UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI CHIMICA

SmartMatLab

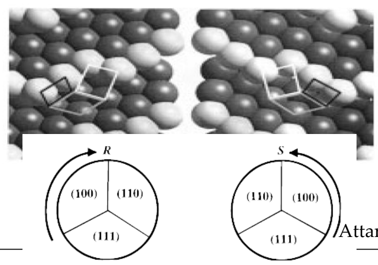
Chiral Electroanalysis

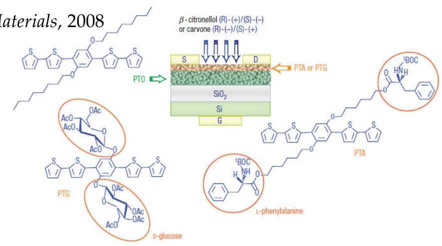
fondazione cariplo

Grants no. 2011-0417
(inherently chiral electrodes)
and no. 2011-1851
(inherently chiral ionic liquids)

Serena Arnaboldi

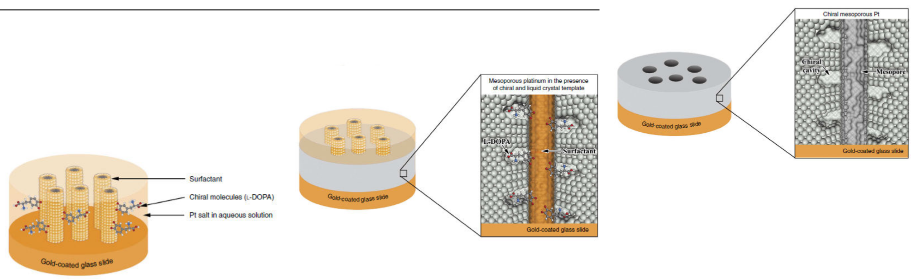
Torsi *et al. Nature Materials*, 2008





Attard, Feliu *et al.*, *Langmuir 1999*

1. Towards artificial enantioselective electrodes



Kuhn *et al.*, *Nature Comm.* 2014

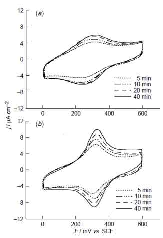
The development of **artificial** "intelligent" electrodes, capable to **discriminate** and **quantify** the **enantiomers** of chiral analytes, particularly of biological and pharmaceutical interest, is a quite attractive issue in electroanalysis.

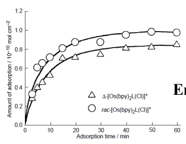
Obviously, selectivity towards specular molecules can only be achieved in an **enantiopure environment**.

For this aim,
many approaches have been proposed in the last years.

Electrodes modified with chiral SAMs

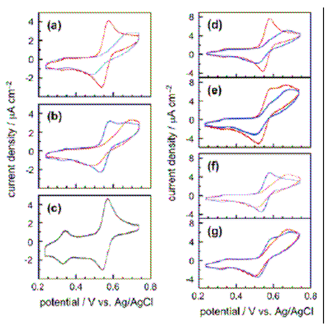
Chiral monolayer of self-assembled Δ-$[Os(bpy)_2L(Cl)]^+$ [bpy = 2,2`-bipyridyl, L = 1,2-bis(4-pyridyl)ethane] on a platinum electrode





Aramata *et al.*,
Chem. Commun. 1997

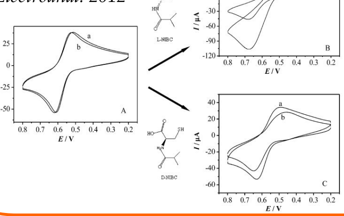
Enantioselectivity of Redox Reaction of DOPA at the Gold Electrodes Modified with a Self-Assembled Monolayer of Homocysteine



Nakanishi, Osaka et *et al.*,
JACS Comm. 2006

Enantioselective Recognition of Dopa Enantiomers in the Presence of Ascorbic Acid or Tyrosine

Fu *et al.*,
Electroanal. 2012



Electrodes modified with molecularly imprinted molecular layers

Chiral Electrochemical Recognition by Very Thin Molecularly Imprinted Sol-Gel Films

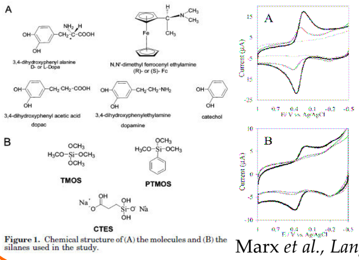
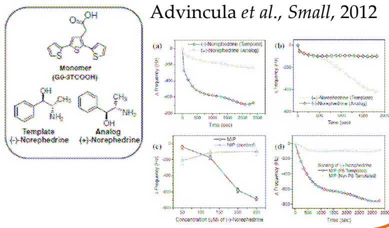


Figure 1. Chemical structure of (A) the molecules and (B) the silanes used in the study.

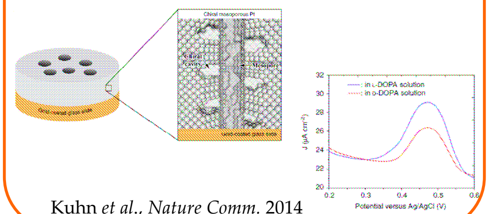
Marx *et al.*, *Langmuir*, 2005

Nanostructured, Molecularly Imprinted, and Template-Patterned Polythiophenes for Chiral Sensing and Differentiation

Advincula *et al.*, *Small*, 2012

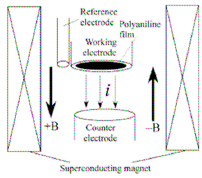


Molecularly imprinted chiral mesoporous Pt



Kuhn *et al.*, *Nature Comm.* 2014

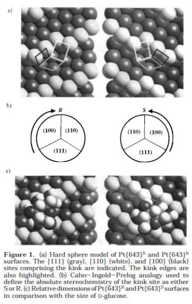
Electrodes modified with asymmetrically grown molecular layers by magnetopolarization

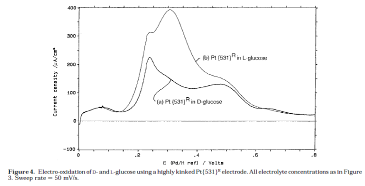


Mogi & Watanabe, *Sci. Tecn. Adv. Mat.* 2006

Oxidation of organic molecules on inherently chiral metal surfaces

Attard, Feliu *et al.*, *Langmuir* 1999 & *other papers in the following years*

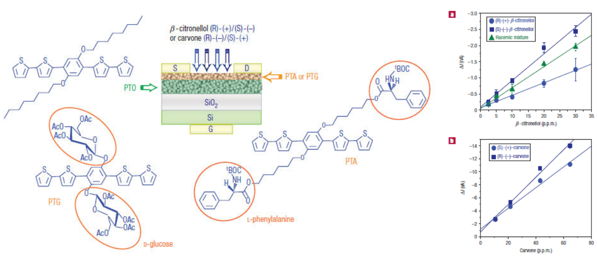




Chiral organic thin-film transistor (OTFT)

A sensitivity-enhanced field-effect chiral sensor

Torsi *et al. Nature Materials*, 2008



However,
- even the most successful attempts at chiral discrimination almost invariably resulted in the detection of a **difference in current intensity** between the signals of the two antipodes of a chiral probe
- the chiral enantioselective layer is in many instances not of general use, but **tailored for a given probe**;
- many preparation procedures are **very sophisticated/expensive**…
- … and/or the active films **fragile**.

Desirable features:
- **both** peak **potential separation** and **current linear dynamic range**
- **easy**, **fast** and **low-cost** preparation
- equal availability in **both enantiomer configurations**
- **general applicability** to many probes
- **reproducibility** and **stability**
- possibility of **recycling** the active surface
- should work on **different supports** and in **different operating media**

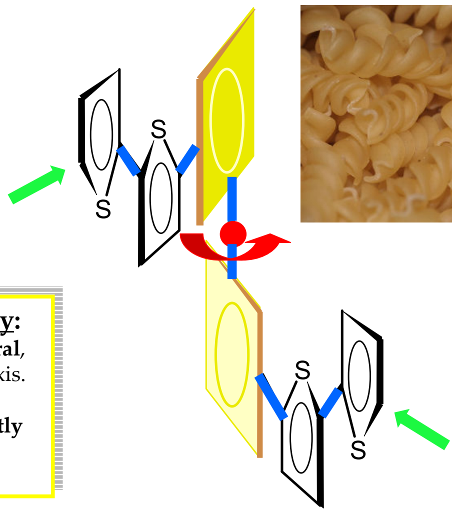
2. Our approach: inherently chiral electroactive oligomer films from inherently chiral heterocycle-based monomers

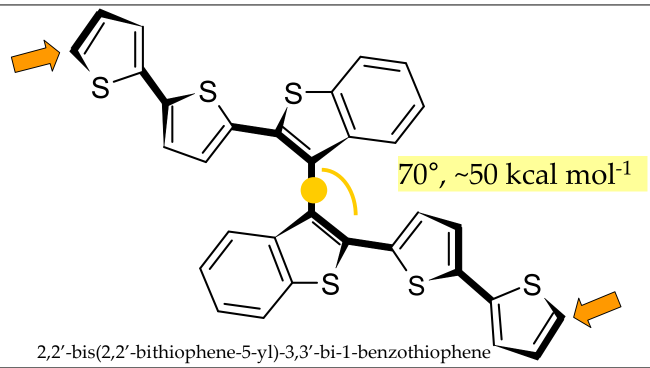
Intrinsic 3D character

Intrinsic regioregularity in polymerization

Inherent dissymmetry:
The whole molecule is chiral, exhibiting a C_2 symmetry axis.

Energy barrier is sufficiently high to yield stable enantiomers.





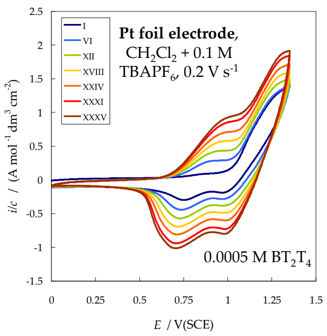
2,2′-bis(2,2′-bithiophene-5-yl)-3,3′-bi-1-benzothiophene

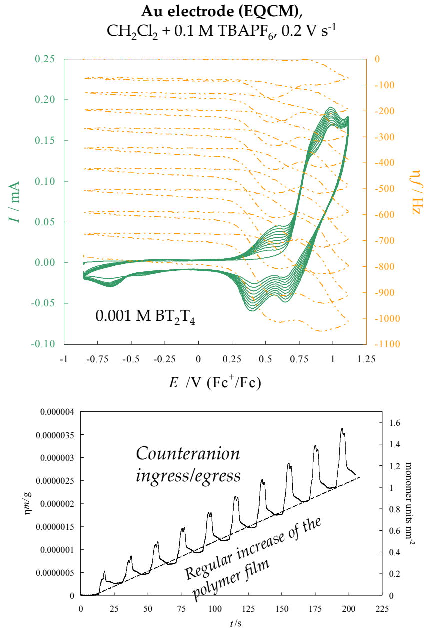
The first example:
BT_2T_4 and oligo-BT_2T_4 films

F. Sannicolò, S. Arnaboldi *et al. Angewandte Chemie Int. Ed.*, 2014, 53, 2623
S. Arnaboldi *et al. Chemical Science*, 2015, 6, 1706

Electrooligomerization of the BT_2T_4 monomer

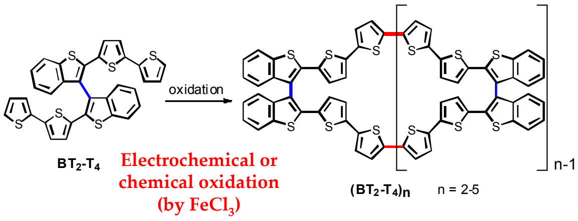
Fast and regular film electrodeposition in a wide range of conditions, even at low monomer concentration

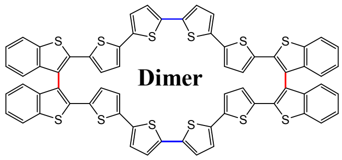




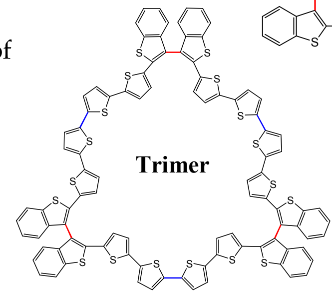
Electrooligomerization yields cyclic oligomers!

Recently, we found by high resolution MALDI that the electrodeposited films mostly consist of **cyclic oligothiophenes**, constituted by 12, 18, 24 … conjugated thiophene units!





The same cycles also constitute a large fraction of the electrodeposited oligomer films.



The cyclic *vs* linear electrodeposited oligomer ratio appears to depend on the electrode surface material (GC>>ITO)

F. Sannicolò, S. Arnaboldi *et al.*, *Chemistry* **2014**
F. Sannicolò, S. Arnaboldi *et al.*, *Pat. Appl.*, **MI2014A000948**

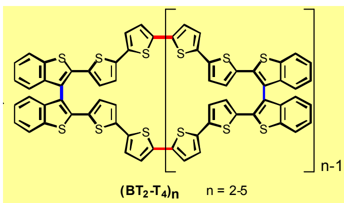
Oligomer properties as racemates

The new molecular materials possess **an outstanding pool of attractive properties**.

Even as **racemates**:

they idealize **conducting polymers without end, with no defectivity** connected with active terminals

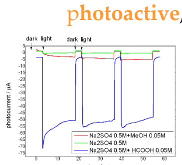
they exhibit **very facile, reversible charge transfer and very fast charge transport**, as revealed by CV and EIS



they provide cavities functionalized with heteroatoms, which, like *e.g* cyclodextrins, **can act as hosts for a variety of guests**

their **redox potentials are convenient for energy applications**, and modulable by structure design

they are **electrochromic**, **photoactive**, and display **charge-trapping effects**



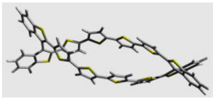
an appropriate protocol affords the oligomer films to be obtained as **self-standing membranes**

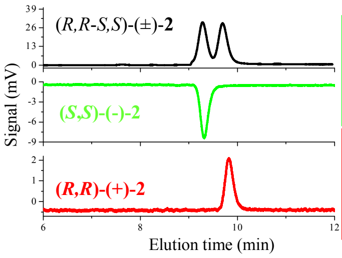
Enantiopure inherently chiral electroactive macrocycles

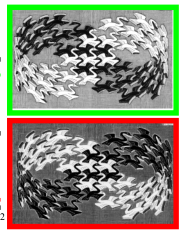
However, chirality can make them even smarter!

Starting from enantiopure monomers,

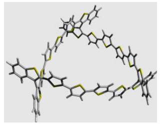
enantiopure inherently chiral macrocycles are obtained

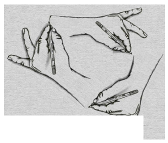


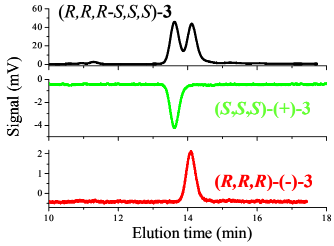




M.C. Escher





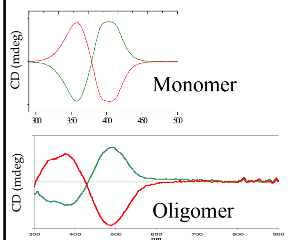


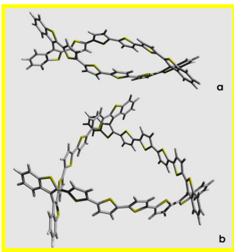
Oligomer properties as enantiopure antipodes

Chirality makes the ringlet films **even smarter,** endowing them with an exceptional series of additional properties!

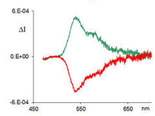
Impressive polarized light rotation angles ($[\alpha]_D^{25}$~2000 for the trimer)

Sharp circular dichroism spectra

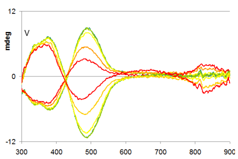




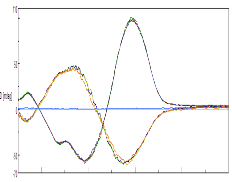
Circularly polarized luminescence



Conformational features and chirality manifestations **reversibly modulable by the electric potential**



New!! **Self-supported electroactive <u>chiral</u> membranes**!



outstanding enantiodiscrimination ability as chiral electrodes

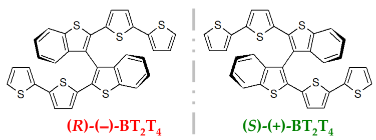
3. Enantiorecognition tests

Potential-Driven Chirality Manifestations and Impressive Enantioselectivity by Inherently Chiral Electroactive Organic Films
Angew. Chem. Int. Ed. 2014, 53, 2623 –262

Inherently chiral electrodes: the tool for chiral voltammetry,
Chemical Science 6 (2015) 1706

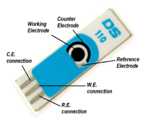
First enantiorecognition tests (I)

(Having identical CV pattern on bare Au SPE)

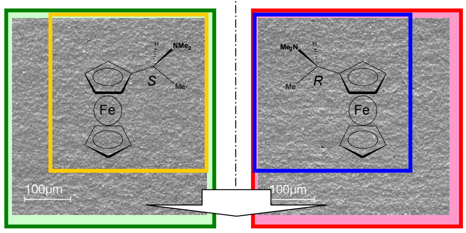


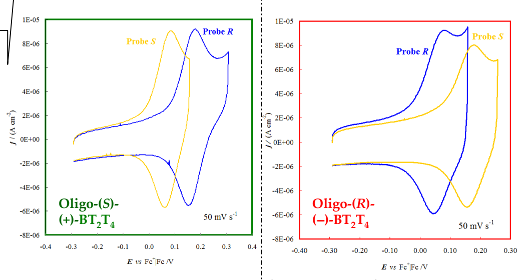
(*R*)-(–)-BT_2T_4 | **(*S*)-(+)-BT_2T_4**

electrooligomerization
at low scan rate (0.05 V/s)
in $BMIMPF_6$ ionic liquid,
on Au screen printed electrodes
(36 cycles, 0.012 M)

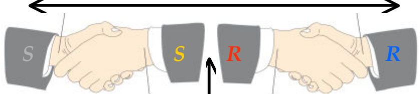


(*S*)-(–)-N,N-dimethyl-1-ferrocenylethylamine | **(*R*)-(+)-N,N-dimethyl-1-ferrocenylethylamine**

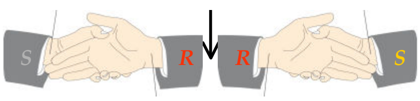




enantiomer redox couples:
$\Delta E°' \approx 0$ mV

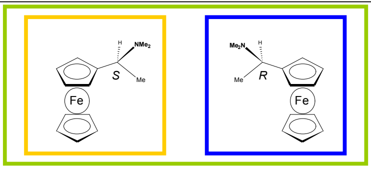


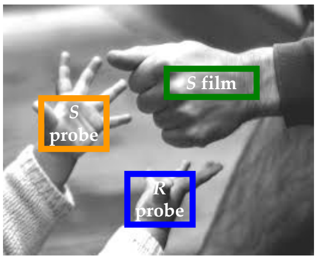
diastereomeric redox couples:
$\Delta E' \approx 100$ mV



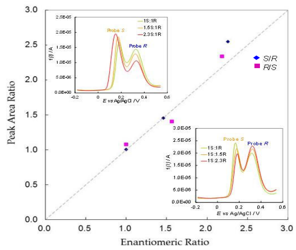
Neat separation between the two enantiomers (~100 mV)!

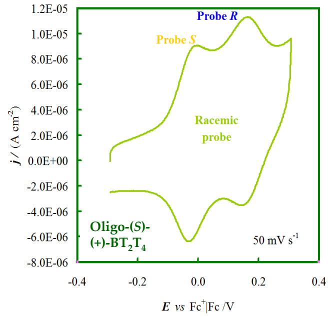
First enantiorecognition tests (II): Racemates and enantiomeric excesses





Inserting the probe racemate,
two neatly separated peaks are observed
(*e.e.* determination)





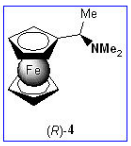
Energetics of a binary system can be significantly **different** from that of a **ternary system**

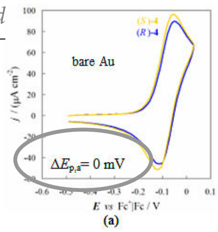
H. Wynberg and B. Feringa, *Tetrahedron*, 1976, **32**, 2831

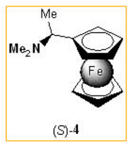
Enantiorecognition tests with a single ringlet kind

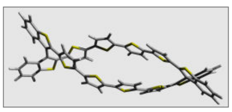
Drop coating of enantiopure ringlet solutions in CH_2Cl_2 on Au SPEs,

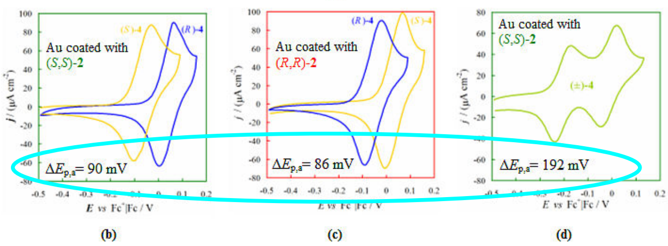
then tests in $BMIMPF_6$

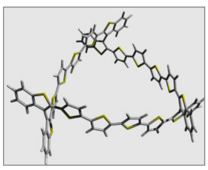


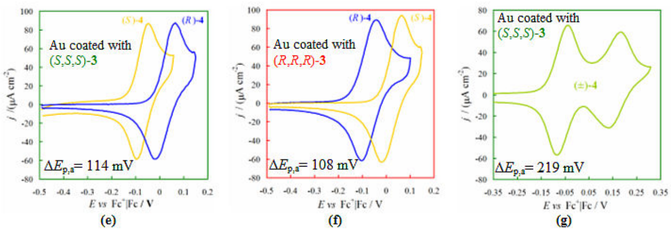






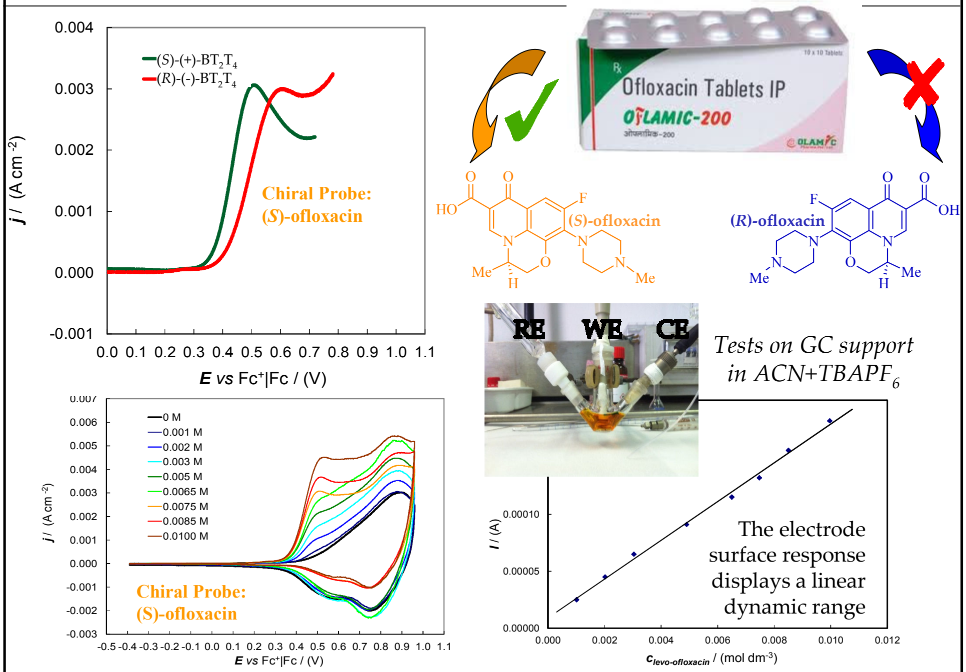




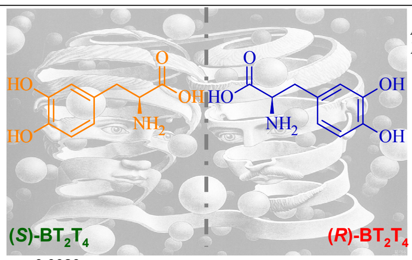


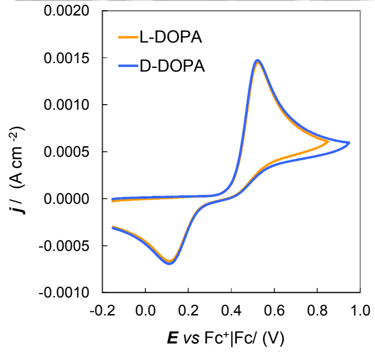
4. Confirming the enantiorecognition capability with different probes

Enantiorecognition Capability using chiral probes with different bulkiness and chemical nature



Enantiorecognition tests towards DOPA probe

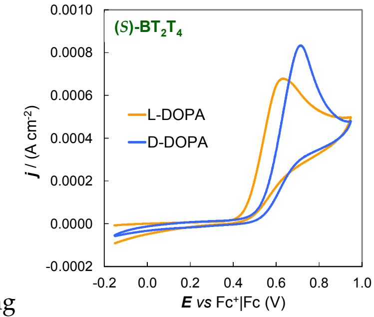


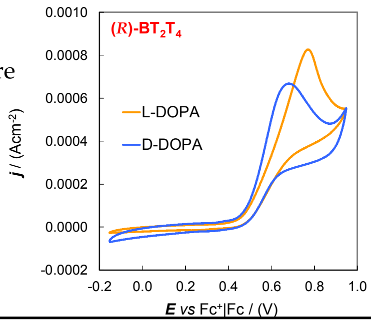


D-DOPA and
L-DOPA signals
on **bare** GC electrode

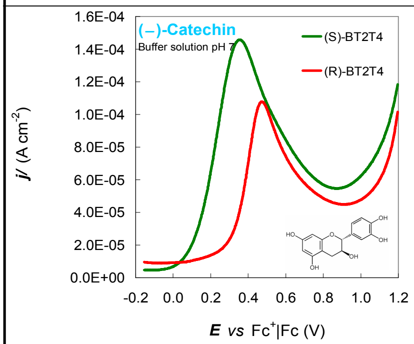
Tests
alternating
D- and L-
DOPA
on both
enantiopure
films

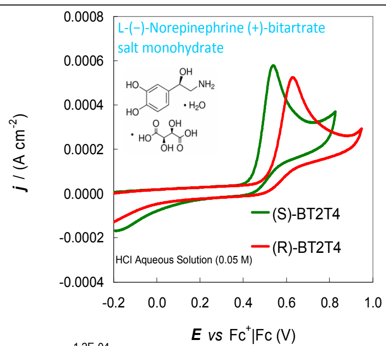
Tests on
GC support
in H_2O+HCl
0.05M

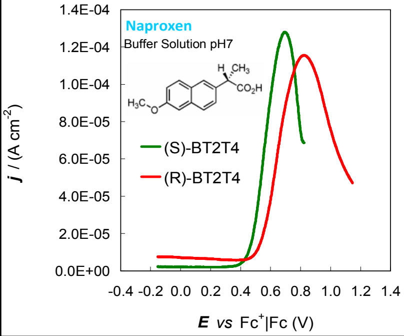


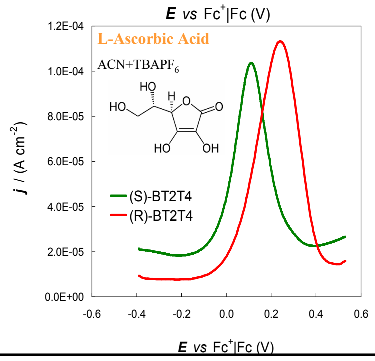


Enantiorecognition tests towards Naproxen, Catechin, Norepinephrine, Ascorbic Acid

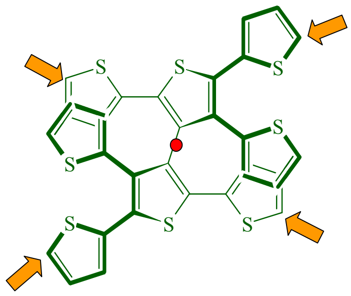


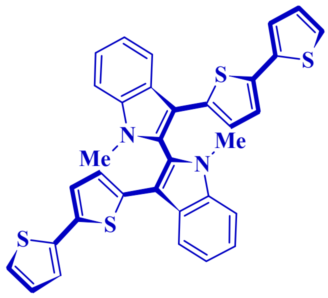




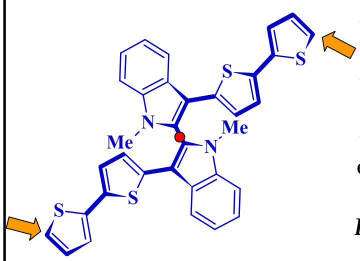


5. Confirming the concept with chemically different starting monomers



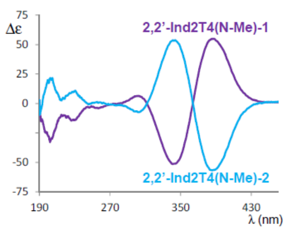


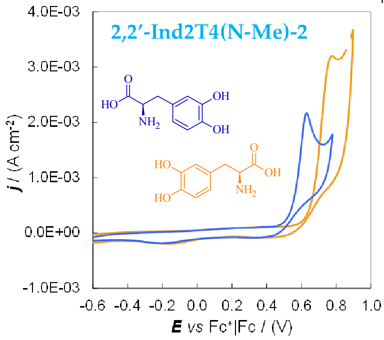
Enantiorecognition tests using pyrrole-based atropisomeric scaffold

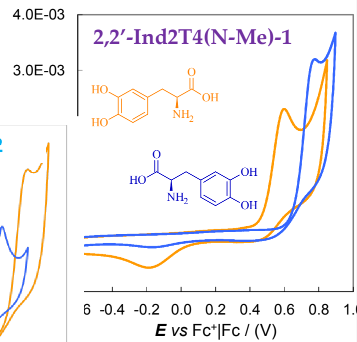


- **100º node angle** between moieties
- Possibility to locate the heteroatom in *ortho* position
- **Two homotopic positions** available for electrooligomerization

Electrooligomerization *on GC electrode in DCM+TBAPF$_6$ 0.1M*

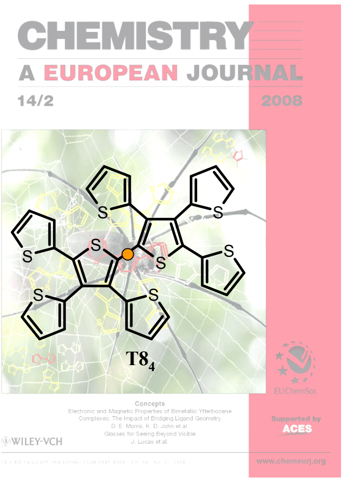


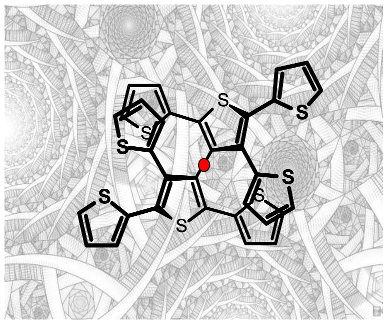




Enantiorecognition *tests on GC electrode in a 0.05 M HCl aqueous solution*

The same concept in all-thiophene materials: inherently chiral spider-like oligothiophenes



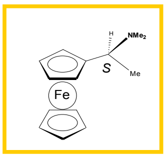


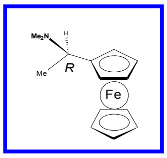
M. C. Escher

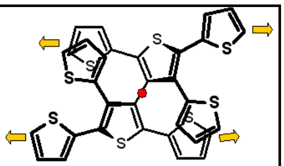
α, α-link: a **node/distortion** arises, but **the energy barrier for rotation is low**

β, β-link: a **node/distortion** with **high energy barrier fo rotation → the molecule is chiral**

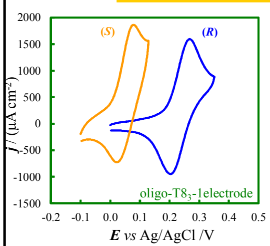
Similar tests on inherently chiral spider-like oligothiophenes (β,β′-bithiophene core)

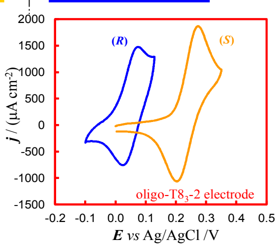




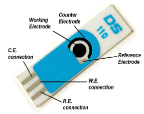


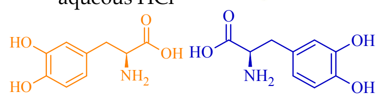
highly 3D, four homotopic α positions for oligomerization, but does not give cyclic oligomers

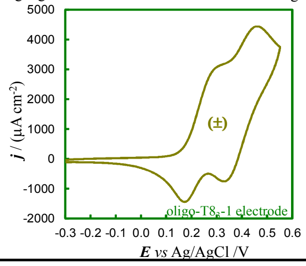


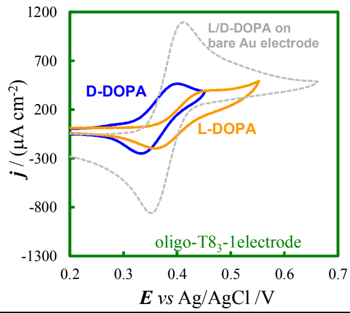


Enantiorecognition tests on SPEs both in $BMIMPF_6$ and in aqueous HCl









Conclusions 1

Coming back to the checklist of desiderable features…

- both peak potential separation and current linear dynamic range COMPLIES
- easy, fast and low-cost preparation COMPLIES
- equal availability in both enantiomer configurations COMPLIES
- general applicability to many probes COMPLIES
- reproducibility and stability COMPLIES
- possibility of recycling the active surface COMPLIES
- efficiency on different supports and operating media COMPLIES

Moreover,
- *The concept works as well in **chemically different** oligomers*
- *The enantiopure film can be also obtained and processed as **self-standing membranes***

Inherently chiral electroactive films are indeed attractive tools for chiral voltammetry

6. An alternative approach: Working on an achiral surface but in an inherently chiral medium

An alternative approach to chiral electroanalysis: chiral working media

As an alternative approach to using a chiral electrode surface, different chiral media for electrochemical processes have been proposed

Chiral organic solvents

Chiral supporting electrolytes

Chiral ionic liquids (CILs)

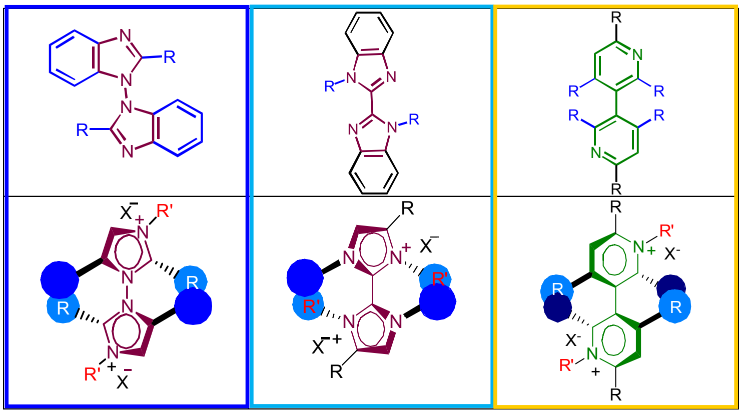
Already adopted in organic chemistry, still to be explored in electrochemistry

Increasingly more ordered at the electrode/solution interphase, resulting in increasing enantioselective effects

Possibly the best:

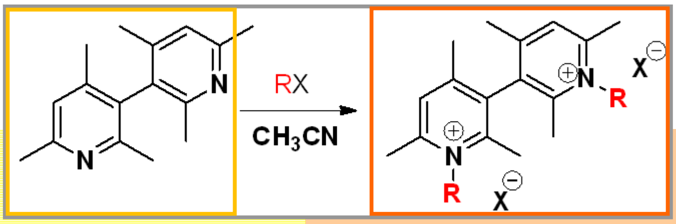
Inherently chiral ionic liquids (ICILs)

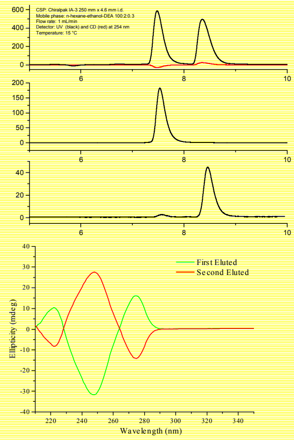
Inherently Chiral Ionic Liquids



The cationic bibenzimidazolium or bipyridinium moiety responsible for the CILs physical properties is also part of the stereogenic element responsible for molecular chirality.

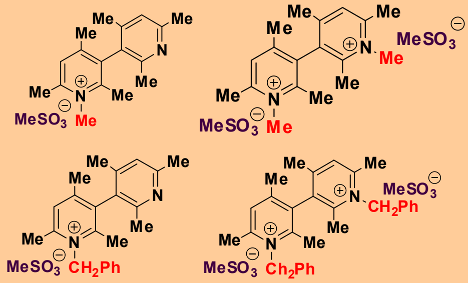
3,3′-Bi(collidinium) cation





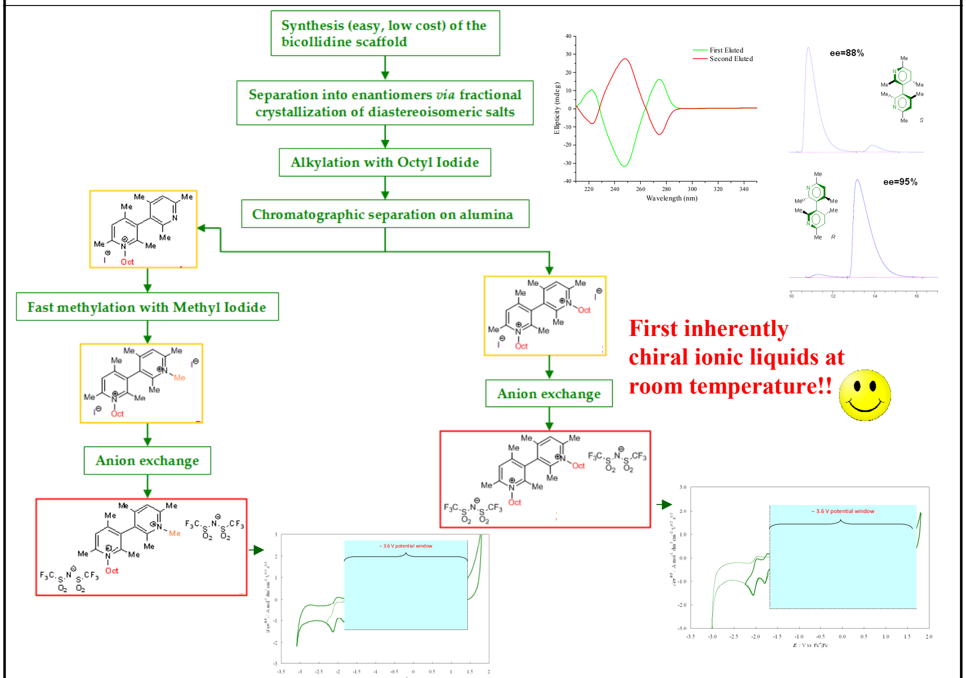
DFT calculation demostrated that **the racemisation barrier of the 3,3′-bicollidine is 42.5 kcal mol^{-1}.**

Mono- and di-alkylation



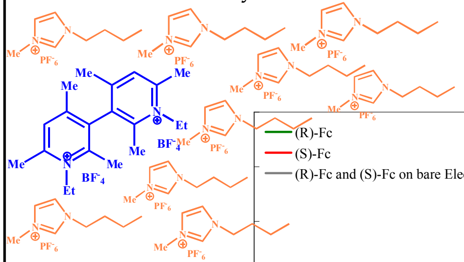
Easy synthesis **Scalable procedures**

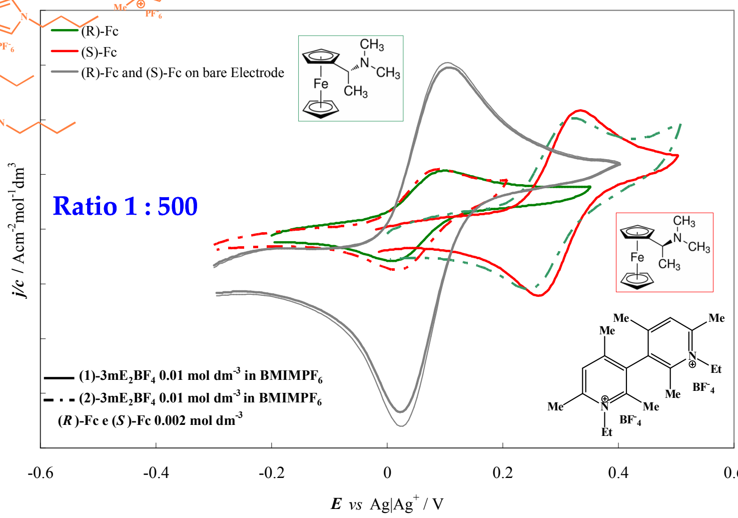
The most promising family: bicollidinium scaffolds and salts



Breaking news: enantiorecognition tests employing bicollidinium salts!!!

Recently we have confirmed that also these materials hold an impressive enantiorecognition ability like a **chiralizing gel** spread on electrodes.





fondazione cariplo

The support of grants no. 2011-0417 (inherently chiral electrodes) and no. 2011-1851 (inherently chiral ionic liquids) is gratefully acknowledged

The Milano researchers are members of the newly set up "SmartMatLab Laboratory and Training Centre"

offering state-of-the-art facilities which will support the preapplicative optimization of these "intelligent" electrode surfaces