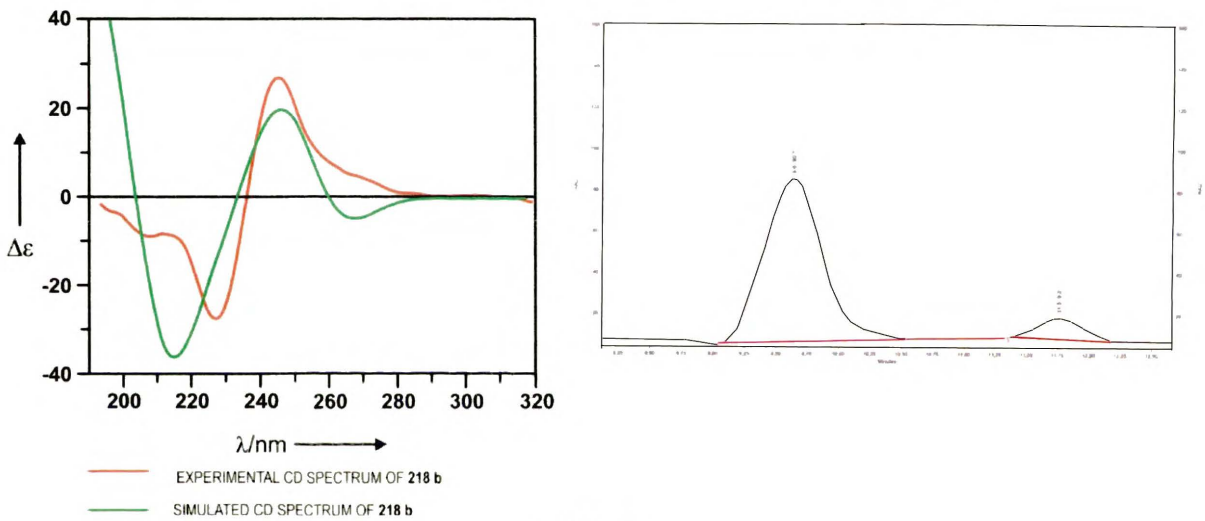




**Figure 11**

In the CD spectrum of compound **218b** also two intensive CD bands round 240 and 230 nm were found (Figure 11). The positive CD couplet [240 nm (positive sign of the CD band), 230 (negative sign of the CD band)] was observed. Upon looking through the centers of the two dipoles, a positive sign is defined when an anticlockwise rotation by an obtuse angle (γ-angel) brings the dipole in the front onto that in the back. It is possible only when compound **218b** has (6*R*) configuration. What is more, we simulated the theoretical CD spectrum of compound **218b**. For this purpose the time-dependent density functional theory (TDDFT) calculation was applied. Also structure of the **218b** was simulated and obtuse γ angel is well seen. As can be seen in Figure 11, the experimental and simulated CD curves are in excellent agreement thus providing an independent proof for the configurational assignment made.

In all cases, enantiomorphic shape of CD curves was observed in the range 290-190 nm, which is a consequence of the opposite absolute configuration at the C-6. What is more, for all (+)-**218** or (-)-**218** similar shape of CD curve were observed. Compounds with (6*S*)-configuration have always negative sign of long-wavelength CD band and negative sign of CD band round 220 nm.



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The CD spectrum of cepham **219** in acetonitrile was also measured. Compound **219** was obtained using (*S*)-3,3'-di-α-naphthyl-BINOL (**236**). On the basis of HPLC analysis **219** was obtained with 48% *ee* (OD-H, 9:1, hexane : isopropanole). The (6*R*) configuration was established as it was expected (Figure 12).

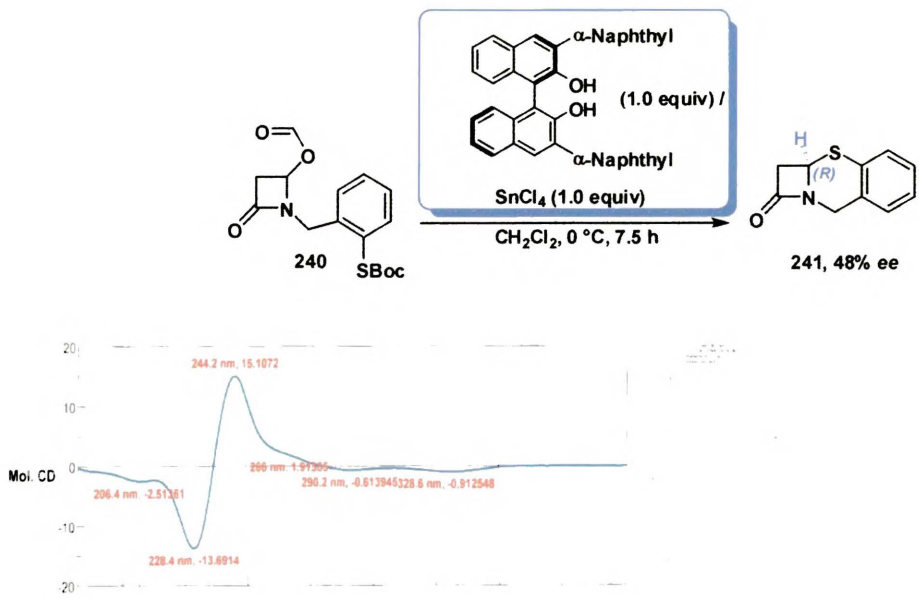
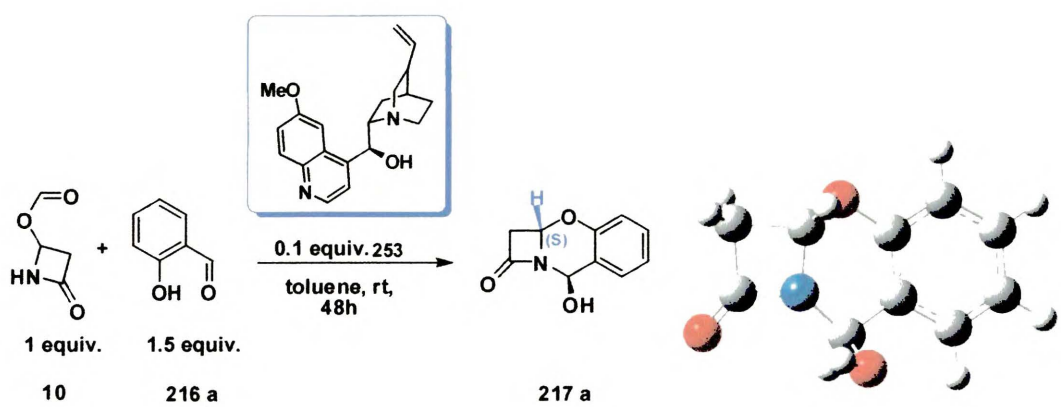



**Figure 12**

In the CD spectrum of **219** also two intensive CD bands round 240 and 230 nm were found (Figure 12). The observed positive CD couplet [240 nm (positive sign of the CD band), 230 (negative sign of the CD band)] corresponds to (6R)-configuration of cepham **219**. It is consistent with stereochemical outcome of the process of the asymmetric destruction.

The assignment of absolute configuration at the bridgehead carbon atom (C-6) of **217** was made by application of the helicity rule previously developed for oxacephams.[142] For compound **217a**, which was obtained with catalytic amount of quinidine **253**, (6*S*)-configuration was assigned. On the base of HPLC analysis (AD-H, 95:5 hexane: isopropanole, 1.0 mL/min) the 49% enantiomeric excess was observed (Figure 13).



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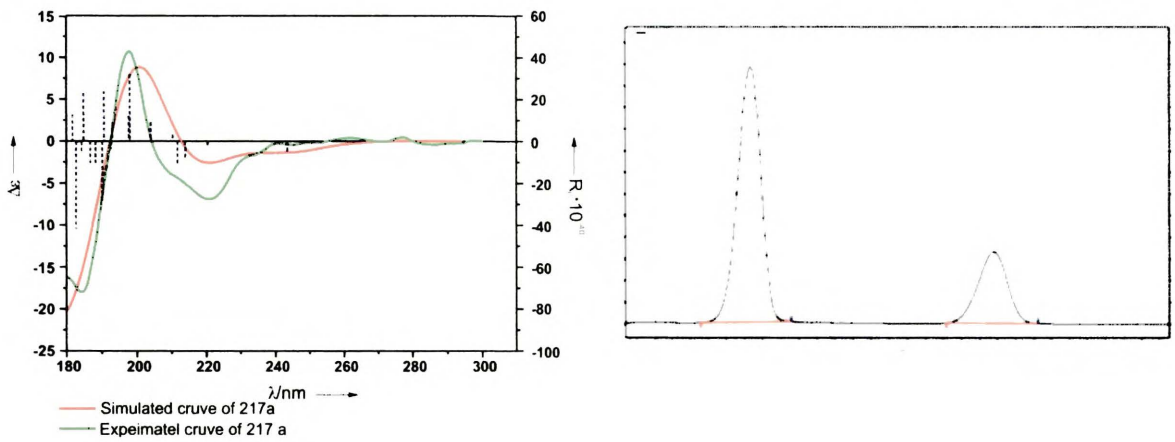
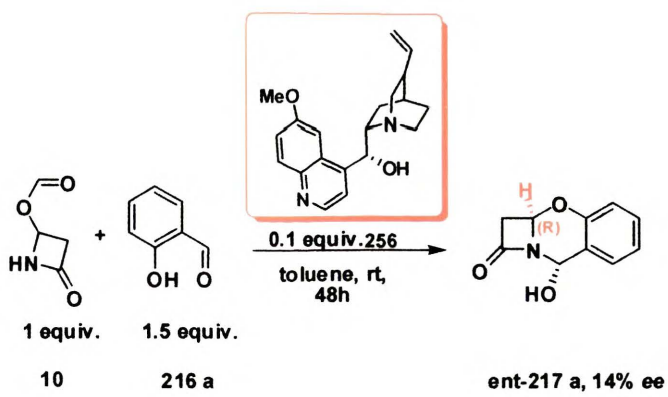



**Figure 13**

The negative sign of the Cotton Effect at 221 nm found for compound **217a** allowed us to assign the absolute configuration as (6*S*). The very good agreement between the experimental and simulated CD spectrum obtained by the TDDFT quantum chemical calculations provided an additional corroboration of the configuration assignment (Figure 13).

The (6*R*) enantiomer *ent*-**217a** was obtained in the presence of catalytic amount of quinine (**256**) which is pseudo-enantiomer of quinidine (**253**). On the base of HPLC analysis (AD-H, 95:5 hexane: isopropanole, 1.0 mL/min) the 22% enantiomeric excess was observed (Figure 14).



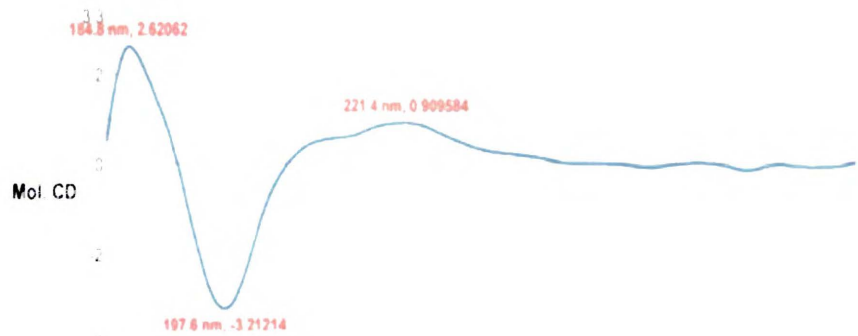




**Figure 14**



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The positive sign of the Cotton Effect at 197 nm for ***ent*-222a** confirms (6*R*) configuration, respectively (Figure 14).

For compounds **217d** and **217f**, the configuration at *N,O*-hemiacetal center (C-2) was established by the NOE's experiments which showed a spin-spin interaction between the hydroxy group proton and the bridgehead proton (H-6). In case of **217d** protons of $CH_3$ group did not show such interaction (Figure 15).

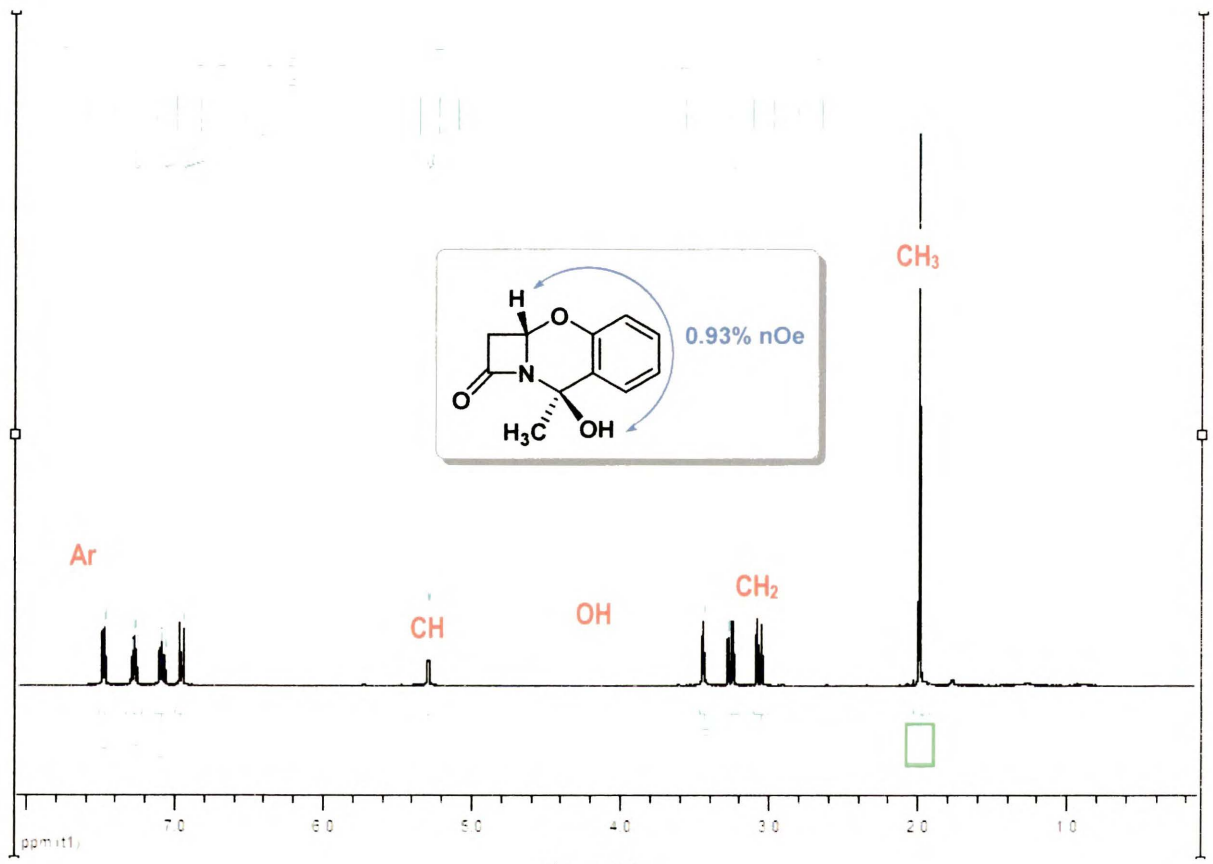


**Figure 15**

NOE experiment was also performed for compound **271a** which was obtained from commercially available non-racemic azetidinone **214** and salicylic aldehyde in the presence of equimolar amount of *t*-BuOK. The obtained compound had *trans* orientation of substituents at C-3 and C-4 of azetidin-2-one ring. The NOE experiment showed a spin-spin interaction between the hydroxy group proton and the bridgehead proton (H-6) and between acetal proton (H-2) and H-7 (Figure 16). On the basis of NMR studies which are consisted with assumed mechanism the (6*R*) absolute configuration can be established.



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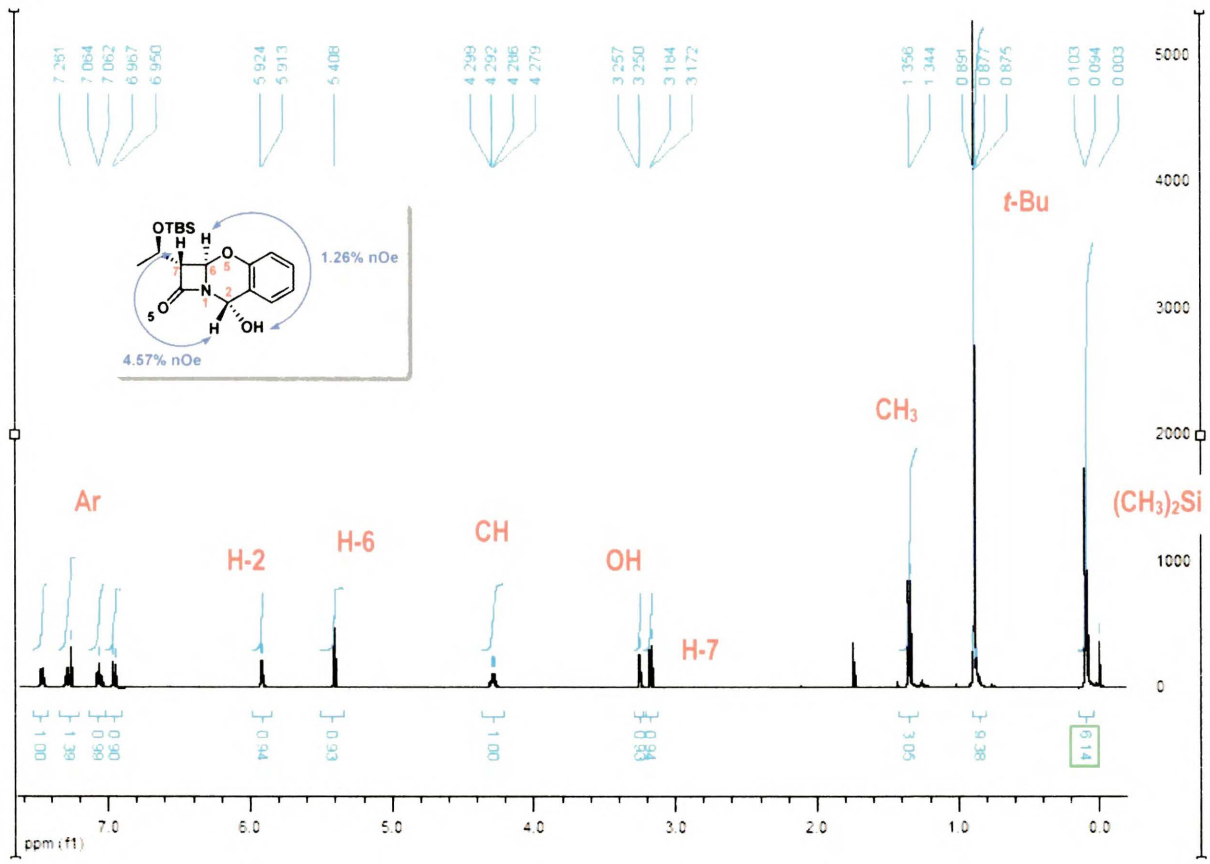


**Figure 16**

Starting form commercially available azetidin-2-one **214**, compound **271b** was also obtained. The CD spectrum of this compound was measured in acetonitrile and compared with CD spectrum of compound **217e** and **222d** (obtained from **10** in the presence of quinidine (**253**)) (Figure 17).

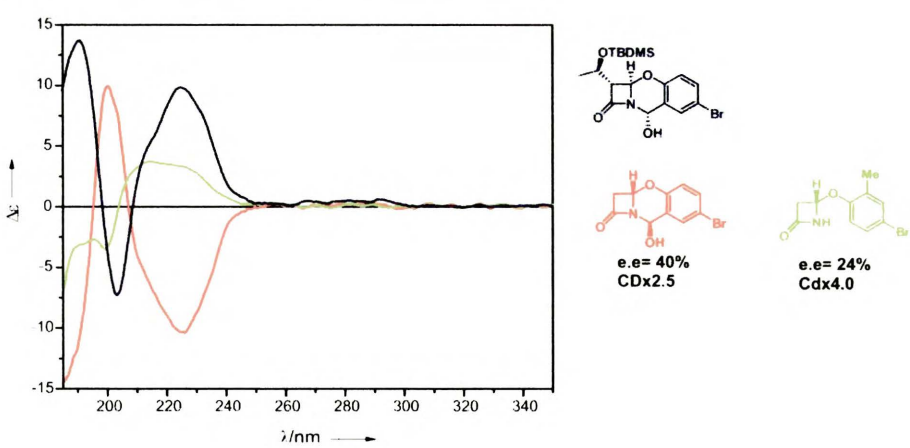


**Figure 17**

As show on Figure 17 the positive sign of Cotton effect round 220 nm observed in the CD curve of compound **271b** confirms absolute configurations as (*6R*). Enantiomorphic shape of CD curves of **271b** and **217d** was observed in the range 290-190 nm, which is a consequence of the opposite absolute configuration at the C-6.



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Both experimental CD curves are in good agreement, thus providing an independent proof for the configurational assignment made (Figure 17). The positive sign of Cotton effect round 220 nm observed for compound **222d** allowed to established (4*S*) absolute configuration (Figure 17). Moreover, the application of helicity rule, allowed to prove (4*S*) configuration for compounds **223** (Figure 18). It remains with agreement with stereochemical outcome of the reaction.

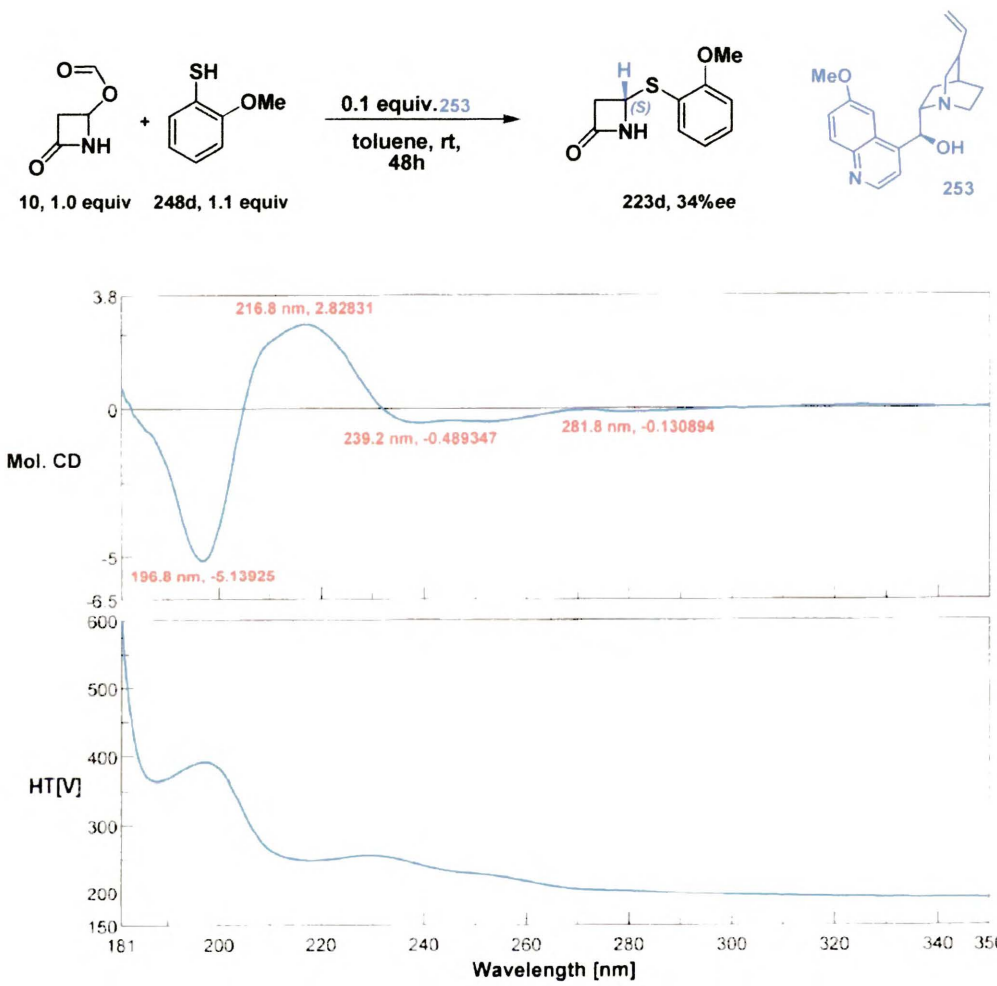


**Figure 18**



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### 3.5. Biological activity of cephams and 4-substitiuted azetidinone

As it was mentioned above, compounds containing β-lactam core display not only antibacterial activity but also are known to have antifungal properties, as well as display excellent enzymes inhibition (β-lactamase). It is important to note, that due to fast mutation of bacteria's antibiotic resistance, novel, save in use and effective antibiotics, are in the center of interest of many pharmaceutic companies. In cooperation with Dr. J. Solecka from National Center of Public Health - National Institute of Hygiene, biological activity tests were performed, while knew enantiomerically enriched structures have been synthesised. An inhibition of DD-peptidase 64-575 activity and, separately, an inhibition of β-lactamase class A and a porcine kidney elastase was measured.

DD-peptidase 64-575, produced by Saccharopolyspora erythrea PZH TZ 64-575, is a very sensitive enzyme to β-lactam antibiotics. One of mode of theirs action is inhibition of DD-peptidase 64-575 enzyme. It is used to assay the affinity of natural and synthetic β-lactam compounds without limitation of solubility (water/organic solvents). Class A β-lactamase (penicillinase-type) is the most common class of β-lactamases.[152] This enzymes are responsible for resistance of some bacteria on β-lactam antibiotics. The genes for class A beta-lactamases are widely distributed in bacteria, frequently located on transmissible plasmids in Gram-negative organisms. It is why the test on this class of enzymes provides the best result of biological activity of a novel compounds. The last tests were concentrated on the inhibition of porcine kidney elastase. It was previously mention, that 4-substitiuted azetidin-2-ones with aryloxy or thioaryl group are potent elastase inhibitors.

For biological activity tests, only representative group of compounds were chosen. All compounds were tested on inhibition of DD-peptidase 64-575 activity and inhibition of β-lactamase class A activity. In the case of inhibition of porcine kidney elastase activity only 4-substitiuted azetidin-2-ones were tested. Any other modification of structure to improved biological activity had not been performed.

In general, 5-oxacephams with (6*R*)-configuration showed inhibition of the DD-peptidase 64-575, expressed by $IC_{50}$(M) between $7x10^{-4}$ and $1.2x10^{-2}$ molar concentration of compound inhibiting the DD-peptidase 64-575 in 50%. The best result $IC_{50}$(M) = $7x10^{-4}$ was achieved for racemic compound with bromine substituent in the aromatic ring. Moreover, in the case o of compound **218d** (entry 8 and 9), which also posses bromine in aromatic ring, both enantiomers showed inhibition of the DD-peptidase 64-575. In other cases 5-oxacephams with (6*S*)-configuration did not show measurable inhibition and were excluded from Table 27. In comparison, the 50% inhibition of enzyme 64-575 by cephamandole, penicillin G and clavulanic acid was achieved at much lower concentration, according to published data: $IC_{50}$(M) = $1.5x10^{-8}$, $6.1x10^{-7}$ and $2.0x10^{-6}$, respectively.[153] Also enantiomericalt pure (6*R*) 3,4-benzo-2-hyroxy-5-oxacephams **271a-b** as well as (6*S*)-**217a** and (6*S*)-**217c** showed inhibition of DD-peptidase 64-575, expressed by $IC_{50}$(M) between $4,6x10^{-3}$ and $1.0x10^{-2}$ .

---

[152] Knox, J. R.; Moews, P. C., *J. Mol. Biol.*, **1991**, *220*, 435

[153] a) Kurzatkowski, W.; Solecka, J.; Filipek, J.; Kurzatkowski, J. D.; Kurylowicz, W., *Appl. Microbiol. Biotechnol.*, **1990**, *33*, 452; b) Rohl, F.; Rabenhorst, J.; Zahner, H. *Arch. Microbiol.*, **1987**, *147*, 315



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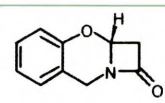
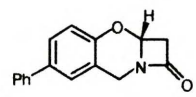
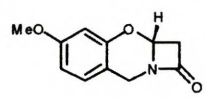
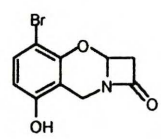
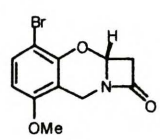
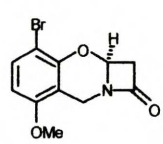
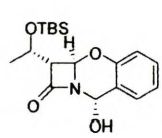
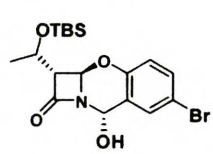
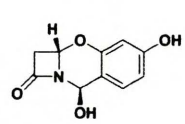
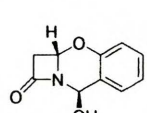
| Entry | Compound | Structure | *ee* [%] | $IC_{50}$ [Mm] |
|---|---|---|---|---|
| 1 | **218a** |  | 99 (*R*) | 12,1 |
| 2 | **218c** |  | 92 (*R*) | 8.2 |
| 3 | **218b** |  | 82 (*R*) | 6.0 |
| 4 | **218e** |  | 0 | 0.7 |
| 5 | **218d** |  | 95 (*R*) | 1.2 |
| 6 | ***ent*-218d** |  | 95 (*S*) | 1.4 |
| 7 | **271a** |  | 100 (6*R*) | 10 |
| 8 | **271b** |  | 100 (6*R*) | 7.3 |
| 9 | **217c** |  | 32 (6*S*) | 4.6 |
| 10 | **217a** |  | 49 (6*S*) | 9 |

**Table 27**

4-Substitiuted azetidin-2-one **222**, **223** showed biologically activity but $IC_{50}$(M) between $1.2x10^{-2}$ and $2.8x10^{-3}$ was achieved at higher concentration than reference compounds (the $IC_{50}$(mM) (Table 28).[153]



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Only two from tested compounds showed the inhibition of β-lactamase class A activity, expressed by the value of $IC_{50}(M) = 9.3x10^{-3}$ and $2.5x10^{-2}$. Other tested compounds did not show measurable β-lactamase inhibition. Moreover, tests of inhibition of porcine kidney elastase turned out to be negative.

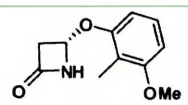
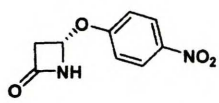
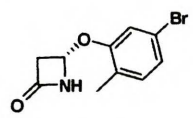
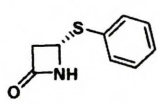
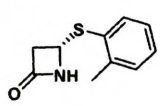
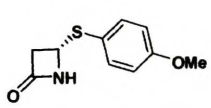
| Entry | Compound | Structure | *ee* [%] | $IC_{50}$ [Mm] peptidase | $IC_{50}$ [Mm] β-lactamase |
|---|---|---|---|---|---|
| 1 | **219b** |  | 46 | 6.8 | 0 |
| 2 | **219g** |  | 43 | 4.4 | 0 |
| 3 | **219d** |  | 24 | 4.6 | 9.3 |
| 4 | **223a** |  | 42 | 12.6 | 0 |
| 5 | **223b** |  | 49 | 0 | 25.0 |
| 6 | **223d** |  | 34 | 12.3 | 24.7 |

**Table 28**



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### 3.6. Summary

My work was concentrated on the novel entry to asymmetric synthesis of azetidinones and cephams. First part of regarded application of chiral Lewis acids. I developed three step synthesis of cyclization precursors – appropriate *N*-benzylated 4-formyloxyazetidin-2-one **231**. I established optimal conditions for enantioselective cyclization leading to 3,4-benzo-5-oxacephams **218**. Application of BINOL/$SnCl_4$ promotor resulted in the excellent enantioselectivities of expected products **218**. However yields of those compounds never exceed 50%. Both yield and enantioselectivity depended form substitiuents in the phenol ring and type of nucleophile used (tiophenols, aliphatic alcohol). The intermolecular reaction promoted by BINOL/$SnCl_4$ was ineffective. On the base of obtained results the kinetic resolution of initially formed cepham was suggested. This hypothesis supported observed kinetic resolution of racemic 5-oxacephams **218** and **224** as well as cephm **219**. Observed slower reaction of cepham **219** than 5-oxacephams **218** and **224** remains in agreement with the fact that *N,S*-acetals are usually more stable under acidic conditions than *N,O*-acetals. The lower enantiomer-differention of cepham *rac*-**219** than *rac*-**218** may be caused by worse matching of the sulphur atom than the oxygen one to the chiral promoter. The worse matching to the chiral promoter of *rac*-**224** than *rac*-**218** is probably coused by lack of aromatic ring. It is why the further decomposition *via* the unstable acylimminium cations provides lower enantioselectivity.

Second part of my work regarded chiral Lewis base catalysed nucleophilic substitution at C-4 of 4-formyloxyazetidin-2-one (**10**). The best catalyst apperd to be quinidine (**253**). This cinchona alkaloid catalyzed intramolecular reaction of *o*-hydoxy-phenons with 4-formyloxyazetidin-2-one (**10**) to proceed in very good yields and moderated enantioselectivities. I applied different nucleophiles like aromatic and aliphatic alcohols, and thiols. On the basis of obtained results, the elimination – addition mechanism was proposed. In case of aromatic compounds the type of nucleophilic atom (oxygen – sulfur) did not affect enantioselectivity of the process. In both cases moderate enantiomeric excesses up to 50% and high yiled up to 90% was observed. However, the use of aliphatic alcohols and thiols in the quinidine promoted process was not so efficient. I obtained corresponding azetidin-2-ones in moderate yields and low enantiomeric excesses.

On the basis of CD spectroscopy the absolute configuration at C-6 for cephams and C-4 for azetidin-2-ones was established. Due to the presence in compounds **218** two chromophores, namely, an amide and a phenyl/phenoxy one, the exciton chirality method (ECCD) was used.[151] In the case of oxacephams **217** obtained with quinidine (**253**), the helicity rule[147] for assignment of the absolute configuration was applied to confirm assignments made by calculations. The biological test of selected compounds shown that (6*R*)-3,4-benzo-5-oxacephams **217** are active, but obtained $IC_{50}$ for DD-peptidase are much more higher (lower activity) than that reported for reference compounds. Tested compound **217** did not show measurable inhibition of $\beta$-lactamse class A and porcine kidney protease.



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## 4. EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA

### 4.1. General Experimental Methods

All reactions involving air- and moisture-sensitive materials were performed under atmosphere of dry argon using dry solvents. Reagents were purchased from commercial supplies and used without further purification, unless noted. Tetrahydrofuran was distilled from Na and bezophenon ketyl, dichloromethane were distilled from $CaH_2$. All processes were performed until disappearance of starting material (TLC monitoring).

Melting points were determinated using Köfler hot-stage apparatus with microscope and were uncorrected. The column chromatography was performed on Merck Kiesel gel (230 – 400 mesh). Thin layer chromatography (TLC) was performed on aluminum sheets Silica Gel 60 $F_{254}$ (20 x 20 x 0.2) from Merck. TLC spots were visualized in UV (254 nm) and by treatment by the solution of ceric acid. Routine NMR spectra were obtained with Bruker DRX 500 Advance Spectrometer at 500 MHz for $^1H$ NMR and 128.5 MHz for $^{13}C$ NMR, using $CDCl_3$ as a solvent and TMS as an integral reference ($\delta$ 0 for $^1H$ and $\delta$ 0 $^{13}C$). The DEPT sequence was used for $^{13}C$ multiplicity assignment. NMR ($^1H$ and $^{13}C$) peak assignments were established using HSQC experiments. Chemical shifts are reported as $\delta$ value in ppm and coupling constants are in Hertz. IR data include only characteristic absorption. They were obtained with FT-IR-1600-Perkin – Elmer spectrophotometer. High resolution mass spectra were recorded on AMD 604 mass spectrometer (EI, 70 eV) and ESI-TOF Mariner spectrometer (Perspective Biosystem). The optical rotations were measured using JASCO J-1020 digital polarimeters. The ozonolysis was carried using Buchi Ozone Generator OZI. The high pressure liquid chromatography (HPLC) was performed using Merck – Hitachi chromatograph with L-2130 pump, diode array detector L-2450, analytical columns : Chiralpark® AD-H, Chiralcel® OD-H and OJ-H and hexane / isopropanole as solvents.

The binaphthol ligands (**234-238**),[138] benzyl bromides (**226**)[135,139] and phenols (**245c**, **245d**)[135] were prepared according to the literature procedure. The thiosalicilic aldehyde was obtained in three step synthesis.[144]

### 4.2. General procedures

**Deprotection of hydroxyl group in *N*-benyzlated-4-vinyloxyazetidin-2-ons. Synthesis of compounds 229**

The solution of *N*-benyzlated-4-vinyloxyazetidin-2-on **228** (0.4 mmol) in THF (5mL) at 0°C was treated with 1M solution of $Bu_4NF$ in THF (1.2 equiv, 0.48 mL) under argon atmosphere. The reaction mixture was stirred for 2h and diluted with saturated $NH_4Cl$ (10 mL) and $CH_2Cl_2$ (10mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 1:1 hexane/acetyl acetate) to yield product **229**.

**Lewis acid promoted cyclization of 230 and 236**

The solution of **230** (75 mg, 0.14 mmol, 1.0 equiv) or **236** (0.14 mmol, 1.0 equiv) in $CH_2Cl_2$ (5mL) at 0°C was treated with Lewis acid (1 equiv) under argon atmosphere. The reaction mixture was stirred for 12h and diluted with saturated $NaHCO_3$ (5mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x10 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield **218** and **232** or only **218**.

**Chiral Lewis acid promoted cyclization of 231**

The solution of **236** (75 mg, 0.14 mmol, 1.0 equiv) in $CH_2Cl_2$ (5mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (140 µL, 1 equiv) under argon atmosphere. After 15 minutes compound **231** (0.14 mmol) was added. The reaction mixture was stirred for 3h and diluted with saturated $NaHCO_3$ (5mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x10 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was



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filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield **218**.

**Chiral Lewis acid promoted intermolecular substitution with phenols 245 a-d and tiophenol 248a**

The solution of **236** / ***ent*-236** (1490 mg, 0.26 mmol, 1.0 equiv) in $CH_2Cl_2$ (5mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (260 µL, 1.0 equiv) under argon atmosphere. After 15 minutes compounds **10** (30 mg, 0.26 mmol) or **246** (53 mg, 0.26 mmol) and **245** (0.37 mmol) or **248** (0.29 mmol) were added. The reaction mixture was stirred for 3h and diluted with saturated $NaHCO_3$ (5mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x10 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography to yield **222a-c** / **223a** / **247** / **249**.

**Brønsted acid promoted intermolecular substitution with phenols 245**

To the solution of chiral Brønsted Acid (16 mg, 0.026 mmol, 0.1 equiv) in toluene compound **245** (0.39 mmol, 1.5 equiv) and **10** (30 mg, 0.026 mmol) were added under argon atmosphere. The reaction mixture was stirred and refluxed for 24h and diluted with saturated $NaHCO_3$ (5mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield **222**.

***t*-BuONa promoted nucleophilic substitution with *o*-hydoxy-aldehydes, ketons, thiosalicilic aldehydes, phenols and thiophenols**

To the solution of **10** (30 mg, 0.26 mmol, 1.0 equiv) or **214** (30 mg, 0.1 mmol, 1.0 equiv) and nucleophile (1.5 equiv) in THF (5mL) at room temperature was added *t*-BuONa (1.0 equiv) under argon atmosphere. The reaction mixture was stirred for 30 minutes till disappearance of starting material and diluted with water (5mL). The aqueous phase was extracted with ether (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography to yield **217**, **221**, **222**, **243**, **271** or **272** respectively.

**Quinidine (253) catalyzed nucleophilic substitution with *o*-hydoxy-aldehydes and ketons or thiosalicilic aldehyde**

To the solution of 4-formyloxyazetidin-2-one (**10**) (30 mg, 0.26 mmol, 1.0 equiv) and **216** (0.39 mmol, 1.5 equiv) or **220** (40 mg, 0.29 mmol, 1.1 equiv) in toluene (5mL) at room temperature was added quinidine (**253**) (9 mg, 0.1 equiv) under argon atmosphere. The reaction mixture was stirred for 48 h till disappearance of starting material and diluted with water (5mL). The aqueous phase was extracted with ether (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography to yield **217** or **221**, respectively.

**Quinidine (253) catalyzed nucleophilic substitution with phenols 245, tiophenols 248**

To the solution of 4-formyloxyazetidin-2-one (**10**) (30 mg, 0.26 mmol, 1.0 equiv) and phenol (**245**) (0.39 mmol, 1.5 equiv) or thiol (**248**) (0.29 mmol, 1.1 equiv) in toluene (5 mL) at room temperature was added quinidine (**253**) (9 mg, 0.1 equiv) under argon atmosphere. The reaction mixture was stirred for 48 h till disappearance of starting material and diluted with water (5 mL). The aqueous phase was extracted with ether (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography to yield **222** and **223**

**Quinidine (253) catalyzed substitution with alcohols 265 at room temperature**

To the solution of 4-formyloxyazetidin-2-one (**10**) (30 mg, 0.26 mmol, 1.0 equiv) and alcohol (**265**) (0.78 mmol, 3.0 equiv) in toluene (5 mL) at room temperature was added quinidine (**253**) (90 mg, 1.0 equiv) under argon atmosphere. The reaction mixture was stirred for 48 h till disappearance of starting material and filtered through small layer of silica gel. The silica layer was washed with toluene (2 mL). Subsequently the filtrate containing 4-alkoxy-azetidin-2-one **250** was slowly added to solution of 50% aqueous NaOH (5 mL), and $Bu_4NBr$ (84 mg, 0.26



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mmol, 1.0 equiv) and benzyl chloride (135 μL, 1.17 mmol, 4.5 equiv) in 1 mL of toluene. The reaction mixture was stirred for 30 min till disappearance of starting material and diluted with water (10 mL). The aqueous phase was extracted with ethyl acetate (3x15 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 2:3 hexane/diethyl ether) to yield **267**.

**Quinidine (253) catalyzed substitution with alcohols 265 at reflux**

To the solution of **10** (30 mg, 0.26 mmol, 1.0 equiv) and alcohol (**265**) (0.39 mmol, 1.5 equiv) in toluene (5 mL) at room temperature was added quinidine (**253**) (90 mg, 1.0 equiv) under argon atmosphere. The reaction mixture was stirred for 12 h at reflux till disappearance of starting material and filtered through small layer of silica gel. The silica layer was washed with toluene (2 mL). Subsequently the filtrate containing 4-alkoxy-azetidin-2-one **250** was slowly added to solution of 50% aqueous NaOH (5 mL), and $Bu_4NBr$ (84 mg, 0.26 mmol, 1.0 equiv) and benzyl chloride (90 μL, 0.78 mmol, 3.0 equiv) in 1 mL of toluene. The reaction mixture was stirred for 30 min till disappearance of starting material and diluted with water (10 mL). The aqueous phase was extracted with ethyl acetate (3x15 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 2:3 hexane/diethyl ether) to yield **267**.

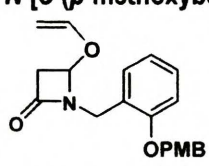
**Quinidine (253) catalyzed substitution with thioalcohols 266**

To the solution of 4-formyloxyazetidin-2-one (**10**) (30 mg, 0.26 mmol, 1.0 equiv) and thioalcohol (**266**) (0.39 mmol, 1.5 equiv) in toluene (5 mL) at room temperature was added quinidine (**253**) (90 mg, 1.0 equiv) under argon atmosphere. The reaction mixture was stirred for 48 h till disappearance of starting material and filtered through small layer of silica gel. The silica layer was washed with toluene (2 mL). Subsequently the filtrate containing 4-thio-azetidin-2-one **251** was slowly added to solution of 50% aqueous NaOH (5 mL), and $Bu_4NBr$ (84 mg, 0.26 mmol, 1.0 equiv) and benzyl chloride (90 μL, 0.78 mmol, 3.0 equiv) in 1 mL of toluene. The reaction mixture was stirred for 30 min till disappearance of starting material and diluted with water (10 mL). The aqueous phase was extracted with ethyl acetate (3x15 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The

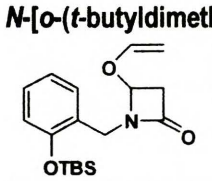
### 4.3. Preparation of *N*-benyzlated-4-vinyloxyazetidin-2-ons 228a-e and 229f[154]

Compounds were prepared from benzyl bromide (**225**, **226** and **242**) and 4-vinyloxyazetidinone (**9**) (226 mg, 2 mmol) following literature procedure.[136]

***N*-[*o*-(*p*-methoxybenzyloxy)-benzyl]-4-vinyloxy-azetidin-2-one (227)**: 380 mg (1.2 mmol); Yield 60%; colorless oil; IR (film) v: 1770 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.84 (d, *J* = 14.8 Hz, 1H, $CH_2$), 3.05 (dd, *J* = 14.8, 3.7 Hz, 1H, $CH_2$), 3.82 (s, 3H, $CH_3$), 4.01 (dd, *J* = 6.6, 2.1 Hz, 1H, $CH_2$=), 4.21 (dd, *J* = 14.2, 2.1 Hz, 1H, $CH_2$=), 4.30 (d, *J* = 15.1 Hz, 1H, CH-N), 4.57 (d, *J* = 15.1 Hz, 1H, CH-N), 5.02 (s, 2H, $CH_2$-Ar), 5.10 (d, *J* = 3.7 Hz, 1H, CH-O), 6.14 (dd, *J* = 14.2, 6.6 Hz, 1H, CH=), 6.91 (d, *J* = 8.5 Hz, 2H, Ar), 6.95 (d, *J* = 8.5 Hz, 2H, Ar), 7.27 (m, 2H, Ar), 7.34 (d, *J* = 8.5 Hz, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 39.9, 44.8, 55.3, 69.9, 80.4, 90.9, 111.9, 114.0, 120.9, 124.2, 129.2, 129.3, 130.4, 148.0, 166.1; HR MS (EI) calcd for $M^+$ $C_{20}H_{21}NO_4$ 339.1471 found: 339.1455;




***N*-[*o*-(*t*-butyldimethylsiloxy)-benzyl]-4-vinyloxy-azetidin-2-one (228a)**: Obtained 466 mg (1.4 mmol); Yield 70%; yellow liquid; IR (film) v: 1774$cm^{-1}$ $^1H$ NMR ($CDCl_3$) δ: 0.24 (s, 3H, $CH_3$-Si), 0.28 (s, 3H, $CH_3$-Si), 1.04 (s, 9H, $(CH_3)_3C$-Si), 2.93 (d, *J* = 14.8 Hz, 1H, $CH_2$), 3.18 (dd, *J* = 14.8 Hz, 3.7 Hz, 1H, $CH_2$), 4.12 (dd, *J* = 6.7 Hz, 2.2 Hz, 1H, $CH_2$=), 4.27 (dd, *J* = 14.2 Hz, 2.2 Hz, 1H,




[154] For the sake of simplicity, names of bicyclic β-lactam compounds were formed using "3,4-benzo-cepham", or "3,4-benzo-5-oxacepham" core. Substituents in the benzene ring were placed to assume C-3 and C-4 of the cepham as C-1' and C-2' of the benzene ring, respectively.



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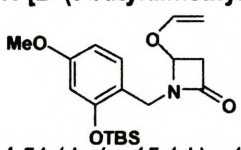
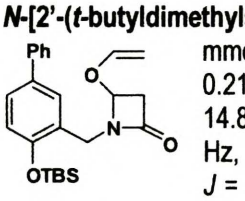
$CH_2$=), 4.35 (d, $J$ = 15.4 Hz, 1H, $CH_2$-N), 4.60 (d, $J$ = 15.4 Hz, 1H, $CH_2$-N), 5.19 (dm, $J$ = 3.7 Hz, 1H, C*H*-O), 6.27 (dd, $J$ = 14.2, 6.7 Hz, 1H, =C*H*-O), 6.85 (d, $J$ = 7.8 Hz, 1H), 6.97 (tm, $J$ = 7.8 Hz, 1H), 7.19 (td, $J$ = 7.8 Hz, 1.6 Hz, 1H), 7.26 (dd, $J$ = 7.8, Hz 1.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: - 4.12, 18.29, 25.79, 39.36, 44.85, 79.79, 90.99, 118.702, 121.35, 125.69, 128.78, 129.89, 147.78, 153.52, 165.55; MS (HR, ESI) m / z (M +Na)$^+$ requires for $C_{18}H_{27}NO_3NaSi$ calcd: 356.1652 found: 356.1637;

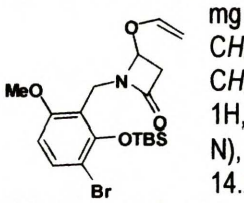
***N*-[2'-(*t*-butyldimethylsiloxy)-4'-methoxy-benzyl]-4-vinyloxy-azetidin-2-one (228b)**: Obtained 145 mg (0.4 mmol); Yield 20%; yellow liquid; IR (film) v: 1765cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 0.24 (s, 3H, $CH_3$-Si), 0.26 (s, 3H, $CH_3$-Si), 1.00 (s, 9H, $(CH_3)_3$C-Si), 2.87 (d, $J$ = 14.8 Hz, 1H, $CH_2$), 3.10 (dd, $J$ = 14.8 Hz, 3.6 Hz, 1H, $CH_2$), 3.77 (s, 3H, $CH_3$), 4.09 (dd, $J$ = 6.7 Hz, 2.1 Hz, 1H, $CH_2$=), 4.21 (d, $J$ = 15.1 Hz, 1H, $CH_2$-N), 4.24 (dd, $J$ = 14.3 Hz, 2.2 Hz, 1H, $CH_2$=), 4.51 (d, $J$ = 15.1 Hz, 1H, $CH_2$-N), 5.11 (dm, $J$ = 3.6 Hz, 1H, C*H*-O), 6.23 (dd, $J$ = 14.3, 6.7 Hz, 1H, =C*H*-O), 6.85 (d, $J$ = 2.5 Hz, 1H), 6.97 (dd, $J$ = 7.8 Hz, 2.5 Hz,1H), 7.19 (d, $J$ = 7.8, 1.6 Hz, 1H), 7.26 (d, $J$ = 7.8 Hz,1H); $^{13}$C NMR ($CDCl_3$) δ: - 4.15, - 4.11, 18.5, 25.8, 38.9, 44.7, 55.3, 79.6, 90.9, 105.5, 106.2, 118.1, 130.8, 147.8, 154.5, 160.1, 165.4; Anal. calcd for $C_{19}H_{29}NO_4Si$ (363.52) C, 62.78; H, 8.04; N, 8.35; O, 17.60; Si 7.73, found C 62.77, H 8.00, N 8.35;



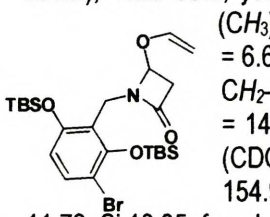

***N*-[2'-(*t*-butyldimethylsiloxy)-5'-phenyl-benzyl]-4-vinyloxy-azetidin-2-one (228c)**: Obtained 204 mg (0.5 mmol); Yield 25%; yellow liquid; IR (film): 1765cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 0.20 (s, 3H, $CH_3$-Si), 0.21 (s, 3H, $CH_3$-Si), 0.95 (s, 9H, $(CH_3)_3$C-Si), 2.85 (d, $J$ = 14.9 Hz, 1H, $CH_2$), 3.09 (dd, $J$ = 14.8 Hz, 3.7 Hz, 1H, $CH_2$), 4.01 (dd, $J$ = 6.7 Hz, 2.2 Hz, 1H, $CH_2$=), 4.18 (dd, $J$ = 14.3 Hz, 2.2 Hz, 1H, $CH_2$=), 4.33 (d, $J$ = 15.4 Hz, 1H, $CH_2$-N), , 4.54 (d, $J$ = 15.4 Hz, 1H, $CH_2$-N), 5.12 (dd, $J$ = 3.6 Hz, 1.9 Hz, 1H, C*H*-O), 6.18 (dd, $J$ = 14.3, 6.7 Hz, 1H, =C*H*-O), 6.81 (d, $J$ = 8.4 Hz, 1H), 7.23 (m, 1H), 7.30-7.36 (complex, 3H), 7.41 (d, $J$ = 2.4 Hz, 1H), 7.46 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ: - 4.1, - 4.0, 18.3, 25.8, 39.5, 44.9, 79.9, 91.1,118.9, 125.9, 126.8, 126.9, 127.4, 128.6, 128.7, 134.4, 140.5, 147.8, 153.1, 165.6; MS (HR, ESI) m / z (M +Na)$^+$ requires for $C_{19}H_{29}NO_4NaSi$ calcd: 386.1758 found 386.1739;



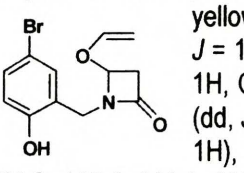

***N*-[3'-Bromo-2'-(*t*-butyldimethylsiloxy)-6'-methoxy-benzyl]-4-vinyloxy-azetidin-2-one (228d)**: Obtained 247 mg (0.56 mmol); Yield 28%; yellow oil; IR (film) v: 1764cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 0.25 (s, 3H, $CH_3$-Si), 0.26 (s, 3H, $CH_3$-Si), 1.00 (s, 9H, $(CH_3)_3$C-Si), 2.81 (dd, $J$ = 14.8 Hz, 1.0 Hz, 1H, $CH_2$), 3.07 (dd, $J$ = 14.8 Hz, 3.7 Hz, 1H, $CH_2$), 3.87 (s, $CH_3$, 3H), 4.03 (dd, $J$ = 6.6 Hz, 2.1 Hz, 1H, $CH_2$=), 4.18 (dd, $J$ = 14.2 Hz, 2.1 Hz, 1H, $CH_2$=), 4.39 (dd, $J$ = 13.9 Hz, 1.1 Hz, 1H, $CH_2$-N), 4.57 (d, J = 13.9 Hz, 1H, $CH_2$-N), 5.08 (dd, J = 3.7 Hz, 1.0 Hz, 1H, C*H*-O), 6.18 (dd, $J$ = 14.2 Hz, 6.6 Hz, 1H, =C*H*-O), 6.53 (d, $J$ = 8.8 Hz, 1H), 7.34 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: - 4.2, - 4.1, 18.4, 25.8, 34.6, 44.8, 61.1, 80.4, 90.8, 115.9, 132.8, 147.6, 152.6, 165.0; MS (HR, ESI) m / z (M +Na)$^+$ requires for $C_{19}H_{28}NO_4NaSiBr$ calcd: 464.0863, found: 464.0867;




***N*-[3'-Bromo-2',6'-(di-*t*-butyldimethylsiloxy)- benzyl]-4-vinyloxy-azetidin-2-one (228e)**: Obtained 380 mg (0.7 mmol); Yield 35%; yellow liquid; IR (film) v: 1766cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 0.25 (s, 6H, $CH_3$-Si), 0.99 (s, 9H, $(CH_3)_3$C-Si), 2.76 (d, $J$ = 14.7 Hz, 1H, $CH_2$), 3.01 (dd, $J$ = 14.7 Hz, 3.8 Hz, 1H, $CH_2$), 3.96 (dd, $J$ = 6.6 Hz, 1.9 Hz, 1H, $CH_2$=), 4.14 (dd, $J$ = 14.1 Hz, 1.9 Hz, 1H, $CH_2$=), 4.42 (d, $J$ = 13.4 Hz, 1H, $CH_2$-N), , 4.50 (d, $J$ = 13.4 Hz, 1H, $CH_2$-N), 4.92 (dd, $J$ = 3.8 Hz, 1.1 Hz, 1H, C*H*-O), 6.18 (dd, $J$ = 14.1 Hz, 6.6 Hz, 1H, =C*H*-O), 6.41 (d, $J$ = 8.8 Hz, 1H), 7.31 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: - 4.1, 18.9, 26.2, 35.8, 44.3, 80.4, 90.8, 107.1, 112.9, 117.7, 132.8, 147.6, 152.6, 154.9, 165.1; Anal. calcd for $C_{24}H_{40}BrNO_4Si_2$ (542.65) C, 53.12; H, 7.43; Br, 14.72; N, 2.58; O, 11.79; Si 10.35, found C, 53.10; H ,7.42; Br, 14.75; N, 2.56;




***N*-[5'-Bromo-2'-hydroxy-benzyl]-4-vinyloxy-azetidin-2-one (229f)**: Obtained 238 mg (0.8 mmol); Yield 40%; yellow liquid; IR (film) v: 1762 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.96 (d, $J$ = 14.8 Hz, 1H, $CH_2$), 3.17 (dd, $J$ = 14.8 Hz, 3.5 Hz, 1H, $CH_2$), 4.15 (d, $J$ = 15.2 Hz, 1H, $CH_2$-N), 4.30 (dd, $J$ = 6.7 Hz, 2.4 Hz, 1H, $CH_2$=), 4.38 (d, $J$ = 15.2 Hz, 1H, $CH_2$-N), 4.42 (dd, $J$ = 14.2 Hz, 2.4 Hz, 1H, $CH_2$=), 5.33 (dd, $J$ = 3.5 Hz, 1.1 Hz, 1H, C*H*-O), 6.40 (dd, $J$ = 14.2, 6.7 Hz, 1H, =C*H*-O), 6.86 (d, $J$ = 8.6 Hz, 1H), 7.34 (dd, $J$ = 8.6 Hz, 2.5 Hz, 1H), 7.42 (d, $J$ = 2.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: 40.5, 44.4, 91.9, 112.4, 114.1, 118.6, 119.6, 126.1, 132.9, 147.7, 155.2, 167.3; MS (HR, ESI) m / z (M +Na)$^+$ requires for $C_{12}H_{12}NO_3NaBr$ calcd: 319.9893 found: 319.9880;



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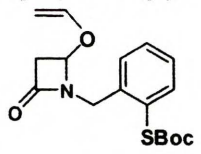
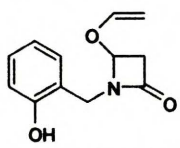
***N*-[2'-(O-*t*-Butyl)-S-benzyl-carbonothioate]-4-vinyloxy-azetidin-2-one (243)**: 335 mg (1.0 mmol); Yield 50%;




IR (film) v: 1764 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.50 (s, 9H, 3x$CH_3$), 2.89 (dm, *J* = 14.9 Hz, 1H, $CH_2$), 3.12 (dd, *J* = 14.9, 3.7 Hz, 1H, $CH_2$), 4.12 (dd, *J* = 6.6, 2.2 Hz, 1H, $CH_2$=), 4.26 (dd, *J* = 14.3, 2.2 Hz, 1H, $CH_2$=), 4.40 (d, *J* = 15.3 Hz, 1H, CH-N), 4.82 (d, *J* = 15.3 Hz, 1H, CH-N), 5.11 (dd, *J* = 3.7, 1.2 Hz, 1H, CH-O), 6.26 (dd, *J* = 14.3, 6.6 Hz, 1H, CH=), 7.34 (m, 1H, Ar), 7.44 (m, 2H, Ar), 7.57 (d, *J* = 7.5 Hz, 1H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 28.1, 42.9, 44.9, 79.9, 86.0, 91.2, 127.8, 128.7, 130.2, 130.6, 137.4, 138.9, 147.8, 165.2, 167.1; HR MS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{21}NO_4NaS$ 358.1083 found:358.1068;

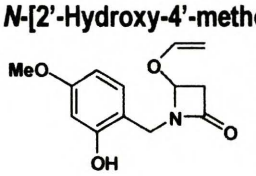
**4.4. Deprotection of hydroxyl group in *N*-benyzlated-4-vinyloxyazetidin-2-ons.**

***N*-[*o*-Hydroxy-benzyl]-4-vinyloxy-azetidin-2-one (229a)**: Obtained 74 mg (0.34 mmol); Yield 85%; yellow liquid;



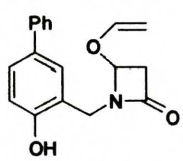

IR (film) v: 1766 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.94 (d, *J* = 15.1 Hz, 1H, C$H_2$), 3.12 (d, J = 3.60 Hz, 1H C$H_2$), 4.16 (d, *J* = 15.2 Hz, 1H, C$H_2$-N), 4.25 (dd, *J* = 6.6 Hz, 2.3 Hz, 1H, C$H_2$=), 4.41 (dd, *J* = 14.2 Hz, 2.3 Hz, 1H, C$H_2$=), 4.53 (d, *J* = 15.2 Hz, 1H, C$H_2$-N), 5.27 (dd, J = 3.6 Hz, 1.2 Hz, 1H, C*H*-O), 6.38 (dd, *J* = 14.2 Hz, 6.6 Hz, 1H, =C*H*-O), 6.89 (td, *J* = 7.4 Hz, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.14 (dd, *J* = 7.4 Hz, 1.6 Hz, 1H), 7.24 (td, *J* = 8.0 Hz, 1.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ: 40.9, 44.4, 79.7, 91.8, 118.1, 121.8, 122.2, 130.2, 130.6, 147.8, 154.8, 167.0; MS (HR, ESI) m / z $(M + Na)^+$ requires for $C_{12}H_{13}NO_3Na$ calcd: 242.0787, found: 242.0796;

***N*-[2'-Hydroxy-4'-methoxy-benzyl]-4-vinyloxy-azetidin-2-one (229b)**: Obtained 80 mg (0.32 mmol); Yield 80%;



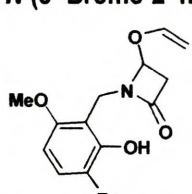

yellow liquid; IR (film) v: 1758 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.94 (d, *J* = 14.9 Hz, 1H, C$H_2$), 3.12 (dd, *J* = 14.9 Hz, 3.6 Hz, 1H, C$H_2$), 3.77 (s, 3H, $CH_3$), 4.09 (d, *J* = 15.2 Hz, 1H, C$H_2$-N), 4.25 (dd, *J* = 6.6 Hz, 2.4 Hz, 1H, C$H_2$=), 4.36 (d, *J* = 15.2 Hz, 1H, C$H_2$-N) 4.39 (dd, *J* = 14.2 Hz, 2.4 Hz, 1H, C$H_2$=), 5.28 (dd, *J* = 3.6 Hz, 1.3 Hz, 1H, C*H*-O), 6.40 (dd, *J* = 14.2 Hz, 6.6 Hz, 1H, =C*H*-O), 6.45 (dd, *J* = 8.3 Hz, 2.5 Hz, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ: 40.7, 44.3, 55.3, 79.6, 91.8, 103.7, 106.7, 114.8, 131.3, 147.8, 156.1, 161.4, 167.2; MS (HR, ESI) m / z $(M + Na)^+$ requires for $C_{13}H_{15}NO_4Na$ calcd: 272.0893, found: 272.0882;

***N*-[2'-Hydroxy-5'-phenyl-benzyl]-4-vinyloxy-azetidin-2-one (229c)**: Obtained 94 mg (0.32 mmol); Yield 79%;



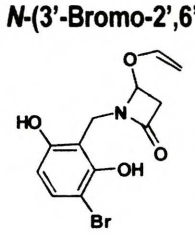

yellow liquid; IR (film) v: 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.91 (d, *J* = 14.9 Hz, 1H, C$H_2$), 3.11 (dd, *J* = 14.9 Hz, 3.6 Hz, 1H, C$H_2$), 4.19 (dd, *J* = 6.6 Hz, 2.3 Hz, 1H, C$H_2$=), 4.23 (d, *J* = 15.0 Hz, 1H, C$H_2$-N), 4.37 (dd, *J* = 14.2 Hz, 2.3 Hz, 1H, C$H_2$=), 4.61 (d, *J* = 15.0 Hz, 1H, C$H_2$-N), 5.25 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H, C*H*-O), 6.40 (dd, *J* = 14.2 Hz, 6.6 Hz, 1H, =C*H*-O), 6.99 (dd, *J* = 8.3 Hz, 1H), 7.29 (tt, *J* = 6.8 Hz, 1.2 Hz, 1H), 7.36-7.40 (complex, 3H), 7.42 (dd, *J* = 8.3 Hz, 2.4 Hz, 1H), 7.48 – 7.52 (complex, 3H); $^{13}C$ NMR ($CDCl_3$) δ: 40.8, 44.4, 79.9, 91.6, 117.7, 122.3, 126.6, 126.7, 128.5, 128.7, 129.9, 133.6, 140.4, 147.8, 154.5, 167.0; MS (HR, ESI) m / z $(M + Na)^+$ requires for $C_{18}H_{17}NO_3Na$ calcd: 318.1101, found: 318.1113;

***N*-(3'-Bromo-2'-hydroxy-6'-methoxy-benzyl)-4-vinyloxy-azetidin-2-one (229d)**: Obtained 105 mg (0.32




mmol); Yield 81%; yellow liquid; IR (film) v: 1762 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.96 (d, *J* = 15.1 Hz, 1H, C$H_2$), 3.11 (dd, *J* = 15.1 Hz, 3.6 Hz, 1H, C$H_2$), 3.87 (s, 3H, $CH_3$), 4.27 (dd, *J* = 6.7 Hz, 2.3 Hz, 1H, C$H_2$=), 4.33 (d, *J* = 15.0 Hz, 1H, C$H_2$-N), 4.48 (dd, *J* = 14.1 Hz, 2.3 Hz, 1H, C$H_2$=), 4.50 (d, *J* = 15.0 Hz, 1H, C$H_2$-N), 5.32 (dd, *J* = 3.6 Hz, 1.2 Hz. 1H, C*H*-O), 6.48 (dd, *J* = 14.1 Hz, 6.7 Hz, 1H, =C*H*-O), 6.71 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H); 7.93 (s, 1H, OH); $^{13}C$ NMR ($CDCl_3$) δ: 34.7, 44.5, 61.4, 80.3, 92.0, 107.2, 116.4, 118.9,133.8, 148.2, 155.7, 155.9, 167.9; MS (HR, ESI) m / z $(M + Na)^+$ requires for $C_{19}H_{28}NO_4NaSiBr$ calcd: 464.0863, found: 464.0845;

***N*-(3'-Bromo-2',6'-dihydroxy-benzyl)-4-vinyloxy-azetidin-2-one (229e)**: Obtained 107 mg (0.34 mmol); Yield




86%; yellow liquid; IR (film) v: 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 2.94 (d, *J* = 15.0 Hz, 1H, C$H_2$), 3.11 (dd, *J* = 15.0 Hz, 3.6 Hz, 1H, C$H_2$), 4.23 (dd, *J* = 6.5 Hz, 2.1 Hz, 1H, C$H_2$=), 4.40-4.52 (complex, 3, C$H_2$-N, C$H_2$= ), 5.32 (d, *J* = 3.6 Hz, 1H, C*H*-O), 6.40 (dd, *J* = 14.1 Hz, 6.5 Hz, 1H, =C*H*-O), 6.61 (d, *J* = 8.6 Hz, 1H), 7.7 (d, *J* = 8.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ: 34.5, 44.4, 80.4, 91.9, 101.2, 109.3, 111.8, 131.9, 148.2, 151.0, 156.1, 167.9; MS (HR, ESI) m / z $(M + Na)^+$



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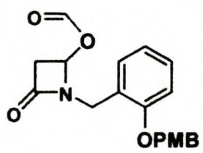
Anal. Calcd for $C_{12}H_{12}BrNO_4$ (314.13) C, 45.88; H, 3.85; Br, 25.44; N, 4.46; O, 20.37; found C, 45.86; H, 3.86; Br, 25.43; N, 4.44;

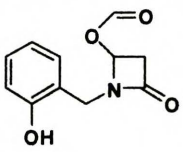
### 4.5. Preparation of *N*-benyzlated-4-formyloxyazetidin-2-ons (230, 231 and 244).

*N*-benyzlated-4-formyloxyazetidin-2-ons (**230**, **231** or **244**) were prepared in 0.3 mmol scale following literature procedure.[136] The crude products **230**, **231** or **244** were used without further purification due to their high instability.

***N*-[*o*-(*p*-Methoxybenzyloxy)-benzyl]-4-formyloxy-azetidin-2-one (230)**: Obtained 72 mg (0.21 mmol); Yield 70%; coloreless oil; IR (film) v: 1772, 1728 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.90 (d, *J* = 15.0 Hz, 1H, $CH_2$), 3.24 (dd, *J* = 15.0, 3.8 Hz, 1H, $CH_2$), 3.85 (s, 3H, $CH_3$), 4.35 (d, *J* = 15.0 Hz, 1H, CH-N), 4.58 (d, *J* = 15.0 Hz, 1H, CH-N), 5.04 (s, 2H, $CH_2$-Ar ), 5.97 (d, *J* = 3.8 Hz, 1H, CH-O), 6.95 (d, *J* = 8.6 Hz, 2H, Ar), 6.97 (d, *J* = 8.9 Hz, 2H, Ar), 7.29 (d, *J* = 8.9 Hz, 2H, Ar), 7.38 (d, *J* = 8.6 Hz, 2H, Ar), 7.77 (s, 1H, CH=O); $^{13}C$ NMR ($CDCl_3$) δ: 40.2, 45.3, 55.3, 69.9, 76.3, 111.8, 113.9, 120.9, 123.6, 128.7, 129.2, 129.4, 130.2, 156.6, 159.5, 159.8, 164.8; HR MS (ESI) calcd for $[M+Na]^+$ $C_{19}H_{19}NO_5Na$ 364.1155 found: 364.1167;

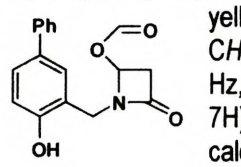



***N*-[*o*-Hydroxy-benzyl]-4-formyloxy-azetidin-2-one (231a)**: Obtained 40 mg (0.18 mmol); Yield 60%; yellow liquid; IR (film) v: 1728 $cm^{-1}$, 1772 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.04 (d, *J* = 15.2 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 15.2 Hz, 3.8 Hz, 1H, $CH_2$), 4.22 (d, *J* = 15.0 Hz, 1H, $CH_2$-N ), 4.53 (d, *J* = 15.0 Hz, 1H, $CH_2$-N), 6.86 – 6.96 (complex, 2H), 7.18 – 7.28 (complex, 2H), 8.10 (s, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) δ: 41.4, 44.2, 75.6, 118.0, 120.9, 122.2, 130.3, 130.8, 160.5, 166.8; MS (HR-ESI) *m/z*: $(M+C3H7OH+Na)^+$ requires for $C_{14}H_{19}NO_5Na$: calcd: 304.1155 found: 304.1144;

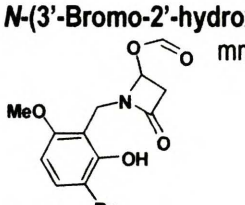



***N*-[2'-Hydroxy-4'-methoxy-benzyl]-4-formyloxy-azetidin-2-one (231b)**: Obtained 53 mg (0.21mmol); Yield 70%; yellow liquid; IR (film) v: 1733 $cm^{-1}$, 1771 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.02 (d, *J* = 15.2 Hz, 1H, $CH_2$), 3.27 (dd, *J* = 15.2, 3.9Hz, 1H, $CH_2$), 3.77 (s, 3H, $CH_3$), 4.13 (d, *J* = 15.1 Hz, 1H, $CH_2$-N ), 4.38 (d, *J* = 15.1 Hz, 1H, $CH_2$-N), 6.09 (d, *J* = 3.9 Hz, 1H, CH-O), 6.45 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H, H-3), 6.51 (d, *J* = 2.4 Hz, H-5), 7.07 (d, *J* = 8.4 Hz), 7.37 (OH), 8.10 (s, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) δ: 40.9, 44.1, 75.5, 103.3, 106.7, 131.4, 160.5;


***N*-[2'-Hydroxy-5'-phenyl-benzyl]-4-formyloxy-azetidin-2-one (231c)**: Obtained 62 mg (0.21 mmol); Yield 70%; yellow liquid; IR (film) v: 1733 $cm^{-1}$, 1774 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.07 (d, *J* = 15.2 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 15.2, 3.9 Hz, 1H, $CH_2$), 4.27 (d, *J* = 15.2 Hz, 1H, $CH_2$-N ), 4.57 (d, *J* = 15.2 Hz, 1H, $CH_2$-N), 6.14 (dm, *J* = 3.4 Hz, 1H, CH-O), 7.10 (d, *J* = 8.4 Hz, 1H, $H_)$, 7.30 – 7.50 (m, 7H), 8.10 (s, 1H, CHO); MS (HR-ESI) *m/z*: $(M+C2H5OH+Na)^+$ requires for $C_{19}H_{21}NO_5Na$: calcd: 366.1312, found: 366.1324;




***N*-(3'-Bromo-2'-hydroxy-6'-methoxy-benzyl)-4-formyloxy-azetidin-2-one (231d)**: Obtained 76 mg (0.23 mmol); Yield 77%; yellow liquid; IR (film) v: 1734 $cm^{-1}$, 1780 $cm^{-1}$,




***N*-(3'-Bromo-2',6'-dihydroxy-benzyl)-4-formyloxy-azetidin-2-one (231e)**: Obtained 82 mg (0.26 mmol); Yield 88%; yellow liquid; IR (film) v: 1733 $cm^{-1}$, 1774 $cm^{-1}$,; $^1H$ NMR ($CDCl_3$) δ: 3.00 (d, *J* = 15.3 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 15.3 Hz, 3.8 Hz, 1H, $CH_2$), 4.39 (d, *J* = 15.0 Hz, 1H, $CH_2$-N ), 4.53 (d, *J* = 15.0 Hz, 1H, $CH_2$-N), 5.94 (b s, 1H, OH), 6.22 (d, *J* = 3.8 Hz, 1H, CH-O), 6.52 (d, *J* = 8.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.60 (b s, 1H, OH), 8.12 (s, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) δ: 35.5, 44.9, 76.1, 112.5, 132.4, 160.4,

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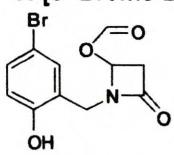
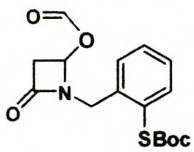
***N*-[5'-Bromo-2'-hydroxy-benzyl]-4-formyloxy-azetidin-2-one (231f)**: Obtained 72 mg (0.24 mmol); Yield 80%; yellow liquid; $^1$H NMR ($CDCl_3$) δ: 2.99 (d, *J* = 15.3 Hz, 1H, C*H*$_2$), 3.29 (dd, *J* = 15.3 Hz, 3.9 Hz, 1H, C*H*$_2$), 4.21 (d, *J* = 15.3 Hz, 1H, C*H*$_2$-N ), 4.50 (d, *J* = 15.3 Hz, 1H, C*H*$_2$-N), 5.95 (d, *J* = 3.9 Hz, 1H, CH-O), 6.81 (d, *J* = 8.6 Hz, 1H), 7.32 - 7.42 (complex, 2H), 7.94 (s, 1H, C*H*O); $^{13}$C NMR ($CDCl_3$) δ: 40.2, 44.9, 76.1, 113.7, 118.9, 124.2, 126.3, 133.3, 154.9, 160.3, 165.3



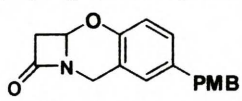

***N*-[2'-(O-*t*-butyl)-S-benzyl-carbonothioate]-4-formyloxy-azetidin-2-one 244**: Obtained 51 mg (0.15 mmol); Yield 50%; yellow oil; $^1$H NMR (500 MHz, $CDCl_3$) δ: 1.49 (s, 9H, 3x$CH_3$), 2.96 (d, *J* = 15.3 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 15.3, 3.7 Hz, 1H, $CH_2$), 4.43 (d, *J* = 15.5 Hz, 1H, CH-N), 4.77 (d, *J* = 15.3 Hz, 1H, CH-N), 5.95 (d, *J* = 3.7 Hz, 1H, CH-O), 7.44 (m, 3H, Ar), 7.57 (d, *J* = 7.3 Hz, 1H, Ar), 7.94 (s, 1H, HC=O);




### 4.6. Lewis acid promoted cyclization of 230 and 236

Reaction was performed accorind to the general procedure.

**3,4-(5'-(*p*-Methoxybenzyloxy)-benzo)-5-oxa-cepham (232)**: Yellow oil; IR (film) v: 1772 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ: 2.99 (dm, *J* = 14.9 Hz, 1H, $CH_2$), 3.34 (ddd, *J* = 14.9, 3.1, 1.9 Hz, 1H, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.85 (s, 2H, $CH_2$), 4.14 (d, *J* = 15.9 Hz, 1H, CH-N), 4.65 (d, *J* = 15.9 Hz, 1H, CH-N), 5.23 (dm, *J* = 3.1 Hz, 1H, CH-O), 6.84 (m, 4H, Ar), 6.99 (m, 1H, Ar), 7.13 (m, 2H, Ar); $^{13}$C NMR ($CDCl_3$) δ: 38.9, 40.1, 46.2, 55.2, 75.3, 113.9, 117.7, 118.3, 118.4, 122.3, 127.2, 128.5, 128.9, 129.7, 152.2, 167.3; HR MS (ESI) calcd for $[M + Na]^+$ $C_{18}H_{17}NO_3Na$ 318.1101 found: 318.1111;



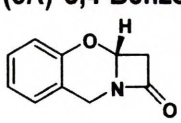

### 4.7. Chiral Lewis acid promoted reactions

#### 4.7.1. Chiral Lewis acid promoted cyclizations

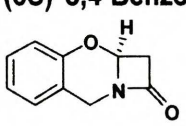
##### 4.7.1.1. Chiral Lewis acid promoted cyclization of 231

Reaction was performed accorind to the general procedure.

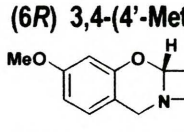
**(6*R*) 3,4-Benzo-5-oxa-cepham (218a)**: Obtained 9.6 mg (0.055 mmol); Yield 39%, 99% *ee;* yellow liquid; $[\alpha]_D^{26}$ = +36 (c = 0.02, $CH_2Cl_2$); IR (film) v: 1774 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.02 (d, *J* = 15.0 Hz, 1H, C*H*$_2$), 3.36 (ddd, *J* = 15.0 Hz, 3.0 Hz, 2.1 Hz, 1H, C*H*$_2$), 4.21 (d, *J* = 16.4 Hz, 1H, C*H*$_2$-N ), 4.57 (d, *J* = 16.4 Hz, 1H, C*H*$_2$-N), 5.27 (d, *J* = 3.0 Hz, 1H, CH-O), 6.94 (d, *J* = 8.2 Hz, 1H), 7.00 (tm, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.20 (tm, *J* = 8.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: 38.9, 46.3, 75.3, 117.8, 118.4, 122.4, 127.2, 128.5, 152.2, 167.3; MS (HR-ESI) *m/z*: $(M+H)^+$ requires for $C_{10}H_{10}NO_2$: calcd: 176.0706, found:176.0697; Anal. calcd for $C_{10}H_9NO_2$ (175.18) C, 68.56; H, 5.18; N, 8.00; O, 18.27, found C, 68.59, H, 5.20, N, 8.03; HPLC [OD-H, hexane/*i*-propanole = 9:1, 1.0 mL/min, $t_R$ [*S*]= 24.5 (minor) $t_R$ [*R*]= 37.2 (major)]




**(6*S*) 3,4-Benzo-5-oxa-cepham (*ent*-218a):** Obtained 10.3 mg (0.059 mmol); Yield 42%, 99% *ee;* yellow liquid; $[\alpha]_D^{26}$ = -35 (c = 0.02, $CH_2Cl_2$), HPLC [OD-H, hexane/*i*-propanole 9:1, 1.0 mL/min, $t_R$[*S*] = 24.5 (major) $t_R$[*R*] = 37.2 (minor)]




**(6*R*) 3,4-(4'-Methoxy-benzo)-5-oxa-cepham (218b)**: Obtained 14.1 mg (0.069 mmol); Yield 42%, 82% *ee;* yellow liquid; $[\alpha]_D^{26}$ = +45 (c = 0.02, $CH_2Cl_2$); IR (film) v: 1788 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 3.00 (d, *J* = 15.0 Hz, 1H, C*H*$_2$), 3.34 (ddd, *J* = 15.0 Hz, 3.1 Hz, 2.0 Hz, 1H, C*H*$_2$), 3.78 (s, 3H, $CH_3$), 4.14 (dd, *J* = 16.1 Hz, 2.0 Hz, 1H, C*H*$_2$-N ), 4.65 (d, *J* = 16.1 Hz, 1H, C*H*$_2$-N), 5.24 (d, *J* = 3.1 Hz, 1H, CH-O), 6.48 (d, *J* = 2.6 Hz, 1H), 6.57 (dd, *J* = 8.5 Hz, 2.6 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H) $^{13}$C NMR ($CDCl_3$) δ: 39.4, 45.7, 55.1, 78.7, 103.4, 109.7, 128.1, 153.9; MS (HR-ESI) *m/z*: $(M+Na)^+$ requires for



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$C_{11}H_{11}NO_3Na$: calcd: 228.0631, found: 228.062; Anal. calcd: for $C_{11}H_{11}NO_3$ (205.21) C 64.38, H 5.40, N 6.83 found C, 64.17, H, 6.53, N, 6.11, HPLC [OD-H, hexane/*i*-propanole 9:1, 1.0 mL/min, $t_R$ [*R*] = 9.0 (major), $t_R$[*S*] = 11.8 (minor)]

**(6*R*) 3,4-(5'-Phenyl-benzo)-5-oxa-cepham (218c)**: Obtained 15.8 mg (0.063 mmol); Yield 45%, 92% *ee*; yellow liquid; $[\alpha]_D^{26}$ = +60 (c = 0.02, $CH_2Cl_2$); IR (film) v: 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.04 (d, *J* = 15.0 Hz, 1H, C*H*$_2$), 3.38 (ddd, *J* = 15.0 Hz, 3.0 Hz, 2.1 Hz, 1H, C*H*$_2$), 4.26 (d, *J* = 16.2 Hz, 1H, C*H*$_2$-N ), 4.77 (d, *J* = 16.2 Hz, 1H, C*H*$_2$-N), 5.30 (d, *J* = 3.0 Hz, 1H, CH-O), 7.01 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.33 (tm, *J* = 7.4 Hz, 1H), 7.42 (m, 3H), 7.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ: 39.0, 46.3, 75.5, 117.9, 118.8, 125.7, 126.8, 127.2, 127.3, 128.8, 135.7, 140.1, 151.7, 167.3; MS (HR-EI) *m/z*: requires for $C_{16}H_{13}NO_2$: calcd: 251.0946, found: 251.0957; HPLC [OD-H, hexane/*i*-propanole 9:1, 0.5 mL/min, $t_R$[*S*] = 12.0 (minor), $t_R$ [*R*] = 17.0 (major)]

**(6*R*) 3,4-(3'-Bromo-6'-methoxy-benzo)-5-oxa-cepham (218d)**: Obtained 19.9 mg (0.070 mmol); Yield 50%, 95% *ee;* yellow liquid; $[\alpha]_D^{26}$ = +55 (c = 0.02, $CH_2Cl_2$); IR (film) v: 1776 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.01 (d, *J* = 15.1 Hz, 1H, C*H*$_2$), 3.36 (ddd, *J* = 15.1 Hz, 2.9 Hz, 2.0 Hz, 1H, C*H*$_2$), 3.85 (s, 3H, $CH_3$), 4.21 (dd, *J* = 15.2 Hz, 2.0 Hz, 1H, C*H*$_2$-N ), 4.70 (d, *J* = 17.2 Hz, 1H, C*H*$_2$-N), 5.23 (d, *J* = 3.2 Hz, 1H, CH-O), 6.64 (d, *J* = 8.9 Hz, 1H), 7.36 (d, J = 8.9 Hz) $^{13}C$ NMR ($CDCl_3$) δ: 35.9, 46.5, 55.4, 75.2, 101.8, 106.7, 111.6, 130.4, 149.3, 152.7, 166.9; MS (HR-ESI) *m/z*: $(M+Na)^+$ requires for $C_{11}H_{11}NO_3NaBr$: calcd: 305.9736, found: 305.9745; HPLC [OD-H, hexane/*i*-propanole 9:1, 1.0 mL/min, $t_R$[*R*] = 14.9 (major), $t_R$[*S*] = 20.7 (minor)]

**3,4-(3'-Bromo-6'-hydroxy-benzo)-5-oxa-cepham (218e)**: Obtained 19.4 mg (0.072 mmol); Yield 52%, 0% *ee*; yellow liquid; IR (film) v: 1776 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 3.02 (d, *J* = 15.1 Hz, 1H, C*H*$_2$), 3.37 (ddd, *J* = 15.1 Hz, 3.1 Hz, 2.0 Hz, 1H, C*H*$_2$), 4.16 (dd, *J* = 17.3 Hz, 2.0 Hz, 1H, C*H*$_2$-N ), 4.68 (d, *J* = 17.3 Hz, 1H, C*H*$_2$-N), 5.24 (d, *J* = 3.1 Hz, 1H, CH-O), 5.64 (s, 1H, OH), 6.48 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H) $^{13}C$ NMR ($CDCl_3$) δ: 35.9, 46.5, 75.2, 101.8, 106.7, 111.6, 130.4, 149.3, 152.7, 166.9; MS (HR-ESI) *m/z*: $(M-H)^-$ requires for $C_{10}H_7NO_3Br$ calcd: 267.9604, found: 267.9616; HPLC [AD-H, hexane/*i*-propanole 9:1, 0.7 mL/min, $t_R$ = 19.6, $t_R$ = 21.5]

#### 4.7.1.2. Chiral Lewis acid promoted cyclization of 241

The solution of **236** (80 mg, 0.15 mmol, 1.1 equiv) in $CH_2Cl_2$ (5mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (308 µL, 2.2 equiv) under argon atmosphere. After 15 minutes compound **241** ( 42 mg, 0.14 mmol) was added and temperature raised to room one. The reaction mixture was stirred for 3.0 h and diluted with saturated $NaHCO_3$ (5mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x10 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield **(6*R*) 3-methylene-5-oxa-cepham (224)** as a yellow oil in 68% yield and 12% *ee*; $[\alpha]_D^{26}$ = +7.2 (c 0.8, $CHCl_3$); HPLC [AD-H, hexane/*i*-propanole 95:5, 1.0 mL/min, $t_R$[*R*] = 14.9 (major), $t_R$[*S*] = 20.7 (minor)]

#### 4.7.1.3. Chiral Lewis acid promoted cyclization of 243

The solution of **236** (660 mg, 1.24 mmol, 2.2 equiv) in $CH_2Cl_2$ (20mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (1.23 mL, 1.24 mmol, 2.2 equiv) under argon atmosphere. After 15 minutes compound **243** (188 mg, 0.56 mmol) was added. The reaction mixture was stirred for 7.5h and diluted with saturated $NaHCO_3$ (20mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x40 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/diethyl ether) to yield **219**.

**(6*R*) 3,4-benzo-cepham (219)**: Obtained13 mg (0.07 mmol); Yield 12%, 48% *ee*; yellow oil; $[\alpha]_D^{26}$ = +20.2 (c 0.41, $CHCl_3$); IR (film) v: 1764 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.97 (dm, *J* = 14.8 Hz, 1H, $CH_2$), 3.51 (ddm, *J* = 14.8, 4.1 Hz, 1H, $CH_2$), 4.25 (d, *J* = 16.6 Hz, 1H, CH-N), 4.79 (d, *J* = 16.6 Hz, 1H, CH-N), 4.81 (dm, *J* = 4.1 Hz, 1H, CH-S), 7.17 (m, 3H, Ar), 7.24 (m, 1H, Ar); $^{13}C$



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NMR ($CDCl_3$) δ: 42.1, 45.9, 49.1, 126.2, 127.7, 128.3, 128.4, 129.5, 130.0, 166.6; HR MS (ESI) calcd for [M + Na]$^+$ $C_{10}H_9NONaS$ 214.0297 found: 214.0288; HPLC [OD-H, hexane/*i*-propanole = 9:1, 1.0 mL/min, $t_R$ [*R*]= 20.9 (major), $t_R$ [*S*]= 25.5 (minor)];

### 4.7.2. Chiral Lewis acid promoted intermolecular substitution with phenols 245 a-d and tiophenol 248a

Reaction was performed according to the general procedure.

**(4*S*) 4-(o-Tolyloxy)-azetidin-2-one (222a)**: Obtained 11 mg (0.065 mmol); Yield 25%, 12% *ee*; white solid; $m_p$ = 99-100 °C; $[\alpha]_D^{26}$ = -5.4 (c 0.40, $CHCl_3$); IR (film) v: 1786 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.24 (s, 3H, $CH_3$), 3.13 (dt, *J* = 15.0 Hz, 1.3 Hz, 1H, $CH_2$), 3.35 (ddd, *J* = 15.0 Hz, 3.8 Hz, 2.4 Hz, 1H, $CH_2$), 5.65 (dd, *J* = 3.8 Hz, 1.3 Hz, 1H, CH-O), 6.58 (s, 1H, NH), 6.69 (d, *J* = 8.0 Hz, 1H, H-1), 7.96 (td, *J* = 7.5 Hz, 1.1 Hz, 1H), 7.15 (td, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: 16.2, 46.3, 76.3, 112.8, 122.4, 126.9, 127.9, 131.5, 154.1, 166.0; MS (HR-ESI) *m/z*: (M+Na)$^+$ requires for $C_{10}H_{11}NO_2Na$ calc: 200.0682 found: 200.0686; HPLC [OD-H, hexane/*i*-propanole 8:2, 0.5 mL/min, $t_R$[*S*] = 24.0 (major), $t_R$[*R*] = 29.4 (minor)]

**(4*S*) 4-(3'-Methyl-4'-phenyl)-phenyloxy)-azetidin-2-one (222b)**: Obtained 13 mg (0.052 mmol); Yield 20%, 24% *ee;* white solid; $m_p$ = 134-136 °C; $[\alpha]_D^{26}$ = -9.8 (c 0.50, $CHCl_3$); IR (film) v: 1785 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.30 (s, 3H, $CH_3$), 3.14 (dt, *J* = 15.0 Hz, 1.1 Hz, 1H, $CH_2$), 3.37 (ddd, *J* = 15.0 Hz, 3.8 Hz, 2.2 Hz, 1H, $CH_2$), 5.69 (dd, *J* = 3.8 Hz, 1.1 Hz, 1H, CH-O), 6.68 (s, 1H, NH), 6.75 (d, *J* = 8.4 Hz, 1H), 7.31 (tt, *J* = 6.8 Hz, 1.2 Hz, 1H), 7.37 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 7.42 (m, 3H), 7.53 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ: 16.4, 46.3, 76.5, 113.0, 125.5, 126.8, 127.0, 128.1, 128.7, 130.3, 135.5, 140.5, 153.7, 166.0; MS (HR-ESI) *m/z*: (M+Na)$^+$ requires for $C_{16}H_{15}NO_2Na$ : 276.0995 found: 276.09919; Anal. calcd: for $C_{16}H_{15}NO_2$ (253.30) C 63.76, H 6.32, N 6.76 found C, 64.31, H, 6.86, N, 5.17; HPLC [AD-H, hexane/*i*-propanole 9:1, 0.5 mL/min, $t_R$[*S*] = 10.6 (major), $t_R$[*R*] = 12.4 (minor)]

**(4*S*) 4-(3-methoxy-2-methylphenoxy)azetidin-2-one (222c)**: Obtained 14 mg (0.068 mmol); Yield 26%, 31% *ee;* white solid; $m_p$ = 104-105 °C; $[\alpha]_D^{26}$ = - 7.4 (c 0.60, $CHCl_3$); IR (film) v: 1784 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ: 2.11 (s, 3H, $CH_3$), 3.12 (d, *J* = 15.1 Hz, 1H, $CH_2$), 3.33 (ddd, *J* = 15.1 Hz, 3.8 Hz, 2.4 Hz, 1H, $CH_2$), 3.83 (s, 3H, $CH_3$), 5.63 (dd, *J* = 3.8 Hz, 1.3 Hz, 1H, CH-O), 6.38 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.75 (s, 1H, NH), 7.11 (t, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ: 8.5, 46.2, 55.7, 76.7, 105.1, 106.0, 116.1, 126.5, 154.7, 158.9, 166.2; MS (HR-ESI) *m/z*: (M+Na)$^+$ requires for $C_{11}H_{13}NO_3Na$ : calc: 230.0787 found: 230.0780; Anal. calcd: for $C_{11}H_{13}NO_3$ (207.23) C 75.85, H 5.97, N 5.53 found C, 75.69, H, 5.93, N, 5.46; HPLC [OD-H, hexane/*i*-propanole 8:2, 0.3 mL/min, $t_R$[*R*] = 16.5 (minor), $t_R$ [*S*] = 18.0 (major)]

**4-Phenylthio-azetidin-2-one (*rac*-223a)**: Obtained 23 mg (0.13 mmol); Yield 50%, 0% *ee*; white solid; m.p. 54-56°C; IR (film) v: 1778 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ: 2.89 (ddd, *J* = 15.2, 2.3, 1.9 Hz, 1H, $CH_2$); 3.36 (ddd, *J* = 15.2, 4.9, 1.9 Hz, 1H, $CH_2$); 5.00 (dd, *J* = 4.9, 2.3 Hz, 1H, CH-S); 6.38 (s, 1H, NH); 7.35 (m, 3H, Ar); 7.45 (m, 2H, Ar); $^{13}$C NMR (125 MHz, $CDCl_3$) *δ*: 45.4, 54.2, 128.6, 129.4, 131.4, 133.5; 165.8; HR MS (TOF MS EI+) calcd for M$^+$ $C_9H_9NOS$ 179.0405 found: 179.0396;

**(4*R*) *N*-Benzyl-(o-tolyloxy)-azetidin-2-one (247)**: Obtained 22 mg (0.08 mmol); Yield 31%, 18% *ee* ; white solid m.p. 130-131°C; $[\alpha]_D^{26}$ = 5.2 (c 0.5, $CHCl_3$); IR (film) v: 1767 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ: 2.16 (s, 3H, $CH_3$), 3.02 (dm, *J* = 14.7 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 14.7, 3.4 Hz, 1H, $CH_2$), 4.24 (d, *J* = 15.2 Hz, 1H, CH-N), 4.68 (d, *J* = 15.2 Hz, 1H, CH-N), 5.45 (dd, *J* = 3.5, 1.1 Hz, 1H, CH-O), 6.60 (dm, *J* = 8.0 Hz, 1H, Ar), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H, Ar), 7.08 (tm, *J* = 8.0 Hz, 1H, Ar), 7.16 (dm, *J* = 7.4 Hz, 1H, Ar), 7.30 (m, 5H, Ph); $^{13}$C NMR ($CDCl_3$) δ: 16.1, 44.6, 45.9, 79.7, 113.2, 122.3, 126.8, 127.7, 128.3, 128.8, 131.3, 135.6, 154.2, 165.4; HR MS (ESI) calcd for [M + Na]$^+$ $C_{17}H_{17}NO_2Na$ 290.1152 found:290.1157; HPLC [OD-H, hexane/*i*-propanole = 9:1, 1.0 mL/min, $t_R$ [*R*]= 14.5 (major), $t_R$ [*S*]= 16.5 (minor)];



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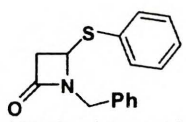
***N*-Benzyl-4-Phenylthio-azetidin-2-one (*rac*-249)**: Obtained 34 mg (0.12 mmol); Yield 45%, 0% *ee*; white solid

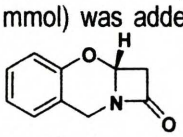


m.p. 129-130°C; IR (film) v: 1779 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 299 (ddd, *J* = 14.9, 2.2, 1.0 Hz, 1H, $CH_2$), 3.29 (ddm, *J* = 14.9, 4.9 Hz, 1H, $CH_2$), 4.58 (d, *J* = 15.1 Hz, 1H, CH-N), 4.73 (d, *J* = 15.1 Hz, 1H, CH-N), 4.79 (dd, *J* = 4.9, 2.2 Hz, 1H, CH-S), 7.14 (m, 2H, Ar), 7.32 (m, 8H, Ar);; $^{13}C$ NMR ($CDCl_3$) δ: 44.3, 44.5, 58.2, 127.8, 128.4,128.7, 128.8, 129.3, 130.4, 134.1, 135.4, 165.1; HR MS (ESI) calcd for $[M + Na]^+ C_{16}H_{15}NONaS$ 292.0767 found:292.0771;

### 4.7.3. Chiral Lewis acid promoted deracemization of azetidin-2-ones

#### 4.7.3.1. Deracemization of 218a

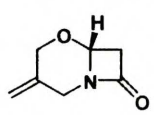
The solution of **233** (129 mg, 0.45 mmol, 1.1 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (450 µL, 1.1 equiv) under argon atmosphere. After 15 minutes compound ***rac*-218 a** (75 mg, 0.42 mmol) was added. The reaction mixture was stirred for 3.0 h and diluted with saturated $NaHCO_3$ (5mL). The



aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield 11 mg (0.06 mmol) of **218a** as a yellow oil in 15% yield and 85% *ee*.

#### 4.7.3.2. Deracemization of 224

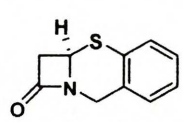
The solution of **236** (240 mg, 0.45 mmol, 1.1 equiv) in $CH_2Cl_2$ (10 mL) at -78°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (450 µL, 1.1 equiv) under argon atmosphere. After 15 minutes compound ***rac*-224** (58 mg, 0.42 mmol) was added. The reaction mixture was stirred for 36 h and diluted with saturated $NaHCO_3$



(10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield 28 mg (0.2 mmol) of **224** as a yellow oil in 48% yield and 22% *ee*.

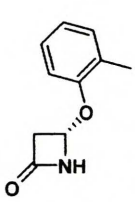
#### 4.7.3.3. Deracemization of 219

The solution of **236** (225 mg, 0.42 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (420 µL, 1.0 equiv) under argon atmosphere. After 15 minutes compound ***rac*-219** (80 mg, 0.42 mmol) was added. The reaction mixture was stirred for 6h and diluted with saturated $NaHCO_3$



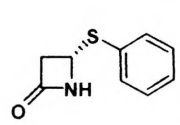
(10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/diethyl ether) to yield 38 mg (0.2 mmol) of **219** as yellow oil in 48% yield and 46% *ee*.

#### 4.7.3.4. Deracemization of 222a



The solution of ***ent*-236** (225 mg, 0.42 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (420 µL, 1.0 equiv) under argon atmosphere. After 15 minutes compound ***rac*-222a** (74 mg, 0.42 mmol) was added. The reaction mixture was stirred for 3h and diluted with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/diethyl ether) to yield 21 mg (0.12 mmol) of **222a** as yellow oil in 28% yield and 17% *ee*.

#### 4.7.3.5. Deracemization of 223a



The solution of ***ent*-236** (225 mg, 0.42 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (420 µL, 1.0 equiv) under argon atmosphere. After 15 minutes compound ***rac*-223a** (75 mg, 0.42 mmol) was added. The reaction mixture was stirred



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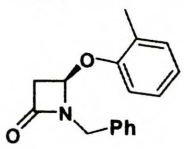
for 6h and diluted with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/acetone) to yield 31 mg (0.17 mmol) of (4*S*) 4-phenylthio-azetidin-2-one **(223a)** as white solid in 41% yield and 42% *ee*. HPLC [OD-H, 8/2 Hexene/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 19.9 (minor), $t_R$ [*S*]= 23.8 (major)]; $[\alpha]_D^{26}$ = -110.7 (c 0.73, $CHCl_3$)

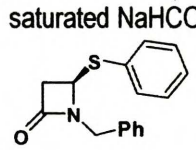
#### 4.7.3.6. Deracemization of 247

The solution of ligand **236** (225 mg, 0.42 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (420 µL, 1.0 equiv) under argon atmosphere. After 15 minutes compound ***rac*-247** (112 mg, 0.42 mmol) was added. The reaction mixture was stirred for 3h and diluted with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/methyl-*t*-butyl ether) to yield 39 mg (0.15 mmol) of **247** as yellow oil in 35% yield and 18% *ee*.



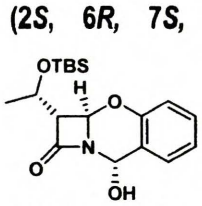

#### 4.7.3.7. Deracemization of 249

The solution of ligand **236** (225 mg, 0.42 mmol, 1.0 equiv) in $CH_2Cl_2$ (10 mL) at 0°C was treated with 1M solution of $SnCl_4$ in $CH_2Cl_2$ (420 µL, 1.0 equiv) under argon atmosphere. After 15 minutes racemic *N*-benzyl-4-phenylthio-azetidin-2-one (***rac*-249**) (113 mg, 0.42 mmol) was added. The reaction mixture was stirred for 6h and diluted with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3x20 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 7:3 hexane/acetone) to yield (4*R*) *N*-benzyl-4-phenylthio-azetidin-2-one **249** as white solid in 40% yield and 37% *ee*. HPLC [OD-H, 9/1 Hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 19.9 (minor), $t_R$ [*S*]= 23.8 (major)]; $[\alpha]_D^{26}$ = +50.7 (c 0.6, $CHCl_3$);

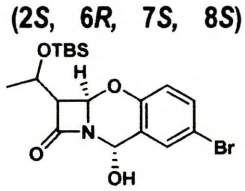



### 4.8. *t*-BuONa promoted nucleophilic substitution with *o*-hydoxy-aldehydes, ketons, thiosalicilic aldehydes, phenols and thiophenols

**(2*S*, 6*R*, 7*S*, 8*S*) 3,4-Benzo-8-(*tert*-butyldimethylsilyloxy)-7-ethyl--2-hydroxy-5-oxa-cepham (271a)**: Obtained 31 mg (0.09 mmol); Yield 90%,; white solid m.p. 134-135°C; $[\alpha]_D^{26}$ = +102.3 (c 1.0, $CH_2Cl_2$); IR (film) v: 1780 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 0.07 (s, 3H, $CH_3Si$), 0.09 (s, 3H, $CH_3Si$), 0.89 (s, 9H, t-Bu), 1.35 (d, *J* = 6.3 Hz, 3H, $CH_3$), 3.04 (d, *J* = 5.9 Hz, 1H, CH), 3.23 (d, *J* = 3.6 Hz, 1H, OH), 4.28 (m, 1H, CH-Me), 5.40 (s, 1H, CH-OH), 5.92 (d, *J* = 5.9 1H, CH-O), 6.97 ( dd, *J* = 8.3, 0.9 Hz, 1H, Ar), 706 (td, *J* = 7.6, 1.2 Hz, 1H, Ar), 7.29 (td, *J* = 8.3, 1.2 Hz, 1H, Ar) 7.46 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: -5.2, -4.3, 17.9, 22.5, 25.7, 29.7, 63.8, 67.4, 67.7, 75.3, 117.9, 120.6, 122.6, 128.8, 130.5, 152.3, 166.7; HR MS (ESI) calcd for [M + Na]$^+$ $C_{18}H_{27}NO_4NaSi$ 372.1602 found 372.1591;




**(2*S*, 6*R*, 7*S*, 8*S*) 3,4-(5'Bromo-benzo)-8-(*tert*-butyldimethylsilyloxy)-7-ethyl--2-hydroxy-5-oxa-cepham (271b)**: Obtained 40 mg (0.095 mmol); Yield 95%,; white solid m.p. 130-131°C; $[\alpha]_D^{26}$ = +90.6 (c 0.26, $CHCl_3$); IR (film) v: 1782 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 0.08 (s, 3H, $CH_3Si$), 0.09 (s, 3H, $CH_3Si$), 0.88 (s, 9H, t-Bu), 1.34 (d, *J* = 6.3 Hz, 3H, $CH_3$), 3.25 (d, *J* = 3.6 Hz, 1H, CH), 3.35 (d, *J* = 5.8 Hz, 1H, OH), 4.26 (m, 1H, CH-Me), 5.38 (d, *J* = 3.6 Hz, 1H, CH-O), 5.88 (d, *J* = 5.8 1H, CH-OH), 6.87 ( d, *J* = 8.8 Hz, 1H, Ar), 7.38 (ddd, *J* = 8.8, 4.6, 2.1 Hz, 1H, Ar), 7.60 (dd *J* = 4.6, 2.1 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ:-5.2, -4.3, 17.9, 22.5, 25.6, 63.7, 67.3, 67.5, 75.6, 114.7, 119.8, 122.5. 131.6, 133.4, 151.5, 166.7; HR MS (ESI) calcd for [M + Na]$^+$ $C_{18}H_{26}NO_4NasiBr$ 450.0707, found:450.0728;



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### 4.9. Quinidine (253) catalyzed nucleophilic substitution

#### 4.9.1. Quinidine (253) catalyzed nucleophilic substitution with *o*-hydoxy-aldehydes and ketons or thiosalicilic aldehyde.

Reaction was performed according to the general procedure.

**(2*R*, 6*S*) 3,4-Benzo-2-hydroxy-5-oxa-cepham (217a)**: Obtained 39 mg (0.20 mmol); Yield 77%, 49% *ee*; white solid m.p. 130-131°C; $[\alpha]_D^{26}$ = -106.0 (c 0.28, $CH_2Cl_2$); IR (film) v: 1785 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.07 (d, *J* = 15.4 Hz, 1H, $CH_2$), 3.37 (dd, *J* = 15.4, 3.3 Hz, 1H, $CH_2$), 3.68 (d, *J* = 5.4 Hz, 1H, OH), 5.37 (d, *J* = 3.3 Hz, 1H, CH-O), 5.92 (d, *J* = 5.4 Hz, 1H, CH-OH), 6.96 ( dd, *J* = 8.1, 1.2 Hz, 1H, Ar), 7. 08 (td, *J* = 7.5, 1.2 Hz, 1H, Ar), 7.30 (td, *J* = 8.1, 1.6 Hz, 1H, Ar), 7.47 (dd, *J* = 7.7 Hz, 1.6 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 46.3, 67.8, 73.4, 117.9, 120.7, 122.8, 128.8, 130.5, 152.0, 164.5; HR MS (ESI) calcd for $[M + Na]^+$ $C_{10}H_9NO_3Na$ 214.0475 found 214.0476; HPLC [AD-H, hexane/*i*-propanole = 95:5, 1.0 mL/min, $t_R$ [6*S*]= 25.2 (major), $t_R$ [6*R*]= 31.9 (minor)]; Anal. calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33; found: C, 62.77; H, 4.71; N, 7.30.

**(2*R*, 6*S*) 3,4-(5'-Bromo-benzo)-2-hydroxy-5-oxa-cepham (217b)**: Obtained 53 mg (0.19 mmol); Yield 76%, 40% *ee*; white solid m.p. 120-121°C; $[\alpha]_D^{26}$ = -52.6 (c 0.9, $CHCl_3$); IR (film) v: 1786 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.08 (ddd, *J* = 15.5, 0.7, 0.3 Hz, 1H, $CH_2$), 3.17 (s, 1H, OH), 3.40 (dd, *J* = 15.5, 3.3 Hz, 1H, $CH_2$), 5.37 (dt, *J* = 3.3, 0.7 Hz, 1H, CH-O), 5.90 (s, 1H, CH-OH), 6.86 ( td, *J* = 8.7, 0.4 Hz, 1H, Ar), 7. 40 (ddd, *J* = 8.7, 2.3, 0.7 Hz, 1H, Ar), 7.61 (ddd *J* = 2.3, 0.7, 0.4 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 46.5, 67.4, 73.7, 115.0, 119.8, 122.4, 131.6, 133.6, 151.2, 166.2; HR MS (ESI) calcd for $[M + Na]^+$ $C_{10}H_8NO_3NaBr$ 291.9579, found: 291.9565; HPLC [AD-H, hexane/IPA = 9:1, 1.0 mL/min, $t_R$ [6*S*]= 13.1 (major), $t_R$ [6*R*]= 23.7 (minor)]; Anal. calcd for $C_{10}H_8NO_3Br$: C, 44.47; H, 2.99; Br, 29.59; N, 5.19; found: C, 44.45; H, 2.94; Br, 29.60; N, 5.21.

**(2*R*, 6*S*) 2-Hydroxy-3,4-(4'-hydroxy-benzo)-5-oxa-cepham (217c)**: Obtained 57 mg (0.28 mmol); Yield 89%, 32% *ee*; white solid m.p. 139-140°C; $[\alpha]_D^{26}$ = -28.4 (c 0.81, $CHCl_3$); IR (film) v: 1792 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.13 (d, *J*= 15.2 Hz, 1H, $CH_2$), 3.42 (ddd, *J* = 15.2, 3.7, 2.4 Hz, 1H, $CH_2$), 5.73 (dd, *J* = 3.7, 1.1 Hz, 1H CH-O), 6.35 (d, *J* = 2.3 Hz, 1H, Ar), 6.53 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar), 6.62 (s, 1H, CH-OH), 7.50 (d, *J* = 8.6 Hz, 1H, Ar), 9.77 (s, 1H, OH), 11.5 (s, 1H, OH); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 46.4, 76.1, 102.1, 108.8, 116.2, 135.8, 162.7, 164.3, 165.0, 194.6; HR MS (ESI) calcd for $[M + Na]^+$ $C_{10}H_9NO_4Na$ : 230.0424, found: 230.0431; HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [6*S*]= 11.3 (major) , $t_R$ [6*R*]= 19.8 (minor)]; Anal. calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76; found: C, 57.95; H, 4.35; N, 6.80.

**(2*R*, 6*S*) 3,4-Benzo-2-hydroxy-2-methyl-5-oxa-cepham (217d)**: Obtained 40 mg (0.19 mmol); Yield 75%, 16% *ee*; white solid m.p. 139-140°C; $[\alpha]_D^{26}$ = -18.6 (c 0.18, $CHCl_3$); IR (film) v: 1777 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.98 (s, 3H, $CH_3$), 3.06 (d, *J* = 15.2 Hz, 1H, $CH_2$), 3.25 (dd, *J* = 15.2, 3.3 Hz, 1H, $CH_2$), 3.43 (s, 1H, OH), 5.28 (d *J* = 3.3 Hz, 1H, CH-O), 6.95 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar), 7.08 (td, *J* = 7.5, 1.2 Hz, 1H, Ar), 7.26 (td, *J* = 8.2, 1.6 Hz, 1H, Ar), 7.47 (dd, *J* = 7.5, 1.6 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 27.8, 45.7, 73.5, 77.8, 118.0, 122.9, 126.5, 126.8, 129.9, 151.3, 164.1; HR MS (ESI) calcd for $[M + Na]^+$ $C_{11}H_{11}NO_3Na$ 228.0631, found: 228.0626; HPLC [AD-H, hexane/*i*-propanole = 95:5, 1.0 mL/min, $t_R$ [6*S*]= 24.6 (major) , $t_R$ [6*R*]= 28.9 (minor)]; Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83; found: C, 64.33; H, 5.38; N, 6.85.

**(2*R*, 6*S*) 3,4-Benzo-2-hydroxy-2-phenyl-5-oxa-cepham (217e)**: Obtained 77 mg (0.28 mmol); Yield 92%, 43% *ee*; white solid m.p. 115-116°C; $[\alpha]_D^{26}$ = -65.7 (c 0.39, $CHCl_3$); IR (film) v: 1785 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.76 (d, *J* = 15.0 Hz, 1H, $CH_2$), 3.17 (ddd, *J* = 2.4, 3.8, 15.0 Hz, 1H, $CH_2$), 5.56 (dd, *J*= 1.3, 3.8 Hz, 1H, CH), 6.34 (s, 1H, OH), 6.90 (d, *J* = 7.9 Hz, 1H, Ar), 7.19 (td, *J* = 0.9, 7.5Hz, 1H, Ar), 7.41 -7.52 (complex, 4H, Ar), 7.58 (tt, *J* = 1.3, 7.4 Hz, 1H, Ar), 7.77 (dd, *J* = 1.2, 8.4 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 46.2, 77.7, 115.5, 123.0, 128.4, 129.6,



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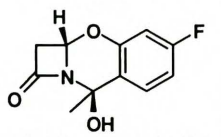
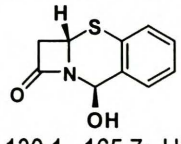
130.4, 130.6, 132.1, 133.2, 137.8, 153.8, 165.3, 195.8; HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [6*R*]= 26.9 (minor), $t_R$ [6*S*]= 35.5 (major)]; Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24; found: C,71.89; H, 4.89; N, 5.29.

**(2*R*, 6*S*) 3,4-(4'-Fluoro-benzo)-2-hydroxy-2-methyl-5-oxa-cepham (217f)**: Obtained 46 mg (0.21 mmol); Yield 79%, 24% *ee*; white solid m.p. 78-79ºC; $[\alpha]_D^{26}$ = -4.7 (c 0.39, $CH_2Cl_2$); IR (film) v: 1778 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.99 (s, 3H, $CH_3$), 2.97 (s, 1H, OH), 3.09 (dd, *J* = 15.3, 1.0 Hz, 1H, $CH_2$), 3.30 (dd, *J* = 15.3, 3.3 Hz, 1H, $CH_2$), 5.32 (dd, *J* = 3.3, 1.0 Hz, 1H, CHO), 6.68 (dd, *J* = 9.6, 2.6 Hz, 1H, Ar), 6.81 (ddd, *J* = 10.6, 8.8, 2.6 Hz, 1H, Ar), 7.45 (dd, *J* = 8.8, 6.3 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ: 27.9 45.7, 73.9, 77.8, 105.2 (d, *J* = 24 Hz), 110.2 ( d, *J* = 22 Hz), 122.4, 128.3 (d, *J* = 10 Hz), 155.6 (d, *J* = 12 Hz), 162.1, 163.8, 164.1; HR MS (ESI) calcd for [M + Na]$^+$ $C_{11}H_{10}NO_3FNa$ : 246.0537, found: 246.0534; HPLC [AD-H, hexane/*i*-propanole = 97:3, 1.0 mL/min, $t_R$ [6*R*]= 24.1 (minor), $t_R$ [6*S*]= 39.9 (major)] ; Anal. calcd for $C_{11}H_{10}NO_3F$: C, 59.19; H, 4.52; F, 8.51; N, 6.28; found: C, 59.15; H, 4.50; F, 8.53; N, 6.31



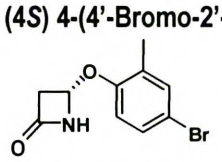
**(2*R*, 6*S*) 3,4-(4'-Fluoro-benzo)-cepham (221)**: Obtained 46 mg (0.22 mmol); Yield 85%, 38% *ee*; white solid m.p. 130-132ºC; $[\alpha]_D^{26}$ = -25.8 (c 1.0, $CHCl_3$); IR (film) v: 1778 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.00 (d, *J* = 15.1 Hz, 1H, $CH_2$); 3.351 (dd, *J* = 15.1, 4.3 Hz, 1H, $CH_2$); 4.58 (s, 1H, OH), 4.93 (d, *J* = 4.3 Hz, 1H, CH-S); 6.04 (s, 1H, CH); 7.26 (m, 3H, Ar); 7.64 (d, *J* = 5.4 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 45.8, 45.9, 69.7, 126.2, 128.6, 129.3, 129.5, 129.9, 130.1, 165.7; HR MS (ESI) calcd for [M+Na]$^+$ $C_{10}H_9NO_2NaS$ 230.0246 found: 230.0257; HPLC [OD-H, 8/2 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [6*R*]= 16.8 (minor), $t_R$ [6*S*]= 21.3 (major)];



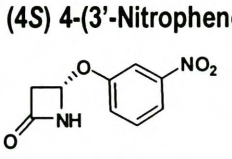
### 4.9.2. Quinidine (253) catalyzed nucleophilic substitution with phenols 245, tiophenols 248.

Reaction was perfomrmed according to the general procedure.

**(4*S*) 4-(4'-Bromo-2'-methylphenoxy)-azetidin-2-one (222d)**: Obtained 91 mg (0.19 mmol); Yield 74%, 24% *ee*; white solid; m.p. 120-121ºC; $[\alpha]_D^{26}$ = -8.1 (c 0.56, $CHCl_3$); IR (film) v: 1788 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.21 (s, 3H, $CH_3$), 3.11 (d, *J* = 15.1 Hz, 1H, $CH_2$), 3.36 (ddd, *J* = 15.1, 3.6, 2.7 Hz, 1H, $CH_2$), 5.62 (dd, *J* = 3.6, 2.7 Hz, 1H, CH-O), 6.56 (m, 2H, Ar, NH), 7. 26 (m, 1H, Ar), 7.32 (d, *J* = 2.1, 1H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 16.0, 46.3, 76.6, 114.3, 114.8, 129.6, 130.3, 134.2, 153.2, 165.6; HR MS (ESI) calcd for [M + Na]$^+$ HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [*S*]= 21.3 (major), $t_R$ [*R*]= 23.6 (minor)]; Anal. calcd for $C_{10}H_{10}NO_2Br$: C, 46.90; H, 3.94; Br, 31.20; N, 5.47; found: C, 46.85; H, 3.92; Br, 31.23; N, 5.50



**(4*S*) 4-(2-tert-Butylphenoxy)-azetidin-2-one (222f)**: Obtained 31 mg (0.14 mmol), yield 54%, 46% *ee*; white solid; m.p. 115-116ºC; $[\alpha]_D^{26}$ = -60.9 (c 0.2, $CHCl_3$); IR (film) v: 1783 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.38 (s, 3H, *t*-Bu); 3.16 (d, *J* = 15.0 Hz, 1H, $CH_2$); 3.38 (ddd, *J* = 15.0, 3.7, 2.5 Hz, 1H, $CH_2$); 5.70 (dd, *J* = 3.7, 1.2 Hz, 1H, CH- O); 6.67 (d, *J* = 8.1 Hz, 1H, Ar); 6.77 (s, 1H, NH); 6.99 (t, *J* = 7.7 Hz, 1H, Ar); 7.17 (td, *J* = 7.7, 1.7 Hz, 1H, Ar); 7.34 (dd, *J* = 8.1, 1.7 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 29.8, 34.8, 46.3, 76.0, 112.9, 122.1, 127.1, 127.5, 138.9, 154.9, 166.1; HR MS (ESI) calcd for [M + Na]$^+$ $C_{13}H_{17}NO_2Na$ 242.1152 found: 242.1158; HPLC [OD-H, 8/2 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 13.3 (minor), $t_R$ [*S*]= 15.0 (major)]; Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; found: C, 71.18; H, 7.77; N, 6.42.



**(4*S*) 4-(3'-Nitrophenoxy)-azetidin-2-one (222g)**: Obtained 44 mg (0.21 mmol); Yield 82%, 43% *ee*; white solid; m.p. 104-105ºC; $[\alpha]_D^{26}$ = -13.8 (c 1.0, $CHCl_3$); IR (film) v: 1791 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) *δ*: 3.15 (d, *J* = 15.1 Hz, 1H, $CH_2$); 3.45 (ddd, *J* = 15.1, 3.7, 2.6 Hz, 1H, $CH_2$); 5.76 (dd, *J* = 3.7, 1.2 Hz, 1H, CH-O); 6.90 (s, 1H, NH); 7.23 (dd, *J* = 8.3, 2.5 Hz, 1H, Ar); 7.51 (t, *J* = 8.2 Hz, 1H, Ar); 7.69 (t, *J* = 2.5 Hz, 1H, Ar); 7.93 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) *δ*: 46.4, 76.7, 109.9, 117.5, 122.5, 130.6, 149.3, 156.4, 165.3; HR MS (ESI) calcd for [M + Na]$^+$ $C_9H_8N_2O_4Na$ 231.0376 found: 231.0365; HPLC [OD-H, 8/2 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*S*]= 33.9 (major), $t_R$ [*R*]= 37.4 (minor)]; Anal. calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46; found: C,51.90; H, 3.85; Br; N, 16.51.



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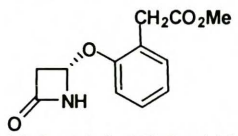
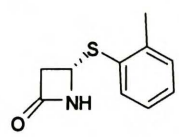
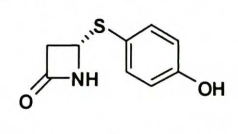
**(4*S*) 4-(*o*-Methoxycarbonylmethyl-phenoxy)-azetidin-2-one (222h):** Obtained 40 mg (0.17 mmol), yield 65%, 11% *ee*; white solid; m.p. 123-124°C; $[\alpha]_D^{26}$ = -7.1 (c 0.58, $CHCl_3$); IR (film) v: 1786, 1738 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 3.06 (d, *J* = 15.1, 1.1 Hz, 1H, $CH_2$); 3.31 (ddd, *J* = 15.1, 3.7, 2.4 Hz, 1H, $CH_2$); 3.62 (d, *J* = 15.7 Hz, 1H, $CH_2Ph$); 3.67 (d, *J* = 15.7 Hz, 1H, $CH_2Ph$); 3.69 (s, 3H, $CH_3$); 5.63 (dd, *J* = 3.7, 1.1 Hz, 1H, CH-O); 6.77 (d, *J* = 8.1 Hz, 1H, H-1); 6.87 (s, 1H, NH); 7.02 (t, *J* = 7.4 Hz, 1H, H-2); 7.24 (m, 3H, Ph); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 35.7, 46.2, 52.0, 76.9, 113.6, 122.7, 124.4, 128.7, 131.6, 154.2, 166.0, 172.1; HR MS (ESI) calcd for $[M + Na]^+$ $C_{12}H_{13}NO_4Na$ 258.07369 found: 258.07413; HPLC [AD-H, 75/25 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 12.1 (minor) , $t_R$ [*S*]= 13.1 (major)]; Anal. calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95; found: C, 61.25; H, 5.53; N, 5.60.



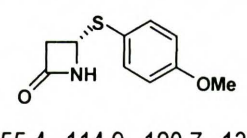

**(4*S*) 4-(o-Tolylthio)-azetidin-2-one (223b)**: Obtained 44 mg (0.23 mmol), yield 89%, 49% *ee*; white solid; m.p. 62-64°C; $[\alpha]_D^{26}$= -15.8 (c 1.0, $CHCl_3$); IR (film) v: 1776 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 2.44 (s, 3H, $CH_3$); 2.93 (ddd, *J* = 15.2, 2.3, 1.9 Hz, 1H, $CH_2$); 3.45 (ddd, *J* = 15.2, 4.9, 1.9 Hz, 1H, $CH_2$); 4.99 (dd, *J* = 4.9, 2.3 Hz, 1H, CH-S); 6.25 (s, 1H, NH); 7.19 (m, 1H, Ar); 7.25 (m *J* = 2H, Ar); 7.37 (m, 1H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 20.9, 45.6, 53.7, 126.8, 128.5, 130.8, 131.4, 132.9, 140.5, 165.8; HR MS (TOF MS E+) calcd for $M^+$ $C_{10}H_{11}NOS$ 193.0561 found: 193.0569; HPLC [OD-H, 8/2 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 17.0 (minor), $t_R$ [*S*]= 22.4 (major)];



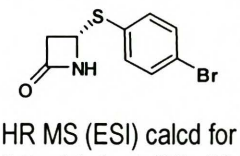

**(4*S*) 4-(4'-Hydroxyphenylthio)-azetidin-2-one (223c):** Obtained 48 mg (0.25 mmol); Yield 95%, 11% *ee*; white solid; m.p. 110-112°C; $[\alpha]_D^{26}$ = -1.8 (c 0.50, MeOH); IR (film) v: 1788 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$: 2.69 (d, *J* = 15.2, 2.1 Hz, 1H, $CH_2$), 3.22 (dd, *J* = 15.2, 4.8 Hz, 1H, $CH_2$), 4.87 (dd, *J* = 4.8, 2.1 Hz, 1H, CH-S), 6.80 (d, *J* = 8.8 Hz, 2H, Ar), 7.37 (d, *J* = 8.8 Hz, 2H, Ar); $^{13}C$ NMR ($CD_3OD$) $\delta$: 44.8, 55.5, 117.2, 120.3, 138.3, 159.9, 169.2; HR MS (ESI) calcd for $[M + Na]^+$ $C_9H_8NO_2NaS$ 218.0246 found: 218.0242; HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [*R*]= 21.3 (minor), $t_R$ [*S*]= 23.6 (major)];




**4-(p-Methoxyphenylthio)-azetidin-2-one (223d):** Obtained 40 mg (0.19 mmol); Yield 75%, 34% *ee*; white solid; m.p. 71-73°C $[\alpha]_D^{26}$ = -24.8 (c 0.755, $CHCl_3$); IR (film) v: 1776 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 2.82 (ddd, *J* = 15.2, 2.2, 1.6 Hz, 1H, $CH_2$), 3.29 (ddd, *J* = 15.2, 4.9, 1.6 Hz, 1H, $CH_2$), 3,81 (s, 3H, $CH_3$), 4.88 (dd, *J* = 4.9, 2.2 Hz, 1H, CH-S), 6.11 (s, 1H, NH), 6.89 (d, *J* = 8.8 Hz, 2H, Ar), 7.43 (d, *J* = 8.8 Hz, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) $\delta$: 44.9, 54.7, 55.4, 114.9, 120.7, 136.7, 160.7, 165.7; HR MS (ESI) calcd for $[M + Na]^+$ $C_{10}H_{11}NO_2NaS$ 232.0402 found: 232.0398; HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [*R*]= 21.2 (minor), $t_R$ [*S*]= 25.4 (major)];



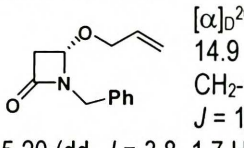

**(4*S*) 4-(4'-Bromophenylthio)-azetidin-2-one (223 e):** Obtained 66 mg (0.25 mmol); Yield 95%, 34% *ee*; white solid; m.p. 107-109°C; $[\alpha]_D^{26}$ = -32.9 (c 0.96, $CHCl_3$); IR (film) v: 1779 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 2.88 (dm, *J* = 15.12, 1H, $CH_2$); 3.39 (ddd, *J* = 15.2, 4.9, 2.0 Hz, 1H, $CH_2$); 4.98 (dd, *J* = 4.9, 2.3 Hz, 1H, CH-S); 6.29 (s, 1H, NH); 7.32 (d, *J* = 8.5 Hz, 2H, Ar); 7.49 (d, *J* = 8.5 Hz, 2H, Ar); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$:45.5, 54.2, 123.3, 132.6, 135.0, 165.5; HR MS (ESI) calcd for $[M + Na]^+$ $C_9H_8NONaSBr$ 279.9402 found:279.9396; HPLC [OD-H, 8/2 hexane/*i*-propanole, 0.5 mL/min, $t_R$ [*R*]= 20.3 (minor), $t_R$ [*S*]= 21.9 (major)];




### 4.9.3. Quinidine (253) catalyzed substitution with alcohols 265.

Reaction was perfomrmed according to the general procedure.

**(4*S*) *N*-benzyl-4-allyloxy-azetidin-2-one (267a):** Obtained 9 mg (0.04 mmol); Yield 15%, 10% *ee*; yellow oil; $[\alpha]_D^{26}$ = -8.3 (c 0.5, $CHCl_3$); IR (film) v: 1759 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 2.89 (dm, *J* = 14.9 Hz, 1H, $CH_2$), 3.05 (dd, *J* = 14.9, 3.8 Hz, 1H, $CH_2$), 3.89 (ddt, *J* = 12.7, 5.7, 1.5 Hz, 1H, $CH_2$-O), 3.95 (ddt, *J* = 12.7, 5.7, 1.5 Hz, 1H, $CH_2$-O), 4.21 (d, *J* = 15.2 Hz, 1H, CH-N), 4.60 (d, *J* = 15.2 Hz, 1H, $CH_2$-N), 4.91 (dd, *J* = 6.1, 1.5 Hz, 1H, $CH_2$=), 5.15 (dm, *J* = 9.7 Hz, 1H, $CH_2$=), 5.20 (dd, *J* = 3.8, 1.7 Hz, 1H, CH-O), 5.80 (m, 1H, CH=), 7.30 (m, 3H, Ar), 7.35 (m, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) $\delta$: 44.4, 44.7, 68.5, 80.7, 117.6, 127.8, 128.3, 128.8, 133.5, 135.7, 165.9; HR MS (ESI) calcd for $[M + Na]^+$



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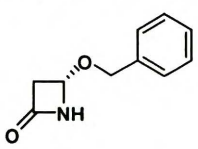
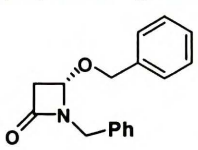
$C_{13}H_{15}NO_2Na$ 240.0995 found:240.0987; HPLC [AD-H, hexane/*i*-propanole = 95:5, 0.5 mL/min, $t_R$ [*R*]= 27.9 (minor), $t_R$ [*S*]= 30.1 (major)];

**(4*S*) *N*-Benzyl-4-propargyloxy-azetidin-2-one (267b)**: Obtained 17 mg (0.08 mmol); Yield 30%, 12% *ee*; yellow oli; $[\alpha]_D^{26}$ = -11.5 (c 0.7, $CHCl_3$); IR (film) v: 1762 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.44 (t, *J* = 2.4 Hz, 1H, CH), 2.97 (dd, *J* = 14.9, 1.2 Hz, 1H, $CH_2$), 3.09 (dd, *J* = 14.9, 3.7 Hz, 1H, $CH_2$), 4.05 (dd, *J* = 16.0, 2.4 Hz, 1H, $CH_2$-C), 4.11 (dd, *J* = 16.0, 2.4 Hz, 1H, $CH_2$-C), 4.23 (d, *J* = 15.2 Hz, 1H, $CH_2$-N), 4.59 (d, *J* = 15.2 Hz, 1H, $CH_2$-N), 5.02 (dd, *J* = 3.7, 1.2 Hz, 1H, CH-O), 7.30 (m, 3H, Ar), 7.36 (m, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 44.6, 44.7, 55.2, 75.3, 78.8, 80.7, 127.8, 128.3, 128.8, 135.6, 165.8; HR MS (ESI) calcd for $[M + Na]^+$ $C_{13}H_{13}NO_2Na$ 238.0838 found: 238.0845; HPLC [AD-H, hexane/*i*-propanole = 95:5, 0.7 mL/min, $t_R$ [*R*]= 34.2 (minor), $t_R$ [*S*]= 35.8 (major)];

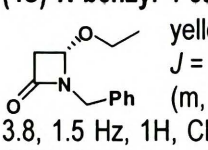
**(4*S*) 4-Benzyloxy-azetidin-2-one (250c)**: The crude reaction mixture containing **250c** was diluted with water (5 mL). Aqueous phase was extracted with ether (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 2:3 hexane/diethyl ether). Obtained 44 mg (0.25 mmol); Yield 78%, *ee* not determinated; yellow oil; $[\alpha]_D^{26}$ = -3.5 (c 0.5, $CHCl_3$); IR (film) v: 1779 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.94 (dm, *J* = 15.0 Hz, 1H, $CH_2$), 3.12 (ddd, *J* = 15.0, 3.8, 1.5 Hz, 1H, $CH_2$), 4.58 (d, *J* = 11.8 Hz, 1H, $CH_2$-O), 4.62 (d, *J* = 11.8 Hz, 1H, $CH_2$-O), 5.16 (dd, *J* = 3.8, 1.4 Hz, 1H, CH-O), 6.20 (s, 1H, NH), 7.36 (m, 5H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 45.6, 70.5, 77.9, 127.9, 128.3, 128.7, 136.7, 166.4; HR MS (ESI) calcd for $[M + Na]^+$ $C_{10}H_{11}NO_2Na$ 200.0790 found: 200.0795



**(4*S*) *N*-Benzyl-4-benzyloxy-azetidin-2-one (267c):** Obtained 53 mg (0.20 mmol); Yield 77%, 4% *ee*; yellow oil; $[\alpha]_D^{26}$ = -4.0 (c 0.5, $CHCl_3$); IR (film) v: 1758 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.90 (dm, *J* = 14.8 Hz, 1H, $CH_2$), 3.04 (dd, *J* = 14.8, 3.8 Hz, 1H, $CH_2$), 4.18 (d, *J* = 15.1 Hz, 1H, $CH_2$-N), 4.42 (d, *J* = 11.7 Hz, 1H, $CH_2$-O), 4.47 (d, *J* = 11.7 Hz, 1H, $CH_2$-O), 4.59 (d, *J* = 15.1 Hz, 1H, $CH_2$-N), 4.98 (dd, *J* = 3.8, 1.3 Hz, 1H, CH-O), 7.19 (m, 2H, Ar), 7.30 (m, 8H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 43.8, 45.5, 70.0, 77.8, 127.5, 127.7, 128.5, 128.7, 128.9, 128.6, 135.3, 136.5, 166.3; HR MS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{17}NO_2Na$ 290.1259 found: 290.1262; HPLC [AD-H, hexane/*i*-propanole = 95:5, 0.7 mL/min, $t_R$ [*S*]= 33.6 (major), $t_R$ [*R*]= 35.9 (minor)];



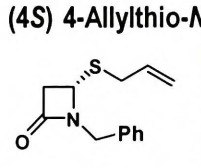
**(4*S*) *N*-benzyl-4-ethoxyazetidin-2-one (267d):** Obtained 6 mg (0.03 mmol); Yield 12%, *ee* not determinated; yellow oil; $[\alpha]_D^{26}$ = -5.2 (c 0.6, $CHCl_3$); IR (film) v: 1758 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.13 (t, *J* = 6.9 Hz, 3H, $CH_3$), 2.87 (dm, *J* = 14.7 Hz, 1H, $CH_2$), 3.03 (dd, *J* = 14.7, 3.8 Hz, 1H, $CH_2$), 3.44 (m, 2H, $CH_2$), 4.20 (d, *J* =15.2 Hz, 1H, $CH_2$-N), 4.59 (d, *J* = 15.2 Hz, 1H, CH-N), 4.86 (dd, *J* = 3.8, 1.5 Hz, 1H, $CH_2$-O), 7.29 (m, 3H, Ar), 7.34 (m, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 15.1, 44.3, 44.7, 63.1, 80.8, 127.7, 128.2, 127.8, 135.8, 166.1; HR MS (ESI) calcd for $[M + Na]^+$ $C_{12}H_{15}NO_2Na$ 228.0995 found: 228.1000



**(4*S*) *N*-benzyl-4-isopropoxyazetidin-2-one (267e):** Obtained 9 mg (0.04 mmol); Yield 15%, 11% *ee*; yellow oil; $[\alpha]_D^{26}$= -3.1 (c 0.71, $CHCl_3$); IR (film) v: 1756 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.09 (d, *J* = 6.1 Hz, 6H, 2x$CH_3$), 2.82 (dm, *J* = 14.7 Hz, 1H, $CH_2$), 3.07 (dd, *J* = 14.7, 3.7 Hz, 1H, $CH_2$), 3.60 (septet, *J* = 6.1 Hz, 1H, CH-$(CH_3)_2$ ), 4.13 (d, *J* = 15.2 Hz, 1H, CH-N), 4.85 (dd, *J* = 3.7, 1.2 Hz, 1H, CH-O), 7.29 (m, 3H, Ar), 7.34 (m, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 22.5, 22.7, 44.2, 45.9, 71.0, 79.5, 127.7, 128.3, 128.8, 135.8, 166.2; HR MS (ESI) calcd for $[M + Na]^+$ $C_{13}H_{17}NO_2Na$ 242.1152 found: 242.1153; HPLC [AD-H, hexane/*i*-propanole = 95:5, 0.5 mL/min, $t_R$ [*R*]= 27.9 (minor), $t_R$ [*S*]= 30.1 (major)];

### 4.9.4. Quinidine (253) catalyzed nucleophilic substitution leading to 268a-c.

Reaction was perfomrmed according to the general procedure.



**(4*S*) 4-Allylthio-*N*-benzylzetidin-2-one (268a):** Obtained 23 mg (0.10 mmol); Yield 40%, 38% *ee*; yellow oil; $[\alpha]_D^{26}$ = -20.3 (c 1.0, $CHCl_3$); IR (film) v: 1755 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 3.10 (m, 3H, $CH_2$, $CH_2S$), 3.34 (dd, *J* = 15.1, 4.9 Hz, 1H, $CH_2$), 4.07 (d, *J* = 15.3 Hz, 1H, $CH_2$-N), 4.53 (dd, *J* = 4.9, 2.2 Hz, 1H, CH-S), 4.70 (d, *J* = 15.3 Hz, 1H, $CH_2$-N), 4.90 (dd, *J* = 16.9, 1.1 Hz, 1H, $CH_2$=), 5.01 (d, *J* = 9.9 Hz, 1H, $CH_2$=), 5.70 (m, 1H, CH=), 7.30 (m, 3H, Ar), 7.35 (m, 2H, Ar);



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$^{13}C$ NMR ($CDCl_3$) δ: 32.5, 44.1, 45.1, 55.6, 117.8, 127.8, 128.3, 128.8, 133.7, 135.5, 165.4; HR MS (ESI) calcd for $[M + Na]^+$ $C_{13}H_{15}NONaS$ 256.0767 found: 256.0769; HPLC [AD-H, hexane/*i*-propanole = 95:5, 0.5 mL/min, $t_R$ [*R*]= 34.2 (minor), $t_R$ [*S*]= 35.8 (major)];

**(4*S*) *N*-benzyl-4-benzylthio-azetidin-2-one (268b):** Obtained 62 mg (0.22 mmol); Yield 86%, 34% *ee*; yellow oil; $[\alpha]_D^{26}$ = -9.3 (c 1.0, $CHCl_3$); IR (film) v: 1758 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.93 (dd, *J* = 15.1, 2.2 Hz, 1H, $CH_2$), 3.26 (dd, *J* = 15.1, 4.9 Hz, 1H, $CH_2$), 3.58 (d, *J* = 13.5 Hz, 1H, $CH_2$-S), 3.67 (d, *J* = 13.5 Hz, 1H, $CH_2$-S), 3.94 (d, *J* = 15.3 Hz, 1H, $CH_2$-N), 4.50 (dd, *J* = 4.9, 2.2 Hz, 1H, CH-S), 4.59 (d, *J* = 15.3 Hz, 1H, $CH_2$-N), 7.13 (m, 2H, Ar), 7.30 (m, 8H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 33.5, 44.1, 44.9, 55.9, 127.3, 127.8, 128.3, 128.6, 128.7, 128.8, 135.4, 137.5, 165.3; HR MS (ESI) calcd for $[M + Na]^+$ $C_{17}H_{17}NONaS$ 306.0923 found: 306.0921; HPLC [OD-H, hexane/*i*-propanole =9:1, 0.5 mL/min, $t_R$ [*R*]= 21.2 (minor), $t_R$ [*S*]= 25.4 (major)];

**(4*S*) *N*-Benzyl-4-tert-butylthio-azetidin-2-one (268c):** Obtained 37 mg (0.15 mmol); Yield 65%, 12% *ee*; yellow oil; $[\alpha]_D^{26}$ = -3.4 (c 0.41, $CHCl_3$); IR (film) v: 1754 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 1.27 (s, 9H, 3x$CH_3$), 2.99 (dm, *J* = 14.8 Hz, 1H, $CH_2$), 3.46 (dd, *J* = 14.8, 4.7 Hz, 1H, $CH_2$), 4.00 (d, *J* = 15.4 Hz, 1H, CH-N), 4.59 (dd, *J* = 4.7, 1.9 Hz, 1H, CH-O), 4.75 (d, *J* = 15.4 Hz, 1H, CH-N), 7.28 (m, 3H, Ar), 7.35 (m, 2H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 29.7, 31.1, 43.7, 48.9, 53.8, 127.6, 128.2, 128.7, 135.9, 165.8; HR MS (ESI) calcd for $[M + Na]^+$ $C_{14}H_{19}NONaS$ 272.1080 found: 272.1085; HPLC [AD-H, hexane/*i*-propanole = 95:5, 1.0 mL/min, $t_R$ [*R*]= 15.1 (major), $t_R$ [*S*]= 19.8 (minor)];

**(4*S*) 4-Tritylthio-azetidin-2-one (251d):** The crude reaction mixture containing **251d** was diluted with water (5 mL). Aqueous phase was extracted with ether (3x10 mL). The organic extracts were combined and dried over $Na_2SO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 2:3 hexane/diethyl ether). Obtained 80 mg (0.23 mmol), yield 89%, 51% *ee* ; white solid m.p. 140-142ºC $[\alpha]_D^{26}$ = 12.5 (c 1.0, $CHCl_3$); IR (film) v: 1772 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.88 (ddd, *J* = 15.2, 2.7, 1.6 Hz, 1H, $CH_2$), 3.27 (ddd, *J* = 15.2, 5.3, 1.6 Hz, 1H, $CH_2$), 4.44 (dd, *J* = 5.3, 2.7 Hz, 1H, CH-O), 7.26 (m, 3H, Ar), 7.32 (m, 6H, Ar), 7.46 (m, 6H, Ar); $^{13}C$ NMR ($CDCl_3$) δ: 45.0, 52.4, 67.3, 127.1, 127.9, 128.3, 129.3, 143.9, 165.7; HR MS (ESI) calcd for $[M + Na]^+$ $C_{22}H_{19}NONaS$ 368.1080 found: 368.1088; HPLC [OD-H, hexane/*i*-propanole = 8:2, 0.5 mL/min, $t_R$ [*S*]= 15.0 (major), $t_R$ [*R*]= 21.2 (minor)];

### 4.10. Bromination of compound 222a

To the solution **222a** (100 mg, 0.56 mmol) in $CCl_4$ (2 mL) was added NBS (1.2 equiv, 119 mg, 0.67 mmol) and AIBN (0.02 equiv, 2 mg, 0.01 mmol) under argon atmosphere. The reaction mixture was stirred and refluxed for 4h. The mixture was filtered and filtrate evaporated. Crude product was used without further purification. 123 mg (0.48 mmol) of 4-(2-(bromomethyl)phenoxy)azetidin-2-one was obtained as white solid. Yield 84%.

$^1H$ NMR ($CDCl_3$) δ: 3.17 (dt, *J* = 15.1 Hz, 1.2 Hz, 1H, $CH_2$), 3.40 (ddd, *J* = 15.1 Hz, 3.8 Hz, 1.2 Hz, 1H, $CH_2$), 4.54 (dd, *J* = 11.9 Hz, 9.8 Hz, 2H, $CH_2Br$), 5.73 (dd, *J* = 3.8 Hz, 1.2 Hz, 1H, CH-O), 6.70 (NH), 6.77 (dd, *J* = 8.2 Hz, 1.7 Hz, 1H), 7.30 (td, *J* = 8.2 Hz, 1.7 Hz, 1H, H-3), 7.39 (dd, *J* = 7.6 Hz, 1.7 Hz, 1H), 7.89 (dd, *J* = 7.6 Hz, 1.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ: 28.2, 46.5, 76.9, 113.8, 122.9, 127.7, 130.3, 131.6, 154.1, 165.8

### 4.11. Intramolecular *N*-benzylation

To the solution 4-(2-(bromomethyl)phenoxy)azetidin-2-one (100 mg, 0.39 mmol) in MeCN (5 mL) was added $K_2CO_3$ (5 equiv, 270 mg, 1.9 mmol) and $Bu_4NBr$ (0.2 equiv, 25 mg, 0.08 mmol) under argon atmosphere. The reaction mixture was stirred for 12h and diluted with water (10 mL) and (AcOEt (10 mL). The aqueous phase was extracted with AcOEt (3x10 mL). The organic extracts were combined and dried over $MgSO_4$. The solution was filtered and filtrate evaporated. The crude product was purified by column chromatography (silica gel, 1:1 hexane/ methyl-*t*-butyl ether) to yield ***ent*-218a** (26 mg, 0.15 mmol, 38%, 17% *ee*).



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### 4.12. The theoretical calculation of CD spectra of selected 5-oxacephams

The theoretical calculation of CD spectra was performed by Magdalena Woźnica from prof. J. Frelek group from IChO PAS. They provide access to detail information referring to this subject. The lowest-energy conformations for each investigated compound were found by the MM3 force field and CONFLEX[148] software and were subsequently reoptimized at B3LYP/6-31 G(d,p) level.[149] To confirm the stability of DFT-optimized structures, the frequency calculations were performed at B3LYP/6-31 G(d,p) level. For the stable structures, the rotational strengths were calculated at the B3LYP/6-31 G(d,p) level. CD and UV spectra were simulated by overlapping Gaussian functions for each transition according to the procedure described by Diedrich and Grimme.[150] No correlation for the medium dielectric constant was implemented. The conformational analysis has been performed with the use of CaChe program package.[148]

### 4.13. Biologial activity tests

Assay of DD-carboxypeptidase, β-lactamase and porcoine kidney elastase activity was performed by Dr J. Solecka from National Center of Public Health – National Institute of Hygiene. She provide access to datial information reffering to methodology used.

#### 4.13.1. Assay of DD-carboxypeptidase activity

The enzyme activity was measured as decribed previously.[154,153] Samples for assay of the DD-carboxypeptidase activity consisted of 10 µL of DD-carboxypeptidase from *Saccharopolyspora erytraea* PZH TZ 64-575 (40 units/mg), 20 µL of substrate solution containing 4.52 mg/mL $N^{\alpha}$, $N^{\varepsilon}$-diacetyl-L-lysyl-D-alanyl-D-alanine in 0.1 M phosphate buffr, pH 8.0 and 10 µL of 0.1 M phosphate buffer, pH 8.0. A standard sample containing 20 µL of D-alanine in distilled water. The reaction mixture for assay of the DD-carboxypeptidase activity consisted of 60 µL of 0.05 mg/mL flavin adenine dinucleotide in 0.1 M phosphate buffer, pH 8.0, 10 µL of 0.05 mg/mL horseradish peroxidase (1230 units/mg) in distilled water, 5.0 µL of 5.0 mg/mL *o*-dianisidine in methanol, and 2.0 µL of 11.77 mg/mL D-amino acid oxidase from procine kidney (6.7 units/mg) in 0.1 M phosphate buffer, pH 8.0. Samples were incubated for 30 minutes at 37°C and than boiled for 2 minutes. After cooling, 77 µL of the reaction mixture was added, and all samples were incubated for 10 minutes at 37°C. Next, was added 350 µL to each sample of a mixture consisting of MeOH, distilled water and sulfuric acid (5 : 5 : 6 by volume). Extinction of the resulting solution was measured at 540 nm.
The inhibition of DD-peptidase 64-575 by the discussed compounds was evaluated. Mixtures of 10 µL of DD-peptidase 64-575 (40 units/mg), 5.0 µL of 0.1 M phosphate buffer, pH 8.0 were incubated for 45 minutes at 37°C. The concentration of tested compounds in the mixture was from 0.04 to 0.0001 M. following the incubation, 20 µL of substrate solution was added to 20 µL of each sample and the resulting mixtures were incubated again.

#### 4.13.2. Assay of β-lactamase activity

The inhibition of penicillinase was evaluated following a literature method. The sample for assay of inhibition of β-lactamase consisted of 10 µL of penicillinase (Penase, $5x10^6$IU/mL, Bacto), 20 µL 0.1 M phosphate buffer, pH 7.0, 10 µL solution of tested compound in methanol. The samples were incubated for 30 minutes at 37°C, than 30 µL of nitrocephin, 430 µL 0.1 M phosphate buffer pH 7.0 were added and all samples were incubated for 10 minutes at 37°C. Absorbtion was measured at 428 nm.



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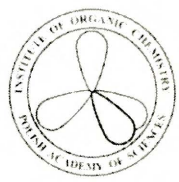

Anna Kozioł

## Streszczenie rozprawy doktorskiej zatytułowanej

# Enancjoselektywna synteza oksacefamów z 4-winyloksyazetydynonu

Praca przedstawiona Radzie Naukowej Instytutu Chemii Organicznej Polskiej Akademii Nauk celem uzyskania stopnia doktora nauk chemicznych

Promotor: prof. dr hab. Marek Chmielewski

Warszawa 2010

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## STRESZCZENIE

Niniejsza dysertacja zatytułowana „Asymetryczna synteza oksacefamów z 4-winyloksyazetydynonu" dotyczy wykorzystania taniego, dostępnego i opatentowanego przez polskich naukowców 4-winyloksyazetydynonu w asymetrycznej syntezie analogów penicylin i cefalosporyn, będących grupą antybiotyków β-laktamowych o dobrze udokumentowanych i ciekawych właściwościach biologicznych i farmakologicznych.

Antybiotyki β-laktamowe swoją karierę zawdzięczają niskiej toksyczność przy wysokiej aktywność przeciwbakteryjnej. Syntetyczne antybiotyki β-laktamowe charakteryzują się znacznie większą skutecznością w leczeniu zakażeń w porównaniu z naturalnymi, a w przeciwieństwie do nich są odporne na działanie β-laktamaz, enzymów powodujących otwarcie pierścienia β-laktamowego i dezaktywacje antybiotyku. Należy podkreślić fakt, że klawamy np. kwas klawulanowy posiadają jedynie słabe właściwości antybakteryjne, lecz ze względu na podobieństwo strukturalne są kompetencyjnymi inhibitorami β-laktamaz przez co w mieszaninie z penicylinami lub cefalosporynami zwiększają aktywność antybakteryjną. Działanie to pozwala na efektywne stosowanie kombinacji obu specyfików w przypadkach infekcji wywołanych szczepami bakterii opornymi na sam antybiotyk.

W ostatnich latach odkryto szereg nowych właściwości terapeutycznych związków zawierających pierścień β-laktamowy. Stwierdzono między innymi, że są to bardzo dobre inhibitory elastaz. β-Laktamy te podawane są osobą z niedoborem α-1-antytrypnsyny. Jej niedobór prowadzi do nieodwracalnego uszkodzenia pęcherzyków płucnych, uszkodzenie wątroby powodującego niezdolność do detoksykacji trucizn i alkoholu jak również zahamowanie wchłaniania witamin czy zapalenie tkanki podskórnej powodujące uszkodzenie, utwardzenie skóry, formowanie się guzków i plam. Ponadto 4-podstawione-azetydynony hamują namnażanie harpes wirusów HCMV (Cytomegalowirus). Wirus ten stanowi śmiertelne zagrożenie dla płodów, noworodków i osób z obniżoną odpornością. Szacuje się, że w USA zakażonych wirusem HCMV jest do 85% ludzi w wieku 40 lat a na rynku jest tylko kilka skutecznych leków.

Czynnikiem determinującym aktywność farmakologiczną azetydynonów jest konfiguracja na węglach C-3 i C-4 pierścienia β-laktamowego co powoduje, że ich stereo- i enancjoselektywna synteza pozostaje wciąż wyzwaniem dla wielu przemysłowych i akademickich grup badawczych. Powstawanie wielu opornych na znane β-laktamy szczepów bakteryjnych i ograniczony dostęp metodami biosyntetycznymi stymuluje rozwój chemicznych metod syntezy układów mono-, dwu- i trójcyklicznych zawierających pierścień β-laktamowy.



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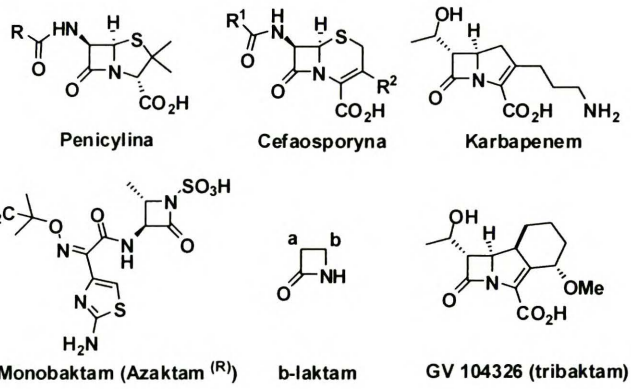
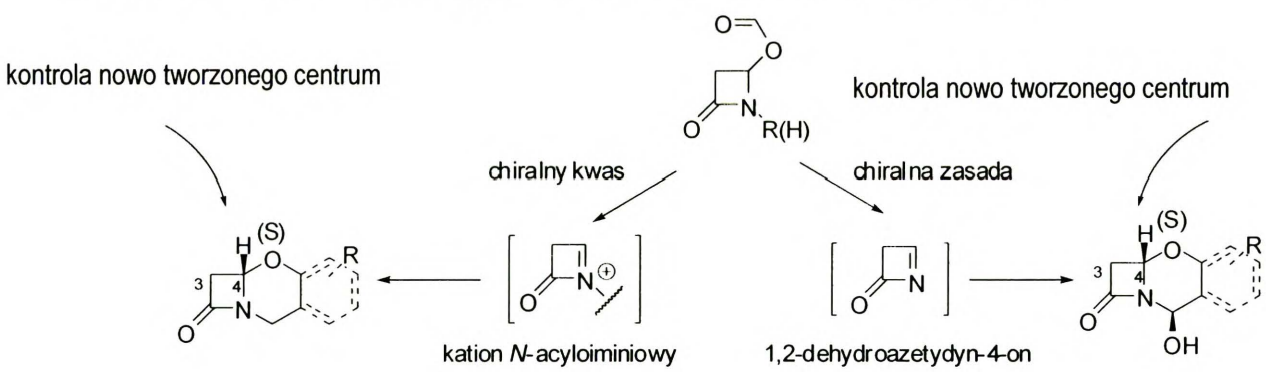



Celem mojej pracy było opracowanie asymetrycznej syntezy oksacefamów, w której kluczowym etapem jest wewnątrzcząsteczkowa wymiana nukleofilowa na węglu C-4 w 4-formyloksyazetydynonach, która przebiega przez etap płaskiego, achiralnego kationu acyloiminiowego. Opierając się na uzyskanych w Zespole II IChO PAN wynikach, została zbadana możliwość wykorzystania opracowanej reakcji w enancjoselektywnej syntezie 3,4-benzo-5-oksacefamów i innych związków pokrewnych będących strukturalnymi analogami antybiotyków *β*-laktamowych (Schemat 1). Druga część niniejszej dysertacji dotyczyła syntezy enancjomerycznie wzbogaconych 3,4-benzo-2-hydroksy-5-oksacefamów i 4-fenoksyazetydynonów na drodze katalizowanej chiralnymi zasadami kondensacji aldehydów salicylowych lub fenoli z 4-acyloksyazetydynonem. W tym przypadku reakcja przebiega przez płaski związek przejściowy mający strukturę 1,4-dehydroazetydyn-2-onu (Schemat 1).




**Schemat 1**

Cześć literaturowa niniejszej pracy została podzielona na cztery części, w których kolejno omawiane są następujące zagadnienia:

- Struktura i reaktywność kationów iminowych
- Strereochemiczny przebieg procesów z udziałem kationów *N*-acyloiminiowych
- Metody syntezy kationów *N*-acyloiminiowych
- Aktywność biologiczna związków zawierających pierścień *β*-laktamowy



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W rozdziale poświęconym badaniom własnym opisałam:

- Enancjoselektywną syntezę cefamów i 4-podstawionych azetydyn-2-onów na drodze wewnątrz- i międzycząsteczkowego, katalizowanego chiralnymi kwasami Lewisa podstawienia nukleofilowego pozycji C-4 w pierścieniach azetydynonów
- Enancjoselektywną syntezę 2-hydroksycefamów i 4-podstawionych azetydyn-2-onów na drodze promowanego chiralnymi zasadami Lewisa międzycząsteczkowego podstawienia nukleofilowego na węglu C-4 w azetydynonach

Pozostałe dwie części dysertacji dotyczą badań przeprowadzonych we współpracy z zespołem prof. J. Frelek z IChO PAN oraz dr J. Solecką z Narodowego Instytutu Zdrowia Publicznego – Państwowego Zakładu Higieny:

- Ustalenie z wykorzystaniem spektroskopii dichroizmu kołowego konfiguracji absolutnej na węglu C-6 w nowo otrzymanych cefamach oraz na węglu C-4 w 4-podstawionych azetydyn-2-onach
- Badania aktywność biologicznej otrzymanych związków



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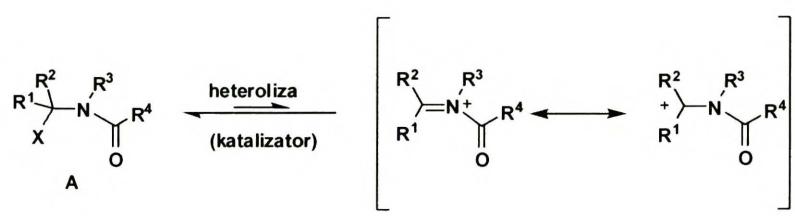
## CZĘŚĆ TEORETYCZNA

Jony *N*-alkiloiminiowe to azotowe analogi kationów oksoniowych jak również aktywowanej grupy karbonylowej, są one elektrofilowymi komponentami w reakcjach tworzenia nowego wiązania węgiel- węgiel jak i węgiel – heteroatom. Kationy iminiowe to jedne z najważniejszych, związków przejściowych w syntezie substancji naturalnych zawierających atom azotu.

Jednymi z najważniejszych typów jonów iminowych są kationy *N*-acyloiminiowe. Jony *N*-acyloiminiowe generowane są *in situ* w kwaśnym środowisku reakcyjnym, głównie poprzez heterolityczny rozpad struktur typu acetalowego **A** (Schemat 2). Grupa X to zazwyczaj hydroksylowa, alkosylowa bądź acetoksylowa funkcja, a jej abstrakcja prowadzi do powstania odpowiedniego jonu. W przypadku gdy X jest grupą metoksylową bądź etoksylową prekursor **A** jest stabilny co umożliwia jego modyfikację w środowisku zasadowym bądź neutralnym przez wygenerowaniem jonu.




**Schemat 2**

Kationy *N*-acyloiminiowe mogą występować w dwóch konformacjach: *s-cis* lub *s-trans*, przy czym forma *s-cis* jest o około 3 kcal·mol$^{-1}$ stabilniejsza od *s-trans*.



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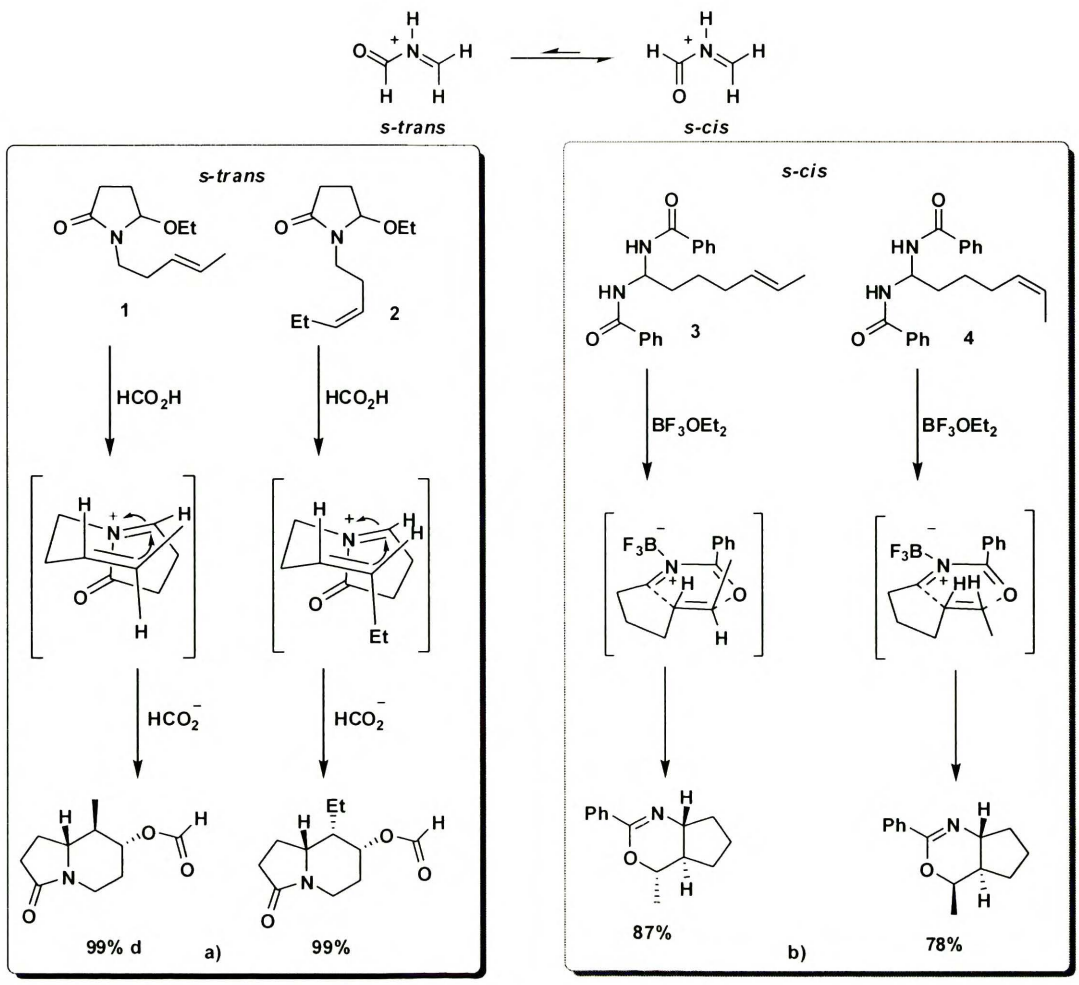


**Schemat 3**

Związki przyjmujące konformacje *s-trans* jak **1** czy **2** w reakcjach z π-nukleofilami zachowują się jak stabilizowane atomem azotu karbokationy a przebieg procesu opisuje teoria π-kompleksu (Schemat 3). Gdy kationy *N*-acyloiminiowe przyjmują konformacje *s-cis* (związek **3** i **4**) przebieg stereochemiczny procesu jest inny. Takie kationy zachowują się jak komponenty 4π-elektronowe z odwróconymi wymaganiami elektronowym i ulegają reakcji Dielsa-Aldera. W większości przypadków proces ten jest wysoce regio- i stereo selektywny.

Kationy iminiowe ulegają wewnątrzcząsteczkowej reakcji Mannicha, tworząc różnorodne związki heterocykliczne (Schemat 4). Przykłady **a** i **b** to przykłady tworzenia związków monocyklicznych w wyniku odpowiednio *egzo*-trygonalnej i *endo*-trygonalnej cyklizacji. Przykłady **c**, **d** i **e** to metody tworzenia związków bicyklicznych.



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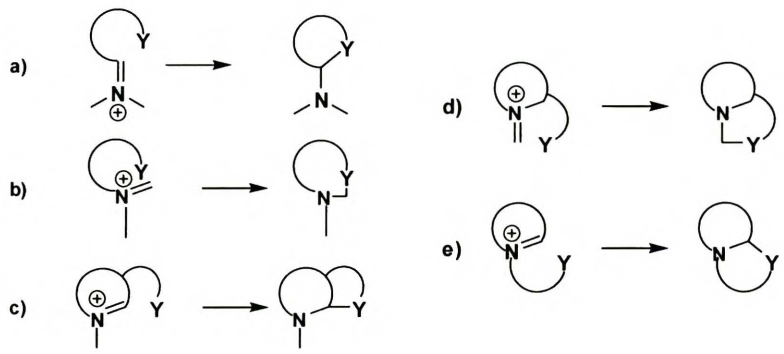
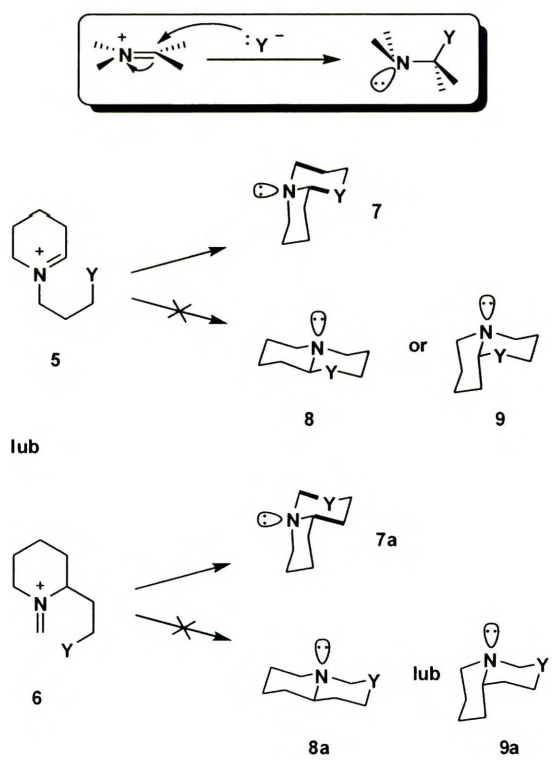



**Schemat 4**

Decydujący wpływ na powodzenie i stereochemiczny przebieg addycji nukleofilowej do jonów iminiowych mają efekty stereoelektronowe. W powstającej aminie wolna para elektronowa atomu azotu położona jest antiperiplanarnie w stosunku do czynnika nukleofilowego (Schemat 5). Prawidłowość ta jest szczególnie widoczna w przypadku reakcji wewnątrzcząsteczkowych. Cyklizacja soli *N*-alkiloiminiowych **5** i **6** prowadzi wyłącznie do *cis*-hydrochinolizydyny **7**, która posiada antiperiplanarne ułożenie niewiążącej pary elektronowej atomu azotu i podchodzącego nukleofila. *Trans*-hydrochinolizydyna **8** i *cis*-hydrochinolizydyna **9** mimo, że trwalsze nie powstają w wyniku przedstawionej na schemacie 5 reakcji.




**Schemat 5**

Enancjoselektywne, katalityczne reakcje imin z czynnikami nukleofilowymi są trudne do przeprowadzenia z silną indukcją asymetryczną. Główną przyczyną tego stanu, jest występowanie izomerów geometrycznych na wiązaniu



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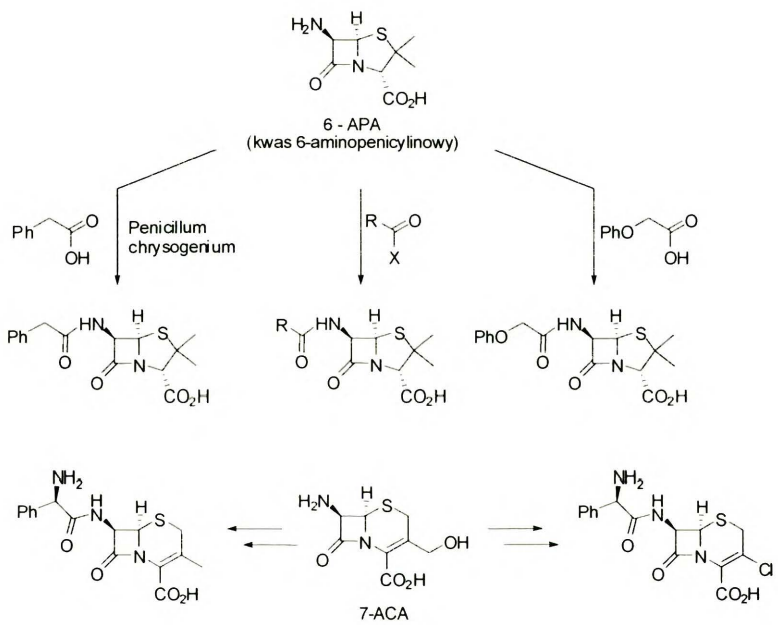
podwójnym C-N przez co możliwe są dwa stany przejściowe odpowiadających kompleksowi kwas Lewisa – imina. Ponadto iminy posiadające protony α ulegają przegrupowaniu do odpowiednich enamin, a otrzymane w wyniku addycji nukleofili aminy wiążą się trwale z chiralnymi kwasami Lewisa, uniemożliwiając przeprowadzenie procesu asymetrycznego.

Asymetryczne transformacje imin można podzielić na dwie grupy: redukcja imin i tworzenie nowych wiązań C-C (addycja nukleofilowa). W przypadku tworzenia nowych wiązań C-C z wykorzystaniem imin można zaproponować dwie strategie syntetyczne: aktywacja nukleofila przez chiralny ligand (wykorzystanie zasad Lewisa) lub aktywacja imin chiralnymi kwasami Lewisa.

Podstawowymi blokami budulcowymi w syntezie antybiotyków β-laktamowy są odpowiednio kwas 6-aminopenicylinowy (6-APA) i kwas 7-aminocefalosporynowy (7-ACA) (Schemat 6).




**Schemat 6**

Poza nielicznymi wyjątkami, antybiotyki β-laktamowe to struktury dwu lub trójpierścieniowe, a czynnikiem determinującym aktywność farmakologiczną jest często konfiguracja na węglach C-3 i C-4 pierścienia azetydynowego co powoduje, że ich stereo- i enancjoselektywna synteza pozostaje wciąż wyzwaniem dla wielu czołowych grup badawczych. Do najczęściej stosowanych metod konstrukcji dwu i trójcyklicznych β-laktamów należą różne strategie cyklizacji (Schemat 7).



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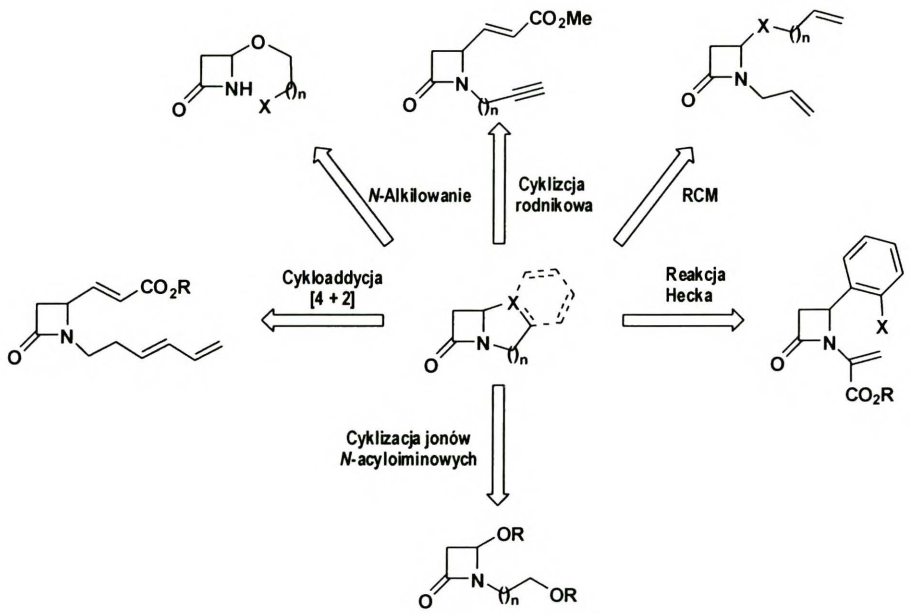
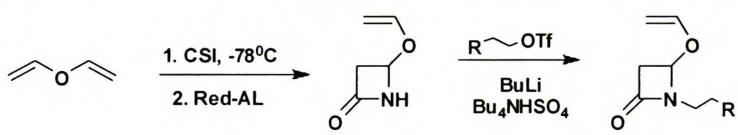



**Schemat 7**

Jedną z najczęściej wykorzystywanych strategii w syntezie 5-oksacefamów i klawamów jest nukleofilowa substytucja na węglu C-4 azetydyn-2-onu, która może być pierwszym lub ostatnim etapem zamknięcia pierścienia. Słabym punktem tej strategii jest niska indukcja asymetryczna w przypadku gdy pozycja C-3 azetydyn-2-onu nie jest podstawiona, a centrum asymetrii umieszczone jest po stronie nukleofila. Inne trudności to powstawianie jedynie związków o względnym *anti*-ułożeniu protonów pierścienia czteroczłonowego w przypadku obecności podstawnika w pozycji C-3 azetydynonu (*anti* podejście nukleofila).

W połowie lat 90-tych w zespole II IChO PAN odkryto 4-winyloksy-azetydynon użyteczny synton do otrzymywania antybiotyków $\beta$-laktamowych. Związek ten w przeciwieństwie do 4-acetoksyazetydynonów nie ulega degradacji w środowisku zasadowym i może być efektywnie *N*-funkcjonalizowany (Schemat 8). Co więcej, grupa winyloksylowa może być łatwo przeprowadzona w acyl umożliwiający łatwą wymianę nukleofilową, bądź, w obecności katalizatora kwaśnego, sama może być grupą opuszczającą (anion acetaldehydu).




**Schemat 8**

Kałuża wykorzystał odpowiednie *N*-alkilowane 4-winyloksyazetydyn-2-ony jako związki wyjściowe w syntezie prostych oksacefamów (Schemat 9).



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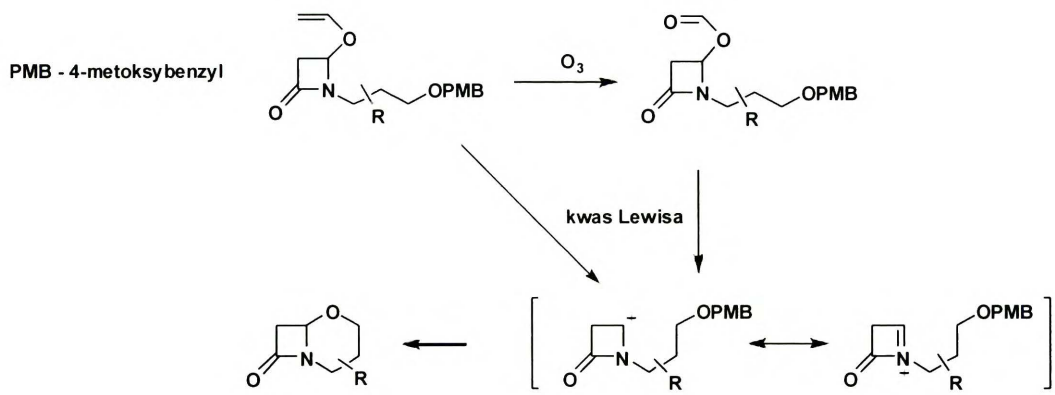
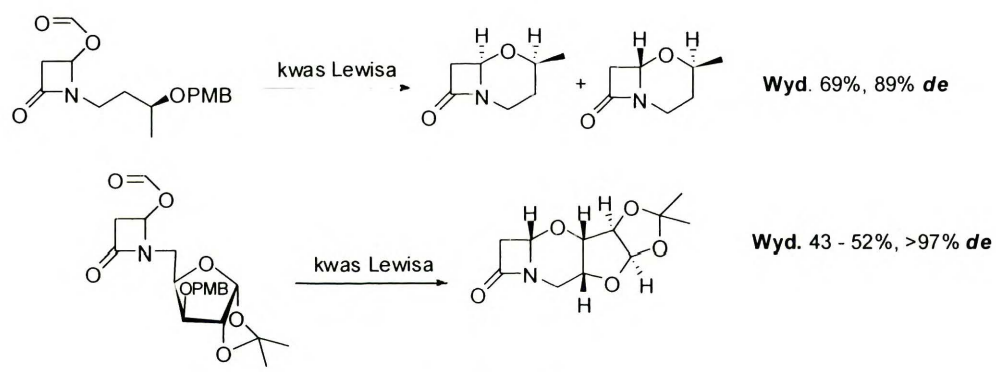



**Schemat 9**

Przedstawiona na Schemacie 9 cyklizacja przebiega przez mezomeryczny kation *N*-acyloiminowy, a jej wydajność zależy od rodzaju zastosowanego promotora kwaśnego.

Opracowano również wariant asymetryczny omawianej przemiany. I tak, dobrą diastereoselekcję w reakcji cyklizacji odnotowano gdy centrum asymetrii znajdowało się po stronie nukleofila (5:1) zaś w przypadku zastosowania reszty cukrowej powstawał wyłącznie jeden stereoizomer (Schemat 10).




**Schemat 10**



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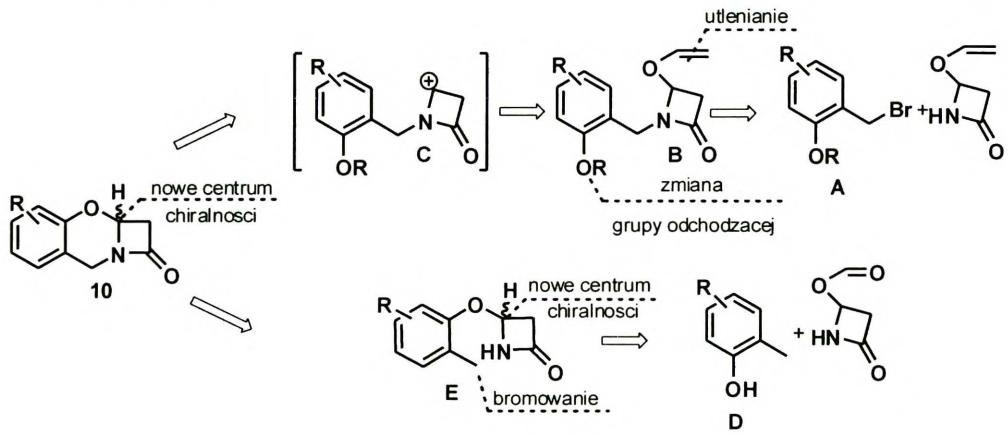
**WYNIKI WŁASNE**

Pierwsza część mojej pracy obejmowała dwie ścieżki syntetyczne prowadzące do odpowiednich oksacefamów typu **10** (Schemat 11). Etapem kończącym cykl reakcyjny pierwszej z nich jest promowana kwasem i prowadząca do kationu *N*-acyloiminowego (**C**) eliminacja grupy acetylowej i wewnątrzcząsteczkowy atak czynnika nukleofilowego na tak otrzymany kation. Dla drugiej drogi najważniejszym etapem jest promowane kwasami międzycząsteczkowe, nukleofilowe podstawienie grupy 4-formyloksylowej w azetydynonie przez atom tlenu odpowiedniego *o*-krezolu (**D**).




**Schemat 11**

Odpowiednie modelowe *N*-benzyloazetydynony (**B**) otrzymałam z zadowalającymi wydajnościami w trzyetapowej syntezie obejmującej N-alkilowanie w warunkach PTC odpowiednimi bromkami benzylowymi, desililowanie i ozonolizę. Tak otrzymane *N*-benzylo 4-formyloksy azetydynony pod wpływem kwasów Lewisa takich jak $BF_3{\cdot}OEt_2$ bądź TMSOTf dawały odpowiednie oksacefamy **10** z dobrymi wydajnościami. W przypadku zastosowania stechiometrycznej mieszaniny chiralnego diolu - BINOL i $SnCl_4$ w 0 °C otrzymałam oczekiwane produkty z umiarkowanymi wydajnościami i wysokimi nadmiarami enancjomerycznymi. Opracowaną przeze mnie metodę syntezy oksacefamów **10** zastosowałam dla procesu międzycząsteczkowego jak również w syntezie pochodnych siarkowych i alifatycznych związku **10**. We wszystkich przypadkach otrzymałam związki typu **E** z umiarkowanymi wydajnościami i średnimi nadmiarami enancjomerycznymi. W przypadku zastosowania chiralnego kwasu fosforowego związki **E** powstawały z bardzo dobrymi wydajnościami jako racematy. W wyniku bromowania wolnorodnikowego związków **E** i *N*-alkilowania w warunkach PTC otrzymałam oksacefamy **10.**

Wstępna optymalizacja pokazała, iż najlepsze wydajności i nadmiary enancjomeryczne uzyskiwane są w 0°C, w chlorku metylenu jako rozpuszczalniku. Obniżenie temperatury pogorszyło nadmiary, podobnie jak zmiana rozpuszczalnika na toluen czy eter. W przypadku zastosowania polowy ekwiwalenta kwasu Lewisa w stosunku do substratów wydajność procesu obniżyła się o połowę.

Po tej wstępnej optymalizacji sprawdziłam wpływ budowy chiralnego diolu na wydajność i nadmiar enancjomeryczny badanej reakcji (Schemat 12) . W przypadku zastosowania (*S*)-3,3'-bisfenyl-BINOLU lub (*S*)-



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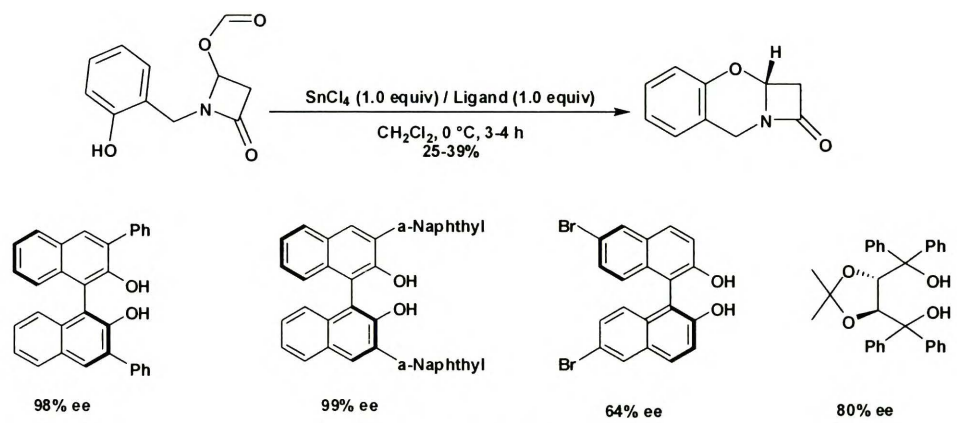
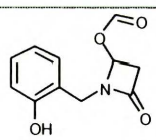
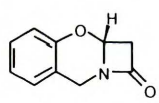
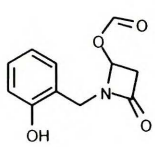
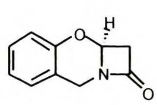
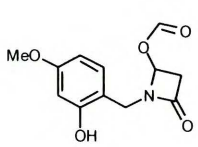
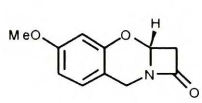
3,3'-bis-α-naftyl-BINOLU oczekiwany produkt otrzymałam z umiarkowana wydajnością (35% i 39%) i doskonałą enancjoselekcją (98%, 99%). Obecność bromu w pozycji 6 i 6' binaftolu ma niewielki wpływ na wydajnośc procesu lecz znacząco obniża enancjoselektywność. Zastosowanie (*S,S*)-TADOLU zamiast BINOLU dało porównywalną konwersje za to obniżyło enancjoselekcję. We wszystkich procesach ligandy były odzyskiwane w 80-90%.




**Schemat 12**

Stwierdziłam również, że na nadmiar enancjomeryczny jak i wydajność istotny wpływ wywierają podstawniki w pierścieniu fenolowym (Tabela 1).

| Lp. | Substrat | Produkt | Wyd. [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 |  |  | 39 | 99 |
| 2[c] |  |  | 42 | 99 |
| 3 |  |  | 49 | 82 |



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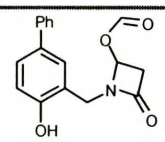
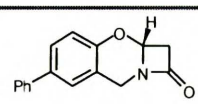
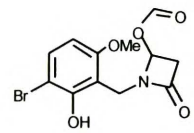
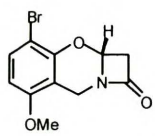
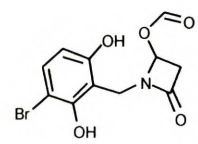
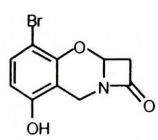
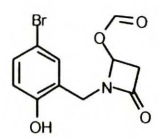
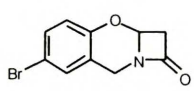
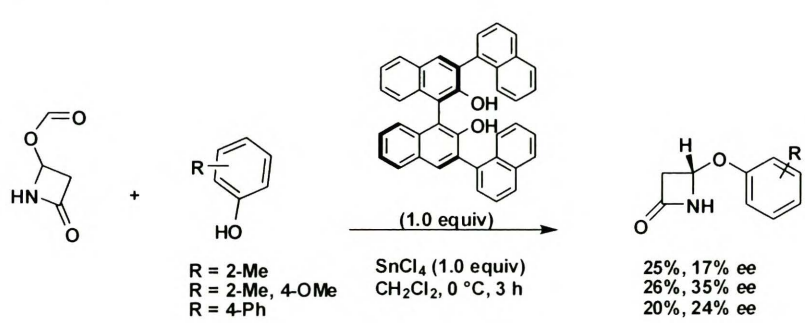
| | | | | |
|---|---|---|---|---|
| 4 |  |  | 45 | 92 |
| 5 |  |  | 50 | 95 |
| 6 |  |  | 52 | 0 |
| 7 |  |  | 0 | - |

[a] Wydajność po wydzieleniu produktu – chromatografia na $SiO_2$. [b] Nadmiar enancjomeryczny określony na podstawie chiralnego HPLC.[c] (R)-3,3'-bis-α-naphtyl-BINOL użyty jako chiralny ligand.

**Tabela 1**

Zakres przedstawionego procesu rozszerzony został na reakcję międzycząsteczkową. We wszystkich przypadkach produkt otrzymałam ze średnią wydajnością chemiczną i dużo niższym nadmiarem enancjomerycznym niż przypadku reakcji wewnatrzcząsteczkowej (Schemat 13). Jednocześnie w przypadku zastosowania 10% molowych chiralnego kwasu fosforowego oczekiwany produkt powstawał z dobrą wydajnością (70-80%) niestety jako racemat.




**Schemat 13**

Związek z R = Me (17% ee) przekształciłam w znany oksacefam bez utraty czystości optycznej w wyniku bromowania grupy metylowej i wewnątrzcząsteczkowego alkilowania atomu azotu.



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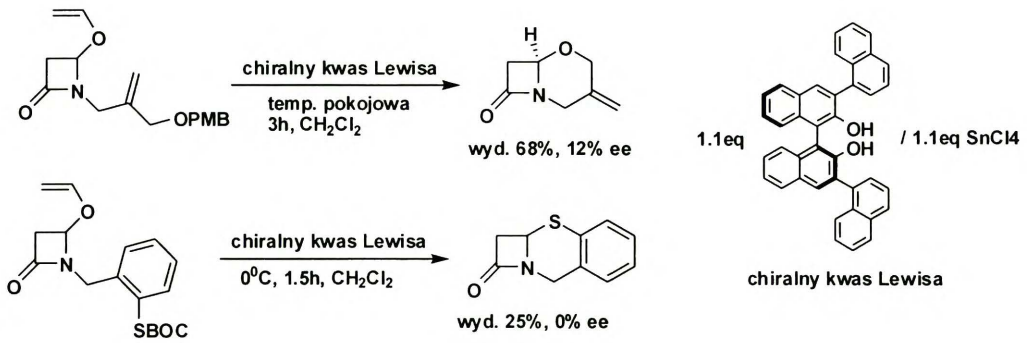
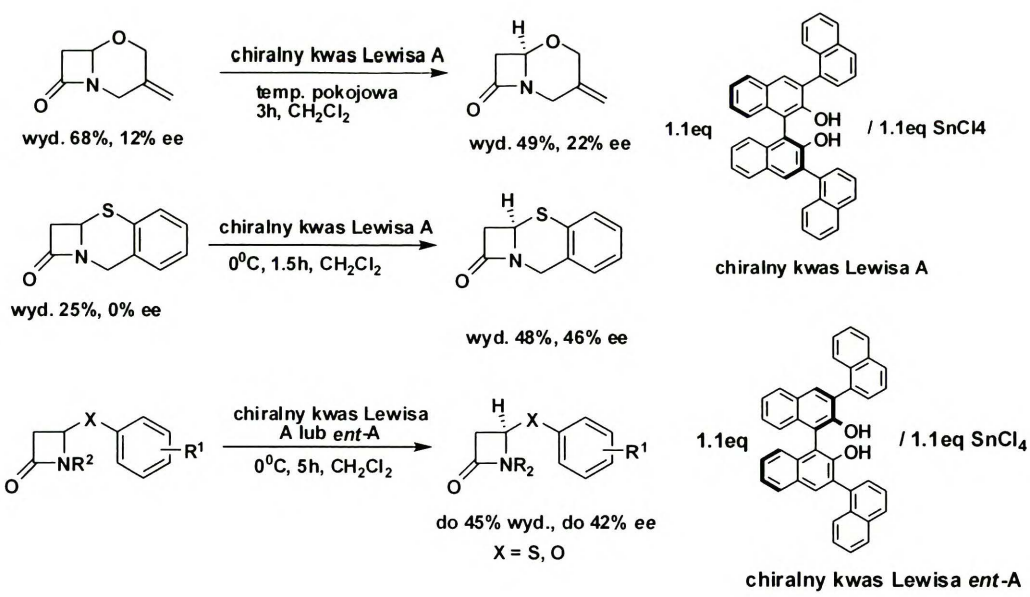
Kolejnym etapem mojej pracy był sprawdzenie czy opracowany układ promujący, enancjoselektywne wewnątrzcząsteczkowe, podstawienie nukleofilowe na węglu C-4 pierścienia $\beta$-laktamowego będzie efektywny w przypadku zastosowania innych nukleofili (Schemat 14).




**Schemat 14**

W wyniku przeprowadzonych eksperymentów stwierdziłam, ze chiralne kwasy Lewisa oparte na chlorku cyny (IV) i pochodnych binaftolu katalizują proces addycji alkoholi allilowych i tiofenoli do winyloksyazetydynonu. Niestety uzyskane nadmiary enancjomeryczne są niskie i nie przekraczają 25 % *ee*. Lepsze wyniki odnotowałam badając proces enancjoselektywnej destrukcji racemicznych oksacefamów, 2,3-benzocefamów i 4-aryloksy- lub 4-tiofenylazetydynonów. I tak, w obecności chiralnego kwasu Lewisa racemiczne addukty ulegają enancjomerycznemu wzbogaceniu, a wyniki indukcji asymetrycznej sięgają 46 % *ee* przy wydajnościach sięgających 49% (Schemat 15).




**Schemat 15**

Drugie opracowane w ramach mojej pracy doktorskiej podejście do enancjoselektywnej syntezy 5-oksacefamów opiera się na łatwo dostępnych, naturalnych i tanich organokatalizatorach – alkaloidach kory chinowca.



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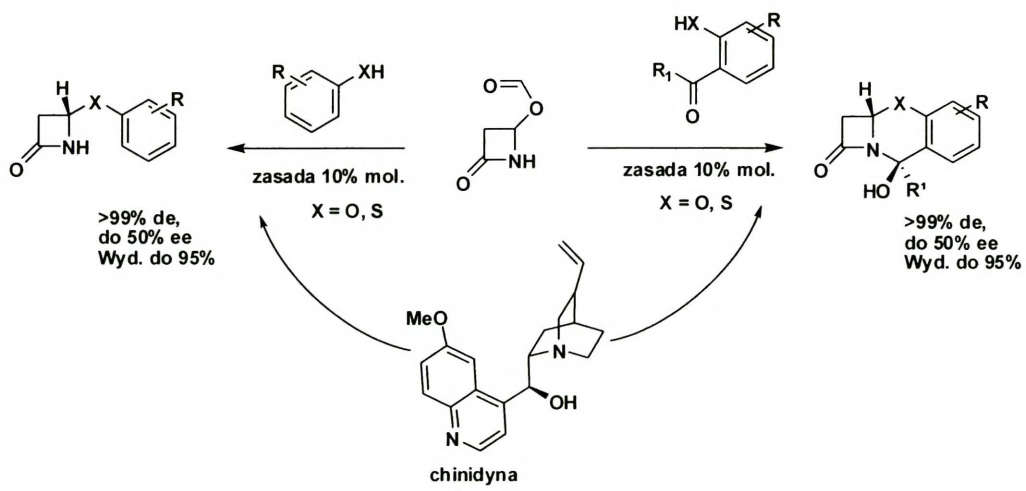
Stwierdziła, że kondensacja aldehydów salicylowych i *o*-hydroksyacetofenonów z 4-formyloksyazetydyn-2-onem przebiega z doskonałą diastereoselekcją, dobrą enancjoselekcją i bardzo dobrymi wydajnościami w obecności jedynie katalitycznych ilości chinidyny w bardzo łagodnych warunkach (Schemat 16). Inne chiralne aminy lub aminoalkohole okazały się całkowicie nieefektywne. Pomimo obserwowanego intensywnego rozwoju organokatalizy w ostatnich latach jest to jak do tej pory pierwszy przykład zastosowania organokatalizy w syntezie *β*-laktamów. Pozytywne rezultaty otrzymano również dla pochodnych fenolu jak i analogów siarkowych. Opracowana przeze mnie metoda daje dostęp do nieracemicznych 4-aryloksyazetydynonów związków będących skutecznymi inhibitorami elastaz.




**Schemat 16**

Kontynuując badania postanowiłam sprawdzić czy inne tlenowe i siarkowe nukleofile (alkohole i tiole alifatyczne, allilowe, propargilowe) są komponentami równie użytecznymi jak fenole i tiofenole.

Tak otrzymane enancjomerycznie wzbogacone *β*-laktamy mogą zostać wykorzystane w syntezie nieracemicznych oksacefamów i oksepenemów. Przeprowadzenie analogicznego cyklu przemian z wykorzystaniem allilotioli pozwoli uzyskać enancjomerycznie wzbogacone cefalosporyny. Jednocześnie odpowiednie 4-alkoksyazetydyn-2-ony w wyniku wewnątrzcząsteczkowego alkilowania atomu azotu dadzą enancjomerycznie wzbogacone pochodne penamów i cefamów.

Pierwszym etapem prac była synteza związków racemicznych. W obecności DBU w roztworze tetrahydrofuranu 4-formyloksyazetydyn-2-on ulegał podstawieniu nukleofilowemu odpowiednim nukleofilem z wydajnościami umiarkowanymi do bardzo dobrych. Jednakże ze względu na lotność nowo otrzymanych związków oraz brak wystarczająco mocnego chromoforu konieczne okazało się benzylowanie azotu w nowo otrzymanych związkach. Wcześniejsze badania pokazały, że *N*-alkilowanie nie wpływa na nadmiar enancjomeryczny. Co wiecej przeprowadzenie benzylowania w obecności 50% NaOH w toluenie z molową ilością $Bu_4NBr$ przebiega prawie ilościowo (Schemat 17).



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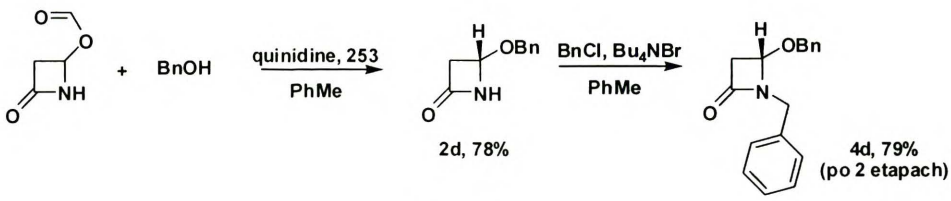
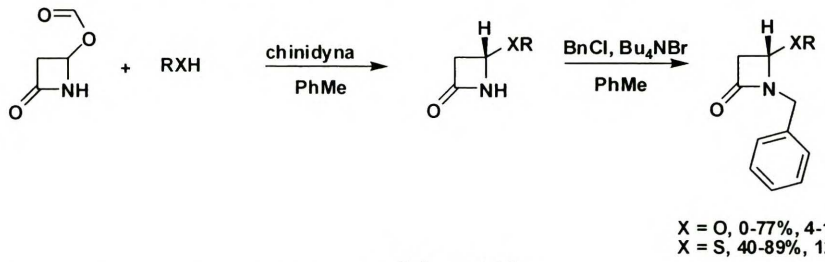



**Schemat 17**

Ta sama reakcja nuleofilowego podstwienia w obecności chinidyny (najefektywniejszego katalizatora w przypadku analogicznego podstawienia fenolami i tiofenolami), przebiega z dobrymi wydajnościami i słabymi nadmiarami enancjomerycznymi. W przypadku alkoholi konieczne okazało się zastosowanie molowej ilości chinidyny. Dla tioli takie zwiększenie ilości promotora niebyło konieczne (Schemat 18).




**Schemat 18**

Podsumowując opracowałam trój etapową syntezę prekursorów do reakcji cyklizacji – odpowiednich *N*-benzylowanych 4-formyloksyazetydyn-2-onów. Określiłam optymalne warunki enancjoselektywnej cyklizacji prowadzącej do 3,4-benzo-5-oksacefamów (**10**). Zastosowanie jako układu promującego kompleksu BINOL/$SnCl_4$ zaowocowało doskonałymi nadmiarami enancjomerycznymi oczekiwanych cefamów **10**. Jednakże wydajność procesu nigdy nie przekroczyła 50%. Stwierziłam, że zarówno wydajność jak i nadmiar enancjomeryczny zależą od rodzaju podstawnika w pierścieniu aromatycznym jak również od typu zastosowanego nukleofila.

Druga część mojej pracy poświęcona była zastosowaniu chiralnych zasad Lewisa w nukleofilowym podstawieniu na węglu C-4 w 4-formyloksyazetydyn-2-onie. Najlepsze rezultaty otrzymałam dla procesu katalizowanego chinidyną. Ten alkaloid kory chinowca promował reakcje *o*-hydroksy-fenonów z 4-formyloksyazetydyn-2-onem z bardzo dobrymi wydajnościami i umiarkowanymi nadmiarami enancjomerycznymi. W badanym procesie sprawdziłam stosowalność różnych nukleofili. Na podstawie otrzymanych rezultatów, został zaproponowany mechanizm eliminacji-addycji. W przypadku związków aromatycznych typ nukleofila nie wpływał na enancjoselekcje całego procesu. Zastosowanie alifatycznych alkoholi i tioli nie było aż tak efektywne. Oczekiwane azetydyn-2-ony powstawały z umiarkowanymi wydajnościami i niskimi nadmiarami enancjomerycznymi.

By określić konfigurację bezwzględną na węglu C-6 w otrzymanych 3,4-benzo-5-oksacefamach zastosowano spektroskopię dichroizmu kołowego (CD). W tym celu wykorzystano metodę chiralnych ekscytonów (ECCD) – obecność dwóch odpowiednio zorientowanych chromoforów amidowego i fenylowego. Na tej podstawie przypisano konfigurację (6*R*) dla związku otrzymanego z (*S*)-BINOLEM. Potwierdziły to symulowane widma CD



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przy wykorzystaniu danych z obliczeń w oparciu o TDDFT. W przypadku 3,4-benzo-2-hydroksy-5-oksacefamów otrzymanych w procesie katalizowanym chinidyną, zastosowanie znalazła reguła helikalności, zaś zwornikowemu atomowi węgla została przypisana konfiguracja (6*S*). Również w tym przypadku występuje zgodność z widmami teoretycznymi.

Wstępne badania DD-peptydazą 64-575 pokazały, że otrzymane przeze mnie oksacefamy o konfiguracji (*S*) na węglu C-4 posiadają umiarkowaną aktywność antybiotyczną



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