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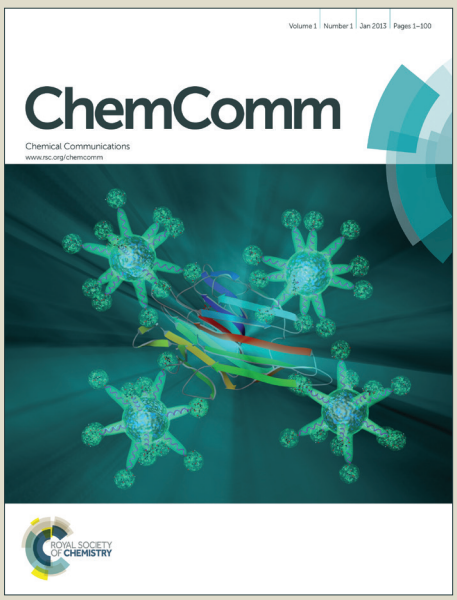

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ARTICLE

Construction of *N*-Containing Heterocycles via Oxidative Intramolecular N-H/X-H Coupling

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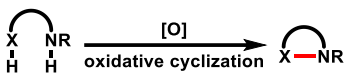
The preparation of *N*-containing heterocycles is always the core of synthetic chemistry. Recently, oxidative coupling between two R-H nucleophiles are gaining more attention due to its atom-economy and step-economy, thus there are numerous reports focus on the *N*-heterocycle construction via oxidative coupling. This feature article is going to cover the methodology related to the construction of *N*-heterocycle through oxidative intramolecular N-H/X-H coupling.

Introduction

N-containing cycles, both aliphatic and aromatic, are of great value since they are key structural features of various functional molecules. Thus the preparation of the *N*-heterocycles is the core of organic synthesis throughout the history of synthesis chemistry. A series of coupling reactions are developed to deal with this topic. In this area, the newly-developed metal-catalyzed cross coupling reactions using organohalides and different N-H bonds is a good way to achieve the C-N bond formation/cyclization since they are known for the relatively mild reaction conditions and good functional group tolerance[1]. However, because the organohalides are always obtained from the functionalization of the corresponding hydrocarbons, although spectacular success was obtained as these methods were employed extensively both in industry and laboratory, problems arisen along with the development of green chemistry that processes with atom-economy and step-economy were required. Therefore, direct coupling of R^1-H with N-H are gaining more attention due to the exclusion of pre-functionalization of the relatively inert R^1-H bonds and N-H bonds. In this case, a proper oxidant is required to accept the redundant hydrogen atoms[2]. Named as oxidative coupling or dehydrogenative coupling, this type of reaction is also employed to synthesize the cyclic compounds through an intramolecular pathway.

As fundamental part of modern synthetic chemistry, oxidative ring-closing methodologies to construct *N*-heterocycles deserved to be summarized and catalogued. Considering that the oxidative intermolecular cyclization was reviewed thoroughly, this article is going to cover the oxidative dehydrogenative intramolecular ring-closing reactions to construct *N*-heterocycles (Scheme 1).



Scheme 1.

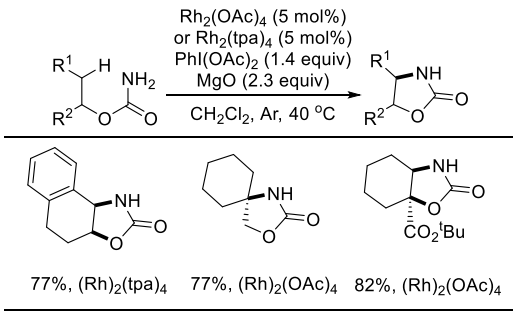
Aliphatic *N*-heterocycle construction via C-N bond formation

Aliphatic *N*-heterocycles, including substituted pyrrolidines, piperidines, azetidines, azepanes and the corresponding lactams, are common skeletons of different molecules that exhibit different bioactivity. Since the traditional method led to the construction of aliphatic *N*-heterocycles was the intramolecular coupling reaction between N-H bonds and organohalides. It is a significant task to replace the R-X (X = Cl, Br, I) bonds by the R-H bonds.

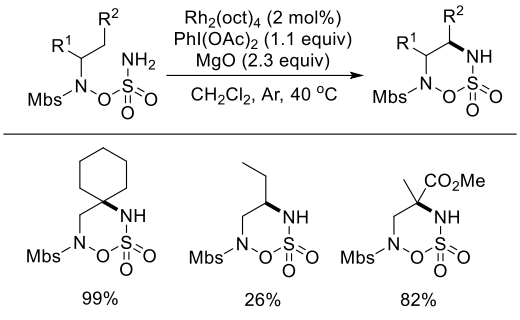
Aliphatic *N*-heterocycle construction through Rh-catalyzed C-H/N-H coupling.

Although the activation of C(sp^3)-H bond remained an undeveloped task, remarkable achievements have been made using Rh catalyst. The first Rh-catalyzed amination of C(sp^3)-H bond was developed in 2001[3]. Du Bois reported an oxidative γ-C(sp^3)-H amidation of carbamate to afford oxazolidinone using $Rh_2(OAc)_4$/$Rh_2(tpa)_4$ (tpa = triphenylacetate) as the catalyst and $PhI(OAc)_2$ as the oxidant (Scheme 2). The *cis*- selectivity suggested that Rh participated in the C-H bond activation. Then, Du Bois switched the carbamate to sulfamate ester, and thus another amidation of γ-C(sp^3)-H was realized under similar condition[4] (Scheme 3) that a combination of $Rh_2(oct)_4$ (oct = octanoate) and $PhI(OAc)_2$ was utilized. It was noteworthy that the sulfamate group was easy to remove to obtain corresponding 1,2-diamine (Scheme 4). In these Rh-catalyzed reactions, the

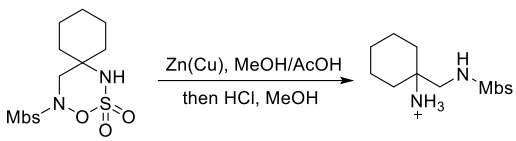
insertion of Rh-nitrenes to C-H bonds were believed to be the route that led to the C-N bond formation.



Scheme 2.



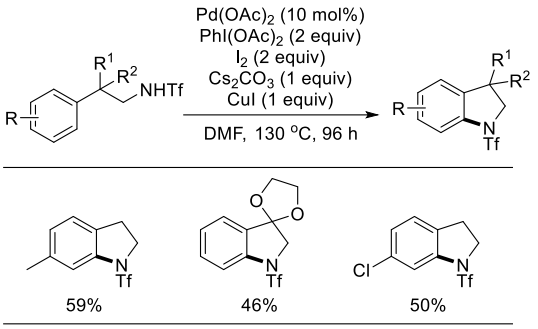
Scheme 3.



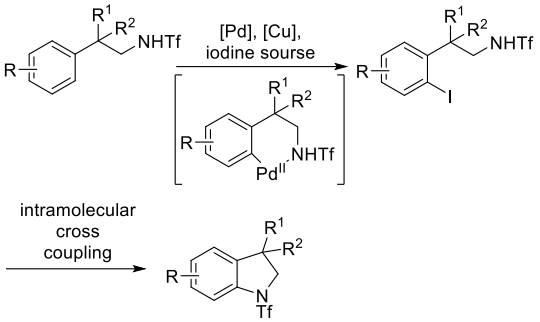
Scheme 4.

Aliphatic *N*-heterocycle construction through Pd-catalyzed C-H/N-H coupling.

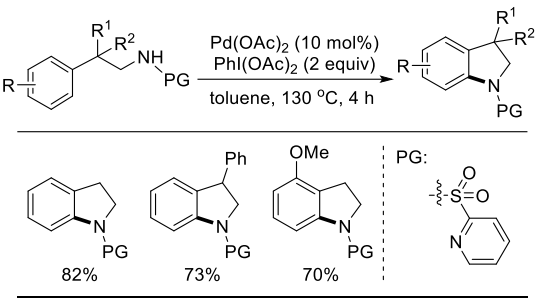
After that, palladium was chosen to catalyse this type of reaction. In 2008, Yu and coworkers reported a Pd-catalyzed intramolecular amination of C(sp^2)-H. With the employment of $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant, β-aryl amines underwent the amination smoothly to afford the corresponding 2,3-dihydroindoles[5] (Scheme 5). A tandem iodization/amination route was believed to be the mechanism (Scheme 6). Also, the Tf group was easy to remove by using $LiAlH_4$. They soon improved the methodology by replacing the oxidant by $Ce(SO_4)_2$ or F^+ reagent. The employment of the above two strong oxidants indicated that a Pd^{IV} intermediate was involved among the transformation[6]. This protocol was soon updated using the cheaper 2-pyridylsulfonyl protecting group instead of the Tf group[7] (Scheme 7). In this case, the iodine, base and copper salt were excluded from the protocol, which simplified the reaction condition. Then, an intramolecular amidation of C(sp^2)-H was also reported by Yu. In this case, *N*-alkoxy-α-aryl amides were utilized to achieve the transformation to afford indolin-2-ones in the presence of catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of AgOAc and $CuCl_2$[8]. Besides, 6-membered lactam was also obtained when the reaction was started from *N*-alkoxy-β-aryl amides (Scheme 8).



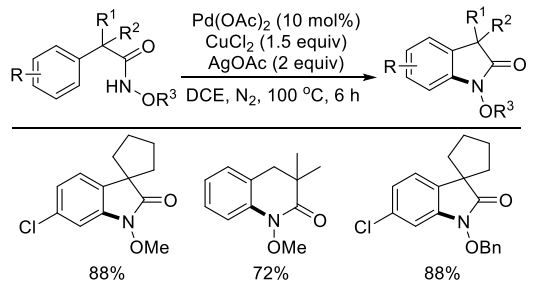
Scheme 5.



Scheme 6.



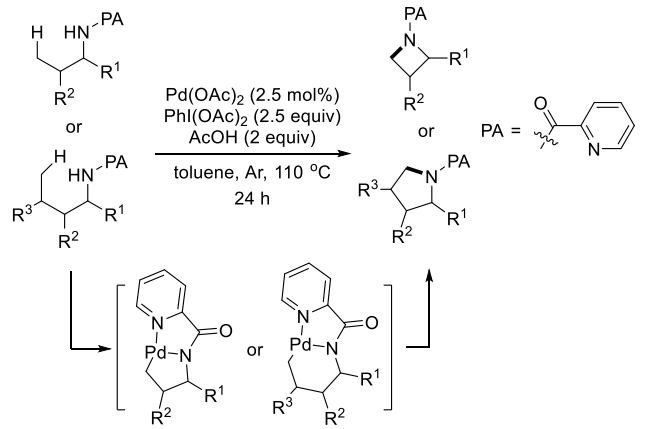
Scheme 7.



Scheme 8.

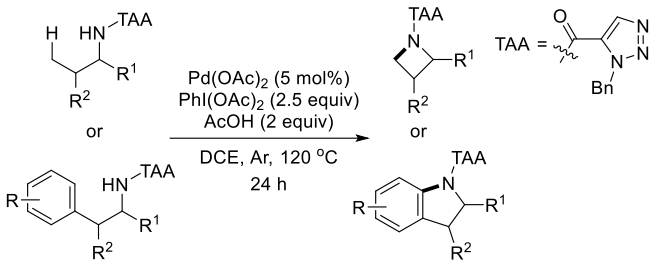
Despite the Pd-catalyzed C(sp^2)-H bond activation was well-known, the C(sp^3)-H activation catalyzed by Pd remained challenging. To overcome this problem, additional directing

group was introduced to the substrates. In 2011, Daugulis reported a intramolecular amination of C(sp^3)-H bond. With $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant, γ and δ-C(sp^3)-H aminations led to the formation of azetidines and pyrrolidines was achieved under acidic condition[9] (Scheme 9). The key to the C-H bond activation was the use of picolinamide group as the additional directing group. 5 and 6-membered palladacycles were believed to be the active intermediates and a Pd^{II}/Pd^{IV} catalytic cycle was believe to be the mechanism. At the same year, similar work was also done by Daugulis[10]. Since the reaction condition was similar to the previous Yu's report, the same amination of C(sp^2)-H bond was also achieved.

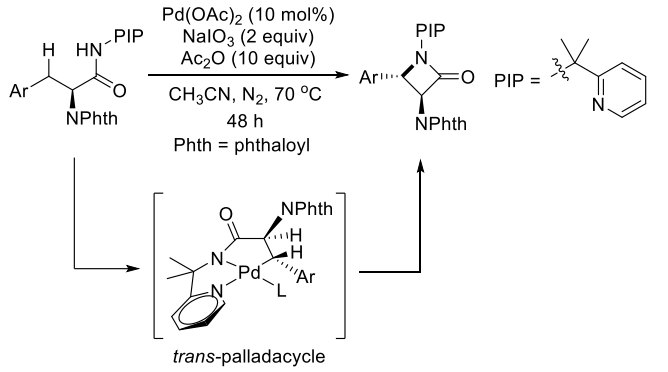


Scheme 9.

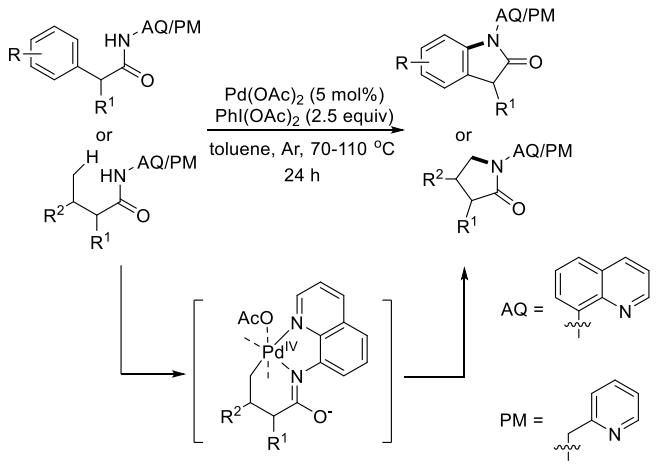
Two years later, several other removable directing groups, including 1,2,3-triazole[11], 2-(pyridin-2-yl)isopropyl[12], quinoline[13] and 2-pyridylmethyl[13], were introduced to this methodology as the additional directing groups. Similar to the previous results, 4-membered and 5-membered rings were obtained with the direction of the mentioned groups. With the employment of 1,2,3-triazole as the directing group, $Pd(OAc)_2$ and $PhI(OAc)_2$ were used as the catalyst and oxidant respectively and azetidines were the cyclizative product[11] (Scheme 10). Then, β-lactams were obtained from the amidation of benzylic C-H bond. In this report, $Pd(OAc)_2$ was chosen to be the catalyst and $NaIO_3$ was chosen to be the oxidant. It was noteworthy that only one diastereoisomer of the product was observed, which may be ascribe to the structure of the *trans*-palladacycle intermediate[12] (Scheme 11). The steric effect of the large NPhth group and Ar group led to the stereoselectivity. By switching the directing group to 8-aminoquinoline and 2-pyridylmethyl, γ-lactam was obtained instead of β-lactam[13] (Scheme 12). The combination of $Pd(OAC)_2$ and $PhI(OAc)_2$ was again utilized and a Pd^{IV} complex was proposed to be the active intermediate. These articles reported amination/amidation of β-aryl amines to afford 2,3-dihydroindoles/indolin-2-one as well as the preceding report[11, 13].



Scheme 10.

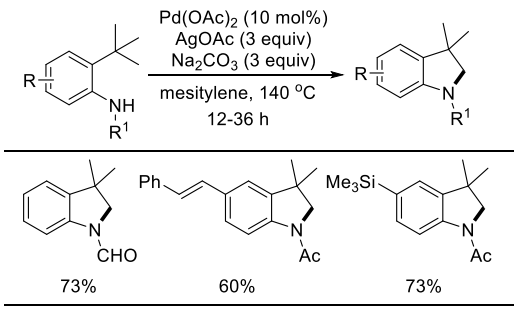


Scheme 11.



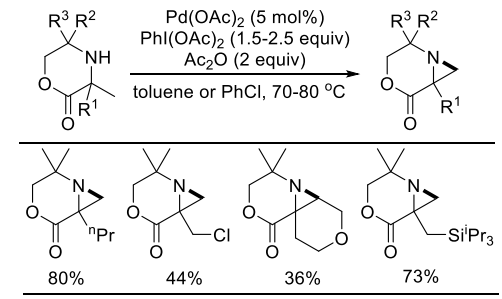
Scheme 12.

Amination of C(sp^3)-H bond without additional directing group was also achieved under Pd catalysis. In 2009, Glorius reported an intramolecular C-N coupling of 2-*tert*-butyl-anilides to afford corresponding indolines in the presence of catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of AgOAc and Na_2CO_3[14] (Scheme 13). As usual, the C(sp^3)-H bond activation was oriented by the anilide group and the C-N bond formed through reductive elimination.

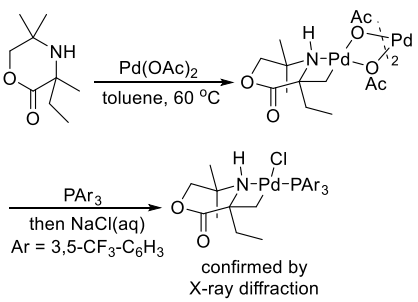


Scheme 13.

The previous reports focused on the construction of 4-6 membered *N*-containing rings and thus the formation of 3-membered rings via direct dehydrogenative C-N bond formation remained unexplored. In 2014, Gaunt filled in this blank that ethyl amines were utilized to prepare the aziridines through oxidative N-H/C-H coupling[15] (Scheme 14). Various aminolactones were converted into corresponding aziridine in the presence of catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of $PhI(OAc)_2$ and Ac_2O. An unusual 4-membered palladacycle, which was confirmed by stoichiometric experiment and underwent reductive elimination to afford the product, was involved in the mechanism (Scheme 15).

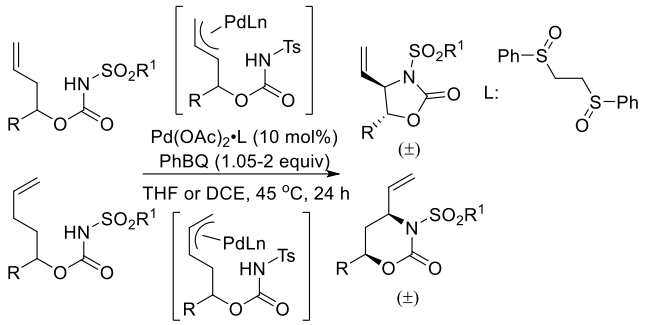


Scheme 14.



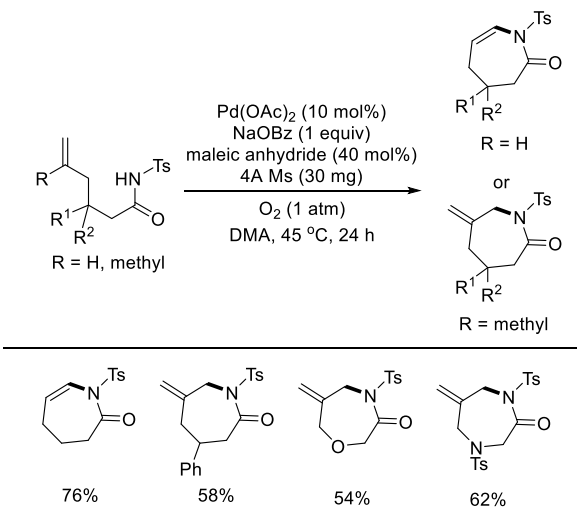
Scheme 15.

Another method to achieve the amination/amidation of $C(sp^3)$-H bonds was to look for proper activated $C(sp^3)$-H bonds. To the best of our knowledge, the Pd-catalyzed allylic C-H bond activation was fully investigated, thus this type of $C(sp^3)$-H bond may be a good choice. Thus, White realized a series of intramolecular Pd-catalyzed amidation of allylic C-H bond. His reports described the construction of 5-membered *anti*-oxazolidinone and 6-membered *syn*-oxazinanone employing $Pd(OAc)_2$ as the catalyst and quinone as the oxidant with the employment of sulfoxide ligand[16] (Scheme 16). The dr value ranged from 1.7:1 to >20:1 in both cases, which may be ascribed to the π-allylPd intermediate confirmed by stoichiometric studies. Moreover, the product can be deprotected to afford 1,2- and 1,3-amino alcohols. The mechanism of this type of reaction was discussed carefully soon[17].



Scheme 16.

At the same time, Liu reported another intramolecular aerobic amidation of alkene[18] (Scheme 17). In this transformation, $Pd(OAc)_2$ was utilized as the catalyst and O_2 as the oxidant without any co-oxidant. The regioselectivity can be modulated by Brønsted base. With the addition of NaOBz as the base, 7-membered lactam was the major product while traditional 5-membered lactam was obtained without the addition of the base. The mechanistic study suggested that the product may form through C-N reductive elimination, and the role of the base may be the accelerator of the Pd-N bond formation.

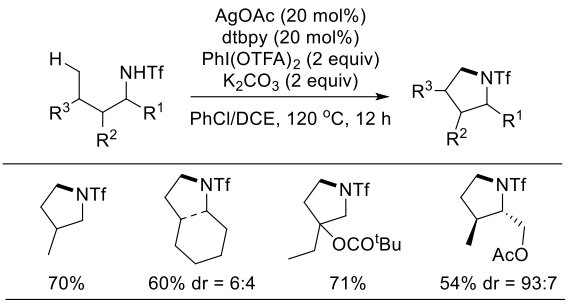


Scheme 17.

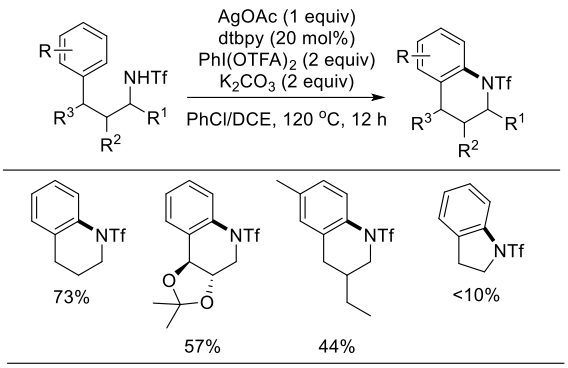
Aliphatic *N*-heterocycle construction through Ag-catalyzed C-H/N-H coupling.

Silver salts also exhibited catalytic activity in the $C(sp^3)$-H and $C(sp^2)$-H amination. Pyrrolidines and 1,2,3,4-tetrahydroquinolines were prepared via the C-H/N-H coupling

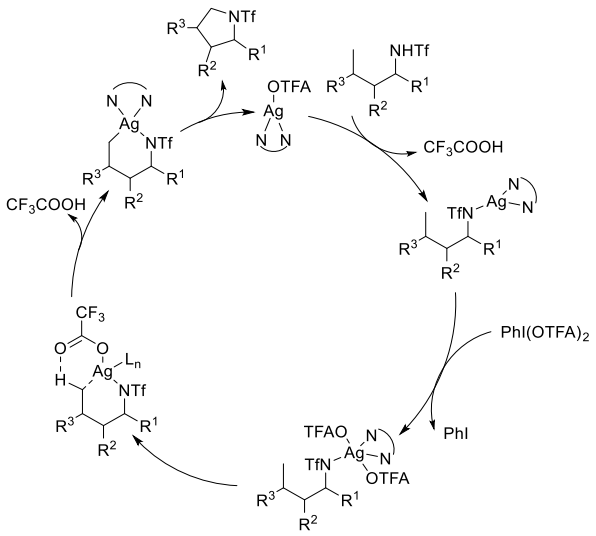
of butyl and 3-aryl propyl amines without additional directing group[19] (Scheme 18, 19). In this transformation, AgOAc together with dtbpy (4,4'-di-tert-butyl-2,2'-bipyridine) were the catalyst while $PhI(OTFA)_2$ and K_2CO_3 were utilized as the oxidant and base respectively. After a series of competition experiments, a mechanism involving a proton abstraction by Ag^{III} was proposed (Scheme 20). With the chelation of the electron-rich ligand, the electron-rich Ag^{I} was oxidized to Ag^{III} by $PhI(OTFA)_2$. Then deprotonation of $C(sp^3)$-H bond occurred through the concerted metallated deprotonation process with the attack of electrophilic Ag^{III} and the assist of $TFAO^-$. The followed reductive elimination produced the pyrrolidine and regenerated the Ag^{I}.



Scheme 18.



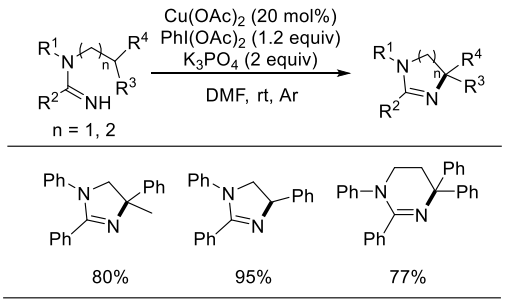
Scheme 19.



Scheme 20.

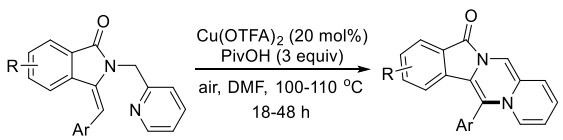
Aliphatic *N*-heterocycle construction through Cu and Fe-catalyzed C-H/N-H coupling.

Since the second-row and third-row transition metals are expensive and hard to obtain, first-row transition metals are gaining attention recently due to their lower cost and nontoxicity. Thereinto, the activity of copper catalysis was investigated in this field. Chiba reported a copper-catalyzed $C(sp^3)$-H amination with amidine motif to obtain dihydroimidazoles and tetrahydropyrimidines[20] (Scheme 21). $Cu(OAc)_2$ was used as the catalyst while $PhI(OAc)_2$ and K_3PO_4 were used as the oxidant and base respectively.

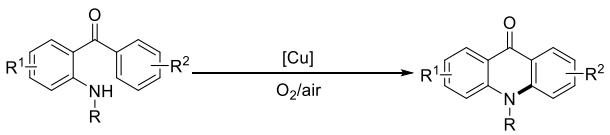


Scheme 21.

Cu-catalyzed $C(sp^2)$-H amination/amidation were also reported. In 2011, Fu reported an aerobic intramolecular alkene C-H amination using pyridine group as the N source and $Cu(OTFA)_2$ as the catalyst (Scheme 22)[21]. Two years later, Xu and Zhu[22], Deng[23] and Cheng[24] achieved the intramolecular amination of 2-amino-benzophenones to afford acridones in the presence of copper catalyst and air/O_2 (Scheme 23). The mechanism of this transformation remained unclear.



Scheme 22.

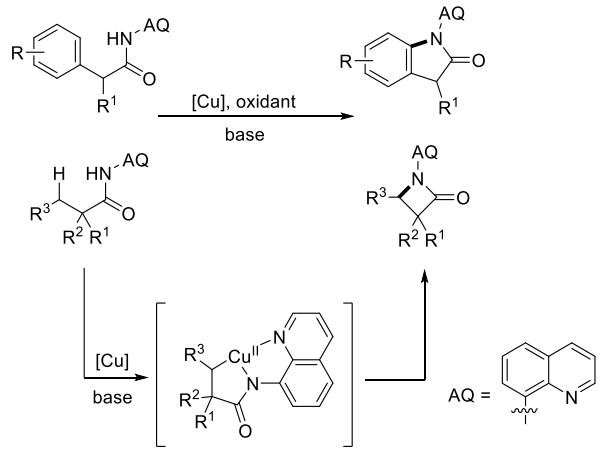


Xu and Zhu's condition:
CuTc (20 mol%), PPh_3 (20 mol%), PivOH (10 mol%), DMSO, 130 °C, O_2, 23-48 h
Deng's condition:
CuI (20 mol%), DMSO, 120 °C, air, 48 h
Cheng's condition:
CuI (1 mol%), bpy (1 mol%), DMAc, 140 °C, O_2, 12-24 h

Scheme 23.

In 2014, Kuninobu and Kanai's group and Ge's group reported Cu-catalyzed intramolecular amidation of $C(sp^3)$-H bonds at the same time[25]. Both reports utilized additional quinolone group to

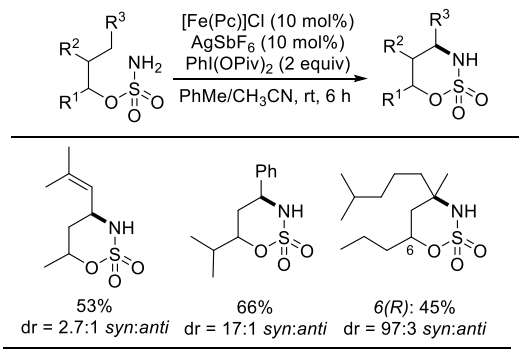
direct the C-H bond activation. Kuninobu and Kanai used $Cu(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant while CuCl and duroquinone were employed as catalyst and oxidant respectively in Ge' work (Scheme 24). Based on the use of bases in both article, a concerted metalation deprotonation type mechanism was proposed to explain the C-H bond activation.



Kuninobu and Kanai's condition:
$Cu(OAc)_2$ (20 mol%), Ag_2CO_3 (3 equiv), DCE, 140 °C, 24 h.
Ge's condition:
CuCl (20 mol%), duroquinone (1.5 equiv), $PhCO_2Na$ (1.5 equiv), xylene, air, 160 °C, 12-24 h.

Scheme 24.

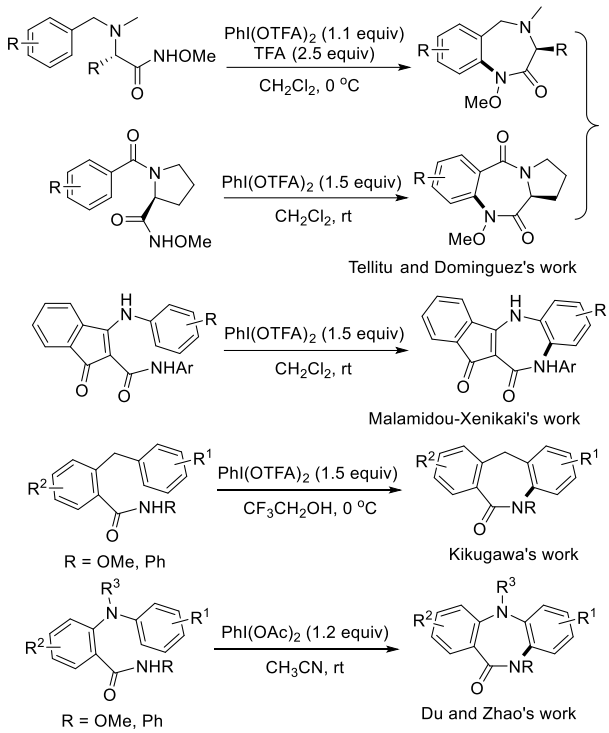
In 2012, the intramolecular C-H amidation was achieved through iron catalysis. Using nontoxic $[Fe^{III}Pc]Cl$ (Pc = phthalocyaninato) and $AgSbF_6$ as the catalyst and $PhI(OPiv)_2$ as the oxidant, an intramolecular oxidative coupling between sulfamate ester N-H bond and allylic C-H bond as well as benzylic and tertiary C-H bonds was realized by White and coworkers[26] (Scheme 25). The well-known [FePc]Cl-catalyzed aliphatic C-H bond activation was the key to realize the chemoselectivity of the reaction.



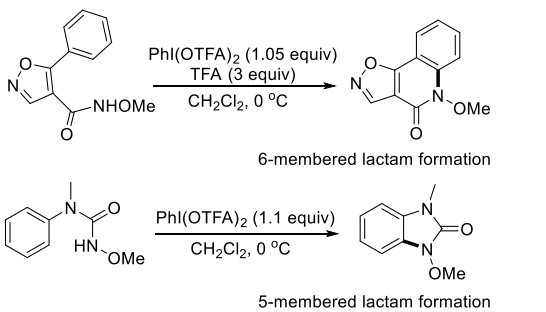
Scheme 25.

Aliphatic *N*-heterocycle construction through metal-free C-H/N-H coupling.

There were also works focus on the metal-free $C(sp^2)$-H amination/amidation. Tellitu and Dominguez[27], Malamidou-Xenikaki[28], Kikugawa[29], as well as Du and Zhao[30], reported a series of hypervalent iodine promoted amidation of $C(sp^2)$-H without the addition of transition metal since 2002 (Scheme 26). In these transformations, different 7-membered lactams were synthesized through similar intramolecular trap of *N*-acylnitrenium ions. This construction of 7-membered *N*-heterocycles was employed as the key step of the synthesis of the nature products[31]. Similarly, 6-membered[32] and 5-membered[33] lactams were also synthesized via the same protocol (Scheme 27).



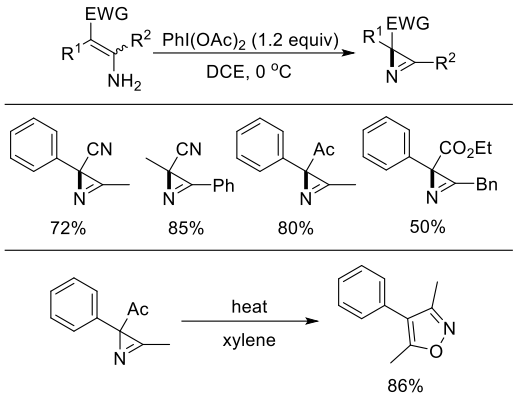
Scheme 26.



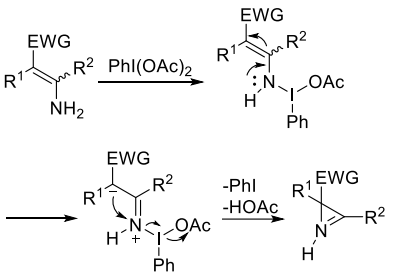
Scheme 27.

Azirins can also be synthesized via oxidative metal-free C-N bond formation. Various enamines were converted into azirins. Such azirins underwent isomerization to obtain isoxazoles easily via thermolysis when they were acetylated with the promotion of $PhI(OAc)_2$[34] (Scheme 28). A plausible mechanism was proposed (Scheme 29). Initially, nucleophilic substitution occurred between the enamine and $PhI(OAc)_2$ to give the intermediate bearing N-I bond. The following tautomerization would provide the charge-separated imine, which was stabilized by the electron-

withdrawing group. Then the carbanion attacked the nitrogen to give the product.



Scheme 28.

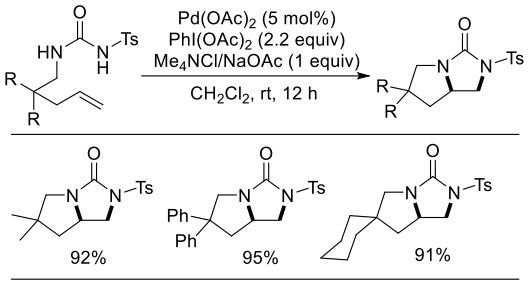


Scheme 29.

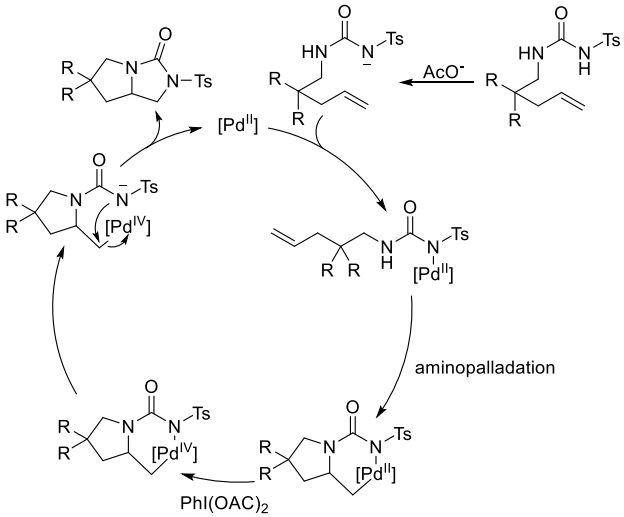
Aliphatic *N*-heterocycle construction via [3+2] annulation.

5-membered *N*-heterocycles are important motif of numerous compounds. One of the most popular method led to the direct construction of 5-membered *N*-heterocycles was the [3+2] cycloaddition which employed 1,3-dipoles and unsaturated bonds as the coupling reagents. However, to the best of our knowledge, 1,3-dipoles were always unstable, which limited its application. Therefore, the newly-developed oxidative annulation of relatively stable acyl and vinyl amines with unsaturated bonds were believed to be a good choice to improve the methodology of the *N*-containing [3+2] annulation[35].

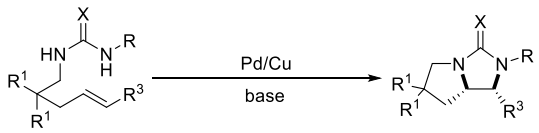
Although the early works focus on the intermolecular annulation in this area, an intramolecular cyclization of alkenes with ureas was reported to construct imidazolidinone[36] (Scheme 30). The reaction employed $Pd(OAc)_2$ as the catalyst, $PhI(OAc)_2$ as the oxidant and Me_4NCl/NaOAc as the additive. A mechanism involving a Pd^{IV} intermediate was given (Scheme 31). First, a base-mediated coordination of palladium to the amide bearing Ts group occured. Then aminopalladation took place and hence a 6-membered palladacycle formed followed by the oxidation of Pd^{II} to Pd^{IV}, which enhance the electrophilicity of the carbon adjacent to it. After that, a nucleophilic attack occurred between the other nitrogen and the electrophilic carbon to give the product. Then a series of similar reaction utilizing Pd/Cu or Pt/Cu co-catalysis was soon realized by Muñiz[37] (Scheme 32). Catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of Cu^{II} salts together with inorganic base was required to promote the reaction. Then they replace the oxidant from stoichiometric amount of Cu salts to O_2. In this case, $PtCl_2$ was employed as the catalyst, and the selectivity totally changed that C-O bond formation happened. In other words, only oxazolidinone, instead of imidazolidinone, was obtained under this condition[38] (Scheme 33). But the cause of this regioselectivity was still unclear.



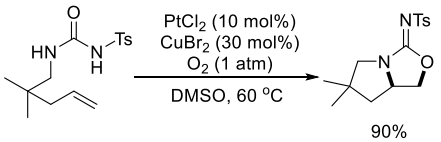
Scheme 30.



Scheme 31.

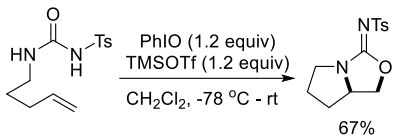


Scheme 32.

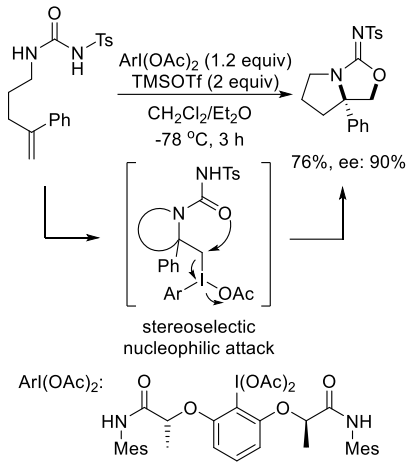


Scheme 33.

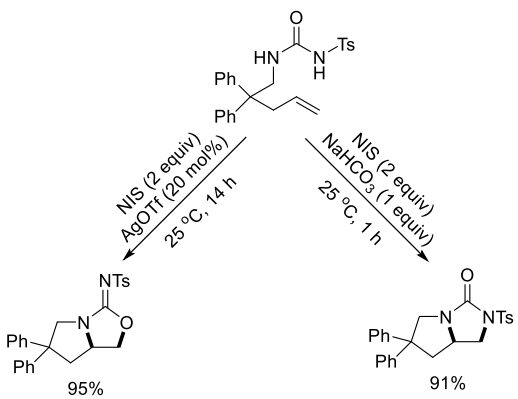
A metal-free condition using hypervalent iodine as the oxidant was also utilized to achieve the construction of oxazolidinone[39] (Scheme 34). Stoichiometric PhIO and TMSOTf were utilized to promote the reaction. When chial hypervalent iodine was utilized as the oxidant, this oxyamination proceed smoothly with high stereoselectivity[40], which may be ascribed to the stereoselectic nucleophilic attack of the oxygen to the hypervalent iodine intermediate (Scheme 35). Soon, this method became regulatable using NIS (*N*-iodosuccinimide) as the oxidant. When the inorganic base $NaHCO_3$ was introduced to the reaction, The oxazolidinone was the major product with the introduction of the inorganic base $NaHCO_3$ to the system while the formation ofimidazolidinone was favored when catalytic amount of AgOTf was added to the reaction[41] (Scheme 36).



Scheme 34.

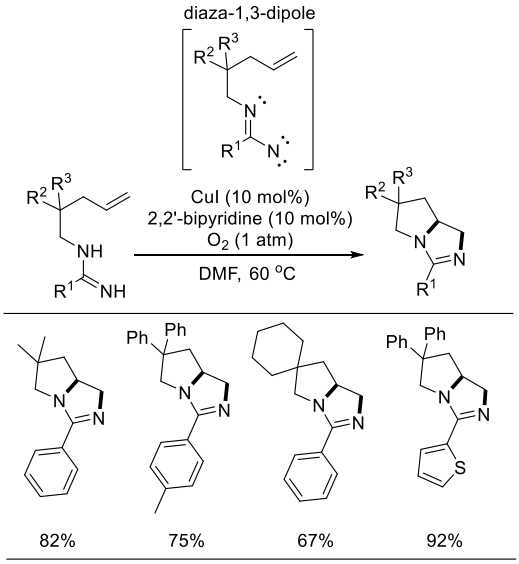


Scheme 35.



Scheme 36.

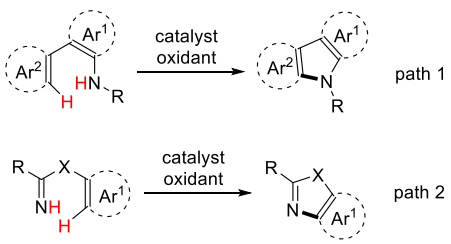
Cu/O_2 was also a powerful catalytic system in this area. Chiba reported an intramolecular [3+2] annulation of amidine bearing two N-H bonds with alkene to afford bicyclic amidine[42] (Scheme 37). In this transformation, CuI together with 2,2'-bipyridine were used as the catalyst and O_2 was used as the terminal oxidant. A diaza-1,3-dipole, which performed annulation with alkene, was believed to be involved in the mechanism.



Scheme 37.

Aromatic *N*-heterocycle construction via C-N bond formation

Generally, the dehydrogenative intramolecular C-N coupling to construct aromatic *N*-heterocycle followed two paths. The most common one is the coupling of C(sp^2)-H with N(sp^3)-H to obtain the pyrrole skeleton (Scheme 38, path 1). And the coupling of C(sp^2)-H with N(sp^2)-H is the other one (Scheme 38, path 2).

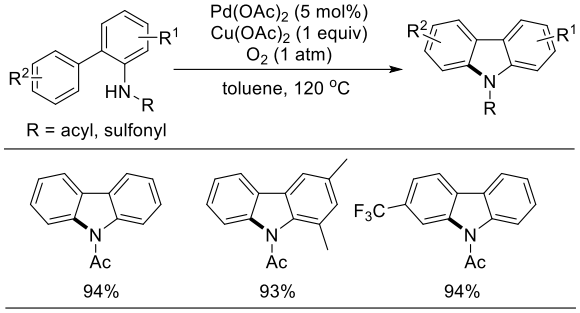


Scheme 38.

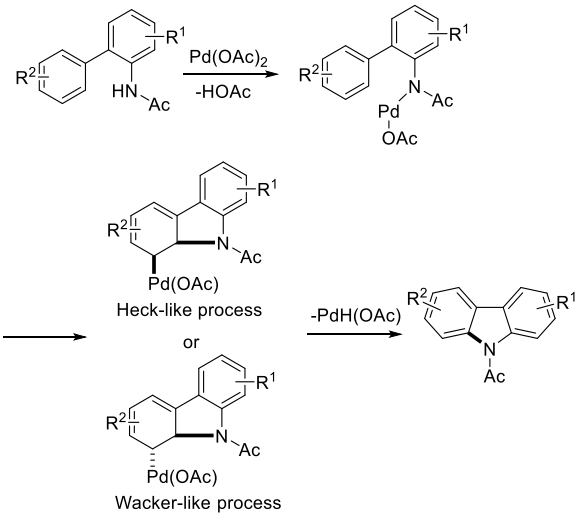
Aromatic *N*-heterocycle construction through C(sp^2)-H/N(sp^3)-H coupling.

In 2005, followed path 1, Buchwald reported an intramolecular C-H/N-H coupling of *N*-acyl/sulfonyl-2-aryl-anilines to construct *N*-acyl/sulfonyl carbazoles in the presence of catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of $Cu(OAc)_2$ under O_2 atmosphere at 120 °C (Scheme 39)[43]. The plausible pathway was proposed after mechanism study. The N-H bond activation took place firstly, followed by the Heck-like or Wacker-like process to form the Pd-C species, which underwent a β-hydrogen elimination to provide the product (Scheme 40).

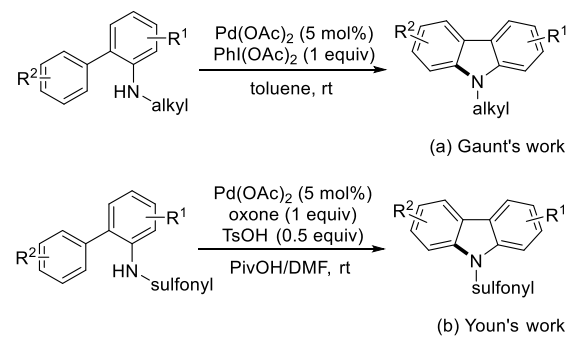
Then much efforts were made to improve this type of methodology. Gaunt replaced the acetyl group by alkyl groups, thus *N*-alkyl carbazoles were obtained using $PhI(OAc)_2$ as the oxidant[44] [Scheme 41(a)]. Youn employed oxone as the oxidant and *N*-sulfonyl carbazoles were the products[45] [Scheme 41(b)]. Both reactions were carried out under room temperature. This milder condition may be ascribe to the easier C-N reductive elimination of the electron-deficient Pd^{IV}, which was oxidized by the strong oxidant $PhI(OAc)_2$ or oxone from Pd^{II}.



Scheme 39.

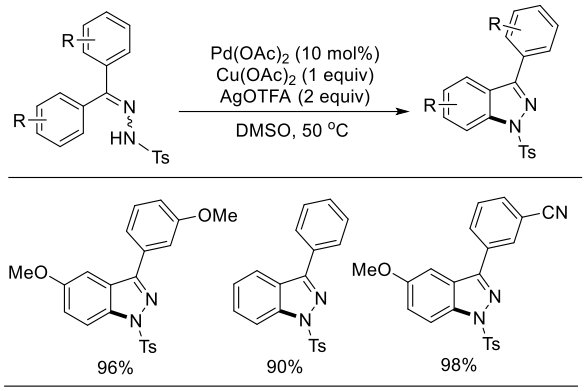


Scheme 40.



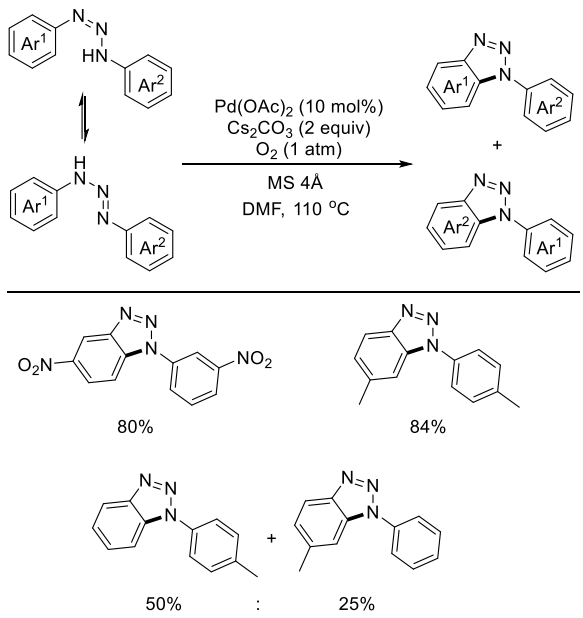
Scheme 41.

Then Inamoto and Hiroya developed an interesting intramolecular C-N bond formation between aryl group and hydrazone group. A variety of indazoles were prepared through this path using a combination of catalytic amount of $Pd(OAc)_2$ and stoichiometric amount of $Cu(OAc)_2$ and AgOTFA[46] (Scheme 42). The C-N bond formation only took place between the electron-rich aryl and the N-H bond. However, poor selectivity was observed when both arenes were electron-rich.



Scheme 42.

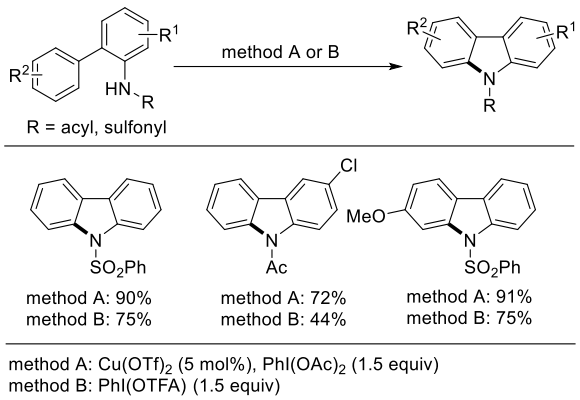
Aryl triazenes can also perform this type of reaction under Pd catalysis. Punniyamurthy reported the intramolecular C-H/N-H coupling of aryl triazenes to obtain benzotriazoles. The reaction was carried out using $Pd(OAc)_2$ as the catalyst and Cs_2CO_3 as the base under O_2 atmosphere[47] (Scheme 43). When the two arenes were distinguishable (for instance, Ar^1 = Ph and Ar^2 = 4-methylPh), a mixture was obtained since the isomerization of the triazene took place easily under standard condition.



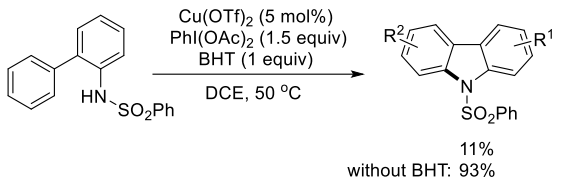
Scheme 43.

Not only Pd, but also Cu catalyst realized this type of reaction. Acyl and sulfonyl carbazoles were again obtained in the presence of $Cu(OTf)_2$ as the catalyst, $PhI(OAc)_2$ as the oxidant[48] (Scheme 44). It was noteworthy that the yield lowered slightly with the

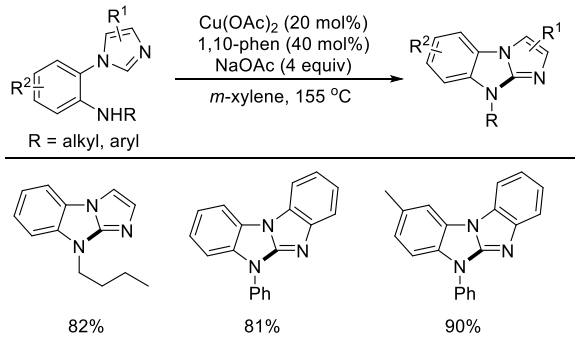
absence of copper. Since the reaction was inhibited by BHT (2,6-di-tert-butyl-4-methylphenol), a general radical scavenger, a radical process may be involved in this transformation (Scheme 45). Then the Cu-catalyzed system extended to the intramolecular coupling between amine and electron-deficient heterocycle[49] (Scheme 46). Thus the direct synthesis of imidazobenzimidazoles was realized using 2-imidazolyl-anilines as the substrates with the combination of $Cu(OAc)_2$ and 1,10-phen as the catalyst and NaOAc as the base.



Scheme 44.

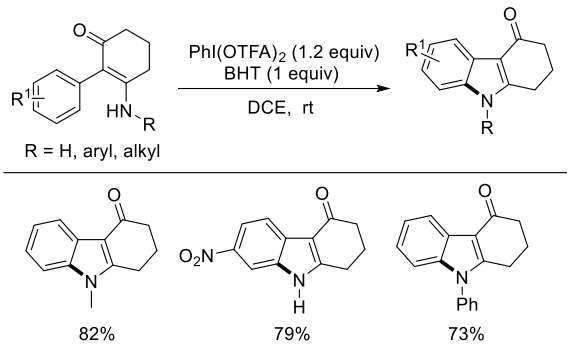


Scheme 45.



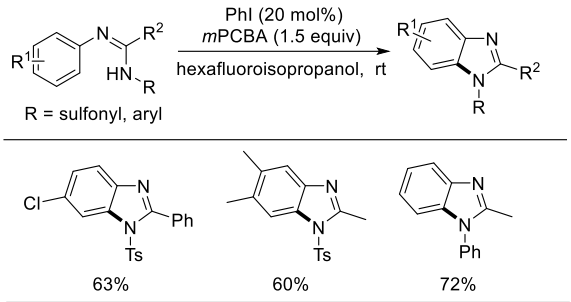
Scheme 46.

Metal-free protocols were also utilized to deal with this type of methodology. A $PhI(OAc)_2$ mediated 3-acetylindoles synthesis starting from 2-aryl enaminones was reported[50] (Scheme 47). The unsubstituted amine, as well as *N*-aryl and *N*-alkyl amine, underwent the transformation smoothly.



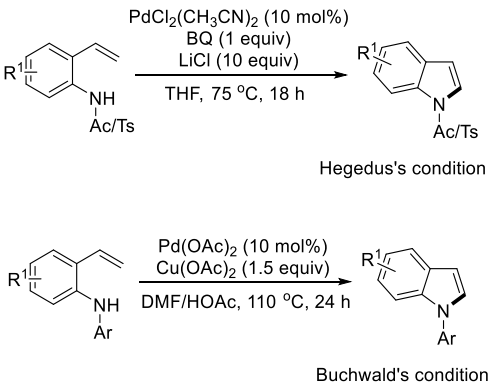
Scheme 47.

Soon, the metal-free intramolecular cyclization of amidine to afford benzimidazole was also reported. The *in situ* generated I^{III} species originated from the oxidation of phenyl iodide by *m*CPBA (*meta*-chloroperoxybenzoic acid) were believed to be the active catalytic species[51] (Scheme 48).



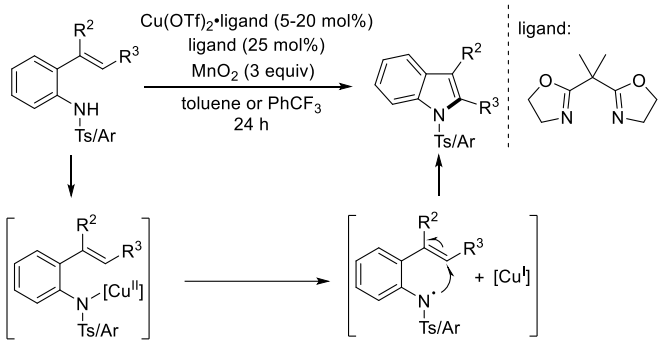
Scheme 48.

The alkenes can also act as coupling partner with N-H bonds instead of arenes. Hegedus developed this type of reaction in 1980s. N-acyl and N-sulfonyl styryl anilines underwent intramolecular cyclization to give corresponding indoles under Pd-catalysis (Scheme 49, Hegedus's condition)[52]. Then in 2010, this methodology was modified by switching the oxidant from BQ to $Cu(OAc)_2$ (Scheme 49, Buchwald's condition)[53]. Unlike the previous reports, the protection of styryl anilines was unnecessary that simple N-aryl indoles can be prepared using this transformation.



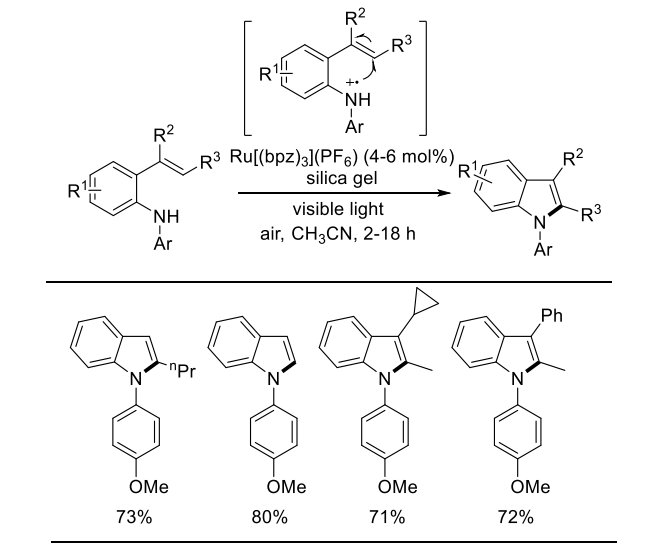
Scheme 49.

Copper is also suitable promoter of this type of reaction. In 2013, Chemler described the same reaction using Cu catalyst. A bis(oxazoline)-ligand-chelated Cu catalyst exhibited good activity to catalyze the intramolecular C-N bond formation using MnO_2 as the oxidant (Scheme 50)[54]. Both *N*-Ts- and *N*-Ar styryl anilines were tolerated in this transformation. A *N*-centered radical addition might be involved in this transformation. Soon, Chemler's group improved this methodology that TEMPO and O_2 was employed as the co-oxidant and terminal oxidant respectively to replace the previous MnO_2[55].



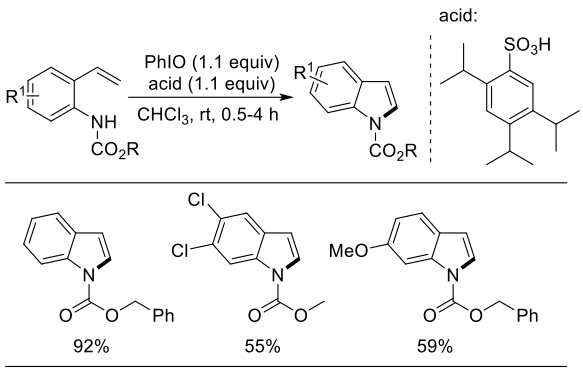
Scheme 50.

In 2012, a similar intramolecular alkenyl C-H/N-H coupling was achieved by Zhang under visible-light-mediated condition. In this case, indoles were obtained starting from styryl anilines using $[Ru(bpz)_3](PF_6)$ (bpz = 2,2'-bipyrazine) as the photocatalyst under air atmosphere (Scheme 51)[56]. The addition of silica gel was also crucial that it might adsorb oxygen and provide protons. The radical addition of the nitrogen-centered radical cation to alkene was believed to be the key process to form C-N bond.

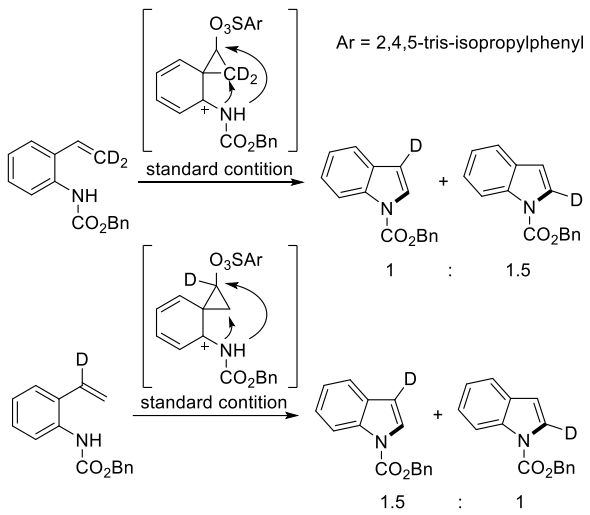


Scheme 51.

Moreover, metal-free synthesis of indoles from styryl anilines was also realized by Muñiz using stoichiometric amount of PhIO and 2,4,5-tris-isopropylbenzene sulfonic acid (Scheme 52)[57]. The mechanism of this reaction is complicated. Based on the results of deuterated experiments, a cyclopropane derivative was proposed to be the key intermediate of the reaction (Scheme 53).



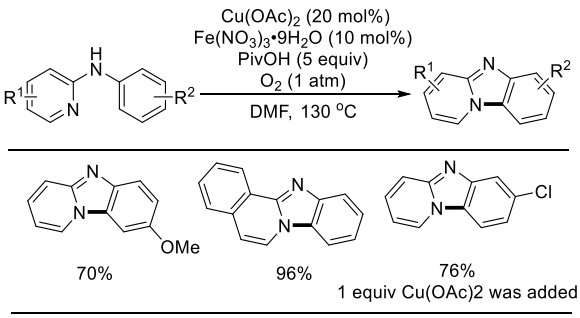
Scheme 52.



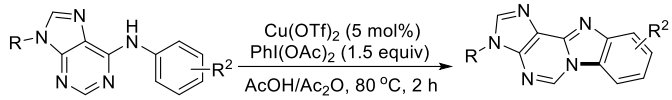
Scheme 53.

Another methodology utilized pyridine group not only as a directing group to promote the C-H activation, but also as a nucleophile to achieve the C-N bond formation. The beginning work was done by Zhang and Zhu, they employed *N*-aryl-2-aminopyridines to perform intramolecular cyclization to obtain pyrido[1,2-α]benzimidazoles[58] (Scheme 54). The combination of $Cu(OAc)_2$ and $Fe(NO_3)_3 \cdot 9H_2O$ was found to be the best choice to catalyze the reaction with O_2 as the oxidant and PivOH as the additive. The unexpected cooperative action of iron salts with cupper catalyst was observed. Then, this methodology was used to construct multifused-ring purine compounds[59] (Scheme 55). In this protocol, the reaction was carried out in acidic condition using Ac_2O/HOAc as the solvent and the common copper/$PhI(OAc)_2$ system was utilized again. Hypervalent iodine reagent was then found a good promoter for this reaction, thus a metal free process led to the construction of pyrido[1,2-α]benzimidazoles was realized by Zhu[60] (Scheme 56, Zhu's

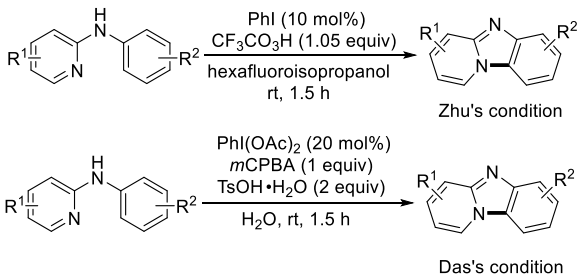
condition). Then another improvement was made by Das that they employed water as the solvent[61] (Scheme 56, Das's condition).



Scheme 54.



Scheme 55.

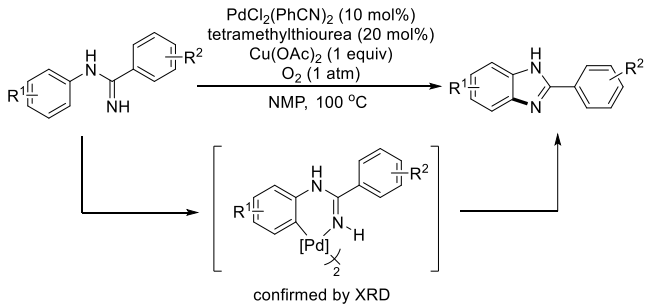


Scheme 56.

Aromatic *N*-heterocycle construction through C(sp^2)-H/N(sp^2)-H coupling.

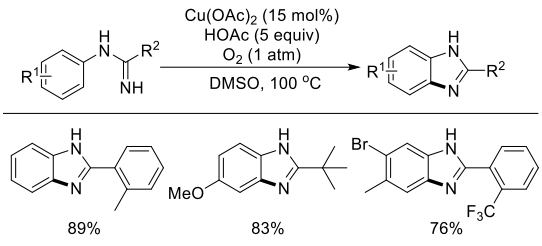
The intramolecular aromatic *N*-heterocycle construction via the coupling of N(sp^2)-H with C-H bonds (Scheme 38, path 2) was not so popular since the imine was relatively unstable.

The way to realized this type of methodology was to employ stable amidines bearing N(sp^2)-H as the substrates. In 2009, Shi achieved the preparation of benzimidazoles started from amidines. In this protocol, $PdCl_2(PhCN)_2$ together with tetramethylthiourea was selected to catalyze the reaction under O_2 atmosphere in the present of stoichiometric amount of $Cu(OAc)_2$[62] (Scheme 57). The confirmed 6-membered palladacycle generated from the *N*-directed C-H bond activation was the intermediate of the reaction. The role of the catalytic amount of tetramethylthiourea was to decompose the relatively inert dimeric palladacycle.



Scheme 57.

This type of reaction was achieved by Cu catalysis as well. With $Cu(OAc)_2$ as the catalyst, HOAc as the additive and O_2 as the oxidant, both 2-aryl and 2-alkyl benzimidazoles were synthesized in high yield[63] (Scheme 58).



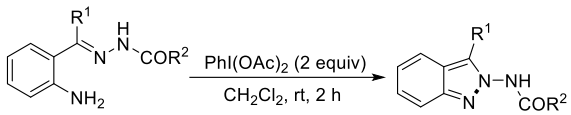
Scheme 58.

N-heterocycle construction via oxidative intramolecular N-N, O-N and S-N bond formation

Beside C-H bonds, hetero-H bonds are also good coupling partner of N-H bonds since the activations of hetero-H bonds are always facile. Moreover, there is a series of hererocycles containing N-N, O-N, S-N skeletons exhibit bioactivities. Thus the oxidative intramolecular N-hetero bond formation are becoming more and more crucial.

N-heterocycle construction via N-N bond formation

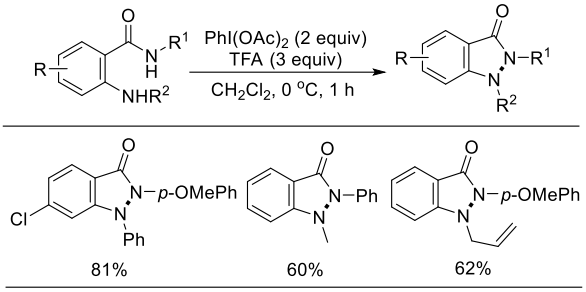
The first report of intramolecular N-H/N-H coupling was published in 1996. *o*-amino ketone acylhydrazines underwent oxidative N-N bond formation smoothly to obtained 2-acylamino indazoles under a metal-free condition that utilizing $PhI(OAc)_2$ as the oxidant[64] (Scheme 59).



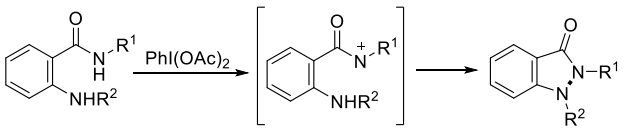
Scheme 59.

In 2006, Dominguez and Tellitu reported the synthesis of indazolones started from 2-aminobenzamides. In this transformation, metal-free condition utilizing stoichiometric $PhI(OAc)_2$ and TFA was employed[65] (Scheme 60). A two-step mechanism was proposed. The *N*-acylnitrenium ions generated

from the oxidation of benzamides was then trapped by the intramolecular nucleophilic attack of amine (Scheme 61).

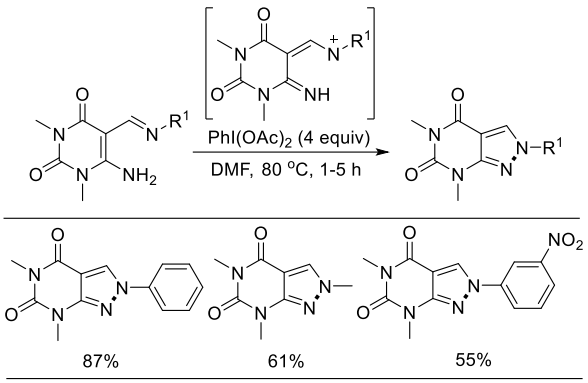


Scheme 60.



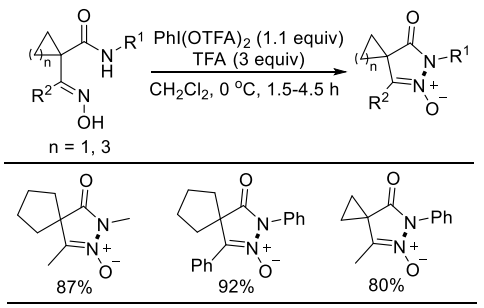
Scheme 61.

Soon, 5-imino-6-aminouracil derivatives were employed to perform N-N bond formation to give pyrazolo[3,4-d]pyrimidin-4-ones using $PhI(OAc)_2$ again as the oxidant[66] (Scheme 62). A plausible mechanism involving the nitrenium ion as the intermediate was discussed.

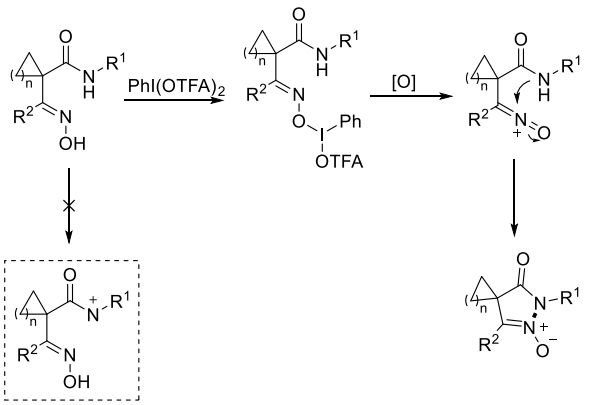


Scheme 62.

After that, the combination of $PhI(OTFA)_2$ and TFA was utilized again to achieve the synthesis of pyrazolin-5-one-*N*-oxides via the intramolecular N-N bond formation of 1-carbamoyl-1-oximylcycloalkanes[67] (Scheme 63). Although the condition was similar to the previous methodology, the *N*-acylnitrenium ions were excluded from the mechanism. In this case, the starting material oximylcycloalkane reacted with $PhI(OAc)_2$ to afford *N*-oxonitrenium ion, which underwent a nucleophilic attack to give the product (Scheme 64).

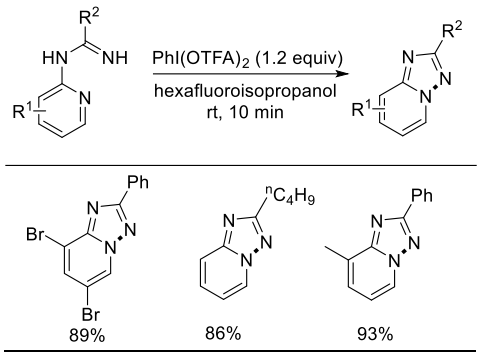


Scheme 63.



Scheme 64.

In 2014, Du and Zhao expanded the topic of intramolecular N-N bond formation. The report described the intramolecular cyclization of *N*-(pyridin-2-yl)-imidamides to give corresponding 1,2,4-triazolo[1,5-a]pyridines[68] (Scheme 65).

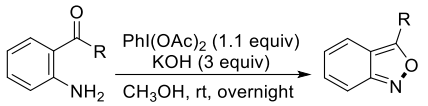


Scheme 65.

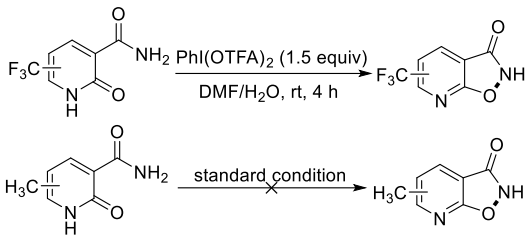
***N*-heterocycle construction via N-O bond formation**

The early intramolecular ring-closing reaction via N-O bond formation was reported by Prakash and Varma in 1997. *o*-acylanilines were converted into benzisoxazoles in the presence of stoichiometric $PhI(OAc)_2$ and KOH[69] (Scheme 66). Soon, similar to the N-N bond formation of 2-aminobenzamides, 3-carboxaide-2-oxo pyridines also underwent the C-O bond formation smoothly using $PhI(OAc)_2$ as the oxidant[65c] (Scheme 67). It is noteworthy that CF_3 group was indispensable for the transformation that no product was detected when the arene was

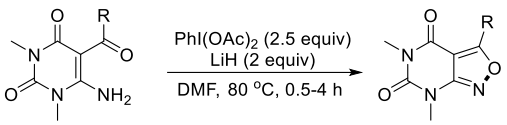
methylated instead of trifluoromethylated. In addition, similar to the N-N formation of 5-imino-6-aminouracil derivatives, 5-acyl-6-aminouracils can also be utilized to perform N-O bond formation[66a] (Scheme 68). This time, except the oxidant $PdI(OAc)_2$, the strong base LiH was required to promote the reaction since it can enhance the nucleophilicity of the amine group.



Scheme 66.

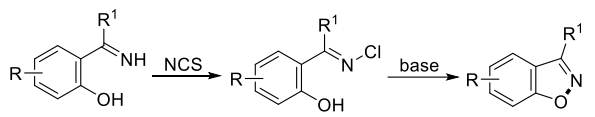


Scheme 67.

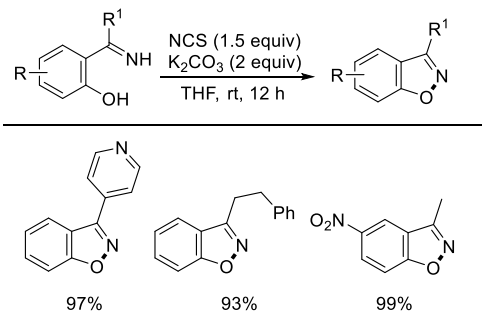


Scheme 68.

In 2011, Li reported the synthesis of benzisoxazoles started from *o*-hydroxyaryl ketimines through an N-H chlorination/substitution process (Scheme 69). After the condition optimizing, NCS and K_2CO_3 were chosen to be chlorination reagent and base respectively, and various 3-substituted benzoisoxazoles were prepared under the optimized condition[70] (Scheme 70).



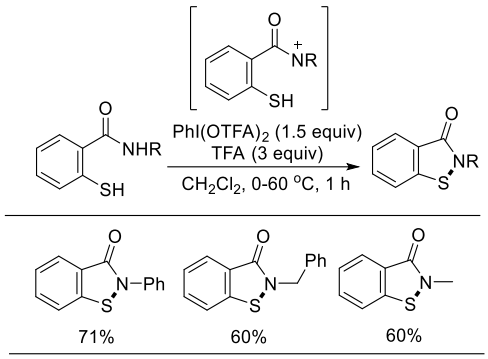
Scheme 69.



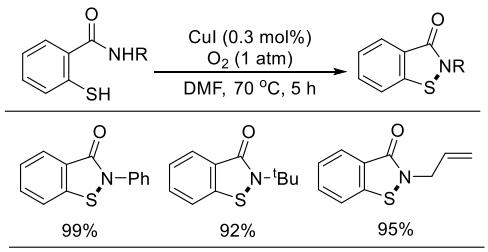
Scheme 70.

***N*-heterocycle construction via N-S bond formation**

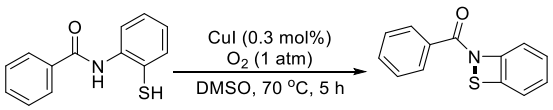
Like the N-N and N-O bond formation, construction of heterocycles via intramolecular N-S bond formation was also achieved. In 2006, *o*-thiol-benzamides were reported to perform N-S bond formation to give corresponding benzisothiazolones[71] (Scheme 71). The combination of $PhI(OTFA)_2$ and TFA led to the realization of the reaction and the well-established *N*-acylnitrenium ion was believed to be the intermediate. After that, the widely-used Cu/O_2 system was utilized to achieve the same reaction with DMF as the solvent[72] (Scheme 72). It was interesting that when *N*-acyl-*o*-thiol-aniline was employed as the substrate, 4-membered heterocyclic product was also obtained (Scheme 73).



Scheme 71.



Scheme 72.



Scheme 73.

Conclusions

The oxidative C-N and X-N bond formation through dehydrogenative pathway have been widely investigated during the past several years. These methods were also utilized to achieve the intramolecular cyclization, especially for the construction of *N*-heterocycles. This feature article provides a summary of this topic. Although more and more novel strategies are applied in this field, there are still many problems remained. The types of catalysts and oxidant remain rare that Pd, Cu and hypervalent iodine are chosen in most cases. The catalytic efficiency is still low that TON/TOF value is seldom discussed. Moreover, the mechanistic understanding of the reaction also

remain lacking. Therefore, efforts should be paid to overcome the problems as usual.

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Notes and references

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