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Copper-Catalyzed Domino Reactions for the Synthesis of Cyclic Compounds

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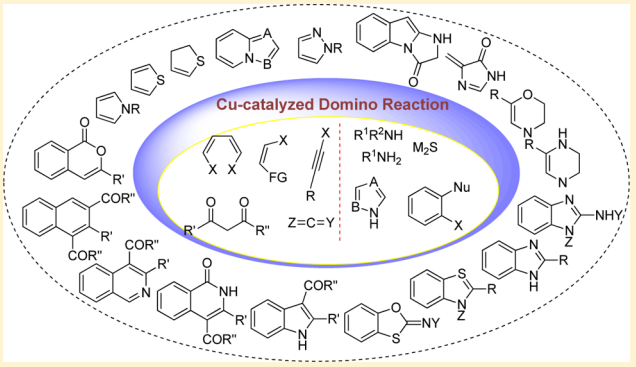
ABSTRACT: Copper-catalyzed domino reactions are one of the most useful strategies for the construction of various cyclic compounds. In this Synopsis, we mainly focus on the latest advances in copper-catalyzed cross-coupling or addition-initiated domino reactions in the synthesis of cyclic compounds, including double alkenylation of *N*- or *S*-nucleophiles, alkenylation or alkynlation followed by cyclization of amides or amines, addition and cyclization of heteroallenes affording heterocycles, and coupling and cyclization of 1,3-dicarbonyl compounds toward heterocycles.



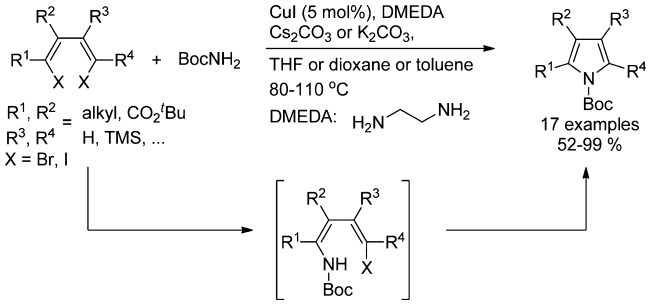
Cyclic compounds, especially heterocycles, have been occupying the center stage of organic chemistry. More than two-thirds of organic compounds are cyclic, and the number is still increasing. Cyclic compounds are widely distributed in nature and essential for life. Moreover, they are frequently used in material science, such as organic conductors, semiconductors, liquid crystalline compounds, and so on. Consequently, development of new methods for efficient synthesis of cyclic compounds is an ongoing subject for organic chemists. Among the myriad of synthetic transformations, the domino reaction is defined as a powerful tool for the synthesis of cyclic compounds, since they can directly construct complicated molecules in one pot under identical conditions from readily accessible starting materials.[1] In particular, transition-metal-catalyzed domino reactions have become a research hotspot during the past decades for their ability to shorten reaction procedures, reduce waste, and use milder conditions.[2] As a member of the transition-metal family, copper not only displays great catalytic potential in many transformations but also has many advantages such as low toxicity, low cost, and easy handling.[3] Thus, copper-catalyzed domino reaction toward cyclic compounds is receiving more attention these days.[4] In this Synopsis, we mainly focus on the latest advances in copper-catalyzed cross-coupling or addition transformation-initiated domino reactions for the construction of cyclic compounds.

1. DOUBLE ALKENYLATION FOR THE SYNTHESIS OF AROMATIC HETEROCYCLES

1,4-Dihalo-1,3-dienes own four π-conjugated carbon atoms and were employed in various methods for the construction of heterocyclic compounds,[5] especially aromatic heterocycles. Many novel procedures for the synthesis of pyrroles, pyrazoles, indoles, and thiophenes have been developed in recent years, based on double alkenylation of the corresponding nucleophiles.

1.1. Double Alkenylation of Amides. A general copper-catalyzed coupling of amides and carbamates with vinyl halides to form enamides was reported by Buchwald and co-workers in 2003,[6] while the synthesis of pyrroles and heteroarylpyrroles via a copper-catalyzed double alkenylation of $BocNH_2$ was described in 2007 (Scheme 1).[7] Compared with conventional methods,

Scheme 1. Cu-Catalyzed Double Alkenylation of Amides



this strategy has advantages in the synthesis of alkyl-substituted electron-rich pyrroles and heteroarylpyrroles. In the same year, Li and co-workers also published a relevant procedure for the synthesis of pyrroles, in which the substrate scope was extended to other amides.[8]

1.2. Double Alkenylation of Amines. Enamines are valuable intermediates in many organic syntheses. We have

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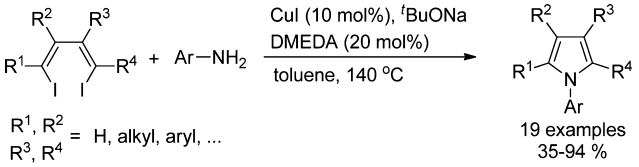
demonstrated that when catalyzed by CuI together with DMEDA (*N*,*N*-dimethylenediamine), amines could be alkenylated by various alkenyl halides, forming the corresponding enamines in good yields.[9] It is crucial to use ^{t}BuONa as the base to deprotonate the amine in this transformation. Complementary to this observation, the synthesis of substituted *N*-arylpyrroles based on double alkenylation of aromatic amines with (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes was established (Scheme 2).[10]

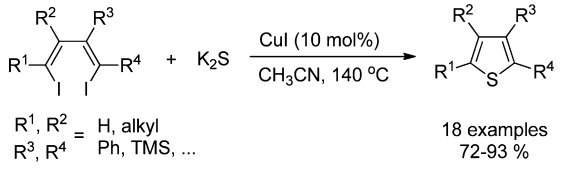
Scheme 2. Cu-Catalyzed Double Alkenylation of Amines



Anilines with electron-donating and -withdrawing substituents as well as pyridylamines reacted very well under such conditions. Not only tetrasubstituted dienyl diiodides but also some tri- and disubstituted dienyl diiodides worked smoothly under such conditions, affording the corresponding substituted *N*-arylpyrroles in good yields. Dienyl diiodides with *trans*-β-H gave lower yields due to the elimination process. No desired product was observed when alkylamines were used.

1.3. Double Alkenylation of Potassium Sulfide toward Thiophenes. Copper-catalyzed cross-coupling reactions applying thiols were extended to vinyl halides by 2004: a general and stereospecific copper-based protocol for the cross-coupling of vinyl iodides and thiols was reported by Venkataraman using Cu(1,10-phen)(PPh_3)NO_3 as the catalyst.[11] Improvements in terms of substrate scope, stability of catalyst, and reaction conditions were then made by Bao[12,13] and Cook.[14] Inspired by these results, we envisioned that besides organic sulfides, inorganic sulfides might also be able to couple with vinyl halides. If an intermolecular/intramolecular tandem alkenylation can proceed on an inorganic sulfide, a straightforward route for the synthesis of a wide range of structurally diverse thiophenes from the corresponding dienyl diiodides might be reached (Scheme 3).[15]

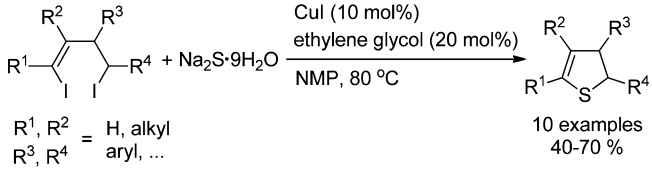
Scheme 3. Cu-Catalyzed Double Alkenylation of Potassium Sulfide



Actually, in the presence of a catalytic amount of CuI, potassium sulfide was double-alkenylated by 1,4-diiodo-1,3-dienes at 140 °C, affording thiophenes in good to excellent yields. Usually, dramatically different effects of ligands were observed in Ullmann couplings, but in this case, to our joy, the C−S coupling proceeded smoothly even in the absence of additional ligands. It is noteworthy that this procedure also applies to silyl groups. The TMS substituent not only acts as a directing group in the synthesis of diiodo dienes from alkynes but also provides a convenient functional handle for further manipulation on the resulting thiophenes.

In a similar catalytic system, 1,4-diiodobut-1-enes were treated with sodium sulfide, forming 2,3-dihydrothiophenes after a sequential alkylation/alkenylation process (Scheme 4).[16] Unlike

Scheme 4. Cu-Catalyzed Alkylation/Alkenylation of Sodium Sulfide

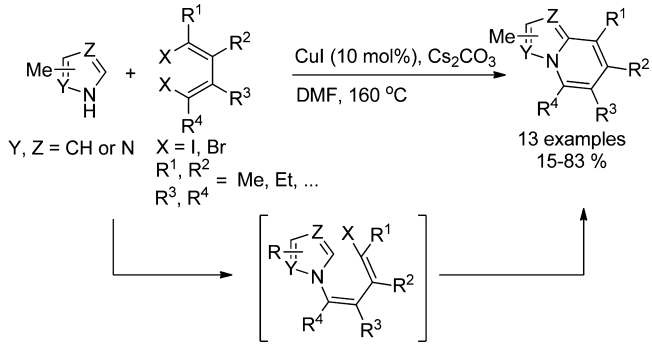


the double alkenylation of potassium sulfide, this cyclization can occur without any copper catalyst with rather low yield. The presence of a copper catalyst can significantly increase the yield of the expected product. Under oxidizing conditions, the resulting 2,3-dihydrothiophenes can be further transformed to di- or trisubstituted thiophenes.

1.4. Double Alkenylation of Azoles. Copper-catalyzed N−H alkenylations of imidazoles and indazoles were achieved by Bao[17] and Lam[18] in 2005 and 2001, respectively. These reactions were then further developed by Taillefer,[19] Cook,[20] and our group.[21] General copper-catalytic systems for N−H alkenylation of various azoles with vinyl halides were established. However, compared with N−H alkenylation, C−H alkenylation of azoles with vinyl halides is much more challenging. One example was the copper-catalyzed 2-alkenylation of 5-phenyloxazoles with bromoalkene in the presence of ^{t}BuOLi.[22]

Inspired by these previous works, we envisioned that in the presence of CuI, N−H/C−H double alkenylation could occur on azoles with dienyl dihalides to afford azolopyridine derivatives, which would constitute an important type of *N*-bridgehead heterocycles (Scheme 5).[23] In most cases, additional

Scheme 5. Cu-Catalyzed Double Alkenylation of Azoles



ligand was not required, which is similar to the double alkenylation of K_2S mentioned above; indicating that azole itself might function as the ligand in the reaction. In order to investigate the reaction course, a dienyl monoiodide was treated with imidazole and an N−H alkenylated product was isolated, suggesting that the annulation was a preferential N−H bond activation followed by a sequent C−H bond alkenylation.

2. DOMINO SEQUENCE ALKENYLATION OR ALKYNYLATION FOLLOWED BY CYCLIZATION

A copper-catalyzed alkenylation of a nucleophile followed by an intramolecular cyclization could also form cyclic compounds. This domino transformation attracted much attention in the field

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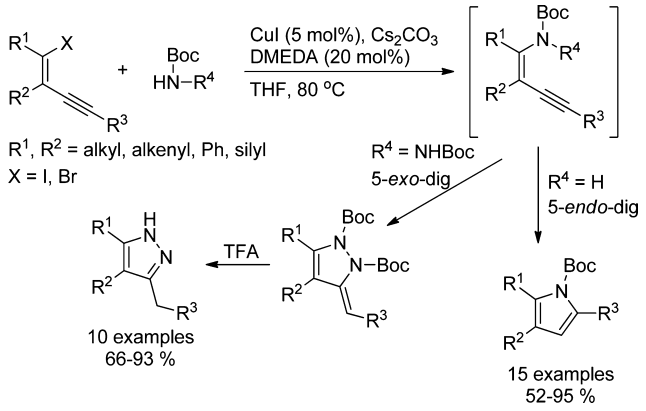
of copper-catalyzed coupling reactions as was well documented, applying the alkenylation/arylation strategy.[24,25] In this part, we focus on some sequential alkenylation (or alkynlation)/cyclization reactions, excluding those with an arylation step.

One pioneering example of the copper-catalyzed domino sequential alkenylation/cyclization reactions was the selective synthesis of pyrrole (or pyrazole) precursors from haloenynes, as reported by Buchwald and co-workers in 2006 (Scheme 6).[26]

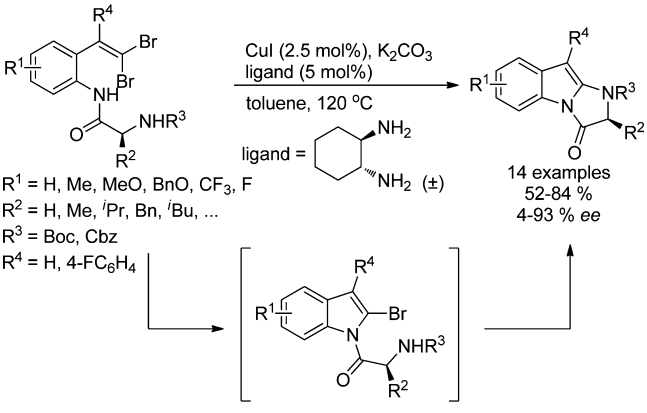
Scheme 6. Cu-Catalyzed Synthesis of Pyrroles or Pyrazoles via Domino Amidation/Hydroamidation of Haloenynes



The initially formed C−N coupling product can be easily isolated, while its cyclization requires the presence of both a base and a copper catalyst. These intramolecular hydroamidations produce exclusively five-membered rings, yielding pyrroles or pyrazole derivatives.

For the construction of annulated fused products, *gem*-dibromovinyl compounds provide a highly efficient way. A representative example was published by Lautens and co-workers in 2006 (Scheme 7).[27] Catalyzed by CuI/racemic *trans*-1,2-

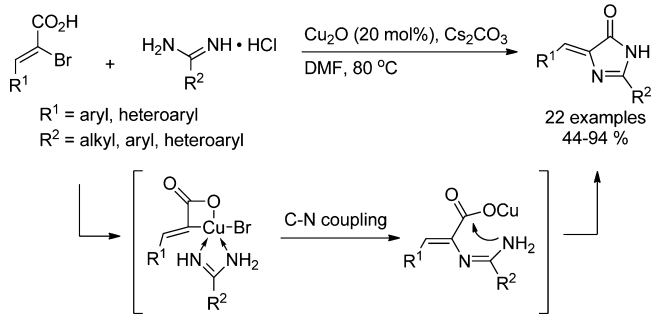
Scheme 7. Cu-Catalyzed Domino Intramolecular Alkenylation Using *gem*- Dibromovinyl System To Sythesize Imidazolones



cyclohexyldiamine, tandem intramolecular C−N coupling occurred on the same carbon atom, and imidazoindolones were formed as the final products in good yields. Monocyclized intermediate, *N*-acylindole, was isolated if there was a substituent on the 3-position. Higher catalyst loading was required to obtain the desired product in this case.

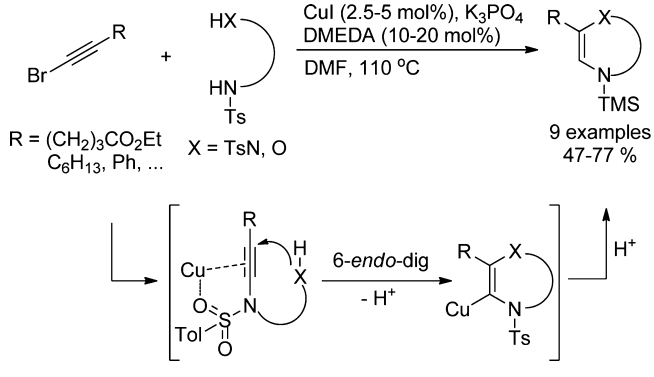
As an unconventional *N*-nucleophile, amidines can also participate in the copper-catalyzed alkenylation reactions. Fu and co-workers described an approach to 2,4-disubstituted imidazolones by domino reactions of 2-bromoacrylic acids and amidine hydrochlorides. The authors proposed a pathway via a copper-catalyzed alkenylation, followed by an intramolecular aminolysis of the carboxylic acid (Scheme 8).[28]

Scheme 8. Cu-Catalyzed Alkenylation/Condensation of Amidines toward 2,4-Disubstituted Imidazolones



Similar to alkenyl halide, alkynyl halide can couple with *N*-nucleophile in the presence of copper species, affording ynamine or ynamide. The triple bond in this reactive compound is ready to undergo further addition reactions. If the process occurs intramolecularly, heterocyclic compounds can be envisioned. An example was the production of tetrahydropyrazines and related heterocyclic compounds via a copper-catalyzed alkynlation of sulfonamides with haloacetylenes followed by a 6-*endo-dig* ring closure (Scheme 9).[29] Note that the formation of isomeric tetrahydroimidazole through the cyclization of 5-*exo-dig* mode was not observed in the reaction.

Scheme 9. Cu-Catalyzed Domino Amidation/Addition of 1-Halo-1-alkynes toward Tetrahydropyrazines and Related Heterocyclic Compounds



3. DOMINO SEQUENCE ADDITION FOLLOWED BY CYCLIZATION WITH HETEROALLENES

Addition reactions are widely used to initiate domino processes. Incorporated with sequential copper-catalyzed cyclizations, a series of novel and promising syntheses of cyclic compounds were developed. Triple bonds such as C≡C and C≡N are often employed in these transformations.[30,31] In addition, heteroallenes that have two cumulated double bonds between three atoms (Y═C═Z, Y and Z are heteroatoms) are also good candidates. Its multiplicity in reaction site qualifies the domino reaction for the formation of heterocycles. For example, its center carbon can be attacked by a nucleophile, and a heteratom then

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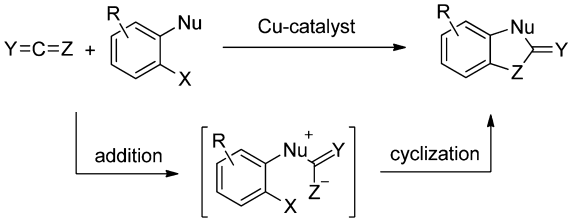
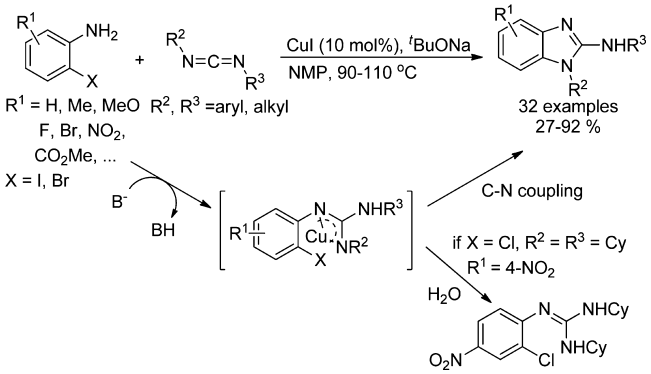
further reacts as the secondary nucleophile for cyclization (Scheme 10).[1d] In general, the synthetic chemistry of heterocycles from heteroallenes is rich and varied.

Scheme 10. Typical Domino Reaction Process of Heteroallenes toward Heterocyclic Compounds



3.1. Reaction of Carbodiimides toward 2-Aminobenzimidazoles. The construction of 2-aminobenzimidazole was reviewed by Rastogi.[32] Recently, carbodiimides were found to be versatile building blocks for the synthesis of such *N*-containing heterocyclic compounds. As the reaction disclosed by Bao and co-workers[33] in 2010, through the nucleophilic attack of o-haloaniline on the electron deficient carbon in diphenylcarbodiimide, 2-aminobenzimidazole was afforded after a copper-catalyzed intramolecular N-arylation process. We also developed a general and practical protocol to 2-aminobenzimidazoles via domino reactions of *o*-haloanilines and carbodiimides, using CuI as the catalyst under ligand-free conditions (Scheme 11).[34] This

Scheme 11. Cu-Catalyzed Addition/Cyclization of *o*-Haloanilines and Carbodiimides

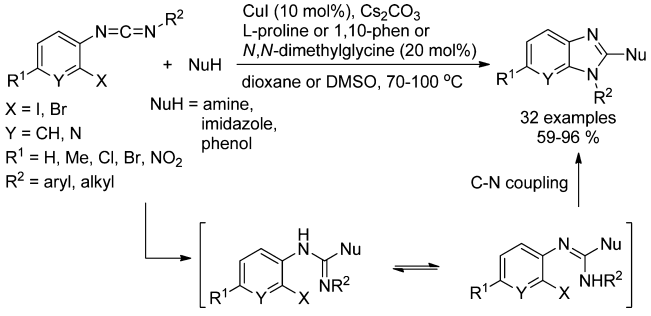


procedure could be applied to *o*-iodoaniline, *o*-bromoaniline as well as *o*-chloroaniline derivatives. Not only symmetrical but also unsymmetrical carbodiimides were found to be suitable substrates. The reaction exhibited a good regioselectivity, affording *N*-alkyl-1-aryl-2-aminobenzimidazoles in good yields, when unsymmetrical carbodiimides possessing both alkyl and aryl groups were employed. This selectivity might be attributed to the preferential copper-catalyzed coupling activity of NH-aryl group in the intermediate, which is formed by the nucleophilic attack of aniline to the center carbon of carbodiimide.

Similarly, when *o*-haloarylcarbodiimides react with suitable nucleophiles, the domino synthesis of 2-aminobenzimidazoles (or other 2-heterobenzimidazoles) was also feasible (Scheme 12).[35]

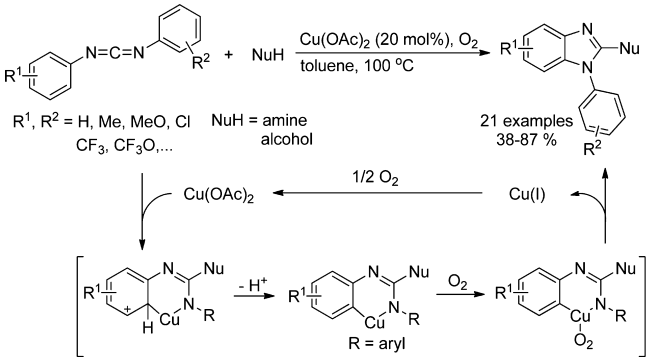
An expansion of the above principle was then documented by Bao's group again, using carbodiimides and amines to synthesize 2-aminobenzimidazoles, through the addition/oxidative C–N

Scheme 12. Cu-Catalyzed Addition/Cyclization of Nucleophiles and *o*-Haloarylcarbodiimides



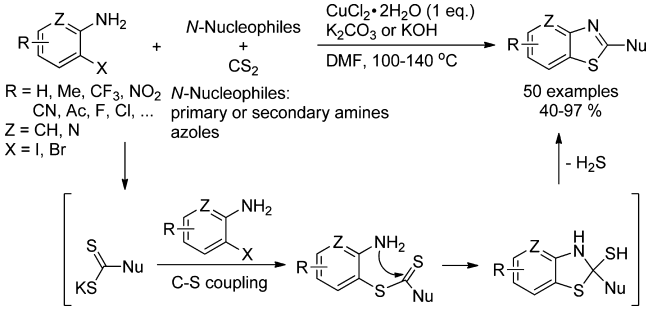
coupling strategy (Scheme 13).[36] Note that quinazolines formed if benzylarylcarbodiimides were used under the same conditions.

Scheme 13. Cu-Catalyzed Synthesis of 2-Aminobenzimidazoles via Addition/Oxidative C–N Coupling Process



3.2. Reaction of Carbon Disulfide toward Polycyclic Compounds. Carbon disulfide can be considered as another type of heteroallene. Its center carbon atom is ready to be attacked by appropriate nucleophiles and the sulfur atom reflects the nucleophilicity in the reaction. In some cases, carbon disulfide releases one H_2S during the reaction, and thus it is used as H_2S equivalent in some transformations involving C–S coupling.[37] In 2011, Ma revealed a synthesis of 2-N-substituted benzothiazoles and the related polycyclic compounds through copper-catalyzed three-component domino condensation/S-arylation/heterocyclization reactions (Scheme 14).[38] It was believed that the dithiocarbamate salt from the addition of nucleophile to CS_2 was the intermediate which cross coupled with *o*-haloanilines. The following cyclization eliminated H_2S

Scheme 14. Cu-Catalyzed Domino Condensation/*S*-Arylation/Heterocyclization Reactions



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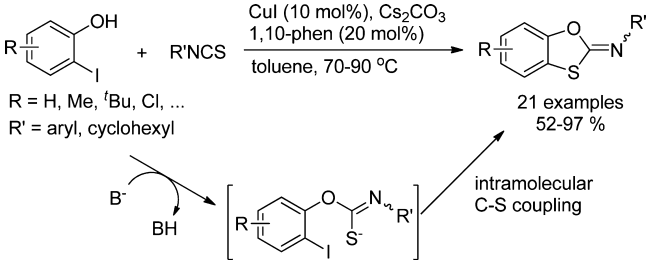
and afforded the aromatic rings. This protocol displayed excellent substrate compatibility, since various *N*-nucleophiles were applicable and many functional groups were tolerated.

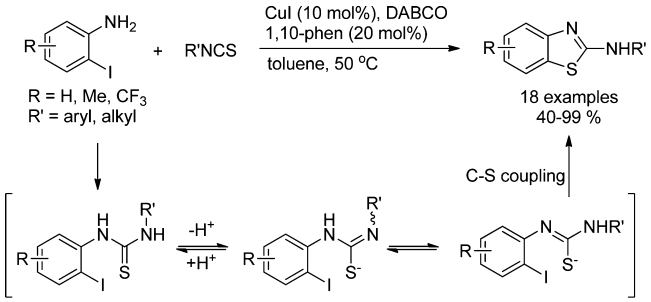
3.3. Reaction of Isothiocyanates toward 2-Iminobenzoxathioles and 2-Aminobenzothiazoles. Following the same principle described above, isothiocyanates are expected to participate domino reactions in a similar way. However, sulfides are usually stronger nucleophiles when compared with *N*-nucleophiles. Therefore, the formations of C−S bonds are usually favored, affording benzoxathioles, benzothiazoles, and related compounds. In 2008, Bao and co-workers first reported a one-pot copper-catalyzed cascade reaction to synthesize 2-iminobenzo-1,3-oxathioles from *o*-iodophenols and isothiocyanates (Scheme 15).[39] Later on, an identical transformation performed in water was published.[40]

Scheme 15. Cu-Catalyzed Addition/Cyclization of *o*-Halophenols and Isothiocyanates



When *o*-iodophenols were replaced by *o*-iodoanilines, 2-aminobenzothiazoles formed (Scheme 16).[41] This transformation was further improved in the substrate scope by Bao's group, using a CuI/Cs_2CO_3/DMSO catalyst system.[42] Almost the same year, a very similar ligand free system using CuBr/TBAB/DMSO was reported by Li and co-workers.[43]

Scheme 16. Cu-Catalyzed Addition/Cyclization of *o*-Haloanilines and Isothiocyanates

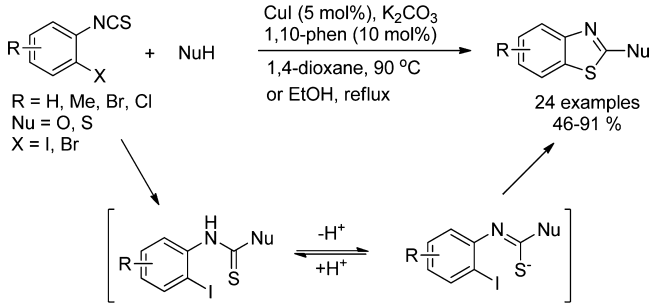


Switching the location of the nucleophile and isothiocyanate groups, copper-catalyzed domino addition/cyclization process provided an alternative route to 2-substituted benzothiazoles, as described by Patel and co-workers in 2009 (Scheme 17).[44]

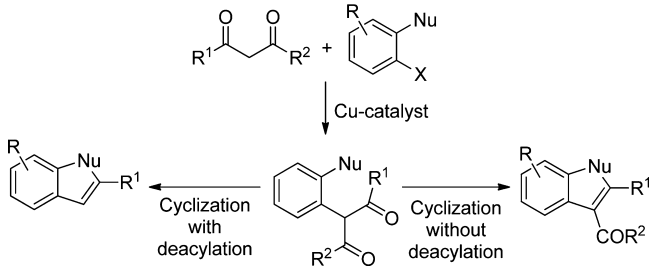
4. DOMINO SEQUENCE COUPLING/CYCLIZATION WITH 1,3-DICARBONYL COMPOUNDS

1,3-Dicarbonyl compounds have two activated C−H bonds which can react as nucleophiles in copper-catalyzed coupling reactions. In addition, their carbonyl groups can also react as electrophiles. It is also known that 1,3-dicarbonyl compounds undergo deacylation under certain conditions. Because of these characteristics, 1,3-dicarbonyl compounds are widely used in organic syntheses.[45] In the copper-catalyzed assembly of cyclic compounds, they usually provide two carbon atoms for ring closure, and their reactions are mainly divided into two types, depending on whether the deacylation occurs or not (Scheme 18).

Scheme 17. Cu-Catalyzed Formation of 2-Substituted 1,3-Benzothiazoles from *o*-Halophenyl Isothiocyanates

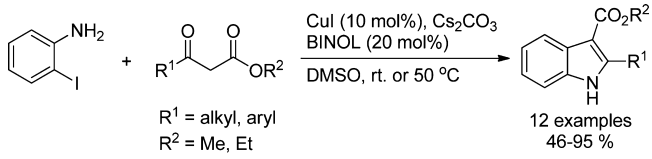


Scheme 18. Typical Cu-Catalyzed Heterocyclic Compound Construction with 1,3-Dicarbonyl Compound



4.1. The Domino Reaction Achieved without Deacylation. In 2007, Tanimori and co-workers developed a copper-catalyzed one-pot synthesis of 2,3-disubstituted indoles from 2-iodoanilines and various β-keto esters. No deacylation occurred after the cyclization; thus, both R^1 and ester groups remained in the products (Scheme 19).[46] In the same period, Ma and co-workers reported a similar transformation with $COCF_3$ masked *o*-haloanilines. The coupling was facilitated by the *ortho*-substituent effect of NHCOR (amido) group, which lowered the reaction temperature and provided better compatibility (Scheme 20).[47] Using the same *o*-halotrifluoroacetanilides, Fu, Qiao et al. reported another Cu-catalyzed indole synthesis from 2-cyanoacetates or malononitrile, which are analogues of 1,3-dicarbonyl compounds.[48] As a further modification of these methods, a ligand-free Cu_2O system was declared by Punniyamurthy and co-workers in 2011.[49]

Scheme 19. Cu-Catalyzed Generation of 2,3-Disubstituted Indoles from *o*-Iodoanilines and β-Keto Esters



Six-membered heterocycles can be assembled if 1,3-dicarbonyl compounds are incorporated with proper four-membered building blocks. Fu and co-workers reported that the reaction of β-keto esters with *o*-halobenzamides afforded isoquinolinone

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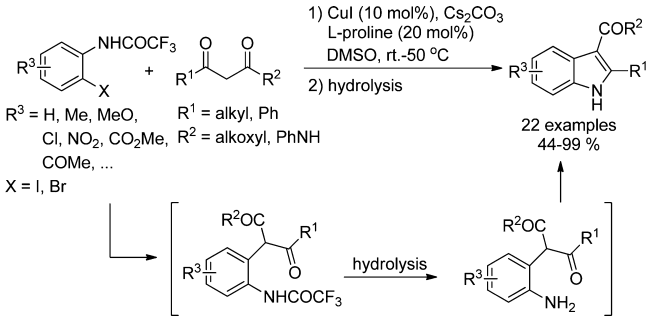
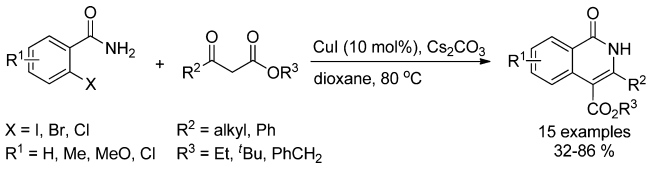
Scheme 20. Cu-Catalyzed Synthesis of Polysubstituted Indoles from *o*-Halotrifluoroacetanilides and 1,3-Dicarbonyl Compounds



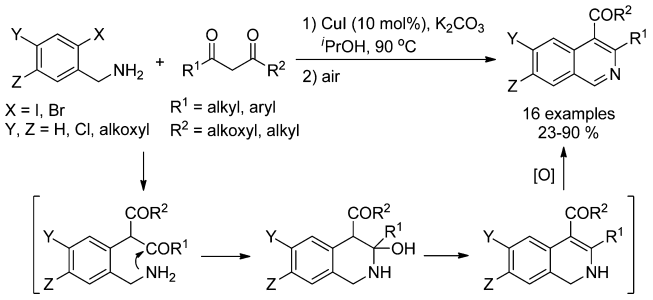
derivatives (Scheme 21),[50] while Ma's group found that the treatment of *β*-keto esters or 1,3-diketones with *o*-halobenzyl-

Scheme 21. Cu-Catalyzed Fabrication of Isoquinolinone Derivatives from *o*-Halobenzamides and *β*-Keto Esters



amines yielded dihydroisoquinolines, which were then in situ dehydrogenated to give isoquinolines (Scheme 22).[51] Alter-

Scheme 22. Cu-Catalyzed Synthesis of Substituted Isoquinolines from *o*-Halobenzylamines and *β*-Keto Esters or 1,3-Diketones

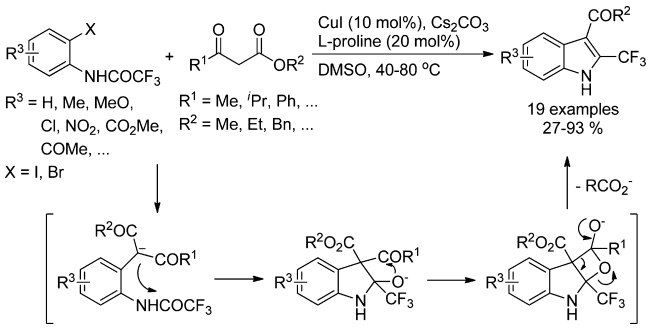


natively, the starting *o*-halobenzylamines could be replaced by a three-components reaction of *o*-bromobenzaldehydes, primary amines and terminal alkynes, and 1-alkynyl-substituted isoquinolines would be the final products.[52]

4.2. The Domino Reaction Achieved with Deacylation. 2-(Trifluoromethyl)indoles were produced in good yields when the same $COCF_3$ masked *o*-haloanilines, which were used in the indole synthesis as mentioned above (Scheme 20),[47] were subjected to similar but anhydrous conditions (Scheme 23).[53] The modification on reaction conditions dramatically changed the pathway from *N*-nucleophilic cyclization to *C*-nucleophilic cyclization followed by a basic deacylation process.

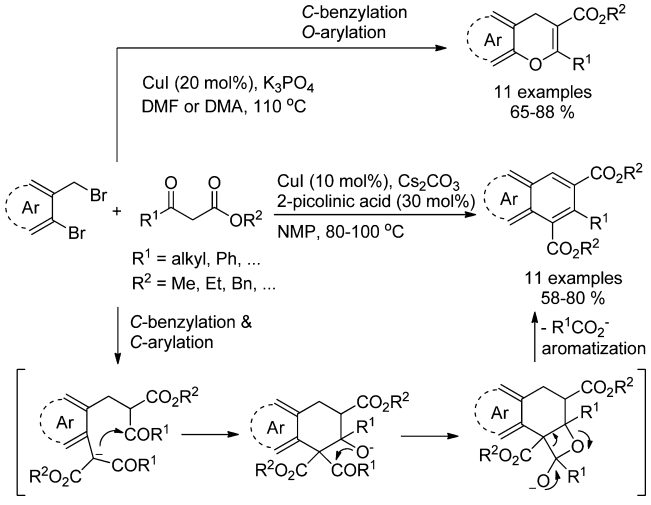
Recently, an interesting copper-catalyzed domino reaction involving 1,3-dicarbonyl compounds was achieved by Beifuss and co-workers.[54] Depending on the ratio of the substrates and the reaction conditions employed, either 4*H*-chromenes or naphthalenes were formed exclusively, starting from 2-bromobenzyl bromides and *β*-keto esters. The former derived from *C*-

Scheme 23. Cu-Catalyzed Formation of 2-(Trifluoromethyl)indoles from *o*-Halotrifluoroacetanilides and *β*-Keto Esters



benzylation and *O*-arylation of one *β*-keto ester molecule, while the latter derived from an intramolecular addition, deacylation, aromatization sequence of the intermediate, which came from *C*-benzylation and *C*-arylation of two *β*-keto ester molecules, respectively (Scheme 24).

Scheme 24. Cu-Catalyzed Selective Construction of 4*H*-Chromenes and Naphthalenes from 2-Bromobenzyl Bromides and *β*-Keto Esters



The cyclization partner of 1,3-diketones was extended to *o*-halobenzoic acids by our group. When *o*-halobenzoic acids were treated with 1,3-diketones in the presence of a catalytic amount of CuI under 90−120 °C, 3-substituted isocoumarins formed (Scheme 25).[55] In the reaction with phenyl or *p*-methoxylphenyl-substituted 1,3-diketone, benzoic acid or *p*-methoxybenzoic acid was obtained as the byproduct, respectively. This indicated that deacylation unambiguously occurred in the reaction process. Disymmetrical 1,3-diketone with two different substituents at the 1- and 3-positions gave rise to a mixture of two different 3-substituted isocoumarins. Monoketones were nonreactive under such conditions. In addition to *o*-iodobenzoic acids, *o*-bromo and *o*-chlorobenzoic acids could also be used, with a relative reactivity order of aryl iodides > aryl bromides > aryl chlorides.

If the reaction between *o*-iodobenzoic acid and acetylacetone was carried out at a lower temperature, 2-(2,4-dioxopentan-3-yl)benzoic acid could be isolated as the intermediate (Scheme 26). But without CuI, no isocoumarin could be detected even

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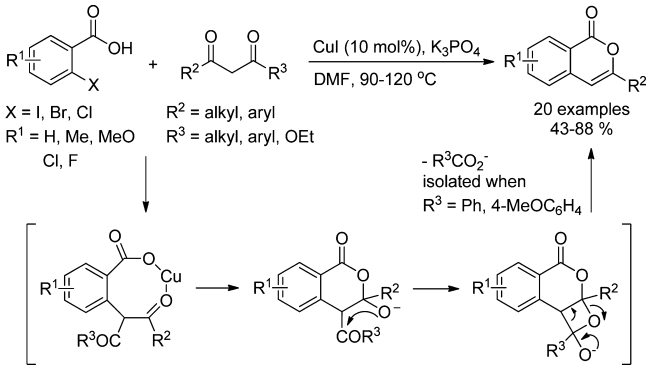
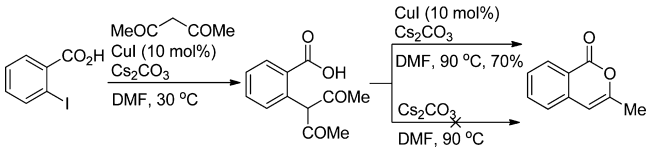
Scheme 25. Cu-Catalyzed Synthesis of 3-Substituted Isocoumarins from *o*-Halobenzoic Acids and 1,3-Diketones



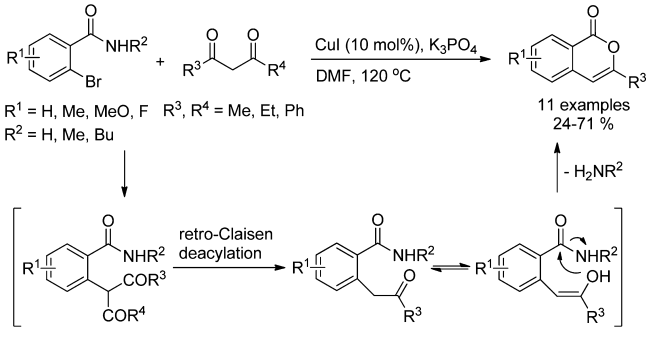
Scheme 26. Preparation and Transformation of the Intermediate in Isocoumarin Synthesis



when the intermediate was heated to 90 °C for 20 h. This suggested that the copper species catalyze not only the cross-coupling but also the ring-closure process.[53]

Interestingly, unlike the reactions described by Fu's group (Scheme 21),[50] isocoumarins rather than the expected isoquinolinones were obtained when *o*-halobenzamides and 1,3-diketones were subjected to slightly different conditions (Scheme 27).[56] The reaction was catalyzed by CuI in DMF and

Scheme 27. Cu-Catalyzed Preparation of 3-Substituted Isocoumarins from *o*-Bromobenzamides and 1,3-Diketones



also proceeded smoothly with *o*-bromobenzamides bearing methyl or methoxyl groups. *N*-Butyl and *N*-methyl *o*-bromobenzamides reacted with acetylacetone to give the same product, confirming the loss of an amine during the process. In 2012, Fan reported a similar catalytic system, in which 3-methylisocoumarin was obtained from the reaction between methyl *o*-bromobenzoate and acetylacetone.[57] According to our observation and Fan's results, the following three-step pathway was proposed: (i) copper-catalyzed C−C coupling, (ii) retro-Claisen deacylation under basic condition, and (iii) intramolecular lactonization.

5. CONCLUSION

As a versatile catalyst, copper can promote many types of reactions accompanied by the formation of important chemical bonds, including cross coupling, addition, and so on. Combination of several fundamental reactions into a copper-catalyzed domino reaction was demonstrated to be a very efficient approach to cyclic compounds. Its considerable impacts on traditional organic chemistry can be seen from the rapid growth of literature citations. Nevertheless, the reaction scope, catalyst loading, and mildness of the reaction conditions remain to be improved, while many mechanism details are unclear. Research in this area is just unfolding.

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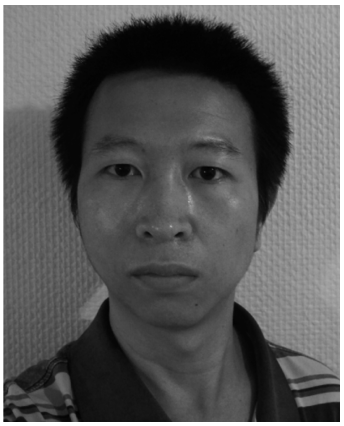
Notes

The authors declare no competing financial interest.

Biographies



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