Recent Advances in the Stereochemical Outcome of Multicomponent Reactions Involving Convertible Isocyanides

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Abstract Multi-component reactions (MCRs) have become an integral part of organic synthesis as short and very efficient routes to molecular diversity with included varying stereochemistry. MCRs have evolved rapidly in terms of the components used in the reactions and their role on the stereo chemical outcomes. This chapter focuses on covering recent contributions towards MCRs including targeted asymmetric control. Furthermore, advances in MCRs, as reported by many researchers, covering the utility of the convertible isocyanides, stereochemical advances of the Passerini and Ugi reactions and finally, the use of carbohydrates as chiral auxiliaries are examined and discussed.

1 Introduction

Carbohydrates are naturally occurring complex chiral molecules that have significant biological significance. They have been used in the laboratory setting as chirons for the transformation into multiple functionalities such as aldehydes, acids, amines, and isocyanides as well as employed in reaction settings such as multicomponent reactions. In recent years, there has been a marked increase in utilizing carbohydrates as key components in multicomponent coupling reactions such as the Ugi, and Passerini reactions to name a few [1, 2]. In the aforementioned reactions, sugars were used as the isocyanide and amine components for understanding diastereoselective roles in the key carbon–carbon bond forming reaction. However, over a period of time the use of carbohydrates in such multicomponent reactions has diminished. In the later

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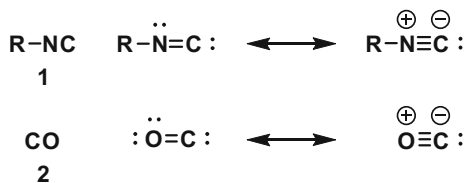OH 43606-3390, USA
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Fig. 1 General
representation of the
isocyanide and carbon
monoxide

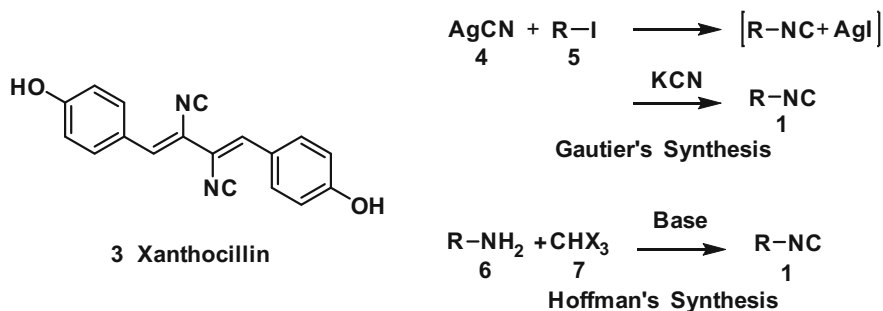R−NC   R−N=C : ⟷ R−N≡C :
1

CO   : O=C : ⟷ O≡C :
2

sections of this chapter, we attempt to discuss the role of carbohydrates in multi-component reactions as both isocyanide and amine functionalities.

An isocyanide, also known as an isonitrile or carbylamine is an organic compound characterized by the functional group $R–N\equiv C$. It is the isomer of closely related cyanide ($R–C\equiv N$), thus the prefix *iso*. Electronically, isocyanides are similar to carbon monoxide and therefore have been used to substitute carbon monoxide in organometallic transformations. Akin to carbon monoxide, the isocyanides are represented by two resonance structures, one with a triple bond between nitrogen and carbon and the other with a double bond (Fig. 1).

Isocyanides are adaptable functional groups having a divalent carbon which acts as a proton acceptor (Brønsted base). Very few compounds belong to this class of proton acceptors. Isocyanides are also stable to basic conditions but under highly acidic conditions, they tend to hydrolyze or polymerize. Some suspect that they may even undergo radical formations depending on reaction conditions [3–6].

The first reported synthesis of an isocyanide was serendipitously discovered in 1859 by Lieke [7] when the synthesis of allyl cyanide was attempted but instead an isocyanide was characterized. The first naturally occurring isocyanide, Xanthocillin, discovered by Rothe in 1950, was later used as an antibiotic (Fig. 2).

Ever since the development of synthetic routes for isocyanides established circa 1867 by Gautier and Hoffman [8, 9], there have been many reports describing further developments, not just in terms of different synthetic routes but also for obtaining varied isocyanides which have been used in the synthesis of biologically important scaffolds. The synthetic importance and utility of isocyanides rocketed following their use in multicomponent reactions (MCRs). MCRs involve the use of

AgCN + R−I   ⟶   [R−NC + AgI]
4   **5**

$\xrightarrow{\text{KCN}}$ R−NC
1

Gautier's Synthesis

3 Xanthocillin

$R–NH_2 + CHX_3$ $\xrightarrow{\text{Base}}$ R−NC
6   **7**   **1**

Hoffman's Synthesis

Fig. 2 First isolated naturally occurring isocyanide **3** and early attempts at isocyanide synthesis. (X = Halogen)

three or more different compounds as starting materials, which can react to give a product comprising the majority of atoms from the starting materials, making them atom economical reactions. Even though there has been an exponential increase in isocyanide published manuscripts over the past 15–20 years, there is a need for novel isocyanides that can be used in the synthesis of various natural products *via* well-known transformations. Isocyanides are used to introduce new functionality in the molecule, which is overshadowed by utilizing harsh reaction conditions to hydrolyze the amide bond formed. This creates complications in highly functionalized compounds and a major drawback for extended uses. To overcome this challenge a new class of isocyanides, now termed "Convertible Isocyanides" (CICs), have been developed. The name convertible is justified by the role it plays in the MCRs and the post-modifications of the products obtained. The labile amide can be easily removed in a single step and be "converted" into a variety of other moieties with augmented diastereoselectivity. These are, at times, referred to as "Universal Isocyanides".

2 Convertible Isocyanides (CICs)

CICs are isocyanides consisting of a moiety that allows for selective cleavage of the terminal amide; for example in an Ugi post-condensation product. They are widely used in MCRs like the Passerini reaction. The concept of CICs was first introduced by Armstrong in the year 1996. There has been a considerable increase in efforts for the development of CICs and some of the famous CICs are shown in Fig. 3.

Despite the fact that isocyanides **13** and **18** do not have the appearance of CICs, recent reports prove that they can be used as such [10, 11]. Recently, Orru and co-workers have reported on the use of 2-bromo-6-isocyanopyrudine **14** as a universal CIC for MCRs to synthesize some biologically important compounds [12].
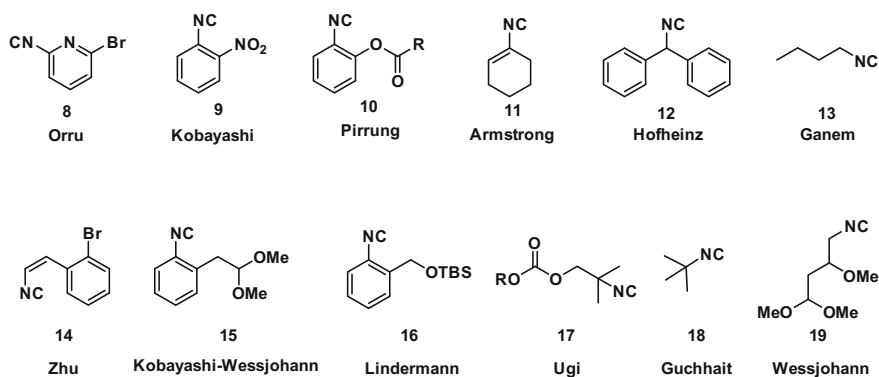

Fig. 3 Some of the more well-known convertible isocyanides

2.1 Methyl Isocyanides

Methyl isocyanides (MICs), can be considered a class of CICs where the substituent is present on the methyl group. Some of the better known MICs are *p*-tolylsulfonylmethyl isocyanide (TosMIC), diphenylmethyl isocyanide (DPMIC), benzotriazol-1-yl-methyl isocyanide (BetMIC), and methyl 2-isocyanoacetate (MICAc). Although the afore-mentioned MICs have been used as CICs in MCRs, the role of methyl isocyanide (MIC) alone as a CIC in an Ugi4-CR was only just first explored and reported by Andreana and co-workers [13] in 2016. The general outline for the reaction using MIC is given in Scheme 1. The required compound **24**, was obtained by mixing benzalde-hyde **22**, methyl isocyanide **20**, propionic acid **21,** and isopropyl amine **23** in methanol at room temperature for 24 h (Scheme 1). Then the dipeptide **24** was reduced to give compound **25** under Bechamp-type reduction conditions. Under microwave reactor conditions, the desired cyclized product **26** was readily obtained. Apart from the role as a CICs, MIC has also been used by the same group as a key component in the one-pot synthesis of diketopiperazine-based natural product Thaxtomin A (±)-*syn* (TA); well known for herbicidal activity [14]. First, the required starting materials 4-nitroindolylacetaldehyde **27**, methyl amine **28**, 3-hydroxyphenylpyruvic acid **29** and compound **20** were reacted in methanol followed by epimerization and cyclization under basic conditions using KOH at 70 °C to afford Thaxtomin A (±-*syn*-**30**) and the corresponding *anti*-diastereomer in a 4:1 ratio (Scheme 2).
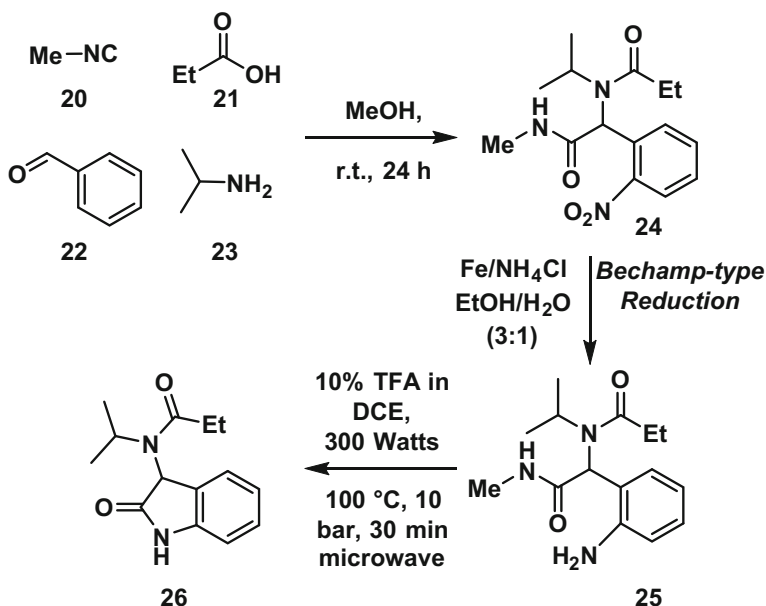
Scheme 1 Synthesis of 3-substituted indolinones
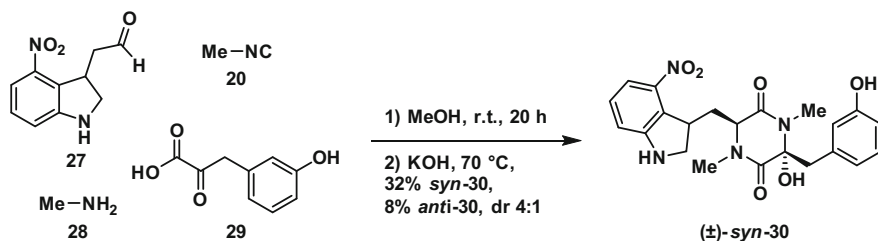
Scheme 2 Synthesis of (±)-Thaxtomin A

3 Asymmetric Control of Isocyanide-Based Multicomponent Reactions

Isocyanides have gained a lot of interest among the organic chemists in view of its importance in the various reactions used to generate a library of compounds and natural products *via* diversity-oriented synthesis (DOS). This is attributed to the generation of new chiral centers implicit in various multicomponent reactions like Passerini, Ugi to name a few. Admitting the fact, that the isocyanide is just one of the components in the MCR, the outcome of the reaction can be controlled by the types of isocyanides used along with the use of chiral catalysts as seen in some of the cases discussed hereafter.
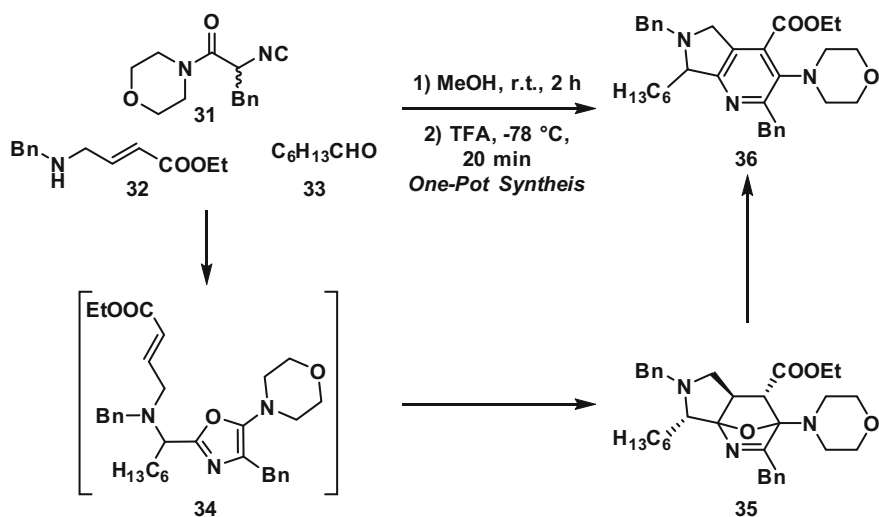
3.1 Diastereoselective Additions

Although isocyanides have been widely used in the MCRs for the synthesis of various scaffolds including natural products and biologically active compounds, there has been a concern lurking over the stereoselectivity of the reactions involving isocyanides. Although there have been stereoselective reactions developed for a myriad of multicomponent coupling reactions, the isocyanide-based reactions seem to be a little more challenging and to date only the asymmetric Passerini reaction has been achieved.

Zhu and co-workers [15] reported the stereoselective synthesis of pyrrolo-pyridine *via* the formation of the oxanorbornene heterocyclic intermediate **35**, followed by the Diels–Alder reaction to give the desired product **36**. Isocyanide **31**, ester **32,** and aldehyde **33** were dissolved in methanol and stirred for 2 h at room temperature followed by the addition of triflouroacetic acid (TFA) at −78 °C and stirred for 20 min which afforded the pyrrolo-pyridine moiety **36** in 80% yield (Scheme 3). Intermediate **35** was obtained in high diastereoselectivity of >90% *de* with an excellent yield of 92%.

Furthermore, Kazmeier et al. [16, 17] reported the use of an enantiomerically pure isocyanide **38** to form oxazoline, ligands (**40a** and **40b**) which were used in

stereoselective additions of Et$_2$Zn to various aldehydes. Due to the instability of the oxazolines, they designed an alternate two-step synthesis of thiazoline ligands (**42a** and **42b**). In both the cases, an excellent stereoselectivity of >92% *ee* was obtained. The oxazoline ligand **40b** was synthesized in one step followed by the addition of Et$_2$Zn to benzaldehyde to yield **43** in 100% yield with a 94% *ee*. The thiazoline ligand **42b** was synthesized in a two-step process followed by the addition of Et$_2$Zn to benzaldehyde to yield **43** in 100% yield with a 92% *ee* (Scheme 4).


Scheme 3 Synthesis of pyrrolo-pyridine derivatives
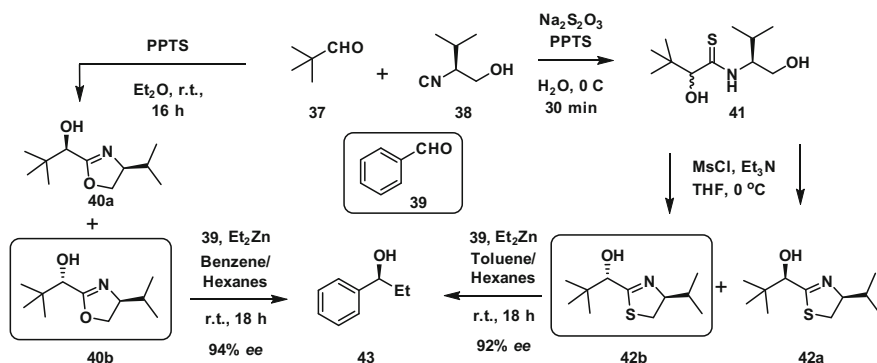
Scheme 4 Synthesis of oxazolines and thiazolines and their application in the addition of Et$_2$Zn to benzaldehydes

3.2 Enantioselective Additions

Denmark and Fan reported the synthesis of α-hydroxyl amides and esters *via* the use of the concept of Lewis base activation of Lewis acids which employs the use of SiCl₄ and a chiral bisphosphoramide (*R,R*)-catalyst [18, 19]. The reaction was carried out using various aldehydes **39, 44a–e** and isocyanide **18** in the presence of SiCl₄ and 5 mol% of the catalyst to give intermediates **46a–f**. It was determined that the intermediates could give two different products based on the workup route selected (Scheme 5). Under saturated aqueous NaHCO₃ workup conditions, α-hydroxyl amides **47a–f** were obtained in good to excellent yields of 76–92% with 82–99% *ee*. Under conditions where methanol and saturated aqueous NaHCO₃ workup conditions, it gives rise to α-hydroxyl esters **48a–f** in good to excellent yields of 70–92% with 80–98% *ee* (Table 1).
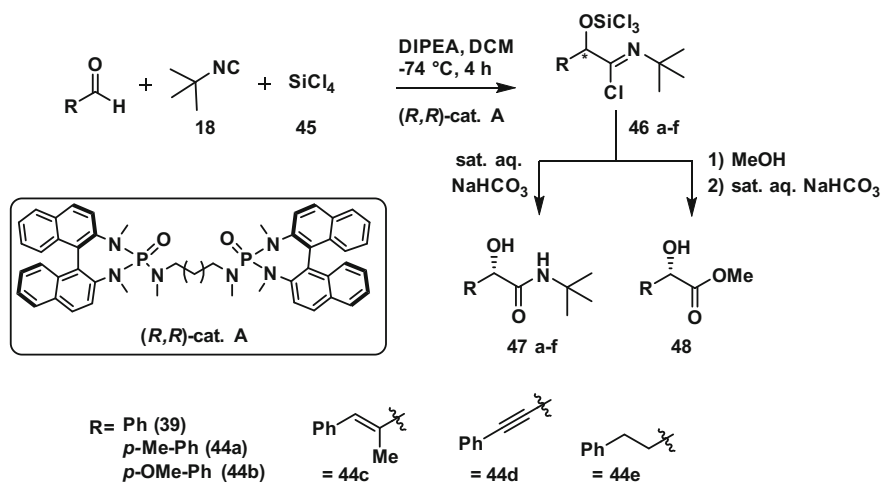
Scheme 5 Enantioselective addition of isocyanides to aldehydes using catalyst

Table 1 Reaction profile of Lewis base activation of Lewis acids

Product	Aldehyde	Yield (%)	er
46a	**39**	91	99.9:0.1
46b	**44a**	91	99.9:0.1
46c	**44b**	89	98.3:1.7
46d	**44c**	86	67.4:32.6
46e	**44d**	76	77.0:23.0
46f	**44e**	92	81.9:18.1

4 Stereoselectivity of Passerini Reactions

4.1 Diastereoselective Passerini Reactions

In recent times, there have been very few reports on the diastereoselective Passerini reaction. Berlozecki and co-workers have reported on Passerini reactions wherein they used N^α protected amino acids, cyclic ketones, and isocyanides [20]. They achieved exceptional diastereoselectivity which they attribute to the protecting groups used to protect the amine group of the amino acids. L-phenylalanine (Scheme 6) with *Boc-* or phthaloyl and trityl protected amine **49** gave a selectivity of 99% *de* with yields of 86, 84, and 66% respectively (Table 2). Whereas the D-valine (Scheme 7) with *Boc-* and phthaloyl protected amine **53** gave a selectivity of 85–96% *de* with the yields of 79 and 74% respectively (Table 3). Albeit high yields and diastereoselectivity was achieved, this approach had a drawback; ketones other than cyclohexanone were not tested for the transformation. They were later tested by Simila and Martin [21].

4.2 Enantioselective Passerini Reactions

Over the years many enantioselective Passerini reactions have been reported, but only a few of them have resulted in good enatioselectivity [22–25]. A recent report by Szymanski imposes the utilization of *wheat germ lipase* enzyme to resolve the Passerini product by hydrolysis of the racemic mixture (desymmetrization) [26]. Although two different products were obtained, the selectivity was excellent giving **58 (R)** in 70% *ee* and **59** in 99% *ee*.

The α-hydroxyl amide **59** was then converted into the corresponding amino acid by six additional steps. First, compound **59** was mesylated, followed by nucleophilic substitution of azide and hydrogenation using Pd/C in methanol afforded the amide **60** (Scheme 8). This was later subjected to hydrolysis under acidic and basic conditions followed by hydrogenation using Pd/C in methanol to yield the amino acid [27] in 71% with an excellent enatioselectivity (98% *ee*).

Similar to the Lewis base catalyzed Passerini reaction, Lewis acid catalyzed Passerini reactions were initially described by Domling [22] and Schreiber groups (2004) [28] using titanium- and copper-based catalysts respectively. However in each case, when these approaches were used, the drawback was lower enantioselectivity when non-chelating agents were employed. This was further explored by Zhu and co-workers (2008) using aluminum-based catalysts [29]. Several catalysts and reaction conditions were optimized which showed that the use of salen-aluminum catalyst could render good enantioselectivities. The reactions were carried out by mixing the aldehyde, carboxylic acid, and the isocyanide in toluene at −40 °C and stirring for 48 h (Scheme 9). The reaction yields were moderate to good (59–70%) affording the amide **65a–i** with moderate to excellent
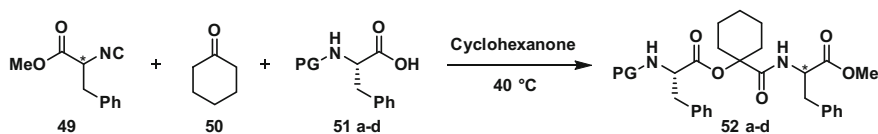
Scheme 6 Diastereoselective P-3CRs of L-phenylalanines

**Table 2** Reaction profile of P-3CRs of L-phenylalanines

Product	PG	Isocyanide configuration	Time (h)	Yield (%)	dr
52a	Bz	S	20	39	94:6
		R	20	48	7:93
52b	Trt	S	24	66	<1:99
		R	20	49	>99:1
52c	Phth	S	14	84	<1:99
		R	40	82	>99:1
52d	Boc	S	20	86	99:1
		R	16	>99	1:99
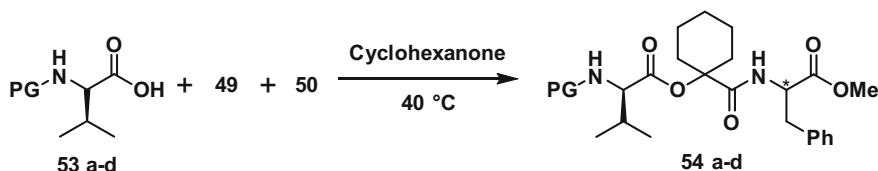
Scheme 7 Diastereoselective P-3CRs of D-valines

enatioselectivity of 63–99% *ee* (Table 4). Screening a set of diversified reagents revealed that the enatioselectivity is greatly dependent on the structures of the aldehydes and isocyanides. It was determined that the carboxylic acid also played a minor role in selectivity. The *S*-selectivity of the product is favored by the attack of the isocyanide on the *Re*-face of the aldehyde.

Table 3 Reaction profile of P-3CRs of D-valines

Product	PG	Isocyanide configuration	Time (h)	Yield (%)	dr
54a	Bz	S	20	30	16:84
		R	35	42	81:19
54b	Cbz	S	27	52	18:82
		R	25	89	87:13
54c	Phth	S	17	74	85:15
		R	20	78	18:82
54d	Boc	S	20	79	5:95
		R	23	87	96:4
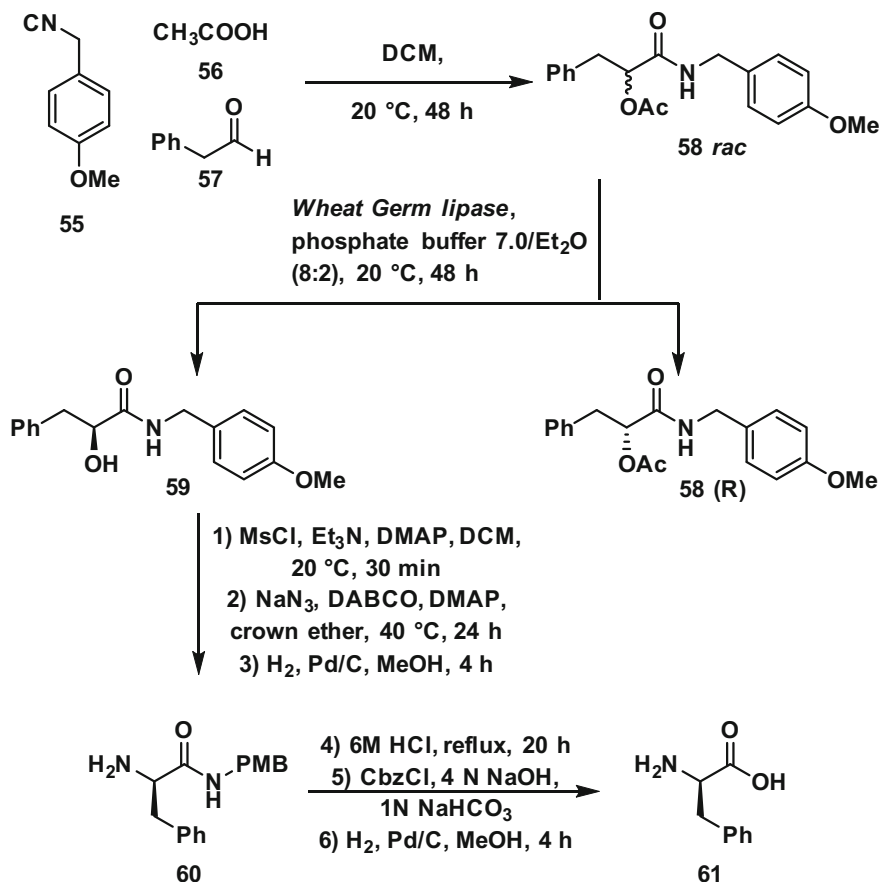
Scheme 8 Enzymatic resolution of the racemic Passerini product

Zhu and co-workers further modified the catalyst and replaced the carboxylic acid with the hydrazoic acid **67** which gave a cyclic product following a 1,5-dipolar cyclization (Scheme 10) instead of the acylation as observed in the previous case [24]. The products were achieved in high yields of 76–95% with excellent enatioselectivity up to 95% *ee* (Table 5). But this approach is also limited due to the fact that it is more suitable for aliphatic aldehydes and very few aromatic aldehydes.

A very recent report by Bin Tan's group has shown that the use of phosphoric acid based catalysts could actually enhance the enantioselectivity of Passerini reactions and could be applied to wide range of aldehydes and carboxylic acids. They have optimized the reaction conditions by screening a wide range of catalysts [30] and selecting the catalyst with the best results (**CP6**) followed by its use to further explore the reaction profile. Moderate to excellent yields of 45–99% with enantioselectivity of 84–99% *ee* were observed (Fig. 4).
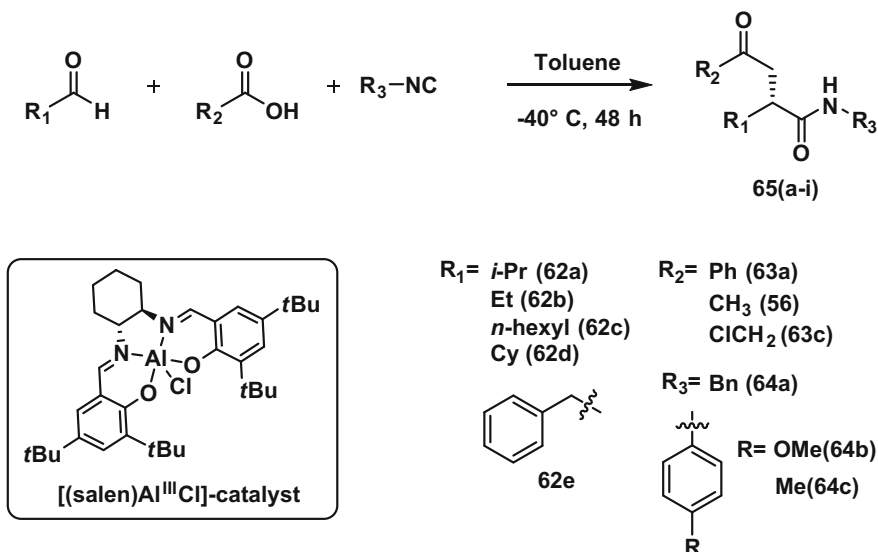
**Scheme 9** Salen-aluminum catalyzed enantioselective P-3CR

Table 4 Reaction profile of Lewis acid catalyzed Passerini reaction

Product	Aldehyde	Acid	NC	Yield (%)	ee (%)
65a	62a	63a	64a	70	63
65b	62a	56	64a	59	63
65c	62a	56	64b	63	84
65d	62b	63c	64b	66	87
65e	62c	63c	64b	67	73
65f	62d	63c	64b	59	87
65 g	62e	63c	64b	68	71
65 h	62a	63c	64c	61	81
65i	62a	63c	64b	64	99

5 Stereoselective Ugi Reaction

Successful attempts at the diastereoselectivity and enatioselectivity of the Passerini reaction encouraged the organic chemists' community to look for ways to access similar success in Ugi reactions. List and co-workers [31] demonstrated the lack of enatioselectivity in Ugi reactions. Recent reports by Zhu and co-workers have given a ray of hope when they reported the enantioselective Ugi reaction [32, 33].

In the past few years, efforts from various research groups have shown that the diastereoselective outcome of the Ugi reaction has been fruitful. Kobayashi and co-workers [34, 35] demonstrated the synthesis of Omuralide, a proteasome
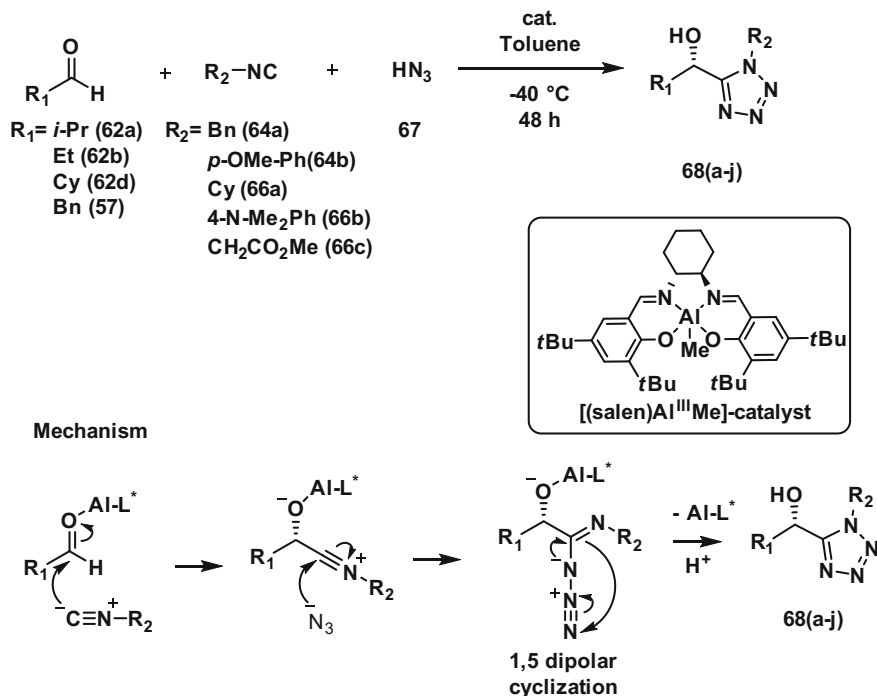
Scheme 10 Enantioselective synthesis of tetrazoles *via* P-3CR and the proposed mechanism

Table 5 Reaction profile of synthesis of tetrazoles *via* P-3CR

Product	Aldehyde	Isocyanide	Yield (%)	*ee* (%)
68a	**62a**	**64b**	90	85
68b	**62a**	**66a**	90	95
68c	**62b**	**64b**	88	87
68d	**62c**	**64b**	90	91
68e	**62a**	**64a**	76	92
68f	**57**	**64b**	97	64
68 g	**62c**	**66a**	93	84
68 h	**62c**	**66b**	95	94
68i	**62c**	**64a**	91	83
68j	**62c**	**66c**	93	75

inhibitor. The synthesis involved the use of beta-hydroxy gamma-keto acid. The starting materials {protected β-hydroxyγ-keto acid intermediate (**I**), isocyanide **15** and amine **71**} underwent the Ugi four center three-component reaction (Ugi-4C-3CR) to afford anti-**72** predominantly with a yield of 78% with the formation of single diastereomer (Scheme 11). This compound **72** further was used to complete the synthesis of Omuralide **74**.
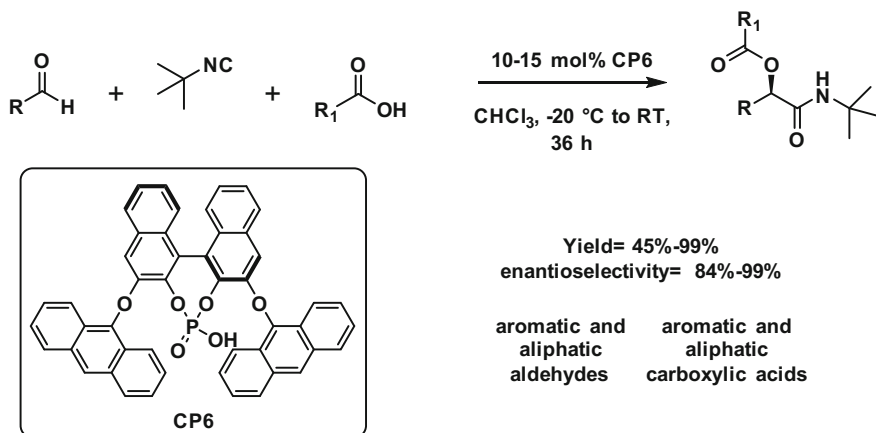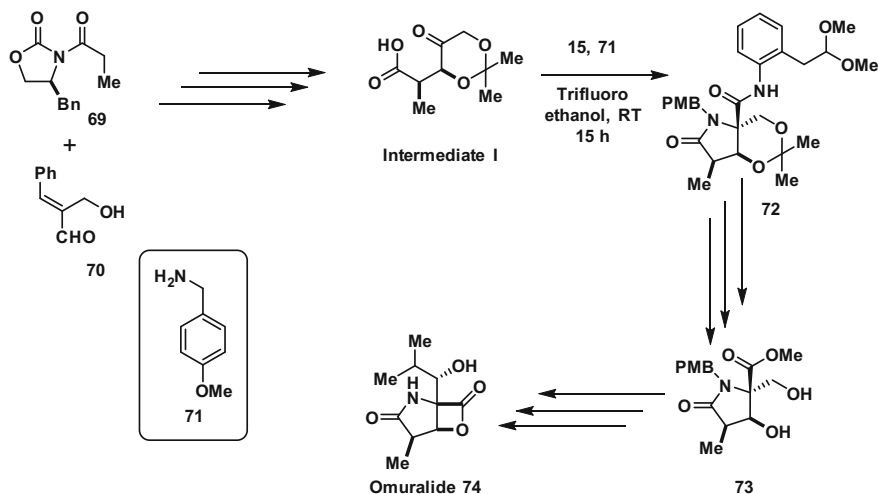
**Fig. 4** Phosphoric acid catalyzed asymmetric Passerini reaction

Scheme 11 Synthesis of Omuralide **74** *via* Ugi reaction

Use of chiral isocyanides was reported by Nenjadenko and co-workers to achieve diastereoselectivity for the Ugi MCRs. They have used the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl derivatives or the chiral oxabicyclooctyl (OBO)esters **78a–e** (previously synthesized by them) to study the role of chiral isocyanide in the stereoselectivity [36]. The OBO esters played a key role in controlling the racemization. The general reaction module for this reaction is, stirring a mixture of amine, aldehyde or ketone, carboxylic acid, and the OBO esters of the isocyanide in methanol at room temperature. They observed the retention of configuration of the Ugi products **80a–**k (Scheme 12). To further
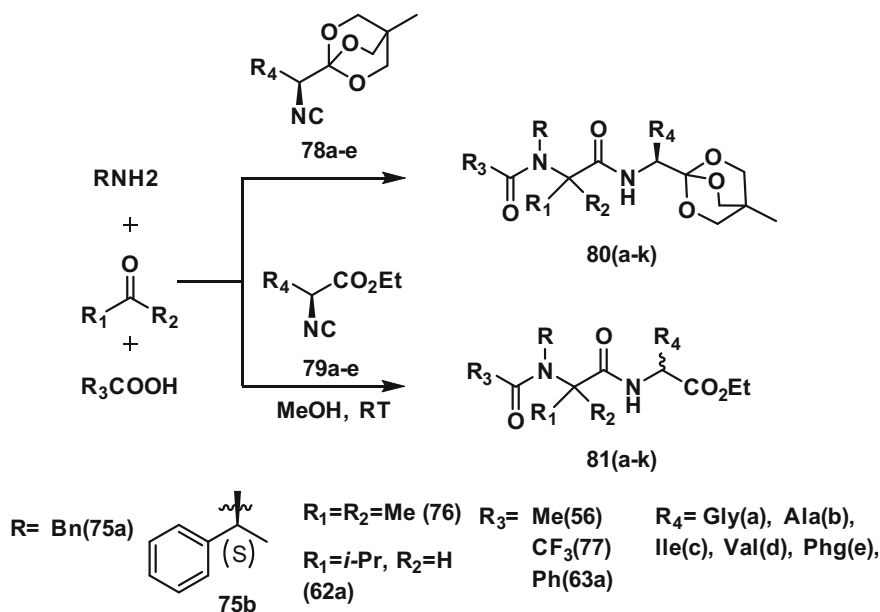
Scheme 12 Diastereoselective Ugi-4CR using chiral OBO esters
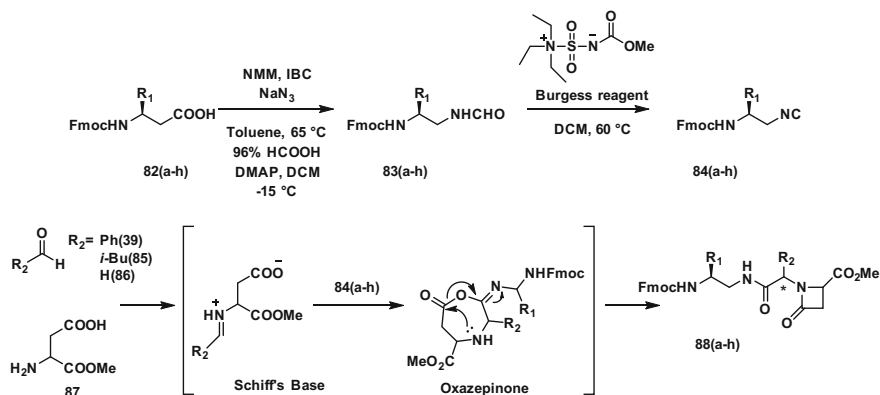
Scheme 13 Synthesis of β-lactams using chiral amino alkyl isocyanides

investigate the reaction profile they used the esters **79a–e**, surprisingly racemization at the chiral center on the isocyanide was observed. This observation suggests that the OBO plays an important role to prevent the racemization.

Along the same lines of using the chiral isocyanides, Sureshbabu and co-workers [37] attempted the utilization of the N^β-Fmoc amino alkyl isocyanides, which were previously synthesized by the same group. They employed those isocyanides for the

synthesis of a series of β-lactam peptidemimics *via* Ugi 4C-3CR (Scheme 13). The reactions were conducted using the isocyanides **84a–h**, aldehydes and methyl ester of the aspartic acid **87** to give the peptidomimics **88a–h** in moderate to good yields (53–78%) with excellent diastereoselectivity {*de* between 85 and 100% (Table 6)}.

The high selectivity can be attributed to the formation of the 7-membered oxazeoinone intermediate [38]. Furthermore, the Fmoc group on the final product can be deprotected and be used in other reactions to synthesize various complex natural products.

A collaborative work between Orru and van der Eycken [39] accomplished a new level of diastereoselectivity. They utilized an aldehyde-carboxylic acid derivative of biphenyl **89**, amine (**71**) and the isocyanide (**18**) for the microwave assisted Ugi 4C-3CR (Scheme 14). The reaction gave a dibenzo[c,e]azepinone derivative as a single diastereomer with an excellent yield of 82%. The reaction proceeds through the formation of iminium ion which is attacked by the isonitrile to form nitrilium ion followed by the intramolecular acylation to give the intermediate IV. This intermediate upon Mumm rearrangement forms the (R_a, S) isomer of the product **90**.

After all the years of hard work put in by various research groups to achieve the enantioselectivity for the Ugi reactions, the initial breakthrough was provided by Zhu's group in 2012, wherein they used chiral phosphoric acids (CPAs) as catalysts for the one-pot four-component Ugi type reaction [32]. The reactions were conducted by adding the first three components (aldehyde, amine and isocyanide) in dichloromethane and stirring for 24 h at −35 °C followed by addition of the fourth component (unsaturated acid chloride) and base and refluxing the mixture for 5 h in toluene. The process gave the desired single diastereomer in yields ranging from 41 to 94% with the enantioselectivity of 81–94% *ee*.

Following up on this work they further explored the role of the CPAs in achieving excellent enatioselectivity for Ugi reactions [33]. There were two different approaches that they followed in order to achieve the desired product. In the first approach, they followed a two-component version wherein they reacted the preformed furan (from carboxaldehyde and amine) and the isocyanide followed by the addition of the catalyst (**CP–NO₂**). Second approach was mixing all the components in a single pot followed by addition of the catalyst (**CP–NO₂**). In both the

Table 6 Reaction profile for the synthesis of β-lactams **88a–h**

Product	R_1	Aldehyde	Yield (%)	*dr*
88a	–H	**39**	65	99:1
88b	–Me	**39**	78	96:4
88c	–Bn	**85**	69	85:15
88d	–*i*-Pr	**86**	72	90:10
88e	–CH₂–OBn	**39**	76	89:11
88f	–CH₂–COOBn	**85**	63	100:0
88 g	–(CH₂)₄–NHZ	**86**	59	98:2
88 h	Pyrrolidine NC	**39**	53	95:5
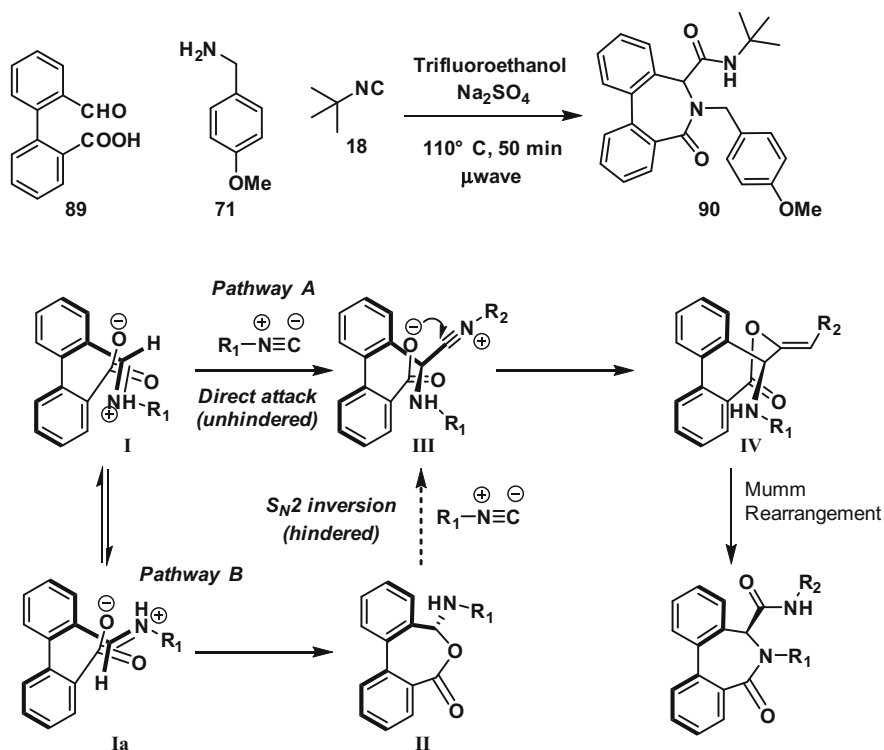
Scheme 14 Microwave assisted Ugi-4C-3CR and the proposed mechanism

cases excellent yields (74–98%) and enantioselectivities (82–97% *ee*) were obtained (Fig. 5).

6   Carbohydrates as Chiral Auxiliaries

There have been efforts in improving the stereoselectivity in the Ugi 4CRs to synthesize the substituted amino acids. Horst Kunz and co-workers have reported the use of carbohydrates as chiral auxiliaries keeping other constituents achiral [1, 2]. The α-D and L-amino acids can be achieved by simply switching the amines between the galactosamine and the arabinosylamine respectively.

When the galactosamine **91** was reacted with isocyanide **18** and formic acid **94,** variety of aldehydes in the presence of ZnCl₂ and tetrahydrofuran at lower temperatures, N-galactosyl amino acid amide derivative **95a–i** were obtained in excellent yields ranging from 80 to 93% and high enantioselectivity (only one chiral center) of 91–94% (Table 7). The derivatives were further processed for the cleavage of the N-glycosidic bond following a two-step acidic hydrolysis
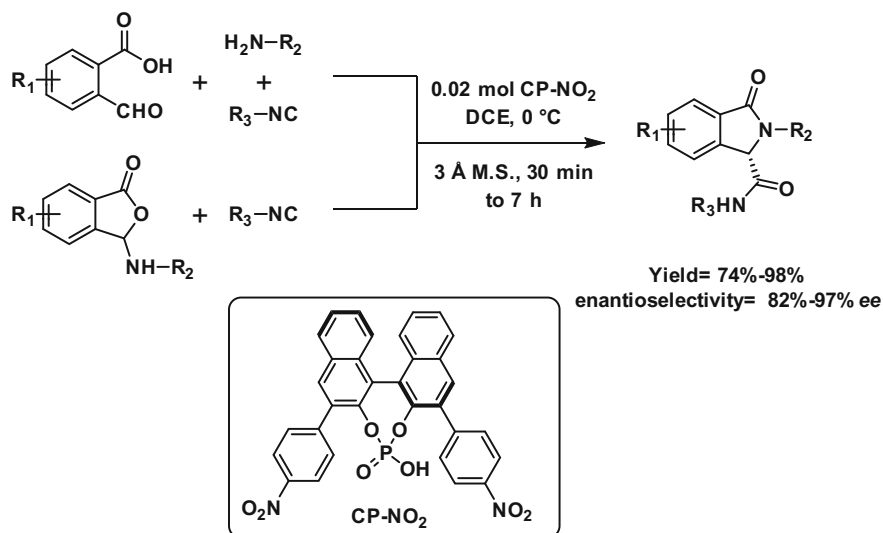
Fig. 5 Chiral phosphoric acid catalyzed enantioselective Ugi reaction

Table 7 Reaction profile for Ugi reaction using D-galactosamine auxiliary

Product	R_1	Aldehyde	Reaction temp (°C)/time	R:S	Yield (%) of pure R
95a	C_3H_7	**92a**	−78/2d	94:6	80
95b	-i-Pr	**62a**	−78/2d	95:5	86
95c	t-Bu	**92b**	−25/3d	96:4	80
95d	Bn	**57**	−78/8	95:5	80
95e	furan-CH₃	**92c**	−25/24 h	95:5	90
95f	thiophene-CH₃	**92d**	-25/24 h	96:4	93
95 g	Ph	**92e**	0/8d	91:9	81
95 h	p-Cl–Ph	**92f**	−25/24 h	97:3	92
95i	p–NO₂–Ph	**92 g**	0/4 h	94:6	91

(Scheme 15) giving the galactose template **96** and the desired free α-D-amino acids **98a–i** in quantitative yields [1].

When the Ugi reaction was conducted using arabinosylamine as the chiral amine, following similar reaction conditions, the derivatives [2] N-formyl-N-arabinosyl amino acid amides **100a–e** were obtained in excellent yields ranging from 85 to 95% and enantioselectivity of >96% respectively as observed in the case of galactosamine (Table 8). The desired L-amino acid derivatives **103a–e** and the arabinose template **101** were obtained in quantitative yields *via* a two-step acidic hydrolysis (Scheme 16).
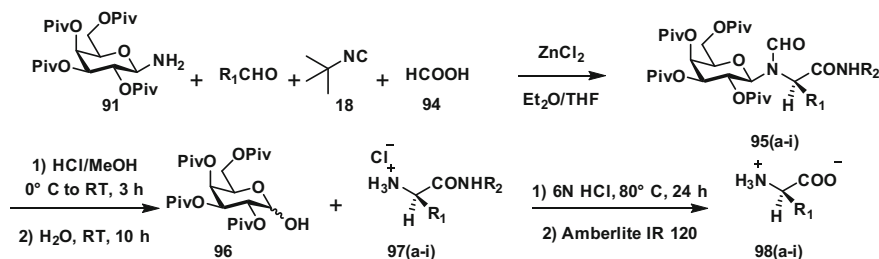
Scheme 15 Galactose derived chiral auxiliary based asymmetric Ugi reaction

Furthermore efforts were put in by Pellicciari's group [40], synthesizing the glycine derivatives with good to moderate yields and excellent diastereoselectivity (Fig. 6) and Ugi and co-workers [41] used a thiosugar to synthesize the D-leucine derivatives with excellent yields and enantioselectivity (Fig. 7). The selectivity could have been achieved due to the formation of the intermediate which directs the attack of the isocyanide at the imine center.

Use of sugars as chiral auxiliaries was further explored by Zeigler and co-workers [42] by employing carbohydrate-based isocyanides in the Ugi and Passerini MCRs to synthesize a library of glycopeptides. The reactions were performed using anomeric glucosyl isocyanides **104a, b** and protected

Table 8 Reaction profile for Ugi reaction using D-arabinosamine auxiliary

Product	R₁	Aldehyde	Reaction temp (°C)./time	R:S	Yield (%) of pure S
100a	t-Bu	**92b**	−25/3d	97:3	85
100b	Bn	**57**	−78/24 h	97:3	87
100c	p-Cl–Ph	**92f**	−25/24 h	98:2	91
100d	(furyl)	**92c**	−25/24 h	96:4	85
100e	(thienyl)	**92d**	−25/24 h	4:96	95 (2R)
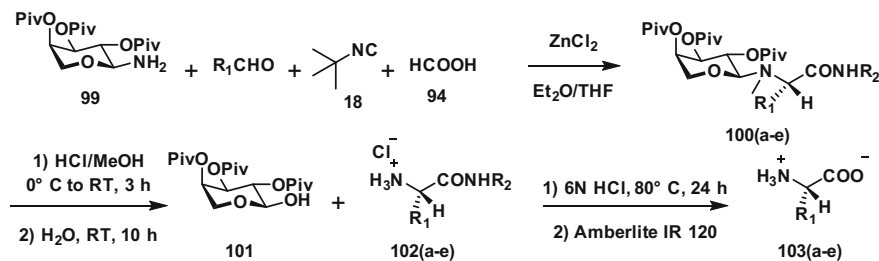
Scheme 16 Stereoselective synthesis of L-amino acid derivatives *via* D-arabinose auxiliary
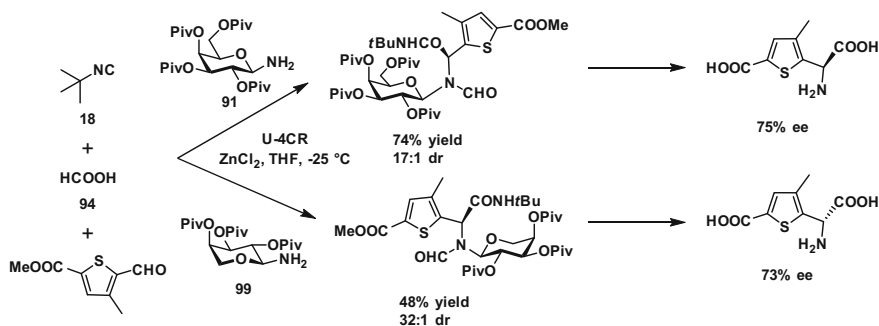
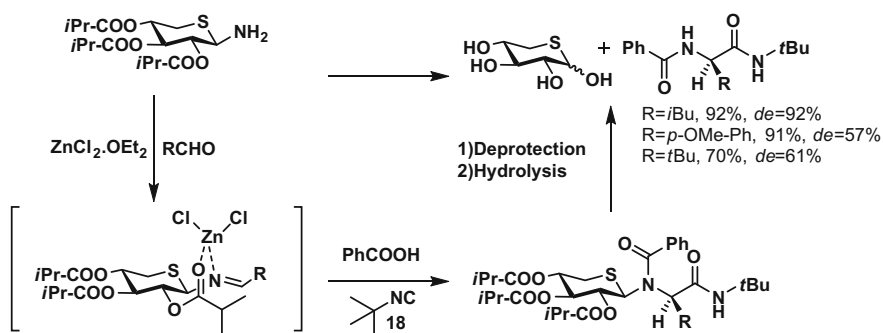**Fig. 6** Pellicciari's stereoselective synthesis of glycone derivatives

Fig. 7 Stereoselective synthesis of D-Leucine derivatives using thiosugars as chiral auxiliary

2-deoxy-2-isocyano-β-D-glucopyranose **104c** with various combinations of aldehydes, carboxylic acids, and amines (Fig. 8). The reactions were characterized by longer reaction time, lower yields and more importantly poor diastereoselectivity with a couple of exceptions as evident from Tables 9 to 10.

The 2-isocyano compound faired well in the Passerini reactions with higher yields and better reaction times. Although the reactions did not result in desired
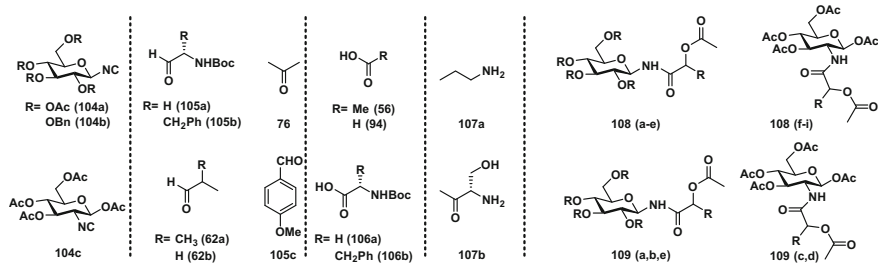

Fig. 8 Passerini and Ugi reactions of isocyanoglucoses

Table 9 Reaction profile for Passerini reaction leading to products **108a-i**

Product	Isocyanide	Aldehyde	Acid	Reaction temp/time	Yield %, *dr*
108a	**104a**	**105a**	**56**	RT/3d	23%, 55:45
108b	**104a**	**105b**	**56**	RT/3d	41%, 58:42
108c	**104a**	**62b**	**56**	RT/24 h	80%, 50:50
108d	**104b**	**105a**	**56**	RT/6d	31%, 57:43
108e	**104b**	**105b**	**56**	RT/8d	35%, 52:48
108f	**104c**	**105b**	**56**	RT/4d	57%, 60:40
108 g	**104c**	**62a**	**56**	RT/8d	23%, 53:47
108 h	**104c**	**62a**	**106a**	RT, 28 h	90%, 53:47
108i	**104c**	**76**	**94**	0 °C, 3 h	14%, –

Table 10 Reaction profile for Ugi reaction leading to products **109a–e**

Product	Isocyanide	Aldehyde	Acid	Amine	Reaction temp/time	Yield %, *dr*
109a	**104a**	**62a**	**106a**	**107a**	RT/37d	22%, 55:45
109b	**104b**	**62a**	**106a**	**107a**	RT/25d	35%, 60:40
109c	**104c**	**62a**	**106a**	**107a**	RT/30d	31%, –
109d	**104c**	**62a**	**106b**	**107a**	RT/18d	19%, –
109e	**104a**	**62a**	**107b**	**107b**	55 °C/11 h	15%, 63:37

diastereoselectivity, there was room for improvement but unfortunately not many researches have followed this work, and thus far not much work has been done in this area. This approach could be a useful tool for synthesizing complex glycopeptides.

7 Conclusions

This chapter describes the recent developments in the application of isocyanides in the multicomponent reactions (MCR) forming chiral products It also describes the first ever application of methyl isocyanide as a convertible isocyanide, which could be useful in the synthesis of various natural product intermediates via Ugi and Passerini reactions involving the multicomponent transformations. In order to achieve higher stereoselectivity, various catalysts were used giving a sign of importance of catalysis in chemical tranformations *en route* to the synthesis of natural products of biological significance. The post-modifications of Ugi and Passerini products can give rise to esters, acids, and thioesters.

Recent reports have shown that the high enatioselectivity can be achieved in the Ugi reactions, opening up the avenues to further explore the results that can be implemented in the synthesis of intermediates for complex natural products.

Use of carbohydrates as chiral auxiliaries has revolutionized the utility of the multicomponent reactions owing to their ease of access and further modifications in those reactions. The carbohydrates have been used for the synthesis of various amino acid derivatives and can further be used to synthesize biologically important amino acid based molecules.

We summarize the chapter with an anticipation that this will galvanize the synthetic chemists to focus on further development of applications of isocyanides in various fields of chemistry to synthesize compounds of biological significance and compounds that can make an impact on environment in a positive way.

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