Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6873

www.rsc.org/obc

PERSPECTIVE

Tandem reactions initiated by copper-catalyzed cross-coupling: A new strategy towards heterocycle synthesis

Yunyun Liu* and Jie-Ping Wan

Received 17th May 2011, Accepted 27th July 2011
DOI: 10.1039/c1ob05769c

Copper-catalyzed cross-coupling reactions which lead to the formation of C–N, C–O, C–S and C–C bonds have been recognized as one of the most useful strategies in synthetic organic chemistry. During past decades, important breakthroughs in the study of Cu-catalyzed coupling processes demonstrated that Cu-catalyzed reactions are broadly applicable to a variety of research fields related to organic synthesis. Representatively, employing these coupling transformations as key steps, a large number of tandem reactions have been developed for the construction of various heterocyclic compounds. These tactics share the advantages of high atom economics of tandem reactions as well as the broad tolerance of Cu-catalyst systems. Therefore, Cu-catalyzed C–X (X = N, O, S, C) coupling transformation-initiated tandem reactions were quickly recognized as a strategy with great potential for synthesizing heterocyclic compounds and gained worldwide attention. In this review, recent research progress in heterocycle syntheses using tandem reactions initiated by copper-catalyzed coupling transformations, including C–N, C–O, C–S as well as C–C coupling processes are summarized.

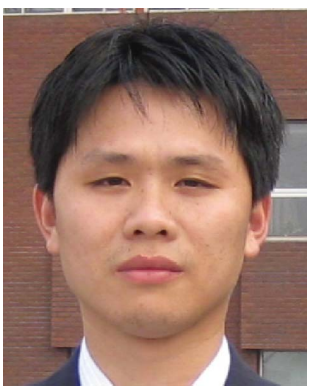
1. Introduction

Transition metal catalyzed coupling transformations are now serving as one of the most useful and powerful tools in organic synthesis. Their application, from laboratory to industrial scale, has permeated to a great number of different subjects.[1] Notably,

College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 33002, China. E-mail: chemliuyunyun@gmail.com; Fax: +86 791 8120380; Tel: +86 791 8120380

Yunyun Liu

Dr Yunyun Liu was born in 1983 in Shandong Province, China. She obtained her Bachelor's Degree in Qufu Normal University in 2005. She then moved to Zhejiang University to continue her graduate study in the Department of Chemistry. Under the supervision of Professor Weiliang Bao, she worked on the field of copper-catalyzed Ullmann reaction and related tandem reactions for her doctorate study. She obtained her doctorate degree in 2010 and presently she is an assistant professor in Jiangxi Normal University. She is currently interested in the research of organometallic chemistry.



Jie-Ping Wan

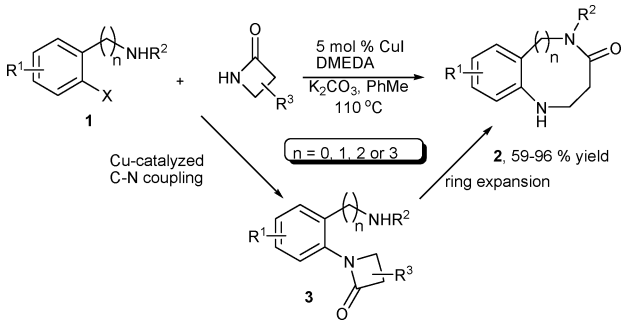
Dr Jie-Ping Wan was born in 1982 in Nanchang, Jiangxi Province in China. He began to study chemistry in Nanchang University in 2000 and finished his undergraduate study there in 2004 with his bachelor degree. He continued his graduate study in Zhejiang University since September, 2005, where he spent 5 years in the group of Professor Yuanjiang Pan. He was awarded the degree of Doctor of Science in 2010. Since July, 2010, he is an assistant professor in the College of Chemistry and Chemical Engineering of Jiangxi Normal University. His present research interest contains the development of new multicomponent reactions (MCRs) for the synthesis of heterocyclic compounds with potential biological function and organometallic chemistry.

the latest decade witnessed an unprecedented blossom in the research of transition metal-catalyzed synthesis.[2] Among the massive numbers of reaction styles catalyzed by transition metals, the coupling process forming C–X bonds (X = C, N, O, S) consists of a central issue.[3] In general, Pd, Au, Ag, Rh, Ni, Cu and Fe *etc.* are the most investigated and employed metal species for these coupling reactions. While different advantages could be specifically ascribed to each of these metals, Cu-catalysis represents a promising direction in C–X coupling reactions for the following reasons: a) Abundant storage of Cu in the earth and low cost; b) high catalyst activity in C–X coupling reactions; c) low toxicity and easy to recycle; d) excellent tolerance to different reaction protocols as well as functional groups.[4] Actually, the past decade witnessed sharp increase on the attention to Cu-catalyzed coupling transformations due to the important discovery on organic ligand facilitated copper catalysis, which significantly lowered the demand on reaction conditions and expanded the compatibility of Cu-catalyzed couplings.[5] Accordingly, the research on exploring new application of Cu-catalyzed coupling also gained extensive interest. The synthesis of natural products and biologically interesting molecules are typical examples and have been comprehensively reviewed.[6] An interesting newly emerging direction in the application of Cu-catalysis is that of tandem reactions providing heterocyclic products in which the Cu-catalyzed C–X bond formation serves as key transformation. In these reactions, the insertion of Cu to unsaturated C-halo or C–H bonds led to the formation of new C–X (X = C, N, O, S) bonds and initiated the construction of various heterocycles. Considering the boom in Cu-catalyzed synthesis and the importance of C-heteroatom bonds forming reactions, it is not surprising that these reactions rapidly gained numerous attention and have been regarded as one of the major strategies for assembling heterocycles. In this review, we systematically summarized the developments in Cu-catalyzed coupling transformation-initiated tandem reactions in the synthesis of heterocyclic compounds. According to the different C–C/heteroatom bonds formed in the reactions, the content was divided into five main sections, including reactions initiated by C–N coupling, C–S coupling, C–O coupling, C–C coupling and reactions involve in double coupling processes.

2. Tandem reactions initiated by Cu-catalyzed couplings for the syntheses of heterocycles

2.1. Reactions initiated by C–N coupling

Cu-catalyzed C–N coupling reactions between N-nucleophiles and aryl halides are the earliest forms of both Ullmann and Goldberg reactions.[7] These reactions therefore attracted most attention among all Cu-catalyzed coupling transformations. One pioneer example on the cascade synthesis of heterocycles based on Cu-catalyzed coupling process was reported by Buchwald and coworkers.[8] As outlined in Scheme 1, the amino group functionalized aryl halides **1** (X = Br or I, *n* = 0, 1, 2 or 3) were able to be converted to corresponding medium heterocyclic products **2** *via* the tandem C–N coupling and ring expansion reaction with *β*-lactams in the presence of 5 mol% CuI and 10 mol% *N*,*N*′-dimethylethylenediamine (DMEDA). Intermediates **3** were observed in some entries and could be transformed into products **2** under transition metal complex catalysis or acidic



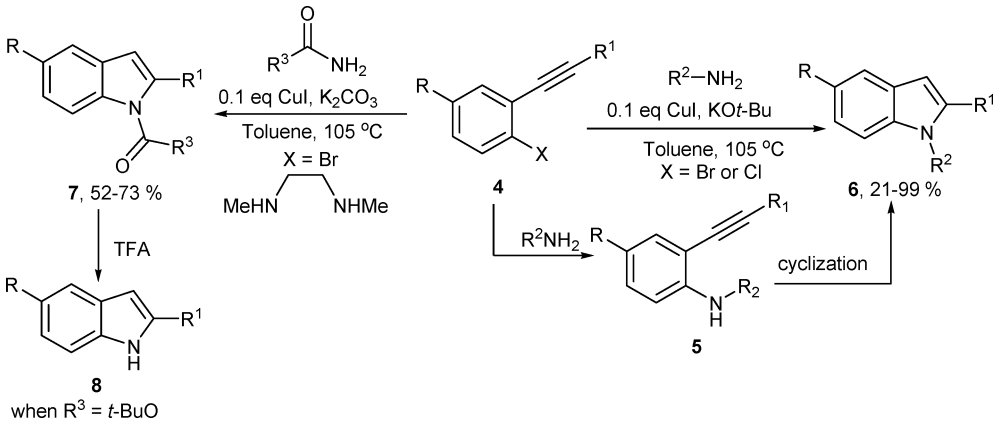
Scheme 1

condition. This protocol provided a highly useful and important new route to prepare medium aza heterocycles. The success of this protocol revealed the excellent tolerance of Cu-catalyzed coupling transformations to other bond-forming processes and therefore paved the way for the later boom in research on Cu-catalyzed coupling-initiated tandem reactions for the synthesis of various heterocycles.

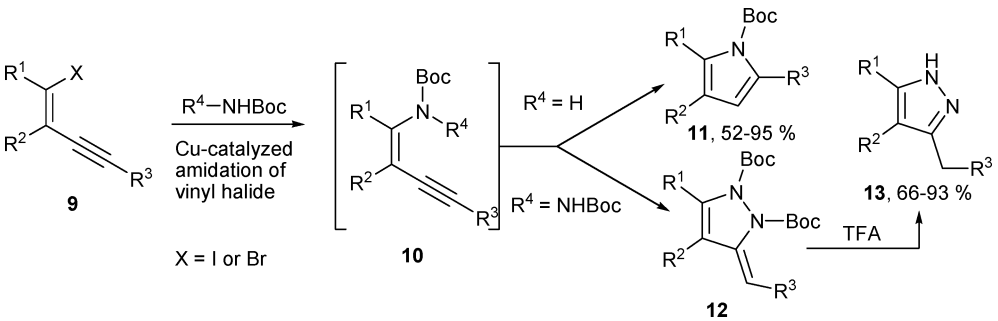
In 2005, Ackermann[9] reported the synthesis of indole using *o*-alkynylaryl bromide **4** and primary amines with the catalysis of CuI. This reaction was also initiated by the C–N coupling of amines and Ar-Br, which led to the production of intermediates **5**, the subsequent intramolecular cyclization of **5** provided indole derivatives **6** (Scheme 2). When corresponding *o*-alkynylaryl chloride was employed, a poor yield of products was obtained by using CuI, while palladium(II) acetate was effective in catalyzing the reaction of *o*-alkynylaryl chloride. Recently, the author expanded the scope of this CuI-catalyzed reaction to carbamates and amides. Under the assistance of DMEDA, *N*-acylindoles **7** were furnished *via* similar transformation, and the products synthesized from *tert*-butyl carbamate could be readily converted to indoles **8** in the presence of TFA.[10]

In modern Cu-catalyzed C–X coupling reactions, vinyl halide is another type of electrophilic partner and could also serve as building block in Cu-catalyzed domino reaction to provide heterocyclic scaffolds. Buchwald[11] *et al.* developed the selective synthesis of pyrroles **11** and pyrazole precursors **12** *via* designed Cu-catalyzed amidation/hydroamidation of haloenynes **9**. The NMR analysis on crude products implied that intermediates **10** were firstly formed in the reaction, and **11** and **12** were respectively produced through 5-*endo*-dig and 5-*exo*-dig cyclization pathways (Scheme 3).

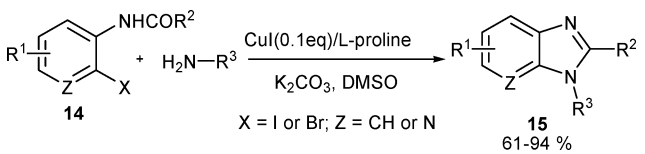
Starting from *o*-halide (I or Br) functionalized *N*-acyl aromatic amines **14**, different *N*-amination based tandem reactions have been devised for the synthesis of different heterocycles, in the presence of CuI, L-proline and base; Ma *et al.* established the one-pot synthetic approach of benzimidazoles **15**, the substitution variation in both the 1- and 2-position (R^1 and R^2) of **15** was allowed in the synthesis.[12] The *ortho*-subtituent effect of the NHCOR group turned out to be an important factor for the transformation (Scheme 4). Later on, the authors modified the structure of **14** to corresponding carbamate elaborated aryl halides **16** to run new tandem reactions. Correspondingly, after amination, subsequent intramolecular amidation of the carbamate fragment led to the formation of heterocyclic products **17**. Both bromide and iodide substituted **16** were good reactants while slight change in the reaction conditions such as ligand, base were necessary



Scheme 2

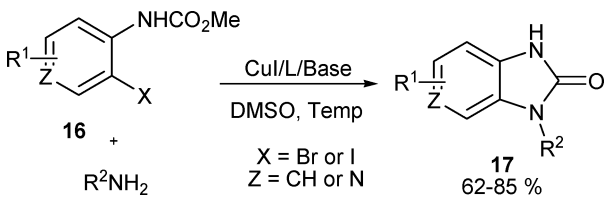


Scheme 3

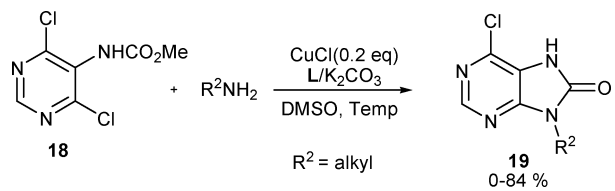


Scheme 4

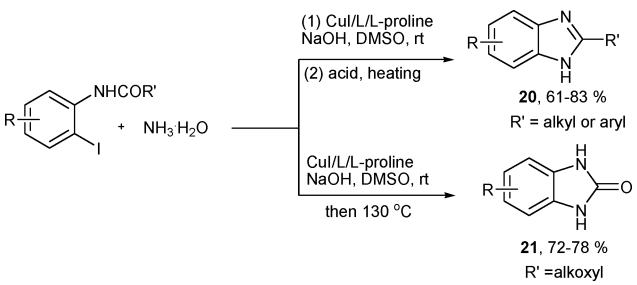
to guarantee satisfactory yields for different aryl halides (Scheme 5).[13] Using a similar strategy, Sun[14] *et al.* developed the tandem synthesis of analogous pyrimidine fused heterocyclic compounds **19** *via* cascade C–Cl bond amination and an intramolecular carbamate amidation reaction of corresponding substrate **18**, CuCl and *trans*-4-hydroxyl-L-proline were employed as catalyst and ligand, respectively (Scheme 6). Additionally, when ammonia was used instead of primary amines, **14** or **16** were able to undergo similar tandem reactions to provide 2-substituted benzimidazoles **20** and 1,3-dihydrobenzimidazol-2-ones **21** (Scheme 7).[15] Besides the utility in the one-pot synthesis of heterocyclic products of **20** and **21**, *o*-haloaromatic amines of type **14** are also capable of serving as starting materials for the assembly of fused heterocycles **24**.[16] Under the catalysis of CuI and assistance



Scheme 5



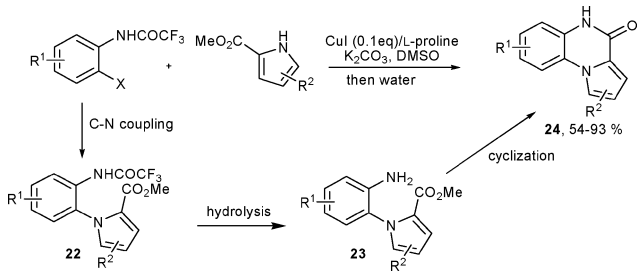
Scheme 6



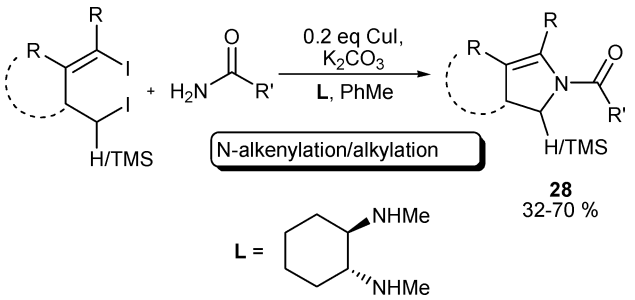
Scheme 7

of L-proline, 2-halotrifluoroacetanilides efficiently reacted with pyrrole-2-carboxylate esters to furnish a class of fused pyrrolo[1,2-*a*]quinoxalines **24**. The whole reaction process involved C–N coupling to give **22** and hydrolysis to give **23** as well as intramolecular condensation of **23** to give **24** (Scheme 8).

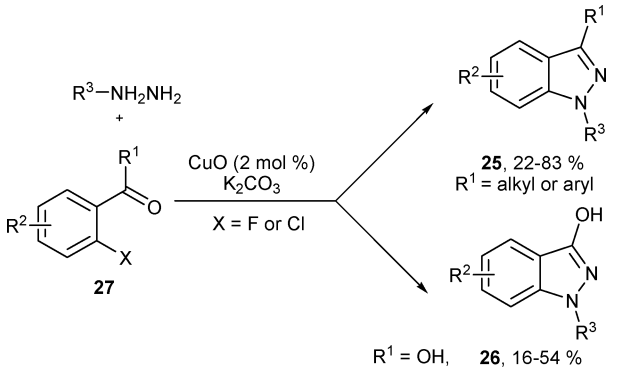
Also employing subsequent transformation of C–N amination and intramolecular dehydration, del Olmo and coworkers[17] devised a CuO-catalyzed one-pot reaction for the synthesis of indazoles **25** or **26** from *o*-haloalkanoylphenones **27** and hydrazines (Scheme 9), no additional ligand was needed in these reactions. It



Scheme 8



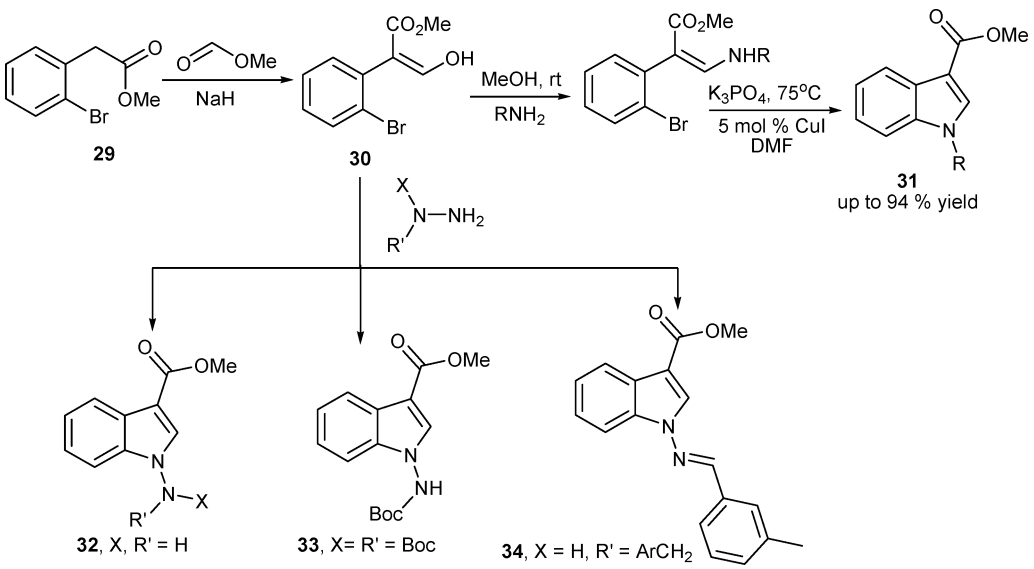
Scheme 10



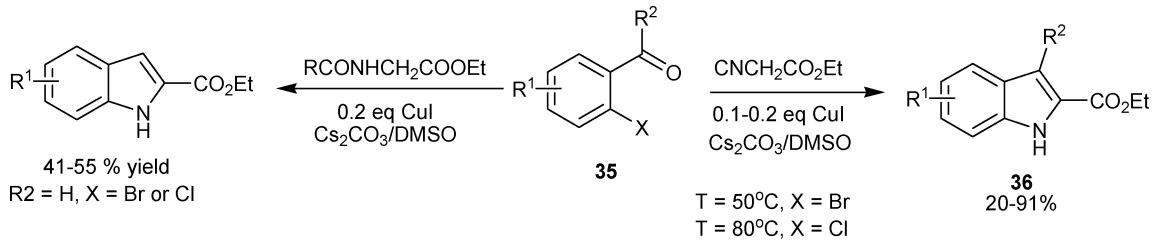
Scheme 9

is noteworthy that the amination conversions were accomplished through C–Cl or C–F bond cleavage and a broad range of functional groups were well tolerated to the system (Scheme 9).

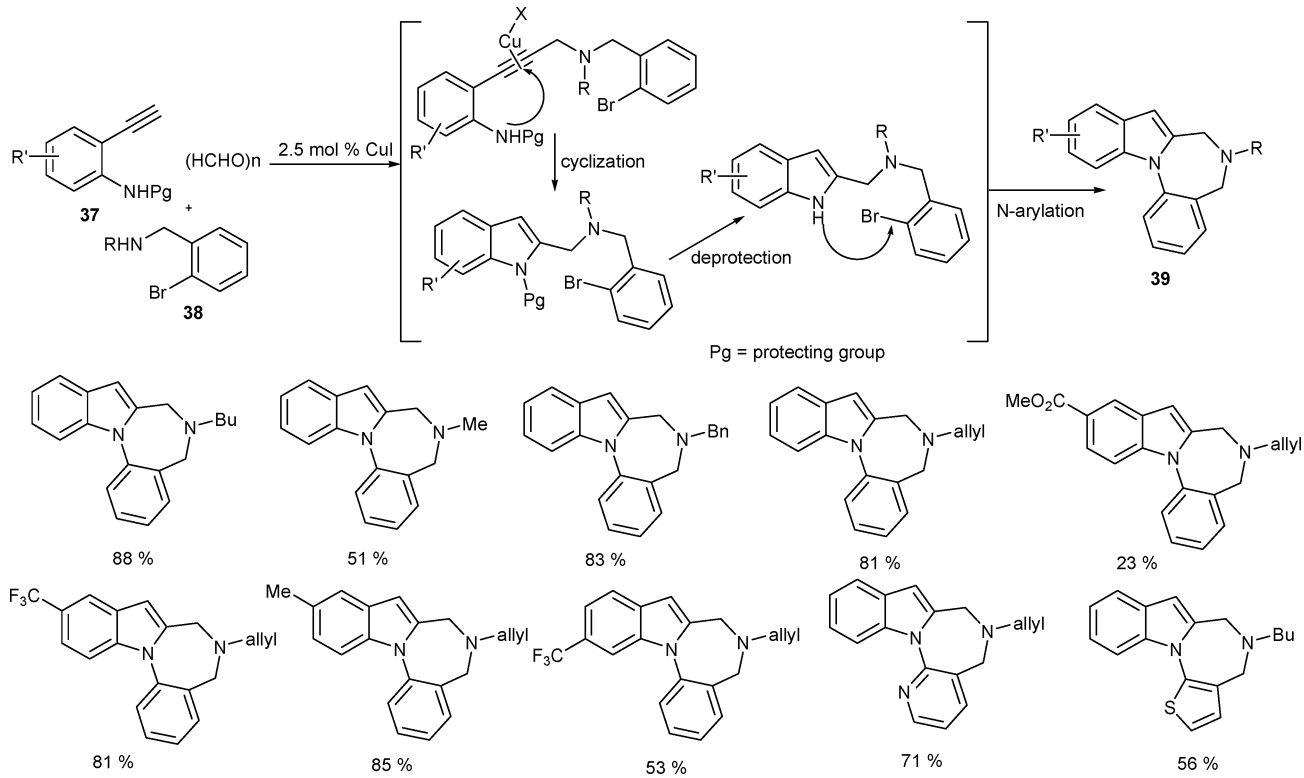
Using 1,4-diiodobut-1-ene derivatives as the partners, the domino reactions of alkenylation/alkylation of amides have been designed to prepare 2,3-dihydropyrroles **28**. Two electrophilic sites in **27** were utilized to construct the heterocycle (Scheme 10).[18] The indole moiety is ubiquitous in natural products as well as pharmaceuticals, indole derivatives are therefore also major targets in Cu-catalyzed domino synthesis. By making use of methyl 2-(2-bromophenyl)acetate **29**, primary amines and methyl formate as building blocks, Karchava[19] *et al.* developed the tandem synthesis of indole derivatives **31** *via* the formation of key intermediates **30** (Scheme 11). The limits of this approach are that only variation in the amine component is allowed and it involves the operation of altering reaction conditions. On the basis of the results, the authors further explored the reaction behavior of hydrazines as the alternative building block of amines. And it was discovered that different reaction routes selectively leading to the formation of indole derivatives **32**, **33** and **34** respectively could be achieved depending on the use of hydrazines of different functionalization (Scheme 11).[20] Similarly by the catalysis of CuI, Cai and coworkers devised a novel reaction for tandem synthesis of indoles **36**, these products were constructed by the assembly of *o*-haloaryl aldehydes or ketones **35** with ethyl isocyanoacetate under ligand-free conditions, bromo- and chloro-functionalized **35** were applicable for the transformation while higher temperature was employed when 2-chloro aryl aldehydes/ketones were used (Scheme 12).[21] Shortly after the publication of this method, a modified method employing ethyl amidoacetate to react with **35** was designed to produce indoles of type **36** (R^2 = H, Scheme 12).[22] This process avoided the use of foul-smelling cyano-substituted materials, while suffered from the limitation on substrate variation. Fujii and coworkers devised the synthesis of indole-fused products **39** *via* three-component reaction of amines **37**, **38** and paraformaldehyde under microwave irradiation in the presence of CuI. These reactions proceeded *via* 4 main steps



Scheme 11

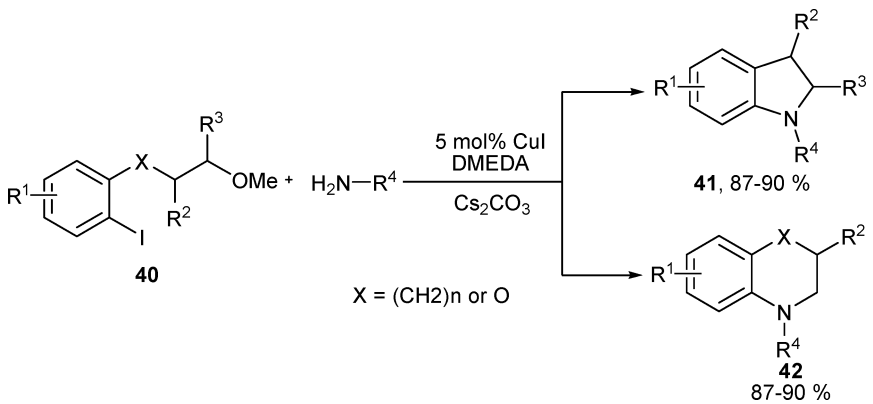


Scheme 12

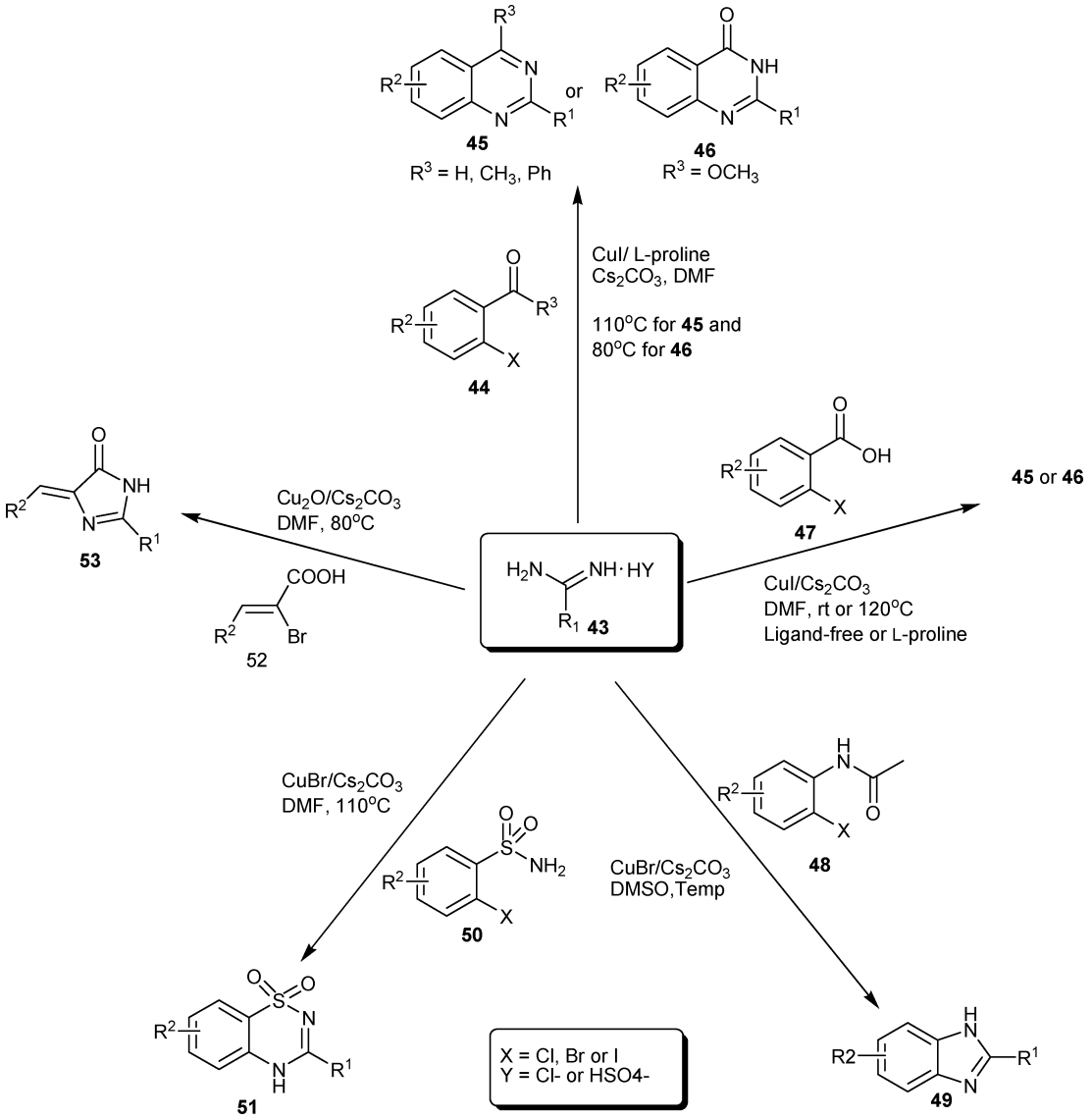


Scheme 13

of three-component Mannich-like condensations, intramolecular cyclization, deprotection and intramolecular *N*-arylation, it is noteworthy that these fused tetracyclic products containing 1,4-diazepine backbone were obtained with sound substructural variation (Scheme 13).[23] Similar to indole, indoline is also important substructure in many natural alkaloids and industrial chemicals. Buchwald[24] *et al.* reported the Cu-catalyzed annulation of functionalized aryl iodides **40** by incorporating primary amines to produce indolines **41**, and the modification on the structure of **40** was also able to generate corresponding homologues **42** (Scheme 14).



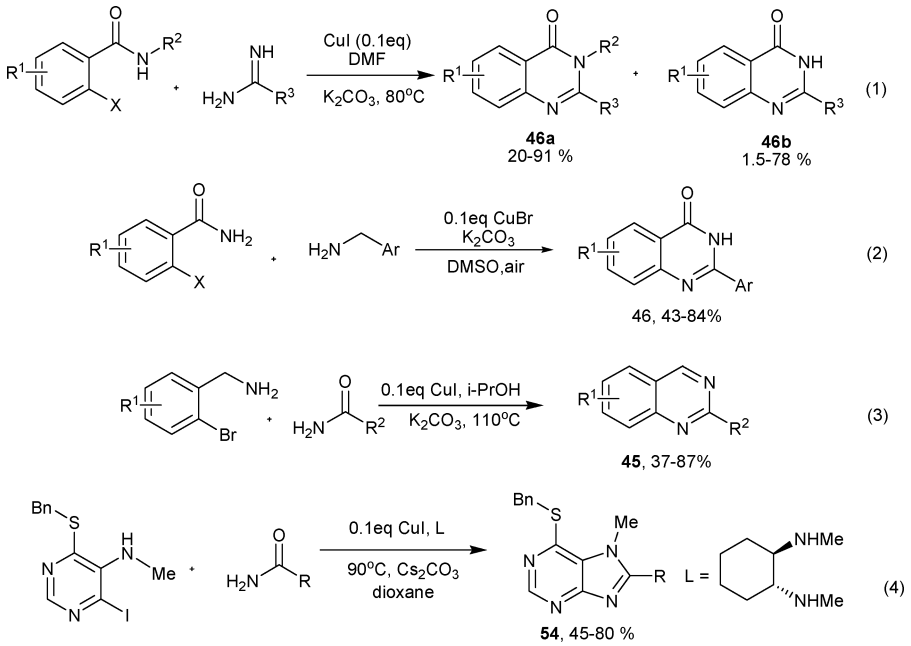
Scheme 14



Scheme 15

The reaction process comprised tandem C–N coupling and intramolecular S_N2 displacement as demonstrated by designed experiments.

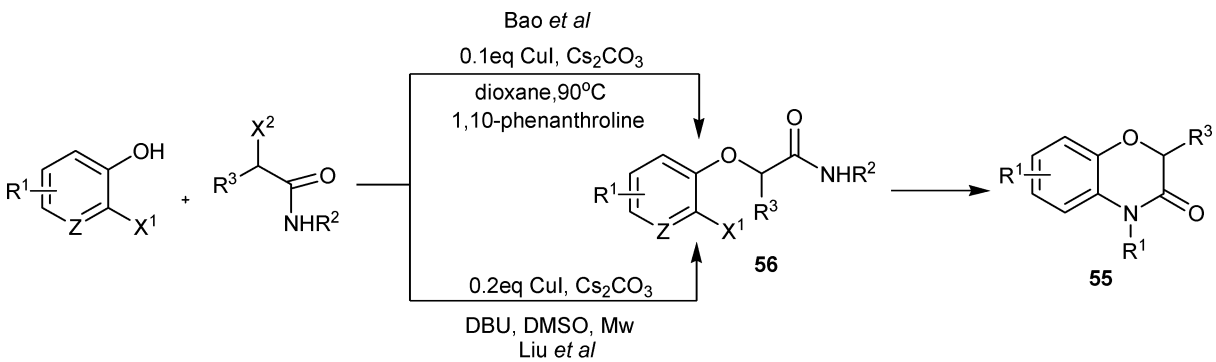
Although amines, amides, hydrazines or azoles were employed as nitrogen sources in most Cu-catalyzed cascade reactions involving C–N coupling process, some unconventional N-containing identities such as amidines were also able to serve as nitrogen source to furnish various heterocyclic motifs *via* Cu-catalyzed transformation. Fu and coworker have performed a pioneering and comprehensive exploration of this subject—a class of useful methodologies in synthesizing heterocyclic compounds were established (Scheme 15). Using *o*-halo aromatic aldehydes, ketones or esters **44** as the reaction partners of amidines **43**, CuI was able to catalyze tandem reactions to yield quinazolines **45** and quinazolinones **46** with the assistance of L-proline and base, the chemo-selectivity was manipulated *via* modifying specific functional groups and reaction temperature.[25] In continuing research, the same group discovered that simple *o*-halophenyl carboxylic acids **47** were also able to react with amidines to selectively provide heterocyclic products **45** or **46**. The important improvements of the new method were that **47** are much more easily accessible than **44**, and the reactions for the synthesis of **45** were performed at room temperature.[26] In addition, guanidines have also been proven to be suitable for analogous transformation to offer corresponding 2-aminoquinazolines and 2-aminoquinazolinones (R^1 = amino) at 110 °C (for 2-aminoquinazolines) or 120 °C/L-proline (for 2-amino quinazolinones).[27] Besides, amidines were also successfully used for the synthesis of benzimidazoles **49**, the synthesis involved the participation of *N*-acyl protected *o*-haloaryl amines. Under the catalysis of CuBr, the products were formed *via* cascade processes of *N*-arylation of amidines, intramolecular deprotection and deamination condendation.[28] Similarly, 2-halobenzenesulfonamides **50** could be employed to construct 1,2,4-benzothiadiazine-1,1-dioxide derivatives **51**, the *N*-arylation step was also suggested as the first intermediate according to the results obtained from designed experiments.[29] Rather recently, the author further explored the reaction behavior of properly elaborated aliphatic reactants. In the presence of Cu_2O and Cs_2CO_3,



Scheme 16

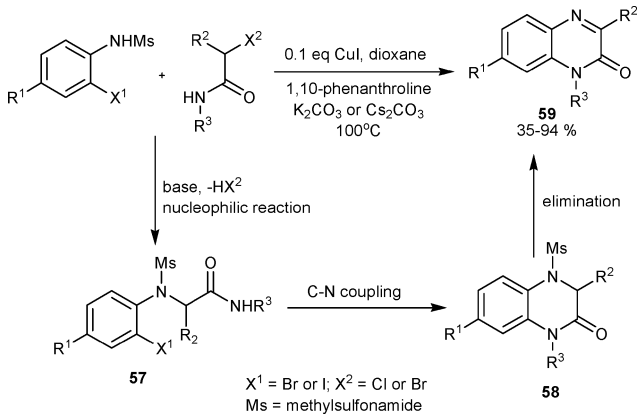
2-bromo-3-alkylacrylic acids **52** efficiently reacted with amidines to give 2,4-disubstituted imidazolones **53**, and 80 °C is effective to secure expected results for most reactions.[30] Interestingly, products of type **46** have also been successfully synthesized by CuI-catalyzed domino reactions of amidines with 2-halobenzamides in 2008, product **46a** and **46b** could be selectively formed depending on the use of reactants containing different functional groups (Eq 1 in Scheme 16).[31] And rather recently, the domino C–N coupling–oxidation–cyclization–oxidation reaction between *o*-halo benzamides and arylmethylamine had been devised to directly prepare **46** (Eq 2 in Scheme 16).[32] Moreover, products of type **45** were also accessed by new CuI-catalyzed cascade reaction of 2-bromobenzylamines with amides (Eq 3 in Scheme 16),[33] while purine derivatives **54** which bear analogous architecture to benzimidazoles **49** were accessed by CuI-catalyzed reactions of methyl masked 2-iodide aryl amines with amides (Eq 4 in Scheme 16).[34] These results strongly exemplified the tremendous diversity of Cu-catalyzed tandem reactions for heterocycle synthesis.

Bao and coworkers reported interesting Cu-catalyzed tandem reactions for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones **55** using readily available *o*-hydroxylaryl halides and 2-haloamides. The reactions were successfully performed using CuI/Cs_2CO_3/1,10-phenanthroline systems in dioxane and the temperature of 90 °C, this protocol exhibited good functional group tolerance by giving a broad variety of **55**.[35] Simultaneously, Liu and coworkers reported the synthesis of the same target products using identical starting materials and DBU under microwave irradiation condition. The reaction was plausibly completed through intermediate **56**, which underwent further intramolecular C–N coupling to provide final products (Scheme 17).[36] Based on this study, the reactions of *o*-halo aryl amines were reasonably examined due to their resemblance with *o*-hydroxyl halides in reactivity. With catalysis of CuI and assistance of 1,10-phenanthroline as well as base, products **59** have been generally formed *via* intermolecular nucleophilic displacement, intramolecular *N*-arylation and elimination processes from

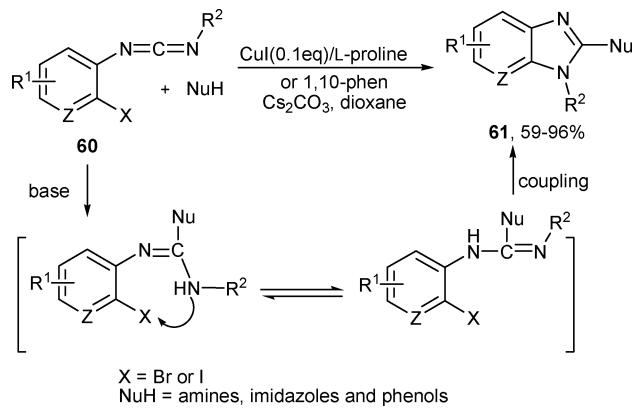


Scheme 17

methylsulfonamide protected *o*-halo aryl amines and 2-haloamides. K_2CO_3 and Cs_2CO_3 were respectively favored when R^3 are aryls and alkyls (Scheme 18).[37] During their further research on new Cu-catalyzed domino reactions, Bao *et al.* also discovered that a diimine motif was a versatile building block in designing Cu-catalyzed cascade reactions. Through the attack of a nucleophile on the electron deficient carbon in diimide **60**, 1,2-disubstiuted benzimidazoles **61** have been formed *via* subsequent intramolecular C–N coupling of the imidamide intermediate. A significant advantage of this protocol is that amines, imidazoles and phenols could all be employed as nucleophilic partners and enabled great structural diversity of products (Scheme 19).[38] Conversely, when the positions of diimine and nucleophile species were exchanged, the cascade synthesis of analogous heterocycles was also feasible. The reactions between *N*,*N*′-disubstituted dimines **62** and *o*-haloaniline/*o*-halophenols **63**, through similar process, gave 2,3-dihydrobenzo[*d*]oxazoles **64**, benzimidazoles **65** and 2,3-dihydro-1*H*-benzo[*d*]imidazoles **66** (Scheme 20).[39]

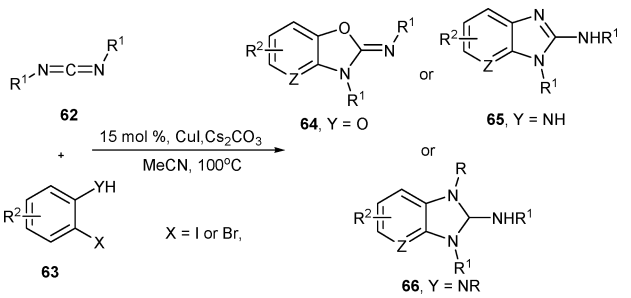


Scheme 18

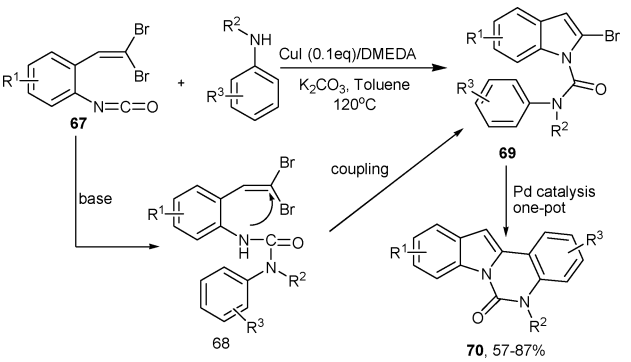


Scheme 19

Recently, the reactions were expanded to the use of *o*-dibromovinyl funtionalized isocyanatobenzenes **67**. In the presence of *N*-alkyl aromatic amines, the reactions efficiently proceed to provide masked indoles **69** *via* CuI-catalyzed nucleophilic displacement and *N*-vinylation process, and **69** are highly useful precursors for one-pot fusion of multicyclic scaffolds **70** through a subsequent Pd-calayzed C–H activation (Scheme 21).[40]

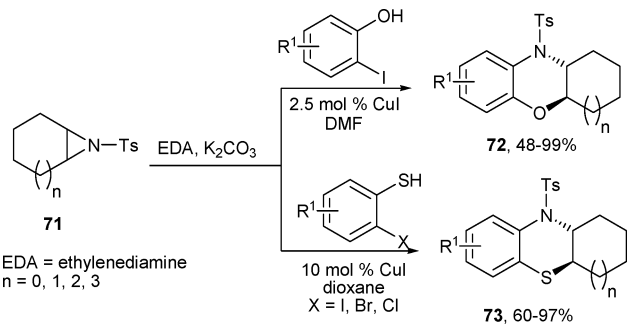


Scheme 20



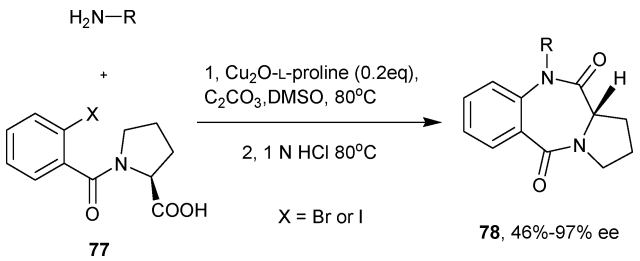
Scheme 21

As an active reactant bearing both electronic and nucleophilic sites, aziridine derivatives have also been found as good precursors for the synthesis of N-containing heterocycles *via* Cu-catalyzed ring-opening/C–N coupling cascade reactions. Seker *et al.* have done representative work of this type. *o*-Halophenols and *o*-halothiophenols could be utilized as the reaction partners of aziridines **70** to initiate the reaction. Under the promotion of CuI, base as well as ligand, *trans*-fused tricyclic products 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazines **72**[41] and 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazines **73**[42] were synthesized with good to excellent yields (Scheme 22). Similar to the results obtained by the reactions based on aziridine, much interest has been afforded to probe new nitrogen sources for devising Cu-catalyzed cascade heterocycle synthesis. Amino acids are amongst the interesting and highly practical examples as there are naturally able to build up products of optical purity. In 2009, Ma[43] and coworkers disclosed the domino reactions between *o*-benzylamines **74** and amino acids. The CuI/base system has been found efficiently mediating reactions to give 1,4-benzodiazepin-3-ones **75** or **76** *via* the reaction sequence of C–N coupling and intramolecular dehydration



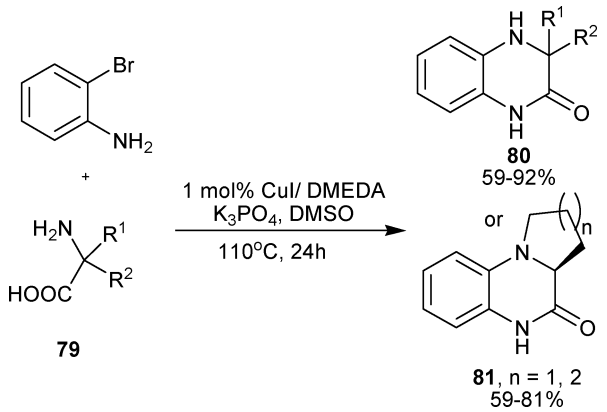
Scheme 22

amidation *via* direct operation or subsequent treatment with DPPA (Scheme 23). When L-proline or L-valine were used, corresponding products were formed in good diastereoselectivity, albeit racemization occurred in some entries. Later on, through modifying the structure of reactants, a new domino reaction had been designed for the synthesis of pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-diones **78** *via* similar sequential conversion. The products were obtained in 46–97% ee by employing chiral reactants **77** depending on the use of different amines (Scheme 24).[44] Compared with the synthesis of the 7-membered ring matrix, the 6-membered hetero ring system was theoretically easier to access using similar tactic. The synthesis of 6-membered heterocyclic compounds from amino acids **79** have been recently demonstrated by Tanimori *et al.*,[45] the key factor to construct this 6-membered ring system was the employment of *o*-bromoaniline which incorporated various optically pure amino acids to give quinoxalin-2-ones **80** or **81**, a notable feature of this methodology was that no loss of optical purity was observed on the products after the reaction according to the authors experimental examination (Scheme 25).



Scheme 23

As a functional group frequently utilized in synthetic chemistry, the formyl group has been also extensively adopted in Cu-catalyzed tandem reactions due to its excellent reactivity towards C- and N-nucleophiles. Cai[46] *et al.* reported the tandem reactions of *o*-halobenzaldehydes with 2-methylene fragment functionalized (benz)imidazoles or pyrroles (**82**, **84** and **85**). The fused polycyclic compounds **83**, **86** or **87** were produced by the transformation of CuI-catalyzed *N*-arylation of azoles and aldol condensation of aromatic aldehydes. Generally, aryl halides of I, Br, Cl were all able to give corresponding products under the catalysis of CuI, but substantially lower yields of products were observed as well as much higher temperatures being required when Cl-, Br-substituted

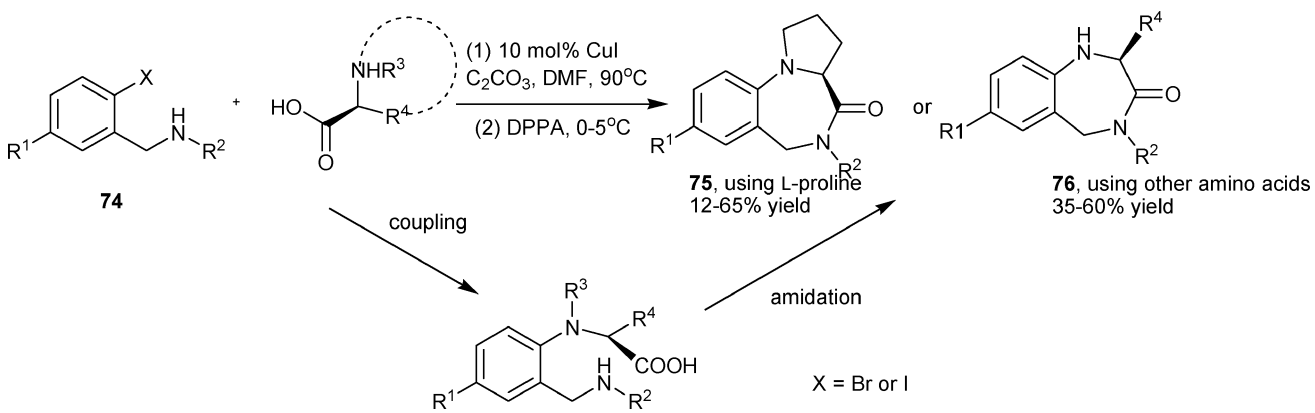


Scheme 25

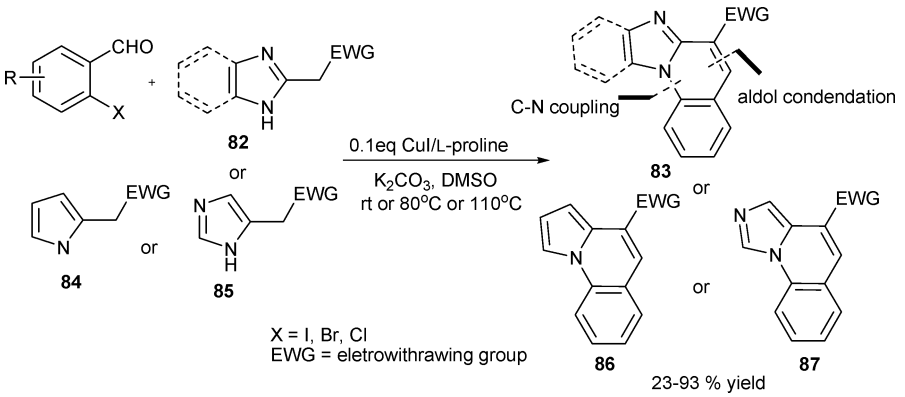
aromatic aldehydes were used (Scheme 26). Another sequential reaction based on the assembly of 2-formyl pyrroles and *o*-iodide anilines affording tricyclic products **89** has also been achieved recently. The reactions in the presence of CuI and sparteine ligand proceeded at 130 °C and consisted of a two-step tandem transformation of C–N coupling and imine condensation (Scheme 27).[47] By making use of the widely investigated ketenimine intermediates, the Cu-catalyzed tandem reactions directly using sulfonyl azides, terminal alkyne and *o*-haloaninline have been found to afford benzimidazoles **92** *via* intramolecular C–N coupling of key intermediate **91** (Scheme 28).[48] Continuous modification removing the haloatom from the amine components to *ortho* position of ethynylbenzenes led to production of new heterocyclic products **94**. The modified reactions were performed under similar conditions, the three-component reactions of sulfonyl azides, amines and *o*-haloethynylbenzenes furnished heterocyclic scaffolds **94** *via* corresponding intermediate **93** (Scheme 28).[49] Rather recently, a new tandem reaction consisting of C–N coupling and intramolecular 1,3-dipolar click cycloaddition using **95** and $TMSN_3$ has been reported by Yao *et al.*, which provided a practical approach for the synthesis of fused heterocyclic compounds **96** (Scheme 29).[50]

2.2. Reactions initiated by C–O coupling

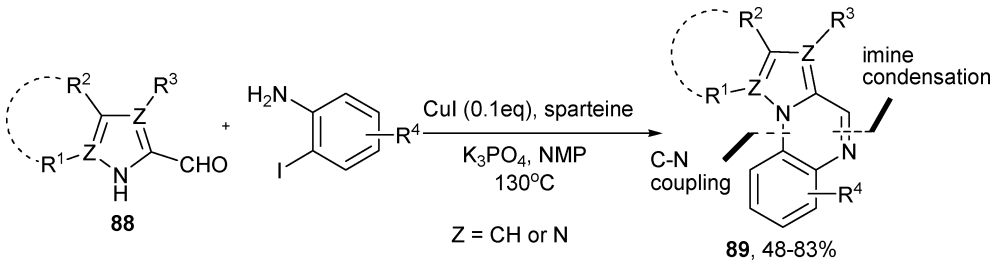
Compared with *N*-nuleophiles, *O*-nucleopiles are much lower in reaction diversity because of the lower valence of the O-atom. Therefore, the known tandem reactions initiated by Cu-catalyzed C–O



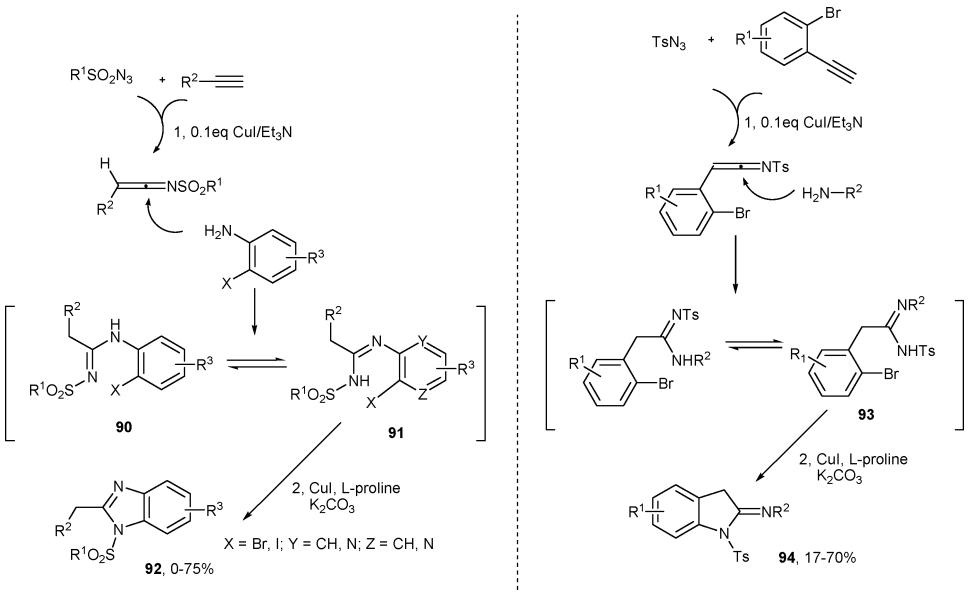
Scheme 24



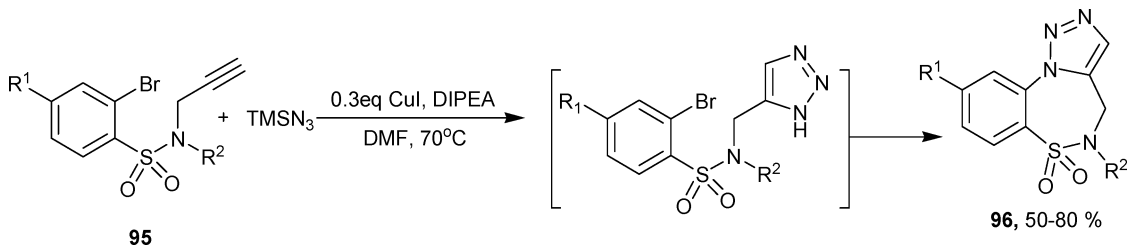
Scheme 26



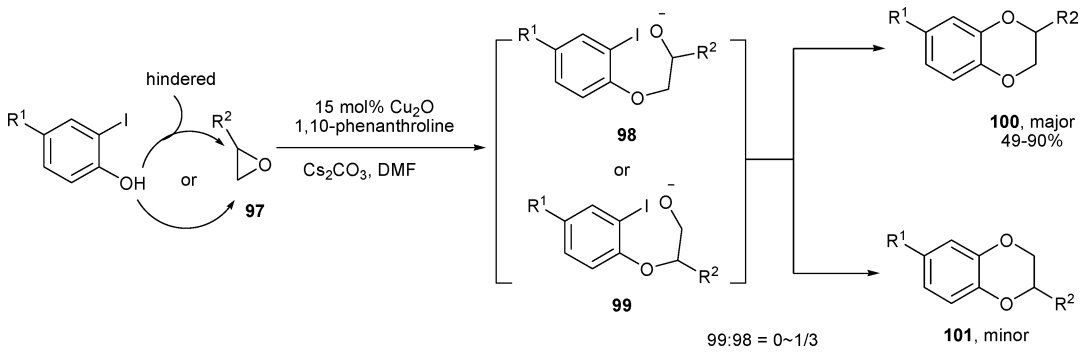
Scheme 27



Scheme 28

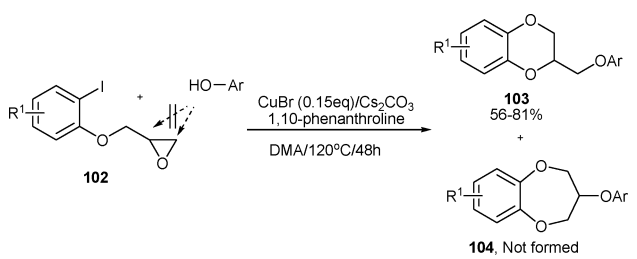


Scheme 29



Scheme 30

coupling are thus also considerably less than those initiated by C–N coupling. Actually, only several reports on sole Cu-catalyzed C–O coupling intrigued tandem reactions dealing with heterocycle synthesis are presently available. Interestingly, our research in Cu-catalyzed tandem reactions began from the Cu-catalyzed domino reactions involving coupling reaction of *O*-nucleophiles. Initially, epoxides **97** were selected as the precursors of nucleophiles to react with *o*-iodophenols. With the catalysis of Cu_2O and assistance of 1,10-phenanthroline/Cs_2CO_3, 2,3-dihydro-1,4-benzodioxins were successfully afforded with satisfactory yields *via* ring opening intermediates **98** or **99**. Compounds of type **100** had been obtained as major products, while **101** occurred as side products in some entries even though good regioselectivity was generated by the steric hindrance of R^2. The ratio of **99** : **98** ranged from 0 to 1 : 3 depending on the use of different substrates (Scheme 30).[51] This kind of transformation was later implemented in Ranu's group by using aluminum supported Cu(II) catalyst system, and it is noteworthy that Ranu's system was able to be expanded to similar reactions of arizidines with *o*-iodophenols to furnish 3,4-dihydro-2*H*-1,4-benzo oxazines.[52] In our continuous efforts improving the regioselectivity of the above C–O coupling initiated tandem reactions, we later revised the structure of the starting materials and designed a new Cu-catalyzed domino reaction to prepare 2,3-dihydro-1,4-benzodioxine derivatives. The tactic was reacting the epoxide group with the hydroxyl of the phenol matrix, the elaborated backbone **102** underwent the nucleophilic attack of another phenol in CuBr-catalyzed conditions to provide 2,3-dihydro-1,4-benzodioxines **103**. The other theoretically possible by-products **104** were not observed in all experiments, probably due to the instability of seven-membered fused ring system (Scheme 31).[53]

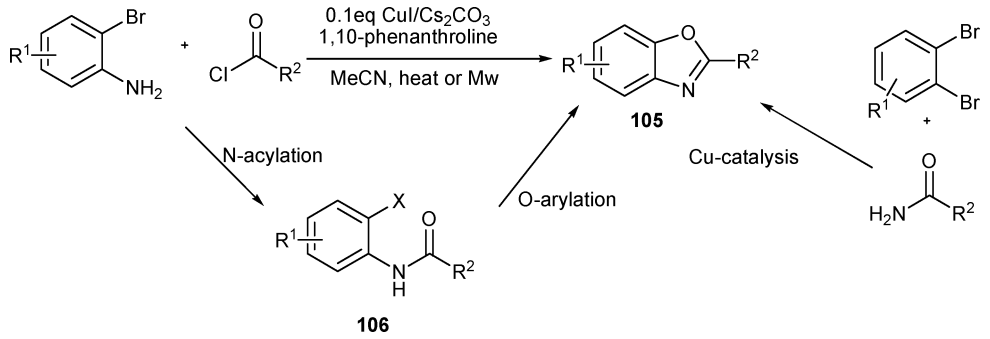


Scheme 31

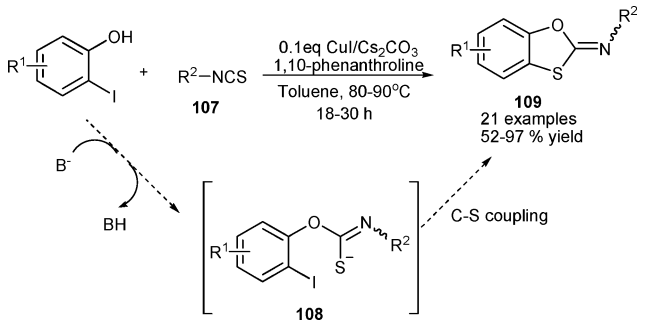
Another synthetic approach of C–O coupling-initiated domino heterocycle synthesis was reported by Batey and coworkers. This strategy targeted benzoxazoles **106** and started from 2-bromobenzenes as well as acyl chlorides. The domino acylation of the amino group and intramolecular *O*-arylation of intermediates **105** resulted in the formation of **106** in a satisfying manner in the catalyst system of CuI/1,10-phenanthroline/Cs_2CO_3 by using microwave irradiation. This method, as declared by the authors, was more versatile and practical than the synthetic route employing Cu-catalyzed tandem reactions between aryl dihalides and amides (Scheme 32).[54]

2.3. Reactions initiated by C–S coupling

In most coupling cases, *S*-nucleophiles exhibited similar reactivity as *O*-nucleopiles. However, *S*-nucleophiles are usually stronger in nucleophilicity, and the resources of *S*-nucleophiles are broader than *O*-nucleophiles. Therefore, the application of C–S coupling in heterocycle synthesis is also wider than C–O coupling initiated tandem reactions. Inspired by C–S coupling, we earlier studied Cu-catalyzed sulfur containing heterocycle synthesis. The original attempt was employing isothiocyanates **107** as reaction partners of *o*-iodophenols, the intermediates **108** could be formed under the promotion of a base, and the intramolecular C–S coupling of **108** led to the production of 2-iminobenzo-1,3-oxathiole products **109** in a one-pot manner. Temperatures as well as reaction time were slightly modified when required in some specific entries (Scheme 33).[55] Ding *et al.* declared identical transformations in the catalyst system of $CuCl_2$/DBACO/1,10-phenanthroline in water.[56] Recently, through similar tactics, the syntheses of benzothiazoles **111** have also been achieved by using isothiocyanate to incorporate *o*-iodoaniline. Besides nucleophilic addition on C═S bonds and intramolecular C–S coupling transformations, as in the assembly of **109**, a further tautormerization of intermediates **110** was involved in the formation of **111** (Scheme 34).[57] Almost in the same period, the same reactions have been finished in Bao group, and the application scope on substrates has been expanded to *o*-bromo- and chloroanilines, while no ligand is needed in the CuI/Cs_2CO_3/DMSO catalyst system.[58] Later on, the same transformation has been reported again under very similar reaction conditions of CuBr/TBAB/DMSO.[59] Additionally, an alternative way to access this heterocyclic system was exchanging the location of the isothiocyanate and nucleophilic groups, Patel *et al.* described the sequential transformation of nucleophilic addition and intramolecular *S*-arylation between isothiocyanates **112** and *O*- or *S*-nucleophiles, which gave benzothiazoles as final products. An interesting point of this method was that



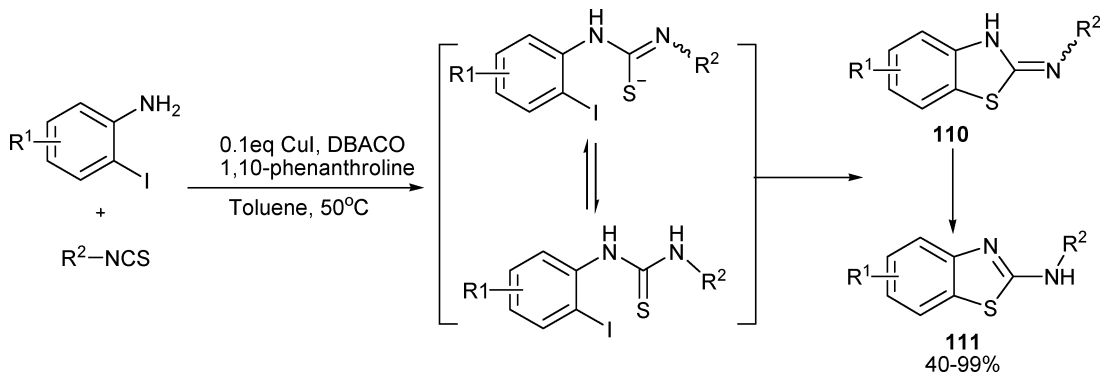
Scheme 32



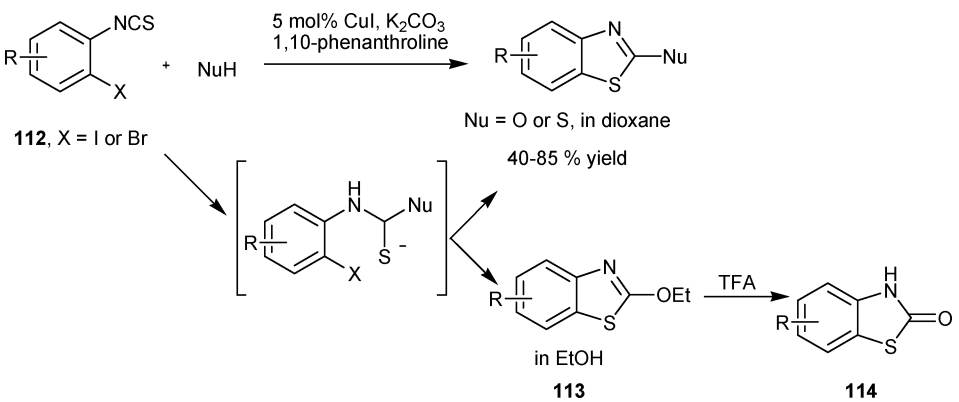
Scheme 33

corresponding benzothizoles **113** obtained in ethanol were able to be converted to 1,3-benzothiazolones **114** by treating with TFA (Scheme 35).[60]

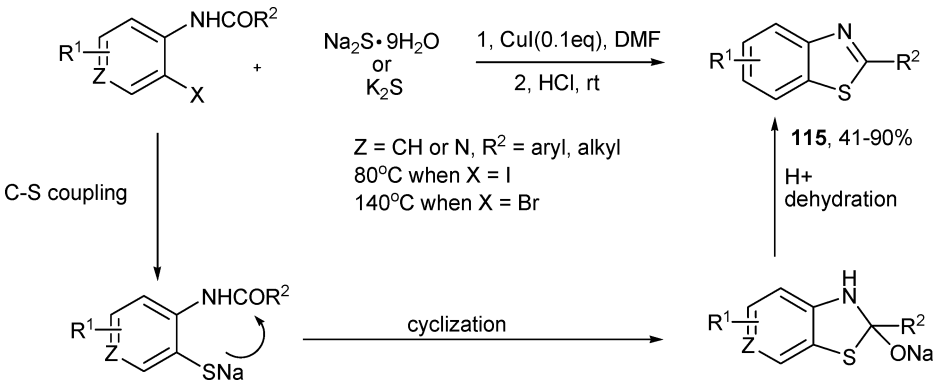
Besides isothiocyanate, some simple and easily available S-containing chemicals such Na_2S have also proven to be capable of serving as sulfur sources in Cu-catalyzed domino S-heterocycles syntheses. Ma and coworkers successfully developed the Cu-catalyzed tandem reaction for one-pot synthesis of benzothiazoles **115** (R^2 = aryl, alkyl) starting from *o*-halo-*N*-acyl aromatic amines and $Na_2S{\cdot}9H_2O$. This protocol displayed wide application scope in terms of reactant tolerance and bears significant advantage of atom economy by using low cost metal sulfides as sulfur source (Scheme 36).[61] Quite recently, the same group discovered that another conventional S-containing species, carbon disulfide, was



Scheme 34



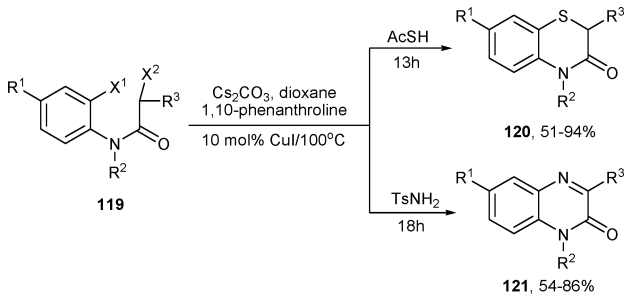
Scheme 35



Scheme 36

also a good reaction partner in C–S coupling initiated domino reaction for synthesizing 2-amino benzothiazole derivatives. More accurately, it is the dithiocarbamate salts **116**, generated *in situ* by base-catalyzed reactions of carbon disulfide and amine nucleophiles, that were utilized for the tandem reactions with *o*-haloanilines. The reactions proceeded in a multicomponent reaction manner by reacting three starting materials at the same time. This protocol has demonstrated excellent substrate compatibility since various primary and secondly amines, cyclic and acyclic amines, aromatic/aliphatic amines as well as azoles had been successfully applied to provide corresponding products (Scheme 37).[62]

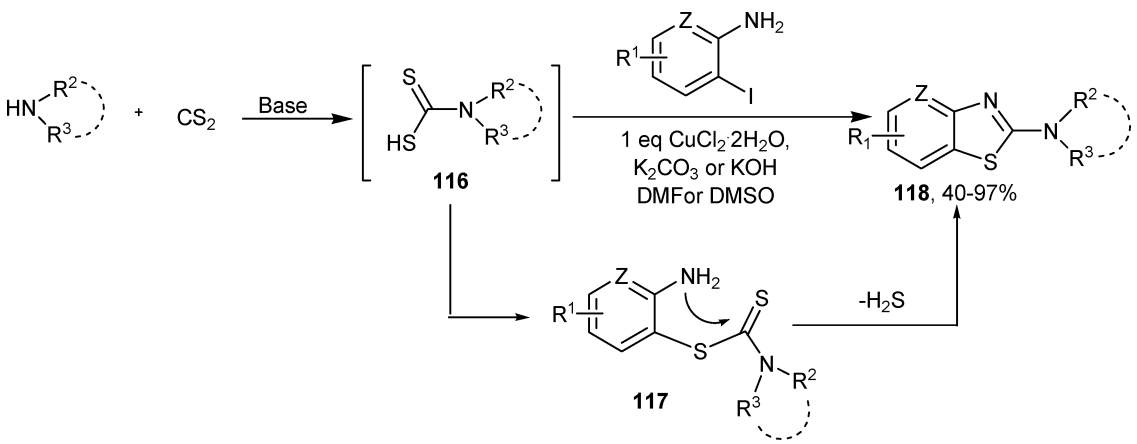
Bao and coworkers have also developed related cascade reactions involving Cu-catalyzed C–S coupling for the synthesis of 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones **120**. The tactic utilized 2-halopheyl masked 1-haloamides **119** as building blocks and AcSH as a novel sulfur source. The reaction sequence of tandem nucleophilic displacement and intramolecular C–S coupling reactions afforded a class of 2*H*- benzo[*b*][1, 4]thiazin-3(4*H*)-ones in moderate to excellent yields. Analogous transformations have been found to be practical by using $TsNH_2$ as nucleophile, which accordingly gave quinoxalin-2(1*H*)-ones **121** (Scheme 38).[63]



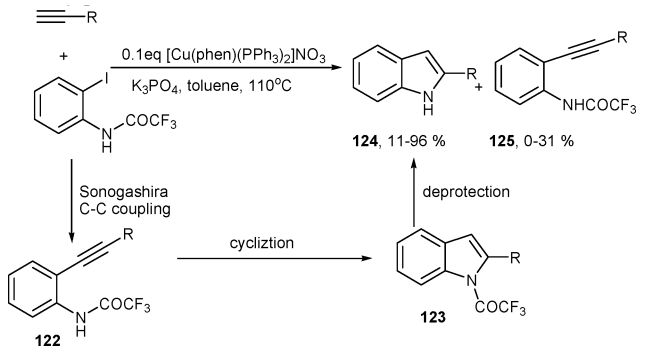
Scheme 38

2.4. Reactions initiated by C–C coupling

As an efficient and practical method for creating C–C bonds, the C–C coupling reactions have been extensively studied and employed in synthetic organic chemistry. When designed in tandem reactions, C–C coupling processes had been found with specific utility in the synthesis of single heteroatom cyclic systems. The pioneer attempt on this type of reaction was reported by Cacchi and coworkers. The approach was developed for one-pot synthesis of N–H free indoles **124** by directly employing terminal alkyne and *N*-trifluoroacetyl protected *o*-iodoaniline. The general process could be divided into a Sonogashira coupling, 5-*endo*-dig cyclization and deprotection sequence *via* intermediates **122** and **123**, **125** have been found as side products in some entries (Scheme 39).[64] Besides the low cost of Cu catalyst, this methodology bears a special advantage to directly provide N–H free indoles. These kind of transformations have later been revisited and modified by Ma *et al.*, who synthesized the same target

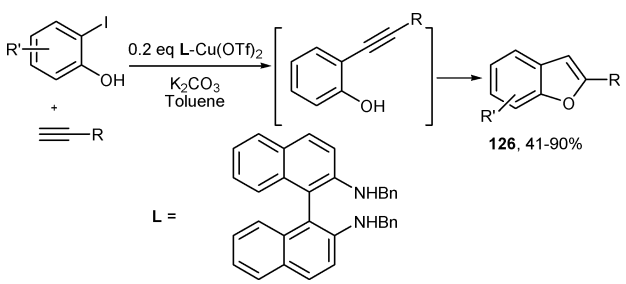


Scheme 37

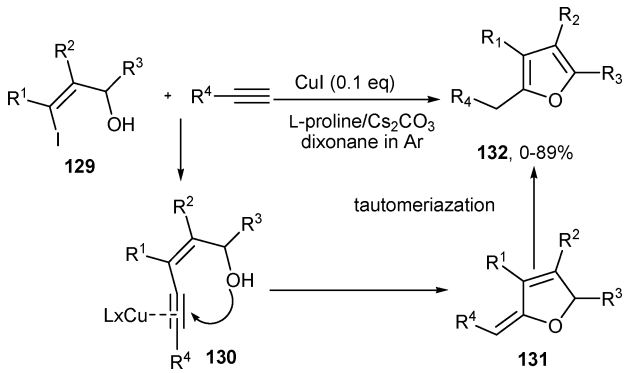


Scheme 39

products using more readily available CuI as catalyst and *N*-masked *o*-bromoaniline derivatives as starting materials under the assistance of L-proline at 80 °C.[65] An interesting further expansion on this strategy was using *o*-iodophenols as alternative building blocks of *o*-haloanilines. The tandem reactions for assembling corresponding benzofurans **126** from terminal alkynes and *o*-iodophenols have been achieved by applying the Cu(II)/L (L = BINAM) catalyst system (Scheme 40), aromatic terminal alkynes were generally tolerated in this protocol.[66] In a further exploration of Sonogashira coupling-initiated domino reactions, Ma *et al.* conducted Cu-catalyzed reactions between terminal alkynes and *o*-halo benzamides. In the catalyst system consisting of CuI, K_2CO_3 and L-proline in polar solvent (*i*-PrOH, DMF or DMSO), *o*-bromobenzamides underwent Sonogashira coupling as well as intramolecular additive cyclization of intermediates **127** to deliver 3-methyleneisoindolin-1-ones **128** by incorporating aliphatic/aromatic terminal alkynes. The 3-methyleneisoindolin-1-one products had been demonstrated as highly useful synthetic precursors in the construction of the natural product lennoxamine (Scheme 41).[67] Analogous to aryl halide, the reactivity of vinyl halide in the Sonogashira coupling reaction has also been employed to design cascade heterocycles syntheses. Through the reactions of vinyl iodide derivatives **129** and terminal alkynes, Ma and coworker disclosed the one-pot synthesis of polysubstituted furans **132** by employing CuI/L-proline catalysis under an argon atmosphere. Intermediates **131** were originally formed *via* the cyclization of **130**, and further tautomerization of **131** led to the formation of products **132** (Scheme 42).[68]

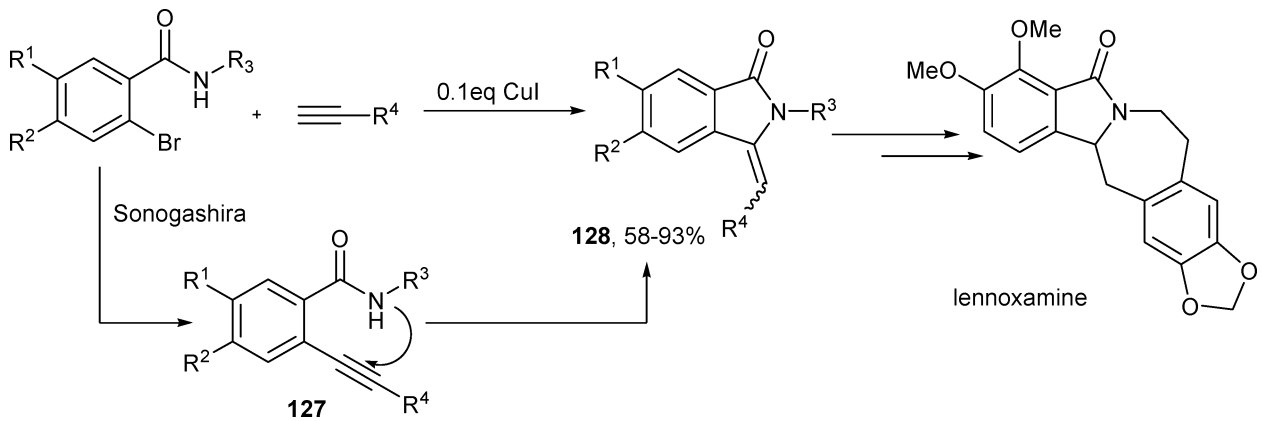


Scheme 40

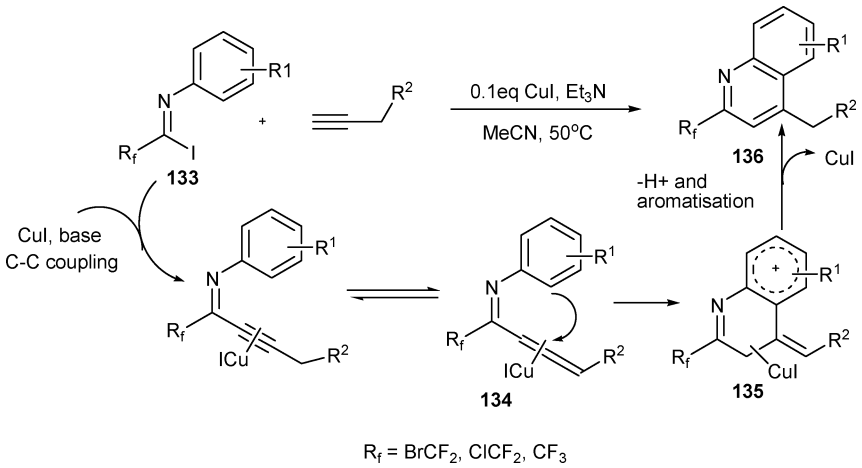


Scheme 42

Another type of building blocks that could be employed for domino synthesis of heterocycles *via* C–C coupling are imidoyl halides. Using 1-fluorinated group functionalized imidoyl iodides **133** and terminal alkynes, Wu and coworkers achieved the synthesis of fluorinated group functionalized quinolines **136** *via* CuI-catalyzed domino reactions in MeCN without assistance of additional ligand. As only alkynes bearing a methylene structure were able to proceed to target products under catalyst conditions, **134** were proposed to be key intermediates, the cyclization of **134** gave **135** which underwent further aromatization transformation to provide aromatic heterocyclic scaffolds **136** (Scheme 43).[69] Recently, Liang *et al.* reported tandem reactions involving Cu-catalyzed Sonogashira C–C coupling and "click" 1,3-dipolar cycloaddition. The starting materials **137** that contained vinyl azide fragments reacted efficiently with terminal alkynes in the presence of $CuCl_2$ and a base to afford triazole fused heterocyclic



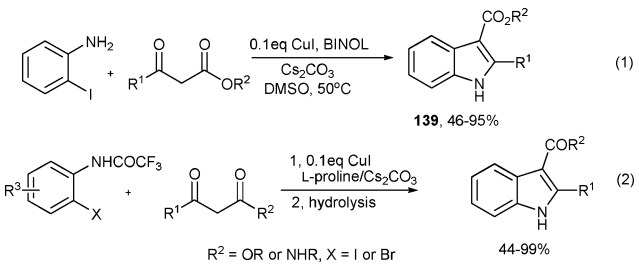
Scheme 41



Scheme 43

products **138**. Based on designed experiments for mechanistic investigation, intermediates formed *via* the C–C couplings of **137** and terminal alkynes have been demonstrated as the first stage of reaction process, and the intramolecular 1,3-dipolar cycloaddition between the azide and alkyne subunits led to the formation of **138**. It is notable that **138** have been proven as good synthetic precursors of isoquinolines based on the authors studies (Scheme 44).[70]

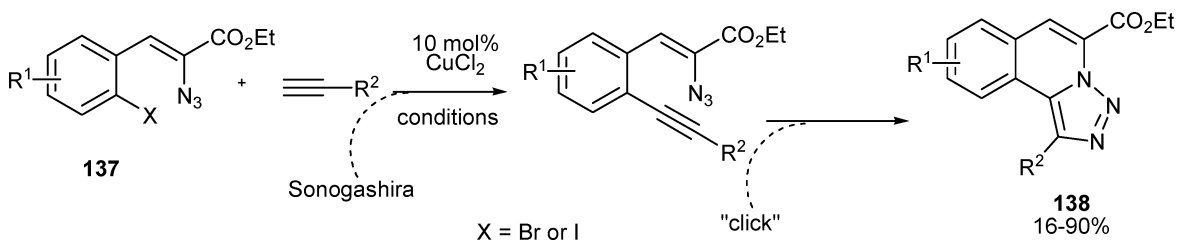
In addition to terminal alkynes, 1,3-dicarbonyl compounds possessing an active methylene nucleophilic site are also highly useful reaction partners in C–C coupling initiated domino reactions. In 2007, Tanimori *et al.* declared the tandem reactions between *o*-iodoaniline and β-keto esters leading to 2,3-disubstituted indoles **139** using CuI catalysis and BINOL as ligand (Eq 1, Scheme 45).[71] Almost at the same time, Ma *et al.* reported CuI-catalyzed domino reactions employing $COCF_3$ masked *o*-haloanilines and β-keto esters/amides and L-proline as additive for the synthesis of indoles. The later protocol had been illustrated to have broader reactant tolerance wherein a further hydrolysis to deprotect $COCF_3$ was required (Eq 2, Scheme 45).[72] Rather recently, a report declaring the same domino reaction using Cu_2O under ligand-free conditions appeared as further modification of this method.[73] Interestingly, in their continuation study, Ma and coworkers discovered that subjecting identical materials of *o*-halotrifluoroacetanilides and β-keto esters to anhydrous conditions in a CuI/L-proline/Cs_2CO_3/DMSO catalyst system lead to the production of 2-trifluoromethyl substituted indoles **143**. Through the modification on reaction conditions, the pathway of reaction had been changed to *C*-nucleophilic cyclization from the *N*-nucleophilic cyclization in the synthesis of **139**. As outlined in Scheme 46, the general reaction sequence is the C–



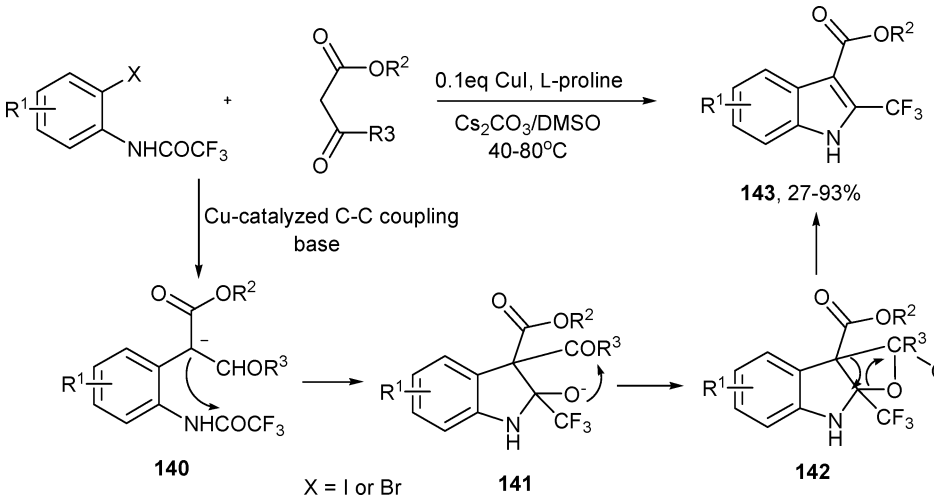
Scheme 45

C coupling to **140**, cyclization to **141** and loss of carboxylic group of **142**.[74] Also using *o*-halotrifluoroacetanilides, Fu *et al.* devised a Cu-catalyzed indole synthesis based on their tandem incorporation of 2-cyanoacetates or malononitrile. The reactions proceed *via* C–C coupling and intramolecular addition cyclization of the amino group to nitrile, leading respectively to indoles **144** or **145** depending on the use of different methylene donors (Scheme 47).[75]

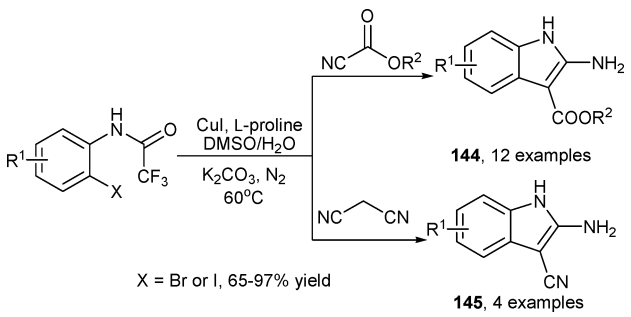
Besides the application in the annulation of five-membered ring systems, 1,3-dicarbonyl compounds are also practical building blocks for the synthesis of six-membered heterocycles by incorporating proper functional reactants. Ma *et al.* developed CuI-catalyzed tandem reactions of β-keto esters or 1,3-diketones with *o*-halobenzylamines. Isoquinolines **146** were assembled *via* the sequential process of C–C coupling, aldol condensation as well as *in situ* dehydration (Scheme 48),[76] while Fu *et al.* employed *o*-halobenzamides as the reaction partners of 1,3-dicarbonyl compounds to run tandem reaction of C–C coupling and aldol



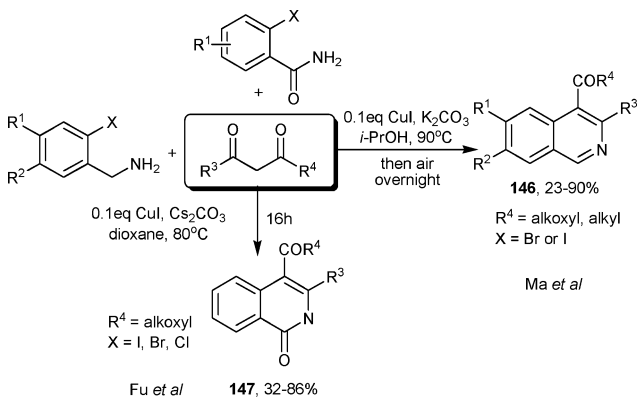
Scheme 44



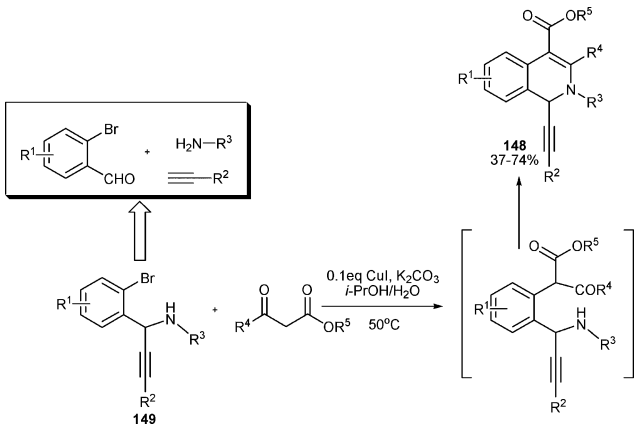
Scheme 46



Scheme 47



Scheme 48

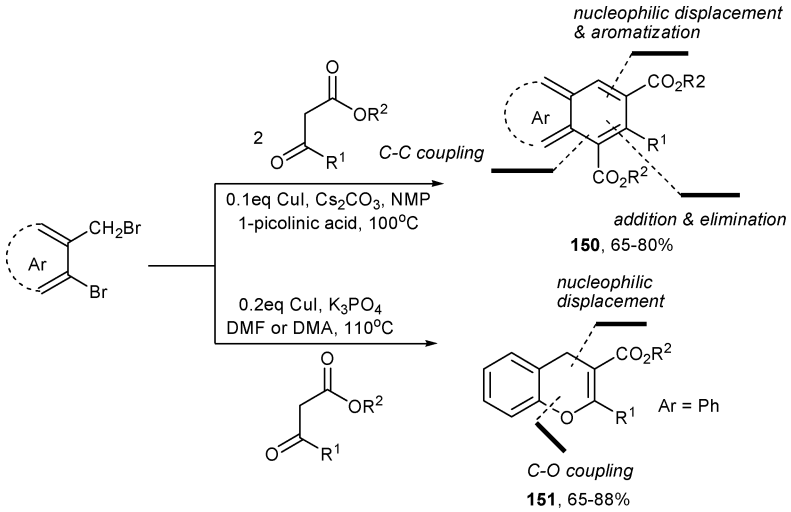


Scheme 49

condendation, which led to the production of isoquinolin-1(2*H*)-one derivatives **147** in the presence of CuI and base (Scheme 48).[77] Later on, a tandem reaction for the synthesis of 1,2-dihydroisoquinoline derivatives **148** using propargylamines **149** and β-keto esters had been devised, the process was similar with that involved in the synthesis of **147**, and the starting materials **149** were prepared by the three-component reactions of *o*-bromobenzaldehydes, primary amines and terminal akynes (Scheme 49).[78]

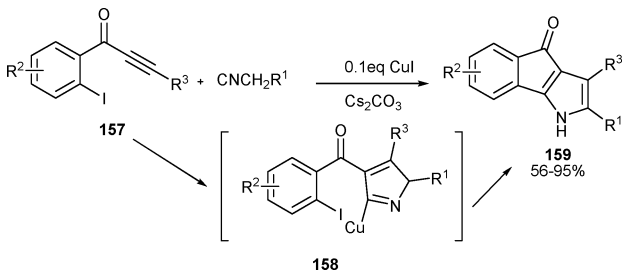
A rather interesting C–C coupling initiated tandem reaction involving multistep transformations using 1,3-dicarbonyl compounds have recently been achieved by Beifuss and coworkers. Starting from 2-bromobenzyl bromides and β-keto esters in CuI/1-picolinic acid and base system, naphthalene derivatives **150** were assembled *via* the reactions of 2-bromobenzyl bromide with 2 equivalent of dicarbonyl substrates. The domino process consisted of nucleophilic displacement, C–C coupling, intramolecular addition, elimination as well as aromatization. The total of 5 C–C bonds formed in this reaction further demonstrate the latent power of Cu-catalyzed tandem reactions in synthetic chemistry. In addition, products **151** could be selectively afforded *via* modifying reaction conditions and the ratio of starting materials (Scheme 50).[79]

As a classical *C*-nucleophilic species, indoles have also been found as useful building blocks in Cu-catalyzed cascade heterocycle synthesis, especially for the construction of fused cyclic systems. Larock and coworkers devised CuI-catalyzed tandem reactions using *o*-bromoarylalkynes **152** and indoles containing a free NH group. Under the catalytic conditions, intermediates **153** were generated from the hydroamination or oxidative addition process of indoles to **152**. A subsequent C–C coupling of C2 in the indole unit and the arene–halide bond led to the formation of fused polycyclic products **154** in moderate to good yields.



Scheme 50

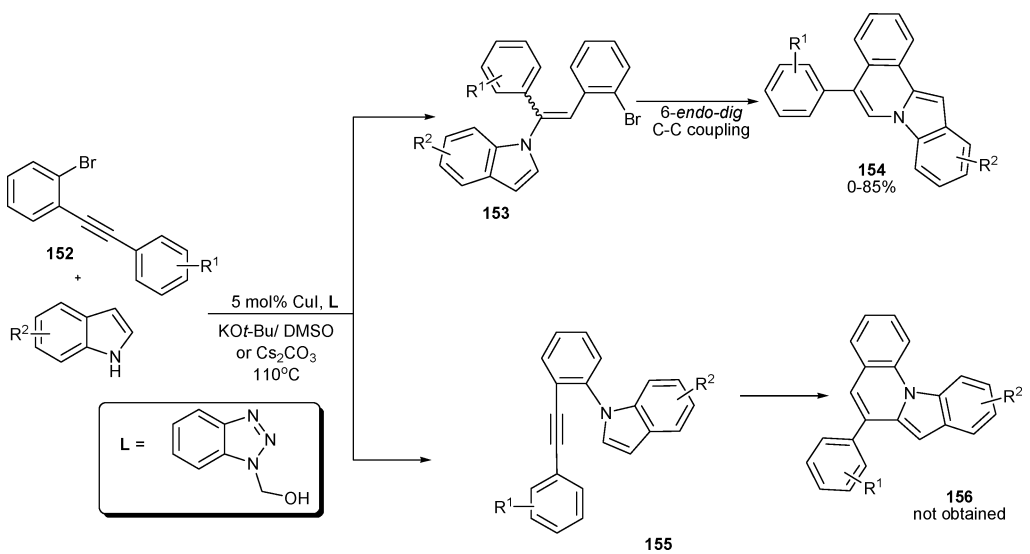
The other potential isomeric products **156**, which might have been given *via* the C–N coupling initiated intermediate **155**, were not observed in the authors experiments (Scheme 51). The proposed reaction process forming **150** was partially illustrated by the designed addition reaction between biphenyl ethyne and 3-methyl indole under standard catalysis conditions.[80] Cai *et al.* recently developed the tandem synthesis of fused heterocyclic scaffolds 4-oxo-indeno[1,2-*b*]pyrroles **159** using CuI catalyzed tandem reactions of alkynyl decorated acetophenones **157** and isocyanides. The indoline-like intermediates **158** were believed to afford target products *via* quick C–C coupling (Scheme 52).[81]



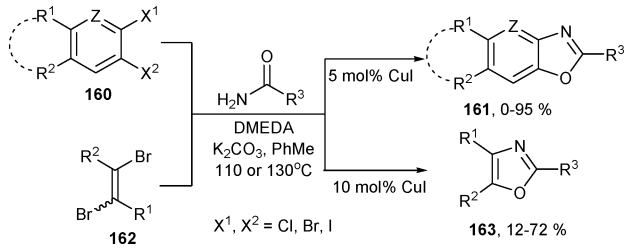
Scheme 52

2.5. Reactions involving a double C–X coupling process

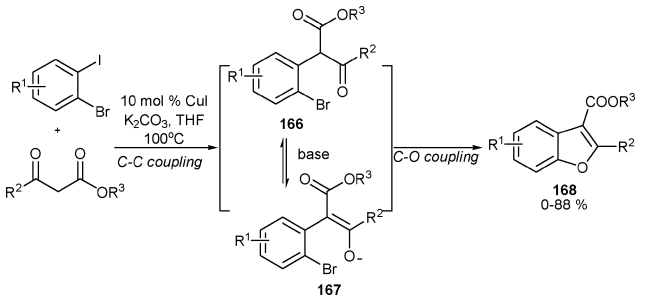
In contrast to the Cu-catalyzed tandem reaction initiated by the single C–X coupling process, reactions involving double C–X coupling are theoretically more manipulable due to the consistency of reactions conditions that are favored by different C–X coupling transformations. The most direct tactic in designing such reactions may be using *o*-dihaloarene derivatives to incorporate proper nucleophiles twice. The limit of this kind of strategy is probably the scarce availability of *o*-halogenated aryl halides or analogous reactants. As early as in 2004, Glorius *et al.* declared the first Cu-catalyzed tandem synthesis of benzoxazoles employing dihalobenzenes **160** and primary amides. The whole reaction process involved a C–N coupling and a C–O coupling, and



Scheme 51



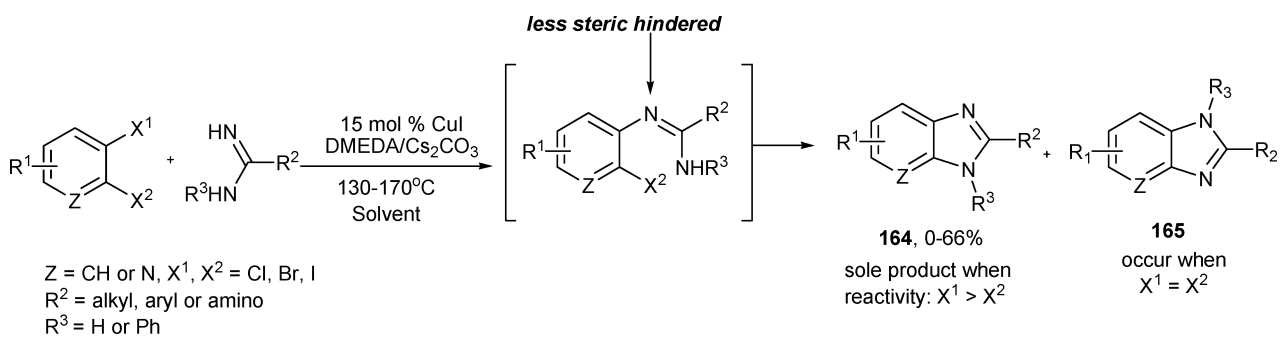
Scheme 53



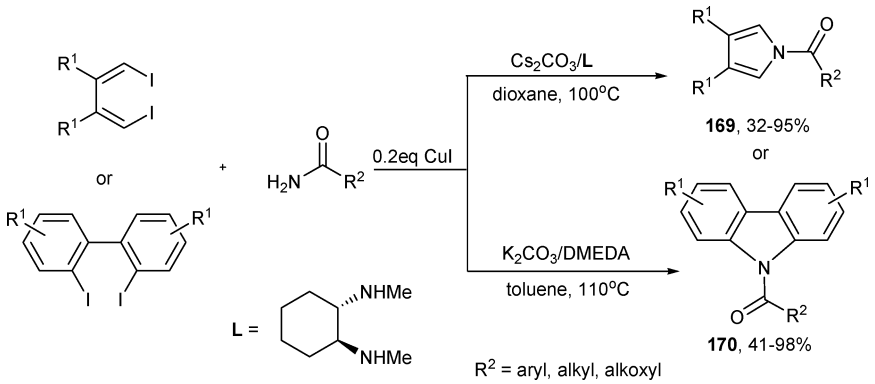
Scheme 55

halo atoms of Cl, Br, I were all applicable for this reactions, while no product was formed when X^1 and X^2 are both chloride (Scheme 53).[82] This synthetic methodology has been later expanded to the reactions of primary amides and vinyl 1,2-bromides **162**, which accordingly afforded oxazoles **163** as the products *via* a double coupling tandem process (Scheme 53).[83] The appearance of the methodology has inspired interest in devising similar tandem reactions using guanidines or amidines as the coupling partner of *o*-dihaloarenes, which led to the production of various benzimidazole derivatives. Deng *et al.* systematically investigated the Cu-catalyzed tandem reactions of dihaloarenes and guanidines/amidines. Their results provided a novel route for the synthesis of benzimidazole derivatives. Interesting regioselectivity in giving benzimidazoles **164** and **165** was observed when substituted *o*-dihaloarenes were employed. As displayed in Scheme 54, the regioselectivity in forming **164** and **165** were disclosed to be determined by the relative reactivity of haloatoms X^1 and X^2, as well the relative steric hindrance effect on the nucleophilic *N* atoms in guanidines or amidines according to the authors' experiments. When X^1 was more reactive than X^2 (for example: X^1 = I, X^2 = Cl), the *N* atom of less steric hindrance in guanidines or amidines coupled X^1 as the first stage, the sequential C–N coupling between X^2 and the second *N* atom provided benzimidazoles **164** as the sole products. However, when $X^1 = X^2$, no evident selectivity was observed as **164** and isomers **165** were both furnished in similar yields.[84–85] Still using *o*-dihaloarenes as the double eletrophilic species, Ma *et al.* developed Cu-catalyzed tandem reactions for the synthesis of benzoxazole derivatives using 1,3-dicarbonyl compounds as binucleophilic partners. As depicted in Scheme 55, 2-bromoiodobenzenes firstly coupled with active methylene to afford intermediate **166** which tautomerized to **167** in the presence of a base, and the tandem intramolecular C–O coupling cyclization led to the production of products **168**. Analogously, the differentiation between the two substituted halides strictly controlled the reaction sequence to selectively afford products of type **168**.[86] In addition to the tandem double coupling process based on *o*-1,2-dihaloarenes for heterocycle synthesis, the dihalides with halo atoms located in the 1,4-positions of conjugated alkenes or analogous building blocks have also been demonstrated as useful starting materials in building up heterocycles. Li and coworker have done representative work of the type. Through CuI-catalyzed double C–N coupling of primary amides with 1,4-diiodo-1,4-dialkenes or 1,2′-diiodobiphenyls, corresponding pyrroles **169** and carbazoles **170** have been prepared in fair to good yields, respectively (Scheme 56).[87–88] The application of this kind of double coupling has recently been expanded to the synthesis of fused products using azoles as the dinucleophilic species to incorporate the 1,4-dihalides, and annulated fused products **171** were readily obtained in fair to good yield by following CuI-catalyzed C–N/C–C coupling transformation (Scheme 57).[89] Alternatively, *o* -*gem*-dihalovinyl anilines have been discovered as another type of applicable architecture for Cu-catalyzed tandem reactions with particular utility for the synthesis of fused heterocycles. Lautens and coworkers developed the one-pot synthesis of imidazoindolone derivatives *via* the tandem coupling reactions of chiral *o*-*gem*-dibromovinylanilines **172**. Under the catalysis of CuI/racemic *trans*-1,2-cyclohexyldiamine/K_2CO_3 in toluene, the tandem intramolecular coupling process occurred in 120 °C. The final products **174** were probably provided through the coupled indole intermediates **173**. In term of the stereochemistry of the chiral center, good *ee* values were obtained in some entries by retaining the configuration of the starting materials, while a different extent of epimerization occurred in some other reactions. One of the rationalizations accounting for the epimerization was that intermediates **173** were not stable with respect to their chiral properties during the reaction process (Scheme 58).[90]

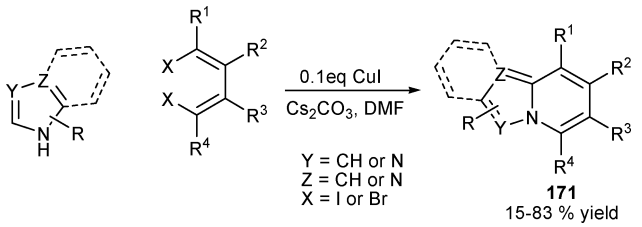
As unconventional compounds containing sp^2 C–X (X = halildes), *N*-aryl fluorinated acetimidoyl halides have been also



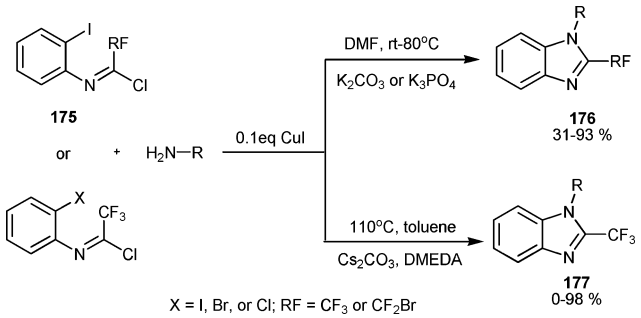
Scheme 54



Scheme 56



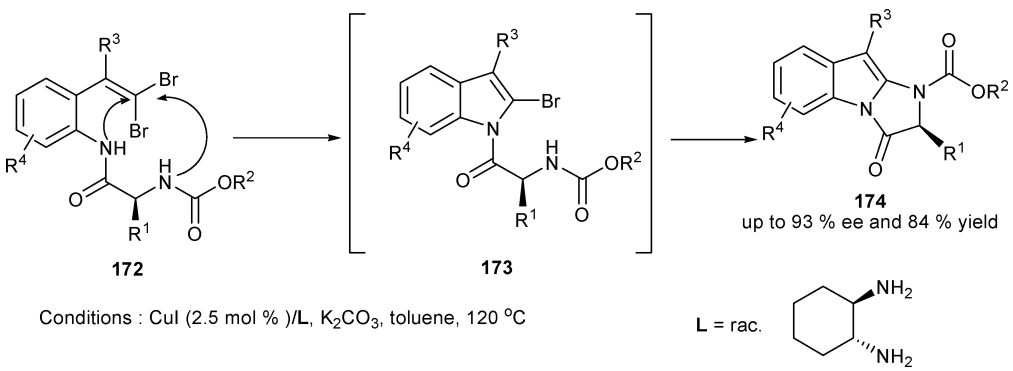
Scheme 57



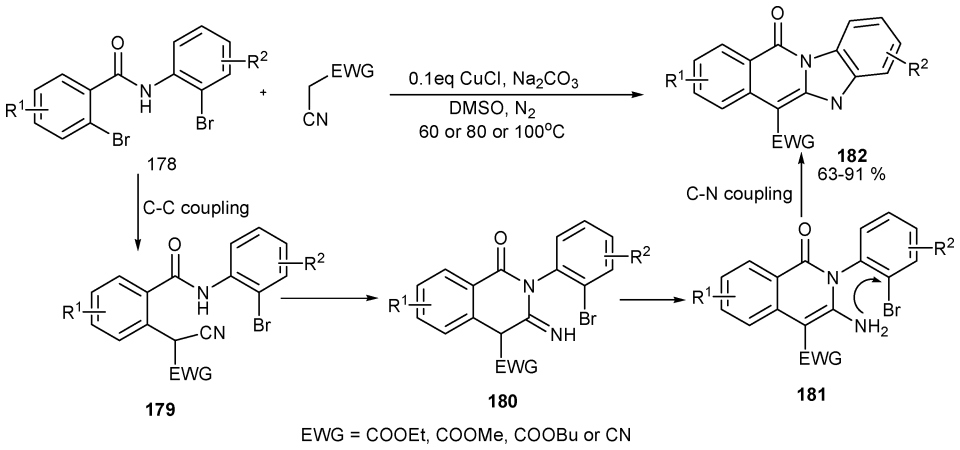
Scheme 59

found as effective materials for Cu-catalyzed C–N couplings. Wu and coworker discovered that *N*-(2-iodophenyl) fluorinated acetimidoyl chlorides (R_F = CF_3 or CF_2Br) were able to be efficiently reacted with primary amines to provide benzimidazoles **176** possessing 2-fluorinated methyl substitution. This protocol involved a double C–N coupling process and completed under mild conditions although an sp^2 C–Cl was cleaved during the transformation (Scheme 59).[91] The application scope of this kind of transformation has turned out to be much broader when performed at higher temperatures based on the results reported by Chen *et al.* in the synthesis of homologous products **177** (Scheme 59).[92] Recently, Fu and coworkers reported a highly novel and interesting tandem reaction for the synthesis of fused tetracyclic compounds bearing both isoquinolinone and benzimidazole moieties. The reactions adapting *N*-bromoaryl substituted 2-bromobenzamides **178** and β-electron withdrawing group functionalized nitriles firstly generate intermediate **179** *via* selective CuCl-catalyzed C–C coupling at the C–Br bond adjacent to the carbonyl groups. **180** Were then produced *via* cyclization initiated by nucleophilic addition on the triple C–N bond of the nitrile group, which were further transferred to isomers **181**. Finally, intramolecular C–N coupling on **181** gave products **182**. The construction of two new heterocycles in the products *via* a one-pot tandem reaction was a notable feature of this methodology (Scheme 60).[93]

Unlike the reactions based on the double coupling reactions taking place at two sp^2 C–X bonds in one reagent, the reactions involving the double coupling process respectively happening at C–X bonds of two different starting compounds is a different and scarcely mentioned approach. Ma and coworkers successively established the tandem reactions between *o*-iodoanilines and *o*-bromothiophenols. Through the catalysis of CuI in the presence of L-proline and K_2CO_3, the C–S coupling occurred as the first transformation in the tandem reaction process to yield intermediates **183**, and phenothiazine derivatives **184** were then

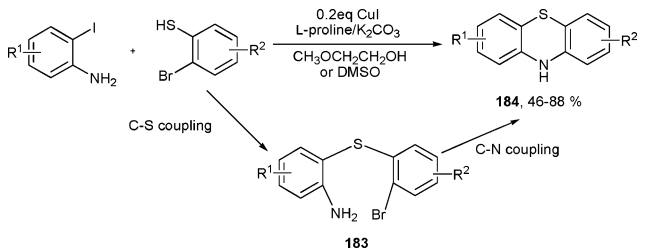


Scheme 58



Scheme 60

efficiently afforded through the intramolecular C–N coupling of **183** (Scheme 61). This method was creative as a synthetic strategy based on a brand-new consideration, and was also highly useful for providing the versatile pharmaceutical backbone of phenothazine.[94]



Scheme 61

3. Conclusions

The Cu-catalyzed C–X coupling reaction is currently making a new era in organic synthesis due to the contribution of ligands. The ready manoeuvrability of these coupling reactions under substantially milder conditions enabled them to be applied in a broad range of research fields such as pharmaceuticals, materials, natural products *etc.* It is unarguable that the Cu-catalyzed coupling reaction is still going to play an indispensable role throughout synthetic development due to the low cost and low toxicity, as well as many other advantages of Cu catalysts. As an important step towards the ideal synthesis of atom economics, employing the Cu-catalyzed coupling reaction in the design of tandem reactions is now gaining worldwide attention for their great efficiency in assembling structurally diversified small molecules, especially heterocyclic identities. Copper catalysts have been proven to tolerate a great variety of different reaction conditions and allowed the presence of various different transformations such as aldol condensation, nucleophilic displacement, nucleophilic addition, "click" dipolar cycloaddition *etc.* in one-pot reactions, which guaranteed the extraordinary power of this kind of synthetic methodology. The presently available reports on Cu-catalyzed tandem reactions covered the synthesis of quite a large number of heterocycles of different styles including ring systems embedding one, two or more heteroatoms, monocyclic compounds as well as polycyclic compounds of fused or non-fused types. These results indicated the fact that the application scope of the Cu-catalyzed coupling reaction is as broad as we can expect.

Despite the large number of presently known protocols in the field of Cu-catalyzed tandem reactions, there is still plenty of room and numerous possibilities to explore in this area. One representative issue is that in most cases of the known reactions, the formation of the aromatic ring system seemed to be important driving force of these transformations. The reports on reactions providing non-aromatic rings, on the other hand, are remarkably fewer. In terms of the diversity of both product and reaction styles, developing new reactions for efficient synthesis of non-aromatic heterocycles is presently a highly desired direction of research. Considering the sustained interest in research into Cu-catalyzed synthesis, much broader applications of Cu-catalyzed tandem reactions are definitely to be expected.

Acknowledgements

The authors gratefully acknowledge the financial support from NSFC (no.21102059) as well as the Doctoral Start-up program (Nos. 3335 and 3336) of Jiangxi Normal University.

Notes and references

1 For selected reviews on transition metal-catalyzed synthesis, see: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*b*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439–2463; (*c*) B. M. Trost and D. L. VanVranken, *Chem. Rev.*, 1996, **96**, 395–422; (*d*) I. Nakamra and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127–2198; (*e*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (*f*) F. M. J. Tappe, V. T. Trepohl and M. Oestreich, *Synethsis*, 2010, 3037–3062; (*g*) S. M. Ma, *Acc. Chem. Res.*, 2003, **36**, 701–712; (*h*) S. Kotha, E. Brahmachary and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741–4767; (*i*) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013–3039.

2 For selected recent examples in transition metal-catalyzed syntheses, see: (*a*) H. Prokopcova, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel and B. U. W. Maes, *Chem.–Eur. J.*, 2010, **16**, 13063–13067; (*b*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 9322–9324; (*c*) D. B. Walker, J. Howqeqo and A. P. Davis, *Synthesis*, 2010, 3686–3692; (*d*) Y. Zhou, J. Zhao and L. Liu, *Angew. Chem., Int. Ed.*, 2009, **48**, 7126–7128; (*e*) Q. Li and Z. X. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 4542–4543.

3 (*a*) D. A. Candito and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 6713–6716; (*b*) Y. B. Zhou and J. G. Verkade, *Adv. Synth. Catal.*, 2010, **352**, 616–620; (*c*) J. R. Wang and K. Manabe, *Synthesis*, 2009,

1405–14207; (*d*) M. C. Willis, D. Taylor and A. T. Gillmore, *Tetrahedron*, 2006, **62**, 11513–11520; (*e*) M. J. Iglesias, A. Prieto and M. C. Nicasio, *Adv. Synth. Catal.*, 2010, **352**, 1949–1954; (*f*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3342.
4 Reviews on Cu-catalyzed coupling reactions see: (*a*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2428–2439; (*b*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096–3099; (*c*) M. Carril, R SanMartin and E. Dominguez, *Chem. Soc. Rev.*, 2008, **37**, 639–647; (*d*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2364.
5 (*a*) H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, 1999, **64**, 670–674; (*b*) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727–7729; (*c*) D. Ma, Q. Cai and H. Zhang, *Org. Lett.*, 2003, **5**, 2453–2455; (*d*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449; (*e*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954–6971.
6 (*a*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (*b*) G. Evano, M. Toumi and A. Coste, *Chem. Commun.*, 2009, 4166–4175.
7 (*a*) F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 2382–2384; (*b*) I. Goldberg, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 1691–1692.
8 A. Klapars, S. Parris, K. W. Anderson and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529–3533.
9 L. Ackermann, *Org. Lett.*, 2005, **7**, 439–442.
10 L. Ackermann, S. Barfüßer and H. K. Potukuchi, *Adv. Synth. Catal.*, 2009, **351**, 1064–1072.
11 R. Martín, R. Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079–7082.
12 B. L. Zhou, Q. L. Yuan and D. W. Ma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2598–2601.
13 B. L. Zhou, Q. L. Yuan and D. W. Ma, *Org. Lett.*, 2007, **9**, 4291–4294.
14 Q.-F. Zhong and L.-P. Sun, *Tetrahedron*, 2010, **66**, 5107–5111.
15 X. Q. Diao, Y. J. Wang, Y. W. Jiang and D. W. Ma, *J. Org. Chem.*, 2009, **74**, 7974–7977.
16 Q. L. Yuan and D. W. Ma, *J. Org. Chem.*, 2008, **73**, 5159–5162.
17 D. Viña, E. del Olmo, J. L. López-Pérez and A. S. Feliciano, *Org. Lett.*, 2007, **9**, 525–528.
18 X. B. Zhou, H. M. Zhang, J. W. Yuan, L. G. Mai and Y. Z. Li, *Tetrahedron Lett.*, 2007, **48**, 7236–7239.
19 F. S. Melkonyan, A. V. Karchava and M. A. Yurovskaya, *J. Org. Chem.*, 2008, **73**, 4275–4278.
20 F. Melkonyan, A. Topolyan, M. Yurovskaya and A. Karchava, *Eur. J. Org. Chem.*, 2008, 5952–5956.
21 Q. Cai, Z. Q Li, J. J. Wei, C. Y. Ha, D. Q. Pei and K. Ding, *Chem. Commun.*, 2009, 7581–7583.
22 S. G. Koenig, J. W. Dankwardt, Y. Liu, H. Zhao and S. P. Singh, *Tetrahedron Lett.*, 2010, **51**, 6549–6551.
23 Y. Ohta, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2008, **10**, 3535–3538.
24 A. Minatti and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 2721–2724.
25 C. Huang, Y. Fu, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Chem. Commun.*, 2008, 6333–6335.
26 X. W. Liu, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348–351.
27 X. H. Huang, H. J. Yang, H. Fu, R. Z. Qiao and Y. F. Zhao, *Synthesis*, 2009, 2679–2688.
28 D. S. Yang, H. Fu, L. M. Hu, Y. Y. Jiang and Y. F. Zhao, *J. Org. Chem.*, 2008, **73**, 7841–7844.
29 D. S. Yang, H. X. Liu, H. J. Yang, H. Fu, L. M. Hu, Y. Y. Jiang and Y. F. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 1999–2004.
30 X. Y. Gong, H. J. Yang, H. X. Liu, Y. Y. Jiang, Y. F. Zhao and H. Fu, *Org. Lett.*, 2010, **12**, 3128–3131.
31 J. Zhao, L. B. Fu, M. Lv, J. S. Liu, D. Q. Pei and K. Ding, *Synthesis*, 2008, 3974–3980.
32 W. Xu, Y. B. Jin, H. X. Liu, Y. Y. Jiang and H. Fu, *Org. Lett.*, 2011, **13**, 1274–1277.
33 C. Wang, S. F. Li, H. X. Liu, Y. Y. Jiang and H. Fu, *J. Org. Chem.*, 2010, **75**, 7936–7938.
34 N. Ibrahim and M. Legraverend, *J. Org. Chem.*, 2009, **74**, 463–465.
35 D. B. Chen, G. D. Shen and W. L. Bao, *Org. Biomol. Chem.*, 2009, **7**, 4067–4073.
36 E. G. Feng, H. Huang, Y. Zhou, D. J. Ye, H. L. Jiang and H. Liu, *J. Org. Chem.*, 2009, **74**, 2846–2849.
37 D. B. Chen and W. L. Bao, *Adv. Synth. Catal.*, 2010, **352**, 955–960.
38 X. Lv and W. L. Bao, *J. Org. Chem.*, 2009, **74**, 5618–5621.
39 G. D. Shen and W. L. Bao, *Adv. Synth. Catal.*, 2010, **352**, 981–986.
40 Z. J. Wang, J. G. Yang, F. Yang and W. L. Bao, *Org. Lett.*, 2010, **12**, 3034–3037.
41 R. K. Rao, A. B. Naidu and G. Seker, *Org. Lett.*, 2009, **11**, 1923–1926.
42 D. J. C. Prasad and G. Seker, *Org. Biomol. Chem.*, 2009, **7**, 5091–5097.
43 H. X. Wang, Y. W. Jiang, K. Gao and D. W. Ma, *Tetrahedron*, 2009, **65**, 8956–8960.
44 X. Lu, L. Shi, H. Zhang, Y. W. Jiang and D. W. Ma, *Tetrahedron*, 2010, **66**, 5714–5718.
45 S. Tanimori, H. Kashiwagi, T. Nishimura and M. Kirihata, *Adv. Synth. Catal.*, 2010, **352**, 2531–2537.
46 Q. Cai, Z. Q. Liu, J. J. Wei, L. B. Fu, C. Y. Ha, D. Q. Pei and K. Ding, *Org. Lett.*, 2010, **12**, 1500–1503.
47 J. T. Reeves, D. R. Fandrick, Z. L. Tan, J. J. Song, H. Lee, N. K. Yee and C. H. Senanayake, *J. Org. Chem.*, 2010, **75**, 992–994.
48 H. W. Jin, X. L. Xu, J. R. Gao, J. H. Zhong and Y. G. Wang, *Adv. Synth. Catal.*, 2010, **352**, 347–350.
49 H. W. Jin, B. W. Zhou, Z. Wu, Y. Shen and Y. G. Wang, *Tetrahedron*, 2011, **67**, 1178–1182.
50 D. K. Barange, Y.-C. Tu, V. Kavala, C.-W. Kuo and C.-F. Yao, *Adv. Synth. Catal.*, 2011, **353**, 41–48.
51 W. L. Bao, Y. Y. Liu, X. Lv and W. X Qian, *Org. Lett.*, 2008, **10**, 3899–3902.
52 S. Bhadra, L. Adak, S. Samanta, A. K. Maidul, M. Islam, M. Mukherjee and B. C. Ranu, *J. Org. Chem.*, 2010, **75**, 8533–8541.
53 Y. Y. Liu and W. L. Bao, *Org. Biomol. Chem.*, 2010, **8**, 2700–2703.
54 R. D. Viirre, G. Evindar and R. Batey, *J. Org. Chem.*, 2008, **73**, 3452–3459.
55 X. Lv, Y. Y. Liu, W. X. Qian and W. L. Bao, *Adv. Synth. Catal.*, 2008, **350**, 2507–2512.
56 Q. P. Ding, X. J. Liu, B. P. Cao, Z. Z. Zong and Y. Y. Peng, *Tetrahedron Lett.*, 2011, **52**, 1964–1967.
57 Q. P. Ding, X. D. He and J. Wu, *J. Comb. Chem.*, 2009, **11**, 587–591.
58 G. D. Shen, X. Lv and W. L. Bao, *Eur. J. Org. Chem.*, 2009, 5897–5901.
59 Y.-J. Guo, R.-Y. Tang, P. Zhong and J.-H. Li, *Tetrahedron Lett.*, 2010, **51**, 649–652.
60 S. Murru, P. Mondal, R. Yella and B. K. Patel, *Eur. J. Org. Chem.*, 2009, 5406–5413.
61 D. W. Ma, S. W. Xie, P. Xue, X. J. Zhang, J. H. Dong and Y. W. Jiang, *Angew. Chem., Int. Ed.*, 2009, **48**, 4222–425.
62 D. W. Ma, X. Lu, L. Shi, H. Zhang, Y. W. Jiang and X. Q. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1118–1121.
63 D. B. Chen, Z.-J. Wang and W. L. Bao, *J. Org. Chem.*, 2010, **75**, 5768–5771.
64 S. Cacchi, G. Fabrizi and L. M. Parisi, *Org. Lett.*, 2003, **5**, 3843–3846.
65 F. Liu and D. W. Ma, *J. Org. Chem.*, 2007, **72**, 4844–4850.
66 E. A. Jaseer, D. J. C. Prasad and G. Sekar, *Tetrahedron*, 2010, **66**, 2077–2082.
67 L. Li, M. Wang, X. J. Zhang, Y. W. Jiang and D. W. Ma, *Org. Lett.*, 2009, **11**, 1309–1312.
68 Y. Wang, L. T. Xu and D. W. Ma, *Chem.–Asian J.*, 2010, **5**, 74–76.
69 S. Li, Y. F. Yuan, J. T. Zhu, H. B. Xie, Z. X. Chen and Y. M. Wu, *Adv. Synth. Catal.*, 2010, **352**, 1582–1586.
70 Y.-Y. Hu, J. Hu, X.-C. Wang, L.-N. Guo, X.-Z. Shu, Y.-N. Niu and Y.-M. Liang, *Tetrahedron*, 2010, **66**, 80–86.
71 S. Tanimori, H. Ura and M. Kirihata, *Eur. J. Org. Chem.*, 2007, 3977–3980.
72 Y. Chen, X. A. Xie and D. W. Ma, *J. Org. Chem.*, 2007, **72**, 9329–9334.
73 M. A. Ali and T. Punniyamurthy, *Synlett*, 2011, 623–626.
74 Y. Chen, Y. J. Wang, Z. M. Sun and D. W. Ma, *Org. Lett.*, 2008, **10**, 625–628.
75 X. B. Yang, H. Fu, R. Z. Qiao, Y. Y. Jiang and Y. F. Zhao, *Adv. Synth. Catal.*, 2010, **352**, 1033–1038.
76 B. Wang, B. Lu, Y. W. Jiang, Y. H. Zhang and D. W. Ma, *Org. Lett.*, 2008, **10**, 2761–2763.
77 F. Wang, H. X. Liu, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Org. Lett.*, 2009, **11**, 2469–2472.
78 Y. Y. Wu, Y. H. Zhang, Y. W. Jiang and D. W. Ma, *Tetrahedron Lett.*, 2009, **50**, 3683–3685.
79 C. C. Malakar, D. Schmidt, J. Conrad and U. Beifuss, *Org. Lett.*, 2011, **13**, 1972–1975.
80 A. K. Verma, T. Kesharwani, J. Singh, V. Tandon and R. C. Larock, *Angew. Chem., Int. Ed.*, 2009, **48**, 1138–1143.
81 Q. Cai, F. T. Zhou, T. F. Xu, L. B. Fu and K. Ding, *Org. Lett.*, 2011, **13**, 340–343.

82 G. Altenhoff and F. Glorius, *Adv. Synth. Catal.*, 2004, **346**, 1661–1664.
83 K. Schuh and F. Glorius, *Synthesis*, 2007, 2297–2306.
84 X. H. Deng, H. McAllister and N. S. Mani, *J. Org. Chem.*, 2009, **74**, 5742–5745.
85 X. H. Deng and N. S. Mani, *Eur. J. Org. Chem.*, 2010, 680–686.
86 B. Lu, B. Wang, Y. H. Zhang and D. W. Ma, *J. Org. Chem.*, 2007, **72**, 5337–5341.
87 X. Y. Yuan, X. B. Xu, X. B. Zhou, J. W. Yuan, L. G. Mai and Y. Z. Li, *J. Org. Chem.*, 2007, **72**, 1510–1513.
88 E. D. Li, X. B. Xu, H. F. Li, H. M. Zhang, X. L. Xu, X. Y. Yuan and Y. Z. Li, *Tetrahedron*, 2009, **65**, 8961–8968.
89 Q. Liao, L. Y. Zhang, S. T. Li and C. J. Xi, *Org. Lett.*, 2011, **13**, 228–231.
90 J. Yuen, Y.-Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 653–656.
91 J. T. Zhu, H. B. Xie, Z. X. Chen, S. Li and Y. M. Wu, *Chem. Commun.*, 2009, 2338–2340.
92 M.-W. Chen, X.-G. Zhang, P. Zhong and M.-L. Hu, *Synthesis*, 2009, 1431–1436.
93 J. Y. Lu, X. Y. Gong, H. J. Yang and H. Fu, *Chem. Commun.*, 2010, **46**, 4172–4174.
94 D. W. Ma, Q. Geng, H Zhang and Y. W. Jiang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1291–1294.

