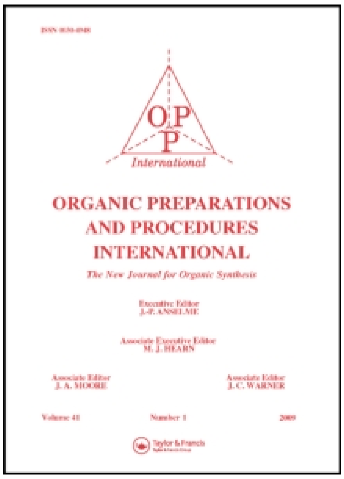

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A DECADE OF ADVANCES IN THREE-COMPONENT REACTIONS

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A DECADE OF ADVANCES IN THREE-COMPONENT REACTIONS. A REVIEW

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A DECADE OF ADVANCES IN THREE-COMPONENT REACTIONS

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INTRODUCTION

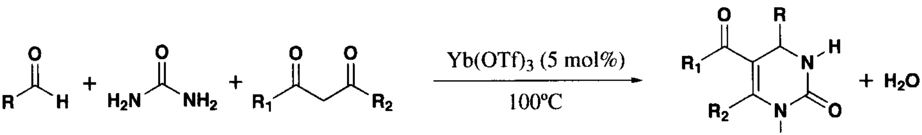
Multi-component reactions have emerged as powerful tools in the drug discovery endeavor[1-4] due to their potential for the generation of molecular diversity in a single synthetic step. Among the multi-component reactions, the three-component processes have been developed into useful organic procedures. Performing efficient chemical transformations by coupling three components in a single operation, *i. e.* making two bonds in one pot by using different catalysts, has attracted the attention of organic chemists. These three-component reactions have elicited enormous interest and several improved procedures have been reported during the last decade. The broad variety of compounds synthesized by these condensations will find important applications both in the academic and industrial fields. The present review covers the decade of advances (1994-2003) in three-component reactions.

I. THREE-COMPONENT NAME REACTIONS

1. Biginelli Condensation

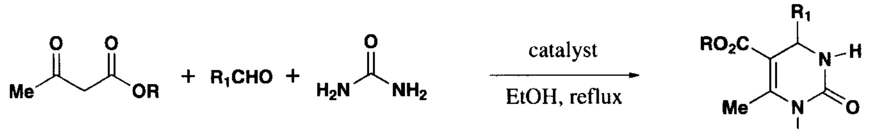
The one-pot cyclocondensation reaction of aldehydes, β-keto esters and urea to afford 3,4-dihydropyrimidine-2-ones was first reported in 1893 by Biginelli under strongly acidic conditions,[5] but often suffers from low yields, particularly for aliphatic and substituted aromatic aldehydes.[6,7] The dihydropyrimidinone derivatives are important due to their therapeutic and pharmacological properties and have emerged as integral backbones of several calcium channel blockers, antihypertensive agents and α-1a-antagonists.[8-10] Several marine alkaloids containing the dihydropyrimidine-5-carboxylate core unit have been isolated,[11] the most important of which are the batzelladine alkaloids which were found to be potent HIV-gp-120-CD_4 inhibitors.[12-14] In view of the importance of dihydropyrimidinones, the Biginelli reaction has been well studied[15-20] and several modifications and improvements have been realized through the discovery of milder and more efficient procedures using variety of catalysts.

An environmentally friendly process for the one-pot synthesis of Biginelli dihydropyrimidinones has been reported by Ma *et al.*[21] by using lanthanide triflate as a catalyst under solvent-free conditions (*Scheme 1*). It is a simple, high-yielding and time-saving process.



Scheme 1

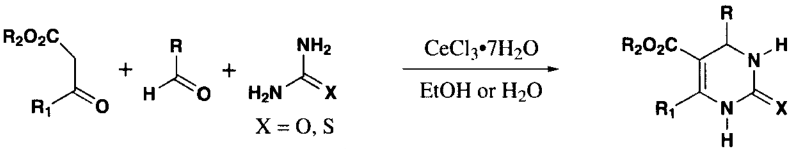
Lu *et al.* have described an efficient synthesis of 3,4-dihydropyrimidinones from an aldehyde, a β-keto ester and urea in ethanol using ferric chloride hexahydrate,[22] nickel chloride hexahydrate[23] or lanthanum chloride heptahydrate[24] as the catalyst (*Scheme 2*). Yields are significantly higher than utilizing the classical Bignelli reaction conditions.



catalyst: $FeCl_3 \cdot 6H_2O$ or $NiCl_2 \cdot 6H_2O$ or $LaCl_3 \cdot 7H_2O$

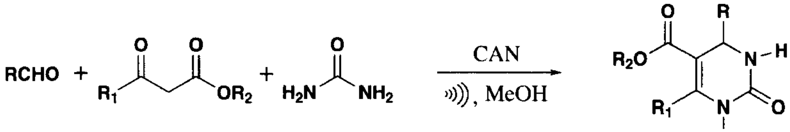
Scheme 2

A novel and improved protocol has been reported by Yadav *et al.*[25] for the three-component condensation reaction of an aldehyde, a β-keto ester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones in high yields under neutral conditions using lithium perchlorate or lithium triflate as the catalyst (*Scheme 3*). This method is effective for aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes. The ultrasound-accelerated synthesis of dihydropyrimidinones with ceric ammonium nitrate (CAN) in methanol in excellent yields has also been described by this group (*Scheme 4*).[26] Other oxidants such as manganese triacetate and oxone were also found to catalyze this reaction under sonication.



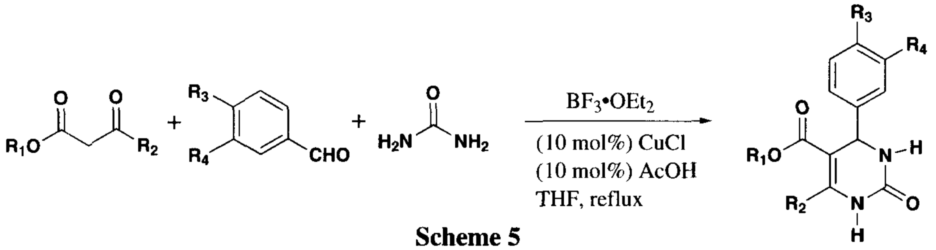
X = O, S

Scheme 17



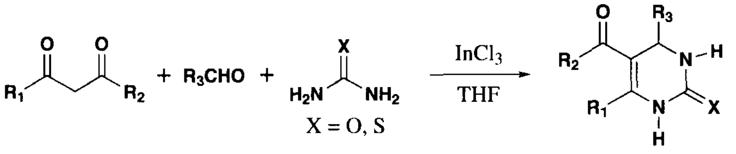
Scheme 4

Hu *et al.* have reported[19] an efficient synthesis of 5-alkoxycarbonyl-4-aryldihydropyrimidin-2(1*H*)-ones by an unprecedented catalytic one-pot condensation using a mixture of boron trifluoride etherate, copper(I) chloride and glacial acetic acid in THF under reflux (*Scheme 5*). These reaction conditions have led to a general method for the direct preparation of substituted dihydropyrimidinones in high yields.



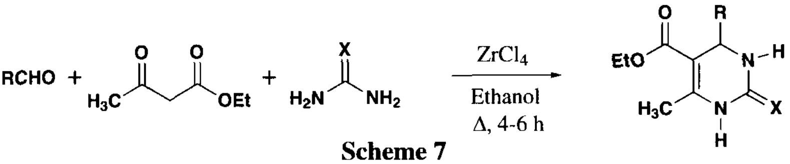
Scheme 5

The remarkable catalytic activity of indium(III) chloride for the one-pot condensation of 1,3-dicarbonyl compounds, aldehydes and urea or thiourea to dihydropyrimidinones or thiones has been described by Ranu *et al.* (*Scheme 6*).[27] It is applicable to a variety of substituted aromatic, aliphatic and heterocyclic aldehydes. These authors have also developed an efficient, cost-effective and green approach for the synthesis of dihydropyrimidinones without the use of solvent or catalyst.[28] Later, Fu *et al.*[29] have reported an indium(III) bromide protocol for the preparation of dihydropyrimidinones which features excellent yields and the possibility of recycling of the catalyst with no loss of activity.



Scheme 6

An efficient zirconium tetrachloride catalyzed method has been described by Reddy *et al.*[30] for the condensation of an aromatic aldehyde, a *β*-keto ester and urea in refluxing ethanol to afford the corresponding dihydropyrimidinones in high yields (*Scheme 7*). They have also reported[31] the same reaction under solvent free conditions at 100°C using *N*-butyl-*N*,*N*-dimethyl-*α*-phenylethylammonium bromide as catalyst.

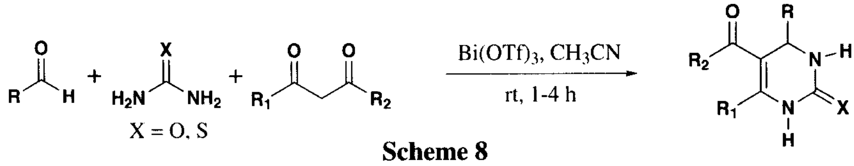


Scheme 7

Kappe and Falsone[32] have described a polyphosphate ester-mediated synthesis of dihydropyrimidines by the one-pot condensation of aldehydes, acetoacetates and ureas. Yields are significantly higher than those obtained using classical Biginelli reaction conditions.

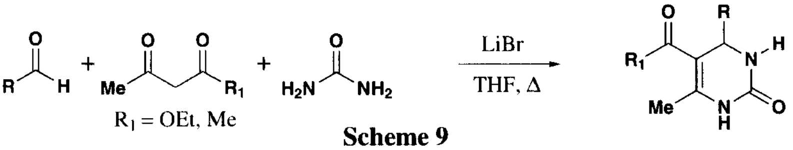
An efficient synthesis of 3,4-dihydropyrimidinones using bismuth triflate as a catalyst has been developed by Adapa *et al.*[33] from an aldehyde, a *β*-keto ester and urea in acetonitrile

(*Scheme 8*). The advantages of this method are high yields and short reaction times.



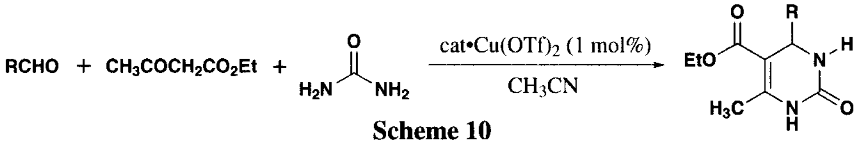
Scheme 8

A novel and efficient regioselective synthesis of dihydropyrimidinones has been reported by Sandhu *et al.*[34] using lithium bromide in tetrahydrofuran for the one-pot reaction of aldehydes, *β*-ketoesters and urea in excellent yields (*Scheme 9*), without any of the side-reactions observed by Biginelli and others. The method is applicable to aliphatic, aromatic and heterocyclic aldehydes. A slightly modified procedure was described by Maiti *et al.*[35]



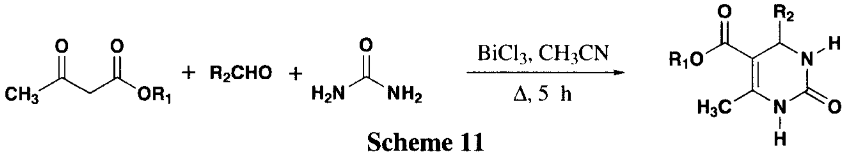
Scheme 9

Sudalai *et al.*[36] have reported a copper(II) triflate catalyzed, high-yield synthesis of dihydropyrimidinones by the condensation reaction of an aldehyde, a *β*-keto ester and urea in acetonitrile (*Scheme 10*). Excellent yields, recycling of the catalyst with negligible loss of activity and application to a variety of substituted/functionalized aryl aldehydes are some of the salient features of this process.



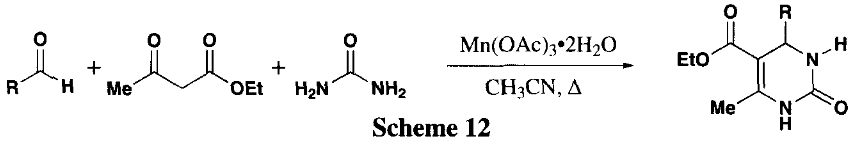
Scheme 10

An efficient synthesis of 3,4-dihydropyrimidines from an aldehyde, a *β*-keto ester and urea in acetonitrile using bismuth chloride as a catalyst has been described by Kaimal *et al.* (*Scheme 11*).[37] This method has the advantage of good yields compared to the classical Biginelli reaction conditions.



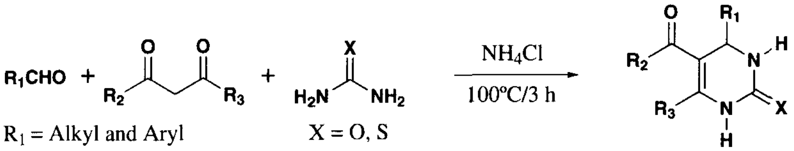
Scheme 11

4-Aryl-substituted 3,4-dihydropyrimidin-2-ones have been synthesized by Reddy *et al.*[38] in high yields by a one-pot cyclocondensation reaction of aldehydes, *β*-keto esters and urea using a catalytic amount of manganese acetate in refluxing acetonitrile (*Scheme 12*); the advantage of this method is the shorter reaction times.



Scheme 12

Shaabani *et al.*[39] have reported solvent-free conditions for the one-pot condensation reaction of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea by using very inexpensive ammonium chloride as a catalyst at 100°C to afford the corresponding 3,4-dihydropyrimidin-2-(1*H*)-ones in high yields (*Scheme 13*).



R_1 = Alkyl and Aryl

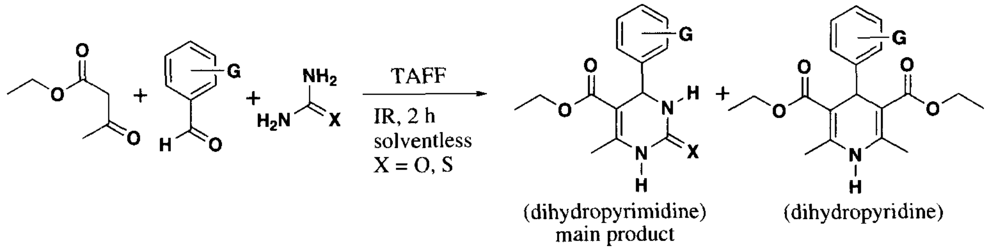
X = O, S

R_2 = Alkyl-O and Alkyl

R_3 = Methyl, Phenyl and 2-Thienyl

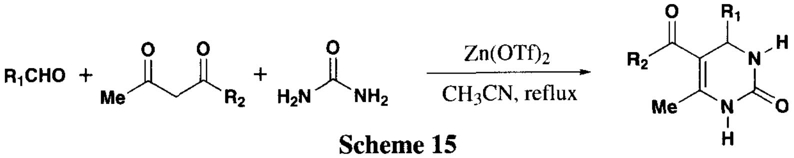
Scheme 13

A green chemistry protocol has been described by Miranda *et al.*[40] They studied the formation of the Biginelli and Hantzsch esters under infrared radiation and solventless conditions with Tonsil Actisil FF (TAFF), a commercial Mexican bentonitic clay as the catalyst (*Scheme 14*).



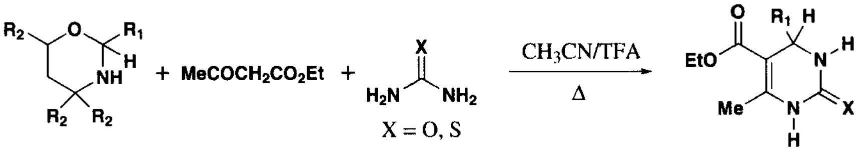
Scheme 14

An efficient synthesis of 4-aryl-5-substituted-6-methyl-3,4-dihydropyrimidin-2(1*H*)-ones has been reported by Wang and Xu[41] by the condensation reaction of aldehydes, 1,3-dicarbonyl compounds and urea using zinc trifluoromethanesulfonate as the catalyst in refluxing acetonitrile (*Scheme15*). When compared to the classical Biginelli reaction conditions, this new method has the advantage of superior yields.



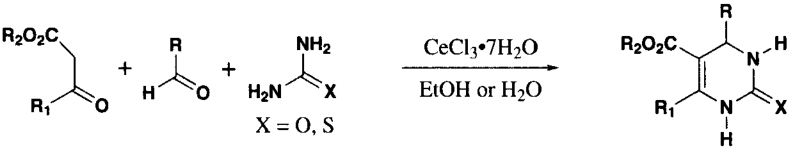
Scheme 15

Singh *et al.*[42] have described an expedient protocol for dihydropyrimidine synthesis with a variety of substituents at C-4 by the one-pot condensation of perhydro-1,3-heterocycle-aldehyde equivalents with ethyl acetoacetate and urea (*Scheme 16*). Yields are comparable or higher than those of the conventional methods.



Scheme 16

A green chemistry route to the Biginelli cyclocondensation reaction has been described by Bose *et al.*[43] for the synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones, in the presence of cerium(III) chloride (25 mol%) (*Scheme 17*).



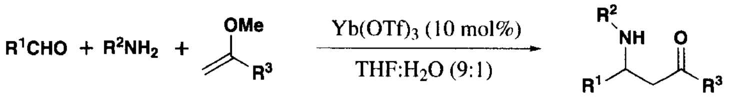
Scheme 17

The Biginelli condensation has also been reported[44] using CBr_4 in methanol. A *p*-toluenesulfonic acid-catalyzed efficient synthesis of dihydropyrimidines has been described[45] by the one-pot cyclocondensation of aldehydes, *β*-keto esters and urea. Dondoni *et al*[46,47] have disclosed the synthesis of C-glycosylated dihydropyrimidine libraries *via* the cyclocondensation of urea with C-glycosylated aldehydes and *β*-keto esters in a combinatorial manner. A vanadium(III) chloride-catalyzed Biginelli condensation has also been reported.[48] One-pot synthesis of dihydropyrimidinones has been described using *in situ* generated iodotrimethylsilane at room temperature.[49] A simple effective approach using boric acid as the catalyst in glacial acetic acid has also been reported.[50]

2. *Mannich Reaction*

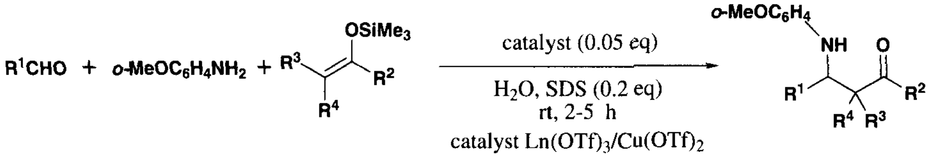
The reaction of an active methylene compound with formaldehyde and an amine to form a *β*-amino carbonyl compound (*Mannich base*) is known as the Mannich reaction.[51-54] Mannich was the first to recognize the significance of this reaction as one of the most important C-C bond forming reactions in organic chemistry. Mannich bases have found wide applications[55-57] in the synthesis of numerous pharmaceuticals and of natural products. The classical Mannich reaction has limited applications, but later developments have resulted in a variety of novel Mannich-type reactions.[58-63]

The first aqueous Mannich-type reaction catalyzed by a lanthanide triflate has been developed by Kobayashi and Ishitani for the reaction between an aldehyde, an amine and a vinyl ether to afford *β*-amino ketones in good yields (*Scheme 18*).[64] Kobayashi *et al.* have also reported Mannich-type three component coupling reactions of aldehydes, amines and silyl

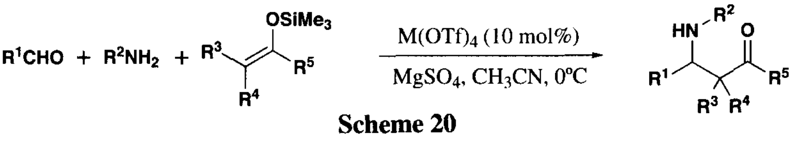


Scheme 18

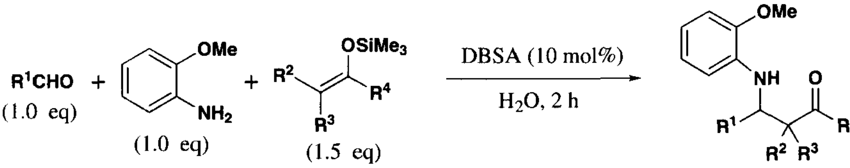
enolates to afford *β*-amino carbonyl compounds using various reagents: in micellar systems using Ln(OTf)$_3$ or Cu(OTf)$_2$ as catalysts in water (*Scheme 19*),[65] in the presence of a catalytic amount of a group 4 metal triflate [Zr(OTf)$_4$ or Hf(OTf)$_4$] (*Scheme 20*),[66] using a catalytic amount of lanthanide triflate and a dehydrating reagent such as 4 Å molecular sieves or MgSO$_4$;[67]/or in the presence of water, dodecylbenzenesulfonic acid (DBSA) as a Brønsted acid-surfactant combined catalyst[68](*Scheme 21*[69] and *Scheme 22*[70]).



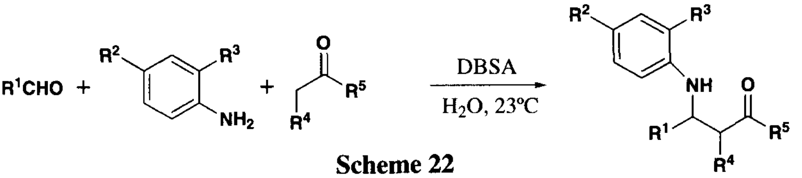
Scheme 19



Scheme 20

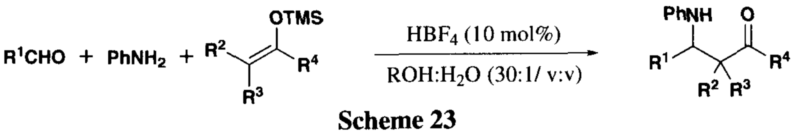


Scheme 21



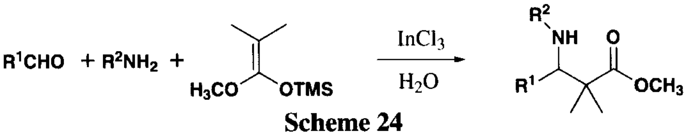
Scheme 22

A one-pot synthesis of *β*-amino carbonyl compounds from an aldehyde, an amine and a silyl enolate has been reported by Akiyama *et al.*[71] using HBF$_4$ as a catalyst in aqueous media (*Scheme 23*). They have also presented another method using the same catalyst in water in the presence of a surfactant.[72]



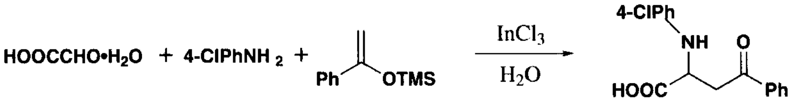
Scheme 23

A novel one-pot Mannich type reaction in water has been described by Loh and Wei[58] for the InCl$_3$ catalyzed condensation of aldehydes, amines and silyl enol ethers to afford *β*-amino esters (*Scheme 24*) and ketones (*Scheme 25*). Under the same conditions, glyoxalic acid monohydrate can also be used directly to give the α-amino acids (*Scheme 26*).



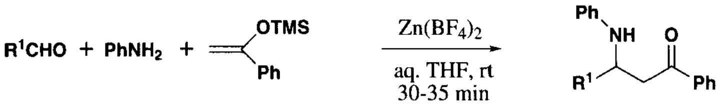
Scheme 24

Scheme 25



Scheme 26

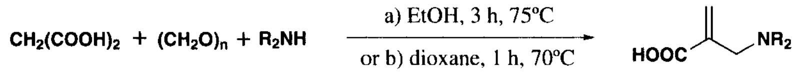
Ranu *et al.*[73] have discovered a zinc tetrafluoroborate catalyzed Mannich-type one-pot reaction of aldehydes, amines and silyl enol ethers for the synthesis of *β*-amino carbonyl compounds (*Scheme 27*).



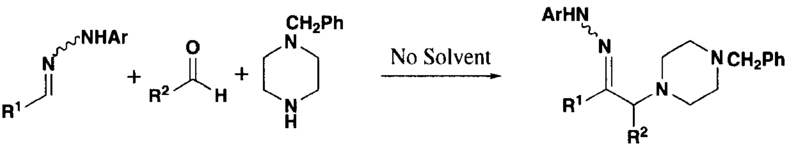
Scheme 27

A one-pot Mannich reaction of electron-rich aromatic compounds using aldehydes, dialkylamines at room temperature in 5 M ethereal lithium perchlorate has been reported by Saidi *et al.*[74] to afford amino alkylated products in good yields. Earlier, the same group has also described a simple one-pot reaction for the preparation of secondary amines and amino esters mediated by lithium perchlorate.[75]

The Mannich reaction of malonic acid with paraformaldehyde and secondary aliphatic amines has been described by Krawczyk (*Scheme 28*).[76] Kaïm *et al.*[77] have reported the use of hydrazones for Mannich reactions and an efficient Mannich-type reaction using hydrazones, aldehydes and diethylamine has been developed to furnish Mannich adducts.[78] They have also described the Mannich type reaction of hydrazones under solvent free conditions (*Scheme 29*).[79]



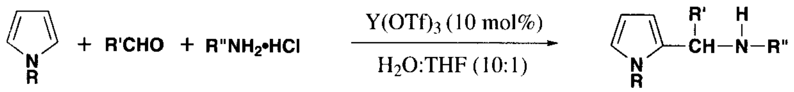
Scheme 28



Scheme 29

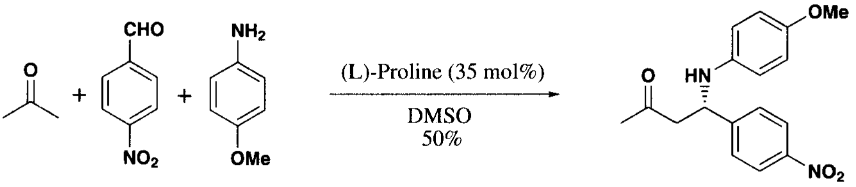
R^1 = RCO, Ar

A novel Mannich reaction between *N*-alkoxycarbonylpyrroles, formaldehyde and a primary amine hydrochloride catalyzed by $Y(OTf)_3$ in aqueous media has been reported by Li *et al.*[80] to afford a monoamino alkylation product in good yields (*Scheme 30*).



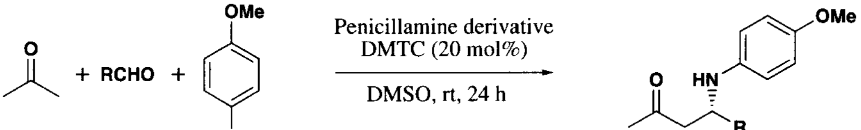
Scheme 30

Mannich-type reactions that produce enantiomerically enriched products are called asymmetric Mannich reactions. The catalytic, asymmetric Mannich reaction is one of the most useful methods for the construction of chiral nitrogen-containing molecules. Shibasaki *et al*[81] have developed a direct catalytic asymmetric Mannich reaction of unmodified ketones by the cooperative catalysis of a heterobimetallic asymmetric complex, AlLibis(binaphthoxide) (ALB) and $La(OTf)_3.nH_2O$ in the presence of MS 3Å. The proline-catalyzed highly enantioselective Mannich reaction has been reported by List (*Scheme 31*).[82] In a later report,[83] the same reaction was utilized for the highly enantioselective synthesis of 1,2-amino alcohols. Catalytic asymmetric Mannich-type reactions using a novel chiral iron complex has been reported by Kobayashi *et al.*[84] Barbas *et al.*[85] have described an amine-catalyzed asymmetric Mannich-type reaction of aldehydes, acetone, *p*-anisidine to furnish the corresponding *β*-amino ketones with 50-89% ee under very mild conditions (*Scheme 32*).



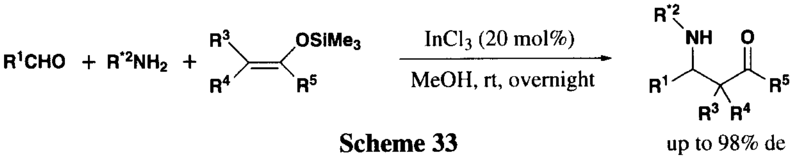
Scheme 31

(*S*)-1 94% ee



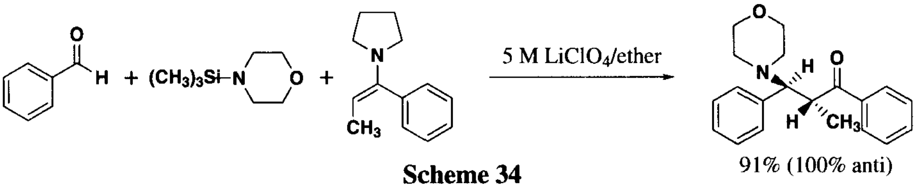
Scheme 32

Loh *et al.*[86] have reported an $InCl_3$-catalyzed one-pot Mannich-type reaction in water for the synthesis of *β*-amino carbonyl compounds. An $InCl_3$-catalyzed asymmetric Mannich-type reaction in methanol has also been developed by the same group in one-pot involving the reaction of aldehydes, amines and silyl enol ethers/silylketene acetals to afford the *β*-amino carbonyl compounds in high yields with high diastereoselectivities (*Scheme33*).[87] Kunz and Allef[88] have described a glycosylation induced asymmetric synthesis of *β*-amino acid esters using Mannich reactions.



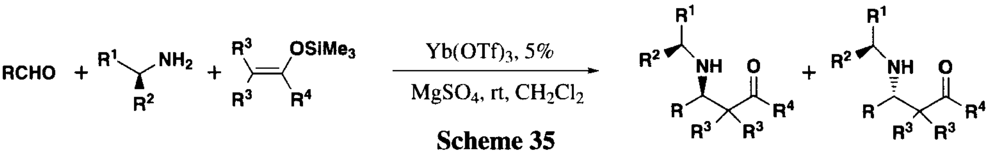
Scheme 33

A diastereo- and enantioselective one-pot Mannich synthesis of *β*-amino ketones has been described by Ipaktschi *et al.*[89] using the addition reaction of enamines, imines or trimethylsilyl enol ethers to aldehydes (enolizable and non-enolizable) and (trimethylsilyl)dialkylamines in concentrated ethereal lithium perchlorate (*Scheme 34*). High diastereoselectivity was achieved with aromatic aldehydes such as benzaldehyde, pyridine-3-carbaldehyde or thiophene-2-carbaldehyde, whereas the aminoalkylation of aliphatic aldehydes such as isobutyraldehyde and pivalaldehyde lacked diastereoselectivity.

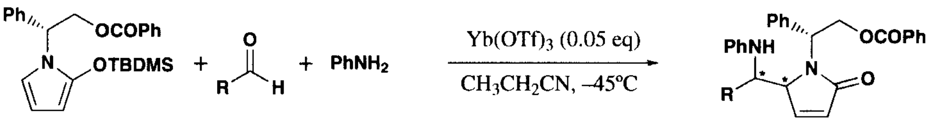


Scheme 34

Umani-Ronchi *et al.*[90] have proposed a one-pot highly diastereoselective synthesis of *β*-amino esters starting from an aldehyde, a chiral amine and a silyl enolate using lanthanide triflate as a catalyst at room temperature (*Scheme 35*). Good to excellent levels of diastereoselection have been achieved by the use of (*S*)-valine methyl ester as chiral amine. Another Yb(OTf)$_3$-catalyzed diastereoselective Mannich-type reaction of the chiral non-racemic silyloxypyrrole has been described by Royer *et al.*[91] for the one-pot reaction of a silyloxypyrrole, an aldehyde and an amine with *erythro* selectivity (*Scheme 36*).

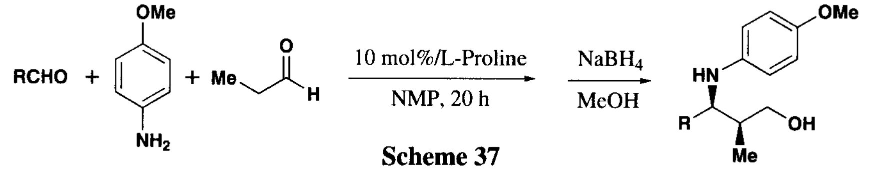


Scheme 35



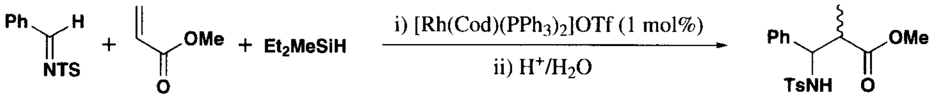
Scheme 36

Hayashi *et al.*[92] have reported a direct and enantioselective, one-pot, cross-Mannich reaction of two different aldehydes in which one aldehyde is employed as the Mannich donor and the other is utilized as a component of the Mannich acceptor to afford a synthetically versatile *β*-amino aldehyde (*Scheme 37*). Since the *β*-amino aldehyde decomposed during purification by column chromatography on silica gel, it was isolated and characterized after reduction with $NaBH_4$ to the corresponding *β*-amino alcohol.



Scheme 37

A rhodium-catalyzed method to give a Mannich type product from the reaction of an aldimine with an α,β-unsaturated ester and a hydrosilane has been reported by Muraoka *et al.* (*Scheme 38*).[93]



Scheme 38

3. *Hantzsch Reaction*

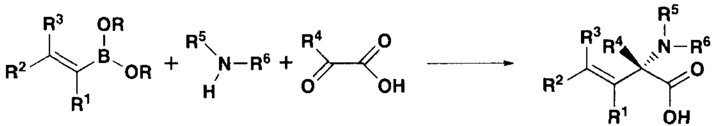
The one-pot condensation of aldehydes, *β*-ketoesters and ammonia in refluxing acetic acid or alcohol solvent to afford 1,4-dihydropyridines was first described by Hantzsch.[94] 1,4-Dihydropyridines are an important class of calcium channel antagonists[95] with widespread pharmacological applications. The dihydropyridine moiety is also common to a variety of bioactive compounds which include various vasodilator, bronchodilator, antihypertensive, antitumor, antiatherosclerotic, hepatoprotective, antimutagenic, geroprotective and antidiabetic agents.[96-98] Several improved procedures have been developed for the Hantzsch three-component condensation which led to increased yields, substantially reduced reaction times and decreased the environmental impact. The major improvements to procedures for Hantzsch-type reactions include microwave (which are mentioned under the microwave-assisted three-component condensations) and solid phase[99,100] methods, in addition to general modified [101-103] methods.

Another type of Hantzsch three-component reaction is the Hantzsch pyrrole synthesis which involves the reaction of *α*-chloromethyl ketones with *β*-ketoesters and ammonia to furnish pyrroles.[104] Pyrroles are the important structural subunit of porphyrins, bile pigments and other natural products. Developments in the Hantzsch type pyrrole synthesis have also been reported.[105]

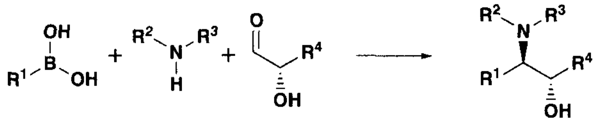
4. *Petasis Reaction*

Petasis *et al.* first reported[106,107] the use of organoboronic acids in a Mannich reaction and later introduced a one-step three-component boronic Mannich reaction based on simple mixing of an aryl- or alkenylboronic acid, an amine and an aldehyde at room temperature to afford *α*-amino acids.[108] It is also a powerful route to *β*-aminoalcohols.[109] The products obtained serve as building blocks in combinatorial chemistry[110] and drug discovery. There are several reports in the literature for this reaction by variation of either the boronic acid, the amine or the aldehyde components.

Petasis and Zavialov[111] have developed a three-component variant of the Mannich reaction for the synthesis of α-amino acids and their *N*-substituted derivatives. It is the condensation of an organoboronic acid or boronate with an amine and an α-keto acid such as glyoxylic or pyruvic acid by simply stirring the three-components at 25-50°C over 12-48 h in a variety of solvents, including ethanol, toluene and dichloromethane (*Scheme 39*). A new synthesis of α-aryl- and α-heteroarylglycines has also been reported[112] by the same group. They have also described a new, practical and highly diastereocontrolled approach to a variety of *anti*-β-amino alcohols[113] using a one-step reaction of an organoboronic acid, an amine and an α-hydroxy aldehyde (*Scheme 40*) in ethanol/dichloromethane or ethanol/water mixtures at ambient temperature for 12-48 h. Direct synthesis of piperazinones has been reported by Petasis and Patel[114] using the reaction of 1,2-diamines, organoboronic acids and glyoxylic acid, most efficiently in refluxing acetonitrile. Petasis and Boral[115] have shown that functionalized Mannich-like products (aminomethylphenol derivatives) can be obtained directly in one-step by the reaction of organoboronic acids, amines and salicylaldehydes at room temperature (*Scheme 41*). Olah *et al.*[116] have also disclosed a facile stereocontrolled synthesis of *anti*-α-(trifluoromethyl)-β-amino alcohols. They have also reported a stereoselective synthesis of anti-α-(difluoromethyl) β-amino alcohols[117] (*Scheme 42*) using the reaction of a difluoro lactaldehyde, an amine and an alkenyl- or arylorganoboronic acid.

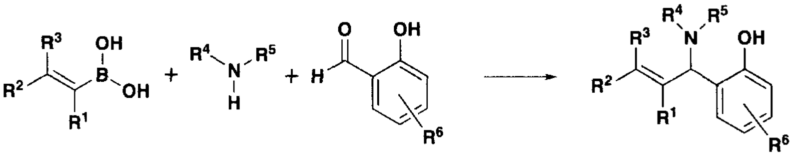


Scheme 39

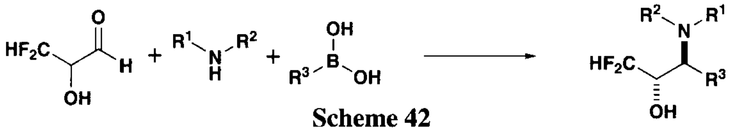


Scheme 40

>99%de, >99%ee

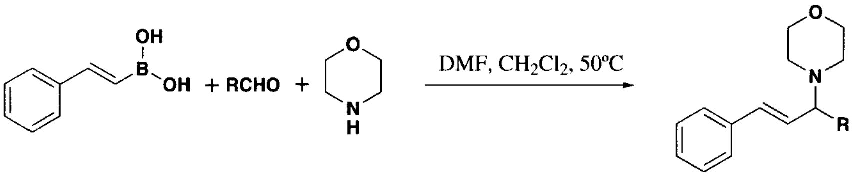


Scheme 41



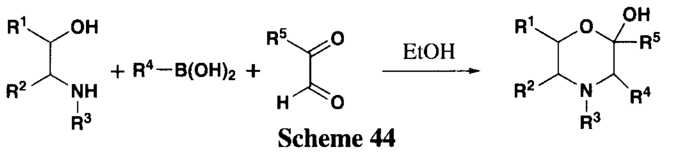
Scheme 42

A range of heterocylic aldehydes as novel components in the boronic Mannich reaction have been shown by Schlienger *et al.*,[118] for the first time, to provide an expedient synthesis of new highly-functionalized small molecules (*Scheme 43*). Carboni *et al.*[119] have reported an efficient one-pot synthesis of substituted 2-hydroxymorpholines (*Scheme 44*) *via* the three-component Petasis coupling reaction of a 1,2-aminoalcohol, an organoboronic acid and a glyoxal derivative.



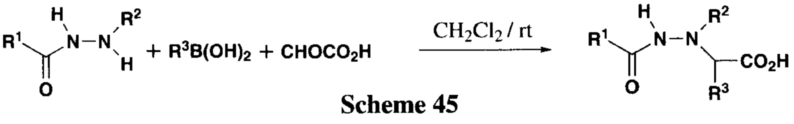
Scheme 43

R = heterocyclic group



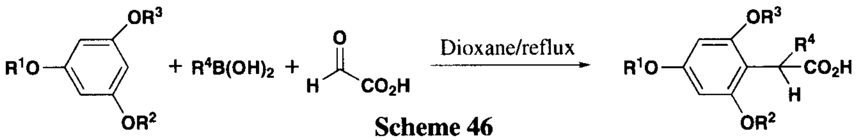
Scheme 44

Pinacolylboronic esters have been used by Scobie *et al.*[120] as components in the Petasis reaction of secondary amines with glyoxylic acid. The enantioselective version of the Petasis reaction using glyoxylic acid, morpholine and a homochiral boronic ester as the chiral auxiliary has been demonstrated by the same group.[121] A highly diastereoselective synthesis of optically active-3-indolyl-*N*-substituted glycines *via* a chiral amine mediated 3-indolylboronic acid Mannich reaction has been reported by Jiang *et al.*[122] A practical synthetic route for the preparation of α-hydrazinocarboxylic acids has been described by Portlock *et al.*[123] for the Petasis boronic-Mannich reaction using *N*-1-(carbonate protected)-*N*-2(alkyl or aryl substituted) hydrazines as amine substrates (*Scheme 45*).



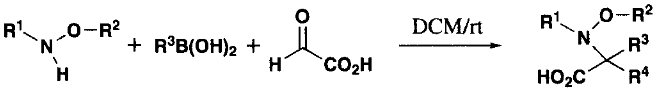
Scheme 45

Naskar *et al.*[124] have developed a route for the synthesis of α-(1,3,5-trioxygenated phenyl)carboxylic acids (*Scheme 46*) using 1,3,5-trioxygenated benzenes as substrates for the

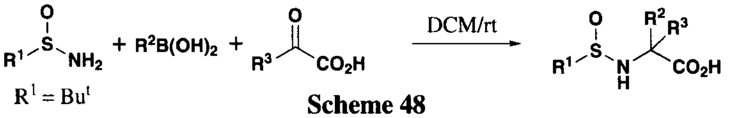


Scheme 46

Petasis boronic acid reaction without incorporating an amine component. They have also investigated the use of substituted hydroxylamines and *tert*-butylsulfinamide as amine components in the Petasis boronic-Mannich reaction for the efficient synthesis of *N*-hydroxy- or alkoxy-α-aminocarboxylic acids (*Scheme 47*) and *N*-(*tert*-butyl sulfinyl)-α-aminocarboxylic acids (*Scheme 48*).[125]



Scheme 47

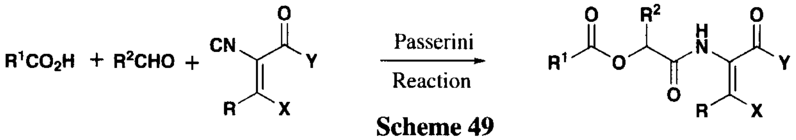


Scheme 48

5. Passerini Reaction

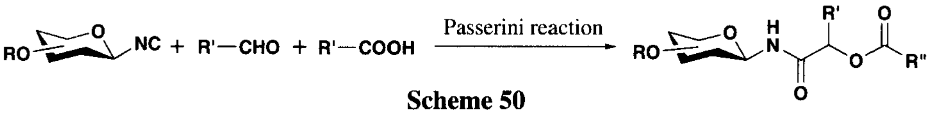
This is the most important reaction among the isocyanide based multi-component reactions. The Passerini reaction is the three-component reaction of isocyanides, aldehydes or ketones and carboxylic acids, preferably carried out in apolar aprotic solvents to afford α-acyloxy carboxamides.[126,127] A novel butenolide synthesis has also been reported[128] using the Passerini reaction and there are several other reports on Passerini-type reactions.

Burger *et al.*[129] have described a methodolgy for incorporation of α-trifluoromethoxy substituted amino acids into the *C*-and *N*- terminal positions of peptides and peptide mimetics *via* a Passerini reaction. Bienaymé[130] has investigated the Passerini reaction providing structurally diverse isonitriles to increase the library size and diversity. Based on the Passerini condensation reaction, Armstrong *et al.*[131] have synthesized a library of dehydroamino acid derivatives (*Scheme 49*).



Scheme 49

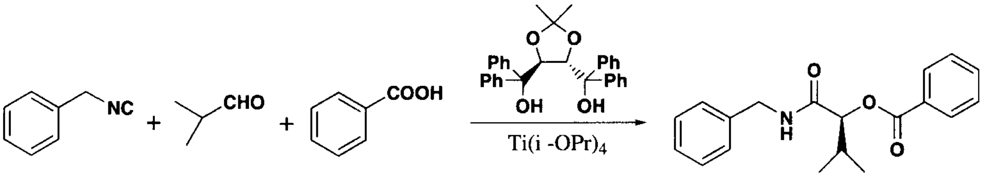
The Passerini reaction of acetyl and benzyl protected β-D-glucopyranosyl isonitriles with aldehydes and acetic acid (*Scheme 50*) has been reported by Ziegler *et al.* [132] They have also



Scheme 50

reported[133] an easy access to complex glycopeptide derivatives using the Passerini reaction of benzyl and acetyl protected isocyano glucose derivatives with carbonyl compounds and carboxylic acids.

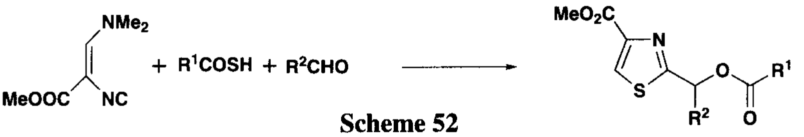
A camphor-derived isocyanide has been employed by Bock and Ugi[134] to induce diastereoselectivity in the Passerini three-component reaction. A new synthetic technology for the efficient construction of α-hydroxy-β-amino amides *via* the Passerini reaction has also been developed.[135] Frey *et al.*[136] have reported a highly stereoselective Passerini reaction in which achiral benzaldehydes and isocyanides could be transformed enantioselectively to chiral mandelamides in a three-component reaction by using a galacturonic acid derivative as the chiral inducer. An enantioselective Passerini reaction using a chiral Lewis acid catalyst has been reported by Dömling *et al.* (*Scheme 51*).[137] Denmark and Fan[138] have reported a chiral-Lewis-base-catalyzed, enantioselective Passerini-type reaction.



Scheme 51

ee = 32-42%

Jenner[139] has examined the effect of high pressure on the Passerini reaction. This study reports that elevated pressures offer an attractive tactic to synthesize sterically congested Passerini products. The application of a $TMSN_3$-modified Passerini reaction for the rapid generation of *cis*-constrained norstatine analogs has been achieved by Nixey and Hulme.[140] Dömling *et al.*[141] have developed an easy access to substituted 2-acyloxymethyl thiazoles by the reaction of thiocarboxylic acids, methyl 3-(*N,N*-dimethylamino)-2-isocyano acrylate and aldehydes (*Scheme 52*).

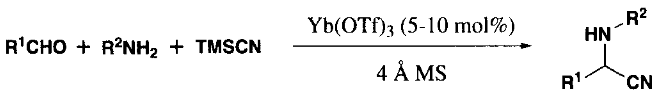


Scheme 52

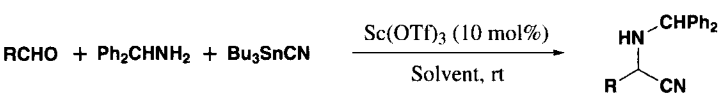
6. *Strecker Reaction*

The first multi-component (three-component) reaction recognized was the Strecker[142] reaction in 1850, which is the one-pot three-component coupling reaction of an amine (masked ammonia), an aldehyde and hydrogen cyanide to give α-amino nitriles. α-Amino nitriles are the precursors for the preparation of α-amino acids and the Strecker reaction provides one of the most efficient methods for the synthesis of various biologically useful molecules.[143] Over the years, the classical Strecker reaction has undergone several modifications with the development of various cyanating agents under different reaction conditions.

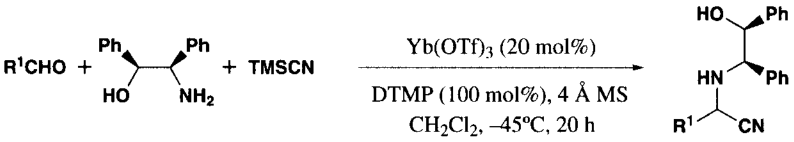
Kobayashi *et al.*[144] have reported a facile synthesis of α-amino nitriles using the three-component reaction of aldehydes, amines and TMSCN in the presence of $Yb(OTf)_3$ and 4 Å MS (*Scheme 53*). They have also developed scandium triflate-catalyzed Strecker-type reactions of aldehydes, amines and tributyltin cyanide (*Scheme 54*) to afford α-amino nitriles in high yields in both organic and aqueous solutions with complete recovery of the tin compounds. This is an environmentally friendly chemical process.[145] The asymmetric reaction using a chiral amine has also been reported[144] to afford α-amino nitriles with excellent diastereoselectivity (*Scheme 55*) in the presence of $Yb(OTf)_3$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTMP). They have also described a catalytic asymmetric version of the Strecker reaction of achiral aldehydes, amines and hydrogen cyanide using a chiral zirconium catalyst to furnish chiral α-amino nitriles with high yields and enantioselectivities (*Scheme 56*).[146,147]



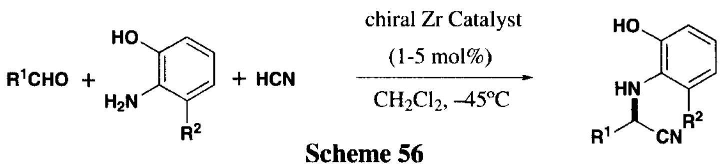
Scheme 53



Scheme 54



Scheme 55



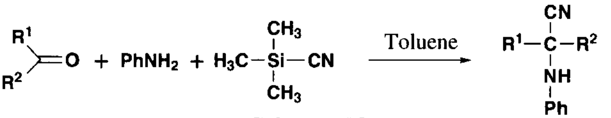
Scheme 56

Heydari *et al.*[148] have developed an efficient one-pot method for the preparation of α-amino nitriles from aldehydes, amines and TMSCN catalyzed by LPDE (lithium perchlorate/diethyl ether). A simple and general method has been elaborated for the synthesis of

α-amino nitriles by Ranu *et al.*[149] using a one-pot condensation of aldehydes or ketones, amines and potassium cyanide in THF in the presence of a catalytic amount of $InCl_3$ (*Scheme 57*).

Scheme 57

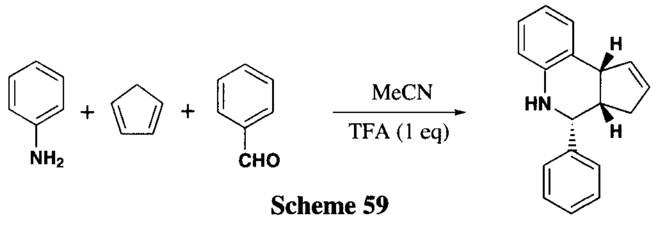
A convenient synthesis of *N,N*-dialkyl-α-cyanoamines has been reported by Sun *et al.*[150] using the condensation reaction of aldehydes, secondary amines and trimethylsilyl cyanide in the presence of 10 mol% of La(O-*i*-Pr)$_3$. A high pressure mediated Strecker synthesis of α-amino nitriles has been described by Jenner *et al.* [151] using the reaction of ketones, aromatic amines and trimethylsilyl cyanide under high pressure (600 MPa) reaction conditions in the absence of a catalyst (*Scheme 58*). The same group has also reported[152] the effect of pressure on the Strecker synthesis of hindered α-amino nitriles from ketones and aromatic amines.



Scheme 58

7. Grieco Condensation

The three-component condensation reaction of aromatic amines, electron-rich olefins and aldehydes in the presence of equimolar trifluoroacetic acid (TFA) in acetonitrile for the synthesis of tetrahydroquinolines has been recently reported by Grieco *et al.* (*Scheme 59*).[153] In view of the importance of tetrahydroquinolines[154,155] as biologically active compounds, this reaction has been extended by others and the use of solid support versions[156-158] has also been reported.



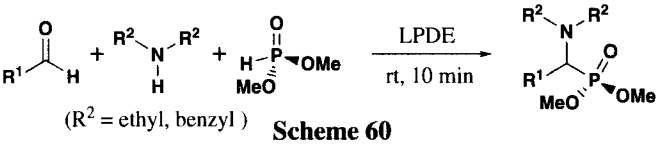
Scheme 59

A one-pot synthesis for the formation of tetrahydroquinolines has been established by Mellor and Merriman,[159] based upon the reaction of aromatic amines and formaldehyde with electron rich alkenes such as styrene, α-methylstyrene, 1-phenylcyclohexene and 3,4-dihydro-2*H*-pyran. They have also reported[160] the extension of this chemistry to aminoanthraquinones by the cyclocondensation reaction of mono- and diaminoanthraquinones with formaldehyde and diverse electron-rich alkenes to afford a series of tetrahydroquinolines in acetonitrile in the presence of trifluoroacetic acid.

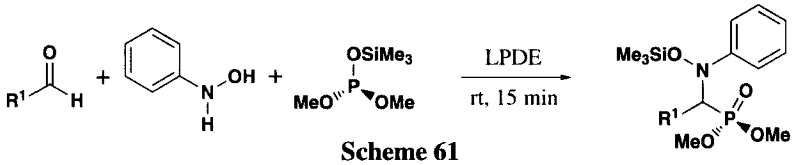
II. SYNTHESIS OF α-AMINOPHOSPHONATES AND RELATED PHOSPHONATES BY THREE-COMPONENT REACTIONS

α-Aminophosphonates, the structural analogues of corresponding α-amino acids, are an important class of compounds, which exhibit a wide range of biological activities such as peptide mimics,[161] enzyme inhibitors,[162] pharmacological agents,[163] antibiotics[164] etc. As derivatives of α-aminophosphonic acids, α-hydrazinophosphonic acids[165] and *N*-hydroxy-α-aminophosphonates[166] are of considerable interest owing to their potential biological activities. A variety of methods have been devised for the preparation of α-aminophosphonates in the literature. The classical approach for their synthesis is the Kabachnick-Fields reaction,[167,168] which is a one-pot, three-component operation with a carbonyl compound, an amine and a dialkylphosphite. This reaction is not known by its name, unlike other three-component "name" reactions, in spite of the development of various catalysts and conditions for the one-pot synthesis of α-aminophosphonates.

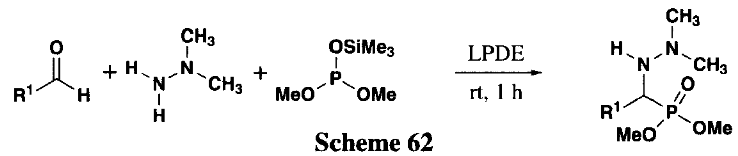
Heydari *et al.* have reported the preparation of four different types of phosphonates using lithium perchlorate/diethyl ether (LPDE) as a catalyst: (a) a one-pot method for the preparation of α-aminophosphonates from aldehydes, amines and dimethyl phosphite, catalyzed by LPDE (*Scheme 60*);[169] this methodology has been extended to the preparation of chiral α-aminophosphonates derived from (*R*)-(+), (*S*)-(–)-α-methylbenzylamines etc; (b) a new approach for the synthesis of *N*-trimethylsilyloxy-α-aminophosphonates from aldehydes, hydroxylamines and dimethyl (trimethylsilyl)phosphonates in high yields using LPDE as a catalyst (*Scheme 61*);[170] (c) a one-pot synthesis of α-hydrazinophosphonates by the reaction of aldehydes, *N*,*N*-dimethylhydrazine and dimethyl (trimethylsilyl)phosphite using LPDE (*Scheme 62*);[171] (d) a practical and cost effective strategy[172] for the preparation of α-hydrazinophosphonates and *N*-hydroxy-α-aminophosphonates using the reaction of aldehydes, *N*,*N*-dimethylhydrazine and trimethyl phosphite/trimethylsilyl chloride (acetic acid) in the presence of 5.0 M LPDE.



Scheme 60

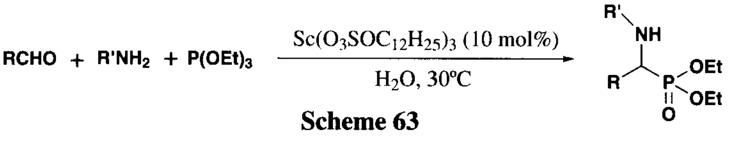


Scheme 61



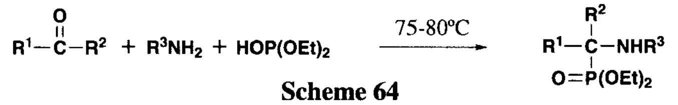
Scheme 62

A facile synthesis of α-aminophosphonates in water using a Lewis acid-surfactant combined catalyst namely scandium tris(dodecyl sulfate) at ambient temperature has been reported by Kobayashi and Manabe[173] using the reaction of aldehydes, amines and triethyl phosphite (*Scheme 63*). Ranu *et al.*[174] have reported an $InCl_3$ catalyzed synthesis of α-aminophosphonates.



Scheme 63

The same group has also developed a simple and greener method for the synthesis of α-aminophosphonates *via* a solvent- and catalyst-free one-pot condensation of a carbonyl compound, an amine and diethyl phosphite (*Scheme 64*).[175]



$$R^1\text{–}C(=O)\text{–}R^2 + R^3NH_2 + HOP(OEt)_2 \xrightarrow{75\text{-}80^\circ C} R^1\text{–}C(R^2)(P(=O)(OEt)_2)\text{–}NHR^3$$

Scheme 64

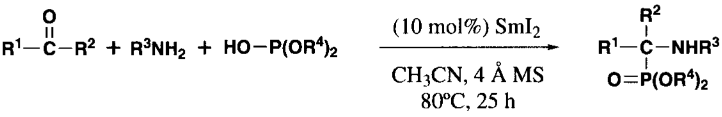
A very mild, efficient and simple method for the synthesis of tertiary α-aminophosphonates has also been reported by Saidi and Azizi[176] using the reaction of an aldehyde, a secondary amine and trialkyl phosphite in LPDE at ambient temparature with high yields. They have also described[177] a one-pot reaction of trialkyl phosphite with imines (obtained *in situ* by reaction of aldehydes and ketones with primary amines) in the presence of trimethylsilyl chloride (TMSCl) in LPDE.

A one-pot synthesis of α-aminophosphonates from aldehydes, amines and phosphites using a lanthanide triflate as the catalyst (*Scheme 65*) has been reported by Qian and Huang.[178]

$$RCHO + R^1CH_2NH_2 + HO\text{–}P(OEt)_2 \xrightarrow[MgSO_4,\ (10\ mol\%),\ rt]{Yb(OTf)_3} RCHP(O)(OEt)_2NHR^1$$

Scheme 65

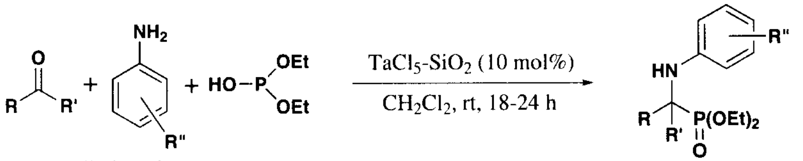
Shen *et al.*[179] have investigated the one-pot synthesis of α-aminophosphonates from aldehydes, amines and dialkyl phosphites using SmI_2 as a catalyst (*Scheme 66*).



$$R^1\text{–}C(=O)\text{–}R^2 + R^3NH_2 + HO\text{–}P(OR^4)_2 \xrightarrow[CH_3CN,\ 4\ Å\ MS,\ 80^\circ C,\ 25\ h]{(10\ mol\%)\ SmI_2} R^1\text{–}C(R^2)(P(=O)(OR^4)_2)\text{–}NHR^3$$

Scheme 66

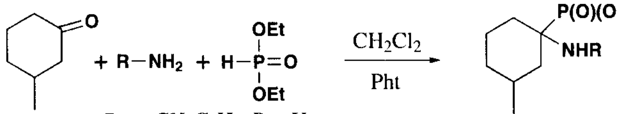
The $TaCl_5$-SiO_2 catalyzed synthesis of α-aminophosphonates has been disclosed by Chandrasekhar *et al.*[180] from the coupling of carbonyl compounds, aromatic amines and diethyl phosphite (*Scheme 67*). The same reaction has also been reported[181] under solvent and catalyst-free conditions at ambient temperature.



R = alkyl, aryl
R' = H, alkyl
R" = H, NO_2, OMe, OH, F

Scheme 67

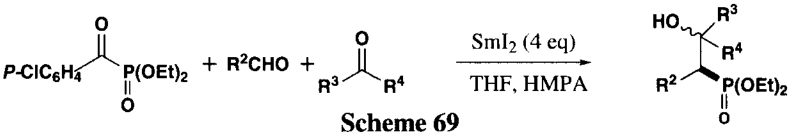
Matveeva *et al.*[182] have developed a novel catalytic route for the preparation of α-aminophosphonates using the *Kabachnik-Fields* reaction of ketones with diethyl phosphite and either benzylamine or ammonium carbonate in the presence of tetra-(*tert*-butyl)phthalocyanines (*Scheme 68*).



$R = -CH_2C_6H_5$, R = H

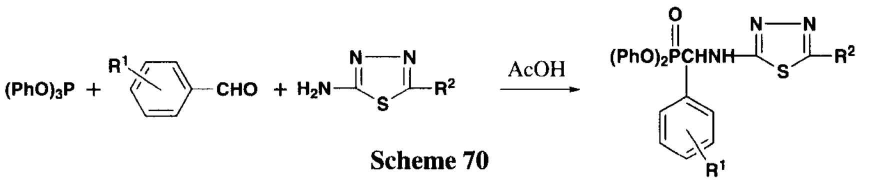
Scheme 68

A simple modification of the original procedure for the preparation of diethyl α-aminophosphonates has been reported[183] by using the reaction of an aldehyde, ammonium acetate and diethyl phosphite. An aluminum chloride catalyzed one-pot synthesis has also been described[184] at an ambient temparature. A one-pot synthesis of β-hydroxyphosphonates has been developed by Takaki *et al.*[185] using the coupling of acylphosphonates with two carbonyl compounds (*Scheme 69*) in the presence of SmI_2.



Scheme 69

Akiyama *et al.*[186] have reported a Brønsted acid-mediated synthesis of α-aminophosphonates by the reaction of aldehydes, amines and diethyl phosphite under solvent-free conditions. A convenient and facile synthesis of *O,O*-diphenyl 1-(5-alkyl-1,3,4-thiadiazol-2-yl)amino-1-arylmethylphosphonates has been described by Lu and Chen,[187] based on the condensation reaction of 2-amino-5-alkyl-1,3,4-thiadiazoles with triphenyl phosphite and aromatic aldehydes in the presence of acetic acid (*Scheme 70*).

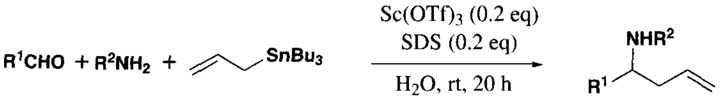


Scheme 70

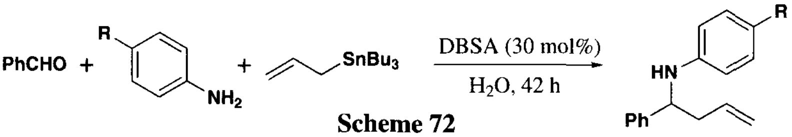
III. SYNTHESIS OF HOMOALLYLIC AMINES BY THREE-COMPONENT REACTIONS

Homoallylic amines are important intermediates in the synthesis of nitrogen-containing compounds such as *N*-heterocycles, *β*-lactams, *β*-amino acids, natural products and other biologically active compounds.[188-190] Various catalytic procedures have been developed for the preparation of these homoallylic amines by coupling of an aldehyde, an amine (or an amide) with different types of allylic organometallics.

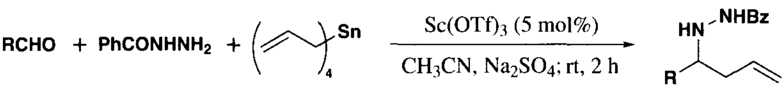
The facile synthesis of homoallylic amines in water has been reported by Kobayashi *et al.*[191] using a three-component reaction of aldehydes, amines and allyltributylstannane in the presence of a small amount of scandium dodecylsulfate (SDS) (*Scheme 71*). They have also carried out the same reaction in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as a Brønsted-acid-surfactant-combined catalyst in water (*Scheme 72*).[70] This group also has developed a reaction of aldehydes, benzoylhydrazine and tetraallyltin for the preparation of homoallylic amines in the presence of a catalytic amount of scandium triflate (*Scheme 73*).[192] Aspinall *et al.*[193] have reported a three-component synthesis of homoallylic amines using La(OTf)$_3$/benzoic acid catalyst system.



Scheme 71

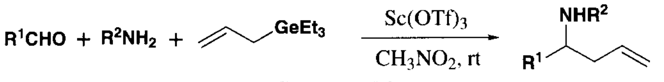


Scheme 72

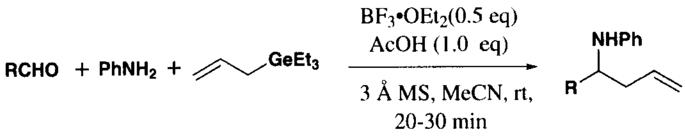


Scheme 73

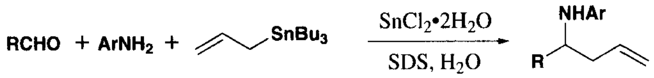
Three-component synthesis of homoallylic amines by the reaction of an aldehyde, an amine and an allylgermane (*Scheme 74*) in the presence of scandium(III) triflate has been investigated by Akiyama and Iwai.[194] Combined use of BF$_3$.OEt$_2$ and AcOH for the same reaction (*Scheme 75*) has been reported by the same group.[195] Another synthesis of homoallylic amines starting from aldehyde, amine and allyltributylstannane by means of tin(II) chloride in water in the presence of sodium dodecyl sulfate (SDS) (*Scheme 76*) has also been developed.[196]



Scheme 74

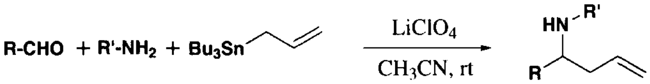


Scheme 75



Scheme 76

A lithium perchlorate catalyzed, facile synthesis of homoallylic amines in excellent yields has been described by Yadav *et al.*[197] using the condensation of aldehydes, amines and allyltributylstannane under mild and neutral conditions (*Scheme 77*).

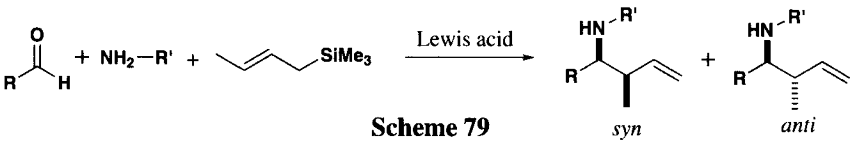


Scheme 77

Veenstra and Schmid[198] have presented a one-pot synthesis of protected homoallylic amines by the reaction of an aldehyde, a carbamate and allyltrimethyl silane in the presence of BF_3•OEt_2(*Scheme 78*).

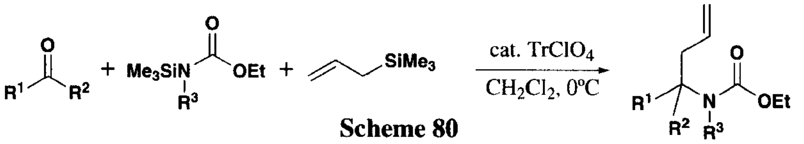
Scheme 78

The synthesis of homoallylic amines with *syn* diastereoselectivity, using crotylsilane in a three-component reaction in the presence of a Lewis-acid has been reported by Mann *et al.*[199] (*Scheme 79*). These authors also described the further conversion of these products in to substituted pyrrolidines or piperidines.



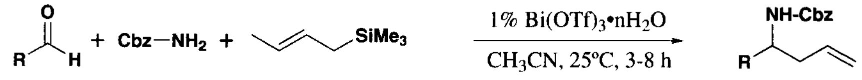
Scheme 79

Yokozawa *et al.*[200] have reported the synthesis of *N*-homoallyl carbamates by the Lewis-acid catalyzed condensation reaction of aldehydes, *N*-silylcarbamates and allylsilane in the presence of a catalytic amount of triphenylmethyl perchlorate ($TrClO_4$) at 0°C (*Scheme 80*).



Scheme 80

An efficient three-component synthesis of homoallylic amines has been developed by Choudary *et al.*[201] A one-pot reaction of an aldehyde, a carbamate and allyltrimethylsilane in the presence of catalytic bismuth triflate has been presented by Ollevier and Ba[202] to afford protected homoallylic amines in good yields (*Scheme 81*).

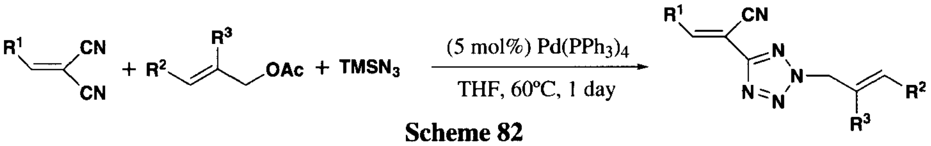


Scheme 81

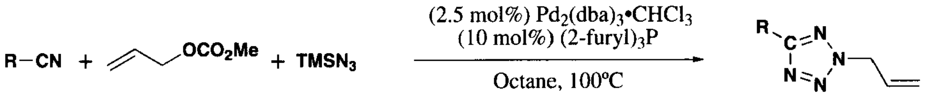
IV. PALLADIUM CATALYZED THREE-COMPONENT REACTIONS

Transition metal-catalyzed multi-component reactions play an important role in the one-step construction of many complex molecules. Among the transition metal mediated reactions, palladium-catalyzed reactions[203,204] are the most versatile for carbon-carbon bond formation due to their generality and ability to tolerate a variety of functional groups. Several groups have reported palladium-catalyzed three-component reactions resulting in the formation of a wide range of products.

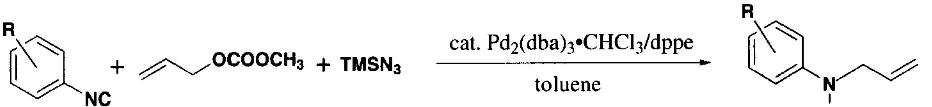
The palladium-catalyzed three-component coupling reaction of activated olefins, allylic chlorides and trimethylsilyl cyanide has been described by Yamamoto *et al.*[205] to give the corresponding cyanoallylation products. The regiospecific synthesis of 2-allyl-5-substituted tetrazoles in excellent yields has been reported by the same group *via* the palladium-catalyzed reactions of nitriles, allyl acetates and trimethylsilyl azide (*Scheme 82*). [206] They have also developed [207] a palladium-catalyzed selective synthesis of 2-allyltetrazoles (*Scheme 83*) by the three-component coupling reaction of nitriles, allyl methyl carbonate and trimethylsilyl azide. A novel synthetic route to allyl cyanamides has been reported[208] *via* the palladium-catalyzed coupling of the isocyanides, allyl carbonate and trimethylsilyl azide (*Scheme 84*). The same methodology has



Scheme 82

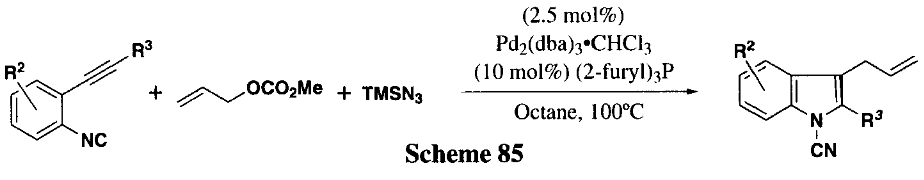


Scheme 83

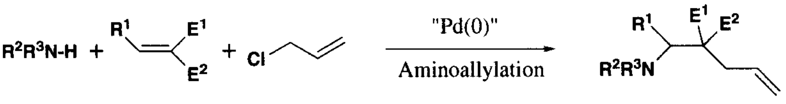


Scheme 84

been utilized for the synthesis of *N*-cyanoindoles (*Scheme 85*).[209] The same group has also developed a palladium-catalyzed aminoallylation of activated olefins with allylic halides and phthalimide to give the corresponding aminoallylated products (*Scheme 86*).[210]



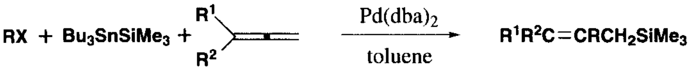
Scheme 85



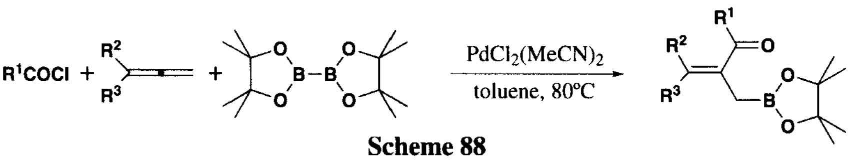
Scheme 86

Laren *et al.*[211] have reported a palladium-catalyzed synthesis of functionalized allyl amines by the reaction between iodobenzene, an allene and an amine.

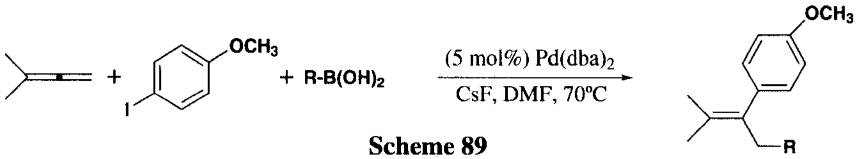
Cheng *et al.*[212] have reported a new method for the synthesis of substituted allyl silanes by the palladium-catalyzed coupling of organic halides, organosilylstannanes and allenes (*Scheme 87*). They have also reported[213] the reaction of aryl or alkenyl iodides with allenes and hexaalkylditins in the presence of Pd(dba)$_2$ to afford the substituted allylstannanes. A highly regioselective method for the preparation of 2-acylallylboronates has also been developed using a reaction of allenes, acid chlorides and a diboron compound catalyzed by palladium complexes (*Scheme 88*).[214] They have further described[215] the reaction of allenes, organic halides and arylboronic acids (*Scheme 89*) using Pd(dba)$_2$ as a catalyst in the presence of CsF in DMF. A novel route to 1,7-enyne derivatives has been reported[216] *via* a highly regio- and



Scheme 87

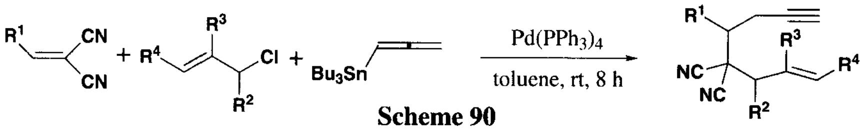


Scheme 88



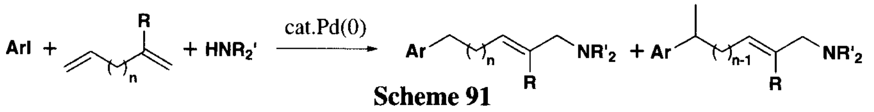
Scheme 89

chemoselective palladium-phosphine-mediated three-component assembly of arylethylidene-malononitriles, allyl chlorides and allenylstannanes (*Scheme 90*).



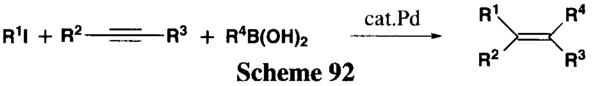
Scheme 90

Synthesis of aryl-substituted allyl amines has been described by Larock *et al.*[217] *via* a palladium-catalyzed coupling of aryl iodides, non conjugated dienes and amines (*Scheme 91*).



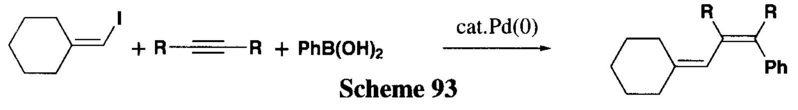
Scheme 91

Larock and Tu have reported[218] a palladium-catalyzed coupling of vinyl halides, alkenes and amines. These authors[219] have also developed an efficient, regio-and stereoselective route to tetrasubstituted olefins (*Scheme 92*) by the palladium-catalyzed intermolecular coupling of an



Scheme 92

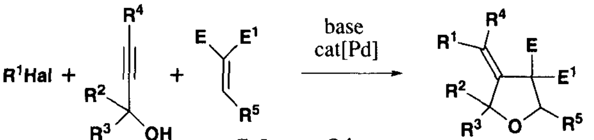
aryl iodide, an internal alkyne and an arylboronic acid. Palladium-catalyzed reaction of vinyl halides, internal alkynes and organoboranes has also been reported[220] to afford highly substituted 1,3-dienes and trienes in good to excellent yields (*Scheme 93*).



Scheme 93

Oda *et al.*[221] have described the use of (*o*-tolyl)diphenylphosphine as a ligand on palladium and tetraethylammonium chloride as additives to increase the yield of the product 5,6-diarylnorbornene obtained from the coupling reaction of aryl bromide, phenyltributyltin and norbornadiene. The same group has also reported[222] the coupling reaction of aryl bromides, phenyltributyltin and 1,3-dioxole using the palladium catalyst, $PdCl_2[P(o\text{-tol})_3]_2$ in THF to afford 4,5-diaryl-1,3-dioxolanes. The palladium-catalyzed coupling reaction of acid chlorides, organodisilanes and 1,3-dienes described by Obora *et al.*[223] affords allyl silanes as products.

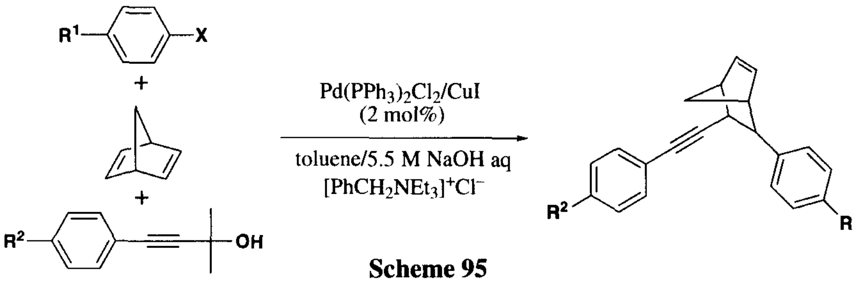
Palladium-mediated synthesis of substituted tetrahydrofurans has been reported by Balme *et al.*[224] using one-pot "three-components" Michael-Carbopalladation-Cyclization process. One-pot syntheses of highly substituted 3-arylidene-(or 3-alkenylidiene-)tetrahydrofurans have been described by the same group using the reaction of propargyl alcohols, Michael acceptors and unsaturated halides (or triflates) in the presence of a palladium(0) catalyst.[225] The most effective catalyst is the one generated *in situ* by reduction of $PdCl_2(PPh_3)_2$ with *n*-butyllithium (*Scheme 94*). The same authors have also reported[226] the same palladium-catalyzed



Scheme 94

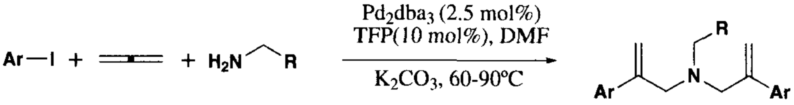
synthesis of functionalized (*Z*)-4-benzylidene- and alkenylidenepyrrolidines from simple and readily available starting materials such as propargylamines, *gem*-diactivated olefin and aryl-halides (or vinyl triflate). Finally, the palladium-mediated synthesis of furo[2,3,6]pyridones has been reported[227] by the one-pot coupling of 4-alkoxy-3-iodo-2-pyridones, terminal alkynes and organic halides.

Kang *et al.*[228] have reported a palladium-catalyzed coupling reaction of nobornadiene and iodonium salts (or diazonium salts) with organostannanes, alkynes and sodium tetraphenylborate. Pd/Cu catalyzed reaction of aryl halides, norbornadiene and alkynols to obtain 2,3-disubstituted norbornenes has been developed by Endo *et al.*[229] in the presence of aqueous NaOH and a phase-transfer catalyst in toluene at 100°C in high yields (*Scheme 95*).



Scheme 95

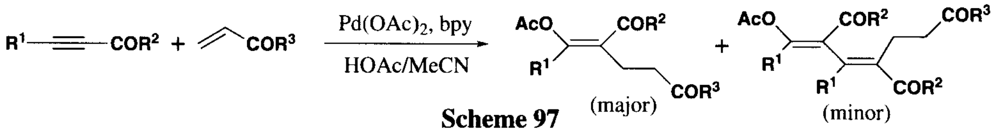
A three-component cascade synthesis of *bis*(2-arylallyl) tertiary amines from aryl iodide, allene and primary aliphatic amines (*Scheme 96*) has been described by Gai *et al.*[230] using palladium catalysis.



Scheme 96

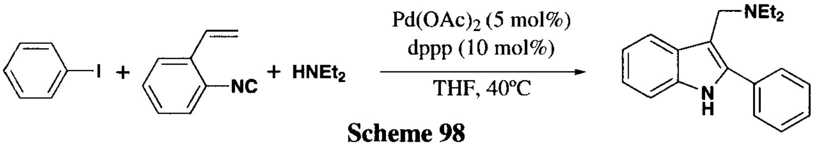
Szabo *et al.*[231] have reported a palladium-catalyzed tandem *bis* allylation of *p*-toluenesulfonyl isocyanates with allylstannanes and allyl chlorides. They have also described[232] the coupling reaction of allylstannanes, allyl chlorides and benzylidene malonitrile with excellent regiochemistry and good yields in the presence of 5 mol% of $Pd(PPh_3)_4$ in CH_2Cl_2 at 40°C. A palladium-catalyzed one-pot procedure for the formation of diarylnorbornene derivatives has also been developed by Goodson *et al.*[233] from readily available aryl halides, arylboronic acids and substituted norbornadienes.

Lu and Zhao[234] have reported an efficient route to γ,δ-unsaturated carbonyl compounds *via* a Pd(II)-catalyzed three-component tandem coupling reaction of acetate ion, an alkyne and an α,β-unsaturated carbonyl compound initiated by acetoxypalladation of alkynes with high atom economy (*Scheme 97*).



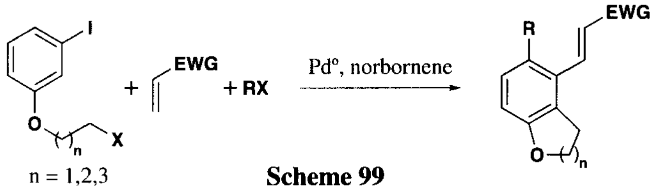
Scheme 97

Saluste *et al.*[235] have described a palladium-catalyzed intramolecular three-component synthesis of aromatic and heteroaromatic *N-tert*-butyl amidines. The same group has also reported[236] the synthesis of imidates and thioimidates using palladium-catalyzed coupling reaction between aryl- or heteroaryl bromides, alkoxides or thioalkoxides and isocyanides. A novel route to 2,3-disubsitituted indoles has been reported by Takahashi *et al.*[237] *via* the coupling reaction of an aryl iodide, an *o*-alkenylphenyl isocyanide and an amine (*Scheme 98*) in the presence of palladium catalysts.



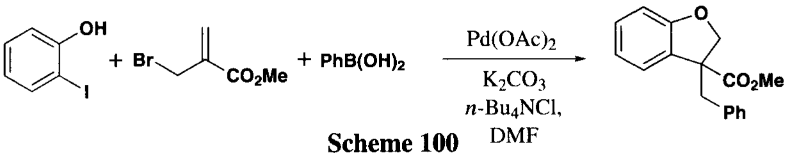
Scheme 98

Pache and Lautens[238] have described a coupling reaction of variety of substrates with an alkyl halide and a Heck acceptor leading to oxacycles catalyzed by palladium (*Scheme 99*).



Scheme 99

A palladium-catalyzed one-pot synthesis of 3,3-disubstituted-2,3-dihydrobenzofurans has been reported by Lamaty *et al.*[239] *via* a novel reaction of 2-iodophenol, methyl α-bromomethylacrylate and an arylboronic acid (*Scheme 100*).

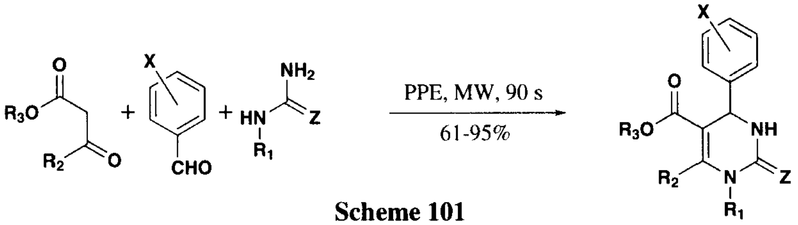


Scheme 100

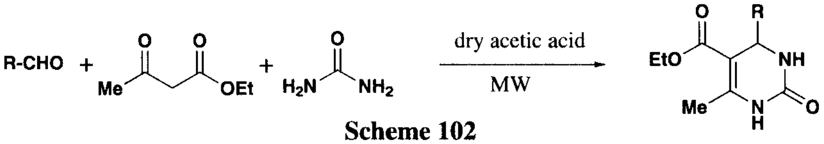
V. MICROWAVE-ASSISTED THREE-COMPONENT REACTIONS

The microwave irradiation of organic reactions has gained popularity in recent years. In 1986, it was Gedye[240] who published the pioneering report on the use of microwave irradiation as a thermal source to carry out organic reactions. The application of microwave energy[241-244] to accelerate organic reactions offers such advantages over conventional techniques as shorter reaction times, cleaner reactions, dry media (thus avoiding the use of solvents), easy work-up and minimization of thermal decomposition products. Along with other organic transformations, several three-component condensations have also been reported using this environmentally benign protocol.

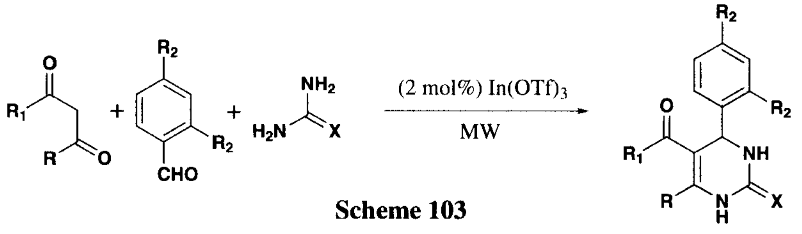
A microwave-assisted solventless Biginelli condensation protocol has been used by Kappe *et al.*[245] for the synthesis of 4-aryl-3,4-dihydropyrimidin-2-(1*H*)-ones using polyphosphate ester (PPE) as a reaction mediator (*Scheme 101*). The same reaction has also been reported under microwave irradiation by Ramalingam *et al.*[246] using various acid catalysts such as Amberlyst-15, Nafion-H, KSF clay[247] and dry acetic acid (*Scheme 102*) and by Perumal *et al.*[248] on water soluble solid support (sodium sulfate) catalyzed by indium triflate (*Scheme 103*). Gupta *et al.*[249] have described the microwave-induced Biginelli condensation in unsealed vessels by acid catalysis using ethanol as the energy transfer medium. Stefani *et al.*[250] and Kidwai *et al.*[251] have also developed microwave-assisted Biginelli conditions. The reaction between 4-hydroxycoumarin with aldehydes in the presence of urea/thiourea using solid inorganic supports under microwave irradiation to afford 4-substitutedbenzopyrano[4,3-d]-pyrimidine derivatives has also been reported.[252]



Scheme 101



Scheme 102



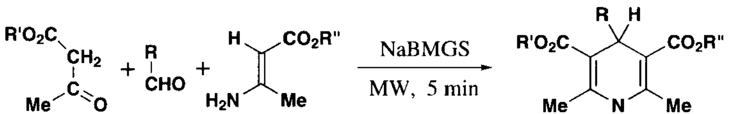
Scheme 103

A convenient synthesis of Biginelli compounds in the presence of ferric chloride hexahydrate using silica gel as carrier under microwave irradiation under solvent-free conditions has been reported.[253] Si-MSM-41-supported $FeCl_3$ catalyzed microwave assisted solvent-free synthesis of dihydropyrimidinones using the Biginelli reaction has been reported by Choudhary *et al.*[254] A regiospecific three-component one-step cyclocondensation to dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones has been described,[255] starting from readily available aminopyrimidin-4-ones, benzoylacetonitrile and benzaldehydes using microwaves under solvent-free conditions. An environmentally benign method has been developed by Kabalka *et al.*[256] for the synthesis of *β*-aminoalkynes using a microwave-enhanced, solventless Mannich condensation on CuI-doped alumina, with terminal alkynes, amines and paraformaldehyde (*Scheme 104*). Another microwave-assisted regioselective synthesis of *β*-aminoketones *via* the Mannich reaction has been developed by Sandhu *et al.*[257]

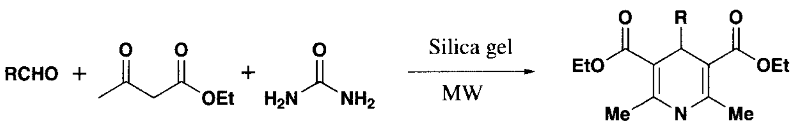
$$R^1C{\equiv}CH + (CH_2O)_n + HNR^2R^3 \xrightarrow[MW]{Cu/Al_2O_3} R^1C{\equiv}CCH_2NR^2R^3$$

Scheme 104

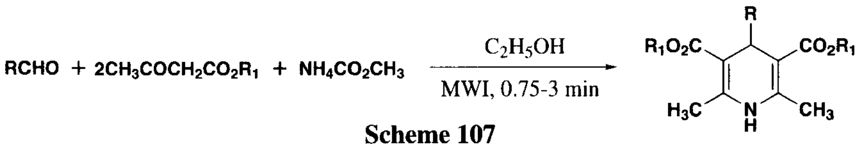
Microwave enhanced Hantzsch dihydropyridine ester synthesis has been reported[258,259] by Khadilkar *et al.* in aqueous hydrotrope solution (sodium butylmonoglycosulfate-NaBMGS) as a safer reaction medium (*Scheme 105*). Microwave assisted synthesis of 1,4-dihydropyridines has also been described by Zhang *et al.*[260]An unprecedented synthesis of Hantzsch 1,4-dihydropyridines under the Biginelli reaction conditions on the surface of silica gel under microwave irradiation in solvent free conditions has been developed by Yadav *et al.* (*Scheme 106*).[261] The Hantzsch reaction under microwave irradiation has also been reported by Perumal *et al.*[262] (*Scheme 107*) and Kidwai *et al.*[251] Khmelnitsky *et al.*[263] have applied a new highly efficient



Scheme 105



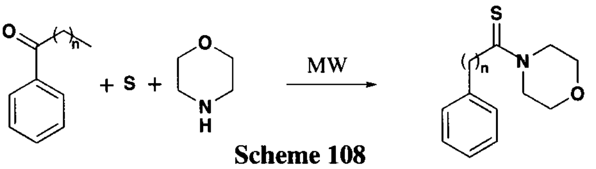
Scheme 106



Scheme 107

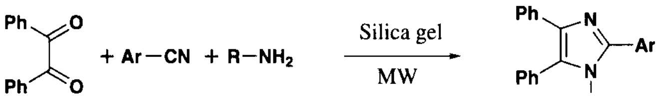
MICROCOS (Microwave-Assisted Combinatorial Synthesis) to the high throughput, automated, one-step, parallel synthesis of diverse substituted dihydropyridines using the three-component Hantzsch synthesis. Öhberg and Westman[264] have developed an efficient and rapid procedure for the Hantzsch dihydropyridine synthesis and synthesized a small library, with acceptable purity under microwave conditions.

The Willgerodt-Kindler reaction of several aryl alkyl ketones with sulfur and morpholine under solvent free conditions was performed by Nooshabadi *et al.*[265] in a domestic microwave oven to afford thiomorpholides in good yields with very short reaction times (*Scheme 108*).



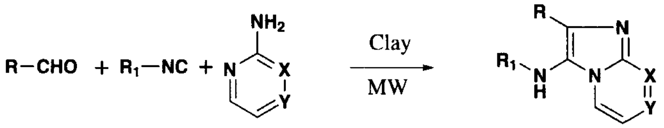
Scheme 108

Balalaie *et al.*[266] have reported a novel, one-pot condensation of benzil, benzonitriles and primary amines on the surface of silica gel under solvent-free conditions by microwave irradiation to provide tetrasubstituted imidazoles in high yields (*Scheme 109*).



Scheme 109

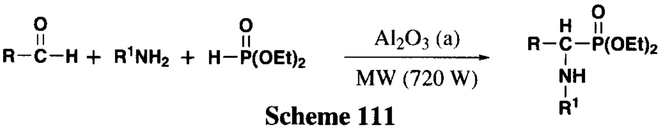
A rapid one-pot synthesis of imidazo[1,2-*a*]annulated pyridines, pyrazines and pyrimidines by the condensation reaction of aldehydes, amines and isocyanides has been described by Varma and Kumar[267] in the presence of recyclable montmorillonite K10 clay under solvent-free conditions using microwave irradiation (*Scheme 110*).



X = Y = C; X = C, Y = N; X = N, Y = C

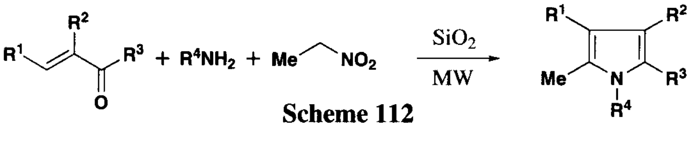
Scheme 110

Microwave assisted one-pot synthesis of α-aminophosphonates in solvent-free conditions has been reported by Yadav *et al.*[268] using montmorillonite KSF clay catalyzed condensation of aldehydes, amines and diethyl phosphite. Kaboudin and Nazari[269] have described the synthesis of 1-aminoalkyl phosphonates through a one-pot reaction of aldehydes, amines and diethyl phosphite in the presence of acidic alumina under solvent-free conditions using microwave irradiation (*Scheme 111*).



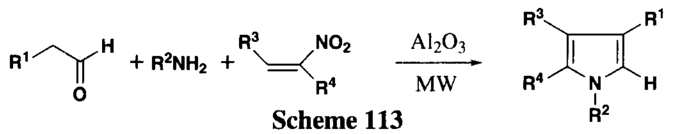
Scheme 111

An efficient microwave assisted one-pot synthesis of alkyl substituted pyrroles has been reported by Ranu *et al.*[270] using the coupling reaction of an α,β-unsaturated carbonyl compound, an amine and a nitroalkane on the surface of silica gel (*Scheme 112*) and also through



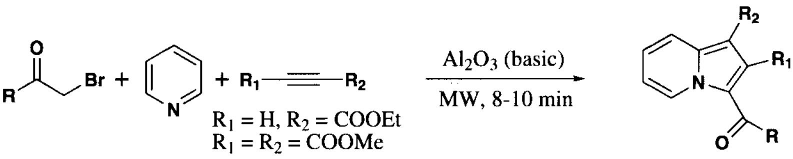
Scheme 112

the use of the three-component coupling of a carbonyl compound, an amine and an α,β-unsaturated nitroalkene on the surface of alumina (*Scheme 113*).[271]



Scheme 113

Microwave assisted one-pot synthesis of 2,4-disubstituted quinolines has been reported by Yadav *et al.*[272] using the condensation of aldehydes, amines and alkynes on the surface of montmorillonite clay impregnated with copper(I) bromide in solvent-free conditions. Boruah *et al.*[273] have reported a one-pot synthesis of indolizines by the reaction of acyl bromide, pyridine and acetylenic esters catalyzed by basic alumina under microwave irradiation (*Scheme 114*).

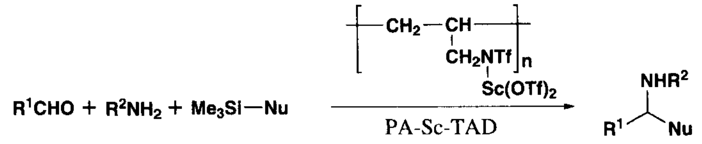


Scheme 114

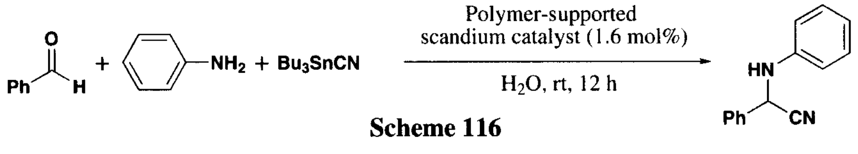
VI. THREE-COMPONENT REACTIONS USING SUPPORTED-REAGENTS

There is growing interest in the use of solid-supported reagents[274,275] as a part of combinatorial methods of synthesis due to facile work-up by simple filtration, regeneration and recycling of the catalyst, *etc.* Three-component reactions have also been reported using this environmentally conscious protocol.

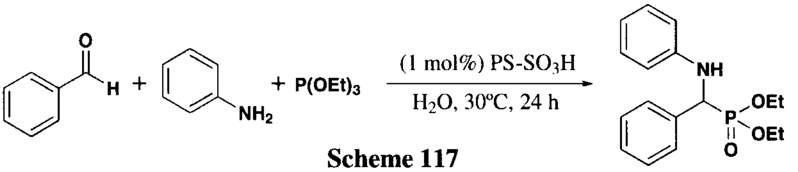
Kobayashi *et al.*[52] have reported a polymer-supported scandium (PA-Sc-TAD) catalyzed three-component reaction (*Scheme 115*) of aldehydes, amines and silylated nucleophiles to afford β-amino ketones, β-amino esters and α-amino nitriles in high yields. The use of the same catalyst by the same group has led to a combinatorial preparation of diverse quinoline derivatives[276] from the reaction of aldehydes, amines and olefins. A polymer-supported, microencapsulated Lewis acid catalyzed Mannich-type reaction has also been developed.[277] These authors have also reported[278] polymer-supported scandium catalyzed Strecker-type reaction of benzaldehyde, aniline and tributyltin cyanide to afford α-amino nitrile derivatives in water (*Scheme 116*). Mannich type reaction using hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H) as catalyst has also been reported[279] in addition to the use of the same catalyst for the preparation of α-aminophosphonates (*Scheme 117*). Microencapsulated $Sc(OTf)_3$ has also been utilized for quinoline-forming reactions by the same group.[280]



Scheme 115



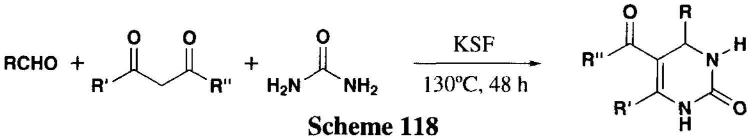
Scheme 116



Scheme 117

Iqbal and Prabhakaran[281] have developed a polymer-supported cobalt-catalyzed protocol for the general synthesis of β-amino acid derivatives. Iqbal *et al.*[282] have also described an efficient one-pot stereoselective synthesis of β-acetamido ketones catalyzed by montmorillonite K10 clay. A catalytic Petasis reaction for the preparation of 2*H*-chromenes using resin bound amine has been developed by Wang and Finn.[283] Three-component condensation reactions of Meldrum's acid with aldehydes and thiols to afford a variety of spirocyclic derivatives has been reported by Yadav and Syamala[284] using a polymer-supported reagent.

Montmorillonite KSF clay has been developed as the solid acid catalyst for the Biginelli reaction by Sartori *et al.*[285] under solventless conditions (*Scheme 118*) or in water. Dondoni and Massi[286] have described a green chemistry approach to a Biginelli reaction for the parallel synthesis of dihydropyrimidinones using solid-supported ytterbium(III) reagent under solvent free conditions. The Biginelli reaction using silica sulfuric acid has been reported by Salehi *et al.* in refluxing ethanol[287] and also under solvent free conditions.[288]



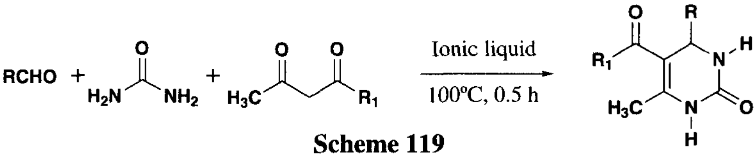
Scheme 118

A facile synthesis of homoallylic amines has been described by Yadav *et al.*[289] using a montmorillonite KSF clay catalyzed coupling reaction of aldehydes, amines and allytributylstannane. The use of the same catalyst has led to the synthesis of quinoline derivatives having a spiro cyclopropyl ring in good to excellent yields by Shi and Shao[290] by the one-pot aza-Diels-Alder reaction of methylene cyclopropanes with arene carbaldehydes and arylamines.

VII. THREE-COMPONENT REACTIONS IN IONIC LIQUIDS

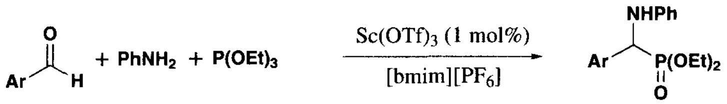
In recent years, room temperature ionic liquids[291-294] have received much attention as novel environmentally benign media for organic synthesis, and their own contribution to green chemistry is well known. Ionic liquids are emerging as an alternative to conventional organic solvents due to their unique properties such as non-volatility, recyclability, etc. Three-component reactions have also been performed in ionic liquids in addition to other organic transformations.

Deng and Peng[295] have reported a one-pot Biginelli condensation for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, in the presence of room temperature ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (bmimBF$_4$) or hexafluorophosphorate (bmimPF$_6$) as catalysts (*Scheme 119*), under solvent-free and neutral conditions.



Scheme 119

Lanthanide triflate-catalyzed three-component reactions in room temperature ionic liquids to give α-aminophosphonates has been reported[296] by Lee *et al.* (*Scheme 120*). Yadav *et al.*[297] have reported an eco-friendly approach for the synthesis of α-aminophosphonates using

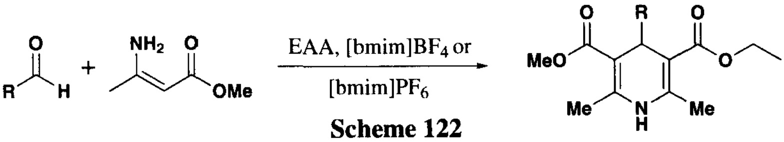


Scheme 120

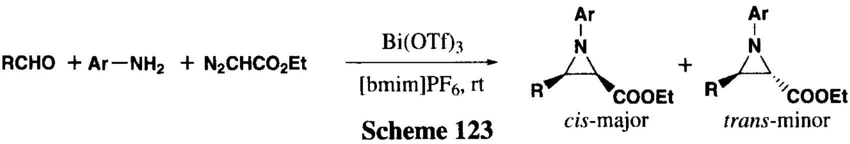
room temparature ionic liquids as catalysts. The same group has also synthesized α-hydroxylaminophosphonates by the coupling reaction of aldehydes, hydroxylamines and diethyl phosphite in [bmim]BF$_4$ or [bmim]PF$_6$ ionic liquids.[298]

A facile synthesis of α-amino nitriles has been reported by Yadav *et al.*[299] using ionic liquids as efficient promoters (*Scheme 121*) for the reactions of aldehydes, amines and trimethylsilyl cyanide. They have also developed an improved protocol for the synthesis of 1,4-dihydropyridines *via* the condensation reaction of an aldehyde, a β-ketoester (EAA) and methyl 3-aminocrotonate in the presence of [bmim]BF_4 or [bmim]PF_6 ionic liquids at room temperature under mild conditions (*Scheme 122*).[300] Synthesis of *cis*-aziridinecarboxylates using Bi$(OTf)_3$-[bmim]PF_6 as a novel and reusable catalytic system has also been reported[301] by the same group *via* the coupling of aldehydes, amines and ethyl diazoacetate (*Scheme 123*).

Scheme 121



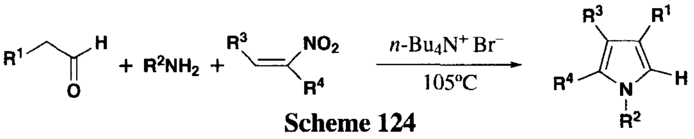
Scheme 122



Scheme 123

Yadav *et al.*[302] have explored the use of [bmim]BF_4 ionic liquid as a promoter and recyclable solvent system for the synthesis of homoallylic amines by the coupling reaction of aldehydes, amines and allyltributylstannane. They have also reported[303] a facile synthesis of pyrano- and furanoquinolines by the coupling reaction of aldehydes, amines and cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran using ionic liquids as promoters. The same group has also investigated the ionic liquids as promoters for the synthesis of *cis*-isoquinolonic acids using the coupling reaction of aldehydes, amines and homophthalic anhydride.[304]

Chen *et al.*[305] have developed a highly asymmetric Mannich-type reaction catalyzed by indium(III) complexes in ionic liquids. A green method for the efficient synthesis of alkyl substituted pyrroles has been reported by Ranu *et al.*[306] *via* a one-pot condensation reaction of a carbonyl compound, an amine and a nitroalkene (*Scheme 124*) in molten tetrabutylammonium bromide.

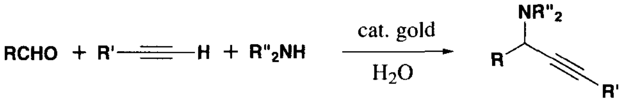


Scheme 124

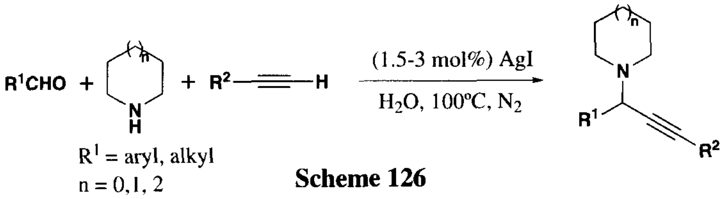
VIII. MISCELLANEOUS THREE-COMPONENT REACTIONS

A number of three-component reactions which were not covered under any of the above specific headings such as the preparation of propargyl amines, aza-Baylis-Hillman reaction, aza-Diels-Alder reaction, Reformatsky type reaction, Ugi three-component condensation and several others have been reported.

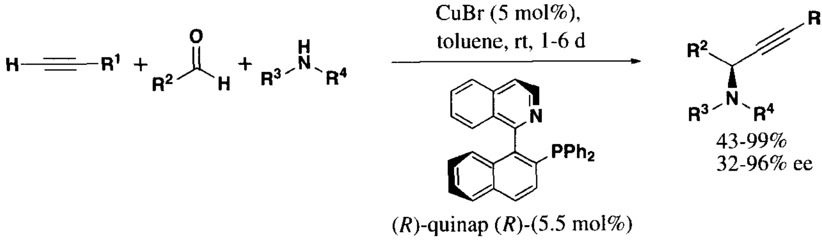
An efficient synthesis of propargylamines has been described by Wei and Li[307] using three-component coupling of aldehydes, alkynes and amines (A^3 coupling), catalyzed by gold in water (*Scheme 125*). They have also reported[308] the first silver salt-catalyzed coupling of aldehyde, alkyne and amine to afford propargylic amines (*Scheme 126*) using silver iodide in water. Enantioselective, copper(I)-catalyzed synthesis of propargylamines has been reported by Knochel *et al.*[309] using the reaction of an alkyne, an aldehyde and a secondary amine (*Scheme 127*). Hoveyda *et al.*[310] have reported an enantioselective synthesis of propargylamines through Zr-catalyzed addition of alkylzinc reagents. A coupling reaction of aldehydes, amines and alkynes in the presence of a catalytic amount of $[\{Ir(cod)Cl\}_2]$ (cod = cycloocta-1,5-diene) has been reported by Ishii *et al.*[311] to afford the coupling products (*Scheme 128*). The reaction of



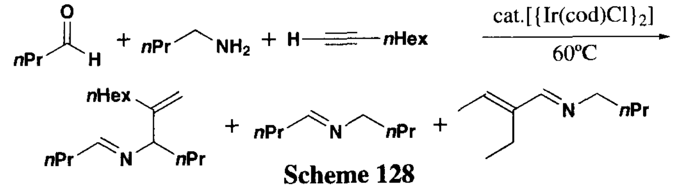
Scheme 125



Scheme 126

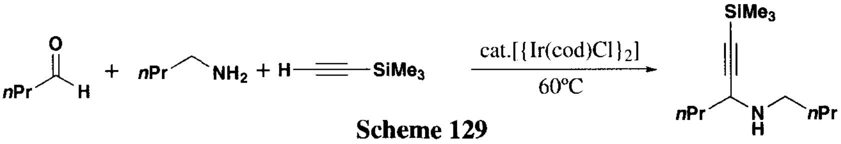


Scheme 127



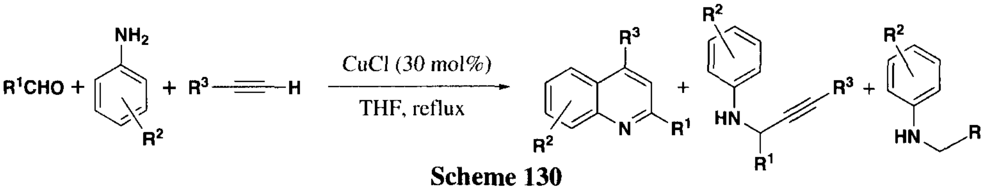
Scheme 128

aldehyde, amine and trimethylsilylacetylene furnished a different adduct (*Scheme 129*). A coupling protocol for the synthesis of quinoline derivatives has been reported by Iqbal *et al.*[312] in



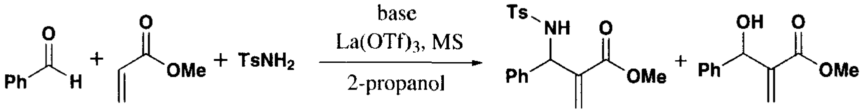
Scheme 129

a one-pot synthesis from an arylamine, an aldehyde and a terminal alkyne (*Scheme 130*) using CuCl. The same group has also described[313-316] a cobalt(II) chloride catalyzed route to *β*-acetamido carbonyl compounds.

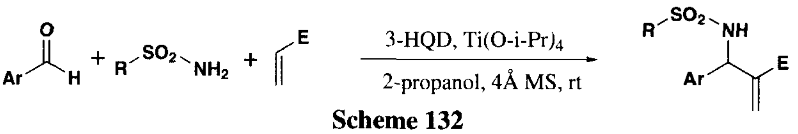


Scheme 130

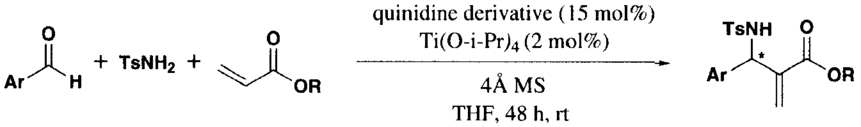
Balan and Adolfsson[317] have developed a one-pot procedure for the selective formation of *α*-methylene-*β*-amino acid derivatives based on the *aza* version of the Baylis-Hillman reaction of aldehydes, sulfonamides and *α,β*-unsaturated carbonyls (*Scheme 131*) catalyzed by base and Lewis acid La(OTf)$_3$, in the presence of molecular sieves (4Å). They have also reported the *aza* version of the Baylis-Hillman reaction of arylaldehydes, sulfonamides and Michael acceptors catalyzed by titanium isopropoxide and 3-hydroxyquinuclidine (3-HQD) in the presence of molecular sieves (*Scheme 132*).[318] An asymmetric version of the one-pot *aza*-Baylis-Hillman reaction of aryl aldehydes, tosylamide and alkyl acrylates or acrylonitrile has also been described by the same group using chiral quinuclidine-based amine catalyst.[319] A quinidine derivative was found to be the most efficient catalyst to afford *α*-methylene-*β* amino acid derivatives in good yields and enantioselectivities (*Scheme 133*) in the presence of a catalytic amount



Scheme 131

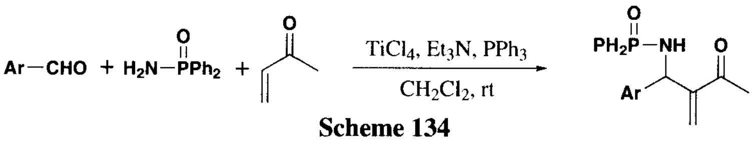


Scheme 132

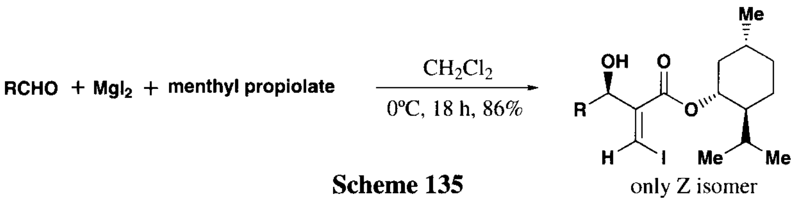


Scheme 133

of Ti(O-i-Pr)$_4$ and by the addition of molecular sieves (4Å) in THF. Shi and Zhao[320] have described a novel one-pot *aza*-Baylis-Hillman reaction of arylaldehydes and diphenylphosphinamide with methyl vinyl ketone (*Scheme 134*) to give the corresponding *aza*-Baylis-Hillman adducts in good yields in the presence of TiCl$_4$, PPh$_3$ and Et$_3$N in dichloromethane. An asymmetric synthesis of chiral *β*-iodo Baylis-Hillman esters has been reported with high yields and modest diastereoselectivities by Pare *et al.*[321] using MgI$_2$ both as the iodide source and as a Lewis acid promoter (*Scheme 135*).

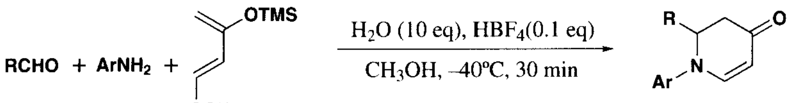


Scheme 134

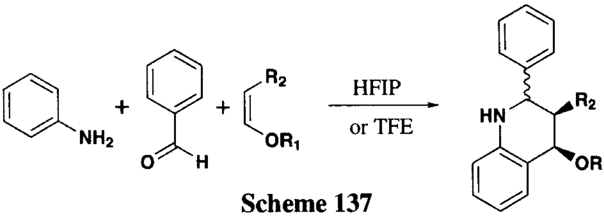


Scheme 135

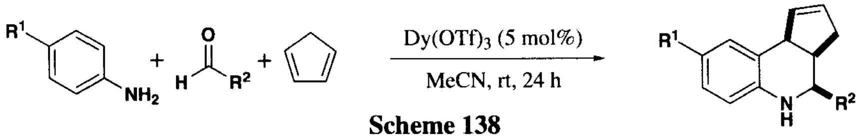
A formal *aza*-Diels-Alder reaction of aminoheterocycles with formaldehyde and electron-rich alkenes to give cyclic amidines and isothioureas has been reported[322] by Mellor and Rataz. Frost *et al.*[323] have described an In(OTf)$_3$ catalyzed coupling reaction between aldehydes, amines and Danishefsky's diene to afford tetrahydropyridine derivatives. A Brønsted acid-catalyzed *aza* Diels-Alder reaction has been performed by Akiyama *et al.*[324] starting from an aldehyde, aniline and Danishefsky's diene in aqueous media to afford dihydro-4-pyridone derivatives in high yields (*Scheme 136*). Chou and Hung[325] have described *aza*-Diels Alder reaction of 2-(phenylthio)-1,3-butadiene. Silver triflate catalyzed *aza*-Diels-Alder reaction has been reported by Kobayashi *et al.*[326] *via* the reaction of aldehydes, amines and Danishefsky's diene to afford dihydro 4-pyridones. The same group has also described[327] the alkaline salt-catalyzed *aza*-Diels-Alder reaction. A one-pot synthesis of tetrahydroquinolines through the imino-Diels-Alder reaction of aldehyde and amine with enol ethers has been reported by Spanedda *et al.*[328] using hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) as promoters or solvents (*Scheme 137*). Lanthanide(III)-catalyzed formal *aza*-Diels-Alder (or Povarov) reaction has been accomplished by Batey and Powell[329] *via* the coupling of anilines with cyclopentadiene and cyclic acetals/aliphatic aldehydes to afford tetrahydroquinolines in good to excellent yields and high diastereoselectivity (*Scheme 138*).



Scheme 136

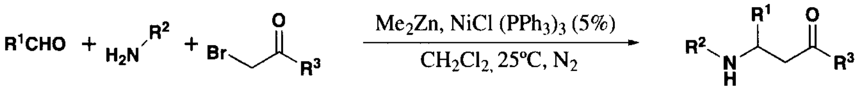


Scheme 137



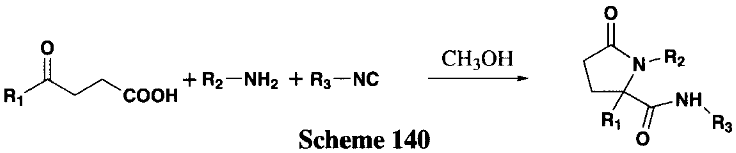
Scheme 138

A one-pot preparation of chiral β-amino esters has been reported by Honda *et al.*[330] *via* three-component coupling of amines, aldehydes and ethyl bromoacetate under rhodium-catalyzed Reformatsky-type reaction conditions. Adrian and Snapper[331] have developed an efficient, nickel-catalyzed Reformatsky-type condensation reaction of an aldehyde, aniline and an α-bromocarbonyl compound to afford β-aminocarbonyl compounds (*Scheme 139*) and its application in parallel synthesis. Saidi *et al.*[332] have described a three-component aminoalkylation of aldehydes by functionalized organozinc compounds. An efficient one-pot method for the preparation of several highly diastereomerically enriched secondary amino esters and secondary amines has been reported by Saidi and Azizi[333] in the presence of trimethylsilyl chloride with 5 M LPDE.



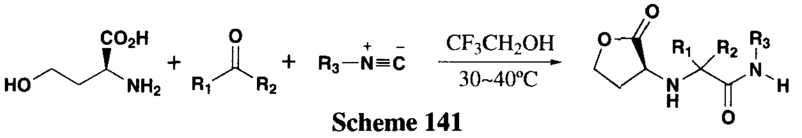
Scheme 139

Ugi and Kompa[334] have generated γ-lactams in a one-pot intramolecular Ugi-4-centered-3-component reaction (*Scheme 140*) using carboxy aldehydes or ketones as bifunctional components. A facile synthesis of *N*-carbamoylmethyl-α-aminobutyrolactones has been reported by Park *et al.*[335] utilizing the intramolecular Ugi five-centered-three-component condensation reaction of L-homoserine, aldehydes or ketones and isocyanides in the presence of 2,2,2-trifluoroethanol (*Scheme 141*). Zhang *et al.*[336] have also explored the Ugi three-component condensation reactions using bifunctional starting materials containing aldehyde and carboxylic acid functional groups to prepare unique lactam structures (*Scheme 142*). Zhu *et al.*[337] have developed an

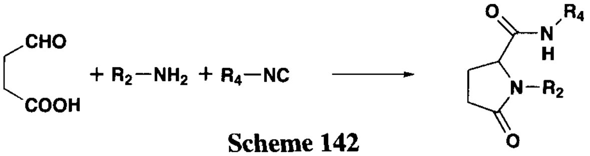


Scheme 140

Ugi-type condensation for the synthesis of bridged tetracyclic tetrahydroquinolines using a novel three-component domino process starting from *o*-aminocinnamate, α-isocyanoacetamide and an aldehyde in toluene containing LiBr.

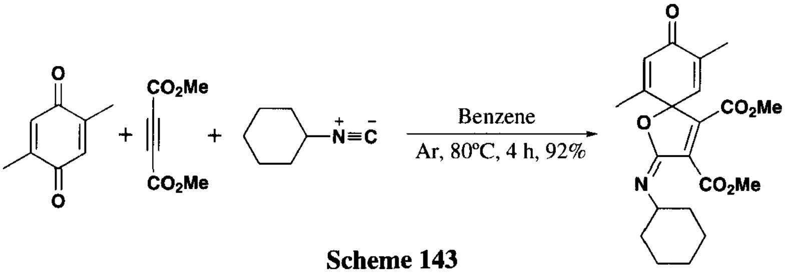


Scheme 141



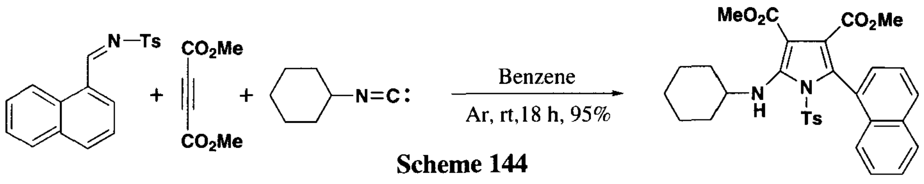
Scheme 142

Nair *et al.*[338] have proposed the preparation of novel spiropyrrolidine derivatives using a three-component reaction involving sarcosine and 1,2-diones such as isatin, acenaphthenequinones and cyclobutene-1,2-dione. The same group has also reported[339] a novel one-pot synthesis of iminolactones in good yields by a condensation reaction of cyclohexyl isocyanide and dimethyl acetylenedicarboxylate (DMAD) with *o*-and *p*-quinones (*Scheme 143*). They have



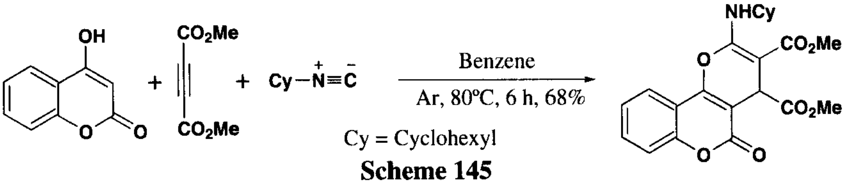
Scheme 143

also developed[340] a novel synthesis of 2-aminopyrroles using a reaction of *N*-tosylimines, DMAD and isocyanides (*Scheme 144*) and also the synthesis of 2-aminofuran derivatives using a one-pot



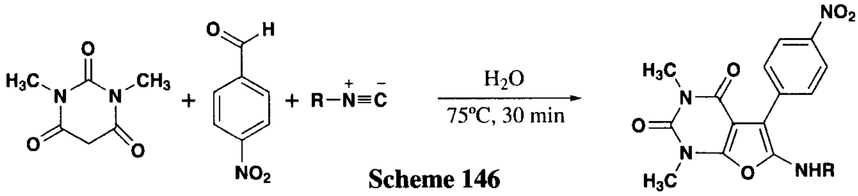
Scheme 144

reaction of isocyanides and DMAD with aldehydes.[341] A facile synthesis of polycyclic pyran derivatives has also been reported[342] by the same group *via* the one-pot reaction of isocyanides and DMAD with various active methylene compounds (*Scheme 145*). The same group has also described[343,344] a synthesis of highly functionalized dihydrofuran derivatives in good yields by the one-pot reaction of carbonyl compounds, DMAD and dimethoxycarbene. In addition to these methods, this group has also reported[345-354] other three-component reactions based on isocyanides and nucleophilic carbenes for the preparation of several heterocycles.



Scheme 145

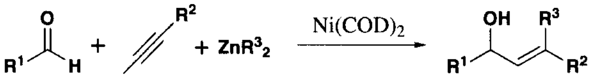
An efficient and improved procedure for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones has been described by Shaabani *et al.*[355] *via* a one-pot condensation reaction of *N,N'*-dimethylbarbituric acid, 4-nitrobenzaldehyde and alkyl or aryl isocyanides (*Scheme 146*) in water at 75°C.



Scheme 146

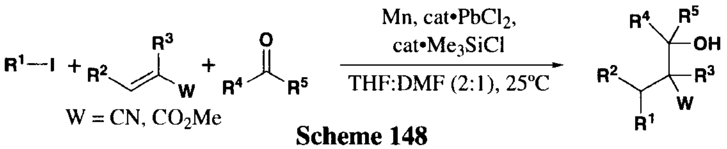
Sato *et al.* [356,357] have reported a nickel-catalyzed coupling reaction of α,β-conjugated enones with alkynes and alkynyltins. The same group has also described[358] a nickel-catalyzed coupling reaction of allyl chlorides, 1-alkynes and alkynyltins.

A new stereoselective method for the preparation of allylic alcohols has been reported by Montgomery and Oblinger[359] using a nickel-catalyzed coupling of alkynes, aldehydes and organozincs (*Scheme 147*). Montgomery and Qi[360] have also described a new synthesis of 1,3-dienes employing nickel catalysis. A nickel(0)-catalyzed reaction of dimethylzinc, 1,3-dienes and carbonyl compounds has been reported by Tamaru *et al.*[361]



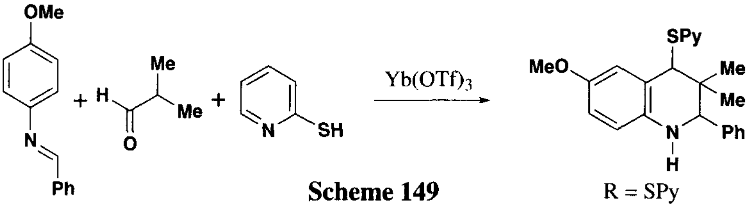
Scheme 147

Takai *et al.*[362] have explored a coupling reaction of alkyl iodides, 1,3-dienes and carbonyl compounds with $CrCl_2$. They have also reported a reaction of iodoalkanes, α,β-unsaturated nitriles (or esters) and carbonyl compounds using manganese and catalytic amounts of $PbCl_2$ and Me_3SiCl (*Scheme 148*). [363,364] Simple one-pot routes to homoallylic alcohols have also been described by Lombardo *et al.* [365,366]



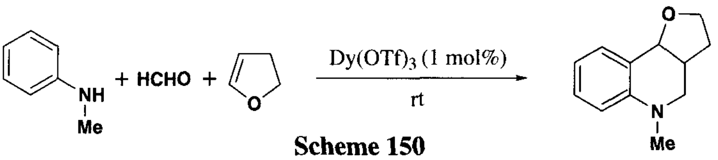
Scheme 148

A one-pot synthesis of β-lactams from a reaction of silyl ketene thioacetals, aldehydes and amines has been reported by Annunziata *et al.*[367] using $Yb(OTf)_3$ as a catalyst. A new reaction of an imine (Ar-N=CHR), an α-branched and enolizable aldehyde (R^1R^2CHCHO), and a nucleophile (ROH, ArSH, $ArNH_2$, H_2O) for the synthesis of 1,2,3,4-tetrahydroquinolines has been described by the same group using $Yb(OTf)_3$ as a catalyst (*Scheme 149*).[368] Qian and Chen[369] have reported a one-pot synthesis of tetrahydroquinolines using a condensation reaction of *N*-methylaniline with commercial formaldehyde solution and electron-rich alkenes (*Scheme 150*) in the presence of $Dy(OTf)_3$ (1 mol%) under mild conditions at ambient temparature and in the absence of any organic solvent. A facile synthesis of pyrano-and furanoquinolines has been described[370] using the CAN catalyzed coupling of anilines, benzaldehyde and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran.



Scheme 149

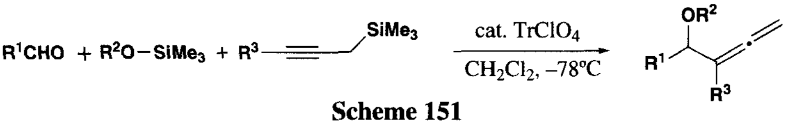
R = SPy



Scheme 150

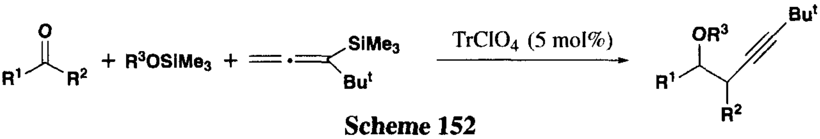
A reaction between aldehydes, hexamethyldisilazane and silylated nucleophiles in the presence of LPDE to afford trimethylsilylated primary amines in good yields has been reported by Saidi *et al.*[371]

Utimoto *et al.*[372] have described a titanium tetrachloride induced coupling reaction of α-haloacylsilane, allylsilane and carbonyl compound. Yokozawa *et al.*[373] have demonstrated a condensation protocol for the synthesis of α-allenyl ethers using Lewis acid-catalyzed reaction of aldehydes, alkoxysilanes and propargylsilanes (*Scheme 151*). This reaction was also applied to the synthesis of a polyether having allenyl side-chains. They have also reported the synthesis of α-propargyl ethers by the Lewis acid-catalyzed condensation reaction of aldehydes, alkoxysilanes and allenylsilanes (*Scheme 152*).[374] Allenylsilanes having bulky substituents such as the *tert*-butyl and isopropyl groups result in the corresponding α-propargyl ethers in high yields, whereas allenylsilanes having methyl and ethyl groups afford not only the corresponding α-



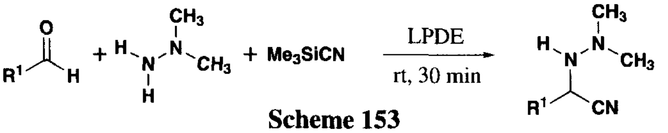
Scheme 151

propargyl ethers in low yield but also cyclopropyl ketones and α-β unsaturated ketones as by-products.



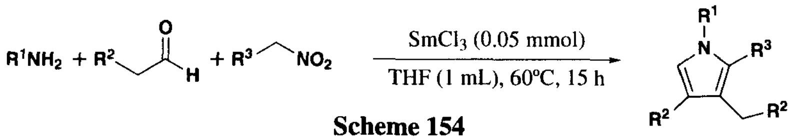
Scheme 152

A reaction of an aldehyde, a carbamate and trimethylpropargylsilane for the preparation of α-aminoallenes has been described by Mann *et al.*[375] in the presence of a Lewis acid (BF_3•OEt_2) as a catalyst. Heydari *et al.*[376] have reported a 5 M LPDE promoted coupling reaction of aldehydes, hydroxylamines and trimethylsilyl cyanide to afford α-cynanohydroxylamines. They have also described[377] a novel, one-pot synthesis of α-C-cyanohydrazines by the condensation of aldehydes, *N,N*-dimethylhydrazine and trimethylsilyl cyanide in the presence of 5 M LPDE (*Scheme 153*).

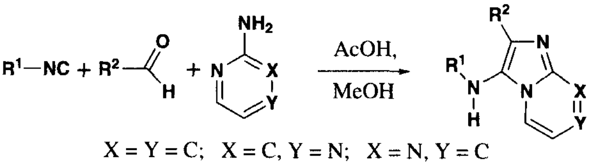


Scheme 153

A coupling protocol for the preparation of substituted alkyl pyrroles has been reported by Ishii *et al.*[378] *via* samarium-catalyzed reaction of aldehydes, amines and nitroalkanes (*Scheme 154*). Groebke *et al.*[379] have developed a facile one-pot condensation reaction of aldehydes, isonitriles and 2-aminopyridine, 2-aminopyrazine or 2-aminopyrimidine to afford 3-amino substituted imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines (*Scheme 155*). Parallel synthesis of these compounds has been reported by Blackburn *et al.*[380] using $Sc(OTf)_3$ as the catalyst.

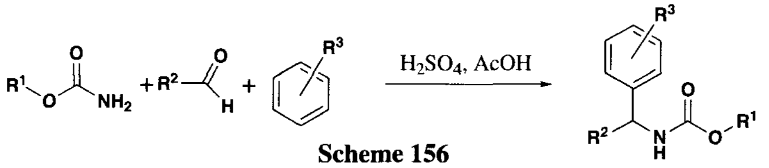


Scheme 154



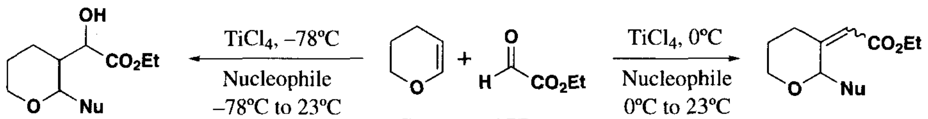
Scheme 155

A new three-component amidoalkylation which provides a flexible route to β-amido aldehydes has been described by Marson and Fallah[381] in the presence of trifluoromethanesulfonic acid. Mioskowski *et al.*[382] have reported a one-pot preparation of *N*-protected benzylic amines by carbamoalkylation of aromatic compounds using a reaction involving a carbamate, an aldehyde and an aromatic substrate (*Scheme 156*).



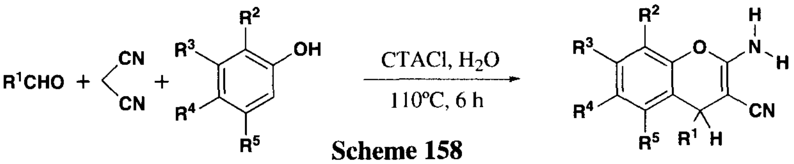
Scheme 156

Ghosh and Kawahama[383] have described a $TiCl_4$-promoted coupling reaction of 3,4-dihydro-2*H*-pyran, ethyl glyoxylate and an appropriate carbon, oxygen or sulfur nucleophile (*Scheme 157*) for the efficient synthesis of substituted tetrahydropyrylidene acetates. The olefinic coupling product formation is dependent upon the reaction temperature. They have also reported[384] the same reaction with allyltrimethylsilane as a nucleophilic trapping agent. Thioalkylation of Meldrum's acid with dialdehydes to afford isopropylidene *cis*-2-hydroxy-6-phenyl thiocyclohexane-1,1-dicarboxylate derivatives has been described by Lawton *et al.*[385] in aqueous acetonitrile with piperidine acetate. List and Castello[386] have described a novel proline-catalyzed reaction of ketones, aldehydes and Meldrum's acid to furnish the keto esters.



Scheme 157

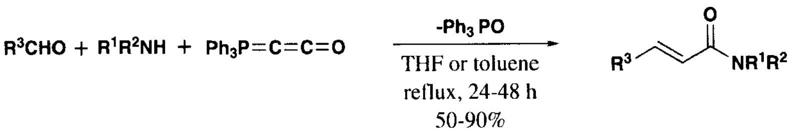
A one-pot synthesis of 2-amino-2-chromenes in aqueous media has been developed by Ballini *et al.*[387] using the reaction of an aldehyde, malononitrile and a phenol in water at reflux in the presence of cetyltrimethylammonium chloride (CTACl) as a catalyst (*Scheme 158*).



Scheme 158

A three-component catalytic asymmetric synthesis of aliphatic amines has been reported by Snapper *et al.*[388] using Zr-catalyzed reaction. A one-pot synthesis of 4-thiazolidinones has been studied by Srivastava *et al.*[389] using a DCC mediated condensation reaction of amines, aldehydes and mercaptoacetic acid.

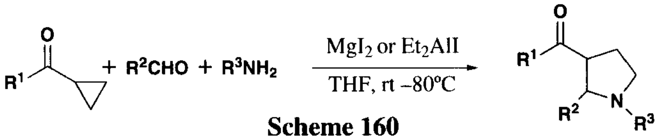
Schobert *et al.*[390] have described the selective formation of (*E*)-α,β-unsaturated amides by intermolecular reaction between aldehydes, amines (1° or 2°) and ketenylidenetriphenylphosphorane ($Ph_3P=C=C=O$) (*Scheme 159*). Natural amides such as fagaramide and piperine, could be prepared by this method and it is also extendable for the preparation of thioesters from thiols and aldehydes.



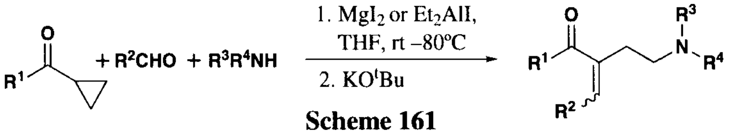
Scheme 159

Devi and Boulton[391] have developed a convenient synthesis of *N*-(α-dialkylaminobenzyl)formamides by the condensation of benzaldehyde, formamide and morpholine or piperidine. A new one-pot cyclocondensation reaction of 2,6-diaminopyrimidin-4-one, an aromatic or aliphatic aldehyde and a *β*-ketoester has been reported by Bagley and Singh[392] for the synthesis of dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones in good yields with total regiocontrol in acetic acid, or dimethyl sulfoxide in the presence of ZnBr$_2$, under thermal conditions. They have also described[393] the synthesis of 2,3,4,6-tetrasubstituted pyridines using a one-pot condensation reaction of a *β*-keto ester, ammonia and alkyne in the presence of a Brønsted or Lewis acid or Amberlyst 15 ion exchange resin.

Olsson *et al.*[394] have developed a novel metal iodide promoted synthesis of substituted pyrrolidine derivatives using the reaction of commercially available cyclopropyl ketones, aldehydes and amines (*Scheme 160*). They have also reported[395] the synthesis of *α*-substituted *α,β*-enones by a new metal iodide-promoted one-pot reaction of commercially available cyclopropyl ketones, aldehydes and secondary amines followed by base treatment (*Scheme 161*).

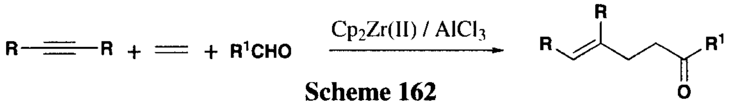


Scheme 160



Scheme 161

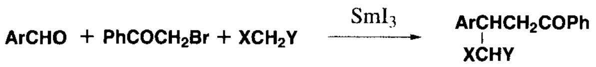
Kobayashi *et al.* [396] have reported a lanthanide triflate catalyzed coupling reaction of aldehydes, hydroxylamines and alkenes leading to isoxazolidine derivatives. A one-pot synthetic route to homoallyl ketones has been developed by Xi *et al.*[397] *via* the selective combination of three different components involving aldehydes, ethylenes and alkynes (*Scheme 162*).



Scheme 162

An efficient one-pot preparation of 1,6-diketones has been reported by Boruah *et al.*[398] *via* a three-component Michael addition reaction from *α*-bromoketone, malononitrile and *α,β*-

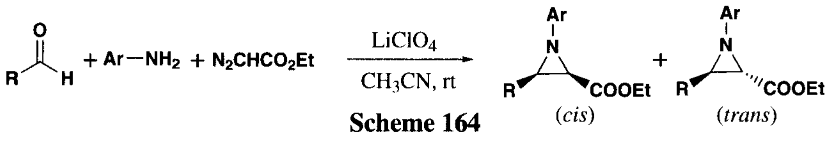
unsaturated keto compounds. Ma and Zhang[399] have developed a SmI_3 promoted coupling reaction of aldehydes, α-haloketones with malononitrile, ethyl cyanoacetate or nitromethane (active methylene or methyl compounds) to form 1,1-disubstituted-2-aryl-3-benzoylpropanes in moderate to high yields (*Scheme 163*).



$$ArCHO + PhCOCH_2Br + XCH_2Y \xrightarrow{SmI_3} \underset{\displaystyle XCHY}{ArCHCH_2COPh}$$

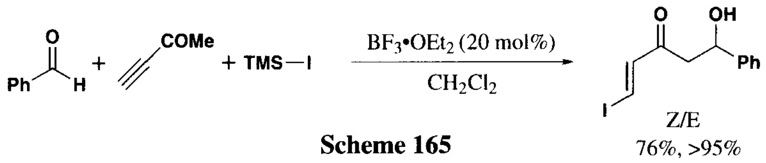
Scheme 163

Nagayama and Kobyashi[400] have reported a facile synthesis of aziridines based on the reaction of aldehydes, amines and ethyl diazoester using $Ln(OTf)_3$ as catalyst in hexane at room temperature. A simple and convenient method for the highly diastereoselective synthesis of *cis*-aziridinecarboxylates has been described by Yadav *et al.*[401] from aldehydes, amines and ethyl diazoacetate using 10 mol% $LiClO_4$ in acetonitrile as a catalytic medium (*Scheme 164*).



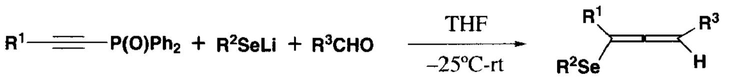
Scheme 164

Gallagher *et al.*[402] have demonstrated the synthesis of vinyl epoxides using a tandem three-component coupling. Three-component synthesis of 2-haloalk-2(*Z*)-en-1-ols *via* tandem haloalkylidenation-aldehyde addition has been reported by Mioskowski *et al.*[403] A new three-component halo aldol reaction has been proposed by Li *et al.*[404] *via* a tandem functionalization of 1,4-positions of ethynyl alkyl ketones (*Scheme 165*).



Scheme 165

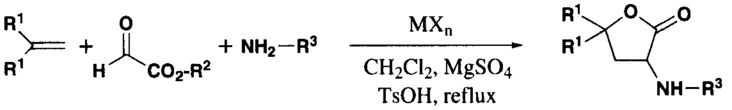
A facile synthesis of selenium-substituted allenes has been developed by Huang and Xiong[405] using a novel one-pot three-component Michael/aldol/Horner-Wadsworth-Emmons tandem reaction of lithium alkylselenolates with 1-alkynylphosphine oxides and aldehydes in THF (*Scheme 166*).



Scheme 166

Barluenga *et al.*[406] have described a coupling reaction of difluoroboroxy Fischer carbene molybdenum complexes, vinyl ketones and aldehydes to furnish *syn*-β-hydroxy ketones diastereoselectively.

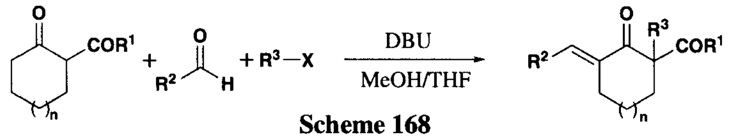
A diastereoselective synthesis of β-amino-α-hydroxyesters has been reported by Clerici *et al.*[407] *via* $TiCl_3$/pyridine system catalyzed reaction between methylphenyl glyoxylate, aniline and aromatic aldehydes. $InCl_3$-mediated or $Sc(OTf)_3$-catalyzed novel tandem three-component reaction of alkenes, glyoxylates and amines has been reported by Li and Huang[408] for the synthesis of α-amino-γ-lactones (*Scheme 167*).



Scheme 167

One-pot synthesis of β-amino esters, β-thio esters or β-thio nitriles has been developed by Reiser *et al.*[409] using a high-pressure induced three-component process by combining a Horner Wadsworth-Emmons reaction with a Michael reaction starting from aldehydes, phosphonates and amines or thiols.

Rodriguez *et al.*[410] have proposed a one-pot three-component domino transformation between 1,3-dicarbonyl compounds, aldehydes and allylic, propargylic or benzylic halides providing a regio-, chemo- and stereoselective access to valuable α,γ-difunctionalized α-ketoesters and amides using DBU (*Scheme 168*). A one-pot access to amino azabicyclo[3.3.1]nonanones and 1,6-hydronaphthyridines has been reported[411] by the same group using a three-component domino reaction of β-ketoester with acrolein and various amines in the presence of 4Å MS.



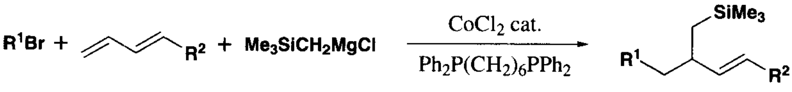
Scheme 168

A one-pot process for the synthesis of α-alkyl β-hydroxy ketone derivatives has been described by Chandrasekhar *et al.*[412] using a triethylborane triggered intermolecular domino Michael-aldol three-component coupling reactions.

Che *et al.*[413] have proposed a ruthenium porphyrin-catalyzed one-pot coupling, reaction involving *N*-benzylidene imine, diazoesters, and alkenes to form functionalized pyrrolidines with remarkable stereoselectivity. A one-pot three-component tandem metathesis/Diels-Alder reaction has been reported by Lee *et al.*[414]

An efficient new methodolgy for the synthesis of aminocyclopropanes using three-component condensation has been described by Wipf *et al.*[415] β-Phenylseleno-α-tolylsulfonyl-substituted alkenes were synthesized by Huang and Xie[416,417] using the reaction of phenylselenomagnesium bromide, acetylenic sulfones and carbonyl compounds, such as aldehydes, aliphatic ketones or α,β-unsaturated enals or enones.

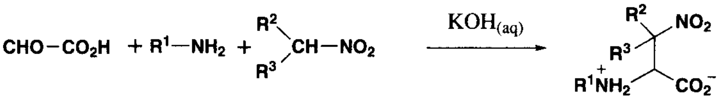
White and Jensen have reported[418] the synthesis of 1,3-dienes of (*E,Z*)-configuration by the coupling of an anionic nucleophile, butadienyltriphenylphosphonium bromide and an aldehyde. Oshima *et al.*[419]have described a synthesis of homoallylsilanes (*Scheme 169*) using a cobalt-catalyzed coupling reaction of alkyl halides, 1,3-dienes and trimethylsilylmethyl magnesium chloride.



Scheme 169

A coupling reaction of alkynes, vinylcyclopropanes, and diphenyl diselenide (or ditelluride) under visible-light irradiation has been developed by Ogawa *et al.*[420] Harada *et al.*[421] have described a novel coupling reaction of *p*-iodobenzyl derivatives, trialkylzincates and electrophiles leading to functionalized *p*-substituted benzenes.

A new procedure for the preparation of *β*-nitroamino acids and their *N*-alkyl derivatives has been reported by Easton and Coghlan[422] using a one-pot condensation of glyoxylic acid, nitroalkanes and amines in basic aqueous solution at room temperature (*Scheme 170*).



Scheme 170

Ni-catalyzed coupling of alkynes, imines and organoboron reagents has been developed by Jamison and Patel[423] for the preparation of allylic amines. Odom *et al.*[424] have reported a titanium-catalyzed preparation of *α,β*-unsaturated *β*-iminoamines using a three-component coupling of an amine, an alkyne and an isonitrile.

CONCLUSION

This review has focused on a variety of three-component methodologies developed during the decade 1994-2003. The topics covered included significant three-component name reactions, three-component routes to *α*-aminophosphonates and homoallylic amines, palladium-catalyzed three-component reactions and such environmentally benign protocols as microwave irradiation and reactions using supported-reagents and ionic liquids. The main goal of this review has been to bring to the attention of organic chemists the newest developments in these important and convenient procedures. It is expected that new three-component reaction methodologies will continue to be explored because of their versatility, molecular economy and exciting potential for the synthesis of complex organic compounds. In a review of this scope, some omissions may have occured and the author regrets any such oversights.

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