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Design for Carbon-Carbon Bond Forming Reactions at Ambient Conditions[#]

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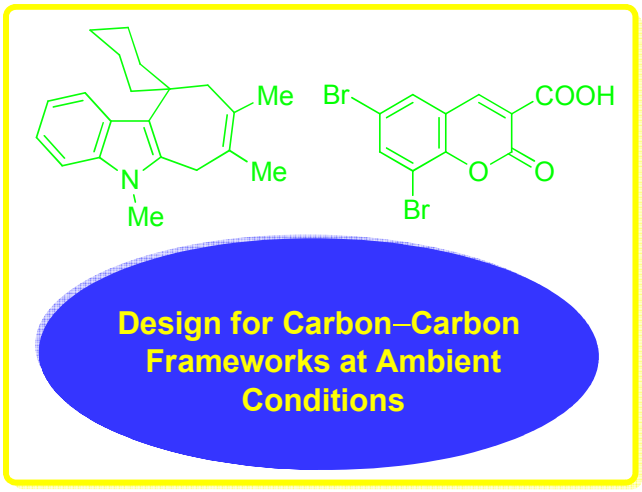
[#]This article is dedicated to Professor Srinivasan Chandrasekaran on the occasion of his 70th birthday

Abstract

Carbon-carbon (C-C) bond forms the '*backbone*' of nearly every organic molecule, and lies at the heart of the chemical sciences! This transformation has always been one of the most useful and fundamental reactions in the development of organic chemistry. Currently, the concept of '*green chemistry*' is globally acclaimed and has already advanced quite significantly to come out as a distinct branch of chemical sciences. Among the principles of '*green chemistry*', one principle is dedicated to "*design of energy efficiency*" – that is to develop synthetic strategies that require less/minimum amount of energy to carry out a specific reaction with optimum productivity. And the most effective way-out to save energy is to develop strategies/protocols that are capable enough to carry out the transformations at ambient temperature and pressure! As part of on-going developments on green synthetic strategies, designing for reactions under ambient conditions coupled with other green aspects is, thus, an area of current choice. This review is aimed to offer an up-to-date development on the design of carbon-carbon bond forming protocols to access a wide variety of organic molecules of topical significance under ambient conditions. The account highlights on the brilliant applications of reaction conditions such as the use of solvents or no solvent, catalysts or no catalyst, and the use of green tools like ball-milling, ultrasonication and visible light in achieving the goal!



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1. INTRODUCTION

Carbon-carbon (C-C) bond formation is the basis for the biogenesis of nature's essential molecules and C-C bond forms the '*backbone*' of nearly every organic molecule. Hence, it lies at the heart of the chemical sciences and is regarded as the key transformation in organic synthesis to set up the carbon backbone of organic molecules.[1] Currently, a plethora of organic compounds are known that find a wide range of applications as fine chemicals, medicinal and pharmaceutical agents, agrochemicals, and many others.[2-16] In the development of organic chemistry, the carbon-carbon bond formation has always been one of the most useful and fundamental reactions, and as a result, there is an ever-growing of methods for carbon-carbon bond formation.[17-28]

With the advent of the 21st century, the public is equally aware of the hazardous substances used and generated by chemical processes, and eventually the concept of '*green and sustainable chemistry*' has evolved.[29-34] The main essence of this concept is to develop a sustainable chemical enterprise that will find creative ways to minimize human exposure to, and the environmental impact of, harmful chemicals while enhancing scientific progress. Current trends of green chemistry practice encompass a number of agenda, such as the avoidance of extensive use of toxic and hazardous reagents and solvents, harsh reaction conditions, and expensive and sophisticated catalysts.[35-40] The last decade has seen a tremendous effort toward savings in energy consumption, use of eco-friendly catalysts and solvents, proficiency in atom economy, and minimization of wastes from reactions in order to design novel green synthetic protocols for organic compounds of interest.[41] Among various energy-efficient processes, the most effective way to save energy is to develop strategies/protocols that are capable enough to carry out the transformations at ambient temperature. Designing reactions under ambient conditions coupled with other green aspects is, thus, a current area of emphasis.[42] The concept of developing reaction strategies at ambient conditions is now an emerging field of research in organic chemistry and is progressing considerably. The purpose of this review is to offer an up-to-date development of carbon-carbon bond forming reactions of topical significance under ambient temperature and pressure. However, no results of any spectroscopic or analytical techniques are supplemented as they are very adequately defined in the original papers and are out of the scope of this article.

2. CARBON-CARBON BOND FORMING REACTIONS AT AMBIENT CONDITIONS

2.1. Carbon-carbon bond forming reactions in solvent medium

This section covers carbon-carbon bond forming reactions occurring in various solvent media under ambient conditions.

2.1.1. Carbon-carbon bond forming reactions in water

The increasing need for more sustainable strategies in organic synthesis has led to a growing interest in the use of water and other nonclassical solvents. In general water is now regarded a

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'*green solvent*' for organic reactions, and a huge number of chemical reactions performed ''*in*- or *on*-*water*'' conditions are known.[43-55] Water is the solvent of choice not only from an environmental standpoint but also from an economic point of view since it is cheap, non-flammable, and abundantly available.[56-59] First reports on the successful use of water as a solvent in organic synthesis are associated with Diels-Alder reactions.[60,61] Although water suffers from certain limiting issues, particularly the low solubility of organic reactants in aqueous medium that generally leads to immiscible and/or biphasic reaction mixtures, still water is the best choice to the organic chemists in present time, and several endeavors have been made to address and solve these issues by designing protocols based on the use of microwaves, ultrasound or pressure reactors, and using other benign (co)solvents.[62-79] Water behaves differently from other commonly used organic solvents in terms of its unique and unusual physical properties such as high surface tension, high dielectric constant, high specific heat, large cohesive energy density and also chemical properties, particularly its amphoteric nature and the ability to form hydrogen bonds.[80,81] Moreover, hydrophobic interactions offered by water molecules with organic reactants sometimes facilitate certain organic processes.[82,83] The present section focuses on both the catalyst-free and catalyst-promoted organic transformations involving C-C bond formation in water.

2.1.1.1. Under catalyst-free conditions

Role of catalysts in organic synthesis is obvious and thus they find huge applications and uses. Efforts have been made to reduce toxicity level of catalysts by multidirectional modifications, but the most fruitful way is to design an organic reaction without catalyst(s), if feasible! If this important achievement can be coupled with energy consideration, one of the most alarming issues in the 21st Century, then it would be the great as far green chemistry practice and sustainability are concerned. Recently, research endeavors directed toward catalyst-free reactions have been the subject of numerous studies.[84-87] This sub-section summarizes catalyst-free C-C bond forming reactions in aqueous media occurring at room temperature and pressure as reported over the last decade.

2.1.1.1.1. Condensation-addition reaction

Knoevenagel condensation and Michael addition are the fundamental reactions in forming C-C bonds in organic synthesis. A catalyst-free tandem Knoevenagel condensation and Michael addition in water was reported by Yu et al.[88] to synthesize a wide range of substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes **3** from the reaction of aldehydes (**1**) with cyclic-1,3-diketones (**2**) at room temperature (Scheme 1). Tetraketonic derivatives (**3**) are key intermediates for the preparation of diverse biologically relevant heterocycles such as xanthendiones, acridindiones and 4*H*-1-benzopyrans;[89-91] in addition such compounds are also reported to possess tyrosinase inhibitory properties.[92]

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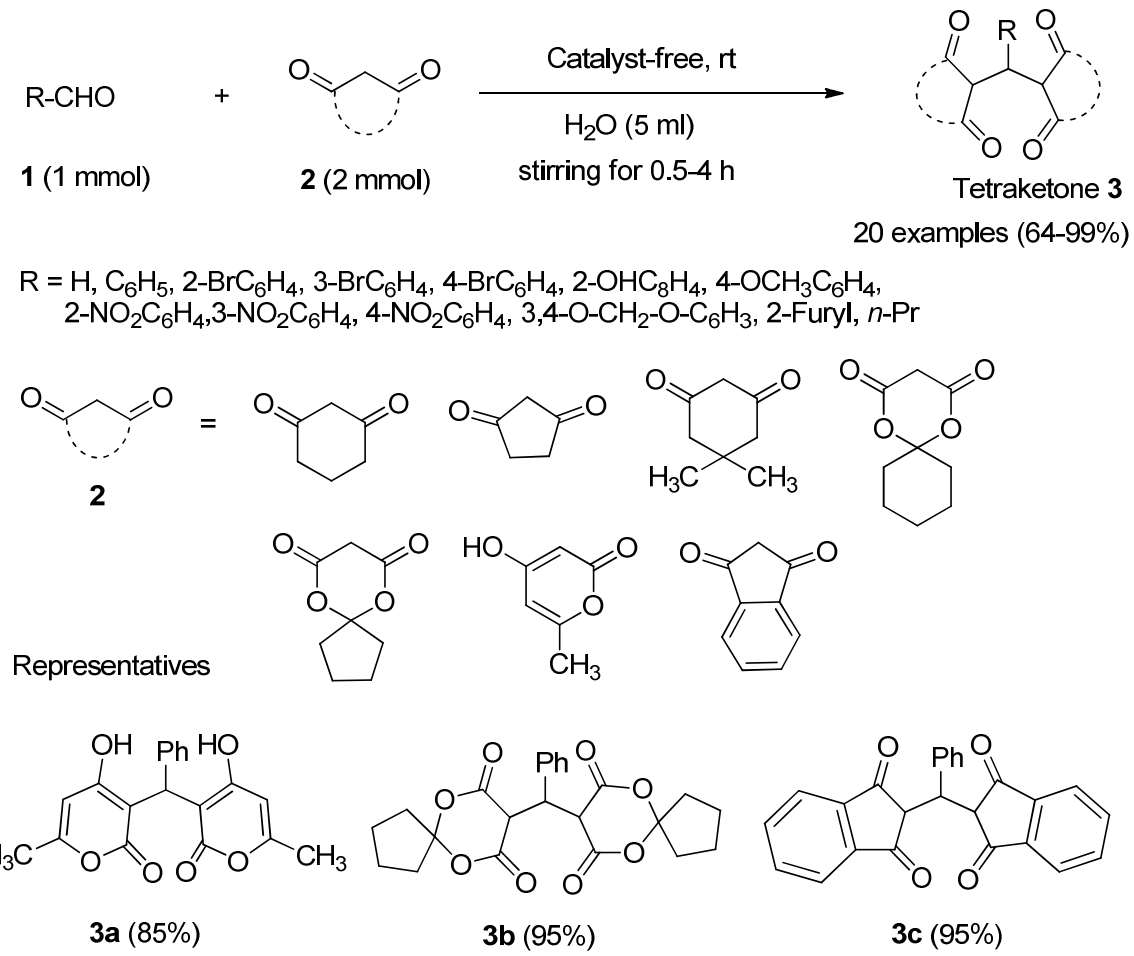

Scheme 1: Synthesis of substituted *bis*(6-amino-1,3-dimethyluracil-5-yl)methanes **3**

In addition to acting as a solvent, water is also supposed to promote enolization process of 1,3-diketone (**2**) through hydrogen bonding with enolic OH, thereby enhancing the nucleophilic character of methylene carbon of this C-H activated acid.[88] Besides, water also increases the electrophilic character of the carbonyl carbon reacting with aldehyde **1** by forming hydrogen bonds with the carbonyl oxygen. A tandem Knoevenagel condensation and Michael addition ultimately affords the desired tetraketone **3** (Scheme 2).[88]

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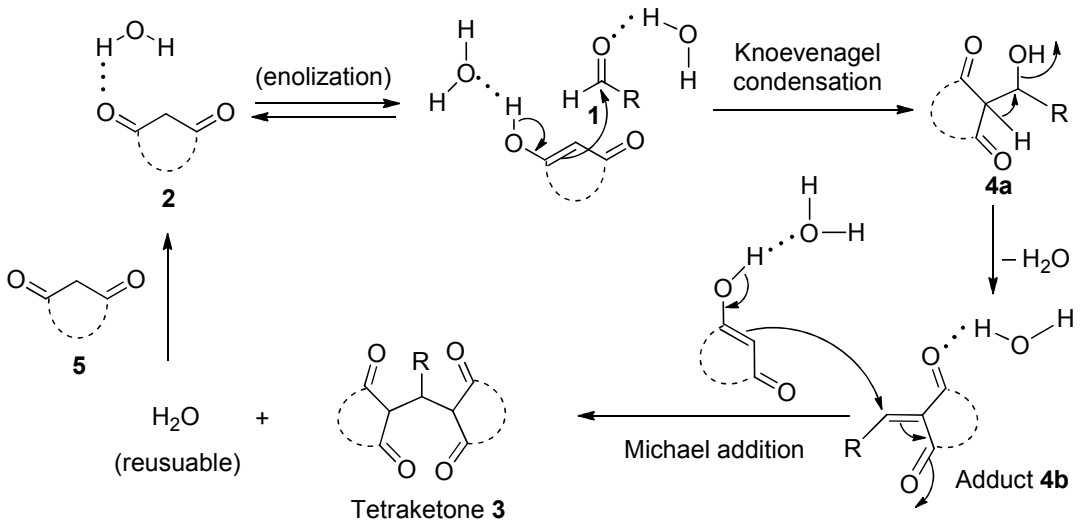
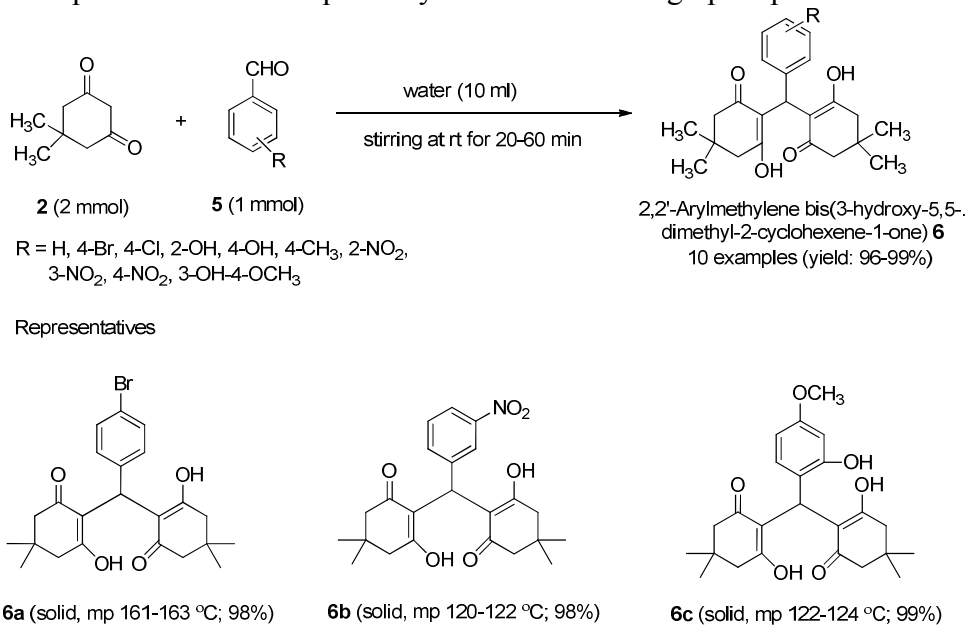


Scheme 2: Plausible mechanism for the one-pot synthesis of tetraketonic derivatives (**3**)

There are several reports available in literature for the efficient synthesis of tetraketones most of which suffer from the use of catalysts, surfactants, and aqueous organic solvent as co-solvent.[89,92,93] Conversely, the present catalyst-free protocol developed by Yu et al. is not only eco-friendly and high yielding but operationally simple and highly efficient in pure water just at ambient temperature.

Bayat et al.[94] developed an efficient protocol for the synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives (**6**) from the reaction of dimedone (**2**) with various aromatic aldehydes (**5**) in water at room temperature (Scheme 3). The work-up procedure is simple and does not require any column chromatographic purification.



Scheme 3. One-pot synthesis of 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **6**

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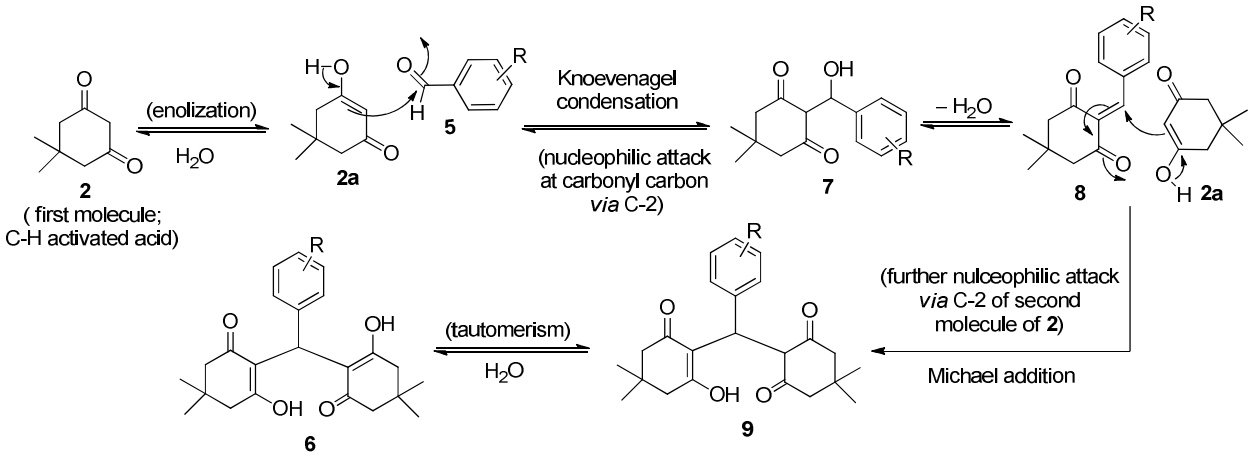
The authors proposed a plausible mechanism for this transformation (Scheme 4).[94] A first molecule of dimedone (**2**) undergoes enolizaton in water medium and the enolized species (**2a**) participates in Knoevenagel condensation with aldehyde **5** generating an intermediate **7**. Enolized form of a second molecule of dimedone thereafter undergoes Michael addition with the intermediate **7** through nucleophilic attack, followed by tautomerisation to afford the desired product **6**.



Scheme 4. Proposed mechanism for the one-pot synthesis of derivatives **6**

2.1.1.1.2 C-C coupling *via* nucleophilic substitution reaction

A catalyst-free 'on-water' direct C-C coupling *via* nucleophilic substitution reaction between indoles (**10**) and 1,4-benzoquinones (**11**) affording both 3-indolyl-1,4-benzoquinones (**13**) and bis(indolyl)-1,4-benzoquinones (**14**) at room temperature was developed by Li and his group (Scheme 5).[95] 3-Indolylquinones, particularly bis(indolyl)quinones, constitute an important structural unit in many natural products with biological and pharmaceutical properties including antitumor, anti-HIV and antidiabetic activities.[96-101]

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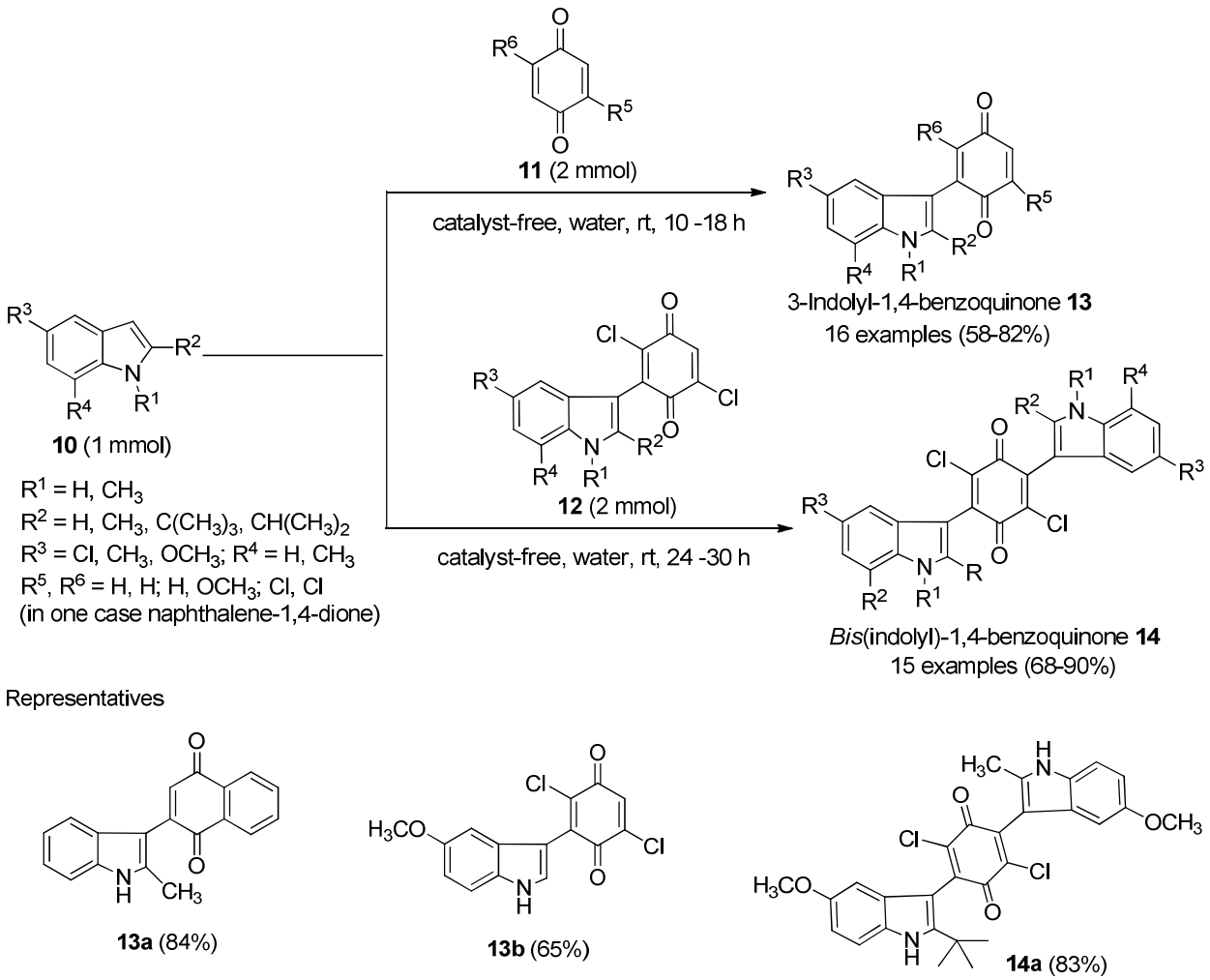

Scheme 5. One-pot synthesis of 3-indolylyquinones and bis(indolyl)-1,4-quinones

2.1.1.1.3 C-C coupling *via* nucleophilic addition

Thakur and Meshram demonstrated an "on water" C-C coupling involving nucleophilic addition of thiazolidinediones (**16**) or oxindoles (**18**) with isatins (**15**) for the diastereoselective synthesis of a novel class of diverse 3-(thiazolidinedione or oxindole)-substituted-3-hydroxy-2-oxindole scaffolds (**17** and **19**) without the aid of catalyst and column chromatographic purification just at room temperature (Scheme 6).[102] A variety of functionalized isatins as well as thiazolidinedione and oxindole derivatives underwent the reaction smoothly with excellent yields from readily available starting materials. 3-(Thiazolidinedione or oxindole) substituted-3-hydroxy-2-oxindole frameworks are regarded as key structural motifs in a large array of alkaloid class of natural products with diverse biological activities such as antioxidant, anticancer, anti-HIV and neuroprotective properties,[103-110] and compounds bearing such a structural motif are widely used as targets for drug design.[111-113]

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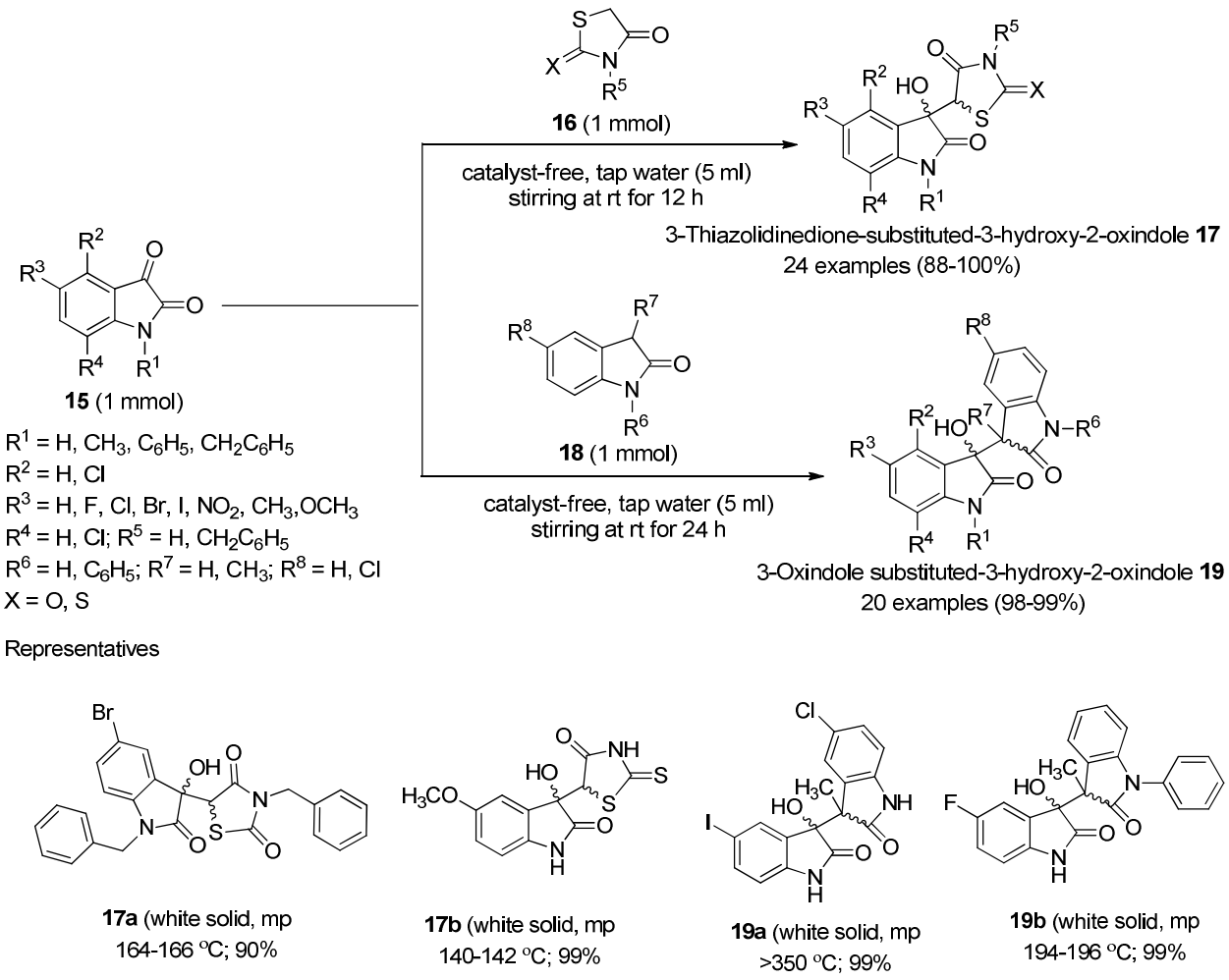

Scheme 6: Synthesis of 3-thiazolidinedione-/3-oxindole-substituted-3-hydroxy-2-oxindoles (**17**/**19**)

The same group of investigators reported in the same year another efficient synthesis of a novel class of diverse 3-(2-pyrazolin-5-one)-substituted-3-hydroxy-2-oxindole scaffolds **21** from the reaction of isatins (**15**) with 2-pyrazolin-5-one derivatives (**20**) following a catalyst-free method at room temperature (Scheme 7).[114] No column chromatographic purification was required in this process.

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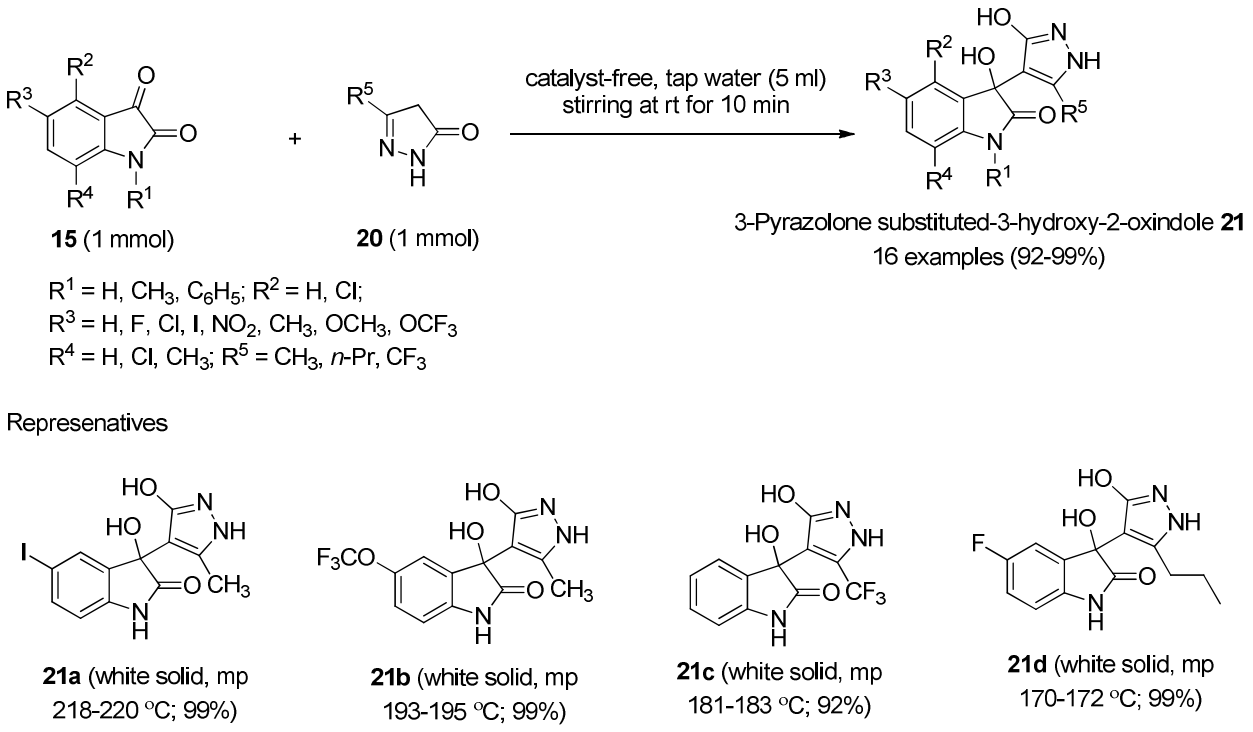
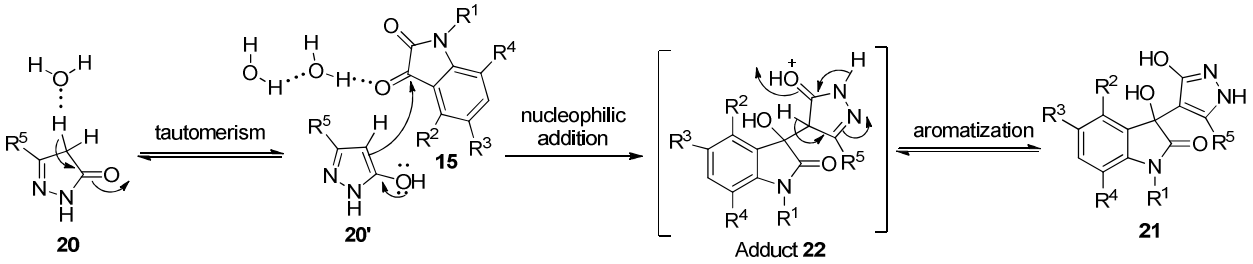


Scheme 7: Synthesis of 3-pyrazolone-substituted-3-hydroxy-2-oxindoles (**21**)

As proposed by the authors, 3-substituted-2-pyrazolin-5-one (**20**) first undergoes tautomerization under the influence of water and the resulting tautomer **20′** then takes part in nucleophilic addition-type reaction with isatin **15** to form the adduct **22**, followed by its aromatization to furnish the desired product **21** (Scheme 8).



Scheme 8: Proposed mechanism for the one-pot synthesis of derivative **21**

In another report, Olyaei et al.[115] described the synthesis of a series of *N*-heteroaryl α-arylglycines (**25**) from the one-pot three-component condensation reaction β-naphthols (**22**), glyoxalic acid (**23**) and heteroaryl amines (**24**) in water at ambient temperature in the absence of any catalyst with moderate to high yields (Scheme 9). From their experimental observations, the investigators also assumed that 2-naphthol undergoes nucleophilic addition with the iminoacid generated *in situ* from a condensation reaction between amine and glyoxalic acid affording the desired α-naphthylglycine compound. Both C-C and C-N bond formations took place in this transformation.

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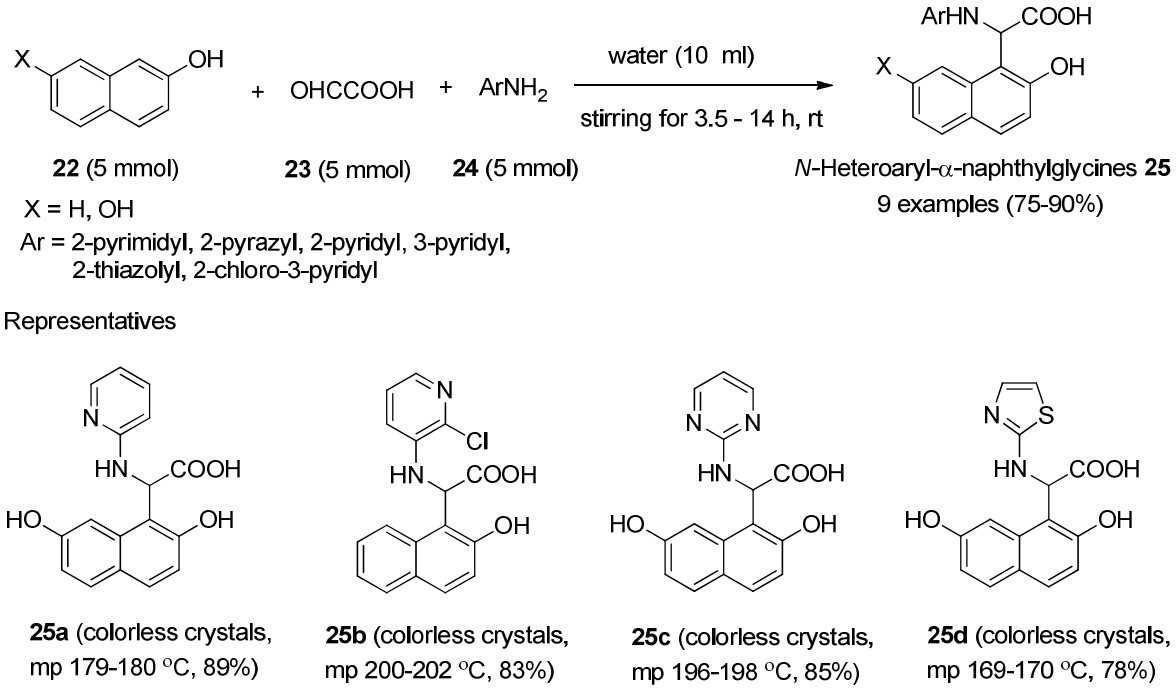

Scheme 9: One-pot synthesis of *N*-heteroaryl α-naphthylglycines **25**

Strecker synthesis of α-aminonitriles follows similar kind of strategy; such organic compounds are regarded as possible prebiotic precursors to porphyrins, corrins, nicotinic acids, and nucleic acids,[116] and find immense applications in the synthesis of a wide range of pharmaceutically relevant natural and unnatural molecules of interest.[117] α-Aminonitriles are the key precursors of diverse α-amino acids for synthesizing proteins,[118] and also as chiral building blocks in pharmaceutical industries.[119] A catalyst-free protocol for the synthesis of racemic α-aminonitriles (**29**) from the reactions of varying carbonyl compounds (**26**), amines (**27**), and acetone cyanohydrin (**28**) *via* one-pot Strecker reaction in water was reported by Galletti *et al.* (Scheme 10).[120] A good number of entries were found to proceed very efficiently at ambient conditions with high selectivity. Moreover, the mild reaction conditions and the operational simplicity of this atom-economic cyanation process offer a possibility for the large-scale syntheses of pharmaceutically important natural and synthetic α-amino acids in a cost-effective, cleaner and environmentally friendlier alternative.

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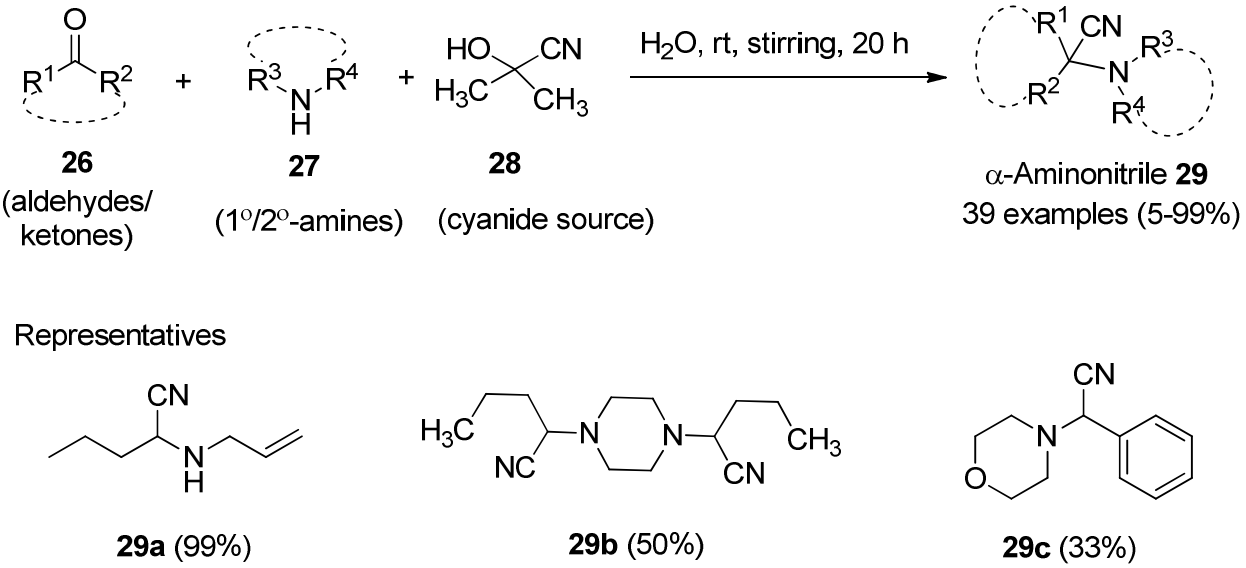

Scheme 10: Three-component Strecker synthesis of α-aminonitriles **29**

Both aliphatic and aromatic aldehydes, and cyclic ketones, in combination with primary and secondary amines were shown to undergo smooth reaction. In some cases, pure α-amino nitriles can be obtained just by direct separation from water. An unusual application of the Strecker reaction to 1,2-diamines to obtain 1,2-diamino nitriles, and to cyclic secondary amines was also reported. However, dialkyl and alkyl aryl ketones practically did not undergo this reaction; in contrast cyclic ketones afforded excellent yields, which is in accordance to the difference in the reactivity and internal strain effect (I-strain) of linear versus cyclic ketones in nucleophilic addition reactions.[120]

2.1.1.1.4 Catalyst-free one-pot multicomponent reactions

In recent past, several catalyst-free multicomponent reactions occurring at ambient conditions were reported so as to design one-pot synthesis of biologically relevant organic scaffolds, and these transformations involve formation of both carbon-carbon and carbon-heteroatom bonds. Such a novel one-pot eco-friendly protocol for the synthesis of 4,5-disubstituted 2-benzazepine derivatives **32** in water under catalyst-free conditions from a domino reaction between 4-chloro-3-formyl coumarin (**30**) and benzyl amines (**31**) at room temperature was demonstrated by Kumar and his group (Scheme 11).[121] Both C-C and C-N bonds are formed in this transformation. Benzazepine is a fused *N*-heterocyclic moiety present as a key structural fragment in various biologically active natural and synthetic molecules.[122-128]

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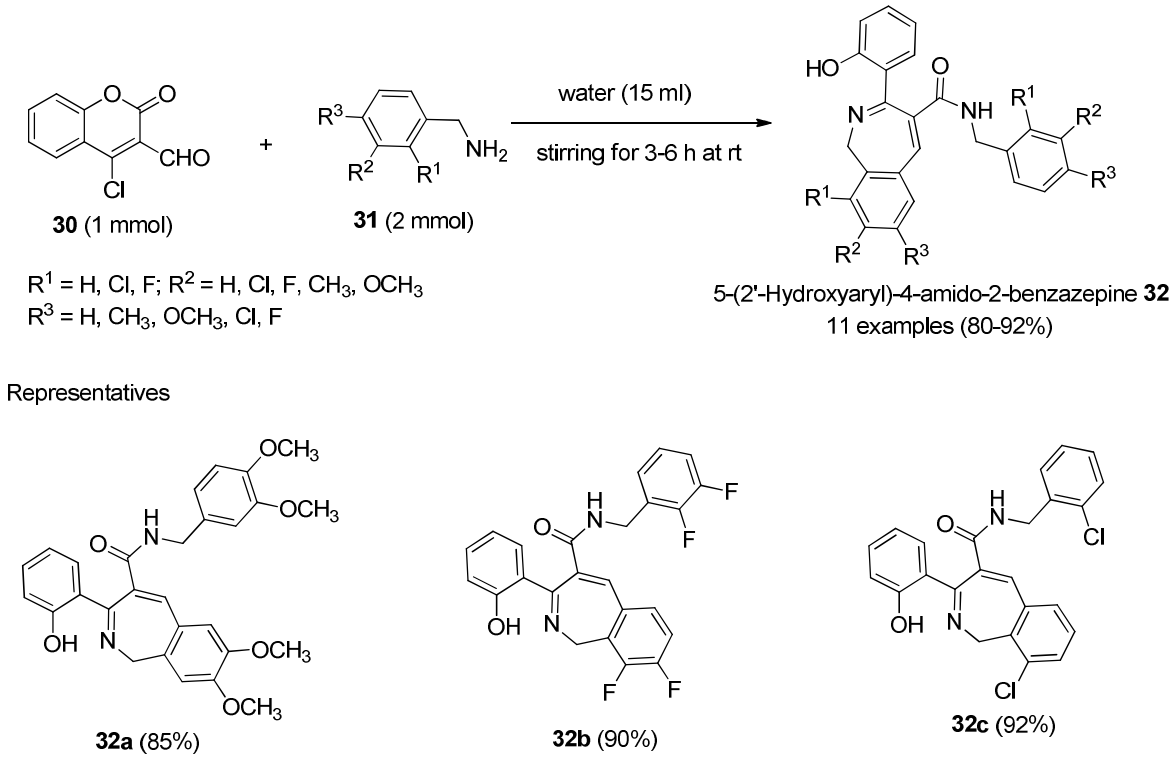

Scheme 11: One-pot synthesis of 4,5-disubstituted 2-benzazepines (**32**)

The investigators proposed a plausible mechanism for the synthesis of 4,5-disubstituted 2-benzazepine (**32**) out of domino reaction of 4-chloro-3-formyl coumarin (**30**) with benzyl amines (**31**) as outlined in Scheme 12. The method does not involve complicated work-up procedures and avoids the use of organic solvents as well. In addition, the investigators also attempted a mixed substrate combination (use of two different benzyl amines) in one exemplary case with a hope to broadening the scope of the reaction to achieve higher product diversity and they became successful in their attempt.

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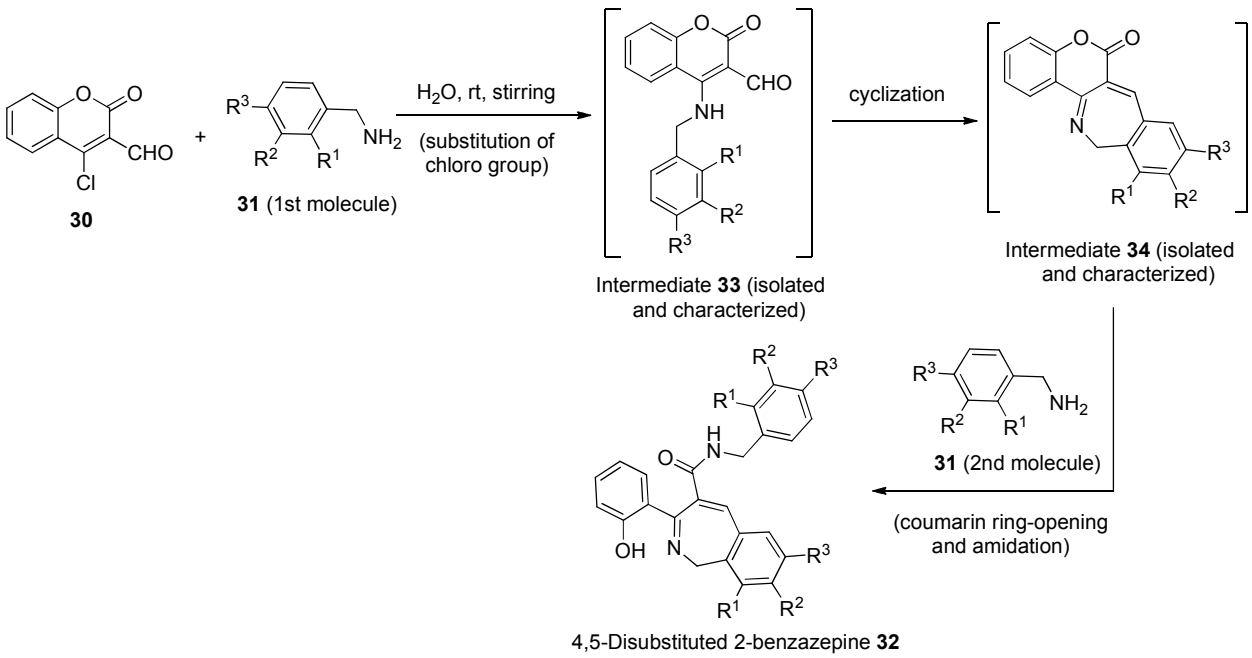
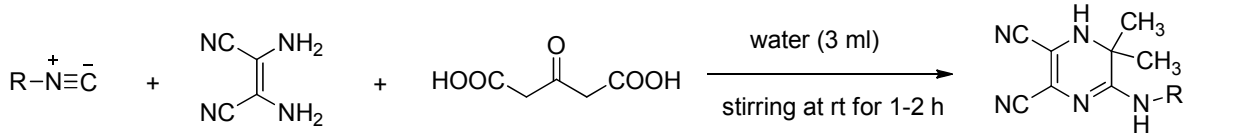


Scheme 12: Plausible mechanism for the construction of substituted 2-benzazepines **32**

Quinoxalines and their derivatives are an important class of benzoheterocycles exhibiting a broad spectrum of biological activities[129-137] and also found applications as dyes[138,139] and as building blocks in the synthesis of organic semiconductors.[140,141] In 2012, Shaabani et al.[142] developed a novel and efficient one-pot multicomponent reaction for the synthesis of 1,6-dihydro-6,6-dimethylpyrazine-2,3-dicarbonitriles (**38**) from the reaction between alkyl or aryl isocyanides (**35**), 2,3-diaminomaleonitrile (**36**) and 3-oxopentanedioic acid (**37**) at room temperature (Scheme 13). The transformation involves formation of both C-C and C-N bonds.

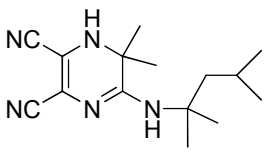


35 (1 mmol) **36** (1 mmol) **37** (1.1 mmol)

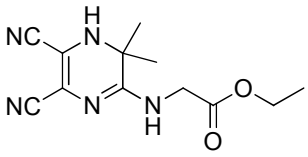
1,6-Dihydropyrazine-2,3-dicarbonitrile **38**
6 examples (75-90%)

R = *c*-C_6H_{11}, ^{t}Bu, $CH_2C_6H_5$, 2,6-di-CH_3-C_6H_3, $CH_2COOC_2H_5$

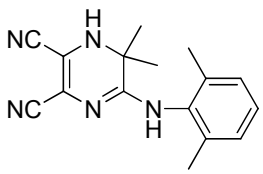
Representatives



38a (white powder, mp 149-151 ^{o}C; 80%)



38b (colorless crystals, mp 190-192 ^{o}C; 78%)



38c (colorless crystals, mp 260-262 ^{o}C; 75%)

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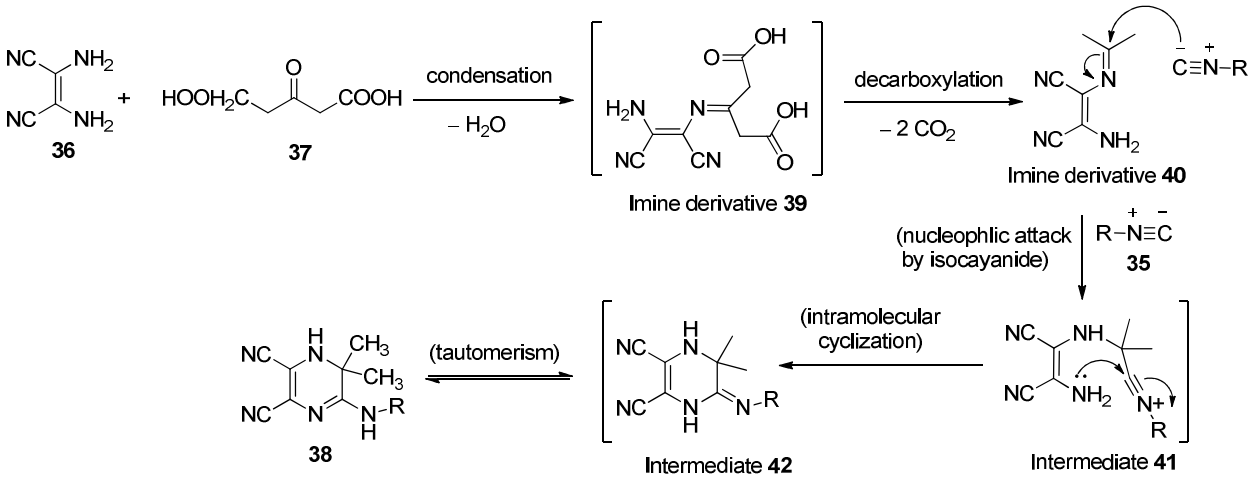
Scheme 13: One-pot three-component synthesis of 1,6-dihydropyrazine-2,3-dicarbonitriles (**38**)

A possible mechanism for the formation of product **38** was suggested by the authors (Scheme 14). Initially, there occurs a condensation reaction between 2,3-diaminomaleonitrile (**36**) and 3-oxopentanedioic acid (**37**) to form an imine derivative **39** which immediately undergoes decarboxylation leading to the formation of another imine derivative **40**. In the next step, an intermediate **41** is produced by a nucleophilic attack of isocyanide **35** on **40**, followed by an intramolecular nucleophilic attack by the -NH_2 group at the activated nitrile moiety to give intermediate **42**. Finally, imine-enamine tautomerization of intermediate **42** affords the 1,6-dihydropyrazine-2,3-dicarbonitrile derivative **38**. Easy reaction set-up, easy work-up procedure, catalyst-free and mild reaction conditions, no column chromatographic purification, high yields are the notable features of this present protocol; however, the investigators synthesized just six compounds of this series. Scope of this present protocol should be explored.



Scheme 14. Plausible mechanism for the synthesis of 1,6-dihydropyrazine-2,3-dicarbonitrile **38**

Ramazani et al.[143] reported an operationally simple, mild and water-mediated synthesis of highly functionalized γ-iminolactone derivatives (**45**) *via* one-pot three-component reaction of alkyl isocyanides (**35**), dialkyl acetylenedicarboxylates (**43**) and phenacyl halides (**44**) at room temperature (Scheme 15). This transformation involves both C-C and C-O bond formations. In their report, the authors discussed that syntheses of such heterocyclic compounds were accomplished previously using various catalysts. Besides, this present protocol offers other significant advantages such as operational simplicity, mild reaction conditions, enhanced rates, ease of isolation of products, cleaner reaction profiles, and water as solvent.

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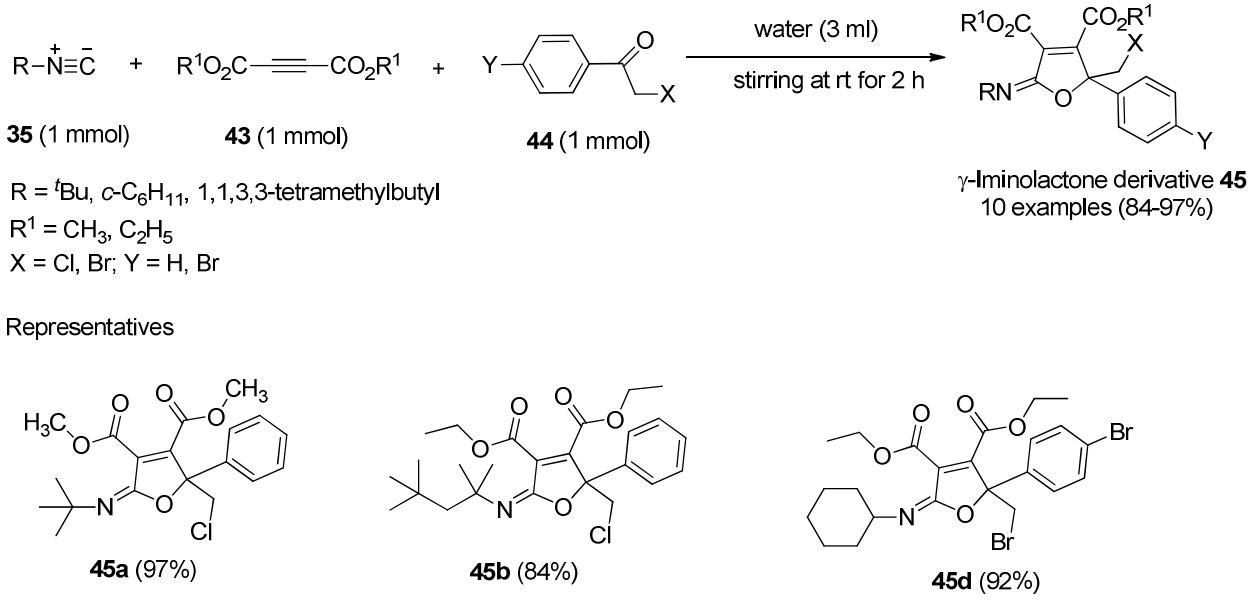
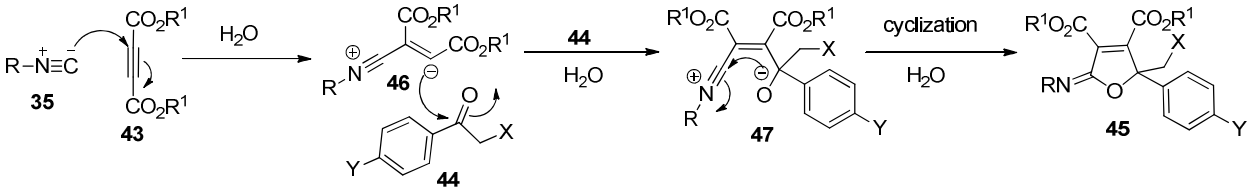


Scheme 15: Synthesis of functionalized γ-iminolactones

The authors proposed a plausible mechanism for the condensation reaction (Scheme 16).[143] Initially, a zwitterionic species (**46**) is formed from the reaction between isocyanide **35** and dialkyl carboxylate **43**. In the next step, the carbanion part of this zwitterion intermediate attacks the electron-deficient carbonyl carbon of phenacyl halide **44**, leading to a dipolar species **47**. Cyclization of **47** eventually yields the γ-iminolactone **45**.



Scheme 16: Plausible mechanism for the synthesis of γ-iminolactones (**45**)

The quinoline scaffold is prevalent in a variety of pharmacologically active synthetic and natural compounds,[144] and are historically among the most important antimalarial drugs ever used.[145] Taran et al.[146] developed an efficient one-pot three-component synthesis of novel α-(acyloxy)- α-(quinolin-4-yl)acetamides (**50**) from the reaction of isocyanides (**35**), quinoline-4-carbaldehyde (**48**), and arylcarboxylic acids (**49**) at room temperature using water as reaction medium involving the formation of both C-C and C-O bonds (Scheme 17). Operational simplicity, mild reaction conditions, ease of isolation of products, cleaner reaction profiles, and excellent yields are the key advantages of this method.

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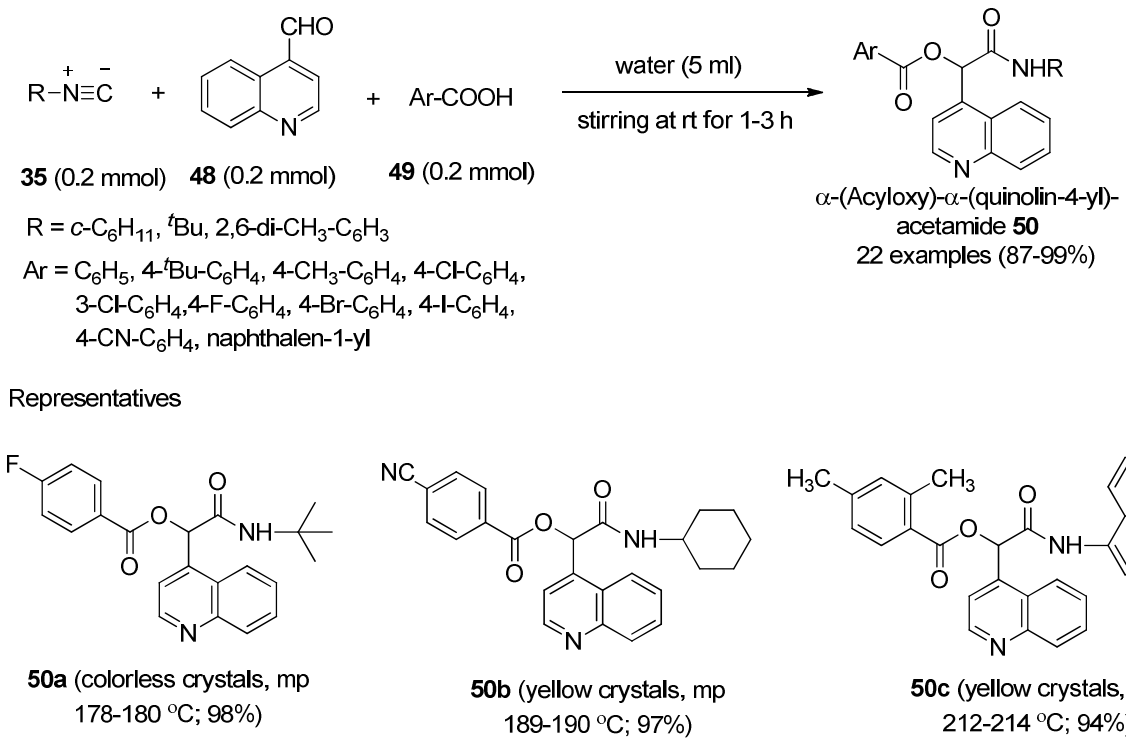
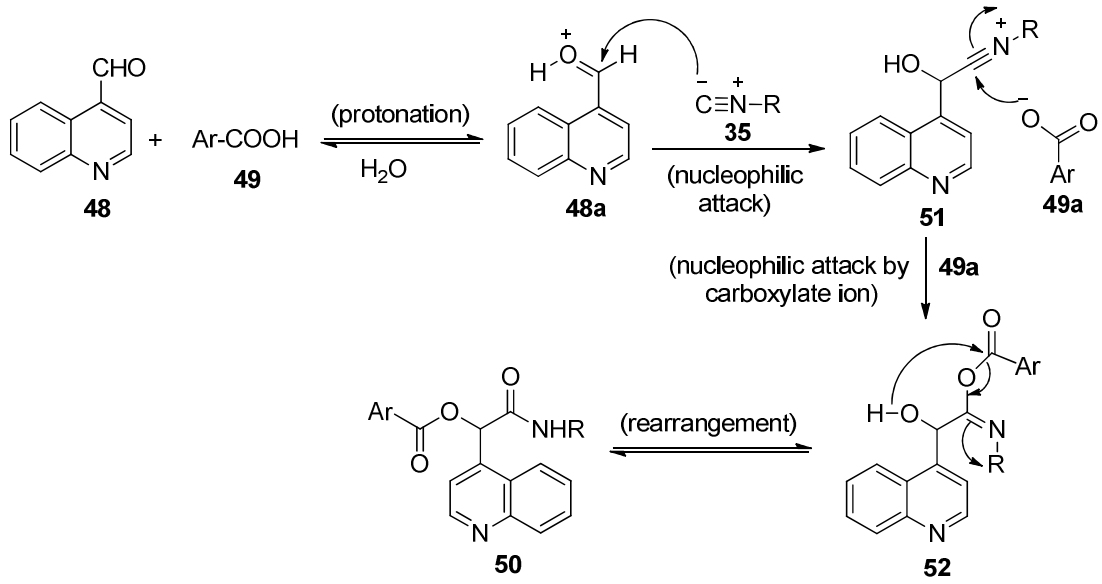


Scheme 17. One-pot three-component synthesis of α-(acyloxy)- α-(quinolin-4-yl)acetamides (**50**)

A possible mechanism for the formation of product **50** was suggested by the authors (Scheme 18). Initially, protonation occurs at the aldehydic carbonyl oxygen by the carboxylic acid (**49**) to generate an electron-deficient species **48a**, which is then attacked by isocyanide (**35**) through its electron-rich carbon centre to form intermediate **51**. The carboxylate ion **49a** adds to the intermediate **51** in the next step *via* nucleophilic attack leading to the formation of intermediate **52** that undergoes a rearrangement reaction to give ultimately the desired product **50**.



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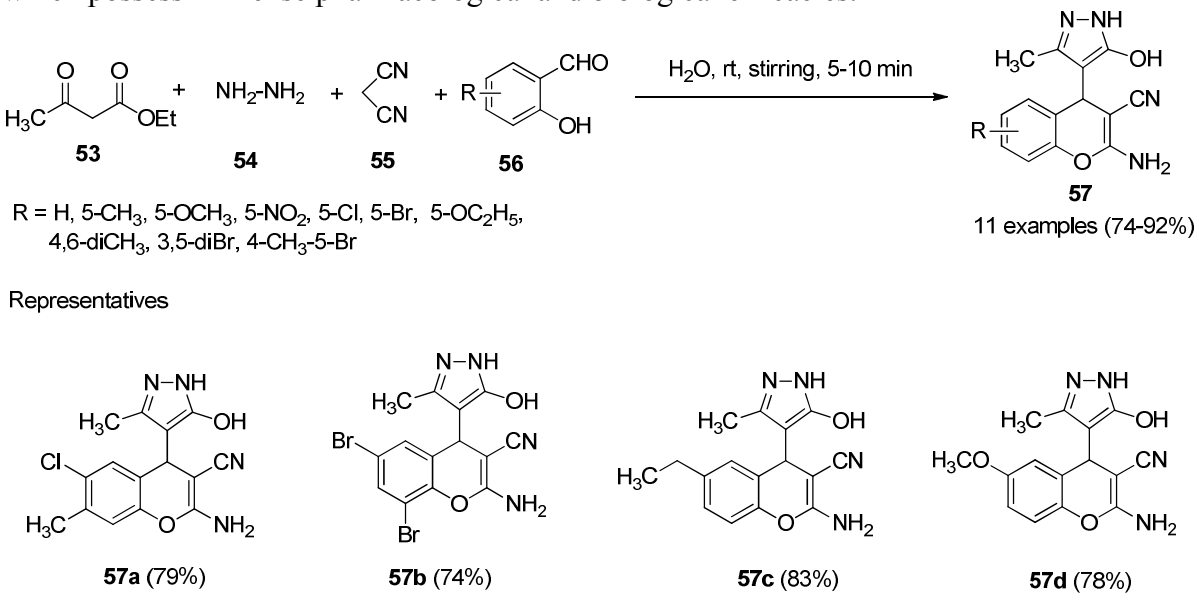
Scheme 18. Plausible mechanism for the construction of α-(acyloxy)- α-(quinolin-4-yl)acetamide moiety **50**

In 2009, Kumaravel and Vasuki reported a rapid synthesis of a series of such scaffolds **57** *via* one-pot four-component reaction of ethyl acetoacetate (**53**), hydrazine hydrate (**54**), malononitrile (**55**) and 2-hydroxybenzaldehydes (**56**) involving both C-C and C-N bond formations (Scheme 19).[147] This reaction protocol offers an easy access to a combinatorial library of these compounds. In addition to C-C, also C-N and C-O bond formations take place in this reaction. Molecular skeleton of a 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)-4*H*-chromene-3-carbonitrile scaffold (**57**) integrates a chromene and a pyrozolone moiety, both of which possess immense pharmacological and biological efficacies.[148-154]



Scheme 19: Four-component synthesis of 2-amino-4-(5-hydroxy-3-methyl-1*H*-pyrazol- 4-yl)-4*H*-chromene-3-carbonitrile derivatives (**57**)

The authors proposed the following plausible mechanism for their reaction which involves a series of the tandem reactions: (i) reaction between hydrazine hydrate (**54**) and ethyl acetoacetate (**53**) resulting in instantaneous formation of pyrazolone **A** that tautomerizes to **B**, (ii) Knoevenagel condensation between 2-hydroxybenzaldehyde (**56**) and malononitrile (**55**) forming 2-imino-2*H*-chromene-3-carbonitrile intermediate (**C**) by 6-*exo*-*dig* cyclization, and (iii) Michael addition of **B** to **D,** followed by subsequent rearrangement. The overall reaction is shown step-wise:

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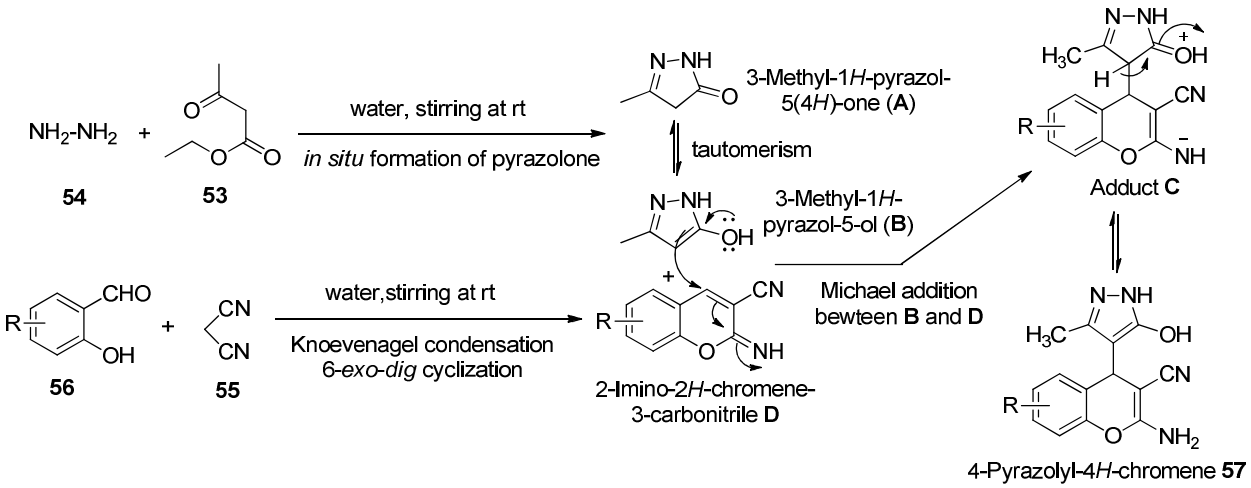

Scheme 20: Plausible mechanism for the one-pot synthesis of 4-pyrazoyl-4*H*-chromeme derivatives **57**

2.1.1.2. Under catalytic conditions

This sub-section summarizes C-C bond forming reactions in water under the influence of both homo- and heterogeneous catalysts at ambient conditions.

2.1.1.2.1. Knoevenagel condensations

In general, reversible dehydration condensation in water is a difficult transformation because the large excess of water pushes the equilibrium in favor of the hydrated compounds; [44,48,59,80,155-158] however, certain naturally elaborated enzymes are capable enough to accomplish homogeneous dehydration in water even under neutral conditions at ambient temperature. Such a special attribute of enzyme catalysis motivated Fujita and his group[159] to introduce a cationic coordination cage-**A** (a 12+ charged M_6L_4 cage) [cage components: (ethylene diamine)$Pd(NO_3)_2$ and 2,4,6-tripyridyl-1,3,5-triazine] that was found to dramatically accelerate the Knoevenagel condensation of aromatic aldehydes with Meldrum's acid in water under neutral conditions (Scheme 21). The addition of a nucleophile to the aldehyde to generate anionic intermediates seems to be facilitated by the cationic environment of the cavity. The products are ejected from the cage as a result of the host-guest size discrepancy.

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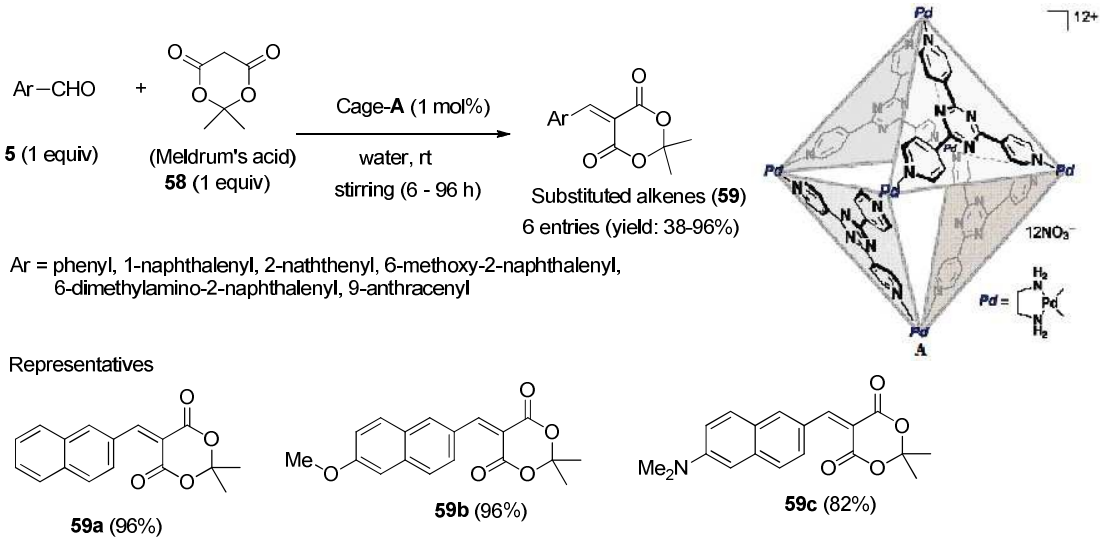

Scheme 21. Synthesis of Knoevenagel condensation products (**59**) in water

This technique demonstrated a unique dehydration condensation under neutral conditions in water catalyzed by the water-soluble synthetic cationic host cage-**A**. An aromatic aldehyde substrate (**5**; an electron-rich guest) first became efficiently encapsulated into the host's (cage-**A**) hydrophobic cavity, which after then attacked by the enolate of Meldrum's acid (**58**) to generate oxyanion intermediate. The condensation reaction seems to be facilitated by the anionic intermediate in the cationic environment of the cage. The eventual loss of water molecule occurs smoothly within the hydrophobic cavity to form the dehydrated product (**59**) which is too large for the cavity and is spontaneously released from the cage, and a new incoming substrate molecule (**5**) occupies the position. The overall phenomenon follows the tricks of enzyme-like catalysis.[159]

Recently, Brahmachari has reported that coumarin-3-carboxylic acids (**60**) can efficiently be synthesized *via* Knoevenagel condensation between substituted salicylaldehydes (**56**) and Meldrum's acid (**58**) in one-pot at room temperature using water for the first time as a green and eco-friendly solvent and commercially available potassium carbonate or sodium azide as inexpensive and less-toxic catalyst (Scheme 22).[160] The present method is not only cost-effective and environmentally benign, but also experimentally safe and simple, easy to handle, clean, and efficient also for the large-scale synthesis eliminating the use of any toxic organic solvent and tedious operation of column chromatographic purification. The feasibility of the present method was also examined for a somewhat scaled-up (on the gram scale) experiment and found to be satisfactory.

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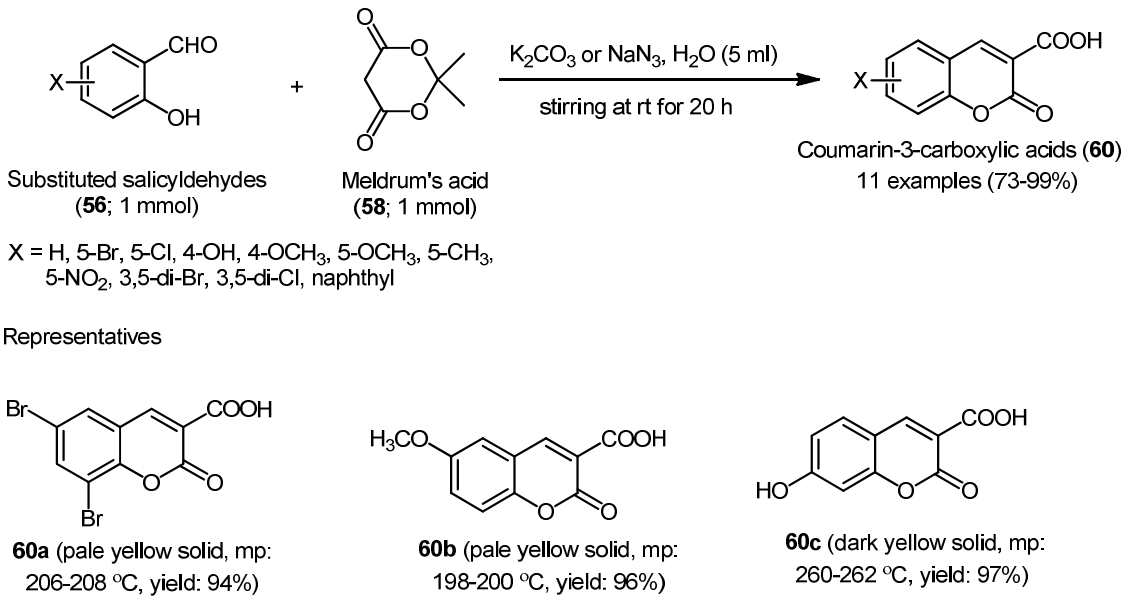
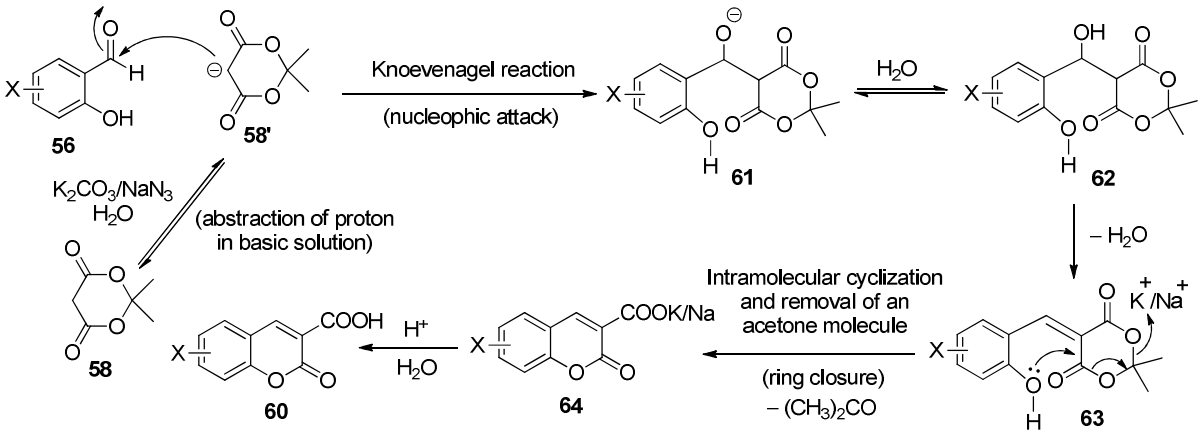


Scheme 22. Potassium carbonate or sodium azide-catalyzed one-pot synthesis of coumarin-3-carboxylic acids (**60**) in water

The transformation involves both C-C and C-O bond formations and a plausible mechanism has been suggested in Scheme 23. Interestingly, azide ion does not act as a nucleophile in this reaction in spite of its use in a 0.5 equivalency. Mild reaction conditions, good to excellent yields, operational simplicity, avoidance of organic solvent, use of water as reaction medium, absence of tedious separation procedures, clean reaction profiles, and energy-efficiency as well as the use of inexpensive and environmentally benign catalysts are the advantages of the present method.



Scheme 23. Plausible mechanism for the base-catalyzed one-pot synthesis of coumarin-3-carboxylic acids **60** in water

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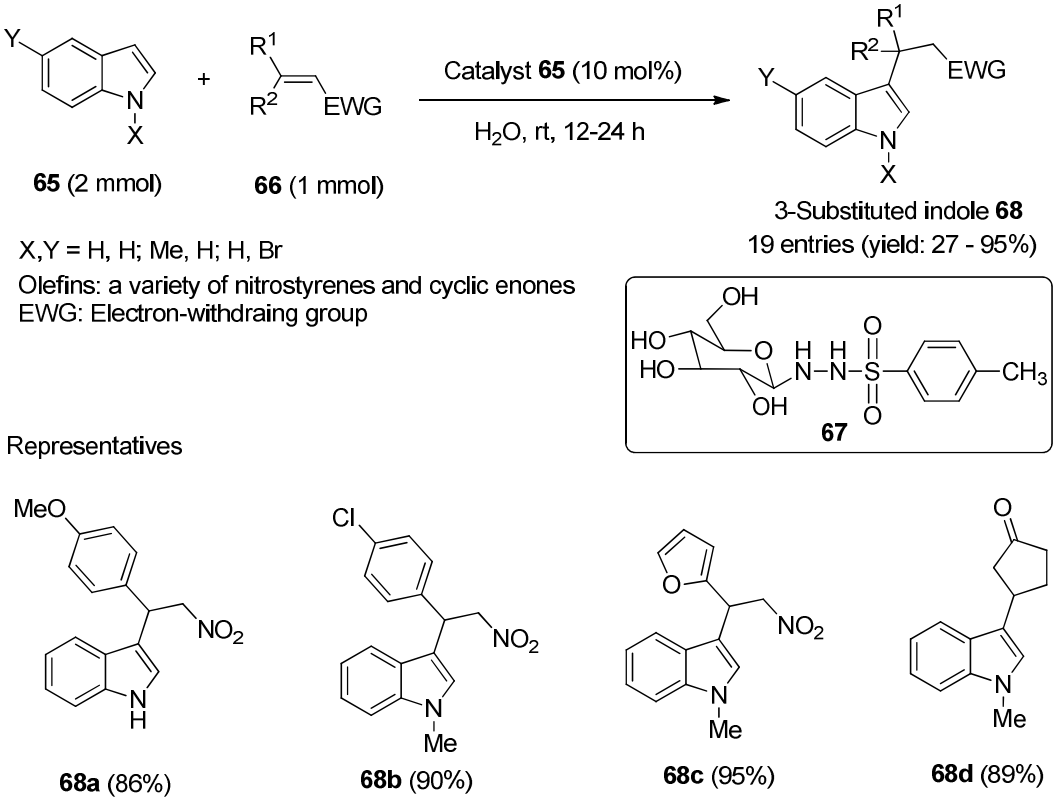
Coumarin-3-carboxylic acids represent a pronounced group of coumarin-heterocyclic compounds with a wide range of applications.[161-165] Literature survey reveals that these compounds find applications as synthons of numerous natural and semi-synthetic pharmacological agents like β-lactams,[166] isoureas,[167] and tetrahydropyridones.[168] Ester and amide derivatives of coumarin-3-carboxylic acid have been evaluated to possess efficient inhibitory activity against cancer cell invasion *in vitro* and tumor growth *in vivo*.[169] Apart from these applications, coumarin-3-carboxylic acids have been widely used as fluorescent probes[170] and triplet oxygen sensitizers.[171]

2.1.1.2.2. Michael addition

In the field of organocatalysis, amine-based catalysts are found to carry out a variety of organic transformations so far;[172,173] however, most of the reactions were typically performed in organic solvents with a few aminocatalysts could be used in water.[174-180] Under this purview, Wu et al.[181] thought to design carbohydrate-based compounds capable to exhibit hydrogen bonding interactions for possible organocatalysts to activate organic reaction in water. The present investigators reported for the first-time that carbohydrate-based tolylsulfonyl hydrazines can effectively accomplish Michael addition of indoles (**65**) to electron-deficient olefins (**66**) in water just at room temperature (Scheme 24). This method provides a green process for the synthesis of biologically relevant 3-substituted indole derivatives **68** under mild conditions with high yield and with good substrate scope.



Scheme 24. Carbohydrate-based tolylsulfonyl hydrazine-catalyzed synthesis of 3-substituted indoles **68**

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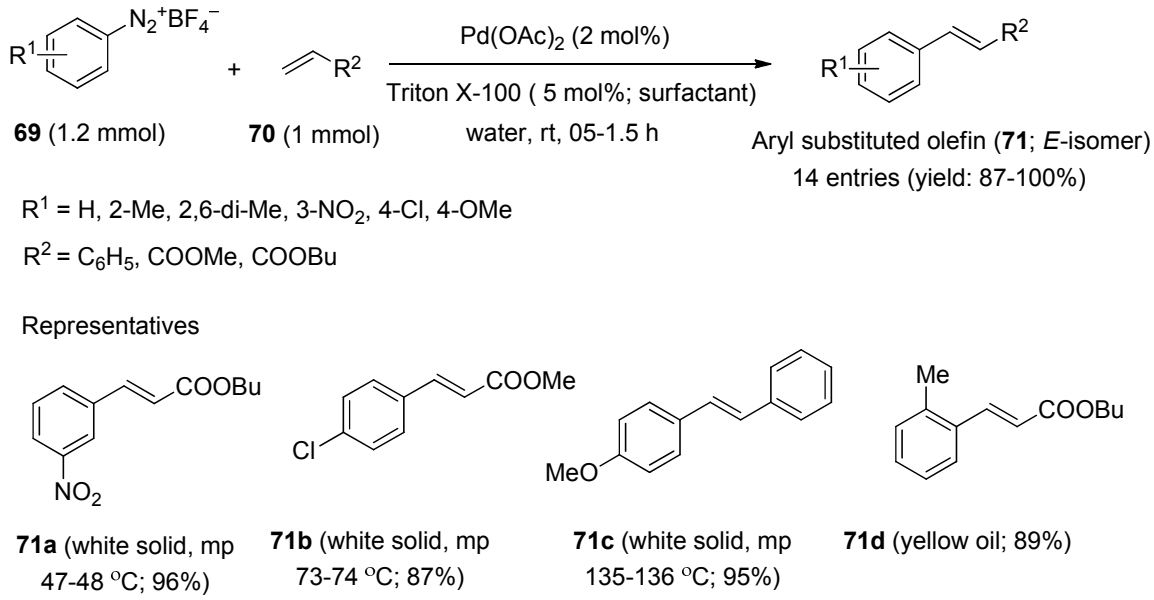
2.1.1.2.3. Matsuda-Heck coupling

In 2012, Gaikwad and Pore introduced a modified eco-friendly and simple method for Matsuda-Heck coupling reaction of olefins with arenediazonium tetrafluoroborate salt catalyzed by *in situ* generated palladium-nanoparticles in the presence of Triton X-100 as surfactant in water at ambient temperature.[182] A variety of arenediazonium tetrafluoroborate salts were coupled with olefins under ligand-free and aerobic conditions to afford arylated products with high yields and stereoselectivity (Scheme 25).



Scheme 25. $Pd(OAc)_2$-catalysed synthesis of aryl-substituted olefins (**71**)

The key advantages of this method include no requirement for additional base, ligand and nitrogen atmosphere that obviously simplify the reaction conditions; in addition the modified method is also associated with excellent yields and high stereoselectivity.

2.1.2. Carbon-carbon bond forming reactions in non-aqueous media

Carbon-carbon bond forming reactions in non-aqueous media under the influence of different catalytic systems are presented herein.

2.1.2.1. Knoevenagel condensations

Inokuchi and Kawafuchi[183] developed the first *E*-selective Knoevenagel condensation of acetoacetic derivatives of TEMPO (2,2,6,6-tetramethylpiperidin-1-yl 3-oxobutanoate) with aldehydes bearing electron-withdrawing substituents using piperidine as catalyst in ethanol at room temperature. Alternatively, they also accomplished the *Z*-selective Knoevenagel condensation of *N*-methoxy-*N*-methyl-3-oxobutanamide with those aldehydes using piperidine/acetic acid as catalyst in the same solvent under identical conditions (Scheme 26).[183]

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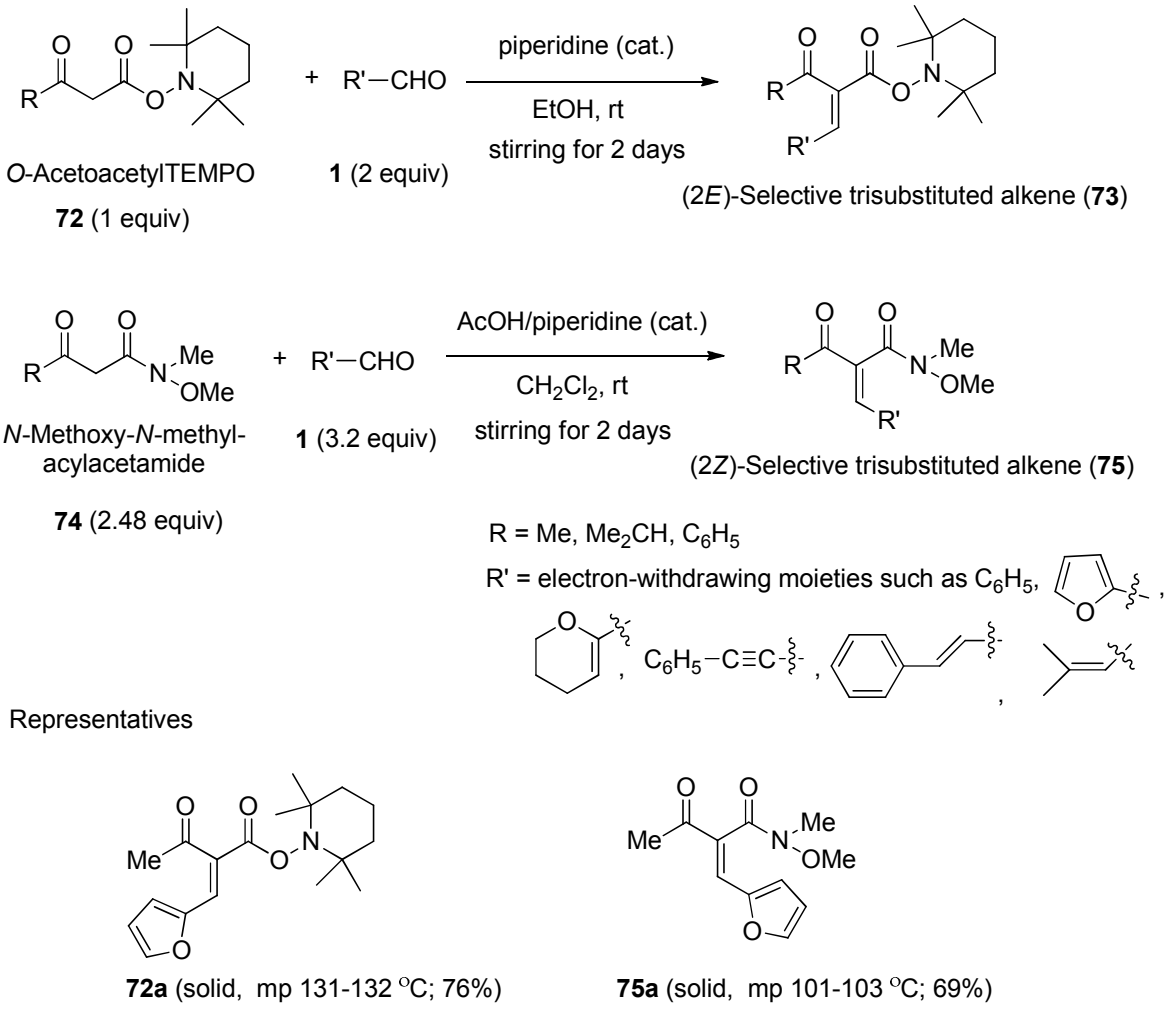

Scheme 26. Synthesis of trisubstituted *E* or *Z*-2-alkenes *via E*- and *Z*-selective Knoevenagel condensation

In another report, Lakshmi Kantam et al.[184] used modified Mg-Al hydrotalcite (MHT) as a heterogeneous reusable catalyst for carrying out Knoevenagel condensations involving various aromatic carbonyl compounds, aliphatic ketone and cyclohexanone with malononitrile/ethyl cyanoacetate in toluene /DMF at room temperature (Scheme 27).

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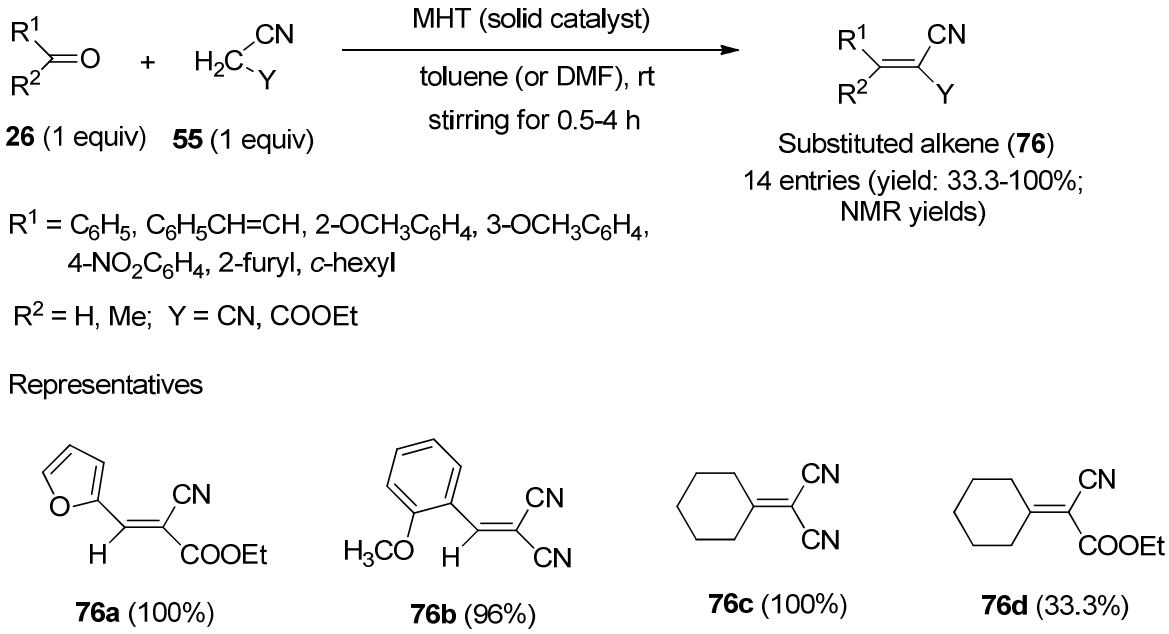

Scheme 27. Synthesis of substituted alkenes **76** via Knoevenagel reaction

Recently, an eco-friendly one-pot synthetic protocol for 3,3-bis(indol-3-yl)indolin-2-one (**16**) along with 2,2-bis(indol-3-yl)acenaphthylen-1(2*H*)-one (**18**) derivatives has been developed by Brahmachari and Banerjee[185] from the pseudo-multicomponent reaction of indole (**14**, 2 equiv.), respectively with isatin (**15**) or acenaphthaquinone (**17**) in aqueous ethanol at room temperature in the presence of a catalytic amount of sulfamic acid (Scheme 28). Bis(indolyl)indolin-2-ones are found to possess various pharmaceutical properties such as anti-inflammatory,[186] anti-HIV,[187] antitumor,[188] spermicidal potential,[189] anticancer,[190] and cytotoxic[191] properties. Interestingly, certain bis(indolyl)indolin-2-one derivatives have been reported to exhibit strong cytotoxicity against a series of cancer cell lines but not against the normal cells.[191] The present protocol offers a number of benefits such as mild reaction conditions at ambient temperature and pressure, excellent yields, operational simplicity and absence of tedious separation procedures, reusability of catalyst, energy-efficiency and high atom-economy as well as the use of inexpensive and environmentally benign catalyst. Moreover, reusability of the reaction media is an added advantage to this protocol. A plausible mechanism for this sulfamic acid-catalyzed transformation has also been suggested (Scheme 29).

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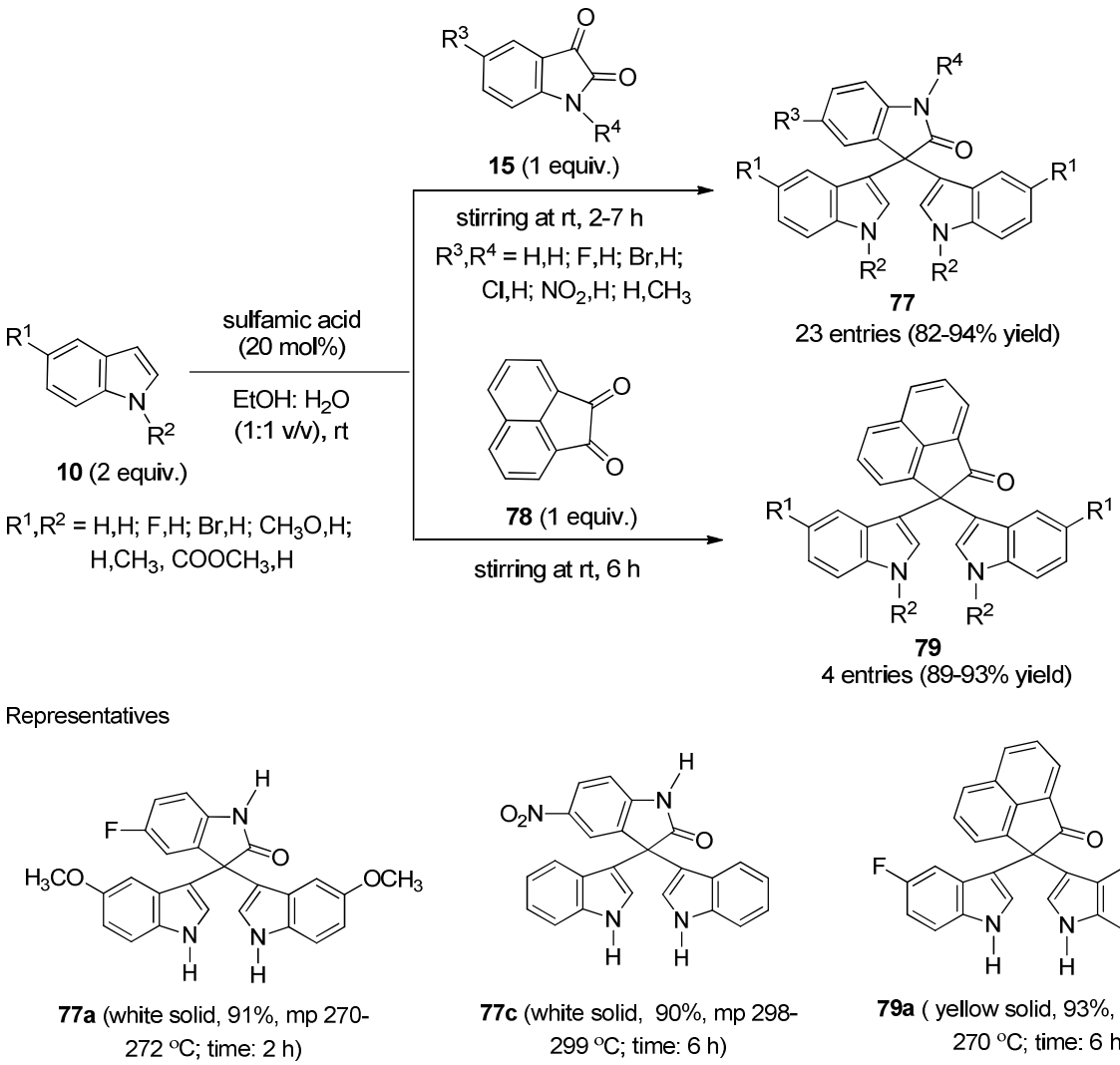

Scheme 28**.** One-pot synthesis of functionalized 3,3-bis(indol-3-yl)indolin-2-ones (**77**) and 2,2-bis(indol-3-yl)acenaphthylen-1(2*H*)-one derivatives (**79**)

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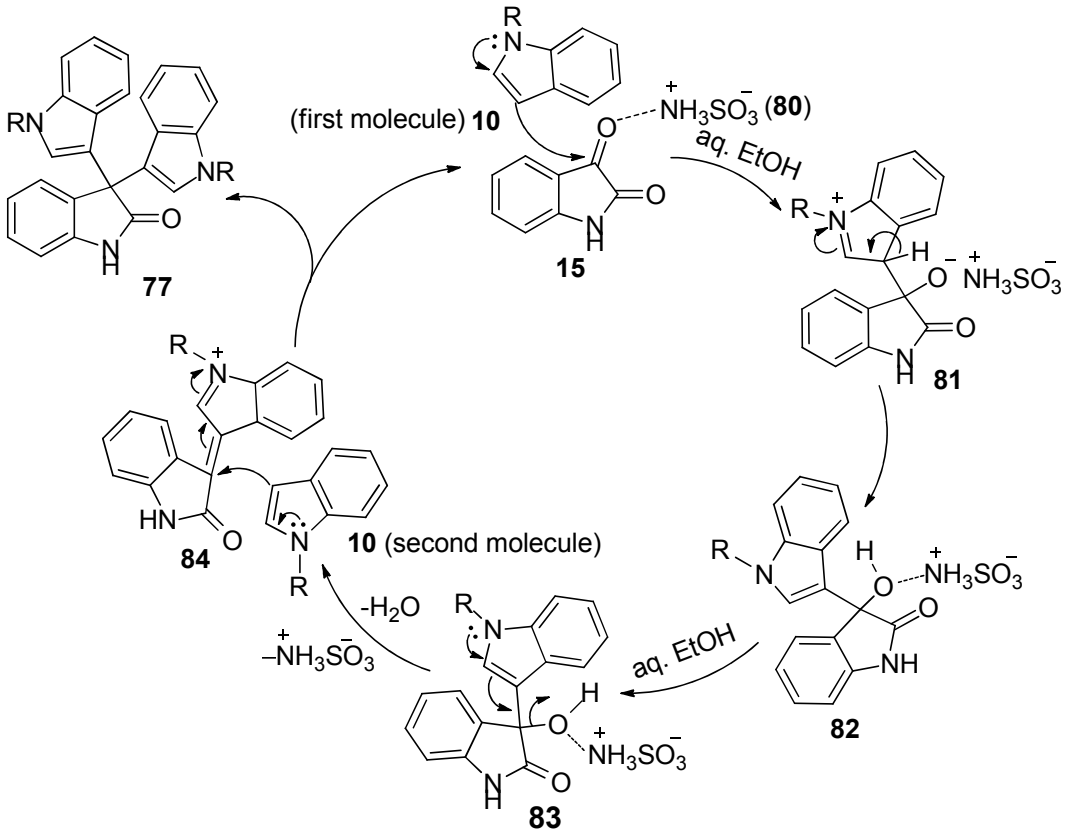

Scheme 29. Proposed mechanism for the sulfamic acid-catalyzed synthesis of 3,3-bis(indol-3-yl)indolin-2-ones (**77**)

6-Aminouracil and its derivatives play a key structural part in numerous natural and synthetic bioactive compounds, and also regarded as a versatile building block for several nitrogen-containing heterocycles possessing a wide range of pharmacological potentials.[192-195] Brahmachari and his group reported a straightforward and efficient *pseudo* three-component one-pot synthesis of a series of substituted bis(6-aminouracil-5-yl)methanes **86** in good yields using either ceric ammonium nitrate (CAN)[196] or sulfamic acid[197] as commercially available, inexpensive and eco-friendly catalyst from the reaction of 6-aminouracils (**85**) and diverse aldehydes (**1**) in aqueous ethanol at room temperature (Scheme 30). Both procedures satisfy many green chemistry parameters, such as mild reaction conditions, good to excellent yields, operational simplicity and absence of tedious separation procedures, high atom-economy as well as the use of inexpensive and environmentally benign catalysts.

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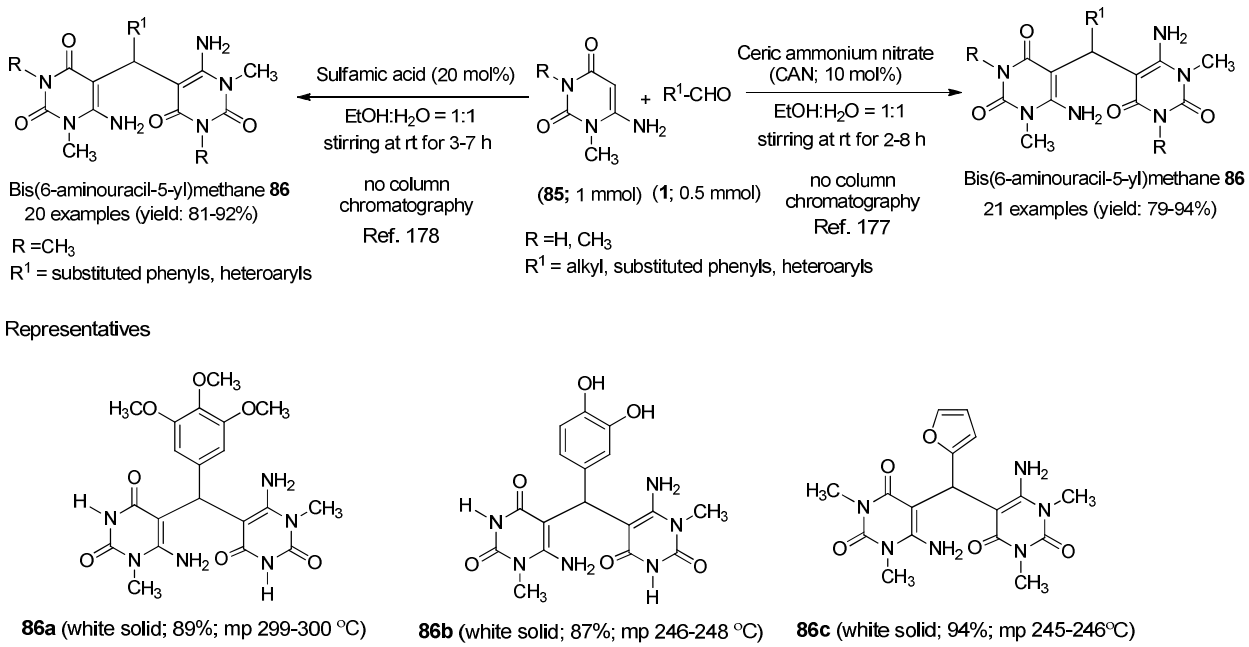

Scheme 30. CAN/sulfamic acid-catalyzed one-pot pseudo-multicomponent synthesis of substituted bis(6-aminouracil-5-yl)methanes (**86**)

Lawsone (2-hydroxy-1,4-naphthoquinone) is a major chemical constituent of the medicinal plant, *Lawsonia inermis* Linn. (Synonyms: *L. alba*, *L. spinosa*; also known as *Henna* or *Mhendi*; family: Lythraceae), different parts of which are traditionally used all over the world as cosmetics (hair dye, body paint and tattoo dye) and herbal remedies in treating various ailments.[198-200] This phenolic quinone compound has been evaluated to possess a wide range of biological and pharmacological activities such as antioxidant,[201] antibacterial,[202] antifungal,[203] cytotoxic,[204] trypsin inhibitor,[205] anticoagulant,[206] advanced glycated end products (AGEs) formation inhibitor,[207] and anti-acute pancreatitis.[208] Under this purview, Brahmachari has recently developed a simple, convenient, clean and highly efficient protocol for the one-pot synthesis of functionalized bis-lawsone derivatives **88** from the pseudo-multicomponent reaction of lawsone (i.e. 2-hydroxynaphthalene-1,4-dione; **87**) and diverse aldehydes (**1**) in aqueous ethanol at room temperature using commercially available sulfamic acid as an inexpensive organocatalyst (Scheme 31).[209] The plausible mechanism for this transformation involving a Knoevenagel-type condensation is presented in Scheme 32. Mild reaction conditions, excellent yields, operational simplicity, absence of tedious separation procedures, clean reaction profiles, energy-efficiency and high atom-economy, as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method.

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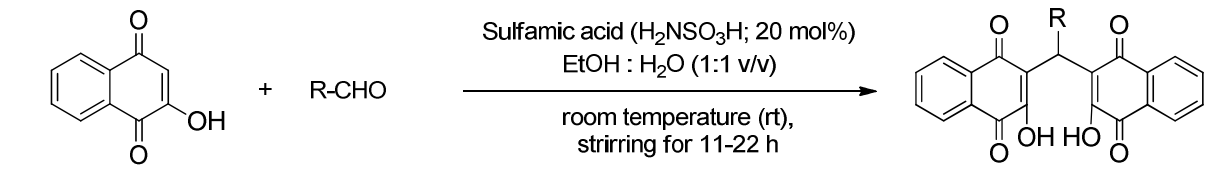
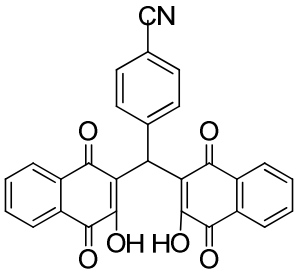
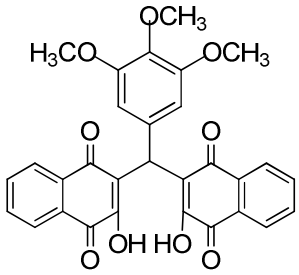


R = C_6H_5, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$, 3-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-CNC_6H_4, 3-$CH_3C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-OH-5-$CH_3C_6H_3$, 2-OH-4-$CH_3C_6H_3$, 3-OHC_6H_4, 4-OHC_6H_4, 3,4,5-$(OCH_3)_3C_6H_2$, naphthyl, 4-CHO-C_6H_4, *n*-Pr

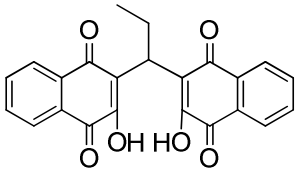
Represenatives



88a (yellow solid; 90%; mp: 150-152 °C)

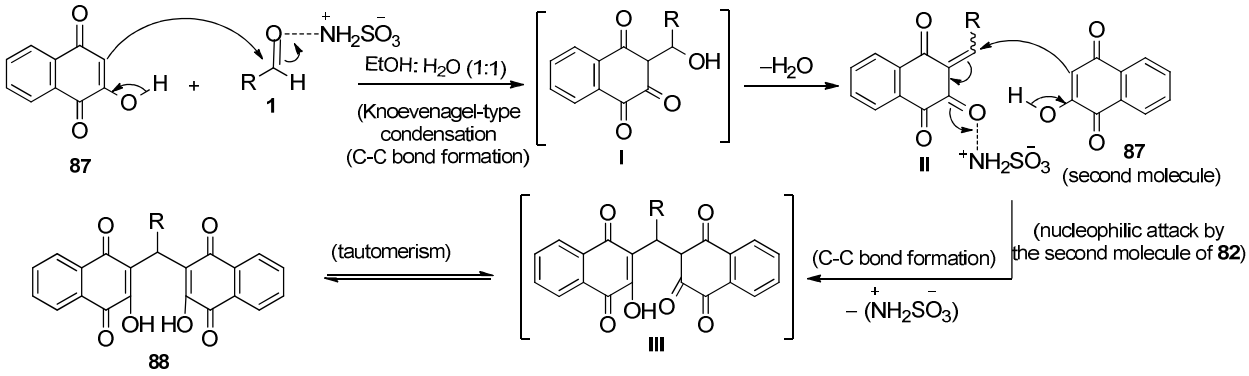


88b (yellow solid; 89%; mp: 201-203 °C)



88c (yellow solid; 66%; mp: 136-138 °C)

Scheme 31. One-pot synthesis of functionalized bis-lawsone derivatives **88**



Scheme 32. Plausible mechanism for the sulfamic acid-catalyzed synthesis of bis-lawsones **88**

2.1.2.2. Addition reactions

Hagiwara et al.[210] reported a facile Mannich reaction of arylaldimine **89** with methylsilyl enol ether **90** catalyzed by lithium chloride in dimethylformamide (DMF) at room temperature resulting the synthesis of a series of β-amino esters **91** with good yields (Scheme 33). The reaction is mild enough to apply to aldimines having the AcO–, TBDMSO–, or MeS– group. The present reaction offers a mild, practical, environmentally and economically benign method

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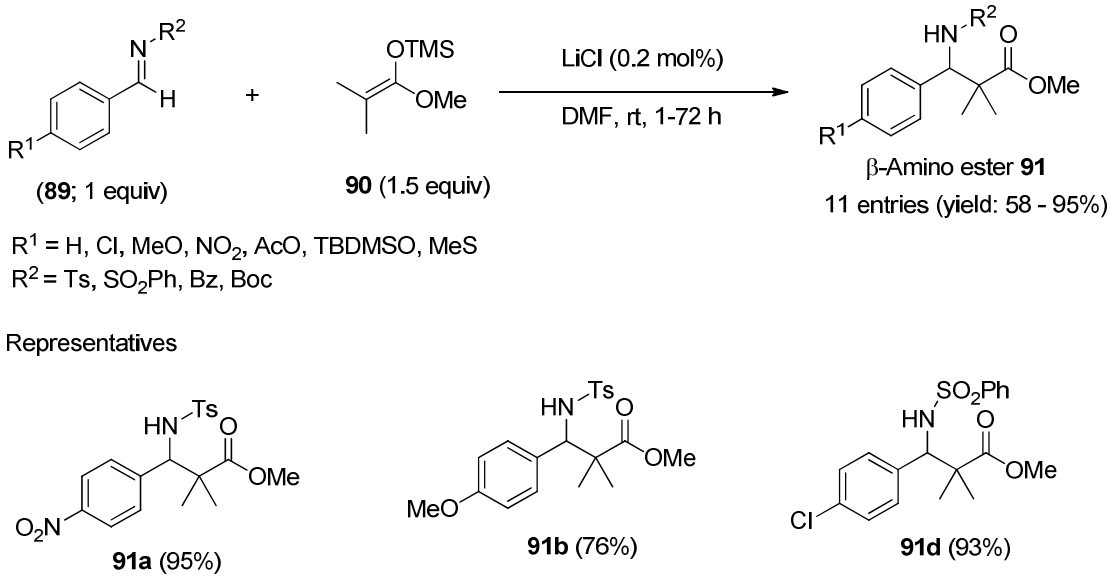
for synthesizing β-amino carbonyl compounds, which are versatile building blocks for the synthesis of various biologically important products.[210]



Scheme 33. LiCl-catalyzed synthesis of β-amino esters **91** *via* Mannich reaction

Wang et al.[211] reported 2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl (XPhos, a phosphine derivative, **93**)-catalyzed Michael addition of α-trifluoromethylated ester (**92**) with α,β-unsaturated ketone (**26**) in *N*,*N*-dimethyformamide (DMF) under an aerobic atmosphere at room temperature resulting to the generation of a series of γ-substituted α-trifluoromethylated ester derivatives (**94**) with moderate to good yields (Scheme 34). Although limited to active Michael acceptors and highly acidic trifluoromethylated nucleophiles, these reactions with α,β-unsaturated carbonyl compounds such as (hetero)aryl vinyl ketones, alkyl vinyl ketones, and phenyl acrylate proceeded efficiently at room temperature, providing many fluorinated compounds with a CF_3-containing quaternary carbon center. Fluorinated compounds are of interest because fluorine often offers organic molecules with many important properties such as high lipophilicity, bioavailability, and metabolic stability.[212-217]

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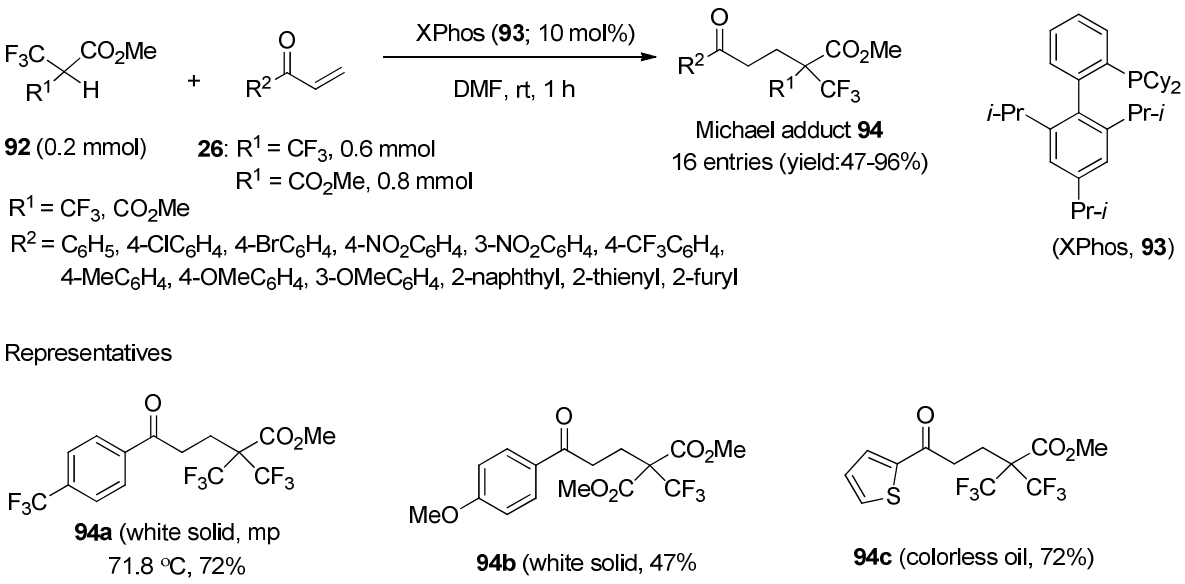

Scheme 34. Synthesis of γ-substituted α-trifluoromethylated ester derivatives *via* Michael addition

In 2012, Kamalraja et al.[218] synthesized a series of 3-(aminomethylene)oxindoles (**97**) *via* one pot Michael addition of α-azido ketones (**96**) and isatylidenemalononitriles (**95**) followed by the conversion of azides to amines using piperidine as an efficient catalyst in ethanol at room temperature with good product diastereoselectivity (Scheme 35). The investigators proposed a plausible mechanism for the transformation (Scheme 36). Initially piperidine reacts with α-azido ketone **96** to form enamine **98**, which undergoes Michael addition with isatylidene malononitrile **95** to form adduct **99**. Elimination of malononitrile from the adduct **99** results in the formation of vinyl azide **100**. Intramolecular cyclization of vinyl azide **100** may take place to form a oxatriazine **102**, which transforms to intermediate **103** by the addition of water. Finally the intermediate **103** rearranges to form product **97** (Scheme 36).

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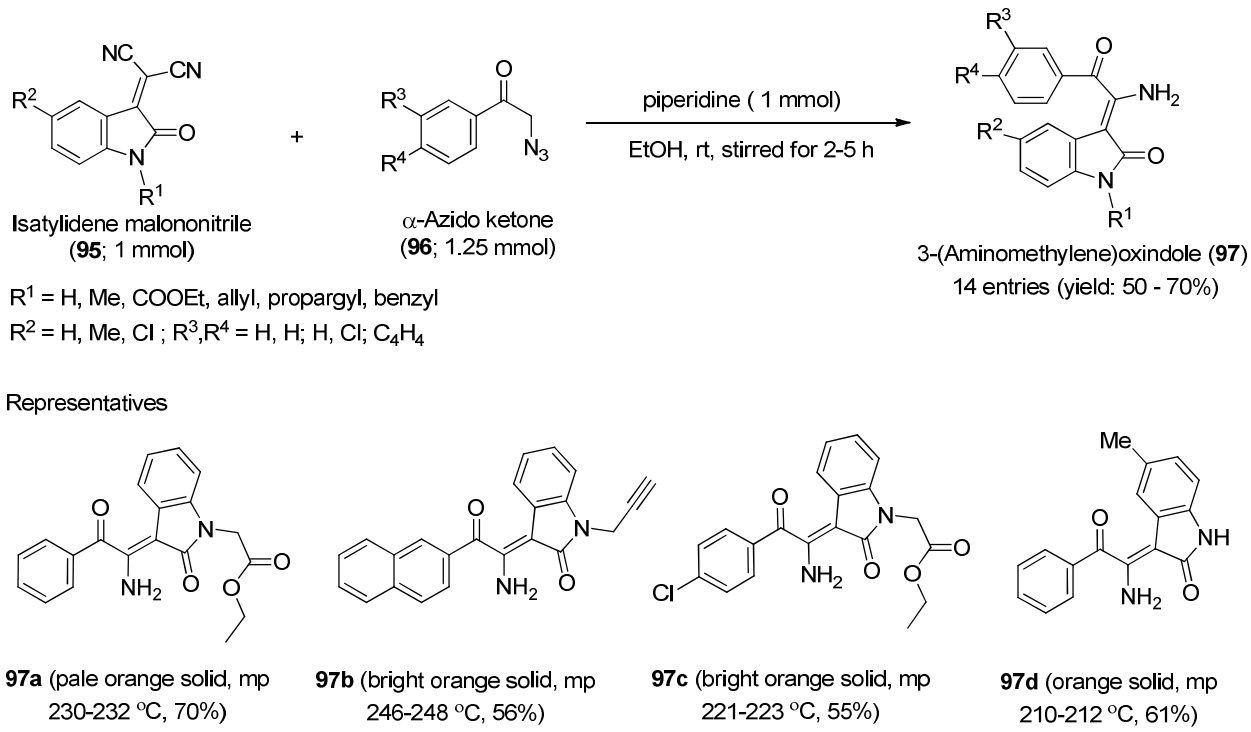
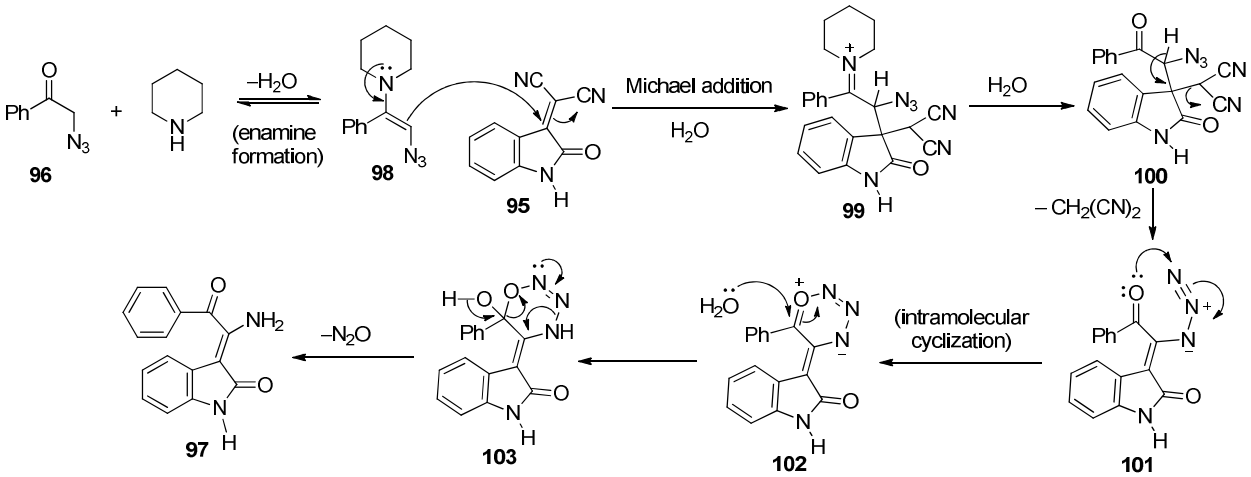


Scheme 35. Piperidine-catalyzed synthesis of 3-(aminomethylene)oxindoles **97** via Michael addition



Scheme 36. Proposed mechanism for bases-catalyzed synthesis of 3-(aminomethylene)oxindole **97**

The Henry (nitroaldol) reaction is one of the most atom-economical carbon-carbon bond-forming reactions in synthetic chemistry. The resulting β-hydroxy nitro compounds have been used in various beneficial transformations to provide chiral β -amino alcohols and α-hydroxy carboxylic acids. To provide the raw materials for research into these biologically significant building blocks, attention has recently been focused on the development of catalytic, asymmetric

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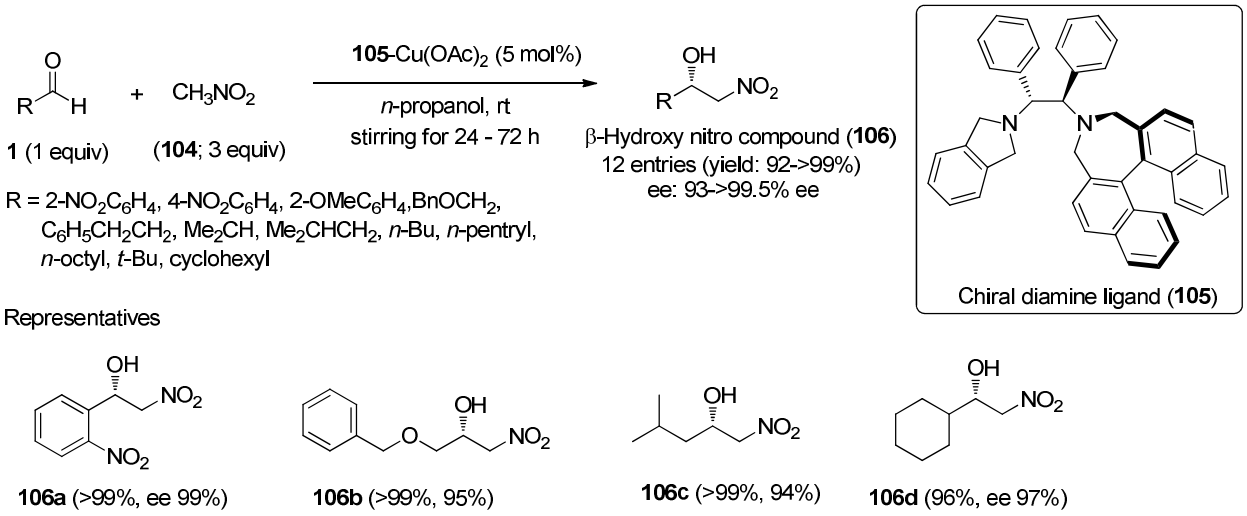
versions of the Henry reaction.[219-221] The most impressive work of heterobimetallic lanthanoid catalysis[222] has stimulated the successful development of various types of asymmetric catalyst.[223-234] Among them, the Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years.[223,225,231-234] As part of the ongoing research in this domain, Arai et al.[235] designed and developed a new chiral diamine ligand **105** using a cheap building block and its $Cu(OAc)_2$ complex is air-stable and can smoothly catalyze the Henry reaction from a variety of aldehydes and nitromethane in *n*-propyl alcohol at room temperature in high yield (up to >99%) with excellent enantiomeric excess (over 90%) (Scheme 37). All these points contribute to the practicality and usefulness of this catalytic system.



Scheme 37. Enantioselective synthesis of *β*-hydroxy nitro derivatives **106** *via* Henry reaction

α-Trichloromethylamines are pharmacologically as well as synthetically interesting compounds.[236-243] Recently, Wahl et al.[244] reported a nucleophilic addition of trimethyl(trichloromethyl)silane (**108**) to *N*-phosphinoyl benzaldimines **107** outlining a tetrabutylammonium difluorotriphenylsilicate (TBAT)-catalyzed route to *N*-phosphinoyl-α-(trichloromethyl)benzylamines **109** in tetrhydrofuran (THF) with good yields within just one hour at room temperature (Scheme 38).

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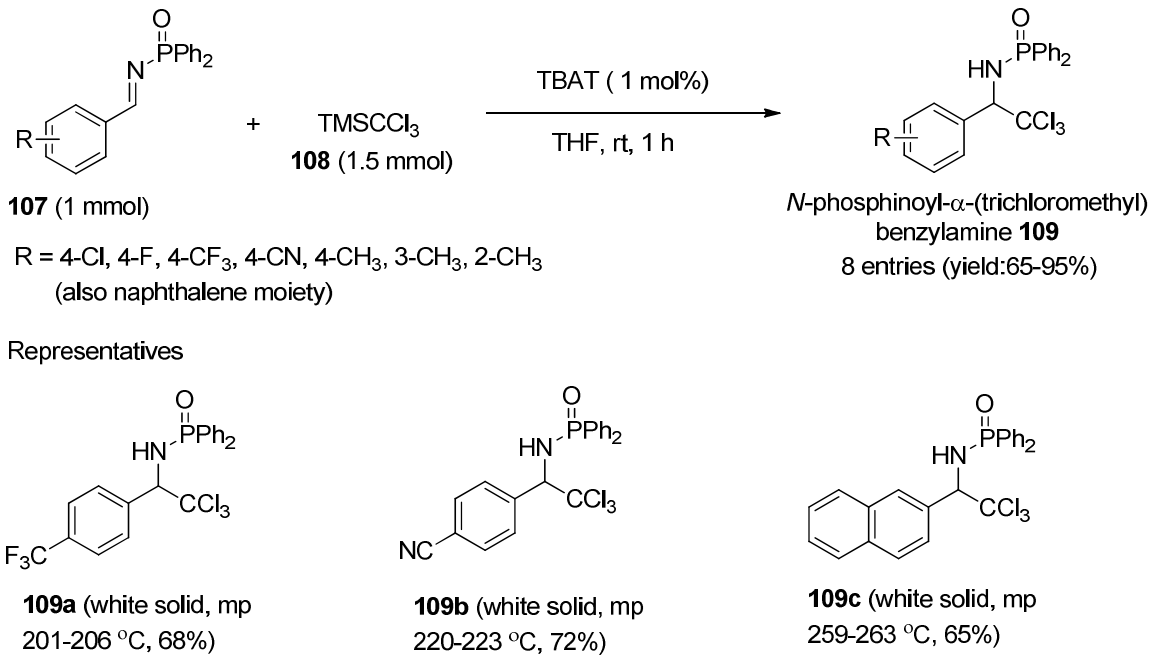
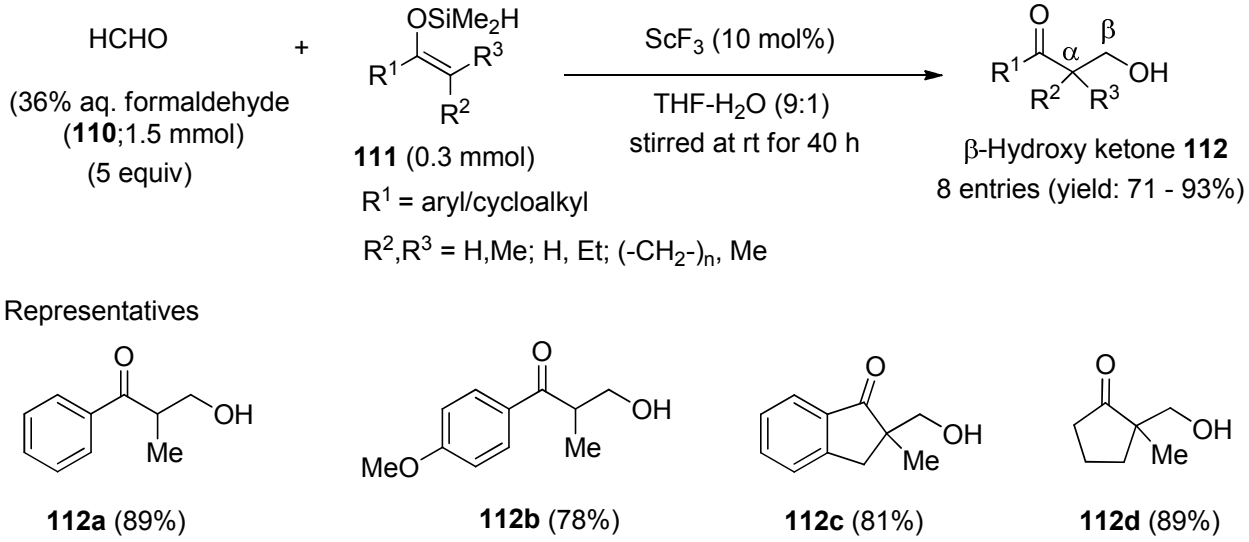


Scheme 38. TBAT-catalyzed synthesis of *N*-phosphinoyl-α-(trichloromethyl)benzylamines **109**

Hydroxymethylation reactions are among the most important C–C bond-forming reactions in organic synthesis. Kokubo and Kobayashi explored scandium(III) fluoride (ScF_3) as a novel catalyst for such a hydroxymethylation reaction of dimethylsilyl (DMS) enolates (**111**) using aqueous formaldehyde solution in aqueous THF media to give the corresponding β-hydroxy ketones **112** in good to excellent yields at room temperature condition (Scheme 39).[245]



Scheme 39. ScF_3-catalyzed synthesis of β-hydroxy ketones **112**

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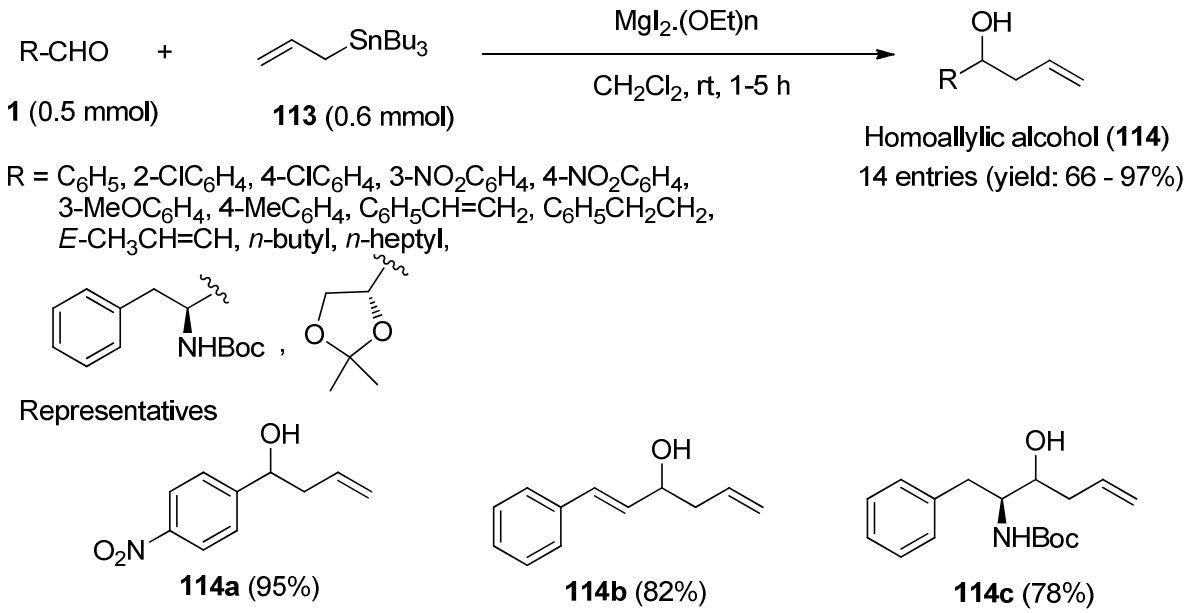
Zhang[246] demonstrated a magnesium-catalyzed allylation addition of aldehydes (aromatic, unsaturated and aliphatic) with allyltributylstannane in the presence of $MgI_2 \cdot (OEt)_n$ etharate in dichloromethane at room temperature, affording homoallylic alcohols with moderate to good yields (Scheme 40). The process is mild, efficient, operationally simple and highly selective.



Scheme 40. $MgI_2 \cdot (OEt)_n$-catalyzed synthesis of homoallylic alcohols **114**

2.1.2.3. Cycloaddition reactions

Angucyclinones are a large group of naturally occurring quinones that have a benz[*a*]anthracenequinone framework and exhibit a broad range of biological activities.[247] Hsu and Huang performed Diels−Alder reaction of juglone (**115**) with various styrenes (**116**) in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dichloromethane catalyzed by boron triacetate at room temperature to generate such derivatives **117** in good yields and with excellent regioselectivity (Scheme 41).[248] The investigators successfully applied strategy to the total syntheses of tetrangulol[249] and anhydrolandomycinone[250] in the present report as well.

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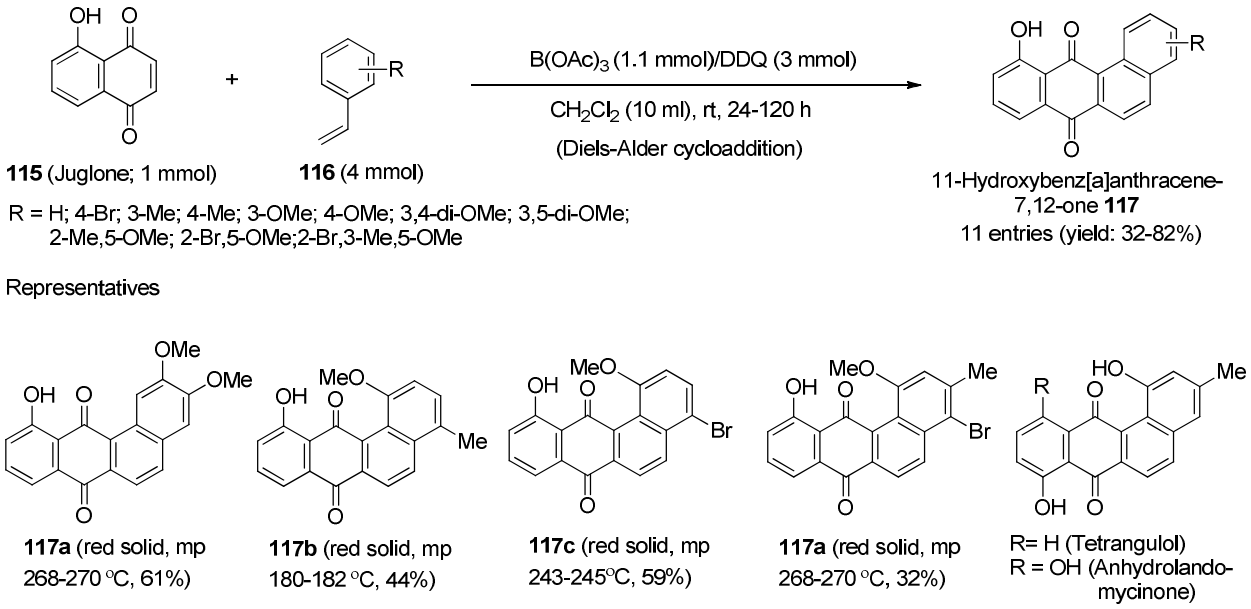
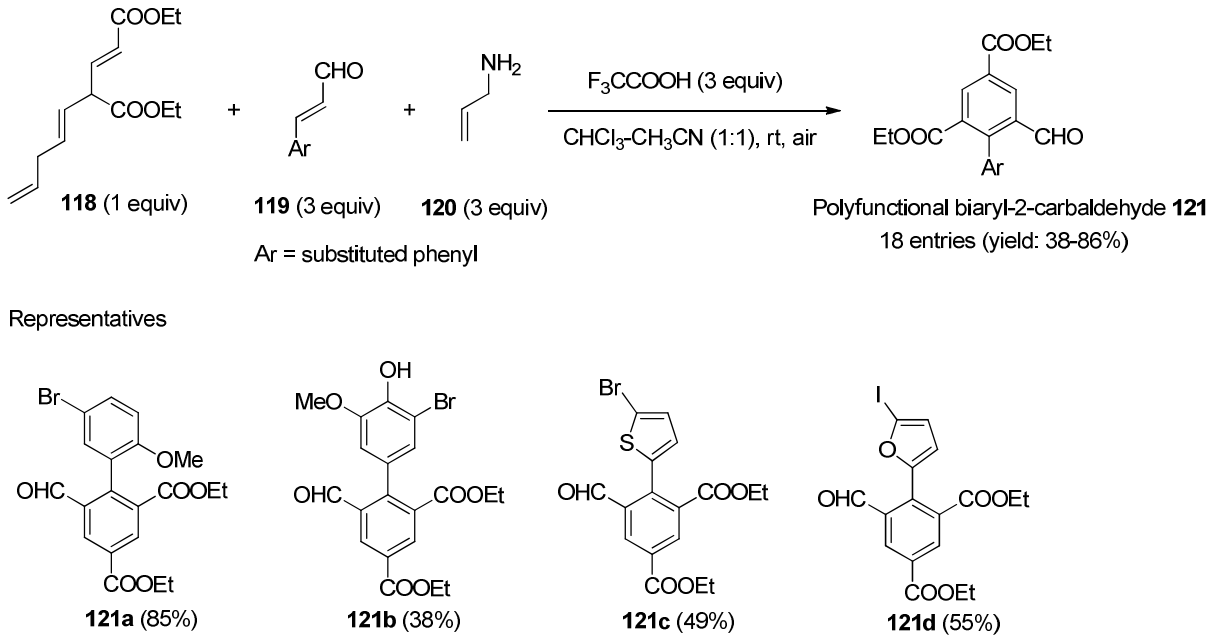


Scheme 41. $B(OAc)_3$/DDQ-promoted synthesis of angucyclinones **117** via Diels-Alder cycloaddition

Challa et al.[251] also developed a metal-free one-pot cascade annulation of acyclic substrates such as dienaminodioate (**118**), cinnamaldehydes (**119**) and allyl amine (**120**) using trifluoroacetic acid as a catalyst for the synthesis of polyfunctional biaryl-2-carbaldehydes **121** at ambient conditions (Scheme 42). The reaction proceeds through Diels–Alder pathway. The investigators also demonstrated synthetic applications of the resulting biaryl-2-carbaldehyde by their conversion into an array of diverse molecules with biological and materials chemistry relevance.



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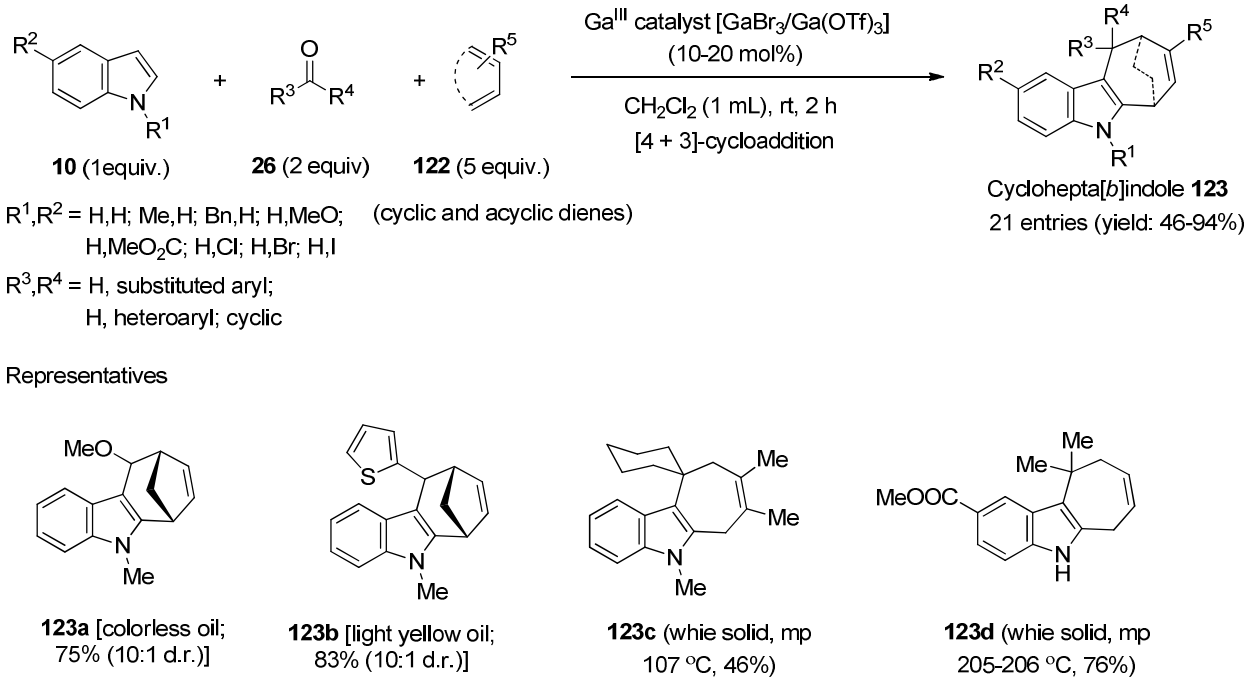
Scheme 42. Acid-catalyzed metal-free one-pot synthesis of polyfunctional biaryl-2-carbaldehydes (**121**) through Diels-Alder pathway

Han et al.[252] synthesized biologically potent cyclohepta[*b*]indoles (**123**)through one-pot three-component [4 + 3]-cycloaddition reaction of indoles (**10**), carbonyl compounds (**26**) and cyclic/acyclic dienes (**122**) using gallium(III) salts ($GaBr_3$/$Ga(OTf)_3$) as catalytic system in dichloromethane at room temperature (Scheme 43); this is the first instance of a (4+3) cycloaddition where the 2π component is derived from indole.



Scheme 43. Ga(III)-catalyzed synthesis of cyclohepta[*b*]indoles **123** through one-pot three-component [4 + 3]-cycloaddition

2.1.2.4. Substitution reactions

Recently, Cacciuttolo et al.[253] have reported bismuth(III) triflate-catalyzed intermolecular reaction between differently substituted electron-rich arenes (**124**) and unactivated 1,3-dienes (**125**) at room temperature leading to the efficient synthesis of substituted indane derivatives **126** through a tandem bis-hydroarylation involving C-C bond formation reaction (Scheme 44). This process is highly atom-economic and regioselective.

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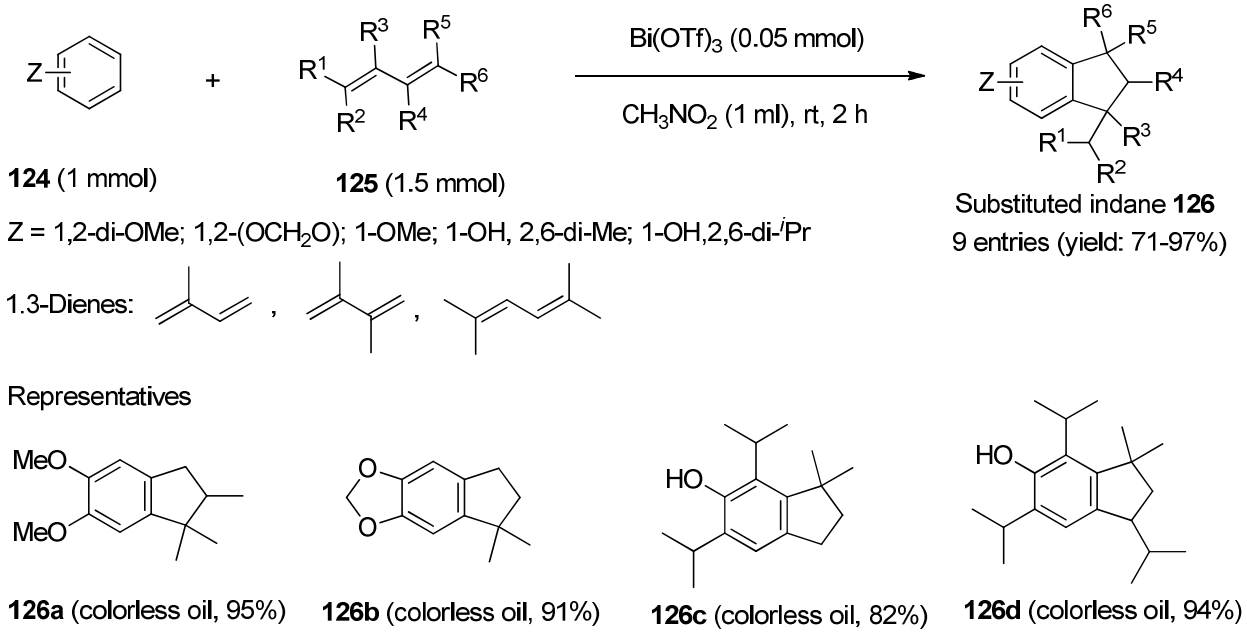

Scheme 44. $Bi(OTf)_3$-catalyzed synthesis of substituted indanes **126**

p-Tolenesulfonic acid (PTSA), a simple Brønsted acid was found to catalyze smoothly C_3-selective *tert*-alkylation of indoles using tertiary propargylic (**127**) and benzylic alcohols in acetonitrile at room temperature resulting to the functionalization of indoles with a quaternary carbon at the propargylic position (Scheme 45).[254] The availability of the reagents used, mild conditions and the fact that only water was generated as a side product, make this method an attractive and environmentally friendly process for the synthesis of C_3-substituted indoles **128** and **130**.

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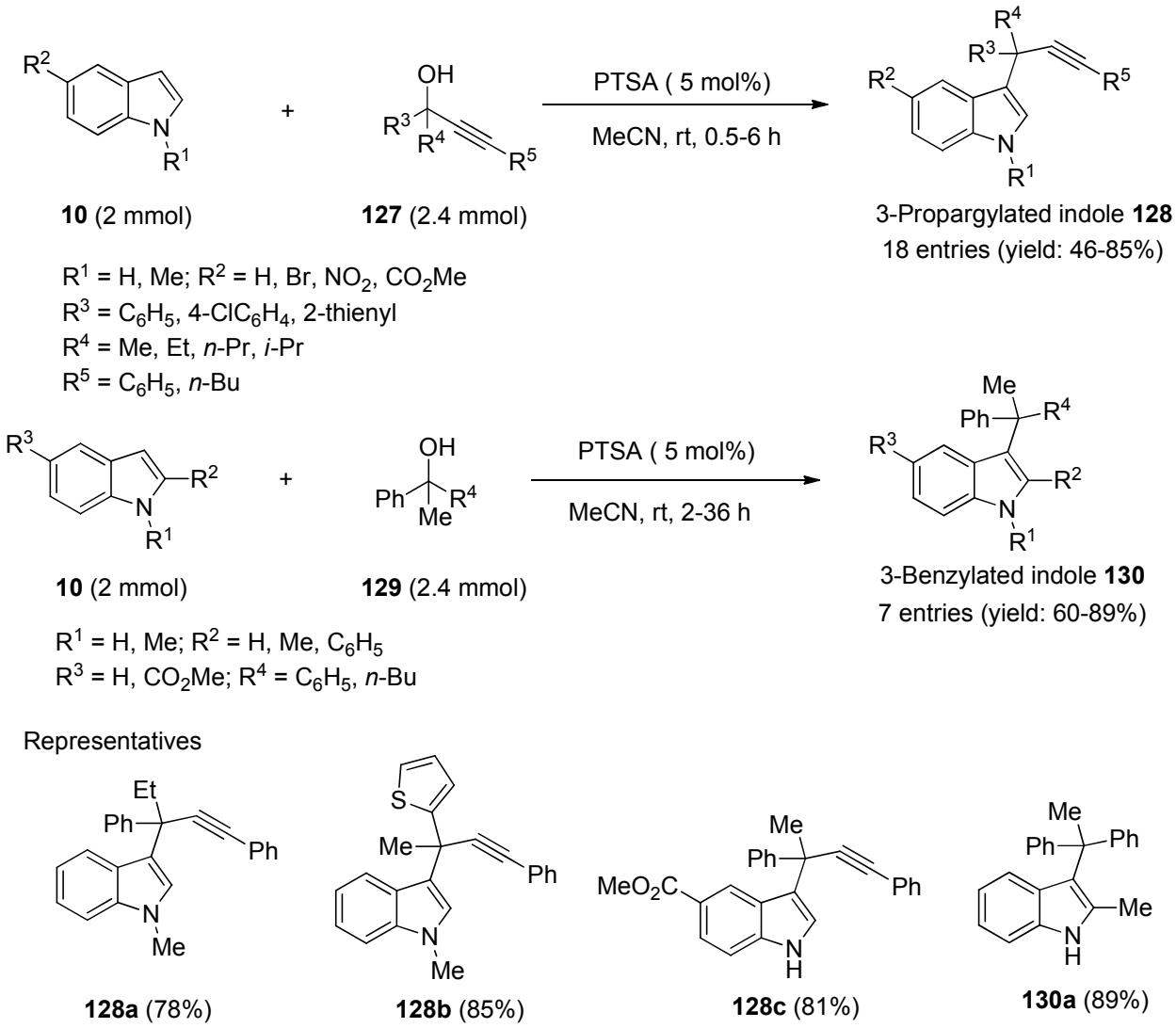

Scheme 45. PTSA-catalyzed synthesis of 3-propargyl/benzyl indole derivatives **128/130**

Xu et al.[254] also reported on the substitution reaction of ferrocenyl alcohols **131** with various nucleophiles **132** catalyzed by cerium ammonium nitrate (CAN) at ambient conditions (Scheme 46); this methodology offers an efficient and direct C–C bond formation from alcohols and nucleophiles in acetonitrile at room temperature condition leading to the synthesis of ferrocene functionalities **133** with moderate to high yields.

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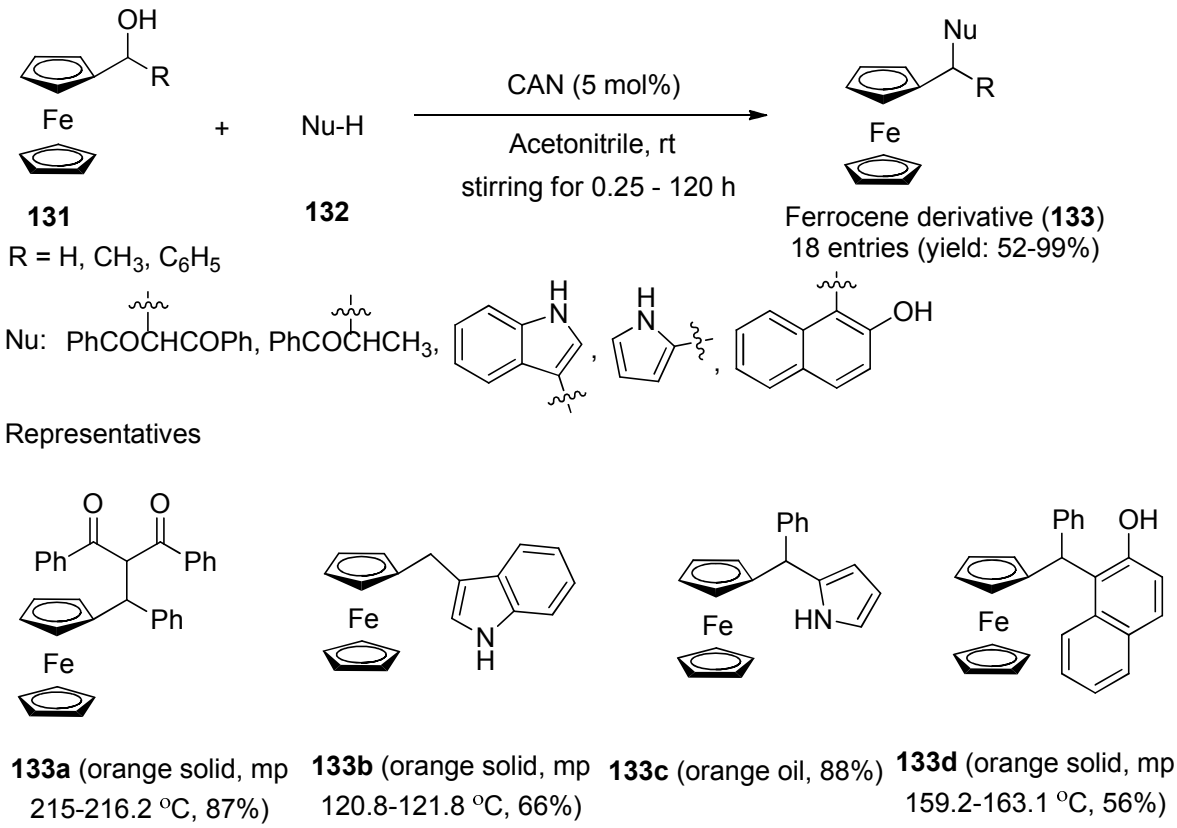

Scheme 46. CAN-catalyzed synthesis of ferrocenyl derivatives **133**

2.1.2.5. C-H activations

Zhang et al.[256] developed a convenient and efficient method for the synthesis of heteroaryl-group-containing compounds via the palladium-catalyzed C–H activation of heteroarenes leading to direct conjugate addition of heteroarenes (**134**) to α,β-unsaturated ketones (**135**) under mild reaction conditions to afford Michael adducts **136** in moderate to excellent yields (Scheme 47).

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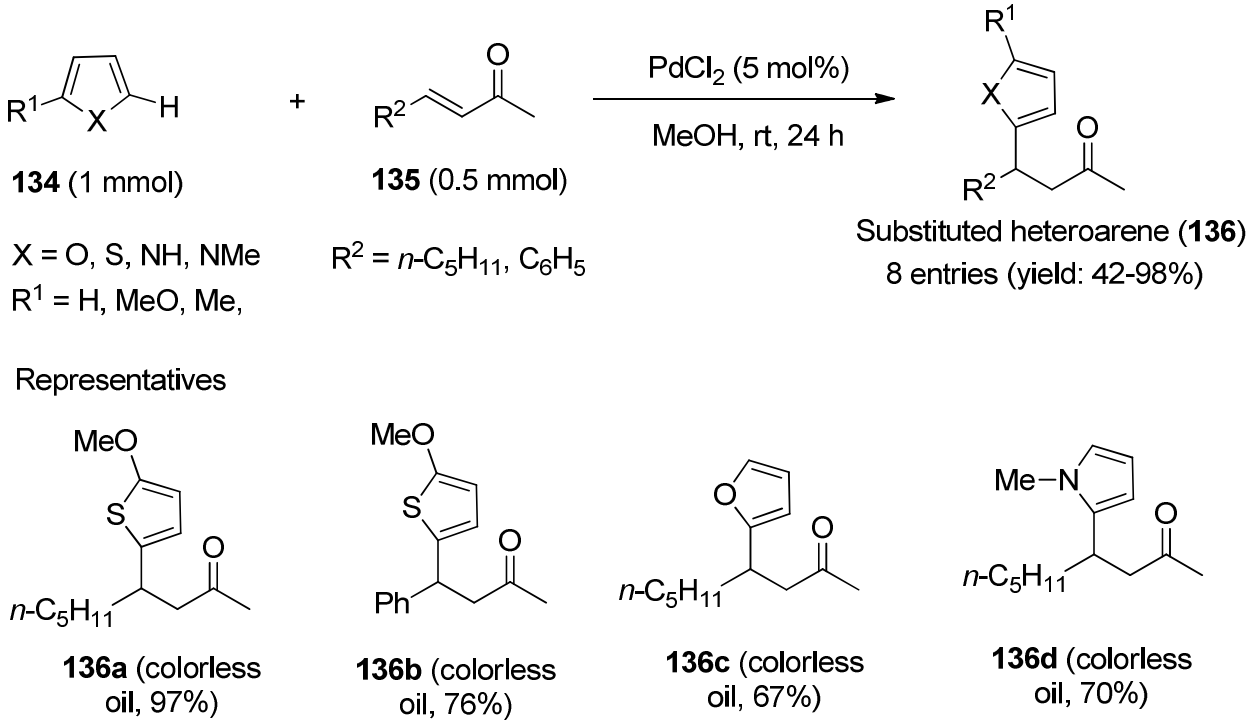
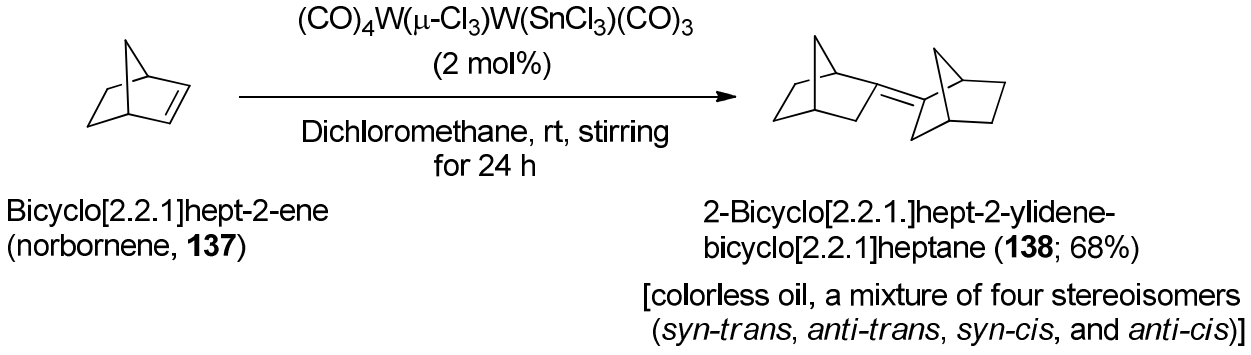


Scheme 47. $PdCl_2$-catalyzed synthesis of substituted heteroaryl derivatives **136**

A new and straightforward catalytic route to 2-bicyclo[2.2.1]hept-2-ylidenebicyclo[2.2.1]-heptane **138** involving C-H bond activation of bicyclo[2.2.1]hept-2-ene (**137**; norbornene) using a tungsten(II) carbonyl complex $[(CO)_4W(\mu\text{-}Cl)_3W(SnCl_3)(CO)_3]$ as a catalyst in dichloromethane was developed by Malinowska et al.[257] at ambient conditions (Scheme 48).



Scheme 48. Tungsten(II) carbonyl complex-catalyzed synthesis of 2-bicyclo[2.2.1]hept-2-ylidenebicyclo[2.2.1]-heptane **138**

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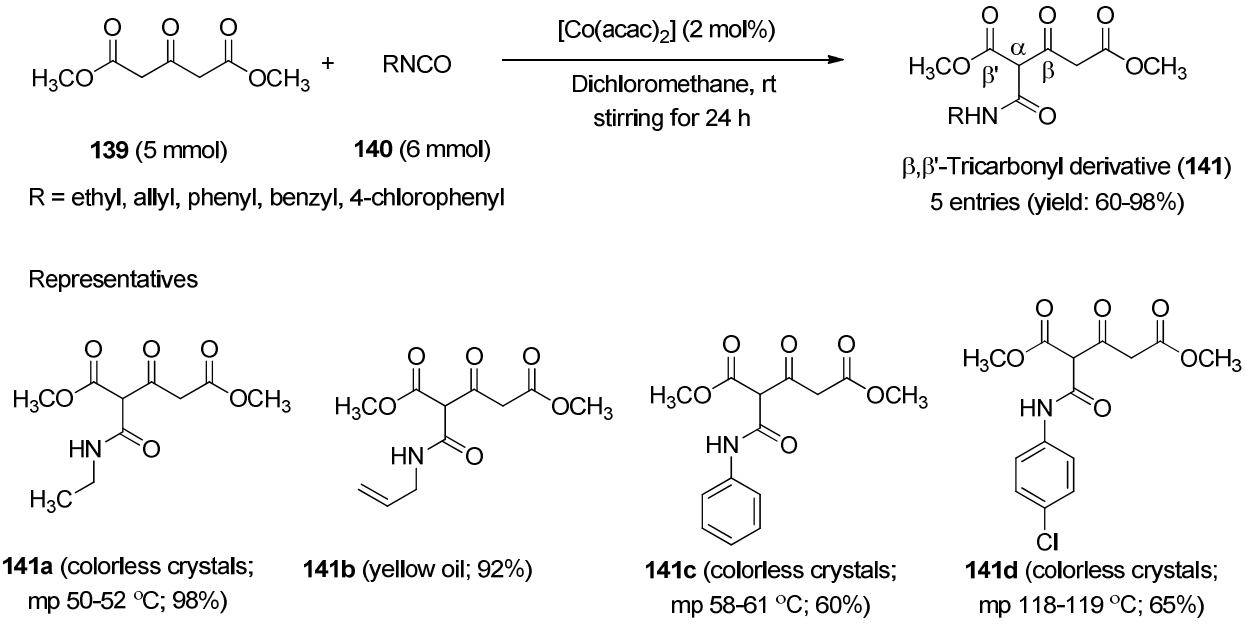
Substituted β,β′-tricarbonyl derivatives **141** were prepared by Veronese et al.[258] from reaction of β,β′-tricarbonyls (**139**) with isocyanates (**140**) using cobalt acetylacetonate [$Co(acac)_2$] catalyst in dichloromethane at room temperature (Scheme 39). The catalyst accomplished the 1:1 adduct involving the formation of a new C-C bond between the intercarbonylic methylene of **139** and the isocyanato group. This is also an example of C-H activation reaction occurring at ambient conditions.



Scheme 49. Cobalt acetylacetonate-catalyzed synthesis of substituted β,β′-tricarbonyls **141**

The quinone moiety is a privileged structure in medicinal chemistry for the discovery of pharmaceutical leads, and quinone-based compounds find immense applications in pharmaceutical chemistry.[101,259-267] Lamblin et al.[268] developed a facile route for 2-aryl-1,4-benzoquinones (**142**) via direct C-H arylation of *p*-quinone (**11**) with anilines (**24**) in the presence of *tert*-butyl nitrite in aqueous DMSO at room temperature under neutral, additive-free and metal-free conditions (Scheme 50). The investigators proposed that the reaction proceeds through *in situ* formation of a diazonium hydroxide **143**, which on homolytic decomposition generates free radical species and such radical intermediate, in turn, takes part in the arylation of quinone (Scheme 51).

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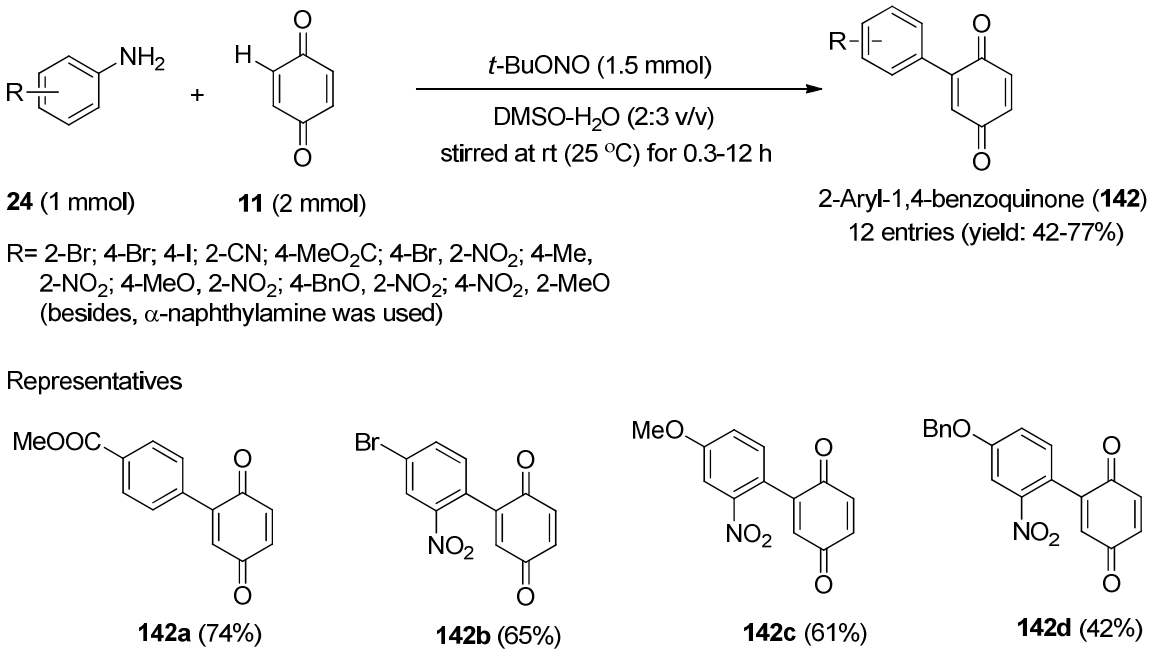
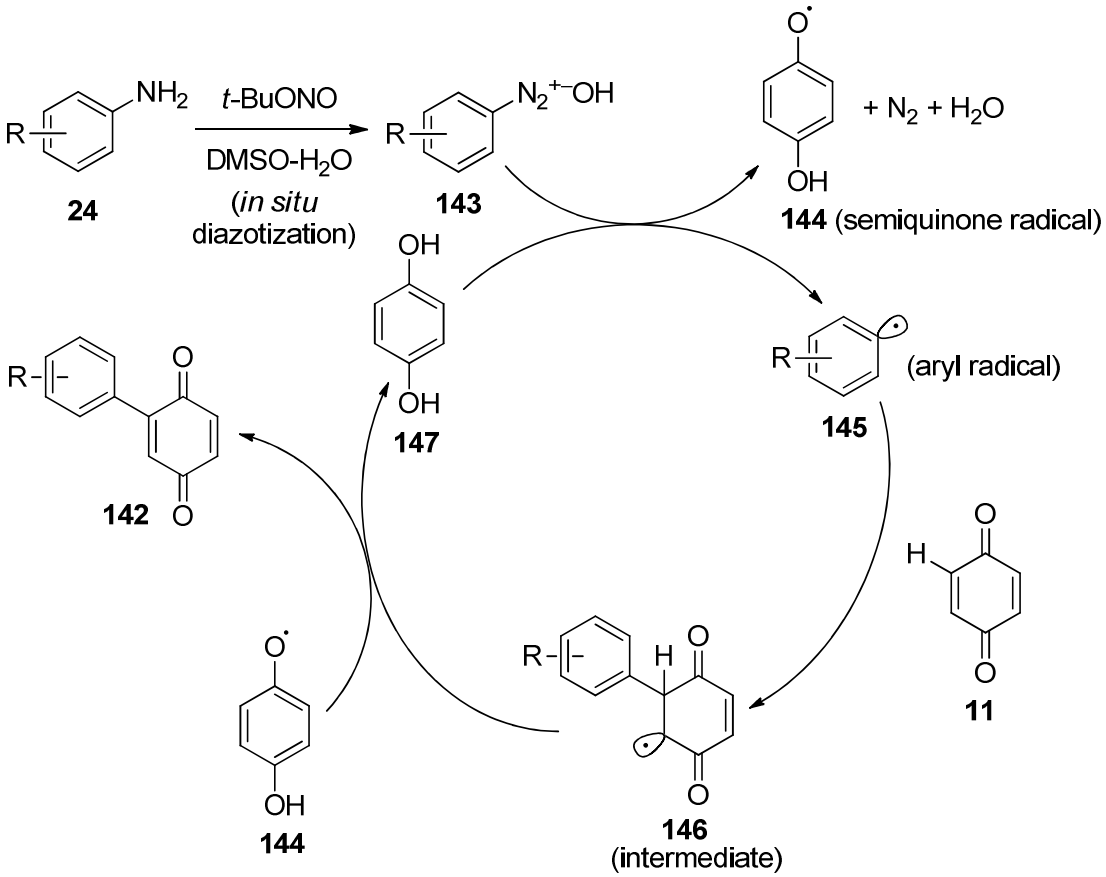


Scheme 50. Metal-free synthesis of 2-aryl-1,4-benzoquinones under neutral conditions



Scheme 51. Proposed mechanism for the direct C-H arylation of *p*-quinone

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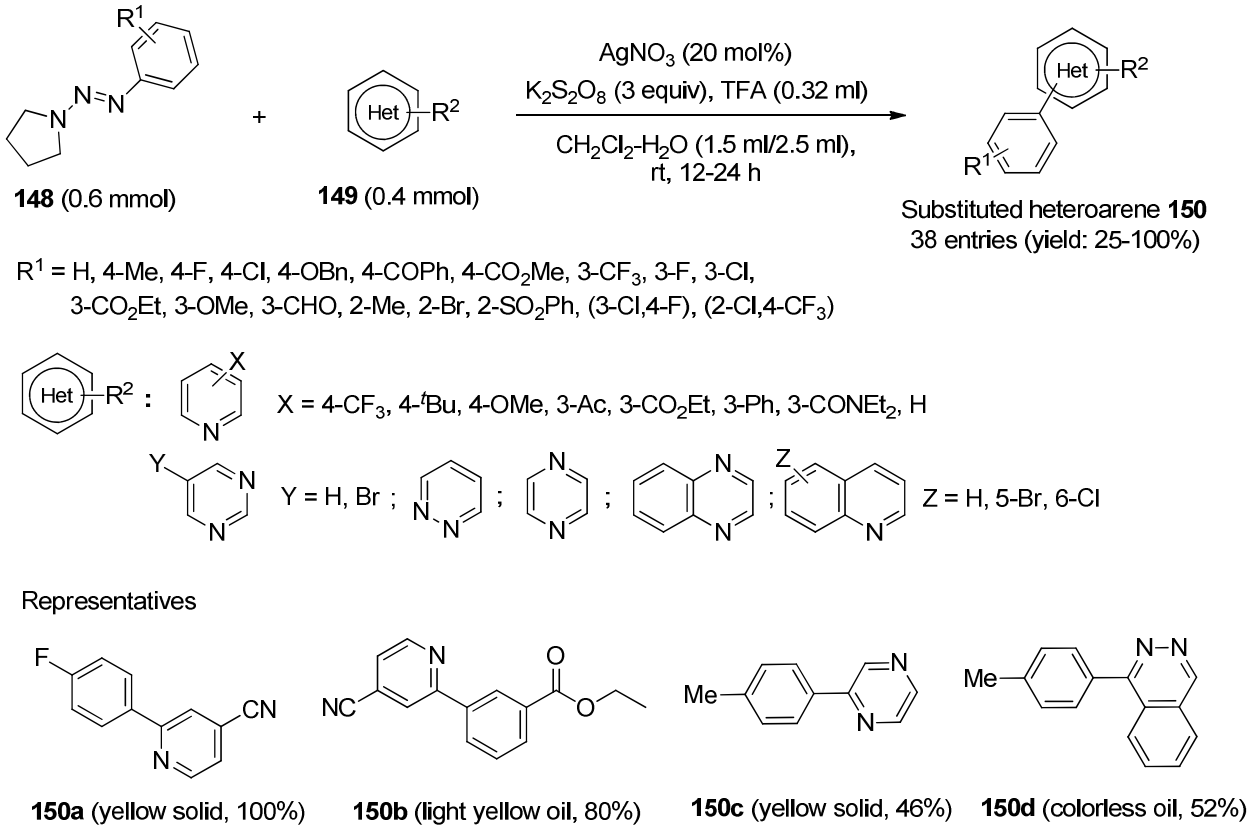
2.1.2.6. Coupling reactions

Wang and Falck[269] reported the first example of a rapid, open-flask, single-pot, and scalable process in which aryl radicals derived from aryl triazenes **148** were coupled with heteroarenes **149** *via* C–H functionalization to produce heterobiaryls **150** in moderate to good yields in dichloromethane-water (3:5 v/v) at room temperature (Scheme 52). Best results were obtained with electron-deficient heteroarenes, while both electron donating and withdrawing substituents in the triazene moieties were tolerated.



Scheme 52. Synthesis of heteroarene derivatives (**150**) *via* C-H functionalization

Fluorinated biphenyl derivatives are fundamental building blocks in fluorinated liquid crystals. Guo et al.[270] synthesized a variety of fluorinated biphenyl derivatives (**153**) in good yields *via* Pd-catalyzed Suzuki coupling reaction of aryl bromides and fluorinated phenylboronic acids in aqueous THF solvent at room temperature (Scheme 53). This approach with high activity, good selectivity, mild reaction condition and aqueous phase reaction, as well as potential recycling of the catalytic species offers an environmentally sustainable chemical processes and provides a practical procedure for the synthesis of fluorinated liquid crystals in industry applications.

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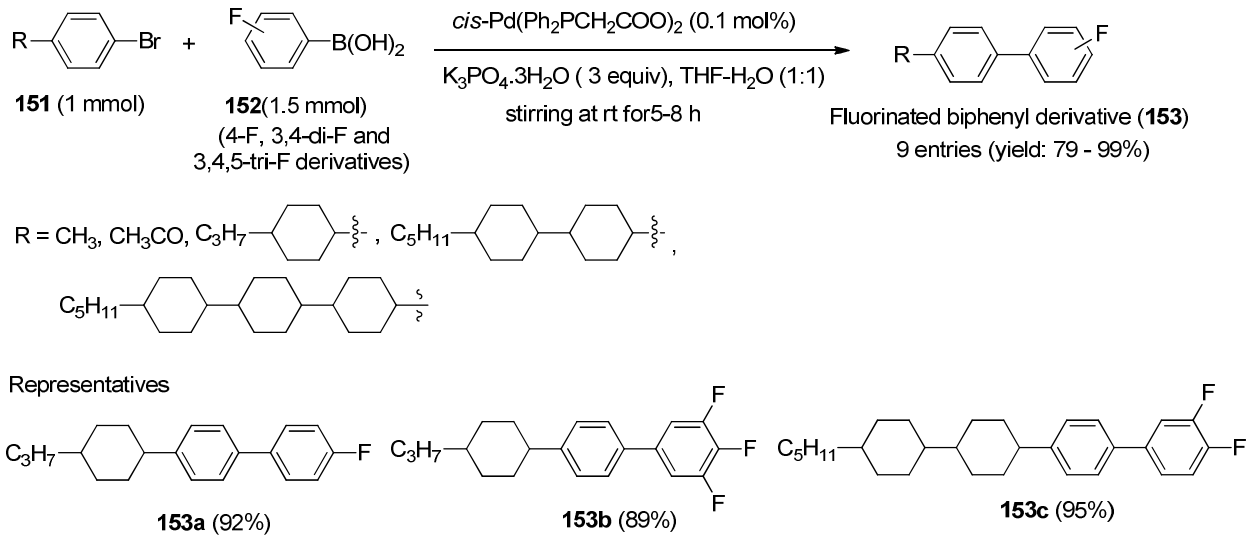
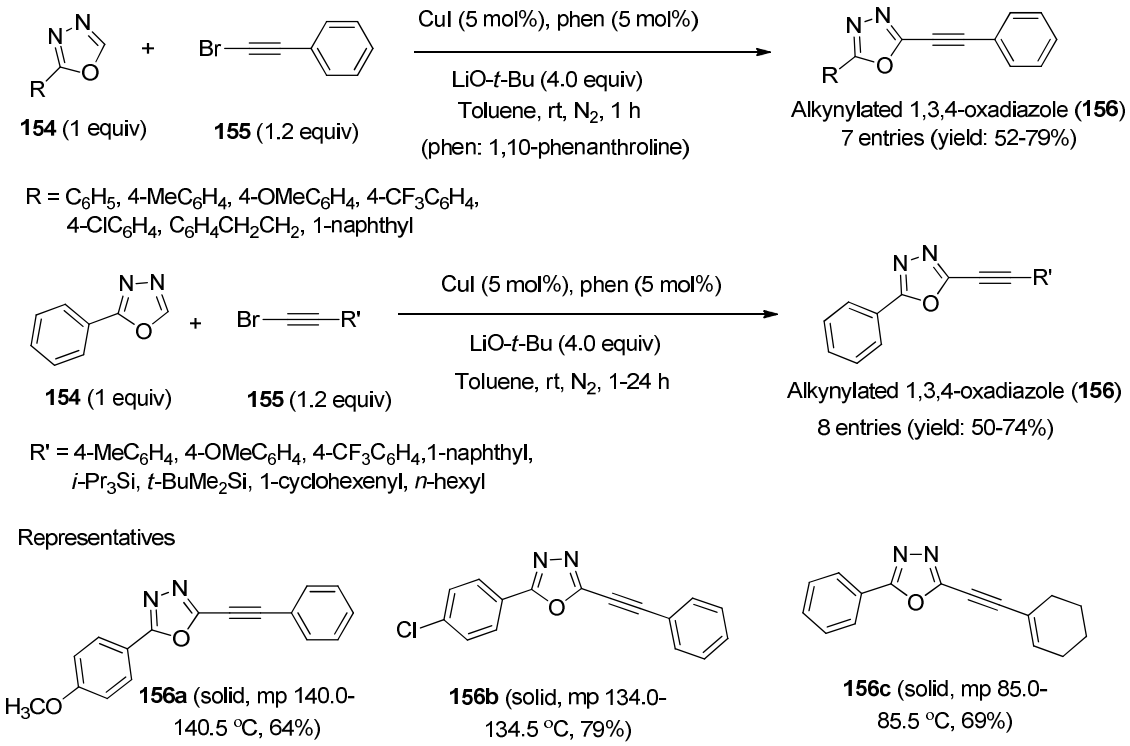


Scheme 53. Synthesis of fluorinated biphenyls **153** *via* Pd-catalyzed Suzuki coupling

2-Aryl- and 2-alkyl-1,3,4-oxadiazoles (**154**) were found to efficiently undergo direct alkynylation upon treatment with readily accessible alkynyl bromides in the presence of a copper catalyst at room temperature, offering a facile approach to the synthesis of biologically interesting substituted oxadiazoles **156** with an oxadiazole core attached with π-conjugated systems (Scheme 54).[271]



Scheme 54. Cu(I)-catalyzed synthesis of substituted 1,3,4-oxadiazoles **156**

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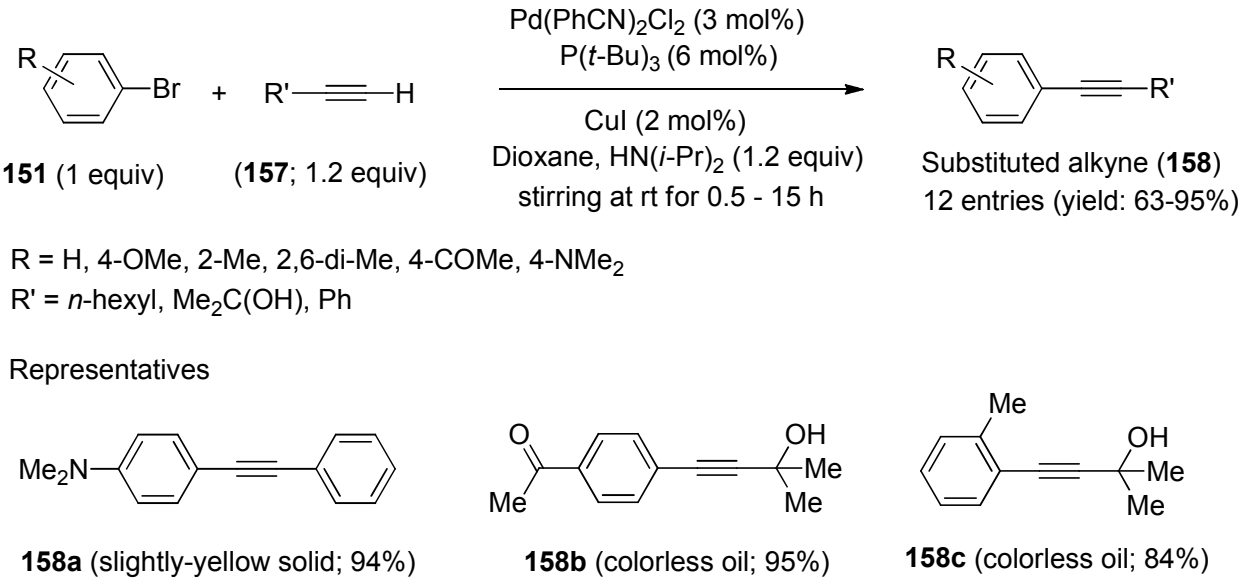
The Sonogashira coupling reaction of terminal acetylenes with aryl and vinyl halides provides a powerful method for synthesizing conjugated alkynes, an important class of molecules that have found application in diverse areas ranging from natural product chemistry to materials science.[272-278] In 2000, Hundertmark et al.[279] observed that $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ can as an efficient and a versatile catalyst for room-temperature Sonogashira reactions of aryl bromides **151** with terminal alkynes **157** in the presence of *N*,*N*-di-isopropylamine/dioxane in dioxane (Scheme 54).



Scheme 55. Synthesis of di-substituted alkynes **158** *via* Sonogashira coupling

However, Finke et al.[280] developed an optimized conditions for a general and convenient copper-free Sonogashira cross-coupling between aryl bromides and alkynes using Pd(I)-dimer as catalyst (**158**) and $ZnCl_2$ as promoter in the presence of *N*,*N*-di-isopropylamine/THF at room temperature to generate substituted alkynes in good yields (Scheme 56).

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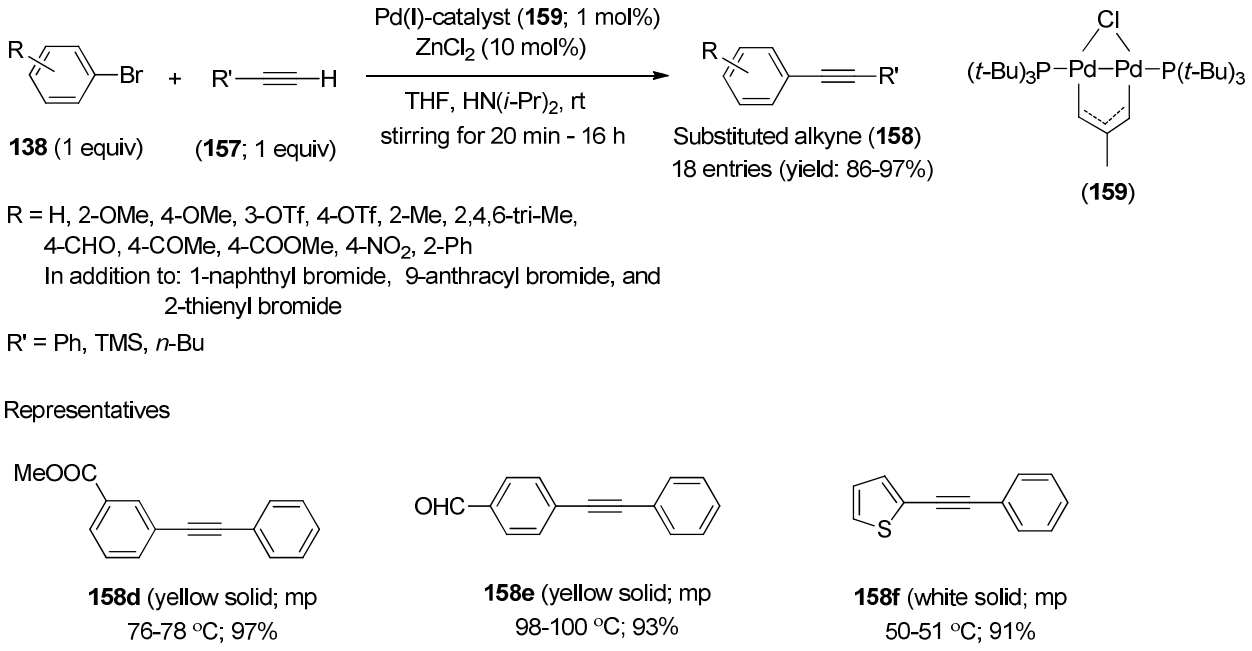

Scheme 56. Copper-free Sonogashira cross-coupling for the synthesis of di-substituted alkynes **158**

Copper-free Sonogashira coupling of aryl bromide with alkynes using $(AllylPdCl)_2$/P(*t*-Bu)$_3$ catalyst in the presence of piperidine or DABCO in acetonitrile at room temperature was also reported by Soheiji et al.[281] Another mild protocol for the copper-free Sonogashira coupling of aryl iodides with terminal acetylenes in water under aerobic conditions was accomplished using 1 mol % $PdCl_2$ in the presence of pyrrolidine at room temperature.[282]

2.1.2.7. Ring-expansion

Medium- and large-size ring systems are widespread, ranging from naturally occurring compounds to macrocyclic synthetic receptors or ligands, and their synthesis is still a challenging job for organic chemists.[283-288] Huang et al.[289] successfully demonstrated the ring-expansion reaction of bicyclic vinylidenecyclopropanes (**160**) in the presence of titanium chloride ($TiCl_4$) as a Lewis acid catalyst in dichloromethane, providing an efficient method for the synthesis of naphthalenes with annulated carbocycles of various ring sizes (**161**) in good to excellent yields under mild conditions at room temperature (Scheme 57).

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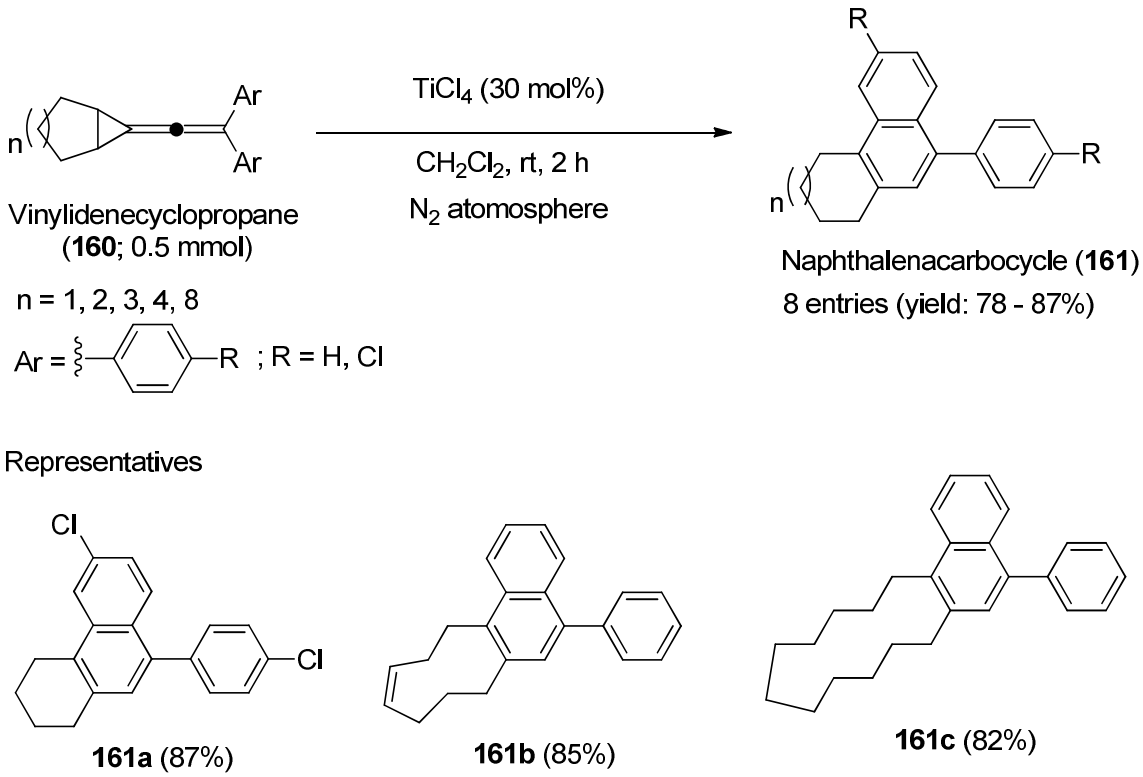

Scheme 57. $TiCl_4$-catalyzed synthesis of naphthalenacarbocycles **161**

2.2. Carbon-carbon bond forming reactions in solvent-free/neat conditions

Solvent-free reaction protocols offer several advantages like reduced pollution, lower cost, and simplicity in processing, which are beneficial to the industry as well as to the environment.[8,36,290-296] In recent years, mechanochemistry (i.e. chemical synthesis using mechanical force) has attracted much attention because it allows promotion of reactions under solvent-free conditions by grinding reactants together.[297,298] Mechanochemical synthesis affords many advantages, such as greater efficiency with regard to time, materials, and energy usage, as well as the discovery of new or improved reactivity and products, as an alternative approach to synthesis. Planetary ball mill has now also come-up as an effective tool to carrying out a plethora of organic transformations with substantial improvements in reaction time, selectivity and energy efficiency, compared to conventional solution-based synthesis.[299-303] The present section focuses on the applications of various solvent-free protocols in implementing carbon-carbon bond forming reactions reported in recent times.

2.2.1. Substitution reactions

Ballini et al.[304] developed a cetyltrimethylammonium hydroxide (CTAOH)-catalyzed general method for the formation of carbon–carbon bond using nitroalkanes **162** with several electrophilic alkenes **70** (such as α,β-unsaturated ketones, α,β-unsaturated esters, α,β-unsaturated sulphones, and α,β-unsaturated nitriles) and both aromatic and aliphatic aldehydes **1** under solvent-free conditions at room temperature (Scheme 58). The process is easy t o handle and high yielding with short reaction time.

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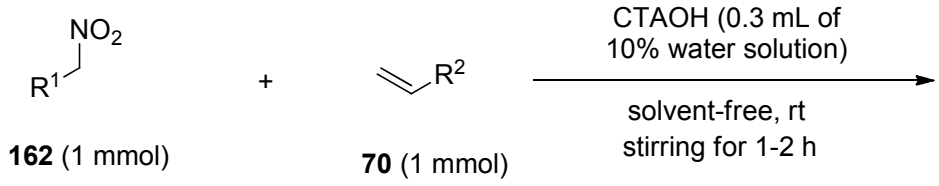
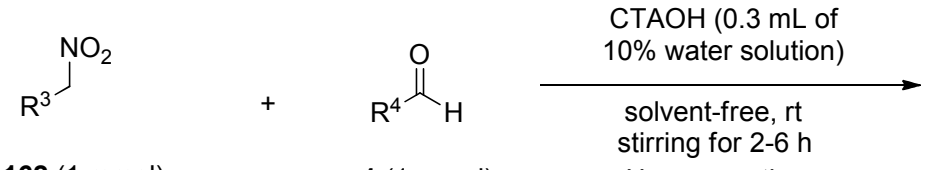


162 (1 mmol) **70** (1 mmol) Michael adduct (**163**)

14 entries (yield: 65-90%)

R^1= CH_3, C_2H_5, *n*-Pr, *n*-Bu, *n*-Pentyl, $CH_3OCO(CH_2)_3CH_2$, $CH_3COCH_2CH_2$, $CH_3CH(OH)CH_2CH_2$

R^2= $COOCH_3$, $COOC_2H_5$, COC_2H_5, CN, SO_2Ph, $COCH_3$ (2-cyclohexenone was also used in two entries)

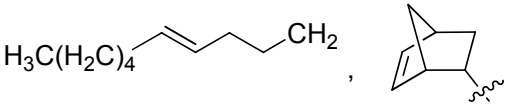


162 (1 mmol) **1** (1 mmol) β-Nitroalcohol (**164**)

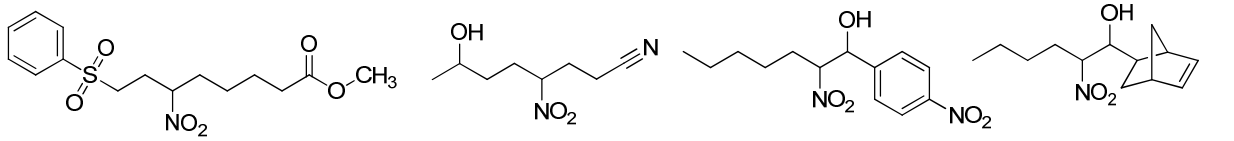
11 entries (yield: 68-86%)

R^3= C_2H_5, *n*-Pr, *n*-Bu, *n*-Pentyl, $CH_3OCO(CH_2)_3CH_2$, C_2H_5OCO, $PhCH_2$; nitrocyclopentane was also used in one entry)

R^4= H, *n*-Pr, $CH_3(CH_2)_8$, $CH_3(CH_2)_4$, Ph, $PhCH_2CH_2$, 4-$NO_2C_6H_4$,



Representatives



163a (yellow oil; 73%) **163b** (yellow oil; 72%) **164a** (yellow oil; 76%) **164b** (white solid, mp 43-45 °C, 85%)

Scheme 58. CTAOH-catalyzed one-pot synthesis of substituted nitroalkanes **163** and β-nitroalcohols **164**

An efficient solvent-free protocol for Friedel-Crafts acylation of aromatic compounds using nontoxic, inexpensive and reusable ZnO powder as solid catalytic surface was developed by Sarvari and Sharghi[305] under ambient conditions. The advantages of this environmentally benign and safe protocol include a simple reaction setup not requiring specialized equipment, very mild reaction conditions, high product yields, very short reaction times, and the elimination of solvents.

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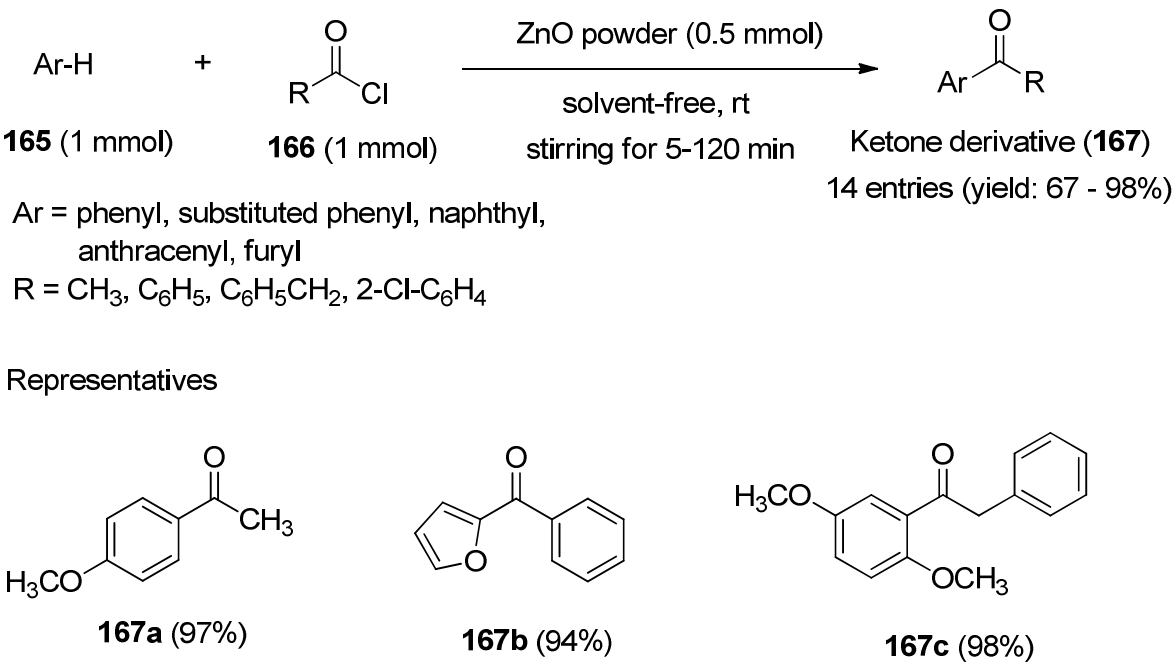

Scheme 59. ZnO-catalyzed one-pot synthesis of substituted ketones **167** via Friedel-Crafts acylayion

In another report, Lakshmi Kantam et al.[306] demonstarted a simple and recyclable room temperature protocol for direct alkylation of nitrogen-heterocyles such as indoles and pyrroles with epoxides *via* Friedel-Crafts reaction by using ionic liquid [bmim][OTf] as an efficient catalyst and reaction medium (Scheme 60). The process takes place with high regio- and chemoselectivity. The synthesized compounds are of pharmacological and biological importance.[307-313]

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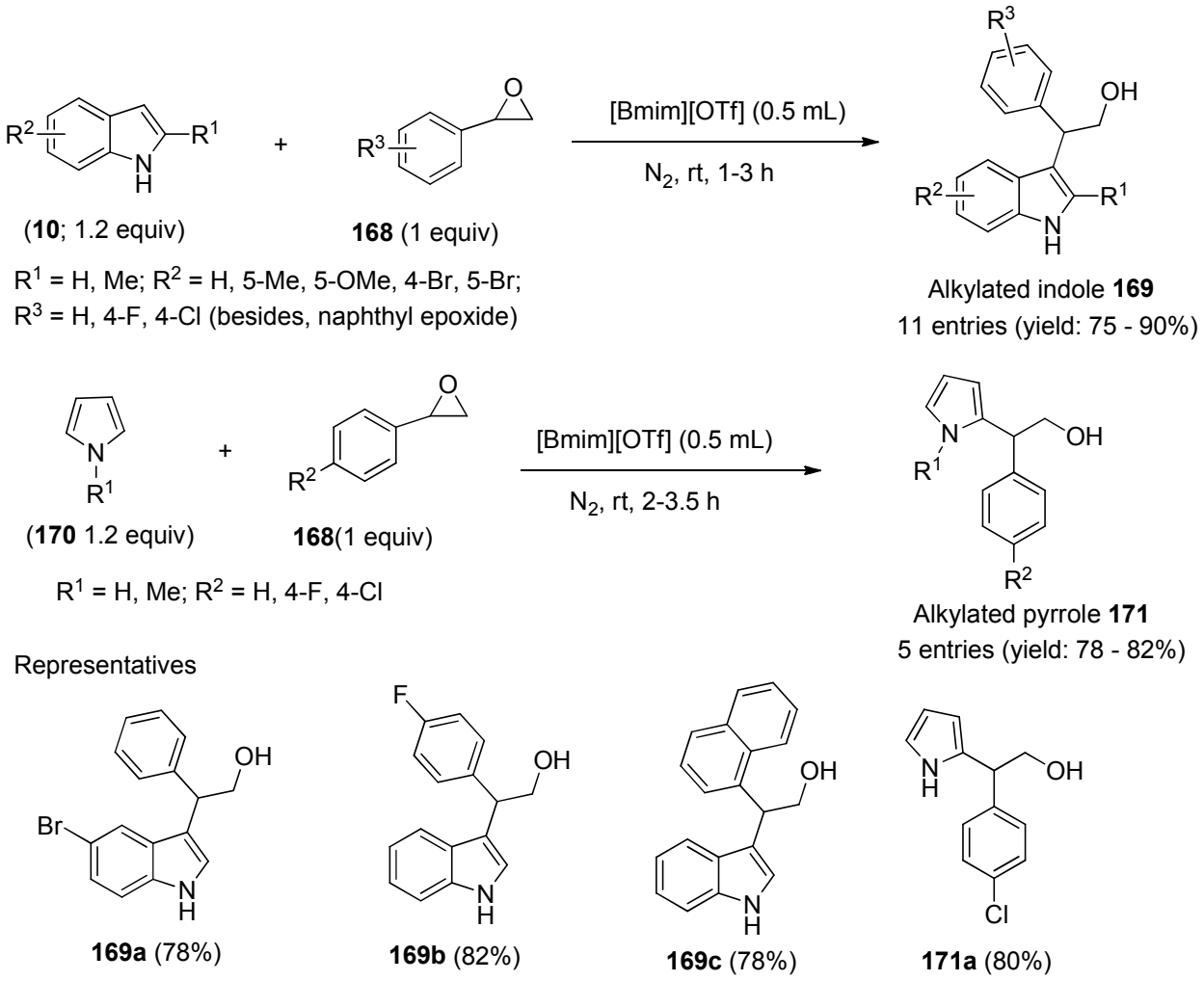

Scheme 60. Ionic liquid-catalyzed synthesis of alkylated *N*-heterocycles **169** and **1171** *via* Friedel-Crafts reaction

Zhang et al.[314] also reported that Friedel–Crafts alkylation of indoles by *tert*-enamides (**172**) proceeds effectively in the presence of acetic acid to afford the pharmacologically and biologically active 2-oxo-1-pyrrolidine derivatives **173** in moderate to good yields under neat condition at room temperature (Scheme 61).

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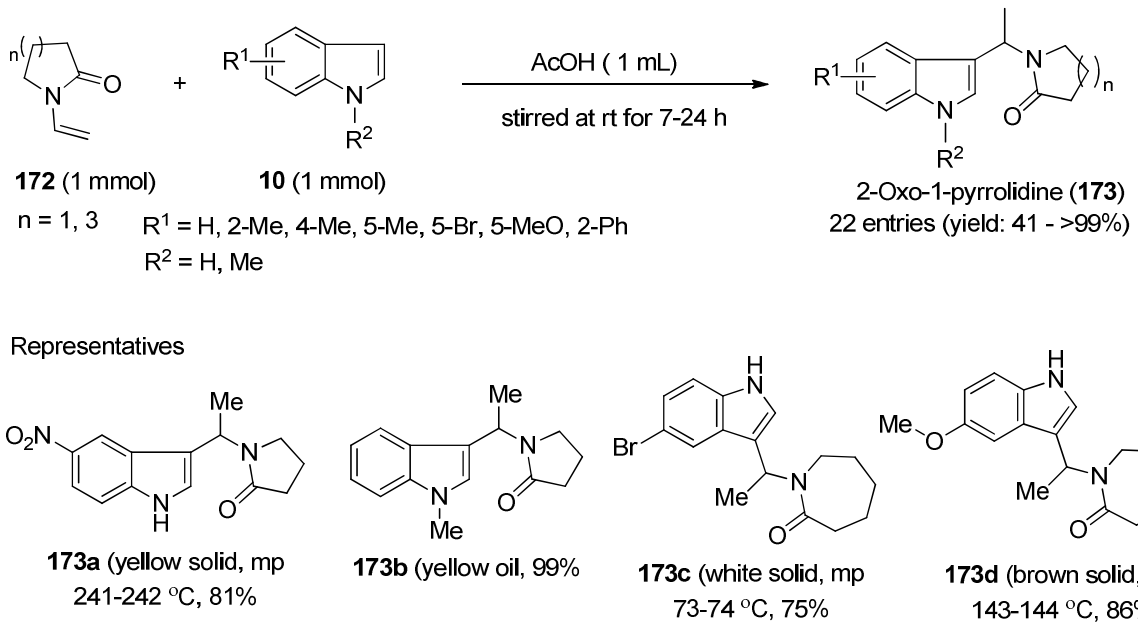
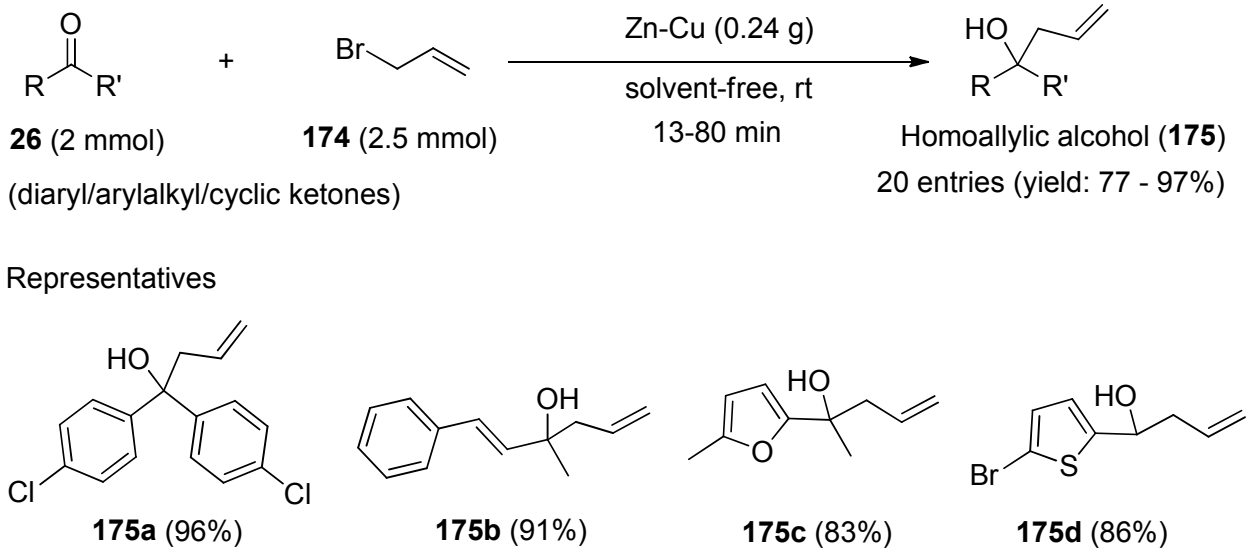


Scheme 61. Acid-catalyzed synthesis of 3-substituted indoles **173** *via* Friedel-Crafts reaction

2.2.2. Addition reactions

Homoallylic alcohols are important synthons of many biologically active molecules such as macrolides, polyhydroxylated natural products, and polyether antibiotics.[315,316] Zhou et al.[317] observed that zinc-copper couple could efficiently mediate the Barbier-type reaction of ketones and allyl bromide to furnish the corresponding homoallylic alcohols **175** in high to excellent yields at room temperature under solvent-free conditions (Scheme 62). Mild conditions, short reaction time, eco-friendliness and high yields are the key advantages of this method.



Scheme 62. Zn-Cu couple-catalyzed one-pot synthesis of homoallylic alcohols **175** *via* Barbier-type reaction

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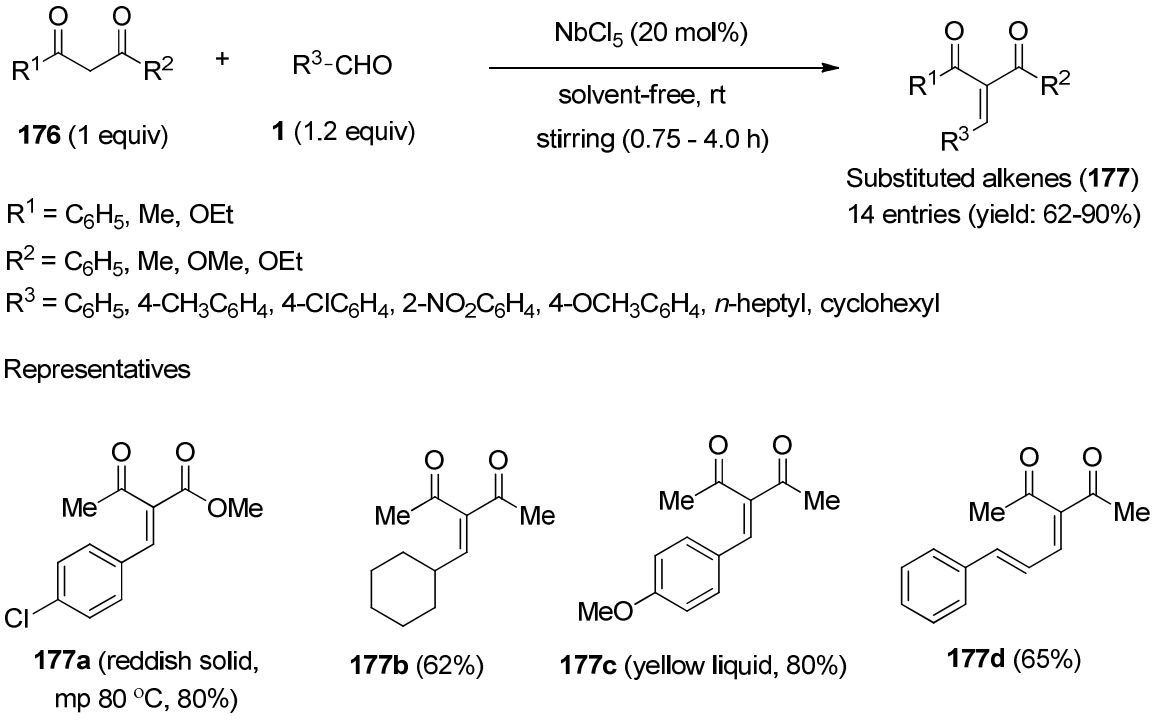
2.2.3. Condensation reactions

A series of trisubstituted alkenes were synthesized by condensation of β-diketones or β-ketoesters (**177**) with aldehydes **1** in presence of $NbCl_5$ as a Lewis acid catalyst in solvent-free conditions at room temperature (Scheme 61).[318] A solvent-free reaction with a shorter time and mild reaction conditions involving room temperature and single product formation are the key features involved in the present protocol.



Scheme 63. $NbCl_5$-catalyzed one-pot synthesis of trisubstituted alkenes **177**

Palmieri et al.[319] developed an eco-friendly simple and heterogeneous synthetic approach for the preparation of potentially interesting (*Z*)-α-bromonitroalkene compounds (**179**) with overall good yields *via* a two-step transformation involving Henry reaction under solvent-free conditions at room temperature (Scheme 64). It is to be noted that the final dehydration of nitroalkanol proceeds in this process under acidic conditions, contrary to the standard procedures that usually employ basic conditions.

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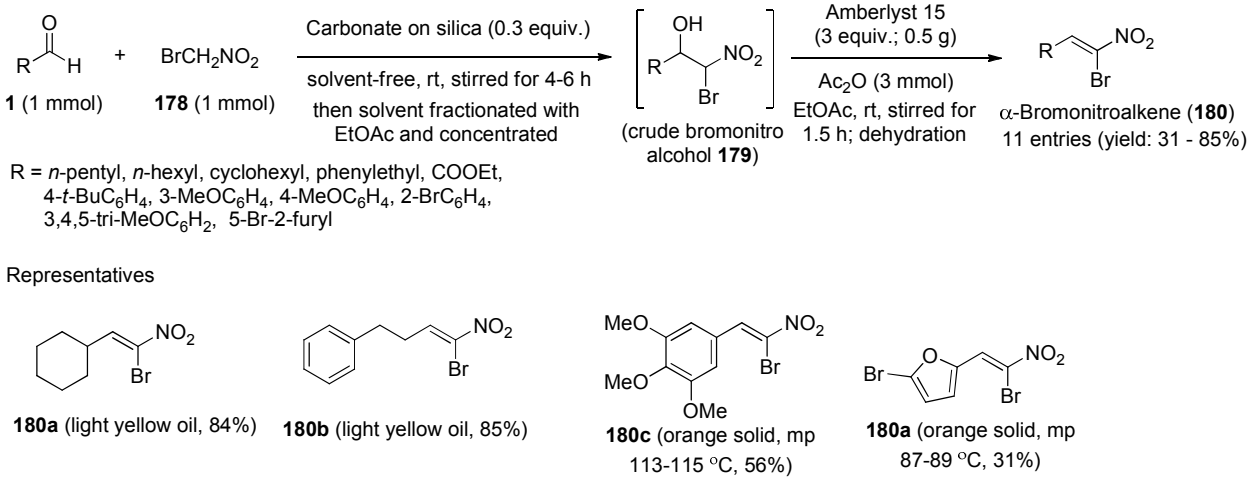
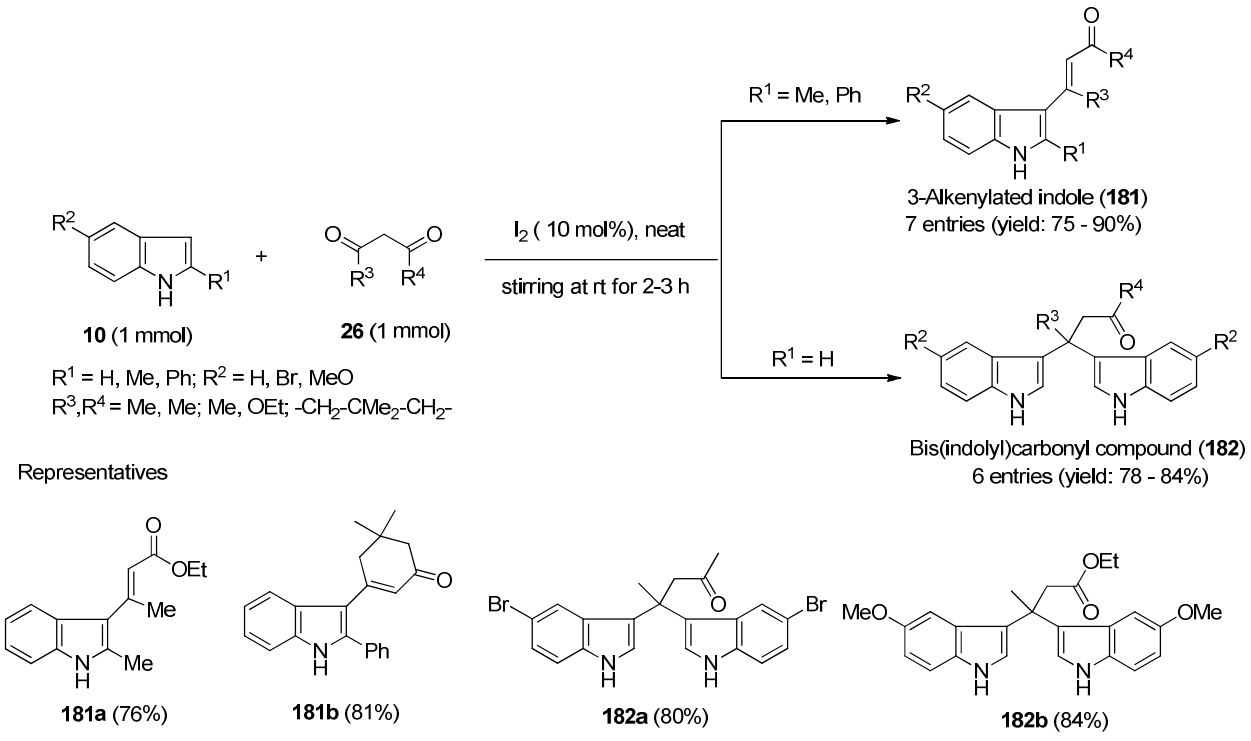


Scheme 64. Base-catalyzed one-pot synthesis of (*Z*)-α-bromonitroalkenes **180** *via* Henry reaction

Molecular iodine has been found to be as an efficient, inexpensive, and easy-to-handle catalyst for C-3 alkylation/alkenylation of diverse indoles with 1,3-dicarbonyl compounds at room temperature under solvent-free conditions with excellent yields (Scheme 65).[320]



Scheme 65. Iodine-catalyzed synthesis of 3-alkenylated indoles **181** and bis(indolyl)carbonyls **182**

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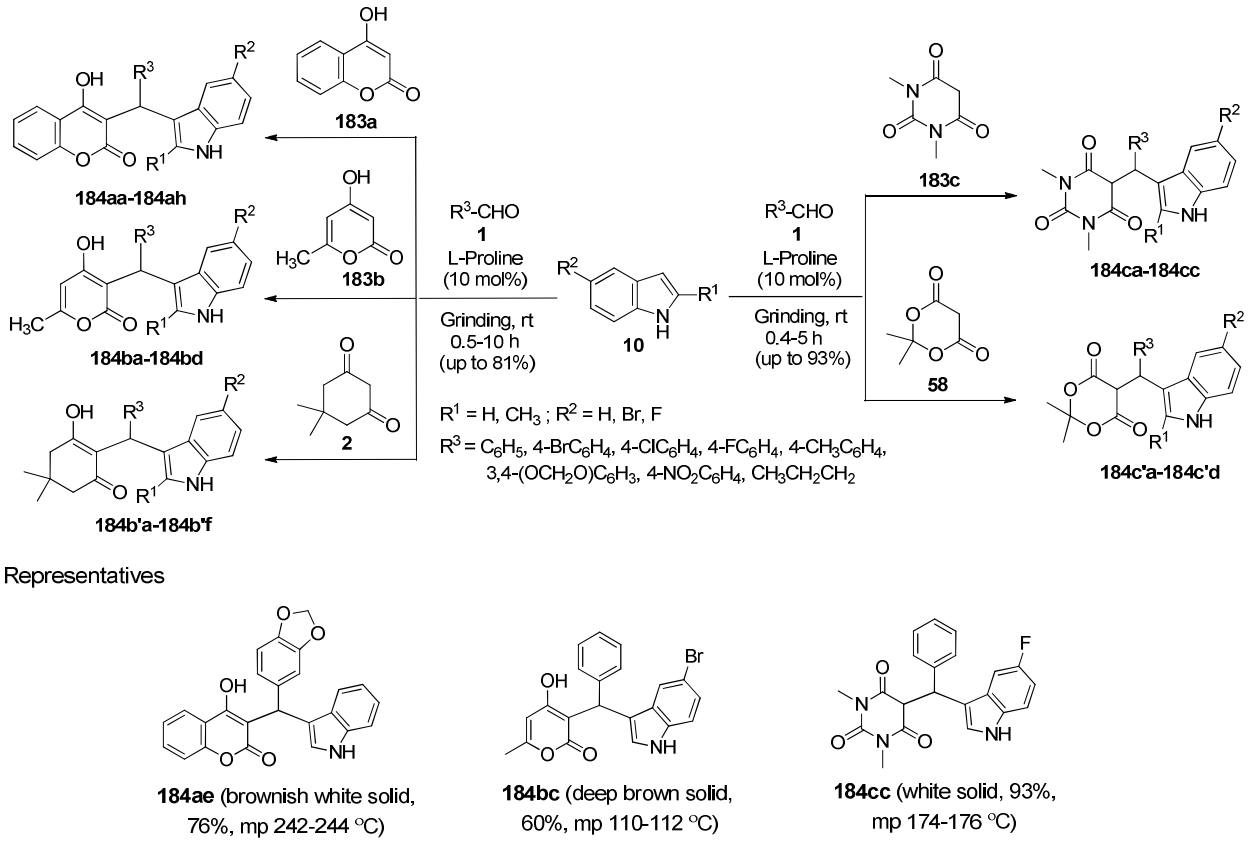
2.2.3. One-pot multicomponent reactions

Both 1,1-dihomoaryl- and 1,1-diheteroaryl-methane scaffolds, particularly involving indolyl and coumarolyl moieties represent 'privileged' structural motifs in pharmaceutical drugs and numerous potentially bioactive natural products.[321-326] Recentgly, Brahmachari and Das have reported a convenient, clean and highly efficient protocol for the synthesis of *gem*-(β-dicarbonyl)arylmethanes (**184**) *via* multicomponent reaction simply by grinding the mixture of indoles (**10**), C-H activated acids (4-hydroxycoumarin, 4-hydroxy-6-methyl-2*H*-pyran-2-one, dimedone **2**, *N*,*N*-dimethylbarbituric acid, Meldrum's acid **58**) (**183**) and aldehydes (**1**) in the absence of solvent under L-proline catalysis at room temperature (Scheme 66).[327] L-Proline is a very useful and environmentally friendly organocatalyst to validate this useful transformation in a facile manner. In addition to other notable outcomes such as mild and solvent-free reaction conditions, operational simplicity and good yields, the major advantage of our present protocol is an improved conditions for the synthesis of *gem*-(β-dicarbonyl)arylmethane derivatives instead of the formation of usual *bis*-indoles.[327]



Scheme 66. L-Proline-Catalyzed three-component one-pot synthesis of *gem*-(*β*-dicarbonyl)arylmethanes **184**

A plausible mechanism for this transformation has also been suggested (Scheme 67). The initially formed iminium salt (**164**) arising out of the reaction between aldehyde (**1**) and L-proline, undergoes Mannich reaction with C-H activated acid (**162**) to generate intermediate **166** which immediately takes part in Michael addition with the indole moiety (**10**) affording the desired product **163**. L-proline releases out for the next cycle.

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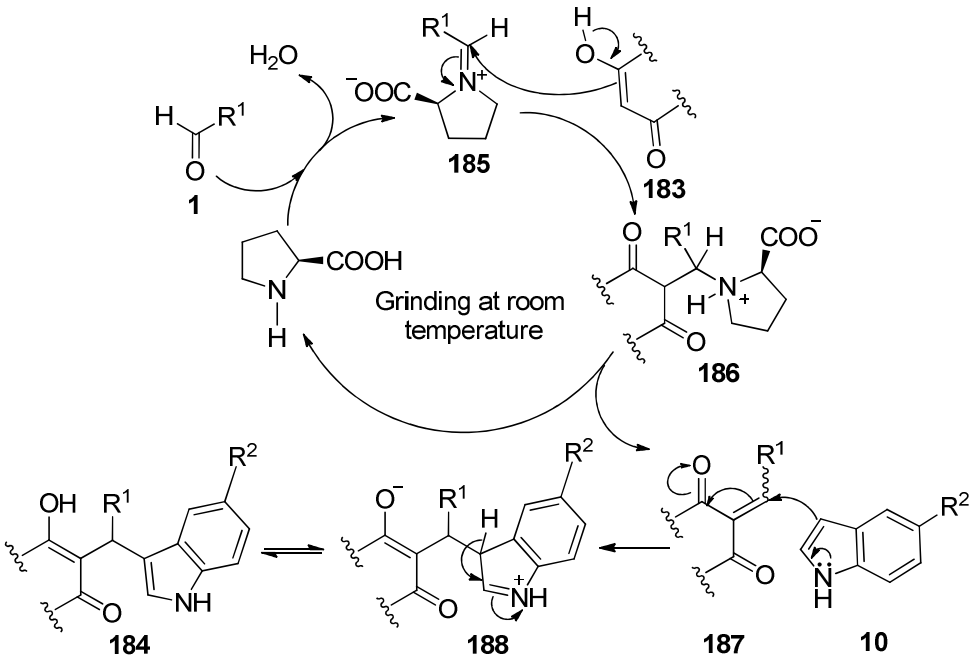

Scheme 67. Proposed mechanism for the L-proline catalyzed multicomponent synthesis of the *gem*-(β-dicarbonyl)arylmetahnes **184**

Sulfamic acid has been reported to behave as a highly efficient organocatalyst for the condensation of indoles with various aldehydes or ketones. An et al.[328] demonstrated an efficient and cost-effective protocol for the synthesis of *bis*(indol-3-yl)methanes **189** at room temperature under neat conditions (Scheme 68). Mild reaction conditions, easy product separation, reusability of the catalyst are some of the major advantages of this protocol.

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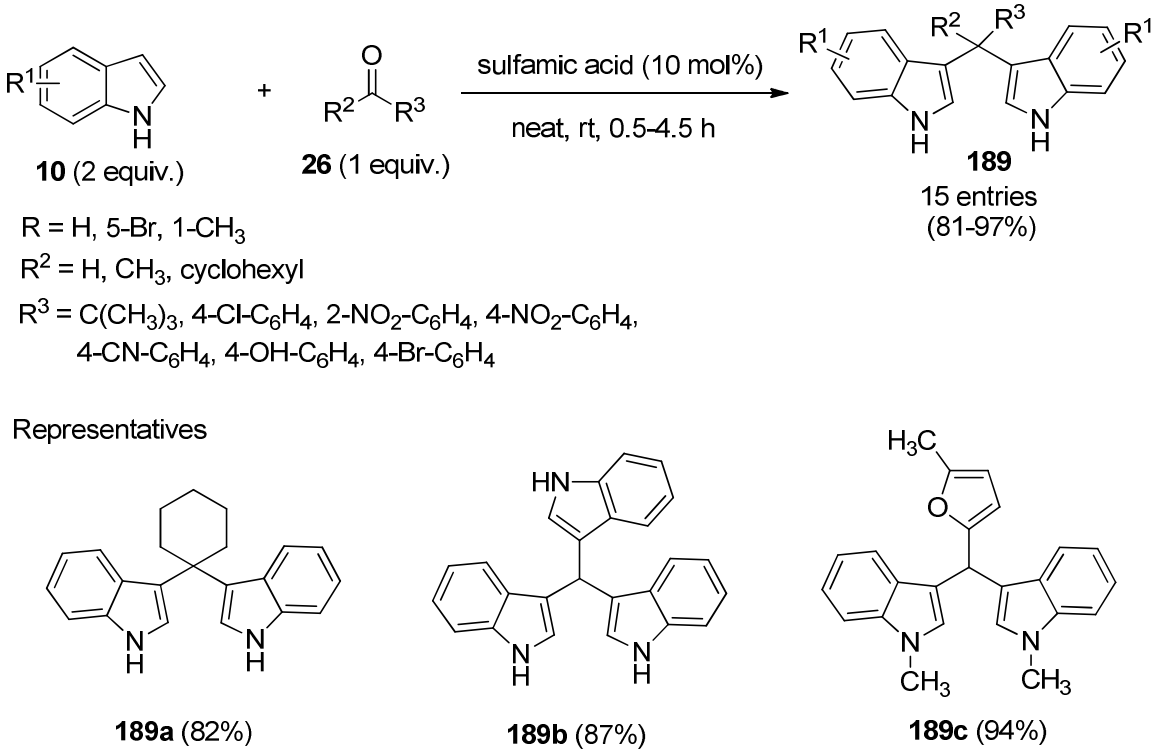

Scheme 68: Sulfamic acid-catalyzed synthesis of *bis*(indol-3-yl)methanes **189**

Kumar et al.[329] developed L-proline catalyzed efficient protocol for one-pot synthesis of 3-amino-alkylated indoles **187** *via* a three-component Mannich-type reaction of secondary amines (**186**), aldehyde (**1**) and indoles (**10**) under solvent-free conditions at room temperature (Scheme 69). The notable advantage of this methodology is an improved condition for the synthesis of such compounds without the formation of bis-indoles.

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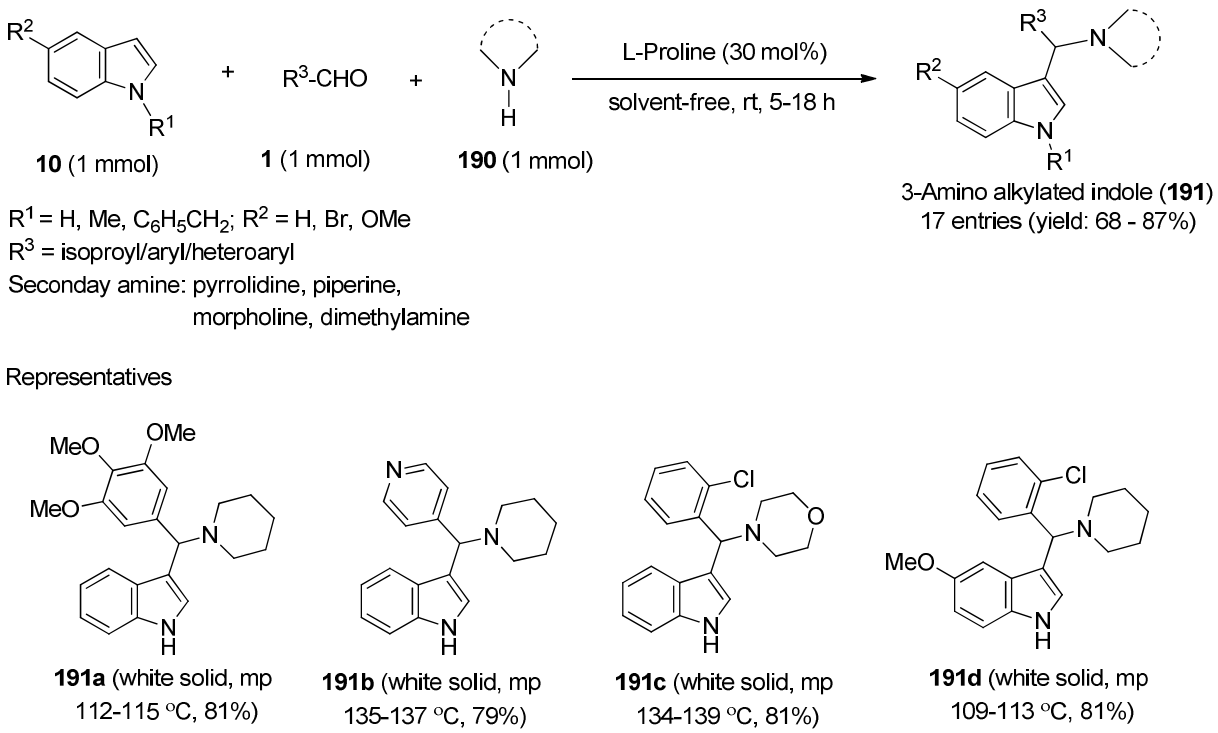

Scheme 69. L-Proline-catalyzed one-pot synthesis of 3-amino-alkylated indoles **191**

A solvent-free, environmentally clean and a general protocol was developed by Mulla et al.[330] for the efficient synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols **194** in good to excellent yield via one-pot three-component condensation of various aldehyde, amide/urea/carbamate, and naphthols/phenols using ethylammonium nitrate (EAN) as reusable ionic liquid catalyst under neat reaction condition at ambient temperature (Scheme 70). EAN was recovered and recycled several times without loss of catalytic activity.

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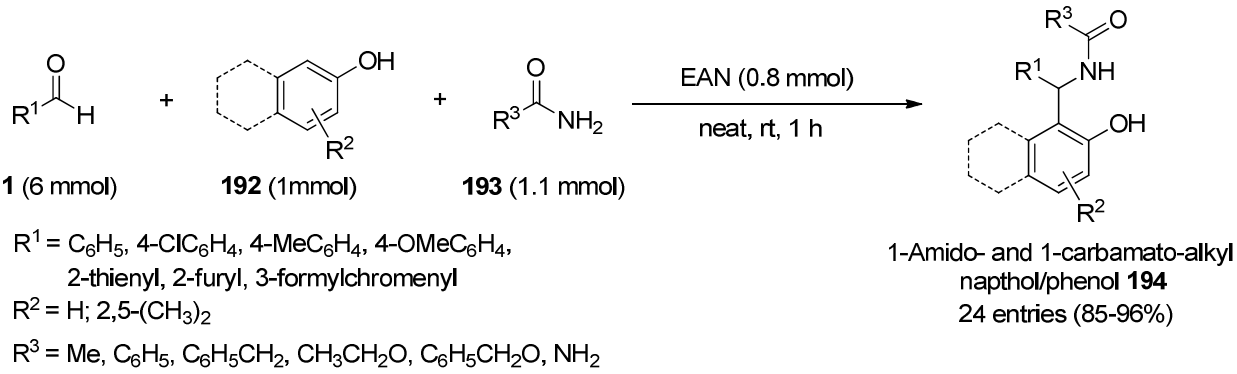
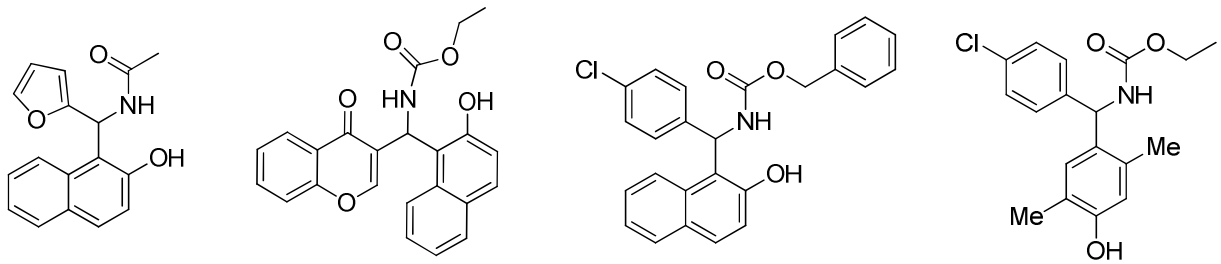


Representatives



194a (brown solid, mp 226-228 °C, 87%)

194b (yellow solid, mp 181-183 °C, 85%)

194c (white solid, mp 154-156 °C, 90%)

194d (yellow solid, mp 166-168 °C, 95%)

Scheme 70. EAN-catalyzed one-pot synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols **194**

The investigators proposed a plausible mechanism for the transformation. The reaction involves first the activation of carbonyl group of aldehyde by EAN (intermediate **195**) followed by the nucleophilic addition of beta-naphthol to obtain complex **196**. The removal of water from complex **196** produces intermediate **197** as an *ortho*-quinonemethide. The subsequent activation of **197** by EAN to generate **197′** as a Michael acceptor is followed by *in situ* Michael addition of amide or carbamate or urea to release instantly the corresponding product **194**.

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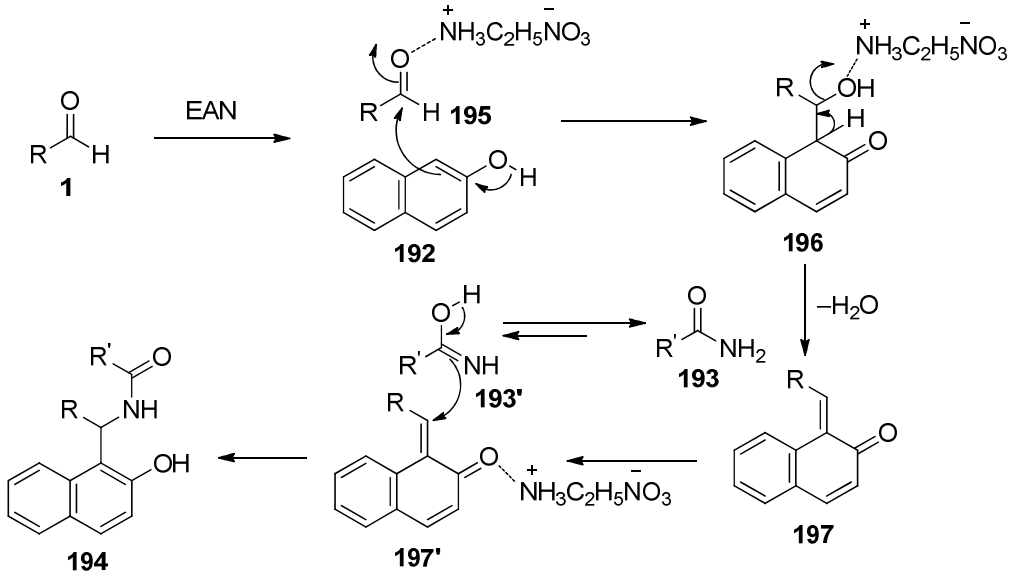
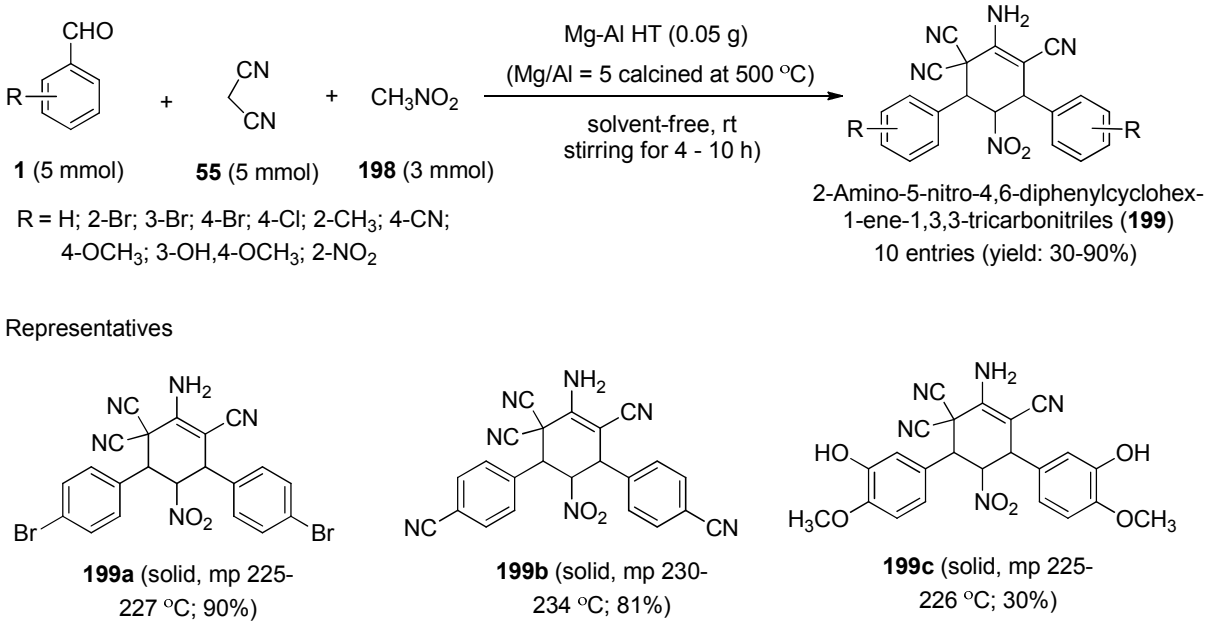


Scheme 71. Proposed mechanism for EAN-catalyzed synthesis of 1-amido- and 1-carbamato-alkyl naphthols/phenols **194**

Kshirsagar et al.[331] reported for the first time on one-pot synthesis of functionalized cyclohexenes **199** through a three-component reaction in the presence of a solid catalyst; the investigators demonstrated that Mg-Al hydrotalcite (Mg-Al HT calcined at 500 °C) acts as an efficient solid heterogeneous catalyst for solvent-free one-pot three-component synthesis of a series of 2-amino-5-nitro-4,6-diarylcyclohex-1-ene-1,3,3-tricarbonitriles (**199**) from the condensation of aryl aldehyde, malononitrile, and nitromethane at ambient temperature (Scheme 72). The catalyst can be easily separated and is recyclable.



Scheme 72. Mg-Al hydrotalcite-catalyzed one-pot synthesis of functionalized cyclohexenes **199**

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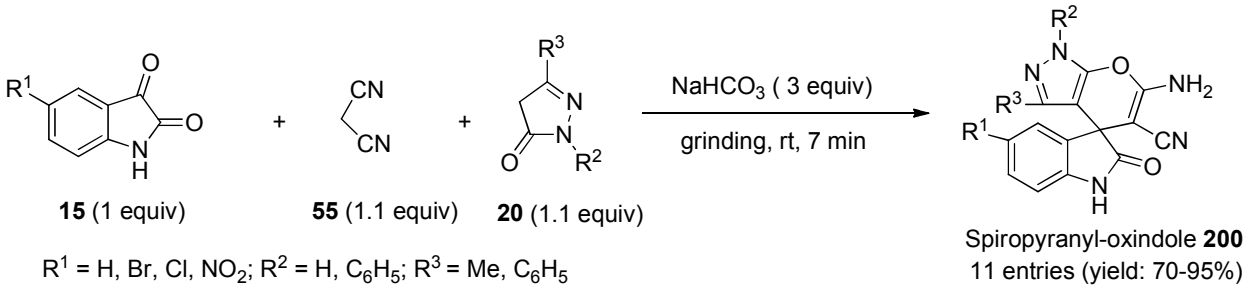
Liu et al.[332] developed a solvent-free and fast one pot synthesis of spiropyranyl-oxindoles **200** in the presence of $NaHCO_3$ under grinding at room temperature with good to excellent yields (Scheme 73). Short reaction times, good yields, operational simplicity, and eco-friendliness are the key features of this procedure for the synthesis of a series of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazol]-2-ones, spiro-oxindole framework of which is an important structural motif in a number of bioactive natural products and pharmaceuticals.[333-336]



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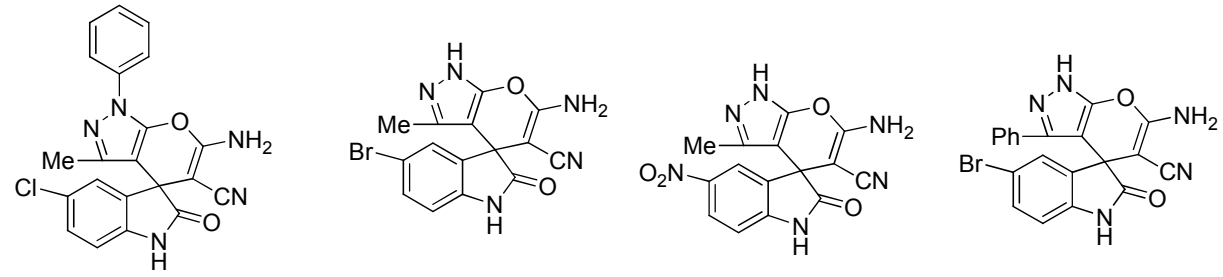

200a (solid, mp 223-224 ^{o}C, 70%) **200b** (solid, mp 282-283 ^{o}C, 95%) **200c** (solid, mp 270-271 ^{o}C, 82%) **200d** (solid, mp 258-259 ^{o}C, 95%)

Scheme 73. Sodium bi-carbonate-catalyzed one-pot synthesis of spiropyranyl-oxindoles (**200**) under grinding operation

2.3. Carbon-carbon bond forming reactions under ultrasonication

Ultrasonication is a process of irradiating a liquid sample with ultrasonic (>20 kHz) waves resulting in agitation, and this technique is now-a-days a well-regarded eco-environmental technology in green chemistry being advantageous over the traditional thermal methods as enhanced reaction rates, formation of purer products, improved yields, increased selectivities, easier experimental procedures, and use of milder conditions both in case of homogeneous and heterogeneous reactions.[337-344] Successful applications of ultrasound in synthetic organic chemistry have been demonstrated in recent years in carrying out a handful of organic transformations with enhanced reaction rates, yields and selectivity just at ambient conditions which otherwise require drastic conditions of temperature and pressure.[334-362]

On propagation into the liquid media, sound waves result in alternating high-pressure (compression) and low-pressure (rarefaction) cycles. During rarefaction, high-intensity sonic waves create small vacuum bubbles in the liquid, and the rapid nucleation, growth and collapse of these micrometerscale bubbles constitute the phenomenon of cavitation, generating very high local temperatures in short times. This is the driving force of smooth chemical transformations

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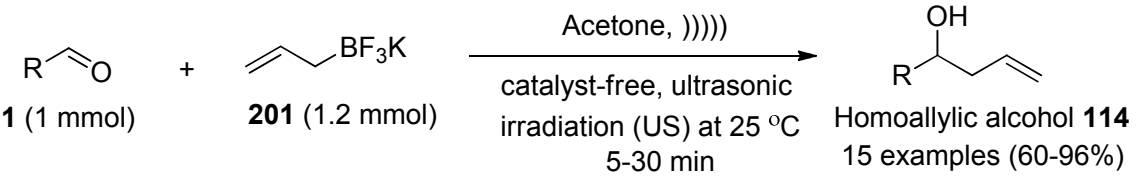
under ultrasound irradiation.[363-371] Number of organic reactions promoted by ultrasonication have been revisited in recent times.[63,372-375] The present section just offers a highlight on certain recently reported carbon-carbon bond forming reactions occurred under the influence of ultrasound irradiation at ambient conditions.

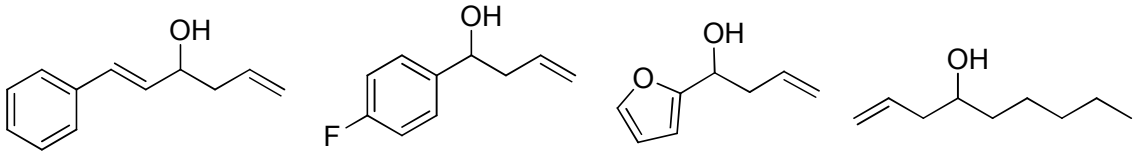
2.3.1. Addition reactions

The addition of an allylic organometallic reagent to a carbonyl compound affording the formation of a new carbon–carbon bond and the introduction of two new functionalities, an alcohol and a double bond, is regarded as an important synthetic method because the homoallylic alcohols, thus formed, can be used for further transformations.[376-378] Freitas et al.[379] developed a metal- and catalyst-free protocol for the efficient allylation of aldehydes at room temperature under the influence of ultrasound irradiation. The investigators synthesized a series of homoallylic alcohols **114** from the reaction of diverse aldehydes with potassium allyltrifluoroborate (**201**) in acetone, without any other catalyst or promoter (Scheme 74). The present method avoids the preparation of unstable allyl organometallics, and it is simple to operate, efficient and the products are obtained in short reaction times with moderate to high yields and purity at room temperature.



R = C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 2-FC_6H_4, 4-FC_6H_4, 2-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, C_6H_5CH=CH, Naphthyl, 2-Furyl, *n*-Pentyl

Representatives



114d (95%) **114e** (75%) **114f** (60%) **114g**(60%)

Scheme 74. Catalyst-free ultrasound-assisted synthesis of homoallylic alcohols in acetone

Narayanaperumal et al.[380] developed an efficient solvent-free conjugate Michael addition of 2,4-pentanedione (**203**) to various nitroalkenes (**202**) in the presence of a catalytic amount of 1-methyl-3-(2-(piperidin-1-yl)ethyl)-1*H*-imidazol-3-ium chloride, a base-behavior task-specific ionic liquid (TSIL), under ultrasonication furnishing the desired conjugate adducts **204** in good to excellent yields (Scheme 75). The investigators reported on the successful recovery and recycling of the ionic liquid in further reactions for at least four successive runs without observing significant decrease in yield.

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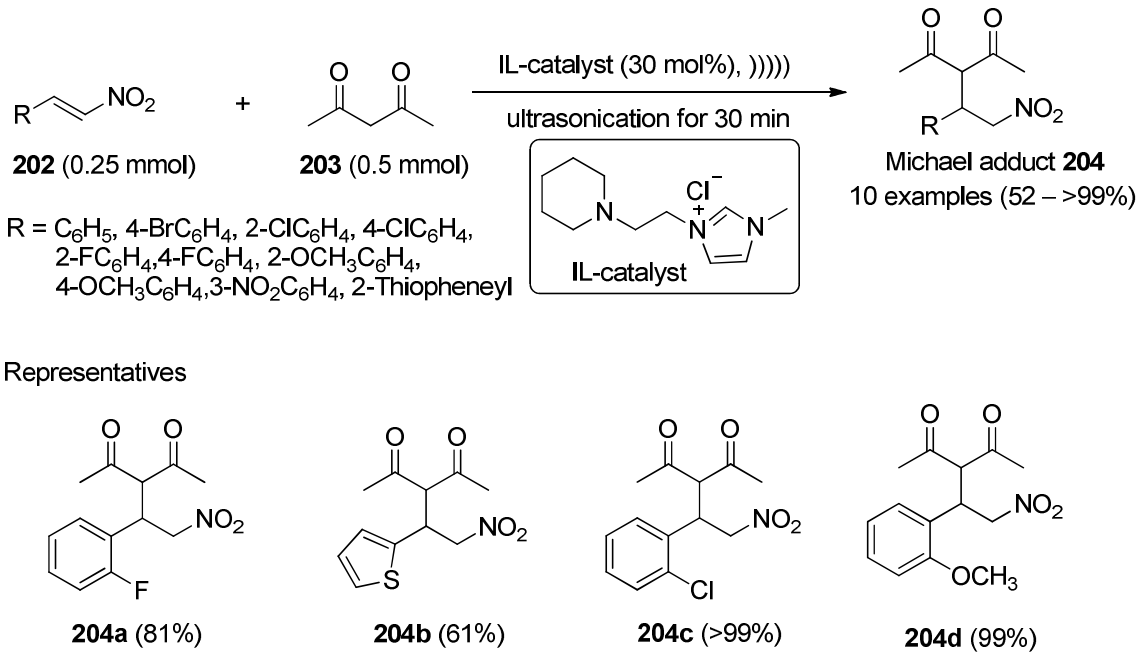
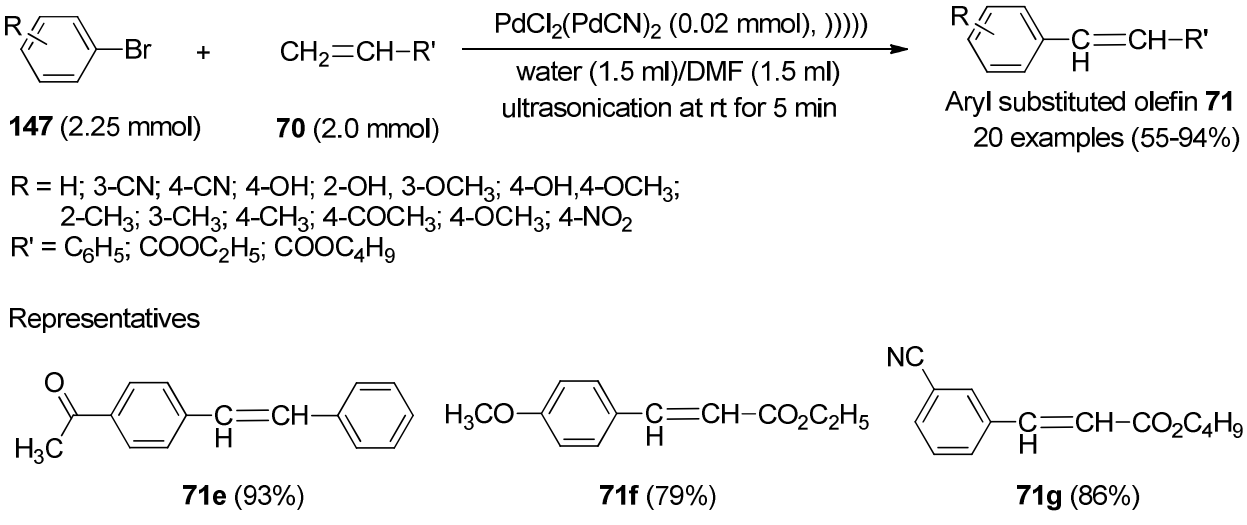


Scheme 75. Ionic liquid (IL)-catalyzed ultrasound-assisted synthesis of Michael adducts **204**

2.3.2. Heck-type coupling reaction

Saïd et al.[381] developed a base- and ligand-free rapid and high yielding ultrasound-promoted Heck reaction involving different aryl bromides (**147**) with styrene and acrylic esters (**70**) using $PdCl_2(PhCN)_2$ as catalyst in the presence of Aliquat-336 in water-DMF mixtures (Scheme 76). The reaction is nearly quantitative within 5 min. The use of Aliquat-336 plays an important role in the reduction of Pd(II) as well as in the stabilisation and solubilisation of Pd(0) by formation of an ionic complex in the reaction media.



Scheme 76. Ultrasound-promoted Heck type arylation reactions of α,β-ethylenic compounds in water

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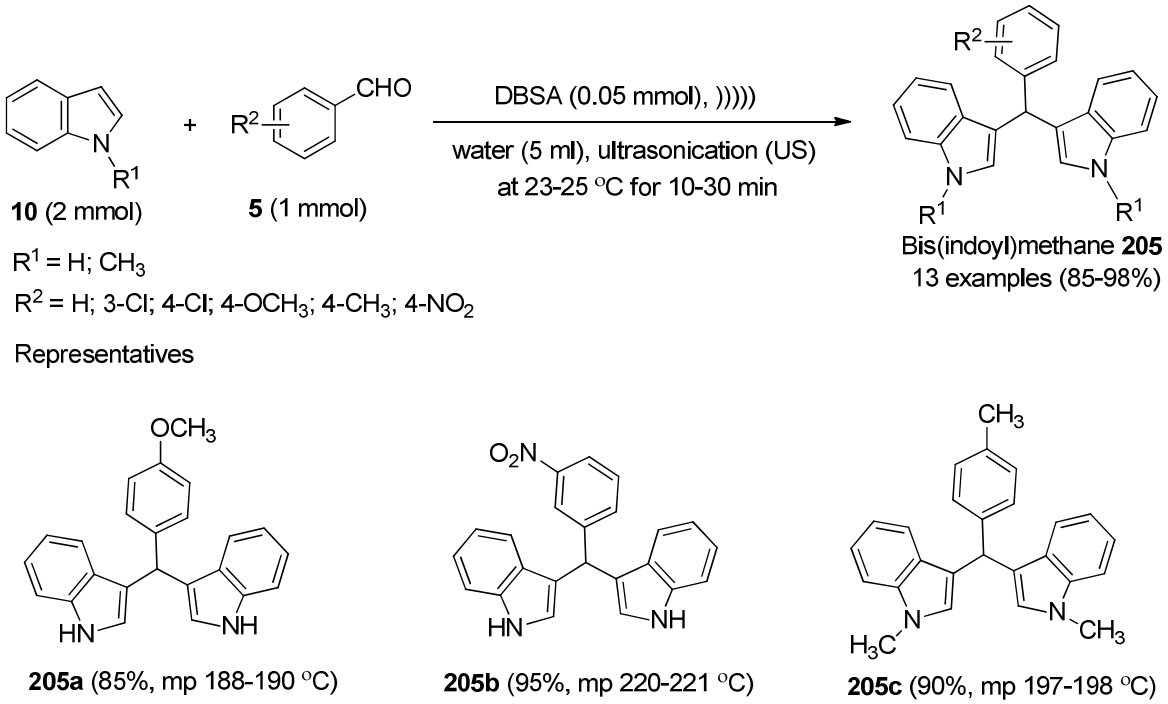
2.3.3. One-pot multicomponent reactions

Li et al.[382] developed an ultrasound-promoted synthesis of bis(indolyl)methanes from the reaction of indoles (2 equiv.) with aromatic aldehydes (1 equiv.) in the presence of dodecylbenzenesulfonic acid (DBSA) in water (Scheme 77) at 23-25 ^{o}C. The present procedure offers many advantages such as short reaction time, good yields, mild conditions and easy operation procedures among others.



Scheme 77. Dodecylbenzenesulfonic acid (DBSA)-catalyzed synthesis of bis(indoyl)methanes in water

Xanthene derivatives are useful pharmacological as well as optical properties.[383-386] Khaligh and Shirini[387] have recently designed a room temperature and solvent-free one-pot synthesis of a series of such compounds under the influence of ultrasound irradiation from the reaction of aromatic aldehydes (**1**; 1 mmol) and a varying substrates such as 2-naphthol (**22**; 2 mmol), 2-hydroxynaphthalene-1,4-dione (**87**; 2 mmol), mixture of 2-naphthol (1 mmol) and indane-1,3-dione (**206**; 1 mmol) or 2-hydroxynaphthalene-1,4-dione (1 mmol) and indane-1,3-dione (1 mmol) using a heterogeneous and reusable *N*-sulfonic acid poly(4-vinylpyridinium) hydrogen sulfate (NSPVPHS) catalyst (Scheme 78). Compared with traditional methods, the present methodology offers several advantages such as the accelerated reaction rate and good yields, minimization of the energy consumption, ease of preparation and handling of the catalyst, simple experimental procedure, and mild reaction conditions. The transformation involves formation of C-C and C-O bonds. Previously, Venkatesan et al.[388] also reported on the use of ultrasonication in synthesizing 1,8-dioxo-octahydroxanthene derivatives in the presence of the ionic liquid, [Hbim]BF_4 (IL) as a catalyst and reaction medium with methanol as co-solvent at ambient temperature.

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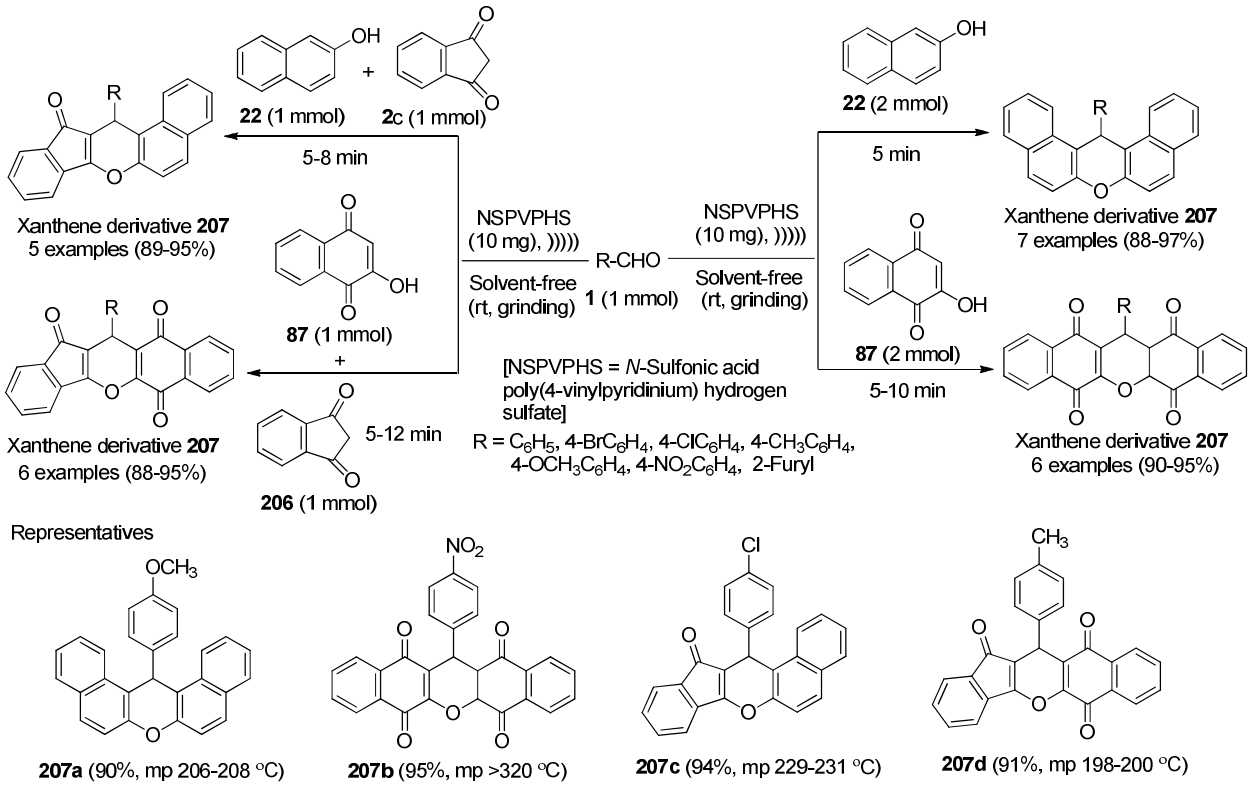

Scheme 78. *N*-Sulfonic acid poly(4-vinylpyridinium) hydrogen sulfate (NSPVPHS)-catalyzed one-pot solvent-free synthesis of xanthenes

Datta and Pasha[389] reported a one-pot multicomponent synthesis of a series of 2-amino-3-cyanao-4*H*-chromenes (**209**) from the reaction of diverse aromatic aldehydes (**5**), malononitrile (**55**) and resorcinol (**208**) at 28–30 °C in water under ultrasonication, using glycine as a cost effectiveness and non-toxic organocatalyst (Scheme 79).

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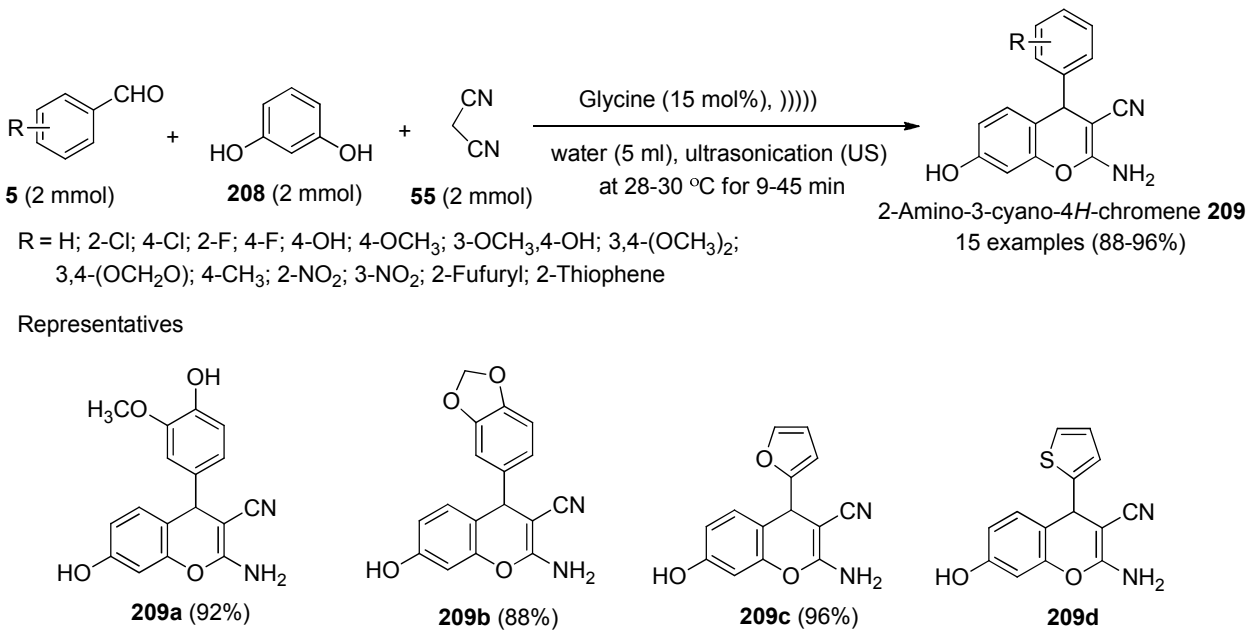

Scheme 79. Glycine-catalyzed one-pot multicomponent synthesis of 2-amino-3-cyano-4*H*-chromenes (**209**) in water

Ziarati et al.[390] developed an efficient protocol for the synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones (**211**) with the aid of synergetic effect of ultrasonication and Cu-nano catalysis from a four-component one-pot condensation reaction of hydrazines, ethyl acetoacetate, aldehydes and β-naphthol in water (Scheme 80). The authors commented that US can increase the surface area of the catalyst and supply additional activation through efficient mixing and enhanced mass transport. This multicomponent protocol in water gave excellent yields in short reaction times and showed a wide range of applicability as it could be used with different substrates, including aromatic aldehydes and hydrazines to provide the corresponding pyrazolones in good yields.[390]

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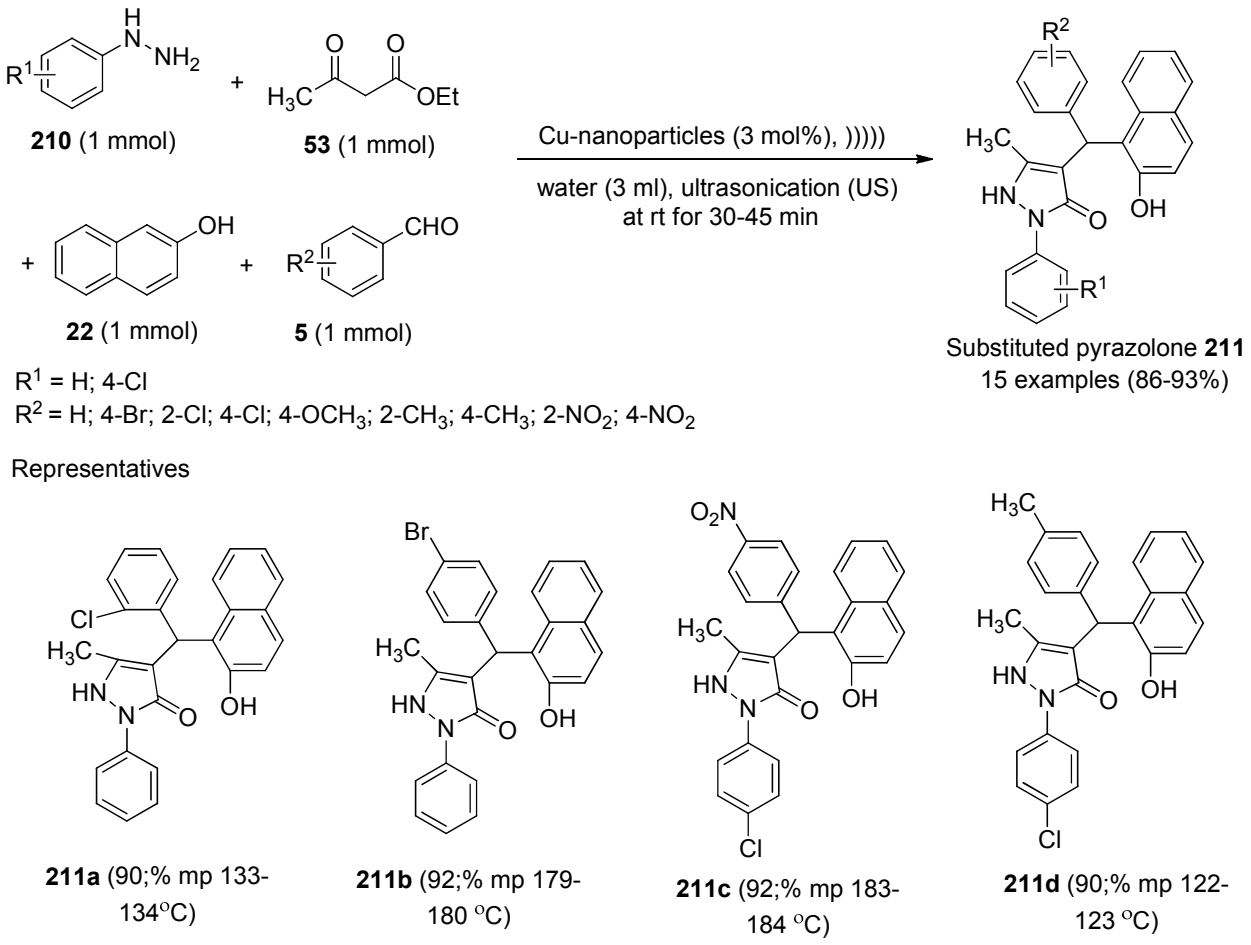

Scheme 80. Cu-nanoparticles-catalyzed one-pot multicomponent synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones (**211**) in water

2.4. Carbon-carbon bond forming reactions driven by visible-light

Application of visible-light as a clean, inexpensive, and sustainable alternative energy source to promote chemical transformations has received increasing attention from the chemistry community in recent times. Actually, a hundred years ago G. Ciamician had already recognized that sunlight could be utilized as an inexpensive, abundant, clean and renewable energy source for organic chemistry.[391] The ability to convert solar energy into chemical energy in an efficient manner, thus, continues to be an important issue from the viewpoint of environmental sustainability. However, due to inability of most common organic substances to absorb light in the visible region, the major part of photochemical reactions of organic substrates described to date involve the use of high-energy UV light.[392] UV-light-induced reactions not only require the use of specialized light sources, but they are also accompanied by many side reactions that limit their broad application. Under this purview, sincere drives have been made so far to develop visible-light photocatalysts to channel energy from the visible light spectrum to organic molecules capable to mediate the desired chemical transformations. This approach originates from the unique property of metal complexes and organic dyes to become engage in single-electron-transfer (SET) processes with organic substrates upon photoexcitation with visible light. As a result, many of the most commonly employed visible light photocatalysts are thus

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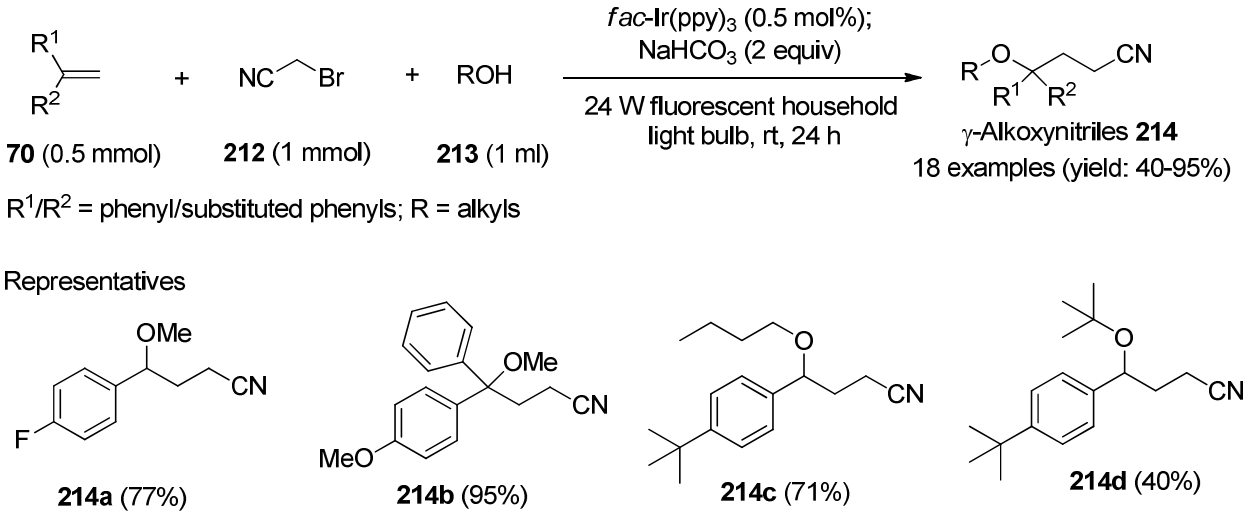
polypyridyl complexes of ruthenium and iridium [393,394] or organic dyes.[395] Generally, irradiation of the photocatalyst with visible light produces a redox-active excited state, which can be either reduced or oxidized by single electron transfer (SET) from or to the substrate; in addition, the photoexcited states of photocatalysts can serve as energy donors, activating organic substrates through an energy transfer process.[396,397] A number of good reviews are already in literature summarizing the developments in the field of photocatalysts and their useful applications in synthetic organic chemistry.[398-412] The present section summarizes most recent developments in visible-light-driven carbon-carbon bond forming reactions at ambient conditions.

2.4.1. Visible light-induced three-component alkoxycyanomethylation of alkenes

Yi et al.[413] have accomplished visible-light induced difunctionalization of alkenes at room temperature using the iridium photoredox catalyst [*fac*-Ir(ppy)$_3$] in the presence of sodium bicarbonate and alcohol (acting both as a solvent and alkoxylating agent) furnishing γ-alkoxynitriles **214** in good yields (Scheme 81). Both cyanomethylation and alkoxylation of alkenes were achieved in one-pot three-component reaction with this catalytic radical difunctionalization with varying alcohols, and the introduced cyano group can undergo further transformations into various useful functional groups.



Scheme 81. Synthesis of γ-alkoxynitriles (**214**) *via* visible light-induced three-component alkoxycyanomethylation of alkenes

2.4.2. Visible light-induced trifluoromethylation reactions

The trifluoromethyl (–CF_3) moiety is well-regarded as an important structural motif for biologically relevant compounds and functional materials as found in many useful agrochemicals, pharmaceuticals and materials.[215,217,414-418] It has also been observed that introduction of a trifluoromethyl group into organic compounds usually leads to improvement of their biological and physiological characteristics attributed to developing and/or improving unique physical and chemical properties in the trifluoromethyl-substituted derivatives, such as chemical and metabolic stability and bioavailability, by the incorporated trifluoromethyl

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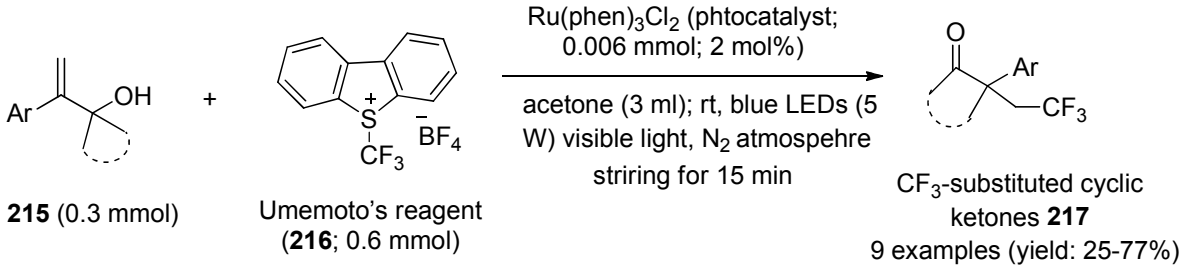
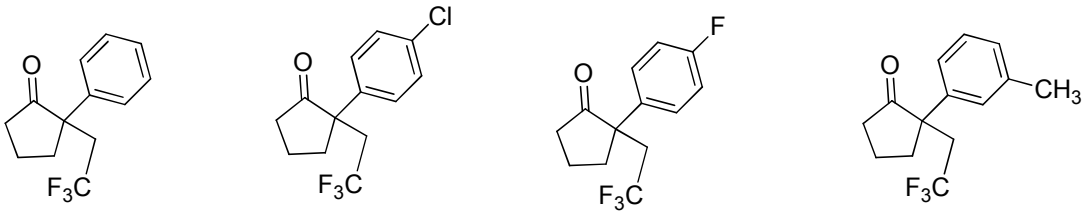
group.[419-426] Consequently, extensive efforts have been made to explore the incorporation of trifluoromethyl moiety into organic molecules in recent years.[427-447]

Recently, Woo and Kim[448] have developed a visible-light-induced photoredox-catalyzed rapid protocol for the synthesis of CF_3-substituted cyclic ketones (**217**) *via* trifluoromethylation and 1,2-carbon migration of 1-(1-arylvinyl)cyclobutanol derivatives **215** using $Ru(phen)_3Cl_2$ as photocatalyst and Umemoto's reagent **216** as a source of CF_3-moiety at ambient temperature (Scheme 82).



Ar = C_6H_5, 4-ClC_6H_4, 2-FC_6H_4, 4-FC_6H_4, 3-$CH_3C_6H_4$

Representatives



217a (77%) **217b** (70%) **217c** (70%) **217d** (73%)

Scheme 82: Synthesis of CF_3-substituted cyclic ketones (**217**) *via* photocatalytic trifluoromethylation/1,2-carbon migration sequences

In the same year (2015), Zheng et al.[449] have reported on the development of a viable visible-light-induced method for smooth implementation of trifluoromethylarylation/1,4-aryl shift/desulfonylation cascade reaction of α,β-unsaturated imide alkenes (**218**) using CF_3SO_2Cl as CF_3 source in the presence of $Ru(bpy)_3Cl_2$ as the photocatalyst at room temperature, thereby yielding trifluoromethyl isoquinolinediones (**219**), trifluoromethyl oxindoles (**220**) and α-aryl-β-trifluoromethylamides (**221**) under varying conditions in moderate to good yield (Scheme 83). Operational simplicity, low catalyst loading (5% catalyst), and less additives are the advantages of this method.

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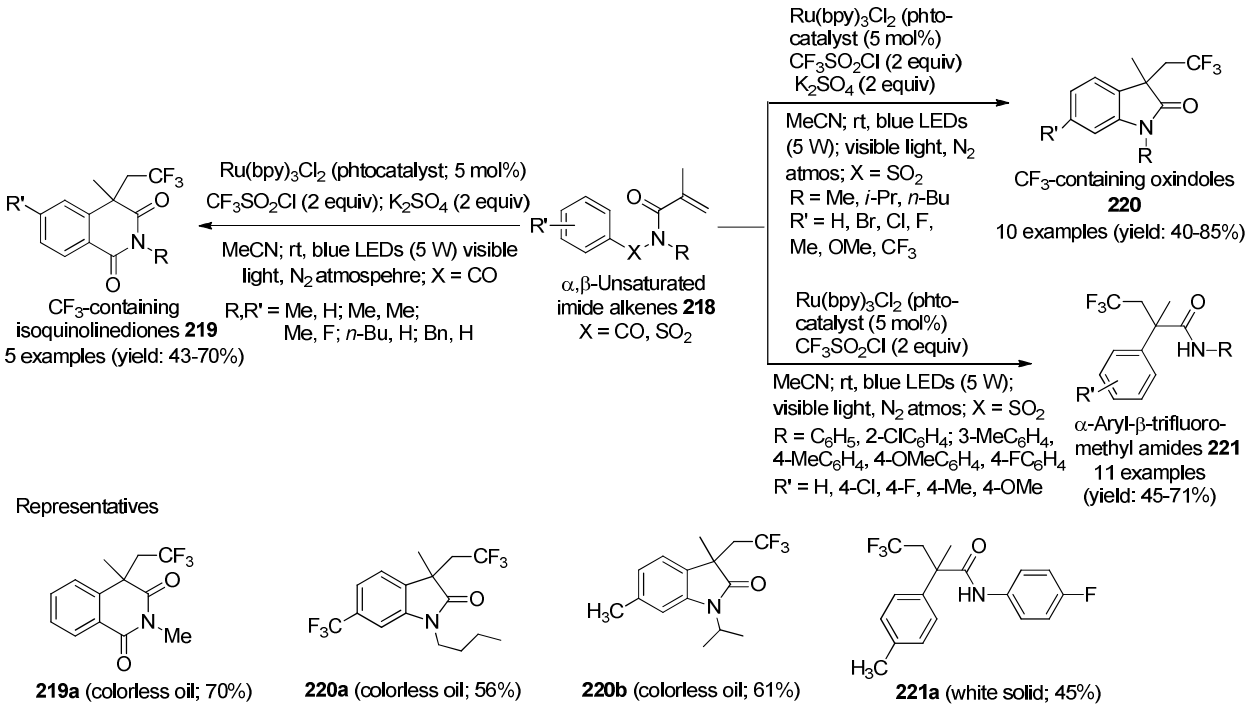

Scheme 83: Synthesis of CF_3-containing isoquinolinediones (**219**), trifluoromethyl oxindoles (**220**) and α-aryl-β-trifluoromethylamides (**221**) *via* trifluoromethylarylation/1,4-aryl shift/desulfonylation cascade reaction

In another report, Deng et al.[450] have recently described an efficient method for photocatalytic oxytrifluoromethylation reaction of *N*-allylamides (**222**/**224**)for the first time under the influence of visible light leading to the synthesis of biologically relevant CF_3-containing diversely functionalized oxazolines (**223**) and benzoxazines (**225**) at room temperature (Scheme 84). The transformation involves formation of both C-C and C-O bonds.

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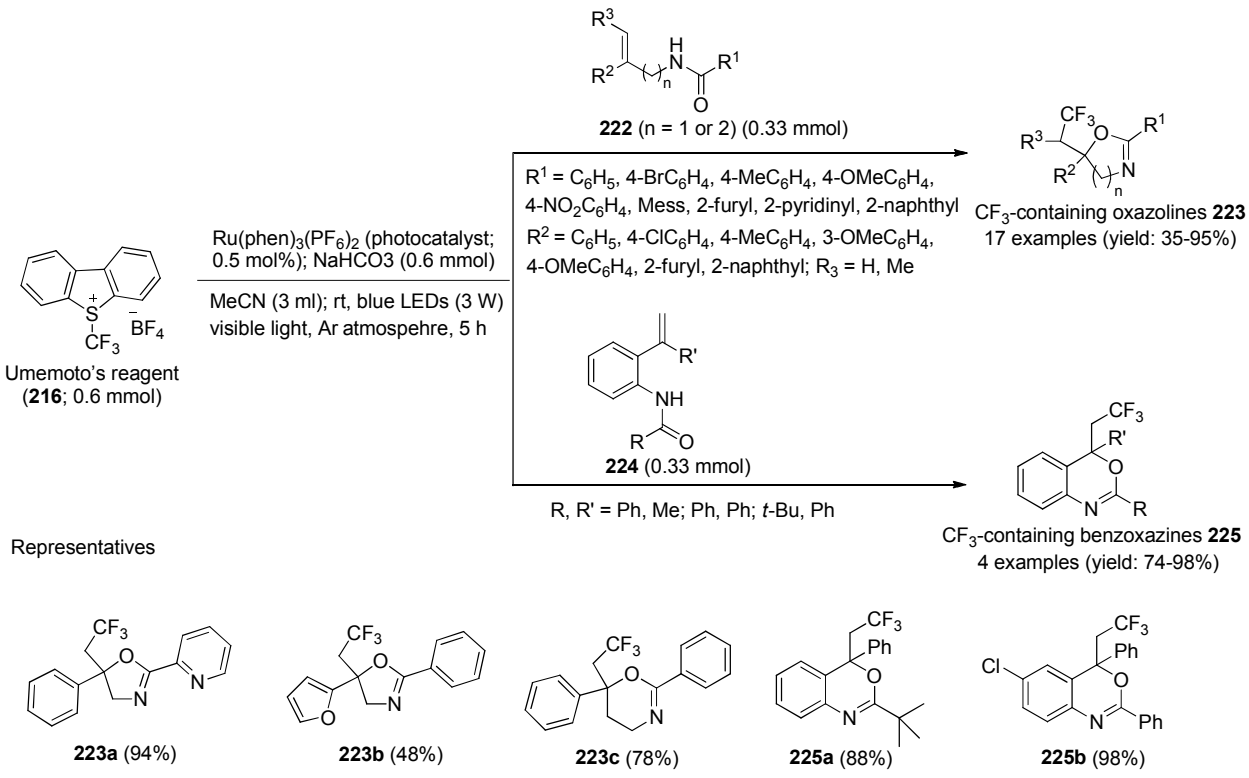

Scheme 84: Synthesis of CF_3-containing diversely functionalized oxazolines and benzoxazines

Oh et al.[451] developed a new photoredox-catalyzed protocol for vicinal chlorotrifluoromethylation of alkenes (**226**) in the presence of $Ru(Phen)_3Cl_2$ as photocatalyst using CF_3SO_2Cl (**227**) as a source for the CF_3 radical and chloride ion under visible light irradiation (Scheme 85). Various terminal and internal alkenes were transformed to their vicinal chlorotrifluoromethylated derivatives **228**.

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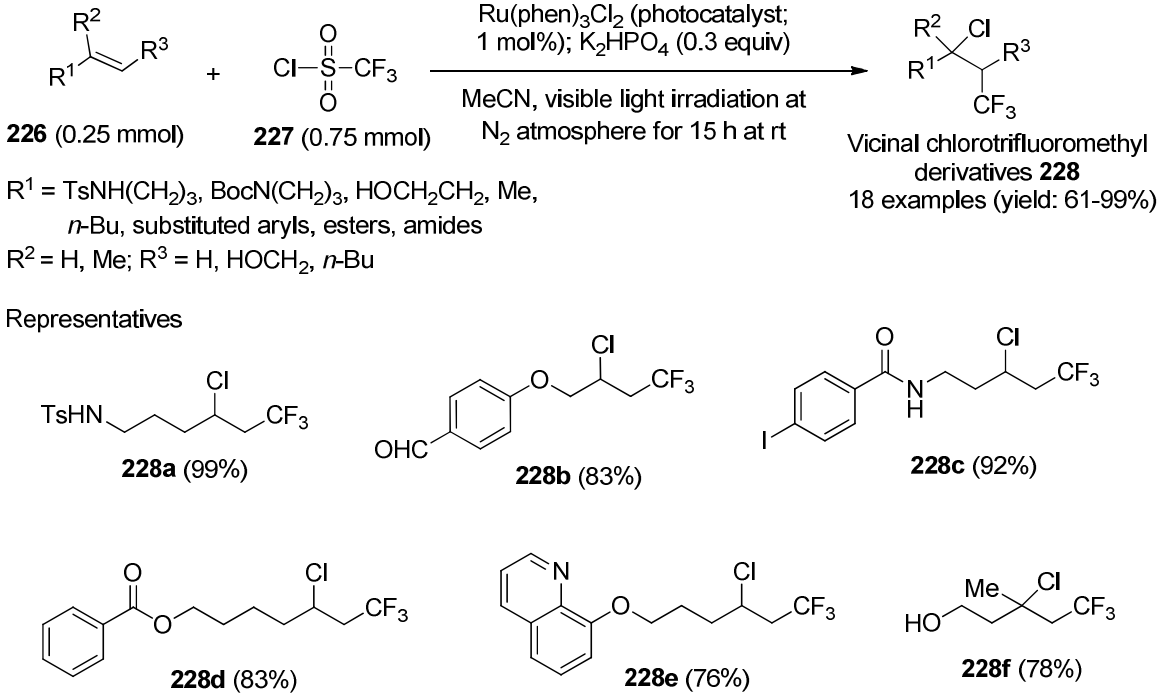
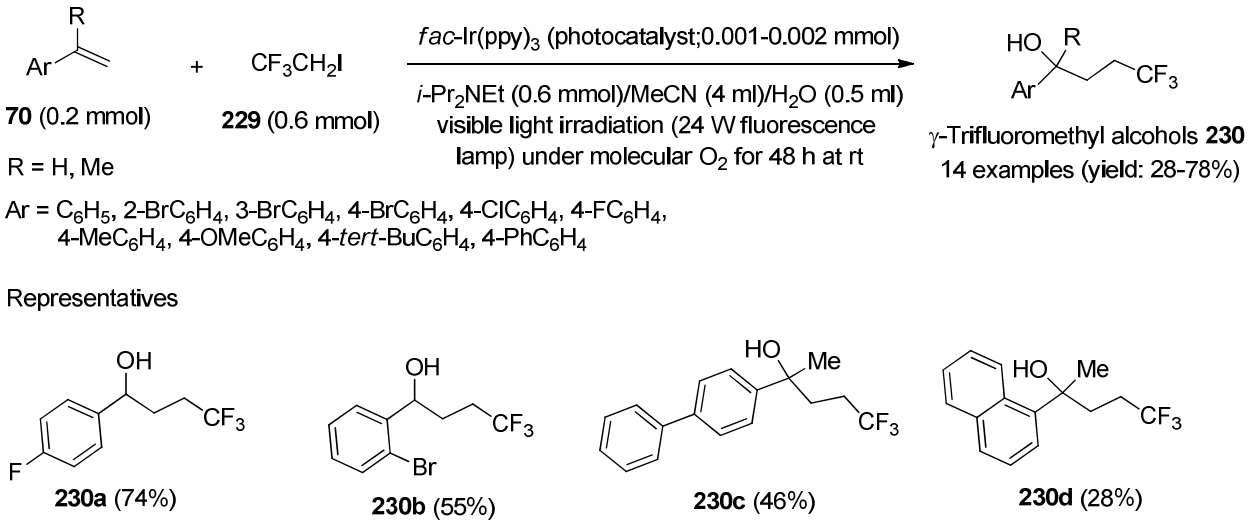


Scheme 85: Vicinal chlorotrifluoromethyaltion of alkenes

Very recently, Li et al.[452] have reported visible-light-induced photoredox difunctionalization reactions of diverse substituted styrenes **70** with 1,1,1-trifluoro-2-iodoethane (**229**) under an oxygen atmosphere in the presence of water yielding a series of γ-trifluoromethyl alcohols **230** (Scheme 86). They used *fac*-Ir(ppy)$_3$ as a photocatalyst in this light-induced radical reaction, and it has also been demonstrated that the oxygen atom in the product originates from molecular oxygen. The investigators have observed that water plays a key role in this reaction, and instead of the desired product, 2,2,2-trifluoroethanol has been found to form in the absence of water; no difunctionalization of styrenes is observed.[452]



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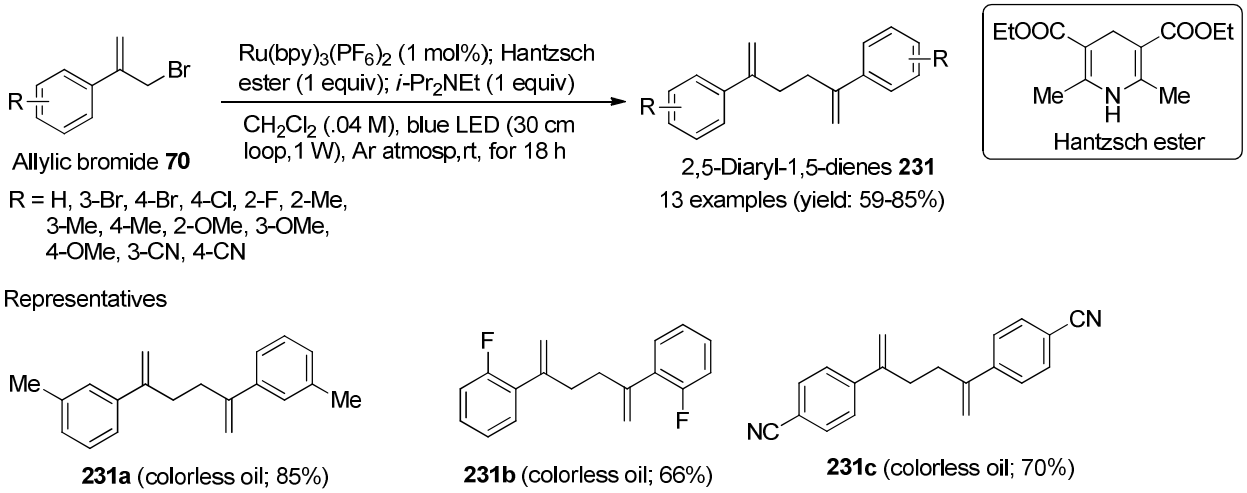
Scheme 86: Synthesis of γ-trifluoromethyl alcohols (**230**) on light-induced difunctionalization of styrenes

2.4.3. Visible light-induced coupling reactions

Visible light-induced facile synthesis of 2,5-diarylhexa-1,5-dienes has been achieved by Pratsch and Overman[453] at room temperature in moderate to good yields via reductive coupling of 2-arylallyl bromides (**70**) in the presence of 1 mol % of the commercially available photocatalyst $Ru(bpy)_3(PF_6)_2$, Hantzsch ester and ethyl di-*i*-propylamine under argon atmosphere (Scheme 87). This method avoids the use of stoichiometric metal reductants and is compatible with the presence of halogen, alkyl, electron-donating, and electron-withdrawing substituents on the aromatic ring. It is supposed that the coupling proceeds largely *via* dimerization of photogenerated allylic radical intermediates.[453]



Scheme 87. Synthesis of 2,5-diarylhexa-1,5-dienes (**231**) in dichloromethane

α,β-Epoxy ketones are regarded as important intermediates and precursors in synthetic organic chemistry.[454-456] Li and Wang[457] have recently demonstrated the visible-light induced straightforward protocol for the synthesis of such compounds **232** from a range of styrenes and benzaldehydes under the influence of $Ru(bpy)_3Cl_2$ (as photocatalyst), *tert*-butyl hydroperoxide (*t*-BuOOH) and cesium carbonate as a base at room temperature (Scheme 88). The investigators have proposed that the process proceeds through visible-light-enabled photocatalytic generations of acyl radicals as key intermediates as depicted in Scheme 89.[457] The transformation involves the formation of both C-C and C-O bonds.

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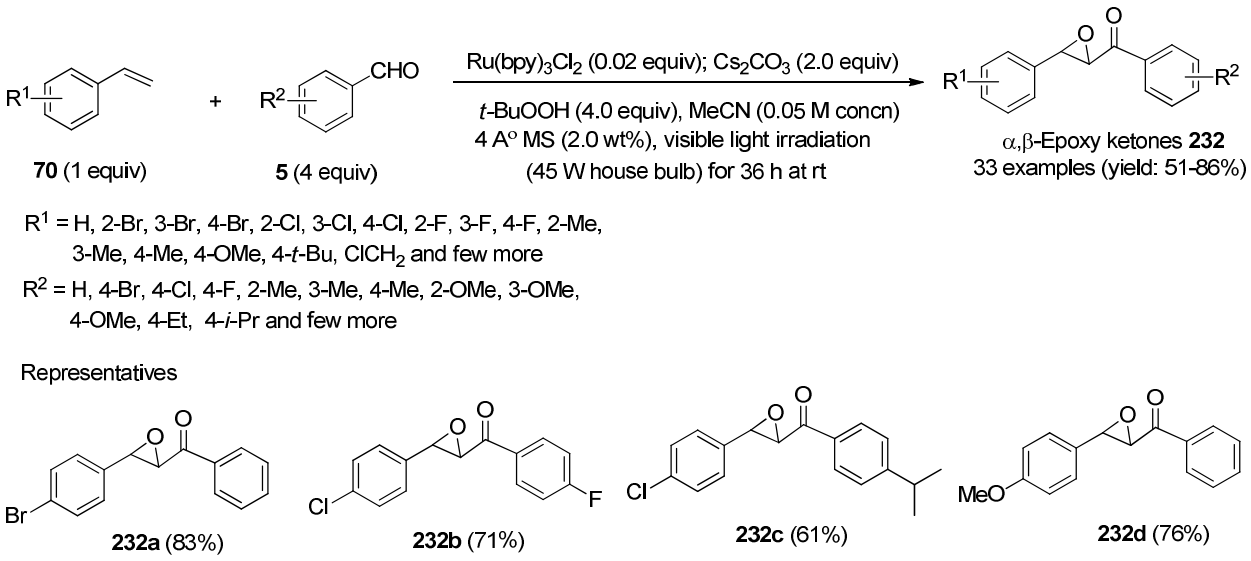
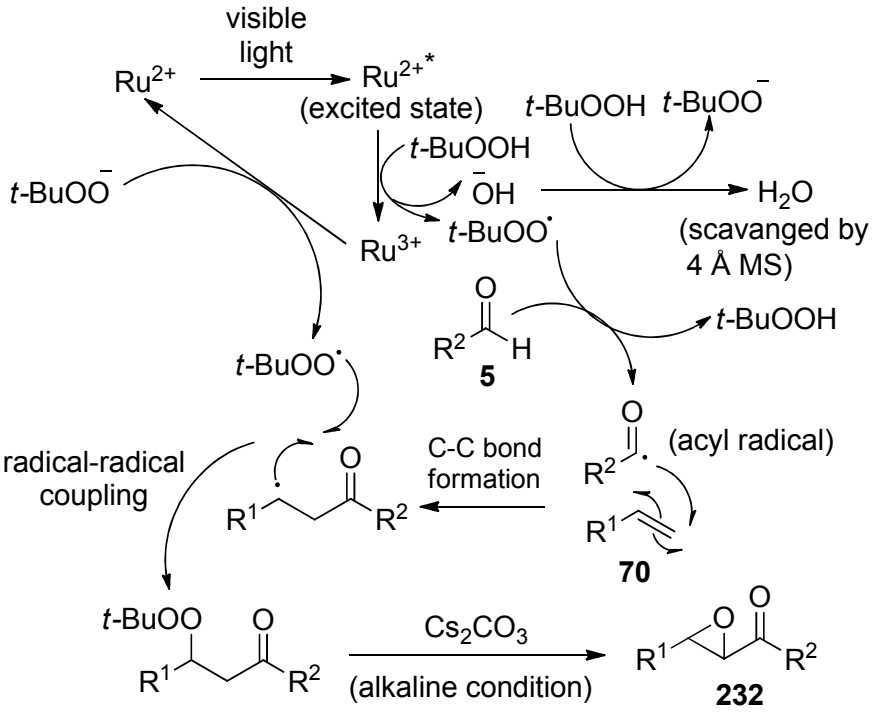


Scheme 88: Synthesis of α,β-epoxy ketones (**232**) in acetonitrile



Scheme 89: Proposed mechanism for visible-light-driven synthesis of α,β-epoxy ketones (**232**)

In recent time, an effort to merging photoredox and nickel catalysis for better dual catalytic activation mode in exploring C-C bond formations has been initiated. In a recent report, Noble et al.[458] have successfully accomplished decarboxylative C_{sp3}-C_{sp2} cross-coupling of diverse carboxylic acids (**49′**) with vinyl halides (**233**) through the synergetic merger of photoredox and nickel catalysis under mild conditions under the influence of visible light at

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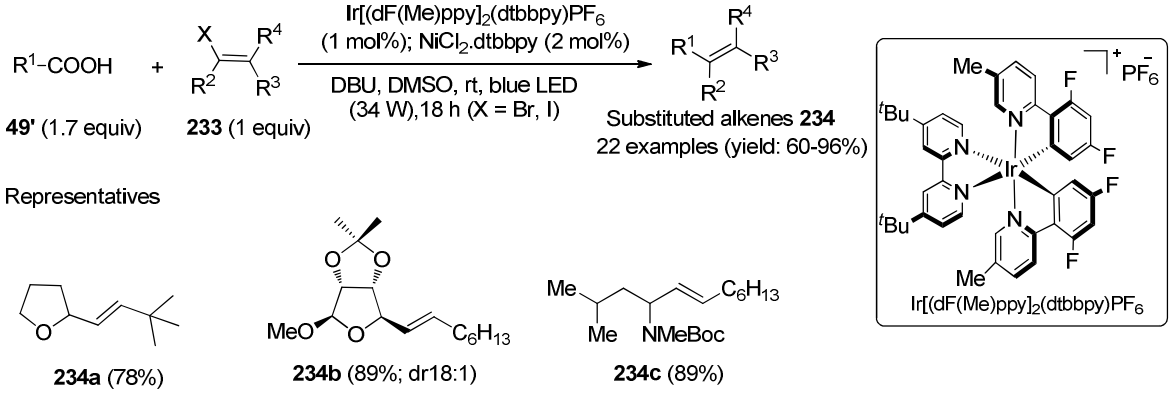
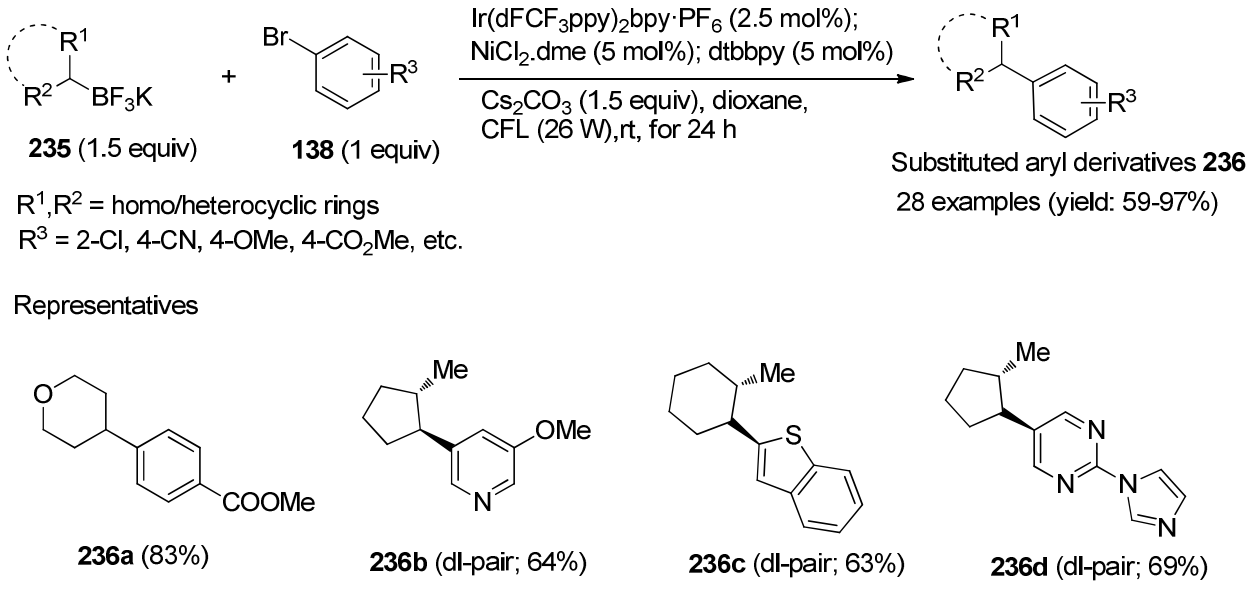
room temperature (Scheme 90). The investigators have extended their new methodology to a variety of α-oxy- and α-amino acids, as well as simple hydrocarbon-substituted acids; diverse vinyl iodides and bromides yielded vinylation products in high efficiency under mild, operationally simple reaction conditions.



Scheme 90. Synthesis of substituted alkenes through decarboxylative olefination with vinyl halides

Recently, Primer et al.[459] have developed visible-light induced single-electron-mediated alkyl transfer as a novel mechanism for transmetalation, enabling a general C_{sp^3}-C_{sp^2} cross-coupling of secondary alkyltrifluoroborates (symmetrical and both unsymmetrical and sterically encumbered) **235** with an array of substituted aryl bromides effected by an Ir-photoredox catalyst and a Ni cross-coupling catalyst under mild conditions at room temperature (Scheme 90). The investigators have claimed their method as operationally simple and superior to previously reported such cross-coupling protocols.



Scheme 91. Synthesis of substituted aryl derivatives **236**

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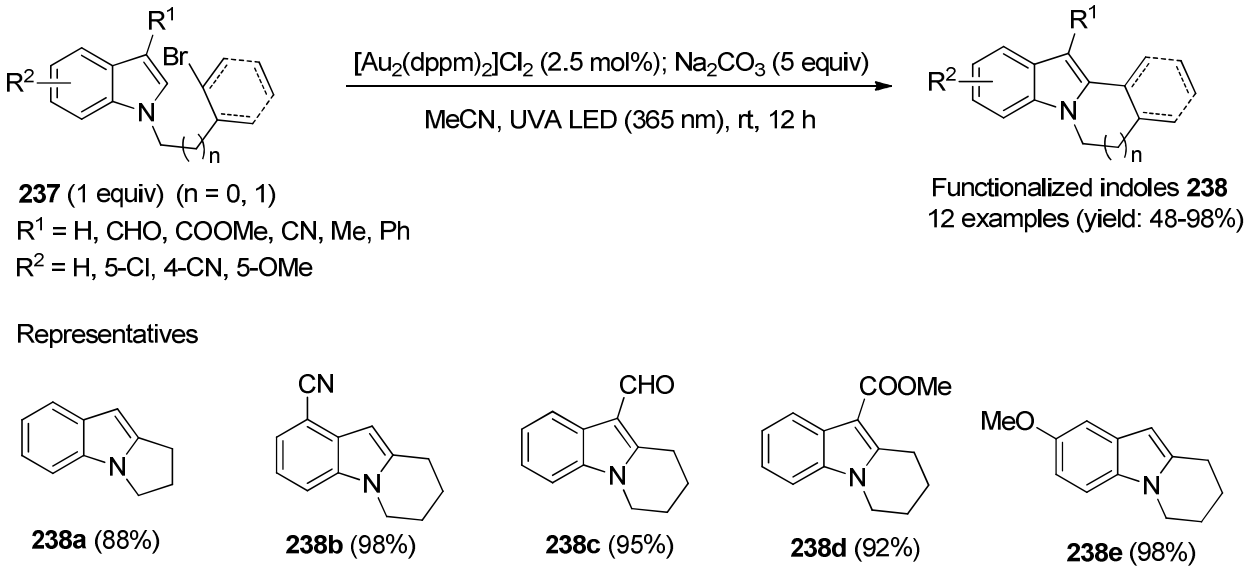
Kaldas et al.[460] have developed a light-mediated process for the generation of organic free radicals with unactivated bromoalkanes/arenes (**237**) using dimeric Au(I) photocatalyst under basic conditions at room temperature for functioanlization of substituted indoles (**238**) (Scheme 92). This method may be a mild and relatively safe alternative to organostannanes and pyrophoric initiators used for accessing high energy radicals that were previously inaccessible through catalytic or stoichiometric means.



Scheme 92: Synthesis of functionalized indoles **238**

3 CONCLUDING REMARKS AND OUTLOOK

Practice of green and sustainable chemistry, thus, encompasses so many criteria during carrying out organic transformations, and those which can satisfy these criteria to a greater extent are welcome! Under this purview, designing of methods for promising and useful organic reactions under ambient conditions coupled with other green aspects is, thus, a hot area in current trends in green chemistry research. Carbon-carbon (C-C) bond forms the '*backbone*' of nearly every organic molecule, and is essentially regarded as the key transformation in organic synthesis to set up the carbon backbone of organic molecules. It is needless to mention that the carbon-carbon bond formation has always been one of the most useful and fundamental reactions in the development of organic chemistry, and continues to be. The present review offers an up-to-date development on the design of carbon-carbon bond forming protocols to access a wide variety of organic molecules of topical interest under ambient temperature and pressure. The account categorically focuses on the brilliant applications of reaction conditions such as the use of solvents or no solvent, catalysts or no catalyst, and the use of green tools like ball-milling, ultrasonication and visible light in achieving the goal! These reported protocols for developing carbon-carbon frame-work are associated with a handful of advantages such as mild reaction

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conditions, good yields, operational simplicity and absence of tedious separation procedures, clean reaction profiles, high atom-economy, inexpensive starting materials, and environmentally benign catalysts and their reusability. The author of this article hopes that this account would motivate the young minds of the coming generation in chemistry as well as the experts and professionals practicing green and sustainable chemistry at large.

ACKNOWLEDGEMENT

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Biography of the Author

Goutam Brahmachari was born at Barala in the district of Murshidabad (West Bengal, India) in 1969. He received B.Sc. (Honours) in Chemistry and M.Sc. with specialization in Organic Chemistry from Visva-Bharati (a Central University), West Bengal, India in 1990 and 1992, respectively. Thereafter he received Ph.D. (Organic Chemistry) in 1997 from the same University. In 1998, he joined his alma mater as assistant professor. He became associate professor in 2008, and promoted to full professor in 2011. His research interests include (i) synthetic organic chemistry with special emphasis on green chemistry; (ii) isolation, structural determination, and/or detailed NMR study of new natural products from medicinal plants; (iii) semi-synthetic studies with natural products, and (iv) evaluation of biological activities and pharmacological potential of natural and synthetic compounds. With more than seventeen years of teaching experience, he has produced so far about 160 scientific publications including original research papers, review articles, books and invited book chapters in the field of organic chemistry. He has authored/edited seventeen books and more than 30 book chapters so far published by internationally reputed major presses such as Elsevier/Academic Press, Wiley-VCH, CRC Press/Taylor & Francis Group, Royal Society of Chemistry, World Scientific Publishing Co., Alpha Science International, Research Signpost, *etc*. He is the Series Editor of the Elsevier Book Series '*Natural Product Drug Discovery*' (forthcoming in 2016). He serves as a member of the *Indian Association for the Cultivation of Science* (IACS) and *Indian Science Congress Association* (ISCA), Kolkata. He also serves as an editorial advisory board member for several journals. He is regularly consulted as a referee by leading international journals. He is a Who's Who in the World-2015 & 2016 Listee, and also a recipient of Academic Brilliance Award-2015 (Excellence in Research).

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