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Organocatalytic enantioselective multicomponent reactions (OEMCRs)

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Abstract—The achieved level of expertise in organocatalytic processes has allowed synthetic chemists to apply this useful synthetic strategy to enantioselective multicomponent reactions. Although, this new methodology is still in its infancy, the reported results show the possibilities and versatility of this type of reaction, with an extraordinary level of atom efficiency being reached. All examples, from classical Mannich, Biginelli, Michael, and Diels–Alder reactions to new amination–reduction and Tietze reactions, allow the synthesis of complex chiral molecules with several stereogenic elements created in just one process. In fact, the organocatalyst acts in this type of process as a clear enzyme mimic, but with an ample substrate scope.

Contents

1. Introduction and definitions

Chirality nowadays plays a major role in almost all chemical fields.[1] The interest of the pharmaceutical and agrochemical industries in chiral products has prompted the intensive search for more efficient methods of synthesis. The development of enantioselective methods has allowed high levels of atom efficiency in transformations to be reached.[2] In the pursuit of more efficient protocols for synthesis, multicomponent reactions[3] should be regarded as a suitable option. In such a process, the time consuming isolation and purification of synthetic intermediates disappears and, in general, the energy, solvents, manipulations and, therefore, cost are reduced, compared to other one-pot synthetic methods, such as domino,[4] tandem[5] or cascade[6] transformations.[7] Moreover, the old idea that the

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presence of an extra reagent could have a detrimental effect on the level of enantioselectivity (or diastereoselectivity) is not in agreement with our current knowledge of this type of reaction.[3c,f]

In the area of catalytic enantioselective transformations, the use of a so-called organocatalyst (small organic molecules) has become a revolution in this century.[8,9] These metal-free processes, excluding silicon and boron derivatives not only from catalyst partner but also from the reagents, have shown their utility and advantages, namely, stability and availability of the catalysts, less demanding reaction conditions, reduced toxicity of reagents and products, and suppression of protection–deprotection steps.

Unsurprisingly, the marriage of both aforementioned concepts has led to an important batch of examples, which will be presented in this overview, reaching a formidable level of efficiency. Firstly, a clear definition of this new synthetic method should be formulated to prevent confusion with other related one-pot organocatalyzed processes.[10] Thus, an organocatalytic enantioselective multicomponent reaction (OEMCR) is a reaction between three or more achiral reagents in a single vessel, which have been added at the same time (or nearly), in the presence of a substoichiometric amount of a chiral organic compound, which forms a new chiral product containing portions of all reagents, with the reagents and the catalysts being small molecules containing only C, H, N, O, P, S, and halogen atoms.

According to this strict definition, all reactions using enzymes, antibodies, even in some extent polymers and, of course, organometallics are excluded. Reactions where any reagent or catalyst has a silicon atom should be excluded. Reactions where the silyl group has only a steric role will however be included in this overview.

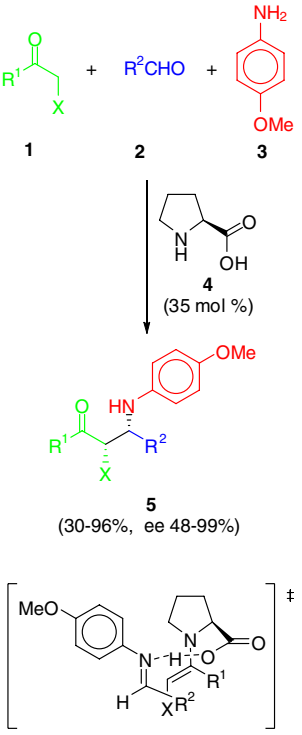
Finally it should be noted that, according to the clearest classification,[7] the multicomponent reactions described here are tandem processes since in all cases two differentiated cycles can be drawn and the connection between them is always products and not reaction intermediates. It is clear for us that tandem etymology does not fit exactly to the definition of these processes, but it is the usually employed word.

2. Mannich multicomponent reactions

The classic Mannich reaction is an aminoalkylation of carbonylic compounds involving ammonia (or an amine derivative), a non-enolizable aldehyde (source of electrophile) and an enolizable carbonyl compound (source of nucleophile). From a modern viewpoint, the potential application of this reaction is rather modest (limited range of application, undesired by-products, unsatisfactory regio- and stereocontrol, etc.). However, the exceptional attractiveness of the final products makes the challenge of overcoming these initial drawbacks worthwhile.[11]

2.1. Ketones as source of nucleophile

The first OEMCR was reported at the beginning of this century, it being an example of a Mannich reaction.[12] The catalyst chosen for this pioneering work was proline **4**, using different ketones **1**, such as acetone and α-hydroxyacetone as a source of the nucleophile, aniline derivatives **3** and aldehydes **2** as the source of the electrophile (Scheme 1). The nature of the aldehyde has some influence on the results, with the chemical yields being lower for aromatic aldehydes, while maintaining the high enantioselectivity (up to 99%). A correlation between the Hammett σ_p-values and the enantioselectivity for 4-substituted aldehydes suggested a negative charge formation in the enantioselective-determining step.[13] The proposed transition state is formed by the in situ generated imine (arising from the condensation of aldehyde and aniline derivative) and the enamine resulting from the reaction of ketone **1** with organocatalyst **4**. The approach of both reagents is governed by steric repulsion between both the aniline and pyrrolidine moieties, as well as by the formation of a hydrogen bond between the iminic nitrogen atom and the carboxylic group. The formation of this transition state was corroborated by DFT-calculations, explaining also the preferential *syn*-diastereoselectivity.[14] However, the presence of an important autocatalytic effect draws a more complicated picture of a possible catalytic cycle.[15]



Scheme 1.

The scope of this multicomponent reaction has been studied further using other different ketones **1**, such as unsymmetrical ketones[16] and diverse protected dihydroxyacetone derivatives.[17] Although the aldol reaction could compete with the formation of compounds **5**, it is worthy to note

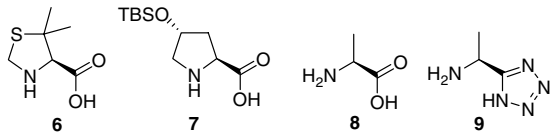
that Mannich compounds **5** were obtained with a very high regio-, diastereo- and enantioselectivity. Different aldehydes **2**, such as branched and linear aliphatic ones, formaldehyde[17c,18] and ethyl glyoxylate[17] were also used successfully. Instead of *p*-anisidine **3**, other aniline derivatives can be used to obtain similar results. However, due to the possibility of an easy removal of the *p*-methoxyphenyl protecting group, aniline **3** is the ideal partner, although for some concrete examples the deprotection step is not so easy.

The only drawback of this reaction is the low chemical yield in certain examples, as well as the long reaction times. In order to improve these aspects several new reaction conditions have been tested. Thus, the replacement of a typical organic media by an ionic liquid,[19] such as *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ([bmim]BF_4) increased the reaction rate by 4–50 times, probably owing to the imine activation by the solvent, maintaining the aforementioned diastereo- and enantioselectivity.

The pressure in the reaction was expected to have a great impact, since the activation volume of this multicomponent reaction is negative. In fact, when the reaction was performed under high pressure induced by water-freezing conditions (≈200 MPa) at −20 °C, the yields and enantioselectivities were improved.[20] Furthermore, electron-rich aromatic aldehydes **2** could be used for the first time.

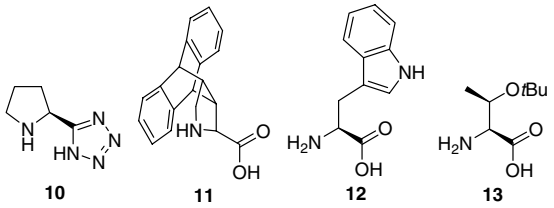
The use of microwave (15 W) or conventional oil bath heating (75–77 °C) also increased the reaction rates, allowing the reaction to be performed under very low catalyst loading (**4**, 0.5 mol %).[21] Finally, it should be noted that the use of ultrasound conditions also had a beneficial effect on the reaction rates.[22]

Proline **4** is not the only suitable catalyst for this multicomponent Mannich reaction but other small organic molecules have been proposed as an alternative. In the early stage of this reaction, thiazoline derivative **6** was used as a catalyst, affording slightly lower results than compound **4** (38–58%, ee 50–89%).[23] Conversely, catalyst **7** gave similar results to those obtained using proline (70–98%, ee 81–96%), with an interesting enhancement on the reaction rate due to its higher solubility.[24]



Simple acyclic amino acids such as alanine **8** and its tetrazole derivative **9** have been successfully employed, to give the best results when cyclic ketones **1** were used, and in the presence of one equivalent of dicyclohexyl amine.[25]

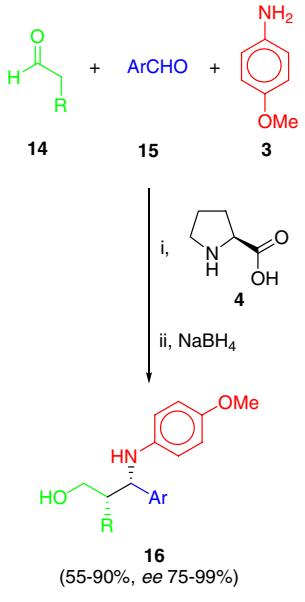
The proline tetrazole derivative **10** catalyzed the multicomponent Mannich reaction using azido ketones as a source of the nucleophile (**1**: X = N_3). The results obtained ranged from good to excellent depending on the nature of aldehyde **2** used and were attributed to the high solubility of the catalyst.[26] However, the very soluble roof-shaped antracene-fused chiral proline derivative **11** did not improve upon the previous results obtained with proline.[27]



The high *syn*-diastereoselectivity found for all catalysts presented could be changed to *anti* just by the use of the amino acid derivatives **12** and **13**. This fact was rationalized on the basis that this primary amine catalyst forms the corresponding *Z*-enamine when reacted with α-hydroxy ketones (instead of the *E*-enamine represented in Scheme 1). The reaction provided the corresponding products *anti*-**5** with high yields, diastereoselectivities (up to 98%) and good to excellent enantioselectivities (53–98%), with the reaction catalyzed by compound **13** being faster than by **12**.[28]

2.2. Aldehydes as source of nucleophile

The multicomponent Mannich reaction using aliphatic aldehydes **14** as a source of the nucleophiles and aromatic aldehydes **15** as electrophiles were simultaneously published by different groups using proline **4** as a catalyst (Scheme 2).[29]



Scheme 2.

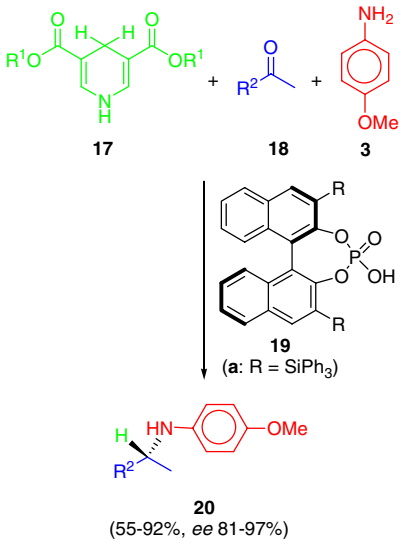
The very strict control of the temperature (below 4 °C) was compulsory in order to avoid the undesired aldol reaction, as well as the sequential in situ reduction of aldehyde formed to the corresponding primary alcohol (by adding

$NaBH_4$), in order to prevent the epimerization and racemization process during the isolation and purification steps. Under these reaction conditions, the corresponding 3-amino primary alcohols **16** could be obtained with very high yields, diastereo- and enantioselectivities. A further study expanded upon the range of possible electrophiles used to hetereoaromatic aldehydes and glyoxylate, as well as nucleophiles to long chain aldehydes bearing carbon–carbon double bonds and α-hydroxy aldehydes.[30]

The usefulness of the former reaction has been exemplified by the synthesis of the *N*-terminal amino acid moiety of nikkomycis B and B_x, a nucleoside peptite antibiotic isolated from the culture broth of *Stremptomyces tendae*,[31] and different imino sugar derivatives through a sequential multicomponent Mannich reaction followed by a Horner–Wittig–Emmons reaction with the in situ formed aldehyde instead of the reduction with $NaBH_4$.[32]

3. Amino-reductive multicomponent processes

The enantioselective amino reductive[33] multicomponent reaction has been performed successfully using the chiral Brønsted acid **19a** (R = $SiPh_3$ in Scheme 3).



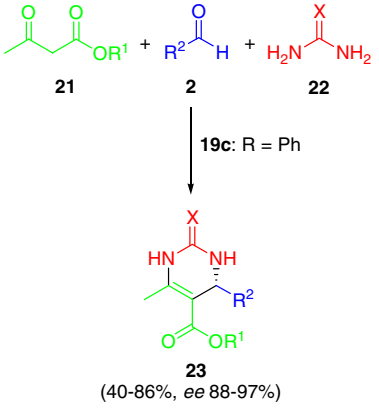
Scheme 3.

The reaction of different methyl ketones with *p*-anisidine and the Hanztsch ester **17** (R^1 = Et) gave the expected chiral α-branched secondary amine **20** with excellent results.[34] In order to obtain these results, the amount of water should be controlled strictly by the addition of 5 Å molecular sieves, since the presence of water has a negative effect on the iminium formation, and in the further hydride reduction. The scope of the ketone component is very broad, admitting substituted aryl and alkyl derivatives, even permitting the discrimination between methyl carbonyl moieties from other alkyl carbonyl ones.

The aforementioned reaction has been further expanded to the dynamic kinetic resolution of enolizable α-branched aldehydes. In this case, the final β-branched secondary amine could be obtained with good chemical yield and enantioselectivities, independently of the electronic nature of the starting aldehyde when the chiral BINOL-phosphoric derivative **19b** [R = 2,4,6-(iPr)$_3$C$_6$H$_2$] was used as chiral organocatalyst.[35]

4. Biginelli multicomponent reactions

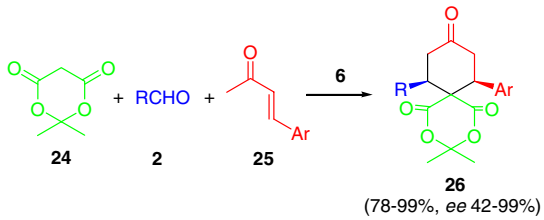
The Biginelli dihydropyrimidine synthesis consists of the condensation of urea, an aldehyde and a 1,3-ketoester. The accepted mechanism involves the condensation of urea with the aldehyde to yield the corresponding iminium intermediate, which is then trapped by an aldol-type reaction with the enol derived from the ketoester.[36] The chiral BINOL-phosphoric derivative **19c** (R = Ph) has also been shown to be an excellent organocatalyst for also the classical Biginelli multicomponent reaction, which permitted the synthesis of chiral polyfunctionalized 3,4-dihydropyrimidin-2-(1*H*)-ones **23** (Scheme 4).[37] Electron rich and poor aromatic aldehydes and less reactive aliphatic aldehydes, as well as different 1,3-ketoesters underwent the reaction with excellent enantiomeric excess, providing access to an ample scope of pharmaceutically interesting products **23** without any transition metal contamination.



Scheme 4.

5. Tietze multicomponent reactions

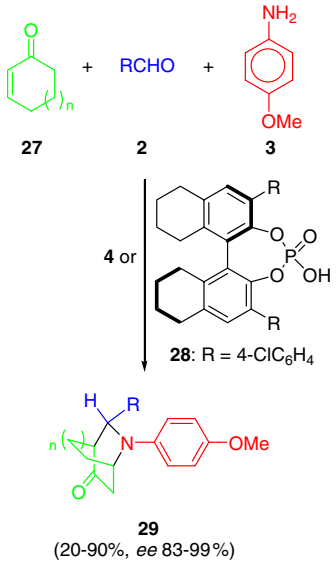
The Tietze multicomponent reaction (Knoevenagel/Diels–Alder process) between Meldrum's acid **24**, aldehydes **2** and α,β-unsaturated methyl ketones **25** catalyzed by the thiazoline derivative **6** gave spirolactones **26** (Scheme 5).[38] The reaction rates obtained, yields and enantioselectivities were better in protic solvents, such as methanol, probably owing to the enhanced stabilization of charged intermediates and the more facile proton-transfer reactions. The scope of the reaction has been extended to other 1,3-dicarbonyl compounds,[39] and even the α,β-unsaturated ketone could be prepared in situ through a Wittig reaction,[40] previously to the one-pot multicomponent process, with the whole sequential processes giving the same results as the previous multicomponent reaction.



Scheme 5.

6. Aza-Diels–Alder multicomponent reactions

The formal aza-Dields–Alder multicomponent reaction was initially performed using proline **4** and formaldehyde (R = H in **2**) to give bicyclic compounds **29** with excellent enantioselectivities (Scheme 6), not only with cyclohexenone but also with other cyclic enones.[41]

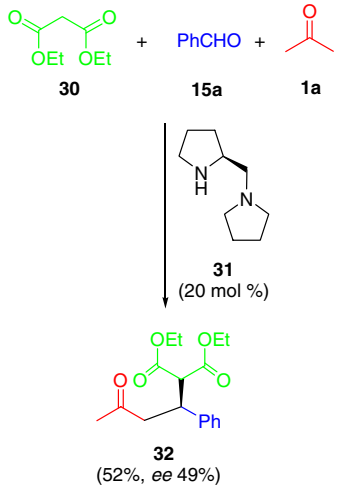


Scheme 6.

The scope of aldehydes was further enlarged to aromatic aldehydes by the use of chiral phosphoric derivative **28**, to give good enantioselectivities, and diastereomeric ratios never higher than 70%.[42] The outcome of the reaction was explained on the basis of a Mannich reaction of the enamine (enol) of the cyclic ketone (see Scheme 1), followed by a Michael type addition to form the new ring in the final compound **29**.

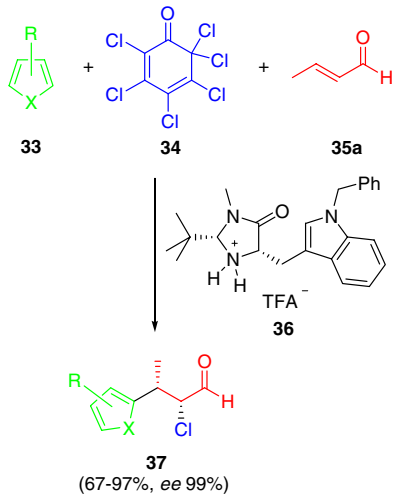
7. Michael-type multicomponent processes

The nucleophilic 1,4-addition to electron-poor olefins, generally α,β-unsaturated carbonylic compounds, is known as the Michael addition, although it was first reported by Komnenos.[43] The usual enantioselective version of this reaction could employ a sequential process.[44] In recent years, different sequences of reaction highlighted the possibility of using an organocatalytic enantioselective multicomponent process. The first example of Michael-type multicomponent reaction was performed by an aldol reaction of benzaldehyde **15a** with acetone **1a** to give the corresponding benzylidenacetone, which suffered the 1,4-addition of diethyl malonate in the presence of substoichiometric amounts of proline amine derivative **31** (Scheme 7). The final product **32** was obtained with moderate results but it opened the field to this type of reactions.[45]



Scheme 7.

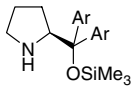
More interesting is the Michael-type multicomponent process outlined in Scheme 8.[46] The success of the reaction was based in the formation of a chiral iminium derivative between aldehyde **35a** and catalyst **36**, which is an active electrophilic agent able to react with electron-rich heteroaromatic compounds **33** to form the corresponding chiral enamine intermediate. This intermediate is in situ trapped by the chlorinating agent **34**, yielding the highly functionalized compounds **37** with excellent levels of diastereo- and enantioselectivity. Instead of using electron-rich heteroaromatic compounds **33**, as the initial nucleophiles, other nucleophiles could be used, such as Hanztsch ester **17**.



Scheme 8.

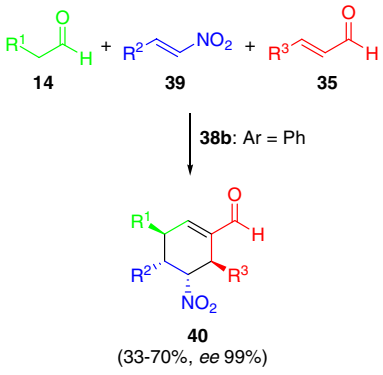
Based on this strategy, the addition of aliphatic thiol derivatives (nucleophiles) to different α,β-unsaturated aldehydes

of type **35** and subsequent amination of the enamine intermediate with azodicarboxylates gave access to 1,2-aminosulfanyl aldehydes with diastereomeric excess up to 98% and enantioselectivities up to 99%.[47] In this case, the organocatalyst used was the prolinol derivative **38a**, the addition of substoichiometric amounts of a carboxylic acid, as well as the control of temperature, being mandatory in order to prevent the racemization processes and to increase the reaction rates.



38a: Ar = 3,5-$(CF_3)_2C_6H_3$

A more complicated sequence of chiral iminium-enamine formation permitted the construction of cyclohexane carbaldehdyes **40** (Scheme 9).[48] In this process, the more electrophilic reactive nitroalkene **39** reacts with the chiral enamine, formed in situ by the reaction of the prolinol derivative **38b** with aldehyde **14**, to give the expected Michael type product. The α,β-unsaturated aldehyde **35** reacts with the liberated prolinol to give a new chiral Michael acceptor, which in turn suffers a new Michael addition by the previously formed nitro alkane. A final intramolecular aldol condensation and dehydration gives the corresponding cyclic compound **40**. The results obtained could not be improved upon, since from 16 possible stereoisomers, only two were obtained, in all cases with good diastereoselectivities (68–89%; the epimerization occurred on the carbon bearing the nitro functionality) and enantioselectivities (99%).

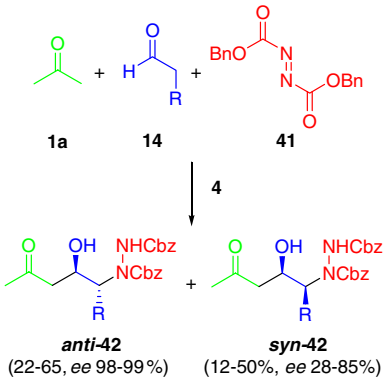


Scheme 9.

This multicomponent reaction, followed by an intramolecular Diels–Alder reaction (R^1 = dienyl moieties) has been successfully applied to the synthesis of functionalized decahydroacenaphthylene and decahydrophenalene derivatives, which are typical units of diterpenoid natural products.[49]

8. Amination-aldol processes

Finally a multicomponent reaction between acetone **1a**, aldehydes **14** and azodicarboxylates **41** catalyzed by substoichiometric amounts of proline **4** yielded a ≈1:1 mixture of the corresponding diastereoisomers **42** (Scheme 10).[50] The success of the reaction can be attributed to the higher reactivity of aldehydes over acetone (about 100-fold). The disappointing diastereomeric ratio was attributed to the easy and fast racemization of the initial α-amino aldehyde formed, compared to its reaction with acetone.



Scheme 10.

9. Conclusions and perspectives

The aforementioned highly efficient processes show that organocatalytic enantioselective multicomponent reactions are a very promising chemical strategy of synthesis, which allows the rapid access to chiral structurally complex molecules, starting from simple, readily available precursors, mimicking biological systems and using environmentally friendly reaction conditions. Moreover, the use of small, robust and easy prepared organic molecules as catalyst is an unforgettable advantage.

Acknowledgments

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