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Review

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Catalytic alkynylations through the activation of C-N bonds

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Dedicated to my beloved teacher Professor Tien-Yau Luh in his 75th birthday

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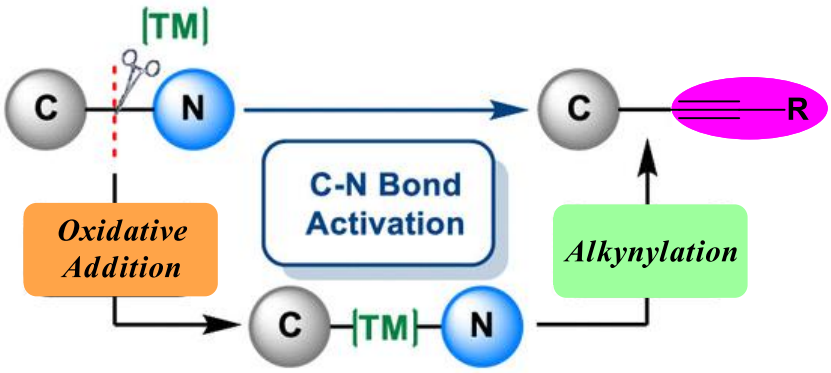
Abstract

Activation of carbon-nitrogen sigma bonds has attracted significant attention in recent years as a promising approach for bond-breaking and bond-making with a wide range of applications. Although C-N bonds are inert, due to their high bond energy, breaking them is feasible in the presence of a suitable catalyst. This approach has been successfully applied to numerous reactions, including cross-coupling reactions, making it a popular choice in the field of organic synthesis. Among the cross-coupling reactions, the alkynylation reaction occupies a significant position since alkynes are one of the privileged intermediates for the synthesis of foremost molecules with great importance in biology, medicine, and material science. This mini-review described the developments of various efficient strategies for the alkynylation reactions through the catalytic cleavage of both C(sp^2)–N and C(sp^3)–N bonds with mechanistic insights.



Keywords: C–N Bond activation, Transition metal catalysis, Alkynylation, Cross-coupling, Alkynes, Nitrogen containing compounds

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1. Introduction

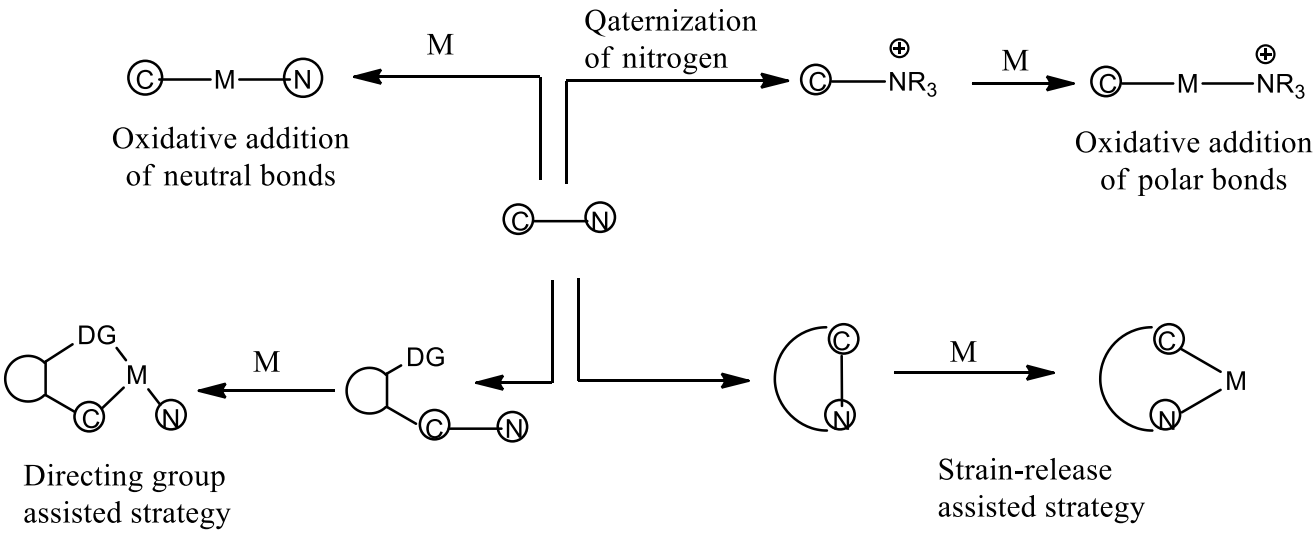
Organic compounds containing carbon-nitrogen bonds are widespread in nature and have significant importance in medicinal chemistry and materials science. The breaking of the bond between a carbon atom and a nitrogen atom in a molecule is called "C-N bond activation" and is often facilitated by a suitable catalyst or through the formation of other reactive species.[1] The ability to form new C-N bonds or modify existing ones, both of which are required for the synthesis of various organic compounds, medicines, and functional materials, makes this reaction of great interest to organic as well as inorganic chemists.[2] In recent years, C-N bond activation has been intensively explored to create new and effective catalytic methods for organic synthesis.[3] The application of the C-N bond activation reaction has a wide scope including cross-coupling reactions, carbo- and heterocycle synthesis. The development of unique and new chemical reactions depends on a deep understanding of reaction mechanisms and strategies of C-N bond activation, which can impact numerous areas of science in the academy as well as in the industry.

Generally, bonds with greater bond energies are difficult to cleave since they require more energy. The energy typically required to break the C-N bond, can be provided thermally, photochemically, or electrochemically under suitable experimental conditions. For this purpose, various factors, including the nature of the C-N bond and the conditions of the reaction, the nature of the catalyst used, roles of solvent, and additives also need to be taken care of. Considering the bond energies, the cleavage of C-N bonds is commonly easier than C-C bonds but more difficult than C-H bonds.

Since the bond dissociation energy is high in the case of the C-N bond, one of the common strategies is the conversion of neutral compounds into quaternary salts, where lowering the LUMO energy of the C-N bond facilitates the oxidative addition by the transition metal. On the other hand, the activation of neutral C-N bonds is limited due to the high thermodynamic stability and high coordination susceptibility of their N center. In these cases, directing group-assisted strategy are helpful to activate the C-N bond selectively.

One of the most significant techniques to obtain complex structures is the application of transition metals for bond activation. C-H activation was the first area to acquire momentum, owing to its statistical richness, and modern C-H activation-based techniques are plentiful and extensively investigated.[4-6] Interestingly, development in C-N bond activation has been slow until recently; this is due mainly to the higher dissociation

energy of C-N bonds and the overall stability of inactivated nitrogen-containing molecules. One of the biggest obstacles in this field is that most C-N bonds are rather inert, making activation difficult. The most common techniques have used strain release or quaternization of the nitrogen center, but other cutting-edge techniques have been also developed, such as oxidative addition to neutral C-N bonds and successful utilization of directing groups (Scheme 1). As a result, new and innovative approaches for activating C-N bonds might pave the way for novel strategies that could facilitate the synthesis of a large number of complex scaffolds and building blocks. The breaking of C–N bonds by transition metals is a mild and easy way to get excellent nitrogen and/or carbon substrates for the synthesis of valuable products.[7]



Scheme 1. Various strategies of metal catalyzed activation of C-N bonds.

Alkynes are versatile substrates that may readily be converted into a range of different substances because of the broad reactivity of triple bonds toward various electrophiles and nucleophiles.[2] Various natural products [8-10] and biologically important molecules[11] as well as carbo-[12] and heterocyles [13-15] were synthesized through utilization of alkynes as suitable substrates. As a consequence, finding an effective and sustainable technique for synthesizing alkynes has been a key consideration in organic chemistry. Several methods for the production of alkynes were explored, and transition metal-catalyzed cross-coupling has been identified being one of the most convenient.[16-17] Classically, the Sonogashira coupling[18] of aryl halides or vinyl halides with aryl or alkyl terminal alkynes is carried out in the presence of a redox-active transition metal catalyst (generally Pd (0)), a copper(I) salt (generally CuI) as a suitable co-catalyst, and a base (generally amine), under inert atmosphere, to produce aryl alkynes and enynes. There are certain disadvantages in using copper salt as a co-catalyst in the Sonogashira coupling. Along with the primary Sonogashira coupling product, copper acetylide, generated in situ under the reaction conditions, usually produces the undesired homocoupling product of terminal alkynes (Glesser/Hay coupling). As a result, various copper(I) co-catalyst substitutes have been developed in different laboratories over the years to address the difficulties caused by competitive homocoupling of terminal alkynes to the diyne. The use of a stoichiometric quantity of silver oxide or tetrabutylammonium salts,[19] gold catalyst,[20,21] silver catalyst,[22] or a palladium-only[23] method are examples of these. Nevertheless, for traditional alkynylation processes, aryl halides, specifically aryl iodides, and bromides, are the preferred starting materials. The application of aryl halides as suitable electrophilic partners has a certain downside, including (i) the high cost of aryl bromides and iodides, (ii) comparatively very low reactivity of the

aryl chloride towards oxidative addition of transition metal due to the high C-Cl bond energy, (iii) some organic halides exhibit environmental toxicity. Thus, the aryl halides may not be suitable for large-scale industrial use due to these drawbacks. As a result, the development of environment friendly, sustainable, and cost-effective catalytic techniques is always desirable. Greener methods aim to reduce waste materials, increase percentage of catalyst recovery, and develop step economic strategies for necessary target molecules. Alkynylation by C-N activation can accomplish some of these goals. The aim of this review is to highlight current advances in alkynylation reactions involving C–N single bond cleavage that proceeds by the oxidative addition to transition metals.

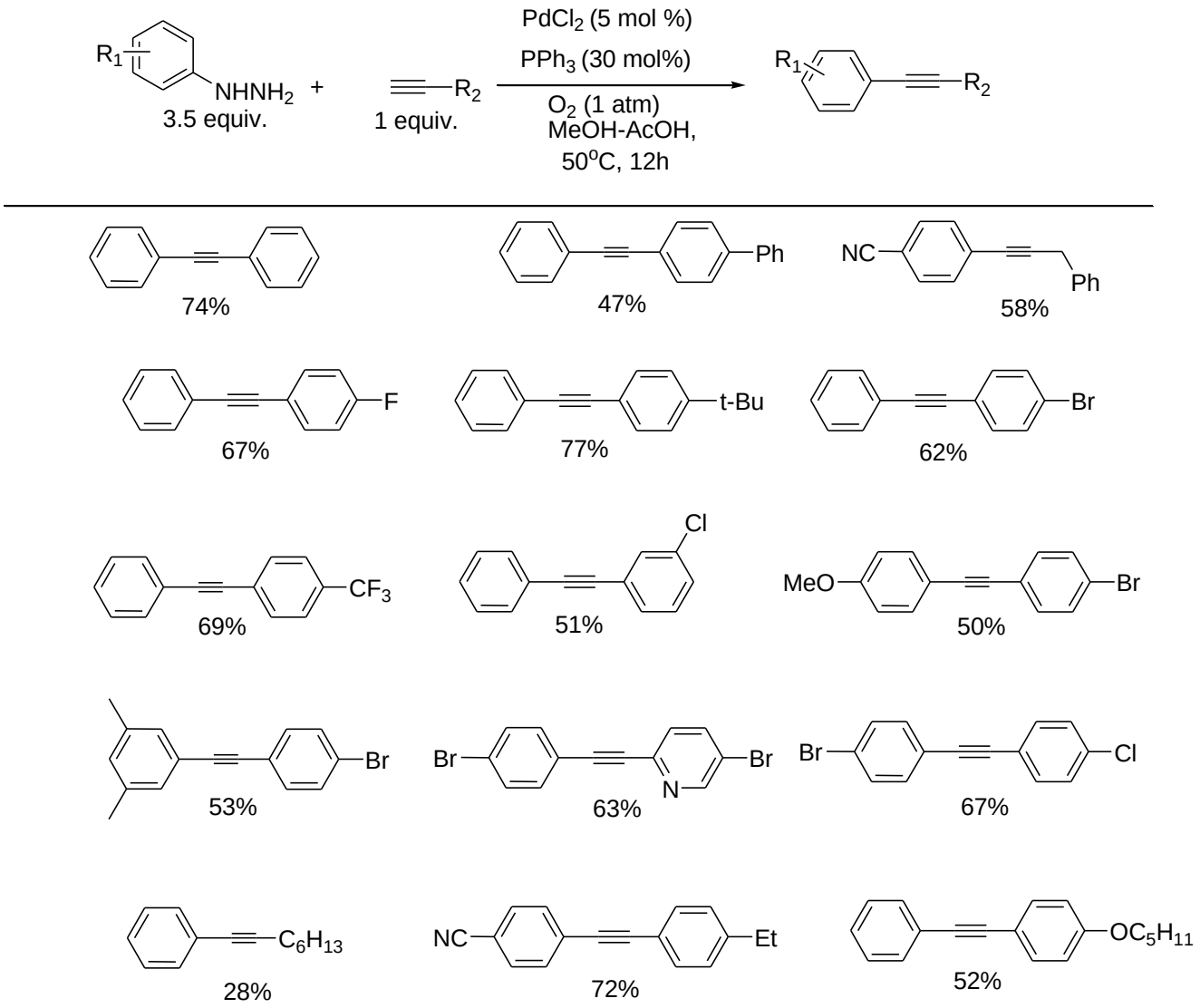
2. Activation of C-N bond

2.1. Activation of aryl hydrazines

Aryl hydrazines are found to be very efficient arylating agents for oxidative cross-coupling processes, and to produce environment-friendly byproducts such as water and nitrogen gas after the reaction. Thus, aryl hydrazine was employed in oxidative coupling reactions as a suitable aryl surrogate. As they are readily available and inexpensive, these compounds are ideal for broader applications. There are several routes to prepare the aryl hydrazines, including the aromatic nucleophilic substitution of aryl halides with hydrazine, reduction of aryldiazonium salts, and through the transition metal-catalyzed cross-coupling reactions between aryl halides and hydrazine. Over the last two decades, researchers have developed various methodologies for the utilization of arylhydrazines as aryl synthons in organic reactions, generally by forming free aryl radicals or aryl-transition metal complexes under oxidative conditions.[24]

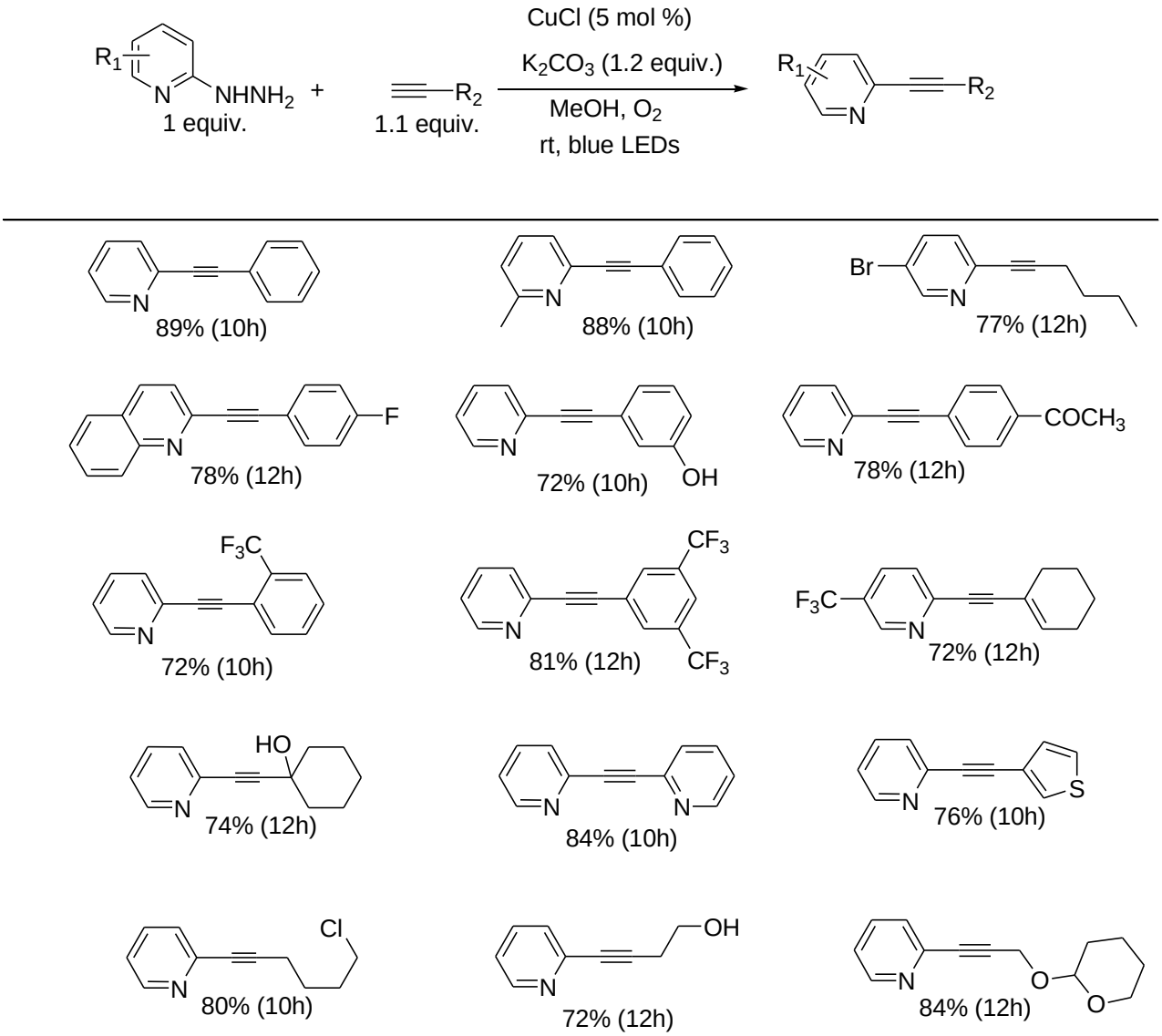
Previously, stoichiometric amounts of high-valent metal oxidants, such as lead (IV) acetate, manganese (III) acetate, barium ferrate, or hypervalent iodine(V) reagents, were used for the conversion of phenylhydrazine to phenyl radical. However, these oxidants have several disadvantages like, toxicity, being environmentally hazardous, and being expensive. To overcome these issues, researchers are intended to develop efficient and cost-effective methods that use molecular oxygen as a cheap, abundant, and eco-friendly oxidant. This is an attractive alternative to green and sustainable chemistry.

In 2015, Zhao and Song reported a palladium catalyzed protocol for arylation of terminal alkynes using arylhydrazines as aryl source for the first time.[25] This method provides an alternate strategy to conventional Sonogashira coupling reactions. In their protocol, a $PdCl_2$ was used as precatalyst and PPh_3 as suitable ligand in a mixture of solvent with acetic acid and DMF. Various electronically diverse arylhydrazines were successfully coupled with a range of aromatic terminal alkynes to generate corresponding internal aromatic alkynes with moderate to good yields (Scheme 2). It is known that bromine-substituted internal alkynes are difficult to synthesis through classical Sonogashira coupling due to the selectivity issues, coupling of arylhydrazines with bromine-substituted terminal alkynes under this protocol successfully provided the desired product in high yields. Good substrate scope, mild reaction conditions, and large scalability are the merits of this protocol. The authors found that, this protocol did not work well in case of coupling of arylhydrazine with aliphatic terminal alkynes. It is important to note that, in this method commercially available arylhydrazine hydrochlorides are unable to provide the desired products, and thus, pretreatment of arylhydrazine hydrochlorides with NaOH is necessary.

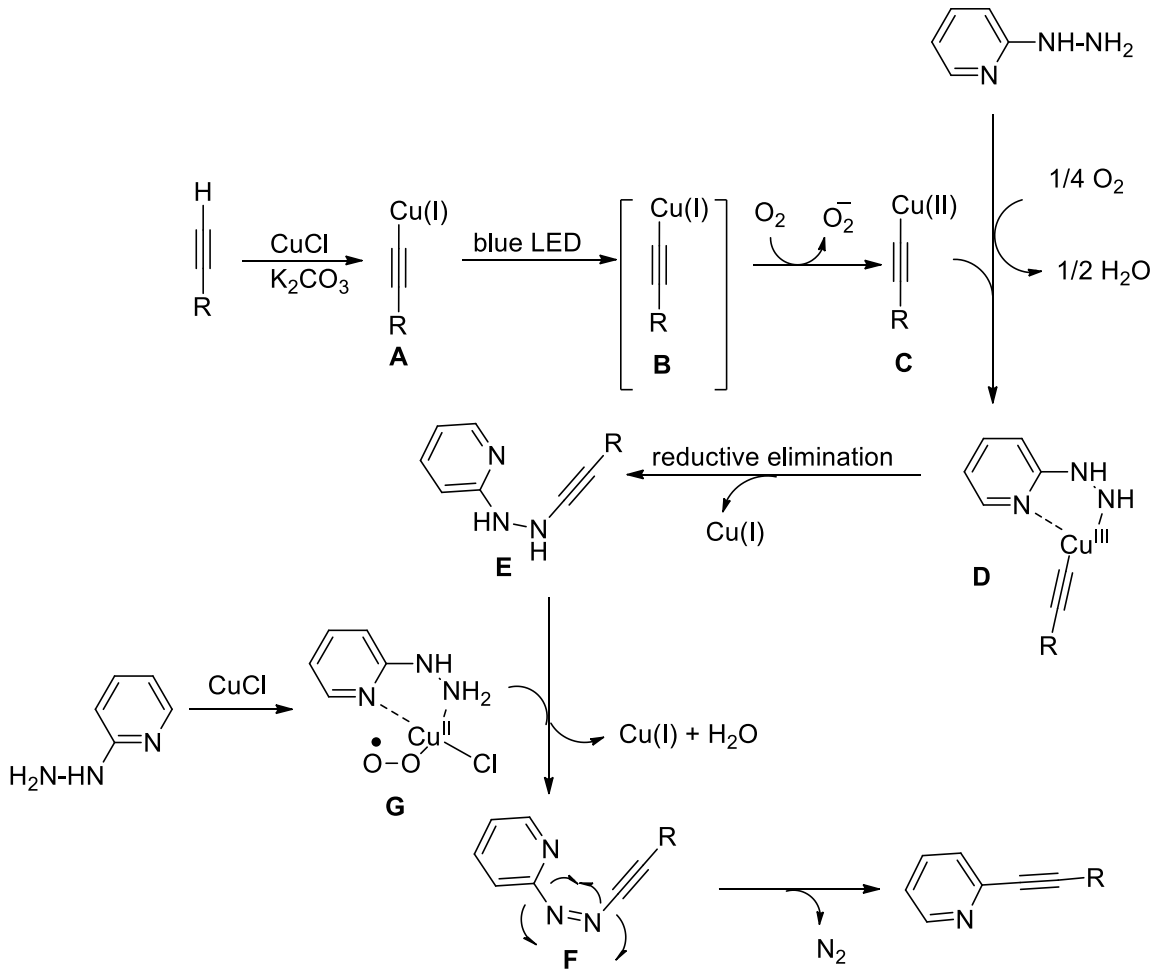


Scheme 2. Alkynylation of Aryl hydrazines.

Hwang and co-workers reported a convenient method for copper-catalyzed denitrogenated oxidative coupling of hydrazinylpyridines with terminal alkynes (Scheme 3) that was triggered by visible light.[26] In the presence of O_2 at room temperature, a variety of 2-(alkyl/aryl ethynyl) pyridines could be effectively produced in moderate to high yields. Because the only byproducts are N_2 and water, this reaction provides a cost-effective and ecologically friendly way to produce alkyne-substituted pyridines. According to Hwang et al., photoexcitation of in situ-produced Cu(I) phenyl acetylide **A** results in the formation of a long-lived triplet photo-excited Cu(I) phenyl acetylide **B** (Scheme 4). Cu(II)-phenyl acetylide intermediate **C** and a superoxide radical anion are produced via a single electron transfer (SET) reaction in the presence of molecular oxygen. The Cu(III) species **D** is formed by the oxidative addition of 2-hydrazinopyridine to **C**. Following the reductive elimination of **D**, intermediate **E** is obtained. Meanwhile, leftover 2-hydrazinopyridine may serve as a bidentate ligand for Cu, allowing it to bind with the metal, and subsequently converted into the bidentate chelated Cu(II) superoxo/-peroxo complex **G**. This complex **G** might remove the acidic protons from **E** to create **F**, which could then be converted to the desired product by removing N_2.



Scheme 3. Alkynylation of pyridyne-2- hydrazines.



Scheme 4. Mechanism of alkynylation of pyridyne-2- hydrazines.

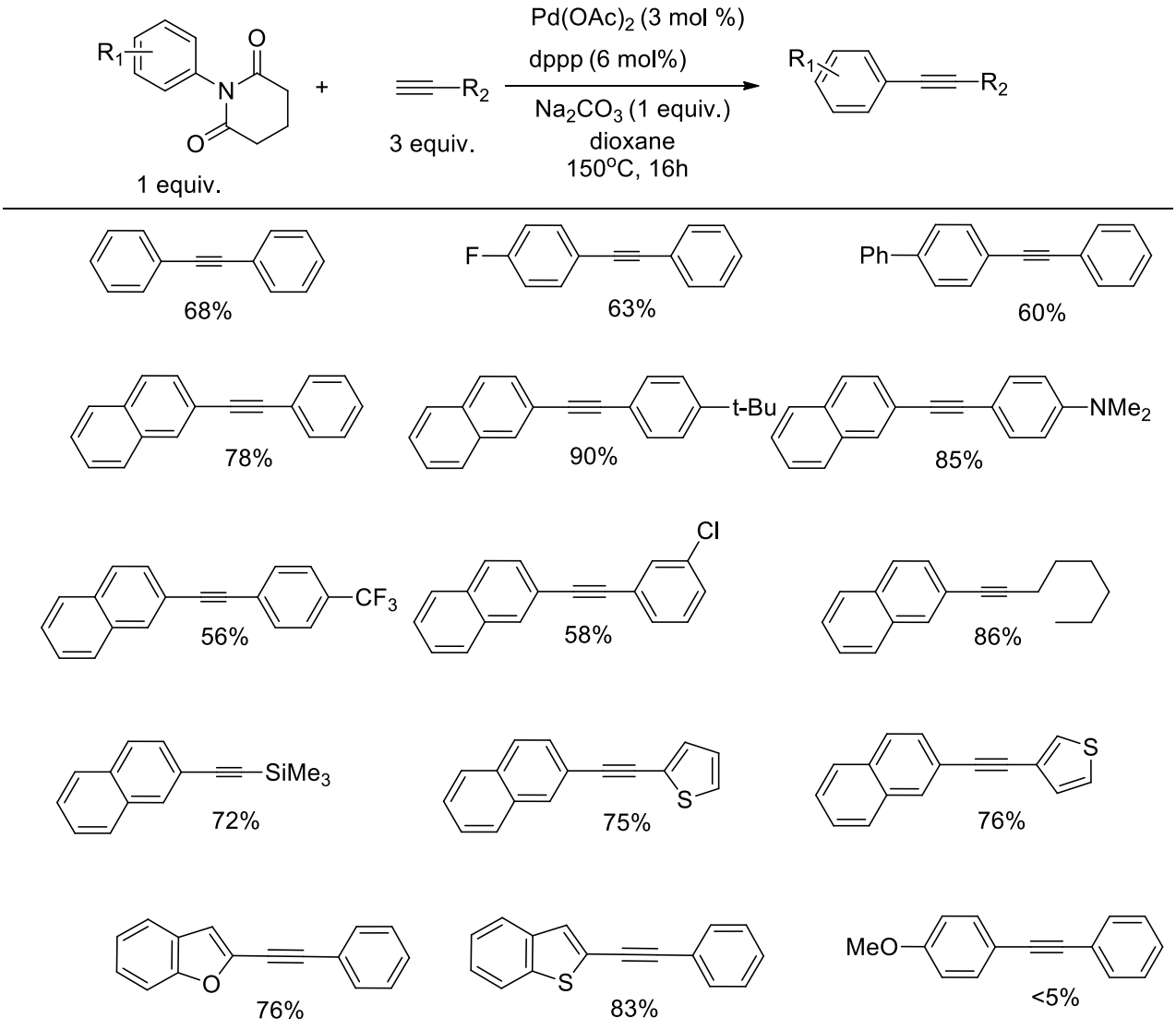
2.2. Activation of amides

Amides are advantageous coupling partners in cross-coupling reactions due to their low cost, stability under various conditions. They are also potential for functional group conversion.[27] However, the activation of the amide C(acyl)–N bond by transition metals has historically been difficult due to strong $n_N \rightarrow \pi^*_{C=O}$ conjugation. Recent studies have shown that with the help of electronic activation and steric distortion, such as electron deficiency, weak π–π interactions, amide bond twisting, and chelation assistance, C(acyl)–N bond activation is now more feasible, allowing amides to be used as electrophiles in cross-coupling reactions for the synthesis of valuable molecules through previously unknown catalytic processes.[28]

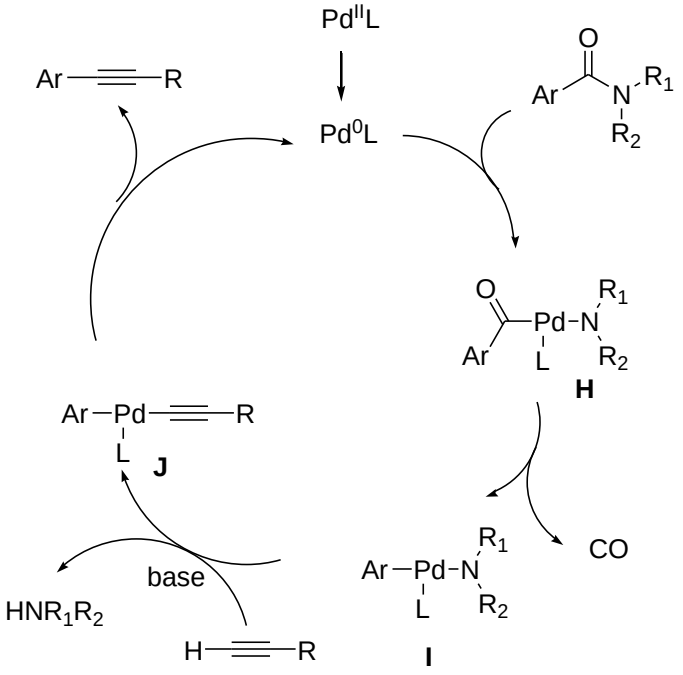
Carbonyl-retaining acyl cross-coupling reactions have been developed using C(acyl)–N bond cleavage by transition metals, representing an intriguing class of amide cross-coupling reactions. These transformations allow for the retention of the carbonyl group and enable synthetically valuable functional group conversion of amides. On the other hand, decarbonylative cross-coupling reactions involve the entire amide group acting as a leaving group, producing a new chemical bond and allowing for further functional group conversion of amides. These reactions have gained considerable attention in recent years due to their potential in synthetic chemistry.[29]

Chen et al. described a Sonogashira-type cross-coupling reaction of amides with terminal alkynes (Scheme 5) through decarbonylation of amides.[30] This reaction makes it simple to access a variety of internal alkynes, including those with aryl, alkyl, and silyl substituents. The reactive Pd(0) species is produced from the Pd catalyst

in the proposed catalytic cycle (Scheme 6). Intermediate **H** is produced by the oxidative addition of reactive Pd(0) species to the C–N bond in amide, followed by decarbonylation to produce intermediate **I**. In the presence of a base, ligand exchange with a terminal alkyne yields intermediate **J**, as well as the release of HNR_1R_2. The catalytic cycle is closed with the final reductive elimination of **J**, which yields the internal alkyne and regenerates the reactive Pd(0) species. This method proffers some advantages compared to traditional methods for the synthesis of internal alkyne with a large substrate scope and milder reaction conditions.

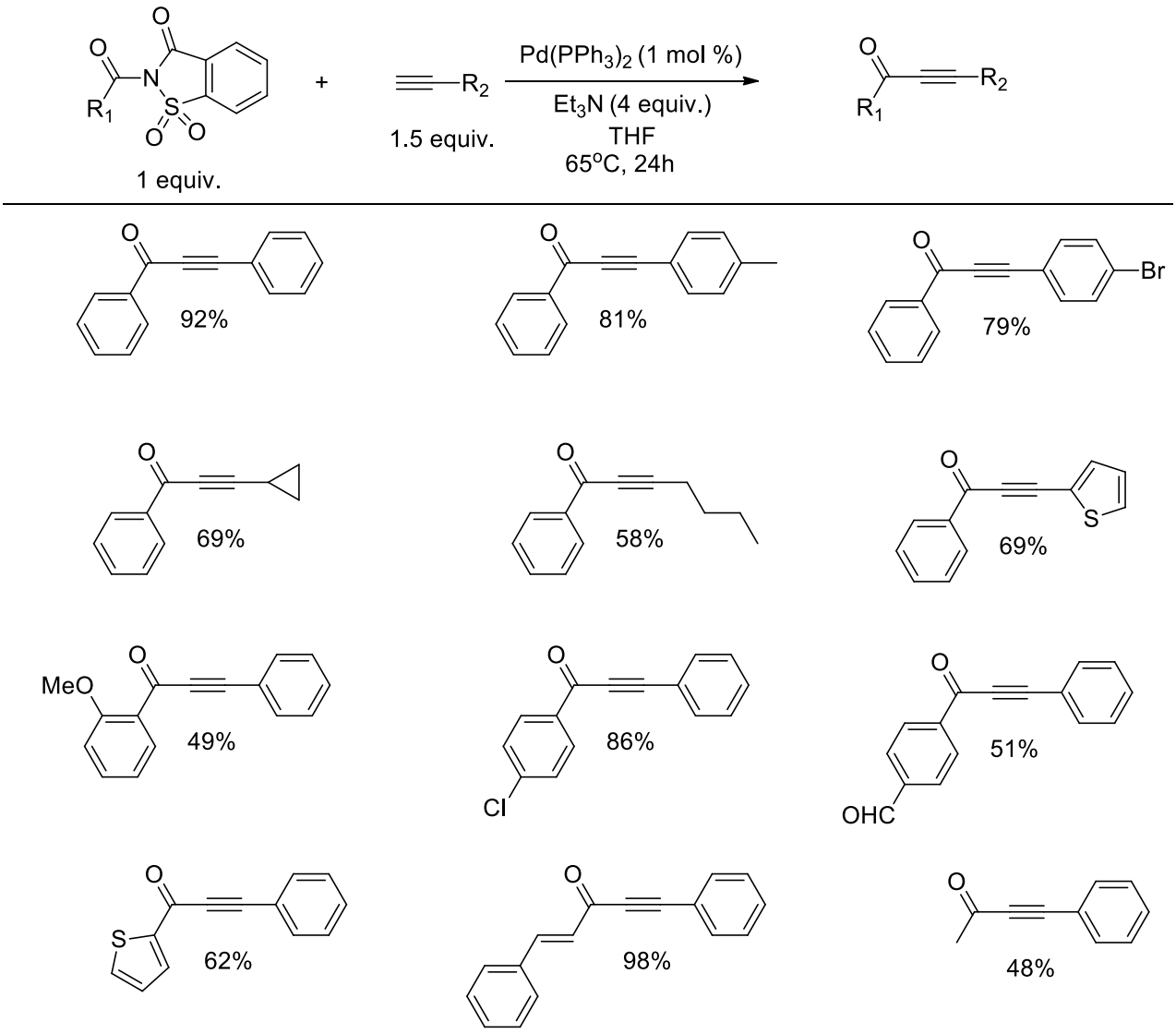


Scheme 5. Decarbonylative alkynylation of amides.

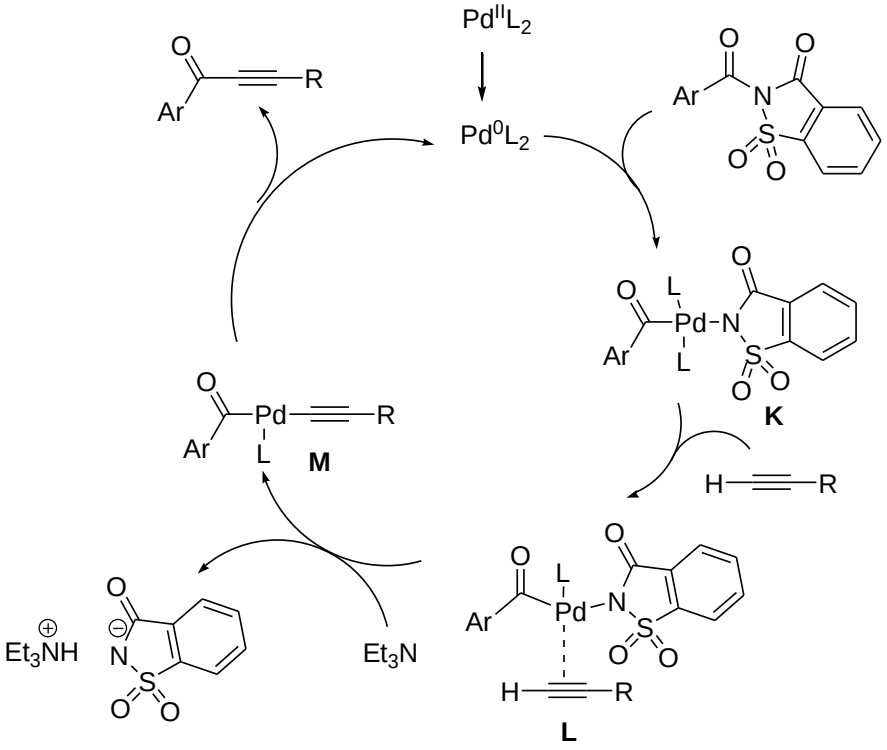


Scheme 6. Mechanism of decarbonylative alkynylation of amides.

In 2016, Zhang and co-workers reported an efficient method for Pd-catalyzed Sonogashira coupling of amides with terminal alkynes with retention of carbonyl group (Scheme 7).[31] With great selectivity, several terminal alkynes and N-acyl-saccharine derivatives may be converted to corresponding ynones. N-Acyl-saccharine derivatives were initially utilized in the synthesis of ynones as electrophilic acyl antecedents. In Scheme 8, a suggested mechanism is provided. The acyl palladium intermediate **K** is formed by the first oxidative addition of N-acyl-saccharine to the Pd (0) species. After a ligand exchange with a terminal alkyne, **L** is formed, which is subsequently deprotonated by the triethylamine to yield intermediate **M**. Finally, the required product is obtained by reductive elimination of **M**, which regenerates the Pd(0) species and completes the catalytic cycle. This strategy offers several merits over traditional methods of the synthesis of ynones, like higher selectivity, milder reaction conditions as well as broader substrate scope. This protocol has a significant impact on organic synthesis since ynones are important building blocks for the synthesis of heterocycles, various biologically active compounds, and natural products.

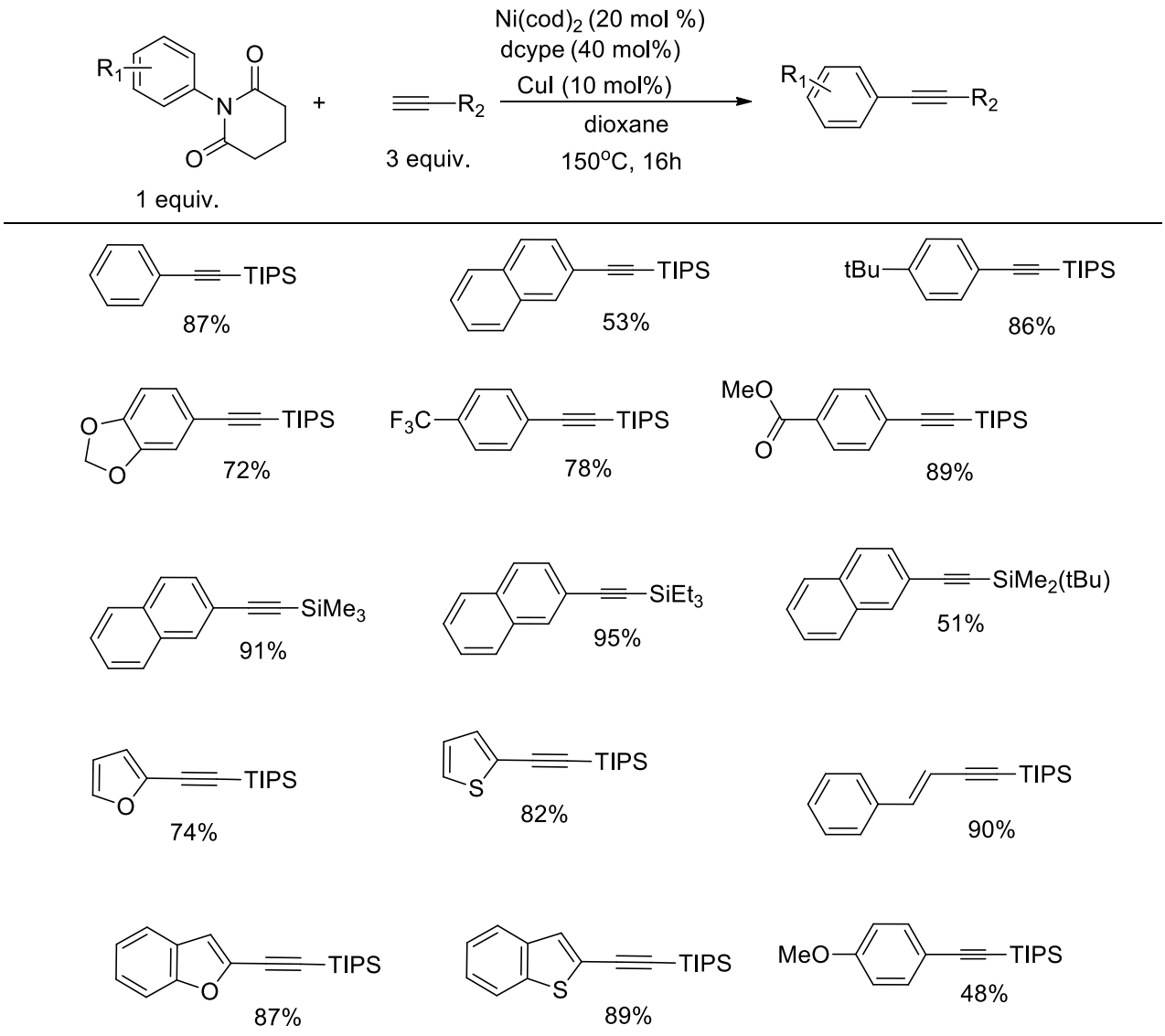


Scheme 7. Cross-coupling of amide with retention of carbonyl group.



Scheme 8. Mechanism for cross-coupling of N-acyl-saccharines with alkynes.

In 2017, Rueping and co-workers used N-acyl-glutarimides for the decarbonylative Sonogashira coupling employing a Ni/Cu-co-catalytic system(Scheme 9).[32] In this transformation, $Ni(Cod)_2$ was used as a suitable precatalyst in presence of CuI as co-catalyst and dcype (1,2-bis(dicyclohexylphosphino)ethane) as an effective ligand. The reaction proceeded through oxidative addition of the C-N bond by Ni(0)-complex. The authors proposed that the transmetallation step is very crucial since it occurs before the decarbonylation step. It is interesting to note that this method is also suitable for the synthesis of sensitive π-conjugated enynes. This technique is a typical example of Ni-catalyzed alkynylation where the substantial stability of N-acyl-glutarimides and perpendicular N-C(O) twist speed up this coupling reaction.

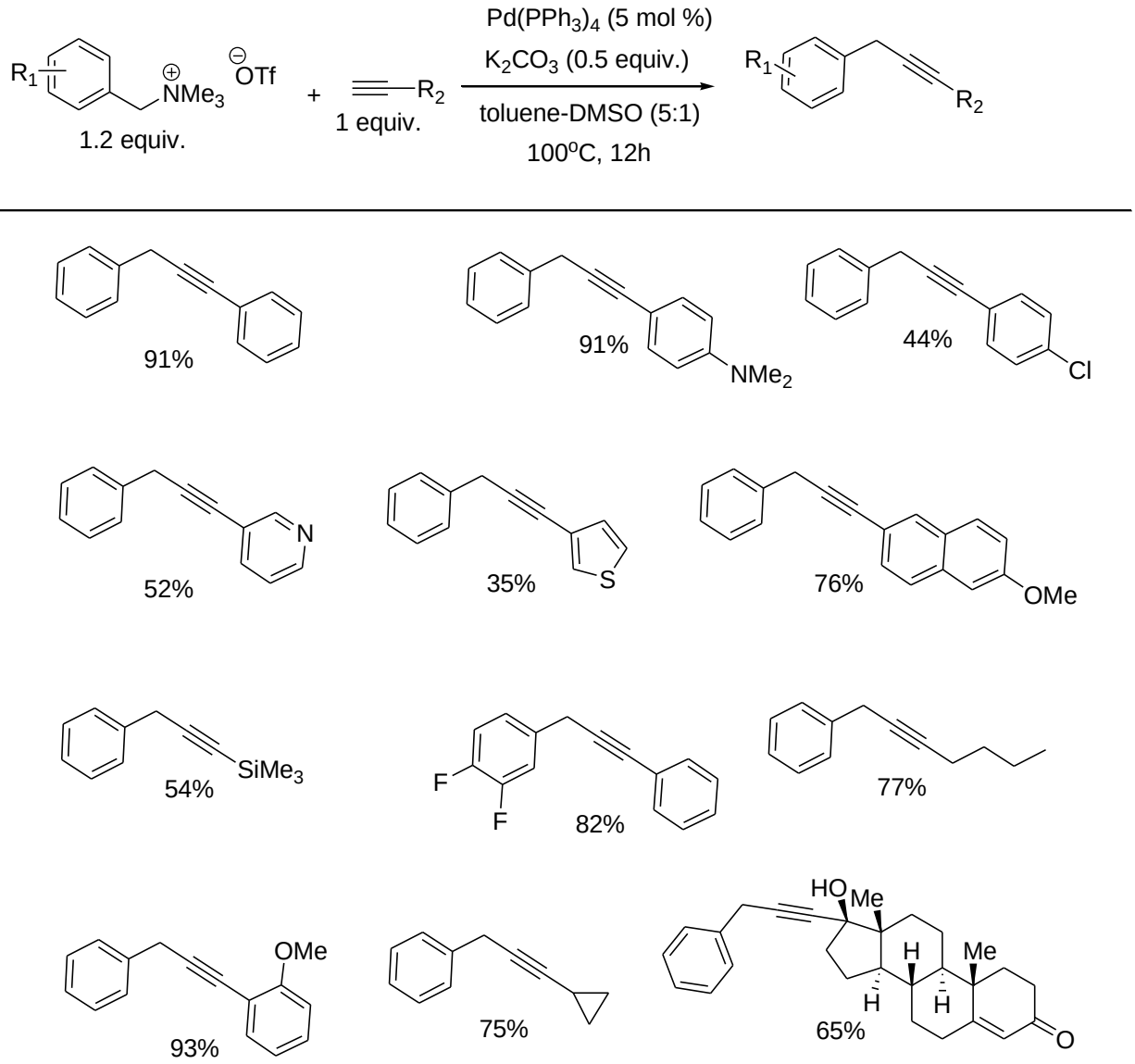


Scheme 9. Ni-catalyzed cross-coupling of amides with alkynes.

2.3. Activation of benzylammonium salts

Although palladium-catalyzed formation of the C(sp2)-C(sp) bond is well known in literature, formation of the C(sp3)-C(sp) bond under palladium-catalyzed protocol remains challenging due to the possibility of side reaction involving β-hydride elimination of C(sp3)-Pd complex formed through oxidative addition of alkyl electrophiles. Due to their widespread availability and superior reactivity, quaternary ammonium salts are significant as compared to other C-N bonds containing electrophiles. Since Wenkert's groundbreaking work in 1988, the activation of the C-N bond has been a popular topic for organic chemists who carry out their research in this area.[33] Among the various alkyl ammonium salts as electrophilic partners in cross-coupling reactions, benzylammonium salts have been extensively used as effective electrophiles in numerous cross-coupling reactions like carbonylation, borylation, phosphorylation, and C-H activation, etc. through the activation of $C(sp^3)$-N bond under transition metal catalytic conditions.[34] Additionally, benzyl ammonium salts are simple to prepare from corresponding amines and also these salts are highly stable for long-term storage. Noteworthy, several catalytic asymmetric techniques or conventional resolution can produce highly enantioenriched benzyl

amines. These amines can easily be convertible to corresponding benzyl ammonium salts and these salts can participate in an alkynylation reaction to finally produce highly enantioenriched alkynyl products.

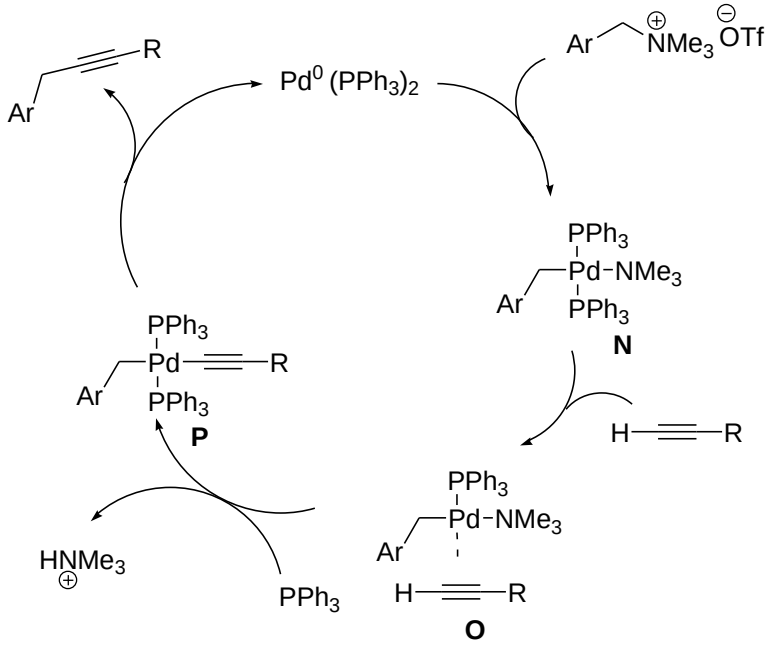


Scheme 10. Cross-coupling of benzyl ammonium salts with alkynes.

In 2019, Zhao and co-workers reported a very efficient palladium-catalyzed Sonogashira coupling of benzylic ammonium salts with terminal alkynes (Scheme 10).[35] By cleaving the C-N bond and forming the C(sp^3)-C(sp) bond, this approach allows the obtainment of a variety of internal alkyne derivatives in moderate to good yields. In this protocol, $Pd(PPh_3)_4$ was used as a catalyst, and K_2CO_3 as a suitable base without the necessity of any additional ligand. This reaction is appealing for organic synthesis because of its large substrate scope and strongly functional group tolerance. A diverse variety of substituents on the phenyl ring of benzyl trimethylammonium salts that contain both an electron-donating group (Me and OMe) and a weak electron-withdrawing group (F and Cl) could react efficiently with phenylacetylene to produce the desired products in good to excellent yields. Furthermore, the naphthyl-substituted ammonium salt easily participated in this coupling process, yielding the desired product in 90% yield. Notably, a number of terminal alkynes containing sensitive functional groups, such as $SiMe_3$ and $Si(iPr)_3$, were tolerated by the reaction, providing synthetic

handles for subsequent modification. Interestingly, a terminal alkyne containing drug molecule, ethisterone nicely coupled with benzyl ammonium salts under this protocol and yielding the corresponding internal alkyne in good yield. However, heteroaryl acetylenes, like pyridine and thiophene ring, containing terminal alkynes, provided the desired coupled product, albeit in lower yields (52 % and 35 % respectively).

Scheme 11 describes a probable reaction mechanism for this palladium-catalyzed Sonograshira coupling of benzylammonium salts. The oxidative addition of Pd(0) to benzyl trimethylammonium salts produced the benzyl palladium intermediate **N**. The palladium complex **O** is formed through the coordination of intermediate **N** to the carbon-carbon triple bond of alkyne. The coordinated alkyne is then deprotonated by the base, resulting in complex **P**. Lastly, the desired product is obtained by reductive elimination of intermediate **P** and regenerates the active Pd(0) catalyst. which is then inserted into the next catalytic cycle. The author proposed that NMe_3 produced during the reaction in situ was co-ordinating the palladium center thereafter oxidative addition and later promoted the deprotonation step as a base. However, this proposal needs to be proven by further mechanistic investigation with evidence.



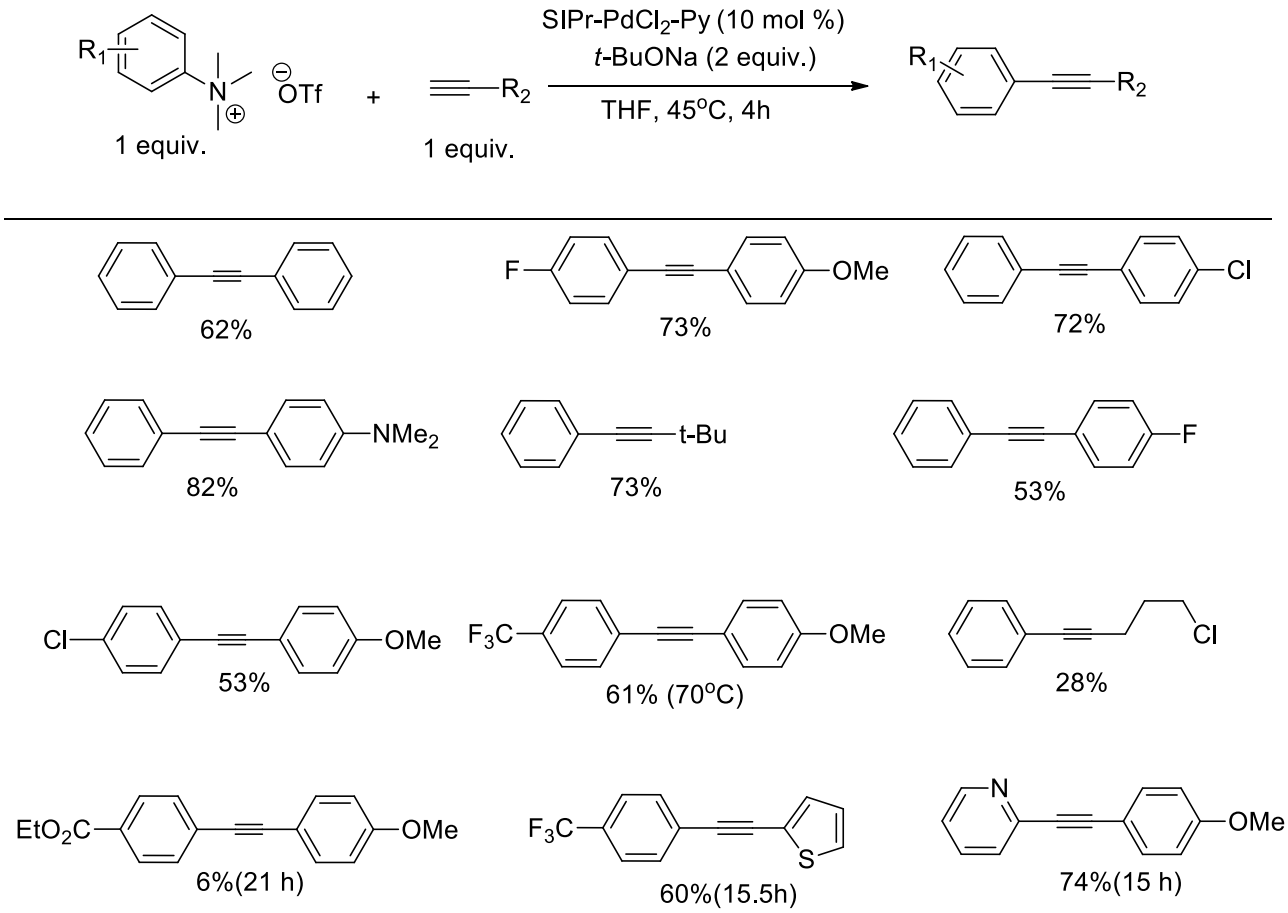
Scheme 11. Mechanism for cross-coupling of benzyl ammonium salts with alkynes.

2.4. Activation of aryltrimethylammonium salts

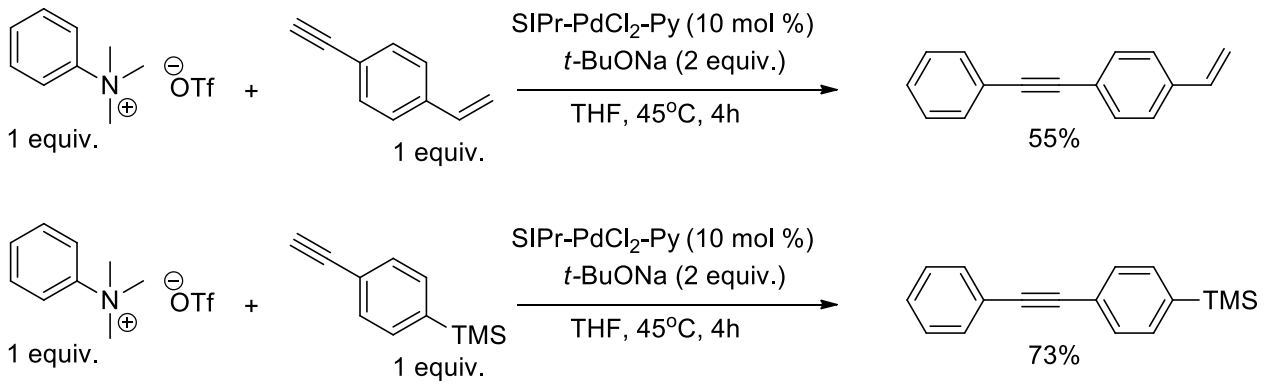
Quaternary ammonium salts are sufficiently stable, have a long shelf life, and may be synthesized from a range of inexpensive amines, including primary, secondary, and tertiary amines.[36] Numerous Ni or Pd-catalyzed procedures utilizing quaternary ammonium salts have been described for the production of $C(sp^2)$-$C(sp^2)$ or $C(sp^3)$-$C(sp^2)$ bonds since Wenkert used aryl trimethylammonium iodides for the first time as an effective coupling partner in the Kumada coupling under nickel catalyzed reaction conditions. These reactions include a variety of others, such as the Kumada, Suzuki, Negishi, Buchwald-Hartwig, Stille, Suzuki, and Negishi reactions.[37,38]

In 2019, Cao and co-workers reported a palladium-catalyzed Sonogashira cross-coupling of aryltrimethylammonium salts with terminal alkynes (Scheme 12).[39] In this protocol SIPr-$PdCl_2$-Py (SIPr – 1,3-Bis(2,6-diisopropylphenyl)imidazolidine, Py-Pyridine) was used as effective catalyst in presence of *t*-BuONa as base. Alkynes having various functional groups are tolerated well, including alkyl, aryl, and heteroaryl

substituents. Authors have found that the counter ion effect of the ammonium salts is not much significant except for the iodide salts which provide lower yields. The electronic effect of the substituents in the aromatic ring of phenylacetylene shows that phenylacetylene-bearing electron-donating groups provide better yields compared to phenylacetylene-containing electron-withdrawing groups. Aryl ammonium salts bearing an electron-withdrawing group in the aromatic ring provide better yields compared to the aryl ammonium salts substituted with the electron-donating group in the aromatic ring. Authors also performed competitive experiments to investigate the selectivity of alkynylation over the Heck and Hiyama reaction. The reaction of aryl ammonium salt was reacted with an enyne and phenylacetylene containing a TMS-group in the phenyl ring separately and get in both cases only alkynylation product without Heck or Hiyama reaction product (Scheme 13). The catalytic cycle appears to entail oxidative addition, alkyne coordination, deprotonation, and reductive elimination, according to a DFT calculation study.



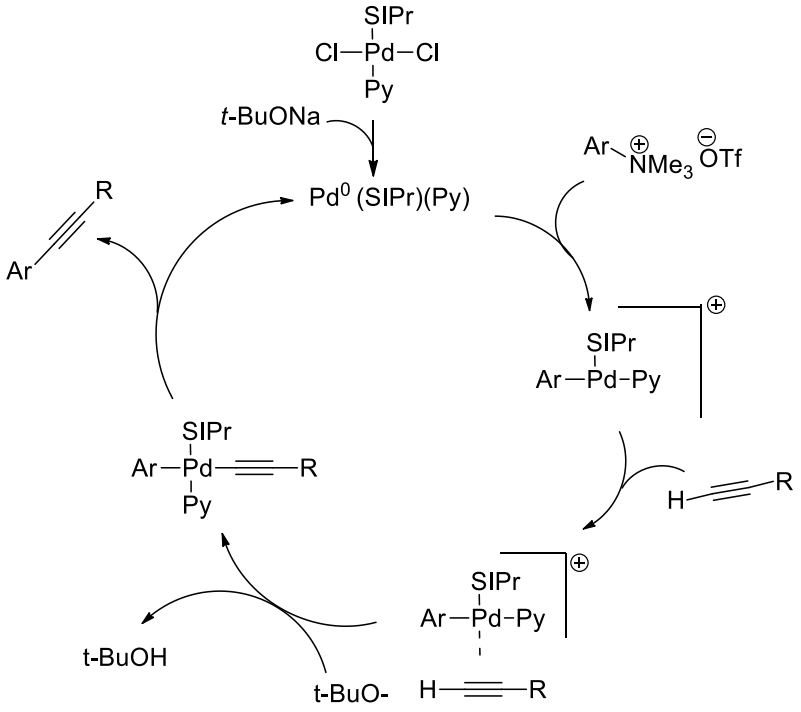
Scheme 12. Sonogashira coupling of Aryltrimethylammonium salts with terminal alkynes.



Scheme 13. Competitive studies of Sonogashira reaction with the Heck and Hiyama reaction.

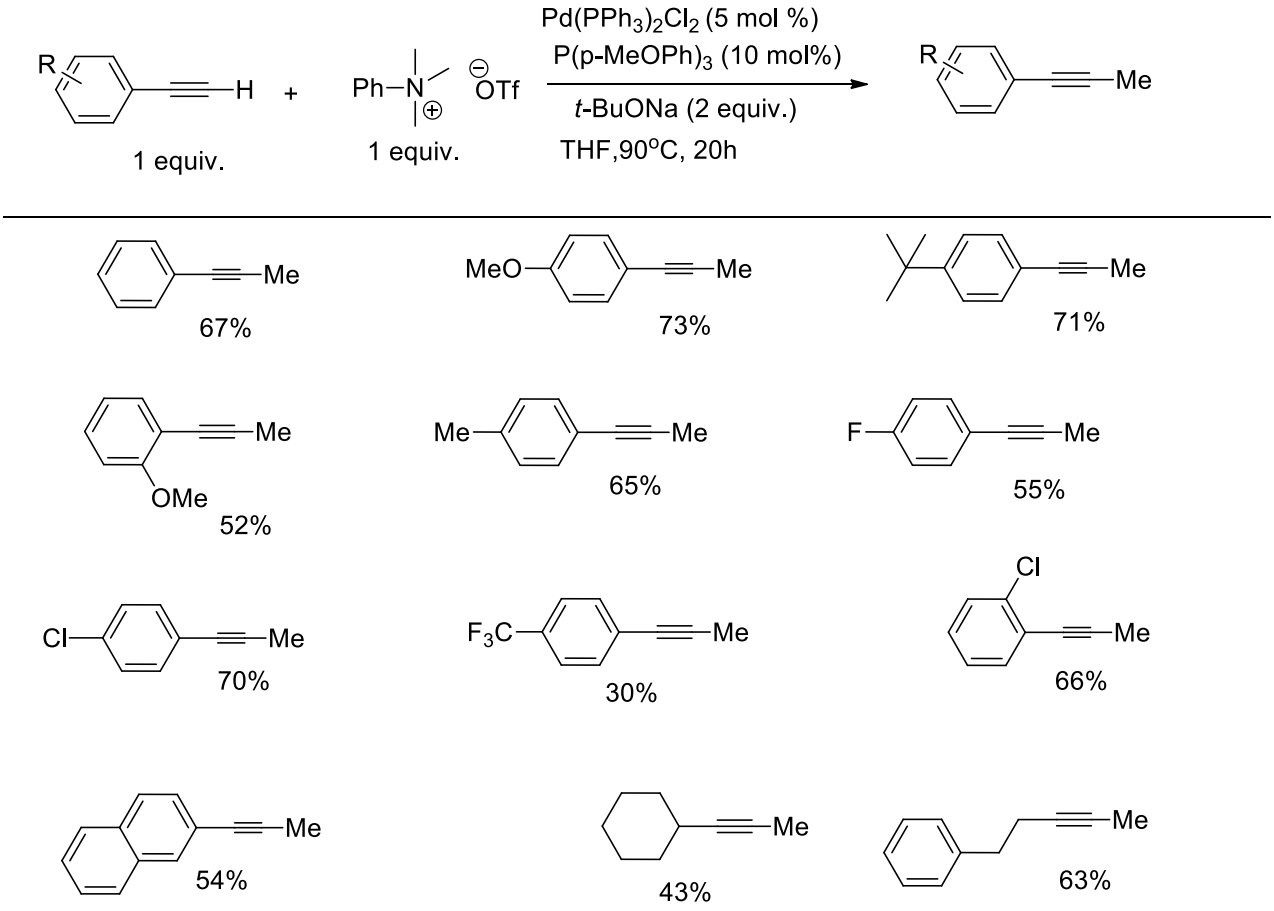
A possible mechanism for this afore-discussed alkynylation reaction has been proposed. Initially, the active palladium(0) catalyst cleaves the C-N bond through oxidative addition and generates an aryl palladium(II) complex (Scheme 14). In the second step, terminal alkyne coordinates the generated aryl palladium(II) complex, and thus acidity of the acetylenic hydrogen increases. The third step is the deprotonation of alkyne by the base which produces palladium(II) acetylide by shifting the coordination from η^2 to η^1. The last step is the reductive elimination of palladium(II) acetate complex to the final alkynylation product with the regeneration of the palladium((0) catalyst for the next catalytic cycle.

The high reactivity of aryl trimethylammonium salts with transition metals for oxidative addition and remarkable selectivity for alkynylation as well as the viability of gram-scale reaction makes this protocol attractive. Moreover, the feasibility of one-pot alkynylation of dimethylaniline reduces the number of steps necessary to obtain the desired products, and purification of intermediate could be avoided which leads to improvement of efficiency and low waste production.



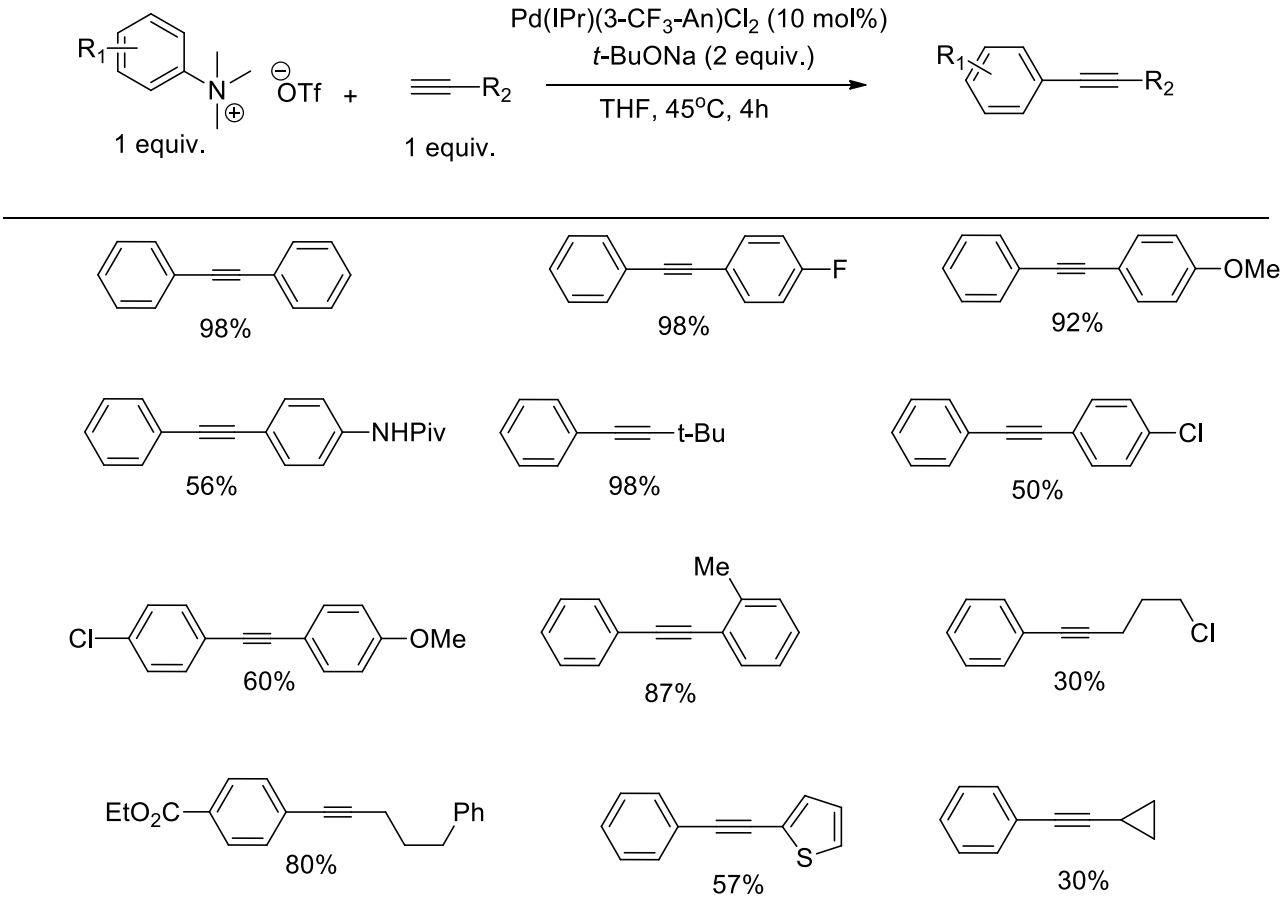
Scheme 14. Proposed mechanism for cross-coupling of aryl ammonium salts with alkynes.

Wang and Wu successfully developed a pleasing method for the palladium-catalyzed methylation of terminal alkynes using *N,N,N*-trimethylbenzenaminium trifluoromethanesulfonate as methyl source (Scheme15).[40] Under optimized reaction conditions, aromatic terminal alkynes containing various substitutions in the aromatic ring smoothly participated in this reaction and gave the desired methylated products in moderate to good yields. Furthermore, aliphatic alkynes are also nicely coupled and provide methylated products in good yields. Although, coupling of some terminal alkynes such as 3-ethynyl pyridine, prop-2-yn-1-ylbenzene, and but-3-yn-1-yl benzoate was found to be ineffective in this protocol. Notably, ethylated alkynes were also accessible, albeit in low yield, under these experimental conditions employing *N,N,N*-triethylbenzenaminium trifluoromethanesulfonate as a source of ethyl group.



Scheme 15. Pd-catalyzed Sonogashira coupling of aryl trimethylammonium salts.

In 2022, Lei and co-workers reported an efficient method for the Sonogashira cross-coupling of aryl ammonium salts using their own palladium catalyst. According to their report, the catalyst [Pd(NHC)(3-CF_3-An)Cl_2] (An = aniline) was air- and moisture-stable. This prepared Pd(II)–NHC catalyst exhibits high activity and a broad substrate scope for the alkynylation reaction, with excellent C–N activation selectivity. Detailed structural characterization and computational studies have established the effectiveness of replacing pyridine with aniline as a highly effective stabilizing ancillary ligand in well-defined Pd(II)–NHCs. They have also commercialized the prepared catalyst .



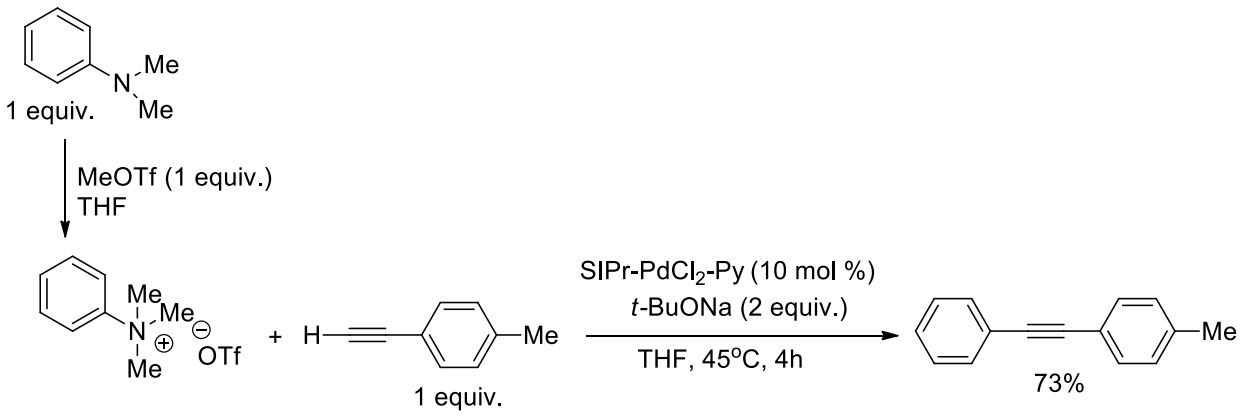
Scheme 16. Pd-catalyzed alkynylation of aryl trimethylammonium salts.

2.5. Activation of tertiary amines

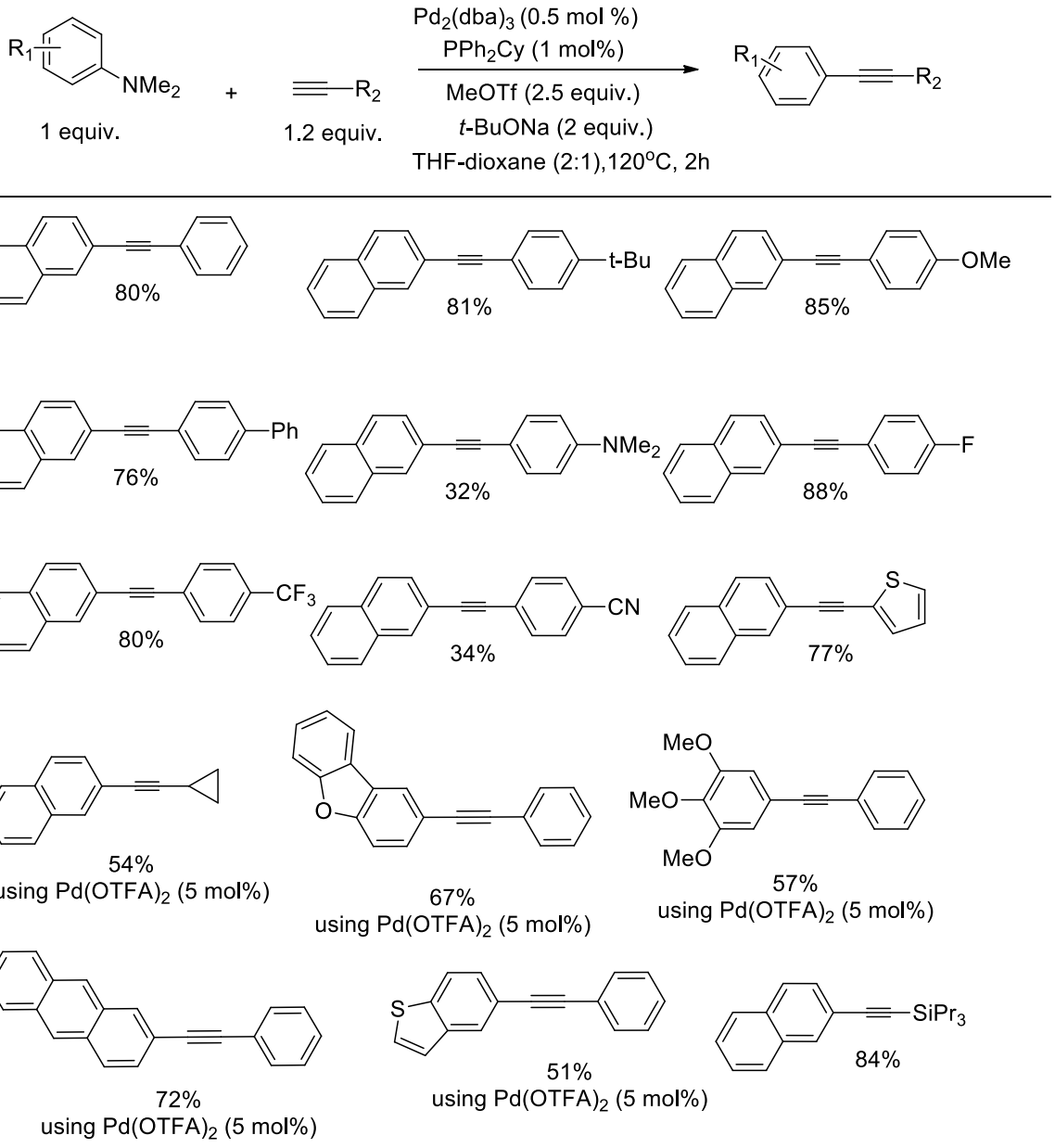
Tertiary amines are a significant group of compounds that are widely used in organic synthesis. Tertiary amine C-N bonds must be activated in order to undergo a number of chemical changes, including C-N bond functionalization, and cleavage. Due to their great efficacy, selectivity, and versatility, transition metal catalysts have drawn a lot of attention in recent years for their application in activating the C-N bond of tertiary amines. The coordination of the amine to a metal center, which creates an electrophilic center for the nucleophilic attack, also accelerates the breaking of the C-N bond through the metal-catalyzed oxidative addition of tertiary amines. The activation of the C-N bond of tertiary amine can be made feasible through direct oxidative addition by transition metal or through the *in situ* generation of quarternary salts by alkylation of tertiary amines, followed by oxidative addition of transition metals.

In 2019, Cao and co-workers showed that dimethylanilines can be directly alkynylated in a one-pot method under mild conditions without the need to isolate ammonium salts, resulting in high yields of the desired alkynylated products (Scheme 17).[39]

In 2020, Chen et al. reported a palladium-catalyzed alkynylation of aromatic amines with terminal alkynes through in situ-generated trimethylammonium salts (Scheme 18).[42] In contrast to the previous system, which used ammonium salts as starting materials and a high loading of pre- formed-NHC-Pd catalyst (10 mol percent Pd), this reaction used amines as coupling partners and commercially available $Pd_2(dba)_3/PPh_2Cy$ (1 mol percent Pd) as the catalyst, greatly simplifying manipulation and lowering costs. This reaction not only offers an alternate way of transforming aromatic amines effectively into important internal alkynes, but it also enhances the organic chemistry arsenal of amines.

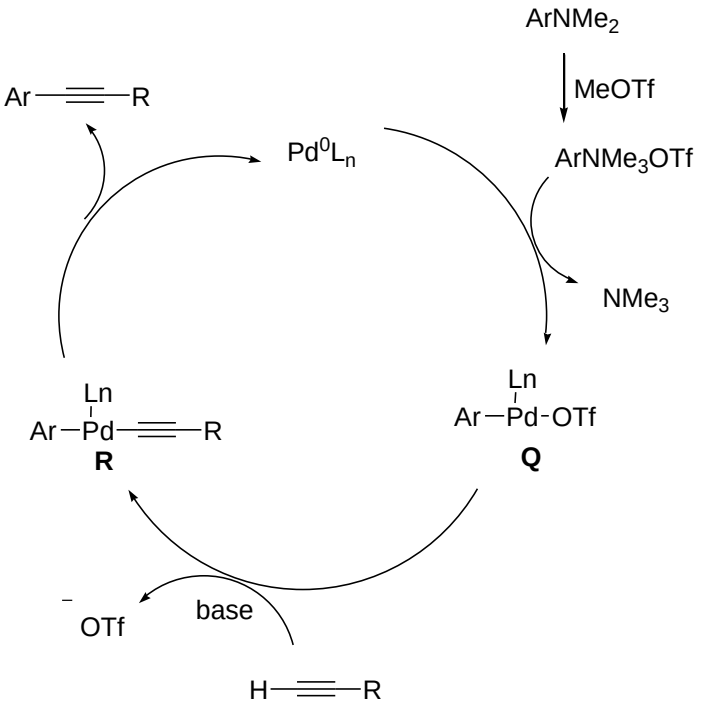


Scheme 17. In situ methylation and Sonogashira coupling of dimethylanilines.



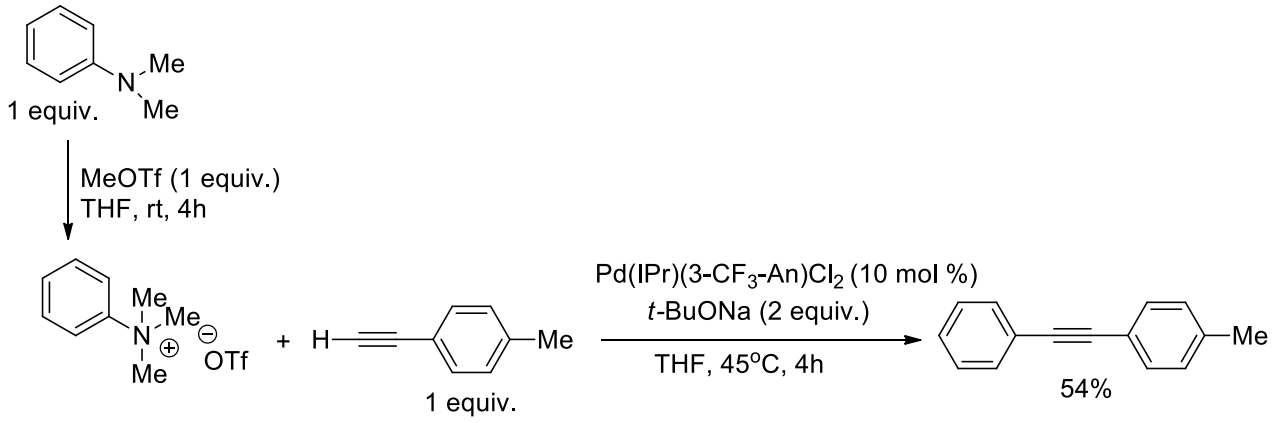
Scheme 18. Pd-catalyzed alkynylation of aromatic amines.

In Scheme 19 a feasible mechanism of the reaction is shown, based on prior literature reports. Pd(0) complex was initially added to the in-situ formed aryl trimethylammonium salts to generate species **Q**. Species **Q** subsequently performed ligand exchange with a terminal alkyne in the presence of a base, creating intermediate **R**. Reductive elimination of **R** provides the desired internal alkynes and regenerated the Pd(0) complex to accomplish the catalytic cycle.



Scheme 19. Mechanism of Pd-catalyzed alkynylation of aromatic amines.

Lei and co-workers reported a one-pot strategy for methylation of dimethylaniline to form aryltrimethyl ammonium salts which successfully coupled with terminal alkynes and provided the desired internal alkynes in moderate yields (Scheme 20). [41]

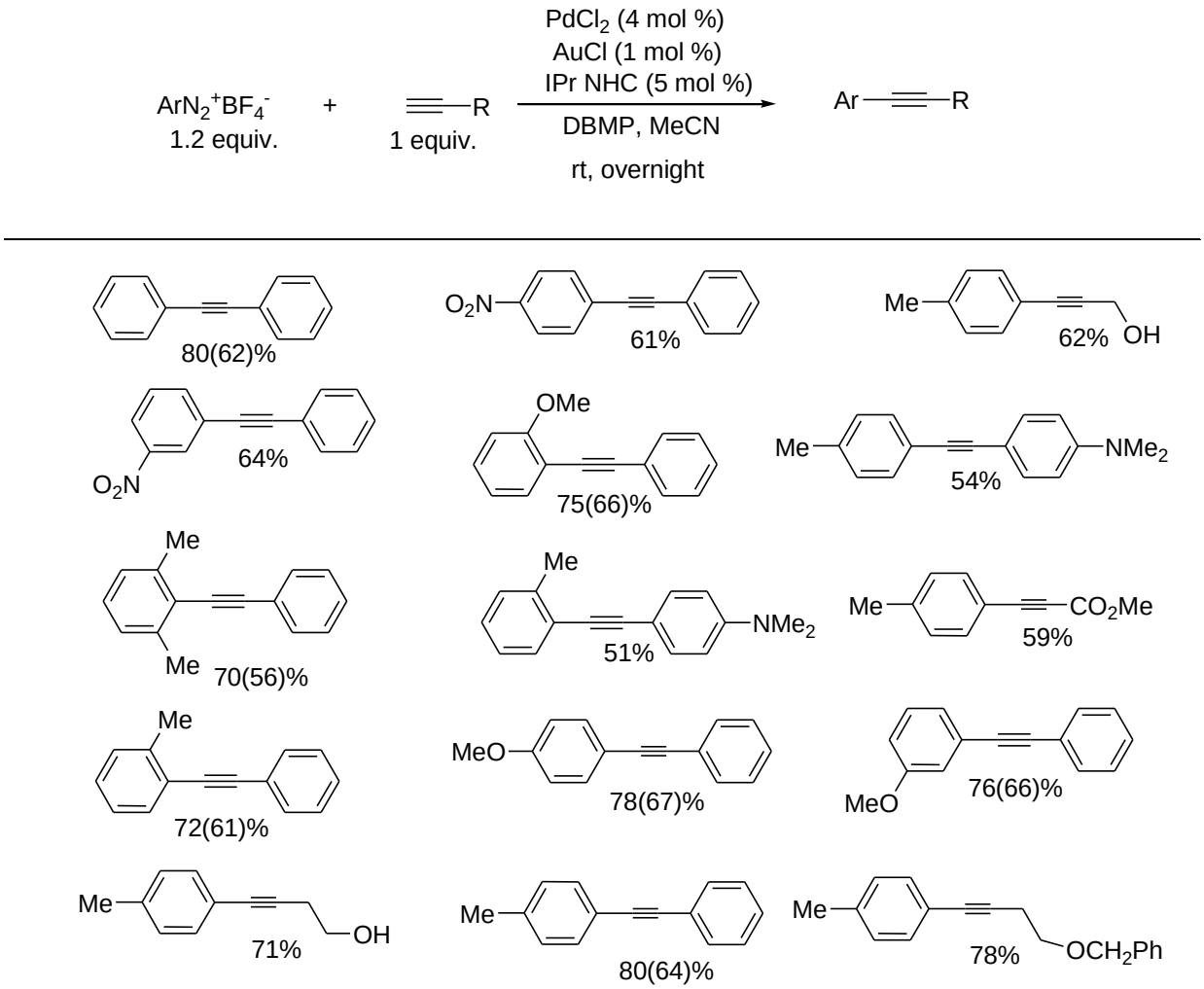


Scheme 20. One-pot methylation and Sonogashira coupling of dimethylanilines.

2.6. Activation of primary aromatic amines through diazonium salts

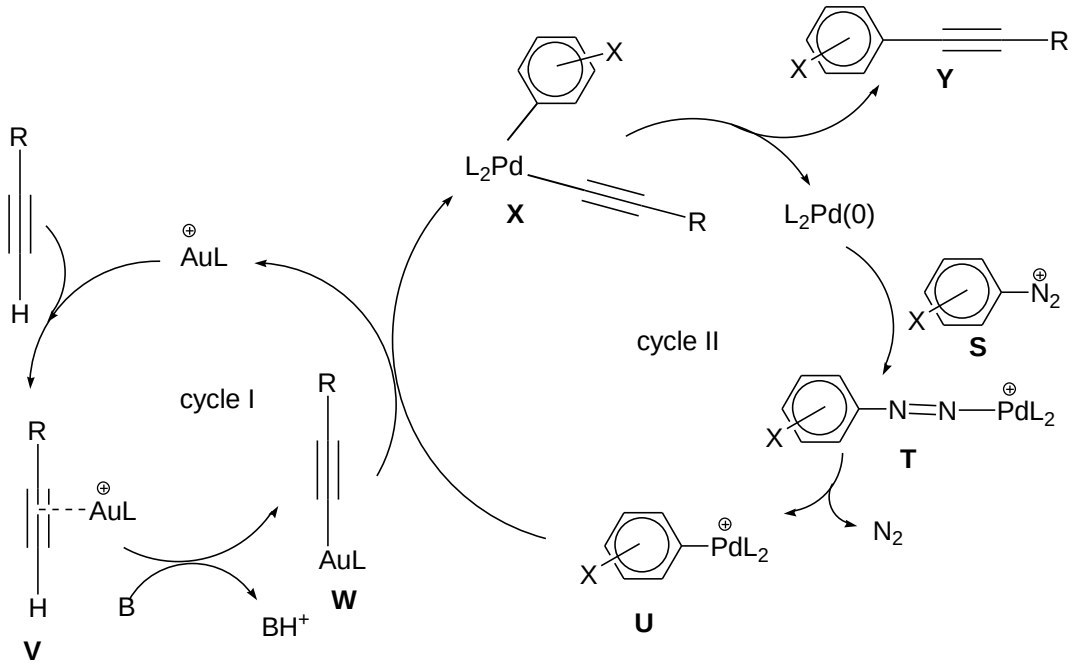
Recently, attention has focussed towards metal-catalyzed coupling reactions that include arenediazonium tetrafluoroborate salts as aryl surrogates. Aryl diazonium salts was discovered in the mid-19th century, when Johann Peter Griess was investigating azo compounds as dyes and pigments. These salts are a kind of super electrophile having the general formula of R-N_2X, where R is an aryl or heteroaryl component and X is a weakly nucleophilic organic or inorganic anion. Although some diazonium salts are available commercially, due to their high nucleofuge properties these are hazardous when used on a large scale. The stability of aryl diazonium salts depends mainly on the related counterion, although the electronic nature of aryl component should also be considered. Therefore, while aryl diazonium chlorides and acetates are unstable above 0°C, their tetrafluoroborate, tosylate, and disulfonamide salts are typically more stable and can be isolable as crystalline salts. Arene diazonium salts offer several noteworthy advantages as aryl halide substitutes. Firstly, they can be easily prepared with good yields from corresponding aromatic amines. Secondly, they are more reactive in palladium-catalyzed cross-coupling reactions compared to aryl halide. Thirdly, these reactions can be generally carried out at lower temperatures (between 20 and 50 °C) without the requirement of additional base or salt, expanding the range of substrates, with sensitive functional groups, that can be tolerated. Fourthly, high levels of chemo- and regioselectivity can be achieved in cross-coupling reactions by employing arenediazonium salts. Finally, the N_2 leaving group in the cross-coupling reaction of arenediazonium salts does not interfere with the reaction mixture.

Although aryldiazonium salts were used as aryl halide surrogates in several Pd-catalyzed cross-coupling reactions, such as the Heck,[43-45] Suzuki–Miyaura,[46-48], carbonylative coupling,[49] carbon-heteroatom coupling, [50-52] and Stille reactions,[53] the Sonogashira cross-coupling has remained a challenge until our findings in 2010.[54,55] The first Sonogashira coupling of arene diazonium salts utilizing a Pd-Au synergistic dual catalytic system has been successfully developed.[56,57] The coupling of arene diazonium salts with terminal alkynes was performed at room temperature omnipresence of carbene ligand bis-2,6-diisopropylphenyl dihydroimidazolium chloride (IPr NHC) (5 mol %) and base DBMP(2,6-Di-*tert*-butyl-4-methylpyridine) in acetonitrile using AuCl as a co-catalyst along with $PdCl_2$ as catalyst. The synthetic efficiency of this reaction was investigated with a range of electronically and structurally varied arene diazonium salts and terminal alkynes. Arenediazonium salts, both electron-rich, and electron-deficient, were effectively coupled with both aryl and alkyl acetylenes to produce desirable arylated alkynes in high yields (Scheme 21). This method tolerates nitro, alcohol, benzyl ether, methoxy, methyl, ester, *N,N*-dimethylanilino, and other functional groups. Terminal alkynes couple lucidly with ortho-substituted arenediazonium salts and even highly sterically hindered 2,6-disubstited benzene diazonium salts. The one-pot direct in situ diazotization with *t*-BuONO and boron trifluoride followed by a cross-coupling reaction starting with anilines was proved to be effective using this strategy. In one-pot diazotization and cross-coupling processes, the yields given in parentheses in Scheme 3 are achieved directly from aniline.



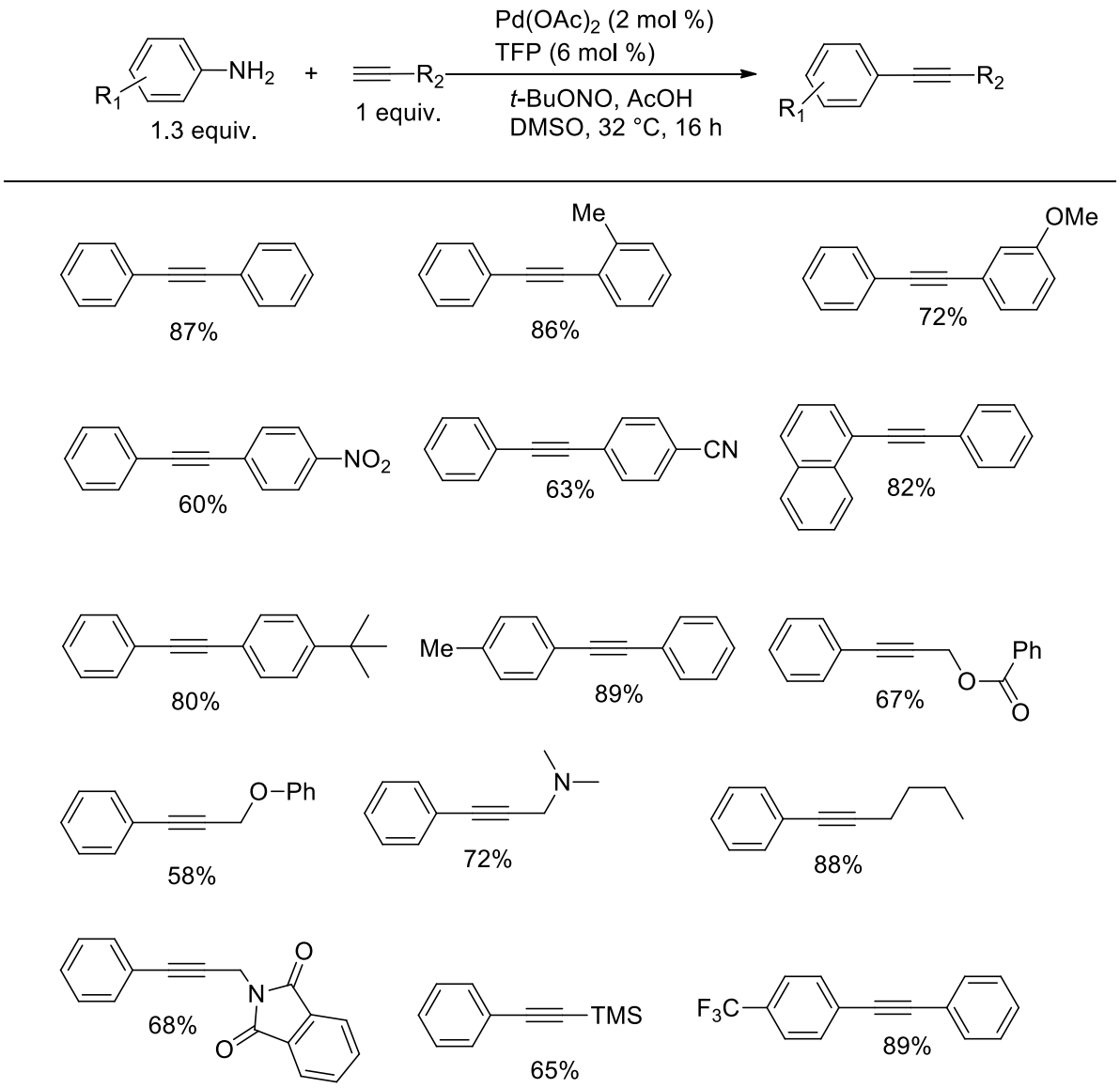
Scheme 21. Pd-Au dual catalytic Sonogashira coupling of arenediazonium salts.

Scheme 22 depicts a possible mechanism for Sonogashira coupling of arenediazonium salts utilizing the Pd-Au dual catalytic system.[58-76] This reaction is thought to have three stages: First, the cation **S** can coordinate the palladium(0) produced in situ to form cation **T** and then arene-palladium cation **U**, in which the palladium(0) has raised its oxidation number by two units. In the second step, the palladium species **X** is produced by transmetalation of the in situ generated alkynyl gold species **W**, which is synthesized by the initial coordination of gold to the alkyne followed by the abstraction of a proton from **V** by the base. The reductive elimination is the final step to yield the product **Y** and allow the regeneration of active palladium(0) complex for the next catalytic cycle.



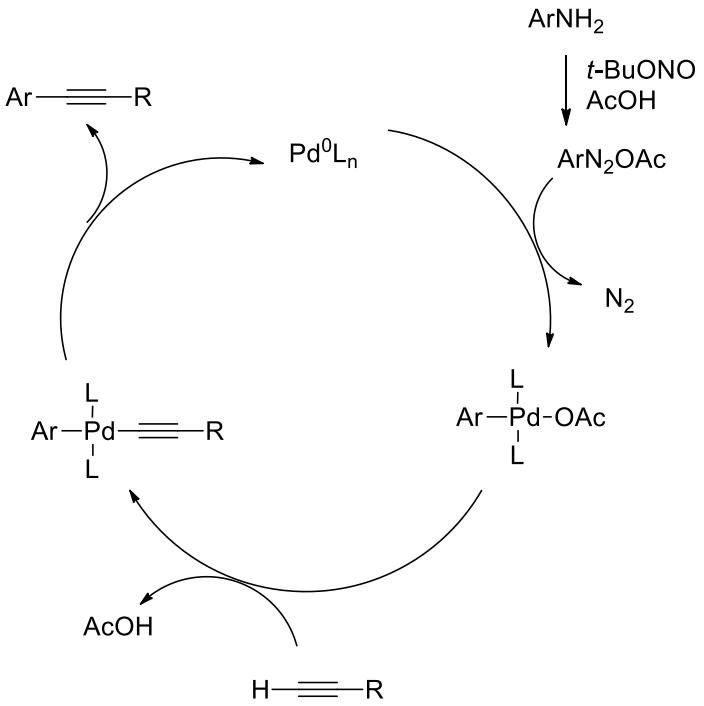
Scheme 22. Mechanism of Pd-Au dual catalytic Sonogashira-coupling of arenediazonium salts.

In 2011, Beller et al. described an efficient Sonogashira coupling of in situ-produced arene diazonium salts with alkynes to accomplish a range of arylated alkynes.[77] Of course, this approach is more direct and allows for a general and efficient palladium-catalyzed Sonogashira coupling of arene diazonium salts to produce good yields of internal aryl alkynes (Scheme 23). In this pleasant method $Pd(OAc)_2$ is utilized as a catalyst and a tri-heteroarylphosphane, such as tri(2-furyl)phosphane (TFP), is used as a ligand. Arenediazonium salts substituted with both electron-donating and electron-withdrawing groups are well tolerated in this process. This procedure has included a significant number of aryl, alkyl, and trimethylsilyl acetylenes in addition to a variety of arene diazonium salts. Use of base or co-catalyst being avoided as well as toleration of thermally unstable propargyl alcohol derivatives, such as phenyl propargyl ether, propargyl benzoate and others, were the merits of this protocol.



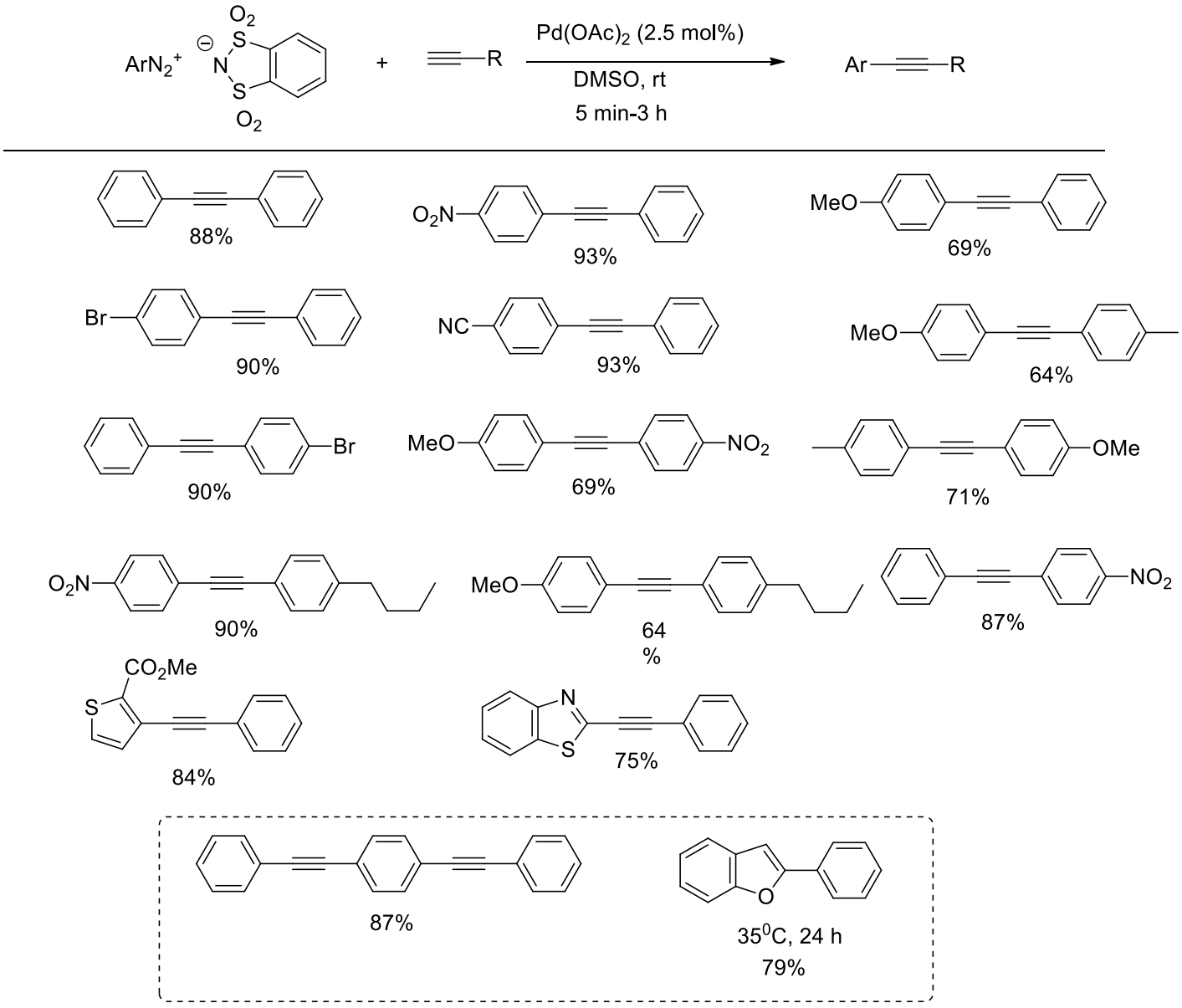
Scheme 23. Pd-catalyzed Sonogashira coupling of arenediazonium salts.

Scheme 24 depicts a simplified reaction mechanism for this innovative Sonogashira procedure. The aryl palladium (II) intermediate is formed by the oxidative addition of the in situ-produced diazonium salt to a Pd(0) phosphine complex, which is created from $Pd(OAc)_2$. Following acetate-assisted deprotonation of phenylacetylene, the aryl(alkenyl)palladium(II) species is generated, which then forms the final product by reductive elimination and regenerates the catalytically active Pd(0) species for the next cycle.



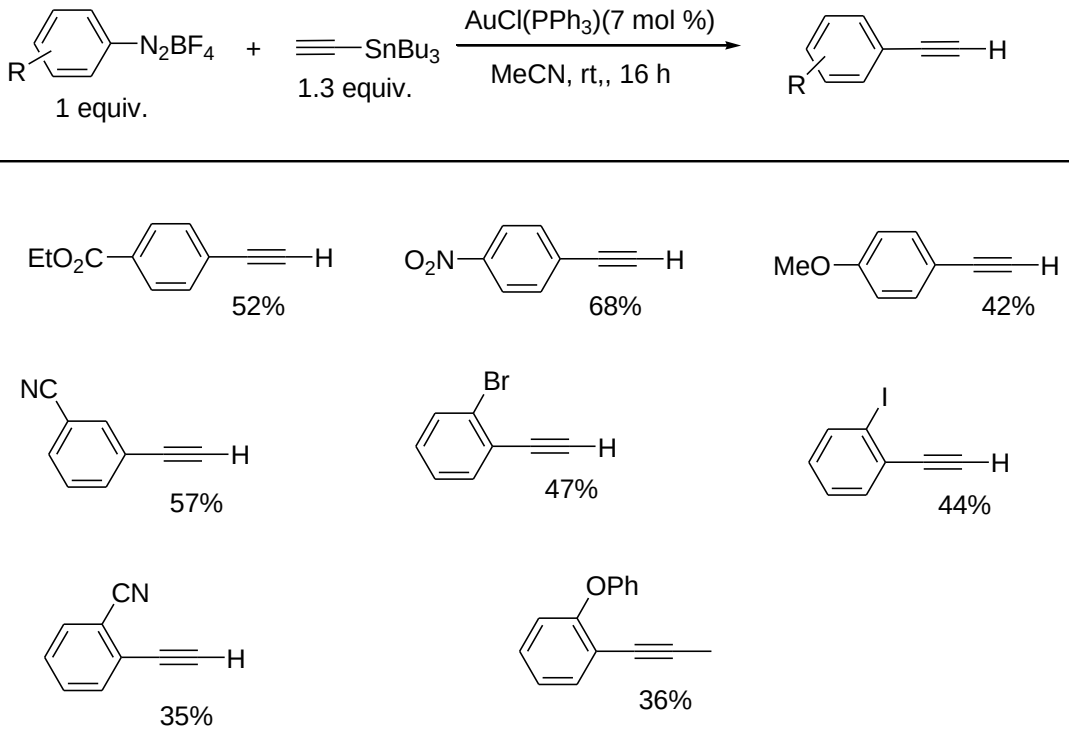
Scheme 24. Mechanism of palladium catalyzed Sonogashira-coupling of arenediazonium salts.

Dughera and co-workers developed a methodology for Sonogashira coupling of arene diazonium O-benzenedisulfonimides using palladium-catalyst and under copper- and phosphane-free conditions in 2014. (Scheme 25).[78] This procedure was made user-friendly by the use of arene diazonium O-benzenedisulfonimides, which are simple to prepare and have greater stability than arene diazonium halides. It did not need the use of a base, ligand, or co-catalyst. The advantages of this strategy are the high yield and cleanness of the processes. The anion of O-benzenedisulfonimides and DMSO both play important roles in the formation of the real Pd(0) catalyst, according to a mechanistic analysis. It was also discovered that DMSO plays an important part for increasing alkyne reactivity. Under these conditions, aromatic rings with two diazonium groups can also be engaged in cross-coupling. In the presence of two equivalents of phenylacetylene, benzene-1,4-bis(diazonium) O-benzenedisulfonimide coupled effectively to provide the bis-alkyne product in good yield (shown in dashed box). The coupling of 2-hydroxybenzene diazonium salt with phenylacetylene yields 2-phenylbenzofuran in a good yield, through the spontaneous cyclization of initially produced 1-(2-hydroxyphenyl)-2-phenylacetylene.



Scheme 25. Sonogashira-coupling of arene diazonium O-benzenedisulfonimides salts.

In 2015, Patil and co-workers reported various cross-coupling reactions of aryldiazonium salts with organostannanes in the presence of a gold catalyst.[79] In this protocol, they showed that arylation, vinylation, and alkynylation were feasible using the corresponding organostannanes with the reaction of arenediazonium salts. The reaction proceeds at room temperature in an acetonitrile solvent. The alkynylation using alkynylstannane successfully provided the desired product in good yields (Scheme 26). Various functional groups substituted on the aromatic ring of arenediazonium salts, such as –CO_2Et, -NO_2, -OMe, -CN, -Br, -I, -OPh, etc., were well-tolerated under this protocol.



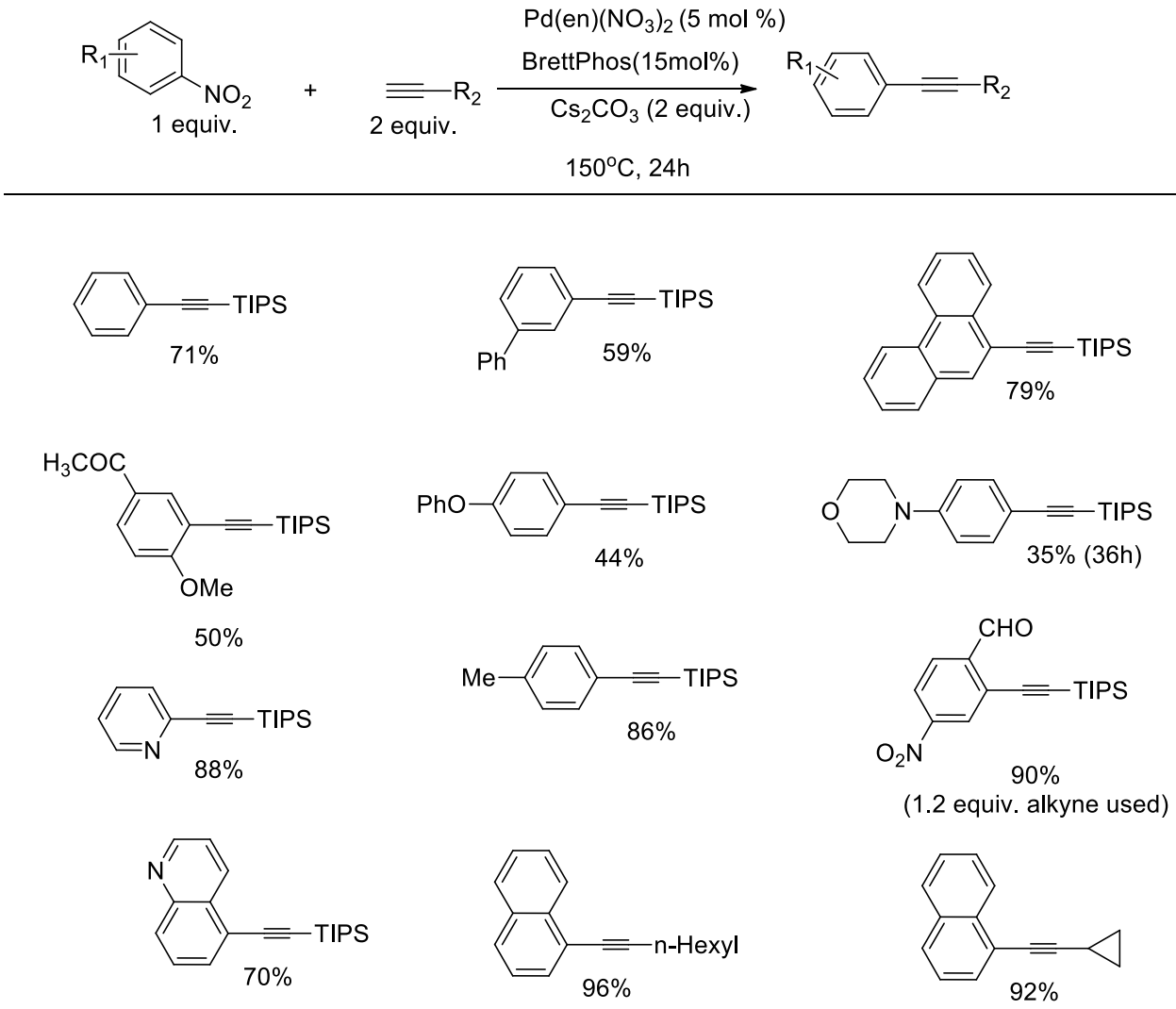
Scheme 26. Gold-catalyzed alkynylation of arenediazonium salts with alkynylstannanes.

2.7. Activation of nitroarenes

Nitroarenes are common chemically important raw materials that may be prepared by the nitration of arenes. Recent advancements in the development of milder nitration techniques using highly electrophilic reagents have made it possible to avoid the use of highly acidic conditions. Consequently, late-stage nitration of complex compounds has become feasible. Nitroarenes have not been widely used in cross-coupling, most likely because there isn't an efficient metal catalyst that can effectively cleave the C–NO_2 bond.[80] The NO_2 group itself frequently results in the unwanted deactivation of metal catalysts, considering the inherent inertness of C-NO_2 bonds against transition metal catalysts. Additionally, phosphene reagents, which are frequently employed as a ligand for most of the metal catalysts, have the power to reduce nitro groups, resulting in the production of nitroso compounds and species similar to nitrene and creating a dead-end catalytic pathway. Because of these limitations, the application of nitroarenes as suitable electrophilic coupling partners in denitrative cross-coupling processes has been considered a challenging task. Two issues must be resolved to create denitrative alkynylation reactions involving transition metals: (1) the suppression of alkyne homocoupling and addition-based enyne formation; and (2) the activation of the C_{Aryl}-NO_2 bond, which is generally inert in transition metal-catalyzed coupling reactions. In the year 2017, Nakao and coworkers showed that nitroarene can be a coupling partner in the Suzuki-Miyaura cross-coupling reaction in the presence of a palladium catalyst.[82] This study proved that Ar-NO_2 bonds may be added oxidatively to a transition-metal core. After that, various methods for the palladium-catalyzed denitrative Buchwald-Hartwig amination, denitration under reductive conditions, and C-H arylation were published.

Feng and coworkers described an effective method for forming a Csp^2–Csp bond through the cross-coupling reaction between nitroarenes and terminal alkynes in the presence of a palladium catalyst in 2019 (Scheme 27).[83] It was found that XPhos, RuPhos, dppb, and SIPr were shown to be inappropriate ligands for $Pd(OAc)_2$, but BrettPhos (2- (Dicyclohexylphosphino) 3,6-dimethoxy-2',4',6'-triisopropyl -1-1-biphenyl) had a favorable impact. According to optimization studies, $Pd(en)(NO_3)_2$ and $Pd(acac)_2$ have nearly identical performances. In

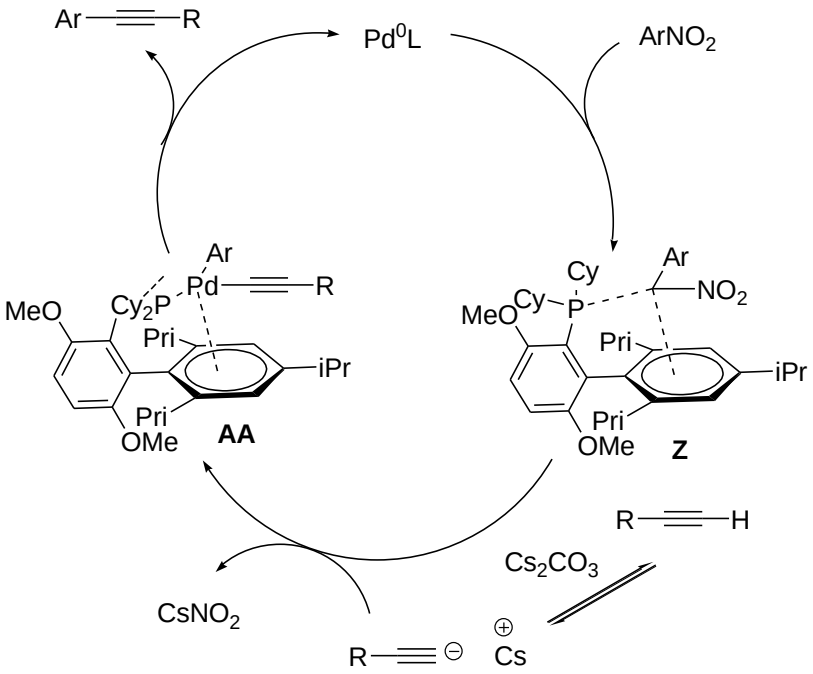
the absence of the catalyst, the reaction failed. CuI and CuF_2 were shown to cause alkyne homocoupling and Pd catalyst deactivation when used as additives. Cs_2CO_3 was identified to be an effective base for obtaining the required product in good yields after screening organic and inorganic bases. The screening of various reaction conditions revealed that raising the temperature to 150 °C was beneficial in achieving this transition. As a result, a wide spectrum of nitroarenes, including hetero-nitroarenes, may be converted to the desired products in moderate to excellent yields. C–H activation resulted in the C2 position via the directing activity of the formyl group when 2,4-dinitrobenzaldehyde was used as one of the coupling partners. When 4-fluoronitrobenzene was used as a substrate, selective denitration was found, whereas 4-bromo- and 4-chloro-1-nitrobenzenes resulted in mono- and di-alkynylation. Although the reaction was unsuccessful in the presence of phenylacetylene, it was effective in the presence of aliphatic acetylenes. The synthesis of phenanthrene, 9,90-bifluorenylidene, and spirobifluorene derivatives was carried out using this technique.



Scheme 27. Sonogashira coupling of aromatic nitro compounds.

The authors have proposed a possible mechanism for the dinitrative alkynylation of nitroarenes as depicted in Scheme 28. The reaction begins with the oxidative addition of the Pd(0)/BrettPhos complex with the C-NO_2 bond of nitroarene which formed the intermediate **Z**. On the other hand, terminal alkyne coordinates the metal complex and the base Cs_2CO_3 abstracts the proton from the activated terminal alkyne to generate cesium

acetylide, which then enters into the catalytic cycle and reacts with intermediate **Z** to form intermediate **AA**. Finally, the desired product was obtained through reductive elimination together with the regeneration of the active catalyst, which can further participate in the next catalytic cycle.



Scheme 25. A proposed mechanism for alkynylation of nitroarenes.

The reaction systems, where organic nitrogen compounds were used as aryl or alkyl surrogates for the alkynylation reaction that proceeds through the activation of carbon-nitrogen bonds, are summarized in Table 1 to acquire a clear outline of this research area. The comparative studies of catalyst stability reveal that when nickel catalysts are used, higher loading is required compared to the palladium catalysts. Additionally, the N-heteroatom-containing carbene palladium complex is more reactive in oxidative addition proceeding at low temperature compared to palladium phosphine complexes due to strong σ-donation as well as π-back-bonding of NHC ligands.

Table 1. Summary of alkynylation reactions proceeds through C-N bond activation

Nitrogen compounds	Scheme	Catalyst(s)	Oxidant	Temp.	Ref.	Authors
Aryl Hydrazines	2	$PdCl_2$ (5 mol%), PPh_3 (30 mol%)	O_2	50 °C	25	Zhao et al.
	3	CuCl (5 mol%)	O_2	rt	26	Hwang et al.
Amides	5	$Pd(OAc)_2$ (3 mol%), dppp(6 mol%)	-	150°C	30	Chen et al.
	7	$Pd(PPh_3)_2Cl_2$ (1 mol%)	-	65°C	31	Zeng et al.
	9	$Ni(cod)_2$ (20 mol%), dcype (40 mol%), CuI (10 mol%)	-	150°C	32	Rueping et al.
Benzylammonium Salts	10	$Pd(PPh_3)_4$ (5 mol%)	-	100°C	35	Zhao et al.
Aryltrimethylammonium Salts	12	SIPr-$PdCl_2$-Py (10 mol%)	-	45°C	39	Cao et al.
	15	$PdCl_2(PPh_3)_2$, (5 mol%), P(p-OMe Ph)$_3$ (10 mol%)	-	90 °C	40	Wang and Wu
	16	Pd(IPr)(3-CF_3-An)Cl_2 (10 mol%)	-	45°C	41	Lei et al.
Tertiary Amines	17	SIPr-$PdCl_2$-Py (10 mol%)	-	45°C	39	Cao et al.
	18	$Pd_2(dba)_3$ (0.5 mol%), PPh_2Cy(1 mol%)	-	120°C	42	Chen et al.
	20	Pd(IPr)(3-CF_3-An)Cl_2 (10 mol%)	-	45°C	41	Lei et al.
Arenediazonium Salts	21	$PdCl_2$(4 mol%), AuCl(1 mol%) IPr NHC (5 mol%)	-	rt	56	Panda and Sarkar
	23	$Pd(OAc)_2$ (2 mol%), TFP(6 mol%)	-	32 °C	77	Beller et al.
	25	$Pd(OAc)_2$ (2.5 mol%),	-	rt	78	Dughara et al.
	26	PPh_3AuCl (7 mol%)	-	rt	79	Patil et al.
Nitrobenzenes	27	$Pd(en)(NO_3)_2$ (5 mol%), Brettphos (15 mol%)	-	150°C	83	Feng et al.

3. Conclusions

This review explores recent advancements in the alkynylation process through the oxidative addition of transition metals to activate C-N bonds. Several alkynylation methods have been devised to facilitate the

activation of challenging C-N bonds, as exemplified in this discussion. In the realm of aryl carbon-nitrogen bond activation, the range of suitable substrates has progressed from aryldiazonium salts to aryltrialkylammonium salts, and ultimately to anilines and aryl nitro compounds. This development of abundant C-N bonds enables chemists to access functionality more directly from raw materials, thereby reducing the number of intermediary steps. Since C-N bonds are prevalent in numerous organic molecules, utilizing them as functional inputs opens up new possibilities for route design and scaffold diversification. In order to further advance the field of C-N bond activation, the development of more efficient and high turnover catalyst designs will undoubtedly be necessary. Despite significant progress, a deeper understanding of the activation processes and improvements in atom economics are still required to advance this research area. The methods and mechanistic insights outlined in this review can serve as a source of inspiration for the chemical community in the pursuit of further developments in this field.

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Abbreviations

AcOH	acetic acid
An	aniline
BrettPhos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6' -triisopropyl-1,1' -biphenyl
COD	cyclooctadiene
cy	cyclohexyl
dba	dibenzylideneacetone
DBMP	2,6-Di-tert-butyl-4-methylpyridine
DFT	density functional theory
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPPP	1,3-bis(diphenylphosphino)propane
dcype	1,2-Bis(dicyclohexylphosphino)ethane
dppb	1,4-diphenyl phosphinobutane
equiv	equivalent
en	ethylenediamine
IPr	1,3-bis(2,6-diisopropylphenyl)imidazolium
OAc	acetate
OTf	triflate
Py	pyridine
RuPhos	2-dicyclohexylphosphino-2', 6' -diisopropoxy-1,1' -biphenyl
SET	single-electron transfer
SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine

TFA	trifluoroacetic acid
TMS	trimethylsilyl
TFP	tri(2-furyl)phosphane
Xphos	2-(dicyclohexylphosphino)-2', 4', 6' -triisopropylbiphenyl

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Author's Biography

Dr. Biswajit Panda was born in West Bengal, India, in 1984. He started his academic journey by earning a Bachelor of Science degree in Chemistry from Vidyasagar University, West Bengal, India, in 2004. After receiving his undergraduate degree, he pursued higher education and obtained a Master of Science degree in Chemistry from the prestigious Indian Institute of Technology, Kharagpur (IIT KGP), India.

Inspired by his passion for chemistry, Dr. Panda pursued his doctoral studies in Organic Chemistry at IIT KGP under the guidance of Professor Tarun K. Sarkar. In 2012, he successfully defended his thesis and was awarded his Ph.D. degree. During his doctoral studies, he gained expertise in organic synthesis, total synthesis of natural products, and development of new methodologies in organic reactions. After completion of doctoral degree, Dr. Panda joined the research group of Professor Tien Yau Luh at National Taiwan University, Taiwan as a postdoc fellow. His postdoctoral research focused on the synthesis of cyclopropene fused azetidine monomers and their polymerization to obtain a new type of two-dimensional covalent organic framework, namely stromaphane.

In 2015, Dr. Panda returned to India and joined City College, Kolkata, West Bengal, India, as an Assistant Professor of Chemistry. He is associated with teaching organic chemistry to undergraduate, graduate, and postgraduate students. He has published several research articles in peer-reviewed journals, presented his work at various national and international conferences. His research interests include developing new reaction methodologies and natural product synthesis.