Review

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Non-Isocyanide-Based Three-Component Reactions: From Strecker to Nowadays

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Abstract. Almost two centuries have passed since Strecker synthesized for the first time the α-aminoacid DL-alanine *via* a sequential combination of acetaldehyde with aqueous ammonia and hydrogen cyanide, coupled to a further hydrolysis of the resulting α-aminonitrile using an acid aqueous solution. Since then, a broad variety of high valued products in various fields of science and technology have been synthesized *via* three-component reactions (3CRs) or *via* one-pot methodologies involving 3CRs coupled smartly to further processes like functionalizations, condensations, cross couplings, cyclizations, ring openings, and so on. In the same way, very interesting and useful computational calculations behind understanding reaction mechanisms related to 3CRs, conformational analyses, and energy profiles have been performed. All these topics are on the scope of the present review, which covers selected and elegant based 3CRs (except for the Ugi-3CR or its variants), and other unclassified 3CR-based works from 2010 to nowadays.
Keywords: MCRs; isocyanides; multicomponent reactions; DFT-based calculations; reaction mechanisms.

Resumen. Han pasado casi dos siglos desde que Strecker sintetizó por primera vez el α-aminoácido DL-alanina mediante una combinación secuencial de acetaldehído con amoníaco acuoso y cianuro de hidrógeno, acoplada a una hidrólisis posterior del α-aminonitrilo resultante utilizando una solución acuosa ácida. Desde entonces, se ha sintetizado una amplia variedad de productos de gran valor en diversos campos de la ciencia y la tecnología mediante reacciones de tres componentes (3CR) o mediante metodologías en un mismo reactor que implican 3CR acopladas a procesos posteriores como funcionalizaciones, condensaciones, acoplamientos cruzados, ciclizaciones, aperturas de anillos, etc. Del mismo modo, se han realizado cálculos computacionales muy interesantes y útiles para comprender los mecanismos de reacción relacionados con 3CR, análisis conformacionales y perfiles energéticos. Todos estos temas están dentro del alcance del presente artículo de revisión, que considera trabajos seleccionados y elegantes basados en 3CRs (excepto Ugi-3CR o sus variantes), y otras 3CRs no clasificadas desde 2010 hasta la actualidad.
Palabras clave: MCRs; isonitrilos; reacciones de multicomponentes; cálculos basados en DFT; mecanismos de reacción.

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Introduction

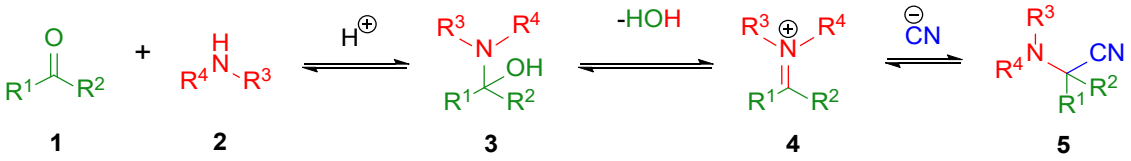
Multicomponent reactions (MCRs) are defined as highly convergent one-pot processes in which three or more reagents are simultaneously, sequentially, or consecutively combined to assemble complex products that contain most of atoms coming from reactants (efficient atom economy) [1]. MCRs can be classified into two main groups: a) MCRs based on the use of isocyanides, and b) non-isocyanide-based MCRs [2]. We recently reported a review-type manuscript discussing reactions based on the use of isocyanides, particularly the Ugi three-component reaction and its variants [3]. In 2009, M. Syamala reported a review focused on three-component reactions (3CRs) [4].

Polyheterocyclic structures are found in a wide variety of products with interesting applications in medicinal chemistry, materials science, agrochemistry, optics, etc. [5-8]. MCRs have been considered as synthetic methodologies of choice to construct polyheterocyclic structures which contain heteroatoms mainly like oxygen, nitrogen, and/or sulfur, just to name a few [9].

This review is focused on non-isocyanide-based 3CRs such as Strecker, Biginelli, Mannich, and Petasis reactions, to name the most known, highlighting applications of synthesized compounds, mainly polyheterocycles. It is important to highlight that the present review includes the literature since 2010.

Strecker-type 3CRs

Strecker reaction was performed for the first time by Adolph Strecker in 1850. This 3CR allows the synthesis of α-aminonitriles **5** (Scheme 1) as result of condensation between a carbonylic compound **1** and an amine **2** (*e.g.*, primary or secondary amines, or ammonia) to afford aminoalcohols **3** which after a dehydration performed iminium ions **4**, followed by the addition of a cyanide source (HCN, TMSCN, etc.) in the same reactor to give the compounds **5**. Moreover, it is known an asymmetrical version of this coupling consisting of sequential combinations of chiral imines, carbonylic components, and cyanide anions but using organocatalysts or chiral metal-based compounds as catalysts to achieve enantio-enriched mixtures of α-aminonitriles. The α-aminonitriles are adequate precursors of α-amino acids. This 3CR owing to its simplicity and atomic economy is appropriate for further transformations [10].



Scheme 1. Three-component Strecker reaction.

In 2011, Stocker *et al.* reported the synthesis of various aminoiminohexitols or azasugars (Scheme 2). Some of these compounds show glycosidase inhibitory activity. The synthesis starts from *D*-ribose **6**. The key step of this methodology involved a diastereoselective Strecker reaction between the *D*-ribose-derived aldehyde **7**, NH_4OAc, and TMSCN to afford the α-aminonitrile **8** in excellent yield (92%). The major diastereomer was placed in *syn* configuration (*syn/anti* 8:1). Diastereomer **8** was isolated and then treated with $NaHCO_3$ and I_2 promoting carbamate annulation to afford the bicyclic compound **9**. After hydrogenation, and deprotection it was achieved the compound **10**. Finally, a hydrolysis of compound **10** completes the total synthesis of the aminoiminohexitol **11** in 36% overall yield [11]. It is worth noting the high stereoselectivity of the Strecker reaction as well as the absence of metal catalysts.

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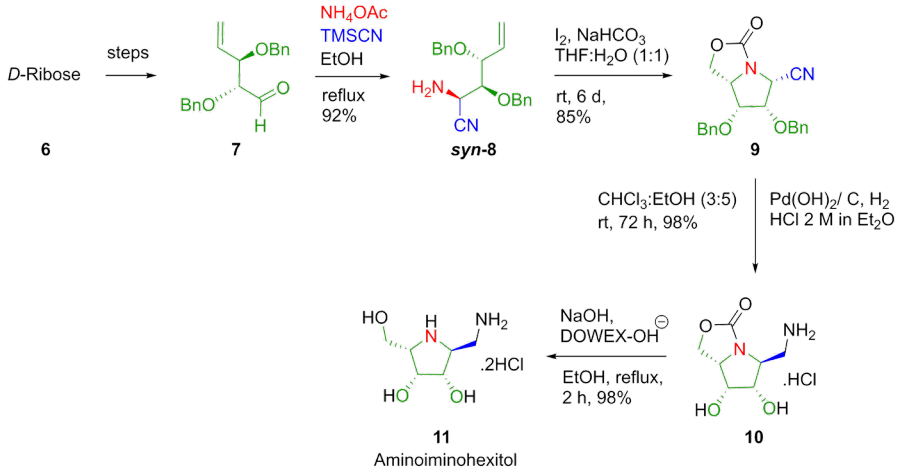
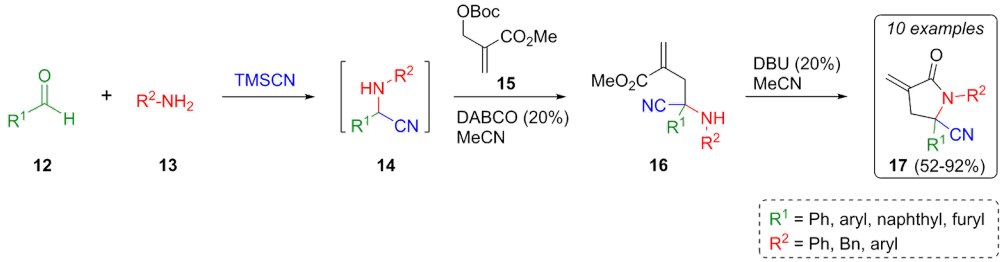


Scheme 2. Synthesis of aminoiminohexitols.

A tandem Strecker-Lewis base-catalyzed reaction was employed by Liao *et al.* in the synthesis of γ-lactams [12]. As the first step, amino nitrile intermediates **14** were achieved through a sequential combination of aldehydes **12**, amines **13**, and TMSCN under basic conditions generated *in situ* (Scheme 3). Then, functionalization of amino nitriles **14** *via* allylic alkylation was furnished by reacting with methyl acrylate **15** to provide the precursors **16**. Thus, the new γ-lactams **17** were synthesized in moderate to good yields (52-92 %) from the intermediates **16** through the assistance of DBU in acetonitrile as solvent. This Strecker reaction was an excellent option for synthesizing highly functionalized aminonitriles that for the allylic-alkylation-cyclization strategy is regioselectively driven by polar solvents such as acetonitrile.



Scheme 3. Synthesis of γ-lactams.

Another nice example of a Strecker reaction is found in a report by Cardona *et al.* [13]. Aldehyde **19** was previously prepared starting from D-mannose (**18**) in four steps (Scheme 4). Then, a catalytic hydrogenation of ketal **19** was performed to give the aldehyde **20**, which then was subjected to a Strecker reaction in mild conditions using benzylamine and trimethylsilyl cyanide. Finally, nitrile **21** was acetylated under basic conditions affording the piperidine-containing acetate **22**. Noteworthy, Strecker reaction was the step key as stereo and regio-selective due to the following reasons:1) it was taken the stereochemistry of compound **20** to carry out the Strecker reaction, where the formation of the iminium ion favored a chelated intermediate in which the cyanide anion performed the addition on the *Si* face to the double bond forming the diastereomer *S* as the major product. In the same way, reductive amination at the C-1 position was promoted by the C-5 position of aldehyde.

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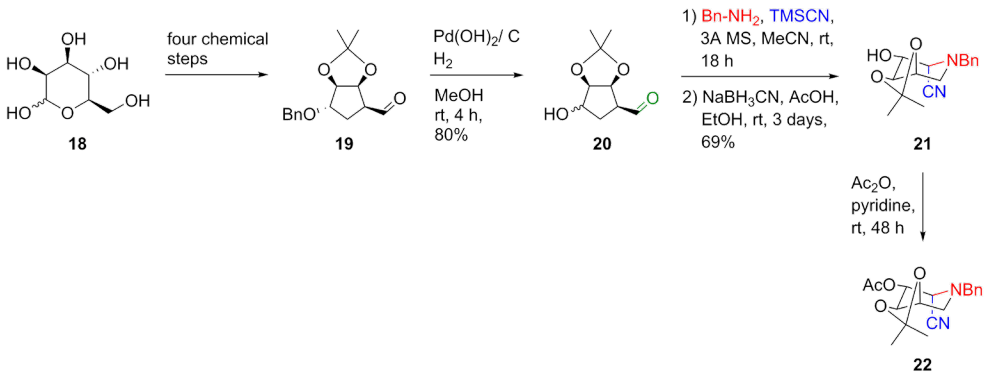
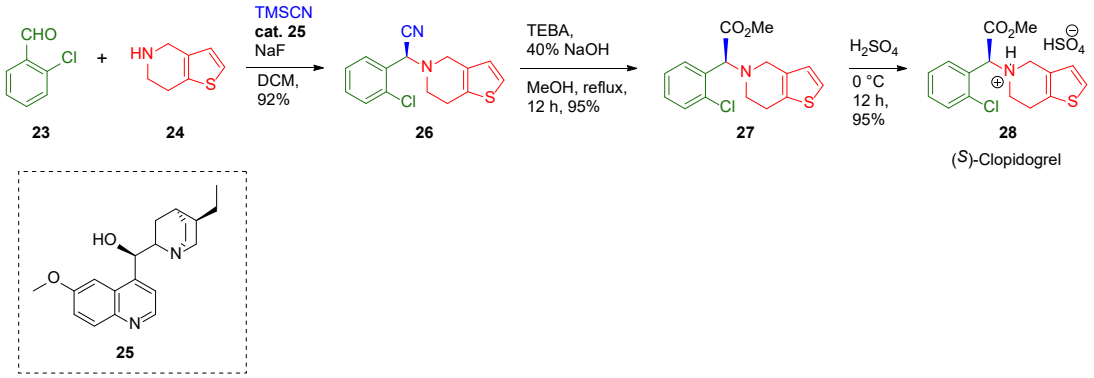


Scheme 4. Synthesis of piperidine adducts.

Khan *et al.* reported a short and original asymmetric Strecker reaction to synthesize (*S*)-Clopidogrel (antiplatelet agent) [14]. 2-Chlorobenzaldehyde (**23**) in the presence of *bis*-heterocycle **24** as the amine generated *in situ* an iminium salt, which was trapped by TMSCN. The chiral alkaloid **25** as an organocatalyst was included. The reaction gave a good yield (92 %) and enantioselectivity (er 78:22). A further Pinner reaction with nitrile **26** achieved compound **27**, and its acidic hydrolysis afforded the (*S*)-Clopidogrel (**28**) (Scheme 5). Authors suggested that the use of NaF as a polarizer of the Si-CN bond facilitated the nucleophilic attack by CN. Coupled with it, it is noted that the use of this kind of organocatalysts made it possible to perform Strecker reactions in enantioselective manner. This was the first time where a *Cinchona alkaloid* derivative was used in an asymmetric Strecker reaction, in this case occurred a process of dynamic kinetic resolution to generate quantitative yields in one of the enantiomers [15].



Scheme 5. Synthesis of (*S*)-Clopidogrel.

In 2013, Liu, Hao *et al.* designed an unusual strategy with extreme atom economy towards the synthesis of Trigonoliimine A (hexacyclic bisindole alkaloid isolated from *Trigonostemon lii*), in which one of the key steps was a Strecker-type reaction [16]. Oxidation of tryptamine **29** gave the ketone **30**. Thus, the TMSOTf-catalyzed sequential combination of *N*-phthaloyl-derivative aldehyde **30**, tryptamine (**31**), and TMSCN gave the Strecker-intermediate **32**. Seven-membered ketone **33** was obtained from nitrile compound **32** *via* Houben-Hoesch-type cyclization in 60% yield. Trigonoliimine A (**34**) was provided in 85% yield by treatment of seven-membered ketone **33** with hydrazine in ethanol (Scheme 6). It is noteworthy that Strecker reactions with ketones are hard to perform.

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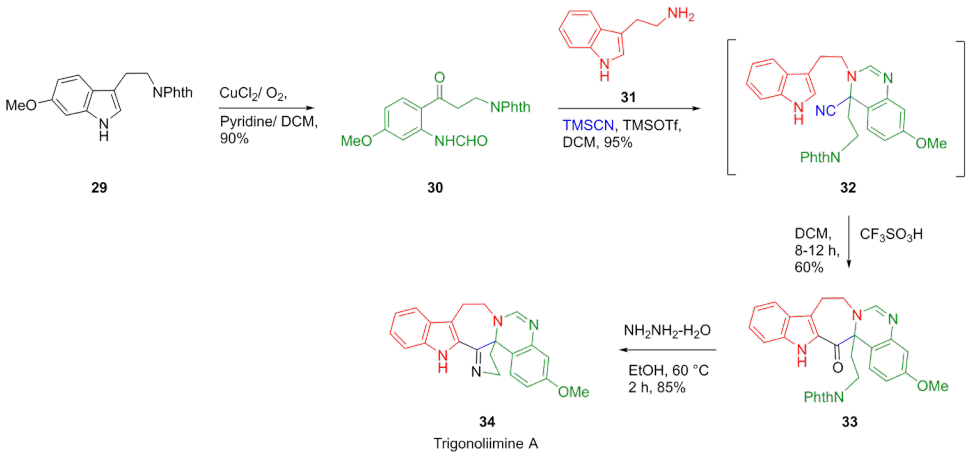
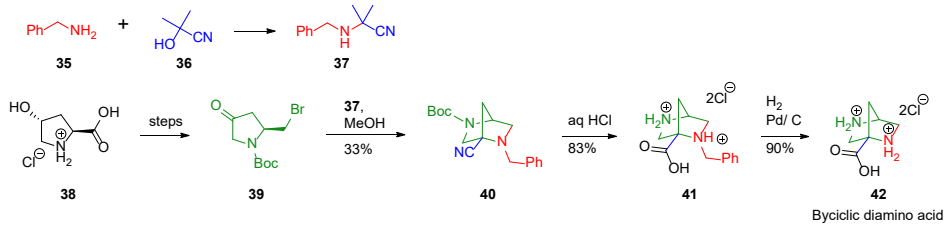


Scheme 6. Synthesis of (±) Trigonoliimine A.

In 2015, Grygorenko *et al.* continued developing their strategic route called tandem Strecker Reaction–Intramolecular Nucleophilic Cyclization (STRINC) (Scheme 7) [17]. Thus, pyrrolidine-derived γ-bromoketone **39** was synthesized from L-4-hydroxyproline **38** after several chemical steps. After optimization, STRINC process was carried out between ketone **39** and reagent **37**, previously generated through a combination between amine **35** and nitrile **36**, affording bicyclic aminonitrile **40**. Acid hydrolysis of aminonitrile **40** and deprotection of acid **41** completed the synthesis of bicyclic amino acid **42** in an overall yield of 7 % after 10 steps. This one is a peculiar kind of methodology giving good atom economy to develop bicyclic scaffolds.



Scheme 7. Synthesis of bicyclic diamino acid.

In 2016, Kurosu *et al.* reported a stereocontrolled total synthesis of Muraymycin D1 [18]. Due to the complexity of the latter, its synthesis was divided in two crucial sides. a) Starting from carbamate **43**, it followed a sequence of reactions such as ureido-muraymycidine tripeptide builded by epimerization-lactone opening and a cyclic guanylation as key steps. b) The other moiety, starting from carbohydrate **45**, the chemical steps comprise a complex of 3-aminopropyl amino acid involving several processes such as oxidation, Carreira's asymmetric alkynation, β-selective ribosylation, hydration with $HgCl_2$, a selective deprotection, and a stereoselective Strecker reaction as one of determining steps of this route. The reaction between aldehyde **47** (precursor of Strecker reaction) with Cbz-monoprotected 1,3-diaminopropane **49** and TMSCN catalyzed by thiourea **48** or magnesium sulfate produced the desired aminonitrile **50** with absolute selectivity in (*S*)-diastereomer form (Scheme 8). Authors proposed thiourea **48** or magnesium sulfate to promote separation of the mixture of enantiomers. The join of the peptidic chains **44** and **51** was promoted by glyceroacetonide-oxyme **52** through a decomplexation process with compound **44**. Finally, after a deprotection step of compound **53** afforded Muraymycin D1 (**54**). It is worth highlighting the complexity of this synthetic strategy, its stereoselectivity, and the implementation 'for the first

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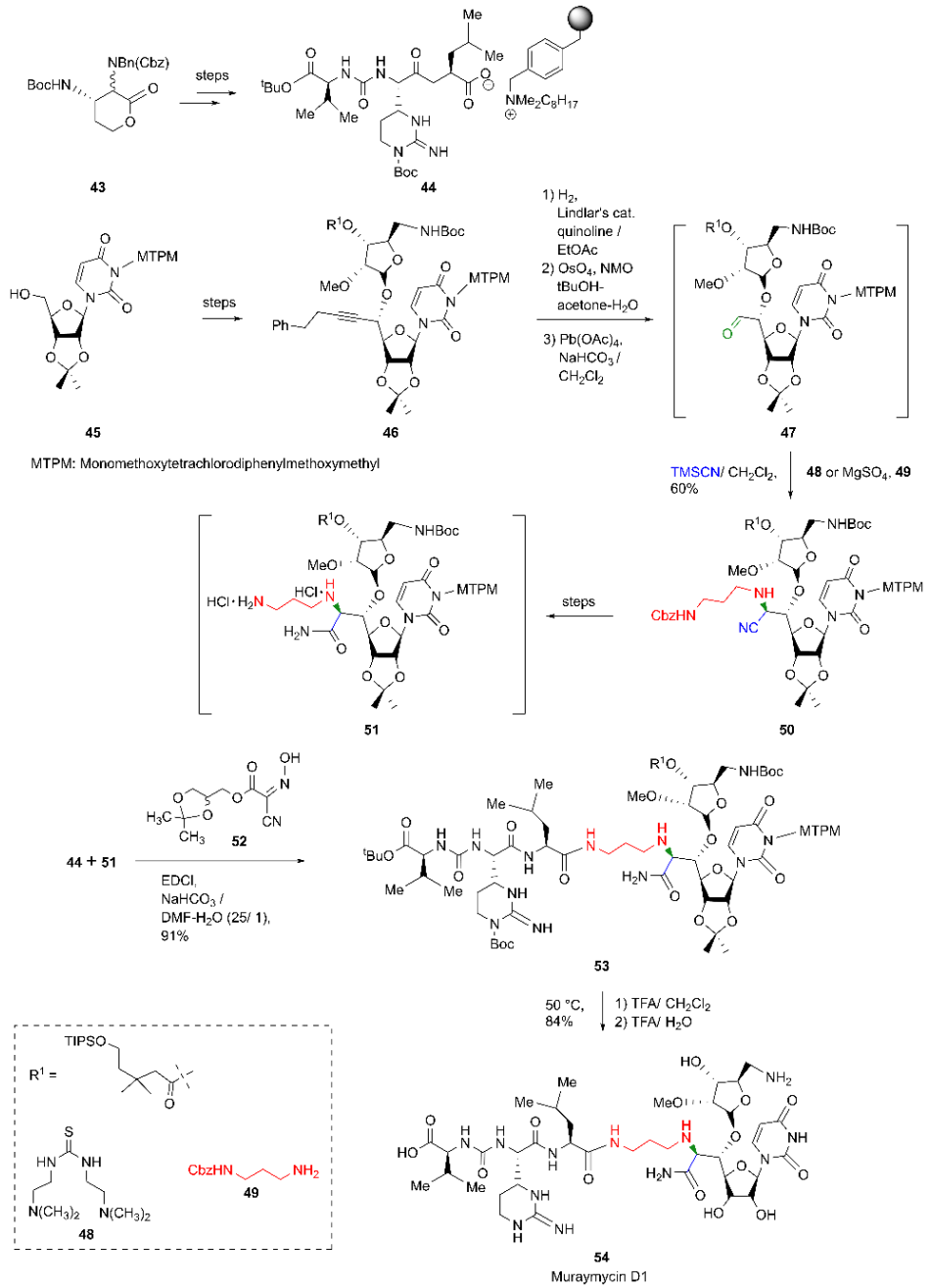
time' of a stereoselective Strecker reaction as the key step. Also, it played an extremely important role in the joining of fragments **44** and **51**, leading to a high proportion of the (*S*)-diastereomer.



Scheme 8. Synthesis of Muraymycin D1.

Chaturbhuj *et al.* reported an efficient and low toxic strategy involving the use of a solvent-free organocatalyzed Strecker reaction between aldehydes **55**, amines **56**, TMSCN and borate catalyst **57** at room temperature to afford in up to 30 minutes the products **58** shown in Scheme 9 in good to excellent yields (87-

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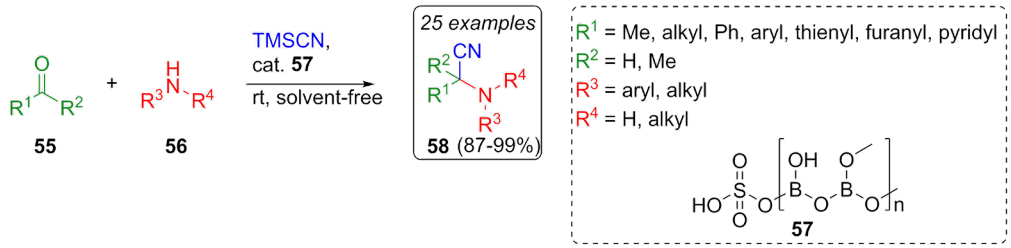
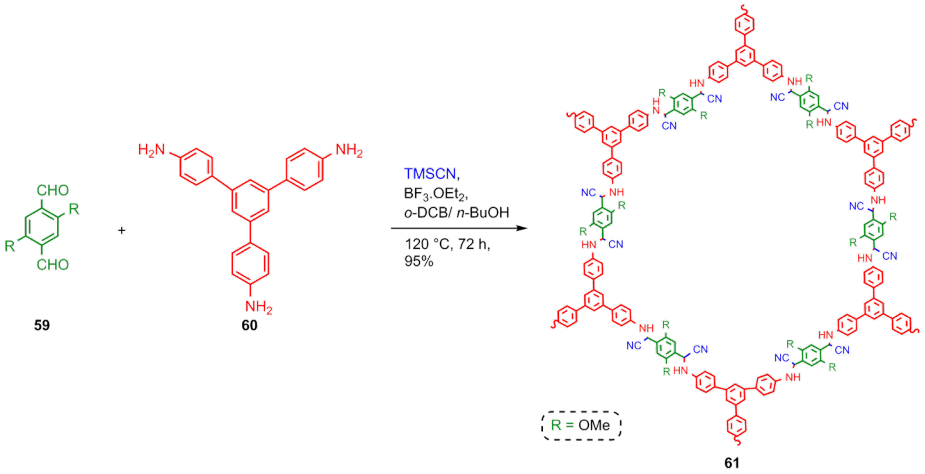
99%) [19]. In scope, different electron-donating and electron-withdrawing groups were evaluated, as well as polar and non-polar solvents, finding that the best reaction condition was under a solvent-free environment. In addition, the effect of the catalyst on the reaction was proven using a panel of Lewis and Brønsted acids, resulting to be the sulfated polyborate the best one. Finally, many advantages of the trimethylsilyl cyanide (TMSCN) as a cyanide source were demonstrated, but mainly safe use, ease of handling, and effectiveness.



Scheme 9. Sulfated polyborate-catalyzed Strecker reaction.

Covalent Organic Frameworks (COFs) belong to a special type of crystalline porous materials, that have caught the attention of synthetic and material chemists for their applications such as catalysts or gas storage materials [20]. The approach of Chen, Dong *et al.* involved a mixture of aromatic aldehydes **59**, amine **60**, and TMSCN catalyzed by a Lewis acid to afford the products **61** in 95 % yield (Scheme 10) [21]. There are currently a few examples of COFs designed and synthesized through multicomponent reactions due to their complexity, but these methods turn out to be good choices for the preparation of these types of materials.



Scheme 10. Covalent organic frameworks approach.

Marder *et al.* reported a chemoselective strategy to synthesize α-amino boronates *via* a new named Borono-Strecker reaction [22]. Thus, aldehydes **62** coordinate with titanium to give intermediates **63**, which were combined with amines **64** in the presence of Lewis acid $Ti(OEt)_4$ promoting imine's **66** formation after an ethanol release in compounds **65**. A proton source is necessary for the hydroboration of imines **66**. This latter is due to the formation of a fluoride assisted by ethoxide anion, activating B_2pin_2 (*bis*(pinacolato)diboron) for copper transmetalation in compound **67**, using MTBE as a solvent to give the α-aminoboronates **68** in moderate to good yields (42-95 %) (Scheme 11). As seen, the key idea was to use a Lewis acid together with a proton source (Brønsted acid) to avoid side reactions between carbonylic compounds and B_2pin_2.

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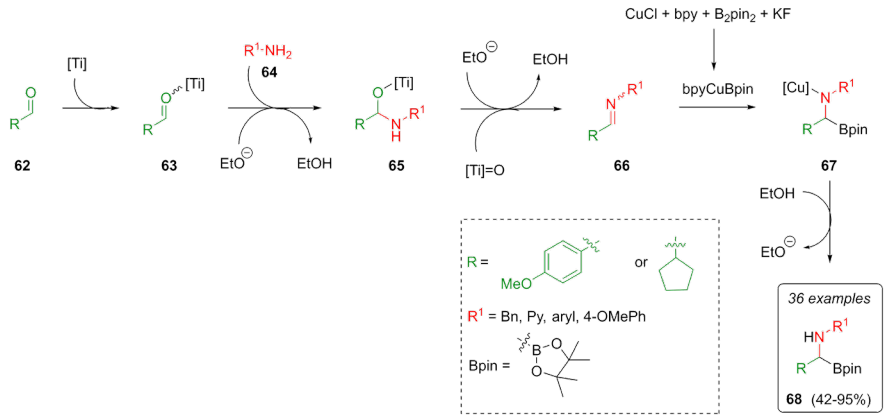
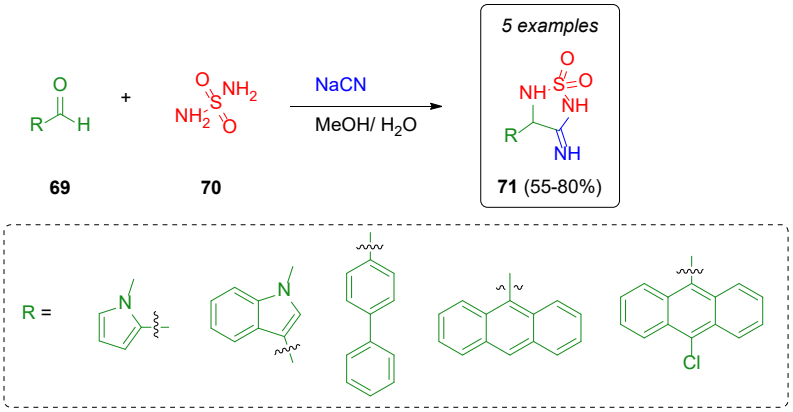


Scheme 11. Synthesis of α-aminoboronates *via* a Borono-Strecker reaction.

In 2022, Başkan *et al.* reported the synthesis and *in vitro* evaluation of 3-imino-sulfahydantoins on bacteria and cytotoxicity studies [23]. These compounds were prepared through a Strecker reaction by a combination of different aromatic and heterocyclic aldehydes **69**, sulfamide **70**, and sodium cyanide to give 1,1-dioxides **71** in moderate to good yields (55-80 %) (Scheme 12). These compounds exhibited potential antibacterial properties and cytotoxic effects on SPC212 cells related to malignant pleural mesothelioma, a type of lung cancer.



Scheme 12. Synthesis of 3-imino sulfahydantoins.

Biginelli-type 3CRs

In 1893, Pietro Biginelli made possible another kind of a three-component reaction by protonation of carbonyl compounds **72**. Then, protonated aldehydes **73** were combined with urea or thiourea (**74**) to give aminoalcohols **75,** which after dehydration performed iminium ions **76**. The addition of a *β*-ketoesters **77** (*e.g.* ethyl acetoacetate) achieves 3,4-dihydropyrimidin-2(1*H*)-ones **80** after a cyclization step of compounds **78** and dehydration of intermediates **79** (Scheme 13) [24]. Also, this kind of condensation could be catalyzed by many Brønsted or Lewis acids. Asymmetric synthesis of many dihydropyrimidinones has been also reported to develop new compounds with pharmaceutical interest [25].

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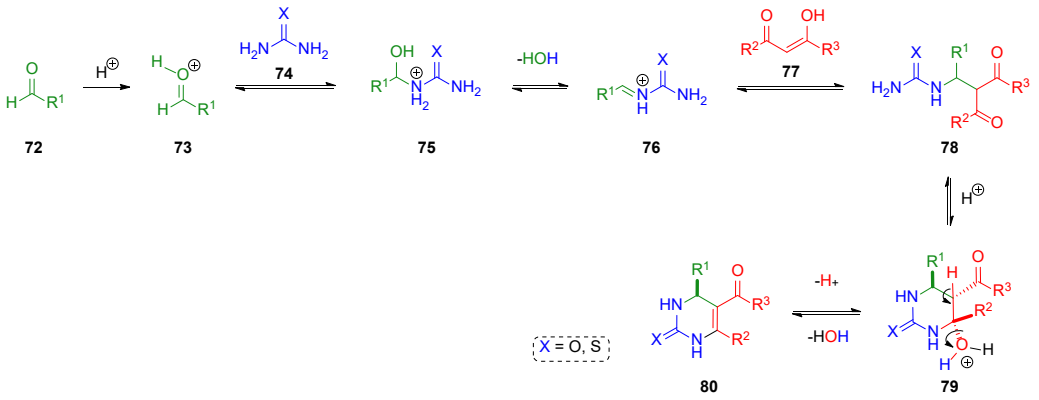
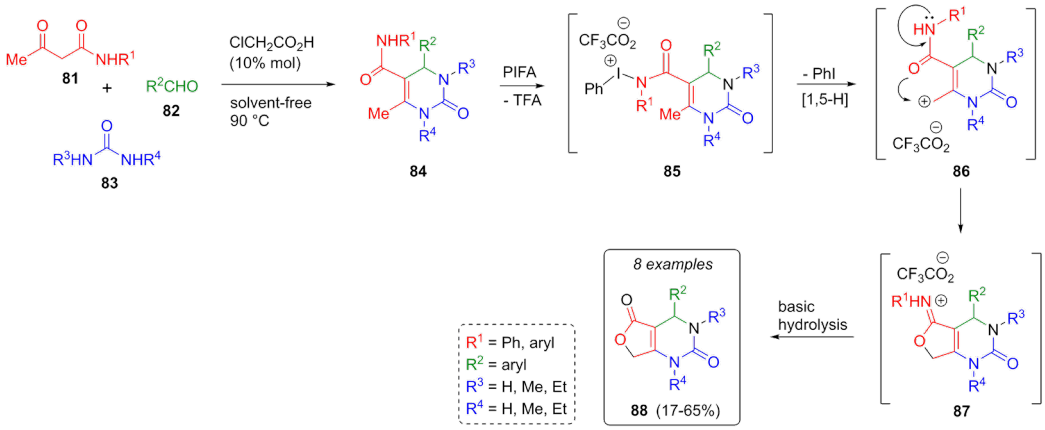


Scheme 13. Biginelli reaction.

In 2010, Tellitu, Dominguez *et al.* developed an interesting methodology to achieve furo[3,4-*d*]pyrimidinones **88** using a Biginelli reaction as the key step [26]. After corresponding optimizations, 5-carboxamido-dihydropyrimidines **84** were afforded from 3-ketoamides **81**, aldehydes **82**, and urea-derivates **83** using chloroacetic acid as catalyst, under solvent-free conditions (Scheme 14). Compounds **84** in the presence of PIFA [phenyliodine(III) bis(trifluoroacetate)] promote formation of iodine complexes **85**. Then, a 1,5-hydride shift achieved intermediates **86**, where the allylic position was attacked by oxygen of amide fragment to give the iminolactones **87**. Finally, a hydrolysis step developed corresponding furo[3,4-*d*]pyrimidine-2,5-diones **88** in moderate yields (17-65%). PIFA plays an important role in intramolecular oxycarbonylation. Also, electronic or steric effects into aryl groups promote the corresponding yields.



Scheme 14. Synthesis of furo[3,4-*d*]pyrimidinones.

A closer work was reported by Singh *et al.* in 2010, where it was performed for the first time a silica-sulfuric acid-catalyzed Biginelli-type reaction [27]. It was proposed the use of β-oxodithioesters as β-dicarbonyl components. After corresponding optimizations, oxodithioesters **91**, aldehydes **92**, and urea (**93**) were combined with SiO_2-H_2SO_4 as acid catalyst to generate the Biginelli-derivatives **97** in moderate to good yields (65-85%). It was proposed a plausible mechanism where condensation between aldehydes **92** and urea (**93**) performed iminium cations **95**. After the addition of dithioester enols **91** (previously afforded through condensation between ketones **89** and thioate **90**), an intramolecular cyclocondensation, and dehydration performed dihydropyrimidinones **97**

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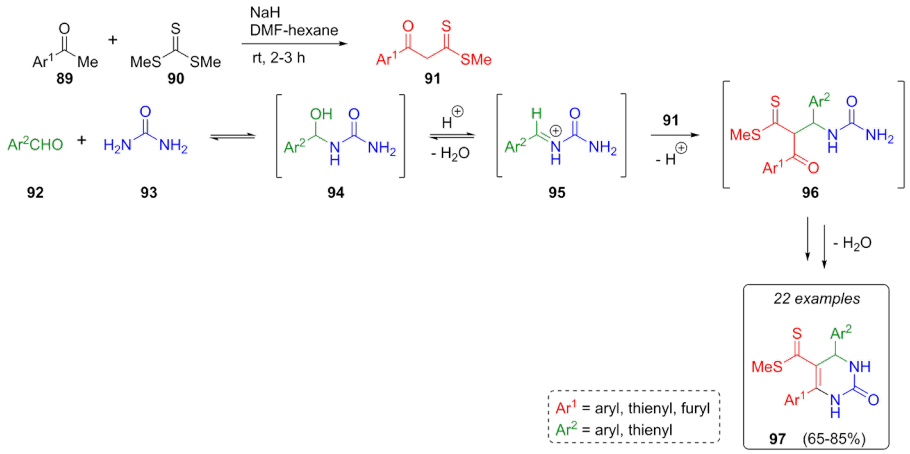
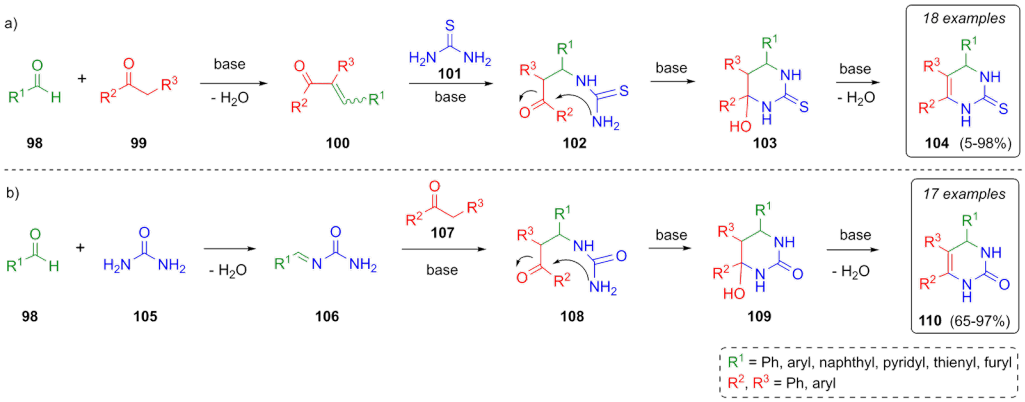
(Scheme 15). It has been used different electron-withdrawing and electron-releasing substituents. The authors mentioned that it was unable to know the role of thiourea in thiocoumarin-derivatives. However, it is worth noting the role of silica-sulfuric acid to promote the involved cyclizations in this methodology.



Scheme 15. Synthesis of dihydropyrimidinones.

In 2010, Ji *et al.* reported the synthesis of a series of novel dihydropyrimidinones through a Brønsted-base (*t*-BuOK)-catalyzed Biginelli-type reaction [28]. In the first pathway, aldehydes **98** were combined with ketones **99** to give the compounds **100** under basic conditions. Then, the addition of thiourea (**101**) achieved intermediates **102**, which after a ring closure afforded the compounds **103**. Finally, a dehydration step performed the thiones **104** (Scheme 16a). In the second pathway, a condensation of aldehydes **98** and urea (**101**) gave the compounds **106**. After the addition of ketones **107**, cyclization of compounds **108**, and dehydration of cyclic compounds **109**, dihydropyrimidin-2(1*H*)-ones **110** were obtained (Scheme 16b). After several optimizations, two series of compounds were prepared depending on the reagents used. In the same way, the mechanism may take two different pathways in function of the reagents used (Scheme 16 a) thiourea, or b) urea), where the important intermediates are furnished after corresponding condensations in each pathway. It is important to note that this was the first Biginelli reaction developed under basic conditions.



Scheme 16. Brønsted base-catalyzed synthesis of a) thiones, and b) 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-ones.

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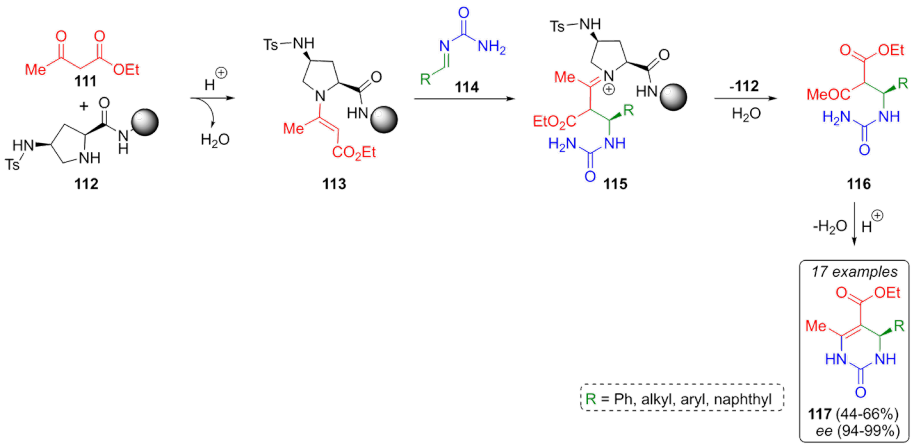
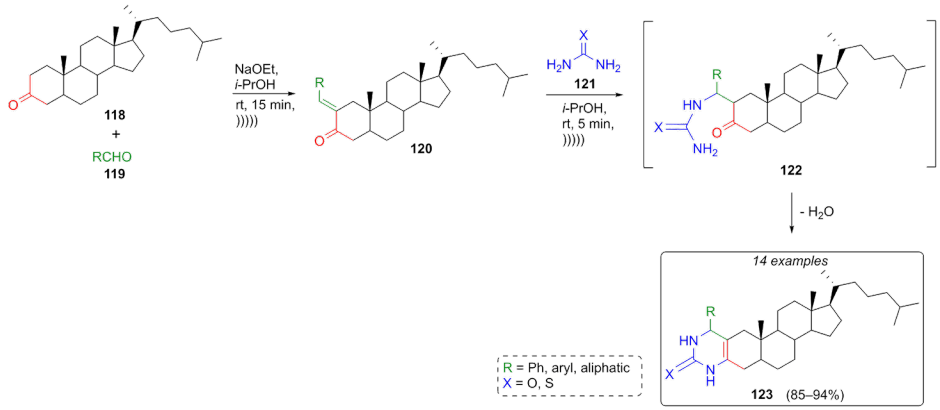
The search behind better organocatalysts with associated lower costs and toxicity, but even with enantioselective efficiency led to Moorthy and Saha developed a Biginelli reaction including mechanistic studies of sterically hindered organocatalysts (Scheme 17) [29]. After exhausting studies, it was found that catalyst **112** worked in high selectivity on Biginelli reaction from a series of electron-rich and electron-deficient aldehydes combined with ethyl acetoacetate (**111**) and urea to afford the products **117** in up to 66 % yields but in excellent enantiomeric excess (94-99 %). Mechanism pathway proposed involves condensation between catalyst **112** and dicarbonilic compound **111** to give the enamine **113**. Then, nucleophilic attack from enamine **113** to iminoamides **114** performed pyrrolidinium cations **115**. Finally, cyclization of precursors **116** achieved the products **117**. Despite the moderate yields, the enantioselectivity found was good because the catalyst used is bulky and contains a proton donor group, which favors the *re*-facing attack of complex **113** towards the iminoamide **114**.



Scheme 17. Organocatalytic Biginelli reaction.

Gogoi, Baruah *et al.* developed an ultrasound-assisted Biginelli-type reaction [30] to efficiently synthesize some new 3,4-dihydropyrimidin-2(1*H*)-ones and 3,4-dihydropyrimidine-2(1*H*)-thiones. In this one-pot reaction, steroidal ketone **118** was combined sequentially with aldehydes **119**, urea, or thiourea (**121**) using ultrasound conditions and sodium ethoxide as the base. Biginelli-species **123** were formed with excellent yields (85–94 %). It was proposed a plausible mechanism that proceeds through an aldol condensation between ketone **118** and aldehydes **119** to give the compounds **120**, which through a nucleophilic attack by urea or thiourea (**121**) gave intermediates **122**, which after releasing water furnished the steroids **123** (Scheme 18). It is well-known that ultrasound-assisted reactions have an important impact on green chemistry, giving added value to one-pot reactions. In the particular case of this work, ultrasound energy improved the yields probably due to mechanical stress in the process.



Scheme 18. Synthesis of fused-ring steroidal derivatives.

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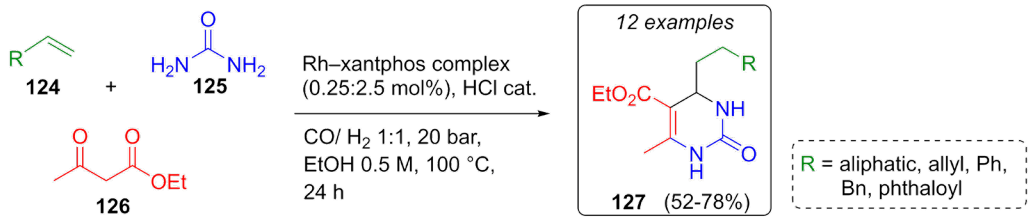
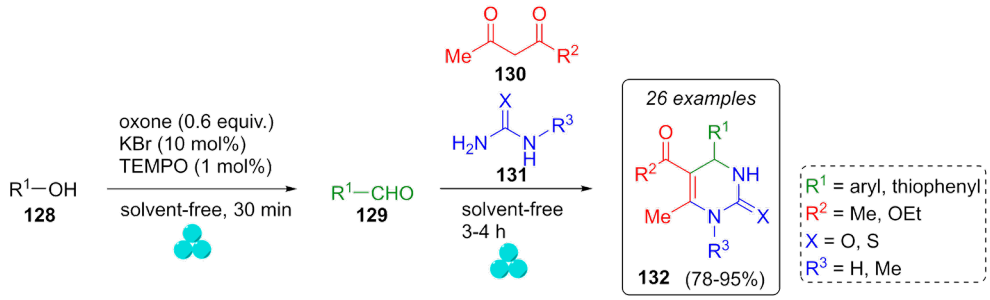
The synthesis of a dozen of new Biginelli compounds developed by Breit *et al.* involved the use of alkenes to generate aldehydes through a hydroformylation process catalyzed by a rhodium-xantphos complex [31]. After corresponding optimizations, alkenes **124** were combined with ethyl acetoacetate (**126**) and urea (**125**), HCl was added in catalytic amounts (Scheme 19). Functionalized dihydropyrimidones **127** were synthesized in moderate yields (52-78 %). Rh-xantphos catalyst usually used in hydroformylation reactions was employed here in a Biginelli reaction and by-products derived from carbonylation reaction were not observed, except when large chain alkenes **124** were used, resulting in low yields for the Biginelli products.



Scheme 19. Tandem hydroformylation–Biginelli reaction.

Another example of an eco-friendly methodology is the synthesis of Biginelli products under ball-milling assistance reported by Mal *et al.* in 2015 [32]. First, the aldehydes **129** were prepared through alcohols **128** oxidation under solvent-free conditions by ball-milling using a catalytic amount of oxone (peroxymonosulfate ion), KBr, and TEMPO [(2KHSO$_5$·KHSO$_4$·K$_2$SO$_4$)-2,2,6,6-tetramethylpiperidin-1-yl-oxy radical]. With aldehydes **129**, and reagents **130** and **131** in hands, Biginelli reaction proceeded also under solvent-free conditions and using a ball-milling device to give products **132** in moderate to good yields (78-95 %) (Scheme 20). Acid subproduct in the oxidation reaction served as the catalyst in Biginelli reaction. Notably, this method employed electron-withdrawing and electron-releasing aldehydes to afford new dihydropyrimidones in a one-pot process. Also, regioselectivity was directed by using *N*-methyl urea to obtain just a single regioisomer.



Scheme 20. Mechanochemistry-assisted synthesis of dihydropyrimidones.

Silvani *et al.* developed an organocatalytic asymmetric method for the construction of spiro-compounds *via* a Brønsted acid-catalyzed Biginelli-type reaction [33]. Thus, isatin derivatives **133** were combined in a one-pot process with *β*-ketoesters **134** and urea (**135**) using the chiral organocatalyst **136** to give the spiro(indoline-pyrimidine)-diones **137** in moderate to good yields (49-93%) with moderate ee values (50-80%) (Scheme 21). This report was the first one to describe an asymmetric Biginelli-type reaction from ketones under acid-organocatalytic conditions in which 3,3'-positions of the catalyst have a strong influence on the yields and ee. Best yields and enantioselectivity were observed for the *N*-methyl isatin derivative rather than others with substituents like benzyl.

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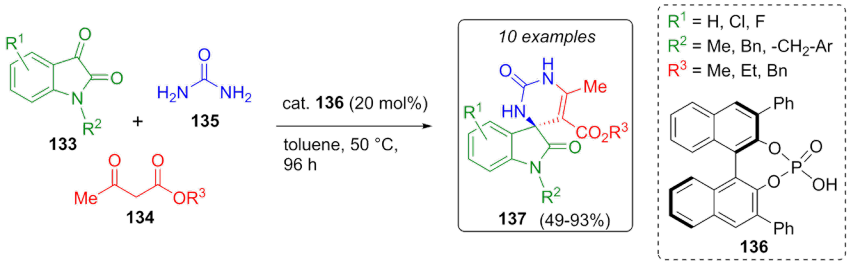
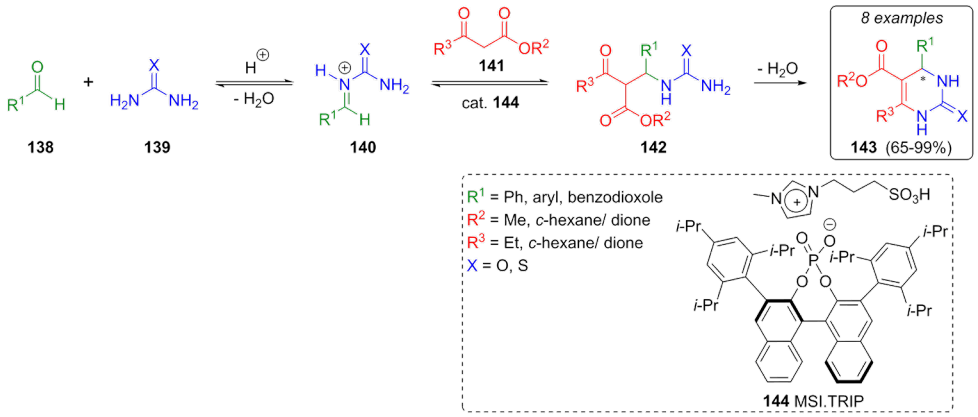


Scheme 21. Synthesis of spiro(indoline-pyrimidine)-diones *via* an organocatalytic asymmetric Biginelli reaction.

Amarante, Neto *et al.* developed a synthetic strategy where a chiral catalyst was used in a Biginelli reaction [34]. The catalyst **144** containing a chiral phosphoric acid moiety in ionic liquid media resulted in a creative method called Asymmetric Counteranion-Directed Catalysis (ACDC). Thus aldehydes **138** were combined with urea or thiourea (**139**) to give the intermediates **140**. Further addition of keto-esters **141** to compounds **140**, and dehydratation of precursors **142** gave good to excellent yields (65-99 %) and ee (37-99 %) of compounds **143**. It was proposed that Biginelli reaction followed the iminium pathway (Scheme 22). The catalyst **144** was recovered in 95 % amount and reused many times. This feature joined to solventless conditions results in another example of an environmentally friendly multicomponent reaction toward heterocyclic compounds.



Scheme 22. Asymmetric counteranion-directed catalysis for an enantioselective Biginelli reaction.

Yu, Ying *et al.* used a cyclic enol ether as the main reagent in a Biginelli reaction [35]. In this approach, it was necessary to optimize reaction conditions, being found as the best catalyst $PdCl_2$ and trifluoroacetic acid as solvent. Sequential combination of aldehydes **145** with alkynol **148** and urea or thiourea (**146**) afforded the spiro-compounds **155** in moderate to good yields (45-87 %). A plausible mechanism involves a catalytic cycle involving the use of palladium (Scheme 23). As the first step, vinyl palladium complex **149** was trapped by *N*-acyliminium intermediates **147** through an intermolecular addition furnishing intermediates **150**. Then, palladium catalyst promoted the formation of endocyclic enol ethers **151** *via* double bond isomerization. Enol ethers **151** perform a nucleophilic attack to aldehydes **145** to give the intermediates **152**. After intramolecular cyclization of complexes **153**, protonation, and dehydration of intermediates **154**, the catalytic cycle was completed regenerating the palladium complex **149**. Formation of spiro compounds was achieved in a combination of metal and Brønsted acid catalytic cycle in excellent enantioselectivity and with the best yields in a wide variety of electron-donating and withdrawing groups.

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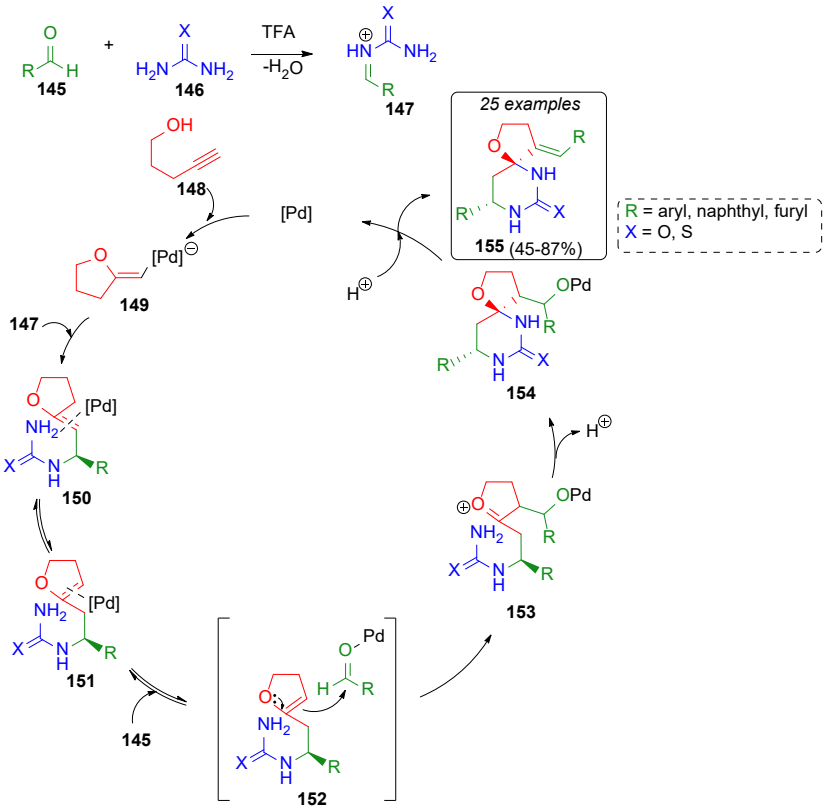
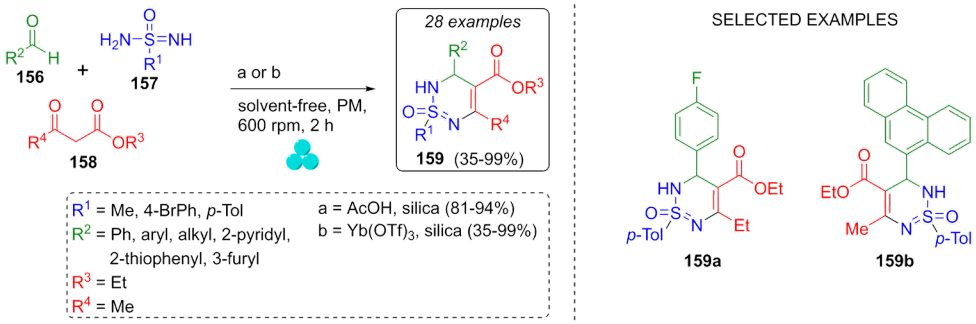


Scheme 23. Synthesis of spiro-furan pyrimidinones.

In 2021, Bolm *et al.* reported the synthesis of a series of dihydro-thiadiazine-oxides *via* a one-pot mechanochemical Biginelli-like process [36]. Optimal reaction conditions were found and were using acetic acid and silica gel as Brønsted and Lewis acids, respectively (Scheme 24). Thus, towards series *a*, aldehydes **156**, sulfonimidamides **157**, and ethyl acetoacetate (**158**) were placed in acetic acid/silica under mechanochemical conditions to afford products **159a** in good to excellent yields (81-94 %). Then, toward series *b*, same starting materials were combined but under mechanochemical and solventless conditions to synthesize products **159b** in moderate to excellent yields (35-99 %). Both series were obtained in a good diastereomeric ratio (up to 2:1). Aromatic and aliphatic aldehydes with releasing and withdrawing groups were used. Also, it is noteworthy the role of silica as a dehumidifier and partial-acidic agent at the grinding time.



Scheme 24. Biginelli-type mechanochemical approach.

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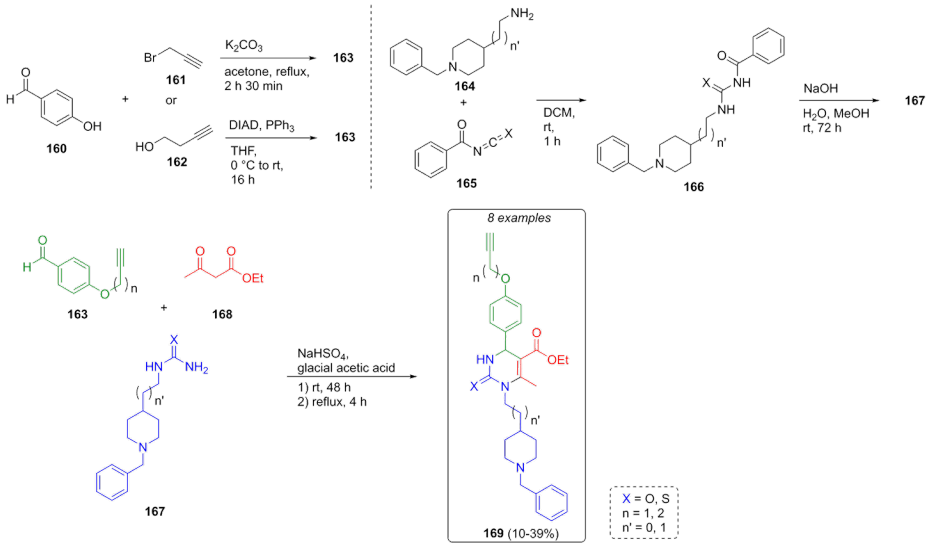
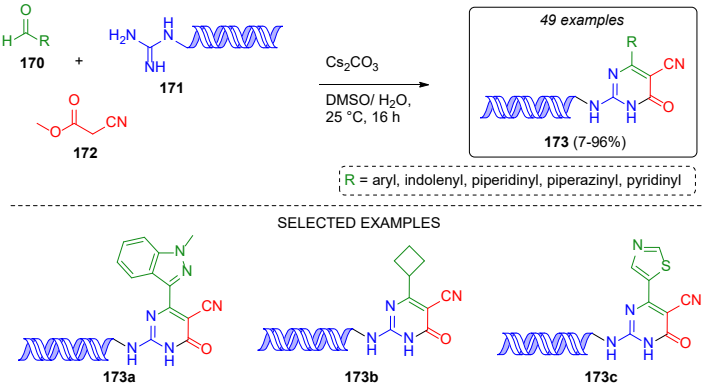
Ismaili *et al.* reported the synthesis of many new heterocyclic compounds *via* Biginelli reaction which were evaluated toward three different biological targets [37]. Thus, the key substrates were the alkynyl-aldehydes **163**, which were synthesized previously through two routes: a) Williamson reaction between 4-hydroxybenzaldehyde (**160**) and propargyl bromide (**161**), and b) 4-hydroxybenzaldehyde (**160**) and alcohol **162** *via* a Mitsunobu reaction (Scheme 25). On the other hand, ureas **167** were prepared from benzylpiperidines **164** and benzoyl isocyanate or benzoylthioisocyante (**165**). Thus, aldehydes **163**, ureas **167** and ethyl acetoacetate (**168**) furnished the compounds **169** in moderate yields (10-39 %) making use of sodium bisulfate as catalyst. These kinds of compounds have potential activity as Ca^{2+} channel blockers, cholinesterase inhibitors, and activators of nuclear erythroid 2-related factor 2.



Scheme 25. Multitarget-directed ligands.

Qi, Peng *et al.* developed a innovative strategy in which DNA-derivatives were obtained [38]. After optimization of reaction conditions, aromatic and heterocyclic aldehydes **170**, DNA-conjugated guanidine **171**, and methyl cyanoacetate (**172**) were sequentially combined using cesium carbonate as the base to achieve DNA-dihydropyrimidinones **173** in low to good yields (7-96 %) (Scheme 26). Thus, isocytosine scaffolds were developed taking advantage of DNA-conjugated guanidine fragment. A variety of electron-donating and releasing groups were tolerated in such reactions even 5-membered heteroaromatic compounds participated therein. It is important to highlight that this is the first report in which a DNA-amine fragment was used in an organic reaction.



Scheme 26. DNA-compatible Biginelli-type reaction.

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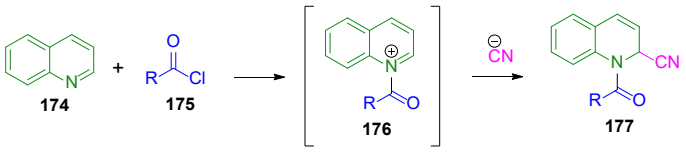
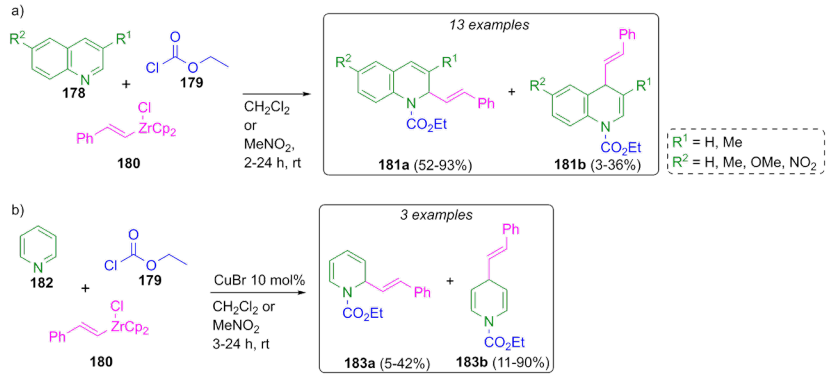
Reissert-type 3CRs

Cooney's manuscript from 1982 described that Arnold Reissert reported in 1905 a multicomponent reaction involving combinations of quinoline with acyl chlorides, and potassium cyanide in aqueous media (Scheme 27) [39]. Thus, the formation of *N*-acyl quinoliniums **176** by the reaction of quinoline (**174**) and acyl chlorides **175** is followed by cyanide anion addition to promote the formation of the Reissert products **177**. The preparation of such compounds in aqueous media has some common complications. For instance, the low solubility of the reagents because of their different polarity that may be solved by using mixtures of solvents. Reissert reaction works well on a wide range of pyridine-containing reagents, acyl chloride-derivatives, and different kind of nucleophiles [40].



Scheme 27. Reissert reaction.

Reissert-type reactions have been developed using a variety of nucleophiles instead of cyanide anions. Thus, Saito, Hanzawa *et al.* reported a methodology where alkenylzirconocene chloride was used as a nucleophile in a Reissert-type 3CR (Scheme 28**(a)**) [41]. This synthetic methodology consisted of a sequential combination of quinoline derivatives **178** or pyridine (**182**), styrylzirconocene **180** and ethyl chloroformate (**179**) in dichloromethane or nitromethane to give quinoline- or pyridine-containing products **181** or **183**, respectively, in moderate to good yields (up to 93 %). The use of nitromethane instead of dichloromethane as the solvent improved the 1,2-additions on the quinoline derivatives. However, the use of nitromethane in the reaction of pyridine afforded a mixture of regioisomers with a poor 1,2-addition selectivity (Scheme 28**(b)**). On the contrary, the 1,4-addition was improved by employing a catalytic amount of CuBr (10 mol%) at -78 °C to the pyridine, whilst using quinoline derivatives irrelevant selectivity was found (Scheme 28).



Scheme 28. Alkenylzirconocene-based Reissert-type alkenylation.

Later in 2013, Saito *et al.* continued developing a similar strategy, finding that the orientation of the reaction can be controlled by the addition of copper or rhodium catalysts (Scheme 29) [42]. Thus, a sequential combination of polysubstituted quinolines **184**, acylzirconocene chloride (**186**), and ethyl chloroformate (**185**) under copper iodide (I) or rhodium/silver catalysts afforded a mixture of regioisomeric products **187** in moderate to good yields (up to 71 %). A mechanism pathway was proposed where chloride **186** was coordinated with

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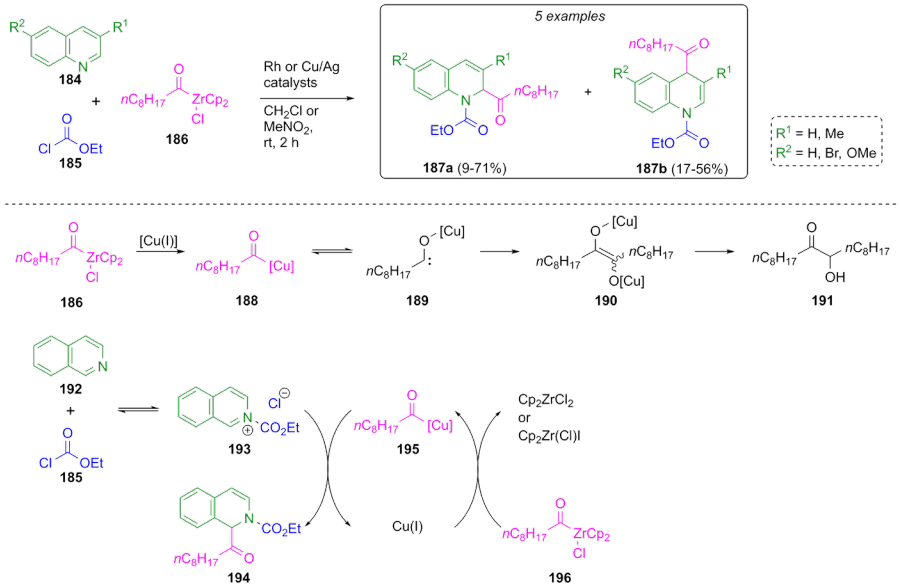
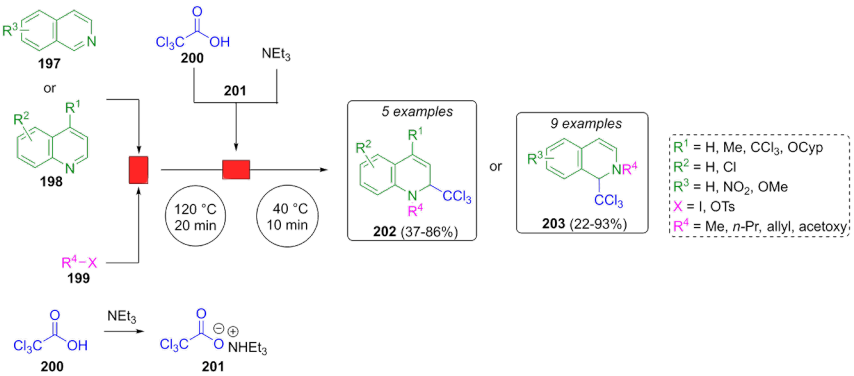
Cu(I) to give the complex **188** which performed compound **191** after the formation of carbene **189** and its precursor **190**. Thus, there is an equilibrium between the addition of isoquinoline (**192**) and chloride **185** with *N*-acylisoquinolinium **193** and acylated product **194**. Acyl cooper product **195** was carried out through acyl transfers from the chloride **196** to Cu(I). In the case of the combination of rhodium (2.5 mol%) and silver (5 mol %) catalysts, it was promoted 1,2-addition in nitromethane as solvent. Instead that, under copper catalyst (10 mol %), 1,4-addition is promoted in dichloromethane. Then, *N*-acylation of isoquinoline occurred at the 2-position through an addition of the corresponding nucleophile.



Scheme 29. Acylzirconocene-based Reissert-type acylation.

Lindhardt *et al.* developed a methodology to obtain isoquinolines and quinolines *via* a decarboxylative Reissert-type reaction through a continuous flow [43]. Isoquinolines **197** or quinolines **198**, triethylammonium trichloroacetate (**201**), and electrophilic iodides or tosylates **199** were combined in neat DMF or a mixture of DMF/ MeCN under continuous flow afforded dihydroquinolines **202** or dihydroisoquinolines **203** in moderate to good yields (up to 93 %) (Scheme 30). *N*-alkylations were carried out with different types of alkylic chains. 4-Addition was promoted by trichloromethyl anion to afford the products **202**. On the other hand, alkyl iodides or allyl tosylates promote the corresponding alkylations to give the products **203**.



Scheme 30. Continuous flow-Reissert approach.

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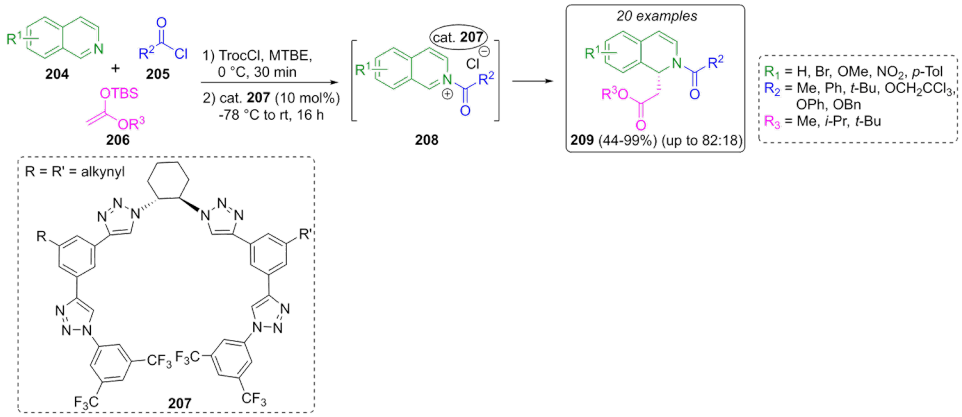
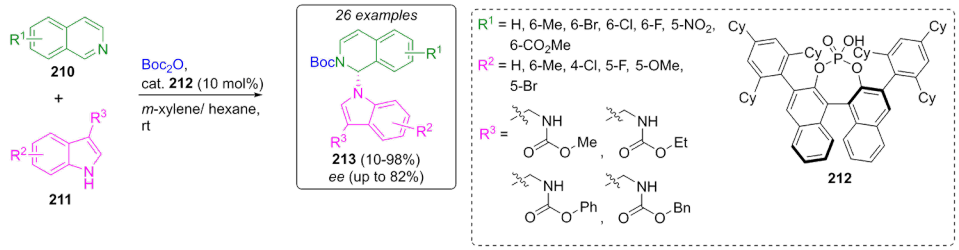
García-Mancheño *et al.* used a chiral triazole-based organocatalyst to synthesize some new Reissert-type dihydroisoquinolines (Scheme 31) [44]. After optimizing reaction parameters, a sequential combination of isoquinolines**204**, acid chlorides **205**, and silyl ketene acetals **206** in methyl *tert*-butyl ether (MTBE), catalyzed by the triazole-containing organocatalysts **207** resulted in the synthesis of isoquinolines **209** in moderate to good yields (up to 99 %) and good enantioselectivity (up to 82:12 (*R*/*S*). The use of chiral-triazole through anion-binding activation and MTBE as solvent had a strong influence on the enantioselectivity. 1*H*-1,2,3-triazoles are excellent H-bond donors due to the high polarizability of their C-H bond and the acidity at the C-5 position. In addition, triazole catalysts exhibit chloride counterion binding, which results in chirality transfer. This type of catalysis is most efficient in the case of counterion catalysts with halogen-halogen interactions [45].



Scheme 31. Chiral-triazoles in enantioselective Reissert-type reactions.

You *et al.* developed an asymmetric *N*-alkylation of indoles *via* a Reissert reaction (Scheme 32) [46]. Thus, once the optimal reaction conditions were identified, a sequential combination of isoquinolines **210**, indoles **211,** and protective group reagent Boc_2O catalyzed by the chiral phosphonic acid **212** in the solvent mixture (*m*-xylene/hexane) at room temperature allowed the synthesis of compounds **213** in good to excellent yields (up to 98 %) and with moderate to good enantioselectivities (up to 82 %) as (*R*) absolute configuration. Indole alkylation occurred in the *N*-1 position assisted by the catalyst. The best yields and enantioselectivities were obtained when the reaction occurred at position 2 of the isoquinoline ring, which is due to steric hindrance at the other reactive positions.



Scheme 32. Chemoselective N-H functionalization of indoles *via* a Reissert-type 3CR.

Kang *et al.* reported the synthesis of a series of new quinolinyl phosphonamides *via* a Reissert-type reaction (Scheme 33) [47]. A plausible mechanism involves the formation of quinolinium salts **216** through a mixture of quinolines **214** and chloroformates **215**. Thus, thiourea **217** reacts with quinolinium salts **216** to give the salt-complexes intermediates **218**. Finally, an intramolecular nucleophilic attack on intermediates **219** occurs

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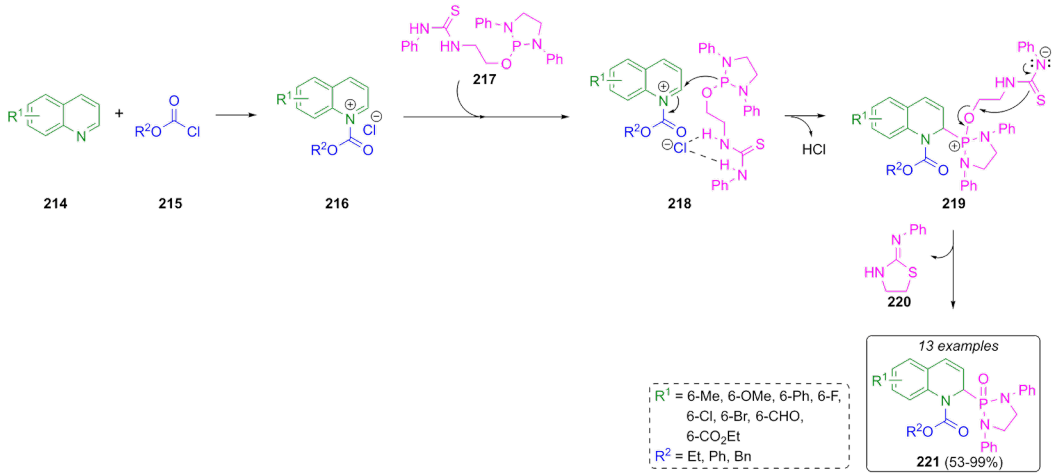
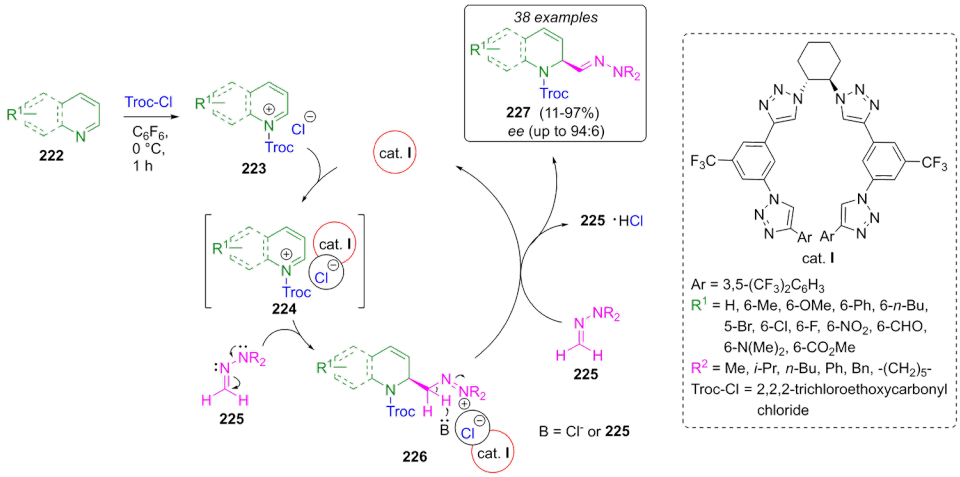
to release cyclic compound **220**, achieving the products **221** in moderate to good yields (53-99 %). The salt-complexed thioureas **218** as Brønsted acids promote 1,2-regioselective additions of the phosphine moiety through a ion paring process between chloride and thiourea fragments.



Scheme 33. Synthesis of α-amino quinolinyl phosphonamides from *N*-heterocyclic phosphines.

In 2021, García-Mancheño *et al.* developed a robust strategy to synthesize 2-hydrazone-1,2-dihydroquinolines **227** *via* a Reissert-type reaction using a triazole-containing organocatalyst and dimethylhydrazone as the nucleophile with reversed-polarity [48]. The best reaction conditions were employing CF_3-tetrakistriazole as the catalyst and hexafluorobenzene as the solvent at low temperatures. Thus, quinolines **222**, trichloroethoxycarbonyl chloride (Troc-Cl), and formaldehyde dimethylhydrazones **225** were reacted together to give the products **227** in moderate to good yields (11-97 %) and enantiomeric ratio (er) up to 94:6 (Scheme 34). It was proposed a plausible mechanism in which quinolinium salts **224** and **226** were formed after a chloride activation with Troc-Cl to give intermediates **223**. Then, the later were activated through an anion-binding catalysis. Finally, a nucleophilic attack of the hydrazones followed by deprotonation afforded products **227**. It is to highlight that the use of hexafluorobenzene as the solvent and tetrakestriazole as the organocatalyst promoted a high regio- and chemoselectivity through anion-binding strategy; which is probably due to the presence of triazoles-CF_3 moieties as a key fragment in the organocatalyst, as discussed above.



Scheme 34. Synthesis of hydrazones *via* organocatalytic under reversed-polarity approach.

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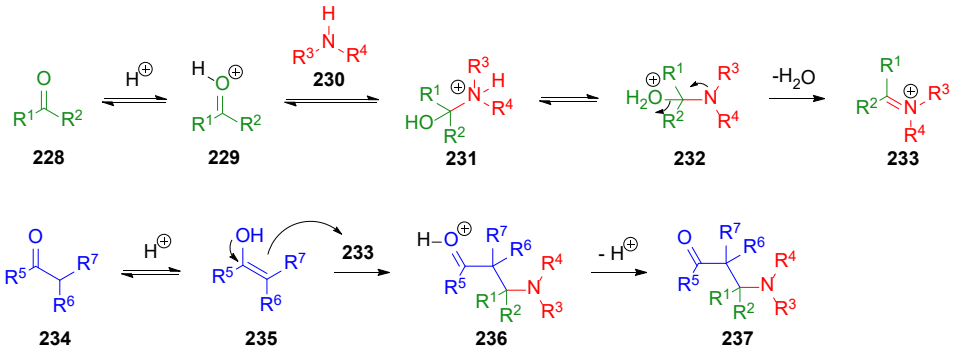
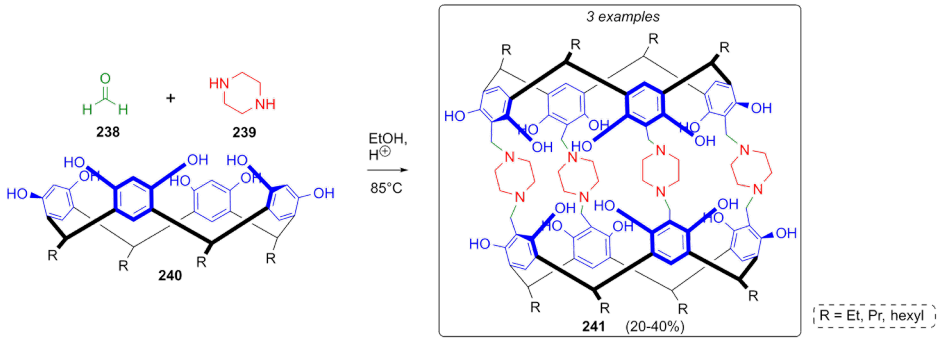
Mannich-type 3CRs

Around 1917, Carl Mannich reported a 3CR that consists of the combination of a non-enolizable carbonyl compound (usually aldehyde or ketone), a primary or secondary amine (even ammonia), and an enolizable aldehyde or ketone to access β-amino carbonyl compounds. A mechanism accepted begins with the formation of oxoniums **229** through protonation of carbonyl compounds **228**. Then, addition of amines **230** to give species **231** which after prototropic exchange achieve intermediates **232**, and the formation of iminium ions **233** through water release. Besides, carbonyl compounds **234** perform corresponding enols **235**. Then, a nucleophilic attack from enols **235** to iminium ions **233** achieved oxonium salts **236**. Finally, a proton releases complete formation of alkaloid-type compounds **237**(Scheme 35) [49]. This procedure can also be carried out as intramolecular manner [50]. The asymmetric version of this process could be catalyzed by organic and inorganic complexes. This reaction has been applied successfully for the synthesis of several natural products, even some alkaloids [51].



Scheme 35. Mannich reaction.

Rissanen *et al.* developed a one-pot synthetic approach based on the Mannich reaction to synthesize three complex macrocycles **241** [52]. Formaldehyde (**238**) in solution of ethanol was combined with piperazine (**239**) and cyclic tetrabenzoxazines **240** to assemble the macrocyclic dimers **241** in modest yields (20-40 %) (Scheme 36). Piperazine links both moieties through covalent bonds giving rigidity to these supramolecules. Despite the size of the compounds, the yields were moderate highlighting that the one-pot process was favored by the solvent being encapsulated on cage structures.



Scheme 36. Synthesis of piperazine-bridged resorcinarene cages *via* a Mannich-type reaction.

Aza crown-ether-derivatives have been utilized as fluorescent sensors in different biological targets. Lombardo, Trombini *et al.* synthesized eleven new diaza crown-ethers *via* a Mannich one-pot process using microwave radiation as a heat source [53]. Paraformaldehyde **242**, and the crown-ether **243** were combined

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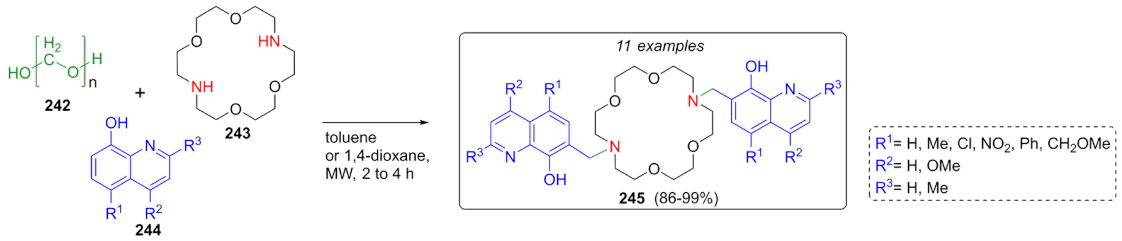
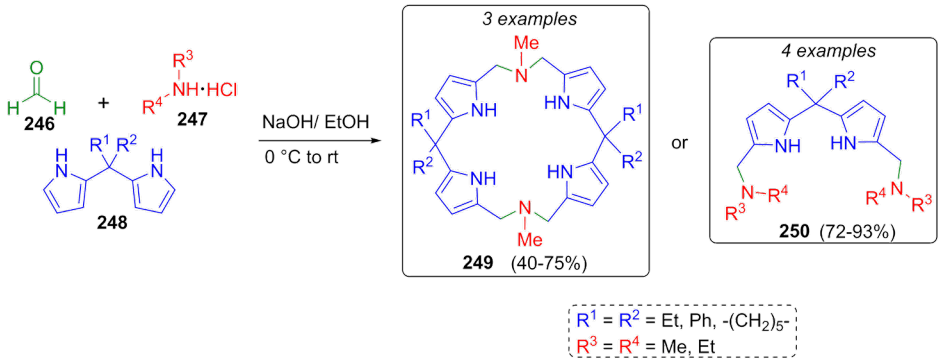
sequentially with 8-hydroxyquinolines **244** reaching ligands **245** in good yields (86-99%) *via* a microwave-assisted Mannich-type 3CR (Scheme 37). It is important to highlight the high atom economy of this innovative experimental protocol. Also, microwave-assisted catalyst-free conditions decreases the formation of by-products. Strategic substituents at positions 2, 4 and 5 in isoquinoline moiety contributed to higher yields due to a high activation on such ring.



Scheme 37. Synthesis of diaza crown-ethers substituted symmetrically with quinoline moieties.

Mani *et al.* reported the synthesis of a series of diazacalix[2]dipyrrolylmethanes (macrocyclic **249** and acyclic **250**) *via* a Mannich 3CR from formaldehyde (**246**), amine hydrochlorides **247**, in the presence of dipyrrolylmethane-derivatives **248** in moderate to good yields (40-93%) (Scheme 38) [54]. It is exemplified by another three-component approach where flexible anion-receptor supramolecules were assembled. Also, these reactions were carried out under catalyst-free conditions. These kinds of compounds by containing both hydrogen donors and acceptors can act as ion-pair receptors or anion receptors, which is important mainly in medicinal chemistry.



Scheme 38. Synthesis of azacalixarenes.

Coined for the first time by C.-J. Li, the A^3 coupling is a 3CR of amines, aldehydes, and alkynes to synthesize propargyl amines. [55]. This coupling, which is characterized by its high atom economy and ecofriendly conditions, is commonly applied for the formation of several kind of N, O, and S-heterocycles [56]. In 2011, Wu *et al.* reported an interesting methodology to generate macrocycles *via* a Mannich reaction based on an early A^3 coupling [57]. Thus, a copper(I)-catalyzed sequential combination of formaldehyde (**251**), polysubstituted piperazines **252**, and dialkynes **253** gave the macrocycles **254** and **255** in moderate yields (29-31 %) (Scheme 39**(a)**). In addition, another Mannich-type 3CR coupled to an Eglinton–Glaser dimerization was performed (Scheme 39**(b)**) by using formaldehyde (**251**), 1,4-diazepane (**256**), and aryl-dialkynes **257** to give the macrocycles **258** and **259**. Both terminal dialkynes **253** or **257** fulfilled the double function in the Mannich reaction and dimerization process. Also, these kind of reactions proceed correctly using secondary amines, which is not common.

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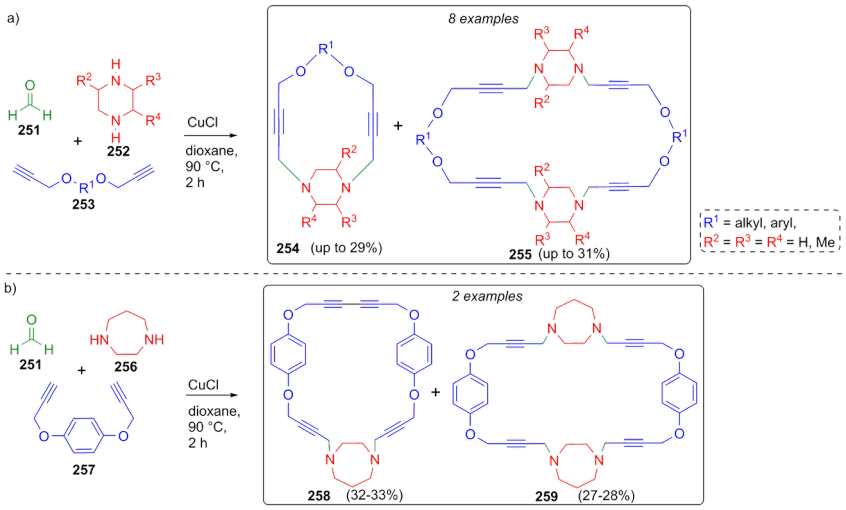
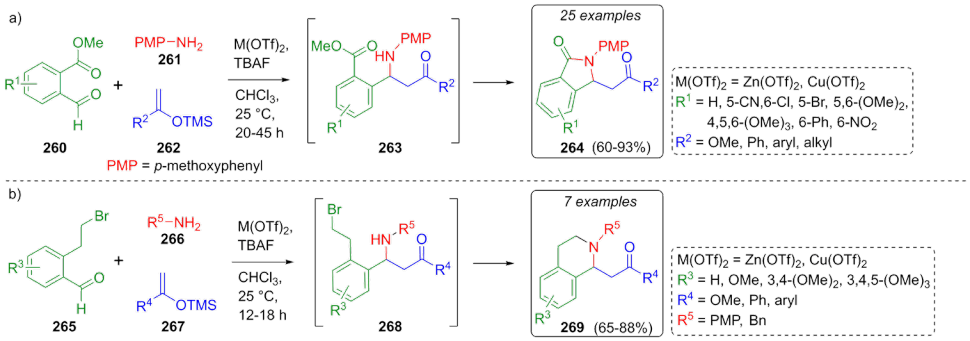


Scheme 39. Synthesis of macrocycles.

In 2015, Singh *et al.* reported an interesting procedure to synthesize a new series of isoindolinones and tetrahydroisoquinolines *via* a domino Mukaiyama−Mannich lactamization/alkylation process [58]. Thus, to synthesize the isoindolinones **264**, the methodology was optimized using metal triflates as catalysts and electron-donor-acceptor substituted benzaldehydes **260** and amine **261**, finding that electron-withdrawing amines do not promote such reaction. In the same way, *o*-anilines do not allow the corresponding isoquinoline formation due to steric hindrance (Scheme 40**(a)**). Thus, the same strategy was improved to assemble the corresponding tetrahydroisoquinolines **269**. Thus, the combination of aldehydes **265**, amines **266**, and silyl enol ether- derivatives **267** catalyzed by Lewis acids achieved the products **269** in moderate to good yields (65-88 %) (Scheme 40**(b)**). To note, a decrease in reaction time was found for the synthesis of tetrahydroisoquinolines **269** probably due to a higher reactivity of intermediates **268** in comparison to intermediates **263**.



Scheme 40. Synthesis of isoindolinones and tetrahydroisoquinolines *via* metal-catalyzed Mannich-type 3CR.

Gu *et al.* reported a procedure to synthesize the quinoline-fused 1-benzazepines **277** *via* an intramolecular Mannich 3CR [59]. Thus, *o*-aminobenzaldehydes **270**, indoles **271** as the nucleophile/amine-containing components, and ketones **275** were sequentially combined using a Lewis acid catalyst to give the benzo-annulated species **277** in moderate to good yields (20-90 %) (Scheme 41). The most plausible reaction mechanism involves the formation of intermediates **272** followed by nucleophilic attack at C2 position on the indole ring to give cyclized intermediates **273**. Then, a ring-opening achieved compounds **274**. Finally,

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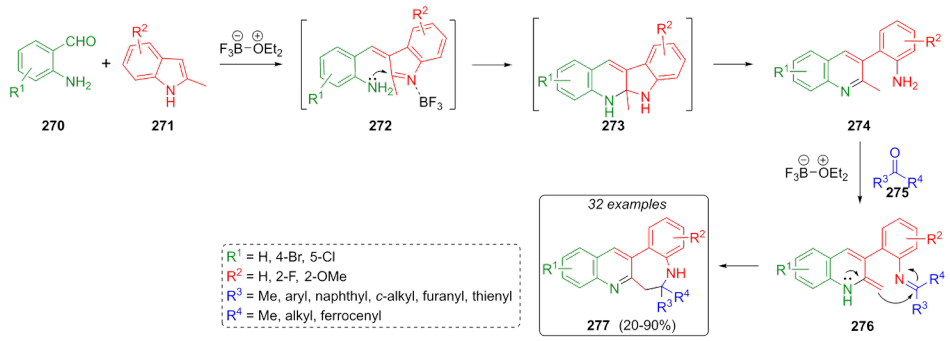
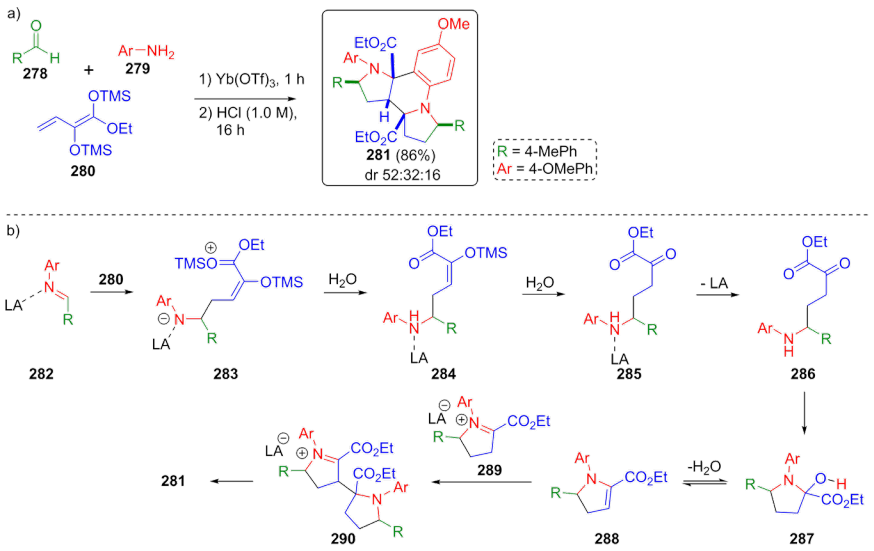
compounds **277** were achieved through intramolecular cyclizations of activated enamines **276**. A wide range of electron-donating and electron-deficient groups was included in the substrate scope. Even bulky groups such as ferrocene and cyclooctanone gave moderate yields. Formation of C, *N*-bis nucleophile intermediates **274** through a combination of aldehydes **270** and indoles **271** was the key step in this strategy.



Scheme 41. Synthesis of quinoline-fused 1-benzazepines *via* Mannich reaction.

In 2018, Schneider *et al.* developed a synthetic procedure to obtain dipyrroloquinolines *via* a Mukaiyama−Mannich reaction [60]. The strategy involved a key mixture between the Lewis-acid activated imines **282** and a bis(silyl) dienediolate **280**, which after a few steps gave the products **281** (Scheme 42). To carry out this synthesis, it was achieved a three-component reaction through sequential combination of aldehydes **278**, amines **279,** and TMS-dienediolate **280** under catalysis with Ytterbium (III) in acid medium to give a diastereomeric mixture (52:32:16) of products **281** in good chemical yield (86 %). The Lewis-acid catalyzed imines **282** and dienediolate **280** furnished desilylated enol ethers **283**which after the addition of water performed compounds **284** and **285** and release of Lewis acidafforded the keto esters **286**. Then, it was promoted an intramolecular cyclization to furnish compounds **287** in equilibria with compounds **288**. Finally, it was carried out the Mannich reaction followed by Pictet-Spengler cyclization. In this strategy, several C-C and C-N bonds were formed with excellent stereoselectivity using both Brønsted and Lewis acids, where Brønsted acids enhanced better the stereoselectivity. DFT-based calculations by using the functional M06-D3 at LACVP**/PBF level of theory support the proposed mechanism.



Scheme 42. Modular synthesis of dipyrroloquinolines.

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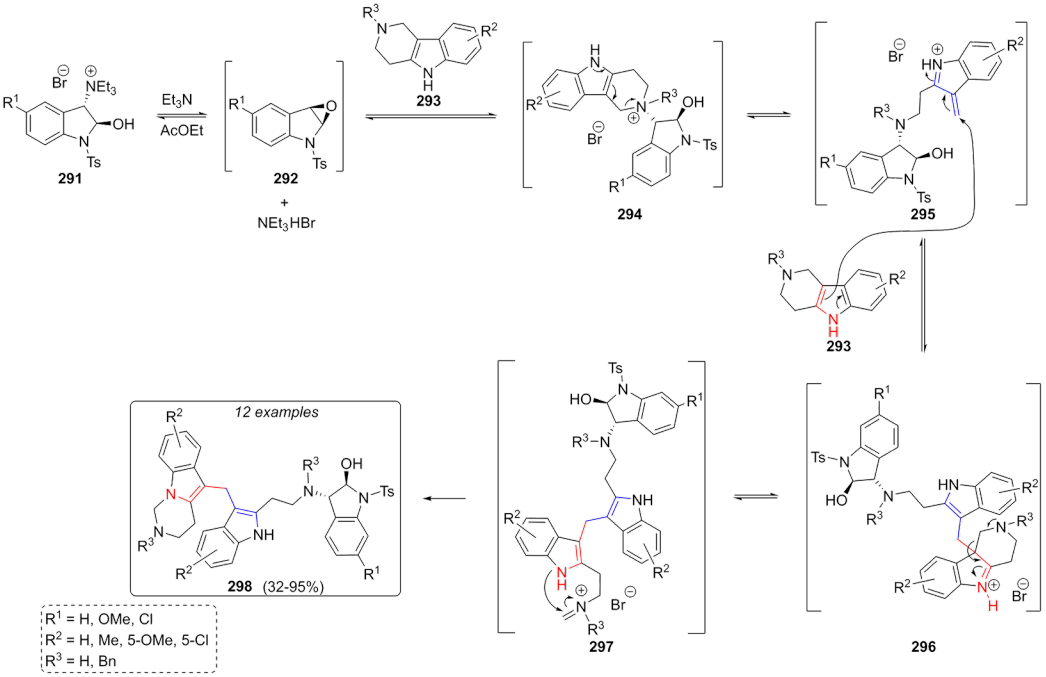
Abe, Yamada *et al.* developed a robust methodology to synthetize polyheterocycles *via* a ring-opening/vinyl closure cascade strategy [61], involving a key vinylogous Mannich/retro Mannich process (Scheme 43). Thus, indoline-salts **291**, carbolines **293**, and triethylamine reacted together in a one-pot fashion to assemble the polyheterocycles **298** in moderate to excellent yields (32-95 %). A plausible mechanism was proposed where epoxides **292** were achieved from salts **291** and triethylamine, followed by the formation of ammonium salts **294** through addition of indols **293** to epoxides **292**. Then, an ammonium exchange promotes a Hoffman elimination to give intermediates **295**, followed by a vinylogous Mannich reaction between carbolines **293** and intermediates **295** to afford alkylated intermediates **296**. A retro-Mannich process achieved intermediates **297**. Finally, aintramolecular cyclization on the intermediates **297** complete the synthesis of compounds **298**. It is worth mentioning the absence of catalysts in all cascade processes, and the high atom economy obtained. Electron-donating and electron-deficient groups had a strong influence on the yields, especially substituents at the C-5 position of the indole and piperidine rings. On the other way, electron-withdrawing groups placed at the C-6 on the carbolines caused the lowest yields.



Scheme 43. Synthesis of polyheterocycles *via* a double 'open and shut' vinylogous Mannich/retro Mannich process.

Yan *et al.* reported an interesting method involving a waste and reuse-based tandem Mannich reaction (Scheme 44) [62]. Amido sulfones **300**, activated-methylene compound **299**, and alkynes **301** reacted together under organocatalytic and mild basic conditions affording both chiral products, the b-amino acid-derivatives **303** (asymmetric compounds) and naphthyl-styrenes **304** (rotation-restricted naphthalene-type enantiomers) in moderate to excellent yields (31-96 % and 65-91 %, respectively). Thus, good enantioselectivity for each asymmetric product was found. Besides, a wide variety of electron-withdrawing and electron-releasing groups were efficiently employed in Mannich 3CR through a waste-reuse process to afford at the same time sulfone-containing naphthyl-styrenes and amino acid derivatives.

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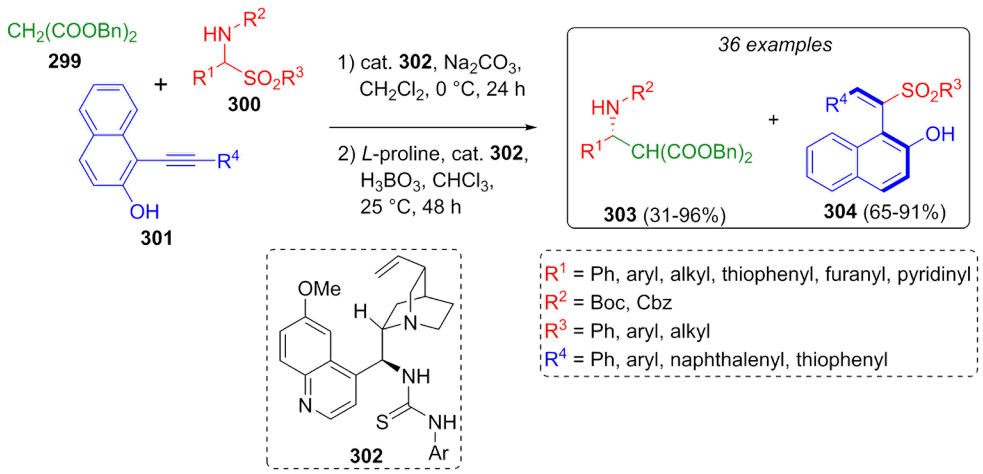
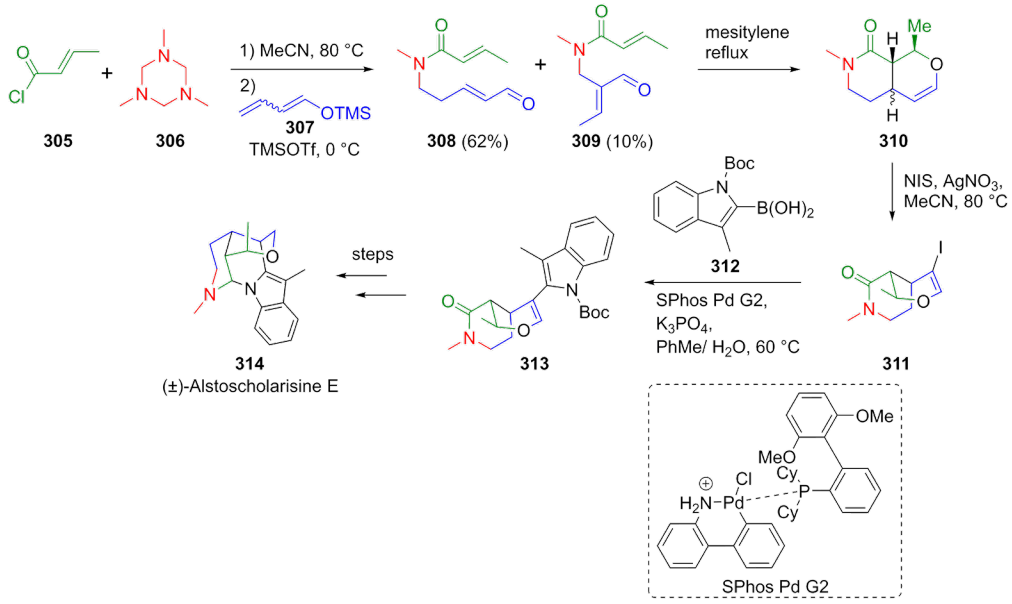


Scheme 44. Organocatalyzed Mannich-type reaction.

Martin *et al.* achieved the total synthesis of (±)-Alstoscholarisine-E (**314**) in seven steps with high stereoselectivity employing a vinylogous Mannich-type reaction as the initial key process [63]. Thus, acid chloride **305** and triazine **306** were combined in a solution of acetonitrile at 80 °C affording the *in situ* formed *N*-acyliminium ion, to which protected diene **307** was added to provide regioisomeric amides **308** and **309** in 62 % and 10 % yield, respectively (Scheme 45). Subsequent transformation of such compounds included a hetero-Diels-Alder cycloaddition, stereoselective enol ether reduction, a Suzuki-coupling, and a Lewis acid-catalyzed reduction. The three-component vinylogous Mannich reaction had a key role in this creative and short total synthesis of the natural product **314**.



Scheme 45. Synthesis of (±)-Alstoscholarisine E.

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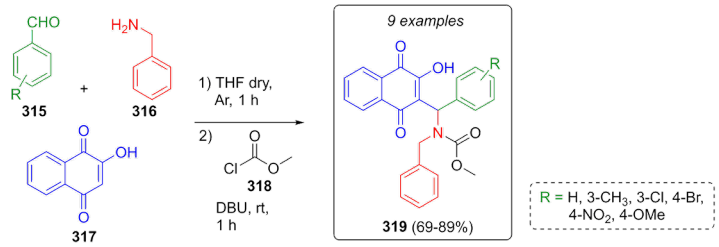
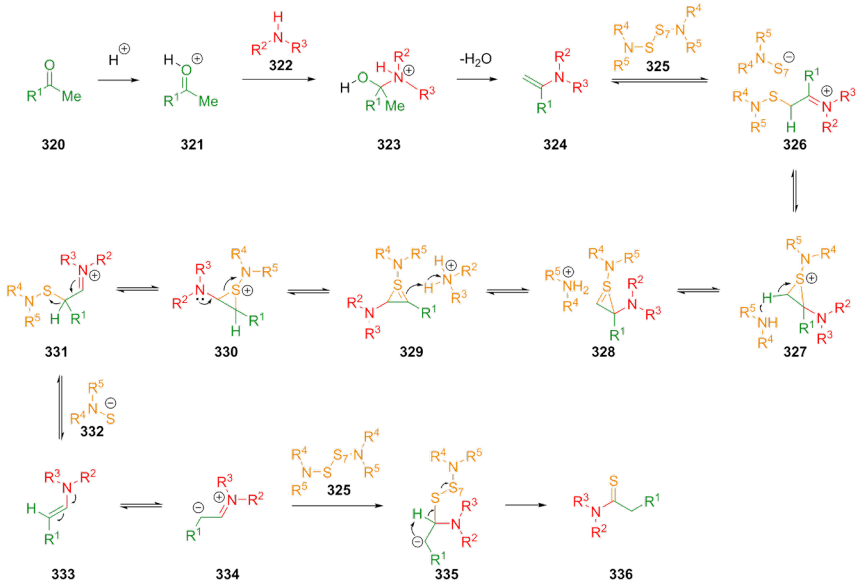
Forezi, Robbs *et al.* reported the synthesis of nine new naphthoquinones *via* a Mannich one-pot reaction, and their evaluation against oral squamous cell carcinoma was conducted [64]. Aromatic aldehydes **315**, benzylamine (**316**), and hennotannic acid (**317)** also known as lawsone were combined sequentially at room temperature (Scheme 46). Then, DBU and methyl chloroformate (**318**) were added to obtain the naphthoquinone derivatives **319** in moderate to good yields (69-89 %). Also, dialkylated products were also obtained but changing the base by K_2CO_3. Naphthoquinones reported exhibited potential activity for preclinical trials against oral squamous cell carcinoma.



Scheme 46. Synthesis of 1,4-naphthoquinones with potential anticancer activity *via* a chemoselective Mannich reaction.

Willgerodt-Kindler-type 3CRs

In 1887 (C. Willgerodt) and in 1923 (K. Kindler) the reaction between carbonylic compounds, disulfide compounds (or elemental sulfur), and secondary amines was developed, and later named asWillgerodt-Kindler reaction. In its classical version, this kind of one-pot process involves combinations of a carbonylic compound (aldehydes or ketones), elemental sulfur, and amines. Other non-carbonylic (or unsaturated) reactants such as imines, amines, alkenes, alkynes, or acetals may be used in these kinds of reactions [65]. In 1989, M. Carmack reported the mechanism in which the main steps consisted in the formation of enamines **324** between ketones **320** and amines **322** in acid media. Then formation of iminium ions **326** through reaction of enamines **324** and amino-sulfur compounds **325**. Thus, it were performed annulated intermediates through a set of thiirene-type rearrangements **327** to **330** to achieve enamines **331**.Finally, an oxidation on compound **333** in equilibria with **334** promoted by sulfur-containing reagents **325** afforded the products **336** (Scheme 47) [66].



Scheme 47. Willgerodt-Kindler reaction.

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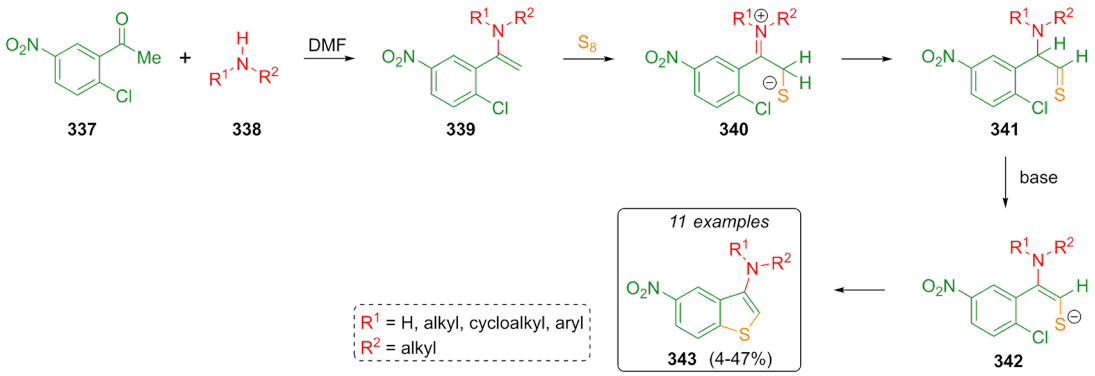
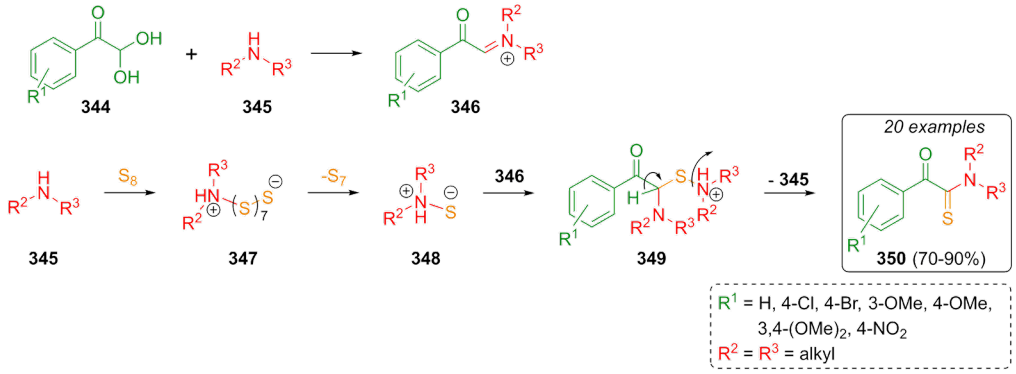
Androsov *et al.* reported a strategy based on the Willgerodt-Kindler reaction to synthesize 3-amino benzo[*b*]thiophenes. Thus, acetophenone **337**, amines **338**, and elemental sulfur were mixed obtaining the products **343** in modest to good yields (4-47 %) [67]. A plausible mechanism of reaction was proposed (Scheme 48). Enamines **339** were formed by condensation of ketone **337** and amines **338**, and the sulfur-was added to give the intermediates **341**. Finally, the ring closure step took place by a nucleophilic substitution on intermediates **342** assisted by the nitro group, which activates its para-position substituted by the chlorine atom. Yields may be affected by the steric hindrance of the secondary bulky amines and low temperatures.



Scheme 48. Synthesis of 3-aminobenzo[*b*]thiophenes.

In 2013, Eftekhari-Sis, Büyükgüngör *et al.* reported the first Willgerodt–Kindler reaction using arylglyoxals as carbonylic reagents. Thus, phenylglyoxals **344**, amines **345**, and elemental sulfur were combined to achieve products **350** in good to excellent yields (70-90 %). It was proposed a plausible reaction mechanism where a pathway involving an iminium ion was followed instead of one involving formation of enamines. Thus, it was proposed the classical mechanism. Iminium ions **346** were formed from glyoxals **344** and amines **345**. Zwitterions **348** were performed through intermediates **347**. Then, the addition to iminium ions **346** to iminium ions **348** furnished the intermediates **349**, which after a release of protonated amine performed the products **350** (Scheme 49) [68]. It is important to underline the high efficiency obtained under solventless conditions. Also, the reaction worked well using aryl-glyoxals with electron donator and deficient groups, as well as using secondary cyclic amines. On the other hand, the reaction did not proceed with primary amines or nitro-containing glyoxals.



Scheme 49. Synthesis of α-ketothioamides from aryl glyoxals.

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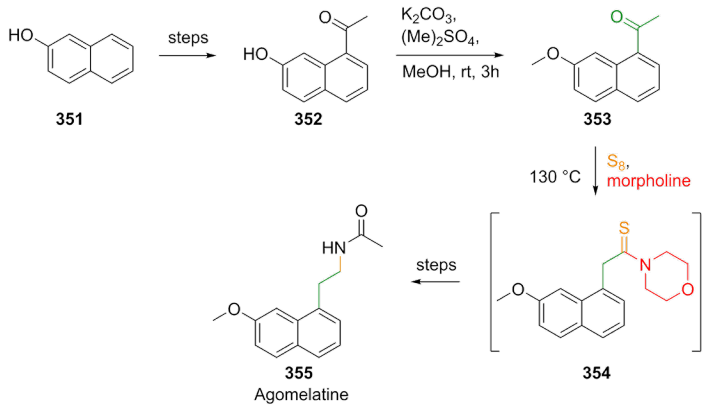
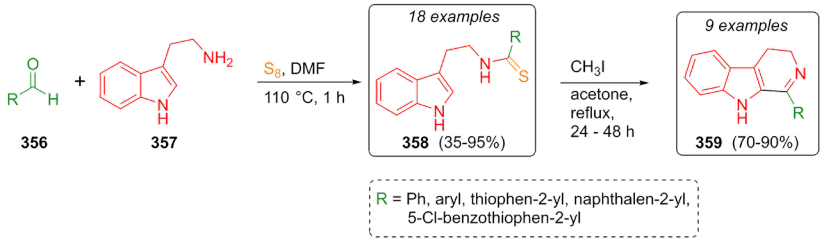
Cherukupally *et al.* furnished the total synthesis in eight steps of the antidepressant drug agomelatine (**355**) by a synthetic strategy in which the key step was a Willgerodt–Kindler reaction [69]. The procedure began with 2-naphthol **351**, which was transformed into ketone **352**. The latter was methylated with dimethyl sulfate in mild basic conditions to give ketone **353**. Then, ketone **353**, morpholine, and elementary sulfur were converted into thiomorpholide-type intermediate **354** (Scheme 50). Further transformations such as esterification, reduction to alcohol, and hydrogenation completed the synthetic route in 27 % overall yield. The use of a Willgerodt–Kindler reaction in a total synthesis, since this process regularly provides moderate to good yields.



Scheme 50. Total synthesis of agomelatine.

Volk *et al.* performed the first Willgerodt–Kindler 3CR-based synthetic strategy towards *N*-thioacyltryptamines **358**, and their further transformations into the corresponding β-carbolines **359** (Scheme 51) [70]. Thus, aldehydes **356**, tryptamine (**357**), and sulfur were combined to afford the *N*-thioacyltryptamines **358** in moderate to good yields (35-95 %). At the same time, a portion of these products were carried to subsequent ring-closure transformations promoted by iodomethane to give β-carbolines **359**. In addition, this procedure was furnished using a broad range of electron-releasing and electron-withdrawing groups placed in the aldehydes **356**.



Scheme 51. Synthesis of carbothioamides as precursors of 1-substituted 3,4-dihydro-β-carbolines.

In 2017, Darehkordi *et al.* performed a rapid route to synthesize novel heterocycles incorporating fragments of antibiotic fluoroquinoline-derivatives such as enoxacine, norxacine, and ciprofloxacine *via* a Willgerodt–Kindler reaction [71]. Thus, arylglyoxals **365**, fluoroquinolones **363**, and elemental sulfur were combined sequentially using sodium sulfide in catalytic amounts to reach products **369** in good to excellent yields (83-95 %). The mechanism proposed suggests that Na_2S (**360**) and sulfur (**361**) allowed the formation of ions **362** that combined with amines **363** gave the anions **364**, which perform a nucleophilic attack on iminium ions **367** to achieve the products **369** through a release of amines **363** from the intermediates **368** (Scheme 52). It is worth emphasizing the key role of Na_2S (**360**) in the addition to uncommon amine source and the role of sulfur as an oxidant. Also, this one-pot reaction allowed easily and efficiently incorporation of fluorodihydroquinoline as an antibiotic pharmacophore fragment.

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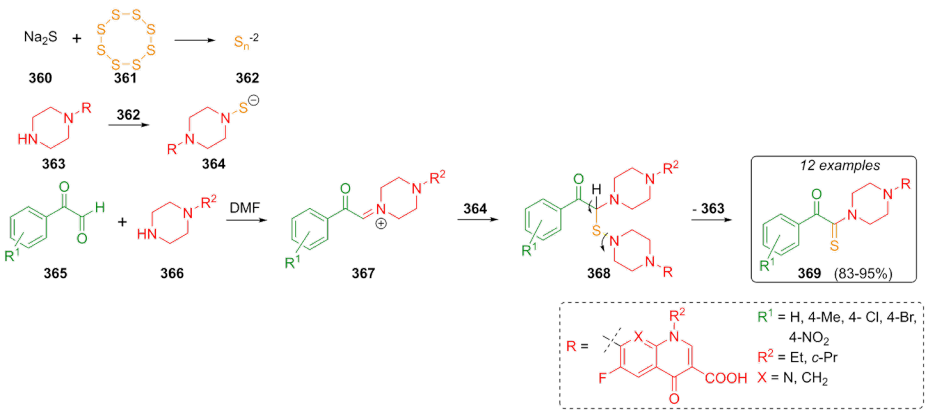
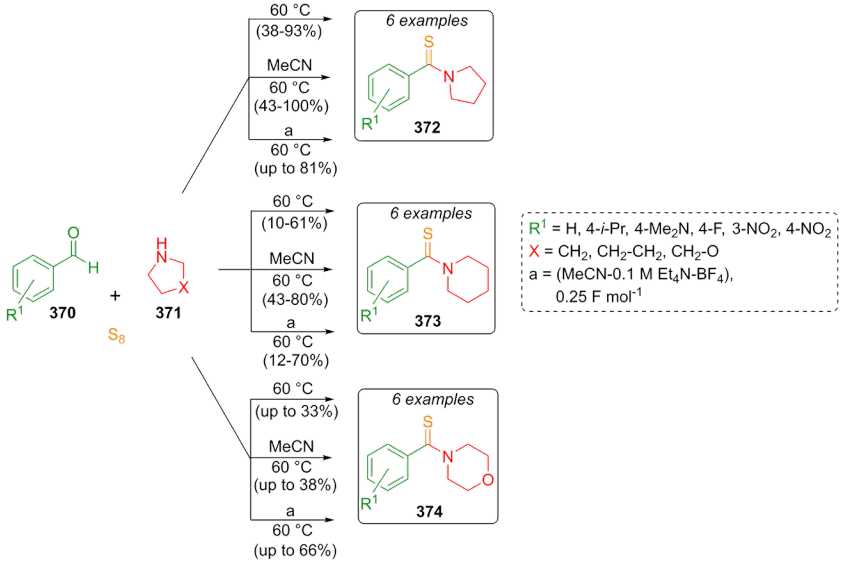


Scheme 52. Synthesis of piperazine-linked fluorodihydroquinoline-3-carboxylic acids with potential antibiotic activity.

Feroci *et al.* reported a sustainable method to synthesize thiobenzamides *via* a Willgerodt-Kindler reaction [72]. Benzaldehydes **370**, cyclic amines **371**, and elemental sulfur were sequentially combined in three different reaction pathways: under solventless conditions, in solution, and by electrochemical conditions at the same temperature (60 °C) for 3 h to achieve products **372**, **373**, and **374** (Scheme 53). The yields were varied (up to qualitative yields) due to the variety of substituents in the aromatic aldehydes. Regarding the electrochemical reactions, it is not easy to carry out this type of reactions with electro-attracting groups, but in the case of this methodology, it worked satisfactorily. Also, in electrochemical conditions, formation of tetraethylammonium cations was observed. Low yields were obtained for morpholine-containing analogues probably due to the interactions between oxygen from the morpholine moiety and the sulfur source even though stoichiometric amounts of sulfur were used at low temperatures.



Scheme 53. Eco-friendly approach for the synthesis of thiobenzamides.

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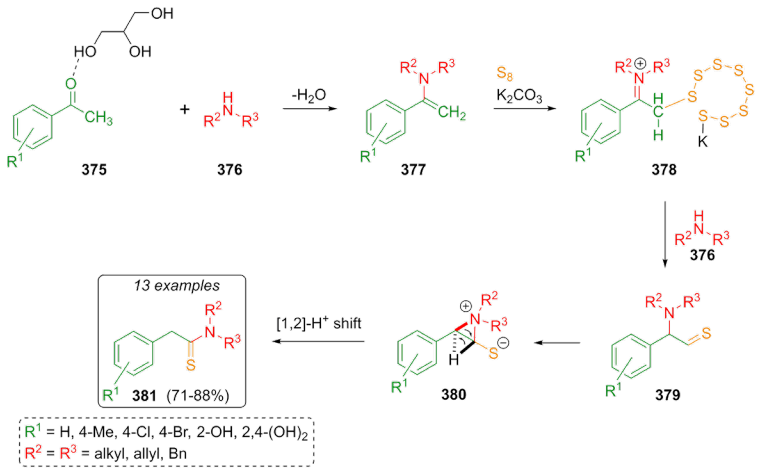
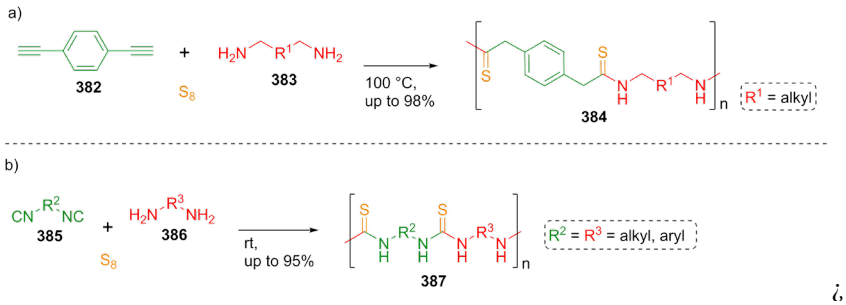
In 2017, Heydari *et al.* developed a green approach to synthesize ethanethioamides under a basic deep eutectic solvent *via* the Willgerodt-Kindler reaction [73]. After optimizing solvent conditions, thioamides **381** were obtained in good yields (71-88 %) by sequential combination of acetophenones/glycerol **375**, amines **376**, and sulfur under glycerol/carbonate-assisted solvent. A plausible mechanism was described in Scheme 54, where glycerol plays an important role in capturing water producing the corresponding enamines **377**. Then, the base promoted the formation of sulfur anion and deprotonation of iminium ions **378**, which after the addition of amines **376** achieved compounds **379** that through a rearrangement afforded intermediates **380**, and a 1,2-proton shift performed the products **381**. Moreover, the deep eutectic solvent, glycerol-K_2CO_3, increases collisions in the reaction medium promoting a better chemical environment.



Scheme 54. Synthesis of ethanethiones using an environmentally friendly basic deep eutectic solvent.

In 2018, Theato *et al.* published a seminal manuscript in which two types of multicomponent polymerizations *via* a Willgerodt–Kindler reaction are described [74]. Reaction a) combining dialkynes **382** with aliphatic diamines **383** , and reaction b) using diisonitriles **385** and aliphatic diamines **386**. Both reactions were carried out under typical Willgerodt–Kindler conditions and without catalysts, yielding up to 98 % and 95 % for both kind of polymeric products **384** and **387** respectively (Scheme 55).



Scheme 55. Multicomponent-sulfur polymers approach.

In 2019, Dalal *et al.* developed a methodology to synthesize thioamides *via* a Willgerodt-Kindler reaction [75]. Thioamides **393** were assembled by combining aromatic aldehydes **390**, cyclic amines **388**, and a sulfur source under catalyst-free conditions. The products were prepared in good to excellent yields (80-94 %). Electron-withdrawing and electron-donating groups were included in the substrate scope. A plausible reaction mechanism

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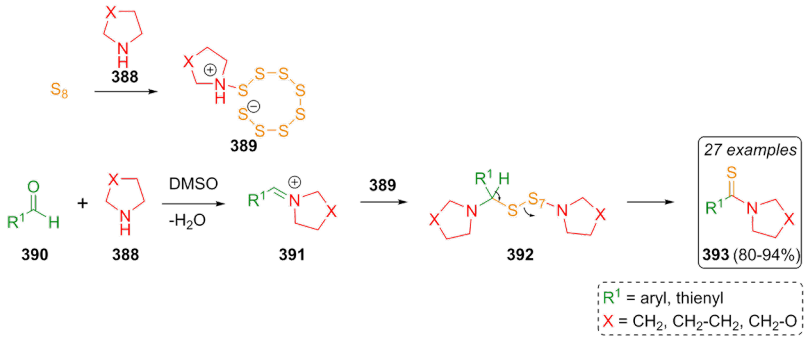
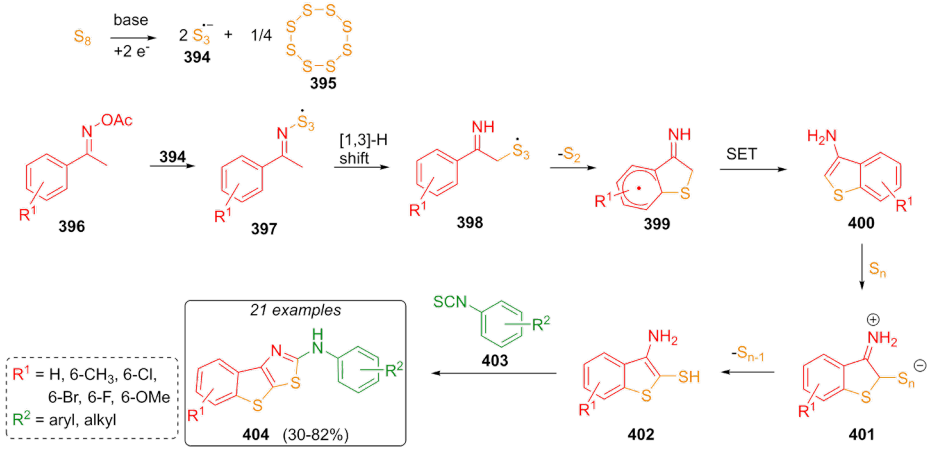
starting from zwitterionic compounds **389**, which were prepared by reacting sulfur and amines **388.** Then, zwitterions **389** performed a nucleophilic attack on cyclic iminium ions **391** to give intermediates **392** (Scheme 56). Finally after releasing of sulfur, the products **393** were achieved. The best yields were directed by three important factors: a) nucleophilicity of cyclic secondary amines; b) DMSO as an environmentally friendly solvent; and c) low amounts of sulfur used.



Scheme 56. Synthesis of thioamides at room temperature from a zwitterionic sulfur source.

In 2019, Huang, Ji *et al.* reported an interesting 3CR approach which includes a cascade process under transition metal-free conditions, and employing the Willgerodt–Kindler-type reaction [76].Polyheterocyclic thiazoles **404** were synthesized up to 82 % yield through sequential combinations of ketoximes **396**, isothiocyanates **403**, and a sulfur source promoted by two bases. A plausible mechanistic pathway suggests formation of a base-promoted sulfur radicals **394** s, which are inserted into ketoximes **396** followed by a [1,3]-H shift in the intermediates **397** to give radicals **398**. Then, it was promoted a radical cyclization on compounds **398** to achieve intermediates **399**, which after a single electron transfer (SET) performed heterocycles **400**, and finally, a Willgerodt–Kindler-type reaction between thiols **402** and isothiocyanates **403** (Scheme 57). Notability, sulfur-assisted cascade process formed trisulfur radical anion **394**, which activated compound **396**. The base-containing acetates promoted the formation of subproducts. Ketoxime acetates proceed accurately when they are substituted in *meta* instead of *ortho* position. On the other hand, other reagents were explored instead of isocyanates such as urea, thiourea, DMF, etc. but those attempts did not proceed.



Scheme 57. Three-component *bis*-heterocyclization approach.

In 2022, Iraji, Mahdavi *et al.* developed a synthetic procedure to achieve ciprofloxacin derivatives through a Willgerodt–Kindler-3CR, incorporating a pharmacophoric fragment behind the search for potential

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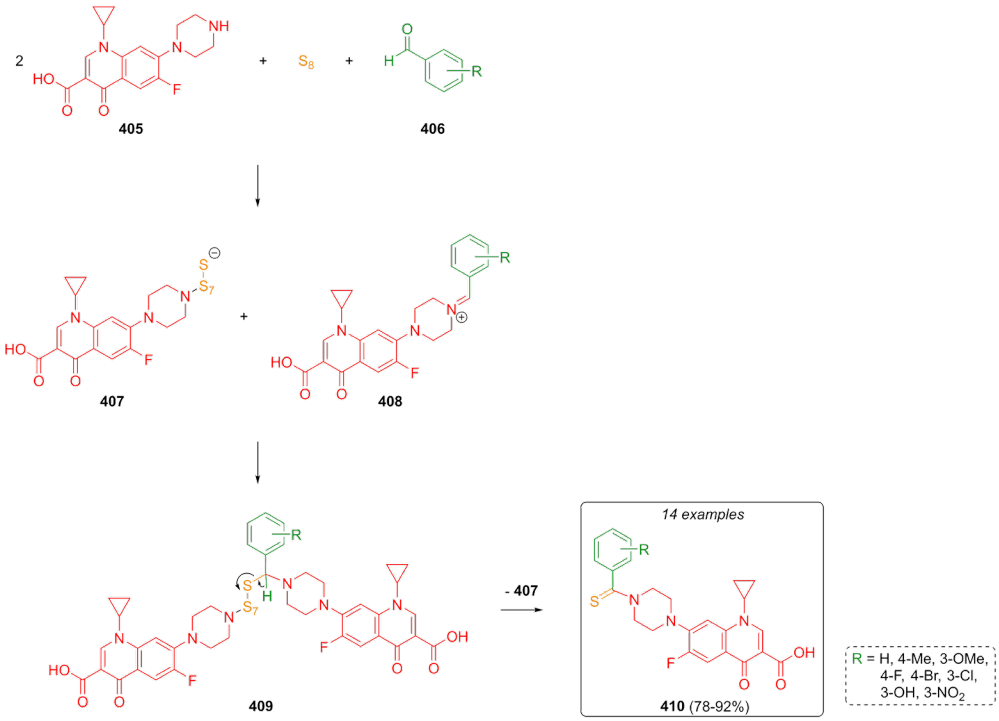
antibacterial activity [77]. The combination of aromatic aldehydes **406**, a couple of equivalents of ciprofloxacin (**405**), and sulfur allowed the synthesis of ciprofloxacin derivatives **410** in moderate to good yields (78-92 %). A plausible mechanism was proposed (Scheme 58). Condensation of aldehyde and amine-fragment from ciprofloxacin performed iminium ions **408**. Besides, nucleophilic attack from sulfur to ciprofloxacin (**405**) gave the polysulfide anion **407**. Finally, a reaction between iminium ions **408** and anions **407** after an oxidation process, ciprofloxacin derivatives **410** were obtained *via* elimination of ciprofloxacin anion **407** from the precursors **409**. It is worth noting that a modest to good antibacterial activity was exhibited by compounds **410** with the ciprofloxacin pharmacophoric fragment included.



Scheme 58. Synthesis of *N*-thioacylated ciprofloxacin derivatives.

Bücherer-Bergs-type 3CRs

In 1934, H. T. Bucherer reported a mechanism for hydantoin formation which was previously patented by H. Bergs in 1929 [78]. Thus, Bucherer-Bergs reaction is a multicomponent reaction between carbonylic compounds (aldehydes or ketones), a cyanide source (KCN), and ammonium carbonate. The general reaction pathway involves the formation of imines **412**, which are attacked by cyanide anions to afford the corresponding aminonitriles **413** followed by a nucleophilic addition to CO_2 to furnish intermediates **414**. A ring-closing process occurs to give the cyclic compounds **415**, which undergo a rearrangement toward formation of isocyanate-type intermediates **416** to finally furnish the hydantoin-based compounds **417** (Scheme 59) [79].

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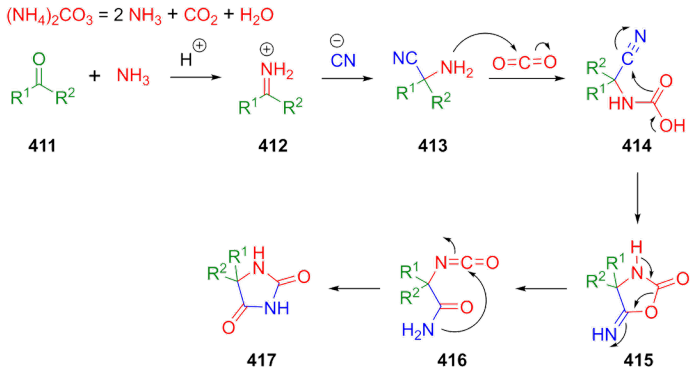
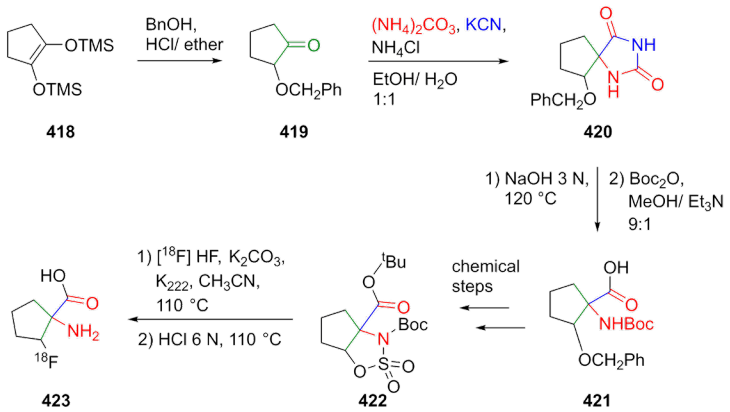


Scheme 59. Bucherer-Bergs reaction.

Goodman *et al.* reported in 2010 the synthesis of an amino acid employed as a tracer in chemotherapy *via* a Bucherer-Bergs-Strecker reaction as a key step [80]. This tandem-type methodology began with the disubstituted cyclopentene **418**. Thus, ketone **419** was treated with KCN, ammonium carbonate, and ammonium chloride to obtain the product **420**. After hydrolysis of hydantoin **420** to furnish compound **421** and several further transformations from this latter, precursor **422** was ^{18}F labeled in 39 % radiochemical yield (Scheme 60). In this 3CR, majoritarian product **420** was found to be in a *syn/anti* (ca. 8:1) stereoselectivity. It was not possible to carry out the direct halogenation in the C-2 position concerning the spiro center in compound **420**.



Scheme 60. Synthesis of fluorine-18-labeled radiotracer.

Midura, Mikołajczyk *et al.* developed a stereocontrolled strategy to prepare compound **428** and its analogue **432** utilizing a Bucherer-Bergs 3CR [81]. Thus, the synthesis of **428** (LY354740) started with the treatment of sulfoxide **424** with ethyl (dimethylsulfuranylidene)acetate (EDSA) obtaining a mixture of diastereomers *ent*/*exo* **425**. Cyclopentanone **426** was then obtained with by treatment of alcohol **425** with isopropyl magnesium chloride. Then, oxobicyclo **426** was sequentially combined with potassium cyanide and ammonium carbonate to afford the spiro-compound **427**. Finally, the synthesis of biomarker **428** was completed through hydrolyzation of its precursor **427** in 26 % overall yield from the sulfoxide **424**. To obtain the (+)-LY354740 analogue **432**, it was used the same strategy but needing only three experimental steps. From phosphonate **429**, sulfur moiety was removed and promoted by isopropyl magnesium chloride to give the bicyclo **430**. Thus, applying Bucherer-Bergs conditions to the later compound, the precursor **431** was assembled. Finally, its hydrolysis afforded the product *endo*-**432** in 45 % yields by

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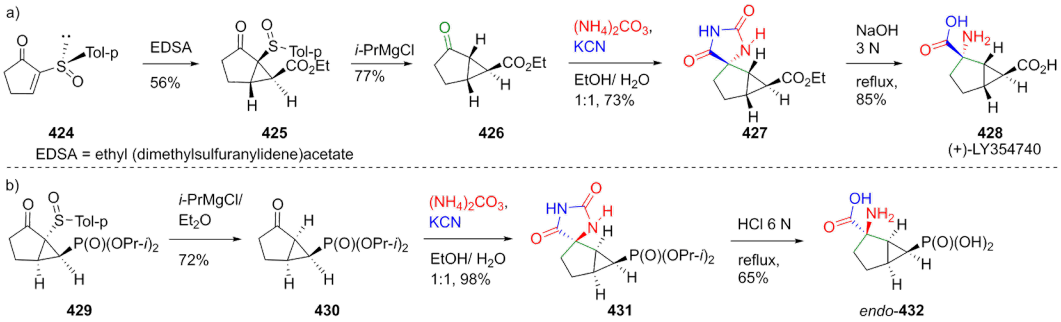
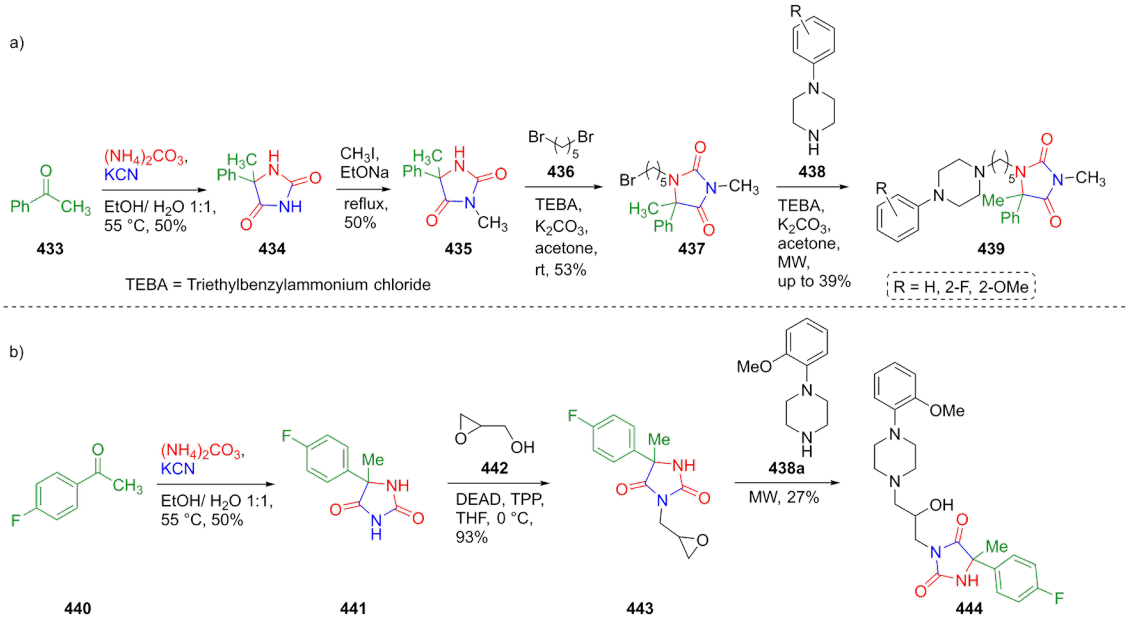
the three-steps (Scheme 61). In both strategies, a single diastereomer was afforded, where Bucherer-Bergs reaction was the key step.



Scheme 61. Synthesis of (+)-LY354740 and its analogue *via* a Bucherer-Bergs-based strategy.

In 2014, Handzlik *et al.* used a Bucherer-Bergs reaction as the key experimental step to achieve a series of arylpiperazine-containing compounds which were evaluated as 5-Ht$_7$ receptor ligands [82]. There are two synthetic procedures. The first one began with the combination of acetophenone (**433**), KCN, and ammonium carbonate to assemble the corresponding hydantoin **434** in 50 % yield, followed sequentially by an alkylation in different basic conditions to give the compound **435**. Then, after a nucleophilic substitution with dibromide 436, the compound **437** was obtained. After a second nucleophilic substitution of this latter with piperazines **438,** the spaced-type *bis*-heterocycles **439** were obtained. The second procedure involved also in a Bucherer-Bergs reaction starting from 4-fluoroacetophenone (**440**) to furnish hydantoin **441**. After the one-pot process, compound **444** was formed through a Mitsunobu reaction coupled with an *N*-alkylation under microwave conditions (Scheme 62). According to the pharmacological studies carried out in this work, the existence of a substituent in position 3 of the hydantoins favors the ligand-protein affinity. In this strategy, two modifications were made in positions 1 and 3 of the hydantoin moiety, being the most favorable in position 3 by incorporating lipophilic groups, potentiating their affinity to the 5-Ht$_7$ receptor ligand, which is involved in neurodegenerative disorders like the Alzheimer disease.



Scheme 62. Synthesis of phenylpiperazine hydantoins.

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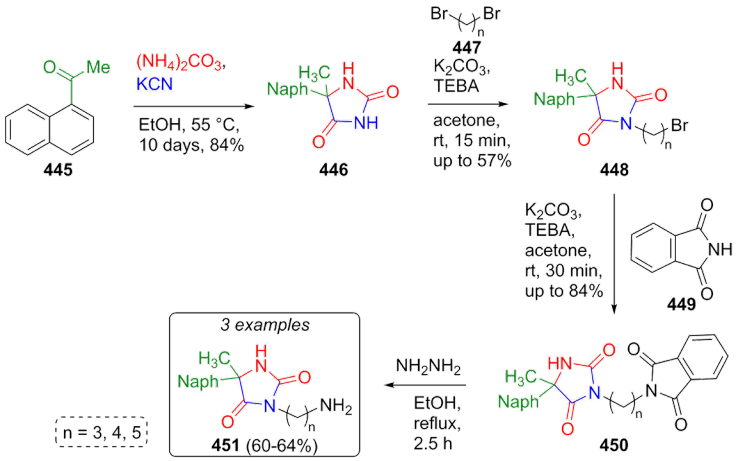
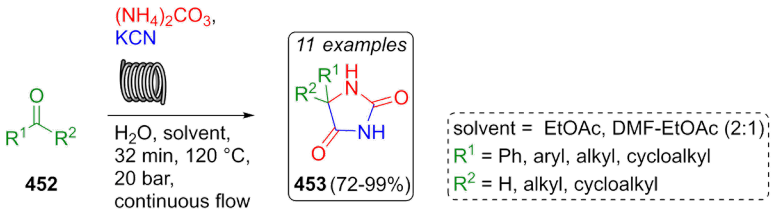
Later in 2015, Handzlik *et al.* again reported a procedure to achieve some new imidazolidine-4-ones *via* a Bucherer-Bergs as the key reaction of the process. The products were evaluated as chemosensitizers of *S. aureus* [83]. The naphthylacetophenone (**445**) was subjected to a Bergs-Bucherer reaction promoted by KCN and ammonium carbonate to afford the imidazolidine-2,4-dione (**446**). After two sequential C3-C5 alkylations (the first one on hydantoin **446**, and the second one in compounds **448**), phthalimides **450** were treated with hydrazine to finally afford products **451** (Scheme 63). Further modifications in N-3 position on the hydantoin ring are expected to potentiate the biological activity of such compounds.



Scheme 63. Synthesis of imidazolidine-4-ones.

Kappe *et al.* reported the development of a creative and interesting approach to synthesize hydantoins *via* Bucherer–Bergs reaction under continuous flow conditions [84]. It was performed a two-feed setup with an organic solution of carbonylic compounds **452** and an aqueous solution of KCN and ammonium carbonate to afford hydantoins **453** in moderate to excellent yields (72-99 %) (Scheme 64). By employing polar solvents like alcohols, an unexpected issue of clogging occurs, which was easily solved by increasing the temperature of the system. However, in the case of alcohols, there is not a correct mixture of phases, so it was necessary to employ ethyl acetate or a mixture of solvents such as DMF-EtOAc in 2/1 v/v proportion.



Scheme 64. Synthesis of hydantoins through continuous flow conditions.

Tanaka *et al.* developed a new protocol to prepare peptides *via* the Bucherer-Bergs reaction used to increase annulated amino acids-chains [85]. The first step is just a Bucherer-Bergs reaction starting from chiral ketone **454** to give hydantoin cyclic-derivatives **455** in diastereomeric major product with *R*, *R* configuration (Scheme 65). After a separation of diastereomers, pure spiro-compound **455** was *N*-protected with Boc to give the product **456**. Then, it was hydrolyzed with LiOH, and the carboxylate esterified to give the product **457**. Stereoselective Bucherer-Bergs reaction is carried out due to steric hindrance between 1,3-diaxial H and C=NH groups. Moreover, it is worth noting that the cyclohexane ring has an axial methyl making a repulsion with to amino esther type group in **457.**

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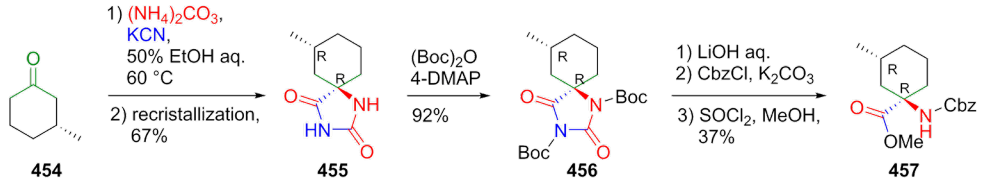
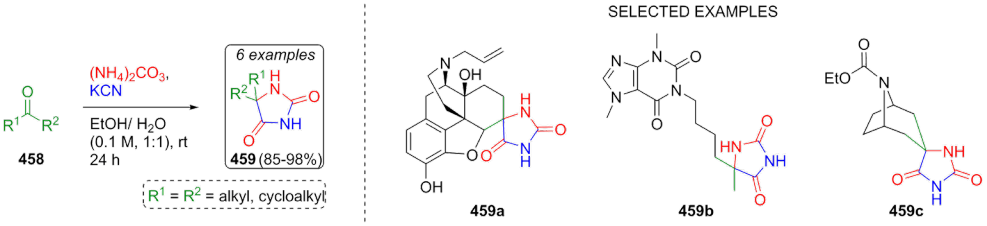


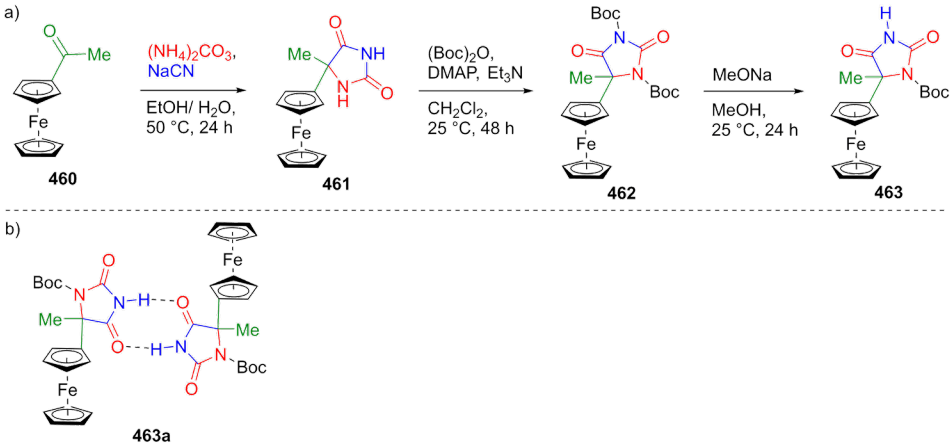
Scheme 65. Amino acid synthesis *via* Bucherer-Bergs reaction.

In 2016, Tomohara, Adachi *et al.* worked on the synthesis of hydantoins from extracts of *Curcuma zedoaria via* a Bucherer-Bergs reaction [86]. This strategy involved a direct chemical derivatization to synthesize the hydantoins **459**. Thus, ketones **458** were combined sequentially with KCN, and ammonium carbonate to afford the products **459** in good to excellent yields (85-98 %) (Scheme 66). In the case of reactions with natural products, at high temperatures, it could produce undesirable compounds or fragmentation of the hydantoin ring in such compounds. On the other hand, it also could be produced other undesirable side reactions if concentrations of reagents are not optimal due to the wide variety of functional groups contained in such natural products.



Scheme 66. Derivatization *via* Bucherer-Bergs reaction.

Santi *et al.* have been focused on the synthesis of aminoacids containing the ferrocenyl-moiety as a metallocene unit to provide H-bonded dimers through the Bucherer-Bergs reaction [87]. Thus, acetylferrocene (**460**) was subjected to mild Bucherer-Bergs conditions to give the product **461**. Then, *N*-Boc protection was performed under the treatment of hydantoin **461** with $(Boc)_2O$, DMAP, and triethylamine to give the *bis*-*N*-Boc-protected hydantoin **462**. Finally, compound **462** was combined with sodium methoxide in methanol to afford the product **463** (Scheme 67**(a)**). Dimerization of hydantoin derivative **463** was carried out in a solution of $CDCl_3$ (Scheme 67**(b)**). These kinds of compounds are suitable for recognizing cationic species due to the strategic position of the ferrocene fragment.



Scheme 67. Synthesis of hybrid ferrocenyl-hydantoin dimers.

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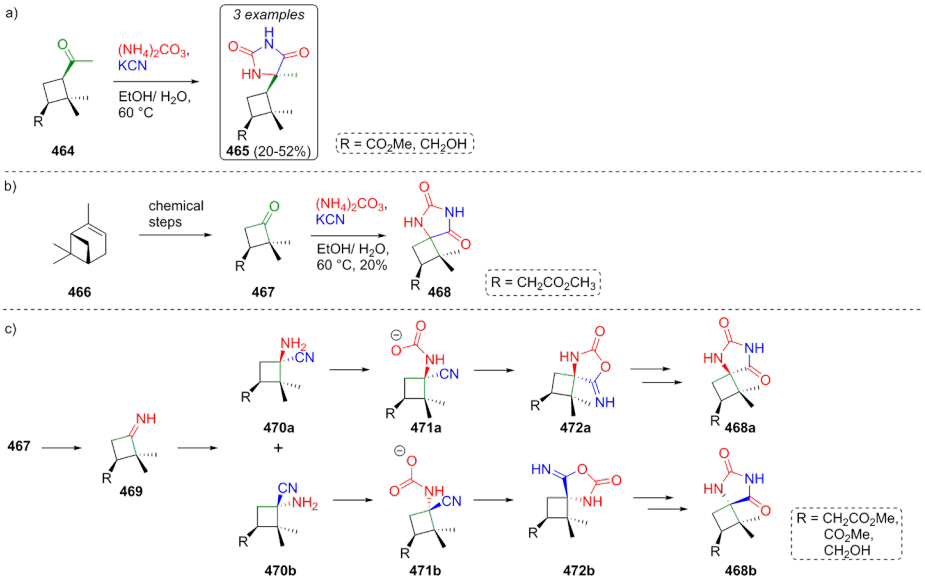
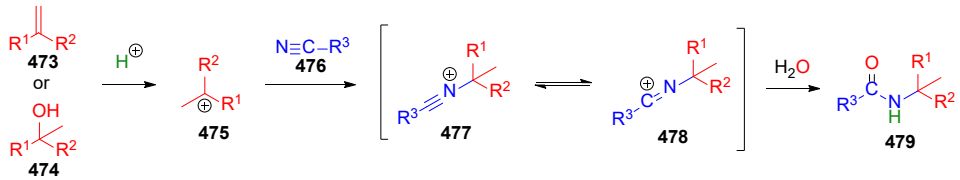
In 2018, Moglioni *et al.* reported the synthesis *via* Bucherer-Bergs of a series of some new hydantoins, which contain cyclobutyl rings [88]. Cyclobutanones **464** and **467** were sequentially combined with KCN and ammonium carbonate in water-methanol as the solvent system at 60 °C affording two types of hydantoins **465** and **468** (Scheme 68**(a)**,**(b)**). A plausible mechanism for the synthesis of hydantoins **468** was displayed in Scheme 68c, where the main feature involves a carbamate-type intermediates **471a** and **471b**, which determine diastereoselectivity since they do not form diastereomeric mixtures in the conversion of precursors **467** into products **468**, producing only a compound isolable while in the process from precursors **464** into **465** achieved a mixture of products.



Scheme 68. Synthesis of cyclobutyl-hydantoins.

Ritter-type 3CRs

In 1948, John J. Ritter developed a pioneering method to synthesize amides. Formation of carbocations **475** coming from alkenes **473** or alcohols **474** in an acid medium is the first step of this methodology. Then, addition of nitriles **476** furnished nitrilium ion intermediates **477** and their resonance form **478**, which in presence of water (or other kind of nucleophiles) finally provide the amides **479**, eventually in good to excellent yields (Scheme 69) [89]. Even, Ritter reaction has been used in an intramolecular way to give heterocycles, for instance, lactams and other kind of related aza-heterocycles [90].



Scheme 69. Ritter reaction.

In 2011, Togni *et al.* developed a Ritter-type reaction to generate compounds with N-CF_3 bonds [91]. In this approach, triazoles **480** were combined sequentially with iodine-containing compound **481** in acetonitrile

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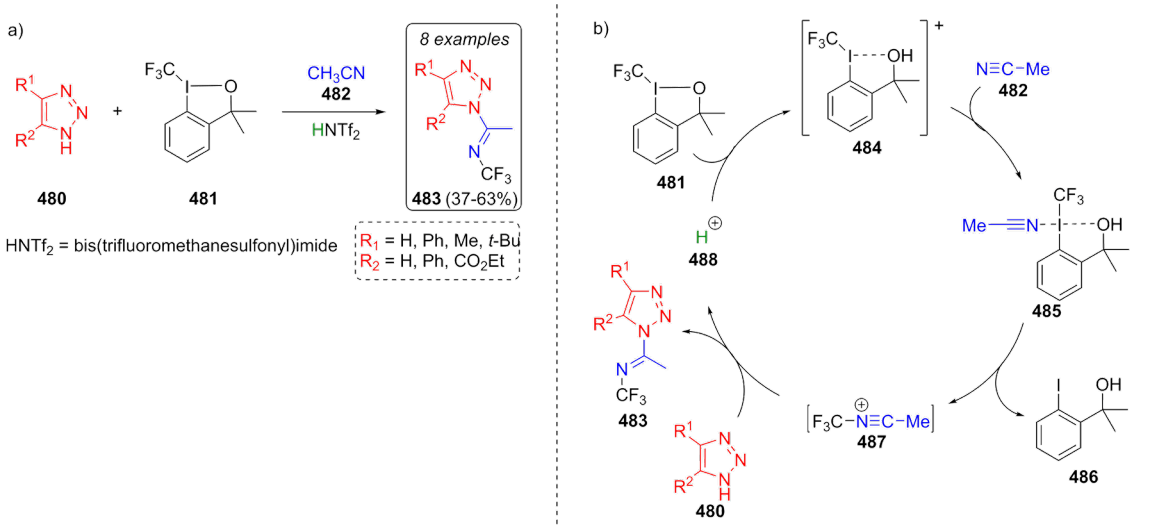
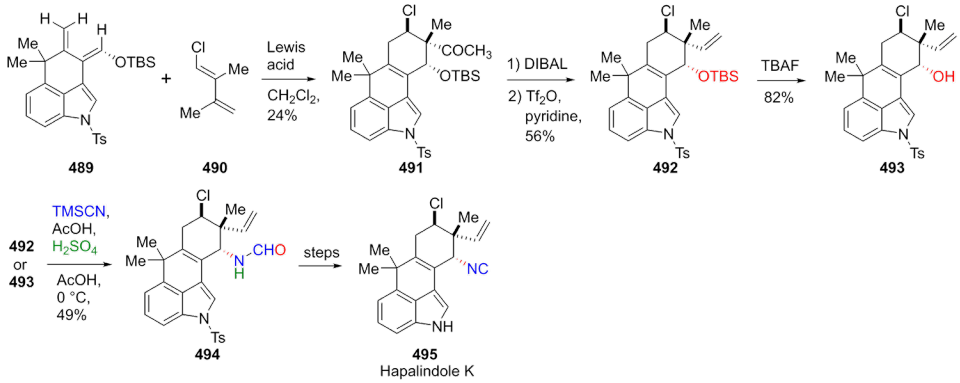
under mild acidic conditions to furnish *N*-(trifluoromethyl)imidoyls **483** as the main products in modest yields (37-63 %) (Scheme 70**(a)**). It was proposed a plausible catalytic mechanism, where protonated iodine-containing compound **481** and acetonitrile **482** gave the complex **485**. Then, nitrilium ion **487** was formed through a reductive-elimination step. Imines **483** were constructed by a reaction between triazoles **480** and ion **487**. Finally, it was released a proton to complete the catalytic cycle (Scheme 70**(b)**). This strategy allows the formation of a N-CF_3 bond since regularly it was formed through another kind of methodologies. Two by-products were formed due to stereoelectronic nature of reactants. For instance, an excess of triazole **480** promotes a trifluoromethylation process, while an excess of iodaoxole (**481**) produces a Ritter addition of nitrile, which was controlled by stoichiometric quantities of the corresponding reactants **480** and **481**.



Scheme 70. *N*-Trifluoromethylation approach.

Johnston *et al.* reported in 2011 the total synthesis of Hapalindoles K, A, and G in twelve steps where a Ritter reaction was the key one [92]. Starting reagents **489** and **490** were previously synthesized. Thus, it was performed a Diels-Alder cycloaddition between them (**489** and **490**) to give the compound **491**, which was reduced with DIBAL to provide alkene **492**. This latter was treated with TBAF to obtain the alcohol **493**. Then, reagents **492** or **493** were subjected to acidic Ritter conditions with TMSCN affording the compound **494** in good stereoselectivity. After several chemical steps, the synthesis of hapalindole K was completed (Scheme 71). It is noteworthy that Ritter reaction was useful for stereoselective formation of a C-N bond.



Scheme 71. Synthesis of Hapalindole K.

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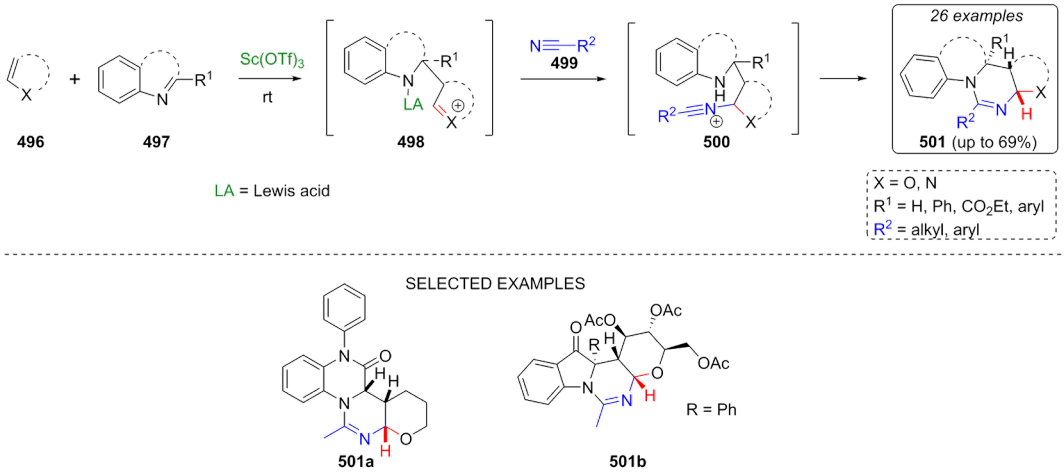
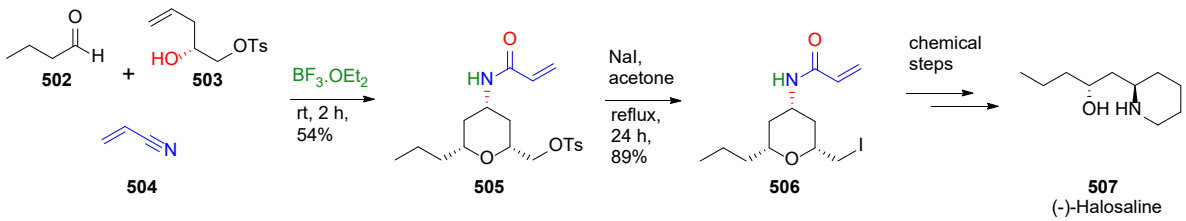
In 2012, Lavilla *et al.* developed a unusual multicomponent approach through a tandem Mannich-Ritter-type strategy [93]. Thus, unsubstituted compounds **496** and imines **497** were sequentially combined with nitriles **499** to afford products **501** in yields up to 69 % under Lewis-acid catalytic conditions at room temperature. Plausible mechanism comprises the formation of Mannich-type intermediates **498** from olefine and imine reagents, followed by the addition of nitriles to give the Ritter-intermediates **500**. Finally, amidines **501** were furnished by means of an intramolecular C-N bond formation (Scheme 72). As first step, it was proposed that cyclic compounds **496** and imines **497** react *via* Povarov reaction but, it was observed a high ring strain in that intermediate formed so that the mechanism pathway was directed to run *via* a Mannich sequence. This reaction works well with some restrictions: a) it was necessary to carry out the reaction using an excess of nitriles; b) some compounds such as dimethylindolenine do not perform MCR due to steric hindrance; c) other products with poor yields were the aromatic imine derivatives which were epimerized; d) it was used different *N*-olefins such as lactams, enamides or thiazolones, which afforded Mannich-type products.



Scheme 72. Tandem Mannich–Ritter approach.

Yadav *et al.* reported in 2013 a creative three-component procedure involving a cascade Prins-Ritter process as a key step to synthesize tetrahydropyranes as precursors of anti 1,3-aminoalcohols [94]. To demonstrate the effectiveness of this approach, it was achieved the total synthesis of (-)-Halosaline. Chiral alcohol **503** was previously prepared starting from epoxides through Jacobsen's hydrolytic kinetic resolution followed by a protection. Thus, aldehyde **502**, alcohol **503**, and nitrile **504** were sequentially combined using a Lewis-acid as catalyst to give product **505**, which was treated with sodium iodide to give acrylamide **506**. Eight steps from compound **506** were performed, some of them were a ring closing and alkene reduction to complete the total synthesis of (-)-Halosaline (**507**) (Scheme 73). After MCR, substituents found in equatorial position allowed stereocontrol behind the synthesis of *anti*-1,3-aminoalcohols, which can be further functionalized.



Scheme 73. Synthesis of anti 1,3-aminoalcohols *via* a strategy involving a Prins-Ritter cascade sequence.

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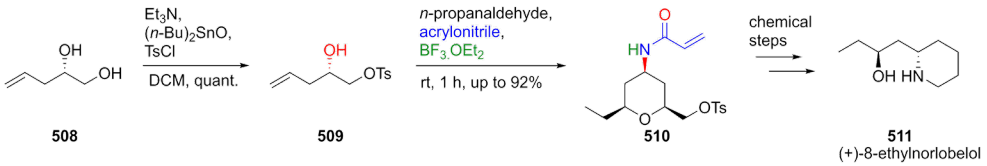
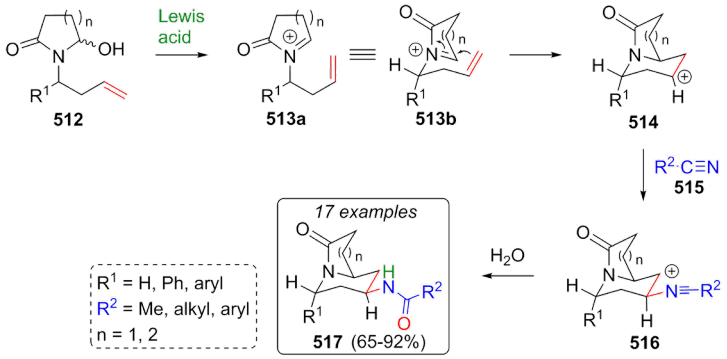
In 2013, Reddy *et al.* completed and reported for the first time the total synthesis of the alkaloid (+)-8-ethylnorlobelol (**511**) *via* a multistep strategy in which a Prins-Ritter cascade reaction was the key process [95]. Synthetic procedure began with the chemoselective protection of dialcohol **508** with tosyl group selectively in the primary alcohol affording product **509**. Combination of secondary alcohol **509** with *n*-propanaldehyde and acrylonitrile under Lewis acid catalysis resulted in the formation of *cis*-diastereomer of tetrahydropyran **510**. Total synthesis was completed in ten steps with high diastereoselectivity (Scheme 74). In the same way, the stereoselectivity key feature was directed since the cascade multicomponent process.



Scheme 74. Synthesis of (+)-8-ethylnorlobelol.

Saikia *et al.* developed an interesting tandem sequence *via* an aza-Prins reaction coupled with an intermolecular Ritter reaction to give azabicyclic species **517** [96]. Previously, it was prepared starting reagents **512**. Thus, lactams **512** were mixed with nitriles **515** under Lewis acid catalysis to achieve azabicyclic products **517** in good to excellent yields (65-92 %) and with high diastereoselectivity. It was suggested a plausible mechanism where iminium ions **513** were promoted by a Lewis acid. Then, carbocations **514** in chair-like favored conformation lead trapping nitriles **515** affording nitrilium ions **516**, which were hydrolyzed completing the synthesis of products **517** (Scheme 75). It was observed that Lewis acids have a favorable effect on the yields and diastereoselectivity, better than Brønsted acids. Also, yields of this MCR depend directly on substituents from the allylic chain, giving the best yields to electron-withdrawing groups. *Endo-trig* cyclizations of compounds **513** were carried out in axial substitution due to steric hindrance between substituents R^1 and carbonyl group from *N*-acyliminium ions as well as strong ring strain.



Scheme 75. Tandem Aza-Prins-Ritter approach.

The synthesis of new pyrrolidin-2-ones reported by Grellepois, Ben-Jamaa *et al.* involved a diastereoselective Ritter-type reaction [97]. The first step was the formation of *N*-acyliminium ions **519**, which were trapped by nitriles **520** affording isomeric mixtures of nitrilium ions **521a** and **521b**. Then, two routes continued from isomers **521a**: 1) *cis*-nitrilium ions **521a** promoted the synthesis of oxazolines **524** in 63 to 89 % yields through intermediates **522**, and 2) hydrolysis of intermediates **522** allowed the formation of *cis*-amides **523** (Scheme 76). These MCRs were carried out under Lewis acid conditions. During the processes, side products like amides or a diastereomeric mixture of products were obtained due to the presence of water in reaction media, which was solved using adequate quantities of acetonitrile to obtain **521a** as the major products. In contrast, compounds **521b** were obtained as by-products.

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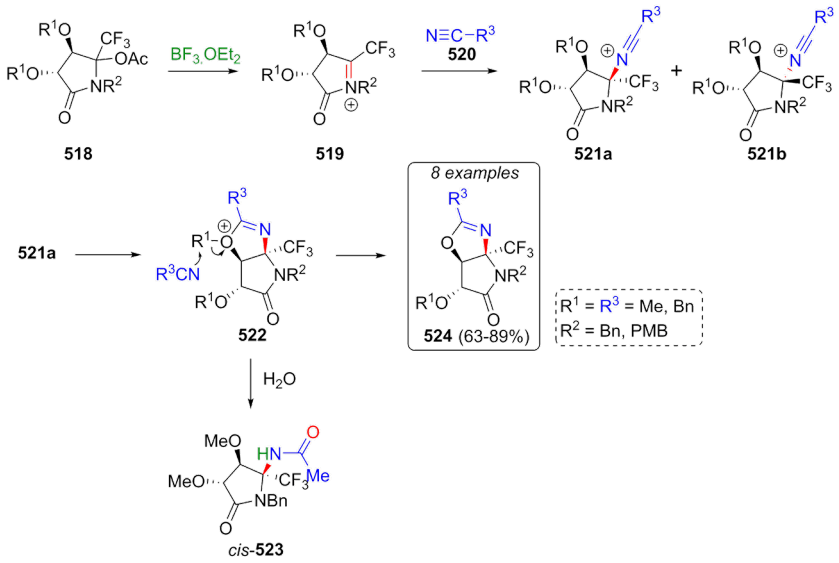
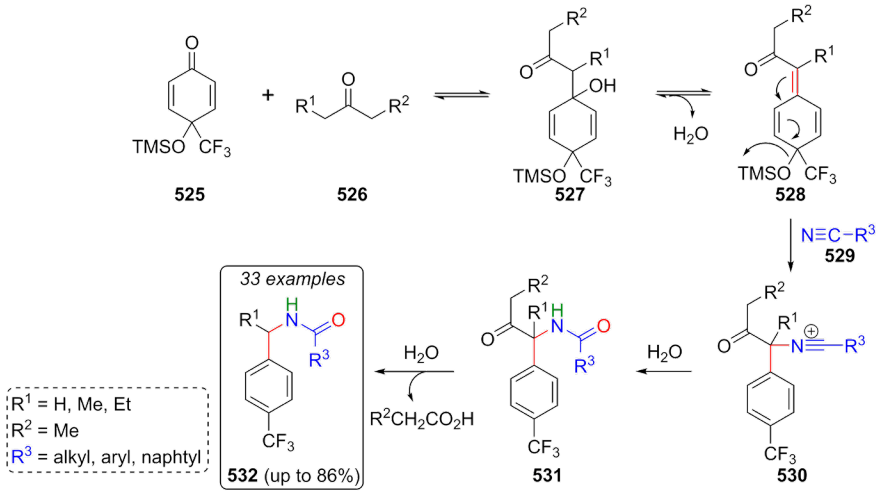


Scheme 76. Synthesis of CF_3-containing pyrrolidin-2-ones.

Li, Liu *et al.* developed an interesting method for preparing *N*-benzyl amides **532** through a cascade Ritter-type reaction [98]. In this process, the enolic form of ketones **526** performed a nucleophilic attack on carbonyl compounds **525** generating the intermediates **527**. Dehydration of these later affords intermediates **528**, which were trapped by nitriles **529** gave the nitrilium ions **530**. Thus, after their hydration to give compounds **531**, the elimination of leaving group completed the synthesis of *p*-(trifluoromethyl)benzyl amides **532** in up to 86 % yields (Scheme 77). As seen, best yields were obtained using dichloroethane as solvent, and TMSCl as Lewis acid catalyst, and water as an additive. In particular, the addition of water promoted hydrolysis of acyl group. Regarding to nitriles, multisubstituted benzonitriles do not promote reaction due to steric hindrance. On the other hand, benzonitriles substituted in *ortho* or *para* position decrease considerably the yields due to electronic inductive effects. A variety of electron-donating and electron-deficient groups were used in this approach, which indicates the viability of this process.



Scheme 77. Ritter-type synthesis of *p*-(trifluoromethyl)benzyl amides.

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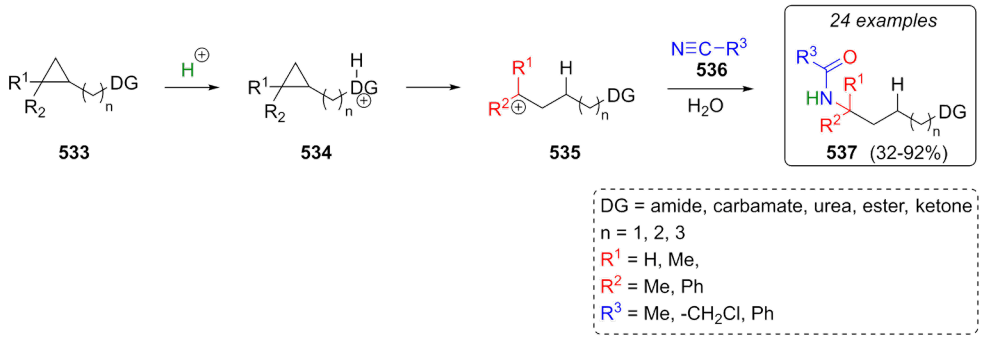
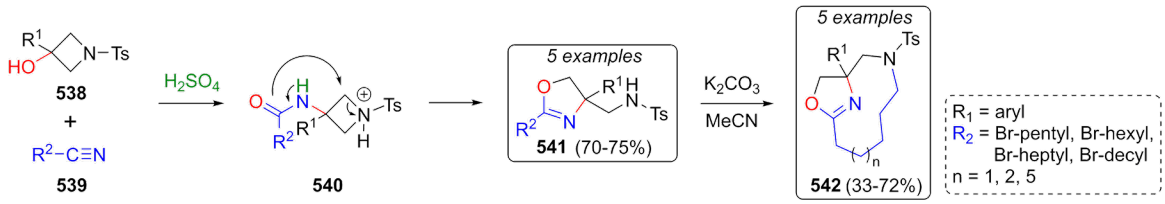
Protonolysis of cyclopropane-containing compounds was developed by Jirgensons *et al.* in 2019. This strategy makes use of amides, carbamates, ureas, esters, and ketones as reagents to generate corresponding amides *via* a Ritter-type reaction [99]. Thus, cyclopropanes **533** were protonated in a directing group (amide, carbamate, urea, and so on) through proton C-C transference to form the carbocations **534**. Products **537** were achieved through cations **535** trapping the nitriles **536** (Scheme 78). The reaction was carried out in acidic media under mild conditions. The use of trifluoroacetic acid, chloroacetonitrile, and acetic acid in a 1:1:1 proportions and heating the reaction at 60 °C gave the best yields. When a phenyl substituent was placed into the cyclopropane ring, the yields decreased considerably due to its interference at protonolysis step. In the same way, phthalimide and urea as directing groups of the reaction afforded the products in low yields, obtaining various byproducts.



Scheme 78. Protonolysis of cyclopropane-based compounds.

An elegant methodology developed by Baxendale *et al.* towards the synthesis of the new and complex macrocycles **542** involved a Ritter-type reaction as the first step of such procedure [100]. To achieve oxazolidines **541**, Ritter conditions from alcohols **538**, nitriles **539**, and sulfuric acid afforded amides **540**, where the oxygen of the amides attacked the ring releasing the ring strain to give the products **541**. With 4,5-dihydrooxazoles **541** in hands, compounds **542** were synthesized *via* intramolecular cyclizations in basic conditions (Scheme 79). The corresponding Ritter-intermediates were not formed in this approach. Moreover, in this strategy, several acids were evaluated, sulfuric and fluoroboric acids were the best ones, where sulfuric acid was chosen for its economy and ease of access. On the other hand, authors examined solvent effects in chloroform, dichloromethane, toluene, xylene, among others; DCM was selected as the best one.



Scheme 79. Macrocyclic approach under Ritter-type conditions.

Bao *et al.* reported in 2021 the synthesis of vicinal diamines **549** *via* a Ritter-type multicomponent reaction [101]. The optimal reaction conditions were using the strong Brønsted acid HPF_6, and $Cu(CH_3CN)_4PF_6$ as catalyst . Diethyl azodicarboxylate (**543**) and styrenes **545** were mixed to achieve the corresponding products in moderate to good yields (39-97 %). Authors proposed a plausible reaction mechanism, that was supported by DFT calculations. Thus, azodicarboxylate (**543**) was protonated by a Brønsted acid to assemble the intermediate **544**, which in the presence of styrenes **545** afforded carbocations **546**. Finally, products **549** were obtained following a Ritter reaction route after a nucleophilic attack of acetonitrile to intermediates **546**, and the addition

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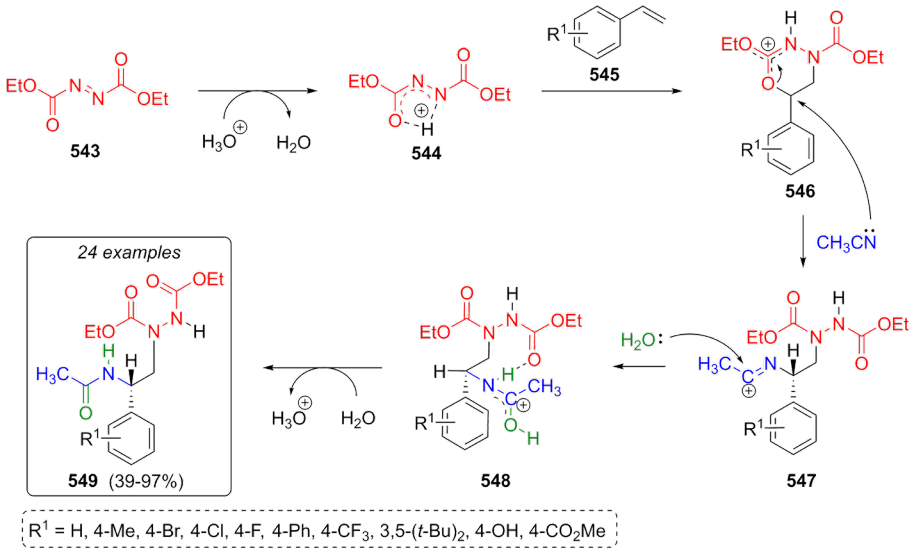
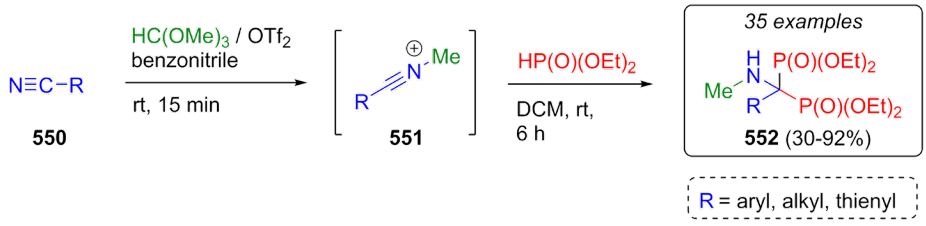
of water to carbocations **547** and dehydration of intermediates **548** (Scheme 80). Acetonitrile not only worked as the solvent but also contributed to the multicomponent process as one of the three reagents. Electronic effects influenced the yields because in the substitution from compounds with electro-donating or electro-withdrawing groups, the *ortho* or *meta* positions in the aromatic moiety gave the best yields, whereas in the *para* position, the yields were lower. In addition, the yields are affected by the amount of Brønsted acid used.



Scheme 80. Three-component vicinal diamination approach.

In 2022, Ye, Huang *et al.* worked on the synthesis of bisphosphonates through an interrupted version of Ritter reaction [102]. The methodology started with nitriles **550**, and their sequential combination with trimethyl orthoformate and triflic anhydride (1:1), nitrilium ions **551** were afforded. Then, These later ones were trapped by phosphite ester to assemble the bisphosphonates **552** in moderate to good yields (30-92%) (Scheme 81). Yields were affected by electronic effects of electron-withdrawing groups and steric hindrance in bulky groups from benzonitriles such as 4-*tert*-butyl or 4-propylcyclohexyl ones, as well as *ortho*-methyl-substituted benzonitriles and *para*-halogenated-substituted benzonitriles. Instead that, alkylic nitriles gave the best yields.



Scheme 81. Synthesis of α-amino bisphosphonates *via* an interrupted Ritter-type reaction.

Kabachnik-Fields-type 3CRs

Another multicomponent reaction was developed in 1952 by Martin I. Kabachnik and Ellis K. Fields. This 3CR involves a reaction between carbonylic compounds (usually aldehyde but, a few examples using

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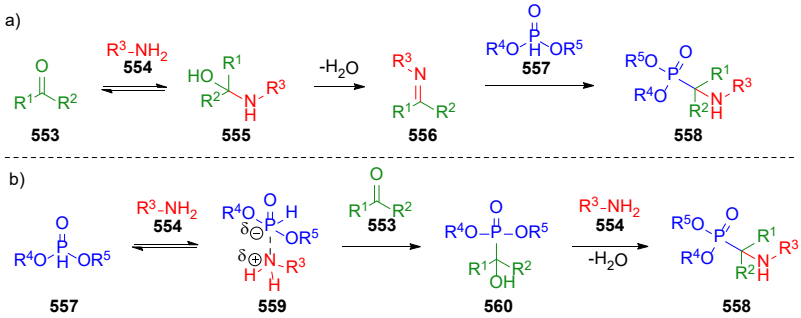
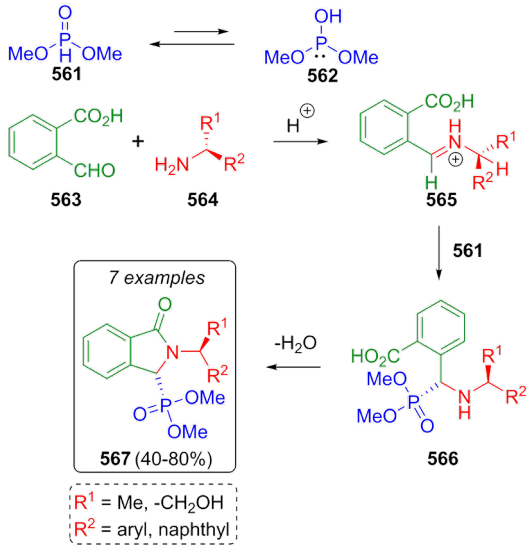
ketones have been reported), an amine, and a dialkyl phosphite [103]. The mechanism may take two pathways depending on the nature of reagents and mainly of the order of addition: a) condensation between carbonyl compounds **553** and amines **554**, followed by addition of P-H anions **557** to the corresponding imines **556** to complete the synthesis of phosphonates **558**; or b) addition of phosphites **557** to amines **554** to afford phosphonate complexes **559**. Then, zwitterions **559** are mixed with carbonyl compounds **553** to achieve compounds **560**, which through a condensation with amines **554** furnish products **558** (Scheme 82**(a)**,**(b)**) [104].



Scheme 82. Kabachnik–Fields reaction pathways.

Ordóñez *et al.* developed a synthetic methodology based on the Kabachnik–Fields three-component reaction to synthesize a few isoindolin-1-one-3-phosphonates [105]. Thus, condensation between aldehydes **563** and amines **564** afforded iminium ions **565**, which were nucleophilically attacked by phosphites **562**. After a dehydration process, products **567** were obtained under solvent and catalyst-free conditions (Scheme 83). It must be noted that the determinant step that allowed the high degree of diastereoselectivity is the nucleophilic attack of phosphites to imines due to a less hindered attack in *re*-face.



Scheme 83. Synthesis of isoindolin-1-one-3-phosphonates.

Berlicki *et al.*reported in 2012 the use of Kabachnik-Fields reaction to synthesize some new hydroxmethylphosphonic acid[106]. This synthetic procedure was used to evaluate the inhibitory properties of synthesized compounds towards bacterial urease. Thus, aldehydes **569** and phosphinic acid (**568)** were

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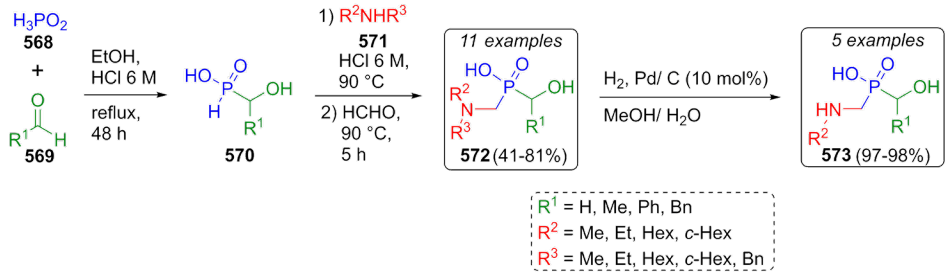
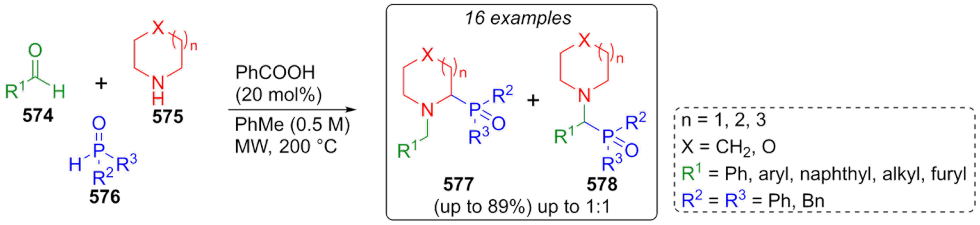
combined to achieve the a-hydroxy phosphinic acids **570**, which were trapped with secondary amines **571** followed by addition of formaldehyde in acidic conditions to afford the bioactive compounds **572** in yields up to 81 %. Phosphinic acid derivatives **573** were obtained by further catalytic hydrogenation of compounds **572** (Scheme 84). This procedure involves a modification of the amine moiety and the incorporation of a hydroxymethyl fragment for modulating biological activity.



Scheme 84. Synthesis of phosphonic acids.

Seidel *et al.* worked on a new Kabachnik-Fields-type reaction for the preparation of α-amino phosphine oxides (Scheme 85) [107]. This synthetic strategy involves a sequential combination of aldehydes **574**, cyclic secondary amines **575**, and phosphine oxides **576** using benzoic acid as the catalyst and under microwave heating conditions to give the α-amino phosphine oxides **577** and **578** in moderate to good yields (up to 89 % in the sum of yields for both isomers) and regioselectivity 1:1. The procedure promoted formation of C-P bond through functionalization of C-H bond using electron-withdrawing aldehydes and carboxylic acid as catalyst which accelerate the iminium ion formation.



Scheme 85. Synthesis of phosphine oxides.

Čikotienė *et al.* reported the preparation of many condensed pyrrolylphosphonates through a Kabachnik−Fields reaction-based methodology [108]. With reagents in hand, they proceeded to implement Kabachnik−Fields process through a sequential combination of aldehydes **579** with anilines **580** and dimethylphosphite under copper (I) catalyst to give the complex intermediates **582**, which performed an intramolecular cyclization to prepare a set of phosphonate-containing cyclized products **583** or **584** in moderate yields (48-69 %) (Scheme 86). Electron-releasing groups placed in aldehydes do not promote the reaction. On the other hand, pyridines and quinolines activate the triple bond of alkyne moiety, which decreases electron density from imine, thus promoting nucleophilic attack of phosphite *via* an *endo*-dig cyclization.

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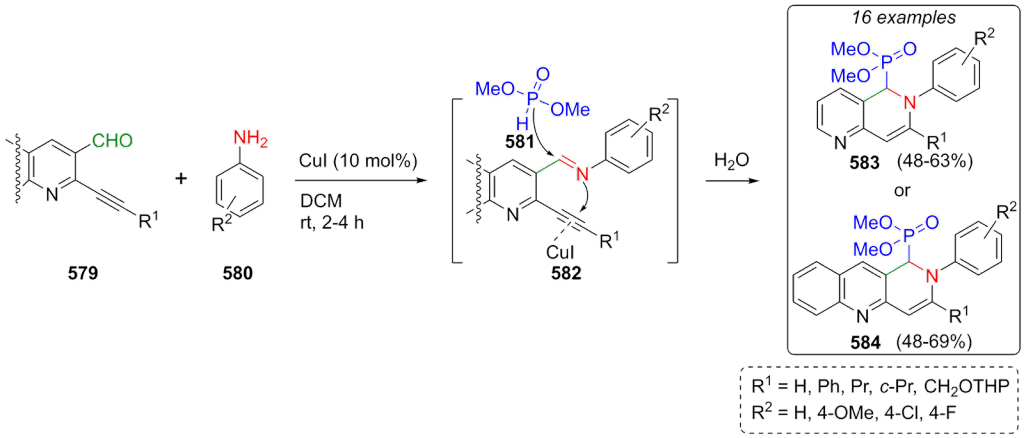
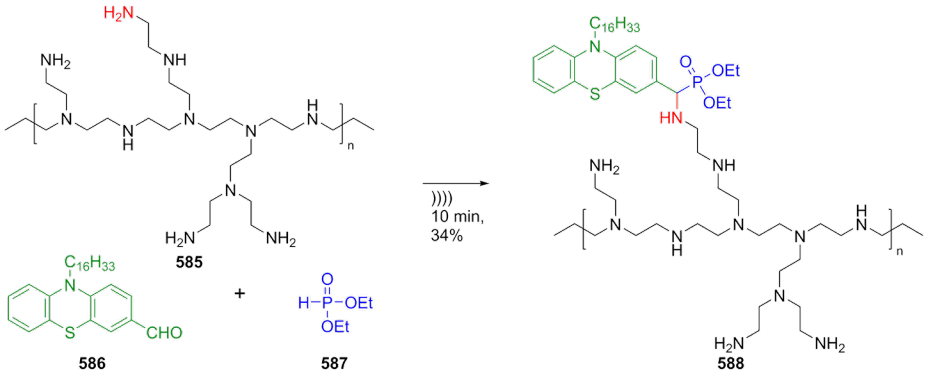


Scheme 86. Synthesis of fused dihydropyridine phosphonates.

Based on recent studies of fluorescent nanoparticles, Wan, Zhang, Wei *et al.* developed the first synthetic procedure to prepare active organic nanoparticles *via* the Kabachnik-Fields reaction, which were further evaluated in HeLa cervical cancer cell line [109]. Aggregation-induced emission-active aldehyde **586** was mixed with polyetherimide **585** and diethyl phosphite **(587)** under solvent and catalyst-free conditions using ultrasound heating affording product **588** in moderate yield (Scheme 87). This compound was synthesized under environmentally friendly conditions, and it exhibits potential activity for bioimaging due to its amphiphilic character. Likewise, this polymer may work as a cell biomarker because it exhibits biocompatibility with HeLa cell line.



Scheme 87. Synthesis of fluorescent nanoparticles.

In 2018, Wilhelm, Silva *et al.* reported the synthesis of twelve novel selanyl-a-amino phosphonates *via* a Kabachnik-Fields reaction [110] (Scheme 88). After the previous preparation of selenide amines **590**, the combination of aldehydes **589** with selenide amines **590**, and phosphonates **592** under solvent-free conditions catalyzed by niobium oxide allowed the preparation of organylselanyl α-amino phosphonates **593** in moderate to good yields (48-90 %). The use of diphenylphosphite and 3,5-dimethoxybenzaldehyde decreased the yields. Instead that, aldehydes substituted at the *ortho* position gave the best yields in the same way that the aryl groups in the selenide amine. These compounds were evaluated behind their antioxidant properties, as well as enzymatic inhibition properties.

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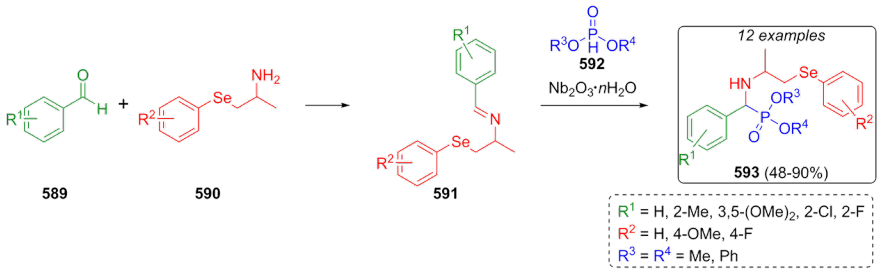
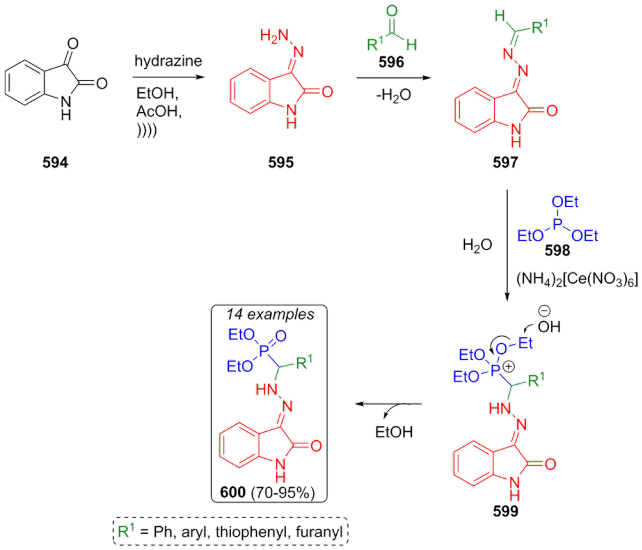


Scheme 88. Synthesis of selanyl α-aminophosphonates approach.

Nikalje *et al.* worked in 2018 on the synthesis of some new phosphonate-containing indolinones *via* a Kabachnik-Fields reaction. The synthesized compounds were probed against a panel of cancer cell lines such as MCF-7, IMR-32, SK-MEL-2, MG-63, to name a few [111]. Starting from indoline **594**, it was was formed the hydrazone **595** in the presence of hydrazine and acidic conditions. Thus, aldehydes **596**, hydrazone **595,** and triethylphosphite **(598)** were sequentially combined in the presence of ceric(IV) ammonium nitrate as a green catalyst at room temperature to synthesize the products **600** in good to excellent yields (70-95 %) (Scheme 89). Mechanism suggests that first were achieved imines **597**. Then, the catalyst promotes imines **599** formation, as well as the nucleophilic attack of phosphite **598** to give the intermediates **599**. Finally, water in the media reacts with phosphonium ions to achieve the Kabachnik-Fields products **600**. It is noteworthy the environmentally friendly conditions (EtOH, AcOH and ultrasound irradiation) involved in this synthetic strategy as well as potential biological activity on cancer cell lines.



Scheme 89. Synthesis of 2-oxoindolin phosphonates.

In 2019, Bálint *et al.* developed a methodology consisting of a double Kabachnik-Fields from aminoalcohols as key reagents (Scheme 90) [112]. Thus, paraformaldehyde (**601**), 2-aminoethanol (**602**), and phosphine oxides **603** were reacted together using microwave irradiation as a heat source in acetonitrile as a solvent and under catalyst-free conditions to afford products **604** and **605** in good yields (up to quantitative yields in the case of **605**). In this procedure, it was a functional range of temperatures (from 80 to 100 °C), and a quantity of reagents that gave both products. Authors found also that the use of an excess of paraformaldehyde at 80 °C, promotes the formation of both Kabachnik-Fields products.

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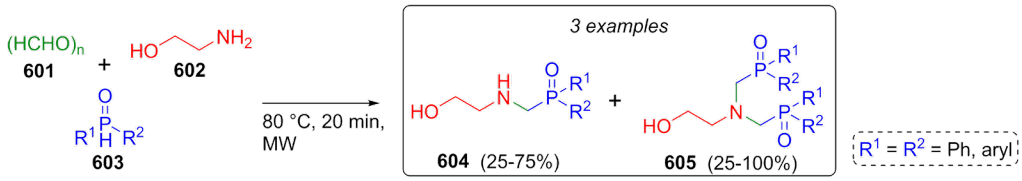
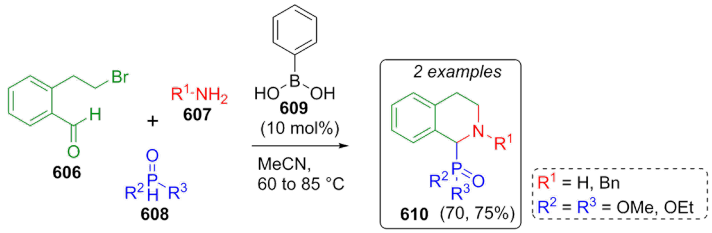


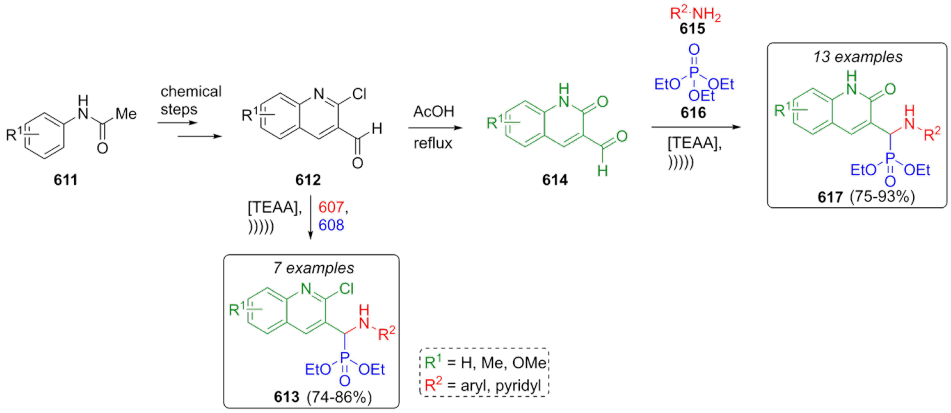
Scheme 90. Double Kabachnik–Fields reaction.

Ordóñez *et al.* reported in 2019 a new strategy to synthesize 1,2,3,4-tetrahydroisoquinoline-1-phosphonic- and -1-phosphinic acids **610** *via* a Kabachnik–Fields reaction (Scheme 91) [113]. Thus, aldehyde **606**, amines **607**, and phosphites **608** were combined in acetonitrile at 60 to 85 °C under catalytic amounts of phenylboronic acid (**609**) (10 % mol) to afford the products **610** in moderate yields (70-75 %). This study aimed to obtain analogues of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid through isosteric replacement of phosphonic acid instead of carboxylic acid fragment *via* an MCR-based synthesis under mild reaction conditions.



Scheme 91. Synthesis of 1,2,3,4-tetrahydroisoquinolin-1-phosphonates.

Bazine *et al.* developed a rapid and efficient methodology to prepare new α-amino phosphonates through a Kabachnik-Fields reaction as a key step. The synthesized compounds were evaluated as antioxidants and enzymatic inhibitors (Scheme 92) [114]. To prepare the quinoline-type reagents **612** it was employed a Meth-Cohn multistep reaction sequence starting from amides **611**. Then, compounds **612** were treated under mild acidic conditions to afford oxoquinolines **614**. Thus, quinolines **614**, amines **615**, and triethyl phosphate (**618)** were then subjected to Kabachnik-Fields reaction conditions in liquid ionic TEAA (triethylammonium acetate) using ultrasound irradiation to synthesize the corresponding products **613** and **617** in moderate to good yields (up to 93 %). Liquid ionic TEAA promoted high yields and in short reaction time. In addition, this procedure has a few advantages over previous ones. For instance, short reaction times, high yields in one-pot procedure, the products were afforded without purification by chromatography, and ease of experimental operation.



Scheme 92. Synthesis of novel quinoline-aminophosphonates.

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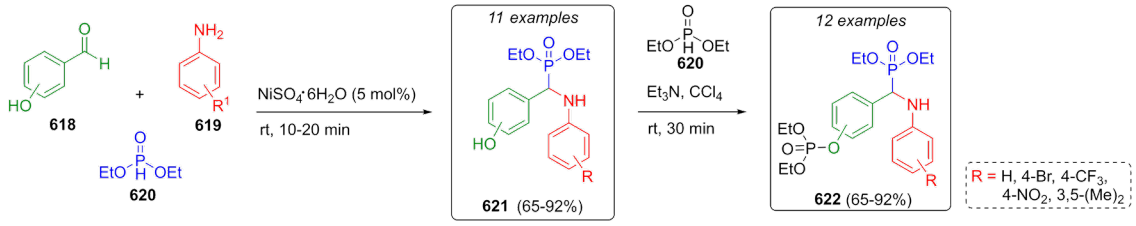
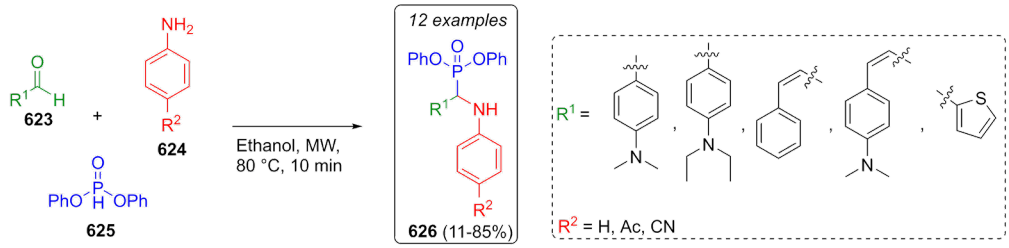
Guezane-Lakoud *et al.* developed a synthetic strategy towards the synthesis of new phosphates a-aminophosphonates through a Kabachnik-Fields-3CR as the first step of such procedure, followed by an Atherton-Todd reaction [115]. Sequential combination of hydroxybenzaldehydes **618**, anilines **619**, and diethylphosphite (**620**) using nickel(II) sulfate as a catalyst allowed the formation of the new α-aminophosphonates **621** in moderate to good yields (65-92 %) (Scheme 93). Then, phosphates α-aminophosphonates **622** were obtained through an Atherton-Todd reaction condition from compounds **621**. Precursors with substitution at *ortho* and *para* positions of benzaldehydes afforded the best yields in comparison to those from benzaldehydes substituted in *meta* position. The use of anilines with electron-rich or deficient groups did not affect the yields. Also, it is worth highlighting the solventless conditions, room temperature, and short times for all the processes.



Scheme 93. Synthesis of phosphates α-aminophosphonates.

Hernández-Fernández, Robledo-Leal, López-Cortina *et al.* reported the synthesis of a-aminophosphonates and their antifungal evaluation against *L. prolificans* [116]. Thus, aromatic, and heterocyclic aldehydes **623**, *para*-substituted anilines **624,** and diphenyl phosphite (**625**) were reacted together in a one-pot process using MW as a heat source without catalysts to produce the a-aminophosphonates **626** in moderate to good yields (11-85 %) (Scheme 95). It is important to highlight the eco-friendly reaction conditions that were used. Low reactivity was observed in some products probably due to the use of low activated 4-dimethylaminocinnamaldehyde, which promoted the formation of undesirable side products.



Scheme 94. Synthesis of a-aminophosphonic derivatives.

Gewald -type 3CRs

The reaction developed by Karl Gewald in 1966 has two experimental ways to be carried out. One of them is a 3-CR [117]: a) the first version (Gewald-2CR): mercaptocarbonyl reagents **628** are condensed with base-activated nitriles **627** to achieve intermediate-type mercaptonitriles **629**, which after a rearrangement/cyclization process on compounds **630**, **631** and **632** gave the 2-aminothiophenes **633** (Scheme 95a); and b) second version (Gewald-3CR): the first step consists of a Knoevenagel condensation between carbonyl compounds (aldehyde or ketone) **635** and base-activated nitriles **634** to give cyano alcohols **636**, that after a deprotonation achieved intermediates **637**, and a dehydration to furnish intermediates **638** was ensembled towards the corresponding

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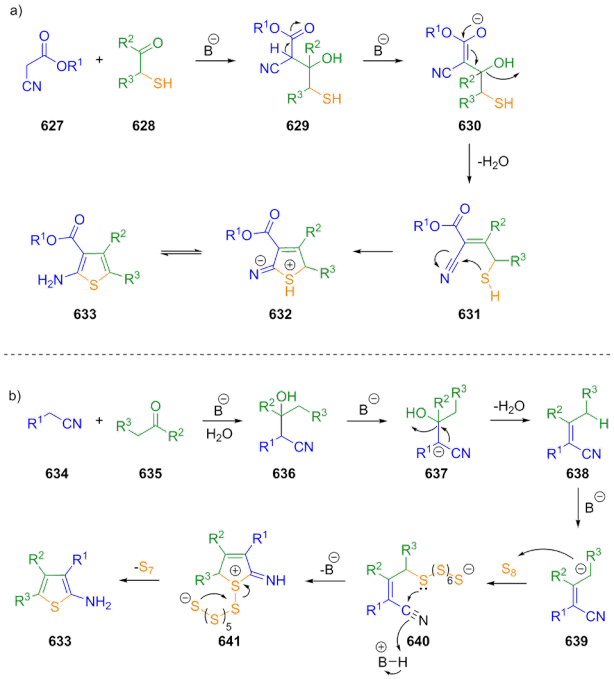
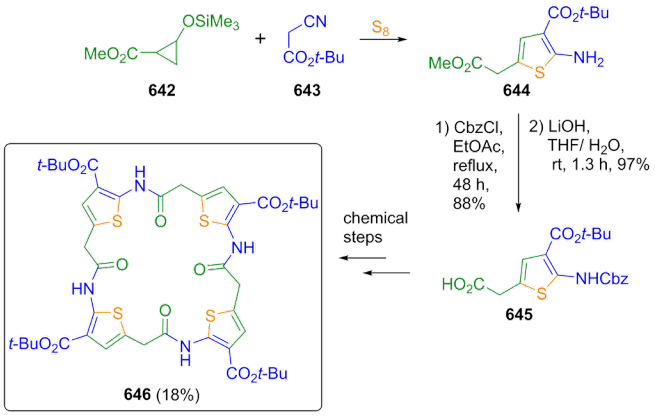
acrylonitriles **639**, which were thiolated with elemental sulfur at active methylene position to give the sulfur-containing-intermediates **640**. Finally, 2-aminothiophenes **633** were furnished through annulation promoted by intramolecular nucleophilic attack by mercaptide in precursors **641** (Scheme 95b) [118].



Scheme 95. (a) Gewald-2CR, **(b)** Gewald-3CR.

Reissig *et al.* developed a synthetic procedure to synthesize complex macrocyclic peptidomimetics containing the 5-aminothiophene moiety as the main building block [119]. For this one, it was necessary to improve a Gewald three-component reaction. Thus, after combining cyclopropanecarboxylate **642**, methylene-activated nitriles **643,** and elemental sulfur, thiophene **644** was afforded in a sequence involving a ring-opening process from compound **642** and a further condensation with nitrile **643** and elemental sulfur (Scheme 96). Amine functionalization of compound **644** furnished the product **645**, which was used as unit for construction of the peptidic macrocycle **646**. The key step in this methodology was the Gewald reaction, which allowed the incorporation of thiophene fragment into macrocycle **646**.



Scheme 96. Synthesis of macrocyclic peptidomimetics *via* aGewald-type 3CR.

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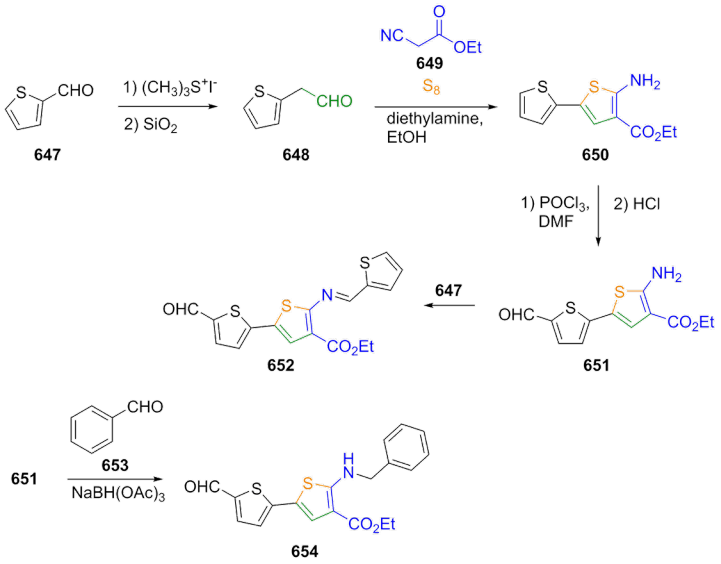
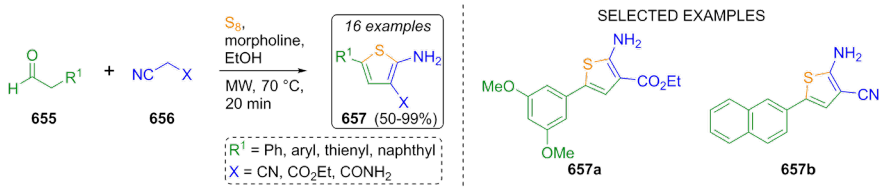
In 2011, Skene *et al.* synthesized a couple of fluorescent aminobisthiophenes *via* a Gewald reaction as second step of both synthetic procedures (Scheme 97) [120]. Starting from 2-thiophene carboxaldehyde (**647**), trimethylsulfonium iodide and SiO_2 were added to give the 2-thienylacetaldehyde (**648**), which was combined under a Gewald 3CR protocol with nitrile-ester **649** and sulfur to obtain the product **650** in 25 % yield per two steps. Compound **650** was then formylated using $POCl_3$ under Vilsmeier-Haack conditions. Then, Base *bis*-thiophene containing Schiff **652** was prepared by treatment of aldehyde **647** with *bis*-thiophene **651**. Additionally, subsequent reductive alkylation of aminobisthiophene **651** with benzaldehyde (**653**) achieved the *bis*-thiophene-containing product **654**. Gewald reaction allowed incorporating a second thiophene ring, which increases the optical activity of the whole compounds helped by the presence at the same time of electron-rich and deficient groups (*push-pull* effect).



Scheme 97. Synthesis of 2-aminobisthiophenes.

Hesse *et al.* reported a rapid and efficient procedure to prepare the new 5-aryl 2-aminothiophenes **657** *via* a Gewald reaction under microwave heating conditions (Scheme 98) [121]. Thus, aldehydes **655**, nitriles **656**, and elemental sulfur were mixed under microwave- heating conditions to achieve the products **657** in moderate to good yields (50-99 %). Also, the synthesis of **657** was performed but under conventional heating conditions, and the products were afforded in lower yields. It can be noted that microwaves as a heat source are optimal for decreasing reaction times. This approach allowed synthesizing 2,4,5-substituted thiophenes in short times and with high chemical yields.



Scheme 98. Microwave-assisted synthesis of 2-aminothiophenes.

Based on the idea that polysiloxanes are environmentally friend catalysts, Lai, Xu *et al.* worked in 2012 on a creative and green approach, in which amine-functionalyzed polysiloxanes were used as catalysts in a Gewald

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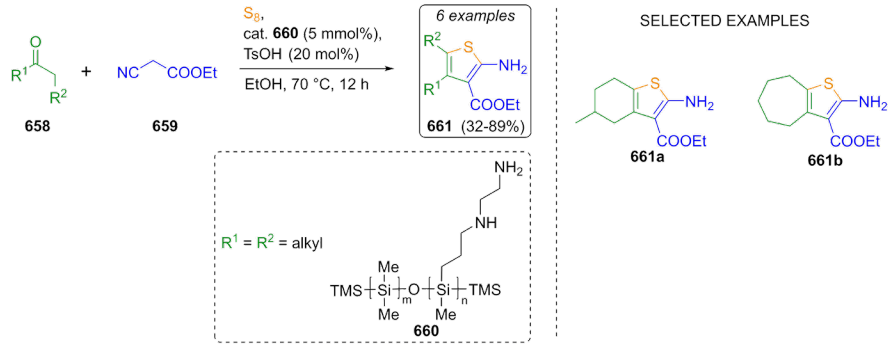
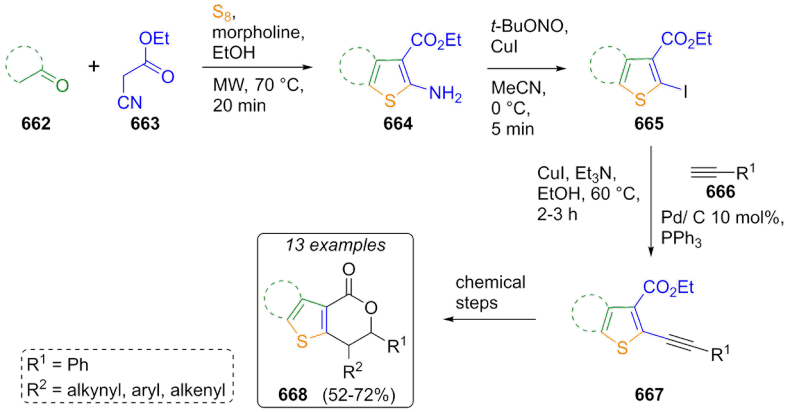
reaction (Scheme 99) [122]. Ketones **658**, methylene-activated nitrile **659**, and elemental sulfur were sequentially mixed using the amino catalyst **660** to generate the aminothiophenes **661** in moderate to good yields (32-89 %). Ketones worked well in such reaction, regardless of low reactivity mainly by stereoelectronic effects. Thus, to solve the problem that ketones afforded low yields due to their limited reactivity, catalyst **660** helped the process successfully. The size of the ketone ring influenced yields, 6-membered ring ketones afforded the best yields instead of 5 or 7 membered ketones.



Scheme 99. Amino catalyst approach.

Pal *et al.* developed a methodology to synthesize anticancer agents containing the fused-type *bis*-heterocyclic thieno[3,2-*c*]pyran-4-one core [123]. Thus, the synthesis of the 2-aminothiophenes **664** as key reagents were carried out *via* a Gewald reaction through a sequential combination of cyclic ketones **662**, ethyl cyanoacetate (**663**), and elemental sulfur. Further transformations involved Sandmeyer iodination to give compounds **665**, cyclization promoted by iodide, and various C-C couplings catalyzed by palladium-based reagents from alkynes **666** achieved the compounds **667**, and the products **668** (Scheme 100). The thiophene ring is the key fragment in this strategy because it was found in several biological active compounds. Gewald reaction allows often incorporating thiophene fragments in short reaction times and high yields.



Scheme 100. Synthesis of thieno[3,2-*c*]pyran-4-ones.

Parsa, Pal *et al.* developed a multistep methodology to prepare a series of fused-type thieno[2,3-*d*]pyrimidines **674**, that include a Gewald 3CR as the first and key step. Synthesized compounds were evaluated as inhibitors of PDE4 enzyme [124]. Thus, cyclic ketones **669**, ethyl cyanoacetate (**670**), and elemental sulfur were combined in morpholine to afford the products **671**, which performed a ring closing promoted by formamide or formimidine acetate to give the products **672**. Besides, compounds **673** were constructed by treatment of

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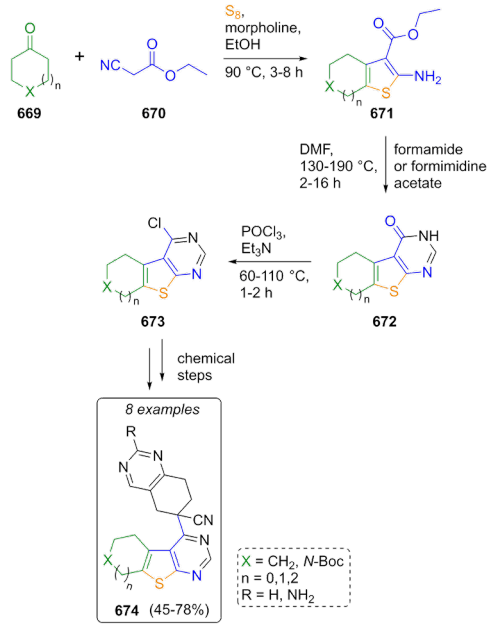
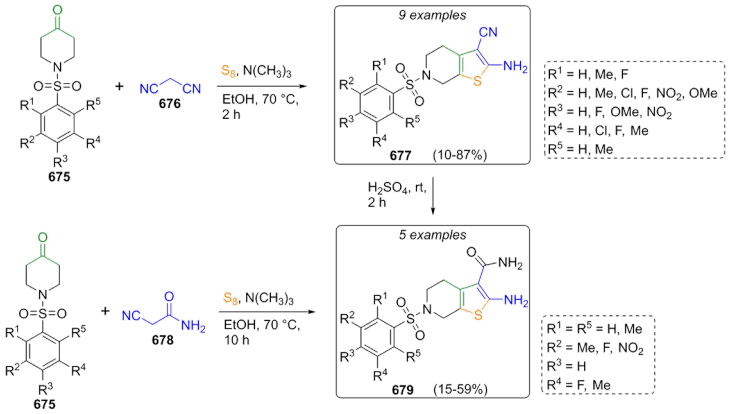
polyheterocycles **672** with stoichiometric amounts of $POCl_3$. After a few further chemical steps, it was accomplished the synthesis of the target compounds **674** (Scheme 101). As seen, Gewald reaction acts as the key step in constructing thieno[2,3-*d*]pyrimidine core, which is present in a relatively wide variety of bioactive compounds, even in some current drugs.



Scheme 101. Synthesis of thieno[2,3-*d*]pyrimidines.

Kanizsai *et al.* developed in 2019 a synthetic strategy to obtain novel β-aminonitriles, for instance the 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines **677** and **679** *via* a Gewald reaction [125]. These compounds were evaluated as antitumoral by tyrosine-kinase inhibition. Thus, piperidones **675**, malononitrile (**676**), and elemental sulfur were mixed under basic conditions to assemble the compounds **677** in moderate to good yields (10-87 %) (Scheme 102). Also, a few compounds **677** were hydrolyzed toward the formation of their amide-analogues **679** in moderate yields (15-59 %). A direct way to synthesize compounds **679** using a Gewald reaction was by combining the piperidones **675**, cyanoacetamide (**678**), and elemental sulfur. This last pathway is less efficient than the procedure in two steps. In other way, products **677** and **679** have a potential antitumoral activity due to influence of *N*-sulfonyl pharmacophoric fragment.



Scheme 102. Synthesis of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines.

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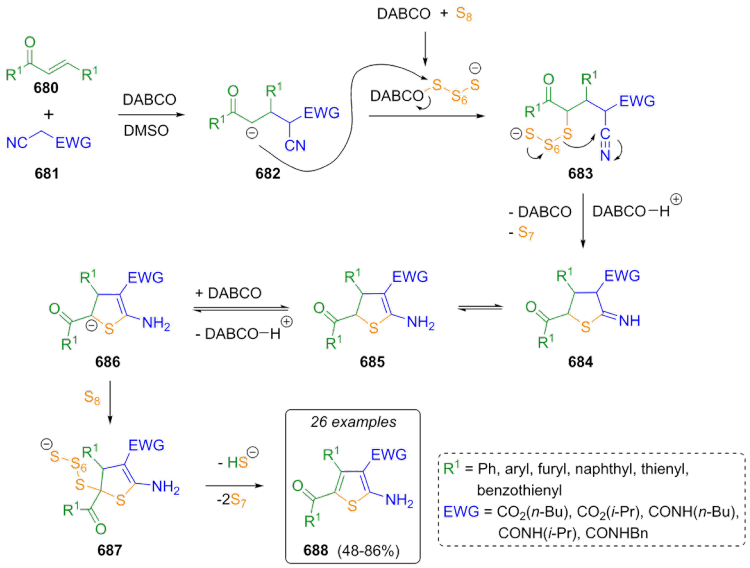
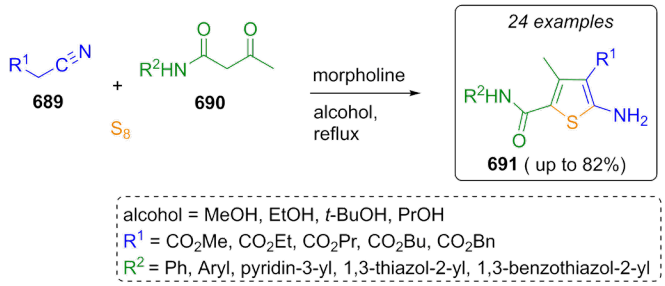
Nguyen, Mac *et al.* worked in 2021 on the synthesis of 2-aminothiophenes through a Gewald reaction [126]. Thus, α-cyanoacetates **681**, chalcones **680**, and elemental sulfur were combined under basic catalytic conditions to provide the 2-aminothiophenes **688** in moderate to good yields (48-86 %). Authors proposed a plausible mechanism where the first step was a nucleophilic attack of cyanoacetates **681** to chalcones **680** producing the anions **682** (Scheme 103). Steric hindrance inhibits Knoevenagel condensation as the first step. Then, DABCO-sulfur complex was attacked by anions **682** affording the products **683**, which were cyclized to give the tetrahydrothiophenes **684** and came into equilibrium with dihydrothiophenes **685**. Finally, an aromatization process occurs from compounds **686** and then **687** due to the presence of elemental sulfur to produce compounds **688**. The sulphuration process is favored in the *cis* intermediate due to steric hindrance. The regioselectivity was promoted by appropriate chalcones. Moreover, there are no reports about the use of cyanoacetates and chalcones as starting materials in Gewald-type processes.



Scheme 103. α-Cyanoacetates and Chalcones approach.

Yeh, Tsai, Lee *et al.* reported the synthesis of many thiophenes *via* a Gewald reaction, as well as the evaluation of synthesized compounds as Cisd2 (CDGSH iron sulfur domain 2) protein activators that cause childhood diabetes. [127]. A sequential combination of methylene-activated amides **690**, nitriles **689**, and elemental sulfur in mild reaction conditions achieved the new thiophene derivatives **691** in moderate to good yields (8-82 %) (Scheme 104). Synthesis of compounds was focused on the effect of substituents R^1 or R^2 on the activator Cisd2 to potentiate their activity. In the case of substituents R^1, bulky esters decrease the activity as well as groups like amide or nitrile. On the other way, R^2 substituents exhibited higher activity in 3 and 4-substituted phenyl rings with electron-donating groups such as methyl or methoxy, instead electron withdrawing groups that showed lower activity.



Scheme 104. 2-aminothipphenes as Cisd2 activators.

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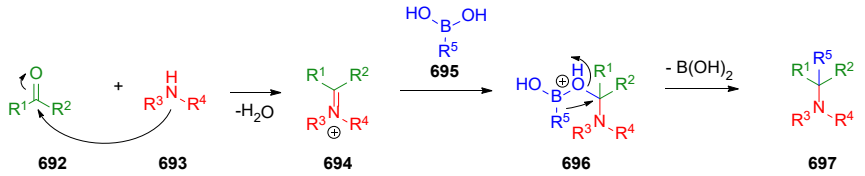
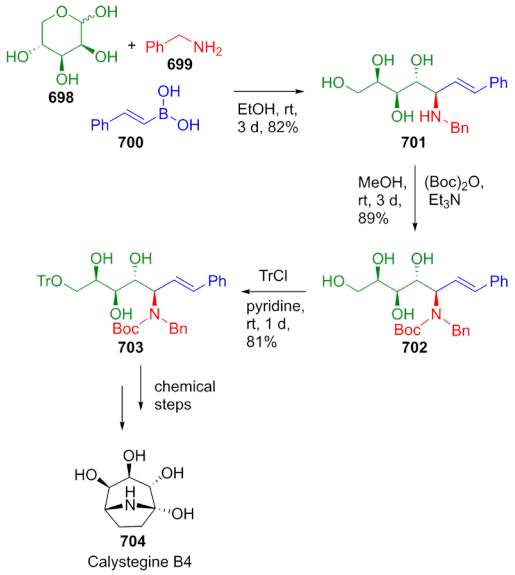
Petasis-type 3CRs

The Petasis reaction, also known as Petasis-Boron-Mannich reaction, was reported in 1993 by Nicos A. Petasis, who modified the original Mannich reaction by employing a boronic acid as a nucleophile. This three-component reaction involves a sequential combination of carbonyl derivatives with secondary amines and boronic acids. The reaction mechanism is still under discussion [128]. However, the most plausible and accepted one proceeds *via* a hemiaminal-type condensation between aldehydes or ketones **692** and secondary amines **693**. Then, iminium ions **694** react with boronic acids **695** to give the complex **696**, which through a C-C bond migration gave amine derivatives **697** (Scheme 105) [129].



Scheme 105. Petasis reaction.

Pyne *et al.* reported in 2010 a procedure that allowed the total synthesis of Calystegine B_4 using a Petasis reaction as the first key step [130]. Thus, a combination of (-)-*D*-lyxose (**698**) as a carbonylic compound, benzylamine (**699**), and boronic acid **700** afforded the product **701** in 82 % yield. Then, the amino group from compound **701** was protected using Boc to give the aminoalcohol **702**, which was treated with trityl chloride to give the advanced intermediate **703**. After seven additional transformations from this later, it was obtained the natural product **704** (Scheme 106). Notably, the Petasis reaction allowed obtaining stereoselectivity of the amino group, which could be used for further transformations.



Scheme 106. Synthesis of Calystegine B_4 *via* a Petasis-involved methodology.

Hutton *et al.* reported a creative process to synthesize g,b-dihydroxyhomotyrosines through a Petasis reaction as one of keys steps [131]. Thus, glyoxylic acid (**705**) as carbonylic component, sulfinamide **706**, and boronic acids **707** were combined to afford products **708** in good to excellent yields (90-99 %) and good

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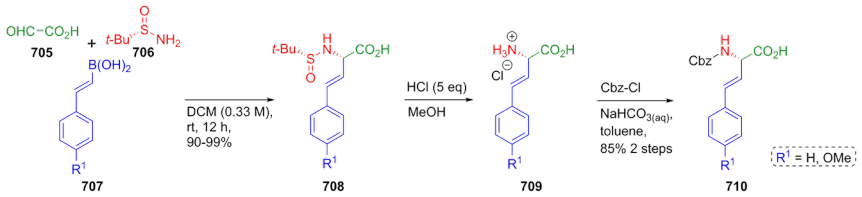
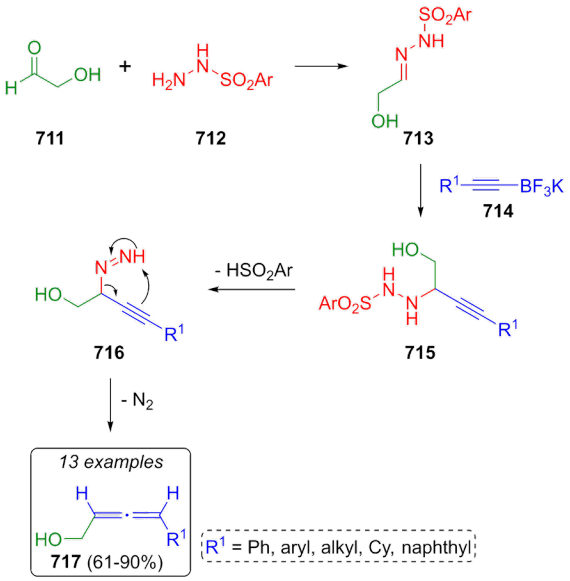
diastereoselectivity. Then, compounds **708** were treated in concentrated acid media to give ammonium salts **709**. Then, authors protected amino position to further transformations and completed preparation of dihydroxyhomotyrosine derivatives **710** (Scheme 107). As seen, the use of *tert*-butylsulfinamide in the Petasis reaction facilitated the incorporation of protective groups on the amine moiety. The olefin fragment was compatible with all conditions throughout the process, so it could be used for further transformations.



Scheme 107. Synthesis of γ,b-dihydroxyaminoacid derivatives.

Thomson *et al.* reported an interesting methodology to provide allenes *via* a traceless Petasis reaction [132]. The reaction mechanism suggests that the first step is the formation of hydrazones **713** through the combination of sulfonylhydrazides **712** and glycoaldehyde (**711**). Then, the addition of alkynyl trifluoroborate salts **714** to hydrazones **713** gave propargyl hydrazides **715**, which releases sulfinic acid to give diazines **716**. Finally, loss of nitrogen molecule provided allenes **717** in moderate to good yields (61-90 %) (Scheme 108). Best yields were afforded under Lewis acid catalyst La(OTf)$_3$ and acetonitrile as solvent. Alkyne was used as an activator of borate because the reaction does not work well with aldehydes that do not contain an α-hydroxyl group. This process may be considered as a reaction that did not follow the expected Petasis mechanism.



Scheme 108. Traceless Petasis reaction towards allenes.

Shaw, Ghosal *et al.* reported in 2012 a creative methodology involving a diastereoselective Petasis reaction [133] from the carbohydrate galactose (**718**). Thus, iodide **719** was treated with Zn and Vitamin B12 in catalytic amounts to generate hemiacetal **720**, which was combined in a one-pot process with *trans*-2-phenylvinyl boronic acid (**721**) and *tert*-butylamine to furnish the chiral alcohol **722**, which after several chemical steps afforded the natural product (+)-Conduramine E (**723**) (Scheme 109). Petasis reaction was the key step to achieve in a diastereoselective way the key alcohol **722,** as well as for reducing the number of synthesis steps.

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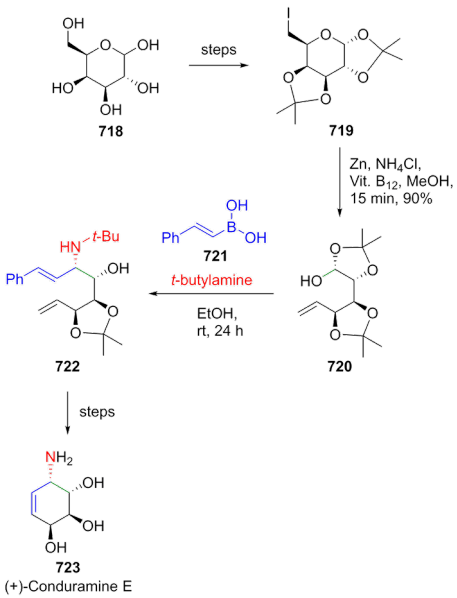
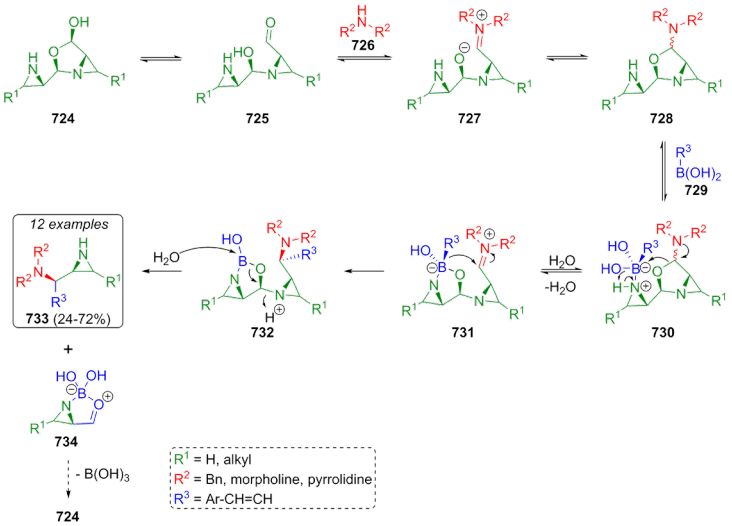


Scheme 109. Synthesis of (+)-Conduramine E.

Yudin *et al.* reported a different approach to obtain aziridine-containing diamines *via* a Petasis-type reaction [134]. The mechanism proposed involves ring-openings in the substrates **724** toward aldehydes **725** as the first step. The addition of secondary amines **726** to aldehydes **725** in tautomeric equilibria with intermediates **727** promotes amine adducts **728**, which in the presence of boronic acids **729** gave the hemiaminals **730**. Thus, aqueous media afforded chelates **731**. *Si* face attack is preferred over *Re* one to give the intermediates **732**, which are hydrolyzed to yield products **733** in up to 72 %. Finally, a dimerization of the released compounds **734** may occur to recover the initial reagents **724** after losing an equivalent of boronic acid(Scheme 110). Products were synthesized in excellent diastereoselectivity (up to 95:5 ee). Through Petasis reaction, the key chelated intermediate **732** was assembled, which contributes in a high stereoselective way to form the *syn* products. On the other hand, the efficiency of the reaction depends on the halogenated solvent and the nucleophile used.



Scheme 110. Synthesis of aziridine-containing diamines.

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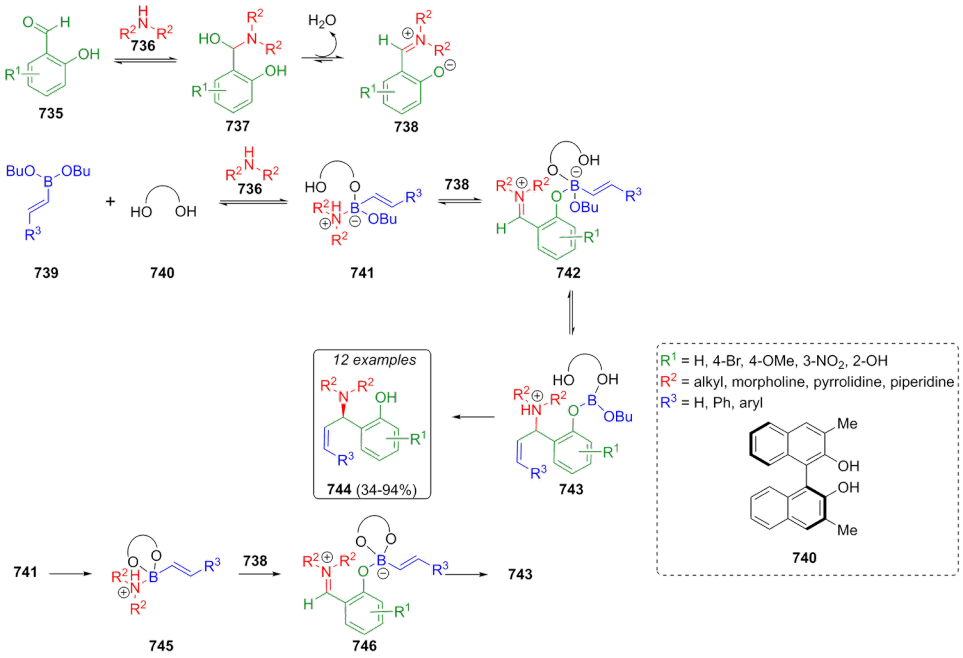
Around 2013, Shi *et al.* reported a version of the Petasis reaction in which salicylaldehydes **735**, secondary amines **736**, and vinylboronates **739** are combined sequentially under organocatalytic conditions to obtain the corresponding Petasis products in moderate to good yields (34-94 %) and in excellent enantioselectivity [135]. A plausible reaction mechanism suggests an initial formation of iminium ions **738** by condensation of salicylaldehydes **735** and amines **736**. Besides, boronates **739** react with diols **740** and amines **736** under catalysis conditions to produce intermediates **741** in equilibria with **742**, which were treated with preformed iminium ions **738** to afford the intermediates **743**, which migrates a vinyl group after hydrolysis to finally obtain products **744** (Scheme 111). Another pathway in the formation of intermediates **746** was carried out through precursors **745** and iminium ions **738**, which could be promoted by triethylamine in reaction media. Also, vinylboronates promote higher yields instead of other types of boronates such as dioxaborolanes or dioxaborinanes.



Scheme 111. Catalytic asymmetric version of Petasis reaction from vinylboronates.

Seeberger *et al.* developed the total synthesis of legionaminic acid **754** using a stepwise methodology in which a Petasis reaction was the key step [136]. Synthetic procedure starts from *D*-threonine (**747**) (Scheme 112). After corresponding chemical transformations, diester **748** was treated with lithium borohydride to give the diol **749**. Oxidation of compound **749** provided the less hindered aldehyde **750** as a reagent for Petasis reaction. Thus, a combination of aldehyde **750**, amines **752**, and styrylboronic acid (**751**) in ethanol afforded products **753** in 76 % yield as a diastereomeric mixture. All procedure was accomplished in eleven steps. Petasis reaction allowed obtaining products with good stereoselectivity, avoiding epimerization processes.

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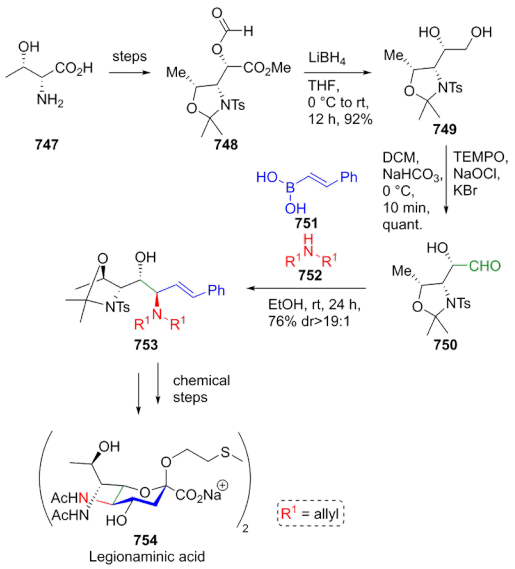
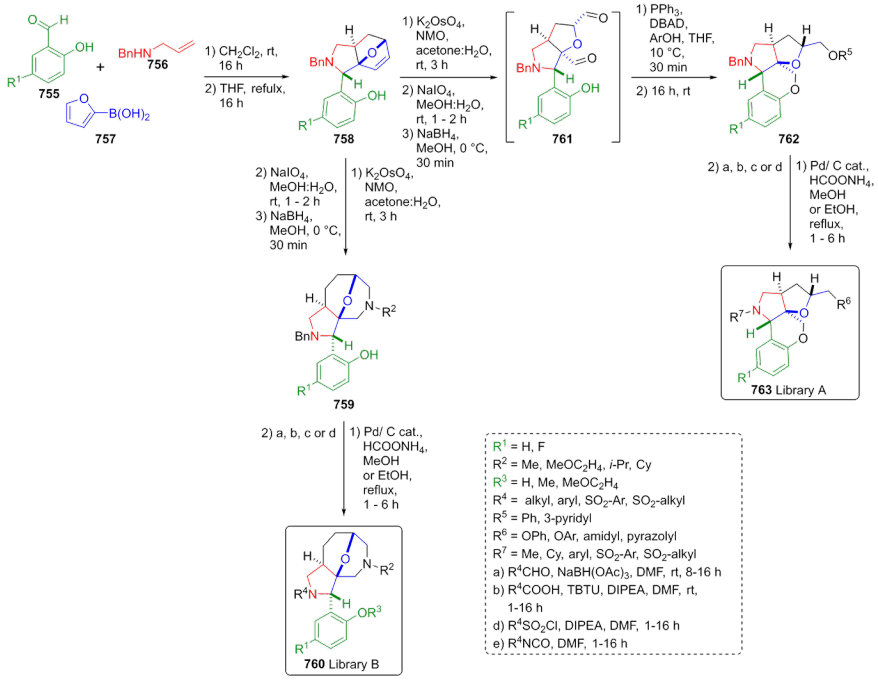


Scheme 112. Synthesis of Legionaminic acid.

Clausen, Nielsen *et al.* reported a Petasis-based strategy to develop new scaffolds containing four stereogenic centers [137]. Thus, salicylic aldehydes **755**, benzyl allyl amine (**756**), and furan-2-boronic acid (**757**) were reacted together to give the products **758** after a domino process Petasis / Diels-Alder cycloaddition. Then, cyclic compounds **758** were oxidized using K_2OsO_4 and methylmorpholine oxide affording the intermediate s**759**. Finally, products **760** (library B) were synthesized through a reductive cyclization promoted by osmium salt, NMO, and sodium periodate. Moreover, Library A was afforded after reduction of intermediates **761** coupled to cascade Mitsunobu conditions from precursors **762** (Scheme 113).



Scheme 113. Sp^3-rich approach.

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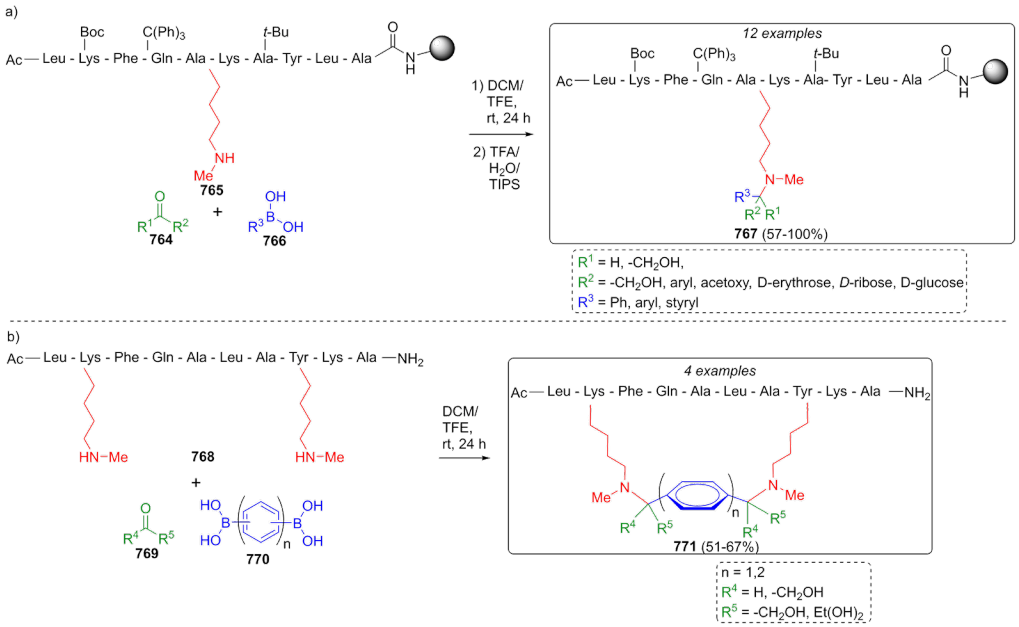
Wesjohann, Rivera *et al.* developed for the first time a synthetic procedure for labeling and stapling peptides *via* a new Petasis-type reaction without charge modifications [138]. The peptide chain was modified by protecting amino groups and linking an amino-end chain to lysine. Thus, the peptidic chain in polypeptide substrates **765** was reacted with aldehydes or ketones **764** and boronic acids **766** to afford peptide labeled on lysine side chain **767** (Scheme 114**(a)**). In the same way, a diversification of resin peptide was performed changing sugars such as *D*-erythrose or *D*-ribose, fluorescent peptides, or steroidal peptides instead of aldehydes. A Petasis-stapled reaction was carried out mixing resin-peptide **768**, carbonylic compounds **764** or **769,** and diboronic acids **770** to give peptides **771** (Scheme 114**(b)**). Due to polypeptide size, the authors carried out the MCR in two stages, to avoid a second Petasis reaction.



Scheme 114. Labeling and stapling of peptides approach.

Zhang, Yang *et al.* reported a distinct procedure to obtain functionalized dihydropyrones *via* a regioselective Petasis reaction [139]. It proposed a mechanism pathway where iminium ions **775** were formed through condensation of glyoxylic acid (**772**) as a carbonyl compound and secondary amines **773** (Scheme 115). Oxaborols **776** were coordinated with carboxylates of **775** to achieve the intermediates **777**. A further intramolecular nucleophilic attack of the vinyl moiety to iminium furnished intermediates **778**, which after releasing a molecule of water achieved products **779** (78-98 %). Finally, thermal isomerization gave the products **780** in moderate to good yields (45-98 %). The authors found that its methodology cannot be applied using anilines as reagents as well as alkylic chains as substituents on the R^3 position. Final isomerization processes are promoted by increasing temperature up to eighty Celsius degrees.

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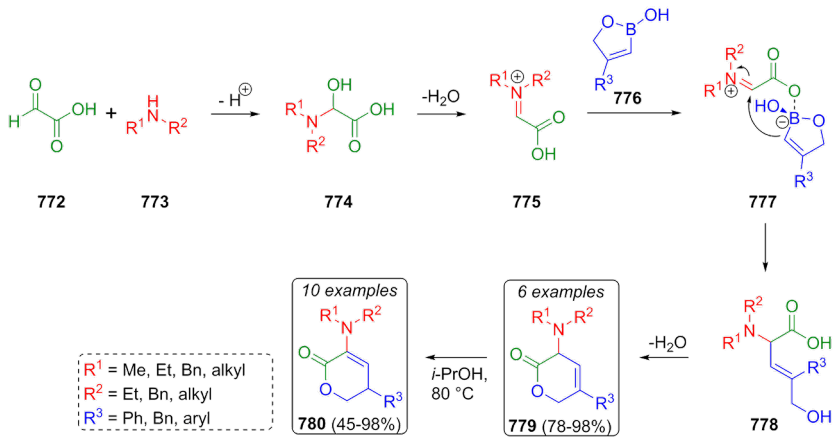
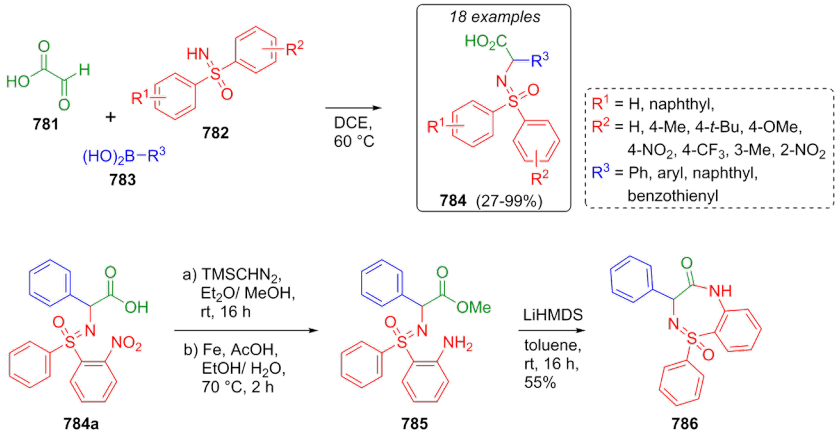


Scheme 115. Regioselective synthesis of functionalized dihydropyrones.

Bolm *et al.* reported in 2021 another approach to synthesize benzodiazepine analogues using a Petasis reaction under catalyst-free conditions as the key step [140]. With optimal reaction parameters in hand, glyoxylic acid (**781**), sulfoximines **782,** and aryl boronic acids **783** were mixed without catalysis to afford products **784** in moderate to excellent yields (27-99 %) and diastereomeric ratio up to 1:1. Thus, product **784a** was selected to perform further transformations involving esterification of its acid moiety assisted by trimethylsilyl diazomethane, and a further nitro reduction with iron in dust and acetic acid to give the precursor **785**. Finally, its amidation with lithium hexamethyldisilazane promoted a ring closure to give corresponding benzothiadiazepine **786** in 55 % overall yield (Scheme 116). The authors noted that steric hindrance has no effects on the yields, except for *S*-alkyl substituent from sulfoximines. On the other way, electronic effects decrease the yields in alkyl-substituted *S*-aryl of sulfoximines.



Scheme 116. Efficient synthesis of benzodiazepine sulfoximines analogues.

Povarov-type 3CRs

In 1967, L. S. Povarov reported the first reaction which involved a sequential combination of aromatic imines and alkenes reacting through an inverse electron demand Diels-Alder [4+2]-cycloaddition [141]. Later, this reaction was retaken and discussed into a 3-CR between aldehydes, amines, and olefins. The mechanism

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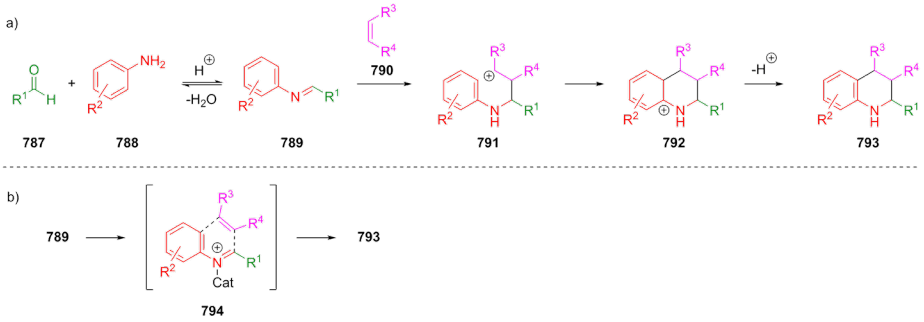
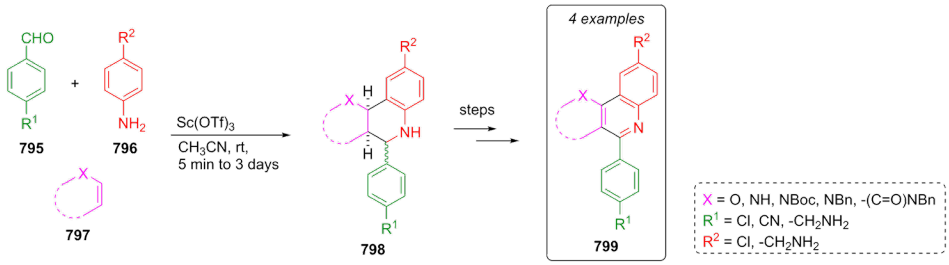
pathway is still under discussion, as the first step is a condensation between aldehydes **787** and amines **788** to give corresponding imines **789** in catalytic conditions. Then, two routes have been proposed (Scheme 117): a) *via* a Mannich addition to alkenes **790** to achieve the intermediates **791**, followed by Friedel-Crafts alkylation, and finally an aromatization step to produce the compounds **793**; and b) same route Mannich addition and Friedel-Crafts alkylation were carried out to construct the concerted intermediates **794**, which react through a cycloaddition-type reaction to give the products **793** [142].



Scheme 117. Povarov reaction.

In 2015, Muñoz-Torrero *et al*. reported the synthesis of quinoline-derivatives using a Povarov reaction as a first key step synthesis and their biological evaluation against protozoan parasites *T. brucei*, *T. cruzi*, and *L. infantum* [143]. The synthetic strategy of the more active compounds begins with a Povarov reaction between corresponding aldehydes **795** and amines **796**; in the case of the olefinic compounds **797**, lactams, enamines, or pyrans were used. Further transformations such as oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) reagent, protection/deprotection processes, and reduction of nitriles or lactams were carried out in each sequence (Scheme 118). To improve the activity of the compounds as well as higher bioavailability, the authors proposed a bioisosteric replacement of NH to O or the incorporation of heterocyclic rings instead of cyclic amide.



Scheme 118. Synthesis of tricyclic heterofused quinolines.

Menichetti *et al*. reported in 2019 the synthesis of heterohelicenes *via* the Povarov-oxidation process through a one-pot manner [144]. A combination of benzaldehyde (**800**), naphthylamines **804** or anilines **801** and **805** , and as cyclic aromatic dienophiles, alkenes or chromenes **806**, **807**, and **808** respectively afforded the products **803** or **809**, under different reaction conditions. Reaction conditions a) it was carried out using boron trifluoride ethyl etherate as a catalyst to achieve a diastereomeric mixture *cis*/ *trans* of tetrahydroquinoline **803** in moderate yield. Then, under reaction conditions b) scandium triflate or ytterbium triflate were used as catalysts in different amounts, magnesium sulfate as an additive, and DDQ as an oxidative reagent to achieve the compounds **809** in moderate to good yields (34-75 %) (Scheme 119). The authors proposed that involved imines act as dienes to afford the compound **803** (depending on the amount of amine) but also participates into oxidations to give compounds **809**. Naphthylamine directs towards products **809** regioselectively due to a-carbon or b-carbon that participates in cyclizations.

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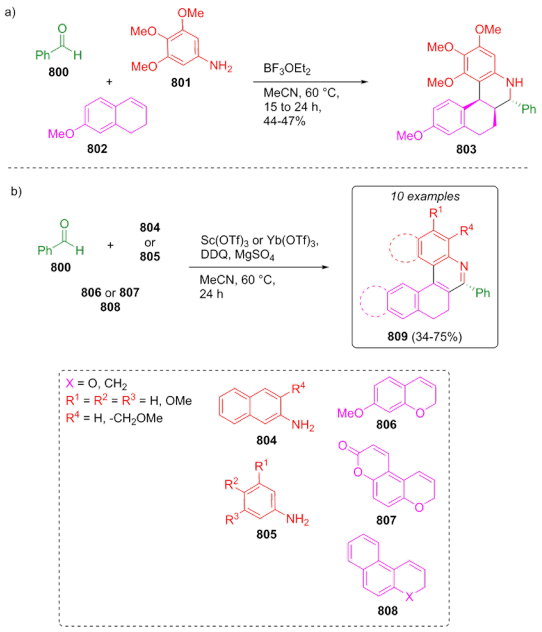
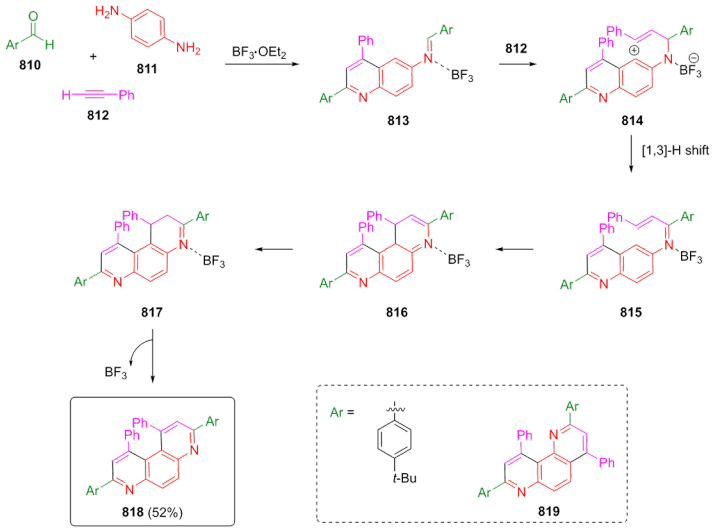


Scheme 119. Synthesis of azaoxahetero helical-shaped compounds.

Kuwabara *et al*. reported in 2021 the synthesis of some new triazatriphenylenes *via* a double Povarov reaction [145]. Aromatic aldehydes **810**, dianiline **811**, and phenylacetylene (**812**) were sequentially combined under Boron trifluoride etherate as a catalyst, and DQQ as an oxidative reagent to afford a mixture of products **818** and **819**, being 4,7-phenanthroline derivative **818** the majoritarian product (52 %). Authors proposed a mechanism pathway where the first step is the Povarov cyclization under a Lewis catalyst to give the compound **813**. Then, the addition of acetylene **812** achieved zwitterionic compounds **814**, which through [1,3]-H shift afforded the compounds **815**. Compounds **818** were obtained after a ring closure, prototropic tautomerization, and oxidation (Scheme 120). To know about the second cyclization, DFT studies were performed and showed that in compound **815** there is a HOMO charge distribution in the a-position of the quinoline core that favored the cyclization. Also, steric repulsion from the phenyl neighboring fragment did not interfere with the cyclization process.



Scheme 120. Synthesis of 4,7-phenanthrolines.

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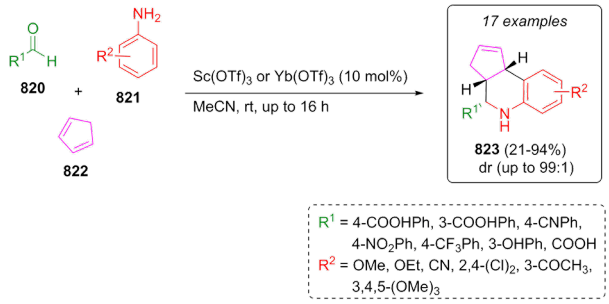
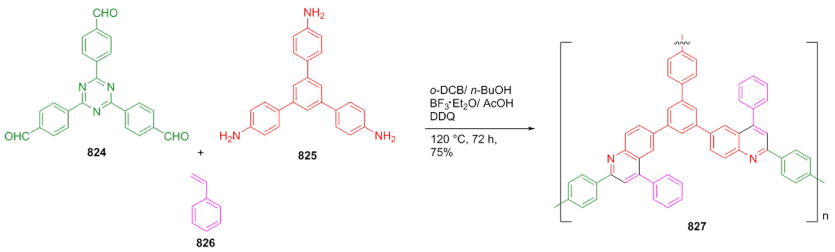
Wu *et al.* reported the synthesis of various new tetrahydroquinolines in 2022 which were evaluated behind their interactions with micro RNA-binding protein LIN28 and let-7 micro RNAs, both related to human tumor cells. After finding optimal conditions, a combination between aromatic and non-aromatic aldehydes **820**, anilines **821**, and cyclopentadiene (**822**) using scandium triflate or ytterbium triflate as catalysts achieved tetrahydroquinolines **823** in moderate to good yields (21-94 %) and diastereomeric ratio (up to 99:1). Based on the stereoelectronic properties of the anilines **821**, mixtures of *cis*/ *trans* products or *syn* products as major diastereomers were obtained. Authors were inspired for this work in the compound LI71, which was previously reported [146]. The goal of synthesizing these molecules is to have greater interactions with the non-coding RNA molecules LIN28 and let-7.



Scheme 121. Synthesis of tricyclic tetrahydroquinolines.

Thomas *et al.* reported in 2024 the synthesis of a covalent organic framework (COF) *via* a Povarov reaction [147]. Sequential combination of aldehyde **824**, aniline **825**, and styrene (**826**) afforded the COF **827** under Lewis acid catalysis and DQQ as oxidant in good yield (75 %) (Scheme 122). COF **827** exhibited stability under strong acids and bases. Povarov reaction allowed affording a complex product in one step. Also, the porous and crystalline rearrangement was favored due to Povarov reaction being performed after the oxidation process resulted in a π-π stacking interactions of extended frameworks.



Scheme 122. Synthesis of a new COF *via* Povarov reaction.

Miscellaneous

Unnamed 3CRs

Katsumura *et al.* reported the first asymmetric total synthesis of (-)-Hippodamine by an unclassified three-component reaction as the first step [148]. Thus, after optimal conditions were found, a sequential combination of aminoalcohol **828**, ester **829**, and vinylstannane **831** under palladium catalyst achieved the product **834** in 81 % yield as single diastereoisomer (Scheme 123). It is proposed a mechanism pathway where reagent **828** in the presence of ester **829** allowed the formation of compound **830**. Then, an addition of stannane **831** occurred to promote further aza-electrocyclization to give compound **833**. Further sequential transformations such as hydrogenations, alkylations, and intramolecular Mannich reactions completed the synthetic methodology toward the natural product **837**.

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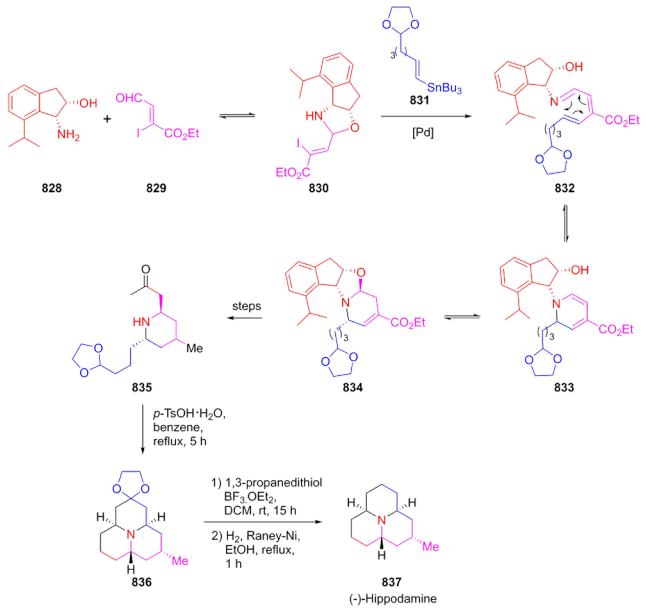
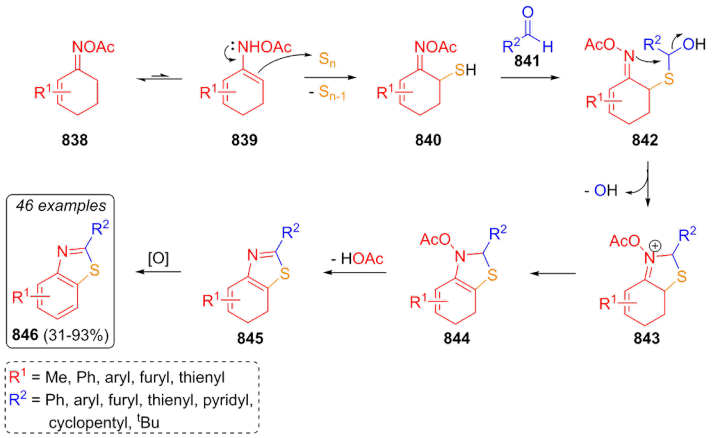


Scheme 123. Asymmetric total synthesis of (-)-Hippodamine.

In 2019, Huang, Deng *et al.* developed a synthetic route to obtain naphthothiazoles **846** *via* a three-component reaction under catalyst and additive-free conditions [149]. A plausible reaction mechanism was proposed, where tautomerization of cyclohexenone oximes **838** provided the enamines **839** (Scheme 124). Then, elemental sulfur was attacked probably *via* a Willgerodt–Kindler process by compounds **839** to give the intermediates **840**, which were annulated after the addition of aldehydes **841** to give intermediates **844**. After releasing water and acetic acid, the intermediates **845** were obtained. Finally, it was oxidized with sulfur present in the medium affording the products **846** in moderate to good yields (31-93 %).



Scheme 124. Synthesis of naphthothiazoles.

In 2019, Lomas-Romero, Gonzalez-Zamora, Islas-Jacome *et al.* developed a procedure to synthesize a few symmetrical tetrazoles **849** through a non-named 3CR involving a heterocyclization as a key step [150]. Thus, a sequential combination of anilines **847**, trimethyl orthoformate (**848**), and sodium azide gave the products **849** in moderate to good yields (30-83 %). The plausible reaction mechanism starts with the formation

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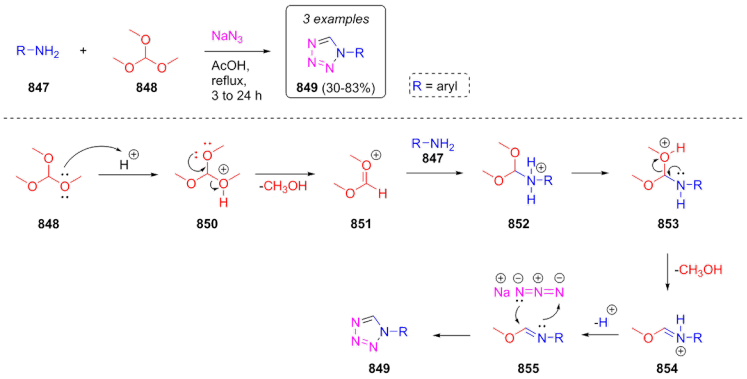
of activated carbonyl intermediate **851** from trimethyl orthoformate (**848**) (Scheme 125). This latter reacts with the amines **847** *via* a condensation reaction to give the dipoles **854** after releasing a molecule of methanol. Then, these later intermediates carry out a dipolar cycloaddition with azide anion to assemble the symmetrical tetrazoles **849**. These compounds are potential linkers to fabricate tetrazole-based MOF-type materials. Tetrazole as a functional group is considered an isostere of carboxylic acid. In this context, tetrazole-based ligands have some advantages over carboxylate-based MOFs, like enhanced resistance to harsh conditions like higher temperatures, a wide range of pH, and a higher degree of humidity.



Scheme 125. Synthesis of *bis* tetrazoles.

Computational calculations on 3CRs

Over time, it is commonly found collaborations between experimental and theoretical chemists behind searching mechanism pathways. This one provides greater robustness to the work reported. In this subsection, we discuss some works describing energy profiles through computational studies.

One of the most controversial MCRs without using isocyanide is the Biginelli reaction, whose mechanism is still under discussion. In 2015, Morokuma *et al.* reported mechanistic studies about the most favorable pathway in the Biginelli reaction between benzaldehyde, urea, and ethyl acetoacetate [151]. It is necessary to mention that urea performed a double function as a reactant and catalyst. The three routes of Biginelli mechanism (iminium, enamine, and Knoevenagel pathways) were evaluated under artificial force-induced reaction method computed using DFT formalisms at M06-2X/6-31+G(d) level of theory, in ethanol as the best solvent, Fig. 1.

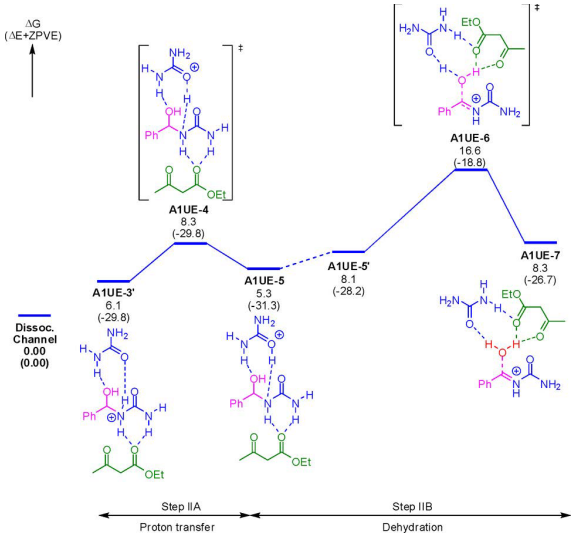


Fig. 1. Revised mechanism of the Biginelli reaction determined by the artificial force-induced reaction method. Reproduced from ref 150. Copyright 2015 American Chemical Society.

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In Mannich-type reactions (previously discussed) [60], a combination of dienediolates and imines follows a pathway giving stable intermediates produced after a Pictet−Spengler-type cyclization. A nice energy profile was computed by Schneider *et al.* through DFT formalism using M06-D3/LACVP**/PBF method including London dispersion interactions using acetonitrile as the best solvent, Fig. 2.

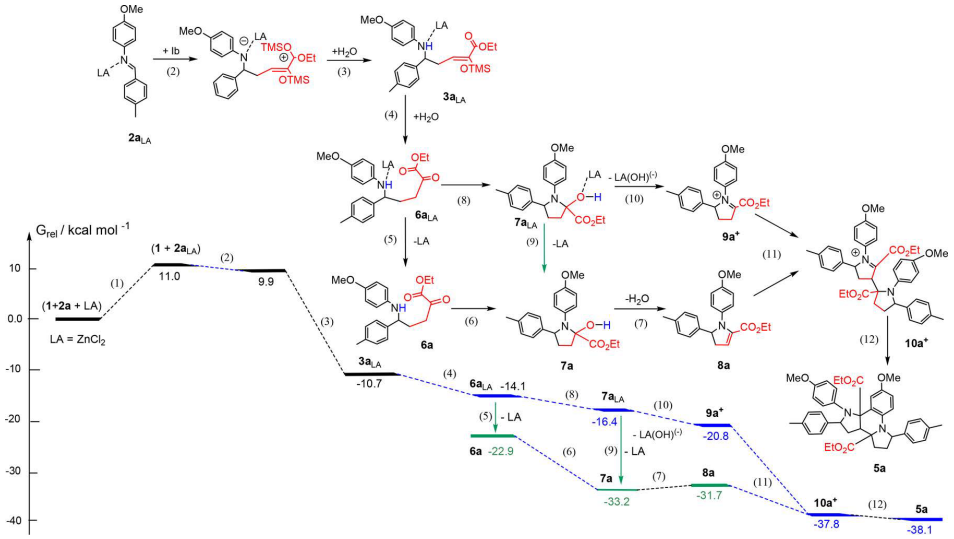

Fig. 2. Energy profile for dipyrroloquinoline synthesis. Reproduced from ref 60. Copyright 2018 American Chemical Society

Conclusions and outlook

Every year several examples of multicomponent reactions without using isocyanides are published, mostly emphasized in "most popular" three-component reactions like Strecker, Biginelli, or Mannich. However, in the last ten years, many other examples “less common” like Petasis, Reissert, Ritter, Gewald, Povarov, Bucherer-Bergs, Willgerodt-Kindler or Kabachnik-Fields have gained their importance in various fields of science and technology. Thus, the present comprehensive review is focused on medicinal applications, total synthesis, green conditions, and novel mechanisms (or variants) proposed, directed towards experts and those who are not specialized in multicomponent reactions, but from different areas of chemistry.

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