2.1 Introduction

The synthesis of complex organic molecules is conventionally performed by a sequence of multi step syntheses having its own conditions, reagents, solvents and catalysts. The intermediate products thus obtained are separated and purified in each and every step. This would be rather time consuming and laborious, moreover the solvent and the waste products should be removed and discarded. Now, environmental and economic pressures are forcing the chemical community to search for more efficient ways of performing chemical transformations in an eco friendly and more economic manner. It is obvious that the use of multicomponent transformations or domino reactions is a very efficient strategy for the production of compound ensembles of high diversity necessary in modern search for required structures.1

2.2 Multicomponent reactions

Multicomponent reactions are more versatile and efficient technique to execute the desired requirements for the compound ensembles of different substitution patterns. The multi step solid phase method by Merrifield and
co-workers laid the basement and the library chemistry became active in 1982 when Furka introduced the peptide libraries.\textsuperscript{2} Other solid phase libraries were also introduced. The U-4CR is a new method to synthesize amino acid libraries by a four-component reaction in solution phase. The U-4CR introduced by Ugi \textit{et al} involves a combination of a carboxylic acid 1, an amine 2, an aldehyde 3 and an isocyanide 4 to afford highly substituted amino acids 5 (Scheme 1).\textsuperscript{3}

\[
\begin{array}{c}
\text{O} \\
R^1\text{COOH}
\end{array} + \begin{array}{c}
\text{O} \\
R^2\text{NH}_2
\end{array} + \begin{array}{c}
\text{O} \\
R^3\text{R}^4
\end{array} + \begin{array}{c}
\text{NC} \\
R^5
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
R^1\text{N}
\end{array} + \begin{array}{c}
\text{O} \\
R^2\text{R}^4\text{H}
\end{array} + \begin{array}{c}
\text{N} \\
R^5
\end{array}
\]

\textbf{Scheme 1}

The synthetic potential of U-4CR and its combinations with further reactions have been developed. Such reactions have been modified into a large extent for synthesizing important amino acid derivatives, \(\beta\)-lactams\textsuperscript{4} or phosphorous triesters.\textsuperscript{5} Carbohydrate combinatorial libraries\textsuperscript{6} were generated by Gobel and Ugi, using the multicomponent reaction approach. In 1995 the libraries of U-4CR products were industrially introduced by Weber \textit{et al},\textsuperscript{7} and since then this chemistry is one of the most favorable strategies for searching new suitable chemical products.\textsuperscript{8}

The compounds obtained from U-4CR and subsequent reactions can form extensive libraries of great interest. For instance, Keating \textit{et al} have reported a synthesis of substituted pyrroles starting from cyclohexanamide 6. The acid catalyzed cyclization gave the 1,3-dipole 7 which on cycloaddition with acetylenic dienophiles gave the adduct 8 which on loss of carbon dioxide afforded pyrroles 9 (Scheme 2).\textsuperscript{9}
As the result of an Ugi-5-center-4-component reaction of methyl trimethylsilyloxy-cyclopropanecarboxylates 10 with amino acids 11, \textit{t}-butylisonitrile and methanol furnished amino diacid derivatives. The adduct obtained underwent thermal cyclization to provide \(\gamma\)-lactams 13 in good yields (Scheme 3).\textsuperscript{10}

Isomers of the antibiotic \textit{furanomycin} 18 and 19 have been prepared in 55\% overall yield via an Ugi four component condensation reaction of 5-methyl-2,5-dihydrofuran-2-carbaldehyde 14, 1-phenylethylamine 15, benzoic acid 16 and \textit{t}-butyl isocyanide 17 (Scheme 4).

\textsuperscript{11}
Some strategies for the multicomponent N-arylation of primary amines 21 with isocyanides 22, aldehydes 20, and phenols 23 have been put forward by El Kaim et al (Scheme 5).\(^{12}\)

Acid-free, aminoborane-mediated Ugi-type reaction leading to general utilization of secondary amines 25 with aldehyde 20 and isocyanide 26 have been put forward by Tanaka et al (Scheme 6).\(^{13}\) Corresponding α-amino amides 27 are obtained in good yields. The nonacidic reaction conditions are beneficial for unique chemoselectivity, where the aldimine functionality is left intact in the present Ugi-type reaction.

Optimisation of a microwave assisted Ugi reaction by Tye et al for the formation of 2-methyl-5-oxopyrrolidine-2-carboxamides 29 from the reaction of 4-oxopentanoic acid 28 with amine 21 and isocyanide 22 (Scheme 7).\(^{14}\) The optimal procedure developed using this approach has enabled the preparation of lactam derivatives in moderate to excellent yields
(17–90%) in a reaction time of only 30 minutes compared to the conventional methodology which required up to 48 hours.

\[
\text{HOOC} + R^1\text{NH}_2 + R^2\text{N} = \text{C} \xrightarrow{\text{MW, 100°C}} \text{MeOH, 30 min} \rightarrow \text{NHR}^1 \\
\text{O} \quad \text{O} \\
\text{N} \quad \text{C} \quad \text{R} \quad \text{2} \quad \text{M} \quad \text{W}, \quad 100^\circ \text{C} \\
\text{Me} \quad \text{O} \quad \text{H}, \quad 30 \text{min} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{N} \quad \text{H} \quad \text{R} \quad \text{1} \\
28 \quad 21 \quad 22 \quad 29
\]

Scheme 7

A straightforward approach towards thiazoles and endothiopeptides 32 via Ugi reaction was put forward by Kazmaier et al via the reaction of thioic acid 30, secondary amine 31 and ketone 3 (Scheme 8). If isonitriles with an acetal group are applied, the endothiopeptides can directly be converted into thiazoles using TMSCl-NaI under microwave irradiation.

\[
\text{R}^1\text{SH} + \text{R}^2\text{NH} + \text{R}^3\text{R}^4\text{C} = \text{N} \xrightarrow{\text{NC} = \text{O} \text{(OMe)}} \text{MeOH, rt, 15 hr} \rightarrow \text{R}^1\text{N} = \text{S} = \text{R}^2\text{S} = \text{R}^3\text{NH} = \text{R}^4\text{NH} \quad \text{OMe} \\
30 \quad 31 \quad 3 \quad 32
\]

Scheme 8

A modified U-4CR reaction with acid 33, aldehyde 34, isocyanide 22 and 2-nitrobenzylamine 35 as an ammonia equivalent was put forward by Sung et al (Scheme 9).

\[
\text{R}^1\text{CHO} + \text{C}_{\text{NO}} \text{H}_2 + \text{R}^2\text{NC} \xrightarrow{\text{MeOH, rt}} \xrightarrow{\text{hν (254 nm)}} 6-13 \text{hr} \rightarrow \text{R}^2\text{N} = \text{O} = \text{R}^1 \quad \text{R}^1 \quad \text{R}^2 \quad \text{NH} \\
33 \quad 34 \quad 22 \quad 35 \quad 36 \quad 37
\]

Scheme 9

Balme et al have reported a three component synthesis of stereo defined 4-benzylidene-(or alkenylidene)-pyrrolidenes 41 from simple, readily
available starting materials. This one-pot process is initiated by a conjugate addition of propargylamine 38 to a gem-diacivated olefin 39 followed by a carboxylation involving an aryl halide 40 (or vinyl triflate) (Scheme 10).\textsuperscript{17}

\[
\begin{align*}
\text{H} & \rightarrow \text{H} \\
R^1R^2 & + \text{EWG} \rightarrow \text{Y} \\
X & = I, Br, OTf \\
Y & = O, NR
\end{align*}
\]

Scheme 10

Recently biologically active \(\alpha\)-oximinoamides 44 have been prepared by a simple three-component reaction between nitro derivatives 42, isocyanides 22 and acetic anhydride 43 (Scheme 11).\textsuperscript{18}

\[
\begin{align*}
\text{R}^1\text{NO}_2 & + \text{R}^2\text{NC} + \text{H}_2\text{C} & \text{O} & \text{O} \rightarrow \text{O} & \text{R}^1 & \text{O} & \text{O} & \text{CH}_3 \\
42 & 22 & 43 & 44
\end{align*}
\]

Scheme 11

The reaction of an aldehyde 34, malononitrile 45 and phenol 46 in water at reflux in the presence of cetyltrimethylammonium chloride (CTACl) as catalyst affords a one-pot synthesis of 2-amino-2-chromenes 47 (Scheme 12).\textsuperscript{19}

\[
\begin{align*}
\text{R}^1\text{CHO} & + \text{NC} & \text{CN} & + \text{OH} \rightarrow \text{CTCl} & \text{H}_2\text{O} \\
34 & 45 & 46 & 47
\end{align*}
\]

Scheme 12
Similarly a one-pot condensation of \( \alpha,\beta \)-unsaturated ester 48, amidine 50 and malononitrile/cyanoacetate 49 building blocks affords multifunctionalized pyrido[2,3-d] pyrimidine scaffolds 51 (Scheme 13).$^{20}$

![Scheme 13](image)

The reaction of N-silylated iminoethers 52 with 2-substituted acetyl chlorides 53 yields activated 2-azadienes. They were shown to react with electron deficient acetylenic dienophiles 54 to yield pyridones 55. The reaction of 2-azadienes with activated nitriles 56 provided a very convenient route towards polysubstituted pyrimidones 57 (Scheme 14 and 15).$^{21}$

![Scheme 14](image)

![Scheme 15](image)

The construction of dihydropyrimidinones via the Biginelli reaction certainly ranks as one of the most recognized and frequently used MCRs for the generation of novel pyrimidine scaffolds. The reaction of aldehydes 34, \( \beta \)-ketoesters 58 and urea 59 leads to dihydropyrimidinones 60 having an ester moiety in the 5-position (Scheme 16).$^{22}$

16
N-Substituted ureas and thioureas in Biginelli reaction promoted by chlorotrimethylsilane were found to be very effective in the synthesis of N1-alkyl-, N1-aryl-, and N1,N3-dialkyl-3,4-dihydropyrimidin-2(1H)-(thi)ones from aldehyde, ethyl acetoacetate and substituted ureas (Scheme 17).

Ferric chloride/tetraethyl orthosilicate was also used as an efficient system for the synthesis of dihydropyrimidinones by Biginelli reaction from aldehyde, urea and ethyl acetoacetate (Scheme 18).

Ruthenium(III) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones from aldehyde, ester and urea under solvent-free conditions was put forward by Schauble et al. (Scheme 19).
N-Bromosuccinimide as an almost neutral catalyst for efficient synthesis of dihydropyrimidinones 68 from aldehyde 20, ester 63 and urea 67 under microwave irradiation was done by Karimi et al (Scheme 20).²⁶

One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones 70 from aldehyde 34, ester 69 and urea 59 via the catalysis of the Biginelli reaction by ferric and nickel chloride hexahydrates have been reported (Scheme 21).²⁷

A new three component condensation of an imine 71, an α-branched enolizable aldehyde 72 and a nucleophile, under ytterbium(III)trifluoromethane sulfonate [Yb(OTf)₃] catalyst condition would afford a variety of 1,2,3,4-tetrahydroquinolines 74 (Scheme 22).²⁸
Nair et al have reported MCRs involving diisopropylaminoisocyanide and DMAD. For example a variety of aldehydes and dicarbonyl compounds were reacted with diisopropylaminoisocyanide and DMAD leading to the formation of 1-aminopyrrolin-2-one derivatives (Scheme 23).

Recently the same group has explored the multicomponent reactions involving N-heterocyclic carbenes, activated acetylenes and aldehydes; t-butyl substituted imidazolin-2-ylidene, generated by the deprotonation of corresponding imidazolinum salt using NaH in dry toluene, on treatment with methyl phenylpropiolate and 4-trifluoromethylbenzaldehyde at 90°C afforded the aminofuran derivative in good yield. For 1,3-di-t-butylimidazol-2-ylidene the carbene formed insitu failed to react with methyl phenylpropiolate and aldehydes. However the reaction of the carbene with dimethyl acetylenedicarboxylate affords an acyclic four component adduct (Scheme 24 and 25).
Efficient synthesis of N-protected β-aryl-β-aminoketone compounds 86 have been carried out by transition metal salt-catalyzed direct three-component Mannich reactions of aldehydes 62, ketones 85, and carbamates (Scheme 26).  

Silver acetate catalyzed asymmetric Mannich reactions of enol ethers 88 with aryl, alkyl, alkenyl, and alkynyl imines have been reported (Scheme 27).  

A large variety of β-aminoketones 89 can be synthesized in the presence of 1-5 mol % of AgOAc and an inexpensive and readily available amino acid-derived phosphine. Ag-catalyzed asymmetric Mannich reactions can be run in undistilled THF and air.
The direct and enantioselective, one-pot, three-component, cross-Mannich reaction of aldehydes 62 with 4-methoxyaniline 90 have also been reported (Scheme 28).\textsuperscript{33}

In organocatalysis, proline derivatives are found to be improved catalysts for the asymmetric Mannich, nitro-Michael and aldol reactions (Scheme 29).\textsuperscript{34}

3-Pyrrolidinecarboxylic acid and related pyrrolidine derivatives are found to be efficient catalysts in enantioselective \textit{anti}-Mannich type reactions
Importance of the carboxyl group on pyrrolidine for stereocontrol have also been explored. Evaluation of a series of pyrrolidine-based catalysts indicated that the acid group at the β-position of the pyrrolidine ring of the catalyst played an important role in forwarding the carbon-carbon bond formation and in directing anti-selectivity and enantioselectivity.

Scheme 30

Diarylborinic acid derivatives can be used as a catalytic iminium ion generators in Mannich-type reactions using secondary amines 25, aldehydes 20, and ketenesilylacetals 97 (Scheme 31).

Scheme 31

Stereoselective synthesis of β-aminoketones from aldehyde 62, amine 99 and ketone 100 have been carried out by direct Mannich type reactions, catalyzed with ZrOCl₂·8 H₂O under solvent free conditions (Scheme 32).

Scheme 32

Matsuo et al have reported oxidative Mannich reaction of N-carbobenzyloxy amines with 1,3-dicarbonyl compounds (Scheme 33).
Efficient carbon–carbon bond formation at the α-position of nitrogen was established by one-pot oxidative Mannich reaction of N-carbobenzyloxy (Cbz) amines 103 with 1,3-dicarbonyl compounds using N-t-butylbenzenesulfinimidoyl chloride as an oxidant.

Scheme 33

A highly stereoselective direct vinylogous Mannich reaction using propylidenepropanedinitriles have been reported by Liu et al using an organic catalyst (Scheme 34). 39 The first direct asymmetric vinylogous Mannich (AVM) reaction of α,α-dicyanoolefins 106 and N-Boc aldimines 107 was described, promoted by a simple chiral bifunctional thiourea-tertairy amine organocatalyst. The reaction was highly efficient, regioselective, and stereoselective (generally >99% de, 96 to >99.5% ee) at room temperature for a broad array of substrates. Enantiomerically pure δ-amino acid could be smoothly prepared from the adduct.

Scheme 34

Asymmetric Mannich reactions have also been carried out by using protected amine 109 and 1,5-diphenylpentane-2,4-dione with an organic catalyst providing in situ generation of carbamate protected imines 111 (Scheme 35). 40
Scheme 35

Efficient synthesis of α,β-diamino acid derivatives 113 have been carried out by direct type catalytic three component Mannich reactions involving aldehyde 20, amine 25 and methyl[(diphenylmethylene) amino]acetate 112 (Scheme 36).\textsuperscript{41}

Scheme 36

Welch et al have derived spiro hydantoin aldose reductase inhibitors 116 from 8-aza-4-chromanones 115 (Scheme 37).\textsuperscript{42} The standard Bucherer-Bergs conditions had to be drastically modified to increase yields from less than 1% to an acceptable 50% range.

Scheme 37
Modified Bucherer-Bergs reaction for the one-pot synthesis of 5,5′-disubstituted hydantoins 119 have been reported from nitriles 117 and organometallic reagents (Scheme 38).\(^{43}\)

\[
\begin{align*}
&\text{R-CN} & \xrightarrow{\text{R'MgX, 5 mol% CuI}} & \text{THF, 70°C, 24 hr} & \xrightarrow{\text{NM}} & \text{R}^1\text{R}^1\text{N}\text{MgX, 5 mol% CuI} \\
&\text{117} & & & \text{THF/ EtOH/ H2O(1:4:4)} & \text{75°C, 24 hr} & \xrightarrow{\text{(NH4)2CO3 / KCN}} & \text{NH}_2\text{O} \\
&\text{118} & & & & & \text{119} \\
\end{align*}
\]

**Scheme 38**

Practical synthesis of tetrasubstituted thiophenes 122 have been carried out by using alkyl cyanoacetates 121 and esters 120 for use in compound libraries (Scheme 39).\(^{44}\)

\[
\begin{align*}
&\xrightarrow{\text{"S", Et2NH}} \text{pyridine, 25°C} & \text{18-48 hr} & \xrightarrow{\text{R O O}} \text{122} \\
&\text{120} & \text{121} & \text{R O O} \\
\end{align*}
\]

**Scheme 39**

Kumar et al have reported the efficient synthesis of Hantzsch esters 124 and polyhydroquinoline derivatives in aqueous micelles (Scheme 40).\(^{45}\)

\[
\begin{align*}
&\xrightarrow{\text{NH}_2\text{OAc / PTSA}} \text{SDS (0.1M in H2O)} & \text{123} & \text{125} & \text{124} \\
&\text{20} & \text{20} & \text{124} \\
\end{align*}
\]

**Scheme 40**

Synthesis of new dihydropyridine glycoconjugates 126 have been carried out by solvent-free Hantzsch reaction at room temperature from aldehyde 20 and ester 125 (Scheme 41).\(^{46}\)
Scheme 41

One-pot synthesis of 1,4-dihydropyridines 127 via a phenylboronic acid catalyzed Hantzsch three-component reaction have been carried out by Debache et al from aldehyde 20 and ester 63 (Scheme 42).47

Scheme 42

An environmentally benign approach toward the synthesis of pyridines 128 from aldehyde 20 and ester 63 have been done by the multicomponent domino cyclization-oxidative aromatization on a bifunctional Pd/C/K-10 catalyst (Scheme 43).48

Scheme 43

Covalently anchored sulfonic acid on silica gel have been found to be an efficient and reusable heterogeneous catalyst for the one-pot synthesis of Hantzsch 1,4-dihydropyridines 129 from aldehyde 20 and ester 65 under solvent-free conditions (Scheme 44).49
Yb(OTf)$_3$ catalyzed an efficient, operationally simple and environmentally benign Hantzsch reaction via a four-component coupling reaction of aldehydes 20, dimedone 130, ethyl acetoacetate 63 and ammonium acetate at ambient temperature to yield polyhydroquinoline derivatives 131 in excellent yield (Scheme 45).\(^{50}\)

An extremely efficient three-component reaction of aldehydes/ketones 132, amines 133, and phosphites 134 (Kabachnik-Fields Reaction) for the synthesis of $\alpha$-aminophosphonates 135 catalyzed by magnesium perchlorate have been reported under solvent-free conditions. The use of solvent retards the rate of the reaction and requires a much longer reaction time than that for neat conditions. The reactions involving cyclic ketones, aromatic amines with an electron-withdrawing substituent, and aryl alkyl ketone (e.g., acetophenone) require longer reaction times at room temperature or heating. (Scheme 46).\(^{51}\)

A facile and highly efficient route to $\alpha$-aminophosphonates 138 have been reported via three-component reaction of aldehyde 62, amine 136 and
diethyl phosphonate 137 catalyzed by Mg(ClO₄)₂ or molecular iodine (Scheme 47).⁵²

![Scheme 47]

Lee et al. have put forward a microwave-assisted Kabachnik-Fields reaction using aldehyde 62, amine 139 and diethyl phosphonate 137 in ionic liquid (Scheme 48).⁵³

![Scheme 48]

A novel catalytic three-component synthesis (Kabachnik-Fields Reaction) of α-aminophosphonates 142 from ketones 141 and amine 2 have also been reported (Scheme 49).⁵⁴

![Scheme 49]
Direct access to enantiomerically enriched α-aminophosphonic acid derivatives was obtained by organocatalytic asymmetric hydrophosphonylation of imines (Scheme 50).\(^{55}\) By using 10 mol % of quinine as the catalyst in the enantioselective addition of diethyl phosphonate 137 to N-Boc protected imines 143, α-aminophosphonates 144 are obtained in moderate to good yields and with up to 94% ee.

\[
\begin{align*}
\text{Ar} & \quad \text{H} \\
+ & \quad \text{O}_2\text{P(OMe)}_2 \\
\text{N-BOC} & \quad \text{H} \\
\text{Xylene, 20°C, 2-7 hr} & \quad \text{quinine} \\
\text{143} & \quad \text{137} & \quad \text{144}
\end{align*}
\]

**Scheme 50**

Supramolecular catalysis of Strecker reaction in water under neutral conditions in the presence of β-cyclodextrin have been reported by Rao et al (Scheme 51).\(^{56}\) An environmentally benign and highly efficient procedure for the nucleophilic addition of trimethylsilyl cyanide 146 to imines 145 (Strecker reaction) has been developed under biomimetic conditions in water in the presence of β-cyclodextrin to afford α-aminonitriles 147 in quantitative yields. The use of cyclodextrin precludes the use of either acid or base, and the catalyst can be recycled a number of times without loss in activity.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{N} & \quad \text{TMSN} \\
\text{H}_2\text{O} / \text{MeOH (10:1)} & \quad \text{r.t, 1-2 hr} \\
\text{145} & \quad \text{146} & \quad \text{147}
\end{align*}
\]

**Scheme 51**

Baeza et al have carried out solvent-free synthesis of racemic α-aminonitriles 149 from ketone 141 and amine 148 (Scheme 52).\(^{57}\)
Yadav et al have put forward a montmorillonite KSF clay catalyzed one-pot synthesis of α-aminonitriles 150 from ketone 20 and amine 21 (Scheme 53).\(^{58}\)

Catalytic one-pot, three-component acyl-Strecker reaction of aldehyde 20, amine 21 and nitrile have been reported by Pan et al (Scheme 54).\(^{59}\) Strecker reaction of aldimines catalyzed by a nucleophilic N-heterocyclic carbene have also been reported.\(^{60}\)

Zhu et al have put forward a one-pot three-component synthesis of α-iminonitriles 154 from aldehyde 20, amine 21 and trimethylsilyl cyanide 146
by IBX/TBAB mediated oxidative Strecker reaction (Scheme 55). \(^{61}\) The reaction of aldehydes, amines, and TMSCN in the presence of 2-iodoxybenzoic acid (IBX) and tetrabutylammonium bromide (TBAB) afforded \(\alpha\)-imino nitriles in good to excellent yields under mild conditions. The presence of TBAB is essential for this transformation. The methodology was applied to a two-step synthesis of indolizidine via a microwave-assisted intramolecular cycloaddition of \(\alpha\)-imino nitrile.

\[
\begin{align*}
\text{RCHO} & \quad + \quad \text{H}_2\text{N-R}^1 & \quad + \quad \text{TMSCN} & \quad \xrightarrow{\text{IBX, TBAB}} \quad \text{R-CN}
\end{align*}
\]

**Scheme 55**

Efficient synthesis of thiobenzanilides 156 by Willgerodt-Kindler reaction using aldehyde 62, sulfur and amine 99 with base catalysts have been put forward by Okamoto *et al* (Scheme 56). \(^{62}\)

\[
\begin{align*}
\text{ArCH} & \quad + \quad \text{S} & \quad + \quad \text{H}_2\text{N-Ar}^1 & \quad \xrightarrow{\text{5 - 15 mol % Na}_2\text{S.9H}_2\text{O}} \quad \text{Ar-S-Ar}^1
\end{align*}
\]

**Scheme 56**

Preparation of thioamide building blocks via microwave-promoted three-component Kindler reactions involving aldehyde, sulfur and amine have been put forward by Kappe *et al* (Scheme 57). \(^{63}\) Taking advantage of the sealed vessel capabilities of a dedicated single-mode microwave reactor, a diverse selection of thirteen aldehydes and twelve amine precursors was utilized in the construction of a representative 34-member library of substituted thioamides. The three-component condensations of aldehydes 20, amines 25, and elemental sulfur were carried out using 1-methyl-2-pyrrolidone (NMP) as solvent employing microwave flash heating at 110–180°C for 2–20 minutes. A simple workup protocol allows the isolation
of synthetically valuable primary, secondary, and tertiary thioamide building blocks $158$ in 83% average yield and >90% purity.

$$\text{O} R^1 \text{H} + S_8 + \text{NH}_2 \text{H} \rightarrow \text{S} R^1 \text{N} \text{R}^2$$

**Scheme 57**

Experiments showing stereochemical control of the Passerini reaction using acid $33$, aldehyde $34$ and isocyanide $22$ have been proposed by Schreiber *et al* (Scheme 58).$^{64}$ A catalytic asymmetric Passerini reaction using tridentate indan (pybox) Cu(II) Lewis acid complex with substrates capable of bidentate coordination has been achieved. The reaction occurs *via* ligand-accelerated catalysis.

$$\text{O} \text{OH} + \text{R}^1 \text{H} + \text{C}^{\ominus} \text{N} \text{R}^2 \rightarrow \text{O} \text{OH} \text{R}^1 \text{R}^2$$

**Scheme 58**

Alves *et al* have carried out the Passerini reaction using isocyanide $160$, aldehyde $34$ and acid $161$ under eco friendly reaction conditions (Scheme 59).$^{65}$

$$\text{R} \text{NC} + \text{R}^1 \text{H} + \text{HO} \text{R}^2 \rightarrow \text{R} \text{R}^1 \text{R}^2$$

**Scheme 59**
A three-component reaction of isocyanides 163, phenol derivatives 23 and aldehydes 20 in methanol forms O-arylated compounds 164 in a new Passerini-type reaction (Scheme 60). The key step is an irreversible Smiles rearrangement of intermediate phenoxyimidate adducts. It represents the first use of a Smiles rearrangement in a Passerini reaction.

Scheme 60

Veenstra and Schmid described a one-pot, three-component condensation of an aldehyde 165 and a carbamate with allyltrimethylsilane 167, to give the protected homoallyl amines 168 in high yields under boron trifluoride etherate as catalyst (Scheme 61).

Scheme 61

1-Substituted propan-2-ones 170 were prepared by the ring opening of 1-alkyl-2-methylene aziridines 169 with organocopper reagents in the presence of boron trifluoride diethyl etherate in 42-88% yield. This MCR has been applied to the synthesis of (Z)-6-heneicos-11-one 171, an important sex attractant of the Tussock moth (Scheme 62 and 63).

Scheme 62
The above reactions show the diversity of multicomponent reactions for the preparation of synthetically significant molecules in a one-pot manner.

The pyridine moiety is one of the important heteroaromatic ring systems present in numerous natural products and biologically active substances.\(^69\) The modification of the pyridine nucleus to various annulated heterocycles or naturally occurring alkaloids attracts considerable interest in organic chemistry.\(^70\) Halogenated pyridines are useful intermediates in drug research as they can be further elaborated to desired structures by Stille and Suzuki cross coupling reactions.\(^71\) Our literature survey revealed that there are only limited reports on the synthesis of 2-halopyridines.\(^72\) In some cases the existing heterocycles are functionalized by various halogenating reagents. Often cyclization reaction of substituted propylidene malononitriles, under acid catalyzed condition lead to the formation of 2-pyridone derivatives.\(^73\) In the literature there are some reports on alkylidene malononitriles, which undergo cyclization reactions under the Vilsmeier-Haack reaction conditions to afford functionalized 2-chloropyridines.\(^74\)
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