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# Towards click chemistry: Multicomponent reactions *via* combinations of name reactions

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ABSTRACT

In this report, we try to show the importance of incorporation of name reactions in the sequential cascade reaction in which significantly decreasing the number of steps towards an ideal and practical multi-step synthesis of natural products as well showing virtually all the advantages already mentioned for "Click Chemistry". In addition, since the chiral inductions are desired for most of these sequential name reactions, their asymmetric catalyzed reactions were also described.



**Contents**



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## 1. Introduction

*The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole'.*

Sir John Cornforth.[1,2]

Molecular diversity, modularity and efficiency are intrinsic in organic synthesis, and expected being involved in the synthesis of complex and multifunctional compounds. Generally speaking, "Click Chemistry" is the class of biocompatible reactions anticipated principally to link substrates of choice with specific biomolecules. Natural products are generated by joining small modular units *via* biosynthesis as well as photosynthesis. Thus, the first criteria required for "Click Chemistry" is well met by reactions occur in nature and their mimic in laboratory is the closest and most desirable to the brain and heart of most synthetic organic chemists. Two classic modern total synthesis are the quinine total synthesis[3–11] and total synthesis if Taxol.[12]

On the other hand "Click Chemistry" is a term that was initially devised by K. B. Sharpless in 1998 and fully described in 2001.[13,14] According to Sharpless et al. a click reactions should be proceeded to completion in one-pot reaction fashion, they are high yielding, wide in scope, generate minimal offensive by-products that can be easily eliminated. Where appropriate, they are stereo and region-selective and specific, simple to conduct in conventional safe organic solvents, less toxic solvents or even better done in either water or under solvent-free conditions thus, meaningfully more benign from environmental point of view They are "spring-loaded"-characterized by a high thermodynamic driving force resulting in a single reaction product in high yield and with high reaction specificity. These salient features represent a part of the field of chemical biology. Thus, click chemistry is expected to plays a key role in the total synthesis of natural products.[13] Huisegn 1,3-dipolar azide/alkyne cycloaddtion reaction[15] was a precious phenomenon which the broad scope and molecular diversity of this reaction was first realized and reported by German chemist, Rolf Huisgen in 1961. Generally speaking, Huisegn 1, 3-dipolar cycloaddition is a reaction between an azide and a terminal or internal alkyne, resulting in 1, 2, 3-triazoles.[16]

It was particularly stirred up the courtesy of the American chemist K. Barry Sharpless (Nobel prize laureate in chemistry, 2001) who referred, to this 1,3-dipolar cycloaddition as "*the cream of the crop*" of "Click Chemistry".[17] Although, several reactions may show such perfection as far as synthetic organic chemistry concerns nowadays, the Cu(I)-catalyzed Huisgen cycloaddtion reaction is recognized as one of the best transformations out of the complete collection of those reactions which are in agreement with the "Click Chemistry" criteria.[18,19]

1,2,3-Traizoles are biologically important class of compounds[20,21] and are present as framework in several natural products.[22] Thus, triazoles as a safe and mild connecting framework can be assembled in several circumstances during total synthesis of natural products *via* "Click Reaction". In addition, the extremely stable and aromatic nature of the triazole ring with large dipole moment along with hydrogen bonding aptitude, make it a moiety of great impending usefulness. Above all, the term "Click Chemistry" may has been influenced and coined by the giant organic chemist of 20th Century, K. Barry. Sharpless.[17,23,24]

There are several important name reactions in organic chemistry. Among the tens of thousands of organic reactions that are known, hundreds of such reactions have reached such status to be named after its discoverers or developer. Well-known examples include the Grignard reaction, the Sabatier reaction, the Wittig reaction, the Claisen condensation, the Friedel-Crafts acylation, and the Diels-Alder reaction. Some cases of reactions that were not actually discovered by their names discovers are also known. Examples include the Pummerer rearrangement,[25] the Pinnick oxidation[26] and the Birch reduction.[27]

Shall we contemplate that the click chemistry is not attributed to a single specific reaction, but defines a route of forming molecules that follows the biosynthesis of naturally occurring compounds. In nature, substances are generated by joining small modular units. Nowadays, Click Chemistry" is not considered being limited to biological conditions.

One of the most challenging aspects of designing a route to total synthesis is devising sequences of reactions that will lead from a designated starting materials to a desired target. Generally speaking, an ideal design of synthetic pathway for any total synthesis is the one which lead to the desired target with lowest possible steps. This route then should be studied from different points of view and being found reasonable and operational. Thus, the designers should try to decrease the number of steps as many as possible. One of the most appropriate ways to make a total synthesis more concise is combining steps together. To do so, it is absolutely essential to become comfortable with each step, considering the sequential steps, and examine the possible combination of two or more steps together. On the other hand, the status of organic synthesis is hindered by costly and time-consuming protection-deprotection protocol.[28]

Each protection and deprotection steps also need purification procedures in a multistep synthesis. To avoid these draw backs, the synthetic potential of multicomponent, cascade, cascade and domino reactions should be considered in designing an ideal route for the total synthesis of natural products as well as efficient and stereoselective construction of complex molecules from simple precursors in a single process. In particular, domino reactions mediated by organocatalysts are in a way biomimetic[29,30] as this principle is used very efficiently in the biosynthesis of complex natural products starting from simple precursors.

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more commercially available or readily accessible starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. "MCRs convert more than two molecules straightly to the expected products". Remarkably, a name reaction is a chemical reaction, which has reached to such status from different points of view, being named after its discoverers or developers. Among the tens of thousands of organic reactions that are known, hundreds of such reactions are well-known enough to be named after people.

As organic chemistry developed during the 20th century, chemists started associating synthetically useful reactions with the names of the discoverers or developers; in many cases, the name is merely a mnemonic.

Since MCRs are one-pot reactions, expectedly, they can be conducted much easier than multistep reactions. Combined, with high-throughput library screening, this protocol can be considered as an important development in the rational drug design in the terms of rapid and unambiguous identification and optimization of biologically active lead compounds. Libraries of small-molecule organic compounds are perhaps the most desired class of potential drug candidates, because standard peptides and oligonucleotides have limitations as bioavailable therapeutics. In the last decade, with the introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and

development of several MCRs for the generation of libraries of heterocycles.[31–42]

As far as the organic synthetic chemists concern an ideal reaction pathway for the synthesis of structurally complex substances should involve sequences in which stereocontrolled formation of multiple carbon-carbon bonds take place in a single step starting from simple commercially available or easily accessible compounds.

Several organic reactions and reaction sequences have been developed for the construction of structurally natural products and non-naturally occurring complex compounds. Obviously, these reactions and reaction sequences are not expected being as effective and superior as enzymatic reactions in terms of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) or in the environmental science and economic feasibility for chemical reactions. Consequently, much attention has been paid to the development of multicomponent reactions (MCRs), because of the aforementioned advantages and merits[43–48] In spite of concentrated interest, there are only few reports of diastereo- or enantioselective MCRs for the preparation of stereochemically complex polycyclic compounds and total synthesis of natural products.[46–48] A key to many useful MCRs is the amalgamation of a Diels-Alder and Sharpless Click Reaction sequences for the construction of complex polycycles and as few steps of total synthesis of natural products in a completely stereocontrolled fashion.[49–55]

Recent investigations have resulted in development of novel organocatalytic MCRs or asymmetric installation reactions of simple substrates in one pot manner, such as organocatalyzed asymmetric Michael/aldol, Knoevenagel/Michael, self-aldol, aldol/aldol, amination/aldol, Knoevenagel/Diels-Alder, and Knoevenagel/Diels-Alder/epimerization reaction sequences.[56]

Cascade reactions establish an attractive section of organic synthetic chemistry and one which has been the subject of concentrated study in the last decade, as perceived by a several of reviews that have appeared in chemical literature covering different aspects and issues of these processes.[57–61] The undisputable remunerations of cascade reactions are fully recognized, having been described on plentiful occasions, and include atom economy,[62,63] as well as financial prudence, labor, resource management, and waste generation. Thus, cascade reactions are nowadays considered as the outstanding examples falling under banner of “green chemistry”.[64] In another word, a synthetic operation can be performed only using a single solvent, workup procedure, and purification step, which may would otherwise have to be achieved over the course of several distinct steps. Cascade reactions thus subsidize immensely to both the science and art of total synthesis, providing not only improved operational effectiveness but also increase visual demand to design of multi-steps synthesis. In cascade reactions, isolation of intermediates is not required, as each reaction, composing the sequence occurs spontaneously. In the strictest definition of the term, the reaction conditions do not change among the consecutive steps of a cascade and no new reagents are added after the initial step. Although often composed solely of intramolecular transformations, cascade reactions can also occur intermolecularly, in which case they also fall under the category of domino, cascade and MCRs.[65]

Now, the question is what are the challenges for the future? The click chemistry symbolizes an ideal approach in organic synthetic chemistry. This domination has been growing and applied over the 15 years in biology and material science due to its reliability and simplicity but most importantly to it is impeccably orthogonal to the acid-base reactivity, which is vital to bio-organic and life chemistry.[66–68]

In the past decade our group has been engaged and studied the application of name reaction in the total synthesis of natural products and regioselective synthesis of 1,2,3-triazoles *via* “Click Reaction” from different points of view[69] including the computational study.[70–72] Our group also is practically engaged in the synthesis of heterocycles[73–77] asymmetric synthesis,[78] applications of sharpless asymmetric epoxidation in total synthesis[79] and total synthesis of natural products.[80–86]

Armed with these experiences, we can realize that *click chemistry actually cannot be inferred to one specific reaction*: Thus, the click chemistry is not attributed to a single specific reaction but defines a route of forming molecules that follows the biosynthesis of naturally occurring compounds. In nature, substances are generated by joining small modular units but nowadays “Click Chemistry” is not considered being limited to biological conditions. Actually, some specific examples can have a comparable or even superior impact as the click reaction, for example, Diels-Alder (DA)[87] or even more profound hetro-Diels-Alder (HAD) cycloaddtion reactions,[88,89] which are frequently used a key step(steps) in the total synthesis of biologically active naturally occurring compounds. Thus, we thought it is worthwhile to attempt to collect and introduce some new sequential cascade organic transformations, which almost fulfill all of the criteria required for a “Click Reaction”. It is also worthy to think about the appetite of such tools and approaching towards other similar reactions which may provide chief benefit to the chemical as well as material communities alike.

It has been already shown that the combination of Cu-catalyzed Hiusegn cycloaddition reaction (Click Reaction) with other well-established reactions such as name reactions in organic chemistry is most beneficial to MCRs resulted in their applications in the total synthesis of natural products.[90] An interesting cascade reaction is the incorporation of a Diels-Alder and Huisgen cycloaddition reaction sequences which can construct complex polycycles in a completely stereocontrolled fashion as reported, previously.[50–55]

In this review, we try to underscore the incorporation of name reactions in the multicomponent reactions, which can be used in the total synthesis of natural products in order to decrease the number of steps by emphasizing to have the advantages already mentioned for sequential cascade reactions and being accepted ideally and practically by synthetic organic chemists. Naturally, since the asymmetric installation is desired, most of these reactions have favorably should have been asymmetrically catalyzed. Remarkably, one type of these cascade reactions are the combination of name reactions which can be effectively used in the total synthesis of natural products. Following their and our paces, in this review we try to highlight the applications of combined cascade name reactions in MCRs in order to introduce some selected reactions proceeding towards the criteria required for Click Chemistry.

## 2. Multicomponent reaction *via* combinations of name reactions

### 2.1. Knoevenagel reaction/Michael reaction

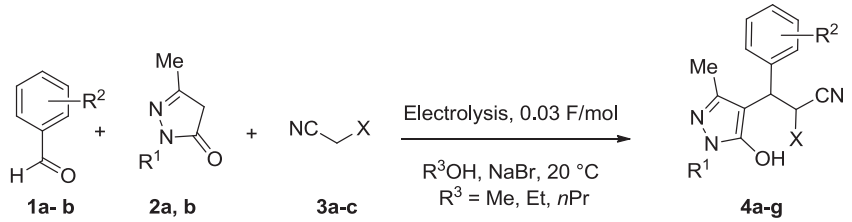
An efficient and operational electrocatalytic system was designed work under neutral and mild reaction conditions. This system provided a rapid and selective sequential Knoevenagel/Michael reaction of 3-methyl- 2-pyrazolin-5-ones **2**, aryl aldehydes **1a-g** and malononitrile or cyano-functionalized C–H acids **3a-c** using an undivided cell in the presence of NaBr as an electrolyte in EtOH as solvent to give 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles **4a-g** in excellent yields at room temperature. This facile electrocatalytic sequential reaction opened an effective and simple multicomponent gateway to afford 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles **4a-g**. These compounds

were found as the auspicious small-molecules for human cardiovascular diseases therapy and other various biomedical applications. This effective electrocatalytic method which efficiently provided the desired 3-(5-hydroxy-3-methylpyrazol-4-yl)-3- arylpropionitriles **4a-g** exemplifies a new, facile and environmentally synthetic concept for MCRs, permitting for the arrangement as well as combination of the synthetic qualities and merits of orthodox MCR with ecological welfares and suitability of simple electrocatalytic method (Scheme 1).[91]

Sequential Knoevenagel condensation of the anion **5** with aryl aldehyde **1** occurred by the removal of a hydroxide anion with generating of compound **6**. Subsequently, hydroxide ion catalyzed Michael addition of 3-methyl-2-pyrazolin-5-one **2** to electron-deficient Knoevenagel adduct **6** resulted in the formation of the desired 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitrile **4** with the renewal of the alkoxide anion in the last step of reaction. The catalytic chain reaction was then followed *via* the interaction of the alkoxide anion with another molecule of C–H acid **3**. The above-mentioned process in the solution exemplifies a classical cascade reaction (Scheme 2).[91]

An asymmetric silica supported cupreine (CPN)-organocatalyzed one-pot, three-component reactions was designed in 2010 by Yuan and co-workers.[92] A one-pot sequential Knoevenagel/Michael/cyclization in the presence of cupreine as catalyst was performed to afford a wide variety of chiral spiro[4*H*-pyran-3,3′ oxindoles] in excellent chemical yields (up to 99%) and with high to excellent *ee*s (up to 97%) using either commercially available or readily accessible starting materials under mild and relatively environmentally reaction conditions. Under secured optimized reaction conditions a one-pot three-component reaction involving differently substituted isatins **9**, malononitrile **3a**, and **10a-e** proceeded smoothly to produce the expected corresponding products chiral spiro[4*H*-pyran-3,3′ oxindoles] **12a-p** in excellent chemical yields and good to excellent *ee*s (Scheme 3).[92] Spirooxindoles usually are considered as promising candidates in drug discovery and medicinal chemistry.[93] Notably, silica supported cupreine (CPN),[94] is frequently used efficiently in different organocatalyzed asymmetric synthesis.[54,55]

A proposed mechanism for the synthesis of spiro[4*H*-pyran-3,3′-oxindoles] **12a-p** is depicted in Scheme 4 just as a hypothesis. In accordance with this suggested mechanism initially, isatin **4** undergoes condensation with malononitrile **3a** to generate compound **13** *via* rapid Knoevenagel condensation. Consequently, it can be suggested that the Michael addition of **10** to **13** mediated by **CPN 11** passes through of transition-state **14** creating **15**. Then, **15** and **16** co-occur as a known keto-enol tautomerism equilibrium in the reaction mixture. Subsequently, the intramolecular cycloaddition, comprising the CN group already activated by OH phenolic group as the electrophile, takes place through **16** to generate **17**. At last, molecular tautomerization resulted in the construction of the anticipated corresponding spiro[4*H*-pyran-3,3′-oxindole] derivatives **12,** which simultaneously discharges catalyst **CPN 11** back into the catalytic cycle. As depicted by transition-state models **14**–**17** in Scheme 4, the stereochemical outcome of this stereoselective cascade reaction mediated by organocatalyst **CPN 11** results from a network of H-bonding interactions among the sequential Michael addition, keto-enol tautomerization, cyclization, and tautomerization steps.[92]




**1a- b** **2a, b** **3a-c** **4a-g**

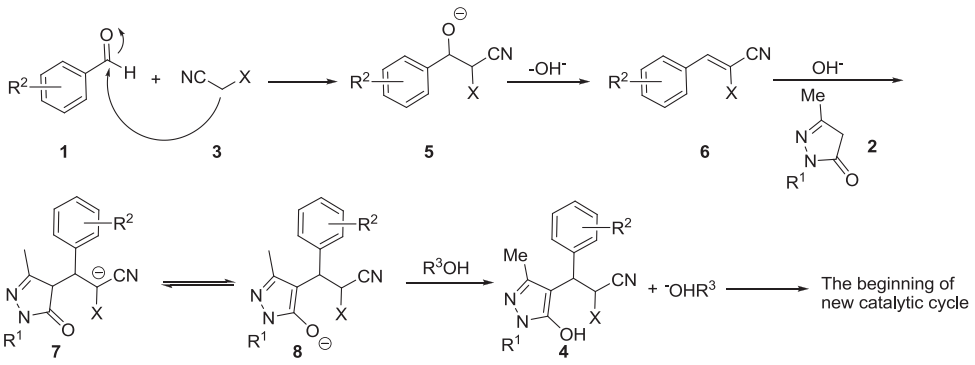
**1a**: $R^2$ = H
**1b**: $R^2$ = 4-Me
**1c**: $R^2$ = 4-Et
**1d**: $R^2$ = 4-F
**1e**: $R^2$ = 4-Cl
**1f**: $R^2$ = 3-Br
**1g**: $R^2$ = 2-OMe

**2a**: $R^1$ = H
**2b**: $R^1$ = Ph

**3a**: X = CN
**3b**: X = $CO_2$Me
**3c**: X = $CO_2$Et

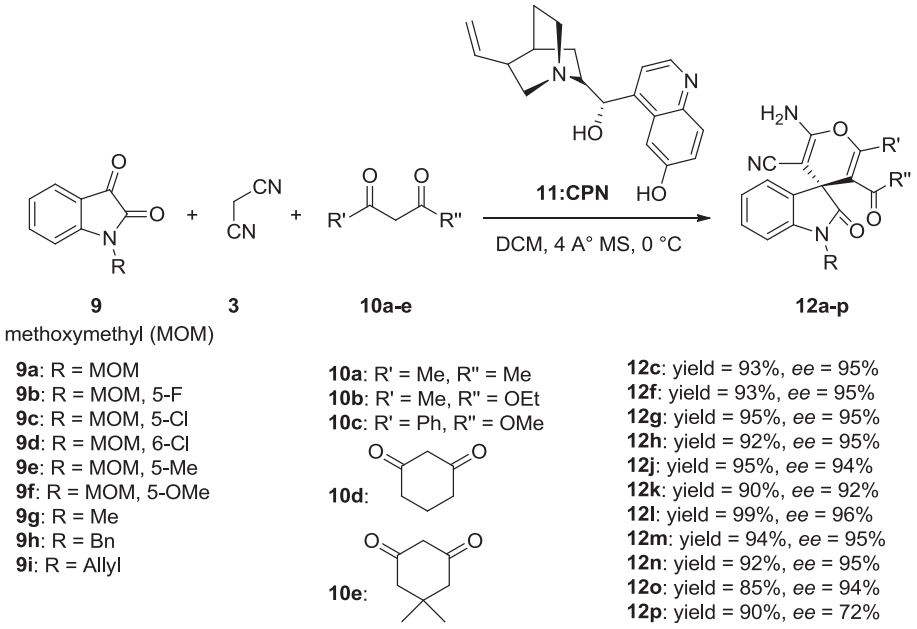
**4a**: $R^1$ = $R^2$ = H, X = CN, yield = 97%
**4b**: $R^1$ = $R^2$ = H, X = $CO_2$Me, yield = 84%
**4c**: $R^1$ = $R^2$ = H, X = $CO_2$Et, yield = 91%
**4d**: $R^1$ = H, $R^2$ = 4-Me, X = CN, yield = 80%
**4e**: $R^1$ = H, $R^2$ = 4-Et, X = CN, yield = 76%
**4f**: $R^1$ = H, $R^2$ = 4-F, X = CN, yield = 82%
**4g**: $R^1$ = H, $R^2$ = 4-Cl, X = CN, yield = 75%

**Scheme 1.** MCR for the synthesis of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3- arylpropionitriles **4a-g**.




**1** **3** **5** **6** **2** **7** **8** **4**

**Scheme 2.** Probable mechanism for the synthesis of 3-(5-hydroxy-3-methylpyrazol-4-yl)-3- arylpropionitriles **4**.




**Scheme 3.** Asymmetric synthesis of spiro[4*H*-pyran-3,3′-oxindoles] **12a-p** *via* one-pot, three-component reaction.

A direct and effective approach for the preparation of nitriles or β-cyanocarbonyls through sequential Knoevenagel condensation and Michael addition reaction involving barbituric acid (one-pot three-component reaction), differently substituted aldehydes and sodium cyanide in the absence of any catalyst or additive in water was accomplished and reported.[95] One of the best approaches for the introduction of a nitrile group in different molecules is the Michael addition of nitrile anions to α,β-unsaturated carbonyl compounds mediated by either strong base or Lewis acid catalysts.[96]

To evaluate the substrate scope of this protocol, this process was then extended to two different CH-acids, barbituric acid and 1,3-dimethyl barbituric acid, and differently substituted aromatic aldehydes, diversely. A broad range of aromatic aldehydes, bearing eitherelectron-withdrawing or electron-releasing substituents, signifying that this protocol can be applied to the syntheses of a wide range of products. Interestingly, in all cases, regardless of the nature of substituents on aromatic aldehydes excellent chemical yields were obtained. It also water as green solvent tested in this reaction, which was found works ideally, in the synthesis of alkyl cyanides. Moreover, in this environmentally synthetic strategy, the solvent water itself is able to promote the reaction *via* H-bonding, therefore evading the utilization of any other catalysts. Thus, the work up procedure will be much more easier besides, this approach can be categorized as non-catalyzed reaction (Scheme 5).[95]

Fascinatingly, alkyl cyanides **19** were converted into its sodium salts that could be easily transformed to product **21**. After treatment with conc. HCl. classically, barbituric acid and 3-hydroxybenzaldehyde were stirred at 70 °C. The none equivalent of NaCN was added to this reaction mixture. After a while, one equivalent of conc. HCl was added and the resulting mixture stirred for couple of min. at ambient temperature. Upon easy conventional work-up procedure the expected product (protonated salt and product of hydrolysis of cyano group) was obtained in excellent chemical yield (Scheme 6).[95]

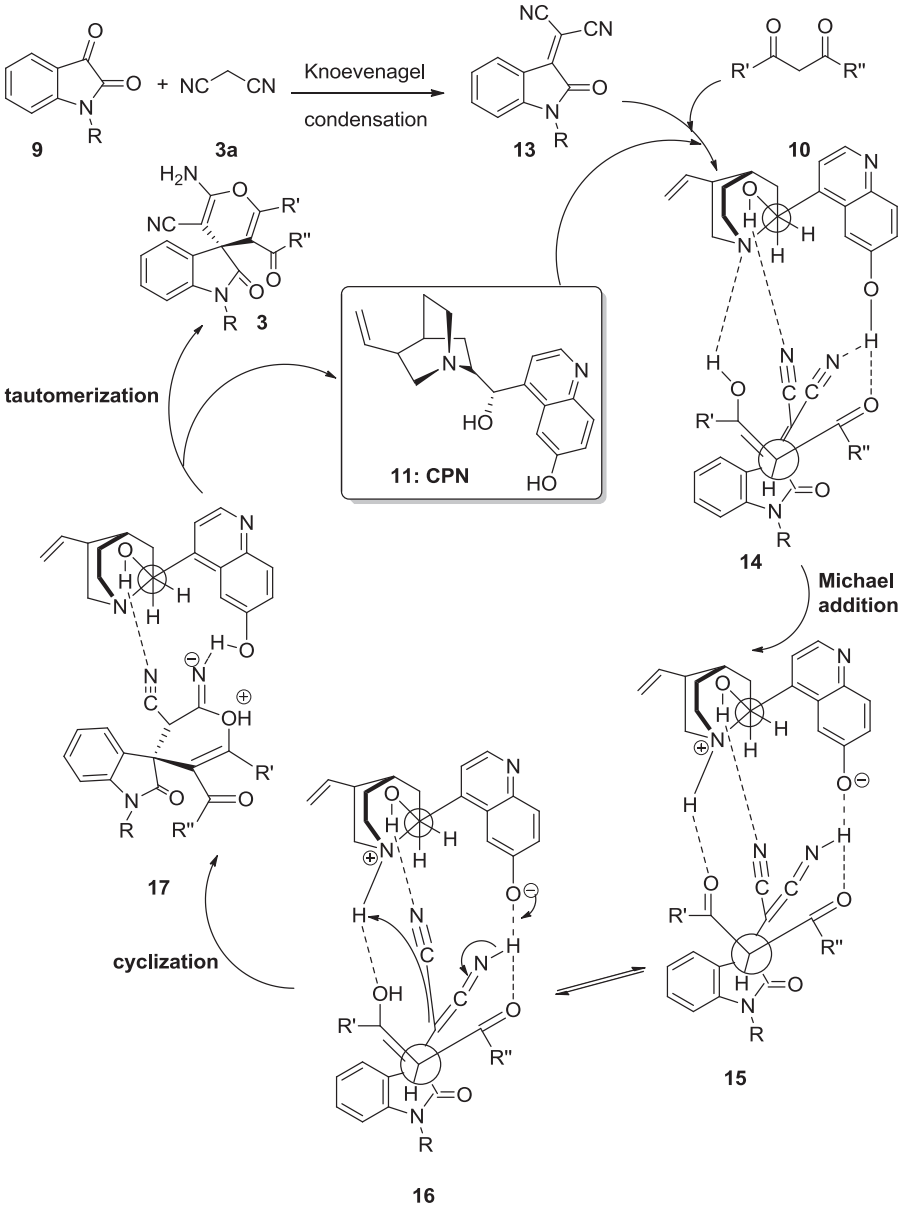
A probable mechanism for the synthesis of alkyl cyanides **19** is shown in Scheme 7.[95]

An ecological benign, practically facile and highly effective one-pot MCR for the synthesis of spiro[indoline-3,4′-thiopyrano[2,3-*b*]indole] derivatives was achieved and reported in 2012 by Majumdar and co-workers.[97] A three-component sequential reaction of commercially available or readily accessible starting materials such as indoline-2-thione, isatin and ethyl cyanoacetate or malononitrile were reacted in EtOH under reflux in the absence of any catalyst. The important merits of this methodology are short reaction times, excellent yields, operationally simple, more significantly directed towards the "Click Reaction", creation of three new bonds in one operation as Sir John Cornforthstated stated.[98] Moreover, this approach is appropriate for the synthesis of diversity-oriented heterocycles with biological activity, thus will be seemingly proper for the generation of a library of pertinent for the total synthesis of natural products.

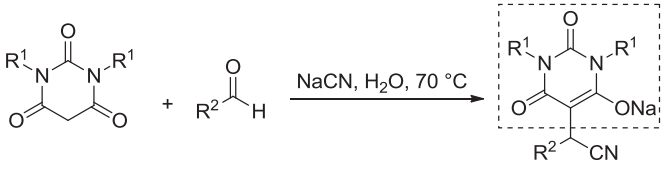
The corresponding products spiro[indoline-3,4′-thiopyrano[2,3-*b*]indole] derivatives were provided *via* one-pot sequential Knoevenagel condensation/Michael addition/cyclization reaction by using a wide range of substrates under the already secured optimal reaction conditions to obtain a wide variety of the corresponding spiro compounds **25a-h**. To the purpose, reactions of different indoline-2-thiones **24**, a broad range of *N*-substituted isatin derivatives **9** and ethyl cyanoacetate or malononitrile **3** were diversely studied. Delightfully, all of the reactions examined, afforded high to excellent yields (89–99%) of the corresponding products under the optimal reaction conditions (Scheme 8).[97]

A plausible mechanism for this un-catalyzed reaction is illustrated in Scheme 9. Accordingly, at first, a cyanoolefin intermediate **26** is generated *via* the Knoevenegal condensation between compounds **9** and **3**. Then, Michael addition of A to indole-2-thione **24** in its enol form may provide the intermediate **28** which can be subjected to an intramolecular *S*-acylation to give the spiro[indoline-3,4′-thiopyrano[2,3-*b*]indole] derivative **25** as sole product. Noticeably, in most cases the corresponding products were formed as a solid in the reaction mixture, which were easily separated by simple filtration under vacuum.[97]

Several 3,3′-pyrrolidonyl spirooxindoles derivatives were prepared in satisfactory yields from the sequential Knoevenagel/Michael reaction followed by cyclization in one-pot manner. MCRs of various derivatives of compound **9**, malononitrile **3** and α-isothiocyanato imide **29** were reacted in the presence of

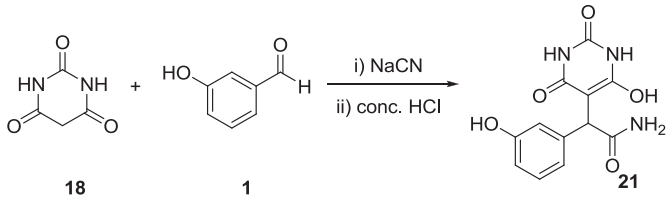



**Scheme 4.** Suggested mechanism for the synthesis of spiro[4*H*-pyran-3,3′-oxindoles] **12**.




**19a**: $R^1$ = H, $R^2$ = 4-OH-$C_6H_4$, yield = 99%
**19b**: $R^1$ = H, $R^2$ = 4-Cl-$C_6H_4$, yield = 99%
**19c**: $R^1$ = H, $R^2$ = 4-OMe-$C_6H_4$, yield = 99%
**19d**: $R^1$ = H, $R^2$ = 3-OH-$C_6H_4$, yield = 98%
**19e**: $R^1$ = $CH_3$, $R^2$ = 3-$NO_2$-$C_6H_4$, yield = 98%
**19f**: $R^1$ = $CH_3$, $R^2$ = 4-Br-$C_6H_4$, yield = 98%
**19g**: $R^1$ = $CH_3$, $R^2$ = 4-$CH_3$-$C_6H_4$, yield = 98%
**9h**: $R^1$ = $CH_3$, $R^2$ = 4-$NO_2$-$C_6H_4$, yield = 989%

**Scheme 5.** MCR of aldehydes, barbituric acids and sodium cyanide in water.



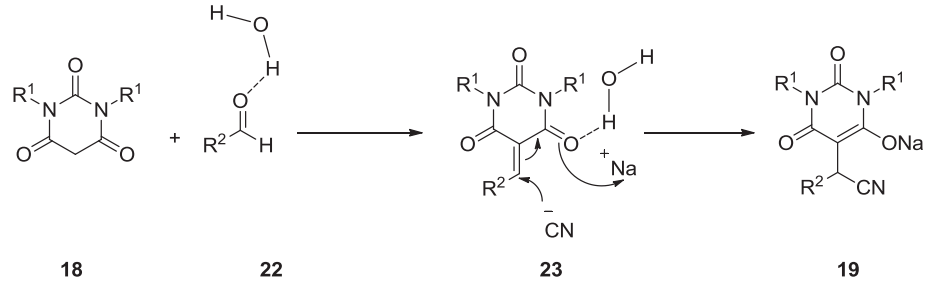

**Scheme 6.** MCR of 3-hydroxybenzaldehyde, barbituric acid and sodium cyanide with conc. HCl.

trimethylamine as catalyst on water under ultrasonic irradiation as a harmless source of energy to give the corresponding 3,3′-pyrrolidonyl spirooxindoles **30**. The merits of this methodology are showing high level of efficiency, exhibiting acceptable functional group tolerance, can be done under mild reaction conditions and using ecologically benign starting materials. Thus, this cascade reaction can be considered as green protocol for generating diversity-oriented important class of compounds, 3,3′-pyrrolidonyl spirooxindoles **30** with potential biological activities. It is worthy to mention that compound **30** is obtained as racemic mixture of two inseparable enantiomers (Scheme 10).[99]

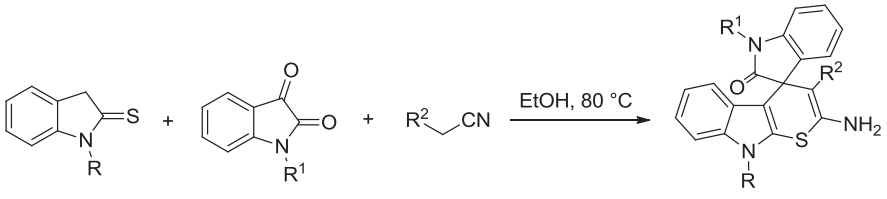
A plausible mechanism for this sequential domino reaction MCR was suggested and depicted in Scheme 11. In accordance with the proposed mechanism, initially the Knoevenagel reaction of isatin **9** with malononitrile **3** occurs to generate a dicyanoalkene as an intermediate **26**. Then, the Michael addition of this generated Knoevenagel adduct, **26** reacted with α-isothiocyanato imide **29** in the presence of triethylamine to create another intermediate, the enolate **33**, leading to simultaneous generation of intermediate **34**. The latter then is subjected to an intramolecular cyclization giving the product **30** *via* the intermediate **35**. According to this plausible mechanism, this sequential three-component reaction overall resulted in the creation of three C–C bonds, ideal from atom economy point of view.[99]

A facile, safe, and highly effective approach to the functionalized spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine] derivatives **37a-j** was achieved *via* a pseudo three-component domino reaction of differently substituted aromatic aldehydes **1** and barbituric acids or thiobarbituric acid **18/36**, promoted by urotropine ebromine (UB) complex in aqueous media at ambient temperature in a one-pot manner. The advantages of this cascade reaction were mentioned by being performed under mild reaction conditions, easy work-up procedure for the isolation of the products, giving excellent yields, showing high atom economy due to bond-efficiency of sequential generating of three new bonds (including two C–C and one C–O bonds) as well as generation of one stereogenic center in a single process (Scheme 12).[100]

A plausible mechanism for the synthesis of spiro[furo[2,3-*d*]-pyrimidine-6,5′-pyrimidine] derivatives is suggested as depicted in Scheme 13. It is assumed that the reaction proceeds in a stepwise fashion. It is thought that initially, the reaction proceeds through a Knoevenagel condensation between barbituric acid **18/36** and an appropriate aromatic aldehyde **1** to generate the arylidene barbituric acid **38** that is immediately subjected to Michael addition of the second barbituric acid molecule **18/36** to give aryl bis(barbitur-5-yl)methane **39**. Consequently, the Michael-adduct **39** brominated at α position affords substituted 5-bromo-5-[aryl(barbitur-5-yl) methyl]pyrimidine **40**. Ultimately, intramolecular Williamson cycloetherification of **40** in a 5-exo-tet fashion occurs to provide the




**Scheme 7.** Possible mechanism for the synthesis of alkyl cyanides **19**.



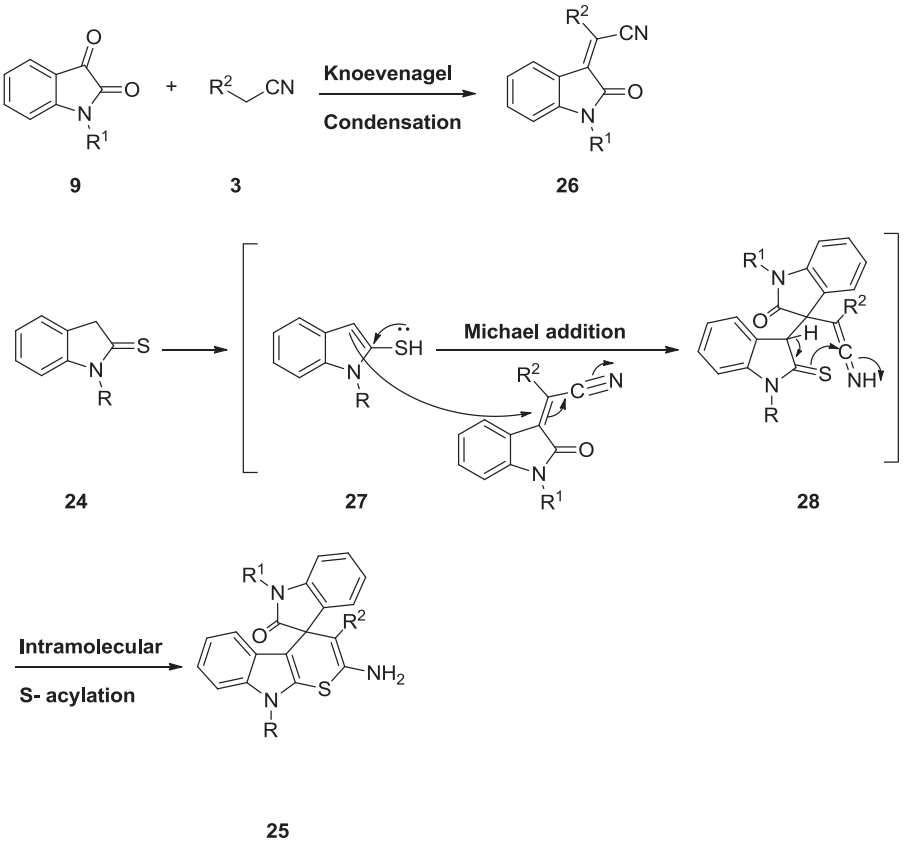

**24a**: R = Et
**24b**: R = Me
**24c**: R = H

**9a**: $R^1$ = Me
**9b**: $R^1$ = Et
**9c**: $R^1$ = H

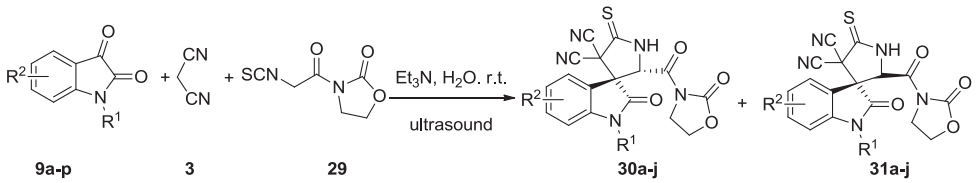
**3a**: $R^2$ = $CO_2Et$
**3b**: $R^2$ = CN

**25a**: R = Et, $R^1$ = Me, $R^2$ = $CO_2Et$, yield = 99%
**25b**: R = Et, $R^1$ = Me, $R^2$ = $CO_2Et$, yield = 96%
**25c** R = Et, $R^1$ = H, $R^2$ = CN, yield = 96%
**25d**: R = Et, $R^1$ = Et, $R^2$ = $CO_2Et$, yield = 97%
**25e**: R = Et, $R^1$ = Et, $R^2$ = CN, yield = 98%
**25f**: R = Me, $R^1$ = Et, $R^2$ = CN, yield = 93%
**25g**: R = Me, $R^1$ = Mr, $R^2$ = $CO_2Et$, yield = 95%
**25h**: R = Me, $R^1$ = Me, $R^2$ = CN, yield = 92%

**Scheme 8.** Synthesis of various spiro[indoline-3,4′-thiopyrano[2,3-*b*]indole] derivatives **25**.




**Scheme 9.** Proposed mechanism for the formation of spirooxindolethiopyrans **25**.

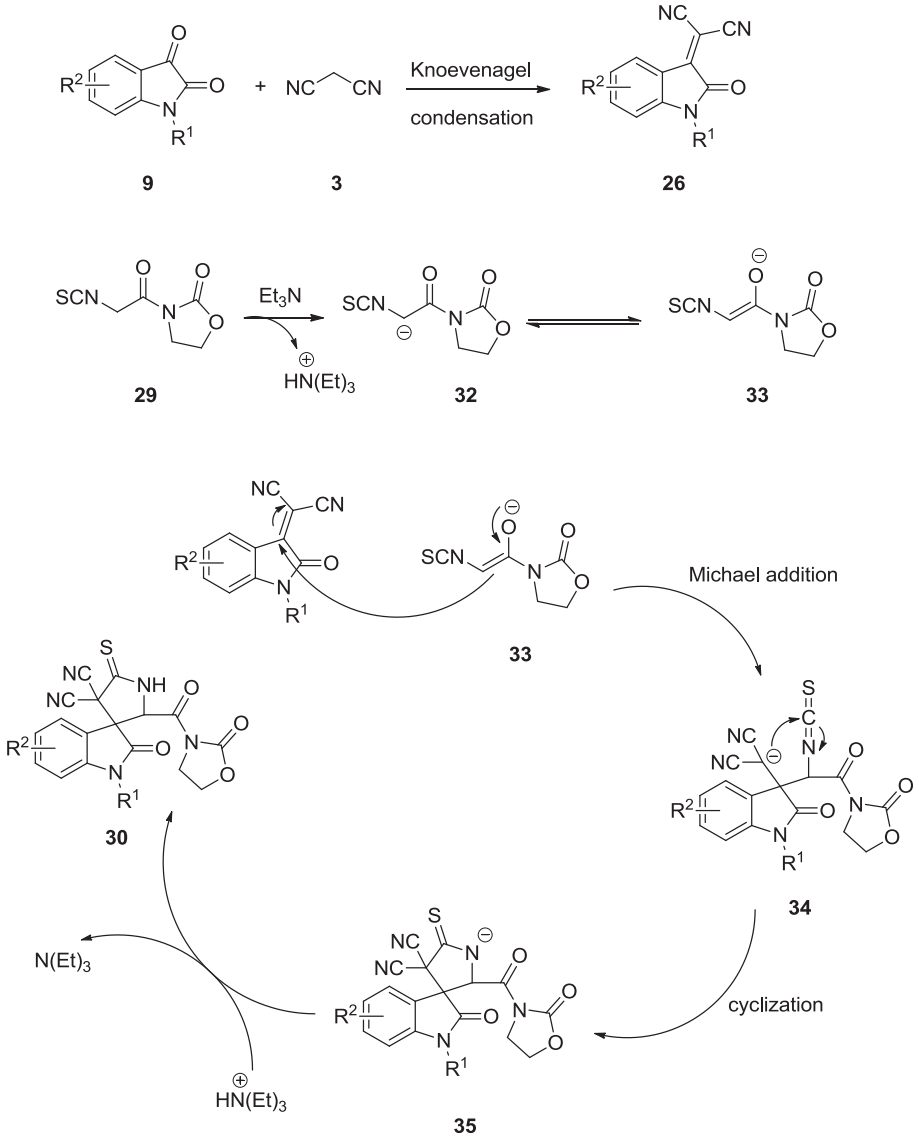



(**30, 31**): **a**: $R^1 = CH_3$, $R^2$ = H, yield = 98%
**b**: $R^1 = CH_3$, $R^2$ = 5-$CH_3$, yield = 98%
**c**: $R^1 = CH_3$, $R^2$ = 5-$NO_2$, yield = 91%
**d**: $R^1 = CH_3$, $R^2$ = 5-Br, yield = 98%
**e**: $R^1 = CH_3$, $R^2$ = 5-Cl, yield = 98%
**f**: $R^1 = CH_3$, $R^2$ = 7-$CH_3$, yield = 98%
**g**: $R^1$ = H, $R^2$ = H, yield = 95%
**h**: $R^1$ = H, $R^2$ = 5-$CH_3$, yield = 98%
**i**: $R^1$ = H, $R^2$ = 5-$OCH_3$, yield = 93%
**j**: $R^1$ = H, $R^2$ = 5-$NO_2$, yield = 83%

**Scheme 10.** MCR for the synthesis of 3,3′-pyrrolidonyl spirooxindoles **30** *via* cascade Knoevenagel-Michael-cyclization reaction.

oxaspirotricyclic furobarbiturate **37**. It is feasible to accept that the three basic nitrogen atoms, which are present in the Urotropine-bromine (UB) complex can support all steps of the reaction including base-mediated Knoevenagel condensation/Michael addition/α-bromination/enolization and finally Williamson cycloetherification.[100]

Amphiphile (SDS) catalyzed synthesis of the 4-amino alkylated-1*H*-pyrazol-5-ol **42a-r** through a Mannich type reaction was found favorite in comparison with Knoevenagel/Michael type reaction regarding atom economy, efficiency and green reaction conditions. Differently substituted arylaldehyde **1**, appropriate secondary amine **41** and 3-methyl-1-phenyl-5-pyrazolinone **2** reacted in water to give the corresponding aromatized 4-amino alkylated-1*H*-pyrazol-5-ol **42**. It is believed that the reaction proceeds through selective Mannich aromatization. Initially a micelle stabilized imine intermediate is formed with subsequent nucleophilic addition to 3-methyl-1-phenyl-5-pyrazolinone followed by aromatization in aqueous media. The merits mentioned for this protocol for the synthesis of substituted 4-amino alkylated-1*H*-pyrazol-5-ol derivatives are including the improvement of reaction conditions as well as detection of the formation no side product which showed the formation of even no bis product (Scheme 14).[101]



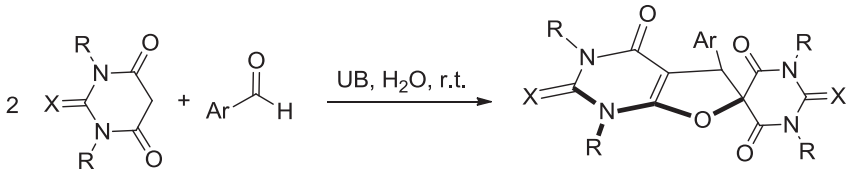

**Scheme 11.** A plausible reaction mechanism for the synthesis of 3,3′-pyrrolidonyl spirooxindoles **30**.

Brønsted acidic hydrogensulfate ionic liquid immobilized SBA-15:[MPIm][HSO $_4$]@ SBA-15 as an eco-friendly, halogen- and metal-free reusable catalyst for Knoevenagel-Michael-cyclization methods. Brønsted acidic-IL@SBA-15 was prepared *via* immobilization of ionic liquids (IL) of halogen-free imidazolium hydrogensulfate into SBA-15.[102,103]

It was used a powerful, heterogeneous and water-tolerant supported Brønsted acid catalyst in the synthesis of tetrahydrochromenes and hexahydroquinolines *via* MCR. Three-component reaction involving an appropriate aromatic aldehyde **1**, malononitrile **3** and **43**, and in the presence of catalytic amount of IL@SBA-15 in water, which gave the corresponding tetrahydrochromenes **45a-i** in satisfactory yield. Noticeably, IL@SBA-15 showed significant catalytic activity as well as of all merits attributed to an ideal heterogeneous catalyst such as recyclability in MCR synthesis of tetrahydrochromenes **45a-i**, which is in turn accomplished through sequential Knoevenagel-Michael-cyclization under eco-friendly conditions. It is assumed that the hydrophobic nature of the IL offers the effective mass transfer of substrates to the active sites of supported within SBA-15 pores. It may also increase the Brønsted acid strength as a result of a novel proposed acid site at the same time, cooperatively.

As illustrated in Scheme 15, the model reaction in the presence of catalyst verifies being optimum, in term of the yield of reaction. Water was used as the solvent of choice not only because it is inexpensive, and environmental friendly but it is known that the highest dispersion of IL@SBA-15 is accomplished in water. To establish the diversity of the immobilized IL of halogen-free imidazolium hydrogensulfate and in order to extend the substrate scope of this strategy under secured optimal reaction conditions a series of substrates **43**, and **1** were reacted with malononitrile **3** to give the corresponding desired products **45** in satisfactory yields.[102]

Then, the substrate scope of this strategy was examined in the synthesis of polyhydroquinolines **47**, through the three-component reaction involving dimedone, an appropriate aldehyde and enaminone **46**. Encouraged by this gifted result, the same authors further studied the catalytic activity of compound **47** in a one-pot synthesis of polyhydroquinolines. Differently substituted aryl aldehydes bearing electron-releasing and electron-withdrawing groups and also *ortho*-substituted aldehydes were smoothly and cleanly

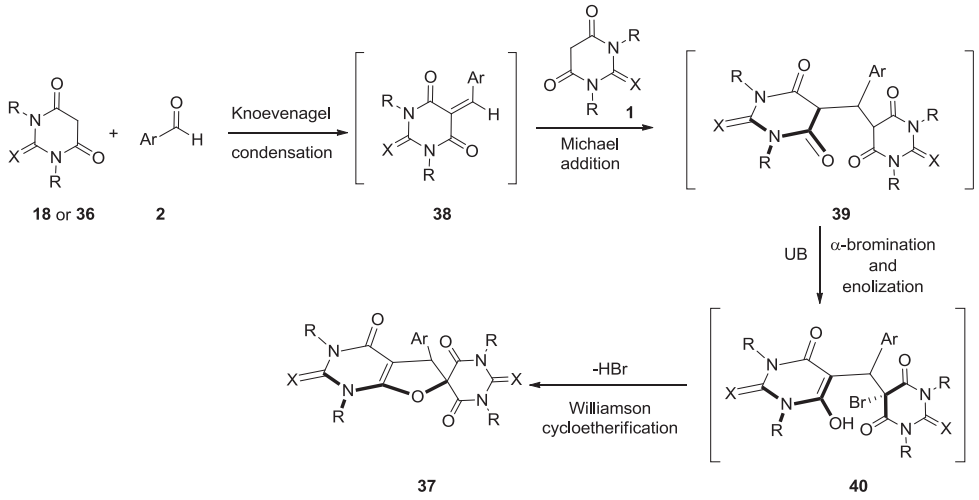



**18, X = O** **1** **37a-j**

**36: X = S**

**37a**: R = H, X = S, Ar = 4-$NO_2$-$C_6H_4$, yield = 91%
**37b**: R = H, X = S, Ar = 2-Cl-$C_6H_4$, yield = 86%
**37c**: R = H, X = S, Ar = 4-Cl-$C_6H_4$, yield = 89%
**37d**: R = $CH_2CH_3$, X = S, Ar = Ph, yield = 81%
**37e**: R = $CH_2CH_3$, X = S, Ar = 4-Cl-$C_6H_4$, yield = 80%
**37f**: R = $CH_2CH_3$, X = S, Ar = 4-$NO_2$-$C_6H_4$, yield = 82%
**37g**: R = H, X = O, Ar = Ph, yield = 90%
**37h**: R = H, X = O, Ar = 3-OH-$C_6H_4$, yield = 85%
**37i**: R = H, X = O, Ar = 4-Br-$C_6H_4$, yield = 90%
**37j**: R = H, X = O, Ar = 4-Cl-$C_6H_4$, yield = 86%

**Scheme 12.** Synthesis of spiro[furo[2,3-*d*]pyrimidine-6,5′-pyrimidine] derivatives **37a-j**.




**18** or **36** **2** **38** **39** **37** **40**

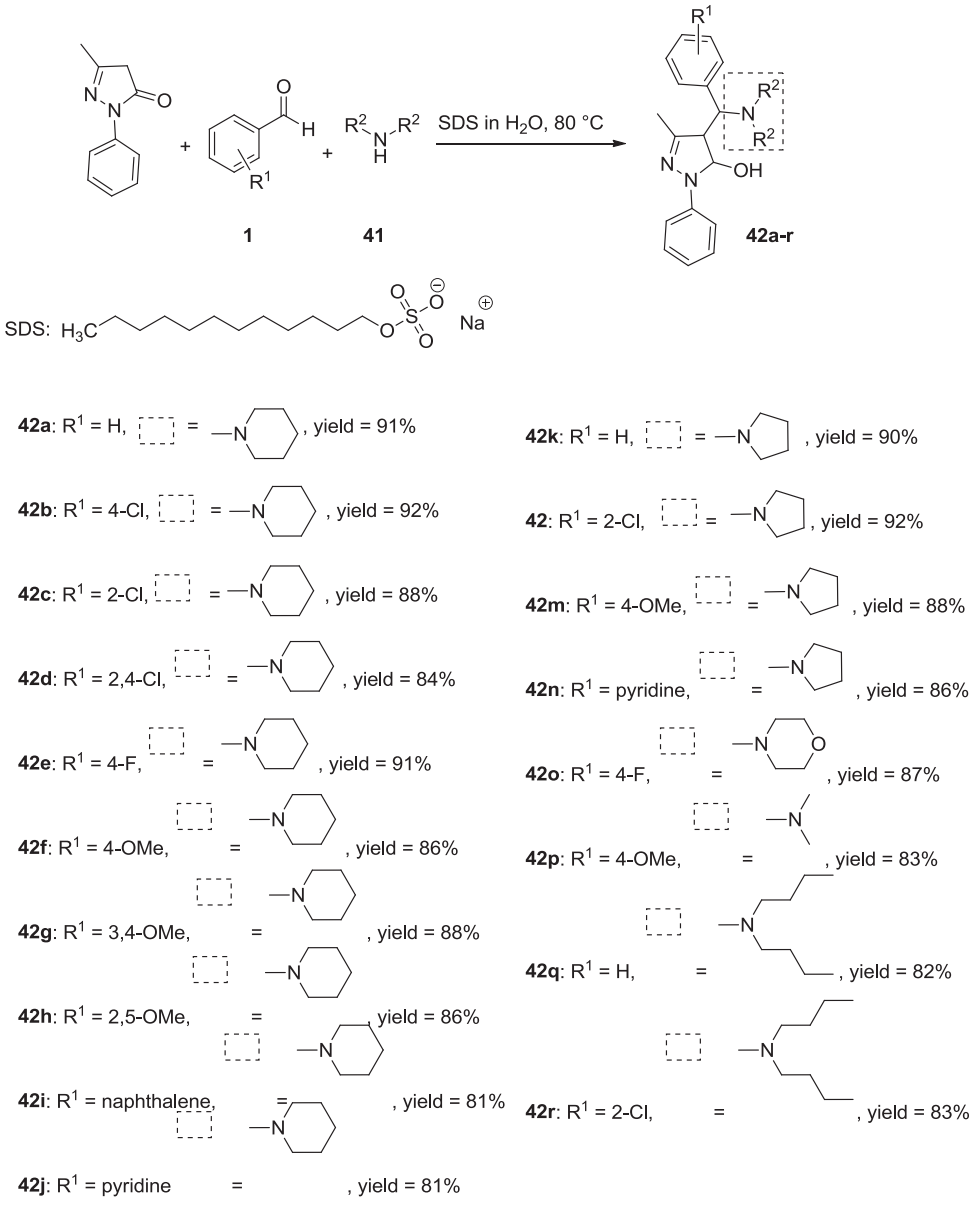
**Scheme 13.** A possible mechanism for the synthesis of oxaspirotricyclic furobarbiturate **37**.

transformed rapidly to the desired corresponding polyhydroquinolines **47a-h** in satisfactory yields (Scheme 16).[102]

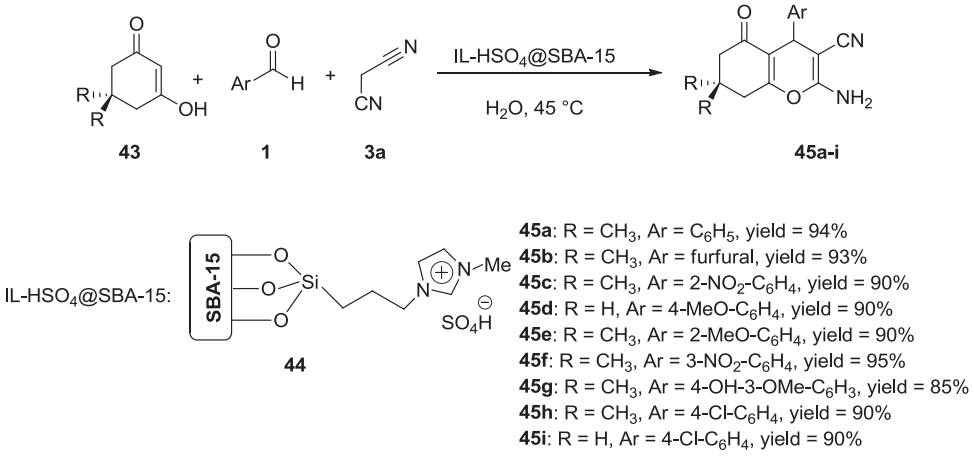
Noticeably, a definite mechanism for this one-pot synthesis of the compounds **45** and **47** utilizing aldehyde over the IL-$HSO_4$@SBA-15 as catalyst *via* experimental fashion has not been reported (Scheme 17). It is known that ionic liquid has the hydrophobic nature. Due to this quality, IL has the advantage of the rapid diffusion of reaction substrates to the catalytic core in SBA-15 mesoporous channels. IL can also enhance the Brønsted acidity in terms of acid-cite assistance in this proposed mechanism.[102]

The preparation of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one derivatives **53a-m** was accomplished *via* a three-component reaction involving 4-hydroxycoumarin **50**, differently substituted aldehydes **1**, and 3-amino-5-methyl-pyrazole **51** in the presence of tetrabutylammonium tribromide (TBATB) in refluxing $CH_3CN$, in one-pot fashion. This reaction proceeds *via* sequential cascade Knoevenagel condensation/Michael addition followed by simultaneous cyclization (Scheme 18).[104]

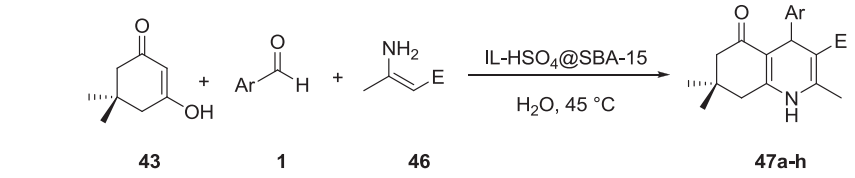
A reasonable mechanism for this one-pot synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one **53** was proposed. It is suggested that initially, 4-hydroxycoumarin **50** reacts with aldehyde *via* Knoevenagel condensation to afford intermediate **54**. Here, two mechanistic pathways (**a** and **b**) are possible which is illustrated in Scheme 19. In accordance with 'path a', the intermediate **54** reacts with 3-amino-5-methylpyrazole **51** *via* the Michael addition to give intermediate **55**, which can be submitted into simultaneous tautomerization in the form of **56**, which can then be subjected to intramolecular cyclization to give the expected corresponding product **53**. Then again, *via* 'path **b**', 3-amino-5-methyl-pyrazole **51** can also react with the already generated intermediate **54** through 1,4-addition conjugate reaction to generate intermediate **57,** which then can be subjected into simultaneous intramolecular cyclization followed by tautomerization to give the corresponding product **58**. Nevertheless, in spite of such possibility the authors claimed no observation for **58** thus, the above-mentioned reaction should have proceeded *via* superior 1,4-addtion of amino group present in 3-amino-5-methyl-pyrazole to intermediate **54** to generate **55** followed by tautomerization to **56**

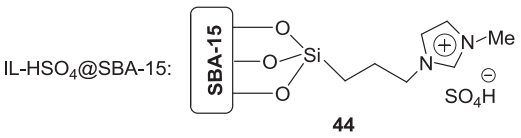



**Scheme 14.** Amphiphile (SDS) catalyzed mediated synthesis of the 4-amino alkylated-1*H*-pyrazol-5-ol **42a-r**.



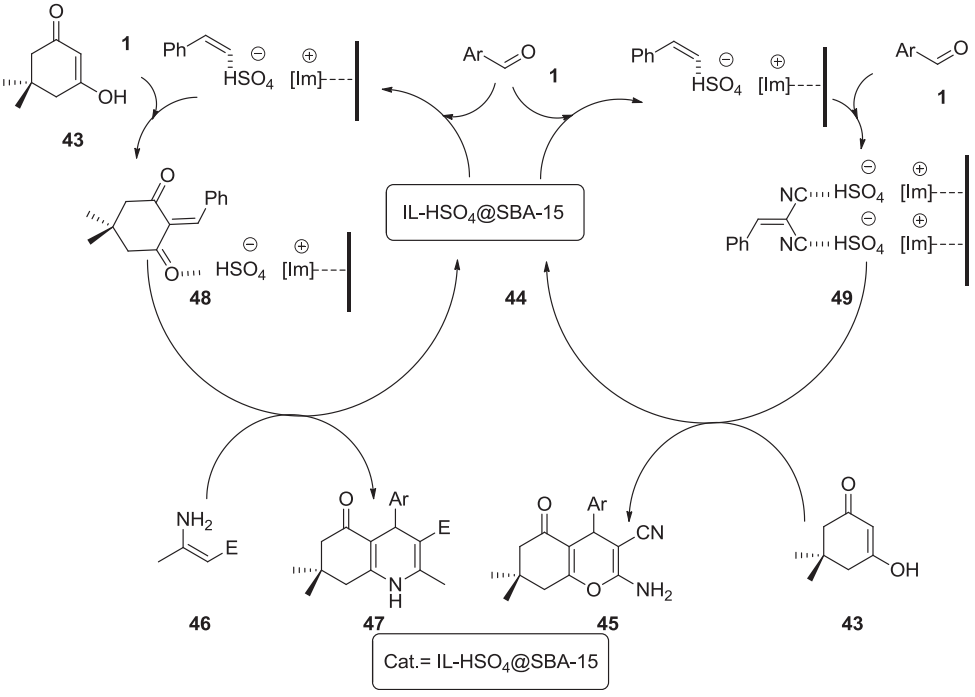

**Scheme 15.** The synthesis of tetrahydro-4*H*-chromenes **45a-i** using IL-$HSO_4$@SBA-15.




**47a**: Ar = $C_6H_5$, E = $CO_2Me$, yield = 90%
**47b**: Ar = 4-Cl-$C_6H_4$, E = $CO_2Me$, yield = 93%
**47c**: Ar = 2-Me-$C_6H_4$, E = $CO_2Me$, yield = 90%
**47d**: Ar = 2-Cl-$C_6H_4$, E = $CO_2Me$, yield = 92%
**47e**: Ar = 4-MeO-$C_6H_4$, E = $CO_2Me$, yield = 88%
**47f**: Ar = 2-Me-$C_6H_4$, E = $CO_2Et$, yield = 91%
**47g**: Ar = 2-Cl-$C_6H_4$, E = $CO_2Et$, yield = 91%
**47h**: Ar = 4-Cl-$C_6H_4$, E = $CO_2Et$, yield = 96%

**Scheme 16.** One-pot synthesis of polyhydroquinolines **47**.




**Scheme 17.** Plausible mechanisms for the catalytic conversion of the synthesis of products **45** and **47**.

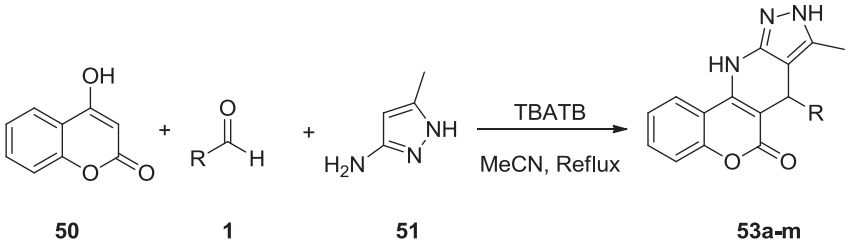
to afford compound **58**.[104]

MWI-prompted, chemoselective and ecologically benign successful and rapid synthesis of a variety of wide range of bioactive oxazolo[5,4-*b*]quinoline-fused spirooxindoles **60a-m** through three-component sequential knoevenagel condensation/Michael addition was achieved and reported in 2015 by Reddy and co-workers.[105] 5-Amino-3-methylisoxazole **59**, β-diketones **10** and isatin **9** were reacted in the absence of catalyst in solventless system to give the corresponding products **60** in satisfactory yield. This protocol opens a promising gateway for the synthesis of libraries of a broad range of bioactive spirooxindoles for biological screening and examination (Scheme 20).[105]

A plausible mechanism for this well-recognized MCR is depicted in Scheme 21. It is well rationalized that initially the β-diketone reacts with isatin under the Knoevenagel condensation reaction conditions to give **61** that submitted rapidly to a Michael-type addition with present 5-amino-3-methylisoxazole **59** in the reaction vessel. Subsequently, the cyclo condensation of the intermediate adduct **63** gives the expected desired products **60**.[105]

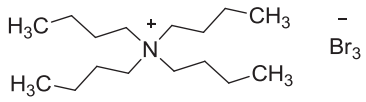
A highly versatile and regioselective synthesis of 4-amino-1,2-dihydropyridines **65** was achieved by Presset and co-workers reported in 2015.[106] This synthetic approach proceeds through three-component sequential reaction of (3CDC) of α-oxoketene-*N*,*S*-arylaminoacetals **64**, differently substituted aldehydes **1**, and malononitrile **3** catalyzed by $InCl_3$ in solvent-less system to give the desired products **65** in satisfactory yields. The salient feature of this sequential domino Knoevenagel condensation/Michael addition/cyclization was mentioned by its atom-economy, efficiency of generating successive three new bonds including two C–C and one C–N bonds and one ring in a one-pot manner. Noticeably, the presence of cyano and amino moieties at 3- and 4-positions of 1,2-dihydropyridine ring provides these compounds as valuable precursors for further synthetic endeavors. Significantly, one of the novel synthesized 4-amino-1,2-dihydropyridine showed high selectivity and sensitivity for $Fe^{3+}$ ion over other metal ions, which can be used as for the removal of ferric ion from a mixture (Scheme 22).[106]

A possible pathway for the above-mentioned MCR cross-



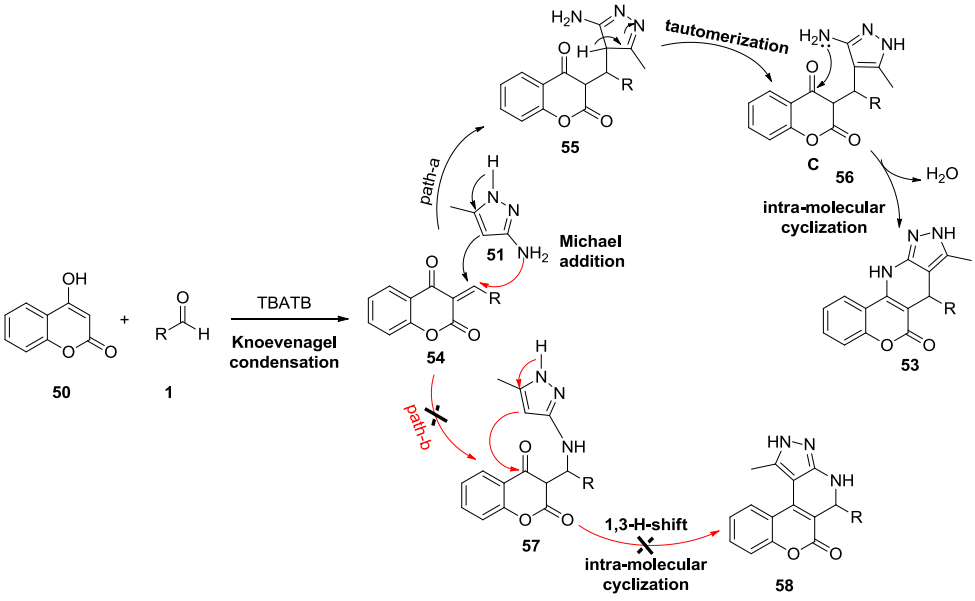

**50** **1** **51** **53a-m**

**TBATB**: Tetrabutylammonium tribromide



**53a**: R = 4-OMe-$C_6H_4$, yield = 84%
**53b**: R = $C_6H_5$, yield = 78%
**53c**: R = 2-F-$C_6H_4$, yield = 64%
**53d**: R = 3-F-$C_6H_4$, yield = 70%
**53e**: R = 4-F-$C_6H_4$, yield = 74%
**53f**: R = 2-Cl-$C_6H_4$, yield = 70%
**53g**: R = 4-Cl-$C_6H_4$, yield = 76%
**53h**: R = 2,6-Cl-$C_6H_3$, yield = 68%
**53i**: R = 4-Br-$C_6H_4$, yield = 74%
**53j**: R = 4-CN-$C_6H_4$, yield = 72%
**53k**: R = 2-$NO_2$-$C_6H_4$, yield = 70%
**53l**: R = 4-$NO_2$-$C_6H_4$, yield = 72%
**53m**: R = 4-Me-$C_6H_4$, yield = 80%

**Scheme 18.** Synthesis of various dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones **53.**

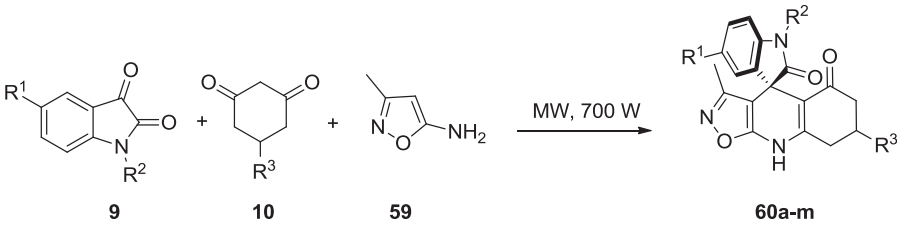



**Scheme 19.** Plausible mechanism for the formation dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-one **53**.

dehydrative coupling approach is illustrated in Scheme 23. Initially, Knoevenagel condensation between aldehyde **1** and malononitrile **3** occurs generating the expected Knoevenagel product **66** that serves as Michael acceptor, stimulately. It means, Michael acceptor **66** reacts with α-oxoketene-*N,S*-acetal **64** in the presence of Lewis acid, which assists Michael addition process. Apparently, the attack of α-oxoketene-*N,S*-acetal could have occurred *via* two routes (path a and II) to give the open chain intermediates **67** and **67′**, respectively. The intermediates **67** and **67′** concurrently is subjected into intramolecular *N*-cyclization to yield compounds **65** and **68**. However, during the investigation, which is described even a trace of **68**, and **65** detected, suggesting that the reaction proceeds, highly regioselectively.[106]

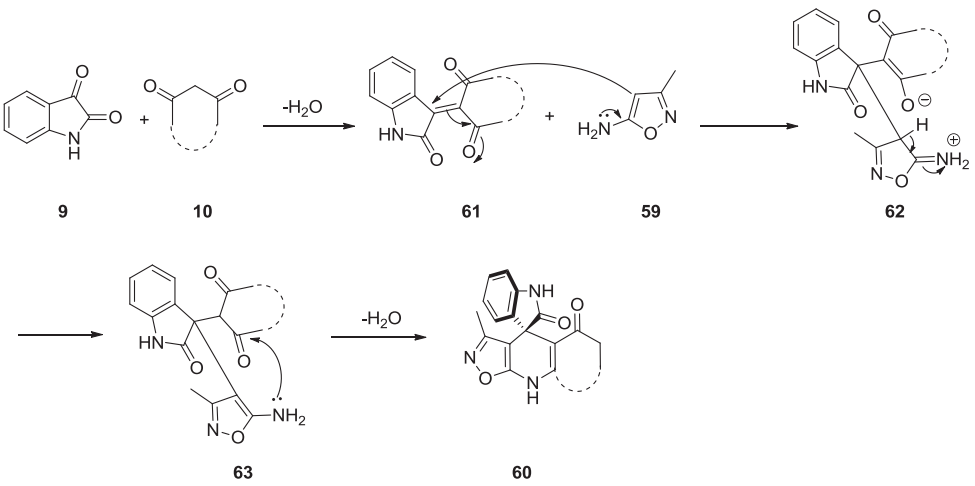
A MCR of differently substituted isatin **9a-i**, malononitrile **3**, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **69** in the presence of piperidine as a basic organocatalyst for the synthesis pyranocoumarin fused spirooxindoles **70a-i** was reported in 2015 by Choudhury and co-workers.[107] The merits of this stately are metal-free reaction conditions, tolerance to a differently substituted isatins with satisfactory yields and production of just one regioisomer as sole product among the three other possible isomers (Scheme 24).[107]

Also, in this approach, when ethyl cyanoacetate **3c** was employed instead of malononitrile the expected *trans* esterified




**60a**: $R^1$ = H, $R^2$ = H, $R^3$ = H, yield = 95%
**60b**: $R^1$ = F, $R^2$ = H, $R^3$ = H, yield = 88%
**60c**: $R^1$ = Cl, $R^2$ = H, $R^3$ = H, yield = 85%
**60d**: $R^1$ = Br, $R^2$ = H, $R^3$ = H, yield = 89%
**60e**: $R^1$ = $NO_2$, $R^2$ = H, $R^3$ = H, yield = 84%
**60f**: $R^1$ = H, $R^2$ = $CH_3$, $R^3$ = H, yield = 89%
**60g**: $R^1$ = F, $R^2$ = $CH_3$, $R^3$ = H, yield = 86%
**60h**: $R^1$ = Cl, $R^2$ = $CH_3$, $R^3$ = H, yield = 85%
**60i**: $R^1$ = Br, $R^2$ = $CH_3$, $R^3$ = H, yield = 88%
**60j**: $R^1$ = $NO_2$, $R^2$ = $CH_3$, $R^3$ = H, yield = 92%
**60k**: $R^1$ = H, $R^2$ = H, $R^3$ = $(CH_3)_2$, yield = 87%
**60l**: $R^1$ = F, $R^2$ = $CH_3$, $R^3$ = $(CH_3)_2$, yield = 87%
**60m**: $R^1$ = Cl, $R^2$ = $CH_3$, $R^3$ = $(CH_3)_2$, yield = 89%

**Scheme 20.** Synthesis of oxazolo[5,4-*b*]quinoline-fused spirooxindole derivatives **60a-m**.




**Scheme 21.** Proposed mechanism for the synthesis of oxazolo[5,4-*b*]quinoline-fused spirooxindoles **60**.

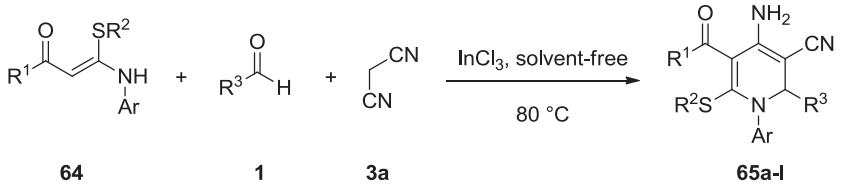
was formed (Scheme 25).[107]

A MCR of four-components, *o*-phenelyne diamine **73**, ninhydrin **72**, 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **69** and malononitrile **3a**, using the same catalyst proceeded smoothly to give the corresponding pyranocoumarin fused spirooxindoles **74**. The salient features of this strategy are the use of advantageous organocatalyst in MCRs, simple reaction approach, obtaining satisfactory yields, and most importantly gaining excellent regioselectivity (Scheme 26).[107]

A reasonable reaction mechanism for the synthesis of spirooxindole pyrans **71a-d** was suggested as illustrated in Scheme 27. In accordance to this proposed mechanism, initially, intermediate **13** is generated from the Knoevenagel condensation of **9** and **3a**. Then, intermediate **13** undergoes Michael addition with **69** prompted by piperidine generating intermediate **76** that is subjected to intramolecular cyclization to create intermediate **77**. Finally intermediate **76** upon tautomerization to more favorable tautomer as product **71**.[107]

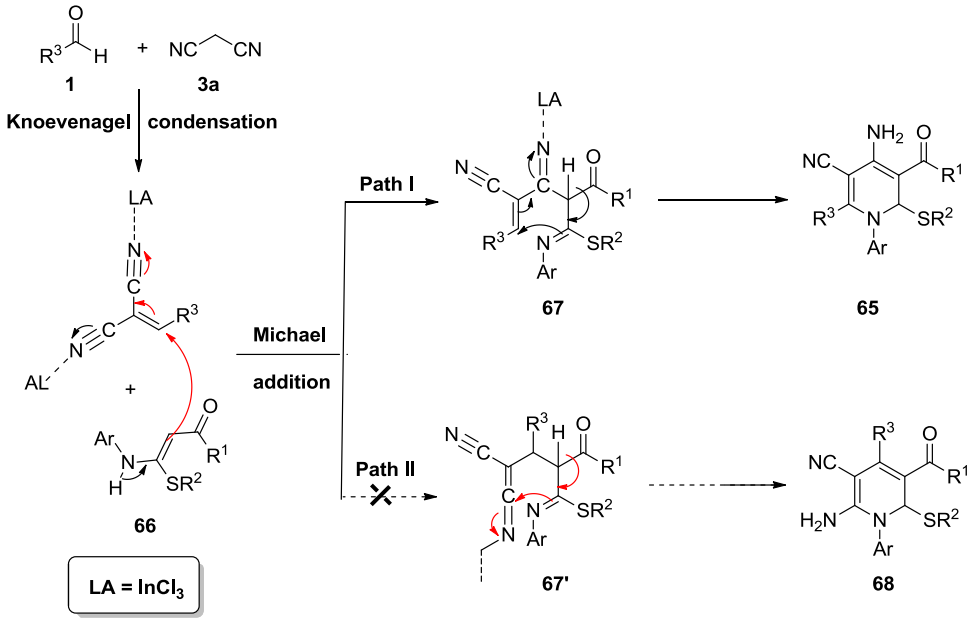
A highly effective, strategy was achieved and reported by Chavan and co-workers in 2016 for the synthesis of several fused 7-azaindoles **80** and **82** in high yields *via* MCR reaction in one-pot manner involving the installation of cyclic 1,3-dicarbonyls (dimedone and indane-1,3-dione) with differently substituted aromatic aldehydes **1** and 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile **78**. This transformation took place *via* domino Knoevenagel/Michael reaction with subsequent intramolecular cyclization in catalyzed by $InCl_3$ (10 mol%). The merits, mentioned for this attractive sequential one-pot reaction are which being performed under mild reaction conditions, and giving well to excellent yields in a relatively short reaction times. These silent features of this strategy make it quite close to “Click Reaction” (Schemes 28 and 29).[108]

A suggested mechanism for the generation of fused 7-azaindoles is illustrated in Scheme 30. Initially, Knoevenagel reaction occurs between cyclic 1,3-dicarbonyls and aromatic aldehydes to afford adduct **83**, which is well known to acts as a Michael




**65a**: $R^1 = C_6H_5$, $R^2$ = Me, $R^3 = C_6H_5$, Ar = Ph, yield = 80%
**65b**: $R^1 = C_6H_5$, $R^2$ = Me, $R^3$ = 4-OMe-$C_6H_4$, Ar = Ph, yield = 77%
**65c**: $R^1 = C_6H_5$, $R^2$ = Me, $R^3$ = 4-F-$C_6H_4$, Ar = Ph, yield = 71%
**65d**: $R^1$ = 4-Me-$C_6H_4$, $R^2$ = Me, $R^3$ = 2-Br-$C_6H_4$, Ar = Ph, yield = 72%
**65e**: $R^1$ = 4-Me-$C_6H_4$, $R^2$ = Me, $R^3$ = 4-OMe-$C_6H_4$, Ar = Ph, yield = 79%
**65f**: $R^1$ = 4-Me-$C_6H_4$, $R^2$ = Me, $R^3$ = 4-Cl-3-F-$C_6H_3$, Ar = Ph, yield = 69%
**65g**: $R^1$ = 4-OMe-$C_6H_4$, $R^2$ = Me, $R^3$ = 4-OMe-$C_6H_4$, Ar = Ph, yield = 78%
**65h**: $R^1$ = 4-OMe-$C_6H_4$, $R^2$ = Me, $R^3$ = 4-Br-$C_6H_4$, Ar = Ph, yield = 75%
**65i**: $R^1$ = 4-OMe-$C_6H_4$, $R^2$ = Pent, $R^3 = C_6H_5$, Ar = Ph, yield = 78%
**65j**: $R^1$ = 3-OMe-$C_6H_4$, $R^2$ = Bu, $R^3$ = 4-Me-$C_6H_4$, Ar = Ph, yield = 79%
**65k**: $R^1$ = furan, $R^2$ = Et, $R^3$ = 2,4-di-Cl-$C_6H_3$, Ar = Ph, yield = 73%
**65l**: $R^1$ = furan, $R^2$ = Et, $R^3$ = 3-$NO_2$-$C_6H_4$, Ar = Ph, yield = 70%

**Scheme 22.** MCR for the synthesis of 4-amino-1,2-dihydropyridines **65**.

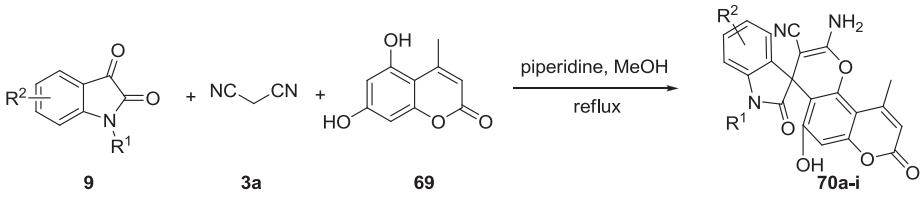



**Scheme 23.** Plausible mechanism for the formation of 4-amino-1,2-dihydropyridines **65**.

acceptor. Therefore, adduct **83**instantaneously is subjected to Michael type addition with amino pyrrole **78** to generate intermediate **84**, which exists in its tautomeric form. At the end, intramolecular cyclization of **84** with subsequent dehydration resulted in the formation of non-aromatic product **79**. DDQ as a dehydrogenating agent along with driving force of aromatization converts compound **79** to aromatic fused 7-azaindoles **80** while in other case ofindane-1,3-dione impulsive oxidation occurs to afford the stable aromatic products **82**.[108]

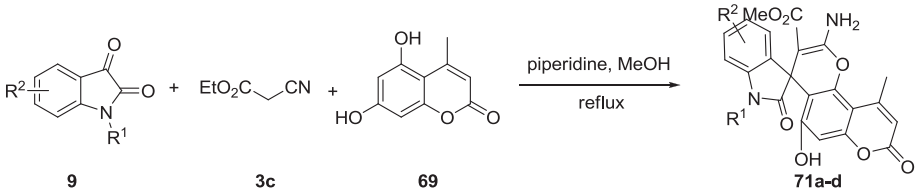
Recently, Deka and co-workers performed and presented a facile, highly efficient and ecologically benign strategy for regioselective synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines **86** and pyrido[2,3-*d*]pyrimidin-2-amines **88** in the presence of L-proline *via* MCR sequential Knöevenagel/Michael reaction involving 2-aminobenzimidazole **85** and 2,6-diamino-pyrimidin-4-one an appropriate aldehydes and β-ketoesters. This reaction was performed to obtain the optimized reaction conditions.[109]

Under optimal reaction conditions, the substrate scope of the reaction was examined *via* the reaction of 2-amino-benzimidazole **85** with differently substituted aldehydes **1** and β-ketoesters **10**, which afforded the corresponding benzo[4,5]imidazo[1,2-*a*]pyrimidines **86** in high to excellent yields. The presence of electron-withdrawing or releasing group in *ortho*-, *meta*- and *para*-position of benzene ring of benzaldehyde did not show any remarkable effect on the rates or yields of the corresponding products **86**. The reaction of heteroaromatic aldehydes such as furfural and 2-pyridinecarboxyldehyde also proceeded smoothly to afford the corresponding products **86** in 80% and 93% yields respectively. Delightfully, several aliphatic aldehydes such as valeraldehyde and phenylacetaldehyde also were successfully reacted to create their



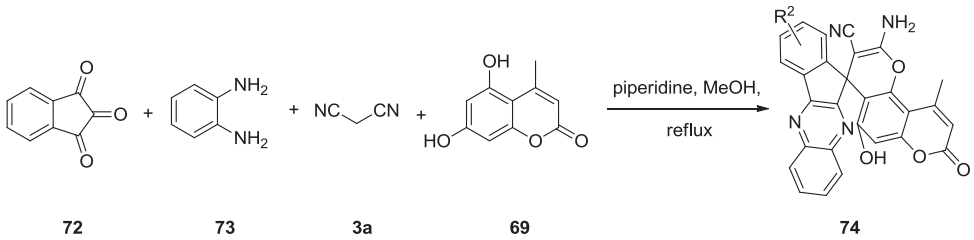

**70a**: $R^1$ = H, $R^2$ = H, yield = 79%
**70b**: $R^1$ = H, $R^2$ = 5-OMe, yield = 76%
**70c**: $R^1$ = H, $R^2$ = 5-Cl, yield = 74%
**70d**: $R^1$ = H, $R^2$ = 5-Br, yield = 67%
**70e**: $R^1$ = H, $R^2$ = 5-F, yield = 72%
**70f**: $R^1$ = H, $R^2$ = 5-I, yield = 71%
**70g**: $R^1$ = 1-Me, $R^2$ = H, yield = 76%
**70h**: $R^1$ = 1-Ph, $R^2$ = H, yield = 80%
**70i**: $R^1$ = H, $R^2$ = 7-Cl, yield = 72%

**Scheme 24.** Synthesis of pyranocoumarin fused spirooxindoles **70a-i** from the MCR of isatins, malononitrile, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **69**.




**71a**: $R^1$ = H, $R^2$ = H, yield = 68%
**71b**: $R^1$ = H, $R^2$ = 5-OMe, yield = 66%
**71c**: $R^1$ = H, $R^2$ = 5-Br, yield = 64%
**71d**: $R^1$ = 1-Ph, $R^2$ = H, yield = 71%

**Scheme 25.** Synthesis of spirooxindole pyrans **71a-d** from the reaction of isatins, ethyl cyanoacetate, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **69**.

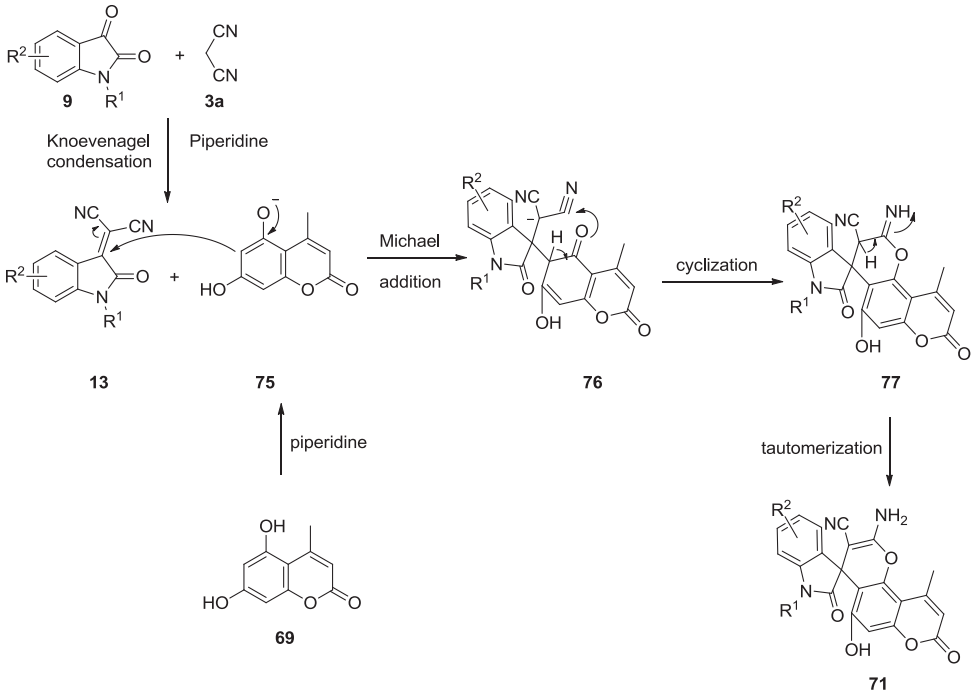



**Scheme 26.** Four-component reaction of ninhydrin **72**, *o*-phenelyne diamine**73**, malononitrile **3a**, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **69**.

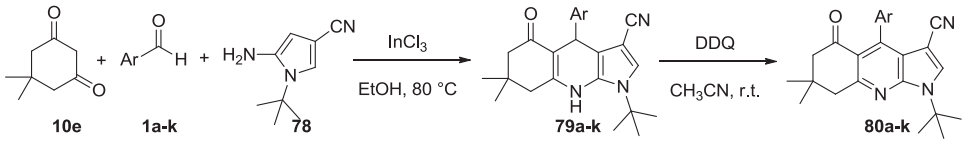
corresponding products **86** with in yields of 75% and 80%, respectively. This protocol was also extended using polyaromatic aldehyde like 2-naphthaldehyde in which its respective product **86** was provided in high yield. Generality of the scope of this strategy was further investigated by using methyl acetoacetate, instead of ethyl acetoacetate, with 2-aminobenzimidazole **85** and differently substituted aldehydes **1,** which successfully afforded the methyl analogs of benzo[4,5]imidazo[1,2-*a*]pyrimidines. Use of water as solvent along with L-proline as a commercially available organocatalyst were mentioned as merits of this approach since performing of domino reactions in aqueous media is rarely reported. The efficiency of the catalyst along with broad substrate scope conducting the reaction under mild reaction conditions and providing enormous library of biologically significant benzo[4,5] imidazo[1,2-*a*] pyrimidines **86** and pyrido[2,3-*d*]pyrimidin-2-amines **88** are other advantages which can be realized for this approach (Scheme 31).[109]

In addition, the scope of the methodology was also widen by investigation of regioselective synthesis of pyrido[2,3-*d*]pyrimidin-2-amines **88**, under the same optimal reaction conditions. The synthesis of 2,6-diaminopyrimidin-4-one **87** was studied using various aldehydes **1** and β-ketoesters **10**. Differently substituted benzaldehydes were reacted with compound **87** and ethyl acetoacetate **10** to obtain the expected product in satisfactory yields, meaning electronic and steric hindrances from the substituents of the benzene ring do not have substantial effects. Also, heteroaromatic aldehyde such as furan-3-carbaldehyde afforded the corresponding product in satisfactory yield. Furthermore, aliphatic aldehydes such as phenyl acetaldehyde was reacted fruitfully giving pyrido[2,3-*d*]pyrimidin-2-amine **88** in high yield. Furthermore, when methyl acetoacetate, was used instead of ethyl acetoacetate, the same aptitude was observed giving their corresponding methyl derivatives of pyrido[2,3-*d*]pyrimidin-2-amines **88** (Scheme 32).[109]

A suggested mechanism for the synthesis of pyrido[2,3-*d*]pyrimidin-2-amines **88** is illustrated in Scheme 33. It is assumed that initially Knöevenagel condensation between benzaldehyde **1** and β-ketoester **10** creates the corresponding adduct **89** with subsequent Michael addition of 2-amino-benzimidazole **85** or 2,6-




**Scheme 27.** Plausible mechanism for the synthesis of synthesis of spirooxindole pyrans **71a-d**.




Ar = 4-Cl$C_6H_4$, yield of **79a** = 90%, yield of **80a** = 94%
Ar = 4-OMe$C_6H_4$, yield of **79b** = 93%, yield of **80b** = 93%
Ar = 3-OMe-4-OH$C_6H_3$, yield of **79c** = 91%, yield of **80c** = 95%
Ar = 3,4,5-$(OMe)_3C_6H_2$, yield of **79d** = 89%, yield of **80d** = 92%
Ar = 3,4-(O-$CH_2$-O)$C_6H_3$, yield of **79e** = 92%, yield of **80e** = 96%
Ar = 2,4-$(Cl)_2C_6H_3$, yield of **79f** = 90%, yield of **80f** = 91%
Ar = 4-OMe-3-F$C_6H_3$, yield of **79g** = 88%, yield of **80g** = 90%
Ar = 4-CN$C_6H_4$, yield of **79h** = 89%, yield of **80h** = 92%
Ar = thiophene, yield of **79i** = 86%, yield of **80i** = 93%
Ar = furan, yield of **79j** = 87%, yield of **80j** = 94%
Ar = 2,4-$(F)_2C_6H_3$, yield of **79k** = 90%, yield of **80k** = 90%

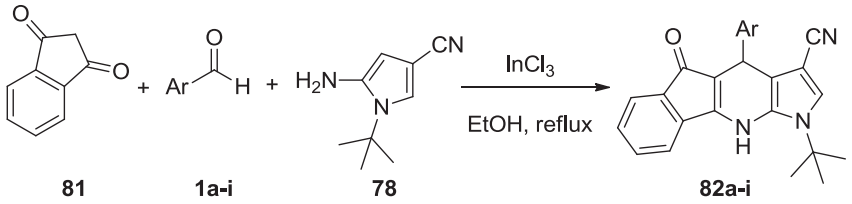
**Scheme 28.** MCR of dimedone **10e**, aldehyde **1** and aminopyrrole **78** catalyzed by $InCl_3$ to synthesis of fused 7-azaindole derivatives **80**.

diaminopyrimidin-4-one **87**, which the resultant consequently cyclized and dehydrated *via* the intermediate **90** and **91** or **93** and **94** to afford the final product **92** or **88** respectively.[109]

In 2016, Xu and co-workers accomplished and reported a facile and highly effective MCR *via* sequential Knoevenagel/Michael reaction approach for the synthesis of several bisenols. They used 1,4-diazabicyclo[2.2.2]octane (Dabco)-based ionic liquid as a catalyst system. This catalyst is commercially and inexpensively available and ecologically benign with the potentiality of being recyclable. Under the secured optimized reaction conditions, different aldehydes **1** was reacted with 4-hydroxycoumarin **50** in the presence of [Dabco-H][AcO] in water at 80 °C to obtain biscoumarins **96a-i** *via* Knoevenagel/Michael reaction. Notably, the ionic liquids are soluble in water thus, could be readily recovered and directly reused in the next reaction under the same reaction conditions. Besides, using water as the most abundant, safe, non-toxic, readily available free of charge, is another merit for this sequential Knoevenagel/Michael reaction for the easy access to bisenol derivatives (Scheme 34).[110]

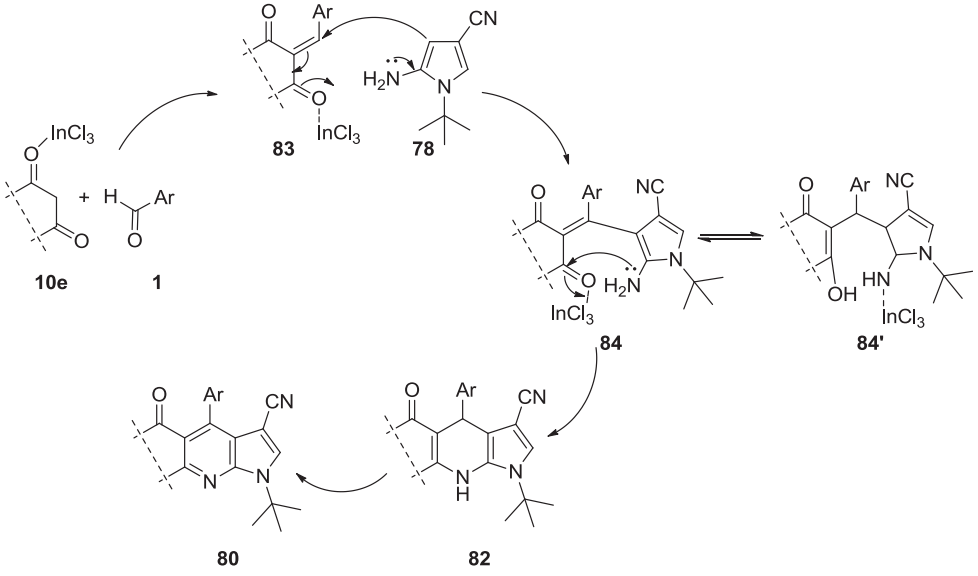
As a model reaction, terephthaldehyde was reacted with 4-hydroxycoumarin in the presence of [Dabco-H][AcO] in water at 80 °C to afford the bis[bis(4-hydroxycoumarinyl)methanes] **98** in virtually quantitative yield (99%). To establish the generality of the method under the optimized reaction conditions, the substrates, such as 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, 3-methyl-1*H*-pyrazol-5(4*H*)-one, dimedone and cyclohexane-1,3-dione, were reacted in one-pot fashion to afford the respective products **100**–**105** in almost quantitative yields (Schemes 35 and 36).[110]

A suggested reasonable mechanism for the construction of bisenols catalyzed by [Dabco-H][AcO] is depicted in Scheme 37. The pathway exhibits a classical MCR *via* double-activation. Initially, the catalytic cycle, double-activation occurs on the carbonyl group of aldehydes and enols (for example, 4-hydroxycoumarin) by the catalyst ([Dabco-H][AcO]) to generate a Knoevenagel intermediate. Next, the catalyst can activate both the Knoevenagel intermediate

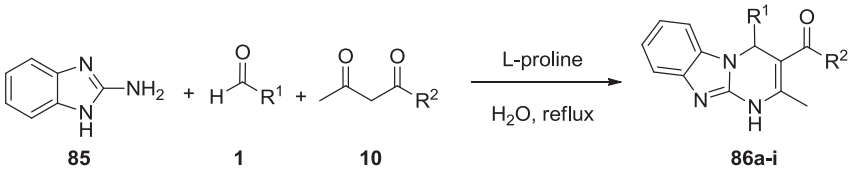



**82a**: Ar = 4-$ClC_6H_4$, yield = 95%
**82b**: Ar = 3-$OHC_6H_4$, yield = 93%
**82c**: Ar = 3,4,5-$(OMe)_3C_6H_2$, yield = 96%
**82d**: Ar = 3,4-(O-$CH_2$-O)$C_6H_3$, yield = 91%
**82e**: Ar = 2,4-$(Cl)_2C_6H_3$, yield = 90%
**82f**: Ar = 4-OMe-3-$FC_6H_3$, yield = 91%
**82g**: Ar = 4-$CNC_6H_4$, yield = 90%
**82h**: Ar = thiophene, yield = 88%
**82i**: Ar = 2,4-$(F)_2C_6H_3$, yield = 95%

**Scheme 29.** Synthesis of fused 7-azaindole derivatives **82** using indane-1,3-dione **81**.

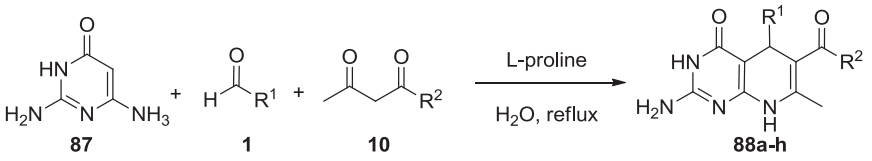



**Scheme 30.** Suggested mechanism for the synthesis of fused 7-azaindoles **80** and **82**.



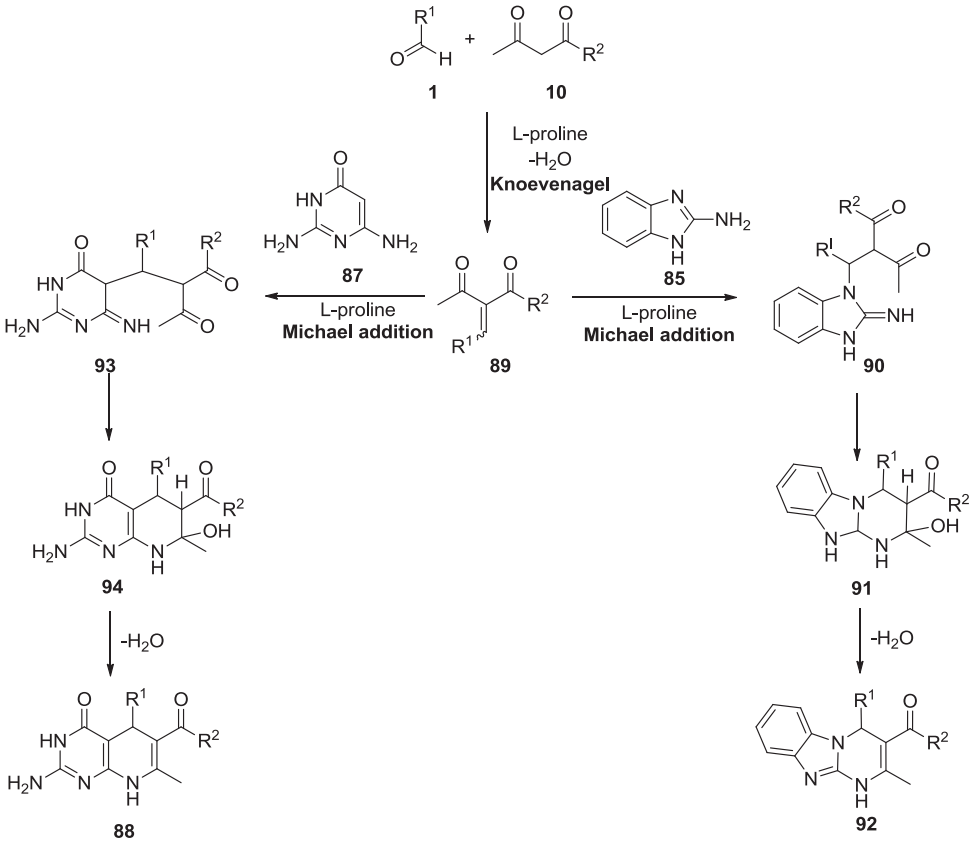

**86a**: $R^1$ = Ph, $R^2$ = OEt, time = 3 h, yield = 91%
**86b**: $R^1$ = 2-$ClC_6H_4$, $R^2$ = OEt, time = 3 h, yield = 92%
**86c**: $R^1$ = 3-$FC_6H_4$, $R^2$ = OEt, time = 3 h, yield = 90%
**86d**: $R^1$ = 4-$OMeC_6H_4$, $R^2$ = OEt, time = 2.5 h, yield = 88%
**86e**: $R^1$ = 3,5-$(OMe)_2C_6H_3$, $R^2$ = OEt, time = 3 h, yield = 85%
**86f**: $R^1$ = 2-Furan, $R^2$ = OEt, time = 3.5 h, yield = 80%
**86g**: $R^1$ = 2-Pyridyl, $R^2$ = OEt, time = 3.5 h, yield = 93%
**86h**: $R^1$ = 2-Naphthyl, $R^2$ = OEt, time = 4 h, yield = 80%
**86i**: $R^1$ = $PhCH_2$, $R^2$ = OEt, time = 4 h, yield = 80%

**Scheme 31.** Synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines **86**.




**88a**: $R^1$ = Ph, $R^2$ = OEt, time = 3 h, yield = 82%
**88b**: $R^1$ = 3-$NO_2C_6H_4$, $R^2$ = OEt, time = 2.5 h, yield = 88%
**88c**: $R^1$ = 4-$MeC_6H_4$, $R^2$ = OEt, time = 3 h, yield = 81%
**88d**: $R^1$ = 2,5-$(OMe)_2C_6H_3$, $R^2$ = OEt, time = 3 h, yield = 80%
**88e**: $R^1$ = $PhCH_2$, $R^2$ = OEt, time = 3.5 h, yield = 82%
**88f**: $R^1$ = 2-$BrC_6H_4$, $R^2$ = OMe, time = 3 h, yield = 83%
**88g**: $R^1$ = 3-$ClC_6H_4$, $R^2$ = OMe, time = 3.5 h, yield = 76%
**88h**: $R^1$ = 3-Furyl, $R^2$ = OMe, time = 3.5 h, yield = 80%

**Scheme 32.** Synthesis of pyrido[2,3-*d*]pyrimidin-2-amines **88**.

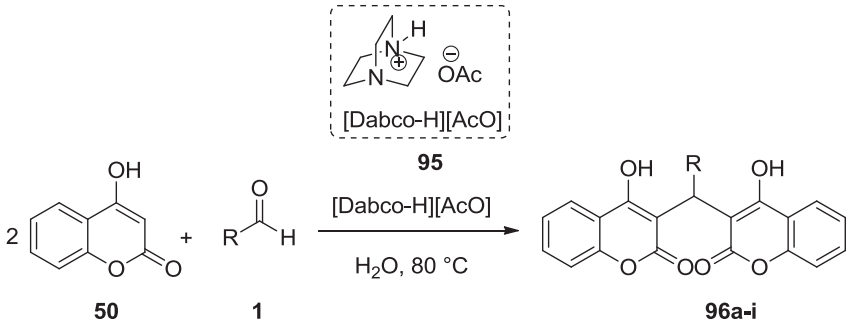



**Scheme 33.** The possible mechanism for the synthesis of pyrido[2,3-*d*]pyrimidin-2-amines **88**.

and another molecule of enol for the occurrence of the Michael addition taking the $H^+$ away from enol by the right N and give the $H^+$ attaching to left N of −C═O. At the end, a tautomerization *via* H [1,3] shift occurs to give the desired target.[110]

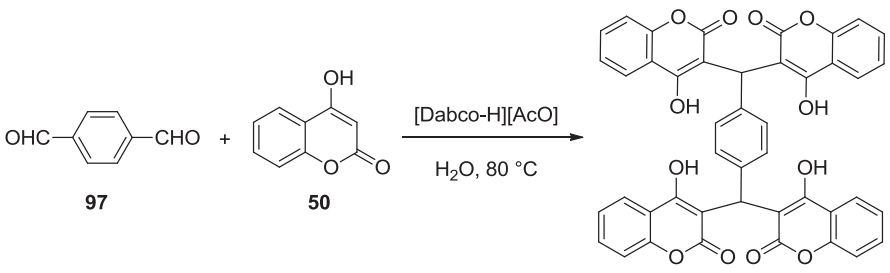
Recently, Gupta and co-workers accomplished and reported the synthesis of 2,2′-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **110** through sequential Knoevenagel/Michael reaction involving differently substituted aryl aldehydes and dimedone by employing diphenic acid immobilized onto silica **109** as a recyclable heterogeneous catalyst is clearly illustrated. In this Scheme 38, the mild and selective role of diphenic acid immobilized on silica in the construction of the aforementioned products **110** is clearly revealed. This mild conditions resulted in discontinuing the reaction after the construction of product **110**, stopping the reaction undergoing further cyclization to produce product **111**.[111]

The suggested mechanism involves the reaction of aldehydes (1 mmol) and dimedone (2 mmol) mediated silica-diphenic acid a mild and highly effective and heterogeneous catalyst. Initially, aldehyde **1** is activated *via* protonation by the catalyst, which then subjected to Knoevenagel condensation with dimedone**10a** to generate intermediate **113**. Since the latter can be further activated by the present catalyst in the reaction mixture, it is subjected into Michael addition with another molecule of dimedone **114** to give




**96a**: R = 4-$MeC_6H_4$, time = 15 min, yield = 96%
**96b**: R = Ph, time = 3 min, yield = 98%
**96c**: R = 4-$MeOC_6H_4$, time = 3 min, yield = 98%
**96d**: R = 4-$ClC_6H_4$, time = 2 min, yield = 99%
**96e**: R = 4-$BrC_6H_4$, time = 2 min, yield = 99%
**96f**: R = 3-$BrC_6H_4$, time = 3 min, yield = 98%
**96g**: R = 2-$BrC_6H_4$, time = 3 min, yield = 98%
**96h**: R = 4-$NO_2C_6H_4$, time = 5 min, yield = 99%
**96i**: R = 2,4-$Cl_2C_6H_4$, time = 15 min, yield = 96%

**Scheme 34.** MCR sequential [Dabco-H][AcO]-catalyzed Knoevenagel/Michael reaction of aromatic/heter-oaromatic/aliphatic aldehydes with 4-hydroxycoumarin.




**Scheme 35.** Synthesis of bis[bis(4-hydroxycoumarinyl)methanes] **98**.

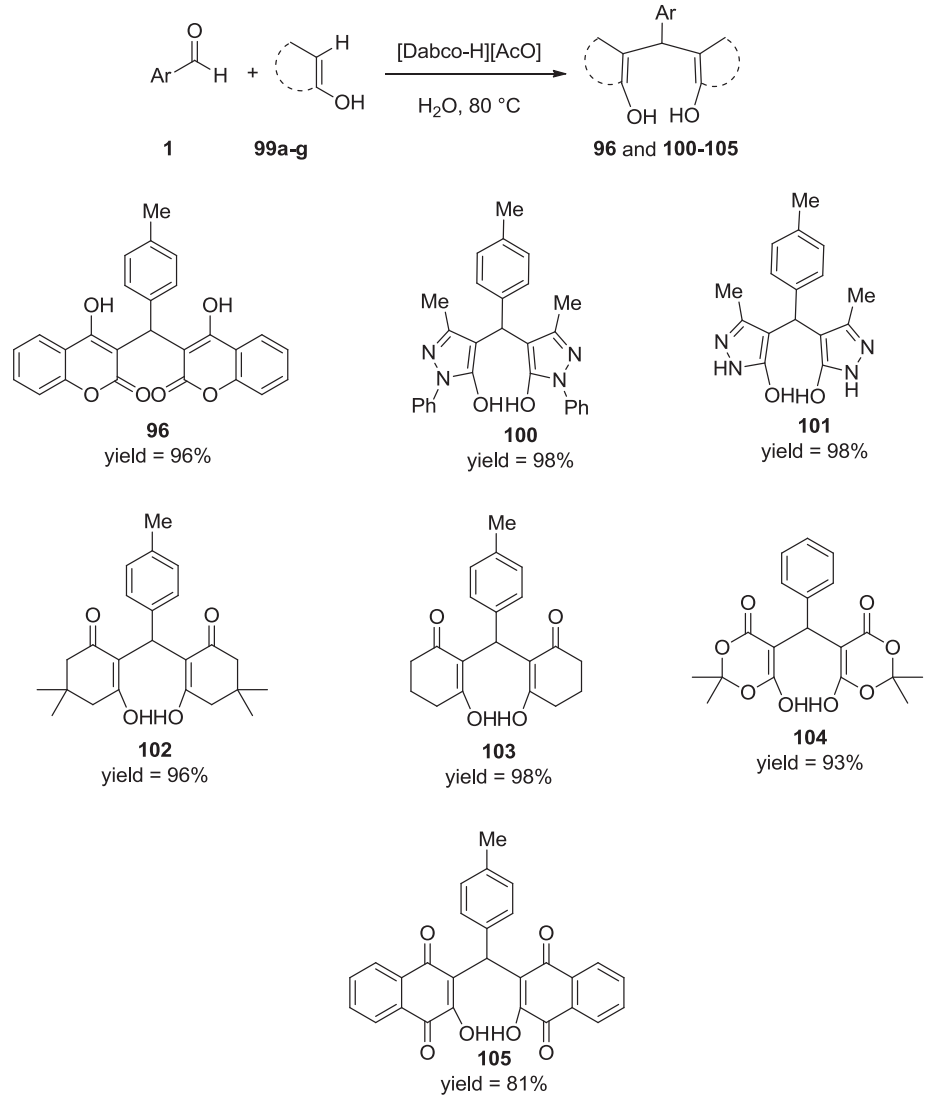
the desired target **111** (Scheme 39).[111]

A highly effective and green approach was reported for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) **118** *via* cyclocondensation-Knoevenagel-Michael sequential reaction. A *pseudo*-five-component reaction involving 2 mol of phenyl hydrazine, 2 mol of ethylacetoacetate, and differently substituted aromatic aldehydes catalyzed by acetic acid functionalized pyridinium salt (1-(carboxymethyl)pyridinium chloride {[cmpy]Cl}) in solvent-less system and in one pot fashion (Scheme 40).[112]

A reasonable mechanism for this strategy was suggested in Scheme 41. It involves the initial activation of ethylaceto acetate **119** by [cmpy]Cl. Next, phenyl hydrazine attacks to **119** for the generation of intermediate **120** *via* elimination of one molecule of water. Intramolecular cyclization in intermediate **120** along with removal of one molecule of EtOH, 3-methyl-1-phenyl-5-pyrazolone **121** was created which converted to **122** after tautomerization. Intermediate **123** is created *via* the condensation of **122** with already activated aldehyde by the catalyst to give **124** through removal of one molecule of water, is actually a Michael acceptor thus is reacted with another intermediate **122** to give **125**. Ultimately, upon the tautomeric proton shift, the desired target **118** is produced.[112]

An efficient and operationally facile and rapid synthesis of synthesis of tetrahydrobenzo[*b*] pyrans **127** was designed and practiced *via* Knoevenagel/Michael cyclocondensation.[113] In this strategy the reaction of dimedone, differently substituted aromatic aldehydes and malononitrile was performed at ambient temperature under solvent-less system in the presence of 1-methylimidazolium tricyanomethanide {[HMIM]C$(CN)_3$} nano molten salt (NMS) **126**. In a similar method, 3,4-dihydropyrano[*c*] chromene derivatives **128** were also prepared *via* the reaction of 4-hydroxycoumarin **50**, differently substituted aryl aldehydes and malononitrile catalyzed {[HMIM]C(CN)}NMS as the green catalyst. Notably, it was realized that the nature and electronic properties of the substituents on the aryl ring has influence in the rate of reaction. Benzaldehydes bearing electron-withdrawing groups react faster than electron-releasing groups (Scheme 42).[113]

A plausible mechanism for the preparation of the tetrahydrobenzo[*b*]pyran **127** is illustrated in Scheme 43.[114] Initial activation of carbonylaldehyde by, {[HMIM]C$(CN)_3$} as a NMS catalyst gives intermediate **129**. The catalyst also tautomerize malononitrile **50** to **130**. The Knoevenagel condensation of intermediate **129** with **130** takes place leading to the arylidene malononitrile **113**. Consequently, dimedone **10e** tautomerizes to **114**, which attacks as nucleophile to **113** affording the Michael adduct **131**. The latter tautomerizes by the aid of {[HMIM]C$(CN)_3$} as a NMS catalyst to generate intermediate **132**, which upon cyclization yields **133** and then upon tautomerization to give the tetrahydrobenzo[*b*]pyran




**Scheme 36.** The reaction of aromatic aldehydes with various enols **99**.

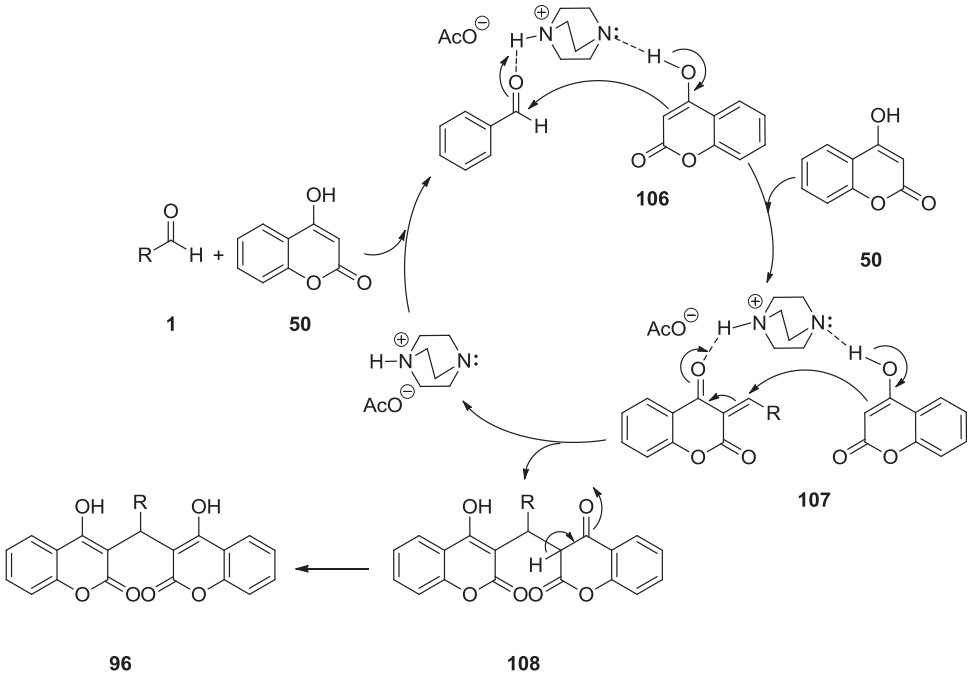
**127** as an aromatic compound.[113]

A similar mechanism for the synthesis of 3,4-dihydropyrano[*c*] chromene derivatives **128** is shown in Scheme 44.[113]

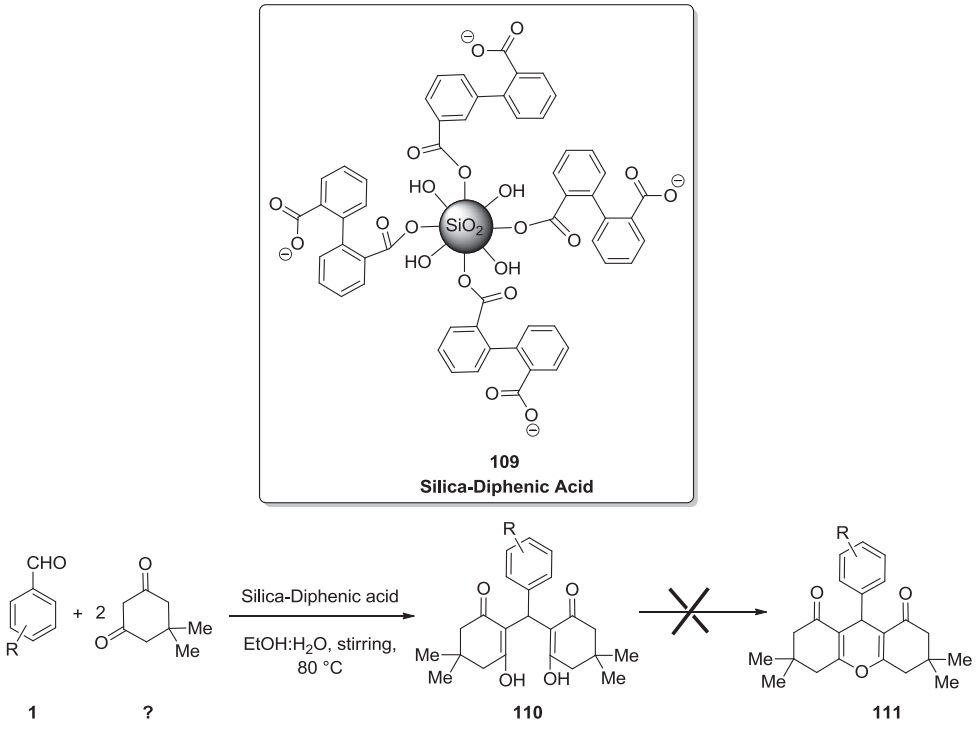
Anatase and rutile forms of $TiO_2$ nanoparticle was successfully used as an effective heterogeneous catalyst in the synthesis of 1,8-dioxo-decahydroacridines **138**/**139** *via* MCR of dimedone with differently aryl aldehydes ammonium acetate or various aromatic amines under mild reaction conditions in solvent-less system. The generality and effectiveness of the catalyst, were examined by the reaction of dimedone with differently substituted aromatic as well as aliphatic aldehydes bearing electron-withdrawing groups, electron-donating groups and halogens and ammonium acetate. All reactions proceeded smoothly to completion to afford the desired target 1,8-dioxo-decahydroacridine **138**/**139** in satisfactory yields and irrelative short reaction times (Scheme 45).[115]

The reaction is believed to proceed *via* sequential Knoevenagel/Michael cyclocondensation. The suggested mechanism involves the initial activation of carbonyl group of aldehyde by nano-$TiO_2$ next, dimedone attacks to the activated carbonyl group of aldehyde providing intermediate **140**. Then, one molecule of water is removed from **140** giving **141** as a Michael acceptor. The intermediate **141** is activated by Nano-$TiO_2$ activates. Subsequently, Michael addition of dimedone with intermediate **141** provides **142**. Then ammonia, generated from ammonium acetate, attacks the already activated carbonyl group of **142** to generate intermediates **143** and **144**, respectively by removal of water. Then, **144** is transformed to **145** *via* tautomerization, which by cyclocondensation reaction of $NH_2$ group with the already activated carbonyl group of **145** and removal of one molecule of water gives the desired product (Scheme 46).[115]

An efficient, rapid and one-pot three-component reaction was performed by using MWI in EtOH to synthesize spiro-benzimidazoquinazolinones **148**/**149**. This MCR involves a one-pot reaction of acenaphthoquinone or isatin, 1,3-diketone and 2-aminobenzimidazole in EtOH under MWI. The notable merits of this strategy is being performed under the mild reaction conditions with practical simplicity. Under the optimal reaction conditions, the substrate scope of the reaction was further expanded by using various diversities of **147** or **9** with **10** and **85** to give varied **148** or **149**, respectively. Both acenaphthoquinone **147** and isatins **9** gave the desired compounds **148** and **149** with satisfactory yields and relatively short reaction times since it is under MWI. Various substituents on the isatin ring were well tolerated, thus can be employed in transition metal catalyzed coupling reactions for




**Scheme 37.** Proposed mechanism for the synthesis of bisenols.

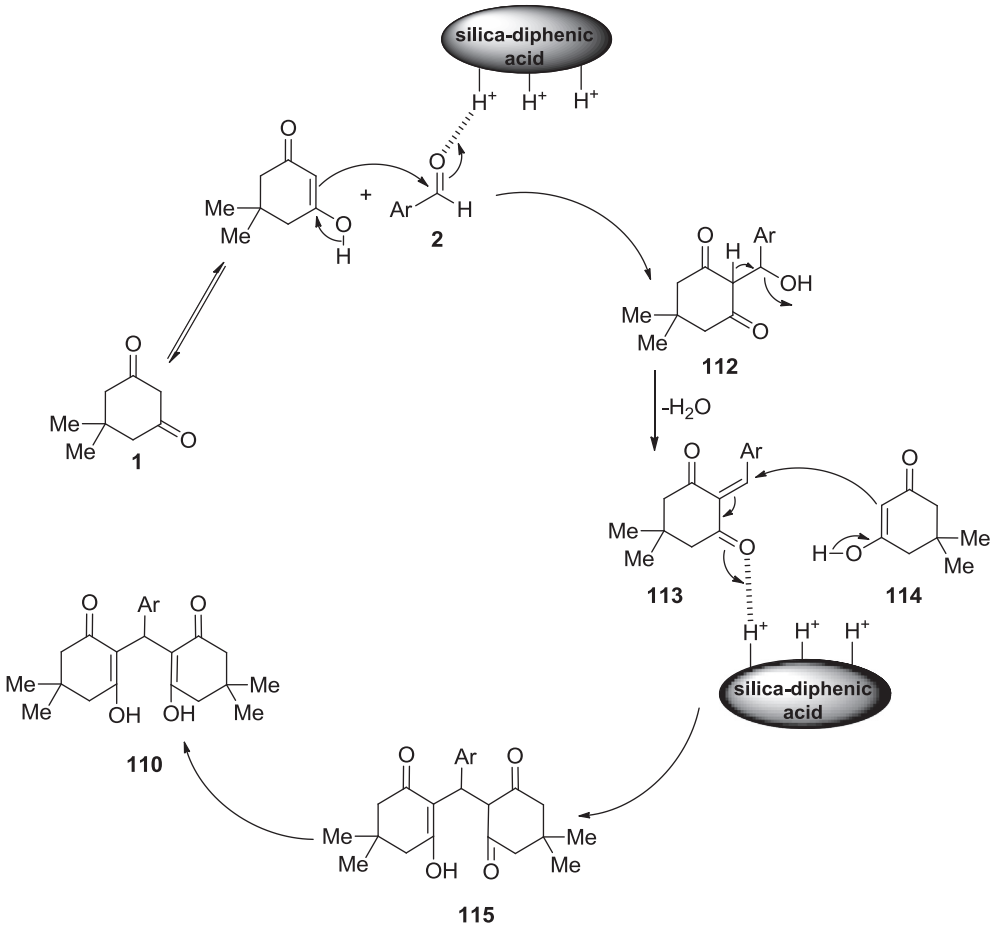



**Scheme 38.** Reaction scheme terminating after formation of product **110**.

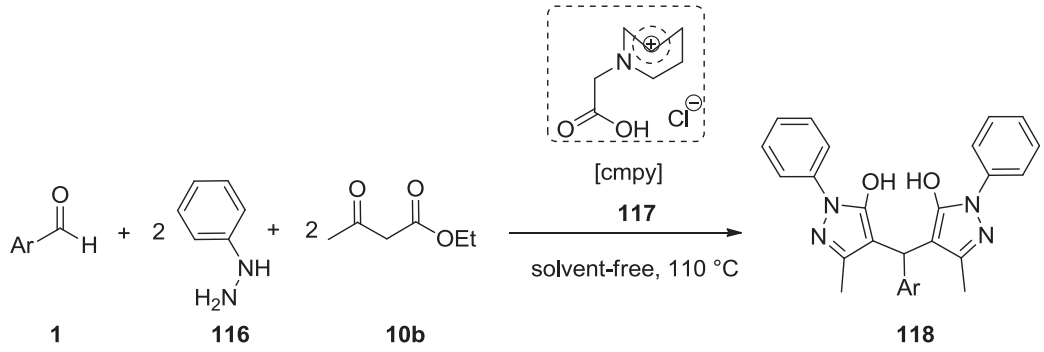
preparation of several other diversified frameworks (Scheme 47).[116]

In this route, for the synthesis of spiro-heterocycle **148**, three plausible reasonable mechanistic pathways can be proposed as illustrated in Scheme 48. Initially, Knoevenagel condensation of **147** and **10e** occurs creating acenaphthylidene **151**, which can react with **85** in two possible ways. The first possible route is Michael addition of *p*-nitrogen of benzimidazole to α, β-unsaturated ketone **151** creating intermediate **150** with subsequent imine condensation to give **148** (Knoevenagel/Michael-imine route, path A1). b) In the second route, imine condensation of 2-amino-benzimidazole **85** and **151** created intermediate **152** and with subsequent intramolecular Michael addition afforded **148**.[116]

Pyridine derivatives having diverse biological activities were synthesized by MCR Knoevenagel-Michael addition without use of any catalyst. This strategy employs various substituted aryl aldehydes, malononitrile, and 1,3-indandione **81**. Notably, the



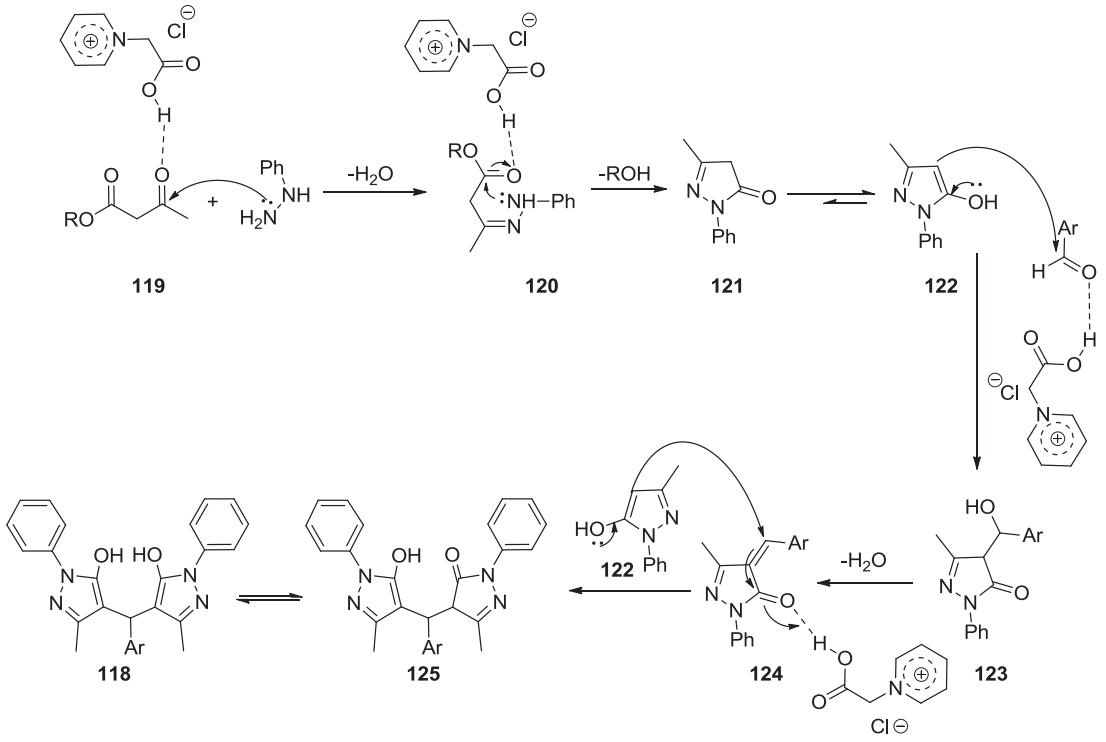

**Scheme 39.** Plausible mechanism for the silica-diphenic acid-catalyzed synthesis of 2,2′-arylmethylenebis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) **110**.



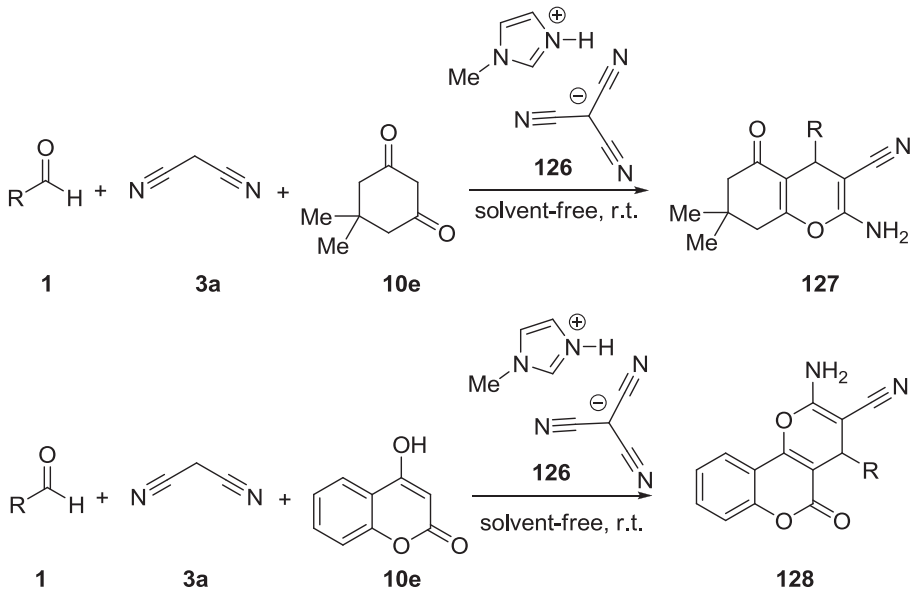

**118a**: Ar = Ph, time = 17 min, yield = 82%
**118b**: Ar = 2-$ClC_6H_4$, time = 8 min, yield = 87%
**118c**: Ar = 4-$ClC_6H_4$, time = 5 min, yield = 92%
**118d**: Ar = 2-$NO_2C_6H_4$, time = 7 min, yield = 85%
**118e**: Ar = 4-Br-2-$OHC_6H_3$, time = 13 min, yield = 82%
**118f**: Ar = 4-$MeC_6H_4$, time = 20 min, yield = 80%
**118g**: Ar = 2-$BrC_6H_4$, time = 7 min, yield = 85%
**118h**: Ar = 4-$BrC_6H_4$, time = 3 min, yield = 90%

**Scheme 40.** The solvent-free synthesis of 4,4'-(arylmethylene)-bis (3-methyl-1-phenylpyrazol-5-ol) derivatives **118** catalyzed by [cmpy]Cl.

difference between the MCR and sequential multicomponent reaction is underscored by this methodology. The reaction is conducted at room temperature in the absence of commonly used ammonium salt as N-source for the construction of aza-




**Scheme 41.** The suggested mechanism for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1H -pyrazol-5-ol)s **118** using [cmpy]Cl.

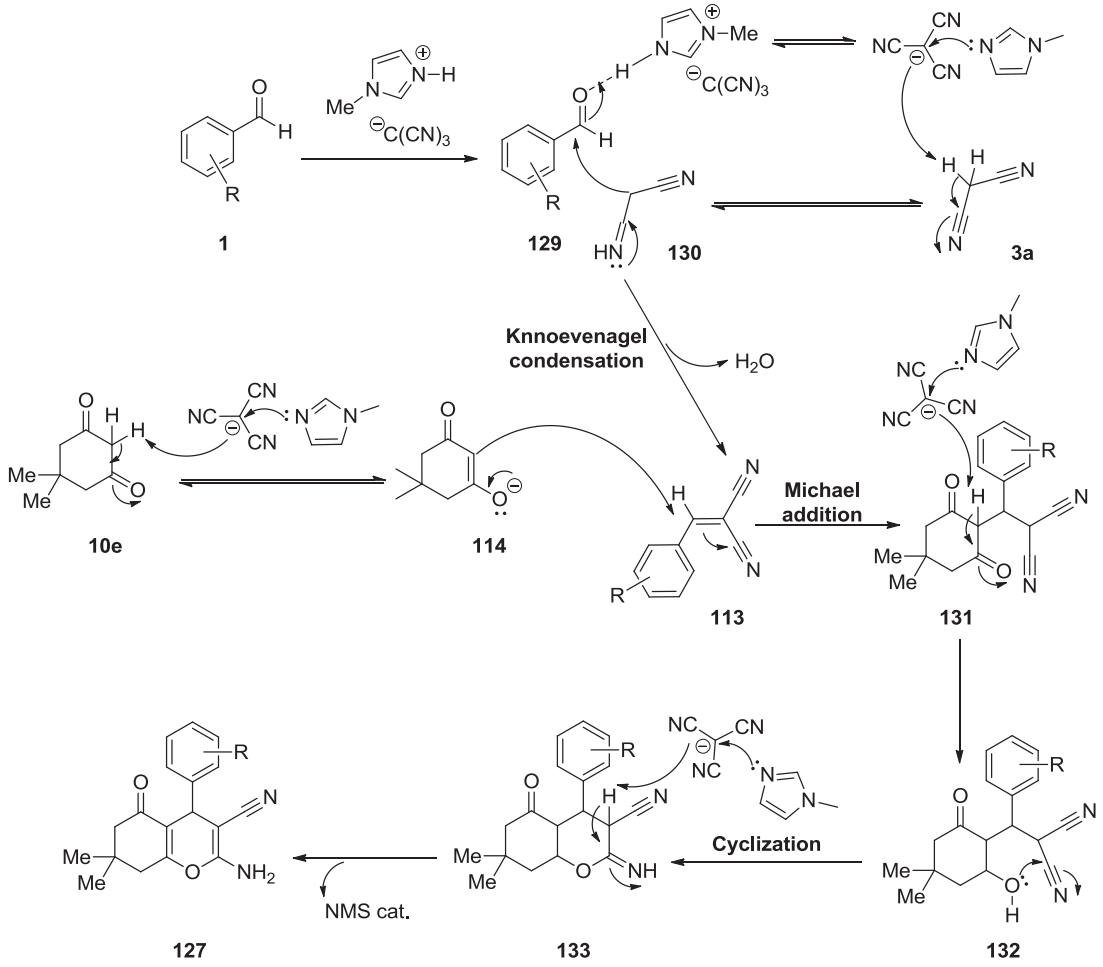



**Scheme 42.** Synthesis of tetrahydrobenzo[*b*]pyran derivatives **127** and 3,4-dihydropyrano[*c*]chromene derivatives **128**

heterocycles, which makes this strategy as a novel synthetic pathway for the synthesis of the in denopyridine skeleton (Scheme 49).[117]

The proposed mechanism for the construction of products **154** may be described on the base of the pathways depicted in Scheme 50. Accordingly, first an aryl aldehyde **1** reacted with malononitrile **3a** *via* a Knoevenagel condensation to generate a Knoevenagel adduct (in this case 3-nitrobe nzylidene)propanedinitrile **155**, which behaves as a Michael acceptor during the addition of the enol form of 1,3-indandione **81** to generate an intermediate **156**. Next, the intermediate **156** upon rearrangements gives ketoimine derivatives **157**, which tautomerizes to become reactive species enol imine derivatives **158**. At the end, the reactive enol imine derivative is subjected to intramolecular cyclization to give a corresponding pyridine derivative **154**.[117]

A sequential Knoevenagel/Michael reactions catalyzed by diethylamine in aqueous medium were successfully conducted for the facile one-pot synthesis of bis-dimedone derivatives. The MCRs of differently substituted benzaldehyde (1 equiv.) and dimedone (2 equiv.), mediated by diethylamine at ambient temperature gave




**Scheme 43.** The proposed mechanism for the synthesis of tetrahydrobenzo [*b*]pyran derivatives **127**.

bis-dimedone derivatives **160a-n** in high to excellent yields (87–95%) within a relatively short reaction time. Thus a highly efficient, green and cost effective process for the synthesis of bis-dimedone derivatives was developed.

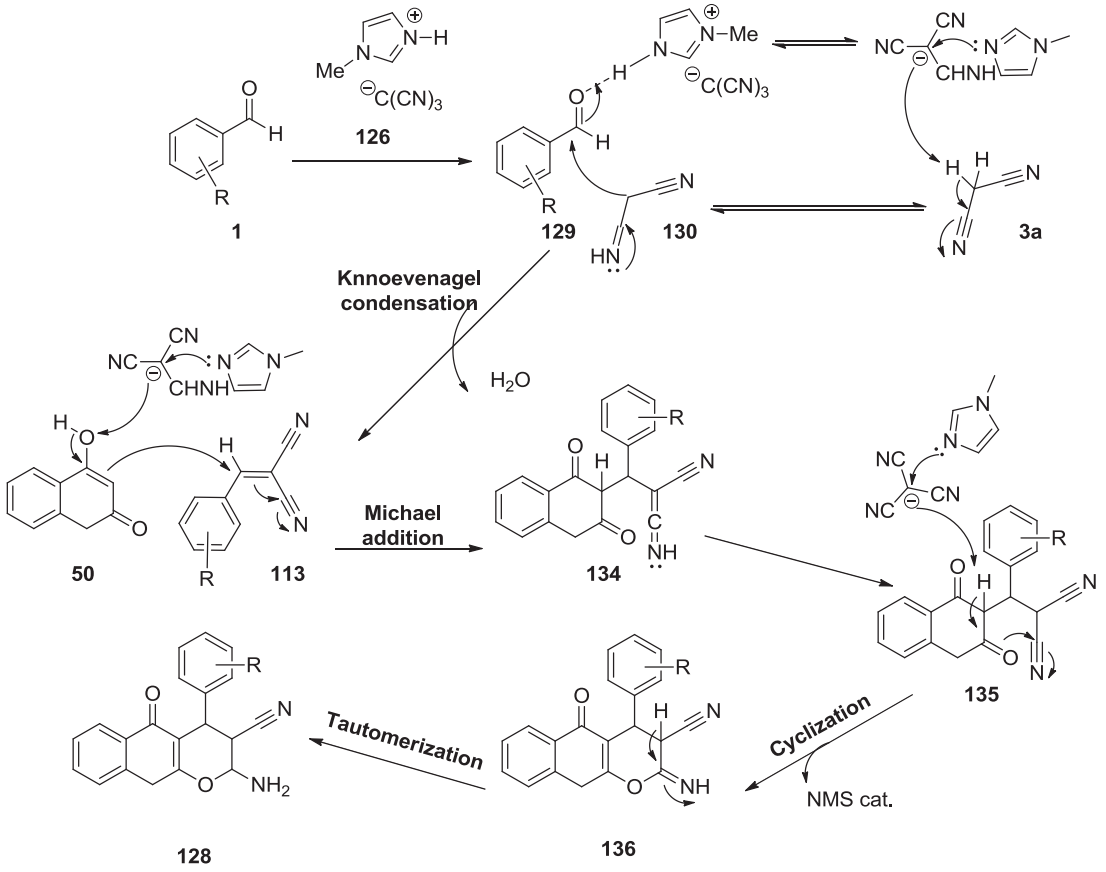
As shown in Scheme 51, differently substituted benzaldehydes bearing electron-releasing or electron-withdrawing groups at the ortho-, meta- or para -, even bulky group at ortho-position on the aromatic ring irrespective of nature of the substituted groups were well tolerated, giving the corresponding bis-dimedone derivatives **160b-n** with in good to high yields (85–93%. Furthermore, reactions with substrates **159g**, **159k** and **159** bearing strictly hindered group, proceeded smoothly to completion affording the products with very satisfactory results (85%, 92% and 91% respectively). Relied on the above results, this strategy was then expanded to heterocyclic aldehyde, but undelightfully, the reactions did not proceed at all. The merits mentioned for this strategy involved were use of inexpensive, environmentally friendly, commercially available or easily accessible readily reagents, and obtaining high purity products makes the procedure a facile and healthy methodology for the synthesis of sequential Knoevenagel/Michael adducts.[118]

A plausible mechanism for this sequential Knoevenagel/Michael reaction was proposed and illustrated in Scheme 52. Water molecule initially generates H-bonding with the keto group of compound **10e** thus, the C'O functional group is activated, therefore the deprotonation of methylene proton by diethylamine resulted in the enolate intermediate **162**. Next, the enolate **163** attacks the nucleophilic center of the carbonyl group of aldehyde with subsequent Knoevenagel condensation to generate Knoevenagel condensation adduct as intermediate **164** *via* the removal of a molecule of water. Ultimately, the second molecule of enolate further attacks the double bond of Knoevenagel product **164** and then is subjected to Michael addition to afford the Knoevenagel-Michael product **160a-n** and in which water and diethylamine are regenerated.[118]

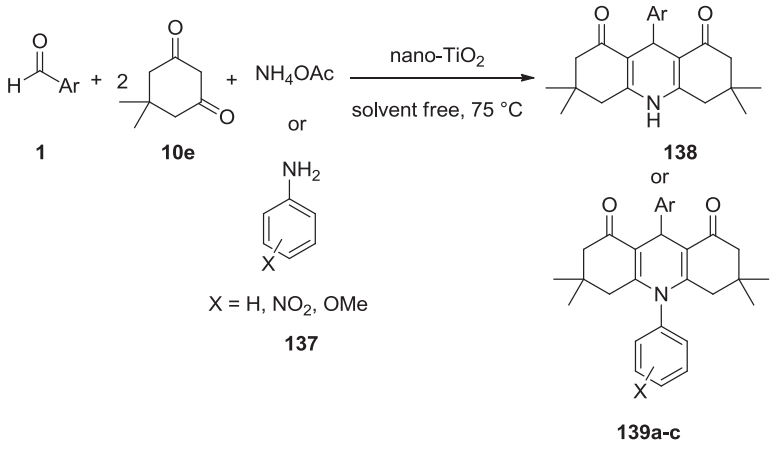
Very recently, Xu and co-workers successfully achieved a facile, ecologically benign and highly effective protocol for synthesis of the 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives **167**. In 2017, they reported a *pseudo*-five-component one-pot reaction involving 2 mol of phenylhydrazine **116**, 1 mol of dialkylacetylenedicarboxylats **165** or 2 mol of β-ketoesters and differently substituted aryl aldehydes mediated by Dabco-base ionic liquids in water. With this optimal reaction conditions, next, the substrate scope of the reaction was studied. For such purpose sequential cyclocondensation Knoevenagel/Michael addition of phenyl hydrazine, various dialkylacetylene dicarboxylates **165** and aromatic aldehydes bearing both electron-releasing and electron-withdrawing groups in the presence of ionic liquid catalyst [Dabco-$C_4$]Cl in aqueous media was investigated which all gave the corresponding 1-phenyl-5-pyrazolone derivatives **167**, in good to excellent yields within fairly short reaction times (Scheme 53).[119]

Also, the generality of this protocol for the synthesis diverse substituted bis(pyrazol-5-ol)s **169** was established by using various β-ketoesters **168** to replace dialkylacetylene dicarboxylates (Scheme 54).[119]

A proposed route for the construction of the 4,4'-



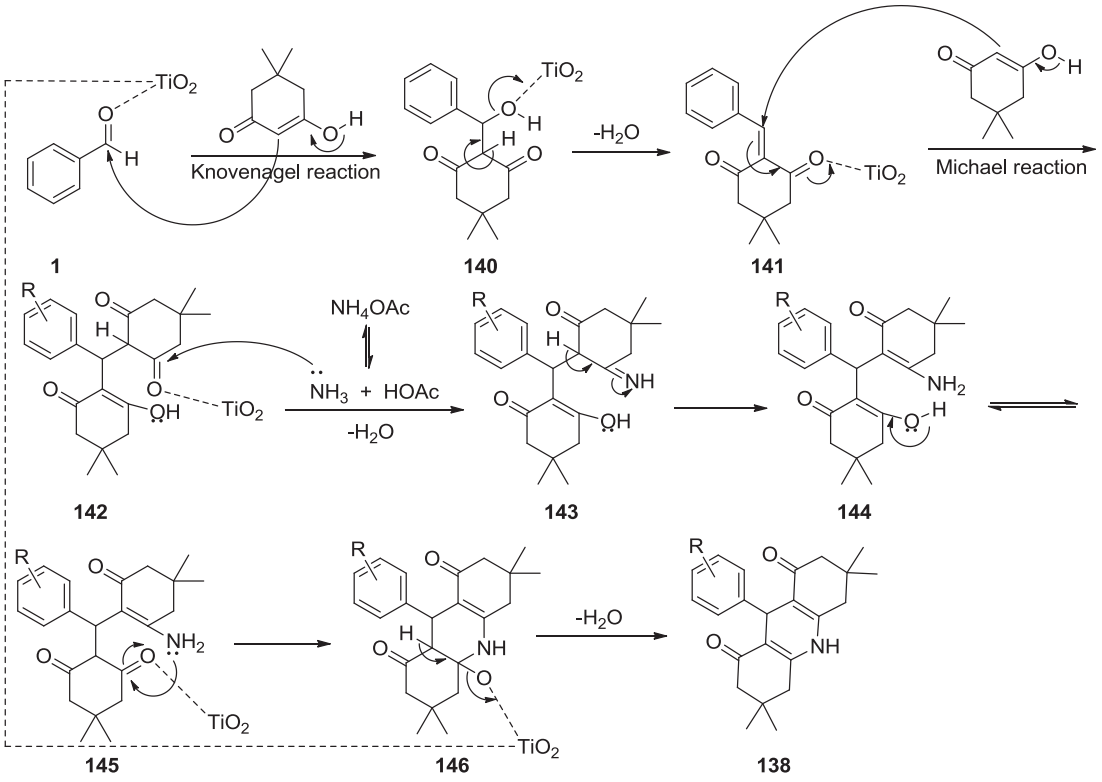

**Scheme 44.** The probable mechanism for the synthesis of 3,4-dihydropyrano[*c*]chromene derivatives **128**.



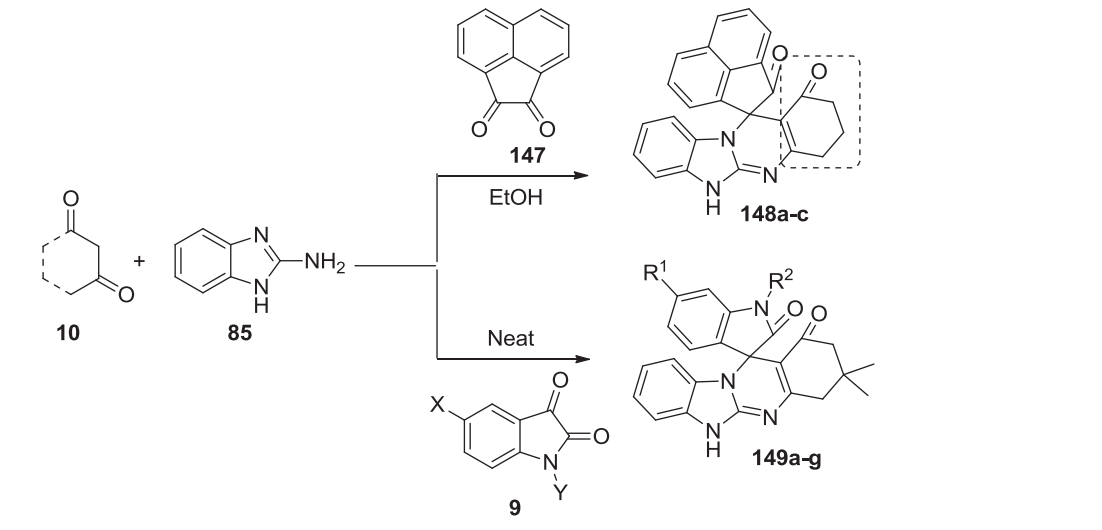

**138a**: Ar = Ph, time = 30 min, yield = 80%
**138b**: Ar = 2,4-$Cl_2C_6H_3$, time = 25 min, yield = 81%
**138c**: Ar = 2-OMe-4-$OHC_6H_3$, time = 60 min, yield = 83%
**138d**: Ar = 4-$CNC_6H_4$, time = 30 min, yield = 85%
**138e**: Ar = 4-$NO_2C_6H_4$, time = 30 min, yield = 80%
**138f**: Ar = 4-$FC_6H_4$, time = 15 min, yield = 90%
**138g**: Ar = 4-$BrC_6H_4$, time = 20 min, yield = 80%
**138h**: Ar = 3-$BrC_6H_4$, time = 15 min, yield = 90%
**138i**: Ar = 3-$ClC_6H_4$, time = 20 min, yield = 90%

**139a**: Ar = Ph, X = H, time = 30 min, yield = 80%
**139b**: Ar = Ph, X = 4-OMe, time = 25 min, yield = 81%
**139c**: Ar = Ph, X = 4-$NO_2$, time = 80 min, yield = 83%

**Scheme 45.** Preparation of 1,8-dioxo-decahydroacridines**138** and **139** employing Nano-$TiO_2$ as catalyst.




**Scheme 46.** The suggested mechanism for the synthesis of 1,8-dioxo-decahydroacridines **138** using nano-$TiO_2$.

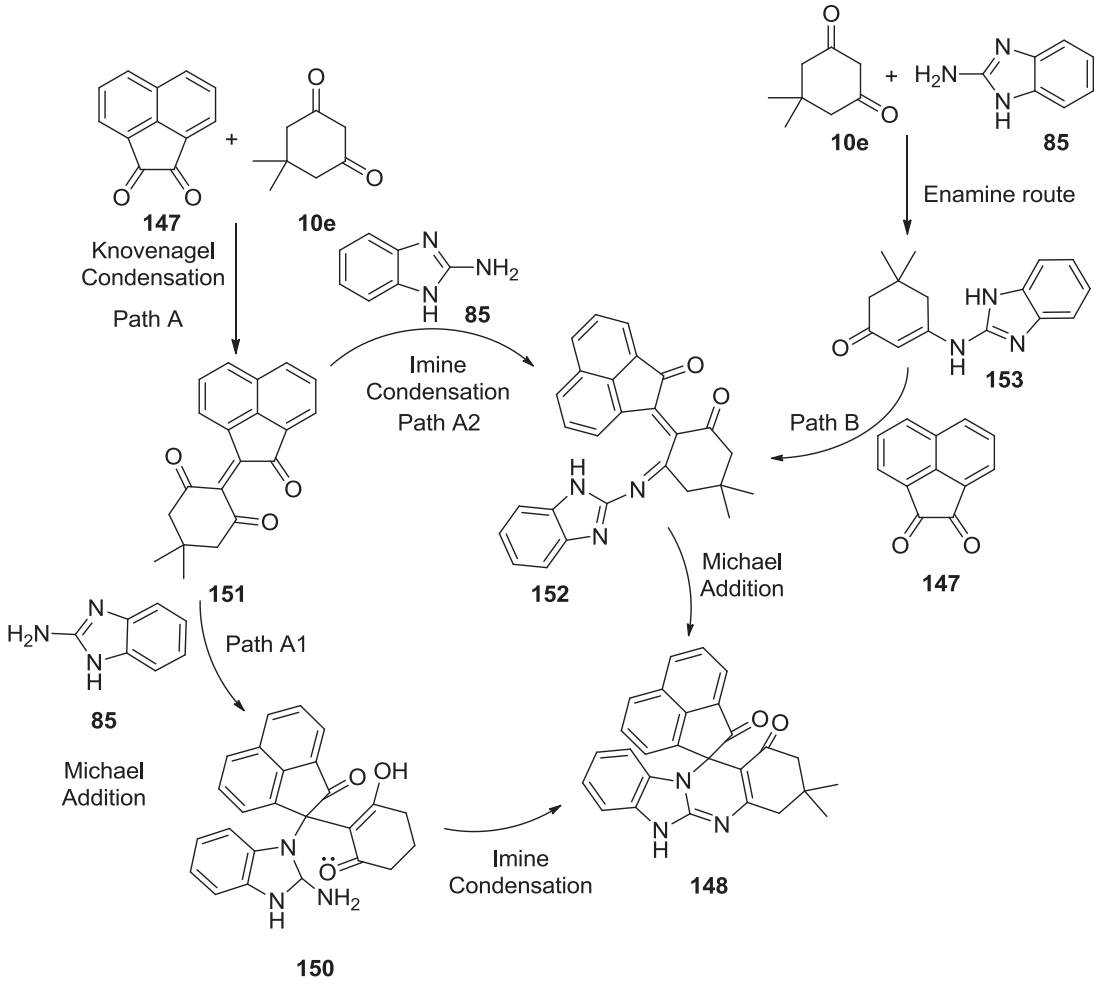



**148a**: 5,5-dimethylcyclohex-2-enone, yield = 75%
**148b**: 1*H*-inden-1-one, yield = 72%
**148c**: cyclohex-2-enone, yield = 75%

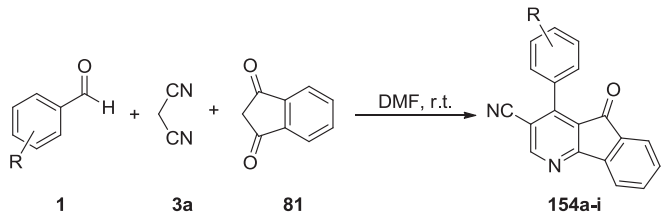
**149a**: $R^1$ = H, $R^2$ = H, yield = 77%
**149b**: $R^1$ = Me, $R^2$ = H, yield = 78%
**149c**: $R^1$ = Br, $R^2$ = H, yield = 80%
**149d**: $R^1$ = H, $R^2$ = Me, yield = 82%
**149e**: $R^1$ = Cl, $R^2$ = H, yield = 76%
**149f**: $R^1$ = H, $R^2$ = $CH_2CH_2Me$, yield = 78%
**149g**: $R^1$ = H, $R^2$ = $CH_2CH_2CH_2Me$, yield = 77%

**Scheme 47.** One-pot MCR synthesis of spiro-benzimidazoloquinazolinones **148a-c** and **149a-g** under MWI.

(arylmethylene)bis(1*H*-pyrazol-5-ol) derivatives **169** mediated by [Dabco-$C_4$]Cl is illustrated in Scheme 55. In accordance with this suggestion, initially pyrazolone **173** or **177** as an intermediate is formed from the condensation of hydrazines with dialkylacetylene dicarboxylates or β-ketoesters. Next, [Dabco-$C_4$]Cl, catalyzes the Knoevenagel condensation of the intermediate **173** or **177** with an




**Scheme 48.** Three proposed mechanisms for the synthesis of spirobenzimidazoquinazolinone **148**.




**154a**: R = 4-$NO_2C_6H_4$, time = 3 h, yield = 86%
**154b**: R = 4-$NMe_2C_6H_4$, time = 5 h, yield = 88%
**154c**: R = 2,4-$Cl_2C_6H_3$, time = 3.5 h, yield = 90%
**154d**: R = 4-$BrC_6H_4$, time = 3.5 h, yield = 90%
**154e**: R = anthracene-9-carbaldehyde, time = 3 h, yield = 85%
**154f**: R = 4-$CNC_6H_4$, time = 3 h, yield = 90%
**154g**: R = furan, time = 3 h, yield = 94%
**154h**: R = 3-OMe-4-$OHC_6H_3$, time = 3.5 h, yield = 93%
**154i**: R = thiophene-3-carbaldehyde, time = 3 h, yield = 92%

**Scheme 49.** Synthesis of 4-(3,nitrophenyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile **154**.

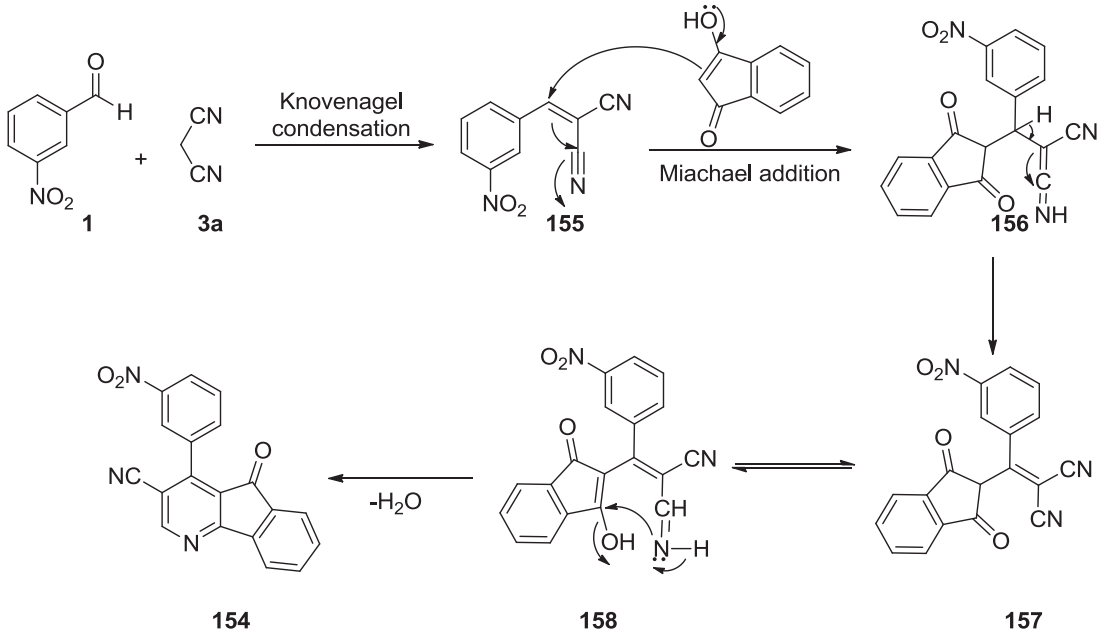
appropriate aldehyde followed by dehydration, resulting in the generation ofintermediate**179.** Subsequently, another intermediate **173** or **177** reacts with **179** *via* Michael addition to afford the adduct **181**. Ultimately, upon proton shift, *via* tautomerism gives the desired target **167** or **169**.[119]

### 2.2. Knoevenagel/Diels-Alder reaction

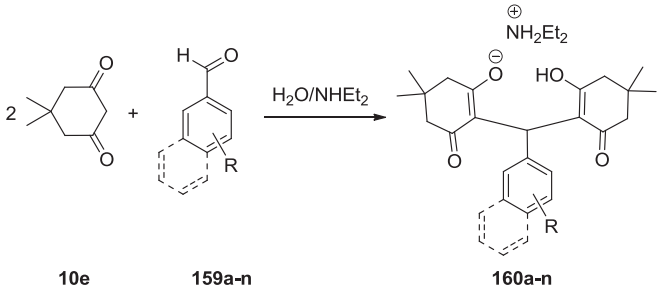
A simple concept in combinatorial chemistry that takes advantage of merits of reactions being done in solution with those of solid-phase synthesis was disclosed. In such strategy, the reagents can be used in excess, and the products can be isolated in purities up to 99% by simple filtration. The procedure includes a MCR sequential Knoevenagel/hetero-Diels-Alder reaction involving a 1,3-dicarbonyl compound, an amino aldehyde and an enol ether, which followed by a reductive amination upon formation of a betaine that can be separated by precipitation from the solution in high purity. Other by-products and excess used reagents were separated by simple filtration. By the using of α-, β-, and γ-amino aldehydes libraries of pyrrolidine, piperidine, and azepane derivatives were obtained, respectively.

The merits mentioned for this reaction is the use of expensive resins as well as the development and optimization of appropriate coupling and decoupling reactions are non-required. The sequential Knoevenagel/hetero-Diels-Alder reaction, and reduction allows fast access to a number of N-heterocycles with different ring sizes and substitution patterns a generated betaine structure that can be gained by simple high precipitation in high purities. Importantly, it was found this process is also appropriate for automation (Scheme 56).[120]

An effective organocatalyzed diastereospecific and enantioselective sequential Knoevenagel/Diels-Alder reactions was




**Scheme 50.** Mechanistic pathway for the synthesis of Synthesis of 4-(3,nitrophenyl)-5-oxo-5*H*-indeno[1,2-*b*]pyridine-3-carbonitrile **154**.




**160a**: R = Ph, time = 30 min, yield = 95%
**160b**: R = 4-MePh, time = 45 min, yield = 93%
**160c**: R = 4-ClPh, time = 45 min, yield = 92%
**160d**: R = 4-BrPh, time = 45 min, yield = 90%
**160e**: R = 3-BrPh, time = 45 min, yield = 88%
**160f**: R = 4-OMePh, time = 45 min, yield = 89%
**160g**: R = 2,4,6-$(Me)_3$Ph, time = 90 min, yield = 85%
**160h**: R = 4-$NO_2$Ph, time = 60 min, yield = 90%
**160i**: R = 3-MePh, time = 60 min, yield = 91%
**160j**: R = 4-OHPh, time = 60 min, yield = 88%
**160k**: R = 2,4-$Cl_2$Ph, time = 90 min, yield = 92%
**160l**: R = 2,6-$Cl_2$Ph, time = 90 min, yield = 91%
**160m**: R = 2-$NO_2$Ph, time = 60 min, yield = 87%
**160n**: R = 2-naphthaldehyde, time = 60 min, yield = 93%

**Scheme 51.** Knoevenagel/Michael addition sequence of dimedone **10e** with aromatic aldehydes **159b-n** in aqueous diethylamine medium.

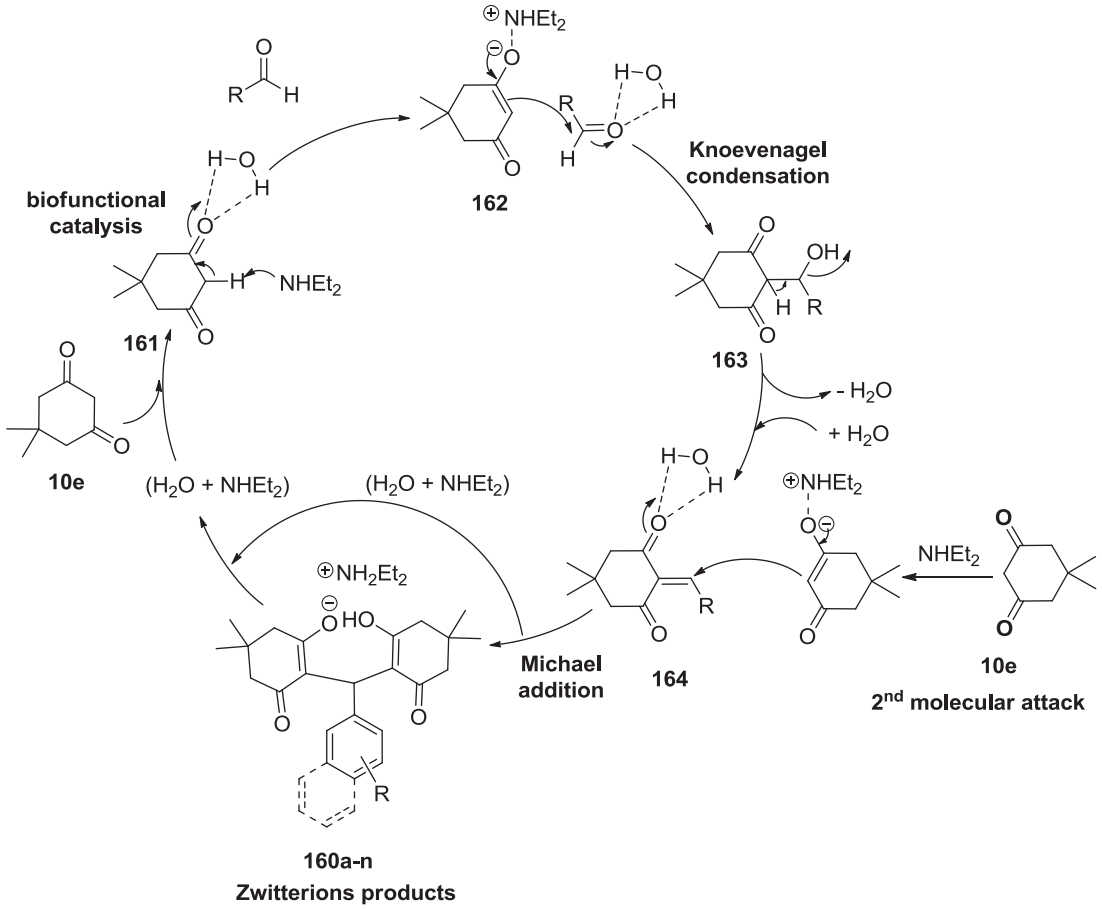
accomplished and provided fully substituted spiro[5,5]undecane-1,5,9-triones **194** starting with market purchasable 4-substituted-3-buten-2-ones **192a-e**, differently substituted aldehydes **1a-d**, and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, **192**.[121] Spirocyclic ketones **194** are important intermediates in the total synthesis of several naturally occurring and complex molecules showing significant biological activities.[122,123]

According to the designed above-mentioned strategy an amino acid catalyzed the sequential Knoevenagel condensation[124] of aldehyde **1** with Meldrum's acid **192** to produce the corresponding alkylidene derivative of Meldrum's acid that subsequently was subjected to a concerted [4 + 2] cycloaddition with a 2-amino-1,3-butadiene resulted in the creation in situ of enone **191** and an amino acid to afford substituted spiro[5,5]undecane-1,5,9-triones **194** in a highly *ee* and *de*.[125] The sequential Knoevenagel/Diels-Alder reaction would then takes place to produce a quaternary center with generation of three new carbon-carbon bonds *via* amino acid catalysis process (Scheme 57).[121]

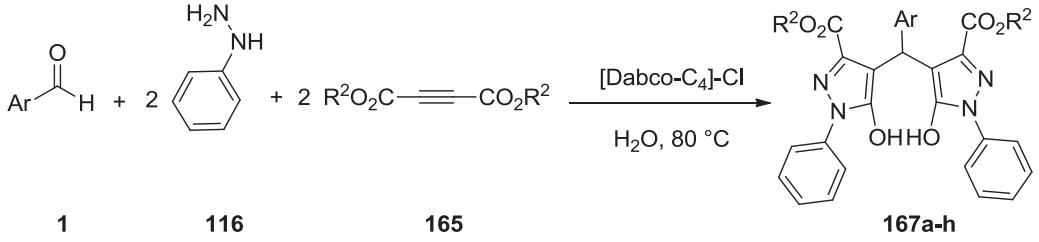
Generation of the unanticipated symmetric triketone **195** from the reaction of **191a**, **1**, and **192** can be clarified as depicted in Scheme 58. Amine-mediated Knoevenagel condensation of **1**with **192** gives the 4-nitrobenzelidene derivative of Meldrum's acid **197** that subsequently is subjected to Diels-Alder or a double Michael reaction with the soft nucleophilic 2-amino-1,3-butadiene, generated in situ from enone **191a** and an amine to provide product **194aa**. At that moment, the in situ provided hard nucleophile methoxide ($MeO^-$) reacts with **197** to recreate acetone. Noticeably, it was found that the yield of this recreation actually depends on the basicity of the amine, which is used as the catalyst. Regenerated acetone is submitted to amine mediated aldol condensation with aldehyde **1** to afford enone **200** that subsequently reacts with an amine to give2-amino-1,3-butadiene **201** as a reactive species which subsequently is subjected into a diastereospecific Diels-Alder reaction with dienophile **197** to give the ketone **195**.[121]

Upon combination of enamine-based activation of enones in Diels-Alder reactions with the amine-mediated Knoevenagel reaction of malonates with differently substituted arylaldehydes and1,3-indandione **81** or Meldrum's acid **192**. In this strategy, if 1,3-indandione **81** is employed instead of Meldrum's acid, after thermodynamic equilibration, the *cis*-configured corresponding Knoevenagel Diels-Alder products **206** are obtained in virtually quantitative yields (Scheme 59).[126]

The application of a synthetic pathway analogous to the creation of a small library of irregular biphenyl-substituted 6-phenylspiro [cyclohexane-1,2′-inden]-1′,3′,4′-triones and terphenyl- and biphenyl-substituted 2,4-dioxa-spiro[5,5]undecane-1,5,9-triones was deigned. Conceptually, this strategy shows attraction for the sequential domino Knoevenagel/Diels-Alder epimerization reaction. This strategy resulted in the formation of a spirocyclic ketone



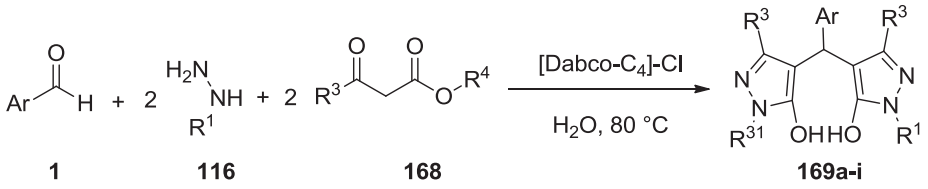

**Scheme 52.** A possible mechanistic pathway for the synthesis of Knoevenagel-Michael product **160a-n**.




**167a**: Ar = 4-$MeOC_6H_4$, $R^2$ = Me, time = 60 min, yiield = 95%
**167b**: Ar = 4-$MeOC_6H_4$, $R^2$ = Et, time = 120 min, yiield = 81%
**167c**: Ar = 4-$ClC_6H_4$, $R^2$ = Me, time = 50 min, yiield = 96%
**167d**: Ar = 4-$ClC_6H_4$, $R^2$ = Et, time = 180 min, yiield = 87%
**167e**: Ar = 4-$BrC_6H_4$, $R^2$ = Me, time = 60 min, yiield = 90%
**167f**: Ar = 4-$BrC_6H_4$, $R^2$ = Et, time = 75 min, yiield = 97%
**167g**: Ar = 4-$MeOC_6H_4$, $R^2$ = Me, time = 50 min, yiield = 95%
**167h**: Ar = 4-$MeOC_6H_4$, $R^2$ = Et, time = 75 min, yiield = 92%

**Scheme 53.** Synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol) **167**.

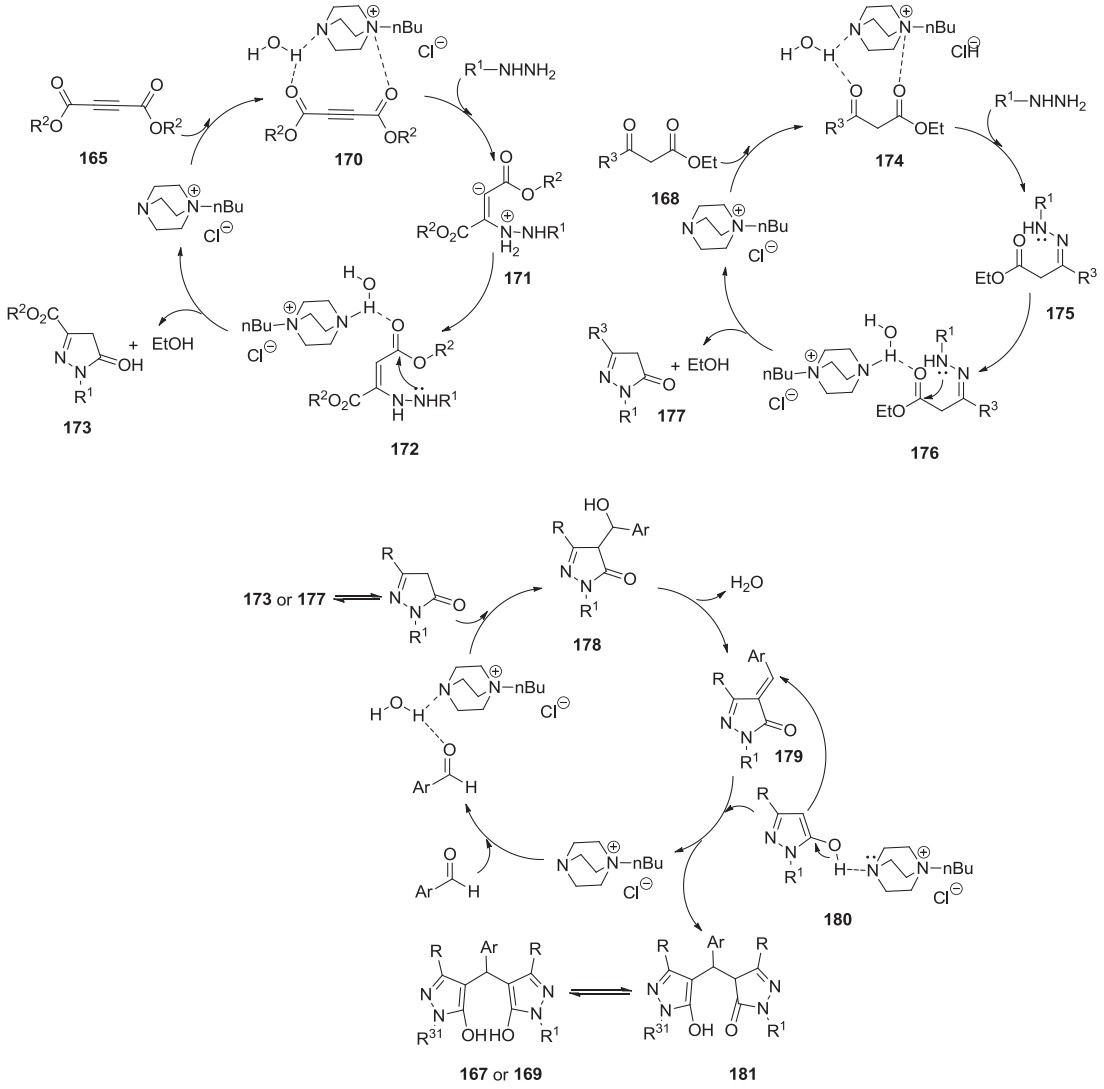
core *via* the concurrent generation of three carbon-carbon-bonds in a single step. Base-catalyzed three-component reaction of differently substituted aromatic aldehydes **1**, cyclic methylene-activated compounds and 4-substituted-3-buten-2-ones **212** resulted in the construction of corresponding spiro compound **210**. It was found that the reaction is highly diastereospecific giving the thermodynamically more stable *cis*-spirane as a main diastereomer because of the epimerization of the minor trans isomer, taking place under the similar reaction conditions except a prolonged reaction time. Furthermore, this sequential reaction can be conducted in similar efficacy resulted in the fast synthesis of a group of differently substituted derivatives (Scheme 60).[127]



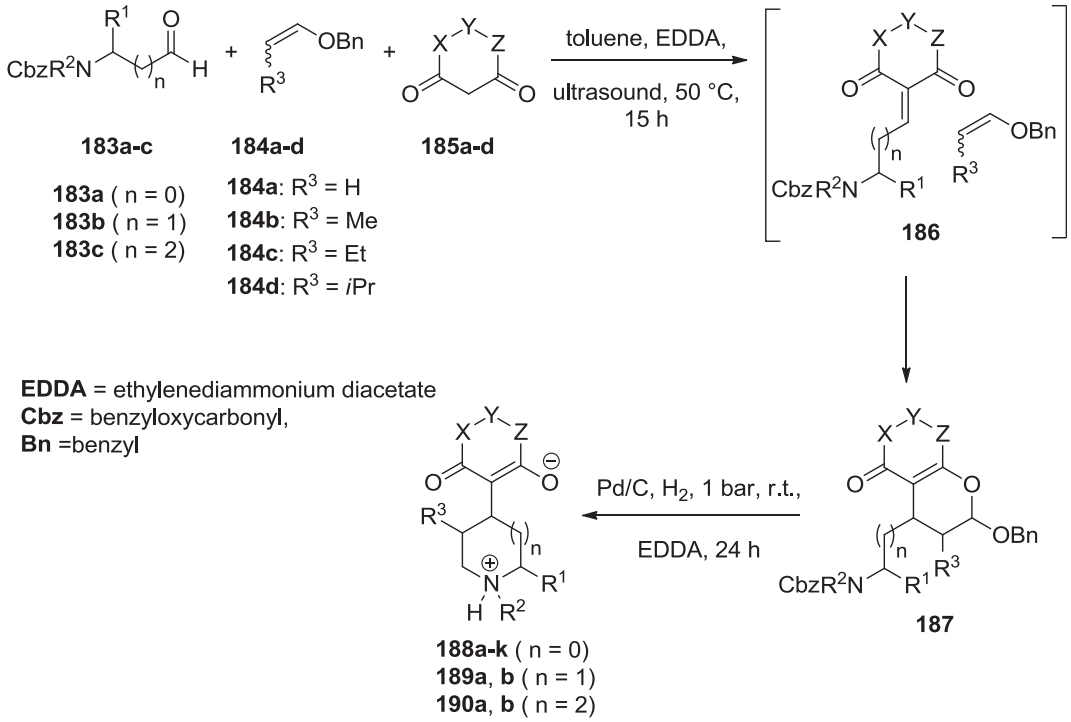

1 116 168 169a-i

**169a**: Ar = 4-$MeOC_6H_4$, $R^1$ = Ph, $R^3$ = Me, $R^4$ = Et, time = 30 min, yiield = 94%
**169b**: Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^3$ = Me, $R^4$ = *i*-Pr, time = 30 min, yiield = 90%
**169c**: Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^3$ = Et, $R^4$ = Et, time = 60 min, yiield = 93%
**169d**: Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^3$ = *n*-Pr, $R^4$ = Et, time = 60 min, yiield = 89%
**169e**: Ar = 4-$MeOC_6H_4$, $R^1$ = H, $R^3$ = Ph, $R^4$ = Et, time = 10 min, yiield = 98%
**169f**: Ar = 4-$MeC_6H_4$, $R^1$ = Ph, $R^3$ = Me, $R^4$ = Et, time = 50 min, yiield = 95%
**169g**: Ar = 4-$MeC_6H_4$, $R^1$ = H, $R^3$ = Me, $R^4$ = Et, time = 10 min, yiield = 98%
**169h**: Ar = 4-$BrC_6H_4$, $R^1$ = Ph, $R^3$ = Me, $R^4$ = Et, time = 45 min, yiield = 95%
**169i**: Ar = 4-$BrC_6H_4$, $R^1$ = H, $R^3$ = Ph, $R^4$ = Et, time = 10 min, yiield = 97%

**Scheme 54.** Synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol)s **169**.

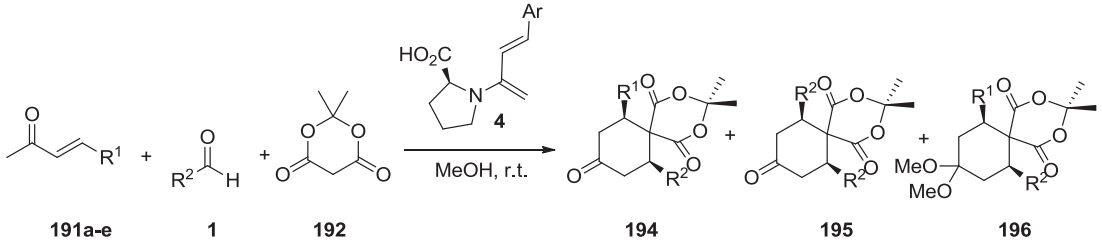



**Scheme 55.** Suggested mechanism for the synthesis of 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol)s **167** and **169**.




**188a**: $R^1$ = H, $R^2$ = H, $R^3$ = Et, purity = 97%, yield = 53%
**188b**: $R^1$ = H, $R^2$ = Me, $R^3$ = *i*Pr, Purity = >90%, yield = 47%
**188c**: $R^1$ = Me, $R^2$ = H, $R^3$ = Me, Purity = 97%, yield = 45%
**188d**: $R^1$ = *i*Pr, $R^2$ = H, $R^3$ = H, Purity = 95%, yield = 55%
**188e**: $R^1$ = *i*Bu, $R^2$ = H, $R^3$ = H, Purity = 99%, yield = 59%
**188f**: $R^1$ = *i*Bu, $R^2$ = H, $R^3$ = Et, Purity = >95%, yield = 41%
**188g**: $R^1$ = $R^2$ = $CH_2CH_2CH_2$, $R^3$ = H, Purity = >90%, yield = 51%
**188h**: $R^1$ = Bn, $R^2$ = H, $R^3$ = H, Purity = 97%, yield = 65%
**188i**: $R^1$ = Me, $R^2$ = H, $R^3$ = H, Purity = >95%, yield = 71%
**`188j**: $R^1$ = Me, $R^2$ = H, $R^3$ = H, Purity = >95%, yield = 59%
**188k**: $R^1$ = Me, $R^2$ = H, $R^3$ = H, Purity = 95%, yield = 61%
**189a**: $R^1$ = H, $R^2$ = H, $R^3$ = H, Purity = >95%, yield = 60%
**189b**: $R^1$ = H, $R^2$ = H, $R^3$ = H, Purity = >95%, yield = 69%
**190a**: $R^1$ = H, $R^2$ = H, $R^3$ = H, Purity = 98%, yield = 58%
**190b**: $R^1$ = H, $R^2$ = H, $R^3$ = Me, Purity = >95%, yield = 55%

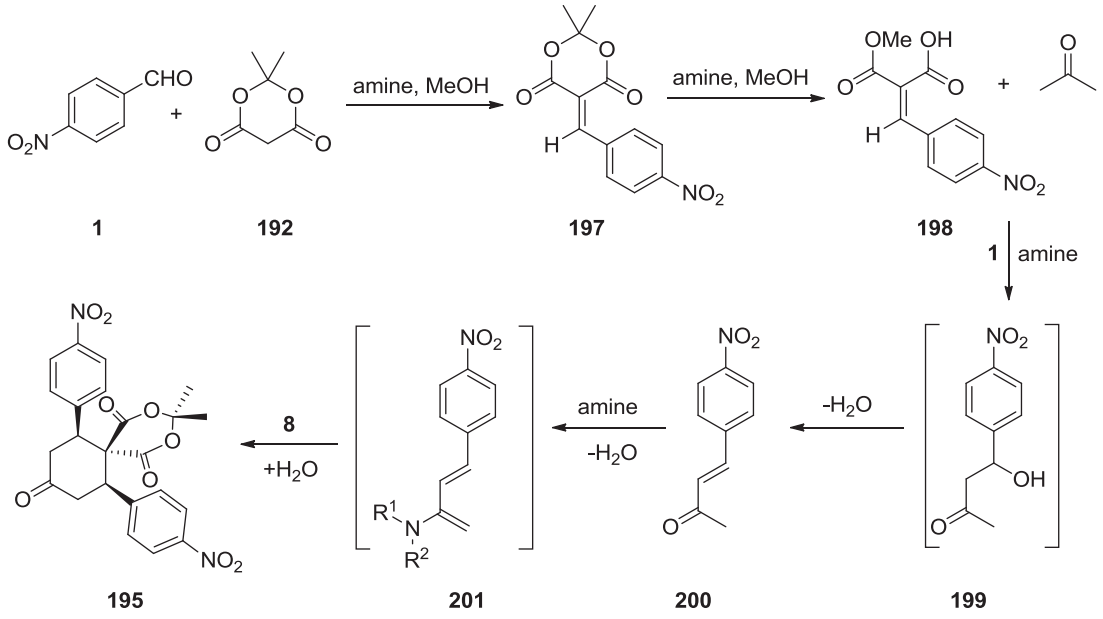
**Scheme 56.** Domino sequence comprising Knoevenagel, hetero-Diels-Alder reaction, and hydrogenation starting from amino aldehydes, 1,3-dicarbonyl compounds, and enol ethers.



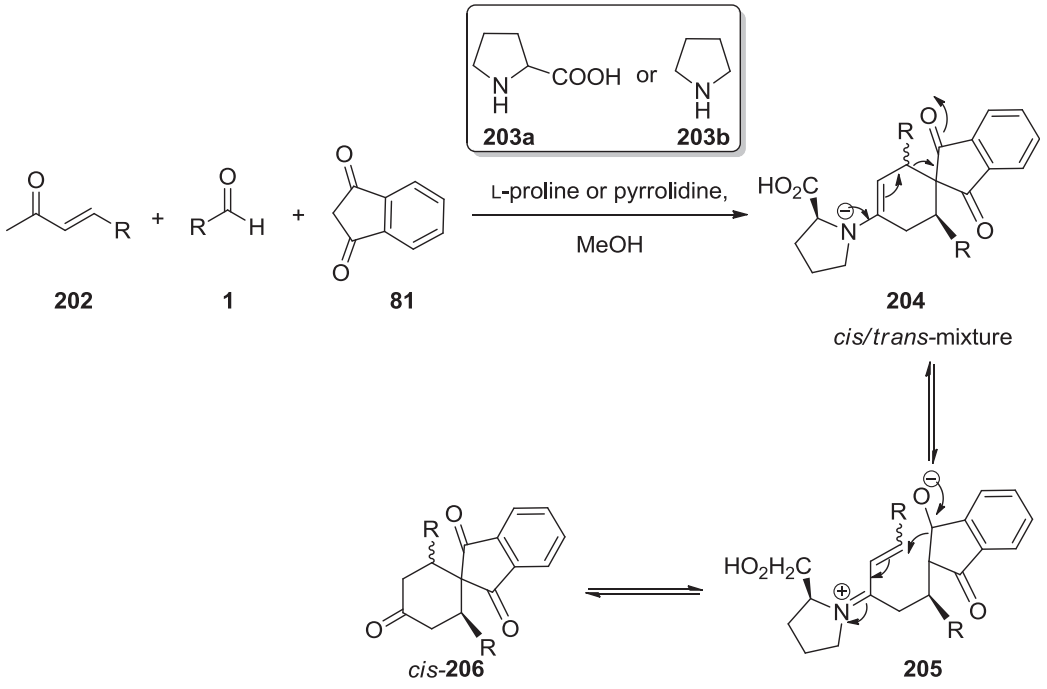

**191a**: $R^1$ = Phenyl
**191b**: $R^1$ = Piperonyl
**191c**: $R^1$ = 1-Naphthalenyl
**191d**: $R^1$ = 2-Furanyl
**191e**: $R^1$ = 2-Thiophenyl

**1a**: $R^2$ = 4-$NO_2C_6H_4$
**1b**: $R^2$ = 4-$CNC_6H_4$
**1c**: $R^2$ = Ph
**1d**: $R^2$ = 3,4-$(OCH_2O)C_6H_3$

**Scheme 57.** Amino acid catalyzed asymmetric, three-component Diels-Alder reaction.



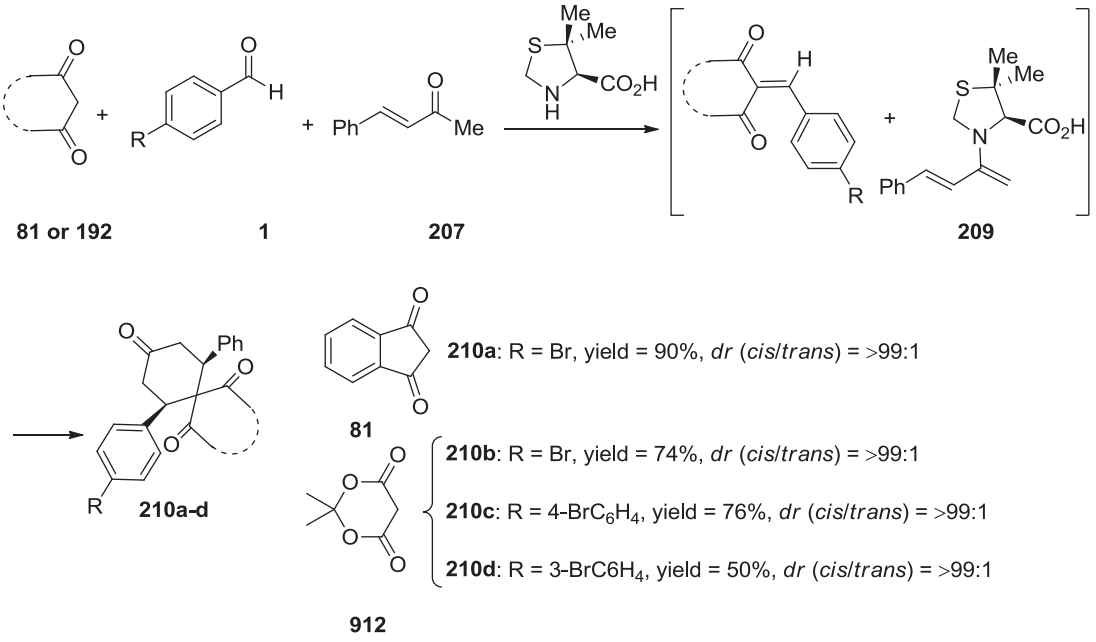

**Scheme 58.** Proposed reaction mechanism for the formation of the unexpected product **195**.



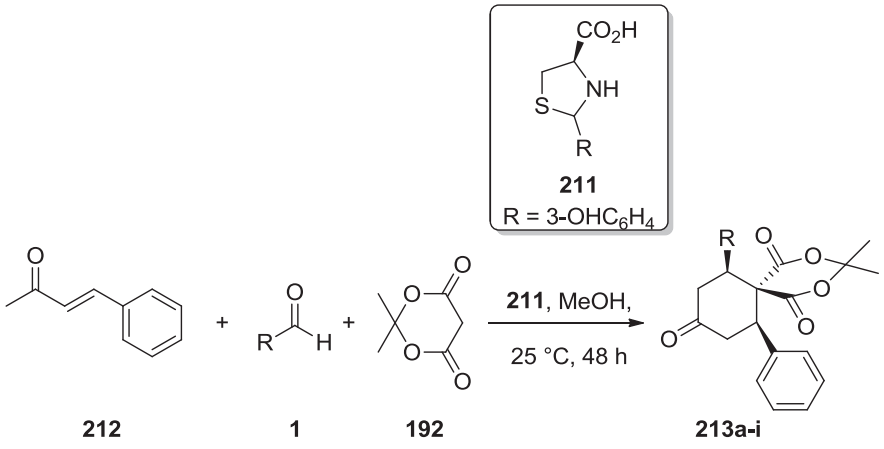

**Scheme 59.** Hetero domino Knoevenagel-Diels-Alder epimerization reaction.

A sequential Knoevenagel/Diels-Alder reaction has been established as a highly effective protocol for the synthesis of a wide variety of heterocyclic compounds. This approach was used in a three-component reaction comprising aromatic aldehydes, benzylideneacetone and meldrum acid in the presence of several organocyclic amino acid as catalysts. This facile and ecologically benign approach was found advantageous to provide numerous biologically multi substituted spiro[5,5]undecane-1,5,9-trione derivatives in satisfactory yields (up to 81%) with excellent diastereolectivities (>99:1 *dr*).[128] Moreover, the substrate scope of the stereoselective three-component reaction was studied using differently substituted aldehydes under optimized reaction conditions using compound **211** as catalyst. In general, aryl aldehydes bearing electron-withdrawing substituents gave higher yields, whereas, lower yields were obtained when aldehydes bearing electron-withdrawing substituent on the phenyl group. Also, various 2-napthyl aldehydes afforded the corresponding products in satisfactory yields. The effect of electronic nature of aldehyde is attributed to the assortment of the key alkylidene intermediate produced *via* the Knoevenagel reaction of aldehyde and Meldrum's acid (Scheme 61).[128]

Nevertheless, when other substrates such as 1,3-dimethylbarbituric acid, was used this reaction was not mediated by cyclic amino acid but mediated by L-proline. Thus, a three-




**Scheme 60.** Domino Knoevenagel/Diels-Alder epimerization reaction.

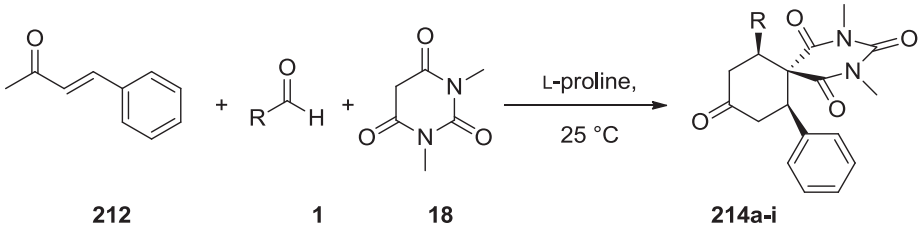



**213a**: R = 4-$NO_2C_6H_4$, yield = 52%, *dr* = >99:1
**213b**: R = 4-$FC_6H_4$, yield = 79%, *dr* = >99:1
**213c**: R = 4-$MeOC_6H_4$, yield = 52%, *dr* = >99:1
**213d**: R = 3-$ClC_6H_4$, yield = 64%, *dr* = >99:1
**213e**: R = 3-$BrC_6H_4$, yield = 44%, *dr* = >99:1
**213f**: R = 3,4-$ClC_6H_3$, yield = 61%, *dr* = >99:1
**213g**: R = 2,4-$ClC_6H_4$, yield = 82%, *dr* = >99:1
**213h**: R = 2-$CNC_6H_4$, yield = 51%, *dr* = >99:1
**213i**: R = 2-naphthyl, yield = 73%, *dr* = >99:1

**Scheme 61.** Substrate scope of the asymmetric three-component reactions.

component reaction including aromatic aldehydes **1**, benzylideneacetone **212** and 1,3-dimethylbarbituric acid **18** were reacted in the presence of L-proline, which gave various biological multi-substituted spiro[5,5]undecane-1,5,9-triones **214** in satisfactory yields (up to 81%) and excellent des (>99:1 *dr*) (Scheme 62).[128]

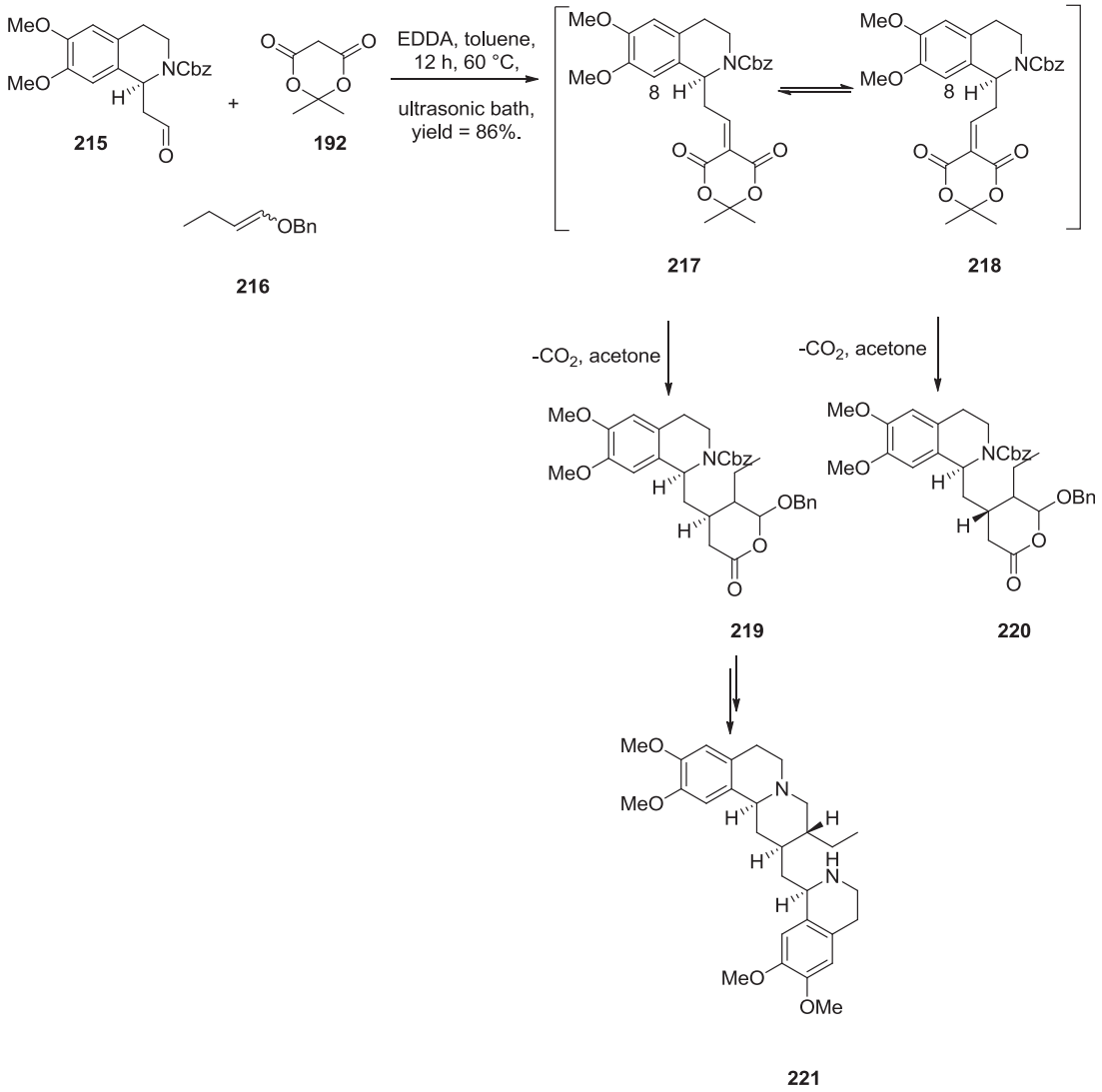
In this route, for the synthesis of emetine **221,** the enantiorich aldehyde **215** initially was condensed with Meldrum's acid **192** to provide the 1-oxa-1,3-butadiene **217** that was subjected to a hetero-Diels-Alder cycloaddtion with the enol ether **216**. From this initial reaction, the two diasteromeric cycloadducts **219** and **220**were gained as a 1:1 mixture. Therefore, it seems likely in this reaction the chiral centers in **215** and **217**, did not influence a facial distinction. As other justification attributed to the absence of selectivity in this Diels-Alder reaction could be coexistence of the two conformers **217a** and **217b**, which both may subjected into a facial selective cycloaddition. Therefore, it can be accepted that the




212 1 18 214a-i

**214a**: R = 3,4-$ClC_6H_3$, yield = 52%, *dr* = >99:1
**214b**: R = 4-$NO_2C_6H_4$, yield = 79%, *dr* = >99:1
**214c**: R = 4-$FC_6H_4$, yield = 52%, *dr* = >99:1
**214d**: R = 4-$CNC_6H_4$, yield = 64%, *dr* = >99:1
**214e**: R = 4-$OMeC_6H_4$, yield = 44%, *dr* = >99:1
**214f**: R = 4-$BrC_6H_4$, yield = 61%, *dr* = >99:1
**214g**: R = 3-$BrC_6H_4$, yield = 82%, *dr* = >99:1
**214h**: R = 3-pyridine$C_6H_4$, yield = 51%, *dr* = >99:1
**214i**: R = 2-F-4-$BrC_6H_3$, yield = 73%, *dr* = >99:1

**Scheme 62.** MCR for the synthesis of spiro[5,5]undecane-1,5,9-triones **214**.




215 192 216 217 218 219 220 221

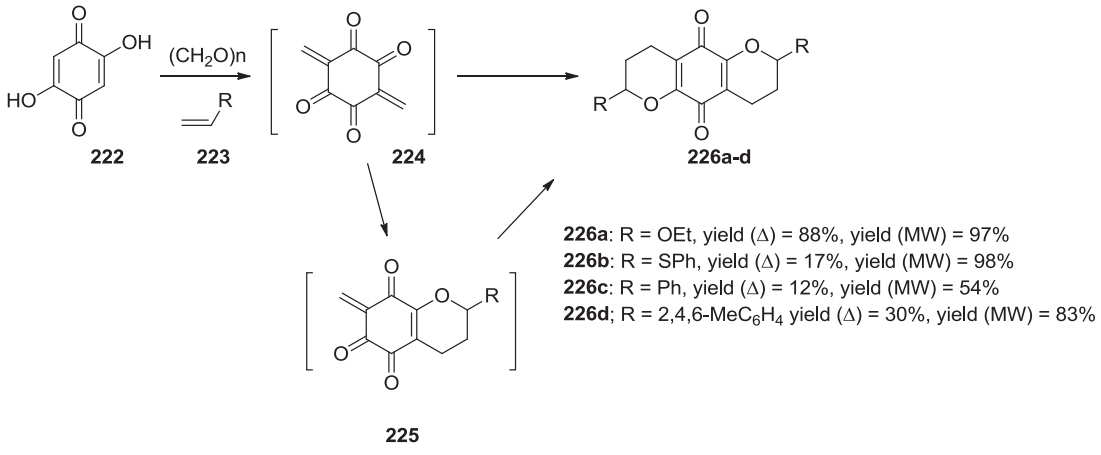
**Scheme 63.** Facial selectivity in the three-component domino Knoevenagel-hetero-Diels-Alder process of **215**, **216** and **192**.

attack of the enol ether **216** takes place at the (*E*)-oxabutadiene scaffold in both **217a** and **217b**from below where are the least hindered side to provide **219** and **220**, selectively. High level 1,3-induction in this reaction then should be anticipated if one of the conformers **217a** and **217b** each stabilized or destabilized. Therefore, it can be assumed that a bulky substituent at C-8 in **217** is responsible for destabilization of the conformer **217b** (Scheme 63).[129]

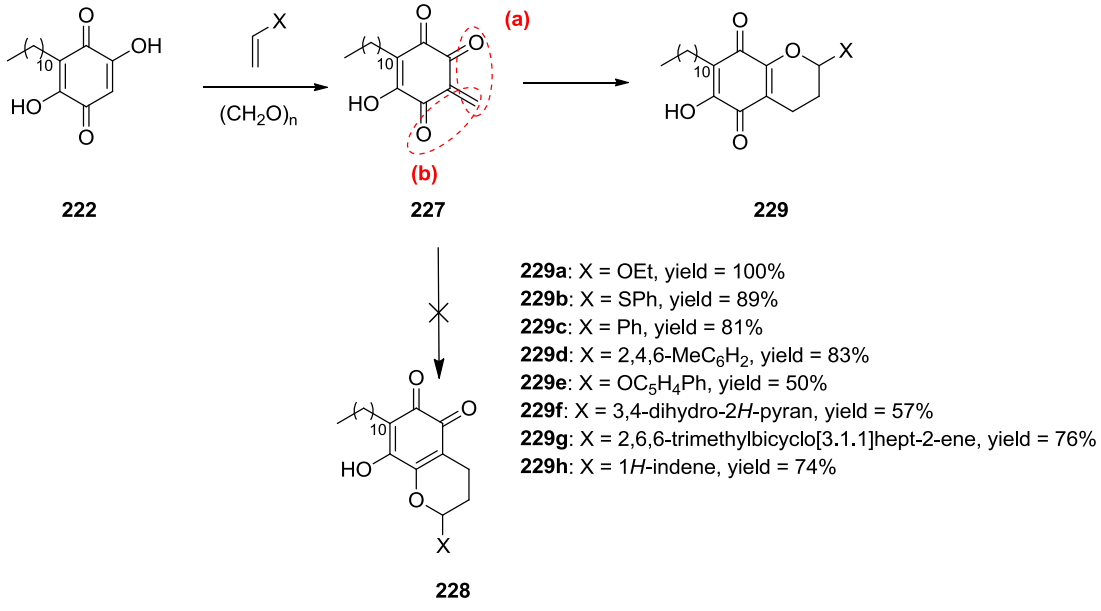
A series of bis-pyrano-l,4-benzoquinones were prepared *via* a double sequential Knoevenagel/hetero Diels-Alder reaction. The synthetic strategy was found being highly effective permitting the preparation of complex polycyclic framework containing six new s-bonds. These reactions showed more efficacies and being completed faster when were done under MWI. The obtainedbis-pyrano-1,4-benzoquinones can be considered as the first examples of such strategy. This method offers a new contribution to the chemistry of importantly bioactive 2,5-dihydroxyl, 4-benzoquinones and was the first general and well-established methodology for the development of bis-pyranobenzoquinones.[130]

The synthesis of bis-pyranol, 4-benzoquinones, bearing two well-recognized privileged structures, *via* a direct and highly effective methodology based on direct Knoevenagel/hetero Diels-Alder reaction was achieved. 2,5-Dihydroxy-1,4-benzoquinone **222** as a suitable and symmetric synthetic equivalent to 1,3-dicarbonyl compound was accomplished. In this line, the Knoevenagel condensation of 2,5-dihydroxy-1,4-benzoquinone **222** and paraformaldehyde resulted in the generation of a reactive intermediate **224**. The latter is subjected to a double hetero Diels-Alder reaction using different electron-rich alkenes as dienophiles, giving the expected bis-pyrano-1,4-benzoquinonesin one-pot fashion. The construction of the two pyran rings may take place concurrently commencing from the intermediate **224**. On the other hand, initially, one of the two pyran rings is constructed to generate a second intermediate **224a**, which subsequently, subjected to hetero Diels-Alder reaction. The hypothetical intermediates **224** and **224a** exhibit the similarities with *o*-quinone methides that constitute other examples of very active and transitory intermediates. These momentary species are reacted with nucleophiles *via* 1,4-Michael-type addition reaction as well as with a series of dienophiles, to implement [4 + 2] cycloadditions (Scheme 64).[130]

The synthesis of a series of pyrano embelin derivative was accomplished *via* sequential Knoevenagel/hetero Diels-Alder




**Scheme 64.** Plausible formation of bis-pyranobenzoquinones.




**Scheme 65.** Synthesized embelin adducts.

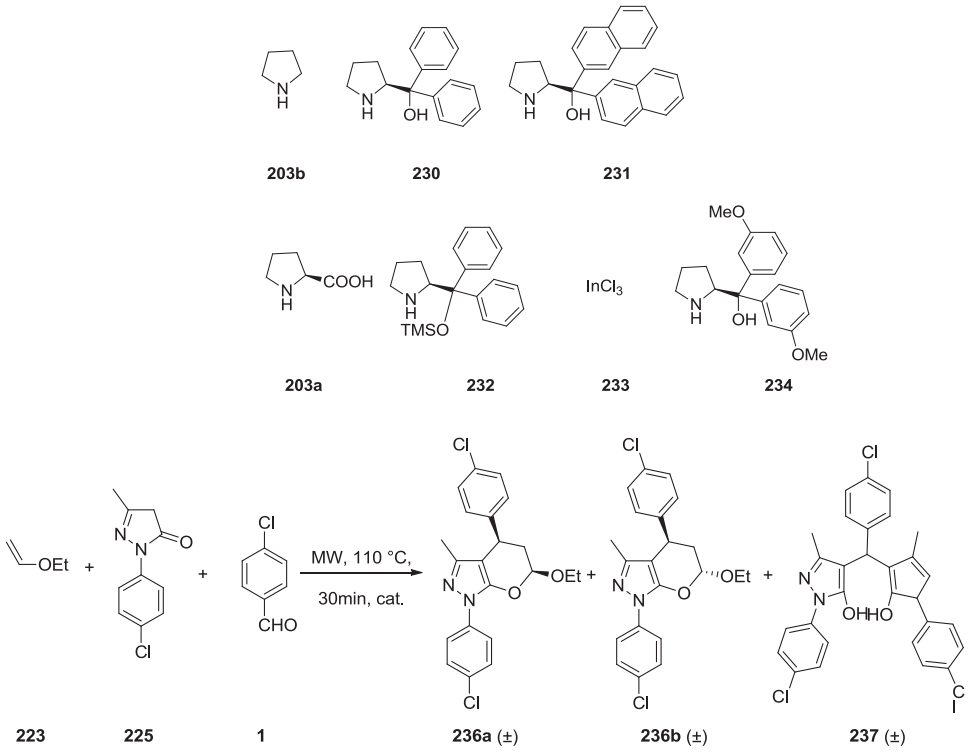
reactions of embelin **222** with paraformaldehyde and electron rich alkenes. This synthetic method was found being highly effective when is performed under MWI. These reactive intermediates offer regioselective hetero Diels-Alder cycloadditions when reacted with electron rich alkenes to give pyrano-1,4-benzoquinone adducts in satisfactory yields. As depicted in Scheme 65, two possible heterodynes can be formed from the intermediate b to be converted into the desired ortho and para-pyranobenzoquinones. As a matter of fact, the reaction of embelin, paraformaldehyde, and alkenes proceeds in regioselective manner, since just 1,4-benzoquinones were obtained from the more electron-poor heterodiene (a). Under already secured optimal conditions a series of dihydropyran-embelin derivatives by using different dienophiles were synthesized. Noticeably, this reaction proceeds smoothly to give the expected products in satisfactory yields, and being noticed to tolerate several types of electron-donating groups in the used alkenes.[131]

An efficient and fast protocol for the MWI-prompted organocatalyzed sequential domino Knoevenagel/hetero Diels-Alder reaction was developed for the synthesis of 2,3-dihydropyran[2,3-*c*] pyrazoles with anti-tuberculosis (ant-TB) activity. Employing the diaryl-prolinol as catalyst in *t*-BuOH as the solvents in this strategy provided compounds **236a** and **236b** in good and poor yields, respectively (56% and 12%) as well as it high-graded diastereoisomeric ratio (4:1) in comparison to the results obtained for similar compounds, reported previously.[132]

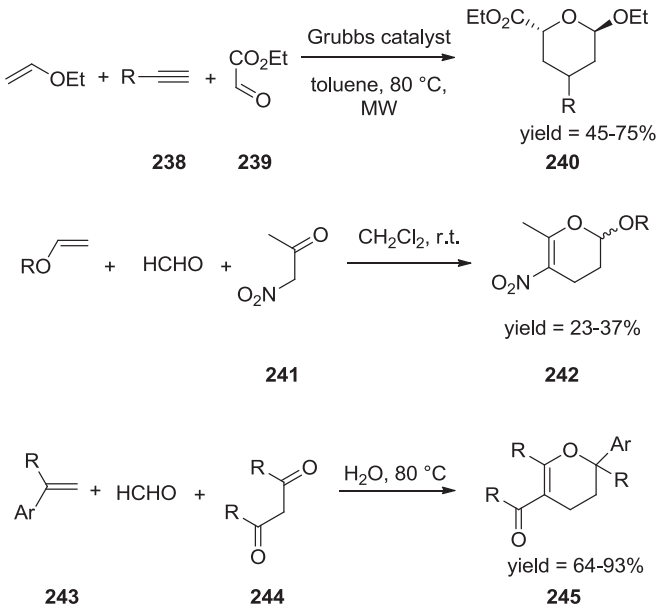
By the verification of expediency of diaryl-prolinols as the catalysts in the hetero Diels-Alder reaction under MWI, sequential Knoevenagel/hetero Diels-Alder reaction was also examined under similar reaction conditions. In a typical procedure, a model reaction involved pyrazolone **235**, aldehyde **1**, and ethylvinyl ether was performed. Except, pyrrolidine that exhibited the enhanced in the generation of the side-product **237**, several other catalysts **230**–**233** were employed in the sequential Knoevenagel/hetero Diels-Alder reaction. The frequently employed L-proline **203b** and the indium-chloride **233** as Lewis acid were also used for obtaining a broader insight of the catalyst's influence. In Scheme 66, the highlighted results disclose the significance of the catalyst both for the Knoevenagel reaction between **235** and **1** and the subsequent hetero Diels-Alder reaction with ethylvinyl ether. It was found that the aforementioned reaction does not proceed in the absence of catalyst, at all. The best results were obtained in the presence of diaryl-prolinols **230** and **231**. L-Proline, in terms of yields and low generation of side-product **237**. Furthermore, the $InCl_3$ -catalyzed reaction gave poor yields.[132]

During this investigation, in 2009, Tietze and co-workers reported another kind of MCR as depicted in Scheme 67.[133] Importantly, they illustrated that dihydropyrans can be directly prepared from nitrobutenone, alkyl vinyl ether, and formaldehyde in the absence of catalyst.

The suggested mechanism for this MCR included a Knoevenagel/hetero Diels-Alder sequential reaction. It was also found that the yields is related to the nature of the solvent in which $CH_2Cl_2$ was found the solvent of choice. Although the study reported by Tietze et al., indubitably opened a gateway to greener approach to the construction of dihydropyran skeleton, the selectivity of their MCR was inappropriately rather low since the desired dihydropyrans were obtained in poor to moderate yields (23–37%). Delightfully, when this reaction was conducted in/on water, the selectivity of the reaction was greatly improved, just one isomer was formed and the corresponding dihydropyrans were obtained in good to high yields(64–93%).[134] This aqueous MCR showed a very wide range of substrate scope thus, presenting an economical and ecologically benign approach for the synthesis of dihydropyranderivatives. Practically, it was shown that in this reaction water acts as an efficient solvent and promoting the synthesis of dihydropyrans. Another factor at work is the solubility of formaldehyde in water comparing to that of in organic solvent. Water can play a key role in a several MCRs including the sequential reaction of styrene, 2,4-




**Scheme 66.** MW-assisted organocatalytic three-component Knoevenagel/hetero Diels-Alder reaction.




**Scheme 67.** MCR for the synthesis of dihydropyran derivatives.

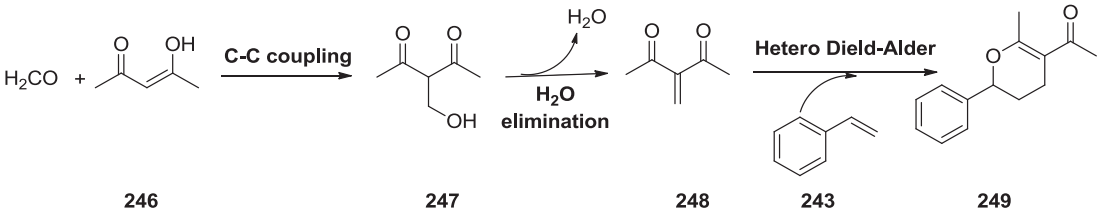
pentanedione, and formaldehyde. While, water free conditions gave no reaction, the MCR in the presence of water fruitfully proceeded to completion in the presence of water, giving the desired dihydropyrans in satisfactory yield. The mechanism of this sequential Knoevenagel/hetero Diels-Alder studied was studied with and without presence of water molecules. In accordance with this proposed mechanism in Knoevenagel step, water acts as a proton donor for preferable construction of more supple six-membered ring transition state both in concerted reaction *via* direct removal of water and stepwise reaction involving keto-enol tautomerization and dehydration). pathways.

An un-catalyzed MCR was achieved *via* a one pot sequential reaction including (step 1) formation of C–C bond between formaldehyde and the *cis*-keto-enol isomer of the 2,4-pentanedione, (step 2) followed by removal water resulting in the formation of the α,β-unsaturated carbonyl intermediate **248**, and eventually (step 3) a hetero-Diels-Alder reaction between **248** and styrene, leading to the expected dihydropyran (Scheme 68).[135]

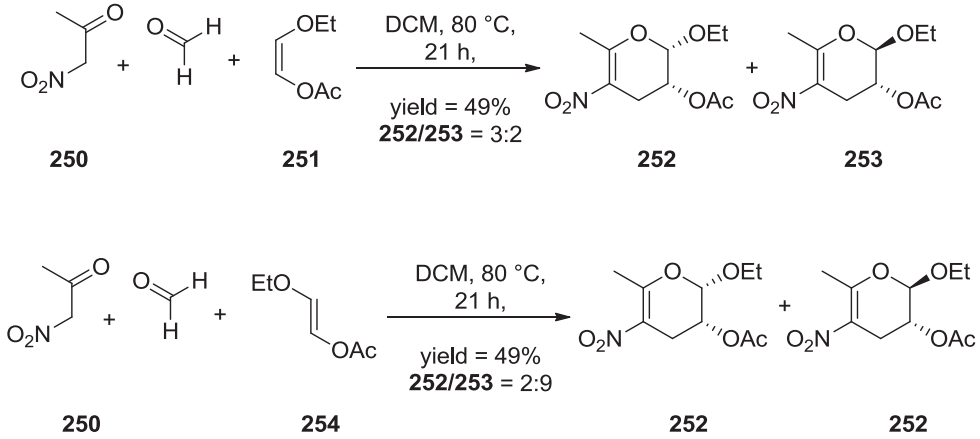
The three-component sequential Knoevenagel/hetero-Diels-Alder reaction of nitroacetone **250**, formaldehyde and ethoxy vinylacetate **251** results in the formation of dihydropyrans **252** and **253**. Deoxyamino sugars present in many in several biologically compounds, such as spinosyns (highly potent insecticides) are significant compounds. For the asymmetric construction of the β-glycosidic bond in such compounds, the utilization of a 2-acetoxy sugar is greatly suitable. Such compounds can readily be obtained *via* a sequential a three-component Knoevenagel/hetero Diels-Alder reaction of nitroacetone, formaldehyde and either (*Z*)- or (*E*)-ethoxyvinylacetate. From this MCR several dihydropyrans were obtained which can easily be converted into the corresponding desired compounds *via* two-fold hydrogenation and reductive amination, respectively using such approach, various sugars of the for osamine and jessamine series were efficiently prepared.

Therefore, MCR sequential of Knoevenagel/hetero-Diels-Alder reaction of (*Z*)-ethoxyvinylacetate **251** with **250** that can be readily provided from nitromethane and aqueous formaldehydein $CH_2Cl_2$ resulted in a 3:2 mixture of the racemic dihydropyrans **252** and **253** in satisfactory yield. Under the same reaction conditions, using (*E*)-ethoxyvinylacetate **254** as the dienophile, racemic **253** and **252** in a ratio of 9:2 obtained virtually in an identical yield (49%). In both cases, just one regioisomer was generated (Scheme 69).[136]

Relied on the results obtained a nonconcerted two-step mechanism can be suggested. Accordingly, the generation of transition state **257**containing the zwitterionic intermediates **258** and **259** in




**Scheme 68.** The three elementary steps involved in the MCR.



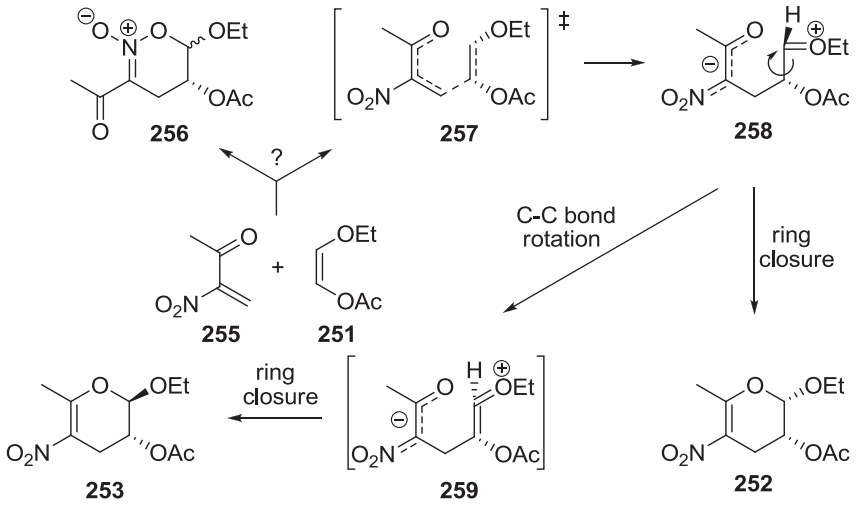

**Scheme 69.** Synthesis of dihydropyrans **252** and **253**.

such proposed mechanism can be contemplated. As depicted for the reaction of *Z*-dienophile **251** in Scheme 70, the first generated intermediate **257** could provide either **252** or, **259** upon rotation of the dienophile scaffold about the C–C bond. Due to the limited lifetime of **258** and **259**, it can diastereomeric product ratios, regardless of the geometry of **251** and **254**. Therefore, by just a partial inter conversion the ultimate ring closing of **258** may produce **253** as well as **252.** Therefore, the ratio of the product mixture should be based on the relative stability of the zwitterionic intermediates, their corresponding lifetimes and in particular, and ease of rotation around the carbon-carbon bond. Nevertheless, the possibility of the generation of the products are formed *via* a concerted mechanism cannot be totally excluded. In such circumstances, the configuration of the dienophile actually defines the configuration of the product.[136]

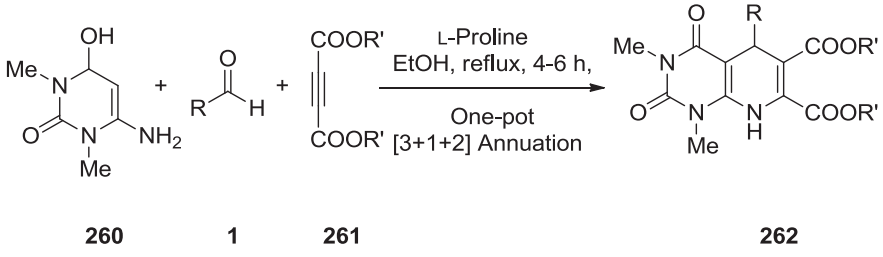
A literature survey disclosed that, in spite of various biological activities reported for pyrido[2,3-*d*]pyrimidines **262**, the developed synthesis of this bicyclic system has been largely overlooked.[137] For instance, there was no report on the one-pot synthesis of pyrido [2,3-*d*]pyrimidines *via* MCR (Scheme 71).[138]

An efficient and brief synthesis of poly functionalized pyrido [2,3-*d*]pyrimidines was achieved and reported in 2011 by Singh and co-workers.[138] A one-pot three-component sequential reaction utilizing 6-amino-1,3-dimethyluracil, aldehydes, and dialkyl acetylenedicarboxylates catalyzed by L-proline under mild reaction conditions gave the corresponding products. This MCR process includes sequential Knoevenagel/hetero-Diels Alder reaction [4 + 2] cycloaddition reaction in the presence of only L-proline and no co-catalyst or activator was needed.[138] A rationale and plausible mechanism for this reaction suggested and illustrated in Scheme 72. It is feasible that initially the 1,3-dimethyl-6-amino uracil **260** in the presence (L-proline) of Knoevenagel condensation with aldehyde **263** to generate the ortho-iminemethide **264** as an intermediate. As soon as intermediate **264** is generated, it is subjected to simultaneous hetero-Diels-Alder reaction with dialkyl acetylenedicarboxylate **261** to afford the corresponding pyrido[2,3-*d*]pyrimidine **262**. Clearly, the intermediate **264** is very reactive thus cannot be isolated and its intermediacy can be only confirmed by isolation and identification of product through the reaction with the second molecule of 1,3-dimethyl-6-amino uracil. The condensation and cycloaddition were found being independent the electronic and steric influence of the substituents. Therefore, by this approach, two new carbon-carbon bonds and one carbon-nitrogen bond are generated *via* a single hit, resulting in the effective installation of two rings by using commercially available or easily accessible starting materials.[138]

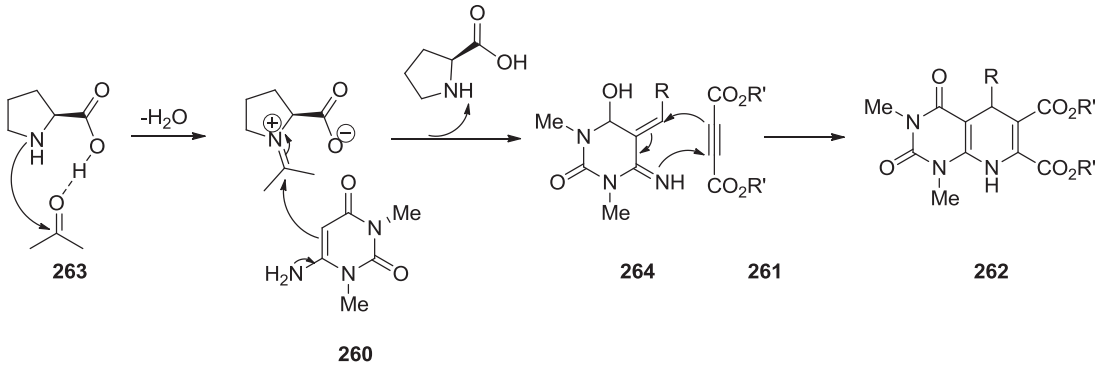
An effective *pseudo*-five-component one-pot strategy under MWI and solvent-free conditions was developed for the synthesis of complex and novel spiroindenopyridines through a sequential Knoevenagel/hetero Diels-Alder reaction. Practically, both diene and dienophile were made in situ.[139] As a classical procedure, a three-component reaction involving 1,3-indanedione **81**, *p*-fluorobenzaldehyde **1**, and ammonium acetate was performed under MWI in the absence of any catalyst in solvent-less system giving the corresponding spiropyridine **265a** in high (85% yield). The substrate scope of the reaction was studied by using differently substituted aryl aldehydes resulted in the synthesis of a series of compounds **265b–i**. Different aromatic aldehydes bearing either electron-donating or electron-withdrawing groups gave more and less similar yield of the respected products. Nevertheless, in case of heterocyclic aldehydes such as furan-2-carbaldehyde, thiophen-2-carbaldehyde and aliphatic aldehydes such as butyraldehyde and




**Scheme 70.** Proposed mechanism for the formation of **252** and **253** from **251**.




**Scheme 71.** Synthesis of pyrido[2,3-*d*]pyrimidines **262**.




**Scheme 72.** A plausible mechanism for the synthesis of pyrido[2,3-*d*]pyrimidines **262**.

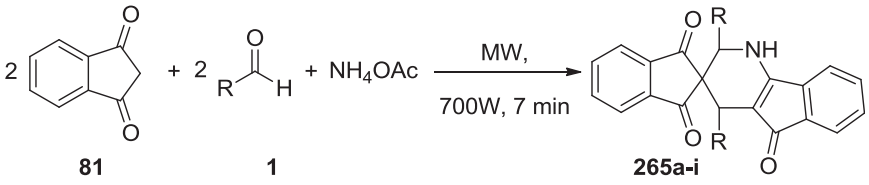
acetaldehyde, this reaction did not proceed to completion even in longer reaction time and just resulted in decomposition of the starting materials (Scheme 73).

The construction of the spiropyridines can be reorganized mechanistically, through a sequential Knoevenagel/hetero Diels-Alder reaction.[140] A plausible mechanism involved the initial in situ formation of dienophile A from the reaction of indanedione **81** and aldehyde **1** through a Knoevenagel condensation. Next, **266** reacts with ammonium acetate to give imine **267** that acts as a diene. Ultimately **266** and **267** is subjected into hetero Diels-Alder reaction to give the product **265**. On the other hand, it is possible for the reaction to proceed through an ionic mechanism *via* the formation of iminium ion (path B) (Scheme 74).[141]

### 2.3. Michael addition/aldol reaction

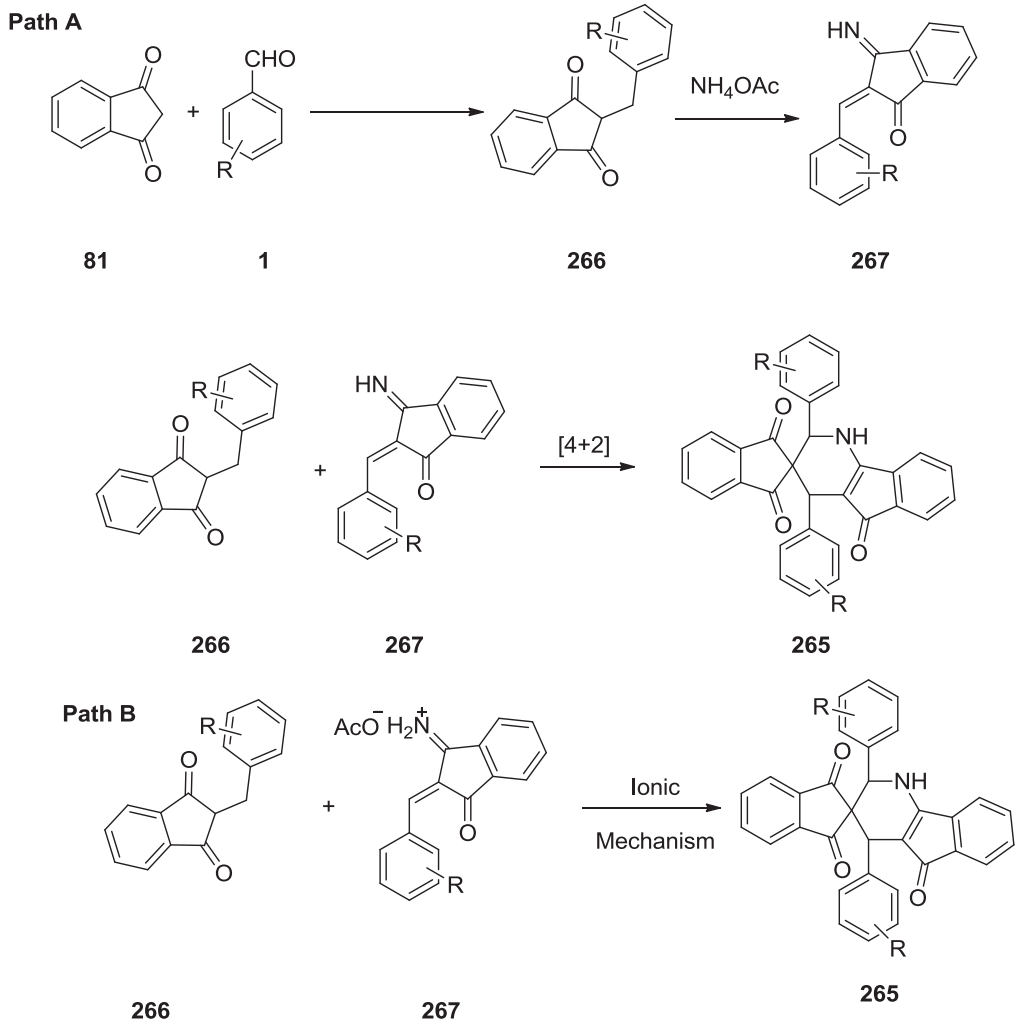
A three-component reaction was conducted using an appropriate primary amine, a dialkylacetylenedicarboxylate **261**, and 1,3-dimethylalloxan, which resulted in the construction of corresponding oxaspirobicyclic γ-butenolidobarbiturates **268**. The reaction started by easy run Michael-addition of primary amines to dialkyl acetylenedicarboxylates with subsequent aldol-like reaction of the resultant with 1,3-dimethylalloxan, followed by γ-lactonization to give the desired products **268**.[142] As a matter of fact, this is a cascade reaction sequence illustrating a fast and exceptional pathway to the important biologically potent compounds. Strictly speaking this attempt is a cascade strategy for the preparation of alkyl 3-(alkyl or arylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylates through a Michael addition followed by stereocontrolled aldol-type reaction, with subsequent γ-lactonization *via* a one pot reaction fashion. This one-pot MCR reaction showed the most advantages attributed to "Click Reaction" showing superior atom economy, facile work-up procedures, higher efficacy, and higher overall yields as well as other discrete merits over sequential multi-step reaction (Scheme 75).[142]

A mechanism for the present reaction is shown in Scheme 76 that visualizes a cascade sequence. Relied on the well-known chemistry of trivalent nitrogen as nucleophilic species, the fruitful nucleophilic attack of amines on a carbon atom is smoothed when the latter is activated by conjugation to a carbonyl moiety, or when it is activated by being a part of an unsaturated bond system. Initially, the primary amine as a nucleophile species attacks to the β-carbon of the electron-deficient alkyne **261** *via* Michael-addition, creating the aminobutendioate **269**, which is an electron-rich enaminone.[143] Notably, the central carbonyl moieties of the adjacent *tri*-carbonyl compounds, such as alloxan derivatives show significant electrophilic possessions.[144] Then, carbanion-like (electron rich) species, such as enaminones is subjected to the polar nucleophilic addition to the carbonyl moieties leading to carbon-carbon bond formation.[145] Consequently, aminobutendioate **269** is attacked by nucleophilic aldol-like on the central carbonyl moiety of the 1,3-dimethylalloxan resulted in generation of iminium-oxyanion intermediate **270**, which is tautomerically in

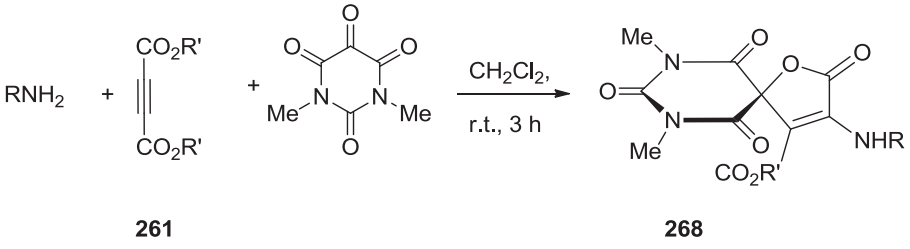



**265a**: R = 4-$FC_6H_4$, yield = 85%
**265b**: R = 3-$BrC_6H_4$, yield = 83%
**265c**: R = 2-$ClC_6H_4$, yield = 81%
**265d**: R = 4-$ClC_6H_4$, yield = 82%
**265e**: R = 4-$BrC_6H_4$, yield = 82%
**265f**: R = 4-$NO_2C_6H_4$, yield = 78%
**265g**: R = 3-$NO_2C_6H_4$, yield = 79%
**265h**: R = 2-$BrC_6H_4$, yield = 83%
**265i**: R = Ph, yield = 82%

**Scheme 73.** Synthesis of spiropyridine derivatives **265a-i** under MWI.



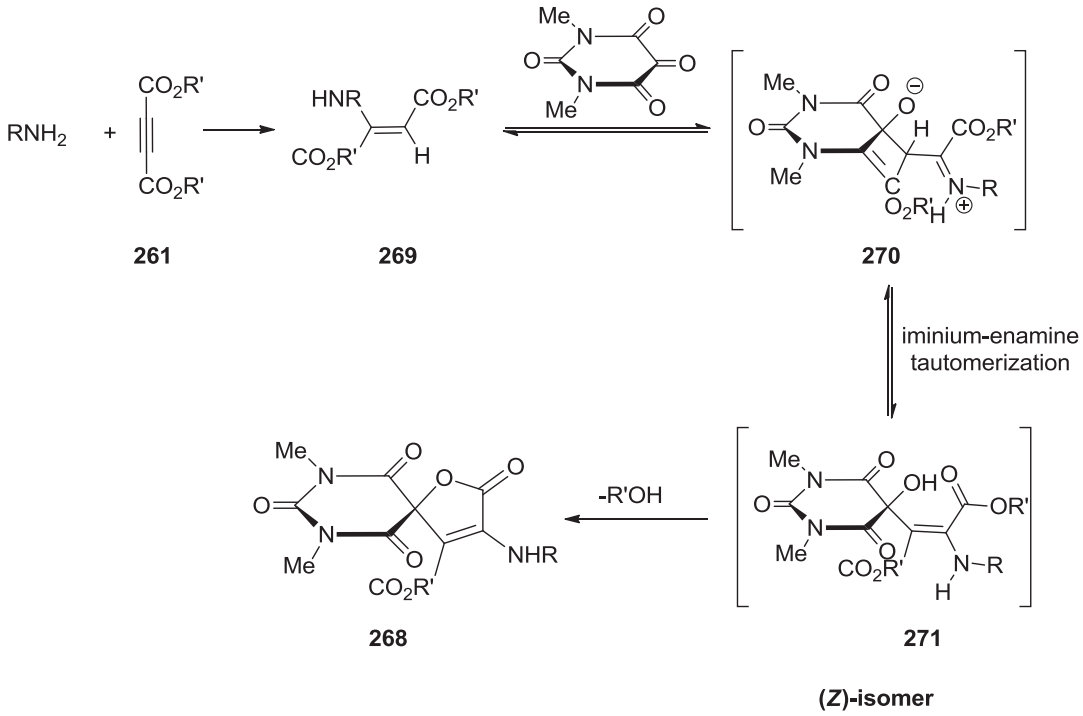

**Scheme 74.** Suggested mechanism for the synthesis of spiropyridine derivatives **265a-i**.




**Scheme 75.** MCR of primary amines, dialkyl acetylenedicarboxylates and 1,3-dimethylalloxan.

equilibrium with the hydroxy barbiturates **271**. Compound **271** with the Z-geometry around the C=C double bond is then subjected to γ-lactonization of affording the oxaspirobicyclic γ-butenolidobarbiturates **268**. At least three distinctive reactions including Michael addition, stereocontrolled aldol-type reaction followed by lactonization takes place in a one-pot fashion. All these aforementioned steps occur sequentially to produce the desired compound by simultaneous formation of three chemical bonds. Noticeably, two irreversible steps including the generation of enaminone followed by lactonization leads to the observed reaction sequence as an exceptional and a dynamic procedure.

An operational and viable chemical method for the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones **274** was accomplished *via* stereoselective cascade Michael-aldol reaction of 4-hydroxy-3-alkyl-5*H*-furan-2-ones with alkyl vinyl ketones catalyzed by L-proline or 9-amino-9-deoxyepiquinine/TCA. The stereoselective synthesis of advantaged bicyclic lactones *via* kinetic resolution and its synthetic usefulness for the synthesis of several prescribed medicine and total synthesis of naturally occurring compounds were accomplished. Based on the optimal reaction conditions, the scope of the amino acid- and amine/acid-mediated cascade TCRA and stereoselective Michael-aldol reactions was studied. Several functionalized cyclic β-ketolactones **272a-n** were treated with aldehydes/ketones as well as organic hydride **273** in the presence of L-proline (5 mol%) at 25 °C in dichloromethane to obtain the corresponding desired products **274a-n**. Three-



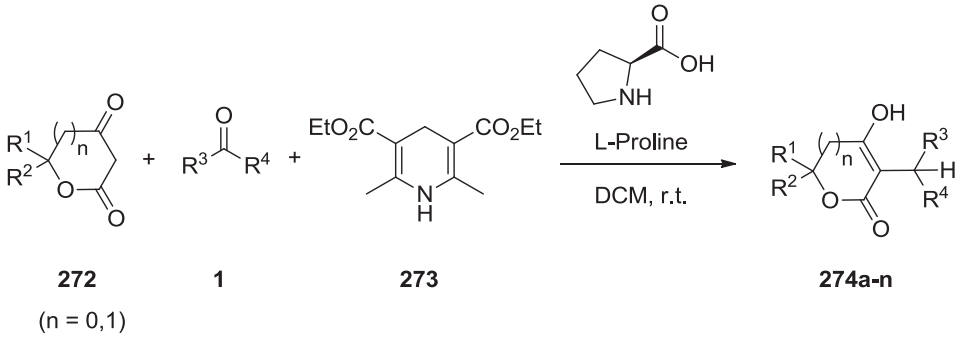

**Scheme 76.** Suggested mechanism for the synthesis of oxaspirobicyclic γ-butenolidobarbiturates **268**.

component reductive alkylation reaction of tetronic acid **272a** and **273** and differently substituted benzaldehydes **1** bearing either neutral or electron-withdrawing and electron-releasing gave the corresponding **274a-n** in excellent yields (Scheme 77).[146]

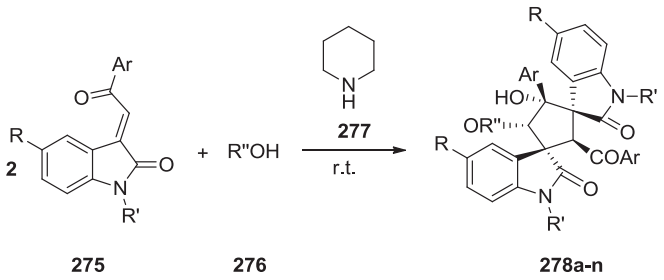
A facile and highly effective strategy for the synthesis of dispirocyclopentane bisoxindoles **278** was achieved *via* the base catalyzed domino reactions involving two molecules of 3-phenacylideneoxindoles **275** and nucleophiles such as amines or thiophenols. In this reaction, solvents such as alcohol can participate and act as nucleophile.[147] Expressively, this simple domino reaction led to the formation of the complex dispiro compounds in high yields and satisfactory *de*. Significantly, this apparently facile reaction resulted in the formation of dispirocyclopentane bisoxindole bearing four and five diastereogenic centers employing commercially available or easily accessible stating materials. The suggested mechanism for such reaction involves domino Michael addition, aldol condensation, and nucleophilic substitution and reduction reaction. Using commercially available or easily accessible starting materials, performing the reaction under mild reaction conditions, practical simplicity, and tolerance of a wide range of substrates are the merits of this domino reaction. This strategy gives a facile synthetic method for the synthesis of the complex dispirooxindole system. The potential application of this reaction may be found useful in the synthesis of some compounds with biological activity (Scheme 78).[147]

The methoxy and ethoxy moieties in the dispirocyclopentane bisoxindoles obtained as above clearly resulted from the nucleophilic substitution of MeOH and EtOH. It can be proposed that by using stronger nucleophiles than MeOH or EtOH in the reaction, the other corresponding nucleophilic-substituted products should be obtained. Therefore, for broadening the scope substrate stronger nucleophiles such as aniline, ptoluidine, *p*-chloroaniline, *n*-butylamine, or benzylamine to the acetonitrile solution of 3-phenacylideneoxindoles in the presence of piperidine as a catalyst, can be add to obtain the expected corresponding amino-substituted dispirocyclopentane bisoxindoles **279a-h** (Scheme 79).[147]

Construction of dispirocyclopentane bisoxindoles can be explained by a plausible reaction mechanism, which is depicted in Scheme 80. Initially, a 1,4-conjugated addition of secondary amine



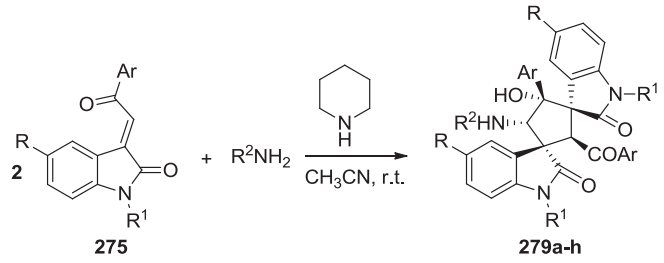

**Scheme 77.** MCR for the synthesis of highly substituted tetrahydro-isobenzofuran-1,5-diones **274**.




275 276 278a-n

**278a**: R = H, R' = Bn, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 85%
**278b**: R = H, R' = Bn, R'' = Me, Ar = *p*-$ClC_6H_4$, yield = 83%
**278c**: R = $CH_3$, R' = *n*-Bu, R'' = Me, Ar = $C_6H_5$, yield = 96%
**278d**: R = $CH_3$, R' = *n*-Bu, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 80%
**278e**: R = F, R' = *n*-Bu, R'' = Me, Ar = $C_6H_5$, yield = 96%
**278f**: R = F, R' = *n*-Bu, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 98%
**278g**: R = F, R' = *n*-Bu, R'' = Me, Ar = *p*-$CH_3OC_6H_4$, yield = 97%
**278h**: R = F, R' = Bn, R'' = Me, Ar = $C_6H_5$, yield = 82%
**278i**: R = F, R' = Bn, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 83%
**278j**: R = F, R' = Bn, R'' = Me, Ar = *p*-$CH_3OC_6H_4$, yield = 89%
**278k**: R = F, R' = Bn, R'' = Me, Ar = *m*-$CH_3OC_6H_4$, yield = 90%
**278l**: R = Cl, R' = H, R'' = Me, Ar = $C_6H_5$, yield = 93%
**278m**: R = Cl, R' = H, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 92%
**278n**: R = Cl, R' = *n*-Bu, R'' = Me, Ar = *p*-$CH_3C_6H_4$, yield = 87%

**Scheme 78.** Synthesis of dispirocyclopentane bisoxindoles **278a-n**.




275 279a-h

**279a**: R = Cl, $R^1$ = *n*-Bu, $R^2$ = *p*-$CH_3C_6H_4$, Ar = *p*-$CH_3C_6H_4$, yield = 80%
**279b**: R = Cl, $R^1$ = *n*-Bu, $R^2$ = *p*-$CH_3C_6H_4$, Ar = *p*-$ClC_6H_4$, yield = 83%
**279c**: R = F, $R^1$ = Bn, $R^2$ = *p*-$CH_3C_6H_4$, Ar = *p*-$CH_3C_6H_4$, yield = 78%
**279d**: R = Cl, $R^1$ = Bn, $R^2$ = $C_6H_5$, Ar = *p*-$CH_3C_6H_4$, yield = 76%
**279e**: R = Cl, $R^1$ = Bn, $R^2$ = *p*-$ClC_6H_4$, Ar = *p*-$CH_3C_6H_4$, yield = 86%
**279f**: R = Cl, $R^1$ = Bn, $R^2$ = $CH_2C_6H_5$, Ar = *p*-$CH_3C_6H_4$, yield = 80%
**279g**: R = Cl, $R^1$ = Bn, $R^2$ = *n*-$C_4H_9$, Ar = *p*-$CH_3C_6H_4$, yield = 74%
**279h**: R = Cl, $R^1$ = Bn, $R^2$ = $(CH_2)_5$, Ar = *p*-$CH_3C_6H_4$, yield = 84%

**Scheme 79.** Synthesis of dispirocyclopentane bisoxindoles **279a-h**.

to the exocyclic carbon atom to one molecule of3-phenacylideneoxindole **275** occurs, generating an adduct A an intermediate. Then, intermediate **280** is subjected to the Michael addition of the carbanion in another molecule of 3-phenacylideneoxindole **275** creating a new intermediate **281**. Next, the intramolecular aldol condensation of carbanion and carbonyl group takes place giving raise to the generation of the cyclized intermediate **282**. Ultimately, the nucleophilic substitution of alcohol or amine to the ammonium cation gives the expected dispirocyclopentane bisoxindoles **278** or **279**. If another nucleophile was not added, the excess secondary amine, present in the reaction mixture, itself as a nucleophile reacted leading to substitution reaction and to furnish the desired dispirocyclopentane bisoxindoles **279**.[147]

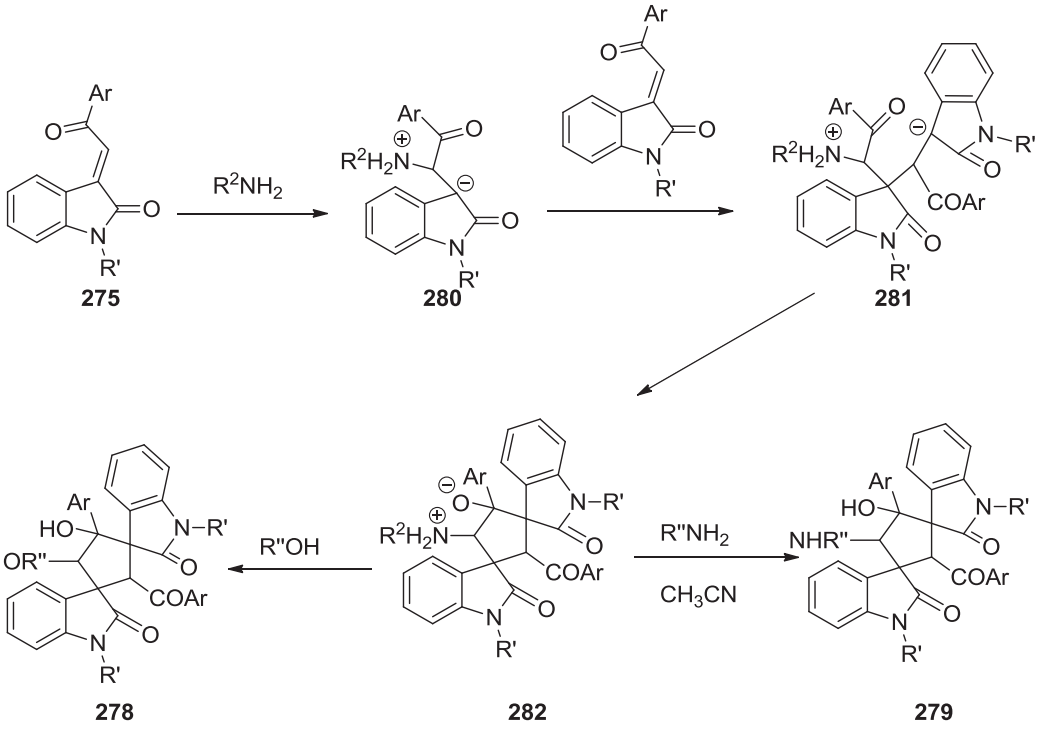
In another attempt, a solution of equivalent molar of 3-phenacylideneoxindole was reacted with thiophenol in the presence of piperidine in $CH_3CN$ at ambient temperature. The reactions were completed in about 3–4 h, which was found being much faster than that of performed in alcohol and in the presence of amine. Upon conventional workup, isolation and purification of the product, it is surprisingly found that the dispirocyclopentane bisoxindoles **284a-i**, being no phenylsulfanyl group have been synthesized in satisfactory yields (Scheme 81).[147]

Notably, the un-catalyzed (in the absence of piperidine) 3-phenacylideneoxindoles reacted with thiophenol or *p*-chlorothiophenol in $CH_3CN$ at ambient temperature affording the phenylsulfanyl or 4-chlorophenylsulfanyl adducts **285** in good to high yields, respectively. Alternatively, when 3-phenacylideneoxindole reacted with 2-mercaptoethanol in the presence of piperidine the 3-phenacyloxindole **286** was identified which isolated in 91% yield. The suggested mechanism for this transformation is depicted in Scheme 82. This mechanism is intensely supported by the isolation of two important and key intermediates. Thus, it can be concluded that the 3-phenacyloxindole is initially created in situ upon the reduction of 3-phenacylideneoxindole with thiophenol **286** that in turn is subjected further to sequential reactions, analogous to the reaction reported by Barbas and co-workers.[148]

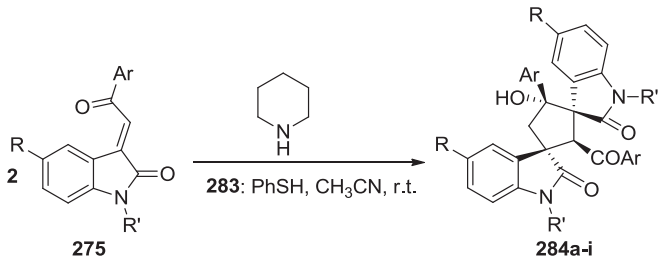
A one-pot electrophilic trifluoromethylthiolation-sulfur-Michael/aldol sequential MCR for the synthesis of $CF_3S$-containing spiro-cyclopentanone-thiochromanes was accomplished using bifunctionals quaramide as catalyst. This facile, one-pot sulfur-Michael/aldol reaction sequence assists as a powerful weapon in the synthetic organic chemists' arsenal for the asymmetric synthesis of biological active spiro-cyclopentanone-thiochromanes **292**. Notably, the latter has one quaternary stereogenic center bearing a $CF_3$-S group and three adjacent stereogeniccenters involving one spiro all-carbon quaternary center, in satisfactory yields and in excellent *ee* (up to 15:1 *dr*, >99%*ee*).[149]

After finding this optimization of the reaction conditions, the substrate scope of this one-pot asymmetric squaramide-catalyzed sulfur- Michael/aldol sequential reaction was discovered for the synthesis of functionalized $CF_3$ S-bearing spiro-cyclopentanone-thiochromanes **292**. (*E*)-3-Aryl idene-2-oxocyclopentane carboxylate containing electron-releasing, electron-neutral, or electron-withdrawing groups on the aromatic rings undergoes an efficient reaction involving 1-(trifluoromethylthio)pyrrolidine-2,5-dione **289** and 2-mercapto-benzaldehyde **290a** smoothly, affording the respecting products **292a-k** in satisfactory yields and good diastereoselectivities, with excellent *ee*s. A small decrease in yield was observed when the substituent on the aryl ring was placed in the ortho or meta position (**292c**, **292e**, **292f,** and **292i**). Moreover, heterocyclic substrates were also undergoes to this reaction smoothly to afford the respective product **292k** and **292l.** Nevertheless, the when substrate provided from 2-furaldehyde is reacted the obtained product **292k** showed a decrease in enantioselectivity (87% *ee*). In addition, (*E*)-ethyl and (*E*)-isopropyl 3-benzylidene-2-oxocyclopentanecarboxylate were tested, with the respective products **292m** and **292o** obtained in relatively lower amount compared to **292a**. Ultimately, the substrate with a 4-$NO_2$ group on the aryl ring was also investigated, but lower *ee* was observed for product 8n(>2:1 *dr*, 92% *ee*). Besides, 2-thio-5-methylbenzaldehyde **290b** was also examined for the further establishment of the generality of this approach, affording the product **292p** in excellent yield and *ee* (Scheme 83).[149]

A highly effective catalyzed asymmetric MCR involving sulfa-Michael/aldol sequential reaction was accomplished, employing achiral multi-functional catalyst. This strategy presented easy access to γ-sulfur-β-nitro-α-hydroxyesters **295** containing three successive linear stereogenic centers in high to excellent yields (up to 97%) and excellent diastereo- (up to >97:3 *dr*) and excellent *ee*s (up to 99% *ee*).[150]




**Scheme 80.** Proposed mechanism for the construction of dispirocyclopentane bisoxindoles **278** and **279**.

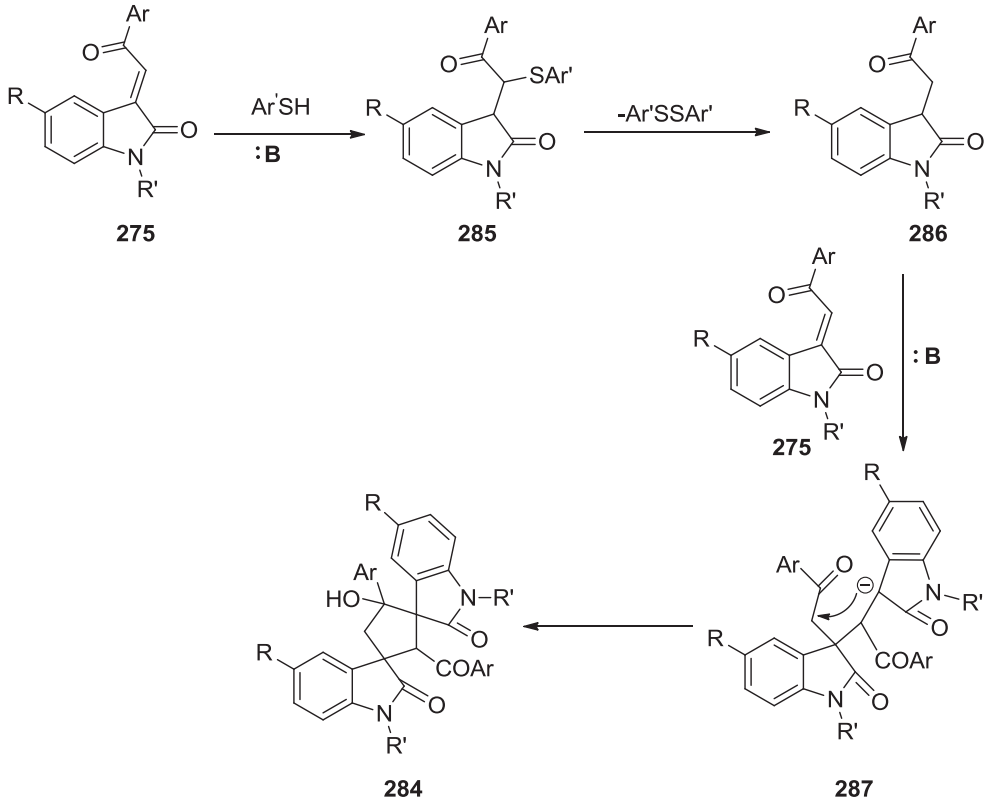



**284a**: R = H, R' = Bn, Ar = *p*-$CH_3C_6H_4$, yield = 75%
**284b**: R = H, R' = Bn, Ar = *p*-$ClC_6H_4$, yield = 68%
**284c**: R = $CH_3$, R' = Bn, Ar = *p*-$CH_3C_6H_4$, yield = 88%
**284d**: R = F, R' = Bn, Ar = *p*-$ClC_6H_4$, yield = 66%
**284e**: R = Cl, R' = Bn, Ar = *p*-$CH_3OC_6H_4$, yield = 79%
**284f**: R = Cl, R' = Bn, Ar = $C_6H_5$, yield = 82%
**284g**: R = Cl, R' = Bn, Ar = *p*-$ClC_6H_4$, yield = 80%
**284h**: R = F, R' = *n*-Bu, Ar = *p*-$CH_3C_6H_4$, yield = 76%
**284i**: R = Cl, R' = *n*-Bu, Ar = *p*-$CH_3C_6H_4$, yield = 91%

**Scheme 81.** Synthesis of dispirocyclopentane bisoxindoles **284a-i**.

With the already found optimal reaction conditions, the substrate scope of the reaction using differently substituted thiols was studied. It was found that the nature of the substituent on the phenyl ring of the aryl thiols had no substantial influence on the diastereo- or enantio-selectivity of the reaction, giving the respective products in excellent diastereo- (>94:6 *dr*) and enantioselectivities (>99.2 *ee*). The substrate scope study of this reaction was extended to different nitrostyrenes **293**. Delightfully, nitrostyrenes containing an electron-releasing or electron-withdrawing substituent on their phenyl ring afforded the desired products in good to excellent yields (85–97%) and high to excellent diastereo- (92:8–97:3 *dr*) and *ees* (99.1–99.8% *ee*). Under optimal reaction conditions, the reactions of nitrostyrenes bearing a phthylorheteroaromatic ring proceeded smoothly under the optimized reaction conditions to give the respective γ-sulfur-β-nitro-α-hydroxy esters in satisfactory yields, 94:6–97:3 *dr* and 98.8–99.5% *ee*. Known less reactive aliphatic nitroalkenes were also responsive to this reaction affording the respective products in modest yield (48–49%) but in excellent diastereo- and enantio-selectivity (95:5 *dr*, 98.6–98.8% *ee*). The scope of the carbonyl compound **1** as substrate was examined. The results revealed that steric hindrance of the alkyl group of the glyoxylate ester had only small effect on the yield, *ee* or *de* of the reaction (Scheme 84).[150]

A facile and highly effective MCR *via* sequential Michael/Michael/aldol was developed for a one-pot synthesis of polysubstituted cyclohexane **297** bearing six adjoining stereogenic centers. A three-component reaction involving acetyl acetone, broad range of nitroalkenes and various unsaturated aldehydes under optimal reaction conditions gave the corresponding, fully-substituted cyclohexanes in satisfactory yields, with excellent diastereoselectivities and enantionselectivities. The substrate scope of this strategy was investigated by using various unsaturated aldehydes, disclosing that both electron releasing and electron-withdrawing groups on phenyl group were well tolerated to afford **297a-f**. Then, for extension of diversity, a wide range of nitroarenes were examined, observing that the sequential Michael/Michael/aldol reactions proceeded smoothly to afford the corresponding desired products with modest to good yields (31%–63%, **297g-j**) and excellent stereoselectivities (>20:1 *dr*., >99% *ee* in all cases). Notably, when furyl or thienyl nitroalkenes and unsaturated aldehydes also gave respective enantioenriched fully-substituted cyclohexane in satisfactory yields (**297k-l**) without loss of stereoselectivities. Encouraged by these results the same authors successfully performed the asymmetric synthesis of poly-substituted cyclohexanes *via* sequential Michael/Michael/aldol reactions in the presence of dual-organo catalyst, squaramide (0.5 mol%) as H-bond donor and achiral secondary amine pyrrolidine (10 mol%).




**Scheme 82.** Proposed formation mechanism of dispirocyclopentane bisoxindoles **284**.

Satisfactory chemical yields (up to 81%), excellent diastereoselectivities (>20:1 in all cases) and enantioselectivities (>99% in all cases) were obtained from above-mentioned reactions (Scheme 85).[151]

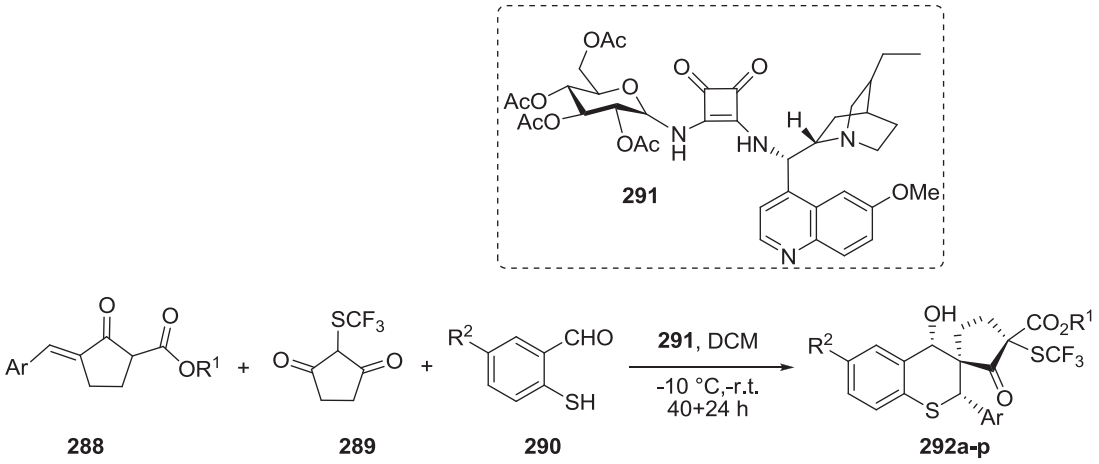
A reasonable mechanism for this approach was illustrated in Scheme 86. Accordingly, at first Michael addition is promoted by chiral squaramide **295b** as an organocatalyst generating enantioenriched intermediate **299**. Expectedly, achiral secondary amine pyrrolidine activates unsaturated aldehyde creating intermediate **301**. Consequently, nucleophilic attack by the intermediates **299** affords **303**. Finally, aldol cyclization followed by hydrolysis gives raise to the desired products **297** and pyrrolidine is recycled. To confirm this proposed mechanism, the reaction is performed using isolated intermediate **299**, and cinnamaldehyde in the presence of achiral pyrrolidine. The result exhibits the same diastereoselectivity (>20:1 *dr*) and enantioselectivity (>99% *ee*) as the sequential reaction carried out in the presence of chiral catalyst, representing that the stereoselectivities of second Michael reaction and the final aldol reaction obtain assistance from substrate controlling and the irreversible cyclization.[151]

In 2016, Lin and co-workers achieved and reported a highly effective organocatalyzed-MCR, involving Michael-Michael-aldol sequence for the formation of spirocyclohexaneoxindoles **307** in good yields and excellent stereoselectivities under mild reaction conditions. These products are bearing six adjoining stereogenic-centers, up to three quaternary stereogeniccenters, including two successive quaternary stereogeniccenters.[152] Based on the optimal reaction conditions, the substrate scope was studied. At first, various 1,3-dicarbonyl compounds, for example ethyl 2-methyl-3-oxobutanoate and pentane-2,4-dionewere examined, found being suitable substrates for such one pot MCR, affording the desired spiroxindole products in 40% and 73% yields respectively, with excellent *ee* (**307b**, **c**). Then, a wide range of methylene indolinones bearing either electron-releasing or electron-withdrawing groups at 5-position or 7-position were fruitfully transformed to the corresponding spiroxindole derivatives in modest yields but with excellent enantioselectivities **307d-f**. Next, this strategy was employed for various α,β-unsaturated aldehydes **307g-l**. Improved results were observed when α,β-unsaturated aldehydes bearing electron-withdrawing group at 4-position comparatively to those containing electron-donating group at 4-position. Delightfully, aliphatic unsaturated aldehyde (*E*)-ethyl 4-oxobut-2-enoate constructed the desired spiroxindoles with 56% and 43% yields respectively with diverse 1,3-dicarbonyl compounds **307k, 307l**. Noticeably, the diastereoselectivities were found being >20:1 in almost all cases (Scheme 87).[152]

### 2.4. Michael addition/Mannich reaction

An effective and operational method was developed for the diversity-oriented synthesis of polysubstituted 2-piperidinones through MCRs involving four commercially available or easily accessible as follows, substituted nitrostyrenes, aromatic aldehydes, ammonium acetate, and dialkyl malonates. This one-pot four-component reaction efficiently afforded wide variety of functionalized alkyl (±)-*trans*-4,6-diaryl-5-nitro-2-oxopiperidine-3-carboxylates and alkyl (±)-trans(C3/C4)-*cis*(C4/C5/C6)-4,6-diaryl-5-nitro-2-oxopiperidine-3-carboxylates in moderate to good yields. They are structurally interesting, pharmacologically important and useful as versatile synthetic intermediates and are potentially biologically active compounds.

It is worthy to mention that the formation of products in the course of reaction was found highly stereoselective. Two different stereochemical types of polysubstituted 2-piperidinones depending on the substituent position on aromatic aldehyde can be obtained. Practical simplicity, being done under reaction mild




**291a**: Ar = Ph, $R^1$ = Me, $R^2$ = H, *dr* = 13:1, yield = 82%, *ee* = >99%
**291b**: Ar = 4-$FC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 7:1, yield = 64%, *ee* = >99%
**291c**: Ar = 3-$ClC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 10:1, yield = 71%, *ee* = >99%
**291d**: Ar = 4-$ClC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 15:1, yield = 73%, *ee* = 99%
**291e**: Ar = 2,4-$Cl_2C_6H_3$, $R^1$ = Me, $R^2$ = H, *dr* = 6:1, yield = 58%, *ee* = 98%
**291f**: Ar = 2-$BrC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 4:1, yield = 67%, *ee* = 98%
**291g**: Ar = 4-$MeC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 13:1, yield = 85%, *ee* = 99%
**291h**: Ar = 4-$OMeC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 13:1, yield = 79%, *ee* = >99%
**291i**: Ar = 3-$CNC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 12:1, yield = 68%, *ee* = >99%
**291j**: Ar = 4-$CNC_6H_4$, $R^1$ = Me, $R^2$ = H, *dr* = 13:1, yield = 73%, *ee* = 98%
**291k**: Ar = furan, $R^1$ = Me, $R^2$ = H, *dr* = 7:1, yield = 63%, *ee* = 87%
**291l**: Ar = thiophene, $R^1$ = Me, $R^2$ = H, *dr* = 12:1, yield = 76%, *ee* = 99%
**291m**: Ar = Ph, $R^1$ = Et, $R^2$ = H, *dr* = 7:1, yield = 83%, *ee* = >99%
**291n**: Ar = 4-$NO_2C_6H_4$, $R^1$ = Et, $R^2$ = H, *dr* = >2:1, yield = 65%, *ee* = 92%
**291o**: Ar = Ph, $R^1$ = *i*-Pr, $R^2$ = H, *dr* = 3:1, yield = 80%, *ee* = 98%
**291p**: Ar = Ph, $R^1$ = Me, $R^2$ = Me, *dr* = 13:1, yield = 74%, *ee* = >99%

**Scheme 83.** One-pot asymmetric squaramide-catalyzed sulfur-Michael/aldol sequential reaction for the synthesis of the target products **292**.

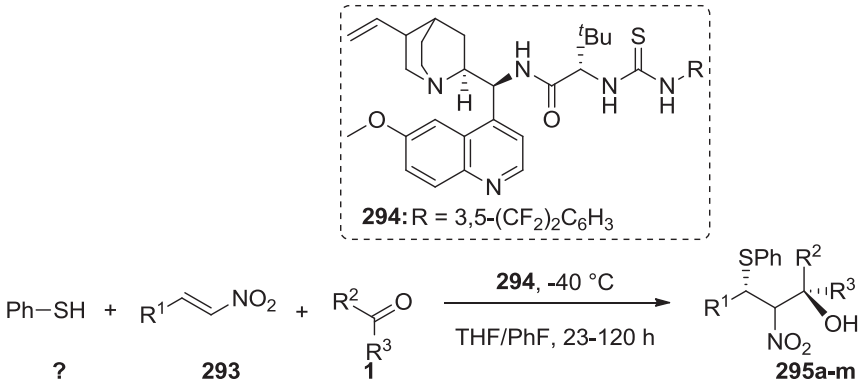
conditions and using market purchasable or easily available starting materials were observed and mentioned as merits for this strategy. To realize the scope of this devised approach, several market purchasable aldehydes **1** and readily available substituted nitrostyrenes **293** provided from aromatic aldehydes and nitromethane were reacted with dialkyl malonates **308** and ammonium acetate under optimal reaction conditions in one pot fashion. Significantly, both electron-withdrawing and electron-releasing groups on aromatic aldehydes were worked equally in the reaction, giving the products in modest to good yields (Scheme 88).[153]

A suggested mechanism for this reaction is depicted in Scheme 89. Initially, the Michael addition of malonate **308** to the substituted nitrostyrene **293** generated 2-(1-aryl-2-nitroethyl) malonate **311** that is followed by nitro-Mannich nucleophilic addition to the already generated intermediate arylimine to create 2-(3-amino-2-nitro-1,3-diaryl propyl)-malonate **312**. Ultimately, intramolecular lactamization in 2-(3-amino-2-nitro-1,3-diarylpropyl)malonate **312** afforded the cyclic amide with removal of alcohol.[153]

A highly efficient stereoselective synthesis of spiro-γ-lactam-oxindoles **315** with three stereogeniccenters was accomplished by Huang and co-workers reported in 2016.[154] Thiol-Michael/Mannich/lactamization reactions catalyzed by easily separable and recyclable fluorous bifunctional cinchona alkaloid/thiourea as an organocatalyst in one pot fashion gave the products **315** in moderate to excellent yields (up to 95% *ee* and 6:1 *dr*). The substrate scope of these sequential thiol-Michael/Mannich/cyclization reactions was studied by preparation of different analogs of **315** employing various thiols as Michael donors and a wide variety of amines and aldehydes. All reactions progressed smoothly to give products **315a-i** in satisfactory yields and high stereoselectivities. Both electron-withdrawing (F, $CF_3$) and electron-releasing (*t*-Bu, SMe) groups as the para-position of benzaldehydes **1** afforded the corresponding products **315b-f** in good to high (68–81%) yields and with >87% *ee* and >4:1 *dr* (Scheme 90).[154]

### 2.5. Ugi reaction/Heck reactions

An efficient synthetic pathway for the preparation of highly substituted indol-2-ones **321** *via* a combination of Ugi and Heck reaction was achieved in 2006 by Umkehrer and co-workers.[155] The synthesized indol-2-ones signify an interesting pharmacological framework with four divergent potential points. Therefore, this reaction-type is agreeable to combinatorial high-output screening. Nevertheless a new one-pot synthetic pathway resulted in the construction of the indol-2-one core structure by adjoining combinatorial and typical; sequential chemistry was developed. This accessible efficient sequential Ugi/Heck reaction designates an extension of the previously reported works. In that work, Gracias and co-workers[156] and Yang et al.[150] independently reported an Ugi/Heck two-step preparation of N-heterocycles, employing the merits of MCR and typical domino chemistry. The amalgamation of




**295a**: $R^1$ = 4-$MeC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 97:3, yield = 89%, *ee* = 99.9%
**295b**: $R^1$ = 3-$MeC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 96:4, yield = 85%, *ee* = 99.1%
**295c**: $R^1$ = 2-$MeC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 97:3, yield = 97%, *ee* = 99.8%
**295d**: $R^1$ = 4-$FC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 94:6, yield = 88%, *ee* = 99.6%
**295e**: $R^1$ = 3-$FC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 93:7, yield = 90%, *ee* = 99.5%
**295f**: $R^1$ = 2-$FC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 96:4, yield = 95%, *ee* = 99.6%
**295g**: $R^1$ = 4-$ClC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 95:5, yield = 95%, *ee* = 99.8%
**295h**: $R^1$ = 3-$ClC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 93:7, yield = 95%, *ee* = 99.6%
**295i**: $R^1$ = 4-$BrC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 95:5, yield = 93%, *ee* = 99.7%
**295j**: $R^1$ = 3-$BrC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 92:8, yield = 94%, *ee* = 99.6%
**295k**: $R^1$ = 4-$OMeC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 94:4, yield = 95%, *ee* = 99.7%
**295l**: $R^1$ = 3-$OMeC_6H_4$, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 97:3, yield = 91%, *ee* = 99.6%
**295m**: $R^1$ = 2-naphthyl, $R^2$ = $CO_2Et$, $R^3$ = H, *dr* = 96:4, yield = 85%, *ee* = 99.5%

**Scheme 84.** Stereoselective sulfa-Michael/aldol for the synthesis of γ-sulfur-β-nitro-α-hydroxyesters **295**.

MCRs and various post-reactions led to high diversity that is or enviously described.[158–164]

The construction of the acyclic products **320** was initially discovered by Ugi and co-workers and the ring-closure was occurred *via* a typical intramolecular Heck cyclization (Scheme 91).[165–169]

These two reaction were combined in a new one-pot fashion synthesis. The Ugi-Heck reaction was conducted *via* a classical fashion. Then, solvent was replaced from polar protic to polar aprotic in addition of 10% of Pd-catalyst. The desired compounds as isomeric mixture **321a-i** were isolated as isomeric mixtures in satisfactory yields. All the obtained products have purity >95%. Thus, it was shown an effective synthesis of different types of 1,3-disubstituted indol-2-ones. The aldehydes, anilines, isocyanides, and acrylic acids were diversely used, affording products with four convergent potential points.[155]

### 2.6. Ugi Reaction/Deils-Alder reaction

The indication of combining the merits of an intramolecular MCR with those of norbornene compounds was initially discovered by Paulvannan and co-workers in 1999.[170] They reported the first synthesis of an Ugi derived oxanorbornenyls *via* combining an intramolecular MCR with an intramolecular Deils-Alder reaction of furan. This was accomplished *via* the utilization of maleic or fumaric acid derivatives **322a** or **322b** and furaldehydes **323** as frameworks for the MCR. Remarkably, in spite of the generation of five new stereogenic centres, it was found that always one diastereoisomer, **326** is prevailed (isomer ratio 83:17–93:7). This predominant formation of **326** could partially described be this fact that when the C-9 stereogenic centres generated during the Ugi reaction is combined into the final tricyclic system, then favorably orients the attack of the diene onto one of the two diastereotopic faces of the dienophile (Scheme 92).[170]

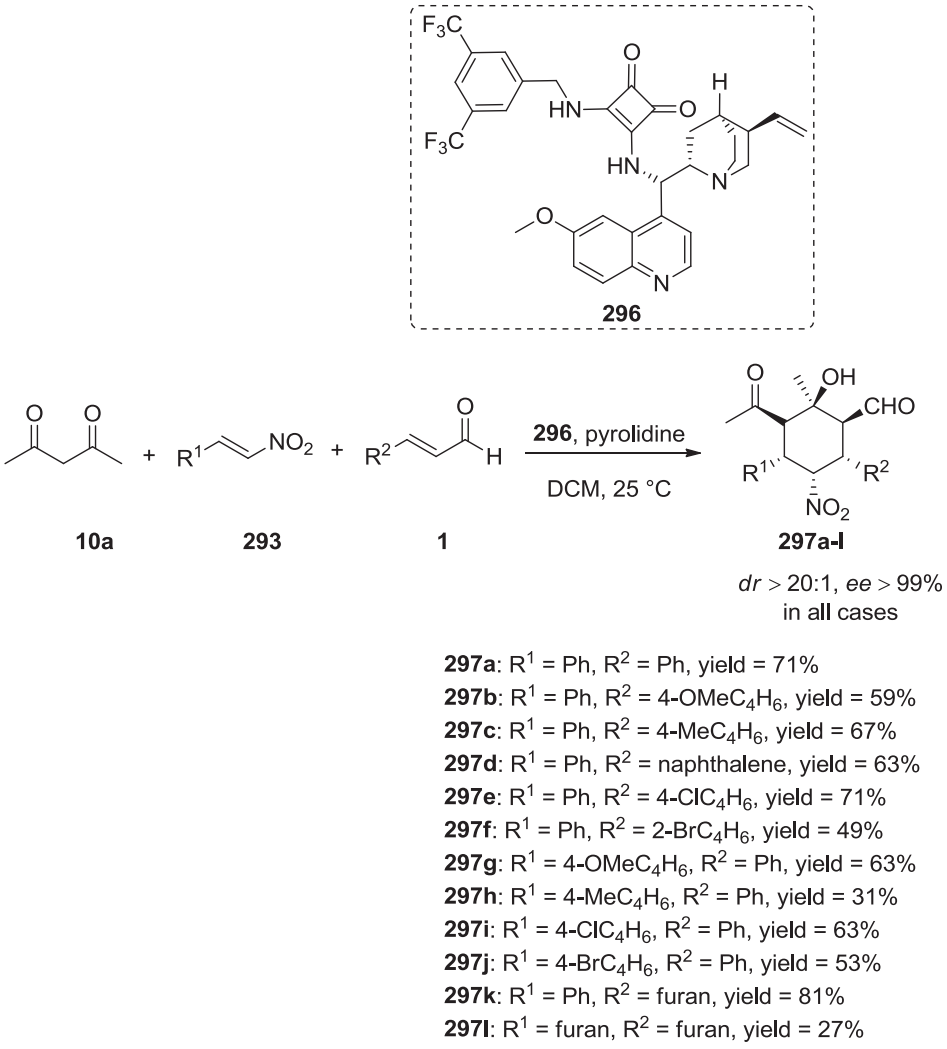
As expected, by changing furaldehyde with substituted furaldehyde such as furfurylamine **327** the C-2 stereogeniccentre, placed outside the tricyclic system, is no longer capable to direct the attack of the diene effectively, thus, isomers **328** were isolated in an approximately 1:1 ratio (Scheme 93).[170]

### 2.7. Ugi reaction/Huisgen reaction

An un-catalyzed Ugi four-component reaction involving β-azido-α-amino acid, propargylamine, an isocyanide and an appropriate aldehyde, was performed and the product was subsequently subjected into thermal azide-alkyne 1,3-dipolar Huisgen cycloaddition to afford a 16-member library of amino triazoloazepinone containing di- and tripeptides with atom economy and up to four points of diversification. A wide variety of aldehydes was also examined in a next step for functionalization of the respective corresponding of side chain of the second amino acid present in these dipeptide-like molecules. The substrate scope of the used aldehydes were evaluated and delightfully it was observed that aryl and heteroaromatic aldehydes can be well tolerated and showed great effect on the time and yield of the reaction (Scheme 94).[171]

### 2.8. Ugi reaction/aldol reaction

A fascinating MCR was developed involving sequential post-Ugi/aldol condensations to have access to poly substituted heterocyclic systems. To obtain the MCR product bearing functionalities useful to partake in an aldol condensation, pyruvic aldehyde and



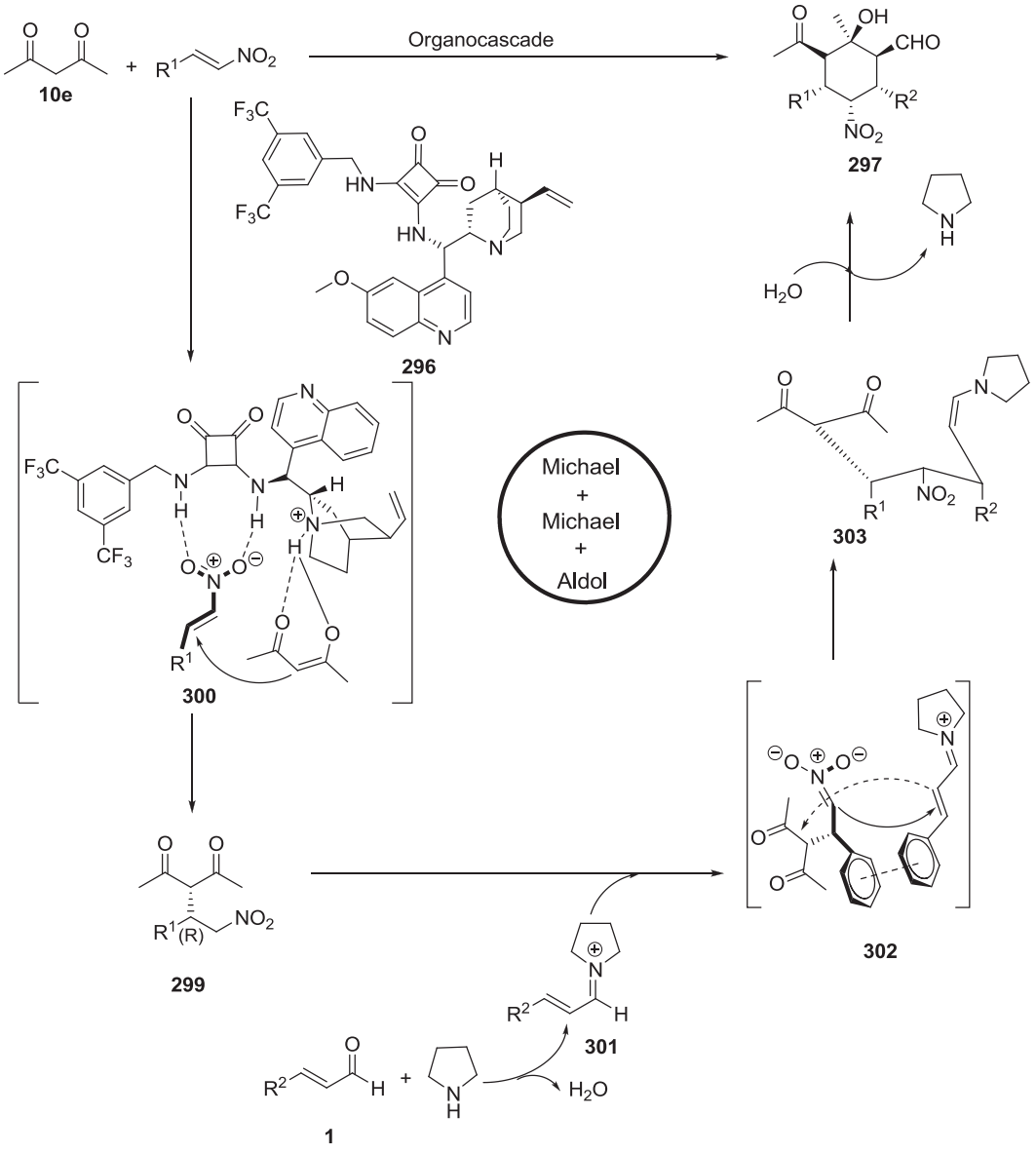

**Scheme 85.** MCR of acetyl acetone **10a**, nitrostyrene **293** and unsaturated aldehydes in the presence of **296** as catalyst.

phenylglyoxylic acid were used, with participation of benzylamine and *n*-butylisonitrile. Unsurprisingly, initially the reaction made progress smoothly in MeOH overnight under mild reaction conditions to provide **326a** in 67% yield. Thus in the first step an acyclic intermediate was generated which is bearing carbonyl groups and an active methyl, available for further reaction (Scheme 95).[172]

The aldol reaction in combination with the Ugi MCR was studied in the installation of decorated mono- and polycyclic systems through swift domino sequential reaction. Few pyrrolinones was provided *via* this strategy thus, the rarely accessible pyridoquinoxalinedione framework was also provided by manipulative of an additional nucleophilic substitution stage in this sequential reaction needing minimum practical energy. In this fashion, two direct and facile and friendly sequential reaction enabling the fast installation of the heterocyclic cores **341** and **347**.[173]

Initially, the synthesis of the pyrrolidone scaffold, as a very interesting biological framework was attempted. The assemblage of the acyclic precursor for this chemo type was achieved *via* employing of the Ugi four-component condensation,[174] which successfully performed under the conventional mild reaction conditions.[175] A four-component reaction involving pyruvic aldehyde, *n*-butylisonitrile, 2,4-dichlorophenylacetic acid, and benzylamine were mixed in MeOH and performed at ambient temperature. Up construction of **340a**, MeOH was evaporated off and the residue was directly subjected to the aldol reaction. The aforementioned reaction was performed under MWI in the presence of an organic base at elevated temperatures to make the cyclization step, facile. To find the optimal reaction conditions, different solvents, temperatures and reaction times were examined in a model reaction. It was found that heating the reaction at160 °C for 20 min in dimethylformamide and in the presence of diisopropylamine are the best reaction conditions. Under these conditions, the reaction proceeds smoothly providing the desired product **341a** in a high yield over two steps.

Under secured optimal reaction conditions for the second step of the sequence to determine the reactivity realm of the Ugi-aldol two-step, one-pot pathway for the assemblage of a small collection of compounds with general structure **341**, and diverse starting materials were used. Overally, various amines, two glyoxaldehydes, four carboxylic acids and three isonitriles were examined to construct a set of collection of **341a-g** in good to high yields in pure form after column chromatography. The merits of this MCR methodology for the synthesis of **341** over already traditional linear approaches are outstanding. As a matter of fact, those reported stepwise routes for the synthesis of pyrrolinones, suffer from using unusual starting materials, different transition metals as catalysts, and/or prolonged multistep routes and slack of generality and




**Scheme 86.** Suggested Mechanism for the synthesis of the target products **297** *via* the Michael/Michael/aldol sequence.

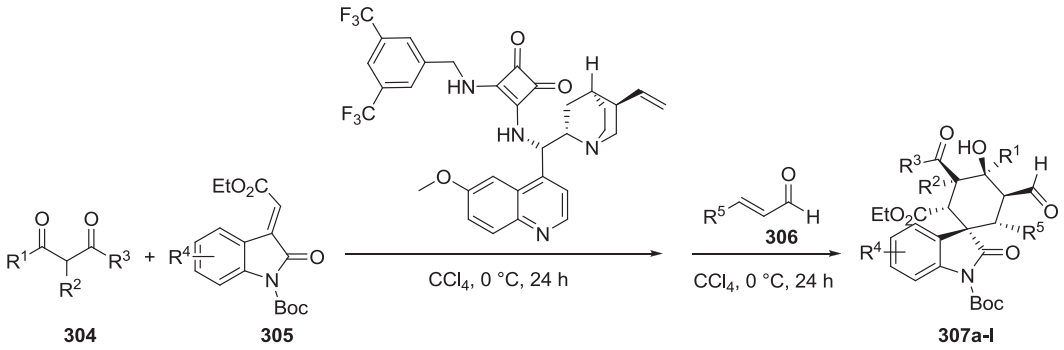
operational ease (Scheme 96).[176]

In this domino sequential reaction, the required nucleophilic partner in the aldol reaction was provided from commercially available pyruvic aldehyde. For assembly of functionality for the cascade reaction, some other atoms such as a fluorine atom placed on the aniline to increase the input of the MCR upon nucleophilic attack by the amidic nitrogen surrounded in the Ugi backbone. The MCR reaction of *tert*-butylisonitrile, phenylglyoxylic acid, 2-fluoro-4-bromoaniline, and pyruvic aldehyde in MeOH at ambient temperature was examined. After evaporation of the solvent, the obtained residue **344** was heated in the presence of an appropriate base that stimulated an aldol-driven cyclization resulting in the construction of **345**, which is susceptible to tautomerization. A second ring closure occurring in a one-pot manner affording the desirable target tricyclic species **347** through the formation of intermediate **346**. As a result, by a non-obvious four-step route, compound **347** can be synthesized *via* two facile synthetic operations in 10% overall yield in pure form after column chromatography. Notably, this reaction represents a high-yielding and operationally easy direct domino sequential reaction giving an unusual tricyclic framework (Scheme 97).[177]

### 2.9. Miscellaneous

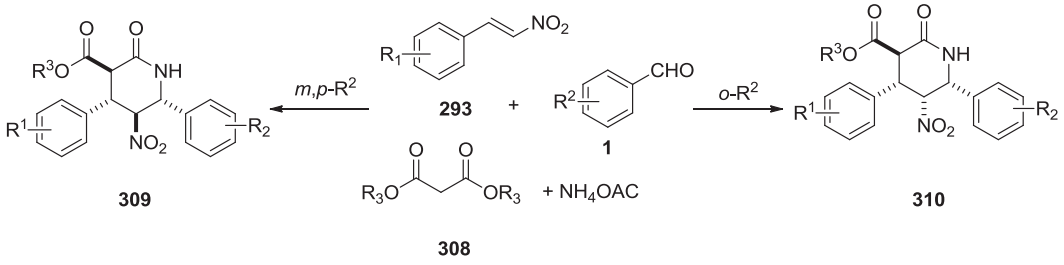
This one-pot methodology was next stretched for the preparation of styrylstilbenes **350**, renown as a significant typical highly conjugated systems.[178] The synthesis pathway commenced from terephthaldehyde **97** as the appropriate aldehyde component, which was condensed with two molecules of the phosphonium salt provided from 4-bromobenzyl bromide. As the result, initially Wittig product **349** was formed, this latter was reacted with the reagents of the Suzuki reaction to afford the desired target **350**. Interestingly, such molecules were proven to possess many electrical and optical applications (Scheme 98).[179]

A two-step MCR involving acrylic aldehydes, bromoanilines, acids and isocyanides in one pot fashion gave polysubstituted indoles.[180] The reaction is relied on the combination of four-component Ugi reaction with subsequent an intramolecular Heck-

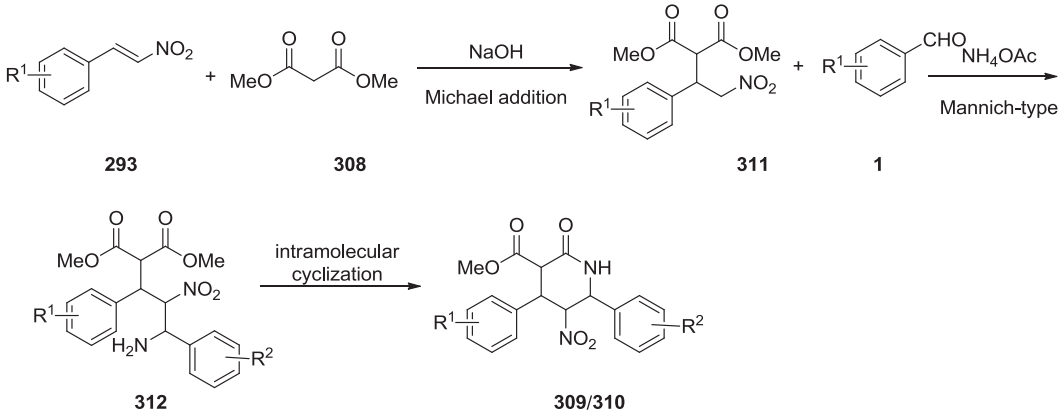



**307a**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = H, $R^5$ = Ph, yield = 80%, *dr* = >20:1, *ee* = 96%
**307b**: $R^1$ = Me, $R^2$ = Me, $R^3$ = OEt, $R^4$ = H, $R^5$ = Ph, yield = 40%, *dr* = >20:1, *ee* = 97%
**307c**: $R^1$ = Me, $R^2$ = H, $R^3$ = Me, $R^4$ = H, $R^5$ = Ph, yield = 73%, *dr* = >20:1, *ee* = 94%
**307d**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = Me, $R^5$ = Ph, yield = 56%, *dr* = >20:1, *ee* = 94%
**307e**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = Cl, $R^5$ = Ph, yield = 64%, *dr* = >20:1, *ee* = 92%
**307f**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = F, $R^5$ = Ph, yield = 71%, *dr* = >20:1, *ee* = 95%
**307g**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = H, $R^5$ = Cl, yield = 72%, *dr* = >20:1, *ee* = 97%
**307h**: $R^1$ = Me, $R^2$ = Me, $R^3$ = OEt, $R^4$ = H, $R^5$ = Br, yield = 51%, *dr* = >20:1, *ee* = 94%
**307i**: $R^1$ = Me, $R^2$ = H, $R^3$ = Me, $R^4$ = H, $R^5$ = Me, yield = 42%, *dr* = >20:1, *ee* = 97%
**307j**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = Me, $R^5$ = OMe, yield = 32%, *dr* = >20:1, *ee* = 91%
**307k**: $R^1$ = Me, $R^2$ = Me, $R^3$ = Me, $R^4$ = Cl, $R^5$ = $CO_2$Et, yield = 56%, *dr* = >20:1, *ee* = 97%
**307l**: $R^1$ = Me, $R^2$ = Me, $R^3$ = OEt, $R^4$ = F, $R^5$ = $CO_2$Et, yield = 43%, *dr* = >20:1, *ee* = 98%

**Scheme 87.** MCR for the synthesis of spirocyclohexaneoxindoles **307**.

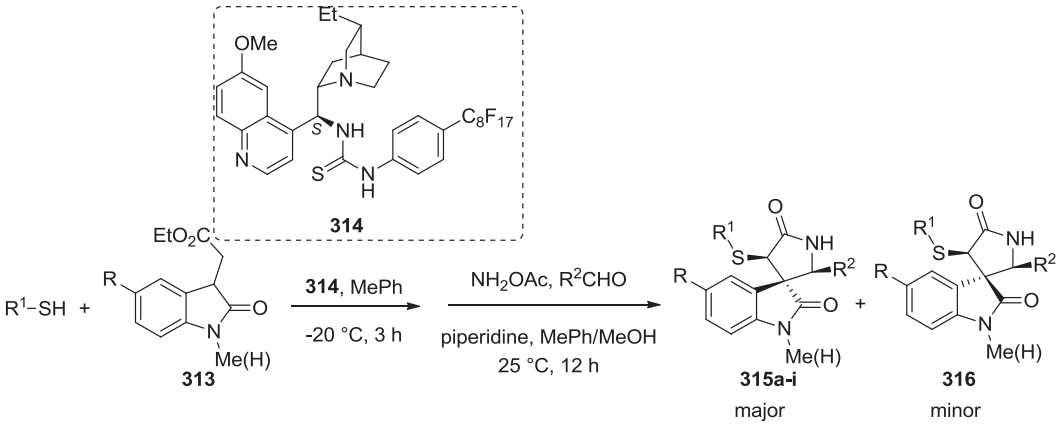



**Scheme 88.** MCR for the synthesis of products **309** and **310**.



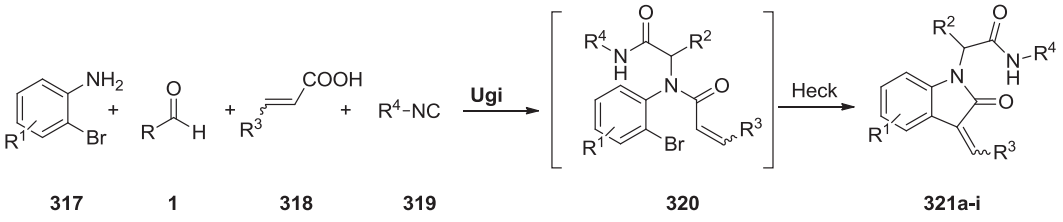

**Scheme 89.** probable mechanism for the synthesis of the cyclic amide **309/310**.

reaction. The concurrent utilization of HCOOH and cinnamaldehydes led to in situ construction of 1*H*-indoles. Transformable isocyanides were also successfully used with success in this Ugi/Heck combination reaction to afford 1*H*-indole-2-carboxylic acid framework. Encouraged by this post-condensation modifications, the same authors have examined another variant of combination the Ugi/Heck reaction for the synthesis of highly substituted indol-2-ones *via* a one-pot reaction.[155] The extension of usage of potentiality of the Ugi/Heck reaction developed for the synthesis of wide range of indole derivatives, almost at the same time by Gracias[156] and Xiang and co-workers.[157] In this line the synthesis of four novel substituted dihydro-indoles including 2-bromoanilines **351a-**



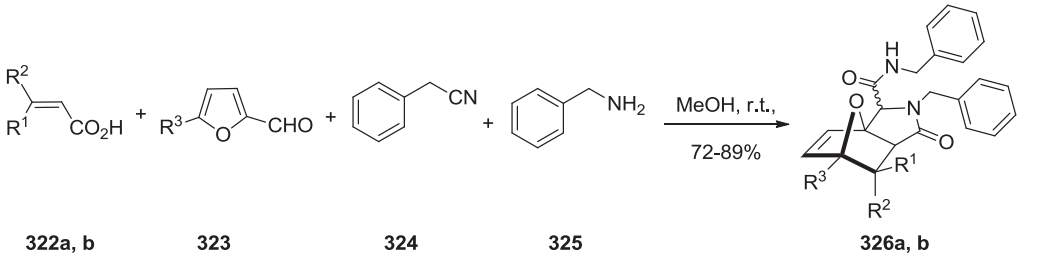

**315a**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = Ph, *dr* = 6:1, yield = 78%, *ee* = 93%
**315b**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = 4-$FC_6H_4$, *dr* = 6:1, yield = 79%, *ee* = 87%
**315c**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = 4-$MeC_6H_4$, *dr* = 4:1, yield = 72%, *ee* = 94%
**315d**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = 4-$^t$Bu$C_6H_4$, *dr* = 5:1, yield = 68%, *ee* = 94%
**315e**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = 4-$SMeC_6H_4$, *dr* = 5:1, yield = 71%, *ee* = 91%
**315f**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = 4-$CF_3C_6H_4$, *dr* = 6:1, yield = 81%, *ee* = 89%
**315g**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = thiophene, *dr* = 6:1, yield = 75%, *ee* = 82%
**315h**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = cyclopropane, *dr* = 3:1, yield = 67%, *ee* = 85%
**315i**: R = H , $R^1$ = 4-$MeC_6H_4$, $R^2$ = Me, *dr* = 2.5:1, yield = 59%, *ee* = 83%

**Scheme 90.** One-pot synthesis of spiro-γ-lactam-oxindoles **315**.



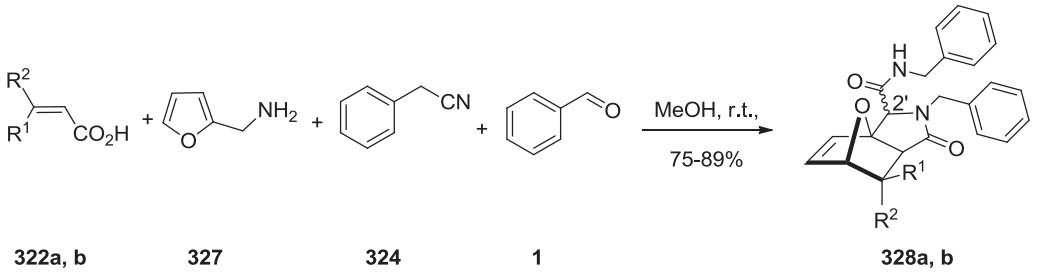

**321a**: $R^1$ = H, $R^2$ = Ph, $R^3$ = Ph, $R^4$ = $CH_2CO_2Me$, yield = 59%
**321b**: $R^1$ = H, $R^2$ = $CHMe_2$, $R^3$ = Ph, $R^4$ = $CH_2CO_2Me$, yield = 63%
**321c**: $R^1$ = H, $R^2$ = H, $R^3$ = Ph, $R^4$ = $CH_2CO_2Me$, yield = 52%
**321d**: $R^1$ = H, $R^2$ = Ph, $R^3$ = Ph, $R^4$ = $CMe_3$, yield = 54%
**321e**: $R^1$ = H, $R^2$ = H, $R^3$ = Ph, $R^4$ = $CH_2Ph$, yield = 48%
**321f**: $R^1$ = H, $R^2$ = H, $R^3$ = 4-$NO_2C_6H_4$, $R^4$ = $CH_2CO_2Me$, yield = 43%
**321g**: $R^1$ = H, $R^2$ = H, $R^3$ = 4-$NO_2C_6H_4$, $R^4$ = $CH_2Ph$, yield = 58%
**321h**: $R^1$ = H, $R^2$ = H, $R^3$ = 3-$CF_3C_6H_4$, $R^4$ = $CH_2CO_2Me$, yield = 46%
**321i**: $R^1$ = H, $R^2$ = Ph, $R^3$ = 3-$CF_3C_6H_4$, $R^4$ = $CH_2CO_2Me$, yield = 62%

**Scheme 91.** One-pot indol-2-one synthesis through Ugi-Heck sequential reaction.

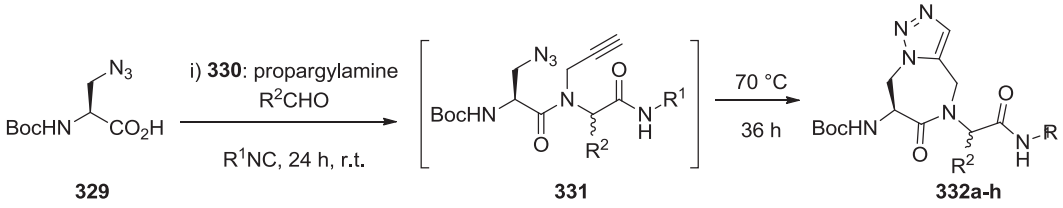



**322a, 326a**: $R^1$ = ester, amide, $R^2$ = H, $R^3$ = Me
**322a, 326a**: $R^1$ = H, $R^2$ = ester, amide, $R^3$ = H, Me

**Scheme 92.** Four-component Ugi reaction with subsequent intramolecular Deils-Alder cycloaddition with furaldehydes as diene source.

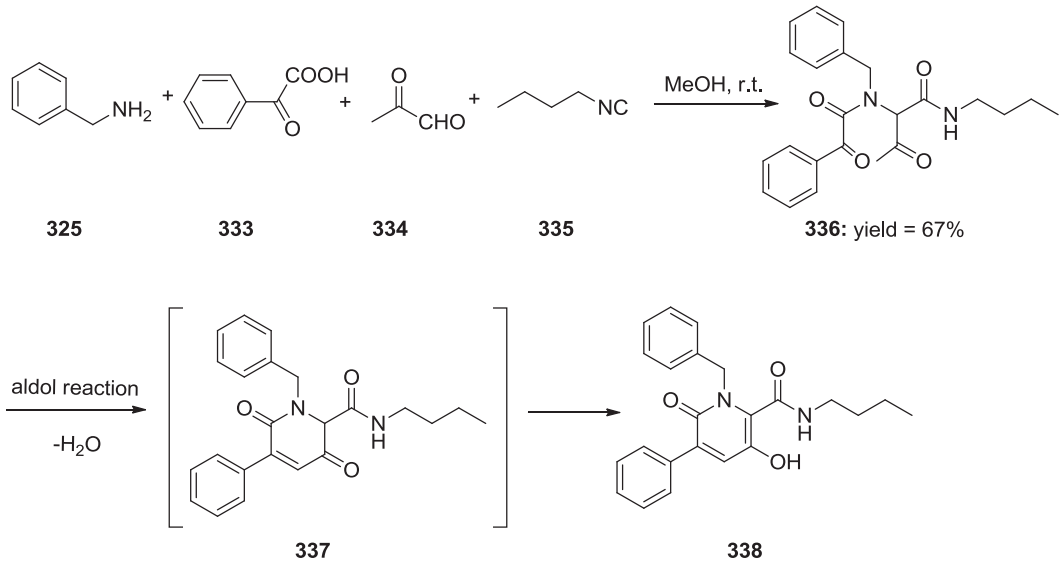



**Scheme 93.** Four-component Ugi reaction with subsequent intramolecular Deils-Alder cycloaddition with furafurylamine as diene source.



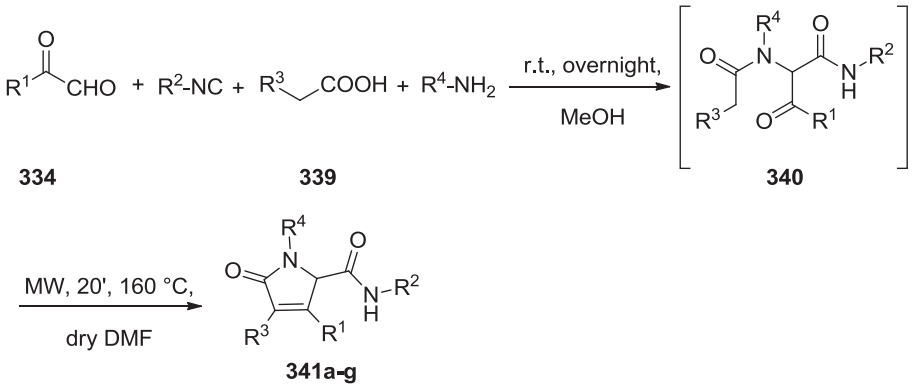

**332a**: $R^1$ = *t*-Butyl, $R^2$ = Ph, yield = 94%, *dr* = 55/45
**332b**: $R^1$ = Cyclohexyl, $R^2$ = Ph, yield = 78%, *dr* = 50/50
**332c**: $R^1$ = Benzyl, $R^2$ = Ph, yield = 76%, *dr* = 50/50
**332c**: $R^1$ = *t*-Butyl, $R^2$ = 4-$BrC_6H_4$, yield = 74%, *dr* = 53/47
**332d**: $R^1$ = *t*-Butyl, $R^2$ = 3-Indolyl, yield = 41%, *dr* = 58/42
**332e**: $R^1$ = *t*-Butyl, $R^2$ = $Me_2NC_6H_4NCO$, yield = 74%, *dr* = 52/48
**332f**: $R^1$ = *t*-Butyl, $R^2$ = Me, yield = 54%, *dr* = 51/49
**332g**: $R^1$ = *t*-Butyl, $R^2$ = Cyclohexyl, yield = 39%, *dr* = 64/36
**332h**: $R^1$ = *t*-Butyl, $R^2$ = Piperonyl, yield = 67%, *dr* = 55/45

**Scheme 94.** Substrate scope for the generation a-dipeptides *via* four-component Ugi-reaction.




**Scheme 95.** Ugi/aldol reaction for the synthesis of the target product **338**.

**b** and acrylic aldehydes **352a-b** as starting materials for the Ugi-reaction was completed. The synthesis of the acyclic products **353** was formerly achieved and reported by Ugi co-workers and the ultimate ring-closure was conducted by a conventional intramolecular Heck-reaction.[181] The Ugi and Heck reactions then were combined and performed in one-pot fashion. The sequential Ugi/Heck reaction was conducted *via* an already established conventional procedure. In next attempt, the solvent of choice was

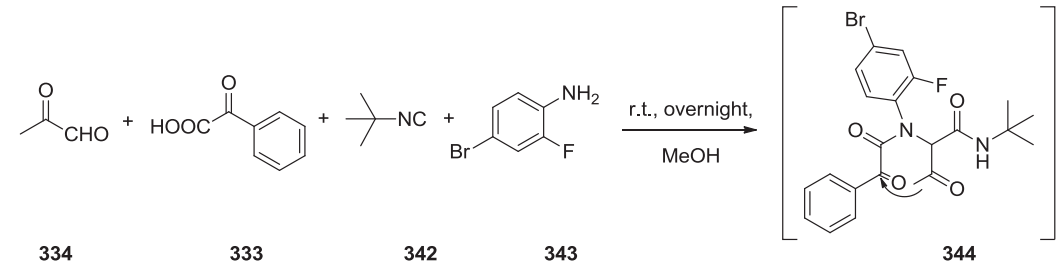



334 339 340

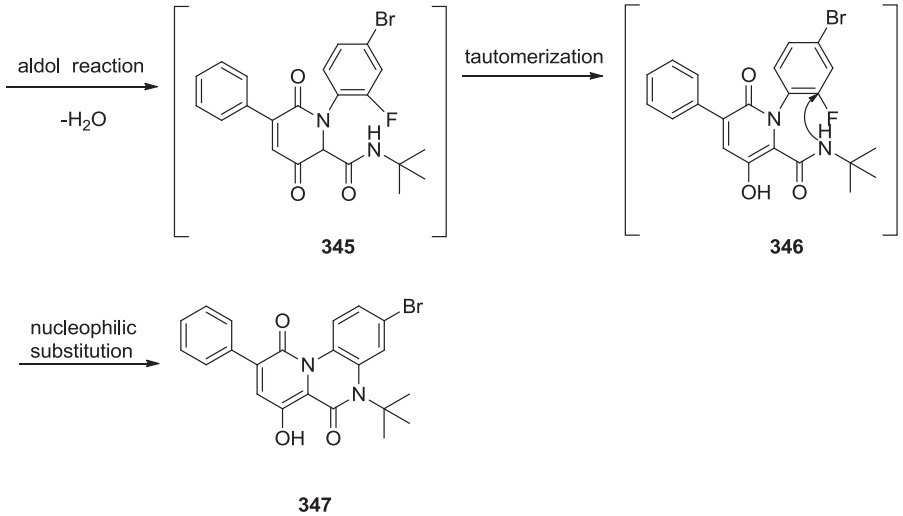
341a-g

**341a**: $R^1$ = Me, $R^2$ = *n*Bu, $R^3$ = 2,4-$ClC_6H_4$, $R^4$ = Bn, yield = 75%
**341b**: $R^1$ = Me, $R^2$ = *n*Bu, $R^3$ = 2,4-$ClC_6H_4$, $R^4$ = 2,4-$OMeC_6H_4$, yield = 68%
**341c**: $R^1$ = Me, $R^2$ = *n*Bu, $R^3$ = 2,4-$ClC_6H_4$, $R^4$ = 2-furylmethyl, yield = 62%
**341d**: $R^1$ = Me, $R^2$ = Bu, $R^3$ = 3,4-$OMeC_6H_4$, $R^4$ = 3,4-$OMeC_6H_4$, yield = 82%
**341e**: $R^1$ = Me, $R^2$ = *n*Bu, $R^3$ = 3,5-$FC_6H_4$, $R^4$ = 2-ClBn, yield = 73%
**341f**: $R^1$ = Ph, $R^2$ = *n*Bu, $R^3$ = 3,5-$CF_3C_6H_4$, $R^4$ = Bn, yield = 67%
**341g**: $R^1$ = Ph, $R^2$ = *n*Bu, $R^3$ = 3,5-$CF_3C_6H_4$, $R^4$ = 4-$BrC_6H_4$, yield = 72%

**Scheme 96.** The Ugi-aldol Sequence toward pyrrolinones **341**.

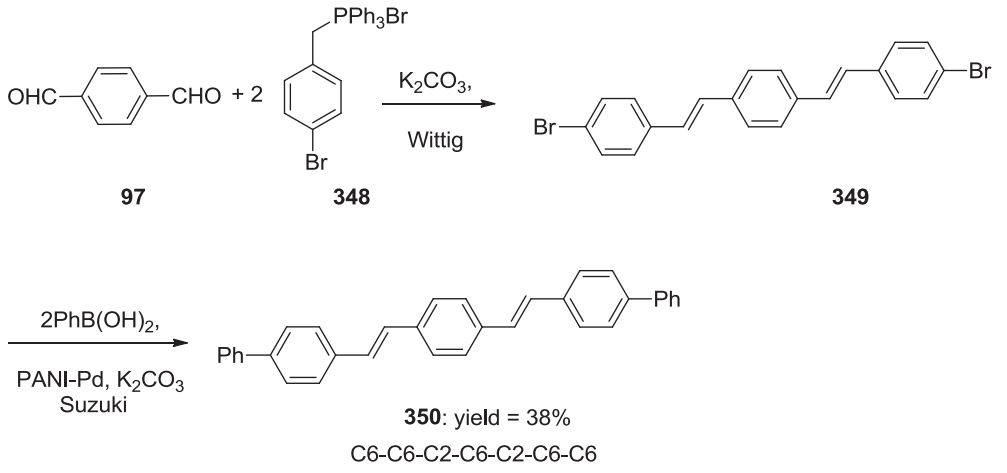



334 333 342 343 344

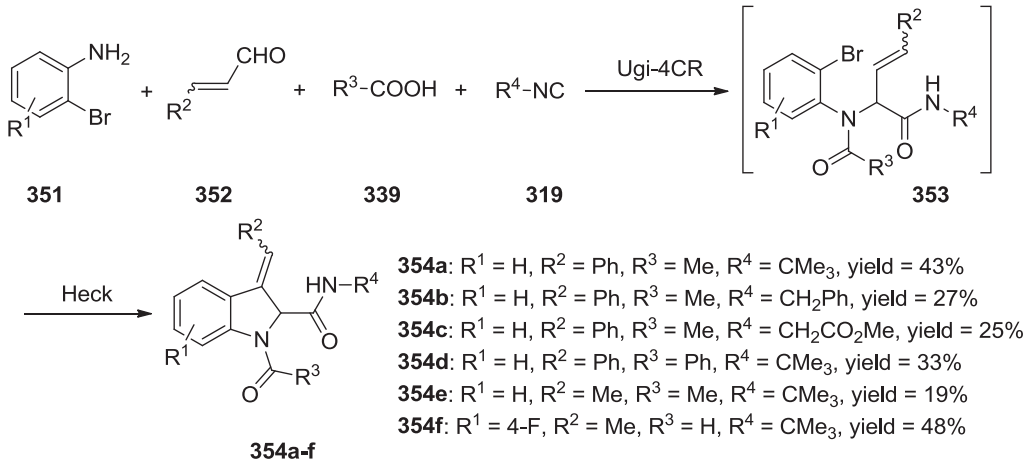



345 346 347

**Scheme 97.** Suggested mechanism for the synthesis of pyridoquinoxalinediones **347**.




**Scheme 98.** Wittig/Suzuki reaction for the synthesis of styrylstilbenes **350**.

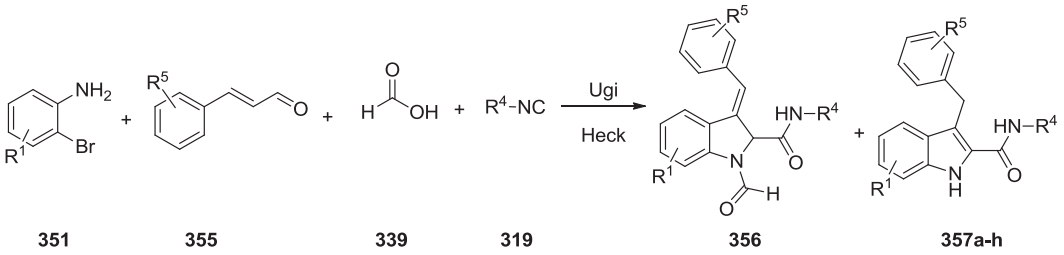



**Scheme 99.** Ugi-Heck synthesis of substituted indoles **354**.

identified, in which the polar aprotic solvent using 10% of Pd-catalyst was found as the suitable solvent and catalyst loading for the above-mentioned reaction. The expected compounds **354a-f** were prepared and isolated as a mixture of isomers in modest to good yields. For the all prepared compounds the purities >95% were determined. The used bromoanilines, acids, acrylic aldehydes and isocyanides could be varied broadly, producing products with four potential points of diversity. Delightfully, the synthesis of substituted 1*H*-indoles was achieved *via* the reaction of cinnamaldehydes **352a** and **352c** and formic acid **339** in one-pot manner. Worthy to mention that under Heck-reaction conditions, the obtained formyl group was partially subjected to cleavage. Subsequent isomerisation resulted in 1*H*-indoles in modest to good yields. After success of this strategy, various 1*H*-indoles **357a-h** from obtained from the reaction of substituted 2-bromoanilines **351a-b**, cinnamaldehydes **352 a,c** and different isocyanides **319**. The obtained compounds were fruitfully isolated in modest to good yields. All the prepared compounds showed purities >95%. By utilization of substituted 2-bromoanilines further derivatization of the 1*H*-indole frame work were achieved. Noticeably, this sequential reaction tolerates the use of 'adaptable' isocyanides **319** (Schemes 99 and 100).[180]

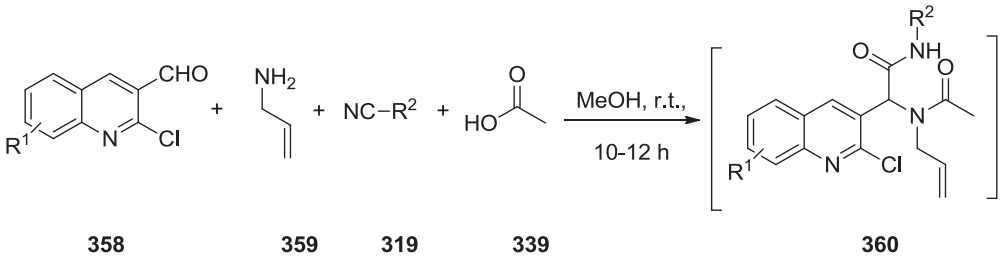
A simple, operational and highly efficient synthesis of functionalized 1,2-dihydrobenzo[*b*][1,6]naphthyridines was achieved through four-component Ugi MCR utilizing allyl amine, substituted 2-chloroquinoline-3-carboxaldehydes, acetic acid, various isocyanides and ligand free *via* Heck reactions in satisfactory yields. The yields of reactions were modified when it was performed in a one-pot manner and avoiding purification of intermediate as the Ugi adducts.[182] Encouraged by these results, the same authors employed the Ugi adducts obtained from four-component reaction of 2-chloroquinoline-3-carboxaldehydes, allyl amine, isocyanides and acetic acid. Then they focused on an alternative pathway to prepare five and six membered nitrogen heterocycle dedicated to quinolones through metal-mediated cyclization reactions. Nevertheless, up on three times implementation of these reaction, a four-component sequential Ugi and ligand free Heck reaction in one of fashion an effective pathway to poly functionalized 1,2-dihydrobenzo[*b*][1,6] naphthyridines has been achieved. To establish the generality of these one-pot reactions, differently substituted 2-chloroquinoline-3-carboxaldehydes **358** were reacted with allyl amine, *tert*-butyl isocyanide and $CH_3COOH$ in MeOH at ambient temperature (Ugi reaction) followed by Heck reaction under the already secured optimal reaction conditions. It was found that all reactions progressed to completion giving the products **361b-h** in satisfactory yields but relatively in long reaction times (Scheme 101).[182]

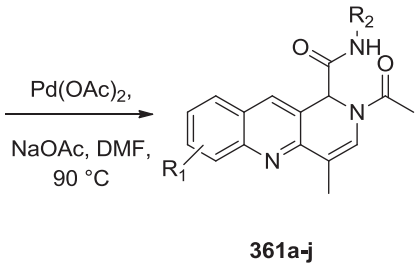
A combination of aldol condensation/Michael addition of 4,4-




**357a**: $R^1$ = H, $R^5$ = H, $R^4$ = $CH_2Ph$, yield = 21%
**357b**: $R^1$ = H, $R^5$ = H, $R^4$ = $CMe_3$, yield = 17%
**357c**: $R^1$ = H, $R^5$ = H, $R^4$ = $CH_2CO_2Me$, yield = 15%
**357d**: $R^1$ = H, $R^5$ = H, $R^4$ = $CMe_3$, yield = 23%
**357e**: $R^1$ = 4-F, $R^5$ = H, $R^4$ = $CH_2Ph$, yield = 31%
**357f**: $R^1$ = 4-F, $R^5$ = H, $R^4$ = $CH_2Ph$, yield = 38%
**357g**: $R^1$ = H, $R^5$ = H, $R^4$ = 1-cyclohexen-1-yl, yield = 29%
**357h**: $R^1$ = H, $R^5$ = H, $R^4$ = 4-phenyl-1-cyclohexen-1-yl, yield = 32%

**Scheme 100.** 1*H*-Indoles **357a**–**h** synthesized by the Ugi-Heck reaction.



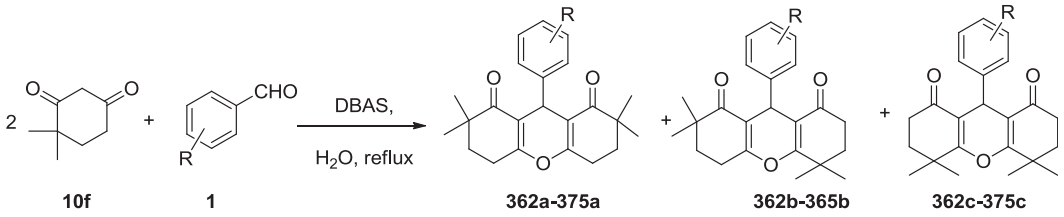




**361a**: $R^1$ = 6-Me, $R^2$ = $CMe_3$, time = 1 h, yield = 84%
**361b**: $R^1$ = H, $R^2$ = $CMe_3$, time = 1 h, yield = 85%
**361c**: $R^1$ = 7-Me, $R^2$ = $CMe_3$, time = 1 h, yield = 83%
**361d**: $R^1$ = 8-Me, $R^2$ = $CMe_3$, time = 1.5 h, yield = 81%
**361e**: $R^1$ = 6-OMe, $R^2$ = $CMe_3$, time = 1 h, yield = 85%
**361f**: $R^1$ = 7-OMe, $R^2$ = $CMe_3$, time = 1 h, yield = 84%
**361g**: $R^1$ = 8-Et, $R^2$ = $CMe_3$, time = 1.5 h, yield = 80%
**361h**: $R^1$ =7-Cl, $R^2$ = $CMe_3$, time = 1.5 h, yield = 80%
**361i**: $R^1$ = 6-Br, $R^2$ = $CMe_3$, time = 2 h, yield = 77%
**361j**: $R^1$ = 6-Me, $R^2$ = $(CH_2)_3Me$, time = 1.5 h, yield = 82%

**Scheme 101.** One-pot synthesis of benzo[*b*][1,6]naphthyridines **361**.

dimethylcyclohexane-1,3-dione and differently substituted aromatic aldehydes was achieved by Muharrem and co-workers in 2011. Upon cyclization of 4,4-dimethylcyclohexane-1,3-dione with differently substituted aromatic aldehydes the resulted product was identified as divers xanthene regioisomers. It was found that electronic and steric effects on aromatic aldehydes have influence in this reaction. Notably, xanthene regioisomers were actually formed as a result of the reaction of 4,4-dimethylcyclohexane-1,3-dione **10f** with differently aromatic aldehydes **1**. It is proposed that initially, a Claisen-Schmidt condensation occurs between ketones and aldehydes. Thus, the generated enone *via* the attack of an enol compound that is obtained by the protonation of a ketone attacked the carbonyl carbon of aldehyde followed by elimination of 1 mol $H_2O$. Elimination of water is assisted by the increasing conjugation. The resulted of highly reactive α,β-unsaturated carbonyl compound (enone) was treated with **10f** mol of 4,4-dimethylcyclohexane-1,3-dione and the product of Michael addition was obtained. For the finding substrate scope, differently substituted aromatic aldehydes were used in this reaction. Thus, the relationship among the three xanthene isomers and the reaction mechanism were realized. In case of using benzaldehyde, structural isomers **a** and **b** were obtained in which the isomer **b** was obtained as a main product (65%) (Scheme 102).[183]

A facile one-pot, one step atom economic three-component reaction for the synthesis of 5-monoalkylbarbiturates **378** involving barbituric acids **18**, aldehydes **1** and α,β-unsaturated ketones **377** was achieved and reported in 2015.[184] It is believed that this reaction proceeds *via* a domino aldol-Michael reaction. This approach with the features required for green chemistry presents an alternative but a more cost-effective approach for the synthesis




**362**: R = PhCHO, time = 1.5 h, yield = 94%, product rate: **a** = 35%, **b** = 65%, **c** = -
**363**: R = 4-OHC$_6$H$_4$CHO, time = 2 h, yield = 86%, product rate: **a** = - , **b** = 30%, **c** = 70%
**364**: R = 4-OH-3-Br-C$_6$H$_3$CHO, time = 1.5 h, yield = 83%, product rate: **a** = - , **b** = 73%, **c** = 27%
**365**: R = 2-NO$_2$C$_6$H$_4$CHO, time = 2 h, yield = 89%, product rate: **a** = - , **b** = 92%, **c** = 8%
**366**: R = 3-NO$_2$C$_6$H$_4$CHO, time = 2.5 h, yield = 82%, product rate: **a** = 81%, **b** = 19%, **c** = -
**367**: R = 4-NO$_2$C$_6$H$_4$CHO, time = 2.5 h, yield = 80%, product rate: **a** = - , **b** = 82%, **c** = 18%
**368**: R = 4-PhC$_6$H$_4$CHO, time = 2.5 h, yield = 77%, product rate: **a** = - , **b** = 10%, **c** = 90%
**3690**: R = 4-MeSC$_6$H$_4$CHO, time = 2 h, yield = 70%, product rate: **a** = 91%, **b** = 9%, **c** = -
**370**: R = 4-MeOC$_6$H$_4$CHO, time = 1.5 h, yield = 87%, product rate: **a** = 100%, **b** = - , **c** = -
**371**: R = 3,4-(MeO)$_2$C$_6$H$_3$CHO, time = 2 h, yield = 77%, product rate: **a** = - , **b** = 7%, **c** = 93%
**372**: R = 2,4-(MeO)$_2$C$_6$H$_3$CHO, time = 2.5 h, yield = 80%, product rate: **a** = - , **b** = - , **c** = 100%
**373**: R = 2,4-Cl$_2$C$_6$H$_3$CHO, time = 2 h, yield = 81%, product rate: **a** = 75%, **b** = 9%, **c** = 16%
**374**: R = 2-Pyridine carbaldehyde, time = 2.5 h, yield = 75%, product rate: **a** = - , **b** = 100%, **c** = -
**375**: R = 3-Pyridine carbaldehyde, time = 2.5 h, yield = 80%, product rate: **a** = - , **b** = - , **c** = 100%

**Scheme 102.** Synthesis of the 1,8-octahydroxanthenes **362**–**375**.

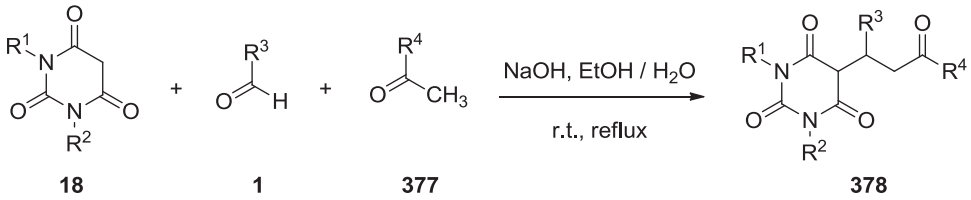
of 5- monoalkylbarbiturates (Scheme 103).[184]

From the mechanistic point of view, it is assumed that initially base (NaOH)-mediated aldol condensation between aldehyde and ketone provides an α,β-unsaturated ketones, which is subsequently undergoes Michael addition by barbituric acid (Scheme 104).[184]

A domino Heck-aza-Michael sequential three-component reaction leading to the synthesis of functionalized benzisothiazoline-3-acetic acid 1,1-dioxides **385** was achieved in a one-pot manner. By combination of sequential Heck-aza-Michael reaction initially, functionalized benzylsulfonamides is assembled which is then subjected to Pd-mediated domino Heck reaction in an operationally direct fashion (Scheme 105).[185]

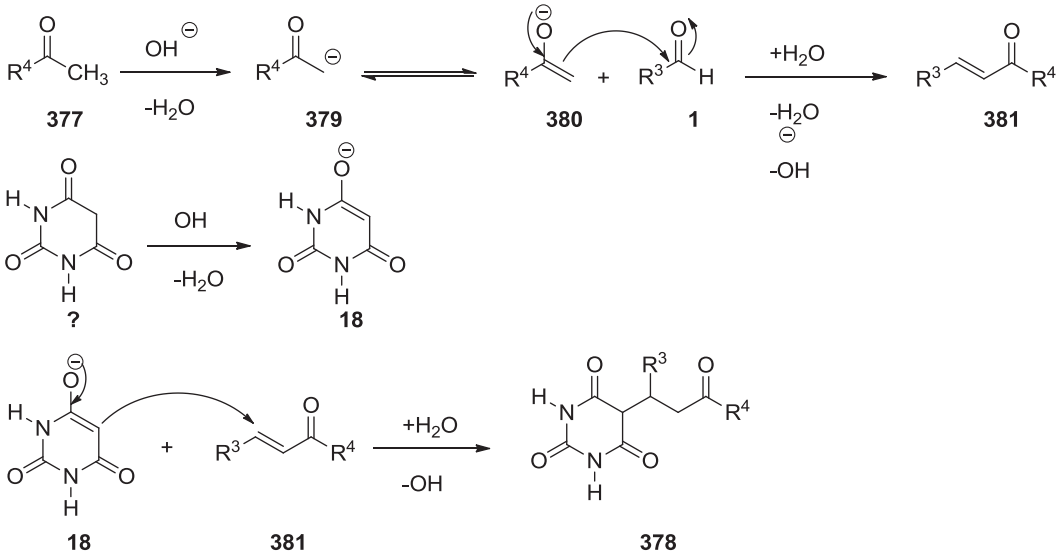
A small proof of concept expressive library by employing the Heck-aza-Michael strategy was created for 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides and its derivatives **385**.[186] Based on this concept, the utilization of a domino, Heck-aza-Michael strategy in the synthesis of three combinatorial. Sub-libraries using a range of reaction podiums was established and reported. In addition, a wider variety of coupling partners was employed to give the final structural divergence around the central core. Generally, the utilization of a domino Heck-aza-Michael reaction caused the fast combination of functionality through the operation of the three distinct components, permitting to design a library of various drug-like small molecules (Scheme 106).[185]

A domino Heck-aza-Michael sequential reaction was developed for a one-pot reaction in 2011 by Pfeffer and co-workers.[187] Initially the reaction between acryloyl chloride and an amine provided an appropriate electron-deficient alkene generated which then subjected to domino Heck–aza-Michael process to give a several C1-acetamide tetrahydroisoquinolines. As a matter of fact, this reaction was known as the first example of a domino Heck-aza-Michael sequential reaction permitting an electron-deficient terminal

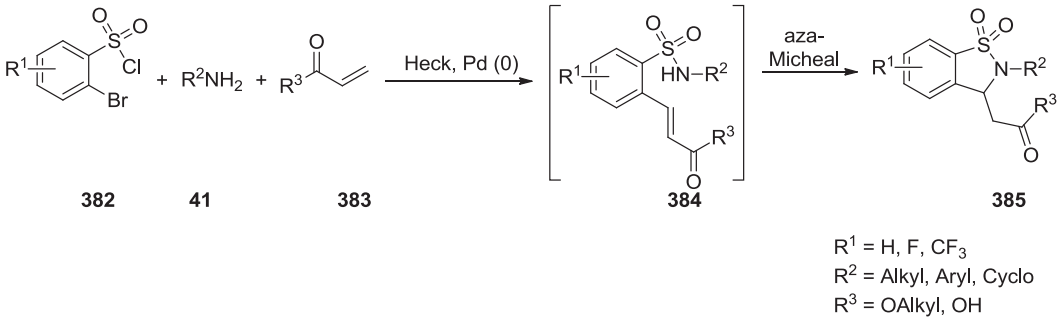



**378a**: R$^1$ = H, R$^2$ = H, R$^3$ = C$_6$H$_5$, R$^4$ = C$_6$H$_5$, yield = 85%
**378b**: R$^1$ = H, R$^2$ = H, R$^3$ = 3-CH$_3$OC$_6$H$_4$, R$^4$ = C$_6$H$_5$, yield = 85%
**378c**: R$^1$ = H, R$^2$ = H, R$^3$ = 4-ClC$_6$H$_4$, R$^4$ = C$_6$H$_5$, yield = 87%
**378d**: R$^1$ = H, R$^2$ = H, R$^3$ = thiophene, R$^4$ = C$_6$H$_5$, yield = 82%
**378e**: R$^1$ = H, R$^2$ = H, R$^3$ = butane, R$^4$ = C$_6$H$_5$, yield = 71%
**378f**: R$^1$ = H, R$^2$ = H, R$^3$ = C$_6$H$_5$, R$^4$ = CH$_3$, yield = 93%
**378g**: R$^1$ = H, R$^2$ = H, R$^3$ = 2-ClC$_6$H$_4$, R$^4$ = CH$_3$, yield = 87%
**378h**: R$^1$ = H, R$^2$ = H, R$^3$ = 2-CH$_3$OC$_6$H$_4$, R$^4$ = CH$_3$, yield = 80%
**378i**: R$^1$ = H, R$^2$ = H, R$^3$ = 3-FC$_6$H$_4$, R$^4$ = CH$_3$, yield = 87%
**378j**: R$^1$ = H, R$^2$ = H, R$^3$ = 4-NO$_2$C$_6$H$_4$, R$^4$ = CH$_3$, yield = 90%

**Scheme 103.** MCR for the synthesis of 5-monoalkylbarbiturates **378**.




**Scheme 104.** Possible reaction mechanism for the synthesis of 5-monoalkylbarbiturates **378**.

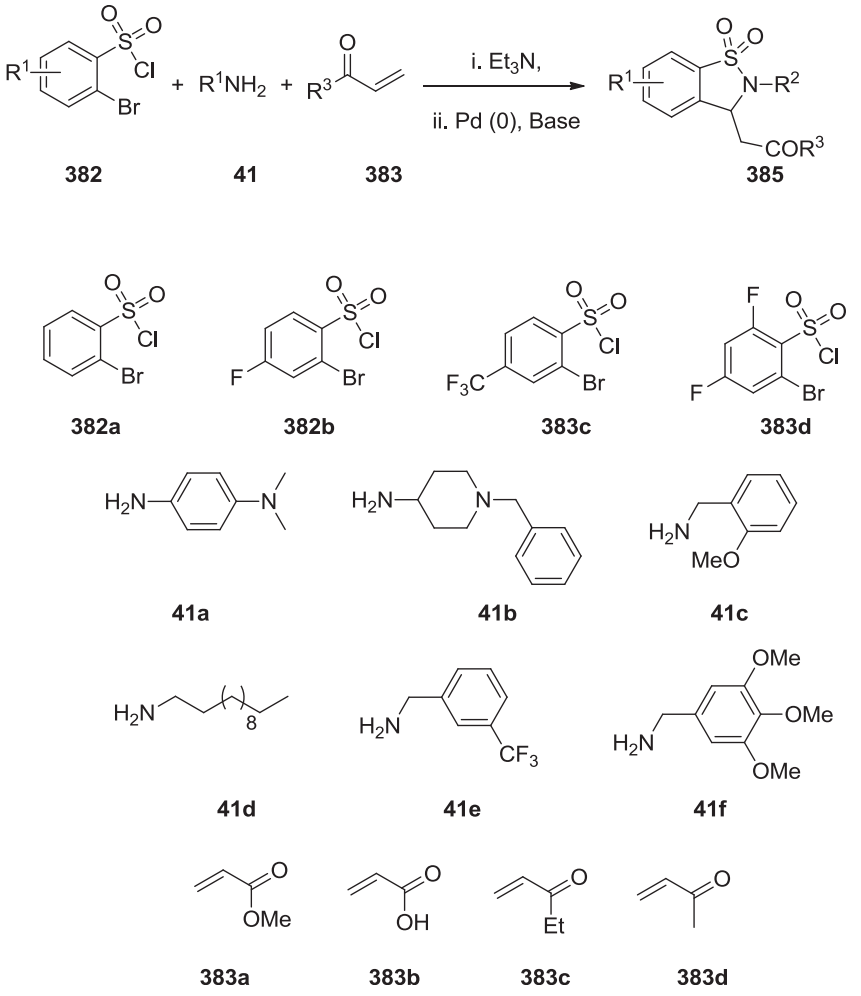



**Scheme 105.** Sequential three-component domino Heck-aza-Micheal for the synthesis of functionalized benzisothiazoline-3-acetic acid 1,1-dioxides **385**.

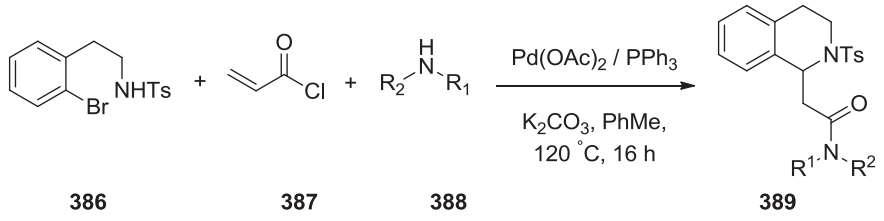
alkene being conveniently entered in a reaction performed in a one-pot manner. This MCR reaction was proven to be reasonably general concerning the substrate scope. A wide variety of primary and secondary amines were examined resulting in the formation of functionalized tetrahydroisoquinolines, in modest to excellent yields (28–97%). As it can be realized if this one-pot sequential reaction, employed in a medicinal chemistry, the background would simplify the fast creation of compound libraries.[187] Using this approach tetrahydroisoquinolines **389** were prepared through the reaction of 2-bromophenethylamine **386** with commercially available acrylates utilizing either the $Pd(OAc)_2/PPh_3$ or the $Pd(OAc)_2$/DavePhos in the presence of $K_2CO_3$ in toluene. This method permitted for the combination of different functionalities at R involving ester, cyano group and ketone; nevertheless, neither the reaction with acrylic acid nor acrylamide was acquiescent (most probably because of the occurrence of deprotonation under the reaction conditions) Since the formation of tetrahydroisoquinolines having C1-acetamide functionality is a usually desirable, it was thought worthwhile to modify the original domino sequential reaction. Thus, a three-component domino Heck-aza-Michael sequential reaction, which will provide a fast and effective access to C1-functionalized tetrahydroisoquinolines was designed. Primary or secondary amines **388** as nucleophiles were added to acryloyl chloride **387**, before the above-mentioned domino reaction would give a wide variety of acrylamides. Since for the formation of acrylamide a similar moderate basic conditions were required for both the Heck and aza-Michael steps in this sequential one-pot three-component reaction, acylation in this domino Heck-aza-Michael reaction for the synthesis of tetrahydroisoquinolines was quite possible (Scheme 107).[187]

Unpredictably, by mixing bicyclopropylidene **390**, iodobenzene (**391**-Ph) and methyl acrylate **392a**, the best yields for the sequential Heck/Diels-Alder products **394** were obtained achieved *via* the Jeffery reaction [$Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN].[188] By increasing and using high concentration of all reactants to 4 folds, in the presence of 1 mol% of precatalyst almost quantitative yields for **391a**-Ph are obtained. Therefore, the tetra substituted alkene **390** is more quickly carbopalladated than even methyl acrylate, which is realized being especially good substrate in Heck cross coupling reactions. This high reactivity of **390** is attributed to its unique nucleophilicity,[189] which make the facile attack of the electrophilic organopalladium species. Nevertheless, just the trans-spiro[2.5]oct-4-ene-7,8-dicarboxylate **394f**-Ph was formed and isolated from the one-pot Heck/Diels-Alder reaction of bicyclopropylidene **390** and phenyl iodide (**391**-Ph) with dimethyl *cis*-but-2-ene-1,4-dioate (dimethyl maleate) **392b** *via* Heck as well as Jeffery reactions (Schemes 108 and 109).[190]

Upon treatment of 1,4-diiodobenzene **408** with bicyclopropylidene **390** and a dienophile **392**, in the presence of the Pd catalyst as catalyst products **409** of a double Heck/Diels-Alder reaction in moderate yields. Worthy to mention when the aforementioned reaction was performed under high pressure the yield of compound



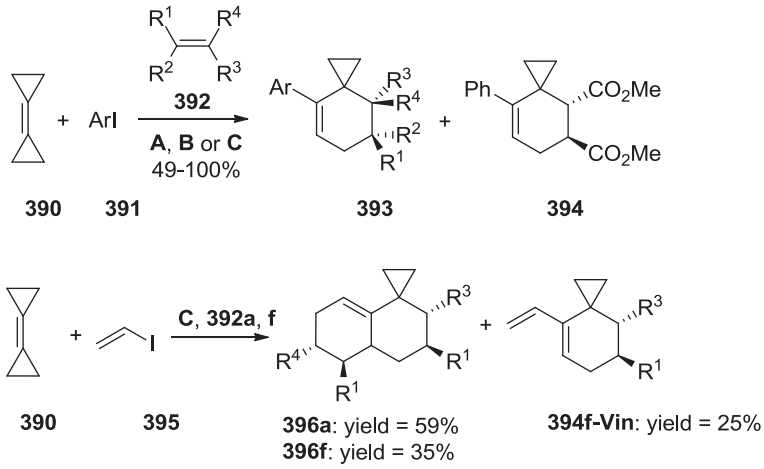

**Scheme 106.** Heck-aza-Michael reaction for the synthesis of 1,2-benzisothiazoline-3-acetic acid 1,1-dioxides and its derivatives **385**.




**Scheme 107.** Synthesis of tetrahydroisoquinolines **389**.

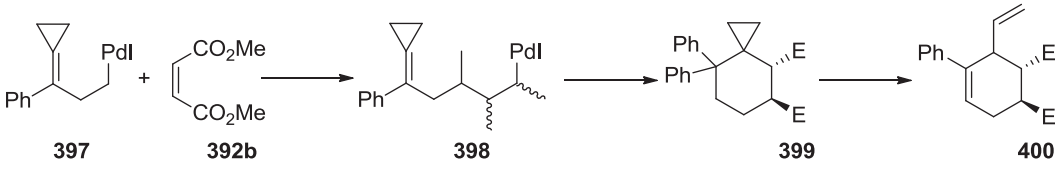
**409** was increased to 87%. Conducting the reaction at lower concentrations of the starting materials completed to the mono-coupling-cycloaddition giving 18-$C_6H_4I$ mainly as well as just tiny amounts of **409**. Unpredictably, the product **409** a was constructed as a sole diastereomer, by analysis of its X-ray crystal structure.[191] Interestingly, even the crude product exhibited just a single set of signals in the 13C NMR spectrum, showing the high purity of compound **409a** (Schemes 110–112).

1,1-Bicyclopropylidene **390** has a highly strained structure. Due to this structure, this alkene is highly reactive, undergoing different chemical conversion, easily.[192] It is remarkable that **390**, dissimilar to most other tetra substituted alkenes, shows higher reactivity in Heck reactions.[193,194] Carbopalladation of **390** proceeded more smoothly or even more rapidly than that of alkyl acrylates that allows for the conduction of MCR sequential reactions involving compounds **390** and an acrylate with in a Pd-precatalyzed one-pot reaction.[193,194] Therefore, a divergent sequential Heck/Diels-Alder reaction of **390** gave differently substituted spiro[2.5]octenes.[190] Under the conditions of Heck cross coupling reaction [Pd-$(OAc)_2$, $PPh_3$, triethylamine, dimethylformamide] or another name reaction so-called Jeffery reaction[195] [$Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN] bicyclopropylidene initially was subjected into carbopalladation with an initial formation of arylpalladium halide resulted in the formation of an intermediate **416** bearing a (cyclopropylmethyl) palladium halide scaffold. The latter was rapidly submitted into a homoallylpalladium halide **417** rearrangement followed by removal of $\beta$-hydride affording an allylidenecyclopropane derivative of type **418**, that instantaneously reacted with a dienophile **419** present in

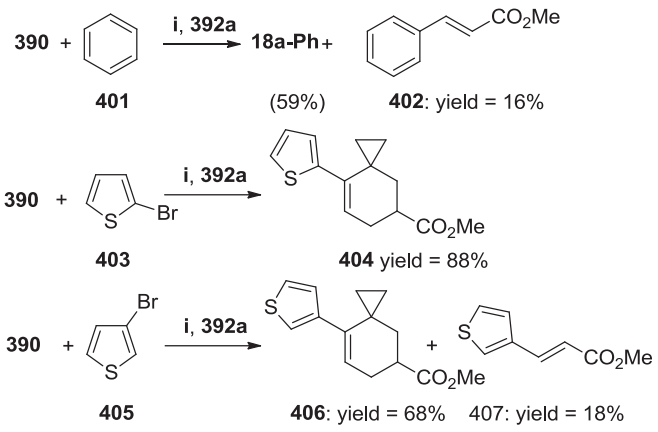



**A**: $CDCl_3$ ,12 h; **B**: $Pd(OAc)_2$ , $PPh_3$, $C_6D_6$ ; **C**: $Pd(OAc)_2$ , $PPh_3$ ,$Et_3N$, DMF

**392a**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = H$
**392b**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = H$, $R^4 = CO_2Me$
**392c**: $R^1 = CO_2Et$, $R^2 = H$, $R^3 = CO_2Et$, $R^4 = H$
**392d**: $R^1 = CO_2Et$, $R^2 = H$, $R^3 = H$, $R^4 = H$
**392e**: $R^1 = CO_2tBu$, $R^2 = H$, $R^3 = H$, $R^4 = H$
**392f**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = CO_2Me$, $R^4 = H$
**392g**: $R^1 = CO_2NH_2$, $R^2 = H$, $R^3 = H$, $R^4 = H$
**392h**: $R^1 = CO_2Me$, $R^2 = Me$, $R^3 = H$, $R^4 = H$
**392i**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Me$, $R^4 = H$
**392j**: $R^1 = CO_2Me$, $R^2 = H$, $R^3 = Ph$, $R^4 = H$
**392k**: $R^1 = CH_2CO_2Me$, $R^2 = CO_2Me$, $R^3 = H$, $R^4 = H$




**Scheme 108.** Three-component reactions with bicyclopropylidene **390**.



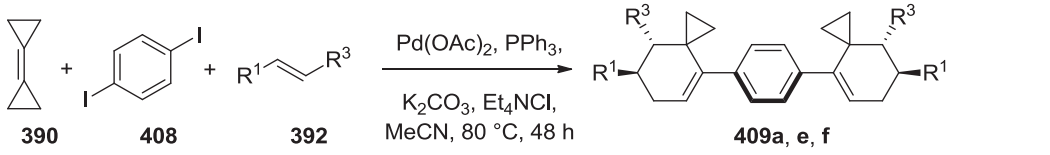

**i**: $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN, 80 °C.

**Scheme 109.** Heck- Diels-Alder reactions of bicyclopropylidene **390** with bromoarenes and methyl acrylate **392a**.

the reaction mixture to yield a spiro[2.5]octene derivative **420** (Scheme 113).[190]

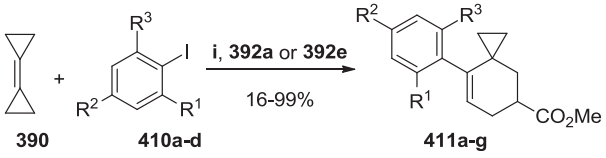
Sequential reactions of the functionalized bicyclopropylidenes **421a** and **421b,** phenyl iodide **391** and *tert*-butyl acrylate **422** gave *tert*-butyl 4-phenylspiro[2.5]oct-4-ene-7-carboxylate **424** in 49 and 25% yield, respectively. Although, a presence of mixtures of the spirooctenes *syn*/*anti*-(*E*)-**423c**, **d** and/or *syn*/*anti*-(*Z*)-**423c**, **d** were observed in the $^1H$ NMR spectra of the residue obtained from reaction mixture, these other compounds could not be isolated, thus their exact configurations as well as their yields could not be determined (Scheme 114).[196]

An efficient and one-pot synthesis of biaryls **426** was achieved *via* sequential Suzuki cross coupling reaction/Knoevenagel condensation of bromobenzaldehyde and phenylboronic acid in the along with activated methylene compounds in aqueous isopropyl alcohol at ambient temperature. Importantly, this protocol gave a straightforward and effective methodology for construction of original biaryls in which a new carbon double bond attached to activated groups such as cyano, ester and amide is generated from three commercially available or easily accessible compounds in a one-pot fashion. The generality and scope of this approach was




**409a**: $R^1$ = $CO_2Me$, $R^3$ = H, yield = 64%
**409e**: $R^1$ = $CO_2tBu$, $R^3$ = H, yield = 69%
**409f**: $R^1$ = $CO_2Me$, $R^3$ = $CO_2Me$, yield = 54%

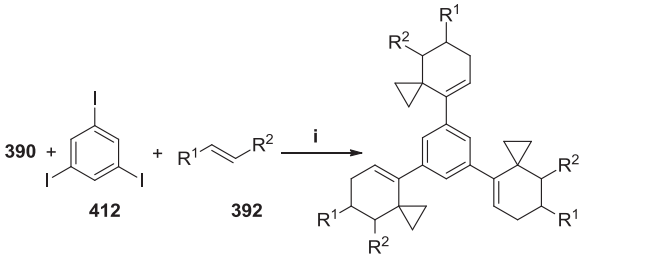
**Scheme 110.** Two-fold Heck-Diels-alder reaction of bicyclopropylidene **390** with 1,4-diiodobenzene **408**.



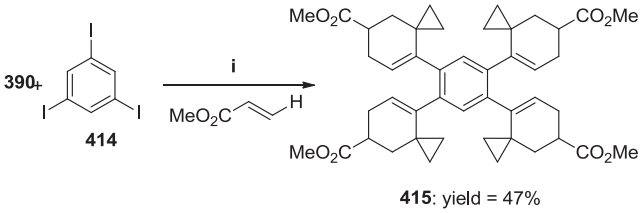

**i**: $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN, 80 °C, 48 h

**411a**: $R^1$ = Me, $R^2$ = H, $R^3$ = H, with **392a**, yield = 99%, *syn*/*anti* = 2:1
**411b**: $R^1$ = Me, $R^2$ = H, $R^3$ = H, with **392e**, yield = 76%, *syn*/*anti* = 3:1
**411c**: $R^1$ = Bn, $R^2$ = H, $R^3$ = H, with **392a**, yield = 85%, *syn*/*anti* = 2:1
**411d**: $R^1$ = Bn, $R^2$ = H, $R^3$ = H, with **392e**, yield = 39%, *syn*/*anti* = 3:1
**411e**: $R^1$ = Me, $R^2$ = Me, $R^3$ = H, with **392a**, yield = 98%, *syn*/*anti* = 2.5:1
**411f**: $R^1$ = Me, $R^2$ = Me, $R^3$ = H, with **392e**, yield = 16%, *syn*/*anti* = 2.7:1
**411g**: $R^1$ = Me, $R^2$ = H, $R^3$ = Me, with **392a**, yield = 56%, *syn*/*anti* = -

**Scheme 111.** Heck- Diels-Alder reactions of **390** with substituted iodoarenes **410** and methyl **392a** or *tert*-butyl acrylate **392e**.




**413a**: $R^1$ = $CO_2Me$, $R^2$ = H, yield = 73%
**413e**: $R^1$ = $CO_2tBu$, $R^2$ = H, yield = 60%
**413f**: $R^1$ = $CO_2Me$, $R^2$ = $CO_2Me$, yield = 57%




**415**: yield = 47%

**i**: $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN, 80 °C, 48 h

**Scheme 112.** Multicomponent domino reactions of **390** with 1,3,5-triiodobenzene **412** as well as 1,2,4,5-tetraiodobenzene **414** and dienophiles **392**.

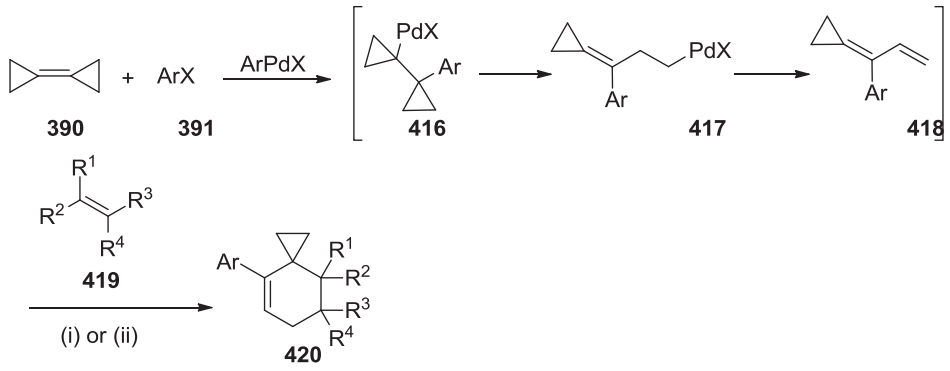
investigated with the reaction of 4-bromobenzaldehyde **1** with differently arylboronic acids **425** and activated methylene compounds **3** under the aforementioned optimal conditions. In most cases, satisfactory yields along with good selectivity were obtained. Worthy to mention when the more active malononitrile used higher yields were obtained in comparison of those if ethyl cyanoacetate, methyl cyanoacetate, and cyanoacetamide were employed (Scheme 115).[197]

The MCR of unsymmetrically-substituted stilbenes was accomplished *via* sequential Hiyama/Heck reaction between *p*-iodonitrobenzene, triethoxy(vinyl)silane, and differently substituted aryl iodides in one-pot manner. Under obtained optimal reaction conditions, a double Heck/Hiyama-Heck reactions were fruitfully accomplished in one-pot fashion. Delightfully, a three-component synthesis of unsymmetrical stilbenes from triethoxy(vinyl)-silane and two differently aromatic iodides was achieved in a one-pot fashion in satisfactory yields. By controlling the experimental parameters, it was suggested that the Hiyama reaction with 1-iodo-4-methoxybenzene or 1-iodo-4-fluorobenzene occurs first which followed by Heck reaction of 1-iodo-4-nitrobenzene with the resulting *p*-substituted styrene (Scheme 116).[198]

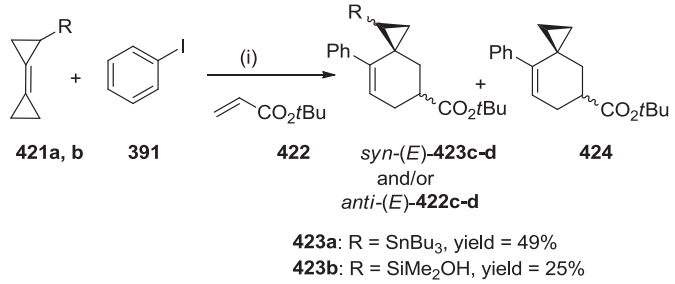
Synthesis of a library of structurally diverse alkynyl/alkenyl-substituted pyridine derivatives **431** were achieved and established through heterocyclization followed by Pd-catalyzed structural expansion under Sonogashira/Heck coupling reactions in a one-pot manner. Significantly, the Heck cross coupling reaction with terminal alkenes occurs regioselectively with exclusive generation of the *E*-isomers. A series of 2-amino-4-(3/2-(alkynyl)/3-(alkenyl)phenyl)-6-phenylnicotinonitriles **431** were synthesized in pure form and in good to excellent isolated yields by MCR (five component) of bromobenzaldehyde **1**, malononitrile **3a**, acetophenone **3**, $NH_4OAc$ and several terminal alkynes/alkenes mediated by pyrrolidine and Pd as catalysts in a refluxing mixture of $H_2O$-DME (1:4 ratio) in a one-pot fashion. The Heck cross coupling reaction with terminal olefins occurs regioselectively to obtain *E*-isomers as sole products. As a matter of fact, this efficient MCR protocol opens novel gateways in the development of a) diversity-oriented novel cyano pyridine based compound library and novel chemical moieties other than the previously reported compounds (Scheme 117).[199]

MCR using boron substituted 1,3-dienes have attracted much attention of synthetic organic chemist and being used as powerful tools in organic synthesis. Norsikian, Beau and co-workers reported an efficient MCR sequential reaction involving the combination of the Petasis reaction/intramolecular [4 + 2]-cycloaddition/cross metathesis/Michael reaction. This process resulted in to polycyclic heterocyclic framework **438** with good yields and complete stereoselectivity (Scheme 118).[200,201]

A series of prevailing, reliable, and selective MCRs for the fast preparation of new compounds and combinatorial libraries *via* organo/CuI-mediated [4 + 2] and [3 + 2] cycloaddition were designed and conducted in 2004 by Barbas and co-workers.[202] The most popular approach of these kindsis“organo-click chemistry,”




**Scheme 113.** Three-component domino Heck-Diels-Alder reaction involving bicyclopropylidene **390** an aryl halide **391** and a dienophile **419**.



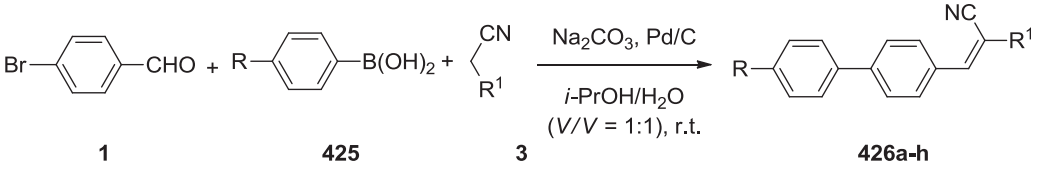

**Scheme 114.** Three-component domino Heck-Diels-Alder reactions involving mono-substituted bicyclopropylidenes **421a** and **421b**, iodobenzene **391** and *tert*-butyl acrylate **422**.

which introduced by K. B. Sharpless et al., which initiated the strategies so called click reaction.[203] Superlatively, catalyzed and especially organocatalyzed MCRs justify all crucial aspects and is usage of click chemistry.

For example a series of complex polycyclic compounds were synthesized *via* asymmetric design and installation of simple substrates such as acetone or phosphorane, two different aldehydes, and 1,3-cyclic diketones in the presence of organoamine catalyst. This reaction proceeds *via* aldol-condensation/Knoevenagel/Diels-Alder reaction, Wittig/Knoevenagel/Diels-Alder reaction, Wittig/Michael and Knoevenagel/Michael reaction sequences in one-pot manner.

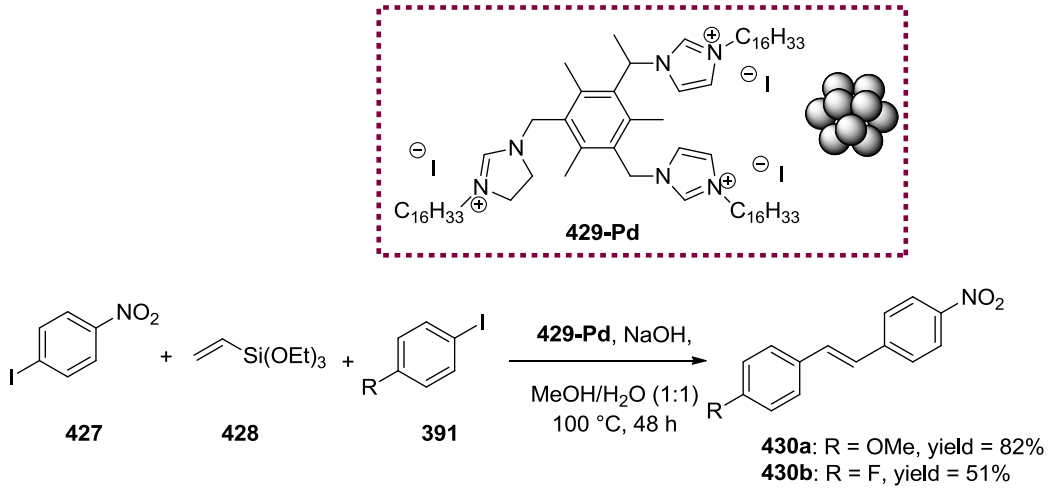
Both diene and dienophiles concurrently were prepared under very mild and ecologically benign conditions, therefore affording the ingredients for a stereocontrolled Diels-Alder reaction that gives compounds **445** to **449**. An attempt for the organocatalyzed, stereospecific asymmetric installation of polysubstituted 1,4-disubstituted 1,2,3-triazoles **448**, dispiro[5.2.5.2]hexadecanes **447**, spiro(cyclohexane-1,2′-indan)-triones **446**, spiro[5.5]undecanes **445**, simple substrates in one-pot fashion, was made. Dispirolactones **447** are biological active molecules showing antioxidant and radical trapping qualities[204] and substituted 1,2,3-triazoles **449** showed multiple applications in chemistry, biology as well as materials science.[204]An efficient technique for the synthesis of both chiral isomers of spirotriones **445** that includes an easy change in the order of addition of the reactants rather than a change in catalyst.

Amino acids and amines can catalyze the sequential aldol condensation of an aldehyde with acetone(with phosphorane in Wittig reaction) to afford *trans*-enone **441** (diene source). Knoevenagel condensation of an aldehyde with 1,3-cyclic diketones gives arylidene–cyclic diketones (2; dienophile) that would then is

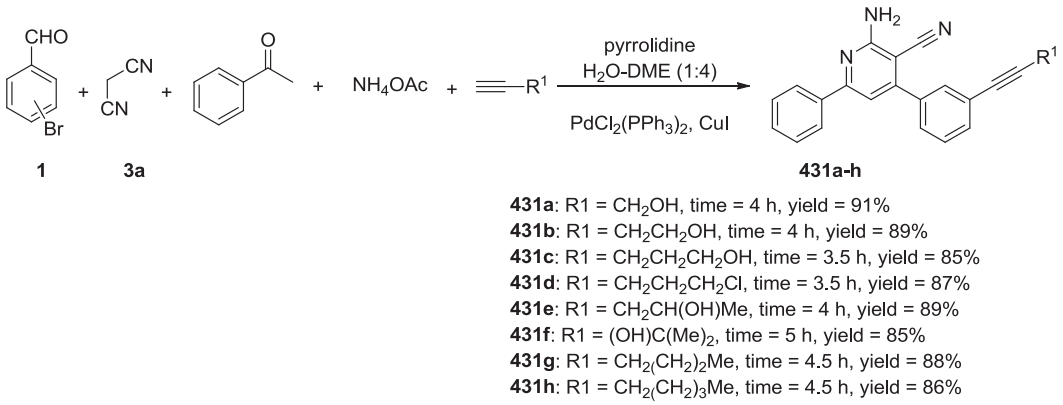



**426a**: R = OMe, $R^1$ = CN, time = 2.5 h, yield = 75%
**426b**: R = Me, $R^1$ = CN, time = 4.5 h, yield = 81%
**426c**: R = Cl, $R^1$ = CN, time = 5.5 h, yield = 84%
**426d**: R = F, $R^1$ = CN, time = 5.5 h, yield = 74%
**426e**: R = OMe, $R^1$ = $CO_2Et$, time = 3 h, yield = 45%
**426f**: R = Me, $R^1$ = $CO_2Et$, time = 5 h, yield = 57%
**426g**: R = Cl, $R^1$ = $CO_2Et$, time = 6 h, yield = 57%
**426h**: R = F, $R^1$ = $CO_2Et$, time = 6 h, yield = 39%

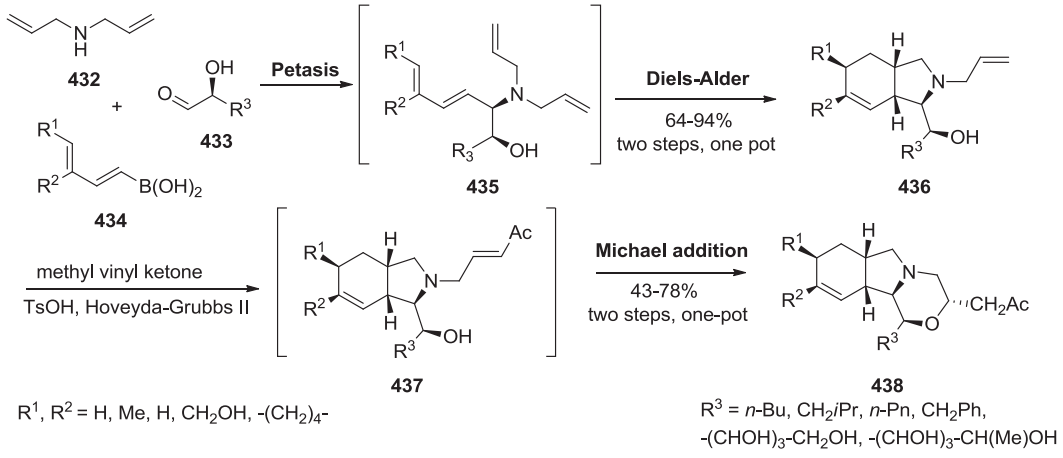
**Scheme 115.** MCR for the synthesis of biaryl derivatives **426**.




**Scheme 116.** One-pot Hiyama-Heck reactions for the synthesis of the target products **430**.




**Scheme 117.** MCR based synthesis of 2-amino-4-(3-(alkynyl)phenyl)-6-phenylnicotinonitriles **431** *via* heterocyclization followed by Sonogashira reaction.

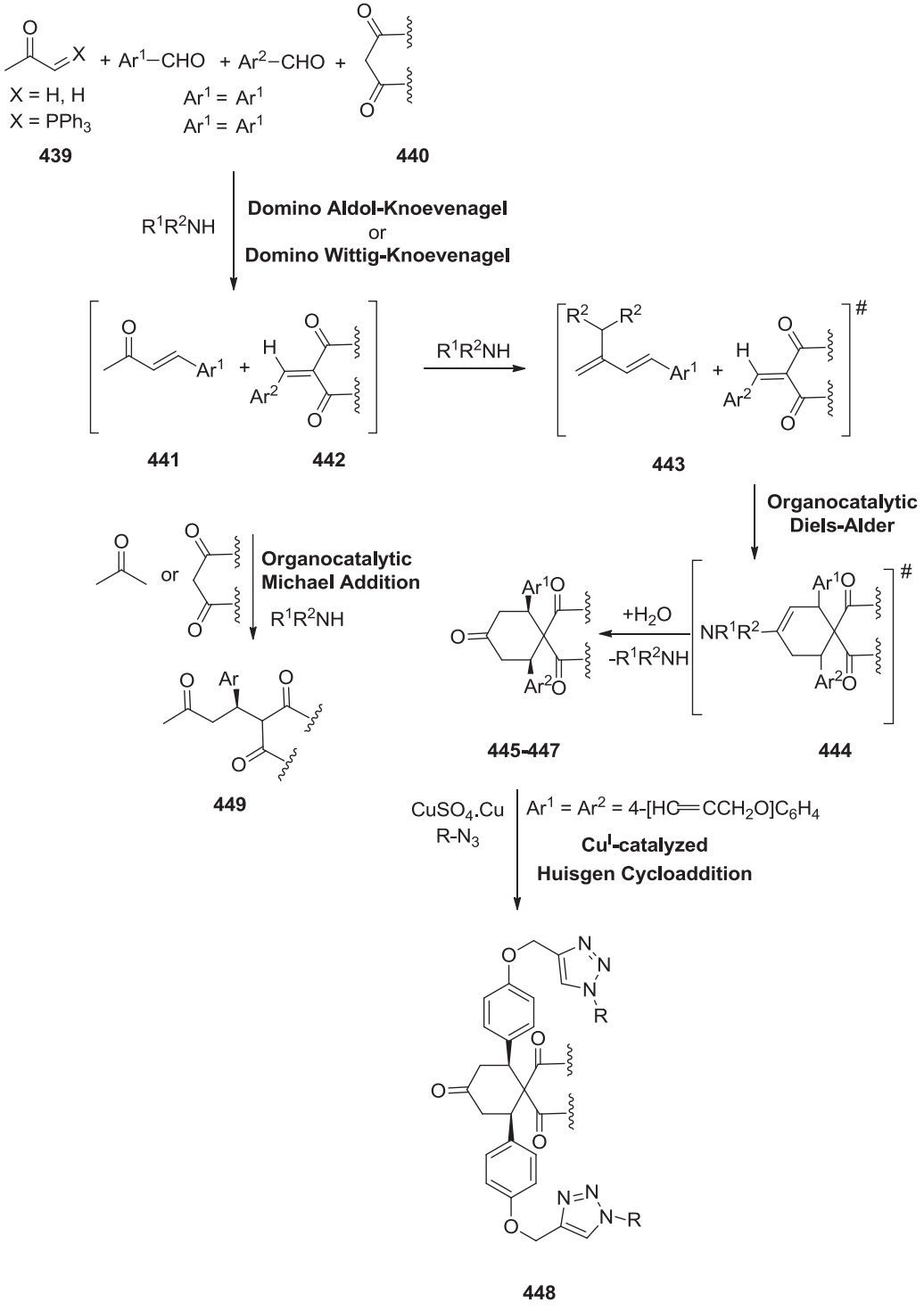



**Scheme 118.** Cascade sequence based on the Petasis borono-Mannich reaction as first key step.

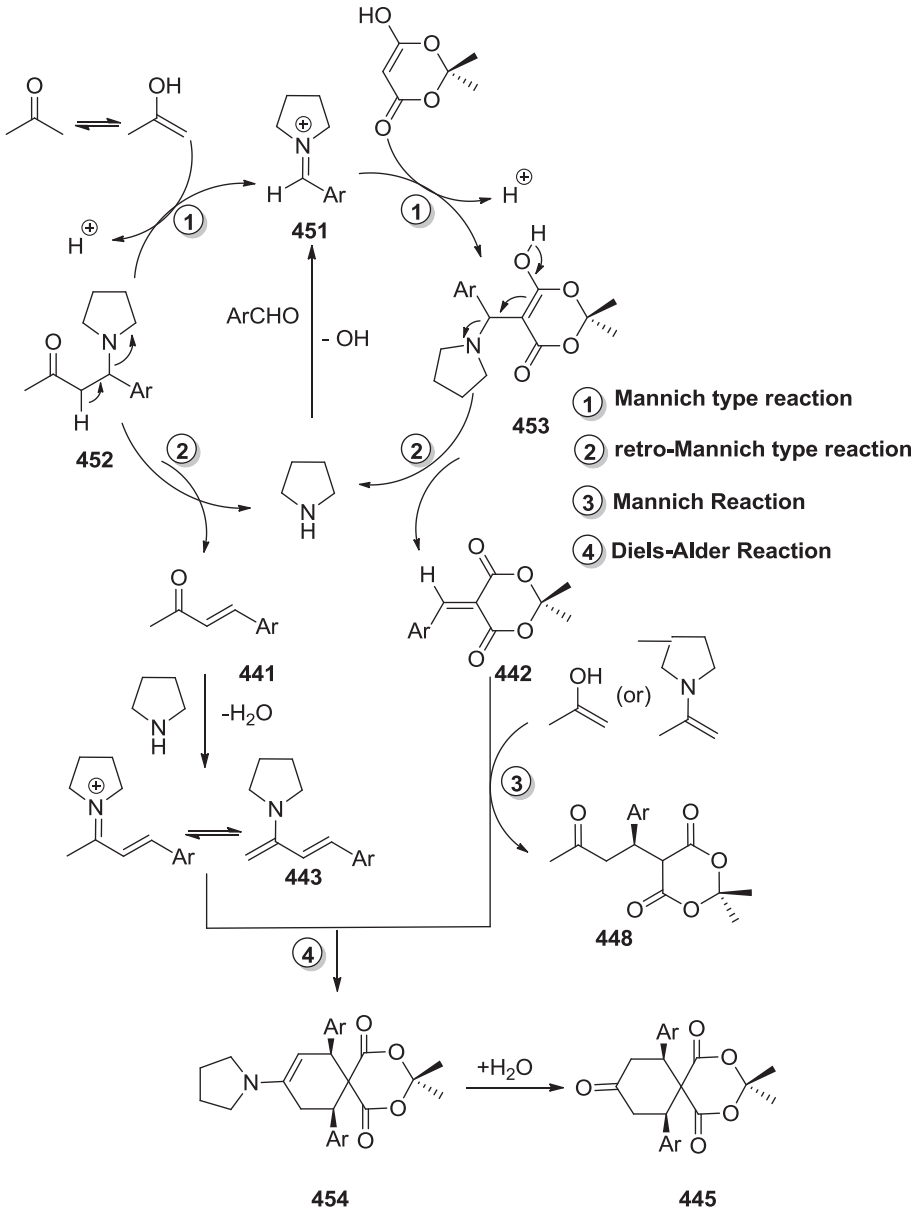
subjected to a concerted [4 + 2] cycloaddition with a 2-amino-1,3-butadiene **443**providing from in situ reaction of trans-enone **441**and amino acid or amine to give substituted spirotriones **445** to **447** in a diastereoselective fashion. Propargyl substituted spirotriones **445**–**447**are subjected into regiospecific [3 + 2] cycloaddition with azides to construct 1,2,3-triazoles **449** catalyzed by $CuSO_4$/Cu in one-pot fashion. Enones **441** and **442** were also submitted to stereoselective Michael additions with 1,3-cyclic diketones or acetone in the presence of amino acid or amine catalysis to give compounds **448**. The sequential Aldol/

Knoevenagel/Diels-Alder or Wittig/Knoevenagel/Diels-Alder and Wittig/Knoevenagel/Diels-Alder/Huisgen cycloaddition reaction would then generate a chiral center with construction of four new C–C bonds and four new C–N bonds, respectively (Scheme 119).[202]

The suggested mechanism of diastereospecific installation of *cis*-spiranes **445** and Michael adducts **448** in the MCRs involving acetone, aldehyde, and Meldrum's acid in the presence of pyrrolidine depicted in Scheme 120. Initially, pyrrolidine reacted with aldehyde producing the imine cation **451**. The latter is an excellent electrophile, which is subjected to Mannich type reactions with enolates or enamines of acetone and Meldrum's acid to create the products **452** and **453**, respectively. Retro-Mannich or base-induced removal of amino-ketones **452** and **453** under basic conditions gives *trans*-enone **441** and benzylidene-Meldrum's acid




**Scheme 119.** Suggested organo/CuI-catalytic assembly of spirotriones and spirotrione-triazoles through Wittig)/Knoevenagel/Diels-Alder and Wittig/Knoevenagel/Diels-Alder/Huisgen cycloaddition reaction sequences in one-pot.




**Scheme 120.** Suggested catalytic cycle for the simultaneous organogeneration of diene and dienophiles in pyrrolidine-mediated aldol/Knoevenagel/Diels-Alder and Knoevenagel/Michael reaction sequences in one-pot.

**442**, respectively. The latter is a reactive dienophile which is subjected to Diels-Alder or a double Michael reaction with 2-amino-1,3-butadiene **443**, as a soft base which is produced in situ from the reaction of trans-enone **441** and an amine catalyst, affording the products aldol/Knoevenagel/Diels-Alder and Knoevenagel/Michael **445**. Compound **442** can also interact with enolate (or enamine) of acetone to give Knovenegal/Michael product **448**. The ratio of sequential products **445** and **448** dependents on the electrophilicity of imine **451**, dienophile **442**, temperature the reaction is performed as well as concentration of acetone in the reaction. Creation of transenones **441** (diene source) and dienophiles **442** *via* Mannich and retro-Mannich reactions is a good proof of this hypothesis that aldol products **450** cannot be obtained during these reactions. However, the reaction with the highly reactive 4-$NO_2C_6H_4$–CHO is an exception. This proposition is also sustained by the study of pyrrolidine-mediated enal generation *via* aldehyde self-condensation.

## 3. Conclusion

In synthetic organic chemistry, a multi-component reaction (MCR), sometimes referred to as a "Multi-component Assembly Process" (MCAP), is a chemical reaction where three or more component react to form a single product. By definition, MCRs are those reactions whereby more than two reactants combine in a sequential fashion to afford highly selective products that preserve majority of the atoms of the starting material.

There are several important *name reactions* in organic chemistry. Among the tens of thousands of organic reactions that are known, hundreds of such reactions have reached such status to be named after its discoverers or developer. Some cases of reactions that were not actually discovered by their names discovers are also known.

Cascade reaction, also known as a domino reaction or cascade reaction, is a chemical process that comprises at least two consecutive reactions such that each subsequent reaction occurs

only in virtue of the chemical functionality formed in the previous step. Cascade reaction, also known as a domino reaction or cascade reaction, is a chemical process that comprises at least two consecutive reactions such that each subsequent reaction occurs only in virtue of the chemical functionality formed in the previous step.

In this review, we tried to show the importance of incorporation of name reactions in the cascade reactions leading to an ideal and practical chemical process in order to decrease the number of steps in a multi-step reaction, showing an approach towards the definition for click chemistry, being accepted ideally and practically by synthetic organic chemists. The selections of name reactions were based on general interest, recurrence in the literature, and the contributions of these name reactions in the total synthesis of natural products and synthetic complex organic molecules. Furthermore, since in virtually all of them, the chiral induction is desired, most of these reactions have favorably should have been asymmetrically synthesized. In summary, we tried to collect some sequential name reactions, which are comparable in many features and aspects with the “Click Reactions”.

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