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Transition Metals Catalyzed Element-Cyano Bonds Activations

Rui Wang^{1,2} and John R. Falck¹

¹Department of Biochemistry, Division of Chemistry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

²Department of Chemistry, State University of New York at Albany, Albany, New York, USA

Abstract

Cyano group as a versatile functionalized intermediate has been explored for several decades, as it readily transfers to many useful functionalization groups such as amine, amide, acid, etc., which make it possess high popularization and use value in organic synthesis. Reactions involved with element-cyano bond cleavage can provide not only a new cyano group but also a freshly functionalized skeleton in one-pot, consequently making it of high importance. The highlights reviewed herein include H-CN, Si-CN, C-CN, B-CN, Sn-CN, Ge-CN, S-CN, Halo-CN, N-CN, and O-CN bonds cleavages and will summarize progress in such an important research area. This review article will focus on transition metal catalyzed reactions involving element-cyano bond activation.

Keywords

Bond activation; Carbon-carbon formation; Dehydrogenative coupling reactions; Elements-cyano; Transition metals

1. INTRODUCTION

Synthetic organic chemistry has advanced significantly during the past few decades. These achievements made it much simpler to construct complex molecule through manipulation of the classic strategies from commercially available starting materials, which predominantly included the carbon bond-formation reactions, *viz.* Aldol reaction, Diels-Alder reaction, Grignard reagent addition reaction, Heck reaction, Michael reaction, Wittig reaction, and most recently the RCM reaction (RCM or Ring Closing Methathesis, is a variation on olefin metathesis that especially allows the closing 7–8 member rings).

Although these carbon-carbon formation methods have made considerable use in pharmaceutical and medical chemistry, there is additional high demand for these reactions via green chemistry and sustainability technology. Other bond-bond construction reactions such as carbon-nitrogen and carbon-oxygen formations are reported to a less extent.

Address correspondence to Rui Wang, Department of Biochemistry, Division of Chemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9038, USA. rui.wang@utsouthwestern.edu.

Actually, one of the unremitting efforts that modern chemists are pursuing constantly is to develop efficient methods for bond activation and related synthetic reactions. Moreover, less or even no waste intermediates will be generated during the transformations of new and efficient types. However, before these expectations can realize, there are still challenging tasks. The breaking of existing C-H bonds to form new bonds is one of the difficulties to be resolved. Although impressive achievements have also been made in this field, there are still unsolved issues, e.g., selective cleavage of a specific carbon-hydrogen bond in a random molecule which seems to be a very challenging topic nowadays.

Fortunately, organic chemists have been successful in broad aspects of relevant fields. In the past, in the process of dehydrogenative coupling reactions, toxic reagents and tedious steps were needed to make the transformation successful. However, things have been changed greatly in the last few decades. By applying suitable catalyst, the formation of new carbon-carbon bond has been achieved via cleavage of carbon-hydrogen bond.

These reactions, namely dehydrogenative coupling reactions, are required to be catalyzed by the transition metal complexes or enzyme. The transformation enables the most straightforward manipulation of organic synthesis accompanied only with the release of hydrogen molecule. Compared with traditional pre-activation methods, this strategy will be highly appreciated in the future as it is today:

Notably, it has been popular to investigate regio- and chemo-selective activation of traditional inert bond, particularly due to the aspect of atom economy. Among these classes of reactions, carbon-carbon bond activation is undoubtedly in the central field of current research. Given the most common C-C bond and the C-H activations, many of other elements such as silicon, boron, tin, sulfur, oxygen, nitrogen, etc., are of the same importance, or maybe more important if taking the use of the versatile cyano group in consideration.

Cyano groups as versatile intermediates can be easily transferred to many functionalized groups, as summarized in Fig. 1. These include most common functionalization groups, *viz.*, (i) amine; (ii) amide; (iii) acid; (iv) ester; (v) aldehyde; (vi) thioamide; (vii) hydroxyimide; (viii) ketone, etc. Recently, several new strategies have been reported. The cyano groups were replaced subsequently by hydrogen atom, silicon group, boronic group, amino group and phosphonic group (19–24). All these methods make the cyano groups important precursors in many transformations.

Actually, the relevant bonds dissociation energies are summarized in Table 1, which intuitively indicate the strength of bonds between different atoms such as C-H, C-C, C-O, C-N, etc. The data directly show the nature (i.e., cleavage energy of C-C bond is much higher than C-H bond) of these transformations in the reactions involving bond cleavage.

In view of these data, we herein report on bond activations between the elements (H, Si, C, Sn, Ge, S, B, Br, I, O, and N) and cyano groups, and address their useful applications. All of

the reactions were realized via transition metals catalyzed elements-CN bond cleavages. Other processes such as photochemical reactions involving cyano groups will not be included herein.

Interestingly, a nitrile group can also serve as a directing group for the C-H activation (1). In this transformation, the π -electrons obtained from the nitrile group seem to participate in directing the ruthenium atom in the catalyst $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ close to the ortho C-H bond (Eq. (2)). The exclusive ortho selectivity indicates that a nitrile group can assist geometric proximity of the ruthenium to the ortho C-H bond. When the reaction was conducted using 1 equiv of the vinylsilane, both the single addition product and the double adduct were formed in 18% and 19% yields, respectively. The case definitely indicated that as a useful directing group, the cyano can be of importance due to the *ortho*-functionalization followed by its further manipulation:

(2)

Notably, Yu et al. (2) recently disclosed a cyano group assisted meta selective C-H bond activation. This template design is based on the interaction between Pd(II) and a nitrile group in a tail-on fashion. This novel strategy for directing meta selective C-H bond activation provides a powerful route for the preparation of aromatic derivatives that are difficult to obtain via existing C-H activation methods (Eq. (3)). As a directing group, the cyano group assisted the alkenyl group to be predominately attached to the *meta* position of arenes. The aromatic C-H bond can be functionalized efficiently to provide *meta*-alkenylated aryl derivatives in moderate to good yields. In view of the effective alkenylation of the aryl group, this method can be of considerable importance.

In addition to useful precursors and interesting directing groups, which were previously presented, the cyano groups serve as strong electron-withdrawing species were also with significant applications.

For example, in 2011, Falck et al. (3) disclosed a Pd (II)-mediated cross-coupling of α -cyanohydrin triflates with boronic acids (aryl, hetero-aryl, and vinyl) under mild conditions (Eq. (4)). The process proceeds with total inversion of configuration at the stereogenic carbon. The products can be easily transferred to valuable functional groups and consequently achieve a higher level of molecular diversity than the products of Suzuki reactions. This case demonstrated that, as a strong electron-withdrawing group, cyano can realize useful transformation.

(3)

(4)

(5)

A similar strategy was employed in the coupling reported by Liu et al. (Eq. (5)) (4). The palladium-catalyzed decarboxylative coupling process of the cyano-acetate salt as well as its mono- and disubstituted derivatives with aryl chlorides, bromides, and triflates are described. This reaction is valuable for the preparation of a wide range of α -aryl nitriles and its good functional group tolerance. These two cases clearly demonstrated the useful properties of cyano group, namely, electron-withdrawing nature.

Another interesting case is a Lewis base catalyzed enantio-selective addition of an *N*-silyl vinyl ketene imine to aldehyde (Eq. (6)) (5). In the title reaction, the nucleophile represents a synthetic equivalent of nucleophilic allylic nitriles and addresses some of the current limitations associated with reactions of allylic nitrile anions. Unsaturated nitriles containing a trisubstituted double bond are obtained in high yield, with excellent regio selectivity and good to excellent stereo-selectivity. This case demonstrated the unique and useful electron

withdrawing nature of cyano-containing compounds and expands their usefulness in synthetic applications.

(6)

All of the cases reported above represent the valuable applications of cyano group. Reactions involved with additional bond cleavage/generation along with cyano group manipulation can be of high importance due to the inert nature of cyano group, which have been presented in the text above.

Owing to its considerable applications, the cyano group has gained vast research focus in organic chemistry nowadays. Herein, we will focus on the tandem transformations, including: *viz.* H-CN, Si-CN, C-CN, B-CN, Sn-CN, Ge-CN, S-CN, Halo-CN, N-CN, and O-CN bonds activation. Plausible mechanism studies and their useful applications will be highlighted therein.

2. ELEMENT-CN BONDS ACTIVATION REACTIONS

2.1. Hydro-cyano Bond

Hydrogen cyanide is a colorless, poisonous liquid. It boils at ambient temperature (26°C), which significantly hinders its synthetic usefulness. HCN is produced on an industrial scale and is a highly valuable precursor to plenty of products ranging from polymers to pharmaceuticals, thus making it be of high importance in organic synthesis. However, due to the volatile nature, HCN has also been used as inhalation rodenticide and as human poison, or animal poison. All of these aspects of hydrogen cyanide led to the important as well as limited aspects of practical usefulness in synthetic organic chemistry.

The original discovery dealing with a homogeneously catalyzed HCN addition to non-functionalized alkenes was disclosed by Arthur et al. in 1954 (6). They revealed that several alkenes were transformed to the corresponding nitriles using $\text{Co}_2(\text{CO})_8$ as a pre-catalyst. Considerable results were disclosed using this method. A cyano group is a synthetic equivalent of carbonyl and related functionalities, and its introduction into organic molecule, particularly by transition metal catalysis, has been a major challenge in synthetic organic chemistry. Therefore, the addition of HCN to alkene is a very useful reaction for the synthesis of functional organic substrates in view of atom-economy.

Industrially, the nickel-catalyzed hydro-cyanation has gained considerable interest, mainly due to the production of adiponitrile in the DuPont process, with a total annual production of approximate one million tons in late 1960s (7).

Relevant knowledge of these steps is summarized and elucidated. The DuPont process comprises three separate steps (Scheme 1): (i) the hydro-cyanation of 1,3-butadiene and other conjugated dienes; (ii) the isomerization of 2-methyl-3-butenenitrile to 3-pentenitrile; and (iii) the hydro-cyanation of 3-pentenitrile and other mono-alkenes. Further mechanistic investigation is still in progress for the improvement of catalyst performance and for development of this process to its full potential in organic synthesis.

Another useful aspect of hydrogen cyanide is the hydro-cyanations of α,β -unsaturated carbonyl compounds. The competition is between 1,2-addition vs. 1,4-addition. Direct addition adduct versus conjugate addition product depends on several factors. The structure of the carbonyl compound is important, as β -substitution and adjacent angular substituents sterically disfavor 1,4-addition. The nature of the cyanated reagent also plays an important role. When dialkylaluminum cyanides are used, the transformation of a six-member transition state with *s-cis* enones may favor 1,4-addition. Low steric cyanated reagents such as alkali metal cyanides and cyano-aluminates prefer to add in a 1,4-fashion, whereas Lewis acidic cyanides, such as TMSCN (trimethylsilyl cyanide), favor 1,2-addition.

Actually, the asymmetric conjugate addition of cyanide to α,β -unsaturated carbonyl compounds is a highly versatile reaction. Significant achievement has recently been made in the catalytic asymmetric variant using α,β -unsaturated carboxylic acid derivatives (imides and *N*-acylpyrroles). Synthetically useful catalytic asymmetric conjugate addition of cyanide to enones, however, has been developed rarely. This sharp contrast with respect to substrates is due to the ambient characteristics of enones. There are two possible pathways from enones, 1,2-addition vs. 1,4-addition (Scheme 2). Therefore, differentiation of the two pathways, in addition to enantio-selection, is necessary.

However, catalytic control of even one of these two factors is not easy. Interestingly, Shibasaki et al. reported the first synthetically useful catalytic enantio-selective conjugate addition of cyanide to enones (Scheme 3) (8). This powerful synthetic strategy allowed the selective generation of β -cyano ketones (1,4-adducts) from enones with high enantio-selectivity via catalytic Gd complex. Alkyl and cyclo-alkyl substituted olefins are also compatible in these transformations. In contrast to most cases of aldehydes as substrates, the alkyl- and aryl-substituted ketones are tolerated. This process afforded corresponding adducts in good to excellent yields (up to quantitative) and up to 98% ee (enantiomeric excess). This makes it a useful process for the introduction of chiral cyano group in the systems.

Notably, the selective production of α -cyano hydrins (1,2-adducts) from enones with high enantio-selectivity using catalytic Gd complex have also been disclosed in 2001 (9) by Shibasaki and co-workers (Scheme 4). Catalytic enantio-selective synthesis of the key intermediate for (20*S*)-camptothecin family by (*S*)-selective cyano-silylation of ketones was also reported (9). Interestingly, alkyl and aryl substituents in the α -position of olefins were

tolerated. Two examples indicated that only aliphatic-substituted ketone was realized in such transformation. Combining the previous results, the regio- and enantio-selectivity of adducts can be obtained separately.

Acetone cyanohydrin has been employed as a source of HCN for several decades (Scheme 5), which can prevent the use of toxic cyanohydrin. The addition of cyanide to a carbonyl compound to provide a cyanohydrin is one of the fundamental carbon-carbon bond formation reactions in organic chemistry and has frequently been at the forefront of advances in chemical transformations.

Cyanohydrin synthesis was firstly reported by Winkler in 1832 using hydrogen cyanide as the cyanide source (10a). In 1837, Wöhler identified an oxynitrilase enzyme (this class of enzymes is also called hydroxynitrile lyases) which is existed in almonds (10b). The inert role of this enzyme is to decompose mandelonitrile (2-hydroxyphenyl-acetonitrile) to benzaldehyde and hydrogen cyanide, the reverse of the synthetically more useful synthesis of cyanohydrins from aldehyde and hydrogen cyanide. In 1908, Rosenthaler successfully employed an extract of almonds to mediate the asymmetric addition of hydrogen cyanide to benzaldehyde (10c). This was one of the first asymmetric syntheses ever reported and the first to be catalyzed by an enzyme, thus placing asymmetric cyanohydrin synthesis at the leading edge of asymmetric organic synthesis. In 1903, Lapworth carried out early mechanistic studies on cyanohydrin synthesis and demonstrated that the reaction was base catalyzed, with the role of the base being to convert hydrogen cyanide into the nucleophilic cyanide ion (10d). The reaction is also known to be reversible, with the position of equilibrium being determined by a combination of steric and electronic factors.

Pioneering discoveries on cyanohydrin synthesis were all carried out with hydrogen cyanide as the cyanide source. The volatility and extreme toxicity of this reagent cause obvious difficulties, and numerous alternative cyanide-based reagents have since been developed. Since the addition reaction is base catalyzed, the simplest approach is to use a metal cyanide salt as the cyano source in the presence of a slightly less than stoichiometric amount of acid.

As a well-established strategy, HCN as a source of cyano functioned group has been broadly investigated, although mostly in a non-enantio-selective manner. However, the enantio-selective construction of chiral cyanides are also reported.

One interesting case is disclosed by Chang et al. (10e) A procedure for the Cu-catalyzed hydro-cyanation of α -aryl diazoesters has been developed using acetone cyanohydrin as the source of hydrogen cyanide. It was observed that the addition of trimethylsilyl cyanide significantly accelerates the conversion presumably by generating free cyanide ion in situ, thus affording various types of α -aryl cyano-acetates in high yields under mild conditions (Scheme 6). Variable substituents on the arenes were compatible and up to 93% isolated yields were realized. In view of the interesting H-CN bond cleavage, the method disclosed herein is valuable due to the easily accessed of chiral cyanates generated from α -aryl diazoesters, which was mediated by a copper(I) catalyst.

As a surrogate of hydro-cyanation, acetone cyanohydrin was employed in the hydro-cyanation of styrenes by Ni(0) and chiral phosphine ligand via cleavage of the H-CN bond (Scheme 7).

In 2013, Schmalz et al. (11) disclosed an enantio-selectively nickel-catalyzed hydro-cyanation of vinylarenes using HCN accompanied with chiral P-P (phosphorus-phosphorus) ligands. A wide range of substrates, i.e., substituted-arenes, terminal olefins, and α -alkyl-substituted olefins were tolerated (these functionalized groups are not reacted under these reaction condition). This case indicated the useful prospects of acetone cyanohydrin, which can be used as a chiral cyano group equivalent.

Chiral catalytic Ru(II) assisted cyano-hydride addition to amines has also been disclosed via cleavage of H-CN bond, which can produce chiral amino nitriles. In 2012, Ohkuma et al. reported an enantio-selective hydro-cyanation of *N*-benzyloxycarbonyl aldimines catalyzed by a Ru[(*S*)-phgly]₂ [(*S*)-binap]. C₆H₅OLi system or a bimetallic complex [Li{Ru[(*S*)-phgly]₂ [(*S*)-binap]}]Cl, which successfully affords the amino nitriles (Scheme 8) (12). Primary, secondary, and tertiary alkyl amines as well as the aromatic and hetero-aromatic substrates are smoothly cyanated to afford the desired products in up to quantitative yield and 99% ee value. The compatible substrates allow broad application due to the wide range and ready manipulation of the cyano groups to a vast variety of functional groups.

Actually, this catalyst system has been utilized by Ohkuma and co-workers in 2011 (Scheme 9) (13). A wide range of aromatic, hetero-aromatic, and α,β -unsaturated aldehydes as well as a *tert*-alkyl aldehydes are transformed to the corresponding cyanohydrins in high yields (up to 99%) and high enantiomeric excess (up to 99% ee). The current method allows an efficient construction of α -substituted (alkyl, aryl, and styryl) chiral cyanates initiated from benzaldehydes, which were mediated by catalytic ruthenium complex via activation of the H-CN bond.

2.2. Silyl-cyano Bond

As an equivalent of hydro-cyanide, silyl-cyanide was frequently employed in modern transformation owing to its commercial availability and easy manipulation. In most instances, silyl-cyanide served the same function as HCN. Owing to the inert nature of cyanohydrins, especially the high toxic property (the easy evaporation of cyanohydrin even at ambient temperature), silyl-cyanide is frequently used as a powerful surrogate of cyanohydrins in modern organic chemistry.

A large number of relevant research have been reported. Representatively, one of the interesting cases is shown below in Scheme 10. During the synthesis of PDE₄ inhibitor, TMS-CN is the source of cyano group (Scheme 10) (14). On the top of Scheme 10, Lewis acid catalyzed dehydroxylation of free hydroxyl group occurred and corresponding replacement with cyano group was realized in excellent yield. On the bottom of Scheme 10, the starting material was transferred to an alkene derivative, consequently, the Brønsted acid mediated cyanation of the olefin to afford the product in good yield (up to 89%). This example indicated in a straightforward fashion that the introduction of cyano groups into molecules can be easy, which may be initiated from hydroxyl or alkene precursors. This

case also demonstrated that as a surrogate of cyanohydrins, silyl-cyanide has been extensively employed in organic synthesis. Silyl-cyanide is commercially available, and has been broadly investigated owing to the versatile function of cyano group in organic chemistry.

Apart from functionality, trimethylsilyl cyanide was also employed as a silyl cyanation precursor *via* activation of Si-CN bond. In 1988, Chatani et al. first reported a palladium catalyzed silicon-cyano bond cleavage and subsequent insertion to the terminal alkyne (15). The addition of trimethylsilyl cyanide to acetylenes in the presence of transition-metal complex was investigated. It was revealed that the structures of starting acetylenes, catalysts, amount of solvent, and trimethylsilyl cyanide highly affected product distributions. The PdCl₂/pyridine catalyzed reaction of phenylacetylene and para-substituted phenylacetylenes with trimethylsilyl cyanide to afford cyano-substituted vinylsilanes in good to high yields (up to 90% isolated yield) with high regio- and stereo-selectivity (up to 95:5 selective isomer). *Ortho*-substituted phenylacetylenes provided additional products with less stereo-selectivity. This reaction afforded *Z* adducts (indicated that the cyano and silyl groups are on the same side of the double bond), which decreased in the order of *para*-> *meta*-> *ortho*-substituted phenylacetylenes (Scheme 11). Actually, both aromatic and hetero-aromatic acetylenes are tolerated in this transformation. As a result, a wide range of cyano-substituted styryl derivatives are accessible via direct cleavage of the Si-CN bond.

Interestingly, with the assistance of molecular oxygen, the functionalization of alkyne can be realized twice by cyano group. In 2009, Arai et al. disclosed a stereo-selective 1,2-dicyanation of various alkynes in the presence of trimethylsilyl cyanide by Pd(II) catalysis under aerobic conditions (16). High syn-selectivities were observed by employing terminal alkynes that have bulky substituents at a propargyl position and aliphatic internal alkynes (Scheme 12). Notably, excellent tolerance of the acetylenes was also observed. The terminal, aryl- and alkyl-substituted acetylenes provided corresponding α,β -dicyano olefins in moderate to good yields (up to 86%).

Another interesting case was reported by Ito et al. (17) Intramolecular cyano-silylation was achieved by the reaction of chlorodiphenylsilyl ether generated from homopropargylic alcohols with trimethylsilylcyanide in the presence of Pd(0). The in situ generated Si-CN intermediates were activated by palladium catalyst and subsequently underwent intramolecular insertion into the alkyne (Scheme 13) (17). The reaction proceeded with regio- and stereo-selectivity to afford (*Z*)-3-(1-cyano alkylidene)-2-silatetra-hydrofurans, whose silyl groups can be transformed into various functional groups. This intramolecular cyano-silylation reaction provides a new entry into the synthesis of regio- and stereo-defined α,β -unsaturated nitriles. A wide range of functional groups are compatible. Alkyl-substituted, vinyl-substituted and terminal alkynes were successfully transformed to corresponding olefins in up to 84% yields. One interesting case was also presented, by applying palladium catalyzed coupling of the silyl group with allylic bromide, and useful building block was successfully constructed in excellent yield. Considering the readily available starting material and good tolerance of the substituents, the current strategy and its further modification are highly valuable, which efficiently afford both cyano- and silyl-substituted olefins.

2.3. Carbo-cyano Bond

Owing to its broad existence and central role in organic chemistry, C-C bond activation has been one of the most frequently investigated areas nowadays.

It was discovered that the C-CN bonds are readily activated and suitable for coupling reactions. Carbo-cyanation via cleavage of the C-CN bonds by nickel *et al.* has been one of the most powerful tools for the introduction of a cyano functionality. One interesting carbo-cyanation is Pd(II) catalyzed 1,2-dicyanation through a unique nucleophilic cyanation (cyanopalladation). Despite extensive investigations to identify cyanation mechanisms catalyzed by transition metal complexes, no examples that install both alkyl and cyano components in an anti fashion have been reported until the 1980s.

In 1982, Yamamoto *et al.* disclosed an electron-rich Co(I) catalyzed carbon-cyano cleavage process (Scheme 14) (18).

This is the first time that the activation of C-CN bond was examined. The inert C-CN bond was cleaved under ambient temperature by Co(I) (18). Although stoichiometric cobalt is necessary for the transformation, this case definitely indicated that the inert C-CN bond can be activated with the use of a proper metal even at ambient temperature, which laid the foundation for the future progress.

In 2006, Chatani *et al.* disclosed a Rh(I)-catalyzed disilicon reagent mediated C-CN bond cleavage reaction. Consequently, aromatic silicon compounds were formed (Scheme 15) (19). At elevated temperature, with the assistance of silyl reagent, the cleavage of C-CN bond was realized using more common Rh(I) complexes. Notably, aryl, hetero-aryl, styryl and alkenyl cyanides were all tolerated, providing corresponding decyanated silyl products in moderate to excellent yields (35–97%). These authors first demonstrated that with the assistance of a silicon reagent, the release of cyano group from aryl, etc., cyanides was practicable.

In 2009, based on the initial discovery, Chatani *et al.* disclosed a rhodium-catalyzed reductive cleavage of carbon-cyano bonds with hydrosilane, which provide a catalytic pathway for the removal of cyano groups (20a). Recently, Maiti disclosed a similar strategy, wherein the hydride source was replaced with TMDSO and metal was changed to Ni(0) (21). And most recently (22), the hydride source was replaced by hydrogen gas (Scheme 16), which made it more valuable for the cleavage of cyano group. As stated in the introduction, cyano group can be employed as a useful directing group. Specifically, cyano as a directing group, can first introduce another ortho-functional group, and subsequently it can be removed if not needed or further transformed to another group. In view of the functional diversity, the method disclosed herein will definitely expand the application of cyano groups.

Notably, one important example was also disclosed in this article (20b). A catalytic C-H bond borylation of benzonitrile derivatives (20b) followed by decyanation afforded borylated arenes, which are difficult to access by direct borylation of the corresponding

arenes. Importantly, both aromatic and aliphatic cyanates are tolerated. The transformation is efficient, with the isolated (obtained yield after purification) yield up to 99%.

With all these important results in hand, Chatani et al. developed this method into a more practical form, which the previous silyl group was replaced by a more versatile boronic one. In 2012, Chatani et al. reported a rhodium catalyzed borylation of nitriles through the cleavage of the carbon-cyano bonds (Scheme 17) (23). Aryl, hetero-aryl, and benzyl cyanides are tolerated in such transformation, providing its boronic derivatives in moderate to excellent yields (up to 91%) using Rh(I) catalyst under elevated temperature. In view of the broad and frequent usage of boronic compounds in modern organic chemistry, the methodology disclosed herein is of high importance and valuable. For example, the *ortho*-selective arylation of benzonitrile followed by replacement of borylation of the cyano group was realized, which can efficiently provide regio specific boronic derivatives. Interestingly, this is also the first time that breaking of inert C-CN bond and formation of useful C-B bond was realized simultaneously, which will expand the scope of the strategy.

Recently, Yang et al. developed a highly efficient protocol for the preparation of various diphenylphosphoryl ligands through nickel-catalyzed C-CN bond cleavage (Scheme 18). The availability of the substrates and the remarkable scope (both aromatic and hetero-aromatic cyanates) observed make this method attractive to synthetic chemists (24). Under relatively mild reaction condition, phosphoryl derivatives were synthesized through cleavage of the C-CN bond by catalytic Ni(II). In the perspective of phosphoryl ligand in modern organic synthesis, the current strategy provides a new and applicable synthesis alternative.

Actually, as early as 1994, Takaya et al. (25) reported two different electron-withdrawing carbon substituents (aryloyl and cyanides) were introduced into terminal arylacetylenes by a new method, palladium-catalyzed intermolecular acylcyanation of the acetylenic bonds (Scheme 19). Considering that the $C(sp^2)(C=O)$ was activated both by the aryl and oxygen groups, the acylcyanation process can be easily realized by Pd(II). Aryl-substituted terminal acetylenes and substituted-aryloyl cyanates are compatible in such transformation, with the isolated yield up to 99%. This method provides a new strategy for the synthesis complex olefins with cyano and carbonyl functional groups.

As mentioned above, intermolecular addition of aryloyl cyanides to arylacetylenes has been reported since 1994 (Scheme 19) (26).

Takemoto et al. prepared five-to seven-membered α -alkylidene lactams in 45–99% yield by the palladium catalyzed cyanoamidation of alkynyl cyano-formamides (Scheme 20) (26). The reaction proceeded exclusively in a 5-exo mode, giving the corresponding (*Z*)-alkenes as major products. The reaction was also applied to 1,1-disubstituted alkenes to afford oxindoles bearing a quaternary carbon center.

Not surprisingly, Takemoto et al. developed this intermolecular reaction into an intramolecular process and expand its coupling partners. This transformation was not only restricted to acetylenes, alkenes was also compatible. Importantly, by applying the present method (the key step is the intramolecular cyano-acylcyanation of alkene to provide the

intermediate), these authors provided a useful synthesis route for the construction of natural molecule-physostigmine, which is anticipated to attract broad readership.

Another interesting case has also been reported. Palladium-catalyzed cyano-esterification of norbornenes proceeds stereo-selectively via NC-Pd-COOR (R = Me and Et) complexes as intermediates (Scheme 21) (27). Nishihara et al. developed an unprecedented palladium catalyzed cyano-esterification of alkenes that was initiated by the oxidative addition of the NC-COOR bond. This work offers another useful demonstration of the power of transition metal catalysis to activate unstrained C-C σ -bonds with compatible functional groups. A related discovery was reported by Hiyama et al. (Scheme 23), wherein activated alkenes (norbornenes) were added to cyano-ester mediated by Pd(0) in 66% yield and excellent stereo-selectivity.

Actually, Takemoto et al. disclosed the first enantio-selective cyanoamidation of olefins, which provides rapid access to a variety of 3,3-disubstituted oxindoles (Scheme 22) (28a). The combination of Pd(dba)₂, an optically active phosphoramidite, and N,N-dimethylpropylene urea (DMPU) in decalin were found to be the best conditions. Substituents on the arenes, alkyl-substituted on the nitrogen derivatives and the alkyl/aryl substituted olefins are all tolerated in the transformation, which provided corresponding products in good to excellent yields (up to quantitative) and 86% ee value. Plausible mechanism was indicated such that the reaction proceeds through oxidative addition of the C-CN bond to Pd(0), followed by amidopalladation and reductive elimination. An interesting example utilizing the current method was also presented, which efficiently constructed the natural eserine.

In 2006, Hiyama et al. disclosed a Ni/PMe₂ Ph catalyst, which was found to effect regio-selective addition of cyanoformate esters across allene, giving rise to 3-alkoxycarbonyl-3-butenitriles (Scheme 23) (29). Functional groups such as cyano, protected hydroxyl, and amino groups in the allene substrates are tolerated with the isolated yields up to 84% under very mild reaction condition (50°C). Limitation of the reaction is that only alkyl-substituted allenes are compatible. Isomerization of the initial products to thermodynamically more stable isomers takes place possibly through further oxidative addition of the C-CN bond of 3-alkoxycarbonyl-3-butenitriles to Ni(0) followed by reductive elimination. The cyano-esterification products undergo further addition across alkynes in the presence of a Ni/P(4-CF₃-C₆H₄)₃ catalyst. Notably, a similar strategy (see Scheme 30) by activation of the C-CN (in allylic position) in the presented substrates was also reported, providing the corresponding product in 81% yield, although the stereo-selectivity is not good.

Based on the results that Hiyama et al. previously achieved (see Scheme 23), these authors developed the method to a more practical one. As mentioned, cyano-formate esters add across 1,2-dienes in the presence of a nickel/PMe₂ Ph catalyst to afford β -cyano- α -methylenealkanoates with regio-selectivity at high temperatures catalyzed by the nickel complex, possibly through oxidative addition of the C-CN bond (Scheme 24, top) (30). Similar cyano-esterification products are produced from chloroformate esters, trimethylsilyl cyanide, and 1,2-dienes in the presence of a nickel/dppp catalyst, in which process the cyano-formate esters can be generated in situ. The resulting cyano-esterification products

have a structure of allylic cyanide and thus undergo further allyl cyanation reaction across alkynes with the aid of a nickel/ $P(4-CF_3-C_6H_4)_3$ catalyst to afford highly substituted acrylonitrile derivatives. Good tolerance has also been observed in the process (Scheme 24, lower section), in which the aryl and alkyl allenes can react with vast chloroformate esters along with TMS-CN mediated by Ni(0) catalyst.

Apart from these results, plenty of other carbon-cyano bond activation reactions were also reported. As early as 2001, Matsubara and Kurahashi (31) disclosed an intermolecular cycloaddition reaction, where *o*-arylcarboxy benzonitriles react with alkynes to afford coumarins in the presence of Ni(0)/ $P(CH_2Ph)_3$ /MAD as a catalyst (Scheme 25).

The reaction process displays an unusual mechanistic feature which is the simultaneous cleavage of two independent C-CN and C-CO bonds. As for the cyano part, different substituents on the arenes and variable aryl ester are all compatible. In contrast, alkyl, aryl, and silyl substituted acetylenes are all tolerated for such transformation, with the isolated yield up to 99%. Notably, the title reaction represented the first example of intermolecular cycloaddition involving the cleavage of two carbon-carbon σ bonds of two independent C-CN and C-CO bonds simultaneously.

Most recently in 2013, Matsubara and Kurahashi reported an interesting and similar C-CN activation reaction (32). They illustrated the efficacy of the nickel-catalyzed reaction based on carbon-carbon bond cleavage of amides for the synthesis of quinolones. Different from the previous ester derivatives, these authors demonstrated that amide starting material were also compatible substrates for such an interesting transformation, with the yield up to 99%. This technique should prove useful for the synthesis of a variety of complicated quinolones from simple substrates via the cleavage of C-CN and release of benzonitrile (Scheme 26).

For more practicable C-CN activation methods, there currently is considerable progress, as reported herein.

In 2004, Hiyama et al. (33) disclosed a nickel catalyst coordinated by trimethylphosphine which is found to effect the addition reaction of Ar-CN bonds in aromatic nitriles across alkynes to give rise to various β -aryl-alkenenitriles (Scheme 27). Aliphatic-substituted acetylenes were tolerated in the process, with the isolated yield up to 96%. Even though the afforded cyano-substituted olefins are more common in natural and/or medicinal chemistry, the shown method indicates to possess broader applications.

In 2006, Hiyama et al. disclosed a nickel catalyst having a bulky tri(*sec*-alkyl)-phosphine ligand catalyzed simultaneous cyanation and arylation of alkynes at 35°C (Scheme 28) (34). Interestingly, selective activation of an Ar-H bond over an Ar-CN bond of N-protected 3-cyanoindoles is achieved by a proper choice of ligand and/or an N-protecting group. The process affords *cis*-hydrohetero-arylation products in highly chemo- and stereo-selective manner. Excellent regio-selectivity is observed with unsymmetrical alkynes to give the corresponding hetero-aryl-substituted ethenes having a larger substituent *trans* to an aryl group. With the wide range of functional groups (i.e., alkyl, aryl and silyl-substituted acetylenes are compatible), the unique transformation allows a rapid construction of indole-substituted cyano-containing olefins, which expand the scope of olefin diversity in synthesis.

Hiyama et al. demonstrated that Ni-LA catalysts are effective for carbocyanation of alkynes, and thus not only aryl cyanides but also alkenyl and alkyl cyanides can be employed as substrates for the reaction (35). They demonstrated that a nickel catalyst prepared from $\text{Ni}(\text{cod})_2$ (cod, 1,5-cyclooctadiene) and PMe_3 is found to effect aryl-cyanation reaction of alkynes, namely, cleavage of a C-CN bond of an aryl cyanide followed by the addition of each fragment across an alkyne. Plenty of functional groups on aryl cyanides (aromatic and hetero-aromatic) and various acetylenes are compatible using the current reaction conditions. This method has afforded various functionalized β -aryl-alkenenitriles stereo-selectively, with the isolated yield up to 96% (Scheme 29). On the contrary, compared with previous discoveries (Schemes 22 and 23), the current method expanded the applicable scope and provided complementary synthesis routes.

Apart from these discoveries, cyano group in allylic position can also be activated under certain reaction conditions. In 2007, Hiyama et al. disclosed an interesting reaction in which allyl cyanides are found to add across alkynes in the presence of a nickel/ $\text{P}(\text{4-CF}_3\text{-C}_6\text{H}_4)_3$ catalyst to give poly-substituted 2,5-hexadienenitriles with defined stereo- and regio-chemistry (Scheme 30) (36).

The terminal, alkyl/aryl/silyl-substituted acetylenes were all tolerated in such transformation.

Notably, substituents on the same allylic position, such as aromatic and aliphatic ones, are both compatible in the transformation, with the isolated yield up to 89%. Interestingly, they disclosed that use of AlMe_2Cl or AlMe_3 as a Lewis acid cocatalyst accelerates the reaction and expands the substrate scope significantly. By applying this valuable carbo-cyanation reaction, the stereo-selective construction of the trisubstituted double bond of plaunotol, an antibacterial natural product active against *Helicobacter pylori* has also been reported.

In 2008, Hiyama et al. reported a catalyst system derived from $\text{Ni}(0)$ complex along with PMe_3 or PMe_2Ph ligand and co-catalytic AlMe_2Cl effects for the intramolecular aryl-cyanation of alkenes (Scheme 31) (37). The reaction takes place in an exclusive exo-dig manner to give a wide range of nitriles having a benzylic quaternary carbon in isolated yields up to 93%. A wide range of substituted olefins were all tolerated in such a process, and the linkers between the aryl group and the alkenes are also variable (i.e., $\text{X} = \text{C}, \text{N}$, and Si ; moreover, with or without carbonyl etc.), which definitely expand the scope of applications. Detailed investigations are described (37) on the scope and mechanism as well as preliminary results on the asymmetric version of the reaction to provide novel access to chiral quaternary stereo-centers. Importantly, by applying the current methodology, these authors developed two practicable synthesis pathways towards the synthesis of (–)-esermethole and (–)-eptazocine, respectively. The concise and efficient synthesis demonstrated the powerful and useful tools of the current synthetic strategy. Interestingly, the current transformation, featuring the asymmetric synthesis of complex molecules via activation of C-CN bond, was actually a pioneering research of C-C bond activation in an asymmetric manner.

Simultaneously, Jacobsen *et al.* disclosed that the enantio-selective, intramolecular aryl-cyanation of unactivated olefins via the C-CN bond activation has been accomplished using a Ni(0) catalyst and BPh₃ co-catalyst (Scheme 32) (38a,38b). A plausible reaction mechanism was presented, which involved Lewis acid coordination, migratory insertion and reductive elimination. High enantio-selectivities are achieved using TangPHOS (38c) as a chiral ligand. This method allows the generation of two new C-C bonds and one new quaternary carbon stereogenic center in a single synthetic step, converting readily available benzonitrile substrates to 1,1-disubstituted indanes in 49–85% yield and 92–97% ee. Notably, good compatibilities (different substituted groups on arenes and linkers) were also detected. A wide range of the arenes, the linkers (X = C, O, etc.) and the terminal non-substituted olefins (aryl and alkyl) are all compatible in the transformation. This method is useful in organic community, especially for enantio-selective syntheses.

2.4. Boron-Cyano Bond

Boronic derivatives anticipated transformations have been a vibrant topics since the renowned Suzuki reaction (39a). The versatile usage of boronic functional group makes it of high importance nowadays. As stated previously, the cyano group is an accomplished functional group, thus, reactions that bear both transformations of boronic derivatives and cyano groups will definitely be a powerful and practical method (39b).

In 2002, Suginome *et al.* first reported an efficient Strecker-type aminative cyanation of carbonyl compounds using bis(dialkylamino)cyano-boranes via cleavage of the boron-cyano bond (Scheme 33) (40). In this transformation, different aldehydes (aryl and alkyl-substituted) and ketones (alkyl, aryl, styryl, and hetero-aryl-substituted) are tolerated, and the α -dialkylamino nitriles are formed in yields up to 99% under very mild reaction condition (THF, 50°C). Notably, this study demonstrated for the first time the synthetic utility of cyano-boranes as a nucleophilic cyanation reagent.

Although many addition reactions of the cyano-containing σ -bond have been largely disclosed, cyano-boration activation is still highly attractive due to these two synthetically valuable functionalities. In addition, if the cyanoboration process can be introduced in a regio-and stereo-selective fashion and thus produce useful synthetic intermediates, it will definitely be of high useful.

In 2003, Suginome and Murakami first disclosed an intramolecular cyanoboration reaction, which is catalyzed by palladium and nickel complexes (Scheme 34) (41–44). Mechanistic studies provided a plausible pathway for this reaction, with zerovalent metals {Pd(0) or Ni(0)} first effecting oxidative addition to give an intermediate which the newly formed metal species (the transition state intermediate in the middle of the mechanism part of Scheme 34) incorporated to the triple bond; subsequently, in one possible route, B-M (boron-metal intermediate) was added to the triple bond via activation of boron and metal bond; finally, reductive elimination to provide the desired products, along with the zerovalent metal to circle the process (it means that zerovalent metal will repeat this process, firstly oxidative addition, secondly insertion and final elimination, and the overall reaction is a circle process). A series of cyano-boryl ethers were subjected to intramolecular cyano-borations. Tertiary internal homo-propargylic ethers, the primary and secondary propargylic

ethers, sec-propargylic ether bearing a terminal alkyne group, internal alkynes were all tolerated, to afford the corresponding products in good to excellent yields (83–99%). Notably, in view of the diversity of the obtained product, this transformation is valuable. Boronic groups can be transferred into plenty of groups through hydroxylation, fluorization, trimethylsilylation, cross-coupling reactions, etc. (illustrated in Scheme 34, bottom). The cyano group can also be transformed to amide, amine, acid, etc., and the considerable manipulation of the double bonds.

In 2005, Suginome and Murakami developed the previous process into an intermolecular one (Scheme 35) (45). Different cyano-boranes sources led to regio- and stereo-selective synthesis of α,β -unsaturated β -boryl nitriles by the Pd(II) catalyst. Symmetric acetylenes, such as aryl acetylenes, provided corresponding coupled products in high yields. In contrast, asymmetric acetylenes resulted in moderate yields with a stereochemistry of cyano group attached in the alkyl direction. The coupled products can be obtained in yields up to 97%. Compared with intramolecular reaction, this transformation dramatically expands the application scope. Furthermore, based on the current strategy, these authors completed a convenient synthesis of the potential squalene synthetase (SQS) inhibitor P-3622 by applying the palladium catalyzed intermolecular cyano-boration as the key step. Cyano-boration of 1-(4-methoxyphenyl)-1-butyne with cyano-borane, followed by exchange of the diamine ligand on the boron atom for a pinacol ligand, affording the corresponding 2-boryl-1-cyano-alkene with good regio-selectivity. Suzuki-Miyaura coupling with *p*-chloriodobenzene gave desired product, which was converted into the SQS inhibitor P-3622 and relevant compounds.

In 2009, a Pd(II) catalyzed intramolecular cyano-boration of allenes reaction was realized by Suginome and Murakami (Scheme 36) (46). Owing to the reactive nature of allene (highly reactive), intramolecular oxidative addition is easier than the previous route involving acetylene (45).

Actually, the process can be carried out with a wide range of functional groups, and the isolated yields were up to 86% (46). The cyano-boration products have an allylborane substructure with a cyano group at their β -positions, which is expected to serve as new β -cyano-allylation reagents. Mechanism revealed a plausible pathway, *viz* (i) oxidative addition of boron-cyano bond into zerovalent metal; (ii) intramolecular insertion of the double bond; and (iii) reductive elimination. This case indicated that intramolecular oxidative addition of cyano boronate to allene can be a valuable tool for further applications.

2.5. Germyl-cyano Bond

Synthetic application of trimethylgermyl cyanide has not been developed until 1990. In 1990, Chatani and co-workers disclosed a new synthetic method for the preparation of alkenylgermanes with a high regio- and stereo-selectivity to give corresponding cis-cyano alkenylgermanes in high yields (up to 99%) and regio-selectivity (Z/E up to 99:1) (Scheme 37) (47,48).

In such a transformation, terminal aryl-acetylenes are compatible. Not surprisingly, terminal aliphatic acetylenes also reacted with germyl cyanide in the presence of catalytic PdCl₂ (10

mol%), and provided β -cyano alkenylgermanes in high yields. Notably, the reaction was tolerated with many functional groups (including methoxy, fluoro, chloro, acetoxy, and cyano groups), which will expand the scope of the application. Plausible mechanism are provided, which included oxidative addition, insertion of the double bond and reductive elimination process. In contrast, the reaction of the internal acetylenes, 4-octyne, and diphenyl-acetylene with germyl cyanide did not give additional products. Further transformation of such product is under the way and definitely be of high interest.

2.6. Tin-cyano Bond

The notable Stille reaction (49–51) represents the most valuable reaction with tin-cyano bond cleavage. Examples of the palladium-catalyzed coupling of organo-tin compounds with carbon electrophiles were first reported in 1977 by Kosugi, Shimizu, and Migita (51b–d). The first study by Stille appeared in 1978 (49). The early work of Beletskaya (51e–f), using “ligandless” catalysts in cross-coupling reactions, also often employed organo-stannanes. Nowadays, in recognition of Stille’s comprehensive synthetic and mechanistic studies, this coupling is now referred to as the Stille reaction. The Stille reaction belongs to the larger family of palladium and nickel-catalyzed cross-coupling reactions which features, i.e., organo-magnesium, organo-zinc, organo-tin, organo-boron, and organo-silicon reagents.

Organo-tin reagents are air and moisture stable organometallics, and can be conveniently purified and stored. Since they do not react with most common functional groups, the use of protecting groups is almost always unnecessary in conjunction with the Stille reaction (Scheme 38). This is a very unusual and attractive feature for an organometallic process. As depicted in Scheme 38, the reaction of tributyltin cyanates with halo-arenes mediated by catalytic Pd(0) are successfully realized in excellent yield up to 94%. Additionally, the reaction is often neither air nor moisture sensitive. In some cases, water and oxygen have actually been shown to promote the coupling. Although the reaction as initially described by Stille is often carried out under rather severe conditions (temperatures of 100°C are not uncommon), newly developed ligands and the addition of copper(I) salts have solved some of the problems associated with low reactivity. The utility and mildness of the Stille reaction are demonstrated by its frequent use in the final stages of complex natural product syntheses.

An interesting Pt(II) complex catalyzed cyano-stannylation of alkynes via tin-cyano bond cleavage was reported by Tsuji et al. (52).

In this transformation, in the presence of a catalytic amount (5 mol%) of a platinum complex, tributyltin cyanide reacts with dimethyl- or diethyl acetylenedicarboxylate to afford cyano-stannylation adducts in 92% and 73% yields, respectively. Notably, the reaction proceeds highly selectively affording only a (*Z*)-isomer. This adducts are novel products which possess synthetically useful cyano, alkenylstannyl and alkoxycarbonyl functionalities in the same molecule (Scheme 39).

2.7. Thio-cyano Bond

In 2006, Nomoto and Ogawa first reported a case of transition-metal-catalyzed cyano-thiolation of terminal alkynes with thiocyanates, which attains simultaneous introduction of

both sulfur and cyano groups into carbon-carbon triple bonds with moderate yields (up to 84%) and excellent regio-selectivities (Scheme 40) (53). Good tolerances were also observed in the current process. Aliphatic and aromatic alkynes are acceptable in such transformations. Moreover, functional groups such as cyano and olefinic group are compatible, which make the current method considerable useful for the catalytic introduction of both thio and cyano groups into the internal and terminal positions of alkynes, respectively.

Mechanistic studies revealed that process of this transformation are: (i) the oxidative addition of PhSCN to Pd(PPh₃)₄ proceeds with the cleavage of a sulfur-cyano bond (PhS-CN) not a carbon-sulfur bond (Ph-SCN); (ii) resultant complex reacts with alkynes to give the cyano-thiolation product probably via either a thio-palladation or a cyano-palladation process; and (iii) by reductive elimination, the zerovalent palladium completes the catalytic circle.

Later, Chuang et al. disclosed a microwave-assisted palladium-catalyzed regio-selective cyano-thiolation of alkynes with thiocyanates (Scheme 41) (54). The advantage of this microwave-assisted reaction is that the reaction time can be shortened and, in some cases, much higher yields than those obtained in conventional thermal reactions have been achieved. For the cyano-thiolation process, only the Z-isomers were obtained. Functionalities such as secondary amine, cyano, and olefinic groups are also tolerated the reaction conditions. Aryl and alkyl terminal alkynes provided good to excellent yields, which the internal alkyne failed to yield any desired product. This present methodology will expand the application of such process, which is a modified route for conventional thermal reactions.

Importantly, in 2006, Liebeskind and co-workers disclosed a new method for the synthesis of nitriles via cleavage of the sulfur-cyano bond (Scheme 42) (55). As a complement to the classic cyanation of aryl halides using cyanide sources and a transition metal catalyst, the palladium catalyzed cross-coupling of thiocyanates with boronic acids in the presence of copper(I) thiophene-2-carboxylate (CuTC) affords nitriles in good to excellent yields (up to 95%). In contrast to the benzylic sulfur cyanate as cyano source, aryl, hetero-aryl, seryl, and hetero-seryl boronic acid are all tolerated, which makes it a highly useful tool for the introduction of cyano group. Using this protocol, a variety of nitriles can be easily synthesized in high yields.

Mechanistic studies showed that the coupling may start with an oxidative addition of the thiocyanate to Pd(0), followed by a trans-metallation from boron to palladium. Carbon-cyanide reductive elimination would afford the nitrile and regenerate a catalytically active Pd(0). It is suggested by early results that the copper(I) carboxylate used here functioned as a unique dual activator, acting through the soft Cu(I) ion as a thiophilic agent to help polarize the palladium thiolate bond, while simultaneously providing borophilic activation by coordination of the carboxylate to the trivalent boron atom.

As similar to thio group, the cleavage of sulfonyl-cyano bond in the Ts-CN molecule is also investigated.

In 2007, Carreira et al. disclosed a mild cobalt (II or III) catalyzed hydro-cyanation of olefins with tosyl cyanide via cleavage of the S-CN bond (Scheme 43) (56). These authors reported the conceptually new hydro-cyanation reaction of non-activated olefins that gives access to secondary and tertiary nitriles. It is a transformation for which, to date, few procedures have been available. The salient features of this process are the broad functional-group tolerance, mild reaction conditions (room temperature, EtOH as solvent), readily available starting materials (TsCN, PhSiH₃, catalyst, olefins), and ease of execution. Moreover, the reaction can be conducted on preparatively useful scales and essentially no workup is necessary.

2.8. Halo-cyano Bond

The catalytic addition reactions of X-Y (X,Y are two different elements, i.e., X = H and Y = C) type substrates to carbon-carbon multiple bonds are of continued interest due to the facile access to α,β -bifunctional units from simple alkenes, alkynes and allenes with ideal atom efficiency.

Among these transformations, addition reactions of X-CN to alkynes simultaneously form vinyl-X and vinyl-cyano bonds, both of which can be used to construct complex structures. Several notable examples of palladium or nickel catalyzed regio- and stereo-selective addition reactions to alkynes with several X-CN groups have been previously reported. These included: X = H (hydro-cyanation),⁶⁻¹³ X = C (carbo-cyanation) (18-38), X = Si (cyano-silylation) (14-17), X = Ge (cyano-germylation) (47,48), X = Sn (cyano-stannylation) (49-52), X = B (cyano-boration) (39-46), and X = S (cyano-thiolation) (53-56).

However, much less attention has been paid to catalytic regio- and stereo-selective halo-cyanation of alkynes or alkenes using cyanogen halides. In 2011, Ohe et al. reported a gallium-catalyzed bromo-cyanation of alkynes with cyanogen bromide. It provided an efficient route to (Z)- β -bromo-acrylonitriles in a high regio- and stereo-selective fashion (Scheme 45) (57). Terminal aryl-substituted, alkyl, aryl-substituted and aryl, aryl-substituted acetylenes are all compatible, providing the valuable vinyl derivatives in yields up to 72%. Taking advantage of (Z)- β -bromoacrylonitriles, these authors established efficient routes to a wide range of α,β -unsaturated nitriles, which are of synthetic value (illustrated in Scheme 45, bottom).

In 2013, Ohe et al. disclosed a copper-catalyzed reaction of terminal alkynes with cyanogen iodide (ICN) that produces alkynyl cyanides (Scheme 46) (58).

Aromatic and aliphatic substituted terminal acetylenes are compatible in the transformation in moderate yields up to 78%. Interestingly, the use of tetramethylpiperidine as a sterically congested base was successful in this transformation. Some control experiments revealed that the reaction involves the non-catalyzed formation of alkynyl iodides followed by copper-catalyzed cyanation of the iodides without the formation of Cu(I) acetylide. This observation contrasts with what is normally observed in various copper mediated reactions using terminal alkynes.

2.9. Oxygen-cyano Bond

The most important cases disclosed above are C-CN bond activation reactions (18–38). Other element-cyano bond cleavages, such as silyl-cyano (14–17), germyl-cyano (47,48), stannyl-cyano (49–52), boryl-cyano (39–46), sulfur-cyano (53–56), and halo-cyano (57,58) have also been achieved, a useful synthetic transformation of oxy-cyano has not been reported until recently (59).

In 2012, Nakao et al. reported a reaction of the palladium and triphenylborane catalyzed the intramolecular oxy-cyanation of alkenes via the cleavage of O-CN bonds and the subsequent insertion of double bonds (Scheme 47) (59a). The reaction illustrated the cyano-functionalization of a double bond through cleavage of an oxygen-cyano bond, which is rare. As benzofuran derivatives broadly existing in natural and medical chemistry and the versatile manipulation of cyano group (precursors to amine, amide, acid, etc.), the methodology disclosed herein can construct benzofuran derivatives and functionalized cyano group in one pot. Considering the demand of atom-economy in modern chemistry, this will attract great interest nowadays. Preliminary mechanistic studies supported a process wherein a LA (BPh₃) mimics the silicon reagent. The Lewis acid catalyst is crucial for the oxidative addition to O-CN bonds whereas it has also been shown to promote C(sp³)-CN bond-forming reductive elimination from palladium(II) through coordination of a cyano group to the Lewis acid.

2.10. Nitrogen-cyano Bond

Examples of N-CN bond activation are very rare (bond dissociation energy is ca. 497 KJ/mol) (60). In 2011, Beller et al. disclosed an interesting example of an N-CN cleavage reaction, as shown in Scheme 48 (60b). Rh(I) catalyzed activation of the N-CN bond, followed by transformation of an aryl boronic acid to aryl cyanide. Aryl and styryl boronic acids are also tolerated in the process, providing the cyanated products in moderate to good yields up to 90%. The regio-selective borylation of the arene via C-H bond activation followed by cyanation of the boronic group was realized, which can efficiently afford a wide range of cyano derivatives. This is the first example of a rhodium catalyzed cyanation of aryl and alkenyl boronic acids via N-CN bond activation. Notably, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamides are unique cyanation reagents, i.e., the N-CN bond is activated both by Ts(toluenesulfonyl) and phenyl groups.

These authors postulated a plausible mechanism, viz: (i) aryl boronic acid trans-metallation by the Rh(I) complex; (ii) coordination with the N-CN; (iii) aryl migration from rhodium to carbon; and (iv) reductive elimination connecting the cyano group to the aryl.

At the same time in 2011, Wang and Falck observed that metals such as Pd(0) and Rh(I) can activate the N-CN bond in an intramolecular process to provide a series of 3-aryl-acrylonitriles from styrenes (Scheme 49) (61). Substitution on the arenes and α -position of the styrenes was well tolerated, gave the desired product in moderate to good yields up to 87%. This was the first example of an intramolecular cyanation of a C_(sp2) through N-CN bond cleavage. This case indicated that intra-molecular cyanation of styrene can be realized through the rarely reported N-CN bond cleavage strategy under related mild reaction

condition. This will add one new type of N-C bond activation and will inspire future discovery of bond-bond activation. Moreover, the stereo-specific 3-aryl-acrylonitriles products obtained in this transformation are also useful intermediates, which will expand the application scope of such transformation.

While mechanistic studies are still under the way, previously established discoveries suggests this transformation is consisted of several steps, specifically: (i) oxidative addition of the rhodium complex into the N-CN bond, (ii) double bond insertion into the newly generated N-Rh bond, and (iii) β -elimination to regenerate the reactive Rh(I) allowing the catalytic cycle to continue.

In 2013, Liu and Fu reported an interesting and potentially highly useful intermolecular cyanation reaction (62) using the previously reported Beller cyanation reagent, *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) (Scheme 50). This reaction allows intramolecular cyanation of arenes via C-H bond activation mediated by rhodium catalyzed N-CN bond cleavage. By applying a rhodium catalyst along with silver carbonate, a wide range of aromatic and hetero-aromatic cyanation adducts are obtained in good to excellent yields up to 94%. Notably, regio-selectivity can be controlled by many common directing groups. Although the cyanation reagent (NCTS) was firstly introduced by Beller and co-workers, Liu and Fu's work disclosed herein made it more practicable and useful. That is, synthesis was not only restricted to manipulation of boronic derivatives, but also was applied in the transformation of C-H activation with the assistance of DGs. To illustrate the application of the current strategy, the *O*-methyl oxime of Zaltoprofen was subjected to the standard condition, the corresponding cyanation product via C-H bond activation was obtained in 74% isolated yield in the presence of thioethers.

Related mechanistic studies were also presented. The kinetic isotope (KIE) experiment revealed the transformation is typical of Rh catalyzed C-H activation processes, followed sequentially by coordination with the N-CN moiety and elimination to provide the cyanated products. Thus Liu and Fu have developed an unprecedented and practical Rh catalyzed C-H cyanation reaction that uses less toxic and the readily available NCTS as the cyanation reagent.

3. CONCLUSIONS AND PERSPECTIVES

In conclusion, cyano group is useful for synthetic applications in organic, medical and polymer chemistry as versatile and functional intermediate. Fundamental elemental atoms such as hydrogen (H), oxygen (O), nitrogen (N), silicon (Si), boron (B), germanium (Ge), tin (Sn), halo (Br, I), etc. are in the central role of organic chemistry. These elemental atoms along with the many-sided cyano group, simultaneously, functionalized allenes, alkynes and olefins, undoubtedly will be of high appreciated in organic community. This article provided a continuous summary of progress that has been made in such valuable fields. Notably, as their importance in organic synthesis (e.g., cyano group can readily be transferred to many functional groups which has summarized at the very beginning), investigations involved with elements (such as hydrogen, oxygen and nitrogen *et al.*)-cyano bond activations are considerably attractable, either in racemic or enantio-selective manners. However, although

comprehensive elements-cyano activations have already been reported, more efficient methodology and useful application are still needed. Additionally, all these transformation are catalyzed by transition metals, less loading of the catalyst and/or mild reaction condition are of highly valuable. Further application of those transformations, especially mechanistic studies, aiming for the efficient and concise synthesis of natural and/or medical compounds, is still ongoing.

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for R = aryl, benzyl, alkenyl etc.

Figure 1.
Versatile transformation of cyano group.

Scheme 1.
DuPont's procedure of adiponitrile synthesis.

Scheme 2.
Hydro-cyanide addition reaction.

Scheme 3.
Catalytic enantio-selective conjugate addition.

Scheme 4.

Catalytic enantio-selective addition of ketones.

Scheme 5.
Aceton cyanohydrin.

Scheme 6. Cu-catalyzed hydrocyanation of α -aryl diazoesters.

Scheme 7.
Asymmetric synthesis of cyanided styrene.

Scheme 8.
Asymmetric synthesis of cyanide via imine.

Scheme 9.
Asymmetric synthesis of cyanided aldehyde.

Scheme 10.
Applications via activation of silyl–cyano bond.

Scheme 11.
Silyl-cyanation via activation of silyl-cyano bond.

Scheme 12.

Double cyanation via activation of silyl-cyano bond.

Scheme 13.
Activation of in situ generated silyl-cyano bond.

Scheme 14.
Activation of cyano group.

Scheme 15.

Cyano replaced with silyl group.

Scheme 16.

Cyano replaced with hydro group.

Scheme 17.

Cyano replaced with boronic group.

Scheme 18.
C-P coupling via C-cyano bond activation.

Scheme 19.

Addition of aryloxy cyanides to arylacetylenes.

Scheme 20.
Addition of hetero-aryl cyanides to aryl-acetylenes.

Scheme 21.

Addition of cyano esters to norbornenes.

Scheme 22.

Ni-catalyzed intramolecular cyanation of alkenes.

Scheme 23.

Addition of cyano esters and allylic cyanates to allenes and acetylene.

Scheme 24.

Ni-catalyzed intermolecular cyanation of allenes.

Scheme 25.
Activation of carbon-cyano bond.

Scheme 26.
Activation of carbon-cyano bond.

Scheme 27.
Addition of aryl cyanides to aryl-acetylenes.

Scheme 28.

Addition of hetero-aryl cyanides to aryl-acetylenes.

Scheme 29.

Addition of alkyl cyanides to aryl-acetylenes.

Scheme 30.
Addition of alkyl cyanides to arylacetylenes.

Scheme 31.

Ni-catalyzed intramolecular cyanation of alkenes.

Scheme 32.

Ni-catalyzed intramolecular cyanation of alkenes.

Scheme 33.

Aminative cyanation of carbonyl compounds.

Scheme 34.

Addition of alkynes via activation of boronic-cyano bond and synthesis usage.

Scheme 35.

Intermolecular addition alkyne via activation of boronic-cyano bond and useful application.

Scheme 36.

Addition to alkene via activation of boronic-cyano bond.

Scheme 37.
Addition via activation of germyl-cyano bond.

Scheme 38.

Selective still reaction via cleavage of Sn-CN.

Scheme 39.

Addition to alkyne via activation of stannyl-cyano bond.

Scheme 40.

Addition alkyne via activation of thio-cyano bond.

Scheme 41.

Addition alkyne via activation of stannyl-cyano bond.

Scheme 42.

Pd-catalyzed cyanation of boronic acids mediated by CuTC. (TC = thiocyanate).

Scheme 43.

Hydro-cyanation of olefins with tosyl cyanide.

Scheme 44.

Catalytic addition reactions of X-CN to alkynes.

Scheme 45.

Addition to alkyne via activation of bromo-cyano bond

Scheme 46.

Addition to alkyne via activation of iodine-cyano bond.

Scheme 47.
Addition of alkynes via activation of oxygen-cyano.

Scheme 48.

Cyanation via activation of the nitrogen-cyano bond.

Scheme 49.

Cyanation via activation of the nitrogen-cyano bond.

Scheme 50.

Cyanation via activation of the nitrogen-cyano bond.

Table 1

Selective bonds dissociation energies

Bond	Bond Dissociation Energies (KJ/mol)
H-C ^a	413
C-C	607
N-C	305
O-C	360
H-CN	540(25)
O-CN ^b	ca. 358–799
N-CN ^c	ca. 497
C-CN ^c	ca. 555
Si-C	435(21)
Br-CN	381
I-CN	305(4)
B-C	356
Sn-C	ca. 238
Ge-C	ca. 238
S-C	ca. 272

Notes:

^a C_{sp2} in arene group;^b estimated values between C-O and C=O bonds (59a, 61b);^c essential information (63)