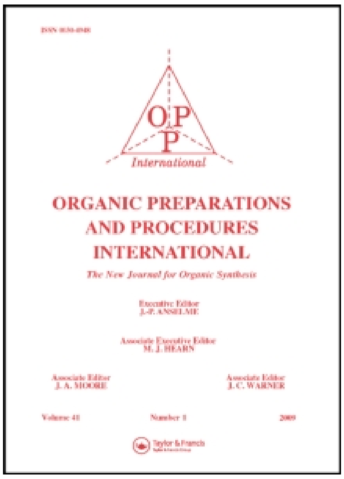

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Recent Progress in Three-Component Reactions. An Update

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Recent Progress in Three-Component Reactions. An Update

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Introduction

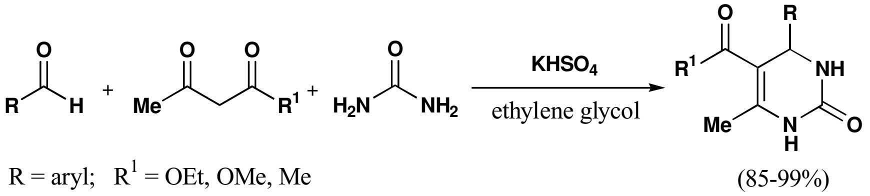
Three-component reactions have emerged as useful methods because the combination of three components to generate new products in a single step is extremely economical, among the multi-component reactions.[1–5] The usefulness and importance of these processes is underscored by the large number of publications since our previous review[6] published in early 2005 summarized the advances in this area for the period 1994–2003. The present review describes the results for the period January 2004–March, 2006.

I. Three-Component Name Reactions

1. *Biginelli Condensation*

The original Biginelli condensation[7] involving the reaction of aldehydes, urea, and β-ketoesters under strongly acidic conditions to give 3,4-dihydropyrimidin-2-ones often suffers from low yields for aliphatic and substituted aromatic aldehydes. Several modifications and improvements have resulted in milder and more efficient procedures and catalysts.[6]

An efficient synthesis of 3,4-dihydropryimidin-2(1*H*)-one derivatives has been described by Tu and co-workers[8,9] using potassium hydrogen sulfate as the promoter in glycol solution for the Biginelli reaction (*Scheme 1*). It can be applied not only to open-chained



Scheme 1

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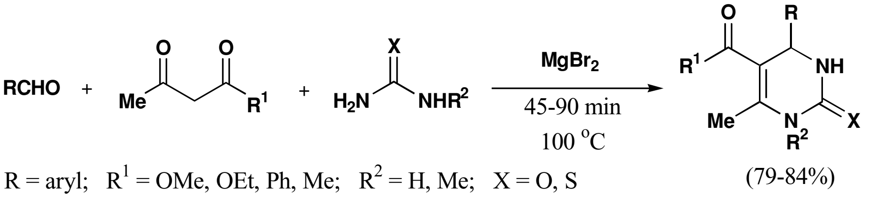
1,3-dicarbonyl compounds, but also to cyclic 1,3-dicarbonyl compounds. Bifunctional compounds containing two dihydropyrimidinone units have also been synthesized using isophthalaldehyde and terephthalaldehyde.

Salehi and Guo[10] have reported a magnesium bromide-catalyzed facile and efficient one-pot synthesis of dihydropyrimidinones under solvent-free conditions (*Scheme 2*).

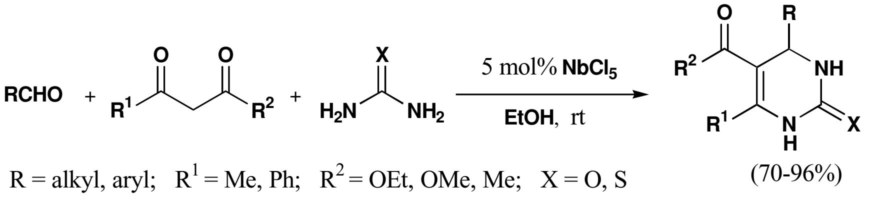


R = aryl; R^1 = OMe, OEt, Ph, Me; R^2 = H, Me; X = O, S

Scheme 2

Besides β-ketoesters, β-diketones have also been employed and thiourea/*N*-methylurea were also used to furnish the corresponding dihydropyrimidinones, which are also of much interest from a biological activity point of view.

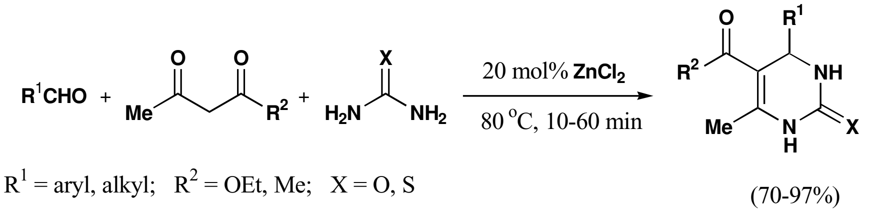
An efficient niobium(V) chloride-catalyzed synthesis of 3,4-dihydropyrimidinones has been described by Yadav and co-workers[11] *via* the condensation reaction of an aldehyde, a β-keto ester, and urea or thiourea under ambient conditions (*Scheme 3*). The study of this reaction using other Lewis acids such as indium(III) chloride, cerium(III) chloride, gadolinium(III) chloride, tantalum(V) chloride, and yttrium(III) chloride revealed that niobium(V) chloride was found to be superior in terms of conversion and reaction time. The other advantage of this catalyst is the reaction proceeded at room temperature where as the other Lewis acids required reflux conditions. The same group has also reported[12] a novel *L*-proline catalyzed Biginelli reaction under solvent-free conditions. The advantages are short reaction times under solvent-free conditions at room temperature and participation of β-diketones also in the reaction. The use of L-proline methyl ester hydrochloride as a catalyst for the preparation of these dihydropyrimidinones *via* Biginelli reaction has been studied by Mabry and Ganem.[13]



R = alkyl, aryl; R^1 = Me, Ph; R^2 = OEt, OMe, Me; X = O, S

Scheme 3

Li *et al.*[14] have reported a zinc-chloride, catalyzed, solvent-free protocol for the preparation of 3,4dihydropyrimidin-2(1*H*)-ones by the condensation of an aldehyde, a 1,3-dicarbonyl compound, and urea or thiourea at 80°C with shorter reaction times (*Scheme 4*). The important feature of this method is that 2-furaldehyde furnished the desired products in 94–95% yields in 10 mins, which normally gives low yields. The use of zinc sulfamate as a catalyst for the one-pot preparation of these compounds *via* the condensation reaction



R^1 = aryl, alkyl; R^2 = OEt, Me; X = O, S

Scheme 4

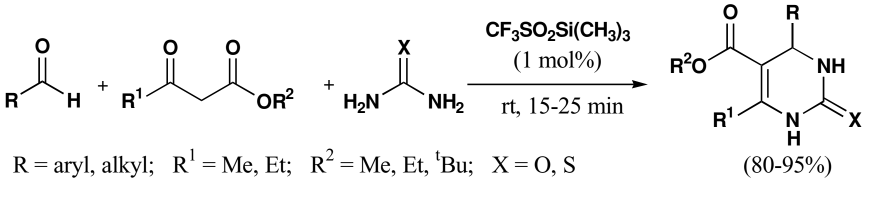
of aromatic aldehydes, β-keto esters, and urea (or thiourea) in refluxing ethanol has been described by Zhang and Li.[15]

The preparation and characterization of a series of eleven transition metal methanesulfonates [Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), La(III), Ce(III), Pr(III), Nd(III), Yb(III)], and their catalytic behavior in Biginelli condensation of aldehydes, 1,3-dicarbonyl compounds and urea in absolute ethanol under reflux temperature has been investigated by Wang and co-workers.[16,17] The study revealed that except for Mn(II) methanesulfonate, the activities of the other ten methanesulfonates are relatively close exhibiting good catalytic effects. With Zn(II) methanesulfonate as a catalyst, the reactions were complete in (0.3–2 h).

The use of titanium(IV) chloride as a catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones has been presented by Nagawade *et al.*[18] *via* the condensation reaction of an aldehyde, a 1,3-dicarbonyl compound, and urea (or thiourea).

Combination catalytic systems such as tin chloride-lithium chloride[19] and cupric chloride-lithium chloride[20] have been proposed by Rao *et al.* for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by Biginelli reaction. Cepanec and co-workers[21] have reported the use of ferric chloride/tetraethyl orthosilicate as an efficient catalyst system for the Biginelli reaction of aldehydes, acetoacetate esters, and urea to afford dihydropyrimidinones.

Trimethylsilyl triflate (1 mol %) mediated one-pot cyclocondensation reaction of aldehydes, β-keto esters and urea at room temperature in acetonitrile with shorter reaction times has been described by Bose *et al.*[22] (*Scheme 5*). By using this procedure, a mitotic kinesin Eg5 inhibitor monastrol has been prepared in 95% yield within 15 min. One mol% triethylsilyl triflate can also be used as a catalyst in acetonitrile at room temperature. Ghosh *et al.* have reported[23] the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using indium(III) triflate (2 mol%) as a catalyst. The use of strontium(II) triflate as a reusable catalyst has also been reported by Su *et al.* [24] for the Biginelli reaction under solvent-free conditions.

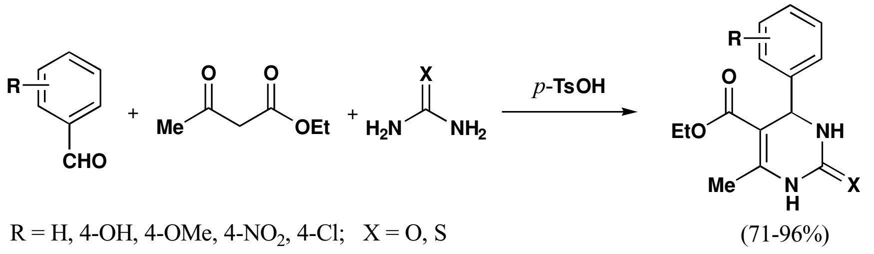


R = aryl, alkyl; R^1 = Me, Et; R^2 = Me, Et, ^{t}Bu; X = O, S

Scheme 5

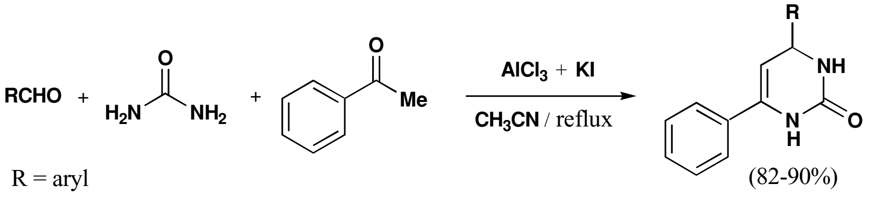
The use of iodine as a catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has been documented.[25,26] A cadmium chloride catalyzed Biginelli reaction has also been developed.[27] Jenner[28] has noted the effect of high pressure on Biginelli reactions.

A simplified green chemistry protocol for the Biginelli reaction catalyzed by *p*-toluenesulfonic acid using grindstone chemistry has been developed by Bose *et al.*[29] (*Scheme 6*). This technique is convenient, time-saving, and also useful for kilogram scale operation. The same group has also reported[30] the large-scale preparation of dihydropyrimidinones *via* water-based biphasic reaction media using *p*-toluenesulfonic acid as a catalyst. This procedure is useful in process development programs. Jin *et al.*[31] have described a methanesulfonic acid-catalyzed efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones from aldehydes, β-keto esters, and urea in ethanol.



Scheme 6

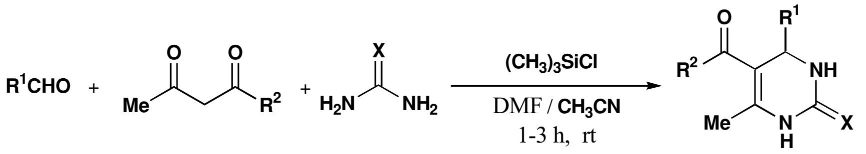
An efficient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones has been published by Wang *et al.*[32] *via* iron(III)-catalyzed Biginelli-like cyclocondensation of urea with aldehydes and ketones in acetonitrile. The facile preparation of these compounds by one-pot condensation of aldehydes, urea, and enolizable ketones (*Scheme 7*) has been reported by Sandhu *et al.*[33] using bimetal system aluminum(III) chloride and potassium iodide in acetonitrile under reflux condtions. Some combinations of catalytic systems have also been studied and out of these, the most effective combination worked out to be the aluminum(III) chloride and potassium iodide system.



Scheme 7

Martins *et al.*[34] have presented the one-pot synthesis of a series of trichloromethylated tetrahydropyrimidinones *via* Biginelli-type condensation of chlorinated 1,3-dicarbonyl compounds and aromatic aldehydes with urea (or thiourea) using indium(III) bromide as a catalyst.

Pan and co-workers[35] have reported the use of trimethylsilyl chloride (TMSCl) as a facile and efficient reagent for the one-pot condensation of aldehydes, 1,3-dicarbonyl compounds, and urea (or thiourea) at room temperature to afford the corresponding dihydropyrimidinones (*Scheme 8*). The advantages are a simple work-up by filtration, and



R^1 = aryl, alkyl; R^2 = OEt, Me; X = O, S

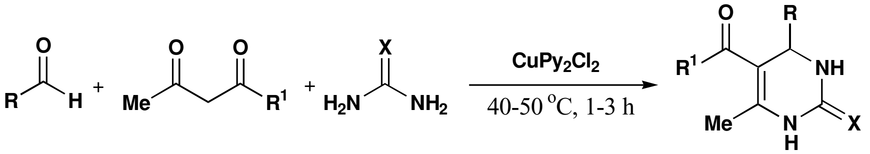
(76-97%)

Scheme 8

aliphatic aldehydes also gave products in good yields. The same group has also reported[36,37] the Biginelli-type condensation reaction of cycloalkanones, urea (or thiourea), and aldehydes by the use of TMSCl as a Lewis acid and also the synthesis of two families of fused heterobicyclic and spiro-fused heterobicyclic compounds. An iodotrimethylsilane-catalyzed Biginelli-like reaction of ketones with aldehydes and urea for the preparation of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones has also been reported.[38]

Khodaei *et al.*[39] have reported the use of aluminum hydrogen sulfate as a catalyst for the efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones *via* the condensation of aromatic aldehydes, β-keto esters, and urea (or thiourea) in methanol under solvent-free conditions. The same group[40] has also prepared these products using bismuth nitrate pentahydrate[41] as a catalyst by the condensation reaction of an aromatic aldehyde, urea, and a β-keto ester or β-diketone under solvent-free conditions. A green protocol for the synthesis of these dihydropyrimidinones brings together an aldehyde and a β-dicarbonyl compound with the hydrogen sulfate salt of urea (or thiourea) under solvent-free conditions.[42]

Rajitha *et al.*[43,44] have reported a bismuth subnitrate and bismuth oxide perchlorate-catalyzed Biginelli reaction for the preparation of 3,4-dihydropyrimidinones. The same group has also reported[45] the one-pot condensation reactions of aldehydes, β-keto esters, and urea or thiourea using copper dipyridine dichloride as a catalyst (*Scheme 9*). In both of



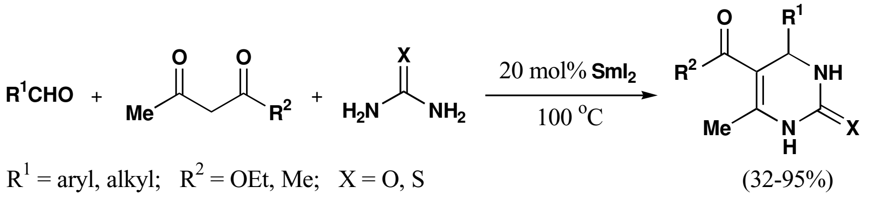
R = aryl; R^1 = OEt, Me; X = O, S

(82-90%)

Scheme 9

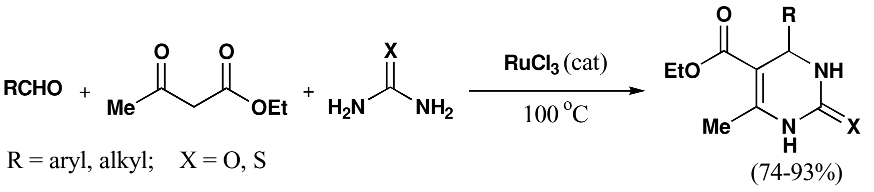
these methods, aliphatic aldehydes were not used for the reaction to give the corresponding dihydropyrimidinones.

Shen and co-workers [46] have reported the use of samarium diiodide as a catalyst for an efficient one-pot synthesis of dihydropyrimidinones *via* Biginelli reaction under solvent-free conditions (*Scheme 10*). However, low yields were observed in the case of cinnamaldehyde and hydroxy and methoxy substituted benzaldehydes. Steric effects influenced the yields of aliphatic aldehydes in the case of reaction with urea and ethyl acetoacetate.



Scheme 10

A one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions has been developed by De and Gibbs[47] using ruthenium(III) chloride as a catalyst (*Scheme 11*). By using this procedure, monastrol, a mitotic kinesin Eg5 motor protein inhibitor, and a potent anti-cancer drug, lead was obtained in 89% yield in 65 mins. The same group has also reported[48] the use of scandium(III) triflate as a reusable catalyst for the preparation of these compounds *via* the reaction of an aldehyde, a β-keto ester, and urea in refluxing acetonitrile.



Scheme 11

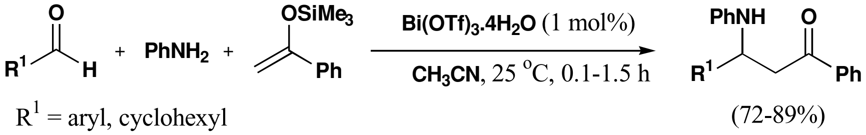
Novel boron-containing dihydropyrimidinones have been prepared by Blacquiere *et al.*[49] *via* the addition of formylphenylboronic acid derivatives to urea and ethyl acetoacetate in the absence of an additional Lewis acid catalyst.

2. *Mannich Reaction*

The formation of β-aminocarbonyl compounds (Mannich bases) from the reaction of an active methylene compound with formaldehyde and an amine was first recognized by Mannich.[50] Its application in the synthesis of numerous pharmaceuticals and natural products, and the later developments of this reaction[6] are significant.

Ollevier and Nadeau[51] have reported a bismuth, triflate-catalyzed, Mannich-type reaction of aldehydes, anilines, and silyl enol ethers to afford the corresponding β-aminoketones (*Scheme 12*). The advantages are low catalyst loading (1%) and no formation of by-products. Probably due to enamine formation, aliphatic aldehydes did not react under these conditions, except cyclohexanecarboxaldehyde, which furnished the corresponding product in good yields. The same group has also developed[52] a bismuth triflate-catalyzed protocol for the reaction of an aldehyde, an amine, and a silyl ketene acetal to furnish β-aminoesters.

Janda and co-workers[53] have reported the use of molecular iodine (neutral conditions) for the preparation of β-aminoketones *via* a three-component Mannich reaction. A zinc(II) triflate-promoted reaction of electron-deficient aromatic amines with electron-deficient

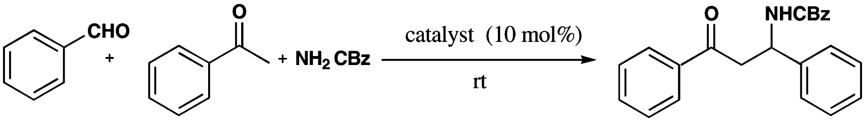


Scheme 12

aromatic aldehydes and diethyl malonate has been described by Wang *et al.*[54] for the synthesis of β-aminoesters.

A Mannich-type reaction in the fluorous phase has been described by Shi *et al.*[55] An unprecedented tandem Mannich reaction involving ammonia has been observed by Chan *et al.*[56] to afford 2,2-dimethyl-6-aryl-4-piperidones.

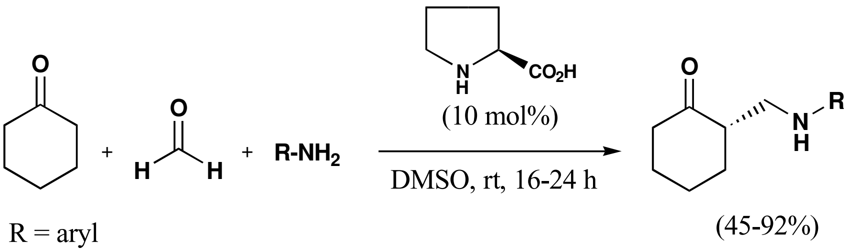
Xu *et al.*[57] have reported an efficient synthesis of *N*-protected β-aryl-β-aminoketones *via* transition metal salt ($RuCl_3.xH_2O$-, $AuCl_3$-PPh_3-, and $AlCl_3$)-catalyzed direct Mannich-type reaction of aryl aldehydes, aryl ketones, and carbamates (*Scheme 13*). The survey conducted using various transition metal salts (10 mol%) and *L*-proline for the Mannich reaction of benzaldehyde, acetophenone, and benzyl carbamate revealed that $Cu(OTf)_2$, $Pd(CH_3CN)_2Cl_2$, $RuCl_2(PPh_3)$, $NiCl_2.6H_2O$, and $CuCl_2$ were not effective including L-proline for the reaction. The same group has also investigated[58] the combined use of $FeCl_3.6H_2O$ and TMSCl as a catalytic system for the reaction of carbamates, aldehydes, and ketones to afford *N*-protected β-aminocarbonyl compounds.



Scheme 13

Hardemare and co-workers[59] have developed a convenient solvent- and catalyst-free, selective Mannich reaction of a variety of *p*-substituted phenols or catechols with paraformaldehyde and ethyl iminodiacetate. A solvent-free, one-pot protocol for the preparation of a series of methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenylmorpholinyl phenols using infrared irradiation has been reported[60] *via* the reaction of phenols and their derivatives with formaldehyde and the corresponding amino groups of piperidine, morpholine, or thiomorpholine. The advantages of this method are short reaction times (within a few min) and high yields without the use of any metal catalyst or solvent. An iminodiacetic acid catalyzed reaction for the synthesis of alkoxymethyl derivatives of resorcinarene has been described by Urbaniak and Iwanek.[61] Finally a Mannich-type reaction for selective tyrosine bioconjugation has been reported by Francis *et al.*[62]

Córdova *et al.*[63–69] have reported a variety of direct catalytic, asymmetric, three-component Mannich and cross-Mannich reactions using amino acids (proline and its derivatives), acyclic chiral amines, and related compounds as catalysts to afford the corresponding products with excellent enantioselectivities (*Scheme 14*). For example, the (*S*)-proline

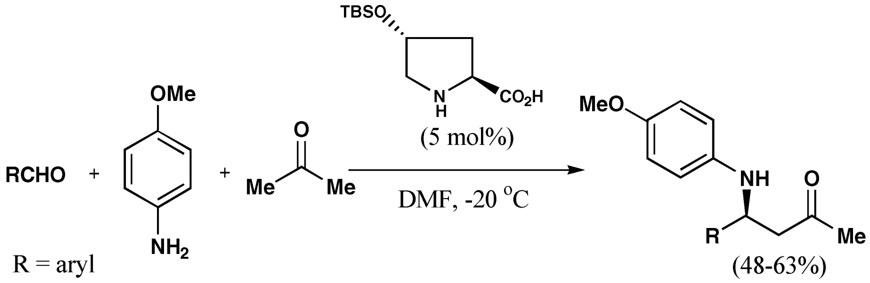


Scheme 14

catalyzed reaction of substituted aniline derivatives with cyclohexanone and formaldehyde afforded the α-arylaminomethylated ketones with $>99\%$ *ee*.

Barbas *et al.*[70] have presented a wide scope of the proline-catalyzed, one-pot asymmetric, Mannich-type reaction between a variety of structurally different ketones as effective donors and aldehyde acceptors and *p*-anisidine. A proline-catalyzed, Mannich-type reaction between glyoxylate, *p*-anisidine, and dihydroxyacetone has been carried out by Westermann and Neuhaus[71] in the presence of 2,2,2-trifluoroethanol as a solvent. Enders *et al.*[72] have reported a proline-catalyzed, direct asymmetric reaction between dioxanone, an aldehyde, and an amine.

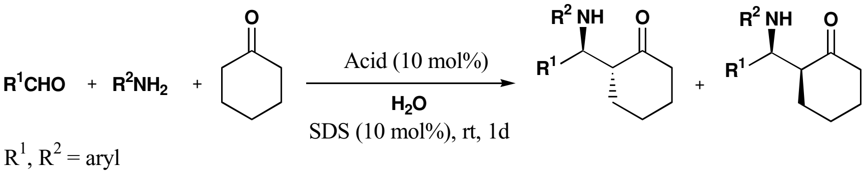
The use of 5 mol% of *trans*-4-*tert*-butyldimethylsiloxy-*L*-proline as a catalyst with greater catalytic activity than the parent proline has been reported by Hayashi and coworkers[73] for the Mannich reaction of aldehydes such as benzaldehyde, 2-naphthaldehyde, *p*-anisaldehyde, and 3,4-dimethoxy-benzaldehyde with *p*-anisidine and ketones. The corresponding Mannich adducts were formed in moderate yields with excellent enantioselectivity in the presence of DMF at −20°C (*Scheme 15*).



Scheme 15

An asymmetric Mannich-type reaction for the synthesis of C-glycosyl β-amino acids has been reported by Dondoni *et al.*[74] *via* a one-pot indium(III) chloride-catalyzed, three-component condensation by combining the corresponding formyl C-glycoside, *p*-methoxybenzylamine, and a ketene silyl acetal, and the reaction was highly stereoselective. Adrian *et al.*[75] have developed a stereoselective titanium enolate-based condensation reaction for the preparation of α,β-disubstituted-β-aminocarbonyl derivatives. Acyl-Mannich reactions of isoquinolines catalyzed by a chiral thiourea derivative has been reported by Jacobsen *et al.*[76]

Wu and co-workers[77] have reported the use of a new class of metal-free catalysts for direct diastereo- and regioselective Mannich reactions in aqueous media. For example, D-camphorsulfonic acid efficiently (with 91% yield) catalyzed the reaction of benzaldehyde, aniline, and cyclohexanone along with three other sulfonated amino acids. HCl-catalyzed Mannich reaction of a cyclic ketone, an aromatic aldehyde, and an aromatic amine to afford β-aminoketones (*Scheme 16*) with high *anti* selectivity has been reported by Akiyama *et al.*[78] in the presence of H_2O-SDS system. Tetrahydro-4-pyrone and tetrahydro-4-thiopyrone also afforded the corresponding Mannich adducts with high yields and high *anti* selectivity.



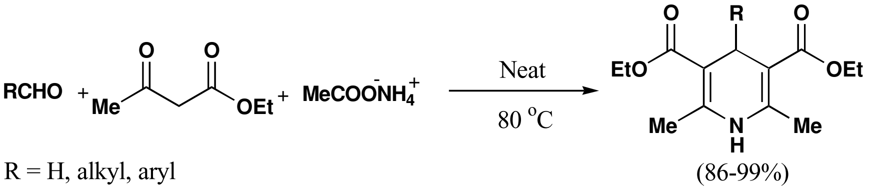
Scheme 16

A temperature-dependent diastereoselective synthesis of chiral *o*-1,2-diaminoalkyl phenols has been described by Rondot and Zhu[79] *via* the Mannich reaction of an electron-rich phenol, an amine, and a chiral α-*N*,*N*-dibenzylaminoaldehyde.

3. *Hantzsch Reaction*

1,4-Dihydropyridines with widespread pharmacological applications were first described by Hantzsch[80] *via* a one-pot condensation of aldehydes, β-keto esters, and ammonia in refluxing acetic acid or alcohol solvent. Later improvements in the procedures[6] were developed for Hantzsch-type reactions including the Hantzsch pyrrole synthesis.[81]

A mild and solvent-free regime for the synthesis 1,4-dihydropyridines from ethyl acetoacetate and a range of aldehydes in the presence of ammonium acetate has been reported by Zolfigol and Safaiee[82] (*Scheme 17*). For example, 2-furyl- and 2-thienylaldehydes furnished the corresponding dihydropyridines in high yields of 91% and 86% within 10 mins and 15 mins, respectively. Wang *et al.*[83] have developed an eco-friendly protocol for the synthesis of Hantzsch esters by the one-pot reaction of aldehydes with ammonium acetate and 1,3-dicarbonyl compounds in water without any additives under refluxing conditions.



Scheme 17

A Hantzsch reaction between ferrocenecarboxaldehyde, ethyl acetoacetate, and ethyl β-aminocrotonate to afford the corresponding dihydropyridine has been described by Contelles *et al.*[84]

Tripathi *et al.*[85] have developed an efficient method for the synthesis of glycosyl 1,4-dihydropyridines *via* the three-component reaction of β-keto esters (or ketones), enamines, and glycosyl aldehydes in the presence of tetrabutylammonium hydrogen sulfate as a catalyst in diethylene glycol. The use of HCl generated *in situ* from 2,4,6-trichloro[1,3,5]triazine as a catalyst for the preparation of new dihydropyridine glycoconjugates has been reported by Sharma *et al.*[86] *via* Hantzsch reaction at room temperature under solvent-free conditions.

4. Petasis Reaction

The use of organoboronic acids in the Mannich reaction, first reported by Petasis *et al.*,[87] involves a one-pot, three-component condensation of an aryl- (or alkenyl-)boronic acid, an amine, and an aldehyde at room temperature to furnish α-amino acids by simple mixing. Various modifications and advances[6] of this reaction resulted in the products that serve as building blocks in combinatorial chemistry and drug discovery.

Tremblay-Morin and co-workers[88] have reported a Lewis acid-catalyzed, three-component Mannich-type (modified Petasis) reaction using potassium organotrifluoroborates (aryl, vinyl, and allyl reagents). This has been developed as an extension of the standard Petasis reaction.

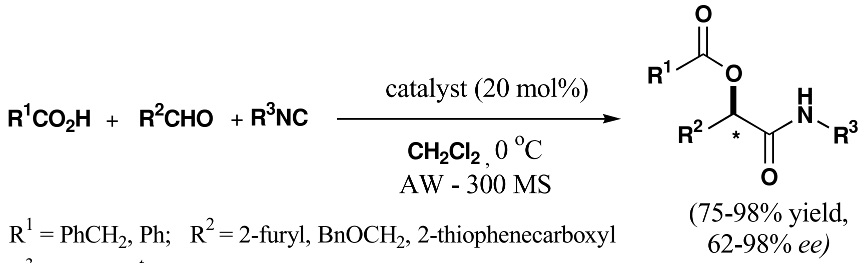
A diastereoselective synthesis of pyrrolidine-derived arylglycines has been developed by Nanda and Trotter[89] *via* the Petasis boronic acid reaction. The acceleration of this reaction upon the addition of hexafluoroisopropanol as a co-solvent has also been reported, which has reduced the reaction times from multiple days to less than 24 h.

5. Passerini Reaction

Among the isocyanide-based, multi-component reactions, the Passerini reaction is the most important one, involving the three-component reaction of isocyanides, aldehydes (or ketones), and carboxylic acids to give α-acyloxy carboxamides.[90,91] It is preferably carried out in aprotic solvents. Several other Passerini-type reactions[6] have also been reported.

Schreiber *et al.*[92] have developed a catalytic asymmetric Passerini reaction giving rise to α-acyloxy carboxamides enantioselectively using tridentate indan (pybox) Cu(II) Lewis acid complex as catalyst (*Scheme 18*). The most commonly used acid component is benzoic acid; the use of phenylacetic acid did not give high enantioselectivities. The best carbonyl substrate is benzyloxyacetaldehyde. The choice of isocyanide also played an important role in both the rate of reaction and selectivity. The highest yields and *ee*'s of products were observed in the case of *tert*-butyl isocyanide and *p*-methoxyphenylisocyanide.

Pirrung and Sarma[93] have reported the rate acceleration of Passerini reaction in water compared to those in organic solvents. Since the products are insoluble in water, the isolation is easy and the crude reaction products showed adequate purity for initial biological testing. The rate accelerating effect for the Passerini reaction in the presence of nucleophilic additives has been studied by Mironov *et al.*[94]



R^1 = $PhCH_2$, Ph; R^2 = 2-furyl, $BnOCH_2$, 2-thiophenecarboxyl

R^3 = $PhCH_2$, ^{t}Bu, *n*-pentyl, *p*-MeOPh

Scheme 18

6. Strecker Reaction

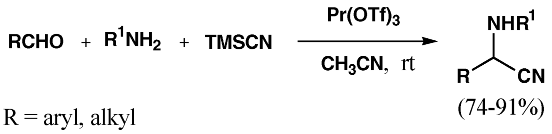
The Strecker reaction,[95] discovered in 1850, is the first multi-component reaction that involves the one-pot coupling reaction of an amine (masked ammonia), an aldehyde, and hydrogen cyanide to afford α-aminonitriles. These are precursors for the synthesis of α-amino acids and several modifications of this reaction have been reported in the literature[6] under different reaction conditions with the development of various cyanating agents.

An efficient one-pot method has been developed for the synthesis of α-aminonitriles by De and Gibbs[96] by combining aldehydes, amines, and trimethylsilyl cyanide using a catalytic amount of bismuth trichloride (*Scheme 19*). This methodology can be applicable to both primary and secondary amines, a variety of aldehydes (aromatic, aliphatic, and heterocyclic), but not to ketones. The catalyst used is inexpensive and relatively non-toxic. The same group[97] has also synthesized α-aminonitriles using praseodymium trifluoromethylsulfonate as an efficient and recyclable catalyst (*Scheme 20*). The advantage of the

R = aryl, alkyl

R^1 = Ph, $PhCH_2$, morpholine, pyrrolidine, furfuryl, 3-methoxybenzyl

Scheme 19

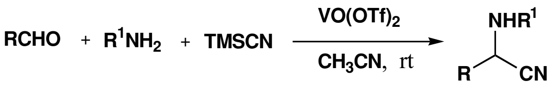


R = aryl, alkyl

R^1 = Ph, $PhCH_2$, morpholine, pyrrolidine, furfuryl, 3-methoxybenzyl, Bu, 3,4,5-trimethoxyaniline

Scheme 20

methodology is that the catalyst can be readily recovered and reused, but the ketones did not give satisfactory results. De[98] has also reported the same Strecker-type reaction for the efficient synthesis of α-aminonitriles (*Scheme 21*) using vanadyl triflate as a recyclable catalyst. The catalyst is commercially available, recoverable, and reusable and the catalytic comparison study showed that the catalytic reactivity of the praseodymium triflate is higher than the indium(III) chloride and KSF-clay in terms of the amount of catalyst and yields of the product.

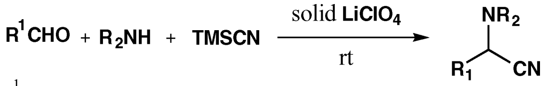


R = aryl, alkyl (74-95%)

R^1 = Ph, $PhCH_2$, morpholine, pyrrolidine, furfuryl, 3-methoxybenzyl, Bu, 3,4,5-trimethoxyaniline

Scheme 21

A solvent-free protocol has been reported by Azizi and Saidi[99] for the preparation of α-aminonitriles from the lithium perchlorate-mediated reaction between an aldehyde, an amine, and trimethylsilyl cyanide (*Scheme 22*). The catalyst is not expensive, and can be recovered and reused after activation. Even though a variety of aldehydes and secondary amines afforded the corresponding α-aminonitriles, no product was obtained when morpholine was used as the secondary amine under the same reaction conditions. However, a 76% yield of the morpholine derivative was obtained when *N*-(trimethylsilyl)morpholine was used as the amine component. A neutral protocol for the preparation of these compounds using molecular iodine has also been reported.[53]



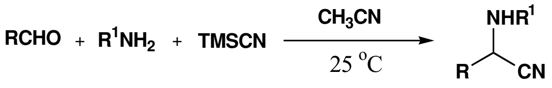
R^1= aryl, alkyl (74-94%)

R_2NH = pyrrolidine, *N*-(trimethylsilyl)morpholine, piperidine, dimethylamine

Scheme 22

Jenner and co-workers[100] have investigated the uncatalyzed Strecker reaction between ketones, aromatic amines and trimethylsilyl cyanide under high pressure[101] to afford α-aminonitriles in high yields.

Yus *et al.*[102] have developed a simpler approach for the preparation of α-aminonitriles *via* a catalyst-free Strecker reaction in acetonitrile using trimethylsilyl cyanide (*Scheme 23*). The advantage is that the use of expensive and toxic Lewis acids were



R = aryl, alkyl; R^1 = aryl, alkyl (53-99%)

Scheme 23

avoided as the catalysts. In some cases, the purification of the products after usual work-up was not necessary. Cyclic secondary amines, such as pyrrolidine and morpholine, also gave the corresponding α-aminonitriles in good yields.

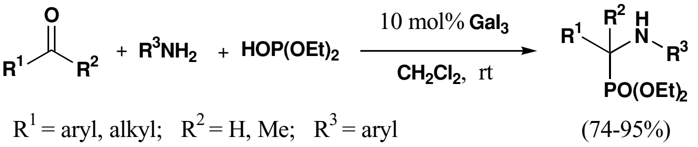
A magnesium bromide ethyl etherate-catalyzed, one-pot method for the preparation of α-aminonitriles from aldehydes, amines and trimethylsilyl cyanide under solvent-free conditions has been developed by Mojtahedi *et al.*[103]

II. Synthesis of α-Aminophosphonates and Related Phosphonates by Three-Component Reactions

α-Aminophosphonates are an important class of compounds owing to their potential biological activities. The classical approach[104,105] for the preparation of these compounds is a one-pot, three-component coupling reaction of a carbonyl compound, an amine, and a dialkyl phosphite. Several new catalysts and conditions have recently been reported in the literature.[6]

The use of different metal triflates as catalysts for the one-pot coupling of carbonyl compounds, amines, and diethyl phosphite in the absence of a solvent to prepare α-aminophosphonates has been reported by Firouzabadi *et al.*[106] The preparation of these compounds using ceric ammonium nitrate as a catalyst has also been reported.[107]

A convenient synthesis of α-aminophosphonates has been developed by Sun *et al.*[108] *via* gallium triiodide-catalyzed coupling of carbonyl compounds, amines, and diethylphosphite in dichloromethane (*Scheme 24*). The catalyst, gallium triiodide, was generated *in situ* very easily by the reaction of gallium metal and iodine. The methodology is applicable for both primary and secondary amines. The reactivity of ketones is slower than that of the aldehydes.



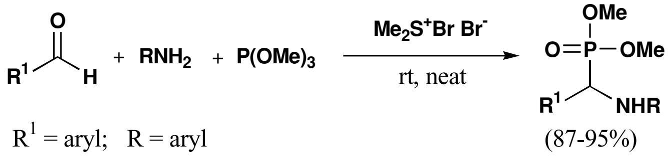
Scheme 24

Rajitha *et al.*[109] have reported an efficient protocol for the one-pot synthesis of α-aminophosphonates (*Scheme 25*) by the condensation of aldehydes, amines, and trimethylphosphite in acetonitrile using VCl_3 as a catalyst. The products were obtained in high yields with short reaction times (5–15 min) at room temperature. The catalyst is inexpensive and the method does not require any additive for promoting the reaction. A

Scheme 25

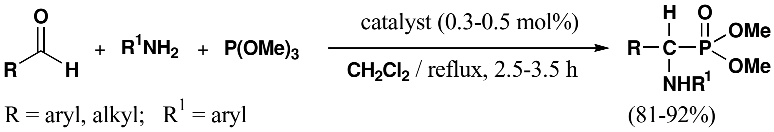
bismuth(III) chloride-catalyzed, one-pot synthesis of α-aminophosphonates has also been reported by Zhan and Li.[110]

A solvent-free method for the one-pot synthesis of α-aminophosphonates has been developed[111] in the presence of catalytic (bromodimethyl)sulfonium bromide at room temperature (*Scheme 26*). Using this catalyst, aromatic as well as α,β-unsaturated aldehydes participated in the reaction to give products without the bromination of the aromatic rings.



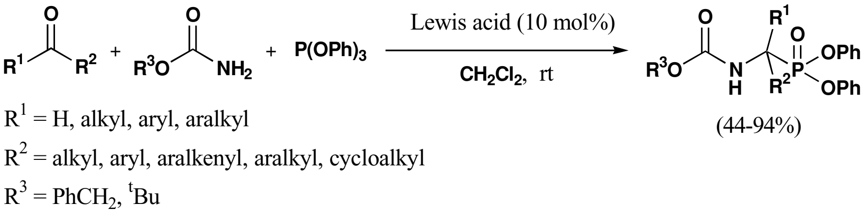
Scheme 26

Reddy *et al.*[112] have reported the use of butyldimethyl(1-phenylethyl)ammonium bromide as a catalyst for the synthesis of α-aminophosphonates (*Scheme 27*) *via* the one-pot reaction of an aldehyde, an aromatic amine, and trimethylphosphite in refluxing CH_2Cl_2. The catalyst is not sensitive to moisture unlike the other conventional Lewis acid catalysts and can be prepared easily in the laboratory. The reaction was even extended to ketones and secondary amines.



Scheme 27

Haemers *et al.*[113] have reported the Lewis acid catalyzed Birum-Oleksyszyn reaction[114,115] (one-pot condensation reaction of an aldehyde with benzyl carbamate and triphenyl phosphite) for the synthesis of *N*-protected diphenyl 1-aminoalkylphosphonates (*Scheme 28*). Yields were comparatively higher than the yields obtained using the usual protocol (heating in acetic acid). The reaction has been extended to ketones also, but required longer reaction times and resulted in lower yields than those obtained with aldehydes.



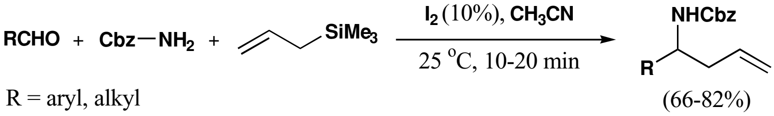
Scheme 28

A solvent-free protocol for the preparation of α-aminophosphonates has been reported by Wu *et al.*[116] *via* NBS or CBr_4 catalyzed reaction of aldehydes, amines, and diethyl phosphite.

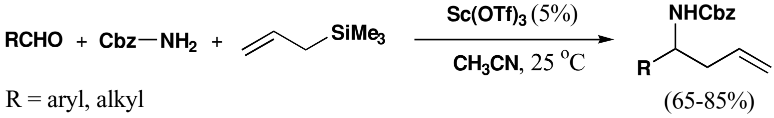
III. Synthesis of Homoallylic Amines by Three-Component Reactions

Homoallylic amines can be synthesized *via* the coupling reaction of an aldehyde and an amine (or amide) with different types of allylic compounds such as allylic organometallics. These are important intermediates in the synthesis of natural products and several catalytic procedures[6] have been developed for the preparation of these compounds.

Phukan[117] has reported a rapid one-pot procedure for the synthesis of protected homoallylic amines (*Scheme 29*) by the three-component condensation of aldehydes, benzyl carbamate, and allyltrimethylsilane using iodine as a catalyst in acetonitrile. The Cbz-protected homoallylic amines were obtained in short reaction times (10–20 min) with high yields using a cheap and easily available catalyst. The same reaction has also been reported[118] using scandium triflate as a catalyst (*Scheme 30*) to afford the products in 2–5 h. Relatively poor yields were observed with 4-nitrobenzaldehyde and isobutyaraldehyde, even though very good yields were observed in the case of both aromatic and aliphatic aldehydes. Stereoselective synthesis of homoallylic primary amines has been described by Kobayashi and co-workers[119] *via* the three-component reaction of aldehydes, allylboronates, and ammonia. The same group has also reported[120] this reaction using aqueous ammonia and several effective conditions were also explored such as the use of dodecylbenzenesulfonic acid as an additive.



Scheme 29



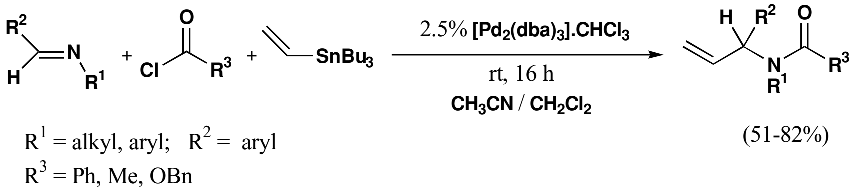
Scheme 30

Kim *et al.*[121] have disclosed an indium-mediated, one-pot protocol for the preparation of *N*-aryl-substituted homoallylic amines from aromatic amines, enol ethers, and allylic bromides in THF at room temperature.

IV. Palladium-Catalyzed Three-Component Reactions

Palladium-catalyzed reactions are the most versatile for carbon-carbon bond formation among the transition-metal mediated reactions, owing to their generality and ability to tolerate a variety of functional groups. There are several reports in the literature[6] on palladium-catalyzed, three-component reactions resulting in the formation of a variety of products.

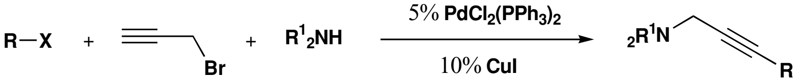
A direct and modular approach to pyrrole synthesis has been reported by Dhawan and Arndtsen[122] *via* a palladium-catalyzed coupling of alkynes, imines, and acid chlorides. The same group has also reported[123] a convenient one-pot synthesis of α-substituted amides and *N*-protected amines by a palladium-catalyzed three-component coupling of imines, acid chlorides (or chloroformates), and organotin reagents (*Scheme 31*).



R^1 = alkyl, aryl; R^2 = aryl
R^3 = Ph, Me, OBn

Scheme 31

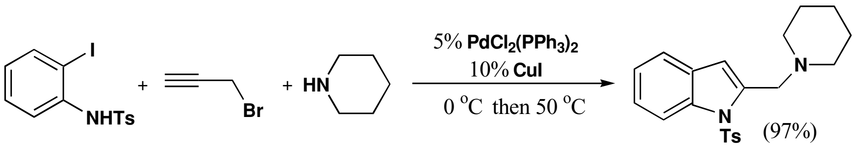
Alami *et al.*[124] have reported an efficient synthesis of highly functionalized propargylic amines (*Scheme 32*) *via* the reaction of propargyl halides, amines, and organic halides using



R = aryl; X = I, Br
R^1 = alkyl, pyrrolidine, dimethyl piperidine, morpholine, piperidine

Scheme 32

palladium-copper catalysis. The reactions proceeded at ambient temperature for the aryl iodides within a short reaction time of 15–30 min. But for the aryl bromides, heating at 60°C was required for the reaction to proceed and will take several hours to give the corresponding coupling product efficiently. An extension of this coupling has also been described (*Scheme 33*) for the synthesis of indole and benzofuran derivatives. The use



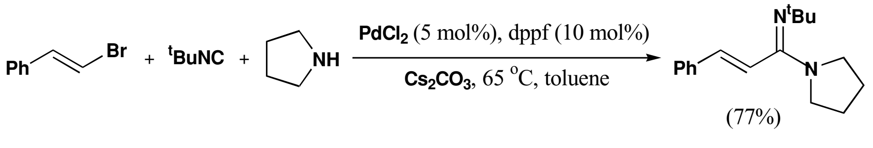
Scheme 33

of a multi-catalytic system consisting of a *N*-heterocyclic carbene palladium complex and copper(I) iodide has been reported[125] for the synthesis of substituted indoles from *ortho*-dihaloarenes, terminal alkynes and various substituted amines. A one-pot synthesis of polysubstituted furans has been developed by Liang *et al.*[126] *via* palladium-catalyzed, three-component, cyclization-coupling reaction of propargyl carbonate, β-keto esters and aryl iodide.

A one-pot synthesis of polysubstituted 4-(phenoxymethyl)-3-pyrrolines and their isomers has been reported by Balme and co-workers[127] *via* coupling of propargyl amines, vinyl sulfones (or nitro alkenes), and phenols. The same group[128] has also achieved the one-pot synthesis of highly functionalized 4-benzyl-(and allyl-)pyrrolidines by the palladium-catalyzed coupling reaction of allylic amines, *gem*-diactivated alkenes, and unsaturated halides (or triflates). A novel and diverse route to 3-aryl/heteroaryl/vinyl substituted heterocycles has also been developed[129] *via* a sequential three-component Pd-cascade / RCM process.

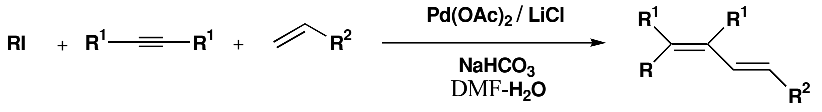
Akiyama *et al.*[130] have described the three-component synthesis of optically active 4-arylated dehydroprolines. A synthesis of highly fluorescent indolizines and bisindolizines has also been reported[131] *via* a consecutive one-pot, three-component process involving a coupling/1,3-dipolar cycloaddition sequence.

The synthesis of α,β unsaturated amidines and imidates has been reported[132] by the palladium-catalyzed coupling of an alkenyl bromide, an isonitrile, and an amine (or alkoxide/phenoxide) (*Scheme 34*). In the synthesis of alkenylamidines, the attempts to replace *tert*-butyl isonitrile with *n*-butyl-, cyclohexyl- or benzyl isonitriles was unsuccessful, even though a variety of primary and secondary amines were tried under the reaction conditions. But, in the synthesis of alkenylimidates, not only *tert*-butyl isonitrile, but *n*-butyl and cyclohexyl isonitriles also furnished the desired imidates.



Scheme 34

Hulin *et al.*[133] have reported a three-component, stereoselective synthesis of functionalized bicyclopentanoids under palladium-catalysis. A palladium-catalyzed route to 1,3-butadiene derivatives has been disclosed by Miura *et al.*[134] *via* intermolecular coupling of aryl iodides, diaryl acetylenes, and monosubstituted alkenes (*Scheme 35*). By using this protocol, butadienes having multiple aryl groups can also be prepared which are of interest for their photo and electrochemical and biological properties.

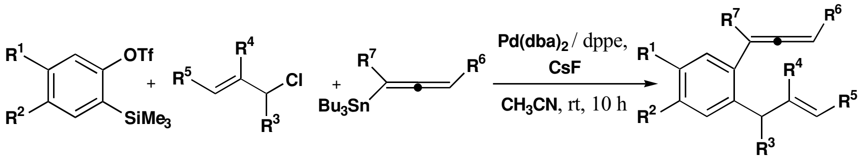


R = aryl; R^1 = aryl; $R^2 = CO_2Bu, CO_2Et, CONMe_2, CN, Ph$

Scheme 35

Zhou and Larock[135] have studied and provided a full account of the scope and limitations of the chemistry of palladium-catalyzed synthesis of tetrasubstituted olefins involving the intermolecular coupling of an aryl iodide, an internal alkyne, and an arylboronic acid and also developed mild, room temperature conditions. By using this protocol, tamoxifen and its analogues were synthesized in a concise, regio- and stereoselective manner. Larock *et al.*[136] have reported the synthesis of a series of C-5 aminoalkyl-substituted nucleosides *via* the palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides, a wide range of dienes and amines in the presence of a Lewis acid such as zinc(II) chloride.

Jeganmohan and Cheng[137] have developed a new palladium-catalyzed route to substituted 1-allyl-2-alkynylbenzenes *via* a three-component assembling reaction of arynes with allylic chlorides and alkynylstannanes. Arynes were generated *in situ* from 2-(trimethylsilyl)aryl triflates and cesium fluoride. The same group has also reported[138] the one-pot preparation of 1-allyl-2-allenylbenzenes by the palladium-catalyzed reaction of benzynes, allylic chlorides, and allenylstannanes (*Scheme 36*). The reactions were performed in the presence of Pd(dba)$_2$ /dppe (5 mol%) and cesium fluoride at ambient temperature in acetonitrile. The selection of the phosphine ligand and the solvent are important for the reaction. Out of the solvents tested, acetonitrile, is effective, but other solvents such as tetrahydrofuran, dimethylformamide and dichloromethane were totally ineffective for the reaction. A highly efficient method for the preparation of *o*-allylbiaryl derivatives has also been reported[139] *via* palladium-catalyzed coupling of benzynes, allylic halides, and aryl organometallic reagents (*Scheme 37*). For example, the reaction of 2-(trimethylsilyl)phenyl triflate with allyl chloride and phenylboronic acid in the presence of 5 mol% of Pd(dba)$_2$/dppb and cesium fluoride in acetonitrile at ambient temperature for 8 h, furnished the corresponding 2-allylbiphenyl derivative in 88% isolated yield.



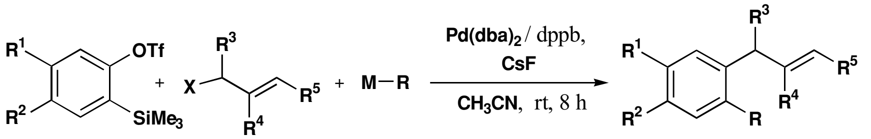
$R^1 = R^2 = H$, alkyl, F

(79-93%)

$R^3 = R^4 = H$, Me; $R^5 = H$, Me, Ph; R^3, R^4, R^5 = 3-chloro cyclohexene

$R^6 = H$, Me; $R^7 = H$, D

Scheme 36



(66-88%)

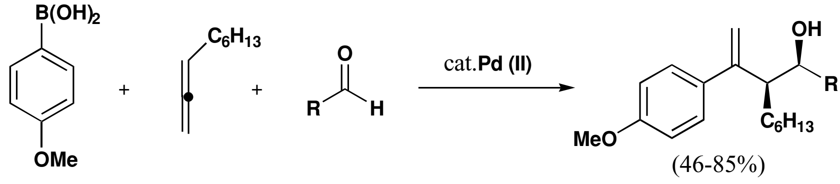
$R^1 = R^2 = H$, Me; R^1, R^2 = -(CH$_2$)$_3$ -

X = Cl; $R^3 = R^4 = R^5 = H$, Me

M = B(OH)$_2$, Si(OMe)$_3$, SnBu$_3$; R = aryl

Scheme 37

Hopkins and Malinakova[140] have described the preparation of highly substituted homoallylic alcohols *via* palladium-catalyzed coupling reaction of an arylboronic acid, an allene, and an aldehyde (*Scheme 38*). Among the different aldehydes tried, electron-deficient *p*-nitrobenzaldehyde is the most reactive aldehyde with 85% yield, whereas aliphatic aldehydes such as cyclohexylcarboxaldehyde led to only a modest yield of alcohol in 46%. Out

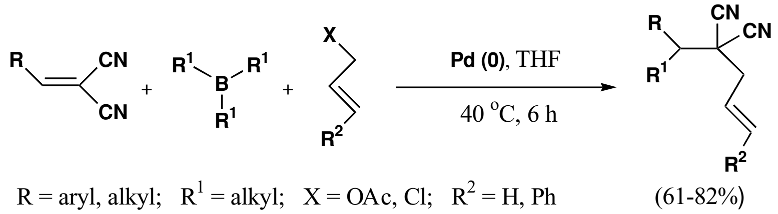


R = aryl, heteroaryl, cyclohexyl

Scheme 38

of the diastereomeric alcohols obtained, the major diastereomer was *syn*. The same group has also reported[141] a palladium-catalyzed protocol for the preparation of highly substituted α,β-unsaturated δ-lactones with excellent chemo-, regio- and diastereoselectivity *via* coupling of boronic acids, allenyl esters and aldehydes.

The palladium-catalyzed linking of activated olefins, trialkylboranes, and allylic substrates has been reported by Yamamoto *et al.*[142] to afford the corresponding β-alkyl-α-allylated products (*Scheme 39*). For example, the reaction between benzyledenemalononitrile, triethylborane, and allyl acetate using 5 mol% of $(PPh_3)_4$ as a catalyst in the presence of THF at 40°C, afforded the corresponding β-ethyl-α-allylated product in 81% yield.



R = aryl, alkyl; R^1 = alkyl; X = OAc, Cl; R^2 = H, Ph (61-82%)

Scheme 39

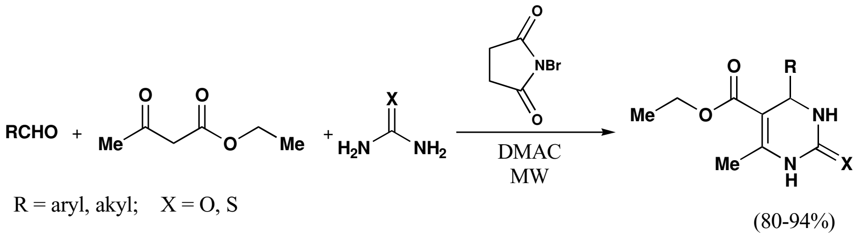
V. Microwave-Assisted Three-Component Reactions

In recent years, the application of microwave energy to accelerate organic reactions has gained popularity after Gedye's[143] pioneering report on the use of microwave irradiation as a thermal source to carry out organic reactions in 1986. This technique[144,145] is advantageous over conventional methods due to shorter reaction times, dry media (thus avoiding the use of harmful solvents), cleaner reactions, easy work up, and minimization of thermal decomposition products. Using this environmentally benign protocol, several three-component reactions[6] have been reported.

An easy access to spiro-fused heterocycles has been reported by Sandhu *et al.*[146] *via* Biginelli-like reaction mediated by nickel chloride hexahydrate in the solid state under microwave irradiation. Cobalt chloride hexahydrate is also found to be equally effective. The same group has also described[147] a microwave-assisted protocol for the one-pot preparation of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones by using cobalt chloride hexahydrate or manganese chloride tetrahydrate or tin chloride dihydrate.

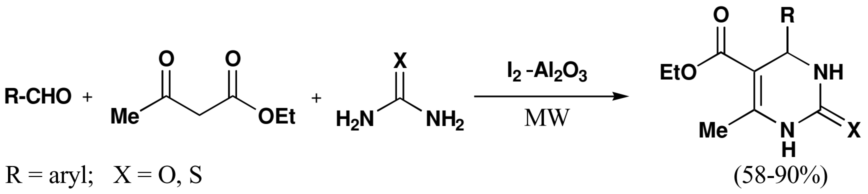
A cupric chloride dihydrate- or cupric sulfate pentahydrate-catalyzed Biginelli reaction under solvent-free conditions using microwave irradiation has also been reported.[148]

Hazarkhani and Karimi[149] have introduced *N*-bromosuccinimide as a mild catalyst for the efficient synthesis of dihydropyrimidinones (*Scheme 40*) using microwave irradiation. The advantages are the use of very cheap and safe reagent, nearly neutral reaction conditions, high yields and shorter reaction times under microwave irradiation. *N*,*N*-Dimethylacetamide proved to be a more superior solvent than EtOH, owing to the higher solubility of the substrate and the excellent energy transfer property.



Scheme 40

Sarma *et al.*[150] have reported a quick method for the condensation reaction of an aldehyde, ethyl acetoacetate, and urea or thiourea to synthesize substituted 3,4-dihydropyrimidin-2(1*H*)-ones using iodine-alumina as the catalyst under microwave irradiation and solvent-free conditions (*Scheme 41*). The method is quick (1 min) with a variety of aromatic, substituted aromatic, and heterocyclic aldehydes; however, no aliphatic aldehyde has been used. Microwave-assisted synthesis of 3,4-dihydropyrimidinones from an aldehyde, a keto ester and urea or thiourea using ferric chloride hexahydrate as a catalyst under solvent-free conditions has been described by Mirza-Aghayan *et al.*[151]

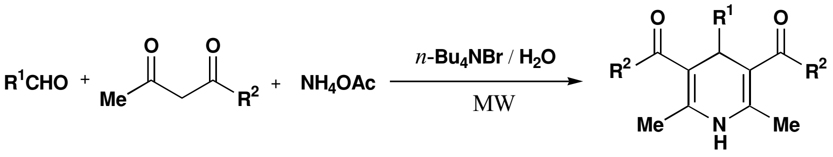


Scheme 41

Zinc chloride-catalyzed one-pot preparation of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones has been proposed by Pasha *et al.*[152] using microwave irradiation in the absence of solvent. The same group has also reported[153] a cobalt(II) acetate-catalyzed, microwave-assisted Biginelli reaction under solvent-free conditions. A microwave-assisted, solvent-free protocol for the synthesis of 3,4-dihydropyrimidinones has been reported by Wang *et al.*[154] using poly(ethyleneglycol)-bound sulfonic acid as a catalyst.

A synthesis of benzofuran Mannich bases has been presented by Rajitha *et al.*[155] under solventless *p*-toluenesulfonic acid or phase-transfer catalytic conditions in a domestic microwave oven. Thermal effects in the organocatalytic asymmetric Mannich reaction have been studied by Rodriguez and Bolm[156] and found that under microwave irradiation, with only 0.5 mol% of catalyst (proline), products with up to 98% *ee* have been obtained after a short period of time in the reaction between cyclohexanone, formaldehyde, and various anilines.

Salehi and Guo[157] have reported the synthesis of 1,4-dihydropyridines in water using tetrabutylammonium bromide as a phase-transfer catalyst under microwave irradiation by the reaction of aldehydes, ethyl/methyl acetoacetates, and ammonium acetate (*Scheme 42*). The reactions were completed in 3–10 mins. It was found that the same reactions carried out without microwaves, even at 100°C did not result in significant yields in 10 mins. Terephthalaldehyde, a dialdehyde, has also been used as precursor for the bifunctional compounds containing two units. A Lewis acid Zn[(L)proline]$_2$ catalyzed one-pot synthesis of Hantzsch 1,4-dihydropyridines has also been described by Sivamurugan *et al.*[158] using microwave irradiation under solvent-free conditions.

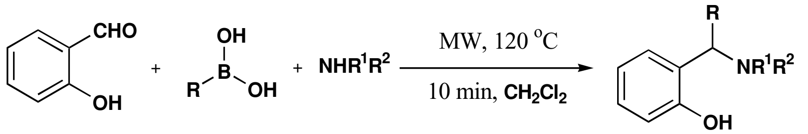


R^1 = H, aryl, alkyl; R^2 = OMe, OEt

(77-92%)

Scheme 42

Follmann *et al.*[159] have described a rapid and straightforward, microwave-induced protocol for the Petasis reaction of electron-poor aromatic amines such as aminopyridines and compared it with conventional heating. The utility of the design of experiments (DOE) approach has been reported by Tye *et al.*[160] to optimize a microwave-assisted protocol for the Petasis boronic-Mannich reaction employing either glyoxylic acid or salicylaldehyde as the carbonyl component along with a wide range of aryl/heteroarylboronic acids and amine components (*Scheme 43*). In the case of reaction with salicylaldehyde, only secondary amines gave the desired products. The advantage of this method is the shorter reaction time (10 mins) when compared to several hours required in the other reported methods at room temperature. The same group has also demonstrated[161] the utility of the DOE approach for the rapid and efficient optimization of a microwave-assisted procedure for the Ugi three-component condensation of levulinic acid with an amine and an isonitrile to afford lactam derivatives (*Scheme 44*) in shorter reaction times (30 min) compared to the conventional procedure (48 h) in methanol as a solvent. Ethanol was also used as a solvent in the case of ethyl isocyanoacetate substrate to avoid problems with transesterification.

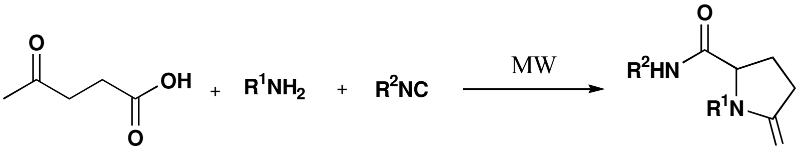


R = aryl

(10-83%)

R^1, R^2 = morpholine, aminodiphenyl methane, *p*-ansidine, dibenzyl

Scheme 43

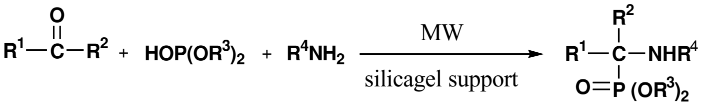


(17-90%)

R^1 = $PhCH_2$, cyclohexyl, 3-methylthiophene-2-methyl, 3-methoxy propyl
R^2 = $PhCH_2$, ethyl isocyanoacetate

Scheme 44

A one-pot synthesis of α-aminophosphonates under microwave irradiation has been developed by Zhan *et al.*[162] *via* a three-component coupling using silica gel-supported reagent (*Scheme 45*). The reaction is applicable to both aldehydes and ketones and aromatic



$$R^1-\overset{O}{\overset{\|}{C}}-R^2 + HOP(OR^3)_2 + R^4NH_2 \xrightarrow[\text{silicagel support}]{\text{MW}} R^1-\underset{O=\underset{}{P}(OR^3)_2}{\overset{R^2}{\overset{|}{\underset{|}{C}}}}-NHR^4$$

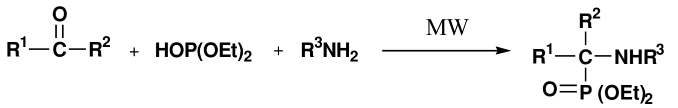
R^1 = aryl, alkyl; R^2 = H, alkyl
R^1, R^2 = cyclopentyl, cyclohexyl
R^3 = aryl, alkyl; R^4 = alkyl

(80-95%)

Scheme 45

as well as aliphatic amines. The silica gel can be easily recovered by filtration, washed with methanol, and activated at 100°C for 1 h and can be reused. The other advantages are that silica gel is cheap and the solvent-free conditions.

The application of microwave irradiation for the preparation of α-aminophosphonates has been presented by Kabachnik *et al.*[163] using ketones in a three-component system under catalyst-free conditions (*Scheme 46*). The ketones used were aliphatic, aromatic,



$$R^1-\overset{O}{\overset{\|}{C}}-R^2 + HOP(OEt)_2 + R^3NH_2 \xrightarrow{\text{MW}} R^1-\underset{O=\underset{}{P}(OEt)_2}{\overset{R^2}{\overset{|}{\underset{|}{C}}}}-NHR^3$$

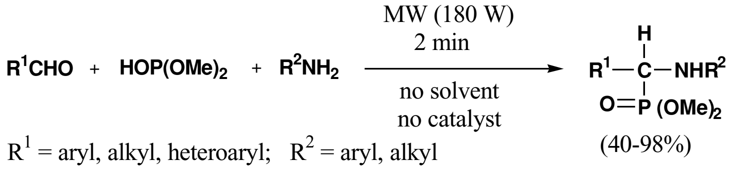
R^1 = R^2 = alkyl, aryl; R^3 = alkyl, $PhCH_2$

(72-92%)

Scheme 46

heterocyclic, and carbocyclic along with a ketone from a natural porphyrin derivative for the preparation of these compounds. A comparative study has also been done on the synthesis of these compounds from ketones both under microwave irradiation and under conventional heating. The application of microwave irradiation is very useful for the preparation of α-aminophosphonates from ketones such as benzophenone and adamantanone-2 which gave poor yields by conventional heating.

A solvent-free and catalyst-free, microwave-assisted method for the synthesis of α-aminophosphonates has been reported by Mu *et al.*[164] *via* the reaction of an aldehyde, an amine, and a dimethyl phosphite (*Scheme 47*). The reactions conducted using pivalaldehyde,

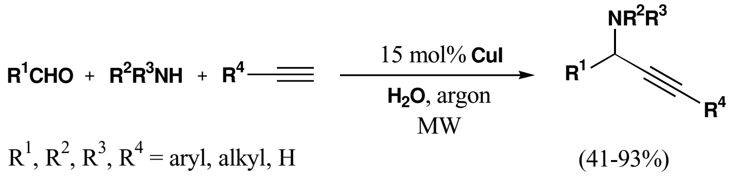


R^1 = aryl, alkyl, heteroaryl; R^2 = aryl, alkyl

Scheme 47

p-toluidine or 2,6-dimethylaniline resulted in much lower yields (53% and 40%) when compared to the reactions using other substrates.

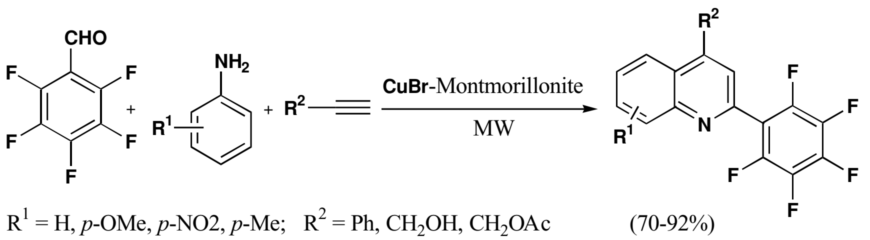
Shi and co-workers[165] have developed a facile method for the construction of propargylamines *via* a microwave-promoted coupling reaction of aldehyde, alkyne, and amine *via* C-H activation catalyzed by copper(I) iodide catalyst without the noble metal co-catalyst (*Scheme 48*). Instead of using commercial catalyst, it is necessary to use freshly prepared catalyst. A very low yield 41% of product was observed with 4-nitrobenzaldehyde as a substrate and none of the expected product was observed in the case of diphenylamine. A diastereoselective coupling has also been developed using chiral amine substrates like (*S*)-proline methyl esters.



R^1, R^2, R^3, R^4 = aryl, alkyl, H

Scheme 48

A microwave-promoted approach for the synthesis of 2-pentafluorophenylquinoline derivatives has been presented by Zhang and co-workers[166] *via* the one-pot reaction of pentafluorobenzaldehyde, anilines, and alkynes on the surface of montmorillonite clay impregnated with a catalytic amount of CuBr under solvent-free conditions (*Scheme 49*).

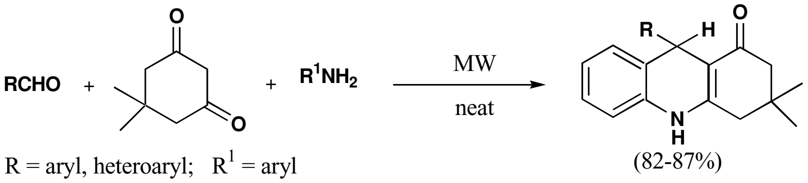


R^1 = H, p-OMe, p-NO2, p-Me; R^2 = Ph, CH_2OH, CH_2OAc

Scheme 49

Improved yields and enhanced reaction rates are the advatages, since the same reaction under the traditional thermal conditions (80°C, oil bath) afforded the expected quinoline derivatives in only moderate yields. The same group has also developed[167] a microwave-promoted protocol for the synthesis of [60]fulleropyrrolidine derivatives *via* a one-pot reaction of C_{60}, an amino acid and an aldehyde under solvent-free condtions.

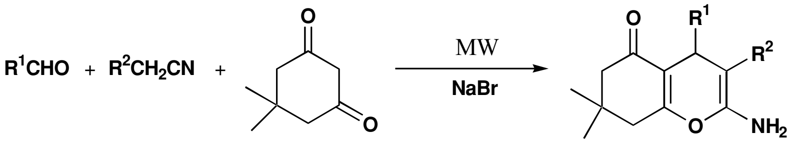
Kidwai and co-workers[168] have reported the synthesis of thiadiazolopyrimidin-2-thiones in dry media using microwave irradiation. A solvent-free synthetic route for the synthesis of tetrahydroacridinones has been reported[169] by the same group *via* the microwave-assisted condensation reaction of an aldehyde, dimedone and a primary aromatic amine (*Scheme 50*). The best microwave method was found to be the "neat reaction" technology without the use of any solvent or inorganic solid supports. The reactions were completed within 5 mins with 82–87% yields, when compared to the conventional solution phase method with longer reaction times (hours) and comparitively lower yields. The other microwave solvent-free methods studied involved the use of inorganic solid supports (basic and neutral alumina). Out of these two supports, basic alumina gave better results than the neutral alumina. The same group has also advanced[170] a new route for the synthesis of acridine and quinazoline derivatives *via* the microwave assisted cyclocondensation of an aldehyde, dimedone, and ammonium acetate/thiourea performed on thin layer chromatography plates. A neat technology has also been developed[171] by the same group for the synthesis of antimalarial agents such as 1-aryl-4,6-diamino-1,2-dihydrotriazine derivatives *via* a one-pot microwave reaction.



Scheme 50

A microwave-induced, solvent-free protocol for the one-pot synthesis of 4-aminobenzoxazinone derivatives has been reported by Yadav and Kapoor[172] *via* montimorillonite K-10 clay-supported reactions of substituted salicylaldehydes, *N*-substituted ureas (or carbamates), and ammonium acetate (or an amine). An expeditious synthesis of polyfunctionalized 1,3-thiazines has also been developed[173] by the one-pot, three-component reaction from 2-methyl-2-phenyl-1,3-oxathiolan-5-one, an aromatic aldehyde and *N*-aryl dithiocarbamic acid under microwave irradiation using solvent-free conditions.

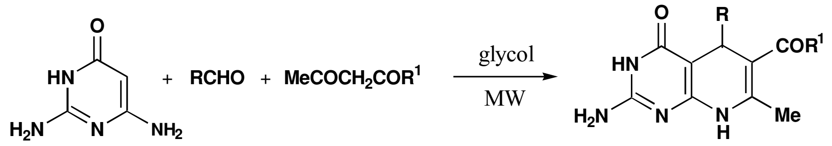
Bhuyan *et al.*[174] have reported a novel one-pot synthesis of pyrano[2,3-*d*]pyrimidines *via* the cyclocondensation of barbituric acids, benzaldehyde, and aliphatic nitriles under microwave irradiation in the solid state. The synthesis of pyrido[2,3-*d*]pyrimidines has also been performed under identical conditions *via* condensation of 6-aminouracils or 6-hydroxyaminouracils, benzaldehyde, and aliphatic nitriles. The same group has also developed[175] another microwave protocol for the synthesis of these derivatives in the presence of acetic anhydride using triethyl orthoformate as one of the substrates. A one-pot synthesis of highly functionalized tetrahydrobenzo[*b*]pyrans (*Scheme 51*) has also been reported[176] by the same group *via* sodium bromide catalyzed cyclocondensation of aryl aldehydes, aliphatic nitriles, and dimedone under solvent-free microwave irradiation conditions. Among the aliphatic nitriles tried, the activity of cyanoacetamide is poor, when compared to malononitrile and ethyl cyanoacetate.



R^1 = aryl; R^2 = CN, CO_2Et, $CONH_2$ (60-95%)

Scheme 51

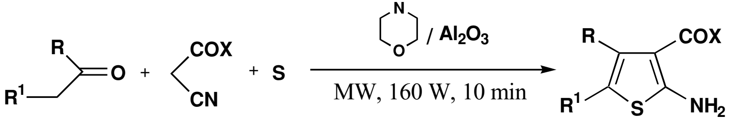
A microwave-assisted, one-pot synthesis of dihydropyridopyrimidine derivatives (*Scheme 52*) has been reported by Tu *et al.*[177] *via* condensation of 2,6-diaminopyrimidin-4-one, aldehydes, and acyclic 1,3-dicarbonyl compounds in glycol without the use of a catalyst. The advantages are shorter reaction times, environmentally benign methodology and it can also be applied to aliphatic as well as aromatic aldehydes. The same group has also disclosed[178] an efficient synthesis of a series of pyrimidoquinoline derivatives through a one-pot condensation of 2,6-diaminopyrimidin-4-one, an aldehyde, and a cyclic 1,3-dicarbonyl compound in glycol under microwave irradiation without a catalyst. A microwave-induced, one-pot procedure for the preparation of pyridopyrimidine-spirocyclohexanetriones has been described by Quiroga *et al.*[179] *via* the three-component reaction of 6-aminopyrimidin-4-ones with dimedone and formaldehyde solution.



R = aryl, alkyl; R^1 = Me, OMe (89-95%)

Scheme 52

An extension of the Willgerodt-Kindler reaction has been studied by Darabi *et al.*[180] using oximes, hydrazones, and semicarbazones as substrates for the preparation of thiomorpholides in a solvent-free reaction, under both classical and microwave conditions. Lagrenée *et al.*[181] have reported a rapid synthesis of 2,5-disubstituted-1,3,4-thiadiazoles *via* the one-pot condensation reaction of aromatic aldehydes, hydrazine, and sulfur in ethanol under microwave irradiation. A Gewald synthesis of 2-aminothiophenes has been reported by Hu *et al.*[182] under microwave conditions using a functional ionic liquid as a soluble support. Microwave-assisted synthesis of 2-aminothiophene-3-carboxylic derivatives (*Scheme 53*)

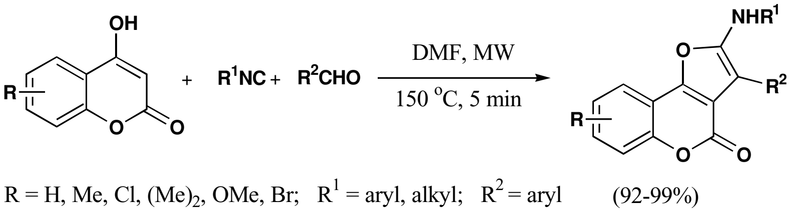


(51-95%)
R = alkyl; R^1 = COMe, CO_2Et; X = OMe, OEt, NH_2, NHaryl

Scheme 53

has been reported by Huang *et al.*[183] *via* the reaction of cyanoacetates (cyanoacetamides) with ketones and sulfur using morpholine as a base catalyst and aluminium oxide as a solid support under solvent-free conditions. The yields of the products were improved substantially using microwave conditions compared to the yields obtained using thermal conditions.

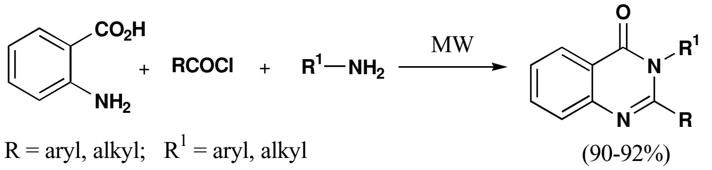
Shaabani and co-workers[184] have reported a solvent-free synthesis of furopyrimidines, furocoumarins, and furopyranones by a microwave-assisted, one-pot reaction of *N*,*N'*-dimethylbarbituric acid or 4-hydroxycoumarin or 4-hydroxy-6-methyl-2-pyrone with *p*-substituted benzaldehydes and alkyl or aryl isocyanides in the presence of montmorillonite K10 as a solid support. An expedient synthesis of functionalized furo[3,2-*c*]chromen-4-ones has been reported by Wu[185] *via* microwave-assisted reaction of common 4-hydroxycoumarins, isocyanides, and aldehydes (*Scheme 54*) in the presence of DMF at 150°C for 5 mins. The advantages of this methodology over the traditional heating methods are shorter reaction times (5 mins), improved yields of 92–99%, easy experimental procedure, complete conversions by suppression of side-products, which has extended its utility for use in high throughput library synthesis.



Scheme 54

Microwave-assisted synthesis of 4(3*H*)-quinazolinone derivatives has been reported by Dabiri *et al.*[186] *via* a one-pot condensation reaction of isatoic anhydride, primary amines, and ortho esters in the presence of catalytic amounts of *p*-toluenesulfonic acid. The same group[187] has also prepared these derivatives using an $AlCl_3/ZnCl_2$ mixture on silica gel as an efficient medium under microwave irradiation.

Dandia *et al.*[188] have presented an improved procedure for the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones by the reaction of anthranilic acid, acid chlorides, and amines under microwave-irradiation using neat reaction conditions (*Scheme 55*).

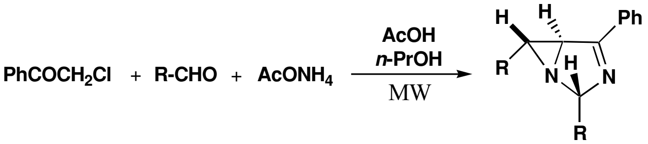


Scheme 55

Comparison studies revealed that the advantages of the microwave method are higher yields of 90–92% and shorter reaction times (4–5 mins) over conventional method yields of

61–60% and 12 h of reaction time. The same group has also studied[189] the one-pot synthesis of these fluorinated 2,3-disubstituted quinazolin-4(3*H*)-ones by a microwave-induced, solvent-free protocol and their anti-fungal activity.

A novel one-pot synthesis of stereo-defined bridgehead aziridines (*Scheme 56*) has been described by Risitano and co-workers[190] *via* the reaction of an aldehyde with phenacyl chloride and ammonium acetate in acetic acid and *n*-propanol using microwave irradiation. The same procedure has been extended to aliphatic aldehydes but no significant result has been observed. An analogous bicyclic product has been obtained in reduced yields with bulkier substrates such as pivalaldehyde. A comparative study has been done with conventional heating which took longer reaction times (2–3 h) and gave lower yields in comparison with microwave protocol (short reaction times 5–10 min).

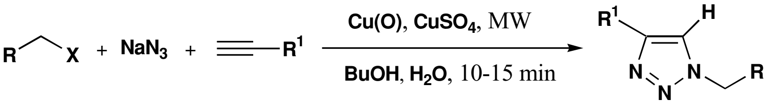


R = aryl, $(CH_3)_3C$

(35-92%)

Scheme 56

Appukkuttan *et al.*[191] have developed a microwave-assisted synthesis of a series of 1,4-disubstituted-1,2,3-triazoles *via* a copper(I)-catalyzed reaction from corresponding alkyl halides, sodium azide, and alkynes (*Scheme 57*). This methodology is more user-friendly, safe, and eliminates the need to handle organic azides, as they were generated *in situ*. For example, methyl iodide reacted with sodium azide and phenylacetylene to afford the corresponding product in 89% yield within 10 mins, whereas its synthesis is otherwise difficult owing to the hazardous nature of methyl azide. An efficient one-pot synthesis of substituted 1,2,4-triazoles has also been reported by Li *et al.*[192] *via* a microwave-assisted three-component reaction.



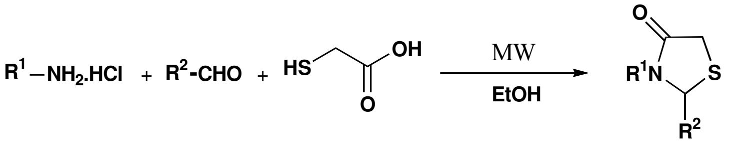
R = aryl, alkyl; X = Cl, Br, I; R^1 = aryl, alkyl

(84-93%)

Scheme 57

The effect of microwave irradiation under solvent-free conditions has been investigated by Sridharan *et al.*[193] for the three-component stereoselective synthesis of tetrasubstituted isoxazolidines.

Miller *et al.*[194] have reported a convenient rate enhanced microwave method for the synthesis of 4-thiazolidinones (*Scheme 58*) *via* the one-pot condensation of a primary amine, an aldehyde, and mercaptoacetic acid. The reactions were conducted using an environmentally benign solvent ethanol in open vessels at atmospheric pressure in the presence of Hünig's base and molecular sieves. Amine components bearing a chiral center have also participated in the formation of diastereomeric products.



R^1 = alkyl; R^2 = aryl (55-91%)

Scheme 58

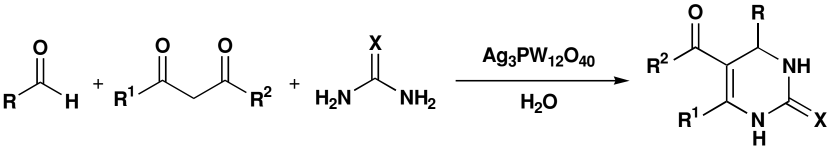
The one-pot synthesis of series of some γ-spiroiminolactone derivatives has been demonstrated by Azizian *et al.*[195] *via* a microwave assisted condensation reaction of isocyanides, dialkyl acetylenedicarboxylates and indenoquinoxilin-11-ones in DMF or in a solventless operation on montmorillonite K10 support.

Meijere and co-workers[196] have reported a new three-component cascade reaction under microwave heating for the direct conversion of alkylhydroxylamine hydrochlorides, formaldehyde (or an alkyl glyoxylate), and bicyclopropylidene to 3-spirocyclopropanated 2-azetidinones in the presence of sodium acetate in ethanol.

VI. Three-Component Reactions Using Supported Reagents

In view of the continuous demand for combinatorial methods of synthesis, there has been growing interest in the use of solid-supported reagents due to facile work-up by simple filtration, regeneration and recycling of the catalyst, etc. Application of this environmentally-conscious protocol to the three-component reactions has been the subject of numerous recent reports.[6]

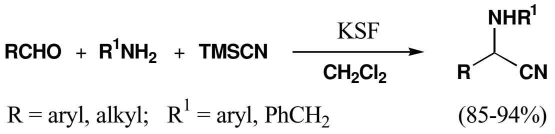
A convenient method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has been described[197] by using silica gel-supported sodium bisulfate as a heterogeneous catalyst. Yadav *et al.*[198] have disclosed a green protocol for the Biginelli reaction (*Scheme 59*) using



R = aryl, alkyl; R^1 = Me, Ph; R^2 = OEt, Me, OMe; X = O, S (82-93%)

Scheme 59

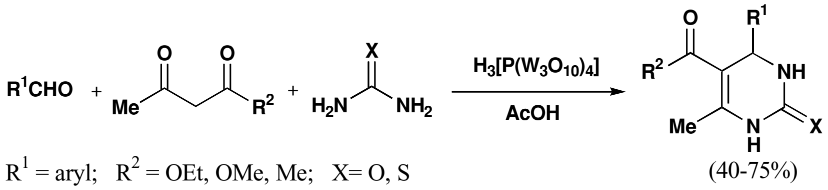
silver salt of heteropolyacid, *i.e.*, $Ag_3PW_{12}O_{40}$, in water. This catalyst was found to be superior in terms of conversion and reaction times when compared to other solid acid catalysts such as KSF clay, acid resin (Amberlyst-15), and acid-washed silica gel (H_2SO_4-SiO_2). The reusability of the catalyst in an eco-friendly solvent such as water is an added advantage. The same group has also reported[199] a simple, convenient, and efficient protocol for the one-pot synthesis of α-amino nitriles by the coupling of aldehydes, amines, and trimethylsilyl cyanide using a heterogeneous solid acid catalyst, montmorillonite KSF clay, under mild reaction conditions (*Scheme 60*). Under these condtions, ketones did not yield any product.



Scheme 60

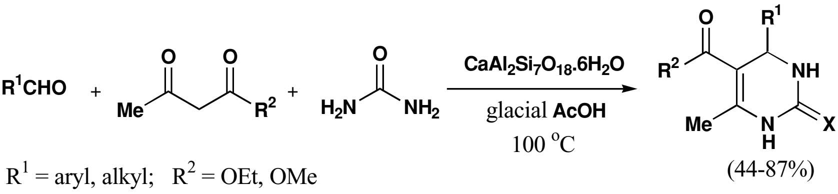
The use of poly(4-vinylpyridine-co-divinyl benzene)-Cu(II) complex as a recyclable catalyst for the synthesis of 3,4-dihydropyrimidinones has been reported[200] *via* the one-pot condensation of aldehydes, β-keto esters, and urea. Polyaniline-bismoclite complex has been used as a facile and reusable catalyst for the one-pot preparation of dihydropyrimidinones by Palaniappan *et al.*[201] Other polyaniline salts have also been reported[202,203] as catalysts for the Mannich-type and Biginelli reactions.

Heravi and co-workers[204] have reported the use of 12-tungstophosphoric acid as a recyclable catalyst for the one-pot cyclocondensation of a 1,3-dicarbonyl compound, an aldehyde, and urea (or thiourea) to afford 3,4-dihydropyrimidin-2(1*H*)-ones (*Scheme 61*).



Scheme 61

The catalyst is non-corrosive and reusable retaining the same activity as that of the freshly used catalyst even after five runs. The same group has also developed[205] a natural Heulandite type of zeolite-catalyzed protocol for the synthesis of these compounds (*Scheme 62*). In this case also, the catalyst can be used up to five times without any loss of activity and also without appreciable changes in yields of the products. Aliphatic aldehydes afforded products in lower yields of 44–46% with longer reaction times (12 h), when compared to aromatic aldehydes with yields of 60–87% in 4–5 h.



Scheme 62

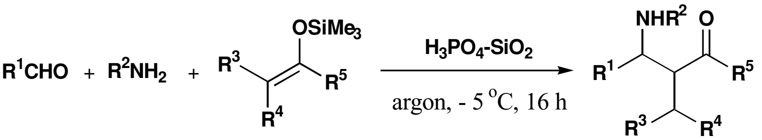
A Lewis acid-doped natural phosphate catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones has been reported by Badaoui *et al.*[206]

Sulfated zirconia-catalyzed synthesis of 3,4-dihydropyrimidinones has been reported by Reddy *et al.*[207] *via* a one-pot condensation of an aldehyde, a β-keto ester, and urea (or thiourea) under solvent-free conditions. The same group has also reported[208] the synthesis and application of sulfated-ceria-zirconia, a solid superacid catalyst for the preparation of β-aminoketones *via* Mannich reaction under solvent-free conditions.

The use of modified zeolite-type adsorbent E4a as a suitable catalyst for the convenient one-pot synthesis of dihydropyrimidinones *via* Biginelli reaction has been reported.[209] A facile one-pot procedure for the preparation of these compounds has been described by Azizian and co-workers[210] using $KAl(SO_4)_2.12H_2O$ (alum) supported on silica gel under solvent-free conditions at 80°C.

The use of alumina impregnated with antimony(III) chloride for the one-pot condensation of an aldehyde, a β-keto ester and urea (or thiourea) to afford dihydropyrimidinones has been reported by Kapoor *et al.*[211] The Biginelli preparation of these compounds using ion-exchange resins as recyclable and heterogeneous solid acid catalysts has been reported by Sain and co-workers.[212]

A convenient solvent-free procedure for the synthesis of β-aminocarbonyl compounds has been reported by Lock *et al.*[213] *via* an imino-aldol, three-component coupling between aldehydes, aromatic amines, and silylenol equivalents using a reusable phosphoric acid-silica gel solid support (*Scheme 63*). When benzylamine was used as the amine component, none of the desired product was obtained. Very poor reactivity has been observed in the reaction of [1-phenyl-1-(trimethylsiloxy)]ethylene as a silylenol ether with benzaldehyde and aniline.



(7-94%)

R^1 = aryl, alkyl; R^2 = aryl; R^3 = Me, H

R^4 = Me, H; R^5 = OMe, Ph; R^4, R^5 = $-(C_4H_8)-$

Scheme 63

The use of silica gel-supported sodium bisulfate as a heterogeneous catalyst has been described[214] for the one-pot synthesis of Hantzsch 1,4-dihydropyridines by the reaction of an aldehyde, a β-ketoester, and ammonium acetate in acetonitrile at room temperature.

A modified Hantzsch method for the synthesis of isoxazole-substituted 1,4-dihydropyridines has been reported by Rajanarendar *et al.*[215] by utilizing ketoamides in place of ketoesters on a neutral alumina support.

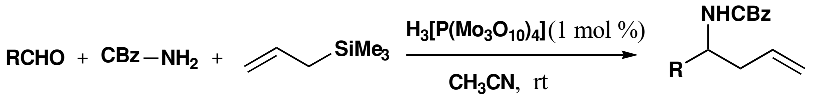
Chen and Lu[216] have developed a silica sulfuric acid-catalyzed, one-pot method for the synthesis of α-aminonitriles *via* coupling of aldehydes, amines, and trimethylsilyl cyanide (*Scheme 64*) at room temperature. The advantages are that reactions were performed using inexpensive, commercially available chemicals without the use of any other additive for promoting the reaction, recyclability of the catalyst with comparable activity. Ketones did not give any good results even though both aromatic and aliphatic aldehydes furnished the corresponding products effectively. However, under these reaction conditions, acid-sensitive aldehydes like furfuraldehyde did not give the product due to the decomposition or polymerization.

Williamson *et al.*[217] have developed an efficient method for the synthesis of protected homoallylic amines (*Scheme 65*) *via* the phosphomolybdic acid-catalyzed reaction

R = aryl, alkyl; $R^1 = H$; R^2 = aryl or alkyl,
R^1, R^2 = morpholine, piperidine, pyrrolidine

(69-91%)

Scheme 64



R = aryl, alkyl

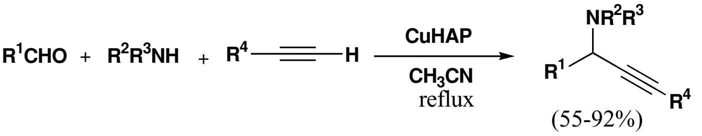
(78-95%)

Scheme 65

of aldehydes, carbamate and allyltrimethylsilane. Cbz-protected homoallylic amines were obtained in high yields in short reaction times (10–30 min). The conversion of aldehyde group to homoallylic amine in the presence of keto group shows the chemoselectivity of the reaction.

A macroporous polystyrene-bound sulfonic acid catalyzed enantioselective synthesis of homoallylic carbamates has been reported by Lipomi and Panek[218] from corresponding aldehydes, carbamates, and chiral (*E*)-crotyl silanes. The three-component reaction of an aldehyde, an amine, and allyltributyltin promoted by a recoverable and reusable polymer-supported sulfonamide of *N*-glycine to prepare homoallylic amines has been reported by Li and Zhao.[219]

The use of hydroxyapatite-supported copper catalyst (CuHAP) has been reported by Choudary *et al.*[220] for the preparation of propargylamines (*Scheme 66*) *via* the coupling



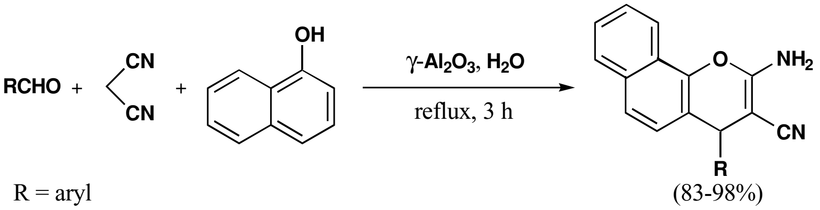
R^1 = aryl, cyclohexyl; R^2, R^3 = dialkyl, dibenzyl; R^4 = Ph, alkyl

Scheme 66

of aldehydes, amines, and alkynes without any co-catalyst or additive. The advantages are the readily recoverable, reusable catalyst, non-leaching of catalyst during the reaction and more rapid reactions than that of the reported[247] method using silver in ionic liquids. This reaction has also been reported[221] using layered double hydroxide-supported gold as a catalyst.

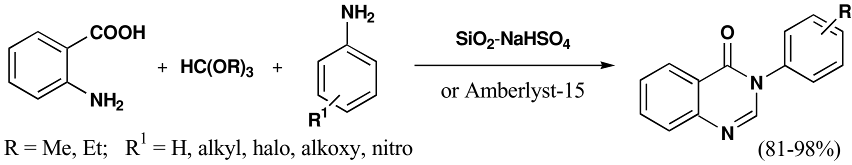
The use of a polymeric π-acid (poly-DCKA-1) as a recyclable catalyst for the inverse-electron-demand aza-Diels-Alder reaction of a benzaldehyde, an aniline, and 2,3-dihydro-4*H*-pyran at room temperature not only in aqueous systems but also under solvent-free conditions has been reported by Masaki and co-workers.[222]

Maggi *et al.*[223] have described the use of basic alumina as a heterogeneous and reusable catalyst for the three-component synthesis of substituted 2-amino-2-chromenes (*Scheme 67*). The reaction is highly regioselective. This process is industrially viable due to the use of water as a solvent and γ-alumina as an inexpensive and reusable catalyst. However, one drawback of this methodology is α-naphthol can only be used as an activated phenol. The preparation of these compounds has also been reported by Wang *et al.*[224] using KF-alumina as a catalyst. Using the same catalyst, they have reported[225,226] the one-pot preparation of pyranoquinoline derivatives and also pyrido[2,3-*d*]pyrimidine derivatives. Li *et al.*[227] have described a one-pot synthesis of tetrahydrobenzo[*b*] pyran derivatives *via* the condensation of aromatic aldehydes with cyanoacetic esters and dimedone catalyzed by KF-basic alumina at room temperature under ultrasound irradiation.



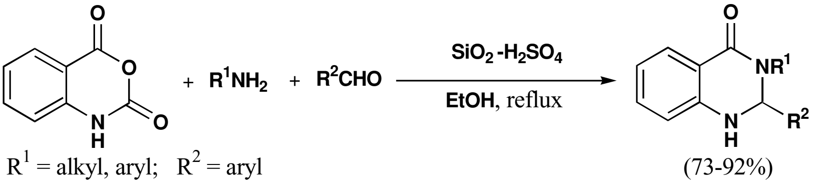
Scheme 67

The use of silica chloride or Amberlyst-15 as a heterogeneous catalyst has been reported by Das *et al.*[228] for the synthesis of pyrano- or furanoquinolines *via* the coupling of anilines, benzaldehydes and 3,4-dihydro-2*H*-pyrans or 2,3-dihydrofurans. The same reaction has also been reported[229] using two reusable solid acids (Fe^{3+}-K10 montmorillonite clay and HY-zeolite) for the one-pot synthesis of pyrano- and furanoquinolines. A solvent-free protocol for the one-pot synthesis of 4(3*H*)-quinazolinones (*Scheme 68*) has also been developed[230] *via* the coupling reaction of anthranilic acid, ortho esters, and amines using silica-supported sodium hydrogen sulfate or Amberlyst-15 as a heterogeneous catalyst. The products were obtained in shorter reaction times (5–15 mins). Most of the reactions proceeded at room temperature, but in the case of anilines containing a nitro group, the products were obtained by heating the reaction mixture at 60°C requiring more time (15 mins). Heating the reaction mixture for 10 mins is necessary for 2,5-dimethoxyaniline. The catalyst Amberlyst-15 can be recovered and reused.



Scheme 68

A novel method for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (*Scheme 69*) has been developed by Salehi and co-workers[231] *via* the condensation reaction of isatoic anhydride, a primary amine or ammonium carbonate and an aromatic aldehyde using silica sulfuric acid as a catalyst in refluxing ethanol. The catalyst is reusable



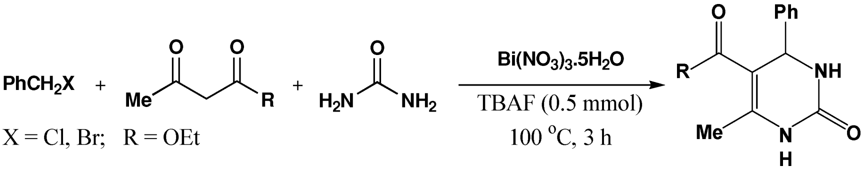
Scheme 69

several times, without any decrease in product yields. Aliphatic amines furnished the corresponding products in shorter reaction times, compared to aromatic analogues. Aliphatic aldehydes were not used for this reaction, as they undergo aldol condensation under these reaction conditions. The same group has also reported[232] an efficient method for the preparation of a series of mono- and disubstituted quinazolin-4(3*H*)-ones *via* silica sulfuric acid-catalyzed, one-pot reaction of isatoic anhydride and an ortho ester with ammonium acetate (or a primary amine) under solvent-free conditions.

VII. Three-Component Reactions in Ionic Liquids

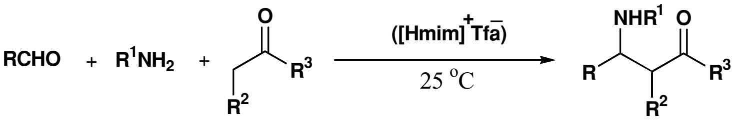
The contribution of room temperature ionic liquids[233] to green chemistry as novel environmentally benign media for organic synthesis is well known due to their unique properties such as non-volatility and recyclability, and these ionic liquids are emerging as alternatives to conventional organic solvents. A variety of three-component reactions[6] have also been performed in ionic liquids.

Gholap *et al.*[234] have developed an ionic liquid protocol under ultrasound irradiation for the efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones at ambient temperature. The use of the ionic liquid [bmim]Cl.2AlCl$_3$ for the one-pot Biginelli preparation of dihydropyrimidinones has been described by Bahekar *et al.*[235] A new process for the synthesis of dihydropyrimidinones has been developed by Khodaei *et al.*[236] *via* a one-pot condensation using benzyl halides in place of aldehydes in the presence of bismuth nitrate pentahydrate in molten tetrabutylammonium fluoride (*Scheme 70*). It is an *in situ*, one-pot oxidation-cyclocondensation and the advantage of this type of reaction is that several commercially available alkyl halides are used rather than aldehydes and the intermediate aldehydes do not require isolation. This reaction is particularly useful for aldehydes that are unstable (*e.g.*, volatile or prone to polymerization or hydration). 1,1,3,3-Tetramethylguanidinium trifluoroacetate as a room temperature ionic liquid promoted preparation of 3,4-dihydropyrimidin-2(1*H*)-ones has been reported[237] at 100°C.



Scheme 70

Zhao and co-workers[238] have synthesized several Brønsted acidic ionic liquids and studied their use as the catalyst and solvent for the Mannich reaction[239] of aldehydes, amines, and ketones at 25°C (*Scheme 71*). Out of these catalysts, 1-methylimidazolium trifluoroacetate was found to be the best, resulting in comparitively higher yields and it can be reused four times without appreciable loss of activity. One limitation is that these ionic liquids are not suitable for the Mannich reaction involving aliphatic amines due to the formation of several products; the main product was not even a Mannich base. When *N*-methylaniline or 2-nitroaniline was used as amine components, no reaction occurred. Some new room temperature ionic liquids were prepared by neutralization of 1,1,3,3-tetramethylguanidine with different acids under ambient conditions and their use as media for the Mannich reaction has also been proposed.[240] Kabalka *et al.*[241] have reported an ionic liquid-mediated coupling of potassium alkyltrifluoroborates with amines and salicylaldehydes in the presence of benzoic acid to generate highly functionalized amines.



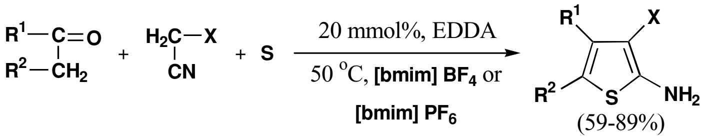
R = Ph, 3-ClPh; R^1 = Ph, 4-BrPh, SO_2NH_2Ph, $3,4(Me)_2Ph$ (36-98%)

R^2 = H; R^3 = Ph; R^2, R^3 = $-(CH_2)_4-$

Scheme 71

A facile synthesis of 4-pyrazolyl-1,4-dihydropyridines has been reported by Perumal and co-workers[242] *via* the cyclocondensation of ethyl 3-aminocrotonate, pyrazole aldehyde, and a *β*-keto ester in ionic liquid media using 3,4,5-triflurobenzeneboronic acid as a catalyst at room temperature. A one-pot synthesis of substituted pyridines has also been reported[243] by the reaction of 1,3-dicarbonyl compounds, ammonium acetate, and alkynones in the presence of the Brønsted acidic ionic liquid 1-methylimidazolium trifluoroacetate.

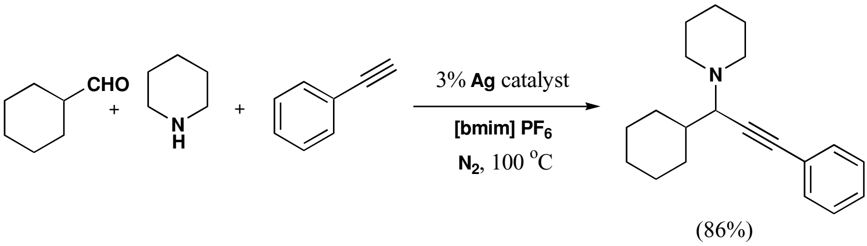
Hu *et al.*[244] have demonstrated an ethylenediammonium diacetate (EDDA)-catalyzed Gewald synthesis of 2-aminothiophenes (*Scheme 72*) using ionic liquids as recyclable reaction media. The advantages are comparatively significant rate enhancement and higher yields over some of the reported methods in addition to being an environmentally benign protocol avoiding the use of volatile organic solvent.



R^1 = Me, H; R^2 = Me, CO_2Et, $-(CH_2)_3-$, $-(CH_2)_4-$; X= CN, CO_2Et

Scheme 72

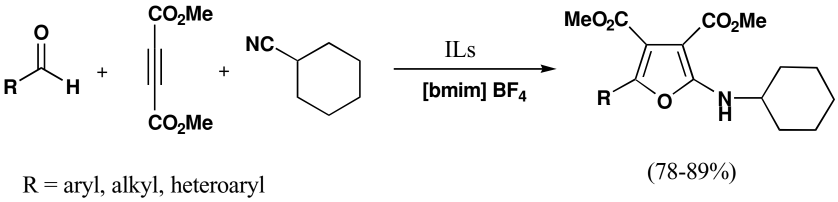
An efficient synthesis of propargylamines *via* the coupling reaction of aldehydes, amines, and alkynes has been reported[245,246] in ionic liquids using copper catalysts. Silver-catalyzed synthesis of propargylamines has also been described[247] by the coupling of aldehydes, amines, and alkynes in ionic liquid (IL) specifically butylmethylimidazolium hexafluorophosphate [bmim] PF_6 (*Scheme 73*). Among various silver salts used such as



Scheme 73

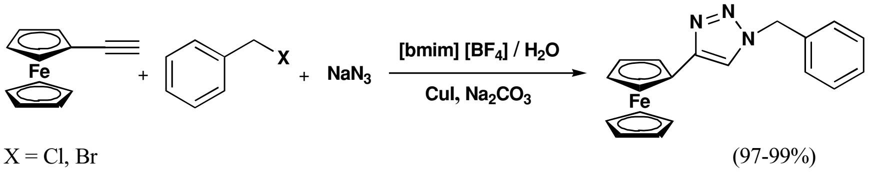
3% $AgNO_3$, AgOTf, AgBr, and AgI, it was observed that AgI was found to be the best and additionally, no further additives were required. The advantage of the reaction in ionic liquid, when compared to that in water, is the participation of other dialkyl- or alkylarylamines apart from piperidine analogues. Moreover, the reaction of aliphatic aldehydes was clean with high conversions.

Yadav *et al.*[248] have described a green approach for the synthesis of highly substituted 2-aminofuran derivatives (*Scheme 74*) by the ionic liquid-promoted coupling of aldehydes, dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide under extremely mild conditions. The advantages are short reaction times (0.5–2 h), recyclability, and reusability of the ionic liquid with consistent activity by avoiding the use of high temperatures and environmentally unfavorable solvents such as benzene. The same group has also reported[249] a diastereoselective one-pot preparation of *cis*-fused pyrano- and furanobenzopyrans by the coupling reaction of *o*-hydroxybenzaldehydes, aromatic amines, and cyclic enolethers using bismuth(III) triflate in ionic liquid $[bmim]PF_6$ as a recyclable catalytic system.



Scheme 74

A series of pyrano[2,3-*d*]pyrimidine derivatives has been synthesized by Li *et al.*[250] *via* a one-pot reaction of aromatic aldehydes, malononitrile, and pyrimidine-4,6-diol in ionic liquid medium $[bmim]BF_4$ at 80°C. Liang *et al.*[251] have reported the one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles in good to high yields from the reaction of halides, sodium azides, and alkynes using a copper(I) catalyst in a mixture of the ionic liquid $[bmim]BF_4$ and water. Triazoles, including a ferrocene substituent, have also been synthesized using ferrocenylacetylene as an alkyne component (*Scheme 75*). The ionic liquid can be recycled and reused without substantial loss in activity within five times. The positive role of water was presumed to be due to the good water solubility of sodium azide.

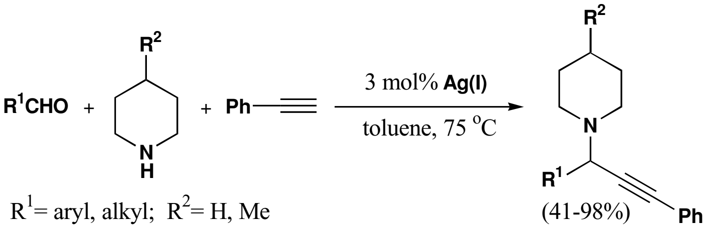


Scheme 75

VIII. Miscellaneous Three-Component Reactions

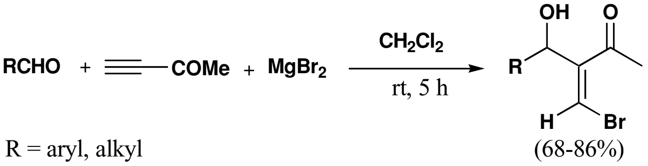
Several other three-component reactions such as the preparation of propargylamines *via* A^3 coupling,[252] *aza*-Baylis-Hillman reaction, *aza*-Diels-Alder reaction and many more which were not covered under any of the above specific headings have been reported.[6]

Gommermann and Knochel[253] have described a practical and highly enantioselective synthesis of terminal propargylamines *via* a one-pot, three-component reaction and application of this as a key intermediate to the synthesis of the alkaloid (*S*)-(+)-coniine. The same group has also reported[254] the highly enantioselective synthesis of these propargylamines using (mesitylmethyl)benzylamine as an efficient amine component for the copper-catalyzed three-component reaction. The preparation of propargylic amines in 90–99% *ee* has been demonstrated by Carreira *et al.*[255] *via* a copper-catalyzed reaction using biaryl P, N ligands. Black and Arndtsen[256] have developed a copper-catalyzed coupling reaction of imines, alkynes, and acid chlorides (or chloroformates) for the preparation of propargylamides and *N*-protected propargylamines. Ultrasound-promoted synthesis of propargylamines has been reported by Sreedhar *et al.*[257] *via* coupling of an aldehyde, an amine, and an alkyne using copper iodide as the catalyst in water at ambient temperature. Acetonitrile ligated silver complexes with the perfluorinated weakly coordinating anions and their activity towards the coupling reactions of terminal alkynes with aldehydes and amines (*Scheme 76*) has been studied by Zhang *et al.*[258] Three types of silver(I) complexes were used as catalysts. Both aromatic and aliphatic aldehydes participated in the coupling of phenylacetylenes with substituted or unsubstituted piperidines and pyrrolidines. Mostly, the coupling reaction was highly influenced by the nature of aldehydes involved. For example, the lowest product yield of 41% was observed with 2-pyridinealdehyde as the aldehyde component.



Scheme 76

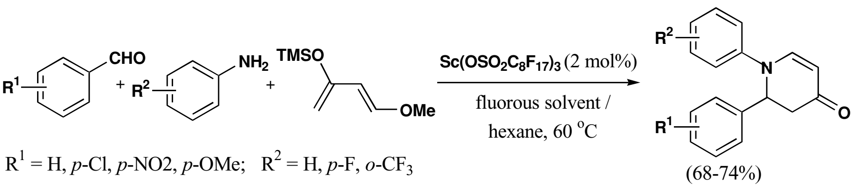
Stereoselective synthesis of (Z)-β-bromo Baylis-Hillman ketones *via* a one-pot, three-component reaction has been reported by Wei *et al.*[259] using magnesium bromide as a promoter (*Scheme 77*). In this reaction, the bromine anion source is magnesium bromide,



Scheme 77

which gives much higher yields of the desired products (*Z*-isomer) compared to the $TiBr_4$-based system which mainly produces the *E*-isomer of the Baylis-Hillman adducts. Yadav *et al.*[260] have developed a highly stereoselective method for the synthesis of (Z)-β-iodo Baylis-Hillman ketones *via* a coupling reaction of aldehydes, 3-butyn-2-one, and sodium iodide using $CeCl_3.7H_2O/NaI$ as a novel reagent system. A new procedure for the stereoselective synthesis of β-branched Baylis-Hillman adducts has been developed by Xue *et al.*[261] *via* a one-pot coupling reaction of β-acetylenic ketones with organozinc species and aldehydes. A titanium tetrachloride-promoted, one-pot coupling of α-oxo cyclic ketene *S,S*-acetals, aryl aldehydes, and nitriles has been described by Sun *et al.*[262] to afford aza-Morita-Baylis-Hillman adducts.

Shi and Cui[263] have reported the *aza*-Diels-Alder reaction of Danishefsky's diene with aryl aldehydes and aromatic amines in a fluorous phase using perfluorinated metal salts (*Scheme 78*). Out of different perfluorinated rare earth metal salts and fluorous solvents



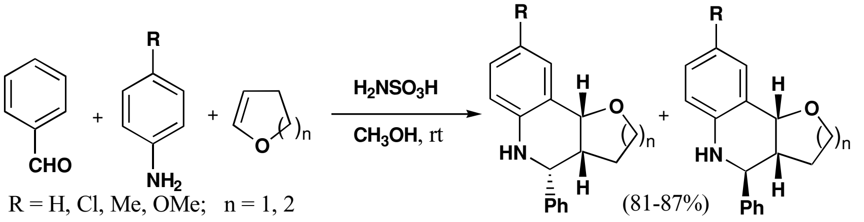
Scheme 78

studied for this reaction, the $Sc(OSO_2C_8F_{17})_3$ was found to be the best catalyst and perfluorodecalin ($C_{10}F_{18}$ *cis*- and *trans*- mixture) is the best fluorous solvent for this reaction. The advantage of the fluorous phase is that the catalytic phase can be reused four times without reloading the fluorous solvent and for the catalyst to give a similar outcome or results. A three-component, one-pot *aza*-Diels-Alder reaction of aldehydes, amines, and the dienes catalyzed by ytterbium(III) triflate under solvent-free conditions has been described by Feng *et al.*[264] to give the corresponding dihydro-4-pyridones. A novel, solvent-free synthesis of polysubstituted tetrahydropyridines using $BF_3.OEt_2$ as a catalyst has also been reported[265] through a one-pot reaction starting from aldehydes, anilines, and Brassard's diene. An enantioselective *aza*-Diels-Alder reaction catalyzed by proline and its derivatives has been developed by Córdova and co-workers.[266,68] For example, the reaction between aqueous formaldehyde, α,β-unsaturated cyclic ketones and aromatic amines furnished the desired azabicylic ketones with up to $> 99\%$ *ee*.

Barbas *et al.*[267] have developed an amino acid-catalyzed approach to the diastereospecific and enantiospecific construction of highly substituted spirotriones by an asymmetric, three-component Diels-Alder reaction of aldehydes, enones, and Meldrum's acid. An organocatalytic asymmetric, three-component Michael reaction has also been reported by the same group.[268]

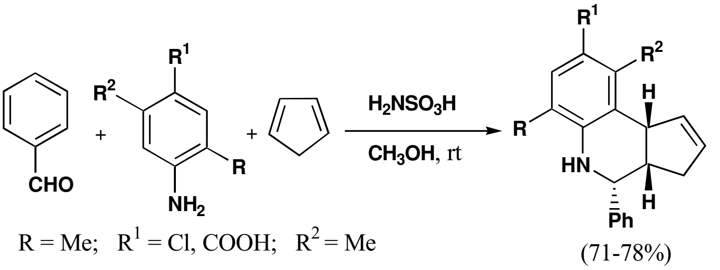
One-pot synthesis of pyrano-and furoquinolines has been reported by Das *et al.*[269] using Lewis acids (e.g. $ZrCl_4$, $SnCl_4$, $TiCl_4$,, and $PtCl_4$) to catalyze the coupling of anilines, aldehydes, and 3,4-dihydro-2*H*-pyran (or 2,3-dihydrofuran).

Perumal *et al.*[270] have reported an efficient one-pot synthesis of tetrahydroquinolines *via* the coupling reaction of benzaldehyde and anilines with electron-rich dienophiles such as 2,3-dihydrofuran, dihydropyran, and cyclopentadiene catalyzed by sulfamic acid in methanol at room temperatue. In the case of pyrano- and furoquinolines (*Scheme 79*), a mixture of isomers were obtained whereas for cyclo-pentaquinolines (*Scheme 80*), only one isomer resulted. Moreover, the catalyst used is mild and commercially available. The same group has also reported[271] a potassium hydrogen sulfate-catalyzed, diastereoselective one-pot synthesis of pyranobenzopyrans, furanobenzopyrans, and tetrahydroquinoline derivatives by the coupling of aldehydes, anilines, and electron-rich dienophiles (both cyclic and acyclic). A coupling reaction of phenylglyoxal monohydrate, aniline, and 2,3-dihydro-2*H*-furan using a chiral salen-AlCl complex to afford pyranoquinolines that act as potential antibacterial agents, has also been reported.[272]



R = H, Cl, Me, OMe; n = 1, 2

Scheme 79

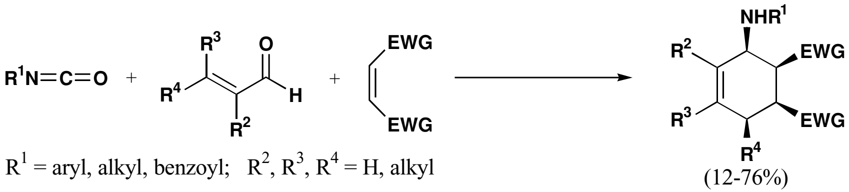


R = Me; R^1 = Cl, COOH; R^2 = Me

Scheme 80

Semwal and Nayak[273] have described the copper(II) bromide-catalyzed, one-pot imino Diels-Alder reaction of aromatic amines, aromatic aldehydes, and electron-rich olefins for the synthesis of pyrano[3,2-*c*]- and furo[3,2-*c*]- tetrahydroquinolines.

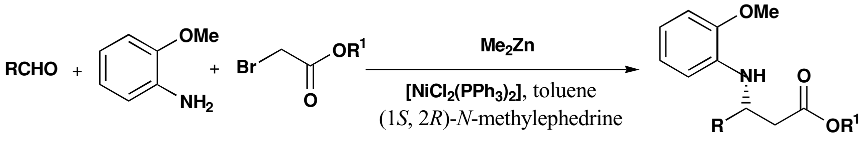
The preparation of *N*-phenylacetamidocyclohexene derivatives *via* the coupling of aldehydes, phenylacetamide, and dienophiles has been reported by Kragl *et al.*[274] The enzymatic kinetic resolution of these products has also been presented. Beller's group has described[275] an efficient one-pot preparation of substituted 1-acylaminocyclohex-2-enes utilizing ubiquitously available aldehydes, amides and dienophiles.[276] The same group has also developed *i)* an operationally simple one-pot method for the synthesis of functionalized bicyclo[2.2.2]oct-2-ene derivatives using a coupling reaction of α,β-unsaturated aldehydes, carboxylic acid anhydrides, and dienophiles,[277] *ii)* the coupling reactions based on aldehydes, dienophiles, and carboxylic acid anhydrides or alcohols for an efficient one-pot preparation of *O*-acyl-substituted and *O*-alkoxy-substituted cyclohexenes,[278] *iii)* a novel one-pot procedure for the preparation of 1-amino-2-cyclohexene derivatives (*Scheme 81*) *via* the coupling reaction of isocyanates, aldehydes, and dienophiles.[279] Out of the isocyanates tried, for example, alkyl substituted isocyanates such as *n*-butyl isocyanate, cyclohexyl isocyanate did not react to give the corresponding products whereas benzyl isocyanate furnished the corresponding product in low yield of 12%.



R^1 = aryl, alkyl, benzoyl; R^2, R^3, R^4 = H, alkyl
dienophile = *N*-methyl maleimide, maleicacid anhydride, acrylonitrile

Scheme 81

A highly enantioselective, nickel-catalyzed, Me_2Zn- mediated, one-pot, three-component imino-Reformatsky reaction has been presented by Cozzi and Rivalta[280] to afford β-amino esters using *N*-methylephedrine as a chiral ligand (*Scheme 82*). The advantages of this methodology are the use of inexpensive nickel salt, recovery and reuse of the inexpensive chiral auxiliary, *N*-methylephedrine with up to 64–92% *ee* of the products.

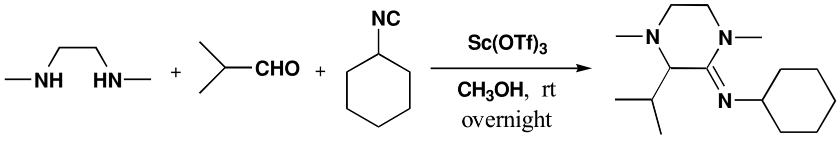


R = aryl, alkyl, heteroaryl, alkenyl; R^1 = Me, Et

(30-90%)

Scheme 82

Keung *et al.*[281] have reported a scandium(III) triflate mediated three-component Ugi condensation involving aldehydes, amines, and isonitriles to afford α-aminoamidines (*Scheme 83*). Preparation of β-lactams *via* a protocol of accelerating the Ugi reaction of β-keto acids in aqueous solution has been proposed by Pirrung and Sarma.[93,282]

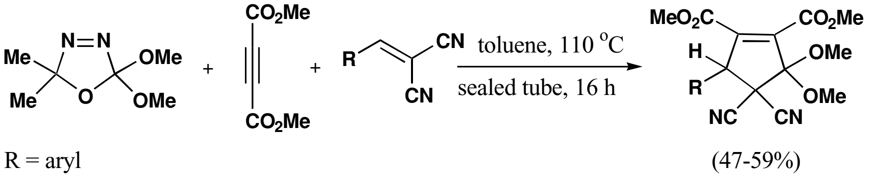


(70%)

Scheme 83

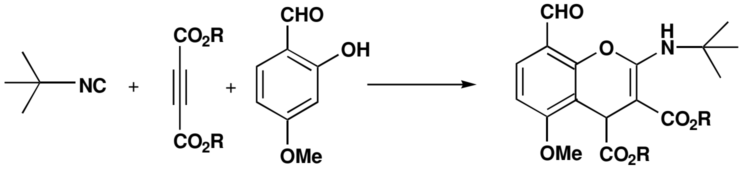
Dömling *et al.*[283] have described a new reaction of cyanamide, an enamine, and an isocyanide to produce arrays of substituted α-amino-N-cyanoamidines.

Nair and co-workers[284] have demonstrated the rhodium(II)-catalyzed stereoselective synthesis of highly substituted tetrahydrofurans *via* a three-component reaction of dicarbomethoxycarbene, aldehydes, and β-nitrostyrene. The same group has also reported[285] the stereoselective synthesis of spirodioxolanes *via* the reaction of acyclic carbonyl ylides generated from dicarbomethoxycarbene and aldehydes with 1,2-and 1,4-dienes. The Nair group has also described a facile synthesis of highly substituted cyclopentadienes[286] *via* the reaction of isocyanides, DMAD, and electrophilic styrenes and in addition, highly substituted cyclopentene derivatives[287] were reported *via* the reaction of dimethoxycarbene (generated *in situ* by the thermolysis of oxadiazolidine in refluxing toluene), DMAD and electrophilic styrenes (*Scheme 84*). In the second case, the zwitterionic species resulting from the addition of dimethoxycarbene to DMAD were trapped by a series of arylidenemalononitriles to yield the corresponding products; a similar type of reaction occurred when cyanocinnamates were used as substrates in the place of arylidenemalononitriles to furnish the corresponding cyclopentenone derivatives, albeit in low yields. The same group also reported *i)* a route to isoquinoline-fused heterocycles *via* a condensation reaction involving isoquinoline, DMAD, and carbonyl dipolarophiles such as *o*- and *p*-benzoquinones and *N*-substituted isatins,[288] *ii)* a three-component reaction involving isoquinoline, DMAD, and electrophilic styrenes for the facile synthesis of tetrahydrobenzoquinolizine derivatives, [289] *iii)* a convenient method for the synthesis of spirofused γ-iminolactams *via* a three-component reaction of the zwitterion generated from DMAD and isocyanides with various quinone imides,[290] *iv)* a one-pot preparation of highly substituted furan derivatives by the reaction of vicinal tricarbonyl compounds with the zwitterion derived from isocyanide and DMAD. [291]



Scheme 84

An efficient route to novel coumarins and 4*H*-chromenes has been described by Yavari and co-workers[292] through the reaction of *tert*-butyl isocyanide and dialkyl acetylenedicarboxylate in the presence of 2-hydroxybenzaldehydes (*Scheme 85*). The reactions conducted using 2-hydroxybenzaldehyde and 2-hydroxy-3-methoxybenzaldehyde afforded the 2-oxo-2*H*-chromenes but 2-hydroxy-4-methoxybenzaldehyde resulted in 4*H*-chromenes, whereas 2-hydroxy-5-methoxybenzaldehyde furnished a mixture of 2-oxo-2*H*-chromenes and 4*H*-chromenes in about 2:1 ratio. The same group has also reported[293] the one-pot reaction between alkyl isocyanides and isopropylidene Meldrum's acid in the presence of pyrroles or indoles to afford highly functionalized 4-(1*H*-pyrrol-2-carbonyl)-pyrrolidine-2,5-dione or 4-(1*H*-indole-3-carbonyl)-pyrrolidine-2,5-dione derivatives in good yields. A one-pot synthesis of functionalized 1,2,3,6-tetrahydropyrano[4,3-*b*] pyrroles by the reaction of



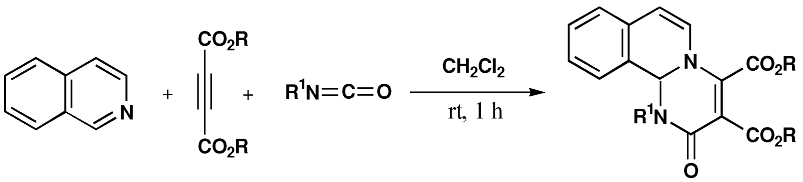
R = Me, ^{t}Bu

(85-97%)

Scheme 85

dialkyl acetylenedicarboxylates with 2,6-dimethylphenyl isocyanide in the presence of methyl 2,4-dioxopentanoate has also been reported.[294]

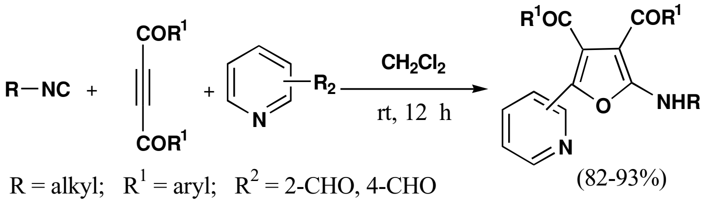
Adib and co-workers[295] have described a simple, one-pot synthesis of functionalized pyrimido[2,1-*a*] isoquinolines *via* the reaction of isoquinolines with dialkyl acetylendicarboxylates in the presence of isocyanates (*Scheme 86*) in CH_2Cl_2 at room temperature within 1h under neutral conditions. When the reaction was performed with quinoline, the corresponding pyrimido[1,2-*a*]quinoline derivatives were obtained in less than 20% yield, whereas the reaction of quinoline only with DMAD and 3-chloro-4-methylphenyl isocyanate gave the corresponding product in 65% yield within 5 h. The same group has also described[296] a facile synthesis of functionalized imidazo[2,1-*b*]-[1,3]oxazines through the one-pot reaction between alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates in the presence of 4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-ones. A one-pot reaction between isocyanides, dialkyl acetylenedicarboxylates in the presence of 2,4-dihydro-3*H*-pyrazol-3-ones at ambient temperature in acetone to afford highly functionalized pyrazolo[1,2-*a*]pyrazoles has been reported by the same group.[297] A facile one-pot, three-component preparation of highly functionalized pyridylfuran-2-amines has also been reported[298] (*Scheme 87*) in CH_2Cl_2 at ambient temperature. The advantages of this method



R = alkyl; R^1 = aryl, alkyl

(75-99%)

Scheme 86



R = alkyl; R^1 = aryl; R^2 = 2-CHO, 4-CHO

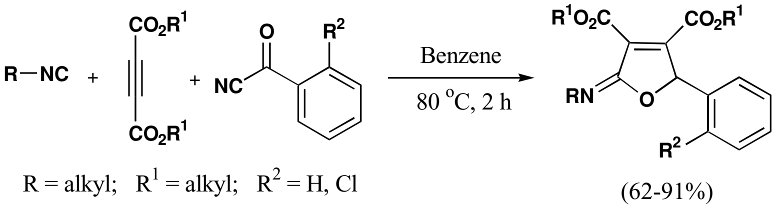
(82-93%)

Scheme 87

are that the reactions can be carried out under neutral conditions and it is an interesting alternative to the multi-step approaches, for the ready preparation of highly functionalized pyridyl furans by a simple method.

A convenient synthesis of highly functionalized 3-aminofuran derivatives has been developed by Ma and Yang[299] *via* the reaction of thiazolium salts, aldehydes and DMAD.

A one-pot synthesis of highly functionalized γ-iminolactones has been described by Esmaeili and Zendegani[300] *via* the reaction between an alkyl isocyanide and a dialkyl acetylenedicarboxylate in the presence of alkyl phenylglyoxylate. Maghsoodlou *et al.*[301] have also reported the one-pot preparation of γ-spiroiminolactones by condensation of alkyl and aryl isocyanides with 2,7-dinitrofloren-9-one and floren-9-one in the presence of dialkyl acetylenedicarboxylates. The synthesis of γ-spiroiminolactone derivatives has also been reported[302] by the reaction of acetylenic esters and α-one-pot dicarbonyl compounds in the presence of aryl isocyanides. Teimouri and co-workers[303] have reported the synthesis of highly functionalized iminolactones (*Scheme 88*) by the one-pot reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of benzoyl cyanides. The advantages are no added catalyst is required, neutral reaction conditions, and the simple mixing of substances without any activation or modifications. The same group has also disclosed[304] a one-pot reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of strong cyclic CH-acids such as 4-hydroxy-6-methyl-2*H*-pyran-2-one or 4-hydroxycoumarin to afford highly functionalized annulated 4*H*-pyrans at room temperature.

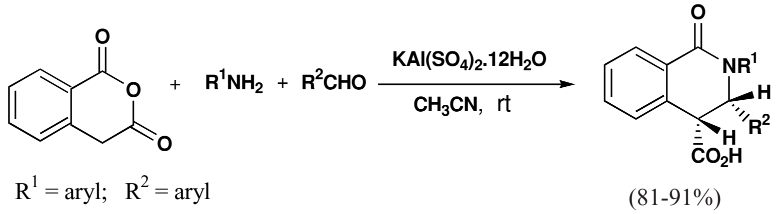


Scheme 88

The preparation of unsaturated amidine derivatives has been reported by Anary-Abbasinejad *et al.*[305] *via* the three-component reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates, and aromatic amides.

Azizian *et al.*[306] have reported a green methodology for the preparation of polysubstituted furans *via* the one-pot reaction of aromatic aldehydes, DMAD, and alkyl isocyanides in water at room tempera-ture. A facile, one-pot, three-component synthesis of alkyl indeno[1,2-*b*]quinoxalin-11-ylideneacetates[307,308] has also been reported by the same group under solvent-free conditions. An efficient and convenient synthesis of *cis*-isoquinolonic acids has also been reported[309] by the same group *via* a stereoselective, one-pot cyclocondensation reaction of homophthalic anhydride, aldehydes and amines using $KAl(SO_4)_2.12H_2O$ as a reusable catalyst (*Scheme 89*). Inexpensive, non-toxic, easy availability of the catalyst and mild reaction conditions are the additional advantages.

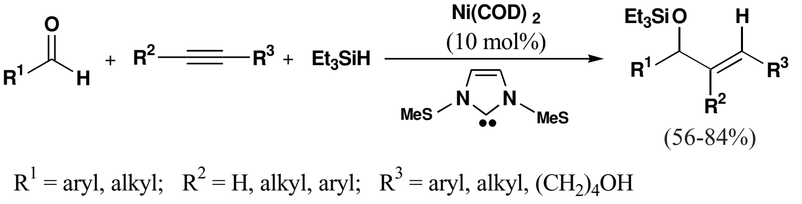
Wang and co-workers[310] have proposed an ytterbium(III) triflate-catalyzed protocol for the one-pot synthesis of *cis*-isoquinolonic acid derivatives. An efficient one-pot cyclocondensation of isatoic anhydride and primary amines or ammonia sources [*i.e.*, $(NH_4)_2CO_3$,



Scheme 89

NH_4OAc, and NH_4Cl] with aromatic aldehydes to afford the corresponding mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones has been reported by Dabiri *et al.*[311] using alum as a reusable catalyst in water and ethanol.

Kambe and co-workers[312] have proposed a nickel-catalyzed,[313] regioselective, three-component, cross-coupling reaction of alkyl halides, 1,3-butadienes, and aryl Grignard reagents (or arylzinc halides). An improved, selective and new procedure for the intermolecular reductive coupling of alkynes, aldehydes, and triethylsilane (*Scheme 90*)

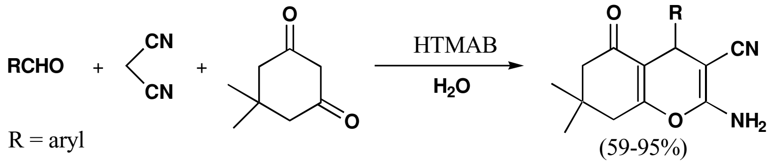


Scheme 90

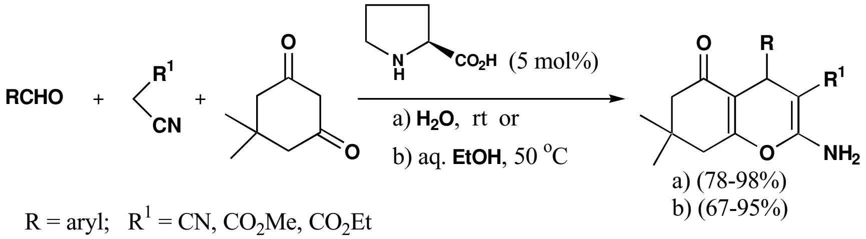
with the catalyst derived from $Ni(COD)_2$ and carbene has been reported by Montgomery *et al.*[314] The mechanistic studies reveal that the Ni(O) catalysts of PBu_3 and heterocyclic carbenes operate by different mechanisms and different scope of these two procedures. A nickel-catalyzed intermolecular coupling of allenes, aldehydes, and organozincs has also been developed[315] for the preparation of homoallylic alcohols.

The development of a nickel-catalyzed enantioselective and regioselective coupling reaction of chiral allenes, aromatic aldehydes, and silanes and its detailed account has been reported by Ng and Jamison.[316,317] The same group has also reported[318] a nickel-catalyzed coupling of aldehydes, silyl triflates, and alpha olefins to form allylic alcohol derivatives.

Jin *et al.*[319] have described a convenient approach to the one-pot synthesis of tetrahydrobenzo[*b*]pyran derivatives *via* the condensation of an aromatic aldehyde, malononitrile, and dimedone using hexadecyltrimethyl ammonium bromide (HTMAB) as the catalyst in aqueous media (*Scheme 91*). Out of the catalyst tested such as tetrabutylammonium bromide, benzyltrimethylammonium chloride, sodium dodecylsulfate, HTMAB was proved to be the best catalyst for this reaction. The same group has also reported[320] the preparation of pyrano[2,3-*c*]pyrazoles by the HTMAB catalyzed reaction of aromatic aldehydes, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one in water. A one-pot synthesis of tetrahydrobenzo[*b*]pyran derivatives has been demonstrated by Balalaie *et al.*[321] *via* a (*S*)-proline-catalyzed condensation of aromatic aldehydes, active methylene compounds, and dimedone in aqueous media (*Scheme 92*). The condensation reaction with malononitrile



Scheme 91

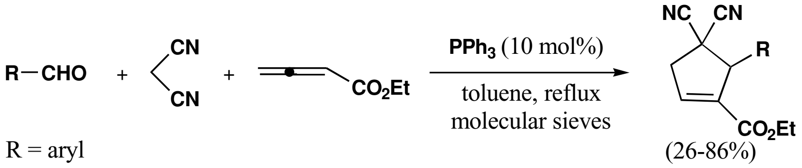


Scheme 92

has been carried out in water at room temperature and required a very short period of time (30 min). However, the reaction with cyanoacetates required higher temperatures in a water-ethanol mixture with longer reaction times due to the lower reactivity of cyanoacetates compared to malononitrile.

A rapid construction of benzopyrans *via* the condensation of phenol, aldehydes and active methylene substrates under $BF_3.OEt_2$ catalysis has been reported by Mashraqui *et al.*[322] The use of rubidium fluoride as a catalyst for the one-pot preparation of polyfunctional 4*H*-pyrans has been reported by Rao *et al.*[323] *via* a three-component coupling.

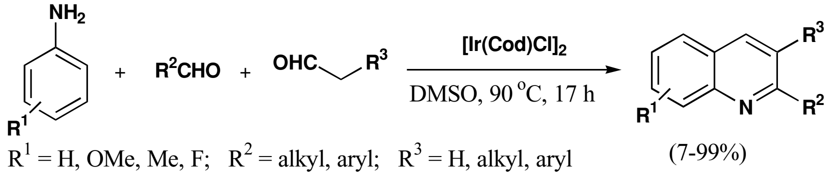
Lu *et al.*[324] have developed a triphenylphosphine-catalyzed, one-pot, three-component protocol for the synthesis of cyclopentenes from aryl aldehydes, malononitrile, and ethyl 2,3-butadienoate (*Scheme 93*). Aliphatic aldehydes failed to give the corresponding products.



Scheme 93

An efficient and regiospecific one-pot protocol has been developed by Stocks *et al.*[325] for the three-component synthesis of substituted 1,2,4-triazoles.

Shimizu and co-workers[326] have presented a convenient, one-pot synthesis of substituted quinolines *via* an iridium-catalyzed coupling of an arylamine, an aromatic or aliphatic aldehyde, and an aliphatic aldehyde (*Scheme 94*). Among the other Lewis acids tried for this reaction, $AlCl_3$,$TiCl_4$, $HfCl_4$, and $Yb(OTf)_3$ also exhibited considerable activities for the synthesis of substituted quinolines. Lewis acid-catalyzed coupling reaction of

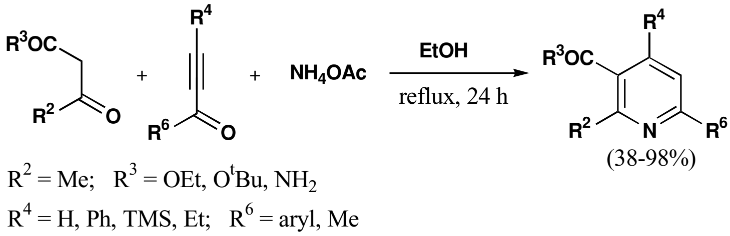


R^1 = H, OMe, Me, F; R^2 = alkyl, aryl; R^3 = H, alkyl, aryl (7-99%)

Scheme 94

aromatic amines, aliphatic aldehydes and ethyl glyoxylate for the one-pot synthesis of ethyl quinaldates has also been reported[327] by the same group.

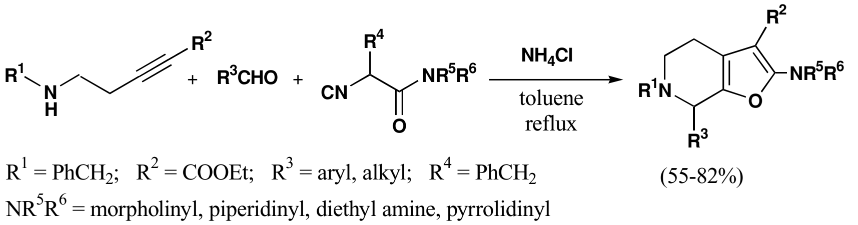
A mild one-pot method for the preparation of polysubstituted pyridines has been developed by Bagley *et al.*[328] *via* a three-component reaction of a 1,3-dicarbonyl compound, an alkynone, and ammonium acetate in alcoholic solvents without the use of an additional acid catalyst (*Scheme 95*). The advantage of this methodology under mild reaction conditions has been applied for the preparation of acid-sensitive pyridine intermediate involved in the total synthesis of dimethyl sulfomycinamate and can be extended to synthesize the components of other thiopeptide antibiotics.



R^2 = Me; R^3 = OEt, O^{t}Bu, NH$_2$
R^4 = H, Ph, TMS, Et; R^6 = aryl, Me
(38-98%)

Scheme 95

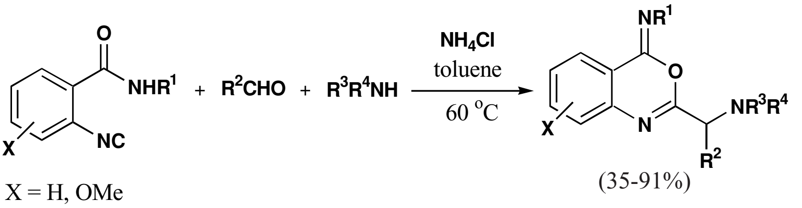
Zhu and co-workers[329] have described the synthesis of polysubstituted 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines *via* a novel three-component reaction (*Scheme 96*) by simply heating a toluene solution of an aminopentynoate, an aldehyde, and an α-isocyano acetamide in the presence of ammonium chloride. The important feature of this methodology is the concomitant formation of a fused ring system from readily accessible starting materials. However, one drawback of this three-component reaction is the lack of atom economy, since phenylacetonitrile was the side-product when phenylalanine-derived isocyanoacetamides were employed. Ultimately, a solution for this problem has also been suggested. A convenient synthesis of 2-imino-4-thiazolidinones has been reported[330] by the same group *via*



R^1 = PhCH$_2$; R^2 = COOEt; R^3 = aryl, alkyl; R^4 = PhCH$_2$
NR^{5}R^6 = morpholinyl, piperidinyl, diethyl amine, pyrrolidinyl
(55-82%)

Scheme 96

one-pot three-component synthesis from aldehydes, chloroform, and thiourea. The Zhu group has also reported *i)* a novel and convenient route for the preparation of polysubstituted 6-azaindolines and its tricyclic derivatives.[331] *ii)* a one-pot process for the synthesis of epoxy-tetrahydronaphthyridine *via* the three-component reaction of an α-isocyanoacetamide, a homoallyl amine, and an aldehyde in methanol at room temperature.[332] *iii)* a Reissert-type three-component synthesis of 1,3-oxazol-2-yl-1,2-dihydroisoquinoline.[333] *iv)* the synthesis of 4-imino-4*H*-3,1-benzoxazines *via* heating a toluene solution of an aldehyde, an amine, and an isonitrile in the presence of a stoichiometric amount of ammonium chloride at 60°C for 12 h (*Scheme 97*). [334] Except for aromatic aldehydes, aliphatic aldehydes including formaldehyde have participated well in the reaction. No reaction occurred when aniline is used as the amine component. In the case of 2-isocyanobenzamides, amides derived from a variety of primary amines including butylamine, benzylamine, phenethylamine, methylphenylalanate, and tryptophan methyl ester were well participated in the reaction.



X = H, OMe

R^1 = *n*-Bu, $PhCH_2$, PhEt, methylphenyl alanate, tryptophanmethyl ester

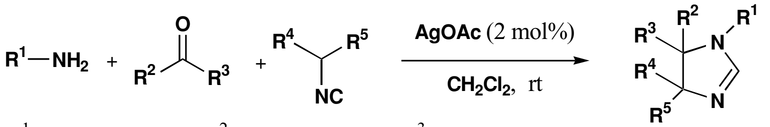
R^2 = alkyl

NR^3R^4 = morpholinyl, alkyl, primary and secondary amine hydrochloride salts

Scheme 97

Glyoxylic acid as a formaldehyde equivalent in the three-component coupling of aminoazines, aldehydes, and isonitriles has been reported by Lyon and Kercher[335] for the one-pot preparation of 2-unsubstituted-3-aminoimidazo heterocycles.

The preparation of highly substituted 2-imidazolines has been reported by Orru *et al.*[336] *via* the reaction between amines, aldehydes, and isocyanides bearing an acidic α-proton using silver(I) acetate as a catalyst (*Scheme 98*). The reactions of ketones as oxo compounds instead of aldehydes which are usually difficult can also be promoted by silver(I) acetate.

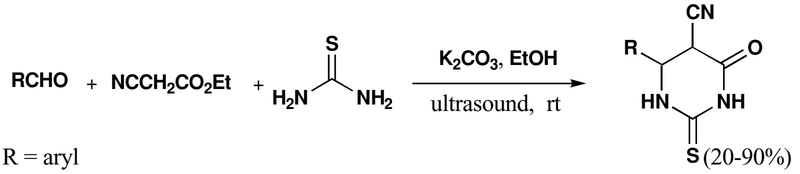


R^1 = H, alkyl, aryl; R^2 = H, alkyl, aryl; R^3 = H

R^4, R^5 = allyl, *p*-nitrobenzyl, isocyanoacetate,
9-isocyanofluorene, methyl isocyanoacetate

Scheme 98

Li *et al.*[337] have described a convenient procedure for the one-pot synthesis of 4-oxo-2-thioxohexahydropyrimidines *via* condensation reaction of aromatic aldehydes, ethyl cyanoacetate and thiourea catalyzed by potassium carbonate in ethanol under ultrasound irradiation (*Scheme 99*). Lower frequency of ultrasound 25 kHz improved the yield. It may



Scheme 99

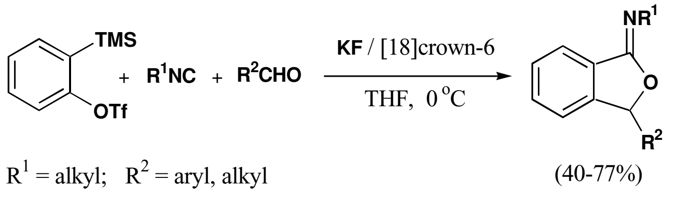
be due to better cavitation created by the lower frequency conditions. Aldehydes possessing electron-donating substituents such as *p*-dimethylamino benzaldehyde gave higher yields of 90%, and aldehydes carrying electron-withdrawing substituents like *p*-nitrobenzaldehyde afforded the products in lower yields of 20%.

A facile one-pot condensation reaction from aldehydes, amines and 3-dimethylamino-2-isocyano acrylic acid methyl ester has been described by Illgen and co-workers[338] for the versatile synthesis of 6-oxo-1,4,5,6-tetrahydro-pyrazine-2-carboxylic acid methyl esters. The same group has also presented[339] a novel one-pot method for the preparation of substituted 2-[(cyanomethyl)-amino]-acetamides *via* the reaction between primary (*S*)-amino acid amides, aldehydes, and isocyanides in the presence of acetic acid. The condensation reaction from aldehydes, *o*-picolylamines, and isocyanides for the one-pot preparation of 1*H*-imidazol-4-yl-pyridines has also been reported.[340] A later paper revised the outcome and mechanism of this reaction.[341]

He and Zhu[342] have developed a facile method for the synthesis of *N*-protected trisubstituted fluorinated oxazolidines *via* the one-pot reaction of ketones, vinyl ethers, and fluoroalkanesulfonyl azides at 0°C within 5 min. The same group has also demonstrated[343] a convenient method for the diastereoselective synthesis of highly fluorinated oxazolidines by the one-pot reaction of fluoroalkane sulfonyl azides, vinyl ethers, and aldehydes at 0°C within 10 min.

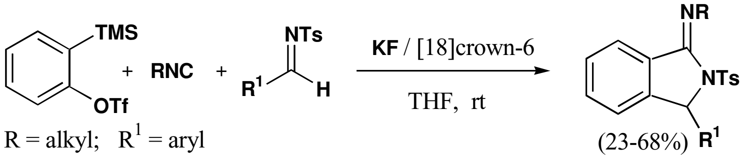
A Yonemitsu-type condensation of indole[344] (or indolin-2-ones) with different types of aldehydes and Meldrum's acid to form the corresponding adducts and their further transformation or application has been well studied by Laronze *et al.*[345–349] The condensation reaction using a sugar hydroxyaldehyde has also been reported. [350]

Straightforward preparation of benzoannulated iminofurans (*Scheme 100*) has been carried out by Yoshida *et al.*[351] *via* the coupling of an aryne (*e.g.*, benzyne, generated



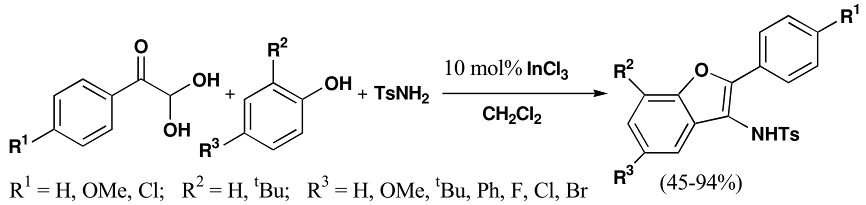
Scheme 100

in situ from 2-(trimethylsilyl)phenyl triflate in the presence of KF and crown ether), an isocyanide, and an aldehyde in THF at 0°C. By using this coupling, diverse benzoannulated iminofurans can be prepared readily, which are difficult to obtain by conventional methods. The same group has also disclosed[352] a straightforward route to diverse 2-iminoisoindolines (*Scheme 101*) by the coupling of arynes, isocyanides, and *N*-tosylaldimines in the presence of tetrahydrofuran (THF) at room temperature. As in the earlier method, benzynes were prepared *in situ* from 2-(trimethylsilyl)phenyl triflate in the presence of KF and crown ether. The reaction has been studied using unsymmetrical arynes and the intermediacy of arynes in the coupling has been verified.



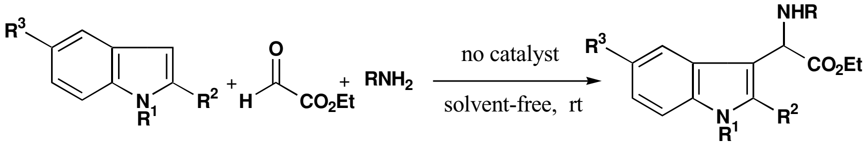
Scheme 101

Chen and co-workers[353] have developed a synthetic approach to 2-aryl-3-aminobenzofuran derivatives *via* indium trichloride-catalyzed reaction of arylglyoxal monohydrates, phenols and *p*-toluenesulfonamide (*Scheme 102*). Some of the advantages are: (i) this method is useful in constructing compound libraries in combinatorial chemistry as structurally diverse benzofuran derivatives were synthesized by using a variety of arylglyoxal monohydrates and phenols containing various functional groups; (ii) by using indium(III) chloride as economical and easily available catalyst, the formation of α-diketones as by-products was inhibited unlike in the other Lewis acid catalyzed present three-component reaction. This group has also developed[354] a solvent-free protocol for the synthesis of (3-indolyl) glycine derivatives by the Friedel-Crafts reaction of indoles, glyoxylate, and amines (*Scheme 103*). It is observed that when aniline was used as an amine component, the reaction was completed in 1 min to give the products. The highest reactivity was shown by 2-methylindole to give the corresponding product in excellent yield of 93%. Low yield of 49% accompanied by 20% formation of another derivative and a longer reaction time (4 h) has been observed with isopropylamine.



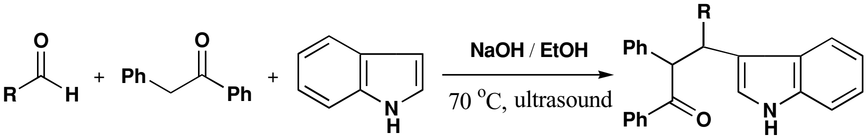
Scheme 102

Ji *et al.*[355] have described a base-promoted, one-pot protocol for the synthesis of β-indolylketones (*Scheme 104*) *via* the condensation of aromatic aldehydes, deoxybenzoin, and indoles under ultrasound irradiation. The influence of different alkalies on the reaction has been studied and it was found that lithium hydroxide, sodium hydroxide, potassium



R = aryl, alkyl; R^1 = H, Me
R^2 = H, Me, Ph, $(CH_3)_2CH$
R^3 = H, OMe, Br, CN

Scheme 103



R = aryl

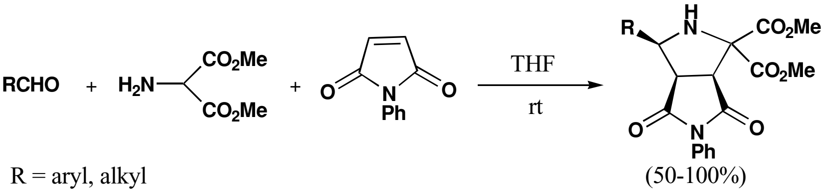
Scheme 104

hydroxide, and sodium ethoxide could promote the reaction effectively to give the desired product. Out of these bases, sodium hydroxide has been used, as it was the cheapest and this route is convenient to synthesize β-indolylketones in one-pot and avoided complexity of two-step synthetic methods. Simoneau and Ganem[356] have developed a new three-component variation of Fischer synthesis of substituted indoles as a one-pot process.

A simple route to halogen-substituted isoxazolidines of mixed composition has been reported by Kuznetsova and co-workers[357] *via* a one-pot reaction of bromotrinitromethane with bicyclobutylidene and methylenecyclobutanes. A one-pot process for the synthesis of *gem*-dinitroaziridines has also been studied[358] by the same group involving reaction of tetranitro- and bromotrinitromethanes with alkoxy acetylenes, mediated by diazomethane (or bicyclobutylidene) *via* sequential electrophile transfer followed by [3+2]-cycloaddition.

An effective three-component, one-pot protocol utilizing a homo [3+2] dipolar cycloaddition for the synthesis of tetrahydro-1,2-oxazines has been developed by Young and Kerr.[359] A diverse array of cycloadducts resulted *via* the reaction of nitrones formed *in situ* by the reaction of hydroxylamines with aldehydes, with 1,1-cyclopropanediesters, in (66–96%) yields, and excellent diastereoselectivity ($>$ 95%).

Nyerges *et al.*[360] have developed a simple, one-pot, three-component method for the preparation of hexahydropyrrolo[2,1-*a*]isoquinolines by an alkylation-dehydrohalogenation-1,3-dipolar cycloaddition sequence. Garner and Kaniskan[361] have reported the one-pot preparation of highly functionalized pyrrolidines *via* a three-component 1,3-dipolar cycloaddition process using dimethyl 2-aminomalonate as the amine component along with aldehydes and dipolarophiles (*Scheme 105*). The dipolarophiles used were *N*-phenylmaleimide, maleic anhydride, and methyl acrylate. Exclusively *endo* selectivity was observed with *N*-phenylmaleimide and maleic anhydride. Good chemo-, regio-, and stereoselectivities were observed with methyl acrylate, though Ag(I) catalysis was necessary with this dipolarophile.



R = aryl, alkyl

(50-100%)

Scheme 105

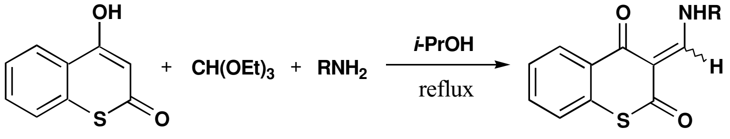
Preparation of 3-spiro[pyrrolidinooxindoles] has been reported by Rehn *et al.*[362] *via* the three-component reaction between isatin, α-amino acids, and dipolarophiles using both N-substituted and N-unsubstituted α -amino acids as the amine component.

The synthesis of 3,3-dialkyl-3,4-dihydroisoquinoline derivatives has been described by Dembitsky *et al.*[363] *via* condensation of activated arenes, isobutyraldehyde, and nitriles.

Che and co-workers[364] have proposed a ruthenium porphyrin-catalyzed, three-component coupling reaction involving chiral diazoesters, N-benzylideneimines, and dipolarophiles for the asymmetric synthesis of multifunctionalized pyrrolines with remarkable diastereoselectivity (up to 92% *de*).

A regioselective, one-pot synthesis of polysubstituted benzene derivatives has been reported by Nakamura *et al.*[365] *via* the reaction of a substituted cyclopropenone acetal and two alkyne molecules.

Park and Lee[366] have reported the synthesis of 3-aminomethylenethiochroman-2,4-diones *via* the condensation reaction of 4-hydroxythiocoumarin and triethyl orthoformate with the substrates containing amino groups such as primary aliphatic and aromatic amines, α-amino acids, ureas, and carbamates, carried out by refluxing in 2-propanol (*Scheme 106*). The condensation with secondary amines gave very low yields or none at all. No condensation reaction was observed with triethyl orthoacetate in contrast to orthoformate even with primary amines.



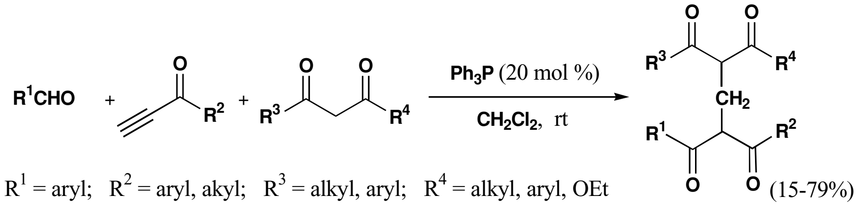
R = aryl, alkyl

(30-99%)

Scheme 106

A base-catalyzed stereoselective preparation of trisubstituted alkenes and 1,3-dienes has been reported by Rodriguez and co-workers[367] *via* a three-component domino transformation between α,β-unsaturated carbonyl compounds, aldehydes, and alcohols.

A facile method for the preparation of acyclic multicarbonyl compounds (*Scheme 107*) has been described by Xue *et al.*[368] *via* triphenylphosphine-catalyzed reaction of aldehydes, acetylenic ketones, and 1,3-dicarbonyl moieties. When an aromatic β-ketoester was used as the 1,3-dicarbonyl moiety, the corresponding product was obtained in 70% yield; however, the product yield was only 26% accompanied by an unidentified complicated mixture in the case of ethylacetoacetate as the 1,3-dicarbonyl moiety.



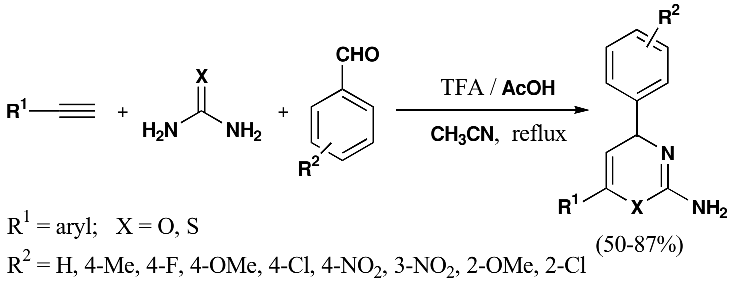
R^1 = aryl; R^2 = aryl, akyl; R^3 = alkyl, aryl; R^4 = alkyl, aryl, OEt

Scheme 107

Boruah *et al.*[369] have reported a facile, base-catalyzed, one-pot synthesis of 1,7-dicarbonyl compounds using a three-component Michael addition reaction of nitromethane with two unsymmetric α,β-unsaturated carbonyl compounds.

A one-pot method for the synthesis of 2-acylimino-3-alkyl-3*H*-thiazoline derivatives has been developed by Manaka *et al.*[370] *via* the condensation of aroylthiourea, primary amine, and α-halo-carbonyl derivatives.

Pan and co-workers[371] have described the one-pot condensation reaction involving alkynes, urea (or thiourea), and aldehydes for the preparation of a series of 2-amino-(4*H*)-1,3-oxazines or 2-amino- (4*H*)-1,3-thiazines (*Scheme 108*). A 1:3 volume ratio of TFA-AcOH in refluxing acetonitrile for 10 h were found to be the best conditions to carry out the reaction.

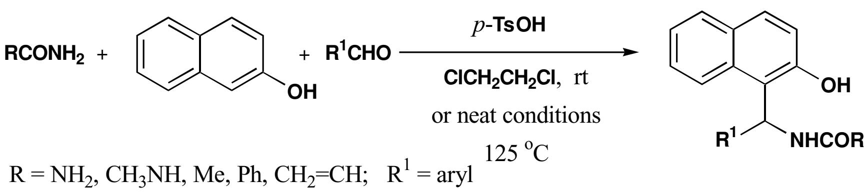


R^1 = aryl; X = O, S

R^2 = H, 4-Me, 4-F, 4-OMe, 4-Cl, 4-NO_2, 3-NO_2, 2-OMe, 2-Cl

Scheme 108

A simple one-pot procedure for the synthesis of amidoalkylnaphthols has been described by Khodaei *et al.*[372] *via* the condensation reaction of aromatic aldehydes, β-naphthol, and ureas (or amides) (*Scheme 109*) catalyzed by *p*-TSA in solution or under



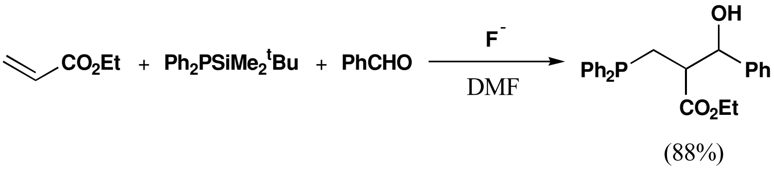
R = NH_2, CH_3NH, Me, Ph, CH_2=CH; R^1 = aryl

Scheme 109

solvent-free conditions. Aliphatic aldehydes, such as isovaleraldehyde and propionaldehyde, did not give satisfactory yields even after 24 h under either conditions. Heteroaromatic aldehydes like furfural and thiophene-2-carbaldehyde did not give any product under solvent-free conditions and no satisfactory results were obtained in solution even after 24 h.

Mironov and co-workers[373] have reported a new approach to the synthesis of substituted propionamides or succinamides by reaction of isocyanides, *gem*-diactivated olefins, and 4-nitrophenol.

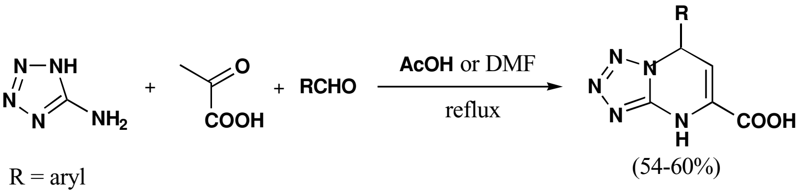
A fluoride-promoted route for the preparation of multi-functional phosphines has been developed by Hayashi *et al.*[374] *via* CsF-catalyzed coupling of a silylphosphine with an activated alkene and an aldehyde (*Scheme 110*). Alkenes having a weak activating group such as styrene did not form any adduct. Both aromatic and aliphatic aldehydes reacted smoothly to afford the corresponding adducts as silyl ethers together with a small amount of the parent alcohols. The parent alcohols were isolated in fairly good yields, after hydrolysis of the silyl ethers with hydrochloric acid. The three-component adduct was not formed even under more drastic conditions, when a ketone is used in place of aldehydes.



Scheme 110

The condensation reaction between 2-formylbenzoic acid, anilines, and hydrogen cyanide to furnish 3-amino-4-(arylamino)-1*H*-isochromen-1-ones has been reported by Opatz and Ferenc.[375] The reactions were conducted using a series of substituted anilines to furnish the corresponding products in 56–88% yields.

Chebanov *et al.*[376] have described a procedure for the synthesis of 5-aryl-5,8-dihydroazolo[1,5-*a*]pyrimidine-7-carboxylic acids by the condensation of pyruvic acid with aromatic aldehydes and some aminoazoles. For example, the three-component reaction of 5-aminotetrazole with pyruvic acid and aldehydes in the presence of DMF or glacial acetic acid at reflux to afford the corresponding products in 54–60% yields (*Scheme 111*).

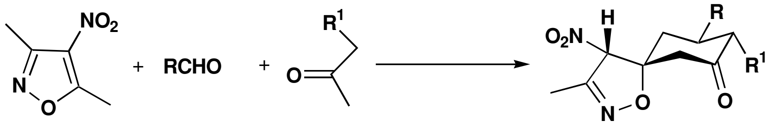


Scheme 111

A three-component coupling protocol, exploiting 2-bromoallyltrimethylsilane as a bifunctional linchpin, has been developed by Smith and Duffey.[377]

Suga *et al.*[378] have developed a new sequential one-pot three-component reaction based on the "cation pool" method.

Synthesis of spiroisoxazolines has been reported by Adamo *et al.*[379] *via* a three-component, one-pot procedure from commercially available materials involving a 3,5-dimethyl-4-nitroisoxazole, an aromatic aldehyde, and a ketone (*Scheme 112*). This methodology does not require column chromatography for purification affording the products in high yields.

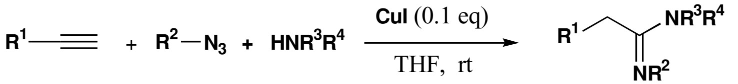


R = aryl; R^1 = COMe, COOEt, H (59-86%)

Scheme 112

Heydari and co-workers[380] have described a general one-pot, three-component, mono *N*-alkylation of amines and amine derivatives in lithium perchlorate/diethyl ether solution.

A highly efficient copper-catalyzed one-pot synthesis of *N*-sulfonylamidines has been described by Chang *et al.*[381] *via* the coupling of a sulfonyl azide, an alkyne and an amine (*Scheme 113*). Copper(I) iodide was selected as a catalyst for the present methodology. One important feature is when an optically active amino ester was used as the amine component, the reaction proceeded without racemization which has broadened its application to chiral compounds.

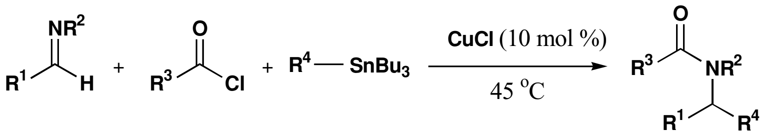


R^1 = aryl, alkyl; R^2 = 4-$MeC_6H_4SO_2$, 2-$C_5H_4NSO_2$, $MeSO_2$ (59-99%)

R^3, R^4 = H, aryl, alkyl, cyclic and acyclic aminoesters

Scheme 113

Black and Arndtsen[382] have developed a copper-catalyzed protocol for the synthesis of α-substituted amides (*Scheme 114*) *via* a cross-coupling reaction of organotin reagents with imines and acid chlorides. *N*-Protected α-substituted amines can also be formed by replacing the acid chloride with a chloroformate and the most important feature of this copper-catalyzed coupling is the use of diverse organotin reagents.

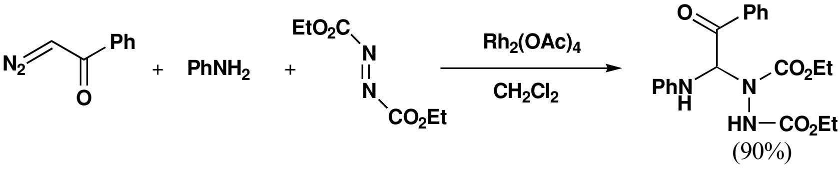


R^1 = aryl, alkyl, heteroaryl; R^2 = aryl, alkyl, $CH_3CH_2CO_2Me$, allyl (68-93%)

R^3 = alkyl, aryl, heteroaryl; R^4 = vinyl, alkyl, aryl, heteroaryl

Scheme 114

Hu and co-workers[383] have reported a rhodium(II)-catalyzed, three-component reaction of aryl diazoacetates, alcohols, and aldehydes (or imines). The same group has also developed[384] a rhodium(II)-catalyzed reaction of diazoacetic esters, titanium(IV) alkoxides, and aldehydes to give α-alkoxy β-hydroxyl acid derivatives. A novel three-component C-N bond forming reaction of diazo compounds with amines and azodicarboxylic esters in the presence of dirhodium acetate as a catalyst to afford corresponding aminals with high selectivity has also been reported[385] by the same group. For example, the reaction of 2-diazo-1-phenylethanone, aniline, and diethyl azodicarboxylate in the presence of 1% dirhodium acetate as a catalyst, afforded the corresponding C-N bond formation products (*Scheme 115*) in 90% yield after column chromatographic purification.



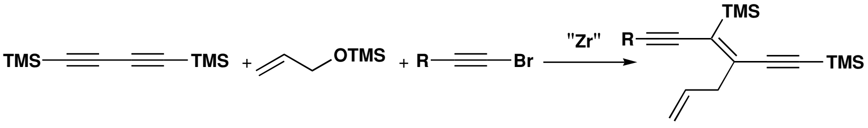
Scheme 115

Regioselective and sequence-selective one-pot, three-component joining reaction of alkyl iodides, α,β-unsaturated esters (or nitriles), and acylating agents in the presence of zinc metal at room temparature has been reported by Yamamoto *et al.*[386]

A platinum-catalyzed approach for the cross-coupling of 3-iodopyridines, terminal alkynes and ArSK has been described by Hirai *et al.*[387] to synthesize functionalized pyridine derivatives.

Xi *et al.*[388] have reported a Lewis acid-promoted one-pot, three-component synthesis of multiply-substituted iminocyclopentadienes.

Liu and Gao[389] have developed a new zirconium-mediated approach for the regio- and stereo-controlled synthesis of *trans*-enediynes *via* the one-pot coupling reactions of 1,4-*bis*(trimethylsilyl)-1,3-butadiyne, allylic ether and alkynyl bromide (*Scheme 116*). This methodology is useful for the ready synthesis of *trans*-enediynes with different substituents in the central double bond which are difficult to prepare by other procedures.



R = aryl, *n*-Bu, cyclohexenyl, CO_2Et or ester substituted (60-76%)

Scheme 116

Conclusion

This review has covered the three-component methodologies reported during the period January 2004–March 2006. The recent progress in these important and convenient procedures provides a platform for future innovation because of the versatility, molecular economy, and exciting potential for the synthesis of complex organic compounds. The author regrets any omissions that may have occurred in this review.

Acknowledgment

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References

1. H. Bienaymé, C. H. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.*, **6**, 3321 (2000).
2. L. Weber, K. Illgen and M. Almstetter, *Synlett*, 366 **(1999)**.
3. R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, **29**, 123 (1996).
4. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, **39**, 3168 (2000).
5. D.J. Ramón and M. Yus, *Angew. Chem. Int. Ed.*, **44**, 1602 (2005).
6. M. Syamala, *Org. Prep. Proced. Int.*, **37**, 103 (2005).
7. P. Biginelli, *Gazz. Chim. Ital.*, **23**, 360 (1893).
8. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang and Q. Zhuang, *Synlett*, 537 **(2004)**.
9. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang and Q. Zhuang, *J. Heterocyclic Chem.*, **41**, 253 (2004).
10. H. Salehi and Q.-X. Guo, *Synth. Commun.*, **34**, 171 (2004).
11. J. S. Yadav, B. V. S. Reddy, J. J. Naidu and K. Sadashiv, *Chem. Lett.*, 926 **(2004)**.
12. J. S. Yadav, S. P. Kumar, G. Kondaji, R. S. Rao and K. Nagaiah, *Chem. Lett.*, 1168 **(2004)**.
13. J. Mabry and B. Ganem, *Tetrahedron Lett.*, **47**, 55 (2006).
14. Q. Sun, Y.-Q. Wang, Z.-M. Ge, T. -M. Cheng and R.-T. Li, *Synthesis*, 1047 (**2004**).
15. M. Zhang and Y.-Q. Li, *Synth. Commun.*, **36**, 835 (2006).
16. M. Wang, Z.-C. Wang, Z.-L. Sun and H. Jiang, *Transition Metal Chemistry*, **30**, 792 (2005).
17. M. Wang, H. Jiang and Z. Wang, *J. Chem. Research*, 691 **(2005)**.
18. R. R. Nagawade, S. A. Kotharkar and D. B. Shinde, *Mendeleev Commun.*, 150 **(2005)**.
19. M. Shailaja, A. Manjula, B. V. Rao and N. Parvathi, *Synth. Commun.*, **34**, 1559 (2004).
20. A. Manjula, B. V. Rao and N. Parvathi, *Synth. Commun.*, **34**, 2665 (2004).
21. I. Cepanec, M. Litvić, A. Bartolinčic and M. Lovrić, *Tetrahedron*, **61**, 4275 (2005).
22. D. S. Bose, R. K. Kumar and L. Fatima, *Synlett*, 279 **(2004)**.
23. R. Ghosh, S. Maiti and A. Chakraborty, *J. Mol. Cat A: Chem.*, **217**, 47 (2004).
24. W. Su, J. Li, Z. Zheng and Y. Shen, *Tetrahedron Lett.*, **46**, 6037 (2005).
25. K. V. N. S. Srinivas and B. Das, *Synthesis*, 2091 (**2004**).
26. R. S. Bhosale, Sidhanath V. Bhosale, Seshanath V. Bhosale, T. Wang and P. K. Zubaidha, *Tetrahedron Lett.*, **45**, 9111 (2004).
27. A. V. Narasaiah, A. K. Basak and K. Nagaiah, *Synthesis*, 1253 (**2004**).
28. G. Jenner, *Tetrahedron Lett.*, **45**, 6195 (2004).

29. A. K. Bose, S. Pednekar, S. N. Ganguly, G. Chakraborty and M. S. Manhas, *Tetrahedron Lett.*, **45**, 8351 (2004).
30. A. K. Bose, M. S. Manhas, S. Pednekar, S. N. Ganguly, H. Dang, W. He and A. Mandadi *Tetrahedron Lett.*, **46**, 1901 (2005).
31. T.-S. Jin, H.-X. Wang, C.-Y. Xing, X.-L. Li and T.-S. Li, *Synth. Commun.*, **34**, 3009 (2004).
32. Z.-T. Wang, L.-W. Xu, C.-G. Xia and H.-Q. Wang, *Tetrahedron Lett.*, **45**, 7951 (2004).
33. A. Saini, S. Kumar and J. S. Sandhu, *Indian. J. Chem.*, **45B**, 684 (2006).
34. M. A. P. Martins, M. V. M. Teixeira, W. Cunico, E. Scapin, R. Mayer, C. M. P. Pereira, N. Zanatta, H. G. Bonacorso, C. Peppe and Y.-F. Yuan, *Tetrahedron Lett.*, **45**, 8991 (2004).
35. Y. Zhu, Y. Pan and S. Huang, *Synth. Commun.*, **34**, 3167 (2004).
36. Y. Zhu, S. Huang and Y. Pan, *Eur. J. Org. Chem.*, 2354 (**2005**).
37. Y. Zhu, Y. Pan and S. Huang, *Heterocycles*, **65**, 133 (2005).
38. G. Sabitha, K. B. Reddy, R. Srinivas and J. S. Yadav, *Helv. Chim. Acta*, **88**, 2996 (2005).
39. M. M. Khodaei, P. Salehi, M. A. Zolfigol and S. Sirouszadeh, *Polish J. Chem.*, **78**, 385 (2004).
40. M. M. Khodaei, A. R. Khosropour and M. Beygzadeh, *Synth. Commun.*, **34**, 1551 (2004).
41. M. A. Chari, D. Shobha, T. K. Kumar and P. K. Dubey, *Arkivoc*, **XV**, 74 (2005).
42. P. Salehi, M. Dabiri, M. A. Zolfigol and M. Baghbanzadeh, *Heterocycles*, **65**, 1177 (2005).
43. Y. T. Reddy, B. Rajitha, P. N. Reddy, B. S. Kumar and G. V. P. Rao, *Synth. Commun.*, **34**, 3821 (2004).
44. Y. T. Reddy, P. N. Reddy, B. S. Kumar, G. V. P. Rao and B. Rajitha, *Indian J. Chem.*, **44B**, 1304 (2005).
45. V. N. Kumar, P. Someshwar, P. N. Reddy, Y. T. Reddy and B. Rajitha, *J. Heterocyclic Chem.*, **42**, 1017 (2005).
46. X. Han, F. Xu, Y. Luo and Q. Shen, *Eur. J. Org. Chem.*, 1500 **(2005)**.
47. S. K. De and R. A. Gibbs, *Synthesis*, 1748 **(2005)**.
48. S. K. De and R. A. Gibbs, *Synth. Commun.*, **35**, 2645 (2005).
49. J. M. Blacquiere, O. Sicora, C. M. Vogels, M. Čuperlović-Culf, A. Decken, R. J. Quellette and S. A. Westcott, *Can. J. Chem.*, **83**, 2052 (2005).
50. C. Mannich and W. Krosche, *Arch. Pharm.*, **250**, 647 (1912).
51. T. Ollevier and E. Nadeau, *J. Org. Chem.*, **69**, 9292 (2004).
52. T. Ollevier and E. Nadeau, *Synlett*, 219 **(2006)**.
53. B. S. Lee, S. Mahajan and K. D. Janda, *Synlett*, 1325 **(2005)**.
54. W.-G. Shou, Y.-Y. Yang and Y.-G. Wang, *Tetrahedron Lett.*, **47**, 1845 (2006).
55. M. Shi, S.-C. Cui and Y.-H. Liu, *Tetrahedron*, **61**, 4965 (2005).
56. L. Feng, L. Xu, K. Lam, Z. Zhou, C. W. Yip and A. S. C. Chan, *Tetrahedron Lett.*, **46**, 8685 (2005).
57. L.-W. Xu, C.-G. Xia and L. Li, *J. Org. Chem.*, **69**, 8482 (2004).

58. L.-W. Xu, Z.-T. Wang, C.-G. Xia, L. Li and P.-Q. Zhao, *Helv. Chim. Acta*, **87**, 2608 (2004).
59. A. M. Hardemare, O. Jarjayes and F. Mortini, *Synth. Commun.*, **34**, 3975 (2004).
60. A. M. Velázquez, L. A. Torres, G. Díaz, A. Ramírez, R. Hernández, H. Santillán, L. Martínez, I. Martínez, S. Diaz-Barriga, V. Abrego, M. A. Balboa, B. Camacho, R. López-Castañares, A. Dueñas-González, G. Cabrera and E. Angeles, *Arkivoc*, **II**, 150 (2006).
61. M. Urbaniak and W. Iwanek, *Tetrahedron*, **62**, 1508 (2006).
62. N. S. Joshi, L. R. Whitaker and M. B. Francis, *J. Am. Chem. Soc.*, **126**, 15942 (2004).
63. A. Córdova, *Acc. Chem. Res.*, **37**, 102 (2004).
64. A. Córdova, *Chem. Eur. J.*, **10**, 1987 (2004).
65. I. Ibrahem, J. Casas and A. Córdova, *Angew. Chem. Int. Ed.*, **43**, 6528 (2004).
66. I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, **46**, 2839 (2005).
67. I. Ibrahem, W. Zou, M. Engqvist, Y. Xu and A. Córdova, *Chem. Eur. J.*, **11**, 7024 (2005).
68. I. Ibrahem, W. Zou, J. Casas, H. Sundén and A. Córdova, *Tetrahedron*, **62**, 357 (2006).
69. I. Ibrahem, W. Zou, Y. Xu and A. Córdova, *Adv. Synth. Catal.*, **348**, 211 (2006).
70. W. Notz, S. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka and C. F. Barbas III, *Adv. Synth. Catal.*, **346**, 1131 (2004).
71. B. Westermann and C. Neuhaus, *Angew. Chem. Int. Ed.*, **44**, 4077 (2005).
72. D. Enders, C. Grondal, M. Vrettou and G. Raabe, *Angew. Chem. Int. Ed.*, **44**, 4079 (2005).
73. Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashzume and H. Koshina, *Adv. Synth. Catal.*, **346**, 1435 (2004).
74. A. Dondoni, A. Massi, S. Sabbatini and V. Bertolasi, *Tetrahedron Lett.*, **45**, 2381 (2004).
75. A. L. Joffe, T. M. Thomas and J. C. Adrian Jr, *Tetrahedron Lett.*, **45**, 5087 (2004).
76. M. S. Taylor, N. Tokunaga and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, **44**, 6700 (2005).
77. Y.-S. Wu, J. Cai, Z.-Y. Hu and G.-X. Lin, *Tetrahedron Lett.*, **45**, 8949 (2004).
78. T. Akiyama, K. Matsuda and K. Fuchibe, *Synlett*, 322 **(2005)**.
79. C. Rondot and J. Zhu, *Org. Lett.*, **7**, 1641 (2005).
80. A. Hantzsch, *Justus Liebigs Ann. Chem.*, **215**, 1 (1882).
81. A. Hantzsch, *Ber.*, **23**, 1474 (1890).
82. M. A. Zolfigol and M. Safaiee, *Synlett*, 827 **(2004)**.
83. G.-W. Wang, J.-J. Xia, C.-B. Miao and X.-L. Wu, *Bull. Chem. Soc. Jpn*, **79**, 454 (2006).
84. J. M. Contelles, R. León, E. Morales, M. Villarroya and A. G. García, *Tetrahedron Lett.*, **45**, 5203 (2004).
85. N. Tewari, N. Dwivedi and R. P. Tripathi, *Tetrahedron Lett.*, **45**, 9011 (2004).
86. G. V. M. Sharma, K. L. Reddy, P. S. Lakshmi and P. R. Krishna, *Synthesis*, 55 **(2006)**.
87. N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, **34**, 583 (1993).
88. J.-P. Tremblay-Morin, S. Raeppel and F. Gaudette, *Tetrahedron Lett.*, **45**, 3471 (2004).

89. K. K. Nanda and B. W. Trotter, *Tetrahedron Lett.*, **46**, 2025 (2005).
90. M. Passerini, *Gazz. Chim. Ital.*, **51**, 126 (1921).
91. M. Passerini, *Gazz. Chim. Ital.*, **54**, 529 (1924).
92. P. R. Andreana, C. C. Liu and S. L. Schreiber, *Org. Lett.*, **6**, 4231 (2004).
93. M. C. Pirrung and K. D. Sarma, *J. Am. Chem. Soc.*, **126**, 444 (2004).
94. M. A. Mironov, M. N. Ivantsova, M. I. Tokareva and B. S. Mokrushin, *Tetrahedron Lett.*, **46**, 3957 (2005).
95. A Strecker, *Ann. Chem. Pharm.*, **75**, 27 (1850).
96. S. K. De and R. A. Gibbs, *Tetrahedron Lett.*, **45**, 7407 (2004).
97. S. K. De and R. A. Gibbs, *Synth. Commun.*, **35**, 961 (2005).
98. S. K. De, *Synth. Commun.*, **35**, 1577 (2005).
99. N. Azizi and M. R. Saidi, *Synth. Commun.*, **34**, 1207 (2004).
100. K. Matsumoto, J. C. Kim, H. Iida, H. Hamana, K. Kumamoto, H. Kotsuki and G. Jenner, *Helv. Chim. Acta*, **88**, 1734 (2005).
101. K. Kumamoto, H. Iida, H. Hamana, H. Kotsuki and K. Matsumoto, *Heterocycles*, **66**, 675 (2005).
102. R. Martinez, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, **46**, 8471 (2005).
103. M. M. Mojtahedi, M. S. Abaee and H. Abbasi, *Can. J. Chem.*, **84**, 429 (2006).
104. M. I. Kabachnik, T. Y. Medved, *Dokl. Akad. Nauk SSSR., 689 (**1952**); Chem. Abstr.*, **47**, 2724b (1953).
105. E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).
106. H. Firouzabadi, N. Iranpoor and S. Sobhani, *Synthesis*, 2692 (**2004**).
107. K. Ravinder, A. V. Reddy, P. Krishnaiah, G. Venkataramana, V. L. N. Reddy and Y. Venkateswarlu, *Synth. Commun.*, **34**, 1677 (2004).
108. P. Sun, Z. Hu and Z. Huang, *Synth. Commun.*, **34**, 4293 (2004).
109. Y. T. Reddy, P. N. Reddy, B. S. Kumar, N. Sreenivasulu and B. Rajitha, *Heterocyclic Commun.*, **11**, 153 (2005).
110. Z.-P. Zhan and J.-P. Li, *Synth. Commun.*, **35**, 2501 (2005).
111. S. Kudrimoti and V. R. Bommena, *Tetrahedron Lett.*, **46**, 1209 (2005).
112. K. R. Reddy, K. S. Reddy, Ch. V. Reddy, M. Mahesh, P. V. K. Raju and V. V. N. Reddy, *Chem. Lett.*, **34**, 444 (2005).
113. P. V. D. Venken, I. E. Sayed, J. Joossens, C. V. Stevens, K. Augustyns and A. Haemers, *Synthesis*, 634 **(2005)**.
114. J. Oleksyszyn and R. Tyka, *Tetrahedron Lett.*, **18**, 2823 (1977).
115. J. Oleksyszyn, L. Subotkowska and P. Mastalerz, *Synthesis*, 985 **(1979)**.
116. J. Wu, W. Sun, X. Sun and H. -G. Xia, *Green Chem.*, **8**, 365 (2006).
117. P. Phukan, *J. Org. Chem.*, **69**, 4005 (2004).

118. H. R. Kalita and P. Phukan, *Synth. Commun.*, **35**, 475 (2005).

119. M. Sugiura, K. Hirano and S. Kobayashi, *J. Am. Chem. Soc.*, **126**, 7182 (2004).

120. S. Kobayashi, K. Hirano and M. Sugiura, *Chem. Commun.*, 104 **(2005)**.

121. T.-S. Jang, I. W. Ku, M. S. Jang, G. Keum, S. B. Kang, B. Y. Chung and Y. Kim, *Org. Lett.*, **8**, 195 (2006).

122. R. Dhawan and B. A. Arndtsen, *J. Am. Chem. Soc.*, **126**, 468 (2004).

123. J. L. Davis, R. Dhawan and B. A. Arndtsen, *Angew. Chem Int. Ed.*, **43**, 590 (2004).

124. N. Olivi, P. Spruyt, J.-F. Peyrat, M. Alami and J.-D. Brion, *Tetrahedron Lett.*, **45**, 2607 (2004).

125. L. T. Kaspar and L. Ackermann, *Tetrahedron*, **61**, 11311 (2005).

126. X.-H. Duan, X.-Y. Li, L.-N. Guo, M.-C. Liao, W.-M. Liu and Y.-M. Liang, *J. Org. Chem.*, **70**, 6980 (2005).

127. B. Clique, S. Vassiliou, N. Monteiro and G. Balme, *Eur. J. Org. Chem.*, 1493 (**2002**).

128. L. Martinon, S. Azoulay, N. Monteiro, E. P. Kündig and G. Balme, *J. Organomet. Chem.*, **689**, 3831 (2004).

129. H. A. Dondas, B. Clique, B. Cetinkaya, R. Grigg, C. Kilner, J. Morris and V. Sridharan, *Tetrahedron*, **61**, 10652 (2005).

130. K. Fuchibe, R. Hatemata and T. Akiyama, *Tetrahedron Lett*., **46**, 8563 (2005).

131. A. V. Rotaru, I. D. Druta, T. Oeser and T. J. J. Müller, *Helv. Chim. Acta*, **88**, 1798 (2005).

132. K. Kishore, R. Tetala, R. J. Whitby, M. E. Light and M. B. Hurtshouse, *Tetrahedron Lett*., **45**, 6991 (2004).

133. B. Hulin, L. S. Newton, S. Cabral, A. J. Walker and J. Bordner, *Org. Lett.*, **6**, 4343 (2004).

134. K. Shibata, T. Satoh and M. Miura, *Org. Lett.*, **7**, 1781 (2005).

135. C. Zhou and R. C. Larock, *J. Org. Chem.*, **70**, 3765 (2005).

136. R. C. Larock, Y. Wang, X. Dong and T. Yao, *Tetrahedron*, **61**, 11427 (2005).

137. M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, **6**, 2821 (2004).

138. M. Jeganmohan and C.-H. Cheng, *Synthesis*, 1693 (**2005**).

139. T. T. Jayanth, M. Jeganmohan and C.-H. Cheng, *Org. Lett.*, **7**, 2921 (2005).

140. C. D. Hopkins and H. C. Malinakova, *Org Lett.*, **6**, 2221 (2004).

141. C.D. Hopkins, L. Guan and H. C. Malinakova, *J. Org. Chem.*, **70**, 6848 (2005).

142. N. T. Patil, Z. Huo and Y. Yamamoto, *J. Org. Chem.*, **71**, 2503 (2006).

143. R. Gedye, F. Smith, K. Westaway, H. Ali and L. Baldisera, *Tetrahedron Lett.*, **27**, 279 (1986).

144. R. A. Abramovitch, *Org. Prep. Proced. Int.*, **23**, 685 (1991).

145. C. O. Kappe, *Angew. Chem. Int. Ed.*, **43**, 6250 (2004).

146. A. Saini, S. Kumar and J. S. Sandhu, *Indian J. Chem.*, **43B**, 2482 (2004).

147. S. Kumar, A. Saini and J. S. Sandhu, *Indian J. Chem.*, **44B**, 762 (2005).

148. M. Gohain, D. Prajapati and J. S. Sandhu, *Synlett*, 235 **(2004)**.

149. H. Hazarkhani and B. Karimi, *Synthesis*, 1239 (**2004**).
150. I. Saxena, D. C. Borah and J. C. Sarma, *Tetrahedron Lett.*, **46**, 1159 (2005).
151. M. Mirza-Aghayan, M. Bolourtchian and M. Hosseini, *Synth. Commun.*, **34**, 3335 (2004).
152. M. A. Pasha, N. R. Swamy and V. P. Jayashankara, *Indian J. Chem.*, **44B**, 823 (2005).
153. M. A. Pasha, J. V. Puttaramegowda, *Heterocyclic Commun.*, **12**, 61 (2006).
154. X. Wang, Z. Quan, F. Wang, M. Wang, Z. Zhang and Z. Li, *Synth. Commun.*, **36**, 451 (2006).
155. G. V. P. Rao, P. N. Reddy, Y. T. Reddy, V. N. Kumar and B. Rajitha, *Indian J. Chem.*, **44B**, 1109 (2005).
156. B. Rodriguez and C. Bolm, *J. Org. Chem.*, **71**, 2888 (2006).
157. H. Salehi and Q.-X. Guo, *Synth. Commun.*, **34**, 4349 (2004).
158. V. Sivamurugan, R. S. Kumar, M. Palanichamy and V. Murugesan *J. Heterocyclic Chem.*, **42**, 969 (2005).
159. M. Follmann, F. Graul, T. Schäfer, S. Kopec and P. Hamley, *Synlett*, 1009 (**2005**).
160. N. J. McLean, H. Tye and M. Whittaker, *Tetrahedron Lett.*, **45**, 993 (2004).
161. H. Tye and M. Whittaker, *Org. Biomol. Chem.*, **2**, 813 (2004).
162. Z.-P. Zhan, R.-F. Yang and J.-P. Li, *Chem. Lett.*, **34**, 1042 (2005).
163. M. M. Kabachnik, E. V. Zobnina and I. P. Beletskaya, *Synlett*, 1393 (**2005**).
164. X.-J. Mu, M.-Y. Lei, J.-P. Zou and W. Zhang, *Tetrahedron Lett.*, **47**, 1125 (2006).
165. L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang and C.-A. Fan, *Org. Lett.*, **6**, 1001 (2004).
166. J.-M. Zhang, W. Yang, L.-P. Song, X. Cai and S.-Z. Zhu, *Tetrahedron Lett.*, **45**, 5771 (2004).
167. J.-M. Zhang, W. Yang, S. Wang, P. He and S.-Z. Zhu, *Synth. Commun.*, **35**, 89 (2005).
168. M. Kidwai, S. Bala and A. D. Mishra, *Indian J. Chem.*, **43B**, 2485 (2004).
169. M. Kidwai and S. Rastogi, *Heteroatom. Chem.*, **16**, 138 (2005).
170. M. Kidwai, S. Saxena and R. Mohan, *J. Heterocyclic Chem.*, **42**, 703 (2005).
171. M. Kidwai, P. Mothsra, R. Mohan and S. Biswas, *Bioorg. Med. Chem. Lett.*, **15**, 915 (2005).
172. L. D. S. Yadav and R. Kapoor, *Synlett.*, 3055 **(2005)**.
173. L. D. S. Yadav, S. Yadav and V. K. Rai, *Tetrahedron*, **61**, 10013 (2005).
174. I. Devi, B. S. D. Kumar and P. J. Bhuyan, *Tetrahedron Lett.*, **44**, 8307 (2003).
175. I. Devi and P. J. Bhuyan, *Synlett*, 283 **(2004)**.
176. I. Devi and P. J. Bhuyan, *Tetrahedron Lett.*, **45**, 8625 (2004).
177. S. Tu, J. Zhang, Z. Xiang, F. Fang and T. Li, *Arkivoc*, **XIV**, 76 (2005).
178. S. Tu, F. Fang, T. Li, S. Zhu and X. Zhang, *J. Heterocyclic Chem.*, **42**, 707 (2005).
179. J. Quiroga, S. Cruz, B. Insuasty, R. Abonía, M. Nogueras and J. Cobo, *Tetrahedron Lett.*, **47**, 27 (2006).
180. H. R. Darabi, K. Aghapoor and M. Tajbakhsh, *Tetrahedron Lett.*, **45**, 4167 (2004).

181. M. Lebrini, F. Bentiss and M. Lagrenée, *J. Heterocyclic Chem.*, **42**, 991 (2005).

182. Y. Hu, P. Wei, H. Huang, S.-Q. Han and P.-K. Ouyang, *Heterocycles*, 375 **(2006)**.

183. W. Huang, J. Li, J. Tang, H. Liu, J. Shen and H. Jiang, *Synth. Commun.*, **35**, 1351 (2005).

184. A. Shaabani, M. B. Teimouri, S. Samadi and K. Soleimani, *Synth. Commun.*, **35**, 535 (2005).

185. J. Wu, *Chem. Lett.*, **35**, 118 (2006).

186. M. Dabiri, P. Salehi, M. S. Khajavi and A. A. Mohammadi, *Heterocycles*, **63**, 1417 (2004).

187. M. Dabiri, P. Salehi, A. A. Mohammadi and M. Baghbanzadeh *Synth. Commun.*, **35**, 279 (2005).

188. A. Dandia, R. Singh and P. Sarawgi, *Org. Prep. Proced. Int.*, **37**, 397 (2005).

189. A. Dandia, R. Singh and P. Sarawgi, *J. Fluorine Chem.*, **126**, 307 (2005).

190. F. Risitano, G. Grassi, F. Foti and S. Moraci, *Synlett*, 1633 (**2005**).

191. P. Appukkuttan, W. Dahaen, V. V. Fokin and E. V. D. Eycken, *Org. Lett.,* **6**, 4223 (2004).

192. D. Li, H. Bao and T. You, *Heterocycles*, **65**, 1957 (2005).

193. V. Sridharan, S. P. Saravanakumar and S. Muthusubramanian, *J. Heterocyclic Chem.*, **42**, 515 (2005).

194. V. Gududuru, V. Nguyen, J. T. Dalton and D. D. Miller, *Synlett*, 2357 **(2004)**.

195. J. Azizian, A. R. Karimi, A. A. Mohammadi and M. R. Mohammadizadeh, *Heterocycles*, **63**, 2225 (2004).

196. A. Zanobini, A. Brandi and A. de Meijere, *Eur. J. Org. Chem.*, 1251 **(2006)**.

197. M. A. Chari and K. Syamasundar, *J. Mol. Cat. A: Chem.*, **221**, 137 (2004).

198. J. S. Yadav, B. V. S. Reddy, P. Sridhar, J. S. S. Reddy, K. Nagaiah, N. Lingaiah and P. S. Saiprasad, *Eur. J. Org. Chem.*, 552 **(2004)**.

199. J. S. Yadav, B. V. S. Reddy, B. Eeshwaraiah and M. Srinivas, *Tetrahedron*, **60**, 1767 (2004).

200. R. V. Yarapathi, S. Kurva and S. Tammishetti, *Catal. Commun.*, **5**, 511 (2004).

201. B. Gangadasu, S. Palaniappan and V. J. Rao, *Synlett*, 1285 (**2004**).

202. S. Palaniappan, A. John, C. Amarnath and V. J. Rao, *J. Mol. Cat. A: Chem.*, **218**, 47 (2004).

203. S. Palaniappan and A. John, *J. Mol. Cat. A: Chem.*, **233**, 9 (2005).

204. M. M. Heravi, F. Derikvand and F. F. Bamoharram, *J. Mol. Catal. A: Chem.*, **242**, 173 (2005).

205. M. Tajbakhsh, B. Mohajerani, M. M. Heravi and A. N. Ahmadi, *J. Mol. Catal. A: Chem.*, **236**, 216 (2005).

206. H. E. Badaoui, F. Bazi, S. Tamani, S. Boulaajaj, M. Zahouily, H. B. Lazrek and S. Sebti, *Synth. Commun.*, **35**, 2561 (2005).

207. B. M. Reddy, P. M. Sreekanth and P. Lakshmanan, *J. Mol. Catal. A: Chem.*, **237**, 93 (2005).

208. B. M. Reddy, P. M. Sreekanth, P. Lakshmanan and A. Khan, *J. Mol. Catal. A: Chem.*, **244**, 1 (2006).

209. A. Hegedüs, Z. Hell and I. Vigh, *Synth. Commun.*, **36**, 129 (2006).

210. J. Azizian, A. A. Mohammadi, A. R. Karimi and M. R. Mohammadizadeh, *Applied Catalysis A: General*, **300**, 85 (2006).

211. K. K. Kapoor, B. A. Ganai, S. Kumar and C. S. Andotra, *Can. J. Chem.*, **84**, 433 (2006).

212. J. K. Joseph, S. L. Jain and B. Sain, *J. Mol. Catal. A: Chem.*, **247**, 99 (2006).

213. S. Lock, N. Miyoshi and M. Wada, *Chem. Lett.*, **33**, 1308 (2004).

214. M. A. Chari and K. Syamasundar, *Catal. Commun.*, **6**, 624 (2005).

215. E. Rajanarender, P. Ramesh, M. Srinivas, K. Ramu and G. Mohan, *Synth. Commun.*, **36**, 665 (2006).

216. W.-Y. Chen and J. Lu, *Synlett*, 2293 **(2005)**.

217. G. Smitha, B. Miriyala and J. S. Williamson, *Synlett*, 839 **(2005)**.

218. D. J. Lipomi and J. S. Panek, *Org. Lett.*, **7**, 4701 (2005).

219. G.-L. Li and G. Zhao, *Org. Lett.*, **8**, 633 (2006).

220. B. M. Choudary, C. Sridhar, M. L. Kantam and B. Sreedhar, *Tetrahedron Lett.*, **45**, 7319 (2004).

221. M. L. Kantham, B. V. Prakash, Ch. V. Reddy and B. Sreedhar, *Synlett*, 2329 **(2005)**.

222. Y. Masaki, T. Yamada, H. Kawai, A. Itoh, Y. Arai and H. Furukawa, *Synlett*, 288 **(2006)**.

223. R. Maggi, R. Ballini, G. Sartori and R. Sartorio, *Tetrahedron Lett.*, **45**, 2297 (2004).

224. X.-S. Wang, D.-Q. Shi, H. Z. Yu, G.-F. Wang and S.-J. Tu, *Synth. Commun.*, **34**, 509 (2004).

225. X.-S. Wang, Z.-S. Zeng, D.-Q. Shi, X.-Y. Wei and Z.-M. Zong, *Synth. Commun.*, **34**, 3021 (2004).

226. X.-S. Wang, Z.-S. Zeng, D.-Q. Shi, X.-Y. Wei and Z.-M. Zong, *Synth. Commun.*, **34**, 4331 (2004).

227. J.-T. Li, W. -Z. Xu, L.-C. Yang and T.-S. Li, *Synth. Commun.*, **34**, 4565 (2004).

228. B. Das, M. R. Reddy, H. Harish, R. Ramu, K. Venkateswarlu and Y. K. Rao, *J. Chem. Res.*, 793 **(2005)**.

229. K. V. N. S. Srinivas and B. Das, *Synlett*, 1715 **(2004)**.

230. B. Das and J. Banerjee, *Chem. Lett.*, **33**, 960 (2004).

231. P. Salehi, M. Dabiri, M. A. Zolfigol and M. Baghbanzadeh, *Synlett*, 1155 **(2005)**.

232. P. Salehi, M. Dabiri, M. A. Zolfigol and M. Baghbanzadeh, *Tetrahedron Lett.*, **46**, 7051 (2005).

233. N. Jain, A. Kumar, S. Chauhan and S. M. S. Chauhan, *Tetrahedron*, **61**, 1015 (2005).

234. A. R. Gholap, K. Venkatesan, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *Green Chem.*, **6**, 147 (2004).

235. S. S. Bahekar, S. A. Kotharkar and D. B. Shinde, *Mendeleev Commun.*, 210 **(2004)**.

236. M. M. Khodaei, A. R. Khosropour and M. Jowkar, *Synthesis*, 1301 **(2005)**.

237. A. Shaabani and A. Rahmati, *Catal. Lett.*, **100**, 177 (2005).

238. G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang and D. Sun, *Green Chem.*, **6**, 75 (2004).

239. S. Sahoo, T. Joseph and S. P. Halligudi, *J. Mol. Catal. A: Chem.*, **244**, 179 (2006).

240. H. Gao, B. Han, J. Li, T. Jiang, Z. Liu, W. Wu, Y. Chang and J. Zhang, *Synth. Commun.*, **34**, 3083 (2004).

241. G. W. Kabalka, B. Venakataiah and G. Dong, *Tetrahedron Lett.*, **45**, 729 (2004).

242. R. Sridhar and P. T. Perumal, *Tetrahedron*, **61**, 2465 (2005).

243. G. Karthikeyan and P. T. Perumal, *Can. J. Chem.*, **83**, 1746 (2005).

244. Y. Hu, Z.-C. Chen, Z.-G. Le and Q.-G. Zheng, *Synth. Commun.*, **34**, 3801 (2004).

245. J. S. Yadav, B. V. S. Reddy, V. N. Kumar, R. S. Rao and K. Nagaiah, *New J. Chem.*, **28**, 335 (2004).

246. S. B. Park and H. Alper, *Chem. Commun.*, 1315 **(2005)**.

247. Z. Li, C. Wei, L. Chen, R. S. Varma and C.-J. Li, *Tetrahedron Lett.*, **45**, 2443 (2004).

248. J. S. Yadav, B. V. S. Reddy, S. Shubashree, K. Sadashiv and J. J. Naidu, *Synthesis*, 2376 **(2004)**.

249. J. S. Yadav, B. V. S. Reddy and P. N. Reddy, *Chem. Lett.*, **33**, 1436 (2004).

250. Y.-L. Li, B.-X. Du, X.-S. Wang, D.-Q. Shi and S.-J. Tu, *J. Chem. Res.*, 157 **(2006)**.

251. Y.-B. Zhao, Z.-Y. Yan and Y.-M. Liang, *Tetrahedron Lett.*, **47**, 1545 (2006).

252. C. Wei, Z. Li and C.-J. Li, *Synlett*, 1472 **(2004)**.

253. N. Gommermann and P. Knochel, *Chem. Commun.*, 2324 **(2004)**.

254. N. Gommermann and P. Knochel, *Synlett*, 2799 **(2005)**.

255. T. F. Knöfel, A. Aschwandne, T. Ichikawa, T. Watanabe and E. M. Carreira, *Angew. Chem. Int. Ed.*, **43**, 5971 (2004).

256. D. A. Black and B. A. Arndtsen, *Org. Lett.*, **6**, 1107 (2004).

257. B. Sreedhar, P. S. Reddy, B. V. Prakash and A. Ravindra, *Tetrahedron Lett.*, **46**, 7019 (2005).

258. Y. Zhang, A. M. Santos, E. Herdtweck, J. Mink and F. E. Kühn, *New J. Chem.*, **29**, 366 (2005).

259. H.-X. Wei, R. L. Jasoni, J. Hu, G. Li and P. W. Paré, *Tetrahedron*, **60**, 10233 (2004).

260. J. S. Yadav, B. V. S. Reddy, M. K. Gupta and B. Eeshwaraiah, *Synthesis*, 57 **(2005)**.

261. S. Xue, L. He, K.-Z. Han, Y.-K. Liu and Q.-X. Guo, *Synlett*, 1247 **(2005)**.

262. S. Sun, Q. Zhang, Q. Liu, J. Kang, Y. Yin, D. Li and D. Dong, *Tetrahedron Lett.*, **46**, 6271 (2005).

263. M. Shi and S.-C. Cui, *New J. Chem.*, **28**, 1286 (2004).

264. K. Cheng, L. Lin, S. Chen and X. Feng, *Tetrahedron*, **61**, 9594 (2005).

265. D. Xiao, L. Wang and X. Feng, *Synlett*, 1531 **(2005)**.

266. H. Sundén, I. Ibrahem, L. Eriksson and A. Córdova, *Angew. Chem. Int Ed.*, **44**, 4877 (2005).

267. D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem. Int. Ed.*, **42**, 4233 (2003).

268. C. F. Barbas III and D. B. Ramachary, *Chem. Eur, J.*, **10**, 5323 (2004).

269. B. Das, M. R. Reddy, V. S. Reddy and R. Ramu, *Chem. Lett.*, **33**, 1526 (2004).

270. R. Nagarajan, C. J. Magesh and P. T. Perumal, *Synthesis*, 69 **(2004)**.

271. R. S. Kumar, R. Nagarajan and P. T. Perumal, *Synthesis*, 949 **(2004)**.

272. C. J. Magesh, S. V. Makesh and P. T. Perumal, *Bioorg. Med. Chem. Lett.*, 2035 **(2004)**.

273. A. Semwal and S. K. Nayak, *Synth. Commun.*, **36**, 227 (2006).

274. D. Strübing, H. Neumann, S. Klaus, A. J. V. Wangelin, D. Gördes, M. Beller, P. Braiuca, C. Ebert, L. Gardossi and U. Kragl, *Tetrahedron*, **60**, 683 (2004).

275. S. Hübner, H. Neumann, A. J. Wangelin, S. Klaus, D. Strübing, H. Klein and M. Beller, *Synthesis*, 2084 **(2005)**.

276. S. Klaus, S. Hübner, N. Neumann, D. Strübing, A. J. V. Wangelin, D. Gördes and M. Beller, *Adv. Syn. Catal.*, **346**, 970 (2004).

277. D. Strübing, A. J. V. Wangelin, H. Neumann, D. Gördes, S. Hübner, S. Klaus, A. Spannenberg and M. Beller, *Eur. J. Org. Chem.*, 107 **(2005)**.

278. D. Strübing, A. Kirschner, H. Neumann, S. Hübner, S. Klaus, U. T. Bornscheuer and M. Beller, *Chem. Eur. J.*, **11**, 4210 (2005).

279. D. Strübing, H. Neumann, S. Hübner, S. Klaus, and M. Beller, *Org. Lett.*, **7**, 4321 (2005).

280. P. G. Cozzi and E. Rivalta, *Angew. Chem. Int. Ed.*, **44**, 3600 (2005).

281. W. Keung, F. Bakir, A. P. Patron, D. Rogers, C. D. Priest and V. Darmohusodo, *Tetrahedron Lett.*, **45**, 733 (2004).

282. M. C. Pirrung and K. D. Sarma, *Synlett*, 1425 **(2004)**.

283. A. Dömling, E. Herdtweck and S. Heck, *Tetrahedron Lett.*, **47**, 1745 (2006).

284. V. Nair, S. Mathai and R. L. Varma, *J. Org. Chem.*, **69**, 1413 (2004).

285. V. Nair, S. Mathai, S. C. Mathew and N. P. Rath, *Tetrahedron*, **61**, 2849 (2005).

286. V. Nair, R. S. Menon, P. B. Beneesh, V. Sreekumar and S. Bindu, *Org. Lett.*, **6**, 767 (2004).

287. V. Nair, P. B. Beneesh, V. Sreekumar, S. Bindu, R. S. Menon and A. Deepthi, *Tetrahedron Lett.*, **46**, 201, (2005).

288. V. Nair, A. R. Sreekanth, N. P. Abhilesh, A. T. N.Biju, L. Varma, S. Viji and S. Mathew, *Arkivoc*, **XI**, 178 (2005).

289. V. Nair, B. R. Devi and L. R. Varma, *Tetrahedron Lett.*, **46**, 5333 (2005)

290. V. Nair, R. Dhanya and S. Viji, *Tetrahedron*, **61**, 5843 (2005).

291. V. Nair and A. Deepthi, *Tetrahedron Lett.*, **47**, 2037 (2006).

292. I. Yavari, H. Djahaniani and F. Nasiri, *Synthesis*, 679 **(2004)**.

293. I. Yavari and A. Habibi, *Synthesis*, 989 **(2004)**.

294. I. Yavari and M. Esnaashari, *Synthesis*, 1049 **(2005)**.

295. M. Adib, M. Mollahosseini, H. Yavari, M. H. Sayahi and H. R. Bijanzadeh, *Synthesis*, 861 **(2004)**.

296. M. Adib, K. Ghanbary, M. Mostofi and H. R. Bijanzadeh, *Tetrahedron*, **61**, 2645 (2005).

297. M. Adib, M. H. Sayahi, B. Aghaaliakbari and H. R. Bijanzadeh, *Tetrahedron*, **61**, 3963 (2005).

298. M. Adib, M. H. Sayahi, S. A. Koloogani and P. Mirzaei, *Helv. Chim. Acta*, **89**, 299 (2006).

299. C. Ma and Y. Yang, *Org. Lett.*, **7**, 1343 (2005).

300. A. A. Esamaeili and H. Zendegani, *Tetrahedron*, **61**, 4031 (2005).

301. M. T. Maghsoodlou, N. Hazeri, S. M. Habibi-Khorasani, R. Heydari, G. Marandi and M. Nassiri, *Synth. Commun.*, **35**, 2569 (2005).

302. M. T. Maghsoodlou, N. Hazeri, S. M. Habibi-Khorasani, G. Marandi and M. Nassiri, *Synth. Commun.*, **35**, 2771 (2005).

303. M. B. Teimouri, A. Shaabani and R. Bazhrang, *Tetrahedron*, **62**, 1845 (2006).

304. M. B. Teimouri, R. Bazhrang, V. Eslamimanesh and A. Nouri, *Tetrahedron*, **62**, 3016 (2006).

305. M. Anary-Abbasinejad, M. H. Mosslemin, S. Tahan and H. Anaraki-Ardakani, *J. Chem. Res.*, 170 **(2006)**.

306. J. Azizian, M. R. Mohammadizadeh, A. A. Mohammadi and A. R. Karimi, *Heteroatom. Chem.*, **16**, 259 (2005).

307. J. Azizian, M. R. Mohammadizadeh, N. Karimi, A. A. Mohammadi and A. R. Karimi, *Heterocycles*, **65**, 143 (2005).

308. J. Azizian, M. R. Mohammadizadeh, N. Karimi, Z. Kazemizadeh, A. A. Mohammadi and A. R. Karimi, *Heteroatom. Chem.*, **16**, 549 (2005).

309. J. Azizian, A. A. Mohammadi, A. R. Karimi and M. R. Mohammadizadeh, *J. Org. Chem.*, **70**, 350 (2005).

310. L. Wang, J. Liu, H. Tian, C. Qian and J. Sun, *Adv. Syn. Catal.*, **347**, 689 (2005).

311. M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A. A. Mohammadi, *Tetrahedron Lett.*, **46**, 6123 (2005).

312. J. Terao, S. Nii, F. A. Chowdhury, A. Nakamura and N. Kambe, *Adv. Syn. Catal.*, **346**, 905 (2004).

313. J. Montgomery, *Angew. Chem. Int. Ed.*, **43**, 3890 (2004).

314. G. M. Mahandru, G. Liu and J. Montgomery, *J. Am. Chem. Soc.*, **126**, 3698 (2004).

315. M. Song and J. Montgomery, *Tetrahedron*, **61**, 11440 (2005).

316. S.-S. Ng and T. F. Jamison, *J. Am. Chem. Soc.*, **127**, 7320 (2005).

317. S.-S. Ng and T. F. Jamison, *Tetrahedron*, **61**, 11405 (2005).

318. S.-S. Ng and T. F. Jamison, *J. Am. Chem. Soc.*, **127**, 14194 (2005).

319. T.-S. Jin, A.-Q. Wang, X. Wang, J. -S. Zhang and T. -S. Li, *Synlett*, 871 **(2004)**.

320. T.-S. Jin, A.-Q. Wang, Z.-L. Cheng, J. -S. Zhang and T. -S. Li, *Synth. Commun.*, **35**, 137 (2005).

321. S. Balalaie, M. Bararjanian, A. M. Amani and B. Movassagh, *Synlett*, 263 **(2006)**.

322. S. H. Mashraqui, M. B. Patil, H. D. Mistry, S. Ghadigaonkar and A. Meetsma, *Chem. Lett.*, **33**, 1058 (2004).

323. B. P. V. Lingaiah, G. V. Reddy, T. Yakaiah, B. Narsaiah, S. N. Reddy, R. Yadla and P. S. Rao, *Synth. Commun.*, **34**, 4431 (2004).

324. X. Lu, Z. Lu and X. Zhang, *Tetrahedron*, **62**, 457 (2006).

325. M. J. Stocks, D. R. Cheshire and R. Reynolds, *Org. Lett.*, **6**, 2969 (2004).

326. T. Igarashi, T. Inada, T. Sekioka, T. Nakajima and I. Shimizu, *Chem. Lett.*, **34**, 106 (2005).

327. T. Inada, T. Nakajima and I. Shimizu, *Heterocycles*, **66**, 611 (2005).

328. X. Xiong, M. Bagley and K. Chapaneri, *Tetrahedron Lett.*, **45**, 6121 (2004).

329. A. Fayol and J. Zhu, *Org. Lett.*, **6**, 115 (2004).

330. J. Blanchet and J. Zhu, *Tetrahedron Lett.*, **45**, 4449 (2004).

331. A. Fayol and J. Zhu, *Org. Lett.*, **7**, 239 (2005).

332. A. Fayol and J. Zhu, *Tetrahedron*, **61**, 11511 (2005).

333. G. C. Tron and J. Zhu, *Synlett*, 532 **(2005)**.

334. D. Bonne, M. Dekhane and J. Zhu, *Org. Lett.*, **7**, 5285 (2005).

335. M.A. Lyon and T. S. Kercher, *Org. Lett.*, **6**, 4989 (2004).

336. R. S. Bon, B. V. Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. B. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen and R. V. A. Orru, *J. Org. Chem.*, **70**, 3542 (2005).

337. J. -T. Li, Z. -P. Lin, J. -F. Han and T. -S. Li, *Synth. Commun.*, **34**, 2623 (2004).

338. K. Illgen, S. Nerdinger, T. Fuchs, C. Friedrich, L. Weber and E. Herdtweck, *Synlett*, 53 **(2004)**.

339. D. Behnke, R. Taube, K. Illgen, S. Nerdinger and E. Herdtweck, *Synlett*, 688 **(2004)**.

340. K. Illgen, S. Nerdinger, D. Behnke and C. Friedrich, *Org. Lett.*, **7**, 39 (2005).

341. S. Carballares and J. F. Espinosa, *Org. Lett.*, **7**, 2329 (2005).

342. P. He and S. Zhu, *Synthesis*, 2137 **(2005)**.

343. P. He and S. Zhu, *Tetrahedron*, **61**, 6088 (2005).

344. J. Sapi and J.-Y. Laronze, *ARKIVOC*, **VII**, 208 (2004).

345. Y. Oikawa and O. Yonemitsu, *Tetrahedron Lett.*, **19**, 1759 (1978).

346. B. Nemes, L. Jeannin, J. Sapi, M. Laronze, H. Seghir, F. Augé and J.-Y. Laronze, *Tetrahedron*, **56**, 5479 (2000).

347. F. Cochard, J. -Y. Laronze, *Tetrahedron Lett.*, **42**, 6291 (2001).

348. F. Cochard, M. Laronze, E. Prost, J. -M. Nuzillard, F. Augé C. Petermann, P. Sigaut, J. Sapi and J. -Y. Laronze, *Eur. J. Org. Chem.*, 3481 **(2002)**.

349. E. Dardennes, A. Kovács-Kulyassa, A. Renzetti, J. Sapi and J.-Y. Laronze, *Tetrahedron Lett.*, **44**, 221 (2003).

350. G. Sabitha, M. R. Kumar, M. S. K. Reddy, J. S. Yadav, K. V. S. R. Krishna and A. C. Kunwar, *Tetrahedron Lett.*, **46**, 1659 (2005).

351. H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Angew. Chem. Int. Ed.*, **43**, 3935 (2004).

352. H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Tetrahedron Lett.*, **45**, 8659 (2004).

353. C. -X. Chen, L. Liu, D. -P. Yang, D. Wang and Y. -J. Chen, *Synlett*, 2047 **(2005)**.

354. J. -L. Zhao, L. Liu, H. -B. Zhang, Y. -C. Wu, D. Wang and Y. -J. Chen, *Synlett*, 96 **(2006)**.

355. Z. -L. Shen, S. -J. Ji, S. -Y. Wang and X. -F. Zeng, *Tetrahedron*, **61**, 10552 (2005).

356. C. A. Simoneau and B. Ganem, *Tetrahedron*, **61**, 11374 (2005).

357. E. M. Budynina, O. A. Ivanova, E. B. Averina, Y. K. Grishin, T. S. Kuznetsova and N. S. Zefirov, *Synthesis*, 286 **(2005)**.

358. E. M. Budynina, E. B. Averina, O. A. Ivanova, T. S. Kuznetsova and N. S. Zefirov, *Tetrahedron Lett.*, **46**, 657 (2005).

359. I. S. Young and M. A. Kerr, *Org. Lett.*, **6**, 139 (2004).

360. M. Nyerges, B. Somfai, J. Tóth, L. Tőke, A. Danscó and G. Blaskó, *Syntheis*, 2039 **(2005)**.

361. P. Garner and H. U. Kaniskan, *J. Org. Chem.*, **70**, 10868 (2005).

362. S. Rehn, J. Bergman and B. Stensland, *Eur. J. Org. Chem.*, 413 **(2004)**.

363. Y. V. Shklyaev, M. A. Yeltsov, Y. S. Rozhova, A. G. Tolstikov and V. M. Dembitsky, *Heteroatom. Chem.*, **15**, 486 (2004).

364. H.-W. Xu, G.-Y. Li, M.-K. Wong and C.-M. Che, *Org. Lett.*, **7**, 5349 (2005).

365. S. Sato, H. Isobe, T. Tanaka, T. Ushijima and E. Nakamura, *Tetrahedron*, **61**, 11449 (2005).

366. H.-J. Park and K.-I. Lee, *Synth. Commun.*, **34**, 2053 (2004).

367. H. H. Zahmani, S. Hacini, C. Bories, R. Faure and J. Rodriguez, *Synthesis*, 2151 **(2005)**.

368. S. Xue, Q.-F. Zhou, L.-Z. Li and Q.-X. Guo, *Synlett*, 2990 **(2005)**.

369. A. Chetia, C. J. Saikia, K. C. Lekhok and R. C. Boruah, *Tetrahedron Lett.*, **45**, 2649 (2004).

370. A. Manaka, T. Ishii, K. Takahashi and M. Sato, *Tetrahedron Lett.*, **46**, 419 (2005).

371. S. Huang, Y. Pan, Y. Zhu and A. Wu, *Org. Lett.*, **7**, 3797 (2005).

372. M. M. Khodaei, A. R. Khosropour and H. Moghanian, *Synlett*, 916 **(2006)**.

373. M. A. Mironov, M. N. Ivantsova and V. S. Mokrushin, *Synlett*, 615 **(2006)**.

374. M. Hayashi, Y. Matsuura and Y. Watanabe, *Tetrahedron Lett.*, **46**, 5135 (2005).

375. T. Opatz and D. Ferenc, *Eur. J. Org. Chem.*, 817 **(2005)**.

376. V. A. Chebanov, Y. I. Sakhno, S. M. Desenko, S. V. Shishkina, V. I. Musatov, O. V. Shishkin and I. V. Knyazeva, *Synthesis*, 2597 **(2005)**.

377. A. B. Smith III and M. O. Duffey, *Synlett*, 1363 **(2004)**.

378. S. Suga, T. Nishida, D. Yamada, A. Nagaki and J.-I. Yoshida, *J. Am. Chem. Soc.*, **126**, 14338 (2004).

379. M. F. A. Adamo, D. Donati, E. F. Duffy and P. Sarti-Fantoni, *J. Org. Chem.*, **70**, 8395 **(2005)**.

380. A. Heydari, H. Tavakol, S. Aslanzadeh, J. Azarnia and N. Ahmadi, *Synthesis*, 627 **(2005)**.

381. I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, **127**, 2038 (2005).

382. D. A. Black and B. A. Arndtsen, *J. Org. Chem.*, **70**, 5133 (2005).

383. C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu, and A.-Q. Mi, *Org. Lett.*, **7**, 83 (2005).

384. C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu and A.-Q. Mi, *Chem. Commun.*, 2624 **(2005)**.

385. H. Huang, Y. Wang, Z. Chen and W.-H. Hu, *Adv. Syn. Catal.*, **347**, 531 (2005).

386. Y. Yamamoto, S. Nakano, H. Maekawa and I. Nishiguchi, *Org. Lett.*, **6**, 799 (2004).

387. T. Hirai, H. Kuniyasu and N. Kambe, *Tetrahedron Lett.*, **46**, 117 (2005).

388. J. Lu, G. Mao, W. Zhang and Z. Xi, *Chem. Commun.*, 4848 **(2005)**.

389. Y. Liu and H. Gao, *Org. Lett.*, **8**, 309 (2006).