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June 2007

3rd Conference on Pericyclic Reactions

New Frontiers in Theoretical Approaches and Synthetic Strategies

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SCIENTIFIC PROGRAM

Wednesday, June 13th

Afternoon

14:00-16:00		***Registration***
16:00-16:20		***Opening Ceremony***

Chairman: **Domenico Spinelli (Bologna University, Italy)**

16:20-17:20	PL1	***Albert Padwa (Emory University, USA)*** Cascade Reactions for Alkaloid Synthesis

17:20-17:50		***Tea break***

Chairman: **Giovanni Desimoni (Pavia University, Italy)**

17:50-18:30	IL1	***Volker Jäger (Stuttgart University, Germany)*** [3+2] and [2+1] Cycloadditions Related to the Quest for New Glycosidase Inhibitors
18:30-18:50	OC1	***Francesca Clerici (Milan University, Italy)*****, Donato Pocar** From Isothiazoles to New or Known Heterocycles *Via* Cycloaddition Reactions
18:50-19:10	OC2	***Alessandro Contini (Milan University, Italy)*****, Gianluigi Broggini, Michela Martinelli, Gaetano Zecchi** Regioselectivity in Intramolecular Nitrone Cycloadditions: a DFT Study on the Role of Dispersive and Weak Hydrogen Interactions
19:10-19:30	OC3	***Maria Luisa Gelmi (Milan University, Italy)*****, Sara Pellegrino, Donato Pocar** Cycloaddition Reactions: Key Reactions to Build Constrained Carbocyclic and Heterocyclic Amino Acids
19:30		**End of session**

20:30		***Welcome to participants: Refreshment offered by Chancellor of Catania University and the Mayor of the city***

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

Thursday, June 14th

Morning

Chairman: **Leon Ghosez (European Institute of Chemistry and Biology, France)**

9:00-10:00	PL2	***Janusz Jurczak (Warsaw University, Poland)***
		Enantioselective Cycloaddition Reactions: The High-Pressure Approach Revisited
10:00-10:40	IL2	***Alexander F. Klebnikov (St. Petersburg State University, Russia)***
		Recent Aspects of the Chemistry of Iminium Ylides Generated from Carbenes
10:40-11:00	OC4	**Olga Bortolini, Antonio De Nino, *Loredana Maiuolo (Calabria University, Italy)*, Antonio Procopio, Giovanni Sindona, Amedeo Tocci**
		Catalytic 1,3-Dipolar Cycloaddition of Nitrones in Ionic Liquid: an Easy Access to Isoxazolidines
11:00-11:30		***Coffee Break***

Chairman: **Harwood M. Laurence (Readings University, UK)**

11:30-12:10	IL3	***Francesco Fringuelli (Perugia University, Italy)***
		Cycloaddition Reactions in Water under Solvent Free Conditions
12:10-12:30	OC5	***Franca M. Cordero (Firenze University, Italy)*, Federica Pisaneschi, Vanni Mannucci, Alberto Brandi**
		Stereoselective Synthesis of Polyhydroxyindolizidines
12:30-13:10	IL4	***Heinz Heimgartner (Zürich University, Switzerland)***
		New Pericyclic Reactions with Thiocarbonyl Ylides
13:10		***Lunch Break***

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

Thursday, June 14th

Afternoon

Chairman: **Gianfranco Scorrano (Padova University, Italy)**

15:00-16:00	PL3	***Laurence M. Harwood (Reading University, UK)***
		Morpholinones and Dehydromorpholinones as Chiral Memory Systems
16:00-16:20	OC6	***Stefano Cicchi (Firenze University, Italy)*, Giacomo Ghini, Pierangelo Fabbrizzi, Alberto Brandi**
		The Huisgen Reaction as a Tool for the Construction of Light Harvesting Antennae
16:20-17:00	OC7	**Gregory R. Unruh, Hua Ji, *David M. Birney (Texas Tech University, USA)***
		Multiphoton Infrared Initiated Pericyclic and Pseudopericyclic Reactions
17:00-17:30		***Tea Break***
17:30		**End of Session**
		Free afternoon: Classical Drama in Syracuse's Amphitheatre: Eracle of Euripide (19:00) or Catania sightseeing tour

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

Friday, June 15th

Morning

Chairman: **Marek Chmielewski (Warsaw University, Poland)**

9:00-10:00	PL4	***Ray C. F. Jones (Loughborough University, UK)***
		Dipolar Cycloadditions: Making Pyrrolidines, Peptide Mimics, and Polycarbonyl Metabolites
10:00-10:40	IL5	***Oliver Kappe (Karl-Franz University, Austria)***
		The Use of Microwave Irradiation to Enhance Pericyclic and related Processes
10:40-11:00	OC8	***Paolo Quadrelli (Pavia University, Italy)*****, Andrea Piccanello, Pierluigi Caramella**
		The Ene Reactions of Nitrosocarbonyl Intermediates: Mechanism and Synthetic Applications
11:00-11:30		***Coffee Break***

Chairman: **Marcello Tiecco (Perugia University, Italy)**

11:30-11:50	OC9	**Paola Conti, Andrea Pinto, Lucia Tamborini, Giovanni Grazioso, Gabriella Roda, *Marco De Amici (Milan University, Italy)*, Carlo De Micheli**
		Synthesis of Novel Enantiopure 2-Isoxazoline and 2-Pyrazoline Amino Acids and their Activity at Glutamic Acid Receptors and Transporters
11:50-12:10	OC10	***René Peters (ETH Zurich, Switzerland)*****, Florian M. Koch**
		Catalytic Asymmetric Synthesis of β-Hydroxysulfonyl Derivatives
12:10-12:30	OC11	***Roberto Romeo (Messina University, Italy),*** **Pedro Merino, Daniela Iannazzo, Luisa Borrello, Antonio Rescifina**
		Synthesis of Enantiomeric Thiazofurin Analogues via Zinc(II) Triflate Controlled 1,3-Dipolar Cycloaddition under Microwave Irradiation
12:30-13:10	IL6	***Juan C. Carretero (Madrid Autonomous University, Spain)***
		Novel Chiral Sulfur Ligands in Catalytic Asymmetric Cycloadditions
13:10		***Lunch Break***

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

Friday, June 15th

Afternoon

15:00-17:00		**Poster Section**
17:00-17:30		***Tea Break***

Chairman: **Ray C. F. Jones (Loughborough University, UK)**

17:30-18:10	IL7	***Marcus Kalesse (Leibniz University, Germany)*** Pericyclic Reactions in Natural Product Synthesis
18:10-18:50	IL8	***John K. Gallos (Thessaloniki Aristotle Univrsity, Greece)*** Cycloaddition Chemistry as a Tool for the Synthesis of Sugar Mimics from Sugars
18:50-19:30	OC12	***John E. Baldwin (Syracuse University, USA)*, Phyllis A. Leber** Thermal Pericyclic Reactions and [1,3] Carbon Sigmatropic Shifts
19:30		**End of Session**
20:30		***Social Dinner***

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

Saturday, June 16th

Morning

Chairman: **Alberto Brandi (Firenze University, Italy)**

9:00-10:00	PL5	***Leon Ghosez (European Institute of Chemistry and Biology, France)*** Pericyclic Reactions: from Serendipity to Planning
10:00-10:20	OC13	***Stefano Menichetti (Firenze University, Italy)*****, Maria Grazia Bartolozzi, Margherita Campo, Francesca Catarzi, Giuseppe Lamanna, Caterina Viglianisi** Recent Synthetic Achievements of the Inverse Electron Demand Hetero Diels-Alder Reaction of Ortho-Thioquinones and Related Species
10:20-10:40	OC14	***Venerando Pistarà (Catania University, Italy),*** **Elisa Vittorino, Anna Piperno** Synthesis of Methylene Isoxazolidine and Tetrahydrothiophene Nucleoside Analogues by 1,3-Dipolar Cycloaddition Chemistry
10:40-11:00		***Coffee Break***

Chairman: **Pedro Merino (Zaragoza University, Spain)**

11:00-12:00	PL6	***Francesco De Sarlo (Firenze University, Italy)*** Isoxazoles and Isoxazolines from Primary Nitrocompounds: Past and Present
12:00		***Conclusions***

PL: Plenary Lectures; IL: Invited Lectures; OC: Oral Contributions

PROGRAM OVERVIEW

Wednesday June 13th 2007	Thursday June 14th 2007	Friday June 15th 2007	Saturday June 16th 2007
	GHOSEZ	**CHMIELEWSKI**	**BRANDI**
	9:00 – 10:00 PL2 (Jurczac)	9:00 – 10:00 PL4 (Jones)	9:00 – 10:00 PL5 (Ghosez)
	10:00 – 10:40 IL2 (Klebnikov)	10:00 – 10:40 IL5 (Kappe)	10:00 – 10:20 OC13 (Menichetti)
	10:40 – 11:00 OC4 (Maiulo)	10:40 – 11:00 OC8 (Quadrelli)	10:20 – 10:40 OC14 (Pistarà)
	11:00 – 11:30 Coffe Break	11:00 – 11:30 Coffe Break	10:40 – 11:00 Coffe Break
	HARWOOD	**TIECCO**	**MERINO**
	11:30 – 12:10 IL3 (Fringuelli)	11:30 – 11:50 OC9 (De Amici)	11:00 – 12:00 PL6 (De Sarlo)
	12:10 – 12:30 OC5 (Cordero)	11:50 – 12:10 OC10 (Peters)	12:00 Conclusions
	12:30 – 13:10 IL4 (Heimgartner)	12:10 – 12:30 OC11 (Romeo)	
	13:10 – 15:00 Lunch Break	12:30 – 13:10 IL6 (Carretero)	
14:00 – 16:00 Registration	**SCORRANO**	13:10 – 15:00 Lunch Break	
16:00 – 16:20 Opening Ceremony	15:00 – 16:00 PL3 (Harwood)	15:00 – 17:00 Poster Section	
	16:00 – 16:20 OC6 (Cicchi)	17:00 – 17:30 Tea Break	
SPINELLI	16:20 – 17:00 OC7 (Birney)	**JONES**	
16:20 – 17:20 PL1 (Padwa)	17:00 – 17:30 Tea Break	17:30 – 18:10 IL7 (Kalesse)	
17:20 – 17:50 Tea Break	17:30 End of session	18:10 – 18:50 IL8 (Gallos)	
DESIMONI	Free afternoon: Classical Drama in Syracuse's Amphitheatre: Eracle of Euripide (19:00) or Catania sightseeing tour	18:50 – 19:30 OC12 (Baldwin)	
17:50 – 18:30 IL1 (Jäger)		19:30 End of session	
18:30 – 18:50 OC1 (Clerici)		20:30 Social Dinner	
18:50 – 19:10 OC2 (Contini)			
19:10 – 19:30 OC3 (Gelmi)			
19:30 End of session			
20:30 Welcome to participants: Refreshment offered by Chancellor of Catania University and the Mayor of the city			

SOCIAL PROGRAM

Opening Ceremony
The Opening Ceremony will take place on Wednesday afternoon, June 13th 2007, at 04:00 p.m. in the conference room of the Hotel des Étrangers et Miramare in Syracuse.

Welcome to Participants
A refreshment offered by the Chancellor of Catania University and Mayor of the city will be held on Wednesday evening at 08:30 p.m. in the Borsellino room of Syracuse city hall.
All the registered participants and their accompanying persons are cordially invited.

Classical Drama in Syracuse's Amphitheatre
The Classical Drama, "*Eracle*" of Euripide, will take place on Thursday, June 14th 2007 at 07:00 p.m. in the Amphitheatre of Syracuse.
All the registered participants and their accompanying persons are cordially invited.

Excursion to Catania
An short sightseeing tour to Catania city, in alternative to the Classical Drama in Syracuse's Amphitheatre, will take place on Thursday afternoon, June 14th 2007 at 06:00 p.m.
All the registered participants and their accompanying persons are cordially invited.
Contact the Organizing Secretariat for furthermore information.

Social Dinner
The social dinner will be held on Friday evening, June 15th 2007, starting at 08:30 p.m. in the banqueting hall of the Hotel des Étrangers et Miramare in Syracuse.
All the registered participants and their accompanying persons are cordially invited.

Excursion for accompanying persons
An excursion will take place on Friday morning, June 15th 2007, 08.30 a.m. – 07.30 p.m., which has Noto, Modica and Ragusa, as destination.
All the registered participants and their accompanying persons are cordially invited.
Contact the Organizing Secretariat for furthermore information.

PLENARY LECTURES

PL 1

CASCADE REACTIONS FOR ALKALOID SYNTHESIS

Albert Padwa

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Sequential transformations enable the facile synthesis of complex natural products from simple building blocks in a single preparative step. Their value is amplified if they also create multiple stereogenic centers. Our research program at Emory has focused on using new cascade reactions of push-pull dipoles and amidofurans for alkaloid synthesis. Our interest in using these domino sequences originated from some earlier work centered on the Rh(II)-catalyzed cyclization/cycloaddition cascade of α-diazoimides containing tethered π-bonds. Making use of these cascade reactions, we have been able to rapidly assemble several alkaloidal systems in excellent yield.

PL 2

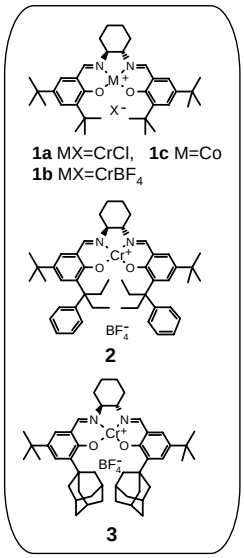
ENANTIOSELECTIVE CYCLOADDITION REACTIONS: THE HIGH-PRESSURE APPROACH REVISITED

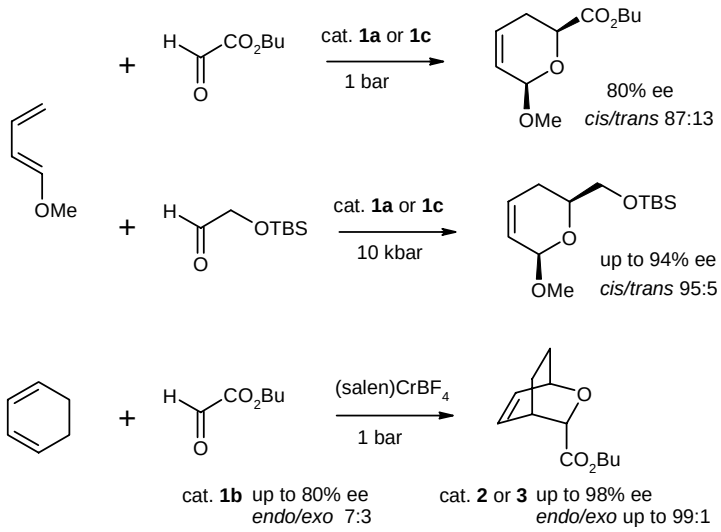
Janusz Jurczak

Department of Chemistry, Warsaw University, 02-093 Warsaw, Poland
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

jurczak@icho.edu.pl

The synthesis of chiral compounds in optically pure form is one of the crucial requirements of modern organic chemistry. We focused our attention on enantioselective methods for the synthesis of 3,6-dihydro-*2H*-pyran derivatives from activated carbonyl compounds such as alkyl glyoxylates or less reactive *O*-protected glycolaldehydes, using hetero-Diels-Alder (HDA) reaction. In our investigations we applied readily available chiral metallosalen complexes as catalysts. The (salen)Cr(III) and (salen)Co(II) complexes turned out to be most efficient, concerning enantioselectivity, in the investigated reactions.[1]





When enantioselectivity of some HDA reactions with classic Jacobsen-type catalysts was not satisfactory, we applied modified complexes. We have synthesised a novel salen ligands and found its chromium complexes to be a highly selective catalyst for some HDA reactions e.g. that with cyclohexa-1,3-diene.[2] Unfortunately, metallosalen complexes, are not effective in some reactions under thermal conditions owing to their relatively low Lewis acidity, however this problem can be solved by application of high-pressure technique.[3]

To conclude, we have shown that the sterically-modified complexes **2** and **3** catalyse the HDA reaction with high enantioselectivity (up to 98% ee). Our results show also how low-active salen catalysts under thermal conditions can be successfully applied for reactions accelerated under high-pressure conditions usually with increase of enantioselectivity.

1. (a) Kwiatkowski, P.; Asztemborska, M.; Caille, J.-C.; Jurczak, J. *Adv. Synth. Catal.* **2003**, *345*, 506-509. (b) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3189-3194.
2. Chaładaj, W.; Kwiatkowski, P.; Jurczak, J. *Synlett* **2006**, 3263-3266.
3. (a) Malinowska, M.; Kwiatkowski, P.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 7693-7696. (b) Kwiatkowski, P.; Chaładaj, W.; Malinowska, M.; Asztemborska, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2959-2964.

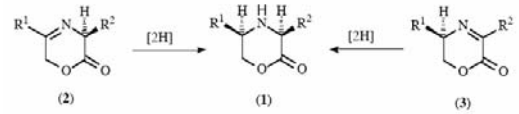
PL 3

MORPHOLINONES AND DEHYDROMORPHOLINONES AS CHIRAL MEMORY SYSTEMS

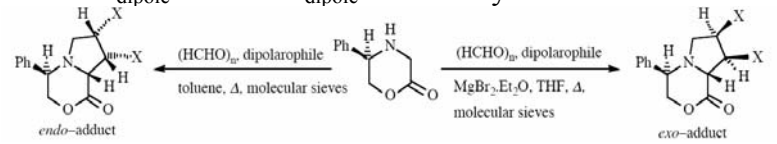
Laurence M. Harwood

Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK

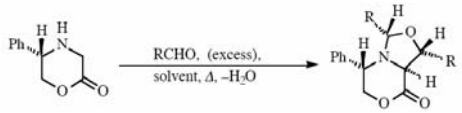
Excellent 1,3–diastereocontrol is displayed in the reactions of enantiomerically pure 4,5–dehydro– and 3,4–dehydromorpholinones (**2**) and (**3**); especially hydrogenations to give 3,5–disubstituted morpholinones (**1**). The parent enantiomerically pure substrates (**1**) and (**3**) (R^2 = H) may also be prepared and act as chiral glycine equivalents.



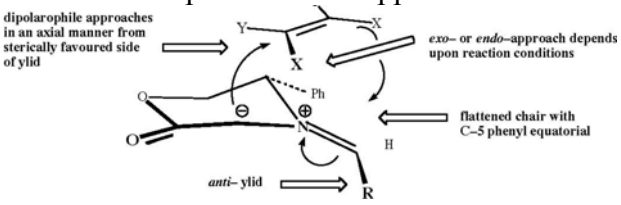
Much of our early work was directed towards establishing the scope of 3 + 2 dipolar cycloadditions of stabilised azomethine ylids generated from (**1**) with a range of aldehydes with doubly activated dipolarophiles. It was found that diastereo- and regiocomplementary cycloadditions could be achieved with *endo*–selectivity being observed under thermal conditions and *exo*–selectivity under mild Lewis acid catalysed conditions corresponding to a change over from $HOMO_{dipole}$ to $LUMO_{dipole}$ directed cycloaddition.



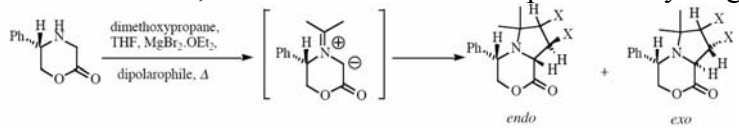
In the absence of the C–C dipolarophile we serendipitously discovered that excess aldehyde can take part in cycloaddition, providing a diastereocontrolled means of generating enantiomerically pure *threo*-β–hydroxy–α–amino acids and, by an extension of the methodology to using imines, α,β–diamino acids.



A working model explaining the diastereoselectivities observed demonstrates that stereocontrol is governed by the centre at C–5 causing the ring to exist as a flattened chair and not in a boat conformation as proposed by other workers. The consequence is that to obtain diastereocontrol does not require any additional stereochemical infrastructure (e.g. at C–6). X–ray crystallographic evidence will be presented to support this rationale.



In our studies to find alternative methods of generating the azomethine ylid which do not involve using analdehyde, we have demonstrated for the first time that it is possible to generate stabilised azomethine ylids derived from ketones, providing access to 5,5– disubstituted prolines. Depending upon the amount of Lewis acid used, *endo*– / *exo*–diastereocomplementarity is again possible.



PL 4

DIPOLAR CYCLOADDITIONS: MAKING PYRROLIDINES, PEPTIDE MIMICS, AND POLYCARBONYL METABOLITES

Raymond C.F. Jones, Carole Law, Chris Lumley, Terence A Pillainayagam, Shabana Rafiq, Maria Sanchis-Amat, and Laura E Seager

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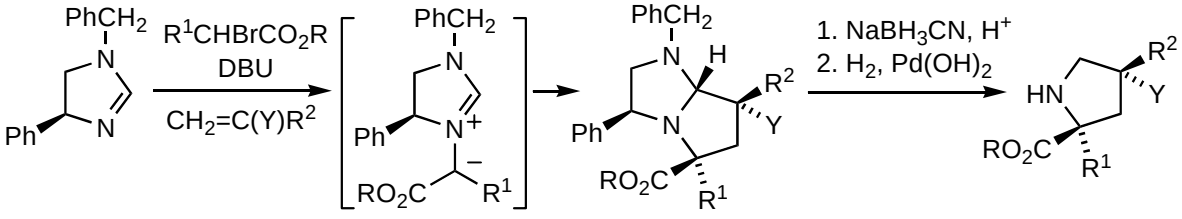
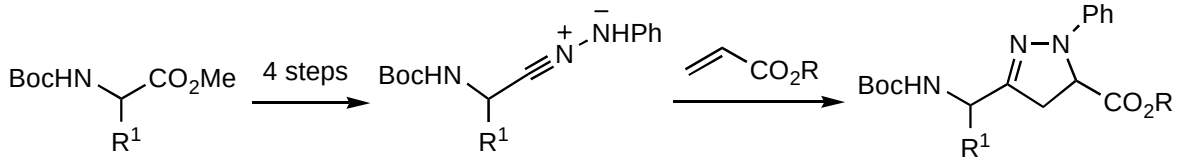
1,3-Dipolar cycloadditions are a rapid way to assemble five-membered ring heterocycles, and because of their highly ordered transition states, they can also display good stereoselectivity. We have employed dipolar cycloadditions in a variety of ways and the lecture will present highlights from three different applications, all using dipoles prepared from amino acids.

1. We have used optically active *azomethine ylides* such as **1** based on the imidazoline structure, to generate (after removal of the templating atoms) optically active pyrrolidines wherein three bonds in the new ring are formed in one pot (e.g. Scheme 1). The chiral imidazoline substrates are prepared from an amino acid.



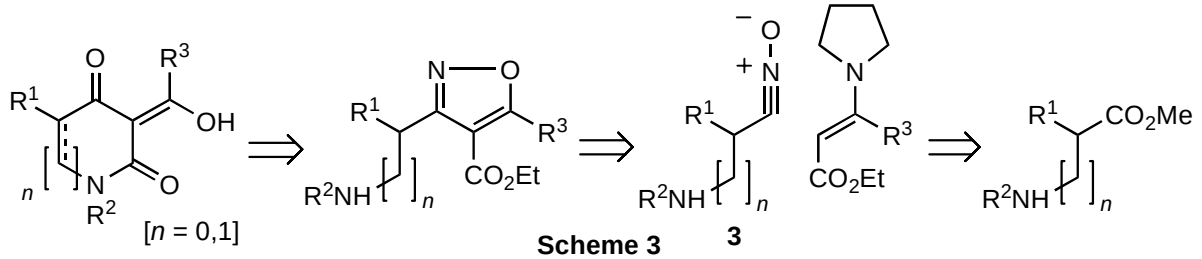
1 **Scheme 1**

2. Amino acids also serve as starting materials for α-amino *nitrile imines* such as **2**. We have explored cycloadditions of these dipoles to prepare pyrazolines as dipeptide mimics (e.g. Scheme 2), and demonstrated their incorporation into peptide synthesis.



2 **Scheme 2**

3. In an application to natural product synthesis, we have used 4-carboxyisoxazoles as masked forms of the polar heterocyclic tricarbonyl moiety of 3-acyltetramic acids or 3-acyl-4-hydroxypyridone metabolites, and their unnatural analogues. The strategy is illustrated in Scheme 3. The isoxazoles are prepared from α- and β-amino *nitrile oxides* such as **3** (again available from amino acids) in cycloaddition to enaminoesters.



Scheme 3 **3**

PL 5

PERICYCLIC REACTIONS: FROM SERENDIPITY TO PLANNING

Léon Ghosez

Institut Européen de Chimie et Biologie, 2, rue Robert Escarpit, 33600 Pessac, France

The Diels-Alder reaction is a prototype of the class of pericyclic reactions which is one of the most widely used method to construct six-membered ring. The combination of a diene and a dienophile in a regio-, stereo- and chemocontrolled manner offers unique opportunities to synthezise a wide diversity of carbo- and hetero- six-membered rings. A serendipitious discovery of an electrocyclic rearrangement of a 1-aminoazirine into an aminocarbene followed by a sigmatropic rearrangement led to a new class of azadienes which showed a good enophilic activity. This initiated a research programme aiming at developing a short, practical and productive method of synthesis of pyridines, pyrimidines, piperidines and many other nitrogen heterocycles by a combination of three reagents. This represents a unique method for the creation of "molecular complexity and diversity" in a very efficient and quick operation. The application to the synthesis of natural alkaloids and their analogs will be illustrated. We will also a fall-out of these strudies in the field of Lewis acids catalysis.

In an attempt to reverse the reactivity of 2-azadienes, we found a new type of rearrangement which results from two successive sigmatropic shifts. This led to a new method for ortho-thioalkylation of aryl acetic esters or γ-functionnalisation of α,β-unsaturated esters. The scope and the mechanism of these unusual transformations will be discussed.

PL 6

ISOXAZOLES AND 2-ISOXAZOLINES FROM PRIMARY NITRO COMPOUNDS. PAST AND PRESENT

Francesco De Sarlo

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email: fdesarlo@unifi.it

The conversion of primary nitro compounds into nitrile oxides and into isoxazole derivatives will be briefly reviewed, considering the reagents commonly employed and the mechanisms proposed.

A new approach will be illustrated, leading to isoxazole derivatives from primary nitro compounds and dipolarophiles, with no need of dehydrating reagents. Condensation takes place in fact under catalysis with suitable bases for "activated" nitro compounds or with metal salts for primary nitroalkanes.[1-4]

1. Cecchi, L.; De Sarlo, F.; Machetti, F. Isoxazoline derivatives from activated primary nitro compounds and tertiary diamines. *Tetrahedron Lett.* **2005**, *46*, 7877 – 7879.
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INVITED LECTURES

IL 1

[3 + 2] AND [2 + 1] CYCLOADDITIONS RELATED TO THE QUEST FOR NEW GLYCOSIDASE INHIBITORS

Volker Jäger, Zeynep Gültekin, Han-Qing Dong, Jörg Williardt, and Christof Schöberl

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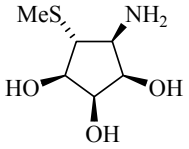
Based on mannostatin A **1** as a natural glycosidase inhibitor, a series of amino-hydroxymethyl-cyclopentanetriols **2** had been prepared and shown to present highly active carbohydrate mimetics (K_i values down to 0.6 nM).[1] The syntheses of **2** relied on intramolecular 1,3-dipolar cycloadditions[2] of nitrile oxides or nitrones of 5-hexenoses **3**, in turn obtained from the corresponding hexoses by vitamin B_{12}-catalyzed fragmentation of respective 6-deoxy-6-iodo pyranosides.[3]

The 5-hexenoses **3** constitute versatile intermediates for various types of cycloadditions or cyclizations, aimed to elaborate monosaccharide mimetics as further potential glycosidase inhibitors. New examples concerning 1,3-dipolar azomethine cycloadditions will be shown, as well as attempts to construct disaccharide mimetics **5** from the combination of hexenoses **3** and hydroxylamino-pyranosides such as **4**. The hydroxylamines **4** were obtained via respective cyclic ketones, i. e. ulose-pyranosides, which also show promise as easily available organocatalysts for enantioselective epoxidations,[4] complementing Shi's[5] and Shing's[6] ketones.



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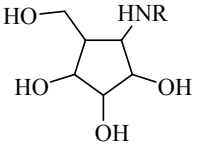

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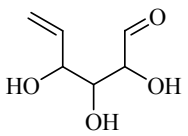

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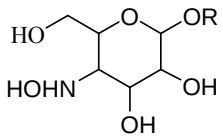

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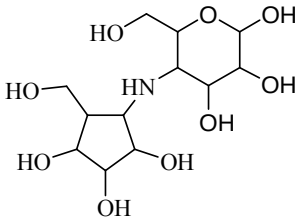

5

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IL 2

RECENT ASPECTS OF THE CHEMISTRY OF IMINIUM YLIDES GENERATED FROM CARBENES

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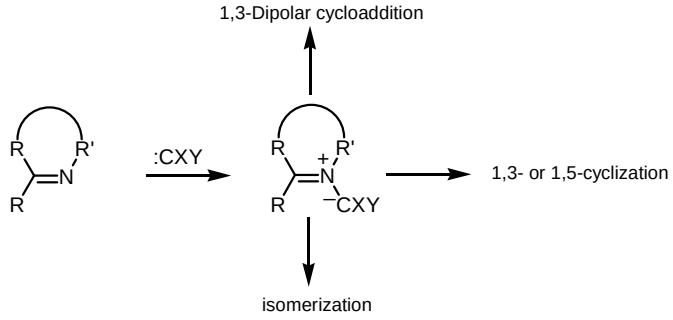
This presentation will give an overview of the recent developments in the chemistry and synthetic utility of azomethine ylides derived from carbenes and imines.



It was found that reaction pathways of halogenated ylides (from halogenated carbenes) are highly halogen-dependent: difluoroylides tend to undergo 1,3-dipolar cycloaddition to multiple bonds, rather than to cyclize into aziridines, whereas with dichloroylides the opposite situation is generally observed. In search for the reasons of such a dramatic difference in the reactivity of these species, DFT computations were carried out.

Reaction of azirines with difluorocarbene involves intermediate formation of azirinium ylides which in the presence of dipolarophiles give rise to strained fused azirinopyrrole or azirinoxazole derivatives as a result of 1,3-dipolar cycloaddition reaction. Azirinium ylides derived from azirines and carbenoids from diazocarbonyl compounds do not give 1,3-dipolar cycloaddition or 1,5-cyclization products but undergo isomerization to heterotrienes which can (in domino fashion) cyclize to 6-membered heterocycles.

We gratefully acknowledge the Russian Foundation for Basic Research (project no. 05-03-33257) and Russian Foundation for Basic Research - the Government of Flanders “Bilateral Scientific Cooperation” program (project no. 05-03-34811) for support of this research.

IL 3

CYCLOADDITION REACTIONS IN WATER AND UNDER SOLVENT FREE CONDITIONS

Francesco Fringuelli

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Nowadays chemists are exploring innovative ways to reduce pollution by devising new industrial processes that eliminate, or significantly reduce waste in the first place. For this goal is necessary both a new mentality and to develop a new chemistry, commonly called Green Chemistry.

In an effort to give a contribute in this field, for several years we have been studying organic reactions in water and under solvent-free conditions and we have developed new and efficient methodologies in these unconventional media.

This lecture is focused on some our more recent results on [3+2] and Diels-Alder cycloadditions carried out in water and under solvent free conditions and their application in the synthesis of targets molecules.

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IL 4

NEW PERICYCLIC REACTIONS WITH THIOCARBONYL YLIDES

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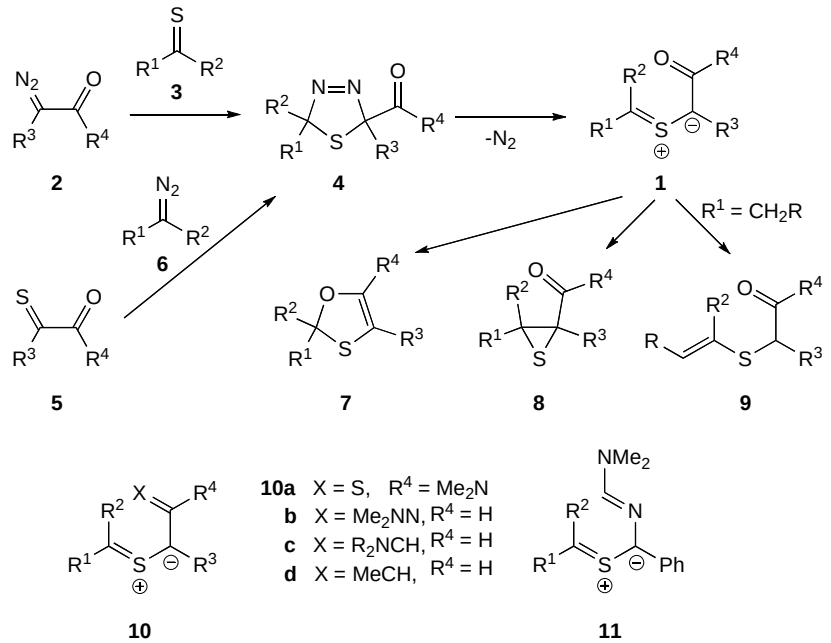
Thiocarbonyl ylides are useful building blocks for the synthesis of sulfur heterocycles.[1,2] A convenient approach to these reactive intermediates is the thermal decomposition of 2,5-dihydro-1,3,4-thiadiazoles, which are accessible by [2+3] cycloaddition of thiocarbonyl compounds with diazo compounds. In addition to *inter*molecular 1,3-dipolar cycloadditions and dimerizations, thiocarbonyl ylides undergo *intra*molecular stabilizations *via* 1,3-dipolar electrocyclization and 1,4-H shift. Recently, we have shown that acyl-substituted thiocarbonyl ylides **1** can be generated by the reaction of α-diazo ketones **2** with thiocarbonyl compounds **3** to give 1,5-dihydro-1,3,4-thiadiazoles **4** and subsequent N_2-elimination. The dominant stabilization of **1** is the 1,5-dipolar electrocyclization to give 1,3-oxathioles **7**.[3,4] In an analogous manner, 1,3-oxathioles **7** have been prepared by the reaction of 1,2-diphenyl-2-thioxoethanone **5** and diazoalkanes **6**.[4,5] Competitive reactions are the formation of thiiranes **8** and enethiolethers **9**. Scope and limitation of these reactions will be discussed. Of special interest is the extension to thiocarbonyl ylides of type **10** and **11**, which bear different π-systems at C(α).



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IL 5

THE USE OF MICROWAVE IRRADIATION TO ENHANCE PERICYCLIC AND RELATED PROCESSES

C. Oliver Kappe

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High-speed microwave synthesis has attracted a considerable amount of attention in recent years.[1] Since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986, more than 3000 articles have been published in the area of microwave-assisted organic synthesis (MAOS).[2] The initial slow uptake of the technology in the late 1980s and early 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns. Since the late 1990s the number of publications related to MAOS has therefore increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid reaction optimization, for the efficient synthesis of new chemical entities, or for discovering and probing new chemical reactivity.[3]

This lecture will highlight contributions from our laboratory in the field of microwave-assisted organic synthesis, in particular as they relate to pericyclic reactions such as intra- and intermolecular hetero-Diels-Alder reactions and thermal Dimroth-type rearrangements.

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IL 6

NOVEL CHIRAL SULFUR LIGANDS IN CATALYTIC ASYMMETRIC CYCLOADDITIONS

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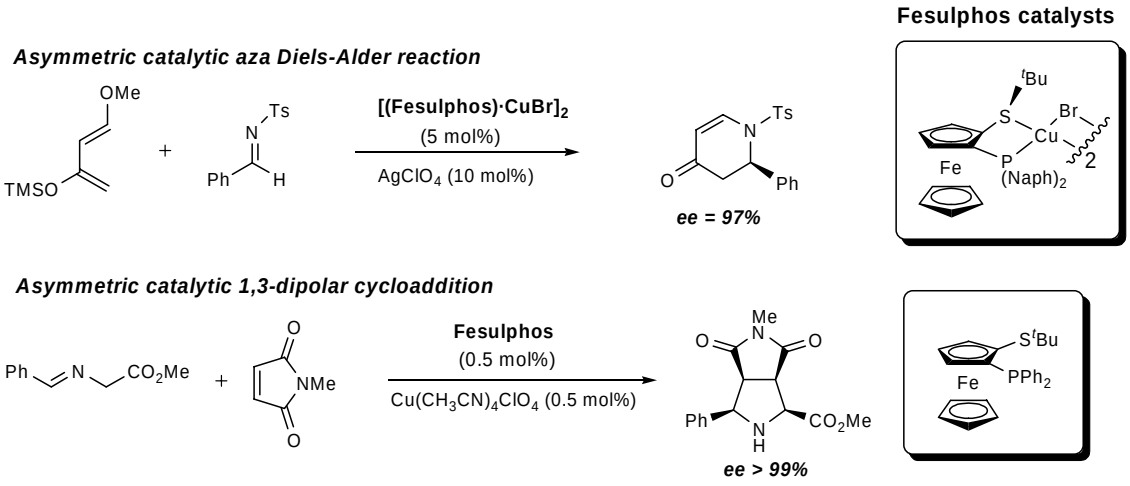
In the last few years we have developed a novel family of P,S-bidentate ligands having only planar chirality, named Fesulphos ligands (1-sulfenyl-2-phosphinoferrocenes).[1] These enantiomerically pure 1,2-disubstituted ferrocenes are readily prepared from ferrocene following the straightforward three-steps sequence sulfinylation of ferrocene, selective *ortho*-phosphination, and sulfoxide to sulfide reduction. This approach allows the easy fine-tuning of the steric and electronic properties around both sulfur and phosphorus metal-coordinating atoms.[2]

The efficiency of these ligands in a variety of asymmetric metal-catalyzed cycloadditions will be presented. Particular attention will be paid to some highly enantioselective Diels-Alder[3] and aza Diels-Alder[4] reactions, and 1,3-dipolar cycloadditions with azomethine ylides.[5]



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IL 7

PERICYCLIC REACTIONS IN NATURAL PRODUCT SYNTHESIS

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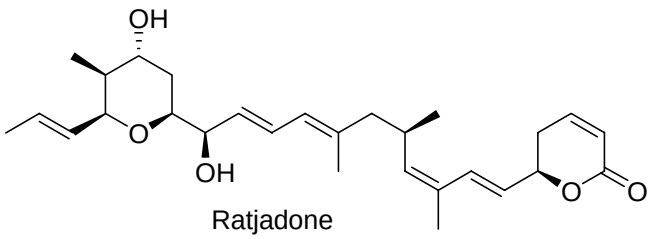
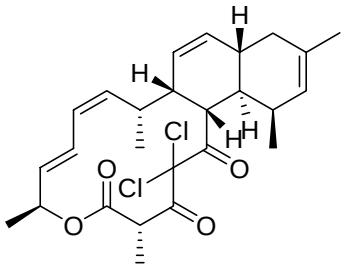
Markus.Kalesse@oci.uni-hannover.de

Natural products are one of the very important aspects in medicinal Chemistry. Besides the more classical fields as isolation and structure elucidation a special focus is put on the efficient and selective synthesis of biologically important natural products. Also, the synthesis of complex natural products which is judged by the highest synthetic standard can not be the sole reason for the initiation of research programs. The variety of different techniques and new methods in organic chemistry makes it possible to synthesize complex natural products and to further evaluate the biological mechanism and targets.

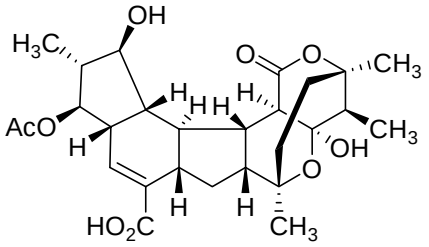
The lecture will cover the synthesis of natural products such as members of the leptomycin familie (e.g. ratjadone), hexacyclinic acid and chlorotonil in which pericyclic reaction pay a pivotal role. The pericyclic reactions involved are hetero-Diels-Alder reactions and intramolecular Diels Alder reactions with a special focus on enantio and diastereoselctive transformations. The synthesis of chlorotonil utilizes a discrimination of two possible *endo* transition states using an intermediate vinyl bromide as the differentiating element. The synthesis together with its biological profile will we discuss.



Ratjadone



Chlorotonil



Hexacyclinic Acid

IL 8

CYCLOADDITION CHEMISTRY AS A TOOL FOR THE SYNTHESIS OF SUGAR MIMICS FROM SUGARS

John K. Gallos

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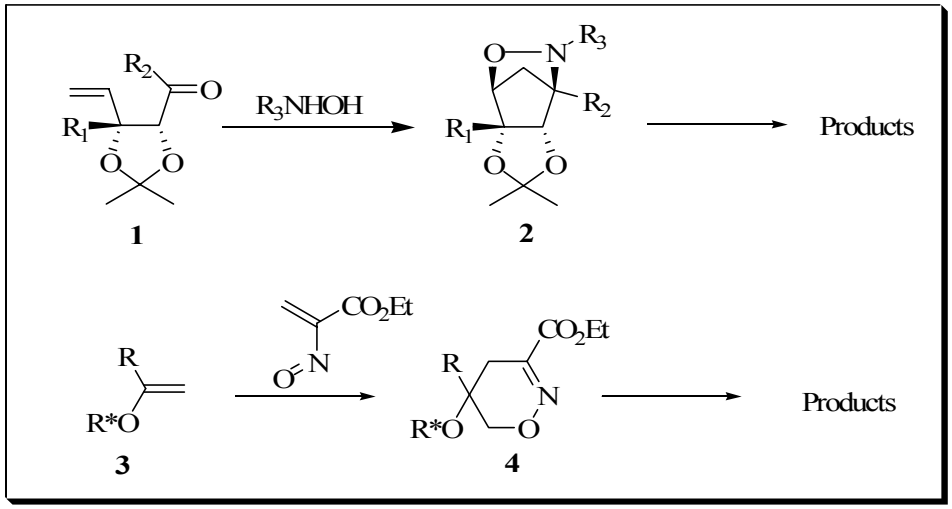
Sugar mimics are molecules that mimic a natural sugar or resemble the transition state of an enzymatic transformation.[1] Nature itself, in an intriguing manner, has designed such molecules, which have shown remarkable biological activities, being thus potential drugs.

More than a century since the original discovery and four decades since the systematic organization, cycloaddition chemistry has greatly evolved as an exceptionally versatile strategic tool for the fabrication of a plethora of organic molecules. Our group has successfully applied last decade the 1,3-dipolar and hetero-Diels-Alder cycloaddition chemistry to the synthesis of sugar mimics and biomimetic molecules, in general.[2]



Some of our results covering this topic will be presented in this talk. They include (i) the development of new synthetic methods for conversion of sugars to carbocyclic or aza-analogues (aza- and carba-sugars, aminocyclopentitols, C-glycosides, carbocyclic nucleosides, polyhydroxylated pyrrolizodine and indolizidine alkaloids), (ii) the total synthesis of some naturally occurring carbohydrate mimics, and (iii) the design and synthesis of new synthetic analogues.

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ORAL COMMUNICATIONS

OC 1

FROM ISOTHIAZOLES TO NEW OR KNOWN HETEROCYCLES *VIA* CYCLOADDITION REACTIONS

Francesca Clerici and Donato Pocar

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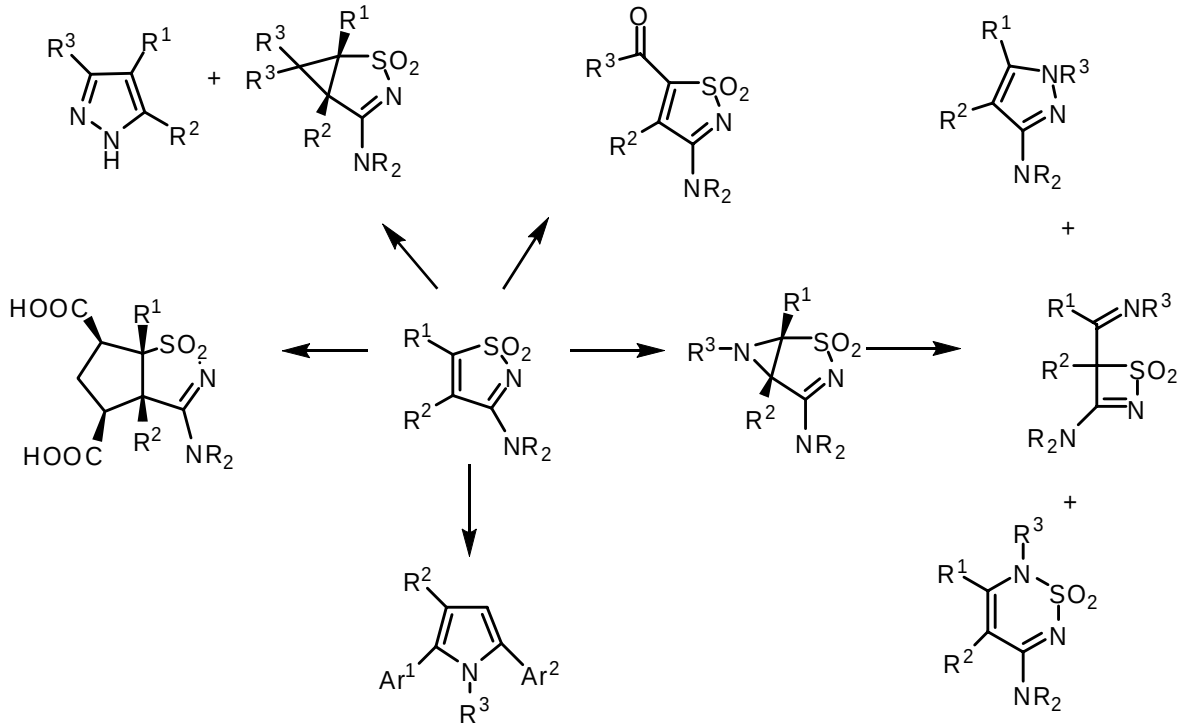
The synthesis and chemical reactivity of 3-amino-isothiazole S-oxides have been studied by us for many years and important transformations and uses of these compounds have been found as precursors both of N- and/or S-containing heterocycles and of open chain compounds through ring opening reactions. In particular, 3-amino-isothiazole S-oxides have been demonstrated to be a versatile system and an effective reaction partners in cycloaddition reactions all of which occurred with high regioselectivity at the C-4-C-5 double bond.[1] The resulting cycloadducts are susceptible to transformation in new or known heterocycles through the cleavage of one of the rings present in the primary cycloadduct. Their cleavage depends on several factors such as the reaction conditions and the substitution pattern. The combination of the cycloaddition reactions and ring transformation represents a good strategy affording mono or bicyclic compounds of both chemical and pharmacological interest. A survey of the synthetic possibility of this combination of reactions will be shown.



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OC 2

REGIOSELECTIVITY IN INTRAMOLECULAR NITRONE CYCLOADDITIONS: A DFT STUDY ON THE ROLE OF DISPERSIVE AND WEAK HYDROGEN INTERACTIONS

Alessandro Contini,[a,c] Gianluigi Broggini,[b,c] Michela Martinelli,[b,c] Gaetano Zecchi[b,c]

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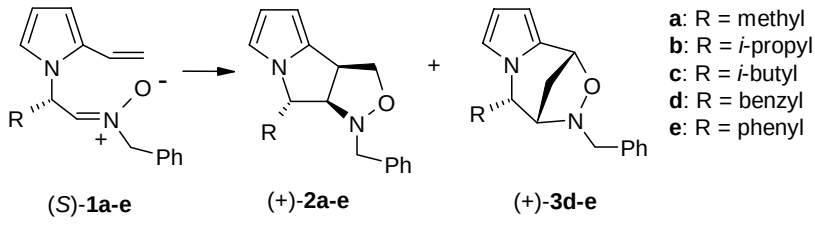
The intramolecular cycloaddition of nitrones **1** provides the two cycloadducts **2** and **3**. The reaction regiochemical outcome strongly depends on the nature of the R substituent. Indeed, the fused-rings **2a-e** are obtained from all nitrones (*S*)-**1**, while the bridged-rings are observed only for (*S*)-**1d-e**. However, it's quite hard to explain the observed regioselectivity only by invoking the R steric hindrance. Indeed, **1c** and **1d** provide a different products distribution even if the encumbrance of the R group is comparable, while **1a** and **1c** lead to a similar outcome even if the steric hindrance of the R substituent is different. Several theoretical investigations on intermolecular[1a-e] and intramolecular[1f-i] nitrone cycloadditions were found in the literature, but none of the reported studies provided us with a rational interpretation of our results. Thus, we performed a DFT computational analysis to clarify the observed behaviour. The B3LYP functional, our first choice for the geometry optimization of reactants **1a-e**, products **2a-e** and **3a-e** and transition structures TS–**2a-e** and TS–**3a-e**, did not provide energetic results consistent with the experiments. However, the analysis of the optimized geometries, highlights that π–π and CH/π interactions between R and the benzylic nitrone substituent could play a role in determining the regiochemistry at the transition state level. It's known that the description of dispersive interaction by DFT methods is challenging and that the B3LYP functional often predict a repulsive instead of an attractive interaction.[2] Thus, reactants, products and TSs were reoptimized using the HCTH functional. This method provides a net improvement in the description of the kinetics and thermodynamics of the reactions herein considered, confirming the importance of a correct evaluation of dispersive and weak hydrogen interactions in determining the regioselectivity of dipolar cycloadditions.



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OC 3

CYCLOADDITION REACTIONS: KEY REACTIONS TO BUILD CONSTRAINED CARBOCYCLIC AND HETEROCYCLIC AMINO ACIDS

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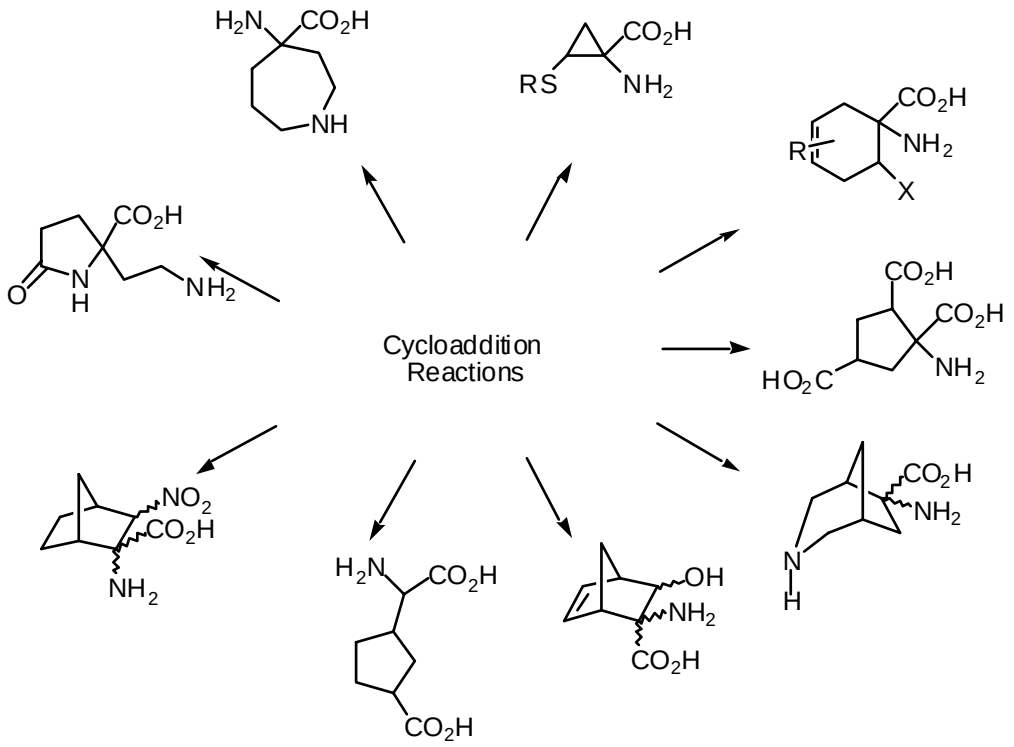
Heterosubstituted alkylidene-oxazolones and aminoacrylates are versatile key starting materials to prepare constrained carbocyclic amino acids functionalized with heteroatoms on the ring by using the Diels-Alder or 1,3-cycloaddition reactions. These reactions allow to control the stereochemistry of the substituents on the carbocyclic ring and to prepare each diastereomeric compound in enantiopure form. Furthermore, the substitution pattern on the ring of the primary cycloadducts allows further interesting transformation and new non proteinogenic carbocyclic and heterocyclic amino acids can be prepared.



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OC 4

CATALYTIC 1,3-DIPOLAR CYCLOADDITION OF NITRONES IN IONIC LIQUID: AN EASY ACCESS TO ISOXAZOLIDINES

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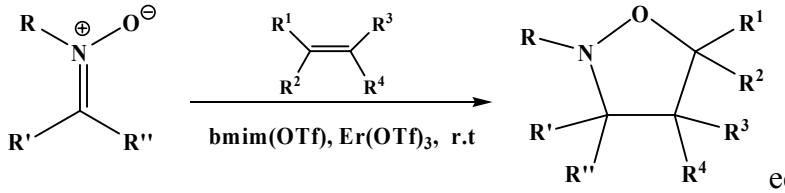
The 1,3-dipolar cycloaddition represents the favourite reaction for the construction of five and six-membered ring heterocycles. Particularly, when the reaction occurs between nitrones (dipoles) and alkenes (dipolarophiles) the products are isoxazolidines, key intermediates for the preparation of important products like isoxazolidinyl nucleosides.[1]

Our group owns a good experience in 1,3-dipolar cycloaddition[2] and similarly in the use of new Lewis acid catalysts such as Erbium (III) triflate,[3] that has shown significant catalytic activity in selective removing of a great number of protecting groups and during the synthesis of acetonides, acylals, enol esters, ecc.

Because of their interesting physical properties such as non-volatility, non-flammability and thermal stability, ionic liquids (ILs) have emerged in recent years as a novel alternative to traditional volatile and carcinogenic solvents, allowing an easy product recovery, a solvent recycling and, in some cases, different product selectivity.

Taking into account the advantages of these new reaction media, we have combined our past experience in the field of cycloadditions and catalysis with the versatile proprieties of ILs with the aim to find new routes for appealing isoxazilidine synthesis. Starting from differently substituted nitrones and alkenes in the presence of $Er(OTf)_3$, we have obtained the corresponding substituted isoxazolidines using bmim(OTf) (bmim = 1-butyl-3-methyl imidazolium, $TfO^- = CF_3SO_3^-$) as solvent, at room temperature, according to eq.1.



eq. 1

If compared with similar 1,3-cycloadditions in conventional media i.e. toluene, our reaction appeared much faster even at room temperature, with conversion and product yields in the range 80-90%.

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OC 5

STEREOSELECTIVE SYNTHESIS OF POLYHYDROXYINDOLIZIDINES

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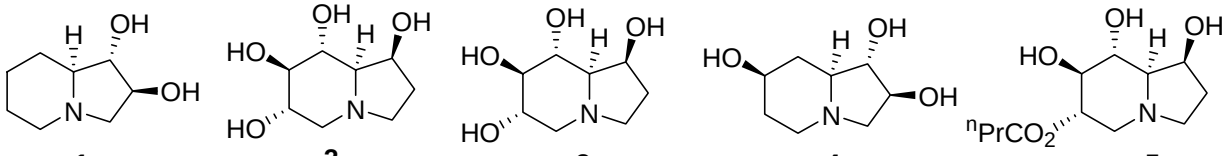
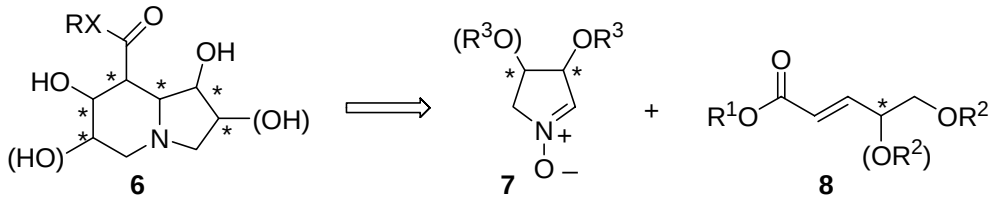
Glycosidase inhibition is important not only in the study of enzyme mechanism, but also in therapies targeted at, for example, cancer, viral infections including HIV and influenza, lysosomal storage diseases, and diabetes. Several polyhydroxylated indolizidines have shown an inhibitory action toward various glycosidase enzymes. Among others, very interesting compounds are the natural alkaloids lentiginosine (**1**), swainsonine (**2**) and castanospermine (**3**) and some of their unnatural analogues and derivatives such as **4** and **5**.



1 lentiginosine; **2** swainsonine; **3** castanospermine; **4** (*7R*)-idrossi-lentiginosine; **5** 6-*O*-butanoyl-castanospermine

In this communication, a general and versatile method for the divergent and diastereoselective synthesis of polyhydroxylated indolizidines will be presented. The synthetic approach is based on the 1,3-dipolar cycloaddition of enantiopure hydroxylated pyrroline *N*-oxides **7** followed by a suitable elaboration of the adducts. Nitrones **7** easily derived from chiral pool compounds such as tartaric acid, malic acid and arabinose can be reacted with dipolarophiles **8** to obtain octahydroindolizine-8-carboxylic acids **6** (XR = OH) with complete control of the relative and absolute configuration of up to six adjacent stereocenters. In particular, the intra- and intermolecular approaches applied to the same starting materials lead to the selective formation of different diastereomers. Moreover, the carboxylic group on C-8 can be reduced to hydroxymethyl moiety or used to introduce lipidic chains to generate new glycolipid mimetics.



6 **7** **8**

X = O, NH; R = H, alkyl, benzyl; * = stereocenter with defined configuration

Eventually, the synthesized compounds having a different number of hydroxyl moieties, different configurations of the stereocenters and various substituents at C-8 will be tested as glycosidase inhibitors and antivirals.

OC 6

THE HUISGEN REACTION AS A TOOL FOR THE CONSTRUCTION OF LIGHT HARVESTING ANTENNAE

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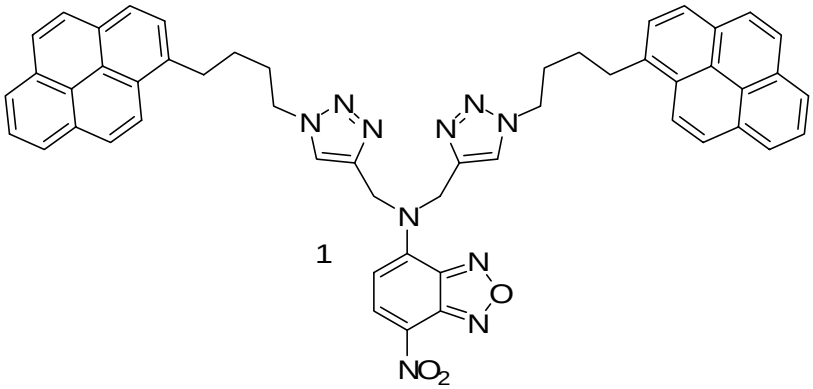
The azide-alkyne cycloaddition has revealed a very efficient tool for the construction of complex molecules. This is an ideal tool for assembling several different molecular fragments which impart a new property to the resulting macromolecule. This efficiency has been demonstrated by several examples in the fields of dendrimers as well as glycobiology.[1,2] We have used this tool to produce new examples of light harvesting antennae. These molecules are characterized by an external layer of fluorescent chromophores whose emission is absorbed by an acceptor chromophore placed in the core. These compounds resemble the behavior of natural systems and have attracted the attention of the research community both for the help that can provide in understanding the mechanism of the energy transfer and for the application that they can find. We have focused our attention on compounds containing pyrene units to take advantage of the formation of excimers, whose fluorescence is adsorbed by chromophores like substituted benzofurazanes (compound **1**) or pyridine salts.



Finally the results obtained with molecular systems will be compared with those obtained with supramolecular antennae based on low molecular weight organogelators[3] substituted with the same chromophores, showing the potential and the limits of these two different approaches.

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OC 7

MULTIPHOTON INFRARED INITIATED PERICYCLIC AND PSEUDOPERICYCLIC REACTIONS

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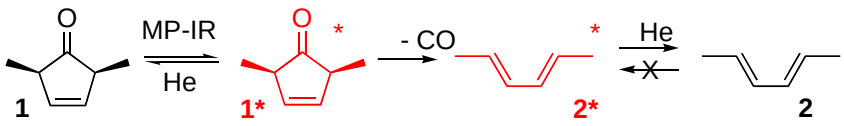
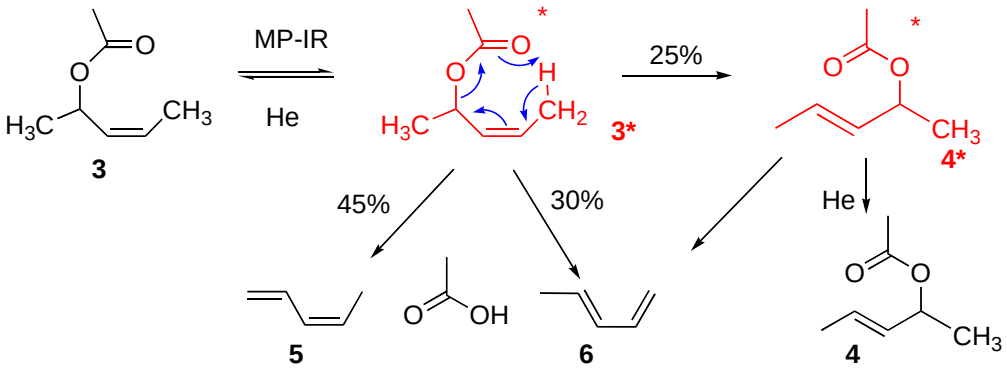
Multiphoton infrared (MP-IR) excitation using a pulsed IR laser results in the vibrational excitation of molecules. In the gas phase, a molecule can be heated in the presence of a room-temperature buffer gas; judicious choice of the exciting wavelength allows the selective heating of one component and the rapid cooling of intermediate products. Thermal decarbonylation of *cis*-2,5-dimethyl-3-cyclopentenone (**1**) was predicted to form *trans,trans*-2,4-pentadiene (**2**). The temperatures required lead to scrambling of the stereochemistry. However, using MP-IR with He as the buffer gas demonstrated that **2** is indeed the initial product.[1]



Pseudopericyclic reactions have bonding changes around a ring, yet they lack cyclic orbital overlap. This has at least four consequences – planar transition states, non-aromatic transition states, low barriers and most significantly, any pseudopericyclic reaction is allowed, regardless of the number of atoms involved.[2] Consideration of the orbitals involved in ester eliminations suggests that this reaction is pseudopericyclic. Thus, pyrolysis of *cis*-2-acetoxy-3-pentene (**3**) would be predicted to lead directly to *trans*-1,3-pentadiene (**6**) via an eight-centered transition state. However, a two-step process via sigmatropic rearrangement to *trans*-2-acetoxy-3-pentene (**4**) followed by elimination is also possible. MP-IR of **3** gives three products, *cis*-1,3-pentadiene (**5**), **6** and **4**. Adding He as a buffer gas gives more **4** as a percentage of products, at the expense of **6**. This would be expected by cooling the first-formed, vibrationally excited **4**. Extrapolation to complete cooling still predicts approximately 30% of the reaction of vibrationally excited **3** gives **6** directly, via what must be a pseudopericyclic pathway.



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OC 8

THE ENE REACTIONS OF NITROSOCARBONYL INTERMEDIATES: MECHANISM AND SYNTHETIC APPLICATIONS

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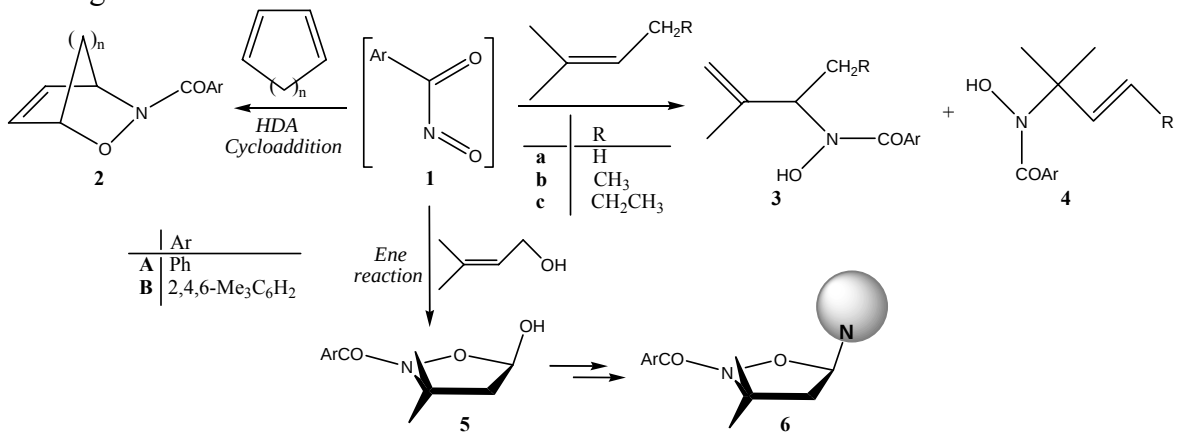
Nitrosocarbonyl intermediates **1** (RCONO) are highly reactive species discovered by Kirby and usually generated by periodate oxidation of hydroxamic acids.[1] Recently we have proposed a mild alternative for their generation through the oxidation of nitrile oxides with tertiary amine *N*-oxides.[2] The protocol easily lead to a variety of fleeting aromatic and aliphatic nitrosocarbonyl intermediates **1**, which can be trapped with dienes to afford the corresponding hetero Diels-Alder (HDA) cycloadducts **2** in high yields (Scheme 1).[3] Nitrosocarbonyls **1** also behave as "super enophiles" in ene processes[4] with a variety of olefins affording the ene adducts **3** and **4**.



The ene adducts were obtained in quantitative yields with tri-substituted olefins, but the regioselectivity changes dramatically upon variation of the nitrosocarbonyl substituent. Moreover suitable stereochemical probes highlight the remarkable "cis" stereoselectivity of these ene reactions. In the present communication the variable Markovnikov orientation and the "cis effect" in the Ene reactions of nitrosocarbonyls are discussed in the light of model calculations which fully clarify the reaction mechanism.[5]

The findings allow for a rational control of the Ene reaction in synthetic applications such as the preparation of 5-hydroxy-isoxazolidines **5** as valuable intermediates to nucleoside analogues **6**.

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OC 9

SYNTHESIS OF NOVEL ENANTIOPURE 2-ISOXAZOLINE AND 2-PYRAZOLINE AMINO ACIDS AND THEIR ACTIVITY AT GLUTAMIC ACID RECEPTORS AND TRANSPORTERS

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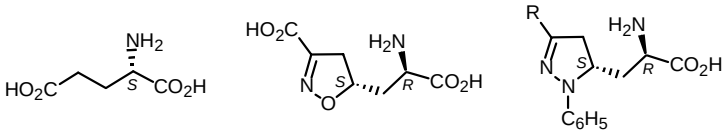
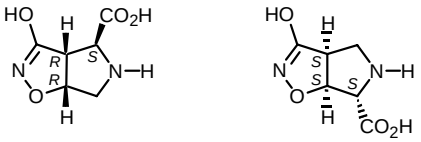
L-Glutamic acid (Glu) is the main excitatory neurotransmitter in the mammalian central nervous system and mediates neurotransmission across most excitatory synapses. Among the different ionotropic and metabotropic receptors which transduce the Glu signal, the NMDA receptor family plays a pivotal physiological role. On the other hand, an overstimulation of this cluster of ionotropic receptors leads to an acute neurodegeneration termed excitotoxicity. Accordingly, a number of efforts has been devoted to the development of selective NMDA receptor antagonists as potential neuroprotective agents. Our interest in the field focused on the synthesis of novel enantiopure 2-isoxazoline and 2-pyrazoline acidic amino acids by applying the principles of chain homologation and structural rigidification. The key step in the preparation of the designed compounds was the 1,3-dipolar cycloaddition of nitrile oxides and imines to suitable dipolarophiles. In the set of stereoisomers under study, amino acids (–)-**1**,[1] (+)-**2**, and (+)-**3** behaved as the most potent and selective NMDA receptor antagonists.



Glu (–)-**1** R = CO_2H: (+)-**2** R = PO_3H_2: (+)-**3**



(–)-**HIP-A** (+)-**HIP-B**

In a parallel investigation, we characterized the interaction of conformationally constrained aspartate and glutamate analogs with the excitatory amino acid transporters (EAATs), which represent a promising molecular target for a therapeutic intervention on neurological as well as mental disorders. In particular, the new bicyclic acidic amino acids (–)-**HIP-A** and (+)-**HIP-B**, with no or slight effects on glutamatergic receptors, efficiently inhibited the [^{3}H]L-glutamate uptake in rat brain cortical synaptosomes.[2,3] Worth noting, (–)-**HIP-A** displayed a high degree of enantioselectivity when compared to its less potent mirror image (+)-**HIP-A**.

The synthetic strategies leading to target compounds as well as the most relevant results of the bio-pharmacological screening will be illustrated and discussed.

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OC 10

CATALYTIC ASYMMETRIC SYNTHESIS OF β-HYDROXYSULFONYL DERIVATIVES

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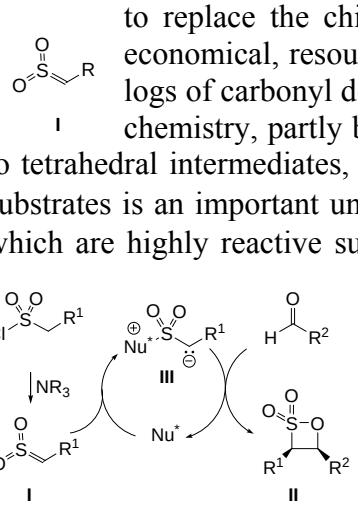
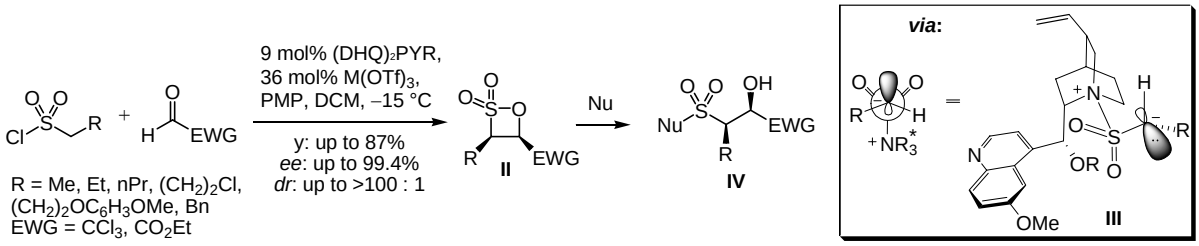
Sulfenes I are the sulfonyl equivalents of ketenes.[1] An unsolved problem was prior to work by our group the application of sulfenes as substrates in asymmetric catalysis providing a tool to replace the chiral auxiliary controlled sulfonyl carbanion chemistry by more economical, resource and time saving approaches. Since enantiopure sulfonyl analogs of carbonyl derivatives are playing an increasingly important role in medicinal chemistry, partly because they mimic the properties of the transition states leading to tetrahedral intermediates, the development of catalytic asymmetric methods using sulfene substrates is an important undertaking. In this context we became interested in β-sultones **II** which are highly reactive sulfonyl analogues of β-lactones. β-Sultones are a rarely investigated substance class despite their potentially high value as ring strained synthetic building blocks. Our work was based on the hypothesis that it should be possible to carry out the β-sultone formation enantioselectively by the action of a catalytic amount of an enantiopure chiral nucleophile which would trap and at the same time activate the sulfene intermediate **I** by the formation of a zwitterionic sulfene-amine adduct **III**. The reactivity of a sulfene normally acting as an electrophile would thus be reverted by the formation of the nucleophilic zwitterion **III**.





R = Me, Et, nPr, $(CH_2)_2Cl$, $(CH_2)_2OC_6H_3OMe$, Bn
EWG = CCl_3, CO_2Et

The sulfene amine adducts **III** must have significantly different structural properties than ketene derived zwitterionic enolates due to pyramidalization of both the sulfonyl sulfur and the C_α-atom (for R = alkyl). Consequently, the formation of diastereomeric adducts is possible (in contrast to ketene-derived enolates). The key to achieve both good yields and high enantioselectivities was the co-activation by a Lewis acid co-catalyst ($In(OTf)_3$ or $Bi(OTf)_3$).[2] Ring opening reactions of the strained heterocycles with alcohol, amine or Grignard reagents gave regioselective access to highly enantioenriched β-hydroxysulfonates, -sulfonamides or -sulfones **IV**. Enantiopure β-hydroxysulfonyl derivatives are attractive synthetic targets as they exhibit a variety of biological activity and are investigated for the treatment of diseases such as diabetes, cardiac failure, Alzheimer's disease, atherosclerosis or thrombosis.

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OC 11

SYNTHESIS OF ENANTIOMERIC TIAZOFURIN ANALOGUES *VIA* ZINC (II) TRIFLATE-CONTROLLED 1,3-DIPOLAR CYCLOADDITION UNDER MICROWAVE IRRADIATION

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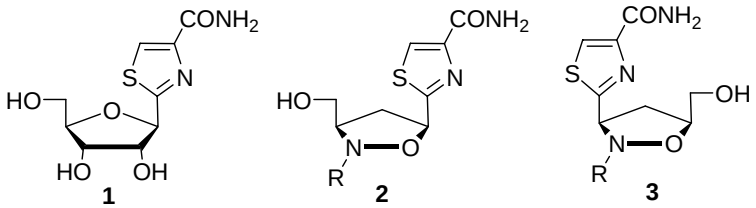
In the search of new antiviral and anticancer agents several modifications of nucleosides have been extensively studied.[1] Tiazofurin **1** is a tiazole-containing C-nucleoside, which has demonstrated significant activity in vitro against a number of model tumor systems.[2] We planned the design and synthesis of the isoxazolidinyl analogues of tiazofurin of type **2** and **3**.

Two different reaction pathways have been developed for the construction of 2-deoxyribo-analogues **2** and ribo- analogues **3**. The synthetic strategy towards the preparation of compounds **2** involves as key step a 1,3-dipolar cycloaddition between acrylonitrile and chiral nonracemic nitrones.[3] An opposite diastereofacial was observed when the chiral group was placed at either the carbon atom or the nitrogen one of the nitrone function. The 2-cyano isoxazolidines obtained were converted into the enantiomeric target compounds by constructing the thiazole ring via condensation with L-cysteine. Compounds type **3** have been prepared by cycloaddition reaction of C-(2-thiazolyl) nitrones and allyl alcohol. The rate of the reactions is increased enormously when the reactions are carried out in the presence of zinc triflate under microwave irradiation.[4]



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OC 12

THERMAL PERICYCLIC REACTIONS AND [1,3] CARBON SIGMATROPIC SHIFTS

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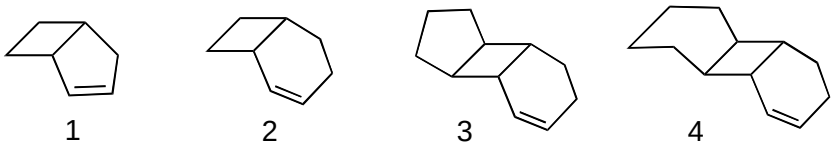
The literature concerned with thermal pericyclic reactions has evolved significantly since the terminology was introduced in 1968. The number and diversity of reactions categorized in this broad class continues to burgeon, and applications to challenging synthetic objectives have achieved hundreds of impressive successes. Yet some conceptual issues remain unsettled. When one reads in today's literature of "concerted pericyclic reactions" the possibility of "non-concerted pericyclic reactions" materializes awkwardly in the offing. Or when experimental evidence suggests that a pericyclic reaction does take place through a step-wise path and the intrusion of a short-lived reactive intermediate, it may provoke more confusion than clarity.

Our experimental studies of thermal pericyclic reactions of relatively small hydrocarbons over the years have addressed a variety of transformations, gaining kinetic and stereochemical data relevant to the basic concerted/non-concerted mechanistic distinction, and prompting valuable theoretical work in other laboratories. Most recently investigations of [1,3] carbon sigmatropic shifts of simply substituted variants of bicyclo[3.2.0]hept-2-ene (**1**), bicyclo[4.2.0]oct-2-ene (**2**), and the more conformationally constrained tricyclic analogs **3** and **4** have uncovered significant system-specific differences in reaction stereochemistry for the [1,3] carbon rearrangements they all exhibit and in the relative importance of such isomerizations compared with competing thermal reactions. The dominant importance of non-concerted, diradical-mediated mechanisms seems unmistakable.



1 2 3 4

We believe that concerted and non-concerted pericyclic reactions are amenable to experimental and theory-based distinctions, and to rational understanding. Investigations and applications of both will contribute to mechanistic and synthetic organic chemical progress.

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OC 13

RECENT SYNTHETIC ACHIEVEMENTS OF THE INVERSE ELECTRON DEMAND HETERO DIELS-ALDER REACTION OF *ORTHO*-THIOQUINONES AND RELATED SPECIES

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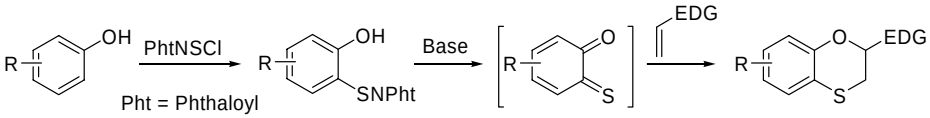
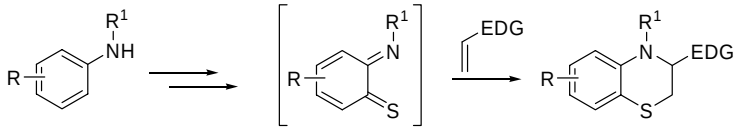
Several years go we developed a simple and general methodology for the generation and trapping of *ortho*-thioquinones that were previously considered as elusive intermediates of scarce utility in synthetic organic chemistry. Our approach is based on the regioselective *ortho*-sulfenylation of properly substituted phenols with the phthalimidesulfenyl chloride, followed by a 1,4-elimination at sulfur promoted by tertiary bases, like pyridine of triethylaminne, that occurs under exceptionally mild conditions, in chloroform at temperature ranging from 25 to 60 °C. Once liberated in solution the *ortho*-thioquinones can be trapped as electron-poor heterodienes in inverse electron demand hetero Diels-Alder reactions providing the corresponding benzoxathiin cycloadducts.[1]



In the last decade we use several tens of phenols and various classes of electron-rich alkenes demonstrating the feasibility and the generality of this approach. In particular using hydroxy and methoxy substituted phenols, as precursors of the dienic *ortho*-thioquinones, and styrenes, as electron-rich dienophiles, we prepared benzoxathiin cycloadducts having a 4-thiaflavane skeleton. In analogy with the Flavonoids, the corresponding family of natural polyphenols, these compounds exhibit a broad range of biological activities including the antimicotic and the antioxidant activity.[2] The latest results on this field obtained by a keen optimization of the structure activity relationship, will be presented in this communication.

Recently a study on the possibility to exploit this chemistry for to the generation and trapping of *ortho*-iminothioquinones has been undertaken.



The challenge and the opportunities offered moving from a phenol to an amine as starting material will be discussed as well.

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OC 14

SYNTHESIS OF METHYLENE ISOXAZOLIDINE AND TETRAHYDROTHIOPHENE NUCLEOSIDE ANALOGUES BY 1,3-DIPOLAR CYCLOADDITION CHEMISTRY

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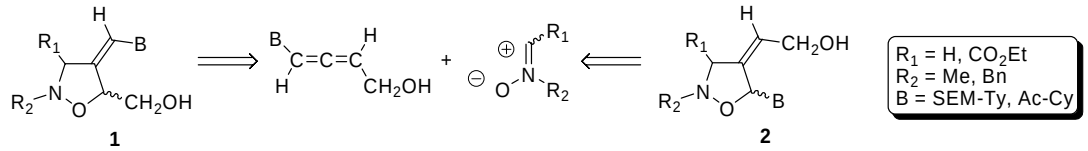
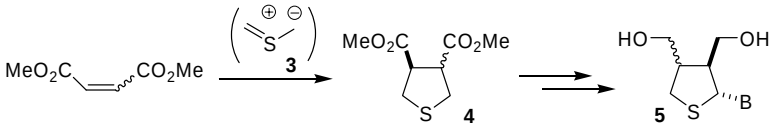
In the last years a wide variety of nucleoside analogues, modified in the carbohydrate moiety and/or in the nucleobase, have been prepared and tested for antiviral and antitumoral activities.[1] The isosteric substitution in the furanosyl moiety of a methylene with a nitrogen atom, affording the isoxazolidine nucleosides[2] with interesting activities as inhibitors of HIV reverse transcriptase, and that one of the oxygen atom with a sulfur atom, affording the corresponding 4'-thio-derivatives,[3] are two of these modifications, object of our interest.[4]

Following our recent interest in the synthesis of new series of alkylidene isoxazolidinyl nucleosides as potential anti-HIV agents, where the sugar spacer is replaced by the more rigid methylene isoxazolidine group, we have planned the construction of new conformationally controlled modified *N*,*O*-nucleosides **1** and **2** by investigation of the cycloaddition reaction of the *C*-ethoxycarbonyl-*N*-methylnitrone with protected thymallene.



1 **2**

Since tetrahydrothiofene syntheses based on sugars have often met various difficulties, we have performed a few steps synthesis of 4'-thionucleosides involving the 1,3-dipolar cycloaddition of the simplest thiocarbonyl ylid **3**[5] with a variety of appropriate alkenes bearing electron-withdrawing substituents, affording tetrahydrothiofene adducts **4** and **5**.[6] 4'-Thionucleosides were then constructed by the coupling reaction of the corresponding sulfoxides, converted into 2-acetoxy derivatives *via* a Pummerer-type reaction, with a silylated nucleobase.[7]



3 **4** **5**

In this communication the syntheses of conformationally blocked *N*,*O*-nucleosides and a new series of 4'-thionucleosides are reported.

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POSTER COMMUNICATIONS

P 1

GLYCOSULFENIC ACIDS AS EFFICIENT SCAFFOLDS IN THE SYNTHESIS OF PSEUDOTHIOSUGARS

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Carbohydrate-protein recognition is an essential process for the biological transfer of information in living organisms. An approach to the comprehension of this process is realized by the use of native proteins and unnatural carbohydrates for understanding the site geometry in the protein. These unnatural carbohydrates should be resistant to the enzyme and competitor of other possible inhibitors.[1]

Carbohydrate derivatives with a sulfur atom instead of the anomeric oxygen, such as 1-tioglycosides, are much more resistant to the glycosidase bond breaking than O-glycosides.[2] Thus, the accomplishment of simple strategies for the obtainment of 1-thiopseudosugars represents a stimulating synthetic problem. The presence of a sulfur atom replacing the glycosidic oxygen atom constitutes also an element of interest from a chemical point of view, since the sulfur atom can undergo several transformations, displays many types of reactivity, and can be a stereogenic centre in the sulfoxide oxidation state.

Recently, we have described an easy methodology for generating *in situ* transient 1-α- and 1-β-glycosulfenic acids that can be regarded as effective scaffolds for the stereocontrolled connection among thioglycons and aglycons or further glycosidic moieties, thus offering the basis for the elaboration of new molecules incorporating thiosugar residues.[3]

In this comunication we will report the development of our synthetic pathway for the obtainment of modified thiosaccharides. Our method starts from commercially available or easily prepared thioglycopyranoses, and allows, in three steps only, the generation of the corresponding glycosulfenic acids. The *syn*-addition of such transient species onto the triple bond of different enynes gives an easy access to glycosulfinyl dienes.

We will describe also the results of the stereoselective Diels-Alder cycloadditions of the prepared glycosulfinyl dienes with suitably substituted dienophiles, performed with the idea of developing a versatile procedure for the access to novel multivalent pseudothiosaccharides.

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Work carried out in the framework of PRIN **2005** (**2005**038048) "Cicloaddizioni a basso impatto ambientale per la sintesi di sostanze d'interesse biologico" supported by the Italian Ministero dell'Università e della Ricerca (MiUR) and the Università di Messina.

P 2

ENANTIOPURE PIPERIDINE-2-ETHANOL AND PERYCICLIC REACTIONS AS VERSATILE TOOLS IN DIVERSITY-ORIENTED SYNTHESIS

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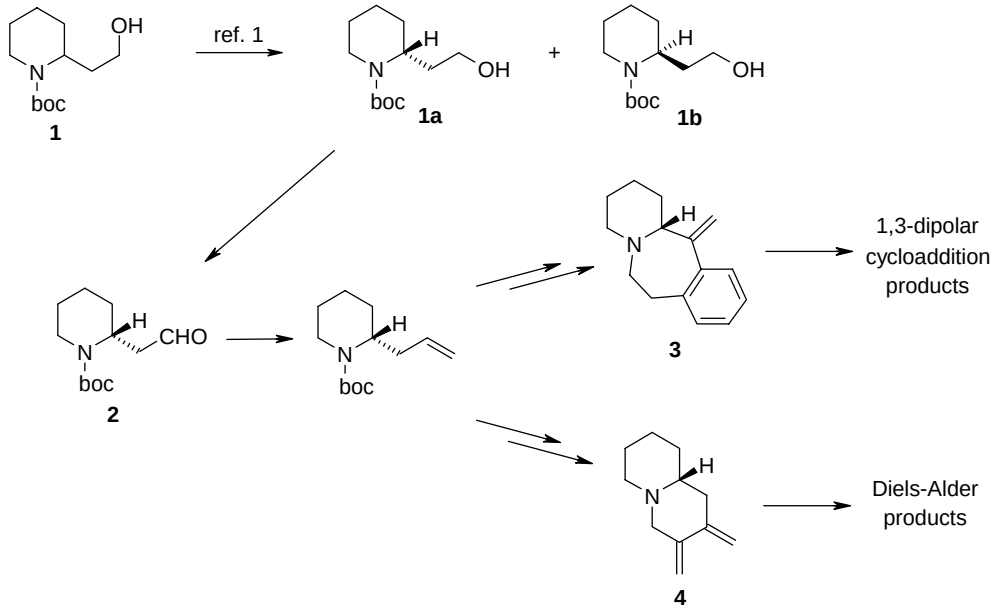
The configurational stability of **1** and the wide spectrum of reactivity of the corresponding aldehyde make possible to employ one of the enantiomers **1a** and **1b**[1] as starting material for a number of natural products.[2] Diversity-oriented syntheses are aimed at a collection of many compounds having structural complexity and diversity. Complexity is important because many biological processes are critically dependent on protein-protein interactions, and many of the small molecules known to disrupt these interactions are structurally complex natural products. Increasing the size and number of rigidifying and protein-binding elements in small molecules is generally viewed as essential in order for these compounds to bind tightly to sites of protein.[3]



For these reasons we used aldehyde **2** for the preparation of the olefin **3** and the 1,3-diene **4**, which were submitted respectively to 1,3-dipolar cycloadditions and Diels-Alder reactions. The key step of the synthetic sequence consisted in an intramolecular Heck reaction, performed in different conditions to enter to compounds **3** and **4**.

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P 3

REVERSIBILITY OF [4+2]CYCLOADDITION OF FULVENES TO DICYANOFUMARATES AS A MODEL REACTION FOR GENERATION OF DYNAMIC COMBINATORIAL LIBRARIES

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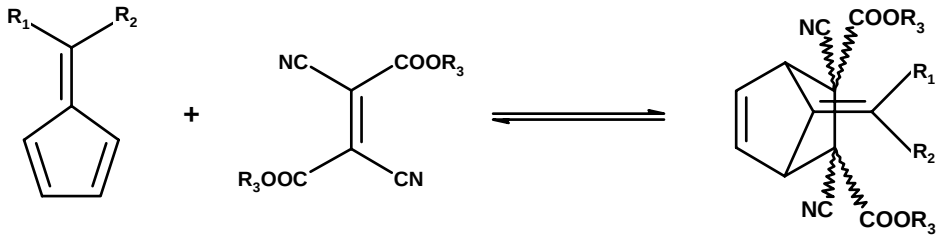
Dynamic combinatorial chemistry[1] (DCC) paves new prospects for drug discovery[2] and for material science.[3] DCCs based on target-driven selection of optimal products from dynamic combinatorial library (DCL) whose covalent elements are generated by exchange of their components. DCLs can only be formed by using fast reversible reactions, among them by some [4+2]cycloadditions. Recently, Lehn *et al*[4] have shown that the reaction of fulvenes with cyanoolefines fulfills above-mentioned conditions.

In this communication we present the preliminary studies on the Diels-Alder reaction of both symmetric and non-symmetric fulvenes of type **1** with dicyanofumarates of type **2**, leading in reversible way to [4+2]cycloadducts of type **3**.



1 **2** **3**

Reversibility of the reaction was studied by diene exchange experiments. The process was followed by ^{1}H NMR spectroscopy. The influence of experimental variables (e.g. solvents, the presence of silica gel, alumina, etc.) on the [4+2]cycloaddition was investigated. These results as well as our preliminary experiments of freezing the DCLs by catalytic hydrogenation and establishing their composition will be presented and discussed.

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P 4

4,5-DIHYDROISOXAZOLES BY 1,3-DIPOLAR CYCLOADDITION (1,3-DC). COPPER(II) CATALYSED CONDENSATION OF PRIMARY NITROALKANES WITH DIPOLAROPHILES

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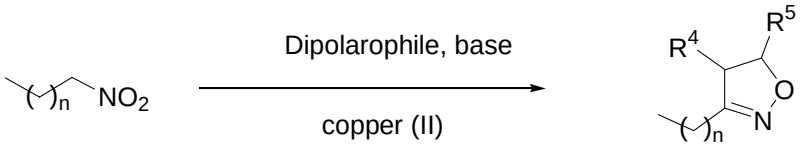
We have recently described a convenient procedure for the preparation of 4,5-dihydroisoxazoles and isoxazoles by base catalysed condensation of primary nitro compounds with alkenes and alkynes respectively.[1-4] Among the bases, those with two basic centres, e.g. 1,4-diazabicyclo[2.2.2]octane (DABCO), appear to favour the condensation much better than monobases, e.g. triethylamine, irrespective of the strength. We proposed a rationalisation of this behaviour based on the collapse of an H-bonded intermediate: indeed the reactivity is related to H-bonding basicity, rather than to Brønsted basicity.[3]



This reaction only occurred using "activated" nitro compounds (nitroacetates or nitroacetamides or nitroketones or phenylnitromethane), and other nitro compounds such as nitroalkanes failed to undergo condensation.

In this communication we wish to report the results obtained by a further extension of this procedure: preliminary data have shown that nitroalkanes and alkenes condense to give isoxazolines in the presence of a copper(II)/base catalytic system.

*Authors thank the Ministero dell'Università e Ricerca (MUR, Italy, project COFIN-PRIN **2005** – prot. **2005**038048) for financial support.*

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P 5

[4+2] CYCLOADDITION OF SINGLET OXYGEN TO NOVEL α,α'-DIGLYCOSYL FURANS*

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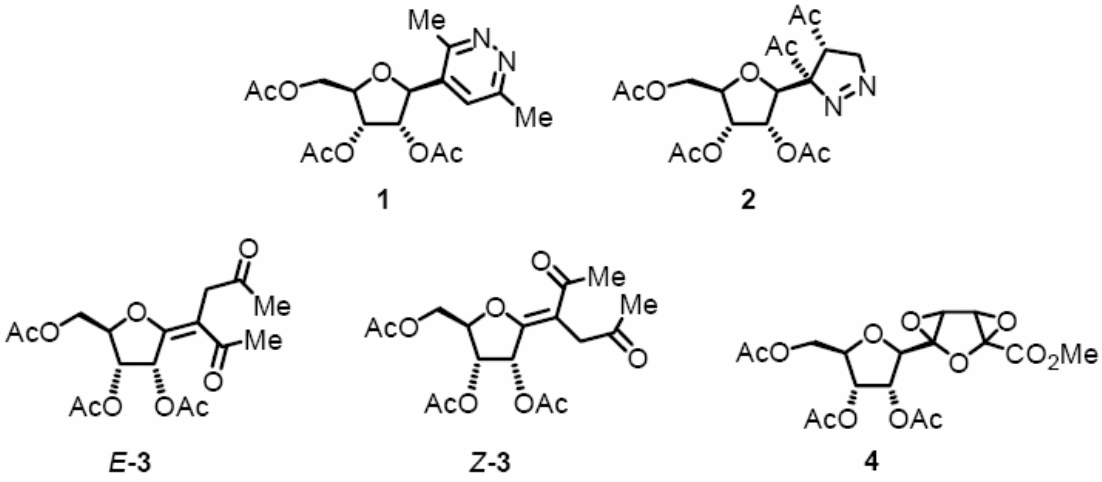
Recently we investigated the use of singlet oxygen in the [4+2] cycloaddition to glycosyl furans as starting reaction for the synthesis of new O- or C-glycosides as well as new *C*-nucleosides of pharmacological interest.[1-3] The high selectivity of the electrophile $^1O_2$, together with the quantitative reaction yields, provided an efficient strategy based on construction of the heterocycle by transformation of the aglycone of a pre-existing *C*-glycoside. This strategy allowed simple one-pot approaches to the novel pyridazin and pyrazolin *C*-nucleosides **1** and **2**, respectively, and to the *E*,*Z*-*exo*-glycals **3**, which are compounds of pharmacological interest.[1,2] Furthermore, the use of methyl furoate as the starting aglycone in the reaction provided the novel bis-epoxide **4** which was easily formed by thermal rearrangement of the [4+2] cycloaddition products.[3] The same functionality is related to the feature present in crotepoxide, a well-known antitumoral compound.



These excellent outcomes have suggested further synthetic uses of the $^1O_2$ cycloaddition reaction. In this communication we report the first [4+2] cycloaddition of singlet oxygen to α,α'-diglycosyl furans carried out with the purpose to generate novel disaccharides structurally related to mimics of the Sialyl Lewis-X (sLe^X), a tetrasaccharide involved in inflammatory processes.[4]

* Lavoro finanziato dal MIUR (PRIN 2005-2007).

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P 6

1,3-DIPOLAR CYCLOADDITION OF NITRONES WITH ALKYLIDENECYCLOPROPANES: A VERSATILE TOOLS FOR HETEROCYCLIC SYNTHESIS

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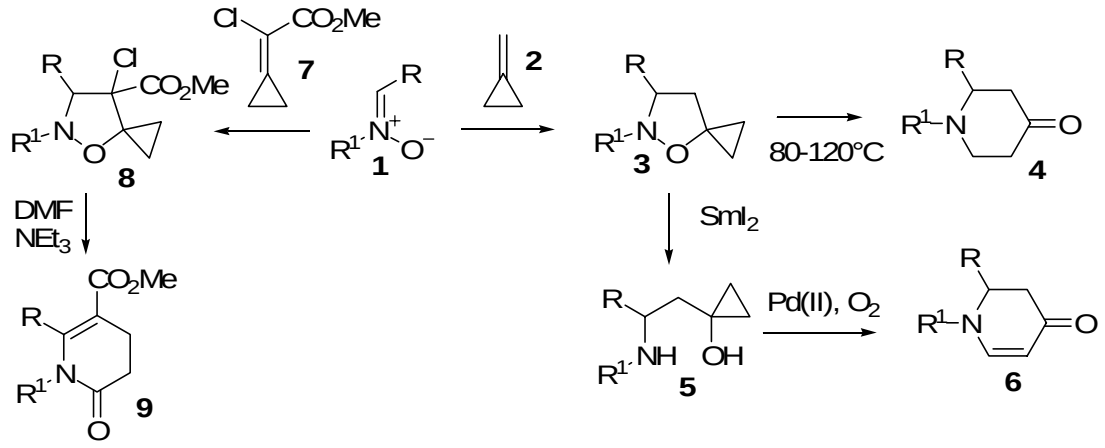
The versatile reactivity of alkylidenecyclopropanes has found an useful counterpart in the 1,3-dipolar cycloaddition with nitrones providing isoxazolidines substituted with a spirofused cycloprane ring. The reactivity of these compounds is extremely influenced by the nature of the substituents and by the reaction conditions. While the simple methylenecycloprane (**2**) affords isoxazolidines that upon thermal treatment afford the tetrahydropyridone **4**,[1] the use of 2-chlorocyclopropilidene acetate (**7**) affords isoxazolidine **8** that rearrange to lactam **9**.[2] The reductive ring cleavage of the isoxazolidine ring affords the corresponding aminocyclopropanol **5** which, in a process catalysed by Pd(II) salts, is transformed into the dihydropyridone derivative **6**.[3] Extending the same processes to other alkylidenecyclopropane derivatives bearing more than one cyclopropyl group, it is possible to access cyclopropyl substituted derivatives.



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P 7

SYNTHESIS OF PYRROLE[1,2-C]THIAZOLE-3-CARBOXYLATE DERIVATIVES VIA MESOIONIC THIAZOLO[3,4-C]OXAZOLATE CYCLOADDITIONS

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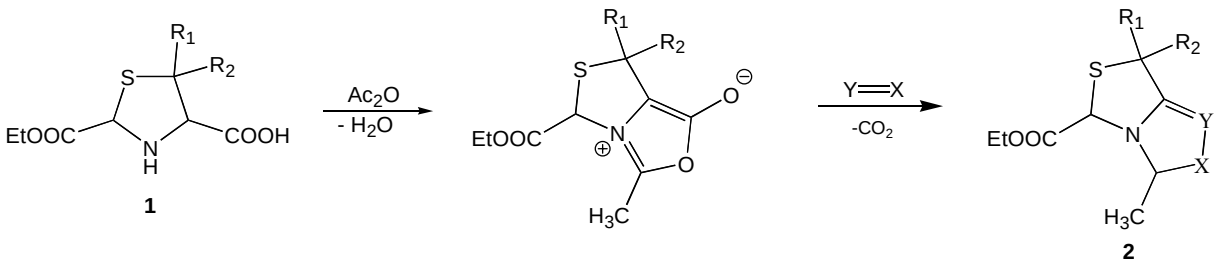
Sulfur-containing cyclic α-aminoacids, such as 1,3-thiazolidine-4-carboxylic acids, are interesting building blocks and were utilized in the synthesis of natural penicillins. In addition to their ability to transform into mesoionic derivatives, which makes them particularly suitable for use in cycloaddition reactions, they can also be employed as chiral auxiliaries and appear able to construct molecules with antibacterial properties.[1]

Within the field of our studies of mesoionic compounds,[2] a focus of special interest has been synthesis and the study of the reactivity of 1,3-thiazolidine-2,4-dicarboxylic acids in 1,3-dipolar cycloaddition processes. In particular, acid monoesters **1** were reacted with selected dipolarophile substrates and acetic anhydride in a typical one-pot procedure to produce fused pyrrole-thiazole derivatives **2**.



The carboxythiazolidine substrate **1** participates in a domino process initially undergoing acylation and subsequently dehydration-cycloaddition-cycloreversion.

Stereochemical and mechanistic aspects will be discussed in the presentation.

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P 8

STEREOSELECTIVE SYNTHESIS OF SPIRO-β-LACTAMS AND THEIR USES AS SYNTHONS

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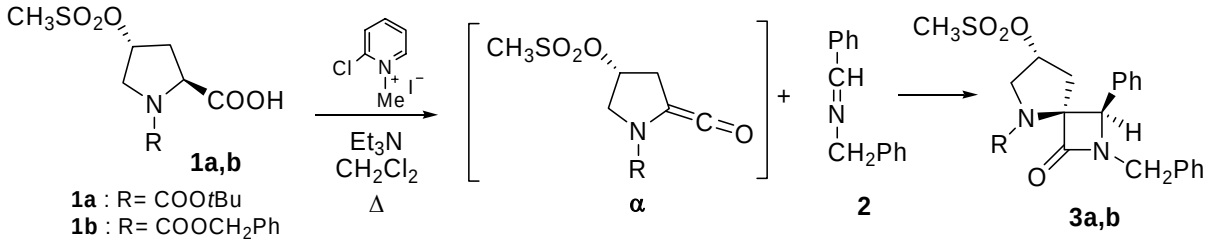
Continuing our studies of the synthesis and reactivity of spiro-β-lactams,[1] we reported here the synthesis of new pyrrolidine-derived 4-spiro-β-lactams and the study about some possible transformations of the pyrrolidine ring.

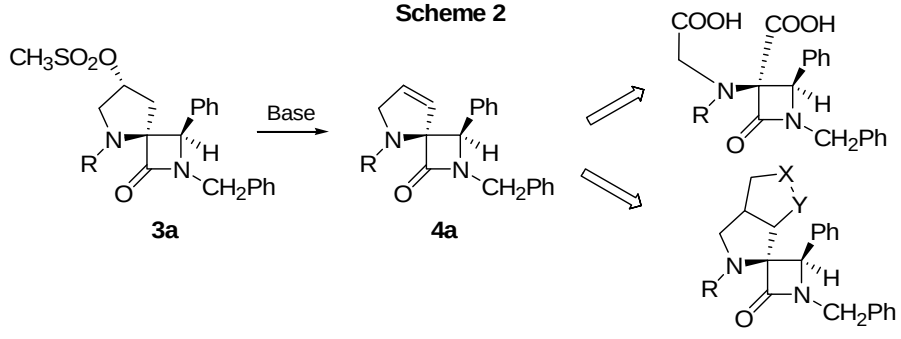
The pyrrolidine-derived 4-spiro-*β*-lactams **3a**,**b** were obtained by means of a [2+2] ketene-imine cycloaddition (*Staudinger*'s reaction) between imine **2** and the chiral non-symmetrical cyclic ketenes *α*. These ketenes were generated starting from (2*S*,4*R*)-4-methanesulfonyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester **1a** or 1-benzyl ester **1b** (prepared starting from the natural *trans*-4-hydroxy-L-proline) using the *Mukaiyama*'s reagent and triethyl-amine. The reaction of ketenes α with imine **2** afforded with total stereoselectivity the spiro-β-lactams **3a**,**b** with a relative *cis*-disposition of *N*-R and the phenyl group (Scheme 1).

Scheme 1



Spiro-*β*-lactam **3a** was successively treated with a base to eliminate methansulfonic acid and to afford the corresponding pyrroline-derivative **4a** susceptible of further transformations. For example the reactivity of the C-C double bond will be tested with oxidants or 1,3-dipoles to give functionalized monobactams or three-membered heterocycles, respectively (Scheme 2).

Scheme 2



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P 9

ENANTIOSELECTIVE GLYOXYLATE-ENE REACTIONS CATALYSED BY (SALEN)CHROMIUM(III) COMPLEXES

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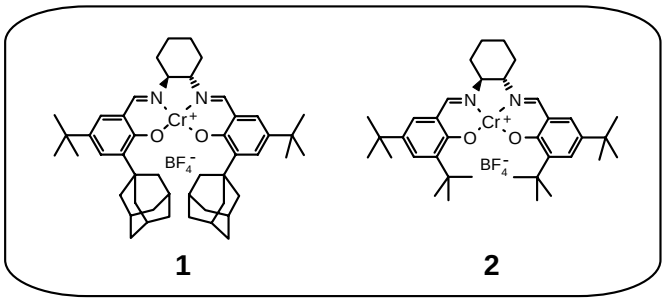
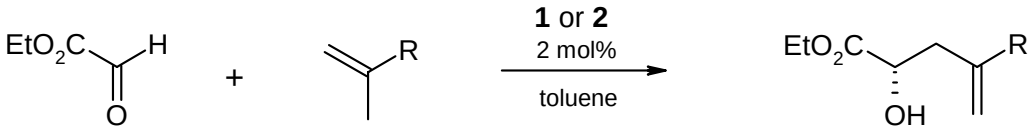
The reaction of olefins with glyoxylates is one of the most efficient methods for constructing α-hydroxy acids containing a double bond at γ,δ-position or, after reduction, the corresponding 1,2-diols. Such optically pure products are of great synthetic importance.

We focused our attention on asymmetric version of this pericyclic reaction[1] using chiral metallosalen complexes as catalysts.[2] In this communication we present studies on enantioselective carbonyl-ene reaction of alkyl glyoxylates with various 1,1-disubstituted olefins, catalysed by modified chiral (salen)Cr(III)BF_4 complexes. We found that the chromium complex **1**, bearing adamantyl substituents at the 3,3'-positions of the salicylidene moiety, catalyse the reaction much more selectively than the classic Jacobsen catalyst of type **2**. The reaction proceeded effectively under undemanding conditions in the presence of 2 mol% of the catalyst **1** in an acceptable yield (56–79%) and with 59-92% ee.[2]





cat. **1**	R=Ph, Me, *i*-Pr, *t*-Bu	59-92% ee
cat. **2**	R=Me	15% ee

To conclude, we have shown that the sterically-modified complex **1**, readily accessible on a multigram scale, catalyse the ene reaction of alkyl glyoxylates with moderate to good enantioselectivities (up to 92% ee), while the classic Jacobsen-type catalyst led to nearly racemic mixtures.

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P 10

ONE-POT SEQUENTIAL 1,3-DIPOLAR CYCLOADDITION/Pd-CATALYZED CYCLIZATION AS A ROUTE TO NITROGENATED POLYHETEROCYCLIC SYSTEMS

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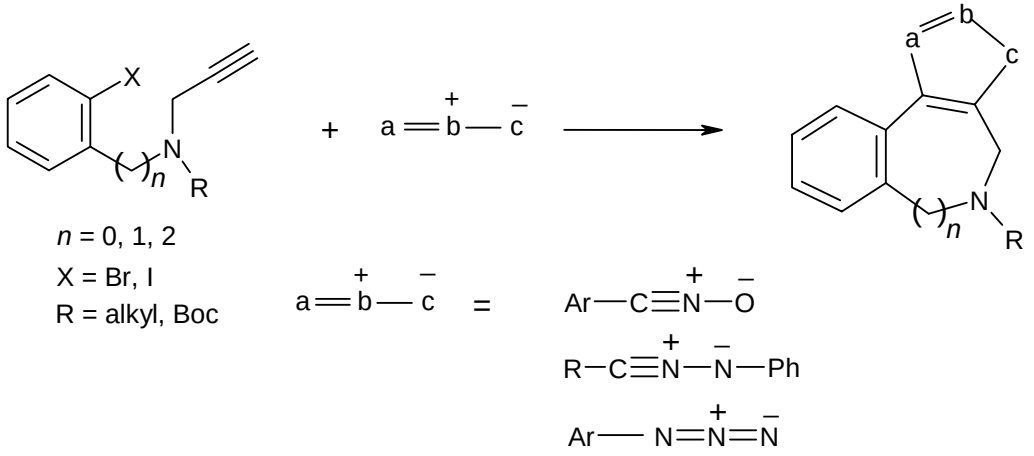
One-pot sequential reactions represent a fruitful approach in organic synthesis due to the possibility to give rise to complex structures by simultaneous formation of two or more bonds, coupling simple and flexible building blocks in a one sequence without isolating the intermediate or changing the reaction conditions. As a consequence, the one-pot sequential reactions are versatile tools of "Green Chemistry" owing to minimization of waste since, compared to stepwise reactions, the amounts of solvents, reagents and energy would dramatically decrease.

Tandem process involving intramolecular Pd-catalyzed reactions have found a broad range of applications but only one report has been previously described in the literature concerning the combined methods with 1,3-dipolar cycloadditions.[1] We previously exploited the application of the sequence Pd-catalyzed reaction/1,3-dipolar cycloaddition obtaining spiroannulated tricyclic system based on tetrahydroisoquinolines nucleus.[2]

With the aim to widen the scope of the sequential methodology we decided to develop the reverse sequence applying first the 1,3-dipolar cycloaddition followed by Pd-catalyzed intramolecular reaction. The advantage of this sequence is the possibility to use different 1,3-dipolar substrates affording to isoxazolo, pyrazolo and triazolo-fused aza-heterocyclic systems. The intramolecular Pd-catalyzed process was unusually carried out on five-membered rings having more than one heteroatom, giving rise to the formation of quinoline, benzazepine and benzazocine.



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P 11

A NEW APPROACH TO THE SYNTHESIS OF *C*-GLYCOSYLATED α-AMINO ACIDS

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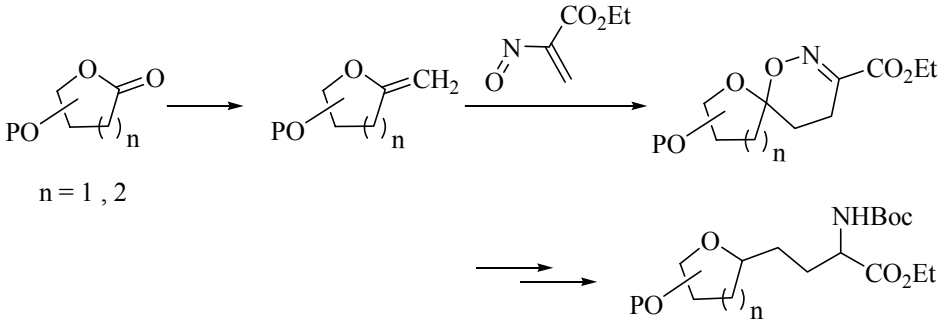
Glycosylation is one of the most common and widespread post-translational modifications of proteins, that exerts influence upon the properties of the parent proteins. Furthermore, glycopeptides are involved in a variety of biological processes like cell recognition and cell-cell communication. In contrast to the natural *O*- and *N*-glycopeptides, *C*-glycopeptides are more stable against chemical and enzymatic hydrolysis and may have applications in many areas of modern medicine such as the control of bacterial and viral diseases, cancer therapy, and treatment of inflammatory processes.

In accordance with our interest in applying the hetero-Diels-Alder additions towards the synthesis of biomometic molecules,[1,2] our approach involved conversion of the appropriate protected sugar lactones to the respective enol ethers, followed by hetero-Diels-Alder addition of ethyl 2-nitrosoacrylate, in situ generated from the oxime of ethyl bromopyruvate, as the key-step. Subsequent C=N reduction by sodium cyanoborohydride, protection of the correspondent amine and N-O bond scission by catalytic hydrogenation over Raney Ni, generated the protected glycosylated amino acid. Further reduction of the O-H group yielded the C-glucosylated amino acid.



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P 12

HIGH PRESSURE DIELS-ALDER REACTIONS OF 4-ETHYNYL[2.2]PARACYCLOPHANES. AN INNOVATIVE ROUTE TO THE SYNTHESIS OF 4-ARYL[2.2]PARACYCLOPHANES

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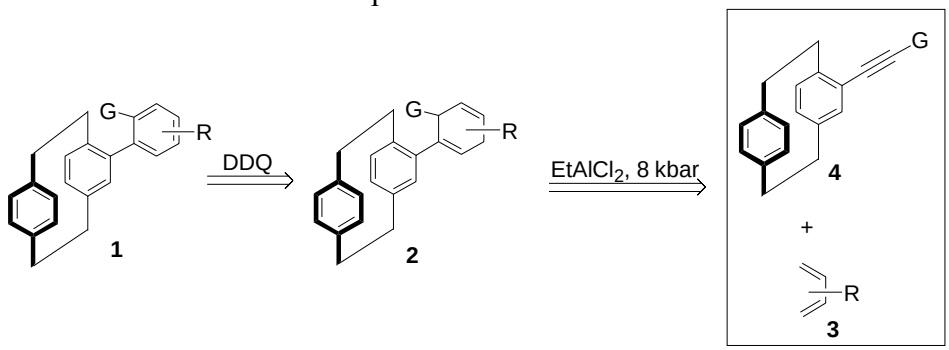
4-Aryl[2.2]paracyclophane derivatives **1** are an attractive class of compounds for their pharmacological and/or optoelectronic properties because of their structure containing the biaryl subunit and the three-dimensional π-electron system of phane.

Biaryl represents, indeed, an important structural motif in a brod range of bioactive molecules, chiral ligand for metal catalyst and new optoelectronic materials.[1]

Although the Diels-Alder cycloadditions of arylacetylenes with 1,3-butadienes could in principle represent a valuable approach for the preparation of arylcyclohexadienes as precursors of biphenyls, this procedure is still largely unexplored due to the low reactivity of arylacetylenes as dienophile. To our best knowledge, only one example of synthtic approach to biaryls via Diels-Alder reaction is reported.[2]



As a continuation of our interest in the synthesis of novel [2.2]paracyclophane derivatives,[3] in this communication we report the study of the Diels-Alder reaction of 4-carbomethoxyethynyl[2.2]paracyclophane **4** (G = CO_2CH_3) with various 1,3-butadienes **3** and the conversion of the relative cycloadducts **2** into the 4-aryl[2.2]paracyclophanes **1**.

Despite the activation by the electron-withdrawing carboxymethyl group, the arylacetylene **4** behaves as poorly reactive dienophile in [4+2]cycloadditions, then the Diels-Alder reactions have to be accelerated by Lewis acid catalysis in combination with high pressure.

The structure of the products have been assigned by NMR spectroscopy.

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P 13

COPE REARRANGEMENTS VERSUS RING CLOSURE IN THE FLASH VACUUM PYROLYSIS OF ACYCLIC DIENES AND ENYNES

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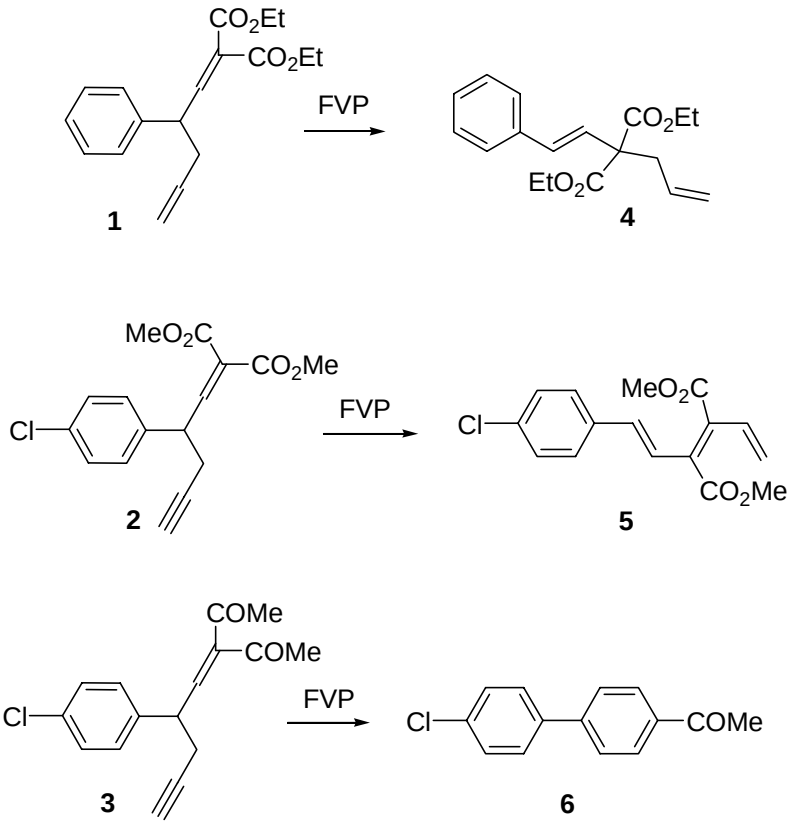
The thermal reaction of the 1,5-hexadiene (**1**) and the 1-hexen-5-ynes (**2**) and (**3**) have been studied at temperatures between 300-500ºC, contact times of 0.01 s and at pressures of 0.01 Torr (Flash Vacuum Pyrolysis-FVP). The experimental results show that malonate derivatives **1** and **2** underwent a Cope rearrangement under reaction conditions. In the case of **1** the initial Cope product **4** could be obtained, while compound **2** suffered a Cope rearrangement followed by a 1,2-acyl migration to give triene **5**. A different behavior was observed when the enyne **3** was submitted under FVP conditions. Thus, this compound underwent a cyclization reaction (*via* an alkenylidene carbene intermediate) followed by aromatization to give the biaryl **6** (Scheme 1). The results reported in this work reveal that there is a strong influence of the substituents of the C=C bond in the course of the thermal reaction.



Scheme 1

P 14

EXPERIMENTAL STUDIES OF RETRO DIELS ALDER REACTION (RDA) OF 4A,5,8,8A-TETRAHYDRO-2-ARYLQUINAZOLIN-4(3*H*)-ONES IN FLASH VACUUM PYROLYSIS

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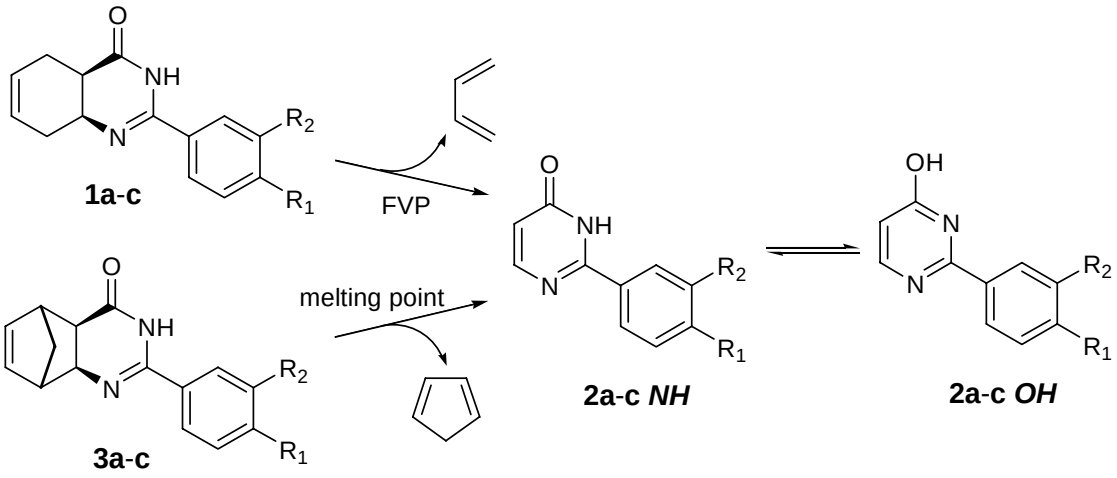
In our earlier investigations on the retro Diels Alder (RDA) reactions by Flash Vacuum Pyrolysis (FVP), we found that FVP of *cis* 2-quinazolin-2,4-ones affording butadiene are of higher energy than the pyrolysis of the norbornene analogous that split off cyclopentadiene.[1,2] In this work we present the result of FVP experiments of 4a,5,8,8a-tetrahydro-2-arylquinazolin-4(3*H*)-ones **1a-c**, where the mayor products are the corresponding heteromonocyclic compounds **2a-c** in very good yields (84-91% crystallized from ethyl acetate), Scheme 1. A comparison with FVP reactions of some heterocycles with similar structures show that RDA reaction depends on the endocyclic tautomerism in the starting heterocycle and on the aromaticity of the products **2a-c**. The FVP experiments were carried out between 460-600 ºC with contact times of 0.01 s and at pressures of 0.01 Torr.



a: R_1= Cl, R_2= H. **b**: R_1= H, R_2= Cl. **c**: R_1= H, R_2= H.

Scheme 1: Thermolysis of 2-arylquinazolin-4(3*H*)-ones.

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P 15

[4+2] CYCLOADDITION REACTIONS OF 4-ALKENYLTHIAZOLES WITH TRIAZOLINEDIONES

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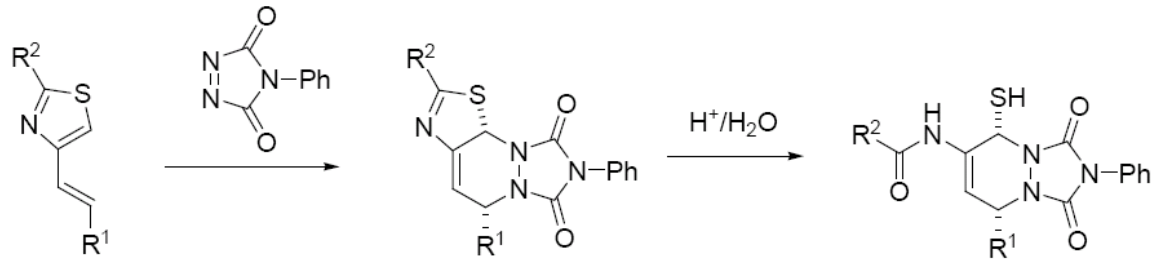
Recently, we have demonstrated that 4-alkenylthiazoles **1** behave as reactive all carbon dienes in Diels-Alder reactions with *N*-substituted maleimides, maleic anhydride and naphtoquinone.[1] 1,2,4-Triazoline-3,5-diones (TADs) are among the most reactive dienophiles and have been used extensively in organic synthesis.[2] Nevertheless, the mechanism of this cycloaddition process, i.e. concerted or stepwise, has brought some controversy along the years. Experimental studies with TADs indicate that both concerted and stepwise pathways may occur, depending upon the diene structure.[3]

In this communication we will report on the experimental and mechanistic details of the [4+2] cycloaddition of 4-alkenylthiazoles **1** with PTAD. As expected, these reactions take place quantitatively and with high levels of stereocontrol. These processes have been also investigated theoretically with the density functional theory in order to elucidate if a concerted or stepwise mechanism is taking place.

The asymmetric version of the cycloaddition step by using chiral 4-alkenylthiazoles as dienes will be also presented. Finally, we will also report on the treatment of the cycloadducts **2** under acidic conditions, which interestingly leads to the 1,2-aminothiol derivatives **3** by means of the hydrolytic cleavage of the 2-thiazoline ring.



1 **2** **3**

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P 16

4-ALKENYL-2-DIMETHYLAMINOTHIAZOLES: EXCELLENT DIENES FOR DIELS-ALDER REACTIONS

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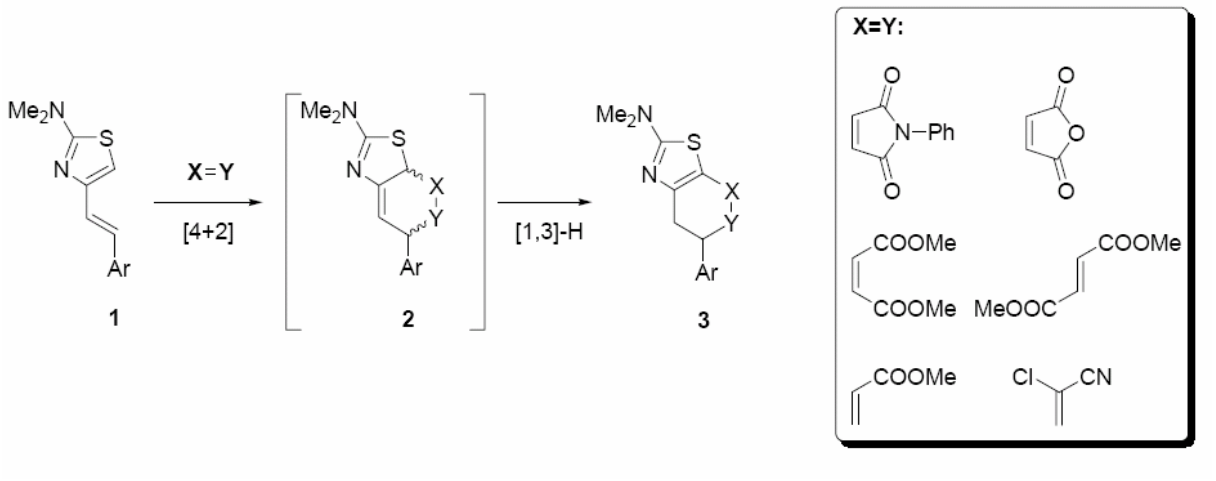
Recently, we have demonstrated that 4-alkenyl-2-alkyl(aryl)thiazoles react under heating with *N*-substituted maleimides, maleic anhydride and naphtoquinone to give the corresponding Diels-Alder cycloadducts.[1] Nevertheless, these reaction products further transform *in situ* through either a 1,3-hydrogen shift, dehydrogenation, or an ene reaction or Michael addition with another molecule of dienophile.

The accelerating effect of electron-donating subtituents at the diene on the rate of the cycloaddition step has been established for a long time.[2] In addition, it is also known the activating effect of an amino group at 2 position of the thiazole ring in their electrophilic substitution reactions.[3] In this communication we will present the Diels-Alder reaction of 4-alkenyl-2-dimethylaminothiazoles **1** with classical dienophiles such as *N*-phenylmaleimide, maleic anhydride, dimethyl maleate and dimethyl fumarate. In spite of these processes take place under soft conditions, the primary cycloadducts **2** were not isolated. Instead, they further transform trough a 1,3-hydrogen shift step under the reaction conditions to give compounds **3**, which were obtained in excellent yields. The regioselectivity of the cycloaddition step, when asymmetric dienophiles are used (i.e. methyl acrylate or α-chloroacrylonitrile), has been also investigated.



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P 17

HIGHLY DIASTEREOSELECTIVE INTRAMOLECULAR DIELS-ALDER REACTIONS OF 4-ALKENYLTHIAZOLES

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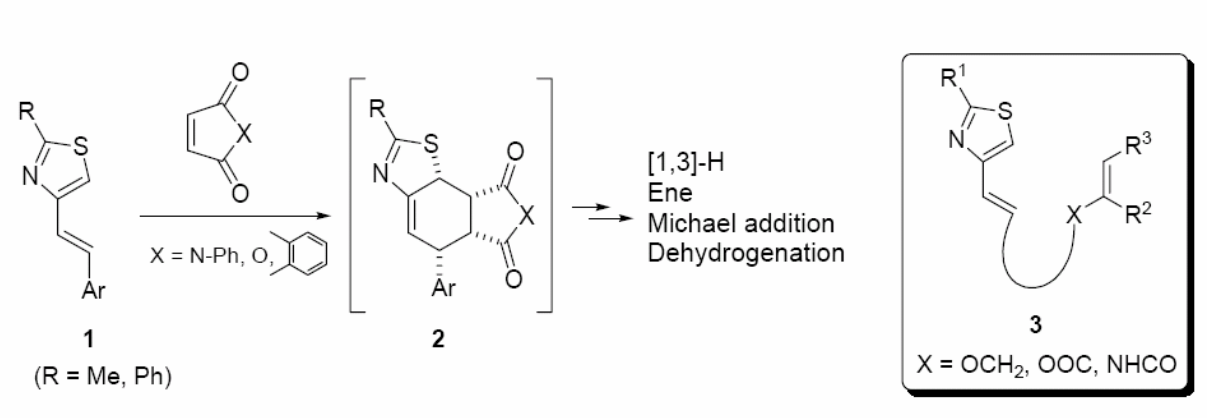
The Diels-Alder reaction is one of the most widely used methods in organic synthesis due to its connective nature. The intramolecular version of the Diels-Alder reaction, where the diene and dienophile are constrained in the same structure, allows the simultaneous formation of two rings and, in a single step, complex structures such as those contained in many drugs and natural products can be assembled.[1] Recently, we have demonstrated that, contrary to some expectations, 4-alkenylthiazoles **1** behave as reactive all-carbon dienes in Diels-Alder reactions with *N*-phenyl maleimide, maleic anhydride and naphtoquinone.[2] Depending on the dienophile, the cycloadduct further transforms under the reaction conditions through either a 1,3-hydrogen shift, dehydrogenation, or an ene reaction or Michael addition with another molecule of dienophile. In this communication we will present the intramolecular version of this process for which thiazole derivatives **3** were selected as substrates.

Thiazoles **3** react under heating to give the corresponding heteropolycycles in high yields and high levels of diastereoselection. Expectedly, the electronic nature of the substituents located either at the tether or the dienophilic moiety (X, R^2 and R^3) has a significant influence on the reaction rate. Stereochemical analysis of the corresponding cycloadducts was accomplished following accurate measurement of coupling constants and with the aid of ^{1}H,^{1}H-NOESY experiments. Confirmation of the configurational assignment was accomplished by single-crystal X-ray analysis.



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P 18

ASYMMETRIC 1,3-DIPOLAR CYCLOADDITIONS OF CHIRAL CARBOXYLOYL NITRILE OXIDES TO CYCLOALKENES

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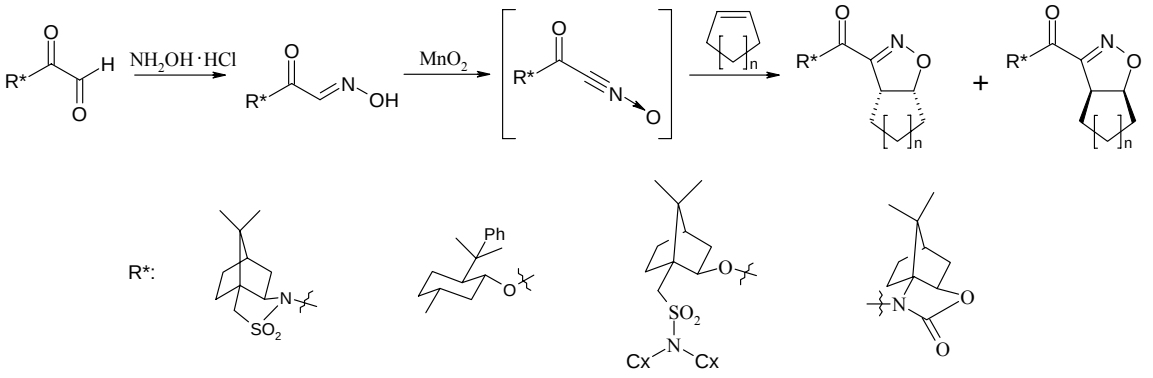
Asymmetric 1,3-dipolar cycloaddition of nitrile oxides to alkenes provides a powerful tool for the stereocontrolled synthesis of 4,5-dihydroisoxazoles.[1] With respect to the easy cleavage of their weak N-O bond, their readily hydrolysis as well as potential nucleophilic or electrophilic reactive centers, these heterocycles demonstrate a high practical usefulness for the syntheses of several types of ligands, pharmaceuticals or natural products.[2,3]

The literature offers only few examples of diastereoselective 1,3-dipolar cycloadditions of optically active nitrile oxides. We would like to present a representative examples of diastereoselective 1,3-dipolar cycloaddition of optically active nitrile oxides to cycloalkenes.



Carboxyloyl nitrile oxides were generated from corresponding aldoximes via mild oxidation with MnO_2 and trapped *in situ* with cycloalkenes to furnish 2-isoxazolines.[4] The cycloadducts were obtained in good chemical yields and with moderate diastereomeric excesses.

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P 19

HETEROCUMULENE EFFECT IN [1,3]- AND [1,5]-H SHIFTS

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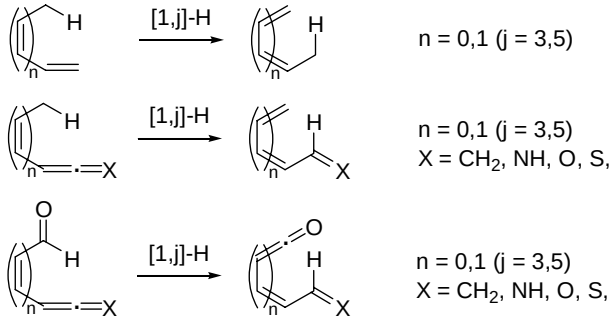
Pseudopericyclic reactions are a subset of pericyclic reactions which has been placed on a solid foundation thanks to the works of Birney and others.[1]

The pseudopericyclic nature of some [1,3] and [1,5] shifts has been well documented, although there are scarce examples of pseudopericyclic [1,5]-H shifts.[1a,2]

Jensen, in a theoretical study on sigmatropic [1,j] (j = 3, 5, 7, 9) rearrangements described that in the [1,3]- and [1,5]-H shifts a decrease of the energy barrier takes place when the terminal double bond is substituted by an allene unit, the so-called "allene effect".[3]

In this communication we will report that the substitution of the terminal double bond by a heterocumulenic moiety favors in all cases the existence of pseudopericyclic orbital interactions in the corresponding transition states, and consequently decreases the energy barrier of the process (*heterocumulene effect*).

We have studied the mechanism of the [1,3]- and [1,5]-H shifts depicted below at the B3LYP/6-31+G** level of theory, with the aim of: a) probing the existence of the heterocumulene effect in these reactions; b) classifying the transition states of [1,3]-H and [1,5]-H shifts in these heterocumulenes as pseudopericyclic or pericyclic, and c) investigating the influence of the atom linked to the migrating hydrogen in the energy barriers of the processes and the orbital topology of the corresponding transition states.



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P 20

HIDRICITY–PROMOTED [1,5]-H SHIFTS IN ACETALIC KETENIMINES

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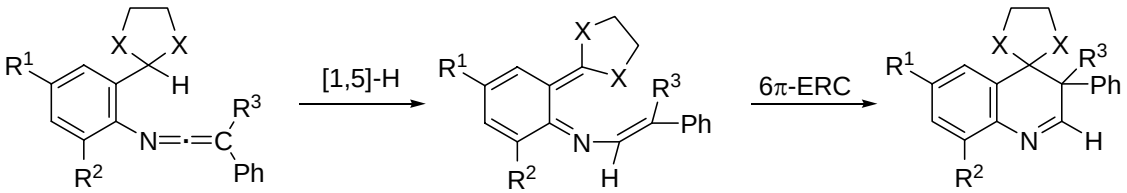
Ketenimines are known to participate in a great variety of cycloaddition reactions and 6π-electrocyclizations, whereas there are only few examples of their participation in sigmatropic rearrangements and sigmatropic shifts. To the best of our knowledge, only four cases of [1,5] sigmatropic shifts involving a H transfer to the central heterocumulenic carbon atom have been reported so far.[1]

We have recently reported[2] that 2-monosubstituted 1,3-dioxolanes and 1,3-dithiolanes act as hydride-releasing fragments, transferring intramolecularly their acetalic H atom to the central carbon of ketenimine functions. The presumed products of these migrations, *o*-quinomethanimines, undergo *in situ* 6π-electrocyclization leading to spiro-quinolines. These new [1,5]-H shifts occur under unusually mild thermal conditions. We have rationalized this fact on the basis of the hydride-releasing character of the 1,3-dioxolane and 1,3-dithiolane functions.



We will report in this communication a full account of our investigations on ketenimines containing new grouping capable to promote [1,5]-H shifts due to their presumable hydricity-imparting functionalities (1,3-dioxanes, 1,3-dithianes, 1,3-oxathianes, acyclic acetals, acyclic dithio acetals, and acyclic monothio acetals).

Computational calculations have been carried out with the aim of elucidating the mechanism of these transformations and explaining the positive role of acetal and dithio acetal functions in these [1,5]-H shifts.

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P 21

PYBOX/LANTHANIDE CATALYSED DIELS-ALDER Vs. HETERO-DIELS-ALDER REACTIONS BETWEEN CYCLOPENTADIENE AND METHYL (*E*)-2-OXO-4-PHENYL-3-BUTENOATE AND THE SIGMATROPIC REARRANGEMENT OF THE HDA ADDUCT

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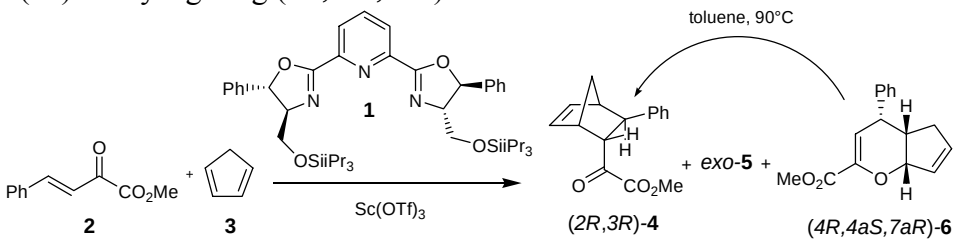
A new pybox class of catalysts[1] has been obtained from (4'*S*,5'*S*)-2,6-bis[4'-(tri-isopropylsilyl)oxymethyl-5'-phenyl-1',3'-oxazolin-2'-yl]pyridine (**1**) and lanthanide(III) triflates, which works nicely with the Diels-Alder (D.A.) and with the Mukaiyama-aldol reactions.[2]

To compare the behaviour of α- and β-dicarbonyl derivatives, coordinated to the cationic site of the catalysts through a five- or a six-membered ring chelation respectively, the D.A. reaction of methyl (*E*)-2-oxo-4-phenyl-3-butenoate (**2**) with cyclopentadiene (**3**) was studied with the catalysts derived from seven lanthanide triflate complexes of **1**. In addition to the expected normal D.A. adducts **4** and **5**, the less expected *endo*-**6** product of the [4+2] hetero-D.A. (H.D.A.) reaction derived from the α-keto-β,γ-unsaturated ester **2** behaving as heterodiene was obtained. This behaviour is rather unusual as it was observed with unsaturated phosphonates only.[3]

The enantioselectivity of the normal D.A. *endo* product **4** is strongly influenced by the nature of the cation: the Eu, Ho and Y-based catalysts give unsatisfactory ee's, while the Yb and Lu ones give results (82-86% ee) better than those reported in the literature.[4] The best catalyst is the Sc complex that induces a high diastereoselectivity and an almost complete enantioselectivity giving >99 ee of (2*R*,3*R*)-**4**, while the La-based one furnishes 31% ee of the opposite enantiomer. An almost parallel enantioselectivity is observed for the H.D.A. adducts that, with the Sc(III) catalyst giving (4*R*,4a*S*,7a*R*)-**6** with >99 ee.



The thermal behaviour of **4** and **6** was investigated with the aim to correlate their absolute configuration. A prolonged heating of the D.A. adduct **4** gives the cycloreversion to **2** and **3**, whereas the H.D.A. adduct 6, through a [3.3]-Claisen rearrangement, gives stereospecifically the *endo* D.A. product (2*R*,3*R*)-**4**.

A rationale of the stereochemical outcome of the catalyzed reaction will be proposed as well as further developments of the rearrangements of D.A. and H.D.A. adducts.

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P22

CARBOCYCLIC NUCLEOSIDES SYNTHETIC METHODOLOGIES

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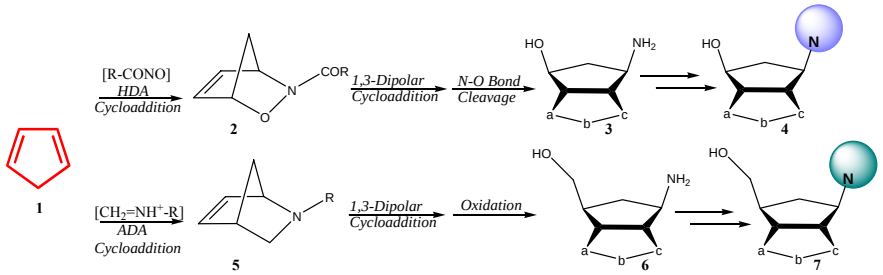
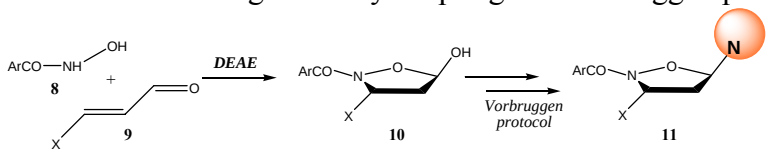
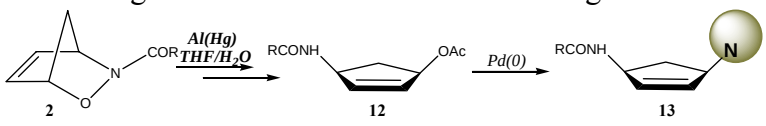
The preparation of carbocyclic and heterocyclic nucleosides has been extensively pursued due to the importance in the development of new antiviral drugs. Most of the nucleoside analogues refer to a general structure defined by the presence of a 5-membered ring of a carbocyclic or heterocyclic nature.[1] In this context, we have recently developed a synthesis of the isoxazoline-carbocyclic nor-nucleosides[2] **4** by the linear construction of the desired heterobases on the regioisomeric aminols **3** obtained from the hetero Diels-Alder (HDA) cycloadducts **2** of nitrosocarbonyl intermediates (RCONO) to cyclopentadiene **1**.[3] A complementary approach affords the "normal" nucleosides **7**, starting from a convenient source, the 2-azanorborn-5-enes **5**, which are readily available through the Grieco cycloaddition of cyclopentadiene **1** with iminium salts and highly reactive toward nitrile oxides.[4] By unmasking the aminols **6**, their prolific elaboration allowed preparation of the desired purine nucleosides **7**.



A novel approach to useful aminols for the nucleoside syntheses is also reported starting from the 5-hydroxy-isoxazolidines **10**, which were prepared through the addition of hydroxamic acids **8** to α,β-unsaturated carbonyl compounds **9**, and are excellent synthons for the preparation of *N,O*-nucleoside analogues **11** by adapting the Vorbrüggen protocol.[5]



A few Pd(0)-catalyzed addition of commercial heterobases to an allylic acetate **12** allowed to prepare nucleoside analogues **13** with retention of the starting material stereochemistry.[6]



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