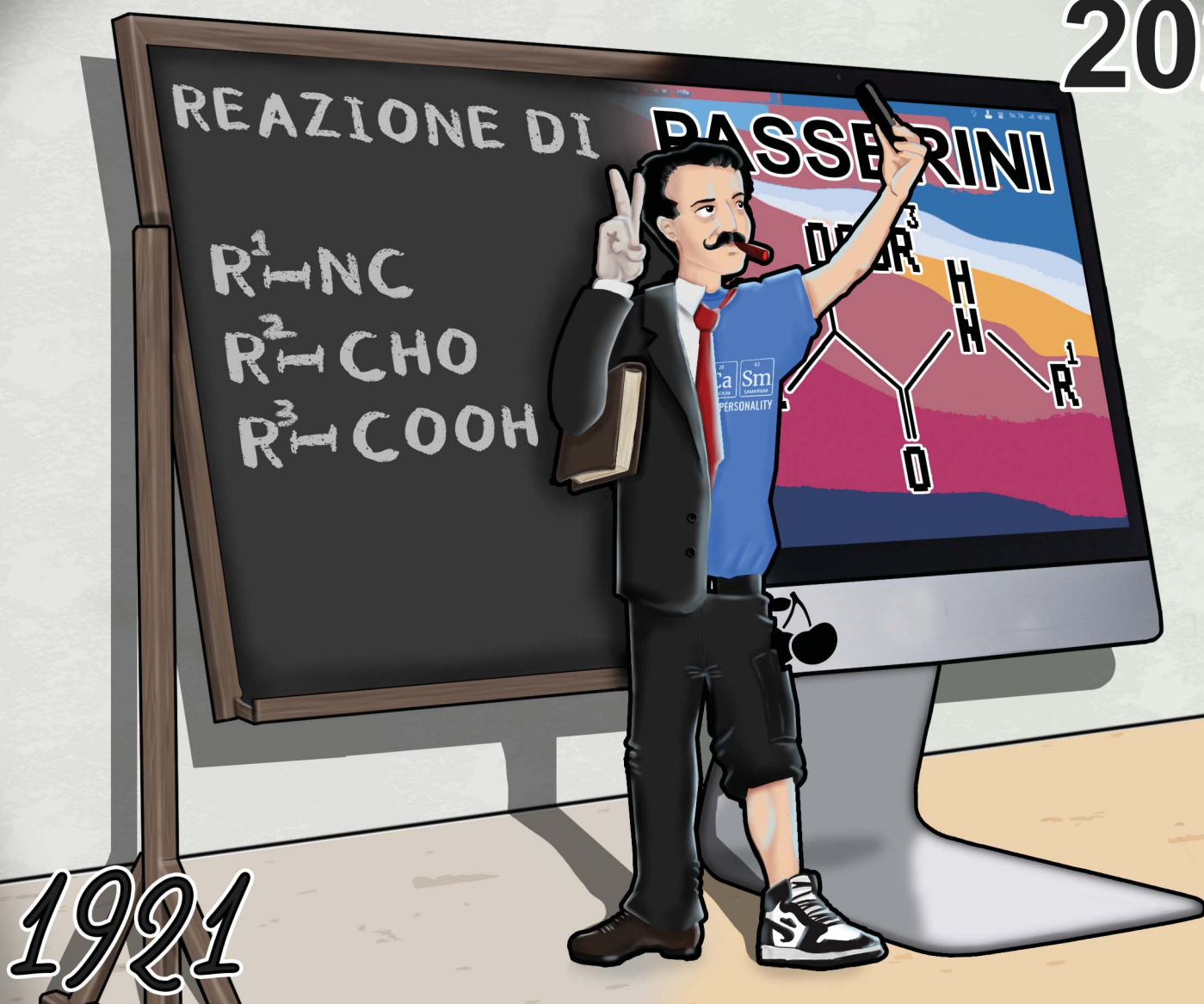


Chemical Science

Volume 12
Number 47
21 December 2021
Pages 15431–15778

rsc.li/chemical-science

2021



ISSN 2041-6539

Cite this: *Chem. Sci.*, 2021, 12, 15445

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 13th July 2021

Accepted 29th September 2021

DOI: 10.1039/d1sc03810a

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The 100 facets of the Passerini reaction

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This perspective aims at celebrating the 100th anniversary of the discovery of the Passerini three component reaction. After being nearly neglected for many years, now this reaction has become quite popular, thanks to the achievements of the last 30 years, which have revealed several chances of exploitation in organic synthesis. Though not being comprehensive, this review means to show the various ways that have been used in order to expand the utility of the Passerini reaction. Post-MCR transformations to give heterocycles or peptidomimetics, variants through single component replacement, stereochemical issues, and applications in total syntheses will be especially covered.

1. Introduction

The reaction of isocyanides, aldehydes/ketones and carboxylic acids to give α -acyloxyamides (Scheme 1) is the oldest isocyanide-based multicomponent reaction (IMCR). It was discovered in Florence by Mario Passerini (Fig. 1) and first reported in 1921.¹ Therefore, 2021 represents an important anniversary, not only for the Passerini reaction, but also for all IMCRs.

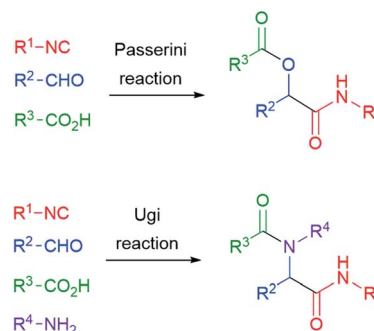
This valuable reaction was nearly neglected for 40 years after its discovery. In 1959, Ivar Ugi added a fourth component, a primary amine, obtaining α -acylaminoamides (Scheme 1). Most importantly, he was able to recognize the great potential of multicomponent reactions in the fast generation of large collections of similar molecules. His pioneering work provided the basis for the upsurge of combinatorial chemistry and diversity-oriented synthesis that took place in the 90's. In those years, the Ugi and Passerini reactions became well known to most organic chemists, and the publications related to them and to other IMCRs have continued to steadily increase in the new century till nowadays.

Nevertheless, in the 90's, the Passerini reaction was still much less exploited than its daughter, the Ugi reaction, probably because esters are less attractive than amides in medicinal chemistry. The renewal of interest in this reaction was thus achieved by extending the scope from simple α -acyloxyamides (depsipeptides) to a variety of different products, including heterocycles and peptidomimetics. Italy, which has been the cradle of the Passerini reaction, had an important role in this renaissance too, especially thanks to Stefano Marcaccini[‡] (Florence University), but from 1998 also to our own group.

During the last 30 years, several new variants and/or applications of the Passerini reaction were reported, eventually granting to it a well deserved place in the Olympus of organic named reactions.²

1.1 Main features of the Passerini reaction

The generally accepted mechanism of the Passerini reaction is shown in Scheme 2.³ This is a concerted mechanism, where the H-bonded cluster formed by the interaction of the carboxylic acid with the carbonyl compound reacts with the isocyanide in a single step. Overall, this is an α -addition of the carbonyl component (as an electrophile) and of the carboxylate (as a nucleophile) to the isocyanide to give the intermediate **2**. The intermediacy of a relatively non-polar cyclic transition state **1** agrees with the fact that the reaction is faster in apolar solvents. Then the α -addition adduct **2** rearranges to the final product **3**. A still unresolved question is whether the rate limiting step is the α -addition or the rearrangement, which may have important consequences on the stereochemical course. A recent theoretical study⁴ suggests that the rate-limiting step may be the last one and that an additional molecule of the carboxylic acid is



Scheme 1 The Passerini and Ugi reactions.

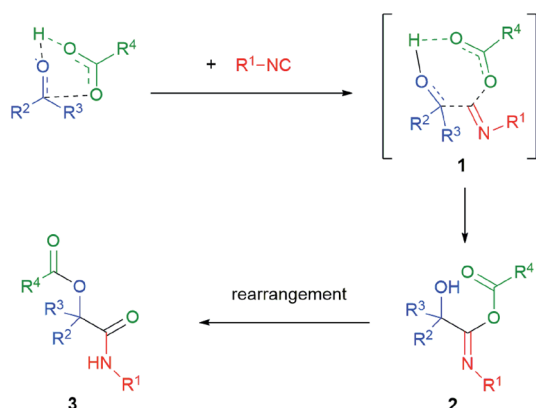
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[†] All the authors equally contributed to this paper.

[‡] Unfortunately, Stefano Marcaccini passed away in 2012 and thus he cannot celebrate with us this anniversary, as he would have certainly liked.



Fig. 1 Mario Passerini. This picture, was taken in 1921 and was kindly given us in 2003 by Passerini's son, Pietro. We thank his granddaughter Sara Passerini for authorizing the publication of this photography. © reserved; photo courtesy of the Passerini family.



Scheme 2 The mechanism of the Passerini reaction.

involved in the transition state. However, an old study,⁵ carried out using a ketone as the carbonyl component, reported that the Passerini reaction is first order in each of the three reactants. We think that both the rate limiting step and the intervention of an additional carboxylic molecule in the T.S. may strongly depend on the nature of substrates. This may explain the apparent contradiction between the theoretical study (done on formaldehyde) and the experimental one.

Being faster in a low polarity medium, the Passerini reaction is typically carried out in solvents such as dichloromethane, ethyl acetate, diethyl ether and tetrahydrofuran. In contrary to the related Ugi reaction, alcohols are not well suited as reaction solvents. Actually, when the Passerini reaction occurs as an unwanted side reaction in an Ugi process, it may be suppressed by using high polar alcohols, such as trifluoroethanol. The classical Passerini reaction is typically carried out at rt, with the reaction times varying from a few hours to several days (in the case of ketones). With bulky ketones, the reaction may be sluggish. Thus, in general yields are much better with aldehydes. The reaction takes place under mild conditions in

a slightly acidic medium and thus tolerates a variety of different functional groups, which is very useful for the introduction of additional functionalities described in chapter 2. Only electron-poor phenols or primary and secondary amines are not accepted, giving the Passerini–Smile (see chapter 3) or the Ugi reaction instead. With aldehydes or unbulky ketones the scope is quite broad, although we found that some heteroaromatic aldehydes may be unreactive.⁶ Also α,β -unsaturated aldehydes/ketones are poor substrates.

As for the carboxylic acids or the isocyanide components, the scope is very broad. Aromatic isocyanides tend to be somehow unstable. In these cases, their *in situ* preparation may be advantageous.⁷

1.2 Organization of this perspective

In this perspective, we would like to review these advancements, demonstrating the many facets of this reaction. The Passerini reaction and its variants have been already reviewed in a comprehensive manner in 2005 and 2014 by us.^{3,8} This perspective, on the other hand, was created with the aim of rationally guiding the reader through the four main lines of research that have characterized this multicomponent reaction, in which our research group has often played an important role: (1) the introduction of post-condensation transformations; (2) the use of non-classical components; (3) the control of diastereoselectivity and enantioselectivity; (4) the synthesis of natural products and APIs.

Each chapter will describe the more interesting, original, and recent applications; in addition, a “future perspective” paragraph will describe what, in our opinion, are the strategies and improvements, not yet explored, that could characterize the Passerini reaction of the second centennial.

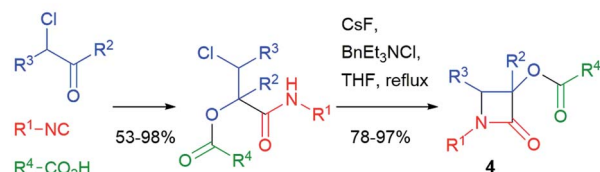
2. The power of post-Passerini transformations: from cyclization to heterocycles to the PADAM strategy

2.1 Post-Passerini cyclizations to give heterocycles^{9,10}

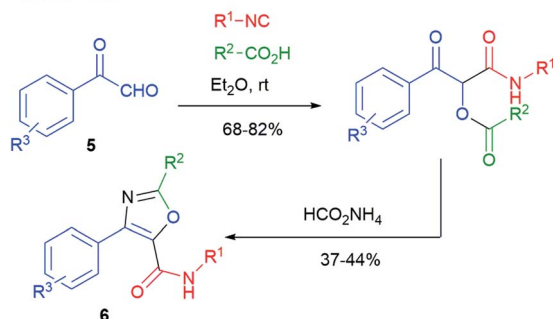
The typical Passerini products are acyclic depsipeptides, which are not much interesting, from a medicinal chemistry point of view, because of the lability of ester groups under physiological conditions. Cyclization to heterocycles can solve this problem. For this purpose, the presence of one or two additional functionalities in the three components is typically needed, although some cyclization may take advantage of the isocyanide-derived secondary amide, which can act either as a nucleophile or an electrophile. The oldest example of this approach was reported in 1983 by Sebt and Foucaud (Scheme 3)¹¹ and involved a halogen as a single additional group. β -Lactams **4** were obtained through an S_N2 reaction, where the secondary amide nitrogen acts as a nucleophile. A few years later, in 1991, Marcaccini reported a Paal–Knorr cyclization that used carboxylic derived $C=O$ and an additional oxo group installed in the aldehyde component. In this way, arylglyoxals **5** have been converted into oxazoles **6**.¹²



Sebtì:



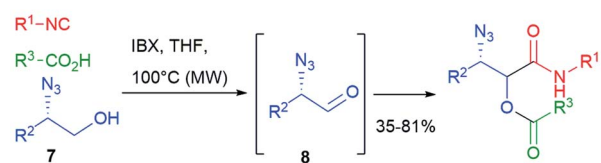
Marcaccini:



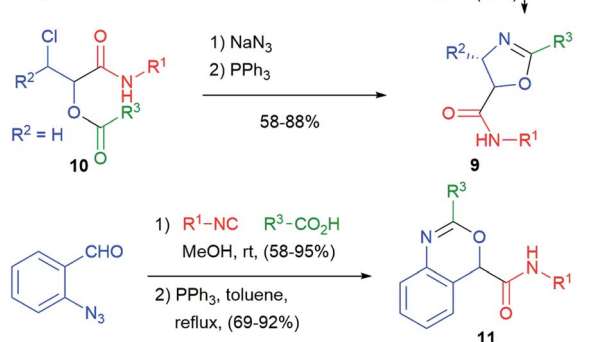
Scheme 3 The oldest syntheses of heterocycles through post-Passerini cyclizations.

In 2010 we have obtained oxazolines **9**, this time exploiting, as an additional functional group, an azide placed on the aldehydic component (Scheme 4).¹³ Since α -azidoaldehydes **8** are rather unstable, we used an *in situ* oxidation protocol¹⁴ of α -azidoalcohols **7** with IBX. The Passerini adducts were then cyclized using supported triphenylphosphine in a Staudinger–aza-Wittig reaction. The use of a supported reagent makes this protocol well suited for combinatorial synthesis of these entities. Diastereomeric mixtures of oxazolines **9** were obtained, with poor stereoselectivity. The same products have been later

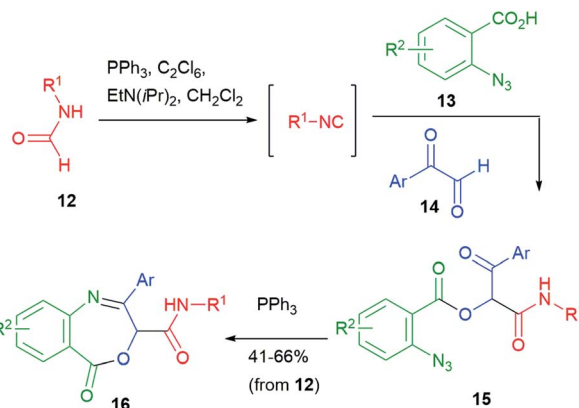
Our work:



Ding:



Scheme 4 Post-Passerini Staudinger–aza-Wittig protocols involving the ester carbonyl.



Scheme 5 Synthesis of heterocycles via post-Passerini Staudinger–aza-Wittig involving an additional ketone.

obtained by Ding from chloroacetaldehyde derived Passerini products **10**, by introducing the azide just before the Staudinger–aza-Wittig step.¹⁵ Using α,β -unsaturated azidoenals, oxazoles (instead of oxazolines) were obtained by Wang.¹⁶ Finally, benzoxazines **11** were prepared by Ding applying a similar protocol with *ortho*-azidobenzaldehyde.¹⁷

A wider exploration of chemical space can be achieved starting from two additional functional groups, such as an azide and a ketone. For example, the Staudinger–aza-Wittig protocol was applied by Wang to azidoketones **15**, in turn obtained by a Passerini reaction of azidoacid **13** and aryl glyoxals **14** (Scheme 5).¹⁶ Interestingly, the authors employed a one-pot procedure, which also involved an *in situ* generation of the isocyanide from the corresponding formamide **12**. Triphenylphosphine was used both for formamide dehydration (together with hexachloroethane) and for azide reduction.

Dihydrobenzazepines **16** were obtained and thus this work represents one of the rare examples of use of the Passerini reaction for the synthesis of seven-membered heterocycles.¹⁸

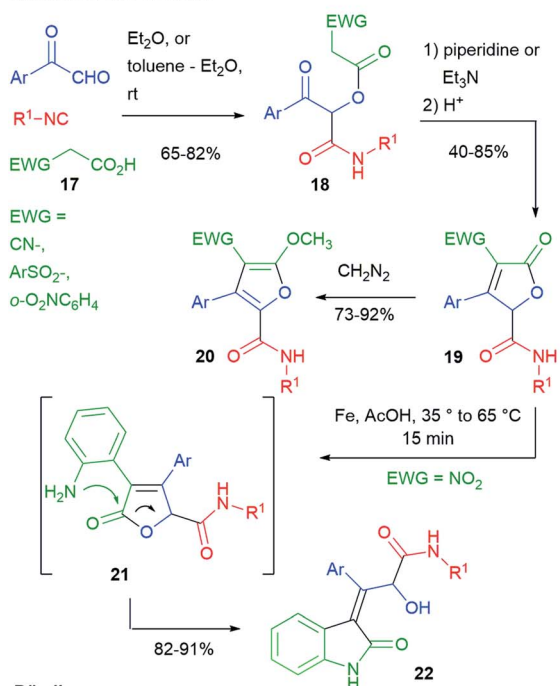
Several researchers have studied post-Passerini $\text{C}=\text{C}$ bond formation through Knoevenagel-type or Wittig-type reactions to give furanones (butenolides) (Scheme 6). The first ones have been Marcaccini and Torroba. In 1993 (ref. 19), they reported that, by using carboxylic acid **17**, containing an electron-withdrawing group (EWG), the Passerini products **18** were acidic enough to undergo an intramolecular Knoevenagel-type reaction in the presence of an amine, affording furanones **19**. The electron-withdrawing group can be either CN ,¹⁹ a sulphonyl group,²⁰ or an *o*-nitroaryl.²¹ Treatment with diazomethane gave methoxyfurans **20**.

Moreover, furanones **19** with $\text{EWG} = o$ -nitrophenyl have been submitted to a second post-MCR transformation, leading to indoles **22**, through a domino process involving the reduction of the nitro group to **21** and acyl migration.²¹

Similar butenolides **23** have been prepared by Dömling in 2001 through a tandem (one pot) Passerini–HWE (Horner–Wadsworth–Emmons) strategy.²² Butenolides **26** were prepared in 2014 by Koert,²³ through a Passerini–Knoevenagel sequence, using this time α,β -dioxoamides **24**, instead of aryl glyoxals. The Passerini reactions were highly regioselective, involving the keto



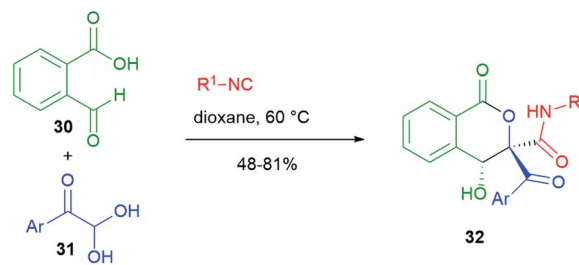
Marcaccini and Torroba:



Scheme 6 Synthesis of butenolides via tandem Passerini-Knoevenagel or Passerini-HWE or Passerini-Dieckmann.

group α to the amide, thus providing **25**. In this work, a broader variety of electron-withdrawing groups was exploited. Interestingly, when $\text{EWG} = \text{P(O)OEt}_2$, the phosphonyl group was retained (only 6% of the HWE product was detected).

By using α -oxoesters **27** as the carbonylic component, Dömling has combined the Passerini reaction with a subsequent Dieckmann cyclization, affording hydroxybutenolides **29**.



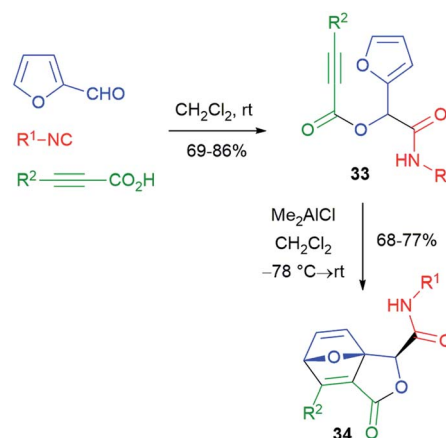
Scheme 7 Synthesis of isocoumarins via the domino Passerini-Aldol reaction.

The procedure can be carried out in a one pot manner, without the need to isolate intermediate diesters **28**. In this case, the presence of an electron-withdrawing R^3 substituent was not needed, since a stronger base (LDA) was employed.²⁴

In the cyclizations reported in Scheme 6, the nucleophilic part is always played by the α -carbon of the carboxylic component of the Passerini reaction. On the other hand, Scheme 7 shows an interesting post-Passerini aldol-type reaction, where it is the carbon α to the secondary amide that plays the nucleophilic role. For this strategy, Jiang and Tu, in 2014,²⁵ employed a system containing two aldehydes, 2-formylbenzoic acid **30** and an arylglyoxal **31**. Substrate selectivity depends upon the solvent employed. In dioxane, the isocyanide selectively attacks aldehyde **31** and the resulting adduct, easily deprotonated, spontaneously cyclizes onto the aromatic aldehyde to give isocoumarins **32**. This aldol reaction is highly diastereoselective.

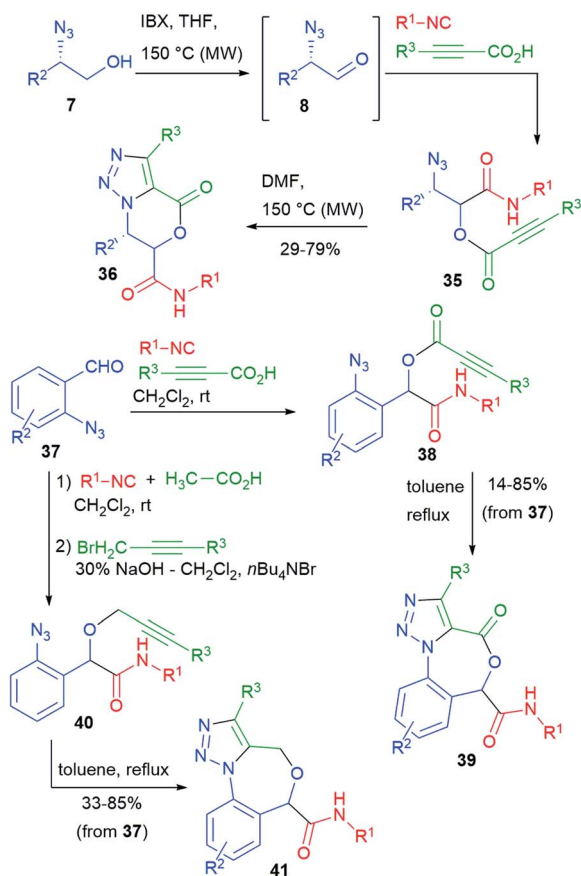
Various post-Passerini cycloaddition reactions have been implemented. The first example was reported by Wright²⁶ in 2002 (Scheme 8), and furfural and a propiolic acid were used in order to install the needed reactive groups for an intramolecular Diels-Alder reaction. The thermal cycloaddition of Passerini adducts **33** did not work, but it could be promoted under Lewis acid catalysis, affording labile tricyclic lactones **34**.

Our group has studied post-Passerini alkyne-azide 1,3-dipolar cycloadditions (Huisgen reaction).²⁷ Towards that goal, we performed a series of Passerini reactions on α -



Scheme 8 Tandem Passerini-Diels-Alder sequence.





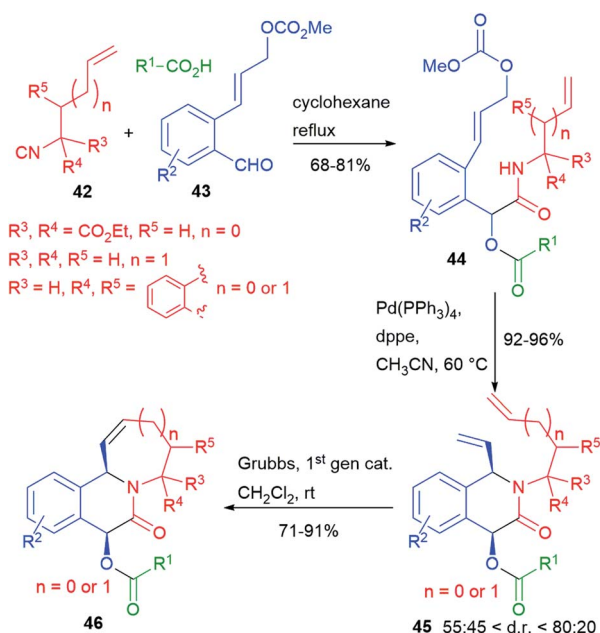
Scheme 9 Tandem Passerini – azide–alkyne cycloaddition.

azidoaldehydes **8**, obtained *in situ* from azidoalcohols **7** (cf. Scheme 4), using as the carboxylic component a propiolic acid (Scheme 9). In some cases (e.g. with trimethylsilylpropionic acid), we could not add all the reagents from the beginning, because of the instability of the propiolic acids under oxidative conditions. It is well known that the intramolecular variant of the Huisgen reaction must be carried out thermally, since the needed regiochemistry is opposite to the one strongly favoured by copper catalysis. Nevertheless, the cyclization of azidoalkynes **35** proceeded efficiently by warming at 150 °C, affording triazolo-fused dihydrooxazinones **36**.²⁸

By using different azidoaldehydes, namely **37**, the same strategy leads to Passerini product **38** first, and then to seven-membered triazolo-fused benzoxazepinones **39**.²⁹

On the other hand, benzoxazepines **41** could be obtained by the thermal cyclization of azidoalkynes **40**. The synthesis of **40** will be described in paragraph 3.3. The overall yields were in most cases good.

We have recently reported (2016)⁷ a double cyclization of a Passerini adduct by performing, in sequence, two metal catalyzed processes (Scheme 10). Towards this goal, we have designed a family of unsaturated isocyanides **42** and a family of aldehydes **43**, containing an allyl carbonate. The Passerini adducts **44**, obtained from various carboxylic acids, could be cyclized in a very high yield, and with moderate diastereoselectivity, through a Pd(0) catalyzed Tsuji–Trost process.



Scheme 10 Tandem Passerini–Tsuji–Trost – RCM.

Then, the resulting dienes **45** have been further cyclized by ring closing metathesis (RCM).

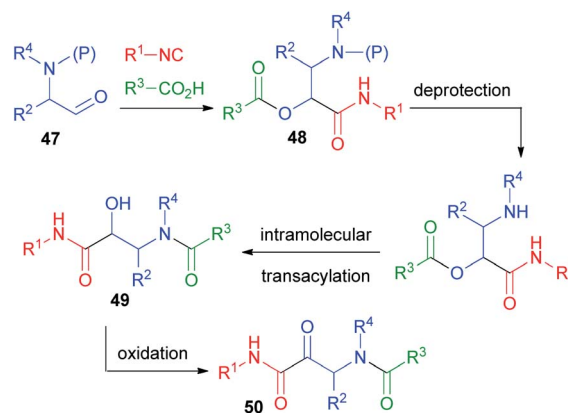
Complex tricyclic adducts **46**, resembling some natural alkaloids, were obtained, displaying either 6- or 7-membered rings.

Passerini reactions followed by RCM cyclizations were also reported by Dömling³⁰ and Martens.³¹ In the first case, various natural-like macrocycles were obtained using unsaturated isocyanides and unsaturated carboxylic acids as MCR inputs. In the second case, six-membered lactones were synthesized starting from allyl ketones and β,γ -unsaturated carboxylic acids.

In chapter 4, we will describe the synthesis of other heterocycles by cyclizations after a diastereoselective Passerini reaction of erythritol derivatives.

2.2 The PADAM approach to peptidomimetics

In 1998, in order to overcome the problem of the physiologically labile ester functionality in the typical Passerini adducts, we



Scheme 11 The PADAM protocol.

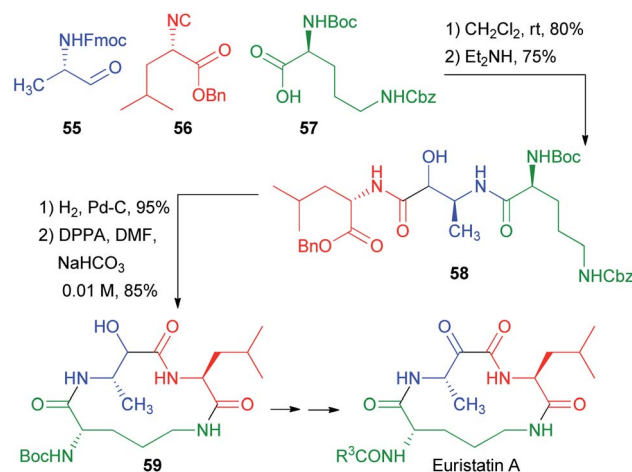


designed a rapid and efficient way to convert the Passerini adducts into peptides, starting from protected α -aminoaldehydes **47** (Scheme 11).³² In this design, we have also been inspired by the work of Hulme on the UDC strategy (Ugi/De-Boc/Cyclize).³³ After the Passerini reaction to afford **48**, a simple deprotection of the amine promotes $O \rightarrow N$ acyl migration, to form α -hydroxy- β -acylaminoamides **49**. With this protocol, which we called PADAM (Passerini-Amine Deprotection-Acyl Migration),³⁴ we could produce, in just two easy steps, peptides **49** containing α -hydroxy- β -amino acid units (norstatine) or, after oxidation, ketones **50**, characterized by an α -oxo- β -amino acid unit. These classes of compounds are widely explored for their potential as inhibitors of aspartic proteases (**49**) or of serine proteases (**50**). Prior to our work, they were typically synthesized through longer sequences of 6–7 steps. α -Aminoaldehydes can be obtained in a wide variety and in enantiomerically pure from α -amino acids, and thus the final peptidomimetics may be obtained in an optically pure form.

Initially, we used the Boc protecting group.³² A library of Passerini adducts **48** was produced in good yields (59–95%) and with moderate stereoselectivity ($52 : 48 < \text{d.r.} < 71 : 29$). Then, adducts **48** were transformed into **49** using first $\text{CF}_3\text{CO}_2\text{H}$, and afterwards triethylamine in a one-pot procedure (yields ranging from 75 to 99%). Recently, the major stereoisomers have been recognized as *syn*.³⁵ The moderate stereoselection is obviously not a problem if the desired final products are α -ketoamides **50**, derived by the oxidation of **49**.

Additionally, we developed the same method on the solid phase, using a photocleavable linker³⁴ (maintaining the Boc group on aldehyde **47**) or employing an acid-labile linker (this time shifting to the Fmoc protection).³⁶

The PADAM approach can be even more potent if a protected amino acid is used as the carboxylic component. This concept is exemplified in Scheme 12 by the synthesis of a known inhibitor of *Cytomegalovirus* protease, a serine protease.³⁷ During the deprotection/acyl migration step, the protecting group of the amino acid (in this example, the asparagine derivative **51**) is concurrently removed, affording **52**, leaving a free amino group available for the introduction of a fourth component by

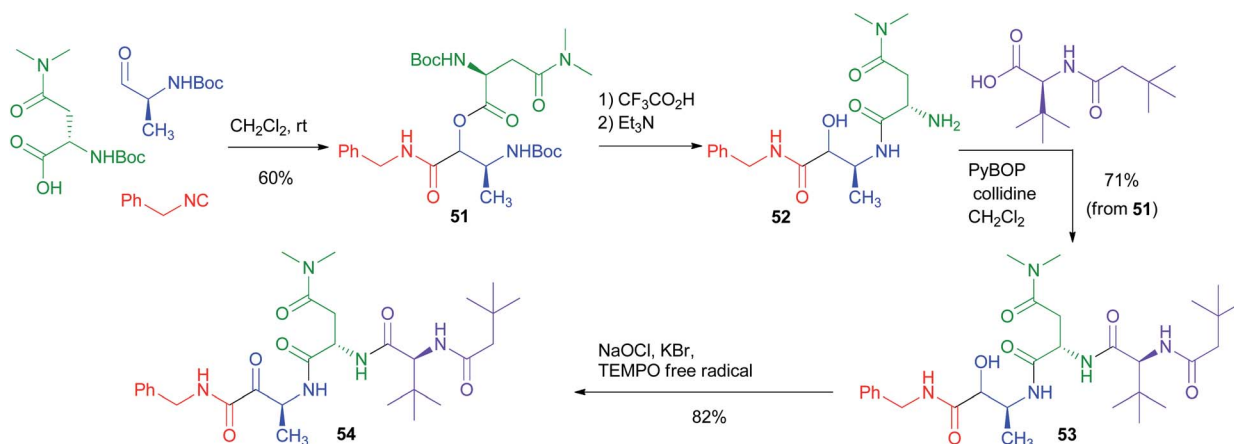


Scheme 13 Synthesis of Eurystatin A.

standard peptide coupling. Finally, the oxidation of **53** gives α -oxoamide **54**. It should be noted that **52** was not isolated and thence the synthesis of **54** involves just three steps with the introduction of 4 diversity inputs.

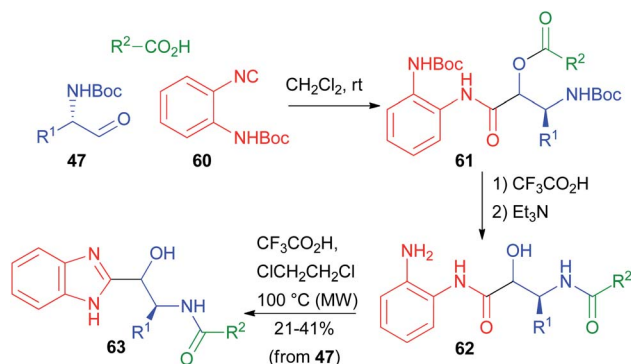
In 2001, Semple used the protected amino acid **57** as the carboxylic component for a total synthesis of Eurystatin A (Scheme 13).³⁸ This time, however, orthogonal protections were used for the acid and the α -aminoaldehyde **55**. The third component, isocyanide **56**, was also derived from a α -amino acid. The chosen aldehyde protecting group was Fmoc, and thus the deprotection–acyl migration stage was accomplished with Et_2NH . The resulting peptidomimetic **58** already contains all the fragments of the final target. Simultaneous deblocking of benzyl ester and of Cbz afforded an amino acid that was cyclized to **59**. Finally, a few steps afforded Eurystatin A, an α -oxoamide. Thus, also in this case, the poor diastereoselectivity of the Passerini reaction was not problematic, because the stereogenic centre was lost in the final oxidation.

These examples point out PADAM as an ideal protocol for the combinatorial synthesis of libraries of peptidomimetics, in drug discovery.



Scheme 12 Application of the PADAM strategy to the synthesis of an inhibitor of *Cytomegalovirus* protease.



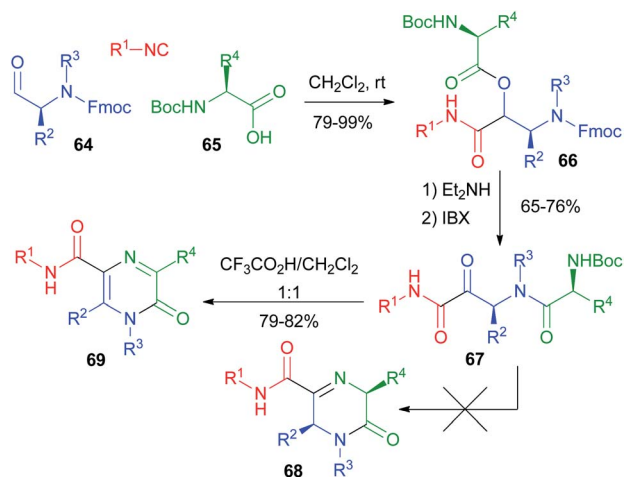


Scheme 14 PADAM followed by cyclization as a route to benzimidazole isosteres of norstatines.

For example, Bode in 2012 used this approach for the synthesis of α -hydroxy- β -acylaminoamides as HIV protease inhibitors, employing branched isocyanides.³⁹ Other total syntheses of peptidomimetics will be described in chapter 5.

In 2012, Hulme coupled the PADAM protocol with a post-MCR cyclization. Using the special isocyanide **60**, he obtained a series of benzimidazoles **63**, isosteres of norstatines (Scheme 14).⁴⁰ After the Passerini reaction, the depsipeptide **61** was converted as usual to **62**. Further treatment under acidic conditions at higher temperatures brought about condensation to give the imidazole ring.

Our group studied post-PADAM cyclization processes as well. In 2011 (ref. 41) we exploited the use of an additional amine placed in the carboxylic component (Scheme 15). In contrast to the above-described Hulme's work, we planned to perform the condensation of the amine onto the ketone resulting from post-PADAM oxidation. Since a free amine was expected to interfere with oxidation, we used orthogonal protections for the α -amino aldehyde **64** (Fmoc) and the α -amino acid **65** (Boc) to obtain **66**. The PADAM protocol was thus implemented using diethylamine for the deprotection/acyl migration step. After oxidation to the α -ketoamide **67**, treatment with $\text{CF}_3\text{CO}_2\text{H}$ was expected to



Scheme 15 PADAM followed by cyclization as a route to pyrazinones.

afford dihydropyrazinones **68**, but an unexpected aromatization took place, giving pyrazinones **69**.

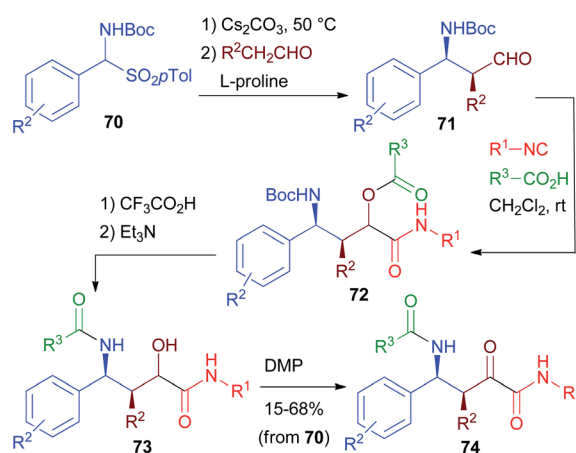
2.3 The homo-PADAM and bis-homo-PADAM protocols

Starting from β -aminoaldehydes, a homo-PADAM protocol could be applied, giving access to a new class of elongated peptidomimetics. However, β -aminoaldehydes are much less easily accessible than α -aminoaldehydes. Moreover, when possessing a stereogenic centre in the α position, they are known to be rather prone to racemisation.

In 2013 (ref. 42), we reported a very efficient and stereo-selective diversity-oriented route towards α -oxo- γ -acylaminoamides **74** and α -hydroxy- γ -acylaminoamides **73**, taking advantage of the asymmetric organocatalytic synthesis of Boc protected β -aminoaldehydes **71** developed by List.⁴³ Towards that goal, we prepared a series of aldehydes **71** from carbamoylsulphones **70** through a proline catalysed Mannich reaction (Scheme 16). These aldehydes are stereochemically labile and for this reason, in previous studies, they were promptly reduced or oxidized. Nevertheless, we found out that the mildness of Passerini conditions allowed the obtainment of products **72** with no epimerization at all. Deprotection-acyl migration to give α -hydroxyamides **73** takes place in high yields. Compared to the standard PADAM, treatment with Et_3N for a longer time is necessary to promote the acyl migration. Finally, oxidation gave α -ketoamides **74**. Thanks to the efficiency of the various steps, the overall sequence from **70** to **74** can be carried out without any intermediate purification, in good overall yields (typically >50% with a few exceptions).

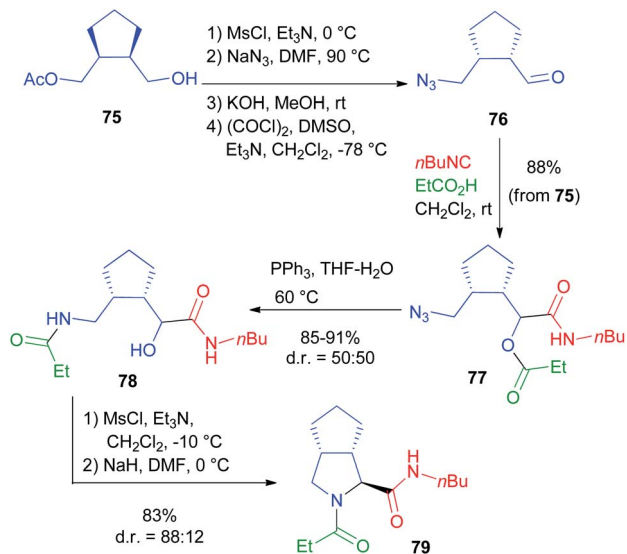
Unfortunately, as expected, the diastereoselection of the Passerini reaction was poor, giving compounds **73** as 1 : 1 diastereomeric mixtures. The back reduction of **74** to **73**, however, can be highly diastereoselective, allowing the obtainment of **73** with high (>9 : 1) d.r. In some cases, both stereoisomers could be selectively obtained by simply changing the reducing agent.

For a bis-homo-PADAM approach, protected γ -aminoaldehydes are needed. Instead of the usual Boc or Fmoc protections, in this case we chose to use an azide, as amine



Scheme 16 The homo-PADAM protocol.





Scheme 17 The bis-homo-PADAM protocol.

synthetic equivalent. Once again, the main problem is the obtainment of γ -azidoaldehydes in an enantioselective form, but we solved it by applying a biocatalytic approach.⁴⁴ Monoacetate **75** (Scheme 17) was obtained by the desymmetrization of the corresponding *meso* diol and was then converted, in a few high yielding steps, into azidoaldehyde **76**. After the Passerini reaction to give **77**, treatment with PPh_3 brought about azide reduction and acyl transfer, to afford α -hydroxy- δ -acylaminoamide **78**, demonstrating the feasibility of the method. On this product, we were able to carry out a cyclization through $\text{S}_{\text{N}}2$ substitution to give pyrrolidine **79**. In this case, no additional functional group was needed. Interestingly, cyclization was found to be stereoconvergent, probably because of the *in situ* epimerization of the stereogenic centre generated during the Passerini reaction. As a result, a 1 : 1 mixture of **78** was nearly completely converted into a single diastereomer of pyrrolidine **79**. An application of this strategy to the total synthesis of an important active pharmaceutical ingredient (API) will be described in chapter 5.

2.4 Future prospects

While a huge variety of heterocyclic systems have been prepared through Ugi reactions followed by post-MCR cyclizations, a similar strategy was less frequently utilized for the Passerini reaction. There are indeed limitations due to the ester nature of the Passerini products and the fewer chances of including additional functional groups (Passerini is a 3-CR, while Ugi is a 4-CR). The PADAM protocol and its daughters (homo-PADAM and bis-homo-PADAM) offer a way to overcome these restraints. We think that coupling these strategies with subsequent cyclizations may offer many possibilities of diversity-oriented heterocyclic synthesis. Nevertheless, these applications are still rather infrequent and thus there is ample room for future achievements. We have already demonstrated that the problem of diastereoselectivity can be solved by the oxidation–reduction

of the secondary alcohol derived from the PADAM protocol, and thus this fact can facilitate the stereocontrolled synthesis of chiral non-aromatic heterocycles.

3. New opportunities for the Passerini reaction by the replacement of one or two components

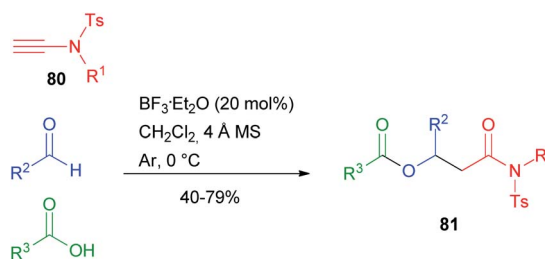
The Single Reactant Replacement (SRR) approach was first coined by Ganem and has been extensively used to improve known MCRs and design new synthetic routes.⁴⁵ The first SRR approach of the Passerini reaction was probably the Ugi reaction, and in the last two decades the scope of the Passerini reaction has experienced further expansion by replacing one or two components, leading to new interesting pathways and different final products. These new products can undergo in some cases post-Passerini transformations, further enlarging the accessible chemical diversity. The isocyanide component usually cannot be changed, although recently Cui reported the Passerini reaction employing tosylamides **80** in place of isocyanides,⁴⁶ affording β -acyloxyamides **81** with broad scope and functional group tolerance (Scheme 18).

Most studies, however, have focussed on the substitution of the carboxylic acid or, less often, of the carbonyl component. The subject has already been reviewed by us,³ while some recent examples will be reported in this chapter.

3.1 The ketene 3-component Passerini reaction

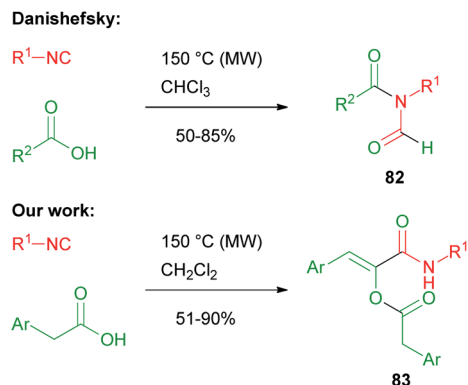
In 2008, Danishefsky reported on the two component reaction of isocyanides with carboxylic acids to yield formylamides **82**.^{47,48}

In the same period, we made a serendipitous discovery, finding that, when an arylacetic acid was employed, a new three component variant of the Passerini reaction took place instead, involving two equivalents of the acid and leading to interesting captodative olefins **83** (Scheme 19).⁶ By studying the mechanism, we understood that the aryl group indeed played a crucial role. The initial α -adduct between an arylacetic acid and isocyanide, in fact, being an activated ester, preferentially underwent a nucleophilic acyclic substitution ($\text{S}_{\text{N}}\text{Ac}$) with an additional molecule of isocyanide, leading to **84**. The $\text{O} \rightarrow \text{N}$ acyl migration, leading to **82** and reported by Danishefsky, was not observed in this case.



Scheme 18 Passerini reaction with tosylamides.

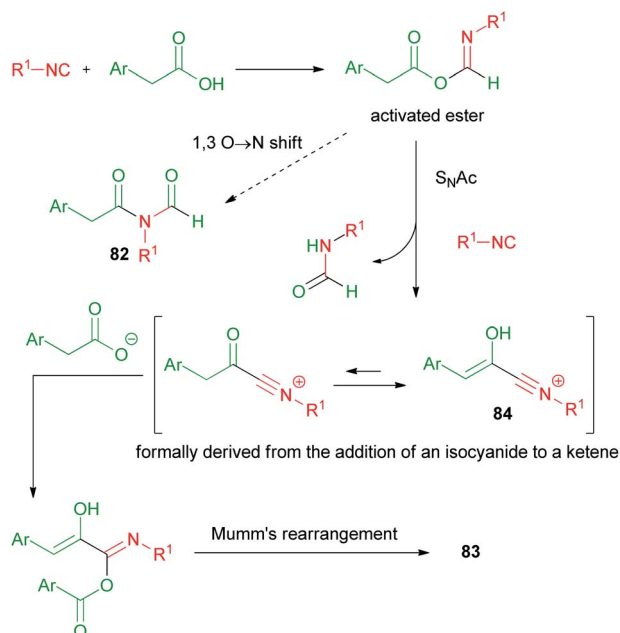




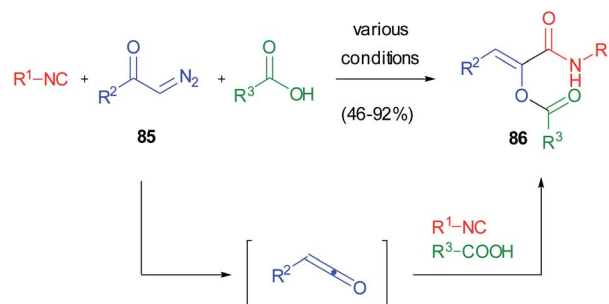
Scheme 19 Different outcomes of the reaction between isocyanides and carboxylic acids.

The formation of adduct **84** was favoured by the stabilization ensured by the aromatic ring, able to generate an extended conjugation in the enolic form. The addition of a second molecule of arylacetic acid onto the nitrilium functionality of **84**, followed by Mumm's rearrangement of the resulting adduct, afforded captodative olefin **83**. Adduct **84** can be considered as formally derived from the addition of an isocyanide to a protonated arylketene, which replaces the protonated carbonyl compound, while the subsequent steps occur similarly to a normal Passerini reaction (Scheme 20).

This serendipitous finding prompted us to investigate if the reaction between ketenes, isocyanides and carboxylic acids could be generalized in a three component reaction involving three real diversity inputs. Due to the intrinsic instability of most ketenes, we devised the possibility to generate them *in situ* from diazoketones **85**. The photoinduced ketene 3-component reaction (K-3CR) was therefore developed, taking advantage of



Scheme 20 Postulated mechanism for the reaction between isocyanides and arylacetic acids.



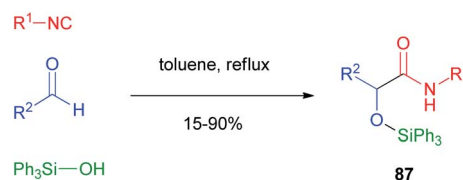
Scheme 21 The ketene 3-component reaction (K-3CR).

the light-induced Wolff rearrangement of diazoketones, while thermal and silver-mediated procedures were unsuccessful (Scheme 21).⁴⁹ This was one of the first examples of photoinduced multicomponent reactions⁵⁰ and has been recently included in the ReactionFlash® App for named reactions.⁵¹

The reaction had a very broad scope, as both aromatic and aliphatic diazoketones could be used indifferently, together with any acid and isocyanide. However, it was poorly selective regarding the stereochemistry of the double bond, since *E/Z* mixtures of the captodative olefins were often isolated. This was a consequence of the UV-mediated isomerization of *Z* olefins **86**, the sole products of the K-3CR, under the reaction conditions. This problem was solved in different ways: (i) by using, as additives, triplet quenchers (piperylene and *trans*-stilbene) able to inhibit the alkene isomerization but not the Wolff rearrangement;⁵² (ii) by performing the reaction under continuous flow conditions, in order to remove the olefin from the irradiation area immediately after its formation;⁵³ (iii) very recently, by using visible light to induce Wolff rearrangement: although diazoketones usually display an absorption maximum around 250–300 nm, we have demonstrated that the molar extinction coefficient at 450 nm is not neglectable, and reactions performed under blue LED irradiation show very high quantum yields and better selectivities.⁵⁴ The captodative olefins originating from this approach have been converted into pyrrolidine-2,5-diones or pyrrolones in a divergent manner, depending on the basic conditions employed.⁵⁵

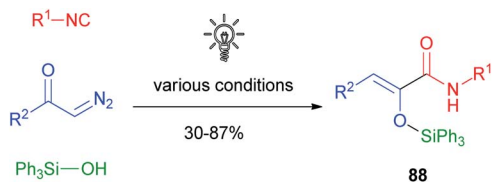
3.2 The modification of the ketene–Passerini reaction using silanols

The silylative Passerini reaction, a modified version where a silanol replaces a carboxylic acid, has been reported by Soeta and Inomata in 2010.⁵⁶ Silanols can effectively act as surrogates of carboxylic acids because they display both a nucleophilic site,



Scheme 22 Silylative Passerini reaction.





Scheme 23 Silylative ketene 3-component reaction (SK-3CR).

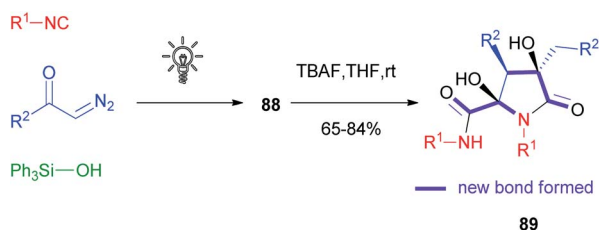
necessary to attack the nitrilium ion, and an electrophilic site, essential for the final Mumm's rearrangement. Due to the lower reactivity of silanols compared to carboxylic acids, the reaction had to be performed with excess reagents, at high temperatures and for prolonged times, affording α -silyloxy amides **87** in moderate to good yields. Triphenylsilanol performed better than other derivatives, due to the EWG character of the aromatic rings (Scheme 22).

Also, the K-3CR could be effectively performed in the presence of silanols replacing the carboxylic acids, but in this case there was no need for excess reagents or higher temperatures. The same solutions used for the K-3CR also made it possible to stereoselectively obtain *Z*-silyloxy acrylamides **88** in this case. The scope of the reaction was quite broad, and also in this case triphenyl silanol performed better than others (Scheme 23).⁵⁷

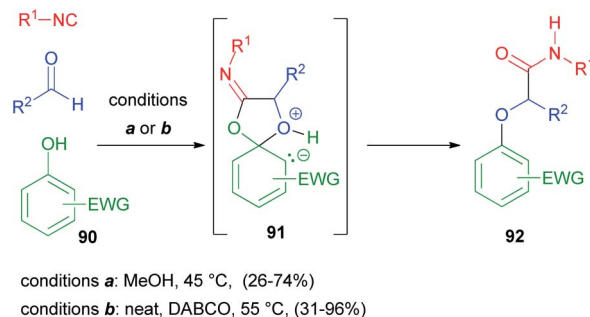
Compared to α -acyloxyacrylamides **86**, silyl enoethers **88** displayed a lower stability, especially during chromatographic purification: the disadvantage in terms of isolated yields turned into an added value in terms of reactivity, as these compounds could be efficiently subjected to the Mannich reaction, Saegusa oxidation, decarboxylative cyclization with α -amino acids, photoredox acetylation⁵⁸ and interestingly to a tandem Michael/aldol dimerization reaction able to afford natural product-like compounds **89** in a very straightforward manner.^{59,60} Six new bonds and three stereogenic centres, including two quaternary carbons, could be formed stereoselectively in just two steps, starting from diazoketones, silanols and isocyanides (Scheme 24).

3.3 The Passerini reaction using alcohols

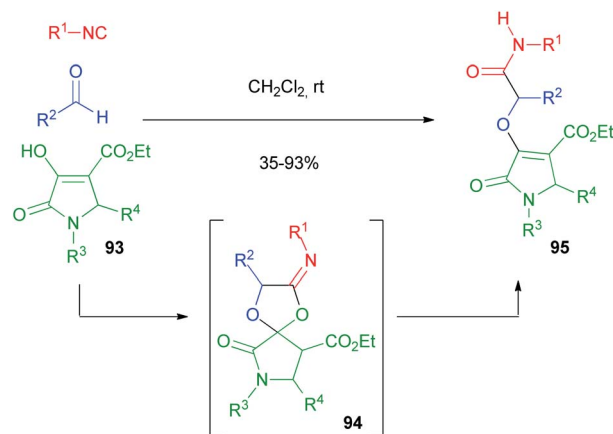
According to what has been discussed in the previous paragraph, alcohols cannot replace carboxylic acids in a Passerini reaction, generating α -alkoxy amides, as they lack an electrophilic site to allow the Mumm rearrangement. However, when electron poor phenols **90** are used, a Smiles rearrangement



Scheme 24 Two-step synthesis of the common skeleton of natural products eusynstyelamides and anchinopeptolides.



Scheme 25 Passerini-Smiles reaction with activated phenols.

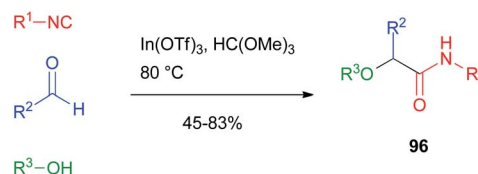


Scheme 26 Enol-Passerini reaction.

through intermediate **91** can occur instead, and α -aryloxy amides **92** can be obtained, as reported in 2006 by El Kaïm and Grimaud.⁶¹ Yields, however, were lower than those of the parent Ugi-Smiles reaction, as aldehydes display a reduced electrophilicity compared to imines. About ten years later, the same authors⁶² reported improved conditions for the Passerini-Smiles reaction, with the use of a tertiary nucleophilic amine as an additive together with solvent free conditions (Scheme 25).

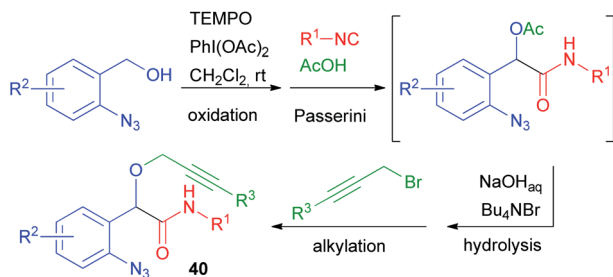
The enol-Passerini reaction recently reported by Neo and Marcos,⁶³ employing enolic pyrrolidin-2,5-diones as substrates **93**, is based on the same Smiles rearrangement. Through the formation of intermediate **94**, it affords enolamides **95**; however, if a polar protic solvent is used, a competitive enol-Ugi reaction is observed, due to the solvent promoted imine formation between the isocyanide and the aldehyde (Scheme 26).

Attempts to achieve a general alkylative Passerini reaction to products **96** were made by Taguchi.⁶⁴ The reaction was



Scheme 27 Alkylative Passerini reaction.





Scheme 28 OPHA strategy as alternative to an alkylative Passerini reaction.

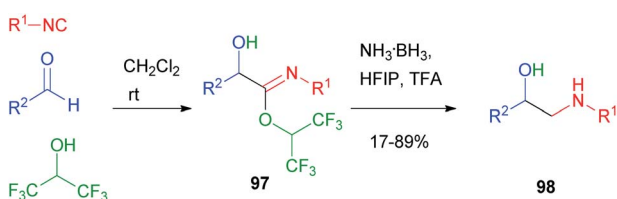
performed with the alcohol used as the solvent in the presence of Lewis acids such as lanthanoid(III) triflates. The method, however, was limited in scope as only aromatic and unsaturated aldehydes could be efficiently used, and the alcohol was also the solvent of the reaction. Therefore, its choice was limited to simple, low-boiling point compounds (Scheme 27).

This limitation proved insurmountable when a few years ago we needed to straightforwardly synthesise α -propargyloxy amides of general structure **40** (cf. Scheme 9).²⁹ The solution was found applying a four-step one-pot reaction involving an Oxidative Passerini reaction, a Hydrolysis, and an Alkylation (OPHA).⁶⁵ Starting from *o*-azido benzyl alcohols and using sacrificial acetic acid, all steps could be performed without isolation of the intermediates. This strategy paralleled a real multicomponent reaction in terms of operational simplicity and atom economy (Scheme 28). In Section 2.1, a Huisgen cyclization of compounds **40** has been described.

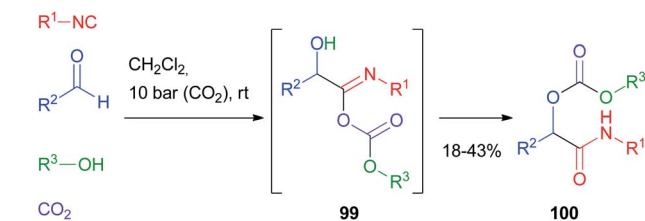
In 2018, Ruijter⁶⁶ reported the Passerini reaction with hexafluoroisopropanol as an acid surrogate: in this case, the intermediate imidate **97**, unable to induce the Mumm rearrangement and to proceed to an alkylated Passerini adduct, was sufficiently stable and could be reduced under mild conditions to β -aminoalcohol **98** (Scheme 29).

3.4 Other recent Passerini variants using different components

Cramail and Meier⁶⁷ have reported the Passerini four-component reaction between aldehydes, isocyanides, alcohols and carbon dioxide. The reaction proceeds through the formation of a carbonate ion, initiated by a base catalyst, and its attack on the nitrilium ion, followed by Mumm's rearrangement of intermediate **99** and formation of an α -alkoxycarbonyl amide **100** (Scheme 30). Final products were isolated in moderate yields and carbonate hydrolysis was observed, together with the



Scheme 29 Passerini reaction with hexafluoroisopropanol (HFIP).



Scheme 30 Passerini reaction with carbon dioxide.

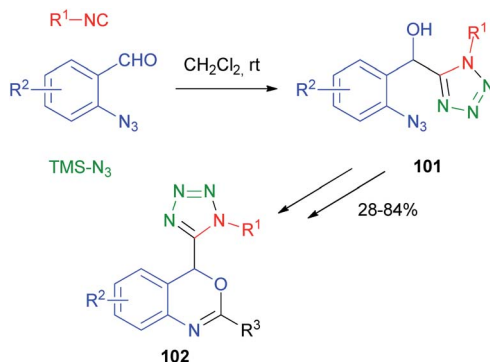
formation of classic Passerini adducts, derived from the oxidation of the aldehyde to carboxylic acid.

The replacement of the carboxylic acid with hydrazoic acid was first reported by Ugi in 1961,⁶⁸ but only in 2002 Nixey and Hulme reported the use of less toxic/explosive and commercially available TMS-N₃ (ref. 69) as the azide source. During the last few years, the methodology has been used independently by Ding⁷⁰ and Xiong⁷¹ to assemble intermediates **101** for the synthesis of 4*H*-3,1-benzoxazine derivatives **102** (Scheme 31).

A new MCR using arynes, carboxylic derivatives and isocyanides has been reported by Stoltz (Scheme 32).⁷² In this reaction, the aryne, generated *in situ* from *o*-silyl aryltriflate **103**, acts as a carbonyl derivative and is subjected to nucleophilic attack by the isocyanide. The resulting zwitterion **104**, in the original design, should have been intercepted by a carboxylate ion, following the typical Passerini mechanism, affording the α -adduct and finally **105** upon the migration of the acyl group onto the carbanionic site. However, the desired product was never isolated, as **104** was not reactive towards carboxylate ions. In contrast, when a carboxylate ester was employed instead, an alternative mechanism occurred, in which the carboxylate was first attacked by the carbanionic site, and then the resulting alkoxide **106** intramolecularly attacked the nitrilium ion, affording the final iminoisobenzofuran derivative **107**. Compounds **105** could be eventually obtained by acid hydrolysis of **107**.

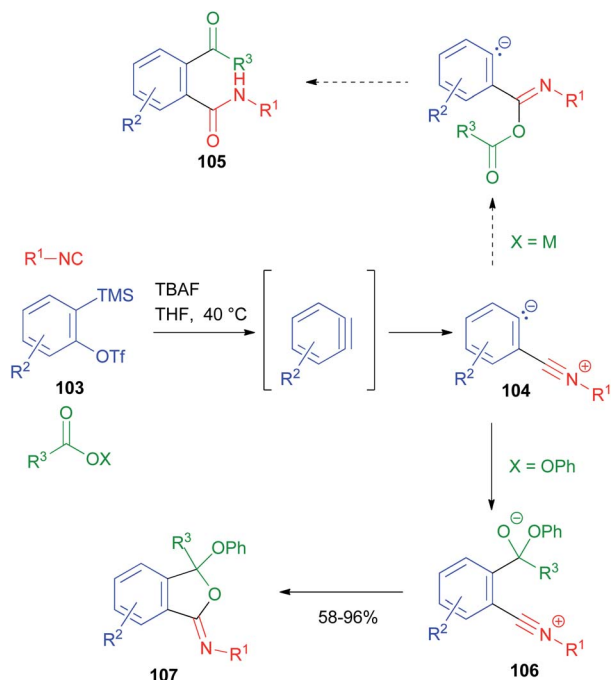
3.5 Future prospects

The substitution of one or two components has attracted high interest over the past two decades, since it has allowed overcoming the inherent limitations of the Passerini reaction.



Scheme 31 Passerini-azide reaction for the synthesis of tetrazole derivatives.





Scheme 32 Three-component reaction between arynes, carboxylate esters and isocyanides.

Carboxylic acids have been replaced by various species, ranging from phenols to azides to silanols and alcohols. Surprisingly, no reports about boron derivatives have been found in the recent literature. Boronic acids, in fact, possess both a nucleophilic hydroxyl group to attack the nitrilium ion and an electrophilic boron atom capable of enabling the Mumm rearrangement. Hopefully, the borono-Passerini reaction will be soon disclosed. If many carboxylic acid surrogates are available, the same does not apply for the electrophilic component, for which the only viable alternatives to aldehydes and ketones are, so far, only ketenes and arynes. Ketenes, in particular, have shown high versatility and could be in principle employed in other Passerini-like reactions, apart from the K-3CR and the SK-3CR. On the other hand, it would be interesting to see whether other electrophilic species, not necessarily carbon-based, could operate by a similar mechanism. Emerging fields such as photocatalysis and electrocatalysis could be used to generate *in situ* such species and widen the range of possible reactions.

4. The still unresolved problem of stereoselectivity in the Passerini reaction

The Passerini reaction always generates a new stereogenic centre when an unsymmetrical carbonyl compound is employed. Therefore, stereoselectivity, either enantio- or diastereoselectivity, represents a major challenge. As it will be illustrated in this chapter, this issue is still in part unresolved.

4.1 The state of the art in the enantioselective catalytic Passerini reaction

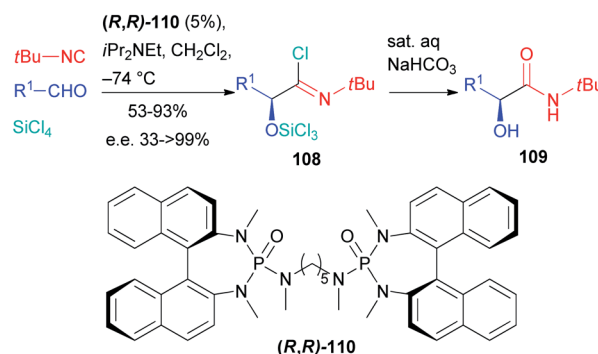
Although the catalytic enantioselective addition of nucleophiles to C=O and C=N double bonds is a well-established procedure, the extension of this protocol to the Passerini (and Ugi) reaction, where the isocyanide is the nucleophile, is an extremely challenging task.⁷³ There are several reasons that hampered the discovery of very efficient enantioselective approaches such as for example: (a) the competition of the not enantioselective MCR reaction, as the Passerini reaction is a spontaneous process and the turnover of the catalyst is usually not efficient; (b) the fact that a Lewis acid, the most logical activating moiety for the aldehyde component, can also interact with other basic sites, first of all with the isocyanide.

The first enantioselective approach to the Passerini reaction was reported by Denmark in 2003 (Scheme 33),⁷⁴ where an efficient enantioselective organocatalytic “truncated” two component Passerini reaction was described. The employment of silicon tetrachloride, a weak Lewis acid, instead of the carboxylic acid, enables interaction with the chiral bisphosphoramide **110**, resulting in the formation of a silicon cation which activates the aldehyde before the selective nucleophilic attack of the isocyanide on one of the enantiotopic faces of the carbonyl.

The intermediate nitrilium ion is trapped by the only available nucleophile, namely chloride, to afford imidoyl chloride **108**, which decomposes under mild basic conditions giving α -hydroxyamide **109**.

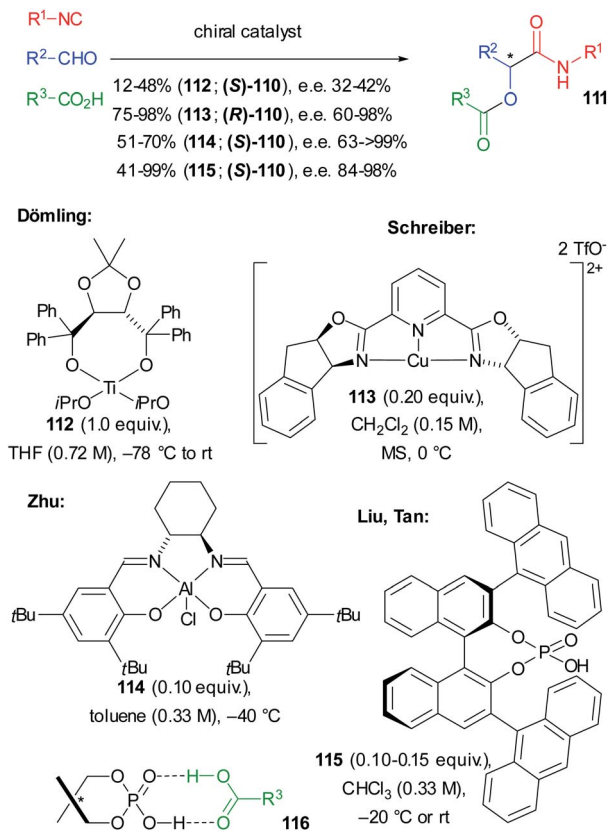
In the same year, in a pioneering study, Dömling reported the first enantioselective not truncated Passerini reaction where a screening of chiral catalysts allowed identifying Ti(IV)-TAD-DOL complex **112** as the best performing one. However, **111** was obtained only with a moderate e.e. and, due to the low turnover number, an equimolar amount of **112** was required (Scheme 34).⁷⁵

Shortly after, an efficient ligand accelerated approach, using 0.20 equivalents of tridentate Cu(II)-PyBOX complex **113**, which usually allows high enantioselectivity, was reported by Schreiber, in particular using chloroacetic acid. High enantioselectivities were obtained, provided that dry conditions were used and that chelating aldehydes were employed. Water, in



Scheme 33 The enantioselective “truncated” Passerini reaction.





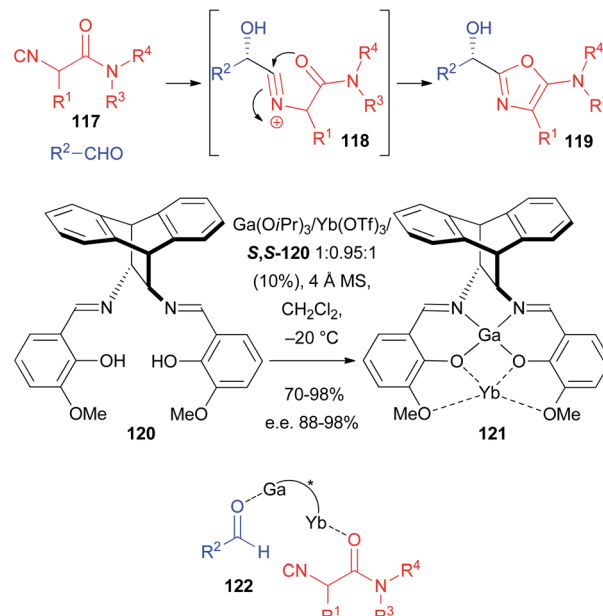
Scheme 34 The enantioselective Passerini reaction.

fact, could deactivate the catalyst, making the underground reaction competitive.⁷⁶

Later Zhu employed (salen)Al(III)Cl complex **114** which allowed the transformation of a variety of nonchelating aldehydes into **111** with good to excellent enantiomeric excess, the best results being achieved with the less reactive aromatic isocyanides.^{73,77}

The first organocatalytic enantioselective Passerini reaction was described by Liu and Tan, who obtained excellent results using chiral phosphoric acid **115** (CPA), which represents the best protocol available to date. With a few exceptions, the yields are high and the e.e.s are almost always >90%. The authors justified the good results as a consequence of the formation of heterodimer **116**, responsible for the double activation of **115** (more acidic CPA) and of the carboxylic acid (enhanced nucleophilicity).⁷⁸

As a matter of fact, the enantioselective Passerini reaction was made possible taking advantage of previous studies on the development of the enantioselective approach to 5-amino-oxazoles **119** through a 2-component reaction involving a particular class of isocyanides, namely α -isocyanoacetamides **117** and aldehydes. In this reaction, with the carboxylate missing, the intermediate nitrilium ion **118** is intramolecularly trapped by the amide oxygen (Scheme 35). Good to excellent results were achieved using a Sn(II)-PyBOX complex,⁷⁹ catalyst **114**,⁸⁰ and CPAs either as ligands for Al,⁸¹ or as Brønsted acid organocatalysts.⁸² In this regard the most efficient ligand,



Scheme 35 The enantioselective synthesis of 5-amino-oxazoles.

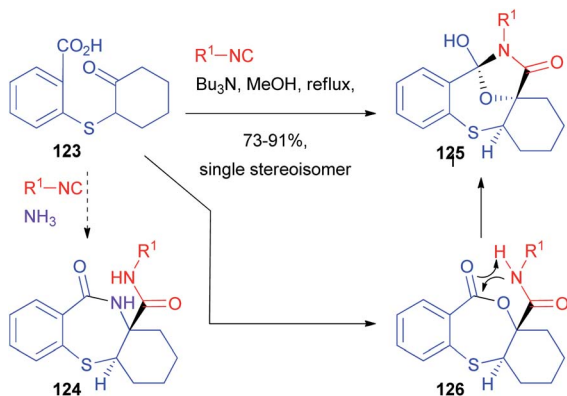
developed by Matsunaka and Shibasaki, is **120** which was transformed into several heterobimetallic Schiff base complexes such as, for example, **121**.⁸³ Despite the complex synthesis of the chiral catalyst, the results are excellent, with e.e.s in the range 95-98%, being lower (88%) only in one case, where 3-phenylpropanal was used as the aldehyde. The concurrent presence of two Lewis acid species allows most likely the concomitant activation of the aldehyde and the coordination of the amide oxygen, bringing the two reacting molecules close together with a controlled orientation during the enantiodiscriminating step (see **122**). The very efficient catalyst **120** has a very peculiar structure, which enables only the coordination of α -isocyanoamides, making the application to the classic Passerini reaction unlikely, as these isocyanides gave 5-amino-oxazoles even in the presence of a carboxylic acid.

Finally, another approach to 5-membered nitrogen heterocycles based on the reactivity of isocyanide **117** was followed by Wang and Zhu to synthesize 5-(1-hydroxyalkyl)tetrazoles in moderate to good enantiomeric excess. This time a three component Passerini-like reaction involved an aldehyde and isocyanide **117**, while the third component, which replaces the carboxylic acid, was hydrazoic acid. Once again a (salen)Al(III) complex, similar to **114** (Me instead of Cl), was used as the catalyst.⁸⁴

4.2 Diastereoselective Passerini reactions

Although the diastereoselectivity control seems in principle much easier, this challenge is still far from being solved.^{85,86} Chiral isocyanides are usually unable to control the diastereoselectivity, one of the very few exceptions being a camphor-derived one described by Ugi with a single example.⁸⁷ The main reason is that they have a linear, not sterically demanding, structure. The main chance to control the stereoselectivity relies on the use of chiral carbonyl compounds, which have been used



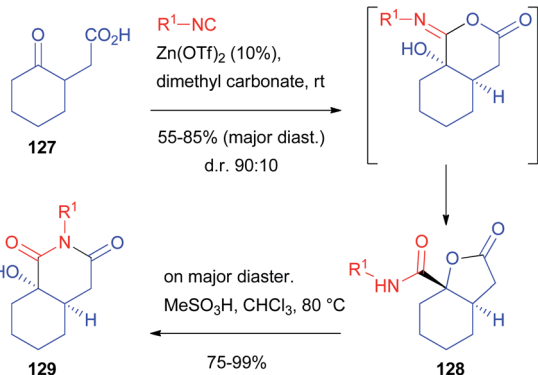


Scheme 36 The diastereoselective synthesis of orthoamides.

both in intramolecular and, most of all, intermolecular processes. Alternatively, chiral carboxylic acids have also been employed, although less frequently.

4.2.1 Intramolecular Passerini reactions on chiral ketoacids. In a study on the diastereoselective intramolecular Ugi reaction using 6-oxo-4-thiacarboxylic acids (**123**), Marcaccini and Torroba found that, if the primary amine is substituted by ammonia, the main product is not the expected Ugi product **124**, but an isomer of the Passerini product.⁸⁸ To this new molecule the bridged orthoamide structure **125** was assigned (Scheme 36). Its formation can be explained by the intramolecular nucleophilic attack of the isocyanide-derived amide on the lactone moiety of Passerini adduct **126**. Finally, if ammonia is substituted by a catalytic amount of tributylamine, single relative stereochemistry was observed, and diastereomerically pure **124** was obtained in high overall yield.

Another report, using racemic as well as enantioenriched ketoacids, was more recently published by Ruijter and Orru, who obtained the functionalized bicyclic scaffold **129** by the Passerini-3-centre-2-component reaction (Scheme 37).⁸⁹ Starting from γ -ketoacid **127**, bicyclic lactone **128** was obtained with moderate stereoselectivity (85 : 15, $R^1 = t\text{Bu}$) using CH_2Cl_2 as solvent. The d.r. could be slightly enhanced performing the reaction in dimethyl carbonate in the presence of catalytic zinc triflate.



Scheme 37 The diastereoselective synthesis of bicyclic derivatives through the Passerini-3 centre-2-component reaction.

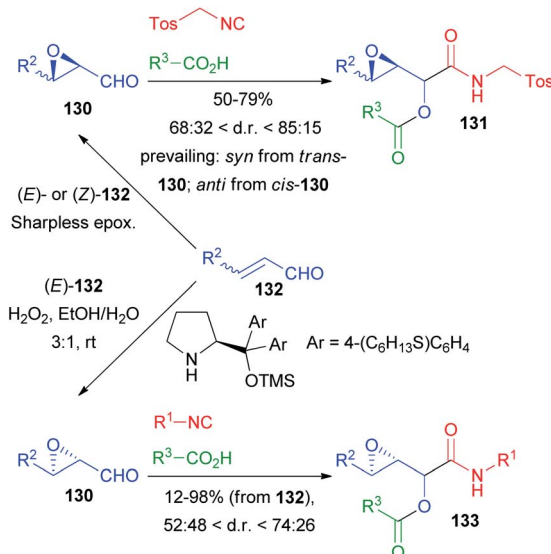
The prevailing formation of *trans*-fused isomer **128** is the result of the preferred axial attack of the not encumbered isocyanide to afford the *cis*-fused α -adduct, which, upon Mumm rearrangement, affords *trans*-**128**. The reaction works well regardless of the employed isocyanide, while the protocol is less tolerant with respect to other cyclic ketones. On the other hand, the diastereomeric ratio is always around 9 : 1. Moreover, by the treatment of the major diastereoisomer with a Brønsted acid, a complete rearrangement occurs, affording the less strained *cis*-hexahydroisoquinolinedione scaffold **129**.

4.2.2 Intermolecular Passerini reactions on chiral carbonyl compounds. The relative asymmetric induction control during the addition of C-nucleophiles to chiral aldehydes is a well-established procedure. In many instances, the diastereomeric ratio can be improved if the carbonyl compound bears a Lewis basic heteroatom in the α or in the β position to the functional group, and the reaction can benefit from the presence of an activating Lewis acid with chelating properties.

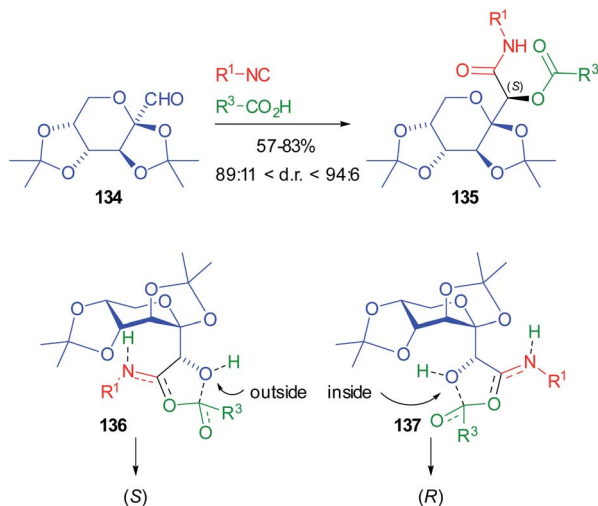
Among the first reports on the Passerini reaction with chiral aldehydes, 2,3-epoxyaldehydes **130**, obtained from **132** by Sharpless epoxidation by Krishna and Lopinti⁹⁰ as well as by an organocatalytic procedure by Corrêa and Paixão,^{91,92} have been used (Scheme 38).

In the first case only TosMIC was used as an isocyanide and the d.r.s are moderate to good; the prevailing diastereoisomer is decided by the relative configuration of the starting 2,3-epoxyaldehyde. Interestingly, the Lewis acid-mediated reaction did not afford **131**, most likely due to the instability of **130** under the reaction conditions. In the second approach, a one pot procedure for the direct epoxidation, followed by the addition of Passerini reagents, afforded **133** with poor to moderate stereoselectivity, and the relative configuration of compounds **133** was not established.

More recently, Jerić used sugar-derived aldehydes for the synthesis of very complex glycomimetics.⁹³ Initially fructose



Scheme 38 Diastereoselective Passerini reaction on 2,3-epoxy aldehydes.



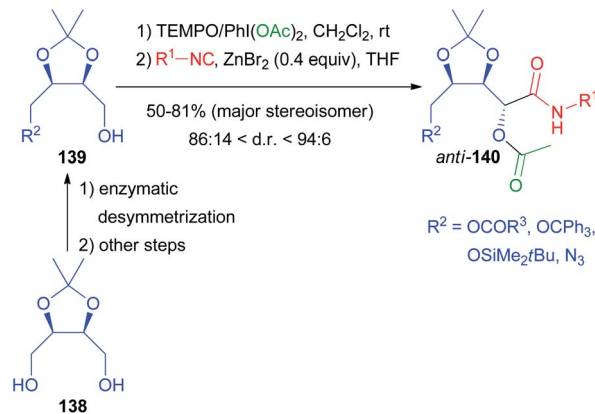
Scheme 39 Diastereoselective Passerini reaction with sugar aldehydes.

derived aldehyde **134** was involved in Passerini reactions with either achiral or chiral sugar isocyanides, and achiral or chiral acids (*N*-protected amino acids or sugar acids) (Scheme 39). However, the control is always exerted by the chiral aldehydes. The yields are moderate to very good, while the d.r.s are up to 94 : 6. The very popular Felkin–Anh model cannot be invoked to explain the stereoselectivity, because of the presence of two oxygens bound to the stereogenic α carbon of **134**. For this reason, the authors carried out DFT calculations, following the mechanistic pathway proposed by Ramozzi and Morokuma, which involves the presence of two molecules of carboxylic acid in the step where the new stereogenic centre is created, which is the one affording the nitrilium ion.⁹⁴

From these calculations, TS **136** with the aldehyde oxygen “outside” seems more stable than **137** with the same oxygen “inside”, which explains the highly preferred formation of the (*S*) configuration for **135**. The same protocol was later applied to the reaction involving other sugar aldehydes (from sorbose, galactose, and allose), and sugar isocyanides and carboxylic acids: the robustness of the methodology was demonstrated and in some cases d.r.s are >99%, while the yields depend on the nature of the reagents.⁹⁵

For more than 35 years, our group has developed biocatalytic methods for the synthesis of small enantioenriched chiral building blocks, through enzyme-catalysed desymmetrizations as well as kinetic resolutions, applying them in asymmetric synthesis and natural product synthesis.^{96–98}

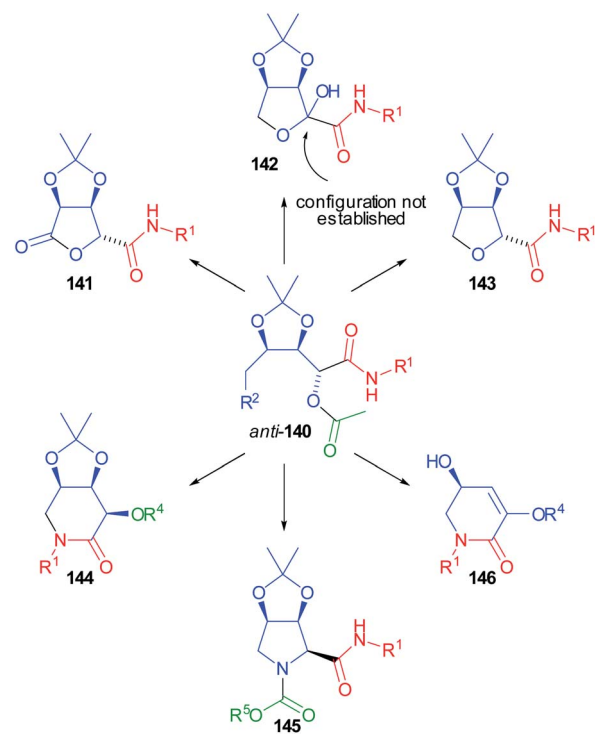
Moreover, since the exploitation of renewable biomass-based feedstocks has become a hot topic, we applied biocatalysis to the valorisation of natural *meso*-diols and the corresponding chiral aldehydes. The enzymatic desymmetrization of protected erythritol **138** allowed the preparation of the chiral building blocks **139** that were transformed into the Passerini products by a one-pot procedure (Scheme 40). After oxidation with TEMPO/PhI(OAc)₂, only the isocyanide was added, because the carboxylic acid is the side product of the oxidation, which represents a nice example of



Scheme 40 Diastereoselective Passerini reaction catalysed by ZnBr₂.

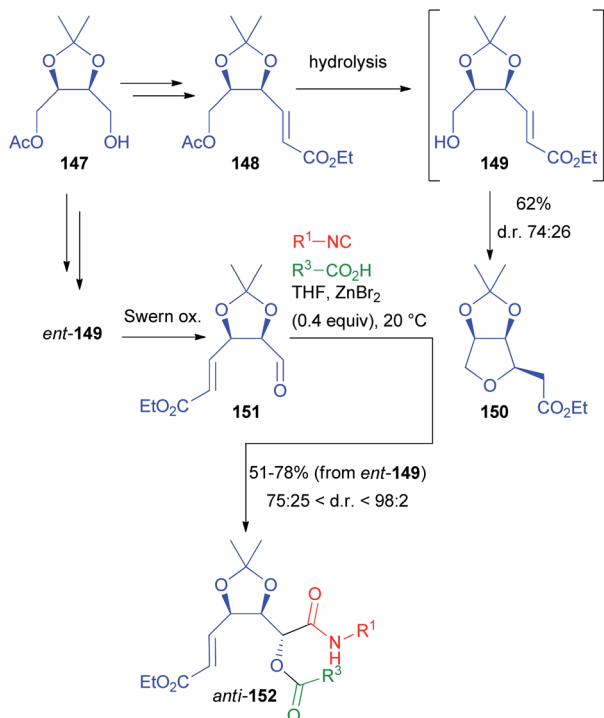
waste recycling in a tandem reaction.⁹⁹ The traditional Passerini reaction in dichloromethane without any additive turned out to be unexpectedly stereoselective, affording *anti*-**140** in a 4 : 1 ratio, while the same reaction on the *trans* isomers of **139** was not stereoselective at all. In order to improve the stereoselectivity, we investigated the effect of different Lewis acids as additives, finding that catalytic ZnBr₂ is able to improve the d.r. up to 96 : 4, depending on R² and on the isocyanide. The reaction is reliable and different isocyanides can be efficiently incorporated.

Compounds **140** were demonstrated to be pluripotent¹⁰⁰ intermediates, as we were able to convert them into six *O*- or *N*-heterocyclic scaffolds (**141–146**) (Scheme 41).



Scheme 41 Transformation of **140** into different heterocycles (actually, the enantiomers of compounds **144–146** were obtained, as they were prepared from the enantiomer of **139**, with R² = N₃ but, for sake of clarity, we reported here only one enantiomeric structure).



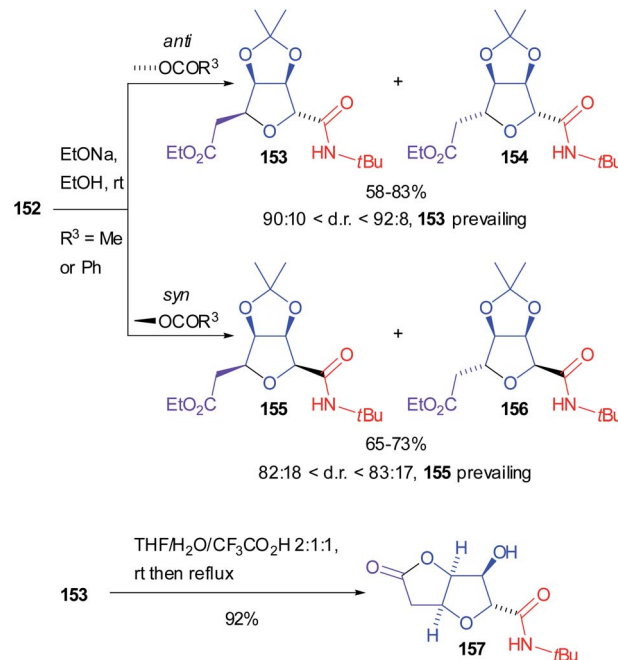


Scheme 42 Another application of erythritol-derived monoacetate 147.

Another application of erythritol-related chiral building blocks is summarized in Scheme 42. Monoacetate **147**, resulting from the desymmetrization of **138**, was homologated to α,β -unsaturated ester **148**, with the aim of converting the acetoxymethyl moiety into the aldehyde.¹⁰¹ However, regardless of the reaction conditions (chemical or enzymatic), as soon as alcohol **149** was released, it immediately underwent a moderately stereoselective intramolecular Michael addition, affording **150** with the *cis* stereoisomer slightly prevailing. To obtain the chiral aldehyde needed for the Passerini reaction, we performed a protecting group exchange on **147** (*tert*-butyldimethylsilyl ether introduction, followed by acetate hydrolysis). The silyl ether was efficiently removed with pyridine·(HF)_x after the introduction of the α,β -unsaturated ester moiety, avoiding the Michael cyclization completely. After oxidation we obtained **151**.

Nevertheless, it is noteworthy that, while **147** can be prepared by enzymatic monoacylation of **138**, also its enantiomer is easily accessible by the enzymatic monohydrolysis of the diacetate of **138**, thus allowing access to both enantiomers of a given target.

As expected, the classic Passerini reaction was poorly diastereoselective (about 6 : 4). Applying the same one-pot protocol (oxidation/ZnBr₂-catalysed Passerini) described for **139**, a partial over-oxidation of aldehyde **151** was observed. Therefore, we preferred to switch to Swern oxidation, also because this allowed us to explore the carboxylic acid diversity. Under the catalysis of ZnBr₂, we were able to obtain **152** in a moderate to excellent diastereomeric ratio (in most cases >4 : 1 and up to 98 : 2), with the *anti*-stereoisomer always prevailing. Again,

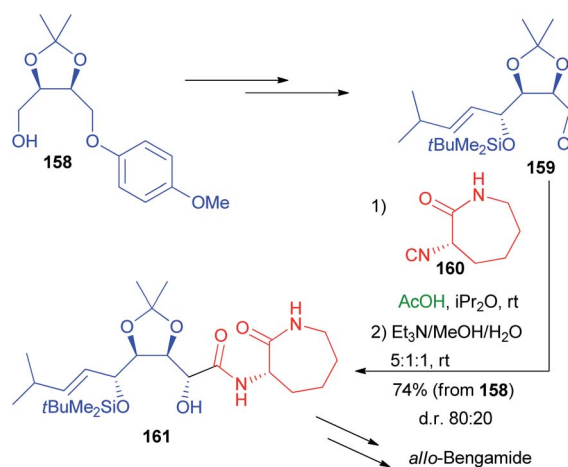


Scheme 43 Further synthetic elaboration of **152**.

a variety of structurally different isocyanides and carboxylic acids could be successfully employed.

Both diastereoisomers of **152**, with R³ either Me or Ph, were separately hydrolysed and the corresponding secondary alcohols underwent spontaneous intramolecular Michael addition to afford preferentially tetrahydrofurans **153** (from *anti*-**152**) and **155** (from *syn*-**152**), highly prevailing over **154** and **156** respectively (Scheme 43). Moreover, submitting **153** to acidic conditions the densely functionalized tetrahydro[3,2-*b*]furan-5-one **157** was isolated, which is an analogue of naturally occurring (+)-goniofufurone.¹⁰¹

More recently, a stereoselective Passerini reaction has been applied on a more functionalized aldehyde, obtained from protected erythritol **138**.¹⁰² Chiral intermediate **158** was



Scheme 44 Synthesis of *allo*-Bengamide.



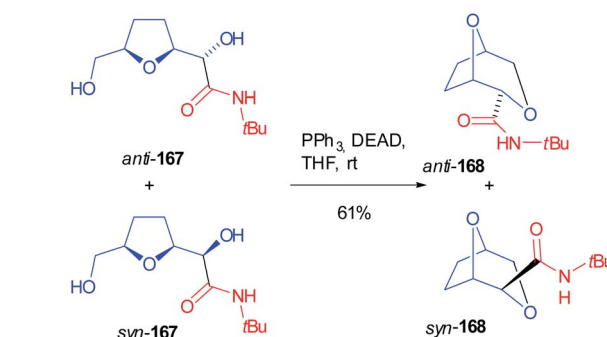
stereoselectively homologated and the other hydroxymethyl group was oxidized, after deprotection, to the key aldehyde **159** (Scheme 44), which underwent a Passerini reaction with enantiopure isocyanide **160** in a double asymmetric induction reaction. The reaction afforded **161** with a moderate preference for the *anti*-stereoisomer, after the hydrolysis of the acetate.

Nevertheless, we were unable to further improve the stereoselectivity taking advantage of ZnBr_2 , because **160** is unstable in the presence of Lewis acids. Intermediate **161** was then converted into *allo*-Bengamide.

Another chiral α -alkoxyaldehyde considered by us is **164**, obtained by lipase catalysed desymmetrization of 2,5-bis(hydroxymethyl)tetrahydrofuran **163**, a reduced derivative of 5-(hydroxymethyl)furfural **162**, an important building block available from lignocellulosic biomass (Scheme 45). The Passerini reaction, performed under standard conditions on a model compound with $\text{R}^1 = t\text{Bu}$ and $\text{R}^2 = \text{Ac}$, was, unlike **139**, poorly diastereoselective, affording **166** as a 59 : 41 diastereomeric mixture.¹⁰³ Then we applied the previously described protocol with ZnBr_2 as the catalyst and we successfully increased the diastereomeric ratio to 81 : 19 (82% yield), provided that a carefully dried aldehyde was used to prevent the formation of the stabilized hydrated form **165**, responsible for not reproducible results. The best results were obtained if a premixed solution of **164** and the carboxylic acid (AcOH) in $i\text{Pr}_2\text{O}$ was added to the mixture of isocyanide and ZnBr_2 . However, the scope of the reaction using the optimized conditions with other carboxylic acids and isocyanides was demonstrated to be troublesome because of the formation of variable amounts of the “truncated” products, as well as due to the insolubility of many carboxylic acids in $i\text{Pr}_2\text{O}$.

For this reason, we developed a more robust and unprecedented methodology using for the first time stoichiometric zinc(II) dicarboxylates. Under these conditions, the d.r. was improved up to 9 : 1 with the *anti*-stereoisomer prevailing, and most reactions affording at least a 4 : 1 ratio.

A mixture of both Passerini products **166** ($\text{R}^1 = t\text{Bu}$) was submitted to the contemporary hydrolysis of both ester

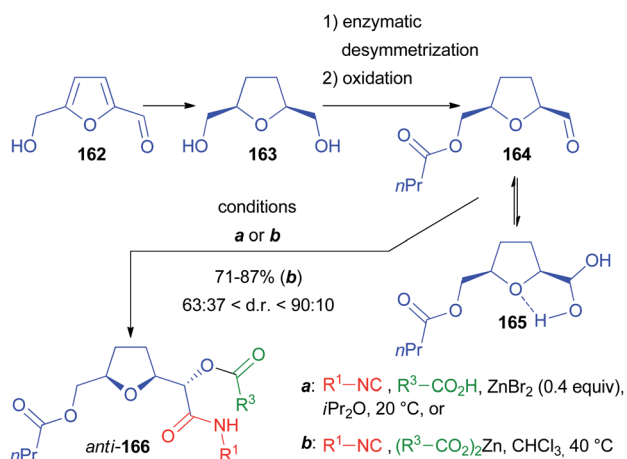


Scheme 46 Synthetic elaboration of **166**.

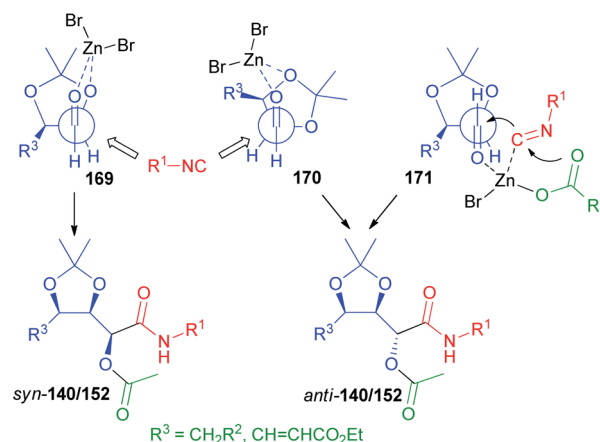
functions and diols **167** were submitted to an intramolecular Mitsunobu reaction, where the primary alcohol cyclized onto the secondary one (**168**) in a stereospecific manner, without losing the initial diastereomeric ratio (Scheme 46).

The rationalization of the stereochemical outcome of these reactions with α -alkoxyaldehydes is not as simple as it might seem at first sight. The increase of stereoselectivity on erythritol-derived aldehydes and on **164** in the presence of ZnBr_2 could be explained if a chelated TS, in which the carbonyl and the α -alkoxy oxygen are both coordinated by the metal (TS **169**, Scheme 47 and **172**, Scheme 48 respectively), is operating. However, this would in all cases preferentially afford *syn* stereoisomers (**140**, **152**, and **166**). For the erythritol-derived aldehydes, another possibility is represented by the coordination of the β -alkoxy oxygen (TS **170**), but this is not possible of course for **164**. Nevertheless, the formation of the *anti*-stereoisomer (**140**, **152**, and **166**) is preferred also in the absence of Zn(II) . The Felkin–Anh model (TS **170** or TS **173**, Scheme 48) can explain the prevailing formation of *anti*-products both for aldehydes from erythritol and for **164**.

However, the well-known Felkin–Anh and chelation models are not always able to explain the stereochemical outcome in the nucleophilic additions to carbonyls,¹⁰⁴ especially those promoted by weak nucleophiles, such as isocyanides. In this

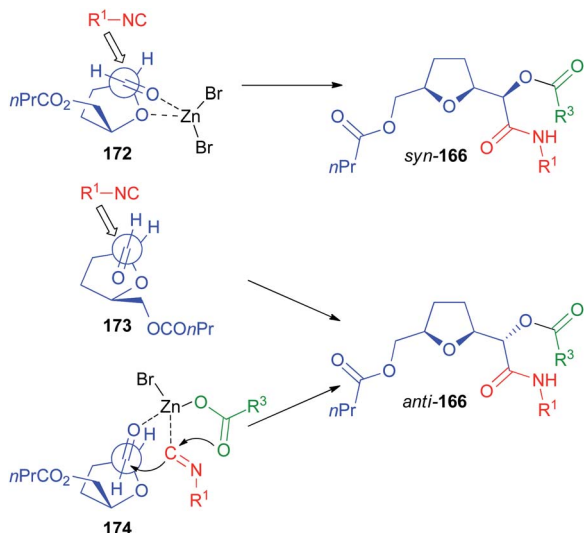


Scheme 45 Diastereoselective Passerini reaction with Zn carboxylates.



Scheme 47 Stereochemical outcome rationalization for Passerini reactions with erythritol aldehydes.





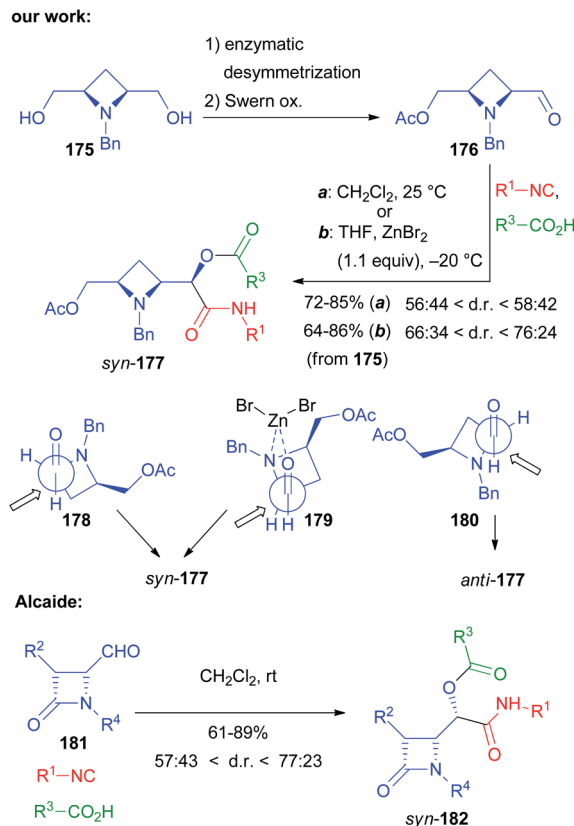
Scheme 48 Stereochemical outcome rationalization for Passerini reactions with aldehyde **164**.

case the addition is most likely endoergonic and the TS is probably more product-like.

Also on the basis of DFT calculations, we think that in the isocyanide addition the position of the carbonyl with respect to the ring plays a crucial role. The “inside” position of the carbonyl (TS **170** and **173**) would be disfavoured by steric interactions with the side arm substituent, and therefore an “outside” arrangement (TS **171** and **174**) is preferred. Moreover, we believe that a concerted mechanism, where the metal, bound to the carboxylate, is coordinated by both the isocyanide and the carbonyl oxygen is working. In this way, a bulkier environment is created around the reaction centre, making one of the two diastereotopic faces more accessible.

Not only chiral α -alkoxyaldehydes but also α -aminoaldehydes were explored as chiral carbonyl inputs. In particular we used biocatalytically derived azetidine aldehyde **176** (Scheme 49), obtained by a chemoenzymatic procedure from *meso*-diol **175**.¹⁰⁵

In contrast to what we experienced with α -alkoxyaldehydes, this time the *syn* stereoisomer **177** prevailed but, using the classic Passerini conditions, the ratio was rather poor. The catalysis by ZnBr_2 still was able to improve significantly the diastereoselectivity, though the best results were only around a 3 : 1 ratio. The explanation of the diastereoselectivity cannot be based on Felkin–Anh or Cram models, with the azetidine nitrogen behaving as a large group, because this would predict the prevailing formation of the *anti*-stereoisomer. For the uncatalyzed Passerini reaction the preference for *syn*-**177** can be explained by the Cram model (TS **178**). The poor stereoselectivity can be justified by the two possible TS **178** and **180**, where the approach of the small nucleophile, the isocyanide, is not able to efficiently discriminate between the two diastereotopic faces of the carbonyl. In the presence of Zn(II) a chelated TS (**179**), where the metal is able to coordinate both the oxygen and the nitrogen, is most likely operating, which explains the observed enhanced stereoselectivity.



Scheme 49 Passerini reaction on chiral α -aminoaldehydes.

The prevailing formation of the *syn* product is in agreement with a previous report by Alcaide, where the classic Passerini reaction was performed using β -lactam aldehydes **181** from isopropylidene-D-glyceraldehyde to afford *syn*-**182**.¹⁰⁶

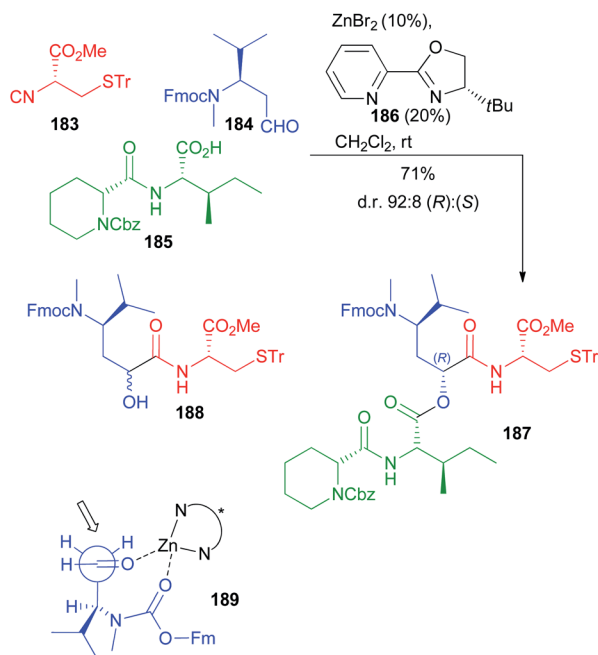
As described in chapter 2, also acyclic α -NBoc-aminoaldehydes **47** (Scheme 11) afford preferentially *syn* derivatives, though with a moderate d.r.^{32,37} In contrast, α -alkyl- β -aminoaldehydes **71** (Scheme 16) gave, as expected, no diastereoselectivity at all, furnishing the homo-PADAM products **73** as a 1 : 1 mixture.⁴²

Very recently Dömling optimized a diastereoselective Passerini reaction on a well-defined combination of 3 chiral reagents, which was aimed at the total synthesis of *N*¹⁴-desacetoxytubulysin H (Scheme 50) reported in detail in chapter 5.¹⁰⁷

This time β -N-Fmoc-aminoaldehyde **184** undergoes a stereoselective attack by chiral isocyanide **183**, and the intermediate is trapped by acid **185**. As expected, the Passerini reaction under conventional conditions (CH_2Cl_2 , 1 M) was not stereoselective at all, while the yield was excellent (90%). Higher dilution (up to 0.01 M) enhanced the stereoselectivity (up to 70 : 30), but the yield dramatically decreased to 15%, as the prevailing product became “truncated” **188**.

In order to improve the stereoselectivity, favouring the formation of **187** with the needed (*R*) configuration at the new stereogenic centre, the authors used chiral CPAs, which recently allowed the first enantioselective Ugi reaction.¹⁰⁸ Despite the high d.r. (95 : 5), the yields were poor, in part because of the

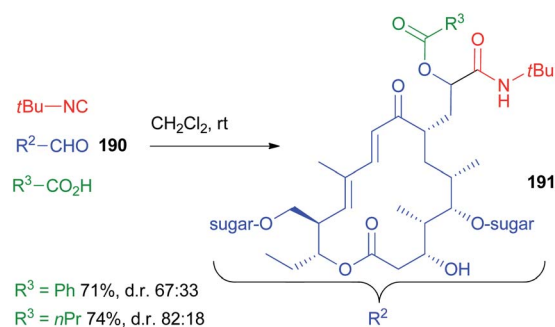




Scheme 50 Stereoselective synthesis of tubulylin fragment **187** through the diastereoselective Passerini reaction (Fm = fluorenylmethyl).

unwanted formation of **188**, which was almost the only product when the CPA was used in the presence of pyridine to mask its acidity. Switching to the activation by an achiral Lewis acid (ZnBr_2), a moderate 80 : 20 diastereoselectivity was obtained with an appreciable 70% yield. Finally, the combination of ZnBr_2 with a chiral ligand, with **186** being the best performing one, allowed obtaining **187** with a remarkable 92 : 8 diastereomeric ratio in 71% overall yield. The proposed TS **189** agrees with a Cram chelated model, where a chelation between the aldehyde and the urethane carbonyls is most likely working. The chiral ligand reinforces the stereoselectivity, favouring the attack of **183** in a matched approach from the less hindered *Si* face of the carbonyl.

A long range highly diastereoselective Passerini reaction is rarely reported, an exception being the reaction on desmycosin **190**, a natural macrolide antibiotic, characterized by a CH_2CHO



Scheme 51 Long range diastereoselection in the Passerini reaction on macrolide aldehyde **190**.

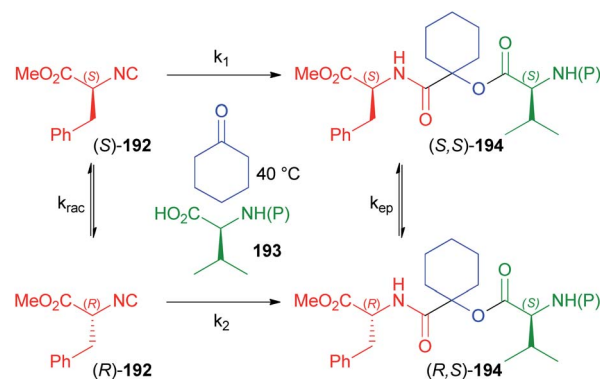
group, reported by Wessjohann (Scheme 51).¹⁰⁹ Only two reactions were reported affording **191** but, using propanoic acid, the d.r. was very good considering the distance between the functional group and the closest stereogenic centre.

4.2.3 Intermolecular Passerini reactions with chiral carboxylic acids. The examples of good asymmetric induction by chiral carboxylic acids are rare. Nevertheless, an exception is represented by peracetylated galacturonic acid, actually used as a chiral auxiliary, though the diastereoselectivity is good only if aromatic isocyanides are used.¹¹⁰ Chiral carboxylic acids (including galacturonic derivatives) have been used in conjunction with sugar-derived aldehydes and TosMIC, affording the expected products in moderate yields and poor to moderate d.r. and just in one case it was excellent.¹¹¹

In another paper by Ostaszewski, aimed at the synthesis of depsipeptides **194**, *L*-phenylalanine methyl ester derived isocyanide **192** was reacted with differently *N*-protected valines **193** using cyclohexanone as the carbonyl component as well as solvent (Scheme 52).¹¹² The reaction itself cannot be diastereoselective as a symmetric ketone is employed, which means that only one product should be obtained in principle. The formation of two diastereoisomers is therefore a consequence of the more or less extended racemisation of the isocyanide, which is heavily dependent on the protecting group of **193**. Actually, the extent of the racemisation is negligible using trityl, phthalyl or Boc (d.r. > 99 : 1 and yield up to 99%) as protecting groups, which suggests that the irreversible Passerini reaction is faster than the racemisation ($k_1 > k_{\text{rac}}$), while the epimerization after the MCR, as well as the possible dynamic kinetic resolution occurring after the racemisation of (*S*)-**192** have been ruled out on the basis of appropriate experiments.

4.3 Future prospects

As witnessed by the relatively small number of papers on this topic, the stereochemistry issues of the Passerini reaction have not been fully solved yet. There is plenty of space to study new conditions and new combinations of catalysts/additives, and to focus on a double asymmetric induction approach. For these reasons, we think that in the future we will be able to better



Scheme 52 Effect of the racemisation of **192**, depending on the protecting group (P) of **193**.

understand the factors affecting the stereochemistry control in the Passerini reaction.

5. The use of the Passerini reaction in the total syntheses of API and natural substances

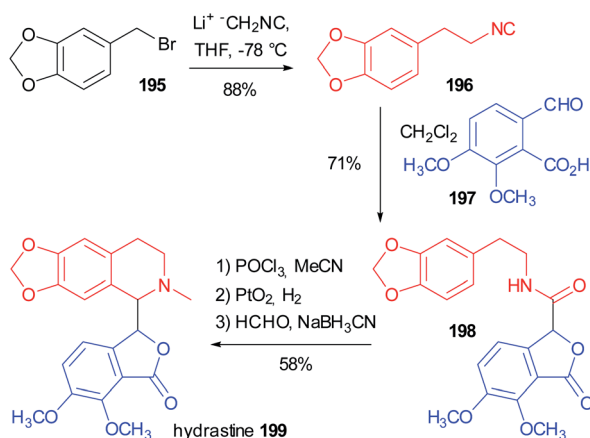
While initially the Passerini reaction, as other isocyanide-based MCRs, was considered useful only in diversity-oriented synthesis, in the last few decades several applications in target-oriented synthesis have appeared. In particular, we can find successful uses of the Passerini reaction and its modifications in the total synthesis of natural compounds and in the preparation of APIs. In this chapter, we report the most significant examples.

5.1 Use of an intramolecular Passerini reaction

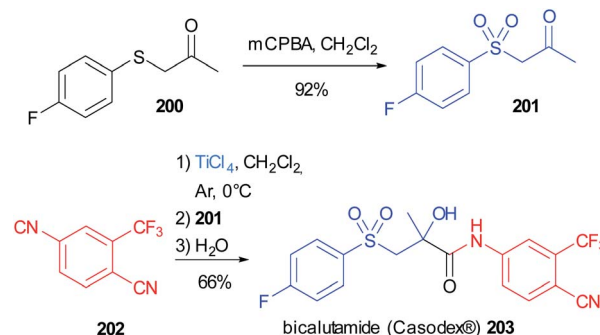
In 1981 Falck reported one of the oldest example, preparing the tetrahydroisoquinoline-based alkaloid hydrastine **199** (Scheme 53).¹¹³ The total synthesis of this compound was already published and involved a Bischler–Napieralski cyclization of **198**, followed by catalytic hydrogenation with PtO_2 of the resulting dihydroisoquinoline and a final methylation by reductive amination. The synthesis of the lactonic amide **198** was troublesome and Falck envisaged the construction of this key intermediate by an intramolecular Passerini reaction between the isocyanide **196** (achievable in one step from piperonyl bromide **195**) and opianic acid **197**. The reaction proceeds well under classical conditions and this example well highlights the power of multicomponent reactions.

5.2 Use of a modified Passerini reaction

The α -hydroxy amide framework is a recurrent motif in biologically active molecules and this important moiety can be obtained in a convergent fashion employing a “truncated” Passerini reaction.



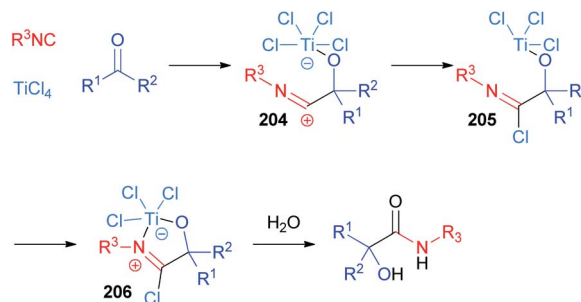
Scheme 53 Synthesis of hydrastine **199** by an intramolecular Passerini reaction.



Scheme 54 Synthesis of bicalutamide **203** through a modified Passerini reaction.

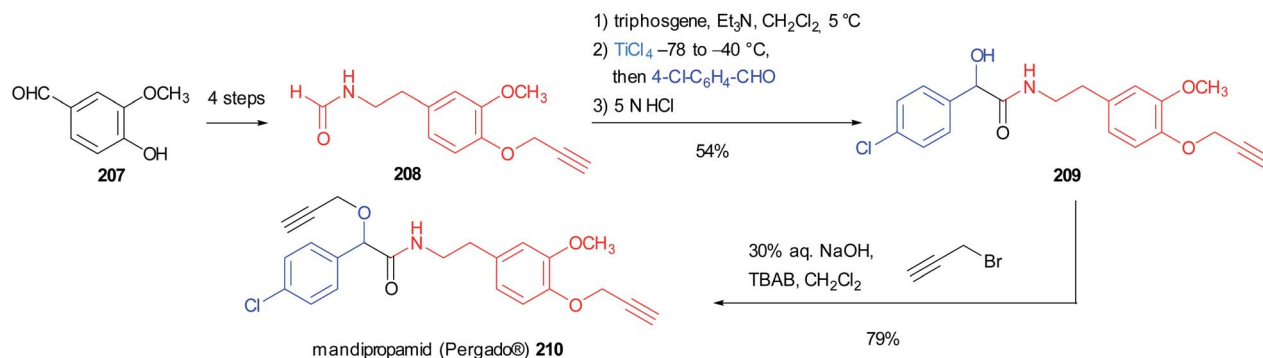
This strategy has been applied to the synthesis of bicalutamide (Casodex®) **203**, an antiandrogen used to treat prostate cancer, which can be conveniently obtained in two steps, starting from commercially available reagents, employing a Passerini reaction assisted by TiCl_4 , as a key step (Scheme 54).¹¹⁴ The thioether group of the commercially available ketone **200** is oxidized to the sulfone **201**, and, together with the isocyanide **202**, was subjected to this modified version of the Passerini reaction, leading directly to α -hydroxy amides, without the need for an additional hydrolysis step. Bicalutamide was obtained with a yield of 66% and a purity >99% after recrystallization.

The use of TiCl_4 as a Lewis acid in the Passerini reaction was first reported by Seebach in 1983 (ref. 115 and 116) and ten years later Floriani definitively clarified the mechanism, thanks to X-ray diffraction studies.¹¹⁷ Although the original hypothesis involved the insertion of the isocyanide into the Ti–Cl bond, nowadays the accepted mechanism proceeds through the initial coordination of the ketone, thanks to the oxophilic nature of titanium(IV). Then, the nucleophilic attack of the isocyanide, to give adduct **204**, is followed by the transfer of a chlorine atom from titanium to carbon (**205**) and the free coordination site is then filled by the nitrogen atom (**206**) (Scheme 55). This reactive imidoyl chloride intermediate **206** is prone to hydrolyse leading to α -hydroxyamide. Therefore, the role of TiCl_4 is to enhance the electrophilicity of the carbonyl group and to bring together the two components of the reaction.



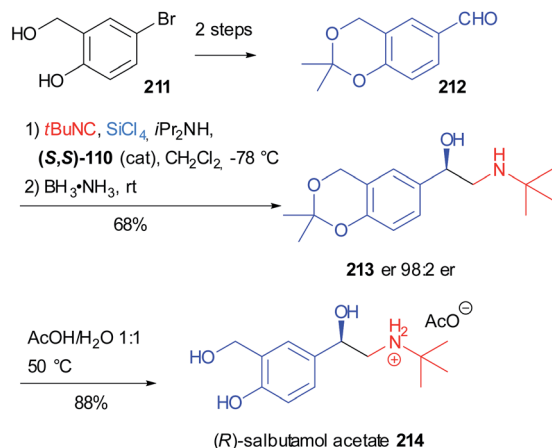
Scheme 55 Mechanism of the TiCl_4 mediated Passerini reaction.



Scheme 56 Synthesis of mandipropamid **210** through a modified Passerini reaction.

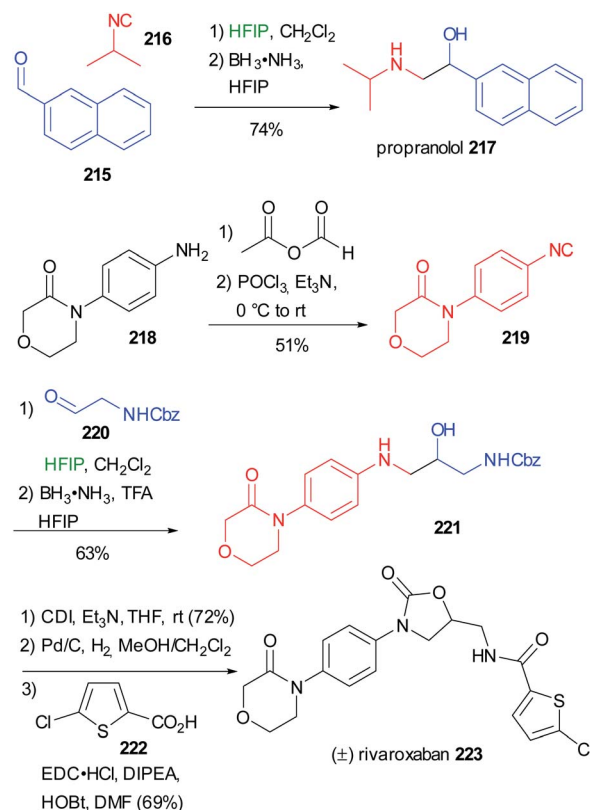
Seebach's Passerini variation was also applied in the synthesis of mandipropamid (Pergado®) **210**, a potent fungicide used to protect crops from downy mildew. The isocyanide precursor **208** could be easily obtained in 4 steps from vanillin **207** through a Henry reaction followed by reduction, formylation and propargylation. It is noteworthy that in this case the isocyanide was not isolated, but the formamide was directly subjected to the one-pot isocyanide formation/modified Passerini reaction, leading to α -hydroxyamide **209** in good yield. The final propargylation of the mandelic acid moiety afforded the marketed agrochemical mandipropamid (Scheme 56).¹¹⁸

Salbutamol (Ventolin®) **214**, also known as albuterol, is one of the most notorious β_2 adrenergic receptor agonists and it is used to treat asthma. In 2020 Virieux, Ayad reported the asymmetric synthesis of the biologically active (*R*) enantiomer of this β -amino alcohol on a gram-scale (Scheme 57)¹¹⁹ exploiting the work of Orru on the two-step one-pot synthesis of *N*-substituted- β -amino alcohol.¹²⁰ This reductive Passerini-type process involves the variation of the asymmetric "truncated" Passerini reaction developed by Denmark,⁷⁴ in which the α -tri-chlorosilyloxy imidoyl chloride intermediate **108** (see Scheme 33, Section 4.1) is reduced *in situ* by an ammonia borane complex.

Scheme 57 Synthesis of (*R*)-salbutamol acetate **214** through a two step one-pot reductive Passerini-type reaction.

The aldehyde **212** could be easily obtained from commercially available 5-bromo-2-hydroxybenzyl alcohol **211** in two steps: isopropylidene acetal protection and formylation *via* bromo/lithium-exchange. The key β -amino alcohol **213** was obtained in good yield and the excellent enantiomeric ratio is due to the attack of the isocyanide on the *Si* face of the aldehyde, thanks to the induction given by the (*S,S*) enantiomer of the chiral bisphosphoramidate Lewis base. The final acetal removal furnished salbutamol **214** as an acetate salt.

Applying the synthesis of β -amino alcohols through the modified Passerini reaction discussed on chapter 3 (Scheme 29), Ruijter reported the preparation of propranolol **217** and

Scheme 58 Synthesis of propranolol **217** and (±)-rivaroxaban **223** through a two step one-pot reductive Passerini-type reaction.

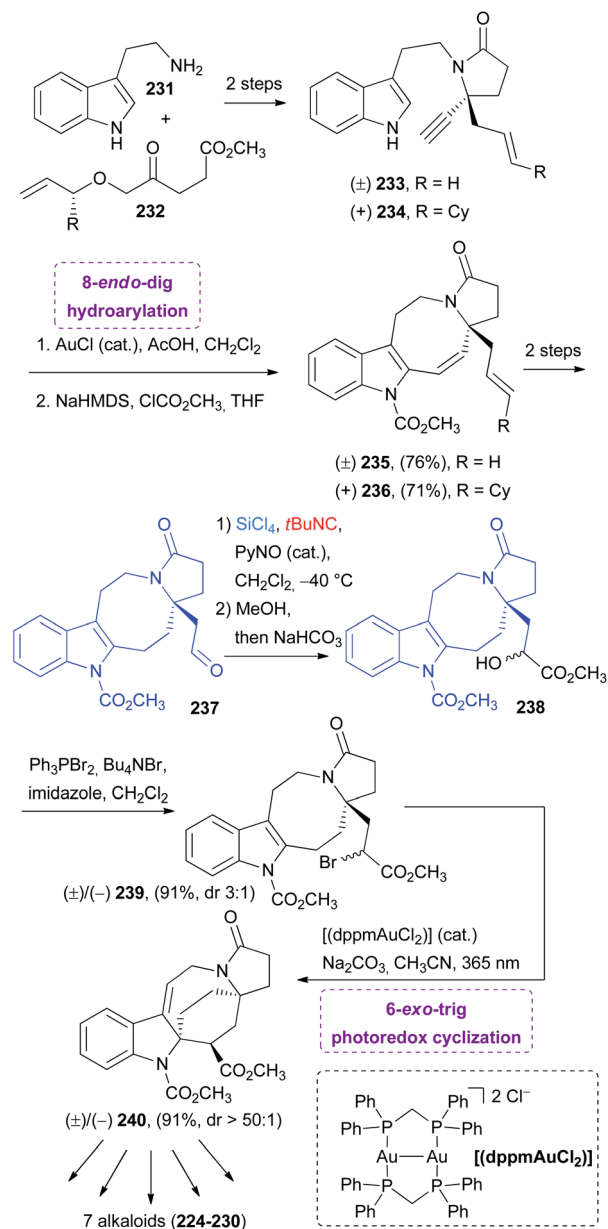
rivaroxaban **223** (Scheme 58).⁶⁶ Starting from (1-naphthyloxy) acetaldehyde **215** and isopropylisocyanide **216**, propranolol can be obtained in one step with excellent yield. The preparation of Rivaroxaban started from the commercially available aniline **218**, which was efficiently transformed into the isocyanide **219** in 2 steps. The reductive Passerini-type reaction of **219** and the Cbz protected aminoacetaldehyde **220** afforded the desired amino alcohol **221** in good yield.

In this case, an excess of trifluoroacetic acid was necessary to activate the imidate toward the reduction, given its lower basicity derived from the use of an aromatic isocyanide. Finally, **221** could be converted into rivaroxaban in three steps involving the formation of a cyclic carbamate with 1,1'-carbonyldiimidazole (CDI), the deprotection of Cbz and the ultimate coupling with 5-chlorothiophene-2-carboxylic acid **222**.

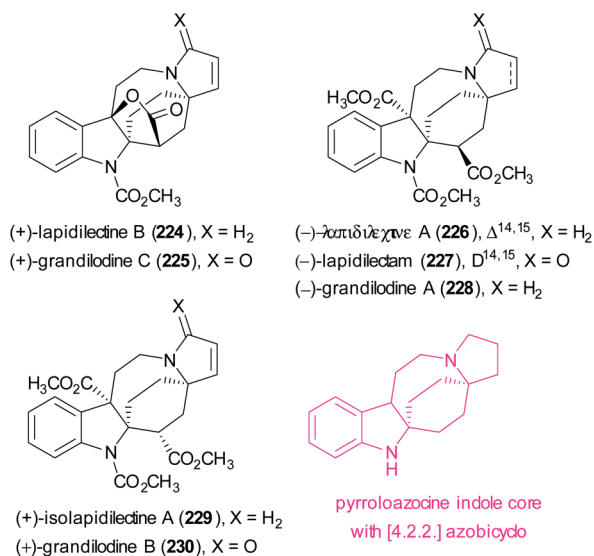
Recently, Echavarren reported the racemic and stereo-selective total synthesis of seven members of the lapidilectine and grandilodine family (**224–230**) (Scheme 59).¹²¹ These natural molecules are indole-based alkaloids and preliminary studies on their biological activity showed their ability to reverse multidrug resistance in vincristine-resistant cancer cells.¹²² These alkaloids have a common pyrroloazocine indole core in which the central 8-membered ring is embedded in a rigid [4.2.2]azabicyclic structure.

The pyrroloazocine indole skeleton was built *via* a gold-catalyzed 8-*endo-dig* hydroarylation, while the azabicyclo was created by a radical 6-*exo-trig* photoredox cyclization, where the catalyst was again an Au complex ([([dppm]AuCl₂), dppm = bis(diphenylphosphanyl)methane) (Scheme 60).

The alkynes **233** and **234** were prepared in two steps starting from tryptamine **231** and the oxoester **232**, with an excellent transfer of chirality in the case of **234**. These alkynes were subjected to gold catalysed hydroarylation, which proceeds with excellent 8-*endo* selectivity (>50 : 1 *endo/exo*) and high yield, and then the methylcarbamate moiety was installed. Compounds **235/236** were converted in two steps into the aldehyde **237** by



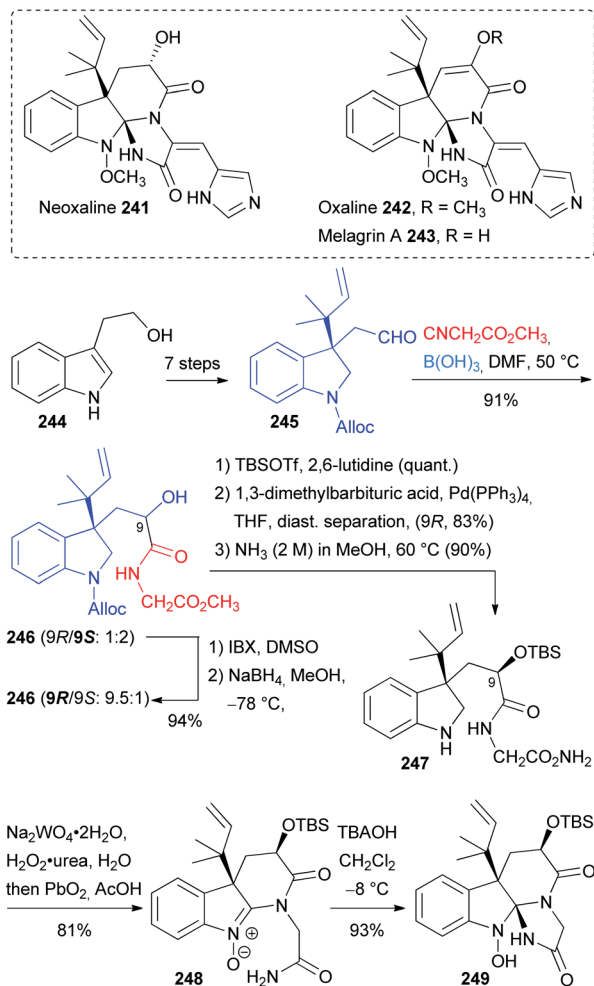
Scheme 60 Synthesis of the key intermediate **240** via hydroarylation "truncated" Passerini and photoredox cyclization.



Scheme 59 Structure of lapidilectine and grandilodine alkaloids.

the oxidative cleavage of the exocyclic double bond by OsO₄/NaIO₄ and hydrogenation of the endocyclic double bond. The substrate necessary for this second key transformation is the α -bromo ester **239**, which in turn could be easily prepared by an Appel reaction from alcohol **238**.

To install the key α -hydroxy methyl ester group, the authors sought a transformation with excellent functional group tolerance, having the labile methyl carbamate moiety, and the Passerini-type reaction reported by Denmark⁷⁴ was again selected. Here, the α -trichlorosilyloxy imidoyle chloride intermediate was treated with MeOH and the subsequent basic hydrolysis of the imino ether afforded the α -hydroxy ester. Thus, the nitrogen substituent of the isocyanide was not retained. In this case, the stereocontrol was not a goal because the



Scheme 61 Synthesis of the key intermediate **249** via "truncated" Passerini and oxidations/cyclizations.

photoredox cyclization proceeds through a radical intermediate; therefore an achiral Lewis base, such as pyridine *N*-oxide, was employed. Compound **240** is a common intermediate in the preparation of the natural alkaloids **224–230**.

Neoxaline **241**, oxaline **242** and melagrin A **243** are indole alkaloids containing a unique indoline spiroaminal framework and possess anti-cancer activity (Scheme 61). Their asymmetric total synthesis was reported by Ōmura and Sunazuka^{123,124} starting from tryptophol **244**. The enantiopure aldehyde **245** was prepared in seven steps and then employed in a "truncated" Passerini reaction with methyl isocyanoacetate in the presence of boric acid affording the α -hydroxyamide **246**, which bears suitable functional groups for the construction of the indoline spiroaminal skeleton. The authors screened many conditions and eventually they found that boric acid was the best reagent to mediate the α -addition of methyl isocyanoacetate to the aldehyde **245**.¹²⁵ The induction given by the chiral aldehyde was poor; in fact the diastereomeric ratio was only 1 : 2 in favour of desired isomer (9*S*)-**246**. Unfortunately, the (9*S*)-isomer was proved unable to give the spiroaminal framework; therefore, the authors tried to reverse the d.r., confident that the stereocentre

C9 could be epimerized later in the synthesis. Through oxidation and reduction by IBX and NaBH₄ at low temperature, the d.r. was reversed in favour of the other diastereoisomer (9*R*)-**246**. The two diastereoisomers could be separated by chromatography after the protection of the alcohol and deprotection of the carbamate.

The final conversion of the ester in the primary amide furnished **247**, which is the substrate for the oxidation/cyclization strategy that produces the spiroaminal framework in two steps. This transformation proceeds through the initial oxidation of the indoline **247** to the nitrone thanks to sodium tungstate, and then PbO₂ and AcOH mediated the cyclization to the diaminal intermediate and its further oxidation to nitrone **248**. Finally, treatment with tetrabutylammonium hydroxide (TBAOH) provided the desired indoline spiroaminal **249**, which is a common intermediate for the preparation of natural alkaloids **241–243**.

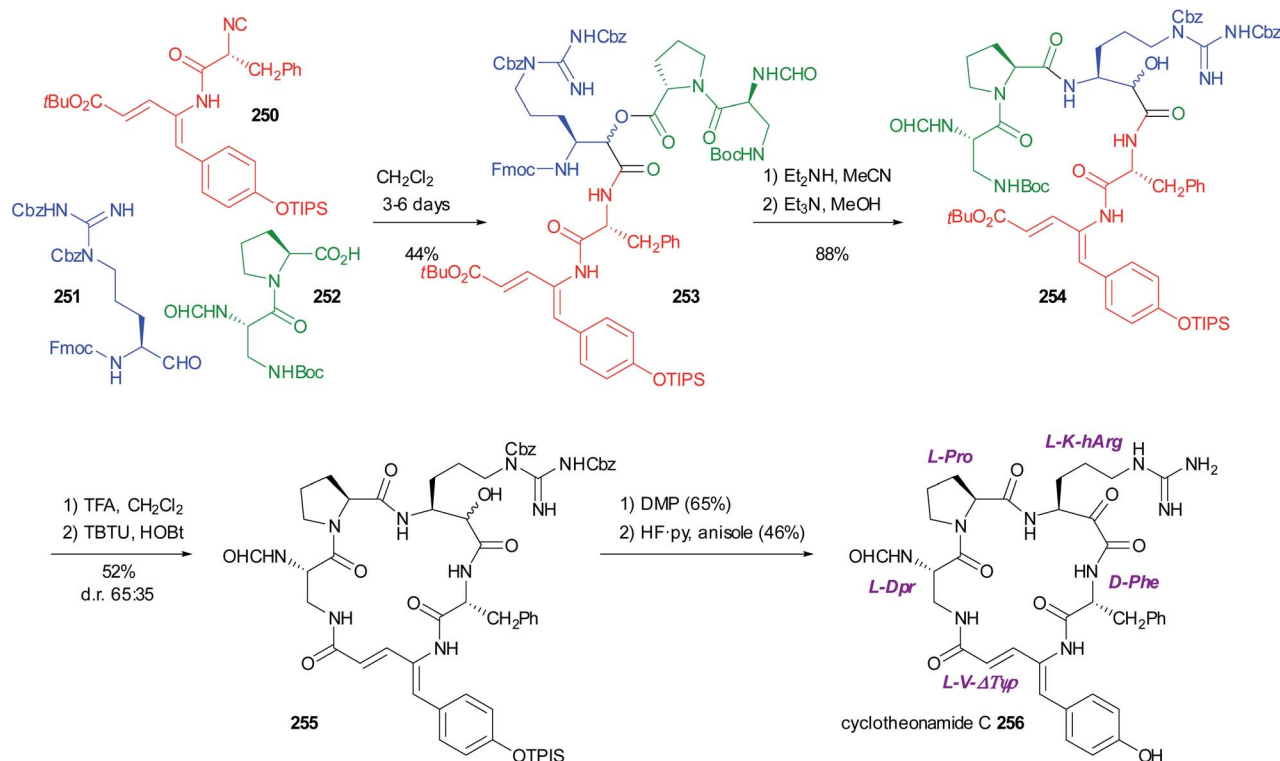
5.3 Use of the PADAM approach

The β -acylamino- α -ketoamide scaffold is present in many natural and synthetic protease inhibitors and can be obtained through the PADAM strategy followed by oxidation (as described in Section 2.2). This approach has been applied to the total synthesis of eurystatin A³⁸ (cf. Scheme 13) and cyclotheonamide C,¹²⁶ two potent inhibitors of serine proteases.

Cyclotheonamide C **256** is a 19-membered pentapeptide containing the unusual amino acids vinylogous *L*-dehydrotyrosine (*L*-V- Δ Tr), *D*-phenylalanine, *L*- α -keto- β -homoarginine (*L*-K-hArg) and *L*-diamminopropanoic acid (*L*-Dpr) that links *L*-proline and V- Δ Tyr residues (Scheme 62). The retrosynthetic approach envisaged by Aitken is highly convergent; in fact cyclotheonamide C is obtained in only four steps after the PADAM protocol. The preparation of the aldehyde **251** and the carboxylic acid **252** was already accomplished by the same authors during previous efforts on the total synthesis of **256**.¹²⁷ The isocyanide **250** was obtained without racemisation by classical *N*-formylation/dehydration with POCl₃, starting from the parent primary amine, the synthesis of which was already reported.¹²⁷ These three components were subjected to the Passerini reaction and the desired product **253** was obtained with respectable yield. It is noteworthy that the reaction does not proceed when the Fmoc protecting group is installed on the acid and the Boc is on the aldehyde. Selective Fmoc deprotection and *O*- to *N*-acyl migration, induced by the addition of Et₃N, provided the key linear pentapeptide **254** in 88% yield. Simultaneous N/C termini deprotection under acidic conditions is followed by macrocyclization mediated by a coupling agent. The late-stage oxidation of **255** with Dess-Martin Periodinane (DMP) and the complete deprotection of the phenol and guanidine moieties with HF·pyridine in the presence of anisole furnished cyclotheonamide C as a single stereoisomer.

Tubulysins are unusual peptides mainly composed of isoleucine (Ile) and non-proteinogenic amino acids, such as *D*-*N*-methyl pipecolic acid (Mep), tubuvaline (Tuv) and tubuphenylalanine (Tup). Recently, Dömling reported the highly convergent total synthesis of *N*¹⁴-desacetoxytubulysin H **263**



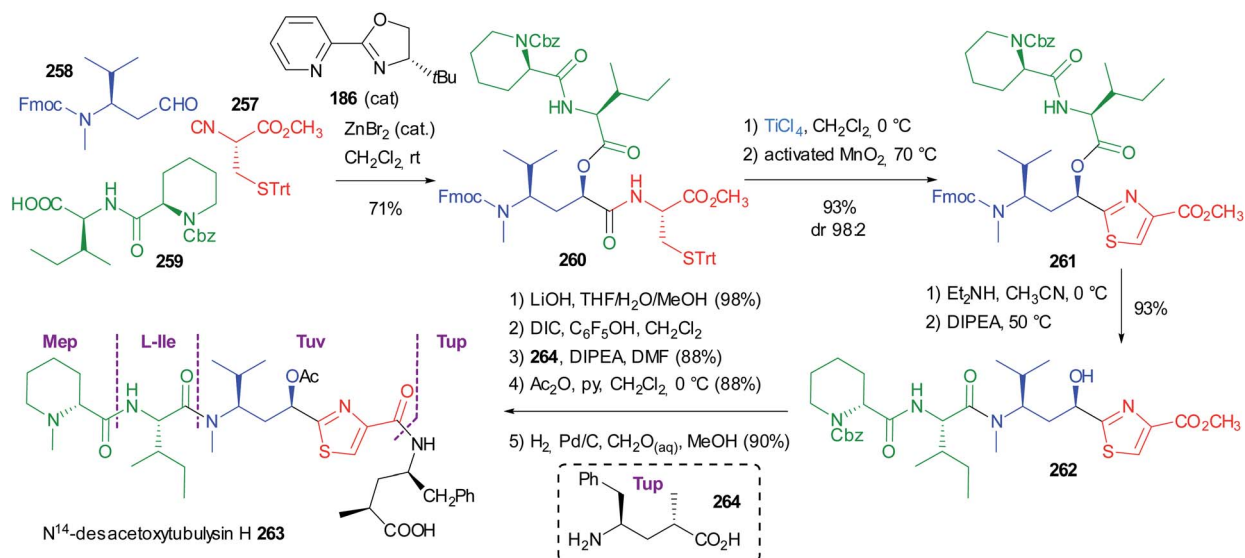


Scheme 62 Total synthesis of cyclotheonamide C 256 via the PADAM/oxidation strategy.

employing a diastereoselective Passerini reaction applied in the PADAM protocol (Scheme 63).¹⁰⁷ The three components needed in the MCR could be prepared on a multi-gram scale from commercially available amino acids. The isocyanide 257 was prepared in three steps from L-cysteine methyl ester by trityl protection and the classical formamide/dehydration protocol; the aldehyde 258 derived from Fmoc L-valine by the Arndt-Eistert homologation reaction and oxidation/reduction steps and

the acid 259 was obtained by coupling Cbz D-pipecolic acid and L-isoleucine methyl ester and final hydrolysis of the ester.

The Passerini reaction proceeded in a highly diastereoselective fashion thanks to the bulky chiral ligand 186 together with ZnBr₂ (cf. Scheme 49). Then the isocyanide residue of product 260 was converted in the peculiar 1,3-thiazole moiety of tubuvaline applying a one-pot two step method using TiCl₄-mediated deprotection-cyclodehydration, followed

Scheme 63 Total synthesis of N¹⁴-desacetytubulysin H 263 via the diastereoselective PADAM strategy.

by MnO_2 oxidation of the resulting thiazoline to afford **261** in excellent yield without racemisation.¹²⁸ Basic conditions promoted Fmoc deprotection and *O*- to *N*-acyl migration ending the PADAM process. The α -hydroxy peptide **262** was converted into the desired product in five trivial steps. The methyl ester of the tubuvaline residue was hydrolysed and coupled with tub-phenylalanine (Tup) **264** *via* the activation of the acid as pentafluorophenyl ester. Finally, the acetylation of the secondary alcohol and a late-stage *N*-methylation, accomplished by catalytic hydrogenation in the presence of formaldehyde, afford **263** in good yield.

To date, the total synthesis of cyclotheonamide **C 256** and N^{14} -desacetoxytubulysin **H 263** has been the most elaborate application of the PADAM strategy. In 2015, we reported a new efficient synthesis of telaprevir **273**, a specific viral serine protease inhibitor, approved by the FDA in 2011 for the treatment of hepatitis C.⁴⁴

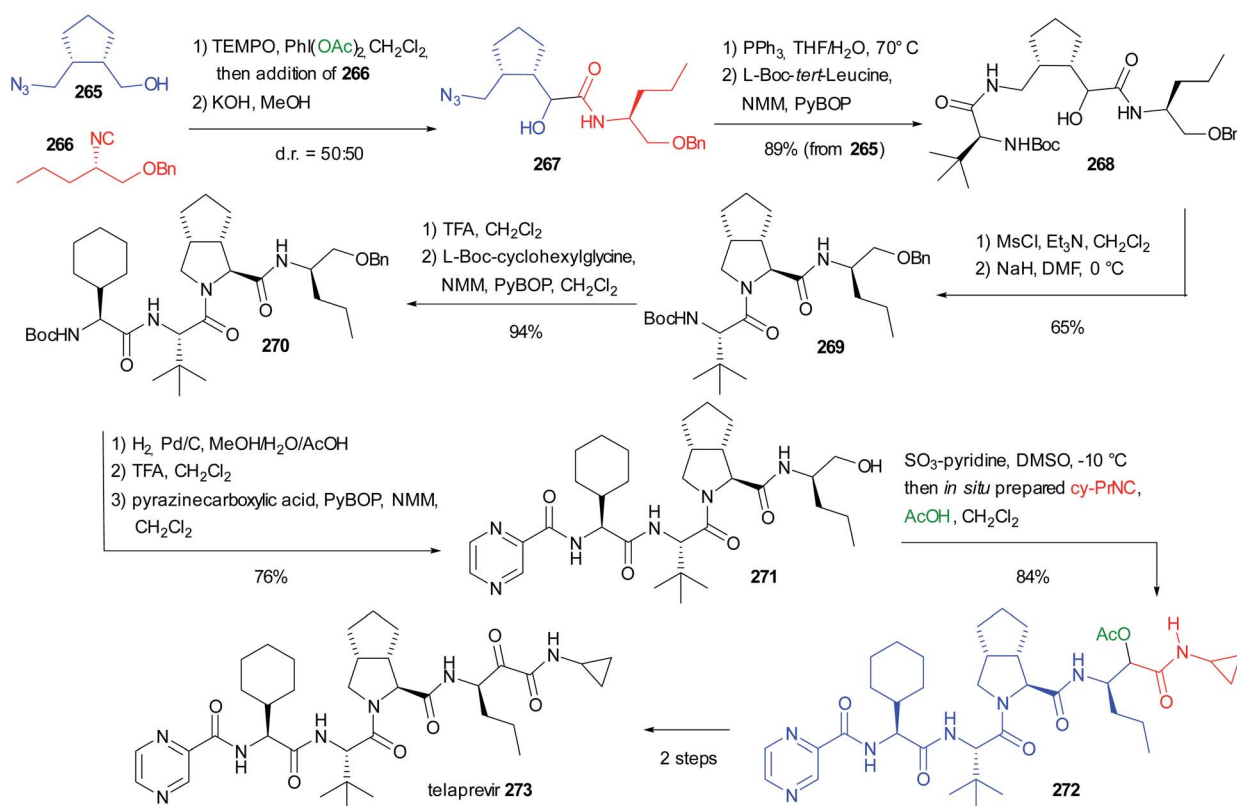
Since in this case, the bis-homo-PADAM approach using γ -azidoaldehyde **76** failed (see Scheme 17), we synthesized the key intermediate **269** exploring an alternative route (Scheme 64). The oxidation of enantiopure azidoalcohol **265** with stoichiometric iodosobenzene diacetate and catalytic TEMPO radical (2,2,6,6-tetramethyl-1-piperidinyloxy) generated the aldehyde **76** and acetic acid as a by-product, which reacted in a Passerini reaction after the addition of chiral isocyanide **266**. The basic treatment of the crude gave alcohol **267** as a 1 : 1 mixture of diastereoisomers. Compound **268** was obtained with remarkable yield after azide reduction and coupling with *L*-Boc-*tert*-

glycine. The lack of diastereoselection was compensated for by the stereoconvergent cyclization performed directly on the mixture, obtaining pyrrolidine **269** as a single diastereoisomer. This product was finally converted into intermediate **270** and, finally, to alcohol **271**, by sequential deprotection and acylation. Finally, a second Passerini reaction was employed to convert **271** into α -acetoxyamide **272** and telaprevir **273** in further 2 steps.

Furthermore, compound **272** represents an advanced intermediate in another total synthesis of telaprevir, reported by Ruijter.¹²⁹ This efficient and convergent approach exploits an Ugi-Joullie three component reaction between chiral cyclic imine **277**, obtained by enzymatic desymmetrization of the commercially available octahydrocyclopenta[*c*]pyrrole, carboxylic acid **278** and the chiral isocyanide **276**, prepared through a Passerini reaction (Scheme 65). *N*-Formylation of commercially available (*S*)-2-amino-1-pentanol furnished alcohol **274**, which was subjected to the one-pot oxidation/Passerini reaction procedure to give formamide **275** in acceptable yield. This protocol avoids the difficult isolation of the aldehyde, which easily dimerized producing a low yield in the Passerini reaction. Dehydration under standard conditions afforded isocyanide **276** without any racemisation.

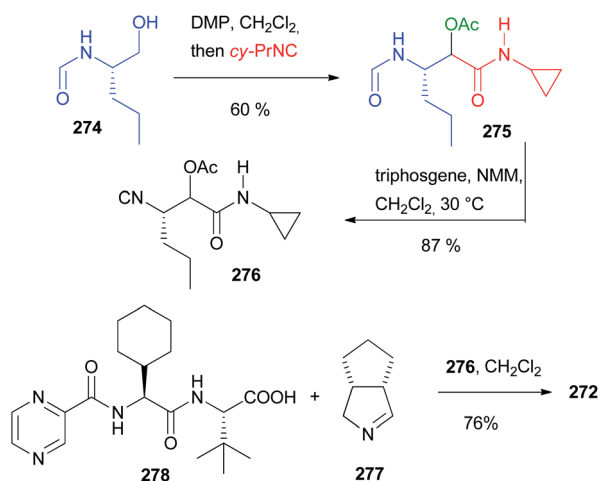
5.4 Future prospects

As highlighted in the Introduction, the esters are rarely found in natural compounds and active pharmaceutical ingredients.



Scheme 64 Total synthesis of telaprevir **273** *via* the Passerini reaction and stereoconvergent cyclization.





Scheme 65 Synthesis of isocyanide **276** via the Passerini reaction and its use for the synthesis of **272** via the Ugi-Joullie three component reaction.

Therefore, the “classical” Passerini reaction is seldom employed in this field. However, its modifications have been successfully applied in the synthesis of important bioactive compounds. Up to now, the most fruitful examples involved the well-studied “truncated” Passerini and the PADAM strategy; however we believe that the more recent modifications developed by the Single Reactant Replacement approach can find future applications in the area of total synthesis.

6. Conclusions

In this review, we have tried to highlight the several facets revealed by this centennial reaction in recent years. Thanks to the brilliant work of many researchers around the world, a reaction that was nearly neglected for many years has now eventually entered the Olympus of the most useful methodologies in organic synthesis. It is a great pity that Mario Passerini has not been able to witness all these advancements and to celebrate with us this anniversary or maybe he is.

Author contributions

Luca Banfi: conceptualization, visualization, writing – original draft, and writing – review & editing. Andrea Basso: conceptualization, visualization, writing – original draft, and writing – review & editing. Chiara Lambruschini: visualization, writing – original draft, and writing – review & editing. Lisa Moni: visualization, writing – original draft, and writing – review & editing. Renata Riva: conceptualization, visualization, writing – original draft, and writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This perspective is dedicated to Prof. Giuseppe Guanti, who was the first to prompt us to engage in research concerning the Passerini reaction.

Notes and references

- 1 M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 126–129.
- 2 L. Kürti and B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Academic Press, 2005.
- 3 R. Riva, L. Banfi and A. Basso, in *Science of Synthesis: Multicomponent Reactions*, ed. T. J. J. Müller, Thieme, 2014, vol. 1, pp. 327–414.
- 4 S. Maeda, S. Komagawa, M. Uchiyama and K. Morokuma, *Angew. Chem., Int. Ed.*, 2011, **50**, 644–649.
- 5 R. H. Baker and D. Stanonis, *J. Am. Chem. Soc.*, 1951, **73**, 699–702.
- 6 A. Basso, L. Banfi, A. Galatini, G. Guanti, F. Rastrelli and R. Riva, *Org. Lett.*, 2009, **11**, 4068–4071.
- 7 M. Spallarossa, L. Banfi, A. Basso, L. Moni and R. Riva, *Adv. Synth. Catal.*, 2016, **358**, 2940–2948.
- 8 L. Banfi and R. Riva, in *Organic Reactions*, 2005, pp. 1–140.
- 9 L. Banfi, A. Basso and R. Riva, in *Synthesis of Heterocycles Via Multicomponent Reactions I*, ed. R. V. A. Orru and E. Ruijter, 2010, vol. 23, pp. 1–39.
- 10 S. Marcaccini and T. Torroba, in *Multicomponent Reactions*, 2005, pp. 33–75.
- 11 S. Sebt and A. Foucaud, *Synthesis*, 1983, **1983**, 546–549.
- 12 R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 1991, 1107–1108.
- 13 F. De Moliner, S. Crosignani, L. Banfi, R. Riva and A. Basso, *J. Comb. Chem.*, 2010, **12**, 613–616.
- 14 L. Moni, L. Banfi, R. Riva and A. Basso, *Synthesis*, 2016, **48**, 4050–4059.
- 15 J. Wu, J.-C. Liu, L. Wang and M.-W. Ding, *Synlett*, 2011, 2880–2882.
- 16 N. Liu, F. Chao, M. G. Liu, N. Y. Huang, K. Zou and L. Wang, *J. Org. Chem.*, 2019, **84**, 2366–2371.
- 17 P. He, J. Wu, Y. B. Nie and M. W. Ding, *Tetrahedron*, 2009, **65**, 8563–8570.
- 18 L. Banfi, A. Basso, C. Lambruschini, L. Moni and R. Riva, *Chem. Heterocycl. Compd.*, 2017, **53**, 382–408.
- 19 R. Bossio, S. Marcaccini, R. Pepino and T. Torroba, *Synthesis*, 1993, 783–785.
- 20 R. Bossio, S. Marcaccini and R. Pepino, *Liebigs Ann. Chem.*, 1994, 527–528.
- 21 S. Marcaccini, R. Pepino, C. F. Marcos, C. Polo and T. Torroba, *J. Heterocycl. Chem.*, 2000, **37**, 1501–1503.
- 22 B. Beck, M. Magnin-Lachaux, E. Herdtweck and A. Dömling, *Org. Lett.*, 2001, **3**, 2875–2878.
- 23 J. Rossbach, K. Harms and U. Koert, *Eur. J. Org. Chem.*, 2014, **2014**, 993–1006.
- 24 N. A. M. Yehia, W. Antuch, B. Beck, S. Hess, V. Schauer Vukasinovic, M. Almstetter, P. Furer, E. Herdtweck and A. Dömling, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3121–3125.



- 25 G.-H. Ma, B. Jiang, X.-J. Tu, Y. Ning, S.-J. Tu and G. Li, *Org. Lett.*, 2014, **16**, 4504–4507.
- 26 D. L. Wright, C. V. Robotham and K. Aboud, *Tetrahedron Lett.*, 2002, **43**, 943–946.
- 27 R. Huisgen, *Proc. Chem. Soc.*, 1961, 357–396.
- 28 F. De Moliner, S. Crosignani, A. Galatini, R. Riva and A. Basso, *ACS Comb. Sci.*, 2011, **13**, 453–457.
- 29 F. De Moliner, M. Bigatti, C. De Rosa, L. Banfi, R. Riva and A. Basso, *Mol. Divers.*, 2014, **18**, 473–482.
- 30 B. Beck, G. Larbig, B. Mejat, M. Magnin Lachaux, A. Picard, E. Herdtweck and A. Dömling, *Org. Lett.*, 2003, **5**, 1047–1050.
- 31 A. Schwaebelin and J. Martens, *Eur. J. Org. Chem.*, 2011, **2011**, 4335–4344.
- 32 L. Banfi, G. Guanti and R. Riva, *Chem. Commun.*, 2000, 985–986.
- 33 C. Hulme, M. M. Morrisette, F. A. Volz and C. J. Burns, *Tetrahedron Lett.*, 1998, **39**, 1113–1116.
- 34 L. Banfi, A. Basso, G. Guanti and R. Riva, *Mol. Divers.*, 2003, **6**, 227–235.
- 35 M. Zimuwandeyi, F. Kola, A. Lemmerer, D. Brady, A. L. Rousseau and M. L. Bode, *Tetrahedron*, 2018, **74**, 2925–2941.
- 36 A. Basso, L. Banfi, R. Riva, P. Piaggio and G. Guanti, *Tetrahedron Lett.*, 2003, **44**, 2367–2370.
- 37 L. Banfi, G. Guanti, R. Riva, A. Basso and E. Calcagno, *Tetrahedron Lett.*, 2002, **43**, 4067–4069.
- 38 T. D. Owens, G.-A. Araldi, R. F. Nutt and J. E. Semple, *Tetrahedron Lett.*, 2001, **42**, 6271–6274.
- 39 D. Gravestock, A. L. Rousseau, A. C. U. Lourens, H. C. Hoppe, L. A. Nkabinde and M. L. Bode, *Tetrahedron Lett.*, 2012, **53**, 3225–3229.
- 40 A. Y. Shaw, F. Medda and C. Hulme, *Tetrahedron Lett.*, 2012, **53**, 1313–1315.
- 41 A. Basso, L. Banfi, G. Guanti, R. Riva and P. Tosatti, *Synlett*, 2011, 2009–2012.
- 42 F. Morana, A. Basso, R. Riva, V. Rocca and L. Banfi, *Chem. – Eur. J.*, 2013, **19**, 4563–4569.
- 43 J. W. Yang, M. Stadler and B. List, *Angew. Chem., Int. Ed.*, 2007, **46**, 609–611.
- 44 L. Moni, L. Banfi, A. Basso, L. Carcone, M. Rasparini and R. Riva, *J. Org. Chem.*, 2015, **80**, 3411–3428.
- 45 B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463–472.
- 46 Y. Y. Shen, B. Huang, L. W. Zeng and S. L. Cui, *Org. Lett.*, 2017, **19**, 4616–4619.
- 47 X. Li and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2008, **130**, 5446–5448.
- 48 G. O. Jones, X. Li, A. E. Hayden, K. N. Houk and S. J. Danishefsky, *Org. Lett.*, 2008, **10**, 4093–4096.
- 49 A. Basso, L. Banfi, S. Garbarino and R. Riva, *Angew. Chem., Int. Ed.*, 2013, **52**, 2096–2099.
- 50 S. Garbarino, D. Ravelli, S. Protti and A. Basso, *Angew. Chem., Int. Ed.*, 2016, **55**, 15476–15484.
- 51 <https://www.elsevier.com/solutions/reaxys/who-we-serve/reactionflash>.
- 52 S. Garbarino, L. Banfi, R. Riva and A. Basso, *J. Org. Chem.*, 2014, **79**, 3615–3622.
- 53 S. Garbarino, S. Protti and A. Basso, *Synthesis*, 2015, **47**, 2385–2390.
- 54 P. Capurro, C. Lambruschini, P. Lova, L. Moni and A. Basso, *J. Org. Chem.*, 2021, **86**, 5845–5851.
- 55 A. Basso, L. Banfi and R. Riva, *Molecules*, 2011, **16**, 8775–8787.
- 56 T. Soeta, Y. Kojima, Y. Ukaji and K. Inomata, *Org. Lett.*, 2010, **12**, 4341–4343.
- 57 F. Ibba, P. Capurro, S. Garbarino, M. Anselmo, L. Moni and A. Basso, *Org. Lett.*, 2018, **20**, 1098–1101.
- 58 M. Anselmo, A. Basso, S. Protti and D. Ravelli, *ACS Catal.*, 2019, **9**, 2493–2500.
- 59 E. Bergamaschi, P. Capurro, C. Lambruschini, R. Riva and A. Basso, *Eur. J. Org. Chem.*, 2019, **2019**, 5992–5997.
- 60 P. Capurro, E. Bergamaschi, A. Basso and L. Moni, *Chem. Heterocycl. Compd.*, 2020, **56**, 467–472.
- 61 L. El Kaim, M. Gizolme and L. Grimaud, *Org. Lett.*, 2006, **8**, 5021–5023.
- 62 E. Martinand-Lurin, A. Dos Santos, E. Robineau, P. Retailleau, P. Dauban, L. Grimaud and L. El Kaim, *Molecules*, 2016, **21**, 14.
- 63 A. G. Neo and C. F. Marcos, *Org. Lett.*, 2018, **20**, 3875–3878.
- 64 H. Yanai, T. Oguchi and T. Taguchi, *J. Org. Chem.*, 2009, **74**, 3927–3929.
- 65 F. De Moliner, M. Bigatti, L. Banfi, R. Riva and A. Basso, *Org. Lett.*, 2014, **16**, 2280–2283.
- 66 J. M. Saya, R. Berabez, P. Broersen, I. Schuringa, A. Kruithof, R. V. A. Orru and E. Ruijter, *Org. Lett.*, 2018, **20**, 3988–3991.
- 67 K. N. Onwukamike, S. Grelier, E. Grau, H. Cramail and M. A. R. Meier, *RSC Adv.*, 2018, **8**, 31490–31495.
- 68 I. Ugi and R. Meyr, *Chem. Ber.*, 1961, **94**, 2229–2233.
- 69 T. Nixey and C. Hulme, *Tetrahedron Lett.*, 2002, **43**, 6833–6835.
- 70 Z. L. Ren, J. C. Liu and M. W. Ding, *Synthesis*, 2017, **49**, 745–754.
- 71 Q. X. Feng, Z. Y. Mu, G. Yao, J. A. Zhang, H. T. He, Y. L. Pang and J. Xiong, *Synlett*, 2020, **31**, 1003–1006.
- 72 K. M. Allan, C. D. Gilmore and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2011, **50**, 4488–4491.
- 73 Q. Wang, D. X. Wang, M. X. Wang and J. P. Zhu, *Acc. Chem. Res.*, 2018, **51**, 1290–1300.
- 74 S. E. Denmark and Y. Fan, *J. Am. Chem. Soc.*, 2003, **125**, 7825–7827.
- 75 U. Kusebauch, B. Beck, K. Messer, E. Herdtweck and A. Dömling, *Org. Lett.*, 2003, **5**, 4021–4024.
- 76 P. R. Andreana, C. C. Liu and S. L. Schreiber, *Org. Lett.*, 2004, **6**, 4231–4233.
- 77 S. X. Wang, M. X. Wang, D. X. Wang and J. P. Zhu, *Angew. Chem., Int. Ed.*, 2008, **47**, 388–391.
- 78 J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu and B. Tan, *J. Am. Chem. Soc.*, 2015, **137**, 14039–14042.
- 79 S. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Eur. J. Org. Chem.*, 2007, **2007**, 4076–4080.
- 80 S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Org. Lett.*, 2007, **9**, 3615–3618.
- 81 T. Yue, M.-X. Wang, D.-X. Wang, G. Masson and J. Zhu, *J. Org. Chem.*, 2009, **74**, 8396–8399.



- 82 X. Zeng, K. Ye, M. Lu, P. J. Chua, B. Tan and G. Zhong, *Org. Lett.*, 2010, **12**, 2414–2417.
- 83 H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 8384–8385.
- 84 T. Yue, M. X. Wang, D. X. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2008, **47**, 9454–9457.
- 85 L. Banfi, A. Basso, L. Moni and R. Riva, *Eur. J. Org. Chem.*, 2014, **2014**, 2005–2015.
- 86 C. Lambruschini, L. Moni and L. Banfi, *Eur. J. Org. Chem.*, 2020, **2020**, 3766–3778.
- 87 H. Bock and I. Ugi, *J. Prakt. Chem.*, 1997, **339**, 385–389.
- 88 S. Marcaccini, D. Miguel, T. Torroba and M. Garcia Valverde, *J. Org. Chem.*, 2003, **68**, 3315–3318.
- 89 R. C. Cioc, V. Estevez, D. J. Van der Niet, C. M. L. Vande Velde, N. G. Turrini, M. Hall, K. Faber, E. Ruijter and R. V. A. Orru, *Eur. J. Org. Chem.*, 2017, **2017**, 1262–1271.
- 90 P. Radha Krishna and K. Lopinti, *Synlett*, 2007, **2007**, 0083–0086.
- 91 D. A. Dos Santos, A. M. Deobald, V. E. Cornelio, R. M. D. Ávila, R. C. Cornea, G. C. R. Bernasconi, M. W. Paixão, P. C. Vieira and A. G. Corrêa, *Bioorg. Med. Chem. Lett.*, 2017, **25**, 4620–4627.
- 92 A. M. Deobald, A. G. Corrêa, D. G. Rivera and M. W. Paixão, *Org. Biomol. Chem.*, 2012, **10**, 7681–7684.
- 93 K. Vlahovick-Kahlina, M. Vazdar, A. Jakas, V. Smrecki and I. Jeric, *J. Org. Chem.*, 2018, **83**, 13146–13156.
- 94 R. Ramozzi and K. Morokuma, *J. Org. Chem.*, 2015, **80**, 5652–5657.
- 95 A. Jakas, A. Visnjevac and I. Jeric, *J. Org. Chem.*, 2020, **85**, 3766–3787.
- 96 G. Guanti, L. Banfi, E. Narisano, R. Riva and S. Thea, *Tetrahedron Lett.*, 1986, **27**, 4639–4642.
- 97 L. Banfi, G. Guanti and R. Riva, *Tetrahedron: Asymmetry*, 1995, **6**, 1345–1356.
- 98 L. Banfi and G. Guanti, *Eur. J. Org. Chem.*, 1998, **1998**, 745–757.
- 99 L. Moni, L. Banfi, A. Basso, E. Martino and R. Riva, *Org. Lett.*, 2016, **18**, 1638–1641.
- 100 W. R. Galloway, A. Isidro-Llobet and D. R. Spring, *Nat. Commun.*, 2010, **1**, 80.
- 101 G. Vitali Forconesi, L. Banfi, A. Basso, C. Lambruschini, L. Moni and R. Riva, *Molecules*, 2020, **25**, 3227.
- 102 L. Moni, 2021, manuscript in preparation.
- 103 L. Moni, L. Banfi, D. Cartagenova, A. Cavalli, C. Lambruschini, E. Martino, R. V. A. Orru, E. Ruijter, J. M. Saya, J. Sgrignani and R. Riva, *Org. Chem. Front.*, 2020, **7**, 380–398.
- 104 N. D. Bartolo, J. A. Read, E. M. Valentin and K. A. Woerpel, *Chem. Rev.*, 2020, **120**, 1513–1619.
- 105 L. Moni, L. Banfi, A. Basso, A. Bozzano, M. Spallarossa, L. Wessjohann and R. Riva, *Molecules*, 2016, **21**, 1153.
- 106 B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz and M. R. Torres, *Org. Biomol. Chem.*, 2015, **13**, 1387–1394.
- 107 T. M. Vishwanatha, B. Giepmans, S. K. Goda and A. Domling, *Org. Lett.*, 2020, **22**, 5396–5400.
- 108 J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk and B. Tan, *Science*, 2018, **361**, eaas8707.
- 109 T. Budragchaa, B. Westermann and L. A. Wessjohann, *Bioorg. Med. Chem.*, 2019, **27**, 3237–3247.
- 110 R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth and M. Zeller, *Synlett*, 2003, 1536–1538.
- 111 P. Radha Krishna, G. Dayaker and P. V. Narasimha Reddy, *Tetrahedron Lett.*, 2006, **47**, 5977–5980.
- 112 S. Berlozecki, W. Szymanski and R. Ostaszewski, *Tetrahedron*, 2008, **64**, 9780–9783.
- 113 J. R. Falck and S. Manna, *Tetrahedron Lett.*, 1981, **22**, 619–620.
- 114 C. Kalinski, H. Lemoine, J. Schmidt, C. Burdack, J. Kolb, M. Umkehrer and G. Ross, *Synthesis*, 2008, **2008**, 4007–4011.
- 115 M. Schiess and D. Seebach, *Helv. Chim. Acta*, 1983, **66**, 1618–1623.
- 116 D. Seebach, G. Adam, T. Gees, M. Schiess and W. Weigand, *Chem. Ber.*, 1988, **121**, 507–517.
- 117 T. Carofiglio, P. G. Cozzi, C. Floriani, A. Chiesi-Villa and C. Rizzoli, *Organometallics*, 2002, **12**, 2726–2736.
- 118 C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H. J. Kempf and R. Zeun, *Bioorg. Med. Chem.*, 2008, **16**, 1531–1545.
- 119 A. Gernet, V. Ratovelomanana-Vidal, J. L. Pirat, D. Virieux and T. Ayad, *Eur. J. Org. Chem.*, 2020, **2020**, 6497–6500.
- 120 R. C. Cioc, D. J. van der Niet, E. Janssen, E. Ruijter and R. V. Orru, *Chem.–Eur. J.*, 2015, **21**, 7808–7813.
- 121 F. M. Miloserdov, M. S. Kirillova, M. E. Muratore and A. M. Echavarren, *J. Am. Chem. Soc.*, 2018, **140**, 5393–5400.
- 122 W. S. Yap, C. Y. Gan, Y. Y. Low, Y. M. Choo, T. Etoh, M. Hayashi, K. Komiyama and T. S. Kam, *J. Nat. Prod.*, 2011, **74**, 1309–1312.
- 123 T. Ideguchi, T. Yamada, T. Shirahata, T. Hirose, A. Sugawara, Y. Kobayashi, S. Omura and T. Sunazuka, *J. Am. Chem. Soc.*, 2013, **135**, 12568–12571.
- 124 T. Yamada, T. Ideguchi-Matsushita, T. Hirose, T. Shirahata, R. Hokari, A. Ishiyama, M. Iwatsuki, A. Sugawara, Y. Kobayashi, K. Otoguro, S. Omura and T. Sunazuka, *Chem.–Eur. J.*, 2015, **21**, 11855–11864.
- 125 J. S. Kumar, S. C. Jonnalagadda and V. R. Mereddy, *Tetrahedron Lett.*, 2010, **51**, 779–782.
- 126 S. Faure, T. Hjelmgaard, S. P. Roche and D. J. Aitken, *Org. Lett.*, 2009, **11**, 1167–1170.
- 127 S. P. Roche, S. Faure, L. El Blidi and D. J. Aitken, *Eur. J. Org. Chem.*, 2008, **2008**, 5067–5078.
- 128 P. Raman, H. Razavi and J. W. Kelly, *Org. Lett.*, 2000, **2**, 3289–3292.
- 129 A. Znabet, M. M. Polak, E. Janssen, F. J. J. de Kanter, N. J. Turner, R. V. A. Orru and E. Ruijter, *Chem. Commun.*, 2010, **46**, 7918–7920.

