

Catalytic Multicomponent Reactions Based on Isocyanides

M.M. Heravi* and S. Moghimi

Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran

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Due to their versatility and diversity, catalytic multi-component isocyanide-based reactions (IMCR), are very interesting and important. Isocyanide group is a unique functional group due to its reactivity toward electrophiles and nucleophiles at the same atom. It participates in many multi-component reactions along with various catalysts which dramatically improve reaction conditions for the achievement of better yields, milder and benign reaction condition and in some cases better stereoselectivities. In this review, we wish to disclose the recent applications of metal, basic, acidic and many other catalytic systems in the IMCRs. In supplementary section we also updated our review with all related publications in 2010.

Keywords: Isocyanide-based reaction, Lewis acids, Bronsted acids, Ugi reaction

INTRODUCTION

The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. The outstanding position of isocyanide-based reactions can be traced back to the exceptional reactivity of the functional group of the isocyanide. No other functional group reacts with nucleophiles and electrophiles at the same atom, leading to the so called α -adduct. Other major primary reaction pathways of isocyanides are radical reactions, α -acidity, and an intrinsic high affinity toward met all organic reagents and their subsequent reactions [1].

The rate of chemical reaction, in the presence of catalyst is faster and unlike other reagents, is not consumed by the reaction itself. Catalysts can be either heterogeneous and homogenous depending on whether a catalyst exists in the same phase as the substrate or not.

In line with the tremendous renewed activity witnessed in recent years in the field of isocyanide-based reactions, remarkable new strategies have been developed based on catalyst processes. Advances in this area take advantage of the myriad of bond-forming processes that can be achieved with catalysts.

On the basis of the rapid growing number of important communications in the area of catalytic isocyanide-based reactions, we felt that it is appropriate and being useful to review the work since 2006, when the last comprehensive review, *Recent Development in Isocyanide Based Multicomponent Reactions in Applied Chemistry*, was Appeared [1]. Here, we wish to summarize current progress in catalytic isocyanide-based chemistry.

STERESELECTIVE IMCR

Although the great utility of isocyanide-based multicomponent reaction in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs widely

*Corresponding author. E-mail: mmh1331@yahoo.com

recognized, the stereochemical issues still represent a challenge. In Passerini and Ugi reactions a new stereogenic center is generated but most reactions reported so far suffer from low or absence of stereoselectivity [2].

Enantioselective Passerini Reaction

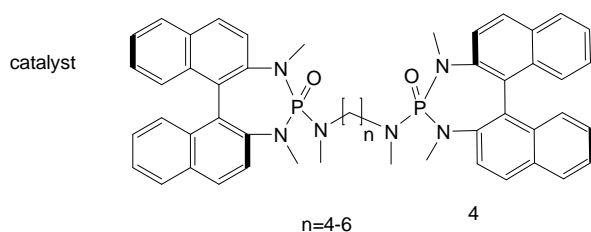
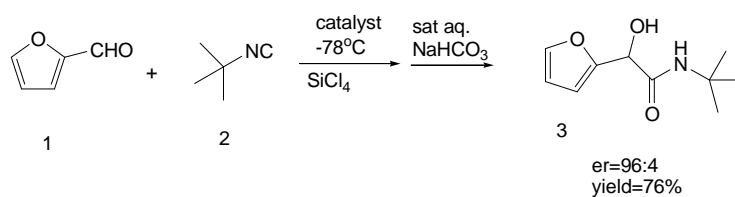
In the classic Passerini reaction (P-3CR), an α -acyloxy carboxamide is formed from the reaction of an isocyanide, an aldehyde, and a carboxylic acid. The mechanism involves an initial nucleophilic addition of the isocyanide on the aldehyde followed by an acyl rearrangement.

Although this reaction has been known since 1921 and is widely applied in natural product synthesis and drug

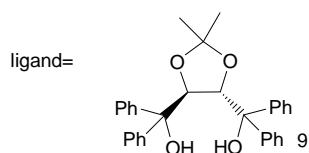
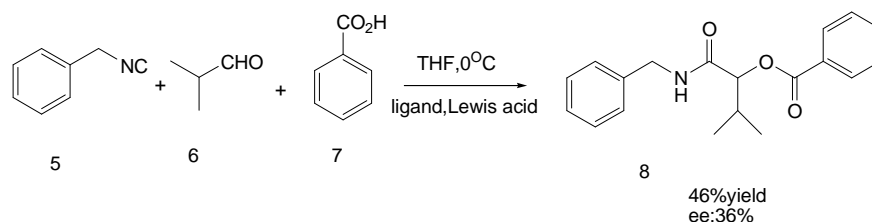
discovery, but catalytic asymmetric variants are rare.

Denmark *et al.* described the first asymmetric Lewis base catalyzed enantioselective Passerini-type reaction (Scheme 1). The yields were good to excellent and the *ee*'s ranged from 70/30 to 99/1. In this reaction water is acting as the acid component [3].

Domling *et al.* identified the first enantioselective Passerini MCR. They screened several hundreds of combinations of Lewis acid-chiral ligands and found that a stoichiometric amount of $\text{Ti}(i\text{-OPr})_4$ in combination with TADDOL **9** turned out to give the best *ee*'s (Scheme 2). This system was capable of promoting reaction to afford product in low to moderate enantioselectivity [4].



Scheme 1



Lewis acid= $\text{Ti}(i\text{-OPr})_4$

Scheme 2

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It has been demonstrated that an indane-pybox-Cu^{II} complex **12** (pybox = pyridinebis(oxazoline)) could catalyze the P-3CR (Scheme 3). Sixteen examples were described to have between 60 and 98% *ee* and 75-98% chemical yield [5].

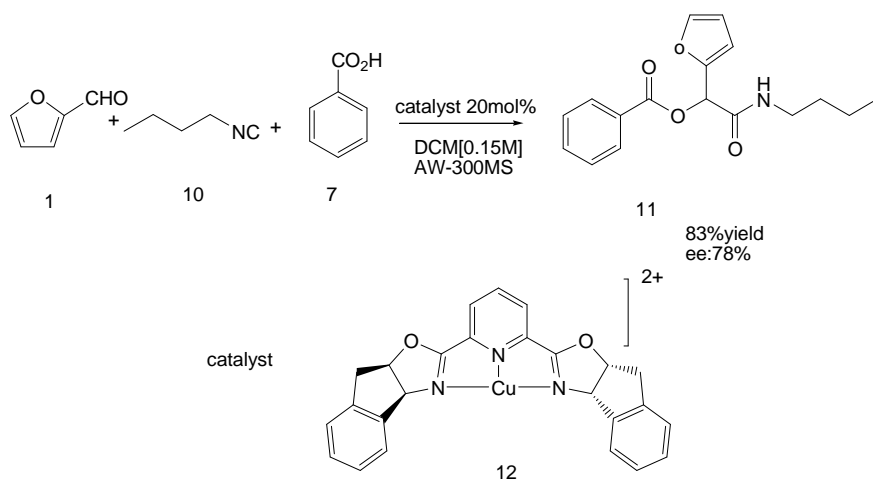
The development of a truly catalytic enantioselective three-component Passerini reaction of wide application scope remains a significant challenge, in sharp contrast to the formidable progress made in the field of asymmetric synthesis in general. A chiral Lewis acid catalyst with one coordination site is essential for the development of enantioselective Passerini- and Ugi-type reactions.

Wang *et al.* described, when *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-(*R,R*)-cyclohexane-1,2-diamine **14** was used as the supporting ligand in association with Et₂AlCl to

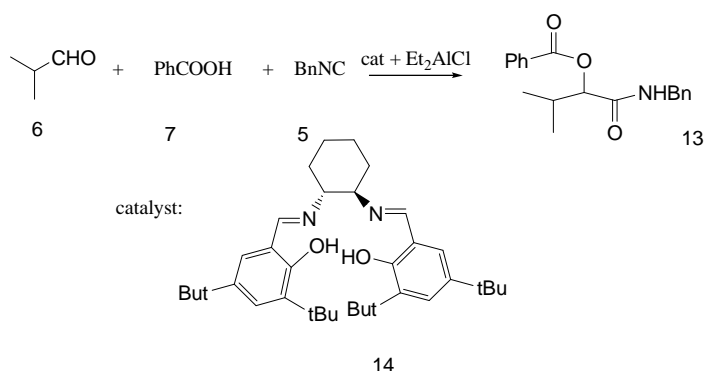
perform P-3CR. Sixteen examples were described to have between 63 and 99% *ee* and 51-70% chemical yields (Scheme 4). Increasing the temperature decrease *ee* values [6].

The Passerini adduct itself is also a bidentate ligand and can therefore compete with the substrate to coordinate to the catalyst. Wang explored to use a chiral catalyst with a single coordination site. As the carboxylic acid itself catalyzed the P-3CR, they designed a protocol involving the slow addition over 1 h of the carboxylic acid to the solution of the catalyst.

The three-component Passerini reaction has seldom been used for the preparation of tetrazoles. Yue and co workers developed the first catalytic enantioselective synthesis of 5-(1-hydroxyalkyl)tetrazoles **18** by a [(salen)Al^{III}Me]-catalyzed three-component Passerini reaction of aldehydes, isocyanides,



Scheme 3



Scheme 4

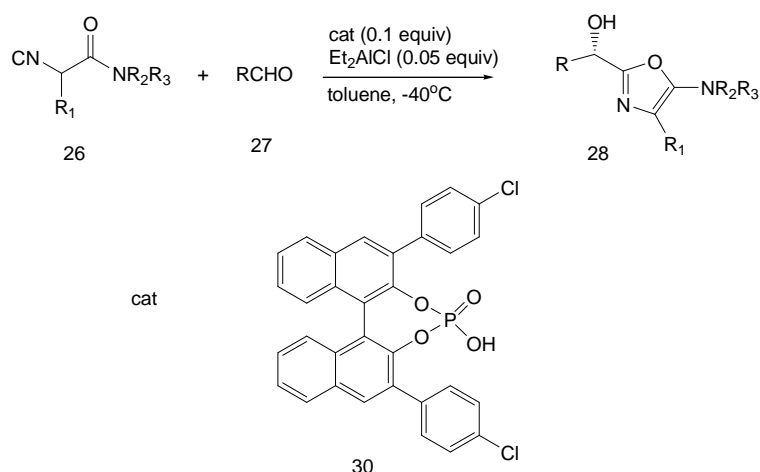
Catalytic Multicomponent Reactions Based on Isocyanides

The absolute configuration of oxazole was determined in this way. Hydrolysis of oxazole under acidic condition furnished amide, that (*S*)-amide can be synthesized by coupling of (*S*)-2-hydroxy-3-methyl butanoic acid with the glycine amide under classic conditions. Comparison of the sign of optical rotation allowed to assign oxazole configuration.

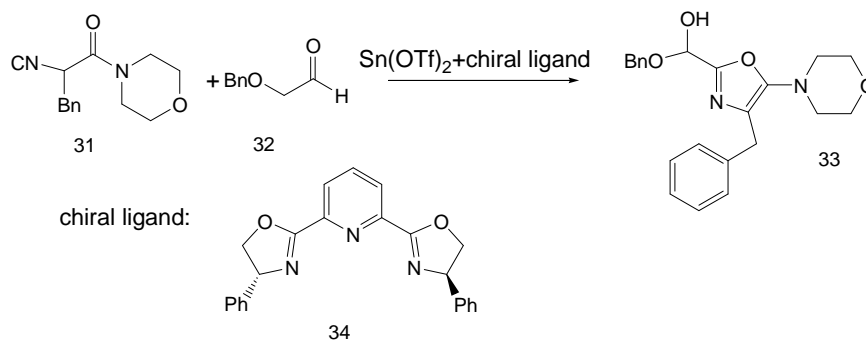
An efficient phosphoric acid-Al complex-catalyzed α -addition of α -isocyanoacetamides **26** to aldehydes for the synthesis of enantio-enriched 2-(1-hydroxyalkyl)-5-amino-oxazoles **28** has been reported (Scheme 8). Eleven examples were described to have between 50-87% *ee* and 75-97% chemical yield [9].

Wang also reported another Lewis acid catalyzed

condensation between α -isocyanoacetamides and aldehydes using an enantioselective version [Sn-(*R*)-Ph-PyBox](OTf)₂ **34** leading to the corresponding 5-amino-2-(1-hydroxyalkyl) oxazole **33** with *ee* values of up to 80% [10]. The reaction between **31** and **32** at -40 °C afforded the desired oxazole **33** in 63% yield and 80% *ee* (Scheme 9). It is interesting to note that a catalyst formed *in situ* from a combination of **34** and Cu(OTf)₂ was capable of catalyzing the P-3CR with simple isocyanides to give the α -acyloxyamide with excellent *ee* values. These results illustrated the significant difference between simple isocyanide and α -isocyanoacetamides in the development of chiral catalysts. The presence of the amide function in α -isocyanoacetamide might interfere with the metal coordination sphere, consequently leading to a different



Scheme 8



Scheme 9

chiral environment.

Mihara [11] developed a new heterobimetallic Ga(O-*i*Pr)₃/Yb(OTf)₃/Schiff base complex for catalytic asymmetric α -addition of α -isocyanoacetamides **36** to aryl, heteroaryl, alkenyl and alkyl aldehydes (88-98% *ee*) (Scheme 10).

Asymmetric Condensation

Chiral-pincer complexes represent a promising new tool in asymmetric catalysis. These species are characterized by strong metal to ligand bonding and a well-defined stoichiometry, which allows an efficient fine-tuning of the catalytic properties and rational ligand design.

The asymmetric condensation of isocyanoacetate **39** and sulfonimines **40** using chiral BINOL and biphenantrol-based palladium-pincer complex was studied by Aydin and co workers [12]. They have investigated the role of the substituent pattern and chirality of the BINOL/biphenantrol ligands on the stereo- and enantioselectivity of the reactions. The chiral palladium catalysts remained completely unchanged in the reaction studied. This suggests that catalyst can be completely recycled after the completed catalytic process. Changing chiral pincer complexes leads to produce each enantiomer predominantly. Using **41** the major enantiomer is (2*S*,3*S*)-*syn* and **42** produce (2*R*,3*R*)-*syn*. The formed imidazoline products can be readily hydrolyzed to the corresponding α,β -diaminoacid derivatives (Scheme 11).

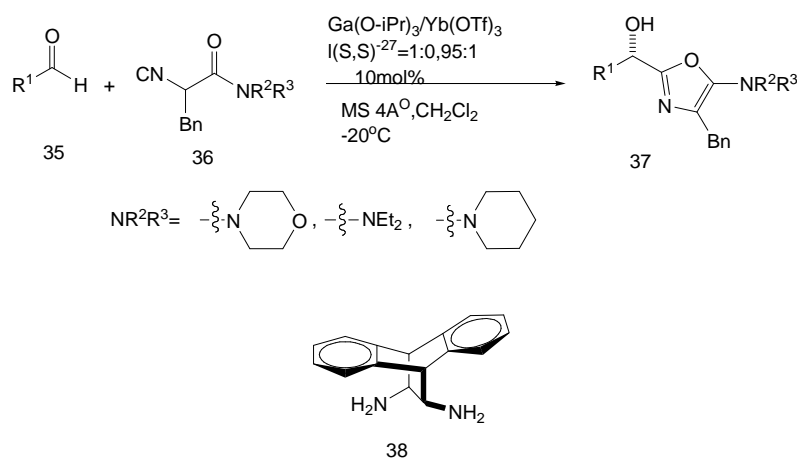
The condensation reaction between various imines and

isocyanoacetate **39** could easily be performed at room temperature in the presence of catalytic amounts (1 mol%) of palladium pincer complexes affording 2-imidazoline derivatives [13]. The reaction proceeds rapidly at 20 °C without addition of base or other additives. The stereoselectivity of the condensation reaction is strongly dependent on the applied pincer ligand. Using the electron-deficient and relatively bulky PCP complex **44** the major product is the *syn* form; however the diastereoselectivity is reversed on applying SeCSe-based catalyst **45**. The condensation reaction proceeds with a poor regioselectivity using common palladium salts such as Pd(OAc)₂, providing mainly the *anti* product (Scheme 12).

LEWIS ACIDS

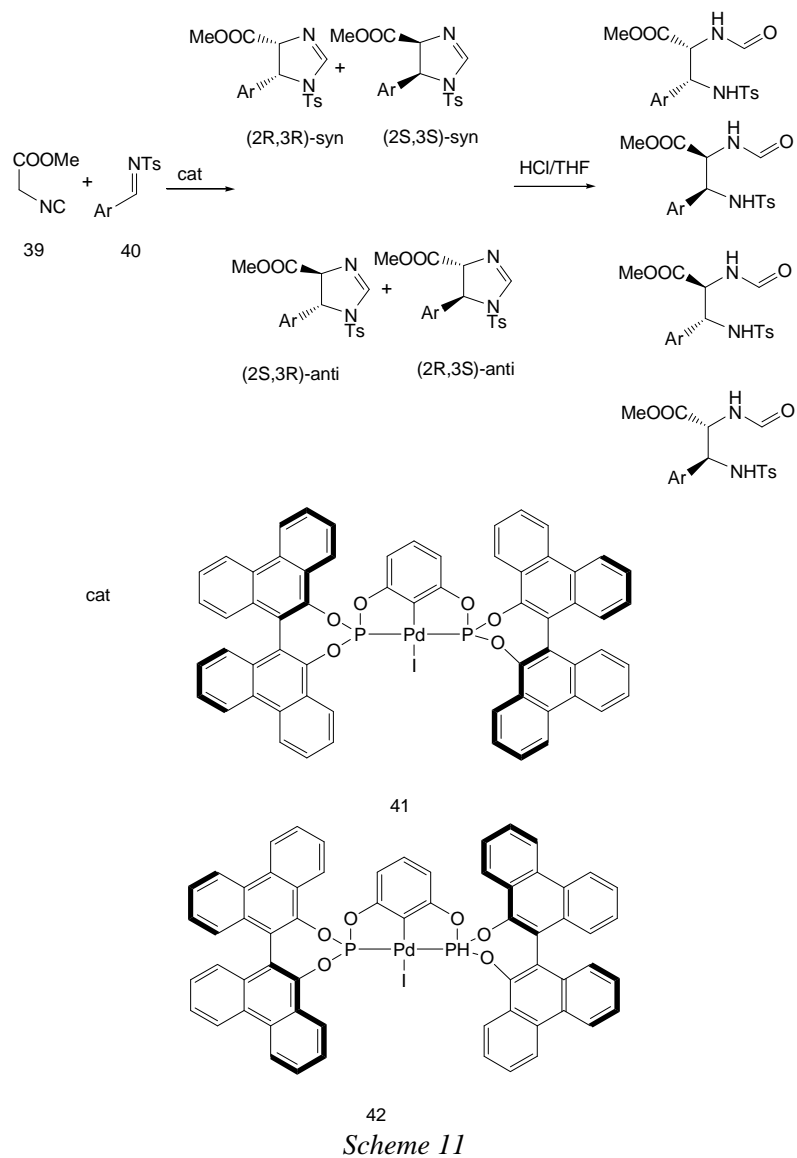
Lewis acid-mediated reactions can be classified into two groups. In the first the complex between substrate and Lewis acid reagent produces the product (type1). Some complexes formed between Lewis acids and substrates are, however, stable enough to react with a variety of reagents from outside the system to generate the product (type2) [14].

Isocyanides could serve as an electrophile and in order to broadening the range of nucleophiles used in this α -addition reaction should further increase the synthetic utility of isocyanides. A simple strategy toward achieving this goal would be enhancing the electrophilicity of isocyanides by

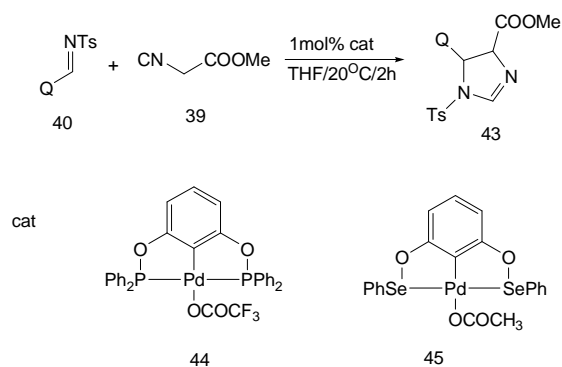


Scheme 10

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 11



Scheme 12

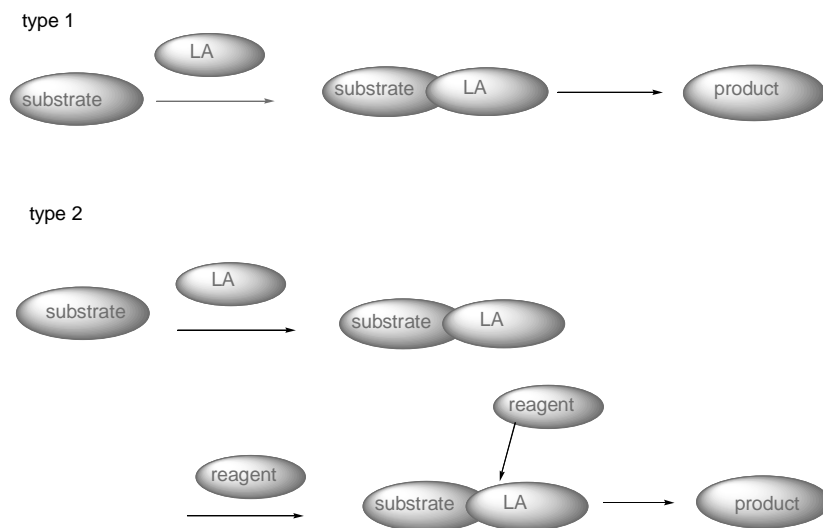
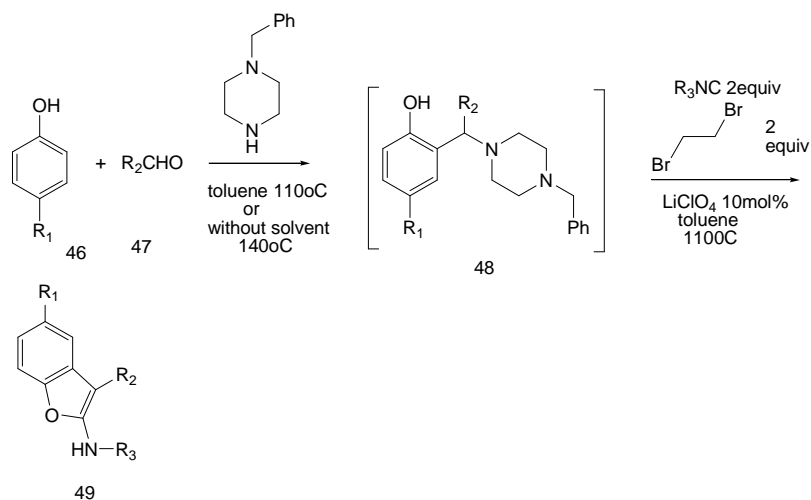


Fig. 1



Scheme 13

Lewis acid complexation.

Group(I) Lewis Acids

Li(I) Lewis acids. Compared with representative, conventional Lewis Acids such as TiCl_4 , alkali metal Lewis Acids are relative newcomers to the group of Lewis Acids used for synthetic organic chemistry, and have been found to be interesting catalysts with inherent and milder Lewis acidity. Perchlorates are potentially explosive and should be handled

with special care [15].

El kaim and co-workers reported a new and efficient three-component one-pot coupling of phenols **46** with aldehydes and [4+1] cycloaddition of isocyanide with transient *o*-quinone methide **48** in the presence of lithium perchlorate as a catalyst to produce aminobenzofuranes [16]. The lithium salt could catalyze both generation and trapping of the *o*-quinonemethide (Scheme 13).

They also synthesized amidophosphonate *via* two step

Mannich/Ugi one-pot procedure under solvent free condition [17]. Amidophosphonates **52** are prepared from primary amines **51**, dialkyl phosphates and carbonyl compounds under LiClO_4 catalysis. After completion, addition of an isocyanide, an aldehyde and acetic acid give access to phosphonate Ugi type adduct in good to moderate yield (Scheme 14). Lithium perchlorate in combination with carboxylic acids allow the Ugi reaction to proceed.

Group (IV) Lewis Acid

Titanium(IV) Lewis acids. The utility of titanium compounds as Lewis acids has been widely accepted in organic synthesis. Compounds of the type TiX_4 are usually used as titanium(IV) Lewis acids; the Lewis acidity is changed from mild to strong by changing the anionic group X in TiX_4 . The Lewis acidity is changed from mild to strong by changing X from alkoxide to halide to OTf [18].

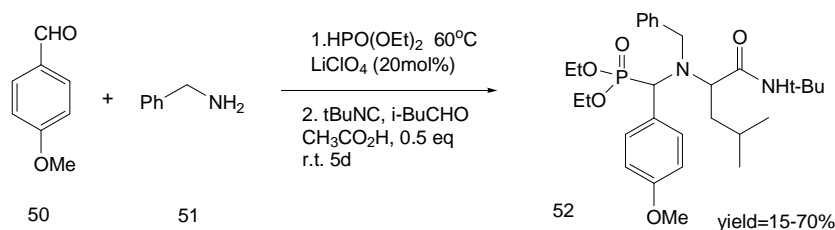
From the reaction of **53**, **54** and **55** in MeOH at 60 °C, Dai obtained an inseparable mixture of the phenol-P-3CR product **56** with a minor byproduct **57** (Scheme 15).

In searching for conditions for selective formation of **57**,

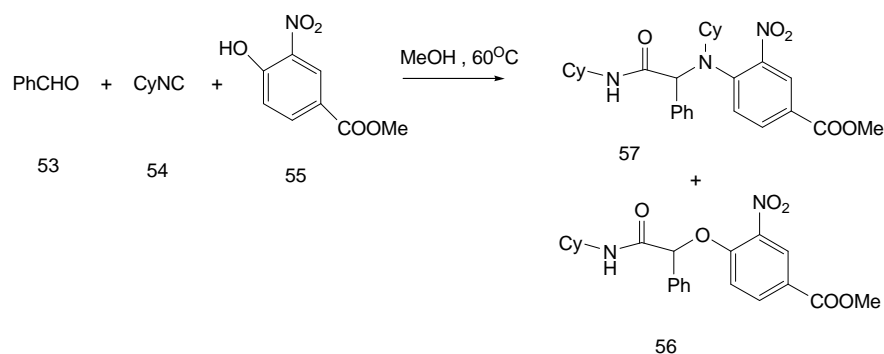
Dai *et al.* examined Lewis acid catalysis and found $\text{Ti}(\text{O}-i\text{-Pr})_4$ in protic solvent, MeOH, produce phenol-U-4CR product **58**. They find out that the reaction took place by using 10 mol% $i\text{-Pr}_2\text{NEt}$ in MeCN at 80 °C for 20 h to furnish phenol-P-3CR **59** (Scheme 16). In conclusion, the presence of a Lewis acid, the phenol-Passerini three-component reaction system is found to deliver a product of the phenol-Ugi four-component reaction.

In continue, Die and his group tried to report on formation of the carboxylic acid-derived U-4CR products from the P-3CR system without an added amine. The reaction proceed in MeOH at 40 °C in the presence of 5 mol% $\text{Ti}(\text{O}-i\text{-Pr})_4$ and obtained the U-4CR product. It is the first demonstration of an isocyanide as an amine equivalent in isocyanide-based multi component reaction (Scheme 17). The U-4CR product **61** was formed in 60% yield. An inseparable mixture of two minor products P-3CR **62**, mandelic acid methyl ester **63** were obtained [19].

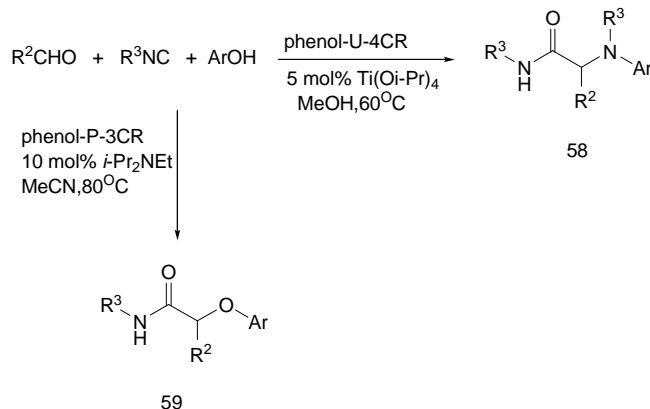
Kalinski *et al.* reported synthesis of anticancer drug (*R,S*)-bicalutamide **66** from commercially available material with a good overall yield. 1-(4-Fluorophenylsulfonyl)propane-2-one



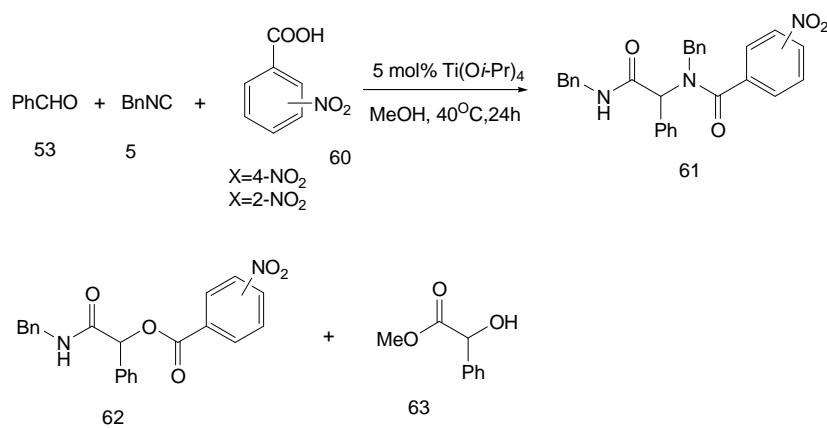
Scheme 14



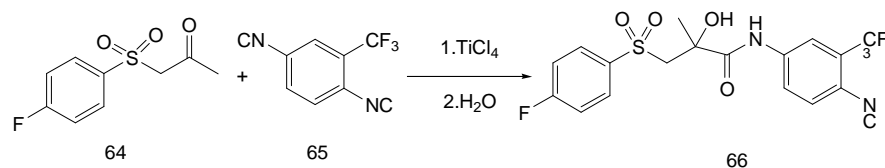
Scheme 15



Scheme 16



Scheme 17

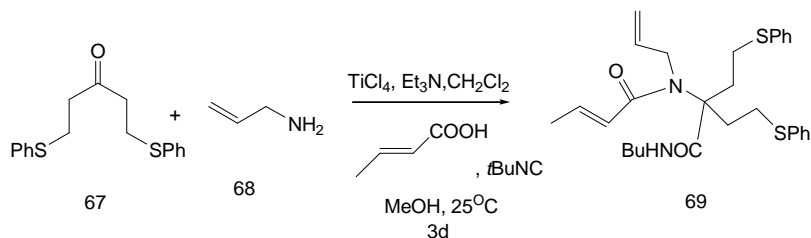


Scheme 18

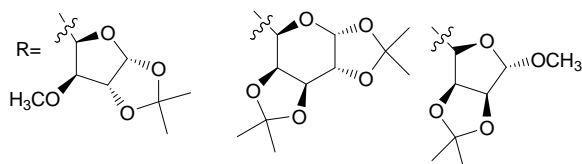
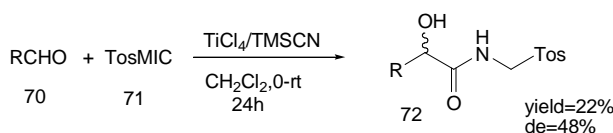
64 was prepared by oxidation of 4-fluorophenylthioacetone with 3-chloroperoxybenzoic acid, the reaction proceeded smoothly with a yield of 92% (Scheme 18). The reaction with 4-cyano-3-(trifluoromethyl)phenyl isocyanide **65** can be promoted by titanium tetrachloride. It has been shown that isocyanide was combined with titanium tetrachloride to form the initial adduct then the carbonyl was added [20].

A reaction in which ketone **67** was condensed with allylamine **68** in the presence of TiCl_4 and triethyl amine has been conducted, and the resultant imine was allowed to react with the carboxylic acid and the isocyanide to provide the allylic amine **69** in 65% yield (Scheme 19). Their goal was getting the participation of ketones in either stepwise or one-pot Ugi MCR to give good to excellent yields of adducts

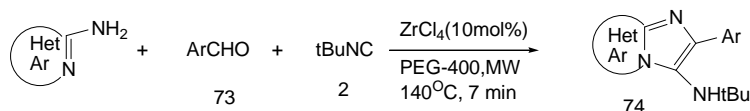
Catalytic Multicomponent Reactions Based on Isonitriles



Scheme 19



Scheme 20



Scheme 21

having a number of different functional groups [21].

Radha Krishna introduced TosMIC for the first time as a novel isonitrile component in diastereoselective Passerini reaction [22]. A two-component Passerini reaction was performed between 1,2-*O*-isopropylidene-3-*O*-methyl- α -D-xylo-pentodialdo-1,4-furanose **70** and TosMIC **71** under Seebach reaction condition to produce amide **72** (Scheme 20).

Zr(IV) Lewis acids. The number of articles on Zirconium Lewis acids is much smaller than that on Titanium, an element in the same group. Zirconium Lewis acids are often mild, which enables to get the reaction done with moderate to good selectivity [23].

Guchhait *et al.* described a microwave-promoted Ugi-type multi component synthesis of *N*-fused imidazoles catalyzed by ZrCl_4 (Scheme 21). The optimized protocol was then tested for

its regioselective efficiency. Very interestingly, 2-amino-pyrimidine in this method catalyzed by ZrCl_4 in PEG-400 afforded the highly regioselective formation of 2-*tert*-butylaminoimidazo[1,2-*a*]pyrimidines over 3-amino regioisomeric products in almost 8:1 ratio with high yields. The reason for regioselective formation of products can be speculated that PEG-400, being polar solvent, stabilizes preferentially the ionic iminium intermediate and ZrCl_4 acting as Lewis acid of high cationic charge potential enhances the formation of pyrimidine-2(1*H*)-imine tautomeric form of 2-aminopyrimidine [24].

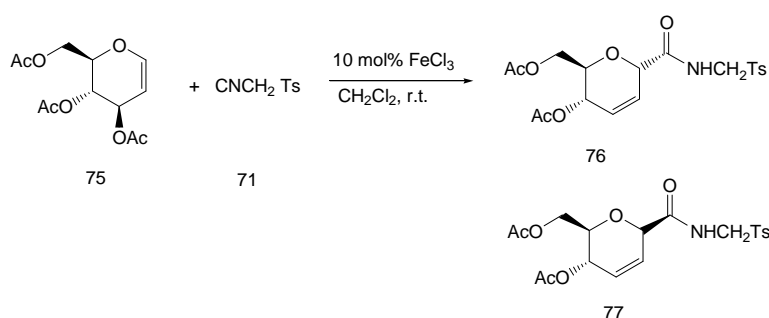
Group (VIII) Lewis Acids

Iron(III) Lewis acids. A novel method for the synthesis of *C*-pseudoglycals from glycals and isonitriles using a catalytic

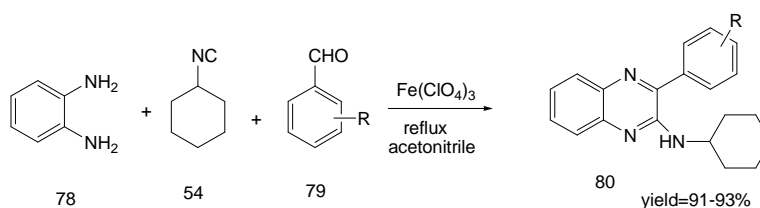
amount of FeCl_3 under mild reaction condition with high α -selectivity has been described [25]. This is the first report on carbon-Ferrier rearrangement using isonitrile as nucleophiles (Scheme 22).

The reaction of 3,4,6-tri-O-acetyl-D-glucal **75** with TosMIC in the presence of 10 mol% of FeCl_3 was complete within 30 min, and the desired product was obtained in 92% yield as a mixture of α -**76**, β -**77** anomers in a 9:1 ratio favoring α -**76** anomers [25].

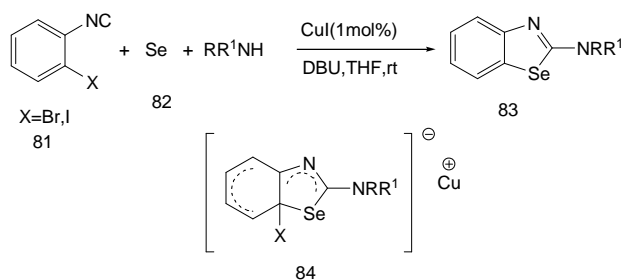
The three-component condensation of cyclohexyl isocyanide **54**, an aromatic aldehyde **79** and *o*-phenylenediamine **78** in the presence of a catalytic amount of ferric perchlorate in acetonitrile to afford *N*-cyclohexyl-3-aryl-quinoxaline-2-amines **80** in good yield have been developed in our laboratory (Scheme 23). In the last step catalytic oxidation was performed by ferric perchlorate [26].



Scheme 22



Scheme 23



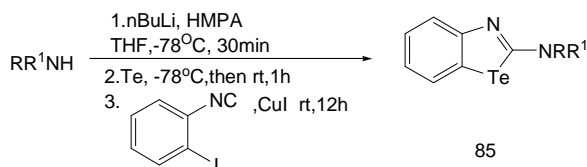
Scheme 24

Group (11) Lewis Acids

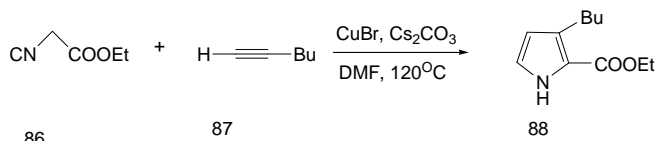
Copper, one of the earliest metals known to mankind, forms a variety of compounds with hydrogens, oxygen, nitrogen, phosphorus, and sulfur donors. Copper, a group 11 metal, can generally exist in three oxidation states; Cu(0), Cu(I) and Cu(II). The Lewis acidity of copper depends on its oxidation state and on the counter ion [27].

Cu(I) Lewis acids. Fujiwara *et al.* developed simple and practical method for the synthesis of 1,3-benzoselenazoles **83** and 1,3-benzotellurazoles **85** having a heteroatom substituent at the 2-position by the copper (I)-catalyzed reaction of 2-bromophenyl or 2-iodo phenyl isocyanides **82** with selenium and heteroatom nucleophiles (Scheme 24). The role of CuI is not clear but Cu^+ may stabilize intermediate or facilitate elimination of the halogen atom from **84** [28]. 1,3-Benzotellurazoles **85** could be prepared according this

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Scheme 25



Scheme 26

procedure (Scheme 25).

The reaction between 1-hexyne **87** and ethyl isocyanoacetate **86** at $120^\circ C$ produce ethyl 3-butylpyrrolcarboxylate **88** in 29% yield in the presence of $CuBr$ and cesium carbonate as a base (Scheme 26). The reaction of **39**, **89** providing pyrroles **90** in 89% yield within 2 h in the presence of $CpCuP(PMe)_3$ as a catalyst (Scheme 27) [29].

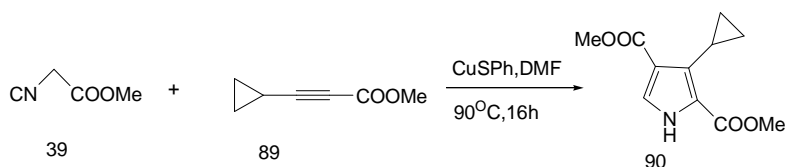
A novel copper-catalyzed synthesis of benzimidazoles **93** from *o*-bromoaryl isocyanides **91** and primary amines **92** has been described (Scheme 28). In this reaction copper catalyzed addition of an amine onto an isocyano group produced intermediate **94** that followed by intramolecular arylation. 2-Bromo-3-isocyanothiophene also can be employed in this reaction [30].

Ligands are employed in copper-catalyzed arylation of

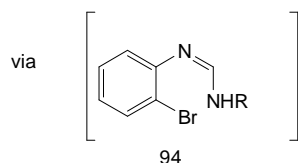
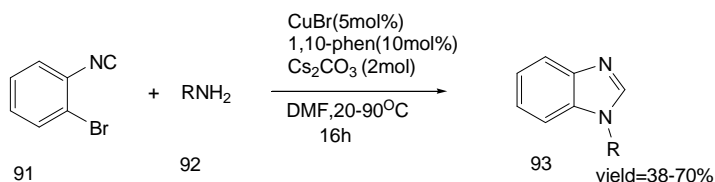
amines. Although the ligand effect was not as significant as one would have imagined.

Yoo *et al.* reported α -aryl β -hydroxy imidates **99** by the four-component reaction of ethyl glyoxalate **95**, aryl acetylenes **96**, sulfonyl azides **97** and alcohols **98** using a copper catalyst (Scheme 29). Copper would catalyzed cycloaddition of 1-alkyne and sulfonyl azide (first step of proposed mechanism) and produce triazole species **100** that loss N_2 and after addition of nucleophile the resultant product would be obtained. β -Hydroxy imidates are amenable to perform Pd-catalyzed [3,3]-sigmatropic rearrangement under mild condition to give *N*-allyl-*N*-sulfonamide in a good yield [31].

A catalytic system for synthesis of *N*-aryl imidazoles **103** through cross cycloaddition between two isocyanides obtained from ethyl *N*-formylglycine esters **101** and *N*-arylformamides **102** has been designed. Phosphorus oxychloride and triethyl



Scheme 27



Scheme 28

Catalytic Multicomponent Reactions Based on Isocyanides

Ag(I) Lewis acids. Silver(I) salts have mild Lewis acidity and have been used as promoters and catalysts in organic synthesis. Among these, salts AgNO_3 , AgClO_4 , AgBF_4 , AgOTf are the most popular reagents [35].

Chen and co workers reported an efficient tandem reactions of 2-alkynylbenzadoximes **112** with isocyanides co-catalyzed by silver triflate and bismuth triflate to produce *N*-(isoquinolin-1-yl)formamides **114** in good to excellent yields (Scheme 33).

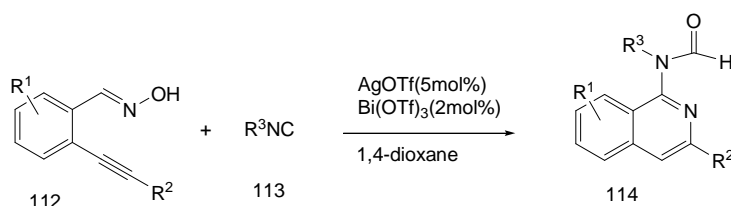
Silver triflate was the best one for the generation of isoquinoline *N*-oxides **115** and bismuth triflate was not effective for this transformation and used for the next step (Scheme 34) [36].

El kaim described for the first time that isocyanide can be synthesized and used without further purification in a one-pot four-component process to afford Ugi-type adducts. The isocyanide formation was catalyzed by silver cyanide and the

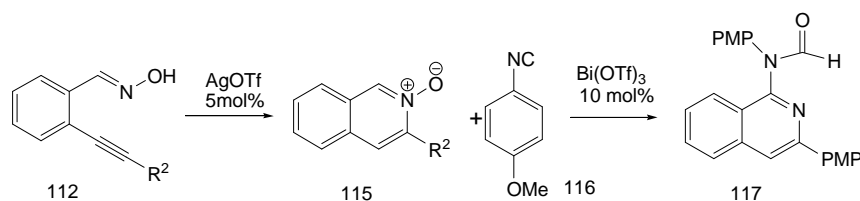
resulting mixture was directly used in Ugi-smiles coupling reaction (Scheme 35). However, it is worth noticing that similar results were obtained using iron(II) cyanide in *N*-methyl pyrrolidone at 110 °C [37].

The reaction between amine **51**, ketone **121** and isocyanamide **122** in methanol at room temperature in the presence of a catalytic amount of AgOAc mainly afforded 2-imidazoline **123** (Scheme 36). The increasing amount of catalyst had a negative effect on the 2-imidazoline formation [38].

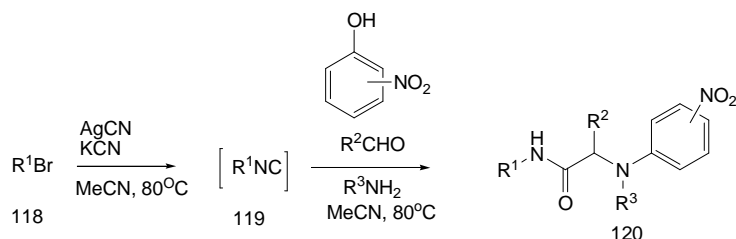
A multicomponent reaction between α -acidic isocyanides **126**, primary amines **125**, and carbonyl compounds **124** under 14 different solvents to produce 2*H*-2-Imidazoline **127** in good yields, has been studied. AgOAc is an efficient catalyst for this reaction (Scheme 37). However, most of the reactions performed very well without this catalyst [39].



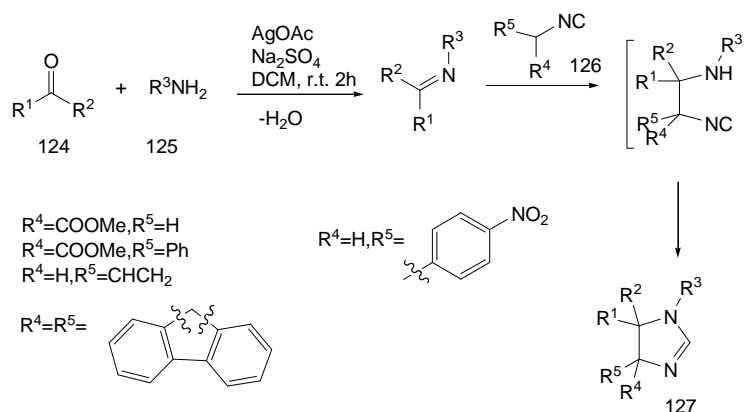
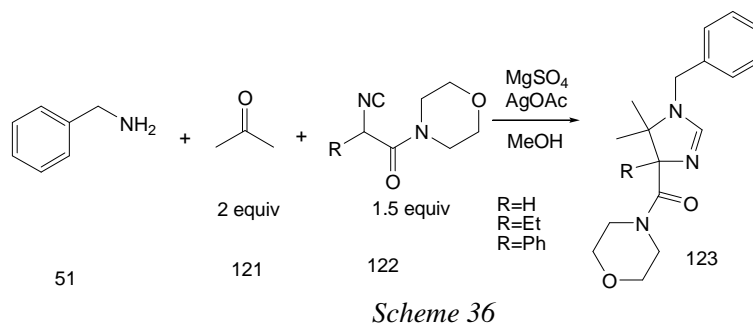
Scheme 33



Scheme 34



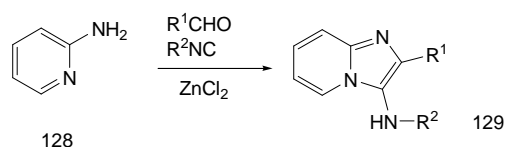
Scheme 35



Group (12) Lewis Acids

Zn(II) Lewis acids. Roussea described the use of zinc chloride, a cheap catalyst, to catalyze one-pot preparation of imidazo[1,2-*a*]pyridines **129** using either conventional heating or microwave irradiation (Scheme 38). This reaction with most aldehydes was catalyzed successfully but some aldehydes such as nicotinaldehyde did not go to completion and the only product isolated from the reaction was the intermediate. Attempts to convert the imine isolated from this reaction to the desired product using a variety of catalyst afforded only low yield of the product, suggesting that zinc chloride forms a stable complex with this imine once it is formed. In order to solve this problem Montmorillonite clay K10 was used as the catalyst in the reaction with nicotinaldehyde [40].

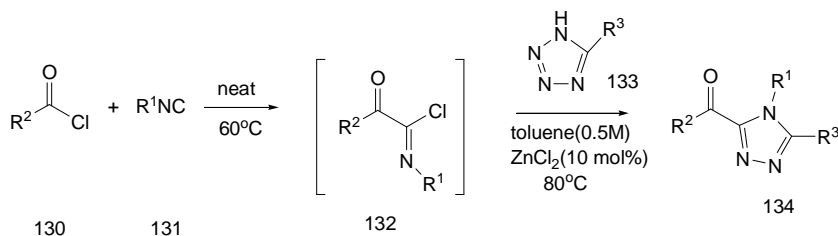
El kaim *et al.* also reported a new three-component reaction involving Nef-Huisgen cascade. The first step is the α -addition of acyl chlorides onto isocyanides (Nef reaction)



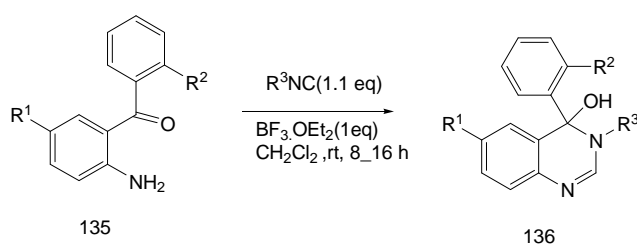
and the resulting imidoyl chloride was prepared. The following Huisgen step was performed in 0.5 M toluene and zinc chloride was introduced as a molar solution in THF. Conversion to the final triazole was achieved by heating overnight at 80 °C (Scheme 39).

Adduct **134** might be trapped by nucleophiles. Due to the poor nucleophilic behavior of neutral tetrazole **133** and to increase the electrophilicity of the Nef adduct under Lewis acid activation appeared to be the best approach. In order to achieve that zinc chloride was used to produce 1,2,4-triazoles **134** as a product [41].

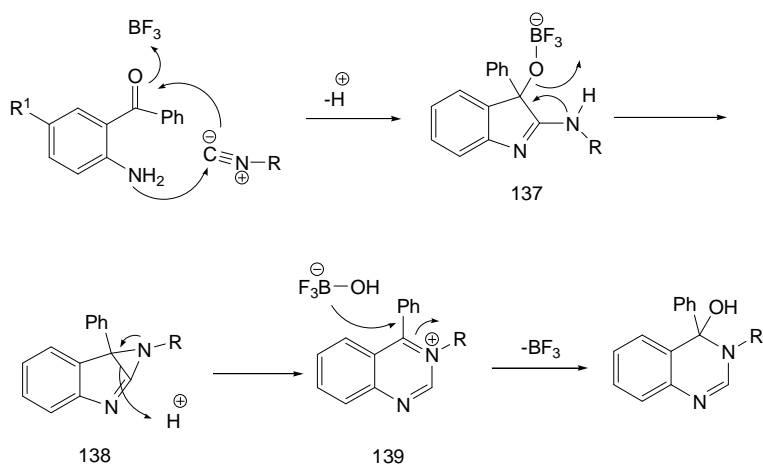
Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 39



Scheme 40



Scheme 41

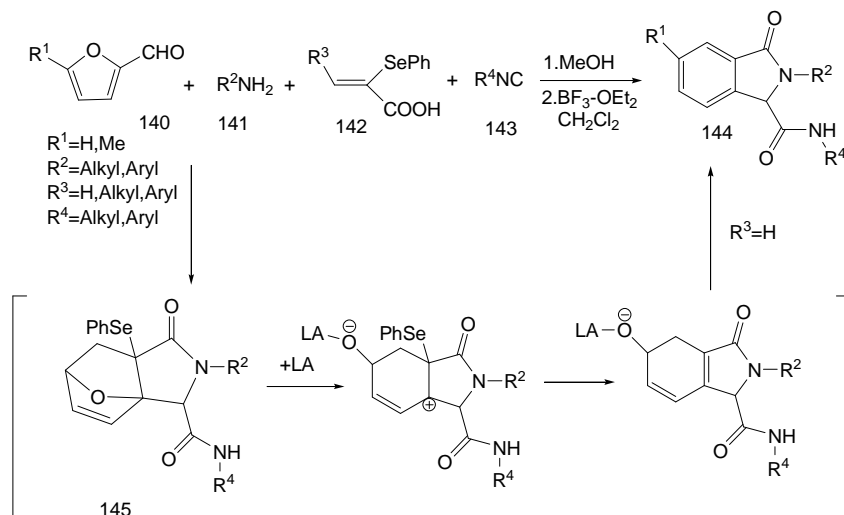
Group (13) Lewis Acids

B(III) Lewis acids. The classical boron Lewis acids, BX_3 are now popular tools in organic synthesis. B(III) can act as a Lewis acid because there is an empty p-orbital on the boron. The BF_3 and BCl_3 complexes of diethyl ether are less stable than those of dimethyl ethers [42].

Krasavin described a novel $BF_3 \cdot OEt_2$ -promoted reaction of *o*-aminobenzophenones **135** with aliphatic isocyanides to produce 4-Aryl-4-hydroxy-3,4-dihydroquinazolines **136** in

good to excellent yields (Scheme 40) [43].

The mechanism requires an initial three-center, two component Passerini-type reaction with subsequent skeletal rearrangement (Scheme 41). The overall process is promoted efficiently by the strong Lewis acidic boron trifluoride, the oxophilic character of which is required for the formal dehydration of **137**. Milder Lewis acids (especially Bronsted acids) do not promote this process efficiently, probably due to their inability to trigger the skeletal rearrangement of **137**.



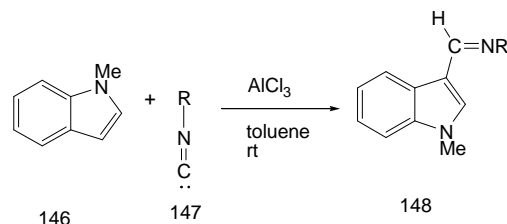
Scheme 42

Relieving strain in **138** could be a substantial driving force for the proposed skeletal rearrangement.

A one-pot synthesis of substituted isoindolinones **144** from 2-furaldehyde **140**, amines **141**, 2-(phenylselenanyl)acrylic acids **142**, and isocyanides **143** has been developed (Scheme 42). The tandem process involves the Ugi four-component condensation/Diels-Alder Cycloaddition, and subsequent deselenization-aromatization promoted by $\text{BF}_3 \cdot \text{OEt}_2$. The Ugi/Diels-Alder reaction was performed in methanol at 25 °C to afford **145**. Traditional methods applied to deselenization did not give desired product. Then Huang used $\text{BF}_3 \cdot \text{OEt}_2$ to perform deselenization/aromatization steps [44].

Al(III) Lewis acids. Because of their availability and low cost, aluminum Lewis acids have been widely used in academia and industry [45].

Tobisu *et al.* reported that Lewis acid promote the addition of weak nucleophiles, specifically, electron-rich aromatic compounds such as 1-methyl indole **146**, onto isocyanides to produce imine **148** (Scheme 43). This reaction promoted by inexpensive Lewis acids, such as AlCl_3 . The method can provide a direct and practical access to a wide array of imines *via* aromatic C-H bond functionalization. The reaction can be extended to other electron-rich aromatics, including pyrroles and thiophenes, which furnish the desired product. The imines are amenable to undergo [4+2] cycloaddition with



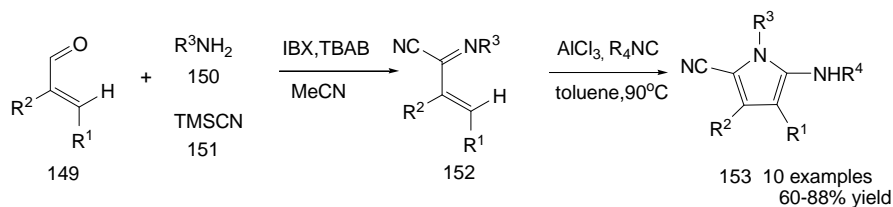
Scheme 43

Danishefsky diene [46].

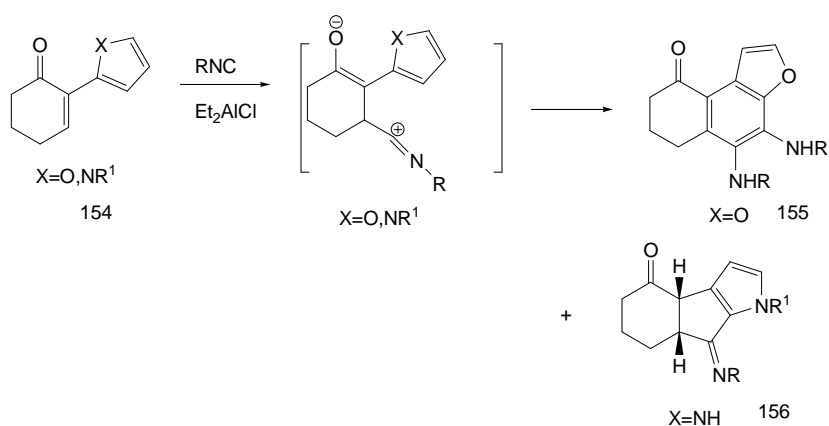
A novel synthesis of 5-amino-2-cyanopyrroles **153** by way of sequential MCR/Cycloaddition strategy has been reported. Heating a toluene solution of α,β -unsaturated imidoyl cyanides **152** (2-cyano-1-azadienes) and isocyanides in the presence of 10 mol% AlCl_3 at 90 °C. [4+1] cycloaddition between **152** and isocyanide occurred with good to excellent yields. The α -iminonitriles **152** were prepared from the respective α,β -unsaturated aldehydes **149**, amines **150**, and TMS-CN **151**. The use of IBX and TBAB was crucial for the success of the oxidative Strecker reaction (Scheme 44) [47].

Winkler and co-worker synthesized novel heterocyclic structures *via* the reaction of *S*-trans enone **154** bearing an internal nucleophilic moiety, *i.e.*, furan or pyrrole with isocyanides. Products formally result from either [4+1] or [4+1+1] cycloaddition products (Scheme 45). The effect of the

Catalytic Multicomponent Reactions Based on Isocyanides



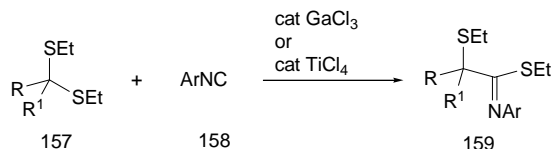
Scheme 44



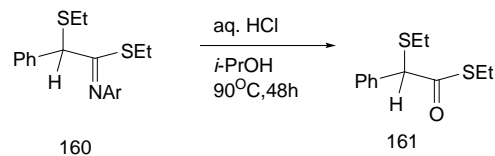
Scheme 45

alkyl substituent of the isocyanide was examined. Increasing the steric effect of the alkyl group R could disfavor the addition of a second equivalent of isocyanide that would promote the formation of monoaddition product **156**. In one of derivatives replacement of diethyl aluminium chloride with stoichiometric or catalytic gallium chloride afforded **155** and none of the monoaddition product was observed [48].

Ga(III) Lewis acids. Tobisu *et al.* demonstrated TiCl_4 - and GaCl_3 catalyzed insertion reaction of isocyanides into C-S bonds in dithioacetals **157** to produce thioimidates **159** (Scheme 46). They envisioned that dithioacetals might be promising candidates in view of the fact that cleavage of the C-S bond in dithioacetals is promoted by the Lewis acid.



Scheme 46



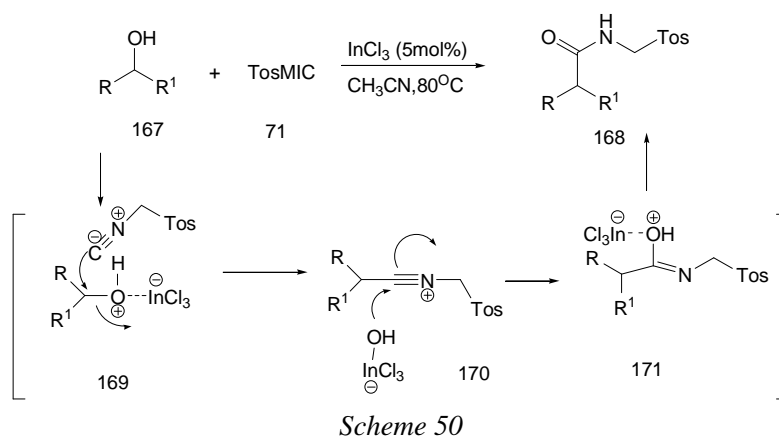
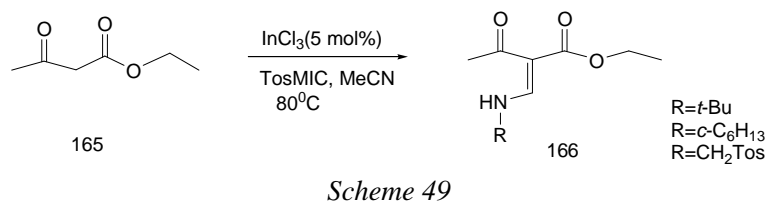
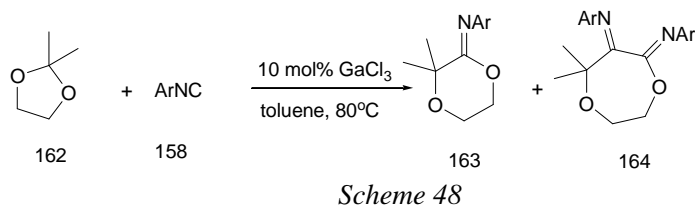
Scheme 47

In this reaction isocyanide behave as a C1 component. In this reaction double-insertion product might be produced and to suppress it slow addition of isocyanide is necessary. TiCl_4 also proved to be an active catalyst for the selective formation of monoinsertion product.

The resultant thioimidates **160** can be converted into the corresponding Thioesters **161** under acidic conditions (Scheme

47) [49]. GaCl_3 can be used for insertion reaction into the C-O bond in cyclic acetals (Scheme 48) [50].

In(III) Lewis acids. Indium(III) are known as mild, soft, and chemically stable Lewis acids and applied in many organic reactions. Krishna have developed an efficient InCl_3



C-C coupling reaction between 1,3-dicarbonyl compounds and TosMIC as a new electrophile for the synthesis of β -keto-(*E*)-enamino esters **166** in good to excellent yields (Scheme 49). The choice of Lewis acid was important in this reaction because *p*-toluenesulfonylmethyl isocyanide decomposes under strong Lewis acid condition [51].

While β -diketones or keto esters displayed good reactivity under these reaction conditions, the diesters remained unreacted probably due to lower acidity and enolizability. TosMIC was the only isocyanide to have reacted under the said reaction condition due to the multiple reactivity of TosMIC.

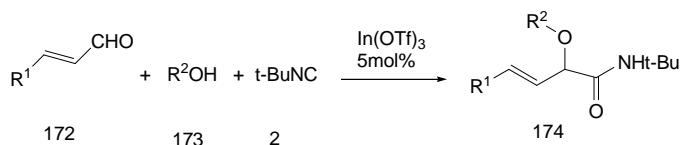
A novel synthetic protocol is reported which leads to the formation of amides **168** from the corresponding aryl alcohols **167** and TosMIC in the presence of Lewis acid catalysis.

The interesting reactivity of isocyanide serving both as an electrophile and nucleophile is exploited here. The Lewis acid coordinates with the alcohol **169** due to its greater nucleophilicity, thereby generating carbocation, to facilitate nucleophilic attack of TosMIC onto **169** resulting in intermediate **170**. Next the alcohol adds to the more electrophile isocyanide carbon to generate the corresponding *N*-substituted acetimidic acid **171** which tautomerises to the stable *N*-substituted amide with regeneration of catalyst [52].

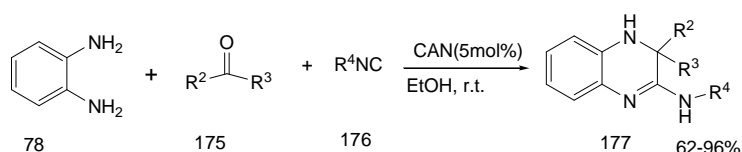
A direct alkylation P-3C reaction of aldehydes, isocyanides and free aliphatic alcohols in the presence of Indium triflate as a Lewis acid catalyst to produce α -alkoxy amide **174** derivatives has been developed (Scheme 51).

This is the first example of the Passerini-type reaction

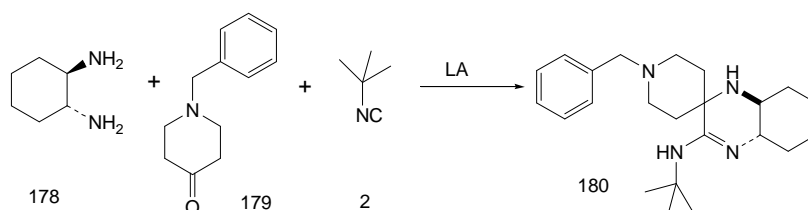
Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 51



Scheme 52



Scheme 53

using free aliphatic alcohols instead of carboxylic acid component [53].

CAN catalyzed reaction. The reaction between *o*-phenylenediamines **175**, ketones and isocyanides were efficiently catalyzed by CAN at room temperature to afford highly substituted 3,4-dihydroquinoxaline-2-amine derivatives **177**. The carbonyl group could be activated by the coordination of the oxygen atom with CAN , thus could facilitate the formation of iminium cation (Scheme 52).

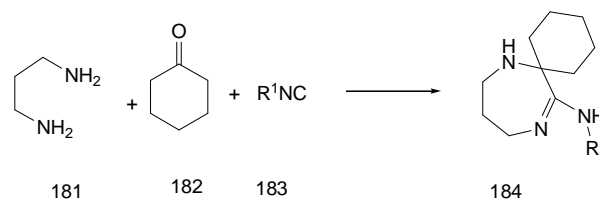
Although $\text{Ce}(\text{IV})$ derivatives are generally employed as single electron transfer (SET) oxidants, we believe CAN serves as Lewis acid in the above processes the same as in other carbon-carbon and carbon-heteroatom bond forming reactions [54].

Metal Free Lewis Acids

TMSCl. The applicability of TMSCl as an efficient equimolar promoter of isocyanide-based multicomponent reaction and reagent, which often appears to be only workable metal free Lewis acid alternative to traditional Bronsted acid catalysts.

Kysil reported a novel TMSCl -promoted multicomponent reaction of *trans*-cyclohexane-1,2-diamine **178** with 1-benzyl-1-piperidone **179** and *tert*-butyl isocyanide **2** that leads to the variety of unique highly functionalized scaffolds with 3,4,5,6-tetrahydropyrazine-2-amine **180** core. These scaffolds are open for further transformation due to an already existing secondary amino-group in their structure (Scheme 53). Silicon Lewis acids have ability to activate carbonyl and imine bonds for an interaction with C-nucleophiles [55].

When Kysil used 1,3-diaminepropane **181**, carbonyl compound **182** and isocyanides, which allows the synthesis of highly substituted 1,4-diazepine-2-amines including spiro heterocycles **184** (Scheme 54). Acidic catalysis is required for



Scheme 54

successful IMCRs. Various Bronsted and Lewis acids are able to promote reaction and TMSCl has been found to be the most efficient among them.

Side reactions could be minimized when TMSCl was used in equimolar ratio. This improved the reaction outcome in yield and purity of target compound and allowed isolation of target material employing chromatography free simple work-up and purification procedure [56].

Krasavin and co-workers tried to run the Groebke-Blackburn reaction with a representative starting material. Simple mixing of the three components in methanol and adding a methanolic solution of a mineral acid resulted in complex reaction mixtures with a target material content of less than 10%. They decided to run reaction using a Lewis acid as promoter instead, to produce 2-piperazin-1-yl imidazo [2,1-*b*] [1,3,4]thiadiazoles **186** (Scheme 55). Because TMSCl produces HCl in methanolic solution, they use aprotic solvent as reaction medium [57].

Krasavin also use TMSCl as a promoter for aminoquinoxaline synthesis, which have best results in comparison of other Lewis acid [58].

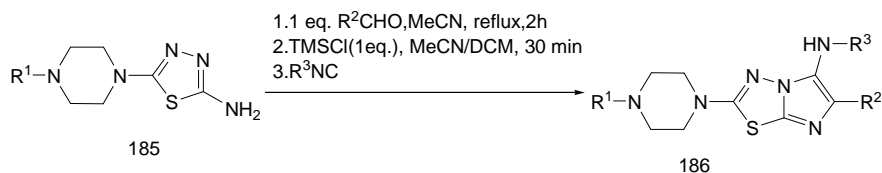
METAL CATALYSTS

Metal-mediated intermolecular reaction cascades proceeding *via* non-isolable intermediates such as catalytic organometallic species, are well suited for the design of “ideal” multi component reactions, those allowing the simultaneous addition of all reactants, reagents, and catalysts at the onset of the reaction with all reactants combining in a unique ordered manner under the same reaction conditions.

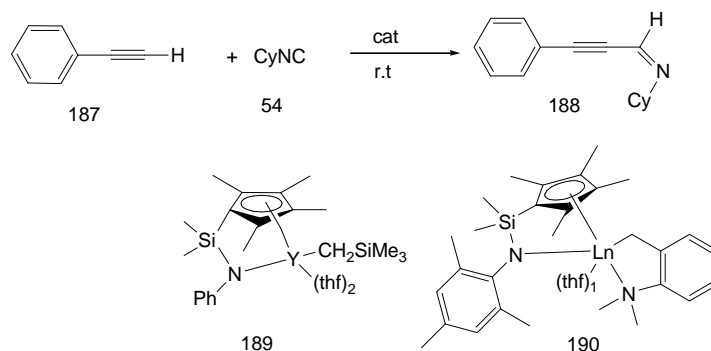
The 1,1-insertion of isocyanides into the C-H bond of terminal alkynes is a straightforward, atom economical route to conjugated 1-aza-1,3-enynes, which are compounds that are bifunctional and are useful synthons in organic synthesis.

Zhang *et al.* reported that half-sandwich rare earth metal complexes can also serve as excellent catalyst for the cross-coupling of isocyanides with terminal alkynes to give an unprecedented selective formation of (*Z*)-1-aza-1,3-enynes **188** (Scheme 56).

Among the rare earth metal complexes surveyed, The yttrium trimethylsilyl methyl complex showed the same activity as that of the aminobenzyl analogue, suggesting that



Scheme 55



Scheme 56

Catalytic Multicomponent Reactions Based on Isocyanides

the activity of the present catalyst system is not significantly affected by the initial alkyl group. If alkynes have a strongly electron-donating substituent, yttrium complex was less efficient and they used larger lanthanum instead [59].

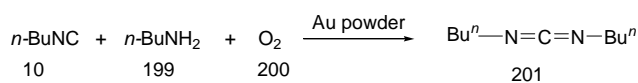
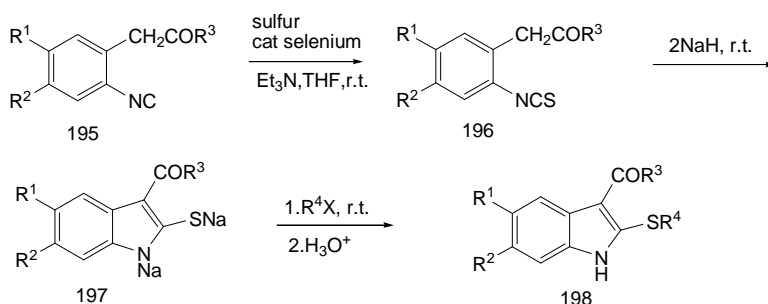
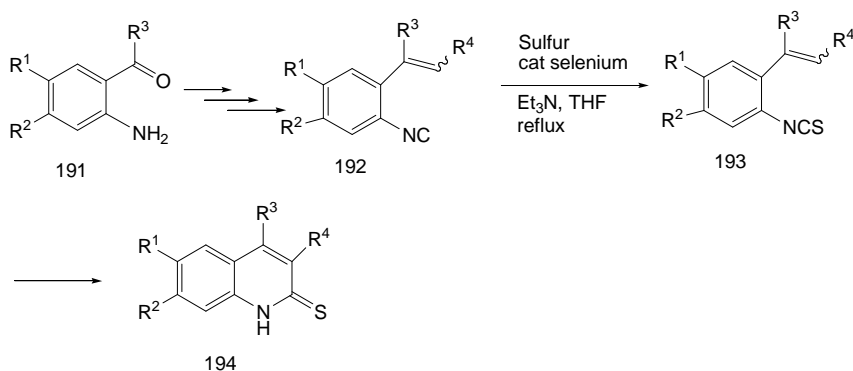
The synthesis of Quinoline-2(1*H*)-thiones **194** by treating α -substituted 2-isocyanostyrenes **192** with sulfur in the presence of a catalytic amount of Selenium has been reported (Scheme 57). α -Substituted 2-isocyanostyrenes was prepared from 2-aminophenyl aryl ketones **191** after three steps. 2-Isothiocyano-styrenes **193** underwent electrocyclic reaction to produce product in one-pot with moderate to good yields [60].

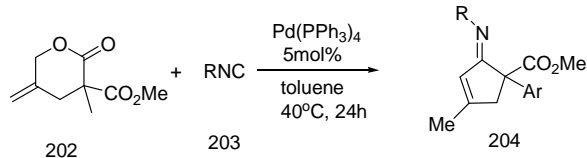
Fukamachi reported that (2-Isocyanophenyl)methyl ketones **195** or ethyl 2-(2-isocyanophenyl)acetates were converted into the corresponding isothiocyanoates **196** by

treatment with sulfur in the presence of a catalytic amount of selenium in tetrahydrofuran at room temperature. Then isothiocyanoates were treated with two equivalents of sodium hydride and then alkyl halides to give the desired indole derivatives **198** via a one-pot process (Scheme 58) [61].

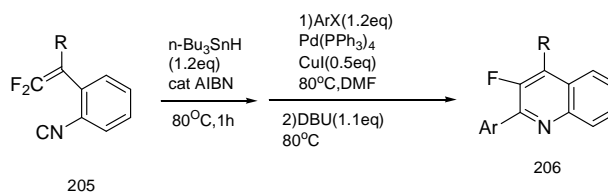
Reactions between isocyanides **10** and primary amines **199** to give formamides are sometimes catalyzed by metal ions. But when this reaction proceeded in the presence of Au powder and oxygen molecules, produces carbodiimides **201** (Scheme 59) [62].

Palladium-catalyzed decarboxylative [4+1] cyclization of γ -methylidene- δ -valerolactone **202** with isocyanides **203** to afford conjugated cyclopentenimines [63] has been developed.





Scheme 60



Scheme 61

When isocyanide **205** was treated with tributyltin hydride (1.2 equiv.) and a catalytic amount of AIBN in toluene at 80°C , 2-stannyl-3,4-dihydroquinoline was observed. We envisaged that the radical cyclization of β,β -difluoro-*o*-isocyanostyrenes would proceed in a normally less favorable *6-endo trig* fashion because of the polarization of their C-C double bond, giving rise to the construction of a quinoline framework. The coupling was conducted using a crude reaction mixture in DMF immediately after the completion of the radical cyclization and palladium-catalyzed coupling reaction occurred to prepare 2,4-disubstituted 3-fluoroquinolines [64].

ACIDIC CATALYST IN IMCR

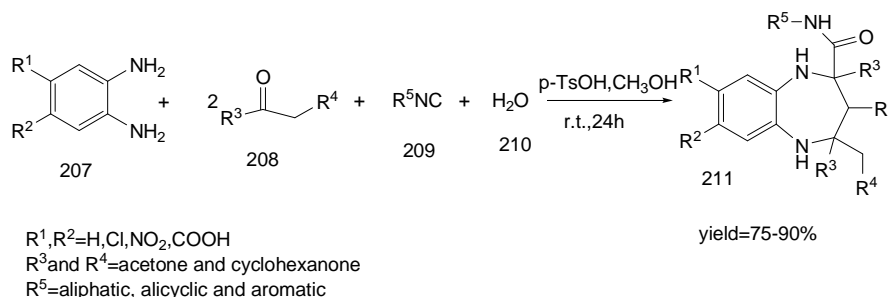
Sulfonic Acid Catalysis

Shaabani *et al.* reported a novel reaction between aromatic

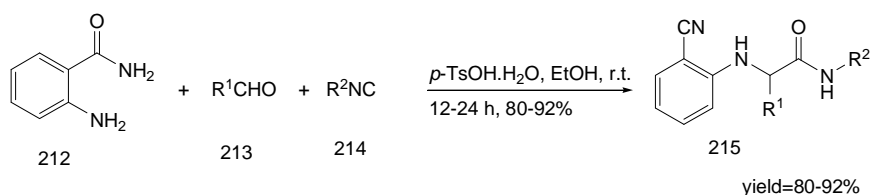
diamines **207**, a linear or cyclic ketones **208**, an isocyanide **209**, and water in the presence of a catalytic amount of *p*-toluenesulfonic acid at ambient temperature in a one-pot manner afforded 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-2-carboxamide derivatives **211** in good yield (Scheme 62) [65].

They also used this catalytic system to synthesize substituted cyanophenylamino-acetamide derivatives **215** in excellent yields from three-component condensation reaction between 2-aminobenzamide **212**, an aldehyde, and an isocyanide at room temperature in ethanol as a green medium (Scheme 63) [66]. This novel reaction can be regarded as an efficient approach for the conversion of primary amides to the corresponding nitriles.

4,5,6,7-Tetrahydro-1*H*-1,4-diazepine-5-carboxamide derivatives **219** synthesis by a new one-pot pseudo-five component condensation was described by Shaabani *et al.* A novel IMCR of readily available inputs including 2,3-



Scheme 62



Scheme 63

Catalytic Multicomponent Reactions Based on Isocyanides

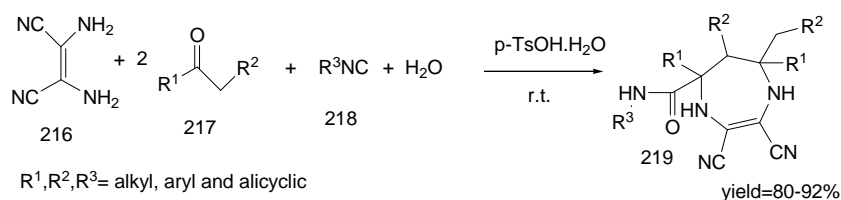
diaminomaleonitrile **216**, a cyclic or acyclic ketone, an isocyanide, and water in the presence of a catalytic amount of *p*-toluenesulfonic acid in aqueous medium at ambient temperature (Scheme 64) [67].

The reaction of diaminomalononitrile **216**, a ketone and an isocyanide in the presence of catalytic amount of *para*-toluenesulfonic acid produced spiro 1,6-dihydropyrazine-2,3-dicarbonitrile **222** in good yields (Scheme 65) [68].

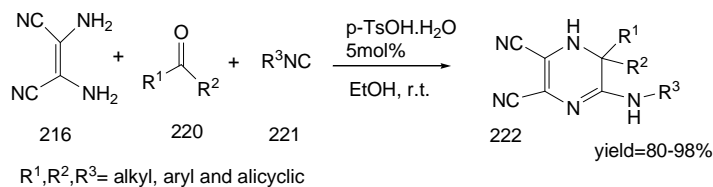
A tandem 3-CR/2-CR reaction sequence using DAMN **216**, a ketone, and an isocyanide component, which provides

1,6-dihydropyrazine-2,3-dicarbonitrile derivatives **222** in good yields. These products can be employed as one of the components in the reaction with an isocyanate or isothiocyanate leading to imidazo[1,5-*a*]pyrazine derivatives **224** (Scheme 66) [69].

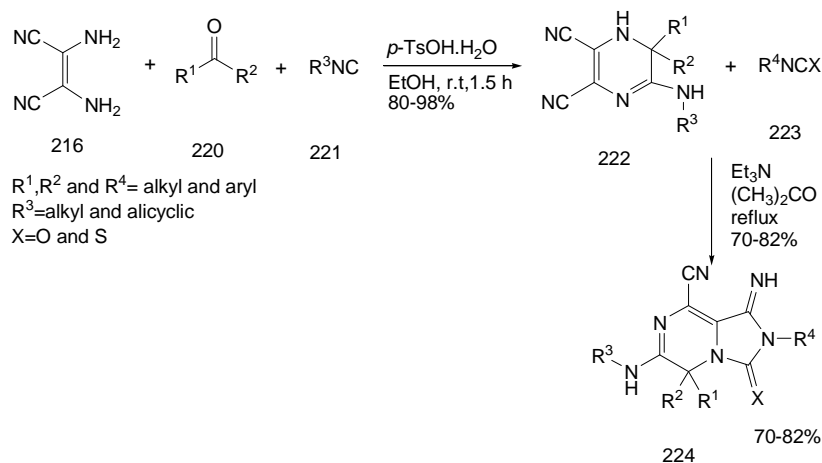
An efficient synthesis of bis-3-aminoimidazo[1,2-*a*]pyridines, pyrimidines and pyrazines **228** as extended pi-conjugated systems via novel pseudo five-component condensation of terephthalaldehyde **226**, 2-aminoazine **225** and isocyanide **227** using *p*-toluene sulfonic acid as a catalyst in



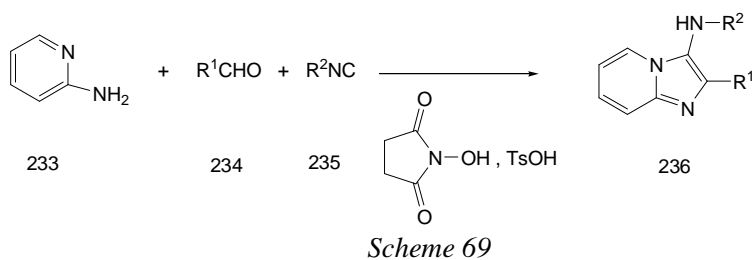
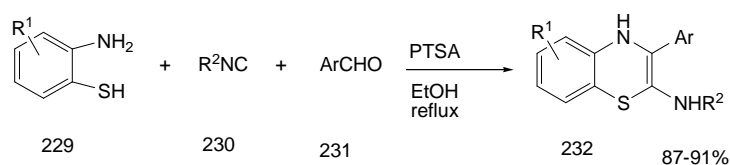
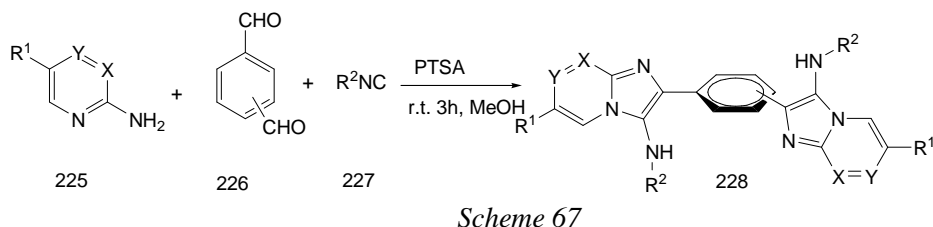
Scheme 64



Scheme 65



Scheme 66



high yield at room temperature (Scheme 67) [70].

We also used PTSA as a catalyst for the synthesis of 3-aryl-4*H*-benzo[1,4]thiazine-2-amine derivatives **232** in three-component condensation of aromatic aldehyde **231**, isocyanide **230**, and *o*-amino thiophenols **229** (Scheme 68). The first step of this reaction is similar to the Ugi reaction. The first step, similar to the Ugi reaction involves reaction of the aromatic aldehyde with the *o*-aminothiophenol followed by isocyanide attack on the resulting intermediate followed by intramolecular trapping by the sulfur nucleophile to give the desired product [71].

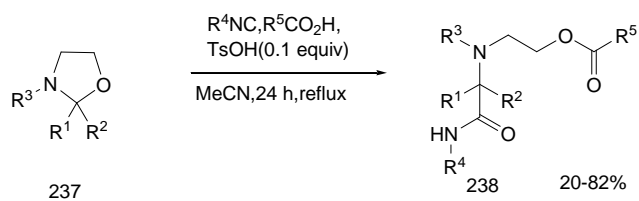
Our group also used *o*-aminophenols instead of *o*-aminothiophenols to prepare 3-aryl-4*H*-benzo[1,4]oxazine-2-amines [72].

Three-component condensation of aromatic isocyanides **235**, aldehydes **234** and 2-aminopyridine **233** can be catalyzed by *N*-hydroxysuccinimide and *p*-toluenesulfonic acid to prepare imidazo[1,2-*a*]pyridine derivatives **236** (Scheme 69)

[73].

A novel multi component condensation between an oxazolidine **237**, an isocyanide, and a carboxylic acid in the presence of catalytic amount of *p*-TsOH in acetonitrile afford *N*-acyloxyethylamino acid derivatives **238**. Without addition of an acid catalyst, the reaction was extremely slow, providing low yields (Scheme 70) [74].

2-Isocyanophenyl ketones **239** is treated with a vinyl ether **240**, at 0 °C in dichloromethane containing a catalytic amount of camphor-10-sulfonic acid to give the corresponding 2-(1-alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazines **241** after



Catalytic Multicomponent Reactions Based on Isocyanides

aqueous workup (Scheme 71).

Isocyanides are rather unstable and must be freshly prepared for satisfactory production of the **241**. This reaction with cyclic vinyl ethers, under this condition resulted in the formation of intractable mixtures of products which no traces of **241** could be isolated [75].

Microwave-assisted three-component reaction between 2-aminopyridines, isocyanides, and 2-carboxy benzaldehyde under acidic condition (methane sulfonic acid produce pyrido[2,1':2,3]imidazo[4,5-c]isoquinoline-5(6*H*)-ones **245** in good yield (Scheme 72). The acid protonated Schiff base and facilitated [4+1] cycloaddition reaction [76].

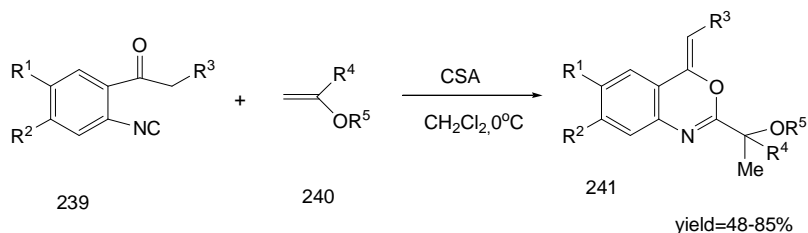
Shaabani and his co-workers also used cellulose sulfuric acid as an efficient and environmentally friendly bio-supported proton source catalyst in one-pot three component condensation reaction between 2-aminoazine **247**, aldehyde **246** and isocyanide **248** to prepare imidazoazines **249** in good

yields (Scheme 73) [77].

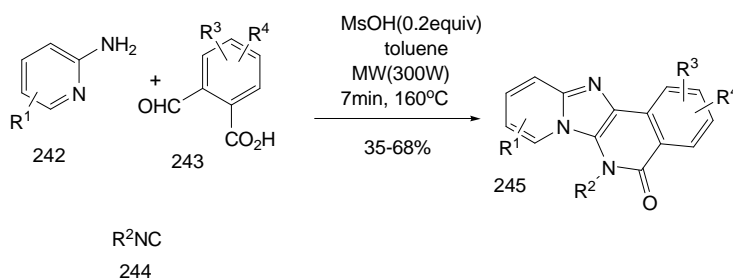
Isocyanides represent promising candidate as an insertion molecule, and can be inserted into a variety of chemical bonds. Tobisu was screening a variety of catalysts for the reaction of acyclic acetal **250** with isocyanides and proved that TfOH is the best. The product is α -alkoxy imidate and the reaction is applicable to a diverse array of acyclic acetals that contain a wide range of functional groups (Scheme 74).

The preferential formation of double-insertion in a major reaction pathway was observed when 2 equiv. of isocyanide were treated with a catalytic amount of TfOH in dioxane. Isocyanide structure also affect on mono- **251** and double-insertion **252** products. Electron-deficient isocyanide selectively formed mono-insertion product and vice-versa. The imidate functionality in the mono-insertion products can be hydrolyzed into an ester **253** (Scheme 75).

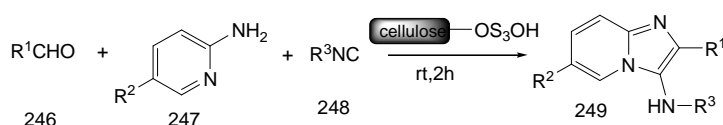
The new Bronsted acid catalyst system can also effect the



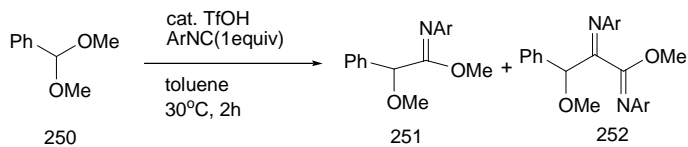
Scheme 71



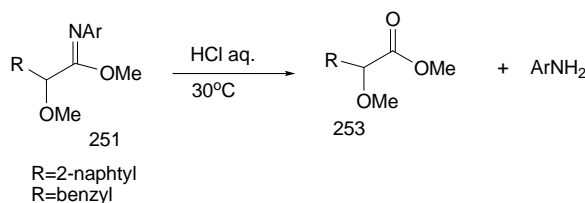
Scheme 72



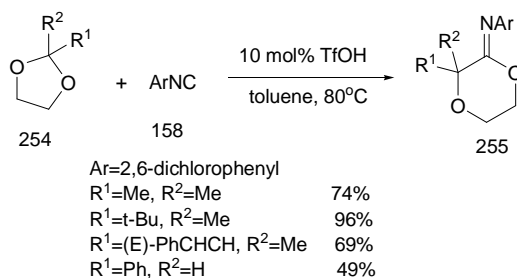
Scheme 73



Scheme 74



Scheme 75



Scheme 76

insertion of an isocyanide into a cyclic acetal, affording the corresponding cyclic imidates in yields comparable to those obtained when GaCl₃ is used as a catalyst [50].

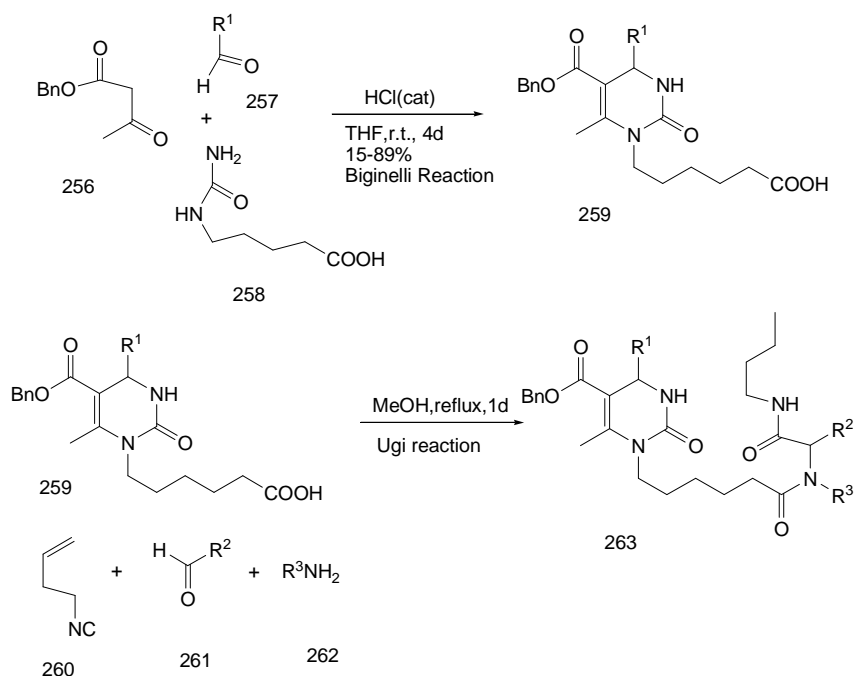
Mineral Acids

Werner *et al.* synthesized tetrahydroprimidnone scaffold from the Biginelli reaction of benzyl acetoacetate, aldehyde, and 6-ureidohexanoic acid in THF in the presence of a catalytic amount of HCl. The product of Biginelli reaction then used as a bifunctional building block that served as the urea component in the Biginelli reaction and as the acid component in the subsequent Ugi condensation (Scheme 77). Tetrahydroprimidineone based on the structure of MAL3-101 that was previously found to block the ability of Hsp70 co chaperones to enhance Hsp70 ATPase activity without affecting the K_{CAT} for ATP hydrolysis. This library demonstrates the utility of TMCRs in SAR studies of

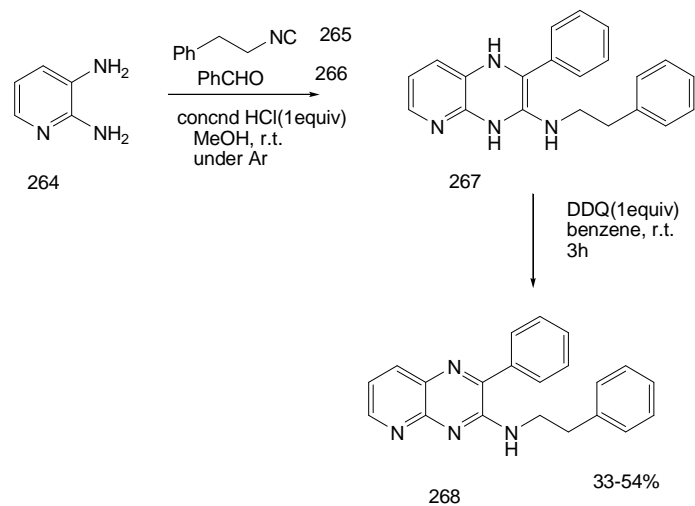
biological lead molecules. The tandem Biginelli-Ugi MCR allowed the synthesis of the library members in a sequence of only two one-pot reactions [78].

The reaction between *o*-phenylenediamine with equimolar amounts of an aldehyde and an isocyanide leads to the formation of 1,4-dihydroquinoxaline **267**. The reaction proceeds in methanol at room temperature using equimolar amount of HCl (conc.) as a catalyst (Scheme 78). The 1,4-dihydroquinoxalines are unstable under reaction condition. Exposure of **267** to air led to the formation of variable amounts of the respective quinoxalines. Efficient conversion of the product mixture into a single isolable product was achieved by brief exposure of crude reaction mixtures to DDQ/benzene system at room temperature furnish quinoxalines **268** as a stable product [79]. If monoalkylated diamines tested in the same multicomponent reaction 1,4-dihydroquinoxalines could be isolated in moderate yields.

Catalytic Multicomponent Reactions Based on Isocyanides



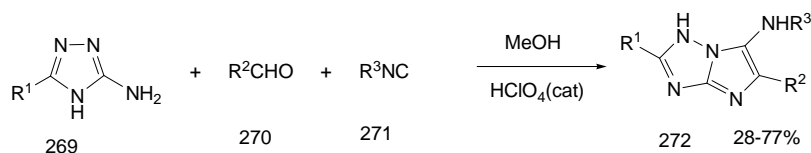
Scheme 77



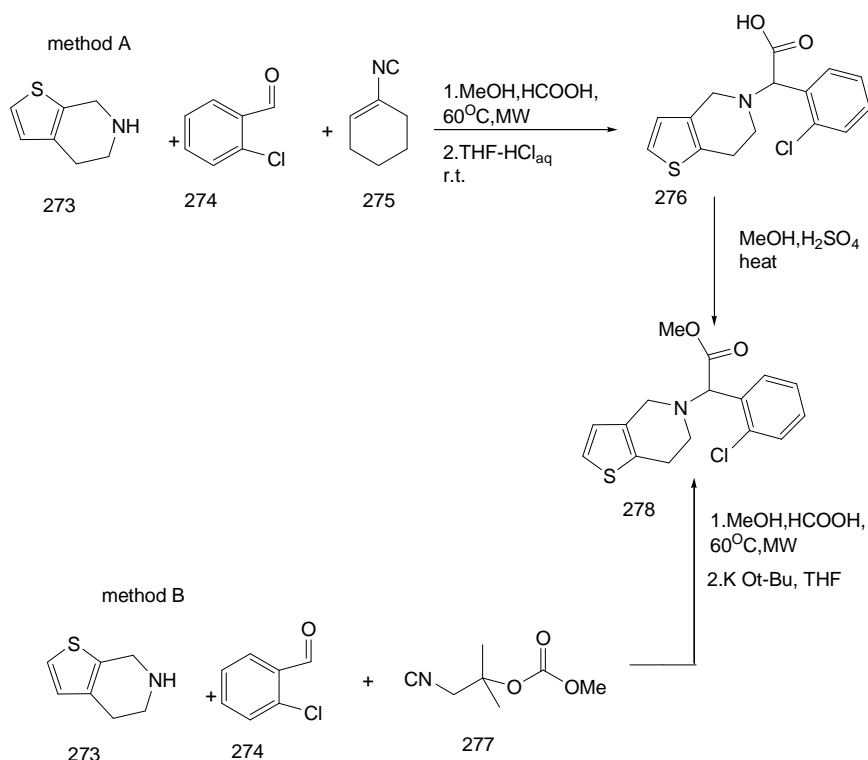
Scheme 78

Huang and co workers synthesized 1*H*-imidazo[1,2-*b*]-1,2,4-triazole-6-amines by treatment of aminotriazoles **269**, isocyanides **271** and aldehyde in the presence of HClO₄ in methanol at room temperature (Scheme 79) [80].

The Ugi reaction involves the 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **273**, which is commercially available, 2-chlorobenzaldehyde **274** and 1-isocyanocyclohexene **275** (Armstrong isocyanide) as acid labile cleavable isocyanide.



Scheme 79



Scheme 80

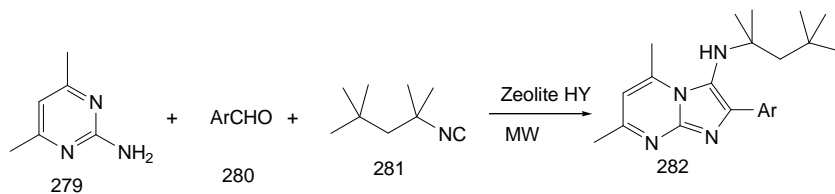
The reaction was performed in methanol under microwave irradiation and formic acid catalysis (method A). This reaction can be operated with a base labile isocyanide, 1,1-dimethyl-2-isocyanoethyl methyl carbonate **277** under same condition to produce (*R,S*)-clopidogrel **278**. The Ugi reaction was performed at 60 °C under microwave irradiation in the presence of an equimolar amount of formic acid, followed by the cleavage of the isocyanide moiety by treatment with potassium *tert*-butoxide in tetrahydrofuran (method B). This reaction can be a powerful tool for generic synthesis of marketed drugs [81].

Thompson *et al.* reported the Microwave assisted, solvent free condensation of 2-aminopyrimidine **279** with aldehydes **280** and isocyanides **281** to produce 3-aminoimidazo[1,2-*a*]pyrimidines **282** regioselectively in the presence of hydrogen zeolite (Scheme 81) [82].

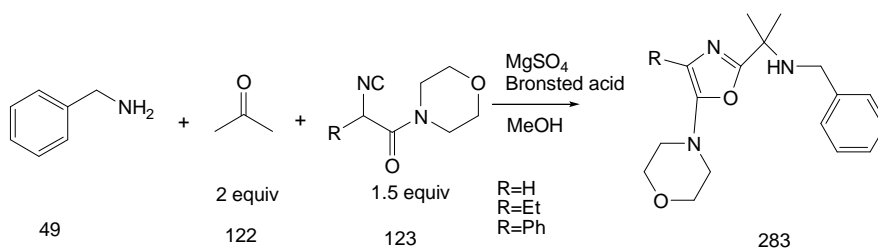
Bronsted Acid Catalysis

The reaction of isocyanoamide **123**, amine **49** and acetone **122** in methanol at room temperature and in the presence of Bronsted acid produce oxazole derivatives **283**. Et₃N.HCl can be used as Bronsted acid [38].

Catalytic Multicomponent Reactions Based on Isocyanides

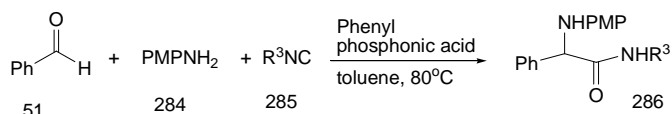


Scheme 81



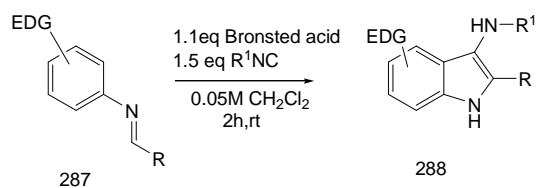
Scheme 82

An efficient and potentially useful new reaction, the phosphonic acid catalyzed three-component Ugi reaction has been developed. The reaction was performed between benzaldehyde, *p*-anisidine and different isocyanides to achieve α -amino amides in good yield. The reaction does not proceed in the absence of catalyst [83].



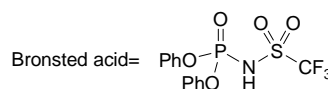
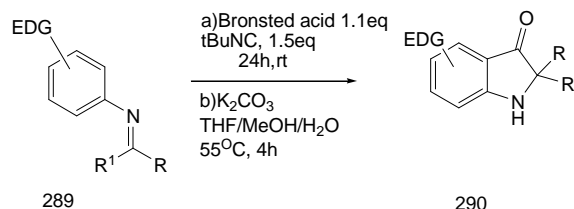
Scheme 83

Phenyl phosphonic acid can be considered a Bronsted acid and, in the form of phenylphosphonous acid tautomer, a Lewis base. It is tempting to speculate that both properties may be required for effective catalysis.



Scheme 84

Reaction between imines **287** and isocyanides can be achieved under strong Bronsted acid condition that reported recently and its presence is critical to obtain high yield under mild condition. This is a replacement of the carboxylic acid component of the Ugi reaction with a Lewis acid or strong Bronsted acid. An imine synthesis by pre condensation markedly improved the chemical yield of product. In general aldimines were prepared by condensation in toluene in the presence of molecular sieves and used without purification to synthesize indoxyls **290** and 3-amino indoles **288**. This reaction is a mild transformation combining mechanistic elements of the Ugi reaction and the Houben-Hoesch cyclization. Two new carbon-carbon bonds and a heterocyclic ring are formed in a single operation [84].



Scheme 85

BASE CATALYZED REACTIONS

Jie *et al.* described a reaction between nitro olefins **291** and TosMIC **71** in the presence of simple base such as KOH and ionic liquids to produce 4(3)-substituted 3(4)-nitro-1*H*-pyrrols **292** (Scheme 86) [85].

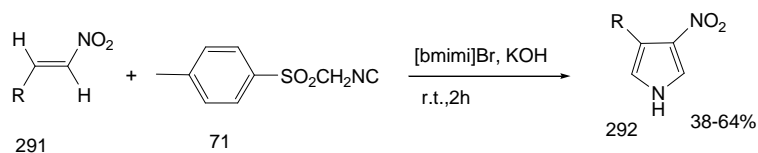
In this paper ILs could efficiently stabilize both the reactants and polar intermediates as solvent to the cyclization process. The reactions were carried out at room temperature to afford the desired products in good yields in a short time.

The synthesis of 4,5-disubstituted oxazoles **293** could be achieved in one-pot from TosMIC **71**, aliphatic halides and aldehydes in ionic liquids as recyclable green solvent, and in the presence of base has been reported. This method is an improvement of van Leuson oxazole synthesis. This procedure was not suitable for tertiary alkyl or aryl halides [86].

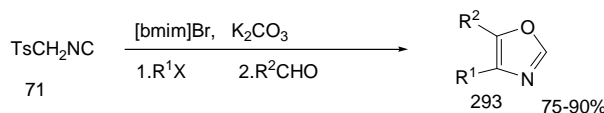
Krishna reported DABCO-catalyzed reaction between the Baylis-Hillman acetate **294** and TosMIC in dichloromethane at room temperature (Scheme 88). The products were obtained in excellent yield (80-92%) and in moderate diastereoselectivity (66-80%) in favor of the *syn*-isomer [87].

A three-component reaction between *o*-phenylenediamine **296**, aldehyde **297** and TosMIC **71** in the presence of DBU or DABCO as base, using toluene as solvent at room temperature for eight hours to afford Quinoxalines [88].

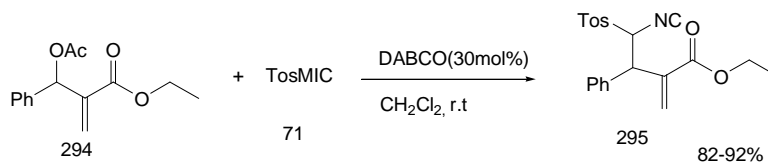
4,5-Disubstituted potassium oxazoline trifluoroborates **300** *via* the condensation of formyl-substituted aryl- and heteroaryl trifluoroborates **299** with tosyl methyl isocyanide has been prepared. The reaction proceeds in the presence of commercially available polystyrene bound DBU (DBU-PS). It could be conveniently removed from the product *via* filtration and reused indefinitely after washing with methanolic NaOH



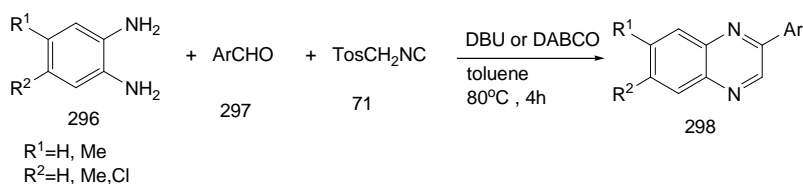
Scheme 86



Scheme 87

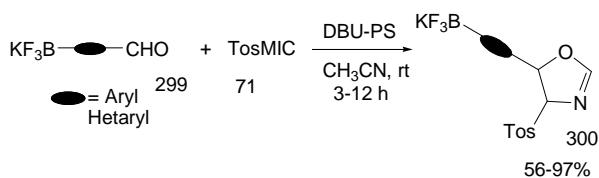


Scheme 88

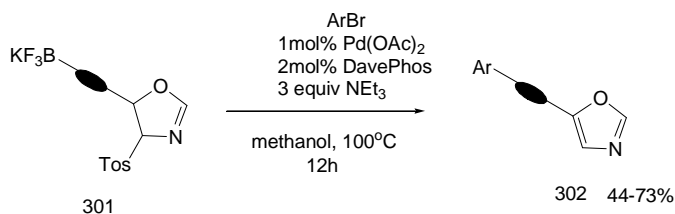


Scheme 89

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 90



Scheme 91

without lowering the yield [89].

Then they achieved the Suzuki-Miyaura cross-coupling of the oxazolynyl-substituted aryltrifluoroborates to various electrophiles using 1 mol% of $\text{Pd}(\text{OAc})_2$ /2 mol% of DavePhos and triethylamine as the base in refluxing methanol (Scheme 91).

Terzidis and co-workers were allowed chromene-3-carboxaldehydes **303** to react with equimolar amounts of TosMIC **71** in the presence of the mild base 1,8-diazabicyclo [5.4.0]undecane in the aprotic nonpolar solvent THF at room temperature for 2 h the 2-tosyl-4-(2-hydroxybenzoyl)pyrroles **304** were isolated in good yields [90].

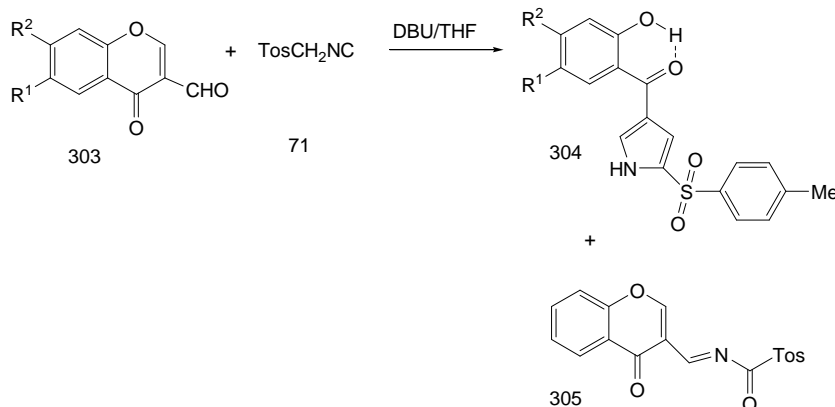
5-Substituted oxazole **307** through the reaction of aldehyde and toluenesulfonylmethyl isocyanide in the presence of sodium methoxide in refluxing methanol has been synthesized. The α,β -unsaturated ester **308** with TosMIC and potassium *tert*-butoxide in THF yielded the paramagnetic 3,4-disubstituted pyrroles **309**. Then condensation of benzaldehyde, pyrrole and aldehyde **1**, to give after DDQ oxidation, the paramagnetic porphyrines, albeit in low yield

due to the formation of tetraphenyl porphyrin [91].

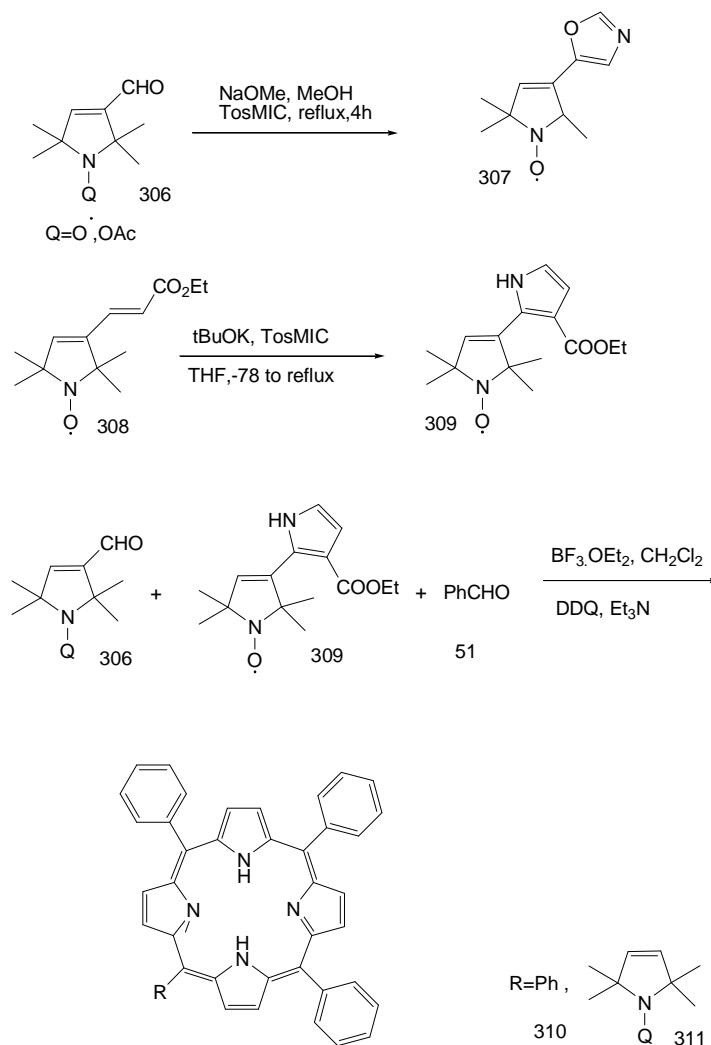
Both C_2 and C_3 -symmetric oxazole derivatives *via* the Suzuki-Miyaura cross-coupling and van Leusen oxazole synthesis have been prepared. Trialdehyde derivatives **314** was treated with TosMIC in the presence of K_2CO_3 in refluxing methanol, the corresponding C_3 -symmetric trisoxazole **315** derivatives. The C_2 -symmetric bisoxazole derivatives **317** can be synthesized according this procedure [92].

Baxendale *et al.* demonstrated a new way to prepare functionalized pyrroles *via* one-pot three-component coupling between tosyl isocyanides and ethyl chloroformate and nitrostyrene to afford nitro-substituted pyrroles **318** in the presence of *n*-butyl lithium as a strong base (Scheme 96) [93].

The reaction of Methyl-3-aryl-2-(*E*-arylethenesulfonyl) acrylate with TosMIC and sodium hydride in a mixture of ether and DMSO has been reported. The solid obtained indicated two spots in TLC which are identified as methyl-3-(4'-aryl-1'*H*-pyrrol-3'-ylsulfonyl)-4-aryl-3*H*-pyrrole-3-carboxylate and methyl-4-aryl-3-(arylethenesulfonyl)-3*H*-pyrrole-3-carboxylate in minor and major amounts, respectively. Repetition of reaction with excess TosMIC



Scheme 92



Scheme 93

resulted in **320** one. In the next steps 1,3-dipolar cycloaddition reaction achieve compounds with greater antimicrobial activity [94].

The reaction between TosMIC, cinnamic or aromatic aldehyde **322** can be catalyzed with triethyl amine to produce trans-5-styryl- or 5-aryl-4-tosyl-4,5-dihydrooxazoles **323** in quantitative yields [95].

The synthesis of various 3-indolylpyrroles has been achieved involving a 1,3-dipolar cycloaddition of TosMIC reagent with different types of N-protected indole-2/3-vinylenes [96].

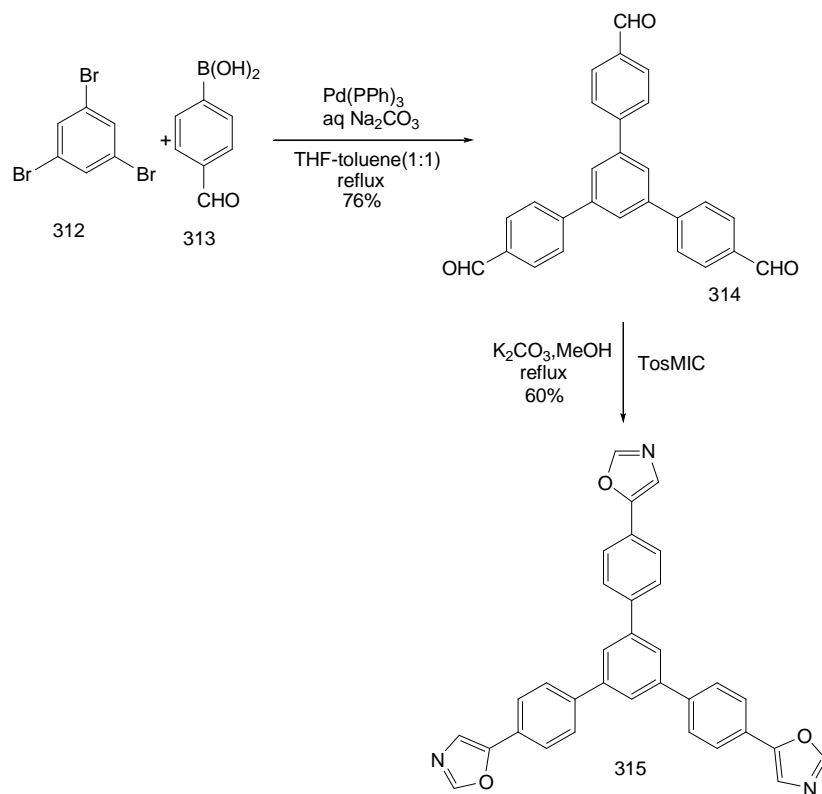
Three component condensation between 2-substituted aza

heterocycles **326**, aldehydes **327** and isocyanides **52** in the presence of catalytic amount (10%) of diaza(1,3)bicyclo [5,4,0]undecane (DBU) to prepare substituted indolizine **328** was reported by Bedjeguelal (Scheme 100) [97].

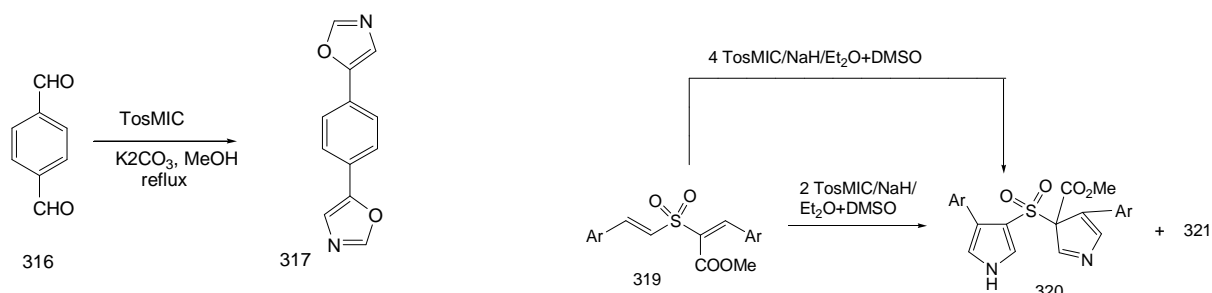
Three-component reaction between aromatic aldehydes, 3-cyanoacetyl indole **329** and isocyanide in the presence of ammonium acetate as a catalyst, produce 3-(2-furanyl) indole derivatives **332** in good yields. In the absence of any catalyst, **332** would obtain in poor yield [98].

Fukamachi *et al.* reported the cyclization of ethyl 2-(2-isocyanophenyl)acetates **333** using sodium hydride at room

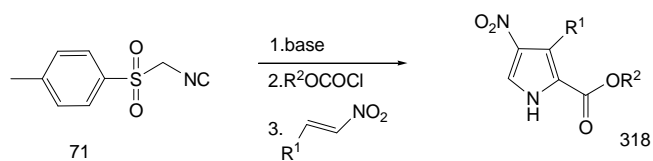
Catalytic Multicomponent Reactions Based on Isocyanides



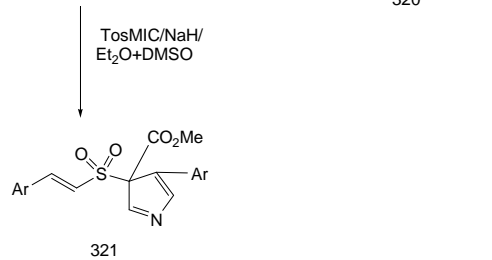
Scheme 94



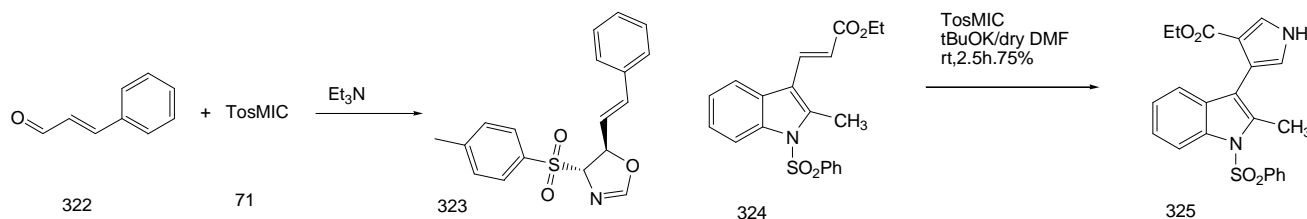
Scheme 95



Scheme 96

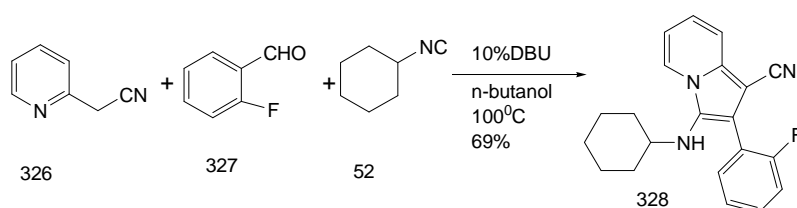


Scheme 97

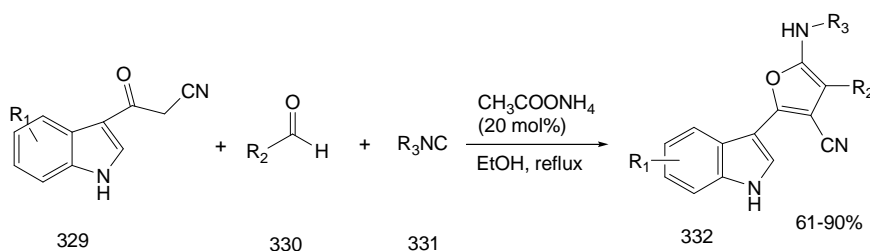


Scheme 98

Scheme 99



Scheme 100



Scheme 101

temperature was followed by 1-arylation of the resulting ethyl 1-sodioindole-3-carboxylates **334** with fluoro(di)nitrobenzenes **335** to give ethyl 1-(di)-nitrophenylindole-3-carboxylate **336** in good yields (Scheme 102) [99].

A three-component one-pot reaction between cyclohexyl isocyanide, aldehyde, and 1,3-dicarbonyl compound *via* weak base catalyzed such as piperidine reaction to afford 5-hydroxy-2*H*-pyrrol-2-one derivatives **339** (Scheme 103) [100].

This reaction could not be used for malonates. When diethylmalonate or ethyl 2-cyanoacetate was employed, no cyclization product was detected due to the difficulty in the enolization step of the carbonyl group during the reaction process.

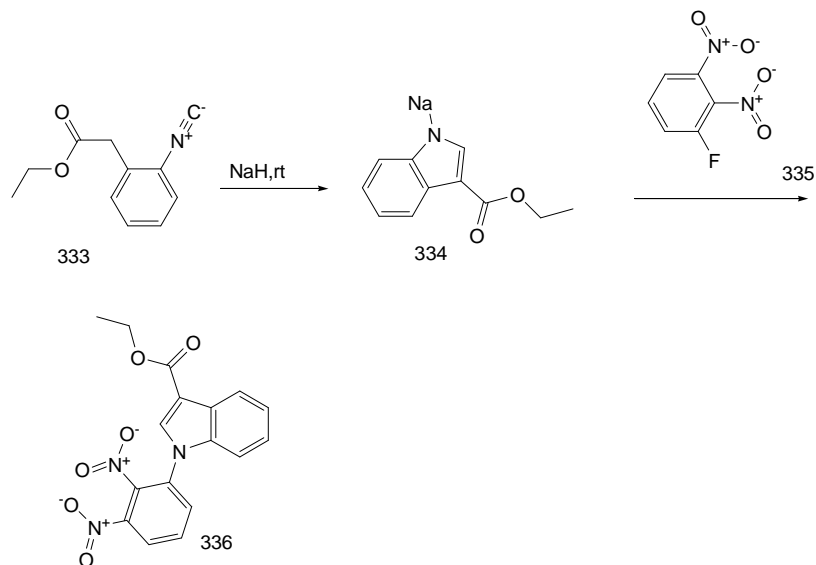
The transformation of (2-isocyanophenylthio)acetonitrile

into 4*H*-1,4-benzothiazine-2-carbonitrile has been attempted by Kobayashi group. The probable pathway is deprotonation of the hydrogen adjacent to the sulfur atom with sodium hydride generates carbanion intermediate, then carbanion attacks intramolecularly on the isocyanide carbon. After proton migration, the stable carbanion is trapped with an electrophiles [101].

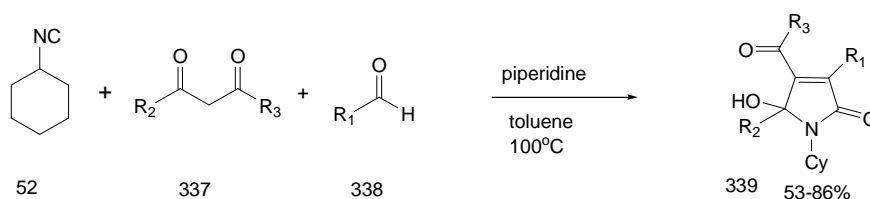
Alkylation of α -isocyanide acetamide can be achieved in the presence of alkyl halide and cesium hydroxide in acetonitrile at 0 °C to afford the monoalkylated Homologues [102].

Shibahara and co-workers discovered that the TosMIC adduct was coupled with 3,5-bis(chloromethyl)pyridine, in the presence of sodium hydride in *N,N*-dimethyl formamide at room temperature for 24 h under nitrogen, followed by

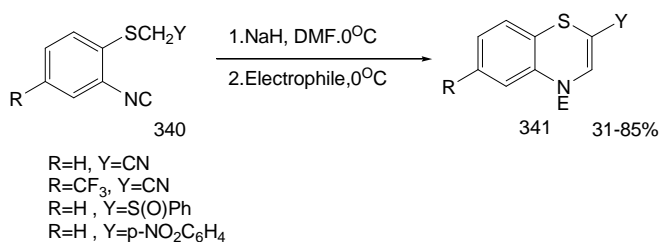
Catalytic Multicomponent Reactions Based on Isocyanides



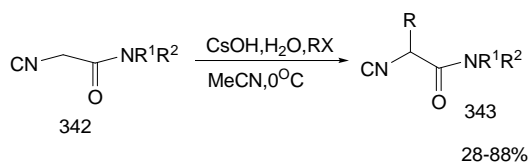
Scheme 102



Scheme 103



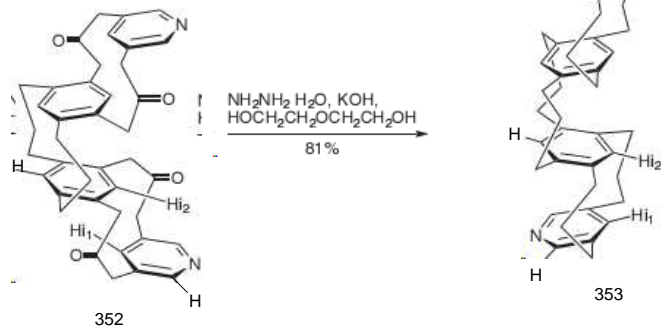
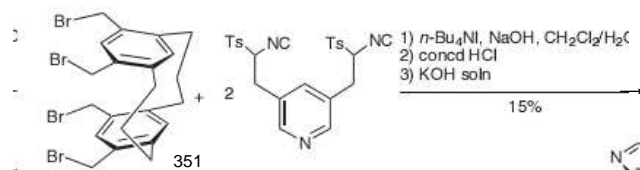
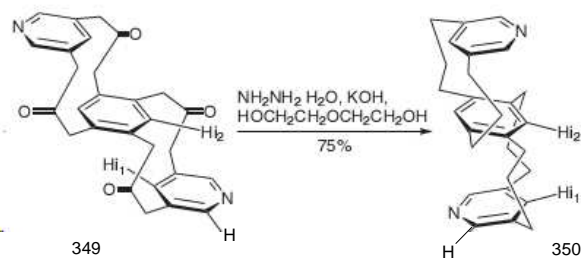
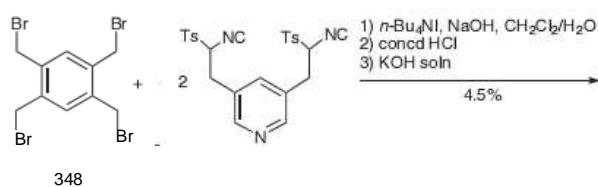
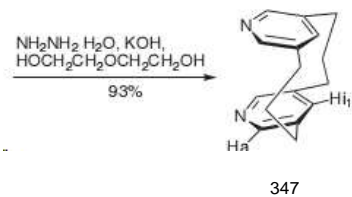
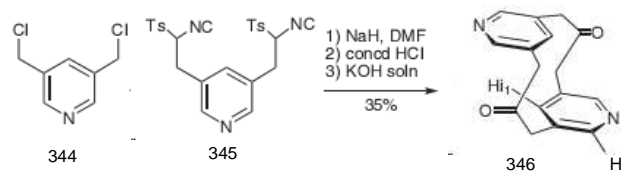
Scheme 104



Scheme 105

hydrolysis of the cyclic adduct with concentrated hydrochloric acid to give the two-layered dione **346** in 35% yield. Wolff-Kishner reduction of **346** afforded the two-layered PyP **347** in 93% yield.

1,2,4,5-Tetrakis(bromomethyl)benzene and 5,7,14,16-tetrakis (bromomethyl)[3.3]MCP was coupled in similar way. [3.3] MCP and its dione adopt different *syn* and *anti* geometry as stable conformers in solution. Similar to the structure of the



Scheme 106

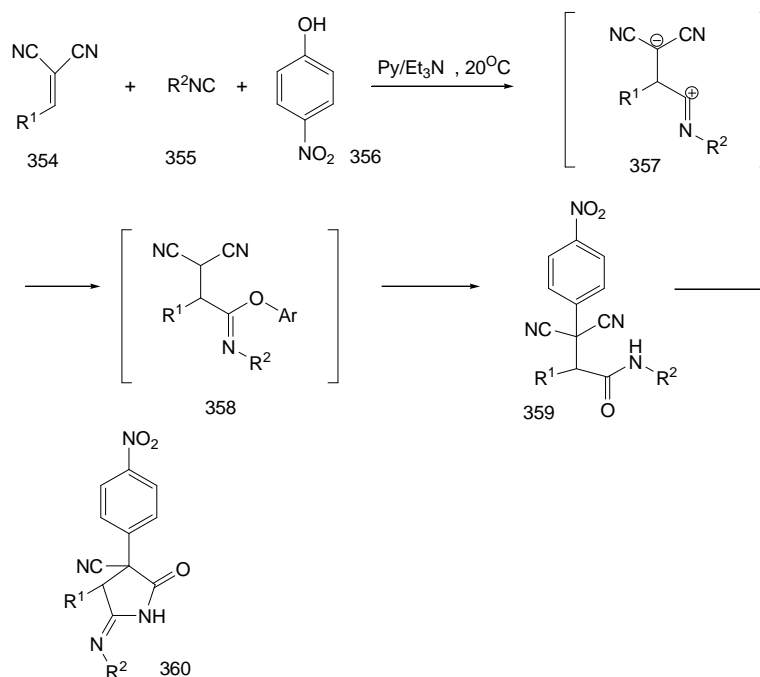
Catalytic Multicomponent Reactions Based on Isocyanides

multilayered [3.3] MCPs in solution, multilayered [3.3](3,5) PyPs 1-3 take the all-*syn* conformation, while the [3.3](3,5) PyP-dione moieties in **7**, **349** and **352** assume anti geometry [103].

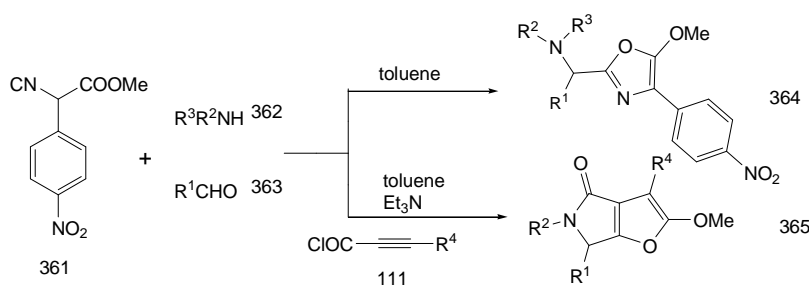
Mironov, discovered a novel MCR leading to propionamides and succinimides. The zwitterionic intermediate formed as a result of the reversible reaction between isocyanide and activated olefin forms **357** by the addition of 4-nitrophenol as an external nucleophile. This reaction is supported by a basic catalyst, the effect of which results in activation of the phenol as well as the olefin. The presence of an activated cyano group and amide fragment in

358 favored intramolecular cyclization by heating the reaction mixture or use an equimolar amount of triethylamine as catalyst. In the case of gem-dicyano olefins containing alkyl substituents, the target compounds **3** were not isolated due to rapid cyclization to substituted succinimides (Scheme 107) [104].

The development of a three-component synthesis of 5-methoxy oxazoles **364** and a four-component synthesis of furopyrrolones **365** on the basis of the unique reactivity of methyl α -(*p*-nitrophenyl)- α -isocyanoacetate **361** has been developed. The latter was performed in basic refluxing toluene solution.



Scheme 107



Scheme 108

The first reaction was conducted in toluene, a possible mechanism is Condensation of the aldehyde with the amine to afford the iminium ion. The hydroxide counterion then furnish the enolate. This reaction also proceed with aqueous potassium hydroxide led to exclusive formation of the enolate. The treatment of enolate with the hydrochloride salt of dimethylamine and cyclo hexanal afforded the corresponding oxazole (Scheme 109).

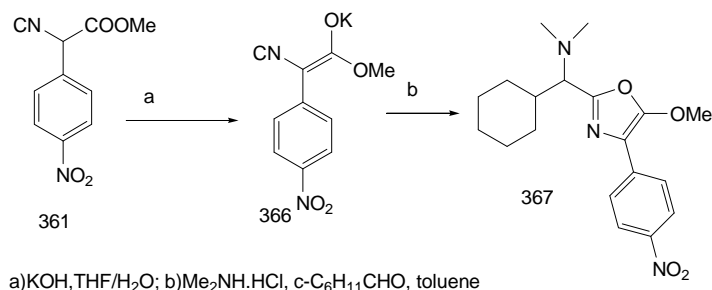
When a toluene solution of amine, aldehyde, and methyl α -(*p*-nitrophenyl)- α -isocyanoacetate was stirred for 4 h, after which time the acyl chloride and triethyl amine were added, and the resulting mixture was heated at reflux for 10 min, the corresponding furopyrralone was obtained [105].

In the first step of total synthesis of (-)-Dysibetaine **371**, a reaction of **368** and convertible isocyanide **369** was performed under basic condition. HFIP, however, is a non-nucleophilic solvent. A key to the success of this synthesis was the discovery that the activated ester **368**, containing the necessary

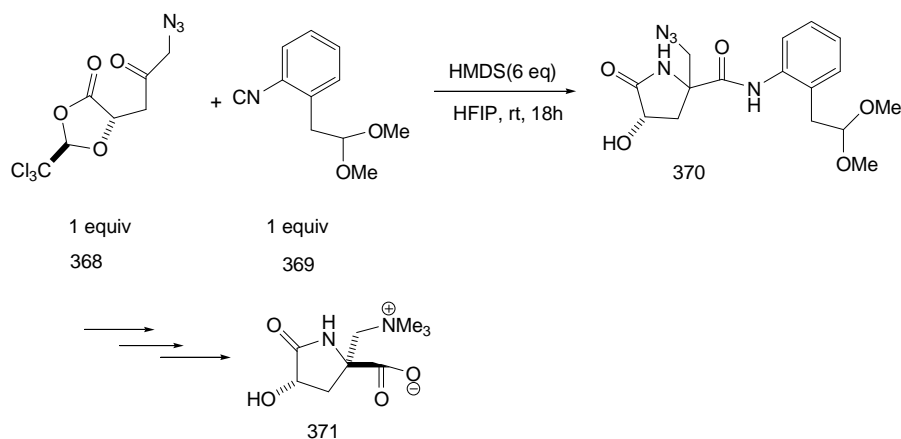
carbon and heteroatom framework, could successfully participate in the Ugi 4-center-3-component cyclization reaction [106].

Treatment of the *N*-benzyl salt with cyclohexyl isocyanide in MeOH with 2 equiv. of AcONa nicely yielded the γ -carbamoylated- β -cyano-1,4-dihydropyridine regioselectively **373**. This is the best way of addition of isocyanide into pyridinium salt. The reaction fails to yield any adduct in the absence of base. The regioselectivity of the process, favoring the 1,4-isomer (Scheme 111) [107].

The reaction of 5-OTBDMS-4''-deoxy-4''-phenyl-sulfinimine-avermectine B₁ **375** with a mixture of pyridine (4 equiv.), trifluoroacetic acid (2 equiv.) and isopropyl isocyanide (1 equiv.) in dichloromethane gave 5-OTBDMS-4''-(*S*)-4''-deoxy-4''-trifluoroacetylamino-4''-trifluoro-acetylamino-4''-isopropylcarbamoyl-avermectin. This substance was prepared through diastereoselective Ugi reaction to phenyl-sulfinimide intermediate.

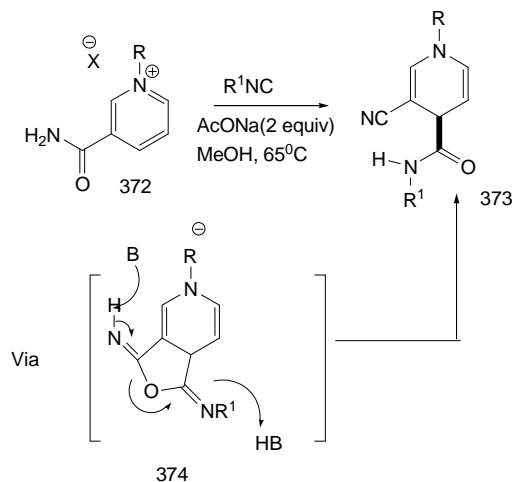


Scheme 109

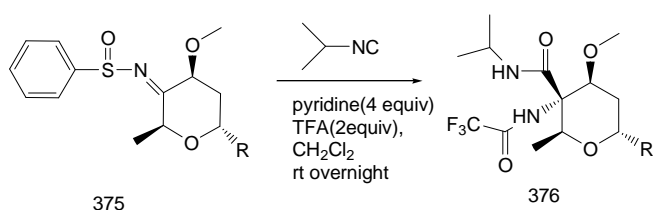


Scheme 110

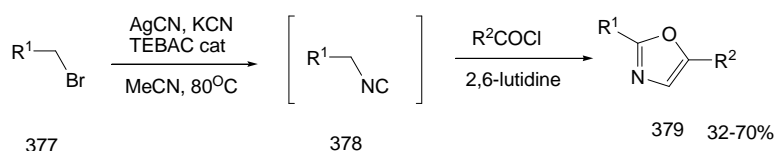
Catalytic Multicomponent Reactions Based on Isocyanides



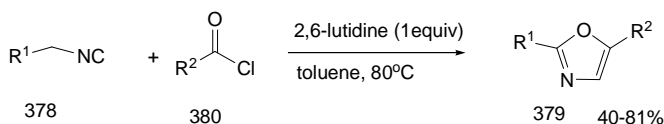
Scheme 111



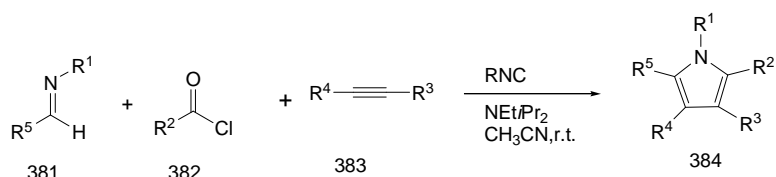
Scheme 112



Scheme 113



Scheme 114



Scheme 115

They isolated compound **376** only with the *S* configuration in 4"-position. One of the side products identified was the compound resulting from the Passerini reaction [108].

El kaim *et al.* [109] reported a simple one-pot synthesis of 2,5-disubstituted oxazoles **379**, starting from benzyl halides and acyl chloride. In this reaction isocyanides prepared *in situ* by AgCN. Addition of an acyl chloride in the presence of a base (2,6-lutidine) leads to desired product in good yield (Scheme 113). This group also reported that this reaction in the presence of isocyanide directly can be performed (Scheme 114) [110].

Cyr and co-workers demonstrated a new isocyanide-mediated synthesis of pyrrols from imines, acid chlorides and alkynes in the presence of base and in the absence of palladium catalyst.

This reaction also proceeds in the presence of palladium catalyst and CO, but in this work, isocyanide display similar reactivity to carbon monoxide, albeit with a higher nucleophilicity [111].

IONIC LIQUIDS

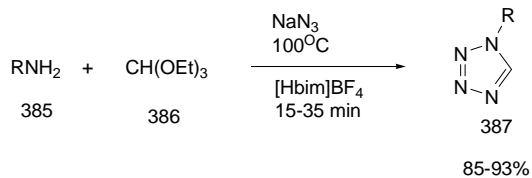
In recent times, ionic liquids have attracted increasing

interest in the context of green synthesis. Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, non flammability, thermal stability, and controlled miscibility. Today they have marched for beyond this border, showing their significant role in controlling reaction as catalyst.

Potewar *et al.* developed [112] a mild and efficient protocol for the synthesis of 1-substituted 1*H*-1,2,3,4-tetrazoles **387** via the one-pot condensation of substituted amines **385**, triethyl orthoformate **386** and sodium azide in stoichiometric portions in a 1-*n*-butyl-imidazolium tetrafluoro borate at 100 °C to afford 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole (Scheme 116).

In this reaction, inherent Bronsted acidity of the ionic liquid play an important role for the breakdown of triethyl orthoformate, and the significantly high polarity of the ionic liquid serves to stabilize sodium azide and facilitates the [3+2] cycloaddition.

Shaabani and his co-worker, introduced an efficient and environmentally friendly approach for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines via condensation of an aldehyde, 2-amino-5-methylpyridine and an isocyanide using [bmim]Br in good to excellent yields at room temperature (Scheme 117). In this reaction ionic liquid was used as a promoter [113].



Scheme 116

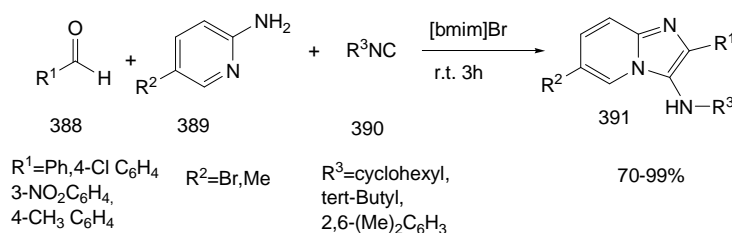
Recently basic ionic liquids offering a new possibility for developing environmentally friendly basic catalysts due to the combination of the advantages of inorganic bases, stability in water and air, easy separation and reusability.

Yavari *et al.* has reported a simple and fast one-pot three component reaction of acid chlorides **392**, amino acids **393**, and dialkyl acetylene dicarboxylates **394** by BIL in water to afford tetrasubstituted pyrroles **395**.

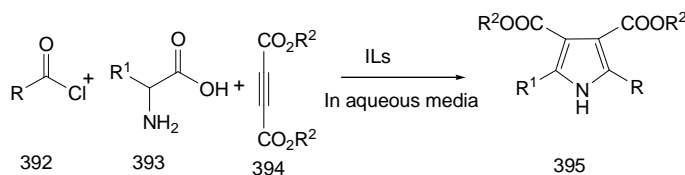
In all cases, the basic IL-catalyzed one-pot reaction proceeded smoothly and gave the corresponding products in excellent yield [114].

DMF CATALYZED REACTIONS

The one-pot three-component reaction of alkyl or aryl isocyanides with *N,N'*-dimethyl barbituric acid in the presence of terephthalaldehyde in DMF at room temperature by shaking provide a facile and efficient method for the



Scheme 117



Scheme 118

Catalytic Multicomponent Reactions Based on Isocyanides

preparation of 1,4-bis(6-alkyl or aryl amino-1,3-dimethyl furo [2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione-5-yl)benzene derivatives **398** in good yields have been revealed (Scheme 119).

High rates of reactions at r.t. have made to establish a significant catalytic role for DMF as urea in Knoevenagel condensation reaction of dimethyl barbituric acid and aldehydes [115].

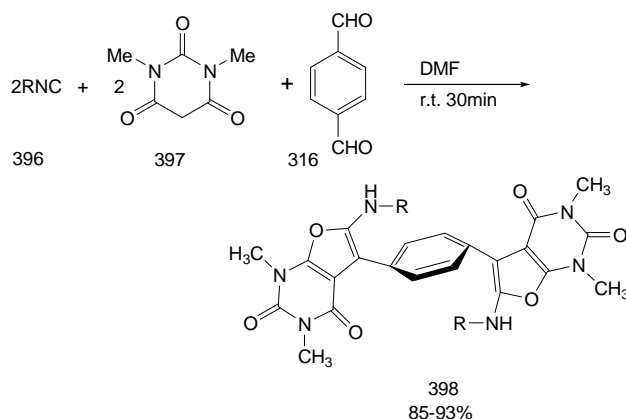
AMMONIUM CHLORIDE PROMOTED REACTIONS

Ammonium chloride as an inexpensive and readily available reagent has been used in various reactions. It effectively promotes the Ugi reaction, Biginelli reaction,

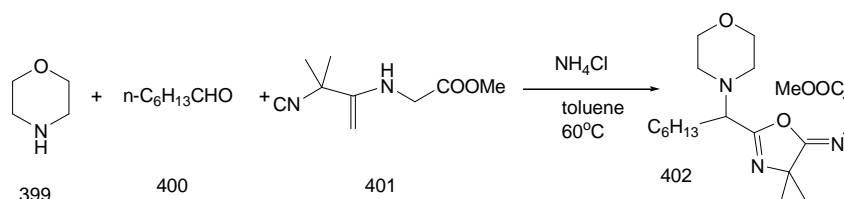
Claisen rearrangement, IMCR for the synthesis of many heterocyclic compounds.

The three-component reaction of α,α -disubstituted α -isocyanoacetamides with heptanal **400** and morpholine **399** in toluene in the presence of ammonium chloride afford the 5-iminooxazoline **402**. The resulting product transformed to Macrocyclodepsipeptide [116].

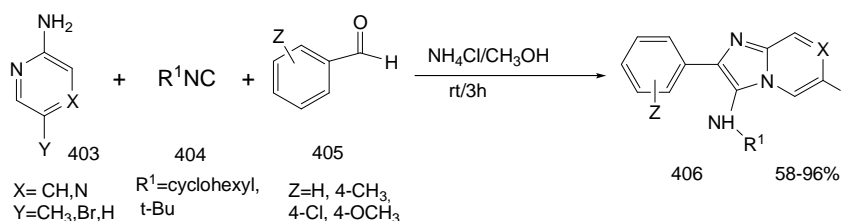
Shaabani *et al.* have developed the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-*a*]pyrazines *via* the condensation of an aldehyde, 2-amino-5-methyl pyridine or 2-amino-5-bromopyridine or 2-aminopyrazine, and alkyl or aryl isocyanide in the presence of ammonium chloride as an inexpensive catalyst and co-reactant in methanol [117].



Scheme 119



Scheme 120



Scheme 121

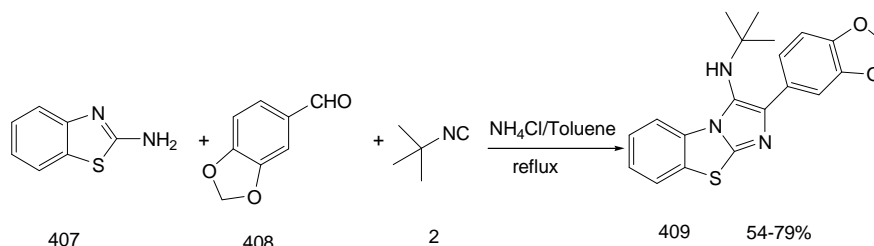
An easy and efficient one-pot synthesis of 3-amino-benzo [2,1-*b*]thiazoles by the reaction of 2-aminobenzothiazole, aldehydes and isocyanide in the presence of ammonium chloride as a promoter has been disclosed (Scheme 122) [118].

SILICA GEL PROMOTED REACTIONS

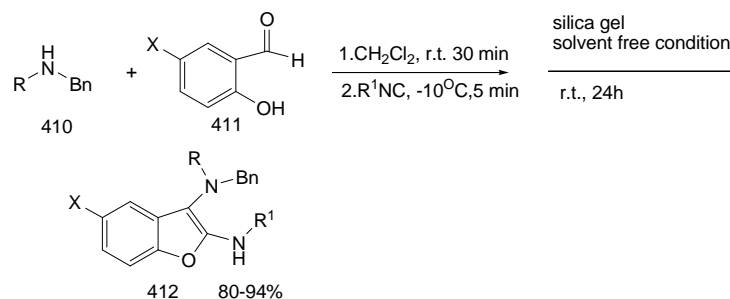
The one-pot three-component reaction between isocyanides, secondary amines and electron poor salicylaldehydes in the presence of silica gel afforded benzo[*b*]furans in good to excellent yields. In the absence of

silica gel the yields were only *ca.*, 20% at room temperature after 24 h and in each case several by-products were observed [119].

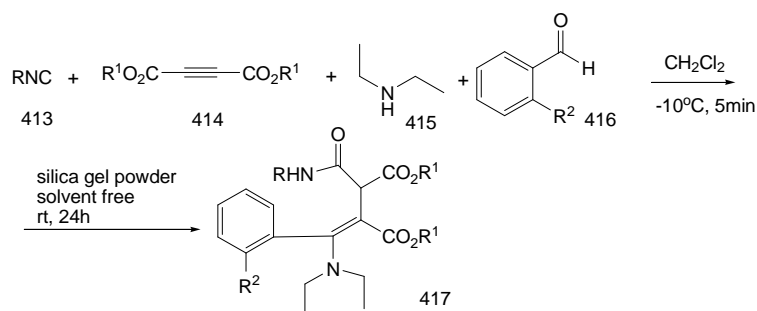
A convenient preparation of densely functionalized alkenes using a simple one-pot four-component reaction between dialkylacetylene dicarboxylates and isocyanides with iminium ions generated from aromatic aldehydes and diethyl amine in the presence of silica gel. The reaction occurs smoothly in the presence of silica gel at ambient temperature, to produce dialkyl-2-[(alkylamino)carbonyl]-3-[(*Z*)-1-(diethylamino)-1-arylmethylidene] succinates **417** in 48-80% yields has been developed [120].



Scheme 122

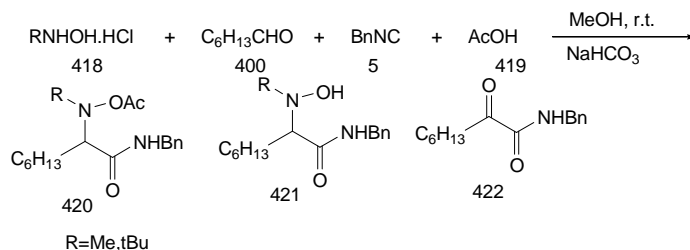


Scheme 123

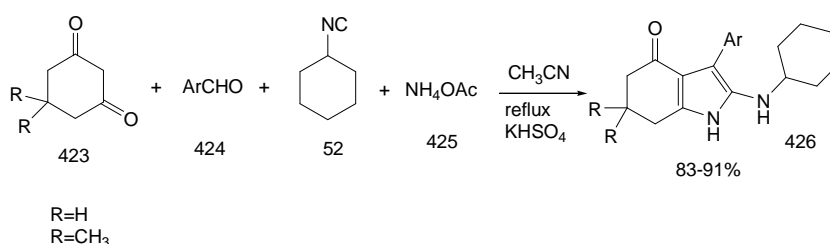


Scheme 124

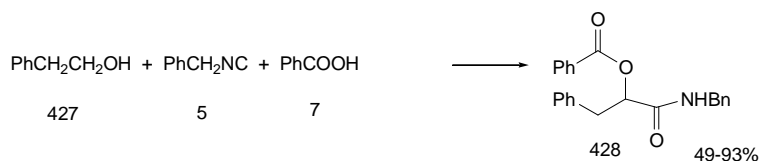
Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 125



Scheme 126



Scheme 127

MOLECULAR SIEVE PROMOTED REACTION

Grassot *et al.* examine the Ugi four-component reaction of *N*-methylhydroxylamine, heptanal, benzyl isocyanide and acetic acid in methanol at room temperature. They obtained Ugi adduct 420 and the non acylated adduct 421. However the unexpected product *N*-benzyl-2-oxooctanamide 422 was also obtained in low yield. The yield of this was increased when they used 4A° molecular sieves. This reaction performed *via* formal oxidative coupling of an aldehyde and isocyanide. Both *N*-methylhydroxylamine and acetic acid are mediators [121].

MISCELLANEOUS CATALYST SYSTEMS

We have recently reported a mild and practical synthesis of 2-(cyclohexylimino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones 426 *via* a one-pot multi component reaction of

cyclohexyl isocyanide, aldehyde and dimedone and ammonium acetate in the presence of KHSO_4 as a catalyst in acetonitrile. KHSO_4 is one of the components of a triple salt with the formula 2KHSO_5 , KHSO_4 , K_2SO_4 which is known as oxone, and is used as a highly efficient oxidant in many organic reagents [122].

Ngouansavanh *et al.* examined IBX as the oxidant in one-pot domino oxidation/P-3CR process relative to the classic two-step sequence. They used nonactivated alcohol, benzoic acid and isocyanide as a substrate to produce α -acyloxy carboxamides [123].

CATALYTIC SYSTEMS BASED ON UPON UGI ADDUCT

Ugi-Heck Combination

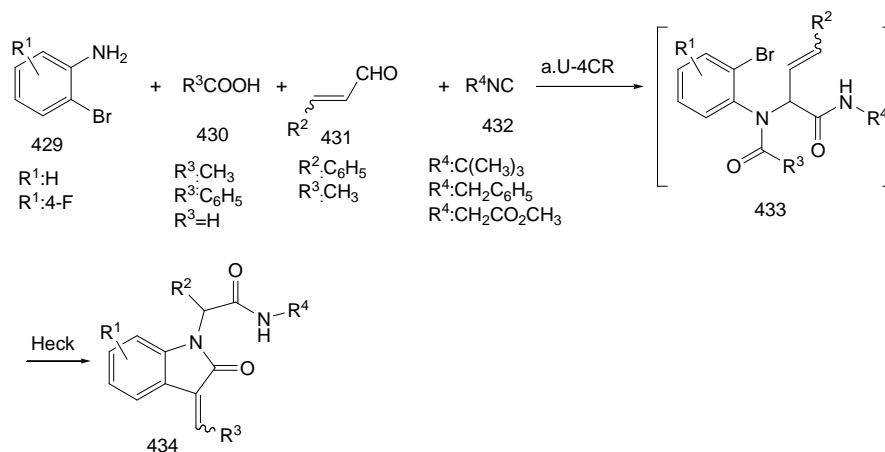
Umekehrer and co-workers developed a novel one-pot synthesis of the indole-2-one core structure by combining Ugi-

Heck reaction. The reaction between 2-bromoanilines **429** and acrylic aldehydes **431** as starting material in Ugi reaction produces acyclic intermediate **433** and the final ring-closing performed by classical Heck reaction (Scheme 128).

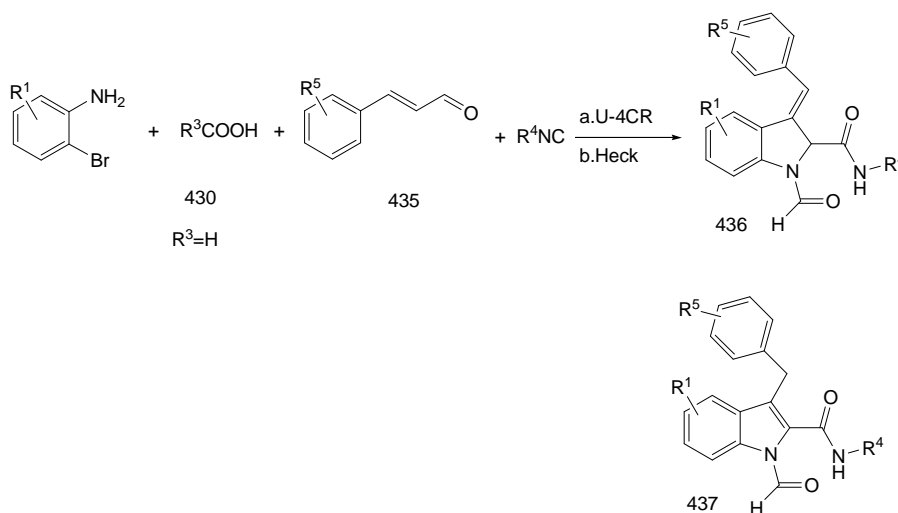
They also found a new route to the synthesis of substituted 1*H*-indoles by involving cinnamaldehyde **435** and formic acid **430** in one-pot procedure. Under the conditions of the Heck reaction, the resulting formic group was partially cleaved under Heck reaction condition [124]. If they used Armstrong isocyanide, the cleavage of isocyanide **437** under acidic condition produce the corresponding carboxylic acid and ester (Scheme 129).

Synthesis of various types of 1,3-disubstituted indole-2-ones can be synthesized by reaction of aldehydes, anilines, isocyanides and acrylic acids **438**. The formation of the acyclic products was originally reported by Ugi *et al.* and the final ring-closing was performed by a classical intramolecular Heck reaction. This two steps were combined in a new one-pot synthesis [125].

A new one-pot two-step procedure Ugi-Smiles/Heck Coupling/Isomerization reaction between allyl amine **68**, iodophenols **443** and various isocyanides and carbonyl derivatives coupled to produce 4CC adducts **444** [126]. After completion of the Ugi-Smiles coupling, addition of 0.2-0.3



Scheme 128



Scheme 129

Catalytic Multicomponent Reactions Based on Isocyanides

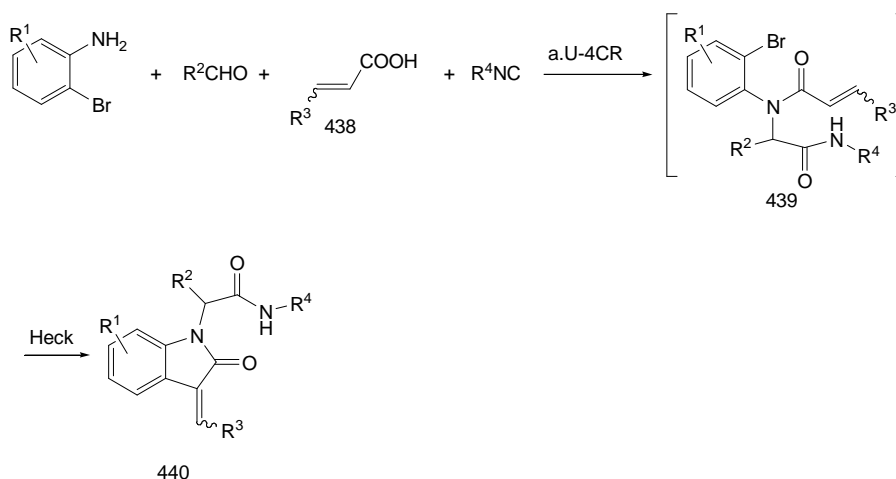
equiv. of trifluoroacetic acid at room temperature allows the hydrolysis of the remaining isocyanide. The following Heck coupling was carried out in the presence of Pd(OAc)₂ and triethylamine and triphenylphosphine in toluene to produce poly substituted indoles **445**.

Metal Catalyzed Reaction Upon Ugi Adducts

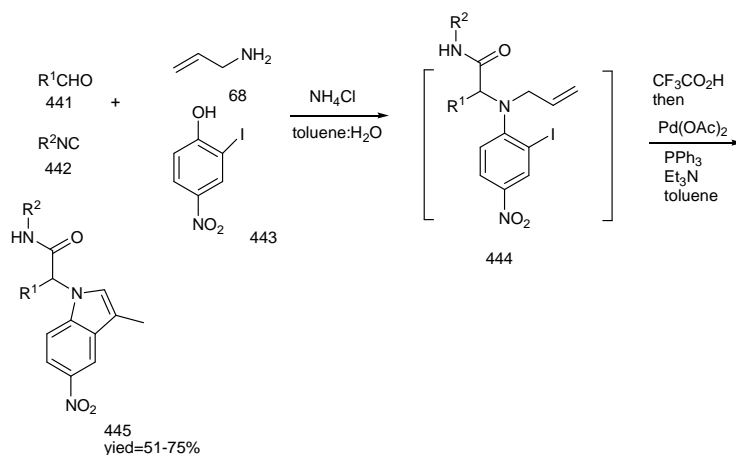
When propargylamine and chloroacetic acid were added to aldehydes and isocyanide in MeOH, the Ugi adduct **450** was efficiently formed after several hours at room temperature. After purification of the amide, the pyridinium salt **452** was formed under heating with pyridine in ethanol. Evaporation of

ethanol and washing of the salt with ether-petroleum ether followed by Sonogashira coupling with iodobenzene derivatives gave the new indolizine. In the last step, the mechanism probably involves a Sonogashira coupling followed by a [3+2] cycloaddition of the more reactive arylalkyne. The indolizine is finally obtained by a spontaneous oxidation to aromatic indolizines [127].

Kalinski and co-workers performed four component Ugi reaction and in the next step palladium assisted intramolecular *N*-aryl amidation to produce indole-2-one **458**, quinoxaline-2-ones **461** and benzodiazepine-2,5-diones **463** [128] with final products containing four points of potential diversity and a



Scheme 130



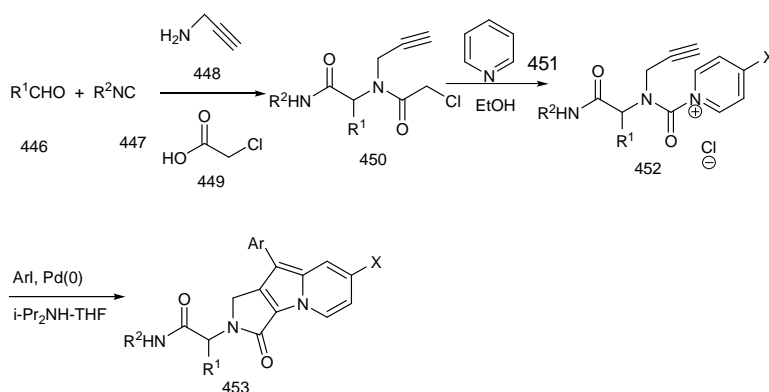
Scheme 131

facile and rapid production protocol, access to thousands of compounds containing the outlined important pharmacophoric scaffolds. With the use of 2-bromobenzaldehyde 455, indole-2-ones are obtained with acceptable yields (Scheme 133).

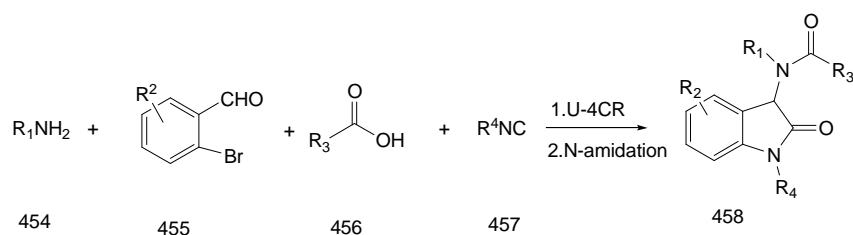
High substituted quinoxaline-2-ones **461** are obtained by the use of 2-bromoanilines **459**. Both aldehydes and ketones could be employed in this reaction. Involving 2-bromobenzoic acid derivatives in the Ugi-*N*-aryl amidation reaction resulted to produce benzodiazepine-2,5-diones.

Banfi, *et al.* first synthesized the special isocyanide **464**,

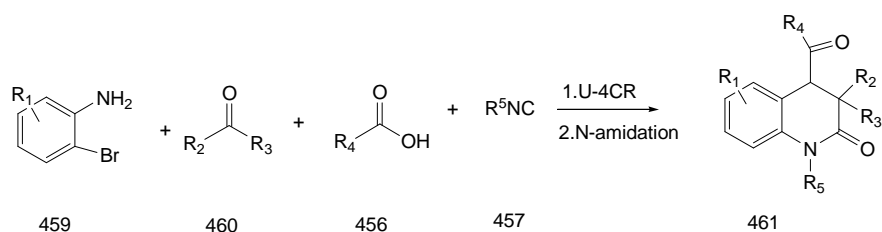
one of the four inputs in the Ugi MCR isocyanide then used, together with a variety of carbonyl compounds, primary amines, and carboxylic acids, in the presence of trifluoroacetic acid for preparing in excellent yield a small library of Ugi derivatives **465**. The Ugi product ($R^5 = \text{CO}_2\text{Me}$), in the presence of $\text{Pd}(\text{PPh}_3)_4$ and *dpe* in acetonitrile at 60 °C produces **466** in quantitative yields. After hydrolysis of the carbonate with aqueous methanol in the presence of KOH, and an intramolecular Pd(II)-mediated ($R^5 = \text{H}$) $\text{S}_{\text{N}}2$ cyclization lead to give highly functionalized *N*-acyl-2-vinylpyrrolidines



Scheme 132

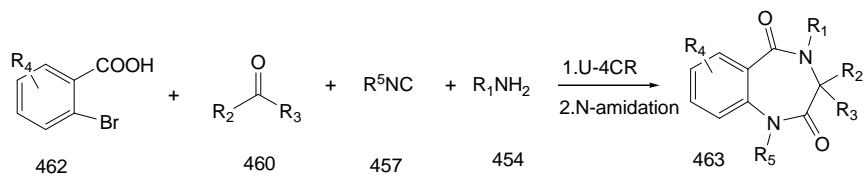


Scheme 133

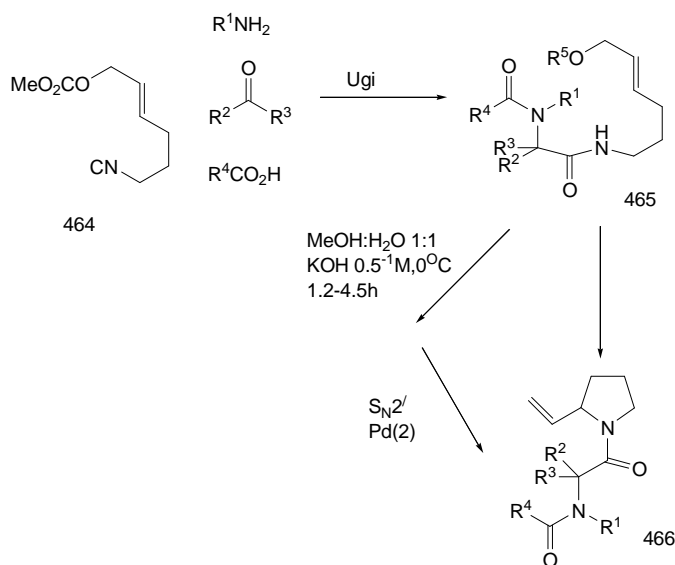


Scheme 134

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 135



Scheme 136

466 (Scheme 136). This protocol represents a further example of how secondary transformation can expand the scope of isocyanide-based multicomponent reaction [129].

Gold-catalyzed reactions have emerged as powerful and highly selective tools for organic synthesis in recent years. Obviously gold complexes exhibit a high reactivity as rather soft Lewis acids. Kadzimirsz used L-valine **467** as chiral amine component and benzaldehyde **468** and isocyanides afford highly functionalized amines **469**. In the next step hydroamination succeeded with just 3 mol% gold chloride as catalyst in acetonitrile at $80^\circ C$ produces dihydro isoquinolines **470** as a result of 6-*endo dig* procedure. Whereas the isoindoles **471** derive from 5-*exo dig* products which of course isomerizes under aromatization under the acidic reaction conditions. Absolutely they combine Ugi reaction and gold-catalyzed cyclization to produce chiral dihydro isoquinolines

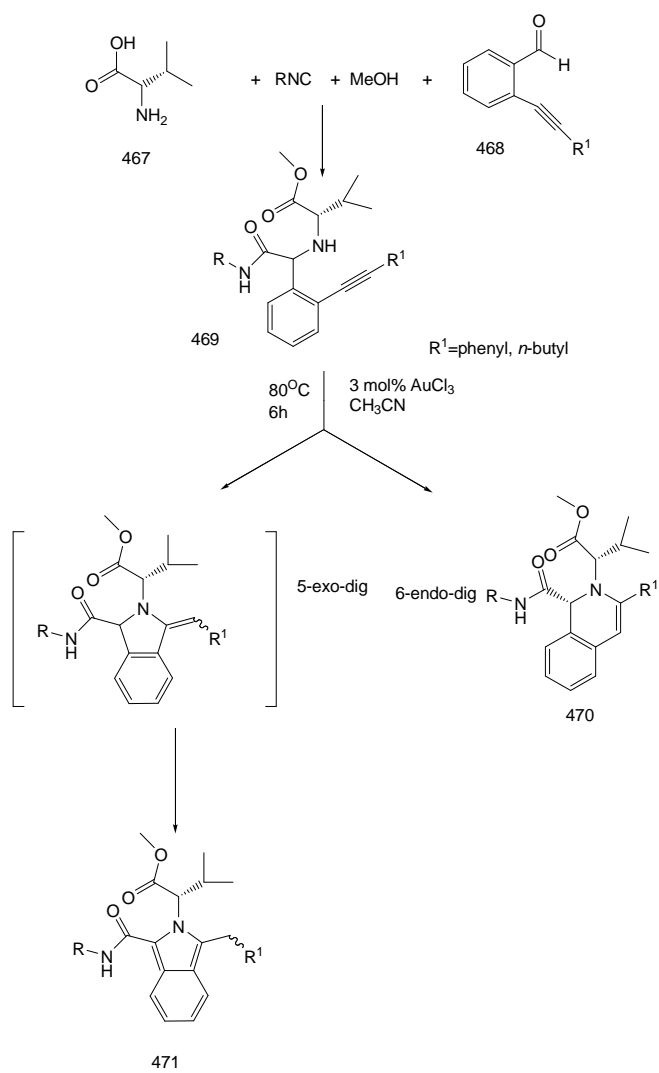
and isoindoles [130].

Ugi-4CR with a copper-catalyzed cyclization have been combined. The Ugi-four component reaction between amine, aldehyde, carboxylic acid **472** and isocyanide **473** proceed to afford peptide-like structure **474**. The subsequent copper-catalyzed cyclization a catalyst combination of CuI (10 mol%), 1,10-phenanthroline (20 mol%) and Cs_2CO_3 (2 equiv.) in DME produce highly substituted benzoxazoles and benzothiazoles [131].

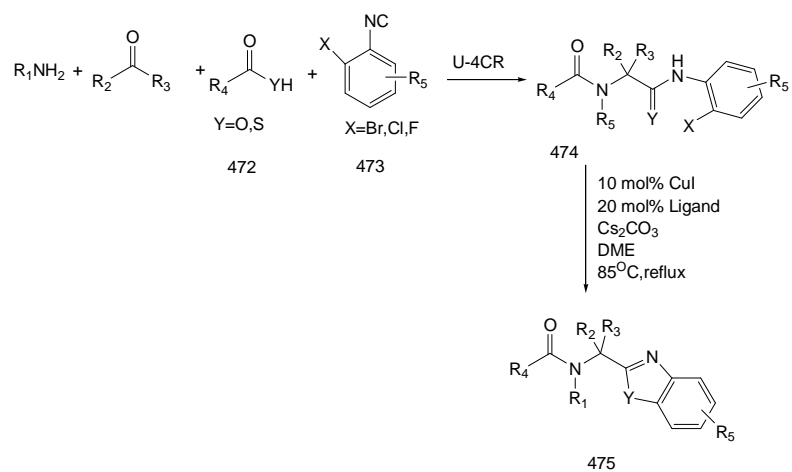
Base-Catalyzed Upon Ugi Adducts

Banfi group has reported the products of an Ugi-4CR employing locate derived *O*-protonated α -hydroxycarbonyl derivatives underwent, during the subsequent *O*-deprotection reaction, an unexpected acyl migration from nitrogen to oxygen. After ester saponification, treatment of the resulting

Heravi & Moghimi

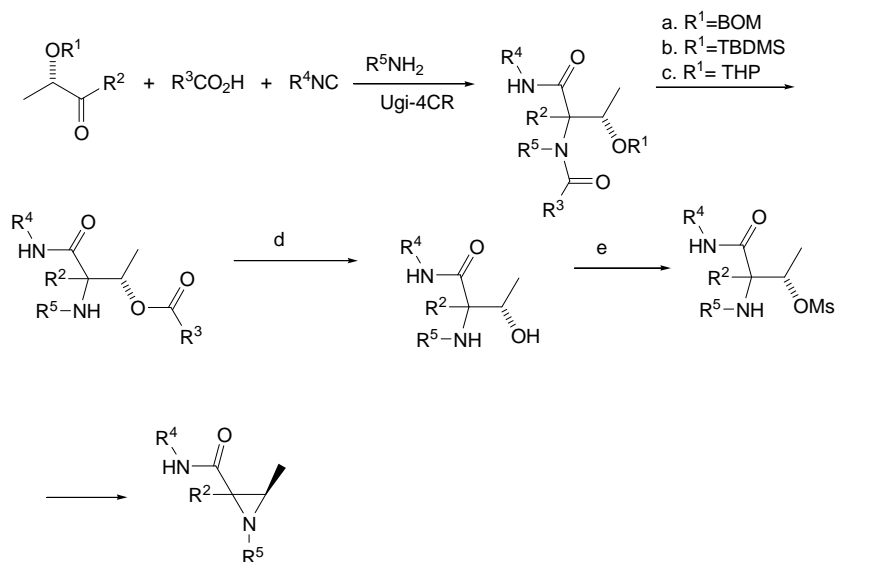


Scheme 137



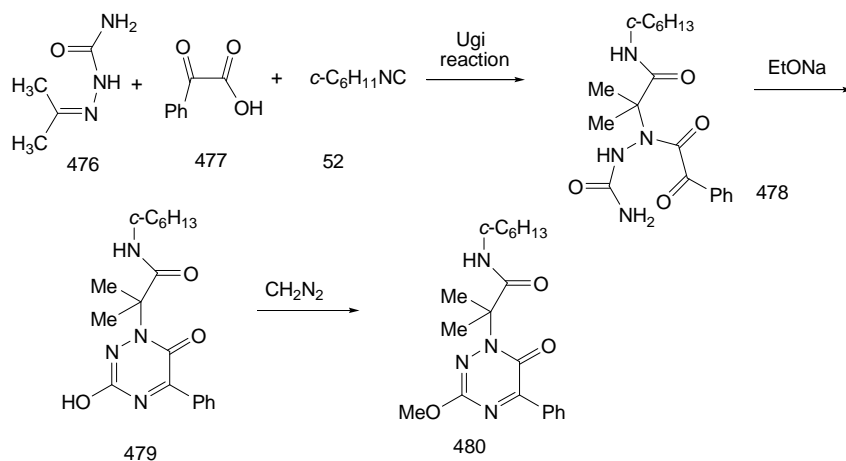
Scheme 138

Catalytic Multicomponent Reactions Based on Isocyanides



a) H₂, Pd/C, EtOH/AcOH 96:4, rt; b) camphorsulfonic acid, MeOH,rt; c) HCO₂H/THF/H₂O 3:2:1 or HCO₂H/NeOH/H₂O 3:1:1, 45°C; d) KOH, MeOH, rt; e) MsCl, Et₃N, CH₂Cl₂, -30° → rt.

Scheme 139



Scheme 140

α -aminoalcohol with mesyl chloride gave rise to a regioselective and stereospecific cyclization to give a series of highly functionalized aziridines in good yield [132].

The Ugi reaction between cyclohexyl or benzyl isocyanide **52**, benzoyl- or 4-methoxybenzoyl formic acid **477** and semicarbazones **476** in methanol for 3 days to give Ugi adducts, which were stirred with sodium ethoxide in ethanol

for 12 h to give 3-hydroxy-6-oxo[1,2,4]triazin-1-yl alaninamides **479**. If **479** treated with diazomethane for 12 h, *O*-methyl derivatives **480** were obtained [133].

The Ugi four-component one-pot condensation between anilines **483**, aromatic aldehydes **482**, isocyanides **481** and α -oxo acids **484**, produces the normal adducts **485** that then cleaved under alkaline hydrolysis and prepare 2,*N*-diaryl

glycines **486** in good yields and purity from the reaction mixture and converted into the corresponding α -amino acids **487**.

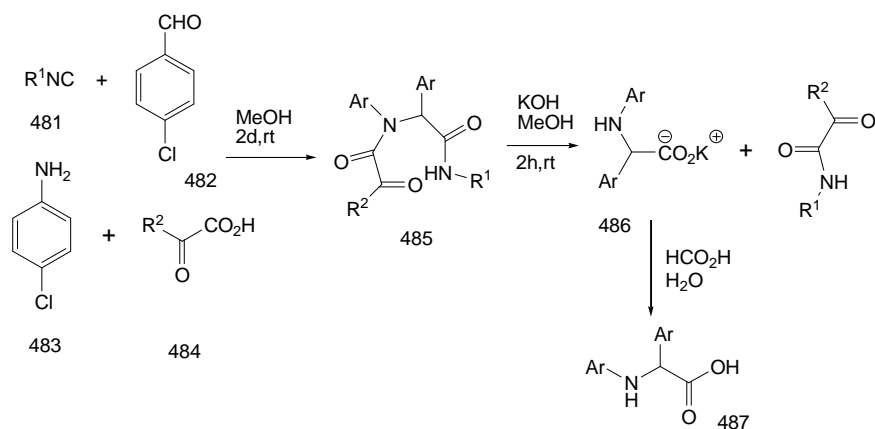
The reaction did not afford α -amino acid salts when Ugi-4CC adducts arising from aliphatic aldehydes, ketones, and alkylamines [134]. When **489** was treated with the base a cyclization to 2,5-dioxo-1,3-diphenyl-3-hydroxy-1,4-diazaspiro [5,5]undecane **490** was produced (Scheme 142).

Methyl *o*-formyl benzoates **491** as bireactive carbonyl component, isocyanides and trimethyl silyl azide participate in the Ugi four component condensation. The Ugi reaction took place by simple stirring the reaction in methanol for 2 days at room temperature. When anilines were employed, the Ugi adduct were isolated and cyclised easily. The Ugi adducts were cyclised to the corresponding isoindolinones **493** in very good yields upon treatment with sodium ethoxide in ethanol. Thus they have developed a method for assembling two interesting heterocyclic systems by means of combination U-4CR/intramolecular amidation [135].

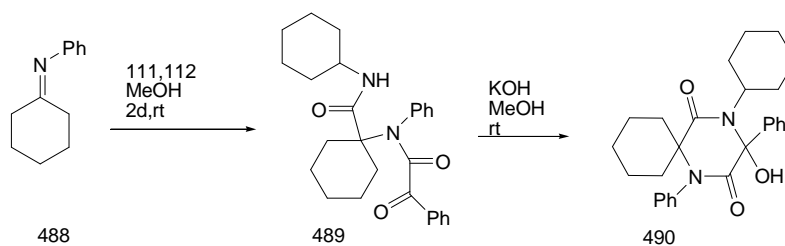
Trifilenkov, have shown that 3-oxoisindoline-1-carboxamides can be efficiently prepared by a novel modification of four component Ugi reaction. They also attempted to use 2-chloro-5-nitrobenzoic acid as the carboxylic acid component in the Ugi reaction. When bifunctional reagent was used, the reaction leads to standard U-4CC products that can undergo intramolecular *O,N*-arylation under elevated temperature in the presence of bases to give the corresponding heterocyclic products.

The reaction of 2-chloro-5-nitrobenzoic acid, aldehyde, acid, isonitrile resulted in formation of the classical U-4CC product. This compound can undergo intramolecular cyclization at elevated temperature in DMF in the presence of Et₃N to the corresponding 3-oxoisindoline-1-carboxamides [136].

Xing *et al.* envisaged that 2-aminophenols could be used in U-4CR as the amine component without protection of the phenolic hydroxyl group. The reaction of 2-aminophenols, aromatic aldehydes, α -bromoalkanoic acids, and isocyanides

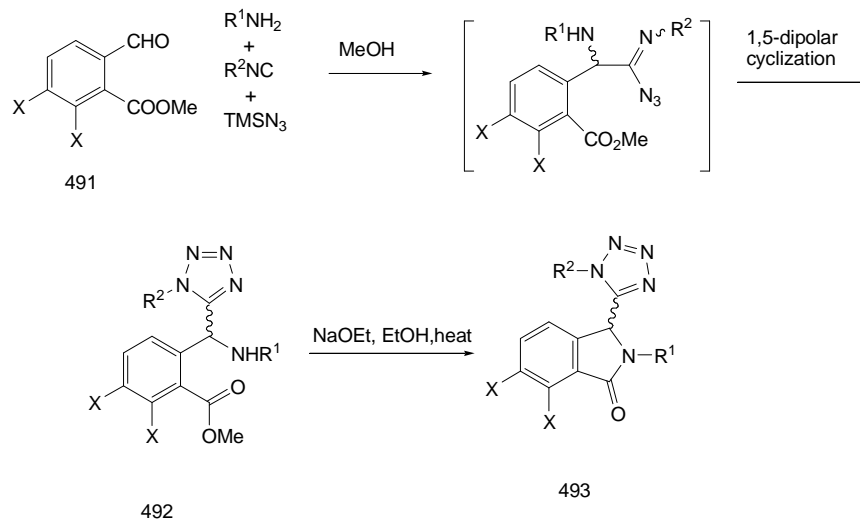


Scheme 141

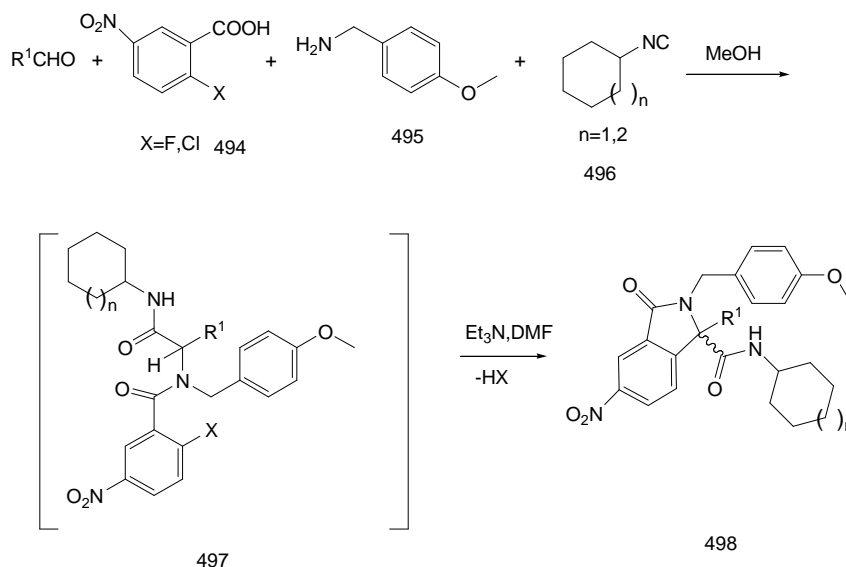


Scheme 142

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 143

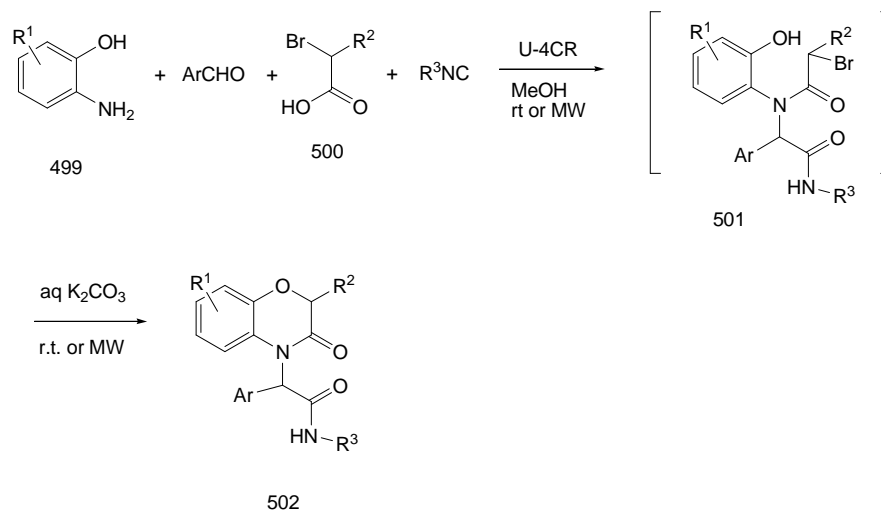


Scheme 144

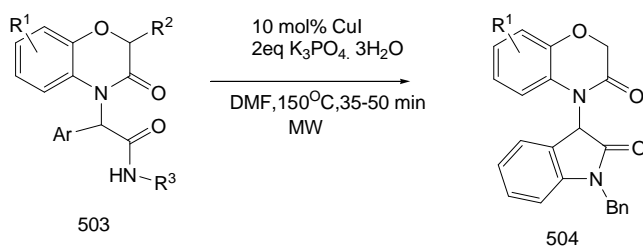
(U-4CR) was carried out in MeOH and then without isolation of the acyclic product, an aqueous solution of K₂CO₃ was added for promoting the intramolecular *O*-alkylation produces highly functionalized 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines in 61-95% yields. To accelerate the one-pot U-4CR and subsequent procedure they used microwave irradiation (Scheme 145).

They used controlled microwave heating for the intramolecular amidation (*N*-arylation) of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines in the presence of 10 mol% CuI as a catalyst and 2 equiv. of K₃PO₄·3H₂O in DMF at 150 °C for 35-50 min [137]. The expected 2-oxindoles **504** were obtained in 80-93% yields (Scheme 146).

Wu carried out the Ugi reaction between 2-aminophenols,



Scheme 145



Scheme 146

2-alkynylbenzaldehyde, 2-chloro-5-nitro-benzoic acid and benzyl isocyanide in methanol at 80 °C in closed vials under microwave heating for 20 min to form the acyclic product. Then 1.2 equivalents of aqueous K₂CO₃ at 100 °C for another 10 min promote the intramolecular nucleophilic aromatic substitution between the phenolic OH and 4-nitrophenyl chloride moieties. This sequence is microwave-assisted, one-pot U-4CR-S_NAr synthesis of dibenzo[*b,f*][1,4]oxazepine-11(10*H*)-ones.

The intramolecular 7-endo-dig hydroamidation reaction is catalyzed by 10 mol% Pd(PhCN)₂Cl₂(THF, 60 °C, 24 h) to afford 1,3-dihydro-2*H*-3-benzazepin-2-ones [138].

Neo and his group [139] performed the reaction between 3-formyl chromone, aniline, cyclohexyl isocyanide and cyanoacetic acid by simply combining the four components in methanol solution and Stirring the mixture at room

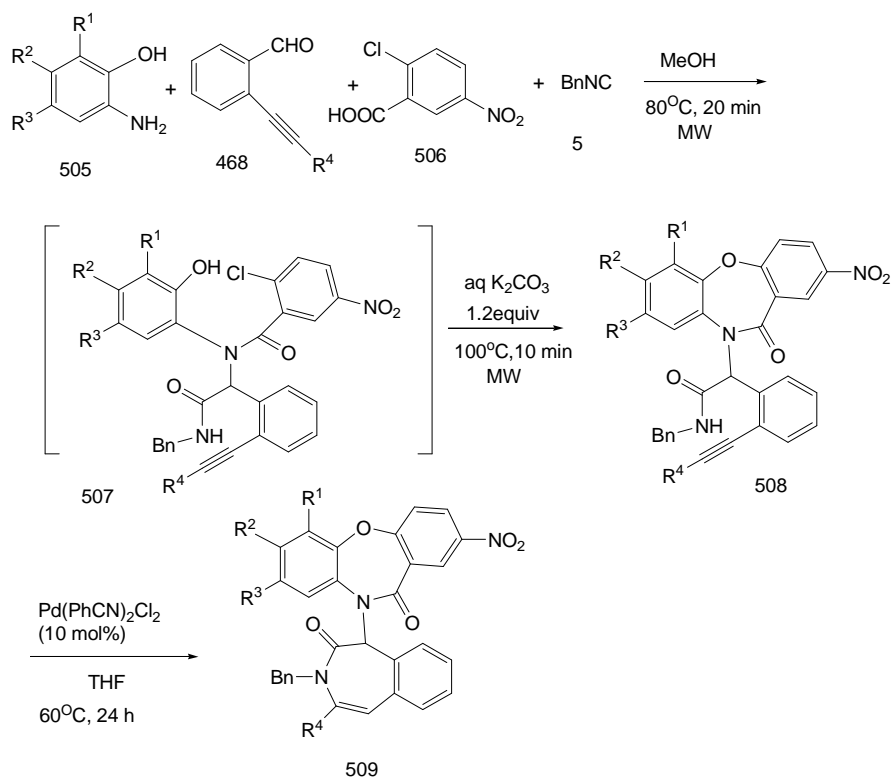
temperature readily led to the formation of a precipitate of the expected Ugi four-component adduct. Subsequent treatment of **513** with potassium hydroxide in methanol resulted in the immediate formation of an orange precipitate. The base promoted an intramolecular addition-elimination reaction of the methylene alpha to the nitrile group onto the chromone endocyclic double bond. Consequently the six-membered pyranone ring was opened and a new pyridone ring was formed.

Convertible isocyanide proved to be well-behaved in U-4CR. The α -aminoacyl amide derivatives are formed in yields ranging from 51-90%. Subsequent transformations to the indolyl amides **518** with catalytic amounts of PPTS in refluxing benzene or toluene was performed in quantitative yields. The saponification of **518** under weak basic conditions at room temperature afforded the carboxylic acid derivatives **519**. After methanolysis of **518** in the presence of catalytic amounts of Et₃N, the methyl esters **520** were obtained in high yields. The transamidation of **518** with allyl amine provided the allyl amide derivatives **521**. This reaction is applicable for Passerini reaction [140].

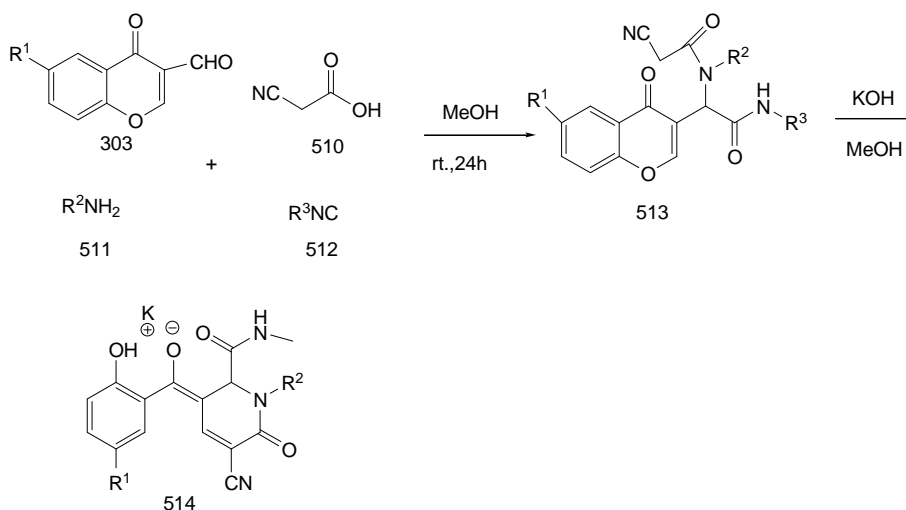
A general and efficient one-pot synthesis of highly functionalized dibenz [*b,f*][1,4]oxazepines *via* microwave assisted one-pot U-4CR and intramolecular *O*-arylation. After producing Ugi adduct, aqueous solution of potassium carbonate afford final product has been established.

In attempt to produce intramolecular amidation, they used

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 147

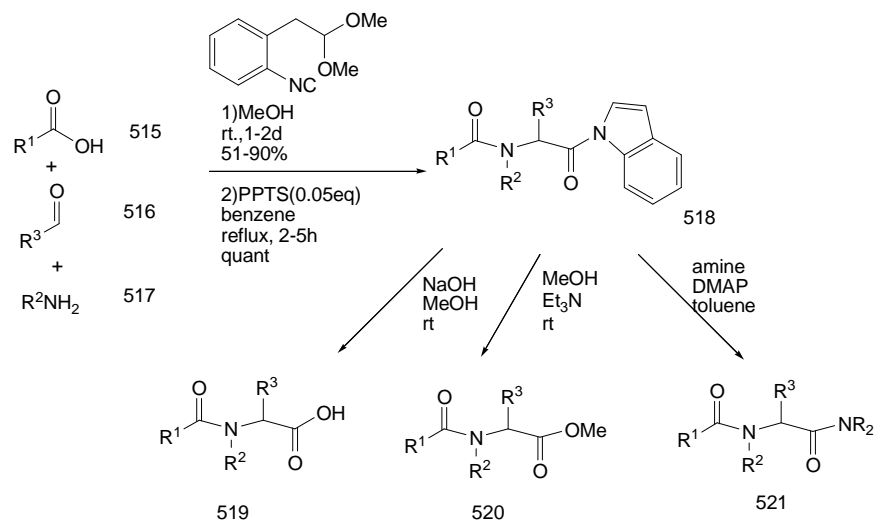


Scheme 148

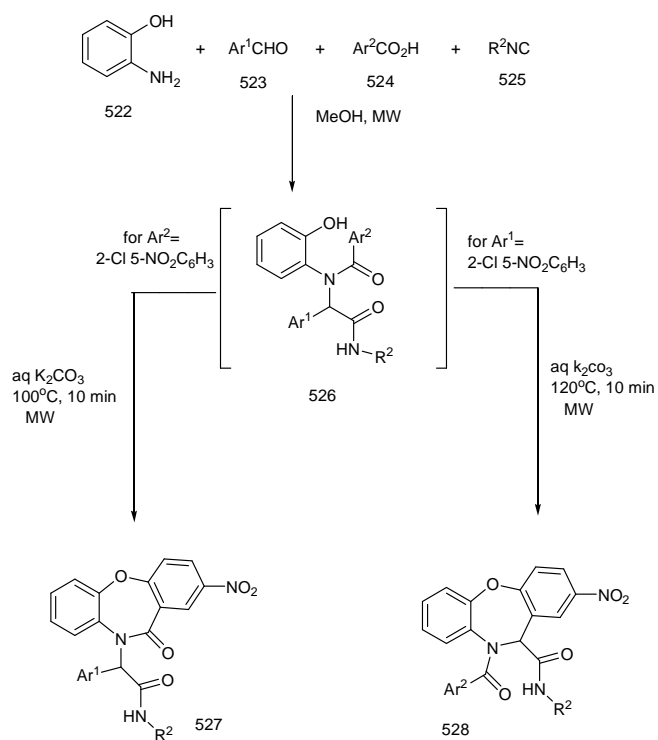
$\text{Pd}(\text{OAc})_2$ and BINAP to produce 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines [141].

Debdashi *et al.* synthesized a series of amines that could be

involved in multicomponent reaction utilizing isocyanides. The amines are connected to the imidazolium entities *via* an ester function that could be cleaved to recycle the ionic



Scheme 149



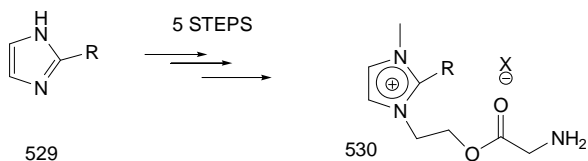
Scheme 150

support.

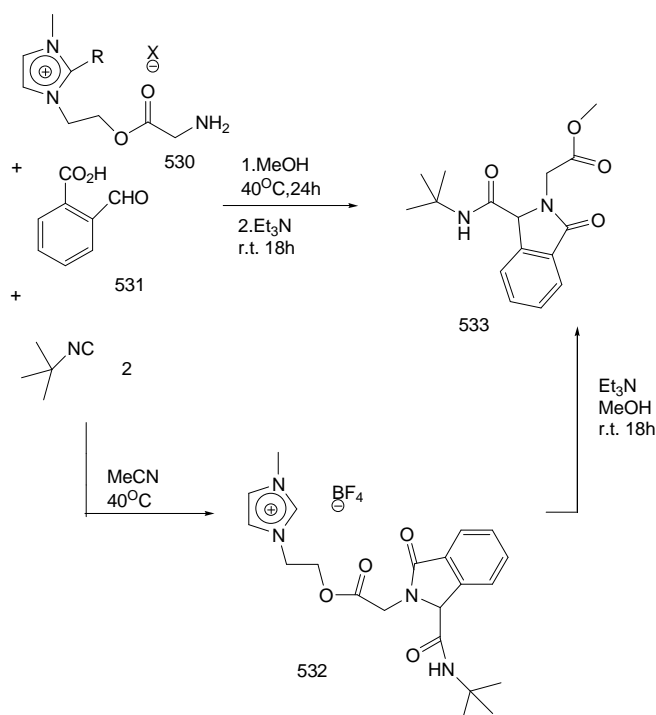
Then the Ugi reaction between an amine, aldehyde, carboxylic acid and an isocyanide was performed in methanol

at 40 °C. If the Ugi compounds were partially cleaved from the ionic support during the reaction furnished a stable compound, it could be seen that the imidazolium ring was compatible with

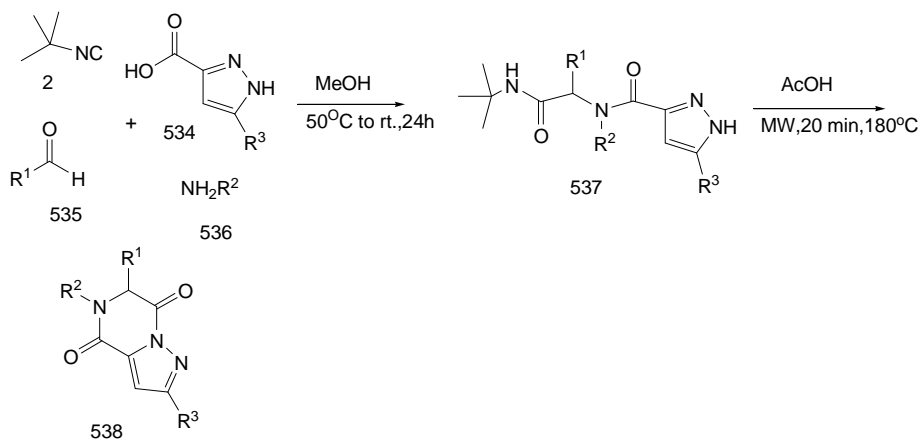
Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 151



Scheme 152



Scheme 153

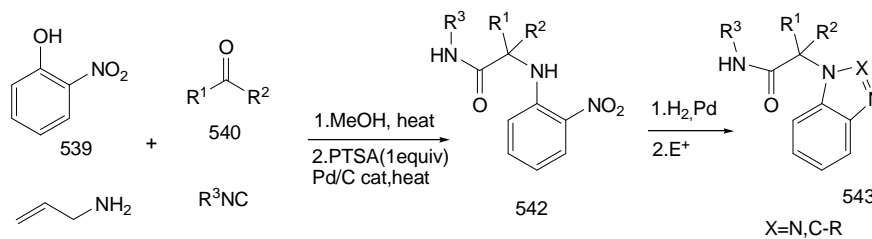
tert-butyl isocyanide under the condition used. To avoid partial cleavage during the Ugi reaction, they decided to use a solvent other than methanol, and performed the reaction in acetonitrile. The solubility of the amine 530 in acetonitrile is very low, but by using a long reaction time (five days), we could obtain the *O*-grafted ester **532** in a 56% yield without observing cleavage or degradation. Subsequent cleavage, under the conditions used before, finally afforded compound **533** in 80% yield [142].

Acid-Catalyst Upon Ugi Adducts

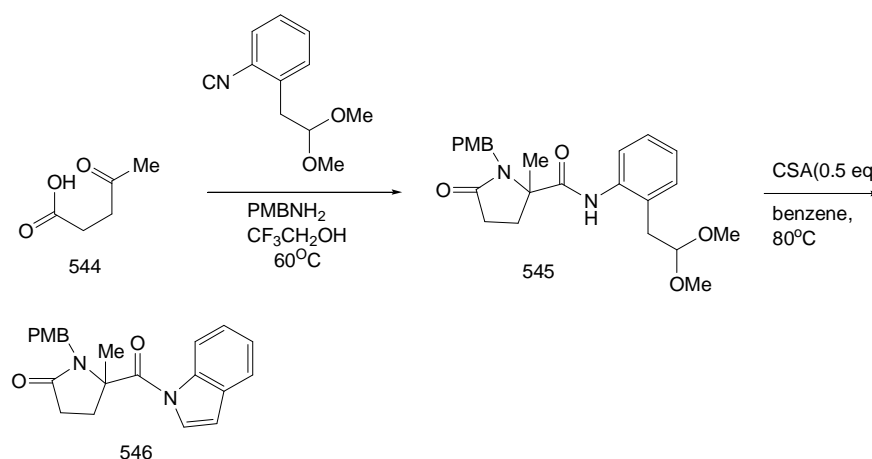
Two-step, one-purification approach to medicinally important 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones using an Ugi 4CR-post-MCR cyclization approach. It is the first time that microwave assists cyclization process has been established [143].

To prepare bisamides, aldehyde, amine, isocyanide and 1*H*-pyrazole-3-carboxylic acid react in methanol at 50 °C. Without further purification, **537** dissolved in acetic acid and heated under microwave irradiation to produce **538** in moderate to good yield.

In The Ugi reaction poor results obtained with ammonia and have led chemists to choose convertible primary amines such as nitro benzylamine that can be deprotected after Ugi reaction [144]. After completion of the Ugi-smiles step, the mixture was treated with 1 equiv. of *p*-toluenesulfonic acid followed by addition of palladium on carbon. After additional heating the expected secondary amines were isolated (Scheme 154).



Scheme 154



Scheme 155

1-Isocyano-2-(2,2-dimethoxyethyl)benzene as a convertible isocyanide which readily affords pyro glutamic acids *via* the Ugi reaction. The initial Ugi product, anilide derived from levulinic acid readily converted to the *N*-acyl indole under mild conditions [145].

SUPPLEMENTARY

Due to prolongation of peer review of this article, it lacked most recent relative reports. Hence we decided to make this review more useful and interesting for the readers by doing another literature survey and create supplementary section.

Shaabani *et al.* have recently published a review article about isocyanides in Iran [146]. The reaction of 2-aryliminophenols with aryl isocyanides catalyzed by Lewis acid produced 2,3-bis(arylamino)-2,3-dihydrobenzofuranes **548** and 2,3-bis(arylamino) benzo furans **549**. Some derivatives are stable toward oxidation and **548** produced as a

main product [147].

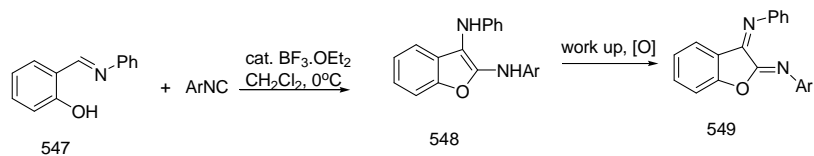
Groebke-Blackburn-Bienyame multicomponent reaction of adenine, guanine and cytosine with aldehydes and isocyanides in the presence of Zirconium chloride afforded *N*-fused aminoimidazole **553-555**.

Condensation of *para*-substituted benzaldehydes and 5-carboxy-2-amino pyridine **556** with catalytic amount of Sc(OTf)₃ occurs at room temperature for 45 min and then phenyl isocyanide were added to yield imidazopyridines **557** (Scheme 158).

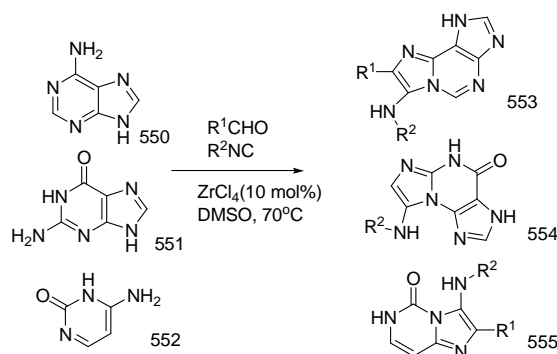
Then they converted the **557** structure to oxadiazoles and phenyl imidazoles to examine their antimicrobial behavior against Gram-positive and Gram-negative bacteria [149].

Condensation between aldehydes, isocyanides and allylamine in the presence of Sc(OTf)₃ as a catalyst and benzene as a solvent produced 5-amino-oxazole. Using Lewis acid and benzene was necessary to obtain high yields. After this step, addition of maleic anhydride and irradiation

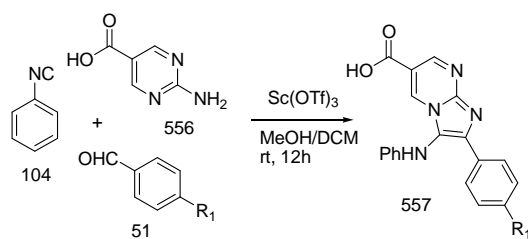
Catalytic Multicomponent Reactions Based on Isocyanides



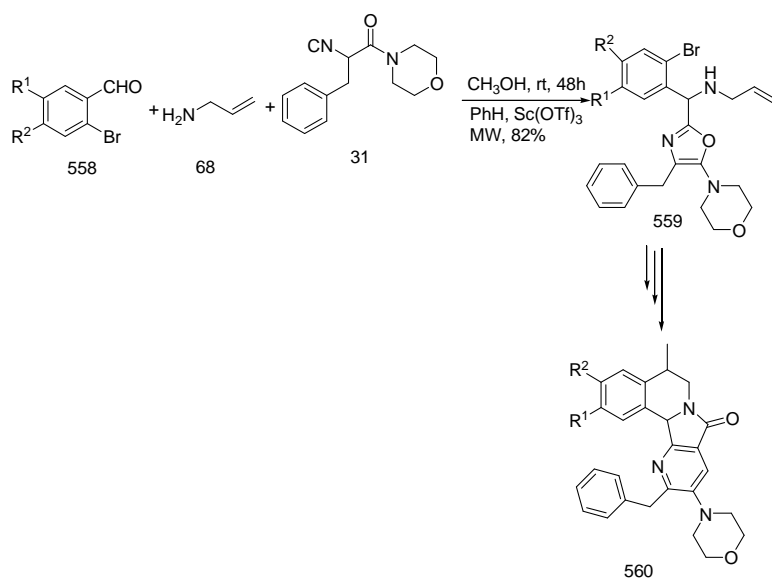
Scheme 156



Scheme 157



Scheme 158



Scheme 159

continued. Finally three portion of Bu_3SnH and irradiation gave in a single one-pot process. This is the way to synthesis of tetracyclic lactam systems which are important due to their biological activities [150].

Akbarzade [151] reported an efficient procedure for the synthesis of ferrocenyl imidazopyridines. The best yield was obtained in the presence of indium chloride as a catalyst.

Bridged imine, phenylglyoxalic acid and homoveratyl isocyanide was chosen for Ugi reaction and then Pictet-Spengler type cyclization of Ugi product was promoted in the presence of TMSOTf as a Lewis acid [152].

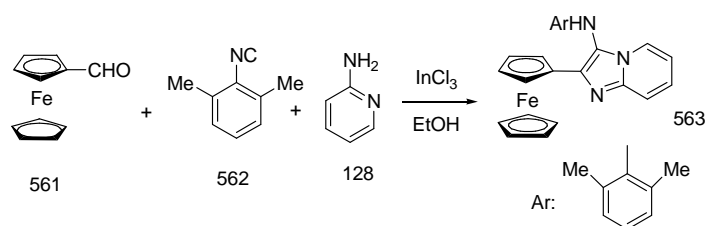
Groebke-Blackburn multicomponent reaction is important because imidazo-fused scaffolds have biological importance [153]. In order to improve this reaction condition Tsurulnikov

used trimethyl silyl chloride as a promoter (Scheme 162).

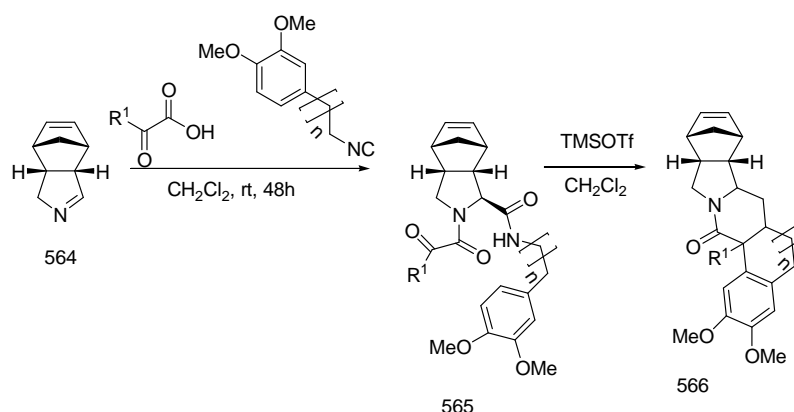
Krasavin investigated the possibility of a new IMCR using various aliphatic keto carboxylic acids and Boc- or Cbz-protected hydrazine which was anticipated to yield *N*-amino lactams. In the absence of ammonium chloride the reaction was slow and only a trace amount of product was obtained (Scheme 163). This reaction required excess amounts of keto acids and the hydrazine to complete. Ammonium chloride acts as mildly acidic promoter [154].

The three-component reaction between *N,N*-dimethyl aniline isocyanide and carboxylic acid produces α -amino amides in moderate yields.

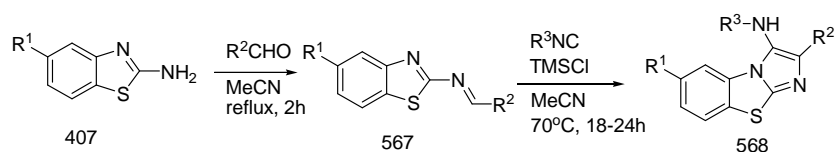
Copper-catalyzed strategies for the activation of $\text{sp}^3\text{C-H}$ α to



Scheme 160

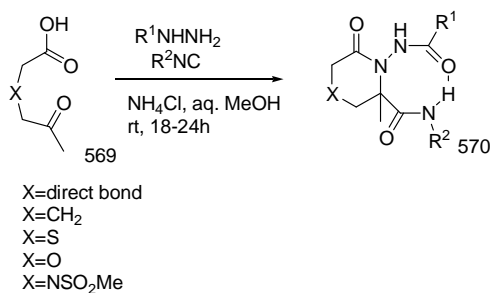


Scheme 161



Scheme 162

Catalytic Multicomponent Reactions Based on Isocyanides



Scheme 166

nitrogen under the promotion of peroxides have been documented [155].

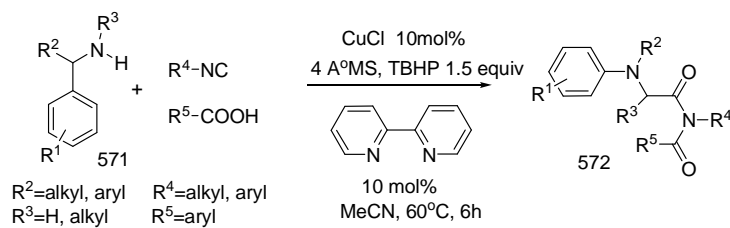
A novel three-component reaction between isocyanides, various thiol **573** and gem-dicyano olefins bearing electron

withdrawing groups was performed in the presence of base to activate thiols [156].

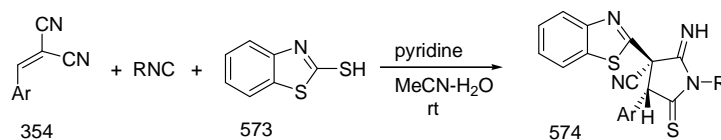
Kolontsova used S-nucleophiles in the reaction with isocyanides and gem-dicyano olefins to obtain 2-aminopyrroles or thioimidates. The reaction proceeds in the presence of organic bases such as pyridine. Water as an additive can enhance the reaction rate. **576** can be obtained when they use 1-adamantyl isocyanide because of steric hindrance during the cyclization step [157].

One-pot reaction between 3-morpholino-3-thioxopropane-nitrile **578**, isocyanides and α -halo ketones in the presence of potassium carbonate afforded trisubstituted thiophenes [158] in moderate yields (Scheme 170).

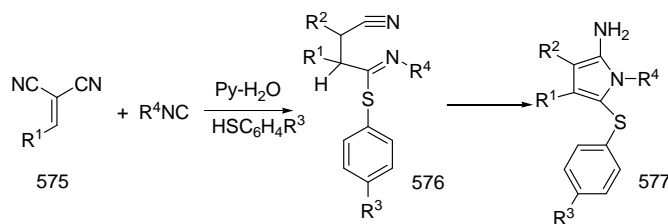
One-pot two step procedure for the synthesis of 2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine-2-carboxamide



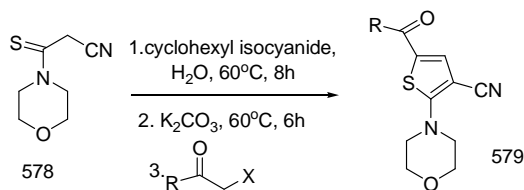
Scheme 167



Scheme 168



Scheme 169



Scheme 170

derivatives was investigated by Shaabani and co-workers (Scheme 171). The reaction was initiated by the reaction of diketene and *o*-phenylene diamine as a limiting reactant. After consumption of *o*-phenylenediamine **78** was reacted with isocyanide in the presence of *p*-TsOH, H₂O [159].

Ugi three-component coupling reaction of phenyl isocyanide, D-xylose and amidine afforded imidazo[1,2-*a*]pyridines among the catalysts, K-10 clay gave the best result

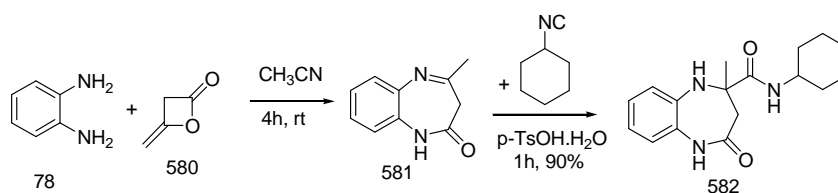
[160].

One-pot three component condensation reaction of aromatic amines, carbonyl compounds and isocyanides in the presence of EDTA afforded 3,4-dihydroquinoxaline-2-amine derivatives [161].

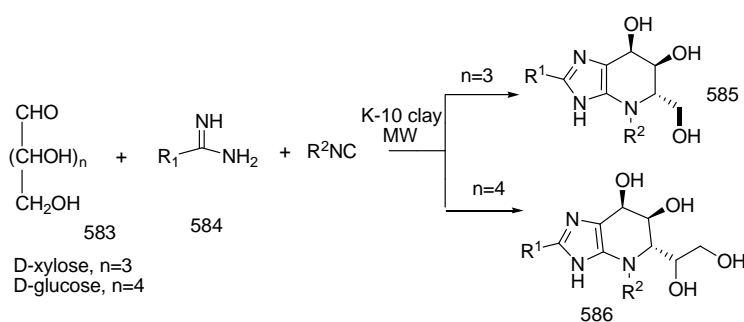
Three-component reaction of isocyanide, acetylenedi-carboxylate and 4-hydroxy coumarine in water in the presence of a phase-transfer catalyst produces pyrano[3,2-*c*]coumarines **589** in good yields [162].

Nanoparticles are important catalysis because of their improved efficiency under mild and environmentally benign conditions [163]. Ramazani *et al.* developed one-pot reaction between isocyanides, dibenzylamine and 2-formyl benzoic acid in the presence of silica NP at room temperature to produce isocoumarine derivatives (Scheme 175).

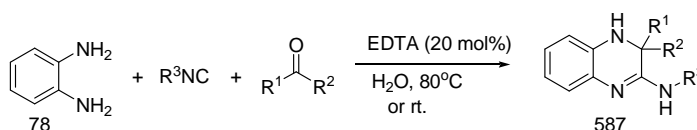
One-pot tandem Ugi/click strategy for the synthesis of triazolo-modified peptide molecules in the presence of



Scheme 171

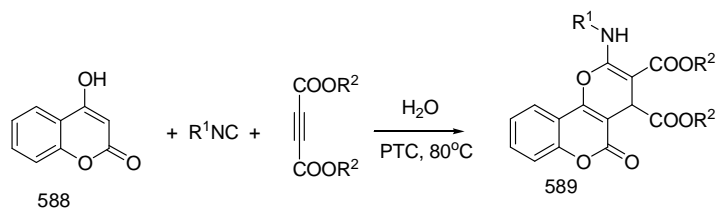


Scheme 172

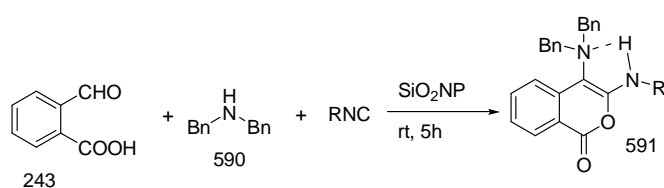


Scheme 173

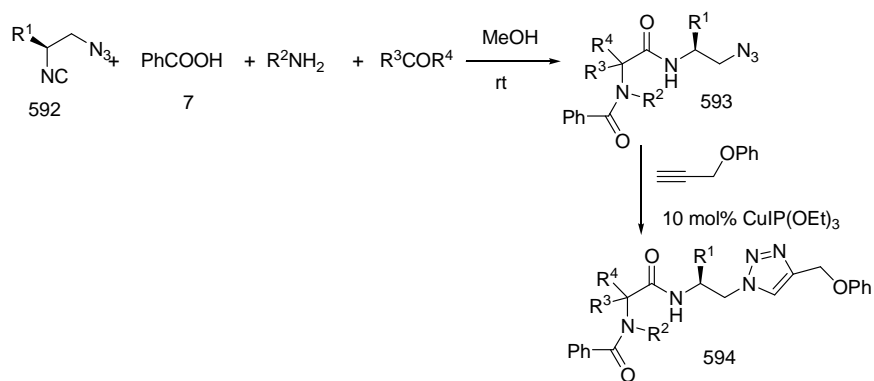
Catalytic Multicomponent Reactions Based on Isocyanides



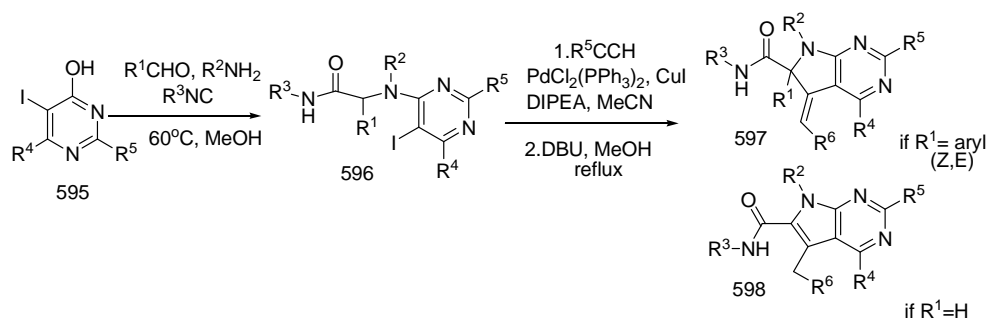
Scheme 174



Scheme 175



Scheme 176



Scheme 177

CuI(OEt)₃ as a catalyst.

Isocyanazides are promising compounds for the preparation of chiral isocyanotriazoles by click chemistry. Copper is coordinated to both the isocyanide and the α -nitrogen of azide group. Complexation of isocyanide with copper can be used as a protection strategy for the isocyanide residue [164].

The Ugi-Smiles adduct can be prepared by reaction of *ortho* iodopyrimidine-4-ol **595**. Then a one-pot procedure for the Sonogashira/cyclization step was performed by adding DBU in the mixture after the palladium-catalyzed step. Under these conditions, both *Z,E* isomers of pyrrolopyrimidines obtained in a 4:3 ratio in a 60% overall yield. The reaction was also proceeded in *tert*-butoxide in refluxing tetrahydrofuran [165].

CONCLUSIONS

In this review, some applications of catalytic systems in isocyanide-based multi component reaction have been discussed. As it was shown, a great number of catalytic systems can catalyze this important MCR and we hope it was in interest of chemists and other readers.

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