Q. Michaudel

Organic Synthesis from France

Baran Group Meeting
10/02/2010

Early French organic chemists (18th and 19th centuries):

Antoine-Laurent de Lavoisier (1743–1794):
* law of conservation of mass
* recognized and named oxygen and hydrogen
* abolished the phlogiston theory (see **Seiple's GM 2010**)
* helped construct the metric system
* wrote the first extensive list of elements
* helped to reform chemical nomenclature

An appeal to delay the execution so that he could continue his experiments was cut short by the judge: *"The Republic needs neither scientists nor chemists; the course of justice can not be delayed."* (This quote may be more part of the legend than the reality)
Lagrange's quote: *"It took them only an instant to cut off his head, but France may not produce another such head in a century."*

Claude Berthollet (1748–1822): discovery of bleach

Jean-Antoine Chaptal (1756–1832):
chaptalization (addition of sugar to unfermented wine to increase the final alcohol level)

Joseph Louis Gay-Lussac (1778–1850):
* work in thermodynamics (Gay-Lussac's law)
* discovery of boron, cyanogen and hydrogen cyanide
* developed a method for quantitative elemental analysis
* named iodine, but also pipette and burette !

Eugène Chevreul (1786-1889): work on fatty acids, explanation of the saponification process and isolation of oleic and stearic acid

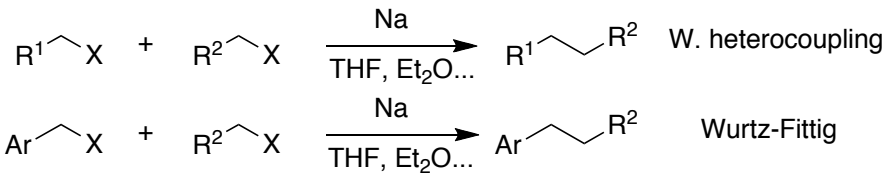
Joseph Bienaimé Caventou (1795–1877) with Pierre-Joseph Pelletier (1788–1842): alkaloids isolation: chlorophyll, emetine, strychnine, brucine, cinchonine, quinine and caffeine

Louis Pasteur (1822–1895): Resolution of tartaric acid racemate ("racemic acid") (first experimental evidence of molecular chirality)

Elemental halogen isolation:
* Br_2 by **Balard** (1826)
* I_2 by **Courtois** (1811)
* F_2 by **Moissan** (1886), Nobel Prize in 1906 for this and the invention of the electric furnace

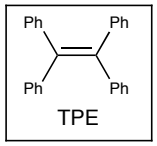
Albin Haller (1849–1925):
* semi-synthesis of camphor from camphoric acid and synthesis of menthol
* use of $NaNH_2$ ("birth of strong bases chemistry")

Wurtz coupling (1855):

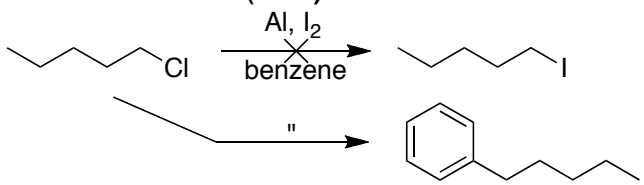


Ann. Chim. Phys. **1855**, *96*, 275

Müller modification: THF, -78°C, TPE (cat) to help Na solubilization
other modifications possible: different metal, sonication...

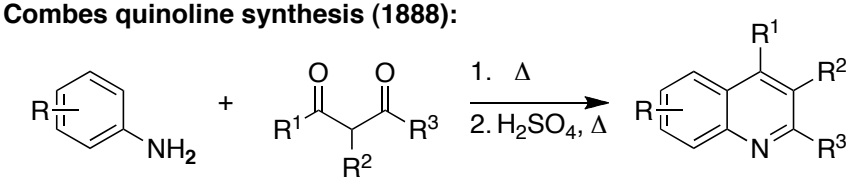


Friedel-Crafts reaction (1877):



Compt. Rend. **1877**, *84*, 1392

Combes quinoline synthesis (1888):



Bull. Soc. Chim. Fr. **1883**, *49*, 89

Notable French chemists from the 20th century outside the field of organic synthesis field:

Marie Curie (1867–1934): Nobel Prize in Chemistry (1911) for discovery of the elements radium and polonium and the isolation and study of radium. (also Nobel Prize in Physics in 1903 !)

Irène Joliot-Curie (1897-1956): Nobel Prize in Chemistry (1935) for their **Frédéric Joliot-Curie (1900–1958)** synthesis of new radioactive elements

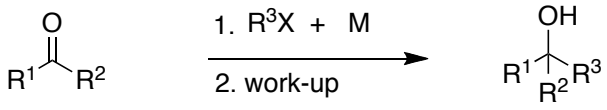
Georges Champetier (1905–1980): polymers, macromolecular chemistry

Organic Synthesis from France

Synthetic methods from the first half of the 20th century:

The "organometallics school":

Barbier coupling reaction (1899):

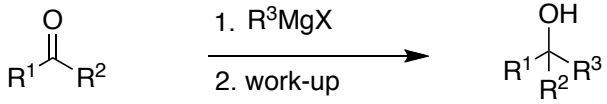


C R. Hebd. Seances Acad. Sci.. **1899**, *128*, 110

* M can be Mg, Sm, Zn, Li...
* When Mg is used, Barbier reaction is an *in situ* Grignard reaction.
* Yield may be improved by sonication and some reactions only work sonication, see *JOC*, **1998**, *63*, 5100.
* In some cases, water can be used as solvent: green chemistry !

Philippe Barbier was Victor Grignard's PhD supervisor...

Grignard reaction (1900):

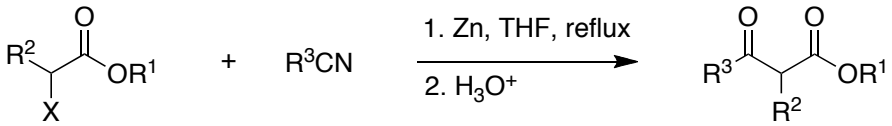


C R. Hebd. Seances Acad. Sci.. **1900**, *130*, 1322

* broad scope of substrate for addition of Grignard reagents: acid derivatives, nitriles, CO_2
* can be used as strong Bronsted bases
* can generate other organometallics like cuprates, organocerium (more nucleophilic), organocadmium (less nucleophilic)

Grignard won the Nobel Prize in Chemistry in 1912 for this discovery

Blaise reaction (1901):



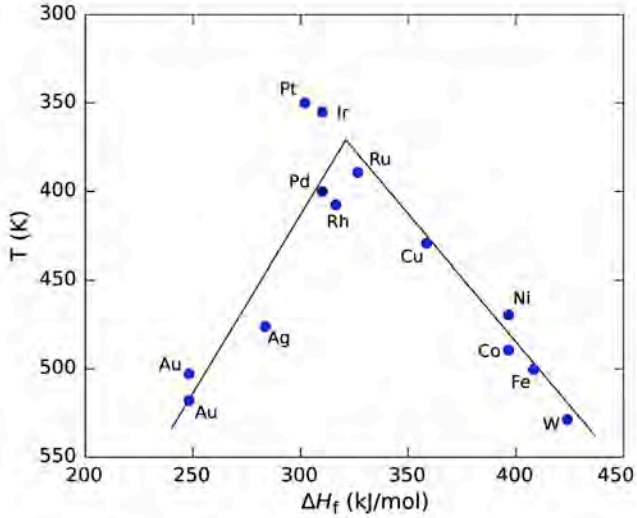
C R. Hebd. Seances Acad. Sci.. **1900**, *132*, 478

Paul Sabatier (1854–1941):

* Nobel Prize in 1912 for hydrogenation catalyzed by metals (Ni...)

* Sabatier process: $CO_2 + 4\ H_2 \rightarrow CH_4 + 2\ H_2O$ (cat. by Ni, Ru or Al_2O_3) *could serve to produce fuel (CH_4/O_2) on Mars or drinkable water source in space from human respiration, according to NASA*

*Sabatier principle: optimal interactions between the catalyst and the substrate have to be neither too strong (product not released after reaction) nor too weak (no binding, so no reaction). (see Volcano plot)

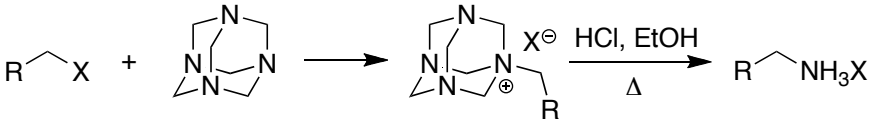


source: Karl Kochloefl (2005). "Heterogeneous Catalysis and Solid Catalysts", Ullmann's Encyclopedia of Industrial Chemistry. Wiley-VCH Verlag

Volcano plot for the decomposition of formic acid on transition metals

Other noteworthy reactions:

Delépine amine synthesis (1895):

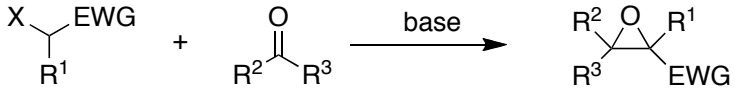


Bull. Soc. Chim. Fr. **1895**, *13*, 352

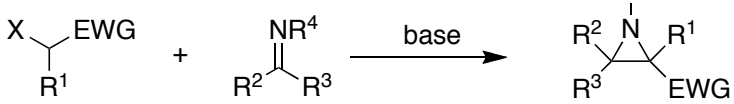
* alternative to Gabriel reaction
* works better with activated halides: benzyl, allyl, α-haloketone...

Organic Synthesis from France

Darzens (1904) and aza-Darzens reactions:



Compt. Rend. Acad. Sci. **1904**, *139*, 1214

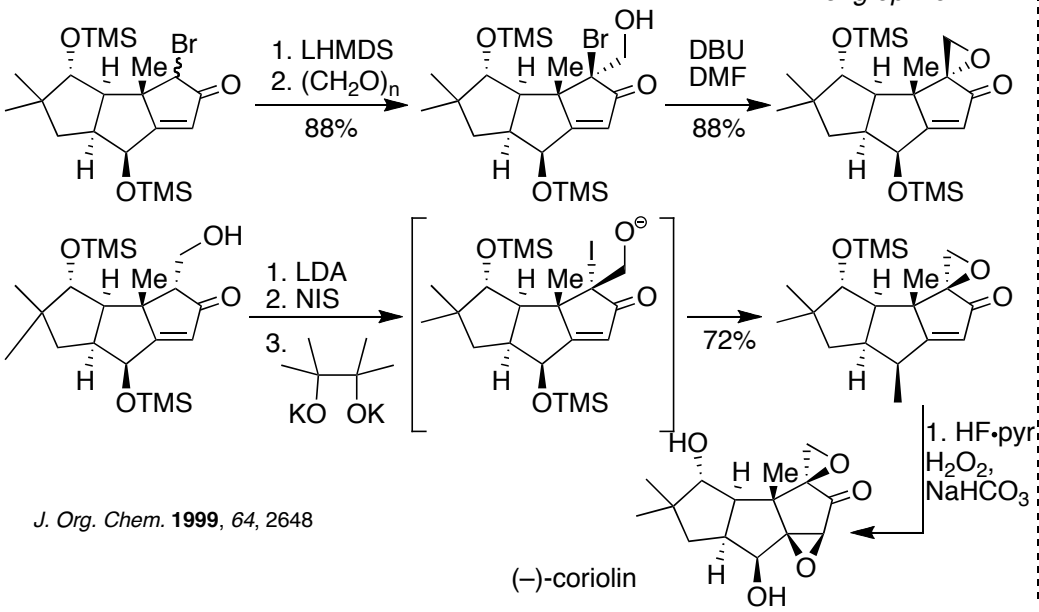


J. Org. Chem. **1969**, *34*, 3600

* EWG = CO_2R, CN, SO_2R, $CONR_2$, C(=O), C(=NR)
* base = NaOEt, NaH, LDA...
* X = Cl > Br or I

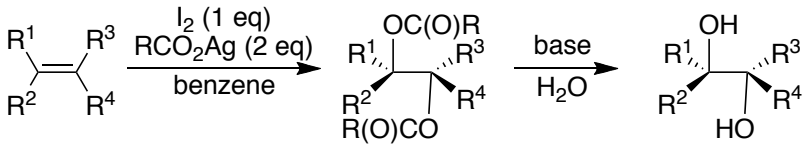
Synthesis of (–)-coriolin by Kuwajima using the *Darzens* reaction

wrong epimer !!!



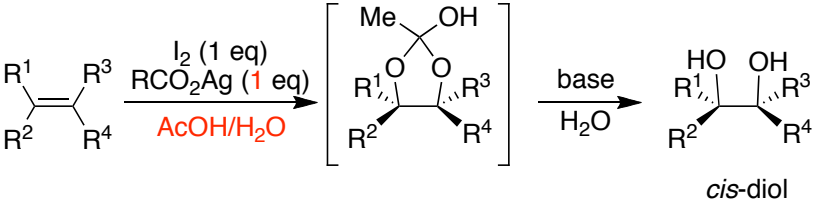
J. Org. Chem. **1999**, *64*, 2648

Prévost *trans*-hydroxylation (1933):

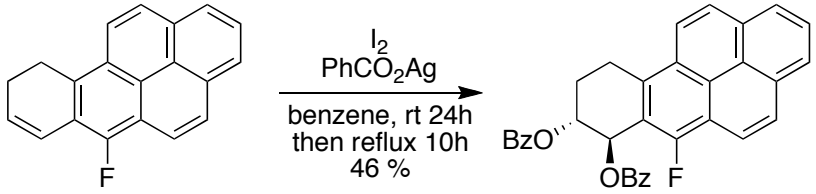


Compt. Rend. **1933**, *196*, 1129

Woodward-Brutcher modification



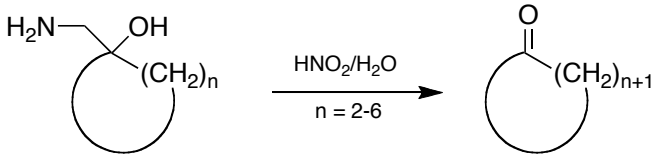
J. Am. Chem. Soc. **1958**, *80*, 209



cis-diol obtained with OsO_4 (70 %)

J. Org. Chem. **1999**, *64*, 1902

Tiffeneau-Demjanov rearrangement (1937):



Compt. Rend. **1937**, *205*, 1411

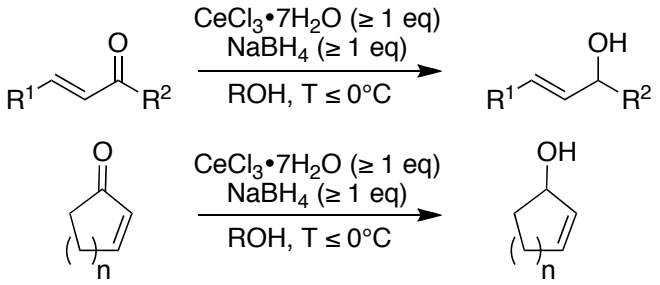
Organic Synthesis from France

Rapid overview of "French" organic chemistry from the last few decades:

Methodology:

Jean-Louis Luche (Université de Grenoble):

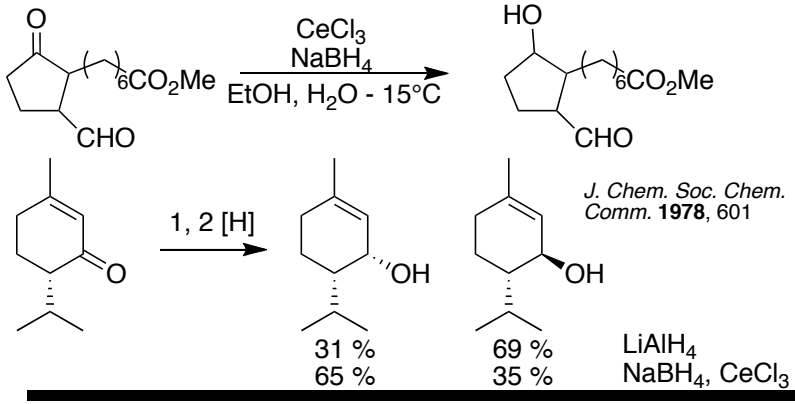
Luche reduction (1978): 1,2-reduction of enones



J. Am. Chem. Soc. **1978**, *100*, 2226

* Ce catalyzes alkoxyborohydride formation and increases acidity of the medium by coordinating to solvent
* ROH : MeOH > EtOH or ^{i}PrOH
* other lanthanide chlorides work (Eu, Yb, La..) but better yield with Ce
* reduction generally done in less than 30 min
* 1,2-selective, very little substrate dependence (e.g., sterics)
* most functional groups are tolerated, H_2O traces (up to 5 %), O_2..
* selective for conjugated or aryl ketones > ketones > aldehydes (because aldehydes are acetalized by ROH)

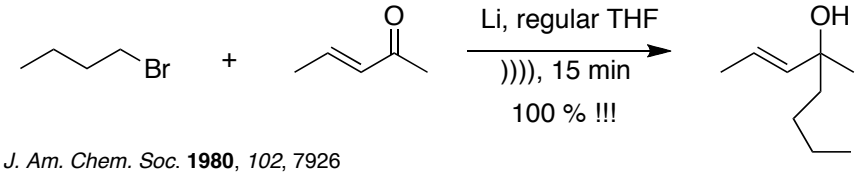
Tetrahedron **1986**, *42*, 2803.



J. Chem. Soc. Chem. Comm. **1978**, 601

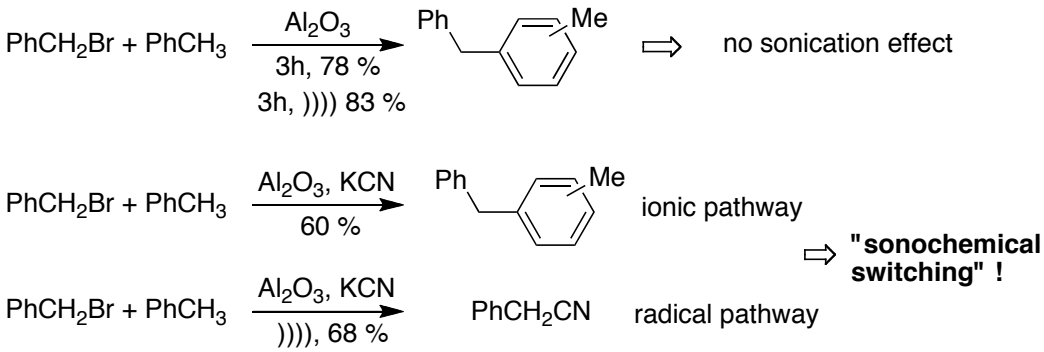
Sonochemistry:

Luche published the first paper that describes a synthetic application of ultrasound in organic synthesis: a Barbier coupling enhanced by sonication (1980).



J. Am. Chem. Soc. **1980**, *102*, 7926

Sonication causes cavitation phenomenon: very small bubbles form in solution, grow and collapse, liberating gas with very high local temperatures (up to 3000 K) and pressure. Cavitation-enhanced reactivity by cleaning the metal surface, improving mass transfer (inhomogeneous) and favoring SET



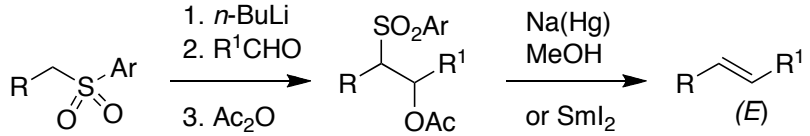
Tetrahedron Lett. **1990**, *31*, 4125.

Reviews on sonochemistry: *Nature* **2002**, *418*, 394 (general)
Synthesis **1989**, *11*, 787 (Luche reviews about reactions improved by sonication)
Luche also works on microwave activation: see *Tetrahedron* **1999**, *51*, 10851.

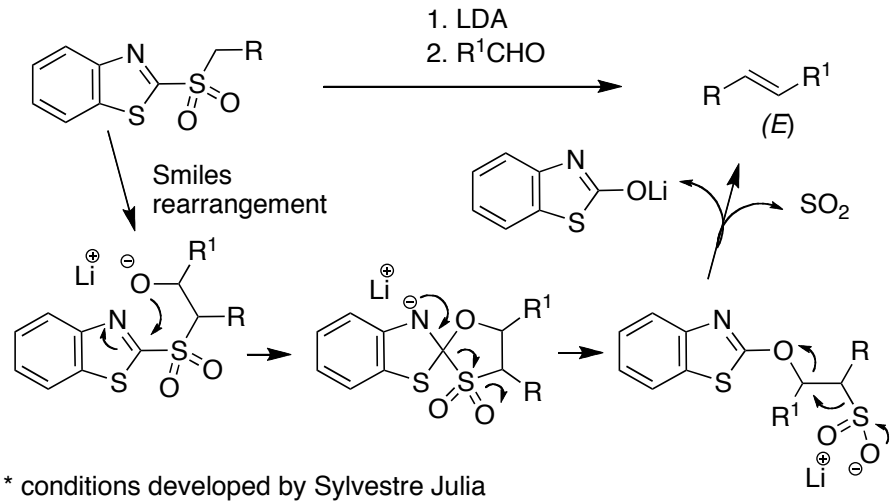
Marc and Sylvestre Julia (École Normale Supérieure):

Julia-Lythgoe olefination (1973):

Tetrahedron Lett. **1973**, *49*, 4833.



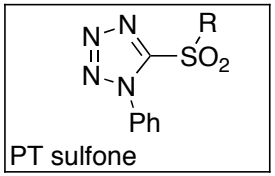
A one-pot Julia olefination (1991): *Tetrahedron Lett.* **1991**, *32,* 1175.



* conditions developed by Sylvestre Julia
* more convenient, scalable
* no need for reducing agents

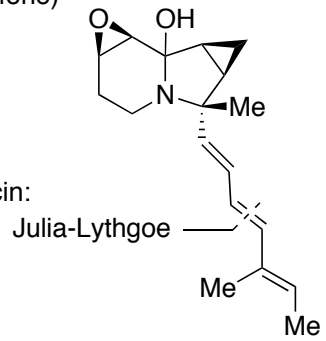
Julia-Kocienski (1998): use of PT sulfone as alkylating agent (same mechanism as BT sulfone)

Synlett **1998**, *26*



Danishefsky's total synthesis of (±)-indolizomycin:

J. Am. Chem. Soc. **1993**, *115,* 30



Marc Julia accomplished some nice total syntheses:

Syntheses of vitamin A, see *Bull. Soc. Chim. Fr.* **1973**, 746

Synthesis of (±)-fredericamycin A, see *Bull. Soc. Chim. Fr.* **1993**, *130*, 447

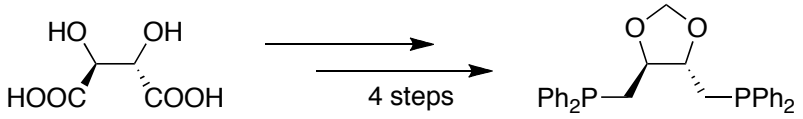
Henri Kagan (Université Paris-XI, Orsay), introduction to future group meeting:

Many contributions including:

* Mild preparation of samarium (II) iodide ("Kagan's reagent") and Kagan-Molander coupling (see **Lewis' GM 2010**)

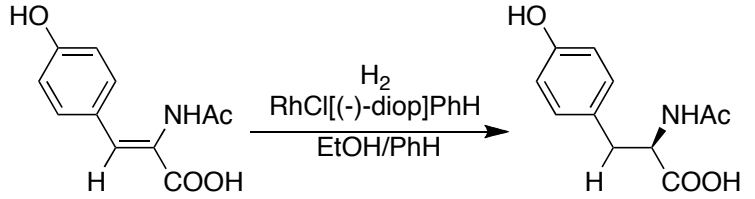
J. Am. Chem. Soc. **1980**, *102,* 2693

* First general method for alkene asymmetric hydrogenation with a chiral ligand



(-) tartaric acid

(-) diop ((-)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)



N-acetyl-(*R*)-tyrosine

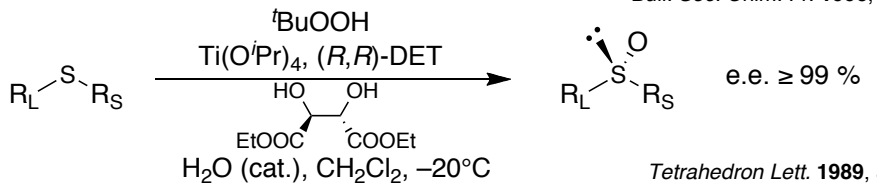
J. Am. Chem. Soc. **1972**, *94*, 6429

yield: 92 %
optical yield: 80 %

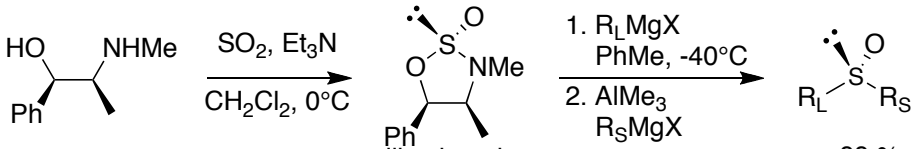
* Rationalization of nonlinear effects in asymmetric synthesis and chiral amplification, *Angew. Chem. Int. Engl. Ed* **1998**, *37*, 2922 (see also **Maimone's GM 2008**)

* Chiral sulfoxide syntheses:

Bull. Soc. Chim. Fr. **1996**, *133,* 1108

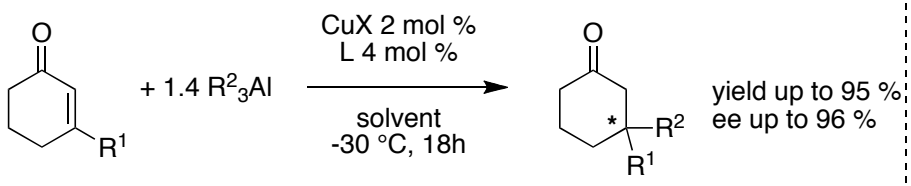


Tetrahedron Lett. **1989**, *30,* 3659



Alexandre Alexakis (Université Pierre et Marie Curie, Paris, then University of Geneva):

enantioselective 1,4-addition:

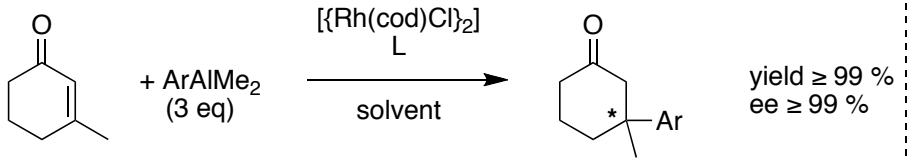


Angew. Chem. Int. Ed. **2005**, *44*, 1376

Tips to improve yield and ee of 1,4-addition (at least with organozincs):

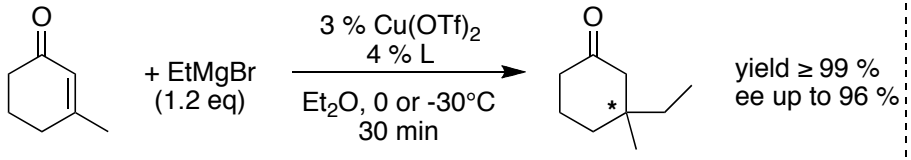
* Solvent choice: acetonitrile gives low conversion, toluene is generally used, but Et_2O, THF, EtOAc show better ee and solubilize substrate better
* $Cu(OTf)_2$ generally used, but Cu carboxylates are more efficient: $Cu(OCOCF_3)_2$ in THF, $Cu(OAc)_2•H_2O$ in Et_2O and copper thiophene-2-carboxylate (CuTC) (the most efficient) in either toluene, Et_2O, or EtOAc, Cu naphthenate soluble in most solvent and the cheapest reagent.
* Of course, ligand choice !

J. Am. Chem. Soc. **2002**, *124*, 5263



Angew. Chem. Int. Ed. **2010**, *49*, 1

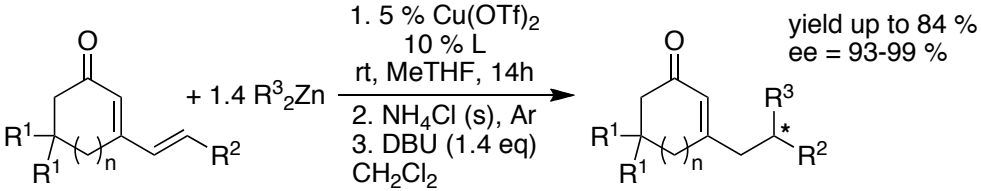
ArLi or ArMgBr + Me_2AlCl --> $ArAlMe_2$



J. Am. Chem. Soc. **2006**, *128*, 8417

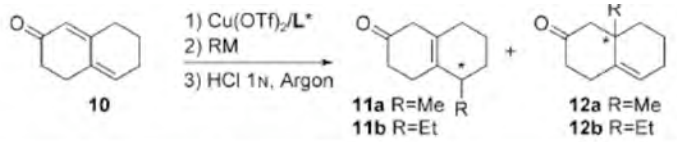
Only one equivalent of the alkylating agent !!

enantioselective 1,6-addition:



Org. Lett., **2010**, *12*, 4335

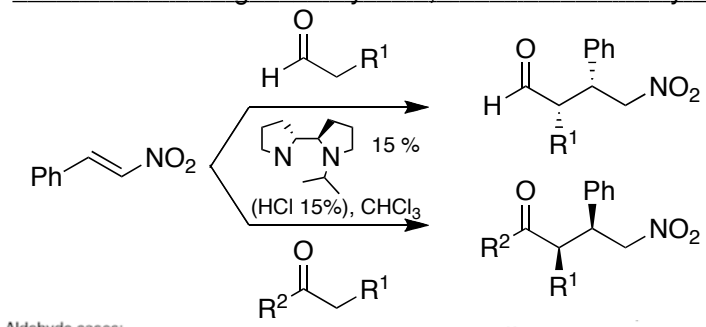
enantioselective 1,4- vs 1,6-addition:



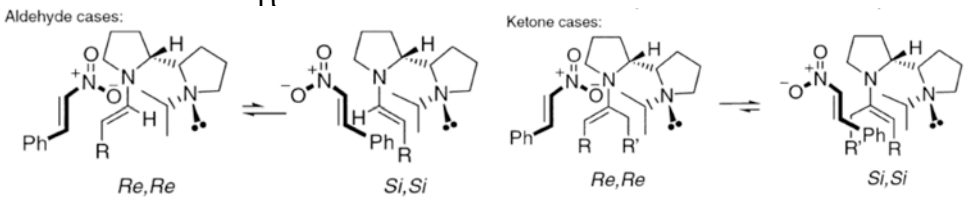
Entry	RM	L*	Solvent	T [°C]	11/12[a]	Conv. [%][a,b]	ee [%][c]
1	Et_2Zn	L2	Et_2O	−10	100:0	11	11
2	Et_3Al	L2	Et_2O	−10	100:0	100 (45)	69
3	Me_3Al[d]	L3	Et_2O	−10	100:0	100 (54)	56
5	EtMgBr	L4	CH_2Cl_2	−10	2:98	100 (73)	96

Angew. Chem. Int. Ed. **2008**, *47*, 1

enantioselective organocatalyzed 1,4-addition on nitrostyrene:



Org. Lett **2002,** *4*, 3611

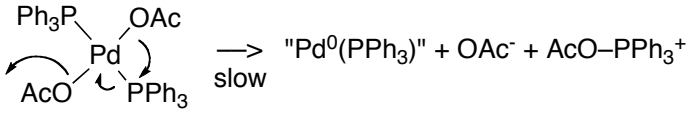


Christian Amatore (École Normale Supérieure): catalysis and mechanism

Evidence that PPh_3 can reduce Pd(II) into Pd(0) for Pd couplings (e.g. Heck):

Thanks to cyclic voltammetry and ^{31}P NMR they propose a mechanism for reduction of Pd(II)

$$Pd(OAc)_2 + 2\ PPh_3 \xrightarrow[\text{fast}]{} Pd(OAc)_2(PPh_3)_2$$

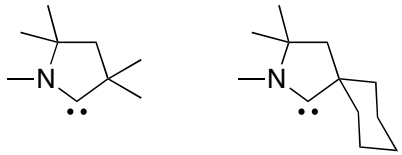


PPh_3 is then oxidized to $O{=}PPh_3$ (2 mechanisms proposed with or without H_2O

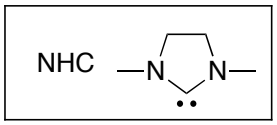
Organometallics, **1992**, *11*, 3009

Guy Bertrand (Université de Toulouse, then UC Riverside):

Synthesis of cyclic (alkyl)-(amino)carbenes (CAACs)

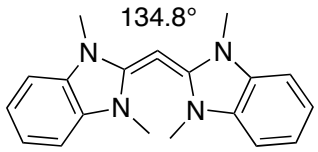


* more electron rich than NHC and steric interactions are different
* CAACs can be mademore or less bulky

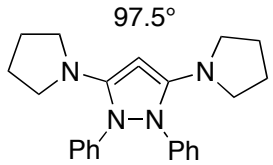


Angew. Chem. Int. Ed. **2005**, *44*, 5705

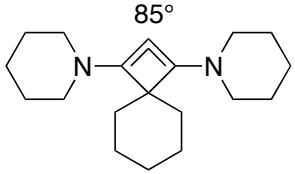
Synthesis of stable bent allenes:



Angew. Chem. Int. Ed. **2008**, *47*, 3206



Angew. Chem. Int. Ed. **2008**, *47*, 5411

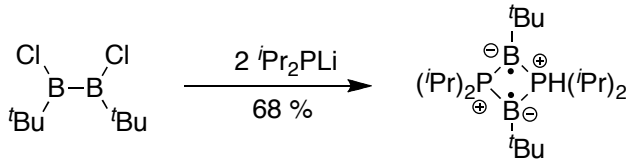


Angew. Chem. Int. Ed. **2009**, *48*, 4792

May serve as very strong donor ligands, but also quite fun!

Synthesis of an indefinitely stable singlet diradical:

(with **Didier Bourissou, Université de Toulouse**)



Science **2002**, *295*, 1880

This diradical may be used as radical scavengers and initiators...

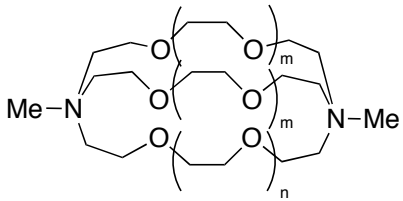
Yves Chauvin: (Université de Lyon) Nobel Prize in Chemistry in 2005 for his mechanistic studies in alkene metathesis

* Dimersol process: nickel-catalyzed dimerization of propylene into isohexenes used as additives in gasoline as octane number boosters or used as plasticizers starting material

* Alphabutol process: titanium-catalyzed dimerization of ethylene into 1-butene used as co-monomer for polyethylene synthesis

Supramolecular chemistry:

Jean-Marie Lehn (Collège de France): Nobel Prize in Chemistry in 1987 for the development of cryptands

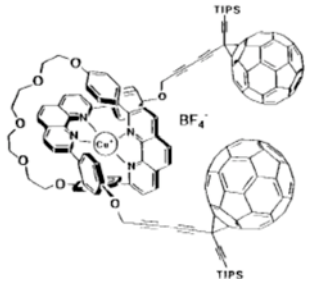


J. Am. Chem. Soc. **1975**, *97*, 6700

One of the first cryptands...

Organic Synthesis from France

Jean-Pierre Sauvage (Université de Strasbourg): Lehn's first PhD student (cryptands), works on rotaxanes, catenanes, molecular motors...

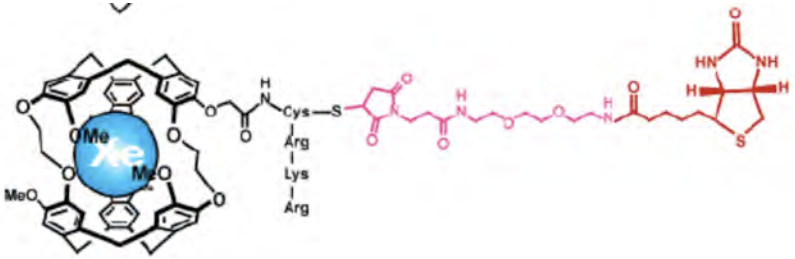


For a review, see *Acc. Chem. Res.* **1998,** *31*, 611

also see **Ishihara's GM 2010**

A fullerene-stoppered rotaxane

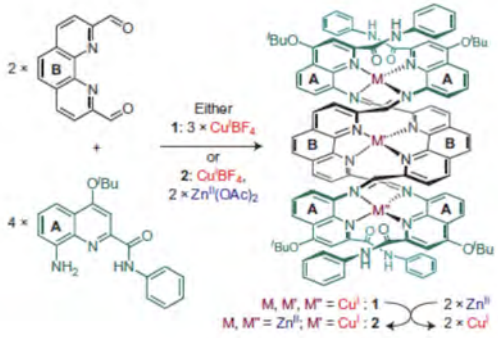
André Collet (École Normale Supérieure de Lyon, deceased): Synthesis of cryptophanes – for a review, see: *Tetrahedron* **1987**, *43*, 5725

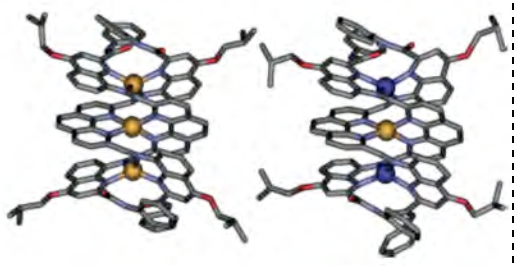


Cryptophanes can be used to make xenon biosensor (P.G Schultz with **N. Winssinger**)

J. Am. Chem. Soc. **2004**, *126*, 15287

Ivan Huc (Institut Européen de Chimie et Biologie, Bordeaux): Dynamic synthesis of self-assembled helicates



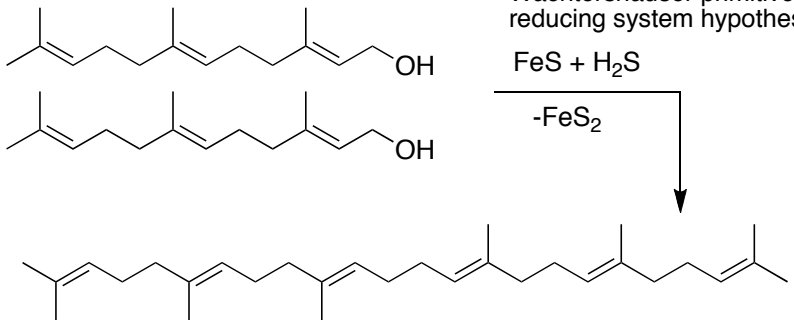


Nature Chem. **2010**, *2*, 684

Methodology applied to total synthesis:

Guy Ourisson (Université de Strasbourg, deceased): One-step synthesis of squalene from farnesol under prebiotic conditions

Wächtershäuser primitive reducing system hypothesis

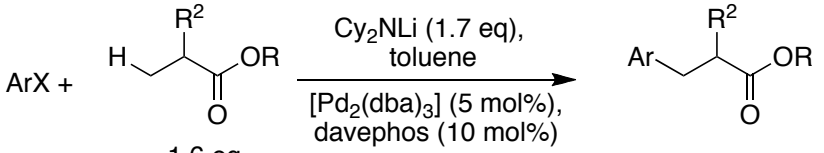


Yield of this reducing coupling: 2 % !!! (compare to vanTamelen-McMurry coupling for this reaction : 30–40 %)

Angew. Chem. Int. Ed. **1995**, *34*, 1898

Olivier Baudoin (Université de Lyon):

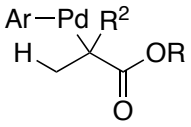
Palladium-catalyzed β-arylation of carboxylic esters:



1.6 eq

yield up to 82 %

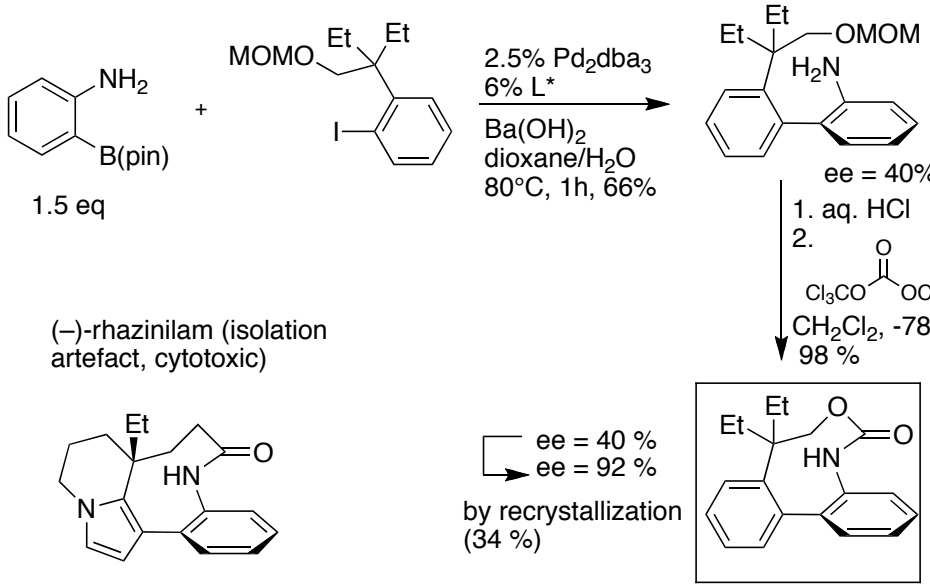
* ArBr reacts better but Cl can be used as well
* often electron donor groups are required at the ortho position (F, OMe...), and some heteroaromatic compounds can be inserted there as well (pyridine, thiophene...)
* enantioselective versions exist: ee around 50 %
* competitive with α-arylation since it generates the same intermediate:



Angew. Chem. Int. Ed. **2010**, *49*, 7261

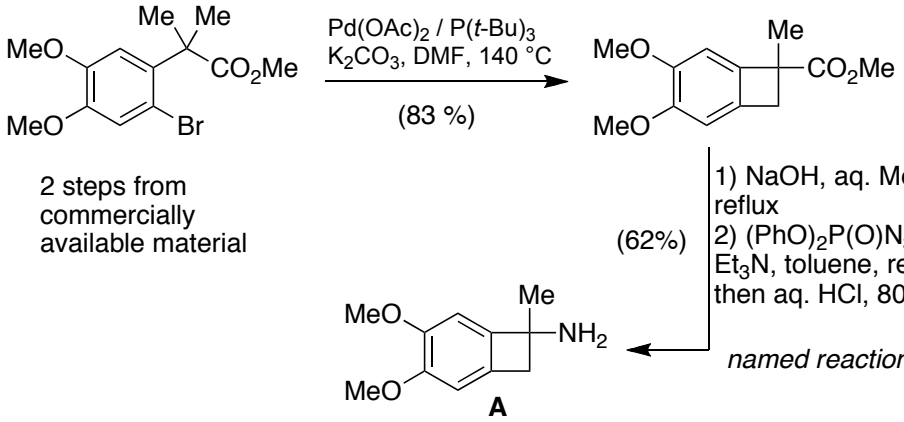
Organic Synthesis from France

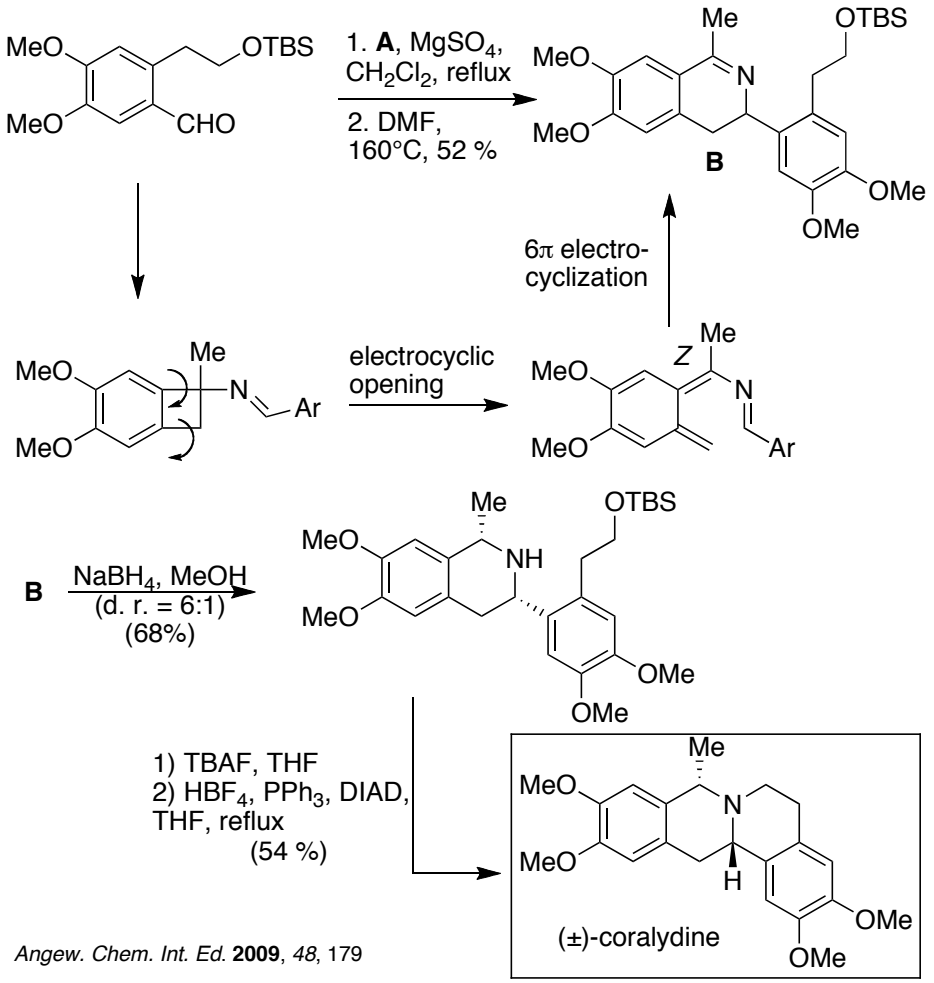
Asymmetric synthesis of atropisomeric biaryl compounds:



J. Org. Chem. **2003**, *68*, 4897

Total synthesis of coralydine:

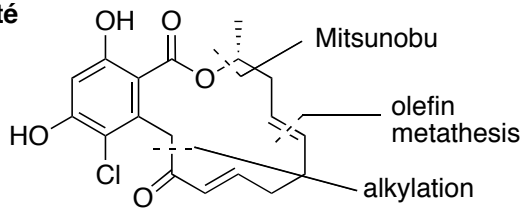




Angew. Chem. Int. Ed. **2009**, *48*, 179

Nicolas Winssinger (Université de Strasbourg):

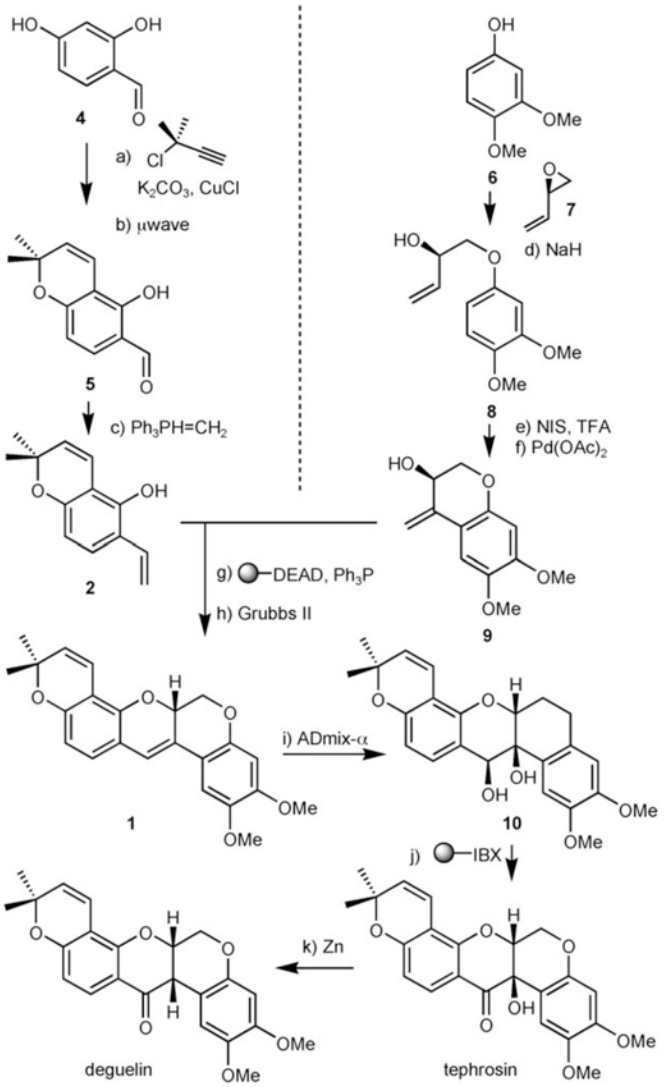
Synthesis of resorcinol macrocycle analogs:



J. Am. Chem. Soc. **2005**, *127*, 6999

Organic Synthesis from France

Total synthesis of deguelin and tephrosin: *Chem. Eur. J.* **2010**, *16*, 9767

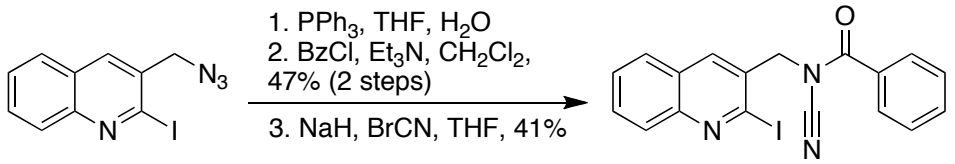


Synthesis of oligosaccharides as a mimic of HIV epitope:
Angew. Chem. Int. Ed. **2009**, *48*, 1

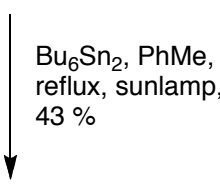
Max Malacria (Université Pierre et Marie Curie Paris 6):

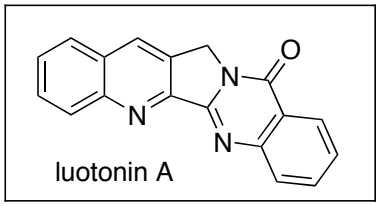
Early works were radical cyclizations, for a review, see: *Chem. Rev.* **1996,** *96*, 289

Recent example: cyclization of *N*-acylcyanamides: Total synthesis of luotonin A



4 steps from quinoline chlorocarbaldehyde in four steps (56% overall yield)

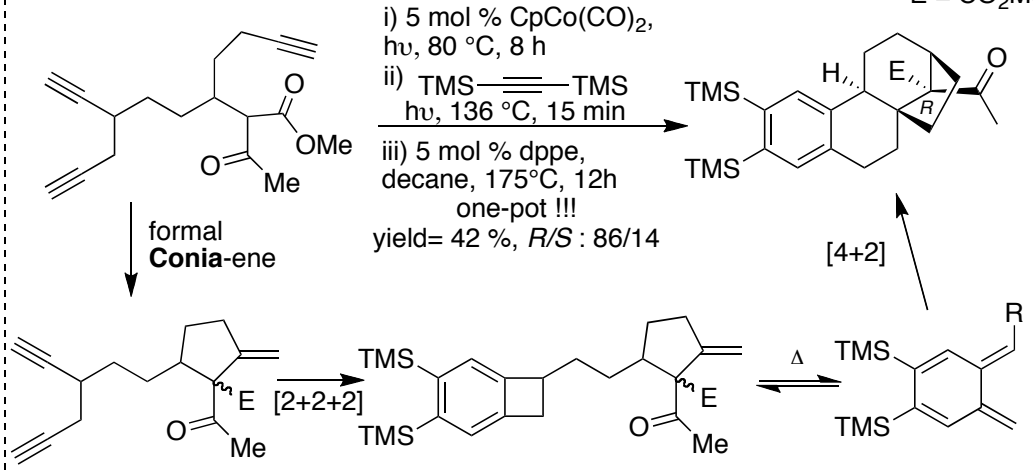




Angew. Chem. Int. Ed. **2007**, *46*, 576

Co-catalyzed cyclizations and cycloadditions:

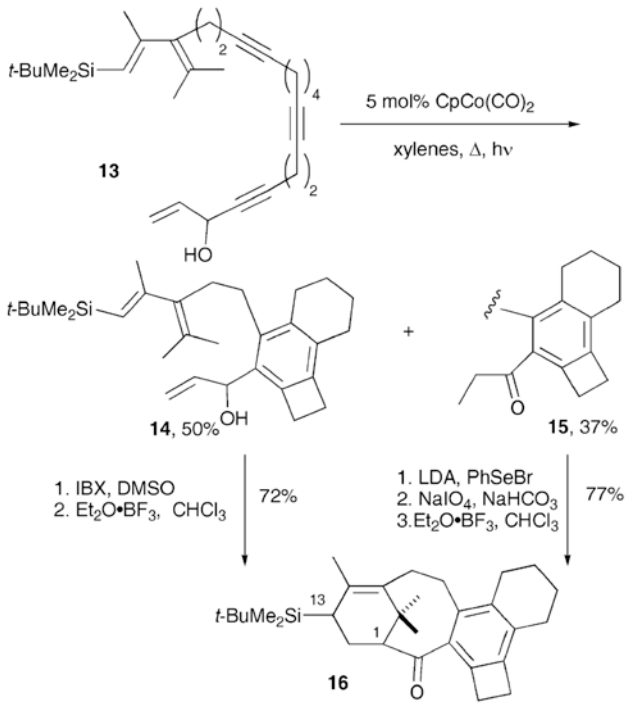
E = CO_2Me



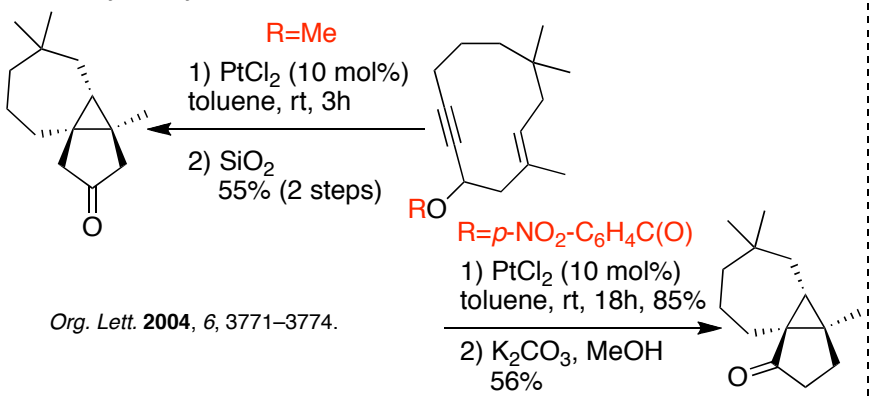
J. Org. Chem. **1996**, *61,* 2699

Organic Synthesis from France

Org. Lett. **2002**, *4*, 1027

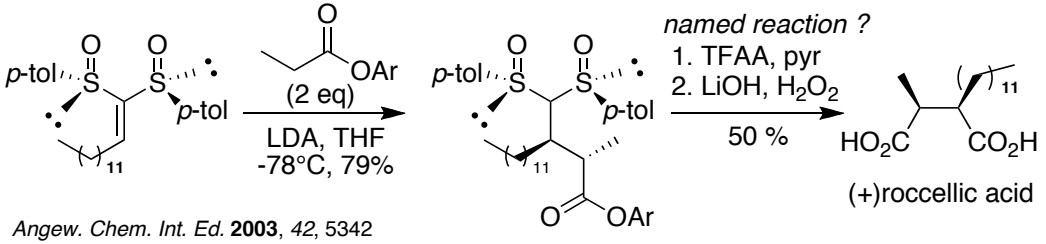


Pt-catalyzed cycloisomerization:

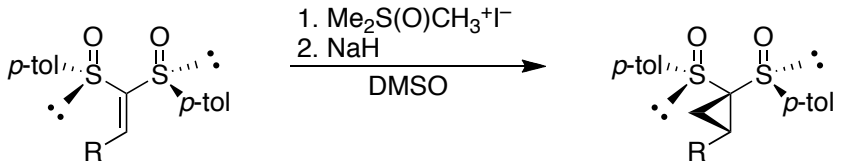


Org. Lett. **2004**, *6*, 3771–3774.

Stereoselective Michael addition on chiral *bis*-sulfoxides:



Angew. Chem. Int. Ed. **2003**, *42*, 5342

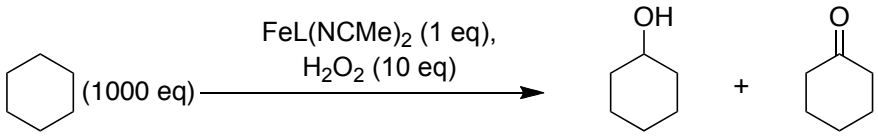


enantioselective synthesis of polyalkylated cyclopropane derivatives

Angew. Chem. Int. Ed. **2008**, *47*, 6865

Sir Derek Barton: he was the director of the Institut de Chimie des Substances Naturelles (ICSN - Gif Sur-Yvette) from 1978 to 1986.

Gif chemistry: biomimetic hydroxylation of alkane catalyzed by Fe.

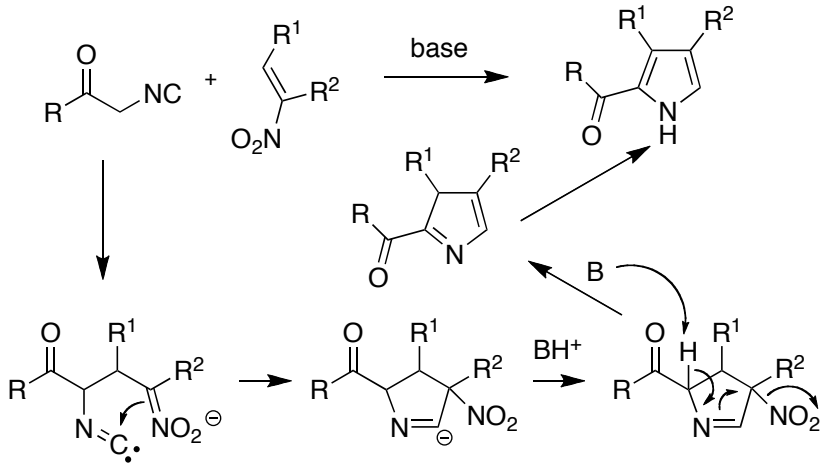


for a review, see Acc. Chem. Res. ***1992****, 25,* 504 and also **Voica's GM 2009**

Samir Zard (École Polytechnique):

works mostly on radical chemistry, like Barton radical decarboxylation, xanthates...

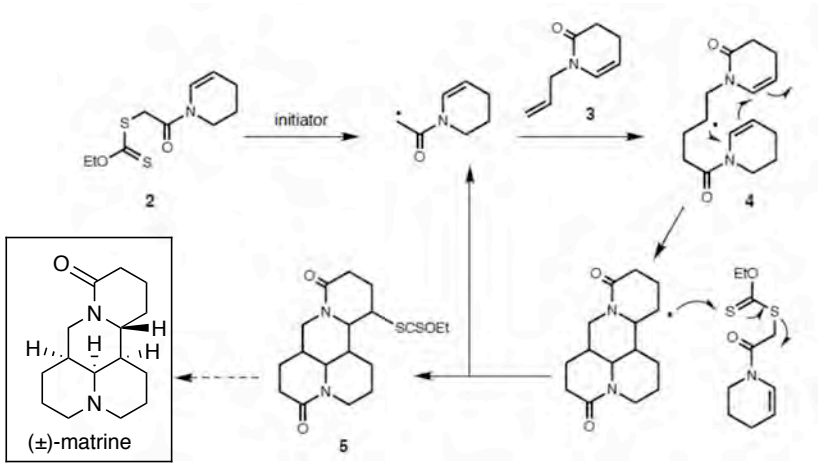
Barton-Zard pyrrole synthesis:



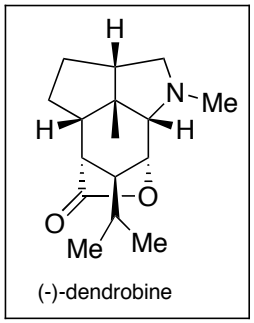
Tetrahedron **1990**, *46*, 7587

Useful synthesis of pyrroles with an ester at the α-position

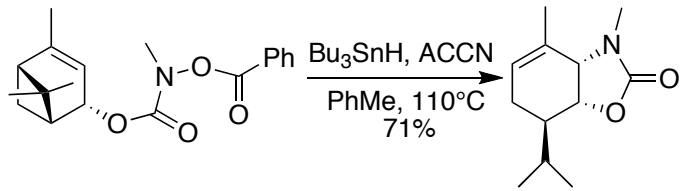
Some total synthesis using radical chemistry:



Angew. Chem. Int. Ed. **1998**, *37*, 1128


(-)-dendrobine

Key steps: radical cascade, Pauson-Khand

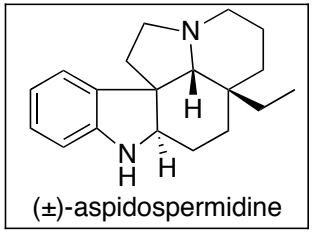


J. Am. Chem. Soc. **1999**, *121*, 6072

See also the synthesis of (±)-aspidospermidine

Org. Lett. **2006**, *8*, 831

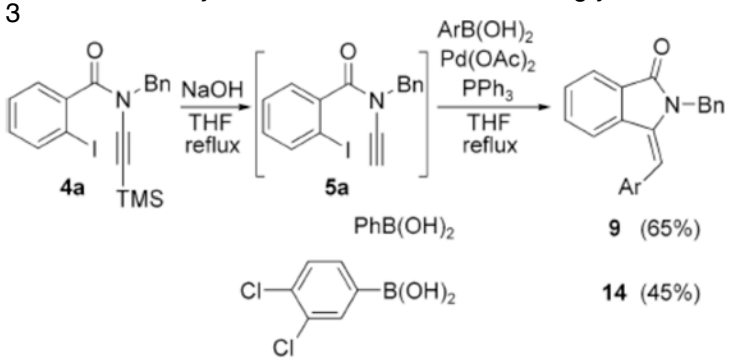
"Thus, in one clean sweep, the side chain we had painstakingly attached was cut off and we were returned to our starting point."


(±)-aspidospermidine

Janine Cossy (École Supérieure de Physique et Chimie Industrielles de la ville de Paris):

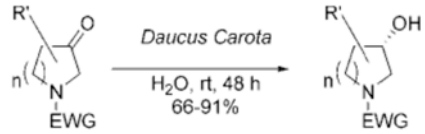
Heck-Suzuki-Miyaura domino reactions involving ynamides:

3



Org. Lett. **2004**, *6* , 2511

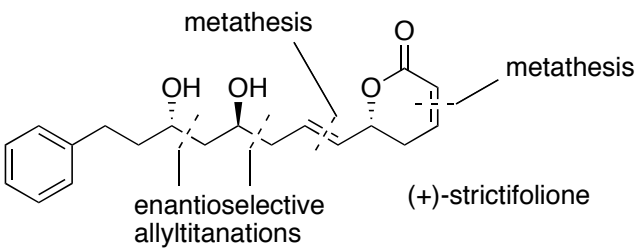
Enantioselective reduction of cyclic aminoketones with carrots:

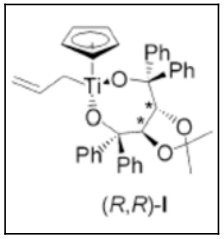


Org. Lett. **2009**, *11*, 1245

Organic Synthesis from France

Sequential enantioselective allyltitanations and metathesis:





Org. Lett. **2003** *5*, 1995

Pierre Potier (Institut de Chimie des Substances Naturelles, deceased):

First semi-synthesis of Taxol from yew leaves: "Meanwhile, we had access to some yew trees, *Taxus baccata* L. (European species), which had to be felled to make way for a new road across the campus at Gif."
Discovery of Docetaxel (Taxotere), commercialized by Sanofi-Aventis: this patent provides one of the most important fundings for CNRS !

Acc. Chem. Res. **1993**, *26*, 160

Other topics of interest:

* Total synthesis: Jieping Zhu and Siméon Arseniyadis (Institut de Chimie des Substances Naturelles)

* Catalysis and organometallics: Pierre Dixneuf (Université de Rennes), Jean-Pierre Genet (École Nationale Supérieure de Chimie de Paris) and Pierre Braunstein (Université de Strasbourg)

To conclude, a quote from Albert Camus (French Nobel Prize for Literature in 1957):

"The struggle itself...is enough to fill a man's heart. One must imagine Sisyphus happy."

The Myth of Sisyphus

Are chemists the modern Sisyphus ???

"Can't you ever relax?"