



Outline:

Reactions included:

- Piria diazotization
- Bertagnini salt
- Bertagnini-Perkin olefination
- Cannizzaro reaction
- Schiff base
- Ciamician-Dennstedt rearrangement
- Ciamician photocoupling
- Biginelli pyrimidine synthesis
- Guareschi pyridine synthesis
- Betti reaction
- Bargellini reaction

Not covered:

- Piria reaction
- Plancher rearrangement
- Ponzio reaction
- Pellizzari reaction
- Ortoleva-King reaction
- Angeli-Rimini reaction

- Paternò-Buchi cycloaddition
- Passerini reaction
- Amadori rearrangement
- Ziegler-Natta polymerization
- Berti olefinination
- Caglioti reduction
- Minisci reaction
- Piancatelli rearrengement
- Lombardo methylenation
- Still-Gennari olefination
- Kagan-Modena oxidation
- Bartoli indole synthesis
- Cacchi reaction
- Catellani reaction
- Gastaldi pyrazine synthesis
- Mascarelli fluorene synthesis
- Guarna-Brandi reaction
- Dondoni homologation
- Rosini-Bartoli reductive alkylation
- Prato reaction
- Only main organic reactions are considered, excluding other close field contributions (inorganic, biological, analytical, etc.).
- This is just an overview of the contributions. Most of the reaction have been widely developed with a huge number of different applications. For more detailed info refer to the cited reviews.
- Francesco Minisci photo was not found.

Relevant review:

Pulici, M. Molecules 2013, 18, 10870-10900. <u>https://doi.org/10.3390/molecules180910870</u>

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- It was discovered by Piria while working on asparagine in 1846.
 - It proceeds through alpha-lactone formation with stereo-retention.
 - Used with analytical purposes for the detection of amino groups.
- It soon became a powerful synthetic method for derivatization of chiral pool amino acids.
- Not to be confused with the "Piria reaction", the reduction of nitroaromatic compounds.

Raffaele Piria



SO₃Na

Piria, R. Il Cimento 1846, 4, 55-73. https://doi.org/10.1007/BF02532918

Bertagnini-Perkin reaction and Bertagnini salt:

- Bertagnini discovered a useful adduct between sulphites and aldehydes (plus some methyl ketones).
- Such reactivity was routinely used in the past to identify and purify aldehydes.
- It is used nowadays to release aldehydes in situ.





<u>Mechanism:</u>



Original reaction:

Applications:

Countless

can be afforded.

Coppola, G.M., Schuster, H.F.

NaNO₂

HCI, H₂O

applications

α-Hydroxy Acids in Enantioselective Syntheses; Wiley-VCH Verlag

syntheses and processes.

In the presence of a different nucleophile lots of derivatives

GmbH & Co. KGaA: Weinheim, Germany, 2002.

in

- This carbon-carbon bond forming transformation was greatly improved later by Perkin using acetic anhydride and a base.





Bertagnini, C. Liebigs Ann. 1853, 85, 179–196. https://doi.org/10.1002/jlac.18530850205





Cannizzaro reaction:

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Original reaction:

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Biginelli synthesis:

- Multi-component-coupling for the synthesis of dihydropyrimidones.
- The mechanism is well defined by ratedetermining step studies.



Applications:

- Widely used for the synthesis of huge libraries of potentially bioactive compounds, thanks to easily tunability of side chains.
- It has also been applied to the total synthesis of (-)-batzelladine D by Overman.





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Guareschi synthesis:

- The reaction proceeds through classic condensation mechanism.
- Used for a rapid synthesis of polysubstituted pyridines.

Original reaction:



Guareschi, I. Mem. Reale Accad. Sci. Torino 1896, 46, 1-30.

The Gazzetta Chimica Italiana:

In 1870, Rome was finally annexed to the newly formed Italian -Kingdom and the Italian Journal of Chemistry was founded.

 H_2N

- The most prominent Italian chemists at the time took charge of it: Cannizzaro, Selmi, Tassinari, Schiff, Gabba, Paternò and Guareschi.
- Between them we can find 4 organic, 2 inorganic and 1 analytical chemists (although the fields were not so separated).
- Issued until 1997, when it joined the new European Journal of Organic Chemistry.







Bargellini reaction:





Mechanism:

- The reaction happens between a phenol, chloroform and acetone in the presence of alkaline base.
- It was first investigated as part of a patent study in which he believed the structure was misassigned.
- The mechanism involved the formation of a dichloroepoxide intermediate, which is often referred as the "Bargellini epoxide".
- Nucleophilic opening affords the corresponding carboxylic acid.



Guido Bargellini



- Numerous variations with different nucleophiles including amines, thiols and alcohols, isonitriles, etc.



Bargellini, G. Gazz. Chim. Ital. 1906, 36, 329–338.

Further reading: Tron, G. C. Molecules 2021, 26, 558. https://doi.org/10.3390/molecules26030558

Applications:

- Used in synthesis, for example by Corey for grisandione.



 The Bargellini reaction has found perfect use for the synthesis of morpholinones or piperazinones.



Also applicable for the synthesis of libraries of medicinal compounds.

Corey, E. J. J. Am. Chem. Soc. 1969, 91, 4782–4786. https://doi.org/10.1021/ja01045a034

Corey-Link modification:



Corey, E. J. J. Am. Chem. Soc. 1992, 5, 1906–1908. https://doi.org/10.1021/ja00031a069

- The "Bargellini epoxide" is also a key intermediate in the Corey-Link reaction
- Sodium azide is used as the nucleophile to open it and then hydrogenated to the amine.



Passerini reaction: The reaction is a multicomponent reaction between an isonitrile, a carboxylic acid and a carbonyl compound. Original reaction: The product is an alpha-acyloxyamide. First important account on the chemistry of isonitriles. Two different mechanisms exist, one ionic and one concerted, depending on the polarity of the solvent. An asymmetric version with copper and chiral ligands exists, but the scope is not so great. Mario Passerini Mechanism: [Cu]* (20 mol%), DCM, 0 °C H Mé 16 examples: 75-98% y, 60-98% ee Ar Schreiber, S. L. Org. Lett. 2004, 6, 23, 4231-4233. https://doi.org/10.1021/ol0482893 Passerini, M. Gazz. Chim. Ital. 51, 126-129. Applications: The Passerini reaction was used by Semple euristatin A in the total synthesis of Eurystatin A. FmocHN FmocHN BocHN, CO₂Me CbzHN DCM, 3 to 5 d NHBoc 75% CbzHN MeO Ö Semple, E. J. Tetrahedron Letters 2001, 6271-6274. https://doi.org/10.1016/S0040-4039(01)01287-4 Berti olefination: Original reaction: In this reaction methyl sulfites are used to prepare unsaturated hydrocarbons. - Similar to the Chugaev reaction, but methyl sulfites are more easily accessible than the corresponding xanthates. Mechanism: The Berti olefination is evidenced to undergo a nonconcerted mechanism with the heterolysis of the carbon-oxygen bond, yielding ion pairs followed by direct proton loss or a 1,2-hydride Giancarlo shift and subsequent proton loss from the cationic species. Berti Berti, G. J. Am. Chem. Soc. 1953, 76, 1207-1210

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Original reaction:



Amadori rearrengement:

- He was doing studies on the Maillard reaction .

H₂N-Ar HO

- This transformation involves the reaction of an aldose with an amine.
- The intermediate rearranges to the corresponding ketoseamine.



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OH





Mario Amadori

Applications:

HO

HO

- Amadori products are formed during Maillard reactions.
- That set of complex reactions that happen between sugars and aminoacids when we cook at high temperature.

OH

- Characteristic is the brownish color of the products.

Amadori, M. Nazionale dei Lincei, 1925, 2, 337-342.

Ziegler-Natta polymerization:

- Nobel Prize winning reaction along with Karl Ziegler.
- "The work of Professor Natta has broken nature's monopoly ability in synthesizing stereoregular polymers".
- The structure of the active catalyst is actually complex and has been studied widely with Zr modification.
- Modifications with Zr, Hf, especially for MgCl₂ supported catalyst.





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Natta, G. Accademia Nazionale dei Lincei 1955.

<u>Applications:</u> - Widely used in industry for the synthesis of several polymers: Polyethylene, Polypropylene, Copolymers of ethylene and 1-alkenes, Polybutene-1, Polymethylpentene, Polycycloolefins, Polybutadiene, Polyisoprene, Amorphous poly-alpha-olefins (APAO), Polyacetylene





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- A lot of recent modifications of the original conditions including:

photoredox of acids, C-H activation by HAT, acyl chlorides, sulphinates,

diazonium salts, alkyl bromides, iodides, xanthates, boronic acids, etc.



Minisci reaction:

- This reaction deals with the alkylation of heteroaromatic bases by a carbon centered radical.

Mechanism:





Giovanni

Piancatelli

OH

NR

RN

Verrier, C. Org. Biomol. Chem. 2018, 16, 676. https://doi.org/10.1039/C70B02962D

NR

Piancatelli rearrengement:

- The reaction entails the synthesis of 4-hydroxycyclopent-2-enones starting from the corresponding 2-furyl carbinols.
- It proceeds with high stereocontrol furnishing a relative trans orientation of the substituents.
- The rearrangement is very renown as it allows accessing advanced intermediates of a lot of natural products. Applications:
- Uncountable modifications exist that allow for nucleophile inclusion, asymmetric control, cascade reactivity, etc.

Mechanism:



Piancatelli, G. Tetrahedron Lett. 1976, 17, 3555–3558. https://doi.org/10.1016/S0040-4039(00)71357-8

Lombardo methylenation:



Useful in synthesis when epimerization needs to be avoided.

Original reaction:



formic acid

acetone, H₂O





Lombardo, L. Tetrahedron Lett. 1982, 23, 4293-4296. https://doi.org/10.1016/S0040-4039(00)88728-6



- Preparation and reactivity of what would later be known as the "Lombardo's reagent", although there is confusion in the literature.
- This is consisting of a modified preparation TiCl₄/Zn/CH₂Br₂ complex, originally disclosed by Takai's group.

the methylenation of ketones.

This organometallic species, enables for

- Luciano Lombardo
- Original reaction:





10 examples: 80-94% yield



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Kagan-Modena oxidation:



- Enantioselective oxidation of sulfides to sulfoxides.
- The two methods are very similar using titanium isopropoxide as the catalyst, diethyl tartrate (DET) as the chiral ligand and TBHP as the oxidant. They differ for the solvent system employed that is dichloromethane and water in the Kagan's method and dichloroethane in the Modena's one.

Giorgio Modena

Bartoli indole synthesis:

- An ortho-substituted nitroarene was reacted with a vinyl Grignard reagent.
- In this case the use of three equivalents of the organometallic species per mole of nitroarene leads to the formation of the corresponding 7-substituted indole.

Original reaction:



THF. -78 °C

6 examples: 55-70% vield

Giuseppe

Bartoli



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Original reaction:





Ti(OiPr)₄, (R, R)-DET, TBHF



- Not used for late-stage indole formation, but it can be very useful for the formation of initial precursors.
- It was used By Stoltz and co workers in the synthesis of Dragmacidin D.
- Wide application in medicinal chemistry.



Bartoli, G. Synthesis 1978, 6, 436-437. https://doi.org/10.1055/s-1978-24770

cannabinoid receptor

antagonist

Applications:





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