Multicomponent reactions: development, scope, and applications

Chandgude, Ajay

Chapter 2

The Passerini Reaction: Scope, Chirality, and Applications

Manuscript in Preparation:

A. L. Chandgude
A. Dömling
2017

Abstract

Passerini reaction is one of the most studied IMCR. It was first reported in 1921. In the last few decades, the importance of this reaction has been increased tremendously with the lots of breakthroughs, such as the report of first catalytic enantioselective Passerini reaction, introduction to polymer science and report of pseudo-four component mechanism. In this review, we focus on the recent developments in the Passerini reaction that have been reported about scope, chirality, and applications.

1. Introduction

Over the last few decades, the research area of isocyanide-based multicomponent reactions (IMCR) has grown rapidly to become one of the exciting and powerful tools for peptidomimetics synthesis. The history of IMCR goes back to the first IMCR by Passerini in 1921.[1] Since the landmark publication of the first IMCR about a century ago, the mechanism, scope, chirality and applications in different areas has been elevated to the rarefied status of being one of the most studied IMCR.

Passerini reaction named after the discoverer, Italian scientist Mario Torquato Passerini. He was born on 29, August 1891, in Casellina/Torri (now Scandicci, Florence, Italy). He graduated from the University of Florence in 1916. In 1920 he joined doctoral studies and in 1921 published the first paper reporting on the "Reaction of an oxo component, an isocyanide, and an acid component to form α-acyloxy carboxamide", which is now known as "Passerini reaction". He worked as a pharmaceutical chemistry professor in Siena from 1930 and from 1933 in the university of Florence. After 1937, he did not continue his work on isocyanide and moved to a characterization of natural products from the lygustrum japonicum leaves and in helichrysum italicum flowers. He died in 1962 in Florence, just after his retirement in a previous year.[2]

His discovery of this first isocyanide-based multicomponent reaction made a robust movement towards the new era of IMCR which was followed by Ivar Ugi. In last decade, this reaction emerging as powerful MCR in the synthetic world which we can clearly see from the high increase in the number of articles on Passerini reaction (Figure 1).

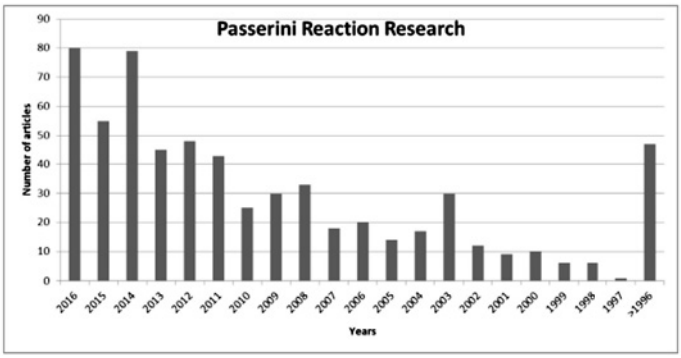


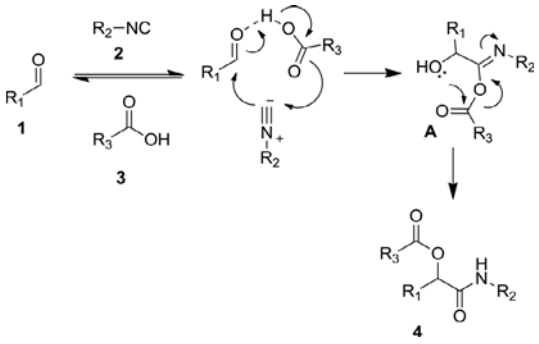
Figure 1. A number of publications on Passerini reaction per year (result derived from SciFinder query on "Passerini reaction").

Many reviews are available from our group and other research groups about the multicomponent reactions which also cover the Passerini reaction.[3] In 2005, L. Banfi and R. Riva made the exclusive review about Passerini reaction with a mechanism, scope, and applications.[4] A. Kazemizadeh and A. Ramazani reviewed the synthetic applications of Passerini reaction.[5] As the remarkable growth of Passerini reaction articles in last decade, an update to this reach area is much needed. The purpose

of this mini-review is to highlight the growing interest in Passerini reaction about scope, chirality and it's applications in the different fields, especially research reported from 2005 to December 2016.

1.1 Mechanism

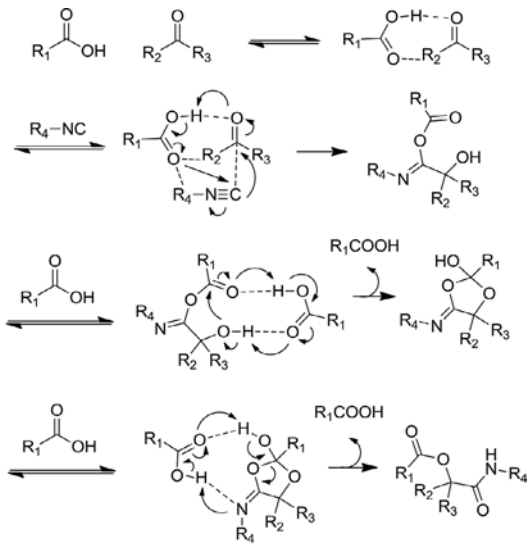
M. Passerini first time proposed that this reaction mechanism might involve the zwitterionic intermediate. An extensive research has been focused on finding the Passerini reaction mechanism, and different literature has shown the different intermediates, such as hemiacetals, carbocation, and hydrogen-bonded adducts.[4] The formation of the hydrogen-bonded intermediate is the most accepted mechanism for this reaction (Scheme 1). It involves the activation of an aldehyde by the carboxylic acid, followed by addition of an isocyanide to form nitrilium intermediate (**A**). Which is trapped by the carboxylate, which undergoes Mumm type rearrangement to form final α-acyloxy amide product (**4**).



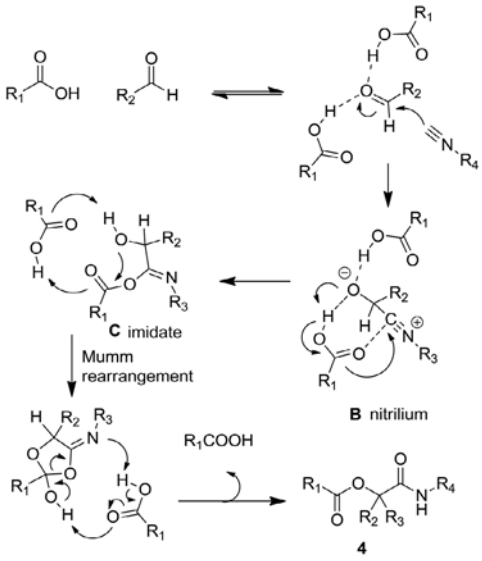
Scheme 1. The proposed Mechanism for the Passerini-3CR.

In 2011, Maeda et al. used the AFIR method for mechanistic studies of Passerini reaction. They show that mechanism involves the extra acidic component before the final product formation, so it shows that Passerini reaction is a pseudo four-component reaction (Scheme 2).[6]

Recently, Ramozzi and Morokuma performed high-level DFT calculations which also support the four component mechanism (Scheme 3).[7] They found the nitrilium intermediate (**B**) is stable in solution and its formation is rate-determining. This step is catalyzed by a second carboxylic acid molecule followed by Mumm rearrangement to form final product (**4**).



Scheme 2. Passerini reaction (pseudo-four component reaction) mechanism based on AFIR method in a gas phase.



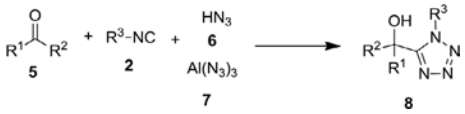
Scheme 3. Passerini reaction (pseudo-four component reaction) mechanism based on high-level DFT in solution.

2. Substrate scope

During the last decade, the substrate scope was extensively studied and the new isosteres have been reported for the acid and aldehyde. The acid isostere use provides the interesting scaffolds and different new bond formations, such as C-Si, C-P, and C-N.

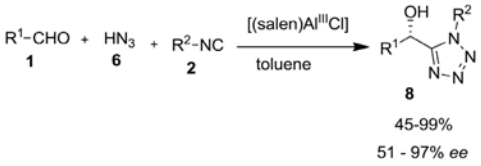
2.1 Acid isosteres in Passerini Reaction

Ivar Ugi reported the use of HN_3 and $Al(N_3)_3$ as first acid isostere in Passerini reaction (PT-3CR) in 1961.[8] This reaction became a model reaction to synthesize α-hydroxy tetrazoles (**8**) (Scheme 4).



Scheme 4. PT-3CR toward a-hydroxy tetrazole.

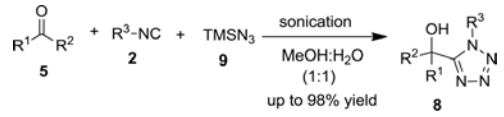
Use of HN_3 or NaN_3 in PT-3CR has been used by many instants.[4, 9] Zhu also used HN_3 in enantioselective Passerini reaction (Scheme 5).



Scheme 5. Enantioselective Passerini-type MCR catalyzed by the [(salen)AlIIIMe] complex.

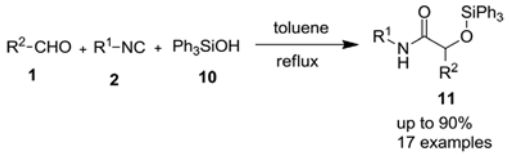
Hulme reported the use of $TMSN_3$ as a safe alternative to NaN_3 and HN_3 for the synthesis of cis-constrained norstatine analogs. Reaction provides the TMS-ether product which was removed by TBAF treatment.[10] Zinc iodide catalyst use with $TMSN_3$ was also reported in PT-3CR where de-etherification done by basic conditions Passerini.[11] Our group reported the PT-3CR in the screening for the X-linked inhibitor of an apoptosis-baculoviral inhibitor of apoptosis protein repeats domain binder.[12]

A significant drawback of this PT-3CR reaction with $TMSN_3$ is, that, TMS-ether will be the product. So always require one extra step for de-etherification and also yields will be very low. Recently, we reported a significant improvement of this method. We reported a sonication accelerated, fast and catalyst free PT-3CR in methanol: water (1 : 1) solvent system which provided good to excellent yields (Scheme 6).[13] Sonication gave high conversion and giving high yields and no TMS-ether side products.



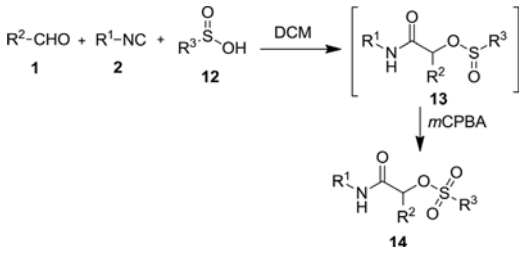
Scheme 6. Sonication accelerated PT-3CR in an aqueous solvent.

In 2010, Soeta and co-workers reported the O-silylative Passerini reaction for the synthesis of α-siloxyamides (**11**) by using silanol (**10**) as an acid isosteric replacement (Scheme 7).[14]



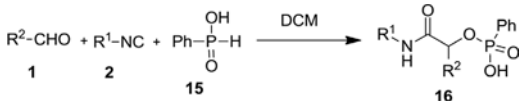
Scheme 7. Passerini reaction with silanol.

The same group reported O-sulfinative Passerini/oxidation for the synthesis of α-(Sulfonyloxy)amide derivatives by using one-pot O-sulfinative Passerini/oxidation reaction (Scheme 8).[15] Passerini reaction carried out with sulfinic acid (**12**) followed by the addition of an oxidant, mCPBA to provide corresponding α-(sulfonyloxy)amides (**14**).



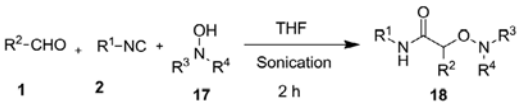
Scheme 8. Passerini reaction with sulfinic acid.

Phosphinic acids (**15**) use in a one-pot O-phosphinative Passerini/Pudovik reaction has been reported for the synthesis of **a**-phosphinyloxy amide (**16**) (Scheme 9).[16]



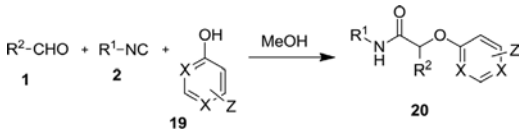
Scheme 9. Phosphinic acids in Passerini reaction.

Recently, we reported the use of *N*-hydroxyimide (**17**) as an acid isostere to get direct access α-aminoxy amides (**18**) (Scheme 10).[17] This sonication-accelerated reaction is compatible with *N*-hydroxysuccinimides and phthalimides.



Scheme 10. *N*-hydroxyimide in Passerini reaction.

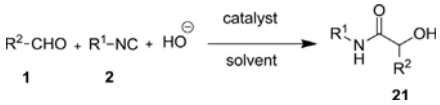
El Kaim and co-workers reported Passerini-Smiles reaction for the synthesis O-arylated compounds just after the report of Ugi-Smiles reaction (Scheme 11).[18] Phenol (**19**) as acid component works well in methanol with the key step of the conversion of an irreversible Smiles rearrangement of the intermediate phenoxyimidate adducts (**20**).



Scheme 11. Passerini-Smiles reaction.

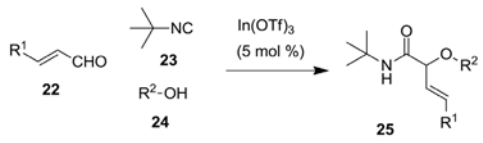
After the report of Passerini-Smiles reaction, they modified the conditions for better yield and substrate scope, also for the synthesis of diverse post-condensations reactions.[19]

Paserini reaction with $TiCl_4$ for the synthesis of α-hydroxy amide is well established and used reaction.[20] The use of water, mineral acid, organic acid and Lewis acid as acid isostere was reviewed by Banfi et all.[4] The use of mineral acids, such as aqueous hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid and sulfuric acid was reported. In Lewis acids, $TiCl_4$, BF_3, $AlCl_3$, $POCl_3$ and combination of $Me_3SiCl/Zn(OTf)_2$ were used to made a-hydroxy amides (**21**) (Scheme **12**). Recently organic acids were also reported, such as diphenylborinic acid/water,[21] and Boric acid/DMF.[22]



Scheme 12. Acid catalyzed P-2CR.

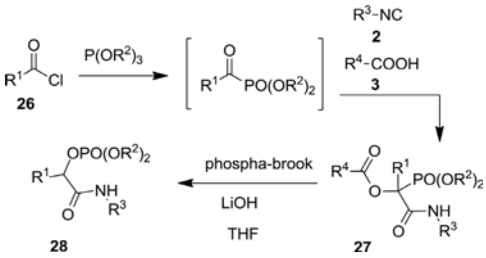
O-alkylative Passerini reaction of aliphatic alcohols catalyzed by $In(OTf)_3$ was reported to access α-alkoxy amide products (**25**) in good yield (Scheme 13).[23] Similar O-alkylative Passerini reaction catalyzed by $AlCl_3$ was also reported to provide access for functional α-alkoxy-β,γ-enamide derivatives.[24]



Scheme 13. O-alkylative Passerini reaction.

2.2 Carbonyl isosteres in Passerini Reaction

Acylphosphonates as carbonyl isostere in Passerini reactions was reported. This reaction involves a phospha-Brook rearrangement to form α-amidophosphates (**28**). Acylphosphonates are formed from acyl chlorides (Scheme 14).[25]



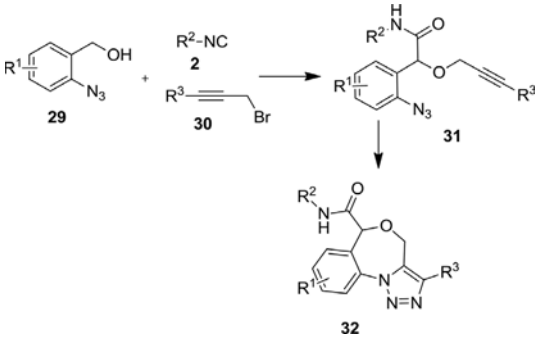
Scheme 14. Acylphosphonates as carbonyl isostere in Passerini reaction.

Direct use of alcohols instead of an aldehyde in the Passerini reaction has been reported by Zhu and co-workers. This reaction worked well by heating O-iodoxybenzoic acid (IBX) at 40°C and then after oxidation/P-3CR to gave α-acyloxy carboxamide (**4**) in good-to-excellent yield (Scheme 15).[26]

Scheme 15. Passerini-alcohol IBX-promoted oxidative Passerini reaction.

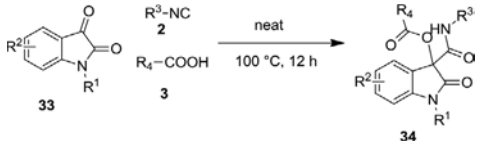
The same group reported the catalytic aerobic oxidative protocol, a catalytic amount of cupric chloride, $NaNO_2$, and TEMPO, under an oxygen atmosphere for the same reaction.[27] This oxidative Passerini reaction with primary alcohols in presence of ferric nitrate and TEMPO and under air also provide good yields.[28] Recyclable magnetic core-shell nanoparticle supported TEMPO use for the one-pot oxidative Passerini reaction of primary or secondary alcohols under metal- and halogen-free reaction conditions have been reported.[29]

Basso and co-workers developed the four-step, one-pot improvement of the alkylative Passerini reaction (Oxidation-Passerini-Hydrolysis-Alkylation strategy) for the synthesis of alkoxyamide and also benzoxazepines (**32**) (Scheme 16).[30]



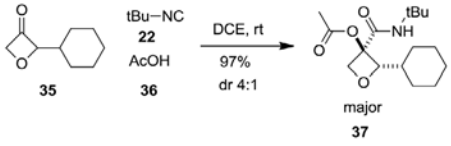
Scheme 16. Oxidation-Passerini-Hydrolysis-Alkylation towards benzoxazepines.

Recently, the use of isatins (**33**) in Passerini reaction to form oxindole derivatives (**34**) in the presence of molecular sieves,[31] and in solvent-free was reported (Scheme 17).[32]



Scheme 17. Isatins in Passerini reaction.

Passerini reactions with oxetan-3-ones for the efficient synthesis of 3,3-disubstituted oxetanes (**37**) has been reported (Scheme 18).[33] Good diastereomeric (*dr* = 4 : 1) products can be achieved when the oxetane with bulky cyclohexyl substitution (**35**) used.



Scheme 18. Passerini reaction with oxetan-3-ones.

2.3 Isocyanide isosteres in Passerini Reaction

Guchhait and co-workers reported the one-pot preparation of isocyanides from amines and used for the Passerini and other MCRs.[34] The nature and quantities of dehydrating agent and base and the function of by-products as promoters for post-transformation were crucial for the success of this reaction. This reaction involves N-formylation of amine by formic acid followed by dehydration by *p*-TsCl and DABCO.

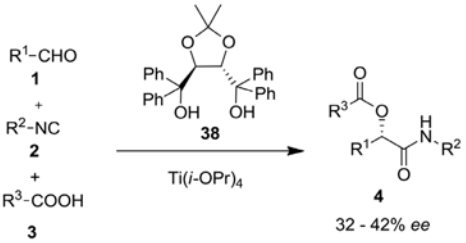
Recently our group described a rapid and highly diverse formamide synthesis via a modified Leuckart-Wallach procedure, with conversion *in situ* into isocyanides, this one pot protocol can be used for different IMCRs.[35]

3. Chirality in Passerini reaction

In 2003, our group developed the first enantioselective Passerini three-component reaction. The development of an enantioselective Passerini three-component reaction remains a significant challenge. Recently, significant breakthroughs were achieved to get high enantioselectivity by Schreiber, Zhu, and Tan.

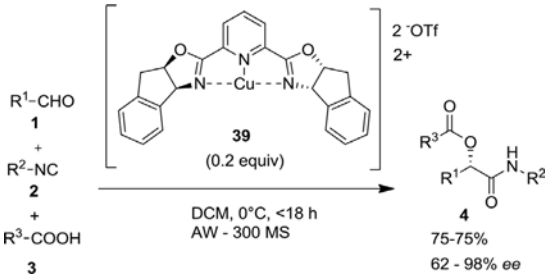
3.1 Enantioselective Passerini three-component reactions

Our group reported the use of a stoichiometric amount of a Ti-taddol complex (**38**) to afford α-acyloxyamides with moderate enantioselectivity.[36] We screened hundreds of Lewis acid/ligand combinations in a parallel fashion for stereochemical induction but only able to get 32–42% *ee* (Scheme 19).



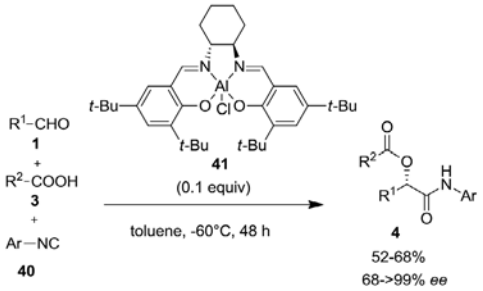
Scheme 19. Enantioselective Passerini reaction by using Ti-taddol complex.

Schreiber et al. used chiral tridentate Lewis acidic Cu-pybox complex (**39**) to activate the carbonyl species and get enantioselective Passerini reaction. However, a good enantioselectivity was observed only with chelating aldehydes (Scheme 20).[37]



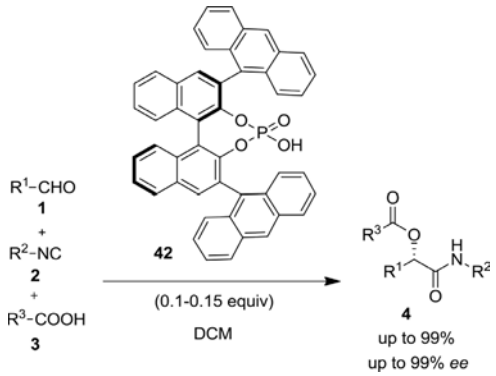
Scheme 20. Cu(II)-pybox-catalyzed enantioselective Passerini reaction.

In 2008, Zhu and co-workers reported the use of stable aluminium salen complex (**41**) as a chiral Lewis acid catalyst in the enantioselective Passerini three-component reaction. This reaction provides the moderate to excellent enantioselectivities (68–>99% ees) with nonchelating aldehydes carboxylic acids, and isocyanides (Scheme 21).[38]



Scheme 21. Enantioselective Passerini reaction catalyzed by the [(salen)-AlIIICl] complex.

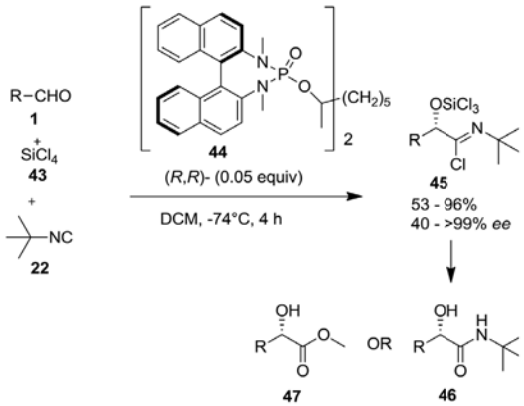
In 2015, Zhang et al. have elegantly demonstrated the use of chiral phosphoric acid (**42**) in P-3CR to activate carboxylic acids, aldehyde, and isocyanide aldehyde to get most efficient and highly enantioselective products. This metal-free Passerini three-component reaction was valid for diverse substrates such as aromatic aldehydes and the very bulky pivalaldehyde (Scheme 22).[39]



Scheme 22. Chiral phosphoric acid-catalyzed enantioselective Passerini reaction.

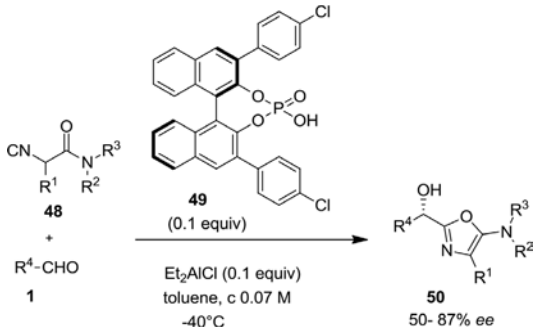
3.2 Enantioselective Passerini-type reactions

In last decade few enantioselective Passerini-type reactions have been reported. In 2003, Denmark reported the first catalytic, enantioselective, Passerini-type reaction. A catalytic system of chiral bisphosphoramide (**44**) and $SiCl_4$ provided good to excellent enantioselectivities for a wide range of aldehydes and isocyanides (Scheme 23).[40]



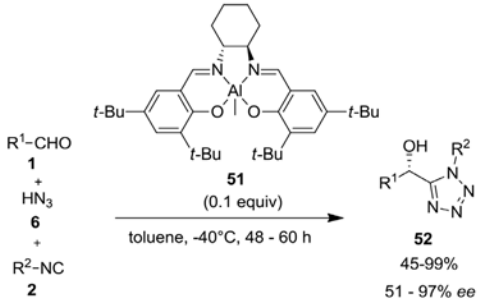
Scheme 23. Lewis base-catalyzed $SiCl_4$-mediated enantioselective Passerini-type reaction.

Zhu reported the different catalytic systems for the Passerini-type reaction to getting access of enantioselective 5-aminooxazoles, such as Chiral Salen-Aluminum Complex,[41] [Sn-(R)-Ph-PyBox] $(OTf)_2$,[42] and Chiral Aluminum-Organophosphate (**49**) (Scheme 24).[43]



Scheme 24. The enantioselective Passerini-type reaction catalyzed by the [(salen)-AlIIICl] complex.

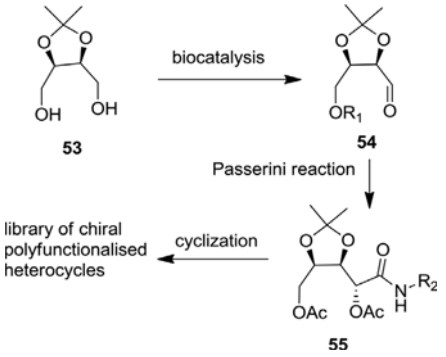
Zhu and co-workers reported an asymmetric Passerini-tetrazole-3CR (Scheme 25). An aluminium salen complex (**51**) was also reported for to get a-hydroxy-tetrazoles (**52**) in modest to high yields (45–99%) with enantiomeric excesses (51–97% ees).[44]



Scheme 25. The enantioselective Passerini-type reaction catalyzed by the [(salen)AlIIIMe] complex.

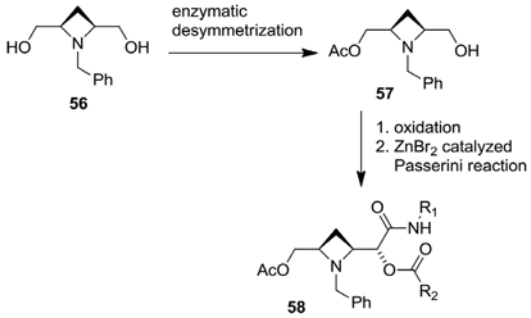
3.3 Diastereoselective Passerini reaction

Recently, Banfi et al. reported a Lewis acid catalyzed diastereoselective Passerini reaction of biobased chiral aldehydes (**54**) derived from desymmetrized erythritol (**53**). Good diastereoselectivity was observed. The P-3CR products used fort he library of polyoxygenated heterocycles (Scheme 26).[45]



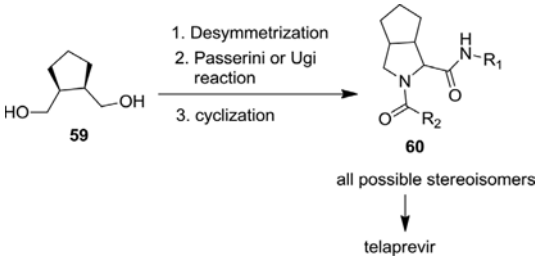
Scheme 26. Diastereoselective Passerini reaction of biobased chiral aldehydes.

Riva and co-workers reported diastereoselective Passerini Reactions on biocatalytically derived chiral azetidines (**58**) (Scheme 27).[46]



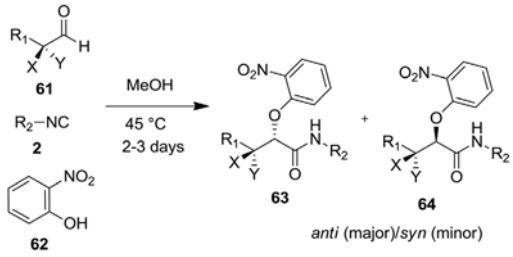
Scheme 27. Passerini Reaction towards chiral azetidines.

The same author reported the Ugi and Passerini reactions of biocatalytically derived chiral aldehydes *meso*-diol (1,2-cyclopentanedimethanol) (**59**).[47] They reported 6 out of all 8 possible stereoisomers of peptidomimetic pyrrolidines (**60**) in good yields and further used this protocol for an efficient synthesis of antiviral drug telaprevir (Scheme 28).



Scheme 28. Passerini reactions of biocatalytically derived chiral aldehydes.

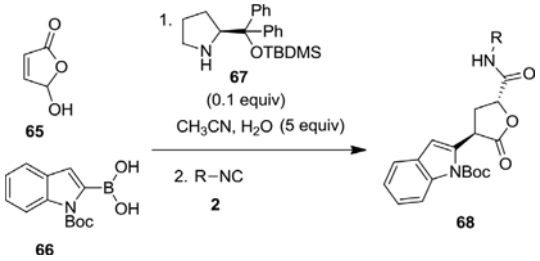
Krishna et al. reported diastereoselective Passerini-Smiles reactions by using chiral aldehydes (**61**) (Scheme 29).[48]



Scheme 29. Passerini-Smiles Reaction of chiral aldehydes.

Different chiral aldehydes have been reported to get diastereoselective Passerini reaction. Szymanski and Ostaszewski reported the enantioconvergent method for the synthesis of chiral α-amino acids by chiral separation.[49] Enantiomerically enriched α-hydroxyamides converted into α-aminoamides and further hydrolyzed to give α-amino acids. Krishna and co-workers reported diastereoselective Passerini reactions by using sugar-derived aldehydes,[50] and 2,3-epoxy aldehydes,[51] with p-toluenesulfonylmethyl isocyanide (TosMIC). Alcaide and co-workers reported the diastereoselective β-lactam-triazole hybrids synthesis via Passerini/CuAAC Sequence by using Azetidine-2,3-diones.[52] and also the synthesis of γ-Lactams and γ-Lactones by using 4-oxoazetidine-2-carbaldehydes.[53]

Deobald et al. reported asymmetric organocatalytic epoxidation/Passerini-3CR for the synthesis of α-acyloxy-α,β-epoxy-carboxamides.[54] Bos and Riguet developed one-pot method for the synthesis of α,γ-substituted Chiral γ-Lactones (**68**) by sequential enantioselective organocatalytic Michael addition of boronic acids (**66**) to 5-hydroxyfuran-2(5H)-one (**65**) followed by diastereoselective intramolecular Passerini reaction (Scheme 30).[55]

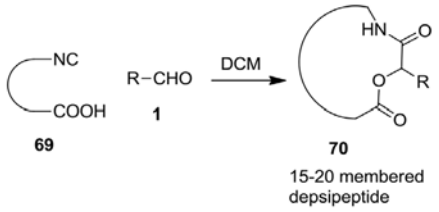


Scheme 30. Diastereoselective intramolecular Passerini reaction towards γ-Lactones.

4. Applications of Passerini reaction

4.1 Passerini reaction for the Macrocycles/Peptidomimetics synthesis

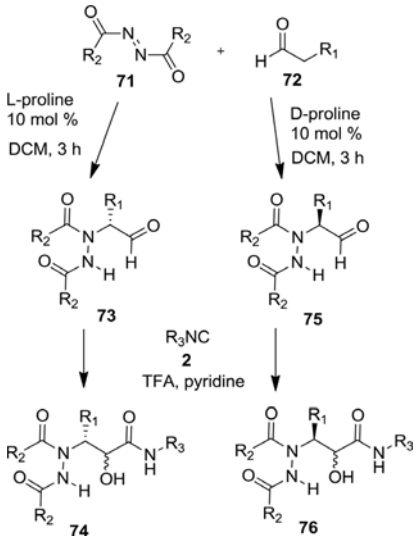
Recently, our group reported the first intramolecular macrocyclization through a Passerini reaction.[56] We reported the easy and one-pot synthesis of macrocycles of a size of 15–20 (Scheme 31).



Scheme 31. Intramolecular macrocyclization by Passerini reaction.

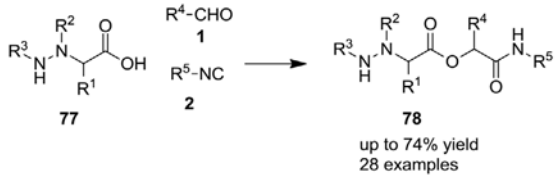
Wessjohann expanded the multiple multicomponent macrocyclizations including bifunctional buildings blocks (MiBs) methodology to Passerini three-component reactions (3CR) fort he synthesis of bis-R-acyloxy carboxamide macrocycles. Reaction with primary alcohols works well under oxidative conditions to form products.[57]

Umbreen et al. demonstrated the use of an organocatalytic, direct, asymmetric α-amination in combination with a Passerini reaction to provide diverse norstatine-based peptidomimetics (Scheme 32).[58]



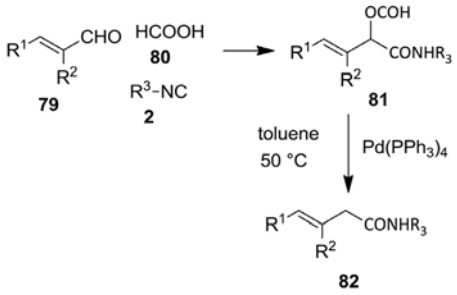
Scheme 32. Two-step synthesis of norstatine intermediates.

The Passerini reaction with α-hydrazino acids (**77**), carbonyl compounds (**1**) and isocyanides (**2**) was reported for the synthesis of hydrazino depsipeptides (**78**) (Scheme 33).[59]



Scheme 33. Passerini for synthesis of hydrazino depsipeptides

El Kaim group reported the Passerini reaction of alpha,beta-unsaturated aldehydes (**79**) with formic acid (**80**) followed by a reductive Tsuji-Trost reaction affords beta, gamma-unsaturated amides (**82**) (Scheme 34).[60] The same group also report the synthesis of α-ketoamides from Passerini adducts of cinnamaldehyde derivatives under basic microwave conditions.[61]

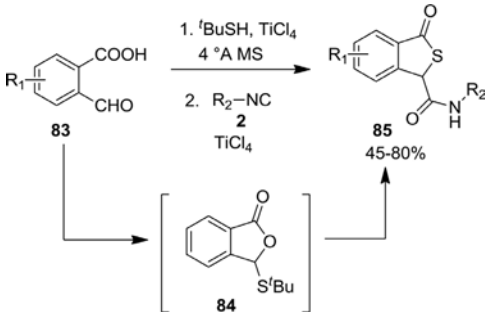


Scheme 34. Passerini for the synthesis of unsaturated amides.

4.2 Passerini reaction post-modifications for heterocycles synthesis

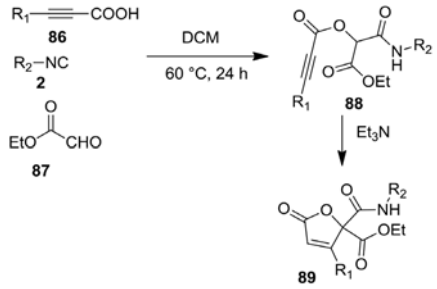
In MCR, use of post-modification reactions for the synthesis of diverse heterocycles is a very important area. As getting diverse heterocycles within 1 or 2 steps make it very useful and convenient tool. Last decade the use of Passerini reaction has been also increased to synthesize diverse heterocycles.

Recently, Ponra et al. reported the $TiCl_4$-mediated synthesis of the thiophthalide derivatives via thio-Passerini reactions (Scheme 35).[62] This reaction involves the formation of a sulfanyl-phthalide intermediate (**84**), followed by thiol dealkylation which undergoes forms Mumm 1,5-acyl transfer to form final product (**85**).



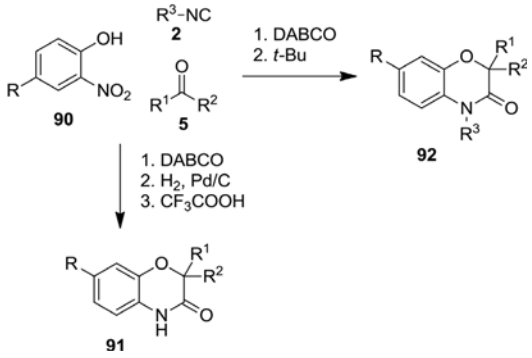
Scheme 35. Thio-Passerini reactions for the synthesis of thiophthalide derivatives.

Van der Eycken reported the one-pot synthesis of butenolides (**89**) using Passerini reaction followed by a triethylamine-promoted cycloisomerization (Scheme 36).[63]



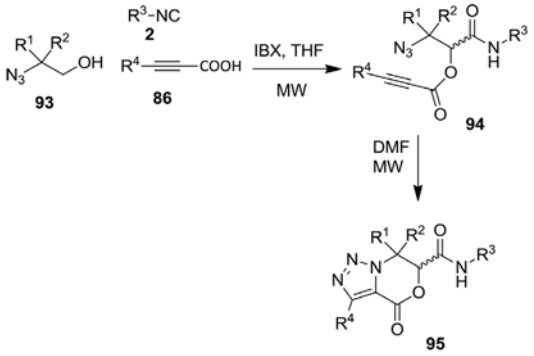
Scheme 36. One-pot Passerini/cycloisomerization towards butenolides.

El Kaim reported the use of double Smiles rearrangement of Passerini adducts for the synthesis of benzoxazinones. This reaction involves the cascade of two Smiles rearrangements coupled with carbon-carbon bond formation (Scheme 37).[64]



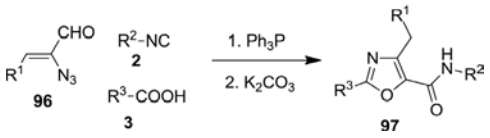
Scheme 37. Passerini-Smiles-Smiles sequence for the synthesis of benzoxazinones.

Basso reported the use of azidoalcohol in Passerini reaction. This two step involves first oxidation by IBX in microwave condition followed azide-alkyne dipolar cycloaddition reaction in MW to form triazolo-fused dihydrooxazinones (**95**) (Scheme 38).[65]



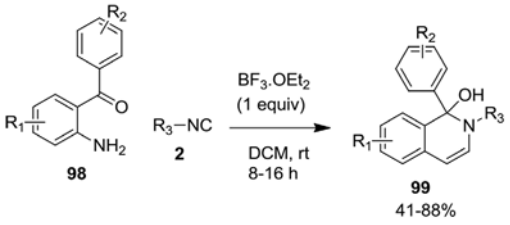
Scheme 38. Passerini reaction/dipolar cycloaddition toward triazolo-fused dihydrooxazinones.

Passerini Three-Component Coupling/Staudinger/Aza-Wittig/Isomerization reaction used for the one-pot synthesis of 2,4,5-trisubstituted oxazoles (**97**), starting from easily accessible α-azido-cinnamaldehydes (**96**), acids (**3**), isocyanide (**2**) and triphenylphosphine (Scheme 39).[66]



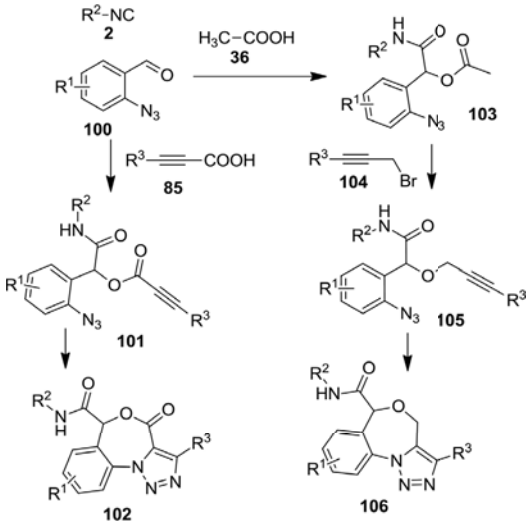
Scheme 39. Passerini reaction coupling/Staudinger/Aza-Wittig/isomerization reaction towards 2,4,5-trisubstituted oxazoles.

Krasavin and co-workers reported the BF_3OEt_2-promoted reaction between o-aminobenzophenones with aliphatic isocyanides to form 4-aryl-4-hydroxy-3,4-dihydroquinazolines (**99**). The reaction involves the initial three-center, two-component Passerini-type reaction followed by skeletal rearrangement of the 3H-indol-3-ol framework (Scheme 40).[67]



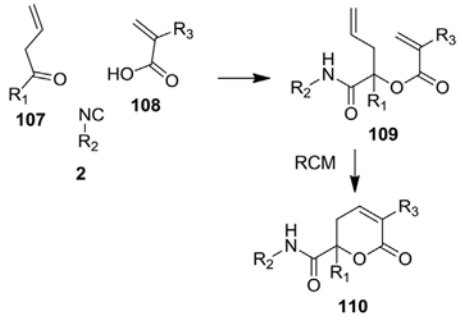
Scheme 40. Passerini type reaction for the synthesis of 3,4-dihydroquinazolin-4-ols.

Basso and co-workers reported the synthesis of triazolo-fused benzoxazepines and benzoxazepinones via Passerini reactions followed by 1,3-dipolar cycloadditions (Scheme 41).[68]



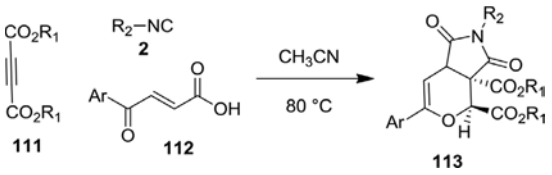
Scheme 41. Passerini reactions towards triazolo-fused benzoxazepines and benzoxazepinones.

Schwablein and Martens reported the synthesis of alpha,beta-unsaturated lactones (**110**) by using the Passerini reaction and ring-closing metathesis (RCM) using a ruthenium catalyst (Scheme 42).[69] Passerini reaction performed with terminal unsaturated carboxylic acids (**108**), allyl ketones (**107**), and isocyanides (**2**).



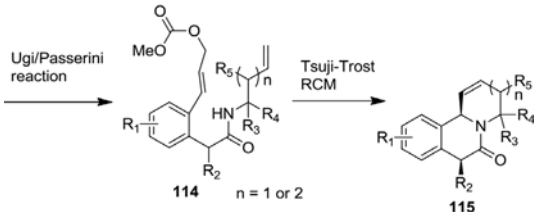
Scheme 42. Synthesis of α,β-unsaturated lactones by Passerini reaction.

Gao et al. reported a three-component bicyclization strategy for the stereoselective synthesis of pyrano[3,4-c]pyrroles (**113**) from dialkyl acetylenedicarboxylates (**111**), 3-aroylacrylic acids (**112**), and isocyanides. This reaction involves a sequence of Huisgen 1,3-dipole formation, Passerini-type reaction, Mumm rearrangement and an oxo-Diels-Alder reaction (Scheme 43).[70]



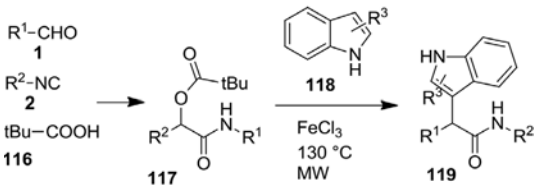
Scheme 43. Synthesis of pyrano[3,4-*c*]pyrroles by Passerini reaction.

Polycyclic alkaloid-like scaffold (**115**) have been prepared by coupling the Passerini and Ugi reactions with Two Sequential Metal-Catalyzed Cyclization (Scheme 44).[71] It involves an intramolecular Tsuji-Trost reaction of the isocyanide-derived amide followed by a ring-closing metathesis with moderate to good diastereoselectivity.



Scheme 44. Passerini/Ugi towards Polycyclic alkaloid-like scaffold.

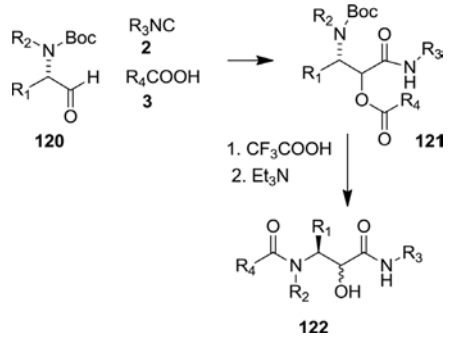
El Kaim recently reported the Passerini adducts (**117**) and indoles (**118**) in $FeCl_3$ catalyzed Friedel-Crafts-type reaction (Scheme 45).[72]



Scheme 45. Passerini /Friedel-Crafts towards indole derivatives.

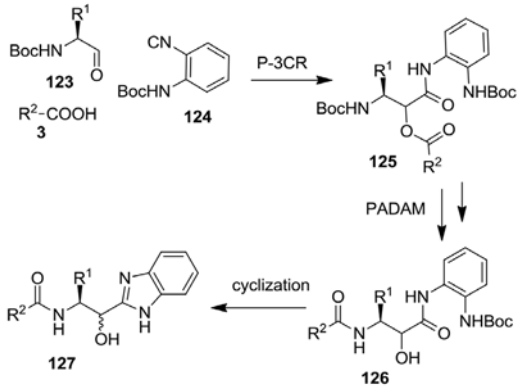
4.3 Passerini reaction-amine-deprotection-acyl-migration strategy (PADAM)

First reported in 2000 by Passerini reaction-amine-deprotection-acyl-migration strategy (PADAM), which was independently described by two group.[73] Three-component Passerini condensation of N-Boc-a-aminoaldehydes (**120**), isocyanides (**2**) and carboxylic acids (**3**) to form (**121**), followed by boc-deprotection/transacylation to complex peptide-like structures containing an a-hydroxy-b-aminoacid unit (**122**) (Scheme 46).



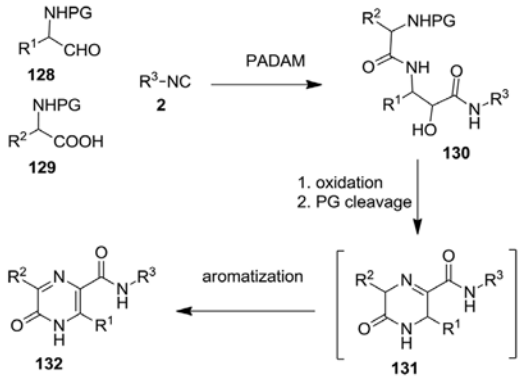
Scheme 46. PADAM strategy for α-hydroxy-β-aminoacid synthesis.

Banfi reported the PADAM strategy for the solid-phase preparation of peptidomimetic compounds.[74] Hulme used PADAM methodology for the synthesis of norstatine isosteres in four steps which involves the benzimidazole formation. This sequence involves a PADAM sequence followed by a TFA-mediated microwave-assisted cyclization to form the benzimidazole isostere of the norstatine scaffold (**127**) (Scheme 47).[75]



Scheme 47. PADAM for benzimidazole synthesis.

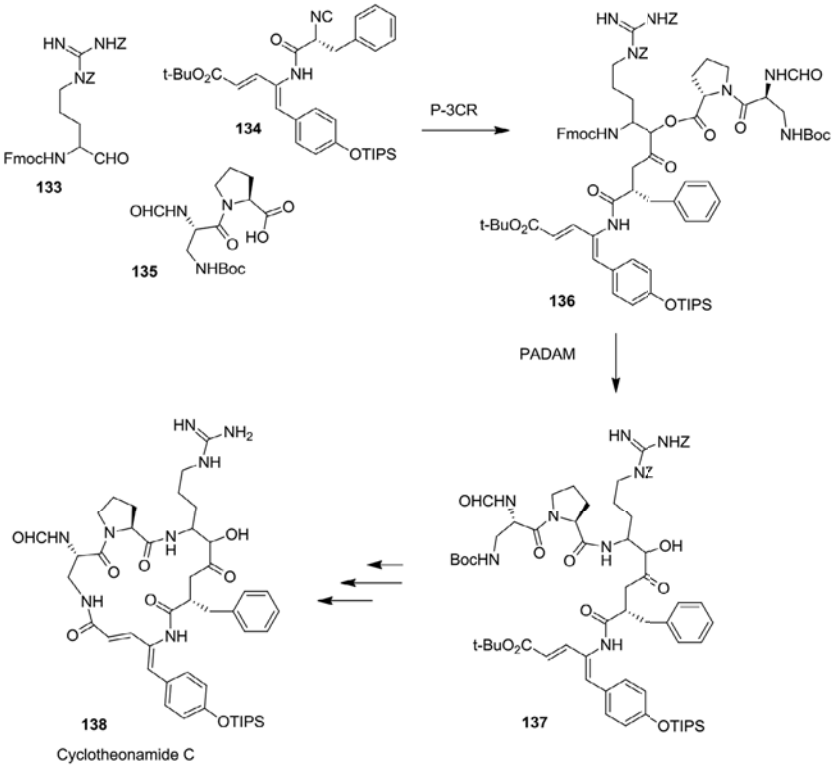
Basso and co-workers reported the PADAM strategy for the synthesis of polyfunctionalised 2(1*H*)-Pyrazinones. Passerini reaction with N-Boc amino acids formed β-acylamino-α-hydroxyamides (**130**) followed by secondary-alcohol oxidation and then Boc deprotection by TFA which undergoes spontaneous aromatisation to form 2(1*H*)-pyrazinones (**132**) (Scheme 48).[76]



Scheme 48. PADAM strategy towards 2(1H)-pyrazinones.

Gravestock et al. used the PADAM strategy for the synthesis of potential HIV-1 protease inhibitors.[77] Different branched isocyanides which have been synthesized from l-serine are used to make Passerini reaction. Furthermore, the homo-PADAM protocol was also used for the stereoselective and operationally simple synthesis of alpha-oxo- or alpha-hydroxy-gamma-acylaminoamides and chromanes.[78]

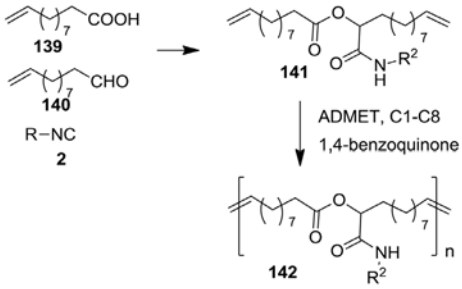
Faure and co-workers used PADAM strategy as a key step for the synthesis of linear pentapeptide intermediate (**137**) in the total synthesis of cyclotheonamide C (**138**) (Scheme 49).[79]



Scheme 49. Cyclotheonamide C synthesis by PADAM.

4.4 Industrial applications of Passerini reaction

In 2003, Wright et al. reported the first use of IMCRs in the syntheses of polymers, where they performed ring-opening metathesis polymerization (ROMP) with Ugi-4CR products and norbornenyl starting materials.[80] The use of IMCRs for direct polymer synthesis via polycondensation was reported by Meier in 2011 (Scheme 50).[81] They introduced the new approach in polymer science by combining IMCRs and acyclic diene metathesis (ADMET) polymerization. The Passerini three-component reaction was used for the synthesis of diverse monomers derived from bio-renewable ricinoleic acid for acyclic diene metathesis (AD-MET) polymerizations.



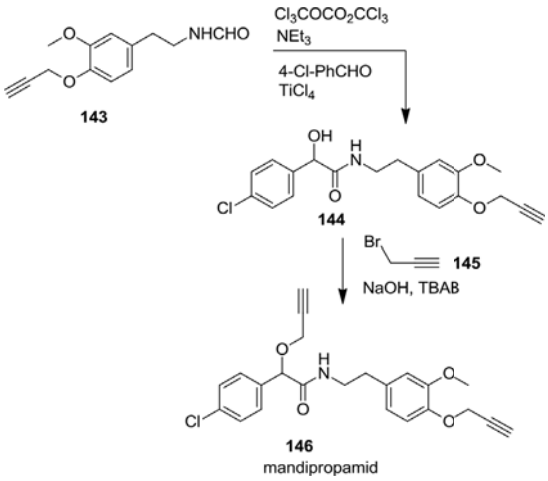
Scheme 50. Macromolecule synthesis via the Passerini reaction.

After this report by Meier, multicomponent reactions use in polymer synthesis have been intensively explored which was also reviewed by him.[82] Kakuchi also reported a brief review about MCR in polymer.[83] Passerini reaction use in this field has been reported many instants, such as synthetis of dendrimers,[84] polyamides,[85] acrylate monomers,[86] photo-cleavable polymers,[87] cross-linked polymers,[88] and highly branched polymers.[89]

4.5 Medicinal/clinical applications of Passerini reaction

Passerini reaction has been used for the many bio-active agents and also in some other pharmaceutical applications. The Passerini 2-CR used for the synthesis of a fungicidal compound, mandipropamid. This two steps synthesis involves the Passerini reaction to form mandelamide (**144**) followed by the alkylation with propargylbromide (**145**) to yield Micora (mandipropamid) (**146**).[90] Trifluoroatrolactamide Library made from one-pot Passerini/hydrolysis reaction sequence was also screened for the fungicidal activities (Scheme 51).[91]

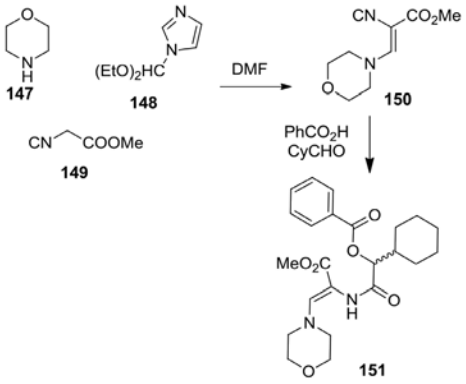
α-Acylamino-amide-bis (indolyl) methane heterocycles as antibacterial potency were synthesized by one pot condensation-Ugi/Passerini reactions.[92] Passerini reaction also used in different pharmaceutical applications like degradable cationic polymer library for gene delivery,[93] and reduction-sensitive amphiphilic copolymers for drug delivery.[94]



Scheme 51. Passerini reaction towards mandipropamid.

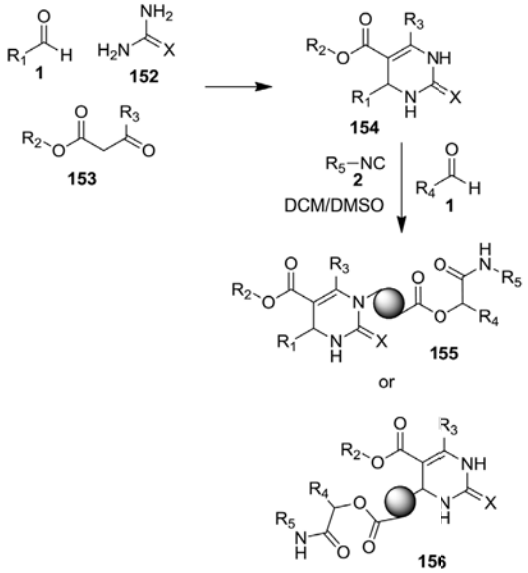
5. Union of Passerini reaction with other MCRs

Two decades ago Dömling and Ugi introduced the concept of the union of MCRs which gained attention to get diverse diversity and complexity. Union of Passerini reaction with other MCRs did not get that much attention as compare to Ugi reaction. Only a few examples have been reported. Long back, Passerini union with Bredereck reaction was reported by Bienayme (Scheme 52).[95] A modified Bredereck reaction used to produce the intermediate isocyanide (**150**) followed by Passerini-3CR to form final product (**151**).



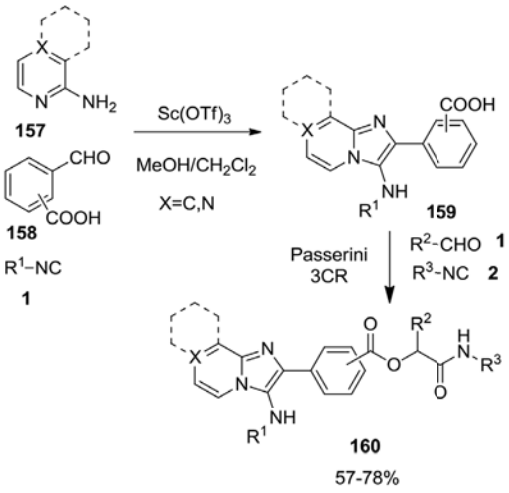
Scheme 52. Passerini-3CR union with Bredereck reaction.

Recently, one-pot Biginelli-Passerini tandem reaction was demonstrated for the synthesis of diverse 3,4-dihydropyrimidin-2(1*H*)-ones via sequential Biginelli and Passerini reactions (Scheme 53).[96]



Scheme 53. Biginelli and Passerini reaction union.

Groebke-Bienayme-Blackburn reaction union with Ugi or Passerini was reported for the synthesis of drug-like heterocyclic compounds, fused pyridine-imidazoles (**160**) (Scheme 54).[97]



Scheme 54. Union of Passerini reaction with Groebke-Bienaymé-Blackburn-3CR.

6. Summary and Outlook

Along with this mini-review, we succinctly highlighted the utility of Passerini reaction in the pharmaceutical and organic industry that has been reported in the last decade. Research momentum in Passerini reaction in last decade has been more than collectively over history, which is proving ground for expanding the chemical space for the medicinal and organic chemist. It has become a powerful and efficient tool in organic chemistry.

The increasing knowledge about the mechanism of Passerini reaction will allow the design of innovative substrates to afford high molecular diversity and complexity. The isosteres use are interesting and it will help to get more interesting bond formations like C-Si, C-P, or C-N. The lack of sufficient examples of Passerini reaction union with other MCR will also take impetus. Recent advances will offer a bright future for the development of novel scaffolds with chemo-, regio-, and stereoselective reactions.

A future trend is definitely the application of this reaction in different fields, such as polymer, agrochemical, explosives and natural products synthesis. This reaction continues to provide inspiration for better and novel research of making diverse and complex molecules. More breakthroughs are to be expected in near future.

Reference

[1] L. S. M. Passerini, *Gazz. Chim. Ital.* **1921**, 51, 126–129.

[2] G. Papeo, *M. Pulici, Molecules* **2013**, 18, 10870-10900.

[3] a) A. Domling, I. Ugi, *Angew. Chem. Int. Edit.* **2000**, 39, 3168-3210; b) A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, 112, 3083-3135; c) E. Marqués-López, R. P. Herrera, **2015**, 283-305; d) A. Domling, *Chem Rev* **2006**, 106, 17-89; e) D. J. Ramon, M. Yus, *Angew. Chem. Int. Edit.* **2005**, 44, 1602-1634; f) I. Ugi, B. Werner, A. Domling, *Molecules* **2003**, 8, 53-66.

[4] L. Banfi, R. Riva, *Organic reactions (A. B. Charette, Ed.). John Wiley & Sons, Inc., Hoboken, NJ, 2005, Vol. 65, pp. 1–140. The Passerini reaction.* **2005**, 1-140.

[5] A. R. Kazemizadeh, A. Ramazani, *Curr. Org. Chem.* **2012**, 16, 418-450.

[6] S. Maeda, S. Komagawa, M. Uchiyama, K. Morokuma, *Angew. Chem. Int. Edit.* **2011**, 50, 644-649.

[7] a) R. Ramozzi, K. Morokuma, *J. Org. Chem.* **2015**, 80, 5652-5657; b) H. G. O. Alvim, E. N. da Silva, B. A. D. Neto, *Rsc. Adv.* **2014**, 4, 54282-54299.

[8] I. Ugi, R. Meyr, *Chemi. Ber.* **1961**, 94, 2229-2233.

[9] T. Sela, A. Vigalok, *Adv. Synth. Catal.* **2012**, 354, 2407-2411.

[10] T. Nixey, C. Hulme, *Tetrahedron Lett.* **2002**, 43, 6833-6835.

[11] E. S. Schremmer, K. T. Wanner, *Heterocycles* **2007**, 74, 661-671.

[12] I. Monfardini, J. W. Huang, B. Beck, J. F. Cellitti, M. Pellecchia, A. Domling, *J. Med. Chem.* **2011**, 54, 890-900.

[13] A. L. Chandgude, A. Domling, *Green Chem.* **2016**, 18, 3718-3721.

[14] T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Org. Lett.* **2010**, 12, 4341-4343.

[15] T. Soeta, S. Matsuzaki, Y. Ukaji, *J. Org. Chem.* **2015**, 80, 3688-3694.

[16] T. Soeta, S. Matsuzaki, Y. Ukaji, *Chem-Eur. J.* **2014**, 20, 5007-5012.

[17] A. L. Chandgude, A. Domling, *Org. Lett.* **2016**, 18, 6396-6399.

[18] L. El Kaim, M. Gizolme, L. Grimaud, *Org. Lett.* **2006**, 8, 5021-5023.

[19] L. El Kaim, L. Grimaud, *Eur. J. Org. Chem.* **2014**, 7749-7762.

[20] a) M. Schiess, D. Seebach, *Helv. Chim. Acta.* **1983**, 66, 1618-1623; b) T. Carofiglio, P. G. Cozzi, C. Floriani, A. Chiesivilla, C. Rizzoli, *Organometallics* **1993**, 12, 2726-2736; c) T. Carofiglio, C. Floriani, A. Chiesivilla, C. Guastini, *Inorg. Chem.* **1989,** 28, 4417-4419; d) T. Carofiglio, C. Floriani, A. Chiesivilla, C. Rizzoli, *Organometallics* **1991**, 10, 1659-1660.

[21] T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Tetrahedron Lett.* **2011**, 52, 2557-2559.

[22] J. S. Kumar, S. C. Jonnalagadda, V. R. Mereddy, *Tetrahedron Lett.* **2010**, 51, 779-782.

[23] T. Soeta, Y. Ukaji, *Chem. Rec.* **2014**, 14, 101-116.

[24] L. Y. Lyu, H. Xie, H. X. Mu, Q. J. He, Z. X. Bian, J. Wang, *Org. Chem. Front.* **2015**, 2, 815-818.

[25] D. Coffinier, L. El Kaim, L. Grimaud, *Synlett* **2008**, 1133-1136.

[26] T. Ngouansavanh, J. P. Zhu, *Angew. Chem. Int. Edit.* **2006**, 45, 3495-3497.

[27] J. Brioche, G. Masson, J. P. Zhu, *Org. Lett.* **2010**, 12, 1432-1435.

[28] S. Kolle, S. U. Dighe, S. Batra, *Arkivoc* **2016**, 82-97.

[29] B. Karimi, E. Farhangi, *Adv. Synth. Catal.* **2013**, 355, 508-516.

[30] F. De Moliner, M. Bigatti, L. Banfi, R. Riva, A. Basso, *Org. Lett.* **2014**, 16, 2280-2283.

[31] A. A. Esmaeili, S. A. Ghalandarabad, S. Jannati, *Tetrahedron Lett.* **2013**, 54, 406-408.

[32] T. Kaicharla, S. R. Yetra, T. Roy, A. T. Biju, *Green Chem.* **2013**, 15, 1608-1614.

[33] B. O. Beasley, G. J. Clarkson, M. Shipman, *Tetrahedron Lett.* **2012**, 53, 2951-2953.

[34] S. K. Guchhait, G. Priyadarshani, V. Chaudhary, D. R. Seladiya, T. M. Shah, N. P. Bhogayta, *Rsc. Adv.* **2013**, 3, 10867-10874.

[35] C. G. Neochoritis, S. Stotani, B. Mishra, A. Domling, *Org. Lett.* **2015**, 17, 2002-2005.

[36] U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Dömling, *Org. Lett.* **2003**, 5, 4021-4024.

[37] P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, 6, 4231-4233.

[38] S. X. Wang, M. X. Wang, D. X. Wang, J. P. Zhu, *Angew. Chem. Int. Edit.* **2008**, 47, 388-391.

[39] J. Zhang, S. X. Lin, D. J. Cheng, X. Y. Liu, B. Tan, *J. Am. Chem. Soc.* **2015**, 137, 14039-14042.

[40] a) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, 125, 7825-7827; b) S. E. Denmark, Y. Fan, *J. Org. Chem.* **2005**, 70, 9667-9676.

[41] S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Org. Lett.* **2007**, 9, 3615-3618.

[42] S. X. Wang, M. X. Wang, D. X. Wang, J. P. Zhu, *Eur. J. Org. Chem.* **2007**, 4076-4080.

[43] T. Yue, M. X. Wang, D. X. Wang, G. Masson, J. P. Zhu, *J. Org. Chem.* **2009**, 74, 8396-8399.

[44] T. Yue, M. X. Wang, D. X. Wang, J. P. Zhu, *Angew. Chem. Int. Edit.* **2008**, 47, 9454-9457.

[45] L. Moni, L. Banfi, A. Basso, E. Martino, R. Riva, *Org. Lett.* **2016**, 18, 1638-1641.

[46] L. Moni, L. Banfi, A. Basso, A. Bozzano, M. Spallarossa, L. Wessjohann, R. Riva, *Molecules* **2016**, 21.

[47] L. Moni, L. Banfi, A. Basso, L. Carcone, M. Rasparini, R. Riva, *J. Org. Chem.* **2015**, 80, 3411-3428.

[48] P. R. Krishna, G. Dayaker, D. V. Ramana, R. Kunde, *Helv. Chim. Acta.* **2014**, 97, 1076-1087.

[49] W. Szymanski, R. Ostaszewski, *Tetrahedron-Asym.* **2006**, 17, 2667-2671.

[50] P. R. Krishna, G. Dayaker, P. V. N. Reddy, *Tetrahedron Lett.* **2006**, 47, 5977-5980.

[51] P. R. Krishna, K. Lopinti, *Synlett* **2007**, 83-86.

[52] B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz, M. R. Torres, *J. Org. Chem.* **2012**, 77, 6917-6928.

[53] B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz, *J. Org. Chem.* **2013**, 78, 10154-10165.

[54] A. M. Deobald, A. G. Correa, D. G. Rivera, M. W. Paixao, *Org. Biomol. Chem.* **2012**, 10, 7681-7684.

[55] M. Bos, E. Riguet, *J. Org. Chem.* **2014**, 79, 10881-10889.

[56] E. M. M. Abdelraheem, K. Kurpiewska, J. Kalinowska-Tluscik, A. Domling, *J. Org. Chem.* **2016**, 81, 8789-8795.

[57] F. Leon, D. G. Rivera, L. A. Wessjohann, *J. Org. Chem.* **2008**, 73, 1762-1767.

[58] S. Umbreen, M. Brockhaus, H. Ehrenberg, B. Schmidt, *Eur. J. Org. Chem.* **2006**, 4585-4595.

[59] J. Suc, D. Baric, I. Jeric, *Rsc. Adv.* **2016**, 6, 99664-99675.

[60] A. Dos Santos, L. El Kaim, *Synlett* **2014**, 25, 1901-1903.

[61] A. Ben Abdessalem, R. Abderrahim, L. El Kaim, *Synlett* **2015**, 26, 2537-2540.

[62] S. Ponra, A. Nyadanu, L. El Kaim, L. Grimaud, M. R. Vitale, *Org. Lett.* **2016**, 18, 4060-4063.

[63] A. A. Nechaev, A. A. Peshkov, V. A. Peshkov, E. V. Van der Eycken, *Synthesis* **2016**, 48, 2280-2286.

[64] a) E. Martinand-Lurin, A. Dos Santos, L. El Kaim, L. Grimaud, P. Retailleau, *Chem. Commun.* **2014**, 50, 2214-2217; b) E. Martinand-Lurin, A. Dos Santos, E. Robineau, P. Retailleau, P. Dauban, L. Grimaud, L. El Kaim, *Molecules* **2016**, 21.

[65] F. De Moliner, S. Crosignani, A. Galatini, R. Riva, A. Basso, *Acs. Comb. Sci.* **2011**, 13, 453-457.

[66] L. Wang, Z. L. Ren, M. Chen, M. W. Ding, *Synlett* **2014**, 25, 721-723.

[67] M. Krasavin, A. Busel, V. Parchinsky, *Tetrahedron Lett.* **2009**, 50, 5945-5950.

[68] F. De Moliner, M. Bigatti, C. De Rosa, L. Banfi, R. Riva, A. Basso, *Mol. Divers.* **2014,** 18, 473-482.

[69] A. Schwablein, J. Martens, *Eur. J. Org. Chem.* **2011**, 4335-4344.

[70] Q. Gao, W. J. Hao, F. Liu, S. J. Tu, S. L. Wang, G. G. Li, B. Jiang, *Chem. Commun.* **2016**, 52, 900-903.

[71] M. Spallarossa, L. Banfi, A. Basso, L. Moni, R. Riva, *Adv. Synth. Catal.* **2016**, 358, 2940-2948.

[72] E. El Mamouni, A. Dos Santos, L. El Kaim, H. Ilitki, *Synlett* **2016**, 27, 2571-2574.

[73] aJ. E. Semple, T. D. Owens, K. Nguyen, O. E. Levy, *Org. Lett.* **2000**, 2, 2769-2772; bL. Banfi, G. Guanti, R. Riva, *Chem. Commun.* **2000**, 985-986.

[74] L. Banfi, A. Basso, G. Guanti, R. Riva, *Mol. Divers.* **2003**, 6, 227-235.

[75] A. Y. Shaw, F. Medda, C. Hulme, *Tetrahedron Lett.* **2012**, 53, 1313-1315.

[76] A. Basso, L. Banfi, G. Guanti, R. Riva, P. Tosatti, *Synlett* **2011**, 2009-2012.

[77] D. Gravestock, A. L. Rousseau, A. C. U. Lourens, H. C. Hoppe, L. A. Nkabinde, M. L. Bode, *Tetrahedron Lett.* **2012**, 53, 3225-3229.

[78] F. Morana, A. Basso, R. Riva, V. Rocca, L. Banfi, *Chem-Eur. J.* **2013**, 19, 4563-4569.

[79] S. Faure, T. Hjelmgaard, S. P. Roche, D. J. Aitken, *Org. Lett.* **2009**, 11, 1167-1170.

[80] C. V. Robotham, C. Baker, B. Cuevas, K. Abboud, D. L. Wright, *Mol. Divers.* **2003**, 6, 237-244.

[81] O. Kreye, T. Toth, M. A. R. Meier, *J. Am. Chem. Soc.* **2011**, 133, 1790-1792.

[82] A. Sehlinger, M. A. R. Meier, *Multi-Component and Sequential Reactions in Polymer Synthesis* **2015**, 269, 61-86.

[83] R. Kakuchi, *Angew. Chem. Int. Edit.* **2014**, 53, 46-48.

[84] a) J. A. Jee, L. A. Spagnuolo, J. G. Rudick, *Org. Lett.* **2012**, 14, 3292-3295; b) J. A. Jee, S. Song, J. G. Rudick, *Chem. Commun.* **2015**, 51, 5456-5459.

[85] a) Y. Z. Wang, X. X. Deng, L. Li, Z. L. Li, F. S. Du, Z. C. Li, *Polymer Chem.* **2013**, 4, 444-448; b) S. C. Solleder, M. A. R. Meier, *Angew. Chem. Int. Edit.* **2014**, 53, 711-714; c) X. X. Deng, L. Li, Z. L. Li, A. Lv, F. S. Du, Z. C. Li, *Acs. Macro Lett.* **2012**, 1, 1300-1303.

[86] A. Sehlinger, O. Kreye, M. A. R. Meier, *Macromolecules* **2013**, 46, 6031-6037.

[87] L. Li, A. Lv, X. X. Deng, F. S. Du, Z. C. Li, *Chem. Commun.* **2013**, 49, 8549-8551.

[88] W. H. Lin, T. T. Sun, M. Zheng, Z. G. Xie, Y. B. Huang, X. B. Jing, *Rsc. Adv.* **2014**, 4, 25114-25117.

[89] X. X. Deng, Y. Cui, F. S. Du, Z. C. Li, *Polymer Chem.* **2014**, 5, 3316-3320.

[90] C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf, R. Zeun, *Bioorg. Med. Chem.* **2008**, 16, 1531-1545.

[91] S. J. Yu, C. Zhu, Q. Bian, C. Cui, X. J. Du, Z. M. Li, W. G. Zhao, *Acs Comb. Sci.* **2014**, 16, 17-23.

[92] G. Kaur, A. Vadekeetil, K. Harjai, V. Singh, *Tetrahedron Lett.* **2015**, 56, 4445-4450.

[93] D. C. Zhu, H. J. Yan, Y. Q. Shen, *Nanomedicine-Nanotechnology Biology and Medicine* **2016**, 12, 474-474.

[94] W. H. Lin, X. G. Guan, T. T. Sun, Y. B. Huang, X. B. Jing, Z. G. Xie, *Colloids and Surfaces B-Biointerfaces* **2015**, 126, 217-223.

[95] H. Bienayme, *Tetrahedron Lett.* **1998**, 39, 4255-4258.

[96] A. C. Boukis, B. Monney, M. A. R. Meier, *Beilstein J. Org. Chem.* **2017**, 13, 54-62.

[97] T. H. Al-Tel, R. A. Al-Qawasmeh, W. Voelter, *Eur. J. Org. Chem.* **2010**, 5586-5593.