Chem Soc Rev

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Journal:	*Chemical Society Reviews*
Manuscript ID	CS-SYN-07-2015-000534.R2
Article Type:	Tutorial Review
Date Submitted by the Author:	15-Dec-2015
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Journal Name

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Transition-metal catalysed C-N bond activation

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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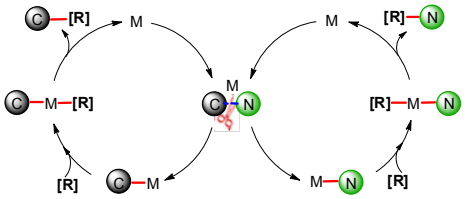
Transition-metal catalysed C-N bond activation has attracted much attention and become one of the most promising bond disconnection and formation strategies that encompass a broad spectrum of applications in many reactions. In this tutorial review, efficient strategies for catalytic cleavage of C(sp)-N, C(sp^2)-N and C(sp^3)-N bond and their applications in new C-C and C-N bond formation reactions are summarized.

Key learning points
(1) The advantages of the synthetic strategy *via* transition-metal catalysed C-N bond activation.
(2) The typical methods of the C-N bond activation *via* transition-metal catalysis.
(3) The general mechanisms.
(4) The potential applications of C-N bond activation in organic synthesis.
(5) The challenge and future perspective.

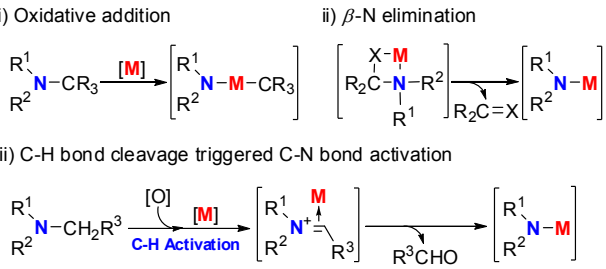
1. Introduction

Transition-metal catalysed C-N bond formation reaction has been widely explored and emerged as a powerful tool for synthesis of amines, amides and some other nitrogen-containing molecules, in which the key C-M and N-M species were typically involved in the catalytic cycle.[1] On the contrary, the cleavage of C-N bond with a transition-metal would also generate C-M and N-M or C-M-N species.[2, 3, 4] In principle, these active nucleophiles could be reacted with other coupling partners to form new C-C and C-N bonds under suitable reaction conditions (Scheme 1). Appealingly, compared to other C-X bond activation methods, two useful nucleophiles could be generated *via* C-N bond activation and both of them might be used as coupling partners for further transformation under transition-metal catalysis. Furthermore, the abundant sources of C-N bond increase the appeal of this strategy and pave the way for large-scale applications. However, the inert nature of unreactive C-N bond and requirement for site selective functionalization make such a process extremely challenging.

Analogous to the most common transformations *via* C–X bond activation, the key to success of the C–N addition reactions was facile occurrence of the C–N bond metalation step, in which an inert C–N bond was converted into more active C–M or N-M species *via* transition-metal catalysis. Typically, there are three general mechanisms for transition-metal-mediated C-N bond metalation: i) oxidative addition with low-valent late transition metals, ii) *β*-N elimination; iii) C-H bond cleavage triggered C-N bond activation (Scheme 2).



Scheme 1 New transformations *via* C-N bond activation.



Scheme 2 Three general mechanisms for transition-metal–mediated C-N bond metalation.

Indeed, with the rapid development of organometallic chemistry, impressive progress has been achieved in the area of transition-metal catalysed new reactions *via* C-N bond activation.[5] In this regard, compared with the well-developed C-H activation reactions, the analogous coupling reactions *via*

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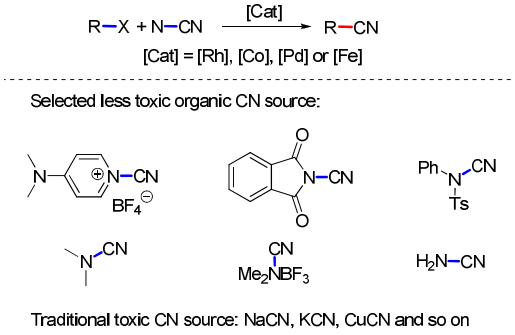
C-N bond activation are still in the development stage. However, two kinds of useful nucleophiles are generated in the C-N bond activation, which enables such reactions more powerful in the construction of functionalized complex molecules. Thereby, more and more attentions have been paying to this research topic.

This tutorial review is to summarize the significant progress in transition-metal catalysed activation reaction and will be classified by the type of C-N bonds (according to the hybridization of carbon atom bond to the nitrogen atom). All C-N bond activation reactions described within this article deal with the reactions involved the formation of C-M or N-M reactive species *via* C-N bond activation.

2 Activation of C(sp)-N bond

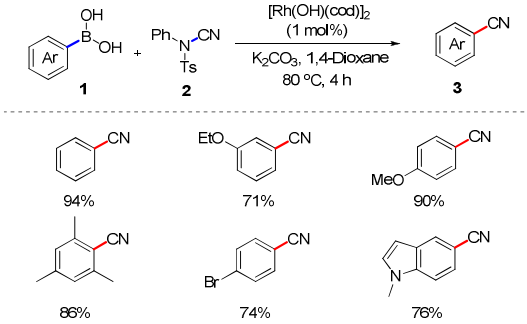
The length of N-CN bond is between that of a normal single C-N bond (1.47Å) and a C=N bond (1.27Å), which indicates that the N-CN is stronger than other single C-N bond. Thus, the cleavage of C(sp)-N bond is more difficult than other single C-N bond. However, the usable CN moiety contained in the "N-CN" compounds stimulates people to develop effective strategy to accomplish new cyanation reactions *via* activation of C(sp)-N bond instead of the traditional methods of preparing nitriles. As such, a number of transition-metal catalysed cyanations were successfully established with "N-CN" as organic cyanation reagents in the past five years (Scheme 3).



Scheme 3 Transition-metal catalysed cyanations with organic N-CN cyanation reagents.

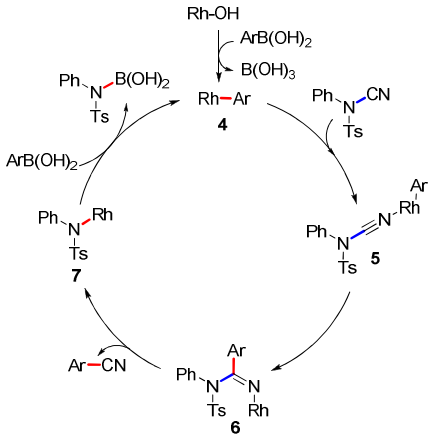
The first breakthrough for activation of "N-CN" bond came from the Nakazawa's seminal discovery in 2009.[6] He found that the inert C-N bond of Me_2N-CN could be cleaved by a silyl-iron complex under photolysis. Wherein an *N*-silylated η^2-amidino iron complex, which was an important intermediate in the C(sp)-N bond cleavage of cyanamide, was isolated and characterized by X-ray crystal structure analysis. Based on these findings, a catalytic coupling reaction of Et_3SiH and Me_2NCN was established *via* C-N bond activation with methyl molybdenum complex as a catalyst. Although only lower catalytic turnover number (TON) could be obtained, this pioneer work paved a way for the C(sp)-N activation in synthetic chemistry.

The first efficient catalytic cyanation *via* N-CN bond activation was developed by Beller and co-workers.[7] With $[Rh(OH)(cod)]_2$ as a catalyst (Scheme 4), the C-N bond of *N*-cyano-*N*-phenyl-p-toluenesulfonamide (NCTS) **2** could be efficiently cleaved and subsequently the CN moiety was coupled with organoboronic acids. Under the optimized conditions, both aromatic and vinyl nitriles could be produced in moderate to excellent yields.



Scheme 4 Rhodium-catalysed cyanation of aryl boronic acids.

On the basis of previous reports on the rhodium-catalysed reaction of aryl boronic acids, a plausible mechanism of the reaction was proposed. Firstly, transmetalation of an aryl boronic acid with the rhodium species would generate the aryl rhodium species **4**, which coordinates with NCTS to form intermediate **5**. Secondly, intermediate **6** would be generated by migration of aryl motif. Thirdly, elimination of intermediate **6** produces the desired product along with the reactive rhodium species **7**. Finally, transmetalation offers the aryl rhodium species **4** to complete the catalytic cycle (Scheme 5).



Scheme 5 Proposed mechanism for rhodium-catalysed cyanation of aryl boronic acids.

In 2013, a catalytic C-H cyanation reaction of arenes with NCTS was developed by Fu and co-workers.[8] $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ was identified as an effective catalyst for the cyanation reaction, providing the desired products in high yields. For facilitating the C-H activation, oxime, pyridine or pyrazole was employed as a directing group. Moreover,

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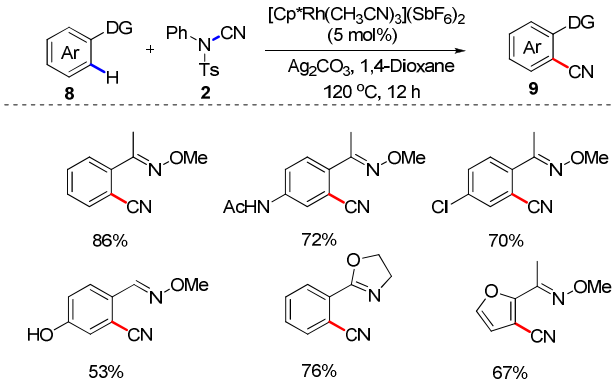
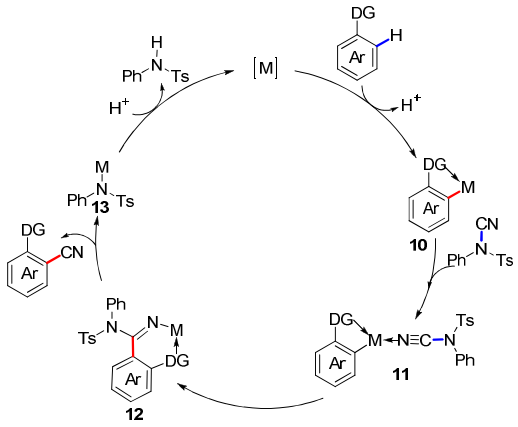
heteroaromatic rings, including furans, thiophenes, pyrroles and indole derivatives, were applicable in the cyanation reaction with oxime as a directing group (Scheme 6).



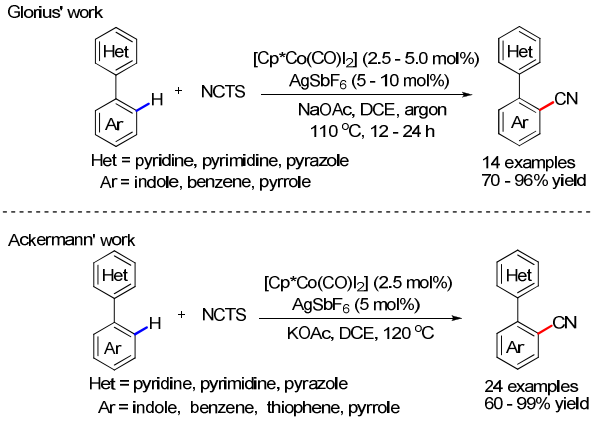
Scheme 6 Rhodium-catalysed cyanation of arenes.

The mechanism of this cyanation reaction was investigated. Intermolecular kinetic isotope effect (KIE) experiment (k_H/k_D = 3) indicated that C-H bond cleavage should be involved in the rate-limiting step of the transformation. Based on the results, the mechanism including the following steps was proposed by the authors: (i) C-H metalation of substrate to generate intermediate **10**, (ii) coordination of NCTS with the metal complex **10** to give **11**, (iii) insertion of NCTS to afford intermediate **12**, and (iv) *β*-N elimination and protonation to offer the desired product together with the metal catalyst (Scheme 7).



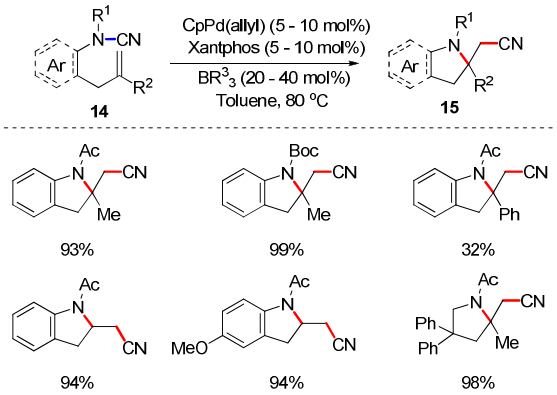
Scheme 7 Proposed mechanism for transition-metal catalysed cyanation.

Soon after, with pyridine, pyrazine or pyrimidine as a directing group, a broad range of substituted aryls were employed in the C-H cyanation with NCTS by Glorius[9] and Ackermann[10] with cobalt complexes as catalysts (Scheme 8).



Scheme 8 Transition-metal catalysed cyanation.

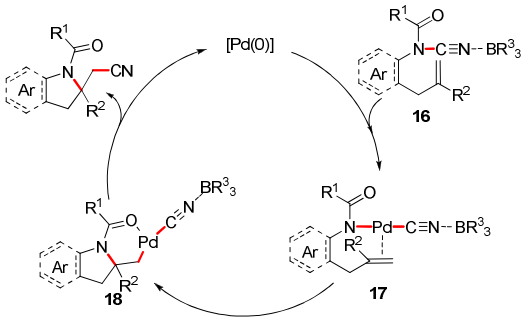
There is no doubt that the cyanation *via* C-N bond activation of NCTS has become a promising method to prepare nitriles. However, the cyanation was inherently restricted to the limited CN resources and low atom economy due to the waste of "N-moiety" which formed by activation of NCTS or analogous CN sources. To address these limitations, the intramolecular aminocyanation of alkenes through the cleavage of N-CN bond was realized by Nakao and co-workers.[4] CpPd(allyl)/Xantphos was identified as the catalytic precursor in the reaction. Under the optimum conditions, a range of substituted indolines and pyrrolidines with cyano functionalities are readily obtained. This transformation serves as an ideal protocol to prepare directly *β*-aminonitriles, which function as synthetic precursors for highly important building blocks such as *β*-amino acids and 1, 3-diamines. It was noteworthy that the oxidative addition could not proceed at all in the absence of BR_3 under the other identical reaction conditions (Scheme 9).



Scheme 9 Palladium-catalysed intramolecular aminocyanation of alkenes.

To gain insight into the mechanism of this transformation, a stoichiometric reaction of Ph-N(Ac)–CN, $Pd(PPh_3)_4$, and BPh_3 in benzene at 80 °C was conducted. Gratifyingly, the oxidative adduct was prepared and characterized by NMR spectroscopy and X-ray crystallography. On the basis of the result, a plausible mechanism was given in Scheme 10. The reaction was initiated by oxidative addition of the N–CN bond of **16**, which was coordinated to the

boron Lewis acid catalyst through a cyano group, to a Pd(0)–Xantphos complex. *Syn*-aminopalladation and subsequent reductive elimination generated the desired product together with the active catalyst.



Scheme 10 Proposed mechanism for palladium-catalysed intramolecular aminacyanation of alkenes.

3. Activation of C(sp^2)-N bond

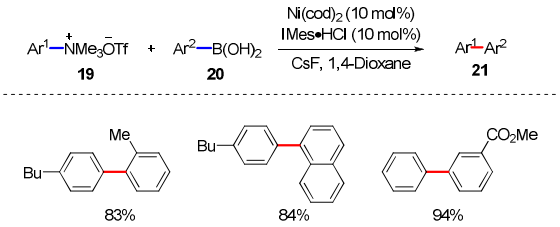
In the past two decades, the activation of C(sp^2)-N bond has become flourishing to afford biaryls, borylation products and ethylene derivatives which are recognized as fundamental structural motifs in myriad of natural products, pharmaceuticals and agrochemicals. In this part, the recent achievements of the activation of C(sp^2)-N bond and the applications in organic synthesis will be discussed.

3.1 Activation of aryl C(sp^2)-N bond

3.1.1 C(sp^2)-N bond in arylammonium salt Aromatic amines are cheap, stable and easily available, which could be potentially used as coupling partners for transition-metal catalysed cross-coupling reactions. However, due to the high bond energy, these amines could not be employed directly as electrophilic partners. One attractive approach to circumvent this problem is transformation of simple arylamines to arylammonium salts.

In 1988, the first nickel-catalysed cross-coupling reaction of aryltrimethylammonium iodides with Grignard reagents *via* C-N bond activation was documented by Wenkert and co-workers.[11] In spite of the limited substrate scope and inherent low reaction efficiency, this pioneering work firstly demonstrated that the C-N bond of arylammonium salt could be cleaved *via* oxidative addition of the low-valent metal to the C-N single bond. Encouraged by this seminal work, other groups popularized this strategy and developed a variety of transition-metal catalysed cross-coupling reactions with arylammonium salts as coupling partners.

For example, a nickel-catalysed Suzuki-type cross-coupling reaction of aryltrimethylammonium triflates with aryl boronic acids was developed by MacMillan and co-workers in 2003.[12] In their work, the coupling partner was extended to the phenylboronic acid, but only a trace amount of cross-coupling product was observed in the presence of Wenkert's $Ni(dppp)Cl_2$. Fortunately, once replacing the $Ni(dppp)Cl_2$ with $Ni(cod)_2$/IMes·HCl, the reactivity was dramatically increased and a wide range of biaryls were obtained with CsF served as a base in excellent yields (Scheme 11).

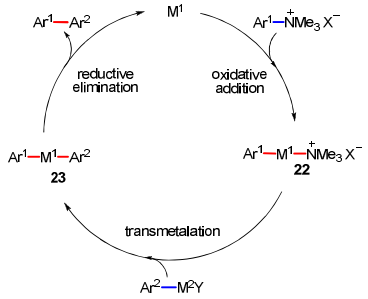


Scheme 11 Nickel-catalysed cross-coupling reaction of aryltrimethylammonium triflates with aryl boronic acids.

Subsequently, with the same C-N bond cleavage strategy, a nickel-catalysed cross-coupling reaction of organozinc reagents with aryltrimethylammonium iodide salts was realized by Wang and Xie.[13] Different from MacMillan's study, PCy_3 was identified as effective ligand to provide the desired coupling products in good to excellent yields. Both the electron-deficient and -rich aryltrimethylammonium iodide salts were applicable to give the desired products.

Other than the aforementioned nickel catalysts, palladium catalysts were also capable of promoting the cross-coupling of arylammonium salts with aryl Grignard reagents. In 2010, Reeves and co-workers found that $Pd(PPh_3)_2Cl_2$ could efficiently catalyse the reaction of aryltrimethylammonium triflates or tetrafluoroborates with aryl Grignard reagents.[14] Notably, good to excellent yields were achieved with various aryltrimethylammonium triflates, whatever electron-donating or -withdrawing substituents were attached on the aryl ring.

The general mechanism for these reactions is shown in Scheme 12, which includes: (i) oxidative addition of aryltrimethylammonium salt to the low-valent metal to cleave the C-N bond, generating species **22**, (ii) transmetalation with organometallic compound, and (iii) reductive elimination of complex **23** to give the desired products.



Scheme 12 Proposed mechanism for cross-coupling.

3.1.2 C(sp^2)-N bond in aromatic amine Several aforementioned examples have been established, in which highly active arylammonium salts were employed to achieve C(sp^2)-N bond activation. Although all of them are powerful methods for utilizing the aromatic amines as coupling partners in cross-coupling reactions, these methods are suffered from the pre-activation of aniline derivatives. Therefore, the development of direct activation of neutral C(sp^2)-N bond in aromatic amine is highly desirable.

As early as 1996, the direct activation of C-N bond of aromatic amines *via* oxidative addition with a Ta-complex was originally reported by Wolczanski and co-workers.[15] In 2007, a

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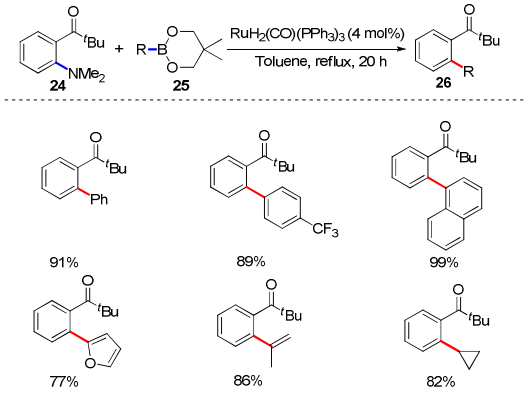
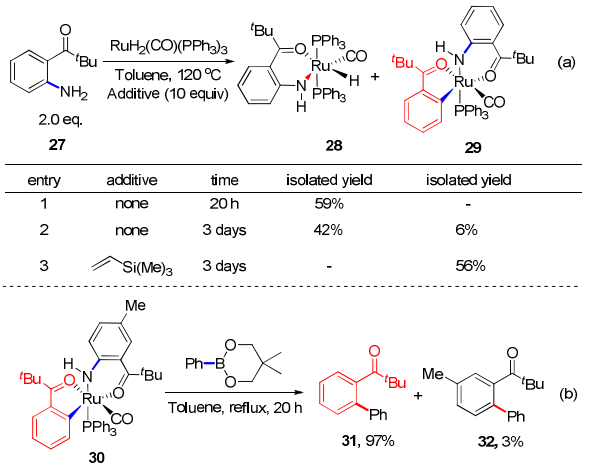
ruthenium-catalysed C-C bond formation reaction of aminoacetophenone with organoboranes *via* C-N bond activation was realized by Kakiuchi and co-workers.[16] The relatively electron-rich $RuH_2(CO)(PPh_3)_3$ was identified as an effective catalyst to activate the aryl C-N bond under the assistance of carbonyl directing group. This reaction was found to be amenable to a wide range of aminoacetophenones with different amino groups, such as -NH_2, -NMe_2 and -N(Me)Ac. Furthermore, both arylboronic acids and alkylboronic acids exhibited good activities for this transformation to give pivalophenones (Scheme 13).



Scheme 13 The ruthenium-catalysed cross-coupling reaction.

To gain further insight into the mechanism of this reaction, some conceivable intermediates were synthesized and investigated by the same research group (Scheme 14).[17] Firstly, the arylruthenium complex **29** could be obtained in 6% yield when aniline derivatives **27** was treated with stoichiometric amount of $RuH_2(CO)(PPh_3)_3$ for 3 days (Scheme 14a). The above results clearly illustrated that a direct observation of C-N bond cleavage on the ruthenium center was possible. The yield of complex **29** could be dramatically improved when 10 equivalents of alkene was introduced into the above reaction system. Similarly, the unsymmetric complex **30** was also prepared and the target coupling product **31** could be obtained in the stoichiometric reaction of intermediate **30** or **29** with organoboronate. Moreover, the target Suzuki-type coupling reaction proceeded well in the presence of catalytic amount of complex **29**.

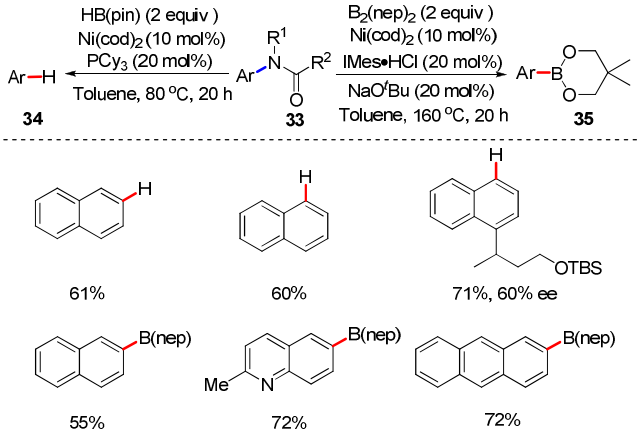
On the basis of these results, a reasonable catalytic cycle was proposed for this transformation: (i) the oxidative addition of the C-N bond to the ruthenium complex, (ii) transmetalation between the ruthenium amido complex and an organoboronate, and (iii) reductive elimination to afford the desired product and regenerate the catalyst.



entry	additive	time	isolated yield	isolated yield
1	none	20 h	59%	-
2	none	3 days	42%	6%
3	$Si(Me)_3$	3 days	-	56%

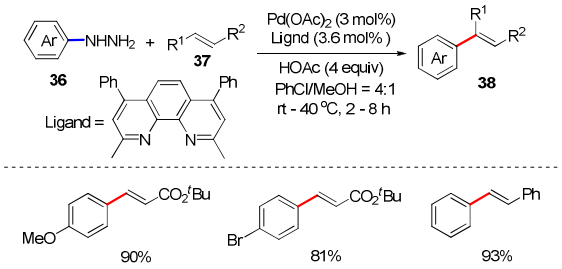
Scheme 14 The ruthenium-catalysed cross-coupling reaction.

3.1.3 C-N bond in *N*-aryl amide Unlike the above studies, the C(aryl)-N bond of electronically neutral *N*-aryl amides could be smoothly cleaved by Ni-catalyst in the absence of the assistance of any directing groups. In 2014, Chatani and Tobisu found that *N*-aryl amides could be transformed into naphthalenes in the presence of HB(pin) *via* C-N bond activation when $Ni(cod)_2/PCy_3$ served as a catalyst.[18] Notably, complete chirality retention was observed, when chiral substrate was used. With the similar C-N bond activation method, the C-B bond formation reaction was also realized when the reaction conducted in the presence of $B_2(nep)_2$ under the catalysis of $Ni(cod)_2$/IMes (Scheme 15).



Scheme 15 Nickel-catalysed cleavage of C-N bond of aromatic amides.

3.1.4 C(sp^2)-N bond in arylhydrazine Apart from the aromatic amines, arylhydrazines could also be used as coupling partners *via* transition-metal catalysed C-N activation. In 2011, the palladium-catalysed Heck-type cross-coupling of arylhydrazines with olefins was reported by Loh and co-workers, in which the C-N bond was selectively cleaved *via* oxidative addition.[19] The transformation proceeded smoothly

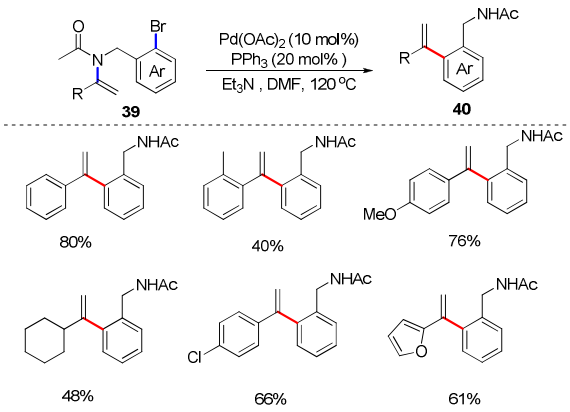


Scheme 16 Palladium-catalysed cross-coupling arylhydrazines with olefins.

at 40 °C with air as an environmentally benign oxidant. Under the optimum conditions, a wide range of arylalkenes were prepared in excellent yields (Scheme 16). It is worthy to point out that excellent chemoselectivities were observed when chloro-, bromo- and iodophenylhydrazines were employed in this coupling reaction, which indicated that the C-N bond was much more facile to be cleaved under these conditions.

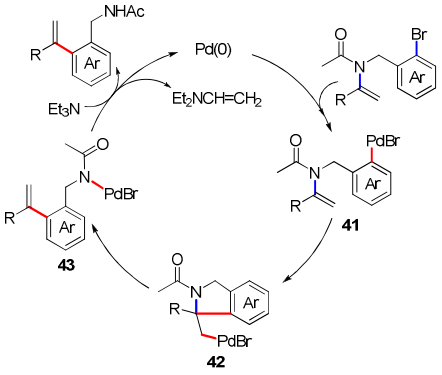
3.2 Activation of olefinic C(sp^2)-N bond

In 2015, Loh and Xu reported a palladium-catalysed intramolecular Heck reaction of *N*-vinylacetamide derivatives.[20] With $Pd(OAc)_2/PPh_3$ as the catalytic system, an intramolecular olefinic C(sp^2)-N bond could be cleaved in the presence of Et_3N to form 1,1'-disubstituted ethylene derivatives in DMF at 120 °C. Additionally, the intramolecular Heck reaction was compatible with both electron-rich and -poor groups on the phenyl ring. Notably, aliphatic enamine (R = alkyl group) could be tolerated during this transformation, as exemplified by the high reactivity of the steric-hindered *tert*-butyl and cyclohexyl-substituted *N*-vinylacetamides (Scheme 17).



Scheme 17 Heck reaction of *N*-vinylacetamide derivatives.

As shown in Scheme 18, the mechanism of this Heck-type reaction was proposed as follows: (i) oxidative addition of C-Br bond to Pd(0) to generate **41**, (ii) intramolecular 5-*exo*-cyclization to give palladium complex **42**, (iii) *β*-N elimination to cleave C-N bond, and (iv) the protonation and sequential reductive elimination to afford the desired product with the regeneration of catalytic palladium species.

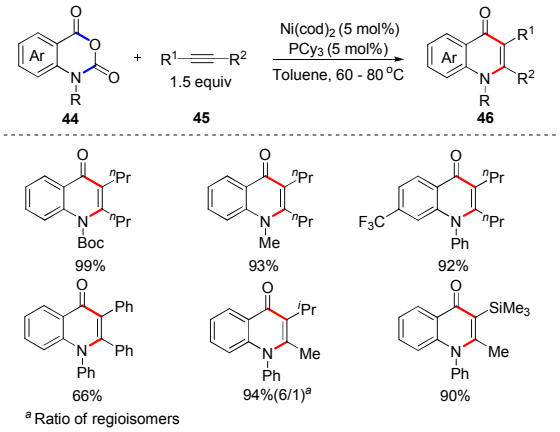


Scheme 18 Proposed mechanism for Heck reaction of *N*-vinylacetamide derivatives.

3.3 Activation of amidic C(sp^2)-N bond

3.3.1 Activation of C(sp^2)-N bond in amide Generally, the C-N bond of amides could be cleaved under harsh reaction conditions in the presence of strong base or acid. However, transition-metal catalysed selective cleavage of C-N bond of amides under mild reaction conditions remains unexplored, which might be partially attributed to the sluggish oxidative addition step of C-N bond of amides with low-valent metal.

A novel nickel-catalysed decarboxylative carboamination reaction of isatoic anhydrides with alkynes *via* C-N bond activation was established by Kurahashi and Matsubara in 2009, in which the amidic C-N bond was cleaved *via* the oxidative addition.[21] Utilizing $Ni(cod)_2/PCy_3$ as the catalyst, the desired quinolones were obtained in excellent yields with various isatoic anhydrides and alkynes as starting materials. Both aryl-substituted and alkyl-substituted alkynes were applicable in this transformation. Although the reaction of unsymmetrical alkynes proceeded in lower regioselectivity, bulky trimethylsilyl-substituted alkynes provided the desired products in excellent yields with complete regioselectivity (Scheme 19).



Scheme 19 Nickel(0)-catalysed decarboxylative carboamination.

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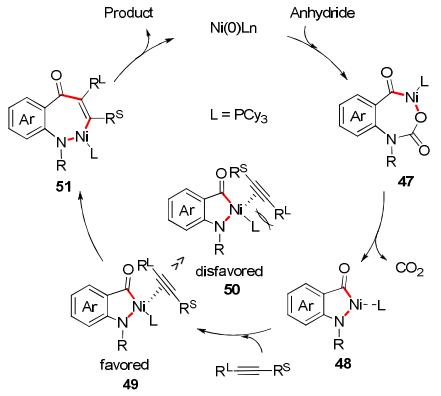
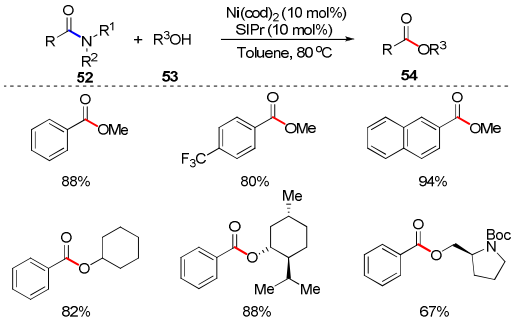


Scheme 20 Proposed mechanism for Nickel-catalysed decarboxylative carboamination.

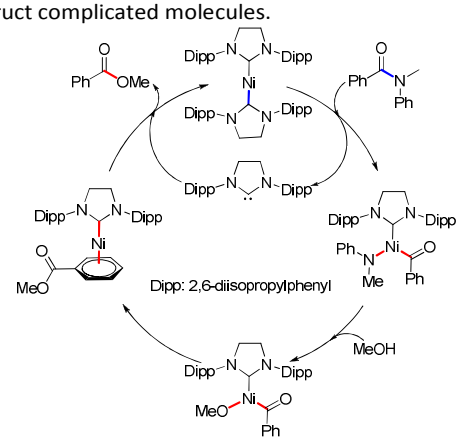
The reaction was initiated by the oxidative addition of an anhydride O-C(O) bond to nickel complex, which provided the intermediate **47**. Subsequent decarboxylation along with the C-N bond cleavage afforded a nitrogen-nickel(II) intermediate **48**. Migratory insertion of the coordinated alkyne into the acyl-nickel bond gave the key intermediate **51**. Interestingly, the studies of ligand effect indicated that the origin of higher regioselectivity with bulky alkynes might be ascribed to the repulsive steric interaction between the ligand and the substituent on the alkyne. Finally, intermediate **51** underwent reductive elimination to give the desired product and regenerate the Ni(0) catalyst (Scheme 20).

In 2015, an important breakthrough for the selective cleavage of the C-N bond of simple amide with transition metal was achieved by Garg, Houk and co-workers.[5] On the basis of density functional theory (DFT) calculations, an efficient nickel-catalysed transformation of inert amides to esters was developed by these authors. With $Ni(cod)_2$/SIPr as the catalytic system, *N*-Methyl-*N*-phenylbenzamide could be efficiently converted to the corresponding methyl benzoate in the presence of MeOH with excellent yield at 80 °C. Under the optimized conditions, both electron-rich and -deficient benzoyl groups, even heterocyclic carbonyl groups, could be well tolerated. Furthermore, a variety of alcohols including sterically hindered alcohols and natural product derived alcohols were suitable for this transformation (Scheme 21).



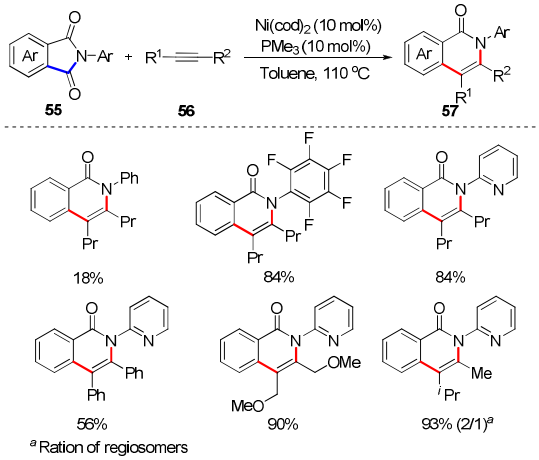
21 Nickel-catalysed esterification of amides.

On the basis of DFT calculations and experimental results, a catalytic cycle with the oxidative addition as rate-determining step was proposed, which included oxidative addition, ligand exchange, reductive elimination and product extrusion (Scheme 22). Although the alkylamide was not applicable in this reaction, the successful explored strategy for activation of C-N bond in arylamides *via* oxidative addition opened a new avenue using amides as synthetically valuable building blocks to construct complicated molecules.



Scheme 22 The proposed mechanism for nickel-catalysed esterification of amides.

3.3.2 Activation of C(sp^2)-N bond in imide Besides that in amide, the imidic C-N bond could also be cleaved by the nickel complex. In 2008, a nickel-catalysed carboamination of alkynes with *N*-arylphthalimides *via* oxidative addition of C-N bond was developed by Matsubara and Kurahashi.[22] Although electron-rich *N*-arylphthalimides only gave the desired isoquinolones in lower yields under the catalysis of $Ni(cod)_2$/PMe_3, this cyclization reaction proceeded efficiently with electron-poor substrates. In addition, various internal alkynes yielded the corresponding isoquinolones efficiently. However, terminal alkynes could not provide the desired products presumably owing to the rapid oligomerization (Scheme 23).

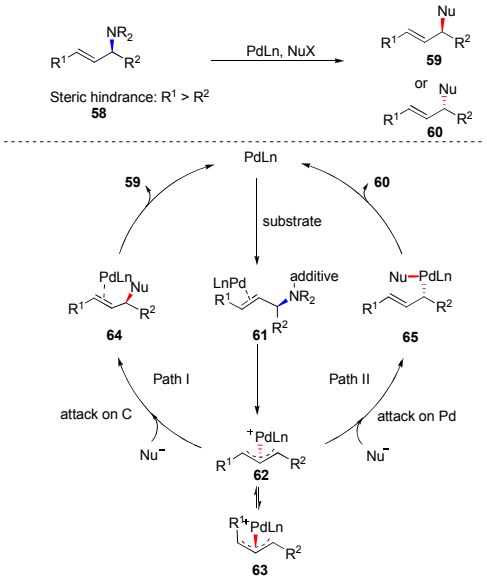


Scheme 23 Nickel-catalysed carboamination of alkynes.

4 Activation of C(sp^3)-N

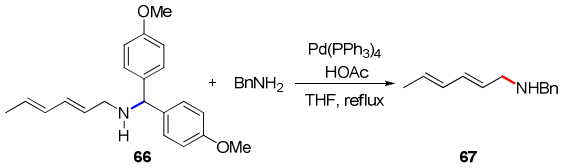
4.1 Activation of C(sp^3)-N bond in amine

4.1.1 Activation of C(sp^3)-N bond in allylic amine Allylic amines are versatile building blocks in synthetic organic chemistry which have attracted much attention during the past several decades. The C-N bond of allylic amines could be cleaved by a low-valent metal *via* oxidative addition. A typical mechanism of palladium catalysed C-N bond activation of allylic amines is shown in Scheme 24. Firstly, palladium-catalyst coordinates with the allylic substrate while the NR_2 group is activated by the Lewis acid to generate the intermediate **61** (The configuration of substrate is supposed to be alternative randomly). Further oxidative addition of C-N bond with Pd(0) give the π-allyl palladium species **62** or **63** which is depended on the used ligands. In the presence of "soft nucleophile" (p*k*a of its conjugate acid < 25), the allylic carbon atom of **62** or **63** is attacked by the nucleophile to form complex **64** with inversion of the configuration, and then the product **59** is obtained along with the regeneration of the low-valent palladium (Path I). Alternatively, the complex **65** would be generated when the palladium atom of *π*-allylpalladium **62** is attacked by a "hard nucleophile" (p*k*a of its conjugate acid > 25) (Path II), which undergoes reductive elimination to provide product **60** with the retention of the configuration.



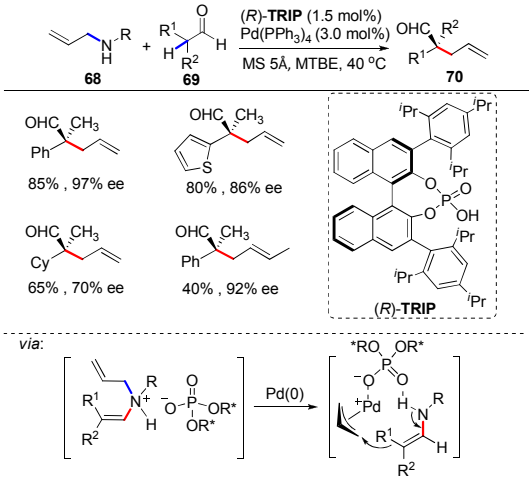
Scheme 24 Proposed mechanism for C-N bond activation of allylic amines.

A pioneering study of the C-N bond cleavage of allylic amine was reported by Trost and co-workers in 1980.[23] Benzylamine was treated with 4, 4'-dimethoxybenzhydrylsorbylamine **66** to give the desired benzylsorbylamine **67** in the presence of $Pd(PPh_3)_4$ in THF. Notably, this transformation could not proceed in the absence of stoichiometric amount of acetic acid. This work paved a way for the development of C-N bond activation reactions of allylic amines (Scheme 25).



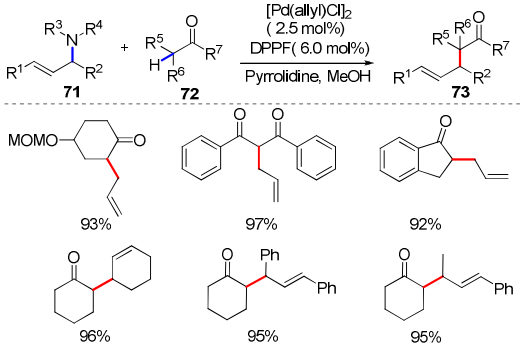
Scheme 25 Palladium-catalysed amine exchange reaction of allylic amine.

Merging with new developments in organic chemistry, the activation of C-N bond in allylic amine has attracted ongoing attention in the past decade. In 2007, List and co-workers developed a palladium-catalysed *α*-allylation of aldehydes *via* C-N bond activation of secondary allylamines.[24] A variety of chiral branched aldehydes containing all-carbon quaternary stereogenic center were synthesized. It is noteworthy that the combination of **TRIP** with palladium(0) complex was used to facilitate the C-N bond activation through *in-situ* formation of ammonium ion pairs and subsequent oxidative addition of Pd(0) (Scheme 26).



Scheme 26 Palladium/Brønsted acid-catalysed allylation reaction of aldehydes with secondary allylic amines.

Four years later, a hydrogen-bond-promoted Tsuji-Trost-type reaction of carbonyl compounds with allylic amines *via* C-N bond activation was developed by Zhang and co-workers.[25]



Scheme 27 Palladium-catalysed allylic alkylation of carbonyl compounds.

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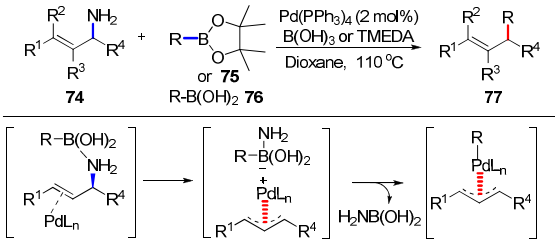
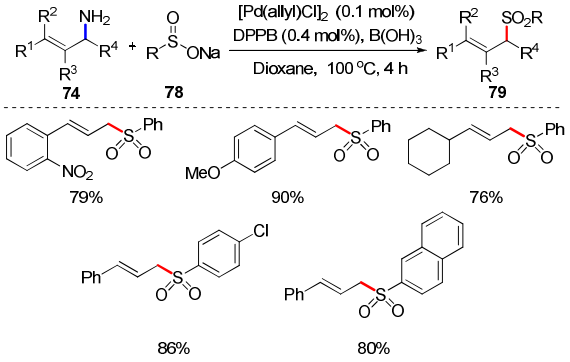
This reaction could proceed efficiently in the presence of $[Pd(allyl)Cl]_2$, DPPF, wherein the active enamine intermediates were generated from the condensation of carbonyl compounds with pyrrolidine. Furthermore, when a chiral ferrocene-based phosphinooxazoline was used as a ligand, chiral *α*-allylic substituted ketones were obtained efficiently with excellent enantioselectivities. It is noteworthy that appropriate hydrogen donor solvent such as methanol was essential for activating the C-N bond of allylic amines (Scheme 27).

In 2012, Tian and co-workers developed a palladium-catalysed highly regioselective cross-coupling of organoboronic acids with allylamines.[26] Moreover, complete transfer of chirality was achieved in the presence of TMEDA as a ligand. It was proposed that organoboronic acids could be employed as Lewis acid to activate C-N bond of primary allylic amines (Scheme 28).



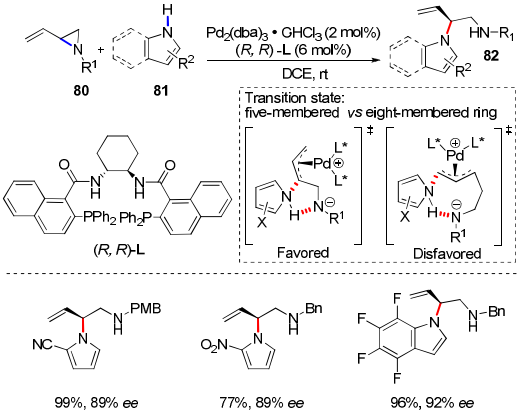
Scheme 28 Palladium-catalysed cross-coupling of organoboronic acids with allylamines *via* C-N bond activation.

Subsequently, the same group disclosed that sulfinate salts were also capable of the similar allylic alkylation reaction.[27] Structurally diverse *E*-type allylic sulfones could be produced efficiently in the presence of 0.1 mol% of $[Pd(allyl)Cl]_2$ and 0.4 mol% of DPPB. Mechanistically, oxidative addition of C-N bond into Pd(0) is facilitated by a Lewis acid (Scheme 29).



Scheme 29 Palladium-catalysed C-N bond activation of allylic amines.

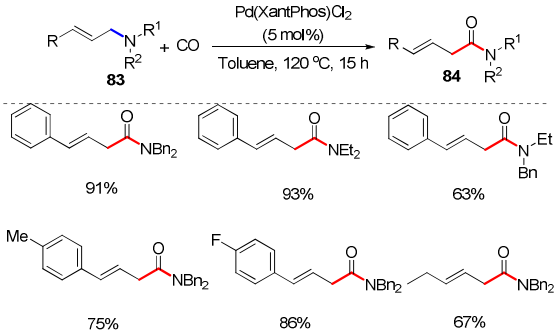
In 2010, a highly chemo-, regio-, and enantio-selective palladium-catalysed dynamic kinetic allylic alkylation of vinyl aziridines was reported by Trost's group (Scheme 30). 28 Both substituted 1H-pyrroles and 1H-indoles as hard nitrogen nucleophiles could react with aziridines to provide a variety of branched N-alkylated products exclusively with excellent enantioselectivities. Moreover, the synthetic application of this protocol was demonstrated by the preparation of several bioactive compounds and bromopyrrole alkaloids. Mechanistically, a nucleophilic attack via a five-membered transition-state following oxidative addition of Pd(0) into aziridines was proposed to rationalize the regioselectivity for the branched products.



Scheme 30 Palladium-catalysed dynamic kinetic asymmetric transformation of vinyl aziridines with nitrogen heterocycles.

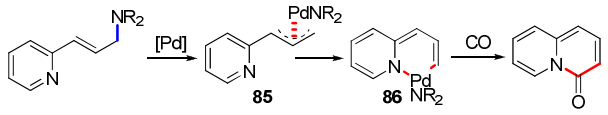
The direct carbonylation of C-N bond was recognized as one of the most powerful ways to access a range of valuable amides. Murahash and co-workers reported the direct insertion of CO into allylamines to form *β, γ*-unsaturated amides in the presence of $Pd(OAc)_2$ and DPPP.[29] It was the first carbonylation of allylamines *via* C-N bond cleavage without any additive. However, high-pressure CO (50 atm) was required in this reaction, presumably due to the slow migratory insertion of CO.

In 2014, a practical and efficient catalytic method for the carbonylation of allylamines *via* C–N activation without any additive was reported by Huang and co-workers.[30] With 5 mol% of $Pd(Xantphos)Cl_2$ as the catalyst, the carbonylation reaction could proceed smoothly to afford the desired *β, γ*-unsaturated amides in good to excellent yields under 10 atm of CO (Scheme 31).



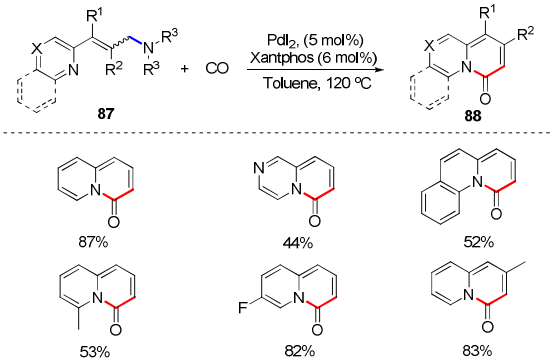
Scheme 31 Palladium-catalysed carbonylation of allylamines.

Different from the aforementioned work, a novel dearomatization/cyclocarbonylation reaction of azaarene-substituted allylamines was developed by Huang and co-workers in 2015.[31]



Scheme 32 Strategy for palladium-catalysed dearomative cyclocarbonylation.

In principle, when introducing azaarene into the allylamine system, the π-allylpalladium species **85** could be smoothly converted into the key species **86**. CO would prefer to insert into the less hindered planar pyridyl N-Pd bond of **86** and the cyclocarbonylation would be occurred (Scheme 32). Indeed, with Pd(Xantphos)I_2 as the catalyst, a wide range of quinolizinone derivatives were obtained in good to excellent yields in the absence of any additives. Notably, the desired cycloadducts could be prepared efficiently from both the *E* and *Z* isomers of allylamines (Scheme 33).

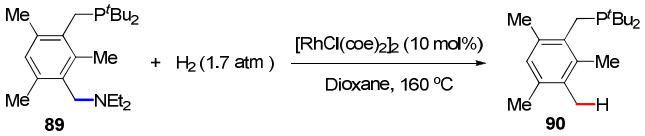


Scheme 33 Palladium-catalysed dearomative cyclocarbonylation.

4.1.2 Activation of C(sp^3)-N bond in aliphatic amine

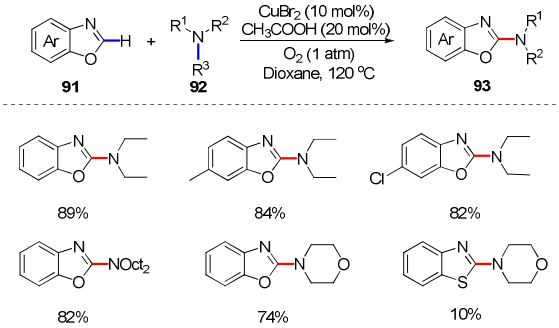
In 1982, the first transition-metal catalysed C(sp^3)-N activation of simple tertiary amines was achieved by Laine and co-workers.[32] The simple $Ru_3(CO)_{12}$, $Rh_6(CO)_{16}$ and $Os_3(CO)_{12}$ were found to be efficient for the alkyl exchange reaction between two different tertiary amines *via* C-N bond activation. Since then, considerable advancements have been achieved in activation of C(sp^3)-N bond with transition-metal catalysts.

In 2000, the rhodium-catalysed reductive hydro-denitrogenation reaction of tertiary amine **89** was first reported by Milstein and co-workers.[33] The desired product was obtained quantitatively with $[RhCl(coe)_2]_2$ as a catalyst under the atmosphere of H_2. As anticipated, a pincer-type rhodium complex generated *in situ* was the active catalyst for the transformation. However, only pincer-type of phosphine-amine could be tolerated in this system, thereby limiting the potential application of this environmentally benign transformation (Scheme 34).



Scheme 34 Rhodium-catalysed hydro-denitrogenation.

Contrary to the reductive cleavage of the simple C-N bond with H_2, a conceptually new strategy for oxidative C-N bond activation triggered by C-H activation was first developed by Huang and co-workers.[3] With simple $CuBr_2$ as a catalyst, C-N bond of tertiary amines was found to be cleaved in the presence of O_2, providing the active copper-amide species which are key intermediates for the copper-catalysed C-N bond formation reaction. Thus, a new and efficient oxidative C-H amination reaction of azoles with tertiary amines as nitrogen sources was established. A variety of azoles and tertiary amines which have α-H adjacent to the nitrogen atom were compatible with the reaction conditions. Reasonably, tertiary amines containing two types of C-N bonds afforded two kinds of aminated products. It is noteworthy that this reaction could be conducted with O_2 as an environmentally benign oxidant (Scheme 35).



Scheme 35 Copper-catalysed oxidative amination of azoles with tertiary amines.

To shed light on the reaction mechanism, isotopic labeling experiments with $H_2{}^{18}O$ and $^{18}O_2$ were conducted and bespoked that the produced aldehyde in this reaction directly resulted from the hydrolysis of the iminium-type intermediate *via* C-N bond cleavage. The KIE experiment suggested that the C-H cleavage of tertiary amine may be the rate-limiting step. A plausible mechanism was proposed on the basis of these experiments. Initially, the C-H bond of tertiary amine was cleaved by the high-valent copper species in the presence of oxygen to form the iminium-type intermeidate **94** together with elimination of H_2O. Subsequent hydrolysis generated the key copper-amide **95**, which coordinated to azole quickly, leading to intermediate **96**. The copper complex **97** would be formed through C-H bond cleavage. Reductive elimination furnished the desired product with the regeneration of copper-catalyst to complete the catalytic cycle (Scheme 36).

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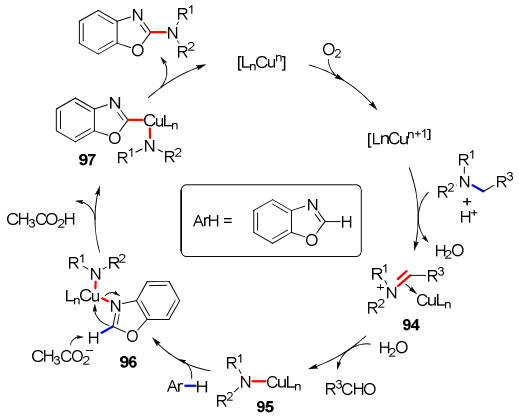
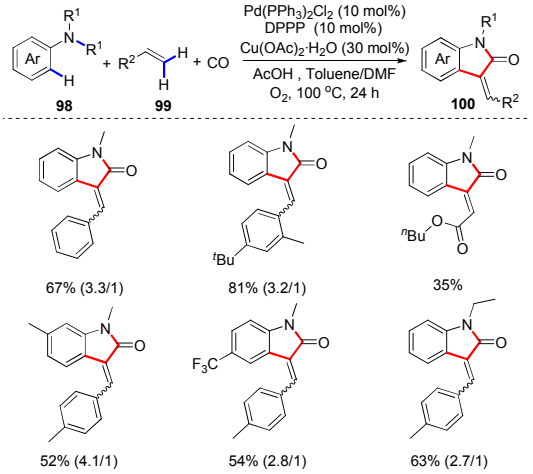


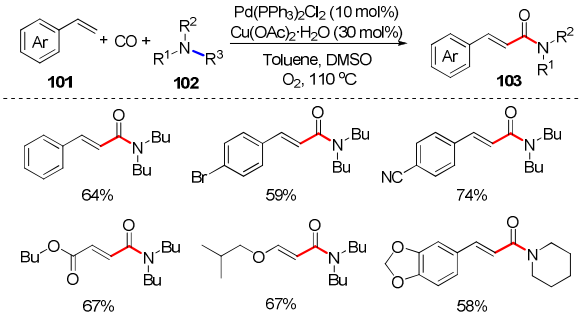
Scheme 36 Proposed mechanism for copper-catalysed oxidative amination.

Soon after, with the same oxidative C-N bond activation strategy, an efficient palladium/copper-catalysed oxidative C-H alkenylation/*N*-dealkylative carbonylation of tertiary anilines was reported by Lei and co-wokers.[34] In the presence of O_2, various *N, N*-dialkylanlines could react with styrene derivatives and CO to give the desired 3-methyleneindolin-2-one derivatives in moderate to good yields (Scheme 37).



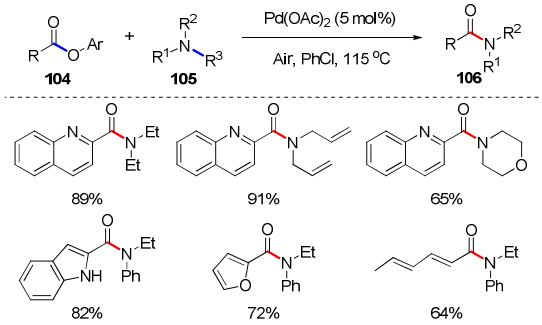
Scheme 37 Palladium/copper-catalysed oxidative C-H alkenylation/*N*-dealkylative carbonylation.

Recently, a convenient palladium/copper-catalysed aerobic oxidative *N*-dealkylative carbonylation reaction was reported by the same group.[35] With $Pd(PPh_3)_2Cl_2$ and $Cu(OAc)_2{\cdot}H_2O$ as the co-catalysts, (*E*)-*α,β*-unsaturated amides could be efficiently synthesized from tertiary amines and olefins under the atmosphere of CO and O_2. Moreover, this reaction could be also employed to synthesize ilepcimide, which is an important marketed drug in the treatment of epilepsy (Scheme 38).



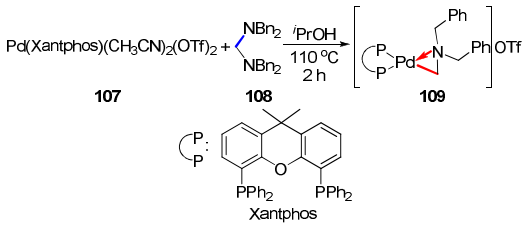
Scheme 38 Palladium/copper-catalysed intermolecular oxidative *N*-alkylative carbonylation

Based on the same oxidative C-N bond activation method, a $Pd(OAc)_2$-catalysed aminolysis reaction of aryl esters with inert tertiary amines was developed by Bao and co-workers.[36] A variety of amines including trialkyl, *N, N*-dialkylaniline and heterocyclic amines could smoothly react with various carboxylic esters to produce the desired amides in 51–91% yields (Scheme 39).



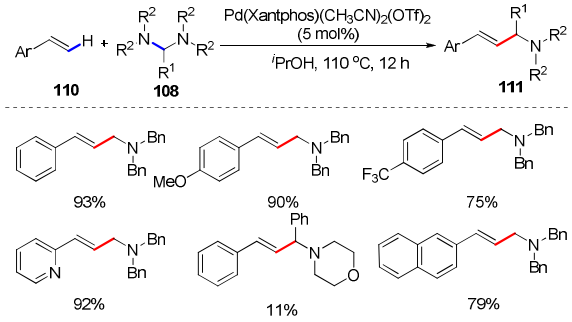
Scheme 39 Palladium-catalysed oxidative coupling.

4.1.3 Activation of C(sp^3)-N bond in aminal Aminal is a type of chemical compound that has two amine moieties attached to the same carbon atom and is easily prepared. Given the higher oxidation state and good leaving ability of the contained amino moiety, these compounds should have good electrophilicity toward organometallic reagents. Inspired by their unique features, Huang and co-workers developed a novel oxidative addition reaction between the aminal and Pd(0) complex *via* C-N bond activation. A unique three-membered cyclopalladated complex was successfully isolated and confirmed by X-ray analysis (Scheme 40).[2]

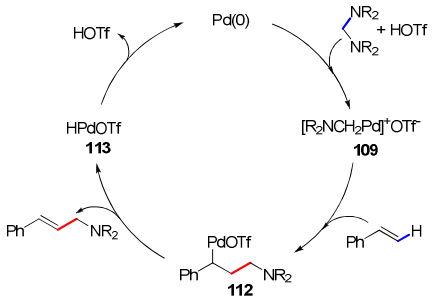


Scheme 40 Synthesis of three-membered cyclopalladated complex *via* C-N bond activation.

A stoichiometric reaction of the three-membered cyclopalladated complex with styrene at 110 °C proceeded well and successfully provided the corresponding allylic amine, which demonstrated a possibility that aminal could undergo a Heck reaction with simple alkenes *via* C-N bond activation in the presence of catalytic amount of palladium complex.[2] Indeed, under the optimized conditons, a series of simple alkenes and aminals were transformed into the desired products with complete regioselectivity (scheme 41). Furthermore, a three-component cascade coupling protocol was realized for the rapid synthesis of cinnarizine with alkene, amine and paraformaldehyde as starting materials.



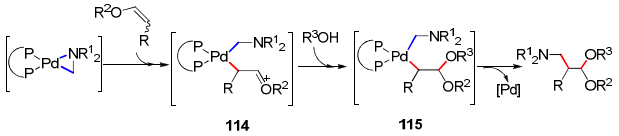
Scheme 41 Palladium-catalysed vinylation of aminals.



Scheme 42 Proposed mechanism for Pd-catalysed vinylation of aminals.

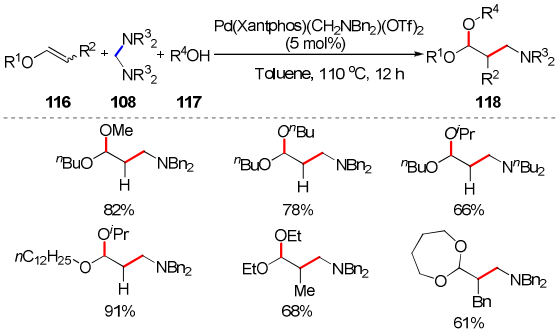
According to the NMR spectroscopy, high-resolution mass spectrometry and X-ray crystal structure analysis, a tentative mechanism for the Pd-catalysed vinylation was proposed involving the following steps: (i) oxidative addition of aminal to Pd(0) complex to generate the cyclopalladated complex **109**, (ii) migratory insertion of alkene into the palladium complex **109** to generate intermediate **112**, (iii) subsequent *syn-β*-hydride elimination to deliver the desired product as well as intermediate **113**, and (iv) reductive elimination to give the active Pd(0) species completing the catalytic cycle (Scheme 42). It is appeared that the rate limiting step is the migratory insertion of alkene to cyclopalladated complex.

Given that an electron-rich alkene could slow down the rate of migratory insertion into the metal-alkyl bond, it would be expected that the migratory insertion of enol ethers to the Pd-alkyl would be slow, resulting in formation of intermediate **114.** The intermediate **114** is prone to be intercepted by alcohol *via* nucleophilic addition to generate the difunctionalization



Shceme 43 New strategy for difunctionalization of enol ethers

product *via* further reductive elimination of intermediate **115** (Scheme 43). This kind of difunctionalization reaction was successfully established by Huang and co-workers when the cationic $Pd(Xantphos)(CH_3CN)_2(OTf)_2$ was utilized as a catalyst.[37] Under the optimized reaction conditions, various terminal or nonterminal enol ethers and aminals were converted into the corresponding amino acetals. Impressively, this method could transform 4-(vinyloxy)butan-1-ol into desired product *via* intramolecular nucleophilic attack (Scheme 44).



Scheme 44 Palladium-catalysed difunctionlization of enol ethers.

Further studies from the same research group demonstrated that the difunctionalization of allenes with aminals could be realized *via* the same C-N bond activation.[38] With the unqiue cyclopalladated complex as a catalyst, the aminomethylamination of allene with aminal proceeded smoothly. A series of aromatic allenes bearing electron-donating or -withdrawing groups on the aryl ring were well tolerated (Scheme 45). Notably, the cyclic aminals could also be successfully employed in this transformation. It is interesting to note that both the "$-CH_2NR_2$" and "$-NR_2$" moieties of the aminal were successfully installed into the product in one step, which provided an atom- and step-economical access to 1,3-diamines.

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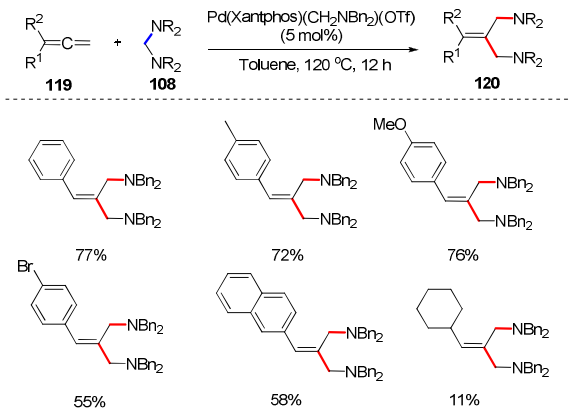
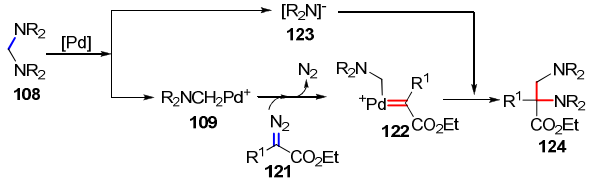
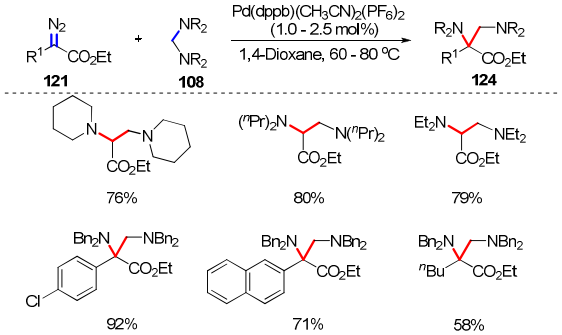


Scheme 45 Palladium-catalysed difunctionalization of allenes with aminals.

In principle, the cationic cyclopalladated complex **109** could react with *α*-diazoesters to give the corresponding palladium-carbenoid intermediate **122**, which might further undergo migratory insertion followed by nucleophilic addition with the released nucleophilic R_2N^- to provide the desired *α,β*-diamino acids **124**(Scheme 46).



Scheme 46 New strategy for insertion of C-N bond of aminal to carbenoid.

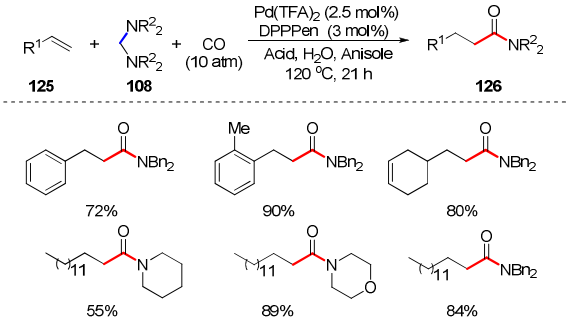


Scheme 47 Palladium-catalysed formal insertion of carbenoids into Aminals.

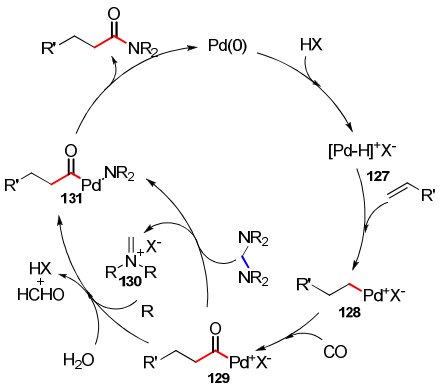
Guided by this strategy, Huang and co-workers realized this novel reaction by using palladium as catalyst, which provided an unusual strategy for insertion of C-N bond to metal carbene.[39] A series of aminals and *α*-diazoesters with different substituents were successfully incorporated into the desired products under the catalysis of palladium, affording a wide range of *α,β*-diamino acid esters. The diamino acid esters not only are key structural motifs in numerous natural products but also serve as important building blocks for the synthesis of important pharmaceuticals (Scheme 47). The mechanism studies demonstrated that the key three-membered cyclopalladated complex was involved in the catalytic cycle.

Transition-metal catalysed hydroaminocarbonylation of alkenes with amines is recognized as one of the most powerful protocols to prepare amides. Unfortunately, aliphatic amines, which are more basic than aromatic amines, could not work well under the palladium catalysis. One attractive method to overcome this basicity barrier is using aminals as the surrogates of aliphatic amines, since the basicity of aminals is lower than aliphatic amines and the active "N-Pd" species could be generated *via* C-N bond activation under suitable reaction conditions.

In 2015, Huang and co-workers succeeded in establishing a palladium-catalysed hydroaminocarbonylation of simple alkenes with aminals *via* C-N bond activation.[40] Using the combination of $Pd(TFA)_2$/DPPPen together with catalytic amount of acid as the catalytic system, a wide range of *N*-alkyl linear amides were obtained in good yields with high regioselectivity under 10 atm of CO in anisole at 120 °C (Scheme 48).



Scheme 48 Palladium-catalysed hydroaminocarbonylation of simple alkenes with aminals.



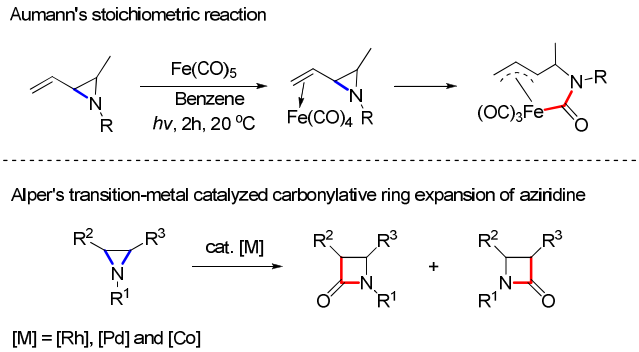
Scheme 49 Proposed mechanism for hydroaminocarbonylation.

This novel hydroaminocarbonylation reaction was believed to proceed through the following mechanism: (i) generation of palladium hydride species **127** in the presence of catalytic amount of acid, (ii) migratory insertion of the alkene into the palladium hydride species to afford intermediate **128**, (iii) insertion of CO

producing the acyl palladium species **129**, (iv) the interaction of B with an aminal to generate **131** *via* C-N bond cleavage and (v) reductive elimination of **131** to give the final hydroaminocarbonylation products and palladium(0)-catalyst (Scheme 49).

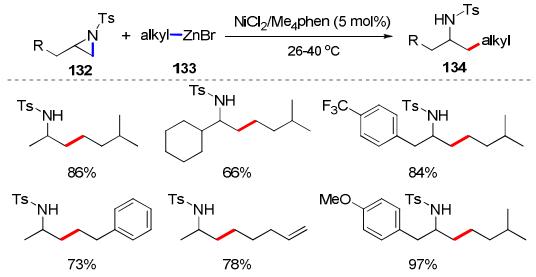
4.2 Activation of C(sp^3)-N bond in aziridine

The intrinsic ring strain of aziridine primes them for facile C-N bond activation in the presence of transition-metal complex. The first breakthrough for carbonylation of aziridines *via* activation of C-N bond came from the Aumann's seminal stoichiometric reaction in 1974 (Scheme 50).[41] The authors found that a ferralactam complex could be isolated in a good yield, which provided a solid evidence that the C-N bond of aziridine was indeed cleaved by the metal. Later, catalytic ring-expansion-carbonylation reactions of aziridines were well developed by Alper and co-workers, wherein cobalt, rhodium or palladium complex could be used as effective catalyst to produce *β*-lactam products. These carbonylation reactions have been previously discussed in a review by Alper and co-workers.[42] Subsequently, Doyle and co-workers summarized the chemistry of aziridines systematically, thus only recent advancements will be mentioned in detail herein.[43]

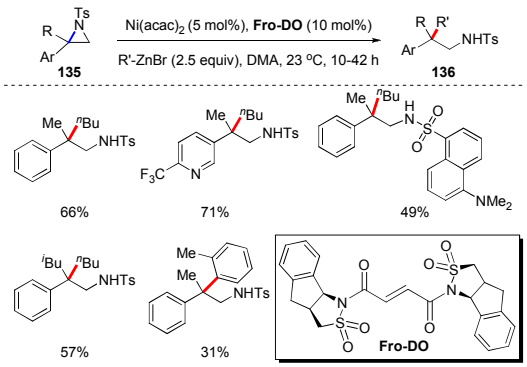


Scheme 50 Transition-metal catalysed carbonylative ring expansion of aziridine.

Several significant developments of C-N bond activation in aziridines have been demonstrated to undergo cross-coupling reactions. In 2014, the first ligand-controlled, nickel-catalysed cross-coupling of aliphatic *N*-tosylaziridines with aliphatic organozinc reagents was achieved by Jamison and co-workers (Scheme 51).[44] With 5 mol% of $NiCl_2$, 6 mol% of Me_4Phen as the catalytic system, the reaction protocol displayed complete regioselectivity at the less hindered C-N bond and worked well for a wide variety of aziridines.



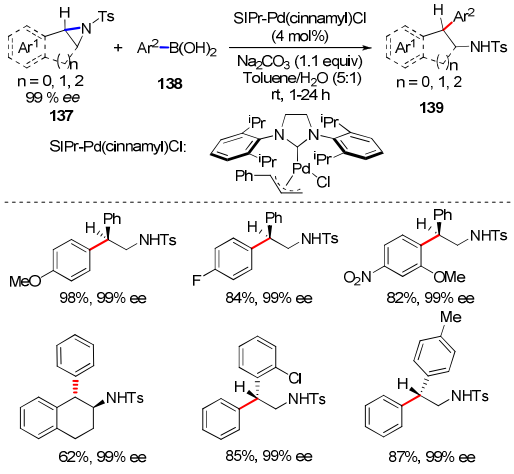
Scheme 51 Nickel-catalysed Negishi-type coupling reaction of aziridines.



Scheme 52 Nickel-catalysed Negishi-type coupling reaction of aziridines.

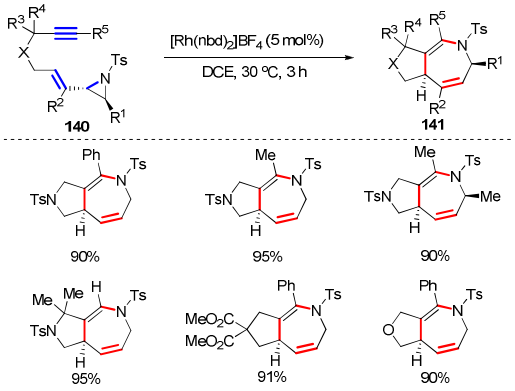
In 2015, Doyle and co-workers developed a nickel-catalysed Negishi-type cross-coupling reaction with 1,1-disubstituted styrenyl aziridines and organozinc reagents to generate quaternary centers under mild conditions (Scheme 52).[45] In presence of 5 mol% of $Ni(acac)_2$ and 10 mol% of Fro-DO, a series of 1,1-disubstituted aziridines could be used for the coupling reaction, forming the corresponding products in moderate to good yields. Both electron-neutral and -poor nucleophiles can be coupled in good yields.

In addition, Takeda and Minakata described a Pd-catalysed Suzuki-type cross-coupling of 2-arylaziridines with arylboronic acids (Scheme 53).[46] With SIPr-Pd(cinnamyl)Cl as a catalyst, this protocol could tolerate a variety of 2-arylaziridines and arylboronic acids. Optically pure 2-arylphenethylamine derivatives were obtained from chiral 2-arylaziridines with inversion of stereochemistry at benzylic carbon. Moreover, the authors demonstrated the utility of this approach in the synthesis of enantiopure fused tetracyclic amine, which was a ubiquitous motif in dopamine D_1 agonists.



Scheme 53 Palladium-catalysed Suzuki-type coupling reaction of aziridines.

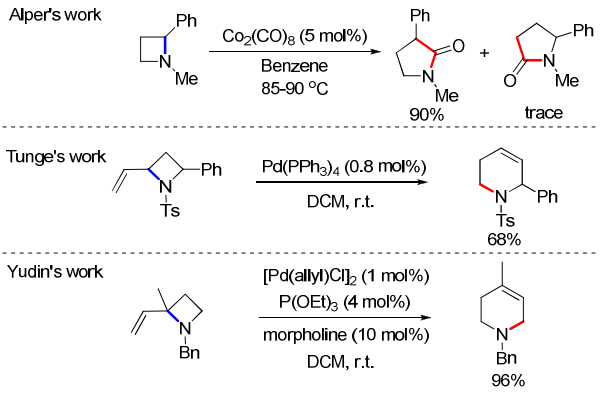
In 2015, an intramolecular formal hetero-[5+2] cycloaddition of vinyl aziridines and alkynes *via* C-N bond activation was developed by Zhang and co-workers (Scheme 54).[47] This reaction can be considered as an ideal pathway for the construction of azepine derivatives *via* C–N bond activation in terms of step and atom economy. With $[Rh(nbd)_2]BF_4$ as a catalyst, this transformation has wide substrate scope and tolerates a broad range of functional groups. Notably, complete chirality transfer could be achieved, providing enantiospecific protocol for the synthesis of 2,5-dihydroazepines. Moreover, an efficient gram-scale reaction and further transformations of the obtained products illustrated that this protocol was a practical and robust method in organic synthesis.



Scheme 54 Rhodium-catalysed hetero-[5+2] cycloaddition.

4.3 Activation of C(sp^3)-N bond in azetidine

Azetidine is another type of ring-strained organic compounds containing C–N bond that could be cleaved in the presence of transition-metal catalysts. Similar to carbonylation of aziridines, the formation of pyrrolidinones could be catalysed by $Co_2(CO)_8$ from azetidines (Scheme 55).[48] Recently, the palladium



Scheme 55 Transition-metal catalysed C-N bond in azetidine.

catalysed conversions of vinyl azetidines to tetrahydropyridine products have been developed by Tunge[49] and Yudin,[50] respectively. They proposed that the Pd(0) complexes were capable of undergoing oxidative addition to vinyl azetidines to form a π-allyl palladium intermediate, producing the desired tetrahydropyridines *via* 6-*endo* cyclization.

Conclusions and Perspectives

The appealing advantage of transition-metal catalysed C-N bond activation has prompted many methods for their applications. It is evident that combining classical coupling reactions with direct C-N bond activation could lead to many new reactions. As demonstrated in this review, the new reactions developed over the past few years via activation of inert C-N bonds have undoubtedly found significant use by synthetic chemists. A wide range of synthetically important molecules, such as nitriles, biaryls, amines and amides, have been prepared efficiently. In addition, various types of transition-metal catalysts such as palladium, nickel, copper, cobalt and rhodium complexes have been explored for these transformations. Although the transition-metal catalysed C-N bond activation reaction has been emerging as one of most promising tools in synthetic organic chemistry, there are still enormous challenges for the development of novel and practical coupling reactions *via* C–N bond activation. Full atom economy C-N bond activation reaction would attract much attention. The application of C–N bond activation for the synthesis of natural products and medical compounds under mild conditions also remains a key future objective, especially in the late-stage functionalization. Furthermore, highly efficient and enantioselective reactions via C–N bond activation are clearly another frontier in this field. Future advances in such research field will require significant efforts in chiral ligand design, substrate design, and mechanistic understanding. We believe that the concepts and results presented in this review serve as effective point to stimulate the search for new methodologies that meet these criteria.

Acknowledgements

We thank the Chinese Academy of Sciences and National Natural Science Foundation of China (Grant Nos. 21133011, 21222203, 21172226, and 21372231) for generous and continuous financial support.

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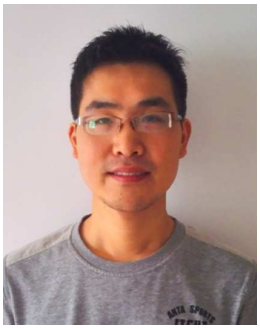

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