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published in

Angewandte Chemie. International Edition
2020

DOI (link to publisher)

[10.1002/anie.201905838](https://doi.org/10.1002/anie.201905838)

document version

Publisher's PDF, also known as Version of record

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Collet, J. W., Roose, T. R., Ruijter, E., Maes, B. U. W., & Orru, R. V. A. (2020). Base Metal Catalyzed Isocyanide Insertions. *Angewandte Chemie. International Edition*, 59(2), 540-558. <https://doi.org/10.1002/anie.201905838>

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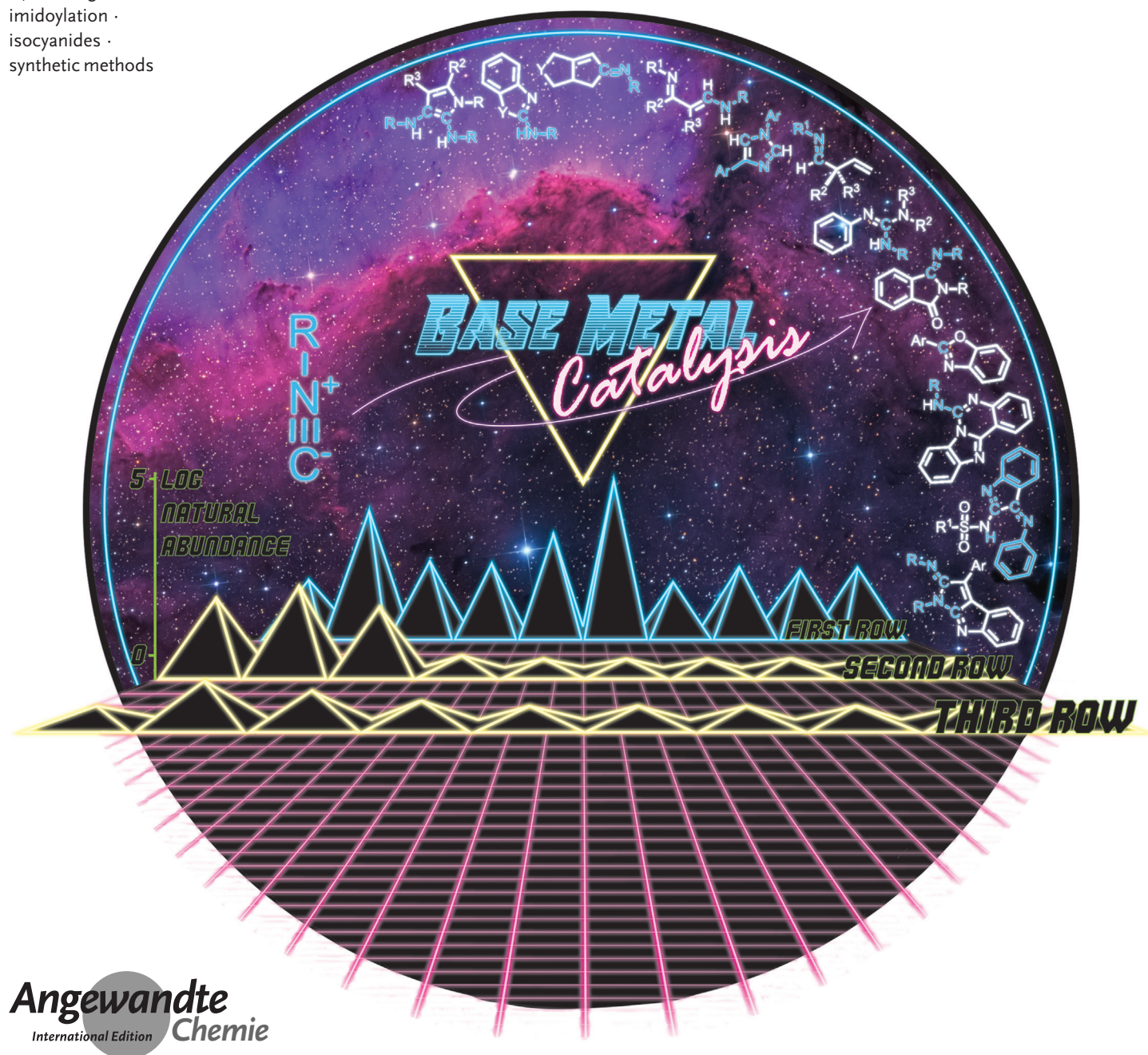
Isocyanides

International Edition: DOI: 10.1002/anie.201905838
German Edition: DOI: 10.1002/ange.201905838

Base Metal Catalyzed Isocyanide Insertions

Jurriën W. Collet⁺, Thomas R. Roose⁺, Eelco Ruijter,^{*} Bert U. W. Maes,^{*} and Romano V. A. Orru^{*}

Keywords:

base metal catalysis ·
C₁ building blocks ·
imidoylation ·
isocyanides ·
synthetic methods

Isocyanides are diverse C_1 building blocks considering 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 that are not possible in the absence of the metal. The tunable 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, reports on the use of earth-abundant and cheap base metals in these types of transformations are scarce and have 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 1) the (hetero)atom bound to and 2) 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 4 base metals are rapidly emerging as equally (or more) efficient alternatives.^[1] 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 the further development of these catalysts.^[2]

Table 1: Earth abundance and bulk cost of fourth-row transition metals and Pd.

Group	Metal	Content in the Earth's crust [ppm] ^[9]	Price [€/mol] ^[10]
IV	Ti	5600	0.21 ^a
V	V	160	4.22 ^a
VI	Cr	100	0.49 ^a
VII	Mn	950	0.12
VIII	Fe	41 000	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

[a] Mined and sold as the bulk ferrous metal.

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

Despite the ubiquity of Pd in these imidoalytic cross-couplings, recent studies increasingly employ base metals (or complexes thereof) 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.

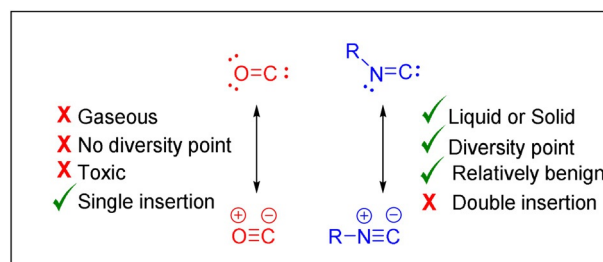


Figure 1. Isoelectronic nature of RNC and CO.

[*] J. W. Collet,^[†] T. R. Roose,^[†] Dr. E. Ruijter, Prof. R. V. A. Orru
Department of Chemistry and Pharmaceutical Sciences and Amsterdam Institute for Molecules, Medicines & Systems (AIMMS)
Vrije Universiteit Amsterdam
De Boelelaan 1108, 1081 HZ Amsterdam (The Netherlands)
E-mail: e.ruijter@vu.nl
r.v.a.orr@vu.nl

J. W. Collet,^[†] Prof. B. U. W. Maes
Organic Synthesis, Department of Chemistry
University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)
E-mail: bert.maes@uantwerpen.be

[†] These authors contributed equally to this work.

The ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.201905838>.

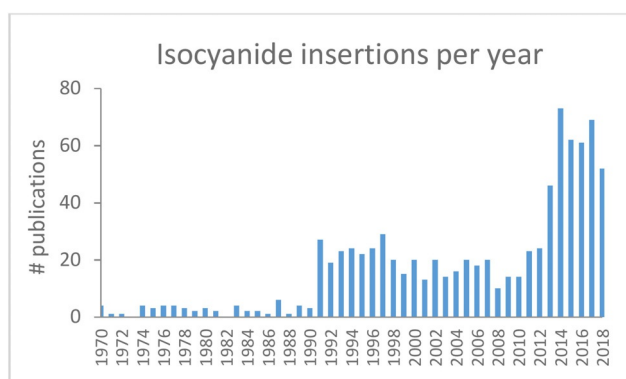


Figure 2. Number of publications reporting on isocyanide insertions since 1970.

This shift poses new challenges and introduces novel catalytic mechanisms of action that offer exciting opportunities for further reaction development.^[11] With this Minire-

view, 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

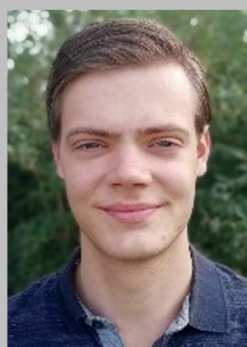
The term “isocyanide insertion” is commonly used by organic chemists to describe TM-mediated or -catalyzed transformations in which the isocyanide moiety is inserted into a σ - or a π -bond. This only refers to the overall result of the reaction and does not suggest a mechanism. Upon studying the reported mechanistic proposals of base metal catalyzed imidoylation reactions, different insertion pathways affording the reactive imidoyl metal intermediates can be distinguished (Scheme 1). First, 1,1-migratory insertion of the isocyanide into a metal–carbon bond (**1**), formed in situ by oxidative addition to TM^n , furnishes the imidoyl metal species



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 the supervision of Prof. Romano Orru and at the University of Antwerp with Prof. Bert Maes. His current research interests include transition-metal catalysis and multicomponent and cascade chemistry.



Bert Maes obtained his PhD in organic chemistry at the University of Antwerp and subsequently received a Post-Doctoral Fellowship of the Research Foundation—Flanders (FWO-Flanders) in Belgium. He worked at the École Normale Supérieure in Paris (mechanisms in catalysis) with Prof. Anny Jutand (CNRS). He 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. In 2019 he was appointed as Collen-Francqui Research Professor by the Francqui Foundation. 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.



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.

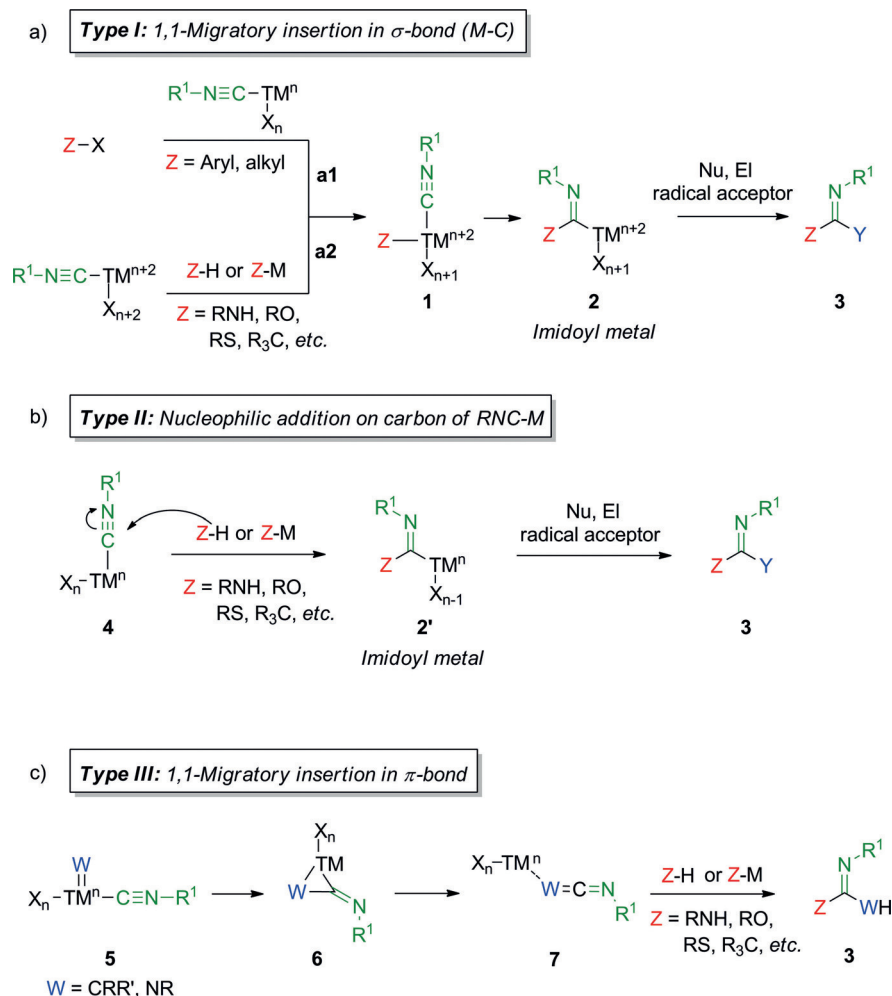


Romano Orru completed his PhD in organic chemistry at the Agricultural University of Wageningen (The Netherlands). From 1996 to 2000, he worked at the Technical University as well as at the Karl Franzens University of Graz (Austria) on synthetic applications of biotransformations. In 2000, he returned to the Netherlands, and was appointed Assistant Professor and later Associate Professor (2003) of Synthetic & Bioorganic Chemistry at Vrije Universiteit Amsterdam. Since 2007, he has held the chair of Synthetic & Bioorganic Chemistry.



Eelco Ruijter obtained his PhD from the Vrije Universiteit Amsterdam and the Leibniz Institute of Plant Biochemistry (Halle/Saale, Germany) in 2005. After a postdoctoral stay at Utrecht University (2004–2006) with Professors 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 added-value molecules.

His research focuses on the utilization of one-pot cascade reactions and multicomponent reactions to improve the efficiency, sustainability, and precision of organic compound synthesis, with emphasis on applications in the field of pharmaceutical science.



Scheme 1. Isocyanide insertion pathways. Nu = nucleophile, El = electrophile.

2 (Type I, Scheme 1 a1). Very similarly, 1,1-migratory insertions of isocyanides into in situ formed metal–heteroatom or metal–carbon 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 imidoylative transformations,^[12] and are observed for most of the fourth row base metal (Sc,^[13] Ti,^[14] V,^[15] Mn,^[16] Fe,^[17] Co,^[18] Ni,^[19] and Cu^[20]). The isocyanide–metal interaction is a coordinate covalent bond. The resulting imidoyl 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 atom, resulting in imidoyl metal species **2'** (Type II, Scheme 1 b).^[6a] This is similar to intermediate **2** in Type I insertion processes, making Type I and II imidoylative pathways often indistinguishable. To date, theoretical and experimental investigations to clarify the exact mechanisms of imidoylative couplings are still limited.^[21]

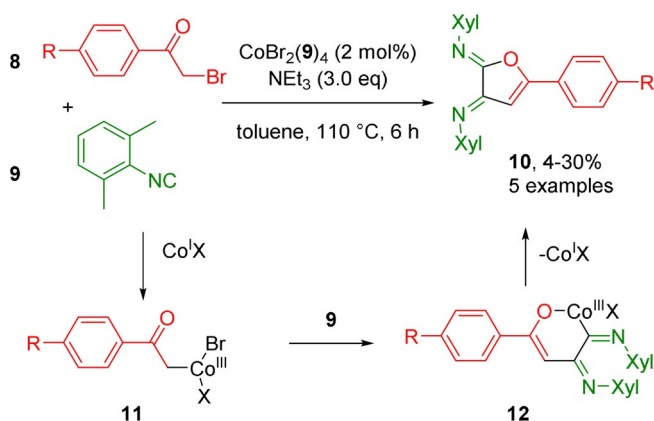
In addition to Type I and II pathways, various other base metal catalyzed and mediated transformations involving carbene or nitrene transfer have been referred to as isocyanide insertion reactions. From a mechanistic point of view, isocyanide migratory insertion occurs into a metal–carbon or metal–heteroatom π -bond rather than the σ -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 1 c). 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.^[22] 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 the reaction rather proceeds through a formal insertion based on a radical relay cascade.

This Minireview aims to highlight the versatile insertion chemistry of isocyanides with fourth-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 that can be used. Therefore, we devoted specific attention to the isocyanides utilized, highlighting current applications in organic synthesis. When applications in multicomponent reactions are discussed, the different components were 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 Organohalides

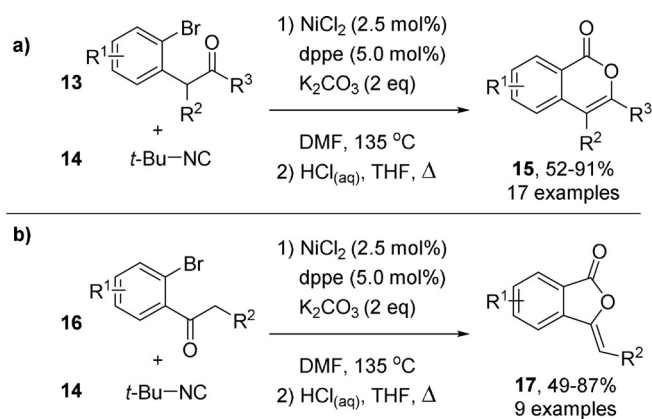
One of the most facile and widespread ways of constructing C–TM bonds is the oxidative addition of aryl (pseudo)-halides to low-valent transition metal centers. Subsequent imidoylation typically occurs through a 1,1-migratory insertion reaction of Type I into the preformed TM–C bond. An early example involving imidoylative cobalt catalysis was reported by Yamamoto and co-workers in 1991 (Scheme 2).^[23]



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

Diiminofurans **10** were obtained in moderate yields, although no optimization was reported. Mechanistic investigations implied that the active catalyst is a Co^I species. Initial oxidative addition of α -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**.^[23]

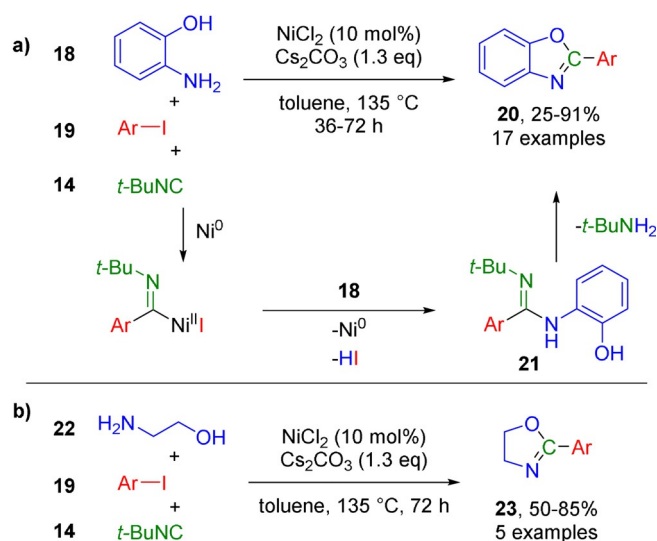
The group of Zhu reported a nickel-catalyzed synthesis of isocoumarins **15** and 3-alkylideneisobenzofurans **17** (Scheme 3). The reaction starts with oxidative insertion of Ni⁰ into a C(sp²)-halogen bond, followed by 1,1-migratory insertion of Type I. The resulting imidoyl nickel species undergoes



Scheme 3. Ni⁰-catalyzed alkoxyimidoylation.

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.^[24] The isocyanide was used as a CO surrogate, and only *tert*-butyl isocyanide (**14**) was employed in these reactions.

Wang and co-workers reported the synthesis of 2-substituted benzoxazoles (**20**) in a Ni-catalyzed reaction (Scheme 4 a).^[25] The 3-CR proceeds via an imidoylative Buchwald–

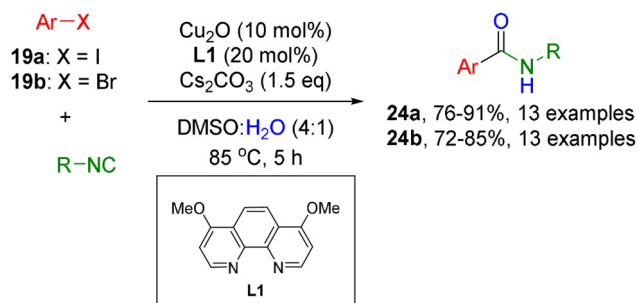


Scheme 4. Ni⁰-catalyzed aminoimidoylation/condensation cascade.

Hartwig-type reaction forming amidine **21**, which subsequently undergoes intramolecular condensation. Only *t*-BuNC (**14**) was used as a C₁ donor. In addition, saturated 2-aminoalcohols **22** afford the corresponding oxazolines (**23**) in good yields (Scheme 4 b). The authors did not comment on how the active Ni⁰ catalyst might be formed from NiCl₂. The efficiency is competitive to that of the analogous Pd-catalyzed process.^[26]

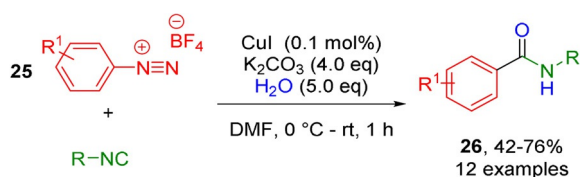
Recently, a copper-catalyzed hydroxyimidoylation of aryl halides was reported as a “CO-free” aminocarbonylation.^[27] The mechanism presumably involves the oxidative addition of

the aryl halide to the Cu^{I} center. The use of aryl iodides or bromides (**19a,b**) afforded 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, whereas primary aliphatic isocyanides were not investigated.



Scheme 5. Cu^{I} -catalyzed hydroxyimidoylation of aryl halides.

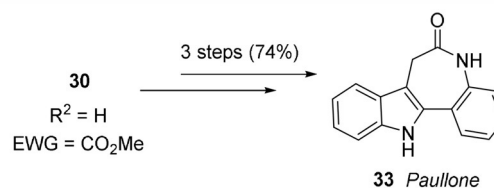
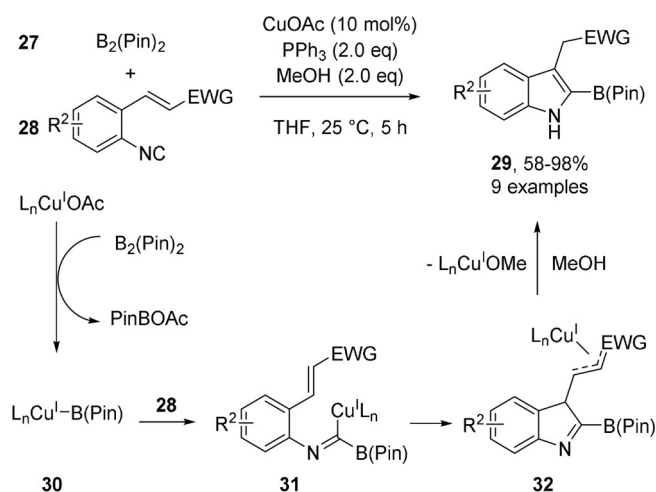
A similar transformation was accomplished by using aryldiazonium salts **25** (Scheme 6). Again, secondary and tertiary aliphatic isocyanides were well tolerated.^[28] The yields of benzamides **26** were substantially lower than reported for the analogous process described in Scheme 5. However, the reaction proceeded at significantly lower temperatures and required a much lower catalyst loading.



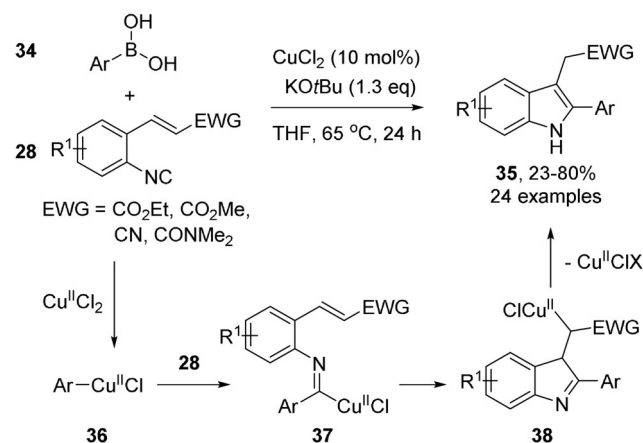
Scheme 6. Cu^{I} -catalyzed hydroxyimidoylation of aryl diazonium salts.

Another interesting Type I process furnishes 2-borylated indoles **29** from *o*-isocyanostyrenes **28** under Cu^{I} catalysis.^[29] Utilizing boronic esters, rather than aryl halides, the in situ formed borylcopper species **30** undergoes 1,1-migratory insertion of isocyanide **28** to afford imidoyl 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 gave lower yields. The synthetic utility of products **29** was demonstrated by several post-cyclization modifications, including a highly efficient total synthesis of the kinase inhibitor paullone (**33**).

In a related process, the transmetalation of aryl boronic 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 imidoylcopper species **37** (Scheme 8). This is followed by a cyclization and protodemetalation of intermediate **38** to afford the 2-arylated indoles **35**.^[30] The proton source is unclear here, and the authors did



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



Scheme 8. Cu^{II} -catalyzed coupling of isocyanostyrenes with aryl boronic acids.

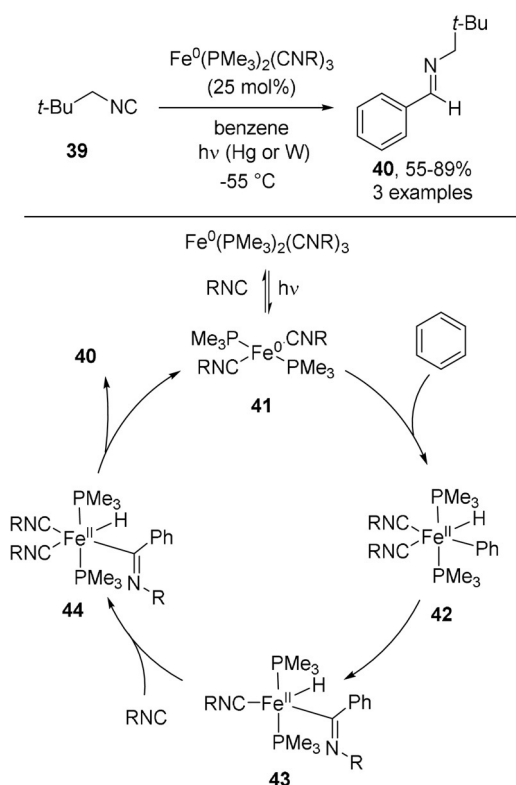
not comment on it. The reaction tolerates electron-donating and electron-withdrawing substituents on both the boronic acid (**34**) and the isocyanide (**28**). However, 2-isocyanostyrenes without an electron-withdrawing group at the conjugated double bond position did not afford the corresponding 2-arylindoles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

2.2. Imidoylations Initiated by C–H Bond Cleavage

Direct C–H functionalization with transition metals is more attractive than the use of preactivated organo-(pseudo)halides in cross-coupling chemistry and can be

considered as a potentially more sustainable process.^[31] Besides oxidative addition, other mechanisms for C–H bond cleavage to form a TM–C bond are possible (e.g., concerted metalation deprotonation (CMD), σ -bond metathesis). Subsequent isocyanide insertion into a TM–C bond then typically occurs through 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,^[32] recently, significant advances have been made in analogous base metal catalyzed processes.

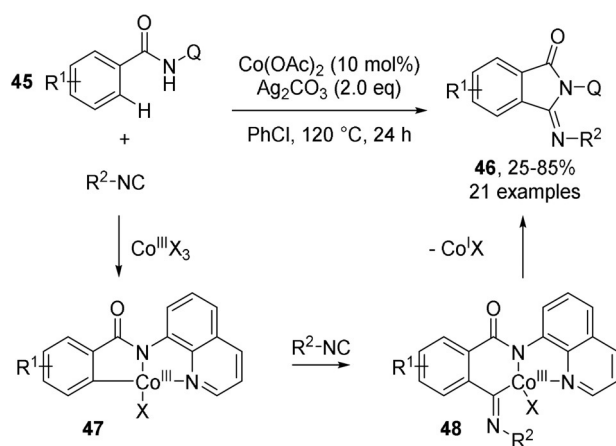
Already in 1987, Jones and co-workers reported the C(sp²)–H activation of benzene by oxidative addition using an electron-rich iron catalyst. Combination of the Fe⁰ catalytic system shown in Scheme 9 with neopentyl isocyanide (**39**) and benzene affords the corresponding aldimine **40**.^[33]



Scheme 9. Aldimine synthesis by Fe⁰-catalyzed imidoylation of arenes.

This reaction also proved successful using toluene or xylene instead of benzene. Curiously, this iron catalyst is deactivated when the irradiation is stopped. The authors propose a light-induced dissociation of isocyanide to the catalytically active Fe⁰(RNC)₂(PMe₃)₂ complex **41**. Increasing the isocyanide concentration leads to formation of Fe(RNC)₃(PMe₃) via ligand exchange, inhibiting imidoylation.

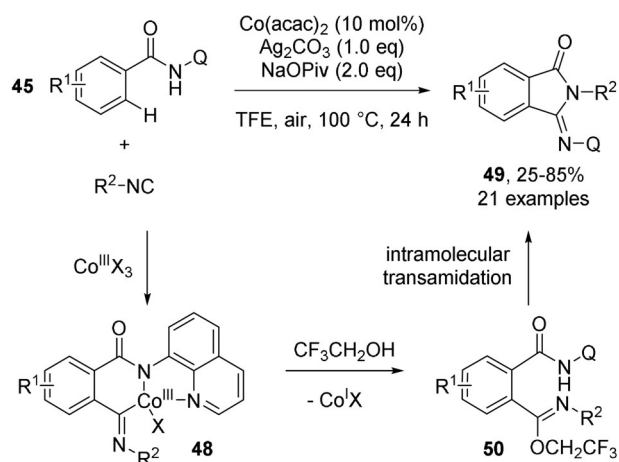
The first cobalt-catalyzed imidoylative process involving C–H activation was reported in 2017. In this process, iminoindolinones **46** were obtained from benzamides **45** by employing Ag₂CO₃ as the optimal stoichiometric oxidant (Scheme 10).^[34] The oxidant brings the cobalt salt to the required oxidation state. The bidentate 8-aminoquinoline functionality is essential and serves as a directing group,



Scheme 10. Co^{III}-catalyzed amidoimidoylation of benzamides in chlorobenzene. Q = 8-quinolinyl.

presumably initiating the formation of cobaltacycle **47**. Though not mentioned, C–H cleavage presumably occurs through a CMD mechanism. Only *t*-BuNC and 2,6-xylyl isocyanide were used successfully in this transformation.

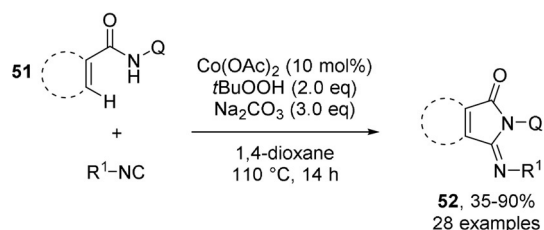
The use of weakly acidic trifluoroethanol (TFE) as a solvent yields other products from benzamides **45** (Scheme 11).^[35] Interestingly, under these conditions, another iminoindolinone isomer **49** was predominantly obtained. The key step in this reaction is most likely the oxidative alkoxyimidoylation 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 imidoyl–Co^{III} moiety followed by protodemetalation generates intermediate **50** (Scheme 11). The resulting Co^I species are subsequently oxidized by Ag^I to the active Co^{III} species. Subsequent intramolecular transamidation of intermediate **50** furnishes product **49** (Scheme 11). Mechanistic studies to determine the kinetic isotope effects, the addition of a radical scavenger, and experiments with isolated Co complexes



Scheme 11. Co^{III}-catalyzed amidoimidoylation of benzamides in trifluoroethanol. Q = 8-quinolinyl.

support the catalytic cycle put forward. C–H activation is not rate-limiting.

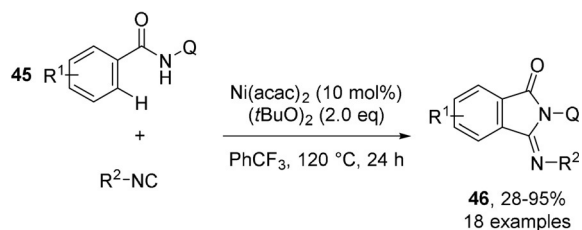
Gu and co-workers reported a similar transformation, employing *t*-BuOOH as an alternative oxidant (Scheme 12).^[36] Their conditions tolerate functionalized



Scheme 12. Co^{III}-catalyzed amidoimidoylation of benzamides and acrylamides. Q = 8-quinolinyl.

acrylamides **51** in addition 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 proposed similar intermediates for this reaction towards **52** as were postulated for the imidoylative C–H functionalization reaction of benzamides **45** described in Scheme 10.

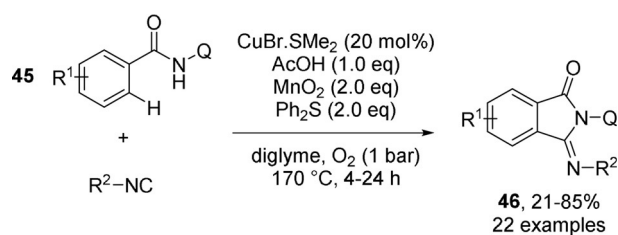
Starting from similar *N*-quinolinylbenzamides **45**, a nickel-catalyzed C–H functionalization is also possible employing *t*BOO*t*Bu as the oxidant, and provides the corresponding iminoisoindolinone **46** in reasonable yields (Scheme 13).^[37]



Scheme 13. Ni^{II}-catalyzed amidoimidoylation of benzamides. Q = 8-quinolinyl.

The 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, the reaction presumably proceeds through a CMD mechanism. No radical mechanism seems to be involved based on TEMPO addition experiments. The reaction is, however, also quite limited in terms of the isocyanide scope (R^2 = xyllyl or *t*-Bu).

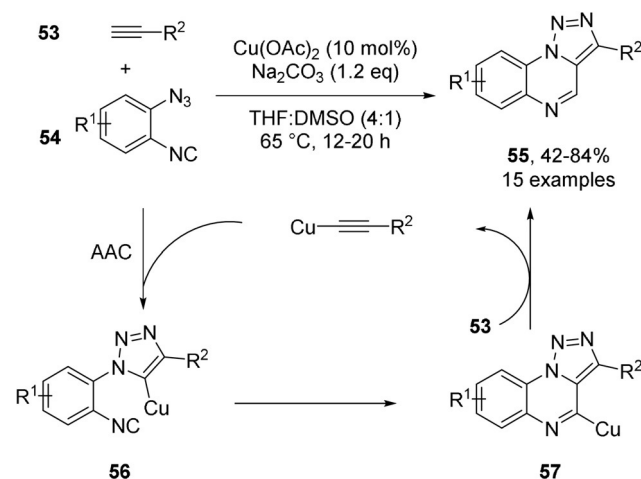
The first copper-catalyzed imidoylative C–H functionalization was reported by Miura and co-workers (Scheme 14). Compared to the above Co- or Ni-catalyzed processes, this Type I imidoylative reaction requires harsher conditions and higher catalyst loadings.^[38] The type and stoichiometry of the additives was optimized experimentally although their role



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

remained 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 xyllyl and tertiary aliphatic isocyanides proved successful.

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).



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

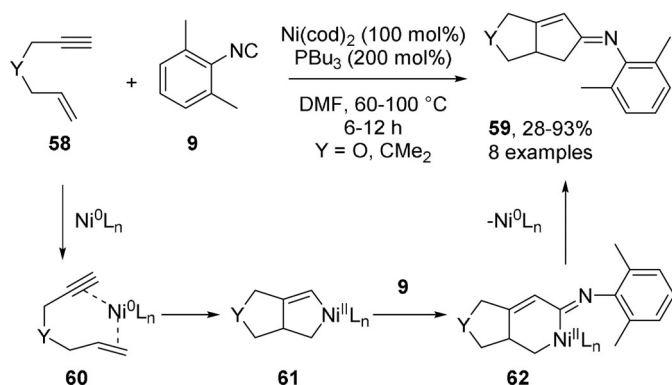
The cycloaddition of azide **54** and an in situ formed copper-alkynyl species followed by intramolecular isocyanide insertion facilitates formation of the organocopper intermediate **57**. The triazoloquinoxalines **55** are generated by subsequent protodemetalation with terminal alkynes, concomitantly regenerating 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.^[39] The authors reported extensive Rh-catalyzed follow-up chemistry with the reaction products.

2.3. Imidoylations Initiated by Cyclometalation

Cycloadditions are widely appreciated as effective C–C bond-forming reactions.^[40] In particular, the Pauson–Khand reaction is a well-known cycloaddition involving CO as a C₁

reactant.^[41] In relation to this, we discuss in the Section 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, and generate relatively high levels of complexity in a single step. The insertion step proceeds through 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 co-workers (Scheme 16).^[42] The reaction presumably proceeds through

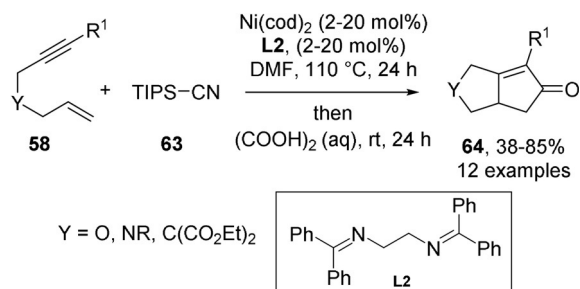


Scheme 16. Ni⁰-mediated imidoylative Pauson–Khand-type reaction to generate enimes **59**.

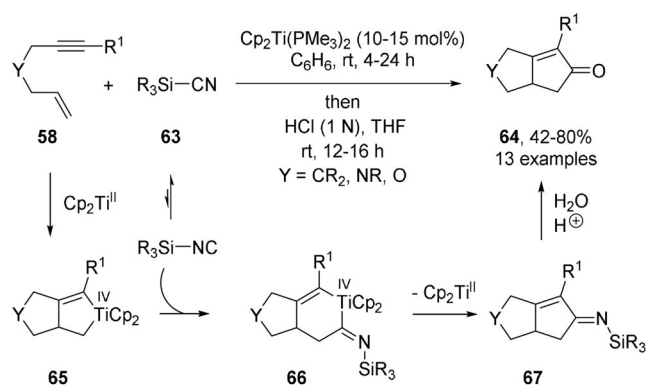
coordination of the enyne (**58**) to the Ni⁰ center followed by oxidative cyclometalation to furnish intermediate **61**. Subsequent Type I 1,1-migratory insertion of xylyl isocyanide (**9**) affords imidoyl nickel intermediate **62**, which can undergo reductive elimination to afford product **59**. As excess isocyanide poisons the Ni⁰ catalyst, stoichiometric Ni(cod)₂ is required to bring the reaction to completion.

A variant of the same reaction was reported by Buchwald and Zhang (Scheme 17).^[43] 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 Ni⁰ catalyst.

Imidoylative Pauson–Khand-type reactions have also been reported with other metals as exemplified by a titanocene(II)-catalyzed process (Scheme 18).^[44] Again, to prevent inhibition, the isocyanide concentration was kept low



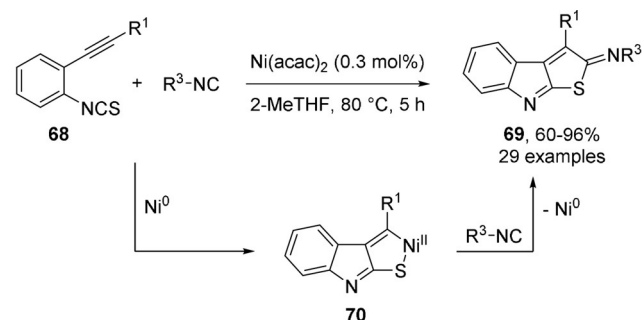
Scheme 17. Ni⁰-catalyzed imidoylative Pauson–Khand-type reaction with silyl cyanides.



Scheme 18. Ti^{II}-catalyzed Pauson–Khand-type reaction with silyl cyanides.

by employing silyl cyanide **63**. Post-cyclization hydrolysis gave the corresponding bicyclic enones **64** in good yields.

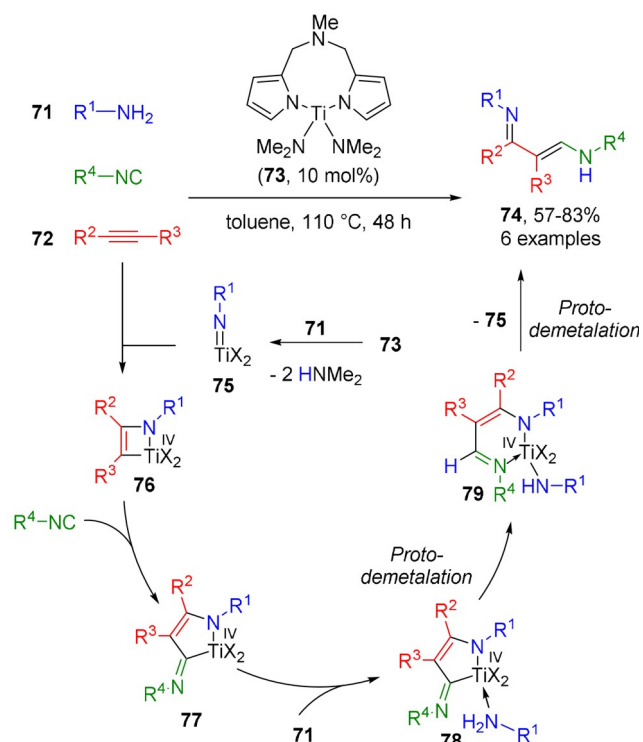
A hetero-[2+2+1] Pauson–Khand-type cycloaddition of 2-alkynylaryl isothiocyanates **68** and isocyanides yields thieno[2,3-*b*]indoles **69** (Scheme 19). The cyclonickelate in-



Scheme 19. Ni⁰-catalyzed imidoylative hetero-Pauson–Khand-type reaction.

intermediate **70** is formed by oxidative cycloaddition.^[45] Control experiments indicated that the active catalyst is indeed a Ni⁰ species, which is generated in situ from the Ni^{II} precursor without addition of an external reducing agent. Notably, the catalyst loading is low, but the reaction still tolerates a rather broad range of aliphatic, aromatic, and α -acidic isocyanides. The yield is somewhat lower for the notoriously unstable naphthyl isocyanide (60%), but in general this transformation proceeds with high efficiency.

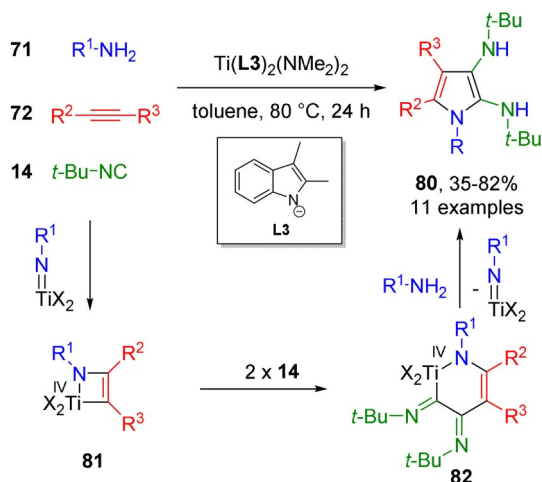
Odom and co-workers reported a three-component reaction of amines, internal alkynes, and isocyanides to give enaminoimines **74**, catalyzed by titanium catalyst **73** (Scheme 20).^[46] With unsymmetrical alkynes, the regioisomers of **74** depicted in Scheme 20 were formed in moderate to good (1.2:1–6:1) selectivity. The reaction proceeds via a meta-thesis-like process of an alkyne (**72**) with the in situ formed titanium nitrene **75**, forming azatitanacyclobutene **76**.^[47] Subsequent isocyanide insertion affords imidoyl intermediate **77**. This intermediate can undergo double protodemetalation by another amine (**71**) to furnish 1-azadienes **74** and regenerate the titanium nitrene **75**. These enaminoimines **74**



Scheme 20. Ti^{IV} -catalyzed three-component reaction of amines, alkynes, and isocyanides.

are precursors to various chemically and medicinally relevant heterocycles.^[48]

Interestingly, when another titanium(IV) catalyst is used, a double isocyanide insertion occurs, affording densely functionalized diaminopyrroles **80** (Scheme 21).^[49] 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 and co-workers argued that

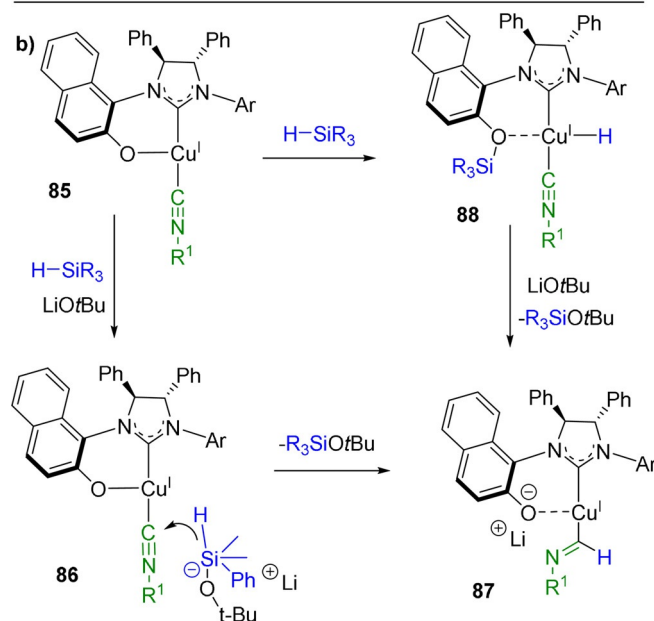
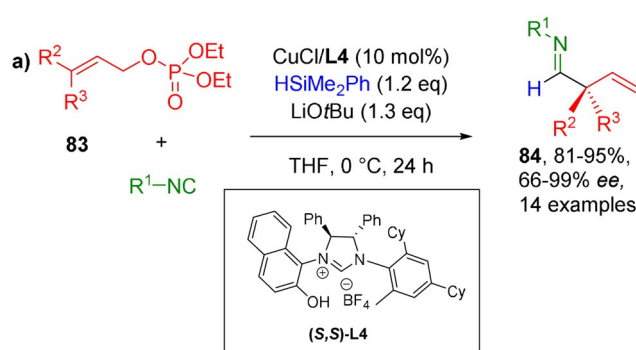


Scheme 21. Ti^{IV} -catalyzed pseudo-four-component reaction to generate diaminopyrroles.

protodemetalation with this ligand system is slower because of 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 tended to react in a three-component reaction comparable to the reaction described in Scheme 20.

2.4. Imidoylations Initiated by Other Processes

In an intriguing report, Sawamura and co-workers disclosed the only known example of a base metal catalyzed isocyanide insertion reaction affording enantioenriched products (Scheme 22 a), by employing Cu^{I} complexed to the chiral NHC ligand **L4**.^[50] While the mechanism was not fully investigated, the authors proposed a Type II process involving hydrosilicate intermediate **86** (Scheme 22 b). However, as the insertion of isocyanides into Cu-H bonds is known,^[51] a 1,1-migratory insertion following a Type I process into copper hydride species **88** cannot be excluded without further studies. Formal enantioselective $\text{S}_{\text{N}}2'$ attack of the organocopper



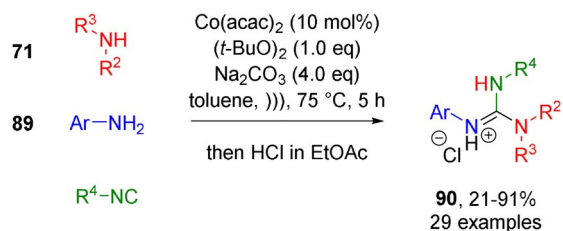
Scheme 22. Asymmetric Cu^{I} -catalyzed synthesis of α -quaternary aldimines employing chiral N-heterocyclic carbenes as ligands.

species **87** onto 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 afforded the corresponding aldimines **84** efficiently. As aldimines derived from non-aromatic isocyanides tend to partially hydrolyze to the corresponding aldehydes during work-up, these aliphatic products required full hydrolysis to prevent the formation of complex product mixtures. As such, the reported yields correspond to the final aldehyde product obtained after hydrolysis.

3. Insertions of Isocyanides into Heteroatom–Metal Bonds

The number of examples in the literature of base metal catalyzed isocyanide insertions involving a TM–Z species where Z is a 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). Applications to the synthesis of several interesting molecular scaffolds have been reported and will be discussed in this Section.

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

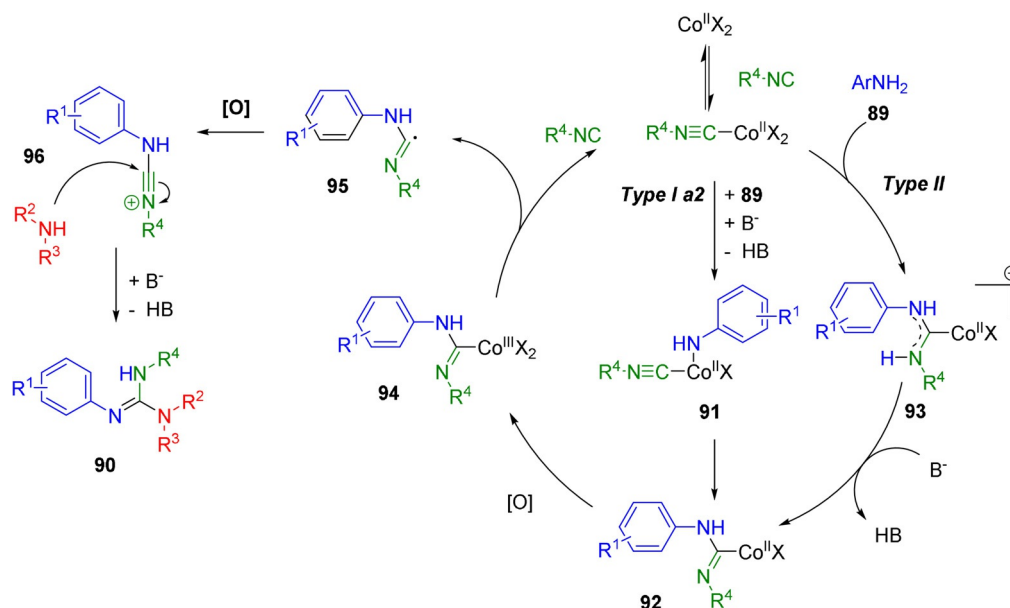


Scheme 23. Co^{II} -catalyzed synthesis of unsymmetrical aryl guanidines.

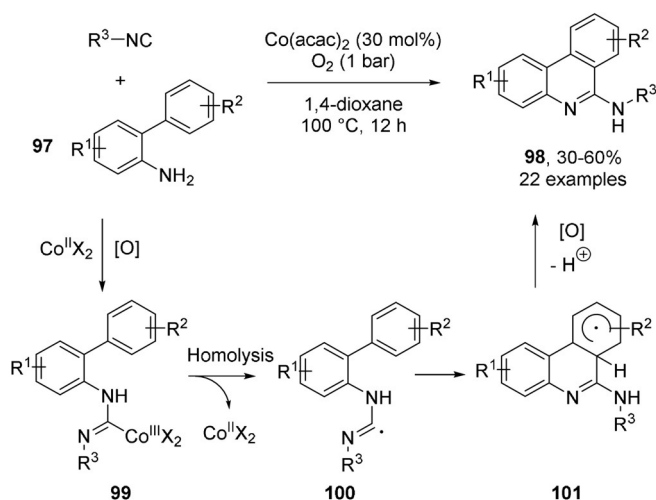
under ultrasound heating (Scheme 23).^[52] The process involves the imidoylative coupling of an aliphatic and an aromatic amine using $(t\text{-BuO})_2$ as the oxidant (Scheme 24). The initially formed aromatic *C*-amidinoylcobalt intermediate **92** can be formed by either a Type I or a Type II pathway. After imidoylation, the authors suggested 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 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**.^[53]

In 2014, Zhu et al. devised a novel approach to the construction of benzo-fused 2-aminoquinolines **98**.^[54] 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 proposed that subsequent homolysis of the cobalt–carbon bond in Co^{III} species **99** furnishes amidinoyl radical **100**, which undergoes an intramolecular homolytic aromatic substitution (HAS), affording the biologically valuable 6-aminophenanthridines **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.

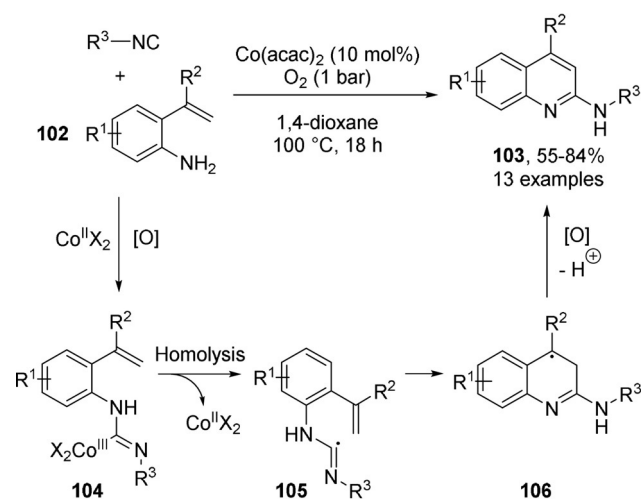
A similar radical relay process was used to access 2-aminoquinolines **103** by using the vinyl group of *o*-aminostyrenes **102** as the radical acceptor (Scheme 26).^[55] Although this reaction proceeds via a similar mechanism as described in Scheme 25, in this case, only tertiary isocyanides led to efficient formation of 2-aminoquinolines **103**. The authors performed radical trapping experiments with TEMPO and



Scheme 24. Proposed catalytic cycle of the Co^{II} -catalyzed synthesis of unsymmetrical aryl guanidines.



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

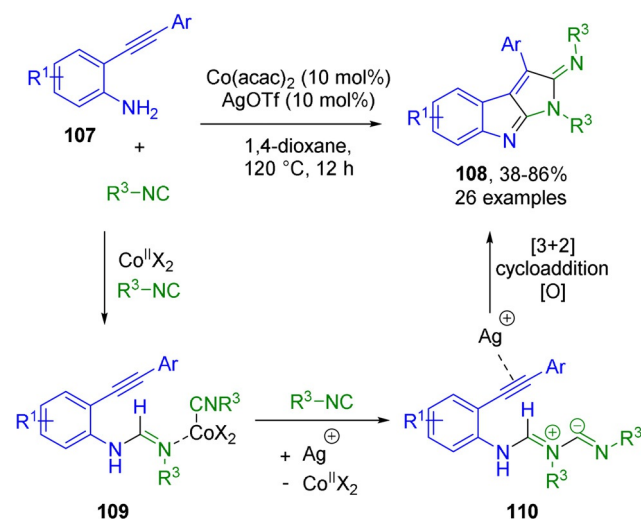


Scheme 26. Co^{II} -catalyzed aminoimidoylation cascade process towards 2-aminoquinolines.

indeed detected the TEMPO–**105** adduct by LC-MS analysis together with a trace amount of product **103**. The authors claimed that this suggests the involvement of a radical process. However, in the studies discussed in Schemes 24 and 25, no further detailed mechanistic investigations were reported in this respect.

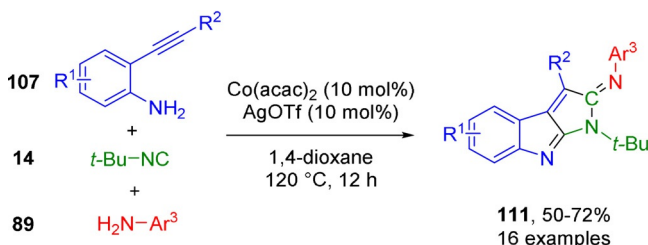
An interesting cobalt-catalyzed double insertion/silver-catalyzed [3+2] cycloaddition cascade approach to iminopyrroloindoles **108** was reported by Gao and co-workers.^[56] Formamidine **109** is formed by isocyanide insertion into an anilincobalt species, formed from 2-alkynylaniline **107** and $\text{Co}(\text{acac})_2$. Subsequently, the authors proposed 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 the uncoordinated forma-

midine in intermediate **109** was subjected to the standard reaction conditions with 1.1 equiv of isocyanide, product **108** did form in excellent yield, which makes the involvement of intermediate **109** plausible (Scheme 27). Initially, the corre-



Scheme 27. $\text{Co}^{\text{II}}/\text{Ag}^{\text{I}}$ tandem catalysis to iminopyrroloindoles.

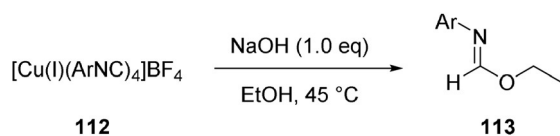
sponding pyrroloindoles are formed, but these oxidize rapidly under air to the observed fused iminopyrroloindoles **108**. The reaction tolerates both aromatic and aliphatic isocyanides. However, an aromatic substituent on the alkyne is required. More recently, the same group extended this protocol to a three-component reaction. By adding an additional aniline (**89**), product **111** was obtained in a thermodynamically and kinetically favored transimination (Scheme 28).^[57]



Scheme 28. $\text{Co}^{\text{II}}/\text{Ag}^{\text{I}}$ tandem catalysis/transimination cascade to **111**.

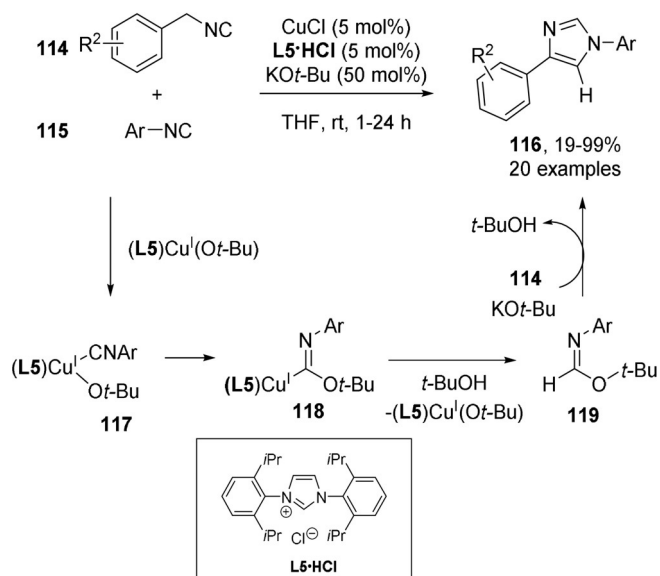
In relation to this, it is perhaps surprising that already in 1974 Knol and co-workers showed that formimidates **113** can be formed by insertion of aryl isocyanides into the O–H bond of ethanol (Scheme 29).^[58] The mechanism has remained largely uninvestigated, but the authors proposed a nucleophilic attack of ethoxide onto the copper-coordinated isocyanide (complex **112**; Type II, Scheme 1b). Several kinetic experiments indeed appear to support this hypothesis.

Similar in situ formed imidates can be used in a one-pot Van Leusen-type formal [3+2] cycloaddition with α -acidic benzyl isocyanides.^[21a] Here, 1,3-diarylimidazoles **116** are formed in high yields and with high chemoselectivity under



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

Cu^{I} catalysis (Scheme 30). Only highly electrophilic aromatic isocyanides (**115**) are sufficiently electron-deficient to be efficiently transformed into the intermediate imidates **119**,

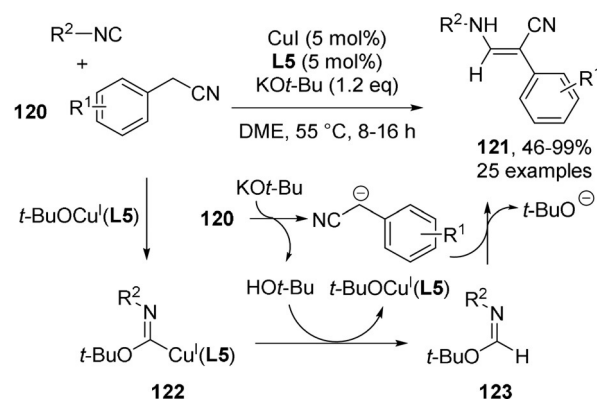


Scheme 30. *N*,3-Diarylimidazole synthesis by a Cu^{I} -catalyzed alkoxyimido-ylation/[3+2] cycloaddition cascade.

which undergo the subsequent cycloaddition with α -acidic benzyl isocyanides **114**. Both experimental results and in silico investigations suggest that the K^+ counterion is essential to obtain high yields of **119**. Various substituted benzyl and aryl isocyanides afford imidazoles **116** in moderate to excellent yields. Additional DFT calculations indicate that the energetic difference between possible Type I 2a and Type II insertion (Scheme 1 a, b) in this reaction is less than 1 kcal mol^{-1} , meaning that both can occur.

Another Cu^{I} -catalyzed alkoxyimido-ylation/condensation cascade reaction was reported by Kim and Hong (Scheme 31).^[59] The in situ formed formimidate intermediate **123** condenses with the α -acidic arylacetonitrile (**120**), affording 3-amino-2-arylacrylonitriles (**121**) in moderate to excellent yields.

In addition to the above discussed substrates, bisnucleophiles are also frequently employed for isocyanide insertion processes. The use of bisnucleophiles has been ubiquitous in imido-ylative 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 imido-ylation of bisnucleophiles was first reported by our



Scheme 31. Cu^{I} -catalyzed alkoxyimido-ylation/condensation cascade.

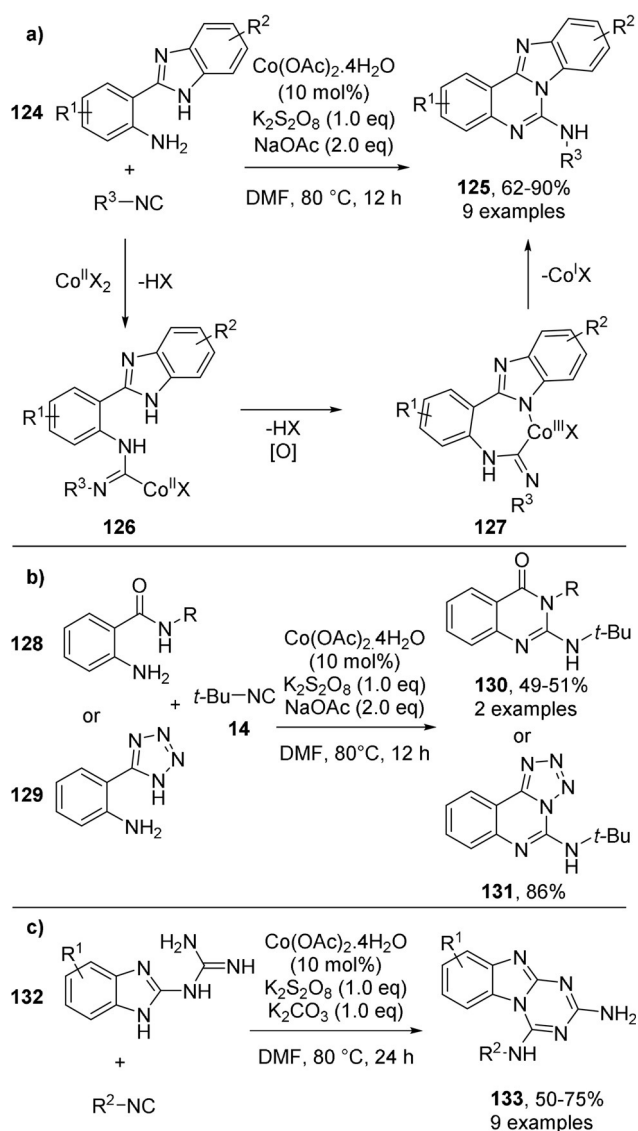
group in 2012.^[60] Since then, various base metal catalyzed variants have been published.

Inexpensive $\text{K}_2\text{S}_2\text{O}_8$ is the preferred oxidant in these reactions. The cobalt-catalyzed insertion of isocyanides into 2-(2-aminoaryl)benzimidazoles **124** (Scheme 32 a) affords benzimidazole-fused 2-aminoquinazolines **125**.^[61] 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 used. In a similar process, 2-(2-aminophenyl)tetrazoles **129** and *N*-(benzimidazol-2-yl)guanidine **132**^[62] proved to be suitable substrates (Scheme 32 b, c). Compared to the Pd-catalyzed process,^[63] cobalt catalysis has a higher tolerance for aliphatic and aromatic isocyanides. Unfortunately, O_2 seems not to be a suitable oxidant.

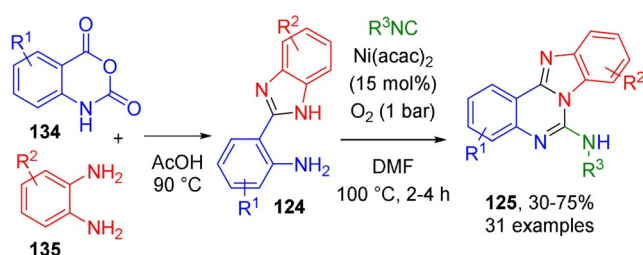
A nickel-catalyzed version with similar substrates **124** was reported to afford aminobenzimidazoquinazolines **125** (Scheme 33).^[64] Interestingly, the scope of isocyanides tolerated by this reaction is broader than that of the comparable cobalt-catalyzed processes discussed in Scheme 32, even tolerating benzylic and α -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% yield.

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

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

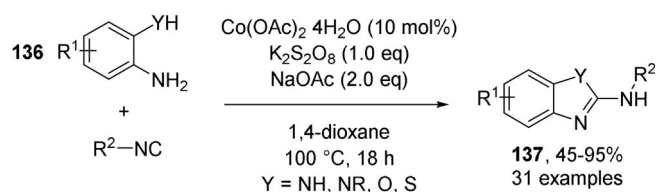


Scheme 32. Fused heterocycles obtained by Co^{II} -catalyzed imidoylation of diamine bisnucleophiles.

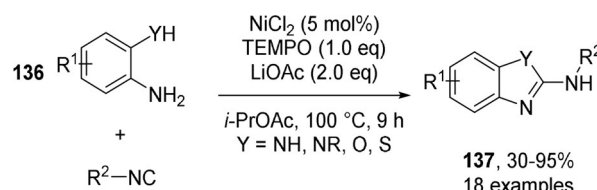


Scheme 33. Ni^{II} -catalyzed imidoylation towards aminobenzimidazoquinazolines (**125**).

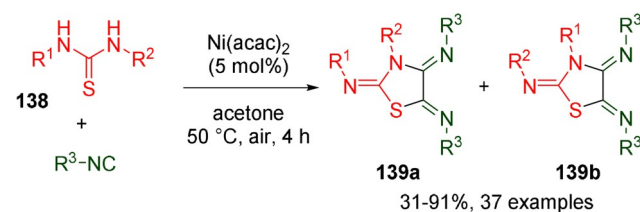
Recently, Li and co-workers reported the first base metal catalyzed aerobic double isocyanide insertion (Scheme 36) to access triiminothiazoles.^[67] The authors proposed that molecular oxygen from air facilitates the oxidation of Ni^0 to Ni^{II} , hereby closing the catalytic cycle. The Ni^{II} -catalyzed reaction tolerates electronically diverse aliphatic and aromatic iso-



Scheme 34. Co^{II} -catalyzed imidoylation of 2-aminoanilines or 2-amino(thio)phenols.



Scheme 35. Ni^{II} -catalyzed imidoylation of 2-aminoanilines or 2-amino(thio)phenols.



Scheme 36. Ni^{II} -catalyzed double isocyanide insertion to 2,4,5-triiminothiazoles (**139**).

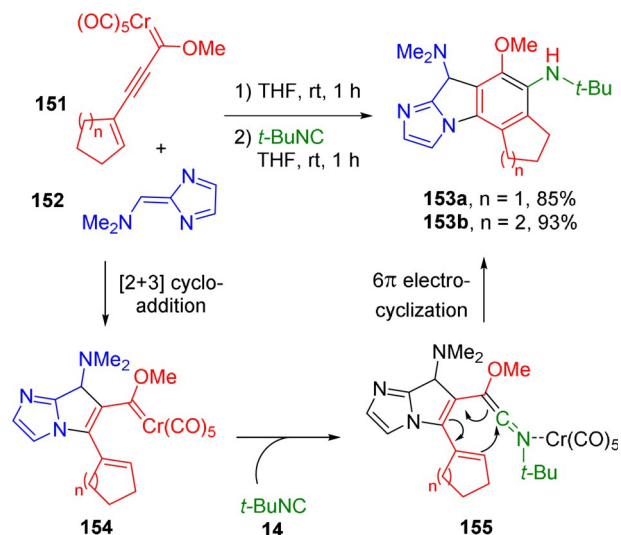
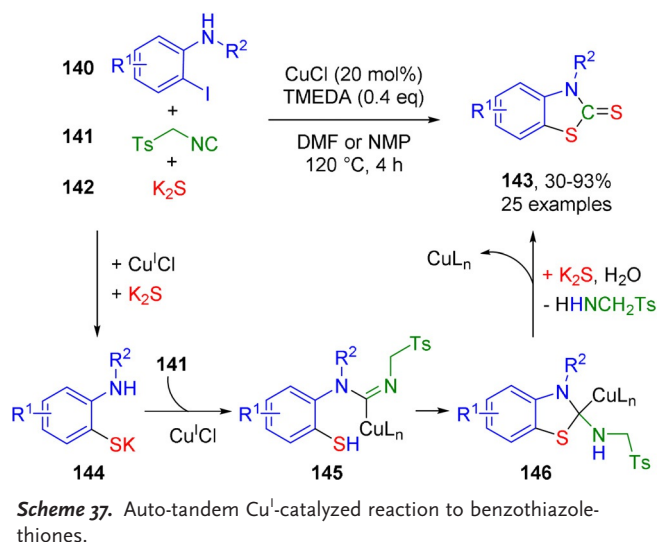
cyanides. Starting from non-symmetrical substituted thiouraeas (**138**), mixtures of regioisomeric iminothiazoles (**139a**/**139b**, 1:1 to 9:1) were obtained in reasonable to good yields.

The final bisnucleophile-based insertion reaction discussed here is the Cu^I -catalyzed synthesis of benzothiazolethiones (**143**) reported by Liang and co-workers. In their reaction, the N,S-bisnucleophile **144** was generated in situ by a non-imidoylative Cu^I -catalyzed Ullmann coupling of iodoaniline **140** and K_2S (Scheme 37).^[68] This is followed by a Cu -catalyzed reaction with isocyanide **141** and K_2S . The oxidation state of copper in the intermediates is unclear. Although the isocyanide in this reaction serves merely as a C_1 donor, the use of toluenesulfonylmethyl isocyanide (**141**) is essential. Employing $t-BuNC$ leads to significant formation of 2-amino-benzothiazoles (**137**; Scheme 35, $R^2 = t-Bu$, Y = S).

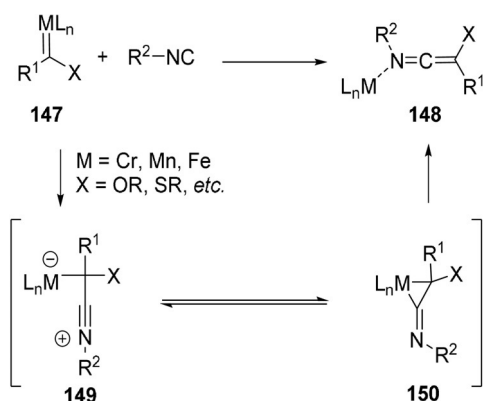
4. Insertions of Isocyanides into $TM=C$ and $TM=N$ Bonds

4.1. Insertion of Isocyanides into Metal Carbene Complexes

Metallocarbenes involving base metals have been used as substrates in reactions with isocyanides. The reaction of an isocyanide with a $TM=C$ π -bond can be categorized as a Type III insertion (Scheme 1c). The general mechanism of the insertion of isocyanides via carbene transfer into the $TM=C$ bond of Fischer carbenes **147** was extensively investigated



in silico by Sierra and co-workers.^[69] They showed that a metallacyclopropanimine intermediate **150** is more likely than the previously considered zwitterionic species **149** (Scheme 38). 1,2-Metallotropic rearrangement of **150** then affords N-metalated ketenimine **148**.^[6a,70]



Scheme 38. General mechanism for carbene transfer to isocyanides.

Although the reported examples make use of stoichiometric metalcarbenes, there is potential for the development of catalytic variants, for example, from diazo compounds, in which the in situ generated ketenimines are immediately used in follow-up reactions.

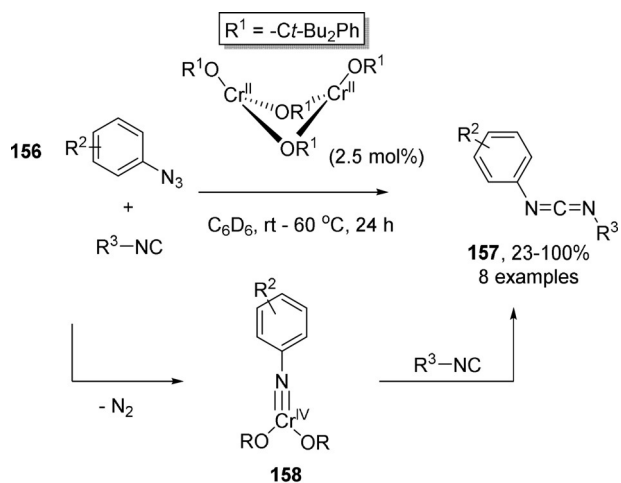
A recent example uses Fischer carbene **151** and gives intermediate species **154** after [3+2] cycloaddition with **152** (Scheme 39). Subsequent isocyanide insertion furnishes the electron-rich ketenimine **155**, which then undergoes a 6 π -electrocyclization to give bis-annulated anisole derivatives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

4.2. Insertions of Isocyanides into Metal Nitrene Complexes

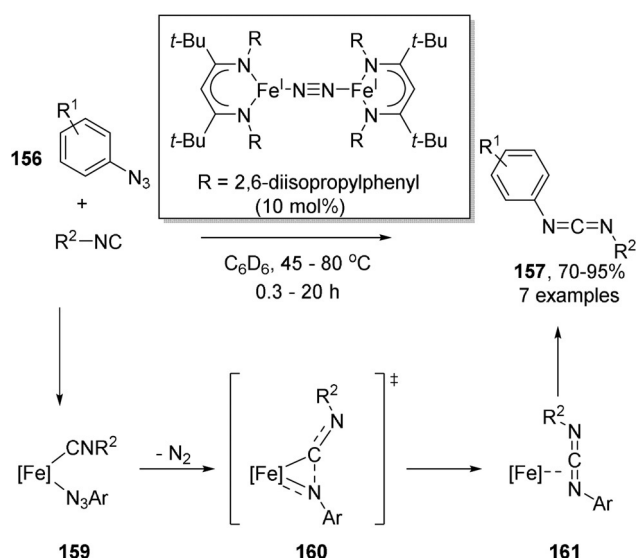
Closely related to the carbene transfer to isocyanides is the insertion of isocyanides into metal nitrene complexes, usually leading to carbodiimides. As metal nitrene complexes are mostly generated in situ from azides, the metal complexes can be used in catalytic amounts. Although some interesting examples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

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.^[72] The bulkiness of both the azide and the isocyanide proved to be highly important. The use of sterically less demanding azides resulted in the formation of an unreactive, saturated Cr^{VI} complex.

Holland and co-workers reported a similar reaction that presumably proceeds via an Fe^I complex of aryl azides **156** and isocyanides (Scheme 41). Mechanistic studies revealed that transition state **160** is involved and that most likely imido



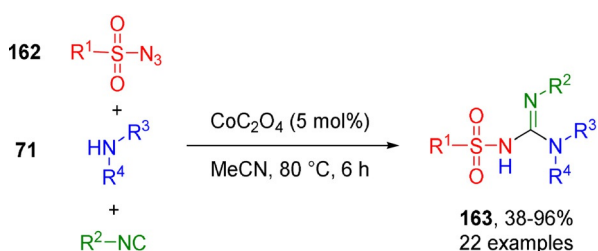
Scheme 40. Cr^{II}-catalyzed carbodiimide formation from aryl azides and isocyanides.



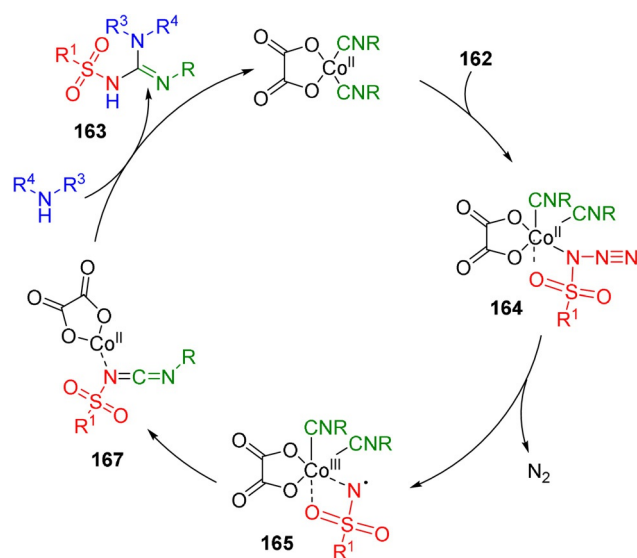
Scheme 41. Fe^I-catalyzed carbodiimide synthesis from aryl azides and isocyanides.

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.^[73] 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 co-workers reported a Ni^I-catalyzed process utilizing similar diamino ligands.^[74] Although the carbodiimides **157** were formed in less reproducible yields than in the Fe-catalyzed process, the reaction with Ni tolerates electronically more diverse azides, such as sulfonyl azides and acylazides. Again, only *tert*-butyl and xylyl isocyanide were employed in this Ni^I-catalyzed process.

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



Scheme 42. Three-component synthesis of unsymmetrical *N*-sulfonylated guanidines by 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.^[75] In this case, the intermediate carbodiimides are trapped with alcohols.

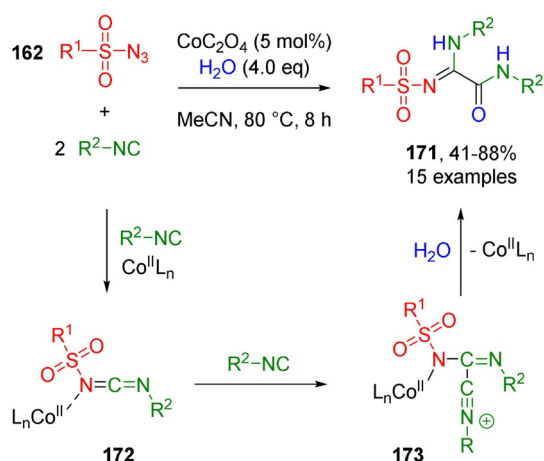


Scheme 44. Co^{II}-catalyzed three-component synthesis of *N*-sulfonyl isoureas.

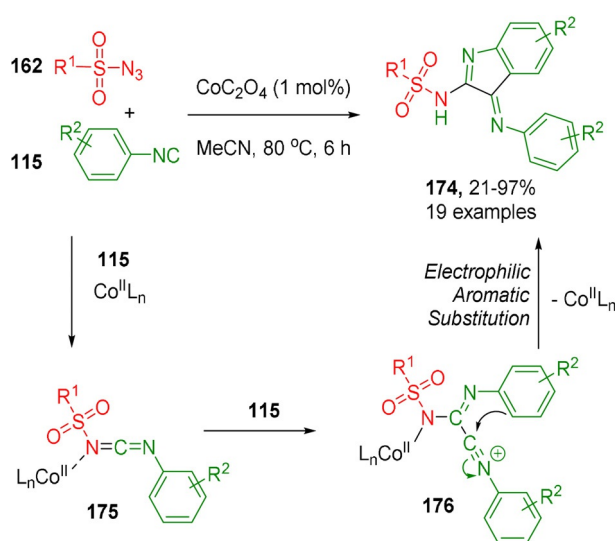
Furthermore, a pseudo-four-component reaction involving two isocyanides, sulfonyl azide, and water affording α -amidoamidines under cobalt catalysis was recently described.^[76] Interestingly, in this reaction, the in situ formed electron-deficient carbodiimide **172** undergoes selective nucleophilic attack by a second isocyanide **2** before addition of less nucleophilic water to nitrilium ion **173** occurs, to give *N*-sulfonyl α -amidoamidines **171** (Scheme 45). On the other hand, utilizing aromatic isocyanides **115** 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.

5. Summary and Outlook

Base metal catalyzed isocyanide insertion processes, although still in their infancy, hold great potential for



Scheme 45. Multicomponent synthesis of α -amidoamidines by Co^{II} catalysis.



Scheme 46. Co^{II} -catalyzed 3-CR to aminoiminoindoles **174**.

applications in organic and heterocyclic synthesis. The (formal) migratory insertion of isocyanides into in situ formed $\text{TM}-\text{C}$, $\text{TM}-\text{X}$, $\text{TM}=\text{C}$, and $\text{TM}=\text{N}$ bonds provides promising pathways to utilize isocyanides as valuable C_1 building blocks in organic synthesis. However, many reports only show applications of rather simple and hindered isocyanides. In particular, the cobalt- and nickel-based reactions discussed here often show a remarkable tolerance for more advanced, functionalized isocyanides. However, when other base metals are used, more challenging unhindered and/or aromatic isocyanides typically cannot be used. This is mainly due to the occurrence of multiple insertions, resulting in competing polymerization. In oxidative processes, the combination with inexpensive oxidants (peroxides, peroxydisulfate, oxygen) has proven quite productive. However, the loading of the base metal catalyst is often still relatively high. On the other hand, toxicity issues related to some specific base metal salts (e.g., for some Co salts) require careful analysis of the alternatives for the traditional noble-TM-based catalytic systems.^[77] To

advance this chemistry towards predictable transformations for synthetic organic chemists, detailed mechanistic studies are of pivotal importance. Most studies reported thus far 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.^[78] 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 thus 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 plays 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.

Acknowledgements

Financial support from The Netherlands Organization for Scientific Research (NWO), the Research Foundation Flanders (FWO; Excellence of Science (EOS) grants G0H0918N and WOG), the Francqui Foundation, and the University of Antwerp (BOF Scholarship to J.W.C.) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

How to cite: *Angew. Chem. Int. Ed.* **2020**, *59*, 540–558
Angew. Chem. **2020**, *132*, 548–566

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Manuscript received: May 10, 2019

Revised manuscript received: July 1, 2019

Accepted manuscript online: July 9, 2019

Version of record online: October 4, 2019