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Review

Recent Synthetic Developments of Asymmetric Multicomponent Transformations: Strecker, Mannich, Passerini and Ugi Reactions

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Multicomponent reactions (MCRs) are important transformations, which allow the attainment of structurally complex derivatives in a single step, starting from three or more compounds with relatively simple structures. These reactions are generally associated with the principles of green chemistry, allowing the incorporation of most (or all) atoms of the starting materials in the products (atom economy) and reducing purification steps (and, consequently, the need for solvents and waste production). For a long time, asymmetric methodologies (in special enantioselective protocols) for most multicomponent transformations remained a gap in the literature, limiting the use of these reactions to produce derivatives only as racemates or in low diastereoselectivities. Over the last two decades, a better comprehension of the mechanisms associated with these transformations allowed the development of efficient enantio- and diastereoselective procedures, attracting the interest of both academia and industry. In this review, selected examples of four important multicomponent reactions (Strecker, Mannich, Passerini and Ugi) will be discussed, presenting a general overview of the development of this field and pointing out possible advantages and limitations of the above mentioned methodologies. In some cases, discussions around mechanisms, proposed transition states and activation modes will be detailed disclosed.

Keywords: Strecker, Mannich, Ugi, Passerini, asymmetric synthesis, multicomponent

1. Introduction

Multicomponent reactions are an important class of transformations in organic synthesis, providing access in a single step to structurally complex compounds from relatively simple substrates.[1-3] These reactions consist of one-pot procedures in which three (or more) reagents are added at the beginning of the reaction and, through sequential reaction steps in which no isolation or separation of intermediates are carried out, affording a product in which most (or all) of the atoms of the starting materials are incorporated, with little or no formation of side-products.[4] These transformations are of great interest to the industry, due to the possibility of obtaining target molecules in a single step, and to combinatorial chemistry, allowing the rapid preparation of libraries of small compounds which are important for biological purposes, considering structure-activity studies.[4,5]

Since three or more components are simultaneously present in the reaction mixture, the mechanism associated with these transformations is generally complex and, in some cases, more than one mechanism can simultaneously occur.[6,7] This makes the development of asymmetric (enantio- and/or diastereoselective) protocols particularly challenging.[8] Recently, studies concerning the stereoselective preparation of multicomponent derivatives have attracted the interest of several research groups, allowing a rapid advent of this area. Figure 1 shows a general overview of this area, revealing a considerable growth of publications covering this topic in the last two decades.

In this review, a general overview of asymmetric methods involving the Strecker, Mannich, Passerini and Ugi multicomponent reactions will be disclosed. In some cases, two-component protocols (e.g., using pre-formed imines) will also be disclosed to provide a general overview of the development of asymmetric methodologies for these

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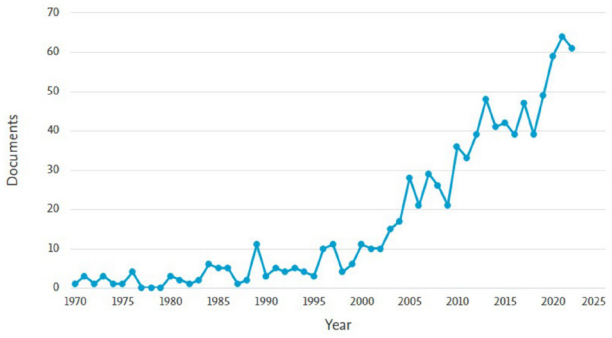
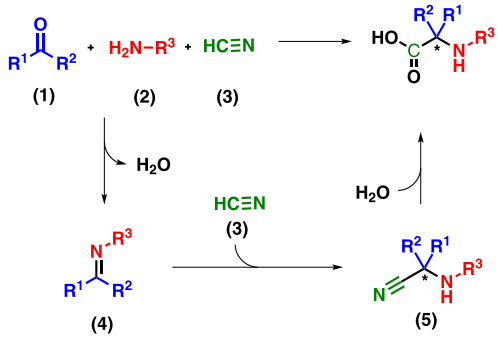


Figure 1. Published documents involving the terms "multicomponent" and "asymmetric" since 1970 (source Scopus database, accessed on March 06, 2023).



Scheme 1. The Strecker reaction.

reactions. In the case of enantioselective protocols, the possibility of the use of different catalytic systems (e.g., transition metal catalysis and/or organocatalysis) will be detailed, pointing out some representative substrate coverage, discussions around mechanisms, activation modes and proposed transition states.

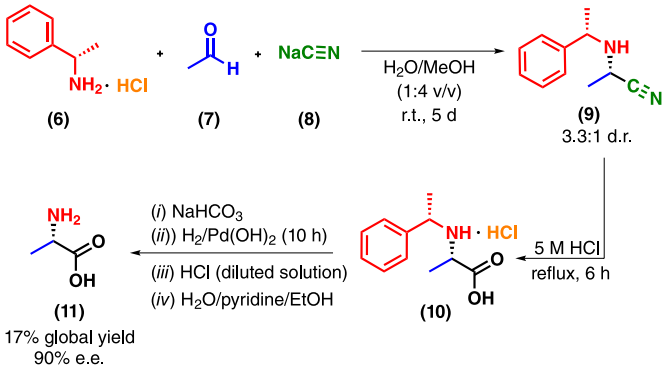
2. Strecker Reaction

The first multicomponent reaction was described by Adolph Strecker in 1850, and received the name Strecker reaction (Scheme 1).[9] The original transformation involved the formation of racemic alanine from the three-component reaction between acetaldehyde, ammonia, and hydrogen cyanide.[9] The substrate scope was further evaluated, allowing the use of a carbonyl compound (**1**) (e.g., ketone or aldehyde), amines (**2**), and a cyanide source (**3**) (e.g., hydrogen cyanide or cyanide salts). The most accepted mechanism for this reaction involves the condensation of amines with the carbonyl compound, affording the imine intermediate (**4**), followed by the addition of cyanide, leading to the α-aminonitrile (**5**).[10] The desired amino acid product is then accessed through hydrolysis of the nitrile function.[11,12]

Considering that this three-step multicomponent transformation leads to the formation of natural and non-natural amino acid derivatives, the development of an asymmetric method for the Strecker reaction remained for a long time as a goal for many research groups.

More than a century after the original study, Harada described in 1963 the synthesis of L-alanine using a diastereoselective Strecker reaction (Scheme 2).[13] The synthetic strategy consisted of the use of the chiral amine D-(−)-α-methylbenzylamine (**6**) (which was used as the chiral auxiliary in both forms the corresponding base free and as its hydrochloride), acetaldehyde (**7**) and sodium cyanide (**8**), affording (*S*)-2-(((*S*)-1-phenylethyl)amino) propanenitrile (**9**). The α-aminonitrile (**9**) was obtained with a low diastereoselectivity (diastereomeric ratio of only 3.3:1) after five days of reaction.[14] Next, sequential steps involving hydrolysis of the nitrile to afford (**10**), selective precipitation and hydrogenolysis of the chiral auxiliary led to chiral L-alanine (**11**) with a global yield of 17% and an enantiomeric excess (e.e.) of 90%. Despite the low global yield and modest diastereoselectivity in the forming stereogenic center step, this work has been guided the development of other important asymmetric procedures for the Strecker reaction.

Since then, several protocols using α-phenylamines as chiral inducers have been described. For example, the diastereomeric synthesis of Streker adducts using substituted ketones (**12**), sodium cyanide (**13**) and the chiral



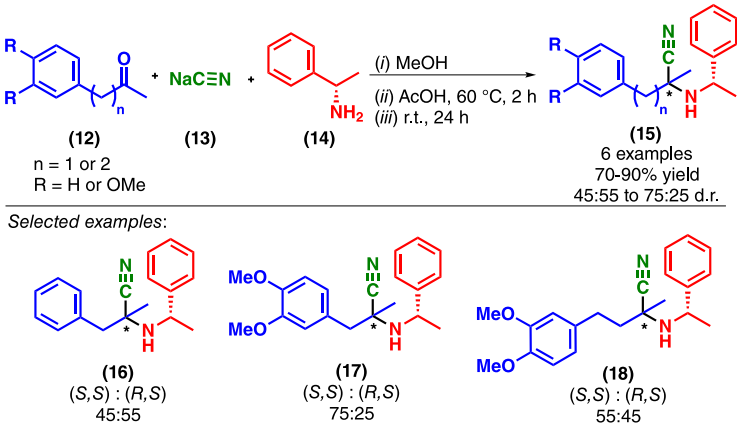
Scheme 2. L-Alanine synthesis through a Strecker diastereoisomeric reaction.

amine (**14**) has been presented by Schrank and co-workers[15] (Scheme 3). Interestingly, the obtained product using ketones bearing non-substituted aryl rings afforded the *S*,*R* diastereomer as the major product (55:45 diastereoisomeric ratio (d.r.)), while the presence of methoxy substituents caused an inversion of selectivity (*S*,*R*:*S*,*S* ratio of up to 25:75). The reaction scope was very limited (only 6 examples) and only a few modifications of the ketone component were presented.

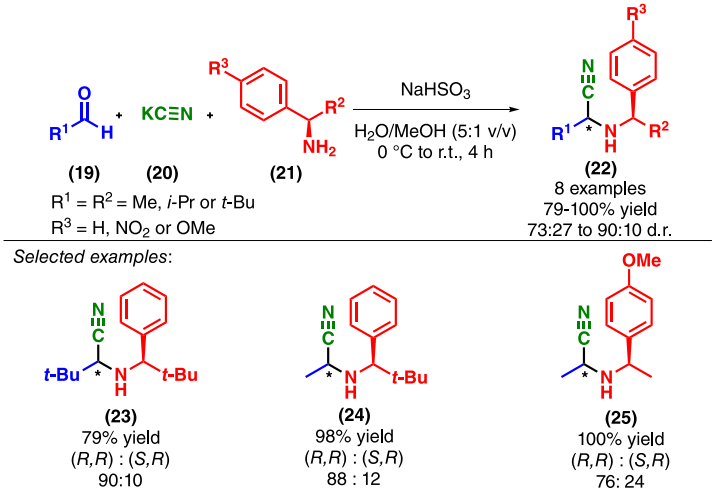
Further development of this area has been reported by Inaba *et al*.,[16] which have described the use of bulkier chiral amines (**21**) as a strategy towards the synthesis of α-amino nitriles (**22**) with diastereomeric ratio of up to 90:10 and yields ranging from 79 to 100% (Scheme 4).[16] The use of steric hindered amines led to the best overall results (e.g., the higher d.r. of derivatives (**23**) and (**24**) in comparison with (**25**)). The authors claimed that a thermodynamic control of the products was responsible for the observed diastereoselectivity. The generality of this method was limited to the use of chiral amines and aliphatic aldehydes.

Wong and co-workers[17] have developed a stereoselective method to obtain glycoalanine derivatives (**29**) using the same enantiopure amine as chiral auxiliary (Scheme 5). The first step involved the Strecker reaction of an aldehyde bearing a protected carbohydrate moiety (**26**), in the presence of the chiral amine (**28**) and cyanohydrin (**27**) as cyanide source. Further steps involving hydrolysis of the cyano group, removal of the chiral auxiliary and debenzylation, affording then the final products. Interestingly, in the absence of the chiral amine (e.g., when benzylamine was used), the chiral aldehyde was not able to induce any diastereoselectivity. Moreover, the solvent played a crucial role in the stereochemical outcome of this transformation, as observed, in some cases, by the inversion of the major diastereomer when the solvent was shifted to tetrahydrofuran (THF). The use of an excess of the cyanide source (5.0 equivalents) appears as a drawback of this procedure.

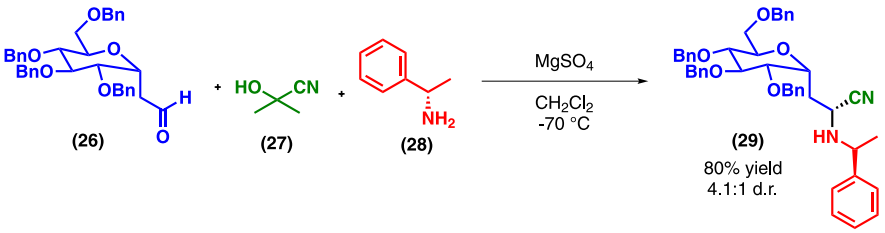
The development of an enantioselective methodology for a Strecker-type reaction was first described in 1996 by Lipton and co-workers.[18] In this protocol, the imine (**30**)



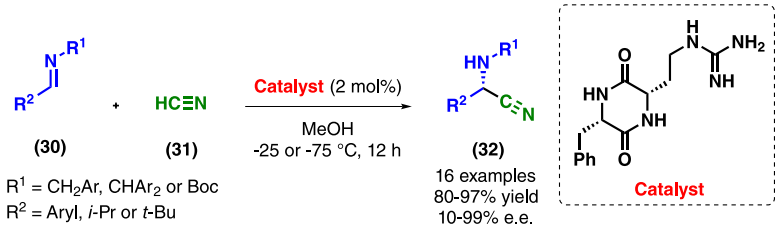
Scheme 3. Diasteroselective Strecker reaction using a chiral auxiliary.



Scheme 4. Diasteroselective Strecker reaction using a bulky chiral auxiliary.



Scheme 5. Diasteroselective Strecker reaction using chiral amine as chirality inducer.

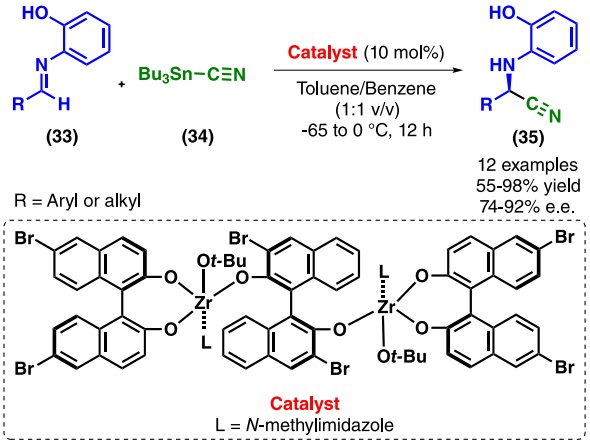


Scheme 6. Enantioselective two-component Strecker-type reaction.

was previously isolated and directly employed in the asymmetric reaction in the presence of cyanide (**31**) catalyzed by a chiral cyclic dipeptide derivative (Scheme 6). Although the study presented a very important concept associated with the Strecker reaction, only two-components were used and, consequently, this procedure cannot be considered a multicomponent transformation. Both the isolated yields (ranging from 80 to 97%) and enantiomeric excesses (varying from 17 to 99%) of the desired products (**32**) were generally satisfactory. The low temperature requirement (–25 or –75 °C) and the need of 2.0 equivalents of the toxic hydrogen cyanide appear as the main limitations of this methodology.

In 1998, the use of metal catalysis was also described for the enantioselective Strecker-type reaction between *N*-(2-hydroxyphenyl aldimines) (**33**) and tributyltin cyanide (**34**) catalyzed by a chiral binuclear zirconium complex as catalyst (Scheme 7).[19] The desired α-aminonitriles were prepared in moderate to excellent yields (up to 98%) and in good to high enantiomeric excesses (up to 92%). As the main drawback, the method was limited to a single substituted amine. Notably, three examples were described involving *in situ* formation of the imine (three-component Strecker reaction), leading to a slightly drop in the isolated yields (55-79%) and moderate to good e.e. (74-83%).

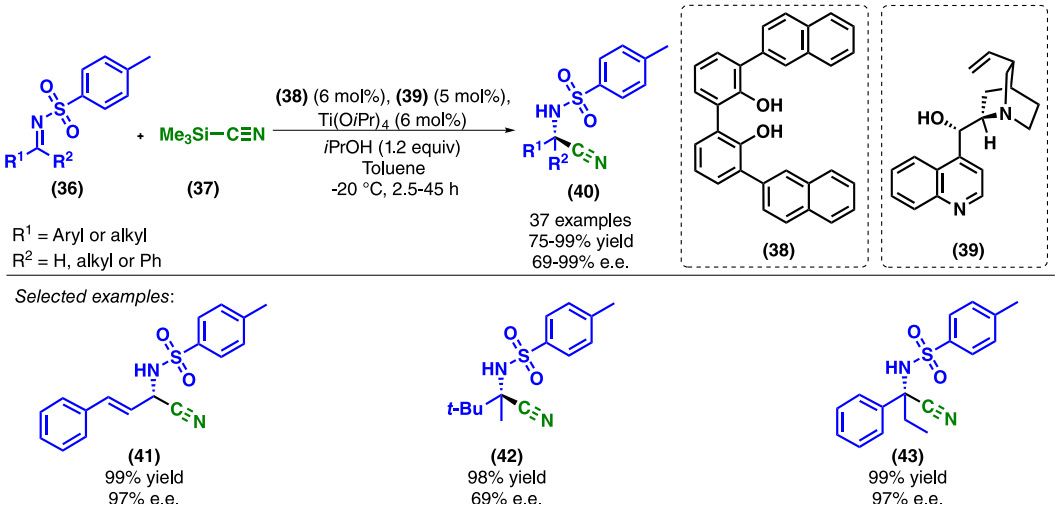
Since the pioneering studies by Lipton,[18] a diversity of enantioselective methods using chiral metal complexes has been described for the two-component reaction between nitriles and imines. These studies include the use of titanium, ytterbium, gadolinium and magnesium based catalysts.[20-23] For example, in 2007, Feng and co-workers[20] described the use of 2,2-biphenol (**38**), cinchonine (**39**), and titanium(IV) isopropoxide for the *in situ* enantioselective



Scheme 7. Enantioselective synthesis of α-aminonitriles using a chiral zirconium catalyst.

Strecker-type reaction between *N*-tosyl imines (**36**) and trimethylsilyl cyanide (**37**) (Scheme 8).[20] The reaction tolerated the use of freshly prepared imines and ketimines, affording a broad substrate scope of α-aminonitriles (**41**-**43**). Notably, excellent yields (up to 99%) and enantiomeric excesses (up to 99%) have been presented for most of the described examples.

In 2019, Ryu and co-workers[24] employed a chiral oxazaborolidinium ion as the catalyst for the enantioselective preparation of Strecker adducts (Scheme 9). The reaction between *N*-(2-hydroxyphenyl) aldimines (**44**) and tributyltin cyanide (**45**) allowed the access to the desired α-aminonitriles (**46**) in good to excellent yields (ranging from 82 to 98%) and moderate to excellent enantiomeric excesses (up to 99% e.e.). The use of aldehydes bearing either aryl groups or bulky alkyl substituents was well tolerated, as shown for derivatives (**47**) and (**48**). In

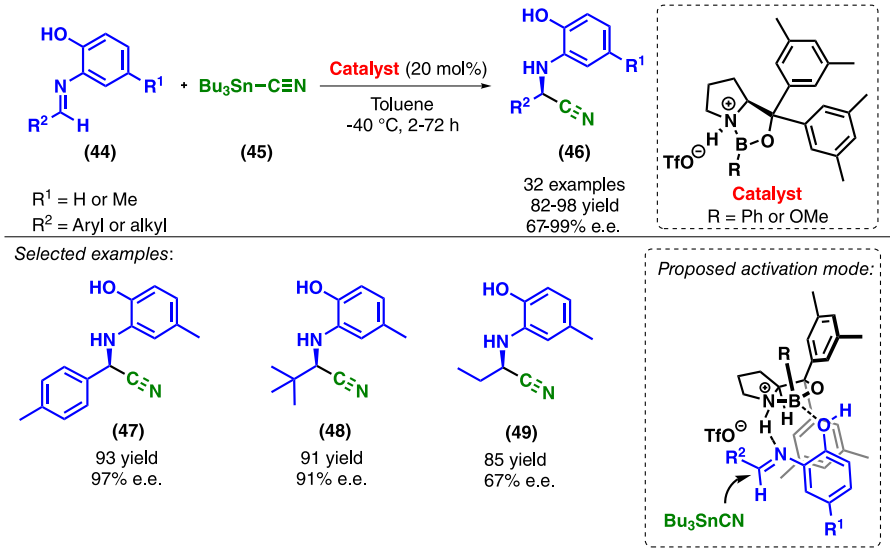


Scheme 8. Titanium(IV) catalyzed enantioselective Strecker-type reaction.

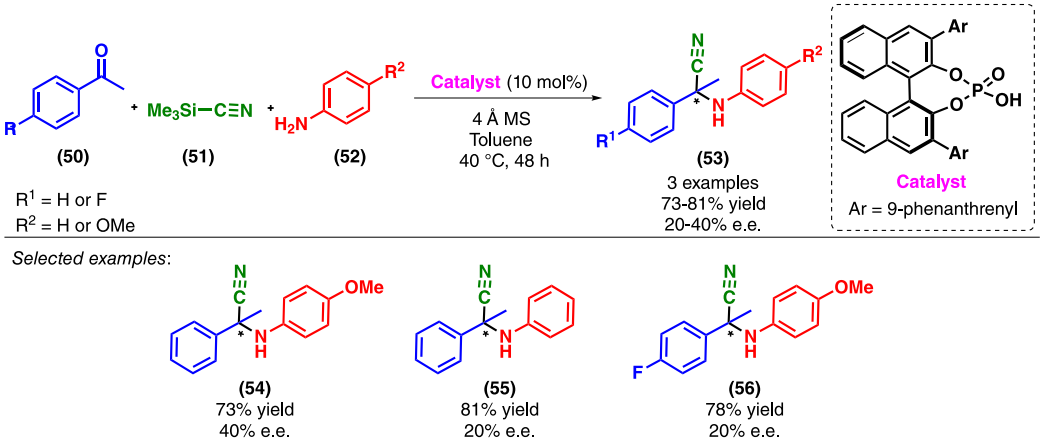
contrast, the use of alkyl groups with a low steric demand, considerably lowered enantiomeric excesses (only 67% e.e. for compound (**49**)). In order to explain the stereochemistry outcome, authors present a plausible dual activation mode. First, a hydrogen bonding interaction between the imine nitrogen and the catalyst N–H group and second, the formation of a boron-oxygen interaction should be involved in the stereoinduction process.

Recently, enantioselective methods using either Brønsted acid or Brønsted base catalysts have been described for the attainment of enantioenriched α-aminonitriles. For example, 1,1'-bi-2-naphthol (BINOL) and its derivatives (e.g., chiral phosphoric acids) have been widely used in the asymmetric preparation of Strecker adducts.[25,26] In this context, in 2010, Ma and co-workers[27] presented an enantioselective protocol for the organocatalytic three-component Strecker reaction between acetophenones (**50**), trimethylsilyl cyanide (**51**) and anilines (**52**) (Scheme 10). Although this study was mainly focused on the development of a Brønsted acid catalyzed methodology, with several prepared racemic examples; preliminary studies (only three examples) were presented using chiral phosphoric acids for asymmetric Strecker reaction. In addition to the limited scope (only two aromatic aldehydes and amines were employed), the corresponding products presented low enantioselectivities (up to 40%) and the absolute configuration of the major enantiomer was not assigned.

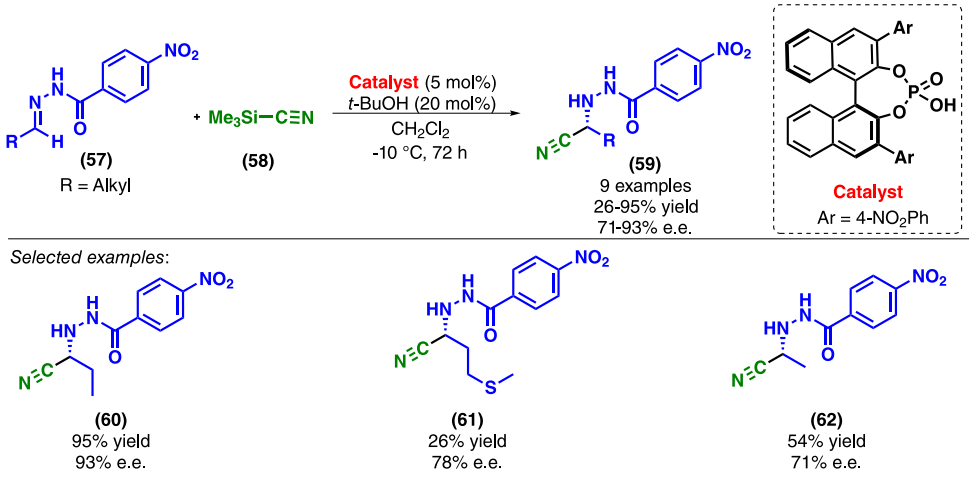
An interesting study in which enantioenriched α-hydrazinonitriles were prepared from the reaction between aliphatic hydrazones (**57**) and trimethylsilyl cyanide (Scheme 11) has been presented by Zamfir and Tsogoeva.[28]



Scheme 9. Oxazaborolidinium catalyzed enantioselective Strecker-type reaction.



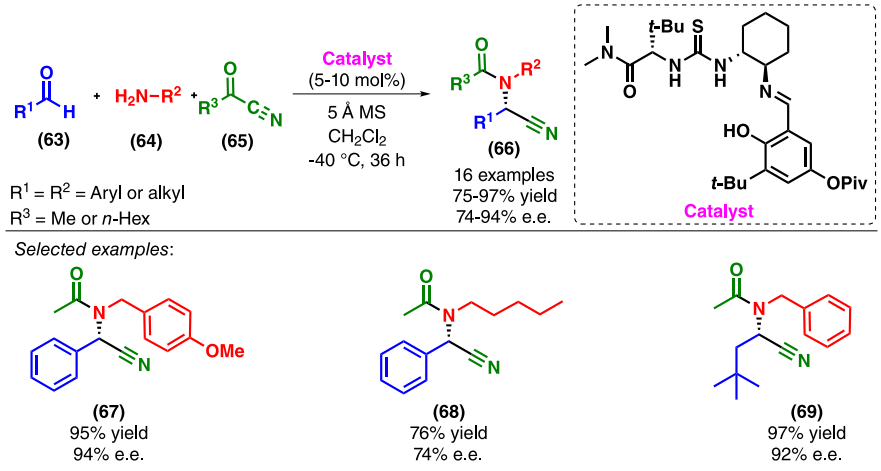
Scheme 10. Chiral phosphoric acid catalyzed asymmetric Strecker reaction.



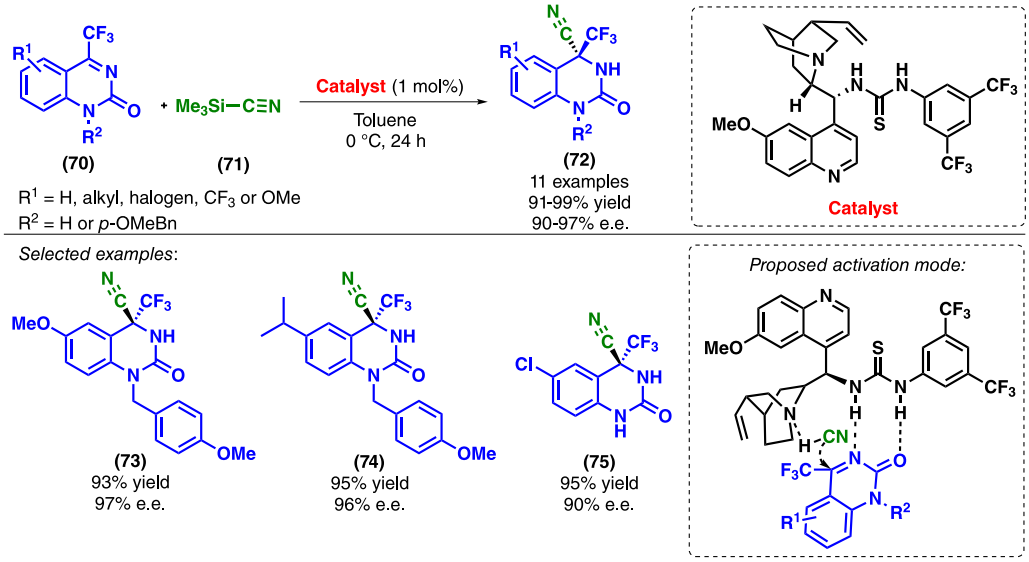
Scheme 11. Chiral phosphoric acid catalyzed enantioselective Strecker-type reaction using hydrazones.

The use of a chiral phosphoric acid as the catalyst allowed the preparation of the desired derivatives (**59**) in low to excellent yields (26-95%) and moderate to excellent enantiomeric excesses (up to 93% e.e.). The use of an excess of the cyanide source (2.0-2.5 equivalent) appears as the main drawback of this procedure.

The use of chiral urea or thiourea based organocatalysts was also described for the preparation of enantioenriched Strecker adducts. For example, in 2007, a thiourea catalyzed asymmetric three-component Strecker-type reaction was described by Pan and List[29] (Scheme 12). Interestingly, by using acetylcyanide (**65**) as a component, the acylcyanation



Scheme 12. Catalytic asymmetric acyl-Strecker reaction by chiral thiourea inductor.



Scheme 13. Enantioselective Strecker-type reaction of cyclic *N*-acyl trifluoromethylketimines.

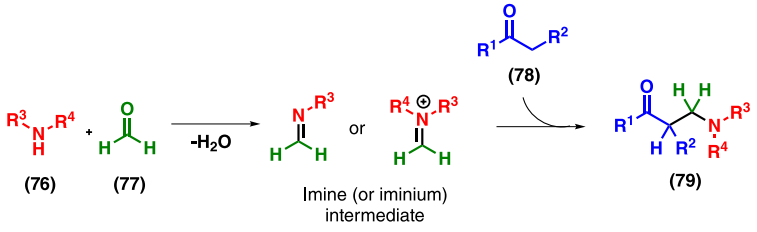
was then carried out, affording α-amido nitriles (**66**) in good to excellent yields (between 75 and 97%) and enantiomeric ratios of up to 93:7. A plausible activation mode for the chiral induction was not provided by the authors.

An enantioselective Strecker-type reaction between cyclic *N*-acyl trifluoromethylketimines (**70**) and trimethylsilyl cyanide (**71**) for the preparation of cyclic α-amino nitriles (**72**), employing a thiourea-cinchone bifunctional catalyst has been reported by Ma and co-workers[30] (Scheme 13). The main advantages of this methodology are the low catalyst loading (only 1 mol%) and the excellent yields and enantiomeric excesses (all above 90%). A plausible activation mode involving bifunctional catalysis was presented, in which the thiourea moiety activates the acyl ketimine group and the tertiary amine of the catalyst interacts with the *in situ* generated hydrogen cyanide, providing an adequate arrangement for the chiral induction step.

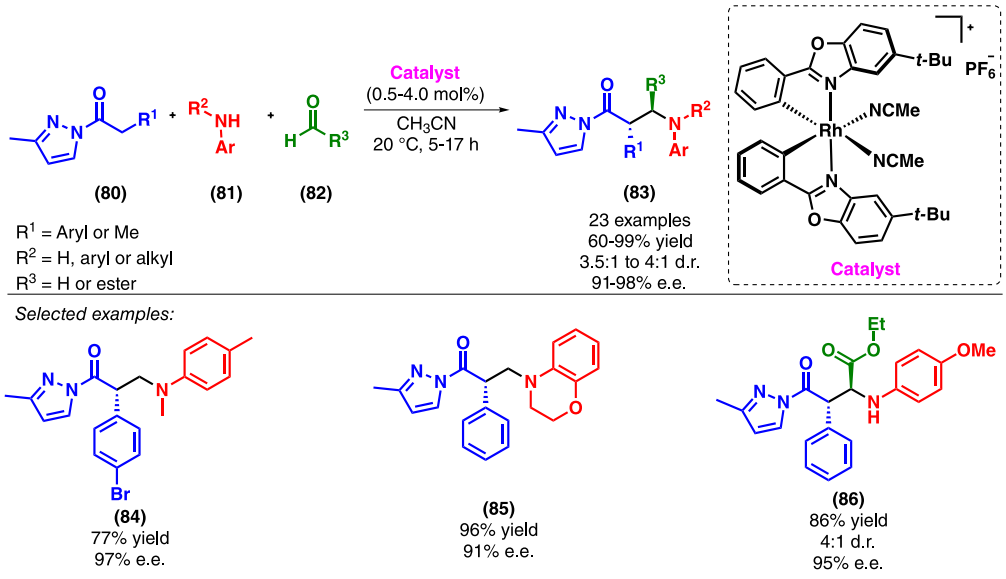
3. Mannich

The Mannich reaction is an important multicomponent transformation in which β-aminocarbonyl compounds are synthesized from an enolizable carbonyl compound (generally an alkyl-substituted ketone or aldehyde) (**78**), a primary or secondary amine (**76**), and a second carbonyl compound (generally non-enolizable, such as formaldehyde (**77**)) (Scheme 14).[31] The mechanism involves condensation between (**76**) and (**77**), forming an imine or iminium ion, which is subsequently attacked by the enol (or enolate) of compound (**78**), providing the Mannich base.[32,33] Since the corresponding adducts are precursors of important classes of compounds,[34-36] such as β-lactams[37] and α-aminoalcohols,[38] the development of asymmetric protocols for this reaction has attracted great interest over the last decades.[39]

Methods using metal complexes as catalysts have been successfully described for the enantioselective Mannich reaction. In this context, recently, the use of a chiral rhodium catalyst for the three-component reaction between 2-acylpyrazoles (**80**), aldehydes (**81**), and primary or secondary amines (**82**) has been reported by Gong and co-workers[40] (Scheme 15). The method employed a mild reaction condition (20 °C and acetonitrile as solvent) and generally required low catalyst loading (for most cases 0.5 mol%), affording the desired products in moderate to excellent isolated yields (up to 99%). When using formaldehyde as a component (enantioselective Mannich reaction), excellent enantiomeric excesses were observed



Scheme 14. The Mannich reaction.

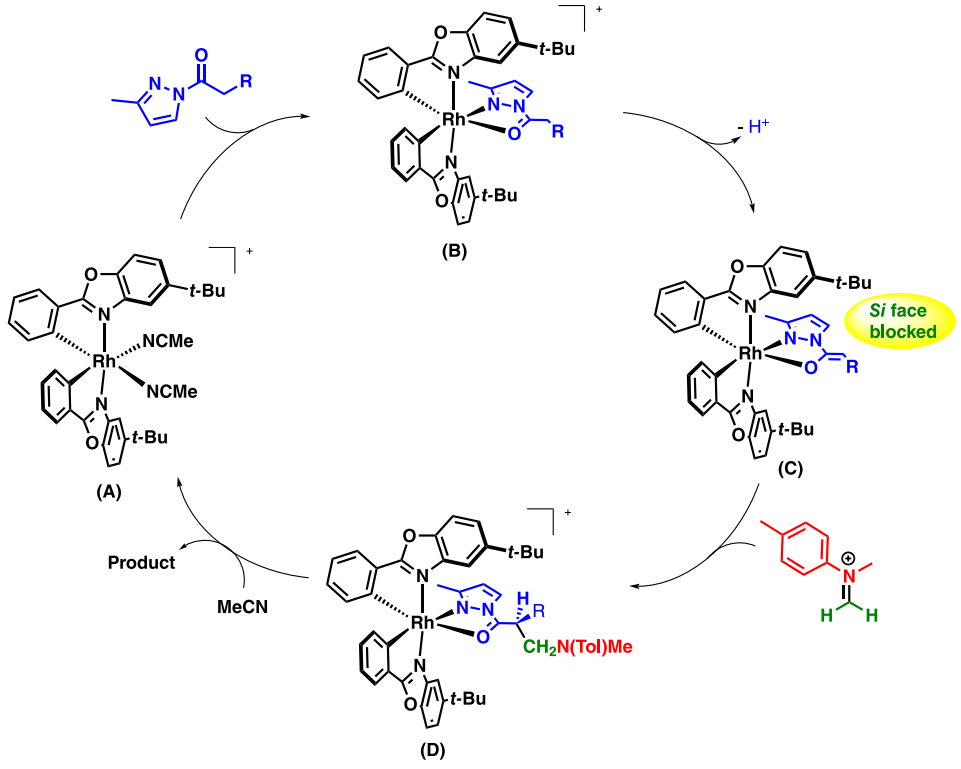


Scheme 15. Enantioselective Mannich reaction catalyzed by a rhodium complex.

(up to 97% e.e., e.g., **84** and **85**). However, when substituted aldehydes were employed, the diastereoselectivity was found to be only moderate (up to 4:1 d.r.), as observed for (**86**). As main limitation, the use of alkyl substituents was not tolerated in some of the components.

A plausible catalytic cycle was proposed for this transformation (Scheme 16). Initially, the complexation of the catalyst (**A**) to 2-acylpyrazole results in the formation of complex (**B**). After, the enolate of the 2-acylpyrazole is formed, affording (**C**) which promptly reacted with the iminium ion. It is important to mention, the *tert*-butyl group blocks the *Si*-face of the enolate, allowing its attack to the iminium ion preferentially through *Re*-face, affording the (*S*)-product as the major enantiomer.

The use of organocatalysts has also been widely described in asymmetrical Mannich reactions.[41,42] In a

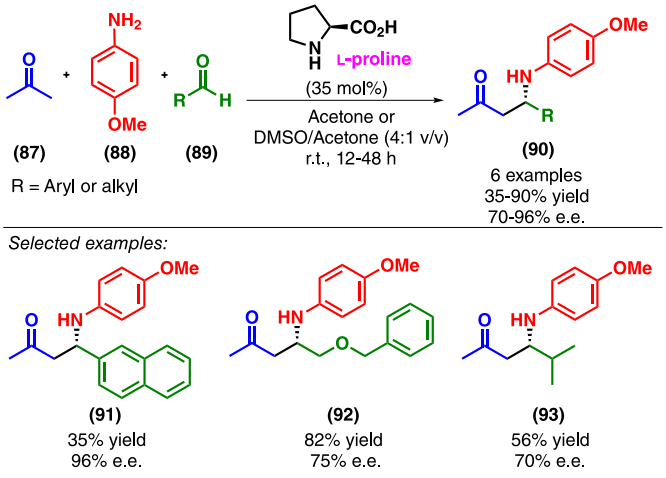


Scheme 16. Proposed catalytic cycle for the asymmetric three-component Mannich reaction using a rhodium complex.

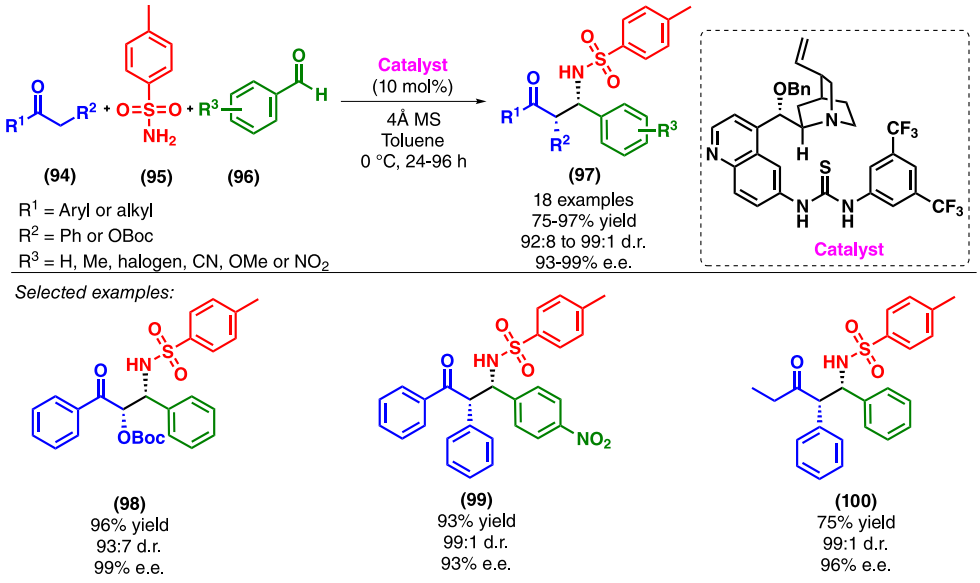
seminal work, in 2000, the use of L-proline as catalyst for the enantioselective three-component Mannich reaction between acetone (**87**), *p*-anisidine (**88**), and aromatic and aliphatic aldehydes (**89**) has been described by List[43] (Scheme 17). Considering that this was the first example of the amino acid catalyzed Mannich reaction (still in the early years of the development of organocatalysis),[44] the required catalyst loading was still considerably high (35 mol%), the scope was limited to only six examples (including **90**, **91** and **92**) and the enantiomeric excesses varied from moderate to excellent (up to 96% e.e.). Nevertheless, this study was an outstanding synthetic contribution, which allowed the further development of this transformation by a diversity of research groups.

Several works[45-49] were later published using amino acids and their derivatives as catalysts for the three-component Mannich reaction, generally allowing the attainment of high diastereomeric ratios and enantiomeric excesses (up to 99%). However, many of them are still limited to the use of *p*-anisidine as the amine component.[50,51]

Bifunctional Brønsted bases are also a commonly employed class of organocatalysts for stereoselective Mannich reactions.[52-57] Among several efficient methods employing this class of organocatalysts, an example involving the use of a bifunctional cinchona-alkaloid catalyst bearing a thiourea moiety for the three-component reaction between ketones or aldehydes (**94**), *p*-toluenesulfonamide (**95**) and aromatic aldehydes (**96**) has been reported by Guo and Zhao.[58] The desired *N*-tosylated-β-aminoketones (**97**) were prepared in good to excellent yields (up to 97%) and with excellent control of both diastereo- and enantioselectivities (up to 99:1 d.r and 99% e.e.) (Scheme 18). Unfortunately, the key interactions involved in the asymmetric induction process was not



Scheme 17. Enantioselective L-proline catalyzed Mannich reaction.

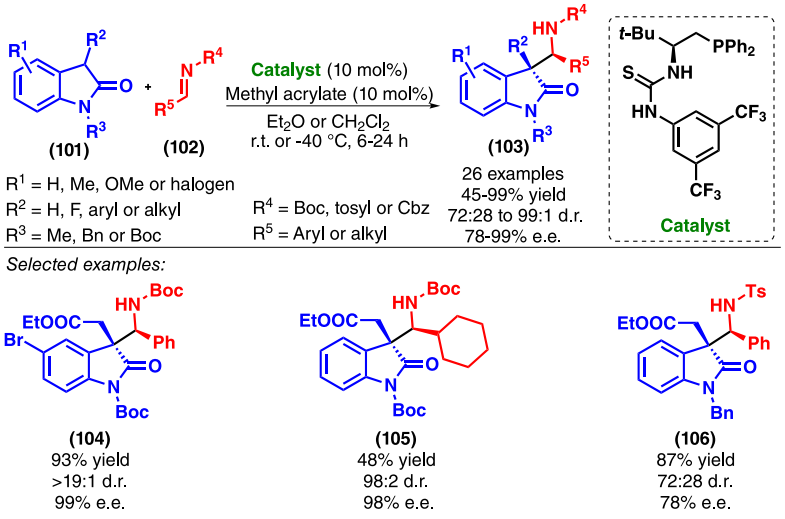


Scheme 18. Mannich reaction catalyzed by a bifunctional cinchona-thiourea organocatalyst.

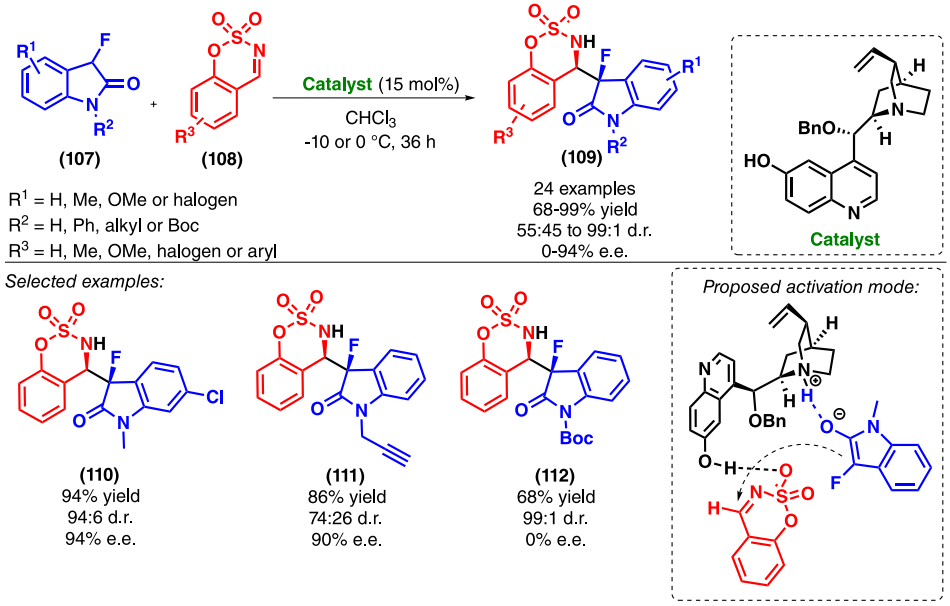
investigated and, consequently, the entire mechanism was not demonstrated.

In 2018, the preparation of optically active 3-tetra-substituted oxindoles (**103**) using a chiral bifunctional thiourea-phosphine catalyst was described by Zou and co-workers[59] (Scheme 19). The reaction between 3-substituted oxindoles (**101**) and imines (**102**) was enabled through a dual-catalytic approach, affording the products in low to excellent yields (up to 99%) and a moderate to excellent control of the stereoselectivities (up to 99:1 d.r. and 99% e.e.). It is worth mention that the products contain two contiguous (a tertiary and quarternary) stereogenic centers. The use of tosyl-imines (e.g., **106**) led to a considerably decrease in both diastereo- and enantioselectivity when compared to Boc-protected imines (e.g., **104** and **105**).

In 2019, Ren and co-workers[60] described the use of a cinchona alkaloid catalyst in the reaction between 3-fluorooxindoles (**107**) and cyclic *N*-sulfamidate aldimines (**108**), affording substituted 3-fluorooxindoles (**109**) (Scheme 20). A broad substrate scope was demonstrated (e.g., **110** and **111**), with most examples presenting high yields (above 90%), and moderate to good both diastereo- and enantioselectivities (up to 99:1 d.r. and 94% e.e.). On the contrary, the use of *N*-Boc-3-fluorooxindole led to the desired product (**112**) as a racemic mixture. The observed stereoselectivity was explained through a transition state proposal, in which the catalyst activates both substrates simultaneously. First, the tertiary amine of the cinchona deprotonates the α-position of 3-fluorooxindole and the resulting enolate is stabilized though a hydrogen bonding



Scheme 19. Enantioselective Mannich-type reaction of 3-substituted oxindoles catalyzed by a thiourea-phosphine organocatalyst.



Scheme 20. Cinchona alkaloid catalyzed enantioselective Mannich-type reaction of 3-fluorooxindoles and cyclic *N*-sulfamidate aldimines.

interaction with the ammonium salt. A second activation involves the aldimine group, which presents a hydrogen bond interaction with the catalyst O–H moiety. Thus, the authors propose that the substrates are oriented in order to favor the *Re*-face enamine attack to the *Si*-face of the imine, giving the (*R*,*R*)-derivative adduct as the major product.

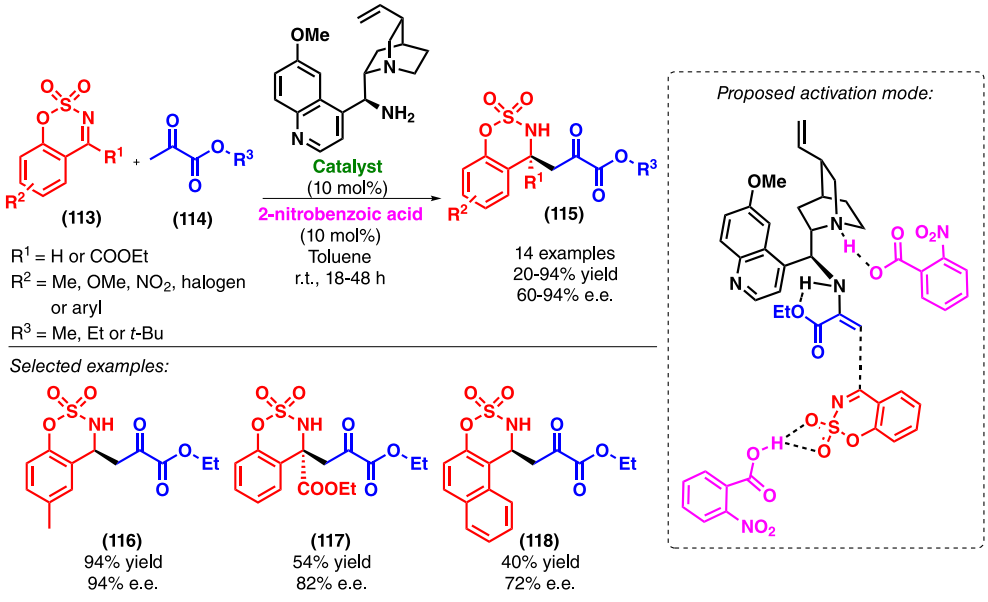
Recently, an asymmetric protocol using a cinchona alkaloid catalyst, associated to 2-nitrobenzoic acid, for the reaction between six-membered cyclic sulfonyl imines (**113**) and pyruvates (**114**) has been reported by Tanaka and co-workers[61] (Scheme 21). The reaction afforded the desired products (**115**) in low to excellent yields (ranging from 20 to 94%), and with an enantiomeric excess of up to 94%. Mechanistic studies revealed the participation of two molecules of 2-nitrobenzoic acid during the reaction. The entire mechanism initiates through the formation of an enamine intermediate from the reaction between the catalyst primary amine group and the pyruvate. The first molecule of the acid is involved in the acid-base reaction with the catalyst tertiary amine, resulting in an ion pairing intermediate which blocks one of the faces of the enamine. Next, the second acid molecule activates the sulfonyl moiety through hydrogen bonding interactions. Finally, the attack of the enamine to the *Si*-face of the imine leads to the formation of the major enantiomer.

The use of other types of organocatalysts, such as chiral squaramides, has also been described in asymmetric Mannich reactions. Most reports employ these catalysts for the two-component Mannich reaction (using pre-formed imines) and generally present promising results (up to 99% yield, 99:1 d.r. and 99% e.e.).[62-64] Although the imine/iminium formation may seem a trivial task at first sight, driving the equilibrium towards its formation while also controlling the reaction stereoselectivity is not simple in most cases.[65,66] Thus, methods involving the three-component Mannich reaction are still scarce in comparison to the direct Mannich reaction (two-component).

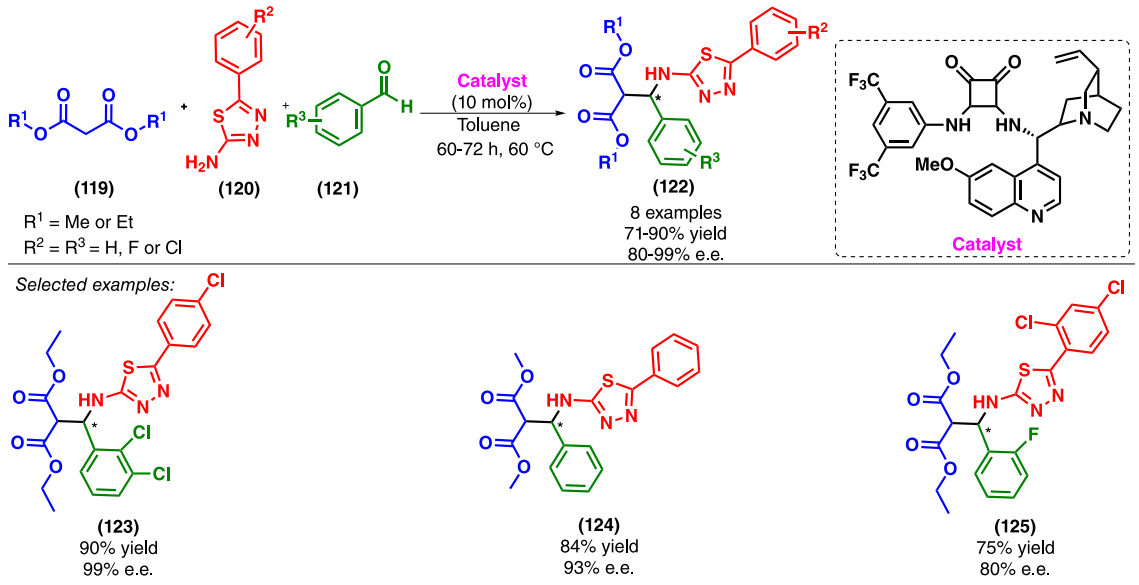
Recently, an enantioselective procedure for the three-component Mannich reaction among dialkyl malonates (**119**), 5-phenyl-1,3,4-thiadiazol-2-amines (**120**), and aromatic aldehydes (**121**), using a cinchona-squaramide catalyst has been presented by Wu and co-workers[67] (Scheme 22). Although the desired compounds (**122**) were attained in up to 90% yield and 99% e.e., the scope was limited to two substituted malonic acids, halide-containing aromatic amines and aldehydes (e.g., **123**, **124** and **125**). The absolute configuration of the major enantiomer was not assigned by the authors.

Brønsted acid catalysts such as BINOL and its derivatives (e.g., chiral phosphates and phosphoric acids) have been used in the asymmetric preparation of Mannich adducts.[68] Recently, Sugiono and co-workers[69] have reported the use of a chiral calcium phosphate salt in the preparation of Mannich derivatives from the two-component reaction between cyclic 1,3-dicarbonyl compounds and imines, with enantiomeric excesses ranging from 39 to 88%.

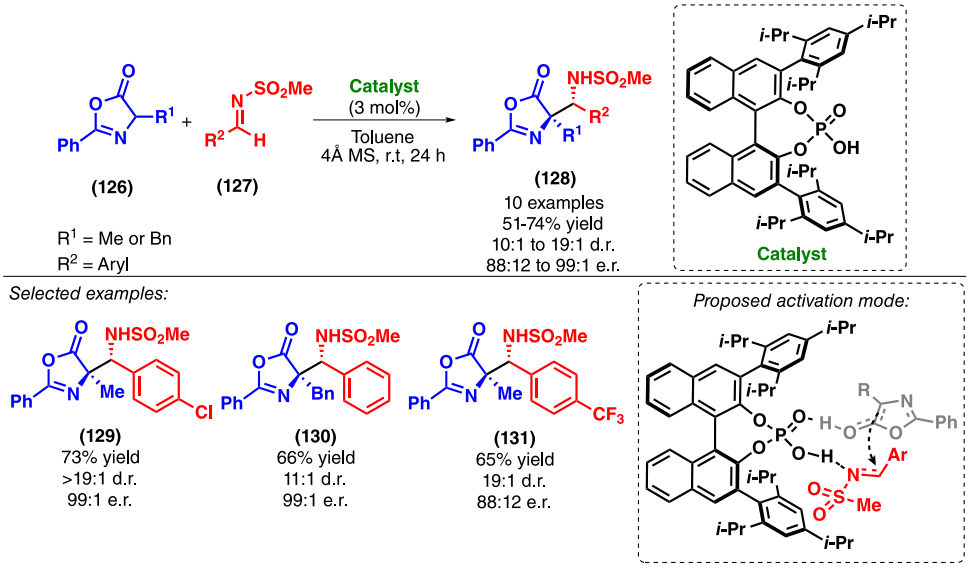
Other synthetic protocols have also employed chiral phosphoric acids for the two-component reaction between enolizable ketones or aldehydes and aldimines.[70-72] For example, in 2015, Amarante and co-workers[73] described the use of a phosphoric acid catalyst for the highly diastereo- and enantioselective Mannich-type reaction between azlactones (**126**) with aldimines (**127**) (Scheme 23).



Scheme 21. Enantioselective Mannich-type reactions of pyruvates and cyclic sulfonylimines catalyzed by a cinchona-alkaloid and 2-nitrobenzoic acid.



Scheme 22. Chiral squaramide catalyzed synthesis of enantioenriched 1,3,4-thiadiazole derivatives.

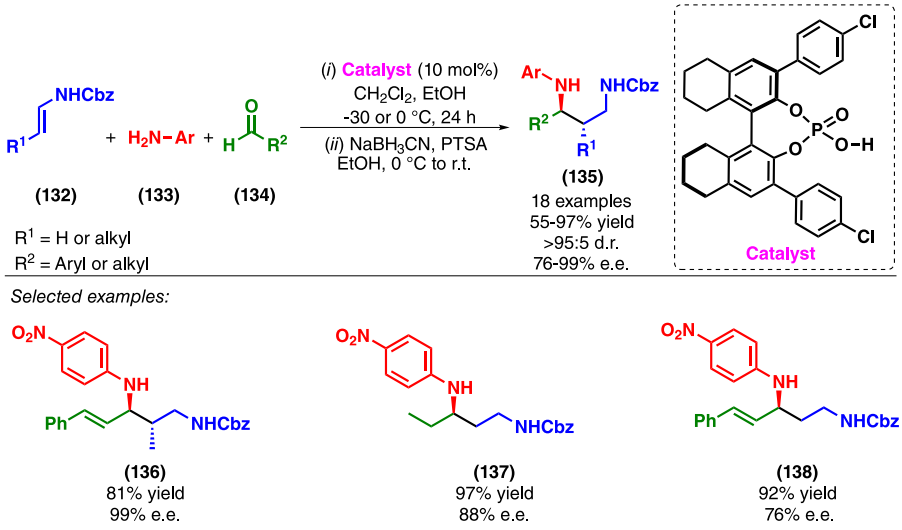


Scheme 23. Phosphoric acid catalyzed Mannich-type reaction between azlactones and aldimines.

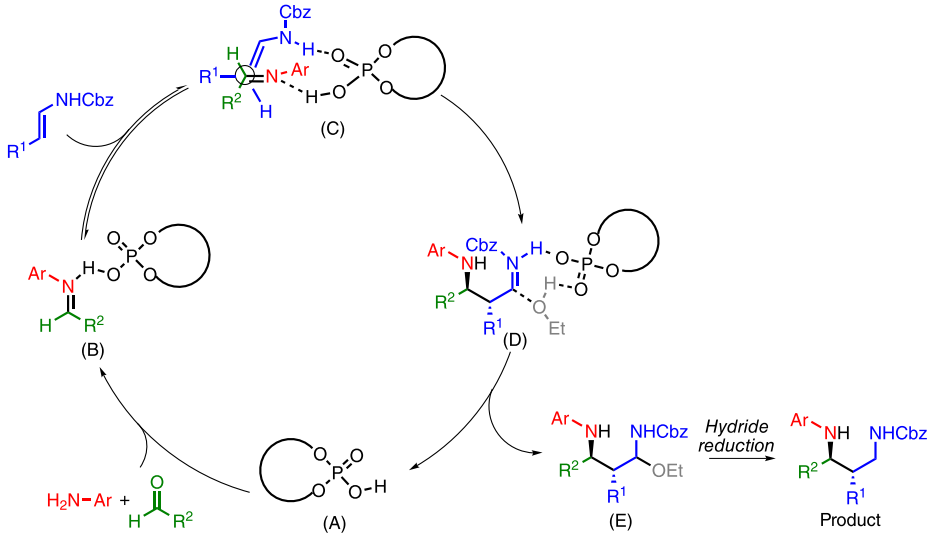
By using 3 mol% of the organocatalyst, the Mannich adducts (**128**) were isolated in moderate to good yields (up to 74%) and with good to excellent control of the stereoselectivities (up to 19:1 d.r. and 99:1 enantiomeric ratio (e.r.)). Notably, these products could also be further transformed in non-natural amino acid derivatives through a sequential ring-opening reaction. The authors proposed that the reaction proceeds through a dual activation mode; a hydrogen bonding between the catalyst and the azlactone enol tautomer, and a second hydrogen bonding interaction between the phosphoric acid group and the imine nitrogen. These interactions provide an adequate arrangement for the nucleophiplic attack of the azlactone to the imine, allowing the attainment of the corresponding Mannich products.

These catalysts have also been employed in the three-component Mannich reaction, as described by Zhu and co-workers.[74] In this study, *anti*-1,2-disubstituted 1,3-diamines (**135**) were stereoselective obtained from the reaction among enecarbamates (**132**), anilines (**133**) and aldehydes (**134**), catalyzed by a chiral phosphoric acid (Scheme 24). The desired products were isolated in moderate to excellent yields (ranging from 55 to 97%), excellent diastereoselectivities (in all cases > 95:5 d.r.) and up to 99% of enantiomeric excess.

A plausible reaction mechanism was then proposed by the authors (Scheme 25). The reaction initiates through the formation of the imine and its interaction with the chiral phosphoric acid catalyst (**A**), affording intermediate (**B**).



Scheme 24. Stereoselective Mannich-type reaction for the enantioselective preparation of 1,3-diamines.

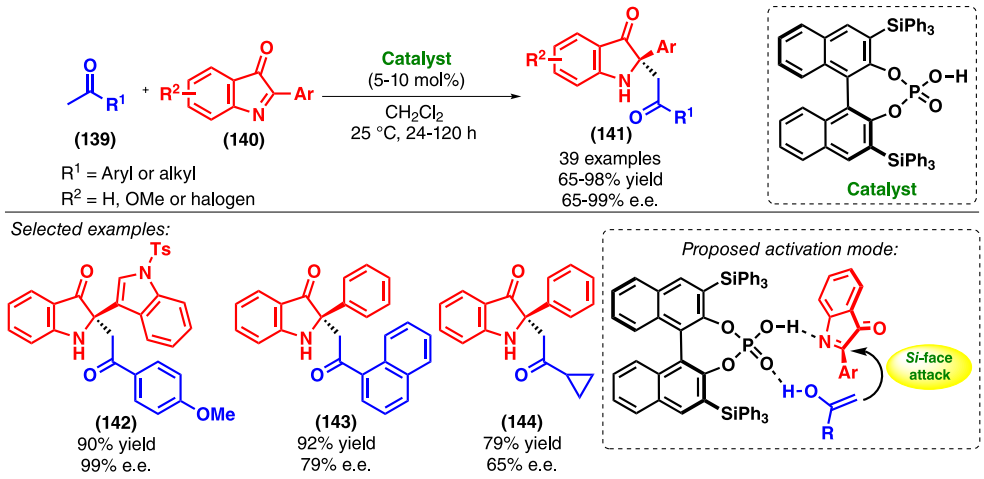


Scheme 25. Proposed mechanism for the phosphoric acid catalyzed preparation of chiral 1,3-diamines.

After, the reaction follows through its interaction with the enecarbamate, producing (**C**). Thus, the catalyst presents a dual activation mode, simultaneously activation both the imine and the enecarbamate, providing an adequate molecular arrangement for the *Si*-face attack of the enecarbamate to the imine, leading to the formation of intermediate (**D**). Finally, ethanol attack to imine, regenerates the catalyst and releases the aminoether (**E**), which is then reduced to the desired product.

Another interesting example involving the use of chiral phosphoric acids was presented by Ma and co-workers,[75] which described the enantioselective preparation of 2-substituted indolin-3-ones (**141**), through the two-component Mannich-type reaction between ketones (**139**) and indolin-3-ones (**140**) (Scheme 26). The developed synthetic method allowed the formation of products bearing a tetra-substituted stereogenic center with a moderate to excellent control of the enantiomeric excess (e.e. ranging from 65 to 99%). Notably, the reaction conditions are mild (25 °C, without the need of inert atmosphere) and a broad substrate scope was presented, involving the use of a diversity of substituents in both substrates. For example, the use of steric hindered acetophenones afforded the desired products (**142**) and (**143**) in 90-92% yield and up to 99% e.e. In contrast, the use of non-aromatic ketones led to a considerable decrease in both yields and enantiomeric excesses (e.g., derivative (**144**), with 79% yield and 65% e.e.)

A plausible activation mode for this transformation was proposed and involved the simultaneous activation of the imine and enol (formed from the keto-enol tautomerism of the ketone) groups of the substrates by the catalyst through hydrogen bonding interactions. Thus, the substrates

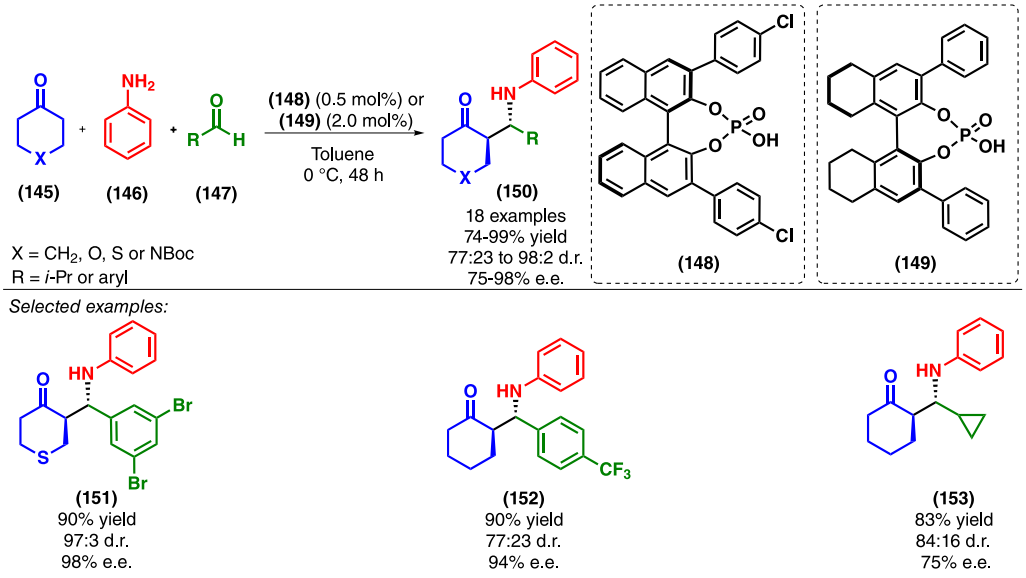


Scheme 26. Enantioselective preparation of 2-substituted indolin-3-ones using a chiral phosphoric acid catalyst.

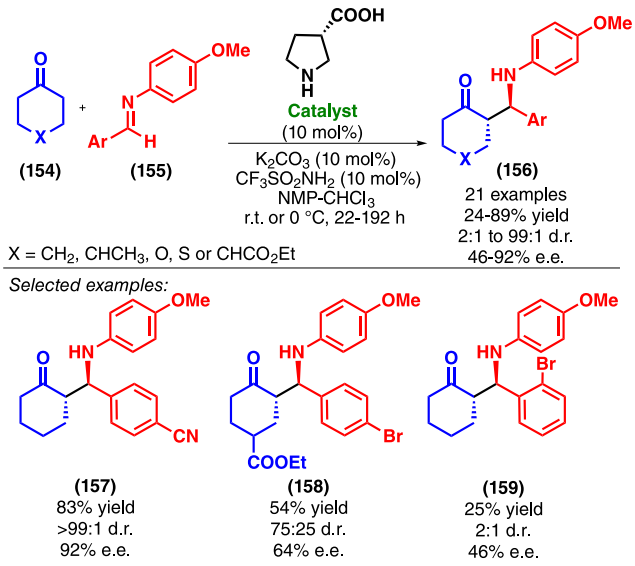
are oriented that the *Si*-face of the imine is preferentially attacked by the enol, affording the major enantiomer as the product.

An *anti*-selective protocol for the three-component Mannich reaction using chiral phosphoric acids was described by Gong and co-workers (Scheme 27).[76] The authors described the reaction among cyclic ketones (**145**), anilines (**146**) and aldehydes (**147**) to afford *anti*-β-amino carbonyl derivatives (**150**) in moderate to excellent yields (between 74 and 99%) and in high stereoselectivities (up to 98:2 d.r. and 98% e.e.). Although the desired adducts (e.g., **151**, **152** and **153**) were generally successfully accessed, the main limitation of this protocol results in the need to alter the reaction conditions, including the catalyst scaffold (**148** or **149**) and loading, according to the employed substrates.

In 2020, Garg and Tanaka[77] described a methodology to access *anti*-selective Mannich adducts (**156**) (Scheme 28). In this case, (*S*)-3-pyrrolidinecarboxylic acid (a proline isomer) was employed as the catalyst for the two-component reaction between cyclic ketones (**154**) and *N*-methoxyphenyl-protected aldimines (**155**). Interestingly, the use of 10 mol% of potassium carbonate and trifluoromethanesulfonamide as additives were required to provide the desired products in low to excellent stereoselectivities (diastereoisomeric ratio ranging from 2:1 to 99:1, and enantiomeric excesses between 46 and 92%). Although a mechanism was not proposed, the authors suggested that potassium carbonate interacts with the imine, providing an adequate molecular arrangement for the selective reaction of the enamine (formed from the reaction between the catalyst and the ketone) to the imine group.



Scheme 27. *Anti*-selective asymmetric Mannich reaction using a chiral phosphoric acid catalyst.



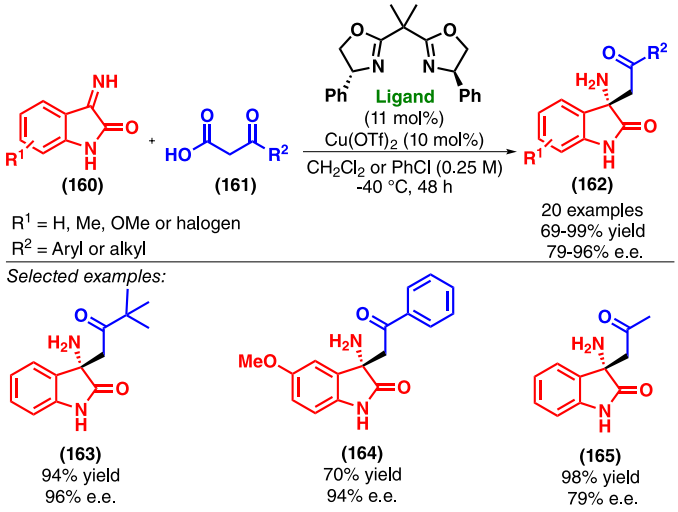
Scheme 28. (*S*)-3-Pyrrolidine carboxylic acid catalyzed *anti*-selective Mannich-type reaction.

Finally, transition metal catalysis still remains as an alternative for the development of novel asymmetric methods for the Mannich reaction.[78] As an example, in 2018, Ohshima and co-workers[79] reported the copper catalyzed enantioselective decarboxylative Mannich-type reaction between *N*-unprotected isatin-derived ketimines (**87**) with β-keto acids (**88**) (Scheme 29). The use of copper triflate catalyst, associated with a chiral bis-oxazoline ligand provided the desired products in good to excellent yields (up to 99%) and enantioselectivities (ranging from 79 to 96%).

4. Passerini

The Passerini reaction is part of a group of transformations called isocyanide-based multicomponent reactions.[4,80-82] These transformations, such as the Ugi (and Ugi-Smiles), Passerini (and Passerini-Smiles) and Groebke-Blackburn-Bienaymé reactions, employ isocyanides (also known as isonitriles) as a key component. It is proposed that the shift from the divalent isocyanide carbon to a tetravalent carbon may act as a driving force in these reactions.[83]

Differently than other multicomponent reactions, the mechanism associated with these transformations are still subject of intense debate.[84,85] Thus, the rational development of catalysts for the stereoselective isocyanide reaction is not a trivial task and, in most cases, only poor to moderate selectivities are observed. Recently, after some groups shed light on the most accepted mechanism for theses reactions,[86-88] highly enantioselective methods have been described using chiral phosphoric acid catalysts and chiral cobalt complexes.



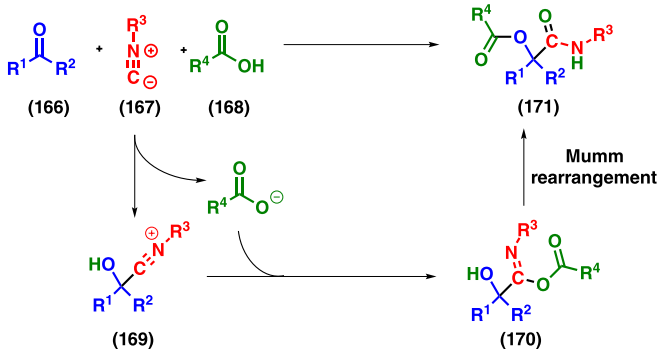
Scheme 29. Asymmetric decarboxylative Mannich-type reaction between *N*-unprotected ketimines and β-keto acids.

The classic Passerini reaction was first described by Mario Passerini in 1921.[89] This reaction consists of the preparation of α-acyloxyamides through the reaction among aldehydes or ketones (**166**), isocyanides (**167**) and carboxylic acids (**168**) (Scheme 30).[89] The most probable mechanism for this reaction involves acid-mediated formation of a nitrilium intermediate (**169**) from the attack of the isocyanide to the aldehyde/ketone, followed by the carboxylate attack, affording intermediate (**170**). The desired Passerini adduct is then released after a sequential Mumm rearrangement of the acyl imidate group.

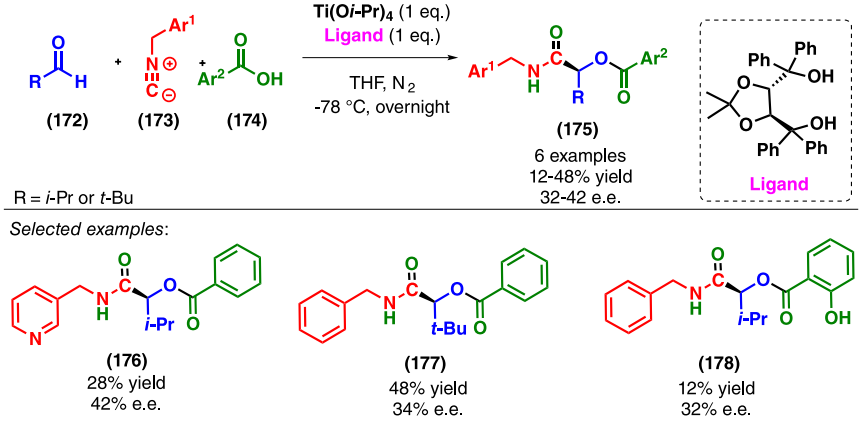
Although good results (up to 99:1 enantiomeric ratio) have been described by Denmark *et al.*[90] for the enantioselective Passerini-type reaction between aldehydes and isocyanides (in the absence of the carboxylic acid) using chiral bisphosphoramides, an enantioselective protocol for the classic three-component Passerini reaction remained for a long time as a gap in the literature. Meanwhile, other methods for the diastereo- and enantioselective two-component Passerini reaction have been described,[91-95] including Zhong and co-workers[96] study, which employed chiral phosphoric acids and served as a starting point to the development of the enantioselective classic three-component Passerini reaction.

Only in 2003, the first enantioselective methodology for the classic Passerini reaction was presented by Dömling's group (Scheme 31).[97] In this study, a large catalyst screening was carried out for the reaction among aliphatic aldehydes (**172**), isocyanides (**173**) and benzoic acids (**174**). It was found that a chiral titanium complex allowed the access to Passerini adducts (**175**) in up to 42% e.e. A small substrate scope of only six products (e.g., **176**, **177** and **178**) was accessed in low yields (up to 48%) and enantioselectivities (only 32 to 42% e.e.). Moreover, the need of a stoichiometric loading of the ligand and the titanium salt, and the use of criogenic temperatures and inert atmosphere appear as drawbacks of this methodology.

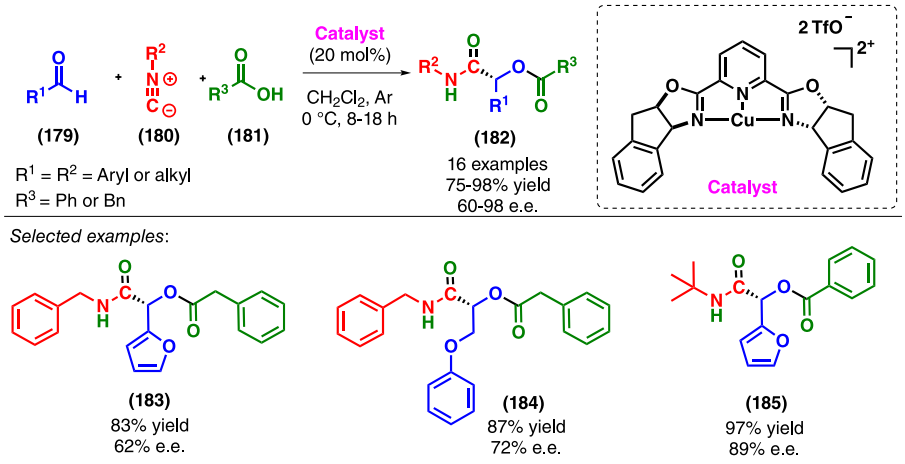
In the following years, other protocols for metal catalyzed Passerini reaction have been described. For example, in 2004, Schreiber and co-workers[98] described the use of a chiral cooper catalyst for the preparation of enantioenriched Passerini adducts (**182**) from the reaction among bidentate coordinating aldehydes (**179**), isocyanides (**180**) and carboxylic acids (**181**) (Scheme 32). In general, the Passerini products (**182**) were isolated in moderate to excellent yields (up to 98%) and enantiomeric excesses (up to 98% e.e.). The high catalyst loading



Scheme 30. The Passerini reaction.



Scheme 31. Enantioselective Passerini reaction catalyzed by a titanium complex.



Scheme 32. Enantioselective Passerini reaction catalyzed by a chiral cooper complex.

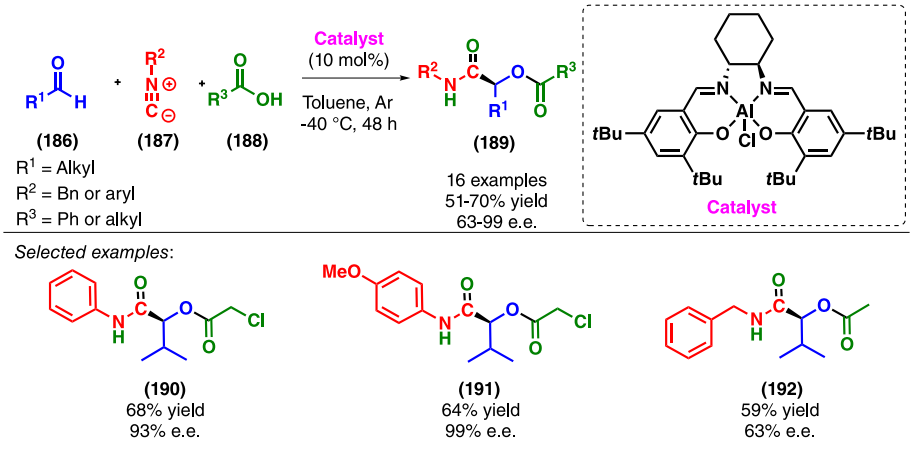
(20 mol%) and the need of inert argon atmosphere are among the drawbacks of this procedure. Besides, the reaction failed for non-bidentate coordinating aldehydes.

Few years later, the use of an aluminum catalyst for the enantioselective three-component Passerini reaction among aldehydes (**186**), isocyanides (**187**) and carboxylic acids (**188**) was described by Zhu and co-workers[99] (Scheme 33). As a result, Passerini adducts were isolated in moderate yields (up to 70%) and in up to 99% e.e., and only aliphatic aldehydes were tolerated in the optimized reaction conditions. Moreover, only two examples, (**190**) and (**191**) presented enantiomeric excesses above 90%. Argon atmosphere and cryogenic temperatures were required in the procedure.

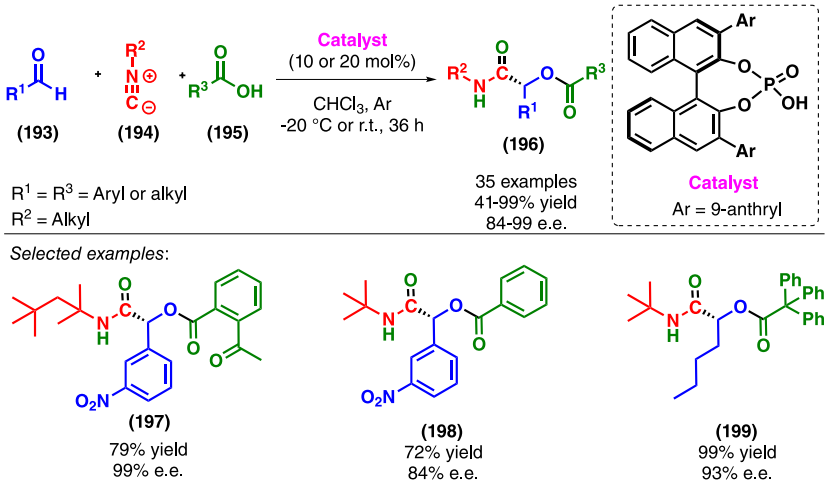
In 2015, the first general protocol to access classic Passerini adducts (**196**) in good to excellent enantiomeric excesses (ranging from 84 to 99%) was described by Tan and co-workers[100] using a chiral phosphoric acid catalyst (Scheme 34). Notably, a variety of aldehydes (**193**), isocyanides (**194**) and carboxylic acids (**195**) were successfully employed in this transformation. Remarkable results, the methodology still presents some drawbacks, though. Long reaction times, the need of altering the reaction conditions according to the substrates (e.g., temperature and/or catalyst loading), and the decrease in e.e. when using non-sterically bulky substrates (especially the carboxylic acid) should be highlighted.

As shown in these examples, the use of ketones was generally not demonstrated. Then, an enantioselective method for the Passerini reaction using these substrates is still a gap in the literature. Thus, despite the considerable advance in the enantioselective Passerini reaction has been achieved, this transformation still requires further development and present opportunities to those willing to complement the existing methods and circumvent their limitations.

Surprisingly, due to the linear and non-steric demanding structure of isocyanides, even reports concerning the diastereoselective Passerini reaction are scarce in the literature.[89,101] The few reports involve the use of chiral aldehydes or ketones (usually sugar-based derivatives),



Scheme 33. Enantioselective Passerini reaction catalyzed by a chiral aluminum complex.



Scheme 34. Phosphoric acid catalyzed enantioselective Passerini reaction.

and generally afford the products in only low to moderate diastereomeric ratios.[102]

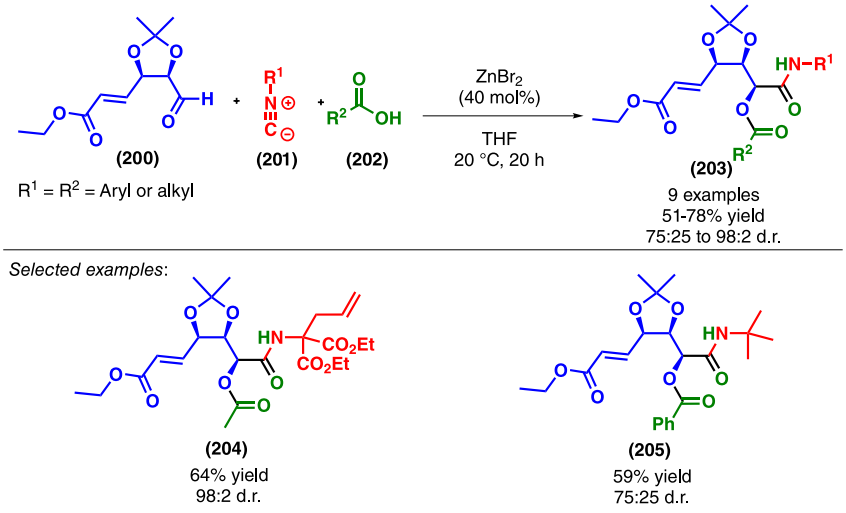
In 2016, Riva and co-workers[103] described the diastereoselective two-component Passerini reaction using chiral aldehydes derived from erythritol. A few years later, the same group described the use of a similar aldehyde (**200**) for the diastereoselective zinc catalyzed three-component Passerini reaction (Scheme 35).[104] By using the optimized reaction conditions, the desired products (**203**) were isolated in up to 78% yield and 98:2 d.r. Although in some cases, such as **204**, an excellent diastereomeric ratio was observed, for most cases only a moderate d.r. was achieved (e.g., derivative **205**). Based on this method, other similar zinc catalyzed protocols have also been recently described.[105,106]

Recently, cyrene (**206**) was described as an interesting substrate for the diastereoselective Passerini reaction (Scheme 36).[107] By using microwave irradiation at 40 °C, the desired products (**209**) were isolated in moderate to excellent yields (ranging from 54 to 99%) and low to excellent diastereomeric ratio (up to 98:2 d.r.). Notably, the reaction was solvent-free and a reaction time of only 5 min was necessary to reach the desired product.

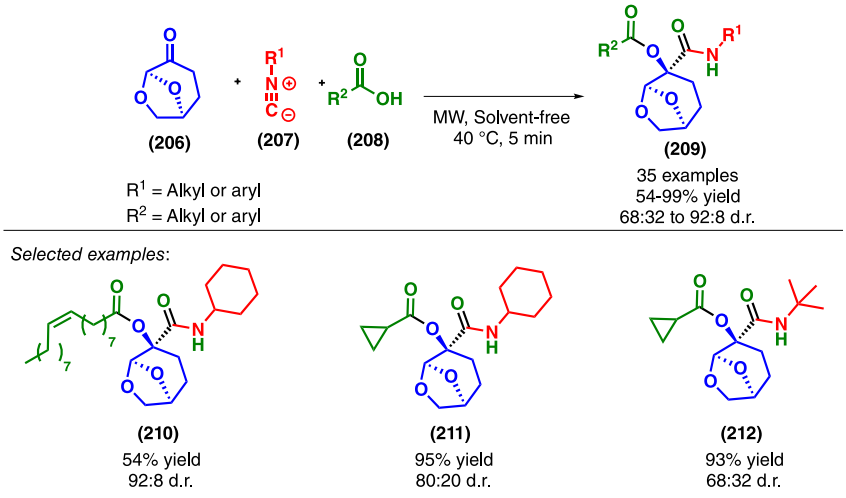
Finally, the preparation of glycomimetics (**216**) through a diastereoselective three-component Passerini reaction has been presented by Jerić and co-workers (Scheme 37).[108] By using sugar-based aldehydes (**213**), a diversity of derivatives was prepared in up to 83% yield and diastereomeric ratio ranging from 89:11 to 95:5 d.r. Notably, sugar-based isonitriles and carboxylic acids were tolerated, affording glycomimetics bearing up to three carbohydrate units (e.g., analogue (**218**)).

5. Ugi

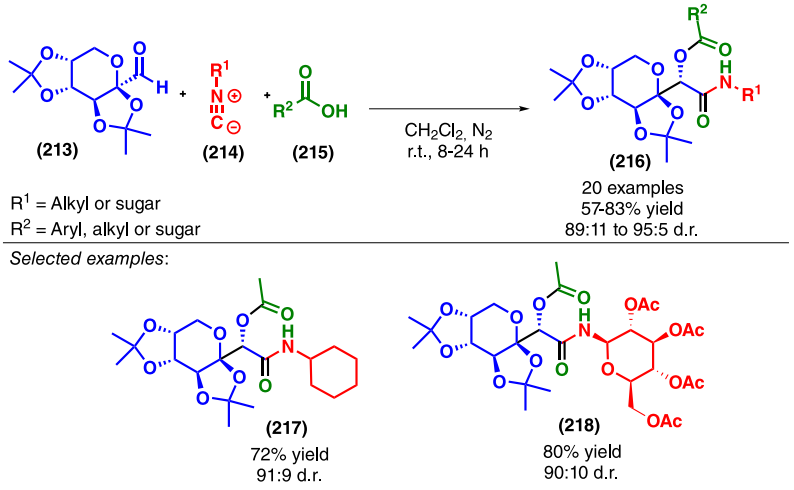
The classic Ugi reaction consists of a four-component reaction involving isocyanides (**219**), aldehydes/ketones



Scheme 35. Diastereoselective Passerini reaction using chiral aldehydes.

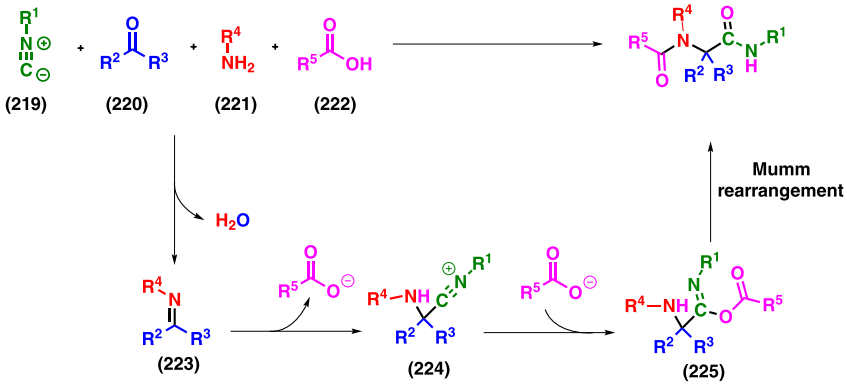


Scheme 36. Diastereoselective Passerini reaction using cyrene.



Scheme 37. Diastereoselective Passerini Reaction using sugar-based aldehydes.

(**220**), amines (**221**) and carboxylic acids (**222**) (Scheme 38). The mechanism of the Ugi reaction is still subject of intense literature debate.[6,32,84] It is generally accepted that it initiates through an imine formation (**223**) from the reaction between aldehydes and amines. A three-component variant using pre-formed imines is also widely employed for the preparation of Ugi adducts. Next, the mechanism proceeds similarly to the previously described for the Passerini reaction, involving the carboxylic acid mediated formation of a nitrilium intermediate (**224**). The attack of the carboxylate to the nitrilium leads to the imidate intermediate (**225**), which after a Mumm rearrangement releases the Ugi adduct.



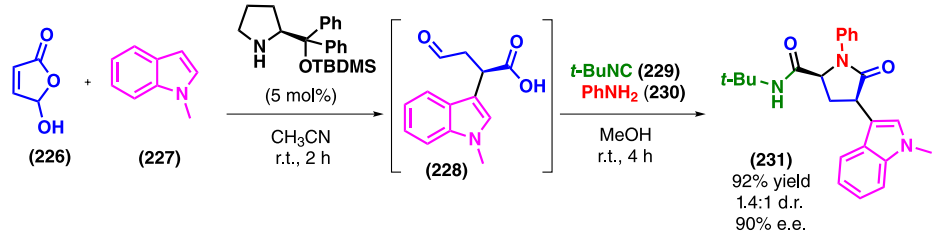
Scheme 38. The Ugi reaction.

Over the last two decades, important asymmetric protocols for the Ugi reaction have been described.[109] Many of these methodologies involve the use of chiral auxiliaries (e.g., aminosugars) for the diastereoselective Ugi reaction.[110] This is of particular interest considering that, after hydrolysis, Ugi adducts can be converted to enantioenriched non-natural amino acids.[111]

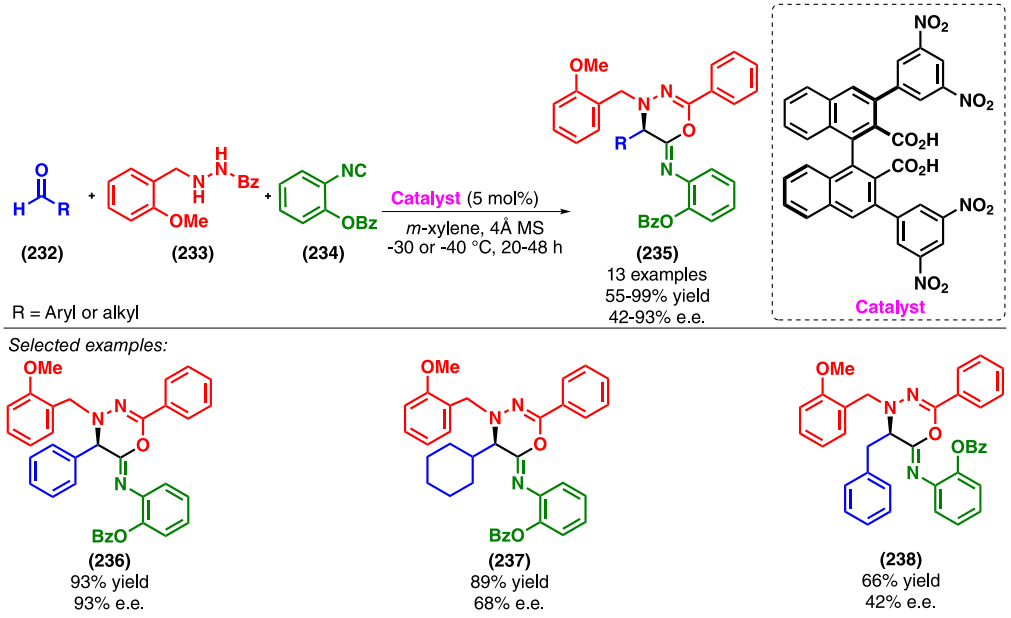
Chiral acids (e.g., amino acids) have been described as important substrates or organocatalysts for the asymmetric Ugi reaction.[112] In this context, Riguet has presented a sequential Friedel-Crafts/Ugi reaction procedure to prepare the chiral lactam (**231**) (Scheme 39).[113] First, by using a diphenyl prolinol catalyst, the reaction between 5-hydroxyfuran-2(5*H*)-one (**226**) and *N*-methylindole (**227**) afforded the chiral intermediate (**228**). Next, a sequential four-center three-component Ugi reaction between (**228**), isocyanide (**229**) and amine (**230**), gave product (**231**) in low diastereoselectivity (only 1.4:1), but in high both yield (92%) and enantiomeric excess (90% e.e.).

In 2012, Maruoka and co-workers[114] reported a methodology for the enantioselective preparation of dihydro-oxadiazines (**235**) using a chiral dicarboxylic acid as the catalyst for a Ugi-type reaction among aldehydes (**232**), benzohydrazides (**233**) and isocyanides (**234**) (Scheme 40). The reaction involved the catalyst-mediated formation of an acyclic azomethine imines from the reaction between (**232**) and (**233**). Next, isocyanide attack to this intermediate and intramolecular ring-closure afforded the desired derivatives in moderate to excellent yields (up to 99%) and enantiomeric excesses (ranging from 42 to 99% e.e.). Although in most cases substituted benzaldehydes gave the products with a good control of the enantioselectivity (e.g., **236**), the use of other aldehydes considerably decreased the e.e., as shown for (**237**) and (**238**).

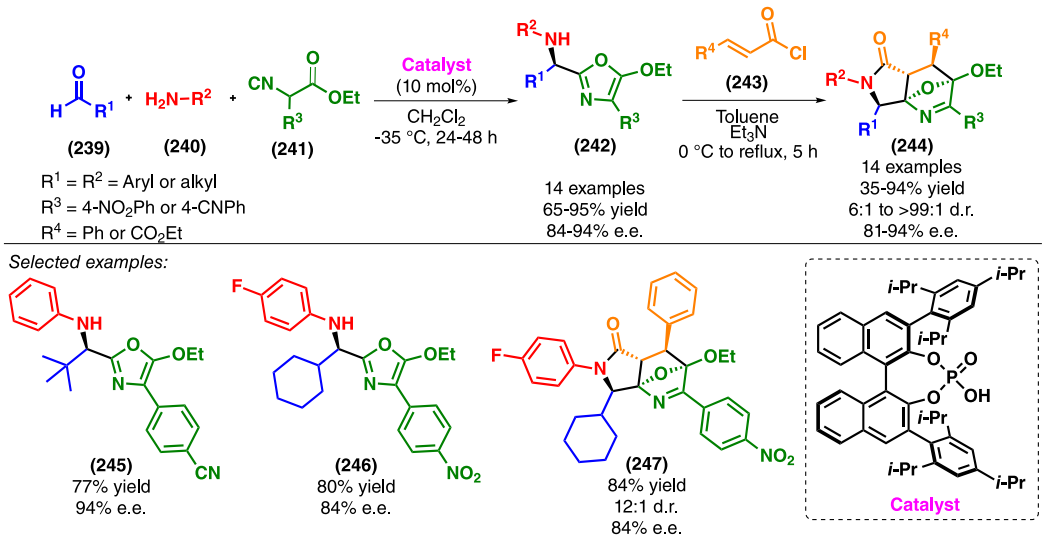
In the same year, Zhu and co-workers[115] developed an enantioselective methodology for another Ugi-type reaction (Scheme 41). By using aldehydes (**239**), amines (**240**) and isocyanoacetates (**241**), in the presence of a chiral phosphoric acid catalyst, a diversity of enantioenriched 5-alkoxyoxazoles (**242**) was prepared through a three-component Ugi-type reaction. Notably, the desired products were attained in moderate to excellent yields (65-95%) and with good to excellent enantiomeric excesses (ranging from 84 to 94% e.e.). Although excellent results were observed when using steric



Scheme 39. Asymmetric four-center three-component Ugi reaction.



Scheme 40. Chiral dicarboxylic acid catalyzed asymmetric Ugi-type reaction.



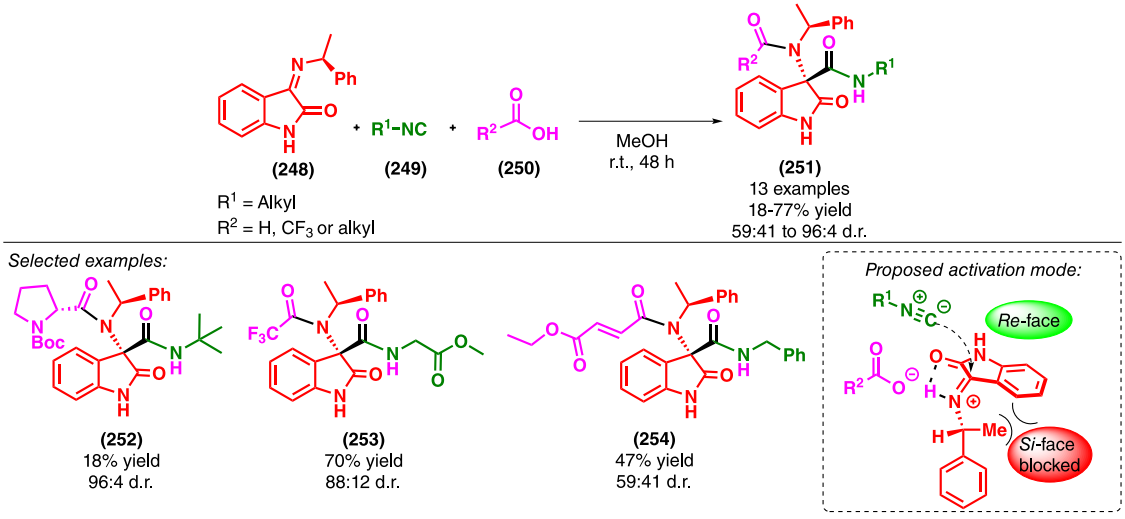
Scheme 41. Organocatalytic enantioselective three- and four-component Ugi-type reaction.

hindered aldehydes (e.g., **245** and **246**), the use of linear aliphatic aldehydes provided the adducts in lower e.e.

The authors also demonstrated that, after the formation of product (**242**), the addition of α,β-unsaturated acyl chlorides (**243**) can provide epoxytetrahydropyrrolo[3,4-*b*]pyridin-5-ones (**244**) in moderate to excellent diastereoselectivities (up to > 99:1 d.r.). The described four-component synthesis generates the adduct with high structural complexity through a sequential of acylation of the amine, followed by intramolecular Kondrat'eva Diels-Alder reaction. A similar Ugi-type transformation was also described by Chen and co-workers.[116]

Another important approach for the diastereoselective three-component Ugi reaction consists on the use of chiral imines as substrates. For example, studies involving the use of chiral pyrrolines[117] and 5,6-dihydro-1,4-oxazin-2-one (or 5,6-dihydropyrazin-2(1*H*)-one) [118] have been described for the diastereoselective preparation of functionalized heterocycles.

In this context, the use of chiral ketimines (**248**), isonitriles (**249**) and carboxylic acids (**250**) in the asymmetric synthesis of 3,3-disubstituted 3-aminooxindoles (**251**) through a three-component Ugi approach has been described Silvani and co-workers[119] (Scheme 42). As commonly observed for Ugi reactions, the diastereosiomeric ratios was generally only moderate (e.g., **254**). However, in some cases, such as (**252**) and (**253**), a high diastereisomeric ratio was observed (up to 96:4 d.r.). It was proposed that the chiral amine partially blocks the *Si*-face of the amine, making the attack of the isocyanide more likely to occur to the *Re*-face, explaining the origin of the diastereoselectivity.

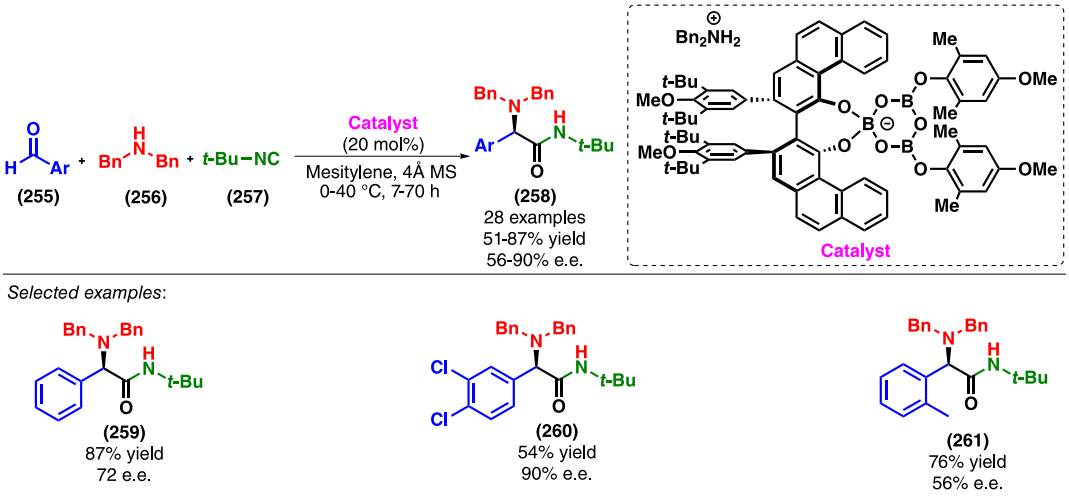


Scheme 42. Diastereoselective Ugi three-component reaction employing chiral ketimines.

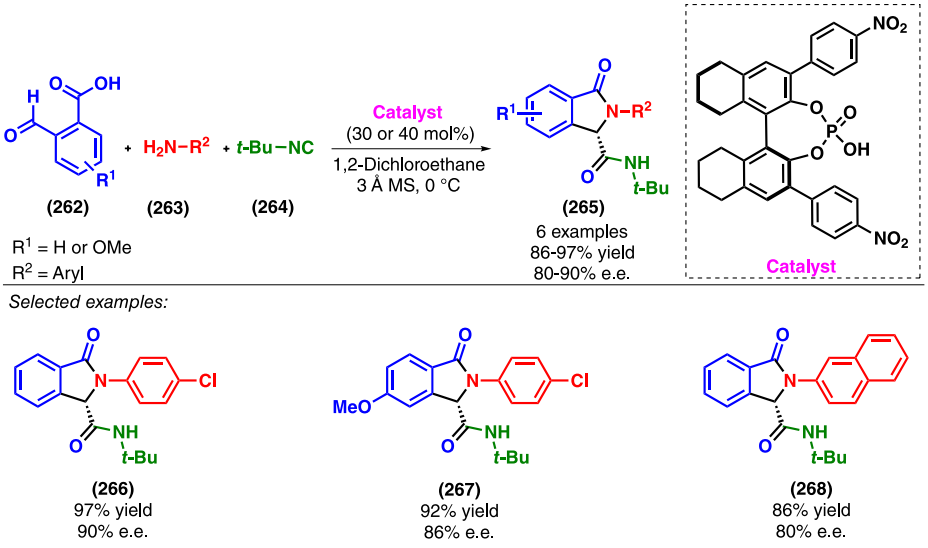
In 2014, Wulff and co-workers[120] developed a boroxinate-based catalyst for the asymmetric preparation of three-component Ugi-type adducts (Scheme 43). By reacting aldehydes (**255**), dibenzylamine (**256**), and *tert*-butyl isocyanide (**257**), the desired (*R*)-α-amino amides (**258**) were accessed in moderate to good yields (51-87%), and enantiomeric excesses (up to 90% e.e.). Although the method efficiently provided the desired adducts, the method was limited to aromatic aldehydes, as shown for (**259**), (**260**) and (**261**).

In 2016, Zhu and co-workers[121] developed a new enantioselective methodology for a four-center three-component Ugi reaction using chiral phosphoric acids as catalysts (Scheme 44). The reaction among 2-formylbenzoic acids (**262**), aromatic amines (**263**) and *tert*-butyl isocyanide (**264**) afforded 3-oxo-2-arylisoindoline-1-carboxamides (**265**) in high both yields and e.e. (up to 97% yield and 90% e.e.). Although a small scope (only six examples) was presented for this reaction, it was also possible to access these derivatives through the use of isocyanides and 3-(phenylamino)isobenzofuran-1(3*H*)-ones (two-component coupling).

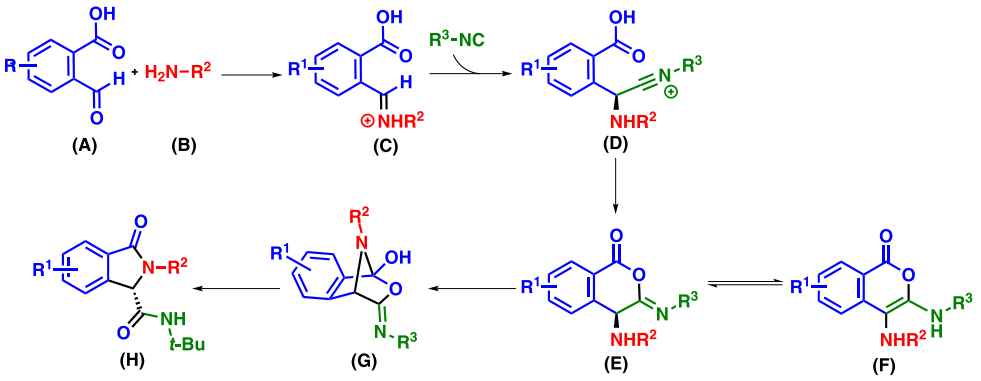
A plausible mechanism for this reaction was then proposed (Scheme 45). First, the iminium (**C**) is formed through the reaction between the amine (**B**) and the aldehyde (**A**). Next, isocyanide attacks this intermediate, affording the nitrilium intermediate (**D**), followed by an intramolecular cyclization to generate (**E**). Interestingly, the enantioselectivity seems to arise from a catalyst-mediated dynamic kinetic resolution involving the imine-enamine tautomerism between (**E**) and (**F**), instead of the C–C bond formation through the attack of the isocyanide to the imine. Finally, the Mumm rearrangement of (**E**), in which (**G**) is formed as a key intermediate, releases the desired product (**H**).



Scheme 43. Organocatalyzed enantioselective three-component Ugi-type reaction.



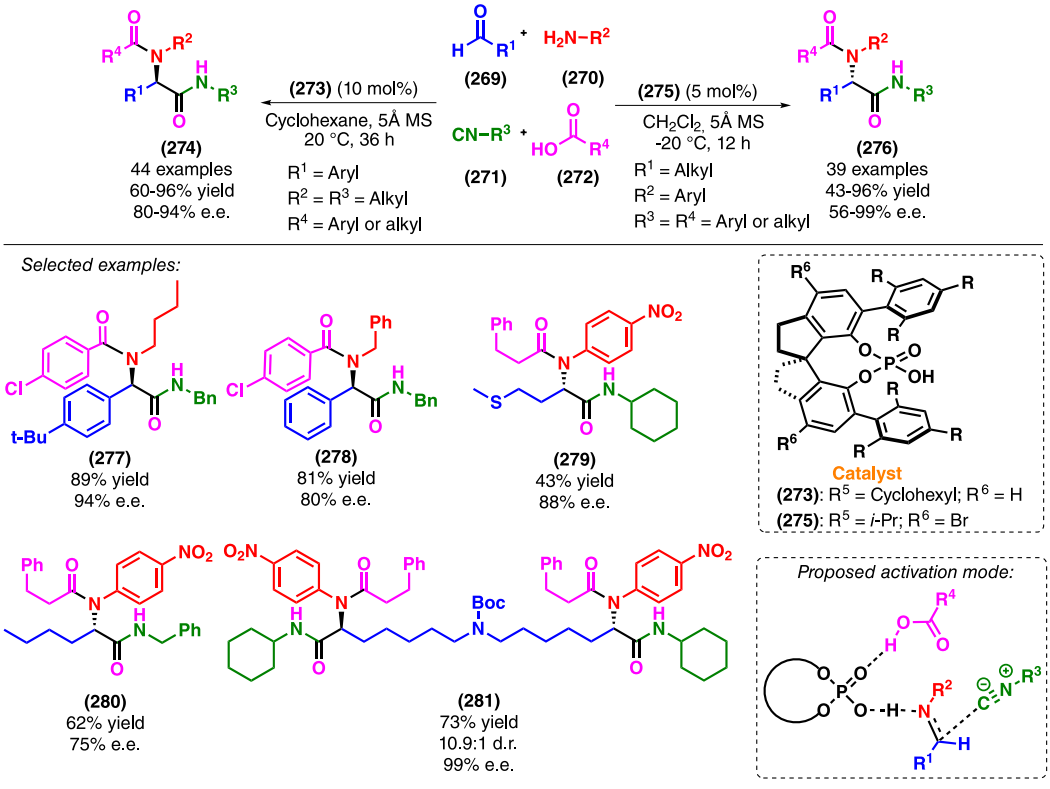
Scheme 44. Enantioselective four-center three-component Ugi reaction.



Scheme 45. Possible reaction pathway for the four-center three-component Ugi reaction.

Recently, a great contribution to the enantioselective synthesis of α-acylaminoamides through the classic four-component Ugi reaction among aldehydes (**269**), amines (**270**), isonitriles (**271**) and carboxylic acids (**272**) has been presented by Tan and co-workers[122] (Scheme 46). By using chiral phosphoric acids as catalysts, a substrate scope of more than 80 examples was described, affording the desired products (**274**) and (**276**) in up to 96% yield and 99% e.e. By subtle alterations in the reaction conditions (e.g., temperature and catalysts), two protocols were described (one for aliphatic aldehydes, such as **279** and **280**, and other for benzaldehydes, e.g., **277** and **278**). Furthermore, the diastereoselective synthesis of (**281**) was demonstrated through two consecutive Ugi reactions (using a total of seven components) in 10.9:1 d.r. and 99% e.e.

Computational investigations using the Density Functional Theory were also carried out to obtain insights concerning the reaction mechanism. Several reaction steps were calculated, demonstrating the energy barriers involved, as well as the role of substrate-catalyst interactions. In this context, the addition of the isocyanide to the imine was found as the enantiodetermining step. In special, the protonation of the imine is mediated by the catalyst, which also simultaneously interacts with the carboxylic acid (Gibbs free energy barriers involved ($\Delta G^{\ddagger}$) = 15.7 kcal mol^{-1}).

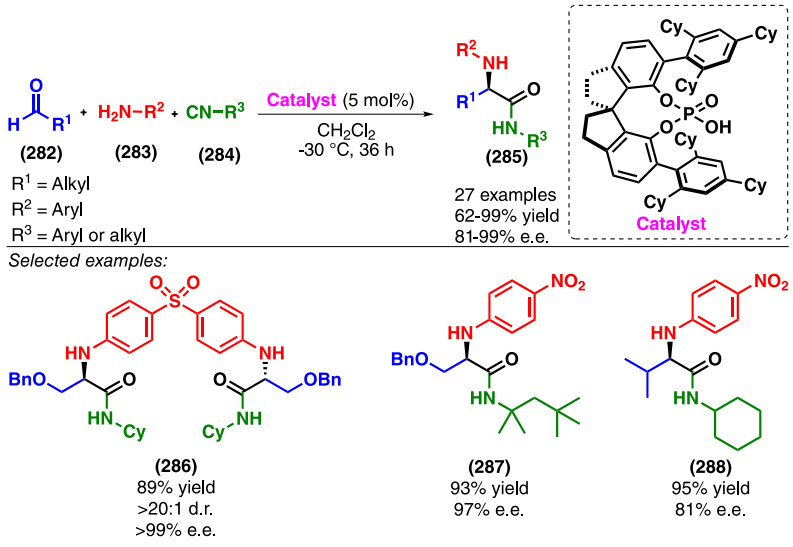


Scheme 46. Enantioselective Ugi four-component reaction using chiral phosphoric acids.

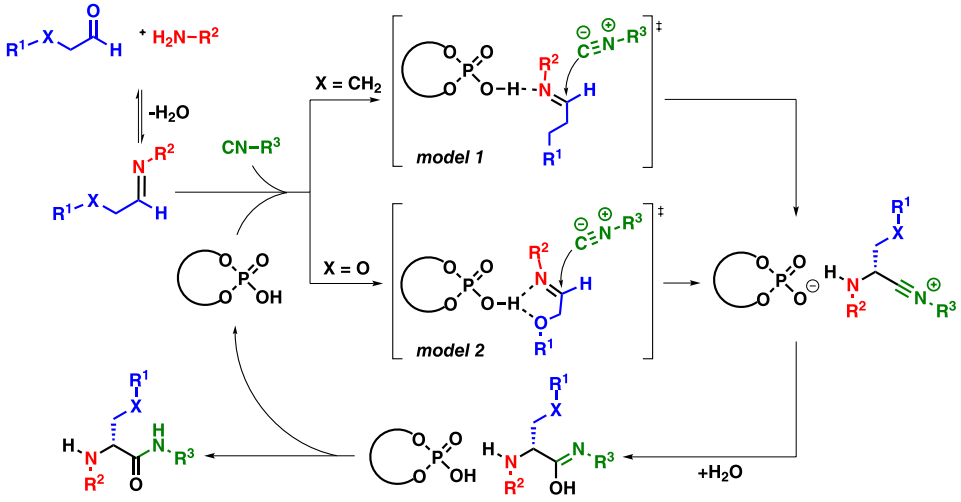
In 2020, the same group[123] presented an asymmetric methodology for the three-component Ugi-type reaction (Scheme 47). A broad substrate scope of (*R*)-α-aminoamides (**285**) was prepared in moderate to excellent yields (62-99%) and good to excellent enantiomeric excesses (up to 99% e.e.) through the reaction among aliphatic aldehydes (**282**), amines (**283**) and isonitriles (**284**). The use of diamines allowed the preparation of adducts involving two consecutive Ugi-type reactions, such as (**286**), in excellent diastereoisomeric ratios and enantiomeric excesses (up to > 20:1 d.r and > 99% e.e.). Notably, this methodology was successfully applied in the three step preparation of the active pharmaceutical ingredient (*R*)-lacosamide, circumventing some limitation of other diastereoselective protocols involving the classic Ugi reaction.[124]

A possible reaction mechanism was presented, in which two possible activation models of the imine were proposed during the enantiodiscriminating step (Scheme 48). For aldehydes without oxygen in the alkyl chain (e.g., **288**), the activation of the imine occurs only by catalyst protonation (model 1). In contrast, when aldehydes bearing oxygen at the side-chain were used, a bidentate model was suggested (model 2), making the substrate-catalyst interaction more rigid and, consequently, enhancing the enantioselectivity (as shown for **287**).

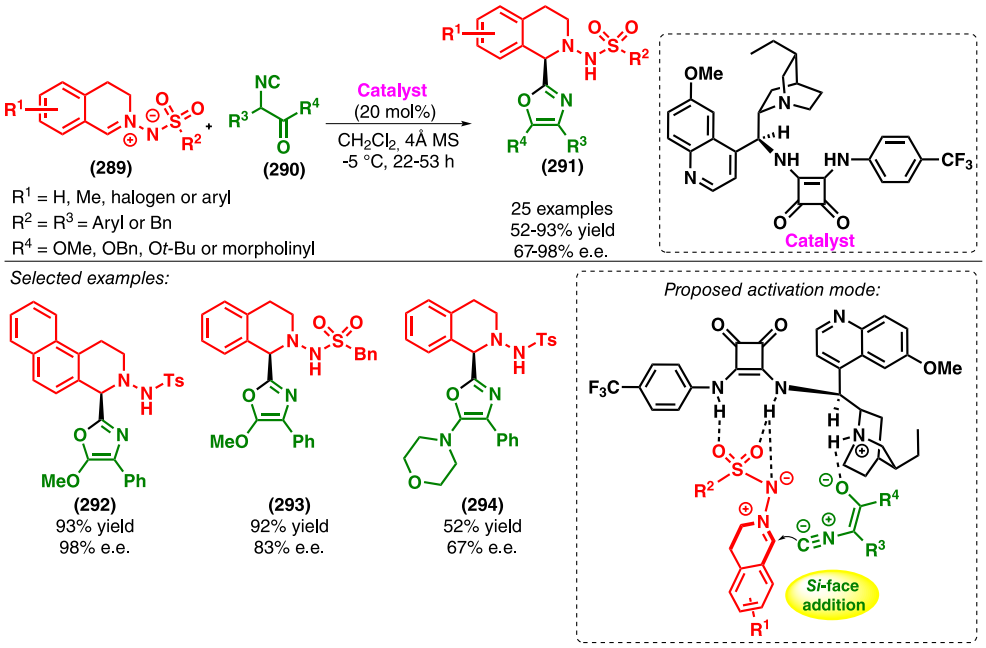
Recently, the use of a cinchona alkaloid-derived squaramide catalyst has been described for the asymmetric two-component Ugi-type reaction of *C*,*N*-cyclic azomethine imines (**289**) and α-aryl-substituted isocyanoacetates (**290**) (Scheme 49).[125] The desired C1-oxazole-substituted tetrahydroisoquinolines (**291**) were isolated in excellent



Scheme 47. Phosphoric acid catalyzed preparation of enantioenriched α-aminoamides.



Scheme 48. Proposed mechanism for the three-component asymmetric Ugi-type reaction.



Scheme 49. Bifunctional cinchona alkaloid squaramide catalyzed two-component Ugi-Type reaction.

yields (86-93%) and moderate to excellent enantiomeric excesses (up to 98% e.e.). The authors propose a dual activation mode, in which the catalyst simultaneously activates the azomethine imine (through a hydrogen bonding interaction with the squaramide) and the isocyanoacetate enolate (involving a second hydrogen bonding with the catalyst ammonium salt). Thus, this molecular complex provides an adequate arrangement for the addition of the isocyanoacetate enolate on the *Si*-face of azomethine imine, providing the derivative with the *R*-configuration as the major product.

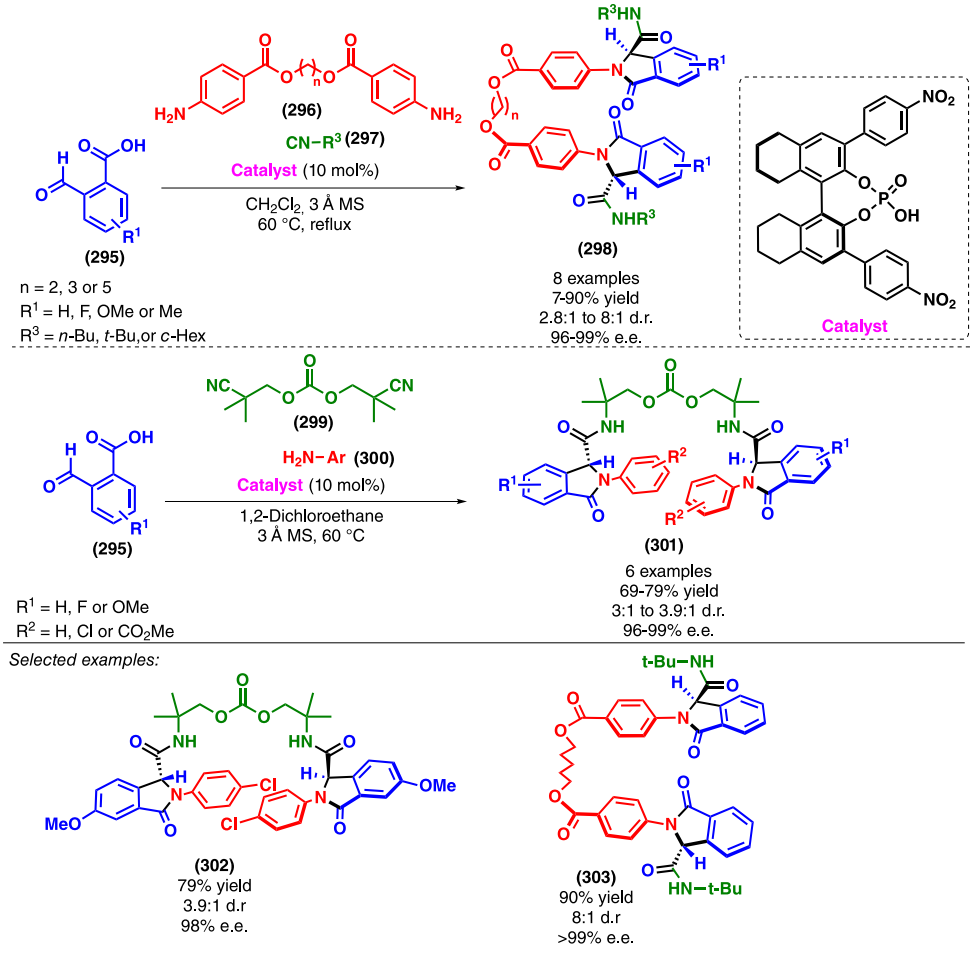
In 2019, an organocatalytic approach to the asymmetric preparation of double Ugi adducts has been reported by Tong and co-workers[126] (Scheme 50). Two approaches were described for the double Ugi reaction: the first involves the reaction among 2-formylbenzoic acids (**295**), diamines (**296**) and isocyanides (**297**), and the second employs 2-formylbenzoic acids (**295**), carbonate-linked bisisocyanides (**299**) and amines (**300**). Both approaches allow the access to the double Ugi adducts (**298**) and (**301**) in moderate diastereomeric ratio (ranging from 2.8 to 8:1) and excellent enantiomeric excesses (ranging from 96 to 99%). This strategy also allowed the access to enantioenriched Ugi adducts after cleavage of the dimers, affording 3-oxo-isoindoline-1-carboxamides with excellent enantiomeric excesses (up to 98% e.e.).

Finally, in 2022, Yu and co-workers[127] reported a method to access enantioenriched Ugi products (**308**) and Ugi-azide analogues (**310**) through the use of anionic chiral cobalt(III) complexes as catalysts (Scheme 51). A diverse substrate scope involving more than 90 examples was presented and highlighted the great utility of this transformation. The classical four-component Ugi reaction, involving the reaction among aldehydes (**304**), amines (**305**), isocyanides (**306**) and carboxylic acids (**307**), provided (*R*)-products in low to excellent yields (up to 99%) and enantiomeric excesses (ranging from 21 to 96% e.e.). By substituting the carboxylic acid for sodium azide (**309**), the authors also accessed α-aminotetrazoles with great efficiency (up to 86% yield and 98% e.e.).

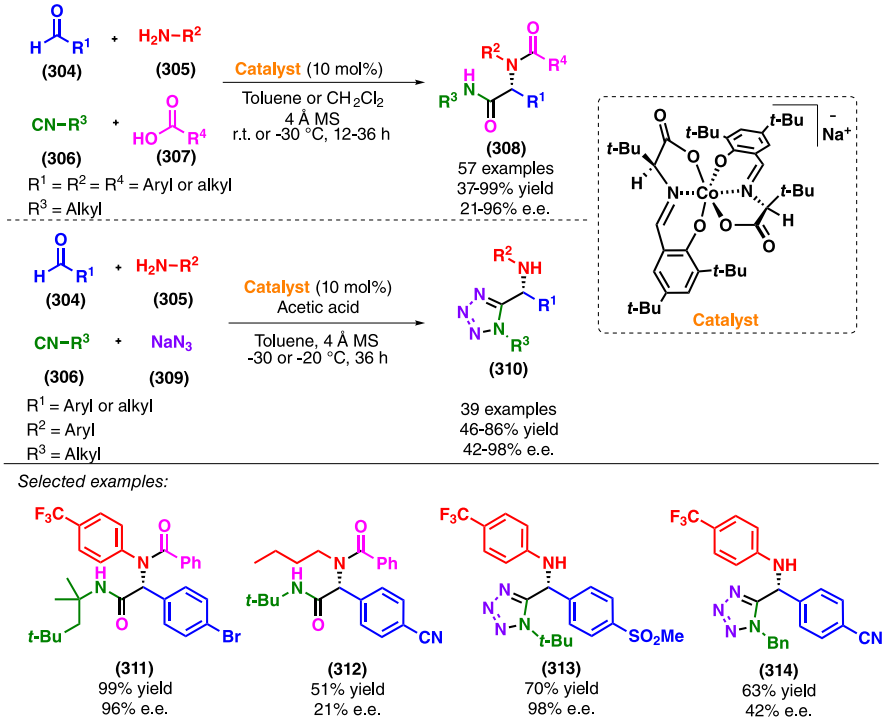
Control experiments were carried out and provided insights involving the catalytic cycle and the activation mode for this reaction (Scheme 52). The formation of the nitrilium intermediate was proposed as the enantiodetermining step. In this particular case, the iminium ion is activated through a hydrogen bonding interaction with the carboxylic acid; simultaneously, a second hydrogen bond between the acid and the catalyst also occurs. This chiral ion-pairing intermediate is then preferentially attacked by the isocyanide at the *Re*-face of the imine (the attack at the *Si*-face is not favorable due to the steric hindrance provided by the catalyst *tert*-butyl groups), affording the enantioenriched (*R*)-product.

6. Conclusions

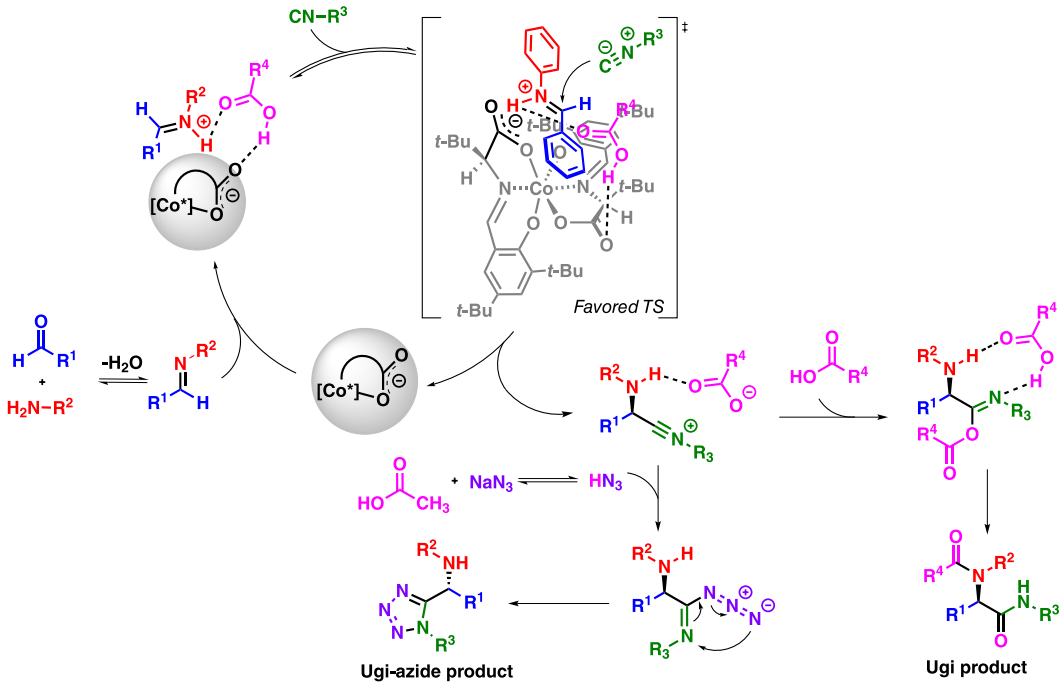
Multicomponent reactions allow a rapid increase in molecular complexity, affording structurally complex adducts in a single procedure from simple starting materials. In contrast, for a long time, the development of efficient



Scheme 50. Dimers obtained by CPA catalysis in double-Ugi reactions.



Scheme 51. Chiral cobalt(III) catalyzed Ugi and Ugi-azide reactions.



Scheme 52. Proposed catalytic cycle (and favored transition state) for Ugi and Ugi-azide reactions catalyzed by a chiral cobalt(III) complex.

asymmetric methods for some of these reactions (e.g., Passerini and Ugi) remained as a gap which limited their application in some fields of science, such as total synthesis. Recently, studies have allowed a better comprehension of the mechanisms associated with these transformations and, consequently, the design of novel catalytic systems and/or activation modes for these reactions. Thus, a great development of asymmetric protocols, especially enantioselective ones, involving multicomponent reactions occurred during the last two decades. In this review, a general overview of asymmetric protocols for four important multicomponent reactions (Strecker, Mannich, Passerini and Ugi) have been covered, pointing out the main developments and opportunities in this area. To date, recently examples showing the power of asymmetric multicomponent reactions, including their representative substrate scope, discussions on their observed selectivities and reactivity were critically exposed.

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