ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Area of Organic Chemistry

Dept. of Industrial Chemistry
University of Bologna

Area of Organic Chemistry – staff

Permanent staff (12):

Prof. Mauro Comes Franchini	full professor
Prof. Andrea Mazzanti	full professor
Prof. Paolo Melchiorre	full professor
Prof. Giorgio Bencivenni	associate professor
Prof. Luca Bernardi	associate professor
Prof. Carla Boga	associate professor
Prof. Mariafrancesca Fochi	associate professor
Prof. Michele Mancinelli	associate professor
Prof. Paolo Righi	associate professor
Prof. Letizia Sambri	associate professor
Prof. Emanuela Marotta	assistant professor
Prof. Paolo Zani	assistant professor

Fixed term staff:

Dr. Binlin Zhao	Fixed term researcher (RTD-A)

PhDs: 4-5; post-docs: 2-3;post-grad grants; 1-2 Master internships: 8-10

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Main area and department research facilities

- NMR spectrometers (300 MHz, 400 MHz, 600 MHz)
- Analytical HPLC on chiral stationary phase
- Preparative HPLC also on chiral stationary phase
- VCD-ECD
- MS spectrometers (GC-MS, ESI);
- Single-crystal X-Ray diffractometer (access to powder XRD);

Topics & Laboratories

- **History of chemistry through XVIII and XIX centuries – chemistry as «*scientia nova*» (Zani)**

- **Development of new catalytic enantioselective reactions (OCSA-Bernardi-Fochi)**
- **«Blue chemistry»: marine biopolymer gels in catalysis (OCSA-Bernardi-Fochi)**

- **New organocatalytic enantioselective vinylogous reactions (OCSA-Bencivenni-Marotta-Righi)**
- **Organocatalytic enantioselective formation of atropisomers (OCSA-Bencivenni-Marotta-Righi)**
- **Study of organic reaction using computational methods (OCSA-Bencivenni-Marotta-Righi)**

- **Making chiral molecules with light – developing new photochemical asymmetric processes (Asymmetric Catalysis and Photochemistry Lab / Melchiorre)**
- **Photoredox catalytic processes for the late-stage functionalization of bio-relevant compounds** (Melchiorre)

Topics & Laboratories

- Synthesis of compounds as anticancer agents and related studies on their drug delivery (Boga)
- Synthesis of highly conjugated organic compounds for applications in optoelectronic field (Boga)
- Detection of labile intermediates of aromatic substitution reactions (Boga)

- DFT Calculations (OCSA-Mancinelli-Mazzanti)
- Structural analysis (OCSA-Mancinelli-Mazzanti)

- Additive Manufacturing (3D-Printing) (ASOM-Comes-Sambri)
- Bio-Ink for biomedical applications (ASOM-Comes-Sambri)
- Theranostic: Therapeutic + Diagnostic (ASOM-Comes-Sambri)
- Sensing for organic electronics (ASOM-Comes-Sambri)

History of sciences (Zani)

Development of chemistry through XVIII and XIX centuries:

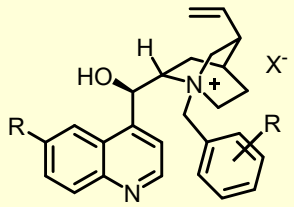
Chemistry as «*scientia nova*», a methodological and documental approach.

For information: paolo.zani@unibo.it

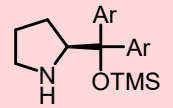
Research topics – OCSA (Bernardi-Fochi)

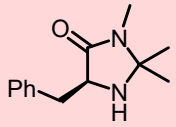
1) Development of new catalytic enantioselective reactions:
Using known organic catalysts (different classes), we explore new chemistry and reactivity.

Phase-Transfer Catalysis

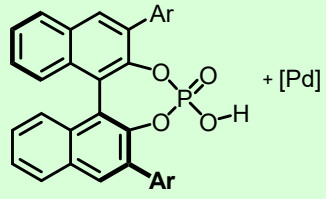


Aminocatalysis

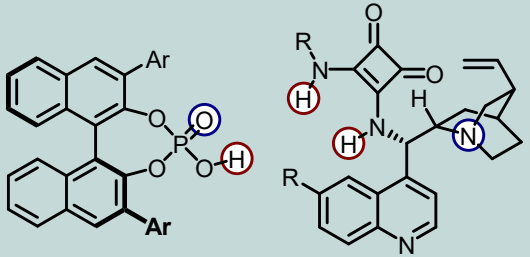




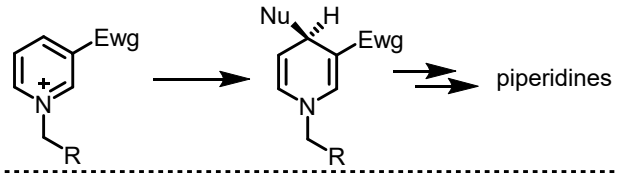
Synergistic Catalysis



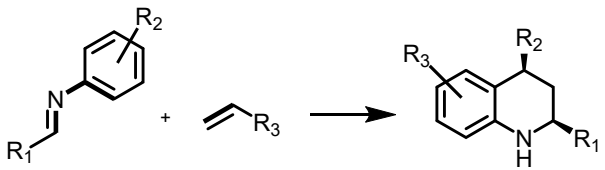
H-Bond and bifunctional catalysts



-Dearomatization of activated pyridines:



-aza-Diels-Alder cycloadditions:



A student involved in such a project will learn how to:
-perform multi-step organic synthesis (catalysts and substrates)
-characterise organic compounds (NMR, HPLC analysis)
-perform extensive optimisation of reaction conditions.

For additional information:
luca.bernardi2@unibo.it
mariafrancesca.fochi@unibo.it

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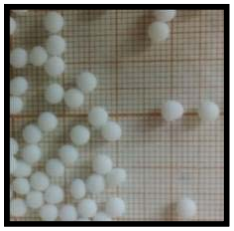
Research topics – OCSA (Bernardi-Fochi)

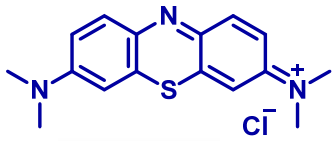
2) «Blue chemistry»: marine biopolymer gels in catalysis:

Aginate biopolymers (algae extracts) readily form gels (solvogels, aerogels) with high surface areas and functional group density: applications in catalysis and adsorption.

1) **Purification**
2) **Acidification and gelification**
3) **From hydrogel to solvogel to aerogel**



Aerogel:
Same properties of a gel (surface are 600 m^2g^{-1})
All functionalities are accessible



A student involved in such a project will learn how to:
-perform simple organic synthesis
-prepare and manipulate hydro and solvogels
-characterise organic compounds (NMR, HPLC analysis)
-perform extensive optimisation of reaction conditions

Currently pursued: is it possible to exploit the intrinsic homochirality for enantioselective processes?

For information:
luca.bernardi2@unibo.it
mariafrancesca.fochi@unibo.it

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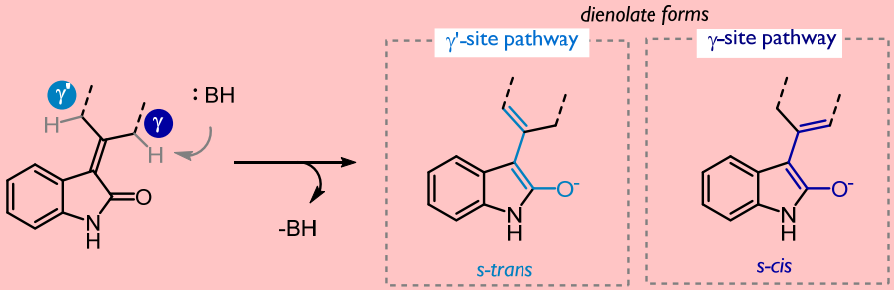
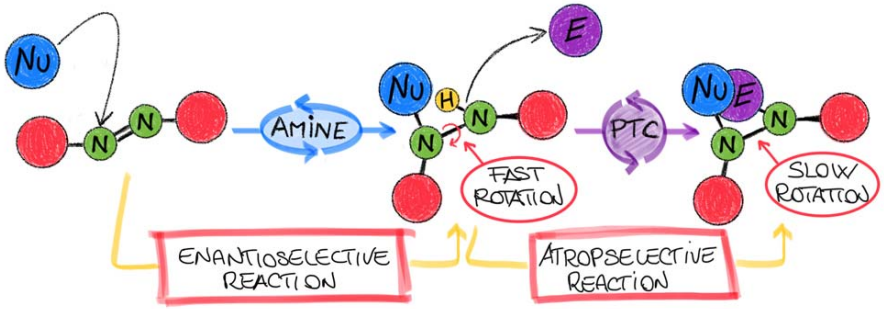
Research topics – ORG (Bencivenni*-Marotta-Righi)

1 - New organocatalytic enantioselective vinylogous reactions:



1 PhD student
1-3 Master (6-9 months) students
1 Bachelor (3-6 months) students
1 post-doc

2 – Organocatalytic enantioselective formation of atropisomers:



3-Collaboration with fine chemical SMEs:

FATRO S.p.A. - Veterinary Pharmaceutical Industry
40064 Ozzano dell'Emilia (BO) Italy

Endura S.p.A. - PBO and synthetic pyrethroids
Headquarters in Bologna, manufacturing and R&D in Ravenna

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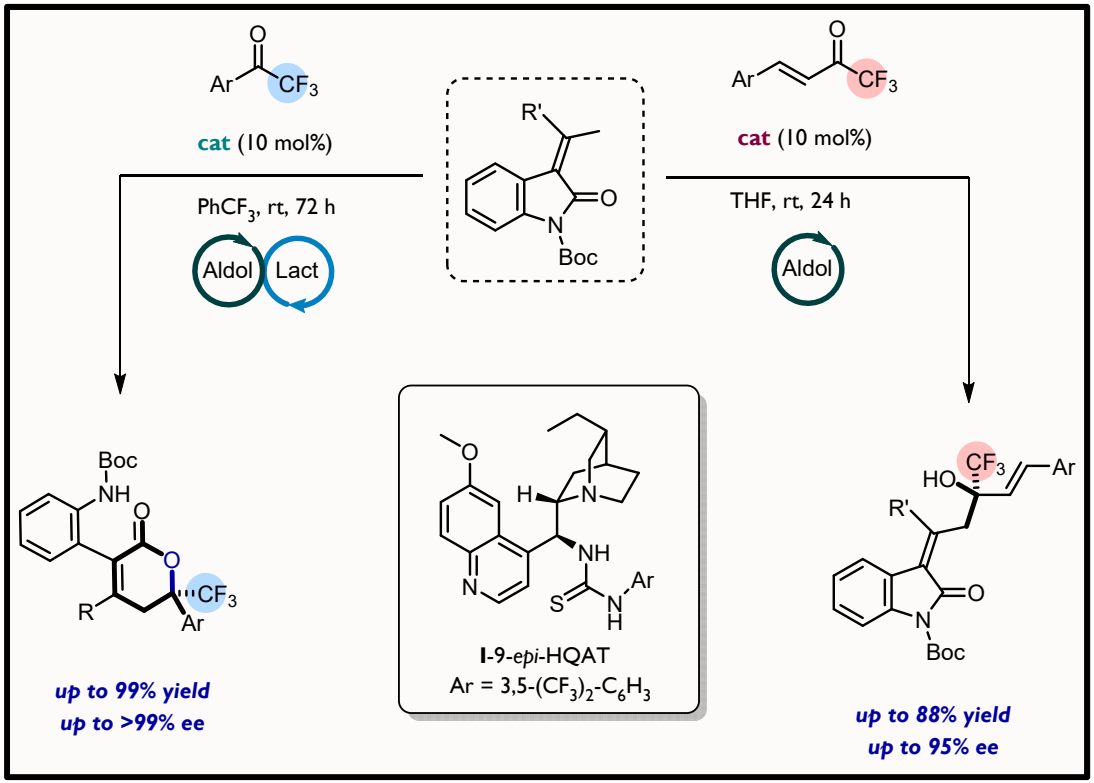
Research topics – (Bencivenni-Marotta-Righi)

1) New organocatalytic enantioselective vinylogous reactions:

- Vinylogous reactivity is a valuable strategy for the remote modification of a molecule.
- Vinylogous addition of alkylidene oxindole on aryl trifluoromethyl ketone resulted in a rare aldol reaction-lactonization cascade. The reaction, catalyzed by a bifunctional tertiary amine, provides an efficient entry to enantioenriched trifluoromethylated a,β-unsaturated δ-lactones.
- The addition on a,β-unsaturated trifluoromethyl ketones provided an efficient preparation of enantioenriched trifluoromethylated allylic alcohols

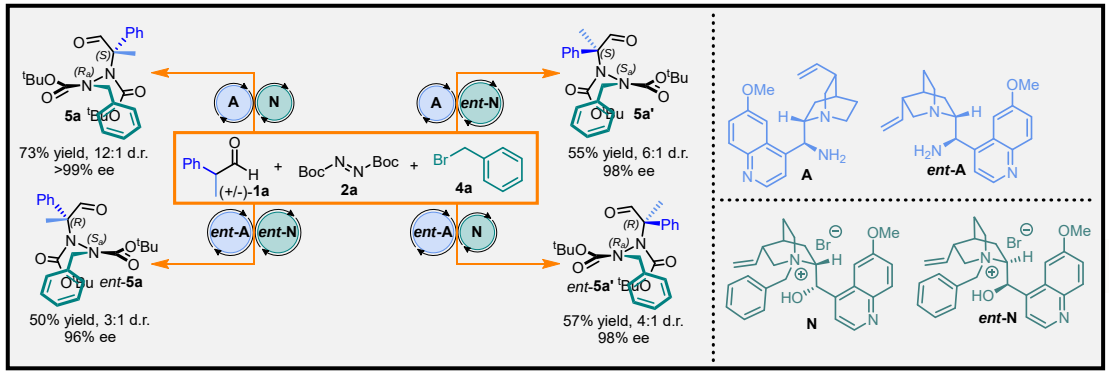


Bencivenni, et al. *J. Org. Chem*. **2018**, *83*, 12440.
Bencivenni, et al. *RSC Adv.*, **2018**, *8*, 33451

Research topics – (Bencivenni-Marotta-Righi)

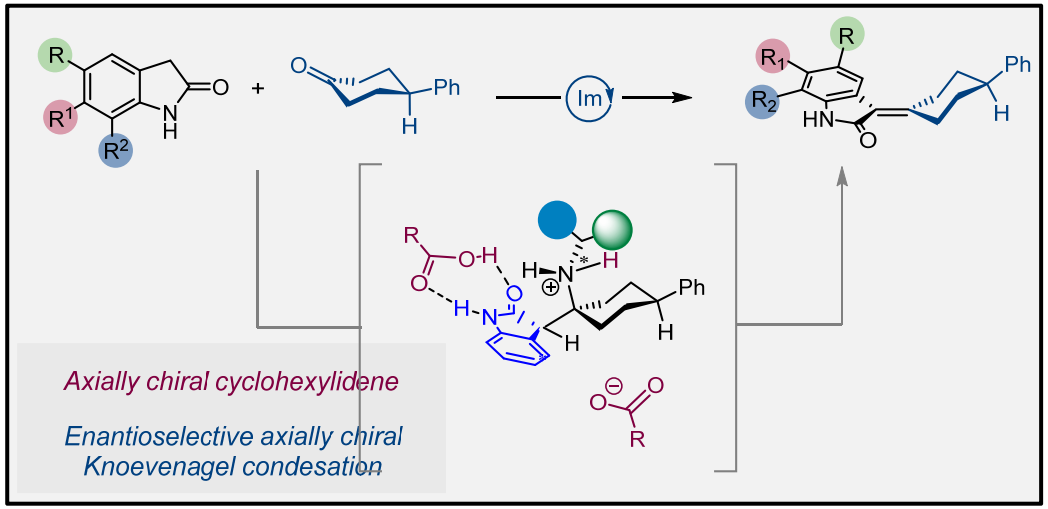
2) Organocatalytic enantioselective formation of atropisomers:

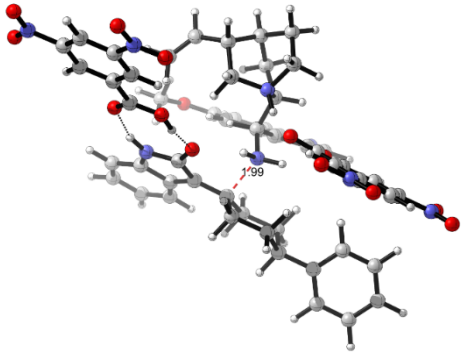
- Enantioselective organocatalysis has been successfully applied to the synthesis of atropisomers
- Synthesis of atropisomeric hydrazides via diastereoconvergent sequential catalysis



Bencivenni, et al. *Angew. Chem. Int. Ed.*, **2022**, *61*, *e202209895*

- Axially chiral cyclohexylidene oxindoles were selectively obtained by means of organocatalytic Knoevenagel condensation. Insights on the mechanism were obtained by DFT methods





Bencivenni, et al. *Org. Lett.*, **2019**, *21*, 3013.

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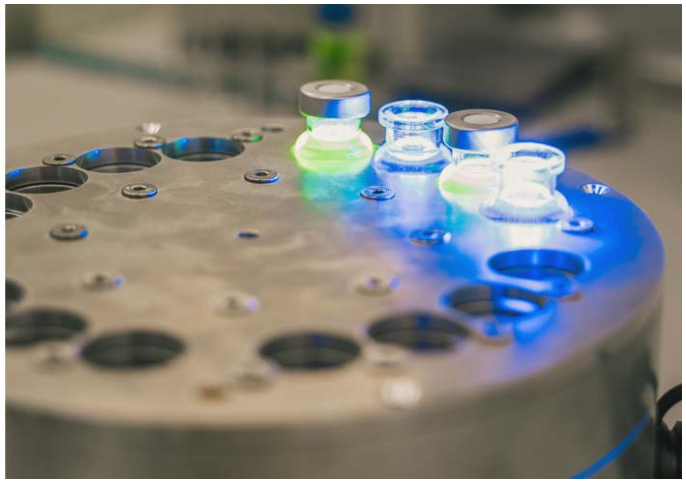
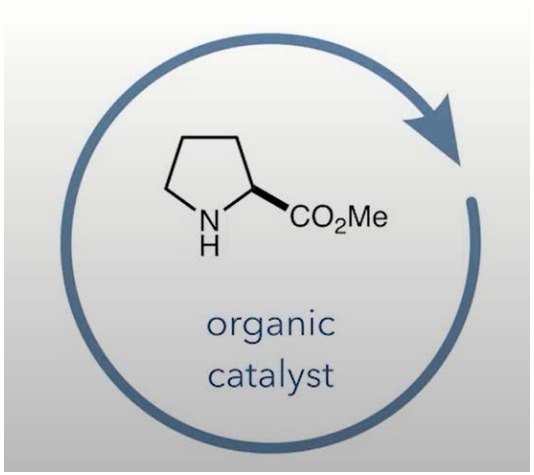
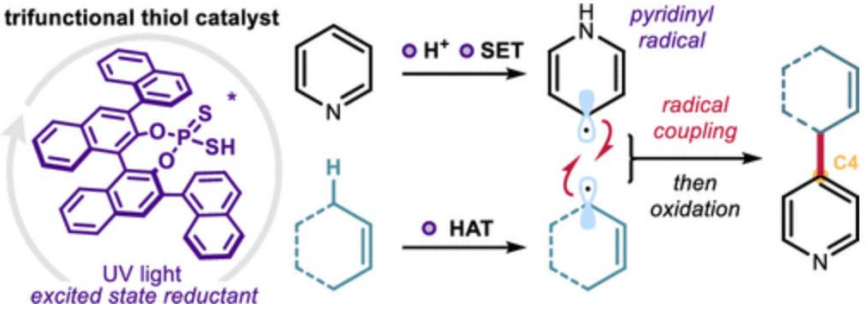
Research topics – (Melchiorre-Zhao)





Photochemistry

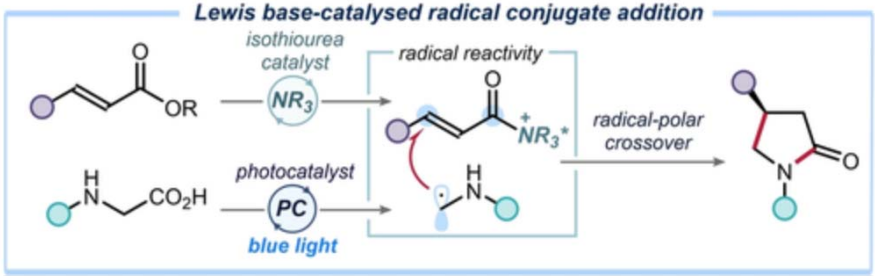
Photoredox processes
Radical reactivity



Recent examples:
J. Am. Chem. Soc. **2023**, *145*, 47–52

Organocatalysis

Asymmetric photocatalysis



Angew. Chem. Int. Ed. **2022**, *61*, e202204735

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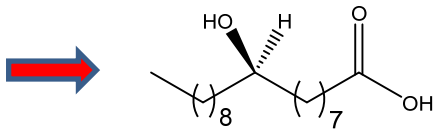
Research topics – (Boga)

Synthesis of compounds as anticancer agents and related studies on their drug delivery

Synthesis of (*R*)-9-hydroxystearic acid [(*R*)-9-HSA] and its derivatives

(*R*)-9-HSA can be obtained in high yield from *Dimorphotheca sinuata* seed oil through a simple multistep procedure.

Dimorphotheca sinuata



(*R*)-9-hydroxystearic acid

(*R*)-9-HSA is an endogenous cellular lipid that, when administered to different human cancer cell lines (colon, bone, leukemia cells, etc.) produces tumor cell growth arrest without effect on normal cell lines.

It acts as an inhibitor of enzymes belonging to the hystone deacetylase classes. Recently the interest has been focused on its drug-delivery: it has been succesfully inserted in hydroxyapatite nanoparticles (*Langmuir* 2016), Keratine nanoparticles (*Mol Pharm* 2019) and, more recently, in magnetite nanoparticles (ACS Omega, in press). (*R*)-9-HSA behaves as organogelator, an interesting property in material field (*Molecules*, 2019). Also the synthesis of structural hybrids bearing the HSA scaffold is work in progress.

Recent studies have been devoted also on the synthesis of novel compounds as substitutes of APCIN in the treatment of acute myeloid leukemia.

RECENT PUBLICATIONS

Boga, C. et al.: **Redox signaling *via* lipid peroxidation regulates retinal progenitor cell differentiation**. *Developmental Cell* **2019**, *50*, 1-17.

Boga, C. et al.: **X-Ray Crystal Structures and Organogelator Properties of (R)-9-Hydroxystearic Acid.** *Molecules* **2019**, 24 (15), 2854.

Boga, C. et al.: **Unprecedented behavior of (9R)-9-hydroxystearic acid loaded keratin nanoparticles on cancer cell cycle.** *Mol. Pharmaceutics* **2019**, 16, 931-942.

Boga, C. et al.: **Synthesis of 9-Hydroxystearic Acid Derivatives and Their Antiproliferative Activity on HT 29 Cancer Cells.** *Molecules* **2019**, 24, 3714.

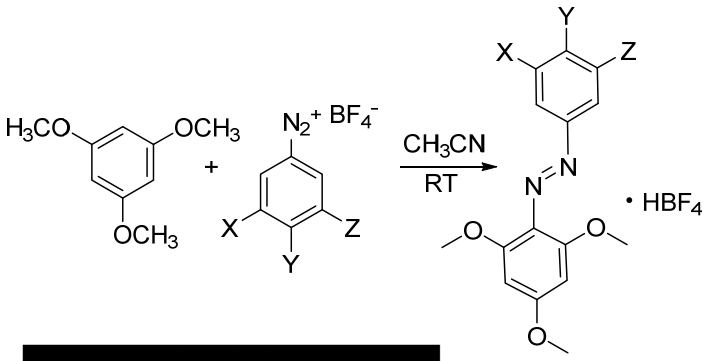
Collaborations

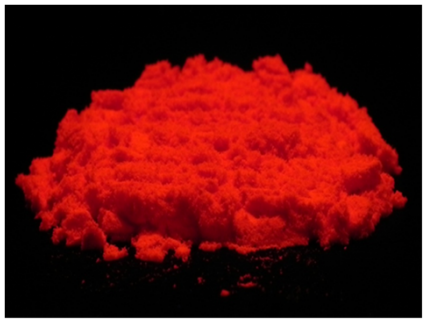
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori Meldola (FC)
Dipartimento FABIT – University of Bologna.
Dipartim. Di Chimica e Scienze Farmaceutiche. Univ. Trieste

Research topics – (Boga)

Synthesis of highly conjugated organic compounds for applications in optoelectronic field

Synthesis and properties of solid state fluorescent materials





Novel highly conjugated architectures from C–C coupling between aminothiazoles, diamino- or sym-triamino-benzenes and benzofurazan- or benzofuroxan- derivatives.

Boga, C. et al.: **New azo-decorated N-pyrrolidinylthiazoles: synthesis, properties and an unexpected remote substituent effect transmission** *Org. Biomol Chem* **2016**,14,7061-7068.

Boga, C. et al.: **Coupling Reactions between Benzofurazan Derivatives and 1,3-Diaminobenzenes**. *Molecules* **2017**, 22, 684.

Boga, C. et al.: **Highly conjugated architectures and labile reaction intermediates from coupling between 10π electron-deficient heteroaromatics and sym-trihydroxy- or triaminobenzene derivatives**." *RSC Adv.*, **2018**, *8*, 41663-41674.

Recent and current topic:

Synthesis of organic compounds for applications as scintillators

Collaborations

Istituto per la sintesi organica e la fotoreattività (ISOF-CNR Bologna)
Proff. Nanni, Cassani, Ballarin (CHIMIND)

Dipartimento di Fisica e Ingegneria dei Materiali e del Territorio, Università Politecnica delle Marche.

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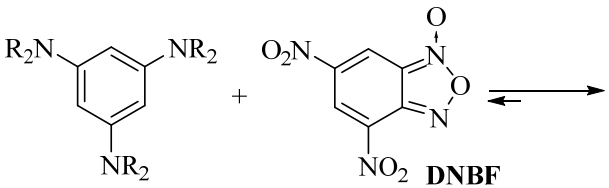
Research topics – (Boga)

Detection of labile intermediates of aromatic substitution reactions

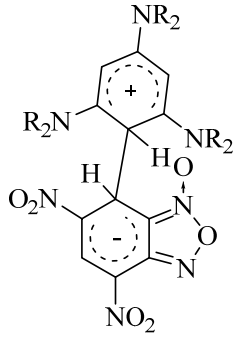
The C-C coupling between strongly activated aromatic neutral nucleophiles (Nu) and electrophiles (E) allowed the first detection and characterization of Wheland-Meisenhemer (**WM**) intermediates, contemporarily of the S_EAr (Wheland) and of the S_NAr (Meisenheimer) (*Boga, C. et al.*: *Angew.Chem.* 2005, 44, 3285-3289).

This paved the way to many other examples, with different Nu/E combinations and the topic is yet in progress.

Neutral carbon supernucleophile **Neutral carbon superelectrophile**

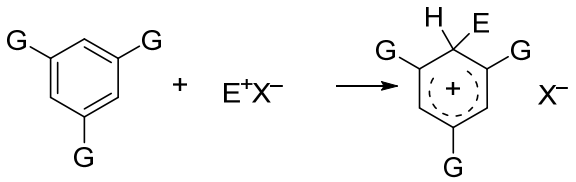


NR_2 = *N*-piperidinyl, *N*-morpholinyl, *N*-pyrrolidinyl



Zwitterionic Wheland-Meisenheimer intermediate (**WM**)

Wheland (W) have also been detected



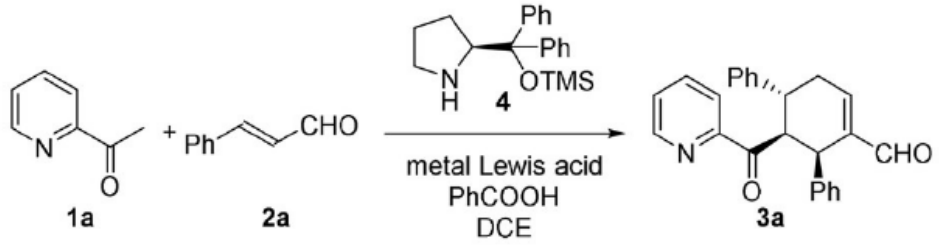
G = electrondonor group
E^+X^- = benzenediazonium salt
$E^+BF_4^-$ = benzhydrilium tetrafluoroborate (in collaboration with Prof.Herbert Mayr Department Chemie -Ludwig-Maximilians-Universität München

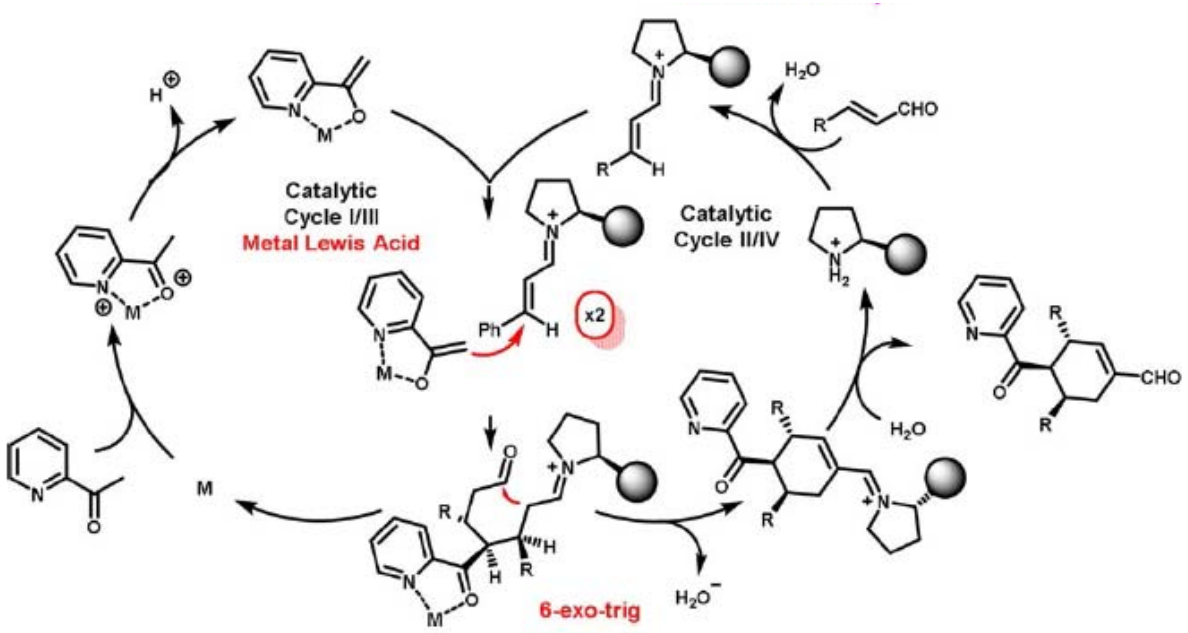
Other WM from the following combinations

Nu = sym-triaminobenzenes, E = 4,6-dinitrotetrazolepyridine (DNTP) (*JOC* 2009)
Nu = sym-triaminobenzenes, E = 2,3,4-trinitrothiofene (*Org. Biomol. Chem*. 2016)
Nu = 2-aminothiazole E = DNBF (*Chem. Eur. J.* 2007)
Nu = 2,4-dipyrrolidinylthiazole E = DNBF e DNTP *(Eur. J. Org. Chem*. 2012)

Research topics – (Mazzanti - Mancinelli)

Synergistic Catalysis: Highly Enantioselective Acetyl Aza-arene Addition to Enals





Chem. Eur. J. 2018, *24*, 13306-13310

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Research topics – (Mazzanti - Mancinelli)

DFT Calculations

The zinc enolate can approach the iminium ion in an ”*endo*” geometry driven by a more favorable interaction between the HOMO of the enolate and the LUMO of the iminium ion, with the zinc and the nitrogen of the iminium ion involved in the HOMO-LUMO interaction. This geometry is more stable than the ”*exo*” by more than 3 kcal/mol, and it accounts for the formation of the *S* enantiomer when *R*-catalyst is used (Fig 1)

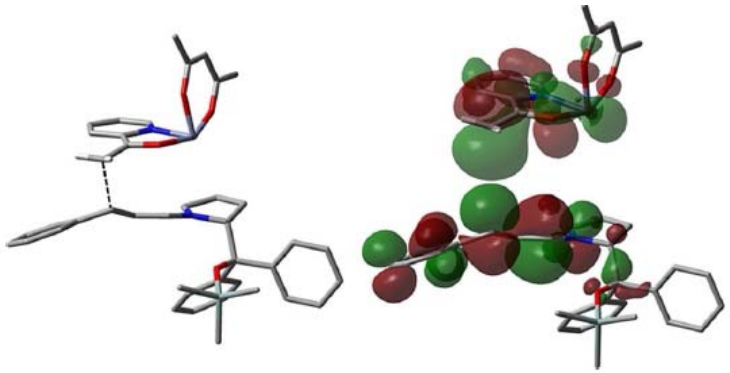


Figure 1. Left: optimized geometry for the addition of the zinc enolate to the iminium ion. Right: shapes of the HOMO of enolate and the LUMO of iminium ion (the distance between the two reagents has been enlarged to show the MOs).

The TS involving the second addition is similar to that of the first step with the E geometry of the iminium ion. Again the endo geometry with zinc over the nitrogen is favored with respect to the exo, and the most stable TS involves the attack the Re face of the zinc enolate. This TS forges the second stereocenter with S-configuration. (Fig 2)

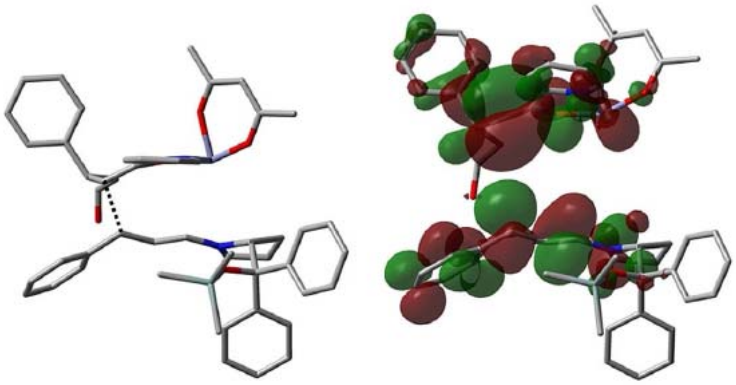
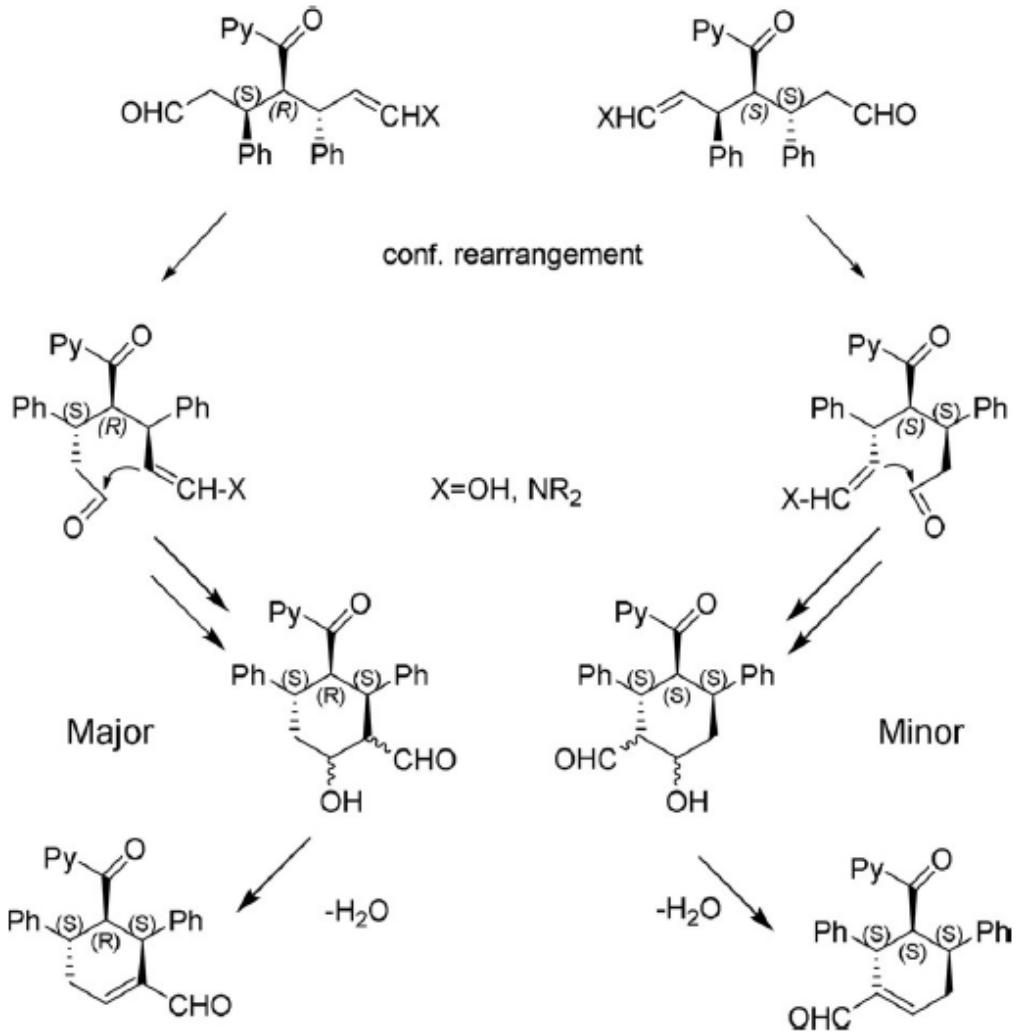


Figure 2. Left: optimized geometry for the addition of the zinc enolate to the iminium ion. Right: shapes of the HOMO of enolate and the LUMO of iminium ion (the distance between the two reagents has been enlarged to show the MOs).

R STUDIORUM
DI BOLOGNA

Research topics – (Mazzanti - Mancinelli)



Scheme 7. Transition states by DFT calculations.

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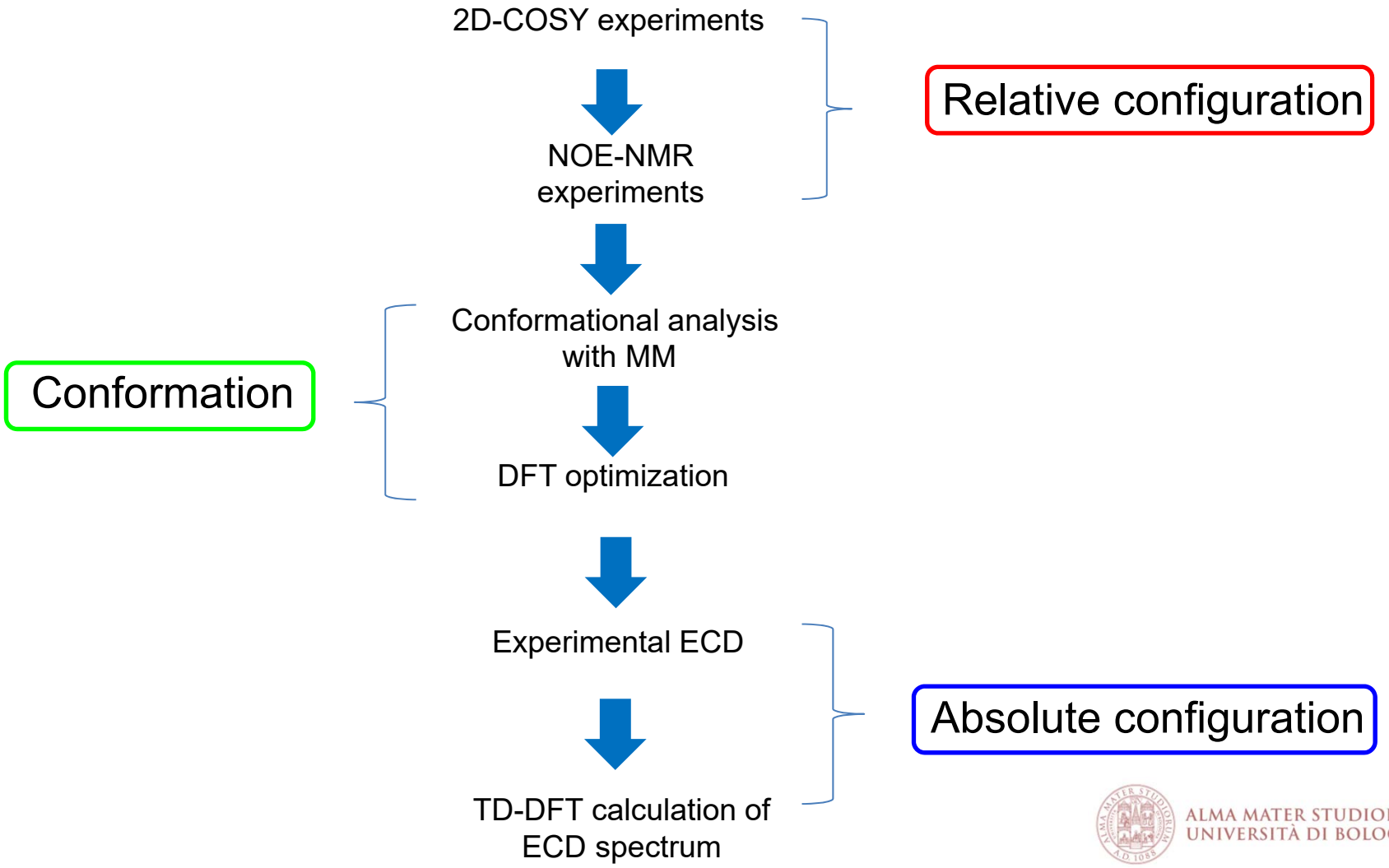
Research topics – (Mazzanti - Mancinelli)

Structural analysis



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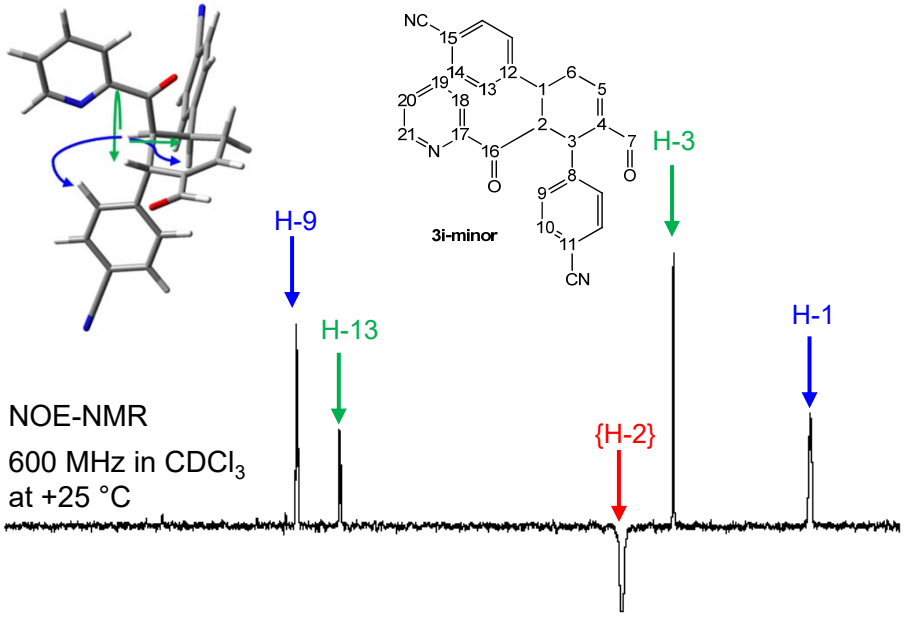
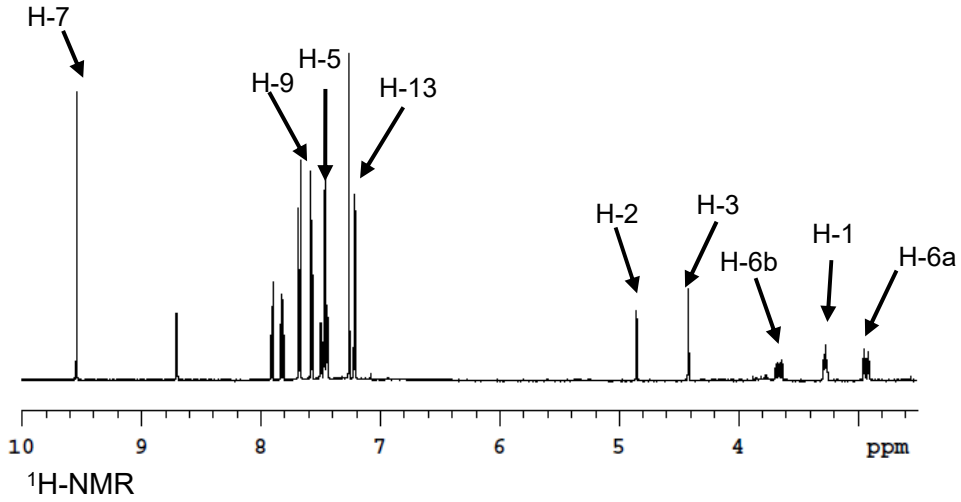
Research topics – (Mazzanti - Mancinelli)

Example for Compound **3i-minor**



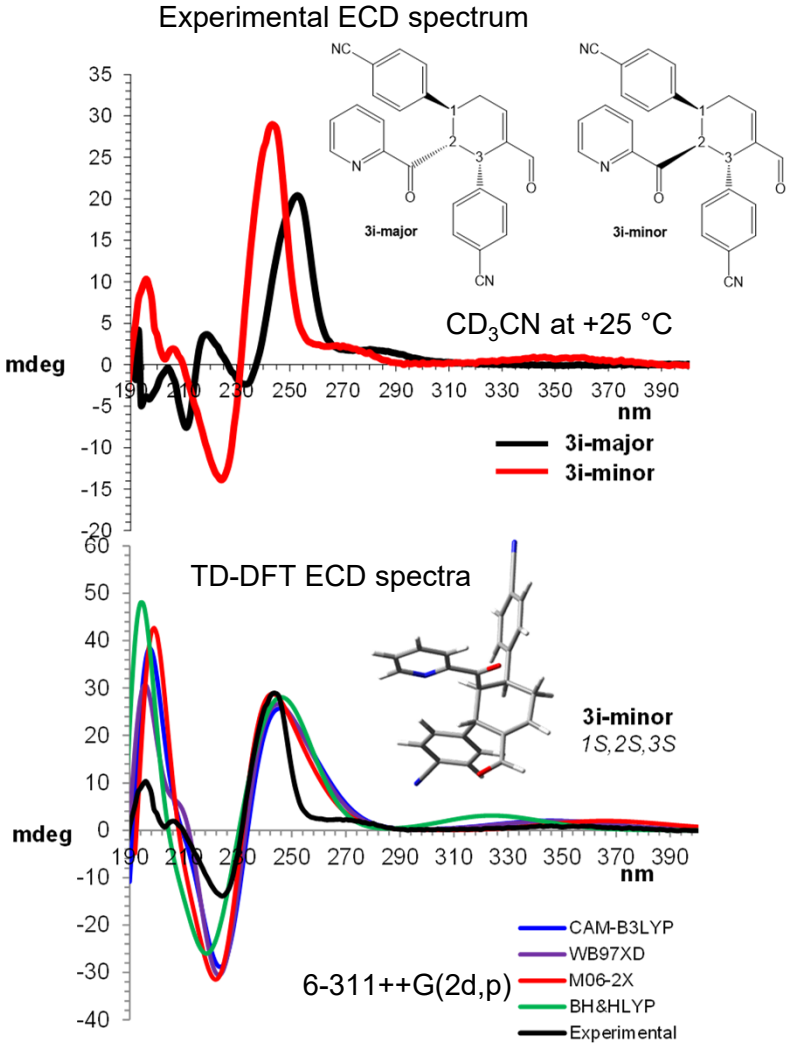


^{1}H-NMR

600 MHz in $CDCl_3$
at +25 °C

Relative configuration

3i-minor *1S*,2S*,3S**



Absolute configuration

3i-minor *1S,2S,3S*

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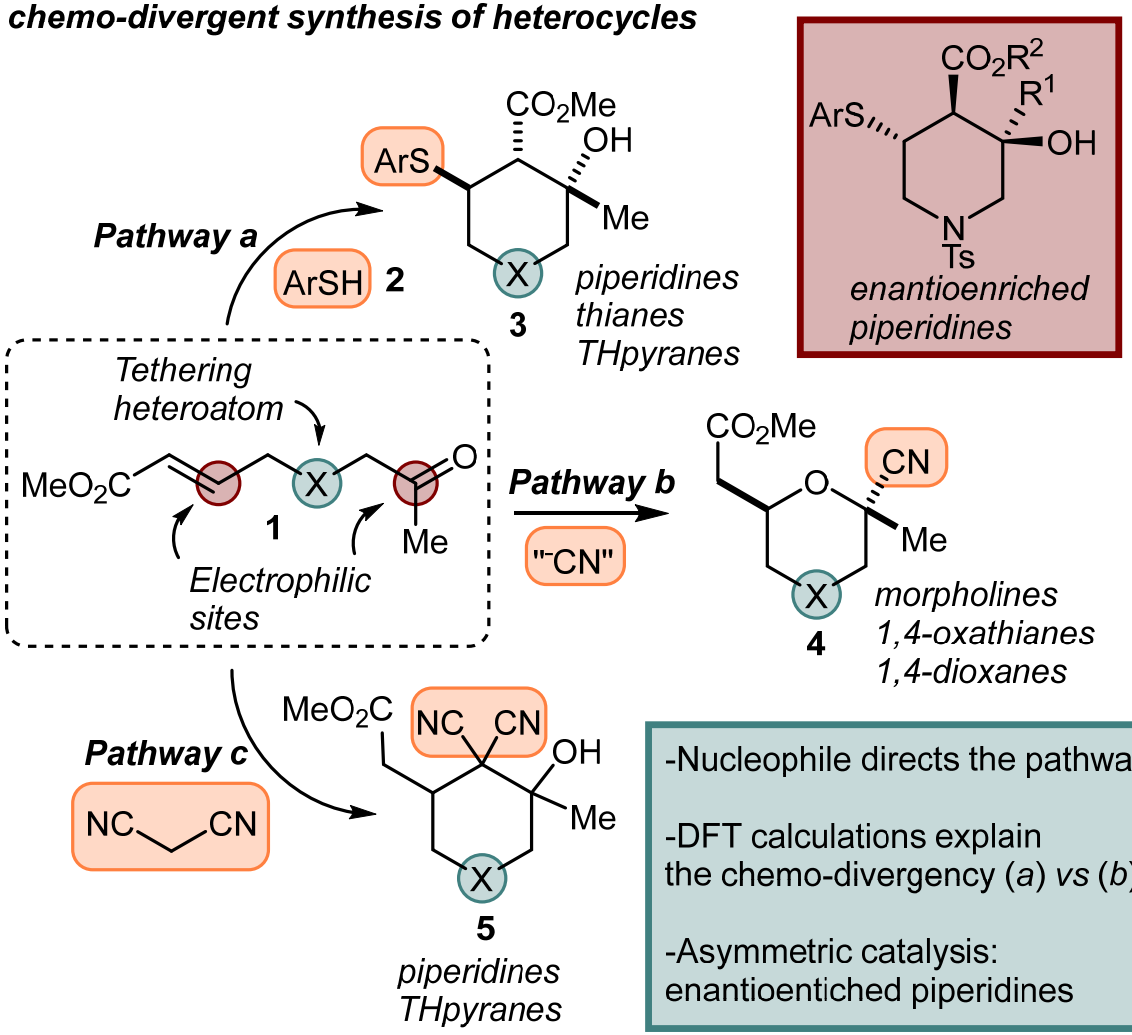
Research topics – (Mazzanti - Mancinelli)

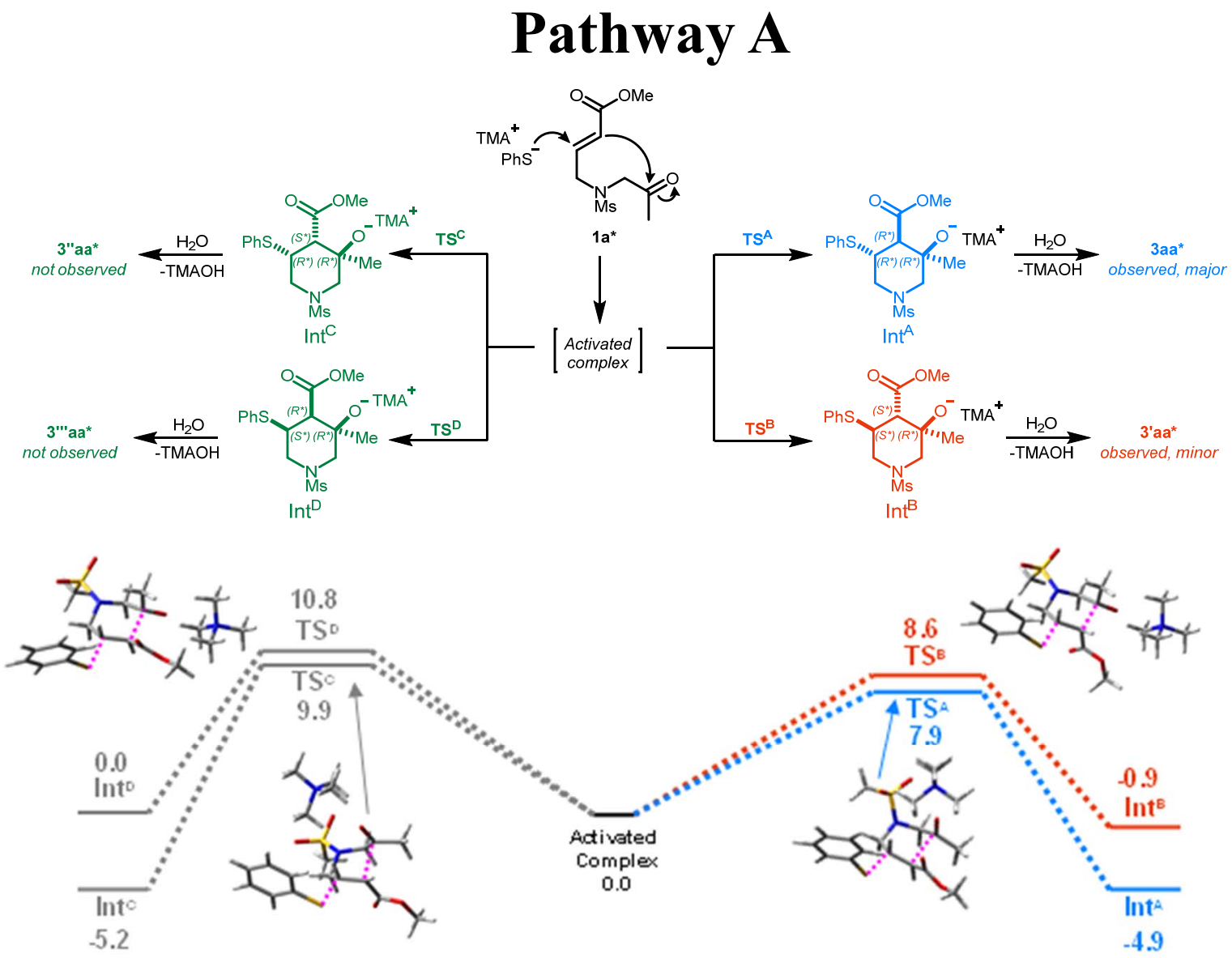
Chemodivergent Preparation of Multiple Heterocycles *via* Phase-Transfer Catalysis: Enantioselective Synthesis of Functionalized Piperidines

-Exploiting the pluripotency of substrates 1 with PTC: chemo-divergent synthesis of heterocycles



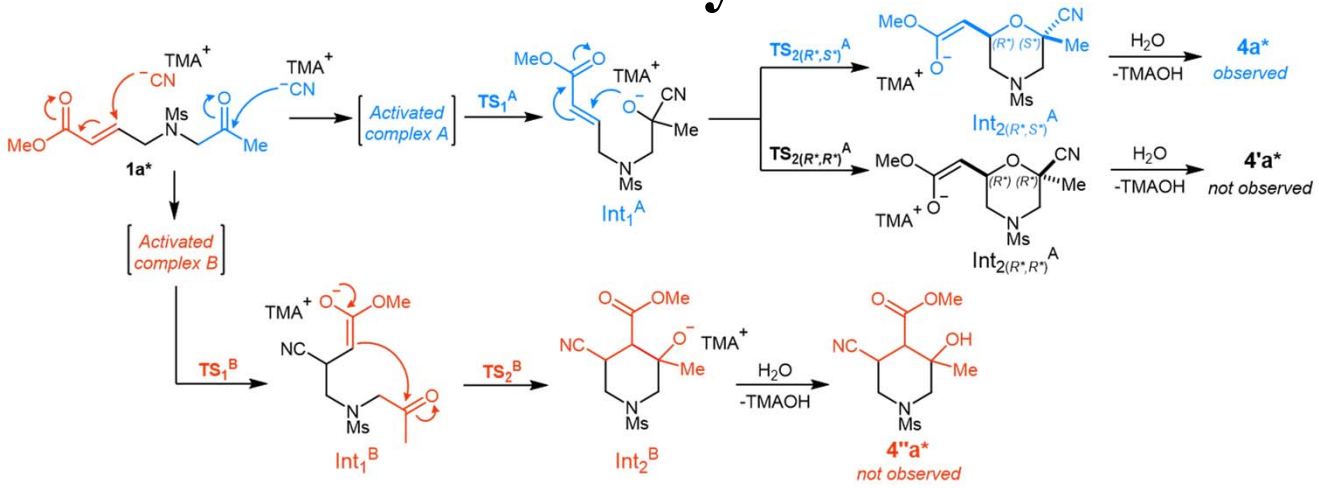
- -Nucleophile directs the pathway
- -DFT calculations explain the chemo-divergency (*a*) *vs* (*b*)
- -Asymmetric catalysis: enantioentiched piperidines

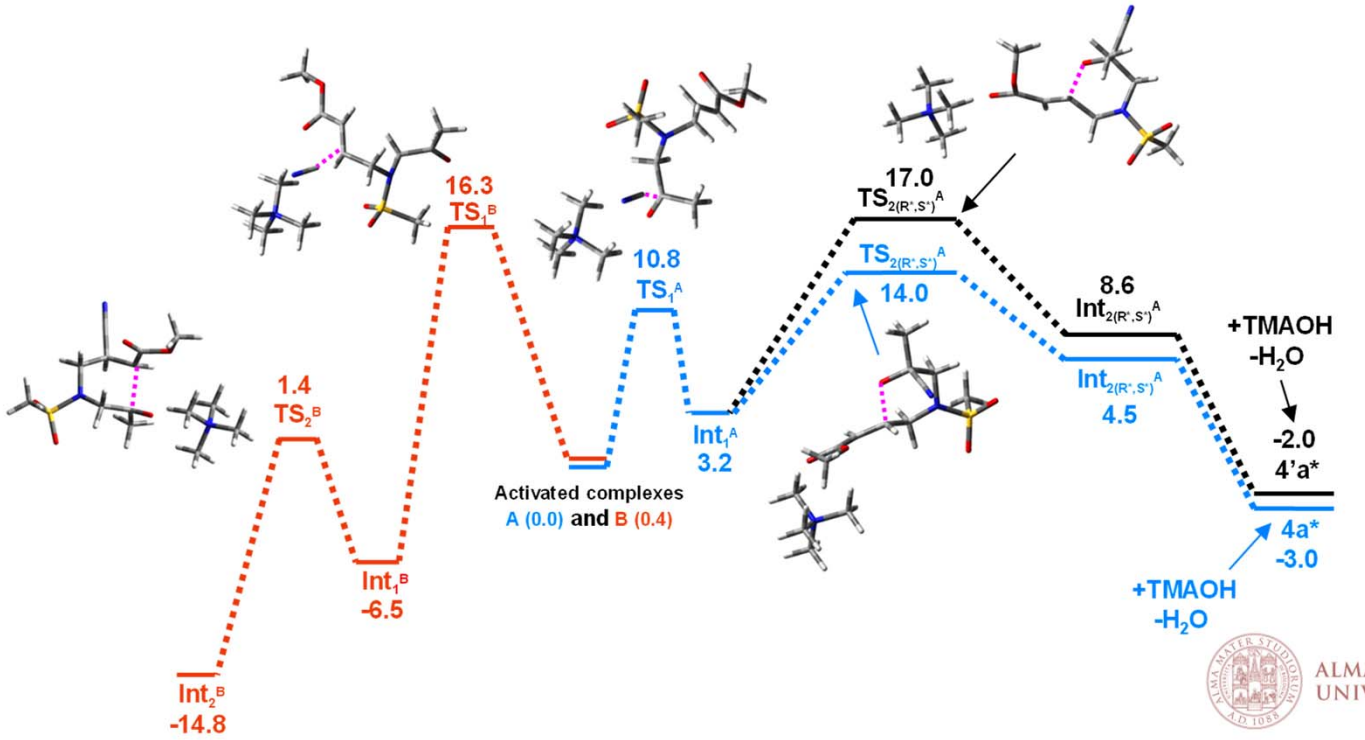
Research topics – (Mazzanti - Mancinelli)



Research topics – (Mazzanti - Mancinelli)

Pathway B





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Advanced Smart Organic Materials (ASOM)



WEB: https://chimica-industriale.unibo.it/it/ricerca/gruppi-di-ricerca/advanced-smart-organic-materials-asom

Prof. Mauro Comes Franchini mauro.comesfranchini@unibo.it Prof. Letizia Sambri letizia.sambri@unibo.it Dr. Erica Locatelli erica.locatelli2@unibo.it

The research group activity is focused on the optimization of **innovative processing techniques** with the aim of **developing new organic materials** for applications in the field of **nanomedicine and organic electronics**, for industrial applications.

Processing techniques include:

- **Additive Manufacturing (3D-Printing)** in order to obtain new materials starting from natural pool sources, such as carbohydrates and proteins. The starting biomaterials are synthetically modified before being applied to the manufacturing**. Collaborations with industries and University of Cadice/Erasmus+ (Spain)**

- **Bio-Ink for biomedical applications** via gel-extrusion deposition. Here too, biocompatible materials are investigated: the formulations are thoroughly explored and optimized in order to obtain suitable rheology for building scaffolds eligible for Tissue Engineering. **Collaborations with Istituto Toscano Tumori (Siena).**

Available Positions: Two october 2023 and Three march 2023

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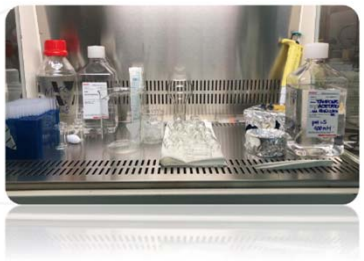
Advanced Smart Organic Materials (ASOM)

The group has proven expertise in synthesis of luminescent molecules and organic functionalization of metal-conductive and piezoelectric nanostructures (gold, silver, metal oxides) with different size and shapes. Integration of these features with the above-mentioned Processing Techniques give main applications as:

Theranostic (Therapeutic + Diagnostic) in medical field: **Breast, Brain and Bladder cancer** Collaborations with CNR (Napoli) in **AIRC project** (**Associazione Italiana Ricerca Cancro**) and Ospedale San Raffaele (Milano)

Sensing for Organic Electronics. Collaborations with **University of Milano** and **Imperial College of London.**



Simone Maturi (PhD 1° y)

Chiara Spanu (PhD 2° y)

Rosario Carmenini (PhD 1° y)

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