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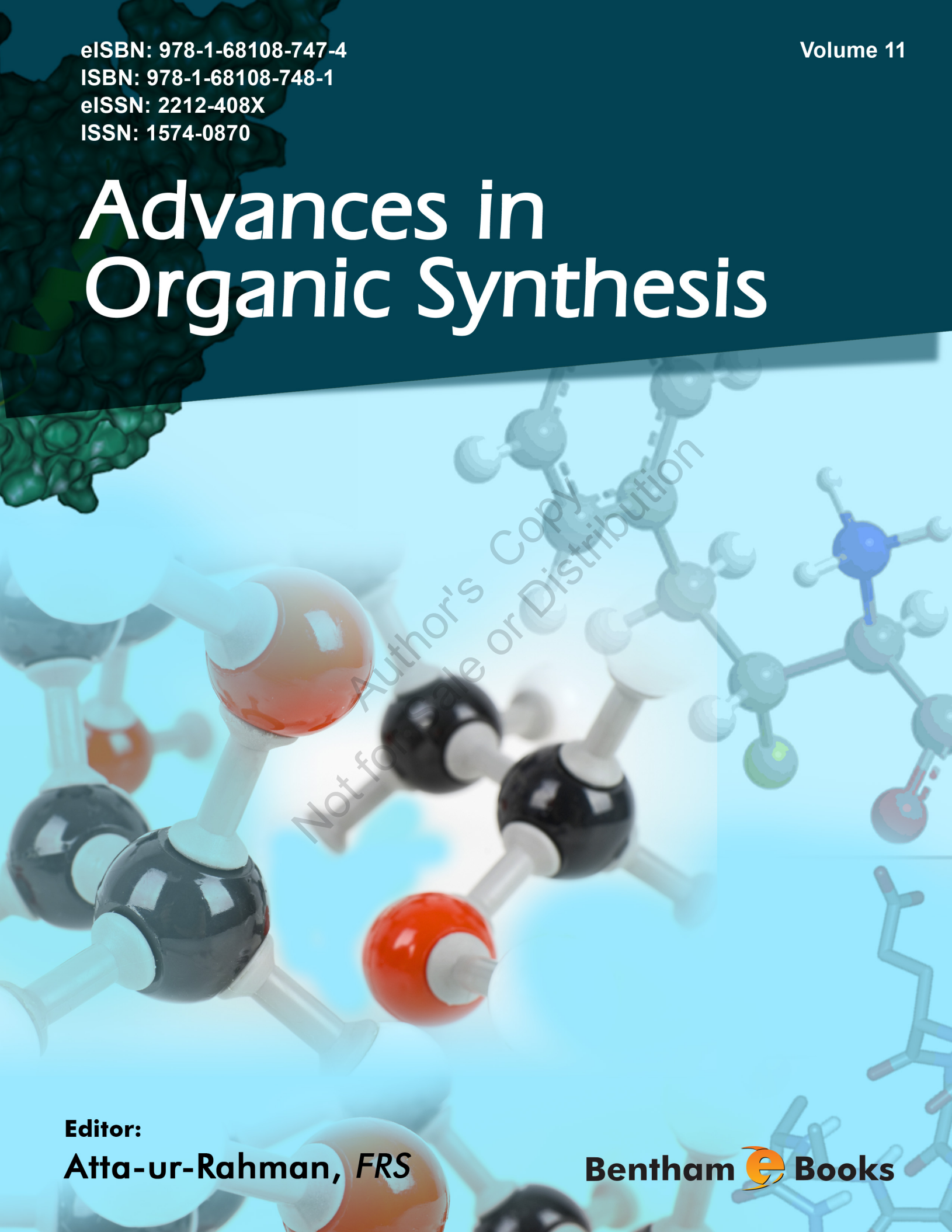

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(Volume 11)

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PREFACE

This volume of ***Advances in Organic Synthesis*** presents some recent exciting developments in synthetic organic chemistry. It covers a range of topics including asymmetric synthesis of chiral flavanones, chromanones and chromenes, supramolecular chemistry of modified amino acids and short peptides, the use of nanocatalysts in the synthesis of heterocycles, synthesis and applications of 1,2,3-triazoles and ring C–H functionalization of aromatic N-oxides. Important and novel approaches to the construction of complex organic compounds are presented.

The book should prove to be a resource for synthetic organic chemists, medicinal chemists, pharmaceutical scientists and postgraduate students seeking critically important information about recent developments in synthetic organic chemistry. The chapters are written by authorities in the field.

I hope that the readers will find these reviews valuable and thought-provoking so that they may prompt further research.

I am thankful to the efficient team of Bentham Science Publishers especially Dr. Faryal Sami (Manager Publications), Mr. Shehzad Iqbal Naqvi (Editorial Manager Publications) and Mr. Mahmood Alam (Director Publications).

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CHAPTER 1

Recent Progress on Asymmetric Synthesis of Chiral Flavanones, Chromanones, and Chromenes

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Abstract: Flavonoids are privileged structural motifs in numerous natural products and pharmaceutical molecules, which show many biological activities such as antitumor, antioxidant, antibacterial and anti-inflammatory properties. Flavanone and chromanone which feature a chiral center are subgroups of flavonoids. The structures of flavanone and chromanone are distinct from that of flavone and chromone by a reduction of C2-C3 double bond. Deoxygenation of flavanones and chromanones provides chromenes which are also important structural motifs present in a number of natural and synthetic products that exhibit a wide range of biological activities. Besides naturally occurring flavanones, chromanone, and chromenes, the benzopyran scaffold is an important intermediate and interesting building block in organic synthesis and design of new lead compounds in drug discovery. Consequently, many attention has been paid to their efficient synthesis, especially in enantiopure forms, and many asymmetric methods for the construction of the chiral flavanone, chromanone and chromene skeletons were reported in recent years.

Keywords: Allylic Cyclization, Asymmetric Synthesis, Chromanone, Chromene, Conjugate Addition, Flavanone, Flavonoid, Reduction.

INTRODUCTION

Flavonoids are one of the largest classes of plant or fungus secondary metabolites which contribute to the main organoleptic and nutritional qualities of common fruits and vegetables [1, 2]. Flavonoids widely exist in thousands of natural products and drugs (Fig. **1**) and provide potential treatment and prevention of many diseases because of their broad spectrum of *in vitro* and *in vivo* bioactivities, including anti-HIV, antitumor, anticancer, antioxidant, anti-aging, antibacterial, and anti-inflammatory properties [3 - 11]. However, most of the

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Atta-ur-Rahman (Ed.)

flavonoids extracted from natural products have some ineluctable limitations such as complex construction, multiple action sites, and poor solubility, which would restrict the development of their applications [12, 13]. Thus, structure constructions and modifications of flavonoids would be more appropriate and feasible to prepare flavonoid analogues that may be more potent [14 - 16]. To date, numerous researches [17 - 24] and review articles [25 - 31] of flavonoids and related derivatives based on synthetic methodology, bioactivity, structure-activity relationship are constantly reported by chemists and biologists.

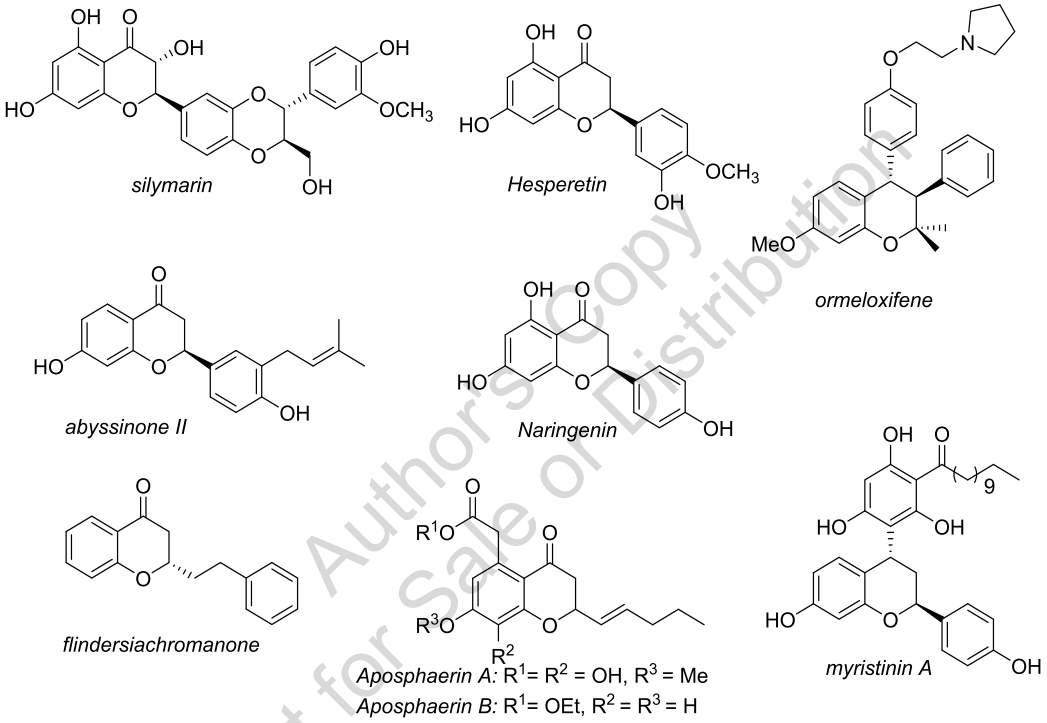


Fig. (1). Some selected pharmaceuticals and natural products.

Chemically, flavonoids contain a basic nucleus of 15-carbon flavan which are arranged into two benzene rings (**A** and **B**) and one heterocyclic ring (**C**) (Fig. **2**). Based on the degree of oxidation and saturation on the heterocyclic ring (**C**), flavonoids can be categorized into three main groups: flavone, flavanone, and flavan-4-ol. The three classes can undergo mutual transformation *via* reduction or oxidation process, in which flavanones are considered as the key intermediates. The 2-arylchromenes, which can be formed by deoxygenation of flavanones, are also important backbones of natural products and drugs which possess various biological activities [32 - 34]. Therefore, the need to develop the synthetic methodologies of flavanones and 2-arylchromenes is apparent and desirable.

Structures of closely related chromanones and 2-alkylchromenes are also discussed in this chapter.

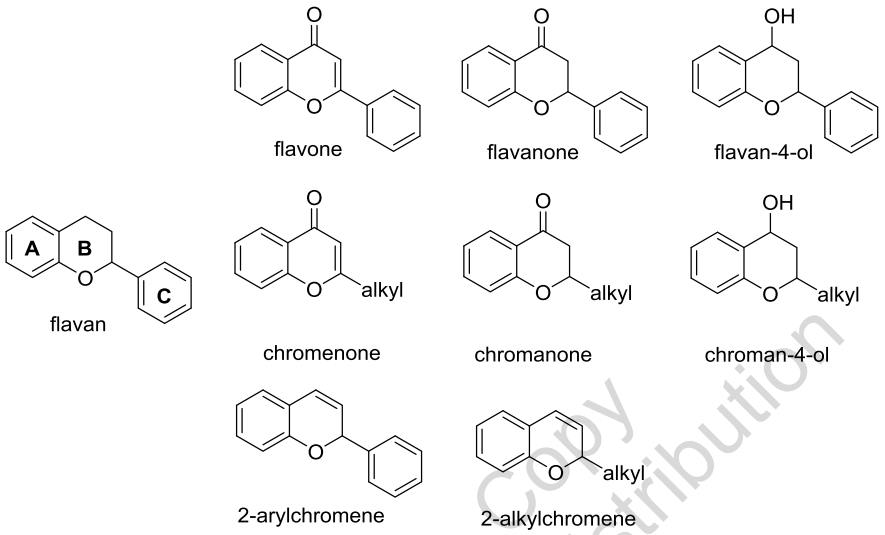


Fig. (2). Structures of flavonoid and its derivatives.

Various researches provide compelling evidences for the fact that only one of the enantiomers is responsible for the effective biological activity and drug safety [35, 36]. Thus, enantioselective synthesis is of great importance in constructing the building blocks of natural products and pharmaceutical molecules. Asymmetric addition reaction [37 - 41] is one of the powerful synthetic strategies to form a new bond by intramolecular or intermolecular ways, which are widely applied in the preparation of chiral flavonoids. Herein, it is desirable to provide a summary of the synthetic approaches of flavanones, chromanones, and chromenes on the basis of different types of addition reactions. Moreover, some other enantioselective methods, such as reduction, metathesis, tandem reaction, are also encompassed in this chapter.

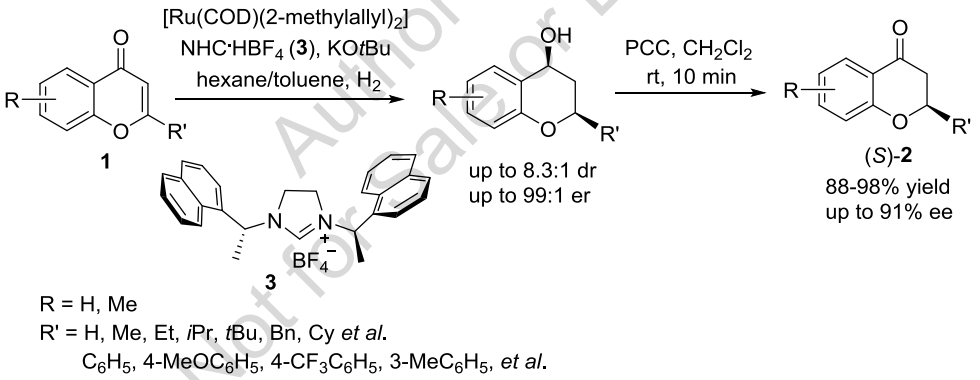
ASYMMETRIC SYNTHESIS OF CHIRAL FLAVANONE AND CHROMANONE

Asymmetric Reduction of Flavone

Asymmetric hydrogenation is an essentially important transformation both in academia and in industry for the preparation of optically active compounds due to its attractive features: high atom economy, operational simplicity, minimal

negative environmental impact [42, 43]. Thus, asymmetric reduction of C2-substituted flavones and chromones seems to be one of the most direct and concise approaches to synthesize flavanones, chromanones and their derivatives. However, the tendencies towards overreduction to chromanol or chromane skeletons always challenge chemists [7, 44, 45].

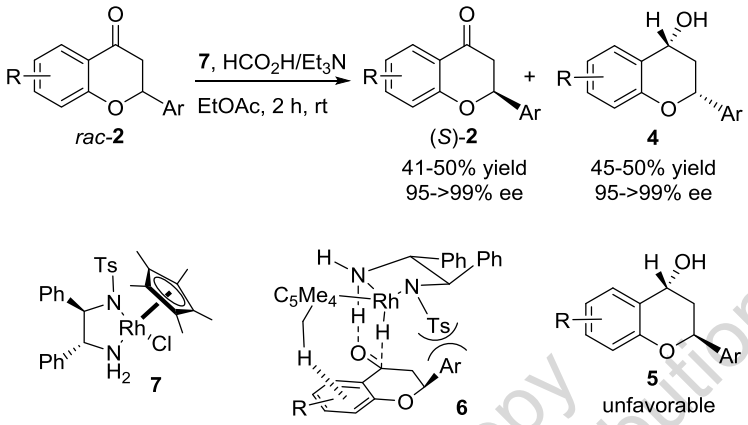
In 2013 Glorius and co-workers [46] reported the first example of ruthenium/NHC complex catalyzed (NHC = N-heterocyclic carbene) asymmetric hydrogenation of flavones and chromones (Scheme **1**). The general condition is that, Ru(COD)(2-methylallyl)$_2$, NHC ligand **3** and KO*t*Bu were stirred in hexane for 16 h after which the reaction mixture was added to substrate **1** and toluene. Then hydrogenation was performed under 120-150 bar of H_2 at 5-25 ^oC for 36 h. Under the above reaction condition, flavonols and chromonols were formed. Therefore, to obtain the desired flavanones and chromanones, additional oxidative procedure was required by using pyridinium chlorochromate (PCC) as the oxidant. This transformation provided the corresponding flavanones and chromanones without compromising the integrity of the newly formed stereocenter at C2. Various substituents, either electron-donating or -withdrawing, were introduced to flavones and chromones, affording chiral flavanones and chromanones in 88-98% yields up to 91% enantioselectivities.



Scheme 1. Ru-catalyzed asymmetric hydrogenation of chromones and flavones.

Metz [47] developed the use of rhodium(III) as catalyst and racemic flavanones as starting materials for kinetic resolution in a mixture of formic acid and triethylamine, producing chiral flavanones **2** and flavanol **4** in high conversion with excellent ee values (Scheme **2**). With 0.5 mol % catalyst loading, both flavanones and 2-alkylchroman-4-ones products can be generated in about 50% yields and up to 97% and 99% enantioselectivity, respectively. They also proposed a model of possible transition state **6** that determined the configuration

of the products. It is much unfavorable to further transfer hydrogen to carbonyl of (*S*)-flavanones to form **5**, because of the hindrance between Ts group on Rh complex and Ar group on (*S*)-**2**.

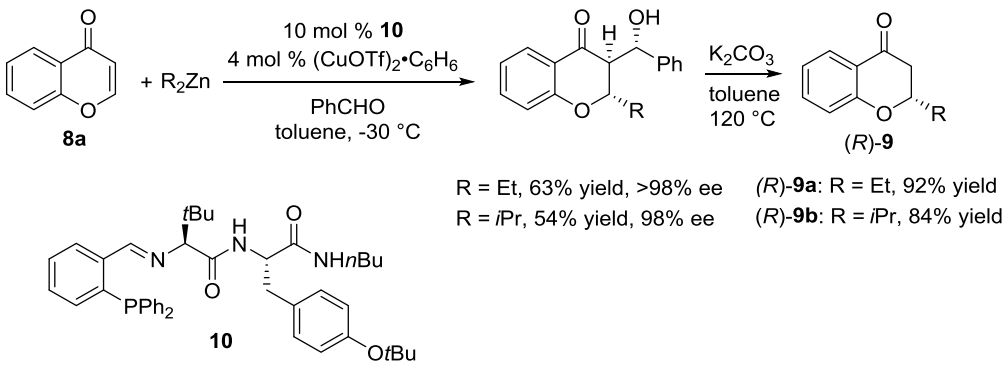


Scheme 2. Rhodium(III) catalyzed asymmetric transfer hydrogenation of flavanone derivatives *rac*-**2**.

C-C Bond Formation *via* Intermolecular Addition to 4-Chromones

The asymmetric catalyzed conjugate addition of nucleophiles to chromones is one of the most convenient and efficient methods to obtain the flavanone and chromanone compounds. However, the reports of synthesis of flavanones and chromanones through 1,4-addition to chromones remain limited due to the ease of phenoxide elimination after enolate formation and less reactivity of these pyran-4-one compounds [7, 44, 45]. In view of these limitations, it is desirable to develop well-tolerant catalyst systems that can make it possible to afford various flavanones and chromanones in good results.

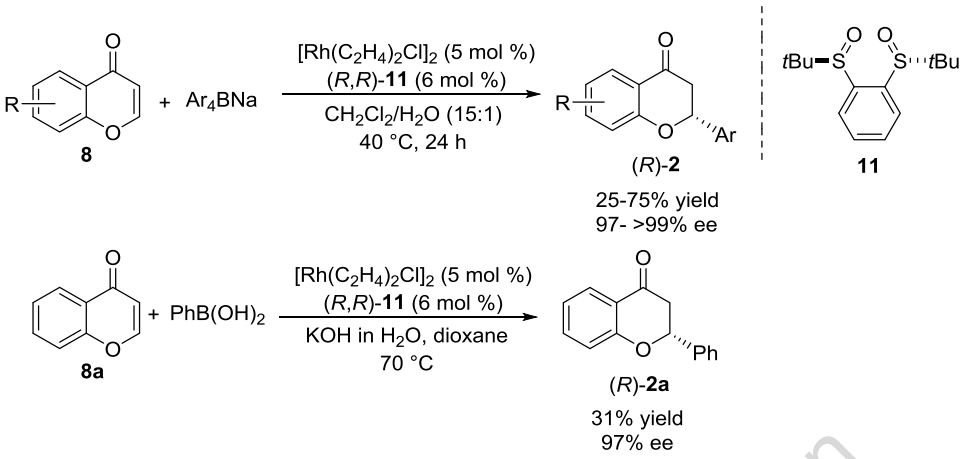
Hoveyda [48] reported Cu/chiral amino acid-based ligand complex catalyzed asymmetric conjugate addition (ACA) of dialkylzinc reagents to furanones and pyranones, which yielded the corresponding adducts with excellent enantioselectivities. Less reactive chromone was subjected to this reaction as well by using diethyl and diisopropylzinc reagents (Scheme **3**). To avoid side reactions, *β*-elimination and intermolecular addition, benzaldehyde was required to trap the forming enolate intermediates. The 2-ethyl and 2-isopropylchromanones can subsequently be obtained in 92% and 84% yield respectively through a retroaldol reaction.



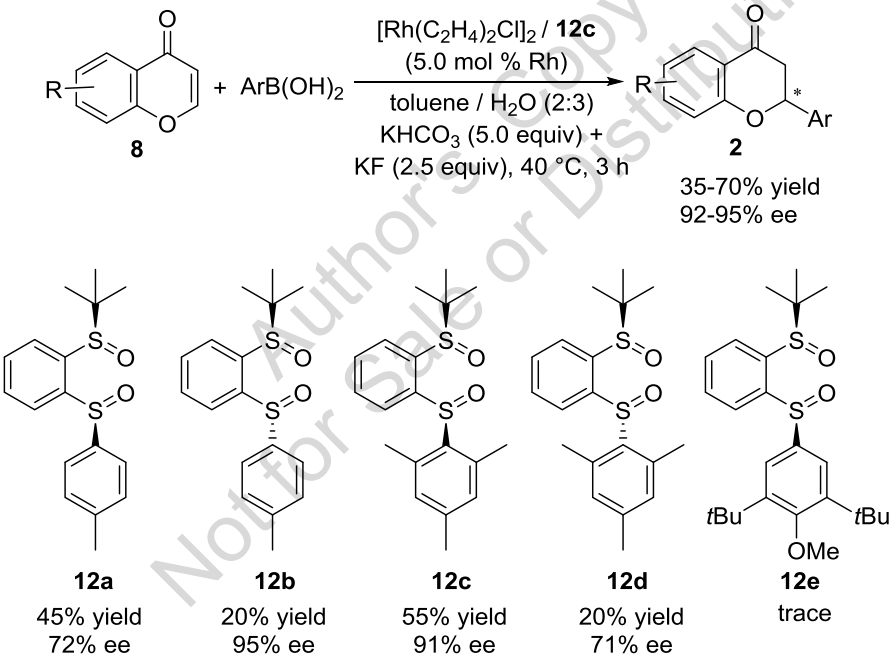
Scheme 3. Cu-catalyzed ACA of alkylzinc reagents to chromone.

In 2010, Liao [49] reported an asymmetric conjugate addition of sodium tetraarylborates (Ar_4BNa) to 4-chromones in the presence of rhodium/chiral bissulfoxide ligand **11** which is less developed than other ligands, such as phosphine, diene, *et al.* (Scheme **4**). Initially, low reactivity was shown (32% yield) when phenylboronic acid ($PhB(OH)_2$) was used as nucleophile. Asymmetric addition can be greatly improved by using Ar_4BNa instead of arylboronic acid. The reason accounted for the phenomenon might be that Lewis acid triarylborane (Ar_3B) generated from the transmetalation step might act as an activator and assist in the insertion step [50 - 52]. The scopes of chromones and nucleophile sodium tetraarylborates were investigated as well to test the activity of the catalytic system. All chromones, no matter with electron-rich or electron-deficient on benzene motif, can give the conjugate addition products in acceptable yields (57-75%) with 99% enantiomeric excess. The sodium tetraarylborates with electron withdrawing group (*meta*-Cl) provided inferior yields (25% yield, 97% ee) while electron rich *meta*- and *para*-methylphenylboranes gave rise to higher yields and ee values (64% and 70% yields, 98 and >99% ee, respectively). However, some limitations still exist: the lack of readily available functionalized Ar_4BNa and the byproducts are generally toxic.

To resolve above limitation, Liao and co-worker [53] challenged the problem that arylboronic acids presented weak reactivity in the Rh-catalyzed asymmetric conjugate addition (Scheme **5**). To achieve their goal, they synthesized and tested a series of disulfoxide ligands (**12a-e**) derived from *tert*-butyl sulfoxide. In the presence of $[Rh(C_2H_4)_2Cl]_2$ as catalyst precursor and KOH as base in CH_2Cl_2/H_2O (10:1) at 40 °C, flavanone was obtained in poor yield (45%) with moderate ee (72%) with **12a** while its diastereomer **12b** gave rise to the desired product in high enantioselectivity (95%) but in very low reactivity (20%). Increased the hindrance by changing *p*-MePh group to 2,4,6-triMePh group instead, **12c** ligand is better than **12d** on both reactivity and enantioselectivity (55% yield with 91% ee *vs* 20%



Scheme 4. Rh-catalyzed asymmetric 1,4-addition of sodium tetraarylborates to chromenones.

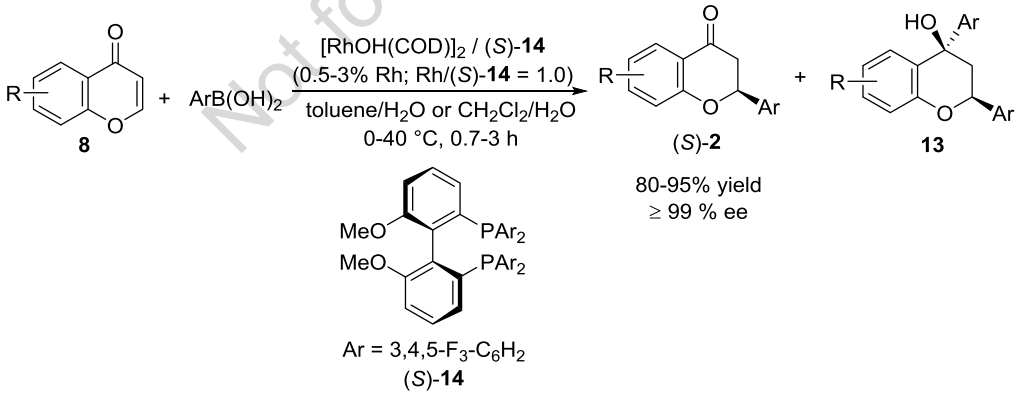


Scheme 5. Rh-catalyzed enantioselective 1,4-addition of phenylboronic acid to chromenone.

yield with 71% ee). Further increasing bulkiness of ligand did not improve the asymmetric reaction. Instead, only trace flavanone was observed. Toluene shows to be the best solvent in the reaction. Various Lewis bases were investigated. The reaction offered the best result by using the combination of $KHCO_3$ and KF as base. With the optimized reaction condition, that is 10 mol % $[Rh(C_2H_4)_2Cl]_2$/**12c**

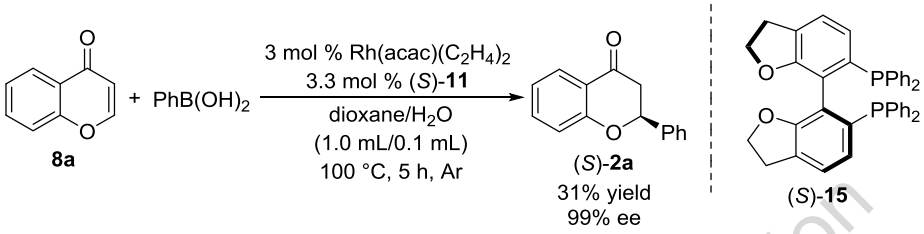
complex as catalyst and $KHCO_3$ and KF as Lewis bases in toluene at 40 °C, a series of flavanones were generated in the yields of 35-70% with high enantioselectivities (92-95% ee) (Scheme **4**). The scope study showed that the position of substituents on arylboronic acids has an affect on yield. For example, *o*-$MeC_6H_4B(OH)_2$ afforded much lower yield than *m*- and *p*-$MeC_6H_4B(OH)_2$ (35%, 60% and 64%, respectively). The electronic property of substituents on chromones did not influence the reactivity significantly. The enantioselectivities were affected by neither position nor electronic property of substituents on substrates (92-95% ee).

In the same year, Sakai and co-workers [54] reported a 1,4-addition of arylboronic acids to chromones **8** in the presence of $[Rh(COD)OH]_2$ with highly electron-poor chiral diphosphine (*S*)-**14**, affording the desired products in moderate to good yields (80%-95%) with excellent ee values (up to ≥99%) (Scheme **6**). Compared with previous work, this transformation was catalyzed by Rh-OH species instead of Rh-Cl species to avoid adding strong base, then suppressing ring-opening side reaction of flavanones. Moreover, Sakai's reactions proceeded in lower Rh catalyst loading (0.5-3 mol %) and a much shorter reaction time. During the reaction process, byproduct **13** generated as well through further addition of arylboronic acids to the carbonyl group of chromones. It was found that using of toluene as a solvent greatly enhanced the catalytic activity of Rh complex, resulting in a faster rate of 1,2-addition to (*S*)-**2**. When dichloromethane or 1,2-dichloroethane was used as solvent, the formation of the 1,2-addition byproducts **13** (up to 10% yields) was restrained due to a decrease in the activity of the rhodium catalyst. Further reaction condition optimization (*i.e.* the amount of $ArB(OH)_2$, temperature, reaction time) for different substrates was required to suppress the formation of the byproduct.



Scheme 6. Rh-catalyzed asymmetric conjugate addition of arylboronic acids to chromenones.

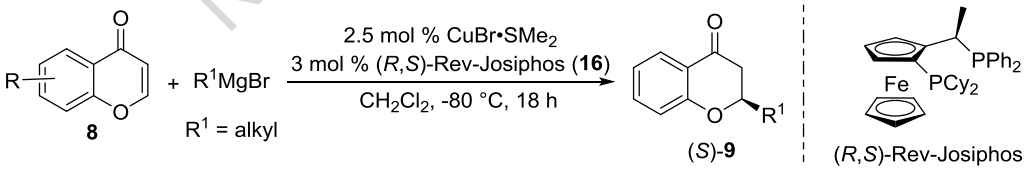
A similar Rh-catalyzed asymmetric addition of an array of arylboronic acids to cyclic enones was reported by Mino [55]. The corresponding products were obtained in moderate to good yields with excellent enantiomeric excesses. However, when they used chromone **8a** as substrate, only 31% yield was obtained even though enantioselectivity was high (99% ee) (Scheme **7**).



8a (*S*)-**2a** 31% yield 99% ee (*S*)-**15**

Scheme 7. Enantioselective synthesis of flavanone.

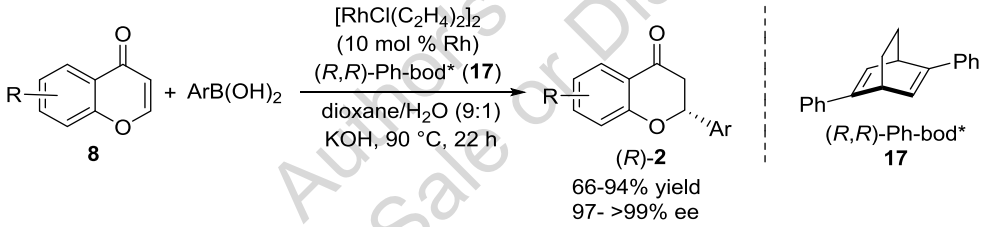
A direct and efficient approach to synthesis 2-alkylchromanones was developed successfully by Feringa's group [56] (Scheme **8**). In the investigation of ligands, they found that no enantioselectivity was observed when BINAP, a binaphthyl-type ligand, was used as ligand. Josiphos ligands showed excellent reactivity and stereoselectivity in this transformation. Almost racemic 2-alkyl substituted chromanone was obtained by using Taniaphos which has ferrocene skeleton as well but different coordination atoms (NP) from Josiphos (PP). THF is not suitable for the catalytic system and offers racemic product may be due to the good coordinating ability. With the optimized reaction condition in hand, a conjugate addition of alkyl Grignard reagents to chromones produced an array of chiral 2-alkylchromanones in moderate to high yields (53-98%) and enantioselectivities (78-98%) in the presence of Cu(I)/Josiphos bisphosphine ligand **16** complex.



8 (*S*)-**9** 53-98% yields 75-98% ee (*R*,*S*)-Rev-Josiphos **16**

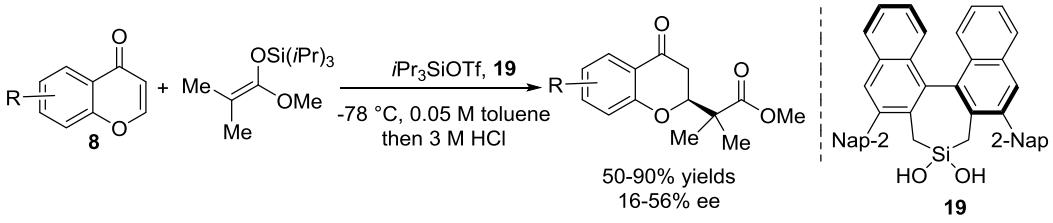
Scheme 8. Cu-catalyzed asymmetric conjugate addition of Grignard reagents to chromones.

After Hayashi [57] (2003) and Carreira [58] (2004) published their works of asymmetric synthesis, chiral diene ligand began emerging into the world of asymmetric synthesis and has now become a member of the most useful and important chiral ligands [59, 60]. In 2015, Wang group [61] developed a Rh/(*R*,*R*)-Ph-bod* **17**-catalyzed asymmetric 1,4-conjugate addition of arylboronic acids to chromones **8** (Scheme **9**). No reaction occurred with (*S*)-BINAP which is a chelating diphosphine ligand. However, when diene ligand (*R*,*R*)-Ph-bod* **17** was subjected to the reaction, the catalytic reactivity and stereoselectivity were increased significantly, providing the desired product in 83% yield with dramatically high enantiomeric excess (>99%). Under optimized reaction condition, that is $[RhCl(C_2H_4)_2]_2$ (10 mol % Rh) coordinated with (*R*,*R*)-Ph-bod* in dioxane/H_2O (9:1) as catalyst precursor and KOH as Lewis base at room temperature, various substituted flavanones were obtained in high yields with remarkable enantioselectivities (99% ee for most substrates). Particularly noteworthy is that no competitive side reactions (1,2-addition or ring opening reaction) were observed with the present catalyst system. The limitation of this catalyst system was relatively high Rh catalyst loading (10% Rh), but 5 mol % Rh catalyst is enough to give high yield and high ee in gram scale reaction.



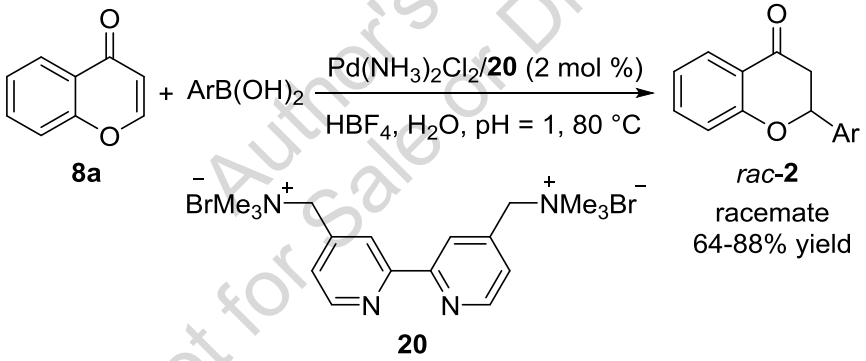
Scheme 9. Rh-catalyzed asymmetric 1,4-addition of $ArB(OH)_2$ to chromone.

In 2016, Mattson's group [62] developed an alkylation reaction of various chromones catalyzed by 3,3′-substituted binaphthyl-based silanediol **19** (Scheme **10**). Initially, the treatment of silyl triflates to chromones gave rise to 4-benzopyrylium triflates. The forming triflates immediately associated with enantioenriched silanediol to form the active chiral catalyst in the reaction. It's a great challenge to control the stereochemistry by the noncovalent interaction (*e.g.*, hydrogen bonding, Π-Π, Π-cation) in the transition state. Moderate enantiomer excesses were obtained in the asymmetric transformation, and the electronic property of substituents on the substrates significantly affected the experiment results. Electron-rich chromones showed much inferior stereoselectivity than electron-poor ones. For example, 7-methylchromone produced 53% yield with 16% ee while 4-nitrochromone provided 50% yield with 49% ee value.



Scheme 10. Silanediol-catalyzed chromenone functionalization.

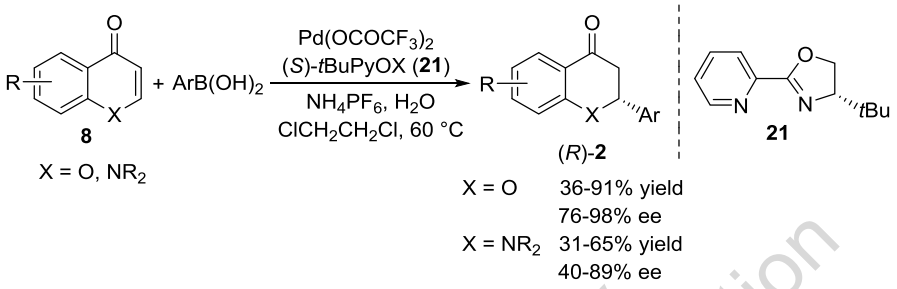
Apart from Rh complex, Pd catalyst could also be utilized in intermolecular conjugate addition to construct the flavanone core. In 2010, Tsai *et al*. [63] reported that Pd(II)/cationic 2,2'-bipyridyl system catalyzed conjugate addition reactions of arylboronic acids to *α,β*-unsaturated enones utilizing water as the reaction medium under air (Scheme **11**). The reaction provided the corresponding products in good to high yield in a racemic mixture. When **8a** was employed instead of simple cycloenones under identical condition, lower yields were afforded than other substrates. This might attribute to the fact that the donation of electron density from the oxygen lone pair to *β*-carbon led to the weakening of the electrophilicity of the *β*-carbon.



Scheme 11. Pd-catalyzed conjugate addition of arylboronic acids to *α,β*-unsaturated chromones in water.

The palladium-catalyzed synthesis of chiral flavanones through conjugate addition was firstly reported by Stoltz and co-workers [64]. The desired enantioenriched flavanones **2** were obtained in 36-91% yield with 76-98% ee in the presence of Pd/PyOX **21** complex (Scheme **12**). Compared with previous catalytic system, this protocol resulted in an unprecedented functional group tolerance. For instance, the unprotected hydroxyl group substituted chromones could provide the desired flavanones with good enantioselectivities. Either electron donating or electron withdrawing groups that arylboronic acids bear, the corresponding adducts can be obtained in good results. It is remarkable that a

hetero group 4-dibenzofuran can be introduced in 64% yield with 77% enantiomeric excess by use of 4-dibenzofuranboronic acid. 4-quinolones were also subjected to the catalytic system, although this transformation showed slightly inferior results than that of chromones.



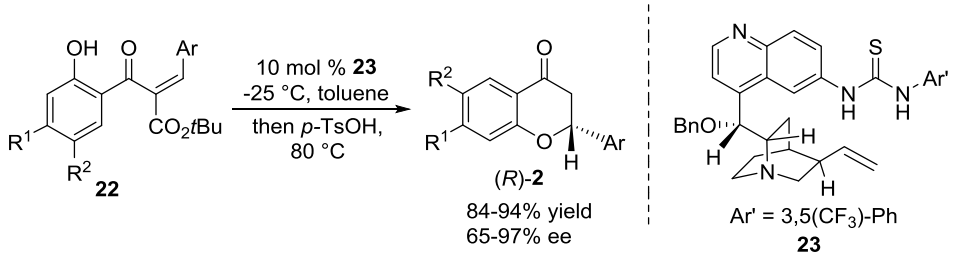
Scheme 12. Asymmetric conjugate addition of arylboronic acids to chromone catalyzed by Pd/PyOX.

C-O Bond Cyclization *via* Intramolecular Oxa-Michael Addition

To synthesize flavanones *via* C-O bond forming is generally based either on an intramolecular conjugate addition reaction of a 2-hydroxychalcone, or on the Mitsunobu inversion of *α*,*β*-hydroxyketone. The former method requires a chiral catalyst for asymmetric induction at C2 and the latter requires the generation of an enantio-enriched aldol or Mannich adduct to introduce stereochemistry at C2 [26].

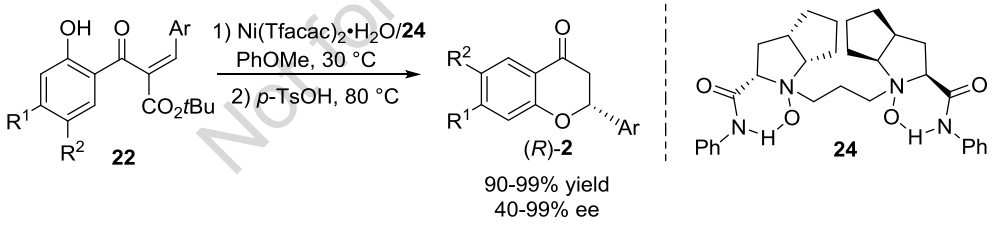
Intramolecular Oxa-Michael Addition

A chiral thiourea **23** catalyzed intramolecular cyclization of R-substituted chalcones **22** to synthesize flavanones and chromanones was firstly reported by Scheidt and co-workers [65] in 2007 (Scheme **13**). To enhance the substrate reactivity, incorporation of an ester group into chalcone was required. The additional ester group can also make the substrate favor intramolecular cyclization and provide a second Lewis basic site for potential interaction with the catalyst. After forming flavanone cores by cyclization, the 3-carboxy group can be removed by treatment with acid in toluene without compromising the integrity of the newly formed stereocenter at C2. From the scope investigation, it was found that the substrates with electron donating groups on the double bond and on aromatic ring could afford better enantioselectivities than those with electron withdrawing. For example, when the R group is 4-$MeOC_6H_4$ and 4-BrC_6H_4, the ee value is 94% and 65% respectively. Chromanones with 2-hexanyl group can be formed as well in the catalytic system (80% yield and 65% ee).



Scheme 13. Enantioselective synthesis of flavanones catalyzed by chiral thioureas.

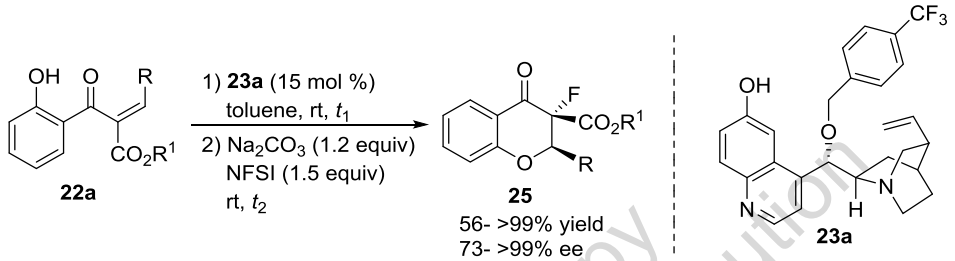
Later that year Feng's group [66] developed a nickel/*N*,*N*'-dioxide complex **24** catalyzed intramolecular oxa-Michael addition to generate a series of flavanones and chromanones (Scheme **14**). The activated group ester was still required in this transition metal catalytic system. With the optimized reaction condition, various olefin substrates with different aryl group were then investigated. The nickel/*N*,*N*'-dioxide complex system has a great tolerance on different group, providing corresponding products in 90-99% yields with 84-99% ee values. Electron-poor substituents led to slightly better enantioselectivities (92-99% ee) than electron-rich substituents (84-93% ee), and 2-ethylchromanone was obtained as well in 90% yield with 85% enantiomeric excess. The phenol motifs of chalcone were also tested and obtained good results. Exception formed when substrate with electron-poor substituents on the phenol moiety was used, offering poor enantioselectivity (40% ee).



Scheme 14. Asymmetric IOM addition of α, β-unsaturated ketone.

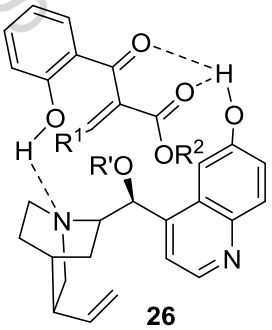
An organocatalytic intramolecular oxa-Michael addition/electrophilic fluorination tandem reaction for the synthesis of various chiral monofluorinated flavanones was reported by Zhao [67] in 2009 (Scheme **15**). A series of cinchona alkaloids were selected as catalysts to be investigated due to their easy availability and well-documented power as bifunctional organocatalysts. The scope of substrates

was extensively tested. When R is an aryl group, most of the substrates generally obtained excellent yields (93-99%) and high ee values (88-96%) regardless of the electronic property of substituents on aryl group. However, the reactivity and/or stereoselectivity were influenced greatly by changing the R group into alkyl or heterocycle group. For instance, when R is the ethyl group, the corresponding product was generated in 93% yield with only 17% enantiomeric excess, and 2-furanylchromanone yielded in 56% with 73% ee value.



Scheme 15. Stereoselective synthesis of fluorinated flavanones.

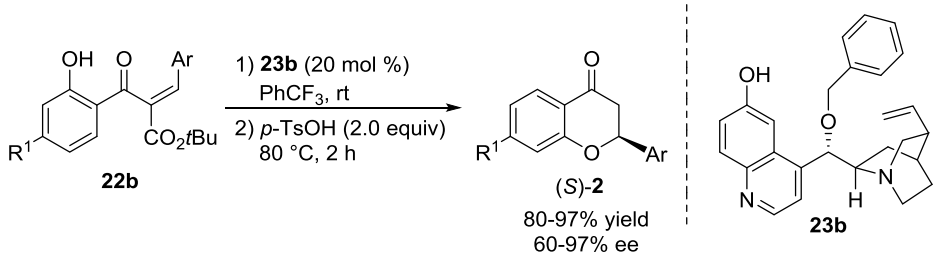
Based on the experimental results and previous researches a transition state model accounted for the *R* configuration of the fluorinated flavanones was built [68 - 70] (Scheme **16**). Both the nucleophile and the electrophilic acceptor were activated by the bifunctional catalyst cinchona alkaloids through a hydrogen-bonding interaction, directing the oxygen nucleophile to attack the *Re* face of the double bond to form the *R*-configured product.



Scheme 16. Proposed transition-state model for the oxa-Michael addition step.

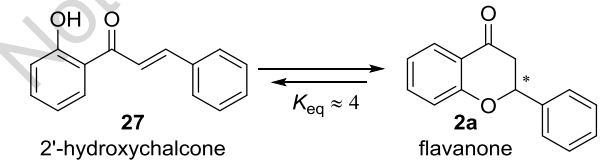
Considering that bifunctional cinchona alkaloids are efficient catalysts in oxa-Michael addition, Zhao [71] disclosed a similar intramolecular oxa-Michael addition reaction of alkylidene *β*-ketoesters **22b** catalyzed by bifunctional cinchona alkaloid **23b** catalysts (Scheme **17**). After cyclization, decarboxylation

proceeded to release the final chiral flavanones. Of all the substrates examined, excellent yields (80-97%) were generally obtained with moderate to high enantioselectivities (60-97% ee).



Scheme 17. Oxa-Michael addition/decarboxylation reaction alkylidene β-ketoesters catalyzed by bifunctional cinchona alkaloids.

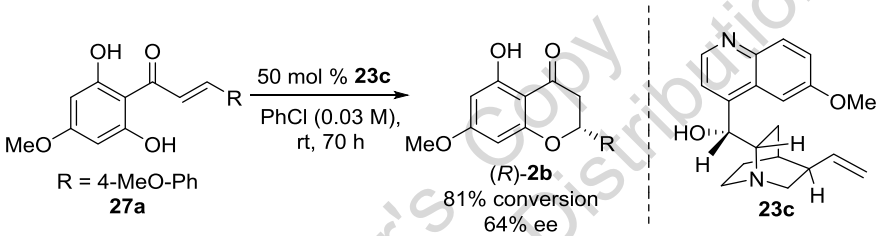
In the plant's metabolic process, 2'-hydroxychalcones **27** can undergo intramolecular cyclization to produce 2*S*-flavanones with an unbelievable enantioselectivity (ee = 99.998%) in the presence of the enzyme chalcone isomerase [72 - 74]. The powerful transformation has forced chemists to develop an appropriate catalyst to facilitate this facile and efficient process. However, various approaches of synthesis of flavanones in common provided products in racemic form. For those asymmetric strategies, multistep involving chiral auxiliaries, protecting groups (*i.e.* ester group at C2) and deprotections is generally required. Moreover, the reversibility of the cyclization process in basic reaction condition and lower reactivity of the substrate makes the transformation more difficult [75, 76] (Scheme **18**). Thus, the development of asymmetric small-molecule catalyzed the cyclization of 2'-hydroxychalcones to flavanones in one step is challenging.



Scheme 18. Most model cyclization of 2'-hydroxychalcone to flavanone.

In 2007, Hintermann [77] took the challenge and successfully achieved asymmetric intermolecular oxa-Michael addition of 2'-hydroxychalcones to flavanones by a nonenzymatic method with organocatalysts **23c** (Scheme **19**).

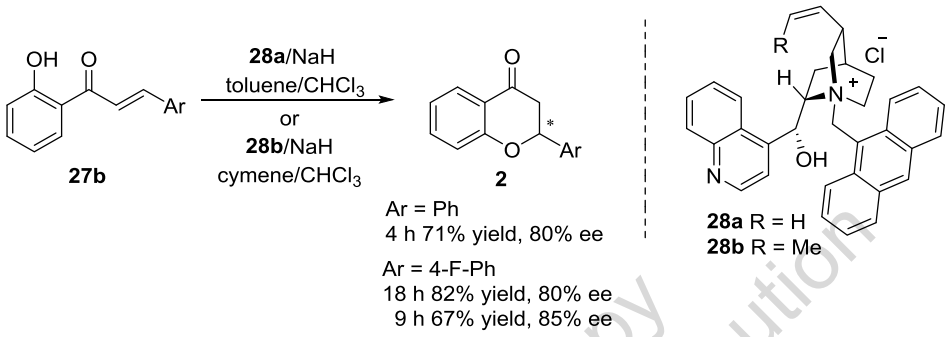
Initially, unsubstituted hydroxychalcone was subjected to Ishikawa's reaction conditions [78 - 80]. However, no expected reaction took place. After careful examination, they found that the kinetic reaction barrier might be overcome by either choosing a more active catalyst, or by using a more reactive substrate. Herein, they synthesized the substrate of 2'-hydroxychalcones **27a** which was incorporated an additional hydroxyl group on 6-position of benzene ring. As expected, the modified substrate underwent successfully cyclization reaction in the presence of cinchona alkaloids and provided the desired flavanone in 81% conversion with 64% enantioselectivity. Nevertheless, the catalyst loading is much higher and the reaction time is long (70 h). It is still desired to develop a more efficient method to synthesize chiral flavanone by cyclization of 2'-hydroxychalcones.



Scheme 19. Asymmetric cyclization of 2',6'-hydroxychalcone to flavanone with cinchona catalyst.

Years later, the same group [81] found that quarternized cinchonidine **28** was a more efficient catalyst for the difficult cyclization of unsubstituted 2'-hydroxychalcones **27b** into enantio-enriched flavanones **2** (Scheme **20**). The author designed and synthesized a series of quaternary cinchonidines, and then they carried out the reactions with co-catalytic sodium hydride (NaH) as base to deprotonate the substrates. When the *N*-alkyl group was 9-anthracenylmethyl, the best result was obtained (59% ee). The presence of the alcoholic hydroxy group was also critical for achieving selective catalysis. The *N*-(9-anthrylmethyl) salts of all major cinchona alkaloids with chloride ion as counter ion were then examined. Finally, they chose two catalyst systems to facilitate the transformation of various of 2'-hydroxychalcones: 1) 9-Am-CD-Cl **28a**/NaH catalyst in toluene/$CHCl_3$; 2) 9-Am-CN-Cl **28b**/NaH catalyst in cymene/$CHCl_3$–The first catalyst system afforded around 60% ee of most of flavanones. Higher enantioselectivities (76-87%) were generated for most of products by using the second catalyst system. Interestingly, the two catalyst systems offered opposite absolute configuration of flavanones. Moreover, the stereoselectivity was dependent on total reaction conversion. For typical example, the reaction was carried out using 4"-fluoro-2'-

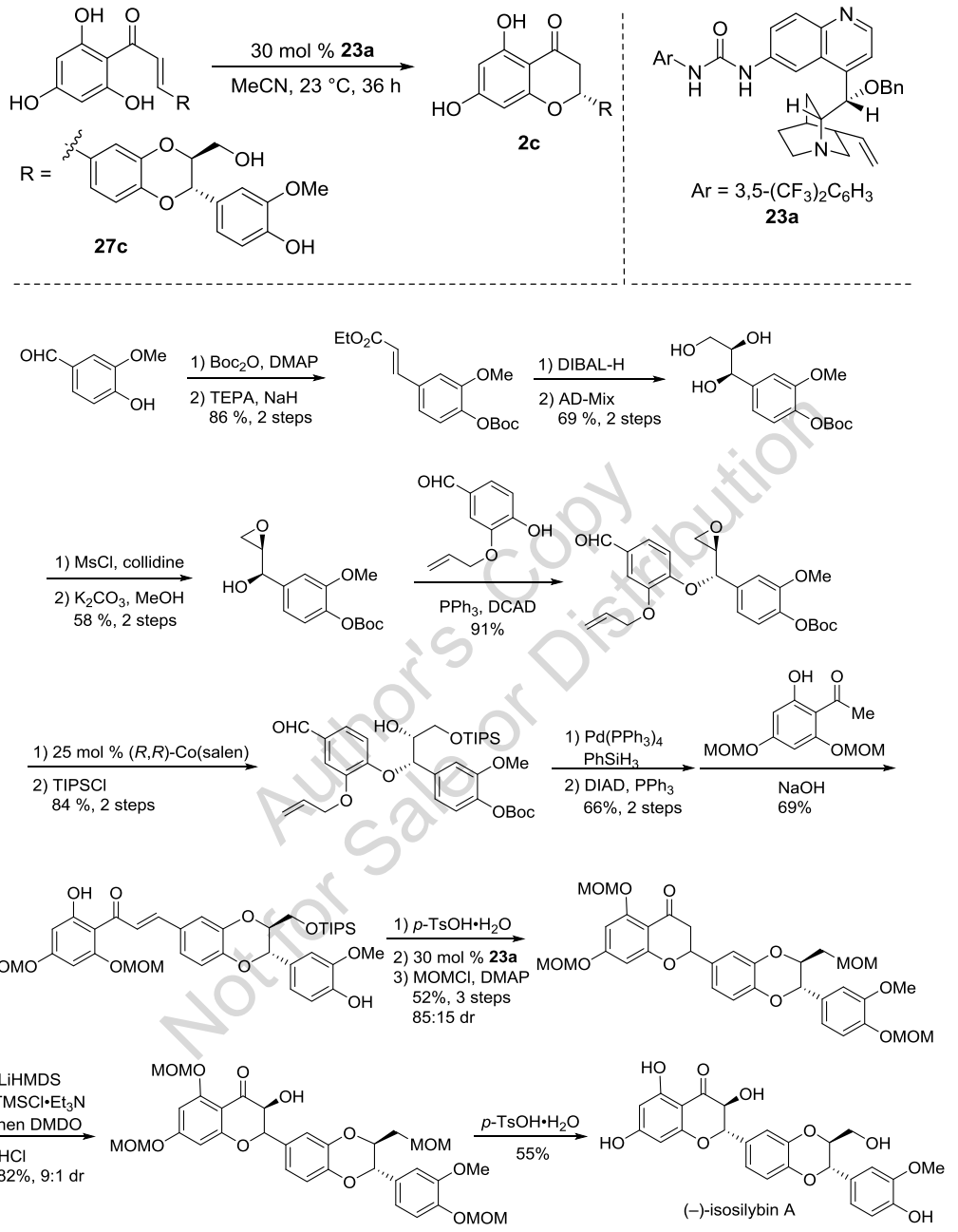
hydroxychalcone as starting material and then quenched after 5 h, offering 4-fluoroflavanone in 45% yield with 87% enantioselectivity. When the reaction time was prolonged to 9 h and 18 h, the desired product was generated in 67% yield with 85% ee and 82% yield with 80% ee, respectively. The use of a mix solvent of toluene and $CHCl_3$ can effectively suppress the side-product.



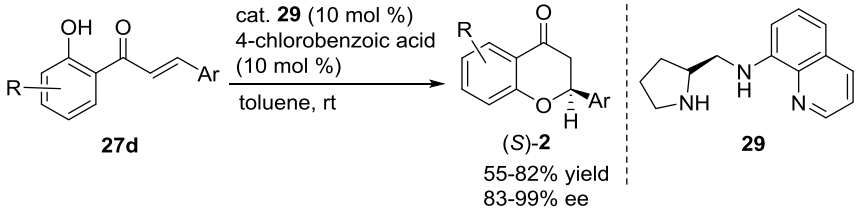
Scheme 20. Asymmetric ion-pairing catalysis of the reversible cyclization of 2'-hydroxychalcone to flavanone.

In 2015, Schiedt [82] reported a total synthesis of (−)-isosilybin through a biomimetic catalytic cyclization of a highly functionalized chalcone, in which urea group was cooperated into quinidine catalyst to accelerate reaction rate and improve the enantioselectivity (Scheme **21**).

In 2014, Wang [83] designed and prepared a series of L-proline derivatives as organocatalysts which can facilitate the ring closing reaction of 2'-hydroxychalcones **27d** (Scheme **22**). Of all the organocatalysts examined, the catalyst **29** showed the best reactivity and stereoselectivity. Various benzoic acid with different substituents were examined due to organic acid could enhance the formation of the iminium-ion intermediate [84, 85]. The experiment showed that catalytic amount benzoic acid does accelerate the reactivity of cyclization, and 4-chlorobenzoic acid was proved to be the best additive, offering chiral flavanones in 68% yield with excellent enantiomeric excess (96% ee). With the optimized reaction condition, that is 10 mol % organocatalyst **29** as chiral catalyst and 10 mol % 4-chlorobenzoic acid as additive in toluene at room temperature, aryl group substituted with either electron-withdrawing or electron-donating groups were introduced onto 2'-hydroxychalcones **27d** and successfully provided the corresponding flavanones in 55-82% yield and 83-99% ee.

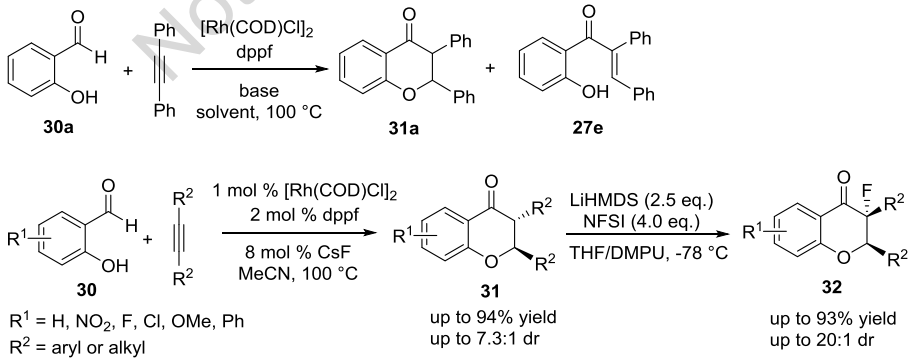


Scheme 21. Total synthesis of (−)-isosilybin.



Scheme 22. Enantioselective biomimetic cyclization of 2'-hydroxychalcones to flavanones.

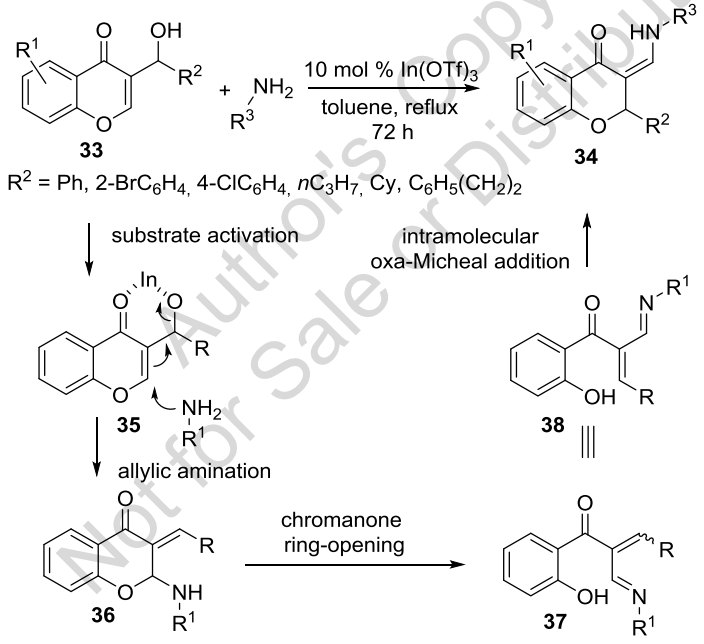
Another rhodium catalyzed intermolecular oxo-Michael additions of 1,2-disubstituted alkynes with 2-hydroxybenzaldehyde **30** to prepare 3-substituted flavanones were reported by Stanley [86] in 2015 (Scheme **23**). In the presence of 5 mol % $[Rh(COD)Cl]_2$ and dppf complex, the transformation afforded not only flavanone but also unexpected byproduct. The base has a significant impact on the reaction to form the flavanone. When the Lewis bases Na_2CO_3, K_3PO_4, and CsF were tested separately, the yields of the desired flavanone were increased from 14% to 84% by suppressing the forming of the side product 1-(2-hydroxyphenyl)-2,3-diphenylprop-2-en-1-one **27e** (yields decreased from 76% to 7%). Finally, under the optimized reaction condition: 1 mol % of $[Rh(COD)Cl]_2$/2 mol % dppf as catalyst and 8 mol % CsF as Lewis base in MeCN at 100 °C, hydroacylation were carried out with various alkynes and salicylaldehydes. When asymmetric alkyne (1-phenyl-1-propyne) was involved in the transformation, a 3.4:1 regioisomeric ratio of 3-methyl-2-phenylchroman-4-one and 2-methyl-3-phenylchroman-4-one was generated, which made the reaction more complicated. Then, symmetric alkynes were preferred in the intermolecular oxo-Michael additions. After hydroacylation process, fluoro group also could be introduced onto 3-position of flavanone, providing 3-fluoro flavanones in 67-91% yield with high diastereoselectivity (>20:1 for most products). 2-ethyl and 2-isopropyl fluorinated chromanones were obtained as well (88% yield with 14:1 dr, 93% yield, 9:1 dr, respectively).



Scheme 23. Tandem alkyne hydroacylation/oxo-Michael addition with salicylaldehydes.

Tandem Reaction of Chromone

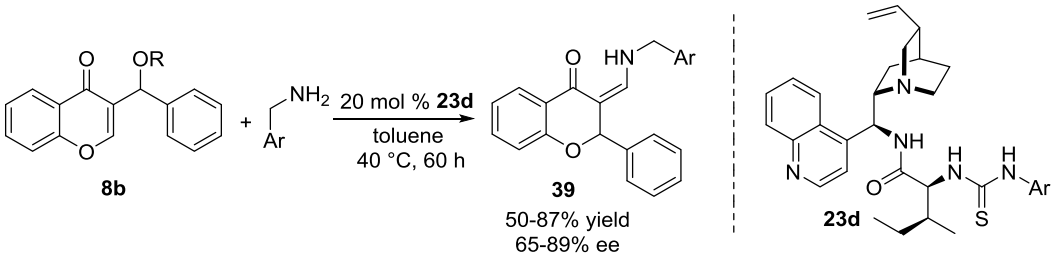
In 2011, Liu [87] developed an interesting approach to synthesize flavanones by the tandem reaction of chromone-based cyclic Morita-Baylis-Hillman alcohols with amines in the presence of Lewis acid $In(OTf)_3$ (Scheme **24**). The reaction conversion required a long time (72 hours) and relatively tough condition (reflux of toluene) to form a series of 2-substituted-3-aminomethylene chromans **34**, although the desired products were generated in good to high isolated yields in racemic form. They have proposed a possible mechanism for the transformation. The Lewis acid $In(OTf)_3$ initially activated chromone-based MBH alcohol **33**, which was attacked by amine at the *γ*-position. The forming intermediate **36** proceeded a chromone ring-opening reaction [75, 76] to generate an active Michael acceptor **35** which could isomerize to **38**. Finally, intermolecular oxa-Michael addition took place to release the terminal product.



Scheme 24. In(III)-catalyzed reaction of MBH alcohols with amines.

Afterwards, the same group [88] discovered that the cinchona alkaloid-based thiourea **23d** is an effective organocatalyst that has access to enantio-enriched flavanones *via* the above tandem reaction (Scheme **25**). Under the optimized reaction condition, that is, 20 mol % cinchona alkaloid-based thiourea as catalyst in toluene at 40 °C for 60 h, both electron withdrawing and electron donating

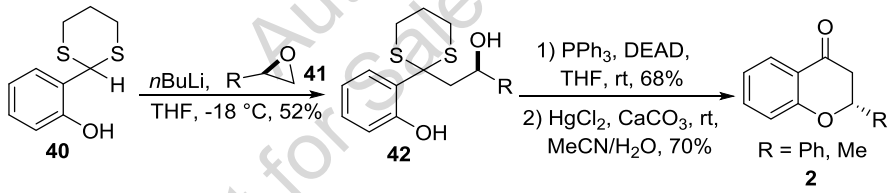
groups can be introduced, offering the desired products in moderate to good yields (50-87%) with ee values (65-89% ee). Compared with their previous work, this reaction required much lower reaction temperature and shorter reaction time.



Scheme 25. The enantioselective tandem reaction of MBH carbonates with amines.

Intramolecular Mitsunobu Cyclization

Noda and Watanabe [89] reported the Mitsunobu cyclization and desulfurization of diol **42** for the preparation of chiral flavanones (Scheme **26**). The diol was synthesized by using dithiane **40** and either (*S*)- or (*R*)-styrene oxide **41** as starting materials in the presence of *n*-BuLi. Since the configuration of flavanones was determined by the use of (*S*)- or (*R*)-styrene oxide, both the (*S*)- and (*R*)-enantiomers of flavanone and 2-methylchromanone could be obtained with exellent enantiomeric excess (95-99%). However, the scope of this transformation was quite limited may due to requirement of multistep preparation of substrates.

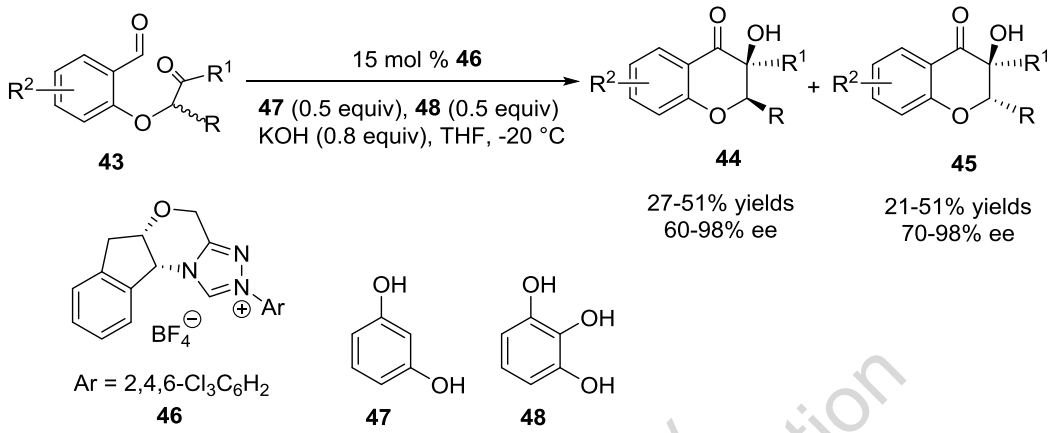


Scheme 26. Enantioselective synthesis of both enantiomers of flavanone and 2-methylchromanone.

Other Related Reactions

Recently, Fang [90] reported a chiral NHC ligand **46** catalyzed cross aldehyde-ketone benzoin condensation to generate a series of chromanones bearing two chiral centers (Scheme **27**). Because of the inherent chiral center of the starting materials, there is only one chiral center that can be controlled in terms of stereoselectivity by chiral catalyst, which means that it is not possible to obtain one optical pure isomer in high yield. It requires a resolution. The enantioselectivities were improved by adding catechol type additives may be due to the H-bonding occurred between the carbonyl group of the ketone moiety and the Breslow intermediate. Not only 2-alkyl but also 2-arylchroman-4-one can be

synthesized in moderate to high ee values.

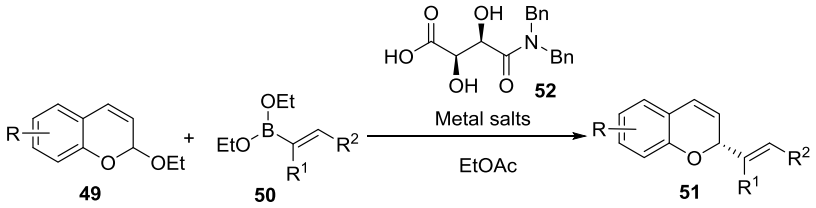


Scheme 27. Stereodivergent benzoin reaction for the synthesis of chromanones/flavanones.

ASYMMETRIC SYNTHESIS OF CHIRAL CHROMENE

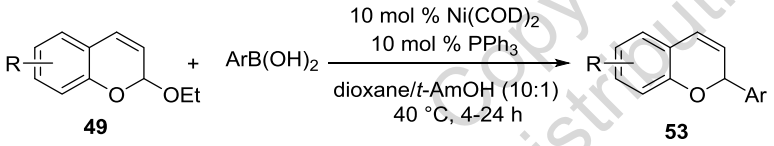
Asymmetric Additions to Chromene Acetals

A chiral Brønsted acid/Lewis acid catalyzed enantioselective addition to chromene acetals **49** was reported by Schaus in 2010 [91] (Scheme **28**). In this methodology, various boronates, which were characterized by their easy preparation, commercial availability, and stability towards storage and isolation, were utilized as electrophiles. Tartaric acid derived amides proved to be the best catalyst for transformation. To achieve high efficiency and enantiomeric excess, further investigations focusing on catalyst loading, additives, solvent, and temperature were carried out. Lower temperatures are preferable in the reaction while Ce(III), Ce(IV), and Yb(III) triflate salts all gave comparably high yields and enantioselectivities. The addition of boronates to chromene acetals catalyzed by Brønsted acid/Lewis acid offers a range of 2-substituted-chromenes in moderate to good yields with high enantioselectivities. However, further optimizations were required to obtain higher yields and selectivity for different substrates, which means that no single set of reaction condition that can be applied to all the substrates evaluated.



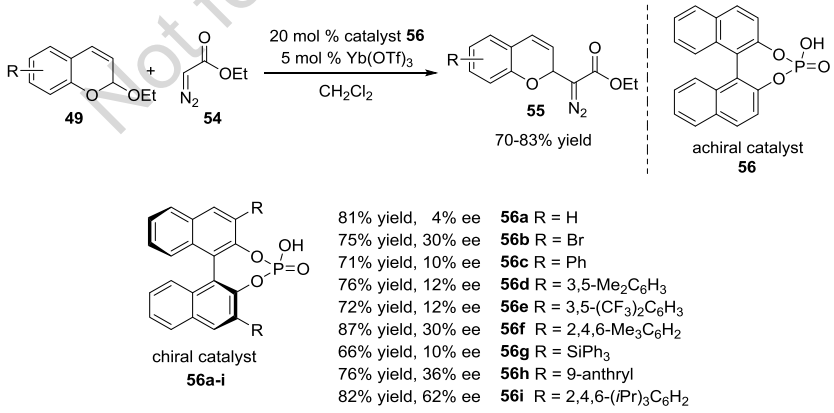
Scheme 28. Enantioselective addition of boronates to 2-ethoxy-2*H*-chromenes **49.**

The boronate partners in the above method are limited to cinnamyl and Π-rich arenes. Lately, Doyle reported a nickel-catalyzed addition of aryl- and heteroarylboronic acids to chromene acetals **49** (Scheme **29**) [92]. The scope of the boronic acids is more general, and many 2-substituted-chromenes could be obtained with 26-97% yields. However, the author did not try this transformation in asymmetric version.



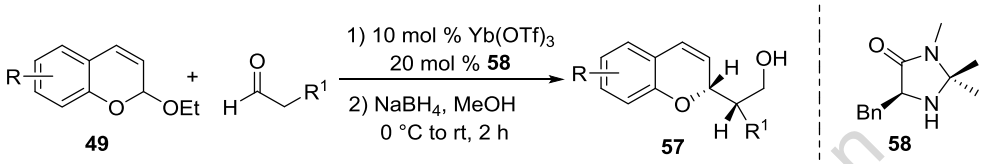
Scheme 29. Ni-catalyzed coupling of arylboronic acids with 2-ethoxy-2*H*-chromene **49.**

In 2014, Schaus reported the application of their Brønsted acid/Lewis acid dual catalyst concept to the addition of diazoesters to chromene acetals, affording racemic products in 70-83% yield (Scheme **30**) [93]. Many chiral (BINOL)-phosphoric acid catalysts were also investigated. However, only one of phosphoric acid **56i** can provide the desired product with moderate enantioselectivity (82% yield with 62% ee).



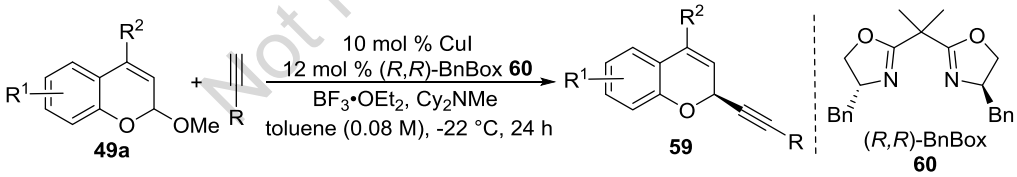
Scheme 30. Brønsted acid/Lewis acid catalyzed addition of diazoesters to 2*H*-chromene acetals **49** .

In 2012, Rueping and co-workers [94] reported a synergistic catalytic system for the asymmetric addition of aldehydes to *in situ* generated oxocarbenium ions which provide access to a series of valuable chromenes with two chiral centers in one step (Scheme **31**). They used Lewis acid $Yb(OTf)_3$ to activate the chromene acetals to generate the prochiral oxocarbenium ions and chiral Lewis base to activate the aldehydes simultaneously. In general, the scope of this transformation was relatively wide as different substituents on the chromenes led to products in 69-89% yields and 72-97% enantioselectivities.



Scheme 31. A dual catalytic system for the synthesis of chromenes.

Watson [95] reported an asymmetric synthesis of 2-alkynyl chromenes in the presence of CuI/(*R*,*R*)-BnBox **60** complex (Scheme **32**). The overall concentration of the reaction influenced the enantioselectivity. By reducing the concentration from 0.31 M to 0.08 M, the enantiomeric excess increased from 63% to 73%. From the view of the author, the base Cy_2NMe promoted the formation of chiral copper acetylide and Lewis acid facilitated the ionization to deliver oxocarbenium ion, which made the catalytic cycle work successfully to form enantioenriched chromenes. Under optimized conditions, a variety of chromene acetal substrates underwent alkynylation in high yields and enantioselectivities. Since numerous biologically active chromene natural products contain 4-aryl substituent, 4-aryl substituted-2-alkynyl chromenes also have been synthesized in good yields (up to 90%) and ee values (up to 95%).

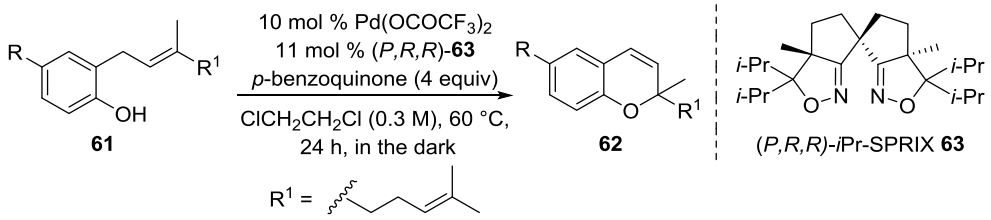


Scheme 32. Cu-catalyzed alkynylation of benzopyranyl oxocarbenium ions to synthesize chromenes.

Intramolecular Allylic Cyclization

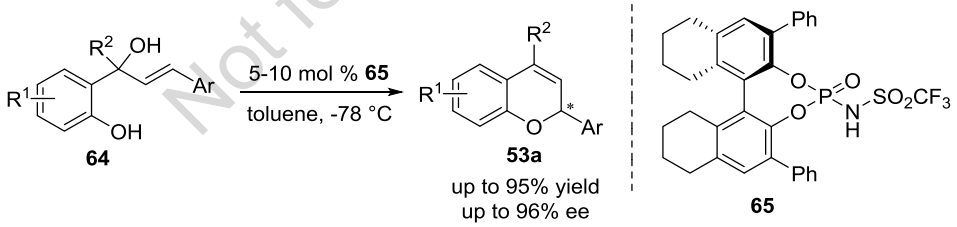
Sasai [96] disclosed a $Pd(OCOCF_3)_2$/(*P*,*R*,*R*)-*i*Pr-SPRIX **63** system catalyzed enantioselective intramolecular Wacker-type cyclization of 2-geranylphenol, which has access to construction of chiral chromenes with a quaternary stereogenic center with moderate yield up to 55% ee (Scheme **33**). Inconvenience

was caused by conducting the reaction in the dark.



Scheme 33. Pd-catalyzed intramolecular cyclization to form chiral chromenes.

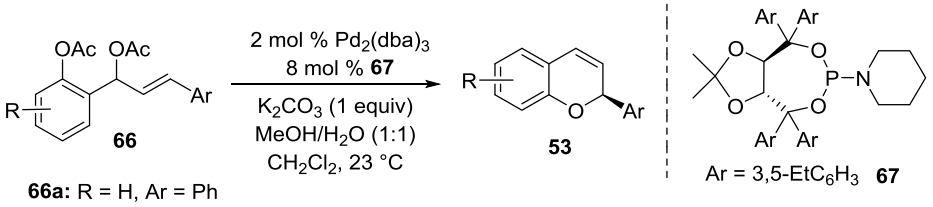
In 2011, Rueping [97] reported an enantioenriched intramolecular allylic alkoxylation to form a series of optical active chromenes derivatives in good to high yields (up to 95%) with high ee value (up to 96%), using chiral Brønsted acid *N*-triflylphosphoramide **65** as catalyst (Scheme **34**). From catalysis investigation, the substituents at the 3,3'-positions of the BINOL framework have a great impact on the enantioselectivity. Low temperature is preferable in this transformation. Considering the reaction mechanism, allylic alkylation pathway is more convinced than other possible postulations. Oxa-6Π electrocyclic reaction in which heating the vinyl *o*-quinone methide structure is needed can be ruled out due to low temperature and the substrates in this reaction. S_N2' substitution, through which enantiomeric excess is preserved during reaction, also exclude from the possibilities. Control reactions indicated that the chiral substrates lost enantioselectivity through an intermediate. Hence, the most possible mechanism for this reaction is that alocholic hydroxyl group of substrate **64** was protonated and subsequent dehydration by chiral Brønsted acid to form allyl-like cation which is associated with phosphoramide anion in a chiral contact ion-pair.



Scheme 34. Asymmetric Brønsted acid-catalyzed allylic alkylation.

In 2014, Scheidt [98] developed an enantioselective Pd-catalyzed 6-*endo-trig* reaction for the synthesis of 2-aryl-chromenes in mild condition (Scheme **35**). Motivated by a report [99] that involved the use of BINOL- and TADDOL-derived phosphoramidites for Pd-catalyzed intermolecular allylic alkylation,

initial ligand investigation began with BINOL-, SIPHOS-, and TADDOL-derived phosphoramidites. The results showed that TADDOL-derived ligands performed

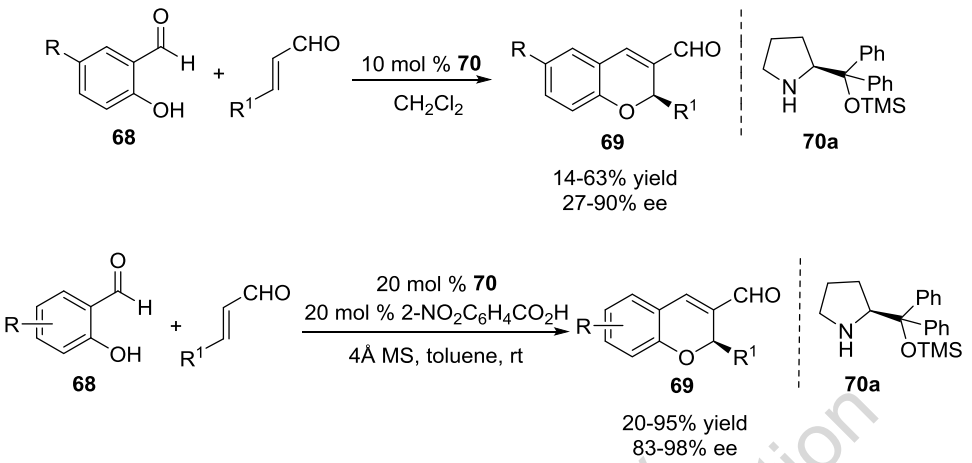


Scheme 35. Enantioselective synthesis of 2-aryl-chromenes catalyzed by palladium complex.

better than the other two types of ligands in terms of shorter reaction time and wider range of ligands. After systematic screening on the backbone of TADDOL-derived ligands, **67** was proved to be the best ligands in the transformation. The catalyst system $Pd_2(dba)_3$/**67** greatly facilitated the formation of 2H-chromenes from various bis-acetate substrates. Under the reaction condition, the cyclization of substrate **66a** gave rise to a 70% yield of 2-phenylchromene with 90% enantiomeric excess. Aryl group of styrenyl component with either electron-withdrawing or electron-donating groups, such as 2-MeC_6H_4, 2-FC_6H_4, 3-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, and 4-FC_6H_4, provided corresponding products with similar enantioselectivities. To the other aryl part of substrates, limited 2-substituted chromenes were offered in the scope table.

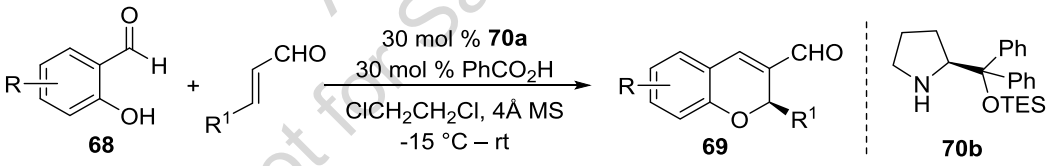
Intermolecular Cyclization

In 2006, Arvidsson reported secondary amine-catalyzed domino reaction involving an oxa-Michael addition of salicylic aldehyde derivatives to *α,β*-unsaturated aldehyde, followed by an intramolecular aldol reaction to construct 3-formylchromenes [100]. TMS protected prolinol **70a** gave C-2 substituent chromene-3-carbaldehyde in 14-63% yield with 27-90% enantioselectivity, which stimulated chemists to develop this method to obtain more satisfied results (Scheme **36**). Almost the same time, Cordova [101] also reported the TMS protected prolinol **70a**–catalyzed domino oxa-Michael/aldol condensations of unsaturated aldehydes with salicylaldehydes, which produced a series of enantioenriched chromenes in 20-95% yields with 83-98% ee (Scheme **36**). There are only a few differences between the two methods. Cordova used 20 mol % **70a** as a catalyst, 20 mol % 2-nitrobenzoic acid as the additive and toluene as solvent which resulted in better yields and ee. They found that the molecular sieves significantly improved the yields of products.



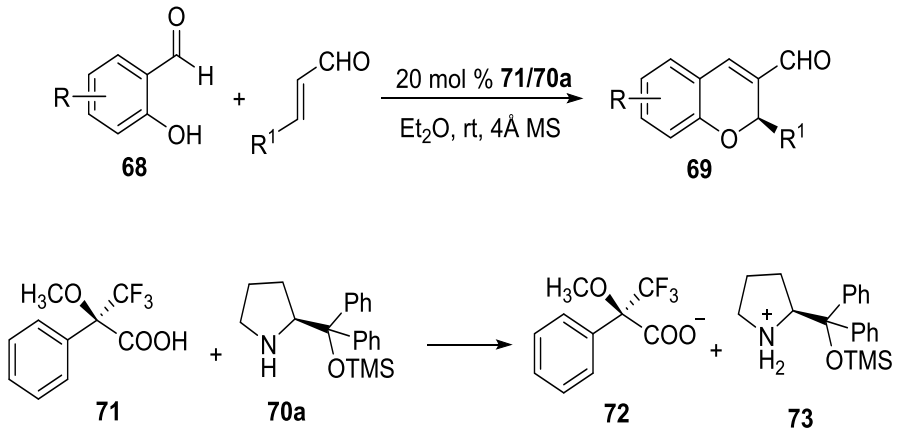
Scheme 36. Organocatalytic synthesis of chiral chromenes.

Simultaneously, a very similar study had been reported by Wang's group [102]. In Wang's work (Scheme **37**), the TES protected prolinol **70b** was a superior catalyst than TMS protected prolinol **70a** which gave 3-formylchromenes with 53-98% yield and 75->99% ee. Before this finding, Wang already demonstrated that 2-mercaptobenzaldehydes can participate in tandem reactions with better yield and higher enantioselectivity since the sulfur of thiophenol is a much stronger nucleophile than that of the oxygen in phenol [103, 104].



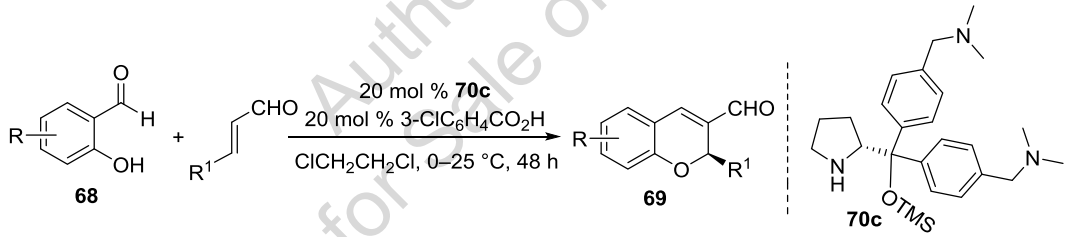
Scheme 37. Preparation of chromenes *via* organocatalytic asymmetric domino oxa-Michael-aldol reaction.

This tandem oxa-Michael-aldol reaction was extensively studied by many groups. Xu and co-workers [105] reported TMS protected prolinol **70a** with chiral acid **71** as organocatalytic system catalyzed the transformation of chromenes (Scheme **38**). They found that the formed chiral ammonium salt can improve the enantioselectivity greatly while the yields and enantiomeric excesses are much poor without adding chiral acid. The structure of the chiral ammonium salt formed *in situ* and the corresponding mechanism were also studied by ^{1}H NMR.



Scheme 38. Tandem oxa-Michael-aldol reactions between unsaturated aldehydes and salicylic aldehydes.

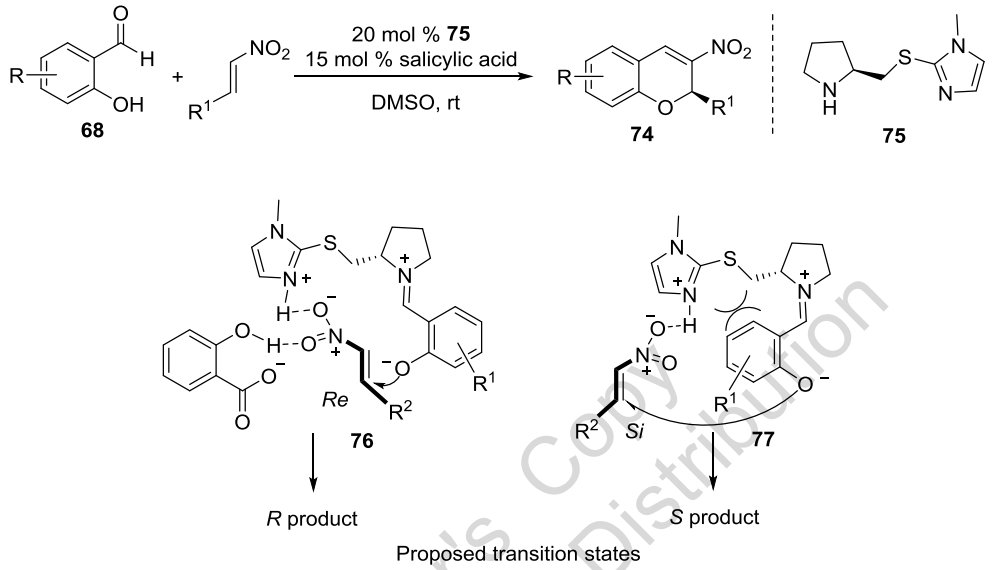
Another Xu group [106] developed a similar approach to obtain various chromenes using a modified TMS protected prolinol **70c** as organocatalyst at 0-25 °C, offering 2-aryl and 2-alkyl substituted chromenes in good yield (up to 93%)with moderate to high ee values (up to 94%) (Scheme **39**). The author also compared the chiroptical properties of the two chiral ligands **70a** and **70c** by UV/Vis and CD spectroscopy.



Scheme 39. Organocatalytic asymmetric oxa-Michael/aldol reactions.

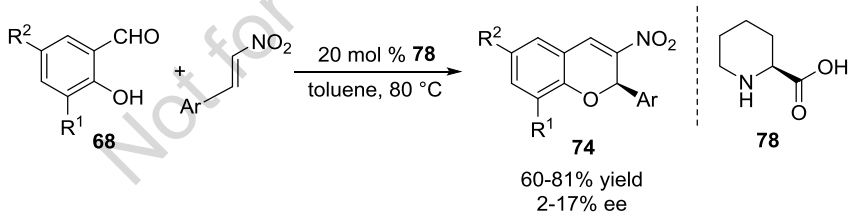
An asymmetric oxa-Michael-Henry reaction of substituted 2-hydroxybenzaldehyde with nitro-activated alkenes was developed by Xu group [107] in 2008 (Scheme **40**). In their study, pyrrolidine-thioimidazole **75** performed best in terms of yield (93%), and addition of salicylic acid can increase the ee value from 5% to 85%, but reduce the yield of product to 67% on the other hand. While the secondary amine part of organocatalyst can react with formyl group of salicylaldehyde, the remote imidazole motif and salicylic acid have hydrogen bonding interaction with nitro group. The enantioselectivity was realized by the combination of the above functions. From the proposed transition state, it is apparently noted that the nitro group is necessary to the alkenes in the

reaction. Apart from the interaction, nitro group can activate the olefins as well. Solvent executed significant impact on the transformation. DMSO proved to be the best solvent regarding reactivity and selectivity when the other solvents gave much poorer results.



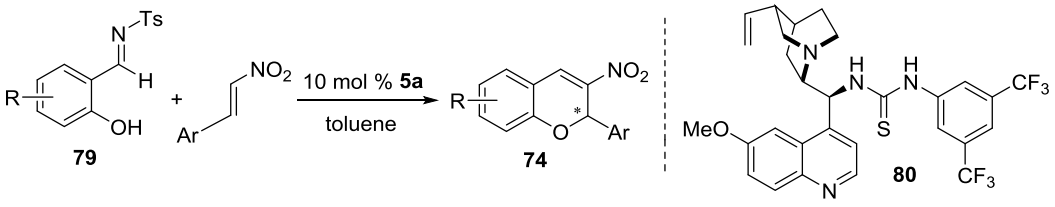
Scheme 40. Organocatalytic asymmetric synthesis of 3-Nitro-2*H*-chromenes.

Piperidine-2-carboxylic acid can also catalyze the ring closing reactions of 2-hydroxybenzaldehyde with nitro-activated styrene, providing the chiral chromenes in 60-81% yield but in almost racemic forms (Scheme **41**) [108].



Scheme 41. Organocatalytic domino oxa-Michael/aldol reactions for synthesis of chromenes.

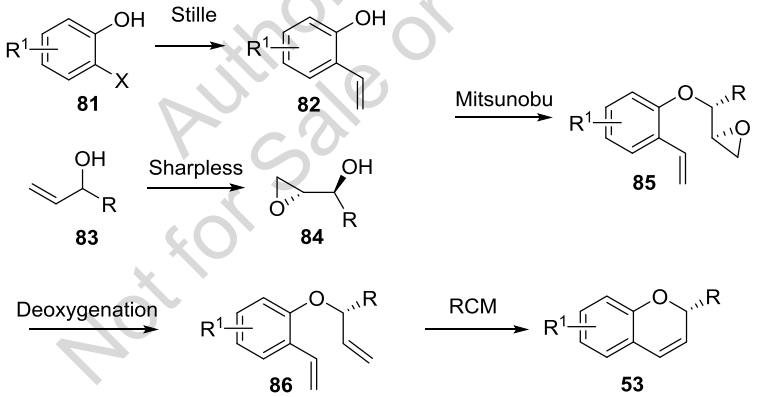
Schreiner [109] came up with a similar idea to prepare chiral chromenes using organocatalyst thiourea **80** to facilitate the asymmetric transformation of salicyl *N*-tosylimine with nitro substituted alkenes to the corresponding 3-nitro-2*H*-chromenes with moderate to good yields and ees (Scheme **42**). Generally, reactions at low temperature afforded the products in high ee, but with the erosion of yields.



Scheme 42. Enantioselective synthesis of 2-aryl-3-nitro-2*H*-chromenes catalyzed by a bifunctional thiourea.

Other Reaction

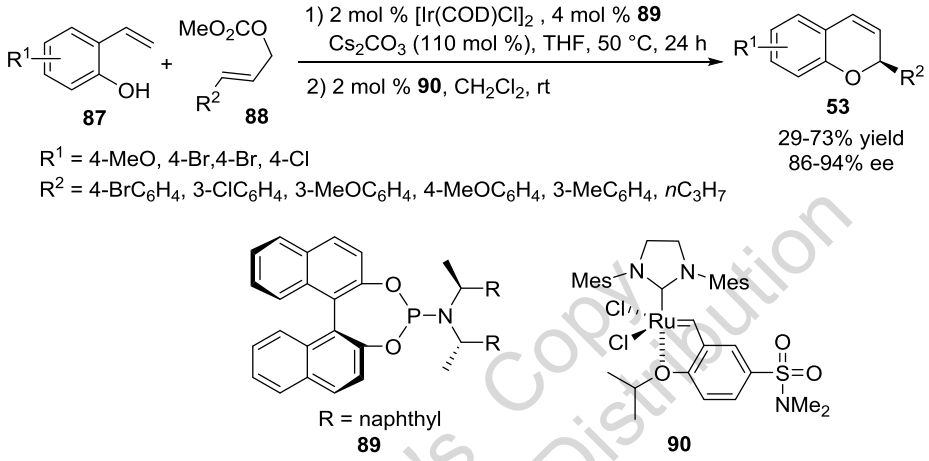
Doris [110] described an approach for the synthesis of chiral chromenes by ring closing metathesis of a C-C double bond (Scheme **43**). In the process, they initially synthesized 2-vinyl phenols **82** through Stille-olefination of the corresponding halogeno-phenols while enantioenriched epoxyalcohols **84** were prepared by Sharpless-kinetic resolution of variously substituted allylic alcohols **83**. Then, Mitsunobu reaction occurred with 2-vinyl phenols and enantioenriched epoxyalcohols to offer the epoxy-ethers **85** which subsequently underwent deoxygenation to generate chiral diene reagents **86**. The epoxy-ethers **85** can serve as a protecting group of the double bond of **83** since the hydroxyl group of phenol **82** can react with **83** in a S_N2' mechanism. Finally, ring closing metathesis gave rise to the desired products with little loss of optical purity.



Scheme 43. Enantioselective synthesis of chromenes.

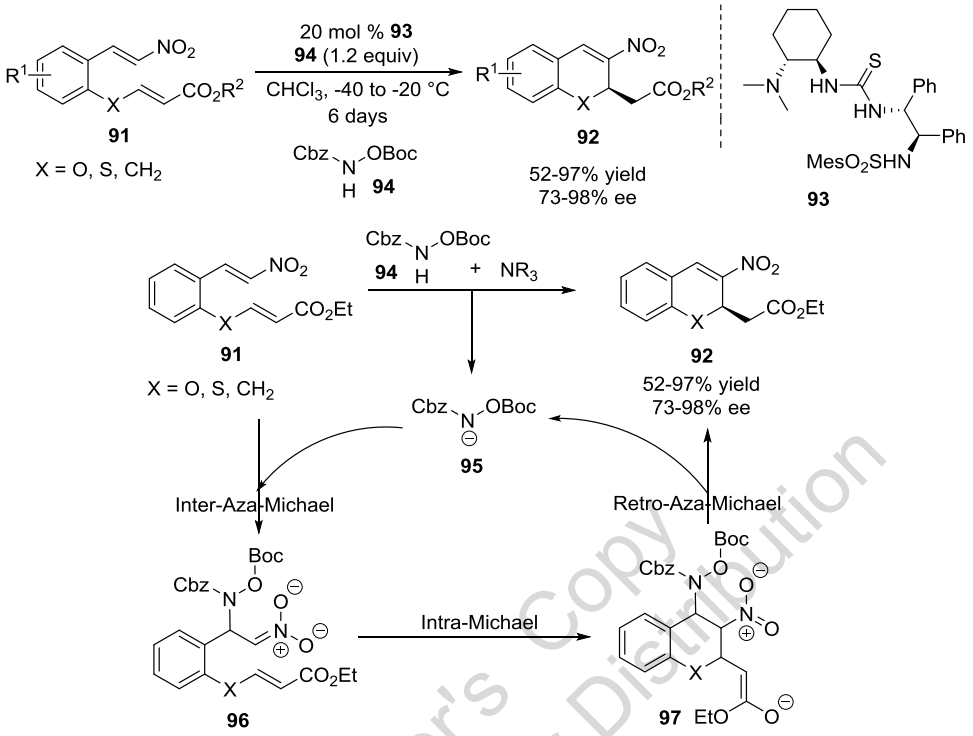
You and co-workers [111] developed a more efficient method for the synthesis of enantioenriched chromene by employing Ir-catalyzed asymmetric allylic etherification and a subsequent RCM reaction (Scheme **44**). The first step is to form chiral diene *via* an allylic vinylation in the presence of $Ir(COD)Cl]_2$/chiral phosphoramidite ligand **89**, which is the forming step of the chiral center of the desired chromene. The products obtained were subjected to a ring closing

metathesis reaction catalyzed by a modified Hoveyda-Grubbs catalyst **90** affording corresponding chromenes in moderate yields (29-73%) with high enantioselectivities (86-94% ee). Notably, aliphatic allyl methyl carbonate also underwent the transformation, producing 2-propylchromene in 52% yield with 93% ee value. The substrates bearing strong electron-withdrawing groups, such as $-CF_3$, $-NO_2$ *etc.,* were not provided in this method.



Scheme 44. Ir-catalyzed allylic etherification and ring closing metathesis for Synthesis of Chromene.

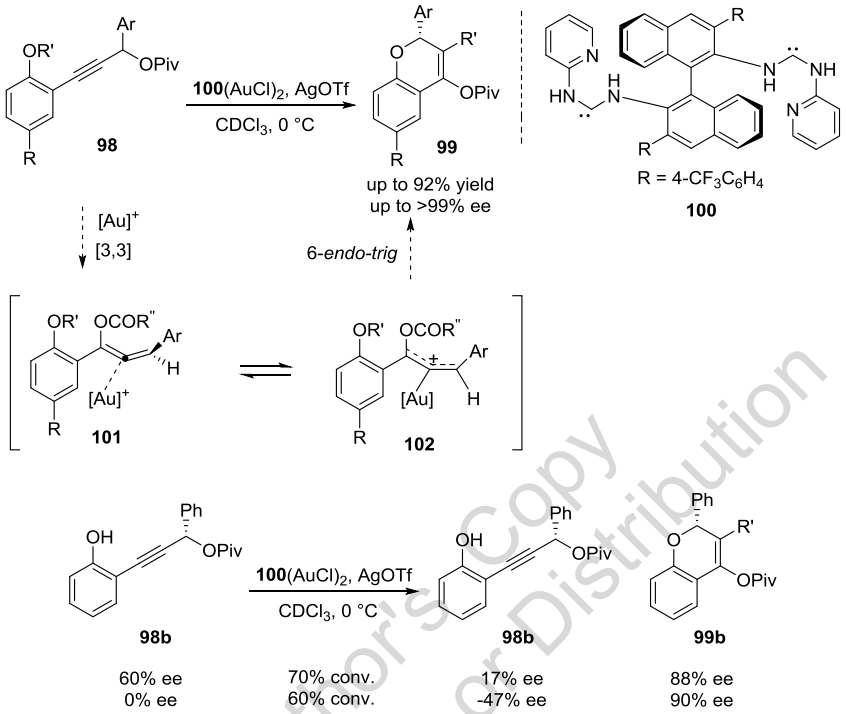
In 2011 Xiao [112] reported a novel approach for the preparation of chiral chromenes *via* intramolecular Rauhut-Currier reaction of conjugated nitroolefin enoate **91** with tethered enonates (Scheme **45**). To optimize the reaction condition, various small-molecular organocatalysts were initially tested. The investigation showed that organocatalyst **93** derived from enantio-enriched 1,2-diaminocyclohexane and 1,2-diphenylethylenediamine provided the best result in CH_2Cl_2 at room temperature (98% yield with 80% ee) by using benzyl *tert*-butoxycarbonyloxycarbamate which can make the substrate more nucleophilic. When the reaction was carried out in the presence of organocatalyst **93** in $CHCl_3$ at 0 °C, the transformation was completed in 16 h and offered the desired product in 94% yield with 86% ee value. When the reaction was carried out at –40 °C for one day and –20 °C for five days, the stereoselectivity increased to 92%. With the optimized reaction condition, either electron donating group (4-Me, 4-MeO, 5-MeO) or electron withdrawing group (4-F, 4-Cl, 4-Br) can be introduced onto benzene ring of nitroolefin enoate **91** with high enantioselectivity (91-93%). Based on their investigation and knowledge, they proposed the possible mechanism of the reaction assisted by DFT calculation as well.



Scheme 45. Enantioselective intramolecular crossed Rauhut-Currier reactions of nitroolefin enoates.

In the same year, Toste [113] disclosed an excellent work describing asymmetric addition to allenes resulting from [3,3]-sigmatropic rearrangement of propargyl esters, using gold catalyst generated from AuCl and 4-trifluoromethylphenyl-substituted NHC ligand (Scheme **46**). Under the optimized reaction condition: 5 mol % **100**/$(AuCl)_2$ complex, 10 mol % AgOTf at 0 °C, and various functional groups can be introduced to the chromenes skeleton in moderate to high yield with high ee. To gain better understanding of the mechanism, some control experiments were performed in standard condition. One is that starting material with 60% enantiomeric excess was subjected to the transformation and then stopped at 70% conversion. The substrate was isolated in 17% ee value and the desired product was obtained in 88% ee, which implies that starting material might undergo racemization *via* **102** species or only one enantiomer can proceed this asymmetric reaction. Another control reaction using racemic **98b** as starting material was carried out and halted at 60% conversion point. Enantio-enriched starting material was observed in –47% ee and chromene was generated in 90% enantioselectivity. These results indicate that starting material undergoes a kinetic resolution and exists a slow equilibration with the gold-coordinated allene intermediate. A dynamic kinetic resolution can be observed due to the rapidly

interconverting isomers of **101** and/or **102** species procceding asymmetric cyclization which is considered as enantioselectivity determining step.



Scheme 46. Enantioselective synthesis of chromenyl pivalate from phenols.

CONCLUSION

Enantio-enriched flavanones, chromanones, and chromenes construct a large family of natural products possessing a broad array of structural diversity and pharmaceutical and biological activities. To date, various efficient methods for preparation of these useful skeletons in chiral forms have been successfully developed in the presence of transition metal catalysis, organocatalysis, and Lewis acid catalysis. Given that most of flavonoids have potentially diverse and efficient bioactivities are often incorporated with various functional groups and/or complicated constructions, no one synthetic methodology can be a panacea for preparation of these charming molecules. Therefore, the highly efficient and concise synthetic methodologies for chiral flavanones, chromanones, and chromenes *via* asymmetric catalysis are still in great demand in the future study.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

ACKNOWLEDGEMENTS

Declare None.

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CHAPTER 2

Supramolecular Chemistry of Modified Amino Acids and Short Peptides

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"Corpora non agunt nisi fixata"
Paul Ehrlich

Abstract: Supramolecular synthesis is a perfect complementary to molecular synthesis in order to create supramolecular assemblies which would not be available by the use of covalent bonds only. The beauty of this advanced synthesis lies in a spontaneous reaction *via* noncovalent intercontacts, offering endless possibilities, without outside help. Recently, short peptides have attracted an increasing interest due to their advantages and applications, *inter alia* supramolecular biofunctional materials, in drug delivery, cancer therapy or immunology. Amino acids, simple building blocks in living systems whose architecture is controlled by a plethora of intermolecular interactions, have a valuable input in understanding highly complex biological systems and processes. Subtle supramolecular intercontacts in precise co-operation just like virtuosos play a symphony of *life*. So, the design of smart bio-inspired materials should be based on the knowledge of intercontacts at a molecular and higher topological level. Nevertheless, information on this subject is very scarce. This chapter is a brief review focused on supramolecular chemistry of short peptides in relation to laboratory synthesis and more comprehensive reaction mechanisms. It summarizes the latest scientific findings scattered across the world literature, the most perspective ways of synthesis and takes a holistic look at the supramolecular landscape in the context of subtle supramolecular effects *via* modern both experimental and theoretical methods. Special attention is paid to the supramolecular H-bond synthon concept, which evolves in various research areas in an intriguing manner. Synthon methodology is as important in supramolecular chemistry as the reaction mechanism in traditional synthesis. For the synthetic chemists, synthons involving relevant intercontacts are invaluable in the synthetic strategy of self-assembly. We hope that this publication highlighting an innovative approach will contribute to the development of short peptide-based supramolecular chemistry.

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INTRODUCTION

Contrary to traditional chemistry, which focuses on the covalent bonds linking atoms into molecules, supramolecular chemistry relies on *synthesis by design* of non-covalently built highly ordered supramolecules. The main merits of supramolecular chemistry, which can be regarded as advanced synthetic science, are reversibility and specificity. Interestingly, the first Nobel prize in the field of supramolecular chemistry (1987) overlapped with the last Nobel prize for traditional synthesis (1990). Nonetheless, there can be no doubt that supramolecular chemistry relies on the molecular information saved in the covalent bonds of assembly components reading at the supramolecular level *via* non-covalent interactions. Supramolecular chemistry became a supramolecular science, covering *exempli gratia* supramolecular crystallography and quantum crystallography and providing a basis for the creativity of scientists from various fields. Experimental and theoretical developments allowed an insight into the amazing complex structures, constructed and stabilized by a large number of different intermolecular interactions. Nowadays, thorough knowing and understanding of those subtle supramolecular effects, playing a prominent role in the biological systems, pose a challenge to scientists. In this context, the aim is to answer the question how the small, important bioactive molecules (*i.e.* amino acids, peptides) cooperate with each other *via* non-covalent association (and also dissociation) forming highly specialized networks underlying life functions. The supramolecular assembly of simple bio-inspired building blocks allows their comparison with bioactive macromolecules (*i.e.* proteins), which enables a preliminary look at complex living systems. In a way, the supramolecular architecture of bio-chemical entities is a key to the origin of *life*. It is noteworthy that short peptides with their numerous advantages (small size, facile synthesis, high biocompatibility, specificity, intrinsic bioactivity, biodegradability, high selectivity for a specific targets) contain all the required molecular data to form well-ordered structures. Therefore, short peptide-based supramolecular assemblies are used to design and develop new smart functional biomaterials with new specific properties for different applications in the biomaterial science, bio- or nanomedicine (*i.e*. in drug delivery, cancer therapy, immunology and so on). The increasing interest in short peptides has been noticeable in the past several years. There is no doubt that peptides are promising modern drugs. Approximately over 100 peptide therapeutics are currently evaluated in clinical trials, most of which are short peptides or even amino acid derivatives. It has now become necessary to explore new routes beyond the traditional peptide design. Nevertheless, despite

the fact that the power and expansion of supramolecular chemistry into various research areas are more and more obvious, which is reflected in a great number of international scientific communications, the information concerning supramolecular aspects in the context of the non-covalent interactions within the supramolecular architecture of short peptides is extremely scarce. This chapter is an updated overview on the subject with an emphasis on the recent progress in the precise study of subtle supramolecular contacts. It identifies the best strategies of both acyclic and cyclic short peptides syntheses, and presents complementary, advanced, experimental and theoretical methods for the profound analysis of short peptide-based supramolecules, keeping a supramolecular H-bonding synthon concept as a new promising approach to short peptides in focus. A holistic investigation of the supramolecular architecture, including a brief description of a few interesting examples from our studies, is discussed in detail.

Supramolecular Chemistry: a Brief Historical Outline, Basic Concepts and Development

To begin with, it is worth mentioning that the scientific community commemorates the 50th anniversary of supramolecular chemistry. Nevertheless, it is disputable to point when exactly this important branch of science started. Looking back, first and foremost we should pay tribute to the pioneers. For the first time the issue supramolecular chemistry was introduced into the literature by Lehn in 1969 [1, 2]. The first example of a supramolecular structure, crown ether, accidentally found as a byproduct of an organic reaction, the first artificial host molecule, was reported by Pederson in 1967 [3] and this year is considered the birth of supramolecular chemistry. However, the Nobel Prize for this achievement, synthesis, development and use of molecules with highly selective structure-specific interactions (crown ethers, carcerands, cryptands) was awarded to Pedersen, Cram and Lehn two decades later, in 1987. Thus, this date is sometimes marked as the emergence of a well-accepted new chemical field. Cram established a host–guest chemistry, where the host molecule can accommodate another molecule (the guest) in unique structural relationships by non-covalent interactions [4]. Interestingly, some synthetic host molecules (*i.e.* cucurbiturils) recognize short peptides (and amino acids) at protein interfaces through supramolecular host−guest interactions [5, 6]. Lehn defined this field as *chemistry beyond the molecule* (*supra* in Latin means *beyond*). Other definitions are as follows: *the chemistry of intermolecular bonds, non-molecular chemistry* or *chemistry of molecular assemblies and of the intermolecular bond*. In other words, it is the chemistry of molecular aggregates, small molecular building blocks assembled in a controlled and desired fashion by non-covalent intercontacts such as electrostatic, hydrogen bonding, π-stacking, π-anion, halogen bonds, hydrophobic effects and van der Waals forces [7, 8]. According to

Vögtle: "*in contrast to molecular chemistry, which is predominantly based upon the covalent bonding of atoms, supramolecular chemistry is based on the non-covalent intermolecular interactions*" [9]. Conceptually, the philosophical roots of supramolecular chemistry go back to the late 19th century, when some very basic principles were initiated [10]. Villiers and Hebd discovered cyclodextrins, naturally occurring cyclic host molecules (cyclic oligosaccharides with hydrophobic cavities, modifying the properties of the included materials), in 1891 [11]. Subsequently, coordination chemistry was formulated by Werner in 1893 [12]. In turn, the lock-and-key concept (*Schlüssel-Schloss-Prinzip*) was introduced by Fischer in 1894 [13, 14]. This system was the origin of molecular recognition - the mechanism of identification by enzymes and their interaction with a substrate (like a key in a lock). Indeed, molecular recognition is the linking of a guest to a complementary host molecule forming a host-guest complex. It is also worth emphasizing that both Fisher and Werner were awarded Nobel prizes. Nevertheless, a half century later, Koshland compiled the induced fit model for binding events with regard to biomolecules persuasible conformational changes in the binding event [15]. It provided a more dynamic view (glove-hand) [16], compared to the static key-lock rule. Ehrlich devised the sentence "*Corpora non agunt nisi fixata",* which means that a molecule can only have an effect if it is bound. In those days, this statement was related to the idea of receptors established in 1906 [17, 18]. However, it can be treated as the basic axiom of supramolecular chemistry. As a consequence, another guiding issue of supramolecular chemistry concerns just the intermolecular interactions. In this regard, a little leeway should be allowed. Interestingly, up to the 19th century there was no difference between the intermolecular interaction and bonding (non-covalent and covalent bonds). The origins of the bond concept evolution can be traced back to long before Christian era, around the 5th century BCE, when famous philosophers such as Democritus and Thales, regarded the existence of atoms as building blocks of matter attracted and pushed back by cohesive and repulsive forces, respectively. On the other hand, the alchemists, known also as the Neoplatonic philosophers, postulated *bonding* idea as the *conjuctio* – union of the opposites (the ultimate synthesis necessary to change lower matter to gold). Next, modern chemists formulated theories concerning *affinities*, which were emphasized to unite substances. It created the fundaments of the modern concept of bonding (and selectivity). In the 17th century, Lemery described selective replacement of the metals (ions) by others using *elective affinity*. Geoffroy, a precursor of Mendeleyev`s periodic table, was probably the first who generalized that a compound is bound by *chemical affinity* between the constituents. It was the basic fundament of modern chemistry. In 18th century, Rouelle revealed a difference between the physical and chemical forces. Chemists perceived that the latter combined chemical elements. The *chemical identities* of substances were

distinguished from the physical mixtures. Dalton suggested compositional rules concerning the combination of the atoms in definitive proportions: *i.e.:* AB, A_2B, AB_2. The chemical bond was like a *Lego* game of atoms. Nevertheless, connectivity of the atoms was not defined and the atomic weights gave the impression of fluctuation, which depended on the establishment of the combined ratio of the atoms. Avogadro established the existence of molecules consisting of identical atoms, *i.e.* O_2 (the elementary molecules or *molecules elemantaires*). Canizzaro proved that Avogadro`s molecular hypothesis created a perfect order defining the atomic weights. As a consequence, valences could be defined from the combining weights and the presence of multiple molecules created from the identical atoms such as H_2O and H_2O_2 was understandable. So, Avogadro and Cannizzaro described the basis for defining the *chemical identity*. In the early 1900s, the Lewis`s idea of the electron-pair bond was a tip for atomic combination rules in *Lego* puzzles. Lewis revealed that an electron is an essential building block of the chemical bond and redefined the term valence number by electron-based language. Next, he proposed the octet rule: separation of the electrons in an atom to the group of eight, using the cubes shared edges (where corners were occupied by electrons), which he called *shared bonds* - prototype of covalent bonds [19 - 24]. The final result of the long-term studies is IUPAC`definition of a bond, first published in 1939 by Pauling: "*there is a chemical bond between two atoms or group of atoms in the case that the forces acting between them are such as to lead to the formation of an aggregate with sufficient stability to make it convenient for the chemist to consider it as an independent molecular species*". Attempts to differentiate between the bond and the intermolecular interaction appeared together with the question of the Greeks: "*why does matter stick together*?". At the end of 19th century, chemists came to the conclusion that chemical identity is determined by the recognition of molecules formed from atoms leading to clear definitions of *structure* and *bond*. The intermolecular interaction was for the first time raised by van der Waals in 1873 [25, 26]. In 1896, Boltzmann postulated *van der Waals cohesive forces*. Finally, Pauling`s definition of a non-covalent bond, presented in his book in 1939 [27], was chosen by the IUPAC for the so-called IUPAC Gold Book [28]. Pauling identified intermolecular bonds as "*in general we do not consider the weak van der Waals forces between molecules as leading to chemical-bond formation; but in exceptional cases, such as the weak bond that holds together the two O_2 molecules in O_4, it may happen that these forces are strong enough to make it convenient to describe the corresponding intermolecular interaction as a bond formation"*. Interestingly, intermolecular interactions were initially of interest to physicists, not chemists. Nevertheless, the discovery of hydrogen bonding interactions changed the scientists` attitude. The omnipresence of H-bonding interactions *as a design force in matter* directed attention to other

intercontacts as well. Currently, exploring new types and a profound understanding of the intermolecular interactions are an extensive area in various branches of chemistry [19]. Therefore, we decided to survey the evidence for hydrogen bonding, the most important of all intermolecular interactions. It goes back to the beginning of the 20th century [29 - 33]. The earliest reports relate to the following understatements: *nebenvalenz* (near valence), *innere komplexsalzbildung* for intra- and intermolecular hydrogen bonding [34 - 36], *weak union* [37] or *Wasserstoffbrücke* (hydrogen bridge) [38]. In 1912, Moore and Winmill described this phenomenon to account for the weaker basicity of trimethylammonium hydroxide than tetramethyl ammonium hydroxide as a weak interaction between the base and water [25, 38, 39]. In 1920, Latimer and Rodebush proposed the following concept of hydrogen bonding: "*the hydrogen nucleus held between two octets constitutes a weak bond"* [40, 41]. Nevertheless, the term *hydrogen bond* or *hydrogen bonding* was used for the first time by Lewis in 1923: "*the most important addition to my theory of valence lies in the suggestion of what has become known as the hydrogen bond*" [31, 42 - 44]. It is worth emphasizing that in spite of its 100-year history the H-bond is still full of surprises, controversies and exciting developments. This led to re-evaluation of the IUPAC definition of H-bond in 2011: "*the H-bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation*" [19, 45].

By continuing major supramolecular considerations, in spite of the fact that the basic rules were established at the turn of the 19th and 20th century, supramolecular chemistry was recognized as an independent research area 50 years later. The reason was the slow development of specialized experimental methods enabling a lot of experiments which changed the mindsets of the scientists who had earlier accepted only the idea "*properties of molecules are properties of the molecules themselves, while the intermolecular interactions with the environment are small"* (or rather negligible) [10]. These above-mentioned principles contributed to the preliminary knowledge and understanding, for example, of proteins structures and biological processes. Chemists began to study synthetic structures based on the non-covalent intermolecular interactions. Considerable and impressive progress has been achieved so far. Nowadays, supramolecular chemistry is a highly interdisciplinary science, widely explored in various areas, playing a main role in the development of chemistry and providing unlimited possibilities for the scientists from almost all disciplines. The molecular self-assembly processes are applied to develop new, smart and advanced supramolecular materials (supramolecular polymers, liquid crystals) [46 - 48]. A vast majority of bottom-up approaches to nanotechnology and nanoscience are based on supramolecular chemistry [49]. The review on the literature let us notice

that supramolecular chemistry led to many worldwide application, like supramolecular analytical sensors [50], gas absorption, nanoreactors, metal extraction from ores and a nuclear waste, as well as drug design (based on the non-covalent interactions between a drug and a protein), delivery or formulation research [51, 52]. What is more, Sauvage, Sir Stoddart and Feringa received, in 2016, the Nobel prize, the second in the history of supramolecular chemistry, for the introduction and advance of molecular machines. Interestingly, Sauvage was a co-author of the first report concerning cryptands, trapping ions, which can be used, for example, in the removal of toxic metals from living systems. The molecular machines (nanomachines), artificial - synthetic and natural - biological, refer to the assemblies designed to perform quasi-mechanical movements (output) in response to external and specific stimuli (input) [53]. Moreover, supramolecular interactions play a vital role in the design of catalysts and catalysis (template-directed synthesis) *via* binding reactants in conformations appropriate for particular reactions. Besides, it could be said that nowadays supramolecular therapeutics and smart functional biomaterials are attracting countinous interest [54, 55]. Exploring weak interactions is essential for the design of supermolecules with tunable activities and the enlargement of new pharmaceutical therapies by the profound knowledge of interactions at drug binding sites [56]. As a side note, the development of several Active Pharmaceutical Ingredients (APIs) in relation to different ways of delivery (encapsulation, targeted release mechanisms) [57] resulted in greater efficiency and minimalization of off-target effects [58]. Additionally, a supramolecular basis is used to create artificial ion (sodium and potassium) channels or to disrupt protein···protein intercontacts, essential to the cellular function [56, 59].

Molecule *vs*. Supermolecule

In molecular chemistry, atoms are linked by covalent bonds leading to more sophisticated molecules. The aim of supramolecular chemistry is to develop large, highly complex chemical systems (supramolecules) formed from the molecules interacting through intermolecular contacts [46]. More specifically, the term supermolecule is used to describe a supramolecular assembly (a molecular assembly at a high level), consisting of two or more molecules spontaneously arranged in higher organization by non-covalent bonds, in a controlled and desired fashion [10]. Interestingly, the issue supermolecule (supramolecule) as *übermolekül* was introduced for the first time by Karl Lothar Wolf and his co-workers in 1937 in order to describe the H-bonded acetic acid dimer, presented in Fig. (**1**) [60].

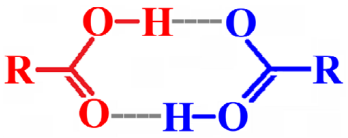
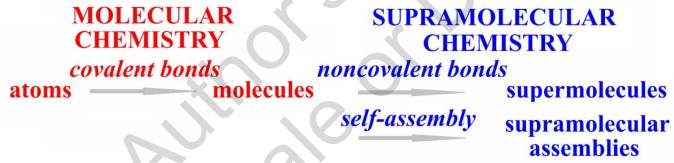


Fig. (1). Schematic diagram of supramolecule.

It is noteworthy that a supermolecule has greater complexity and different physical, chemical and biological features than individual building units (similar to diamond as a carbon assembly or amyloid proteins self-assemblying with regard to Alzheimer's disease) [61, 62]. In recent years, the multicomponent (two or more) peptide supramolecular assemblies evolved as a promising methodology used in various applications, for example, tissue engineering [63, 64]. Supramolecular chemistry progressively became an information science. The chemical data from the molecular level are transferred and read out at the supramolecular level through non-covalent interactions. It is also a dynamic chemistry in relation to the lability of intermolecular intercontacts and the ability of supramolecules to exchange their constituents, *i.e.* molecules [65]. The major differences between the molecular and supramolecular chemistry are highlighted hereafter (Scheme **1**).



Scheme 1. Schematic representations of differences between the molecular and supramolecular chemistry.

Synthesis *vs.* Supramolecular Synthesis

Due to the synthesis of more complicated molecular species with specific properties, chemists still search for and subsequently develop new organic reaction pathways proceeding systematic studies, which enable a better understanding and control of the molecular structure [66]. Supramolecular chemistry may be regarded as an advanced synthetic science. This new approach to synthesis is an interesting alternative, because it offers endless, unlimited possibilities [67]. The supramolecular synthesis is a creation of supramolecular structures by a various noncovalent bonding, complementing covalent (organic) synthesis perfectly and providing fascinating supramolecular architectures (at the nanoscale), which would not be available by the use of the covalent bonds only [68]. In other words, supramolecular chemistry depends on molecular synthesis for the construction of its covalent components in terms of self-assemblies [69].

The beauty of supramolecular chemistry is related to its spontaneous and effective synthesis, without outside help [70].

Synthon vs. Supramolecular Synthon

The term supramolecular synthon was established according to the analogy with the molecular synthon from the molecular chemistry. In the covalent synthesis, synthon means a chemical bonding holding building blocks together. The first definition of the supramolecular synthon was introduced precisely half a century ago (in 1967) by the Nobel laureate, Corey: "*it is repeating structural unit within a molecule which is related to a possible synthetic operation*" [71]. In 1988, he noted that the "*synthon has now come to be used to mean synthetic building block"* rather than retrosynthetic fragmentation structures [72, 73]. In 1995, Desiraju described the supramolecular synthon as *"a sub-structural unit in a molecular crystal that can be assembled with known or conceivable synthetic operations*" [74, 75]. Therefore, the supramolecular synthon is a H-bonding pattern composed of molecular and supramolecular elements and a spatial arrangement of intermolecular non-covalent interactions between two or more molecules (interacting functionalities of building blocks) in a supramolecular unit and repeated in the crystal (Fig. **2**). Synthon has a repetitive, well defined nature, minimum size and contains maximum optimal but indispensible geometrical, topological and chemical information inherent to recognize the phenomenon. The distinction and description of different types of supramolecular synthons, substructural units of the greatest importance in the analysis of supramolecular architecture are constructive from the point of view of rational design strategy. Synthons are used as a practical tool to rationalize the supramolecular synthesis of a crystal structure [19]. For the synthetic chemists, self-assembly is a powerful synthetic strategy leading to the formation of large structures, originated from simple synthons, and involving carefully combined intercontacts [74].

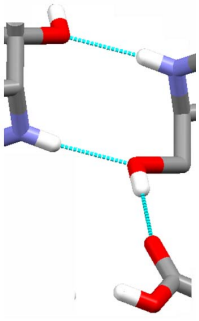


Fig. (2). Supramolecular synthons among various functionalities.

Supramolecular Engineering: Towards "Synthesis by Design"

Crystal engineering, called *state of the art*, is a relatively young scientific genre, sub-discipline of supramolecular chemistry, a solid-state supramolecular equivalent of organic synthesis. In a way, it connects the molecular and supramolecular structures. The first passing mention appeared in the mid-1950s [73], but was described by Schmidt several years later, in 1971, in connection with photodimerization in crystalline cinnamic acid, postulating that self-assembly leads to the crystal formation under suitable conditions [10, 76]. Desiraju played a major role in developing crystal engineering, which involves the synthesis of solid-state structures of polymorphs, pseudopolymorphs and co-crystals with desired properties based on the non-covalent intermolecular interactions [77]. The main idea is *making crystal by design* [78]. Thus, a crystal is a product of supramolecular design, while crystallization can be considered a supramolecular reaction.

A cutting edge aspect of crystal engineering is the development of Crystal Structure Prediction (CSP) theoretical methods, offerring various approaches to the question of prediction of the structures of new compounds, based on their composition. It can be compared to the search of *the Holly Grail* (since the 1950s), because the final crystal structure is the result of a subtle balance among many factors. In 2015, the blind test (a competition for prediction of the new crystal structures, using all software for CSP periodically organized by the CSD Centre) revealed great progress in the setup of plausible ways of predicting the packing of a new structure correctly. Unfortunately, the outcome of the crystallization trial is controlled by kinetics, while CSP acts by considering thermodynamic stability. Furthermore, the observed structures, although possible to obtain, are not always thermodynamically stable [19].

Crystal: "Supramolecule par Excellence"

It is noteworthy that a crystal is an extended and ordered supramolecular self-assembly of numerous molecules linked together by noncovalent intercontacts [74, 79, 80]. As a consequence, a molecular crystal is treated as a solid supramolecule, even a perfect supermolecule [81]. Dunitz stated that a crystal is "*supermolecule par excellence: a lump of matter, of macroscopic dimensions, millions of molecules long, held together in a periodic arrangement by just the same kind of noncovalent bonding interactions as are responsible for molecular recognition and complexation at all levels*" [70, 82 - 84]. More importantly, molecular recognition is significant for crystal engineering [80]. A relatively new paradigm is the co-crystals design, particularly in relation to drugs (pharmaceutical co-crystals) in order to improve their physicochemical properties

(*e.g.* solubility, dissolution, stability, bioavailability) [85, 86]. Co-crystal, representing a host-guest concept, is a solid composed of two or more different molecular (and/or ionic) components, interacting *via* non-covalent interactions, in a stoichiometric ratio which is not solvate or salt [87, 88]. Co-crystals can change the physicochemical properties of APIs without any covalent modification. Quality control aspects, essential for achieving commercial success, are the future prospects. Co-crystal of valsartan-sacubitril (Entresto, *Novartis* company), a new heart failure agent comes into focus in both industry and academia [89]. It is interesting that quinhydrone (Fig. **3**) was the first example of co-crystal of quinone and hydroquinone (quinol), reported in 1844 by Wöhler [90].

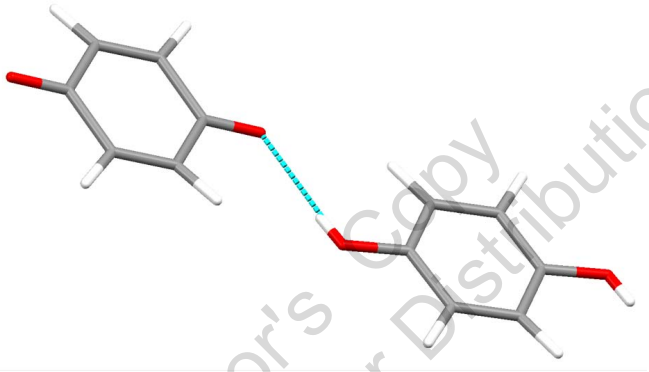


Fig. (3). Co-crystal of quinhydrone (CSD reference code: QUIDON).

It is noteworthy that supramolecular synthesis is the equivalent of traditional synthesis called crystal engineering in a solid state, whilst in a solution it is referred to as molecular recognition. In both cases the principles of identification and the nature of interactions forming supramolecular assemblies are almost the same [91].

Briefly speaking, noncovalent intercontacts lead to reversibility of supramolecular synthesis. Thereby, the making of products is more challenging than in the traditional synthesis, when strong covalent bonds resulted in a multistep synthesis and isolation (with purification) of intermediates. Therefore, great experience in the supramolecular synthesis (from an unexpected to predictable assembly) is crucial. In this context, robust supramolecular synthons should be identified and hierarchically classified. The investigation of the synthons associated with the building blocks leads to new supramolecular assemblies with a high degree of specificity. In summary, the development of supramolecular chemistry is related to the generalization of issues from traditional chemistry. The supramolecular equivalents of molecular chemistry [74, 92] are listed in the Table **1**.

Table 1. Molecular *vs.* supramolecular chemistry issues.

Molecular chemistry	*Supramolecular equivalents*
covalent bonds	non-covalent intermolecular interactions
molecule	supramolecule (crystal)
molecular structure	crystal structure
(covalent) synthesis	crystal engineering (solid state supramolecular synthesis)
(molecular) synthon	supramolecular synthon
reaction	crystallization
single molecules	assemblies of molecules
structure-properties	structure-properties

SHORT PEPTIDES: IMPORTANCE AND SYNTHESIS

Structure and Advantages

The word peptide, meaning derived or digested (gr. *peptós*), was coined in 1902 by Fisher, who synthesized the first peptide as well. On the other hand, the first amino acid asparagine was isolated from asparagus by Vauquelin and Robiquet in 1806 [93, 94]. Peptide contains a chain of amino acids linked by covalent peptide (amide) bonds. There are long chain peptides, also known as polypeptides, high-molecular weight peptides or proteins, and short chain peptides (oligopeptides or low-molecular-weight peptides, consisting of several residues). However, there is no restrictive general upper limit of the number of amino acids for short peptides (usually ≤ 10 residues). Prefixes di-, tri, tetra- indicate the length of the amino acids chain. Proteins have usually over hundred residues. The amino acid with the free amino group is referred to as the *N*-terminus, while that with the free carboxyl group as the *C*-terminus. The shortest peptide is composed of two amino acids. Shorter peptides are more stable than long chain peptides. Amino acids are the elementary units of polypeptides consisting of a central carbon atom connected with an amine group and a carboxylic acid giving a structure of H_2N-C(H,R)-CO_2H, where *R* group is referred to as the side chain. The side chains are classified towards their functionality and are called hydrophobic or hydrophilic, acidic, basic *etc*. However, there are a few exceptions such as glycine, the simplest amino acid, without the side chain, or cysteine and methionine, containing sulfur. The central carbon atom *Cα*, which has four different functional groups, sets out the chirality property (handedness) to the amino acid, meaning that the molecule cannot be superimposed with its mirror image. Glycine is not chiral. The vast majority of natural amino acids are in the *L*-form (left-handed isomer) [95]. According to the Cahn-Ingold-Prelog rules, it means *S* config-

uration. *D*-amino acids occur in certain natural peptide antibiotics, for example, in gramicidin, comprising alternate *D* and *L* amino acids [96 - 99]. *D*-peptides have better bio-stability and antimicrobial activity than their *L*-analogs. It is self-evident that peptides, and particularly amino acids, are scaffold of nature (life) as they are structural elements in biological systems intermediating and playing a vital role in many different biological processes [100, 101]. This diversity is related to a variety of amino acids structures. Interestingly, there are 500 amino acids found in nature. Nevertheless, the basic human genetic code encodes only 20 (Fig. **4**).

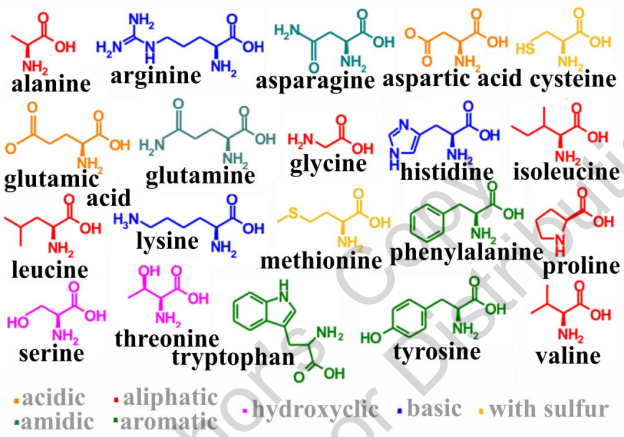


Fig. (4). Twenty common amino acids.

Generally speaking, peptides are flexible molecules. On the other hand, they can have a preferred structure (three-dimensional conformation). At this point, completely flat short peptide molecules, forming planar sheets (graphite-like layers), should be mentioned [102]. The architecture of peptide 3D structures is characterized by well-defined basic turn types such as α-, β- γ-, δ- and ε-turns or helices, and sheets. Ways in which particular residues interact with each other to reach their preferred folding pattern and the diversity of motifs of peptide secondary structures are perfectly described by Professor Claudio Toniolo, Doctor Marco Crisma and their co-workers. For example, the ε-turn is observed in small cyclic peptides formed by four, five, and six amino acid residues, but not in linear short peptides. Amino acids present intramolecular H-bonds, between the main-chain amide N-H donor and the main-chain amide C=O acceptor, determining their folded conformation preferences that are crucial to understand their structure and reactivity. As a consequence, it is important for the investigation of polypetides (and proteins) folding because they can indicate the role of short-range interactions in stabilizing large structures. Subtle changes in conformation are used to modulate/regulate proteins functions. The fundamental biological

activity of peptides depends upon their conformation [103 - 107].

The amino acids, including their analogues, are the most powerful and attractive building blocks [108 - 110]. They offer a great variety of unique advantages in the context of their biochemical and physical properties such as high biocompatibility, great specificity, intrinsic bioactivity, biodegradability, high selectivity for specific targets, organelles or cells, low cellular toxicity, minimal size (relatively low molecular weight), conformation, amide bond rigidity, rich chemical space provided by side-chain functionalities, capability to form specific H-bonding synthons, chemical diversity, (similar to proteins, but more stable). They can also be readily synthesized at a large scale moderate production costs [101, 111, 112]. Hence, peptides are interesting not only for chemists, but also for biochemists, biologists and materials scientists, who cannot overcome the synthetic challenges using non-peptidic small molecules.

Current Progress and Future Outlooks

Generally, the applications of peptides in supramolecular chemistry is quite extensive indeed. The novel peptide-based biomaterials found a wide range of applications in nano- and biomedicine or molecular biology. In particular, smart mechanisms of target oriented drug delivery, tissue engineering, blood substitutes, bio-separation, skin care, bio-mineralization, antibacterial agents, bone regeneration, imaging, biosensors, immunology or hydrophobic coatings are among the most interesting [101, 109]. Peptides are used as artificial ion channels as well. The peptide-based materials will be one of the most promising in the next years because they are perfect models to mimic sophisticated natural processes (dynamic instability, dissipative and adaptative self-assembly) [113, 114]. The peptide amphiphiles spontaneously associate to different nanostructures (tubes, spheres, fibrils, tapes, hydrogels) [111]. Moreover, peptides are able to create advanced, ordered nanostructures, finding multipurpose and numerous applications in other areas such as optical waveguiding and biomimetic energy materials, inclusion complexes with macrocyclic hosts (calixarenes), in photocatalysis, sensing or complexation with metal ions, metal-organic frameworks, ultra-sensitive sensors, energy storage devices and so on [108 - 110]. The applications of short peptides are versatile and their growing relevance is visible. For example, protected oligopeptides, even the very short ones, *Fmoc*-modified Ile-Phe dipeptides, can be used as stable physical hydrogelators intriguing for different technological applications, produced *via* self-assemblies into highly well-ordered supramolecular architectures with various functionalities [115 - 117]. Short peptides are also applied in glioma therapy clinical trials [112]. Keeping in mind that peptides construct living species, it is obvious that they play a key role in biological effects. Peptides are excellent to provide information

about protein-ligand intercontacts. Hence, natural peptides, isolated from biological sources, are attractive substances with great benefits as effective drugs [118]. Large technological advances over the last decade have had a huge influence on the development of attractive peptide agents. Today`s tools can be helpful in the creation of stable, cell permeable, highly biologically active, long lasting and orally bioavailable peptide-based drugs, competiting with conventional APIs. The evolution of therapeutics peptides with unique features and the promising prospects are observed [119]. The pharmaceutical market consists of a growing number of peptide-based medicaments, including short-peptides. At least, two short peptide drugs are worth mentioning: alvimopan (Adolor), *N*-terminal blocked dipeptide, which is a peripherally acting μ-opioid receptor antagonist for the treatment of various gastrointestinal diseases and macimorelin (Macrilen), pseudotripeptide, made by Aib (α-amino isobutyric acid) and two *D*-Trp amino acids, where formyl gem is *C*-terminus, used for adult growth hormone deficiency (Fig. **5**). Peptide-based drugs have short biological half-life and decreasing toxicity. It is evident that amino acids are degradation products of peptides. Consequently, a risk of unwanted drug-ligand interactions is lower. Moreover, it must be said that cyclic peptides are valuable pharmaceuticals due to larger stability and lower flexibility than linear peptides, resulting in higher biological activity. Interestingly, cyclization evolved in various organisms [118]. Therefore, short cyclic peptides are a promising class of therapeutic agents with unique properties [120 - 122]. Peptides are a main target for potential drugs for nearly all disorders. Chemical modifications of peptides lead to the improvement of their properties and medicinal value. Amino acid substitution is one of the ways. Even subtle changes (*e.g.* in sequence) can have a significant influence on the bio-activity. Replacement of amino acids, which are prone to degradation, increases the peptide stability or specific activity [118]. Additionally, the adaptive capability of the supramolecular interactions (*reaction* to external stimuli causing the change of supramolecular structure) is used in the design of stimuli-responsive functional supramolecular materials [120]. The control of sizes and morphologies of the supramolecular materials is possible by a *bottom-up* method. It is vital in nanomedicine. New, highly specialized supramolecular systems can ensure various, new and better diagnostic and treatment platforms [123, 124].

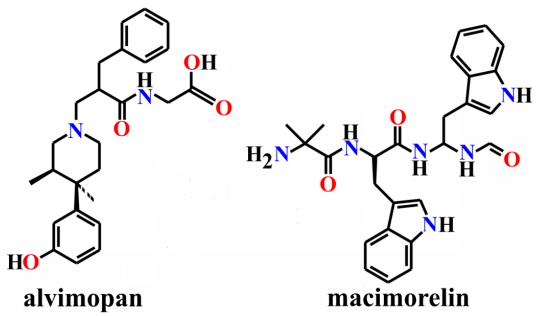
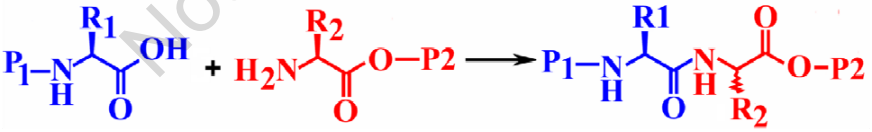


Fig. (5). Molecular structures of short peptide drugs.

Advances in the Synthesis of Short Peptides

The synthesis of modified amino acids and short peptides is a branch of organic chemistry, which is based on reactions of functional groups and the necessity of temporary protection/deprotection of some of them during each particular step. α-Hydroxymethylserine synthesis could be an example of modified amino acids at alpha-carbon atom, while 4-aminopyroglutamic acid can serve as a cyclized dipeptide unit [125 - 128]. A typical chemical peptide synthesis requires the condensation reaction of the carboxyl group of one amino acid with the amino group of another amino acid (Scheme **2**). A proper orthogonal strategy of protecting groups is usually necessary to prevent undesirable side reactions with various amino acid side chains. The two classical approaches to a peptide synthesis are called liquid-phase peptide synthesis (LPPS) and solid-phase peptide synthesis (SPPS). In both methods, different steps in the formation and/or deprotection peptide bond, like introduction of main- and side-chain modifications can be performed. The liquid-phase approach is now used mostly for the synthesis of short peptides such as di- and tri-peptides, and *C*- or *N*-terminally modified peptides.



Scheme 2. Coupling of amino acids in a solution. The unprotected amino group of one of them reacts with the unprotected carboxylic acid group of the other to form a peptide bond. The second reactive group (amino/carboxylic) in each of the substrates bears a protecting group (P_1 and P_2, respectively).

SPPS involves repeated cycles for each added amino acid residue. A single cycle consists of the following four steps: cleavage of the alpha-amino protecting group, coupling of the protected amino acid and washings. Most of these strategies build peptides in the *C* to *N* direction. During the solid-phase peptide synthesis, each

peptide is anchored to an insoluble polymer at the *C*-terminus. A single *N*-protected amino acid unit is coupled to the free *N*-terminal amino group. This unit is then deprotected, revealing a new *N*-terminal amino group to which another amino acid may be attached. Once the synthesis is completed, the desired peptide is cleaved from the resin. Usually, this cleavage step is performed with acids of varying strength. Any functionalized polymer, like, for instance styrene cross-linked with 1–2% divinylbenzene [129], which is a popular carrier resin in SPPS, can be used as a solid support. Other common gel-type supports include polyacrylamide and polyethylene glycol (PEG). A large variety of anchoring groups can be introduced onto the solid support.

Peptide Coupling Reagents

The most commonly used peptide coupling reagents can be divided into two basic classes: carbodiimides and uranium salts. Dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) are frequently used for amide bond formation [130]. DIC is particularly useful for SPPS as it is easily handled as a liquid, and the urea byproduct formed is soluble in most organic solvents, allowing the removal of facile during resin washes. Conversely, the related carbodiimide 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) is often used for solution-phase peptide couplings as the urea byproduct, which is in this case water-soluble, and can therefore be removed easily by washing during aqueous work-up. A danger of racemization during carbodiimide activation can be avoided through the addition of 'racemization suppressing' additives such as triazoles 1-hydroxy-benzotriazole (HOBt) and 1-hydroxy-7-aza-benzotriazole (HOAt) or ethyl cyanohydroxyimino-acetate (Oxyma), a more recently developed additive for carbodiimide coupling with coupling efficiency comparable to HOAt [131]. More recently developed and commonly used coupling reagents incorporate the HOAt/HOBt moiety as an aminium/uronium or phosphonium salt of a non-nucleophilic anion (tetrafluoroborate or hexafluorophosphate) [132]. Examples of aminium/uronium reagents are HATU (HOAt), HBTU/TBTU (HOBt) and HCTU (6-ClHOBt). HBTU and TBTU differ only in the choice of an anion, while phosphonium reagents include PyBOP (HOBt) and PyAOP (HOAt).

Protecting Groups

Amino acids have at least two reactive groups, so they need to be orthogonally protected. One class of the protecting group allows temporary protection of the α-amino group, while the other type is used for permanent protection by blocking the side-chain functionalities of amino acids. Permanent protecting groups have to withstand the repeated cleavages of the temporary protecting group. They are

removed from the final peptide, when the synthesis is complete. Two principle orthogonal protecting group schemes are utilised in a solution and/or solid phase synthesis: the so-called Boc/Bzl (tert-butyloxycarbonyl/benzyl) and the Fmoc/*t*-Bu (fluorenylmethylenoxycarbonyl/tert-butyl) approaches [133]. The fmoc method offers a mild deprotection scheme. This method involves a base, usually piperidine (20–50%) in DMF or NMP in order to remove the Fmoc group and expose the α-amino group so that it may react with an incoming activated amino acid. The advantage of Fmoc is that it is cleaved under very mildly basic conditions, but it remains stable under acidic conditions. This allow to use the mild acid-labile protecting groups such as Boc and benzyl groups to be used on the side-chains of amino acid residues of the target peptide. The Boc/Bzl-strategy requires side chain protecting groups, which tolerate repetitive acidic treatments. SPPS can be automated far more conveniently for Fmoc/tBu than the Boc/Bzl strategies. Other protecting groups used for special cases include: benzyloxy-carbonyl (Cbz, Z), allyloxycarbonyl (Alloc) for the amino group and methyl, allyl or cyclohexyl for the carboxyl group. Most of them could be selectively removed in the presence of Boc/Bzl or Fmoc/tBu protections [118, 134, 135].

Acyclic And Cyclic Modified Short Peptides And Amino Acids Synthesis

Modification of amino acids and/or amide bonds can be achieved using both strategies, solution phase synthesis (SPOS, solid phase organic synthesis) as well as polymer supported synthesis (SPPS). Among modifications popular nowadays are head to tail, head to side chain, side chain to tail and side chain to side chain cyclizations. As it was mentioned above, peptides can be cyclized on a solid support and/or in a solution as well. A variety of condensation reagents can be used such as DPPA, HBTU, PyBOP, HATU or EDC/HOAt. The strategy for the solid-phase synthesis of cyclic peptides in not limited to attachment through Asp, Glu or Lys side chains. Cysteine, which has a very reactive sulfhydryl group at a side chain, can serve as a good example. The disadvantage of the solution phase cyclization is the necessity for substrate high dilution to limit the possible reactions to an intramolecular one.

It is worth emphasizing that less than ten years ago new mechanochemical methods that were proposed as efficient green techniques for the synthesis of different short peptides appeared. They are based on mixing, grinding and/or ball milling in the solid state with no or tiny amounts of solvents [136]. The results obtained by this particular technique in terms of yield and purity are comparable with those obtained by solution and SPPS, but the amount of wastes is definitely much smaller – especially in comparison with SPPS [137].

SUPRAMOLECULAR LANDSCAPE OF MODIFIED AMINO ACIDS AND SHORT PEPTIDES

Supramolecular architecture and interactions are the basis for supramolecules properties. Therefore, a thorough understanding of supramolecular effects is vital to interprete and predict the relationships between the structure and function. Supramolecular chemistry is popularized by a lot of different monographs and scientific articles published in well recognized scientific journals. Nevertheless, the works concerning supramolecular aspects of short peptides and modified amino acids, especially in the context of precise characterization of non-covalent intercontacts, are very scarce indeed. This section introduces the synthon concept to investigate the interplay of strong and weak interactions linking supramolecules, which is pivotal for the development of new functional supramolecular short peptide-based biomaterials or for the understanding of the unique properties describing biological systems. We present a superficial overview, emphasizing a supramolecular landscape of short peptides studied by modern experimental and theoretical methods, developed remarkably in the last years. It is illustrated by examples from our works, as in the following Fig. (**6**).

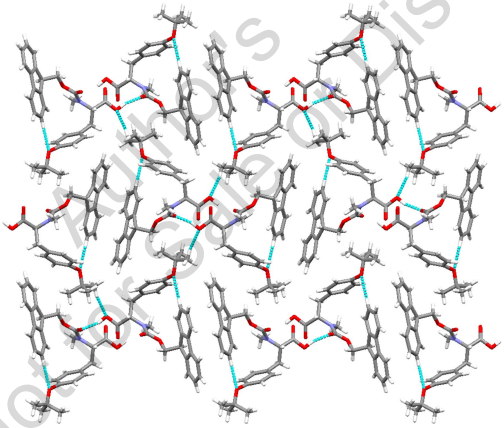


Fig. (6). Supramolecular architecture of modified (by Fmoc group) short peptide (from our studies).

Relevance of the Supramolecular Interactions in Biological Systems

It is obvious, as we have mentioned above, that the multitude of chemical species in living systems is based on non-covalent intercontacts [95, 138]. Thereby, the supramolecular chemistry of bioinspired molecules, highly important *per se* in recognition of the creation mechanisms, evolution of natural organisms and also in the development of new biofunctional materials, has been of great interest recently.

Generally speaking, the supramolecular (noncovalent) interactions are significantly weaker (from ~ 2 to 300) than molecular (covalent) bonds (~ 200-400 kJ/mol for a single bond). The strength of the interactions depends on the type of contact, its directionality, steric considerations and other electronic effects [66]. Nevertheless, a cooperative way of interplay of the noncovalent interactions leads to a stronger bonding and amplifies the stability of supramolecular assembly [139, 140]. Contrary to the covalent interactions, the noncovalent intercontacts have several advantages. They provide a straightforward and facile supramolecular structure construction (supramolecular synthesis) avoiding multiple synthesis steps and a difficult purification process required in the molecular synthesis [122]. The indicated above relative weakness of those contacts together with their dynamic nature guarantees reversibility, further convenient dissociation and reconstruction of the supramolecular systems. Self-repairing is crucial in life processes [65, 141]. It is worth mentioning that the weakest interactions have lately received special attention worldwide [142, 143]. Non-covalent interactions involving aromatic rings such as π···π, cation···π, anion···π or a lone pair (lp)···π play a vital role in biological processes: stabilization of the biological structures or mediating biorecognition [95, 144, 145], DNA repairing [146 - 148], forming complexes in proteins incorporating organic/inorganic cations (host-guest relation) [95], in directing proteins to create correct tertiary structure, in receptor systems which are composed of aromatic residues [66, 149, 150], in anion transport, as activators for reactions, drug-receptor intercontacts, protein-protein recognition and so forth [151 - 155]. Interestingly, the cooperativity effect, which is a general feature of intercontacts in biomolecular systems, in terms of anion-π interactions in biological systems, by the inclusion of other non-covalent contacts (π-stacking or cation-π) forms anion-π-π or anion-π-cation triads [154]. Furthermore, ion-dipole interactions occur in catalysis of DNA polymerization [95]. A non-polar dioxygen interaction with iron in haemoglobin is an example of this weak contact. As a consequence, it is reversed and is strong enough to transport dioxygen from lungs to muscles by haemoglobin. Hydrophobic interactions can have an impact on the significant self-assembly processes of micelles/membranes formation [156, 157]. Moreover, the interest in a new type of intercontacts, halogen bonds, D-X···A, where D is donor, A – acceptor and X = F, Cl, Br or I (and dihalogen bonds, X···X), is noticeable. Surprisingly, the first report of halogens as potential Lewis acids concerning the complexes between molecular halogens (*i.e.* Br_2 or I_2) and methylamines was published in the 19th century [158]. Molecular halogens have high reactivity and halogenation is an important step in synthetic organic chemistry [159]. They have similar properties to H-bond and play an important role in the recognition and supramolecular assembly of biological entities. This bond involves two electron rich centers and the electronegative halogen, resulting

interaction is highly directional, the bond angle centers ~ 180 °, as such it is an architectural element, much like the H-bond [19]. Thus, the relevance of Hal-bond in biological materials is only seemingly irrelevant. The number of X-bonds visible in biomolecular systems increases drastically along with the increasing recognition of Hal-bonding as a substantial factor of specificity. There are examples of naturally halogenated proteins or nucleic acids, thyroid hormones, protein complexes with halogenated ligands. Halogenated compounds can be secondary metabolites, antibiotics or anticancer drugs. X-bonding is useful in the design of therapeutics [159]. The relationship between H-bonds and X-bonding is used to control the structure and function of macromolecules [160]. It leads to a new approach in biomolecular engineering *via* designing the interactions to control specificity or the biomolecules folding. Besides, *"the marriage between computational drug discovery and that of halogen bonding in biological systems has provided renewed impetus and hope for the otherwise thought to be "past-prime" area of drug discovery"* [18, 161]. Another interesting issue is a very week hydrogen-hydrogen (CH···HC) dispersive interaction, which was proposed a decade ago. It is omnipresent in nature. According to CSD analysis, short H···H contacts (with inter-nuclear separation smaller than double vdW radius of an H-atom, 2.4 Å) are common [162]. These unconventional, subtle intercontacts can help considerably through cooperativity in stabilization of C-C bonds and play a role of *sticky fingers* gluing supramolecular structures of macromolecules. H···H contacts are of importance during a chemical reaction and in the crystallization of non-polar molecules, in 3-D crystal growth. X-ray single crystal diffraction and Hirshfeld surface analysis, Bader methods are good experimental and theoretical indicators of H···H contacts, respectively [19].

Supramolecular Synthon Concept Evolution

Supramolecular synthons are the smallest structural units (patterns, motifs) leading, at the atomic level, to the supramolecular structure *via* a specific spatial arrangement of the intercontacts. The concept of supramolecular synthons, was elaborated by Desiraju [74] for the profound examination of the structural effects of crystal packing. It is useful not only for the characterization, offering simplification in structures comparison, but also in the understanding of the biological recognition or drug-enzyme binding [163]. What is more, it is a key step in the design of molecular crystals through supramolecular retro-synthesis, combining chemical information with topological characteristics. The supramolecular synthon idea in crystal engineering became a necessary and convenient method ensuring generality and predictability [75]. Synthon transferability among various supramolecules suggests robustness and interchangeability of synthons. A successful design and synthesis of cocrystals (multi-component crystals), applied mainly in pharmaceutics, but also in catalysis or organic conductors, rely on

identification of robust synthons between the cocrystal constituents [164]. A supramolecular synthon approach is as important in supramolecular chemistry as the reaction mechanisms in traditional organic synthesis [75, 165].

Elementary Synthons Recognition and Classification

Identification and characterization of synthons are difficult because the intercontacts in the crystal are numerous and diverse. Both strong (O-H···O, N-H···O) and weak (C-H···O, π···π, C-H···π and so on) hydrogen bonds form synthons. Weaker non-covalent interactions can be essential in constructing the supramolecular architecture, especially in the absence of the conventional H-bonding [166, 167]. The most popular method of synthons recognition is the Graph Set Theory developed by Etter [168, 169] and Bernstein [170], identifying different types of H-bonds and ranking them by chemical priority and empirical rules for hydrogen bonding. The H-bond with the highest priority generates the so-called motif with the graph set descriptor $G^a_d(n)$, where *G* is the pattern of H-bonding, characterized by the following designators: *C* – an infinite chain, *R* – a ring, *D* – a noncyclic dimer, *S* – an intramolecular ring. The parameter *n* denotes the total number of atoms in the repeat unit, superscript *a* refers to the number of acceptors, while subscript *d* – number of donors, respectively [81] (Fig. **7**).

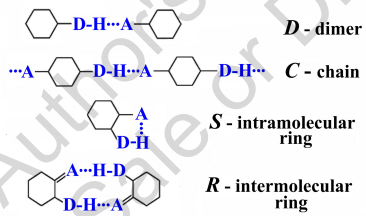


Fig. (7). Schematic representation of different types of synthons (D-donor, A-acceptor).

Etter's hydrogen bond rules are as follows:

- all acidic H-atoms in a molecule are used in H-bonding in the crystal structure,
- all good proton acceptors are used in H-bonding when there are available H-bond donors,
- the best H-bond donor and the best acceptor are preferential to form H-bonds to one another [168, 169].

The supramolecular synthons were further classified by Zaworotko into homo- and heterosynthons based on the identical and different interacting self-complementary functional groups, respectively [171], which will be further explained with the help of the hereunder Fig. (**8**). It is worth mentioning that the list of possible synthons is continuously growing.

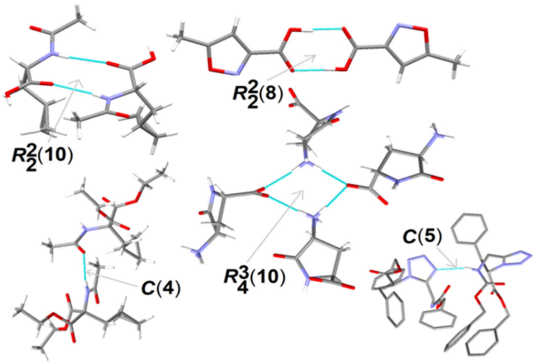


Fig. (8). Representative synthons in short peptides: $R^2_2(10)$ homosynthon between amide dimer, $R^2_2(8)$ homosynthon between carboxylic acid dimer and $R^3_4(10)$ heterosynthon (tetramer), descended from our studies.

The example of interplay of chain and ring synthons as in a cyclic short peptide is demonstrated in the Fig. (**9**).

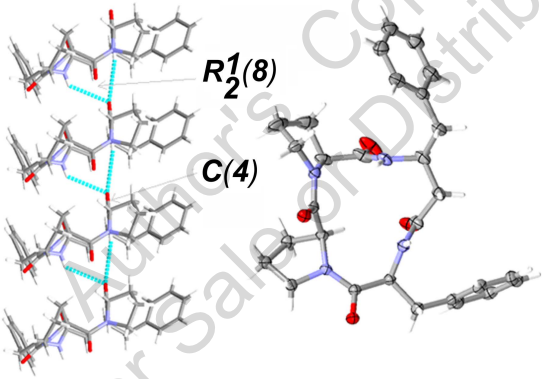


Fig. (9). Fragment of supramolecular architecture of cyclic peptide descended from our studies.

The Long-Range Synthon Aufbau Module (LSAM) Idea

The long-range synthon Aufbau module (LSAM), late synthon, is a large supramolecular synthon containing more than one type of intermolecular interaction [172, 173]. Consequently, H-bonds together with other intercontacts can form larger H-bond motifs [174]. These large synthons, the so-called LSAMSs, fulfill a function of agents between smaller synthons and/or composites of small synthons forming 3-D structure. So, in a way, LSAM is the imprint of the smaller synthons. The LSAMs contain rich geometric and chemical information, which is more representative and characteristic concerning the symmetry, long range order and topology in the crystal structure. Therefore, the analysis of LSAMs packing is often crucial for a proper understanding of crystal structure.

The large synthons are usually one-dimensional, but can also have higher dimensionality. LSAM concept is useful in the crystal structure design, including co-crystals, especially when high level cocrystals are concerned [172, 173].

Synthon Polymorphism

The occurrence of different H-bonding synthons directing supramolecular packing in polymorphic crystal forms is known as synthon polymorphism, which means deep mechanistic implications, indicating the existence of competing crystallization and co-crystalization pathways [66, 175]. The representative example is supramolecular synthon polymorphs of the modified amino acid [176], showing dissimilarities at successive levels of supramolecular architectures. We present the supramolecular assemblies in relation to short-range supramolecular synthons that spontaneously arrange themselves in accordance with Aufbau principles into long-range geometries characteristic of the molecules themselves. The presented supramolecular architectures are composed of completely different large synthons in the form of a layer in (**1**) and specific ribbons in (**2**), sustained by strong hydrogen bonds (alternating catemer-dimer mix) and $\pi\cdots\pi$ contacts, respectively (Fig. **10**).

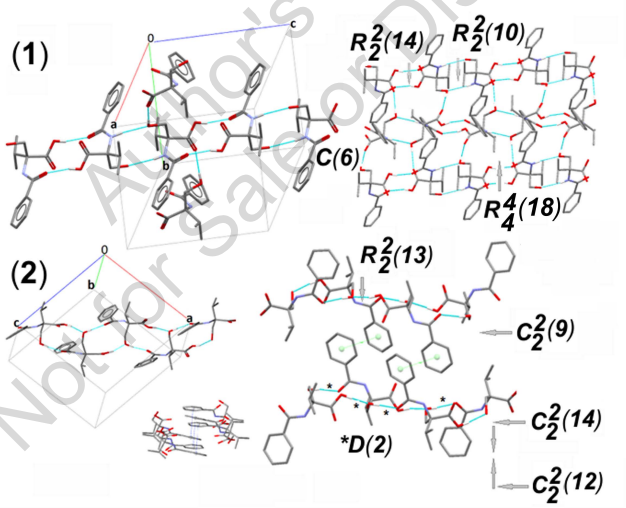


Fig. (10). The supramolecular architectures of two synthon polymorphs of modified amino acid, descended from our studies, showing diverse supramolecular synthon preferences (H-atoms not involved in the H-bonding were omitted for clarity).

Overall, the realization of the desired supramolecule with specific properties is a demanding task due to the dynamic nature of non-covalent reactions. On the other hand, the molecular simplicity results in relatively easy estimation of the

assembly details using the supramolecular synthon concept [177 - 180]. However, different functionalities related to combinations of numerous synthons and/or synthon polymorphism cause that the analysis is not so obvious [181, 182]. Therefore, a carefull identification of all types of synthons, including LSAMs, and a profound knowledge of robustness, reproducibility, transferability and the function of synthons at the particular levels of supramolecular architecture are necessary for a rational design and synthesis of supramolecular systems.

Enlargement and Horizon of Applications: Looking Ahead

The elaboration of the supramolecular synthons concept, a structural device carrying information *via* non-covalent intercontacts [75, 80, 174, 183 - 187], was a milestone in the recognition and understanding of general trends of the supramolecular system (crystal) organization. It highlighted typical ways of arranging molecules [74, 174, 188 - 191]. Unfortunately, in reality this synthons concept has limitations, especially in the crystals with only one type of strong intercontact or those containing different weak H-bonds. In spite of the fact that the synthon methodology is qualitative in nature, quantitative consideration of the H-bonding motifs can be helpful in thorough exploration of the supramolecular architecture. Taking into account the fact that the geometry of the molecular system is the derivative of its energy, it is interesting to consider the role of synthons in the supramolecular assembly construction from the point of view of the energy of the intercontacts (between molecules linked by synthon). Dunitz and Gavezzoti related the energetics of a supramolecule to the synthons concept, providing an insight into the absolute, relative strength of the synthons [192]. Shishkin *et al.* highlighted this phenomenon in more detail and proposed hierarchical classification of the synthons, which is specific to each crystal, into the following groups: basic (or local), responsible for the formation of molecular complexes such as building units of crystals, primary liable for the creation of a basic structural motif of the crystal, secondary, ensuring the packing of basic structural motifs and auxiliary, others involved in the packing of these motifs as well [193]. It is noteworthy that based on the quantum-chemical calculations, it is possible to find pairs of molecules bonded more strongly than others. The basic molecule in the asymmetric unit and two most strongly bonded to the basic molecule determine infinite part of the crystal, namely the basic structural motif (containing the most strongly bonded pairs of molecules), which can have various dimensionalities such as: 2-D (layer), 1-D (column/chain) [194 - 205]. The basic synthons contribute to the lattice energy of the crystal. In contrast, the primary synthons are structure-propagating supramolecular synthons since they are responsible for the construction of infinite fragments of the crystal (columns/ chains or layers). The auxiliary supramolecular synthons do not take part in the generation of the primary and secondary basic synthons. Primary synthons are the

strongest, secondary - weaker, while auxiliary - the weakest. Nevertheless, each type of synthons is important at different levels of supramolecular organization. The ranking of synthons depends on intercontacts energies and is individual for particular crystal. A vital role of those synthons in the creation of the supramolecular architecture is illustrated using the modified amino acid from our studies as an example of supramolecular organization in the crystal (Fig. **11**).

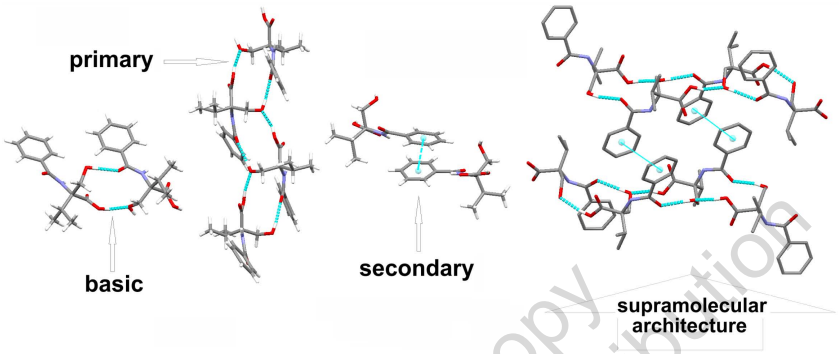


Fig. (11). Supramolecular synthons (basic, primary and secondary) found in the supramolecular structure of modified amino acid, descended from our studies. In supramolecular architecture H-atoms not involved in the interactions were omitted for clarity.

Overall, the analysis should consist of the following steps: identification of all synthons, recognition of the basic structural motifs, classification of the synthons, including LSAMs, at all supramolecular architecture levels and performing synthons ranking taking into account the strength of the intercontacts.

Another interesting issue is conformational polymorphism, which can be used in a broader sense. The supramolecular synthon can exist in different conformations. Hence, a conformational analysis of supramolecular synthons can also be important in the understanding of differences and similarities, for example, among different polymorphic forms [206]. Besides, we would like to emphasize that the new experimental techniques coupled with infrared FTIR or NMR detect supramolecular synthons (even LSAMs) in a solution (prior to crystallization) showing a direct relationship between self-association in the solution and the synthon patterns in the solid-state [207, 184, 185]. A supramolecular synthon concept is a subject of continuous, intensive studies. The applications of this idea not only in the range of mainstream crystal engineering research but also in different fields are worth considering [75, 208 - 212]. Here, we refer to landmark studies only. The synthons concept can be exploited to design new supramolecular functional materials with multiple properties or to design new gel materials [210, 213]. It can also be used to understand the organization of molecules on the surface [214, 215]. Synthon-based fragments analysis (SBFA)

combining the supramolecular synthon concept with charge density studies is approved due to the synthons modularity used for the successful transferring of charge density derived multipolar parameters for structural fragments. In addition, the SBFA method is applicable to single-component crystal structures and/or cocrystals as well [216 - 218]. It is a promising idea which needs future development. The four-step IR method reveals the manner of differentiating slight variations in weak synthons [219]. The H-bond motifs detection in a solution and an understanding of their mutual dynamics may be usable in employing supramolecular synthons in dynamic systems. Furthermore, LSAM concept can be used in designing higher-component co-crystals. More specifically, the main problem lies in the difficulty of establishing synthon hierarchies in systems possessing many functionalities and forming numerous and diverse intercontacts [186, 220 - 223]. Another aspect is the library of real and virtual synthons in a solution [224, 225]. A combinatorial approach based on the virtual synthon library is used to create new design strategies for ternary and quaternary cocrystals [187, 217, 218].

Modern Experimental and Theoretical Methods: Focus on Precise Study of Noncovalent Intercontacts

A precise investigation of supramolecular features and close scrutiny of assemblies need a holistic approach and different high-specialized and advanced techniques.

Supramolecular X-ray Crystallography

It is worth noting that in the past century we learned about *nature* more than ever before. More importantly, supramolecular crystallography played a crucial role in this progress. An understanding of the supramolecular structure in the atomic scale in relation to the intercontacts is still not possible without crystallography. The single-crystal X-ray diffraction (SC-XRD) is the most powerful, invaluable tool for the profound structural investigation of solid-state supramolecular structures and provides essential support for the supramolecular chemistry. The SC-XRD facilitates acquisition of the information concerning the 3-D structure, chemical bonding, intra- and intermolecular interactions to a much greater degree than any other technique. It should be stressed that molecular crystals are an enormous and precious source of intercontacts information. Moreover, this technique also reveals data concerning configuration, stereochemistry, tautomerism of the structures and so forth. Crystallography had a vast impact on the development of other fields such as physics, biology, pharmaceuticals, material science. It provides an insight that no other approach could give [226]. It should be underlined that over the last two decades, substantial progress in the

technology and X-ray diffraction instrumentation, including the advances in the data treatment, structure solution and refinement, has been made. Nowadays, the newest, highly specialized apparatus with incorporated modern generation sources and very fast computers with special software collecting data of superior quality in an intelligent fashion, are an extremely powerful source of physico-chemical data. It enables determination of the crystal structure with the highest precision, including proper assignment of hydrogen atoms and consequently further precise identification and characterization of the structural motifs, which are indispensible in the understanding of the weak intercontacts in the context of supramolecular chemistry [227]. The coincidence of development of crystallographic techniques and supramolecular chemistry merged those two methods in a natural way. Any attempt to distinguish these disciplines is impossible. As a consequence, crystal engineering, being a supramolecular equivalent of synthesis, became a crucial genre of supramolecular chemistry. Research providing an insight at the atomic level revolutionized an understanding of the materials properties and functioning of biological processes. Modern crystallography (supramolecular crystallography) has an interactive and interdisciplinary character and is focused on the investigation of the nature of non-covalent intermolecular interactions, providing unique knowledge according to the following enhanced sequence: conception, design, synthesis, measurements, structure, properties [228]. Supramolecular crystallography played an important role in almost all discoveries in biomedical sciences. A related point to consider is the fact that the x-ray crystallography is a Nobel prize winning technique. The scientists who inform us about the building blocks of life were awarded 30 most prestigious prizes related to X-ray crystallography (Table **2**). The diversity of the significant and impressive number of Nobel prizes for the achievements from the borderland of chemistry, physics, biology, physiology, medicine proves the great importance and wide outreach of this branch of science [226]. Particular importance refers in this context to even the studies of globular proteins structures [229 - 232], the helical structure of DNA, the crystal structures of many biochemical substances (*e.g.* vitamin B12) [233], protein chains folding or *G*-protein-coupled receptors. These X-ray successes in terms of such important biomolecules enabled an insight into non-covalent interactions. The presence of many H-bonds in peptides, proteins or nucleic acids provides highly stable structures [66]. So, in a way the abovementioned accomplishments concern supramolecular aspects. However, the supramolecular chemistry has been awarded two Nobel prizes. The first was in 1987, when the scientists Cram, Lehn and Pedersen discovered crown ethers, cryptands and spherands. The second Nobel Prize (in 2016) highlighted achievement in supramolecular chemistry and structural chemistry [234, 235]. Therefore, the impact of crystallography on supramolecular chemistry cannot be overemphasized.

Table (2). Nobel prizes concerning with X-ray crystallography.

Year	*Nobel laureates*	*Achievement*
1901	W.C. Röentgen	Discovery of X-rays.
1914	M. Von Laue	X-rays diffraction *via* crystals.
1915	W.H. and W.L. Bragg	X-rays for determination of crystal structure.
1917	C.G. Barkla	Discovery of the characteristic X-rays of the elements.
1929	L.V. de Broglie	The wave nature of the electrons.
1936	P.J.W. Debye	Molecular structure knowledge *via* investigation on dipole moments, on the x-rays & electrons in gases.
1937	C.J. Davisson, G. Thompson	Electron diffraction by crystals.
1946	J.B. Summer [236]	Discovery that enzymes can be crystallized.
1954	L.C. Pauling	Nature of the chemical bond, its application to the elucidation of the structure of complex substances.
1962	J.C. Kendrew, M. Perutz	The studies of globular proteins structures.
1962	F. Crick, J. Watson, M. Wilkins	The helical structure of DNA.
1964	D. Hodgin	The crystal structures of many biochemical substances (*e.g.* vitamin B12).
1972	C.B. Anfinsen	Protein chains folding.
1976	W.N. Lipscomb	Boranes structures.
1982	A.Klug	Development of crystallography electron microscopy. Nucleic acid-protein complexes: discovery.
1985	H. Hauptman, J. Karle	Direct methods development for crystal structures determination.
1988	J. Deisenhofer, R. Huber, H. Michel	Photosynthetic reaction centre: determination of 3-D structure.
1991	P.G. de Gennes	Methods of discovering order in simple systems applied to polymers and liquid crystals.
1992	G. Charpak	Discovery of the multi wire proportional chamber.
1994	C. Shull, N. Brockhouse	Neutron diffraction.
1996	R. Curl, H. Kroto, R. Smalley	Discovery of the fullerene.
1997	P. Boyer, J. Walker, J. Skou	Explanation of the enzyme. mechanism in terms of ATP synthesis. Anti on-transporting enzyme:discovery.
2003	R. MacKinnon	Potassium channels.
2006	R.D. Komberg	Eukaryotic transcription: molecular basis.
2009	V.Ramakrishnan, T.Steitz, A.Yonath	Structure and function of ribosome.
2010	A.Geim, K. Novoselev	Groundbreaking experiments concerning the 2-D graphene
2011	D. Shechtman	Discovery of quasicrystals.
2012	R.J. Lefkowitz, B.K. Kobilka	G-protein-coupled receptors.

(Table 2) cont.....

Year	*Nobel laureates*	*Achievement*
2013	M.Karplus, M.Levitt, A.Warshel	Development of multiscale models for complex chemical systems.
2016	J.Sauvage, J. Stoddart, B. Feringa	Molecular machines: design and synthesis.

Crystallographic Experiment

Firstly, the difference between a crystal and crystal structure should be explained. A (single) crystal is a solid which structure is described by a periodic repetition of a motif composed of molecules (or ions). On the other hand, a crystal structure consists of conceptually infinite coordinates, indicating the arrangement of the component atoms relative to one another. In other words, a crystal structure is a model providing knowledge about the molecular structure, packing, intra- and intermolecular interactions. The primary item of X-ray study is to obtain a good quality single crystal with sufficient diffraction power. The crystallization methods such as, solvent evaporation, sublimation, vapor diffusion, gel growth, used for organic molecules can be applied to supramolecules. During the X-ray data collection, symmetry, space group and unit cell are being determined. The unit cell, the smallest 3-D unit into which the atoms in the crystal structure can be arranged, has a certain shape defined by the lengths of the unit cell axes, a, b and c, in [Å] units, and the angles among the unit cell axes, α, β and γ, in [°]s. For the periodic 3-D atoms arrangement, it is possible to imagine and define parallel planes. It is noteworthy that X-rays should have wavelengths comparable to the length of chemical bond and therefore they are proper for visualization of the 3-D crystal structure and interactions between the molecules. When the X-ray beam is diffracted the resulting image contains information about the electron density distribution in the crystal. The geometric description of X-ray diffraction can be schematically simplified as interference of X-rays reflected by adjacent parallel planes according to Bragg's law. All possible reflections have to be measured. Generally, data collection is an automatic process. A set of reflection images with multitude of reflection spots (points in space) is generated. They are converted into a format suitable for special computer software in order to space group determination and subsequently crystal structure solution. This data processing may achieve efficient effects if the data collected are of good quality. In short, higher percentage of reflections signalizes a better quality of the data. Thus, a more real model for the experimental electron density will be generated. A good structure solution results from the well-resolved electron density map. The effect of the solution is a 3-D model of the structure with non-hydrogen atoms. The refinement process includes completion of both non-hydrogen and hydrogen atoms, a possible correction (model disorder). It also models the atom coordinates with atomic displacement parameters. Nowadays, advanced diffractometers are

equipped with a liquid nitrogen cryostat controlling the temperature of the crystal during the measurement. The determination of the crystal structure at a low-temperature (nitrogen or helium atmosphere) together with the developed refinement techniques, aiming at diminishing the atoms thermal motions improves the electron density map visualizing the finest details of the electron density with an increased number of data with very high-resolution, guaranting high-order data. Hydrogen atoms are localized in calculated positions in terms of predefined geometrical criteria and refined by a riding model based on the positions of the parent atoms. If the calculated positions are not properly defined, hydrogen atoms are omitted or refined independently in relation to the peaks at the difference electron density map. However, X-ray diffraction is not the best way to precisely determine the H-atoms positions due to the scattering of X-rays *via* electrons. The single electron of the H-atom is polarized in the direction of a single bond to the parent atom. Thus, an electron density peak for the H-atom will rarely be a good estimator of the atom`s nucleus position. The neutron diffraction, described in the further part of subsection, is the most appropriate. The calculations by the least-squares method are performed. The model is fitted against the measured data. The cycles are repeated until all atoms are found and located properly, and we are sure that is the best possible final model of the structure [10, 77]. The fitting coefficient (*R*-factor) is improved. The rule is as follows: the lower the value expressed as a percentage, the better the model. Data with *R*-factor below 5% are regarded as a good quality structure. The most popular computer software for structure solution and refinement is the SHELX program suite, including SHELXS to solve and SHELXL to refine the crystal structure, respectively [237]. The schematic representation of the general X-ray experiment, including particular steps, is presented in Fig. (**12**). The final effect of the X-ray experiment is written down in the form of crystallographic information file (CIF), containing all necessary information about the crystal structure (the unit cell parameters, space group, atomic coordinates and as well crystal size, morphology, color, chemical formula, weight, atomic displacement and refinement parameters, and so on) [238], which is thereupon submitted to the Cambridge Crystallographic Data Centre for deposition in the Cambridge Structural Database. To sum up, it is important to stress that the X-ray procedure was described just on a very descriptive, indicative level. Finally, it is pertinent to mention the latest techniques such as high pressure crystallography or in situ cryo-crystallization [239].

Structural Databases

Databases, organized sets (also called goldmine) of related plethora data, play a precious role in the study of supramolecular effects. Databases collect secrets of molecular crystals providing a huge knowledge concerning all types of

intermolecular interactions and enable an electronic exchange of structural information among the scientists of various fields.

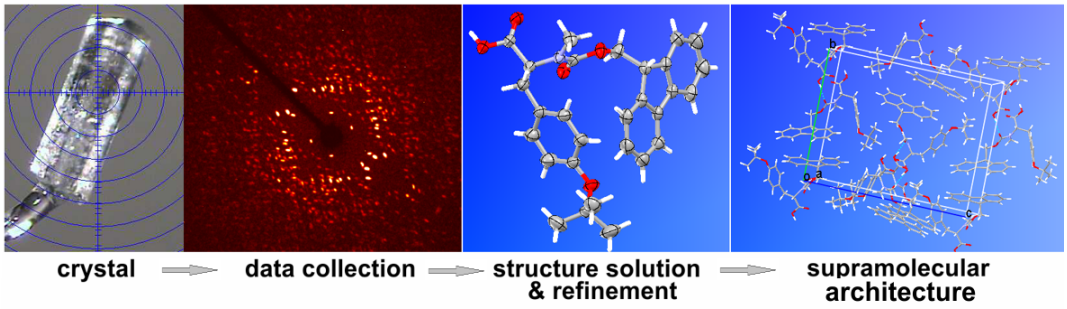


Fig. (12). X-ray experiment using SC-SRD method.

Cambridge Structural Database

The Cambridge Structural Database (CSD) is the world's most comprehensive and up-to-date repository of crystal structures of relatively small (containing less than 1000 atoms) organic and metal-organic compounds derived from X-ray and neutron diffraction experiments provided as *Pivative Communications*, or published as scientific papers. Every database entry has unique reference 6-literal code and is enriched with bibliographic, chemical and physical property information. The CSD was established in 1965. The oldest deposited structure in the database was determined in 1923. Initially, it contained 1500 crystals structures. Today (CSD version 5.39) there are nearly million structures (over 936 000 entries in February 2018, according to data from https://www.ccdc.cam.ac.uk). Crystallographers provide an enormous number of structures per year. Fig. (**13**) demonstrates the exponential growth of the structures deposited in the CSD over the years. The structures before deposition undergo extensive validation to guarantee the highest possible standards. Therefore, before archiving structural data, a CIF file should be tested in a web-based service check CIF (http://checkcif.iucr.org/) in order to find possible errors or shortcomings. The CSD is the most relevant database for intermolecular intercontacts studies and a powerful research tool providing structural information, concerning *inter alia* molecular dimensions or conformations, and an excellent way of structures analysis and comparison, systematic study of the interactions occurring in the deposited structures (mainly as molecular crystals, co-crystals, polymorphic and pseudopolymorphic forms, nanostructures), identification of robust synthons or discovery of new synthons and it also plays an important role of the solvent molecules in the formation of both synthons and supramolecular structure stabilizing them as well. It can be helpful in predicting the H-bonding patterns in synthons. Interestingly, a search for complementary functional groups by CSD increases the likelihood of

occurrence (propensity) of all possible H-bonds in the formation of corresponding homo- or hetero-synthons. The H-bond synthons with high formation probability are preferred in the rational supramolecules design. Thus, the CSD plays a vital role in the development of the supramolecular chemistry (particularly crystal engineering) [240 - 244].

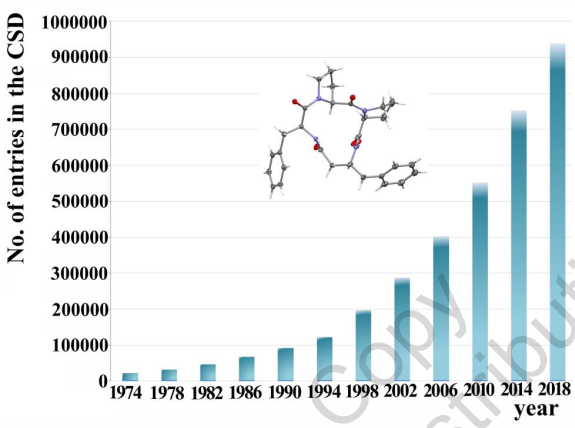


Fig. (13). Growth of the CSD over the years.

The crystallographic programs, compiled with the CSD, *exempli gratia* Mercury [245] (the elementary version is free of charge, available by the Internet *via* http://www.ccdc.cam.ac.uk/products/csd_system/mercury/downloads), are the simplest manners to achieve 3-D visualization, inspect the crystal structure and the molecules packing in the unit cell and compare with the related structure present in the CSD. Mercury program includes the motif search tool optimized for 3D search for ~150 common functionalities. In this program, we can check and compare different details such as bond lengths, angles, identify intra- and intermolecular interactions or prepare molecular graphics for publication, the so-called ORTEPs (Oak Ridge Thermal Ellipsoid Plots) [246] illustrating anisotropic atomic displacement ellipsoids. Thermal displacement images indicate the atoms thermal motion visualized in a manner of qualitative evaluation of the crystal structure quality. Atoms undergo anisotropic thermal motions modeled during the refinement as ellipsoids. Thermal ellipsoids indicate also dynamic disorder, but only in extreme situations. Software applications for data analysis are being continuously upgraded. Interestingly, in 1948, exactly 70 years ago, *Acta Crystallographica* started, a specialist journal providing all aspects of crystallographic research and demonstrating a broad area of X-ray crystallography, a full range of methods, instrumentation and studies from halogen bonds [184, 185], multiferroic materials [247] to serial femtosecond crystallography [248, 249] or

synchrotron radiation serial crystallography [226, 250]. All crystal structures described in this journal are deposited in the CSD. A list of crystallographic databases is accessible on the IUCR web site (http://www.iucr.org/ resources/data). An overview of crystallographic databases is included in the, *inter alia*, special issues of Acta Cryst. B and D [243, 251 - 254]. *Bilbao Crystallographic Server* of crystallographic information, available *via* http:// www.cryst.ehu.es, plays a role of an open access website in relation to databases and programs.

Protein Data Bank

It is a crystallographic database (freely accessible on the Internet, http://www. rcsb.org/, http://www.wwpdb.org/) including 3-D structural data of large biological molecules: polypeptides, for example gramicidin [96 - 99], proteins, nucleic acids and complex assemblies, containing ~ 150 000 entries. The results were obtained by X-ray diffraction, NMR spectroscopy or cryo-electron microscopy.

Biological Macromolecule Crystallization Database

(http://xpdb.nist.gov:8060/BMCD4/index.faces/) includes data concerning crystals and crystallization of macromolecules.

Other databases must be listed such as: Structural Classification of Proteins (http://scop.mrc-lmb.cam.uk/scop/), providing description of the structural relationships between all known protein structures in the context of protein folds or basis for future research, or *Nucleic Acids Database* (http://ndbserver. rutgers.edu/NDB/), the *Crystallography Open Database* (COD) (http://www. crystallography.net/). The latter is the newest tool for scientific community. It is a collection of all available small organic structural data and inorganic, metal-organic (in CIF formats), adopting an open-access type [252].

Neutron Diffraction

Neutron diffraction, as a supplementary technique to X-ray diffraction, played a prominent role in the development of modern structural chemistry (supramolecular chemistry, crystal engineering) in terms of H-bonded systems. It is based on the same theoretical rudiments as X-ray diffraction, but helps to definitely solve structural problems by providing accurate positional and thermal parameters of all atoms. In particular, it makes it possible to correct localization of H-atoms, refine their positions and thermal parameters in a much more reliable way. The main difference between the X-ray and neutron diffraction relies on the size of the interaction potential similar to the electronic cloud for X-rays and

almost punctual for neutrons. Hence, neutron single-crystal diffraction is crucial in defining the synthons of weak interactions in supramolecular structures. Neutron diffraction experiments are performed under extreme conditions (high/low temperature, high pressure, controlled atmosphere). The X-rays and neutrons combination is a powerful tool in finding applications in various areas: host-guest interactions or charge density studies. It is also used for complicated biological systems [77]. Contrary to X-rays, scattered by the electron cloud, neutrons (electrically neutral particles whose mass is close to that of the proton) interact with nuclei through strong nuclear force. Neutron radiation enables the study of microscopic properties due to the thorough penetration of the analyzed crystal. In particular, hydrogen and deuterium nuclei are strongly scattered for neutrons, while X-ray scattering is not sensitive to either. Thus, using neutrons we can determine the position of H-atom in a crystal structure [66, 255, 256]. To conclude, X-ray and neutron diffraction techniques provide complementary information: superficial *versus* thorough H-bond analysis.

Hirshfeld Surface Study

Hirshfeld surface (HS) analysis, which is a relatively new and unique method, visualizes all intermolecular interactions between neighbouring molecules in molecular crystals on the electron density maps at once. The size and shape of the HS are related to the chemical environment which surrounds the molecule, making it ideal for use in comparing different crystal structures incorporating the same molecule. The high resolution 3-D Hirshfeld surfaces of molecules within a crystal are calculated, in program *CrystalExplorer* [257 - 260], based on d_e (external distance), d_i (internal distance) and the van der Waals (*vdW*) radii of the atom, enabling identification based on the electron distribution calculated as the sum of spherical atom electron densities. The external and internal distances mean the distance between the HS and the nearest atom of an adjacent molecule and the distance from the nearest nucleus internal to the calculated HS, respectively. The normalized contact distance (geometric function, d_{norm}) presented by the hereunder eq. (1):

$$d_{norm} = \frac{d_i - r_i^{vdW}}{r_i^{vdW}} + \frac{d_e - r_e^{vdW}}{r_e^{vdW}} \quad (1)$$

The d_{norm} can be a negative or positive sum of d_i and d_e, when the intercontacts are shorter or longer than the sum of the atoms of the *vdW* radii, respectively. The HS map is a color-scheme showing red, white and blue areas, indicating the shortest (shorter than the sum of the vdW radii), weak (around the vdW separation) and free of significant (longer than the sum of the vdW radii) contacts, respectively.

Furthermore, the corresponding 2-D fingerprint plots (FPs), constructed by the combination of d_e and d_i, ensure a rapid quantitative summary of intercontacts (the percentage contribution of each contact to the total HS area) in convenient colors [261 - 266]. These plots provide information about more distant contacts and regions where the contacts are the weakest as well. HS are generated based on the crystallographic information about the structure. For this purpose, the CIF file coming from the SC-XRD experiment is imported into program. In order to obtain the best quality of calculations, very well-characterized results with accurately located all hydrogen atoms should be provided. Next, in the *CrystalExplorer* program all bond lengths to hydrogen are automatically modified to typical standard neutron values [267]. Moreover, except from the d_{norm}, also *shape-index* and *curvedness*, based on the local curvature of H, can be obtained. More specifically, the observed patterns of adjacent red and blue triangles on the *shape-index* surface, a qualitative measure of *which shape*, represent the existence of π···π stacking and related intercontacts. The blue triangles show convex areas (bumps) by the ring carbon atoms of the molecule inside the HS, while the red triangles – concave areas (hollows) in conjunction with the C atoms of the π-stacked molecule above it. Moreover, the presence of C···C contacts can be visible as flat regions by blue outlines on the surface *curvedness,* the measurement of *how much shape*, indicating the electron density surface curves around the intermolecular interactions [257, 264, 268, 269]. Hirshfeld surface method is an enormously helpful tool used for the investigation of supramolecular synthons existing in a particular supramolecular structure. The strong H-bonds such as O-H···O are clearly observed in the d_{norm} profile of Hirshfeld surface map as deep red dots. But at the same time, the supramolecular synthons are drawn with regard to the neighbouring molecules. Interestingly, O-H···O and O···H-O interactions can be distinguished through the d_i and d_e profile of the 3-D surface maps, respectively. Decomposed 2-D fingerprints are quantitative representatives of H···O and O···H traces. Fig. (**14**) summarized the analysis of O-H···O/O···H-O interactions in modified amino acid.

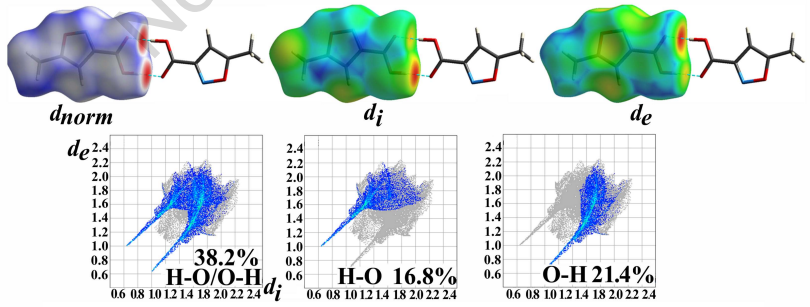


Fig. (14). HS maps (d_{norm}, d_i and d_e profiles) showing supramolecular synthons creating by O-H···O hydrogen bonds and corresponding FPs histograms (results of our studies).

Furthermore, the weakest supramolecular effects can be discovered as well. We demonstrate experimental evidence of the C=O···π interaction as the meaningful motif of the supramolecular architecture and an interesting feature of the modified amino acid structure visualized by HS maps (Fig. **15**). The distance between the carbonyl oxygen and the ring centroid is ~ 3.5 Å, while the corresponding torsion angle ~ 92 °.

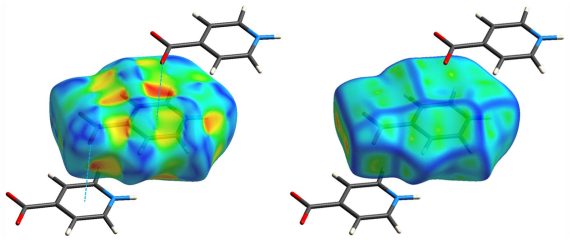


Fig. (15). Hirshfeld surface maps, on the left: *shape-index,* on the right: *curvedness*, presenting C=O···π interactions (descended from our studies).

Hirshfeld surface enables a comparative insight into the packing of polymorphic crystals. At the first glance, discovered intercontacts in polymorphs may seem similar or even identical. Nevertheless, a closer inspection reveals a subtle difference, which in can be extremely important. As an example, we present a quantitative analysis of all intercontacts in the modified isovaline supramolecular structure. Generally, full fingerprints look likewise. In both polymorphs, the H···H, O···H/H···O and C···H/H···C contacts take over a vast majority of total Hirshfeld surfaces, nearly 95%. In fact, the C···C contacts, existing only in one polymorphic form, make a difference. The C···C contacts which are assigned to π···π stacking contacts are clearly visible as a staggered pitch for red and blue triangles on the shape-indexed surface maps and flat regions by blue outlines on the curvedness. Another issue concerns the occurrence of O···O (lone pair···lone pair) and O···C/C···O (lone pair···π) and N···H/H···N contacts in (**1**) and (**2**), but in the vestigial quantities (Fig. **16**).

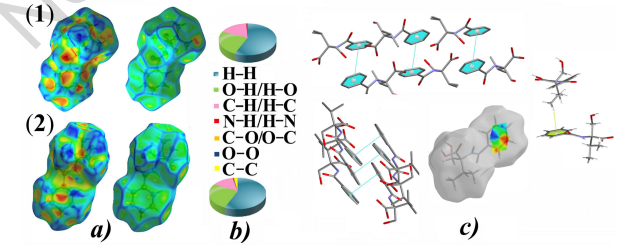


Fig. (16). π···π studies in two polymorphic forms of modified isoleucine: *a) shape-index and curvedness* HS maps visualizing π-stacking contacts only in (**2**) polymorph; *b)* the percentage contributions of all intercontacts found in both polymorphs; *c)* characterization of the π···π and C-H···π contacts in (**2**) polymorphic form.

Theoretical Perspective of Supramolecular Interactions in Crystals of Short Peptides

The emphasis of this sub-chapter focuses on a brief, superficial overview of the current knowledge, including the newest scientific communications which report advances in theoretical chemistry methods that play a vital role in understanding the nature of supramolecular interactions in molecular crystals of amino acids and short peptides. Year by year computational power is increasing. This together with development of experimental techniques makes studies of subtle supramolecular effects feasible. One of the main aims of quantum chemical studies is to obtain information about the energetics (and other properties) of interactions *via* understanding the relation between the crystal structure and intercontacts. The *in silico* procedures of determination of interaction energy are related to both stabilizing and destabilizing interactions. Therefore, it is important to keep in mind that intermolecular interactions (or rather interaction energy) link together the molecules into supramolecular assemblies with a long-distance order stabilizing the structure at the same time. Intermolecular interactions are sometimes called the *supramolecular glue* linking molecules in a crystal. It is noteworthy that the term intermolecular forces, which is sometimes used, is not equivalent because the forces are different to energy. Energy writes the information about the major properties of a crystal [19]. Crystal stability depends on all symmetry-unique pairs of molecules in the unit cell. The most relevant intercontacts are energetically dominant. Among them, interactions with stabilizing energy ($E_{int} < 0$) form a special subset – intermolecular bonds. The sum of all stabilizing interactions should predominate over the sum of the destabilizing ones ($E_{int} > 0$) for stable crystal. So, the term intermolecular interaction means two molecules interacting with each other, while the term intermolecular bond – a dominant stabilizing interaction.

Also the rationalization of the molecular crystal structure by accurate data from first-principles calculations is worth mentioning, which is still not a popular procedure, including the following stages: the identification of all energetically important interactions in the crystal, the determination of the nature of dominant intercontacts, the choice of a proper method and model system (depending on the availability of the computational resources, the model system size, the accuracy of the required results), the computation of the intercontacts strength, the description of the relation between the crystal stability and individual interaction from the most stabilizing until all molecules are linked in the crystal [19, 270 - 272].

Relevance of Charge Density Studies in Understanding of Weak Intercontacts in Biomolecules

Subtle non-covalent interactions are very difficult to represented by classical computational methodologies. On the other hand, proper identification and quantification of intermolecular intercontacts *via* studies of electron densities and charge density distributions in molecular crystals are still not so easy, but possible through modern single crystal X-ray diffraction experiments and high-level theoretical calculations, including improvements in charge density models. Hence, electron density can be determined either from X-ray diffraction (X-rays scatter off the electron density) or theoretical calculations [19]. Nowadays, advanced measurements of charge densities using high-resolution X-ray data of molecular crystals are comparable with highly reliable and high-speed computations. The development of computational methods, which are more and more accessible, in the last years has caused fast and enormous progress and provided huge knowledge concerning supramolecular aspects, especially in the presence of numerous, weak intermolecular interactions in solids. In other words, crystallography and quantum theory are closer than ever before. The so-called quantum crystallography, involving experimental and computational studies, concerns treatment of the X-ray scattering experiment in a way compatible with the quantum mechanics requirements, in relation to the wave function and the topological analysis of electron density distributions. Surprisingly, the term quantum crystallography was introduced by Huang, Massa and Karle [272], referring to the works commenced in the 1960s, connected with first attempts to obtain wave functions from X-ray scattering experiments [273]. However, Tsirelson [274] gave a general definition: "*quantum crystallography is a research area exploiting the fact that parameters of quantum-mechanically valid electronic model of a crystal can be derived from the accurately measured set of X-ray coherent diffraction structure factors."* This area of research is very important in the context of biochemistry. It enables a comparative examination of very subtle but significant differences in energies of the intermolecular interaction in an accurate manner in biological systems.

It is worth mentioning that the popular and powerful topological methodology, deciphering intercontacts nature, in the context of electron densities obtained from both experiment and theory, is *Quantum Theory of Atoms in Molecules* (QTAIM), known also as *Theory of Atoms-in-Molecules* (AIM). Bader together with co-workers constructed and developed (since the early 1960s) this theory "*of great elegance, beauty, generality, and power"* (quoting Matta) [271] derived from quantum mechanics a physical insight into the chemistry. It is based on partitioning of the molecular space in nonoverlapping atomic regions with well-defined boundaries. Bader`s method is a *model free* theory of chemistry. It relies

on quantum Dirac observables such as the electron densities [271]. The electron density has a 3-D topography described by local maxima at the positions of the nuclei. It is worth mentioning that it is one of the most reliable tools of modern studies of electron density (or electron distribution) of molecules or charge density. The electron density distribution is related to the interaction between two nuclei (the chemical bonding). QTAIM allows the determination of all atomic properties and their change. This theory, based on the total density, establishes a frame to classify and understand the chemical structure, its stability, to gain an insight into the nature of covalent and non-covalent (H-bonding, weak van der Waals, π···π, X-H···π, cation···π interactions, halogen bonds) interactions with a particular emphasis on the information concerning the type and strength (as function of charge density) of interatomic interactions. It is noteworthy that QTAIM provided new dimensions to the H-bonding idea. Due to the relative simplicity and low computational cost, QTAIM is extensively used in various fields, *i.e.* in drug-design, prediction and interpretation of *i.e.* physicochemical and biological properties of the amino acids molecules (or the peptides bioactivity), to automate the search for pharmacophores and/or (re)active sites in a series of related molecules or large biological systems at an atomic resolution [275 - 297].

Moreover, the Noncovalent Interaction (NCI) approach [298] identifying inter- and intramolecular intercontacts, is based on the electron density and its derivatives. NCIs is associated with localization of the peaks appearing in the regions of reduced density gradient (RDG), which approaches zero at low electronic densities between atoms. These areas are described as stabilizing, when the density is concentrated, or destabilizing, when the electron density is decreased. NCI calculation is very fast. It serves a function of support for the topological study of non-covalent intercontacts in molecular systems. It is also an index of their visualization in the 3-D space [299]. From the biochemistry point of view, NCI has a great potential value. NCI is also a valuable descriptor in experimental electron densities (from SC-XRD data) [19]. To conclude, NCI is a perfect tool for the studies of supramolecular assemblies and a better understanding of their properties in the biomolecules.

Also, the Interacting Quantum Atoms (IQA) approach based on the quantum theory of atoms in molecules is worthy of note [300]. It is an interpretation tool related to real space energy decomposition [301]. The IQA quantitatively characterizes the energetics of topological interactions and also their internal energy, by a combination of kinetic and potential energies. These energies consist of intra-atomic or an interatomic contribution. So, IQA systematically and precisely evaluates the strength and physics of interactions.

Phenomenon of Cooperativity of Intermolecular Interactions

The name cooperativity was used for the first time in 1957 [302] in order to characterize hydrogen bond interactions between water molecules in aqueous solutions. Generally, it means an increase in the interactions strength in the supramolecular aggregate (crystal structure), when two or more intercontacts are formed among the neighbouring species [19, 303, 304]. The preliminary theoretical study on the H-bond cooperativity revealed that the chain configuration of three water molecules linked together *via* the H-bonds sequence has a stronger effect than two waters [305]. Nevertheless, the cooperativity is a more complex phenomenon with various facets connected with the interdependent changes of various parameters of the analysed system, especially in characterization of different physico-chemical properties. Cooperativity plays an important role in biological systems, due to the prevalence of supramolecular interactions in impressive combinations and crystal engineering due to the necessity of a precise control of weak interactions co-operation. An understanding of cooperativity has relevance in molecular recognition and self-assembly events from the bio-systems and synthetic supramolecular bio-inspired materials point of view. Different classifications of cooperativity are described by Grabowski [19]. It concerns also other, not so common, intercontacts (for example halogen bonds), which are intensively investigated due to their great importance in biological processes. The cooperativity effect can be defined more precisely by quantification based on the interaction energy parameters, using the QTAIM approach. Coopertivity can be defined as nonadditivity in the context of the nonadditive energy of the supramolecular aggregate. So, in other words, it is the difference between the total interaction energy and the sum of the pairwise terms. Interestingly, cooperativity may be referred to the existence of various supramolecular synthons as well. As an example, cooperativity comes from both the existence of the H-bond chain and H-bond ring synthons created by different types and strengths of the intercontacts involved in the synthons [19, 306].

Gavezzotii` Theory vs. Energy Framework

A proper quantification of energetics is crucial to provide a close insight into the nature of intermolecular interactions to establish their hierarchy and role in the stabilization of the supramolecular architecture. This kind of study allows the synthesis of various biologically active peptides. It is also helpful in predicting polymorphs and melting and solubility behavior in understanding the self-assembly during the nucleation and crystal growth processes. Besides, it is a precondition for understanding supramolecular aggregation in condensed phases, and further for predicting and controling structural, thermodynamic, physical properties of supramolecular materials. It is worth emphasizing that the paradigm

of whole-of-molecule viewing, not only at selected intermolecular interactions, is very important for unravelling the nature of the intermolecular interactions in the context of crystal design [188, 307]. A quite popular Gavezzotti's PIXEL method of quantification of intercontacts energies, a partly parametric computational scheme, relies on the consideration and evaluation of pairwise intermolecular interaction energies, partitioned *via* the following physical components: Coulombic, polarization, dispersion (London) and repulsion (Pauli) [308]. The Coulombic terms, important in biological systems, are calculated by Coulomb's law, the polarization terms - in the linear dipole approximation, with the inwards electric field working on local polarizabilities and forming a dipole with its connected dipole separation energy, dispersion terms - in London's opposite sixth power approximation, including ionization potentials and polarizabilities, while repulsion is a modulated function of wavefunction overlap. This CLP (Coulomb-London-Pauli) methodology provides a useful tool for indicating the interaction types [198, 199, 309, 310]. This relatively simple and fast so-called *pixel*-by-*pixel* integration method partitions the electron density into discrete elements *pixels* (an elementary cell in a 2-D picture), which are then used for calculation. The first step of evaluation of the intercontacts energy starts with the *ab initio* calculation of electron densities of an interacting pair (*i.e.* molecules, atoms). The PIXEL method is preferred because it is computationally less demanding and is generally comparable with high level quantum mechanical calculations simultaneously. It suggests the presence of key structural motifs stabilizing the supramolecular architecture. The analysis, despite its empirical nature, is useful for synthetic chemists in drawing up a plan, while making derivatives of similar molecules [310]. In literature survey, we found only a few papers concerning the PIXEL-semi-empirical approach in terms of amino acids (in atypical conditions) [311, 312]. Lately, new computational and graphical tools for precise characterization of the intermolecular interaction energies, including electrostatic and dispersion components, and their use in visualization of the supramolecular architecture as *energy frameworks* have been elaborated, giving a qualitative graphical representation of the 3D-topology of the predominant intercontacts [257, 313 - 316]. Generally, this concept is inspired by Gavezzotti's PIXEL method [198, 199, 308, 317 - 319]. The energy models were implemented in CrystalExplorer17 program [228, 320]. As an example, the intercontacts energies in the short peptide showing polymorphism were investigated using two methodologies: Gavezzotti [198, 199] implemented in the PIXELC and *CrystalExplorer* energy frameworks [320], respectively. The visualizations of molecular clusters corresponding to the presented interactions and synthons, including energy values in polymorphic forms of modified amino acid and calculated with the use of PIXEL are shown in Fig. (**17**).

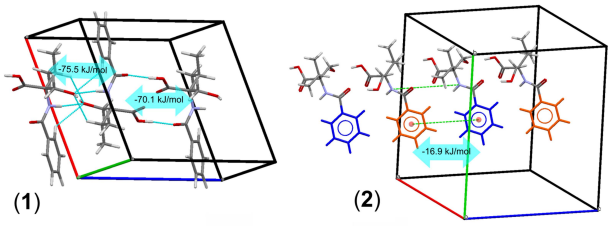


Fig. (17). Examples of interaction motifs and energies in short peptides calculated by PIXEL.

The energy-frameworks, shown in Fig. (**18**), visualize the interactions in a crystal as a network of tubes connecting centres of a molecule to each other. The tube width is proportional to the energy of interactions. The analysis of topology of frameworks enables a quick comparison of interactions that are responsible for crystal packing. The calculations using PIXELC and *CrystalExplorer* programs are in good agreement, revealing far-reaching differences between polymorphs. The detailed discussion of the results will be described in the specialized publication.

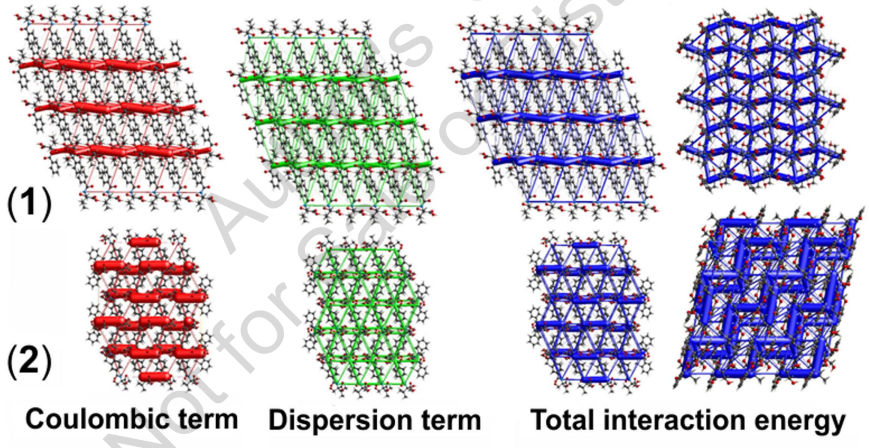


Fig. (18). Energy-framework diagrams for E_{ele}, E_{dis} and E_{tot} for a cluster of molecules in two polymorphs of modified isoleucine (from our studies).

To sum up experimental and theoretical advances over the last years have initiated a breakthrough in the investigations of the weak supramolecular interactions and a subtle interplay between them. The resulting knowledge, provided by modern techniques, is important for the studies of biological supramolecular systems. Understanding supramolecular architectures of bio-inspired molecules in combination with biological systems enables interpretation of biological phenomena in detail. The unique features of synthetic supramolecular systems

allow the creation of structures matching the demands to approach the biochemical problems within reach.

CONCLUSIONS AND PERSPECTIVES

The current chapter is a brief overview presenting the active development of the supramolecular science over one hundred years with a special emphasis put on the latest significant progress keeping the short peptides in focus. The growing interest in these small biomolecules in the last few years is due to their almost unlimited applications. As important of representative bio-inspired moieties, amino acids are the most appealing, programmable building blocks for supramolecular self-assembly. This work highlights frontiers in molecular and supramolecular synthesis of short peptides. We present the modern methods of synthesis of acyclic and cyclic short peptides providing also the most perspective ways of efficient synthesis. Furthermore, we show various ways of investigation of a subtle interplay of strong hydrogen bonds and weak intermolecular intercontacts in short peptides and modified amino acids supramolecular architectures, crucial especially for smart and novel biofunctional supramolecular materials, or an understanding of complex biological systems *via* modern complementary experimental and theoretical methods such as supramolecular X-ray and neutron crystallography, Hirshfeld surface, PIXEL, CrystalExplorer or QTAIM with NCI. Quantum crystallography unlocks the secrets of molecular crystals (supramolecules) concerning nuances of the subtle supramolecular effects. We suggest and examine the role of the supramolecular synthon concept as a new and promising approach to the studies of short peptide-based supramolecules. In the light of the significant advancements taking place in the last few years, synthon methodology has become fascinating and most versatile than ever before, suggesting infinite possibilities awaiting for further exploitating in the nearest future. A holistic view on the supramolecular structure landscape, allowing a profound exploration including proper recognition and precise consideration of the intermolecular interactions, and an understanding of the function of particular synthons on the subsequent levels of supramolecular architectures, is relevant to a better understanding of complex biological systems. Henceforth, an attentive observation of the weakest biosupramolecular interactions, serving a function of virtuosos of *life* symphony, is possible. We hope that this review will be a valuable source of information for both postgraduate students and scientists from other fields, and short peptide-based supramolecular chemistry will continue to advance.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm no conflict of interest, financial or otherwise to declare for this publication.

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In this work some fragments and pictures coming from our recent research were used. All results will be precisely discussed in the successive publications in the specialist international journals.

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CHAPTER 3

The Use of Nanocatalysts in the Synthesis of Heterocycles: A Contemporary Approach

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Abstract: Nanocatalysis is the latest development in the field of synthetic chemistry that has revolutionized the process of chemical transformation. The nanocatalysts offer several advantages as compared to conventional catalyst such as simple and inexpensive methods of preparation, high surface to volume ratio, large number of active sites, high selectivity, enhanced stability, easy recovery and recyclability. In recent years, the nanomaterials have been widely used in the synthesis of heterocylic moieties. The chapter aims to highlight the role of diverse nanocatalysts in the synthesis of various five-, six- and seven- membered heterocycles. An update on catalytic efficiencies of various nanocatalyts such as magnetic nanocatalysts, nanomixed metal oxides, core-shell nanocatalysts, nano-supported catalysts and graphene-based nanocatalysts for the synthesis of heterocycles have been incorporated in this chapter.

Keywords: Core-shell nanocatalysts, Easy recovery, Enhanced stability, Five, Graphene-based nanocatalysts, Heterocyclic moieties, High selectivity, Inexpensive, Magnetic nanocatalysts nanocatalysis, Nanomaterials, Nano mixed metal oxides, Nano-supported catalysts, Recyclability, Six and seven membered heterocycles.

INTRODUCTION

The recent developments in the field of synthetic chemistry have laid emphasis on innovative methods that are environmentally benign. The focus is now on new techniques and methodologies that avoid the use of toxic and hazardous solvents, reagents, long time procedures, harsh reaction conditions, use of non-recyclable and non-selective catalysts, *etc.* Each and every aspect of synthetic procedures is

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dealt with, keeping in mind the significance of sustainable and green methods of synthesis.

The heterocyclic moieties serve as important scaffolds that find applications in pharmaceutical and chemical industries. Consequently, preparation of heterocyclic compounds is one of the most sought after fields of organic synthesis. Numerous methods have been used to synthesize heterocyclic motifs such as using expensive catalyst, solvents, high temperature and multistep reactions. But these methods have several disadvantages as already mentioned above. To resolve these problems, the chemists have devised some new green methods. Amongst one such method is the use of nanocatalysts.

Catalysis is the most efficient process in chemistry that provides sustainable and cost effective methods to transform raw materials into valuable chemicals [1]. A number of homogeneous and heterogeneous catalysts have been used to catalyze a multitude of chemical transformations. However, these catalysts have their limitations such as homogeneous catalysts being in the same phase as reactants are difficult to separate [2] and in case of heterogeneous catalysts, the reaction rate gets restricted due to their low surface area [3]. Therefore, the use of nanomaterials as catalysts can be of great help to overcome the problems of separation, recovery, recyclability and enhanced surface area. Nanoparticle is a microscopic object with at least one dimension less than 100 nm [4]. The extremely small size of nanoparticles leads to large surface area to volume ratio [5] with a high number of exposed active sites; thus, enhancing the contact area with the reactants. The nanomaterials can replace conventional materials to serve as active and stable heterogeneous catalysts [6] or as solid supports for various catalytic groups [7].

Nanocatalysts, owing to a number of advantageous characteristics Fig. (**1**) such as low preparation cost, ease of preparation, excellent activity, great selectivity, high stability, efficient recovery and good recyclability [8] have turned out to be superior to conventional catalysts. Further, the high selectivity of nanoparticles lead to reaction that proceeds through minimization of by-products as impurities and as a result, reducing adverse environmental impact. Hence, nanocatalysis can be considered as an integral part of green science [9]. In the last few years, nanoparticles have been reported to be promising material as heterogeneous catalysts for organic transformations that mainly include oxidation reaction [10], reduction reaction [11], coupling reactions [12, 13] and other reactions related to the synthesis of heterocycles [14, 15]. Here, the role of nanocatalysts in the synthesis of various heterocyclic compounds has been explored.

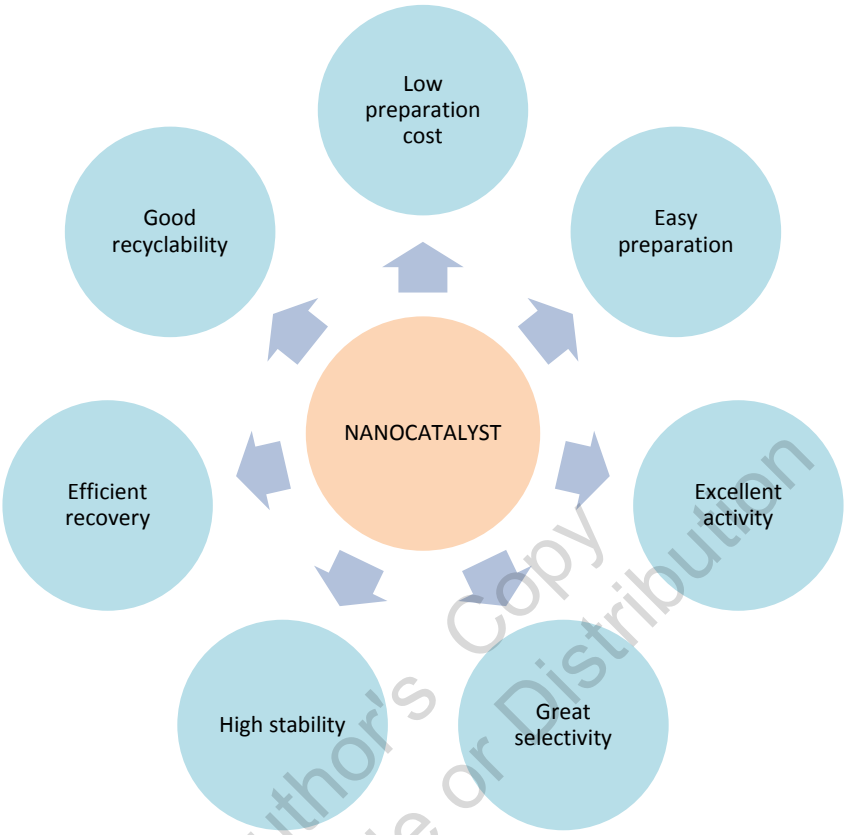


Fig. (1). Advantages of a Nanocatalyst.

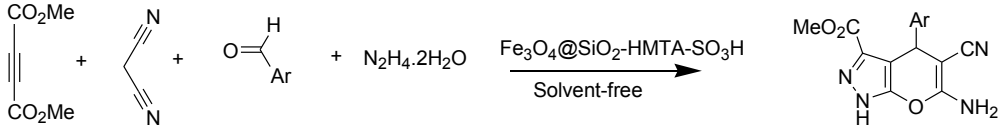
APPLICATIONS OF NANOMATERIALS IN THE SYNTHESIS OF HETROCYCLIC COMPOUNDS

In the following sections, the syntheses of five-, six- and seven- membered heterocycles has been discussed in the presence of different nanocatalysts.

Five Membered Heterocycles-

Functionalized Magnetic Nanoparticles

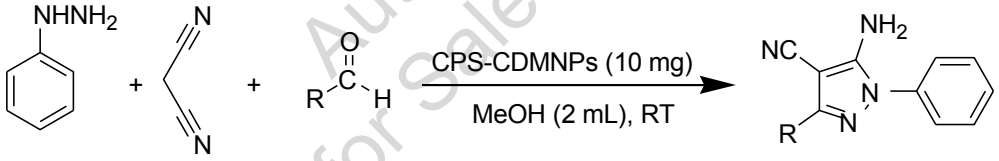
Synthesis of pyranopyrazole derivatives has been reported in the presence of hexamethylenetetramine-functionalized magnetic nanoparticles (average size 60-150 nm) under solvent free condition (Scheme **1**). Ghorbani-Vaghei and Izadkhah [16] synthesized a novel nanocatalyst by surface modification of silica coated magnetic nanoparticles (MNPs) with hexamethylenetetramine followed by its sulphonation and used it to prepare pyranopyrazole derivatives.



Scheme 1. Synthesis of pyranopyrazoles catalyzed by Fe_3O_4@SiO_2-HMTA-SO_3H NPs.

Various methods were reported earlier for the synthesis of pyranopyrazoles but the current method that made use of surface functionalized MNPs is the best method investigated so far. Easy separation of catalyst using an external magnet, recyclability, good yields and short reaction time are some advantages of using magnetic nanoparticles. Moreover it was found that catalytic efficiency of functionalized MNPs was greater than that of Fe_3O_4 and SiO_2@Fe_3O_4 nanoparticles. This proves that functionalization of nanoparticles results in favourable changes in surface morphology of the nanoparticles; thus, improving its efficiency considerably.

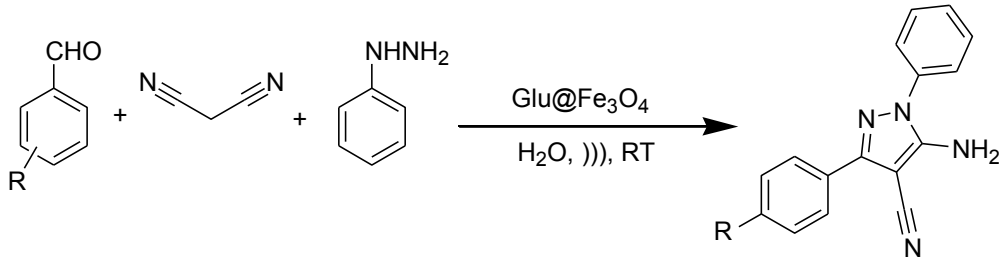
Arora and Rajput [17] synthesized magnetic nanoparticles (MNPs) functionalized with cyclodextrin and Kolliphor P 188 (CDMNPs) and capsaicin (CPS-CDMNPs) and used them to catalyze one pot multicomponent click synthesis of pyrazoles (Scheme **2**). The CDMNPs were prepared by co-precipitation and ultrasonication method and capsaicin was later deposited on CDMNPs by wet impregnation method.



Scheme 2. One pot synthesis of the tetrasubstituted pyrazole derivatives using CPS-CDMNPs.

The low toxicity and biocompatibility of cyclodextrins combined with high surface area, selectivity and recyclability of magnetic nanoparticles make these nanoparticles efficient catalyst. Further, as capsaicin, a vallanoid known for its pharmacological activity, being hydrophobic diffuses to the hydrophobic cavity of cyclodextrin and the hydrophilic surface of cyclodextrin gets linked to magnetic particles. The Kolliphor P 188 provides structural stability to the nanocatalyst as it binds to both, hydrophilic and hydrophobic sites of cyclodextrin. It was reported that the homogeneous nature of cyclodextrin and capsaicin has synergistic effect on the catalytic activity of MNPs. About 91% yield has been reported for reaction catalysed by CPS-CDMNPs (average size 45- 60 nm). The catalyst can be reused up to five cycles without loss of its catalytic activity.

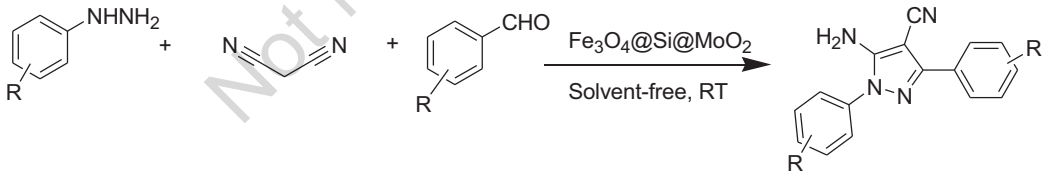
Esfandiary *et al.* [18] synthesized a green, glucose coated superparamagnetic catalyst to prepare pyrazole derivatives from aldehydes, malononitrile and phenylhydrazine (Scheme **3**) in excellent yields.



Scheme 3. Synthesis of pyrazole derivatives in presence of Glu.@Fe_3O_4.

Glucose being a biocompatible material, having polyhydroxy structure displays great catalytic activity. The magnetic nanoparticles with properties like large surface area, recyclability serve as good catalysts. The workers have reported that the surface of magnetic nanoparticles was coated with glucose which reduced the aggregation and enhanced the efficiency of catalyst due to presence of hydroxyl groups of glucose.

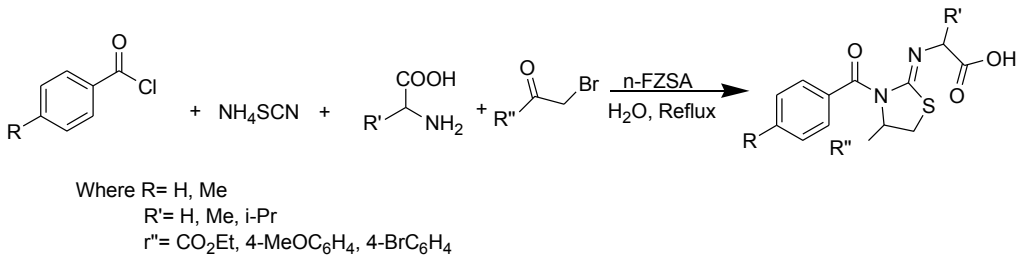
Rakhtshah *et al.* [19] reported an efficient synthesis of 5-aminopyrazole-4-carbonitrile derivatives catalyzed by dioxomolybdenum complex supported on functionalized Fe_3O_4 magnetite nanoparticles containing Schiff base ligand. The average size of the nanoparticles was found to be 10 nm. The Fe_3O_4@Si@MoO_2 complex was prepared and used as catalyst to carry out a multicomponent reaction of aryl aldehyde, malononitrile and phenylhydrazine taken in equimolar ratio to produce pyrazole (Scheme **4**).



Scheme 4. Fe_3O_4@Si@MoO_2 catalyzed synthesis of 5-aminopyrazole-4-carbonitrile derivatives.

The Schiff base coordinates with metals and stabilizes them and improves their catalytic activity [20]. The magnetic nanoparticles have numerous advantages such as large surface to volume ratio and ease of separation but have a tendency of agglomeration also [21]. To overcome this problem a silica coating is used as it exhibits great chemical affinity and thermal stability.

The synthesis of thiazole derivatives by the reaction (Scheme **5**) of acyl chloride with ammonium thiocyanate, amino acids and alkyl bromides in the presence of magnetic nano zirconia–sulfuric acid catalyst (n-FZSA) was investigated by Nakhaei [22].

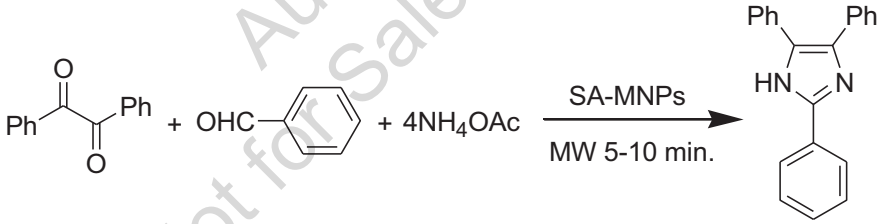


Where R= H, Me
R'= H, Me, i-Pr
r"= CO_2Et, 4-$MeOC_6H_4$, 4-BrC_6H_4

Scheme 5. *n*-FZSA catalyzed synthesis of thiazole derivatives.

The presence of sulphonic acid (-SO_3H) group in the catalyst acts as a Brönsted acid and promotes the reaction by enhancing the electrophilic character of the electrophiles in the reaction.

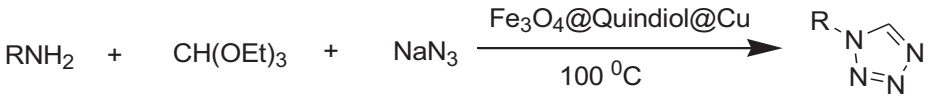
Safari and Zarnegar [23] reported a microwave assisted procedure for the three-component one-step synthesis of 2,4,5-trisubstituted imidazoles by condensation reaction of 1, 2-diketones, aromatic aldehydes, and ammonium acetate using sulphamic acid functionalized magnetic Fe_3O_4 nanoparticles (SA-MNPs, average size of 20 nm) under solvent free condition (Scheme **6**).



Scheme 6. SA–MNPs catalyzed one pot synthesis of 2, 4, 5-trisubstituted imidazoles.

The immobilization of sulphamic acid on magnetic nanoparticles results in a highly efficient recyclable solid acid catalyst. The SA-MNPs catalyzed reaction completes in short time and with minimal waste generation.

A novel nanocatalyst Fe_3O_4@5,10-dihydropyrido[2,3-b]quinoxaline-7,8-diol copper complex was prepared *via* electro-organic synthesis by Habibi *et al.* [24]. The copper complex of Fe_3O_4 MNPs functionalized with quindiol was used for the synthesis of 1-substituted 1*H*-tetrazoles (Scheme **7**).

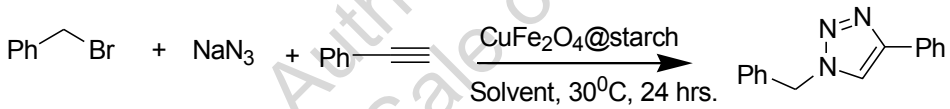


Scheme 7. Synthesis of tetrazoles using Fe_3O_4@Quindiol@Cu nanocatalyst.

The catalyst displays high catalytic performance for synthesis of tetrazoles under solvent free condition and results in excellent yields. It was proposed that the Lewis acidity of the catalyst catalyzes dissociation of triethyl orthoformate resulting in the formation of the intermediate to affect the cyclization producing the desired product.

Spinel Ferrite Nanoparticles

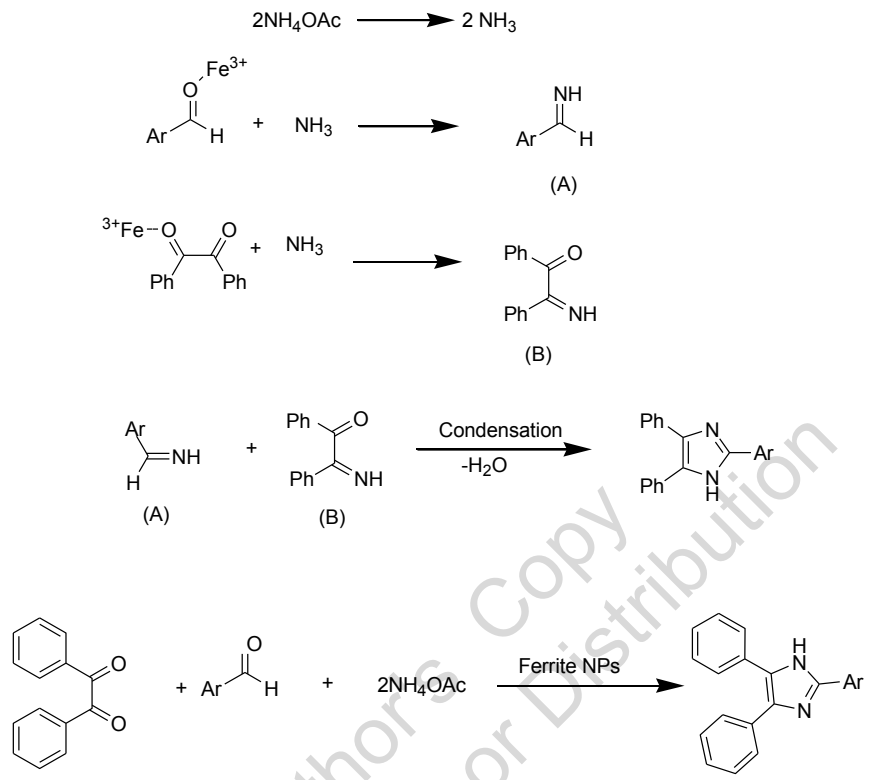
Spinels are a class of minerals that have a cubic closed packed lattice with a general formula AB_2X_4 where X is an anion and A and B are cations occupying tetrahedral and octahedral voids in the lattice. A highly efficient and water dispersible heterogeneous nanocatalyst having spinel structure was reported by Bonyasi *et al.* [25] for the synthesis of 1,2,3-triazoles. The catalyst could be reused up to eleven times. The starch supported copper ferrite nanoparticles were used to catalyze a multicomponent reaction of 1,4-disubstituted 1,2,3-triazoles (Scheme **8**) in high yields.



Scheme 8. Multicomponent synthesis of triazoles using $CuFe_3O_4$@starch catalyst.

The copper ferrite nanoparticles have received huge attention by chemists due to its numerous advantages such as high dispersion, environmental benignity, high reactivity, low cost and effortless separation by an external magnet. Starch is a biodegradable polymer with a complex structure that provides a good support to various materials. Thus, copper ferrite nanoparticles supported on starch (with an average particle size of 20 nm) afforded desired products in good yield.

Sanasi *et al.* [26] synthesized 2,4,5-trisubstituted imidazoles using magnetic recyclable spinel nano copper and cobalt ferrites by the condensation of benzil, aromatic aldehyde and ammonium acetate Scheme (**9**) under benign conditions in high yield.



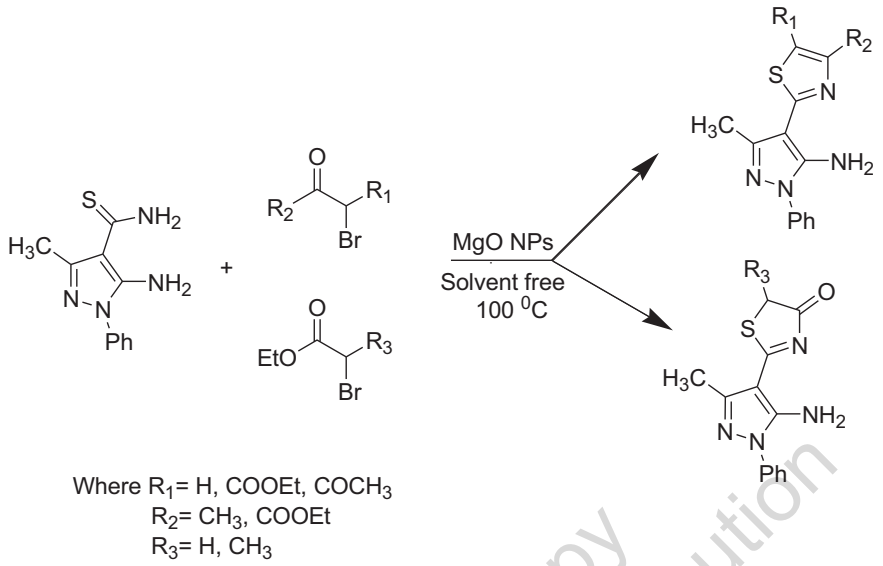
Scheme 9. One-pot synthesis of 2,4,5,-trisubstituted imidazoles using ferrite NPs.

In this reaction, ferrite nanoparticles (Fe^{3+}) activate the aldehyde and 1,2-diketone to afford imine intermediate (A) and 1,2- diketone imine (B) respectively. The imine intermediate (A) undergoes condensation with the carbonyl carbon of 1,2-diketone imine (B) followed by dehydration to afford the imidazole. Thus, the reaction proceeds smoothly in the presence of recyclable nanocatalyst that results in high yield of desired product.

Magnesium Oxide Nanoparticles

A modified Hantzsch method to synthesize some novel 4-thiazolylpyrazoles in the presence of MgO nanoparticles as catalyst under solvent free condition (Scheme **10**) was studied by Beyzaei *et al*. [27].

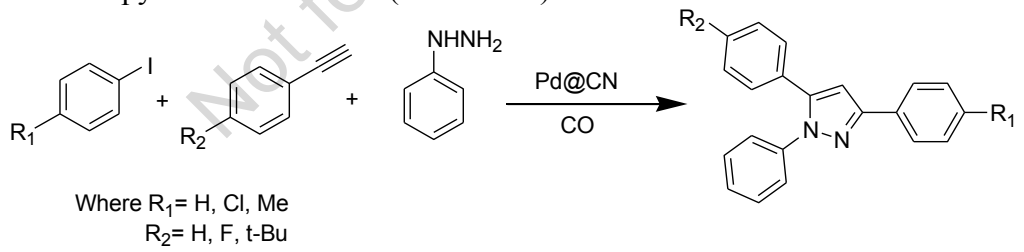
The acidic and basic characters of MgO nanoparticles (average size 23.7-25.7 nm) are quite useful in catalyzing different stages of the reaction, thus, enhancing the rate and yield of the reaction.



Scheme 10. MgO NPs catalyzed synthesis of 4-thiazolylpyrazoles.

Palladium and Platinum Nanoparticles

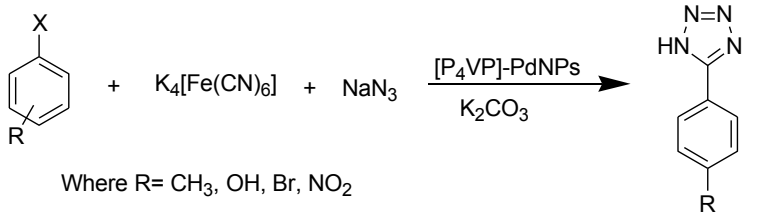
A palladium nanoparticles supported on porous N-doped carbon (Pd@CN) catalyst was prepared by Li *et al.* [28]. They demonstrated that Pd@CN showed high selectivity towards domino carbonylative synthesis of pyrazoles. It was proposed that Pd@CN has widely dispersed Pd nanoparticles on porous N-doped carbon material as stable support. These nanoparticles initiate carbonylative coupling between iodobenzenes and aryl alkynes to yield α,β-alkynyl ketone followed by the addition and cyclic condensation with phenylhydrazine to give the desired pyrazole derivatives (Scheme **11**).



Scheme 11. One pot four-component synthesis of pyrazoles using Pd NPs.

Thus, Pd@CN behaves as a highly sustainable, stable and efficient catalyst. Palladium nanoparticles are well known for catalyzing C-C coupling reactions. Also, polymeric materials have been recently widely used in organic

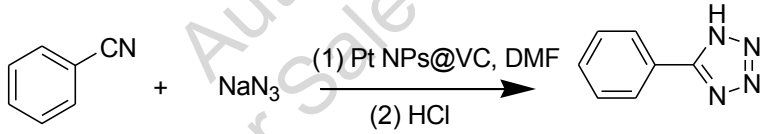
transformations [29]. The polymers serve as matrix for stabilizing nanoparticles. Considering these facts, Abadi and Zarchi [30] reported a one-pot synthesis of 5-substituted 1-*H* tetrazoles. A reaction was carried out with aryl halides, $K_4[Fe(CN)_6]$ and sodium azide in the presence of cross-linked poly(4-vinylpyridine)-stabilized Pd(0) nanoparticles, [P_4-VP]-PdNPs (Scheme **12**).



Scheme 12. Synthesis of 5-substituted 1*H*-tetrazoles using [P_4-VP]-Pd NPs.

The product was obtained in high yield under mild conditions and the catalyst was recyclable with a little decrease in activity.

Baskaya *et al.* [31] synthesized structurally diverse 5-substituated-1*H*-tetrazoles using vulcan carbon decorated platinum nanoparticles (Pt NPs@VC). The nanocatalyst effectively catalyzed cylcoaddition of sodium azide with different nitriles to afford the corresponding tetrazole derivatives Scheme (**13**) in good to excellent yields due to high monodispersity, low crystalline particle size and high percentage contents of Pt (0) in the prepared Pt NPs@VC.

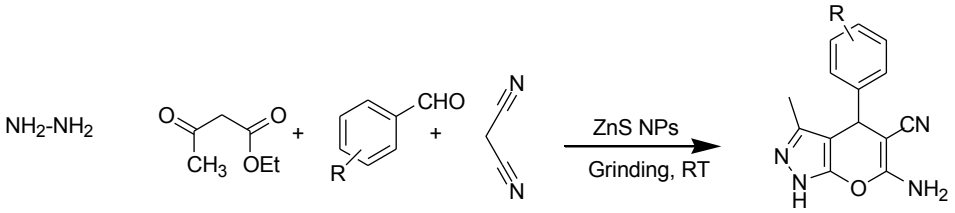


Scheme 13. Pt NPS@VC catalyzed synthesis of 5-substituted 1*H*-tetrazoles.

Thus, Pt NPs@VC acts as an exceptionally stable, reusable and efficient heterogeneous nanocatalyst.

Zinc Oxide/Sulphide Nanoparticles

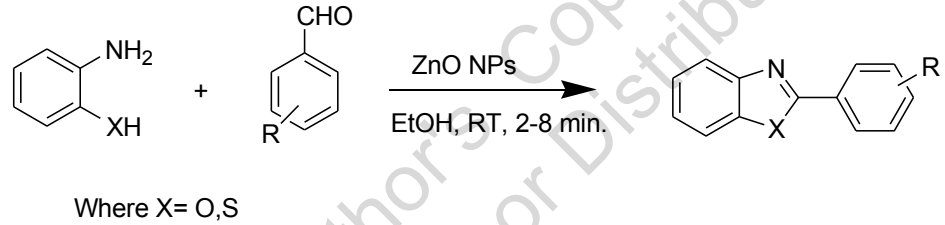
Synthesis 4*H*-pyrano[2,3-*c*] pyrazoles in the presence of ZnS nanoparticles as a heterogeneous catalyst at the room temperature by grinding was studied by Borhade and Uphade [32]. The ZnS nanoparticles of size 20 nm were prepared by hydrothermal method and served as a remarkably effective catalyst for multicomponent reaction comprising benzaldehyde, hydrazine hydrate, ethyl acetoacetate and malononitrile to generate 4*H*-pyrano[2,3-*c*]pyrazoles (Scheme **14**).



Scheme 14. Synthesis of 4*H*-pyrano[2,3-*c*] pyrazoles using ZnS NPs.

The advantages of reusable ZnS nanocatalyst are that it results in simple work-up, excellent yield and solvent-free reaction at room temperature.

A synthetic method to prepare 2-aryl-1,3-benzothiazoles and 1,3-benzoxazoles using ZnO nanoparticles as an efficient heterogeneous catalyst has been demonstrated by Banerjee *et al.* [33]. The reaction was carried out between 2-aminothiophenol/ 2-aminophenol and aryl aldehyde under mild conditions at room temperature (Scheme **15**).



Scheme 15. Synthesis of 1,3-benzothiazoles/1,3-benzoxazoles using ZnO NPs

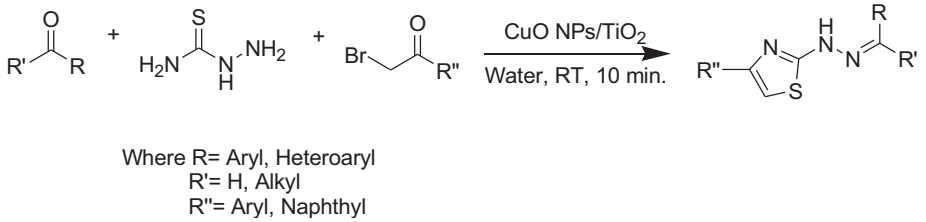
The reaction completed within few minutes along with excellent yield of product. It was proposed that the amino group of 2-aminothiophenol/2-aminophenol gets activated by ZnO nanoparticles due to affinity of nitrogen to the soft Zn^{2+}. Further the electrophilic character of carbonyl carbon of aryl aldehyde increases resulting in condensation reaction. Thus, the ZnO NPs exhibits high chemo-selectivity and is an easily recoverable, reusable, inexpensive, and readily accessible catalyst.

Copper Based Nanoparticles Dispersed on Diverse Supports

The catalytic activity of copper oxide nanoparticles dispersed on titanium dioxide in water for one-pot synthesis of a library of hydrazinyl-thiazoles *via* a three-component reaction Scheme (**16**) of various aldehydes/ketones with thiosemicarbazide and different phenacyl bromides has been investigated by Reddy *et al.* [34].

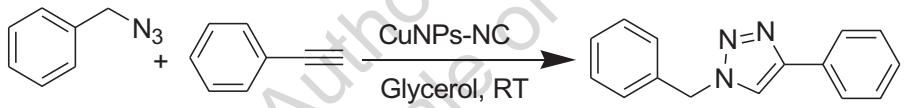
High stability, non-toxicity and large surface area of TiO_2 along with hydrophilic nature of its surface allow dispersion of TiO_2 in water and hence, make it an

excellent support for metal oxide nanoparticles. Further high versatility, reusability and environmental friendly nature of copper oxide nanoparticles result in greater stability and activity of CuO NPs/TiO_2 nanocatalyst. The reaction was accomplished in short time with high yields at room temperature.



Scheme 16. CuONPs/TiO_2 catalyzed multi-component synthesis of hydrazinyl-thiazoles.

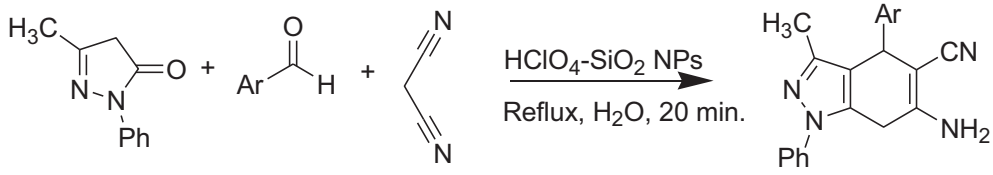
Cellulose is a biopolymer and nanocrystalline cellulose exhibits several unique characteristics such as high crystalline order, well defined size and morphology, a controlled surface chemistry, and superior mechanical strength [35]. Chetia *et al.* [36] prepared copper nanoparticles supported on nanocellulose (CuNPs/NC) with an average size of 6-7 nm and used it as catalyst to synthesize 1,2,3-triazoles by carrying out azide-alkyne cylcoaddition reaction in glycerol (Scheme **17**). It was found that CuNPs/NC acts as a highly efficient and recyclable heterogeneous catalyst with high surface to volume ratio.



Scheme 17. Synthesis of 1,4-disubstituted 1,2,3-triazoles using Cu NPs/NC.

Silica and Silica Supported Nanoparticles

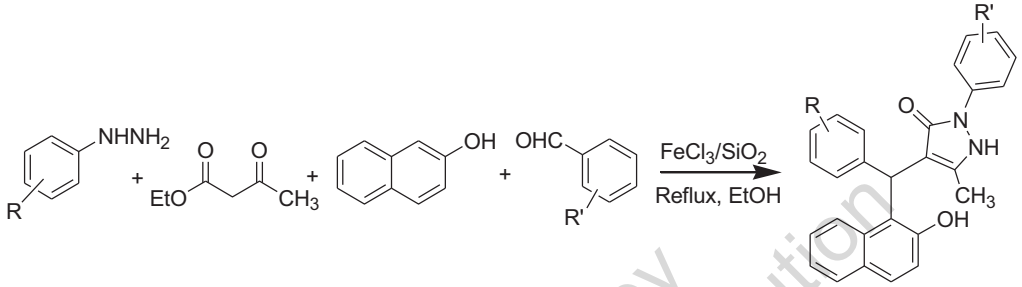
Sadgehi *et al.* [37] reported synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles in excellent yields via a one pot reaction between aromatic aldehydes, malononitrile and 3-methyl-1-phenyl-2-pyrazoline-5-one catalysed by silica supported perchloric acid nanoparticles ($HClO_4$–SiO_2 nanoparticles) in water under reflux (Scheme **18**).



Scheme 18. Synthesis of 1,4-dihydropyrano[2,3-c]pyrazoles using $HClO_4$–SiO_2 NPs.

The advantage of this method was that the reaction completed in short time with high yield of products and the catalyst could be reused several times without any significant loss of its activity.

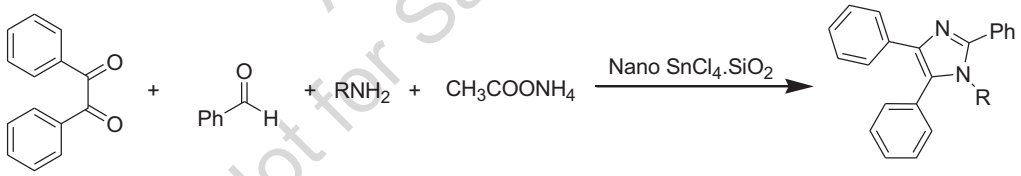
Afkhami and Safaei-Ghomi [38] carried out a one pot four component reaction of phenylhydrazines, ethyl acetoacetate, aldehydes and β-naphthol in the presence of $FeCl_3/SiO_2$ nanoparticles Scheme (**19**) to produce pyrazolones.



Scheme 19. Synthesis of 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones by $FeCl_3/SiO_2$ NPs.

The $FeCl_3/SiO_2$ nanoparticles serve as a highly cost effective, efficient heterogeneous catalyst to produce 2-aryl-5-methyl-2,3-dihydro-1*H*-3-pyrazolones in good to excellent yields and short time under eco-friendly reaction conditions.

Use of nano-$SnCl_4.SiO_2$ as nanocatalyst Scheme (**20**) for the preparation of 2,4,5-trisubstituted imidazoles via three-component reaction of benzil, aldehydes and ammonium acetate was reported by Mirjalili *et al*. [39]



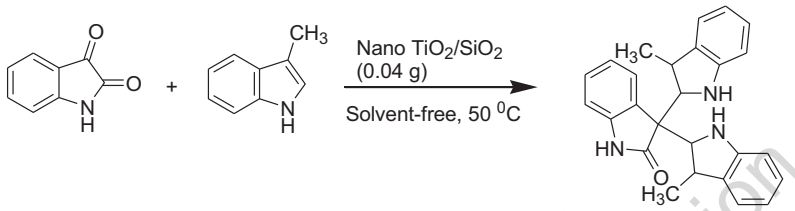
Scheme 20. Synthesis of 2,4,5-trisubstituted imidazoles using $SnCl_4.SiO_2$ nanocatalyst.

Nano-$SnCl_4.SiO_2$ is an extremely efficient Lewis acid solid catalyst with several advantages such as short reaction time, high yield, recyclability of catalyst, solvent free-condition and easy work-up.

A similar multi-component reaction was reported by Alinezhad *et al.* [40] in presence of nanosilica-supported imidazolium ionic liquid as a catalyst under solvent-free conditions. They reported that immobilization of acidic ionic liquids (ILs) on solid support combines the benefits of ILs and heterogeneous catalysts,

such as high design ability, ease of handling and separation, and recyclability. Thus, they made an attempt to prepare nano-silica-bonded (1-imidazolium) propyl chloride and used it to catalyze the synthesis of imidazoles.

Nano TiO_2 supported on SiO_2 (Nano TiO_2/SiO_2) was used by Haghighi and Nikoofar [41] as a solid Lewis acid catalyst for the condensation reaction of indoles with isatins to prepare the corresponding bis(indolyl)oxindoles under solvent-free conditions (Scheme **21**).

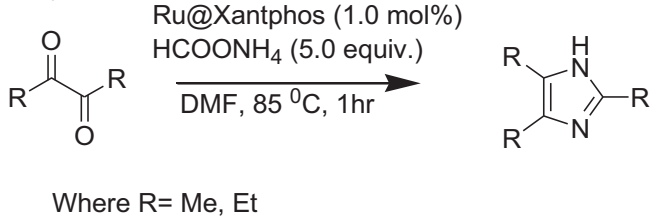


Scheme 21. Synthesis of oxindole derivatives catalyzed by nano TiO_2/SiO_2.

The nano TiO_2/SiO_2 catalyst activates the 3-position carbonyl group of isatin allowing nucleophilic addition of indole to generate 3,3-bis(indolyl)oxindole. It was observed that there was a considerable increase in the yield when nano TiO_2/SiO_2 was used in place of SiO_2 catalyst. This is because loading nano TiO_2 on silica expands its surface area and improves its catalytic efficiency. Further the catalyst was found to be reusable.

Ruthenium Nanoparticles

Ruthenium nanoparticles are well known as catalysts for carrying out chemical reactions such as arene hydrogenations [42], hydrogenation of carbonyl compounds [43], *etc.* Ganji and Leeuwen [44] reported a new method of synthesis of imidazoles catalyzed by phosphine supported ruthenium nanoparticles. The catalyst efficiently catalyzes transfer hydrogenation of α-diketones to synthesize imidazoles (Scheme (**22**).

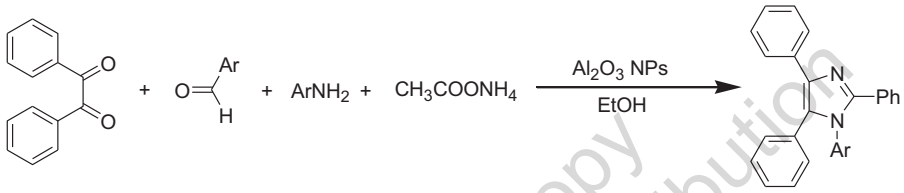


Scheme 22. Synthesis of imidazoles using Ru NPs.

The ruthenium nanoparticle bearing stabilizing ligands such as phosphine is easy to prepare, low cost catalyst that can be removed by adsorption and can be reused. Ruthenium nanoparticles supported with different phosphines such as dbdocphos, dppp, DPEphos, and Xantphos were studied by the workers. Out of these best results were obtained with Xantphos.

Alumina Nanoparticles

A multicomponent reaction of benzil, aryl aldehyde and aryl amines in the presence of γ- alumina nanoparticles to afford the highly substituted 1,2,4,5-tetraaryl imidazoles (Scheme **23**) has been reported by Reddy *et al.* [45].

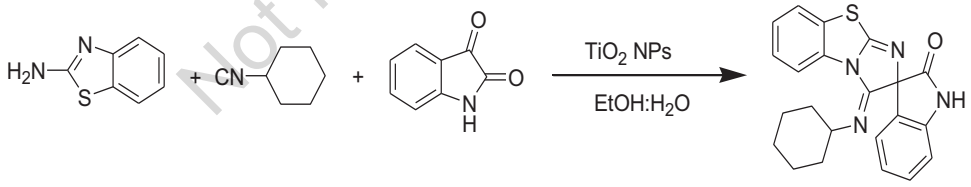


Scheme 23. Tetraaryl substituted imidazoles using Al_2O_3 NPs.

The γ-alumina nanoparticles display effective catalytic activity due to its Lewis acid character and small size of particles, resulting in good yields of the product.

Titanium Dioxide Nanoparticles

An environmentally benign isocyanide-based domino reaction for the synthesis of structurally diverse spiroheterocycles spiroannulated with imidazothiazole (Scheme **24**) involving three-component reaction of 2-aminobenzothiazole, cyclohexylisocyanides and isatin catalyzed by recyclable nanocrytalline TiO_2 was reported by Kumar *et al.* [46].

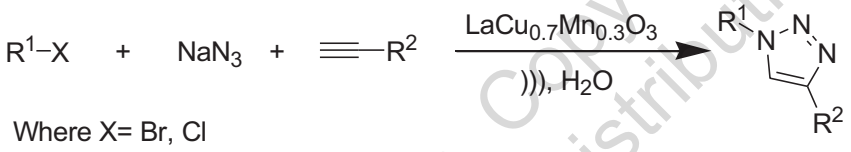


Scheme 24. Synthesis of spiroannulated imidazobenzothiazole using TiO_2 NPs.

The method offers a simple, efficient and atom economic reaction for the synthesis of spiroheterocycles using TiO_2 NPs as catalyst which could be easily separated by simple filtration.

Quarternary Mixed Metal Oxides Nanoparticles

Safa and Mousazadeh [47] carried out synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition of benzyl halides, terminal alkynes, and sodium azide over $LaCu_xMn_{1-x}O_3$ perovskite oxides under ultrasonic irradiation in aqueous medium (Scheme **25**). The perovskites are mixed metal oxides that have received huge attention lately because of their low cost, appropriate redox properties, high thermal stability and catalytic activity. The perovskites have a general formula of ABO_3, where A is lanthanide or alkaline earth metal ion and B is a transition-metal ion. The partial substitution of cations in both places; A and B provided multicomponent oxides with unusual valence in cation sites that usually increased catalytic activity of the perovskite systems [48, 49]. Therefore, they attempted to prepare $LaCu_xMn_{1-x}O_3$ nanoparticles and used it to catalyze the synthesis of substituted triazoles in an environmentally benign and efficient manner.



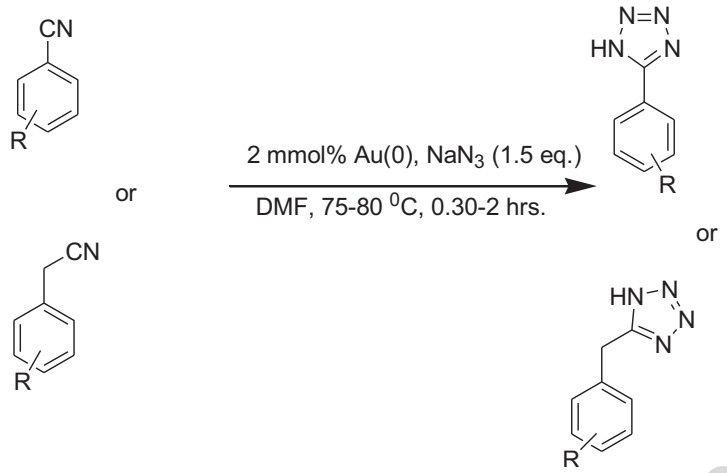
Scheme 25. Synthesis of 2,4,5-triaryl substituted imidazoles using $Ni_{0.5}Zn_{0.5}Fe_2O_4$ NPs.

Khazaei *et al.* [50] prepared $Ni_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticles and used it to carry out one pot synthesis of 2,4,5-triaryl substituted imidazoles. Condensation reaction occurred among ammonium acetate and aromatic aldehydes with various benzil compounds similar to as reported in earlier schemes. The $Ni_{0.5}Zn_{0.5}Fe_2O_4$ nanoparticles act as recyclable heterogeneous catalyst and result in straightforward reaction by activating the carbonyl carbon of aldehyde and benzyl towards condensation reaction followed by dehydration to produce imidazole.

Gold Nanoparticles

Gold being a soft Lewis acid is considered as a suitable catalyst to carry out organic synthesis. Considering this well-known fact, Kumar *et al.* [51] investigated the application of gold nanoparticles for the synthesis of 5-substituted 1*H*-tetrazoles (Scheme **26**).

Due to the acidic character and enhanced surface area of gold NPs, the nitrile functional group coordinates with Au(0) state, which activates nitrile moiety for the (3 + 2) cycloaddition reaction with sodium azide. The product was obtained in substantial yield.

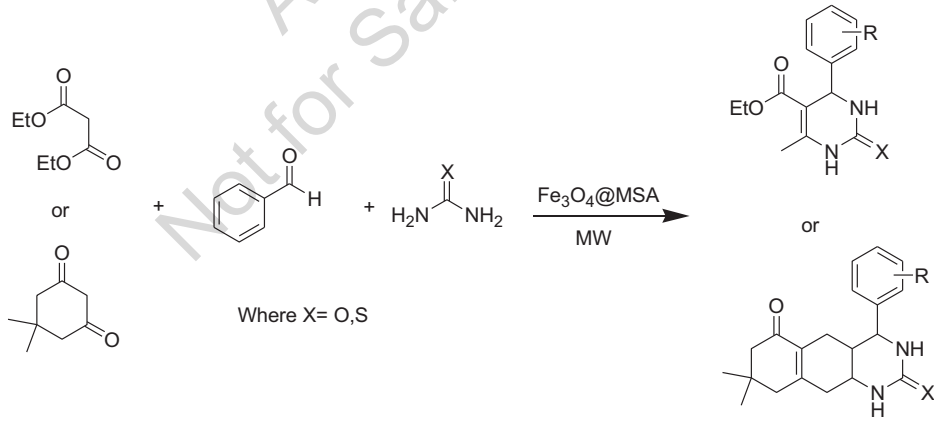


Scheme 26. Au NPs-catalyzed synthesis of 5-substituted 1*H*-tetrazoles.

Six Membered Heterocycles

Magnetic Nanoparticles

A novel nano Fe_3O_4@meglumine sulfonic acid (Fe_3O_4@MSA) catalyst was designed by Moradi and Tadayon [52]. The catalyst was used to carry out microwave assisted one pot green synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/ thiones (Scheme **27**).

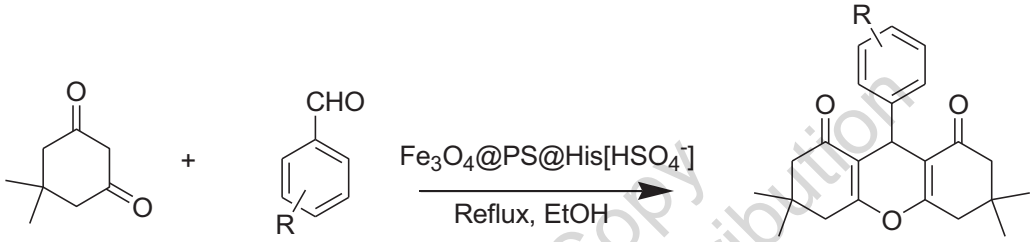


Scheme 27. Synthesis of 3,4-dihydropyrimidinones/ thiones using nano Fe_3O_4@MSA.

To overcome the issue of catalyst separation, the highly efficient homogeneous catalyst (meglumine sulfate) was converted to heterogeneous one (Fe_3O_4@MSA)

that displayed good reusability and high yield of product in short time. The catalyst activates the carbonyl carbon of aldehyde towards nucleophilic addition of urea or thiourea to form an imine intermediate that absorbs a proton from solid acid catalyst and then reacts with ethyl acetoacetate to produce an open chain intermediate, which undergoes condensation and dehydration to afford the product.

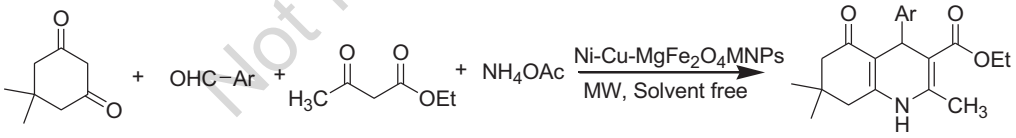
A one-pot synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives Scheme (**28**) in the presence of Fe_3O_4@Propylsilane@Histidine[HSO_4^-] (Fe_3O_4@PS@ His[HSO_4^-]) magnetic nanocatalyst was investigated by Mousavifar *et al.* [53].



Scheme 28. Synthesis of xanthene derivatives using Fe_3O_4@PS@His[HSO_4^-] MNPs.

The Fe_3O_4@PS@ His[HSO_4^-] acts as an environmentally friendly catalyst and shows better efficiency than the conventional homogeneous and heterogeneous catalysts. It is recyclable up to four times without noticeable loss of activity.

Fardood *et al.* [54] synthesized Ni–Cu–Mg ferrite nanoparticles (average size of 19 nm) from tragacanth gum and used it as an efficient and non-toxic catalyst for the synthesis of polyhydroquinoline derivatives *via* multi-component reactions under microwave irradiation (Scheme **29**).

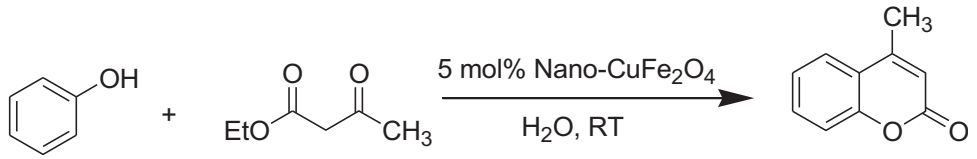


Scheme 29. Synthesis of polyhydroquinoline derivatives using Ni–Cu–$MgFe_2O_4$ MNPs.

The use of natural gum is an economically viable and eco-friendly green method of nanoparticle synthesis. The use of economically convenient catalyst results in good yields in short time in absence of any solvent and can be reused six times without considerable decrease in catalytic activity.

Spinel Nanoparticles

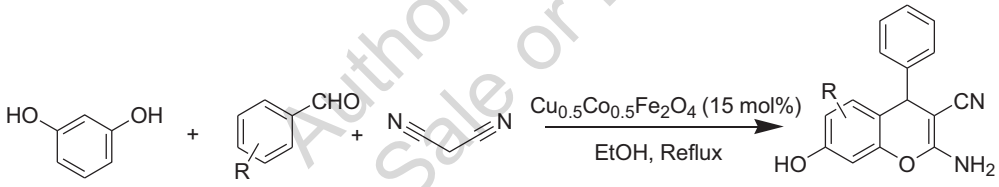
Pechmann reaction for the synthesis coumarins was carried out in the presence of magnetically separable and reusable copper ferrite ($CuFe_2O_4$) nanoparticles in water Scheme (**30**) by Baghbanian and Farhang [55].



Scheme 30. Synthesis of substituted coumarins using $CuFe_2O_4$ NPs.

The advantage of using magnetic copper ferrite nanoparticles over conventional catalyst is that the magnetic separation as compared to filtration or centrifugation methods prevents loss of catalyst and enhances reusability apart from, reducing the cost of catalyst.

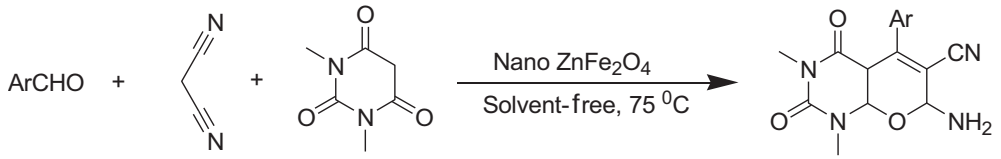
Fareghi-Alamdari *et al.* [56] prepared $Cu_{0.5}Co_{0.5}Fe_2O_4$ magnetic nanoparticles (average size in the range of 40 to 50 nm) and employed them for the synthesis of 2-amino-4*H*-chromene derivatives (Scheme **31**).



Scheme 31. Synthesis of 2-amino-4*H*-chromenes using $Cu_{0.5}Co_{0.5}Fe_2O_4$ nanocatalyst.

High catalytic activity of $Cu_{0.5}Co_{0.5}Fe_2O_4$ magnetic nanoparticles was ascribed to the presence of both, copper and cobalt in its skeleton, which provided a synergistic effect with enhanced activity in comparison to single metal containing spinels. The catalyst was separated by magnetic decantation and reused six times without any depletion in its catalytic efficiency.

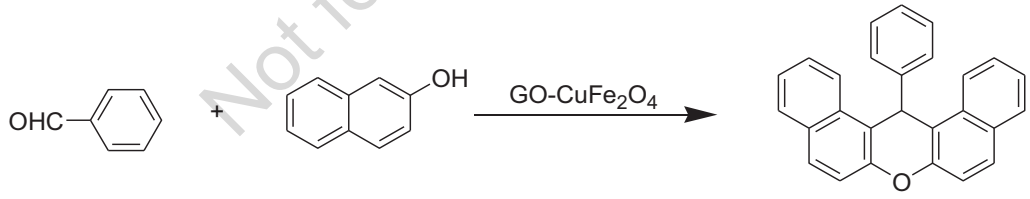
The synthesis of pyrano[2,3-d]pyrimidines by the one-pot three component condensation reaction of 1,3-dimethylbarbituric acid and malononitrile with aromatic aldehydes in the presence of $ZnFe_2O_4$ nanoparticles under solvent-free conditions (Scheme **32**) was reported by by Khazaei *et al.* [57].



Scheme 32. Synthesis of pyrano[2,3-d]pyrimidines using Zn Fe_2O_4 NPs.

They propounded that modification of iron oxide by zinc oxide produces spinel zinc ferrite ($ZnFe_2O_4$) with acidic and basic characters. The basic part of the nanomaterial catalyzes Knoevenagel condensation whereas other steps such as addition, cyclization and dehydration are catalyzed by acidic part of the catalyst. It was also proposed that Lewis acidic behavior of $ZnFe_2O_4$ is derived by the Fe^{3+} of Fe_2O_3 and its basic character is related to the O^{2-} of ZnO. The catalyst is efficient and reusable leading to clean reaction with abundant yield of product.

Kumar *et al.* [58] developed a facile and eco-friendly method for the synthesis of xanthenes by graphene oxide based nanocomposite (GO-$CuFe_2O_4$). Due to several exclusive properties of copper ferrite such as environmental compatibility, moisture insensitive, high dispersion, high reactivity, low cost and easy separation by an external magnet, it is widely used as a catalyst to promote and accelerate various reactions. Further, graphene oxide based nanocatalyst displays dual character both of homogeneous (high surface area and easily accessible) as well as heterogeneous (stable and easy to handle) catalyst systems [59]. Thus, taking into account these factors, a catalytic system was designed comprising of highly porous GO-$CuFe_2O_4$ nanocomposite. The synthesis of xanthene derivatives was carried out *via* one-pot two-component reaction of 2-naphthol with various aryl aldehydes under solventless condition in the presence of GO-$CuFe_2O_4$ nanocomposite (Scheme **33**).

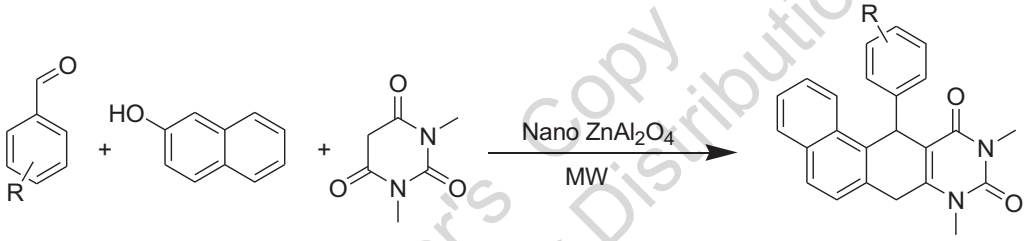


Scheme 33. One pot synthesis of 14-aryl-14*H*-dibenzo-xanthenes using GO-$CuFe_2O_4$ nanocomposite.

The reaction was straightforward, occurred in short period of time and resulted in good yields. Furthermore, the catalyst was recycled and reused up to five cycles. The catalyst enhances the rate of reaction by providing more adsorption and reaction sites during the reaction. It was suggested that the increased catalytic activity of GO-$CuFe_2O_4$ composite is due to the synergistic effect between the

$CuFe_2O_4$ and the graphene oxide sheets. The presence of GO in the composite is responsible for greater adsorption of reactant molecules onto the active sites of the GO-$CuFe_2O_4$ through π-π stacking and electrostatic interactions, resulting in high conversion rate.

A rapid and facile one-pot synthesis of naphthopyranopyrimidines by the three-component condensation reaction of aldehydes, *β*-naphthol, and 1,3-dimethylbarbituric acid using $ZnAl_2O_4$ nanoparticles (average particle size 21-25 nm) under microwave irradiation Scheme (**34**) has been reported by Mohaqeq *et al.* [60]. The synthetic method involves $ZnAl_2O_4$ nanoparticles promoted condensation of *β*-naphthol with aldehyde to produce *α*, *β*-unsaturated carbonyl compound. Then, Michael addition of 1,3-dimethylbarbituric acid to the *α*, *β*-unsaturated carbonyl compound, followed by elimination of water molecule gave the naphthopyranopyrimidine product.

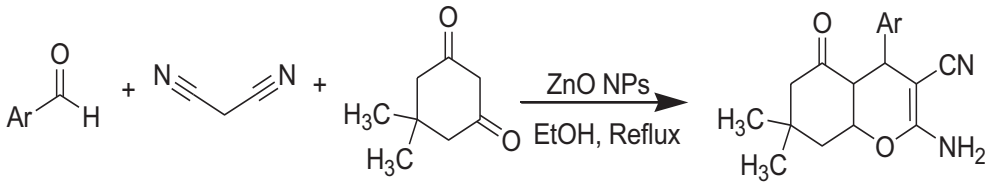


Scheme 34. Synthesis of naphthopyranopyrimidines using nano-$ZnAl_2O_4$.

Excellent yield was obtained and the catalyst could be reused several times without any visible loss in activity.

Zinc Oxide Nanoparticles

A mild procedure for the synthesis of 2-amino-4*H*-chromene derivatives in the presence of nanosized ZnO has been investigated by Zavar [61]. A multi-component reaction involving aldehyde, malononitrile and dimedone was carried out in the presence of ZnO nanoparticles (Scheme **35**).

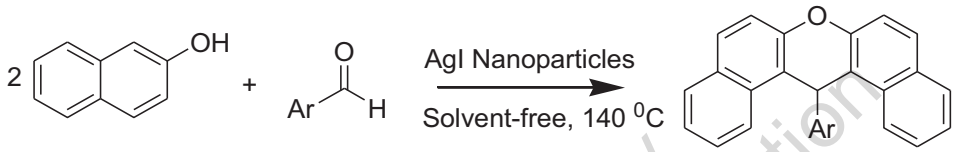


Scheme 35. Synthesis of 2-amino-4*H*-chromenes derivatives using ZnO NPs.

ZnO was used as a green and non-toxic catalyst; ZnO NPs activate the carbonyl carbons of aldehyde and dimedone towards nucleophilic addition by malononitrile and thus, facilitates cyclization to generate chromene derivatives.

Silver Lodide Nanoparticles

Safaei-Ghomi and Ghasemzadeh [62] synthesized recoverable heterogeneous AgI (particle size 48 nm) nanoparticles to catalyze the preparation of 14-aryl-1-H-dibenzo[a,j]xanthenes *via* multi-component reaction of aldehydes and β-naphthol under solvent-free conditions (Scheme **36**).

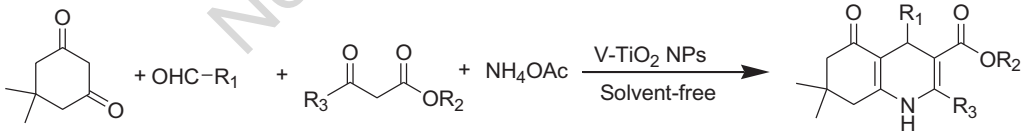


Scheme 36. One-pot synthesis of xanthene derivatives in the presence of AgI NPs.

The efficiency of AgI nanoparticles as catalyst was tested by carrying out the cyclization reaction in presence of diverse catalysts such as AgBr, AgI, CuCl, NiO and CaO. Of all these catalysts, the activity of AgI nanoparticles was found to be the best suited for this condensation reaction. It was suggested that high surface area of AgI nanoparticles as compared to that of bulk AgI is the main reason for the catalytic efficiency of AgI nanoparticles.

Titanium Dioxide Nanoparticles

The synthesis of polyhydroquinoline derivatives was carried out in the presence of mesoporous vanadium ion doped titania nanoparticles (V–TiO_2) Scheme (**37**) by Rao *et al.* [63] *via* Hantzsch reaction of ary laldehyde, β-ketoester, dimedone and ammonium acetate under solvent-free conditions as multi-component synthesis.

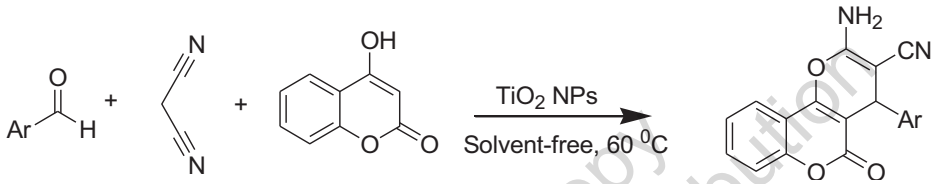


Scheme 37. Polyhydroquinoline derivativesusing V-TiO_2 NPs.

The inclusion of vanadium transition metal into TiO_2 lattice causes increase in the number of Lewis acid sites, Bronsted acid sites and other defects that in turn, enhance the reactivity of metal oxides as a heterogeneous catalyst. It was proposed that the interaction between arylaldehyde with the acidic sites of V–TiO_2

NPs catalyst surface generated the more electrophilic carbon center towards the nucleophilic attack of β-ketoester followed by dimedone to give reactive adduct intermediate. The resulting intermediate undergoes an intramolecular cyclization in the presence of NH_4OAc generating the corresponding desired polyhydroquinoline after dehydration. The use of non-volatile and non-corrosive V–TiO_2 NPs offered several advantages such as easy handling and separation, high yields of products, solvent-free condition and reusability.

Abdolmohammadi [64] performed one-pot three component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin to produce corresponding dihydropyrano[*c*]chromenes in the presence of TiO_2 nanoparticles (Scheme **38**).

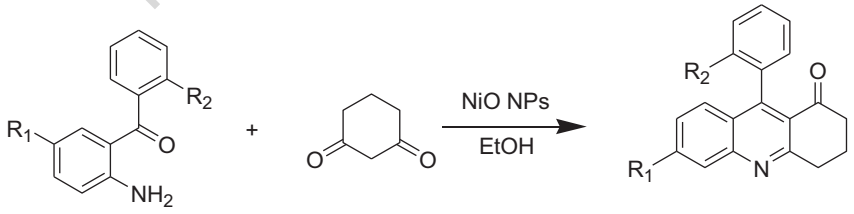


Scheme 38. Synthesis of dihydropyrano[*c*]chromene derivatives using TiO_2 NPs.

The surface area and morphology of TiO_2 nanoparticles promote the reaction in an effective manner resulting in high yields. It was proposed that TiO_2 NPs are coordinated to the oxygen of the aromatic aldehyde and activated it for nucleophilic attack by malononitrile to produce an alkene *via* a Knoevenagel condensation. TiO_2 NPs further facilitate the Michael addition between alkene and 4-hydroxycoumarin to generate the Michael adduct. The cyclization of the latter gives the product.

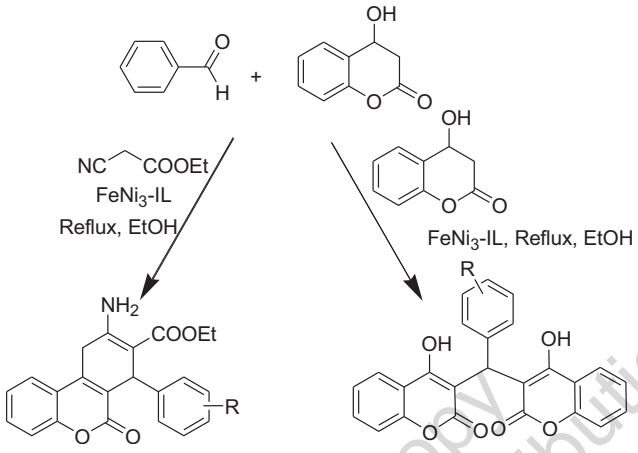
Nickel Based Nanoparticles

Multi-substituted quinolines have been synthesized from 2-aminoaryl ketones and β-ketoesters/ketones *via* Friedlander hetero-annulation reaction Scheme (**39**) in the presence of reusable, acidic nickel oxide nanoparticles [65].



Scheme 39. Synthesis of multi-substituted quinolines using NiO NPs.

A facile and efficient synthesis of dihydropyrano[3,2-*c*]chromenes and biscoumarins Scheme (**40**) was carried out by Safaei-Ghomi *et al.* [66] in the presence of ionic liquids (ILs) supported on nano-$FeNi_3$ as catalyst.



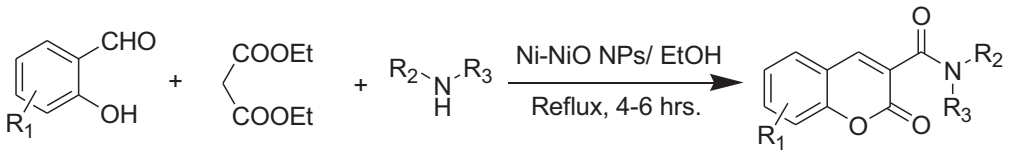
Scheme 40. Synthesis of dihydropyrano[3,2-*c*]chromene and biscoumarin derivatives using $FeNi_3$-IL.

The catalytic system displays several environmental friendly characterstics like high efficiency, easy recovery and reusability without any major loss in performance. Here, ethyl cyanoacetate and aromatic aldehydes undergo aldol condensation in the presence of nano-$FeNi_3$-ILs followed by Michael addition with 4-hydroxycoumarin in the presence of nano-$FeNi_3$-ILs to form dihydropyrano[3,2-*c*]chromene. In the same manner, syntheses of biscoumarins occur.

This method is simple with easy isolation of product and complies with the green protocol.

The use of inexpensive Ni-NiO nanoparticles as catalyst has received considerable attention recently due to their benign nature [67] and interesting catalytic activities [68]. Mallik *et al.* [69] reported a clean and efficient synthesis of coumarin-3-carbamides *via* three-component reaction of 2-hydroxybenzaldehydes, aliphatic primary/secondary amines and diethyl malonate using Ni-NiO nanoparticles of particle size of 25 nm as catalyst in presence of ethanol (Scheme **41**).

Due to several interesting chemical and thermal properties of Ni-NiO nanoparticles, they used the catalytic system to explore the synthesis of coumarins. The desired products were obtained in satisfactory yields and the catalyst was reused seven times without loss in catalytic performance.

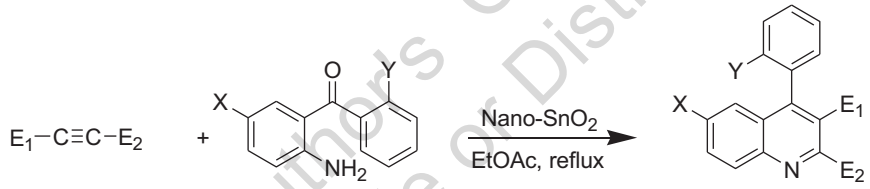


Where R_1= H, Me, OMe
R_2= H or alkyl group
R_3= Alkyl or benzyl group

Scheme 41. Synthesis of coumarin-3-carbamides by use of Ni-NiO NPs.

Tin Oxide Nanoparticles

Nano-SnO_2 displays an excellent surface activity and has been used for the synthesis of quinoline derivatives. Qandalee *et al.* [70] reported two-component reaction of 2-aminobenzophenones with acetylenic mono or diesters to afford quinoline derivatives in high yields using nano-SnO_2 catalyst (Scheme **42**). The nucleophilic amine attacks on the acetylenic ester, which results in the formation of an intermediate on the surface of nano-SnO_2.



Where E_1= COOMe, COOEt, H
E_2= COOMe, COOEt
X= H, Cl
Y= H, F, Cl

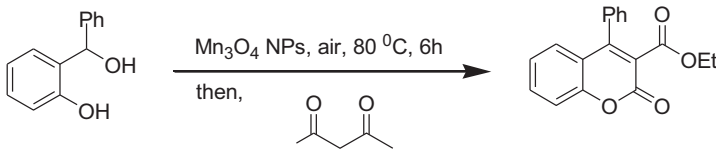
Scheme 42. Nano-SnO_2 catalyzed synthesis of quinoline derivatives.

The nanosized SnO_2 acts as a Lewis acid and increases the electrophilicity of the carbonyl group of 2-aminobenzophenone. This is followed by dehydration leading to the formation of the product.

Manganese Oxide Nanoparticles

A one-pot synthesis of 3,4-disubstituted coumarins from substituted 2-(hydroxymethyl)phenols with β-keto esters catalyzed by Mn_3O_4 nanoparticles Scheme (**43**) was developed by Sun *et al.* [71].

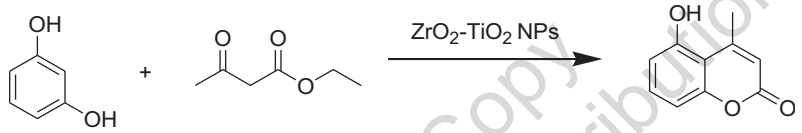
It was found that Mn_3O_4 nanoparticles exhibit several advantages like low catalyst loading, high activity and good recyclability.



Scheme 43. One pot synthesis of 3,4-disubstituted coumarins catalyzed by Mn_3O_4 NPs.

Zirconia Based Nanoparticles

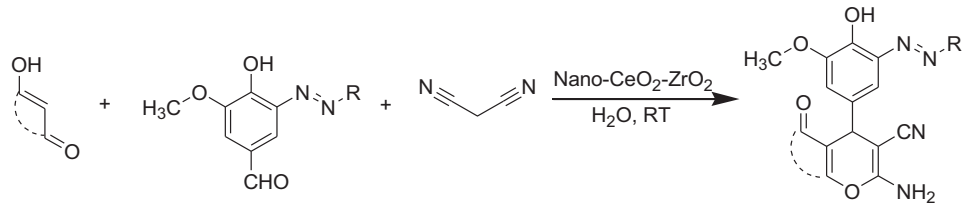
Khan *et al.* [72] carried out the synthesis of coumarins through Pechmann reaction by using zirconia-based heterogeneous catalysts (ZrO_2-TiO_2, ZrO_2-ZnO, and ZrO_2/cellulose) in a solvent-free condition at room temperature (Scheme **44**). It was found that ZrO_2-TiO_2 displayed the best catalytic activity whereas ZrO_2/cellulose was found to be inactive.



Scheme 44. One pot synthesis of coumarins in presence of ZrO_2-TiO_2 NPs catalyst.

Due to acidic and basic nature as well as semiconductor behavior, zirconia (ZrO_2) plays an important role as heterogeneous catalyst [73].

A green protocol for the synthesis of novel phenyldiazenyl−chromene derivatives in the presence of zirconium doped ceria nanoparticles was proposed by Kumar *et al.* [74]. Zirconium doped ceria nanoparticles show some important properties such as the presence of significant number of oxygen defects, high reduction properties, superior acid−base properties, *etc* [75 - 77]. Owing to these properties the nanosized CeO_2−ZrO_2 behaves as a potential catalytic material for organic synthesis. A nano-CeO_2−ZrO_2 catalyzed one-pot reaction of 1,3-dicarbonyl compounds with 4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl) benzaldehydes and malononitrile was carried out in aqueous medium to yield the corresponding 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyl-iazenyl)-chromene-3-carbonitrile derivatives (Scheme **45**).

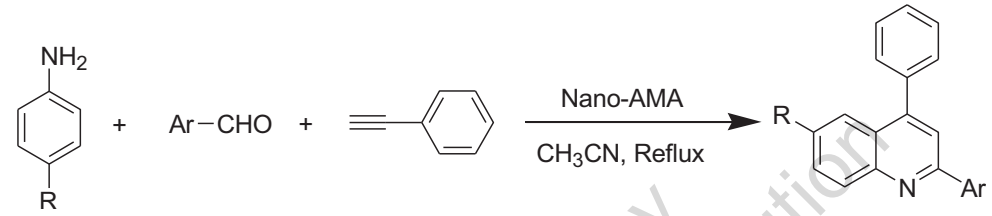


Scheme 45. Synthesis of phenyldiazenyl−chromene derivatives using Nano-CeO_2-ZrO_2.

The products were obtained in excellent yields and the catalyst was reused several times without much loss of its catalytic activity.

Alumina Nanoparticles

An expeditious green synthesis of 2,4-disubstituted quinolines through one-pot three component reaction of aryl amines, aryl aldehydes and phenylacetylene using Al_2O_3 nanoparticles/methanesulfonic acid (nano-AMA) as a novel catalyst Scheme (**46**) has been described by Shargi *et al.* [78].

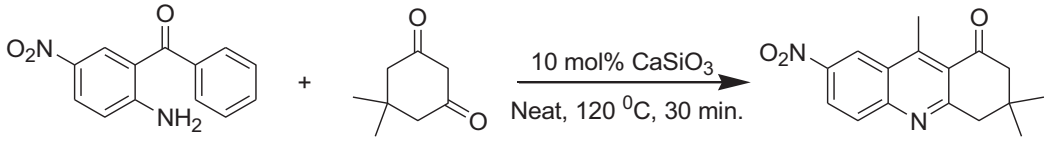


Scheme 46. Synthesis of 2,4-disubstituted quinolines using nano AMA.

The role of nano-AMA as catalyst was elucidated by assuming that in the presence of nano-AMA, aniline reacts with aromatic aldehyde to form an imine. This is followed by the addition of phenylacetylene to imine, which gives a propargylamine intermediate. The cyclization of propargylamine afforded the dihydroquinoline intermediate. Finally, air oxidation of dihydroquinoline intermediate produced an aromatized quinoline. The reaction was clean, resulted in high yields and the catalyst was reused for subsequent reactions. The catalyst was recovered by centrifugation process.

Calcium Silicate Nanoparticles

Palaniraja *et al.* [79] carried out the synthesis of acridines *via* Friedlander reaction Scheme (**47**) in the presence of calcium silicate ($CaSiO_3$) nanoparticles. A novel and economically viable method was developed by them to synthesize wollastonite ($CaSiO_3$) nanoparticles (NP) from tetraethyl orthosilicate and calcium nitrate tetrahydrate in the presence of nitric acid.

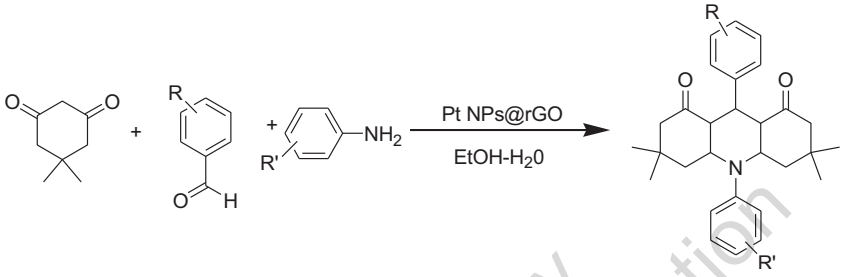


Scheme 47. Synthesis of acridine derivatives using $CaSiO_3$ NPs.

$CaSiO_3$ nanoparticles are non-volatile and display excellent efficiency, recovery and reusability up to five times.

Platinum or Palladium Based Nanoparticles

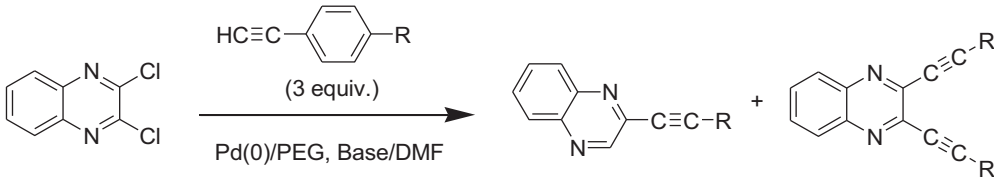
An expeditious method for the synthesis of acridinedione derivatives through one-pot multi component condensation of dimedone, various aromatic aldehydes, and aromatic amines using highly monodisperse platinum nanoparticles supported on reduced graphene oxide (Pt NPs@rGO) as a recyclable heterogeneous catalyst Scheme (**48**) was investigated by Aday *et al.* [80].



Scheme 48. Synthesis of acridinedione derivatives in the presence of Pt NPs@rGO.

Reduced graphene oxide (rGO) has numerous surface functional groups and defects, which act as chemically active sites for use in catalytic reactions and also contains sites for anchoring metal nanoparticles; thus, it has ample potential to serve as supporting material for catalysts for organic reactions. They have used platinum nanoparticles anchored on reduced graphene oxide as a highly efficient and green catalyst. In the reaction, the rGO binds with the oxygen of carbonyl group; this increases the electrophilicity of carbonyl carbon and makes the alpha hydrogen very acidic leading to enolization. This facilitates nucleophilic attack on the aromatic aldehydes resulting in the formation of Knoevenagel product which, then reacts with another C-H active molecule *via* Michael approach to furnish intermediate. Finally, aniline derivatives induce cyclization reaction with the help of Pt NPs@rGO to yield the desired products in satisfactory yields.

Nguyen *et al.* [81] investigated synthesis of monoalkynyl- and dialkynyl-quinoxalines *via* Sonogashira coupling using Pd(0)/PEG nanoparticles as a catalyst (Scheme **49**).

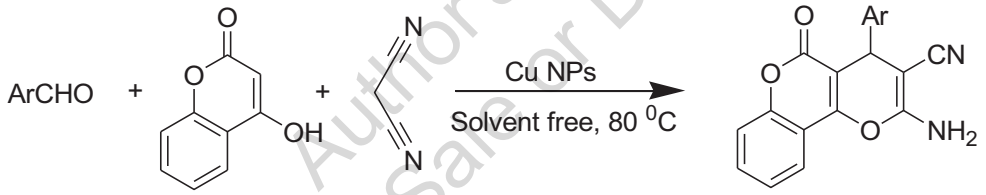


Scheme 49. Synthesis of alkynylquinoxaline derivatives employing Pd(0)/PEG NPs.

It has been reported that palladium nanoparticles have high surface to volume ratio that provides a number of highly active metal uncoordinated sites and thus, Pd NPs have been used to catalyze cross-coupling reactions such as Heck [82, 83], Suzuki [84, 85] or Sonogashira [86, 87] coupling reactions. The Pd(0)/PEG nanoparticles exhibited good catalytic efficiency and resulted in pure products in high yields.

Copper Nanoparticles

Tanna *et al.* [88] reported that copper nanoparticles act as mild and efficient catalyst for organic transformations. A solvent-free green synthesis of 3,4-dihydropyrano[c]chromenes from different aromatic aldehydes, malononitrile and 4-hydroxycoumarin was carried out in presence of reusable copper nanoparticles by stirring at 80 ^{0}C. The study showed that aromatic aldehydes are condensed with malononitrile to afford α-cyanocinnamonitrile derivative in presence of Cu NPs (Scheme **50**). Then, the active methylene group of 4-hydroxycoumarin reacts with electrophilic carbon atom of α-cyanocinnamonitrile giving the Michael adduct, which undergoes cyclization by nucleophilic attack of the carbonyl group on cyano group giving another intermediate. Finally, the expected product is obtained by tautomerisation.



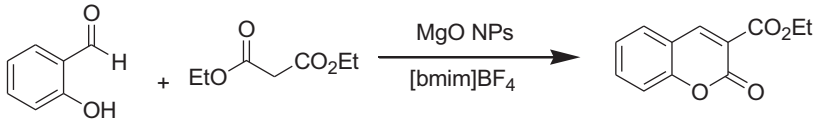
Scheme 50. Solvent-free synthesis of chromene derivatives catalyzed by Cu NPs.

The large surface-to-volume ratio and stability of Cu NPs activate the reactants for the reaction and suppresses the formation of the side products.

Magnesium Oxide Nanoparticles

A facile and expedited synthesis of coumarin derivatives was performed in the presence of MgO nanoparticles of particle size 40 nm in ionic liquid [bmim]BF_4 Scheme (**51**) by Dinparast and Valizadeh [89]. MgO NPs activate the methylene group of diethyl malonate to nucleophilic addition on carbonyl group of salicylaldehyde, which forms an intermediate that undergoes cyclization and dehydration to form coumarins.

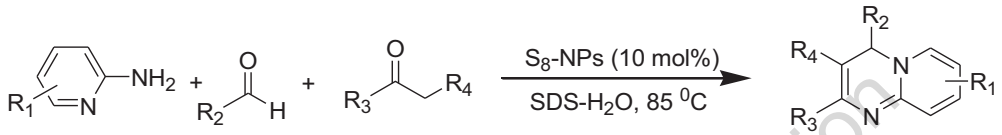
MgO NPs are inexpensive, easily available, and recoverable heterogeneous base catalyst with low toxicity [90].



Scheme 51. MgO NPs catalyzed solvent-free synthesis of coumarins.

Sulphur Nanoparticles

A new and green protocol for the synthesis of substituted 4H-pyrido[1,--a]pyrimidines under admicellar catalysis by sulfur nanoparticles Scheme (**52**) has been described by Sagir *et al*. [91].



Scheme 52. Synthesis of substituted 4*H* pyrido[1,2 a] pyrimidines in presence of S_8-NPs.

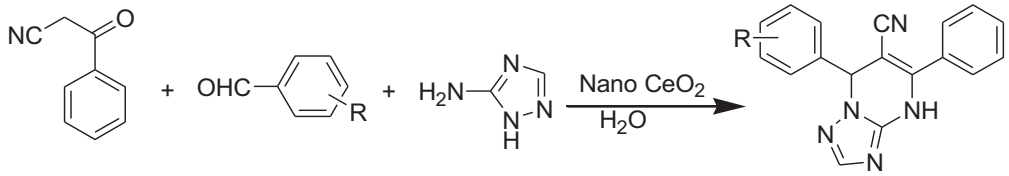
Sulfur-based nanoparticles are non-metallic in nature; this makes their recovery simple and easy. Further sulphur nanoparticles exhibit some important features that include ecofriendly character, economic feasibility, enhanced catalytic efficiency, green method of preparation and reusability that makes them suitable catalyst for several organic reactions. It was speculated that an intermediate is formed *via* S_8-NPs promoted Knoevenagel condensation of aldehyde with ketone. The intermediate then undergoes condensation with 2-aminopyridine to form an imine intermediate in the presence of S_8-NPs. This is followed by intramolecular cyclization to afford the expected product through dehydration catalyzed by S_8-NPs-SDS system (Sodium dodecyl sulphate adsorbed on Sulphur nanoparticles). The catalytic system displayed high efficiency and was recyclable up to the fifth run.

Ceria Nanoparticles

A highly sustainable and efficient protocol for the synthesis of triazolo and tetrazolo[1,5-*a*]pyrimidine derivatives in the presence of ceria nanocatalyst (CeO_2 NPs) has been studied by Lingala *et al.* [92]. The one-pot, multi-component condensation reaction of benzoylacetonitrile, aromatic aldehydes and 5-aminotriazole/5-aminotetrazole proceeds *via* C–C and C–N bond formation giving triazolo/tetrazolo[1,5-*a*]pyrimidine derivatives (Scheme **53**).

The reaction exhibits high selectivity and is accomplished in short time. The CeO_2 NPs bind with the oxygen of carbonyl group of aromatic aldehyde and induces Knoevanagel condensation between aromatic aldehyde and benzoylacetonitrile to generate an intermediate. This intermediate undergoes Michael addition with 5-

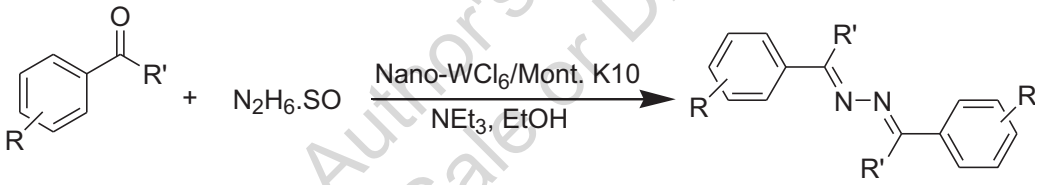
aminotriazole followed by intramolecular cyclization to give the desired product. The benign and recyclable catalyst promotes clean reaction with excellent yields of products.



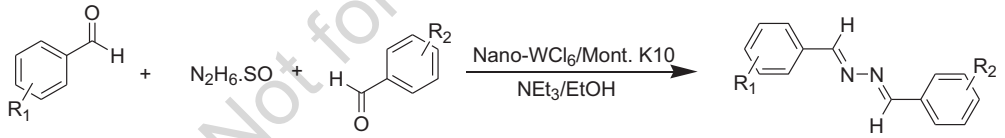
Scheme 53. Synthesis of fused triazolo and tetrazolo pyrimidine derivatives using CeO_2 NPs.

Tungsten Hexachloride Nanoparticles

Safari *et al.* [93] investigated a new methodology to prepare azines using tungsten hexachloride nanoparticles (nano-WCl_6) adsorbed on montmorillonite K10 clay. The nanosized WCl_6/montmorillonite K10 (WCl_6/Mont. K10) was used to promote synthesis of symmetrical and unsymmetrical azines from diverse aldehydes and ketones and hydrazonium sulphate Scheme (**54**), Scheme (**55**) in excellent yields. It was reported that montmorillonite K10 clay acts as a support to enhance the catalytic surface area.



Scheme 54. Preparation of unsymmetrical azines using WCl_6/Mont. K10 catalyst.



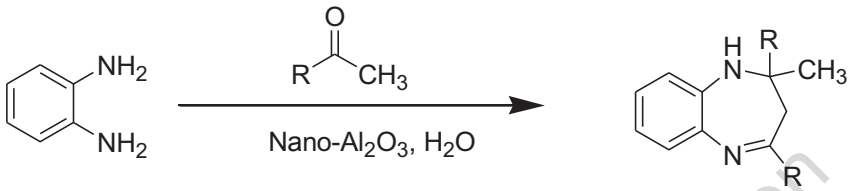
Scheme 55. Synthesis of unsymmetrical azines using WCl_6/Mont. K10 catalyst.

The WCl_6 nanoparticles loaded on montmorillonite K-10 serves as an inexpensive, non-corrosive and readily available catalyst. It was proposed that acidic WCl_6/Mont. K10 catalyzes protonation of hydrazone, which then condenses with enolic form of ketone to form an intermediate. The latter compound undergoes dehydration and deprotonation to produce azine in the presence solid acid catalyst WCl_6/Mont. K10. Thus, the tungsten hexachloride nanoparticles loaded on Montmorillonite K10 clay support displays excellent catalytic performance for the synthesis of azines.

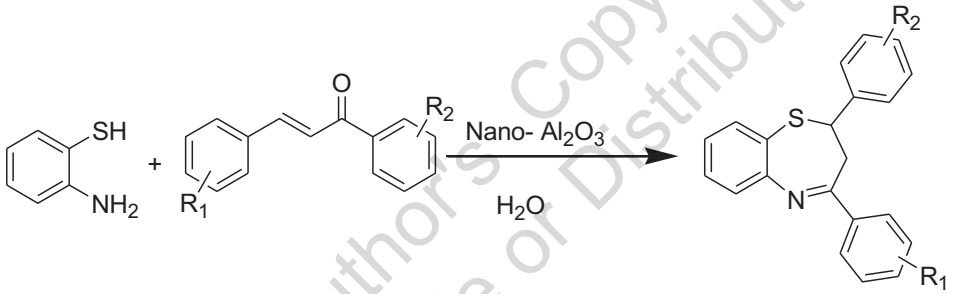
Seven Membered Heterocycles

Alumina Nanoparticles

An efficient protocol for the syntheses of 1,5-benzodiazepine and 1,5-benzothiazepine in the presence of a catalytic amount of nanocrystalline aluminum oxide in aqueous medium Scheme (**56**), Scheme (**57**) was studied by Hekmatshoar *et al.* [94].



Scheme 56. Synthesis of 1,5-benzodiazepines using nano-Al_2O_3 catalyst.

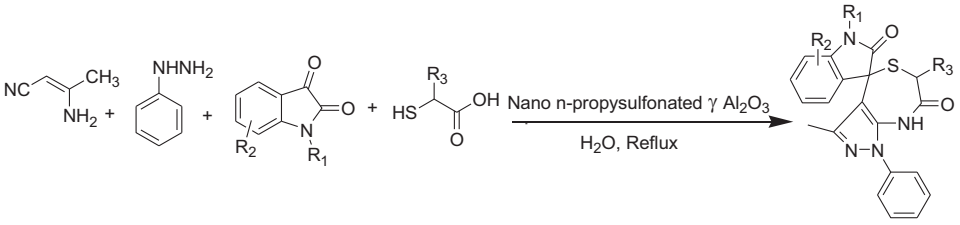


Scheme 57. Synthesis of 1,5-benzothiazepines using nano- Al_2O_3 catalyst.

The catalytic activity of nanocrystalline Al_2O_3 was compared with bulk Al_2O_3 and basic Al_2O_3. It was found that the catalytic efficiency of nano- Al_2O_3 is greater than bulk Al_2O_3 and basic Al_2O_3. This is due to large surface area and high number of reactive sites present on nano-Al_2O_3. It was recylable up to four times without any kind of loss in its activity and selectivity.

Synthesis of spiro[indoline-3,4-pyrazolo[3,4-e] [1, 4]thiazepine]diones has been carried out in excellent yields by Wu [95]. He prepared spiro[indoline-3,--pyrazolo[3,4-e] [1, 4]thiazepine]diones through a one-pot, four-component reaction of 3-aminocrotononitrile, phenylhydrazine, isatins and thioacid using nano n-propylsulfonated γ-Al_2O_3 (average crystalline size 14.9 nm) in presence of water (Scheme **58**).

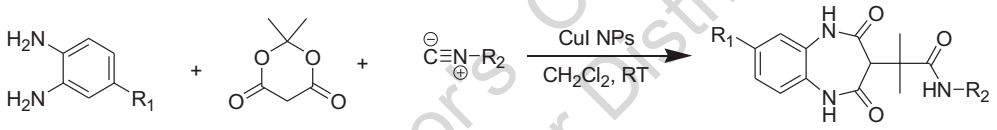
The reaction was highly efficient and completed in short time. Moreover, the non-toxic catalyst was retrievable and reusable up to seventh run without any reduction in its catalytic activity.



Scheme 58. Synthesis of spiro[indoline-3,4-pyrazolo[3,4-e][1,4]thiazepine] diones using nano n-propylsulfonated γ- Al_2O_3.

Copper Iodide Nanoparticles

Ghasemzadeh and Safaei- Ghomi [96] developed an environmental friendly technique for the synthesis of benzo[b] [1, 5]diazepine derivatives *via* copper iodide nanoparticles (CuI NPs) promoted three-component reaction of aromatic diamines, Meldrum's acid and isocyanides (Scheme **59**). The desired product was obtained in excellent yield in short span of time.



Scheme 59. Preparation of benzo[b][1,5]diazepines using CuI NPs as catalyst.

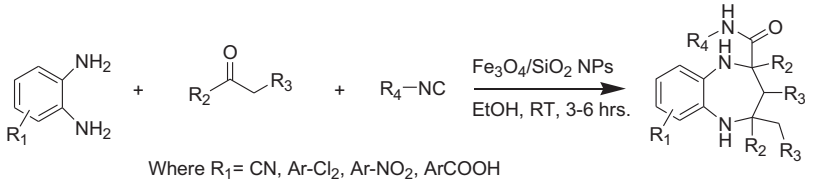
Moreover, the catalyst was easily recovered by filtration and reused five times with minimal decrease in activity. It was reported that due to Lewis acidic character of copper iodide nanoparticles (particle size 25 nm), CuI NPs link with carbonyl groups of Meldrum's acid and speed up the nucleophilic attack of 1,2-phenylenediamine. The driving force behind the reaction is high surface area to volume ratio of nanoparticles, which provides large surface area for diffusion. Thus, use of nanoparticles increase the reaction rate drastically.

Magnetic Nanoparticles

Maleki [97] reported a novel method for the synthesis of diazepine derivatives using a 1,2-diamine, a linear or cyclic ketone, and an isocyanide in the presence of a catalytic amount of silica supported iron oxide (Fe_3O_4/SiO_2) nanoparticles at room temperature (Scheme **60**).

A significant feature of Fe_3O_4/SiO_2 nanocatalyst is easy separation of the catalyst using an external magnet without filtration. In addition, supported magnetic metal nanoparticles (S-MMNPs) catalysts are known to display high catalytic activity as

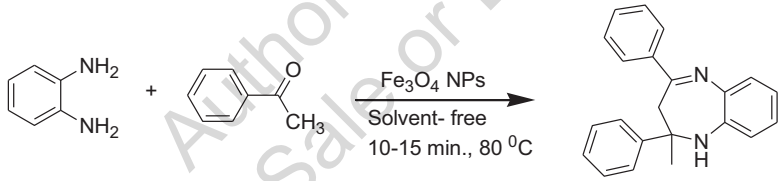
well as high degree of chemical stability in various organic solvents [98, 99]. In this reaction, Fe_3O_4/SiO_2 nanocatalyst catalyzes condensation between *o*-phenylenediamine and ketone (1:2 ratio) to form a diimine intermediate. This is followed by intramolecular imine and enamine cyclization leading to formation of seven-membered ring. Thus, the reusable catalyst promotes a clean reaction with no side reactions and enormous yields of the desired compounds.



Where R_1= CN, Ar-Cl_2, Ar-NO_2, ArCOOH
R_2= R_3= Acetone, cyclohexanone, acetophenone
R_4= Alicyclic/ aliphatic or aromatic group

Scheme 60. Synthesis of diazepine derivatives using Fe_3O_4/SiO_2 nanocatalyst.

Jamatia *et al.* [100] synthesized diazepines in the presence of magnetically recoverable Fe_3O_4 nanocatalyst under solventless condition. A one pot reaction between *o*-phenylene diamine and substituted acetophenones in presence of Fe_3O_4 nanocatalyst resulted in benzodiazepines in high yields and that too in just few minutes (Scheme **61**).



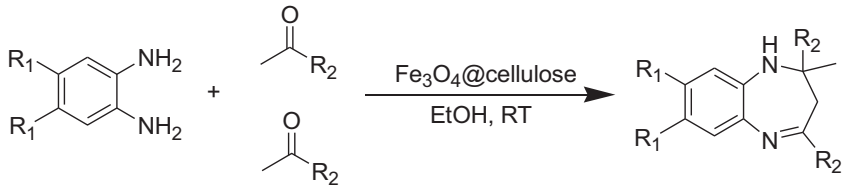
Scheme 61. One pot multicomponent synthesis of diazepines using Fe_3O_4 nanocatalyst.

The advantages of the process are that it avoids use of toxic solvents, involves reusable nanocatalyst without affecting the purity of products.

A cellulose-supported nanocomposite with highly loaded Fe_3O_4 nanoparticles (Fe_3O_4@cellulose) was prepared by Maleki and Kamalzare [101]. The catalyst was employed to promote synthesis of benzodiazepines *via* condensation reaction between o-phenylenediamines (OPDAs) and ketones at ambient temperature (Scheme **62**).

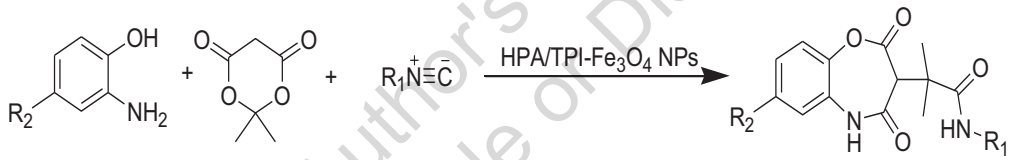
The prepared nanocomposite of average particle size of 25 nm showed good reusability (reusable up to four times) and resulted in satisfactory yields of the products. The Fe_3O_4@cellulose nanocatalyst catalyzes formation of diimine from the condensation reaction between OPDAs and two moles of ketones. The lone pair electrons of oxygen atom of ketones are adsorbed on the surface of acidic

catalyst leading to attack of amino groups on the carbonyl groups. Then intramolecular imine–enamine tautomerization–cyclization occurs to yield the expected products. Thus, the nanocatalyst exhibits high efficiency resulting in a facile and green protocol for the preparation of benzodiazepines.



Scheme 62. Synthesis of benzodiazepines in the presence of Fe_3O_4@cellulose nanocatalyst.

A one pot multicomponent reaction involving *o*- aminophenol, isocyanides and Meldrum's acid in the presence of a magnetic inorganic-organic nanohybrid material (HPA/TPI-Fe_3O_4 NPs) to synthesize 2,3,4,5-tetrahydrobenzo[b] [1, 4]oxazepine derivatives Scheme (**63**) was reported by Vessally *et al.* [102]. The nanohybrid catalyst comprises of $H_6P_2W_{18}O_{62}$ anchored onto the surface of modified Fe_3O_4 nanoparticles (NPs) with N-[3-(triethoxysilyl) propyl]isonicotinamide (TPI) linker.



Scheme 63. Synthesis of 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine derivatives using HPA/TPI- Fe_3O_4 NPs.

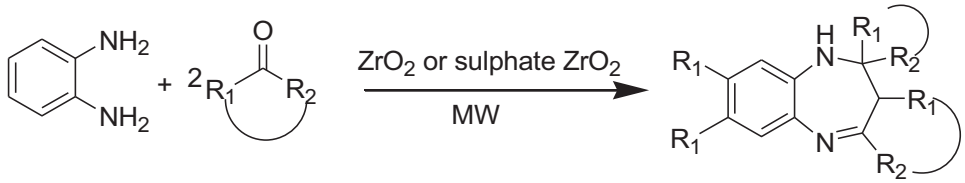
The catalyst displays some significant features, for instance, high catalytic activity, stablility, non-toxicity, economic feasibility and reusability. Therefore, serves as an efficient catalyst giving good yields in short reaction time.

Shabaani *et al.* [103] carried out similar reaction in the presence of an efficient and recyclable nanocatalyst, Cu/GA/Fe_3O_4@SiO_2 (guanidine acetic acid on modified Fe_3O_4@SiO_2 core-shell nanocomposite spheres). The catalyst was retrieved by an external magnet and reused about five times with no loss of catalytic activity. The main advantage of the catalyst is its thermochemical stability that enhances its catalytic activity.

Zirconia Nanoparticles

A similar reaction was carried out by Gondaliya *et al.* [104]. The condensation reaction between *o*- phenylene diamine and ketones to produce 1,5-

benzodiazepines in the presence of zirconia (ZrO_2) and sulfated zirconia nanocatalysts under microwave irradiation (Scheme **64**).

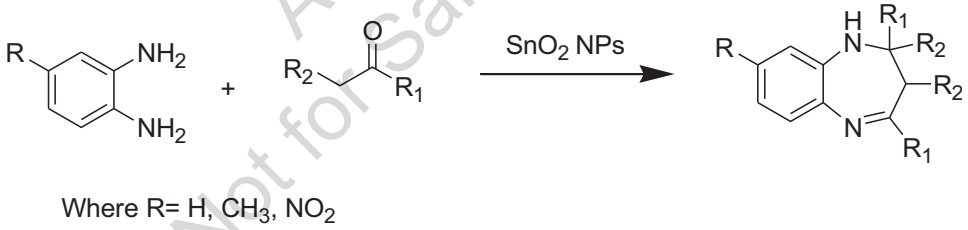


Scheme 64. Synthesis of 1,5-benzodiazepine derivatives using ZrO_2 or sulphate ZrO_2 NPs.

It was reported that both the nanocatalysts displayed excellent catalytic activities but the recyclability of sulfated zirconia was found to be better than that of zirconia.

Tin Oxide Nanoparticles

A green, solventless synthesis of 1,5-benzodiazepines Scheme (**65**) has been reported in the presence of stannic oxide nanoparticles (SnO_2 NPs) by Singh *et al.* [105]. It was proposed that electrophilic activation of carbonyl groups of ketones is due to binding of oxygen through Lewis acid sites (Sn^{2+}) of nanoparticles. This promoted nucleophilic attack by amines due to their activation by Lewis basic sites (O^{2-}) of SnO_2 NPs to form diimine intermediate. Then, 1,3-hydrogen shift of methyl group resulted in formation of enamine that underwent cyclization to yield benzodiazepine.



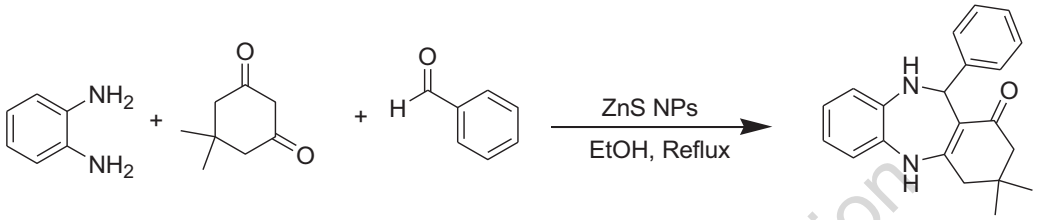
Scheme 65. Synthesis of 1, 5-benzodiazepines promoted by SnO_2 NPs.

They assumed that high surface area and better dispersion of nanoparticles in the reaction mixture are responsible for the superior activities of SnO_2 NPs. Benign nature, reusability of catalyst and excellent yields are some highlights of this synthetic protocol.

Zinc Based Nanoparticles

ZnS nanoparticles show some significant properties such as efficient heterogeneous catalysis, low Curie temperature and high coercivity [106 - 108].

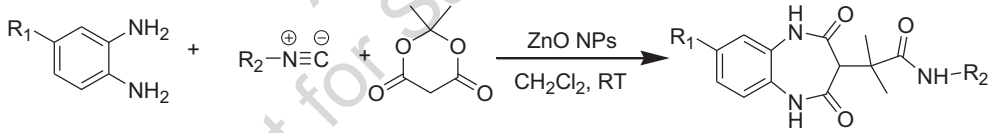
Naeimi and Foroughi [14] reported a new method of synthesis of 4-substituted-1,5-benzodiazepine derivatives *via* a one-pot three-component reaction involving *o*-phenylenediamine, dimedone and aldehyde in the presence of ZnS nanoparticles as a heterogeneous catalyst under reflux conditions (Scheme **66**). They found that ZnS NPs catalyze Michael type coupling of dimedone with *o*-phenylenediamine and that of aldehyde. Further, ZnS NPs promoted Knoevenagel type coupling and cyclization eventually giving 4-substituted-1,5-benzodiazepine.



Scheme 66. Synthesis of 4-substituted-1,5-benzodiazepines using ZnS NPs.

The use of ZnS NPs has several advantages like easy availability, reusability, accelerated reactions, enhanced yields and purity of products.

Multicomponent synthesis of benzo[b] [1, 5]diazepines catalyzed by zinc oxide nanoparticles (ZnO NPs) under mild conditions has been reported by Ghasemzadeh and Safaei-Ghomi [109]. Various different isocyanides, diamines and Meldrum's acid in the presence of ZnO NPs resulted in excellent yields of the products at ambient temperature (Scheme **67**).

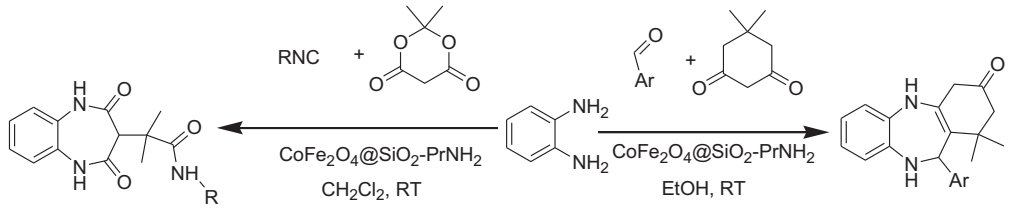


Scheme 67. One pot preparation of benzo[b][1,5]diazepines catalyzed by ZnO NPs.

The catalyst could be easily separated from reaction mixture by centrifugation and could be used subsequently several times.

Spinel Nanoparticles

A novel and expeditious technique for the synthesis of benzodiazepines in the presence of $CoFe_2O_4$@SiO_2-$PrNH_2$ nanoparticles (Scheme **68**) has been described by Miri and Safaei-Ghomi [110].

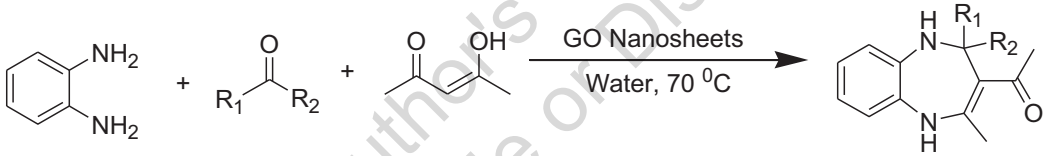


Scheme 68. Synthesis of benzodiazepines catalyzed by $CoFe_2O_4@SiO_2$-$PrNH_2$ NPs.

The use of $CoFe_2O_4@SiO_2$-$PrNH_2$ nanoparticles offer benefits such as low catalyst loading, clean reaction profiles, easy recovery of catalyst and reusability along with enormous catalytic efficiency.

Graphene Oxide Based Nanocatalyst

Kausar *et al.* [111] reported a new synthetic protocol for the synthesis of dibenzo [1, 4]diazepine from multicomponent reaction of *o*-phenylene diamine, diverse aldehydes/ketones and 1,3-diketone catalyzed by highly active graphene oxide (GO) nanosheets (Scheme **69**).

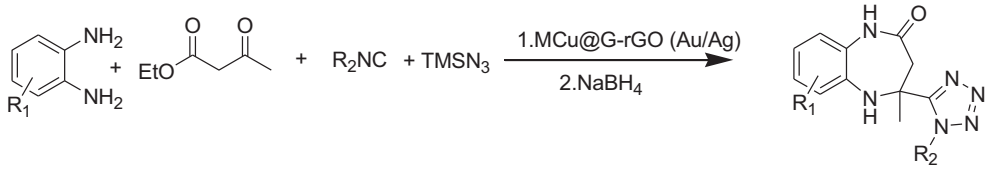


Scheme 69. Synthesis of dibenzo[1,4]diazepine derivatives using GO nanosheets.

The presence of numerous functional groups, such as alcohols, epoxides, carboxylates and sulphates, makes GO a versatile catalyst for several reactions. Additionally, "carbocatalysis" [112] by graphene oxide offers several advantages such as facile and inexpensive methodology, metal free condition and reusability. GO nanosheets have been reported to show high catalytic performance leading to high yields.

Shabaani *et al.* [113] synthesized AuCu and AgCu bimetallic nanoparticles supported on guanidine-grafted reduced graphene oxide nanosheets (AuCu@G-rGO and AgCu@G-rGO). They used the nanosheets as catalyst to promote synthesis of benzo[b] [1, 4]diazepine derivatives Scheme (**70**) and showed that presence of two metals improves the catalytic activity and graphene oxide stabilizes the nanoparticles and enhances their surface area.

The catalyst is recyclable and results in excellent yields. The AuCu@G-rGO shows better catalytic efficiency than AgCu@G-rGO.



Scheme 70. Synthesis of benzo[b][1,4]diazepine derivatives using MCu@G-rGO (Au/Ag).

CONCLUSION

In the present chapter, an attempt has been made to delve into the role of nanocatalysts in the syntheses of various heterocycles. Nanocatalysts display several significant characteristics such as inexpensive and simple preparation, large surface area, suitable surface morphology, low catalyst loading, high dispersion, versatility, excellent activity, great selectivity, high stability, easy recovery, good recyclability and eco-friendliness. Furthermore, functionalization of nanoparticles enhances their catalytic activity by enhancing the surface area and exposing active sites for the reactants. This leads to excellent yields of products in short time. Also, the use of support in the form of synthetic or natural polymers, silica, *etc.* causes stabilization of the catalyst, improves its mechanical strength, enhances its surface morphology, reduces agglomeration and leads to high crystalline order. Moreover, use of naturally occurring materials such as cellulose, starch, glucose, *etc.* adds features like sustainability, biocompatibility and biodegradability to the nanocatalysts. The presence of Lewis acidic and basic sites increases the chemical affinity of nanoparticles, which assists in enhancing the reaction rate. Functionalization of nanoparticles with Bronsted acids such as sulphamic acids, perchloric acids, *etc.* further improves their catalytic action.

The biggest advantage of using nanocatalyst is simple and easy recovery by methods such as using an external magnet (in case of magnetic nanoparticles), centrifugation, adsorption and filtration. Recently, use of graphene oxide as both catalyst and solid support has shown exceptional catalytic effects due to electrostatic and π-π stacking interaction that increases adsorption of reactants on the active sites of the catalyst. Therefore, due to these properties, various magnetic nanocatalysts, nano mixed metal oxides, core-shell nanocatalysts, nano-supported catalysts, ionic liquid supported nanoparticles, graphene-based nanocatalysts have been employed to promote synthesis of diverse heterocycles such as pyrazoles, thiazoles, oxazoles, imidazoles, triazoles, tetrazoles, oxindoles, spiro-azoles, xanthenes, chromenes, azines, pyrimidines, quinolines, isoquinolines, acridines, quinoxalines, coumarins, polyhydroxyquinolines, spiro-acridines, benzodiazepines, benzothiazepines, benzo-oxazepines, spiropyrazolo-thiazepines, *etc.*

The use of nanocatalysts for the synthesis of various heterocycles offers advantages such as short reaction time, high yield, simple and clean protocol, simplified work-up procedure, atom economy, mild reaction condition and in some cases, solvent-free condition, avoidance of expensive and toxic chemicals and reusability of catalyst. Thus, it can be concluded the use of nanomaterials as catalysts helps to achieve the goal of benign and sustainable chemical conversions and processes. In future, nanocatalysis will become an integral part of organic synthesis and will be used to prepare multitudes of pharmacologically active heterocyclic scaffolds resulting in expedited and eco-friendly drug discovery and designing.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 4

Synthesis and Applications of 1,2,3-Triazoles

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Abstract: The chapter is devoted to the recent developments in the synthesis of 1,2,3-triazoles and their selected applications. Since the introduction of a classic Huisgen reaction which involved thermal 1,3-dipolar cycloaddition of alkynes to azides, its catalytic modifications have been elaborated, allowing the regioselective preparation of 1,4- and 1,5-disubstituted derivatives in copper(I)- or ruthenium(II)-catalyzed cyclizations (click reactions). Most of the other synthetic pathways generally also utilize organic azides or sodium azide, although methods based on other starting materials (*e.g.* hydrazine derivatives) are also of importance. A special attention is paid to the preparation of chiral triazole derivatives. Various applications of triazoles are also discussed, with a focus on their use as isosteres of biological functionalities, sensors for ions and neutral molecules, in catalysis and in construction of supramolecular assemblies.

Keywords: Alkyne, Azide, Bioisostere, Chemosensor, Click Reaction, CuAAC Reaction, Cyclization, Heterocyclic Compound, Multicomponent Reaction, Nitrogen Heterocycle, *N*-Tosylhydrazone, RuAAC Reaction, Supramolecular Chemistry, 1,3-Dipolar Cycloaddition, 1,2,3-Triazole.

INTRODUCTION

1,2,3-Triazole, a five-membered diunsaturated heterocycle containing three nitrogen atoms at adjacent positions, ranks among the most important scaffolds used for the construction of bioactive molecules and functional materials. Three tautomeric forms of this compound are found in various derivatives: *1H*-1,2,3-triazole, which can bear substituents at 1, 4, and 5 positions, *2H*-1,2,3-triazole, with the possible 2,4,5-substitution pattern, and relatively rare *4H*-1,2,3-triazole in which stabilization due to delocalization takes place only for certain 4,4,5-substituted rings (Fig. **1**).

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Atta-ur-Rahman (Ed.)

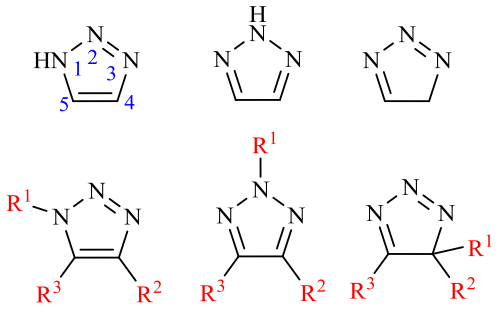

Fig. (1). Tautomers of 1,2,3-triazole (from left to right): *1H*-1,2,3-triazole, *2H*-1,2,3-triazole, and *4H*-1,2,-triazole and their possible substitution patterns.

The story of this heterocycle begins in 1888 with works of Hans von Pechmann (1850-1902), a former assistant of Adolph von Baeyer and a professor of universities in Munich (1886-95) and Tübingen (1895-1902). The name of this brilliant synthetic organic chemist [1] is now associated with his discovery of diazomethane, first (accidental) preparation of polyethylene, syntheses of 1,2-diketones, ketoaldehydes, ketoacids and development of a new route to coumarins (Pechmann condensation). He is also commemorated in the protocol of preparation of pyrazoles (Pechman synthesis). Von Pechmann succeeded in the synthesis of substituted 1,2,3-triazoles from diacetyl (butane-2,3-dione) derivatives, *e.g.* di(phenylhydrazone) (Fig. **2**), and properly identified them as containing a trinitrogen five-membered heterocycle [2, 3]. He was also able to obtain a parent compound [4]. Later, various routes to triazole derivatives have been introduced. In 1893, Arthur Michael (1853-1942), an American chemist, reported the isolation of a product prepared by heating acetylene diester derivative with phenyl azide (Fig. **3**) [5]. Michael, known for the discovery of the reaction which now bears his name, studied in Germany with Robert Bunsen and August Wilhelm von Hofmann, in France with Charles Adolphe Wurtz and Russia with Dmitri Mendeleev, and returned to the United States in 1880 to become a professor of chemistry at Tufts College in Medford, Massachusetts.

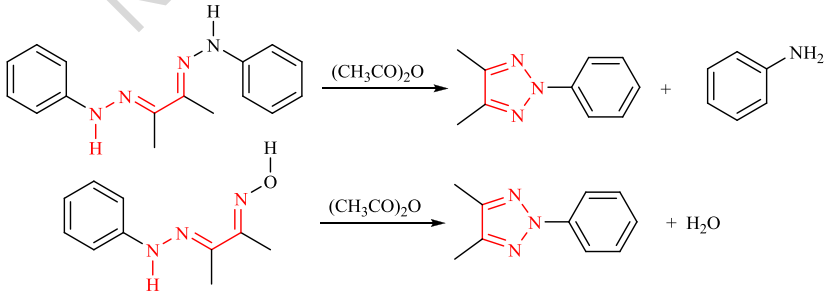

Fig. (2). Von Pechmann's syntheses of 1,2,3-triazole derivatives [2, 3].

The use of acetylene and hydrogen azide for the preparation of unsubstituted 1,2,3-triazole (Fig. **4**) was later described by Otto Dimroth (1872-1940) and Gustav Fester (1886–1963) [6]. Dimroth, a pupil and coworker of Johannes Thiele and Adolf von Baeyer at the University of Munich, worked also with von Pechmann and succeeded him as the Professor at the University of Tübingen. He was later connected with the Universities of Greifswald and Würzburg. The versatility of the cycloaddition has been recognized and the idea has been further developed by Rolf Huisgen (born 1920) [7]. Huisgen prepared his doctorate under the supervision of Heinrich Otto Wieland at the University of Munich in 1943 and worked at his Alma Mater until the retirement in 1988, with a short period at the University of Tübingen (1949-1952). His works on diazoalkanes led him to a general concept of 1,3-cycloaddition conceived in the late 50s. He summarized the idea in two reviews, published in *Angewandte* in 1963, in which the directions of further research were indicated as well [8, 9].

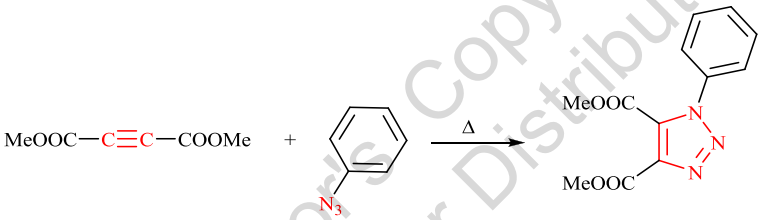

Fig. (3). Michael's synthesis of 1,2,3-triazole derivative [5].

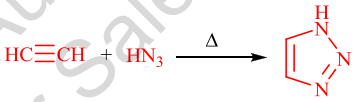

Fig. (4). Preparation of unsubstituted 1,2,3-triazole by Dimroth and Fester [6].

The classical, uncatalyzed reaction of terminal alkynes and azides suffers from several drawbacks: relatively high activation energy which requires elevated temperatures and long reaction times for non-activated alkynes, and limited selectivity: in most preparations, mixtures of 1,4- and 1,5-substituted derivatives are obtained (Fig. **5**). The breakthrough came in 2002 with the publications by the groups of Karl Barry Sharpless (born 1941), a professor in The Scripps Research Institute, USA, a Nobel Prize winner in 2001 [10], and Morten P. Meldal (born 1954), a leader of a group in the Department of Chemistry of the Carlsberg Laboratory in Valby (Denmark) [11]. They described the use of copper(I) catalyst for activation of alkyne substrate that resulted in a great increase of reaction rate and a selective formation of 1,4-adducts (Fig. **5**). Sharpless, in a paper co-authored by Vsevolod V. Rostovtsev, Luke G. Green, and Valery V. Fokin (born

1971), credited by Sharpless for the idea of the use of Cu catalyst [12], reported the application of copper(II) sulphate pentahydrate together with sodium ascorbate for the synthesis of various 1,2,3-traizole derivatives in alcohol-water mixtures at room temperature [10]. *In situ* formation of active catalyst led to better results in comparison with the direct use of copper(I) salts. Meldal, Christian W. Tornøe and Caspar Christensen performed the reaction on a solid support used for peptide synthesis, with CuI catalyst, and afforded a series of 1,4-substituted 1,2,3-triazole derivatives attached to peptide backbones or side chains [11]. The modified version of 1,3-dipolar cycloaddition (usually shortened as CuAAC) meets the standards "click chemistry", the concept introduced by Sharpless in 2001 [13], and now serves as an archetype of click reaction.

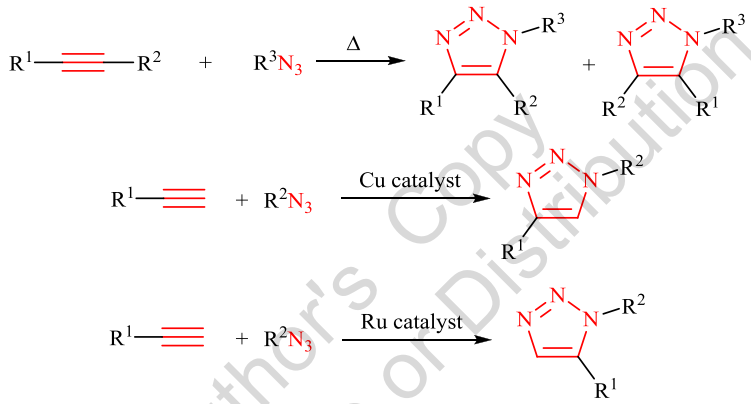

Fig. (5). Thermal 1,3-dipolar cycloaddition and its catalytic modifications [10 - 12, 14]

Shortly, a selective route to 1,5-substituted derivatives has been introduced through the use of ruthenium(II) catalysts (RuAAC, Fig. **5**) [14]. Since internal alkynes are also activated under these conditions, 1,4,5-substituted 1,2,3-triazoles can be prepared with this protocol as well. Both pathways have been widely applied to the synthesis of numerous derivatives which led to a spectacular increase of the number of publications in the field. According to ISI Web of Science database, in 2017 ca. 1400 articles with "triazole" in their title appeared which can be compared with 172 papers in 2000 [15].

Benign reaction conditions, a tolerance for various groups, simple workup and purification led to the application of click reactions to the synthesis of products with desired – and almost any – functionalities. 1,2,3-Triazoles have been used for derivatization of – among others – carbohydrates, peptides and proteins, nucleotides and nucleic acids, variety of polymers, fullerenes, carbon nanotubes and graphene, metal nanoparticles, and for the construction of macrocycles, dendrimers, catenanes and rotaxanes, and other supramolecular architectures. The

synthesized derivatives have found applications in many areas, including interfaces of chemistry with physics, biology and medicine.

Not surprisingly, numerous reviews have appeared devoted to the various aspects of synthesis and applications of 1,2,3-triazoles and, more general, click reactions. In the recent years, books and book chapters summarizing the acquired knowledge have been published [16 - 19]. In some latest review articles on click reaction, its use in modification of alkaloids and isoprenoids [20], polysaccharides [21, 22], porphyrin derivatives [23], nanostructured [24] and π-conjugated polymers [25], fullerenes [26] in construction of chemical sensors [27], luminescent complexes [28], silica-based materials [29], and in radiochemistry [30] has been described. Recent trends and applications of metal-catalyzed azide-alkyne reactions [31 - 35] have been also reviewed. Several articles have been dedicated to advances in the synthesis of 1,2,3-triazoles *via* 1,3-dipolar cyclo-addition and alternative methods [36 - 44]. Applications of these heterocycles in various fields have been also covered [45], in particular, as functional materials [46, 47], as ligands in metal complexes and supramolecular architectures [48 - 51], and the use of triazoles in biomedical studies [52 - 56].

In a preface to his exhaustive review on the synthesis of 1,2,3-triazoles, K. T. Finley stated: "With so many recent and well-written reviews, the desirability of another requires a specific answer." [57]. Such a justification seems also necessary for this particular chapter. Certainly, the fast increase of the number of articles in the field raises the need of new overviews. In our opinion, any fresh approach can give an inspiration for further research. Here, a point of view of organic synthetic chemist, working in the area of asymmetric synthesis (E.W.), and a porphyrin chemist (J.W.) will be presented. Consequently, the review will focus on various methods of preparation of 1,2,3-triazoles, particularly on alternatives for the well-known click reaction. A special attention will be paid to synthesis of chiral derivatives. Examples of various applications of triazoles will be presented to show versatility of functions of these heterocycles in their assemblies. The chapter will concentrate on recent developments, mainly on papers published in the years 2010-2017. Fused systems – benzotriazole and other similar derivatives – will not be covered.

SYNTHESIS OF 1,2,3-TRIAZOLES

Undoubtedly, copper-catalyzed azide-alkyne cycloaddition constitutes the principal method of preparation of 1*H*-1,2,3-triazole derivatives, in most cases substituted at 1 and 4 positions. Well understood CuAAC process offers many benefits: operational simplicity, cheap and easily available catalysts (in most preparations copper sulfate and sodium ascorbate are used), mild conditions, and

tolerance for functional groups. However, this protocol is not free of drawbacks. As it is limited to terminal alkynes, preparation of 1,4,5-substituted derivatives requires the application of ruthenium catalyst, a multicomponent approach, or a modification of the pre-formed triazole. Other drawbacks include a limited availability of necessary reactants, and certain hazards connected with handling of azides – their toxicity and possible explosiveness. The potential of applications of 1,2,3-triazoles in electronics, biomedicine and biological chemistry is hampered by the use of toxic metals in click reaction [34]. These limitations led to substantial developments of various modifications of CuAAC reaction, but also of alternative methods of synthesis of 1,2,3-triazoles.

New Trends in Metal-Catalyzed Click Reactions

Click reactions catalyzed by copper and ruthenium compounds have been further extended to many other metal catalysts as MAAC (metal-catalyzed azide-alkyne cycloadditions), *e.g.* silver, gold, iridium, nickel, zinc and lanthanides. A comprehensive review of these preparations has been recently published [34]. Among the latest achievements, a click reaction of azides, alkynes and aryl halides was reported resulting in various 1,4,5-substituted 1,2,3-triazole derivatives [58]. The application of tandem Cu/Pd catalysis allowed avoiding harsh conditions used for arylation of triazoles (Fig. **6**). The method showed wide substrate scope and only for triarylsubstituted derivative the yield dropped below 50%.

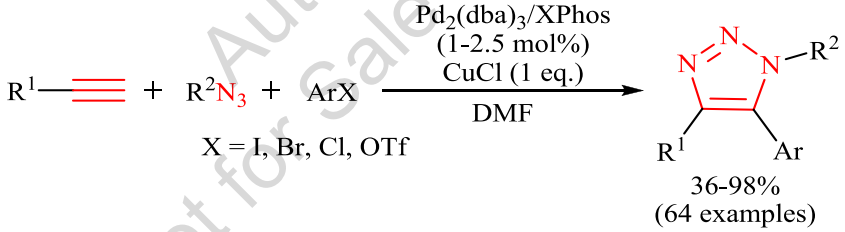

Fig. (6). Mixed Pd/Cu catalyzed three-component click reaction [58].

5-Amino-1,2,3-triazole-4-carboxylates with protected amino groups were prepared *via* Ru-catalyzed cycloaddition of *N*-Boc ynamides to azides and used for the synthesis of triazole-containing dipeptides [59]. With the developed protocol, Dimroth rearrangement was avoided.

Murty and coworkers reported on a one-pot multicomponent synthesis of 1,2,3-triazoles from epoxides or benzyl bromide as organic azide precursors, NaN_3 and terminal alkynes catalyzed by iron oxide nanoparticles in water [60]. Various derivatives were obtained in reasonable yields (73-85%) after 3-5 hours;

nano-Fe_2O_3 could be magnetically separated and reused five times without loss of catalytic activity.

The above example illustrates also modern tendencies in CuAAC reaction: looking for the new protocols allowing an efficient separation of the catalyst from the reaction mixture and its possible recycling. Therefore, the use of a polymer support for catalyst heterogenization and procedures based on the magnetically recyclable catalysts has gained a significant attention [32, 34]. In one of recent articles in this area, Kumar *et al.* applied copper ferrite nanoparticles for the synthesis of 1,4-disubstituted 1,2,3-triazoles performed in tap water [61]. There is also a quest for new ligands for copper that could allow minimizing of the amount of a catalyst [34]. A heterogeneous system based on graphene oxide/poly(vinyl imidazole) nanocomposite containing Cu^{2+} ions was found to catalyze the click, three-component reaction of phenylacetylene, benzyl bromide and sodium azide in the presence of sodium ascorbate in water at 50 °C in only 0.002 mol%; 93% yield was reached after 20 hours [62].

Astruc and coworkers designed a recyclable catalytic dendrimer nanoreactor exhibiting a turnover number of up to 510 000, which allowed to use only 4 ppm (to reach a quantitative yield) or 1 ppm (for 50% yield) of it [63].

Modifications of CuAAC reaction involve also changes of classical reaction conditions [32, 64]. Application of microwave heating in many cases leads to a significant shortening of reaction times [39]. In 2004, Fokin, Van der Eycken and coworkers developed a microwave-assisted three-component synthesis of 1,2,3-triazoles in *tert*-butanol-water mixture; copper metal and $CuSO_4$ were used as catalysts [65]. In a similar procedure, various alkynes and dialkynes were added to benzyl azide (generated *in situ*) in the presence of sodium ascorbate and copper(II) sulfate [66]. Under conventional conditions, the reaction was conducted for 6-12 hours at 50-60 °C, affording triazoles and bis-triazoles in 38-98% yield. Application of microwave conditions (continuous heating at 2455 MHz, 120 °C) allowed to shorten reaction time to 12 minutes with higher and comparable yields. Certain triazole derivatives exhibiting biological activity were efficiently prepared in a copper-catalyzed reaction performed with 10-minute irradiation [67]. Also microwave-assisted copper-free [68], and catalyst- and solvent-free cycloadditions [69] have been recently described.

Ultrasound-promoted cycloadditions, regarded as green and energy-saving procedures, were applied for the preparation of various triazole derivatives [70 - 72]. Again, similar or even better yields as compared with conventional conditions could be achieved after 5-20 minutes of irradiation. In certain cases, the reaction rate was further increased when both ultrasounds and microwaves

were used simultaneously [73, 74]. Pressure-accelerated CuAAC reaction was also studied [75]. Other important modifications include the application of ionic liquids as reaction media and continuous flow processing [32, 64].

Modification of conditions of click reaction was shown to promote reaction products discarded in typical preparations: oxidative formation of 5,5'-bis-triazoles from organic azides and terminal alkynes was optimized by Brassard *et al.* [76] (Fig. **7**).

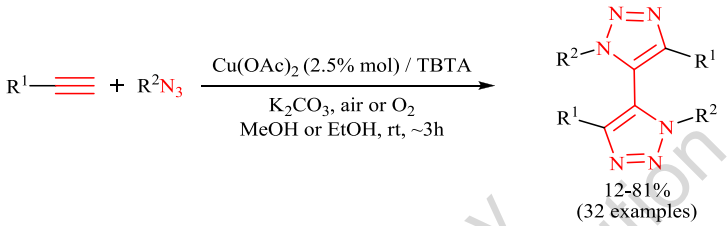

Fig. (7). Preparation of 5,5'-bistriazoles [76].

Alternative Methods of [3+2] Cyclization

Though most popular, [3+2] cyclizations of organic azides and alkynes represent only part of the available methods of 1,2,3-triazole synthesis. In particular, multicomponent reactions broaden the palette of starting materials, and the possibility of introduction of desired functionalities to the formed heterocycle [36]. On the other hand, there is a need of transition metal-free preparations that allow biomedical studies or the use in electronics of formed heterocycles [32, 42]. Organocatalytic procedures, comprising mild reaction conditions and efficiency, are particularly worth mentioning [77, 78].

A review by Krivopalov and Shkurko offers a systematic overview of methods used for the construction of 1,2,3-triazole ring, covering up the literature mainly from the years 1986-2002 [79]. This part will thus focus on the most recent developments in the field. In contrast to 1*H*-1,2,3-triazoles, a versatile approach to their 2-substituted 2*H*-counterparts has not been introduced so far. Methods of their preparation, involving 1,3-dipolar cycloaddition, cyclization of hydrazones or diazocompounds, and electrophilic substitution of the preformed ring, have been recently reviewed [80].

In Situ Generation of Azides

To avoid manipulation with organic azides, modifications to click reaction have been introduced involving *in situ* generation of these potentially hazardous

reactants and their use without isolation from the reaction mixture. Typically, sodium azide or trimethylsilyl azide are reacted with appropriate halides, pseudohalides, epoxides or other organic compounds [36].

A convenient one-pot protocol was proposed by Fokin and coworkers who applied various alkyl and aryl halides for *in situ* generation of desired organic azides that were further reacted with alkynes under copper catalysis [81]. Other preparations make use of halides [60, 61, 65 - 67, 70, 72], epoxides [60], and acyl halides [73]. As an example, 1,4-disubstituted 1,2,3-triazoles were prepared in the three-component, one-pot condensation of α-bromoketones, sodium azide, and terminal alkynes [82]. Copper(I) catalyst was generated by synproportionation of Cu and $Cu(OTf)_2$; under microwave irradiation (700 W, 85 °C, water as solvent) reaction times could be significantly shortened (8-14 minutes). Desired cyclic products were formed in 72-95% yield (Fig. **8**).

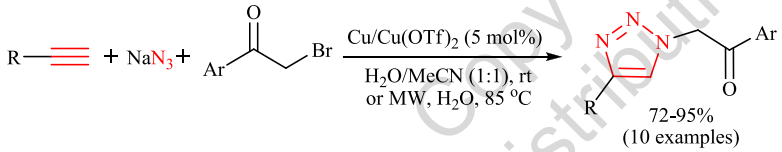

Fig. (8). Three-component synthesis of 1,4-disubstituted triazoles [82].

Alternatives for Alkynes

Part of limitations of click reaction result from an insufficient availability or a high price of alkyne substrates. Some of them were prepared from other compounds bearing a triple carbon-carbon bond [36]. Another possible solution was described by Jiang *et al.* who applied calcium carbide as a source of acetylene [83]. More frequently, various modifications of synthetic methodologies have been developed allowing replacement of alkynes with cheaper and more convenient sources of two-carbon part of triazole ring: appropriately substituted alkenes, alkanes and active methylene compounds (aldehydes, ketones, esters, nitriles *etc.*). Recent trends involve substrate activation through organic catalysts and multicomponent reactions which allow the application of wider scope of starting materials to achieve a desired substitution pattern.

Cyclization of Azides with Olefins

Numerous Huisgen dipolar [3+2] cycloaddition protocols have been developed with the participation of azides and appropriately substituted alkenes. Their condensation yields 1,2,3-triazoline, and its oxidative aromatization results in 1,2,3-triazole formation. This is facilitated by the presence of a good leaving

group at a double bond, as exemplified by nitro-, cyano-, halogen, sulfone, and other substituents [79]. The uncatalyzed reaction of α,β-unsaturated nitro compounds and nitriles with sodium azide was reported by Zefirov and coworkers in 1971 [84]. They observed that triazole products were accompanied by triarylbenzenes. The reaction was reinvestigated by Piet *et al.* [85], Amantini *et al.* [86] and Quiclet-Sire and Zard [87]. A thorough analysis of its mechanism allowed establishing of conditions suppressing a formation of unwanted side products (including additionally substituted triazole), which increased the yield of the desired products to 75-98% and extended the protocol to various nitroalkenes (Fig. **9**) and even nitroalkanes (with 54-55% yield) [87].

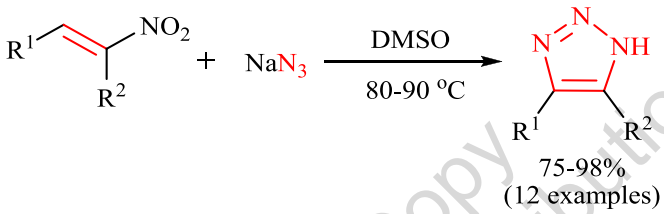

Fig. (9). Preparation of 4,5-disubstituted 1,2,3-triazoles from nitroalkenes [87].

Introduction of catalysts allowed broadening of substrate scope of the reaction. 2-Aryl-1-cyano-1-nitroethenes or 2-aryl-1-carbethoxy-1-nitroethenes treated with $TMSN_3$ under solvent-free conditions with the addition of tetrabutylammonium fluoride gave corresponding triazoles in high yields (70-90%) [86]. Lewis bases (with L-proline leading to the best results) catalyzed a cascade synthesis of 1,2,3-triazoles form nitroalkenes, aldehydes and sodium azide (Fig. **10**) [88].

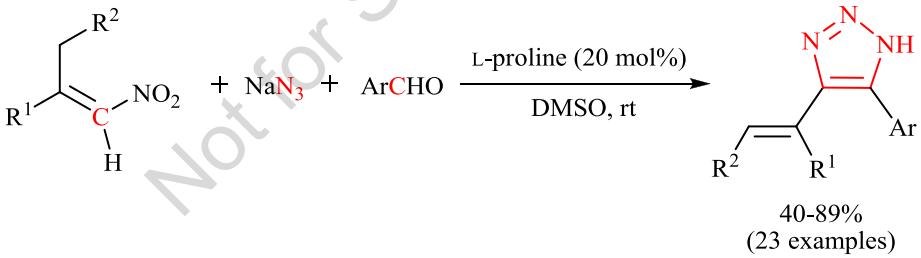

Fig. (10). Cascade synthesis of 4,5-disubstituted 1,2,3-triazoles [88].

Wang *et al.* reported a cerium triflate-catalyzed [3+2] cycloaddition of nitroolefins to organic azides which led to 1,5-disubstituted 1,2,3-triazole derivatives in 68-95% yield (only one of the 24 products was obtained in 45% yield; Fig. **11**) [89]. The reaction was found to tolerate a wide range of functional groups.

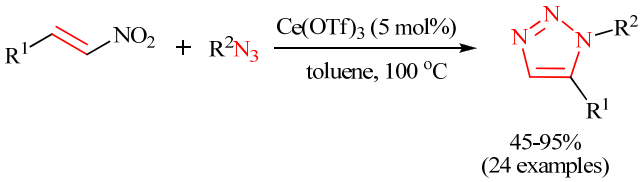

Fig. (11). Preparation of 1,5-disubstituted triazoles from nitroalkenes [89].

para-Toluenesulfonic acid was found to effectively mediate a reaction of nitroalkenes with sodium azide to afford 4-aryl-substituted 1,2,3-triazoles in 66-97% yield (Fig. **12**) [90]. Also organic azides were found reactive under these conditions; cyclotrimerization of nitroolefins was not observed.

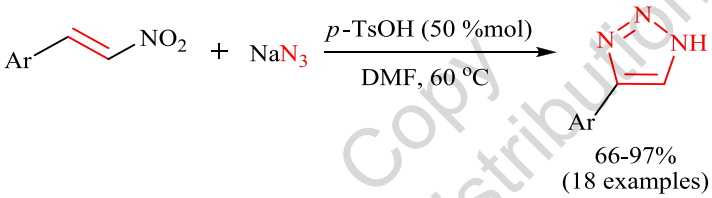

Fig. (12). Synthesis of 4-aryl-1,2,3-triazoles mediated by *p*-toluenesulfonic acid [90].

Copper(II) triflate was used as a catalyst in the synthesis of 4-nitro-5-aryl-1-2,3-triazoles [91]. Instead of elimination of HNO_2, cyclization step was followed by oxidation; Cu(II) catalyzed both steps, and was regenerated by atmospheric dioxygen (Fig. **13**).

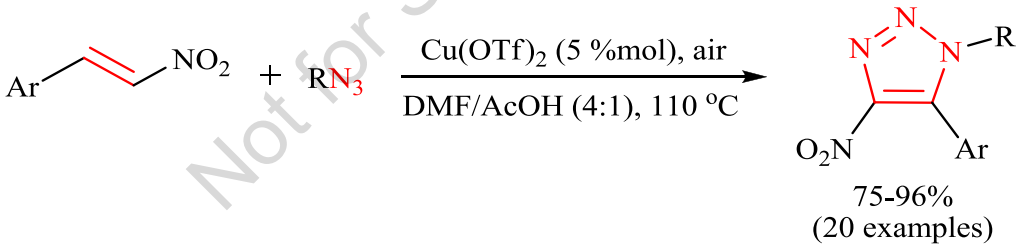

Fig. (13). Preparation of nitro-substituted 1,2,3-triazoles [91]

N-Unsubstituted 4-aryl-1,2,3-triazoles were obtained in a reaction of sodium azide and nitroalkenes in DMF solvent mediated by Amberlyst-15 (Fig. **14**) [92]. The method gave reasonable yields (80-96%), and the catalyst could be recovered and used several times.

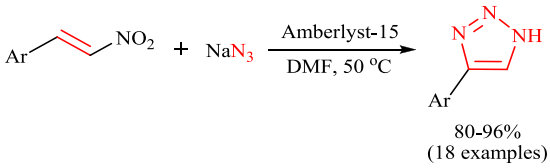

Fig. (14). The use of Amberlyst-15 to the preparation of 4-aryl-1,2,3-triazoles [92].

In 1973, the first application of vinyl sulfone in the synthesis of 1,2,3-triazoles was reported by Beck and Günther [93]. This approach was later used in the preparation of derivatives with antibacterial activity [94]. In a three-step solid-phase synthesis described by Gao and Lam, polymer-bound vinyl sulfones were obtained and reacted with sodium azide in DMF solution (Fig. **15**) [95]. 4,5-Disubstituted 1,2,3-triazole derivatives were formed in 37-78% yield after 20 minutes of microwave heating, and a simultaneous use of benzyl bromide resulted in 2,4,5-trisubstitution.

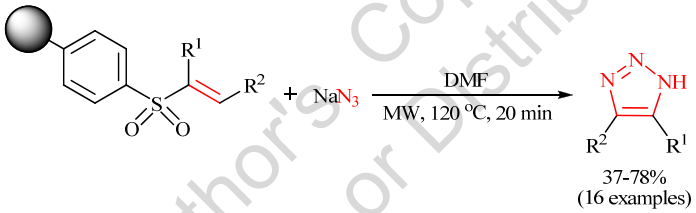

Fig. (15). Solid-phase synthesis of 4,5-disubstituted triazoles [95].

A regioselective route to 1,5-disubstituted 1,2,3-triazoles was reported by Pathak and coworkers who performed "on water" reaction of vinyl sulfones and organic azides (Fig. **16**) [96]. This methodology was applied to the preparation of a series of pyranosides substituted with triazole at C_1, C_2, C_3, C_4 or C_6 position, and triazole-linked disaccharides [97].

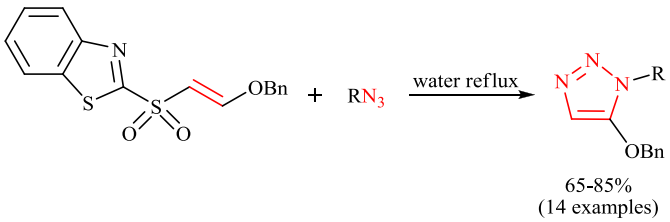

Fig. (16). "On water" synthesis of 1,5-disubstituted 1,2,3-triazoles [96].

4-Trifluoromethylsulfonyl-1,2,3-triazoles were formed in the reaction of organic azides with a zwitterionic reagent serving as a precursor of 1,1-bis(trifluoromethylsulfonyl)ethene (Fig. **17**) [98]. The synthesis was performed at room temperature without any catalysts and additives, leading to high and very high yields.

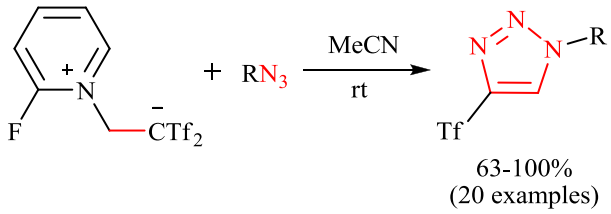

Fig. (17). Formation of 4-trifluoromethanesulfonyl-1,2,3-triazoles [98].

Bromostyrene was quantitatively converted to 4-phenyl-1,2,3-triazole *via* the reaction with sodium azide catalyzed by $[Pd_2(dba)_3]$ in the presence of diphosphine ligands (dpepos or xanthphos) [99]. Using the latter ligand, Barluenga's group prepared various monosubstituted derivatives in 45-94% yield (Fig. **18**).

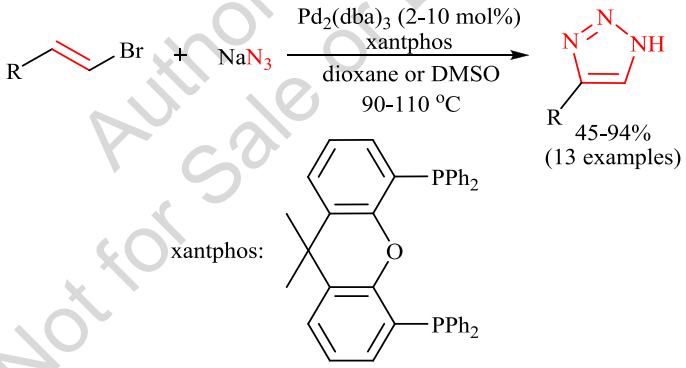

Fig. (18). Palladium-catalyzed preparation of 4-substituted-1,2,3-triazoles [99].

Kuang and coworkers published their study on the copper-catalyzed synthesis of 4-aryl-triazoles from 1,1-dibromoalkenes and sodium azide [100]. Potassium carbonate served as a base in the process, which was promoted by sodium ascorbate and CuI identified as the optimal catalyst (Fig. **19**). Various functionalities of the aromatic ring were tolerated, and respective derivatives were obtained in 60-86% yield.

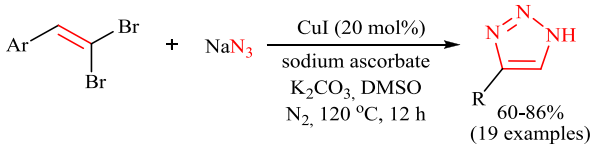

Fig. (19). Synthesis of 4-aryl-1,2,3-triazoles from dibromoalkenes [100].

Enamines and enols serve as intermediates in organocatalytic preparations of triazoles (see 2.2.2.3) [78]. Stable enamines and enols have been also applied in condensation with azides [101, 102]. In one of the recent studies, an approach to 4-azolyl-1,2,3-triazoles *via* the cycloaddition of β-azolylenamines and sulfonyl azides was reported [103]. The reaction was conducted in acetonitrile at room temperature for 12 hours; yields were in the range of 50-93% (Fig. **20**). The potential of enamines in 1,3-dipolar cycloaddition reactions with azides has been recently reviewed [104].

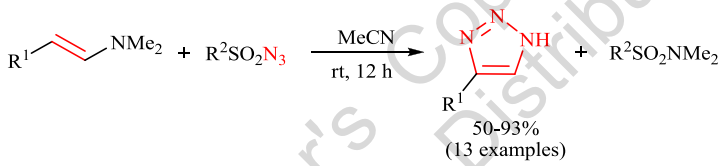

Fig. (20). The use of enamines for the preparation of 4-substituted triazoles (R^1 = thiadiazole, triazole, isoxazole, oxadiazole derivatives) [103].

A route to 5-peptidyl-1,2,3-triazoles was developed by Rademann and coworkers [105]. Polymer-supported peptidyl phosphorous ylide was first obtained; its reaction with azides could be rationalized as resulting from the contribution of enolate resonance structure (Fig. **21**). Peptides with an incorporated 1,2,3-triazole ring were also prepared.

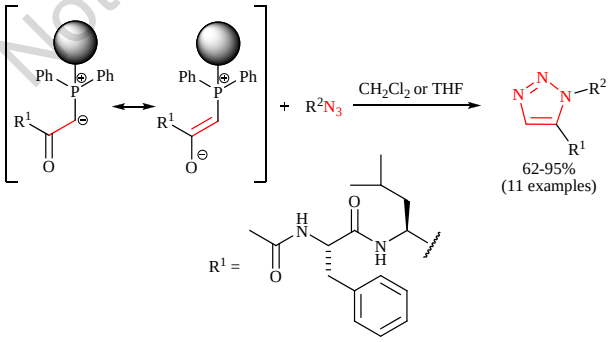

Fig. (21). Preparation of 5-peptidyl-1,2,3-triazoles [105].

Li and Wang described the organocatalytic aerobic synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from phenyl azide and α,β-unsaturated esters [106]. The use of DBU for zwitterion generation resulted in high efficiency of the reaction; chloroform was chosen as the optimal solvent (Fig. **22**). The procedure was shown to work well for various aromatic, but also aliphatic azides, and unsaturated esters as well as other electron-deficient olefins (67-91% yield after 48 hours at 80 °C). Under similar conditions, esters bearing a methoxy group at the C=C bond were converted to 1,4-disubstituted derivatives in very good yields (>82%) [107]. The approach was used to prepare triazoles with known biological activity, isonicotinoyl hydrazide and rufinamide, after an appropriate modification of the cycloaddition products.

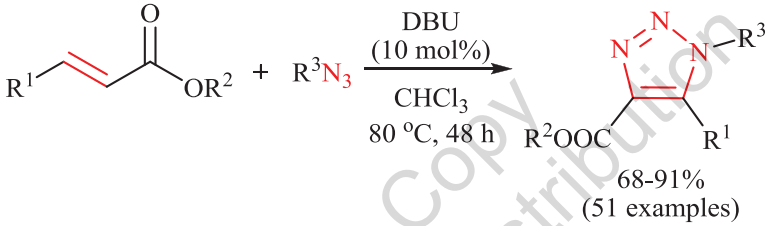

Fig. (22). Synthesis of trisubstituted 1,2,3-triazoles from α,β-unsaturated esters [106].

Piperidine was revealed as the best catalyst in the reaction of unsaturated ketones and organic azides carried out in DMSO at 80 °C for 72 hours [108]. 1,4,5-trisubstituted triazoles were formed in 72-89% yield (Fig. **23**). Wang and coworkers described also the efficient synthesis of triazole-olefins from α,β-unsaturated aldehydes and aryl azides catalyzed by diethylamine and DBU in DMSO [109]. High yields were noted after 2 hours of stirring at 50 °C (Fig. **24**). The use of allyl ketones in a similar reaction with diethylamine catalyst afforded a series of 1,4,5-trisubstituted 1,2,3-triazoles; both aryl and alkyl azides led to satisfactory yields (>75%) after 24 hours of stirring at 80 °C (Fig. **25**) [110].

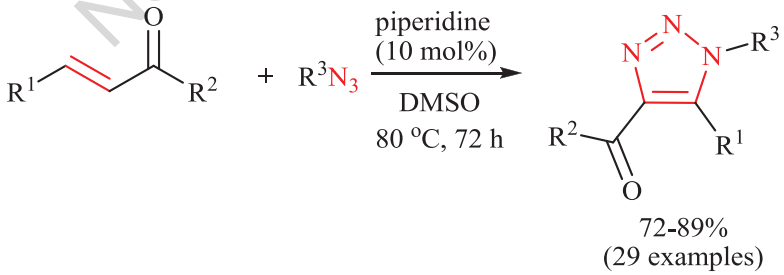

Fig. (23). Piperidine-catalyzed synthesis of 1,4,5-trisubstituted 1,2,3-triazoles [108].

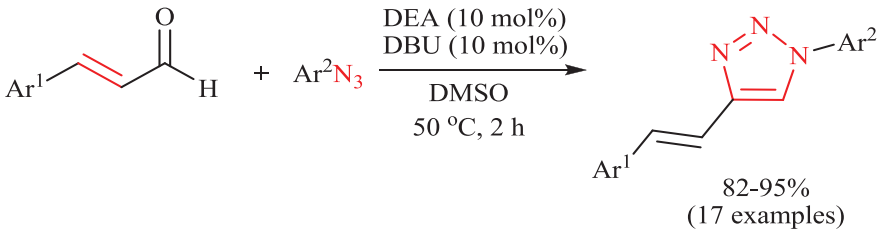

Fig. (24). Preparation of olefin-substituted triazoles [109].

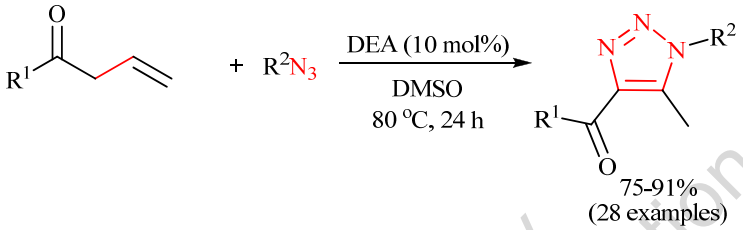

Fig. (25). Synthesis of 1,2,3-triazoles from allyl ketones and azides [110].

Elangovan and coworkers described a TEMPO-promoted oxidative cycloaddition of alkyl azides and various enones performed in water at 90 °C [111]. The control experiments established dioxygen as the best co-oxidant; moderate to excellent yields were noted for internal alkenes, and only 28% for vinyl methyl ketone (Fig. **26**).

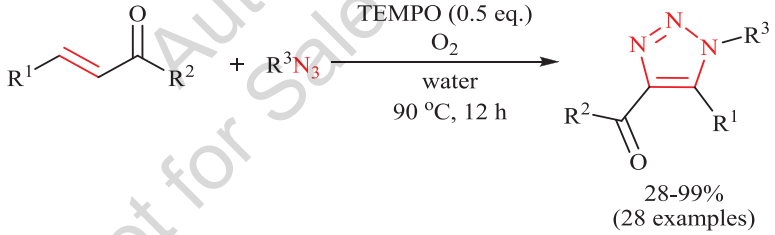

Fig. (26). TEMPO-promoted synthesis of 1,2,3-triazoles in water [111].

Transition metal catalysts were also efficient in preparation of triazoles from alkene derivatives. Copper acetate-catalyzed condensation of unsaturated esters, nitriles, aldehydes, amides, and aldehydes with aryl or benzyl azide was reported by Rohilla *et al.* [112]. The reaction was conducted in dimethylformamide in the presence of air at 85 °C for 6-39 h (Fig. **27**). Terminal alkenes led to disubstituted 1,2,3-triazole derivatives in high yields (with an exception of 4-nitrophenyl azide which gave only traces of desired product), while internal olefins gave moderate yields of trisubstituted derivatives.

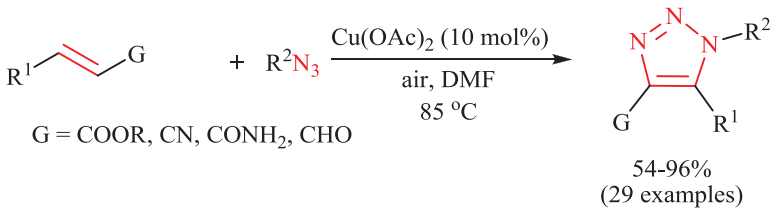

Fig. (27). Copper acetate-catalyzed synthesis of 1,2,3-triazoles from alkenes [112].

The use of copper(I) iodide as a catalyst in the preparation of 1,4-disubstituted triazoles was described by Janreddy *et al.* [113] A reaction of vinyl ketones with benzyl azide was performed in 1,4-dioxane at 80 °C under dioxygen with diisopropylethylamine as a base (Fig. **28**).

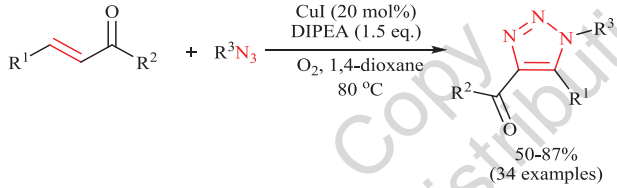

Fig. (28). Copper(I) iodide-catalyzed preparation of 1,2,3-triazoles [113].

A synthesis of trisubstituted triazoles from benzyl azide and enones (chalcone derivatives) catalyzed with $Ce(OTf)_3$ was also reported (Fig. **29**) [114]. Interestingly, a change of solvent from toluene to DMF resulted in formation β-aryl enaminones instead of cyclization products.

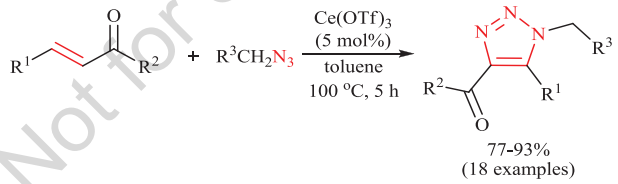

Fig. (29). Synthesis of triazoles from chalcones catalyzed by cerium(III) triflate [114].

An interesting example of tandem [3+2] cycloaddition–retro-Diels-Alder reaction was reported by van Berkel *et al.* [115] Oxanorbornadiene derivatives reacted with azides under ambient conditions yielding 1,4,5-trisubstituted 1,2,3-triazoles and furan. This approach allowed preparation of triazole-linked bioconjugates.

Cyclization of Azides with Alkanes

Various synthetic procedures were based on the condensation of azides with

alkenes generated *in situ* from the appropriately substituted alkanes. In the course of their studies on the reaction of nitroolefins with sodium azide, Quiclet-Sire and Zard found that vicinal acetoxy nitroalkanes formed by Henry reaction of nitroalkanes and aldehydes, treated with sodium azide in DMSO solution gave 1,2,3-triazoles in ca. 55% yield [87]. A highly regioselective, three-component reaction leading to 1,4,5-trisubstituted triazole derivatives was reported by Dehaen and coworkers [116]. Readily available building blocks were used: organic azides were reacted with dipolarophiles generated *in situ* from aldehydes and nitroalkanes in a Knoevenagel condensation catalyzed by morpholinium tosylate (Fig. **30**). The reaction was carried out in toluene at 100 °C under argon atmosphere in a sealed tube for 48 hours in the presence of BHT as additive and 4 Å molecular sieves. The scope of the transformation was considerably high though the yields were in many cases moderate.

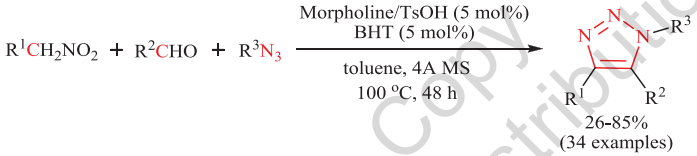

Fig. (30). Three-component reaction leading to1,4,5-trisubstituted 1,2,3-triazoles [116].

Wu *et al.* described a modified one-pot protocol for the preparation of 4-ary--1,2,3-triazoles: aryl aldehydes, simple nitroalkanes, and sodium azide were stirred in DMSO solution for 5 hours in an inert atmosphere at 110 °C in the presence of $NaHSO_3$ and Na_2SO_3 as additives (Fig. **31**) [117]. To avoid side reactions, a control of the concentration of nitroalkane and thus also nitrostyrene intermediate was achieved through the use of syringe pump. Yields were moderate, and the reaction failed for aliphatic aldehydes.

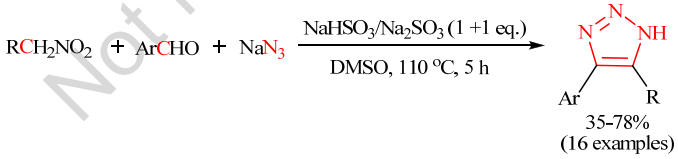

Fig. (31). Three-component synthesis of 4,5-disubstituted 1,2,3-triazoles [117].

Another three-component condensation of aromatic aldehydes, nitroalkanes and sodium azide was reported by Hu *et al.* [118]. The reactants were stirred overnight in DMSO solution at 70 °C in the presence of $AlCl_3$. Mono- or disubstituted 1,2,3-triazoles were obtained in 59-96% yield (Fig. **32**).

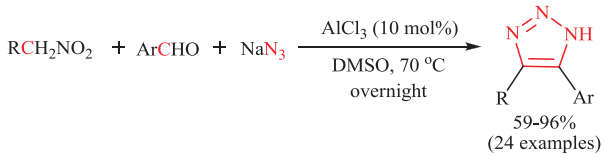

Fig. (32). $AlCl_3$-catalyzed three-component synthesis of 1,2,3-triazoles [118].

The application of Julia reagent for *in situ* generation of vinyl sulfone was tested by Chu and coworkers [119]. In a one-pot protocol, aromatic aldehydes were reacted with benzothiazol-2-yl sulfones and sodium azide under mild conditions (4 hours at 30 °C) to give 4,5-disubstituted 1,2,3-triazoles in moderate to high yields (up to 95%, Fig. **33**). Ammonium acetate was used as a catalyst, and 95% aqueous methanol was identified as the optimal reaction medium.

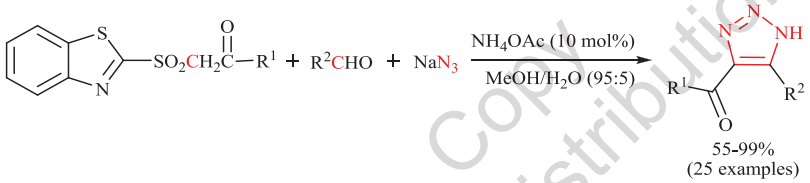

Fig. (33). The use of Julia reagents for the preparation of 1,2,3-triazoles [119].

Kuang and coworkers adopted the method introduced by Barluenga's group for the 1,2,3-triazole synthesis from arylvinyl bromides and sodium azide using palladium catalyst $Pd_2(dba)_3$ and xantphos [99]. In a modified protocol, *anti*--aryl-2,3-dibromopropanoic acids, used as terminal alkyne precursors, were reacted with NaN_3 in DMF at 110 °C for 36 hours affording 4-aryl-substituted triazoles in 50-71% yield (Fig. **34**) [120]. To overcome limitations connected with a high cost of the catalytic system, in the subsequent paper Jiang, Kuang and Yang described its replacement by copper(I) iodide in the presence of sodium ascorbate and cesium carbonate as a base which considerably shortened reaction times to 4 hours (in DMSO at 110 °C) [121]. For various aryl substituents, the yield varied from 52 to 95% (Fig. **34**). A similar catalytic system (however, DBU was found as an optimal base in this case) was applied in the preparation of 1,4-disubstituted 1,2,3-triazoles from *anti*-3-aryl-2,3-dibromopropanoic acids; *para*- or *ortho*-nitrobenzaldehyde and sodium azide served as organic azide precursors [122]. High yields (68-88% for *para*-nitrobenzaldehyde and various aryl derivatives of dibromopropanoic acid) were observed when hexamethyl-phosphoric diamide (HMPT) was used as a solvent, and the reaction was conducted for 3 hours at 80 °C.

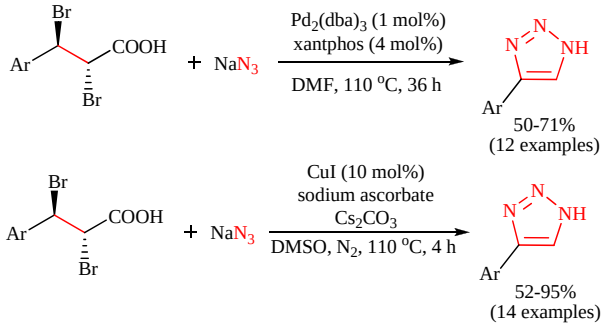

Fig. (34). Synthesis of 1,2,3-triazoles from dibromopropanoic acids [120, 121].

Reactions of Azides with Active Methylene Compounds

The use of dicarbonyl compounds in the synthesis of 1,2,3-triazoles dates back to Dimroth's work on the condensation of ethyl acetylacetate with phenyl azide in the presence of sodium ethoxide [123]. Later, various dicarbonyl compounds and their derivatives have been used for similar preparations, as exemplified by acetylacetone, ethyl malonate, acetoacetate, or cyanoacetate. Recently, this approach has found its application to obtain novel triazole-based systems, including compounds used as bioisosteres of carboxylic acid of phenol functionality [124] or trifluoromethyl derivatives [125]. A continuous flow procedure for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles starting from aniline derivatives was developed by Stazi *et al.* [126]. In a recent report, a library of β-ketophosphonates was prepared from esters and dimethyl methylphosphonate, and applied in a cycloaddition with alkyl and aryl azides in acetonitrile solution (Fig. **35**) [127]. An addition of 2 equivalents of potassium hydroxide resulted in formation of 1,5-disubstituted 1,2,3-triazoles in variable yields (26-97%). Also nitriles – acetonitrile and its derivatives, and particularly maleonitrile were reacted with azides in the presence of bases to yield 1,2,3-triazoles [128, 129]. In a recent report, Ramachary and coworkers used Cs_2CO_3 as a catalyst for the reaction of aryl azides and aromatic derivatives of acetonitrile carried out in DMSO-water mixture at room temperature (Fig. **36**) [130].

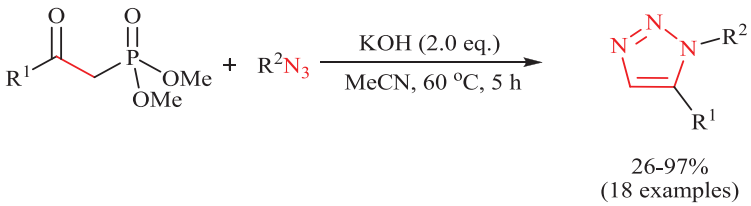

Fig. (35). Synthesis of 1,2,3-triazoles from ketophosphonates and azides [127].

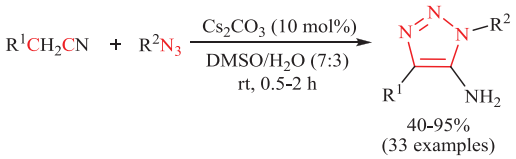

Fig. (36). Azide-acetonitrile click reaction catalyzed with cesium carbonate [130].

As an interesting, though a specific example of azide-carbonyl condensation, trialkylphosphine-induced cyclization of α-azido esters in THF/H_2O observed by Taylor and Lohani is worth mentioning (Fig. **37**) [131]. In contrast, the use of triphenylphosphine or triethyl phosphite led to non-cyclic products.

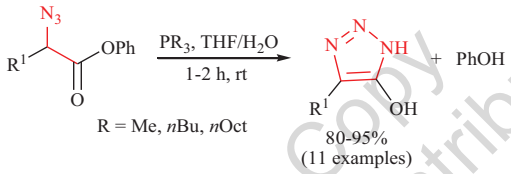

Fig. (37). Trialkylphosphine-induced cyclization of azide esters [131].

In 2008, Ramachary and coworkers reported an organocatalytic approach to bicyclic 1,2,3-triazoles [132]. Reaction of cyclic enones (Hagemann's ester derivatives) with tosyl azide was performed in the presence of L-proline (20 mol%). Formation of dieneamine was postulated as a key step of the reaction mechanism. Secondary amines (diethylamine showed the highest efficiency) were found by Wang's group to catalyze the synthesis of 1,4,5-trisubstituted-1,2-3-triazoles from organic (mostly aryl) azides and diketones, ketoesters and ketonitriles [133]. Reaction performed under relatively mild conditions (DMSO solvent, 70 °C) furnished target compounds in high yields (in most cases >90%) after 1-48 hours (Fig. **38**). Bressy, Pons and coworkers extended this approach to non-activated ketones; in their hands, proline was an optimal catalyst, and the use of microwave heating allowed a significant shortening of reaction times (1 hour at 80 °C, Fig. **39**) [134]. Also Wang's group described an application of enamine-mediated methodology to a broad spectrum of carbonyl compounds (mostly cyclic ketones) and azides; optimization studies indicated pyrrolidine as the most efficient catalyst [135]. For a preparation of 1,4-disubstituted 1,2,3-triazoles, a modified two-step procedure was used involving condensation of organic azides with aliphatic aldehydes followed by oxidation with *meta*-chloroperbenzoic acid (Fig. **40**) [136].

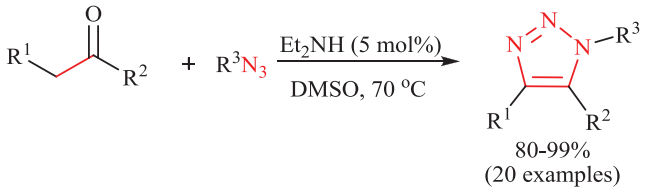

Fig. (38). Diethylamine-catalyzed synthesis of 1,2,3-trazole derivatives [133].

Wang and coworkers reported an enamine-catalyzed green synthesis of trisubstituted triazoles in water as the only solvent [137]. *N,N*-Dioctylprolinamide used as catalyst for the condensation of aromatic azides and various (in most cases cyclic) ketones conducted at 80 °C for 24-28 hours led to moderate to high yields (68-93%).

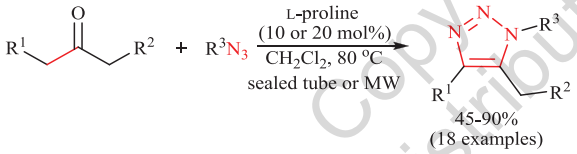

Fig. (39). Organocatalytic triazole synthesis from azides and non-activated ketones [134].

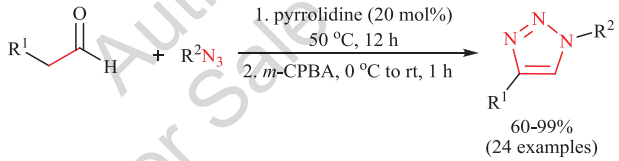

Fig. (40). Organocatalytic one-pot preparation of triazoles from aldehydes and azides [136].

Ramachary's group introduced an alternative organocatalytic strategy based on the formation of enolates from aldehydes upon addition of a tertiary amine (Fig. **41**) [138]. Various 1,4-disubstituted 1,2,3-triazoles were formed in reasonable and high yields, at high rates and under mild conditions (30 minutes at room temperature in DMSO). Best results were obtained for 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) catalyst; it was also most effective in the reaction of ketones with aromatic azides yielding trisubstituted triazole derivatives (Fig. **42**) [139]. The versatile, high-yielding methodology was applied to reactants bearing diverse functional groups. The versatility was further confirmed by its application for the preparation of 4-arylthio-1,2,3-triazoles, which could be oxidized with *m*CPBA to the corresponding sulfoxides or reduced with Raney Ni to remove

sulfur functionality [140]. Ramachary and coworkers reported also an enolate-mediated cycloaddition of carbonyl compounds to vinyl azides which opened a route to *N*-alkyl derivatives (Fig. **43**) [141, 142]. In certain preparations, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) performed better than DBU catalyst [142].

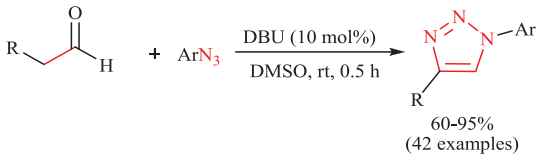

Fig. (41). Enolate-mediated click reaction of aldehydes and azides [138].

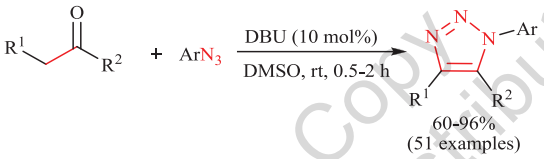

Fig. (42). Enolate-mediated click reaction of ketones and azides [139].

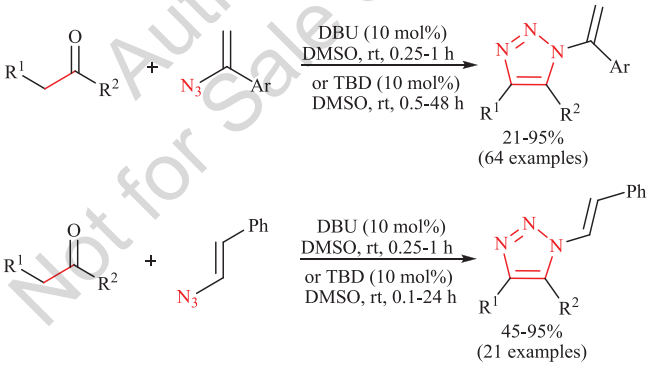

Fig. (43). Ramachary's organocatalytic syntheses of vinyl-substituted triazoles [141, 142].

DBU-catalyzed condensation of β-ketoamides with aromatic azides was reported by Li and coworkers; 24 hours of stirring in chloroform resulted in 84-96% yield (Fig. **44**) [143].

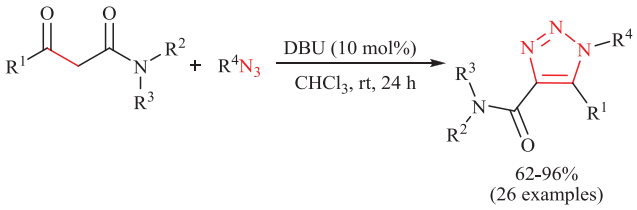

Fig. (44). DBU-catalyzed reaction of ketoamides with azides [143].

Malononitrile was applied as a catalyst for the reaction of aromatic azides with aliphatic aldehydes in the presence of DBU (Fig. **45**) [144]. In a suggested mechanism, supported by DFT calculations, the assistance of active alkylidenes was included, which was in agreement with the fact that isolated alkylidene malononitriles could be reacted with azides as well to give identical products.

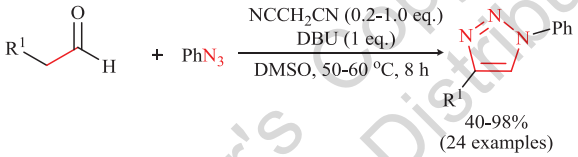

Fig. (45). Malononitrile-catalyzed preparation of 1,4-disubstituted 1,2,3-triazoles [144].

The organocatalyzed reactions of dicarbonyl compounds with azides were successfully applied for the synthesis of various selenium derivatives [71, 145 - 148]. Sulfonyl-substituted triazoles were also prepared [149], including fully substituted glycoconjugates [150]. Pyrrolidine-catalyzed condensation of 4-chloroquinoline azides and ketoesters yielded bifunctional hybrids with promising antioxidative properties [151]. Singh *et al.* used DBU-water system for the reaction of a series of active methylene compounds with aryl and alkyl azides under conventional heating, but also with microwave or ultrasound irradiation [152]. A diethylamine-catalyzed cycloaddition allowed preparation of novel triazole derivatives exhibiting an antiproliferative activity [153].

To avoid post-cyclization triazole modifications, various protocols have been introduced in which desired functionalities are built into the ring during its preparation. In many cases, the desired effect can be achieved through multicomponent reactions [43]. Among recent alkyne-free procedures, 1,4,5-trisubstituted 1,2,3-triazoles were prepared from primary alcohols, sodium azide and active methylene ketones (Fig. **46**) [154]. In a one-pot synthesis performed in DMF-DMSO mixture at 80 °C, KOH acted as a base. Yields were in most cases high, but they dropped down when 2,2-difluoro-2-phenylsulfanylethanol was

used. Benzylic alcohols, ketones, and diphenylphosphoryl azide were condensed in DMF in a procedure described by González-Calderón *et al.* (Fig. **47**) [155]. An excess of DBU was found necessary to afford trisubstituted triazoles in moderate to high yield. In a subsequent report from the same group, organic azides were generated *in situ* from NaN_3 and alkyl halides and reacted with enolate derived from ketone treated with DBU [156]. Desired triazole products were formed in 73-82% yield (Fig. **48**).

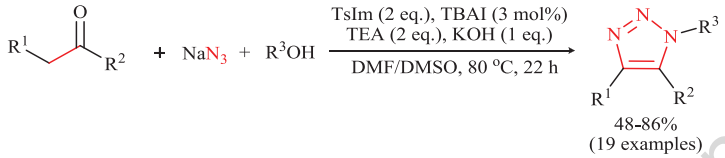

Fig. (46). Three-component synthesis of 1,4,5-trisubstituted triazoles [154].

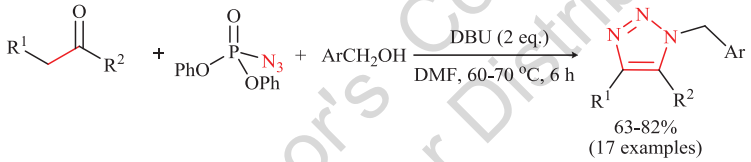

Fig. (47). Synthesis of triazoles from ketones, benzylic alcohols and DPPA [155].

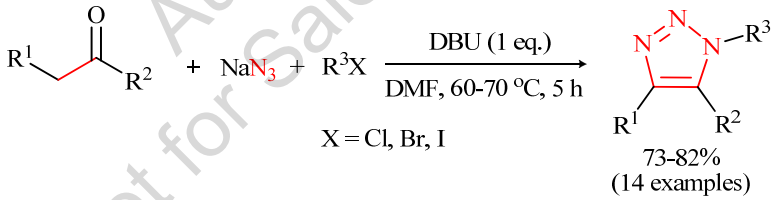

Fig. (48). DBU-catalyzed preparation of triazoles from ketones, alkyl halides, and sodium azide [156].

Other Cyclizations

In a versatile Huisgen [3+2] dipolar cycloaddition, 1,2,3-triazole ring is formed form three-nitrogen and two-carbon fragments. Certainly, alternative approaches have been also explored, in part with an intention to omit the use of azides. However, even in certain preparations in which they have been applied, a diazo transfer has been observed, with the third ring N atom typically incorporated from amine co-reactant.

The Use of Azide as a Dinitrogen Source

During their studies on the Schiff bases – enamines equilibrium, Bianchetti, Dalla Croce and Pocar investigated the reaction of these compounds with tosyl azide and *p*-nitrophenyl azide [157]. To their surprise, heating of *N*-(2-propylidene)propylamine with the latter resulted in 1-propyl-5-methyl-1,2,3-triazole together with 4-nitroaniline, indicating a diazo transfer from the azide. Long forgotten, this approach has been utilized for the base-catalyzed reactions of enaminones with sulfonyl azides or other azides containing electron-withdrawing substituents, as exemplified by papers from the groups of Chakrasali, Ferreira, Donnici, and Dorokhov [158 - 161]. More recently, a series of 5-trifluoromethyl-1,2,3-triazole derivatives, including a rufinamide analogue, was prepared by this route using mesyl azide and DBU as a catalyst (Fig. **49**) [162].

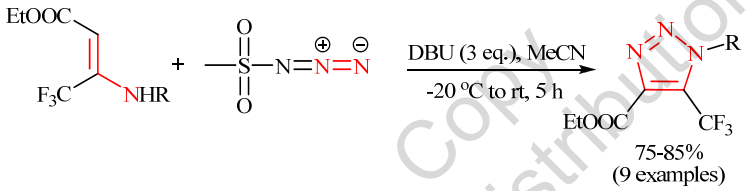

Fig. (49). DBU-catalyzed synthesis of CF_3-substituted triazoles [162].

Cui and coworkers described a metal-free multicomponent synthesis of 1,5-disubstituted 1,2,3-triazoles, starting from primary amines and propynones [163]. The reaction of the *in situ* formed enaminones with tosyl azide in the presence of lithium *tert*-butoxide resulted in a deacylated cyclic product (Fig. **50**).

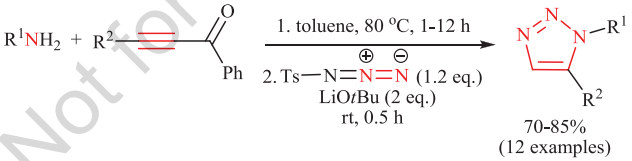

Fig. (50). Synthesis of 1,5-disubstituted 1,2,3-triazoles in a multicomponent cascade reaction [163].

Wan *et al.* showed the possibility to apply NH-enaminones, which could be obtained by transamination of *N*,*N*-dimethylenaminones with aniline derivatives, in the diazo transfer reaction with tosyl azide catalyzed with sodium *tert*-butoxide [164]. Various 1-aryl-4-acyl-1,2,3-triazoles were obtained after stirring for 2 hours at room temperature in 59-90% yield (Fig. **51**).

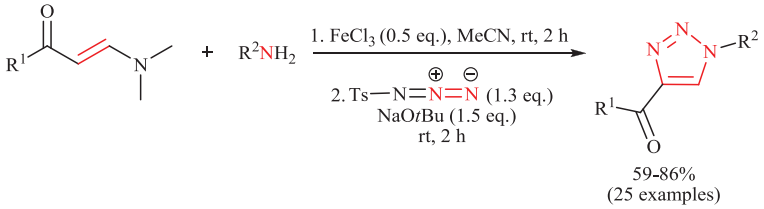

Fig. (51). One-pot preparation of triazoles involving diazo transfer [164].

In a noteworthy development of the diazo transfer procedure reported by Thomas *et al.*, readily available enolizable ketones, primary amines and 4-nitrophenyl azide were subjected to a three-component reaction with acetic acid as a catalyst and 4 Å molecular sieves in toluene at 100 °C (Fig. **52**) [165]. The protocol offered high reaction yields, wide substrate scope, and a possibility to perform it on a gram scale. Moreover, 4-nitroaniline product could be transformed to diazonium salt which was extracted to the aqueous layer and converted back to azide which could be reused (Fig. **53**).

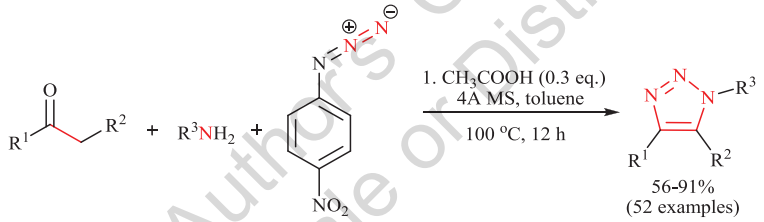

Fig. (52). One-pot synthesis of di- and trisubstituted 1,2,3-triazoles *via* diazo transfer [165].

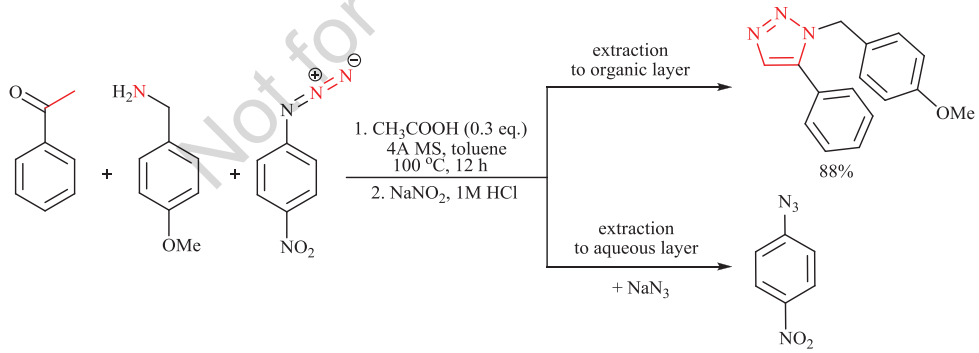

Fig. (53). Bulk synthesis of disubstituted triazole involving azide regeneration [165].

Preparation of *N*-amino-1,2,3-triazoles *via* a diazo transfer was described by Nagarajan *et al.* [166]. Keto esters were treated with Boc-hydrazine, and the

resulting hydrazones reacted with 4-toluenesulfonyl azide or imidazolesulfonylazide in the presence of DBU (Fig. **54**). The procedure worked well for various β-keto esters, including cyclic ones.

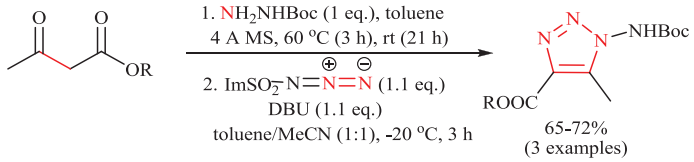

Fig. (54). Preparation of *N*-amino-1,2,3-triazoles [166].

Azide- and Acetylene-Free Protocols

A variety of azide-free procedures have been developed for the synthesis of 1,2,3-triazole system [167 - 169]. Part of them, similarly to the very first preparations by von Pechmann [2, 3], make use of appropriately substituted hydrazones. In 2012, a dimerization of bis-arylhydrazones under aerobic conditions catalyzed by copper(II) acetate hydrate was described (1,2,4-triazoles could be obtained from the same substrates) [170]. Various 2,4,5-substituted derivatives, including unsymmetrical ones, were obtained in 45-90% yield after heating for 3-7 hours in toluene at 60 °C (Fig. **55**). The reaction was also conducted on a gram scale, and 2,4,5-triphenyl-1,2,3-triazole was isolated in 75% yield after 9 hours.

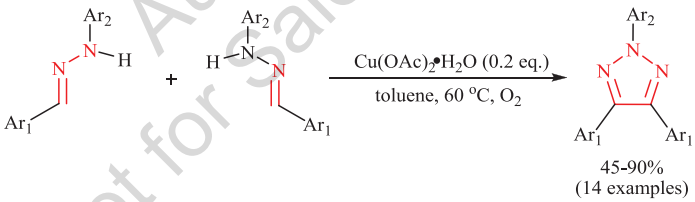

Fig. (55). Dimerization of bis-arylhydrazones [170].

A transition metal-free dimerization of *N*-tosylhydrazones was reported by Panda *et al.* [171]. The reaction was conducted in DMF at 100 °C for 4-10 hours in the presence of Cs_2CO_3; both symmetrical and unsymmetrical 4,5-diaryl-1,2-3-triazoles were formed in 36-91% yield (Fig. **56**). Coupling of hydrazone with nitriles was also attempted, leading to a mixture of hetero- and homocoupling products, while the reaction with imines proceeded smoothly yielding exclusively a regiospecific cross-coupled product.

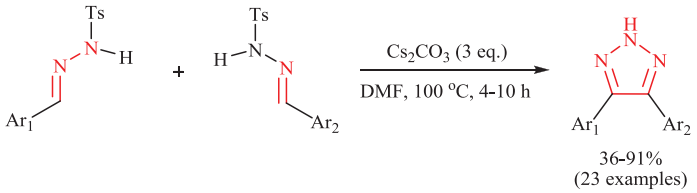

Fig. (56). Heterocoupling of tosylhydrazones [171].

In 1986, Sakai and coworkers introduced a protocol for 1,2,3-triazole synthesis from α,α-dichlorotosylhydrazone and primary amines [172]. 1,4-Disubstituted products were isolated in 83-84% yield (Fig. **57**). This method was applied in the preparation of various derivatives exhibiting antibacterial activity [94, 173, 174] and in a regiospecific solid-phase triazole synthesis [175]. However, the scope and limitations of Sakai's reaction was studied only in 2012 by Westermann and coworkers [176]. Various aromatic and aliphatic amines (including psychosine) and different dichlorotosylhydrazones prepared from the corresponding ketones were tested, proving the versatility of this approach (Fig. **58**).

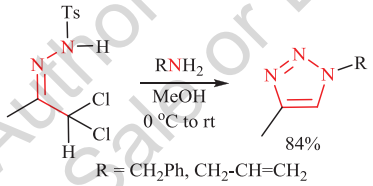

Fig. (57). Sakai's synthesis of 1,2,3-triazole [172].

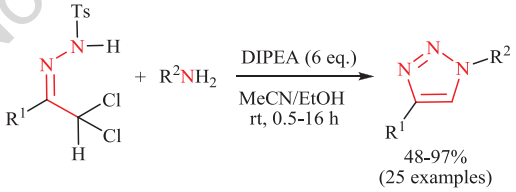

Fig. (58). Reaction of tosylhydrazones with various amines [176].

Zhang's group reported a copper(II) acetate-mediated synthesis of 1,4-disubstituted or 1,4,5-trisubstituted 1,2,3-triazoles from tosylhydrazones and anilines (Fig. **59**) [177]. Later, this methodology was extended to aliphatic amines

by the addition of *N*-acetylglycine to the reaction mixture (Fig. **60**) [178]. In a one-pot metal-free modification, ketones, *N*-tosylhydrazine, and primary amines were heated for 12 hours in DMSO at 100 °C in the presence of molecular iodine used as an activator [179]. Higher yields were noted for aniline derivatives, while aliphatic amines gave more complicated and difficult to separate reaction mixtures (Fig. **61**).

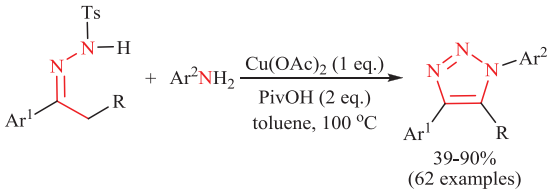

Fig. (59). Condensation of tosylhydrazones with anilines catalyzed by copper(II) acetate [177].

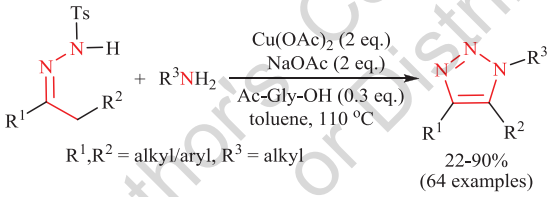

Fig. (60). Synthesis of *N*-alkyl-substituted triazoles from tosylhydrazones [178].

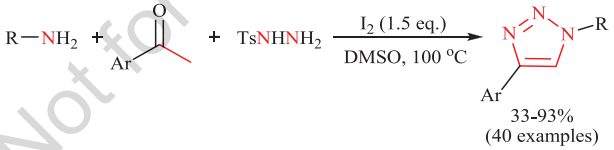

Fig. (61). Iodine-mediated synthesis of triazoles from tosylhydrazine, amines, and aromatic ketones [179].

Independently, Wang, Ji and coworkers described an efficient iodine/TBHP-mediated reaction of tosylhydrazones and anilines, including alkene- and alkyne-substituted derivatives, therefore showing the tolerance for various functionalities (Fig. **62**) [180]. The same group used monochlorotosylhydrazones derived from the respective chloroketones or chloroaldehydes in the reaction with anilines in DMF under air (50 °C, 3 h), yielding 1,4- or 1,5-disubstituted 1,2,3-triazoles (Fig.s **63**, **64**) [181]. A two-step procedure using arylketones and tosylhydrazine

in the first step, followed by addition of aniline derivative, I_2 and TBHP was optimized by Gu *et al.* in a continuous flow reactor system [182]. A possibility to scale up the reaction to a 0.1 mole scale was demonstrated.

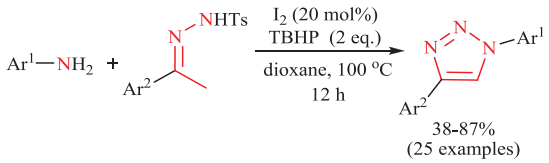

Fig. (62). Iodine/TBHP-mediated synthesis of triazoles from tosylhydrazones and anilines [180].

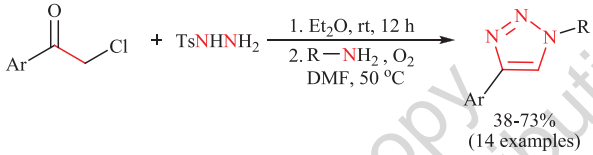

Fig. (63). Synthesis of 1,2,3-triazoles from tosylhydrazine, chloroketones, and amines [181].

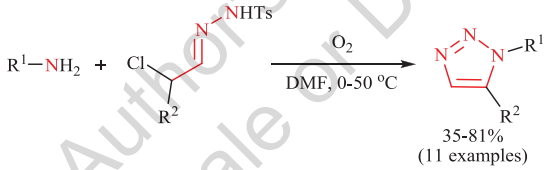

Fig. (64). Synthesis of 1,5-disubstituted triazoles from chlorotosylhydrazones [181].

A multicomponent preparation of 1,5-disubstituted triazole derivatives was reported by Wan *et al.* [183]. Tosylhydrazine, anilines, and enaminone were stirred in DMSO at 110 °C for 12 h in the presence of molecular iodine, leading to 1-aryl-5-acyl-1,2,3-triazoles in reasonable yields (40-71%, Fig. **65**).

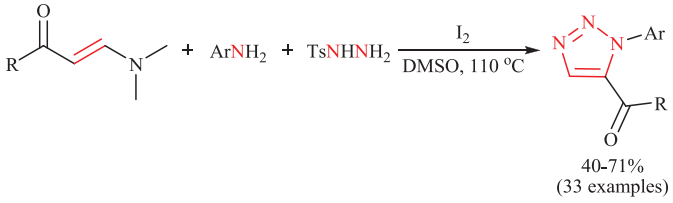

Fig. (65). Reaction of enaminones, anilines and tolsylhydrazine mediated by I_2 [183].

4-Aryl-substituted triazoles were formed by the cyclization of semicarbazones of arylglyoxaldoximes [184]. The reaction required the addition of $Na_2S_2O_4$ as a dehydrating agent, a base ($NaHCO_3$) and the presence of dioxygen, and under the optimized conditions (DMF/H_2O solvent, 110 °C, pure O_2) various derivatives were obtained in 69-98% yield after 10-20 minutes (Fig. **66**).

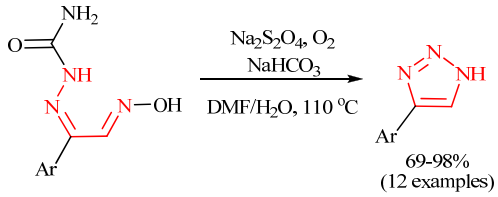

Fig. (66). Cyclization of semicarbazone leading to 1,2,3-triazole [184].

1,2,3-Triazole ring can be constructed in a [3+2] cycloaddition of diazocompounds with amines. Typically, α-diazodicarbonyl derivatives are used, their conversion to diazoimines results in a cyclization to a triazole product [79]. This approach was utilized by Costa *et al.* for the synthesis of compounds exhibiting tuberculosis inhibitory activity, their compounds were prepared through cycloaddition of diazomalonaldehyde with substituted aniline hydrochlorides in water in 73-86% yield [185]. Arylsulfonylhydrazide-1,2,3-triazole derivatives tested as anti-HIV-1 agents were obtained in moderate yields in a two-step procedure, involving the condensation of ethyl 2-diazoacetoacetate with substituted phenylhydrazine hydrochlorides, followed by treatment with hydrazine hydrate [186].

In a report by Li *et al.*, a copper(II)-catalyzed cycloaddition of secondary amines with alkyl diazoacetates was developed (Fig. **67**) [187]. Under optimized conditions, the reaction was conducted with 30 mol% of $CuBr_2$ in DMF for 5-17 hours at room temperature in the presence of 3 equivalents of DBU and under an oxygen atmosphere (1 atm). Various 1,4,5-trisubstituted 1,2,3-triazole derivatives were obtained in moderate to high yields (40-96%), showing the versatility of the approach.

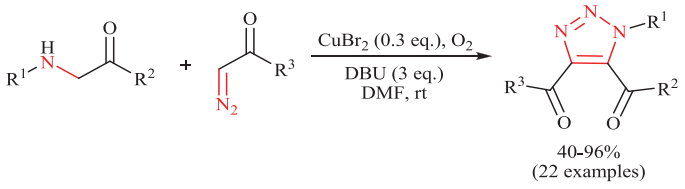

Fig. (67). Synthesis of 1,2,3-triazoles from diazoacetates and secondary amines [187].

The use of dimethyl α-diazo-β-oxopropylphosphonate (Bestmann-Ohira reagent) as the diazo transfer reagent for the synthesis of phosphonylated five-membered triazo heterocycles was described by Mohanan and co-workers [188]. Condensation with aldehydes and aliphatic amines yielded 1,2,3-triazolines, while in case of aniline derivatives a spontaneous air oxidation occurred leading to 1,2,3-triazoles in 31-63% yield (Fig. **68**). The reaction proceeded under mild conditions, at room temperature and with no catalyst; the presence of a base (K_2CO_3 was chosen) was found necessary due to insufficient basicity of aromatic amines.

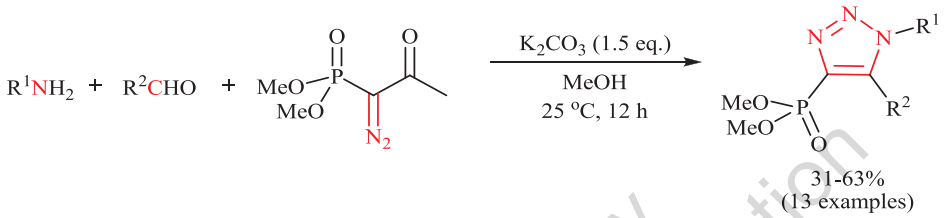

Fig. (68). Preparation of phosphonylated triazoles *via* a three-component domino approach [188].

Cyclocondensation of α-diazoketones with amines catalyzed by iron(II) chloride was performed yielding 1,4,5-trisubstituted 4-amide-1,2,3-triazoles in up to 93% yield (Fig. **69**) [189]. Activation of carbonyl group by an intramolecular hydrogen bond was suggested to be a prerequisite of the efficiency of the reaction.

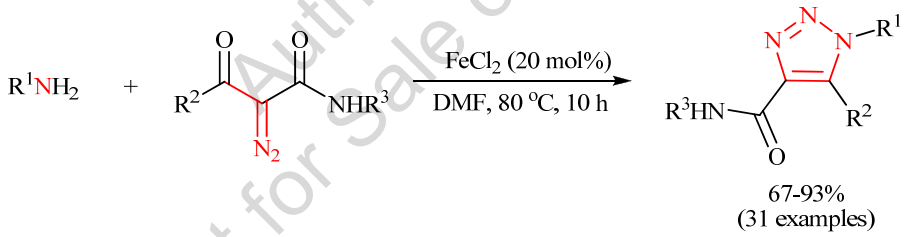

Fig. (69). Cyclocondensation of diazoketones with amines [189].

Diazocompounds have been also reacted with isonitriles. In an uncatalyzed condensation of *N*-fluoropyridinium salts generated *in situ* with various isonitriles and diazocompounds, mixtures of triazoles (12-59% yield) and picolinamides were obtained by Kiselyov [190]. Application of silver carbonate as a catalyst for the reaction of isocyanobenzene derivatives with 2,2,2-trifluorodiazoethane (optimized conditions: DMF solvent, 4Å molecular sieves, 6 hours at 40 °C) resulted in various 1,4-disubstituted triazole products in 52-95% yield; lower yields were observed for aliphatic isonitriles (Fig. **70**) [191]. Diazoacetates and trimethylsilyldiazomethane also afforded the desired cyclic products. Interest-

ingly, a formation of a trisubstituted derivative was detected when an excess of trifuorodiazoethane was used.

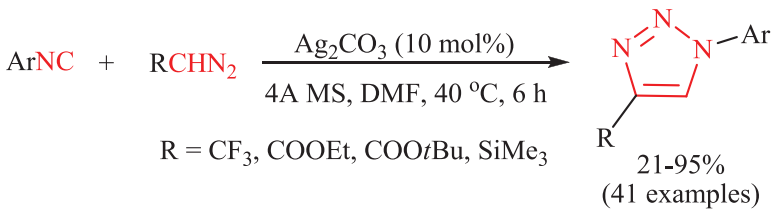

Fig. (70). Silver-catalyzed cycloaddition of isonitriles and diazocompounds [191].

The use of diazonium salts for the diazotization of diaminomaleonitrile was reported by Al-Azmi and Kalarikkal [192]. 1,4,5-Trisubstituted triazole derivatives were obtained under mild conditions in moderate and low yields (up to 44%).

Preparation of Chiral 1,2,3-Triazoles

If appropriately substituted, 1,2,3-triazoles can be chiral. This fact is of key importance for many applications of derivatives of these heterocycles, in particular connected with their biological activities. For example, several triazole-containing drugs that are currently in use or under final phases of tests, tazobactam, solithromycin, cefatrizine and radezolid (Fig. **71**) are administered as single enantiomers [193]. This generates a demand for efficient synthetic procedures of preparation of these compounds in enantiomerically pure or enantiomerically enriched form.

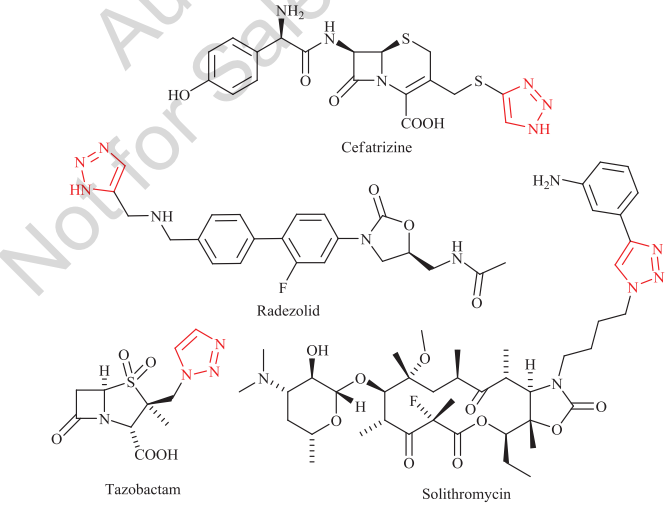

Fig. (71). Enantiopure drugs containing 1,2,3-triazole moiety [193].

In principle, a stereogenic center can be present in the triazole ring. In case of 4*H*-tautomers, two different substituents at 4-C are sufficient to cause the desired

effect. Though various compounds of this kind have been prepared so far [194 - 196], including C-4-spiro derivatives, to the best of our knowledge, all of them have been racemic.

For other tautomers, one has to introduce chiral groups at N or C atoms, leading to N-chiral (substitution on N-1 or N-2) or C-chiral (C-4 or C-5 bearing a chiral substituent) 1,2,3-triazoles (Fig. **72**). In certain cases, triazole moiety connects two carbohydrate or peptide fragments, and a combination of the aforementioned situations can be found.

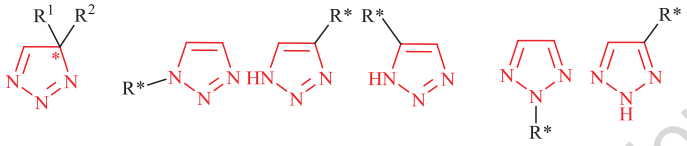

Fig. (72). Types of chiral 1,2,3-triazoles (from left to right): ring-chiral *4H* tautomer, *1H* tautomer bearing chiral substituents at 1, 4 or 5 position, and *2H* tautomer with chiral group at N-2 or C-4.

Most common pathways used to prepare enantiomerically pure triazole derivatives utilize chiral reactants. Typically, a substrate from a chiral pool is converted to a corresponding azide which can be reacted with a terminal alkyne in a Huisgen-type cycloaddition. Under click conditions, it leads to N-1-chiral 1,2,3-triazole product. Alternatively, tosylhydrazone cyclization with an enantiopure amine can lead to a similar effect [178]. Introduction of chirality to C-4 or C-5 most frequently makes use of chiral alkynes and Cu or Ru catalyst, respectively. A great number of enantiomerically pure 1,4-substituted 1,2,3-triazoles have been prepared *via* this route. Though carbohydrate-containing conjugates have been already obtained before the introduction of CuAAC reaction [197 - 199], this protocol is now the method of choice for the synthesis of these assemblies [22, 200, 201]. Starting from the classical Meldal report [11], click reaction have been also utilized with a success to introduce triazole moiety into peptides [202, 203] and glycopeptides [204 - 206]. Various chiral functionalities have been connected to this five-membered heterocycle, as exemplified by *Cinchona* alkaloids [20, 207 - 210] or cyclophane (a rare case of planar chirality) [211, 212]. Less commonly, chiral substituents have been introduced into C-5 atom; RuAAC or alternative cycloaddition methods have been used in this purpose [213, 214].

Post-synthetic modifications have been also used to introduce chirality on a triazole ring [215]. This way, many N-2 chiral derivatives of 2*H*-tautomer have been obtained, including nucleoside analogs and bis-triazoles [216 - 222]. Typically, 2-substituted product is isolated as the main product of alkylation [216, 219 - 221]. Enantiomerically pure derivatives are obtained when a single

enantiomer of substrate is used. In a noteworthy different approach, a chiral thiourea organocatalyst was applied for the asymmetric aza-Michael reaction of 4-aryl triazoles with cyclic enones, leading to 2,4-disubstituted compounds as major products in 62-75% yield and up to over 99% *ee* (Fig. **73**) [223].

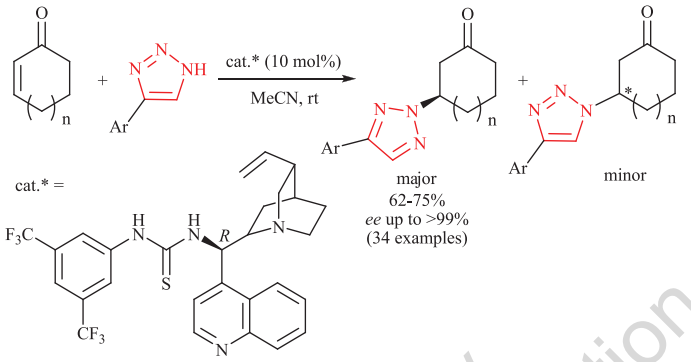

Fig. (73). Organocatalytic stereoselective modification of 1,2,3-triazole [223].

Other methods used for the preparation of enantiomerically enriched 1,2,3-triazoles: kinetic resolution of racemic azides or terminal alkynes, and desymmetrization of prochiral bis-azides and bis-alkynes have been recently reviewed [38].

Summary

When planning a synthesis of a new 1,2,3-triazole derivative, one should be aware that various approaches to this system are possible, with click reaction being the most popular as a versatile and operationally simple methodology. However, alternative cycloaddition methods should be considered as well, even if part of them require long reaction times (microwave heating could be helpful) and harsh conditions. The choice should be based on the availability of reactants and on particular target system, *i.e.* what substitution pattern and functional groups should be present in the desired structure. If possible, also environmental aspects should be taken into account.

SELECTED APPLICATIONS OF 1,2,3-TRIAZOLES

Modifications of 1,2,3-triazole synthesis introduced by Meldal, Sharpless and Fokin have caused these heterocycles to be widely available and thus most limitations for their possible applications are no longer valid. Prepared mainly by means of click reaction, they have become constituents of various assemblies. The use of triazole as a versatile linker that allows the easy and convenient connection of two functionalities can be encountered very frequently; quite often, however, the heterocyclic subunit itself acts as a functional element of the construction.

The unique properties of 1,2,3-triazole system: chemical stability connected with various possible modes of interaction with cations, anions, but also neutral molecules [224, 225] result in widespread applications spanning from chemosensors [225], catalysts [226], materials science [227] (*e.g.* dyes [228], corrosion inhibitors [229], photostabilizers [230]), polymer [24, 25, 41, 231, 232] and supramolecular chemistry [51, 225]. Triazoles are used as building blocks in organic synthesis [233 - 235]. Undoubtedly, however, the main interest is connected with their biomedical applications.

Though 1,2,3-triazole ring is not found in biological systems, it can be utilized to replace a fragment of a biomolecule – another heterocycle (imidazole, pyrimidine, *etc.*), but also a non-cyclic fragment of similar size, rigidity, polarity, and ability of hydrogen bond formation, like amide bond or carboxylic group (*vide infra*) [55]. Introduction of triazole can modify the functions of the original system and its activity, but even if the latter in not affected, other properties (*e.g.* solubility, robustness – triazoles are stable to metabolic degradation or oxidation) can be significantly altered.

Besides these bioisostere applications, triazole moiety itself serves as pharmacophore and is used as a target for drug discovery and modulation [193]. The prepared derivatives exhibit antiviral (including anti-HIV), antibacterial, antifungal, anticancer, antimalarial, antiepileptic, antiallergic, and antioxidant properties and serve as inhibitors of various enzymes [236 - 238].

Use of click chemistry allows labeling of biomolecules (proteins, DNA, and even viruses) by attachment of fluorescent dyes, sugars, peptides [239 - 241]. Though both alkyne and azide are biorthogonal, biological damage caused by catalysts used in CuAAC reaction limits the application of this process *in vivo* [242].

As already mentioned in the Introduction, various applications of 1,2,3-triazoles have been comprehensively covered in numerous review articles [27 - 30, 45 - 56]. Consequently, in this part only general overview will be presented with recent examples showing chosen functions of triazole core in various assemblies.

1,2,3-Triazole As a Bioisostere

The structural properties of 1,2,3-triazole moiety allow its application as a replacement of various biologically important functionalities [55]. In particular, planarity of this heterocycle, its high dipole moment, and the presence of hydrogen bond donors and acceptors make it an ideal amide bond equivalent. These features led to the widespread use of triazoles as peptidomimetics [243 - 246]. Similarities of *trans*-amides with 1,4-disubstituted, and *cis*-amides with 1,5-disubstituted derivatives are depicted in Fig. (**74**) [243]. On the other hand, 5-

amino-1,2,3-triazole-4-carboxylate was used as a peptide turn inducer (Fig. **75**) [59]. The prepared assemblies benefit from the stability of the isostere to enzymatic degradation. Numerous modified peptides have been prepared, many of them exhibit interesting biological activity, in certain cases even higher in comparison with a parent compound [55]. This way, novel chemotherapeutics have been developed, including analogues of Linezolid, Amprenavir, Vorinostat, and many others, also cyclic peptides; examples can be found in the literature [55, 243].

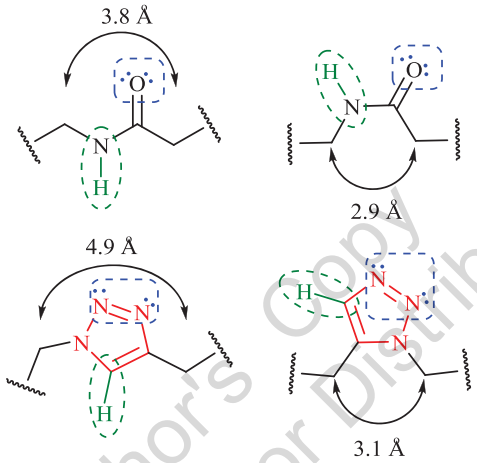

Fig. (74). Similarities between *trans*-amide and 1,4-disubstituted 1,2,3-triazole (left column) and *cis*-amide and 1,5-disubstituted 1,2,3-triazole (right column). Hydrogen bond accepters indicated by blue frames, hydrogen bond donors marked in green [243].

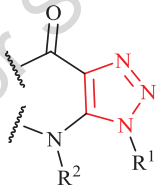

Fig. (75). 5-Amino-1,2,3-triazole-4-carboxylate serving as peptide turn inducer [59].

Isosteric replacement of ester moiety, increasing resistance to enzymatic degradation, has been also described [55]. Also lactones [247] and carboxylic acids [248] have been exchanged to give rigid fragments with the preserved capability of hydrogen bond formation. In particular, hydroxytriazole system was introduced as a bioisostere of carboxylic acid or phenol, exploiting a scaffold hoping approach (Fig. **76**) [124]. An appropriate substitution could be used to tune pK_a value of the synthesized derivative.

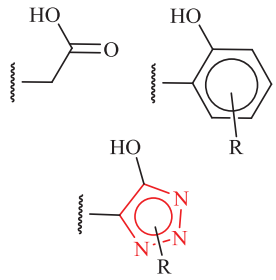

Fig. (76). Hydroxytriazole used as isostere of carboxylic acid and phenol moiety [124].

Di- and trisubstituted 1,2,3-triazoles served as rigid and resistant to isomerization (and other undesired reactions) analogue of *cis*-alkene fragment [55]. Thus prepared combretastatine counterparts were found as potent antiproliferative agents active against various cancer cell lines, including those showing multi-drug resistance [153].

Probably the most obvious analogy, *i.e.* the one between 1,2,3-triazole and other heterocycles encountered in biological systems, particularly imidazole, has been also exploited [55]. Certain histidine analogues containing one more nitrogen atom in the ring component were prepared and efficiently incorporated into a protein *in vivo* by Ikeda *et al.* [249]. Such modified amino acid residues provide additional metal-binding sites close to a peptide backbone [250]. Replacement of imidazole moiety in histamine with 1,2,3-triazole resulted in derivatives exhibiting interesting antihistaminic activity [251, 252]. Bioactive isosteres of imidazole present in pharmacophores (losartan, miconazole) have been also investigated as well as of other heterocycles, including pyrazole (rimonabant), 1,2,4-triazole (ribavirin and fluconazole derivatives), isoxazole, morpholine, and many others [55]. A special attention has been devoted to nucleic acid modification. Nucleoside analogues containing 1,2,3-triazole moiety in place of a nucleobase were shown to exhibit interesting biological (*e.g.* antiviral) activities [54, 129]; however, other strategies (substitution of nucleoside, backbone modification) were explored with a greater success [239, 253 - 255].

Sensors Based on 1,2,3-Triazoles

1,2,3-Triazoles are capable to participate in selective binding of various anions by hydrogen bonds, and several available coordination modes can be utilized in cation complexation [224, 225]. These interactions can be combined, *e.g.*, in ion-pair recognition [224, 225], however, a majority of receptors are designed for anion sensing, their detection, determination and manipulation [256, 257].

Among various assemblies used in this purpose, macrocycles containing several triazole subunits, like triazolophanes or cyclic aryl-triazole oligomers, as well as triazole-based foldamers are of special importance [256]. In many receptors, binding of anions by triazole C-H moiety is enhanced by interactions with other elements of the assembly, including coordination to metal ions. For example, various metalloporphyrin-based receptors have been designed, offering spectroscopic or electrochemical methods of detection. Zinc porphyrin with four triazole substituents attached to *meso*-phenyls appeared an effective host for halide anions; cooperative effects were observed due to coordination to the metal and hydrogen bond formation by 5-CH fragments (Fig. **77**) [258]. A similar system containing zinc porphyrin and four triazole-containing arms was proposed for the determination of cyanide impurity in commercial acetonitrile [259]. Picket-fence nickel(II) porphyrins were prepared with two of *meso*-aryl substituents bearing one or two 1,2,3-triazole functions each as hosts for anion binding, exhibiting strong affinity to cyanide (Fig. **78**) [260]. The participation of triazole rings in anion binding was manifested in the difference in interaction strength observed for various hosts. In a series of multi-porphyrin dendrimers containing a central zinc porphyrin with two 1,2,3-triazole rings appended to *meso*-phenyl substituents, binding of cyanide guest resulted in the change of direction of excitation energy transfer due to the modulation of HOMO-LUMO gap (Fig. **79**) [261]. The process could be reversed by the addition of silver(I) ions for the removal of CN^- ions.

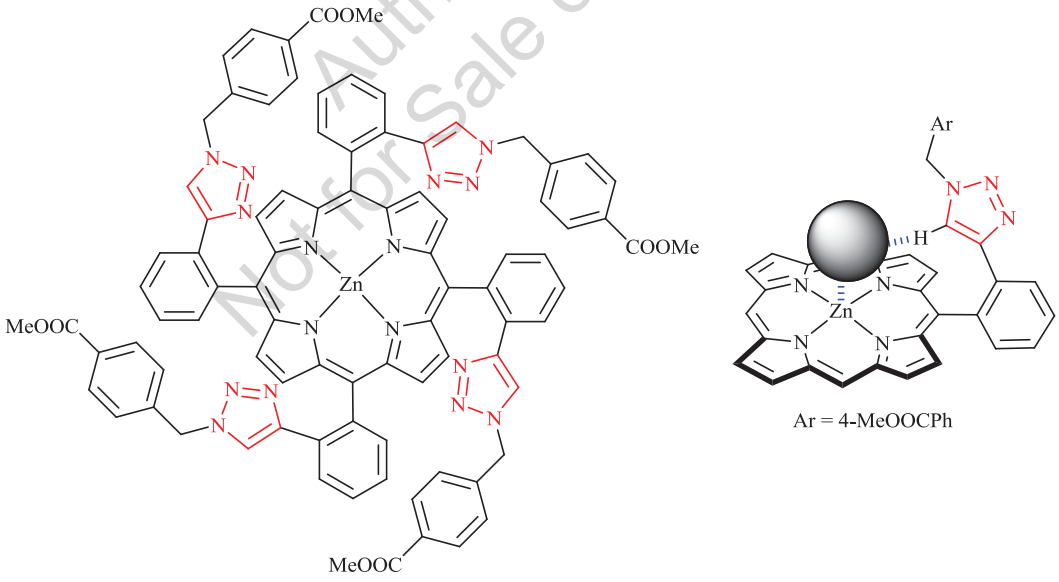

Fig. (77). Structure of triazole-porphyrin receptor for halide anions; interactions of metal ion and one of triazole moieties with an anion shown (the remaining porphyrin substituents omitted for clarity) [258].

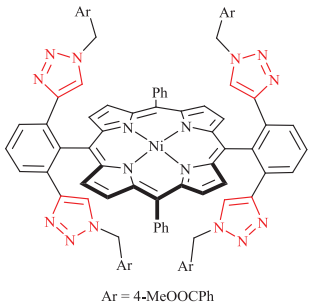

Fig. (78). Nickel porphyrin-based receptor for cyanide ions containing four triazole subunits [260].

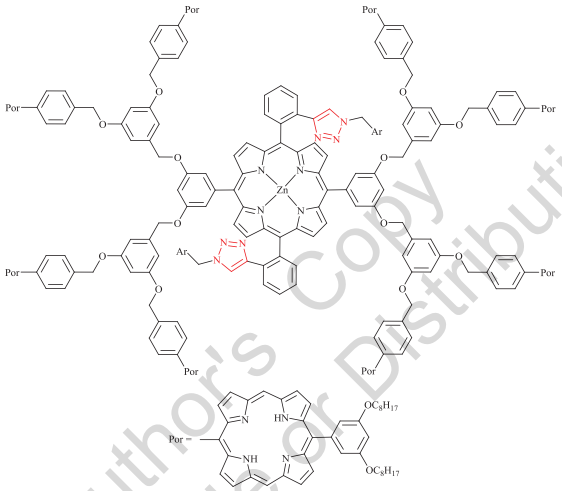

Fig. (79). Porphyrin dendrimers containing triazole moieties participating in a reversible cyanide binding [261].

In the contribution by Gilday, White and Beer, zinc metalloporphyrin-cage receptors for anion binding and recognition were obtained; a capped porphyrin contained four 1,2,3-triazole rings, and a tetracationic derivative was prepared by their methylation [262]. Both hosts were shown to bind various anions in 1:1 ratio in acetone and acetone-water mixture, with a preference for fluoride and sulfate. The same authors described a picket-fence zinc porphyrin containing four 1,2,3-triazole subunits in its arms which was compared with its tetraiododerivative in their anion-binding abilities in organic solvents (Fig. **80**) [263]. The first host capable of hydrogen bond formation exhibited selectivity trend in agreement with anion basicity; the other receptor revealed increased preference for halides which was explained by halogen bonding.

A copolymerizable triazole-based ionic liquid was reported on by Mendecki *et al.* as a simple and robust receptor exhibiting selectivity for iodide anions [264]. Attached to a hydrophobic polymer backbone, it was used in ion-selective electrodes tested for the determination of I^- ions in human urine.

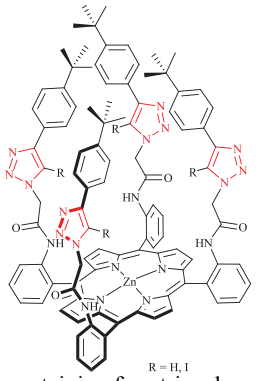

Fig. (80). A picket-fence zinc porphyrins containing four triazoles used for anion sensing [263].

A fluorometric detection was utilized as the mode of action of chemosensors based on naphthylthiourea and disubstituted 1,2,3-triazoles [265]. These assemblies were shown to selectively recognize inorganic phosphates and various phosphorylated nucleosides, such as ATP, ADP and AMP.

A possibility of triazoles to coordinate to metal ions laid a basis for the construction of cation-sensitive ionophores. In a contribution by Ghosh and coworkers, bis-1,2,3-triazoles appended to cholesterol derivative were used as supramolecular gelators for the detection of Ag^{+}, Cu^{2+}, and Hg^{2+} ions (Fig. **81**) [266]. In chloroform-methanol mixture, these compounds formed gels which showed a phase transition upon addition of above-mentioned cations, allowing naked-eye observation.

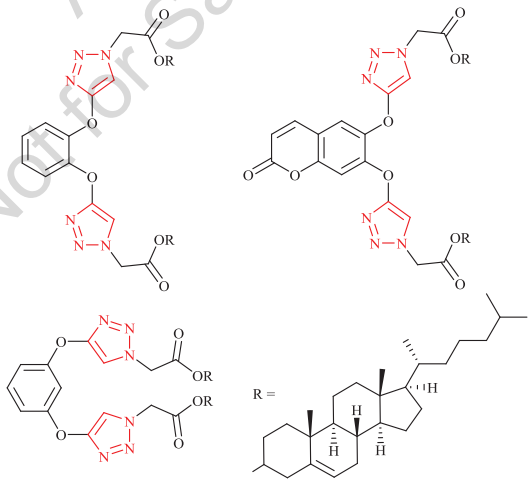

Fig. (81). Structure of bis-triazole gelators for detection of Ag^{+}, Cu^{2+}, and Hg^{2+} ions [266].

Another bis-triazole probe for the detection of cations was described by Aiken and coworkers (Fig. **82**) [267]. Spectroscopic (^{1}H NMR, UV-vis absorption and fluorescence) studies showed the selective behavior with respect to copper(II) ions which could be detected at the micromolar concentration level. A bis-methoxynaphthalene-based ionophore containing two triazole moieties developed by Khurana and coworkers was used for a selective binding of Fe^{3+} ions in methanol or in aqueous solution (Fig. **83**) [268]. Upon addition of EDTA, a reformation of chemosensor resulted in a complete revival of fluorescence which was again quenched after further addition of iron(III). A pyrene-triazol--functionalized calix[3]arene designed by Yamato and coworkers exhibited a high affinity toward Zn(II) in mixed aqueous media (Fig. **84**) [269]. NMR studies suggested a synergistic binding of three triazole fragments to the metal ion in a 1:1 complex.

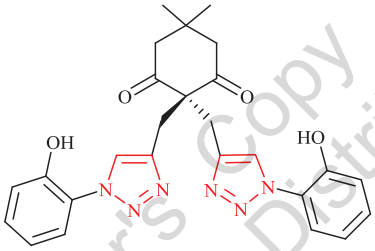

Fig. (82). Structure of a chemosensor for Cu(II) ions [267].

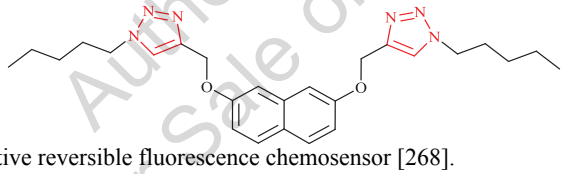

Fig. (83). A Fe(III)-sensitive reversible fluorescence chemosensor [268].

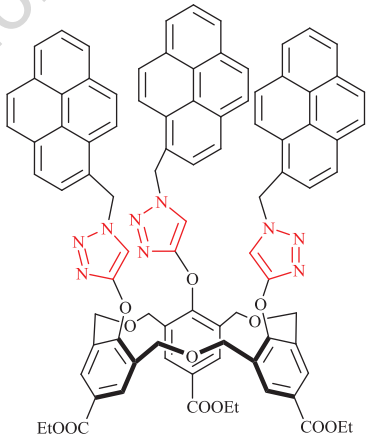

Fig. (84). A fluorescence chemosensor for Zn^{2+} ions [269].

Metal-organic frameworks (MOFs) based on triazole-containing ligands can adopt various guests in their voids. A copper(II)-based network prepared by Li *et al.* showed a high affinity to carbon dioxide and could be used as a size-selective catalyst for CO_2 cycloaddition to small epoxides [270]. A new ligand containing three carboxylic acid moieties and 1,2,3-triazole was obtained and used for the construction of 3D lanthanide MOF (Fig. **85**) [271]. The material based on Tb^{3+} ions was used for a selective luminescence quenching-based detection of Fe^{3+} ions as well as nitrophenol. Sensing of nitroaromatic compounds attracted particular attention due to their military use and contribution to environmental pollution. To this end, a nitrophenyl derivative of 1,2,3-triazolecarboxylic acid and its Cu(II) complexes were prepared (Fig. **86**) [272]. They both were shown to act as selective chemosensors for 2,4,6-trinitrophenol which caused a characteristic fluorescence quenching. Other neutral molecules can be also detected using triazole-based materials, as exemplified by amino acid derivative containing chloroquinoline fluorophoric moiety prepared by Debia *et al.* (Fig. **87**) [273]. Using BSA (bovine serum albumin) as a model, they showed the ability of the receptor as an optical probe for protein detection in solution. Moreover, distinguishing between carbohydrate enantiomers was also achieved as proved by the difference in fluorescence quenching upon addition of L- or D-arabinose.

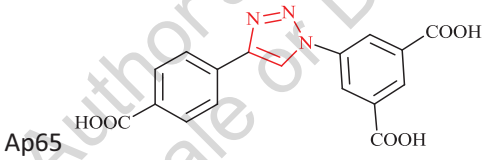

Fig. (85). Ligand used for the construction of lanthanide-based MOFs [271].

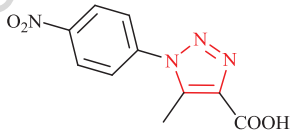

Fig. (86). Triazole-based fluorescence sensor for trinitrophenol [272].

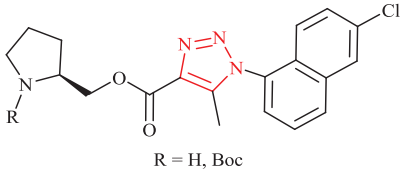

Fig. (87). A receptor sensitive for BSA and monosaccharides [273].

1,2,3-Triazoles in Catalysis

Depending on substitution pattern, and the presence of additional donor groups, neutral 1,2,3-triazoles utilize various coordination modes with metal ions [226]. Deprotonation to give an anionic triazolium ligand further extends these possibilities, and not only nitrogen atoms, but also C-5 can bind to the central ion. To date, triazole complexes with different middle (*e.g.* Mn, Fe, Ru) and late (Cu, Rh, Pd, Ag, Ir, Au) transition metals have been applied in catalytic transformations [226]. In certain cases, the performance with these heterocyclic ligands surpasses the results obtained with pyridine or imidazole analogues, as exemplified by iron-catalyzed dehydration of propargyl alcohol [274].

The presence of triazole moiety can change the course of catalytic reaction due to its possible interactions with reactants or reactive intermediates. For example, iron porphyrins bearing 1,2,3-triazole residues attached to *ortho*-phenyl rings were applied as catalysts in hydrogen evolution reaction in organic and aqueous media (Fig. **88**) [275]. The presence of these substituents lowered the overpotential of the process hence facilitating the catalytic action due to protonation.

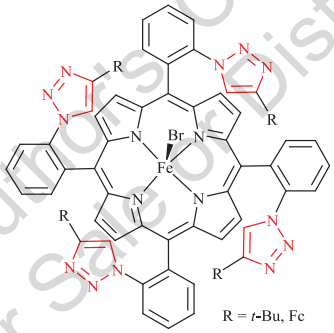

Fig. (88). Structure of catalysts used in electrocatalytic hydrogen evolution [275].

Stable dimeric rhodium(I) complexes bearing bridging 1,2,3-triazolates and COD ligands were prepared and characterized by Shi and coworkers [276]. Applied in Pauson-Khand reaction, they showed high efficiency (60-88% yield, Fig. **89**). A binuclear palladium complex with C5-coordination of 1,2,3-triazolates and bridging acetates was moderately active in hydroarylation of terminal alkynes (Fig. **90**) [277]. Applications of triazole derivatives as ligands in catalytic stereoselective reactions are relatively rare. In a report by Shi *et al.*, enantiopure chiral triazoles were prepared by modification of C-4 vinyl or cyclohexenyl substituent through conversion to racemic hydroxysubstituted derivatives and their resolution by crystallization with quinine with the use of enzyme [215]. The resulting alcohol was applied as N-O type chiral ligand in the asymmetric ethylzinc addition to aldehydes, leading to medium to high enantioselectivity (Fig. **91**).

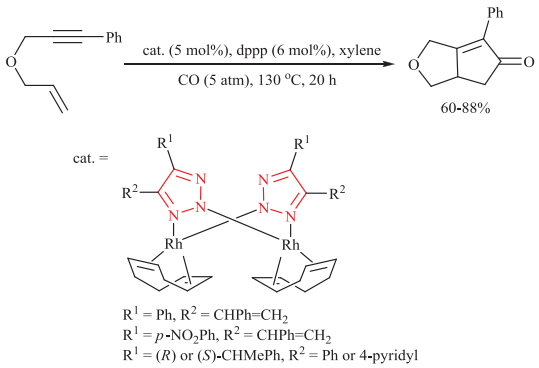

Fig. (89). Pauson-Khand reaction catalyzed by dimeric rhodium triazole complexes [276].

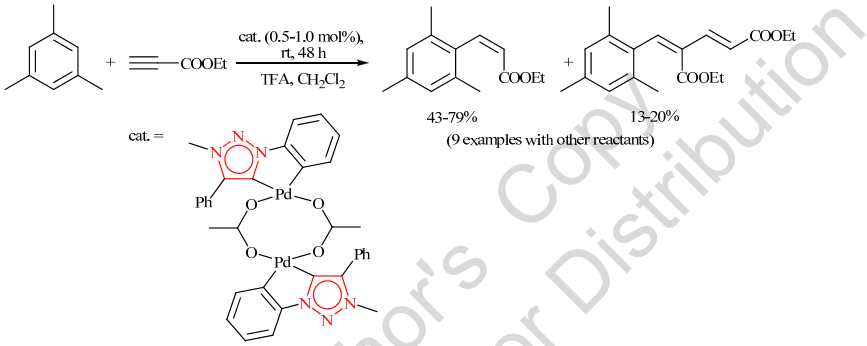

Fig. (90). Hydroarylation catalyzed by binuclear palladium complex with triazolate ligands [277].

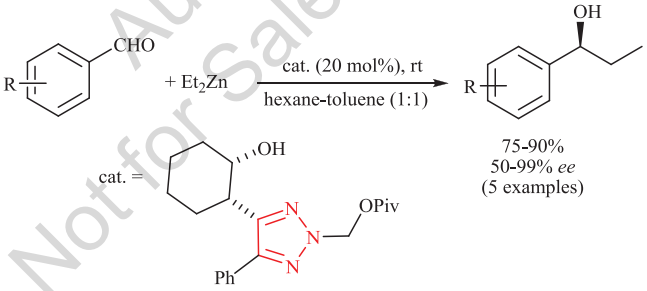

Fig. (91). Stereoselective ethylzinc addition catalyzed with a chiral triazole derivative [215].

Chiral bis-triazole C_2-symmetrical ligands were also prepared and applied in metal-catalyzed asymmetric reactions [210, 278, 279] In a recent report, novel multidendate ligands based on axially chiral 4,4'-bis(aminomethyl)-substituted 5,5'-bistriazole were designed by Pericàs and coworkers [278]. Under optimized reaction conditions, coupling of *N*,*N*-dimethylpropargylamine with benzyl azide led to the desired bis-triazole in 59% yield. Its enantiomers separated with chiral HPLC were prone to racemization in solution, while the derivative bearing *N*-(*S*)-1-phenylethylamine substituents was found resistant to epimerization. Bis-triazole

ligands were used in a scandium-catalyzed Friedel-Crafts reaction of *N*-methylindoles with *N*-methylisatin with high yields and chemoselectivity (Fig. **92**). Unfortunately, no enantioselectivity was observed.

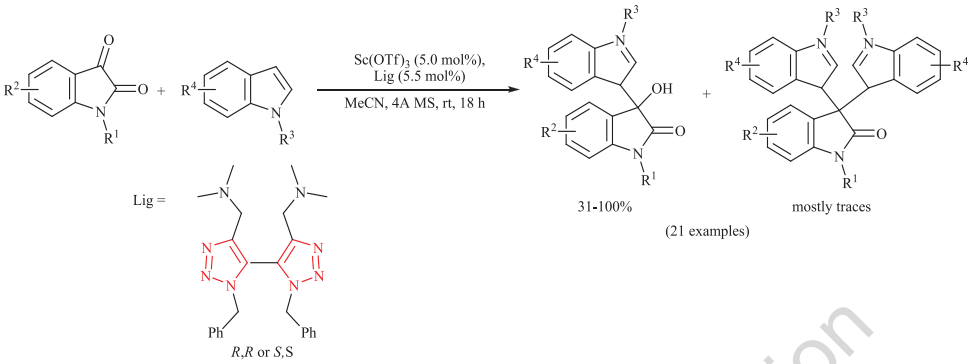

Fig. (92). Scandium-catalyzed Friedel-Crafts reaction with bis-triazole ligands [279].

Tripodal tris(triazolyl)methanol derivatives found application as ligands in metal-catalyzed reactions, including CuAAC [280]. Linked to a Merrifield resin [281], or SiO_2-coated γ-Fe_2O_3 nanoparticles [282], Cu(I) complexes of this type were used in click reaction as efficient and recyclable catalysts (Figs. **93**, **94**).

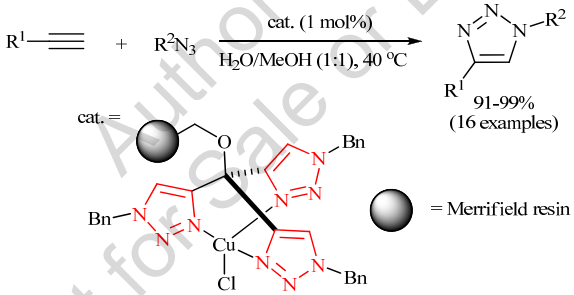

Fig. (93). Resin-appended copper(I) tris(triazolyl)methanol complex used in CuAAC reaction [281].

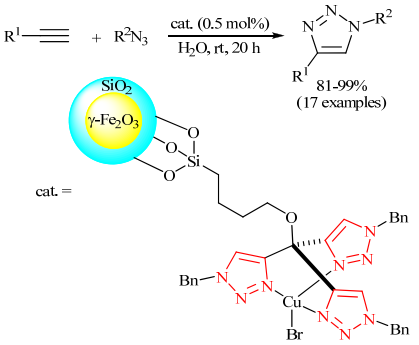

Fig. (94). Use of silica-coated Fe_2O_3 nanoparticles as a support for a copper(I) catalyst for CuAAC [282].

Click reaction was also used for heterogenization of catalysts, facilitating their possible separation from the reaction mixture and further reuse. For example, iron tetraarylporphyrin bearing azide substituent immobilized on polyethylene glycol using click reaction appeared an efficient catalyst for a stereoselective olefination of aldehydes (Fig. **95**) [283]. The activity and selectivity was unchanged after catalyst recycling (10 cycles were checked). Mesoporous silica functionalized with azidopropyl groups was used as a solid support for a series of epoxidation catalysts [284]. CuAAC reaction allowed a covalent attachment of ethynylated ferrocene, pyrene, tris(2-pyridylmethyl)amine and chloroiron(III) tetraphenyl-porphyrin. The latter was used as a catalyst in carbene insertion reaction, providing similar yields to the homogenous catalyst, though longer reaction times were necessary.

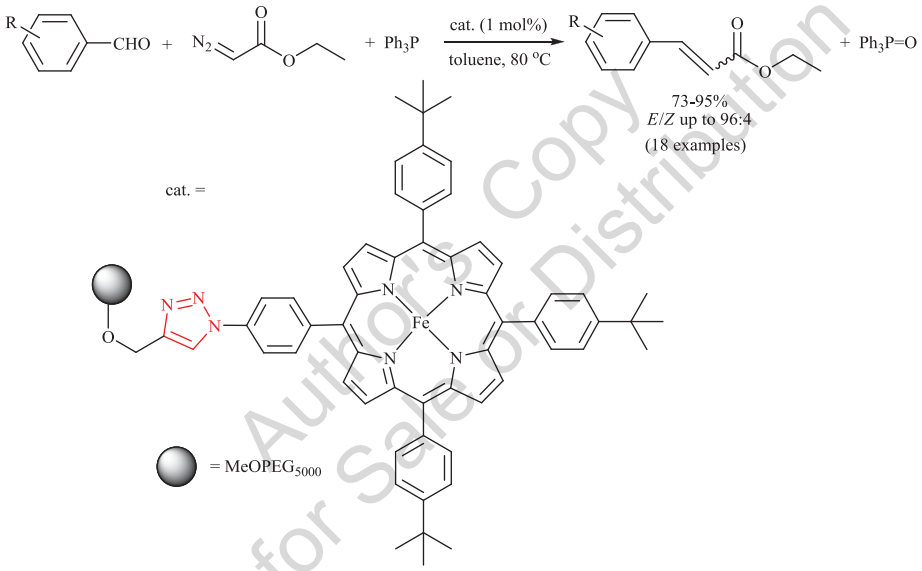

Fig. (95). Stereoselective olefination of aldehydes with a PEG-supported iron porphyrin catalyst [283].

Triazole derivatives were also found as versatile elements of organocatalysts. Click reaction can be used to assemble catalytically active fragments or for covalent immobilization [285]. However, participation of 1,2,3-triazole fragment in substrate binding was also utilized, as described by Chandrasekhar *et al.* who used their chiral conjugates with pyrrolidine in asymmetric Michael and aldol reactions (Fig. **96**) [286, 287]. High enantioselectivity was observed in Michael addition of nitromethane and α,β-unsaturated aldehydes performed in aqueous medium with spiropyrrolidine chiral catalysts (Fig. **97**) [288]. The ability of triazoles to interact with anions was used in a concept of anion-binding organocatalysts (Fig. **98**), used also in asymmetric reaction (dearomatization of *N*-heteroarenes) [289 - 292].

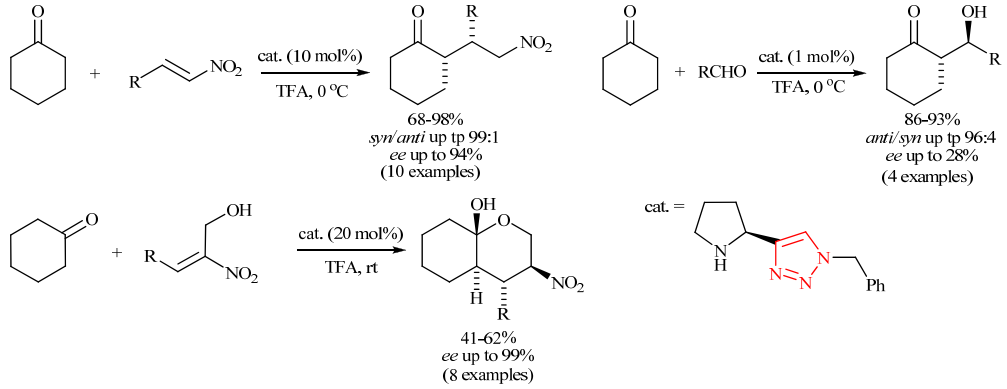

Fig. (96). Chiral pyrrolidine-triazole derivative in organocatalytic reactions [286, 287].

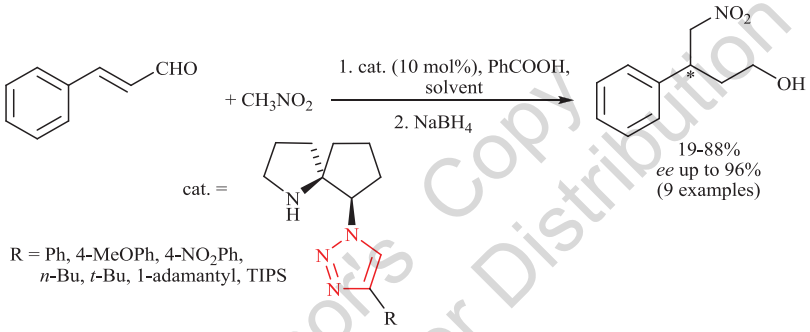

Fig. (97). Asymmetric Michael reaction catalyzed with a chiral spiropyrrolidine-triazole assembly [288].

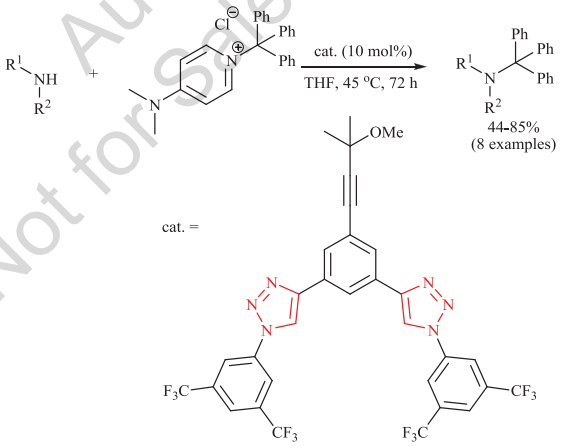

Fig. (98). Bis-triazole derivative as anion-receptor organocatalyst in alkylation reaction [289].

1,2,3-Triazoles in Supramolecular Chemistry

Various possibilities of interactions of triazole derivatives which are of importance from the point of view of their application as sensors and catalysts can

also be applied to the construction of metallosupramolecular architectures [51], and other assemblies, including pilar[*n*]arenes [293] or catenanes and rotaxanes prepared with the use of click reaction [294 - 298]. In this part, chosen assemblies will be presented to give an impression about a diversity of formed structures.

Interesting examples of self-assembly driven by coordination of triazole to the metal center come from metalloporphyrin chemistry. Attachment of 1,2,3-triazole moiety directly to bridging *meso* position of zinc porphyrin resulted in the formation of dimeric assemblies linked with two coordination bonds [299]. Additional stabilization of dimers was possible when 2-ethoxycarbonylphenyl substituent was present in the macrocycle; two hydrogen bonds were found between carbonyl oxygen atom and 2-H of triazole which was thus fixed as 2H-tautomer in this particular structure (Fig. **99**). Larger assemblies – porphyrin squares containing 4 or even 16 macrocycles – were spontaneously formed from 1,2,3-triazole-appended *meso*-*meso*-linked diporphyrins and L-shaped triporphyrins (Fig. **100**) [300]. The oligomers were studied in the context of efficient energy transfer within self-assembled light-harvesting systems.

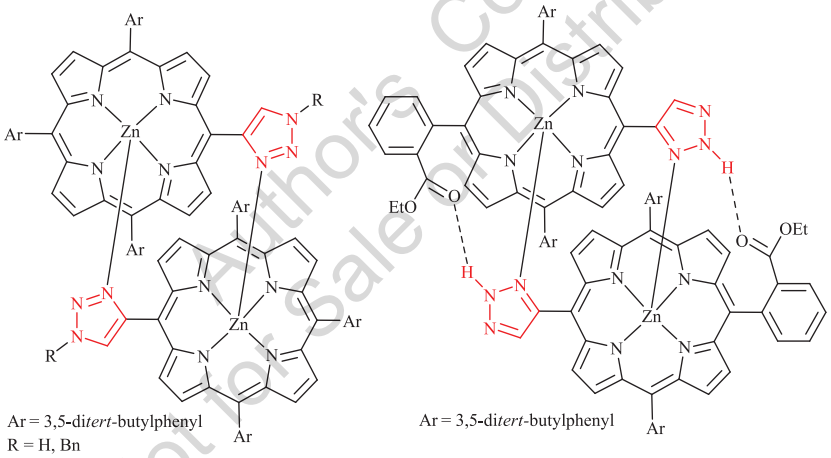

Fig. (99). Dimeric assemblies formed by triazole-appended zinc porphyrins [299].

A triazole linkage was utilized to attach two or four polystyrene, poly(butyl acrylate) and poly(*tert*-butyl acrylate) arms to zinc porphyrin [301]. These conjugates were shown to organize into oligomeric assemblies by zinc-triazole coordination, with the association constant and degree of supramolecular oligomerization tuned by the polymer choice and its length.

1,2,3-Triazole formation was utilized by Kimura *et al.* in the construction of dendrimers containing a zinc porphyrin core [302]. The presence of triazole linkers was crucial for the increased rate of photoinduced electron transfer between the core and peripheral acceptor groups. The properties and function of

dendrimers were affected by the intramolecular coordination of triazole moiety present in one of the arms to the zinc center. A similar intramolecular coordination was observed in deca-zinc porphyrin arrays based on pillar [5]arene [303]. The authors found that external stimuli (temperature change, imidazole addition) could be used to control binding of 1,2,3-triazole moieties to metal centers which resulted also in a significant conformational changes (folding/ unfolding of the molecule).

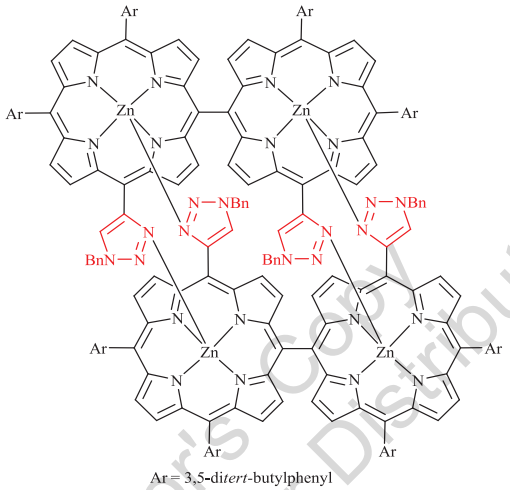

Fig. (100). A porphyrin square formed by four subunits through zinc-triazole coordination [300].

An ease of formation of 1,2,3-triazole linker was utilized in the construction of the thread component of rotaxanes containing strapped metalloporphyrin units [304]. A coordination of triazole to rhodium(III) present in the macrocycle crevice played a crucial role in the synthesis of one of these interlocked systems. Rotaxanes containing a dyad, a triad and a pentad of tetrapyrroles (zinc porphyrin attached to copper(III) corroles through "click" reaction) were prepared with bipyridine-derived "wheels" interacting with triazole bridges with hydrogen bonding [305]. Threading did not influence the possibility of energy transfer between porphyrin and corrole and provided an effective protection from aggregation.

Numerous other assemblies take advantage of coordination abilities of 1,2,3-triazoles. A family of cylindrical, triply-stranded complexes was prepared by Vasdev *et al.* using bis(pyridyl-triazole) ligands and Fe^{2+} or Co^{3+} ions (Fig. **101**) [306]. Coordination polymers, including metal-organic networks [270, 271] can be formed as well. As an example, a one-dimensional manganese(II) complex formed by 4-(2-pyridyl)-1,2,3-triazolates was prepared and characterized by Chen *et al.* (Fig. **102**) [307]. In $[MnL_2]_n$ assembly, bridging was achieved by binding triazolato moieties through N-1 and N-2 to two metal ions.

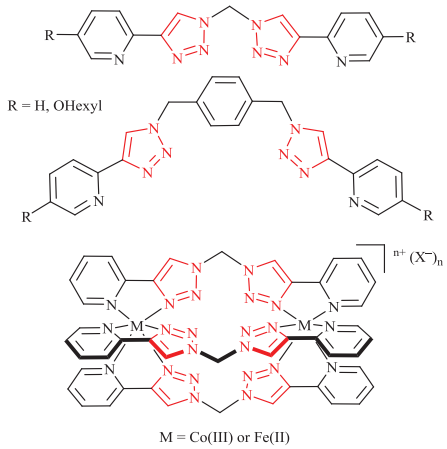

Fig. (101). Bis(pirydyl-triazole) ligands and a coordination cylinder formed with Co^{3+} or Fe^{2+} [306].

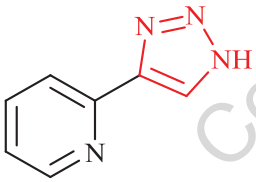

Fig. (102). 4-(2-Pyridyl)-1,2,3-triazole used as for construction of coordination polymer with Mn^{2+} ions [307].

A multifunctional dendron containing coordinating redox-active ferrocene, complexing triazole and hydrophilic termini (Fig. **103**) was used to form silver and gold nanoparticles by reduction of Ag(I) or Au(III) ions, respectively [308]. This compound was also able to stabilize a water-soluble copper(I) catalyst and the obtained nanoreactors were active in CuAAC reaction. In addition, the dendron was shown to reversibly bind a model drug, rhodamine B, encapsulated into a spherical micelles.

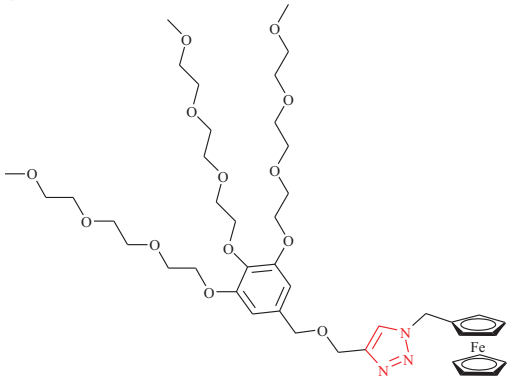

Fig. (103). A triazole-containing multifunctional dendron [308].

Other interactions were also utilized to create supramolecular assemblies, including hydrogen bonds and halogen bonds [309, 310]. 1,4-Diaryl-5-iodo-1-2,3-triazoles prepared by Philp and coworkers were found to form self-assembled dimers in solution and chains of molecules in a solid state [311]. A halogen bond between the pyridine subunit and the iodotriazole of the neighboring molecule was observed (Fig. **104**).

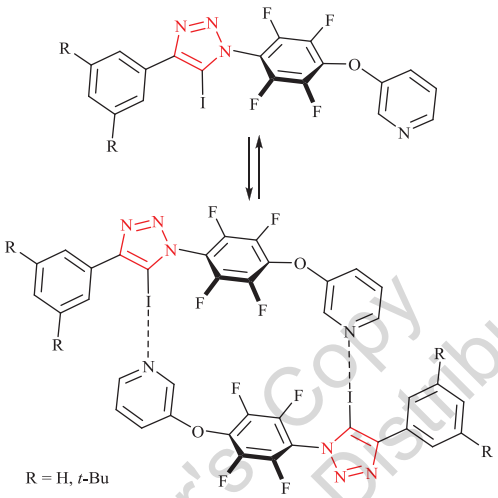

Fig. (104). Dimerization of triazole derivative through a halogen bond formation [311].

Diketopyrrolopyrrole derivatives bearing thiophene and 1,2,3-triazole units were prepared by Punzi *et al.* (Fig. **105**) [312]. Their functionalization with hydrophobic alkyl or hydrophilic polyethylene glycol chains allowed tuning of solubility and formation of aggregates and organic nanoparticles.

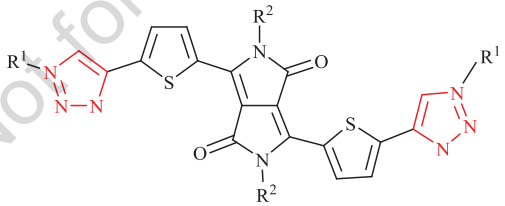

Fig. (105). Bis-triazole derivative containing thiophenylpyrrolopyrrole core [312].

Summary

Selected examples show only part of possible applications of 1,2,3-triazole derivatives. For example, their use as bridging units allowing efficient electron or energy transfer should not be neglected. They are also used to couple pharmacologically active moieties into a one molecule [22, 54, 55, 236 - 238, 244

- 246, 253, 313, 314]. A growing number of publications concerning synthesis and utilization of chiral triazoles is particularly worth mentioning. As described, they are used in asymmetric catalytic reactions as chiral ligands for various metals [209, 210, 215, 278, 279], and organocatalysts [286 - 292]. Other applications include, for example, absolute configuration determination [315], chiral recognition [316], and the use as chiral reactant [213].

Though the great number of publications on 1,2,3-triazoles may suggest that the area has been already exploited, it is still possible to find a niche which deserves attention. In our opinion, this heterocycle, easily available by click reaction, has not yet shown its full potential in the development of diverse functional materials.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author confirms that this chapter contents have no conflict of interest.

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CHAPTER 5

Ring C–H Functionalization of Aromatic *N*-Oxides

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Abstract: Aromatic *N*-oxides occupy a central place in the synthesis of azine and azole derivatives. Unique reactivity of *N*-oxides makes them versatile substrates for introduction of various functional groups into the heterocyclic ring. The area of direct functionalization of $C(sp^2)$–H bonds of aromatic *N*-oxides with various carbon and heteroatom substituents has seen renewed interest in recent years, resulting in introduction of several modern, versatile synthetic protocols into the arsenal of methods available within the chemistry of nitrogen heteroaromatic compounds. The aim of this review article is to provide an overview of these recent developments, together with an appropriate background in more classical *N*-oxide chemistry. It focuses on the most important reaction types characteristic for aromatic *N*-oxides, rather than the type of heterocyclic ring involved.

Keywords: Aromatic compounds, Azines, Azoles, Cine Substitution, C–H-Activation, Cross-Coupling, Cross-Dehydrogenative Coupling, Deoxygenation, Dipolar Cycloaddition, Imidazoles, Isoquinolines, Metalation, *N*-Oxides, Nitrogen Heterocycles, Nucleophilic Substitution, Oxazoles, Pyridines, Quinolines, Radical Substitution, Reaction Mechanisms, Thiazoles.

INTRODUCTION

Heteroaromatic compounds containing in the ring a nitrogen atom with a free electron pair, that is six-membered azines (pyridines, diazines, quinolines, *etc.*) and five-membered azoles (imidazoles, pyrazoles, thiazoles, *etc.*), play a central role in synthetic heterocyclic chemistry. They have also found numerous and diverse applications as pharmaceuticals, agrochemicals, advanced materials, ligands, ionic liquids, *etc.* In fact, it would not be an overstatement to say that azines and azoles are one of the most important classes of substances in the whole organic chemistry.

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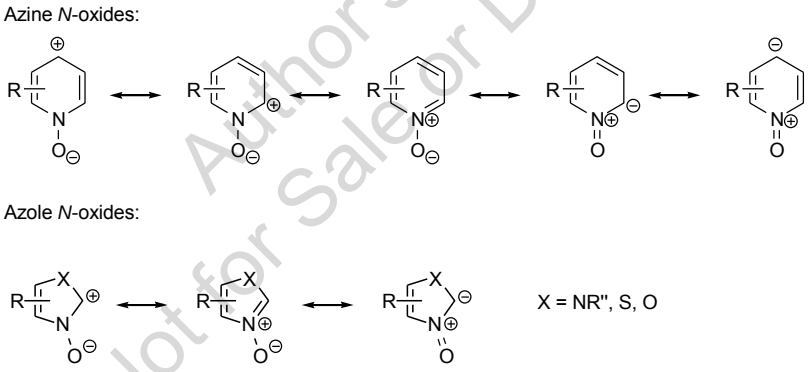
Atta-ur-Rahman (Ed.)

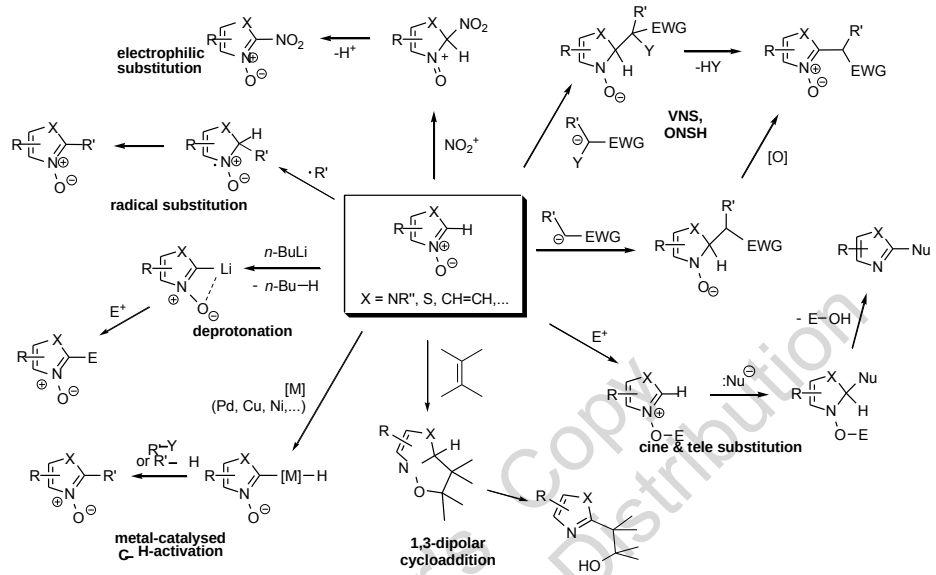
Aromatic *N*-oxides are azine and azole derivatives in which the nitrogen atom of the ring exists in oxidation state higher by 2 than in the parent heterocycle and bears an additional oxygen atom instead of an electron pair. The structure of *N*-oxides can be represented by several resonance structures in which carbon atoms of the ring are either positively or negatively charged (Scheme **1**). This feature, together with the presence of the oxygen substituent bound to the ring by a relatively weak N–O bond, is associated with peculiar and diverse reactivity of aromatic *N*-oxides and makes them key intermediates in the synthesis of azine and azole derivatives of desired structure and properties. Importantly, many reaction types available or even specific for *N*-oxides are associated with introduction of a new substituent into the aromatic ring at the position originally occupied by hydrogen. Such direct aromatic C–H functionalization processes are particularly valuable in synthetic chemistry, owing to their high atom economy and fewer number of steps on the way from readily available substrates to highly ring-functionalized products [1]. A more classical approach to the synthesis of azine and azole derivatives involves pre-functionalization by, for example, introduction of good leaving groups such as halogens and further substitution using S_NAr chemistry. However, the most convenient way of halogenation of nitrogen heteroaromatics utilizes *N*-oxides.



Scheme 1. The structure of azine and azole *N*-oxides.

The aim of this review article is to provide an overview of various types of C–H functionalization reactions of azine and azole *N*-oxides, with particular focus on modern synthetic methods appearing frequently in recent literature. The most important of earlier reactions of *N*-oxides, such that allow introduction of various functional groups at the position occupied by hydrogen, are also covered to provide appropriate context and better mechanistic understanding. Apart from a general textbook on *N*-oxides by Albini and Pietra [2], some reviews dealing with general aspects of *N*-oxide chemistry are available [3], in particular Begtrup's

comprehensive review covering *N*-oxides of diazoles, triazoles and tetrazoles [4]. However, they are either somewhat outdated or deal with limited aspects of the *N*-oxide chemistry, other than the problem of *N*-oxide ring C–H functionalization.



Scheme 2. Reaction of *N*-oxides resulting in ring hydrogen substitution.

General reaction types that enable formal hydrogen substitution in the *N*-oxide ring are shown in Scheme **2**. The ability of the *N*-oxide ring to stabilise positive charge after addition of an electrophile makes classical reactions such as nitration much more facile and orthogonal in terms of regioselectivity compared with nitration of azines themselves. *N*-Oxide rings are also susceptible to nucleophilic attack, thus enabling various types of nucleophilic hydrogen substitution reactions. In particular, the presence of the oxygen atom, that can be transformed into a good leaving group by acylation, sulfonylation, *etc.*, makes *N*-oxides excellent substrates for cine- and tele-type nucleophilic substitution. Addition of radical species is possible as well. Distribution of positive charge in the ring, particularly in the positions neighbouring with the *N*-oxide function (C(2) and C(6) in the pyridine ring), as well as the presence of the N–O bond dipole, makes the vicinal C–H bonds relatively acidic. Their deprotonation enables further functionalization *via* reaction with electrophiles. More importantly from the synthetic point of view, acidity of these vicinal C–H bond(s) and coordinating properties of the formally negatively charged oxygen atom make *N*-oxides extremely useful substrates for metal-catalyzed C–H activation reactions, including not only cross-coupling with substrates containing good leaving groups

(aryl halides, *etc.*), but also cross-dehydrogenative coupling processes, that is oxidative reactions involving double activation of two C–H bonds (or a C–H and heteroatom-hydrogen bond, X–H) in both partners and formation of a new C–C or C–X bond [5]. Finally, an entirely different mode of *N*-oxide reactivity is associated with the presence of a nitrone-like dipole structure in the *N*-oxide ring. 1,3-Dipolar cycloaddition of *N*-oxides is associated with the formation of two new bonds, one of them involving C(2) carbon. Therefore, it may provide another means of ring functionalization, depending on the actual course of further transformations of the initial cycloadduct.

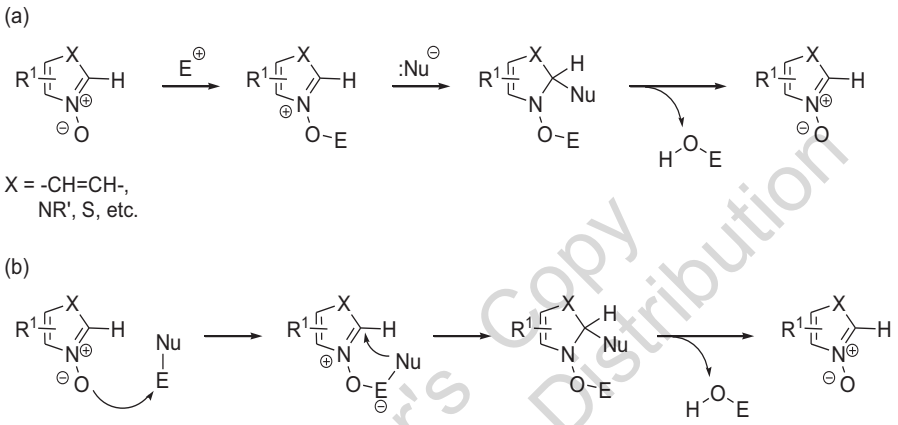
The above reactions of ring hydrogen substitution can be divided into deoxygenative ones, that is reactions accompanied by removal of oxygen from the ring nitrogen atom, and those which leave the *N*-oxide function intact. Reactions of the former class are probably more useful since the desired products of synthesis are usually free azines or azoles with new functionalities in the heterocyclic ring. Synthesis of free (unoxidized) azine and azole derivatives with methods of the latter class requires an additional deoxygenation step. Fortunately, numerous methods of oxygen removal have been developed [6]. On the other hand, aromatic *N*-oxides owe their great synthetic utility to their ready availability [7]. Azine *N*-oxides are usually prepared by oxidation of azines [8], whereas azole *N*-oxides are available *via* a variety of condensation reactions of acyclic precursors [9]. Pyrazole *N*-oxides are formed during *N*-alkylation of 1-hydroxypyrazoles [10].

CINE AND TELE NUCLEOPHILIC SUBSTITUTION

A cine nucleophilic substitution reaction is a process in which the leaving (nucleofugal) group departs from the position vicinal to the one attacked by the nucleophilic species [11]. When the site of the leaving group attachment and the nucleophilic attack site are separated by more than one bond, the term "tele substitution" is applied. Aromatic *N*-oxides are particularly good substrates for cine or tele substitution since the oxygen atom can play the role of the leaving group following a nucleophilic attack on one of the electronically activated positions of the aromatic ring (Scheme **3**) [12]. In general, addition of an electrophile to the *N*-oxide oxygen transforms it into a better leaving group and, at the same time, enhances electrophilicity of the heteroaromatic ring which becomes an *N*-alkoxy, *N*-acyloxy, *N*-sulfonyloxy, *N*-silyloxy or another type of an azinium salt. Nucleophilic addition to this salt, followed by restoration of the ring aromaticity *via* base-assisted C(sp^3)–H proton abstraction from the ring and N–O bond cleavage, provides the product of formal substitution of a ring hydrogen (cine substitution). Successful realization of several reactions of this kind depends on the use of reagents that contain both an electrophilic and a nucleophilic centre

(such as Me_3SiCN, RSO_2N_3, *etc.*) – in such cases, after oxygen atom activation the transfer of the nucleophilic species to the ring carbon occurs in an intramolecular fashion, usually with high regioselectivity for C(2)/C(6) position (Scheme **3**(**b**)).

A mechanistically similar processes, in which the bond between the electrophilic and nucleophilic part of the reactant remains unbroken after a five-membered oxazolidine-type adduct is formed are treated as step-wise dipolar cycloaddition reactions of *N*-oxides in one of the following sections.

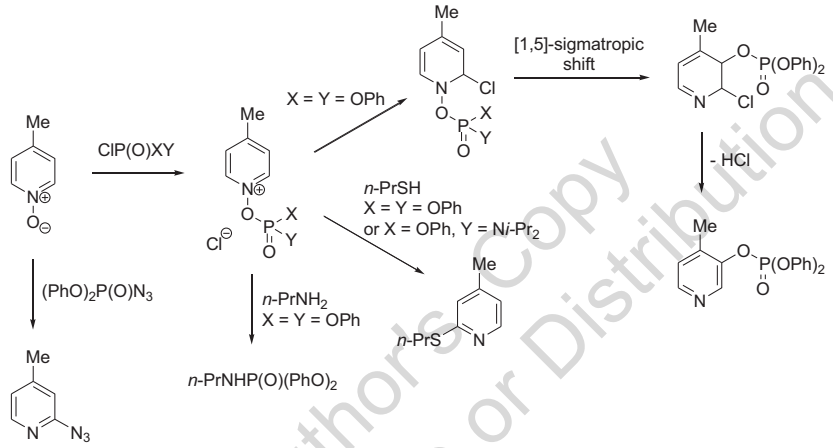


Scheme 3. Cine nucleophilic substitution in *N*-oxides.

The reaction of *O*-activated *N*-oxides with nucleophilic species can follow a few different pathways that lead to various products [13]. Apart from cine nucleophilic substitution in the ring, the initial adduct can undergo electrocyclic ring opening leading to oxime derivatives. Nucleophiles can also attack the atom bound directly to the *N*-oxide oxygen, leading to substitution with unchanged *N*-oxide acting as a leaving group. Finally, under basic conditions *N*-oxides activated by *O*-alkylation may undergo deprotonation of the *O*-alkyl group and elimination of the parent unoxidized heterocycle, leading to oxidation of the *O*-alkyl to a carbonyl compound in a process analogous to Kornblum or Moffat oxidation [14].

The actual course of a reaction between *O*-activated *N*-oxides and a nucleophile largely depends on the nature of the latter reactant. This point can be nicely illustrated by the results of Pratt and co-workers, who investigated the progress of the reactions of *O*-phosphorylated 4-picoline-1-oxide with ^{1}H and ^{31}P NMR techniques [15]. When the starting *N*-oxide was treated with diphenyl phosphoryl chloride in dry $CDCl_3$, phosphorylation of oxygen was followed by nucleophilic addition of chloride to the ring (Scheme **4**). The dihydropyridine intermediate underwent a 1,5-sigmatropic rearrangement with N–O bond cleavage, leading to a

2,3-dihydropyridine derivative. Elimination of HCl accompanied with ring rearomiatisation led finally to a 4-methyl-3-pyridyl phosphate. When *N*-oxide derivatives were *O*-phosphorylated with ClPO(OMe)(N*i*-Pr_2) or ClPO$(OPh)_2$ and treated with *n*-propyl thiol, cine substitution product was formed along with a 3-pyridyl phosphate derivative. On the other hand, the reaction with *n*-propylamine as nucleophile resulted in nucleophilic attack on phosphorous, with *N*-oxide acting as a leaving group, and led to formation of an *n*-propyl phosphoramide. Finally, a phosphate derivative containing a strong nucleophile (N_3) in its structure, that is diphenyl phosphoryl azide (DPPA), gave exclusively 2-azidopyridine.



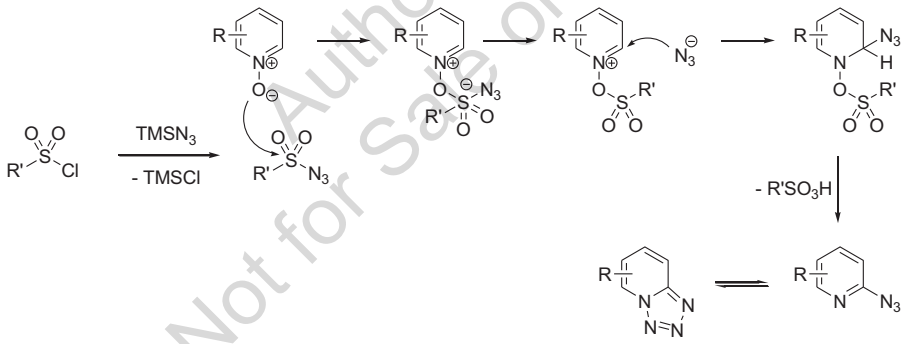
Scheme 4. Reactions of *O*-phosphorylated picoline *N*-oxide with different nucleophiles [15].

Despite the possible complications discussed above, several useful synthetic procedures for introduction of various groups into a hydrogen-occupied position of azine rings, utilizing cine nucleophilic substitution, have been developed. Indeed, this approach to introducing several types of carbon or heteroatom groups into heteroaromatic ring can be considered as complementary to methods based upon classical S_NAr substitution or metal-catalyzed reactions.

The simplest and earliest examples of reactions proceeding according to Scheme **3** are transformations of azine *N*-oxides into azinones with Ac_2O and halogenation with chlorides of inorganic acids, such as POX_3 or SO_2X_2 (X = Cl, Br) [2, 3, 12]. Halogenation generally requires harsh conditions (elevated temperature, strongly acidic reagents) and is hampered by poor regioselectivity [16] and formation of unwanted, overhalogenated or deoxygeated azines as side products. On the other hand, 2-haloazines remain useful synthetic intermediates for further functionalisation of the heterocyclic ring using S_NAr chemistry. In this regard, halogenation of various azine derivatives using the corresponding *N*-oxides as starting materials

has found wide application in the synthesis of biologically active compounds, usually as a means of accessing 2-aminoazines [17]. Recently, a much milder an highly regioselective azine halogenation protocol has been developed [18]. It utilizes tosyl anhydride as an electrophilic activator and tetraalkylammonium halides as nucleophile sources.

In recent years, new synthetic methods appeared that allow direct introduction of nitrogen groups without the need of preparing haloazines as an additional pre-functionalization step. A useful and general reaction of azide introduction *via* cine substitution in *N*-oxides of pyridines, quinolines and isoquinolines, regio-selectively at C(2) position, first mentioned by Iyengar [19], has been developed recently by Keith (Scheme **5**) [20]. The process involves *in situ* generation of sulfonyl azides from sulfonyl chlorides and trimethylsilyl azide, with TMSCl distilling out of the reaction mixture. Electrophilic activation of the substrate oxygen by the sulfonyl group, followed by azide transfer to the C(2) position of the ring and base-assisted elimination provides heterocyclic azides which exist predominantly as bicyclic tetrazoles. The best results were obtained with toluenesulfonyl chloride (TsCl), 2-fluorophenylsulfonyl chloride and phenyl-sulfonyl fluoride. Alternatively, phosphoryl azides generated *in situ* from $TMSN_3$ and appropriate chlorides can be used. Formation of TMSCl by-product can be avoided by employing diphenylphosphoryl azide (DPPA) directly.



Scheme 5. 2-Azidation of azines starting from azine *N*-oxides [20].

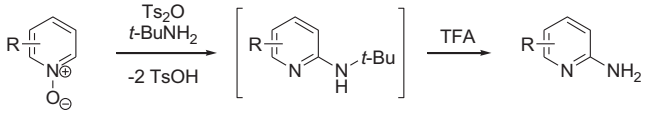
Imidazolyl substituents can be introduced using a similar approach, that is with sulfuryl diimidazole as an activating reagent and a nucleophile source [21]. Decomposition of the initially formed 1-imidazolylsulfonic acids liberates imidazole and SO_3, which complexes the final product causing its precipitation. The complex can be readily cleaved with aqueous NaOH. In some cases, when C(2)/C(6) positions were blocked with methyl groups, slow substitution of CH_3 hydrogen with imidazole occurred. Formation of significant amounts of C(4)

substitution products was observed only with 2,2'-bipyridyl-1-oxide and 3-cyanopyridine *N*-oxide.

Later, Keith extended the above methodology to introduction of other azolyl (triazolyl, imidazolyl and pyrazolyl) groups into the azine ring [22]. Reactions of *N*-oxides with pre-formed *N*-tosylazoles in the presence of DIPEA and without solvent gave good yields of regioisomeric mixtures of products, identified as azines substituted at C(2) with azole rings connected by different nitrogen atoms. Interestingly, isoquinoline *N*-oxide gave some amount of 3-azolylisoquinoline. From the observation that *N*-tosylazoles containing electron-withdrawing groups in the heterocyclic ring reacted faster, it was concluded that electrophilic activation of the *N*-oxide oxygen atom was the rate determining step, followed by liberation of an azolyl anion and its nucleophilic attack on the azinium ring.

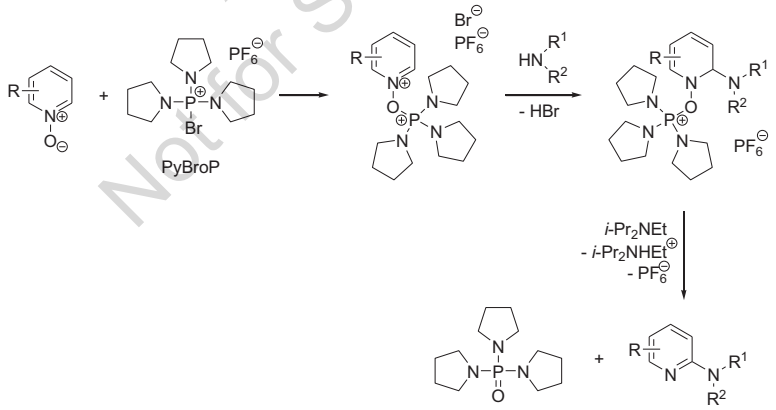
More recently, Keith reported a similar *N*-aryltriflamidation of azines with *N*-aryltriflimides, in which one of the trifluoromethanesulfonyl groups acted as the *N*-oxide-activating electrophile [23]. Another example of cine 2-amidation of pyridine derivatives is a reaction employing saccharin or phthalimide and TsCl activation in the presence of base [24].

2-Aminopyridines are a ubiquitous structural motif in small molecule pharmaceuticals, such as an anti-cancer drug Crizotinib (Xalkori) [25] or new promising drugs for the treatment of malaria [26]. Direct amination of azines *via* cine substitution is associated with difficulties, since strongly nucleophilic amine is prone to react directly with electrophilic reagent needed for activation of the *N*-oxide oxygen. Moreover, the same reagent can *N*-acylate or N-sulfonylate the 2-aminoazine product. Another possible complication is the 2-aminoazine product acting as a nucleophile towards *O*-activated *N*-oxide, leading to dimeric products [27]. For these reasons, for a long time direct amination was restricted to quinoline and isoquinoline *N*-oxides reaction with aqueous ammonia in the presence of TsCl [27, 28]. A useful synthetic protocol avoiding above problems was disclosed by Yin, Xiang and co-workers, who reported mild amination of *N*-oxides with *tert*-$BuNH_2$ and Ts_2O, followed by *in situ* removal of the *tert*-butyl group by treatment with TFA (Scheme **6**) [29]. Careful optimization of the reaction conditions, amine nucleophile and the electrophilic activating agent enabled the authors to reduce the concurrent formation of *tert*-BuNHTs and achieve a general amination reaction applicable to pyridine *N*-oxides containing substituents of various electronic character, as well as quinolines and isoquinolines.



Scheme 6. 2-Amination of azine *N*-oxides [29].

As mentioned above, a nucleophilic attack of amine on the electrophilic reagent bound to the *N*-oxide oxygen is one of the serious side reactions hampering the development of general direct amination reactions of azines *via* cine substitution. A possible solution to this problem is the use of electrophilic activators which bind strongly and irreversibly to the oxygen atom, such as highly electrophillic phosphonium salts. A mild and general synthetic protocol, relying upon activation of azine *N*-oxides with triaminophosphonium salts (particularly (bromotris (pyrrolidino)phosphonium hexafluorophosphate, PyBroP), has been developed by Londregan and co-workers [30]. A wide variety of primary and secondary amines or ammonia could be employed, as well as *N*-oxides of substituted pyridines, quinoline and isoquinoline (Scheme **7**). The success of this reaction is probably the result of particularly strong phosphorus-oxygen bond, which precludes side reactions of the intermediate *O*-phosphorylated *N*-oxyazinium salts. Complete selectivity of the reaction for the formation of 2-aminopyridine regioisomers can be probably attributed to high partial charge at C(2) and C(6) positions of the azinium ring, which is associated with the nature of phosphonium activating electrophile. In several *N*-oxides, this effect is in accord with the LUMO distribution in the azinium aromatic ring [31].



Scheme 7. Amination of azine *N*-oxides activated with PyBroP [30].

In the following years, the same research group extended the PyBroP activation of pyridine *N*-oxides methodology on other nucleophilies with pKa in the range 10-

20, such as electron-rich nitrogen heterocycles, phenols, amides, sulfonamides, thiols and strong C–H acids [31]. Reactions with thiols are valuable as previous cine thiolation methods, employing simple acylating reagents (Ac_2O, carbamoyl or phosphoryl chloride), led to poor regioseletivity of thiopyridines [32]. Cyclic peptides could also be obtained *via* nucleophilic attack of imidazole N–H or phenolic OH on peptide-bound, PyBroP-activated pyridine *N*-oxides [33]. The presence of hexafluorophosphate counter anion in PyBroP, capable of releasing fluoride anions, enabled the use of silyl enol ethers as reaction partners [34]. In some cases, mixtures of 2- and 4- regioisomers were obtained, in accord with different ("soft") character of enol ethers as nucleophiles. Recently, application of PyBroP *N*-oxide activation for 2-alkoxylation of pyridines and diazines has been reported by the same group [35].

An interesting intramolecular version of cine/tele substitution with a nitrogen nucleophile has also been described [36]. In the presence of various activators (sulfonic or carboxylic anhydrides or chlorides, PyBroP) *Z* isomers of *N*-tosylhydrazones derived from *N*-oxides of 3-acylpyridines gave regioisomeric mixtures of pyrazolo[3,4-b]pyridines (cine substitution products at C(2)) and pyrazolo[4,3-c]pyridines (tele substitution at C(4)), with the ratio of isomers depending on the electrophilic reagent employed.

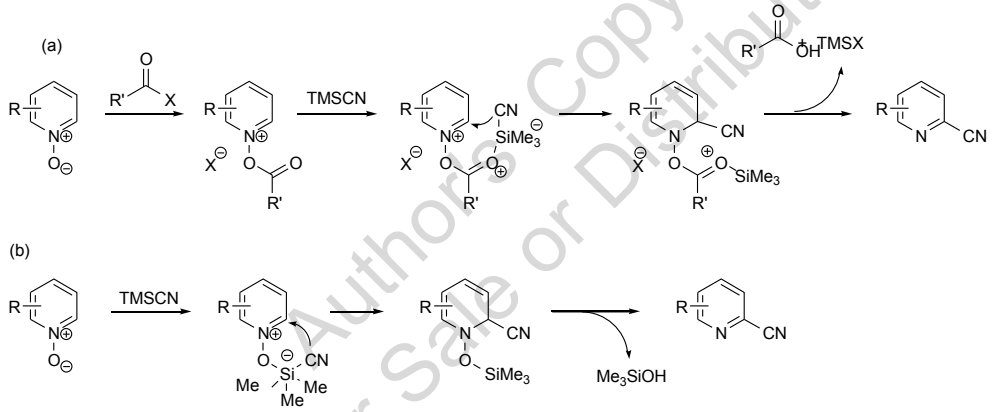
Tertiary amines can also play the role of nucleophiles adding to *O*-activated aromatic *N*-oxides. Pyridine *N*-oxides upon treatment with trifluoroacetic anhydride (TFAA) or Ts_2O in DCM at 0 °C gave *N*-trifluoroacetyloxy- and *N*-tosyloxyazinium salts that added trialkylamines, pyridine or diazabicyclooctane (DABCO) to form 2-ammoniumpyridines [37]. Susceptibility of these products to S_NAr-type reactions has been exploited in their direct transformation to into 2-fluoropyridines upon the action of tetrabutylammonium fluoride. Scalability and simplicity of the last reaction allowed fast preparation of ^{18}F-labelled fluoro-pyridines which are important in PET imagining techniques.

2-Ammonium-substituted azines prepared *in situ* from *N*-oxides and DABCO upon TFAA activation have been treated with nucleophiles (thiols, secondary amines, C*N*-, N_3^-) with opening of the DABCO skeleton [38]. The reaction resulted in azines functionalized at C(2) with nucleophiles separated from the azine ring by a piperazine-ethylene linker.

One of the most extensively studied cine-type substitution reactions occurring in azine *N*-oxides with carbon nucleophiles is cyanation. This process, known as the Reissert-Henze reaction, proceeds readily with the simplest cyanide source (KCN) in the presence of various acylating agents, in a one- or two-phase system (with aqueous KCN solution), to provide predominantly 2-(6-)cyanoazines [39]. An

important modification is based upon the use of trimethylsilyl cyanide (or phosphoryl cyanides), which gives better yields and regioselectivity. These reactions are believed to proceed *via* cyclic intermediates with silicon coordinated to the carbonyl oxygen of the acylating agent (Scheme **8**(**a**)). Formation of such intermediates is not possible with *O*-alkylated *N*-oxides, which in consequence show much lower C(2)/C(4) selectivity. The Reissert-Heinze reaction is also applicable to pyrimidine *N*-oxides [40]. Cyanation of 4-nitropyridine *N*-oxides with chloroformates and TMSCN is accompanied by nitro to chloride exchange [41].

A more direct approach to azine cyanation has been disclosed by Vorbrüggen and Krolikiewicz [42]. Reactions of azine *N*-oxides with TMSCN with only NEt_3 as additive led to 2-cyanoazines, probably *via* coordination of the *N*-oxide oxygen atom to silicon and transfer of cyanide to the ring, without intermediacy of an acylating agent as in Fife's protocol [39] (Scheme **8**(**b**)).

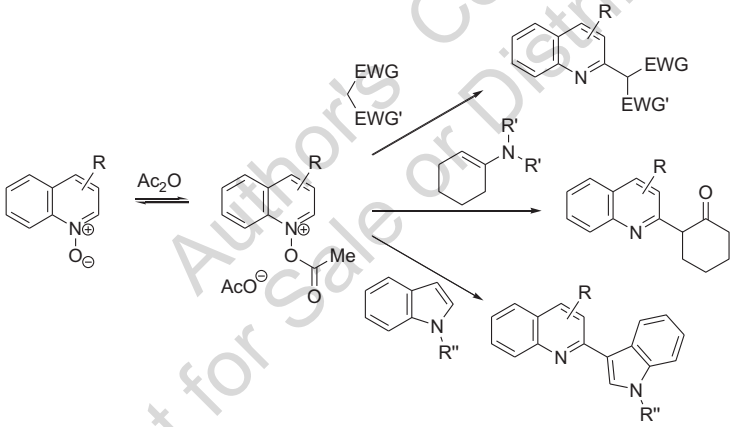


Scheme 8. (a) C(2)/C(6)-regioselective cyanation of *O*-acylated *N*-oxides with TMSCN; (b) Direct reaction of TMSCN with *N*-oxides.

A process mechanistically similar to the above cyanation reaction is the reaction of *N*-oxides with allyl- and benzylsilanes. Coordination of silicon in these reagents to the *N*-oxide oxygen enhances nucleophilicity of the alkyl group, which is transferred selectively to C(2) position of the ring (in the case of allyl presumably in an S_N2' manner) with the departure of trimethylsilanol and rearomatisation of the ring [43]. This interesting methodology has not been developed further; instead, silicon-coordinating properties of *N*-oxides are nowadays utilized in the construction of chiral ligands for asymmetric allylation of aldehydes [44].

Cine substitution in azine *N*-oxides involving carbonyl-stabilised carbon nucleophiles has been investigated since the early 1960s, starting with the works

of Hamana and co-workers. Active methylene compounds (cyanoacetates, malonates, 1,3-diketones, *etc.*) were found to react with quinoline *N*-oxide in the presence of excess of acetic anhydride to give 2-substituted quinolines (Scheme **9**) [45]. Pyridine *N*-oxides were considerably less reactive. A peculiar reaction course was observed with diethyl malonate which gave mainly a double substitution product, resulting from the reaction of one malonate molecule with two molecules of *N*-oxide. Its formation could be explained by good solubility of the mono-substitution product of the reaction mixture and higher acidity of this compound compared with the substrate. More recently, a similar reaction allowed preparation of a chelating ligand containing two quinoline units, *via* consecutive removal of both protons in an active methylene substrate [46]. C–H-acidic compounds containing only one stabilising group could not be employed in the above reaction, but cyclohexanone enamines gave the expected heteroarylation products in good yields, even with pyridine *N*-oxide [47]. In the presence of acylating agents, azine *N*-oxides were also attacked by the nucleophilic C(3) position of indole derivatives [48]. Later, similar reactions were also developed with *N*-oxides immobilized on solid resin [49].

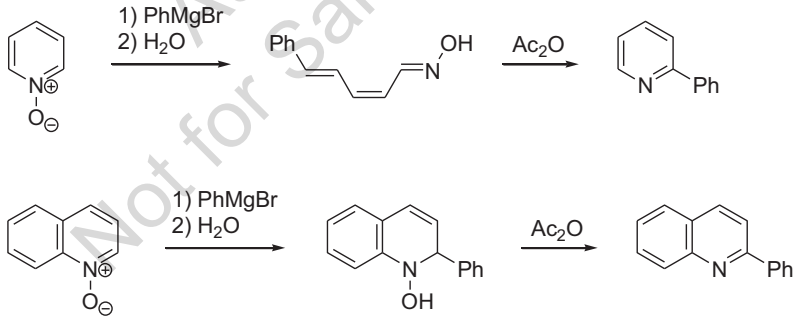


Scheme 9. Reaction of quinoline *N*-oxides with active methylene compounds, enamines and indoles in the presence of Ac_2O [45, 47, 48].

Grignard reagents readily undergo addition to heterocyclic *N*-oxides. According to the first reports on the reaction between phenylmagnesium bromide and pyridine or quinoline *N*-oxide, it leads to 2-phenylazines in poor yields, together with side products such as 2,2'-diphenyl-4,4'-bipyridyl and biphenyl. A careful study of the same reaction performed in THF revealed that under mild conditions it gives stable adducts - 1-hydroxy-2-phenylpyridine and 1-hydroxy-2-phenylquinoline, in highly regioselective manner [50]. The former compound could be transformed into 2-phenylpyridine only under forcing conditions, that is distillation with zinc at > 200 °C or refluxing in Ac_2O, thus accomplishing the

formal nucleophilic substitution of hydrogen in the pyridine ring. Contrary to the expectation based upon the relative resonance stabilisation energies, quinoline adduct underwent rearomatisation much more readily than that of pyridine. Specifically, 1-hydroxy-2-phenylquinoline could be dehydrated to 2-phenylquinoline by refluxing in THF or oxidized with air to 2-phenylquinoline *N*-oxide in an ONSH-type process. 4-Alkyl, 4-alkoxy and 4-chloroquinoline *N*-oxides displayed similar behavior.

In a later study, the same authors examined chemical properties of 1-hydroxy-2-phenylpyridine in detail [51]. They found that upon treatment with BzCl this compound lead to an *O*-benzoyl derivative, which readily underwent an electrocyclic ring opening to an *O*-benzylated oxime. Upon heating, the last compound was debenzylated to nitrile of 5-phenylpentane-2,4-dienoic acid. The same nitrile can be obtained by dehydration of free oxime, by heating of 1-benzoyloxy-2-phenylpyridine in the presence of pyridine, or simply by performing the benzylation reaction of the starting 1-hydroxy-2-phenylpyridine at higher temperatures (30-50 °C). The above results were later verified by van Bergen and Kellog [52], who performed a detailed NMR analysis of phenylmagnesium bromide adduct to pyridine *N*-oxide and concluded that 1-hydroxy-2-phenylpyridine does not exist at all in any noticeable amounts. Instead, a disrotatory opening of the heterocyclic ring occurs directly after addition. Transformation of this product into 2-phenylpyridine upon treatment with Ac_2O is in fact an oxime *O*-acetylation, followed by a Beckmann-like ring closure and AcOH elimination (Scheme **10**).

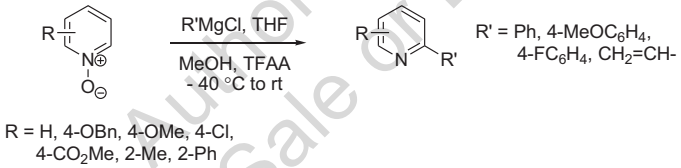


Scheme 10. Addition of PhMgBr to pyridine and quinoline *N*-oxide and transformation of the adducts into 2-phenylazines [50, 52].

In recent years, a reaction of azine *N*-oxides with Grignard reagents of various structures has been developed into a general synthetic method by Andersson, Almqvist and Olsson [53]. They found that treatment of dienal oximes, formed after nucleophilic addition to pyridine *N*-oxides, with Ac_2O under microwave conditions (120 °C), is a general reaction that allows re-formation of the pyridine

ring with elimination of the *N*-oxide oxygen to give aromatized cine substitution products of various substitution pattern [54]. Interestingly, 3-substituted pyridines give the more sterically hindered 2,3-functionalized products with high regioselectivity. Complete selectivity of addition to the positions vicinal to the *N*-oxide function undoubtedly results from coordination of magnesium to oxygen before the addition step. Addition of Grignard reagents to *N*-oxides is a useful method for 2-alkylation and 2-arylation of azines and a convenient alternative to the approach based on the treatment of *N*-acyl- and *N*-alkylpyridinium salts with organolithium and organomagnesium reagents [12, 55].

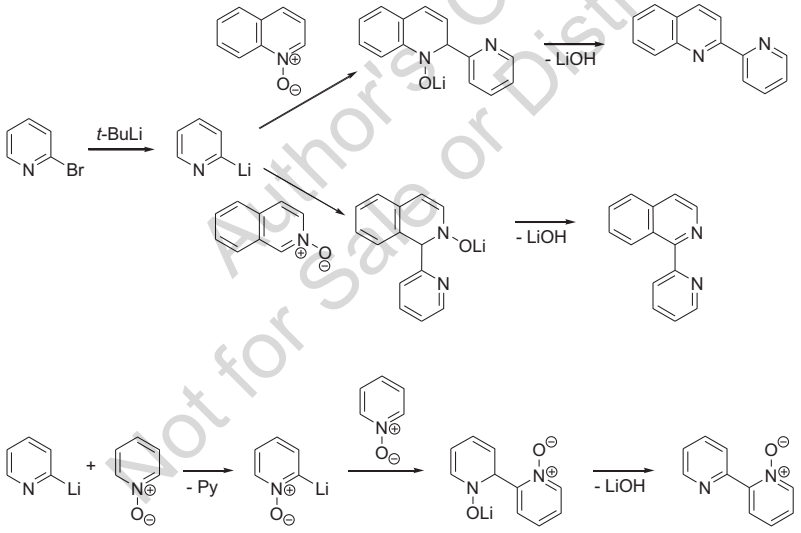
In the course of later studies on nucleophilic addition of organomagnesium compounds to pyridine *N*-oxides, the same group found that heterocyclic ring opening to dienal oximes (see Scheme **10**) does not occur at low temperature [56]. In fact, the ratio close to 1:1 between open and cyclic form was determined at 0 °C. Based upon this observation an improved, mild protocol was elaborated that avoided the second, ring closing step requiring elevated temperatures [57]. Treatment of initial arylmagnesium adducts with TFAA at -40 °C led to the formation of 2-arylated pyridines containing in the ring additional substituents such as alkoxyl, ester or Cl (Scheme **11**). Addition of chloranil instead of TFAA allowed preparation of 2-arylpyridines retaining the *N*-oxide function.



Scheme 11. 2-Arylation reaction of pyridine *N*-oxides at low temperature [57].

A general method of room temperature 2-arylation, 2-alkylation and 2-alkenylation of pyridines, quinolines, isoquinolines and quinoxalines *via* reaction of their *N*-oxides with Grignard reagents in the presence of LiF additive and catalytic amounts of CuCl has been reported recently by Larionov and co-workers [58]. Concerning *N*-oxides of quinoline derivatives, their reactions with a variety of alkyl or vinyl Grignard reagents occur smoothly after *O*-acylation with chloroformates, preferably isobutyl chloroformate [59]. This approach allowed preparation of the whole library of 2-functionalized quinolines for biological activity screening [60]. Cine substitution with aryl Grignard reagents in quinoline *N*-oxides has also found application in the synthesis of biologically active compounds [61]. A similar reaction leading to substitution at C(3) in isoquinoline *N*-oxide derivative was the key step of the synthesis of a complex molecule acting as a MAP kinase inhibitor [62].

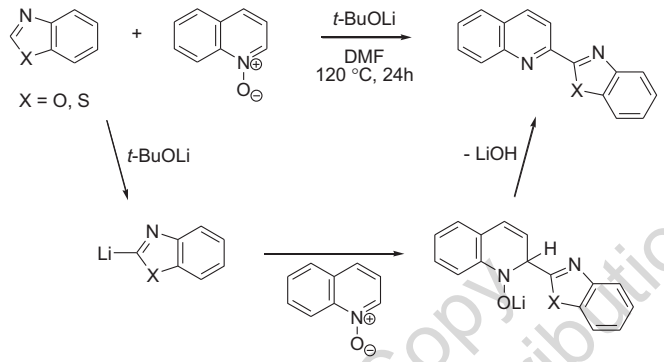
Fast addition of nucleophilic species to hydrogen substituted positions of electron-deficient aromatic rings has been used in the synthesis of bipyridyl derivatives by Chupakhin and co-workers [63]. Reaction of 2-pyridyllithium, obtained in bromine-lithium exchange of 2-bromopyridine and *t*-BuLi, with quinoline and isoquinoline *N*-oxides at low temperature (-78 °C) gave 2-(2--pyridyl)quinoline and 1-(2'-pyridyl)isoquinoline in good yield, formation of which can be expected as a result of nucleophilic attack on the *N*-oxide ring and subsequent rearomatisation *via* elimination of LiOH (Scheme **12**). The course of the reaction of the same organometallic reagent with pyridine *N*-oxide was more complicated, leading to 2,2'-bipyridine 1-oxide. Its formation could be rationalized by lithiation of pyridine *N*-oxide, which is more acidic than the parent pyridine, and subsequent addition to another molecule of *N*-oxide, followed by LiOH elimination and overall cine substitution. A similar reaction has been observed with 2-pyridyllithium and 2,2'-bipyridine 1-oxide, leading to a tetrapyridine monooxide. The above mechanistic proposal has been confirmed in the experiment involving deprotonation of pyridine *N*-oxide with 0.5 equiv. of *t*-BuLi, giving the same 2,2'-bipyridine 1-oxide as before, in good 67% yield.



Scheme 12. Reactions of 2-lithiopyridine with azine *N*-oxides [63].

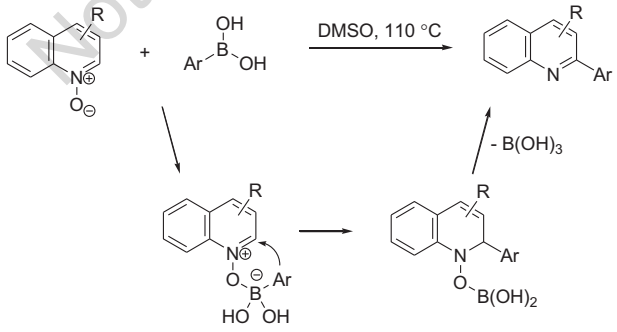
A peculiar example of an organometallic reagent addition to an azine *N*-oxide is the reaction of lithiated 1,2- or 1,7-dicarba-closo-dodecaboranes with 3,6-diaryl derivatives of 1,2,4-triazine 4-oxides [64]. Upon treatment with dimethyl-carbamoyl chloride, anionic adducts underwent elimination to give triazinyl-carboranes.

A reaction in which lithioorganic species generated *in situ* add to aromatic *N*-oxides has been described recently by Cui, Wu and co-workers. Quinoline *N*-oxides reacted with benzo-fused 1,3-azoles in the presence of *t*-BuOLi to afford 2-(2'-azolyl)-quinolines [65]. The reaction probably proceeds *via* deprotonation of azoles at C(2) and subsequent nucleophilic addition and LiOH elimination (Scheme **13**).



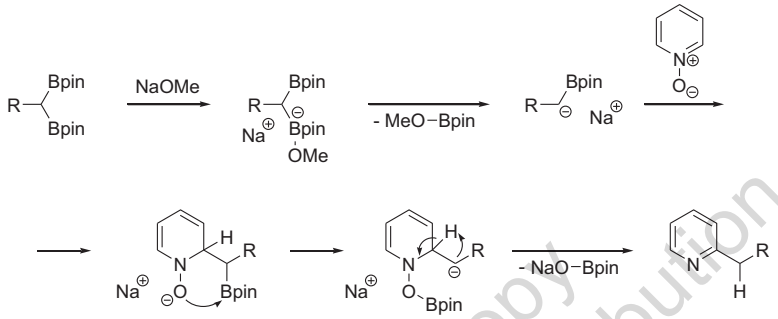
Scheme 13. Heteroarylation of quinoline *N*-oxides with benzothiazole and benzoxazole [65].

Organoboron compounds of the type BR_3 upon addition of Lewis bases become a source of nucleophilic R groups as, for example, in the Petasis reaction [66]. Coordination of BR_3 to *N*-oxide oxygen might lead to nucleophilic transfer of an R group and departure of boronic acid derivative, along with the general pathway shown in Scheme **3**(**b**). In recent years, reactions based upon the above concept and allowing for introduction of carbon substituents into heteroaromatic rings have indeed been developed. Quinoline *N*-oxides have been reported to react with aryl- and heteroarylboronic acids providing 2-arylated quinolines (Scheme **14**) [67].



Scheme 14. 2-Arylation of quinoline *N*-oxides with arylboronic acids [67].

A somewhat similar concept to azine alkylation has been developed by Cho and co-workers, who described a reaction that introduces methylene substituents at C(2) of azine rings [68]. In this process, boryl carbanions generated from 1,1-diborylalkanes and NaOMe add to pyridine and quinoline *N*-oxides. Subsequently, the boron substituent coordinates to oxygen enabling its departure and ring rearomatisation (Scheme **15**).

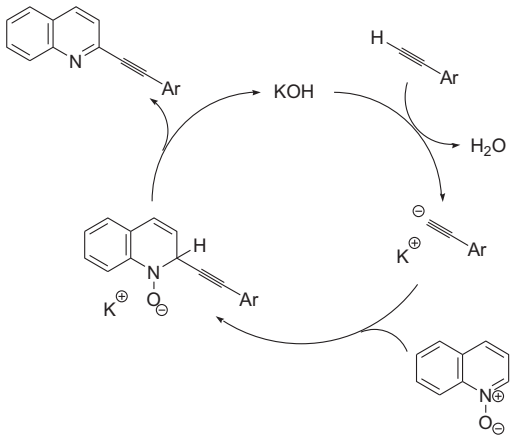


Scheme 15. 2-Alkylation of *N*-oxides with boron-stabilised carbanions [68].

Reaction of *O*-activated azine *N*-oxides with metal acetylides leads to ethynylation of the C(2)/C(6) position of the ring. Upon treatment with silver phenylacetylide, *N*-benzoyloxyazinium salts prepared from BzCl and *N*-oxides of pyridine and its derivatives, quinoline, isoquinoline and pyrimidine (or analogous salts obtained from *p*-TolCOCl, PhCOBr, $PhSO_2Cl$, *t*-BuCOCl) gave moderate yields of 2(6)-alkynylazines [69]. Acetylides of copper or magnesium were less efficient, while sodium phenylacetylide showed preference for an attack on the carbonyl group of the benzoyloxy group. Interestingly, addition to *O*-methylated pyridine *N*-oxide resulted to ring opening rather than elimination, probably due to poorer leaving properties of MeOH as compared with BzOH.

Very recently, a simple and versatile protocol for 2-alkynylation of quinolines has been disclosed by Cui, Wu, and co-workers [70]. Reaction of alkyl-, halo-, methoxy- or unsubstituted quinoline and isoquinoline *N*-oxides with arylacetylenes in boiling toluene, in the presence of KOH and under visible light irradiation, provided the respective 2-alkynylazines in high yields. The authors attributed the role of light to facilitation hydrogen transfer from the azine ring to oxygen and subsequent elimination of KOH, which could be used in substoichiometric amounts (Scheme **16**).

Direct cine substitution in azine, diazine and triazine *N*-oxides with acetylene anions generated with *t*-BuOK or *t*-BuOLi has been described [71].



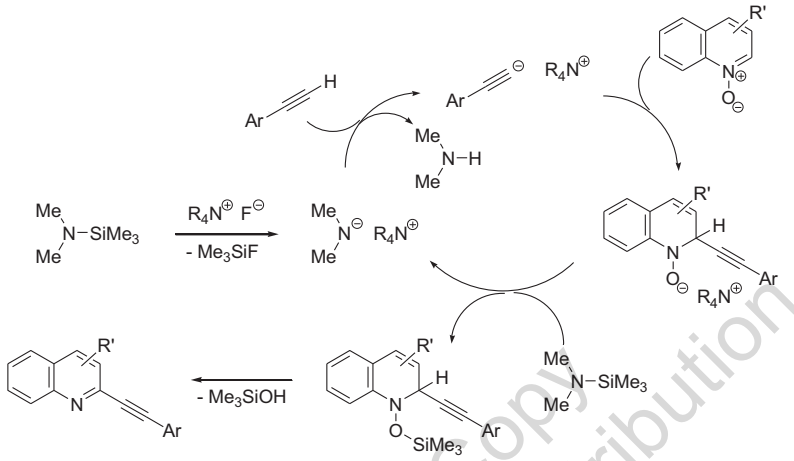
Scheme 16. The proposed catalytic cycle of alkynylation of quinolines in the presence of KOH [70].

Inamoto, Kondo and co-workers developed a reaction of quinoline *N*-oxides with strong nucleophiles, including acetylene anions, which are generated *in situ* by deprotonotion of weak C–H acids with tetraalkylammonium amide salts [72]. The salts were in turn obtained *in situ* in the reaction of aminosilanes with ammonium fluorides. Under these conditions, arylacetylenes, benzothiazole, benzoxazole and *N*-phenylbenzimidazole were all deprotonated efficiently, although heterocyclic substrates required large amounts of fluoride salts and elevated temperatures. Nucleophilic addition to quinoline *N*-oxide and its derivatives (and also 4-phenylpyridine *N*-oxide and isoquinoline *N*-oxide) resulted in the formation of anionic adducts, silylation of which with silylamines regenerated the amide base and, at the same time, probably facilitated elimination resulting in 2-substituted azines (Scheme **17**). Quinoline *N*-oxide itself dimerized under similar conditions *via* deprotonation of C(2) position. A similar alkynylation reaction of quinoline *N*-oxide has been described earlier by the same group, involving activation of silylated nucleophiles by catalytic amounts of phosphazene base P4-tBu [73].

A simple protocol for *N*-oxide dimerization has been reported that exploits a cine-type nucleophilic substitution and at the same time demonstrates considerable acidity of the *N*-oxide C(2)–H bond [74]. Reaction of *N*-oxides of halo-, alklyl- or alkoxyquinolines of simple pyridine derivatives with *tert*-BuOLi in toluene at 120 °C, without any transition metal catalyst, provides mono-oxygenated biaryl products. The reaction most likely begins with proton abstraction from C(2) position of *N*-oxide. Nucleophilic attack of the formed lithium salt on another *N*-oxide molecule is followed by elimination LiOH.

Potentially interesting opportunities in the cine substitution chemistry of *N*-oxides were opened with the recent paper of Wu and Cui, who employed catalytic

amounts of elemental iodine as an electrophilic activator of *N*-oxide [75]. A wide variety of quinoline *N*-oxides were subjected to reaction with styrenes, acting in this case as nucleophilic partners. Reactions performed in air at elevated temperatures provided 2-alkenylquinolines in good yields.



Scheme 17. Alkynylation of quinoline with acetylide anions generated with amide bases [72].

Cine nucleophilic substitution in *N*-oxides has been also investigated as a method of introducing perfluoroalkylated groups into the heterocyclic ring. Already in the 1980's, Uno attempted a reaction of perfluorohexyllithium (generated from *n*-$C_6F_{13}I$ and MeLi·LiBr) to pyridine *N*-oxide complexed at oxygen with boron trifluoride [76]. The expected 2-*n*-perfluorohexylpyridine was obtained in low yield (10%). More recently, Larionov reported trifluoromethylation and perfluoroalkylation of azine *N*-oxides with trifluoromethyl(trimethyl)silane ($TMSCF_3$) or other perfuroralkylsilanes promoted by potassium *tert*-butoxide [77]. The reaction allows preparation of 2-perfluoroalkylquinolines and 1-perfluoroalkylisoquiolines in high yields, but gives only moderate yields of fluoroalkylated pyridines. The process can be probably rationalized by initial nucleophilic attack of *tert*-butoxide anion on silicon, resulting in formation of pentacoordinated silicon species, which coordinates to the *N*-oxide oxygen atom in analogy to Vorbrüggen's cyanation (see Scheme **8**(**b**)). Subsequent transfer of perfluorinated nucleophile to the ring is probably the rate limited step, in agreement with small isotopic effect determined in experiments with deuterated quinoline *N*-oxide. Elimination of trimethylsilanol completes the cine substitution reaction sequence.

Another versatile protocol for azine trifluoromethylation, developed by Kuninobu, Kanai and co-workers, involves activation of *N*-oxides by coordination with trifluoromethyldifluoroborane, which in turn can be generated *in situ* from

$K[BF_3CF_3]$ and $BF_3 \cdot OEt_2$ [78]. The choice of this particular activating electrophile was dictated by DFT calculations, according to which the LUMO level of pyridine *N*-oxide-BF_2CF_3 lies lower than that of a similar BF_3 complex or of *O*-tosylated, mesylated and acylated pyridine *N*-oxides. Moreover, *N*-oxide-BF_2CF_3 complexes proved to be stable and isolable compounds. Their reaction with $TMSCF_3$ in the presence of CsF provided C(2)/C(6)-trifluoromethylated azines regioselectively and usually in high yields. Notably, complex substrates such as quinine could be used as well. The whole procedure starting from free azine to its trifluoromethyl derivative could be performed as a one-pot process.

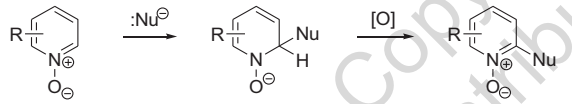
In recent years, considerable attention has been turned towards metal-free sulfonylation of *N*-oxides. 2-Sulfonylation of azine *N*-oxides with arylsulfonyl chlorides has been achieved with dialkyl H-phosphonate [79]. The latter reagent was presumably transformed into electrophilic phosphoryl chloride, acting as an activating agent, with concomitant generation of a sulfinyl nucleophile. At nearly the same time, two groups disclosed iodine-mediated sulfonylation of quinoline *N*-oxides with sulfonyl hydrazides under oxidative conditions (*tert*-butyl hydroperoxide, TBHP, or H_2O_2) [80]. The reaction probably involves hypoiodite anions that coordinate to the *N*-oxide oxygen. Base induces elimination of HN=NH from hydrazide generates sulfinyl anions which attack the azine ring.

OTHER NUCLEOPILIC SUBSTITUTION REACTIONS

Oxidative nucleophilic substitution of hydrogen (ONSH) in aromatic systems is a reaction in which nucleophilic addition to the ring and formation of a σ^H adduct is followed by abstraction of a hydride ion, usually upon the action of an appropriate oxidant [81]. Since heterocyclic *N*-oxides contain a nitrogen atom bearing a formal positive charge, C(2)/C(6) and C(4) positions of the ring are susceptible to attack by strong nucleophiles. Elimination of oxygen atom *via* N–O bond cleavage is just one way of restoring the ring aromaticity and it is typical for cine/tele substitution, described in detail in the previous section. Another possible route is an ONSH reaction (Scheme **18**). Such a process occurring with *N*-oxides has not been explored as extensively as other means of the *N*-oxide ring C–H functionalization, but a few examples exist in the literature.

C–H-Acids, containing only one electron-withdrawing group, such as ketone, ester or nitrile, after deprotonation with *n*-BuLi, *t*-BuOK or alkali metal amides react at low temperature with quinoline, 4-chloroquinoline or 3-bromoquinoline *N*-oxide to provide quinoline *N*-oxide derivatives with the carbon substituent introduced at C(2) [82]. Interestingly, at 30 °C in strongly solvating solvents (DMSO or HMPA) 3-bromoquinoline *N*-oxide reacts with phenylacetonitrile or 2-phenylpropionitrile carbanions with bromine substitution. This fact, as well as

the lack of S_NAr reactivity of *N*-oxide containing Cl substituent at activated C(4) position, is in agreement with the general notion of faster nucleophilic attack at hydrogen-occupied positions of an aromatic ring and a general mechanistic picture of nucleophilic aromatic substitution established in recent years [83]. Addition of free radical scavengers to the reaction mixture indicated that the above ONSH reaction was not a radical process. Performing the reaction in the nitrogen gas flow lowered the yield, whereas bubbling oxygen increased yield. It is then probable that molecular oxygen (O_2) is the oxidant responsible for the further transformation of the initially formed σ^H adducts and hydride removal. *N*-Oxide acting as an oxidant is improbable as the reactions were performed with excess of nucleophile and often proceeded in high yields. Later, the same authors disclosed a similar reaction utilizing deprotonated 2-methyl-*N*-oxides of quinoline and 2-methylquinolines as nucleophiles and leading to bis(quinolinyl)methane mono- or dioxides [84].



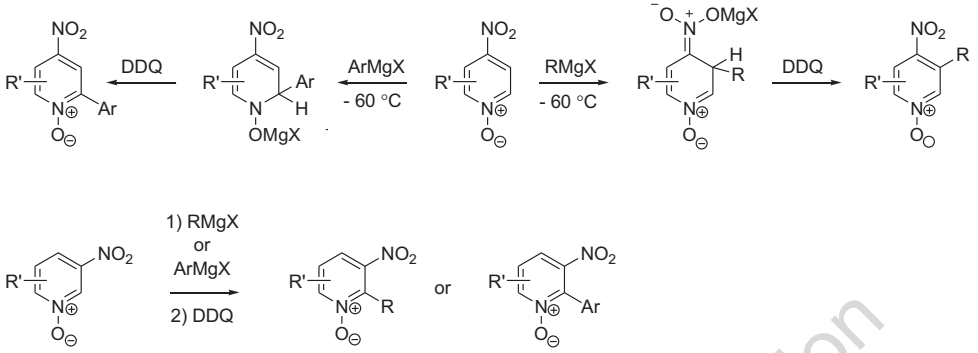
Scheme 18. ONSH reaction in *N*-oxides (an analogous process may occur at C(4) position).

Intramolecular oxidation of a σ^H adduct by a neighbouring *N*-oxide function has been reported as well [85]. The presence of a nitro substituent in the *N*-oxide ring can override the typical directing effect of the *N*-oxide function and an ONSH reaction typical for simple nitroarenes may occur [86].

As mentioned before, the reaction of quinoline *N*-oxides with phenylmagnesium bromide leads to 1-hydroxy-1,2-dihydroquinoline adducts that are prone to air oxidation, leading to 2-phenylquinoline *N*-oxides. This oxidative substitution reaction can be extended to various alkyl- and aryllithium reagents that can be efficiently oxidized to C(2)-substituted *N*-oxides with fluorenone [87].

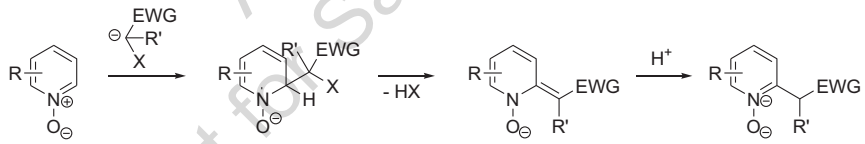
The reaction of pyridine *N*-oxides with Grignard reagents that does not involve deoxygenation, but instead is an example of oxidative nucleophilic aromatic substitution (ONSH), has been developed by Zhang and Duan [88]. *N*-Oxides of 4-nitropyridines undergo addition of aryl and alkyl Grignard reagents at low temperature to give adducts which are stable (or perhaps undergo only reversible ring opening) and can be subsequently oxidized with DDQ to form *N*-oxides with new groups at 2/6- or 3/5 position, depending on the nature of the organomagnesium reagent used (aryl or alkyl, respectively; Scheme **19**). On the other hand, addition to *N*-oxides of 3-nitropyridines proceeded only at C(2)/C(6), which can

be explained by combined activation of the nitro and *N*-oxide functions. Utility of this efficient and transition metal-free protocol has been demonstrated in short syntheses of pyridine alkaloids, Emoxipin, Caerulomycin A and E.



Scheme 19. ONSH reaction in pyridine *N*-oxides with Grignard reagents as nucleophiles [88].

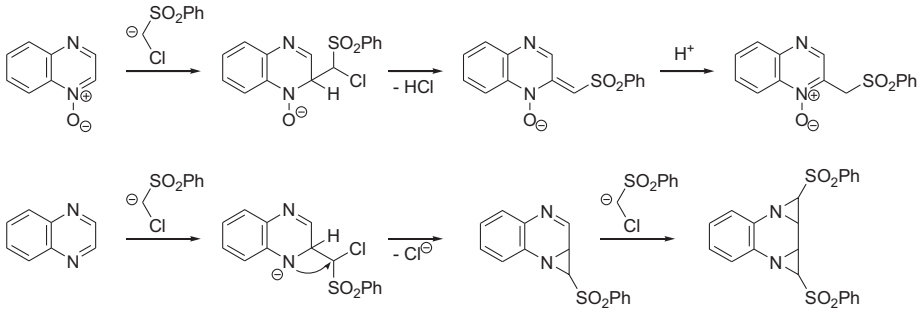
Another general reaction type involving nucleophilic substitution of hydrogen in an aromatic ring that is applicable to aromatic *N*-oxides, is the vicarious nucleophilic substitution (VNS) reaction. In this process, departure of hydrogen from the ring is enabled by the presence of a good leaving group directly attached to the nucleophilic centre (Scheme **20**). Hamana reported 2-cyanomethylenation of quinoline and 4-chloroquinoline *N*-oxides with phenoxyacetonitrile and 2-sulfonylmethylenation of the same substrates with phenyl chloromethyl sulfone [89].



Scheme 20. VNS reaction in aromatic *N*-oxides (X = leaving group; an analogous process may occur at C(4) of the heterocyclic ring).

VNS reactions of quinoxaline provide a good example illustrating the dependence of the reaction course on the presence of the *N*-oxide functionality in the heterocyclic system [90]. Reaction of quinoxaline 1-oxide with chloromethyl phenyl sulfone and KOH in DMSO leads to the expected VNS product, whereas quinoxaline itself gives mono- and bis(aziridination) products resulting from nucleophilic attack of the nitrogen-centred negative charge on the aliphatic carbon atom and substitution of chloride, rather than elimination of HCl (Scheme **21**). Such a reaction course can be explained by poor delocalization of the negative

charge in the system lacking a nitro group.



Scheme 21. The course of VNS in quinoxaline and quinoxaline *N*-oxide [90].

A peculiar case of tele nucleophilic substitution has been reported in which addition of nucleophiles (MeO^-, $HSCH_2CO_2Me$, $HSCH_2CH_2OH$) at C(6) position of 3-trichloromethylpyridine *N*-oxide resulted in departure of C(6)–H proton and chloride from the 3-CCl_3 group [91].

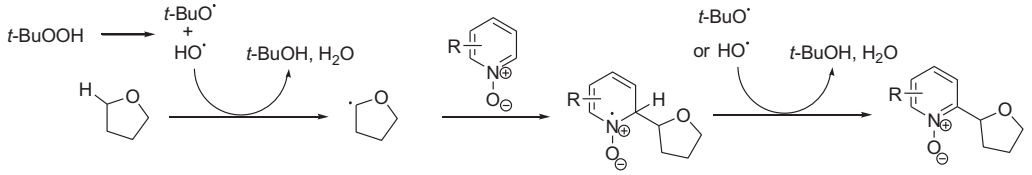
RADICAL SUBSTITUTION

Radical substitution of hydrogen in aromatic *N*-oxides has attracted attention as another metal-free and more "green" process of ring functionalization that is orthogonal to other, more explored methods. Moreover, radical substitution may proceed as a double C–H activation process, if the radical attacking the *N*-oxide has been generated *via* C–H bond homolysis of the other substrate. For example, the pioneering work of Itami, Li, and co-workers involves generation of radicals from cyclic alkanes with *tert*-butoxy radicals formed in thermolysis of *t*-BuOO*t*-Bu [92(a)]. *N*-Oxides of pyridine and its simple alkyl, alkoxyl and aryl derivatives proved much more reactive towards cycloalkyl radicals than unoxidized heterocycles. The reaction led to preferential C(2)–H substitution, although mixtures of mono, bis and even tris-substituted products were usually formed.

A few years later, a similar reaction was published, involving pyridine *N*-oxides and cyclic ethers [92(b)]. At elevated temperature (145 °C) and in the presence of TBHP *N*-oxides were selectively mono-alkylated at C(2) forming products connected *via* α carbon of the starting ether. Adducts of the intermediate ether radicals and TEMPO could be detected in the reaction mixture by HRMS spectrometry (Scheme **22**).

A different approach to generation of radicals capable of addition to azine *N*-oxides leading to C(2) arylation was based upon the use of $K_2S_2O_8$ as oxidant and Ag(I) catalyst [93]. Under these conditions, arylboronic acids reacted at rt

with pyridine and diazine *N*-oxides with formation of C(2)-arylated *N*-oxides with good regio- and chemoselectivity. Intermediacy of aryl radicals could be confirmed in experiments with radical scavengers.

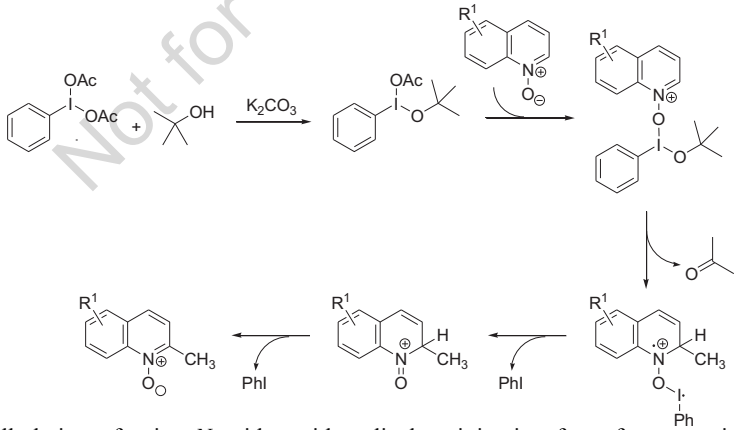


Scheme 22. Alkylation of pyridine *N*-oxides with radicals generated from cyclic ethers [92(b)].

A free-radical pathway probably operates also in C(2)/C(4) decarboxylative acylation of azine *N*-oxides with phenylglyoxylic acids in the presence of Ag(I)/Ag(II) catalytic system and $K_2S_2O_8$ as oxidant [94].

A free-radical methylation of *N*-oxides with dikumyl peroxide has been described [95], as well as arylation with aryl radicals generated by decomposition of aryldiazonium salts, that in turn had been generated by *in situ* diazotization of primary amines [96].

A versatile protocol of 2-alkylation *N*-oxides, which is particularly useful for *N*-oxides of quinolines and isoquinolines, has been reported very recently by Sen and Ghosh [97]. The reaction uses tertiary and secondary alcohols as the alkyl source and is promoted by $PhI(OAc)_2$. Addition of an alkyl radical, abstracted from the α carbon of the alcohol molecule to the heterocyclic ring is probably followed by oxidation of the resultant radical to a heteroaryl cation, which rearomatizes by proton abstraction (Scheme **23**).



Scheme 23. Alkylation of azine *N*-oxides with radicals originating from fragmentation of tertiary or secondary alcohols [97].

DEPROTONATION

Increased acidity of C(2)–H bond at the position vicinal to the N–O group in aromatic *N*-oxides, as well as coordinating and directing group properties of the oxygen atom enable deprotonation of the *N*-oxide ring with strong bases. The resulting anion can be also represented as a carbene resonance structure substituted with a negatively charged oxygen. Acidic properties of C(2)–H bonds in simple azine *N*-oxides were investigated already in the 1960s' by the means of proton deuterium exchange experiments [98].

Deprotonation of pyridine or picolines *N*-oxides with *n*-butyllithium at low temperature leads to 2-lithiated intermediates which can add to electrophiles such as carbonyl compounds, nitriles or carbon dioxide. A serious drawback of this approach is formation of mixtures of products resulting from mono- and bis-deprotonation, as well as low or moderate yields and narrow substrate scope [99]. Deprotonation of pyridine *N*-oxide with LiTMP in the presence of hexafluoroacetone gives much higher yields of addition to the carbonyl group, but selectivity issues remain [100].

Pyridine *N*-oxides substituted with amide groups at C(2) were reported to undergo exclusive C(6) lithiation with LDA [101]. *N*-Oxide of 3,4-dimethoxypyridine was lithiated exclusively at C(2) with *n*-BuLi at 0 °C, but the actual distribution of products of electrophile trapping depends on the reaction time and the nature of the electrophile, since after initial C(2)–H deprotonation equilibration to C(6)-lithiated regioisomer is possible.

Selective deprotonation of pyridine *N*-oxides could be also achieved with Grignard reagents (*i*-PrMgCl or *n*-BuMgCl) at low temperature [102]. Heteroarylmagnesium chlorides prepared in this reaction can be readily trapped with electrophiles such as D_2O, I_2 or carbonyl compounds. 3-Methylpyridine *N*-oxide gave low C(2)/C(6) selectivity, whereas 3-methoxypyridine *N*-oxide was metallated exclusively at C(2) owing to the directing effect of the methoxy group. Magnesium - zinc exchange leads to heteroarylzinc reagents that could be employed in a one-pot process in a microwave-promoted, Pd catalyzed cross-coupling reaction with diphenyliodonium triflate.

Direct formation of zinc *N*-oxide derivatives suitable for Negishi cross-coupling in a one-pot procedure is possible with TMPZnCl·LiCl, originally introduced by Knochel [103]. Metalation of azine *N*-oxides with TMPZnCl·LiCl displays very high selectivity of aromatic C–H bond cleavage *versus* benzylic methyl deprotonation [104]. Azines and diazines containing various substituents, including halogens, were selectively metalated at the position vicinal to the N–O function and used directly in the cross-coupling reaction with heteroaryl bromides

in an efficient and scalable synthesis of unsymmetrical heterobiaryls. Proton-zinc exchange in pyridine *N*-oxide has been also achieved with $Zn(TMP)_2$ [105].

A halophilic reaction of CBr_4 with pyridine *N*-oxides deprotonated with *t*-BuOLi leads to exhaustive bromination of free C(2) and C(6) positions [106].

METAL-CATALYZED C–H-ACTIVATION REACTIONS

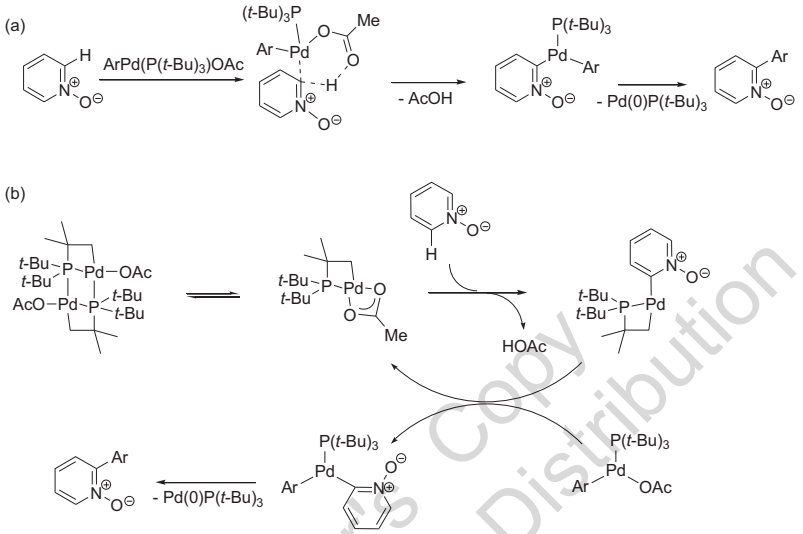
Apart from their considerable acidity, C–H bonds vicinal to N–O group in *N*-oxides of azines and azoles display much lower activation energy for palladium insertion that analogous bonds in the parent, unoxidized heterocycles [107, 108]. Facility of pyridine *N*-oxide C(2)–activation is well illustrated by formation of its stable complexes with actinides, in which the heterocyclic ligand is bound to the metal center *via* C(2) position [109].

Until recently, 2-pyridyl organometallic reagents were difficult to obtain and gave poor yields of cross-coupling products due to limited stability [110]. Therefore, a direct use of *N*-oxides in C–H activation cross-coupling reactions with substrates possessing good leaving groups seemed an attractive alternative. This field of *N*-oxide chemistry has been initiated by a series of seminal works of Fagnou, who already in 2005 reported high-yielding C(2)-selective coupling of pyridine *N*-oxides with aryl bromides, using $Pd(OAc)_2$/*t*-$Bu_3P{\cdot}HBF_4$ catalytic system [111]. Considerably higher activity of electron poor *N*-oxides, as well as large kinetic isotope effect (KIE) between pyridine and pyridine-d_5 *N*-oxide indicated that the reaction did not proceed according to an S_EAr-type mechanism. Later, the same catalytic system was employed in arylation and vinylation of 1,2-, 1,3- and 1,4-diazine *N*-oxides with aryl chlorides, bromides and iodides, as well as vinyl bromides [112]. Changing the catalytic system to Pd_2dba_3 and X-Phos in the presence of NaO*t*-Bu under microwave conditions resulted in complete inversion of selectivity from $C(sp^2)$ arylation to arylation of $C(sp^3)$–H of the 2-methyl group [113]. Impressively, thiazole *N*-oxides could be arylated selectively at either C(2), C(4) or C(5) position [114]. The methodology developed in the Fagnou group become indeed a very general approach to *N*-oxide Pd-catalyzed C–H functionalization of *N*-oxides [7(b), 115].

Computational and experimental investigations led to the establishment of the concerted metalation-deprotonation pathway (CMD) as the most plausible mechanistic hypothesis for the Pd-catalyzed *N*-oxide arylation (Scheme **24**(**a**)) [116]. Such a reaction pathway is in agreement with higher reactivity of electron-deficient substrates, for which proton abstraction is more facile. The presence of a carboxylate ligand is crucial for the formation of the cyclic transition state.

Based upon detailed kinetic measurements, Hartwig proposed an updated

mechanism which is available for catalytic systems capable of forming a cyclometalated palladium species (Scheme **24**(**b**)) [117]. C–H activation of pyridine *N*-oxides with such species is the rate determining step of the reaction and it is followed by transfer of the pyridine moiety to another active Pd species bearing the aryl group.



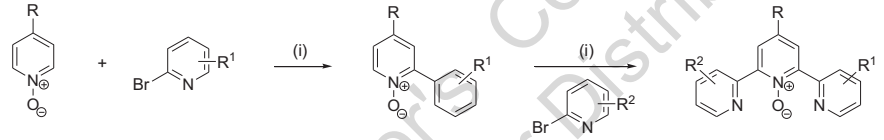
Scheme 24. (a) CMD pathway of C–H activation of aromatic *N*-oxides [116]. (b) An updated mechanism established by Hartwig [117].

In the last few years, methodology based upon *N*-oxide C–H activation catalysed by transition metals has seen a rapid development [118]. Initially, research efforts concentrated on cross-coupling partners containing good leaving group. For example, careful optimization of the catalytic system ($Pd(OAc)_2$, X-Phos, CsF as base) allowed for efficient coupling of various azine and diazine *N*-oxides with aryl and alkenyl tosylates, which generally display low activity in direct C–H arylation reactions [119]. The same reaction conditions were also applicable for much more atom-economical aryl mesylates, as well as cross coupling of electron-deficient 1,2,4,5-tetrafluorobenzene.

Direct heteroarylation of pyridine *N*-oxides based upon transition metal-catalyzed C–H activation of the position adjacent to the oxygen function has been applied in an elegant approach to the synthesis of unsymmetrically substituted 2,2'-bipyridines, elaborated by the Tzschucke group [120]. Cross-coupling of 4-EW--substituted pyridine *N*-oxides, as well as *N*-oxides of 3-fluoropyridine or 2- and 3-cyano- and ethoxycarbonylpyridines with 2-bromopyridine in the presence of $Pd(OAc)_2$/P(*t*-Bu)$_3$ catalytic system provided moderate to good yields of *N*-oxides of 2,2'-bipyridines, which could be subsequently deoxidized by hydrogenation

(H_2, Pd/C), with $NaBH_4$ or PCl_3. With unsubstituted or 4-*t*-Bu-pyridine *N*-oxide the cross-coupling products were formed in lower yields and accompanied by side products (*N*-(2-pyridyl)-2-pyridones, C(3)–H activation products). On the other hand, 3- and 4-halopyridines or 4-haloquinolines could be coupled efficiently with electron-poor *N*-oxides.

The above pyridylation of pyridine *N*-oxides was usually accompanied by the formation of symmetrical terpyridines in a two-fold C–H activation process [121]. This observation led the same research group to develop an efficient, two-step protocol for preparation of unsymmetrical terpyridines, which are useful heterocyclic scaffolds as well. With inverted ratio of the reactants (excess of halopyridine), a two step-protocol enabled the synthesis of terpyridines with two different heterocyclic rings connected to C(2) and C(6) positions of the central *N*-oxide ring (Scheme **25**). Kinetic studies and competitive reactions with 2-bromopyridine and phenyl bromides indicate that the reaction proceeds according to the cooperative catalysis mechanism, proposed earlier by Hartwig (see Scheme **24**(**b**)) [117].



Scheme 25. Synthesis of unsymmetrical terpyridines using Pd-catalyzed pyridine *N*-oxide arylation [121]. (i): $Pd(OAc)_2$, P(*t*-Bu)$_3$, K_3PO_4, toluene, 120 °C, 24 h.

2-Aryl-1,2,3-triazole 2-oxides underwent $Pd(OAc)_2/PCy_3$-catalyzed cross-coupling reactions with aryl and heteroaryl iodides and bromides, selectively at C(5) [122]. Interestingly, phenylboronic acid and (*E*)-2-bromovinylbenzene could be also employed as coupling partners, whereas BnBr, 2-phenylethynyl bromide or cinnamyl bromide were unreactive. Deoxygenation of the products with Pd/C and ammonium formate allowed preparation of 2,4-diaryl-1,2,3-triazoles. Arylation of 2-aryl-1,2,3-triazole 2-oxides at C(5), that is at the position vicinal to the *N*-oxide nitrogen, could be also achieved by cross-coupling with sodium arenesulfinates [123].

The Pd-catalyzed azine *N*-oxide arylation reaction has found application in the synthesis of complex natural products Complanadines A and B [124], as well as in the preparation of paracyclophane-based planar chiral *N*-oxides [125]. Intramolecular vinylation was exploited in an original synthesis of azahelicenes [126]. Arylation of pyridine *N*-oxides with 2-bromoacetanilides was applied on the way to benzisoxazolo[2,3-a]pyridinium tetrafluoroborates, that is cyclic *N*-oxide derivatives [127].

Cross-coupling of azine *N*-oxides with alkyl halides has been initially reported for ring-substituted benzyl chlorides [128]. Selective benzylation of the C(2) position of *N*-oxides of pyridine, cyanopyridines, 1,4-diazine and isoquinoline could be achieved using $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalytic system.

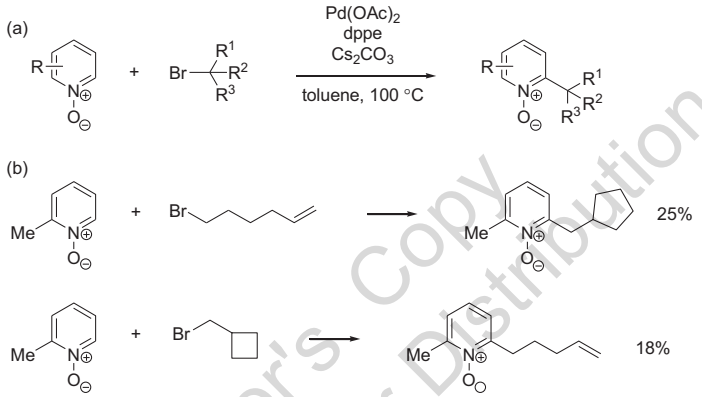
An interesting alkylation protocol, using dialkyl sulfoxides as the alkyl group source, has been developed by Li, Deng, and co-workers [129]. The reaction of 3-alkyl- or 3-arylisoquinoline *N*-oxides or quinoline *N*-oxide with DMSO (reactant and solvent) in the presence of palladium catalyst (preferably $Pd(MeCN)_2Cl_2$), air, $n\text{-}Bu_4NOAc$, ZnO and $n\text{-}Bu_3N$ was found to provide 1-methylisoquinolines or their mixtures with the respective 1-methylated *N*-oxides, depending on the concentration of the reaction mixture. Pyridine *N*-oxides could not be used. A similar reaction with thionyl dihalides ($SOCl_2$ or $SOBr_2$) leads to 1-halogenation and deoxygenation of 3-alkylisoquinoline *N*-oxides. 3-Aryl-substituted substrates undergo double halogenation/deoxygenation, at C(1) of isoquinoline and ortho position of the aryl ring. Based upon control experiments (introduction of CD_3 from DMSO-d_6, no reaction in the absence of air, ^{13}C NMR observation of $CD_3SO_2^-$, facile deoxygenation of isoquinoline *N*-oxides in the presence of Bu_4NOAc, ZnO and $n\text{-}Bu_3N$ and without Pd) the authors proposed a mechanism in which the key steps are coordination of the palladium complex to *N*-oxide, C(1)–H activation, coordination of DMSO to palladium, insertion of palladium into the C–S bond of DMSO and reductive elimination. Formation of the 1-alkylated product is then followed by deoxygenation.

More recently, a much more general cross coupling process of azine *N*-oxides with primary, secondary and even tertiary alkyl bromides using $Pd(OAc)_2/dppf/Cs_2CO_3$ (dppf = bis(diphenylphosphinyl)ferrocene) catalytic system has been developed [130]. Notably, even complex substrates derived from natural products, such as quinine oxide or steroid secondary bromides, could be employed in the reaction. Mechanistic studies revealed that alkyl bromides are converted to radical species in the course of this reaction (Scheme **26**).

Recently, a photoredox catalytic method of pyridine *N*-oxides alkylation with alkyl trifluoroborates has been disclosed [131]. The reaction is catalysed by $[Ru(bpy)_3][PF_6]_2$ in the presence of 1-acetoxy-1,2-benziodoxol-3-(1H)-one upon blue LED irradiation and probably also involves free alkyl radicals; it displays very good functional group tolerance an regioselectivity.

Cross-dehydrogenative coupling (CDC) reactions are particularly valuable synthetic methods in terms of atom economy and reducing the number of synthetic steps [5]. Several reports from the last few years demonstrate that aromatic *N*-oxides are excellent substrates for CDC reactions. An example of

CDC of azine *N*-oxides that allows for introducing alkyl groups at the position vicinal to the *N*-oxide function is an oxidative coupling reaction with cyclic ethers and sulfides, as well as aliphatic alcohols, developed by Cui, Wu and co-workers [132]. The reaction is catalyzed with $Pd(OAc)_2$ with TBHP as a stoichiometric oxidant and is believed to begin with C–H insertion of palladium acetate, followed by coordination of a free radical (generated from the starting ether by the action of *tert*-butoxy radical) to palladium and reductive elimination. On the other hand, it closely resembles free-radical processes developed, for example, by Itami or Liu and Wang [92] that do not require Pd catalysis.



Scheme 26. Pd-catalyzed alkylation of azine *N*-oxides with alkyl bromides (a) and the yield of one of the products (25%) are eclipsed by the compound structures (b) [130].

Kianmehr and co-workers developed a process of two-fold C–H/C–H cross-coupling, involving concomitant arylation and benzylation of pyridine *N*-oxides with toluene derivatives, leading to tricyclic products [133].

Heteroarylation of azine *N*-oxides with azole derivatives is a versatile route of synthesis of unsymmetrical bis(heteroaryls). Such double C–H activation reactions, several of which have been developed in recent years, are usually performed using a Pd(II) source in the presence of oxidant (typically an Ag or Cu salt), which restores +2 oxidation level of the Pd(0) species after the reductive elimination step. You reported *N*-alkylindole coupling with *N*-oxides of azines and diazines, catalysed by $Pd(dppf)Cl_2$/X-Phos/CuBr, with $Cu(OAc)_2 \cdot H_2O$ as a stoichiometric oxidant [134]. The reaction was highly selective for activation of azine C(2) position and C(3) of indole. On the other hand, a similar reaction of indoles containing directing group at nitrogen (2-pyridyl or 2-pyrimidyl) provided products of C(2) indole activation [135].

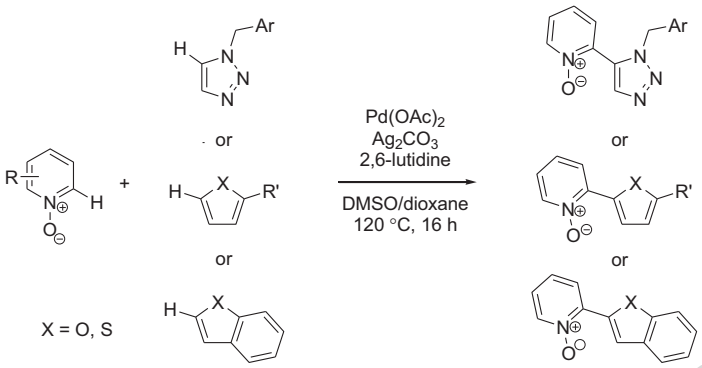
A C–H/C–H cross-coupling reaction between azine and 1,4-diazine *N*-oxides and indoles has been developed using $Pd(OAc)_2/Ag_2CO_3$ system in the presence of

TBAB and pyridine or PivOH additives [136]. The reaction was found to be completely selective for monoarylation of pyridine *N*-oxide and regioselective for C(2) of pyridine and C(3) of indole. 1,2-Dimethylimidazole underwent C–H activation at C(4). Experiments with deuterated pyridine *N*-oxide indicated that activation of the *N*-oxide C(2)–H bond was the rate-determining step. It occurred more readily at the more acidic C(2) position (rather than C(6)) of *N*-oxides of pyridines substituted at C(3) with an electron-withdrawing group. A similar CDC-type reaction was described by Itami, who used indoles and pyrroles as starting materials [137]. *N*-Tosylpyrroles underwent C(3)–H activation, whereas *N*-unsubstituted ones reacted at C(2) position. Pd-catalyzed cross coupling of pyridine *N*-oxides and 2-indolecarboxylic acids was found to occur at C(3) of indole, with protodecarboxylation of C(2) position [138].

Recently, another protocol of coupling of *N*-oxides of pyridine derivatives with *N*-substituted pyrroles has been developed [139]. The reaction provided moderate to good yields of pyridine *N*-oxides substituted at C(2) with 3- or 2-pyrrolyl groups, depending on whether a catalytic amount of $Cu(OAc)_2$ in the presence of air or an excess of AgOAc was used as oxidant. Quinoline and isoquinoline *N*-oxide could be used as well. The reaction exhibited a k_H/k_D KIE of about 2 for pyridine *N*-oxide and about 1 for the pyrrole substrate, which is consistent with a rate limiting *N*-oxide C–H activation step, followed by Heck-type carbo-palladation or an S_EAr-like attack of palladium cationic species on the pyrrole ring. The authors ascribed the dependence of regioselectiovity on the type of additive (Cu or Ag) to the formation of bimetallic Cu-Pd clusters.

Kuang and co-workers developed coupling of pyridine *N*-oxides with five-membered heterocycles: 1,2,3-triazoles, thiophenes and furans [140]. Efficient coupling of electron rich pyridine *N*-oxides (substituted with H, F, or alkoxy groups) at their C(2)–H with C(5)–H position of 1-benzyltriazoles or C(2)–H of furans, thiophenes and their benzo derivatives, has been achieved upon the action of palladium(II) acetate catalyst, in the presence of catalytic amount of 2,6-lutidine and DMSO and excess of Ag_2CO_3 (Scheme **27**). Notably, no homocoupling products were observed. The reaction under the above conditions worked well for isoquinoline *N*-oxides, giving C(1) heteroarylation product selectively, but it failed with quinoline *N*-oxides, oxides of nitropyridines or *N*-phenyltriazole substrates. On the other hand, a 2-aryl-substituted 1,2,3-triazol--1-oxide derivative could be coupled selectively with 2-methylthiophene. The *N*-oxide function could be removed from the pyridine *N*-oxide coupling products upon the action of PBr_3 in refluxing dichloromethane. Mechanistic studies revealed that moderate deuterium incorporation occurs in the ring of benzyltriazole or benzothiophene under the same conditions with D_2O additive, but no deuteration of the pyridine *N*-oxide substrate. On the basis of these

observation the authors proposed that the reaction commences with Pd C–H activation of the five-membered cross-coupling partner.



Scheme 27. CDC reactions between azoles and *N*-oxides of azines and azoles [140].

A similar $Pd(OAc)_2$-catalyzed C(2)-heteroarylation of pyridine, 1,4-diazine and quinoline *N*-oxides with thiazole and benzothiazole derivatives, promoted by DMSO as an additive and with copper(II) pivalate as an oxidant, has been reported by Liu, Li and co-workers [141].

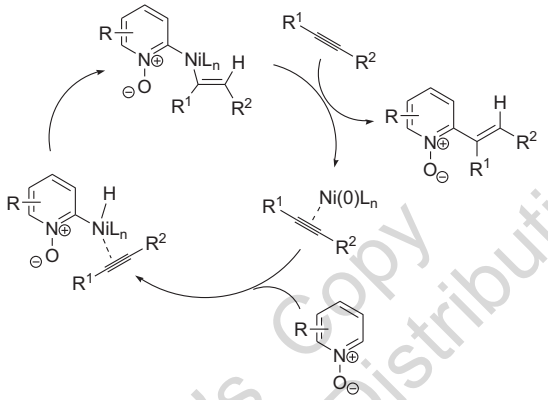
$Pd(OAc)_2/Ag_2CO_3$ catalysis allows also cross-coupling of 2-aryl-1,2,3-triazole 2-oxides with electron-rich (alkyl, alkoxyl) pyridine *N*-oxides [142]. As the reaction with excess of triazole *N*-oxides gave some product of triazole homocoupling, but no bipyridine dioxide, the authors proposed that Pd(II) electrophilic species attack the five membered heterocycle preferably. With pyridine additive, homocoupling products of both triazole and pyridine oxides could be obtained in moderate to good yields.

Homocoupling of 2-aryl-1,2,3-triazole 1-oxides (C-5 to C-5') has been accomplished under $Pd(OAc)_2$ catalysis, in the presence of 1,10-phenanthroline ligand, *t*-BuOK and silver salts as oxidants [143]. Mechanistic studies revealed that C(5)–H of triazole *N*-oxides (unlike parent triazoles) readily undergoes H/D exchange in the presence of *t*-BuOK and CD_3OD, and that no homocoupling occurs in the absence of base or a palladium catalyst. Similar reaction conditions could be also employed for homocoupling of C(2) positions of pyridine *N*-oxide, as well as C(2) of substituted thiazole and imidazole *N*-oxides (with TEMPO instead of Ag salts).

Performing a CDC reaction of pyridine *N*-oxides and thiazoles "on water" has been reported recently [144].

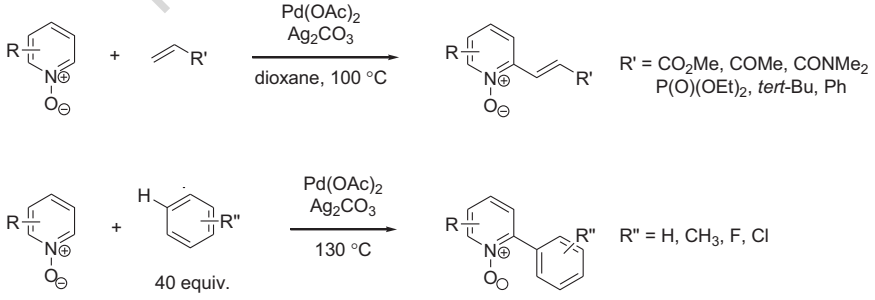
Pd(II) catalysis in the presence of silver salt oxidant allowed double C–H activation in the cross coupling reaction of uracils with *N*-oxides of alkyl, acyl or ester-substituted pyridines [145].

Another class of transition metal-catalyzed C–H activation reaction is alkenylations. In 2007, Ni-catalysed alkenylation of pyridine *N*-oxides with alkynes was disclosed [146]. The reaction proceeded with high *E*/*Z* selectivity, as well as good selectivity for mono-substitution (Scheme **28**).



Scheme 28. Ni-catalysed alkenylation of *N*-oxides with alkynes [146].

In 2008, Chang described Pd-catalysed Heck type alkenylation of *N*-oxides of pyridines and other azines *via* C–H activation of the C(2) position [147]. The reaction proceeded with complete regio- and chemoselectivity (no double alkenylation), in the presence of basic additives and silver salts as oxidants, with electron-poor or neutral olefins (Scheme **29**). Significant kinetic isotope effect suggested that the reaction relays upon cleavage of the acidic C(2)–H bond in the rate-determining step. Interestingly, increasing the temperature allowed performing arylation of the azine *N*-oxide ring under similar conditions, using large excess of benzene or its simple derivatives.



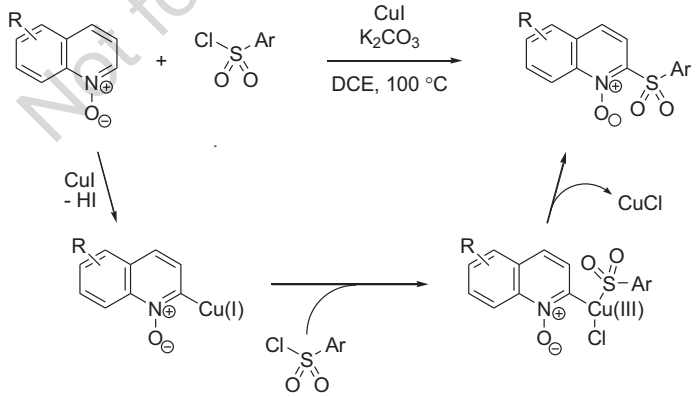
Scheme 29. Alkenylation of azine *N*-oxides with acrylates and styrenes [147].

Quinoline *N*-oxide alkenylation reaction reported by Cui and Wu in 2009 is unique in that it does not require an additional oxidant [148]. Instead, *N*-oxide itself restores palladium to +2 oxidation state, thus maintaining the catalytic cycle. Therefore, it is a rare example of deoxygenative Pd-catalyzed C–H functionalization of *N*-oxides.

Gold catalysis has been used for C–H activation of quinoline N-oxides with deoxygenative introduction of furyl substituents [149].

Some reactions similar to the above Pd-catalysed C–H activation processes of *N*-oxides could be also achieved using copper catalysis. For example, 2-arylation of pyridine *N*-oxides is possible with aryl iodides in the presence of bases and CuI complex with phenanthroline [150]. CDC with oxazoles promoted by $Cu(OAc)_2$ without a Pd catalyst has also been described [151].

Cu(I) catalysed C–H activation of azine *N*-oxides has been used for C–S bond formation, particularly in their direct sulfonylation with aryl sulfonyl chlorides. Cui, Wu and co-workers described a CuI-catalysed synthesis of 2-quinolinyl aryl sulfones (Scheme **30**) [152]. The reaction can be catalysed with Pd salts as well, although less efficiently. The presence of base was found to be crucial, which again points to the importance of C(2)–H bond acidity in azine *N*-oxide rings. Interestingly, moderate yields of sulfones could be obtained even in the absence of any metal salt, which suggests that 2-deprotonated quinoline *N*-oxide can be present in the reaction mixture and react with sulfonyl chloride directly. In the mechanistic proposal forwarded by the authors, such species coordinates to Cu(I), followed by oxidative addition to the S–Cl bond and reductive elimination of copper to provide the final sulfone. Isoquinoline *N*-oxide underwent sulfonylation at C(4).



Scheme 30. Cu-catalysed sulfonylation of azine *N*-oxides with sulfonyl chlorides [152].

Coupling of pyridine, quinoline and isoquinoline *N*-oxides with *N*-tosylhydrazones catalyzed by Cu salts in the presence of a lithium base (*t*-BuOLi) and promoted with microwave irradiation has been developed by Jha and Jain [153]. The reaction yields 2-substituted azines with primary or secondary benzyl groups, or even simple secondary alkyls. The catalytic cycle is believed to commence with deprotonation and metallation of C(2) in azine *N*-oxide. A very similar Cu-catalyzed C(2)-alkylation reaction has been reported for *N*-iminopyridinium ylides [154].

More recently, the same authors reported cross-dehydrogenative homocoupling of 2-arylpyridine *N*-oxides that occurs under similar conditions [155]. On the other hand, the reaction performed in the absence of copper salts provides *N*-monooxides of bis(2,2'-azines) or bis(1,2,3-triazoles). Both reactions probably occur *via* a common intermediate which has the structure of 2-lithiated *N*-oxide. It can further undergo metallation with copper and oxidative coupling with another *N*-oxide molecule, or (in the absence of Cu) act as a nucleophile attacking the second *N*-oxide molecule in a cine-type S_NAr process.

A Cu-catalyzed arylation of azine *N*-oxides with arylboronic acids has been described [156]. The reaction is quite similar to the metal-free process shown in Scheme **14** [67].

Cu(I)/Cu(III) catalysis has been employed in selective C(2)-H amination of alkyl-, halo-, nitroquinoline and quinoxaline *N*-oxides with O-benzoyl hydroxylamines derived from cyclic amines, such as morpholine, piperidine or pyrrolidine [157]. The mechanism proposed by the authors involves *N*-oxide C–H activation to form a Cu(I) derivative, followed by oxidative insertion to the *N*-O bond and reductive elimination of a 2-aminoazine 1-oxide derivative.

Amine function can be also introduced into the *N*-oxide ring *via* dehydrogenative C–H/N–H coupling process. Bolm and co-workers described Cu-catalysed dehydrogenative cross-coupling of quinine *N*-oxides and sulfoximines [158]. The reaction is catalyzed by CuBr in the presence of air, at slightly elevated temperature (50 °C) and without any additives, ligands or bases. It provides high yields of sulfoximinated products with complete C(2) *vs*. C(4) or C(8) regioselectivity for a variety of quinoline and quinoxaline oxides, even halo-substituted ones, but fails for pyridine oxides.

2-Amidation and 2-amination of quinoline and quinoxaline *N*-oxides with cyclic amides and amines using $Cu(OAc)_2/Ag_2CO_3$ catalytic system [159], or of triazole *N*-oxides with amines [160] has been reported.

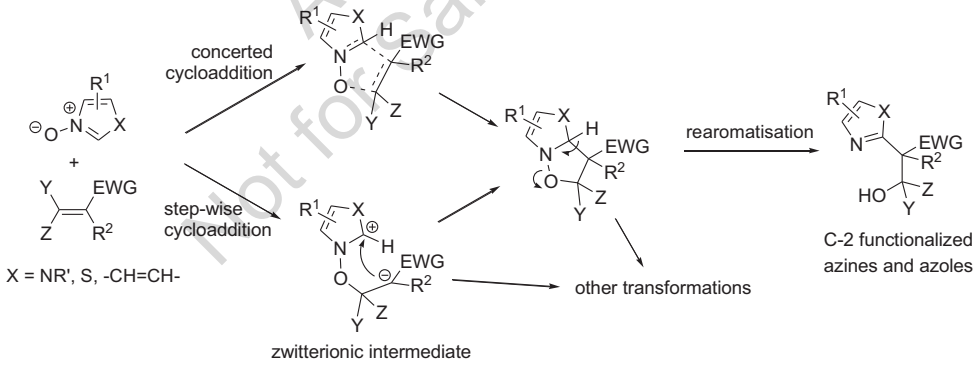
Introduction of oxygen substituents *via* CDC pathway has been achieved using

quinoline *N*-oxides and aldehydes in the presence of CuOTf catalyst and TBHP as the stoichiometric oxidant [161]. The reaction transforms an aromatic aldehyde into an aroyloxy group attached at C(2) of the *N*-oxide ring.

Nickel catalysis has been employed in CDC reaction of 2-aryl-1,2,3-triazole *N*-oxides with thiols [162].

1,3-DIPOLAR CYCLOADDITION

The -C(H)=N^+–O^- fragment present in the *N*-oxide ring is analogous to nitrones and it may participate in cycloaddition reactions with reagents containing multiple carbon-carbon or carbon-heteroatom bonds (Scheme **31**) [163]. Due to loss of aromatic character of the original heterocyclic ring as well as low N–O bond energy, initially formed five-membered cycloadducts (isoxazolidines or isoxazolines) are rather unstable species and usually undergo further transformations - rearomatization, sigmatropic rearrangements, ring expansion, ylide formation, *etc.* [164]. For many years, only few synthetically useful *N*-oxide cycloaddition reactions were known, and they were usually limited to a very small number of (or even single) pairs of *N*-oxides and dipolarophiles. In recent years, however, a few useful and general reactions have been developed which proceed selectively with proton abstraction from the sp^3 ring carbon and N–O bond cleavage, leading to re-aromatized azines and azoles with new substituents at C(2) position of the ring. Such processes are examples of deoxygenative and completely regioselective *N*-oxide C–H functionalization.



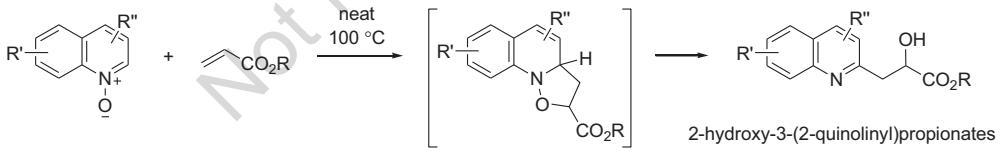
Scheme 31. Dipolar cycloaddition of azine and azole *N*-oxides leading to 2-functionalized heterocycles (addition to triple bonds takes analogous course with formation of isoxazoline adducts).

Owing to their peculiar structure as compared with nitrones (involvement of the C=N bond in the aromatic sextet), aromatic *N*-oxides display greater tendency to undergo cycloaddition in a step-wise manner, especially with highly electrophilic

dipolarophiles. Such reactions begin with nucleophilic attack of oxygen atom on the multiple bond with formation of a zwiterionic intermediate. Subsequent nucleophilic attack of the anionic part of this intermediate on the positively charged C(2) position of the ring leads to a five-membered cycloadduct. Such reactions are akin to cine substitution treated in one of the previous sections, in which one molecule of reactant contained both an oxygen-activating electrophilic centre and a nucleophilic part capable of attacking the heterocyclic ring of *N*-oxide, for example $TMSCH_2CH{=}CH_2$ or TMSCN (see Scheme **3**(**b**)).

Dipolarophiles containing double C=C bonds (acrylates, acrylonitriles, *etc.*) usually react with azine *N*-oxides with formation of 3-(2-hetroaryl)-2-hydroxy-propionates and hydroxypropionitriles. Such regioselectivity indicates addition of *N*-oxide oxygen to C(2) of acrylate, thus it strongly suggests a concerted cycloaddition mechanism rather than initial nucleophilic attack of *N*-oxide on the double bond. Until recently, only few examples of this reaction were known [165, 166] In 2013, a one-pot procedure was reported in which isoquinoline *N*-oxides, generated *in situ* from 2-alkynylbenzaldoximes in an Ag-catalyzed reaction, were subsequently reacted with acrylates, methacrylates and acrylonitriles in DMF at 60 °C to give 1-hydroxyalkylated isoquinolines [167].

Sharma and co-workers developed a general reaction of alkyl acrylates with quinoline *N*-oxides with various substitution pattern of the bicyclic ring system, including acid sensitive groups such as acetals [168]. Heating the reactants mixture without solvent at 100 °C provided 2-hydroxy-3-(2-quinolinyl) propionates, with only small amounts of 3-(2-quinolinyl)acrylates resulting from dehydration (Scheme **32**). Isotopic labelling experiments strongly suggest that the reaction is indeed an example of dipolar cycloaddition, as the hydroxyl oxygen of the products is the one present in the starting *N*-oxides.



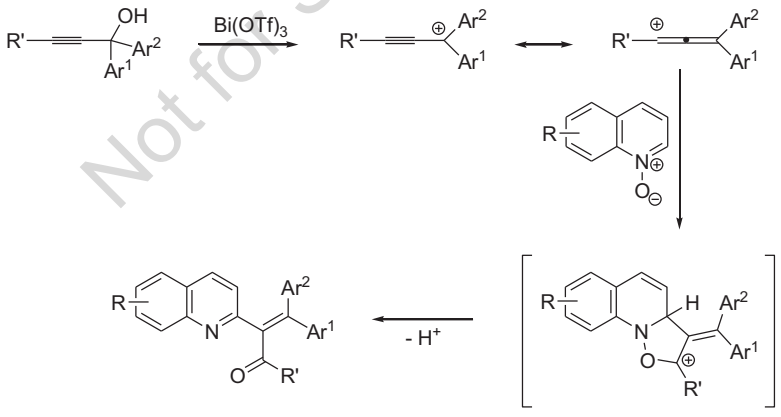
Scheme 32. Cycloaddition of quinoline *N*-oxides and acrylates [168].

A similar reaction of monosubstituted olefins (styrenes and acrylates) with quinoline oxides, performed in DMSO in the presence of AcOH at 120 °C, provided 2-alkenylated products [169]. When the reaction was interrupted after a shorter period of time, 2-hydroxy-3-(2-quinolinyl)propionate intermediate could be isolated along with the expected 2-vinylquinoline derivative.

A similar protocol has been described also by Bower and co-workers, who found that alkenylation of quionoline, isoquinoline and even pyridine *N*-oxides with styrene and its derivatives could be efficiently achieved under Bronsted acid catalysis, in the presence of water (DMSO/water 50:1) [170]. In this case, acrylates displayed low activity. Similarly to the work of Wang [169], intermediates containing an α-hydroxy group (before the water elimination step) could be isolated in some cases. It means that the reaction most probably begins with dipolar cycloaddition between *N*-oxide and alkene. In the absence of $TsOH \cdot H_2O$ catalyst the starting *N*-oxide was recovered nearly quantitatively. It suggests that the role of acid is not just promoting elimination of water, but also facilitating the initial cycloadduct ring opening. The initial cycloaddition must be then a reversible step.

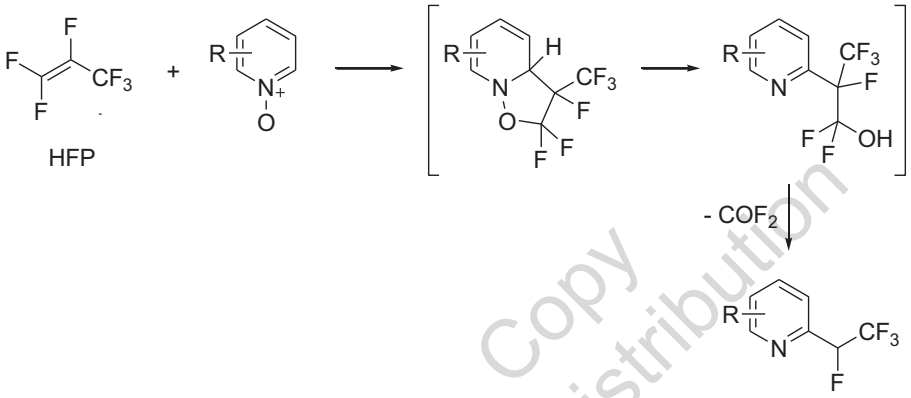
Interestingly, regioselectivity of cycloaddition of imidazole *N*-oxides and acrylates is opposite to that established for azine *N*-oxides [171]. The resulting 3-hydroxy-2-(2-imidazolyl)propanoates could be dehydrated to 2-vinylimidazoles with $Pd(OAc)_2$.

Recently, *N*-oxides of quinoline and its simple derivatives have been reported to react with tertiary α,α-diarylpropargylic alcohols under Lewis acid catalysis, preferably Bi(OTf), to provide derivatives containing an enone substituent at C(2) of the heterocyclic ring [172]. ^{18}O isotope labelling experiments, as well as lack of reactivity of α,β-unsaturated ketones obtained by isomerisation of the starting alcohols suggested that the reaction may proceed as a 1,3-dipolar cycloaddition between *N*-oxide and allenyl carbocation (Scheme **33**). Opening of the alkylidene isoxazolidine intermediate would lead to the observed enone products.



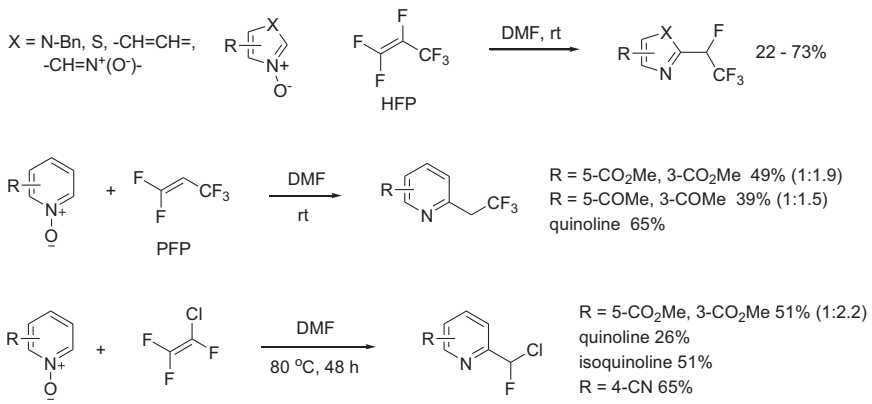
Scheme 33. Cycloaddition of quinoline *N*-oxides and allenyl cations [172].

A group of dipolarophiles cycloaddition of which has been studied in some detail are 1,1-difluoroalkenes. Already in the 1960, it was found that an autoclave reaction of hexafluoropropene (HFP) with *N*-oxide of pyridine and its simple derivatives gives 2-(1,2,2,2- tetrafluoroethyl) pyridines in moderate yields [173, 174]. As difluorophosgene was detected among the gaseous products, it was concluded that the initially formed fluorinated isoxazolidine adduct suffers N–O bond cleavage, followed by a retroaldol C–C bond cleavage (Scheme **34**).



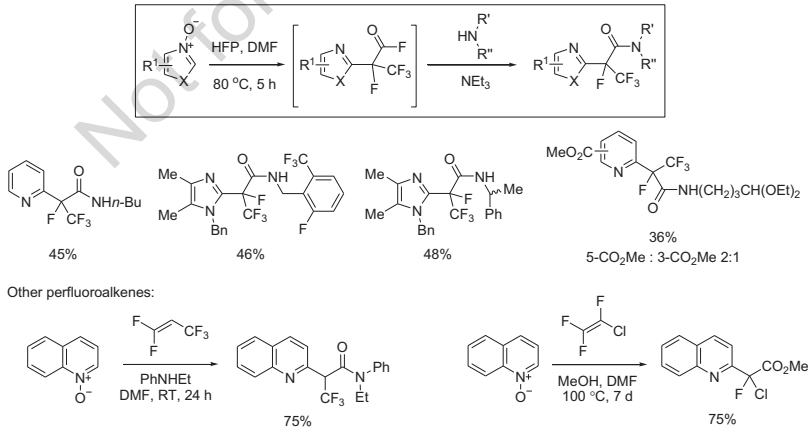
Scheme 34. Early studies on the reaction between HFP and pyridine *N*-oxides [173].

Much later, it was found that the reaction of HFP with *N*-oxides was of a general character in terms of the type of the heterocyclic ring in the substrate as it provided good yields of pyridines, quinolines, imidazoles and thiazoles substituted at C-2 with a 1,2,2,2-tetrafluoroethyl group (Scheme **35**) [175, 176] The reaction was also viable for other perfluoroalkenes such as 2*H*-pentafluoropropene (CF_2=$CHCF_3$; PFP) or chlorotrifluoroethylene (CF_2=CFCl), providing products with a -CH_2CF_3 or -CHFCl substituent, respectively. Moreover, contrary to the first literature reports, the reaction did not require elevated temperatures and pressures. The observed structure of the products indicates regioselective addition of the *N*-oxide oxygen to the terminal CF_2 group of the perfluoroalkene molecule, followed by a loss of a carbon atom, perhaps in the form of difluorophosgene, CF_2=O. Electron-poor azine *N*-oxides reacted considerably more slowly than electron-rich ones. Predominant formation of 2,3-substituted products in the reactions with *N*-oxides substituted at C(3) with electron-withdrawing groups might suggest a step-wise, ionic mechanism for cycloaddition of HFP and other strongly electrophilic fluoroalkenes. On the other hand, elimination of fluoride from β-fluorocarbanions is a very facile process which would certainly occur in a zwitterionic intermediate (see Scheme **31**) formed after nucleophilic attack of *N*-oxide on HFP, leading to side products. However, no such side products were ever observed.



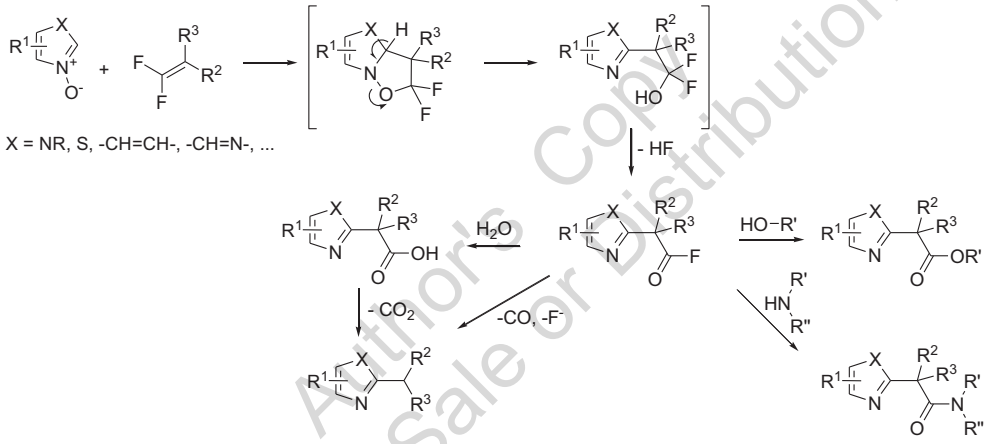
Scheme 35. C(2)-Selective fluoroalkylation of azines and azoles [175, 176].

Further instigation of the mechanism of the fluoroalkene and *N*-oxide cycloaddition revealed that in fact it proceeds *via* an intermediate that has a structure of an α-heteroaryl-α-trifluoromethylacyl fluoride (Scheme **36**) [177]. 1,2,2,2-Tetrafluoroethylazines and similar products observed in the earlier experiments resulted simply from hydrolysis of such acyl fluorides and spontaneous decarboxylation of the respective carboxylic acid. This finding enabled an extension of the reaction to the preparation of azine and azole derivatives with more complex ring substituents that contain ester or amide groups apart from fluorine atoms, by adding an appropriate nucleophile to the reaction mixture. Amines are too nucleophilic to be mixed directly with strongly electrophilic HFP, but high stability of α-heteroaryl-acyl fluorides formed from HFP and *N*-oxides allowed performing the reaction as a one-pot, two-step process (Scheme **36**).



Scheme 36. Preparation of α-heteroarylperfluoropropionic amides by quenching fluoroacyl intermediates with amines [177].

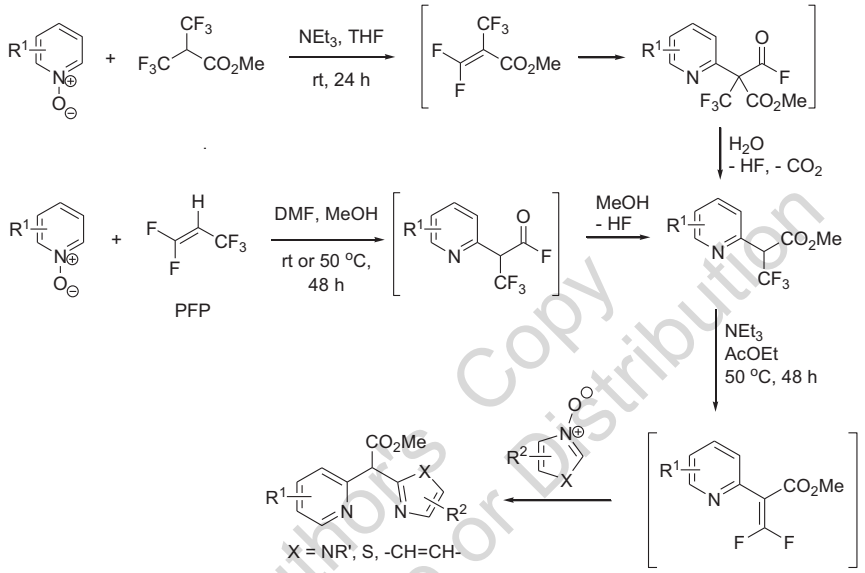
The above synthetic approach to *N*-oxide functionalization is not restricted to gaseous perfluorinated alkenes. In fact, cycloaddition of azine and azole *N*-oxides with 1,1-difluorostyrenes, performed in solvents of moderate polarity at 70 °C and in the presence of alcohols, afforded aryl(heteroaryl)acetates [178]. Similar amides can be prepared in a three component reaction of difluorostrenes, *N*-oxides and amines of diverse structure [179]. The use of difluorostyrenes containing a tetrasubstituted double bond resulted in introduction of substituents with a quaternary carbon centre bound to the heterocyclic ring. A reaction with monofluorostyrene provided the expected α-aryl-α-heteroaryl acetaldehyde. Direct observation of an α-heteroarylacyl fluoride intermediate in the reaction mixture with NMR techniques confirmed that these reactions proceed by a mechanism presented in Scheme **37**.



Scheme 37. The general mechanism of cycloaddition between fluoroalkenes and azine and azole *N*-oxides.

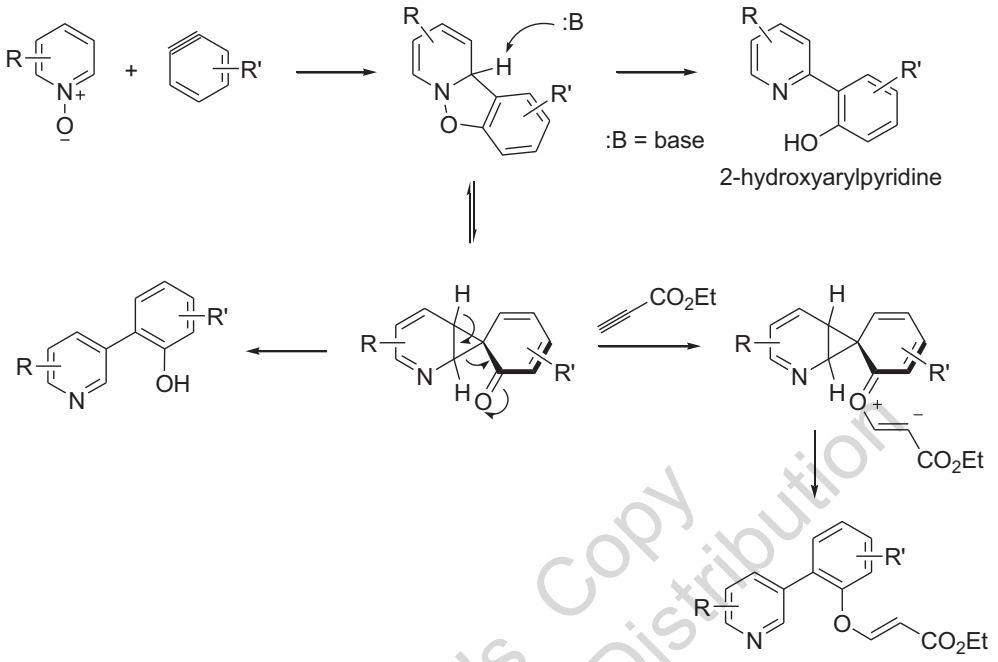
A double cycloaddition strategy could be used for assembly of unsymmetrical bis(heteroaryl)methanes containing two different heterocyclic units from two given aromatic *N*-oxides (Scheme **38**) [180]. First, azines with a -CH(CF_3)CO_2Me substituent at C(2) position were prepared by cycloaddition of appropriate *N*-oxides with either pentafluoropropene or methyl perfluoromethacrylate, which can be generated *in situ* by elimination of HF from methyl 2H-perfluoroisobutyrate ((CF_3)$_2$CHCO_2Me) upon the action of a weak base, for example NEt_3. In the second step, the above fluorinated azine intermediates were subjected to HF elimination in the presence of *N*-oxides, providing the target bis(heteroaryl) cycloaddition products. Compounds containing a quinoline or pyridine ring system exist, at least to some extent, as tautomers with an exocyclic double bond.

Concerning cycloaddition to triple carbon-carbon bonds, reactions of azine *N*-oxides with electrophilic alkynes such as DMAD or PhC≡CCN tend to take complicated course, with the isoxazoline ring opening and elimination route (as shown in Scheme **31**) being only one among other reaction pathways [181]. On the other hand, azole *N*-oxides with DMAD cleanly afford C(2) substitution products [182].



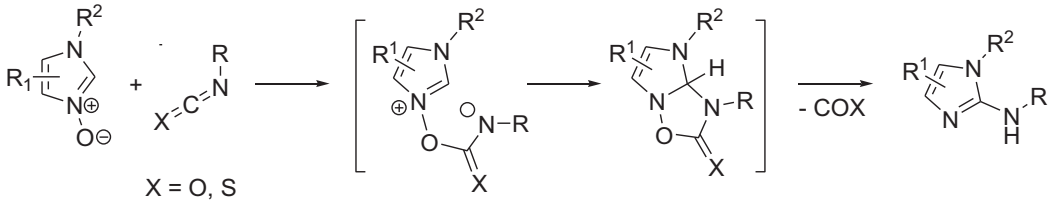
Scheme 38. Application of difluoroalkene cycloaddition in the synthesis of unsymmetrical bis(heteroaryl)methane derivatives [180].

A somewhat more complicated reaction, but still leading to ring-functionalized azines in highly selective manner, is cycloaddition with benzyne. The reaction of pyridine *N*-oxides with *ortho*-trimethylsilylaryl triflates in the presence of CsF, first described by Larock, leads to tricyclic cycloadducts, in which the central isoxazoline ring undergoes a 1,5-sigmatropic rearrangement to a cyclopropane-fused 2,3-dihydropyridine intermediate [183]. Its opening leads to 3-(2-hydroxyaryl)pyridines. Later, Liu and co-workers established that in fact the reaction course described by Larock is only a part of a broader mechanistic picture (Scheme **39**) [184]. They found that excess of basic species in the reaction mixture favoured elimination of proton and N–O bond cleavage in the initial cycloadduct, leading to 2-hydroxyalryl pyridines instead of 3-substituted regioisomers. Formation of the latter products is facilitated by lithium cations. Moreover, vinyl ethers of similar structure can be obtained when electron poor alkynes are present in the reaction mixture.



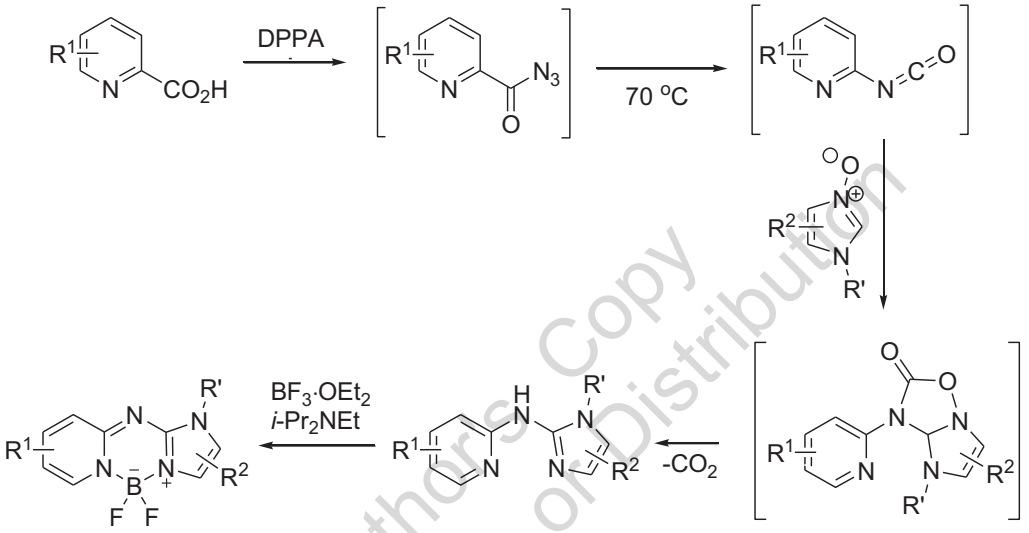
Scheme 39. Reactions of pyridine *N*-oxides and benzyne [184].

Cycloaddition of *N*-oxides to carbon-nitrogen multiple bonds has provided several useful synthetic protocols that enable introduction of nitrogen substituents at C(2) of the heterocyclic ring. Cycloaddition of pyridine *N*-oxides and isocyanates leads to cycloadducts that undergo a fast 1,5-sigmatropic rearrangement to oxazolidinone-fused 2,3-dihydropyridines [185]. Upon heating, they release CO_2 to provide 2-aminoazines. Reactions of pyridyl isocyanates with pyridine *N*-oxides were used in the preparation of bis(pyridyl)amines [186]. Reaction of imidazole *N*-oxides and isocyanates is more straightforward and provides 2-aminoimidazoles directly (Scheme **40**) [187].



Scheme 40. 2-Amination of imidazoles *via* cycloaddition of imidazole *N*-oxides and iso(thio)cyanates [187].

Recently, the methodology of heteroaryl isocyanate generation *via* a Curtius rearrangement of heteroarylacyl azides, followed by their cycloaddition to *N*-oxides, has been used in the synthesis of amines substituted with an azine and azole unit at the central nitrogen atom (Scheme **41**) [188]. Complexation of these products with BF_3 afforded complexes that were unsymmetrical analogues of *aza*-BODIPY fluorescent dyes. Indeed, the new complexes exhibited strong fluorescence and very high Stokes shift values.



Scheme 41. Synthesis of unsymmetrical azine-imidazole BF_2 complexes [188].

For many years, cycloaddition of *N*-oxides to nitrilium cations prepared as free salts or masked in the form of imidoyl chlorides has attracted attention as a possible means of 2-amidation of azines and azoles [189]. However, early attempts suffered from poor yields and selectivity of formation of the desired products. A more practical protocol for 2-amidation of pyridines was later developed by Wachi and Terada, who investigated the reaction between pyridine *N*-oxides and imidoyl chlorides of 1,3-benzoxazines [190]. Appropriate benzoxazines were readily available from salicylamides and ketones. Their addition to *N*-oxides resulted in the formation of *N*-(2-pyridyl)benzoxazinones, acid hydrolysis of which provided 2-aminopyridines in good yields, with the exception of substrates containing a 4-nitro or 4-methoxy substituent. Nowadays, this method still finds application in synthesis of biologically active compounds [191].

In recent years, a few mild, general and selective protocols for azine 2-amidation have been developed. Couturier and co-workers developed *in situ* generation of

acyloyl isocyanates from primary amines and oxalyl chloride [192]. Cycloaddition of these reactive intermediates to azine *N*-oxides proceeds analogously as typical isocyanates. 2-Aminopyridines could be also obtained in reaction with imidoyl chlorides prepared *in situ* from secondary amides and oxalyl chloride or phosgene [193]. Other protocols include a step-wise cycloaddition of nitrillium cations generated from amides with Tf_2O [194] or from isocyanides and TMSOTf [195].

Azine *N*-oxides undergo regioselective, deoxygenative 2-amidation upon the action of arylsulfonamides in the presence of $PhI(OAc)_2$ and PPh_3 [196]. It has been proposed that the reaction proceeds *via* initial formation of an iodoimine intermediate, followed by its PPh_3 -assisted [3+3] cycloaddition to *N*-oxide. Elimination of $PH_3P{=}O$ and PhI provides the final products.

An isolated example of pyridine 2-fluoroalkylation has been reported [197] in which pyridine *N*-oxide undergoes cycloaddition to the double C=S bond of bis(trifluoromethyl)sulfin.

A peculiar case of an *N*-oxide cycloaddition (probably step-wise) is the reaction with Tebbe reagent, $Cp_2Ti{=}CH_2$ [198]. It probably occurs *via* a five-membered titanacycle and it allows 2-methylatioon of azines accompanied with removal of the *N*-oxide oxygen.

CONCLUDING REMARKS

Aromatic *N*-oxide transformations discussed in the preceding sections clearly demonstrate that these substances are versatile intermediates in synthetic heterocyclic chemistry. Even though all general reaction types presented above, with the exception of transition-metal catalysed C–H activation, have been known and understood for several decades, each of them is nowadays actively pursued and brings new developments that provide useful and general methods of preparation of complex azine and azole derivatives. In particular, further seminal discoveries are expected in new cine-type reactions of aromatic N-oxides, as well as transition metal-catalyzed cross-dehydrogenative coupling and radical substitution. There is no doubt that extensive research and discovery of new reactivity modes and reagents capable of interacting with aromatic *N*-oxides will continue in the years to come.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author(s) confirm that this chapter contents have no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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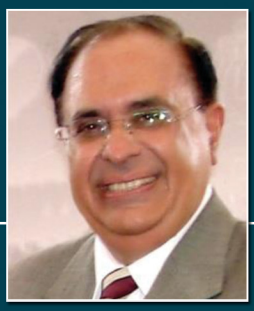

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1080 international publications in several fields of organic chemistry including 751 research publications, 37 international patents, 69 chapters in books and 221 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 54 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.