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## Akzeptierter Artikel

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# Base Metal-Catalyzed Isocyanide Insertions

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**Abstract:** Isocyanides are diverse C1 building blocks given their potential to react with nucleophiles, electrophiles and radicals. Therefore, perhaps not surprisingly, isocyanides are highly valuable as inputs for multicomponent reactions (MCRs) and other one-pot cascade processes. In the field of organometallic chemistry, isocyanides typically serve as ligands for transition metals. The coordination of isocyanides to metal centers alters the electronic distribution of the isocyano moiety and reaction pathways can therefore be accessed which are not possible in the absence of the metal. The tuneable reactivity of the isocyanide functional group by transition metals has evolved into numerous useful applications. Especially palladium-catalyzed isocyanide insertion processes have emerged as powerful reactions in the past decade. However, hitherto, reports on the use of earth abundant and cheap base-metals in these type of transformations are scattered and received far less attention. In this Minireview we focus on these emerging base metal-catalyzed reactions and highlight their potential in synthetic organic chemistry. Although mechanistic studies are still scarce, we discuss distinct proposed catalytic cycles and categorize the literature according to (i) the (hetero)atom bound to and (ii) the type of bonding with the transition metal in which the (formal) insertion occurs.

## 1. Introduction

### 1.1. From Noble to Base Metals

Transition metal catalysis is an established and highly efficient method for the formation of C-C bonds. Although palladium (Pd) is still the most widely employed transition metal (TM), row IV base metals are rapidly emerging as equally (or more) efficient alternatives.<sup>[1]</sup> Although catalyst loadings are often still high, the large earth-abundance and low cost of base metals compared to Pd make them highly attractive from an economic standpoint (Table 1.) Ligand design will play a major role in further development of these catalysts.<sup>[2]</sup>

Isocyanides (RNCs) are versatile building blocks for the synthesis of small molecules, and have found widespread use in medicinal<sup>[3]</sup> and combinatorial chemistry.<sup>[4]</sup> Most prominently, RNCs are highly valuable for multicomponent reactions (MCRs) and one-pot cascade processes in the context of diversity oriented synthesis.<sup>[5]</sup> More recently, RNCs have also been utilized in transition metal-catalyzed cross-couplings, exploiting their isoelectronic nature to carbon monoxide. (Figure 1).<sup>[6]</sup> The interest in transition metal-catalyzed reactions involving isocyanides has increased significantly over the past decade (Figure 2).<sup>[7]</sup> Due to its predictable nature and well-defined catalytic reactivity, Pd in particular has been extensively investigated in these imido-ylative couplings.<sup>[8]</sup>

Table 1. Earth abundance and bulk cost of row IV transition metals and Pd

Group	Metal	Earth's Crust Content (ppm) <sup>[9]</sup>	Price (EUR/mol) <sup>[10]</sup>
IV	Ti	5600	0.21 <sup>a</sup>
V	V	160	4.22 <sup>a</sup>
VI	Cr	100	0.49 <sup>a</sup>
VII	Mn	950	0.12
VIII	Fe	41000	0.004
IX	Co	10	3.17
X	Ni	70	0.62
X	Pd	0.01	4693.12
XI	Cu	100	0.35
XII	Zn	75	0.14

<sup>a</sup> Mined and sold as the bulk ferrous metal

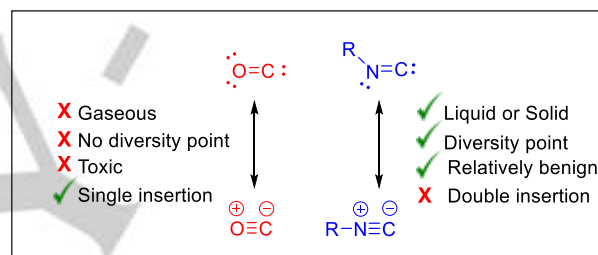


Figure 1. Isoelectronic nature of RNC and CO.

Jurriën Collet obtained his BSc from Leiden University of Applied Sciences in 2012, and his MSc from the Vrije Universiteit Amsterdam. Since 2015, he has been a joint PhD researcher at the Vrije Universiteit Amsterdam under Prof. Romano Orru, and at the University of Antwerp, under Prof. Bert Maes. His current research interests include transition metal catalysis, and multicomponent and cascade chemistry.



Thomas R. Roose studied chemistry at the University of Amsterdam and the Vrije Universiteit Amsterdam (joint degree program). He obtained his BSc in 2016, and his MSc (*cum laude*) in 2018. The same year, he started his PhD under Prof. Romano Orru, in the field of metal-catalyzed isocyanide insertions. His current research interests include transition metal catalysis involving isocyanides, and cascade chemistry.



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# These authors contributed equally

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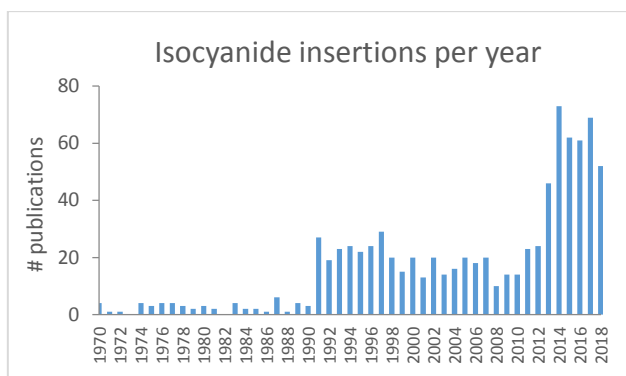


Figure 2. Number of publications reporting on isocyanide insertions since 1970.

Despite the ubiquity of Pd in these imidoxylation cross-couplings, recent studies increasingly employ base metal (complexes) as alternative catalysts. Apart from the economic benefits, base metals are more likely to undergo single electron processes, whereas Pd participates in two-electron processes.

This shift poses new challenges and introduces novel catalytic mechanisms of action that offer exciting opportunities for further reaction development.<sup>[11]</sup> With this review we would like to focus the attention of the synthetic organic chemist to promising base metal-catalyzed processes involving isocyanide insertion and highlight proposed mechanistic aspects of these interesting reactions.

## 1.2. Isocyanide Insertion pathways

The term 'isocyanide insertion' is commonly used by organic chemists to describe TM-mediated or -catalyzed transformations, in which the isocyanide moiety is inserted into a  $\sigma$ - or  $\pi$ -bond. This only refers to the overall result of the reaction and does not suggest a mechanism. Upon studying the reported mechanistic proposals of the base metal-catalyzed imidoxylation reactions, different insertion pathways affording the reactive imidoxylation intermediate can be distinguished (Scheme 1). Firstly, 1,1-migratory insertion of the isocyanide into a metal-carbon bond (**1**) *in situ* formed via oxidative addition to  $TM^n$ , furnishes the imidoxylation metal species **2** (Type I, Scheme 1 a1). Very similar, 1,1-migratory insertions of isocyanides into *in situ* formed metal-hetero or carbon atom bonds, via transmetalation or coordination/deprotonation on  $TM^{n+2}$ , have also been reported (Type I, Scheme 1 a2, Y = C, N, O, S, etc.). These insertion mechanisms have been studied extensively in imidoxylation transformations<sup>[12]</sup>, and are observed for most of the row IV base metals (Sc<sup>[13]</sup>, Ti<sup>[14]</sup>, V<sup>[15]</sup>, Mn<sup>[16]</sup>, Fe<sup>[17]</sup>, Co<sup>[18]</sup>, Ni<sup>[19]</sup> and Cu<sup>[20]</sup>). The isocyanide metal interaction is a coordinate covalent bond. The resulting imidoxylation metal species **2** can react with a variety of coupling partners, including nucleophiles (oxidatively), electrophiles (redox-neutral), and radical acceptors in order to arrive at the overall insertion reaction product **3**. In addition, the increased electrophilicity of coordinated isocyanides, especially when coordinated to higher-valent  $TM^n$  centers (**4**), allows for direct attack of a nucleophile on the isocyanide carbon, resulting in imidoxylation metal species **2'** (Type II, Scheme 1b).<sup>[6a]</sup> This is similar to intermediate **2** in Type I insertion processes making Type I and II imidoxylation pathways often indistinguishable. To date, theoretical and experimental investigations to clarify the exact mechanisms of imidoxylation couplings are still limited.<sup>[21]</sup>

Eelco Ruijter obtained his PhD from the Vrije Universiteit Amsterdam and the Leibniz Institute of Plant Biochemistry (Halle/Saale, D) in 2005. After a postdoctoral stay at Utrecht University (2004-2006) with Profs. Liskamp and Heck, he was appointed assistant professor at the Vrije Universiteit Amsterdam and received tenure in 2012. In 2018, he was promoted to associate professor. His research interests include the development of synthetic methods based on cascade reactions and homogeneous catalysis for the efficient and sustainable production of high value-added molecules.



Bert Maes obtained his PhD in organic chemistry at UAntwerp and subsequently received a Post-Doctoral Fellowship of the National Science Foundation (FWO-Flanders) in Belgium. He worked at the École Normale Supérieure in Paris (mechanisms in catalysis) with Prof. Anny Jutand (CNRS). Bert Maes was appointed Assistant Professor (Docent) in the Department of Chemistry at UAntwerp in 2003 and currently holds a Senior Full Professorship (Gewoon Hoogleraar) of Organic Chemistry at UAntwerp, since 2009 he is a Research Professor. In 2015-2016 he acted as chairman of the Department of Chemistry. His research interests cover the fields of heterocyclic chemistry, organometallic chemistry and homogeneous catalysis with a special focus on the development of sustainable synthetic methodology. The research in his group involves base metal catalysis, aerobic oxidation, strong bond activation, renewables, green metrics analysis. His research group partakes in one of the nine Excellence Centers of UAntwerp. He is an editor of Topics in Heterocyclic Chemistry and an editorial board member of SynOpen.

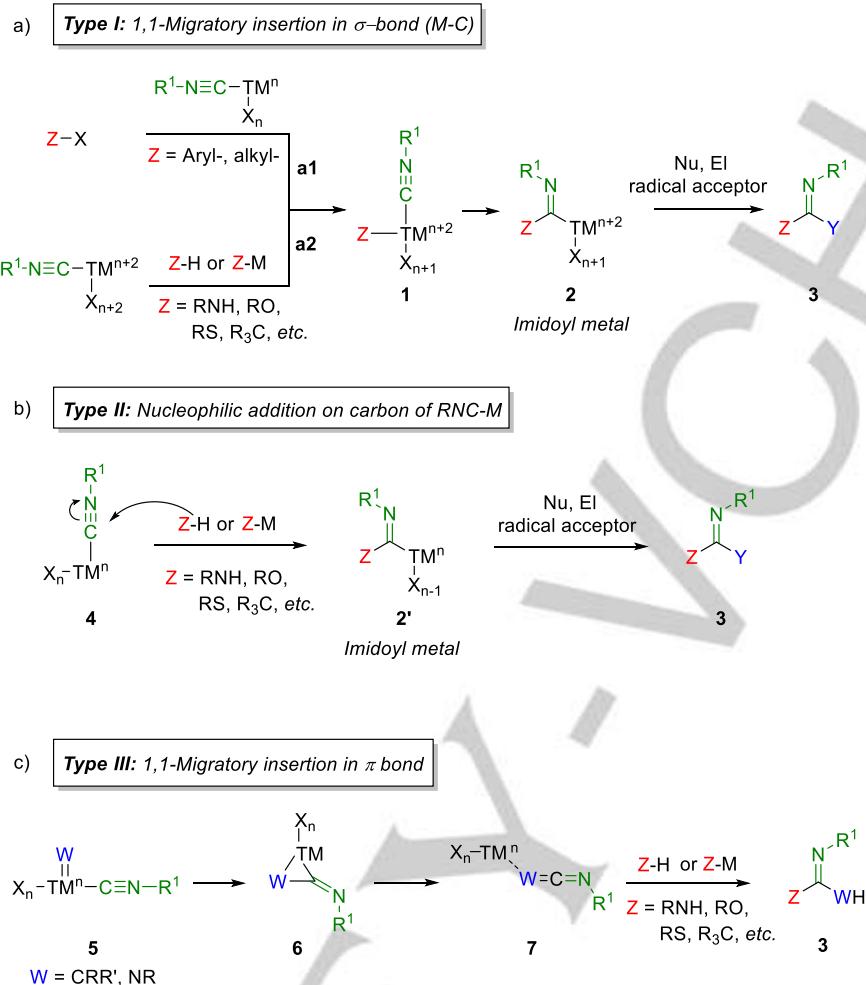


Romano Orru completed his PhD in organic chemistry at the Agricultural University of Wageningen, The Netherlands. From 1996 to 2000 he worked at the Technical as well as at the Karl-Franzens University of Graz, Austria on synthetic applications of bio-transformations. In 2000, he returned to the Netherlands, and was appointed Assistant Professor and later Associate Professor (2003) of Synthetic & Bioorganic Chemistry at Vrije Universiteit Amsterdam.

Since 2007, he holds the chair of Synthetic & Bioorganic Chemistry. His research focuses on the utilisation of one-pot cascade reactions and multi-component reactions to improve the efficiency, sustainability and precision of organic compound synthesis, with emphasis on applications in the field of pharmaceutical science. For that, he develops novel MCRs and employs them in combination with biocatalysts in one-pot processes to access targeted molecules in a stereoselective fashion. In another research line he develops isocyanides as versatile  $C_1$  building blocks in (transition) metal-catalyzed insertion reactions towards privileged heterocyclic scaffolds. He is considered a leader in his field and has contributed much to this emerging area.



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Scheme 1. Isocyanide insertion pathways (Nu = nucleophile, EI = electrophile).

Next to Type I and II pathways, various other base metal-catalyzed and mediated transformations involving carbene- or nitrene transfer have been referred to as isocyanide insertion reactions. From a mechanistic point of view, isocyanide migratory insertion occurs into the metal-carbon or metal-heteroatom  $\pi$ -bond rather than the  $\sigma$ -bond, yielding metallacycle **6** and subsequently *N*-metalated ketenimine/carbodiimide **7**. Upon reaction with a nucleophile product **3** is obtained. Therefore, these reactions can mechanistically be regarded as 'formal insertions' starting from the corresponding metal-nitrene or -carbene species **5** and they will be discussed in a different category (Type III, Scheme 1c). The use of isocyanides as radical acceptors in cyclization reactions will not be discussed here as these reactions were extensively reviewed by Studer in 2015.<sup>[22]</sup> These transformations are often not catalytic, applying the metal as a stoichiometric oxidant. Alternatively, a catalytic base metal can be used in combination with a stoichiometric organic oxidant. In both cases, there is mechanistically no insertion with a metal bound isocyanide involved, but again rather a formal insertion based on a radical relay cascade.

This Minireview aims to highlight the versatile insertion chemistry of isocyanides with first-row transition metals. The quite diverse examples of base metal-catalyzed imidoylations appearing in recent literature were categorized according to the TM species involved in the (formal) insertion proposals. The synthetic utility of these processes largely depends on the variety of isocyanides which can be used. Therefore, we point specific attention in the discussion to the scope regarding the isocyanides utilized, highlighting current applications in organic synthesis. When applications in multicomponent reactions are discussed, the different components have been color-coded so that the origin of the different atoms in the final products is easily recognized

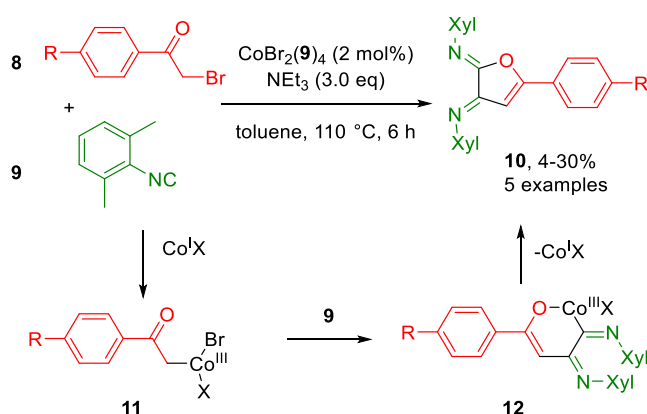
## 2. Insertions of Isocyanides into Carbon-Metal Species

### 2.1. Imidoylations initiated by oxidative addition of carbon halides

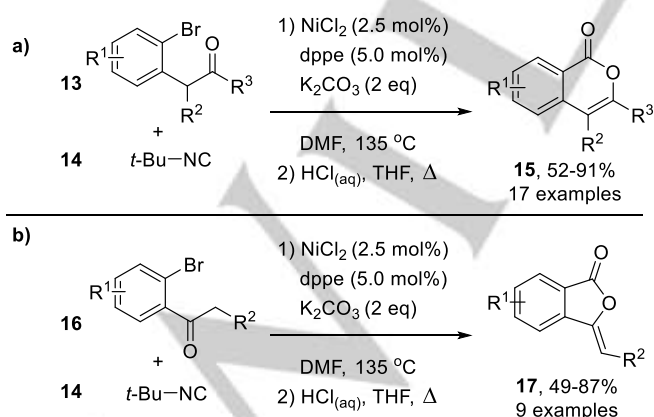


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One of the most facile and widespread ways of constructing C-TM bonds is the oxidative addition of aryl(pseudo)halides to low-valent transition metals. Subsequent imidoylation typically occurs via a 1,1-migratory insertion reaction of Type I into the preformed TM-C bond. An early example involving imidoylative cobalt catalysis was reported by Yamamoto *et al.* in 1991 (Scheme 2). Diiminofurans **10** were obtained in moderate yields, although no optimization was reported. Mechanistic investigations imply that the active catalyst is a Co(I) species. Initial oxidative addition of  $\alpha$ -bromoacetophenone (**8**) is followed by double isocyanide insertion. Then, intramolecular alkoxylation via the corresponding enolate and subsequent reductive elimination of intermediate **12** affords the diiminofurans **10**.<sup>[23]</sup>

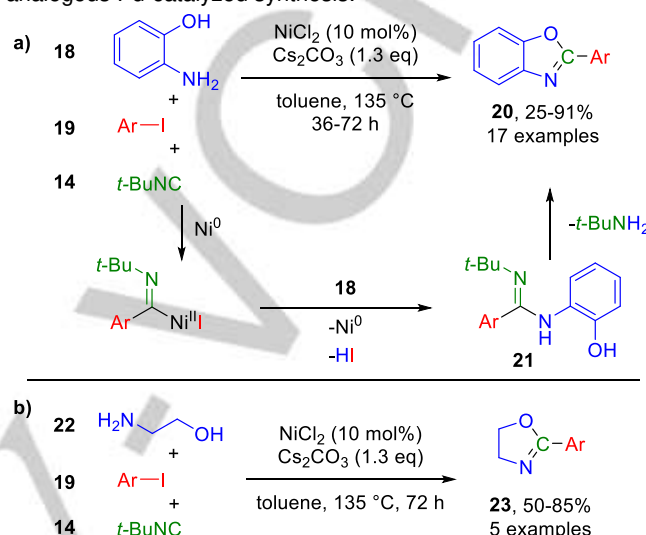
Scheme 2. Co(I)-catalyzed synthesis of diiminofurans **10**.

The group of Zhu reported a nickel-catalyzed synthesis of isocoumarins **15** and 3-alkylidenephthalides **17** (Scheme 3). The reaction starts with oxidative insertion of Ni(0) into a C(sp<sup>2</sup>)-halide, followed by 1,1-migratory insertion of Type I. The resulting imido nickel species undergoes intramolecular nucleophilic attack by an enolate similar to the reaction described in Scheme 2. Acidic hydrolysis of the iminolactone affords the products **15** or **17** in good to excellent yields.<sup>[24]</sup> The isocyanide was used as a CO surrogate and only *tert*-butyl isocyanide (**14**) was employed in these reactions.



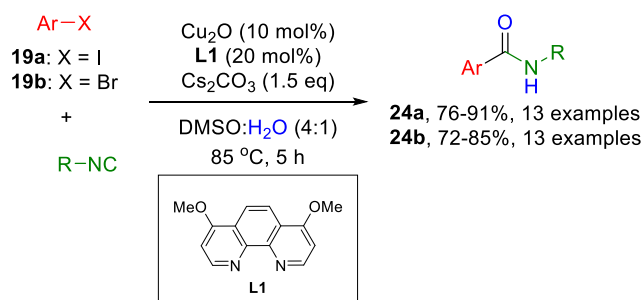
Scheme 3. Ni(0)-catalyzed alkoxyimidoylation.

Wang *et al.* reported the synthesis of 2-substituted benzoxazoles (**20**) via a Ni-catalyzed reaction (Scheme 4a).<sup>[25]</sup> The 3-CR proceeds via an imidoylative Buchwald-Hartwig-type reaction forming amidine **21**, which subsequently undergoes intramolecular condensation. Only *t*-BuNC (**14**) was used as a C<sub>1</sub>-donor. In addition, saturated 2-aminoalcohols **22** afford the corresponding oxazolines (**23**) in good yields (Scheme 4b). The authors do not comment on the proposed formation of the active Ni(0) catalyst from NiCl<sub>2</sub>. The efficiency is competitive to the analogous Pd-catalyzed synthesis.<sup>[26]</sup>



Scheme 4. Ni(0)-catalyzed aminoimidoylation/condensation cascade.

Recently, a copper-catalyzed hydroxyimidoylation of aryl halides was reported as a 'CO-free' aminocarbonylation.<sup>[27]</sup> The mechanism presumably involves the oxidative addition of the aryl halide to the Cu(I) center. The use of aryl iodides or bromides (**19a-b**) affords benzamides **24a-b** in excellent yields (Scheme 5). However, with aryl chlorides the yields were reduced significantly. Both secondary and tertiary aliphatic isocyanides were well tolerated in this reaction, but primary aliphatic isocyanides were not investigated.

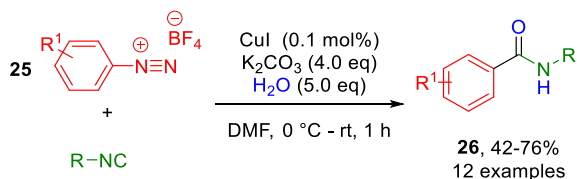


Scheme 5. Cu(I)-catalyzed hydroxyimidoylation of aryl halides.

A similar transformation was accomplished by using aryldiazonium salts **25** (Scheme 6). Again, secondary and tertiary aliphatic isocyanides were well tolerated.<sup>[28]</sup> The yields of the benzamides **26** were substantially lower than reported for the analogous process described in Scheme 5. However, the reaction

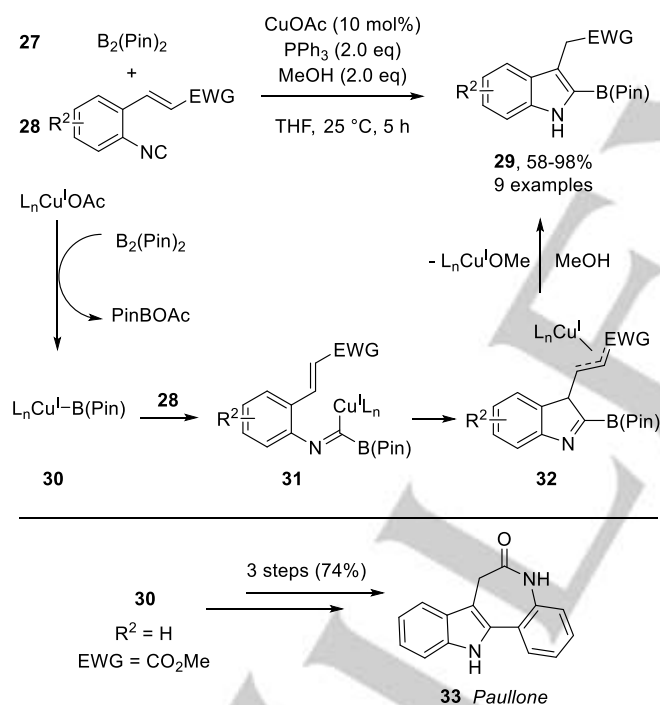
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does proceed at significantly lower temperatures, requiring a much lower catalyst loading.



Scheme 6. Cu(I)-catalyzed hydroxyimidylation of aryl diazonium salts.

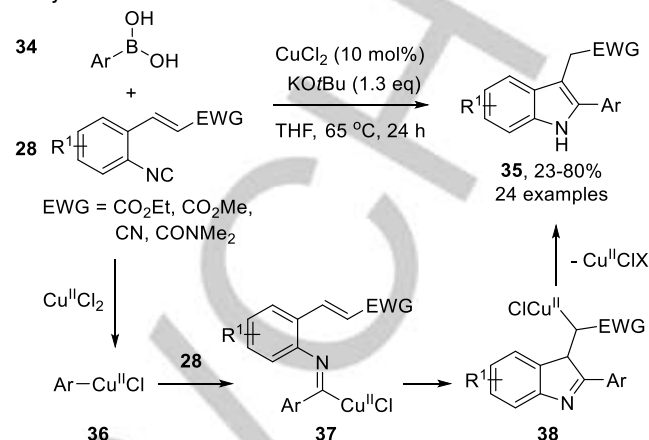
Another interesting Type I process furnishes 2-borylated indoles **29** from *o*-isocyanostyrenes **28** under Cu(I) catalysis.<sup>[29]</sup> Utilizing boronic esters, rather than aryl halides, the *in situ* formed borylcopper species **30** undergoes 1,1-migratory insertion of isocyanide **28** to afford imido copper species **31** (Scheme 7). Hereafter, alkene insertion and methanol-mediated protolysis afford the 2-borylated indoles **29** in good yields. The copper-catalyzed reaction is compatible with diversely functionalized *o*-isocyanostyrenes **28**, although electron-poor substrates give lower yields. The synthetic utility of product **29** was demonstrated by several post-cyclization modifications, including a highly efficient total synthesis of the kinase inhibitor paullone **33**.



Scheme 7. 2-Borylindole synthesis via Cu(I)-catalyzed coupling and application to the synthesis of Paullone (**33**) ( $R^2 = \text{H}$ ; EWG =  $\text{CO}_2\text{Me}$ ).

In a related process, the transmetalation of arylboronic acids **34** to Cu(II) salts furnishes aryl copper species **36**. Subsequent 1,1-migratory insertion of isocyanide **28** into the copper-carbon bond furnishes the imido copper species **37** (Scheme 8). This is followed by a cyclization and protodemetalation of intermediate **38** to afford the 2-arylated indoles **35**.<sup>[30]</sup> The proton source is unclear here and the authors do not comment on it. The reaction

tolerates electron-donating and electron-withdrawing substituents on both the boronic acid (**34**) and the isocyanide (**28**). However, 2-isocyanostyrenes without an electron-withdrawing group at the conjugated double bond position did not afford the corresponding 2-arylindoles **35**.



Scheme 8. Cu(II)-catalyzed borylation.

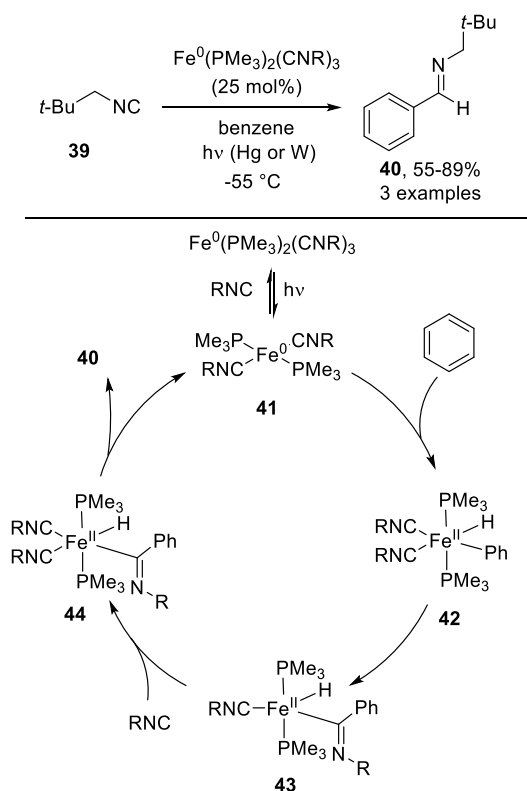
## 2.2. Imidoylations initiated by C-H bond cleavage

Direct C-H functionalization by transition metals is more attractive than using preactivated organo(pseudo)halides in cross-coupling chemistry and can be considered as a potentially more sustainable process.<sup>[31]</sup> Besides oxidative addition, other mechanisms for C-H bond cleavage forming a TM-C bond are possible (e.g. concerted metalation deprotonation (CMD),  $\sigma$ -bond metathesis). Subsequent isocyanide insertion into a TM-C bond then typically occurs via a Type I 1,1-migratory insertion (Scheme 1). Although TM-catalyzed C-H bond functionalization combined with CO or isocyanide insertion is still dominated by Pd,<sup>[32]</sup> recently, significant advances have been made in analogous base metal-catalyzed processes.

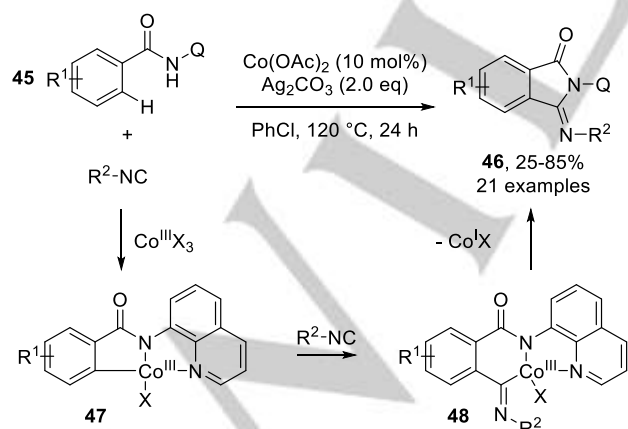
Already in 1987, Jones and coworkers reported the C( $sp^2$ )-H activation of benzene via oxidative addition using an electron-rich iron catalyst. Combination of the Fe(0) catalytic system shown in Scheme 9 with neopentyl isocyanide **39** and benzene affords the corresponding aldimine **40**.<sup>[33]</sup> This reaction also proved successful using toluene or xylene instead of benzene. Curiously, this iron catalyst is inactivated if irradiation is halted. The authors propose a light-induced dissociation of isocyanide to the catalytically active  $\text{Fe}^0(\text{RNC})_2(\text{PMe}_3)_2$  complex **41**. Increasing the isocyanide concentration leads to formation of  $\text{Fe}(\text{RNC})_3(\text{PMe}_3)$  via ligand exchange, inhibiting imidoylation.



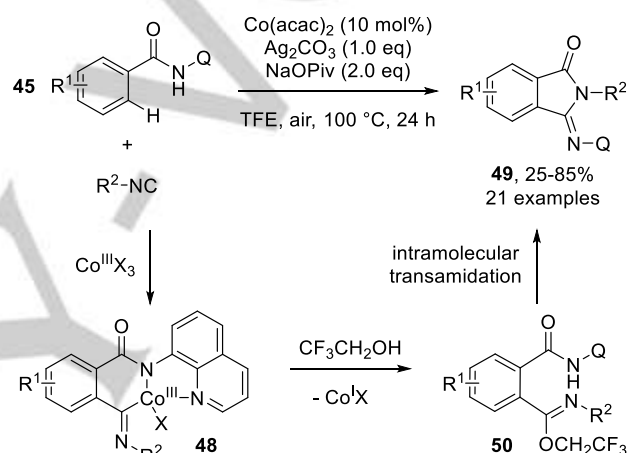
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Scheme 9. Aldimine synthesis by  $\text{Fe}(0)$ -catalyzed imidoxylation of arenes.

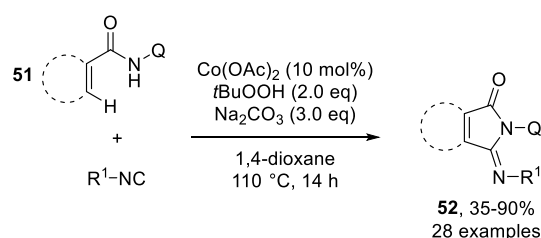
The first cobalt-catalyzed imidoxylation process involving C-H activation was reported in 2017. In this process, iminoindolinones **46** were obtained from benzamides **45** employing  $\text{Ag}_2\text{CO}_3$  as the optimal stoichiometric oxidant (Scheme 10).<sup>[34]</sup> The oxidant brings the cobalt salt to the required oxidation state. The bidentate 8-aminoquinoline functionality is essential and serves as a directing group presumably initiating the formation cobaltacycle **47**. Though not mentioned, C-H cleavage presumably occurs via a CMD mechanism. Only  $t\text{-BuNC}$  and 2,6-xylyl isocyanide were used successfully in this transformation.

Scheme 10.  $\text{Co}(\text{III})$ -catalyzed amidoimidoxylation of benzamides. ( $\text{Q}$  = 8-quinolinyl).

The use of weakly acidic trifluoroethanol (TFE) as a solvent yields other products from benzamides **45** (Scheme 11).<sup>[35]</sup> Interestingly, under these conditions another iminoindolinone isomer **49** was predominantly obtained. The key step in this reaction is most likely the oxidative alkoxyimidoxylation of **45** to eventually form imide **50**. This involves an initial directing group assisted C-H activation via CMD and a 1,1-migratory insertion of the pre-coordinated isocyanide to afford intermediate **48**. From this intermediate the authors propose that a reductive addition of TFE to the imido- $\text{Co}(\text{III})$  moiety followed by protodemetalation, results in intermediate **50** (Scheme 11). The resulting  $\text{Co}(\text{I})$  species are subsequently oxidized by  $\text{Ag}(\text{I})$  to the active  $\text{Co}(\text{III})$  species. Subsequent intramolecular transamidation of intermediate **50**, furnishing product **49** (Scheme 11). Mechanistic studies measuring a kinetic isotope effect, adding a radical scavenger and experiments with isolated  $\text{Co}$  complexes support the catalytic cycle put forward. C-H activation is not rate limiting.

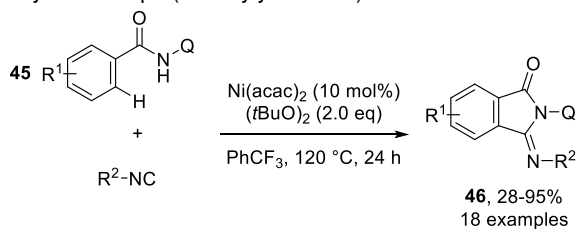
Scheme 11.  $\text{Co}(\text{III})$ -catalyzed amidoimidoxylation of benzamides ( $\text{Q}$  = 8-quinolinyl).

Gu and coworkers reported a similar transformation, employing  $t\text{-BuOOH}$  as an alternative oxidant (Scheme 12).<sup>[36]</sup> Their conditions tolerate functionalized acrylamides **51** next to benzamides (**45**), although also only in combination with tertiary aliphatic and xyllyl isocyanides. The chemoselectivity is sufficiently high to simultaneously tolerate the presence of other directing groups on substrate **51** (e.g. (di)azine, pyrazole), selectively affording quite a range of functionalized iminophthalimides **52** in moderate to excellent yields. The authors propose similar intermediates for this reaction towards **52** as were postulated for the imidoxylation C-H functionalization reaction of benzamides **45** described above in Scheme 10.

Scheme 12.  $\text{Co}(\text{III})$ -catalyzed amidoimidoxylation of benzamides and acrylamides ( $\text{Q}$  = 8-quinolinyl).

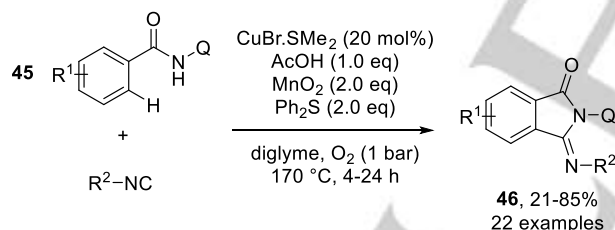
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Starting from similar *N*-quinolinylbenzamides **45**, a nickel-catalyzed C-H functionalization is also possible employing *t*BOOtBu as oxidant and provides the corresponding iminoisoindolinone **46** in reasonable yields (Scheme 13).<sup>[37]</sup> An intramolecular kinetic isotope effect of this Ni(II)-catalyzed reaction indicates that C-H cleavage is a kinetically relevant process (not necessarily the rate limiting step of the cycle). Though not mentioned it presumably occurs via a CMD mechanism. No radical mechanism seems to be involved based on TEMPO addition. The reaction is, however, also quite limited in isocyanide scope ( $R^2$  = xyl- or *t*-Bu).



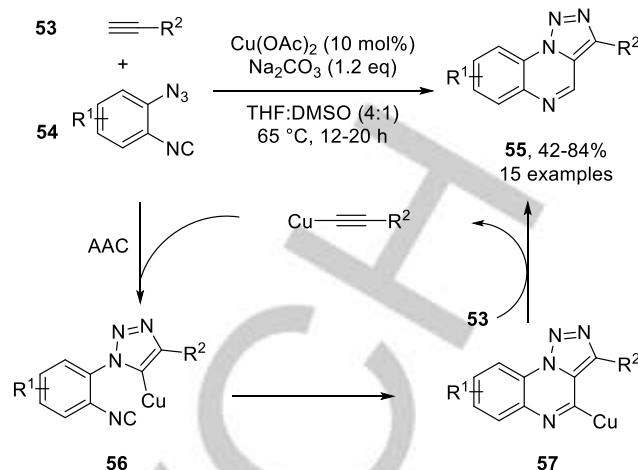
Scheme 13. Ni(II)-catalyzed amidoimidoylation of benzamides (Q = 8-quinolinyl).

The first copper-catalyzed imidoylative C-H functionalization was reported by Miura *et al.* (Scheme 14). Compared to the above Co- or Ni-catalyzed processes this Type I imidoylative reaction requires harsher conditions and higher catalyst loadings.<sup>[38]</sup> The type and stoichiometry of the additives was optimized experimentally though their role is unclear. The regioselectivity of this Cu(I)-catalyzed imidoylative C-H functionalization using 3-substituted benzamides **45** towards the corresponding iminoisoindolinones **46** is moderate to good (1.5:1 – 7.2:1). However, only xyl- and tertiary aliphatic isocyanides proved successful.



Scheme 14. Cu(I)-catalyzed amidoimidoylation of benzamides (Q = 8-quinolinyl).

Finally, a Type I 1,1-migratory insertion process was used to prepare 1,2,3-triazolo-[1,5-*a*]-quinoxalines **55** from 1-azido-2-isocyanoarenes (**54**) and terminal alkynes **53** (Scheme 15). The cycloaddition reaction of azide **54** and an *in situ* formed copper-alkynyl species followed by intramolecular isocyanide insertion facilitates formation of the organocopper intermediate **57**. The triazoloquinoxalines **55** are generated by subsequent protodemetalation with terminal alkynes concomitantly forming back the copper alkynyl species. Although the authors did not comment on the actual oxidation state of the active organocopper species in this reaction, Cu(I)-catalysis seems likely. Both aromatic and aliphatic terminal alkynes are tolerated.<sup>[39]</sup> The authors report extensive Rh-catalyzed follow-up chemistry with the reaction products.



Scheme 15. Triazoloquinoxaline (**55**) synthesis most likely catalysed by Cu(I). (AAC = azide-alkyne [3+2] cycloaddition)

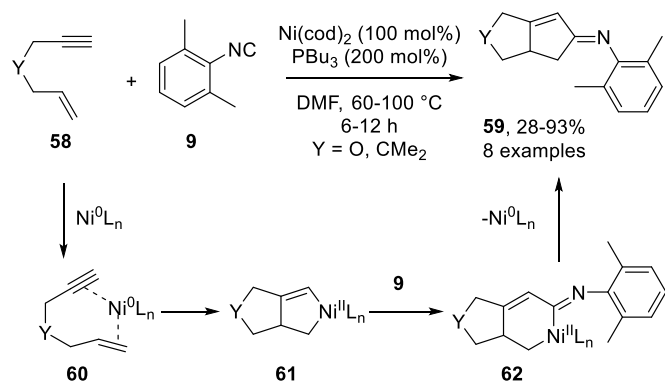
### 2.3. Imidoylations initiated by cyclometalation

Cycloadditions are widely appreciated as effective C-C bond forming reactions.<sup>[40]</sup> In particular, the Pauson-Khand reaction is a well-known cycloaddition involving CO as a C<sub>1</sub>-reactant.<sup>[41]</sup> In relation to this, we discuss in the section below recent advances in combining *in situ* formed cyclometalates with isocyanides. These Pauson-Khand type processes are highly interesting considering the involvement of multiple bond forming transformations generating relatively high levels of complexity in a single step. The insertion step proceeds via a Type I 1,1-migratory insertion into a TM-C bond.

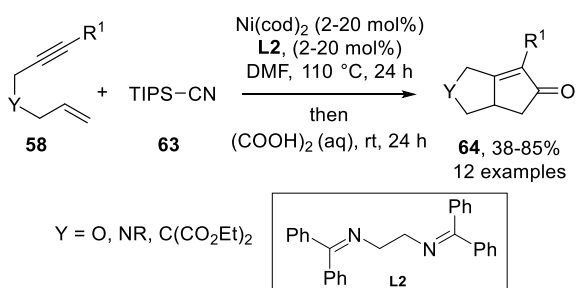
An early example of a Nickel-mediated Pauson-Khand type reaction involving an isocyanide in combination with tethered enynes was reported by Tamao and coworkers (Scheme 16).<sup>[42]</sup> The reaction presumably proceeds via coordination of the enyne (**58**) to the Ni(0)-center followed by oxidative cyclometalation to furnish intermediate **61**. Subsequent Type I 1,1-migratory insertion of xyl- isocyanide (**9**) affords imido nickel intermediate **62**, which can undergo reductive elimination to afford product **59**. As excess isocyanide poisons the Ni(0) catalyst, requiring stoichiometric Ni(cod)<sub>2</sub> to bring the reaction to completion.

A variant of the same reaction was reported by Zhang *et al.* (Scheme 17).<sup>[43]</sup> They used silyl cyanide **63**, which is in equilibrium with its silyl isocyanide isomer (see Scheme 18), to keep the effective isocyanide concentration as low as possible, preventing poisoning of the Ni(0) catalyst.

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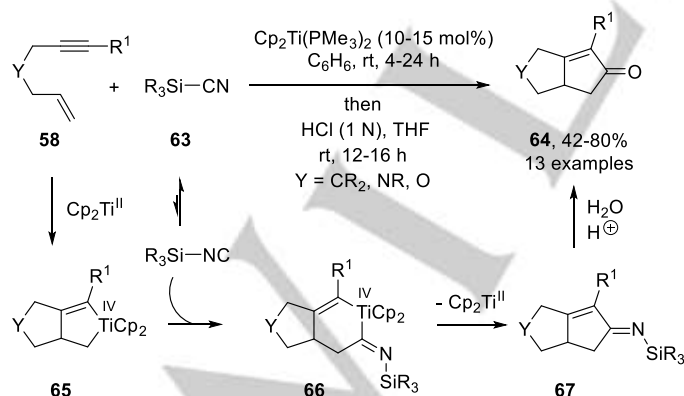


Scheme 16. Ni(0)-mediated imidoylative Pauson-Khand type reaction to enimes **59**.

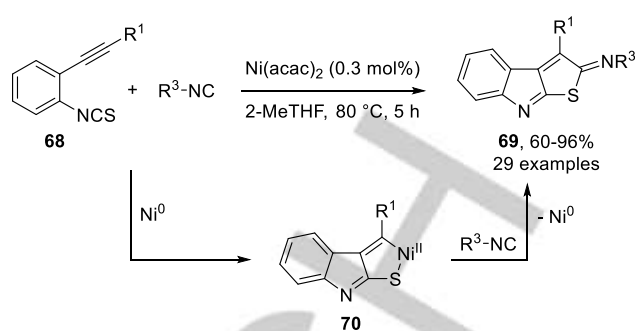


Scheme 17. Ni(0)-catalyzed imidoylative Pauson-Khand type reaction with silyl cyanides.

Imidoylative Pauson-Khand type reactions have also been reported with other metals as exemplified by a titanocene(II) catalyst (Scheme 18).<sup>[44]</sup> Again, to prevent inhibition, the isocyanide concentration was kept low by employing silyl cyanide **63**. Post-cyclization hydrolysis gave the corresponding bicyclic enones **64** in good yields.



Scheme 18. Ti(II)-catalyzed Pauson-Khand type reaction with silyl cyanides.

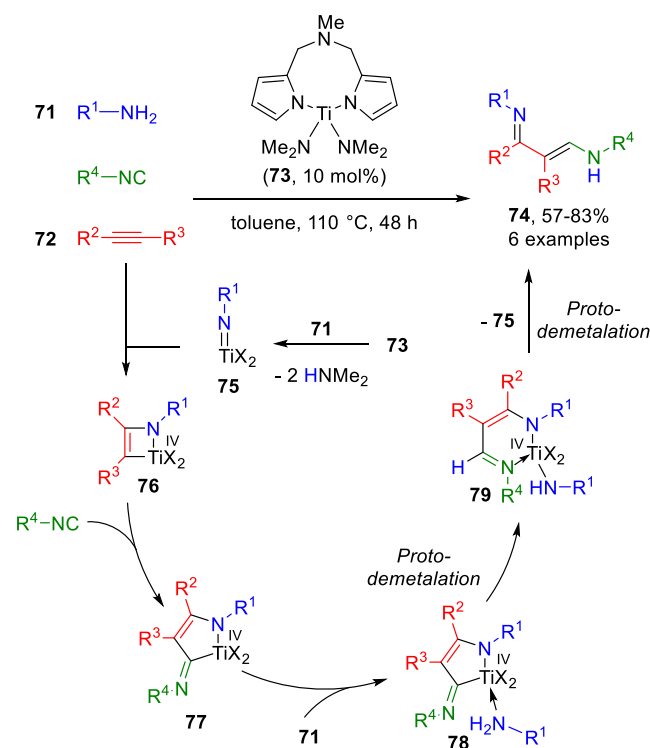


Scheme 19. Ni(0)-catalyzed imidoylative hetero Pauson-Khand-type reaction.

A hetero [2+2+1] Pauson-Khand type cycloaddition of 2-alkynylaryl isothiocyanates **68** and isocyanides yields thieno[2,3-*b*]indoles **69** (Scheme 19). The cyclonickelate intermediate **70** is formed via oxidative cycloaddition.<sup>[45]</sup> Control experiments indicate that the active catalyst is indeed a Ni(0) species, which is generated *in situ* from the Ni(II) precursor without addition of an external reducing agent. Notably, the catalyst loading is low, however still, the reaction tolerates a rather broad range of aliphatic, aromatic and  $\alpha$ -acidic isocyanides. The yield is somewhat lower for the notoriously unstable naphthyl isocyanide (60%), but in general this transformation proceeds with high efficiency.

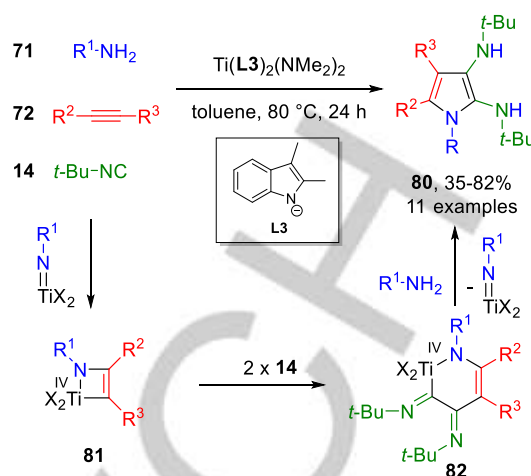
Odom and coworkers communicated a three-component reaction of amines, internal alkynes and isocyanides to give enaminoimines **74**, catalyzed by titanium catalyst **73** (Scheme 20).<sup>[46]</sup> With unsymmetrical alkynes, the regioisomers of **74** depicted in Scheme 20 were formed in moderate to good (1.2:1 – 6:1) selectivity. The mechanism proceeds via a metathesis-like reaction of an alkyne (**72**) with the *in situ* formed titanium nitrene **75**, forming azatitanacyclobutene **76**.<sup>[47]</sup> Subsequent isocyanide insertion affords imido intermediate **77**. This intermediate can undergo double protodemetalation by another amine (**71**) to furnish 1-azadienes **74** and regeneration of the titanium nitrene **75**. These enaminoimines **74** are precursors to various chemically and medically relevant heterocycles.<sup>[48]</sup>

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Scheme 20. Ti(IV)-catalyzed three-component reaction of amines, alkynes and isocyanides.

Interestingly, when another titanium(IV) catalyst is used, a double isocyanide insertion occurs, affording densely functionalized diaminopyrroles **80** (Scheme 21).<sup>[49]</sup> This pseudo-four-component reaction proceeds efficiently with both terminal and unsymmetrical internal alkynes. After initial formation of azatitanacyclobutene **81**, the increased electron density around the metal suppresses the protodemetalation step after the first insertion, favoring a second insertion to furnish intermediate **82**. Odom *et al.* argue that protodemetalation with this ligand system is slower due to the decreased acidity of the coordinated amine prior to protodemetalation after the first insertion (**78**; Scheme 20). In this transformation only the sterically encumbered *t*-BuNC proved successful. Sterically less demanding isocyanides tend to react in a three-component reaction comparable to the reaction described in Scheme 20.

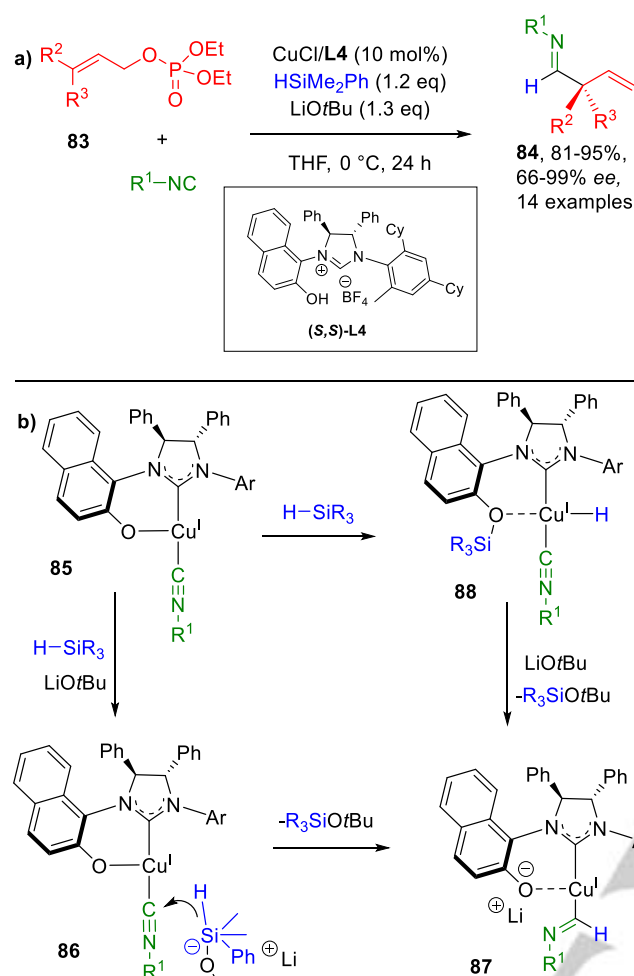


Scheme 21. Ti(IV)-catalyzed pseudo-four-component reaction to diaminopyrroles.

## 2.4. Imidoylations initiated by other processes

In an intriguing report, Hojoh and coworkers disclosed the only known example of a base metal-catalyzed isocyanide insertion reaction affording enantioenriched products (Scheme 22a), by employing Cu(I) complexed to a chiral NHC-ligand **L4**.<sup>[50]</sup> Although the mechanism has not been fully investigated, the authors propose a Type II process involving hydrosilicate intermediate **86** (Scheme 22**Fehler! Verweisquelle konnte nicht gefunden werden.**). However, as the insertion of isocyanides in Cu-H bonds is known<sup>[51]</sup>, the possibility of a 1,1-migratory insertion following a Type I process into copper hydride species **88** cannot be excluded without further studies. Formal enantioselective  $S_N2'$  attack of the organocopper species **87** on the allylic phosphate **83** affords aldimines **84** in excellent yields with moderate to excellent *ee*. Both primary and secondary aliphatic isocyanides as well as *p*-methoxyphenyl isocyanide afford the corresponding aldimines **84** efficiently. As aldimines derived from non-aromatic isocyanides tend to partially hydrolyze to the corresponding aldehyde during work up, these aliphatic products required full hydrolysis to prevent formation of complex product mixtures. As such, the reported yields correspond to the final aldehyde product obtained after hydrolysis.

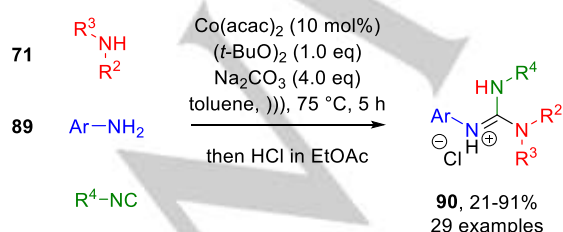
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Scheme 22. Asymmetric Cu(I)-catalyzed synthesis of  $\alpha$ -quaternary aldimines employing chiral *N*-heterocyclic carbenes.

### 3. Insertions of Isocyanides into Heteroatom-Metal Species

The number of examples in literature of base metal-catalyzed isocyanide insertions involving a TM-Z species where Z is heteroatom rather than carbon based (section 2) has increased substantially since 2014. Type I a2 and Type II imidoylations are typically involved in these reactions (Scheme 1). Application to the synthesis of several interesting molecular scaffolds has been reported and will be discussed in this section.



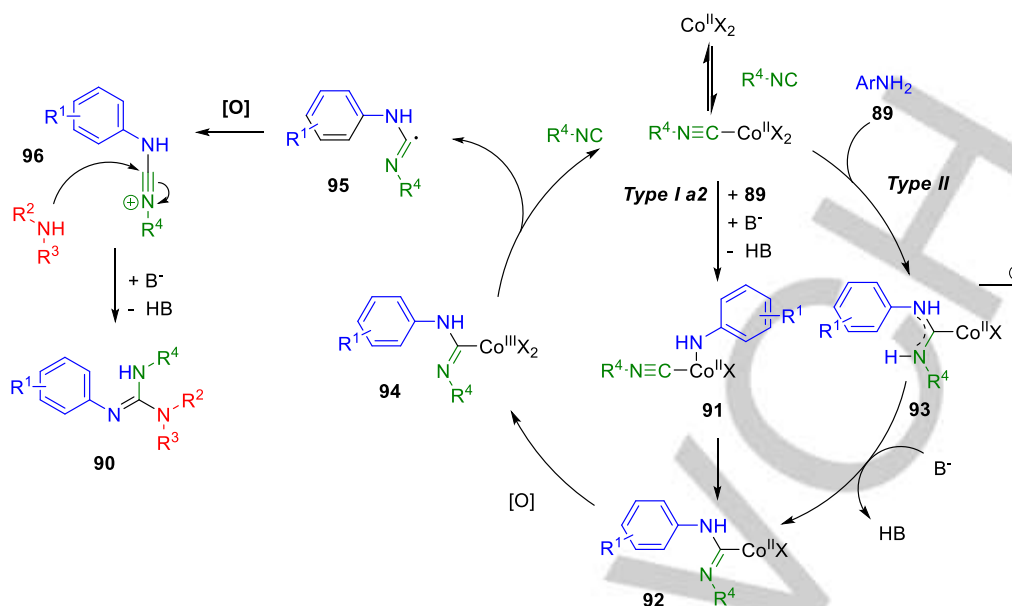
Scheme 23. Co(II)-catalyzed unsymmetrical arylguanidine synthesis.

An interesting example is the synthesis of unsymmetrically substituted arylguanidines **90** using a cobalt catalyst under

ultrasound heating (Scheme 23).<sup>[52]</sup> The process involves the imidoylative coupling of an aliphatic and aromatic amine using (*t*-BuO)<sub>2</sub> as oxidant (Scheme 24). The initially formed aromatic C-amidinoylcobalt intermediate **92** can be formed by either a Type I or a Type II pathway. After imidoylation, the authors suggest that one electron oxidation to intermediate **94** followed by homolysis of the C—Co bond and further oxidation of amidinoyl radical **95**, affords alkylcyanamidium ion **96**, which is trapped by the aliphatic amine. The reaction tolerates both primary, secondary and tertiary isocyanides, but most examples utilize *t*-BuNC (**14**). A similar Co(II)-catalyzed transformation using water or elemental sulfur to quench the intermediate alkylcyanamidium **96** leads to unsymmetrical (thio)ureas, again starting from anilines **89**.<sup>[53]</sup>

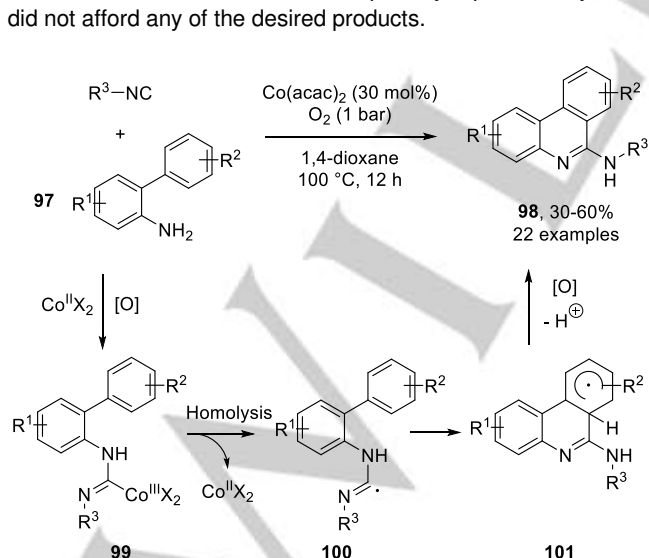


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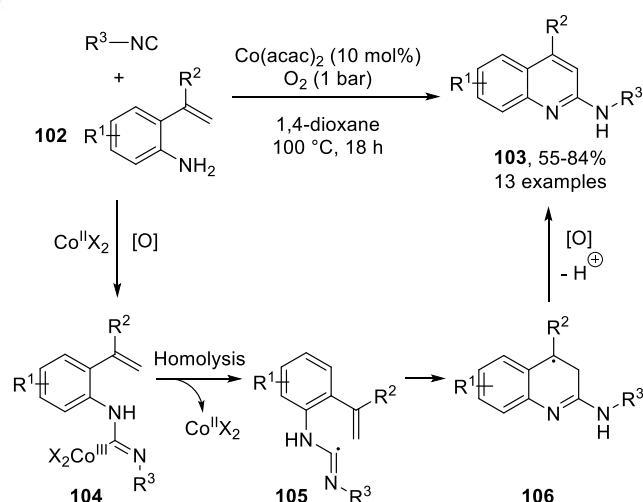
Scheme 24. Proposed catalytic cycle of the Co(II)-catalyzed unsymmetrical arylguanidine synthesis.

In 2014, Zhu *et al.* devised a novel approach to the construction of benzo-fused 2-aminoquinolines **98**.<sup>[54]</sup> Under similar catalytic conditions as described in Scheme 23, a complex of *o*-aminobiphenyls **97** and  $\text{Co}^{\text{II}}\text{X}_2$  undergoes deprotonation, isocyanide insertion and one electron oxidation to afford amidinoyl Co(III) species **99** (Scheme 25). The authors propose that subsequent homolysis of the cobalt-carbon in Co(III) species **99**, furnishes amidinoyl radical **100**, which undergoes an intramolecular homolytic aromatic substitution (HAS), affording the biologically valuable 6-aminophenantridines **98** in low to moderate yields. Molecular oxygen was used as the optimal oxidant. Although tertiary and secondary aliphatic isocyanides react well, reactions of aromatic and primary aliphatic isocyanides did not afford any of the desired products.



Scheme 25. 6-Aminophenantridine synthesis using a Co(II)-catalyzed aminoimidoylation/homolytic aromatic substitution (HAS) cascade process.

A similar radical relay process was used to access 2-aminoquinolines **103** by using the vinyl of *o*-aminostyrenes **102** as radical acceptors (Scheme 26).<sup>[55]</sup> Although this reaction proceeds via a similar mechanism as described in Scheme 25, in this case only tertiary isocyanides led to efficient formation of 2-aminoquinolines **103**. The authors performed radical trapping experiments with TEMPO and indeed detected the TEMPO-**105** adduct by LC-MS analysis together with a trace amount of product **103**. The authors claim that this suggests the involvement of a radical process. However, in the reactions discussed in Scheme 24 & 25, no further detailed mechanistic investigations were reported in this respect.

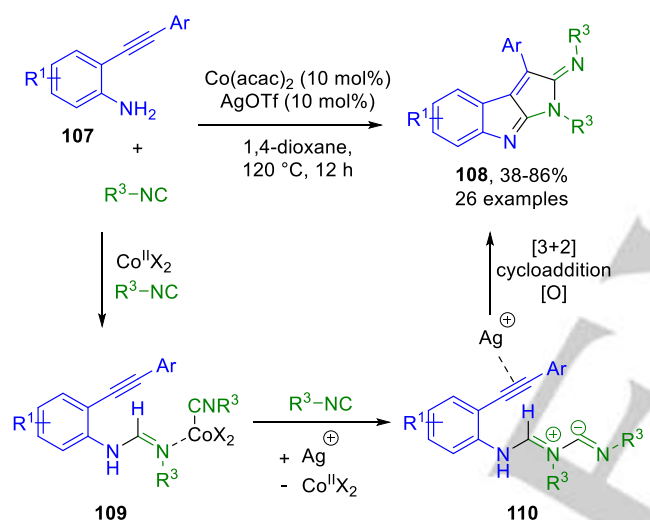


Scheme 26. Co(II)-catalyzed aminoimidoylation cascade process towards 2-aminoquinolines.

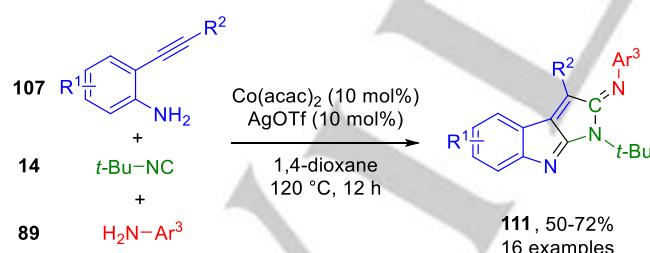
An interesting cobalt-catalyzed double insertion / silver-catalyzed [3+2] cycloaddition cascade approach to iminopyrroloindoles **108**

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was reported by Gao and coworkers.<sup>[56]</sup> Formamidine **109** is formed via isocyanide insertion in an anilino-cobalt species, formed from 2-alkynylaniline **107** and Co(acac)<sub>2</sub>. Subsequently, the authors propose an unconventional second insertion, affording the 1,3-dipole intermediate **110**, which undergoes a silver-catalyzed [3+2] cycloaddition. The authors did not provide detailed mechanistic work to support the formation of 1,3-dipole intermediate **110** from formamidine **109**. However, when subjecting the uncoordinated formamidine in intermediate **109** to the standard reaction conditions with 1.1 equivalent of isocyanide, product **108** did form in excellent yield, which makes the involvement of intermediate **109** plausible (Scheme 27). Initially, the corresponding pyrroloindoles are formed, but these oxidize rapidly under air to the observed fused iminopyrroloindole **108**. The reaction tolerates both aromatic and aliphatic isocyanides. However, an aromatic substituent on the alkyne is required. More recently, the same group extended this protocol to a three-component reaction. By adding an additional aniline (**89**), product **111** was obtained via a thermodynamically and kinetically favored transimination (Scheme 28).<sup>[57]</sup>

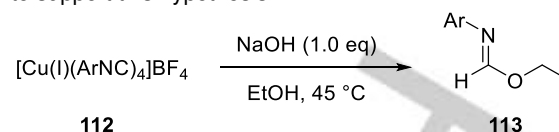


Scheme 27. Co(II)/Ag(I) tandem catalysis to iminopyrroloindoles.

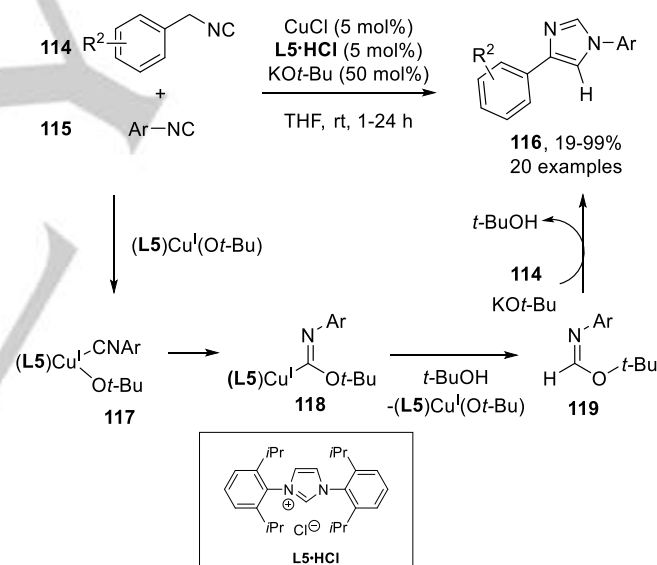
Scheme 28. Co(II)/Ag(I) tandem catalysis/transimination cascade to **111**.

In relation to this, it is perhaps surprising that already in 1974 Knol and coworkers showed that formimidates **113** can be formed by insertion of aryl isocyanides into the O–H bond of ethanol (Scheme 29).<sup>[58]</sup> The mechanism has remained largely uninvestigated, but the authors propose a nucleophilic attack of ethoxide onto the copper coordinated isocyanide (complex **112**)

(Type II, Scheme 1b). Several kinetic experiments indeed appear to support this hypothesis.

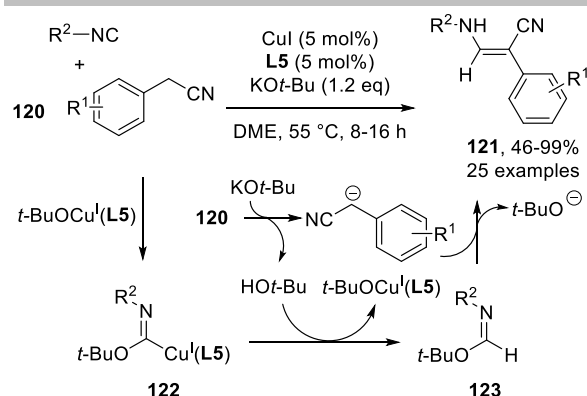
Scheme 29. Early copper-mediated *N*-aryl imidate synthesis.

Similar *in situ* formed imidates can be used in a *one-pot* Van Leusen-type formal [3+2] cycloaddition with  $\alpha$ -acidic benzylic isocyanides.<sup>[21a]</sup> Here, *N*,3-diarylimidazoles **116** are formed in high yields and with high chemoselectivity under Cu(I)-catalysis (Scheme 30). Only highly electrophilic aromatic isocyanides (**115**) are sufficiently electron-deficient to be efficiently transformed to the intermediate imidates **119**, which undergo the subsequent cycloaddition with  $\alpha$ -acidic benzyl isocyanide **114**. Both experimental results and *in silico* investigations suggest that the K<sup>+</sup> counterion is essential to obtain high yields of **119**. Various substituted benzylic and aryl isocyanides afford imidazoles **116** in moderate to excellent yield. Additional DFT calculations indicate that the energetic difference between possible Type I 2a and Type II insertion (Scheme 1a-b) in this reaction is less than 1 kcal/mol<sup>−1</sup>, meaning both can occur.

Scheme 30. *N*,3-diarylimidazole synthesis by Cu(I)-catalyzed alkoxyimidoylation/[3+2] cycloaddition cascade.

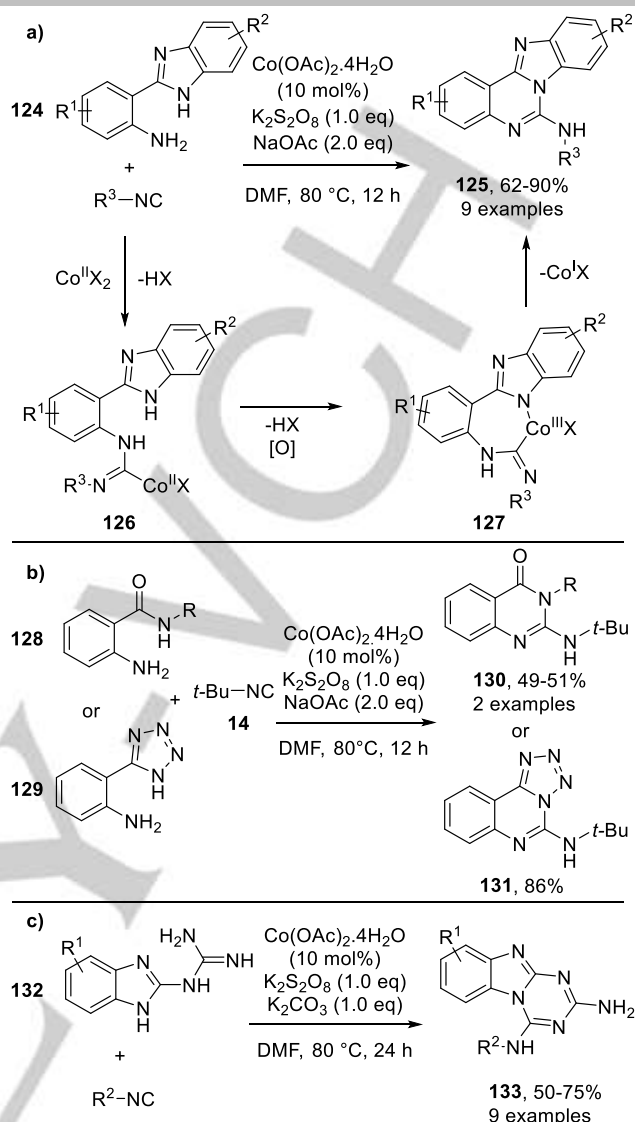
Another Cu(I)-catalyzed alkoxyimidoylation/condensation cascade reaction was reported by Kim *et al.* (Scheme 31).<sup>[59]</sup> The *in situ* formed formimidate intermediate **123** condenses with the  $\alpha$ -acidic arylacetonitrile (**120**), affording 3-amino-2-arylacrylonitriles (**121**) in moderate to excellent yields.

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Scheme 31. Cu(I)-catalyzed alkoxyimidoxylation/condensation cascade.

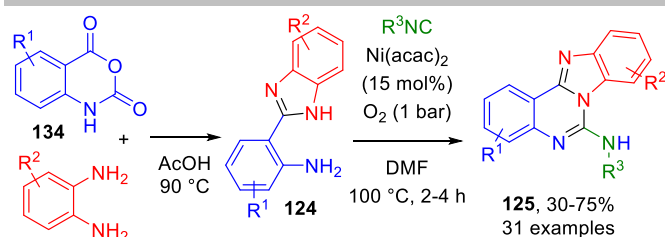
Next to the above discussed substrates, bisnucleophiles are also frequently employed for isocyanide insertion processes. The use of bisnucleophiles has been ubiquitous in imidoxylation transformations as they are valuable precursors to a broad range of heterocycles. This is especially highlighted by the numerous examples of palladium-catalyzed oxidative isocyanide insertion reactions. The Pd-catalyzed oxidative imidoxylation of bisnucleophiles was first reported by our group in 2012.<sup>[60]</sup> Since then, various base metal-catalyzed variants have been published. Cheap  $K_2S_2O_8$  is the preferred oxidant in these reactions. The cobalt-catalyzed insertion of isocyanides into 2-(2-aminoaryl)benzimidazoles **124** (Scheme 32a) affords benzimidazole fused 2-aminoquinazolines **125**.<sup>[61]</sup> A plausible mechanism proceeds via the intermediate amidinoyl cobalt(II) species **126**, which undergoes a single electron oxidation initiating the reductive elimination. Further one electron oxidation of the liberated Co(I) species regenerates the active catalyst. Other nitrogen nucleophiles, such as the anthranilamide **128** can also be involved. In a similar process 2-(2-aminophenyl)tetrazoles **129** and *N*-(benzimidazol-2-yl)guanidine **132**<sup>[62]</sup> proved to be suitable substrates (Scheme 32b-c). Compared to the Pd-catalyzed process<sup>[63]</sup>, cobalt catalysis has a higher tolerance for aliphatic and aromatic isocyanides. Unfortunately,  $O_2$  seems not to be a suitable oxidant.



Scheme 32. Fused heterocycles via Co(II)-catalyzed imidoxylation of diamine bisnucleophiles.

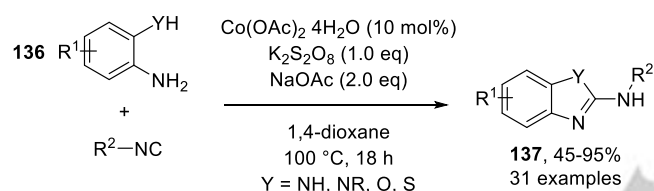
A nickel-catalyzed version with similar substrates **124** was reported to afford aminobenzimidazoquinazolines **125** (Scheme 33).<sup>[64]</sup> Interestingly, the scope of isocyanides tolerated by this reaction is broader than under the comparable cobalt-catalyzed processes discussed in Scheme 32, even tolerating benzylic and  $\alpha$ -acidic isocyanides. Moreover, oxygen, the most abundant and sustainable oxidant, can be used in this reaction. Also, this Ni(II)-catalyzed process could be extended to a one-pot reaction starting from isatoic anhydrides **134**, affording the fused tetracycles **125** in reasonable 30-76% yields.

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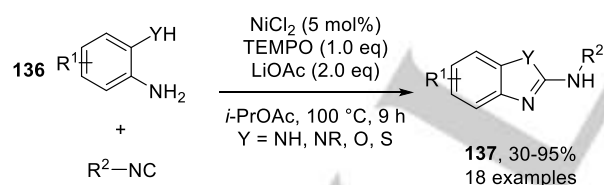
Scheme 33. Ni(II)-catalyzed imidoylation of 2-aminoaniline or 2-amino(thio)phenols (**125**).

In 2013, Ji *et al.* reported the synthesis of 2-aminobenzimidazoles, -benzoxazoles, and -benzothiazoles (**137**) via a Co(II)-catalyzed reaction of isocyanide with 2-aminoanilines, 2-aminophenols and 2-aminothiophenols (**136**), respectively (Scheme 34).<sup>[65]</sup> This exemplifies that bisnucleophiles do not need to be diamines. While the reported yields are lower than for the analogous Pd-catalyzed reactions,<sup>[60]</sup> this transformation is significantly more compatible with aliphatic, aromatic, and  $\alpha$ -acidic isocyanides. Again  $\text{K}_2\text{S}_2\text{O}_8$  is applied as oxidant (Scheme 32).



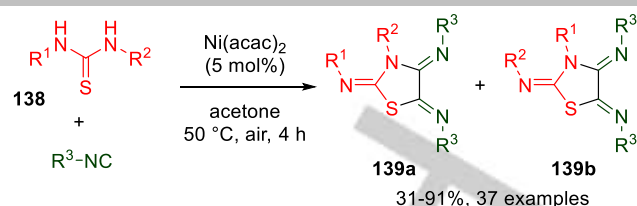
Scheme 34. Co(II)-catalyzed imidoylation of 2-aminoaniline or 2-amino(thio)phenols.

These privileged scaffolds (**137**) are also accessible via oxidative nickel catalysis<sup>[66]</sup> and both primary, secondary, tertiary aliphatic, as well as aromatic isocyanides afforded the products **137** in moderate to excellent yields (Scheme 35). TEMPO was required as oxidant (Scheme 33).



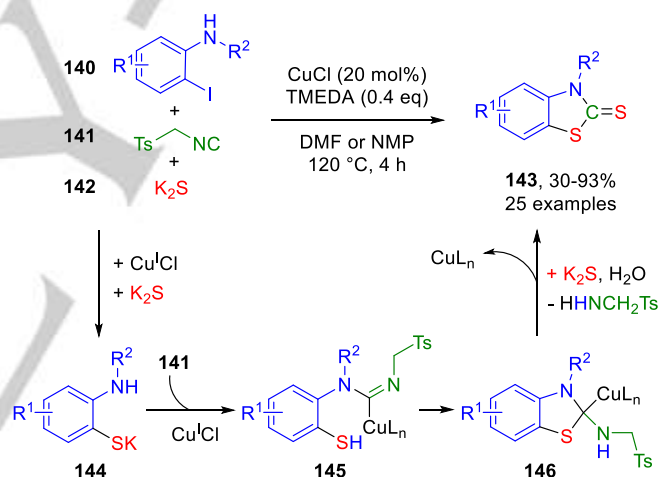
Scheme 35. Ni(II)-catalyzed imidoylation of 2-aminoaniline or 2-amino(thio)phenols.

Recently, the group of Li reported the first base catalyzed aerobic double isocyanide insertion (Scheme 36) to access triiminothiazoles.<sup>[67]</sup> The authors propose that molecular oxygen from air facilitates the oxidation of Ni(0) to Ni(II), hereby closing the catalytic cycle known as oxidase type chemistry. The Ni(II)-catalyzed reaction tolerates electronically diverse aliphatic and aromatic isocyanides. Starting from non-symmetrical substituted thioureas (**138**), mixtures of regioisomeric iminothiazoles (**139a**:**139b**, 1:1 to 9:1) were obtained in reasonable to good yields.



Scheme 36. Ni(II)-catalyzed double isocyanide insertion to 2,4,5-triiminothiazole (**139**).

The last bisnucleophile-based insertion reaction discussed here is the Cu(I)-catalyzed access to benzothiazolethiones (**143**) reported by Liang and coworkers. In their reaction the *N,S*-bisnucleophile **144** was generated *in situ* by a non-imidoylative Cu(I)-catalyzed Ullmann coupling between the iodoaniline **140** and  $\text{K}_2\text{S}$  (Scheme 37).<sup>[68]</sup> This is followed by an interesting Cu-catalyzed reaction with isocyanide **141** and  $\text{K}_2\text{S}$ . The nature of the oxidation state of copper in the intermediates is unclear. Although the isocyanide in this reaction serves merely as a C1 donor, the use of toluenesulfonylmethyl isocyanide (**141**) is essential. Employing *t*-BuNC leads to significant formation of 2-aminobenzothiazoles (**137**; Scheme 35,  $\text{R}^2 = t\text{-Bu}$ ,  $\text{Y} = \text{S}$ ).



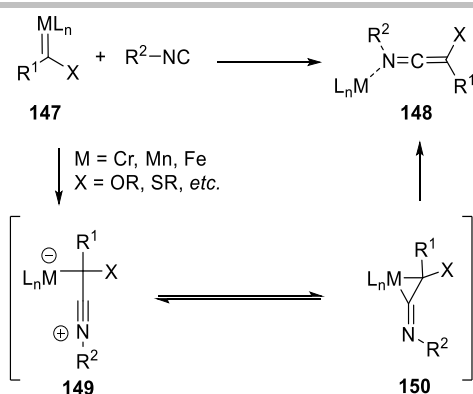
Scheme 37. Auto-tandem Cu(I)-catalyzed reaction to benzothiazolethiones.

## 4. Insertion of isocyanides in TM=C and TM=N Bonds

### 4.1. Insertion of Isocyanides in Metal Carbene complexes

Metallocarbenes involving base metals have been used as substrates in reactions with isocyanides. The reaction of an isocyanide with a TM=C  $\pi$ -bond can be categorized as a Type III insertion (Scheme 1c). The general mechanism of insertion of isocyanides via carbene transfer in the TM=C bond of Fischer carbenes **147** was extensively investigated *in silico* by Fernández *et al.*<sup>[69]</sup> They showed that a metalacyclopropanimine intermediate **150** is more likely than the previously considered zwitterionic species **149** (Scheme 38). 1,2-Metalotropic rearrangement of **150** then affords *N*-metalated ketenimine **148**.<sup>[6a, 70]</sup>

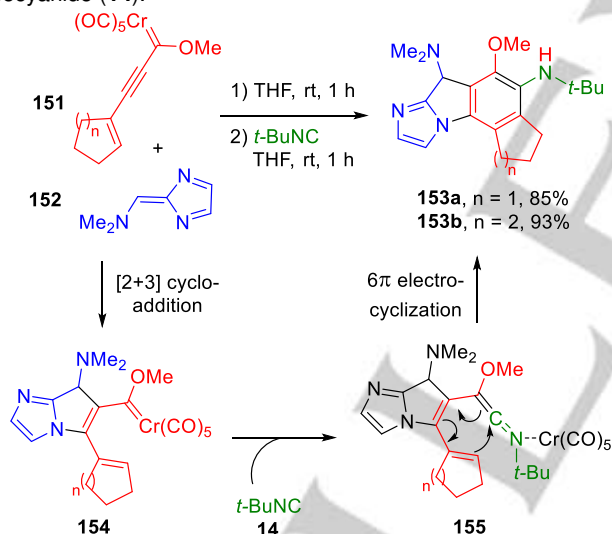
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Scheme 38. General mechanism for carbene transfer to isocyanides.

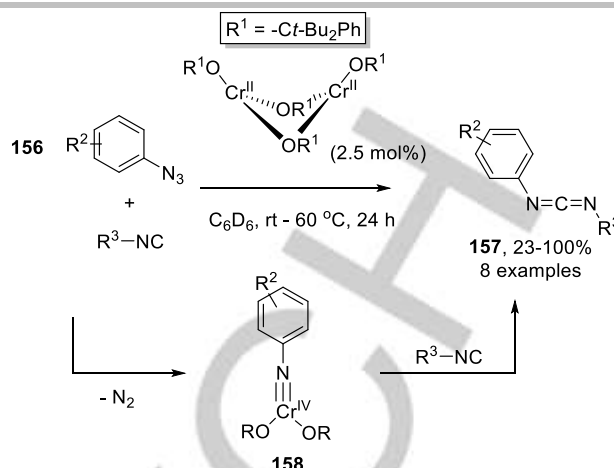
Although the reported examples make use of stoichiometric metallocarbenes, there is potential for being adapted to catalytic variants, e.g. from diazo compounds, in which the *in situ* generated ketenimines are immediately used in follow-up reactions.

A recent example uses Fischer carbene **151** that gives intermediate species **154** after [3+2] cycloaddition with **152** (Scheme 39). Subsequent isocyanide insertion furnishes the electron-rich ketenimine **155**, which then undergoes a 6 $\pi$ -electrocyclization to give bis-annulated anisole derivatives **153**.<sup>[71]</sup> Only two examples of this 3-CR were reported, both with *tert*-butyl isocyanide (**14**).

Scheme 39. Three-component reaction with Fischer carbene **151**.

#### 4.2. Insertion of Isocyanides in Metal Nitrene Complexes

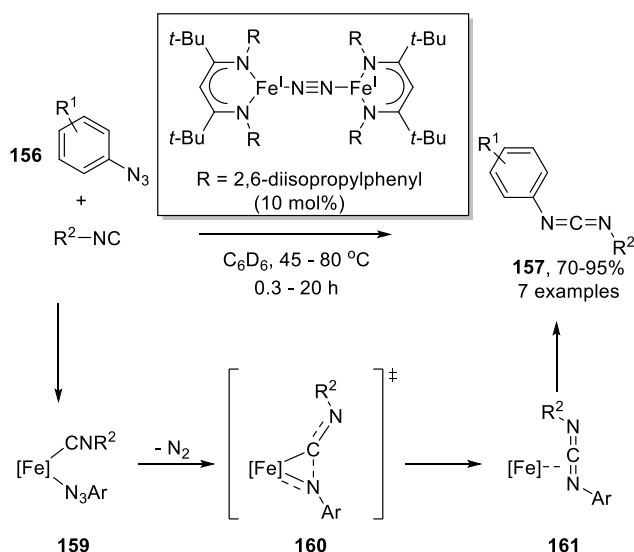
Closely related to the carbene transfer to isocyanides is the insertion of isocyanides into metal nitrene complexes, usually leading to carbodiimides. As metal nitrene complexes are mostly generated *in situ* from azides, catalytic metal complexes can be used. Although some interesting examples have been reported, development of these base metal-catalyzed reactions is still in its infancy.



Scheme 40. Cr(II)-catalyzed carbodiimide formation from aryl azides and isocyanides.

A reaction based on this principle is shown in Scheme 40. The carbodiimides (**157**) can be prepared by a Cr-catalyzed nitrene transfer to isocyanides.<sup>[72]</sup> The bulkiness of both the azide and the isocyanide input proved highly important. The use of sterically less demanding azides results in the formation of an unreactive, saturated Cr(VI) complex.

Holland and coworkers reported a similar reaction that presumably proceeds via an Fe(I)-complex of aryl azides **156** and isocyanides (Scheme 41). Mechanistic studies reveal that transition state **160** is involved and that most likely imido attack occurs to the metal-bound isocyanide (Type III insertion, Scheme 1c). The scope with regard to both the isocyanide and azide is rather limited.<sup>[73]</sup> Only *t*-BuNC and 2,6-xylyl isocyanide gave successful reactions affording the corresponding carbodiimides in good to excellent yields. It should be noted that Wiese and coworkers reported a Ni(I)-catalyzed process utilizing similar diamino-ligands.<sup>[74]</sup> Although the carbodiimines **157** are formed in less reproducible yield compared to the Fe-catalyzed pathway, the reaction with Ni tolerates electronically more diverse azides, like sulfonyl azides and acylazides. Again, only *tert*-butyl and xylyl isocyanide were employed in this Ni(I)-catalyzed process.

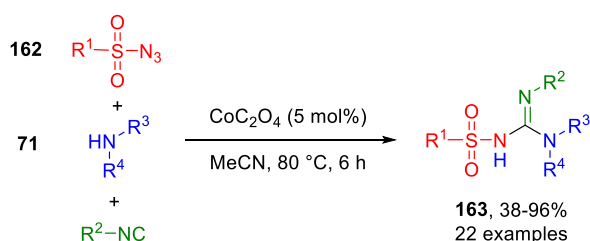
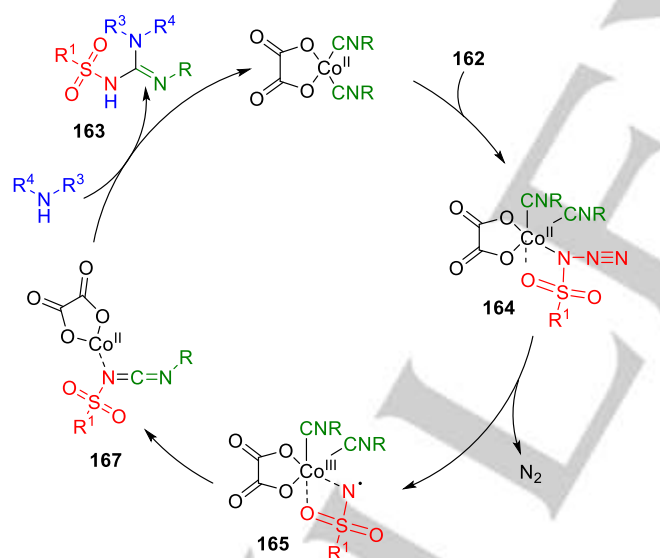




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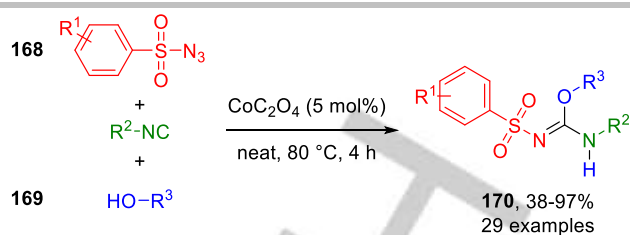
Scheme 41. Fe(I)-catalyzed carbodiimide synthesis from aryl azides and isocyanides.

With an additional nucleophile present these carbodiimides can be *in situ* transformed. The catalyst can then additionally act as a Lewis acid, facilitating addition. Recently, Ji reported a 3-CR affording highly substituted guanidines **163** (Scheme 42).<sup>[21b]</sup> This cobalt-catalyzed process does not require special ligands or glovebox conditions. Extensive EPR analysis and theoretical calculations suggest a catalytic mechanism involving a nitrene radical (**165**; Scheme 43). This pathway allows formation of carbodiimide **167**, via a Co<sup>II</sup>/Co<sup>III</sup>-catalyzed process, which then reacts with amine **71** providing *N*-sulfonyl guanidine **163**. The reaction tolerates a wide variety of aliphatic, aromatic and  $\alpha$ -acidic isocyanides.

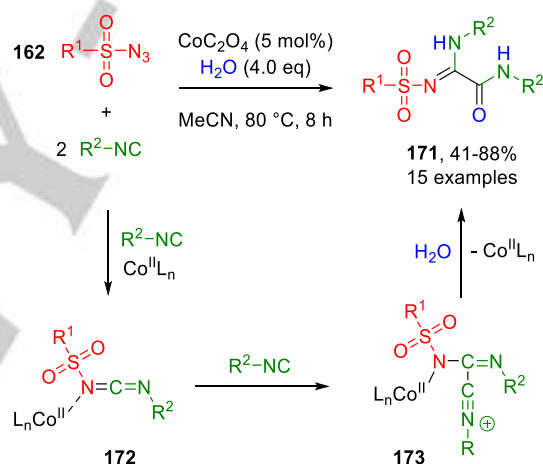
Scheme 42. Three-component synthesis of unsymmetrical *N*-sulfonylated guanidines via Co(II)-catalysis.

Scheme 43. Proposed mechanism for the Co(II)-catalyzed formation of guanidines via intermediate carbodiimide species.

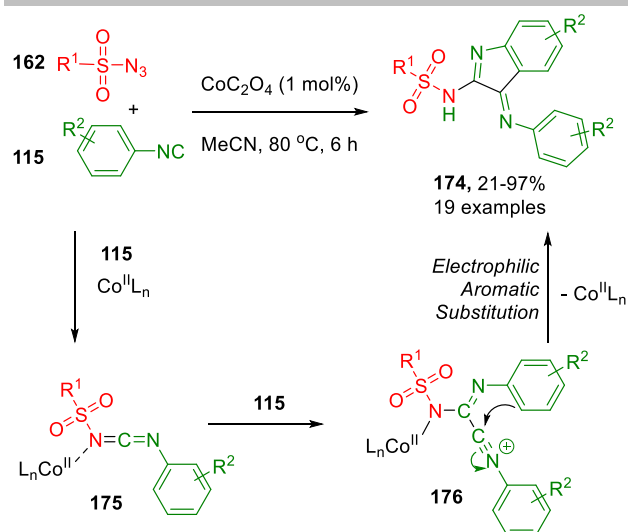
A similar transformation using alcohols instead of amines was developed to furnish the corresponding *N*-sulfonyl isoureas **170** (Scheme 44) in comparable yields to the guanidine synthesis.<sup>[75]</sup> In this case the intermediate carbodiimides are trapped with alcohols.

Scheme 44. Co(II)-catalyzed three-component synthesis of *N*-sulfonyl isoureas.

Furthermore, a pseudo four-component reaction involving two isocyanides, sulfonyl azide and water affording  $\alpha$ -amidoamidines under cobalt catalysis was recently described.<sup>[76]</sup> Interestingly, in this reaction the *in situ* formed electron deficient carbodiimide **172** undergoes selective nucleophilic attack by a second isocyanide **105** before addition of less nucleophilic water to nitrilium ion **173** occurs, to give *N*-sulfonyl  $\alpha$ -amidoamidines **171** (Scheme 45). On the other hand, utilizing aromatic isocyanides in the absence of water (Scheme 46) facilitates an intramolecular electrophilic aromatic substitution of nitrilium ion intermediate **176**, affording stable aminoiminoindoles **174** in moderate to high yields.

Scheme 45. Multicomponent synthesis of  $\alpha$ -amidoamidines via Co(II) catalysis.

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Scheme 46. Co(II)-catalyzed 3-CR to aminoiminoindoles 174.

## 5. Summary and Outlook

Base metal-catalyzed isocyanide insertion processes, although still in its infancy, hold great potential for application in organic and heterocyclic synthesis. The (formal) migratory insertion of isocyanides into *in situ* formed TM-C, TM-X, TM=C and TM=N bonds provides promising pathways to utilize isocyanides as valuable C<sub>1</sub> building blocks in organic synthesis. However, many reports only show application of rather simple and hindered isocyanides. In particular, cobalt- and nickel-based reactions discussed here often show a remarkable tolerance for more advanced functionalized isocyanides. When other base metals are used the more challenging unhindered and/or aromatic isocyanides typically still limit the overall scope. This is mainly due to the occurrence of multiple insertions resulting in competing polymerization. In oxidative processes the combination with cheap oxidants (peroxides, peroxydisulphate, oxygen) proves quite productive. However, the loading of the base metal catalysts applied is often still relatively high. On the other hand, toxicity issues related to some specific base-metal salts (like e.g. some Co-salts) require careful analysis of the alternatives for the traditional noble TM-based catalytic systems.<sup>[77]</sup> To advance this chemistry towards predictable transformations for synthetic organic chemists detailed mechanistic studies are of pivotal importance. Most studies described are still rather phenomenological and do not focus on a clear understanding of what is actually going on in the underlying catalytic process. This, to our opinion, is the major unsolved issue in this field. Mechanistic insight in combination with rational ligand design should, however, bring this methodology to the next level, similar to what has happened in the development of reactions involving Pd-catalyzed isocyanide insertions.<sup>[78]</sup> At present the catalytic cycles are still largely speculative which is not uncommon for an emerging field. Especially the carbene and nitrene transfer processes hold much promise but have only scarcely been reported so far. We believe that the future of this chemistry aligns with the general strive towards the development of more sustainable chemistry, in which the use of catalysts based on more abundant, cheaper and less toxic base metals instead of

noble metals takes a pivotal role. We hope that this Minireview will catalyze further research in this area towards the development of new processes to efficiently assemble high-added value compounds.

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**Keywords:** Isocyanides • base metal catalysis • imidoxylation • synthetic methods • C<sub>1</sub> building blocks

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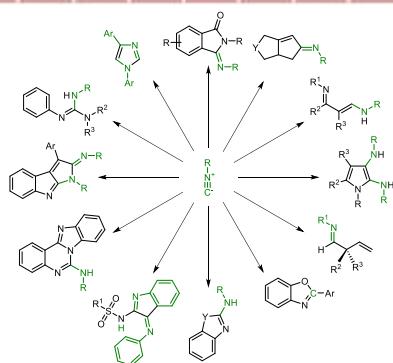
## MINIREVIEW

Entry for the Table of Contents (Please choose one layout)

Layout 1:

## REVIEW

Text for Table of Contents



Jurriën W. Collet<sup>[a],[b]</sup>, Thomas R. Roose<sup>[a]</sup>, Eelco Ruijter<sup>[a]</sup>,\* Bert U.W. Maes<sup>[b]</sup>,\* and Romano V.A. Orru<sup>[a]</sup>,\*

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