University of Warsaw

Department of Chemistry

The organic synthesis as a useful tool to study chemical reaction mechanisms

dr Anna Piątek

Summary of scientific achievements in relation to habilitation procedure

Warsaw, April 2016

1. First Name, last Name

Anna Maria Piątek (nee Kucharska)

2. Obtained diplomas and scientific degrees

Doctor of chemical sciences, Warsaw, 07.11.2001
Title: *The influence of solvents and catalysts on asymmetric induction of [4+2]cycloaddition reaction*
Supervisor: prof. dr hab. Janusz Jurczak

3. Information on academic employment

October 2004 – at present: assistant professor (adjunct), Department of Chemistry, University of Warsaw

4. The main scientific achievement

4.1 Title of the achievement

The organic synthesis as a useful tool to study chemical reaction mechanisms

4.2 List of selected publications related to the achievement

H1. Piątek, A.M., Gray, M., Anslyn, E.V.
"Guanidinium Groups Act as General-Acid Catalysts in Phosphoryl Transfer Reactions: A Two-Proton Inventory on a Model System"
Journal of the American Chemical Society, **2004,** *126* (32), 9878-9879. **IF**=6.903

H2. Koszewska, K.; Piątek, A.; Chapuis, Ch.; Jurczak, J., "X-ray structure analyses of syn/anti-conformers of *N*-furfuroyl-, *N*-benzoyl-, and *N*-picolinoyl-substituted (2*R*)-bornane-10,2-sultam derivatives."
Helvetca Chimica Acta, **2008**, *91*, 1409-1418, **IF**=1.396

H3. Piątek, A., Chapuis, Ch.
„Influence of norbornanone substituents on both the Wagner-Meerwein skeletal rearrangements under sulfonation conditions and the diastereoselectivity of the corresponding *N*,*N*'-bis-fumaroyl sultams in uncatalyzed Diels-Alder cycloadditions to cyclopenta-1,3-diene."
Tetrahedron Letters, **2013**, *54*, 4247-4249. **IF**=2.68

H4. Piątek, A.M., Chojnacka, A., Chapuis, C., Jurczak, J.
"Synthesis and [4 + 2] cycloaddition of (2*R*,2'R)-*N*, *N*'-fumaroylbis[fenchane-8,2-sultam] (=(2E)-1,4-bis[(3a*S*,6*S*,7a*R*)-1,4,5,6,7,7a-hexahydro-7,7-dimethyl-2,2-dioxido-3H-3a,6-methano-2,1-benzothiazol-1-yl] but-2-ene-1,4-dione) to cyclopentadiene."
Helvetica Chimica Acta, **2005**, *88* (9), 2441-2453. **IF**= 1.650

H5. Chojnacka, A., Piątek, A.M., Chapuis, C., Jurczak, J.
"Influence of Lewis acids on the [4+2] cycloaddition of (2R,2'R)-N,N'- fumaroylbis[fenchane-8,2-sultam] to cyclopentadiene and cyclohexadiene"
Tetrahedron Asymmetry, **2006**, *17* (5), 822-828. **IF**=2.468

H6. Piątek, A.M., Sadowska, A., Chapuis, C., Jurczak, J.
"Diastereoselective alkyl Grignard 1,4-additions to para-substituted (2*R*)-*N*-cinnamoylbornane-10,2-sultam derivatives: Influence of N-atom pyramidalization"
Helvetica Chimica Acta, **2011,** *94* (12), 2141-2167. **IF**=1.478

H7. Piątek, A., Chapuis, C.,
"Diastereoselectivity During Ethyl Grignard 1,4-Additions to Fluorine Containing *para*-Substituted (2*R*)-*N*-Cinnamoylbornane-10,2-sultam Derivatives"
Helvetica Chimica Acta, **2016,** in press, DOI: hlca.201500521R1. **IF=** 1.138

H8. Rzymkowski, J., Piątek, A.,
"The development of a stereoselective method for the synthesis of tetrasubstituted derivatives of α,β-unsaturated carboxylic acids"
Helvetica Chimica Acta, **2016,** in press, DOI: 10.1002/hlca.201600079 **IF=** 1.138

Total IF 18.85

5.3 Description of the achievement (aims, results and significance)

The organic synthesis as a useful tool to study chemical reaction mechanisms

1. Introduction.

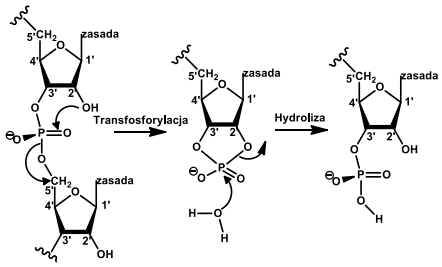
The two main areas of interest in modern organic synthesis are the synthesis of biologically active natural and non-natural organic compounds, and the development of new reagents, catalysts and methods allowing for more efficient and economical organic processes. However, organic synthesis can also be an important tool for studying the mechanisms of organic reactions as well as biological processes. Here, organic synthesis provides model compounds which can be further studied using various physicochemical techniques to elucidate their reaction mechanisms; next, the steric and/or electronic properties of the initial model compounds can be modified to study what impact these modifications have on the reaction mechanisms. Extending the arsenal of model compounds is also an important and sometimes difficult task of organic synthesis. These latter areas of organic synthesis are the main object of my scientific interest and are the main part the research which I will summaries in this report.

2. Kinetic isotope effect studies of hydrolysis of phosphodiester 1.

Ribonucleic acids play a crucial role in many biological processes, from copying DNA (mRNA) by linking genetic code and the protein building blocks (tRNA) to the structural component of ribosomes (rRNA). Importantly, RNA can also act as enzymes (ribozymes), the main function of which is the cleavage or ligation of RNA and DNA. [1]

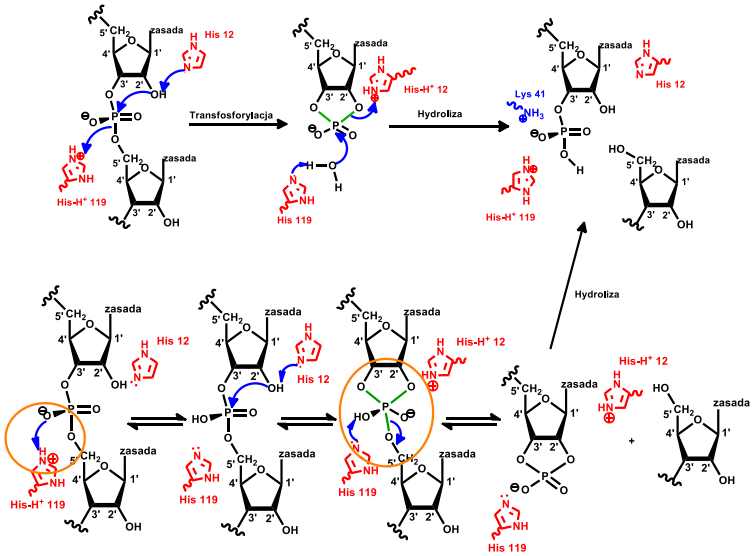
[1] Murray, R.K., Granner, D.K., Mayes, P.A., Rodwell, V.W., *Harper's Illustrated Biochemistyr,* **2003**, McGraw-Hill Companies.

RNA degradation is a major component of overall RNA metabolism, and plays an important role in determining intracellular levels of RNA species. This process requires the action of ribonucleases (RNases) – enzymes that catalyze RNA phosphodiester bond cleavage. In 1997, Anslyn and coworkers published a critical review summarizing the then-current knowledge on RNA degradation.[2] This process proceeds in two steps: transphosphorylation and subsequent hydrolysis (Scheme 1).[2,3] In the transphosphorylation step, the nucleophilic attack of the ribose 2'-OH group on the phosphorus atom induces 5'CH_2O-P bond cleavage and subsequent formation of 2',3'-cyclic phosphoester. The second, hydrolysis step involves the opening of a 2',3'-cyclic phosphodiester and 2'-OH group recovery. For the transphosphorylation step, two mechanisms – "classical" and "triester" – have been proposed.



Scheme 1. *The mechanisms for RNA cleavage.*

The "classical" mechanism involves general-base/general-acid catalysis and it is mostly ascribed to RNAse A (Scheme 2).[4] An imidazole group (His12) acts as a base and deprotonates the 2'-OH group which then attacks a phosphorous atom and forms 2',3'-cyclic phosphodiester. Either in a second step or simultaneously with the nucleophilic attack, an imidazolium group protonates the leaving 2'-O^- group. The subsequent hydrolytic step is also catalyzed by different forms of imidazole group and the negative charge of the final nucleoside-3'-phosphate product is stabilized by the lysine ammonium group.



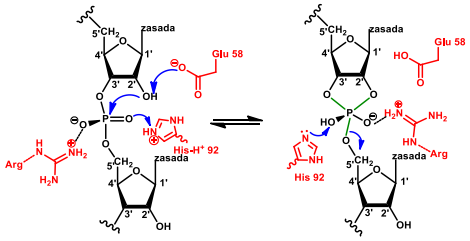
Scheme 2. *The classical mechanism vs "triester" mechanism of degradation of RNA (RNAsa A).*

However, this classical mechanism has often been called into question and alternative mechanisms have been proposed (Scheme 2).[5] The "triester" mechanism, as its name implies,

[2] D. M. Perreault, E. V. Anslyn, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 432.
[3] D. Herschlag, *J. Am. Chem. Soc.*, **1994**, *116*, 11631.
[4] (a) X. Lopez, D. M.York, A. Dejaegere, M. Karplus, *Intern. J. Quant. Chem.*, **2002**, *86*, 10 (b) D. Findlay, D. Herries, A. Mathias, B. Rabin, C. Ross, *Nature*, **1961**, *190*, 781.
[5] K. N. Dalby, A. J. Kirby, F. J. Hollfelder, *Chem. Soc., Perkin. Trans.*, **1993**, 1269.

assumes the formation of phosphotriester as an intermediate compound. In this mechanism, the imidazolium group (His119) protonates the phosphorane, and then another imidazole group (His12) removes a proton from the 2'-OH group, which promotes the nucleophilic attack on the phosphorus atom to yield a monoanionic phosphotriester intermediate.

The "classical" and "triester" mechanisms occur in parallel in buffer-catalyzed RNA cleavage/transesterification. In RNAse A, the classical mechanism receives the most support, where His-12 is the general base, His-119 is the general acid, and Lys-41 acts as either a general acid or an electrostatic catalyst to stabilize the phosphorane-like transition state.[2,6] The triester mechanism receives the most support from RNAse T1. In this enzyme, Glu-58 and His-92 play the roles of the general-base and general-acid catalysts, respectively, while Arg-77 acts as an analogue to Lys-41 in RNase A (Scheme 3). [7]



Scheme 3. *The "triester" mechanism of degradation of RNA (RNAsa T1).*

To probe the roles of individual groups located in the ribonuclease's active sides (RNAsa A and RNAsa T1) during the RNA degradation process, it needs to be investigated whether those groups play the role of general-acid/general-base catalysts (proton transfer) or electrostatic catalysts (hydrogen bond formation).

Towards this end, I designed the model compound **1**, the structure of which resembles an RNA strain and the active site of RNAse.**(H1)**[8] Specifically, a phosphodiester unit with a free hydroxy group (RNA strain mimic) is linked through a phenyl ring to a guanidine group (RNAse T1 mimic) (Figure 1).[1] A guanidine group was chosen because it is least acidic of the groups catalyzing RNA degradation. Therefore, if guanidinium cation can act as an acid, any more acidic group, such as ammonium group from lysine and imidazolium group from histidine, will also act in a similar manner. Modeling of compound **1** revealed that the guanidinium group can coordinate to the phosphoester peripheral oxygen, but not to the phenol oxygen atom.

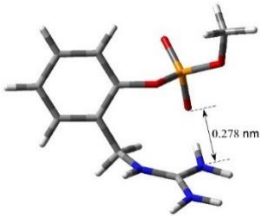
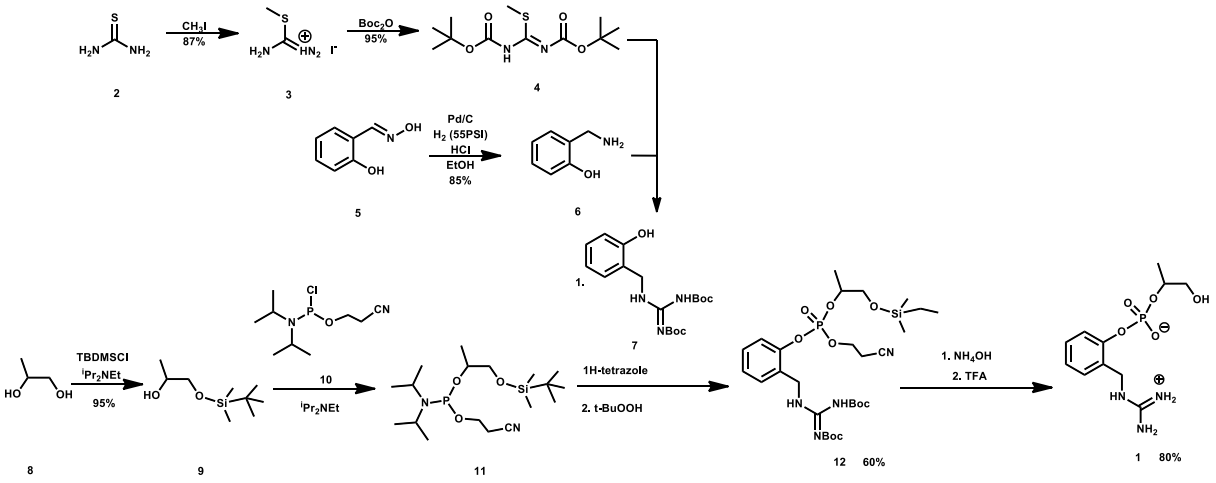


Figure 1. *The modeling structure of **1**.*

Phenol **7** containing a protected guanidine group, required for the preparation of compound **1**, was synthesized in four steps (Scheme 4).

[6] R. T. Raines, *Chem. Rev.*, **1998**, *98*, 1045.
[7] S. Loveriz, A. Winquist, R. Stromberg, Steyaert, *J. Chem. and Biol*., **2000**, *7*, 651.
[8] Piątek, A.M., Gray, M., Anslyn, E.V. *J.Am.Chem.Soc.*, **2004**, *126* (32), 9878-9879.**(H1)**



Scheme 4. *The synthesis of compound **1**.*

Alkylation of commercially available thiourea **2** with MeI lead to salt **3**, which was then protected as t-butoxycarbamates, providing **4**. In parallel, hydrogenation of salicylaldoxyme (**5**) resulted in the formation of aminophenol **6**. The nucleophilic attack of the amine group from compound **6** on the electrophilic carbon in **4** and the simultaneous departure of the leaving group (CH_3S-) yielded phenol **7**.

The other essential substrate for the synthesis of compound **1** is derivative **11**. Its synthesis started from the selective protection of the primary hydroxyl group of 2,3-dihydroxypropane, followed by the addition of 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (**10**), resulting in the formation of derivative **11**. The nucleophilic substitution of phenol **7** to compound **11**, with the departure of the diisopropylamine group and further oxidation of phosphorous atom with di-tert-butyl peroxide, results in the formation of phosphoric ester **12**. Finally, all the protecting groups were removed, yielding the desired compound **1**.

To study the role of the guanidinium group in the hydrolysis of phosphodiester **1**, I employed the proton inventory method (Figure 2).[9] Compound **1** (Chart A) and 2-hydroxypropyl *p*-nitrophenyl phosphate (HPNP), lacking a guanidinium group (Chart B), were hydrolyzed.

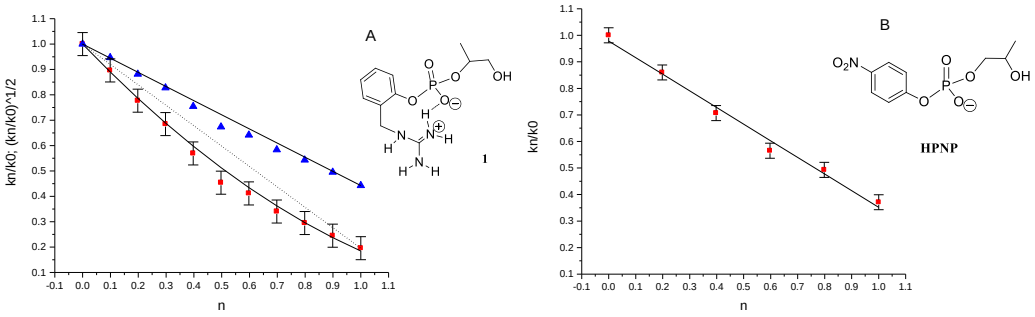


Figure 2. ■ *– Experimental points (kn/k0);* ▲ *– The square root of kn/k0; n-mole fraction of D_2O; kn – the reaction rate (different D_2O mole fraction); k0 – the reaction rate in H_2O.*

The rate of hydrolysis of **1** in various mixtures of H_2O and D_2O was measured via UV/vis spectroscopy, and a first-order kinetics analysis was applied to at least the first three half-lives of the reaction. The resulting "bowl shaped" plot of rate constants of hydrolysis of **1** versus D_2O fraction (n)

[9] (a) Schowen, K.B.; Schowen, R. L. *Methods Enzymol.* **1982**, *87*, 551-606. (b) Anslyn, E.V.; Breslow, R. *J. Am. Chem. Soc*. **1989**, *111*, 8931-8932. (c) Nakano, S.; Bevilacqua, P. C. *J. Am. Chem. Soc.* **2001**, *123*, 11333-11334.

showed that two protons are transferred in the rate determined step of hydrolysis of **1**. The two-proton inventory for **1** relative to a one-proton inventory for HPNP shows that a guanidinium group coordinated to a phosphodiester will act as a general-acid catalyst during cleavage/transesterification, not just as an electrostatic catalyst. Analysis of the results also showed that the presence of guanidinium group in compound **1** causes a 420-fold hydrolysis rate enhancement as compared to HPNP. The proposed mechanism of two-proton transfer during the hydrolysis of **1** is presented in Figure 3.

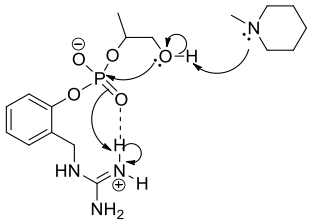


Figure 3. *Proposed mechanism of hydrolysis of compound* ***1.***

In summary, I have found that the guanidinium group can act as general-acid catalyst, not only electrostatically supporting the leaving of the hydroxyl group of ribose during the process of cleavage/transesterification of RNA. These general assumption can be extended to a more acidic group, such as ammonium group (Lys) and imidazolium group (His), which will also act in a similar manner, if they are coordinated to a phosphoester peripheral oxygen.

The above presented study are included to this elaboration because of the experience gained during its performance. That allows me to look at my research interests in new light. My scientific workshop, especially in the area of physical chemistry has been extended, I could combine it with my synthetic skills and applied in study of stereochemical course of asymmetric reaction.

In the next part of my work, I focused my attention on the preparation of novel chiral auxiliaries **14** and **15**. These compounds are analogues of Oppolzer's sultam (**13**) that differ from their parent compound in terms of gem-dimethyl group placement. Problems encountered in efforts to prepare compound **15** simulated my interest in detailed study of sulfonation of camphor and its analogues. In the next part of this report, my work on the influence of chiral auxiliary **14** on the stereochemical course of [4+2] cycloaddition of the fumarate derivative of **14** is presented. Specifically, a detailed explanation is provided of the influence of structural modification of chiral auxiliary **14** on the structure of Lewis acid-dienophile complex formed during the catalyzed cycloaddition reaction. (**H2**,[10] **H3**,[11] **H4**, [12] **H5**[13])

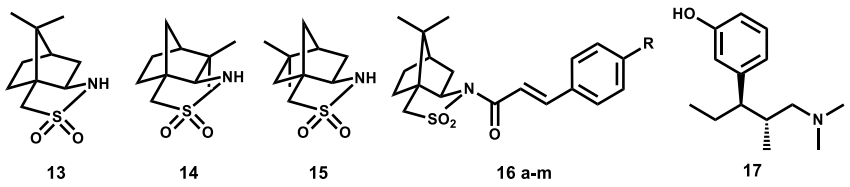


Figure 4

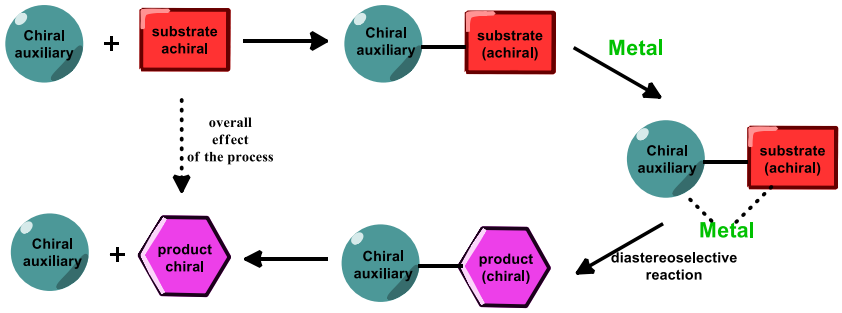
In the last part of this report, I describe my detailed investigations into 1,4-addition of Grignard compounds to chiral derivatives of cinnamic acid (**16a-m)**. The main scientific aim of this project was to establish the influence of phenyl *para*-substituents on the stereochemical course of the addition

[10] Koszewska, K.; Piątek, A.; Chapuis, Ch.; Jurczak, J., *Helv.Chim. Acta*, **2008**, *91*, 1409-1418. **(H2)**
[11] Piątek, A., Chapuis, Ch., *Tetrahedron Letters*, **2013**, *54*, 4247-4249. **(H3)**
[12] Piątek, A.M., Chojnacka, A., Chapuis, C., Jurczak, J., *Helv.Chim. Acta*, **2005**, *88* (9), 2441-2453. **(H4)**
[13] Chojnacka, A., Piątek, A.M., Chapuis, C., Jurczak, J., *Tetrahedron Asymmetry*, **2006**, *17* (5), 822-828. **(H5)**

reaction. These studies initiated my search for new synthetic routes for the preparation of Tapentadol – a modern analgesic drug for neuropathic pain. (**H6**,[14] **H7**,[15] **H8**[16])

3. Influence of the structure of chiral substrates on the course of diastereoselective processes.

Chiral auxiliaries are chiral molecules temporarily introduced into the structure of an achiral substrate to control the stereochemical outcome of a reaction. The chiral environment created by a chiral auxiliary induces the configuration of a newly created stereogenic center (Scheme 5). Most frequently, a metal chelate connects a chiral auxiliary to a functional group of the achiral part of the molecule. This fixes the substrate conformation, as steric hindrance of the chiral auxiliary blocks one side of the prochiral reaction center. Therefore, the reagent approaches the less hindered side of the complex and reaction with the prochiral atom leads to preferable formation of one diasteromeric product.



Scheme 5. The role of the chiral auxiliary in asymmetric synthesis.

After the separation of the major diastereomer from the minor one, the chiral auxiliary is removed to yield a enantiomeric/diastereomeric product. The chiral auxiliary strategy has been applied on numerous occasions for the preparation of natural compounds[17] and biologically active compounds.[18] The most frequently used chiral auxiliaries include 8-phenylmenthol,[19] oxazolidinones,[20] chiral sulfoxides[21] and bornano-10,2-sultam.[22] The latter chiral auxiliary, whose synthesis was proposed by Wolfgang Oppolzer in 1984, is commonly known as Oppolzer's sultam (**13**).[23] It is crystalline, stable and easy to prepare from inexpensive camphor, available in both enantiomeric forms, which makes it one of most frequently used chiral auxiliaries in asymmetric synthesis. The two most important units of Oppolzer's sultam are a norbornane ring, which provides a chiral environment, and a sultam ring, which enables chiral auxiliary functionalization as well as metal complex formation.

Our preliminary results have shown that an Oppolzer's sultam derivative, lacking a gem-dimethyl group in the norbornane ring, is unable to induce any diastereoselection in [4+2]cycloaddition. (**H3**)[3] This fact prompted me to perform a review of the literature, which revealed that there were no

[14] Piątek, A.M., Sadowska, A., Chapuis, C., Jurczak, J., *Helv.Chim. Acta*, **2011,** *94* (12), 2141-2167. **(H6)**
[15] Piątek, A., Chapuis, C., *Helv.Chim. Acta*, **2016,** accepted, DOI: hlca.201500521R1 **(H7)**
[16] Rzymkowski, J., Piątek, A., *Helv.Chim. Acta* **2016**, accepted, DOI: 10.1002/hlca.201600079 **(H8)**
[17] (a) Schultz A. G., Holoboski M. A. and Smyth M. S., *J. Am. Chem. Soc.*, **1996**, *118*, 6210. (b) Paquette L. A., Tae J., Arrington M. P. and Sadoun A. H., *J. Am. Chem. Soc.*, **2000**, *122*, 2742. (c) Miyata O., Shinada T., Ninomiya I. and Naitu T., *Tetrahedron Lett.*, **1991**, *32*, 3519.
[18] Turner, S. T.; et al., *J. Med. Chem.*, **1998**, *41*, 3467–3476.
[19] Corey, E. J.; Ensley, H. E., *J. Am. Chem. Soc.*, **1975**, *97*, 6908–6909.
[20] Evans, D. A.; Chapman, K. T.; Bisaha, J., *J. Am. Chem. Soc.*, **1984,** *106*, 4261–4263.
[21] Ellman, J. A.; Owens, T. D.; Tang, T. P., *Acc. Chem. Res.*, **2002**, *35*, 984–995.
[22] Oppolzer W., *Pure&Appl. Chem.*, **1990**, *62*, 1241-1250.
[23] Oppolzer W., Chapuis C.and Bernardinelli G., *Helv. Chim. Acta*, 1**984**, 1397-1401.

published studies reporting on the influence of the location of gem-dimethyl groups on diastereoselectivity induced by Oppolzer's sultam derivatives. Therefore I began working in this direction by attempting to prepare two new chiral auxiliaries **14** and **15**. These auxiliaries are constitutional isomers of Oppolzer's sultam that have a gem-dimethyl group in positions C(3) and C(5), respectively (Figure 5). (**H3**)[3] Studying the stereochemical outcome of [4+2]cycloaddition reaction of fumaroyl derivatives of **14** and **15** should reveal the role of this gem-dimethyl group.

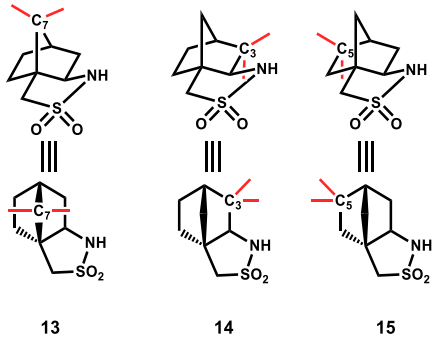
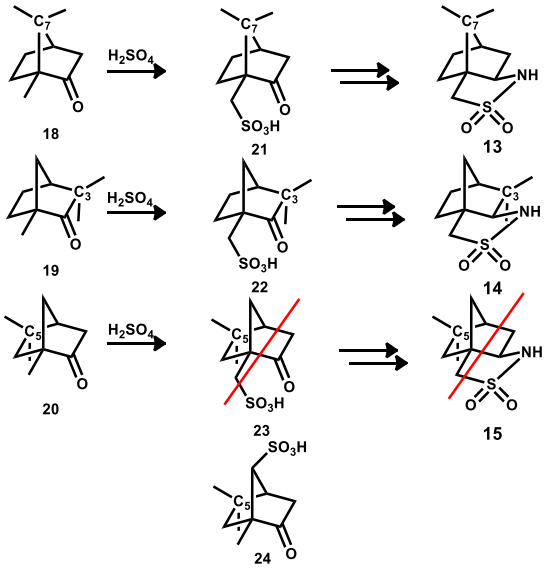


***Figure 5**. The structural differences of chiral auxiliaries **13**, **14**and **15**.*

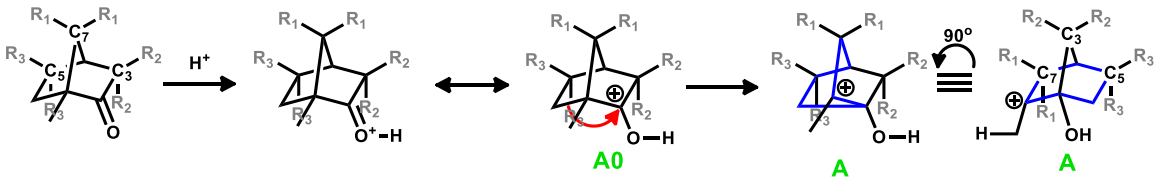
The first step in the preparation of **14** and **15** is the reaction of chiral ketones such as (-)-(1*R*,4*R*)-fenchone (**19**) or (-)-(1*S*,4*S*)-iso-fenchone (**20**) with concentrated sulfuric acid (Scheme 6).



Scheme 6**. The sulfonation reaction of camphor **18** and its derivatives **19** and **20.

However, analysis of the sulfonation reaction products revealed that only sulfonic acid **22** could be prepared. The sulfonation of ketone **20** lead only to secondary sulfonic acid **24**, not to the desired product **23** (Scheme 6). These results motivated me to scrutinize the sulfonation reaction mechanisms in more detail.

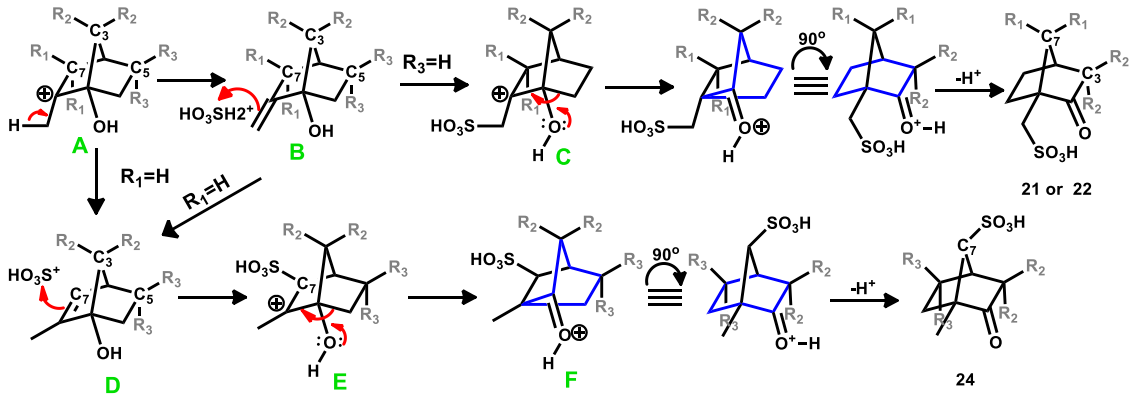
In a first step, concentrated sulfuric acid protonated the carbonyl group, which lead to the formation of carbocation **A0** (Scheme 7).



***Scheme 7**. The mechanism of sulfonation reaction (part 1).*

This carbocation then undergoes Wagner–Meerwein rearrangement to give another carbocation **A**. This process involves 1,2-shifts of H atom or alkyl/aryl groups. I assume that this part of the reaction is similar for ketones **19**, **20** as well as **18**, the latter leading to Oppolzer's sultam.

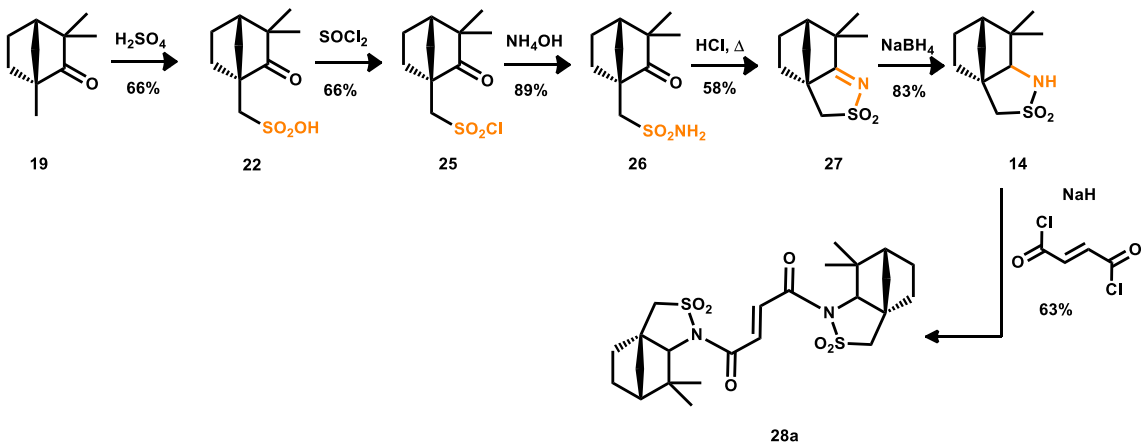
The carbocation **A** eliminates to give *exo*-cyclic allylic alcohol **B** (Scheme 8). When (+)-(1*R*,4*R*)-camphor (**18**) or (-)-(1*R*,4*R*)-fenchone (**19**) was used there is a possibility of HSO_3^+ cation addition to *exo*-cyclic double bond (structure **C**) and subsequent second Wagner–Meerwein rearrangement gave the final sulfonation product **21** or **22**, respectively.



Scheme 8. *The mechanism of sulfonation reaction (part 2).*

If (-)-(1*S*,4*S*)-iso-fenchone (**20**) is a reaction substrate, the intermediate *exo*-cyclic allyl alcohol isomerizes into the thermodynamically more stable *endo*-cyclic isomer **D**, which after sulfonation and Wagner–Meerwein rearrangement affords a secondary sulfonic acid **24**, not the desired product **23**.

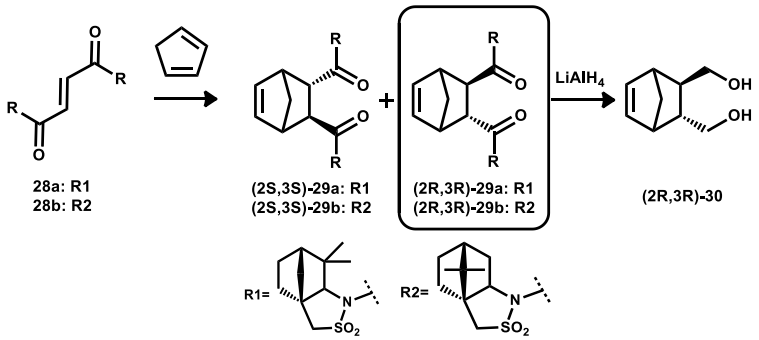
The above presented results clearly show that the preparation of a chiral auxiliary having gem-dimethyl group in position C(5) (**23**) is impossible. Thus I conducted further studies using chiral auxiliary **14**.(**H4**)[4] From commercially available (-)-(1*R*,4*R*)-fenchone (**19**) the corresponding sulfonic acid **22** was prepared (66%), which then was converted into sulfonyl chloride **25** (66%) (Scheme 9). This chloride was treated with aqueous ammonia affording sulfonamide **26** (89%) and subsequent thermal cyclization gave sulfonimide **27** (57%). $NaBH_4$ reduction of this imine afforded the new chiral auxiliary (2*R*)-fenchano-8,2-sultam **14** with 83% yield.



Scheme 9. *The synthesis of dienofile* ***28a***.

Chiral auxiliary **14** was acylated with fumaroyl chloride in the presence of NaH to give *N*,*N*'-fumaroyl bis-fenchano-8,2-sultam **28a**. This chiral, symmetric dienophile was applied to [4+2] cycloadditions

with cyclopenta-1,3-diene (Scheme 10). In this reaction, the influence of Lewis acids, temperature as well as solvent polarity on efficiency and diastereoselectivity was investigated. The results of these investigations were compared with fumaroyl derivative of Oppolzer's sultam **28b**. Table 1 summarizes the results of uncatalysed reactions.



Scheme 10. *The [4+2]cycloaddytion reaction of fumaroyl derivatives of sultams **28a** and **28b**.*

Table 1. *The influence of solvents on the [4+2]cycloaddytion reaction of fumaroil derivatives of sultams **28a** and **28b**.*

			***N,N*-Fumaroyl-bis-fenchane-8,2-sultam (28a)**		***N,N*-Fumaroyl-bis-bornane-10,2-sultam (28b)**	
Solvent	T [°C]	$E_T(30)$	Conversion [%]	d.e. [%]	Conversion [%]	d.e. [%]
CH_2Cl_2	-78	40.7	92	82	95	89
MeCN	+20	45.6	11	65	100	88
DMF	+20	43.8	>99	68	69	84
$PhNO_2$	+20	41.2	>99	85	100	84
CH_2Cl_2	+20	40.7	>99	85	100	84
Pyridine	+20	40.5	>99	76	100	74
$CHCl_3$	+20	39.1	71	72	100	76
THF	+20	37.4	>99	54	100	75
Toluene	+20	33.9	>99	76	100	64
CCl_4	+20	32.4	96	59	100	58

The screening began by varying the reaction medium. In all reactions, as the main product the diastereoisomer (2*R*,3*R*) was isolated. Its absolute configuration was ascertained by chiroptical analysis of the known corresponding diol (+)-(2*R*,3*R*)-**30**. The reaction of dienophile **28a** with cyclopenta-1,3-diene conducted in methylene chloride or nitrobenzene at 20°C affords (2*R*,3*R*)-**29a** with the highest diastereomeric excess of 85%. More polar solvents such as DMF or CH_3CN lead to decreased diastereoselection (68% d.e., 65% d.e., respectively), as do weakly polar solvents such as THF or CCl_4 (54% d.e., 59% d.e., respectively).

Comparison of the above results with analogous data obtained using *N,N*'-fumaroyl bis-(2*R*)-bornano-8,2-sultam **28b** (Table 1) shows that the gem-dimethyl group's location within the chiral auxiliary structure does not notably influence the substrate conversion or diastereomeric excess of the [4+2]cycloaddition products. Moreover, the sense of asymmetric induction is the same for both dienophiles and as the main product the (2*R*,3*R*)-diastereoisomer was obtained.

Next, I focused my attention on studying the influence of the Lewis acid on cycloaddition to cyclopenta-1,3-diene (Scheme 10). (**H5)**[5] Interestingly, the use of $TiCl_4$ as a catalyst results in an

inversion of asymmetric induction compared to uncatalyzed reaction (Table 2). Therefore a series of experiments were conducted to determine the catalyst concentration influence on reaction yield and diastereoselectivity. It was noticed that increasing the amount of $TiCl_4$ from 0.25 to 2.5 mol equivalent resulted in a remarkable reaction yield decrease from 98% to 34%. Simultaneously diastereoselectivity rose from 9% to 27% d.e.

Table 2. *Influence of Lewis acids on [4+2]cycloaddition reaction of fumaroyl derivatives* ***28a****.*

Lewis acid	Equvalents	Conversion (%)	d.e. (%)	Absolute configuration
$TiCl_4$	0.25	98	-9	(2S,3S)
$TiCl_4$	0.5	98	-11	(2S,3S)
$TiCl_4$	1.0	99	-20	(2S,3S)
$TiCl_4$	1.5	73	-27	(2S,3S)
$TiCl_4$	2.5	34	-25	(2S,3S)
$TiCl_3$(O*i*-Pr)	1.0	97	87	(2R,3R)
$TiCl_2$(O*i*-Pr)$_2$	1.0	99	89	(2R,3R)
TiCl(O*i*-Pr)$_3$	1.0	61	82	(2R,3R)
Ti(O*i*-Pr)$_4$	1.0	58	80	(2R,3R)
$AlCl_3$	1.0	98	89	(2R,3R)
$AlCl_2Me$	1.0	93	83	(2R,3R)
$AlCl_2Et$	1.0	90	88	(2R,3R)
$AlClMe_2$	1.0	99	99	(2R,3R)
$AlClEt_2$	1.0	27	88	(2R,3R)
$AlMe_3$	1.0	99	35	(2R,3R)
$AlEt_3$	1.0	31	80	(2R,3R)
$SnCl_4$	1.0	99	99	(2R,3R)

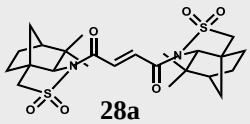
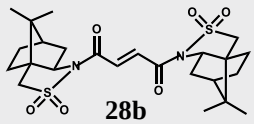
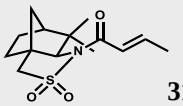
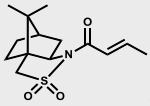
Surprisingly, replacing one chloride atom in $TiCl_4$ with an iso-propyl group again changed the sense of asymmetric induction and led to (2*R*,3*R*)-diastereoisomer with 87% d.e. and 97% yield. Replacement with three or four iso-propoxide ligands resulted in both poorer conversions (58–61%) and poorer diastereoselectivities (80–82%). Application of aluminum trichloride or alkyl aluminum derivatives gave (2*R*,3*R*)-diastereoisomer with stereoselectivity and conversion up to 99%. However, cycloaddition catalyzed with $SnCl_4$, a structural analog of $TiCl_4$, brought another surprising result: in comparison with $TiCl_4$ (27% d.e., (2*S*,3*S*)-diastereoisomer) the use of $SnCl_4$ yielded only practically pure (2*R*,3*R*)-diastereoisomer.

To explain this intriguingly different behavior of these structurally similar Lewis acids, I performed comparative IR studies of dienophiles **28a** and **28b** complexes. Towards this end IR spectra of free **28a** and **28b** as well as *N*-crotonoyl-fenchano-8,2-sultam **31** and *N*-crotonoyl-bornano-8,2-sultam **32** and their 1:1 complexes with $TiCl_4$ and $SnCl_4$ were recorded (Table 3).

In the spectra of free dienophiles **28a**, **28b**, **31** and **32**, C=O and SO_2 absorption bands are clearly visible. In complexes, however, new νC=O bands appear, evidence of strong interactions of this group with Lewis acids. Furthermore, in the presence of $TiCl_4$, the νC=O stretching at 1683cm^{-1} totally disappears for the camphor sultam derivative **32,** while a weak residual signal from uncomplexed dienophile remains for compounds **28a**, **28b** and **31**.

In the case of complexes with $SnCl_4$ new νC=O bands appear, which shows that this weaker Lewis acid also coordinates to the C=O bond. The only exception is *N*,*N*'-fumaroyl bis-(2*R*)-bornano-8,2-sultam **28b** complexation with $SnCl_4$, which did not modify the νC=O band. In contrast to $TiCl_4$ complexation, the intensity of the new bands for $SnCl_4$ coordination is the same or weaker than bands corresponding to uncomplexed dienophile.

Table 3. *Results of infrared spectroscopy study of chiral derivatives **28a**, **28b**, **31** and **32**. The relative intensity of the bands: s-strong, m-medium, in-weak.*

	 **28a**			 **28b**		
	pure	**1:1 $TiCl_4$**	**1:1 $SnCl_4$**	**pure**	**1:1 $TiCl_4$**	**1:1 $SnCl_4$**
νC=O	1674s	1681w	1674m	1676s	1679m	1676s
νC=O···		**1563s**	**1654m**		**1560s**	
ν_aSO_2···		**1404s**			**1413s**	
ν_aSO_2	1341s	1347s	1336s	1340s	1364s	1340s
	 **31**			 **32**		
	pure	**1:1 $TiCl_4$**	**1:1 $SnCl_4$**	**pure**	**1:1 $TiCl_4$**	**1:1 $SnCl_4$**
νC=O	1682s	1682w	1682m	1683s		1683s
νC=O···		**1532s**	**1559w**		**1528s**	**1528s**
ν_aSO_2···		**1396s**	**1441w**		**1410m**	**1412m**
ν_aSO_2	1336s	1338s	1337s	1332s	1338s	1336s

In the analyzed IR spectra, changes of the asymmetric SO_2 stretching band also appear. Complexation of the crotonyl derivatives **31** and **32** with either $TiCl_4$ or $SnCl_4$ causes the development of new band which clearly shows coordination of these Lewis acids to SO_2 group. However for fumaroyl derivatives **28a** and **28b**, only $TiCl_4$ coordination causes new ν_aSO_2 band appearance.

These facts suggest that $TiCl_4$ coordinates strongly and $SnCl_4$ less strongly to all dienophiles studied. This strong $TiCl_4$ coordination could be explained in terms of chelate formation between titanium atom and C=O and SO_2 groups. However, $SnCl_4$ coordinates only to C=O group. $TiCl_4$/$SnCl_4$ chelation of **31** is less favored than **32** due to the presence of the gem-dimethyl group at C(3) of the norbornane ring.

Based on both these comparative IR analyses and the X-ray structure analyses of **31** and **32**[23], I suggest the following hypothesis to rationalize the observed stereochemical course of [4+2]cycloaddition of these dienophiles to cyclopenta-1,3-diene (Scheme 10). The X-ray analyses showed, in both cases, a thermodynamically more stable anti SO_2/C=O s-*cis* C=O/C=C conformation (Figure 6). In both cases, the N atom is pyramidalized in the same direction, but the absence of the C(7) gem-dimethyl substitution in crotonyl derivative **31** allows its S=O(2) bond to adopt a pseudoaxial orientation, in contrast to **32**, which projects its S=O(1) substituent in the opposite pseudoaxial direction.

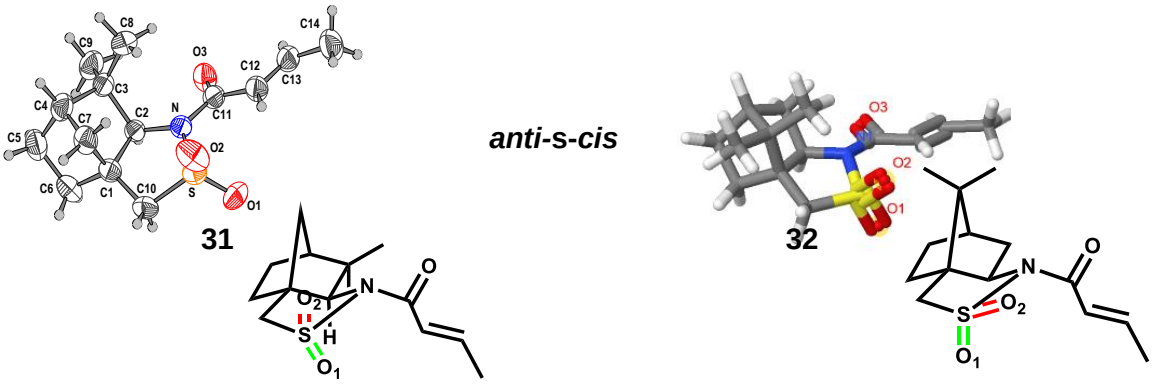


Figure 6. *The crystallographic structures of* ***31*** *and* ***32****.*

The change of relative orientation of S=O groups influence the $TiCl_4$ chelation mode to compounds **31** and **32.** As Figure 7, structure **G** shows, in **32**-$TiCl_4$ complex, the titanium atom coordinates to both S=O(2) and C=O groups. Thus one of the apical Ti–Cl substituents is directed towards the C(7) atom, sterically reinforcing the p-facial shielding of both the Me(8) and C(3) atoms and favoring an attack on the Cα-*re* face.

In the **31**–$TiCl_4$ chelate, by contrast, the titanium atom coordinating to a pseudoequatorial S=O(1) bond orientates both the bottom apical Ti–Cl atom and the Me(9) on the opposite face to the C(3)–Me(8) moiety (Figure 7, structure **H**). As a consequence, both π-faces are sterically hindered and this may possibly explain the poor and reverse selectivity, as well as the lower reactivity of **28a** in the presence of an excess of $TiCl_4$.

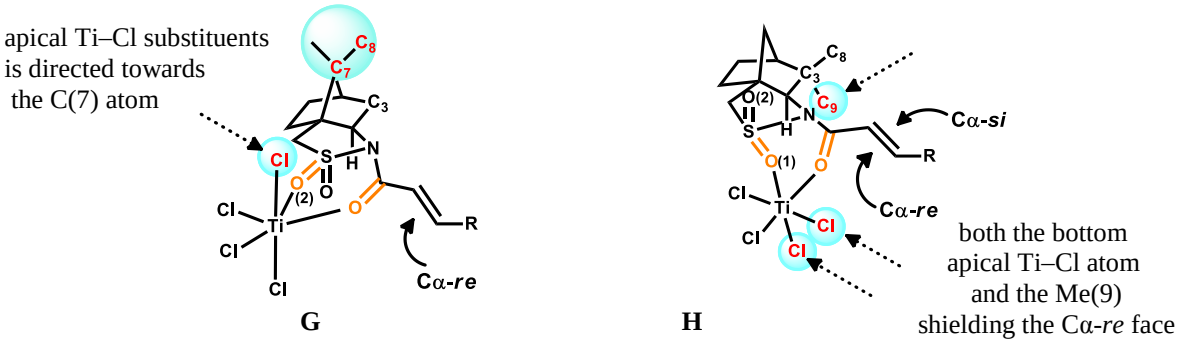


Figure 7*. The structure of complexes of crotonyl derivatives of Oppolzer's sultam* ***13*** *and* ***14*** *with* $TiCl_4$*.*

Due to dipole-moment interactions, *N*-acyl-substituted (2*R*)-bornane-10,2-sultam derivatives are known, in the solid state, to be mostly in the thermodynamically more stable SO_2/C=O *anti*-periplanar conformation. This fact, supported by more than two hundred X-ray-structure analyses, has strongly influenced, under nonchelating conditions, rationalizations for the origin of the diastereoselectivity of this widely used chiral auxiliary. It is also known that the *syn*-periplanar conformation could lead to a more reactive species and thus could potentially participate in the course of the reaction by displacing the *anti*/*syn* equilibrium. This higher reactivity is believed to result from a better electronic delocalization on the sultam moiety through a more planar N-atom. Most of these exceptional *syn*-examples concern substrates which possess a heteroatom in the *β*-position, often connected to a sp^2 C(α)-atom. To study the interactions of the *β*-heteroatom lone pair(s) (lp) with both the SO_2 and C=O moieties, as well as its influence on the *anti*/*syn*-conformations, I decided to prepare some new, simple, conformationally rigid derivatives **33**, **34**, **35**, shown in Figure 8. (**H2**)[10]

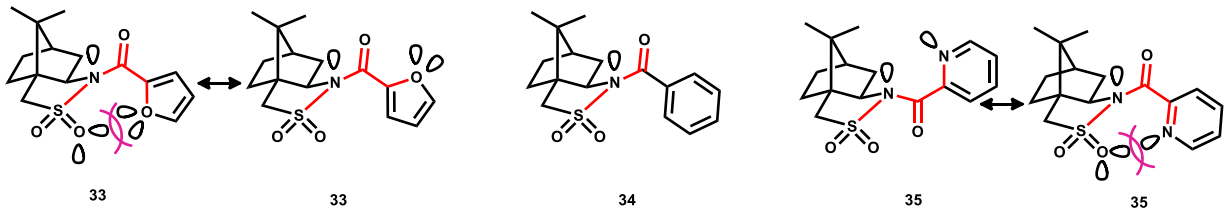


Figure 8. *The structure of N-aryl derivatives of (2R)-bornane-10,2-sultam* ***33****,* ***34*** *and* ***35****.*

The X-ray-structure analysis of **33** showed that although this compound possesses a heteroatom with lone pairs in the *β*-position, it adopts SO_2/C=O *anti*, O=C-C-O s-*cis* disposition similar to derivative **34**, lacking a heteroatom in its aromatic ring. Calculations confirmed that this conformer is indeed the most stable as compared to both the *anti*-s-*trans* and *syn*-s-*trans* conformations, although only by a small difference of approx. 1.1– 1.6 kcal/mol. This may be rationalized in terms of inefficient interference of furan lone pairs with the *syn*-carbonyl lone pair because the furan lone pairs are out of the N-C(1)=O plane. On the other hand, this out-of-plane disposition also disfavors an *anti*-s-*trans* disposition, due to electronic/electrostatic interactions with both S=O substituents.

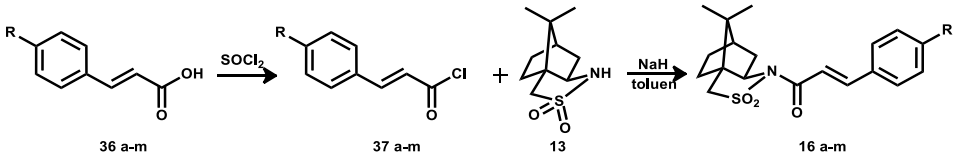
Theoretical calculation for derivative **35** shows that *syn*-s-*trans* conformation is 1.8 kcal/mol higher in energy compared to the *anti*-s-*trans* conformer. Nonetheless, *syn*-s-*trans* conformation can be observed in the X-ray structure of **35**. In fact, three conformers are present in the crystalline cell. Two of them are very similar and express the more stable *anti*-s-*trans* conformer (differing only in terms of picoline nitrogen atom lone pair disposition) while the third one shows the expected *syn*-s-*trans* conformation. All three conformers show trans arrangement of C=O and picoline nitrogen atom. In *anti*-s-*trans* conformers this disposition results in electronic/electrostatic repulsions between the heteroatom lone pair and lone pairs of oxygen atoms of SO_2 group. Only *syn*-s-*trans* conformer does not experience this repulsion. I demonstrated that, with an appropriately designed model compound, it is possible to observe, in the solid state, the higher energy *syn*-s-*trans* conformer of an *N*-acyl-substituted (2*R*)-bornane-10,2-sultam derivatives.

The results presented in this section of this report allow for detailed analysis of the mechanism of sulfonation of camphor and its derivatives. Application of the new, dienophile-containing chiral auxiliary **14** to studying the stereochemical course of [4+2]cycloaddition revealed that gem-dimethyl substituent deposition has a great influence on the sense of asymmetric induction of $TiCl_4$ catalyzed reactions. Based on X-ray-structure analysis of dienophiles **31** and **32** and IR analysis of their complexes, a stereochemical model of Lewis acid catalyzed [4+2]cycloaddition was proposed. I also succeeded in direct observation of the higher energy *syn*-s-*trans* conformer of an *N*-acyl-substituted (2*R*)-bornane-10,2-sultam derivative in the solid state.

4. The 1,4-Addytion reaction of Grignard reagents to *para*-substituted (2*R*)-*N*-cinnamoyl-bornane-10,2-sultams (16a-m). The synthesis of Tapentadol (17).

Most mechanistic studies on stereoselective reactions with (2*R*)-bornane-10,2-sultam auxiliary concentrate on the influence of this chiral auxiliary on the C(*α*) atom of its *N*-alkanoyl derivatives. By contrast, its steric influence on the remote C(*β*) atom is almost inexistent. Therefore, I conducted a series of 1,4-additions of simple Grignard reagents to *para*-substituted (2*R*)-*N*-cinnamoyl-bornane-10,2-sultam derivatives (**16a-m**) to specify the stereoelectronic influence of this chiral auxiliary on the C(*β*) atom (**H6**, **H7**).[14,15] Towards this end, thirteen cinnamamide derivatives

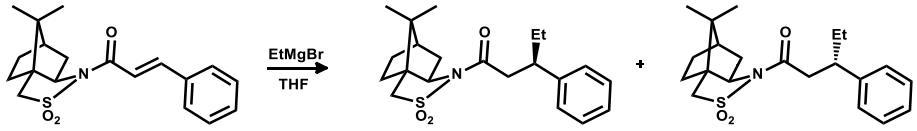
possessing different EWG/EDG groups at *para*-position of the phenyl ring were prepared (Scheme 11).



R=a	**-H**
b	**-OBn**
c	**-Cl**
d	**-Br**
e	**-Me**
f	**-OMe**
g	**-CF_3**
h	**-CN**
i	**-OCF_3**
j	**-SO_2Me**
k	**-SMe**
l	**-F**

Scheme 11. *The synthesis of para-substituted (2R)-N-cinnamoyl-bornane-10,2-sultams* ***16a-m****.*

I started my research by searching for optimal conditions for the 1,4-addition reaction. For this purpose I studied the reaction of ethyl magnesium bromide with Oppolzer's sultam cinnamamide derivative **16a** at different temperatures (Scheme 12). These studies revealed the crucial role of temperature on the conformational equilibrium, with the diastereoselectivities of such reactions being greatest at low temperatures (Table 4). (**H6**)[14]



Scheme 12. *The EtMgBr addytion of cinnamoyl derivative of sultam* ***16a****.*

T	d.e.
0	59
-18	68
-42	68
-63	72
-78	73

Table 4. *The EtMgBr addition of cinnamoyl derivative of sultam* ***16a*** *at different temperatures.*

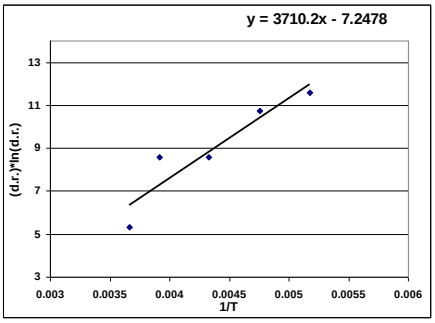
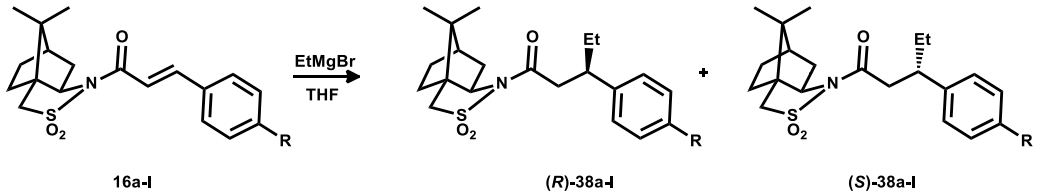


Figure 9. *Eyring plot for* ***16a****.*

Determination of the Eyring plot (1/T vs dr*ln dr) (Figure 9) allowed me to determine the corresponding enthalpic ($\Delta\Delta H^{\#}$= 0.59 kcal/mol) and entropic ($\Delta\Delta S^{\#}$=0.73 cal/(K mol)) factors, obtained from the slope and the intercept, respectively. These values are close to those already reported for the transition states of Diels-Alder reactions, for similar dienophiles.

Steric influence of the nucleophile on 1,4-additions of Grignard reagents of increasing bulkiness were also studied (**H6**).[14] I observed that sterically nondemanding EtMgCl reagent gave product (*R*)-**38** with 78% d.e. The use of the more bulky *n*-BuMgCl nucleophile led to a considerable decrease in diastereoselectivity (58%), while i-PrMgCl afforded the desired product with only 46% d.e. Thus, as the bulkiness of the incoming Grignard reagent increases, the steric directing influence gains in importance and, consequently, the diastereoselectivity decreases due to the poor steric differentiation of the chiral auxiliary on the remote C(*β*) atom.

Next, a series of 1,4-additions of ethyl magnesium bromide to derivatives (**5a-m**) at -78 °C were performed (Scheme 13).



Scheme 13. *The 1,4-addytion of EtMgBr to derivatives 16**a-l**.*

The obtained mixtures of diastereomers were analyzed by means of ^{1}H NMR. Specifically, integration of the Me(8) signals (gem-dimethyl group) of the two diasteroisomers directly provided the diasteromeric ratio of the investigated reaction (Table 5). The investigated compounds are arranged in Table 5 according to the Hammett constant σ-para. This parameter is related to the total polar effect exerted by substituent on the reaction centre. Linear dependence of σ-para and diasteromeric excess can be clearly seen from Table 5. The highest diastereoselectivity in 1,4-additions of EtMgBr was achieved for *N*-cinnamoyl substrates bearing electron donating substituents (Figure 10). However *α,β*-unsaturated substrates with substituents possessing fluoride atoms (-F, CF_3, -OCF_3) deviate appreciably from the calculated line. Intrigued by this discrepancy, I sought an alternative simple method for diasteromeric excess determination. I discovered that two distinct diastereotopic signals can be observed in the ^{19}F NMR spectrum, allowing d.e. to be calculated (**H7**).[15] The resulting d.e. values are lower and better match the linear correlation between the diastereoselectivity σ-para *Hammett* electronic parameter (d.e.^{1}H vs ^{19}F: R=F 78% vs 74%, R=OCF_3 73% vs 68%, R=CF_3 62% vs 60%).

Table 5. *The 1,4-addytion reaction of Grignard reagent to sultam derivatives **16a-l***

R	σ	d.e. (%)	d.r.	log(d.r.)
-OBn	-0.41	79	8.5	0.93
-OMe	-0.27	75	7.0	0.85
-Me	-0.13	79	8.7	0.94
-H	0	73	6.4	0.81
-SMe	0.06	77	7.7	0.89
-F	0.15	78	8.7	0.94
-Cl	0.24	67	5.1	0.71
-Br	0.27	64	4.6	0.66
-OCF_3	0.35	73	6.7	0.83
-CF_3	0.53	62	4.26	0.63
-CN	0.70	49	2.9	0.46
-SO_2Me	0.73	45	2.65	0.42

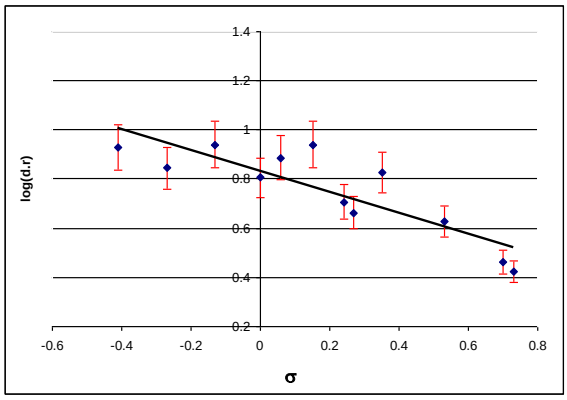
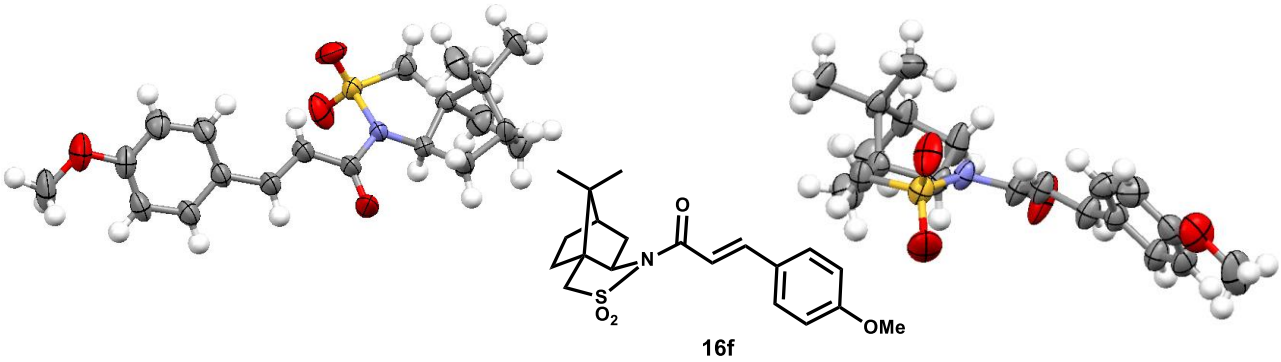


Figure 10. *The plot of the results from Table 5.*

The above results and the resulting conclusion had a great impact on our further studies, prompting me to look closer at stereoelectronic effects. However, the influence of these effects on diastereoselctivity is much more difficult to study and less intuitive to understand.

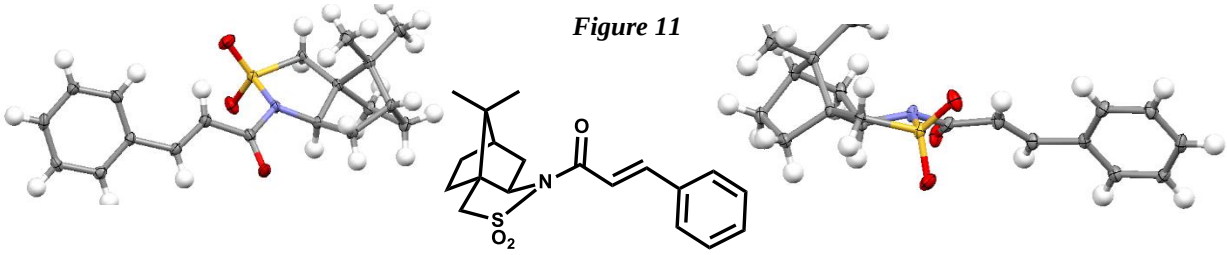
I attempted to illustrate the stereoelectronic effects of Oppolzer's sultam chiral auxiliary on the basis of the influence of the sultam-ring nitrogen atom lone pair on the C(*β*) atom. Thus I analyzed the X-ray structures of three obtained *N*-cinnamoyl derivatives bearing substituents of outermost electronic character (R=NO_2, H, OMe[23])). (**H6**)[14] Regardless of this, all the derivatives studied

adopted both an *anti* disposition of C=O and SO_2 groups and s-*cis* disposition of C=O and C=C bonds, as shown in Figures 11, 12 and 13. The strongest pyramidalization of the sultam-ring nitrogen atom was observed for compound **16f** possessing a strongly electron-donating -OMe group (ΔhN=0.351). Contrarily, the electron-poor p-nitro-cinnamoyl derivative **16m** is almost planar (ΔhN=0.191), whereas the nitrogen atom pyramidalization of unsubstituted N-cinnamoyl derivative **16a** is intermediate (ΔhN=0.285).



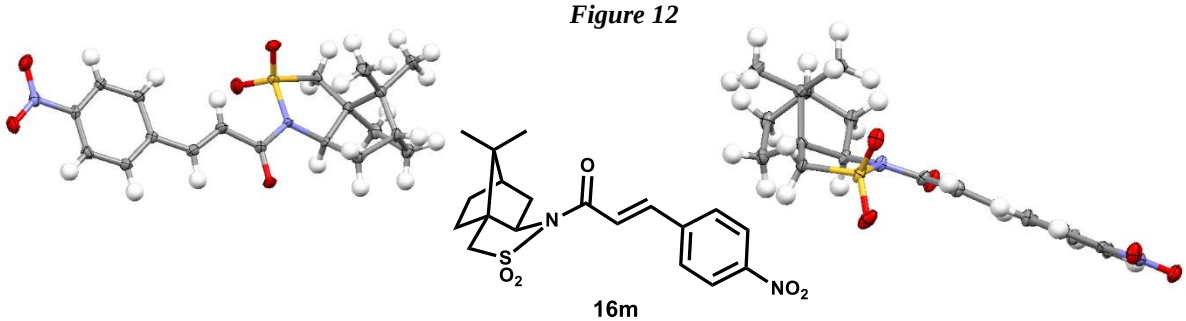
16f

Figure 11



16a

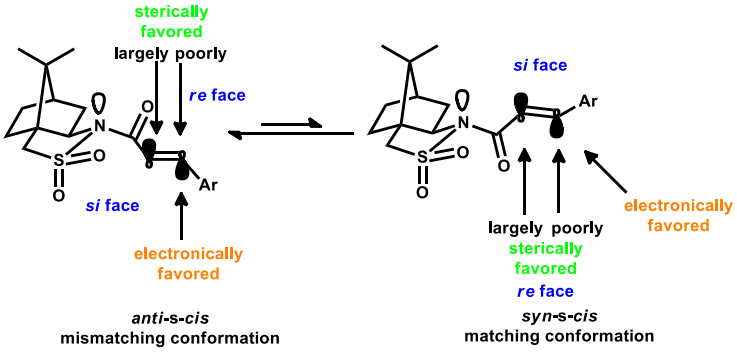
Figure 12



16m

Figure 13

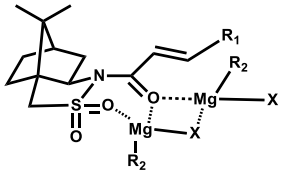
In order to rationalize the observed diastereoselectivity and changes in sultam-ring nitrogen atom pyramidalization, I propose the following stereochemical model. As Scheme 14 shows, in *anti*-s-*cis* conformation, the stereoelectronic effects favor *si*-face approach whereas steric factors favor the opposite *re*-face.



Scheme 14. *The influence of the stereoelectronic effects on observed diastereoselectivity.*

This means mismatch effects occurred in this conformation. In thermodynamically less stable, but more reactive *syn*-s-*cis* conformer both steric and stereoelectronic effects favor the same *re*-face. Thus lower reactivity and diastereoselectivity of electron-withdrawing substituted cinnamoyl derivatives can be rationalized by the fact that the more planar nitrogen atom facilitates better conjugation between C=C, C=O and SO_2 groups. This induces more difficulties in reaching a *syn*-s-*cis* cooperative disposition, and thus results in lower diastereoselectivity of 1,4-additions.

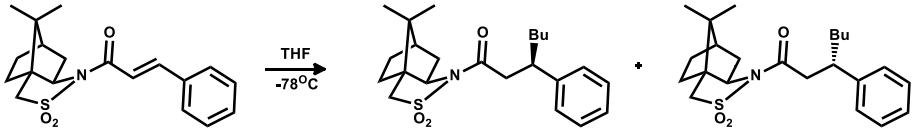
The next part of my studies on 1,4-additions of Grignard reagents to *para*-substituted (2*R*)-*N*-cinnamoyl-bornane-10,2-sultam derivatives (**16a-m**), was devoted to the investigation of the mechanisms involved in the above process. Previous studies assumed that it is necessary to use an excess of at least 2.0 mol. equiv. of Grignard reagent for a complete conversion. It is known, however, that alkyl/aryl magnesium chlorides and bromides exist in solution as aggregates (mainly dimers). It is established that during organomagnesium 1,4-addition to α,β-unsaturated carboxylic acid derivatives, coordination of dimmeric species occurs. One magnesium atom chelatees C=O and SO_2, forcing *syn*-s-*cis* substrate conformation and enabling alkyl/aryl group addition from the "bottom" of the double bond (*re*-face) (Figure 14). On the other hand, organomagnesium iodides rarely form aggregates; therefore, they should not be effective nucleophiles in 1,4-addition.



1,4-addytion from bottom of double bond

Figure 14. *Model of bimetallic complex.*

In a control experiment, treatment of (2*R*)-N-cinnamoyl-bornane-10,2-sultam **16a** with 2.2 mol-equiv. of BuMgI gave product with very low yield and only 29% d.e., confirming the above assumptions (Scheme 15). (**H6**)[14]



16a (*R*)-38a-Bu (*S*)-38a-Bu

conditions	yield	d.e. (%)
2.2eq BuMgI	very low	29
1.1eq $MgBr_2$; 1.1eq Bu_2Mg	83	72
1.1eq $MgBr_2$; 1.1eq BuMgCl	96	72
1.1eq $ZnBr_2$; 1.1eq BuMgCl	22	41

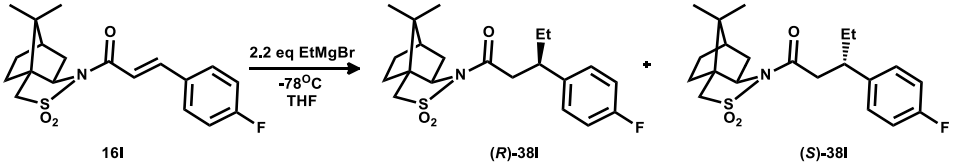
Scheme 15. *The use of 1 equiv. of Grignard reagent in the presence of 1 equiv. of inorganic salt in 1,4-addition reaction.*

Organomagnesium compounds remain in solution in a Schlenk equilibrium ($2RMgX \leftrightarrow MgX_2 + R_2Mg$.). Thus the use of simple magnesium salt in conjunction with dialkylmagnesium should result in similar course of the reaction as for Grignard reagents. Thus I treated the solution of (2*R*)-*N*-cinnamoyl-bornane-10,2-sultam **16a** with $MgBr_2$ and Bu_2Mg. (**H6**)[14] This experiment worked very well, and after complete conversion, **(R)-38a-Bu** was isolated in 83% yield and 72% d.e. This $MgBr_2$ chelating experiment was repeated, but with 1.1 mol-equiv. of BuMgCl as nucleophile, affording product in 96% yield and 72% d.e. Application of $ZnBr_2$ instead of $MgBr_2$ resulted in

considerably lower reaction yield and diastereoselectivity. This suggested that the nature of the chelating salt has a strong impact on 1,4-additions to α,β-unsaturated carboxylic acid derivatives.

The results of this research have practical consequences, showing that one molar equivalent of Grignard reagent can be used in conjunction with chelating salt. This can be especially important when Grignard reagent requires a long preparation sequence.

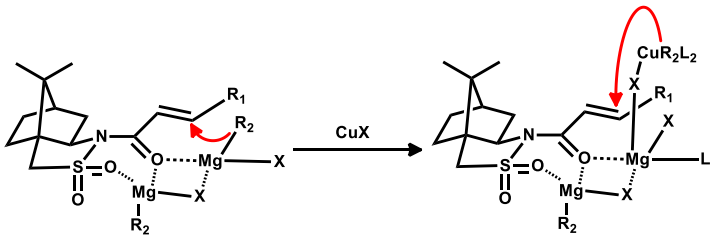
Interestingly, reaction of *para*-fluoride substituted cinnamoyl derivative **16l** with EtMgBr in the presence of copper (I) bromide or iodide gave **(S)-38l**, albeit with low diastereoselectivity (Scheme 16).(**H7**)[15]



additives	convesion	d.e. (%)
1.1 eq CuBr	>99%	-37%
1.1 eq CuI	>99%	-17%

Scheme 16. *The use of copper salts in 1,4-addition reaction of Grignard reagents.*

This product had the inverse absolute configuration as compared to all other products obtained during our studies. This unusual behavior of copper salts requires a new stereochemical model (Scheme 17). I propose the formation of a trimetallic complex, were the CuI is connected, via one of its substituents, to the apical position of the non-chelated Mg atom, opposite to the pseudo axial S=O, thus adding the R_2 nucleophile on the top of the s-*cis* conformer.



syn*-s-*cis
1,4-addytion from
bottom of double bond

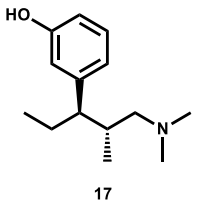
syn*-s-*cis
1,4-addytion from
top of double bond

Scheme 17. *The bismettalic model vs. trimettalic one.*

In summary, my studies regarding 1,4-additions of Grignard reagents to *para*-substituted (2*R*)-*N*-cinnamoyl-bornane-10,2-sultam derivatives (**16a-m**) allow for correlation of reaction diastereoselectivity with the Hammett constant σ-para. Crystallographic studies helped to elucidate the stereoelectronic influence of Oppolzer's sultam chiral auxiliary on the C(β) atom. Instead of the mechanism commonly accepted in the literature for 1,4-additions of Grignard reagents to α,β-unsaturated carboxyl substrates, which assumes the coordination of dimeric species and takes advantage of a Schlenk equilibrium, I have proposed a new hypothesis. Specifically, I have proposed and experimentally confirmed that one equivalent of simple magnesium salt in conjunction with one equivalent of dialkylmagnesium or Grignard reagents can be effectively used in 1,4-additions. My studies also gave results (EtMgBr+CuX) that cannot be rationalized on the basis of well accepted mechanisms. Therefore I have proposed a new model that assumes the formation of trimetallic

complex (Mg-X-Mg-X-Cu). This model explains the inversion in configuration observed for product formed in the presence of copper bromide or iodide salts.

In parallel to the mechanistic study, I also focused on searching for organic compounds, to the synthesis of which I could apply our experience gained during the study of 1,4-addition of Grignard reagents to chiral derivatives of *α,β*-unsaturated acids. My attention was drawn to the medicine Tapentadol (**17**) (Figure 15). (**H8**)[16]

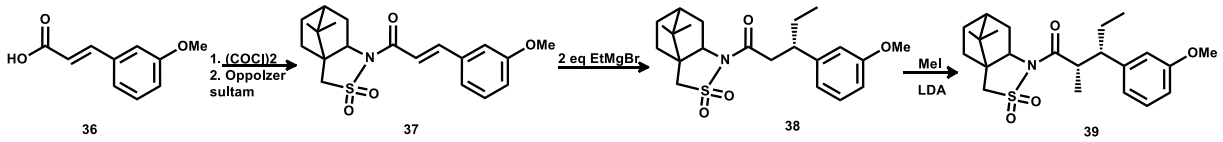


17

Figure 15*. The stucture of Tapentadol.*

This strong painkiller is a very useful complement to analgesic drugs currently in use, such as morphine. It has the advantages of being non-addictive in nature and also causing fewer side effects felt by patients.[24] However, only one of four possible stereoisomers of this analgesic agent is approved for clinical use. This is why searching for new, stereoselective methods for its synthesis is so important.

The method of Tapentadol synthesis I explored started from synthesis of suitable chiral *α,β*-unsaturated derivatives **37**. Then, compound **37** was subjected to 1,4-addition reaction of EtMgBr resulting in derivative **38** with 72% yield and 67% d.e. Single crystallization of the mixture of diastereoisomers yielded clean diastereisomer (*R*)-**38** (Scheme 18). In the next step, using methyl iodide in the presence of a strong base (LDA), proper enol was alkylated to form derivative **39**. The rest of the synthetic steps have to rely on removing the chiral auxiliary and converging the functional groups present.

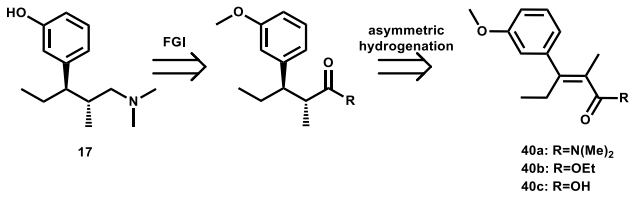


36 37 38 39

Scheme 18. *The asymmetric synthesis of precursor **39**.*

Unfortunately, while my research was underway, a manuscript was published that described synthesis of Tapentadol using a strategy similar to mine, applying the Evans chiral auxiliary.[25] This led me to halt my work on using the asymmetric 1,4-addition reaction for the synthesis of Tapentadol. Nevertheless, this molecule still remains in my scope of interest. Therefore, I have proposed a new synthetic strategy that allows for both new stereogenic centers to be introduced in one synthetic step, using asymmetric hydrogenation reaction of carboxylic α,β-unsaturated derivatives **40a-c** (Scheme 19). (**H8**)[16] This work shows the practical aspect of mechanistic study presented so far, this strategy is general and can be a valuable complement to the synthesis of carboxylic acids and their derivatives containing alkyl or aryl substituents in *α* and *β* positions.

[24] Frampton J. E., *Drugs*, **2010**, *70*(13), 1719-1743
[25] Qiang Z., Jian-Feng L., Guang-Hui T., Rong-Xia Z., Jin S., Jin S., Xin F., Du F., Xiang-Rui J., Jing-Shan S., Tetrahedron: *Asymmetry*, **2012**, *23*, 577-582.



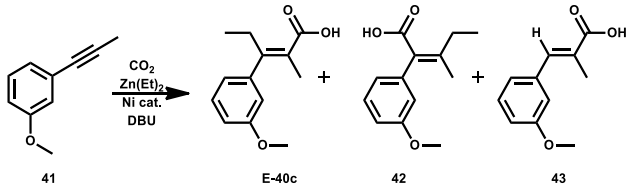
Scheme 19. *The retrosynthesis of Tapentadol.*

The essential substrates for the asymmetric hydrogenation are suitably multi-substituted alkenes. However, the effectiveness and stereoselectivity of traditional double bond formation methods such as Wittig or Horner-Wadsworth-Emmons reactions are usually unsatisfactory for the preparation of tetrasubstituted olefins. Therefore, other synthetic methods are more applicable for the preparation of multisubstituted alkenes. These include the coupling of substituted vinyl halides with organmetallic compounds, elimination reaction, carbometallation of alkynes and carbonyl olefination. After analyzing the literature, I chose several methods that could be of practical application in the regioselective synthesis of tetrasubstituted derivatives of $\alpha\beta$-unsaturated carboxylic acids (**E-40a-c**).

My first attempt involved stereoselective synthesis using method based on reductive elimination of tetrasubstituted-epoxydes or α,β-halohydrynes with SmI_2.[26] Unfortunately, even though I tested many modifications in reaction conditions, including addition of different additives (e.g. HMPA), I was able to obtain the desired product with medium yield and low regioselectivity (max. 60% yield, E/Z 2.8:1).

Next I shifted my attention to ketone olefination by ynolates.[27] Unfortunately, this reaction procedure was unrepeatable, and the best result was 50% yield and 6.7:1 E/Z regioselectivity of major product.

Continuing our search for a more effective and stereoselective synthetic method for tetrasubstituted derivatives of α,β-unsaturated carboxylic acids, I considered the promising approach to such compounds developed by Mori at al.[28] This method is based on nickel-catalyzed addition of carbon dioxide and organozinc reagent to disubstituted alkynes. The proposed mechanism of this reaction excluded the formation of unwanted Z stereoisomer, though the formation of other side products such as isomer **42** or trisubstituted acid (**43**) cannot be ruled out. The synthesis of the desired alkene **E-40c**. (Scheme 20).



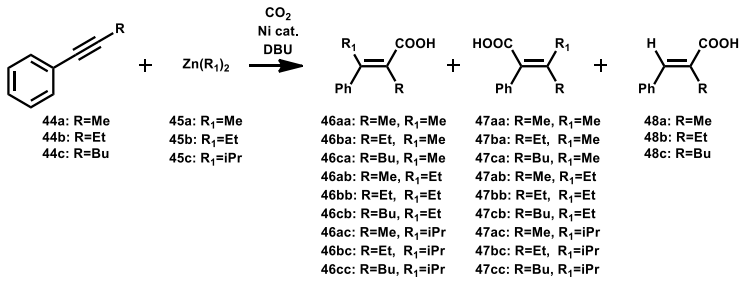
Scheme 20. *The carbometallation reaction.*

The carbometallation reaction of alkyne **41** with diethyl zinc in CO_2 atmosphere, in the presence of $Ni(cod)_2$ (biscyclootadiene nickel (0)) as catalyst and DBU, led to the desired product **E-40c** with 89% isolated yield. I found that pure carboxylic acid could be isolated from the reaction

[26] a) Concellón J. M., Pérez-Andrés J. A., Rodríguez-Solla H. *Chem.Eur.J.*, **2001**, *7*, 3062-3068. b) Concellón J. M., Bardales E., *Org. Lett*., **2002**, *4*, 189-191 c) Concellón J.M., Bardales E., *J. Org. Chem.*, **2003**, *68*, 9492-9495.
[27] Shindo M., Matsumoto K., *Top Curr Chem*, **2012**, *327*, 1–32.
[28] Mori M., *Eur. J. Org. Chem*., **2007**, 4981–4993.

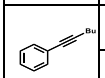
mixture without needing chromatographic purification. The reaction mixture can be purified via bulb to bulb distillation, leading to the separation of clean regioisomer **E-40c**.

To explore the scope of the carbometallation reaction, various alkynes and organozinc reagents were examined (Scheme 21, Table 6).



Scheme 21. *The influence of substituents in alkyne and organozinc compounds on the carbometallation reaction.*

Table 6. *The scope of the carbometallation reaction.*

	$Zn(Me)_2$[a]	$Zn(Et)_2$[a]	$Zn(iPr)_2$[a]
	**44a:46aa:47aa:48a**	**44a:46ab:47ab:48a**	**44a:46ac:47ac:48a**
	41 : 59 : 0 : 0	15 : 61 : 12 : 12	10 : 25 : 5 : 60
	**44b:46ba:47ba:48b**	**44b:46bb:47bb:48b**	**44b:46bc:47bc:48b**
	20 : 66 : 7 : 7	17 : 55 : 11 : 17	40 : 20 : 0 : 0
	**44c:46ca:47ca:48c**	**44c:46cb:47cb:48c**	**44c:46cc:47cc:48c**
	38 : 62 : 0 : 0	21 : 54 : 14 : 10	34 : 15 : 0 : 51

[a] 0.4 mmol of alkyne in 0.5ml THF, 1.2 mmol of organozinc reagent, 4 mmol DBU, 0.08 mmol $Ni(cod)_2$ in 1ml THF, 1atm CO_2, 0°C, the ratio of products was determined based on ^1H NMR analysis.

The influence of the size of the aliphatic substituent of the alkyne on conversion and product yield is rather modest, yet the steric hindrance of the organozinc reagent, by contrast, has a major effect on the product distribution. In the case of $Zn(Me)_2$ the product **46** was observed with 60% yield without formation of side products **48a-c** and **47**. Whereas for $Zn(Et)_2$ a higher conversion of the substrate was observed in favor of unwanted isomer **47** and trisubstituted alkene **48a-c**. Due to the significant steric hindrance of $Zn(iPr)_2$, the Ni-promoted catalyzed carboxylation reaction led mainly to alkene **48a-c**, a product of only CO_2 addition without subsequent organozinc addition.

However, while $Ni(cod)_2$ is an efficient catalyst for carbometallation reaction, it is very air- and water-sensitive and its application requires the use of a glovebox. Therefore, an air sable catalyst would greatly simplify the synthetic procedure. Towards this end I tested the application of other Ni(II) complexes in the carbometallation reaction of alkyne **41** (Scheme 20). Simple nickel (II) chloride is almost inactive in these conditions, leading to product **E-40c** with 8% yield. However, commercially available nickel (II) acetylacetonate ($Ni(acac)_2$) gave 45% of desired product **E-40c**. Then I turned my attention to $Ni(dme)Cl_2$ complex, which is commercially unavailable but easy to synthesize in one step from $NiCl_2$ and 1,2-dimethoxyethane.[29] This complex is air stable, and can be stored in a desiccator without decomposition. Application of this catalyst led to alkene **E-40c** with 61% yield. To evaluate the effectiveness of $Ni(dme)Cl_2$ in a broader scope of substrates (as done previously for $Ni(cod)_2$), the reaction of alkyne **44a** and **44b** with $Zn(Me)_2$ and $Zn(Et)_2$ reagents were examined (Scheme 21). Comparison of the results for the two catalysts revealed similar product

[29] Ward L. G. L., Pipal J. R., *Inorganic Syntheses*, **1972**, *13*, 154-164.

distribution. However, yield of major products **46** is slightly lower for Ni(dme)Cl_2 complex as compared to Ni(cod)$_2$. Nevertheless, the stability of Ni(dme)Cl_2 and its much greater ease of handling make it an alternative catalyst for carbometallation reaction, as compared to Ni(cod)$_2$.

In summary, in this part of this report I have presented work aimed at finding an effective synthetic method for the preparation of a well-known analgesic – Tapentadol. I found an efficient method of synthesis for alkene **E-40c**. A further search for a new, air-stable catalyst suitable for carbometallation reaction showed that the complex Ni(dme)Cl_2 may be an interesting complement to the catalyst already known and used in this process. Currently, I am working on asymmetric hydrogenation reaction of tetrasubstituted alkenes, which will lead to obtaining chiral derivatives of carboxylic acids containing alkyl or aryl substituents in α and β position.

5. Conclusion.

The most important achievements resulting from the studies described in this report are:

- Showing that the guanidinium group can act as a general acid catalyst, not only electrostatically supporting the leaving of hydroxyl group of ribose during the process of cleavage/transesterification of RNA (**H1**).
- Showing that thermodynamically not favored, but more reactive *syn*-s-*trans* conformation can be observed in properly designed *N*-acyl derivatives of Oppolzer's sultam (**H2**).
- Clarifying the mechanism of sulfonation reaction of camphor **18** and its isomeric derivatives **19** and **20** (**H3**).
- Developing an effective method for the synthesis of the new chiral auxiliary (2*R*)-fenchane-8,2-sultam. The use of its fumaroyl derivative in [4+2]cycloaddition reaction (**H4**). Proposing a stereochemical model of Lewis-acid-catalyzed [4+2]cycloaddition reaction of *N*,*N*-fumaroyl-(2*R*)-fenchane-8,2-sultam (**H5**).
- Finding a linear correlation between the electron-donating/accepting character of the *para*-substituent of chiral amide of cinnamic acid and the diastereoselectivity observed during nucleophilic 1,4-addition reaction (**H6**).
- Demonstrating the influence of stereoelectonic parameters that impact on the diastereoselectivity of 1,4-addition reaction and their corelation to observed changes of pyramidalization of nitrogen atom in α,β-unsaturated derivatives of Oppolzer's sultam (**H6**).
- Showing that 1,4-addition reaction of α,β-unsaturated amides can be effectively carried out with only one equivalent of Grignard reagent (**H6** and **H7**).
- Proposing a stereochemical model of trimetallic complex to describe the 1,4-addition reaction of Grignard reagent in the presence of copper salts (**H7**).
- Developing a synthetic method for the synthesis of tetrasubstituted cinnamic acid using the carbometallation reaction. Showing that Ni(dme)Cl_2 can be an effective catalyst in carbometallation reaction, which due to its air stability may be an interesting complement to the catalyst already known and used in this process (**H8**).

5. Description of other scientific achievements

5.1 Bibliographic summary of scientific achievements

Total number of publications 15
Total number of publications after Ph.D degree 11
Total Impact Factor 36.825

Citation report based on Web of Science (WoS) [Scopus] at 10.04.2016 (publications **H7** and **H8**– in press)

Total number of citations: 216 (15.4 citation per paper); [239 (18.4)]
Total number of citations (without self-citations): 187 (13.3 citation per paper); [170 (13)]
Hirsch Index: 7; [9]

5.2 List of publications before the Ph.D. degree

M1 Bauer, T., Chapuis, C., Kucharska, A., Rzepecki, P., Jurczak, J.,
"Influence of Lewis Acids on the [4+2] Cycloaddition of N,N'-Fumaroylbis[(2R)-bornane-10,2-sultam] to Cyclopentadiene and Application to Various Dienes."
Helvetica Chimica Acta, **1998**, *81* (2), 324-329. **IF**=1.833

M2 Chapuis, C., Kucharska, A., Rzepecki, P., Jurczak, J.,
„Influence of the Solvent Polarity on the Stereoselectivity of the Uncatalyzed [4+2] Cycloaddition of Cyclopentadiene to N,N'-Fumaroyldi[(2R)-bornane-10,2-sultam]."
Helvetica Chimica Acta, **1998,** *81* (12), 2314-2325. **IF**=1.833

M3 Chapuis, C., Kucharska, A., Jurczak, J.,
„A comparison of two effective chiral auxiliaries-(2R)-bornane-10,2-sultam and (2R)-bornane-10,2-cyclohydrazide-using the [4+2] cycloaddition of cyclopentadiene to their N,N'-fumaroyl derivatives."
Tetrahedron Asymmetry, **2000,** *11* (22), 4581-4591. IF= 2.386

M4 Kucharska, A., Gorczyńska, R., Chapuis, C., Jurczak, J.,
„Asymmetric Induction in the [4+2] Cycloaddition of Cyclopentadiene and Furan to Chiral Derivatives of Fumaric Acid"
Chirality, **2001**, *13* (10), pp. 631-633. **IF**=1.976

5.3 List of publications after the Ph.D. degree (except these listed in chapter 4.2)

D1 Piątek, A., Chapuis, C., Jurczak, J.,
"Synthesis of a Six-Membered Ring (2R)-Bornane-11,2-sultam and Structural Comparison with Oppolzer's, Lang's and King's Sultams."
Helvetica Chimica Acta, **2002**, *85* (7), pp. 1973-1988. **IF**=1.833

D2 Piątek, A., Chapuis, C., Jurczak, J.,
"Influence of the Solvent Polarity on the Stereoselectivity of the Uncatalyzed [4+2] Cycloaddition of Cyclopentadiene to a N,N'-Fumaroyldi Six-Membered Ring [(2R)-bornane-11,2-sultam]."
Journal of Physical Organic Chemistry, **2003**, *16* (10), 700-708. **IF**=1.211

D3 Piątek, A.M., Bomble, Y.J., Wiskur, S.L., Anslyn, E.V.,
" Threshold Detection Using Indicator-Displacement Assays: An Application in the Analysis of Malate in Pinot Noir Grapes."
Journal of the American Chemical Society, **2004**, *126* (19), 6072-6077. **IF**=6.903