Organic Synthesis from France

Q. Michaudel
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


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

Elemental halogen isolation:
* Br₂ by Balard (1826)
* I₂ by Courtois (1811)
* F₂ by Moissan (1886), Nobel Prize in 1906 for this and the invention of the electric furnace

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 synthesis of new radioactive elements

Frédéric Joliot-Curie (1900–1958) synthesis of new radioactive elements

Georges Chantepetier (1905–1980): polymers, macromolecular chemistry
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Synthetic methods from the first half of the 20th century:

The "organometallics school":

**Barbier coupling reaction (1899):**

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2
\end{array} \xrightarrow{1. \ R^3X + M} \begin{array}{c}
\text{OH} \\
\text{R}^1 \text{R}^2 \text{R}^3
\end{array}
\]

\(\text{C R. Hebd. Seances Acad. Sci. 1900, 128, 110}\)

* 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 on sonication, see JOC, 1998, 63, 5100.
* In some cases, water can be used as solvent: green chemistry!

**Grignard reaction (1900):**

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2
\end{array} \xrightarrow{1. \ \text{R}^3\text{MgX}} \begin{array}{c}
\text{OH} \\
\text{R}^1 \text{R}^2 \text{R}^3
\end{array}
\]

\(\text{C R. Hebd. Seances Acad. Sci. 1900, 130, 1322}\)

* broad scope of substrate for addition of Grignard reagents: acid derivatives, nitriles, CO₂
* 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):**

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2 \text{X} \\
\text{OR}^1
\end{array} \xrightarrow{1. \ \text{Zn, THF, reflux}} \begin{array}{c}
\text{O} \\
\text{R}^1 \text{R}^2 \text{R}^3
\end{array}
\]

\(\text{C R. Hebd. Seances Acad. Sci. 1900, 132, 478}\)

Paul Sabatier (1854–1941):

* Nobel Prize in 1912 for hydrogenation catalyzed by metals (Ni...)
* Sabatier process: \(\text{CO}_2 + 4 \text{H}_2 \rightarrow \text{CH}_4 + 2 \text{H}_2\text{O}\) (cat. by Ni, Ru or Al₂O₃)
could serve to produce fuel (\text{CH}_4/O₂) 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)

Other noteworthy reactions:

**Delépine amine synthesis (1895):**

\[
\begin{array}{c}
\text{R}^1 \text{X} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array} \xrightarrow{1. \ \text{HCl, EtOH}} \begin{array}{c}
\text{R}^1 \text{NH}_3\text{X}
\end{array}
\]

\(\text{Bull. Soc. Chim. Fr. 1895, 13, 352}\)

alternative to Gabriel reaction
works better with activated halides: benzyl, allyl, \(\alpha\)-haloketone...
Darzens (1904) and aza-Darzens reactions:

\[
\begin{align*}
\text{X} & \rightarrow \text{EWG} \\
\text{R}_1 & + \\
\text{O} & \rightarrow \text{R}_2 \text{R}_3 \\
\text{base} & \rightarrow \\
\text{R}_2 & \rightarrow \text{R}_3 \\
\text{EWG} & \\
\text{glycidic ester for EWG}=\text{CO}_2\text{R}
\end{align*}
\]

* EWG = CO₂R, CN, SO₂R, CONR₂, C(=O), C(=NR)
* base = NaOEt, NaH, LDA...
* X = Cl > Br or I

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

\[
\begin{align*}
\text{I}_2 & \text{ (1 eq)} \\
\text{R}_1 & \rightarrow \text{R}_3 \text{RCO}_2\text{Ag} \text{ (2 eq)} \\
\text{benzene} & \rightarrow \\
\text{base} & \rightarrow \\
\text{H}_2\text{O} & \rightarrow \\
\text{trans-diol}
\end{align*}
\]

Prévost trans-hydroxylation (1933):

\[
\begin{align*}
\text{I}_2 & \text{ (1 eq)} \\
\text{R}_1 & \rightarrow \text{R}_3 \text{RCO}_2\text{Ag} \text{ (1 eq)} \\
\text{AcOH/H}_2\text{O} & \rightarrow \\
\text{base} & \rightarrow \\
\text{H}_2\text{O} & \rightarrow \\
\text{cis-diol}
\end{align*}
\]

Woodward-Brutcher modification

\[
\begin{align*}
\text{I}_2 & \text{ (1 eq)} \\
\text{R}_1 & \rightarrow \text{R}_3 \text{RCO}_2\text{Ag} \text{ (1 eq)} \\
\text{AcOH/H}_2\text{O} & \rightarrow \\
\text{base} & \rightarrow \\
\text{H}_2\text{O} & \rightarrow \\
\text{cis-diol}
\end{align*}
\]

Tiffeneau-Demjanov rearrangement (1937):

\[
\begin{align*}
\text{I}_2 & \text{ (1 eq)} \\
\text{PhCO}_2\text{Ag} & \rightarrow \\
\text{benzene, rt 24h then reflux 10h} & \rightarrow \\
\text{46 %}
\end{align*}
\]

Wrong epimer !!!
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

**Chemistry:**

- Ce catalyzes alkoxyborohydride formation and increases acidity of the medium by coordinating to solvent
- ROH: MeOH > EtOH or iPrOH
- 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, H₂O traces (up to 5 %), O₂...
- *selective* for conjugated or aryl ketones > ketones > aldehydes (because aldehydes are acetalized by ROH)

**References:**

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

Sonochemistry:

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

**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

**References:**


Marc and Sylvestre Julia (École Normale Supérieure):

Julia-Lythgoe olefination (1973):

**Chemistry:**

1. n-BuLi
2. R¹CHO
3. Na(Hg)

**References:**


1. LDA
2. R’CHO

1. RLMgX PhMe, -40°C
2. AlMe3

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

Marc Julia accomplished some nice total syntheses:

Syntheses of vitamin A, see Bull. Soc. Chim. Fr. 1973, 746
Alexandre Alexakis (Université Pierre et Marie Curie, Paris, then University of Geneva):

enantioselective 1,4-addition:

\[
\begin{align*}
\text{R}^1\text{C} = \text{O} + 1.4 \text{R}^2\text{Al} & \quad \text{CuX 2 mol \%} \\
& \quad \text{L 4 mol \%} \\
& \quad \text{solvent} \\
& \quad -30^\circ C, 18 \text{h}
\end{align*}
\]

yield up to 95 \%

\[\text{ee up to 96 \%}\]


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\(_2\)O, 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)\(_2\)\(_\cdot\)H\(_2\)O in Et\(_2\)O and copper thiophene-2-carboxylate (CuTC) (the most efficient) in either toluene, Et\(_2\)O, or EtOAc, Cu naphthenate soluble in most solvent and the cheapest reagent.
* Of course, ligand choice!


\[
\begin{align*}
\text{R}^1\text{C} = \text{O} + \text{ArAlMe}_2 (3 \text{ eq}) \\
& \quad \text{[Rh(cod)Cl]}_2 \quad \text{L} \\
& \quad \text{solvent} \\
& \quad \text{ArLi or ArMgBr + Me}_2\text{AlCl} \rightarrow \text{ArAlMe}_2
\end{align*}
\]

yield \geq 99 \%

ee \geq 99 \%

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

Only one equivalent of the alkylation agent!!

enantioselective 1,6-addition:

1. 5 \% Cu(OTf)\(_2\) 10 \% L \\
rt, MeTHF, 14h

2. NH\(_4\)Cl (s), Ar
3. DBU (1.4 eq)
4. CH\(_2\)Cl\(_2\)

yield up to 84 %

ee = 93-99 %

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>RM</th>
<th>L*</th>
<th>Solvent</th>
<th>T°C</th>
<th>11/12 ([%])</th>
<th>Conv. ([%])</th>
<th>ee ([%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et(_2)Zn</td>
<td>L(_2)</td>
<td>Et(_2)O</td>
<td>-10</td>
<td>100.0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Et(_2)Al</td>
<td>L(_2)</td>
<td>Et(_2)O</td>
<td>-10</td>
<td>100.0</td>
<td>100 (45)</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>Me(_\text{Al}^{[\text{p}]})</td>
<td>L(_3)</td>
<td>Et(_2)O</td>
<td>-10</td>
<td>100.0</td>
<td>100 (54)</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>EtMgBr</td>
<td>L(_4)</td>
<td>CH(_3)Cl</td>
<td>-10</td>
<td>2.98</td>
<td>100 (73)</td>
<td>96</td>
</tr>
</tbody>
</table>


enantioselective organocatalyzed 1,4-addition on nitrostyrene:

\[
\begin{align*}
\text{Ph} - \text{NO}_2 + \text{R}^1\text{H} & \quad \text{N} \quad \text{N} \\
& \quad 15 \% \\
& \quad \text{(HCl 15 \%), CHCl\(_3\)}
\end{align*}
\]

Org. Lett. 2002, 4, 3611

Aldehyde cases:

Ketone cases:
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Christian Amatore (École Normale Supérieure): catalysis and mechanism

Evidence that PPh₃ can reduce Pd(II) into Pd(0) for Pd couplings (e.g. Heck):

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

\[
Pd(OAc)₂ + 2 PPh₃ \rightarrow \text{fast} \ Pd(OAc)₂(PPh₃)₂
\]

\[
\text{slow} \ Pd⁰(PPh₃)²⁺ + OAc⁻ + AcO⁻PPh₃⁺
\]

PPh₃ is then oxidized to O=PPh₃ (2 mechanisms proposed with or without H₂O

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


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

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

\[
\begin{array}{c}
\text{N} \\
\text{N}\end{array} \quad \begin{array}{c}
\text{N} \\
\text{N}\end{array}
\]

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

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

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


Synthesis of stable bent allenes:

\[
\begin{array}{c}
\text{N} \\
\text{N}\end{array} \quad \begin{array}{c}
\text{N} \\
\text{N}\end{array}
\]

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

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

Yves Chauvin: 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

One of the first cryptands...

J. Am. Chem. Soc. 1975, 97, 6700
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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-stopped 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

Methodology applied to total synthesis:

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

\[
\text{FeS} + \text{H}_2\text{S} \rightarrow \text{FeS}_2
\]

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:

\[
\text{ArX} + \text{H} \text{OR}^2 \xrightarrow{\text{1.6 eq Cy}_2\text{NLi (1.7 eq), toluene}} \text{Ar} \text{OR}^2 \xrightarrow{\text{[Pd}_2\text{(dba)}_3 \text{] (5 mol%), davephos (10 mol%)}} \text{Ar} \text{R}^2 \text{OR} \xrightarrow{\text{yield up to 82 %}}
\]

\[
\text{ArPd} \text{OR}^2 \xrightarrow{\text{Ar—Pd R}^2 \text{OR}} \text{Ar} \text{OR}^2
\]

* 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
Asymmetric synthesis of atropisomeric biaryl compounds:

\[
\text{NH}_2 + \text{MOMOEtEt} \xrightarrow{2.5\% \text{Pd}_{2}\text{dba}_3, 6\% \text{L}^*} \text{Ba(OH)}_2 \xrightarrow{\text{dioxane/H}_2\text{O}, 80^\circ\text{C}, 1\text{h}, 66\%} \text{ee} = 40\%
\]

(–)-rhazinilam (isolation artefact, cytotoxic)

\[
\text{J. Org. Chem. 2003, 68, 4897}
\]

Total synthesis of coralydine:

\[
\text{MeO} \xrightarrow{\text{Pd(OAc)}_2 / \text{P(t-Bu)}_3, \text{K}_2\text{CO}_3, \text{DMF, 140 }^\circ\text{C}} \text{MeO} \xrightarrow{1) \text{NaOH, aq. MeOH, reflux} \quad 2) \text{(PhO)}_2\text{P(O)N}_3, \text{Et}_3\text{N, toluene, reflux then aq. HCl, 80 }^\circ\text{C}} \text{MeO}
\]

(62%)

(named reaction ?)


Nicolas Winssinger (Université de Strasbourg):
Synthesis of resorcinol macrocycle analogs:

\[
\text{OH} \xrightarrow{\text{Mitsunobu, olefin metathesis}} \text{OMe}
\]

\[
\text{J. Am. Chem. Soc. 2005, 127, 6999}
\]
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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-acylcyranamides: Total synthesis of luotonin A

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

Co-catalyzed cyclizations and cycloadditions:

Synthesis of oligosaccharides as a mimic of HIV epitope:

Angew. Chem. Int. Ed. 2009, 48, 1

Organic Synthesis from France

Stereoselective Michael addition on chiral bis-sulfoxides:

(named reaction?)

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.

Samir Zard (École Polytechnique):

works mostly on radical chemistry, like Barton radical decarboxylation, xanthates...
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Barton-Zard pyrrole synthesis:

$$\text{O} \quad \text{N}\text{C} \quad + \quad \text{R}^1 \quad \text{R}^2 \quad \xrightarrow{\text{base}} \quad \text{R}^1 \quad \text{R}^2 \quad \text{H}$$

$$\text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \xrightarrow{\text{BH}^+} \quad \text{R}^1 \quad \text{R}^2 \quad \text{H}$$

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

Some total synthesis using radical chemistry:

Key steps: radical cascade, Pauson-Khand

See also the synthesis of (±)-aspidospermidine

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

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

Heck-Suzuki-Miyaura domino reactions involving ynamides:

Enantioselective reduction of cyclic aminoketones with carrots:

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Sequential enantioselective allyltitanations and metathesis:

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{O} & \quad \text{O} \\
\text{metathesis} & & \text{metathesis} \\
\text{enantioselective allyltitanations} & & \text{(+)-strictifolione}
\end{align*}
\]


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 ???

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!


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)