Abstract: Isocyanides have long been known as versatile chemical reagents in organic synthesis. Their ambivalent nature also allows them to function as a CO-substitute in palladium-catalyzed cross couplings. Over the past decades, isocyanides have emerged as practical and versatile C\textsubscript{1} building blocks, whose inherent N-substitution allows for the rapid incorporation of nitrogenous fragments in a wide variety of products. Recent developments in palladium catalyzed isocyanide insertion reactions have significantly expanded the scope and applicability of these imidoylative cross-couplings. This review highlights the advances made in this field over the past eight years.

Keywords: isocyanides; palladium; insertion reactions; heterocycles; catalysis

1. Introduction

1.1. Palladium Catalysis

Palladium-catalyzed cross-couplings were discovered close to 50 years ago. Since then, this class of transformations has evolved into one of the most widely applied reactions. Almost a quarter of all chemical reactions performed in medicinal chemistry are palladium-catalyzed cross-couplings [1]. The versatility of palladium-catalyzed couplings originates from the predictable and promiscuous catalytic reactivity of palladium. This also makes these catalysts ideal for cascade-type chemistry, where the active catalyst plays multiple roles [2]. Further developments in palladium catalysis have led to an ever-increasing scope of chemical methodologies, leading to milder conditions, lower catalyst loadings, and more robust and general cross-couplings. The aspects have made palladium-catalyzed cross-coupling reactions a critical staple in the development of chemical pathways to valuable fine chemicals.

1.2. Isocyanides

The usefulness of isocyanides in multicomponent chemistry (e.g., Passerini or Ugi-type reactions) is undisputed [3]. However, many other synthetic applications of these versatile building blocks have been known for a long time [4,5]. A relatively recent use of isocyanide building blocks combines their ambiphilic nature with well-defined transition metal-catalyzed cross-couplings. In these
transformations, isocyanides are inserted into a metal-carbon or metal-heteroatom bond [6–8], similar to better-known carbonylative cross-couplings [9,10]. The ability to insert an isocyanide into two coupling partners also makes this type of reaction interesting for the development of new types of multicomponent reactions (MCRs). While various metals are known to facilitate these ‘imidoylative’ cross-couplings, palladium is by far the most widely used metal in these transformations. In addition, the entire field of palladium-catalyzed isocyanide insertions has matured significantly over the past couple of years, with many new reactivities being reported (Figure 1). In this review we discuss all recent examples in which isocyanides are used as a reactant in palladium-catalyzed cross-couplings. We focus on cascade transformations or processes that couple three or more reactants in a single reaction.

![Figure 1. Publications per year reporting on reactions involving isocyanide reactant using palladium catalysis.](image)

This review augments our earlier comprehensive overviews of both palladium-catalyzed [7] and base metal-catalyzed [8] isocyanide insertions. As the synthetic applicability of these convergent synthetic strategies often hinges on the ability of the catalytic system to tolerate variations of the isocyanide substituent, we will especially discuss the isocyanide scope in each report. While tertiary isocyanides have traditionally been the main focus in most reports, this has changed more recently. Over the past decade, more robust catalytic conversions have been reported, often being much more tolerant of isocyanide input. Additionally, using palladium catalysis to insert an isocyanide, followed by the hydrolysis of the newly formed imine has rendered isocyanide insertions an effective tool for ‘CO-free carbonylation,’ essentially utilizing the isocyanide as a carbonyl surrogate. Nickel-catalyzed polymerization of isocyanides to helical polyimines is extensively reported in literature [11,12]. Recently, significant advances have been made in using palladium catalysis for similar transformations to polyimines [13–18]. Due to the nature of this transformation, affording polymeric structures rather than small molecules, these examples will not be treated in this review.

2. Pd⁰-Catalyzed Isocyanide Insertions

2.1. Imidoylation Initiated by Oxidative Addition of Carbohalides

Since the early discoveries in the 1970s, much of palladium catalysis still utilizes the propensity of aryl halides to undergo oxidative addition to an active Pd⁰ complex. This typically results in the formation of an aryl palladium complex I (Scheme 1). This complex can rapidly undergo 1,1-migratory insertion of isocyanides into the activated aryl palladium bond, furnishing imidoyl...
palladium complex II. Next, a ligand exchange can take place, either with ambient nucleophiles, or the complex II undergoes a transmetalation with metal-based coupling partners, resulting in the formation of complex III or IV. Subsequent reductive elimination then affords the imidoylative cross-coupling imine products, while regenerating the active Pd$^0$ catalyst, thus closing the catalytic cycle. In the following sections, we discuss in more detail the catalytic processes, organized along the nature of the respective coupling partner.

![Scheme 1](image)

**Scheme 1.** Typical catalytic cycle for redox-neutral Pd-catalyzed isocyanide insertion reactions.

### 2.1.1. Cross-Couplings with Organometallic Carbon Nucleophiles

The ‘classic’ palladium-catalyzed cross-couplings almost all follow the typical pattern of oxidative addition, transmetalation, and reductive elimination, thus employing an external R’-M species as the coupling partner. Transmetalation is commonly an integrated step in the catalytic cycle of these processes, except perhaps for the well-known Mizoroki-Heck reaction, which is terminated by alkene insertion and β-hydride elimination. The first example of an imidoylation involving transmetalation by Mitiga et al. (imidoylative Stille coupling) [19] was followed by many studies that report major improvements in coupling partners, catalytic conditions, as well as tolerance for all coupling partners. Current methodologies have thus impressively matured over the past decade.

Although the extension of the well-known Suzuki-Miyaura reaction using isocyanides as starting material was already known [20], a new version of this cross-coupling reaction was introduced in 2014, describing an imidoylative synthesis of biarylketones 4 [21]. This redox-neutral cross coupling of aryl iodides 1, aryl boronic acids 2 and t-BuNC (3) proceeds in good yields, although the use of sterically congested aryl iodides 1 leads to somewhat lower yields (Scheme 2). No attempts were made to investigate isocyanides other than t-butyl isocyanide 3, as post-coupling acid hydrolysis cleaves of the isocyanide residue, liberating the ketone 4.

![Scheme 2](image)

**Scheme 2.** Biaryl ketone synthesis via imidoylative Suzuki-Miyaura reaction.
When the ‘classical’ palladium-catalyzed Negishi conditions are adapted by the addition of an isocyanide, a one-pot selective double isocyanide insertion was observed (Scheme 3) [22]. The choice of ligand is instrumental in the double insertion, as ligands other than dpff give mixtures of mono- and diketone products 8. Although the catalytic system tolerates many different types of alkyl zinc reagents 6, the use of isocyanides other than tert-butyl isocyanide resulted in poor to no conversion. This methodology was used to efficiently generate quinoxalines 7 via double condensation with o-phenylenediamine, in a three-step sequence, without intermediate purification (Scheme 3).

Scheme 3. One-pot double imidoylative Negishi reaction and biscondensation with o-phenylenediamines to quinoxalines.

In an extension of this imidoylative cross-coupling using organozinc compounds (6) as coupling partners, the group of Ogawa reported a similar transformation with tetraaryl lead compounds 9 (Scheme 4) [23]. Generally, this reaction appears to be more difficult to control, typically affording a mixture of mono- and diimidoylated cross-coupling products 10 and 11. However, this reaction proceeds without additives, and is compatible with aliphatic, benzylic, and aromatic isocyanides. Under the optimized reaction conditions, aliphatic isocyanides display a significant preference for coupling product diarylimines 10. When electron-rich aromatic isocyanides were employed, this product distribution switched to diimidoylated structures 11 as the main product. Reactions with electron-deficient aryl isocyanides did not afford any isolable products.

Scheme 4. (Double) isocyanide insertion using tetraaryl lead reactants.

While an imidoylative Sonogashira reaction was already reported in 2013 [24], the initial publication only used i-BuNC as an isocyanide input, and hydrolyzed the formed ynimine in situ. In 2017, our group extended this methodology to include a nucleophile on the α-position of the aryl bromide substrate 12, yielding 4-aminoquinolines (Scheme 5). Formation of the imidoylative Sonogashira intermediate 17 proceeds through transmetalation of an in situ formed copper acetylide to imidoyl palladium 16. The afforded ynimine 17 readily undergoes acid-mediated intramolecular conjugate
addition to directly afford medicinally valuable 4-aminoquinolines 15 [25]. The methodology is compatible with a range of different isocyanides, with secondary and primary isocyanides being well tolerated. Even secondary isocyanides, bearing an additional amine or carbamate moiety, were smoothly incorporated in this Sonogashira-type cross-coupling. The yields are inversely correlated to the electron density of the arenes, as decoration of either the 2-bromoaniline 12 or phenylacetylene 14 with electron-withdrawing groups resulted in lower yields, and more side reactions, most likely due to less facile, and more promiscuous cyclizations. A similar catalytic synthesis of thiochromen-4-ones was reported in 2018. [26]

![Scheme 5](image-url)

**Scheme 5.** One-pot imidoylative Sonogashira reaction and acid catalyzed cyclization.

2.1.2. Cross-Coupling with Other Carbon Nucleophiles

Similar to the imidoylative C-C bond formations via transmetalation with an organometallic reactant, the past decade has seen a significant surge in the use of other carbon nucleophiles as coupling partners, typically formed in situ via deprotonation with readily available bases. The drawback is that this is restricted to active methylenes; additionally, the carbon coupling partner formed should be nucleophilic enough to interact with electrophilic palladium complexes. However, many advancements have been made recently, greatly enhancing the scope of such imidoylative cross-couplings. There are also other ways to generate carbon nucleophiles, involving electrophilic substitutions, e.g., from electron rich enamines or arenes, or via C-H activation.

In 2015, the group of Yang reported the Pd-catalyzed intramolecular C-C imidoylation with enolates of diones 18 to generate the 2-acyl-3-iminoindenes 20 [27]. This palladium-catalyzed isocyanide insertion is highly similar to those reported earlier by Ji et al., who reported an intramolecular isocyanide insertion and trapping of the imidoyl palladium intermediate with enols to afford the corresponding imidates [28]. Deprotonation by the stronger base tert-butoxide favors coupling with the enolate carbon over the enolate oxygen in moderate to good yields (Scheme 6). Similarly, omitting the distal ketone leads to a similar reactivity of \( o \)-bromoacetophenones 19; however, all inputs were hydrolyzed with aqueous hydrochloric acid, leading to 1,3-indanediones 21 in acceptable yields (61–75%).
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enaminones of acetophenones in acceptable yields (61–75%).

However, all inputs were hydrolyzed with aqueous hydrochloric acid, leading to 1,3-indanediones
in a yield of 51%.

Another early example of imidoylation with a carbon coupling partner is shown in Scheme 8.

This methodology was extended in the same year, introducing an additional methylene
functionality to the substrate 22. In this case, medicinally relevant amino-hydroxynaphthyl ketones 23
were obtained in moderate to good yields [29]. The use of tertiary isocyanides typically affords the
4-tert-butylaminonaphth-2-ols in good yields under the optimized conditions (Scheme 7). The authors
did not fully investigate the scope regarding the isocyanide input, although a single cyclohexyl
isocyanide entry afforded the corresponding naphthol 23 in a yield of 51%.

The tether to the internal enolate can also be shortened, and still afford analogous products. In this
manner, acetophenones 25 can also be coupled with the formed imidoyl palladium intermediate,
affording aminoindenones 26 (Scheme 8). The scope of the reaction utilizing the corresponding enolate
of acetophenones 25 is much less broad in terms of isocyanide substituents, as the yields of cyclic enaminones 26 drop significantly even when cyclohexyl isocyanide is used.

**Scheme 6.** Utilizing enolates of 3-(2-bromoaryl)propanediones as coupling partners in imidoylative cyclizations.

**Scheme 7.** Utilizing enolates of 4-(2-bromoaryl)butanediones as coupling partners in imidoylative cyclizations.

**Scheme 8.** Utilizing enamine of N-(2-iodoaryl)enaminones as coupling partners in imidoylative cyclizations.
Another early example of imidoylation with a carbon coupling partner is shown in Scheme 8. The generated imidoyl palladium species is attacked by the electron-rich enamine carbon of enaminoles 27, which affords the medicinally interesting 4-aminoquinazoline derivatives 28 after reductive elimination [30]. The imidoylative cross-coupling proceeds with low catalyst loading, and generally affords annulated 4-aminoquinoline products in yields of around 90%, though the cyclization efficiency is greatly diminished if acyclic enaminoles are used. The use of secondary isocyanides also reduces the yields, and no isolable quantities are formed when aromatic or benzyl isocyanides are employed.

Another example of the redox-neutral cross-coupling with carbon nucleophiles involves the synthesis of indoloquinolines 31 from 2-(2-iodoaryl)indoles 29 and isocyanides 30 [31]. This reaction is postulated to proceed via isocyanide insertion into the generated aryl palladium bond, and subsequent electrophilic aromatic substitution at the highly electron-rich indole C3-position (Scheme 9). N-substituted indoloquinolines 31 were isolated successfully from tertiary and secondary aliphatic isocyanides. A single example was reported starting from 4-nitrophenyl isocyanide, although the corresponding indoloquinoline was formed in much lower yield (26%). The same group later facilitated the same reaction, with double isocyanide insertion, affording amide analogs of 31, which show significant selective cytotoxicity for several cancer cell lines [32].

![Scheme 9](image_url)

**Scheme 9.** Utilizing an electron rich arene of 2-(2-iodoaryl)indoles in imidoylative cyclizations.

An imidoylative cross-couplings using an isocyanide with a tethered carbon nucleophile is highlighted in Scheme 10. Using the readily available tryptophan-derived isocyanides 32, a redox-neutral carboimidoylation was readily facilitated [33]. Regardless of the substituent pattern, all aryl iodides 33 afford β-carbolines 34 in good to excellent yields. The authors suspect that the initially formed dihydrocarbolines are oxidized under aerobic conditions during work-up to the medicinally valuable carbolines 34.

![Scheme 10](image_url)

**Scheme 10.** Intramolecular imidoylation of aryl iodides with isocyanotryptophanes.

A final example of using indoles as cross-coupling partners is shown in Scheme 11, in which the divergent reactivity of 2-(2-bromoaryl)indoles 35 was highlighted [34]. In the case of N-unsubstituted indole, all employed conditions favor the Buchwald-Hartwig-type amidination with the indole nitrogen, affording indoloindolones 36 by post-coupling hydrolysis of the amidine. Implementation of a N-substituent favors formation of indoloindenones 37 via a carboimidoylation rather than an aminoiimidoylation, in comparable yields. In all cases, only tert-butyl isocyanide was used, and the product ketimines were hydrolyzed by addition of aqueous HCl.
A wide variety of aromatic substituents are tolerated on the dibenzyl isocyanoacetates for medicinally valuable dihydroisoquinolines [42], imidoyl palladium species [41] isocyanoacetates [40] afford significant amounts of double isocyanide insertion products. However, if 2,6-disubstituted phenyl and dibenzoxazepines [40] substituted aromatic isocyanides [39], which undergoes an enantioselective carbocyclization to access the medicinally valuable carbolines [34] of a medicinally valuable dihydrocarbolines are oxidized under aerobic conditions during work-up to the medicinally valuable iodides [38]. Utilizing an electron rich arene of 2-(arylxy, arylamino or arylphosphino)aryl isocyanides in imidoylative cyclizations.

Scheme 11. Substrate-dependent intramolecular carboimidoylation or aminoimidoylation.

Recently, the group of Zhu extended this reactivity, reporting a direct imidoylative annulation of substituted aromatic isocyanides [38] and aryl iodides [39], generating medicinally valuable dibenzazepines and dibenzoxazepines [40] (Scheme 12) [35]. The cross-coupling of o-isocyanodiphenylether affords significant amounts of double isocyanide insertion product. However, if 2,6-disubstituted phenyl isocyanides are used, formation of this side product is avoided, forming products [40] with surprising efficacy for a redox-neutral palladium-catalyzed aromatic isocyanide insertion. Dibenzodiazepines [40] (Y = NMe) were synthesized in similar yields via the same method.

Scheme 12. Utilizing an electron rich arene of 2-(aryloxy, arylamino or arylphosphino)aryl isocyanides in imidoylative cyclizations.

In 2017, the same group published an enantioselective desymmetrization of dibenzyl isocyanocacetates [41] [36]. Isocyanide insertion into the formed arylpalladium affords the intermediate imidoyl palladium species [43], which undergoes an enantioselective carbocyclization to access the medicinally valuable dihydroisoquinolines [42] (Scheme 13). Utilization of the chiral spinol-derived ligand L1 affords the products [42] in high yields, and typically in moderate to high ee’s. Additionally, a wide variety of aromatic substituents are tolerated on the dibenzyl isocyanocacetates [41].
Additionally, this method was also compatible with the alkylpalladate (benzylidene)isocyanoacetates (Scheme 14). The reaction proceeds via isocyanide insertion into the formed arylpalladium species. These formal C-H functionalizations can either rely on a classic two step S$_g$Ar, as several examples above, or have a more concerted character, bordering on electrocyclizations.

The redox neutral imidoylation of aryl iodides 39 with biaryl isocyanides 44 was reported in 2015 as a direct method of generating phenanthridines 46 in good to near-quantitative yields (Scheme 14). The reaction proceeds via isocyanide insertion into the formed arylpalladium species. The n, C-H functionalization affords the re-aromatized phenanthridines 48 [38]. Kinetic isotope effect experiments suggest that the annulation proceeds via C-H activation and reductive elimination, although an electrophilic aromatic substitution cannot be excluded. Changing the biaryl isocyanide to (benzylidene)isocyanateacetates 45 affords the corresponding isoquinolines 47 via a similar mechanism. Additionally, this method was also compatible with the alkylpalladate 51 generated by additional intramolecular proximal alkene insertion of methacrylamide 49, affording chemically complex structures 50 in a one-pot fashion (Scheme 15).

![Scheme 13](image)

**Scheme 13.** Enantioselective desymmetrization of dibenzyl isocyanoacetates in a Pd-catalyzed imidoylative annulation.

![Scheme 14](image)

**Scheme 14.** Intramolecular imidoylation of aryl iodides with biarylisocyanide and (benzylidene)isocyanoacetates.
The same group later reported an asymmetric variation of this transformation (Scheme 16). By using (ferrocenyl)vinyl isocyanides 53 and aryl iodides 39 in combination with chiral ligand L2, pyrido-fused ferrocenes 54 could be isolated in good to near-quantitative yields, with high ee [39]. Similarly, with N-(2-iodophenyl)-N-methylmethacrylamide 55 additional alkene insertion occurs prior to isocyanide insertion. This cascade affords the highly complex structures 56 with high ee. However, the chiral induction of the indolinone is moderate, leading to a d.r. of only 1.7:1 of 56a:56b (Scheme 17).

**Scheme 15.** Intramolecular amidation of aryl iodides with biaryl isocyanide involving additional alkene insertion.

**Scheme 16.** Asymmetric synthesis of pyrido-fused ferrocenes.

**Scheme 17.** Asymmetric synthesis of indolinone substituted pyrido-fused ferrocenes.
2.1.3. Cross-Couplings with Oxygen or Nitrogen Nucleophiles

In addition to transmetalation, the Buchwald-Hartwig reaction has received much attention by synthetic and medicinal chemists, as this reaction proved instrumental in the synthesis of many novel pharmaceutical scaffolds and their decoration [1]. The imidoylative variant of the Buchwald-Hartwig reaction involves nucleophilic attack on the transient imidoyl palladium species allowing for the formation of substituted imidates and amidines, and imines, depending on the nucleophile used. The se functionalities are quite useful and ubiquitous in nature and pharmaceutical intermediates. Recent studies in the field of isocyanide insertions are directed towards further development of these imidoylative Buchwald-Hartwig type cross-couplings. To facilitate this, over the past couple of years there have been multiple reports on the mechanistic aspects of these reactions, allowing chemists to easier predict catalytic behavior and develop more effective catalysts [40–42].

In 2014, Schipman et al. extended the imidoylative Buchwald-Hartwig type cross-coupling to include the use of diamines 57 as coupling partners [43]. This reaction is indicative for imidoylative Buchwald-Hartwig couplings, and proceeds via the oxidative addition of an aryl halide 5 to in situ generated Pd⁰, after which a well-documented 1,1-migratory insertion of the isocyanide can take place. The transient imidoyl palladium intermediate 58 is readily attacked by ambient diamine 57, which affords the amidine 60 after reductive elimination. This amidine smoothly undergoes an intramolecular transimination to afford 2-arylated imidazolines 58 (Scheme 18), releasing tert-butylamine. The products are typically formed in good yields, although somewhat lower yields are reported for sterically hindered aryl halides, or less nucleophilic variations of diamine 57, such as o-phenylenediamine. The authors also utilized this methodology to facilitate a direct synthesis of a complex chiral Pybim ligand 63 (Scheme 19).

Scheme 18. Cascade imidoylative Buchwald-Hartwig reaction and cyclization via transimination.

Scheme 19. One-step bisimidoylative synthesis of chiral Pybim ligand.

A related method affords 2-substituted (3H)quinazolin-4-ones from N-acyl 2-bromoanilines 64. [44] This method relies on the direct hydroxyimidoylation of the aryl halides with water as the nucleophile,
affording bisamides 65 at 120 °C from either tert-butyl isocyanide or cyclohexyl isocyanide (Scheme 20). If the temperature is raised to 160 °C, the generated bisamide undergoes a cyclocondensation to quinolinones 66, which is accompanied by spontaneous de-tert-butylation. It should be noted that similar one-pot hydroxyimidoylation/cyclization cascades are also reported in the syntheses of indolin-1-ones [45] and fused dihydropyrrolimines [46].

![Scheme 20. Temperature-dependent hydroxyimidoylation and subsequent condensation cascade.](image)

In a related process, the cyclooxyimidoylation of (2-bromoaryl)ureas 67 proceeds with full selectivity to the urea oxygen, which results in iminobenzoxazinones 68 (Scheme 21) [47]. In contrast to the couplings above, this transformation is highly compatible with various isocyanides, as aliphatic, α-acidic, and aromatic isocyanides all afford the iminobenzoxazinones 68 in high yields, regardless of the isocyanide substituent. The iminobenzoxazinones 68 are readily converted to the medicinally useful corresponding 2-aminobenzoxazinones via hydrolysis with aqueous HCl, or can be converted to the corresponding 2-aminoquinazolin-3H-ones through a piperidine-mediated Mazurkiewicz-Ganesan rearrangement, similar to earlier reports. [48] The same authors reported a similar reactivity for (2-bromophenyl)thioureas [49], and N-(2-bromoaryl)benzamides, yielding 2-aminothiazin-4-imines 2-arylbenzoxazin-4-imines, respectively [50].

![Scheme 21. Intramolecular oxyimidoylation of (2-bromophenyl)ureas.](image)

Early in the development of this research field our group also reported an intramolecular imidoylative Buchwald-Hartwig reaction towards highly electron-deficient (aza)quinazoline 70 (Scheme 22) [51]. The transformation is successful in combination with secondary isocyanides and tert-butyl isocyanide, although no other tertiary isocyanides were investigated. The more electron-deficient N-(2-pyridyl)amidines 69 are more reactive towards imidoylative amidation than the regioisomeric N-(3-pyridyl)amidines, requiring lower temperatures, and affording the corresponding pyridopyrimidines 70 in higher yields.
while 2,6-dimethylphenyl isocyanide gave only trace amounts of quinoline. Although (thio)hydrazides were formed through direct amination, and the follow-up Suzuki coupling proceeds completely without imidoylation. Although (thio)acylamidrazone undergoes a smooth cyclocondensation under the basic reaction conditions.

The imidoylative Buchwald-Hartwig cross-coupling can also be employed in combination with (thio)hydrazides in a redox-neutral synthesis of 1,3,4-oxadiazoles and thiadiazoles. As the isocyanide is only used as a C1 building block, the scope was left uninvestigated, and only t-BuNC was employed in this coupling. The cross-coupling is also successful with aliphatic hydrazides, but results in a significantly reduced yield. The proposed intermediate (thio)acylamidrazone undergoes a smooth cyclocondensation under the basic reaction conditions.

Comparably, an initial Buchwald-Hartwig aminomidoylation can also be followed up by additional palladium-catalyzed cross-couplings in a one-pot fashion. The multicomponent reaction (Scheme 24) generates 2-amino-3-bromoquinolines via an imidoylative Buchwald-Hartwig coupling, after which a subsequent Suzuki coupling takes place, affording 2-amino-3-arylquinolines. Isocyanide insertion is fully selective; no indoles were formed through direct amination, and the follow-up Suzuki coupling proceeds completely without imidoylation. Although (tert-butylamino)quinolines (R3 = tBu) are typically isolated in yields over 70%, changing the isocyanide input significantly hampered the reaction. The use of cyclohexyl isocyanide led to an isolation of the corresponding product of a disappointing 34%, while 2,6-dimethylphenyl isocyanide gave only trace amounts of quinoline. Similarly, in the absence of an internal nucleophile, hydroxyimidoylation of gem-dibromostyrenes to the corresponding alkynylamides is also possible.
An interesting multicomponent cascade reaction with N-tosylaziridines 76 and o-iodophenols 77 affords access to benzoazepines 78 [56]. The cascade is initiated by the base-promoted ring-opening of the aziridine by iodophenol 77 (Scheme 25). A subsequent intramolecular aminoidoylation directly affords the polysubstituted benzoazepines 78 in good yields, and in full trans-selectivity. The regioselectivity is controlled by steric, opening the aziridine on the least hindered carbon. Again, reactions with tertiary isocyanides afford the corresponding benzoazepines in good yields. The only secondary isocyanide (cyclohexyl isocyanide) that was tested afforded the product in a moderate 42%.

An intramolecular Buchwald-Hartwig coupling with aryl iodides 80 bearing an internal nucleophile on the ortho position affords 2-amino-3-iminoindolenines 81 via double isocyanide insertion (Scheme 26) [57]. This reaction is fully compatible with tertiary, secondary, and aromatic isocyanides, but fails to afford any product 81 when primary aliphatic or α-acidic isocyanides are employed.

In an intermolecular variant of this double insertion, the group of Kegl investigated the substituent effects of aryl halides 83 on the imidoylative cross-coupling with tert-butyl isocyanide 3 and secondary amines 82 [58]. Typically, this imidoylative Buchwald-Hartwig type multicomponent reaction affords the ketimine-amidine 85 in good yields, although in most cases a mixture of 85 and the amidine 84 is formed (Scheme 27). No linear Hammett correlation between the electron-donating or -withdrawing
substituents and the yield or selectivity of this transformation was found. Interestingly, the authors note that the use of various bromoarene analogues of 83 (X = Br) typically favor a single isocyanide insertion towards benzamidines 84, implying the halide plays a role in the mechanism. The broad substrate scope investigation was only performed with tert-butyl isocyanide and piperidine; other isocyanides showed no conversion under the reaction conditions.

Scheme 27. Single or double isocyanide insertion in Buchwald-Hartwig reaction.

A Pd-catalyzed imidoylative MCR cascade to β-ketoamidines 90 or 5-aminopyrazoles 91 was reported by the group of Zhu [59]. Oxidative addition of the alkyl halide 87, and subsequent isocyanide insertion is followed by β-hydride elimination of intermediate 92, affording the ketenimine 93 as a common intermediate (Scheme 28). Subsequent addition of either amines 88 or hydrazines 89 as (bis)nucleophiles smoothly affords amidines 90 or 5-aminopyrazoles 91, respectively. A single pyrazole 91 was synthesized using cyclohexyl isocyanide, although further investigations of the isocyanide scope were not performed. Additionally, the ketenimine can also be trapped by hydrazoic acid or Grignard reagents, highlighting the divergent nature of this transformation and the versatility of intermediate ketenimine 93.

Scheme 28. Pd-catalyzed ketenimine formation with alpha bromoketones and isocyanides and interception with nitrogen nucleophiles.

The intramolecular imidoylative Buchwald-Hartwig reaction can also be performed under oxygen atmosphere yielding other products. Thus, imidoylation of the Ugi products 94 affords the
isoindolimines 96, which oxidize spontaneously under O₂ atmosphere, to form α-hydroxy intermediate 97 (Scheme 29). Next, this intermediate isomerizes to form the thermodynamically more stable iminoisoindolinone derivatives 95 [60]. Curiously, the initial Buchwald-Hartwig imidoylation is successful under oxidative atmosphere, and does not require external stabilization by phosphine ligands. The transformation proceeds smoothly using aliphatic isocyanides, but is unsuccessful when aromatic isocyanides are employed, most likely due to their inherent instability.

Scheme 29. Imidoylative Buchwald-Hartwig reaction with Ugi products under O₂ atmosphere.

Carboxylic acids can also be used as nucleophiles, forming intermediate 101 (Scheme 30) [61]. Reductive elimination then affords the O-acylimidate 102 which undergoes a Mumm rearrangement, i.e., a spontaneous intramolecular acyl transfer into the N-arylimides 100. Several examples were performed with bifunctional o-iodobenzoic acids, in which this imidoylative cross-coupling affords phthalimides in comparable yields to the untethered 3-CR variant. The reaction is highly compatible with aryl isocyanides, which is uncommon for redox-neutral palladium-catalyzed imidoylations. Additionally, through this method the authors facilitated late-stage diversification of well-known carboxylic acid pharmaceuticals (e.g., carboprofen, flurbiprofen).

Scheme 30. Imidoylative coupling of aryl iodides and carboxylic acids.
Further application of imidoylative Buchwald-Hartwig coupling includes the synthesis of fused tetracyclic scaffolds 104 (Scheme 31) [62]. The substrate dihydroquinazolinone 103 is formed in a cascade manner from isatoic anhydrides, benzaldehydes, and hydrazines. Fused hydrazide motifs have been reported for their analgesic and anti-inflammatory properties [63]. Although only tert-butyl isocyanide and cyclohexyl isocyanide were employed, both show similar reactivity in this redox-neutral imidoylation. In terestingly, when propargylated isatoic anhydrides are used to synthesize substrate 103 (R<sup>1</sup> = CH<sub>2</sub>C≡CH), the product 104 undergoes a base-promoted, palladium-catalyzed cascade depropargylation, resulting in the aromatized quinazolin-4-ones 105 in good yields.

![Scheme 31. Imidoylative Buchwald-Hartwig cross-coupling of dihydroquinazolinones.](image)

2-Alkynylated aromatic isocyanides 106 occasionally react in redox-neutral palladium-catalyzed isocyanide insertions (Scheme 32) [64]. The only two variations of aryl isocyanide substitutions that were investigated indicate the reaction is less efficient when electron density is withdrawn from the isocyano moiety. The isocyanide insertion of isocyanophenylacetylene 106 is followed by a 6-exo-dig cyclopalladation of the generated intermediate 108. The authors also showed that oxygen is most likely introduced either by residual water, or the carbonate base, which also liberates 3-acylindoles 107 upon hydrolysis.

![Scheme 32. Isocyanophenylacetylene cyclization into 3-acylindoles. R’ = –H, –CO<sub>2</sub>–.](image)

Intramolecular trapping of formed imidoyl palladium species by a nucleophile-bearing isocyanide 110 affords the polysubstituted oxazoles 111 (Scheme 33) [65]. While the reaction is compatible with multiple aryl halides 5, and typically affords the corresponding oxazoles in good yields, the isocyanocacetamide requires a tertiary amide. Further α-substitutions of the isocyanocacetamide were not investigated. Additionally, replacing the aryl halide with vinyl triflates or alkenyl bromides also
generate structural analogues of oxazoles 111 in good yields via the same mechanism. An oxidative homocoupling of isocyanides 110 to afford bisoxazoles was reported later that year [66].

\[ \text{Scheme 33. Imidoylative Buchwald-Hartwig cross-coupling with isocyanooacetamides.} \]

2.2. Imidoylation Initiated by Oxidative Addition of Oximes

Aside from the use of aryl halides as preoxidized substrates, recent reports have repeatedly included the propensity of oxidized amines and imines to undergo oxidative addition to a Pd0 catalyst. These acyloximes or acyloxyamines readily afford a N-Pd active site for isocyanide insertion, leading to more diverse, nitrogeneous cross-coupling products.

The combination of O-acyloximes 113 with isocyanides was first reported by Wang et al. in 2017. Utilizing the inherent nucleophilicity of enamines, the intramolecular double imidoylation of 113 affords the 3-aminopyrrol-2-imines 114 (Scheme 34) [67]. The method is tolerant towards aliphatic and aromatic isocyanides, although utilization of aromatic isocyanides tends to afford the products 114 in moderately lower yields, and typically requires extended reaction times.

\[ \text{Scheme 34. Intramolecular double imidoylation of O-acyloximes.} \]

The same group later exploited this reliable reactivity of isocyanide insertion into O-acyloximes to facilitate the curious dehydrogenative insertion of benzyl isocyanide 116 into these oximes 115 (Scheme 35). This affords the pyrrolediimines 118, which undergo in situ dehydrogenative homocoupling, leading to the diphenylated pyrroloquinoxalines 117 in surprisingly good yields (29–69%) [68]. The benzylc isocyanide substituent is required, as the reaction fails with α-acidic isocyanides. The cross-dehydrogenative homocoupling of the benzylc substituents does not require an external oxidant.

\[ \text{Scheme 35. Imidoylation of O-acyloximes followed by dehydrogenative homocoupling.} \]
The methodology mentioned in Scheme 13 was later expanded by exploiting this oxidative addition of O-benzoylhydroxylamines 120 to the active Pd0 catalyst, and subsequent isocyanide insertion to generate the corresponding imidoyl palladium species (Scheme 36) [69]. Pivalate-assisted C-H functionalization of the tethered arene and reductive elimination affords the 1-aminodihydroisoquinolines 121, typically in good yields. In this case, no asymmetric variations were attempted. The efficacy of this transformation is not hampered by the introduction of electron-withdrawing groups on the arene. No secondary isocyanoacetates (R1 = H) were reported. Additionally, benzoylhydroxylamines derived from primary amines were not tested under these conditions.

![Scheme 36](image)

Scheme 36. Imidoylative coupling of tertiary isocyanoacetates and O-benzoylhydroxylamines.

Related to the above-mentioned phenanthridines synthesis (Scheme 15), but initiated by the oxidative addition of O-benzoylhydroxylamines 123 to Pd0, 6-aminophenanthridines 124 or 1-aminoisoquinolines 125 are rapidly formed through a subsequent imidoylation and electrophilic aromatic substitution cascade [70]. Although the nature of the isocyanide substituents are of little consequence to the overall yield of these transformations, the reaction is only successful when N,N-disubstituted benzoylhydroxylamines are employed introducing tertiary amines on the cores (Scheme 37).

![Scheme 37](image)

Scheme 37. Intramolecular imidoylation of N,N-disubstituted O-benzoylhydroxylamines with biarylisocyanide and (benzylidene)isocyanoacetates.

### 2.3. Imidoylation Initiated by Oxidative Addition of Allyl(pseudo)halides

The first reported palladium-catalyzed imidoylation using allylic (pseudo)halides to initiate isocyanide insertion involves the synthesis of 3H-indolamines 128, bearing a quaternary carbon center at C3, utilizing complex bifunctional 2-(3-acetyloxypropen-1-yl)aryl isocyanide 126 as a coupling partner (Scheme 38) [71]. The use of l-proline methyl ester as an amine component led to moderate stereochemical induction, affording 128 in 44% yield, as a 3:1 mixture of diastereomers.
Scheme 38. Intramolecular imidoylative Tsuji-Trost coupling with amines.

The first intermolecular cross-coupling involving a π-allylpalladium complex and isocyanides was reported by Zhu et al. in 2016 [72]. The y used allylic carbonates 130 to facilitate isocyanide insertion to give the corresponding vinylic ketenimines 133 (Scheme 39), which were subjected to hydration or formal $[3 + 2]$ cycloaddition with azides in a one pot fashion to afford $\beta,\gamma$-unsaturated amides 131 or tetrazoles 132, respectively. The reaction proceeds under remarkably mild conditions, and the products are typically isolated in good yields. As the product regiochemistry is under thermodynamic control, substitution at the R$^1$ or R$^2$ position can lead to formation of some regioisomers, or E/Z-diastereoisomers. While the authors report that the reaction is compatible with secondary and even aromatic isocyanides, these examples were not included in the initial publication.

Scheme 39. Homologation of allyl carbonates into allylic amides and 1H-tetrazoles via ketenimine formation.

An uncommon cyanation via isocyanide insertion into activated allylic (pseudo)halides can also proceed via a radical mechanism (Scheme 40). In a recent report by Zhu et al., the interesting conversion of allylic carbonates 134 and tertiary cyclic isocyanides 135, bearing an α-ester moiety, was described [73]. The ketenimines 138 are formed, similar to Scheme 39, and are postulated to undergo homolysis to generate radical pair 140 and 141. The rapid isomerization is most likely responsible for the mixture of isomers 136 and 137 formed.
The reaction conditions are compatible with secondary and primary aliphatic isocyanides. Extensive mechanistic investigations were not performed, but the authors propose an isocyanide insertion into allylic Pd intermediate 144, followed by reductive elimination to afford imidate intermediate 145. This imidate undergoes an intramolecular acyl migration via Mumm rearrangement to afford the product imides 143. The reductive elimination, generating conjugated intermediates such as 145, has not been reported anywhere else, although similar reactions have been published over the past couple of years [71–73,75,76]. The authors make no mention of a possible hydride transfer. However, a post-coupling “chain-running” allylic isomerization of vinylacetimide towards the more thermodynamically stable conjugated crotonimide seems likely. The se isomerization processes can also be catalyzed by palladium [77].

Zhu et al. reported one of the first controlled palladium-catalyzed triple isocyanide insertion reactions, facilitating the synthesis of highly decorated aminopyrroles 148 [78]. By extending the previously noted Tsuji-Trost activation of allylic acetates to propargylic carbonates 146, an allenylpalladium species is formed that can undergo isocyanide insertion, providing intermediate 149 (Scheme 42). Attack of a second isocyanide 23 forms an electron-deficient nitrilium species 150 that

Scheme 40. Tsuji-Trost imidoylation followed by radical rearrangement into cyanides.

Scheme 41. Imidoylative conversion of allyl benzoates into N-benzoyl-N-substituted crotonimides.
is susceptible to external addition of yet another isocyanide, generating the postulated intermediate 151. Only now is the sequence terminated by the addition of nucleophilic alcohol 147, which performs a conjugate addition to form the aminopyrroles 148. Only tertiary isocyanides were used in this triple insertion process.

Scheme 42. Aminopyrrole synthesis by triple isocyanide insertion cascade.

2.4. Imidoylation Initiated by Oxidative Addition of Activated Sulfur Compounds

Imidoylative variants of less common palladium-catalyzed cross-coupling reactions are also reported. In this respect, the Liebeskind-Srogl coupling, typically involving an activated thioether or thioester, is an interesting example [79,80]. Although early reports rely on both palladium and copper catalysis, new versions of this reaction typically only require either copper or palladium catalysts. The scope of this cross-coupling has recently been extended to include isocyanides, although all imidoylative Liebeskind-Srogl-type reactions reported to date only insert an isocyanide into the activated substrate, retaining the leaving group, and therefore, they are formally not cross-coupling reactions.

An early example (2017) of such an imidoylative Liebeskind-Srogl coupling was performed in a one-pot fashion as depicted in Scheme 43 [81]. The thiophene 156 is formed via an S-demethylation/Thorpe-Ziegler cyclization [82], and is directly subjected to the imidoylative reaction conditions. The reaction reliably affords the thioimidate 155 in 62–74% yield. Even when using cyclohexyl, or 2,6-dimethylphenyl isocyanide, the yields were similar to the reactions performed with the benchmark tert-butyl isocyanide. As this transformation is not affected by the free amine on the intermediate thiophene 156, the product thioimidates could also be further derivatized by Cu/Pd-cocatalyzed amination of arylboronic acids, further increasing the chemical complexity in a one-pot, three-three stage reaction sequence.

Scheme 43. One-pot, two-stage imidoylative Liebeskind-Srogl coupling.
Methyl heteroaryl thioethers 158 can be subjected to imidoylative conditions to selectively afford thioesters 159 (Scheme 44) [83]. It should be noted that without the Zn(OAc)2 additive no scrambling of various mixed methyl- and ethyl thioethers occurred, which suggests that the Lewis acidic zinc ion activates the thioether towards oxidative addition to the palladium catalyst. As the thioimidate product is hydrolyzed, only tert-butyl isocyanide was used in the reported examples.

Scheme 44. Imidoylative Liebeskind-Srogl coupling of methyl heteroaryl thioethers followed by in-situ hydrolysis of the thioimidate yielding thioesters.

Homologation of thiocarbamates 160 with isocyanides was also reported [84]. Treatment of thiocarbamates with a palladium catalyst and aromatic isocyanides results in the transient palladium complex 162 as an active intermediate. In silico experiments indicate the isocyanide insertion proceeds in the labile Pd-S bond. Subsequent reductive elimination affords the thioimidates 161 (Scheme 45). The isocyanide scope was not studied in detail and only 2,6-disubstituted aromatic isocyanides were reported. Although the reaction tolerates different substituents on the thiocarbamate nitrogen, only S-arylated thiocarbamates were employed. Additionally, selenocarbamate analogues of 160 displayed similar reactivity, affording the corresponding products in 41–64%.

Scheme 45. Pd-catalyzed isocyanide insertion into thiocarbamates.

Another unconventional Liebeskind-Srogl-type activation proceeds via the oxidative addition of disulfide 164 to the active Pd0 catalyst, followed by thiopalladation of the internal alkyne 163 (Scheme 46) [85]. The resulting vinylpalladium species 167 can undergo isocyanide insertion, after which δ-hydride elimination of the intermediate imidoyl palladium species 168 affords the β-thiolated acrylonitrile 164, isobutene, and a thiol, while regenerating the Pd0 catalyst. In interestingly, the thiol byproduct does not poison the catalyst towards further catalytic turnover. Unfortunately, the E/Z-stereoisomeric ratio appears to be under thermodynamic control, and affords configurational mixtures in all cases, typically slightly favoring E-configured acrylonitriles 165. Only a single asymmetric internal alkyne was probed, affording total regioselectivity, but still similar mixtures of E/Z-stereoisomers.
Scheme 46. β-thiolated acrylonitrile synthesis from disulfide, t-butyl isocyanide, and internal alkynes.

2.5. Imidoylation of Palladium-Ligated Carbenes and Nitrenes

In 2020, the seminal work of Cai et al. [86] on carbene transfers to palladium isocyanide complexes was significantly extended to a cascade version. In this carbene transfer, which was reported by the group of Liu, the bifunctional nature of tryptamine-derived isocyanides 169 was utilized in an elegant fashion (Scheme 47) [87]. The authors proposed a palladium-catalyzed carbene transfer of diazoacetate 170 to the isocyanide, affording the corresponding ketenimine 175, which readily undergoes dearomatization-spirocyclization upon nucleophilic attack of the indole C3-position, affording indolenines 172. Further intramolecular annulation pathways are available if functionalized diazoacetates 171 are used, affording tetracyclic indolines 173 in moderate to excellent yields. It should be noted that the products 172 were readily derivatized in an enantioselective manner through asymmetric Mannich-type cyclization with chiral phosphoric acids.

Scheme 47. Pd-catalyzed carbene transfer from diazo compounds to tryptamine-derived isocyanides.

Further advancements include generating the intermediate palladium carbene complexes in other ways than via diazo compounds. The palladium carbene complex 179 was obtained via a 5-exo-dig cyclization of conjugated enynones 176, presumably via the zwitterionic intermediate 178 (Scheme 48) [88]. The carbene transfer to the isocyanides 175 proceeds smoothly, affording the
polyfunctionalized furans 177 in isolated yields of 41–72%. In this case, only aromatic 2,6-disubstituted isocyanides were converted.

**Scheme 48.** Pd-catalyzed carbene transfer resulting from 5-exo-dig cyclization to isocyanides.

Analogously, starting from organic azides, the palladium-catalyzed transfers of nitrenes to isocyanide functionalities can be achieved. In a recent example, Sawant et al. reported a ligand-free substrate-dependent synthesis of cyclic systems from bifunctional arylazide substrates [89,90]. Molecular nitrogen is readily extruded from the azide substrates to generate a palladium-bound nitrene intermediate 184, which is subsequently transferred to the isocyanide to afford the short-lived carbodiimide 185, which readily undergoes intramolecular addition (Scheme 49). The substrate scope includes both 2-azidobenzoic acids and amides 180, which afford the corresponding benzoazinones and quinazolinones 182 in good yields. Additionally, 2-azidoanilines and 2-azido(thio)phenols can also be converted to the corresponding amminobenzoazinones, -oxazoles, and -thiazoles 183 in good yields. The syntheses were only attempted with tert-butyl and cyclohexyl isocyanide. Extensive DFT calculations indicate the rate-determining step is the loss of nitrogen from the azide-palladium complex. The resulting nitrene is transferred to the isocyanide, and the resulting carbodiimide undergoes cyclization to afford the heterocycles 182 and 183. In the same year, Ding et al. reported multiple one-pot post-imidoylation cascade transformations based on similar starting materials [91].

**Scheme 49.** Pd-catalyzed nitrene transfer from bifunctional arylazides to isocyanides.
This group further expanded the follow-up chemistry in a one-pot process [92]. The initial nitrene transfer of azide precursors 186 to isocyanides 5 under Pd catalysis proceeds in yields up to 90%. Post-coupling with trimethylsilyl azide in the presence of FeCl₃ affords the medicinally valuable 5-amino-1H-tetrazoles 187 (Scheme 50). This transformation tolerates tertiary, secondary, and aromatic isocyanides affording the corresponding aminotetrazole 187 with full regioselectivity in good to excellent yields. However, only starting materials are isolated if aliphatic azides are employed.

![Scheme 50](image)

**Scheme 50.** Pd-catalyzed nitrene transfer from azide to isocyanides and subsequent [3 + 2] cycloaddition.

An interesting 4-CR, initiated by palladium-catalyzed nitrene transfer of 2-azidobenzaldehydes 190 to isocyanides selectively affords carbodiimide 192 (Scheme 51) [93]. The authors postulate biscondensation with N-tosylhydrazine 189 forms the zwitterionic quinazolines 193. Subsequent cyclcondensation with primary nitrites 188 yields tricyclic pyrazolo[1,5-c]quinazolines 191 bearing a free amine moiety. The products exhibit high EGFR inhibition, and are thus of interest as potential anti-cancer agents.

![Scheme 51](image)

**Scheme 51.** 4-Component reaction towards pyrazolo[1,5-c]quinazolines, initiated by nitrene transfer from 2-azidobenzaldehydes to isocyanides.

Additionally, the formed zwitterionic quinazolines 193 can undergo reaction with other partners than nitrile. A silver-catalyzed annihilation with alkynes 194 cleanly affords the tricyclic pyrazoloquinazolines 196 under remarkably mild conditions (Scheme 52) [94]. The expulsion of p-toluenesulfonic acid occurs upon aromatizing formation of product 195. If alkenes 195 are used in this 4-CR, the coupling generates the corresponding fused N-tosyl-tetrahydro pyrazoloquinazolines 197.
The reaction conditions are remarkably tolerant of various substituents on the aryl halide. The concomitantly formed H-Pd-X can expel HX via reductive elimination, regenerating Pd0. The reaction can be executed at only 1 bar of CO2. A relatively high CO2 pressure is required to prevent this intermediate from undergoing a second isocyanide insertion (see Scheme 53). A similar methodology was simultaneously reported by Ji et al. [96]. Recently, palladium immobilized on an aminated graphene oxide layer was utilized as a heterogeneous catalyst in this imidoylative MCR. This catalyst requires 2-iodoanilines but the reaction can be executed at only 1 bar of CO2 [97].

2.6. Miscellaneous Pd0-Catalyzed Isocyanide Insertions

Our group developed a quite uncommon sequential insertion of isocyanides and carbon dioxide [95]. This reaction proceeds via the Pd0 catalyzed imidoylation of o-bromoaniline 12 to form imidoyl palladium complex 199 (Scheme 53). A relatively high CO2 pressure is required to prevent this intermediate from undergoing a second isocyanide insertion (see Scheme 26), and favoring carboxylation. Subsequent reductive elimination affords benzoazinones 200, which undergo a Mazurkiewicz-Ganesan-type rearrangement under the optimized reaction conditions, resulting in the thermodynamically more stable substituted quinazolinediones 198. This multicomponent cross-coupling tolerates tertiary, secondary, and primary, (including benzylic) isocyanides. The yield of the quinazolinediones 198 does not depend on the type of isocyanide employed, but appears to be correlated to the electron density of the used aniline 12. A similar methodology was simultaneously reported by Ji et al. [96]. Recently, palladium immobilized on an aminated graphene oxide layer was utilized as a heterogeneous catalyst in this imidoylative MCR. This catalyst requires 2-iodoanilines but the reaction can be executed at only 1 bar of CO2 [97].

Another uncommon, but highly interesting formal cyanoimidoylation of aryl halides affords α-iminonitriles 202 through sequential isocyanide insertion/de-tert-butylation (Scheme 54) [98]. The concomitantly formed H-Pd-X can expel HX via reductive elimination, regenerating Pd0. The reaction conditions are remarkably tolerant of various substituents on the aryl halide 201,
including nucleophiles and heterocycles. However, introduction of an o-substitution significantly diminishes the yield. Again, the tertiary isocyanide functionality is required, as the reaction fails with other isocyanide substituents.

Over the past couple of years, alkene insertions involving isocyanide insertion have become an increasingly popular method to generate chemical complexity. Currently, the only report of a true imidoylative Heck-reaction is shown in Scheme 55, effectively inserting the isocyanide between the aryl halide and the activated alkene, in a tunable synthesis of iminoaurones [99].

The iminoaurones 206 are generated in good to excellent yields. Satisfyingly, the catalytic system functions without any ligands, and tolerates various aromatic isocyanides, as even the unstable 2-naphyl isocyanide afforded the corresponding iminoaurone in 54% yield. Post-coupling hydrolysis with aqueous HCl cleanly affords the corresponding aurones 207 with virtually no loss in yield. Curiously, when 2-bromophenoxyacrylates 205 were used, the main product was the dihydrobenzofuran 208. The authors showed that β-hydride elimination leads to the HPdBr, which does not undergo reductive elimination as readily as its iodide analogue, but rather transfers
a hydride to the newly formed imine. Dihydrobenzofurans 208 were isolated in moderate yields, and only tertiary isocyanides were tolerated.

Intramolecular alkene insertion preceding imidoylation are more common. Bringing alkenes in close proximity to an in situ formed aryl palladium species typically leads to 5-exo-dig carbopalladation. In the absence of β-hydrogens, no β-hydride elimination (Heck reaction) can occur, and the formed alkylpalladium intermediate 210 instead undergoes imidoylative cross-couplings. As two insertions selectively and sequentially occur, we treat these examples in this miscellaneous section.

The group of Zhu communicated several excellent examples of this reactivity, reporting a series of palladium-catalyzed reaction cascades. In trinolecular alkene insertion in N-(2-iodoaryl)acrylamides 209 delivers common intermediates 210, which can undergo an isocyanide insertion (Scheme 56). Subsequent cross-coupling with oxadiazoles 211 involving C-H activation gave the ketones 213 after acid-mediated hydrolysis of the formed imine [100]. The authors further highlight the divergent nature of this cascade by changing the nucleophilic coupling partner. Utilization of KOH as a nucleophilic base affords the amides 214, whereas the use of alkoxides leads to formation of the corresponding esters 215. Additionally, substituting tert-butyl isocyanide for aromatic 2-acetoxyphenyl isocyanide 212 in which the acetylated phenol itself acts as a coupling partner, affording benzoazoles 216 in good yields. This specific transformation might also result from the base-mediated decomposition of isocyanide 212 to benzoazole, in which case no formal isocyanide insertion occurs. Additionally, using the chiral DuanPhos ligand, the authors could also isolate analogs of amides 214 with up to 75% ee.

Scheme 56. Imidoylative cross-couplings through alkene insertion/isocyanide insertion/reaction with nucleophiles.

Allenes can also be employed in these type of cascade transformations. The intramolecular carbopalladation of the distal double bond in N-protected N-allenyl-2-idoanilines 217 proceeds selectively prior to isocyanide insertion [101]. The authors highlighted the divergent value of the synthetic method by trapping the intermediate ketenimine 220 with nucleophilic species such as water (Scheme 57). As a proof of concept, the intermediate 220 was also reacted by azides, alcohols, and amines to afford tetrazoles, esters, and amidines, respectively. Unfortunately, this transformation is only successful with tertiary isocyanides.
was reported [104]. Although the reductive isocyanide insertion was only performed using Scheme 59). Subsequent isocyanide insertion, and intramolecular Heck-type cyclization of the formed imidoyl-palladium species affords indolines 223. Unfortunately, isocyanides require slow addition over the course of the reaction, and the final Heck-cyclization is only successful if α-allyl isocyanoacetates are used. Longer or shorter tethers between the alkene and isocyanide moieties do not result in any product formation.

Very recently, Jiang et al. reported the first dearomative imidoylation of indoles [102], extending their earlier work with alkenyl isocyanides [103]. Combining readily available N-(2-bromobenzoyl)indoles 221 with these alkenyl isocyanides 222 gives a cascade reaction. The dearomative intramolecular carbopalladation outcompetes direct isocyanide insertion, forming the tetracyclic intermediate 224 (Scheme 58). Subsequent isocyanide insertion, and intramolecular Heck-type cyclization of the formed imidoyl-palladium species affords indolines 223. Unfortunately, isocyanides require slow addition over the course of the reaction, and the final Heck-cyclization is only successful if α-allyl isocyanoacetates are used. Longer or shorter tethers between the alkene and isocyanide moieties do not result in any product formation.

In 2014, the first reductive synthesis of aldehydes through a hydroimidoylation of aryl halides 5 was reported [104]. Although the reductive isocyanide insertion was only performed using tert-butyl isocyanide, the aryl halide input was varied extensively, affording aldehydes 227 in good to excellent yields, regardless of the steric or electronic influence of the arene substituents (Scheme 59). Triethylsilane 226 gives the best results, although other silanes also afford the target benzaldehydes. The use of silanes as reducing agents ensures the selective reduction of the intermediate
imidoypalladium species, but does not undergo reductive side reactions with the product aldimines. The se aldimines undergo spontaneous hydrolysis upon aqueous workup.

\[
\begin{align*}
5 \text{ Ar-X} & + \text{ Pd(OAc)}_2 (3 \text{ mol\%}) \\
& + \text{ JohnPhos (4.5 mol\%)} \\
& + \text{ Na}_2\text{CO}_3 (1 \text{ eq}) \\
\text{EtSiH} & + \text{ DMF, 65°C, 8 h} \\
3 \text{ CN-t-Bu} & \rightarrow \text{ 226, 49-97\%} \\
\end{align*}
\]

Scheme 59. Reductive Pd-catalyzed isocyanide insertion using triethylsilane.

A similar reductive isocyanide insertion generates benzaldehydes 227 from aryl iodides 5 (Scheme 60) [105]. In this case, sodium formate was found to be an effective reducing agent in polar solvents, allowing for the isolation of the product benzaldehydes in good yields, regardless of the aryl substitution pattern. Post-imidoylative hydrolysis of the aldimines occurred spontaneously upon extraction of the crude mixtures. The use of aryl bromides typically led to diminished yields, even under prolonged reaction times.

\[
\begin{align*}
5 \text{ Ar-X} & + \text{ Pd(OAc)}_2 (4.5 \text{ mol\%}) \\
& + \text{ dppe (9 mol\%)} \\
\text{CN-t-Bu} & + \text{ DMSO, 120°C, 3-30 h} \\
\text{HCO}_2\text{Na} & \rightarrow \text{ 227, 38-95\%} \\
3 & \text{ 30 examples}
\end{align*}
\]

Scheme 60. Reductive Pd-catalyzed isocyanide insertion using sodium formate.

A divergent palladium-catalyzed synthesis of substituted 2-(benzofuran-3-yl)quinoxalines 230 has been shown to be quite effective [106]. The redox-neutral cross-coupling is initiated by the oxidative insertion of Pd\(^0\) into the allyl phenyl ether, which initiates a 5-endo-dig cyclization, furnishing the corresponding benzofuran palladium species (Scheme 61). For reasons that remain uninvestigated, this specific imidoylation proceeds through a double isocyanide insertion. Curiously, the resulting diime complex 231 undergoes protodemetalation rather than hydroxylation. The authors did not investigate whether this process releases allyl alcohol or N-tert-butyl but-3-enamide as a byproduct. The formed glyoxal diimes 232 are subjected to sequential hydrolysis with aqueous HCl and biscondensation with phenylenediamines in a three-stage reaction. Additionally, the authors showed the versatility of this imidoylative synthesis by replacing the diamine condensation with several oxidative follow-up reactions.

\[
\begin{align*}
3 \text{ CN-t-Bu} & + \text{ Pd[PPh}_3]_4 (5 \text{ mol\%}) \\
\text{R}^1 & + \text{ K}_2\text{CO}_3 (1 \text{ equiv}) \\
\text{H}_2\text{O} & (1.2 \text{ equiv}) \\
\text{DMA, 80°C, 12 h} & \rightarrow \text{ 230, 60-90\%} \\
\text{HCl} & \text{examples}
\end{align*}
\]

Scheme 61. Imidoylative synthesis of 2-(benzofuran-3-yl)quinoxalines.
A novel imidoylative Liebeskind-Srogl-type reaction, with interesting mechanistic implications, was reported recently. [107] Oxidative insertion of Pd$^{0}$ into the thioether 233, and subsequent isocyanide insertion affords intermediate 236, which is reduced by triphenylsilane, producing the enmine 237 (Scheme 62). The authors postulate that this enmine is the final product of the reaction, and only oxidizes to the oxaziridine upon aerobic workup, which rearranges to the lactams 235. The role of the water in this process is not fully understood. The resulting 5-hydroxy-$\gamma$-lactams are isolated in good to excellent yields, although the use of isocyanoacetates 234 is critical in this transformation. The use of alkyl isocyanides led to uncyclized acrylamide analogs through a hydroxyimidoylation, whereas TosMIC is completely unreactive under the catalytic conditions.

![Scheme 62. Imidolyative synthesis of 5-hydroxylated $\gamma$-lactams.](image)

### 3. Pd$^{II}$-Catalyzed Isocyanide Insertions

#### 3.1. Introduction

The use of Pd$^{II}$ as an active catalyst in cross-couplings involving isocyanide insertions largely concerns oxidative imidoylations. This allows the use of non-preactivated substrates. An oxidant is required to close the catalytic cycle. Conceptually, these reactions can be considered much more environmentally-friendly, although in reality this may depend on the reoxidizing agent used. In general, for scale-up purposes, oxidants which are cheap, low in mass, only produce benign by-products that can be safely disposed are preferred, such as $\text{O}_2$, $\text{H}_2\text{O}_2$, $\text{NaOCl}$, $\text{AcOOH}$, and $\text{t-BuOOH}$ [108,109].

A generalized catalytic cycle is characterized by a nucleophilic displacement of an anionic ligand from the active Pd$^{II}$ catalyst, generating complex I (Scheme 63). Subsequent 1,1-migratory insertion of the isocyanide affords the imidoyl palladium species II, which is similar to the mechanism described in Scheme 1. In intermediate II can undergo a second nucleophilic displacement, upon which the intermediate III affords the reaction product upon reductive elimination. Finally, an oxidizing agent is needed to regenerate the active Pd$^{II}$ catalyst. It should be noted that nucleophile has to be interpreted in the most general meaning, i.e., C-H activation can also give access to a Pd-C covalent bond without altering the oxidation state, still allowing for the formation of intermediates I and III.
3.2. Pd\textsuperscript{II}-Catalyzed Intermolecular Oxidative Isocyanide Insertions

A direct synthesis of benzamides 240 from arenes 239, isocyanides 13 and water was recently reported by Akbari et al. (Scheme 64) [110]. This C-H functionalization takes place on the most electron-rich position, implying an electrophilic aromatic substitution with the active palladium(II) species for C-H activation, i.e., through intermediate 242 rather than 241, although the mechanism has not been fully elucidated. The authors believe that imidoylation of the afforded aryl palladium intermediate generates 243, which yields benzamides 240 upon reaction with water. (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} was used as the terminal oxidant. Peroxydisulfates are cheap oxidants produced on a large scale, mainly used to initiate polymerization and to etch metal [111]. This oxidative amidation exhibits a remarkable tolerance with regards to the isocyanide scope, as aliphatic, benzylic, aromatic, and α-acidic isocyanides all afford the benzamides 240 in good to excellent yields.

![Scheme 63. General catalytic cycle for cross coupling via oxidative isocyanide insertions.](image)

**Scheme 63.** General catalytic cycle for cross coupling via oxidative isocyanide insertions.

The group of Yu reported an efficient C(sp\textsuperscript{2})-H imidoylation using N-methoxybenzamides 245 as a substrate and a directing group for the rate-determining C-H activation [112]. The active catalyst 247 was later proposed [113] to deprotonate the hydroxybenzamide, forming palladium carboximidamide intermediate 248. The authors found the rearrangement is not a post-imidoylative Mazurkiewicz-type process, but rather occurs via an acyl-migration in this intermediate 248 (Scheme 65). This affords the palladium species 249, which then undergoes C-H activation to 250 and reductive elimination. This reaction tolerates many different substitutions on the benzamide, and also affords the corresponding fused iminophthalimides 246 when heterocyclic N-methoxyamides are employed. However, only t-BuNC was used as an isocyanide input. The reaction still affords...
iminothallimides 246 when the benzamide ring is substituted with other potential directing groups, known to facilitate C-H functionalization. The products 246 are susceptible to catalytic hydrogenation, affording isoindolin-1-ones, effectively using isocyanides as a formal CH₂-donor.

![Scheme 65](image)

Scheme 65. Oxidative C-H functionalization of N-methoxybenzamides with isocyanides providing iminothallimides.

An example of a selective formal double isocyanide insertion is shown in Scheme 66, using an unconventional triaryl bismuth reactant 252 as a transmetallating agent. The authors propose that selective formation of the bisimine product 253 proceeds via Pd species 254 [114]. The reaction is significantly more effective under air atmosphere, implying reoxidation of Pd⁰ is more efficient with molecular oxygen than with Bi(OAc)₃. Surprisingly, cross-coupling with arylbismuths 252 tolerates various isocyanides, inserting aliphatic, benzylic, and even aromatic isocyanides in an effective manner.

![Scheme 66](image)

Scheme 66. Double isocyanide insertion using triaryl bismuth reactants.

The oxidative Pd-catalyzed synthesis of iminomaleimides 257 from alkenes, tert-butyl isocyanide and one equivalent of water has been reported. Electronically and sterically diverse alkenes 256 are compatible with the devised methodology, although no internal alkenes were included [115]. The authors propose copper acetate acts solely as an oxidant, although the possible catalytic activity towards the proposed intermediate 258 was not investigated in more detail. As copper is added in a catalytic amount, air functions as the terminal oxidant. External attack of a second isocyanide is hypothesized to form the cationic intermediate 259. While this transformation was successful with
tertiary isocyanides, all other isocyanides failed to give the corresponding N-substituted analogs of 257 (Scheme 67).

![Image of Scheme 67](image)

**Scheme 67.** Iminomaleimides from two isocyanides, water, and terminal alkynes (X = OAc, Cl).

In the same year, it was reported that maleimides 260 can be synthesized via a similar oxidative double imidoylation of internal alkynes 163 affording the corresponding maleimides 260 in good yields (Scheme 68) [116]. Air acts as a terminal oxidant. In this particular reaction, various substituents on the alkyne are well tolerated, as even ethynamines or phenylpropiolates display high compatibility. Due to the hydrolytic cleavage of the imine, symmetrical maleimides 260 are always obtained, and no investigations were made into the regioselectivity of this coupling. Finally, the compatibility with tertiary, secondary, and primary isocyanides is high, but no further investigations into the isocyanide scope were performed. The same group later reported a similar transformation to phthalimides from o-bromobenzonitriles [117].

![Image of Scheme 68](image)

**Scheme 68.** Maleimides from two isocyanides, water, and alkynes.

Follow-up chemistry using this reaction involved the trapping of the transient yniminyl palladium species with carboxylates (Scheme 69) [118]. Curiously, the utilization of carboxylates as coupling reactants rather than water does not lead to a nucleophilic attack of a second isocyanide, as observed above (Scheme 68). In stead, reductive elimination affords the O-acylimidate intermediate 265, which can undergo a Mumm-type intramolecular acyl transfer to generate the product imides 263. This transformation is highly compatible with primary and aromatic alkynes, as well as with benzylic and aromatic isocyanides. Although this method is highly compatible with benzylic or aromatic isocyanides, this specific transformation did not afford any product when tertiary or secondary aliphatic isocyanides were used. Additionally, in this case, air acts as the terminal oxidant reoxidizing Pd⁰.
Another interesting Pd/Ag dual catalytic method was reported for the synthesis of enol esters [119]. The reaction is initiated by the insertion of the terminal alkyne 256 into the silver carboxylate, generating intermediate 269 (Scheme 70). Transmetalation to PdII, and subsequent hydroxyimidoylation affords the product 267 in moderate to good yields. The formed Pd0 is readily reoxidized by the presence of stoichiometric Ag2O. Silver, therefore, plays a dual role here. This reaction is highly compatible with aliphatic and aromatic alkynes; however, when α-acidic isocyanatoacetates are employed, no product is observed.

In 2013, Zhu et al. performed indole-3-carboximidamides synthesis from N-trifluoroacetyl-2-alkynylanilines 271 via a 5-endo-dig cyclization, and subsequent aminimidoylation [120]. O2 was used as the terminal oxidant. This oxidative cyclization is compatible with various aromatic substituents, regardless of the electronic nature (Scheme 71). Both secondary and primary amines 272 (R3 = H) are also readily converted to the corresponding amidine, but the use of aromatic amines leads to reduced yields of the corresponding products 273. Although secondary and primary isocyanides are tolerated, the yields decrease dramatically when these non-tertiary isocyanides are used (39–45%). It is likely that aqueous workup leads to rapid hydrolysis of the initial N-trifluoroacetylated indole product.

**Scheme 69.** Imide synthesis from alkynes, isocyanides, and sodium carboxylates.

**Scheme 70.** Oxidative Pd/Ag dual catalyzed synthesis of α-acetoxyacrylamides.
with isocyanide as a CN-donor typically utilize tert-butyl and cyclohexyl isocyanides, and proceeds rapidly, using air as the (re)oxidant. An equivalent of amine is formed by the known oxidation of isocyanide to isocyanate, and its subsequent hydrolysis, effectively using the isocyanide as a dual reactant.

Additionally, if the solvent contains trace amounts of water, hydroxyimidoylation is preferred over dealkylation, affording the corresponding isoquinoline-4-carboxamides.

**Scheme 71.** Oxidative Pd-catalyzed 5-endo-dig cyclization followed by aminomidoylation.

A different approach to the utilization of isocyanide as dual reactant is shown in Scheme 73. The cationic intermediate is generated via a 6-endo-dig cyclization of tert-butyl(2-alkynyl)benzaldimines, facilitating the anti-iminopalladation. Subsequent isocyanide insertion provides an imidoylpalladium species that dealkylates affording the 4-cyanoisoquinoline. Regeneration of the Pd$^\text{II}$ catalyst occurs via oxidation with silver triflate. Although cyanations with isocyanide affords the substituted N-acylguanidines (Scheme 72) [121]. This reaction was only tried with tert-butyl and cyclohexyl isocyanides, and proceeds rapidly, using air as the (re)oxidant. An equivalent of amine is formed by the known oxidation of isocyanide to isocyanate, and its subsequent hydrolysis, effectively using the isocyanide as a dual reactant.

**Scheme 72.** Oxidative Pd-catalyzed formation of N-acylguanidines using amides and isocyanides.

**Scheme 73.** 3-Cyanoisoquinoline synthesis via a 6-endo-dig cyclization/isocyanide insertion/double dealkylation cascade.
Similarly, the formation of 3-cyano-N-methylindoles 281 occurs through a one-pot 5-endo-dig palladation/imidoylation/dealkylation/demethylation cascade from 2-alkynyl-N,N-dimethylanilines 280 and isocyanides (Scheme 74) [124]. A similar intermediate imidoyl palladium species as shown above (Scheme 73) is involved. Lack of a suitable coupling partner initiates R3 dealkylation. Here, too, dealkylation occurs if tert-butyl- or cyclohexyl isocyanide is used. The authors do not comment on the active demethylating agent.

![Scheme 74](image)

**Scheme 74.** 3-Cyano-N-methylindole synthesis through an anti-palladation/isocyanide insertion/dealkylation cascade.

Finally, intermolecular oxidative imidoylative cross-couplings can also be initiated by the addition of a boronic acid to an active PdII catalytic center. This effectively generates an aryl palladium intermediate (similar to Scheme 1) that readily undergoes 1,1-migratory insertion of an isocyanide. Such an imidoylation can take place under Pd/Cu co-catalysis, as evidenced by the divergent synthesis of benzamides 283 or biaryl ketones 284 in Scheme 75 [125]. Equimolar amounts of arylboronic acid 282 and isocyanides 13 afford the benzamides 283 where the intermediate imidoyl palladium species is quenched with ambient water. The authors propose that Cu(OH)2 serves to reoxidize the palladium catalyst, but no actual experimental study towards the role of copper in this mechanism was conducted. The isocyanide scope for this amidation is broad, tolerating aliphatic, as well as benzylic isocyanides. Aromatic isocyanides are also compatible with this amidation, even generating phenyl benzamide in 50% isolated yield, starting from the notoriously hard to handle phenyl isocyanide. On the other hand, when this reaction is performed with five equivalents of boronic acid under mild acidic conditions, an imidoylative Suzuki-type homocoupling is observed, affording biarylketones 284 after in situ hydrolysis. Although the isocyanide is cleaved off, the authors showed that this homocoupling is compatible with several isocyanides, mirroring the efficiency shown for the synthesis of benzamides 283.

![Scheme 75](image)

**Scheme 75.** Pd/Cu co-catalyzed formation of benzamides or biaryl ketones.

Isocyanide insertion can be used in the acetoxyimidoylation of boronic acids 282, utilizing t-BuNC as a C3 donor and subsequent hydrolysis (Scheme 76) [126]. The carboxylic acids 285 were formed in good yields, regardless of the electronic nature of the boronic acid. The reaction is sensitive to water during the cross-coupling, but hydrolysis of the formed intermediate 286 occurs upon quenching.
The Cu(OAc)$_2$ additive acts both as a stoichiometric oxidant to reform the active Pd(II) species, and as an acetate donor in the formation of 286. No isocyanide variations were studied besides tert-butyl isocyanide.

Scheme 76. Synthesis of benzoic acids from arylboronic acids using isocyanides as a C$_1$ building block.

Pd-catalyzed imidoylative Buchwald-Hartwig reaction can also be combined with a cascade transition metal-catalyzed cyclization [127]. Transmetalation with arylboronic acids and 1,1-migratory insertion of the isocyanide affords the imidoyl palladium species 290, which is subsequently trapped by the nucleophilic 2-alkynylaniline 296 (Scheme 77). The formed intermediate amidine 291 undergoes a copper-mediated 5-endo-dig cyclization to afford the substituted N-imidoylindoles 289 in varying yields. Copper also acts as a reoxidant for Pd$^0$. The yields drop most noticeably when labile substituents are introduced on the boronic acid. The authors attempted a single deviation from tertiary isocyanides as a substrate, affording the corresponding product 289 in 53% when cyclohexyl isocyanide is used. Aromatic isocyanides are incompatible with this methodology.

Scheme 77. Pd-catalyzed Buchwald-Hartwig imidoylation followed by copper-mediated 5-endo-dig cyclization.

3.3. Pd$^{II}$-Catalyzed Intramolecular Oxidative Isocyanide Insertions

Our group reported one of the first aerobic Pd-catalyzed formation of benzoazinones 293 through the direct coupling of anthranilic acids 292 with isocyanides (Scheme 78) [128]. The reaction is
compatible with several secondary and primary isocyanides, although utilization of non-tertiary isocyanides leads to a moderate yield of 293, even at higher catalyst loadings (10 mol%).

Scheme 78. Oxidative isocyanide insertion into anthranilic acids.

Such bisnucleophilic substrates can also be generated in situ (Scheme 79). The condensation of isatoic anhydrides 295 with various aliphatic or aromatic amines 294 can be followed by addition of isocyanide and a palladium catalyst, without isolation of intermediate 297 or solvent switches, to afford 2-aminoquinazolinones 296 in a one-pot process [129]. For this palladium-catalyzed imidoylation, silver carbonate was found to be the optimal terminal oxidant. Unfortunately, while the reaction does appear to be fully compatible with tertiary and secondary isocyanides, the isocyanide scope was not extensively investigated.

Scheme 79. Oxidative isocyanide insertion into anthranilamides formed from isatoic anhydrides and amines.

An aerobic oxidative Pd-catalyzed imidoylative cross-coupling towards oxadiazoles 300 was performed by Fang et al. [130] Interestingly, the reaction was shown to be much more effective when N-acetylated benzhydrazides 298 were used, compared to N-H free hydrazides (299, R² = H), although no explanation was offered. The acetylated oxadiazoles hydrolyze towards oxadiazoles 300 upon aqueous workup. Additionally, the incorporation of a substituent to the terminal nitrogen of the hydrazide 299 does not hamper the formation of the corresponding oxadiazol-2(3H)-imines 301 (Scheme 80), which have been reported as angiotensin II antagonists, and are typically difficult to prepare via other procedures [131]. Although the reaction is compatible with tertiary and secondary isocyanides, phenyl isocyanide undergoes rapid polymerization under the reaction conditions.
conditions proved incompatible with any aromatic isocyanides. When primary or secondary aliphatic isocyanides are used, the 2-aminoquinolines can also be subjected to oxidative isocyanide insertion, generating the 2-aminoquinoline scaffold (Scheme 81) [132]. The reaction is initiated by the coordination of the aniline to the active Pd\textsuperscript{II} complex. The aminoquinolines 305 are obtained in lower yields if electron-withdrawing aromatic substituents (R\textsuperscript{1}) are present. Limited studies have been performed towards the tolerance for isocyanides. When primary or secondary aliphatic isocyanides are used, the 2-aminoquinolines 305 are obtained in moderate yields (48–61%). Again, the reaction conditions proved incompatible with any aromatic isocyanides.

Scheme 81. Oxidative isocyanide insertion into 2-aminostyrenes.

Treatment of electron-rich 2-indazol-2-yl phenols and -anilines were treated with isocyanides under aerobic oxidative conditions, in the presence of a palladium catalyst furnished the corresponding tetracyclic fused indazole scaffolds 307 (Scheme 82) [133]. While the synthesis of indazolo[2,3-a]quinoxalines 307 is relatively harsh, the use of 2-indazolylphenol (306, Y = O) affords the corresponding cycloimidate product 308 in up to 98% yield, and does not require the addition of either copper or Cs\textsubscript{2}CO\textsubscript{3}. In all cases, only tert-butyl and cyclohexyl isocyanide were successfully converted to the tetracyclic scaffolds 307 and 308.

Scheme 80. Oxidative isocyanide insertion into (N-acetylated) benzhydrazides.
In 2013, our group reported the first palladium-catalyzed imidoylative double C-H functionalization of \( N_1 \text{-diarylethan-1-imines} \) \( 309 \), affording the useful 4-aminoquinoline scaffold [134]. Although the yields of 4-aminoquinolines \( 310 \) are low, we were able to specifically direct imidoylative cross-coupling to two carbon nucleophiles, using molecular oxygen as a sustainable stoichiometric oxidant (Scheme 83). The yield of aminoquinazolines \( 310 \) decreases to only 13% if isopropyl isocyanide is employed (1 example).

Interestingly, a substrate-dependent chemoselective transformation with \( N \text{-arylenaminones} \) \( 311 \) was communicated by Luo et al. (Scheme 84) [135]. Tertiary aliphatic isocyanides afford the carboxamides \( 313 \) via hydroxyimidoylation, which was later corroborated by Luo et al. [136] However, the use of aromatic isocyanides lead to the tacrine derivatives \( 312 \) (Scheme 84). The se oxidative processes proceed via the C-H functionalization of enaminone \( 311 \) and subsequent isocyanide insertion, affording the common intermediate imidoyl palladium species \( 314 \). Bulky aliphatic isocyanide substituents induce a rapid ligand exchange between chloride and water in intermediate \( 314 \), affording \( 316 \). The 1,3-palladium migration was only observed in palladacycles \( 314 \) generated with aromatic isocyanides. The palladium N to C migration forms intermediate \( 315 \), which affords tacrines \( 315 \) in up to 60% yield (Scheme 84).
The authors propose a mechanism in which the palladium hydride expelled in the de-aliphatic isocyanides. Deuteration studies indicate the aminopyrrole NH proton originates from the isocyanide is equally well tolerated, the reaction is incompatible with the use of primary or secondary intermediate that acts as a hydride donor (rather than undergoing reductive elimination), thus reducing the cationic intermediate source through de-

C3 building block in the initial formal [4 + 1] cycloaddition to form intermediate C1, thereby affording aminopyrroles, obtained via isocyanide insertion into the C-Pd bond of 319.

The synthesis of polysubstituted aminopyrroles proceeds via a palladium(II) catalyzed cycloimidoylation of ynimines 317 (Scheme 85) [137]. The isocyanide has a dual purpose, acting as a C1 building block in the initial formal [4 + 1] cycloaddition to form intermediate 319, and as a cyanation source through de-tert-butylation of 320, obtained via isocyanide insertion into the C-Pd bond of 319. The authors propose a mechanism in which the palladium hydride expelled in the de-tert-butylation of 320 acts as a hydride donor (rather than undergoing reductive elimination), thus reducing the cationic intermediate 321, thereby affording aminopyrroles 318 and regenerating Pd(OAc)2. While tert-octyl isocyanide is equally well tolerated, the reaction is incompatible with the use of primary or secondary aliphatic isocyanides. Deuteration studies indicate the aminopyrrole NH proton originates from the tert-butyl fragment, explaining the reason behind this incompatibility.

Imidoylations can also occur through metal-induced cyclization and exo-palladation of unsaturated substrates, generating a heteroaryl palladium intermediate. The se intermediates can undergo various imidoylative cross-coupling, similar to examples mentioned above. These reactions are catalyzed by PdII, and proceed in a redox-neutral manner, as such, these methods do not require an external oxidant to close the catalytic cycle.

3.4. Miscellaneous PdII-Catalyzed Isocyanide Insertions

The synthesis of polysubstituted aminopyrroles proceeds via a palladium(II) catalyzed cycloimidoylation of ynimines 317 (Scheme 85) [137]. The isocyanide has a dual purpose, acting as a C1 building block in the initial formal [4 + 1] cycloaddition to form intermediate 319, and as a cyanation source through de-tert-butylation of 320, obtained via isocyanide insertion into the C-Pd bond of 319. The authors propose a mechanism in which the palladium hydride expelled in the de-tert-butylation of 320 acts as a hydride donor (rather than undergoing reductive elimination), thus reducing the cationic intermediate 321, thereby affording aminopyrroles 318 and regenerating Pd(OAc)2. While tert-octyl isocyanide is equally well tolerated, the reaction is incompatible with the use of primary or secondary aliphatic isocyanides. Deuteration studies indicate the aminopyrrole NH proton originates from the tert-butyl fragment, explaining the reason behind this incompatibility.

Scheme 84. Substrate-dependent oxidative isocyanide insertion into N-arylenaminones.

Scheme 85. Synthesis of cyanated aminopyrroles from substituted ynimines and isocyanides. (X = OAc).
Another report communicated a similar synthesis of 2-aminoquinoline from N-trifluoroacetylated ortho-alkynylanilines 322 and isocyanides [138]. In this study, the authors postulated that amination of the Pd(II) catalyst is followed by isocyanide insertion, generating intermediate imidoyl palladium species 324, which is η²-bonded with the alkyne (Scheme 86). This intermediate subsequently undergoes an anti-carbopalladation presumably involving a second Pd(II) complex. The formed bicyclic carbopalladate 325 affords the 2-aminoquinolines 323 upon protodemetalation and intramolecular acyl migration (endo- to exocyclic nitrogen). This imidoylative annulation works well with tertiary isocyanides. A single secondary isocyanide was also attempted, affording the corresponding aminoquinoline in somewhat reduced yield of 40%. The same group later used this methodology to access tricyclic systems through further functionalization of the intermediate 325 [139].

Scheme 86. Synthesis of 2-aminoquinolines from ortho-alkynylanilines and isocyanides. (X = OAc).

5-Exo-dig cyclization of 2-(1-hydroxyprop-2-yn-1-yl)phenols 326 and subsequent imidoylation affording intermediate imidoyl palladium complex 328 is proposed to lead to benzoxazoles 327 (Scheme 87). Transformation of 328 into 327 is proposed to occur via cycloalkoxylation in 328 and subsequent Pd-mediated reductive ring-opening. However, full elucidation of the reaction mechanism was not performed, and therefore, alternate mechanisms cannot be completely excluded. This transformation is equally successful with tertiary and secondary isocyanides, although the scope was not further investigated. Similarly, trifluoroacetylated aniline analogs 329 react towards indoles 330 under nearly identical conditions (Scheme 88). In this case, the trifluoroacetamide undergoes post-hydrolysis by atmospheric moisture, releasing N-unsubstituted indole derivatives 330. This indole formation was only attempted with tertiary isocyanides [140].

Scheme 87. Synthesis of benzofurans via Pd-catalyzed 5-exo-dig cyclization and isocyanide insertion.
4. Conclusions

Palladium-catalyzed cross-coupling reactions involving isocyanide insertions have matured significantly over the past decade. With an increasing number of intermolecular examples, it is clear that the scope of the coupling partners has also increased significantly, as new types of imidylation catalyzed by palladium are still being reported. The main bottleneck in utilizing palladium for isocyanide insertions still appears to have unpredictable compatibility in various functionalized isocyanide reactants. Although here, too, some impressive advancements have been made in this aspect, replacing tertiary isocyanides with other isocyanides is still challenging. Additionally, imidylylative cross-couplings are increasingly compatible with other occurring cascade processes, opening new avenues for the ever-improving generation of molecular complexity in a single reaction vessel. With the progress in this field made, there have been more and more cases of imidylylative MCRs where the cross-coupling partners no longer need to be linked to achieve high selectivity and efficiency. Continued improvements on all these facets of palladium-catalyzed isocyanide insertions are necessary to increase the synthetic applications of these transformations, and to utilize imidylylative pathways in medicinally relevant synthetic procedures. It is our hope that the coming decade will see further improvements in the field of palladium-catalyzed imidylation, leading to even more robust reactions, i.e., allowing milder reaction conditions and a broader isocyanide scope, leading to a wider coverage of chemical space.

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