Imine-Based Multicomponent Polymerization: Concepts, Structural Diversity and Applications.

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Abstract. Multicomponent reactions (MCRs) are remarkable one-pot combinatorial synthetic tools involving at least three reactants whose nearly all atoms are incorporated in the final product. The development of these high atom-efficient reactions considerably raised the level of molecular complexity and diversity in the last decades. Nowadays, MCRs are no longer confined to organic synthesis and have seen their use extended to polymer science. The latter tend to occupy an
increasingly important place in polymer synthesis and sustain the eager demand for innovative and structurally diverse macromolecules involved in highly valued applications. While MRCs can serve for monomer synthesis and post-polymerization modification, they offer their full potential in one-pot step-growth polymerizations, namely multicomponent polymerizations (MCPs). This review provides a comprehensive and up to date overview of the imine-based MCPs and highlights their great potential for the design of advanced linear, hyperbranched and crosslinked polymers. The focus is placed on MCPs involving imines, the most common and valuable MCRs’ intermediates which are prone to various nucleophilic attacks and give access to a great variety of products. The efficiency, combinatorial feature, substrates versatility and limitations of these imine-based MCPs as well as the polymer diversity they offer are discussed in detail. Some MCPs can also be combined in one-pot to afford unique and highly complex structures. At this stage, several multicomponent step-growth polymerizations are already mature enough to sustain cutting-edge applications in biomedicine, energy, environment and catalysis amongst others. The existing challenges to be addressed are identified and the future research directions are discussed accordingly. MCPs, in particular imine-based ones, will undoubtedly further grow and confirm their status of essential macromolecular engineering tools in the future.

**Keywords:** multicomponent polymerization; multicomponent reaction; imine-based reaction, step-growth polymerization; macromolecular engineering; one-pot polymerization; atom economy.
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Abbreviation

3D     Three-dimensional
Å      Ångström
A-3C-3CP     A³-coupling three-center three-component polymerization
A-3CR     A³-coupling three-component reaction
ACO-3C-2CP     A³-coupling/cycloisomerization/oxidation three-center two-component polymerization
ACO-3C-3CR     A³-coupling/cycloisomerization/oxidation three-center three-component reaction
ADMET     Acyclic diene metathesis
AIE     Aggregation-induced emission
AP-5C-4CP     A³-coupling-Petasis five-center four-component polymerization
B-3C-2CP     Biginelli three-center two-component polymerization
B-3C-3CP     Biginelli three-center three-component polymerization
CMC     Critical micellar concentration
D      Dispersity
D-4C-3CR     Dihydropyrrole four-center three-component reaction
DHPM     3,4-dihydropyrimidin-2(1H)-ones
DMAc     N,N-dimethylacetamide
DMF     N,N-Dimethylformamide
DMSO     Dimethylsulfoxide
equiv.     Equivalent
ESI-MS     Electrospray ionization - mass spectrometry
GSH     Intracellular glutathione
H-4C-3CP     Hantzsch four-center-three component polymerization
H-4C-3CR     Hantzsch four-center three-component reaction
H-4C-4CR     Hantzsch four-center four-component reaction
HBP     Hyperbranched polymer
HIPE     High internal phase emulsion
IL     Ionic liquid
IMCR     Isocyanide multicomponent reactions
IR     Infrared
KF-3CP     Kabachnik-Fields three-component polymerization
KF-3CR     Kabachnik-Fields three-component reaction
M-3C-2CP     Mannich three-center two-component polymerization
M-3C-3CP     Mannich three-center three-component polymerization
MALI-3C-3CP     MALI three-center three-component polymerization
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<tr>
<td>MALI-3C-3CR</td>
<td>MALI three-center three-component reaction</td>
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<td>MALI</td>
<td>Mercaptoacetic acid locking imine</td>
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<td>MCP</td>
<td>Multicomponent polymerization</td>
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<td>MCR</td>
<td>Multicomponent reaction</td>
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<tr>
<td>MeOH</td>
<td>Methanol</td>
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<tr>
<td>$M_n$</td>
<td>Number average molar mass</td>
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<td>MPa</td>
<td>MegaPascal</td>
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<td>MR-4C-3CR</td>
<td>Modified Radziszewski four-center three-component reaction</td>
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<td>NMP</td>
<td>$N$-methyl-2-pyrrolidone</td>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<td>NP</td>
<td>Nanoparticle</td>
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<td>P-3CR</td>
<td>Passerini three-component reaction</td>
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<td>PA</td>
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<td>PAA</td>
<td>Polyamide acid</td>
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<td>PAMAM</td>
<td>Poly(amoedoamine)s</td>
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<td>PEG</td>
<td>Poly(ethylene glycol)</td>
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<td>PIL</td>
<td>Poly(ionic liquid)</td>
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<td>Poly(DHPM)</td>
<td>Poly(3,4-dihydropyrimidin-2(1H)-one)</td>
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<td>PVDF-HFP</td>
<td>Poly(vinylidenefluoride-co-hexafluoropropylene)</td>
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<td>SEC</td>
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<td>Tetrahydropyrimidine five-center three-component reaction</td>
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<td>TFSI</td>
<td>Bis(trifluoromethane sulfonyl)imide anion</td>
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<tr>
<td>$T_g$</td>
<td>Glass-transition temperature</td>
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<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>$T_m$</td>
<td>Melting temperature</td>
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<tr>
<td>TPE</td>
<td>Tetraphenylethene</td>
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<tr>
<td>TREN</td>
<td>Tris(2-aminoethyl)amine</td>
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1. **Introduction**

1.1. **Multicomponent reactions: Basics and definitions.**

Multicomponent reactions (MCR) are commonly described as one-pot reactions involving at least three components reacting to form a product in which almost all atoms of the starting reagents are incorporated.[1,2] MCRs are powerful and straightforward synthetic methods that exhibit key features such as high atom efficiency and ease of implementation. Moreover, these convergent reactions involve the formation of several covalent bonds leading to rather complex structures which can be easily diversified by varying each component of the reaction. For this reason, they are considered as synthetic tools of choice in combinatorial approaches. Although it is generally accepted that MCRs are highly efficient,[3] this aspect needs to be nuanced. Indeed, the conversion depends on the type of MCRs which can be sorted in three categories based on their mechanism (Fig.1).[4]

![Diagram](image)

**Fig.1.** Main classes of MCRs as described elsewhere.[4] Each step represents an elementary reaction. I and P stand for intermediate and product, respectively.
In type I MCR, all steps (elementary reaction) are reversible which can lead to low yields. Nonetheless, it is possible to displace the equilibrium by trapping a byproduct which consists of small molecules like water, nitrogen and low molecular weight acids.[5,6] In type II, the last step is irreversible and drives the overall reaction towards the final product leading to higher conversion. The irreversible step often corresponds to strongly exothermic reactions such as ring-closure, aromatization, rearrangement or formation of a new carbon-carbon bond.[4] Eventually, the most attractive MCRs belong to type III in which each step is irreversible. Although very effective, examples of such MCRs are scarce in preparative chemistry but commonly encountered in biochemical reactions.[4]

In order to clarify the scope of MCRs, it is important to precise the terms of their definition, i.e. “one-pot reactions involving at least three components leading to a product containing most of the atoms of the reactants”. First, the term “component” needs to be specified since it could designate a chemical compound or a chemical function (functional center). In this review, “component” will refer to an individual compound regardless the number of functional groups it contains. For the sake of clarity, throughout the text, reactions will be designated as follows: name (or abbreviation) of the reaction – number of functional centers - number of components. On the other hand, the term “one-pot reaction” describes a set of chemical reactions, whereby a reagent undergoes successive (or concomitant) chemical reactions in a single vessel or reactor.[7] It does not preclude subsequent addition of reagents, mediators or catalysts nor imply that all reactions steps are carried out under the same conditions. Eventually, it does not exclude manipulation (work-up) or isolation of an intermediate. Indeed, a solution containing the intermediate can be extracted or filtered as long as the product remains in the filtrate, the solvent can be exchanged or
concentrated to dryness. Such cases are considered as one-pot processes as long as the intermediate stays in the same reactor.[7]

In the light of these considerations, we will encompass under the term multicomponent reactions “all reactions taking place in a single vessel, involving more than two reagents, whether introduced together at the start or sequentially, whether or not conditions are changed during the reaction, provided that almost all atoms are incorporated into the final product”. Importantly, the function generated at each step must be the reaction centre of the next one. This criterion excludes cases where a reagent bearing two orthogonal chemical functions[8] reacts independently with two other compounds.[9]

The first MCR was reported in 1837 by Laurent and Gerhardt who reacted ammonia with bitter almond oil, a source of benzaldehyde and hydrogen cyanide (Fig.2).[10] Few years later (1850), Strecker published the synthesis of α-amino acids derived from α-aminonitriles obtained by one-pot reaction between aldehyde, amine and hydrogen cyanide (Fig.2).[11] Since these pioneering works, multicomponent reactions have flourished giving rise to a multitude of MCRs notably the well-known Hantzsch, Biginelli, Mannich, Passerini and Ugi reactions to name a few. In the last years, they became very popular tools in combinatorial chemistry for the synthesis of complex products notably in drug discovery and development of biological compounds.[5,12]
1.2. **Emergence of multicomponent reactions in polymer science**

Nowadays, the development of advanced macromolecular synthetic methods is essential to satisfy the demand for more and more complex polymer materials and fulfil the requirements of today’s highly valued applications. In this context, due to their combinatorial character, ease of implementation and atom economy, multicomponent reactions (MCRs) recently emerged as promising and powerful tools for the design of structurally complex macromolecules. MCRs can be exploited via three different approaches for the synthesis of macromolecules, namely monomer synthesis, post-polymerization modification and step-growth polymerization (Fig.3). Briefly, some monomers prepared by MCRs were polymerized by various techniques including ring-opening metathesis polymerization,[13] radical polymerization[14] or acyclic diene metathesis (ADMET) polymerization,[15–17] or step-growth polymerization[18] amongst others (Fig.3A). This approach consists in a multistep process[15–17] but, in some cases, the synthesis of the monomer by MCR and its polymerization can be done sequentially,[18] or even simultaneously,[19–22] in the same pot. Multicomponent reactions were also successfully applied onto preformed polymers.
in order to modify their side chains functions (Fig.3B).[23] Despite the efficiency of MCRs, the level of post-polymerization modification can be limited by steric hindrance factors as it is generally the case for grafting onto strategies. Finally, step-growth polymerization can be achieved by applying MCRs onto multifunctional reagents (Fig.3C). The latter approach was introduced in the second half of the 20th century, with few examples involving notably the well-known Mannich reaction.[24] Nevertheless, the use of MCRs in direct polymerization underwent an impressive expansion following the work of Meier et al. in 2011 consisting in the polymerization of dicarboxylic acids and dialdehydes in the presence of an isocyanide via the Passerini reaction.[15] Since then, examples of polymer synthesis involving MCRs have flourished the literature.[25–33]

In contrast to the two first approaches, the step-growth process requires very efficient MCRs in order to reach decent molar masses since the latter depend on the conversion and follow the Carother’s law. Two different systems are possible for the synthesis of linear macromolecules by step-growth polymerization, i.e. the use of homo-functional monomers (A₂ + B₂ system) or heterofunctional monomers (AB system). While homo-functional monomers are generally stable, a chemical function being often orthogonal with itself, it is sometimes more difficult to get hetero-functional monomers due to reactions between the different chemical functions. Nevertheless, AB monomers allow better control on stoichiometry, an important parameter to aim for high molecular weights. Using MCRs instead of classical reactions broadens the structural diversity of the polymers. Indeed, as illustrated in Fig.3C, if we consider a three-component reaction involving the chemical functions A, B and C, two polymerization systems are possible, i.e. A₂ + B₂ + C and AB + C for homo- and hetero-difunctional monomers, respectively. In both cases, the structure of the polymer backbone is determined by the difunctional monomers and contains the pattern resulting from the multicomponent reaction. On the other hand, the nature of the side chains of the
Macromolecules is ruled by the monofunctional monomer(s) (Fig. 3C). The properties of the polymers can be modulated by varying the linkers or the substituents bearing the chemical functions but also by changing the nature of the difunctional reagents and the monofunctional ones (e.g. $A_2 + B + C_2$ system).

MCRs have been used for the synthesis of hyperbranched polymers (HBPs) and networks as well. A wide variety of combinations is possible to design these architectures (Fig. 3C). Indeed, MCRs applied to monomers bearing three functions ($A_3$ or $AB_2$) with difunctional and monofunctional monomers lead to three-dimensional macromolecules (Fig. 3C). Networks are obtained when functions are close to the stoichiometry whereas an excess of a function favours the formation of HBPs. Moreover, compared to classical step-growth polymerization, multicomponent polymerization (MCP) allows the use of more available difunctional monomers to get HBPs and networks ($A_2 + B_2 + C_2$ and $AB + C_2$). Over the years, all these approaches involving MCRs have led to polymer materials with antioxidant[34,35] or antibacterial[19,36] properties but also to materials finding applications in heavy metal recovery[37], cell-imaging[22], explosives detection,[38] sensors[39], amongst others.
This review gives an overview of the recent progress in the design of polymers via MCRs. In particular, it focuses on multicomponent polymerization (MCP) methods for the
preparation of linear but also branched and crosslinked polymers. Moreover, we concentrated on the imine-based MCPs since the aldehyde/amine condensation is a very common step of numerous MCRs used in organic and polymer synthesis. Also called Schiff base, imines are very interesting MCRs’ intermediates leading to iminiums upon protonation which ultimately facilitates a nucleophilic attack on the sp2 carbon similarly to carbonyl compounds. In addition, the nitrogen atom is able to perform nucleophilic attack allowing a great variety of reactions as will be illustrated. Note that the condensation reaction forming the imine is reversible and often leads to incomplete conversion. Consequently, for an imine-based MCR to be efficient, the following steps must displace the equilibrium by consumption of the formed imine through irreversible reaction steps or at least by subsequent reactions largely displaced towards the formation of products.

Here, we aim to depict the great potential of the imine-based MCRs in step-growth polymerizations for the design of linear macromolecules and networks but also to emphasize their current limitations in terms of molar masses and substrates versatility. Although the field of MCPs is still in its infancy, as will be discussed, this research area already contributed to the development of cutting-edge applications in biomedical, energy, electronic, CO₂ capture, catalysis, heavy metal recycling sectors, to name a few.

2. **Imine-based Multicomponent Polymerizations**

2.1. **Isocyanide-based MCP**

An important class of MCPs relies on isocyanide multicomponent reactions (IMCRs). Isocyanides exhibit unusual reactivity coming from their relatively stable divalent carbon. First synthesized by Lieke in 1859,[40] their electronic structure is still under debate today. They can
either be represented under a zwitterionic form (Lindemann, 1930) or as a carbene (Nef, 1892).[41]

Nevertheless, a recent theoretical study suggests a dominant contribution of the carbene form although the linear geometry is imposed by the zwitterionic contribution.[41] The carbene form explains why isocyanides can act both as a nucleophile or an electrophile on the carbon atom (α-addition). Due to the aforementioned characteristics, the isocyanides became important chemicals in MCRs where they often first react as nucleophiles, to form α-adducts that can subsequently react with other nucleophiles.[42,43] In most IMCRs, the isocyanide divalent carbon is converted into a tetravalent one through the formation of at least one carbon-carbon bond, an exothermic transformation which constitutes the driving force of the reaction and contributes to its efficiency. The use of isocyanides as building blocks in polymer science is increasingly popular,[27–30,44,45] especially upon reactions with imines as described below.

2.1.a. Ugi-4C

The Ugi four-component reaction (U-4CR) usually refers to the reaction between a primary amine, an aldehyde (or a ketone), an isocyanide and a carboxylic acid leading to an α-amido amide (Fig.4). The U-4CR is an extension of the first reported isocyanide-based MCR, namely the Passerini three-component reaction (P-3CR) which involves only three components, i.e. a carboxylic acid, an aldehyde or a ketone and an isocyanide, and produces α-acyloxycarboxylamides. The introduction of a fourth component, that is, the amine, increased the diversity of the possible products and the U-4CR rapidly became one of the most important MCRs in combinatorial and medicinal chemistries.[4] The most plausible and generally accepted mechanism involves the condensation of the amine and the aldehyde to form a Schiff base that is subsequently protonated by the acid to generate an iminium and a carboxylate. The key step consists of the nucleophilic attack of the isocyanide onto the iminium to form a nitrilium
intermediate that undergoes the addition of the carboxylate. Eventually, an α-amido amide is generated through acyl group migration (Mumm rearrangement) with water as the sole byproduct (Fig.4).[46] Electrospray ionization - mass spectrometry (ESI-MS) experiments using charge-tagged reagents allowed the detection of the iminium and the nitrilium intermediates and therefore pointed out the accuracy of the above-mentioned mechanism.[47]

![Ugi four-component reaction and plausible mechanism.](image)

In 2014, Meier and coworkers reported the Ugi four-center four-component polymerization (U-4C-4CP) of homodifunctional reagents (A2 + B2 + 2C + 2D system) towards the synthesis of polyamides.[48] Compared to conventional secondary polyamides (PA 6, PA 6.6 and PA 11) synthesized by ring opening or polycondensation, the U-4C-4CP affords polymers bearing both secondary and tertiary amides. This probably disturbs the formation of hydrogen bonds and changes the overall thermal properties and the solubility of the resulting polyamides. The authors investigated the polymerization of different A2- and B2-type reagents with monofunctional compounds. This approach enables six combinations leading to diversely substituted polyamides (Fig.5).[48] Interestingly, the chemical structure of the backbone and the side groups could be tuned by varying the nature of the difunctional monomers. As a rule, the polymer backbone is composed
The polymerizations were carried without any catalyst and took place at room temperature under air for at least 37 hours. An excess of monofunctional reagents was used to ensure their availability at high conversion. The U-4CR is usually performed in methanol (MeOH)[49] but when considering polymerization, the solvent was adapted to ensure the solubility of the polymer generated during the reaction. In this case, tetrahydrofuran (THF), known as a good solvent for polyamides, was used as cosolvent with MeOH. Although MCRs are usually favoured by high concentration,[49] elevated viscosity was detrimental for the polymerization. On the other hand, the formation of macrocycles was observed when U-4CP was carried out under diluted medium. The concentration was therefore optimized to get the highest possible number average molar masses ($M_n$). Overall, a wide range of aliphatic bifunctional and monofunctional reagents was considered (Fig.5, Meier 2014) and $M_n$ ranging from 7 to 21 kg/mol were obtained. Note that the molar masses were determined by size exclusion chromatography (SEC) as will be the case for all the $M_n$ discussed in this review except if stated otherwise. The resulting polyamides displayed glass-transition temperatures ($T_g$) from 1 to 65 °C but no detectable melting temperature ($T_m$).[48] This behaviour proves the low capability of the chains to form intermolecular hydrogen bonds due to the steric hindrance of the substituents but also due to the presence of tertiary amides at the side of secondary ones. It is noteworthy that the choice of the aldehyde is crucial for the success of the U-4CP. Indeed, aldehydes with blocked α-position prevent the aldol condensation which hampered the polymerization. The orthogonality of the U-4CP towards alkynes was demonstrated with the introduction alkyne-functionalised monomer, which opened the door for post-polymerization modifications (Fig.5, Meier 2014).[48]
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Meier 2014.

Luxenhofer 2015.

\[ M_n = 7-21 \text{ kg/mol} \]

\[ M_n = 1-44 \text{ kg/mol} \]
Since this pioneering work, the scope of possible monomers for the U-4CP has been extended leading to a large library of interesting and functional polymers. Luxenhofer and coworkers considered the six possible combinations to polymerize aromatic monomers such as aromatic aldehydes (mono and difunctional), aromatic and aliphatic carboxylic acids with aliphatic isocyanides and amines (Fig. 5, Luxenhofer 2015).[50] Interestingly, molar masses above 3.5 kg/mol were only achieved for two combinations, i.e. the reactions involving either an aromatic dialdehyde (terephthalaldehyde) and an aromatic dicarboxylic acid or an aliphatic diisocyanide, all other combinations led to oligomers.[50] Encouraged by these results, they further optimized the conditions and finally reached molar masses up to 44 kg/mol. For this purpose, polymerizations were performed under inert atmosphere for prolonged periods (few days). The authors pointed out that the use of aromatic aldehydes and carboxylic acids did not favour the reaction due to their steric hindrance but they ruled out a reduced reactivity coming from the conjugated system.[50]

The U-4CP becoming more mature, various functional polymers and potential applications emerged. In this context, the synthesis of polyampholytes using amino acids as bifunctional compounds was achieved.[51] Protected lysine and protected glutamic acid were reacted with aliphatic and aromatic aldehydes and isocyanides, i.e. the tert-buty1 isocyanide or an oligomer of poly(ethylene glycol) (PEG) functionalized isocyanides (Fig. 6A, Wang 2018). Polymers with molar masses above 10 kg/mol were obtained. These results further confirmed the good reactivity of aromatic aldehydes in U-4CP.[51] Interestingly, the resulting PEG-containing polymers displayed thermoresponsiveness in aqueous solution. Moreover, deprotection of the lysine and the
glutamic acid afforded protein repelling polyampholytes. Eventually, the authors proved the good cytocompatibility of their polymers towards HeLa cells.[51]

Recently, an aromatic dicarboxylic acid, namely the 2,5-furandicarboxylic acid, was used in U-4CP with aliphatic monomers (Fig.6A, Grunwaldt 2019). In this work, the polymerization conditions of one set of monomers were extensively optimized.[52] Depending on the reaction conditions, the $M_n$ ranged from 0.8 to 11 kg/mol highlighting the huge effects of concentration, solvent choice and purity of the bifunctional reagent on the course of MCPs.

In 2020, Deng et al. synthesized oligomers by reacting a diamine linked by a piperazine function with several PEG-diacids of different lengths, various aldehydes and tert-butyl isocyanide (Fig.6A, Deng 2020).[53] High molar masses were obtained ($M_n$ up to 46 kg/mol) which is not surprising given the use of PEG macromonomers. The polymers exhibited thermoresponsive behaviour that could be tuned by changing the lengths of the PEG segment or by changing the hydrophobicity of the aldehyde which constituted the pendant group. Finally, once protonated, the tertiary amines of the piperazine derivative brought antimicrobial activity to the polymers. Interestingly, based on the same PEG-diacids monomers but using dialdehydes and aromatic amines, the same group developed temperature/photo dual sensitive polymers (Fig.6B, Deng 2020).[54] Although aromatic amines are known to be detrimental to the U-4CR[49] and the use of aldehydes with acidic $\alpha$ protons can lead to aldol condensation, they obtained quite high molecular weights, up to 33 kg mol. The introduction of azobenzene moieties endowed the polymers with some photosensitivity and their properties (cloud point temperature, contact angles and particle sizes) could be tuned upon irradiation (at 365 nm).[54]

Eventually, Chen et al. developed some cationic redox-responsive polymers for intracellular protein delivery application. In this case, two different disulfide-containing dicarboxylic acids were
reacted with a diisocyanide in the presence of isobutyraldehyde and primary amine derivatives linked to a tertiary amine or a morpholino moiety (Fig. 6C, Chen 2020).[55] This strategy gave access to polymers with $M_n$ up to 9 kg/mol which contains disulfide bonds in their backbones and protonable tertiary amines as pendant groups. These macromolecules were used to form polyplexes with proteins that facilitate their introduction in the cells where the intracellular glutathione (GSH) rapidly triggers the cleavage of disulfide bonds and thus the release of proteins.[55]

Fig. 6. Scope of reagents used in the Ugi four-center four-component for A) $A_2 + 2B + C_2 + 2D$, B) $2A + B_2 + C_2 + 2D$ and C) $2A + 2B + C_2 + D_2$ systems.
Besides the above-mentioned U-4C-4CP, examples of Ugi four-center three-component polymerizations (U-4C-3CP) involving difunctional monomers bearing different chemical functions (AB system) were reported. This strategy allows a better control over the stoichiometry compared to a $A_2 + B_2$ system which strongly relies on the precision of the operator. Note, however, that not all combinations of chemical functions are possible in the U-4C-3CP approach and that the use of AB monomers also reduces the number of components in the reaction and thus the variability of the products.

Amino acids, containing both an amine and a carboxylic acid, quickly drew attention as reactants for the U-4C-3CP due to their availability and their potential to create peptidomimetic materials.[28][56][57] Several natural $\alpha$-amino acids were first reacted with benzaldehyde and tert-butyl isocyanide.[58] Unfortunately, only oligomers were obtained and the molar masses were limited to 3.4 kg/mol. The polymerization was hampered by a side-reaction consisting of intramolecular cyclisation and subsequent opening via the solvent (MeOH).[58] To tackle this issue, Wang et al increased the distance between the amine and the carboxylic acid functions to disfavour the cyclisation reaction. As an example, they used $N_{\alpha}$-Boc-L-lysine with different aromatic aldehydes and tert-butyl isocyanide and obtained molar masses ranging from 7 to 11 kg/mol (Fig.7, Wang 2016). After the amine deprotection of the lysine, the resulting polycations showed antibacterial properties, good biocompatibility and were able to deliver encapsulated curcumin inside the cytoplasm.[58,59] Decreasing the number of carbons between the amine and the carboxylic acid, from five to four or three, decreased the $M_n$ around 5 kg/mol (Fig.7, Wang 2016). Overall, $\gamma$, $\delta$- and $\varepsilon$-peptoids were synthesized via the U-4C-3CP of amino acids.[58] Recently, the Ugi polymerization of $N_{\alpha}$-Boc-l-lysine, tert-butyl isocyanide and sustainable furfural
was reported in mild conditions (notably in water) leading to polymers with $M_n$ up to 10 kg/mol.[60]

Similarly, Debuigne et al. took advantage of natural dipeptides composed of glycine and alanine to move away the acid and amine functions and avoid intramolecular cyclization.[61] They carried out the polymerization in water with formaldehyde and tert-butyl isocyanide (Fig.7, Debuigne 2017). A series of thermoresponsive alternating peptide-peptoid polymers was produced accordingly. Interestingly, when repeated in the presence of additional monofunctional carboxylic acids, such as acrylic acid or acid-terminated PEG, the U-4C-3CP of dipeptides led to acrylamide-terminated peptide-peptoid macromonomers and thermoresponsive PEG-b-poly(peptide-peptoid) block copolymers, respectively. In a combinatorial approach, the same group extended the scope of poly(peptoid) analogues by using four other amino acids, i.e. glycylglycine, carnosine as well as 4-amino-butryric acid and its hydroxy derivative.[62] These building blocks were reacted with common aldehydes, namely formaldehyde and isobutyraldehyde, in combination with various isocyanides bearing differently substituted aliphatic groups or hydrophilic substituent such as a morpholino function (Fig.7, Debuigne 2021). It afforded ten novel polymers with thermo- and pH-responsiveness as well as good biocompatibility for those tested.[62]

Another hetero difunctional monomer used in U-4C-3CP combines an isocyanide moiety and a carboxylate group. Developed by Koyama and coworkers, this monomer was polymerized in isopropanol for a few days with fluorinated ammonium salts and monofunctional aldehydes such as isobutyraldehyde and aromatic aldehydes (Fig.7, Koyama 2018).[63] Note that, the procedure involves several steps and work-ups but the reaction mixture stays in one-pot. The resulting polymers were notably valued as surface active agents for the chloroform-air interface. In addition, the polymer with biphenyl and perfluoroheptyl pendant groups showed a critical micellar
concentration (CMC) below 1 wt%. In a similar way, difunctional isocyanide/carboxylate-bearing monomers were also reacted with preformed imines leading to a Ugi three-center two-component polymerization (U-3C-2CP, A’ + BC system).[64,65] Since the isocyanide/carboxylate compounds derived from α-amino acids (glycine and phenylalanine), the resulting polymers presented alternating poly(peptide-peptoid) structures (Fig. 7, Koyama 2017 and 2020).[64,65] Except for a few polymers, relatively low molecular weights were obtained but the polymers exhibited good adhesive properties.[65]
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Wang 2016.

Debuigne 2017.

Debuigne 2021.

Koyama 2018.

Koyama 2017 and 2020.
Fig. 7. Ugi polymerizations involving hetero difunctional monomers. a The $M_n$ were determined by NMR.

The last U-4CP example involved levulinic acid, an oxo acids derived from renewable lignocellulosic biomass.[66] Interestingly, when combined with an amine and an isocyanide, oxo acids are known to form lactam via an intramolecular Ugi four-center three-component reaction.[67] Therefore, reacting a diisocyanide, a diamine and the levulinic acid did not produce a network but a linear polyamide containing five membered lactams.[66] Indeed, the reaction of 1,6-diisocyanohexane, ethylenediamine and levulinic acid carried out in MeOH at 100 °C for 30 minutes in a microwave reactor afforded a polymer with a $M_n$ of 9.5 kg/mol. The authors also increased the size of the diamine linker and obtained higher molecular masses around 12 kg/mol (Fig. 8). When an aromatic amine, i.e. the aniline was used, mainly oligomers or macrocycles were formed while the PEG-diamine led to chain extension but the resulting polymer was contaminated with unreacted PEG.[66] Eventually, the use of a triamine, namely the tris(2-aminoethyl)amine (TREN), resulted in a crosslinked material (Fig. 8). To the best of our knowledge, this is the sole example of direct Ugi polymerization of multifunctional monomers towards the synthesis of networks. Note, however, that the Ugi reaction has largely been applied to crosslink pre-existing polymer chains.[68–77]
Fig. 8. Ugi four-center three-component polymerization of levulinic acid toward linear polymers and network.

2.1.b. Ugi-5C

Shortly after its discovery, the Ugi-4CR reaction was extended to a multitude of reagents. The carboxylic acids can be substituted by a variety of other acidic compounds such as carbonic acid monoester, water, activated phenol and hydrogen sulfide to name a few, while the amine can be substituted by hydrazine, urea, sulphonamide, hydroxylamine, etc.[49] A Ugi five-component version (U-5CR) was also reported.[78] The latter implies an alcohol, carbon dioxide, an aldehyde, an isocyanide and a primary amine (Fig. 9). In this case, the alcohol and the carbon dioxide produce a carbonate which reacts with the nitrilium intermediate before rearrangement yielding $N$-
(alkoxycarbonyl)amino amides. Some years ago, this reaction was adapted for polymerization (U-5C-5CP) (Fig.9).[79] The latter involved a difunctional amine and isocyanide (1,12-diaminododecane and 1,6-diisocyanoxyhexane), isobutyraldehyde and methanol in large excess under 10 bar of carbon dioxide. The polymerization was carried out in a mixture of MeOH/THF and the best yield was obtained in concentrated media (up to 56 %) with $M_n$ of 21 kg/mol. The resulting poly(urethane-amide) possessed a methyl carbamate in $\alpha$-position of an amide. Due to this peculiar disposition, additional treatment with aqueous potassium hydroxide solution converted the polymer into the corresponding poly(hydantrons), which further broadened the scope of the macromolecular engineering via Ugi-type reaction.[78]
2.1.c. Ugi-3C

A few years ago, another variant of the Ugi-4CR was reported in literature involving only three component (U-3CR), i.e. amine/aldehyde/isocyanide, and affording an α-amino amide moieties.[80] In the absence of carboxylic acid, it is the water released during the imine formation that plays the role of nucleophile and traps the nitrilium intermediate giving rise to a four-centre three-component reaction (Fig.10). The latter requires the use of a suitable catalyst such as phenylphosphinic acid,[81] aminoborane,[82] zinc chloride,[83] SO$_3$H-functionalized cellulose,[84] aromatic carboxylic acids,[85] boric acid[86] and enzyme.[87] Recently, this reaction was adapted for step-growth polymerization of difunctional amines and isocyanides with monoaldehyde (U-4C-3CP) using the most promising catalytic system, that is phenylphosphinic acid.[88] The polymerizations were generally performed at 50 °C in dimethylformamide (DMF) with a slight excess (2.2 equiv.) in monofunctional reagent and a catalyst loading of 10 mol%. Both aromatic and aliphatic monomers were tested leading to poly(α-amino amide)s with $M_n$ between 2 and 13 kg/mol (Fig.10).[88] Aromatic amines and aldehydes led to higher molar masses than aliphatic ones. Nevertheless, the aliphatic-richer poly(α-amino amide) was soluble in water upon protonation of the amines.
Fig. 10. Ugi four-center three-component reaction and polymerization.

2.2. Phosphorous-based MCP

2.2.a. Kabachnik–Fields

The Kabachnik-Fields three-component reaction (KF-3CR) provides a green procedure for the synthesis of α-amino phosphonates or α-amino phosphonic acids after a further deprotection. These compounds are phosphorous analogues of α-amino acids and exhibit low toxicity towards mammalian cells[89] making them important chemicals for drug research.[90,91] The three-component KF reaction is a one-pot and single step reaction between an aldehyde (sometimes a
ketone), an amine and a dialkyl phosphonate (Fig.11). It can be seen as an upgrade of the Pudovik reaction involving a preformed imine and a dialkyl phosphonate.[92] The mechanism is still debated but a plausible hypothesis consists of an aldehyde/amine condensation followed by the addition of the phosphonate onto the imine.[93,94] The reaction proceeds without any catalyst but is accelerated with various Lewis acids and the assistance of microwaves.[94]

![Kabachnik-Fields three-component reaction and plausible mechanism.](image)

The use of KF-3CR in direct polymerization was first reported by Liu and coworkers to produce halogen-free flame retardants and macromolecular crosslinkers for epoxy resins.[95] They selected terephthalic aldehyde and diethylenetriamine as difunctional monomers while diethyl phosphonate was used in large excess playing the role of both the monofunctional monomer and the solvent (Fig.12, Liu 2014).[95] The polymerization was performed at 120°C for 24 h under inert atmosphere yielding a moderate molecular weight of 3 kg/mol. Increasing the reaction time from 1 to 6 days resulted in slightly higher $M_n$ (4.5 kg/mol) and a broader dispersity. Eventually, when the polymer was incorporated in epoxy resins with a weight ratio equal or higher than 20%, the resulting materials showed good flame retardancy.[95]
Few months later, the higher efficiency of aromatic diamines over aliphatic ones for the KF-3CP was highlighted.[96] According to the authors, it was due to the faster formation of imine. The polymerizations were carried out at lower temperature (80 °C) during 20 hours. The aromatic dialdehyde, namely the 1,10-bis(4-formylphenyl)-1,4,7,10-tetraoxadecane, was polymerized with various aromatic diamines and diisopropyl or dibutylphosphite (Fig.12, Theato 2015).[96] The choice of the amine and the alkyl group of the phosphonate had a huge impact on the molecular
weight ($M_n$ from 5 to 55 kg/mol). Interestingly, after polymerization, the pendant phosphonate moieties could be deprotected upon addition of bromotrimethylsilane to give the corresponding zwitterionic poly(α-amino phosphonic acid). In addition, the authors demonstrated the possible photocleavage of the polymers containing o-nitrobenzyl groups to retrieve the diamines monomers.[96]

More recently, an aromatic diamine dye (Fig.12, Wei 2018) was used in combination with diethyl phosphonate for chain extension of poly(ethylene glycol) and poly(ethylene glycol)-co-poly(caprolactone) α,ω-functionalized with aromatic aldehydes.[97,98] These solvent-free polymerizations were accelerated with microwaves to shorten the reaction time to only 5 minutes. The resulting polymers exhibit low cytotoxicity and photoluminescence upon aggregation (aggregation-induced emission (AIE)) making them good candidates for cell imaging applications.

It is noteworthy that the KF reaction has also been widely used in the modification of pre-existing polymers[99–107] and in one-pot combination with radical polymerization.[108–110] To the best of our knowledge, however, no synthesis of 3D structured materials was reported for the KF-3CR.

### 2.3. Alkyne-based MCP

Alkyne-based MCPs have largely contributed to the development of novel polymeric structures during the past decade. Here, we will describe the combination between an aldehyde, an amine and an alkyne through a condensation reaction named the A$_3$-coupling. However, one must be aware that there are other alkyne-based MCPs that do not involve an imine. Indeed, as reviewed elsewhere,[25–27,111,112] alkynes are precursors of ketenimine or alkynone when reacted with
sulfonyl azides and acyl chloride, respectively. These intermediates are subsequently reacted with various nucleophiles to afford a wide diversity of chemical structures that can be incorporated in a polymer.

### 2.3.a. A$^3$-coupling

Discovered in 2002, the A$^3$-coupling three-component reaction (A-3CR) was reported as a very efficient green synthesis of propargyl amines via the C-H activation of a terminal alkyne with a Cu-Ru catalyst.[113] The accepted mechanism involves the formation of an imine or an iminium depending on the substitution of the amine. The metal activates the alkyne through the formation of a metal acetylide and promotes the nucleophilic addition onto the imine (or iminium) with water as the sole byproduct (Fig.13). Note that for primary amines, a subsequent A-3CR could occur on the newly formed secondary amines depending on its bulkiness. Various transition metals were tested for this reaction extending the scope of reagents to aromatic or aliphatic compounds. Amongst them, indium chloride (InCl$_3$) was reported as a highly efficient catalyst to promote the reaction of aromatic aldehydes and alkynes with aliphatic secondary amines, especially dibenzylamine.[114]

![Fig.13. A$^3$-coupling three-component reaction and plausible mechanism.](image-url)
Based on this research, Tang et al. have developed the A³-coupling three-center three-component polymerization (A-3C-3CP) using dibenzylamine, terephthalaldehyde and a series of aromatic diynes (Fig. 14, Tang 2013).[115] The optimized polymerizations were carried out in o-xylene at 140 °C for 20 hours under inert atmosphere. Molecular sieves were used to trap water and displace the reaction towards the product. Polymers with $M_n$ up to 16 kg/mol were prepared accordingly. They showed a high refractive index due to the presence of polarizable aromatic rings, acetylene units and heteroatoms making them potential candidates for photonic applications (wavelength guide, lenses, etc.).[115] In addition, these polymers readily coordinated cobalt via their triple bonds and a subsequent pyrolysis led to nanostructured magnetic ceramics.[115] Eventually, the polymers synthesized with tetraphenylethene (TPE) or silole-containing monomers (Fig. 14, Tang 2013) exhibited relatively high fluorescence quantum yields in the aggregate state due to aggregation-induced emission phenomenon (AIE).[115]

The same A-3C-3CP was applied with fluorene-like dialdehyde and diynes with dibenzylamine (Fig. 14, Cao 2017) but only oligomers were obtained accordingly.[116] This issue was tackled by using microwaves that ultimately afforded high molecular weights and shorter reaction times (around 1 hour). All the polymers were photoluminescent and the soluble ones were used as cathode interlayers for solar cells improving their efficiency.[116]

Interestingly, primary amines were also used as difunctional monomers in the A-3C-3CP process in combination with diynes and monofunctional aldehydes (Fig. 14, Tang 2014).[117] Although, copper iodide was reported as a good catalyst with primary amine,[118] the degrees of polymerization were significantly lower than those achieved through the A-3C-3CPs involving secondary amines. Indeed, moderate to low yields and molecular weights were obtained except for a few polymers exhibiting $M_n$ above 5 kg/mol.[117] The polymers containing a TPE or a silole
structure were photoluminescent upon aggregation and their potential for photopatterning was demonstrated. Furthermore, they were used as highly sensitive chemo sensors for detecting explosives, especially picric acid that quenched the fluorescence.[117]
Fig. 14. $A^3$-coupling three-component polymerization with primary and secondary amines. The highlighted monomers correspond to the photoluminescent moieties.
2.3.b. A$^3$-coupling / Petasis

The A$^3$-coupling and the Petasis-Borono Mannich reactions are very complementary MCRs. Indeed, in the Petasis-Borono Mannich reaction, a primary (or a secondary amine) is condensed with an aldehyde and the resulting imine or iminium further reacts with boronic acid derivative to yield a secondary (or tertiary) amine. When a secondary amine is formed, the latter can be further used in a A$^3$-coupling reaction (Fig.15).[119] Additionally, to avoid the use of metal catalyst, a decarboxylative version of the A$^3$-coupling[120] has been successfully combined with the Petasis reaction (Fig.15).[121]

Very recently, this combination of MCRs was exploited for the synthesis of functional poly(propargylamine)s (Fig.15).[122] The A$^3$-coupling-Petasis five-center four-component polymerization (AP-5C-4CP) was carried out without catalyst under mild conditions (45°C) in dichloroethane for 10 hours. Formaldehyde and aromatic alkynyl carboxylic acids were used as monofunctional reagents whereas dibenzylamines and diboronic acids compounds containing aromatic fluorene or tetraphenylethene served as difunctional monomers (Fig.15). Polymers with molar masses as high as 12 kg/mol were collected with good yields. Dispersities (Ð ~ 1.02-1.22) were surprisingly low for a polycondensation process but this point was not discussed by the authors. While the fluorene-based polymers did not show photoluminescence in solution, the polymers containing the TPE moieties exhibited a high quantum yield due to aggregation-emission properties. Moreover, the photoluminescence was enhanced upon addition of citric acid.[122] This phenomenon was attributed either to the protonation of the amines or a further ionic crosslinking that induced aggregations.
Fig. 15. $A^3$-coupling / Petasis five-center four-component reaction and polymerization. The highlighted monomers correspond to the photoluminescent moieties.

2.3.c. $A^3$-coupling/cycloisomerization/oxidation

Concomitantly to the discovery of the $A^3$-coupling, it was found that the reaction of aniline derivatives with aldehydes and alkynes in the presence of copper chloride as catalyst produced propargylic amine but also quinoline as side-product (Fig.16).[123] Depending on the substitution of both the aniline and the alkyne, it was possible to favour one product over another. From a mechanistic point of view, the propargylic amine obtained by the $A^3$-coupling is converted into quinoline via subsequent cyclisation and oxidation reactions (ACO-3C-3CR; Fig.16). Since then,
the reaction conditions have been optimized to favour the formation of quinoline, \textit{i.e.} up to 90 \% when \(\text{B(C}_6\text{F}_5\text{)}_3\) was used as the catalyst.\cite{124}

Inspired by these results, Dong \textit{et al} reported an efficient synthesis of poly(quinoline)s \textit{via} the ACO-3C-2CP polymerization of aniline derivatives with monomers bearing both the aldehyde and the alkyne (Fig.16).\cite{125} In brief, different substituted anilines were reacted with various alkyne–aldehyde monomers. It turned out that using aniline compounds with electron-withdrawing groups was detrimental for the polymerization and the yield. Concerning the alkyne–aldehyde
monomer, both functions needed to be directly attached to an aromatic ring or no polymer was observed. High yields were obtained when electron-donating groups, such as ether, separate the phenyl rings bearing the functions (Fig.16). The quinoline moiety endowed the resulting polymers with photoluminescence in solution but the phenomenon was quenched upon aggregation.[125]

2.3.d. Acetylenedicarboxylate-based consecutive MCP

Imines are well-known precursors of nitrogen heterocyclic rings. When they are combined with acetylenedicarboxylate, they efficiently lead to hydrogenated derivatives of pyrimidine and pyrrole depending on the conditions used (Fig.17).[126,127] Briefly, one equivalent of aniline is reacted with the activated internal alkyne through hydroamination and another equivalent combines with formaldehyde to yield the corresponding imine. These two products react together to form a five-membered ring dihydropyrrole when heated[126] (D-4C-3CR) but it can also produce a six-membered ring tetrahydropyrimidine when a second equivalent of formaldehyde is present under milder conditions (T-5C-3CR) (Fig.17).[127]

Few years ago, inspired by this chemistry, Tang and coworkers presented an efficient multicomponent polymerization leading to polyheterocycles.[128] The polymerization was conducted with various aromatic diamines, formaldehyde and two different acetylenedicarboxylates in methanol. When the polymerizations were carried out with an excess of formaldehyde, pure poly(tetrahydropyrimidine)s were obtained (Fig.17, strategy 1) whereas a stoichiometric amount of formaldehyde led to copolymers of tetrahydropyrimidine and dihydropyrrole (Fig.17, strategy 3).[128] The content of tetrahydropyrimidine in the copolymer could be varied from 100 to 8 %. Note that the process used was not strictly speaking a domino reaction like the MCPs discussed above. In other words, the overall reaction occurred via consecutive steps. The first steps consisted of the reaction of one equivalent of amine with the
alkyne during 30 minutes at 25 °C. Next, formaldehyde was added in the mixture as well as acetic acid as catalyst and the reaction was proceeded for 16 hours. The temperature stayed unchanged when pure poly(tetrahydropyrimidine)s were aimed and changed to 70 °C for copolymers. Interestingly, this consecutive approach enables the preparation of sequence-controlled polymers. Indeed, alternating poly(tetrahydropyrimidine)s were formed by the reaction of acetylenedicarboxylate with 0.5 equivalent of a first diamine followed by the reaction with a second diamine (0.5 equiv.) in the presence of formaldehyde and acetic acid (Fig. 17, strategy 2).[128] Concerning the monomers reactivity, acetylenedicarboxylate with methyl substituent (R_2) led to oligomers ($M_n = 2.5$ kg/mol) because of the poor solubility of the corresponding polymer in methanol. Replacing the methyl group by the more polar 2-(2-methoxyethoxy)ethyl increased the $M_n$ up to 30 kg/mol.[128] Moreover, the electron-rich aromatic diamines were more efficient than electron-deficient aromatic diamines or diamines with high steric hindrance.[128] These observations were rationalized by authors based on a reactivity difference in the hydroamination reaction and Schiff base formation. The poly(tetrahydropyrimidine)s (co)polymers showed photoluminescence provided by the newly formed heterocycles as well as aggregation-induced emission properties.[128]
Fig. 17. MCR and MCP toward substituted tetrahydropyrimidines (T-5C-3CR/P) and dihydropyrroles (D-4C-3CR/P) and the corresponding polymers.
2.4. Sulfur-based MCP

Sulfur appears in many different functional groups making its chemistry incredibly versatile. Moreover, sulfur-containing polymers are attractive materials exhibiting various properties. They are used as stimuli-responsive polymers, for metal coordination, in applications requiring high refractive indexes or semiconducting properties as well as lithium-sulfur batteries, to name a few.[129–131] This section highlights the synthesis of sulfur-containing polymers via MCPs using sulfur atoms under the form of elemental sulfur or thiol in combination with an aldehyde/amine condensation.

2.4.a. Willgerodt-Kindler

Elemental sulfur is one of the most abundant elements on Earth and represents a huge byproduct of petroleum industry. Except for sulfuric acid production, other routes for its valorisation have been unsuccessful due to elevated costs of production and operating issues.[130] Consuming the amounts of produced elemental sulfur thus requires the development of high value materials with facile production methods. It can be converted into high sulfur-content polymers with valuable properties.[130] Several MCPs valorising the elemental sulfur enable the synthesis of poly(thiourea)s,[37] poly(O-thiocarbamate)s[132] and poly(thioamide)s.[133] The latter can be obtained via the Willgerodt-Kindler three-center three component reaction (WK-3C-3CR). This reaction involves an aromatic aldehyde with an aliphatic amine and elemental sulfur. The reaction mechanism is still under debate but the first step is widely accepted as the cleavage of the octasulfur ring by the amine with the reversible formation polysulfide anions. This intermediate product then reacts onto the imine formed by condensation of the aldehyde and the amine to yield a thioamide (Fig.18).[134] It should be noted that the third component of the Willgerodt-Kindler reaction,
namely the elemental sulfur, cannot be varied which somewhat reduces the combinatorial character of this MCR to a classical two-component reaction although complex structures can be achieved.

**Fig.18.** Willgerodt-Kindler multicomponent reaction and polymerization. The monomers highlighted in red failed to give polymers.

The Willgerodt-Kindler reaction was adapted to MCP by the group of Kanbara who identified conditions for the polymerization of various aromatic dialdehydes with aliphatic and aromatic secondary diamines in the presence of elemental sulfur $S_8$.\(^{[135]}\) They used $N,N$-dimethylacetamide
(DMAc) as solvent, a temperature of 115 °C and performed the polymerization under inert atmosphere with an excess of sulfur. Three isomers of phthalaldehyde were notably considered with 4,4’-trimethylenedipiperidine and S$_8$ (Fig.18, Kanbara 1999). $M_n$ around 6 kg/mol and yields above 90% were obtained with para and meta-isomers contrary to the ortho-isomer that failed to produce polymers due to steric hindrance. Heteroaromatic dialdehydes were also tested. For example, electron-poor aromatic dialdehydes such as 2,6-pyridinedicarbaldehyde led to polymers with similar $M_n$ (~6 kg/mol) and good yields while both lower yield and $M_n$ (4 kg/mol) were obtained with the electron-rich thiophene dicarbaldehyde.[135] Concerning the diamine monomers, the polycondensation of $m$-phthalaldehyde with piperazine afforded insoluble polymer presumably due to its rigid backbone while acyclic and aromatic secondary diamines ($N,N'$-diethylethylenediamine and $N,N'$-diphenyl-1-phenylenediamine) did not lead to the formation of polymer materials (Fig.18, Kanbara 1999).[135] The same group extended the scope of diamines to aliphatic primary amines such as $p$-xylylenediamine, 1,6-hexamethylenediamine and 2,2’-(ethylenedioxy)bis(ethylamine) (Fig.18, Kanbara 2001).[134] In that work, they obtained higher molar masses (>19 kg/mol) and improved the polymerization conditions, notably by changing the order of monomers addition.[135] In the original procedure, the aldehyde and the amine were reacted together to form the Schiff base before addition of the sulfur. However, the limited solubility of some Schiff bases led to the precipitation of poly(Schiff base-thioamide) copolymers. In order to avoid these solubility issues, aldehyde was added as the last component affording pure poly(thioamide)s in better yields. [135] The poor solubility of some Schiff bases also explained the impossibility to use aromatic diamines even with the modified approach. [134] Eventually, the poly(thioamide)s demonstrated their ability to recover valuable metals like gold and platinum from aqueous and organic solutions.[136] Interestingly, the selectivity towards the different metals could
be tuned with respect to the pH of the solution.[136] Selective separation of palladium from solution containing nickel and platinum was done based on the same principle.[137] Finally, quantitative removal of mercury was achieved in wastewater with pH ranging from 1 to 8.[138] The strong affinity of poly(thioamide)s for Hg allowed its selective removal from water contaminated with Mn(II), Fe(III), Cu(II), Zn(II), and Pb(II).[138]

2.4.b. MALI

As mentioned earlier, the imine is a precursor of several heterocycles via MCRs. Among them, the mercaptoacetic acid locking imine (MALI) reaction affords the formation of 4-thiazolidinone, a compound of interest in the biological and medical fields.[139] In this catalyst-free MALI three-center three-component reaction (MALI-3C-3CR), a primary amine and an aromatic aldehyde are condensed into the corresponding Schiff base that undergoes a nucleophilic attack from the thiol function of mercaptoacetic acid (or derivative). The resulting intermediate then generates the 4-thiazolidinone group by subsequent cyclization via the addition of the amine onto the carboxylic acid (Fig.19). The reaction is accelerated by addition of a desiccant or a molecular sieve that removes the produced water.[140]

MALI three-center three-component polymerization (MALI-3C-3CP) was introduced by Tao and coworkers.[141] They performed direct polymerization of hexamethylenediamine, terephthalaldehyde with an excess of 2-mercaptopropionic acid under mild conditions (room temperature and catalyst-free) for two days leading to complete conversion and polymers with high molar masses (19 kg/mol) (Fig.19, Tao 2014).
Very recently, the MALI-3C-3CP was applied to a telechelic amine-terminated polyamide acid (PAA) preformed in situ from pyromellitic dianhydride and an excess of 4,4’-oxydianiline (Fig.19, Ye 2021).[142] This reaction was conducted in N-methyl-2-pyrrolidone (NMP) in the presence of molecular sieve (4 Å) to capture the produced water. The polymerization was followed by annealing at 400 °C to promote the ring closure and, ultimately, the formation of the corresponding poly(imide-thiazolidinone)s. The latter exhibited exceptional thermal stability with degradation temperature close to 600 °C. In addition, they were casted onto a glass plate as uniform films and showed good adhesion properties with copper, aluminium and stainless-steel plates.[142] Note that the MALI reaction was also used for the modification of pre-formed polymers[143,144] or in combination with radical polymerization.[145–147] However, we found no example of direct MALI polymerization for the synthesis of networks or hyperbranched polymers. The sole example of 3D structures synthesized by MALI concerns photoluminescent nanoparticles obtained by crosslinking of pre-existing polymer chains.[148,149]
Fig. 19. Mercaptoacetic acid locking imine multicomponent reaction and polymerization. NA stands for not available.

2.5. Dione-based MCP

2.5.a. Biginelli

The Biginelli three-component reaction was discovered by Pietro Biginelli in 1891.[150] Unlike the above-mentioned MCRs, it does not involve an amine but urea (or thiourea). The reaction of the latter with an aldehyde and a 1,3-dicarbonyl compound gives access to pyrimidine derivatives, namely 3,4-dihydropyrimidin-2(1H)-ones (or thiones) often abbreviated DHPMs, that
are of great interest in medicinal chemistry.[151] The generally accepted mechanism implies the formation of an iminium by addition of urea onto the aldehyde (Fig.20). This rate-determining step is catalysed by Brønsted acids and followed by a nucleophilic attack of the 1,3-dicarbonyl, generally an alkyl acetoacetate under its enol form. Finally, the nucleophilic attack of the second nitrogen of urea onto the carbonyl and dehydration leads to the final product (Fig.20).[152] This mechanism is supported both by experiments and theoretical calculations.[46] Note that the reaction can also be catalysed by Lewis acids but the mechanism becomes far more complex.[46] As illustrated by previous reviews,[153,154] the Biginelli MCR has been used for a few years in polymer chemistry. The following section consists of an update with a special focus on the Biginelli step-growth polymerization.

**Fig.20.** Biginelli three-component reaction and plausible mechanism.

The Biginelli three-center three-component polymerization (B-3C-3CP) of homo-functional monomers (A₂ + B₂ + C system) was reported by Tao et al.[155] By reacting 8 different bis(β-keto ester) derivatives with 5 aromatic dialdehydes in the presence of urea or thiourea, they synthesized
80 novel polymers highlighting the combinatorial feature of MCPs (Fig.21, Tao 2016). The difunctional monomers differed by the length of the linker between their reactive groups. The bis(β-keto ester)s possessed alkyl linkers while the aromatic dialdehydes were separated by oligomers of PEG linkers (Fig.21, Tao 2016). Typical polymerizations were carried out using an excess of urea or thiourea components (1.5 equiv.) in acetic acid at 100 °C for 24 hours with 20 mol% of MgCl$_2$ as a Lewis acid catalyst. Poly(DHPM)s with molar masses ranging from 7 to 30 kg/mol were obtained accordingly. The systematic variation of the linker allowed to tune the $T_\text{g}$ of the polyDHPMs from 50 to 159 °C with small increments.[155] Interestingly, the poly(3,4-dihydropyrimidin-2(1H)-thiones) synthesized with thiourea instead of urea showed lower $T_\text{g}$. Finally, thiourea was successfully replaced by $N$-methylthiourea broadening the scope of this polymerization method (Fig.21, Tao 2016).[155]

In 2016, Meier and coworkers applied the B-3C-3CP to difunctional monomers that can be derived from renewable feedstock.[156] A series of bis-acetoacetate derivatives with saturated and unsaturated hydrocarbon linkers was prepared and reacted with aromatic dialdehydes such as terephthalaldehyde or divanillin in the presence of urea (Fig.21, Meier 2016). These polymerizations were performed under microwave and catalysed by a Brønsted acid, namely the $para$-toluenesulfonic acid, allowing a reaction time of maximum 4 hours. The obtained poly(DHPM)s had molar masses between 3 and 15 kg/mol.[156] The $T_\text{g}$ were quite high (141-203 °C) and tunable by varying the aliphatic chain length of the diacetoacetate monomer.[156]

Recently, the same group extended the scope of the polymerisarion and considered other renewable monomers. They notably polymerized terephthalaldehyde with a series of bis-acetoacetates and bis-acetoacetamides containing alkyl and isosorbide linkers in presence of urea and methyl-urea (Fig.21, Meier 2021). [157] Overall, $M_\text{n}$ ranging from 4 to 15 kg/mol and broad
dispersities (2.8 to 4.2) were obtained especially with the isosorbide-based monomers (Ð up to 8.71). These results indicate aggregation issues presumably due to hydrogen bonding. Eventually, the polymers exhibited $T_g$ from 160 to 308 °C.[157]
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The Biginelli polycondensation of hetero-functional monomers was made possible by the synthesis of monomers containing benzaldehyde and β-keto ester groups. This “AB” monomer was reacted with thiourea through the Biginelli three-center two-component polymerization (B-3C-2CP) at 100 °C with an excess of thiourea (2 equiv.) in acetic acid with MgCl₂ as catalyst (Fig. 21, Tao 2015).[158] Under these conditions, the reaction was fast and reached almost full conversion after 1 hour. Nevertheless, the reaction time was extended to 9 hours to afford the corresponding poly(dihydropyrimidin-2(1H)-thione) with $M_n$ up to 23 kg/mol. Under basic conditions, the thiourea moiety could be tautomerized into the isothiourea which promoted nucleophilic substitution reactions and ultimately allowed the post-polymerization modifications with haloalkanes.[158] The modification was demonstrated with haloalkane bearing alkene as well as terminal or internal alkynes which served as functions for further modifications (Fig. 21, Tao 2015).[158] The polymer properties such as glass transition temperatures and fluorescence were consequently modified.[158]

Tao’s group also performed the B-3C-2CP with the same AB monomer using urea instead of thiourea.[159] A poly(dihydropyrimidin-2(1H)-one) with a molar mass of 22 kg/mol was obtained after 4 hours (Fig. 21, Tao 2015bis).[159] The resulting poly(DHPM) exhibited interesting metal adhesive properties especially with brass. For the ease of the application, the polymerization of the AB monomer with urea was performed directly between the metal brass sheets without solvent and catalyst. After heating at 130 °C for 20 minutes, the tensile shear strength reached a plateau at 2.8 MPa.[159] Further improvement consisted in the synthesis of hyperbranched polymers and
networks from AB$_2$ and A$_2$B$_2$ monomers which increased the tensile shear strength to 3.6 and 5.9 MPa, respectively (Fig.21, Tao 2015bis).[159] To the best of our knowledge, it is the sole example of direct Biginelli polycondensation leading to 3D structures.

2.5.b. Hantzsch

The original Hantzsch MCR consists in a four-center three-component reaction (H-4C-3CR) involving ammonia or ammonium salt, an aldehyde and two equivalents of a β-keto ester with water as the sole byproduct.[160] The Hantzsch adduct is a 1,4-dihydropyridine derivative well-known in pharmacology.[12] Another version, namely the Hantzsch four-center four-component reaction (H-4C-4CR), in which one equivalent of β-keto ester is replaced by the dimedone, leads to asymmetric 1,4-dihydropyridine (Fig.22).[161] H-3CR and H-4CR share one of the most complex mechanism amongst MCRs. As detailed elsewhere, the latter depends on several parameters like solvent, catalyst, substituent of the reagents, etc.[46] H-4CR has been used in polymer chemistry for monomers synthesis, post-polymerization modifications and in one-pot combination with radical polymerization.[162,163] Hereafter, we describe its use as direct polymerization tool.
**Fig.22.** Hantzsch four-center four-component reaction and Hantzsch four-center three-component polymerization as well as its combination with Biginelli three-center two-component polymerization.

The sole example of synthesis of poly(1,4-dihydropyridine)s by Hantzsch polymerization was reported by Tao *et al.*[164] In this case, an AB monomer containing benzaldehyde and the β-keto ester group was polymerized with ammonium acetate and dimedone by Hantzsch four-center-
three component polymerization (H-4C-3CP) (Fig.22). The H-4C-3CP was almost complete after 40 minutes in acetic acid at 100 °C with MgCl\textsubscript{2} as catalyst. Polycondensates with a molar mass of 17 kg/mol were obtained in these conditions.[164]

Because the Hantzsch and the Biginelli reactions share some common reagents, \textit{i.e.} an aldehyde and a β-ketone ester, their corresponding MCPs, \textit{i.e.} the H-4C-3CP and B-3C-2CP, were combined for the preparation of copolymers.[164] In practice, the AB monomer containing the benzaldehyde and the β-keto ester group was reacted with urea and NH\textsubscript{4}OAc/dimedone yielding copolymers of 1,4-dihydropyridine (Hantzsch adduct) and dihydropyrimidin-2(1H)-one (Biginelli adduct) (Fig.22).[164] By varying the monofunctional monomers concentration, the ratio of Hantzsch/Biginelli adducts in the main chain was tuned.[164] In comparison to the comonomer feed, the copolymers were slightly enriched in the Hantzsch adduct probably due to the higher rate of the latter reaction compared to the Biginelli one in the selected copolymerization conditions. To extend the scope of polymers, urea was replaced with thiourea giving access to poly(1,4-dihydropyridine-\textit{co}-dihydropyrimidin-2(1H)-thione)s.[164] Varying the Hantzsch/Biginelli adduct ratio in these copolymers allowed to tune their \(T_g\) (\(\sim 80-105\) °C) which increases with the content of the Biginelli adduct. [164]

Finally, no report was found in the literature concerning the synthesis of HBPs or networks \textit{via} the Hantzsch polycondensation. Nonetheless, polymers and networks were respectively cross-linked[165] and modified[166] \textit{via} Hantzsch reaction in order to endow them with fluorescent properties coming from the 1,4-dihydropyridine moiety.

2.5.c. Radziszewski
One of the oldest MCR is the Debus-Radziszewski reaction, so named in reference to its first two contributors. It is still nowadays the most employed method to synthesize imidazole compounds. This reaction was discovered by Debus in 1852 who reacted ammonia with glyoxal yielding the simplest imidazole named glyoxaline.[167] Later on, Radziszewski contributed to this field by adding an aldehyde (formaldehyde or substituted aldehyde) to glyoxal and ammonia in mild acidic conditions affording higher yields and broadening the scope of imidazole products.[168] He also extended the reaction to substituted 1,2-diketones affording 2,4,5-trisubstituted imidazoles (Fig. 23, type I) for which harsher conditions were required.[169] The original Debus-Radziszewski reaction, often simply called the Radziszewski reaction, is a three-components reaction with four centers since it requires two equivalents of ammonia considered here as a single component (R-4C-3CR). More than 100 years later, Arduengo introduced a fourth component by replacing one equivalent of ammonia by a primary amine (Fig. 23, type II).[170] The resulting Radziszewski four-center four-component reaction (R-4C-4CR) gives access to tetra-substituted imidazoles. In the last version of this reaction, ammonia is replaced by two equivalents of primary amine (Fig. 23, type III).[171] This reaction, also known as the “modified Radziszewski” reaction, involved four centers and three components (MR-4C-3CR). The final product is not a neutral imidazole but an imidazolium salt which is of great interest in the field of ionic liquid (IL)[172] and medical science.[173] Very few articles deal with the mechanism of each type of Radziszewski reaction, possibly due to the complexity of the subject.[174] All we can say is that condensation reactions take place between the ammonia (or primary amine) and the carbonyl compounds, namely the 1,2-dicarbonyl and the aldehyde, and water is released as byproduct. Moreover, Radziszewski MCRs are generally carried out in acidic media and their driving force is the formation of an aromatic heterocycle. Under appropriate conditions, high conversion can be
reached making these reactions interesting candidates for polymer synthesis. Some years ago, all the approaches, i.e. monomers synthesis, modification or crosslinking of preformed polymers and step-growth polymerization, have been reviewed by Dupuy and coworkers.[175] Hereafter, we focus on the direct Radziszewski MCP and establish the state-of-the-art of this topic.

**Fig. 23.** The different types of Radziszewski reactions toward imidazoles and imidazoliums.

The first attempt to synthesize poly(imidazole) _via_ the Radziszewski type I reaction is one of the oldest example of MCP and dates from 1967.[176] In this work, an aryl bis(1,2-diketone), named bisbenzyl, was reacted with various aromatic dialdehydes in the presence of ammonium acetate in acetic acid at the boil for 240 h under nitrogen (Fig. 24, Manecke 1967). Only oligomers were collected accordingly, with great uncertainty on their molar masses measured by infrared...
spectroscopy (IR), but they showed good thermal and semi-conductive properties with low activation energy (below 1.12 eV).[176]

Forty years later, Mercier et al. enhanced the polymerization efficiency and extended its scope to various dialdehyde monomers (Fig. 24, Mercier 2008).[177] The monomers were solubilized in acetic acid with additional N-methyl-2-pyrrolidone (NMP) to ensure the polymer solubility during the polymerization. In addition, the authors used a ten-fold excess of ammonium acetate and irradiated the mixture for 15 minutes with microwaves in a high-pressure reactor. Only two polymers were sufficiently soluble in SEC solvent (DMF) to determine their molar masses of 10 and 17 kg/mol. All poly(arylimidazole)s exhibited high thermal stability with degradation temperatures above 400 °C and were casted into films after dissolution in NMP suggesting quite high molar masses.[177]

Finally, a poly(arylene-imidazole) was synthesized via the type I R-4C-3CP with the bisbenzyl and a hexamethyl-terphenyl dialdehyde as bifunctional monomers (Fig. 24, Holdcroft 2017).[178] The authors performed the polymerization in conditions similar to those reported by Mercier[177] using microwaves to enhance the conversion and a ten-fold excess of ammonium acetate. The reaction mixture was heated at 120 °C for 35 minutes. The resulting polymer served as a precursor for high molar mass (50 kg/mol) poly(arylene-imidazolium) upon modification with iodomethane (Fig. 24, Holdcroft 2017). The final product exhibited high performance as polyelectrolyte membrane for alkaline fuel-cells.[178] The steric hindrance around the C2-position, that is the carbon between the two nitrogen atoms, prevents its degradation in concentrated hydroxide solution which is usually a severe limitation for the use of poly(imidazolium)s in this application.[179]
Fig. 24. Substrates scope of Radziszewski type I polymerization toward poly(Imidazole)s.

a Determined by infrared spectroscopy. NA stands for not available.

So far, there is only one report on the Radziszewski type II polymerization in the literature.[180] In this work, a series of tetrasubstituted poly(aryl imidazole)s was produced from various bis(aryl 1,2-diketone)s, bis(aryl aldehyde)s, mono-aryl amines and ammonium acetate (Fig. 25). In addition to the use of microwave, an elevated temperature (140 °C) and a high pressure (25 bar), the reaction required a catalytic amount of trifluoroacetic acid. Poly(aryl imidazole)s with molar masses between 18 and 31 kg/mol were formed accordingly in quantitative yield. They
showed very high degradation temperatures (up to 527 °C) and were soluble in common organic solvents (THF, NMP, DMSO, etc.) allowing their casting into films.

Fig. 25. Substrates scope of Radziszewski type II polymerization toward tetrasubstituted poly(imidazole)s.

The modified Radziszewski type III polymerization (MR-4C-3CP) is by far the most common category of Radziszewski MCPs. Instead of neutral poly(imidazole)s, it gives access to poly(imidazolium)s, an important class of poly(ionic liquid)s (PILs). These materials combine some valuable features of ILs with the intrinsic characteristics of polymers and, over the years, became essential in many areas.[173,181,182] The type III is articulated around the amine component which constitutes the attachment points of the imidazolium moiety in the backbone. Replacing two equivalents of monofunctional amine by one equivalent of diamine allows the step-growth polymerization. In the following examples, diamines monomers are used in combination with mono-1,2-dicarbonyls and monoaldehydes. Unlike types I and II Radziszewski polymerizations, the carbonyl compounds involved in the type III MCP are almost not substituted such as formaldehyde and glyoxal (or sometimes pyruvaldehyde).
The MR-4C-3CP was first reported and patented by BASF in 2010[183] and further improved and applied by Lindner (from BASF) few years later.[184–188] These researches were summarized in his paper published in 2016.[189] First, he performed the polymerization of diaminobutane with glyoxal and formaldehyde in aqueous solution using acetic acid as catalyst (Fig.26, Lindner 2016).[189] In this case, the polymerization was highly accelerated at 100 °C compared to room temperature which ultimately shortened the reaction time from 24 to 1 hour to reach the same molar mass. Under optimal conditions, including a slight excess of carbonyl compounds, a poly(imidazolium) acetate with a molar mass about 10 kg/mol was obtained.[189] Various aliphatic diamines were tested affording a series of polymers with $T_g$ ranging from -52 to 48 °C depending on the flexibility of their backbone dictated by the diamine compound (Fig.26, Lindner 2016).[189]

Shortly later, Yuan et al. considered the same strategy to synthesize a series of poly(imidazolium)s from diamines with different aliphatic chains but they used the biomass-derived pyruvaldehyde (methylglyoxal) instead of glyoxal (Fig.26, Yuan 2017).[190] Polymers with $M_n$ of 20 kg/mol were obtained which is higher than those reported by Lindner. The authors claimed for a better reactivity of methylglyoxal over glyoxal due to electron-donating character of the methyl group. They also successfully exchanged the acetate counterion for bis(trifluoromethane sulfonyl)imide anion (TFSI) in order to tune the polymer properties such as the solubility. Importantly, the polymerization was also successful with an aromatic diamine, namely the para-pheylenediamine, leading to poly(imidazolium acetate) with $M_n$ of 20 kg/mol. The acetate counterion was then replaced by a nitrogen-rich dicyanamide followed by carbonization to afford micro/mesoporous nitrogen-doped carbon with almost 70 % of residual weight.[190] This sample was used for CO$_2$ capture and selective aerobic oxidation of benzyl alcohol.[191]
Interestingly, Qian and coworkers synthesized a poly(imidazolium chloride) from para-phenylenediamine, glyoxal and paraformaldehyde (polymeric form of formaldehyde). In addition, they replaced the acetic acid with hydrochloric acid (Fig.26, Qian 2018).[192] The polymerization was carried out in DMSO during 48 h and the resulting poly(imidazolium chloride) was further converted into the corresponding N-heterocyclic carbene-Pd organometallic specie via deprotonation of the C2-carbon and subsequent addition of palladium salt. This complex was valued as a catalyst in the Suzuki-Miyaura reaction between various aryl bromides and phenylboronic acid.[192]

Eventually, a poly(imidazolium) prepared via MR-4C-3CR of hexamethylenediamine, glyoxal and formaldehyde was anchored onto cellulosic substrate (Fig.26, Lucena 2019).[193] The modified cellulose then served as sorptive phase for anti-inflammatory drugs microextraction from urines.[193]
Fig. 26. Substrates scope of the Radziszewski type III polymerization toward poly(imidazolium)s. NA stands for not available.

The linear poly(imidazolium)s prepared by MR-4C-3CP have raised peculiar interest for functional membranes synthesis. Due to their charged cationic structures, they can be further crosslinked by physical interactions. In addition, these polymers generally present amino end-groups, as a result of the diamine involved in their synthesis, which allows subsequent chemical crosslinking. Below, we describe the preparation of membranes based on poly(imidazolium)s synthesized via the Radziszewski reaction.

Yuan et al. prepared reprocessable porous membranes by mixing a poly(imidazolium)-TFSI made of glyoxal, formaldehyde and 1,4-diaminobutane with polyacrylic acid in aqueous ammonia (Fig. 27, Yuan 2018).[194] The crosslinking was achieved by ionic interactions between the carboxylates and the imidazolium moieties. Interestingly, the pores size could be tuned by varying
the molecular weight of the polyacrylic acid. Moreover, the ionic interactions being reversible, the membrane could be dissolved in LiTFSI solution and reprocessed at will by evaporation.[194]

Feng and coworkers combined imidazolium and siloxane groups into a polymer in one step by MR-4C-3P of 1,3-bis(3-aminopropyl)tetramethyldisiloxane, glyoxal and formaldehyde (Fig.27, Feng 2019).[39] Instead of using pure acetic acid as both the catalyst and the counterion precursor, oxalic acid was added to promote an ionic crosslinking. The imidazolium moiety endowed the membrane with ionic conductivity while good healing ability was brought by the dynamic ionic crosslinking. Furthermore, the material emitted a yellow-green fluorescence under UV light and showed a stable and reversible stretching sensitivity (variation of the conductivity upon stretching).[39]

Next, Liu et al. synthesized a poly(imidazolium TFSI) by reacting 1,2-bis(2-aminoethoxy)ethane, glyoxal and formaldehyde with acetic acid followed by ions-exchange reaction (Fig.27, Liu 2020).[195] Porous membranes were prepared from poly(imidazolium TFSI) and poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) by phase inversion method. Physical crosslinking was assumed to occur through ion-dipole interactions between the imidazolium cations and the polar fluorine atoms from PVDF-HFP. The self-supported membrane exhibited good mechanical properties, high liquid-electrolytes uptake, fire-resistance and electrochemical stability making it a high-performance material for Li ion batteries.[195]

Meng’s group synthesized poly(imidazolium)s with low and high molecular weights by performing the polymerization at room temperature or 100 °C, respectively. They used their terminal amine functions for further crosslinking reactions with multifunctional epoxides (Fig.27, Meng 2020).[196] A series of networks with different crosslinking densities were shaped into membranes that were tested in CO₂ capture and diffusivity. The solubility of CO₂ was further
increased with addition of free ILs in the membrane. As a result, the behaviour of the membranes towards CO$_2$ could be precisely tuned by playing with the different parameters.[196]

As mentioned previously, except for pyruvaldehyde, the carbonyl compounds used in the MR-4C-3P are usually not substituted. The recent work from Yan et al. radically changed this limitation.[197] They synthesized a series of substituted poly(imidazolium)s using L-proline as a co-catalyst (Fig.27, Yan 2020), which was already known to efficiently promote the types I and II Radziszewski MCRs.[198] With the alkaline fuel-cell application in mind, the authors anticipated a beneficial effect of the imidazolium group substitution on its stability toward hydroxide-induced ring opening.[178][199] In practice, these PILs were physically entangled in a crosslinked glutaraldehyde-poly(vinyl alcohol) network. All the membranes showed good hydroxide ion conduction but, as expected, only the highly substituted ones retained stable conduction after 120 hours at 80 °C in concentrated alkaline solution.[197]
Fig. 27. Membranes preparation using linear poly(imidazolium)s synthesized by the modified Radziszewski four-center three-component polymerization.

The MR-4C-3CR was also used to crosslink pre-formed polymers with pendant amine functions such as poly(L-Lysine)[200] and chitosan.[201,202] In addition to the proof of concept,
the chitosan-imidazolium gel was used for dye removal.\cite{201} At the frontier between the crosslinking of polymer chains and the polymerization of low molecular weight molecules bearing more than 2 amino groups, Song and coworkers applied the MR-4C-3CP to poly(amidoamine)s (PAMAM) dendrimers (Fig. 28, Song 2017).\cite{203} Different generations of PAMAM dendrimers (from 4 to 128 amines) were considered. The reaction was carried out in ionic liquid (1-ethyl-3-methylimidazolium acetate) using methylglyoxal and formaldehyde as monomers but without acetic acid which therefore led to poly(imidazolium) materials with hydroxide as the counterion. The resulting ionogels presented excellent ionic conductivity at room temperature and good mechanical properties.\cite{203}

The MR-4C-3CP of hexamethylenediamine, glyoxal and formaldehyde, was also conducted in the presence of magnetic iron oxide nanoparticles (NPs) covered by amine functions which served as additional “multiamine” (Fig. 28, Lucena 2017).\cite{204} The resulting nanocomposite composed of poly(imidazolium) attached to magnetic NPs showed its potential for the removal of anionic drugs from aqueous solutions but also from bioanalytical samples such as saliva.\cite{204}

In addition, the MR-4C-3CP was applied to an aromatic tetraamine, the tetrakis(4-aminophenyl)methane, in combination with methylglyoxal and formaldehyde in acetic acid leading to a powdery network of imidazolium acetate (Fig. 28, Bordiga 2017).\cite{205} Several counterions exchanges were made to tune the properties of the materials and tert-butoxide was used to deprotonate the imidazolium yielding the neutral carbene. All these materials showed microporosity that comes from the sterically hindered amine monomer inducing empty spaces inside the networks. These materials demonstrated excellent behaviour in carbon dioxide adsorption.\cite{205}
Finally, two different triamines, namely the tris(2-aminoethyl)amine and the Jeffamine T-403®, were crosslinked via the MR-4C-3CP using formaldehyde and glyoxal (Fig.28 Debuigne 2020).[206] These reactions were implemented in the external aqueous phase of a high internal phase emulsion (HIPE) involving cyclohexane as droplet phase (75 v% of the total volume). Sequential curing by MR-4C-3CP and removal of the internal phase led to the corresponding imidazolium networks with interconnected macroporosity. These materials successfully catalysed the decarboxylation of caffeic acid as well as transesterification reactions and showed good recyclability.[206]
Fig. 28. Networks synthesized by the modified Radziszewski four-center three-component polymerization.

Although it does not match with our MCP definition, it is noteworthy to mention that imidazolium networks with CO$_2$ sorption ability were also produced via a pseudo-Radziszewski reaction carried out in a two-pot, two-step process with the synthesis of the imine-based network from tetraamine followed by its transformation into imidazolium. [207] In the light of these
considerations, the Radziszewski step-growth polymerization appears today as one of the most developed and mature MCPs which gives access to a broad range of linear and crosslinked polymers of practical interest for various applications.

2.6. Miscellaneous-MCP

2.6.a. Active hydrogen compound-based MCP

The Mannich three-component reaction is a hundred years old reaction that significantly evolved since its discovery by Carl Mannich in 1912.[208] The reaction starts with the condensation of a secondary amine with formaldehyde followed by a nucleophilic attack by a compound containing a reactive hydrogen. This reaction is catalysed by Brønsted acids and generates Mannich bases which are important pharmacophores.[209] The versatility of the reaction comes from the numerous possibilities for the acidic hydrogen compound (Fig.29). This active hydrogen was initially located in the α-position of a carbonyl but it can also be in α-position of an imine, a nitrile and a nitro functional group, to name a few.[210] Moreover, aromatic protons from phenols, pyrroles, thiophenes and furans, etc., also present acidic features suitable to perform Mannich reaction.[210,211]

The first examples of the Mannich polymerization date back to the seventies as summarized by Ghedini.[24] Such polymerization can be performed with homo-difunctional monomers and formaldehyde via a Mannich three-center three-component polymerization (M-3C-3CP). First, diamines and compounds with activated protons located on two distinct carbons can polymerize in the presence of formaldehyde (Fig.29, strategy 1). A typical example of such M-3C-3CP involves 1,3-di(piperidin-4-yl)propane, cyclohexanone and formaldehyde (Fig.29, strategy 1).[212] The reactive hydrogens can be carried by carbons as it is the case for cyclohexanone, furan, phenol,
2,6-dimethylpyridine but it can also be carried by the nitrogen of an amide or an urea. All these compounds have been considered and reacted with several secondary diamines.[24] One variant of this MCP consists in using a compound where two reactive hydrogens are on the same carbon, such as acetophenone. The latter could thus react twice with 1,3-di(piperidin-4-yl)propane and formaldehyde (Fig.29, strategy 2).[212] Next, a primary amine can undergo two subsequent Mannich reactions and, therefore, can be used as difunctional monomer as illustrated by the M-3C-3CP of methylamine, pyrrole and formaldehyde (Fig.29, strategy 3).[213] Finally, a Mannich two-component reaction was also considered using arylamine derivatives that behave simultaneously as an amine and an activated hydrogen compound, as exemplified by the M-3C-2CP of para-aminobenzoic acid and formaldehyde (Fig.29, strategy 4).[214] Nevertheless, this approach led to branched and crosslinked polymer products since para-aminobenzoic acid contains four reaction sites, i.e. two acidic protons in ortho positions of the amine and the two protons of the latter which can also react.[214] The Mannich reaction has been extensively employed to synthesize polymer networks.[215–217] These syntheses often involve primary diamines and/or compounds containing multiple carbons bearing two reactive hydrogens.
This section cannot be closed without mentioning the synthesis of benzoxazine and poly(benzoxazine)s via the Mannich reaction. The benzoxazine is a bicyclic compound that consists of a benzene fused with an oxazine. The 1,3-benzoxazine isomer could be formed by reacting a primary amine with formaldehyde and a phenol derivative. In this case, the phenol reacts
at two different sites: the hydroxyl group with a labile hydrogen and the ortho position of the hydroxyl via its active hydrogen (Fig.30). The resulting 1,3-benzoxazine could be polymerized upon heating leading to the expected classical Mannich product (Fig.30, path 1).[220] On the other hand, a polymer containing benzoxazine groups in its backbone is obtained when using a diphenol and a primary diamine (Fig.30, path 2).[220] Interestingly, further heating this material produces a network.[221] Plethora of poly(benzoxazine)s are reported in the literature and have already been reviewed.[218,219]

![Fig.30. 1,3-Benzoxazines synthesis via Mannich reaction and their subsequent polymerization as well as preparation of poly(benzoxazine)s by Mannich polymerization.](image)

### 2.6.b. Preformed imine-based MCP

The last section of this review is dedicated to multicomponent polymerizations involving preformed imines. Compared to the previous MCRs, the imine is no more synthesized in situ by the condensation of an amine and an aldehyde. According to this approach, years ago, Arndtsen
and coworkers developed a one-pot synthesis of münchnones by reacting an imine with an acyl chloride and carbon monoxide in the presence of a palladium catalyst and a base to deal with HCl, the sole byproduct (Fig.31).[222] The münchnones are versatile 1,3-dipolar addition substrates and are thus key intermediates for the synthesis of heterocycles. Subsequent cycloadditions with alkynes and alkenes give access to substituted pyroles while a treatment with tosyl imines leads to imidazoles (Fig.31).[223]

Recently, Arndtsen et al. took advantage of this efficient reaction to synthesize poly(münchnone)s.[224] They used various aromatic difunctional monomers, i.e. diacyl chlorides and diimines combined with carbon monoxide (20 bar) (Fig.31, Arndtsen 2015).[224] The polymerizations were carried out at 45 °C for 64 h with Pd[P(o-tol)]$_2$ and N,N-diisopropylethylamine as the catalyst and the base, respectively. The resulting polymers could be isolated but, due to their moisture sensitivity, they were modified prior to characterization. For the same reason, they were directly transformed into a series of conjugated polymers by one-pot addition of different reagents (alkynes, alkenes and tosyl imines). The final conjugated polymers exhibited fluorescence properties and possessed tunable band gaps which make them good candidates for electronic applications.[224] The munchnone ring could also be opened by addition of an alcohol to produce a poly(amide-ester) (Fig.31).[224] In addition, the authors showed the possibility to perform a four-component reaction by direct addition the alkyne in the reaction medium. Accordingly, CO$_2$ was released and a poly(pyrrole) derivative was formed in good yield (87 %) with a molar mass of 14 kg/mol (Fig.31, Arndtsen 2015).[224] Note that the same group reported a four-component polymerization based on a diacyl chloride, an imine, carbon monoxide and a difunctional tosyl imine compound, affording oligomers of conjugated
poly(imidazole)).[225] In this case, however, the side-product consisting in para-toluenesulfonic acid significantly reduces the atom economy of the reaction.

Phospha-münchnones, analogues to münchnones, were also synthesized by Arndtsen using phosphinite instead of carbon monoxide.[226] Advantageously, no catalyst is required for this reaction but phosphonate is released when the phospha-münchnones is reacted with a dipolarophile which somewhat lowers the atom economy. Recently, this reaction was used for the direct polymerization of a series of aromatic diacyl chlorides and diimines with a phosphinite, i.e. the (catechyl)PPh (Fig.31, Arndtsen 2016).[227] The poly(phospha-münchnone)s were subsequently transformed in one-pot into conjugated poly(pyrrole)s by addition of different alkynes[227] and notably alkynes bearing PEG oligomers.[228] The scope of this reaction was extended to vanillin-based monomers (Fig.31, Arndtsen 2016 bis).[229] While the syntheses of poly(münchnone)s and poly(phospha-münchnone)s conform to the concept of multicomponent polymerizations it should be kept in mind their subsequent transformations do not satisfy the atom economy principles. It is especially true for the transformations of phospha-münchnones releasing significant byproducts which affects the atom economy of the process.
Fig. 31. Synthesis of poly(münchnone)s and poly(phospha-münchnone)s by MCPs and their post-polymerization modification. a SEC measurement performed onto modified polymers due to the moisture sensitivity of münchnones.

3. Conclusion and outlook

For a few decades now, MCRs are employed in polymer chemistry for monomers synthesis, post-polymerization modifications and step-growth polymerizations but this approach has seen a great acceleration in the last years. This general trend is noticeable in the present review dedicated to step-growth multicomponent polymerizations involving an imine as the principal component. The addition of one or more component(s) to the imines generated in situ (or sometimes preformed)
by amine/aldehyde condensation affords a great diversity of valuable polymer structures. The combinatorial feature and versatility of these imine-based MCPs make them very powerful macromolecular engineering tools. Besides large libraries of linear polymers, MCPs give access to unique hyperbranched polymers and networks. Although examples of such macromolecular structures remain limited so far, they illustrate the huge potential of MCPs in this area. Of course, the development of MCPs is still in its infancy and deserves improvements notably in terms of conversion and molar masses for some of them. In this respect, gaining more insight into the MCPs’ mechanism and identifying the potential side-reactions which drive these polymerizations out of stoechiometry should lead to polymers with higher molar masses. For catalysed-MCPs, such as Ugi-3CP, tuning the structure of the catalyst is another key lever for improving the conversion and polymer molar mass. Nevertheless, these polymerization techniques become mature enough to witness the emergence of cutting-edge applications in the biomedical, energy, electronic, gas capture, catalysis, heavy metal recycling sectors and so on.

Future prospects of MCPs are vast and promising. Owing their combinatorial feature, countless substrates could be used to enlarge the already consequent scope of functional polymers. Moreover, most of the MCRs described in organic chemistry have not yet been adapted to polymer chemistry and constitute a huge field of unexplored opportunities. As exemplified by the combination of the Hantzsch/Biginelli and the A3-coupling/Petasis reactions, MCPs can also proceed hand-in-hand towards unique and highly complex polymer structures in one-pot. This strategy is particularly relevant for the imine-based MCPs since they already share two components, i.e. the amine and the aldehyde, and should be pursued. Eventually, the combination of MCP with other techniques such as radical polymerization and click chemistry will certainly constitute a key step in the deployment of this technology. A recent trend in MCR consists in the
development of asymmetric catalysts able to confer chirality to the final product[230,231] which opens a vast field of exploration for the design of more realistic biomimetic macromolecules via MCPs. Overall, there is still a lot of work ahead to extend the scope of MCPs and make them greener, notably by using renewable starting reagents, but there is bright future for the use of MCRs in polymer synthesis and many applications should benefit of it in the coming years.

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