Chem Soc Rev

REVIEW ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Soc. Rev.*, 2022, **51**, 5842

Transition metal-catalysed carbene- and nitrene transfer to carbon monoxide and isocyanides

T. R. Roose, †[a] D. S. Verdoorn, †[bc] P. Mampuys, [c] E. Ruijter, *[a] B. U. W. Maes *[c] and R. V. A. Orru *[b]

Received 26th December 2021

DOI: 10.1039/d1cs00305d

rsc.li/chem-soc-rev

Transition metal-catalysed carbene- and nitrene transfer to the C1-building blocks carbon monoxide and isocyanides provides heteroallenes (*i.e.* ketenes, isocyanates, ketenimines and carbodiimides). These are versatile and reactive compounds allowing *in situ* transformation towards numerous functional groups and organic compounds, including heterocycles. Both one-pot and tandem processes have been developed providing valuable synthetic methods for the organic chemistry toolbox. This review discusses all known transition metal-catalysed carbene- and nitrene transfer reactions towards carbon monoxide and isocyanides and *in situ* transformation of the heteroallenes hereby obtained, with a special focus on the general mechanistic considerations.

1 Introduction

1.1. Group transfer to carbon monoxide and isocyanides

Carbenes and nitrenes are valuable reactive species applied to produce[1] or (late-stage) functionalise[2] various complex organic molecules, including numerous medicinally relevant scaffolds and natural products. Transition metal (TM) catalysis plays a pivotal role in the efficient *in situ* formation of these carbene/nitrene species, starting from mainly diazo (or precursors thereof) compounds (**1**)/azides (**2**), and in fine-tuning their reactivity.[3,4] Typical transformations include the reaction with unsaturated bonds to form cyclopropanes[5] and aziridines,[6] with heteroatoms to form ylides,[7] and the insertion into X–H bonds (X = C, N, O, *etc.*, Scheme 1).[8,9] On the other hand, group transfer of carbenes and nitrenes towards C1-building blocks, such as carbon monoxide (CO) and its isoelectronic counterpart an isocyanide (**5**) (Scheme 1), surprisingly only received attention from the organic chemistry community in the last two decades. In general, CO is well known for its application in TM-catalysis, not only acting as an important ligand in many

[a] *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*
[b] *Organic Chemistry, Aachen-Maastricht Institute for Biobased Materials (AMIBM), Maastricht University, Urmonderbaan 22, 6167RD Geleen, The Netherlands. E-mail: r.orru@maastrichtuniversity.nl*
[c] *Organic Synthesis Division, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium. E-mail: bert.maes@uantwerpen.be*
† These authors contributed equally.

T. R. Roose

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 transition metal-catalysed isocyanide insertions. His current research interests include transition metal catalysis involving isocyanides, and multicomponent and cascade chemistry.

D. S. Verdoorn

Daniël S. Verdoorn obtained his Master's Degree in chemistry in 2021, as a joint-degree title from the University of Amsterdam and the Vrije Universiteit van Amsterdam. In the same year, he started as a joint doctoral student in the research group of Prof. Bert Maes (University of Antwerp) and in the research group of Prof. Romano Orru (University of Maastricht). Currently, his research is focusing on transition-metal catalysed isocyanide insertion, radical isocyanide multicomponent and cascade chemistry.

catalytically active complexes, but also as C1 insertion partner in carbonylative cross-coupling or addition reactions, providing smooth access to carbonyl derivatives.[10] Comparably, isocyanides (**5**) have proven to be valuable C1-building blocks in the construction of imine derivatives *via* TM-catalysed cross-coupling[11] and the stabilisation of catalytic intermediates in catalysis allowing isolation and characterization.[12] More generally, they have found widespread use in the fields of synthetic-organic chemistry[13] in both catalysed and uncatalysed processes, including multicomponent reactions.[14] Furthermore, both carbonylation[15] and imidoylation[16] reactions have shown to be valuable tools towards the synthesis of heterocycles.

The coupling of a carbene or nitrene to CO or an isocyanide provides valuable synthetic intermediates (Scheme 1). More specifically, addition of a carbene to an isocyanide (**5**) results in a ketenimine (**6**), which is a versatile reactive species and can participate in *e.g.* nucleophilic- and radical additions, cycloadditions, electrocyclisations and sigmatropic rearangements.[17] Similarly, the coupling of a nitrene with an isocyanide results in a carbodiimide (**9**), well known for its application in the synthesis of heterocycles and as peptide coupling agent.[18] Similarly, the coupling of CO to a carbene and nitrene provides a ketene (**6**) and isocyanate (**8**), respectively, both considered valuable synthetic building blocks.[19,20] Ketenes are for instance

P. Mampuys

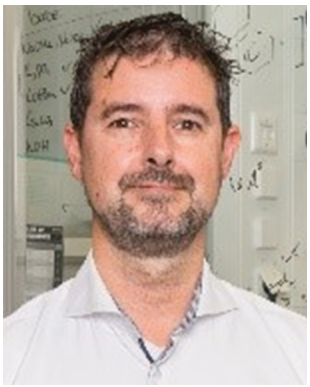
Pieter Mampuys obtained his PhD in organic chemistry both from the University of Antwerp and the Vrije Universiteit Amsterdam under the supervision of Prof. Bert Maes and Prof. Romano Orru in 2017. He also worked at Likat in Germany with Prof. Matthias Beller. From 2018 to 2021 he was appointed as post-doctoral researcher at the University of Antwerp. In 2022 he joined the PCS Chemical Development group at Covestro NV working on phosgene chemistry for polymers. His other research interests include (base) metal-catalyzed multi-component chemistry, organometallics, sulfur chemistry, photoredox catalysis and sustainable method development.

E. Ruijter

Eelco Ruijter (1977) studied Chemistry at the Vrije Universiteit Amsterdam (VUA) and earned his PhD from the VUA and the Leibniz Institute of Plant Biochemistry (Halle/Saale, Germany) under the supervision or Prof. L. A. Wessjohann. After a postdoc in the field of chemistry-based proteomics with Prof. R. M. J. Liskamp at Utrecht University, he returned to the VUA as an Assistant Professor in 2006. After gaining tenure in 2012 and being promoted to Associate Professor in 2018, he was promoted to Full Professor in 2021. His current research interest include transition metal catalysis, cascade reactions, and natural product synthesis.

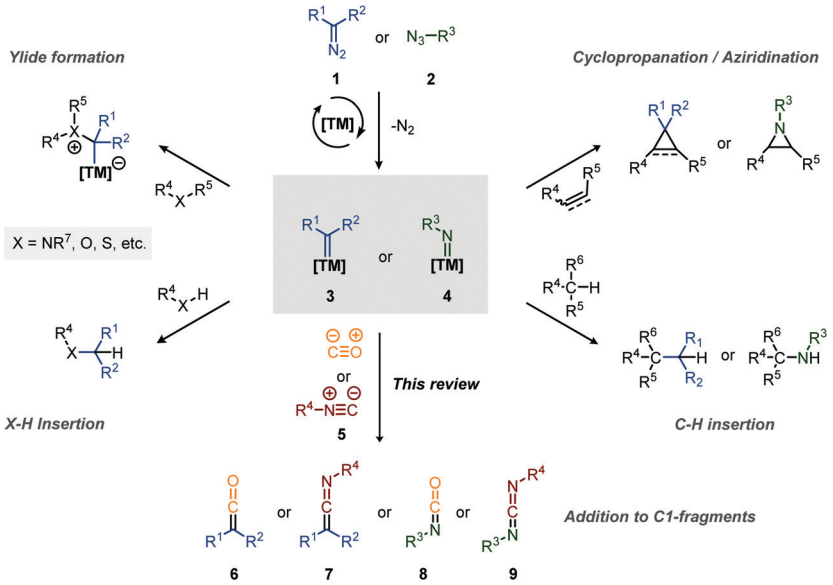
B. U. W. Maes

Bert U. W. Maes obtained his PhD in Organic Chemistry at UAntwerp and subsequently received a Post-Doctoral Fellowship of the Research Foundation in Belgium (FWO – Flanders). He worked at the Hungarian Academy of Sciences in Budapest (G. Hajós) and at the Ecole Normale Supérieure in Paris (A. Jutand). In 2003 Maes was appointed Assistant Professor in the Department of Chemistry at UAntwerp. Currently, he is a Full Professor and spokesman of the Excellence Center CASCH of UAntwerp. In 2019 he was awarded a Collen-Francqui Research Professorship by the Francqui Foundation. His research interests cover the fields of organic synthesis, organometallic chemistry, homogeneous catalysis, and sustainable chemistry. Maes is an editor of Topics in Heterocyclic Chemistry and an editorial advisory board member of SynOpen, Advances in Heterocyclic Chemistry and ACS Sustainable Chemistry & Engineering.



R. V. A. Orru

After my PhD in organic synthesis (1995; Agricultural University Wageningen, NL) I worked on biocatalysis (1996–2000; Technical/Karl-Franszens University Graz, Austria). I continued my independent career at the Vrije Universiteit Amsterdam becoming chair of Synthetic & Bioorganic Chemistry (2007). In 2019, I moved to the Aachen-Maastricht Institute for Biobased Materials (Maastricht University) as professor of Organic Chemistry (2022; Scientific Director). My research focuses on sustainable one-pot cascade reactions and multi-component reactions to synthesize efficiently (poly)heterocycles for therapeutics, materials and catalysis. For this review my world-leading expertise in isocyanides as versatile C1 building blocks in metal-catalyzed insertion reactions is most relevant.



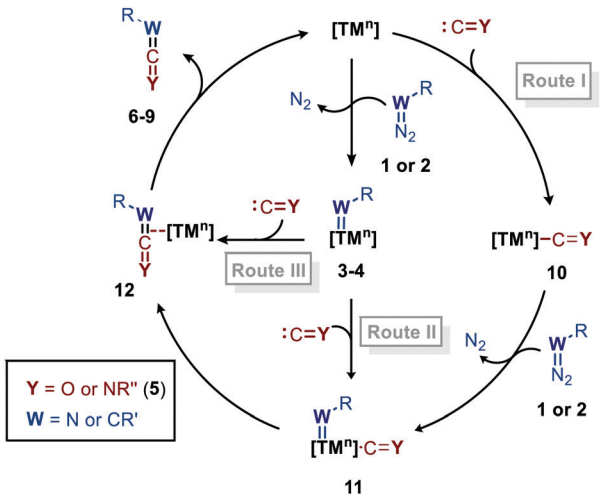
Scheme 1 Overview of common transformations involving transition metal-carbene (**2**) and -nitrene (**3**) species.

involved in the synthesis of β-lactams antibiotics[21] while isocyanates have found major industrial application in the formation of polyurethanes.[20b,22] The value of the polyurethane market was estimated to be around USD 65.5 billion in 2018.[22] Therefore, carbene- and nitrene transfer to CO or isocyanides serve as a foothold for the development of novel cascade processes, exploiting *in situ* formed heteroallene **6–9** as building blocks. This review will highlight such transformations.

1.2. General mechanistic considerations

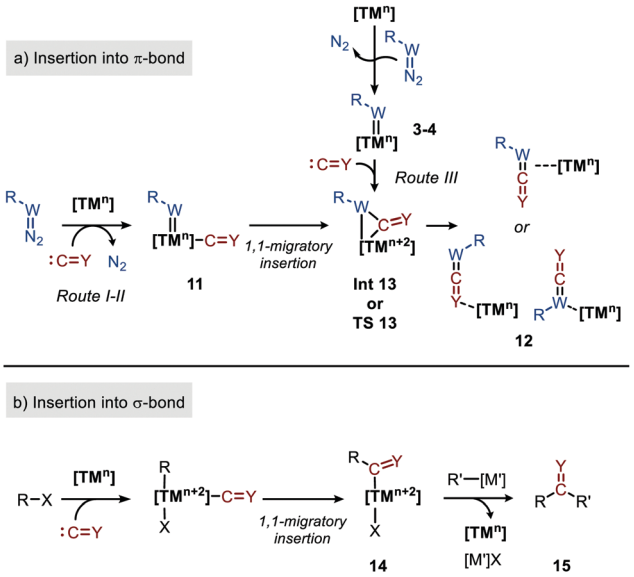
Before highlighting the recent developments in carbene and nitrene group transfer reactions to carbon monoxide and isocyanides affording heteroallenes **6–9**, we will first discuss in this section a general mechanistic rationale based on the available literature. Our analysis is summarized in the cycle depicted in Scheme 2. The general catalytic cycle shows multiple potential pathways.

As both CO and isocyanides (**5**) readily coordinate to TMs,[23,24] route I commences with the formation of the corresponding CO or isocyanide coordinated complex **10**. Important to note is that although CO and isocyanides are isoelectronic the latter are less π-accepting and more sterically hindered affecting TM complexation. Subsequent reaction of diazo compounds and azides with **10** results in the carbene/nitrene coordinated complex **11**. Another possibility is the reverse, *i.e.* formation of the carbene/nitrene complex **3–4** prior to coordination of the C1-fragment, also providing intermediate **11** (route II). In general, TM–carbene and TM–nitrene species are accessed *via* the corresponding diazo-type compounds (**1**) or azides (**2**), respectively, involving extrusion of molecular nitrogen. However, other carbene and nitrene precursors can also be applied, although less frequently encountered in the field of group transfer to CO and isocyanides. Subsequently, formal 1,1-migratory insertion in complex **11** results in the corresponding



Scheme 2 General catalytic cycle for the carbene/nitrene transfer to CO and RNCs.

η^2-coordinated metallacycle **13** as shown in Scheme 3a. However, intermediate **13** may alternatively also serve as transition state in certain catalytic systems[25] towards metallated heteroallene **12**, of which several coordination modes are depicted.[26] The migratory insertion step in intermediate **11** to **13** can be considered as a formal insertion of either CO[3c] or isocyanide[11c,23] into a TM = CRR′ or TM = NR π-bond. Carbonylative and imidoylative transformations relying on the formal 1,1-migratory insertion of CO or isocyanide into a TM-C σ-bond also exists,[10,11,27] forming TM-acyl/imidoyl species **14** (Scheme 3b). Both route I and II in Scheme 2 rely on 1,1-migratory insertion *via* the transfer of metal bound C = Y species towards the carbene/nitrene moiety in complex **11**. Alternatively, non-metal bound species C = Y can be transferred to the coordinated carbene/nitrene moiety *via* an outer sphere



Scheme 3 1,1-Migratory insertion of species C = Y (Y = O, NR″ (**5**)) into: (a) TM = W (W = CR′ (**3**), N (**4**)) double bonds and; (b) TM–R single bonds.

addition to complex **3–4** (route III in Scheme 2).[4a,28] In all routes I–III, intermediate **13** or TS **13** (Scheme 3a) is involved. However, there are also other less common possibilities and these will be highlighted when applicable in the specific section of this review. From intermediate **13** or *via* TS **13**, complex **12** can be accessed, which consists of linear intermediate **6–9** coordinated to the TM centre. These heteroallenes can be transformed *in situ* with *e.g.* nucleophiles while coordinated to, or after dissociation of, the metal centre. The operative mechanism (route I, II or II) depends on both the type of transfer reaction and the TM catalyst used, as well as on the nature and number of additional ligands on the TM center.

1.3. Organisation of the review

The reactions will be categorized based on the heteroallene formed, *i.e.* ketene (**6**), ketenimine (**7**), isocyanate (**8**), or carbodiimide (**9**). First the carbene transfer to CO (Section 2.1) and isocyanides (Section 2.2) will be discussed followed by the nitrene transfer to CO (Section 3.1) and isocyanides (Section 3.2). In each section the formation of the heteroallene is subdivided according to the transition metal catalyst used. In order to demonstrate the synthetic utility of these valuable linear intermediates, all known examples where these are formed and transformed *in situ* have been included. For every transformation several of the reported examples have been selected and shown in the respective scheme to create an awareness of the reader for the scope. The synthesis of several medicinally relevant compounds will also be highlighted when relevant. The suggested reaction mechanism of the processes is discussed referring to the general proposed cycle in Scheme 2. Substrates in multicomponent transformations will be colour coded to account for the origin of the atoms in the resulting product.

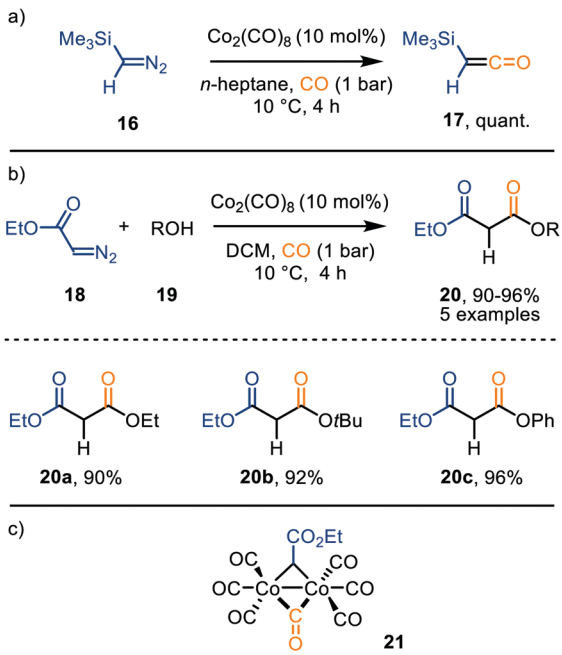
2 Transition-metal catalysed carbonylation and imidoylation of carbenes

In this section, the carbene transfer to carbon monoxide and isocyanides (**5**) will be discussed. Transformations proceeding through linear heteroallene intermediates **6** and **7** (Scheme 1) will be categorized according to the transition metal that was used in heteroallene formation. Mechanistic discrepancies with regard to the general catalytic cycle of Scheme 2 will be highlighted.

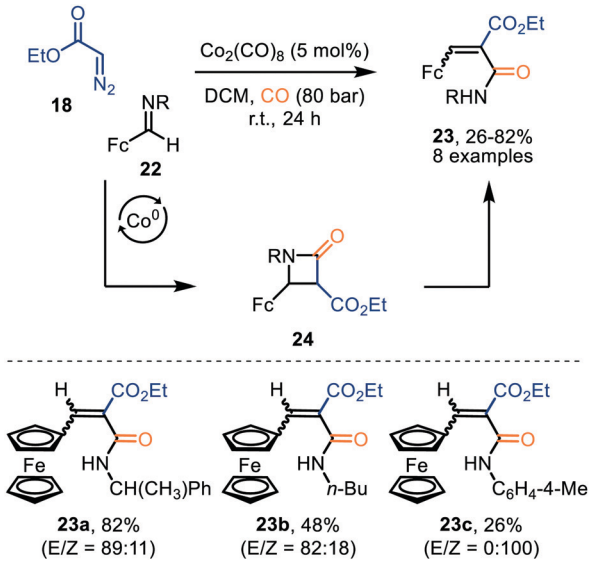
2.1. Carbene transfer to carbon monoxide

Ketenes are considered valuable synthetic building blocks, *e.g.* for the construction of β-lactams *via* [2+2]-cycloaddition with imines.[19b] These are typically accessed *via* Wolff rearrangement of α-diazo ketones or base-mediated elimination of HCl from α-acidic acyl chlorides. However, the TM-catalysed carbene transfer to CO is a valuable alternative for the formation of intermediates **6**. As this topic has been reviewed in 2011 by Wang *et al.*,[29] we will focus on examples reported after 2010. Nonetheless, mechanistically relevant earlier examples will still be briefly mentioned.

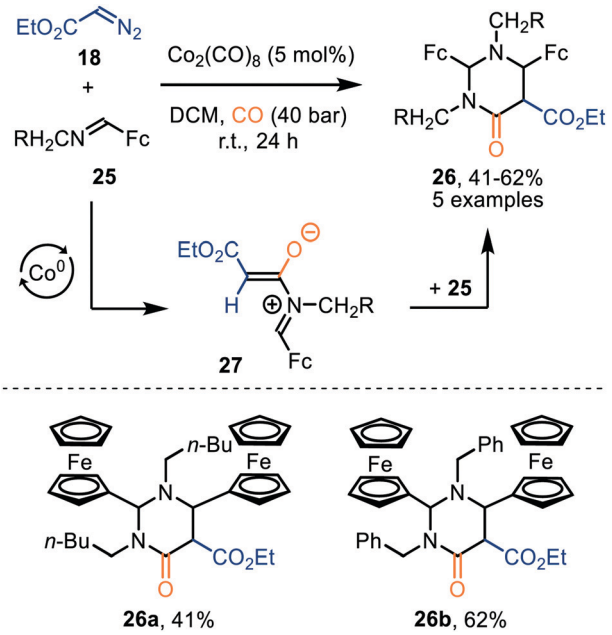
Cobalt. The use of $Co_2(CO)_8$ as base-metal catalyst for the carbonylation of carbenes was nicely demonstrated by Ungváry *et al.* (Scheme 4). The synthesis of trimethylsilylketene **17** from trimethylsilyldiazomethane **16** proceeded in quantitative yield (Scheme 4a).[30] Subsequently, the authors report the formation of malonate derivatives **20** with the same catalyst from α-diazo acetate **18** and anhydrous alcohols **19** (Scheme 4b).[31] The reaction towards malonate derivatives **20** tolerates linear



Scheme 4 Co^0-Catalysed synthesis of (a) trimethylsilylketene **17**, and (b) malonate derivatives **20**. (c) μ^2-Co–carbene intermediate **21**.



Scheme 5 Co^0-Catalysed synthesis of ferrocenyl-α,β-unsaturated amides **23**. Fc = bis(η^5-cyclopentadienyl)iron.



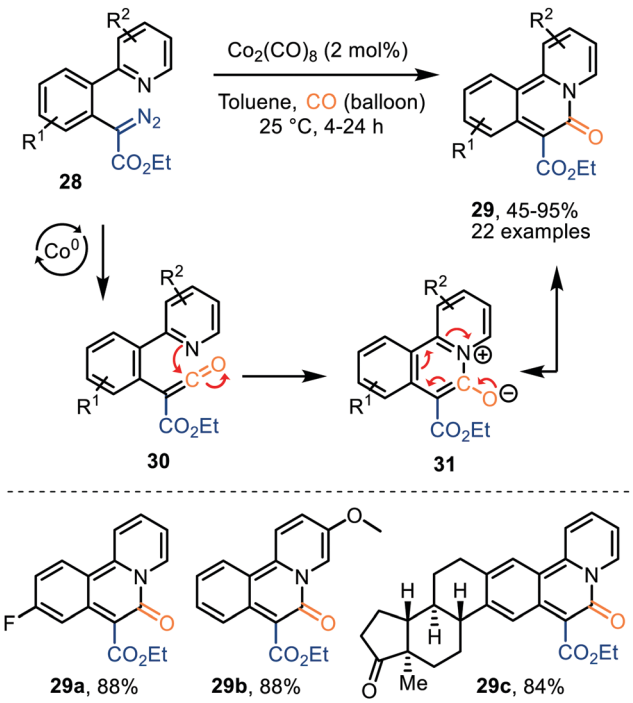
Scheme 6 Co^0-Catalysed formation of tetrahydro-4(1*H*)-pyrimidinones (**26**). Fc = bis(η^5-cyclopentadienyl)iron.

primary and tertiary aliphatic as well as aromatic alcohols to give the corresponding products in near quantitative yield (90–96%). Detailed mechanistic studies indicate that ketene formation proceeds *via* a 1,1-migratory insertion step from bridged Co–carbene intermediate **21** (Scheme 4c).[32] Considering the nature of this catalyst, as the CO fragment is already coordinated to the metal centre, the mechanism follows general route I starting from intermediate **10** onwards in Scheme 2.

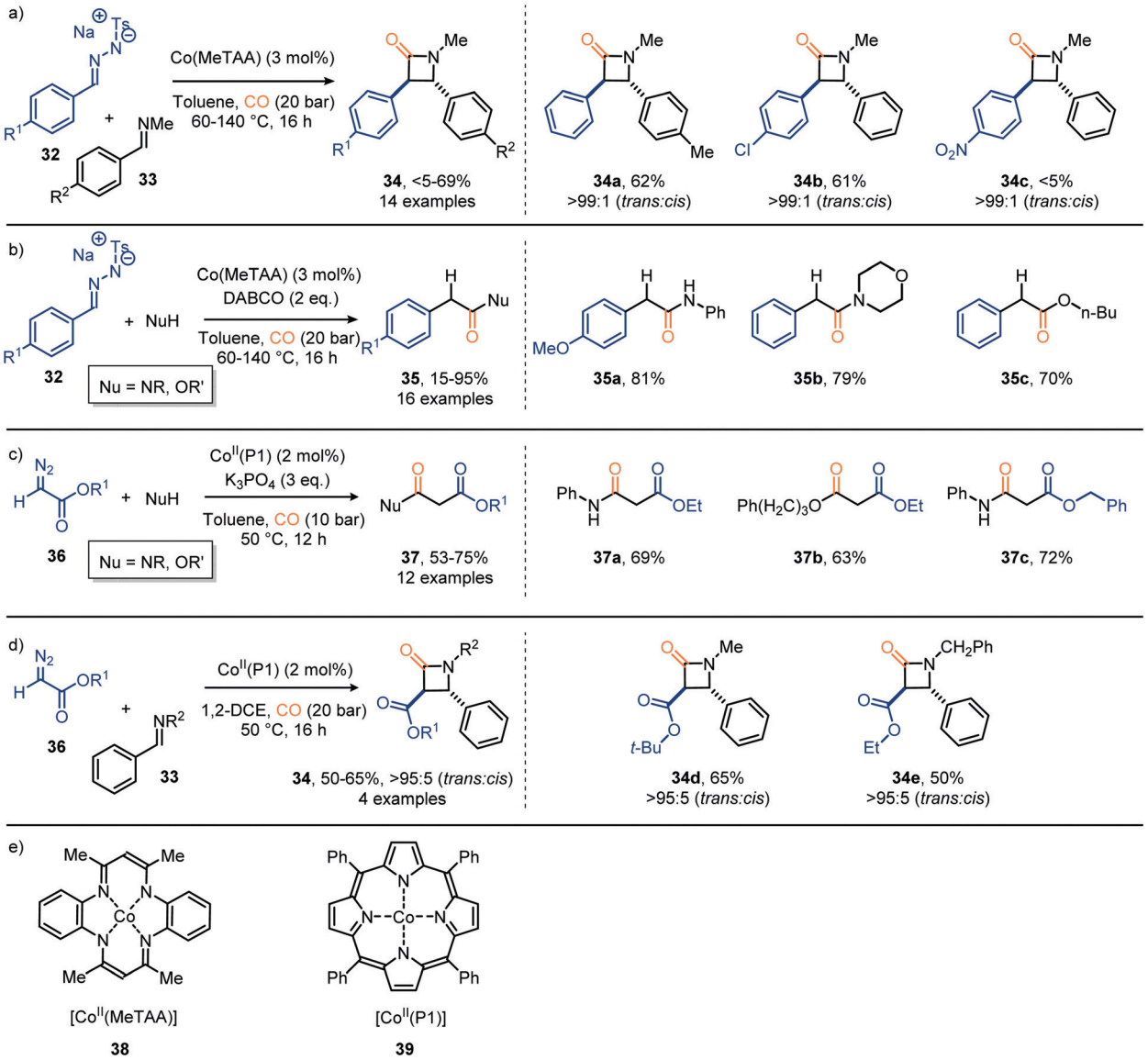
$Co_2(CO)_8$ was also employed for the formation of ferrocenyl α,β-unsaturated amides **23** from ethyl diazoacetate (**18**) and ferrocenyl imine **21**, under high CO pressure (Scheme 5).[33] After CO-catalysed carbonylation of **18**, a [2+2]-cycloaddition occurs between the obtained ketene and imine **22**, generating β-lactam intermediate **24**. The authors highlight that these intermediates **24** are unstable and undergo β-lactam ring cleavage to α,β-unsaturated amides **23**, which were isolated in low to good yields (26–82%). There is precedent in literature that β-lactams rearrange towards the corresponding amide **23**.[34] The transformation tolerates a variety of primary, secondary, tertiary alkyl, and activated aryl substituents on the imine nitrogen.

Interestingly, when a *N*-methylene moiety is present in ferrocenyl imine **25** tetrahydro-4(1*H*)-pyrimidinones **26** are formed as alternative products (Scheme 6).[35a] *N*-Methyleneferrocenylimines **25** (R = alkyl, aryl) were tolerated and products **26** were furnished in moderate yields (41–62%). The formation of the ketenes involved is consistent with our general mechanistic cycle *via* route I (Scheme 2). The reactive species that play a key role in the process are zwitterionic intermediates **27**. Subsequent formal [4+2]-cycloaddition with a second imine **25** affords heterocyclic scaffold **26**. Yields were not optimal as the authors add the diazo ester (**18**) and imine **25** in an equimolar amount.[35b]

Lee *et al.* demonstrated the use of $Co_2(CO)_8$ as catalyst in the formation of pyridoisoquinolinones (**29**) *via* ketene intermediate **30** (Scheme 7).[36] The mechanism complies with route I of our postulated mechanism in Scheme 2, based on the nature of the catalyst. The authors propose that subsequent cyclization of the ketene group with the pyridinyl moiety in **30** provides a zwitterionic pyridinium enolate (**31**), which is in resonance with the product **29**. The presence of both electron-donating and electron-withdrawing -substituents in several positions of α-aryl-α-diazoacetates (R^1 and R^2) **28**, indicates an overall high functional group tolerance for this carbonylative cyclization.

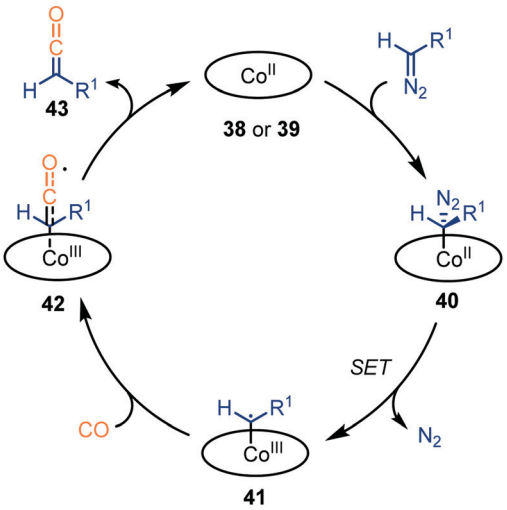


Scheme 7 Co^0-Catalysed formation of benzoannulated pyridin-2(1*H*)-one derivatives **29**.



Scheme 8 Synthesis of (a) β-lactams **34** with [Co(MeTAA)], (b) acyl derivatives **35** with [Co(MeTAA)], (c) malonate derivatives **37** with [Co(P1)], (d) β-lactams **34** with [Co(P1)]. (e) Structure of [Co(MeTAA)] (**38**) and [Co(P1)] (**39**).

Besides $Co_2(CO)_8$ other Co-based catalysts have also been reported to achieve the carbonylation of carbenes staring from diazo compounds and *N*-tosylhydrazones as carbene precursor (Scheme 8). For example, de Bruin *et al.* developed a catalytic route towards β-lactams **34** (Scheme 8a) and acyl derivatives **35** (Scheme 8b) based on Co^{II} tetramethyltetraaza-[1,4]-annulene (Co(MeTAA), **38**, Scheme 8e).[37] Their strategy produces β-lactams in a diastereoselective manner *via* a formal [2+2] cycloaddition of the corresponding *in situ* generated ketene with benzaldehyde imine **33** (Scheme 8a). Electron-donating or halogen substituents (R^1) in the *para*-position of tosylhydrazones **32** as carbene precursor delivered the desired product in moderate yield (33–62%), whereas electron-withdrawing groups were less tolerated. In contrast, electron-withdrawing moieties on the aryl ring of imine **33** (R^2) did not hamper the transformation and delivered the desired β-lactams in moderate yield (36–69%). In addition, the ketene formed from **32** using the same Co^{II} catalyst **38** are compatible with a wide variety of nucleophiles, such as anilines, aliphatic acyclic and cyclic amines primary-, secondary-, and tertiary- aliphatic alcohols, to furnish the corresponding amides and esters **35** (Scheme 8b). Employing catalyst **39**, featuring a related tetra dentate nitrogen ligand, and α-diazo acetate **36** as carbene precursor and nitrogen nucleophiles afforded malonate derivatives **37** (Scheme 8c).[38] The porphyrin-based catalytic system was able to accommodate a broad range of primary aliphatic and aromatic amines, morpholine and a primary alcohol. Next, catalyst **39** was also used in the formation of β-lactams **34**, using diazo ester **36** as the carbene precursor (Scheme 8d).[35] Decent yields were obtained with high *trans* diastereoselectivities (*trans* : *cis* = > 95 : 5). In addition to the use of α-diazo acetate **36**, in both transformations in Scheme 8c and d, *N*-tosylhydrazones also



Scheme 9 General catalytic cycle for the carbene transfer reaction to CO with Co^{II}-catalysts **38** & **39**.

proved suitable carbene precursors in this transformation (not shown).[38]

The authors propose a mechanism, which accounts for both catalysts **38** and **39**, supported by experimental work and DFT calculations (Scheme 9).[37,38] Initially, the diazo compound coordinates to the Co^{II}-centre, resulting in complex **40**. Subsequent extrusion of N_2 *via* SET results in the Co^{III}–carbene radical **41**. Next, CO adds to carbene radical complex **41** *via* an outer sphere mechanism, forming species **42**. Notably, dissociation of the ketene with the [Co^{II}(MeTAA)] complex **38** is less facile than with [Co^{II}(P1)] complex **39**. In case of catalyst **38**, Co^{III}-species **42** can be considered as a short-lived intermediate whereas with porphyrin catalyst **39**, species **42** is found to be a transition state. Subsequently, the liberated ketene **43** can be transformed *in situ*. The mechanism complies with route III of our general proposed catalytic cycle (Scheme 2).

Rhodium. Rhodium was also found to be a suitable metal for the carbonylation of carbenes. De Bruin *et al.* have demonstrated the applicability of cationic Rh^{I}-PNN pincer complex **44** (Fig. 1) for the synthesis of α-amido ester **46** (Scheme 10a), amide **49** (Scheme 10b) or β-lactam **51** (Scheme 10c).[39] Multiple PNN ligands were evaluated, however, catalyst **44** proved to be superior. The *in situ* formed ketenes react either with 4-nitroaniline (**45**) (Scheme 10a and b) or *N*-benzylidenemethanamine **50** (Scheme 10c). A more detailed substrate scope of this carbonylation was not addressed by the authors. Notably, a direct *N*-H bond insertion of the carbene with 4-nitroaniline (**45**) was also observed

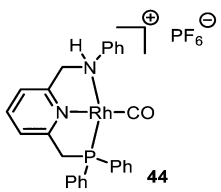
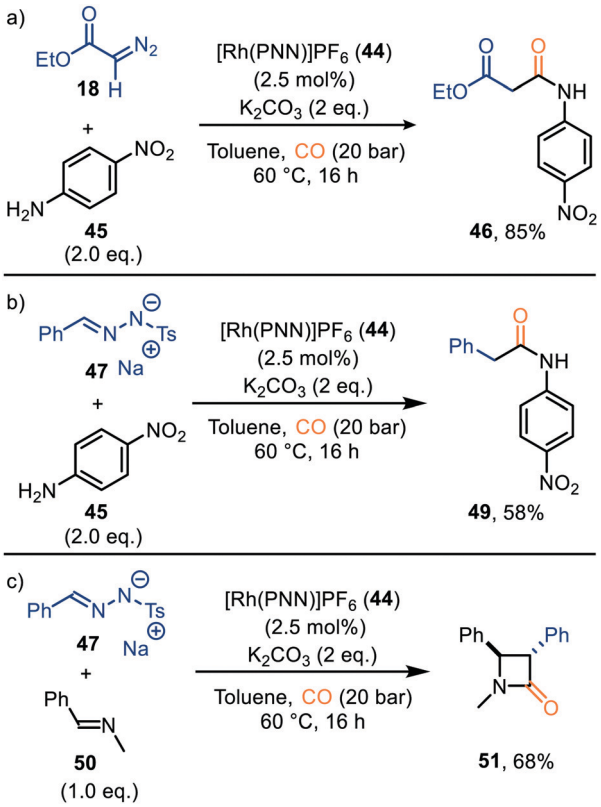


Fig. 1 Rh^{I}-PNN PF$_6$ complex **44**.

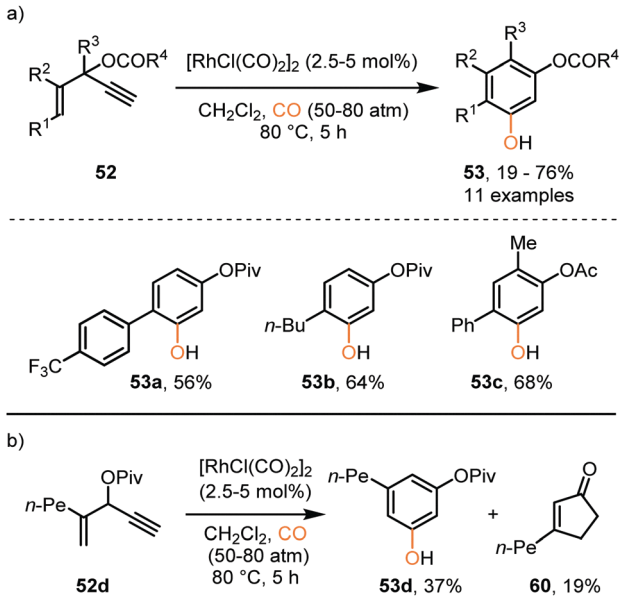


Scheme 10 Formation of (a) malonate monoamide derivate **46**, (b) amide **49**, and (c) β-lactam **51** carbonylation of carbenes catalysed by Rh-PNN PF$_6$ complex **44**.

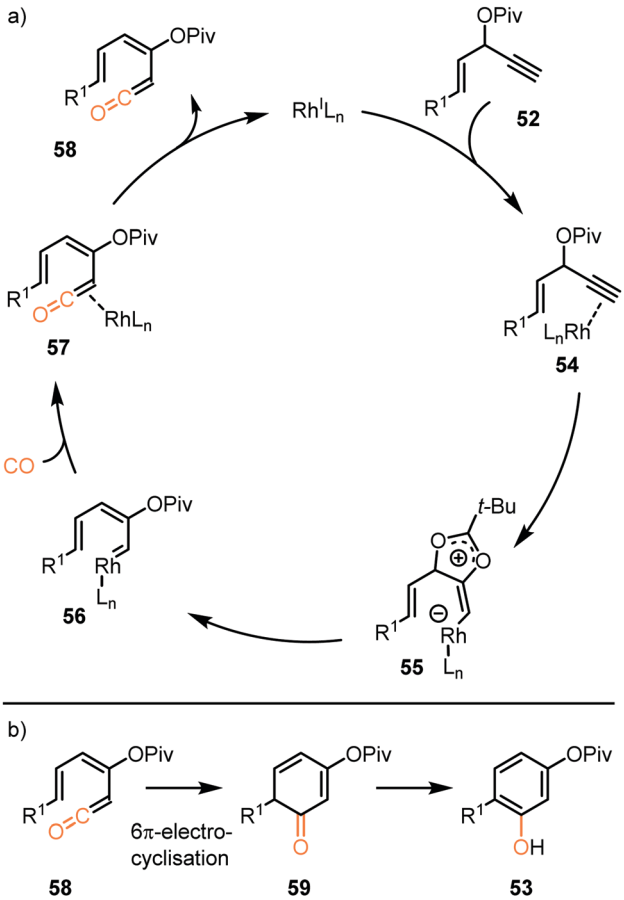
as side product. The mechanism of ketene formation follows the general mechanism in Scheme 2. Although DFT calculations suggest route III is favoured, proceeding *via* an outer-sphere mechanism, routes I and II could not be fully excluded. In this catalytic system, the formation of the metal-carbenoid species is the rate determining step. The η^2-intermediate species (**13**, Scheme 3a) is described by the authors as a Rh^{III}-η^2-CC$_{ketene}$ species, which can be accessed upon 1,1-migratory insertion (route I, Scheme 2) or external attack of CO (route III, Scheme 2).

So far, we discussed only reactions involving carbene sources derived from diazo compounds or deprotonated *N*-tosylhydrazones. However, unsaturated systems can also be efficient precursors. Malacria and co-workers employed 3-acyloxy-1,4-enynes **52** as carbene precursor. An electrophilic Rh^{I}-complex was able to convert **52** and CO to a wide range of mono esterified resorcinol derivatives **53** (Scheme 11a).[40] Various R^1-substituents, such as electron-rich- and electron-poor aromatic groups as well as linear-, and branched aliphatic groups, are accepted and deliver the target resorcinols in poor to moderate yield (19–76%). In addition, primary aliphatic substituents can be decorated on both position R^2 and R^3 of product **53**. Interestingly, for terminal enyne **52d** a non-carbonylated cyclopentenone **60** is in competition with the desired resorcinol derivative (Scheme 11b).

The proposed mechanistic cycle (Scheme 12a)[41] is initiated by electrophilic activation of the alkyne moiety, leading to



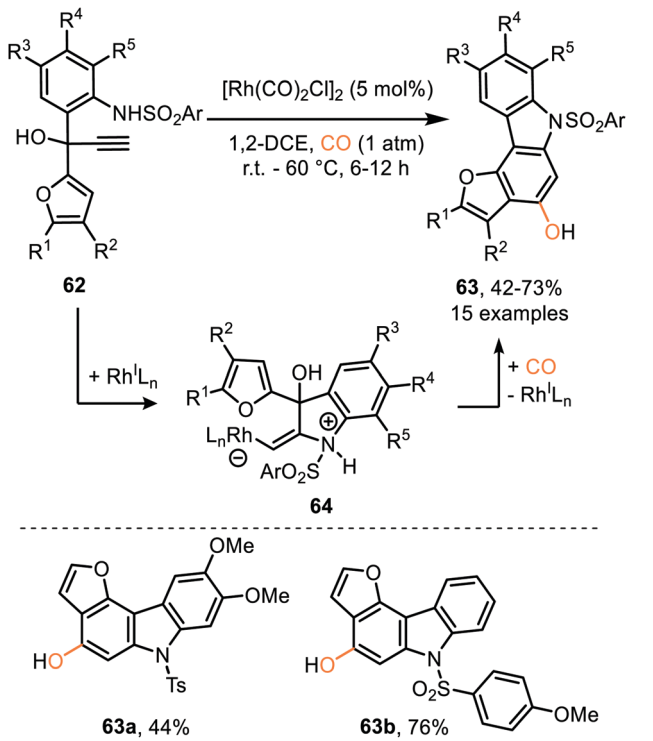
Scheme 11 (a) Rh^{I}-Catalysed [5+1] cycloaddition of 3-acyloxy-1,4-enynes (**52**) with CO. (b) Side reaction that occurs with terminal alkene **52d** forming product **60**.



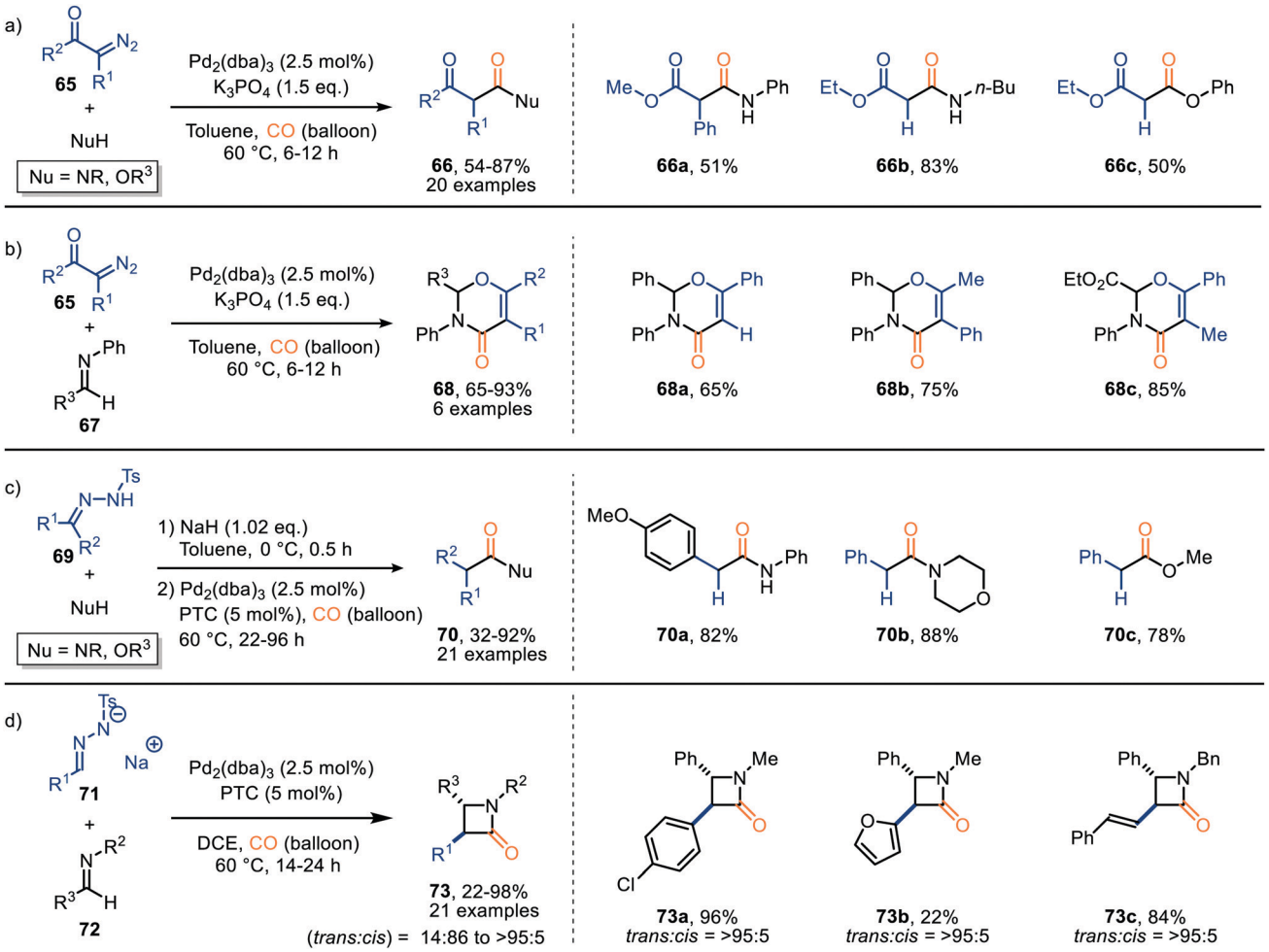
Scheme 12 (a) The mechanism of formation of ketene **58** with carbene precursor **52**. (b) Electrocyclisation of ketene **58**.

an η^2 π-complex **54**. Intramolecular nucleophilic attack from the carboxylate on the activated triple bond affords zwitterionic Rh-complex **55**. Subsequent 1,2-acyloxy migration generates Rh-carbenoid **56**, which in turn undergoes 1,1-migratory insertion with carbon monoxide, finally resulting in Rh-ketene complex **57**. After dissociation from the metal, ketene **58** participates in a 6π-electrocyclization, providing **59** (Scheme 12b), which undergoes spontaneous keto-enol tautomerisation towards aromatic phenol derivative **53**. An important note is that cyclopentenone **60** is produced when the enyne ester has an internal alkyne moiety. This causes the reaction to proceed *via* a 1,3- rather than 1,2-acyloxy migration.

Similarly, Tang *et al.* described a Rh^{I}-catalysed process transforming propargylic alcohol **62** into furo annulated carbazole derivatives **63** (Scheme 13).[42] The sulfonamide moiety performs well with both electron-donating and -withdrawing aryl groups. In addition, the furane and aniline ring could be decorated with a variety of substituents. Furthermore, the furan moiety can be replaced by a pyrrole or thiophene scaffold. The proposed mechanism of carbene formation is similar to the representation in Scheme 12. The crucial difference is the nucleophilic attack of the sulfonamide substituent on the metal activated alkyne of **62** thereby generating zwitterionic Rh-complex **64**, rather than the carboxylate attack in **54** (Scheme 12a) leading to zwitterionic Rh-complex **55**. Elimination of water in complex **64**, Scheme 13, provides Rh carbenoid which upon CO insertion yields ketene. Metal decomplexation and 6π electrocyclisation followed by tautomerisation delivers target compounds **63**.



Scheme 13 Rh^{I}-Catalysed carbene transfer to CO employing **62** as carbene precursor followed by electrocyclisation of ketene.



Scheme 14 Pd-Catalysed carbonylation of carbenes forming: (a) malonate derivatives **66**, (b) 2,3-dihydro-4*H*-1,3-oxazin-4-one derivatives **68**, (c) acylated species **70**, (d) β-lactams **73**. PTC = Aliquat 336 or trioctylmethylammonium chloride.

Palladium. As one of the most chemically diverse and explored noble metals, Pd also proved to be an efficient catalyst in the carbonylation of carbenes. Wang *et al.* described multiple Pd-catalysed carbonylation reactions based on α-diazo compounds **65** which *in situ* generate ketenes (Scheme 14a and b).[43] The authors demonstrate the synthesis of malonate derivatives **66** both from substituted α-diazo ketones and α-diazo esters **65** (Scheme 14a). The formed ketene could be trapped by a range of nucleophiles, such as aniline derivatives, primary, and secondary aliphatic amines, and phenol derivatives. In addition, the ketene could also be trapped with imine **67** in a [4+2] cycloaddition to furnish 2,3-dihydro-4*H*-1,3-oxazin-4-ones **68** in good yield (65–93%) (Scheme 14b).

To further investigate the reaction of ketenes, generated by a Pd-catalysed carbonylation, the authors focused on *N*-tosylhydrazones (**69**), which are *in situ* deprotonated, as carbene precursor (Scheme 14c).[43] With respect to the *N*-tosylhydrazone (**69**) the transformation tolerates aromatic substituents containing electron-donating, and electron-withdrawing groups, biaryl-, and alkyl substituents (R^1 and R^2). Primary, and secondary amines, phenol, and primary alcohols all furnished as nucleophiles providing the corresponding carbonyl compound **70** in moderate to good yields (32–92%). The authors also investigated the use of *N*-tosylhydrazone salts **71** under slightly modified conditions. Ketene formed reacts *in situ* with imine **72** *via* [2+2]-cycloaddition reaction delivering the corresponding β-lactams **73** in moderate to good yield (Scheme 14d).[43] Typically, a high preference for the *trans*-isomer was observed. Especially when α,β-unsaturated *N*-tosylhydrazones were employed (*trans* : *cis* = > 95 : 5). The authors suggest a Pd-assisted isomerisation pathway, which allowed for the interconversion of the *cis*-isomer to the more stable *trans*-isomer of β-lactam **73**. The provided mechanism is based on precedents in literature and DFT calculations. Furthermore, the authors suggest ketene formation to proceed *via* 1,1-migratory insertion where the Pd–CO complex is formed prior to formation of the Pd-carbenoid, which is in accordance with route I in our general proposed mechanism (Scheme 2).

Although several transition metals can catalyse the carbonylation of carbenes, as described in this Section 2.1, the provided examples are still rather limited. As ketenes can undergo a variety of transformations and are reported as intermediates in

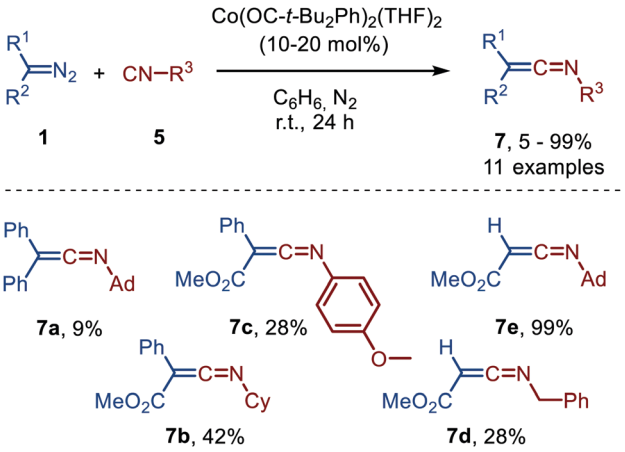
numerous syntheses we believe that further research into its alternative synthesis from metal carbenoids and carbon monoxide will allow for the development of novel cascade processes towards a much broader range of high-value products. While the main focus is still on noble metals, cobalt has been relatively well explored, though successful use of other base metals has not been disclosed. There seems to be a resemblance with other carbonylation reactions here where Co complexes are also common catalysts.[44] Generally Co_2CO_8 is the most common cobalt source and the C1-building block is actually already present in the *in situ* formed catalytic active species without external carbon monoxide supply. Due to the nature of the catalyst the mechanism commences with carbene formation, therefore, reactions catalysed by these complexes are categorized under route I (Scheme 2). So, the nature of the catalyst is important to determine the actual mechanistic pathway *via* which the group transfer proceeds. The same holds for complexes with multidentate ligands such as Co-porphyrin complexes (Scheme 8), where there is no more vacant site to allow for *cis* coordination of the two fragments and, therefore, the carbene transfer to carbon monoxide in this case has to proceed *via* an outer sphere mechanism (route III, Scheme 2). Transition metals in low oxidation state with a lot of d-electrons such as Pd^0 will form strong complexes with carbon monoxide *via* back bonding and therefore favor route I. Clearly, the type of transition metal (early, mid or late) and its oxidation state are at play here. Considering carbon monoxide is a gas the pressure will obviously also play a role in the discrimination between route I and II.

2.2. Carbene transfer to isocyanides

The carbene transfer to isocyanides affords a ketenimine (7) (Scheme 1) and was already discovered in 1919 by Staudinger.[45] Multiple synthetic strategies towards ketenimines have been developed, of which the Wittig reaction with isocyanates is most commonly reported.[17a] Ketenimines display versatile reactivity, in for example nucleophilic and radical additions, cycloadditions and sigmatropic rearrangements. They have shown to be valuable building blocks for the construction of *N*-enriched heterocycles, such as indole-, (iso)quinoline- or carbazole-like scaffolds.[17b] In this section we highlight the formation and *in situ* transformation of ketenimines, accessed *via* the TM-catalysed carbene transfer to isocyanides.

Cobalt. As observed for the carbonylation of carbenes, cobalt is also an efficient catalyst to achieve the carbene transfer to isocyanides (5). For example, Groysman *et al.* demonstrated that a high-valent bis-alkoxy Co^{II}-complex catalyses ketenimine (7) formation from diazo compounds (1) and primary, secondary, tertiary or aromatic isocyanides (Scheme 15).[46]

Unfortunately, poor yields were obtained, when donor-donor carbenes were employed ($R^1 = R^2 = Ph$) and the corresponding ketenimine **7a** could only be obtained efficiently using stoichiometric amounts of Co. Donor-acceptor ($R^1 = Ph$, $R^2 = CO_2Me$) and acceptor ($R^1 = H$, $R^2 = CO_2Me$) carbene precursor smoothly reacted to afford ketenimine **7b**/**7c** and **7d**/**7e**, respectively. The postulated mechanism is based on literature



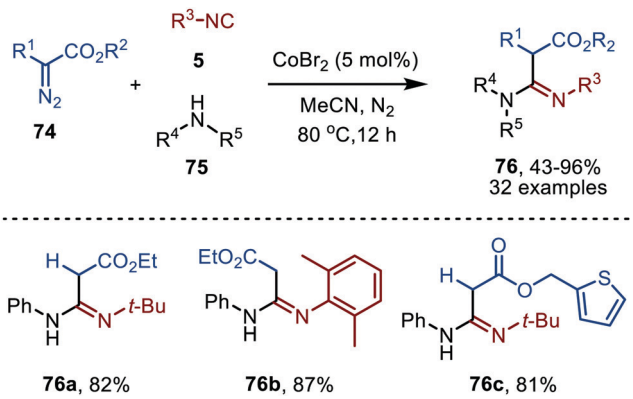
Scheme 15 Ketenimine **7** formation from diazo compounds (**1**) and isocyanides (**5**) catalysed by a bis-alkoxy Co^{II}-complex.

precedents, experimental data, and DFT calculations and is in accordance with route II of the general mechanism (Scheme 2).

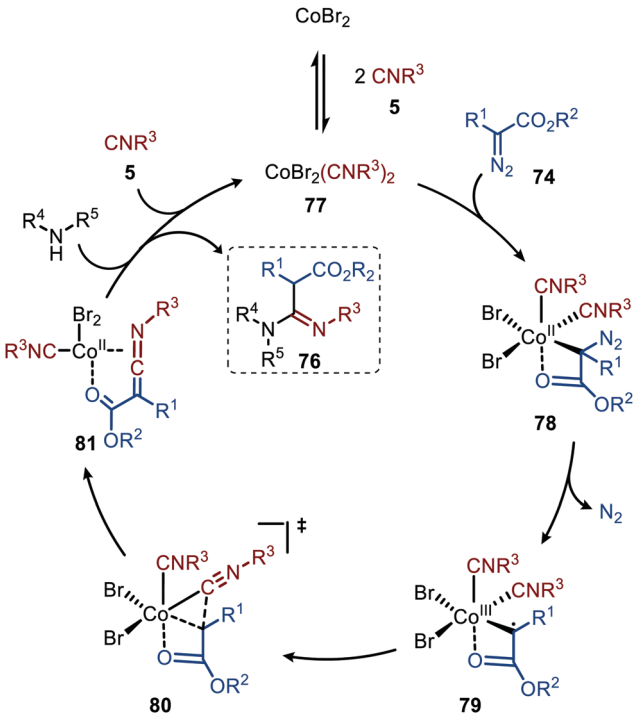
In 2021 a $Co^{II}Br_2$-catalysed carbene transfer to isocyanides was reported, employing α-diazo esters **74** as carbene precursors (Scheme 16).[47] This three-component reaction employs amines (**75**), which capture the ketenimine intermediate to immediately afford amidines **76** in moderate to excellent yield. Notable is that the reaction tolerates tertiary aliphatic isocyanides and aromatic isocyanides as exemplified by amidines **76a**/**c** and **76b**, respectively (Scheme 16).

The authors propose a tentative mechanism, which proceeds *via* Co^{III}-radical species **79**, accessed from complex **78** after nitrogen extrusion (Scheme 17).[47] Radical trapping experiments in the presence of TEMPO support this. The authors suggest that isocyanide complex **77** is formed prior to carbene formation and subsequent migratory insertion, which is in line with general route I of Scheme 2. Control experiments with the isolated ketenimine highlighted that $CoBr_2$ has a dual catalytic role. Besides facilitating the carbene transfer, it also acts as Lewis acid in the activation of the ketenimine in intermediate **81** (Scheme 17).

Nickel. The use of nickel in the carbene transfer to isocyanides was demonstrated by Uyeda *et al.*[48a] Catalytic application

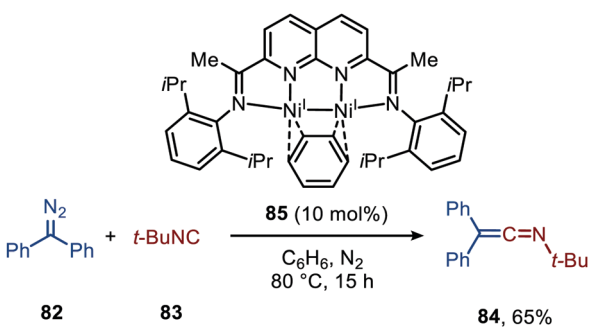


Scheme 16 Co^{II}-Catalysed synthesis of amidines **76** from α-diazo esters (**74**), isocyanides (**5**) and amines (**75**).



Scheme 17 Proposed catalytic cycle of the $CoBr_2$-catalysed carbene transfer to isocyanides (**5**) *via* a Co^{III}–carbene radical intermediate **79** followed by trapping of ketenimine **81** with amine.

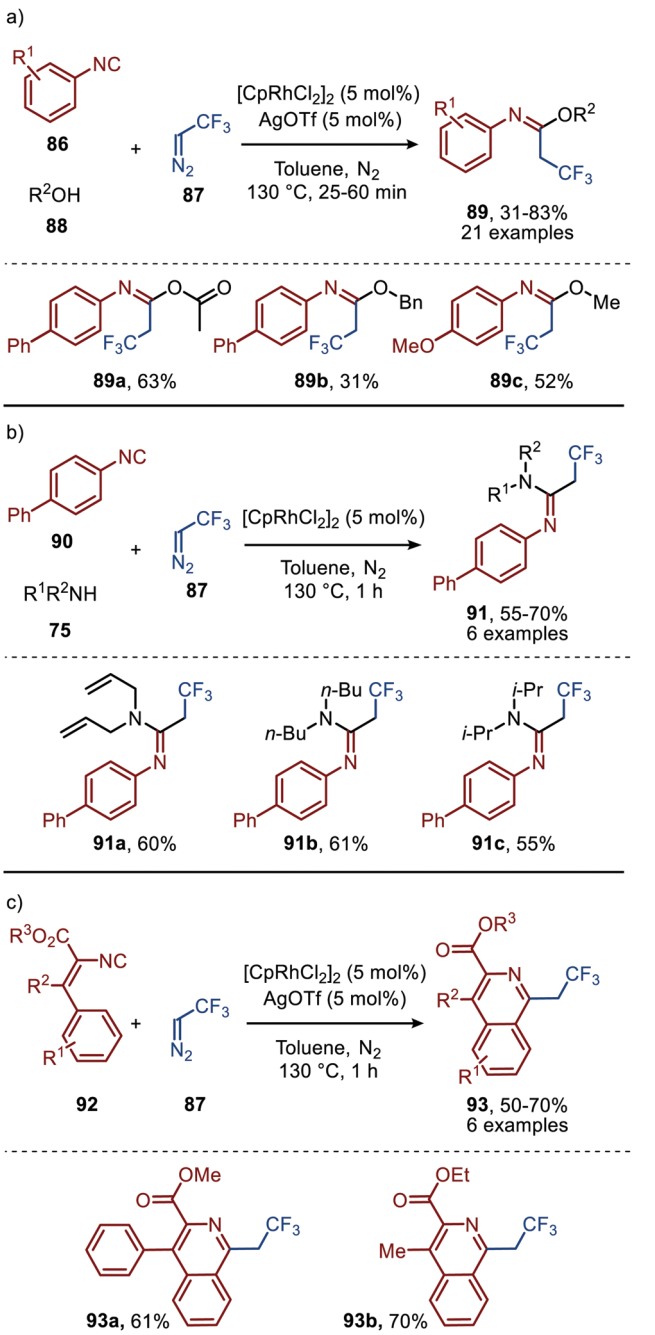
of Ni was feasible using di-nickel(I) complex[48b] **85** in the formation of ketenimine **84** from *t*-BuNC (**83**) and diazodiphenylmethane (**82**) (Scheme 18). However, despite this catalytic example they predominantly discuss the stoichiometric formation of ketenimine **84**, using complex **85**. No extensive optimisation of their catalytic system is reported, and the scope and limitations of the reaction were not studied. The proposed mechanistic pathway is in agreement with route II in Scheme 2. This is based on stoichiometric experiments with the corresponding isolated dinuclear $Ni_2(\mu\text{-}CPh_2)$-complex followed by addition of the isocyanide. The authors state that for catalytic turn over, the isocyanide should be added dropwise over a long period of time. Direct addition of isocyanide **83** results in demetallation and formation of inactive $Ni^0(t\text{-BuNC})_4$. In general, only a handful of examples are found in literature that



Scheme 18 Ketenimine (**84**) formation from diazodiphenylmethane (**82**) *t*-butylisocyanide (**83**) utilising di-nickel complex **85** as catalyst.

describe base-metal catalysed carbene transfer to isocyanides, especially in comparison to the analogous base-metal catalysed carbonylation of carbenes. Therefore, there is plenty of room for further developments within this contemporary area.

Rhodium. Similarly, to the carbonylations discussed in Section 2.1, noble metals have been a major focus of research for the imidoylation of carbenes. For example, Zhao *et al.* reported multiple Rh^I-catalysed carbene transfers based on trifluorodiazoethane (**87**) (Scheme 19a–c).[49] First the authors present a three-component reaction towards imidates (**89**)

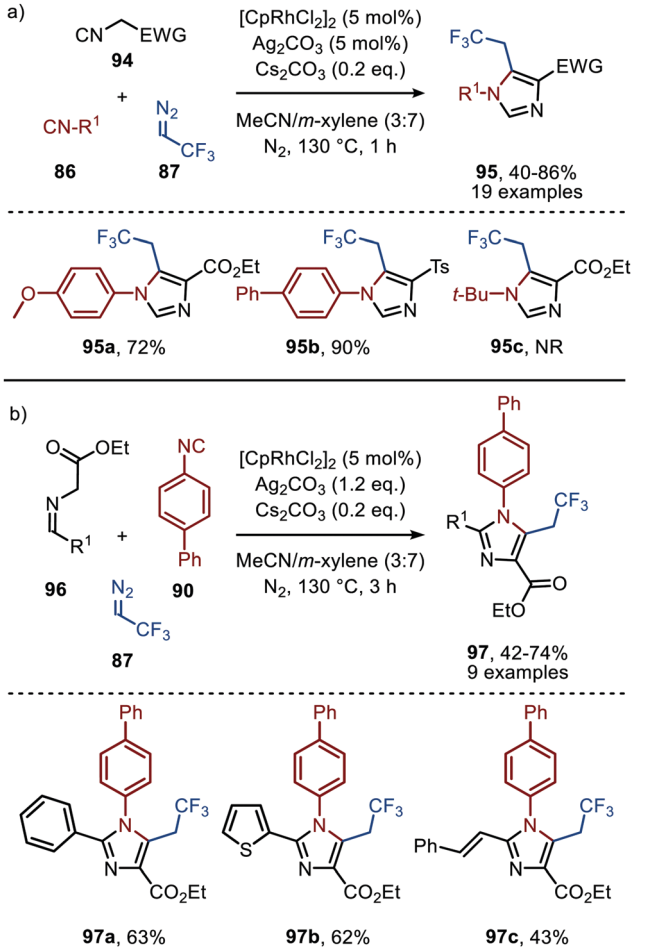


Scheme 19 Rh^I-Catalysed formation of (a) imidates (**89**) (b) amidines (**91**) and (c) isoquinolines (**93**).

using aromatic isocyanides (**86**) and alcohols (**88**) (Scheme 19a). The AgOTf was added as co-catalyst facilitating nucleophilic attack on the *in situ* formed ketenimine. Substituted aromatic isocyanides bearing electron-donating or electron-withdrawing groups are generally accepted. Noteworthy is that the reaction with aliphatic isocyanides did not afford the corresponding imidates (**89**). In addition, the reaction tolerates a wide variety of primary and secondary alcohols furnishing the corresponding imidates **89** in moderate to good yields (31–83%). The alcohols can be decorated with linear, branched, and cyclic alkyl-, allyl-, and benzyl- as well as electron-rich and electron-deficient aryl groups (R^2). Acetate groups also proved to be effective in yielding the desired product **89a** in good yield (Scheme 19a).

The applicability of this tandem reaction was extended towards secondary aliphatic nitrogen nucleophiles (**75**), affording a variety of amidines **91** in moderate to good yield (Scheme 19b), some with functional handles that allow for follow-up chemistry *e.g.* a cyclisation (**91a**, Scheme 19b). No silvertriflate was required due to the increased nucleophilicity of amines compared to alcohols. Furthermore, the authors demonstrate the use of 2-phenylethenyl isocyanide **92** for the synthesis of 2-trifluoroethylisoquinolines (**93**) (Scheme 19c).[49] The reaction proceeds *via* a AgOTf-catalysed intramolecular electrocyclisation of the arene and the corresponding ketenimine, affording heterocycle **93**. The proposed mechanism involves isocyanide coordination prior to carbene formation, which follows route I in our general mechanism (Scheme 2). In continuation of this research the same group reported two additional Rh^I-catalysed three-component reactions towards other heterocycles (Scheme 20a and b), in 2019.[50] The reaction from aryl isocyanides (**86**), 2,2,2-trifluorodiazoethane (**87**), and α-acidic isocyanides (**94**) afforded trifluoroethyl-substituted imidazoles **95** in moderate to good yields (Scheme 20a).

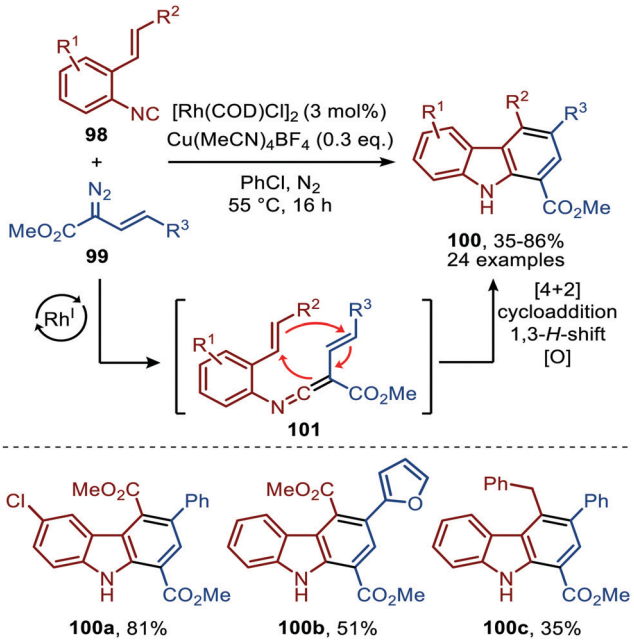
The reaction proceeds *via* selective ketenimine formation between aromatic isocyanide **86** and carbene precursor **87**, followed by an addition of the activated α-acidic isocyanide **94** on the ketenimine intermediate under basic conditions. The authors state that Ag_2CO_3 acts as a Lewis acid in the addition. After a 5-endo-dig cyclization and 1,3-*H* shift imidazoles **95** were obtained. This three-component reaction tolerates a wide variety of aromatic isocyanides (**86**) exceptionally well, but vinyl isocyanides also delivered the desired trifluoroethyl-substituted imidazoles. Unfortunately, the scope of the reaction could not be extended towards aliphatic isocyanides, such as *t*-BuNC (**83**) as illustrated for compound **95c**. Similarly, imidazole scaffolds **97** were obtained from the ketenimine intermediate, formed from aromatic isocyanide **90** and 2,2,2-trifluorodiazoethane (**87**), by reaction with azomethine ylide generated from α-acidic imine **96** with base (Scheme 20b). The cyclisation was followed by a 1,3-*H* shift and oxidative rearomatization with silver carbonate, rationalising it cannot be used catalytically here. The transformation is compatible with a wide variety of R^1 substituents on imine **96**. These groups include electron-rich and electron poor aryls, 1-naphthyl, heteroaryls and alkenes (Scheme 20b). The ketenimine formation presumably proceeds



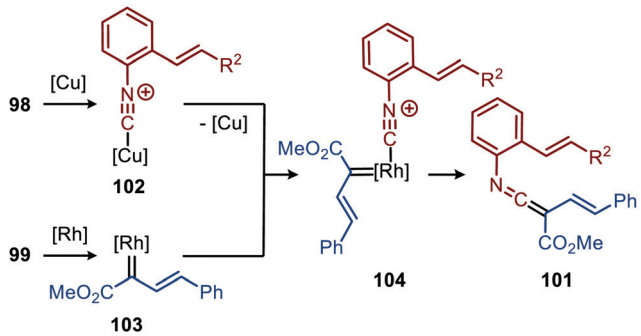
Scheme 20 Rh^I-Catalysed synthesis of trifluoroethyl-substituted imidazoles **95** & **97** based on α-acidic (a) isocyanides (**94**) or (b) imines (**96**). NR = no reaction.

via route I as described in Scheme 2. In related work Zhao *et al.* describe a Rh^I-catalysed carbene transfer to *ortho*-alkenylaryl isocyanides **98** which is *in situ* transformed into carbazole derivatives **100** (Scheme 21).[51] The cascade reaction has a high functional group compatibility (*e.g.* esters (*e.g.* **100a**/**b**), amides, (hetero)aryl (*e.g.* **100b**), and benzyl moieties (*e.g.* **100c**)), including a broad range of substituents on alkenyldiazoacetates **99**, with different electronic characteristics, were tolerated in the reaction.

The authors show in their optimisation that the Cu^I salt co-catalyst is a crucial additive in order to obtain reasonable yields of carbazoles **100**. They propose two plausible roles of the copper(I) additive.[51] First the authors postulate that the Cu^I salt could aid in the aerobic oxidation towards the desired carbazole **100**. Second is that the Cu^I species is actively involved in the proposed mechanism as isocyanide reservoir (Scheme 22). As Cu^I has a high affinity for isocyanides, it could facilitate the transfers of isocyanide **98** towards Rh-carbenoid complex **103**, *via* coordination complex **102**, generating Rh^I-carbenoid **104**. Subsequent 1,1-migratory insertion results in the desired ketenimine **101**. A sequential intramolecular [4+2]



Scheme 21 Rh^{I}-Catalysed carbene transfer of **99** to isocyanide **98** followed by [4+2]-cycloaddition, 1,3-H shift and oxidation on *in situ* generated ketenimine **101**.

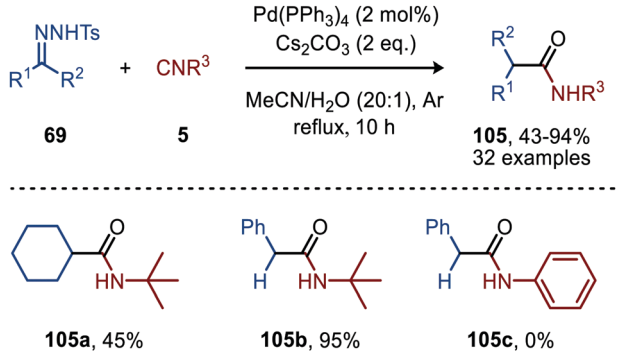


Scheme 22 Rh^{I}-Catalysed ketenimine **101** formation, employing *in situ* formed Cu^{I}-complex **102** as isocyanide reservoir.

cycloaddition, 1,3-H shift, and oxidation finally results in the carbazole reaction product **100** (Scheme 21).

Palladium. As stated before, this noble metal is widely employed in especially homogeneous catalysis. Not surprisingly, Pd has also frequently been reported to catalyse the carbene transfer to isocyanides. In 2011, Cai *et al.*[52] described the first Pd^{0}-catalysed carbene transfer to isocyanides (**5**), using *N*-tosylhydrazones (**69**) as carbene precursor (Scheme 23). For the deprotonation of **69** Cs_2CO_3 is used. The authors demonstrated that in the presence of water acting as nucleophile, the *in situ* formed ketenimine could be converted into amides **105** in moderate to excellent yields.

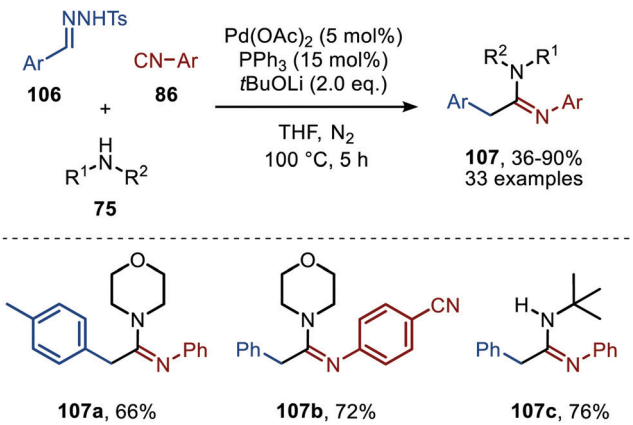
Aryl substituted *N*-tosylhydrazones (**69**) afforded amides **105** without any problem, however (bis)-alkyl *N*-tosylhydrazones required a higher reflux temperature and therefore 1,4-dioxane : H_2O (20 : 1) was used as solvent mixture to obtain a



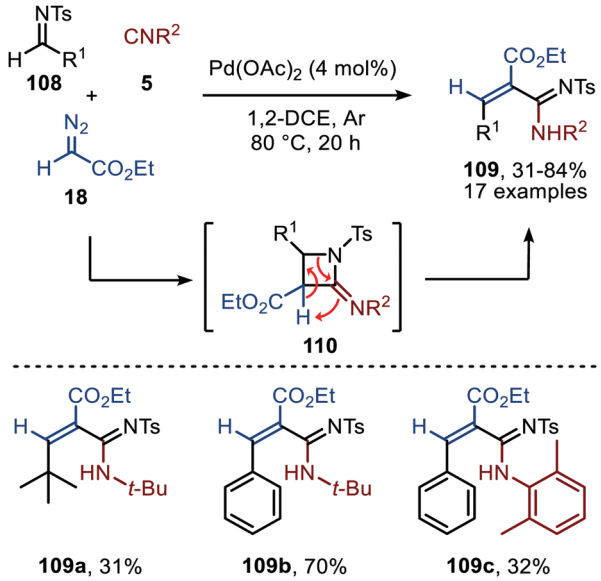
Scheme 23 Pd^{0}-Catalysed formation of amides (**105**) *via* a three-component reaction involving *N*-tosylhydrazones (**69**), isocyanides (**5**) and water.

decent yield of the corresponding amide **105a** (Scheme 23). With regard to the isocyanide scope, primary-, secondary- and tertiary aliphatic isocyanides are accepted (**105b**, Scheme 23). Aromatic isocyanides on the other hand did not lead to any product formation (**105c**, Scheme 23). The authors postulate a mechanism, which is in accordance with route I of our general mechanism (Scheme 2).

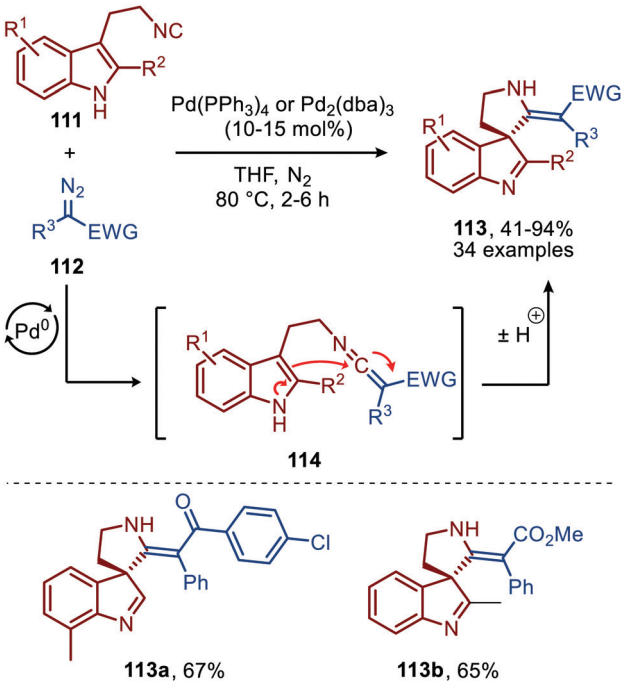
Consecutively, Cheng and co-workers describe a Pd-catalysed imidoylation of carbenes, using amines rather than water to trap the ketenimine *in situ* (Scheme 24).[53] The formation of amidines **107** proceeds in overall reasonable to good yields from benzaldehyde *N*-tosylhydrazones (**106**), aromatic isocyanides (**86**), and amines (**75**). In this case *t*BuOLi was applied as base. The substrate scope with respect to the substituents on the aromatic ring of the benzaldehyde *N*-tosylhydrazones **106** is quite broad. In addition, diverse substituted aromatic isocyanides with both electron-donating and electron-withdrawing groups can be employed. Primary, secondary, and tertiary aliphatic isocyanides were not accepted in this reaction. Additionally, aliphatic primary, secondary, and secondary cyclic amines (**75**) are tolerated in this transformation. The authors propose a mechanism based on some control



Scheme 24 Pd-Catalysed formation of amidines (**107**) *via* a three-component reaction involving isocyanides (**86**), *N*-tosylhydrazones (**106**) and amines (**75**).



Scheme 25 $Pd(OAc)_2$-Catalysed three-component reaction of *N*-tosylimines (**108**), ethyl diazoacetate (**18**), and isocyanides (**5**) towards acrylamidines **109**.



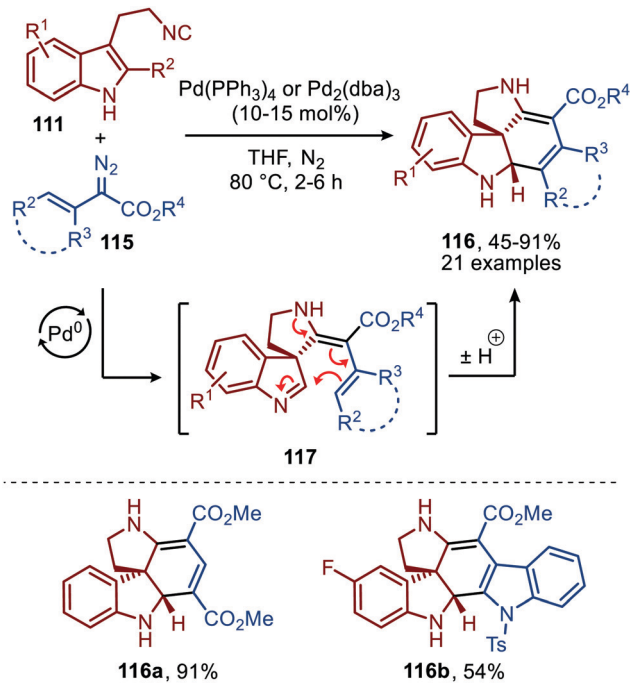
Scheme 26 Synthesis of spiroindolenines **113** *via* spirocylisation of *in situ* generated ketenimine **114** under Pd^0-catalysis.

experiments, which is in compliance with route I of our general mechanism (Scheme 2). However, the oxidation state of the Pd catalyst involved is not specified by the authors.

Cai and co-workers introduce a $Pd(OAc)_2$-catalysed three-component reaction involving an *in situ* ketenimine formation followed by a [2+2]-cycloaddition with *N*-tosylimine **108** (Scheme 25).[54] Interestingly, the expected four-membered 2-iminoazetidines (**110**) were not detected and undergo a ring-opening under the given reaction conditions, providing acrylamidines **109**. Under the optimised conditions, a broad range of benzaldehyde *N*-tosylimines (R^1 = aryl) are tolerated, resulting mainly in the *E*-acrylamidine product **109**. The authors also provide an example of a tertiary alkyl *N*-tosylimine to afford alkenecarboximidamide **109a**, albeit in low yield (Scheme 25). As for the isocyanide scope, the reaction with secondary and tertiary isocyanides afforded high yields, whereas aromatic isocyanides performed less in the reaction as exemplified for structure **109c**. Also in this study the oxidation state of the Pd-intermediates involved is not specified.

Liu and co-workers demonstrated that 3-(2-isocyanoethyl) indoles (**111**) are suitable reactants to synthesise complex spiroindolenines **113** (Scheme 26).[55] These isocyanides **111** react with α-diazo-esters or ketones (**112**) under Pd^0 catalysis to afford the corresponding ketenimine intermediate **114**. Subsequent intramolecular nucleophilic attack of the indole C3-position on the ketenimine carbon in a 5-*endo*-dig fashion results in the target spiroindolenines **113** in moderate to excellent yield. Substituents were well tolerated on the benzene ring and C2-position of the indole moiety of tryptamine-derived isocyanide **111**. The α-diazo scope **112** investigated was predominantly of the donor-acceptor type, bearing a substituted aromatic ring at the α-position (R^3) (Scheme 26).

Noteworthy is that the authors also demonstrated that spiroindolenines **113** could undergo a subsequent annulation in a Mannich type fashion when α-vinyl-, α-aryl and α-heteroaryl diazoacetates (**115**) were employed (Scheme 27).[55] Formation of spiroindolenine **117** (analogous to **113**) is followed by a

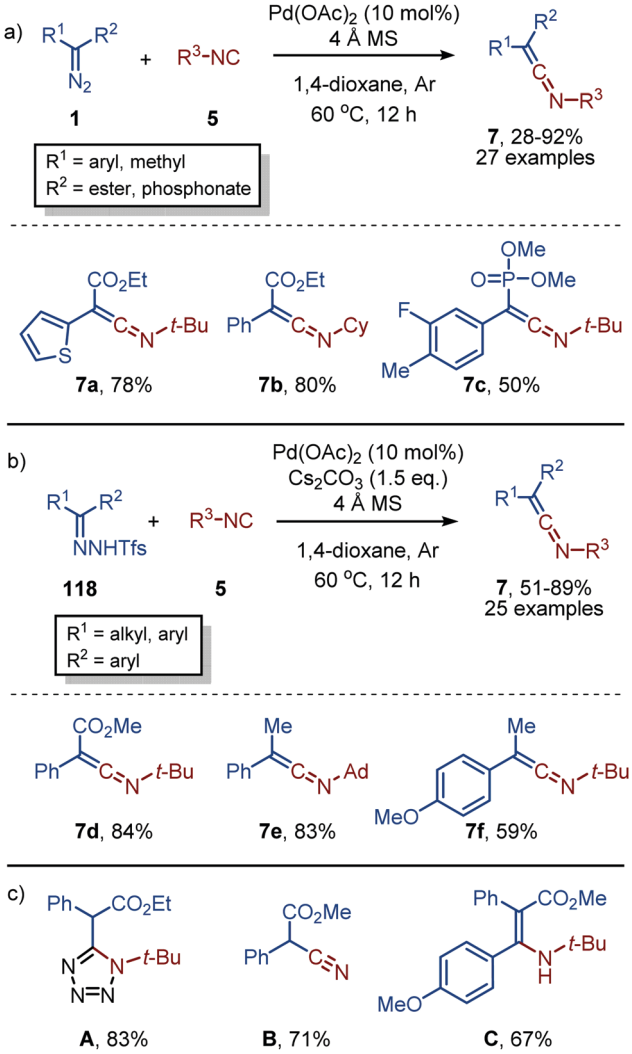


Scheme 27 Carbene-transfer/Spirocyclisation/Mannich cascade using α-unsaturated diazo esters **115** and isocyanide **111**.

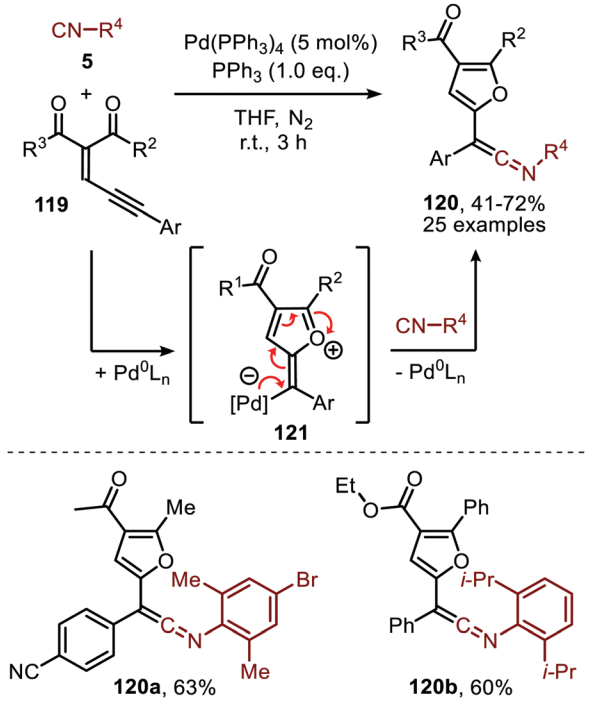
Mannich type cyclisation on the 3*H*-indole affording the corresponding tetra-cyclic spiroindoline scaffolds **116** in moderate to excellent yield.

Recently, Bi and co-workers reported the facile Pd^{II}-catalysed synthesis and isolation of ketenimines (**7**), without further *in situ* transformation. α-Diazo compounds (**1**) were used as carbene precursor featuring an electron-withdrawing ester or phosphonate moiety (Scheme 28a).[56] Similarly, they reported the use of *N*-triftosylhydrazones (**118**) for carbenes bearing electron-donating aryl- and alkyl substituents (Scheme 28b).[56] *N*-triftosylhydrazones were used as novel bench-stable non-stabilized diazo surrogates,[57] omitting the need for an α-electron-withdrawing group. It is interesting that the ketenimines (**7**) synthesised were isolated in moderate to excellent yields, without any decomposition, which is typically observed upon isolation. The isocyanide scope is predominantly limited to tertiary and secondary isocyanides. However, limited examples with aromatic isocyanides afforded the corresponding ketenimines, albeit in low yield. The synthetic utility of ketenimines **7** was illustrated (Scheme 28c) *via* multiple transformations such as a [3+2] cycloaddition towards tetrazoles **A**, the cleavage of the ketenimine N–C bond to afford ethyl 2-cyano-2-phenylacetate **B**, or a Grignard addition towards a ß-amino-acrylate **C**. Experimental and computational mechanistic studies suggest the *in situ* formation of a Pd^{II}-isocyanide complex prior to the formation of a Pd–carbene species, suggesting that the mechanism proceeds *via* route I in our general proposed cycle (Scheme 2). According to their DFT studies, a η^2-metallacycle intermediate (**13**) (Scheme 3a) was not observed and the 1,1-migratoy insertion step proceeds *via* a η^2-metallacycle transition state instead.

As was demonstrated for the Rh-catalysed carbonylation of carbenes (Scheme 11) enynes can be utilized as an alternative carbene source.[58] Li *et al.* demonstrated that enyne **119** could be transformed into furan-containing ketenimines **120** (Scheme 29). Carbene formation commences with activation of the alkyne moiety *via* a Pd-π complexation, which allows for the intramolecular attack of one of the carbonyl oxygens to the triple bond. This results in zwitterionic species **121**, which in turn gives the corresponding carbene that subsequently transfers to the isocyanide resulting in ketenimines **120**. The authors propose the reaction to proceed *via* route II (Scheme 2). However, based on the provided experimental data, the other pathways cannot be excluded. The authors report that aliphatic isocyanides and less bulky aromatic isocyanides are not tolerated in this catalytic transformation. The ketenimine could be isolated and was not transformed *in situ*. When ketenimine **120** is heated in the presence of a second isocyanide fragment (**5**), a



Scheme 28 Pd^{II}-Catalysed formation of ketenimines (**7**) from isocyanides (**5**) and carbenes derived from (a) diazo compounds **1** and (b) *N*-triftosylhydrazones **118**. (c) Synthetic transformations from ketenimine **7**.



Scheme 29 Pd^0-Catalysed synthesis of stable ketenimines **120** using enyne **119** as carbene source.

[4+1] annulation occurs to furnish indenone scaffolds upon acid hydrolysis (not shown).

In this section, we showed that ketenimines can be versatile building blocks towards important functional groups (*i.e.* amide, amidine, imidate) and for the synthesis of numerous heterocycles (*i.e.* isoquinolines, imidazoles, furanes, carbazoles, spiroindolenines). Access of heteroallene **7** *via* carbene transfer to isocyanides is predominantly catalysed by either precious Rh or Pd. For the Rh-catalysed carbene transfer to isocyanides, Rh^{I}-complexes are typically employed and the group transfer reaction presumably proceed *via* route I as multiple authors assume that the isocyano complex is the active catalytic species. Noteworthy is that for the Rh^{I}-catalysed processes, only aromatic or vinylic isocyanides were tolerated, whereas aliphatic isocyanides did not lead to product formation. In addition to Rh, Pd-catalysed carbene transfer to isocyanides are often encountered. Depending on the transformation either aliphatic or aromatic isocyanides are accepted. In some cases, both type of isocyanides are tolerated, but there typically is a large preference for one of the two. A direct rationalisation for this preference is not provided and will require a deeper understanding of the catalysis. The exact nature of the catalytic active species is in most Pd-catalysed examples illusive and the reaction can either proceed *via* route I or II. However, DFT calculations performed by Bi *et al.*[56] indicate that a Pd-isocyano complex is the active species, thereby favoring route I (Scheme 2).

For the base-metals, a simple Co^{II}-salt can catalyse the carbene transfer reaction to isocyanides with high functional group compatibility. For $CoBr_2$ (Scheme 16) a Co-isocyano complex is believed to be the active species,[47] therefore, favouring route I (Scheme 2) as mechanism for the group transfer reaction. However, further research in base-metal catalysis is definately required. The report on Ni catalysis shows feasibility, though there was still a focus on stoichiometric reactions. This will concomitantly stimulate the development of additional applications for *in situ* transformations of the ketenimine products. A notable advantage for the Co-catalysed example is the use of relatively cheap cobalt salt without involvement of additional ligands or additives, which are typically required for the noble-metals, such as Rh and Pd.

Noteworthy is that several non-metal-based processes have been reported in addition to the TM-catalysed processes. The feasibility of this inherently attractive approach towards ketenimines highly depends on the structure of the carbene formed. This include the direct addition of isocyanides to carbenes, *i.e.* various di(amino)carbenes, di(amido)carbenes and (alkyl)(amino)carbenes, under mild conditions.[59] Metal free carbene formation from diazo compounds using direct blue light excitation typically starting from donor-acceptor α-aryl diazoacetates delivers both singlet and triplet carbenes. These carbenes can participate in a wide variety of transformations, *e.g.* in the cyclopropanation of alkenes and alkynes, in the Doyle Kirmse rearrangement with allylic thioethers and insertion in O–H, N–H and C–H bonds.[60] However, extending this to the transfer to isocyanides afforded the corresponding ketenimines in only low to moderate isolated yields (12–64%).[61] The authors mention that the low yields are partly caused by a low selectivity of the free carbene as they do observe by-product formation *via* carbene dimerization. Besides reaction of two diazo compounds into a ketazine and degradation of the triplet ketenimine *via* homolytical C–N single bond fragmentation was noted.[61] Transition metals such as Pd under thermal conditions typically aid in the circumvention of these unwanted side reactions and higher yields for target ketenimine formation plus a broader substrate scope were observed, albeit under typically harsher conditions than room temperature.[56]

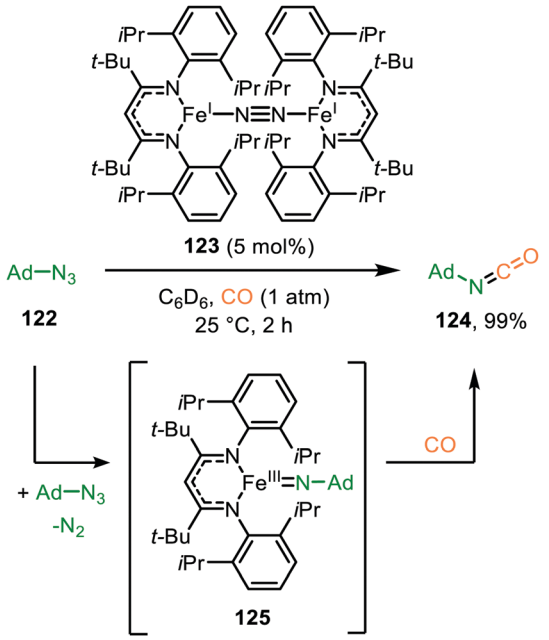
3 Transition-metal catalysed carbonylation and imidoylation of nitrenes

In this section, the nitrene transfer to carbon monoxide and isocyanides (**5**) will be discussed. *In situ* transformations proceeding either through heteroallene intermediate **8** and **9** (Scheme 1) will be categorized according to the transition metal used. In addition, mechanistic discrepancies with regard to the general catalytic cycle of Scheme 2 will be highlighted when applicable.

3.1. Nitrene transfer to carbon monoxide

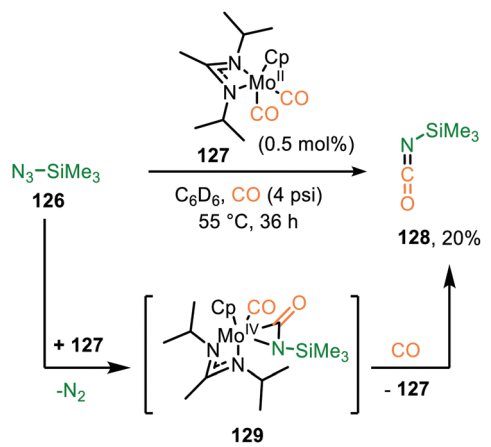
Carbonylation of nitrenes result in the formation of an isocyanate fragment (**8**) (Scheme 1). Isocyanates were already discovered in 1849 by Wurtz[62] and are industrially typically synthesised *via* stoichiometric reaction of an amine with phosgene generating corrosive HCl by-product.[20a] Considering its toxicity, alternatives have been actively sought for.[20b] The transition metal-catalysed carbonylation reaction of nitrenes is one of these interesting alternatives in the formation of **8** as gaseous benign N_2 is the by-product. The *in situ* transformation of the heteroallene **8** avoids the isolation of inherently toxic isocyanates and is, therefore, very appealing. In polymer chemistry blocked isocyanates are an active domain of contemporary research to avoid using diisocyante monomers and hereby reduce the hazards of isocyanates.[63]

Iron. This is one of the most abundant base-metals on Earth,[64] making its utilization highly interesting from an economical as well as ecological point of view. In addition, iron is able to adopt many oxidation states, resulting in versatile reactivity. Therefore, catalytic transformations with iron are highly desired alternatives to noble metal-catalysed processes. However, only one report is published. Holland *et al.* report the catalytic transformation of adamantyl azide (**122**) and CO into isocyanate **124** in excellent yield, using iron catalyst **123** (Scheme 30).[65] The reaction proceeds *via* mono Fe-imido complex **125**. The authors did not perform an optimisation of the catalytic system, nor do they report any substrate scope. However, based on their catalyst and stoichiometric experiments, imido-complex **125** is formed prior to coordination of CO, indicating that the mechanism follows route II in Scheme 2.



Scheme 30 Fe^{I}-Catalysed formation of adamantly isocyanate **124** *via* Fe^{III}-imido intermediate **125**.

Molybdenum. A second still rarely encountered transition metal for the carbonylation and imidoylation of nitrenes is base metal Mo. Mo^{II}-complex **127** was employed by the group of Sita to produce isocyanate **128** (Scheme 31).[66] The authors demonstrate that isocyanate **128** could be obtained under catalytic conditions when treating trimethylsilyl azide (**126**) under CO atmosphere, albeit in low yield (Scheme 31). The proposed mechanism is mainly based on precedents in literature, and presumably proceeds *via* η^2-coordinated metallacycle intermediate **129** (Scheme 31), accessed *via* route I, starting from intermediate **10** of our general mechanism (Scheme 2). Unfortunately, little comment is made on the catalytic cycle that should be operating and synthetic applicability of this Mo^{II}-based system.

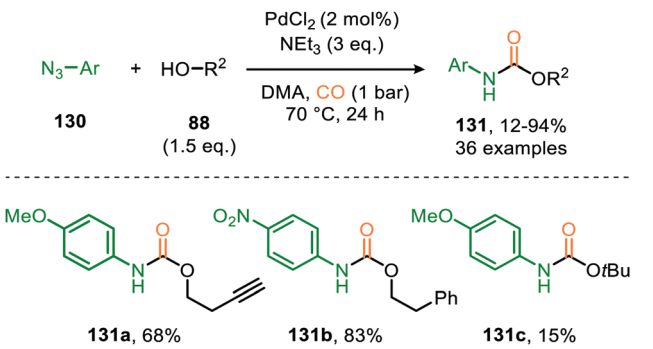


Scheme 31 Mo^{II}-Catalysed nitrene transfer from trimethylsilylazide proceeding *via* metallaaziridine intermediate **129**.

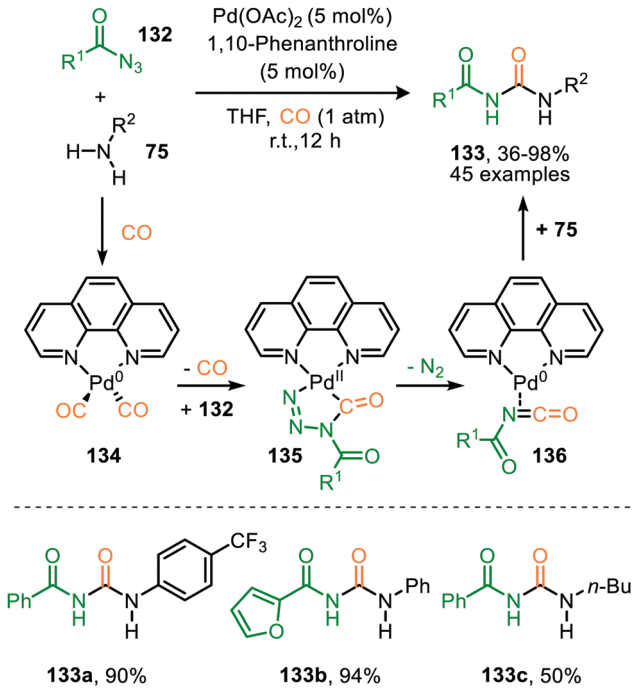
In comparison to the base-metal catalysed examples of carbene transfer to CO, only two catalytic examples are disclosed with nitrenes. Further research into base-metal catalysis, including ligand design, is therefore required. Nowadays, row V noble metals, such as palladium, offer more reliable transformations with a broader applicability.

Palladium. Until today Pd proved to be the superior TM for the nitrene transfer towards CO. Jiao *et al.* demonstrated the use of $PdCl_2$ for the synthesis of carbamates **131**, starting from aryl azides (**130**) and alcohols (**88**) (Scheme 32).[67] The reaction tolerates functionalized primary, secondary, and tertiary alcohols, albeit the yield decreases with increase of steric bulk. In addition, the system is susceptible to aromatic azides (**130**) with different electronic properties, performing exceptionally well in the reaction (60–94%). Noteworthy is that under the given conditions, heteroaryl- and alkenyl azides are also accepted. However, primary alkyl- and benzyl-azides afforded carbamates **131** in rather low yields (12–37%). The authors rationalize this result by the poor stabilisation of the metal nitrene intermediate by the alkyl group (R^1), which is crucial for a facile transfer to CO. Different Pd-sources, such as $Pd(PPh_3)_4$, show no conversion towards carbamate **131**. This indicates that a specific *in situ* generated complex is the active species, of which the exact structure is unknown. The postulated mechanism is solely based on literature precedents as no experimental nor computational mechanistic studies were performed. Both route I and II of the general catalytic cycle are possible (Scheme 2), the η^2-isocyanate metal complex (**13**) is proposed to be a key intermediate (Scheme 3a) transforming into carbamate **131** *via* alcohol addition.

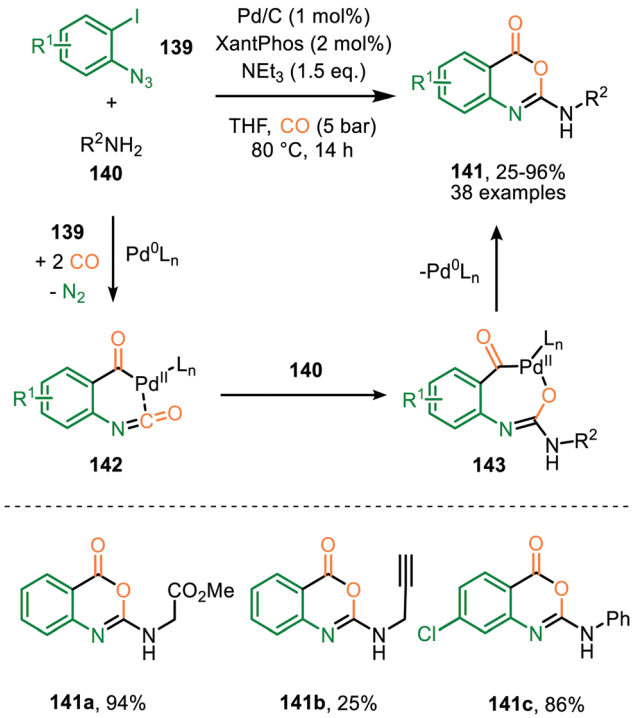
Zhang and co-workers report the use of $Pd(OAc)_2$ and 1,10-phenanthroline as bidentate ligand for the synthesis of *N*-acylated urea derivatives **133** from acyl azides (**132**) employing amine nucleophiles (Scheme 33).[68] A wide variety of electron-withdrawing and electron-donating acyl azides were tolerated providing moderate to excellent yields. Aromatic amines as well as (cyclic) aliphatic amines were compatible as nucleophiles under the reaction conditions. The authors base their proposed mechanism on kinetic and computational studies and suggest that Pd^0-species **134** (Scheme 33) is the active species. Pd-complex **134** forms prior to coordination of acyl azide **132**.



Scheme 32 Pd-Catalysed synthesis of carbamates **131** from azides (**130**), alcohols (**88**) and CO.

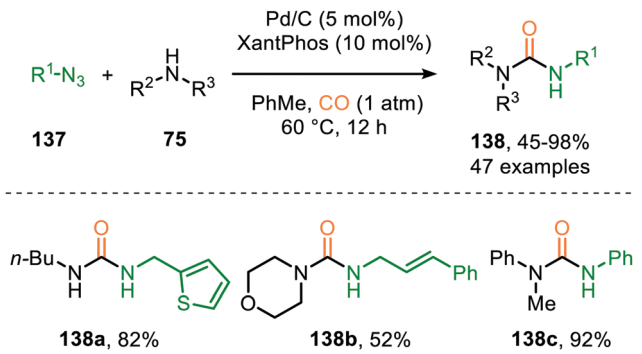


Scheme 33 *N*-Acyl urea (**133**) synthesis *via* Pd^0-catalysed carbonylation of acyl nitrene.



Scheme 35 Pd^0-Catalysed synthesis of 2-aminobenzoxazinones (**141**) *via* carbonylation of nitrene generated from 1-azido-2-iodobenzene (**139**).

Interestingly, instead of the formation of the conventional monometallic nitrene fragment followed by 1,1-migratory insertion of CO (Route I, Scheme 2), the authors suggest that acyl azide **132** reacts with the L_nPd–CO species **134** in an oxidative cyclisation step to provide five-membered metallacycle **135,** from which *via* reduction L_nPd coordinated acyl isocyanate **136** and molecular nitrogen is formed (Scheme 33). The coordinated isocyanate intermediate **136** decoordinates the TM-centre and is then captured by the amine to obtain *N*-acylated urea **133.** The same authors also developed a different catalytic system based on heterogeneous Pd/C and XantPhos ligand for the synthesis of urea derivatives **138** (Scheme 34).[69] The reaction accepts aromatic-, benzylic and aliphatic azides (**137**) and delivers ureas **138** in moderate to excellent yields (45–98%). The proposed mechanism may follow either route I or II of the general catalytic cycle (Scheme 2).

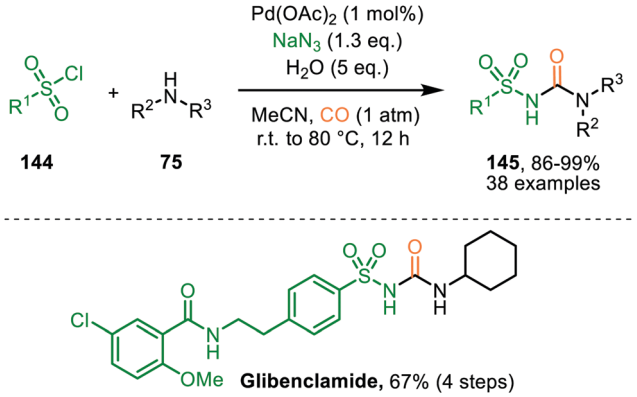


Scheme 34 Synthesis of urea derivatives **138** *via* Pd^0-catalysed nitrene transfer to CO.

However, no experimental or computational data is provided to support the proposed catalytic cycle. The authors propose that a Pd leaching process is highly likely.[70] Presumably, Xantphos scavenges Pd from the carbon support generating a homogeneous catalyst.

A similar catalytic system, based on Pd/C as Pd^0 source, was applied for the carbonylative synthesis of 2-aminobenzoxazinones (**141**) from 1-azido-2-iodobenzenes (**139**) and primary amines (**140**) by Wu and co-workers (Scheme 35), though mechanistically it is completely different.[71] The scope of 1-azido-2-iodobenzenes (**139**) is limited. However, high tolerance is observed for a wide variety of primary, secondary and (cyclic) aliphatic-, and (hetero)aromatic amines. Some examples with interesting functional handles are depicted in Scheme 35. The proposed mechanism is initiated by oxidative addition of 1-azido-2-iodobenzene (**139**) to Pd^0L_n, followed by subsequent 1,1-migratory insertion of CO into the Pd–C σ-bond. This is followed by nitrene transfer to CO, affording intermediate **142** (Scheme 35). Subsequent nucleophilic attack of amine **140** results in palladacycle **143,** which upon reductive elimination furnishes 2-aminobenzoxazinones (**141**). The mechanism is not investigated extensively, and key processes involved, such as isocyanate formation are not addressed.

These authors also reported a Pd-catalysed nitrene transfer for the formation of *N*-sulfonyl ureas **145**, which involves the *in situ* formation of the sulfonyl azide from sulfonyl chloride **144** and NaN_3 (Scheme 36).[72] The reaction tolerated numerous substituents on both the sulfonyl as the amine moiety and the corresponding urea **145** is obtained in excellent yields in all



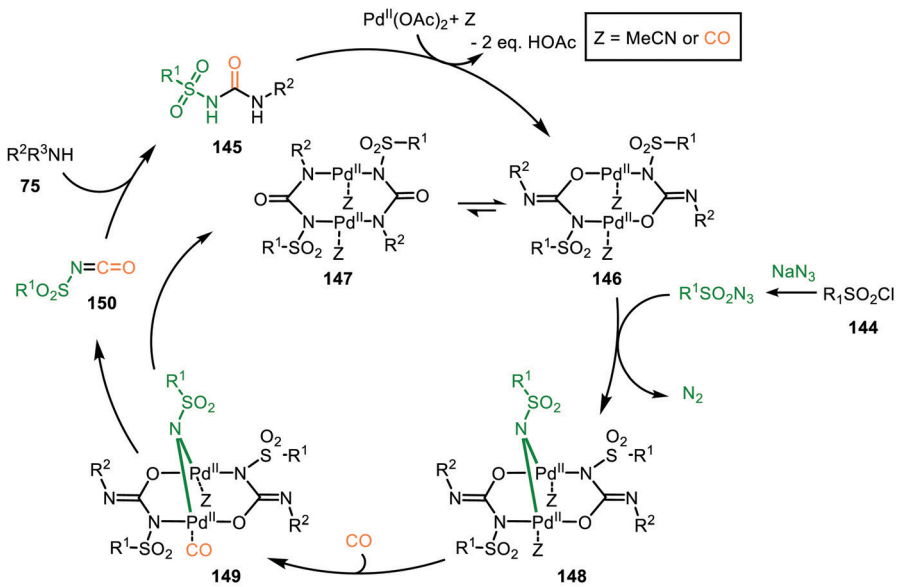
Scheme 36 Pd^{II}-Catalysed synthesis of *N*-sulfonyl urea (**145**) *via* carbonylation of sulfonyl nitrenes from *in situ* generated sulfonyl azides.

cases. The authors demonstrate the synthetic viability of their method by synthesising Glibenclamide with an overall yield of 67% in four steps. The proposed mechanism is based on precedents in literature, HRMS and NMR-studies, and control experiments (Scheme 37). Based on their studies the authors state that the active catalytic species consists of bimetallic Pd-complex, where the urea product **145** acts as a ligand. This was supported by preformation of bimetallic *N*-sulfonylurea complex prior to nitrene transfer, which was far more superior than the system based on $Pd(OAc)_2$ in terms of rate of product formation.

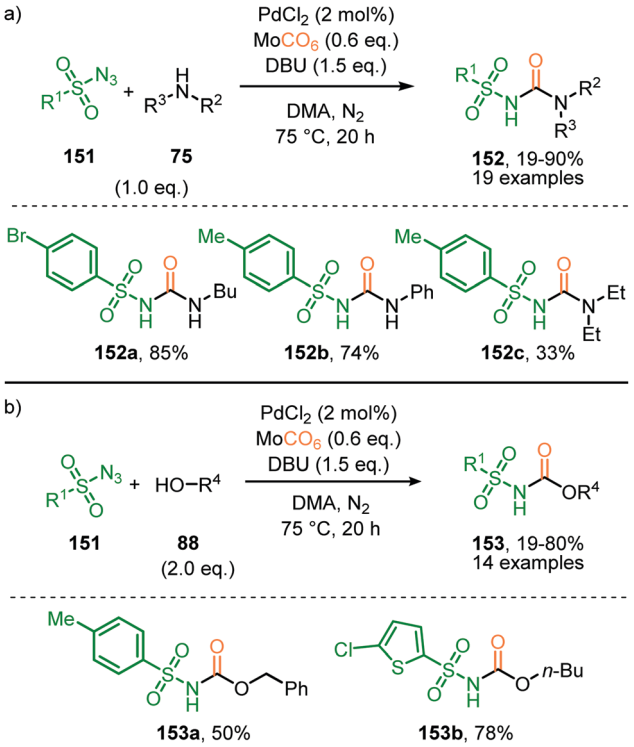
The proposed mechanism commences with the formation of a bi-metallic Pd-complex, where both the *N*,*N*-donor form **147** or the *N*,*O*-donor **146** can be present, and the *N*,*O*-form **146** is the dominant active species according to the authors. Subsequently, bridged nitrene complex **148** is formed from complex **146**/**147** and *in situ* generated sulfonyl azide. Consecutively, CO coordinates to one of the Pd-centres providing **149** followed by 1,1-migratory insertion into one of the Pd–N bonds, affording isocyanate **150**. As CO can already coordinate to the Pd-centre prior to nitrene formation, either route I or II (Scheme 2) is in good agreement with the mechanism depicted in Scheme 37.

In the previous examples, CO was introduced as a gas. However, Odell *et al.* demonstrated the use of $Mo(CO)_6$ as non-gaseous CO-source for the synthesis of *N*-sulfonyl ureas (**152**) and *N*-sulfonyl carbamates (**153**) from sulfonyl azides **151** *via* a Pd-catalysed nitrene transfer to CO (Scheme 38).[73] For both the synthesis of *N*-sulfonyl urea (**152**) and *N*-sulfonyl carbamates (**153**), azides **151** bearing a (hetero)arenesulfonyl moiety perform well in the reaction. Primary and secondary aliphatic and aromatic amines are generally accepted in the transformation of *in situ* generated isocyanate into urea. With respect to the carbamate synthesis, primary-, secondary-, and tertiary aliphatic alcohols are generally tolerated in the reaction, whereas phenol did not afford any product. Their proposed mechanism, based on literature precedents and control experiments, shows that the active catalyst is a Pd^0 species. The mechanism is initiated by the reduction of the pre-catalyst $PdCl_2$ to an active Pd^0L_n species, followed by the generation of a nitrene-palladium complex from *N*-sulfonyl azide **151**. Subsequent CO coordination and 1,1-migratory insertion delivers a sulfonyl isocyanate, which undergoes nucleophilic attack with amines (**75**) or alcohols (**88**) to deliver the corresponding final products. It remains unclear what the exact nature of the active catalytic species is during the reaction as either CO, the azide or the formed products could be involved in generating the active catalytic species.

To conclude, several transition metals can catalyse the nitrene transfer to CO but only palladium is yet well explored. For the Mo-catalysed system the yield was low and no *in situ* transformation of the heteroallene was reported. At first sight,



Scheme 37 Proposed mechanism of the bi-metallic Pd^{II} complex **146**/**147**-catalysed nitrene transfer to CO in the synthesis of *N*-sulfonyl urea (**145**).



Scheme 38 Pd^0-Catalysed formation of: (a) *N*-sulfonyl urea (**152**) and (b) *N*-sulfonyl carbamates (**153**).

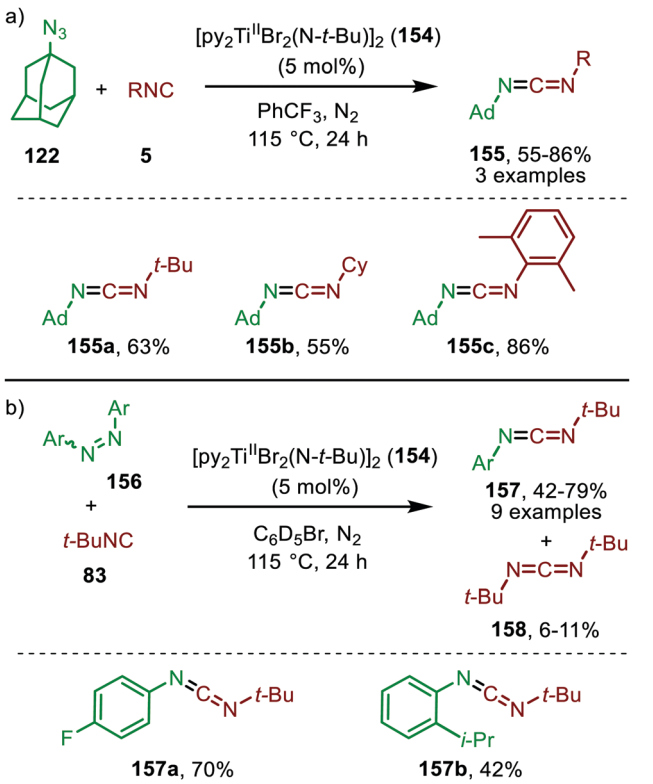
iron seems to be an efficient and promising catalyst, however, no cascade processes have been developed yet. Detailed mechanistic studies point towards route II as the Fe-imido complex forms prior to involvement of CO (Scheme 30). Overall, when looking at the transition metals employed, only palladium has established itself as a mature catalyst in the formation of isocyanates *via* nitrene transfer to CO. The presented catalytic systems also allow *in situ* trapping of isocyanate (**8**) with various nucleophiles as is demonstrated in the formation of carbamates, urea derivatives and aminobenzoxazinones (**141**). The proposed mechanisms indicate that the nitrene transfer can either proceed *via* route I or II (Scheme 2). Interestingly, when a ligand was applied it was of the bidentate type.

3.2. Nitrene transfer to isocyanides

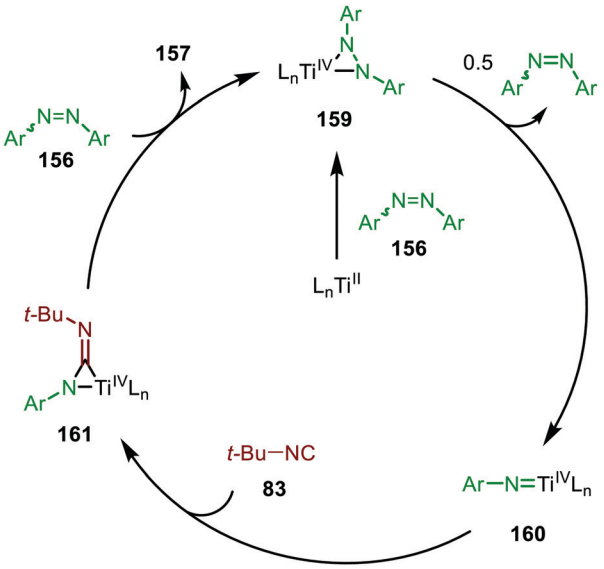
So far, we described in this review the formation of several heteroallenes *via* TM catalysis: ketenes (**6**) and ketenimines (**7**) *via* carbene transfer to CO and isocyanides respectively, and isocyanates (**8**) *via* nitrene transfer to CO. Imidoylation of nitrenes affording carbodiimides (**9**) is also known and described in this section (Scheme 1). Carbodiimides received only limited attention until the late 50's, but are nowadays a widespread building block and reagent in organic synthesis.[18] Common stoichiometric methods[18] for the synthesis of carbodiimide are for example the dehydrosulfirisation of thioureas,[74] the rearrangement of *N*-substituted amidoximes (Tiemann rearrangement) *via* transformation of the hydroxy into a leaving group and the oxidative rearrangement of *N*-substituted amidines.[75] Noteworthy, transition metal mediated processes towards (metallated) carbodiimides (**9**) involving organoazide species and isocyanides have been covered in a review by Beck *et al.* in 2015,[76] but no catalytic examples or cascade processes with the formed **9** were included.

Titanium. Early TMs are less frequently applied as catalyst for group transfer reactions towards CO and isocyanides. However, the work of Tonks *et al.* illustrated that Ti^{II}-catalyst **154** is able to realise nitrene transfer to isocyanides, using adamantyl azide (**122**) (Scheme 39a) or diazenes (**156**) (Scheme 39b) as nitrene precursor for the synthesis of carbodiimides (**155** and **157**), respecitvely.[77]

The adamantyl azide (**122**) reacts either with cyclohexyl isocyanide, *tert*-butyl isocyanide, or aromatic 2,6-xylyl isocyanide to afford the corresponding carbodiimides (**155**) in good yield (Scheme 39a). Important note is that sterically encumbered azide **122** is crucial to prevent catalyst inhibition *via* multiple isocyanide coordination. In the nitrene transfer with diazenes, the reaction tolerates aromatic diazenes **156** bearing aliphatic- or inductively electron-withdrawing substituents on the aryl moiety (Scheme 39b). The formation of carbodiimides **157** deviates from the general proposed mechanism in Scheme 2 as here a different activation mode of nitrene precursor **156** is involved. Extensive mechanistic studies rationalize the formation and further transformation of Ti-imido complexes from diazenes **156**.[77–79] The catalytic cycle commences with oxidative addition of diazene **156** to the



Scheme 39 Carbodiimide synthesis *via* Ti^{II}-catalysed imidoylation of nitrenes using: (a) adamantyl azide (**122**) and (b) diazenes (**156**).

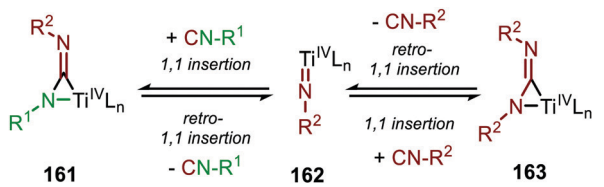


Scheme 40 Proposed mechanism of the Ti^{IV}-catalysed carbodiimide formation from diazenes (**156**) and *t*-BuNC (**83**).

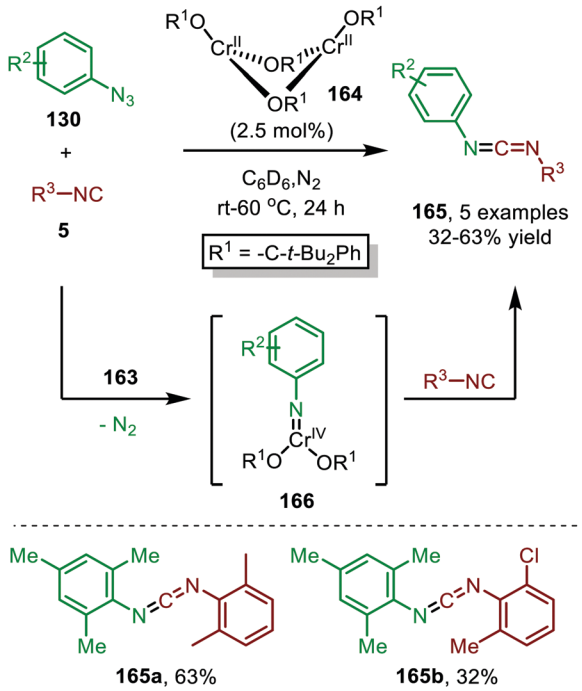
Ti^{II}-centre forming Ti^{IV}-species **159** (Scheme 40). Subsequently, Ti^{IV}-imido complex **160** is formed by formally liberating 0.5 equivalent of diazene. Unfortunately, the authors provide no further comments to support this step. Coordination of isocyanide **83**, and subsequent 1,1-migratory insertion, provides the η^2-carbodiimide intermediate complex **161**, which is in accordance with route II of the general cycle in Scheme 2. Subsequent release of the carbodiimide proceeds in an associative fashion involving diazene **156**. The release is triggered by an electron transfer from the Ti-bound η^2-carbodiimide (**161**) to the Ti-coordinated diazene ligand, releasing carbodiimide **157** and forming complex **159**. Noteworthy is that the associative release prevents the formation of a discrete Ti^{II}-intermediate.[77]

Another important note is the formation of homo-coupled by-product **158**, with diazene **156** as nitrene source (Scheme 39b). The authors suggest the formation of the by-product *via* an uncommon isocyanide metathesis mechanism (Scheme 41). The occurrence of this retro 1,1-insertion, also known in the literature as *isocyanide scrambling*, implies the presence of a η^2-carbodiimide intermediate (**161**) in the catalytic cycle as commonly proposed in the general mechanism (**13**, Scheme 3a.)

Chromium. In 2015, Groysman *et al.* reported the coupling of aryl isocyanides with aryl azides **130** in the synthesis of



Scheme 41 Metathesis mechanism of isocyanide scrambling *via* a retro-1,1-migratory insertion.

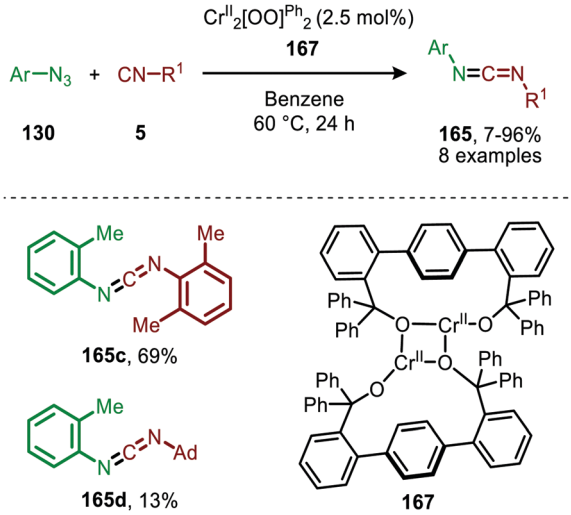


Scheme 42 Cr^{II}-Catalysed nitrene transfer of aromatic azides **130** to isocyanides **5** providing carbodiimides **165**.

asymmetrically substituted *N*-aryl carbodiimides **165**, utilising bis-alkoxide Cr^{II}-complex (**164**) as pre-catalyst (Scheme 42).[80] The authors postulate that the pre-catalyst is converted to active mono-Cr^{IV}-imido species **166** by reaction with aryl azides (**130**).

This trigonal-planar imido-Cr^{IV} intermediate **166** was isolated and fully characterized by the authors and could only be formed with sterically demanding aromatic azides. Decreasing the steric bulk of the azides or the alkoxide ligand of the pre-catalyst, resulted in the formation of a coordinatively saturated Cr^{VI}-bis(imido) complex, which was unreactive in the subsequent nitrene-transfer step. However, the formation of an isocyano complex prior to nitrene formation could not be ruled out and the mechanism could proceed *via* either route I or II in Scheme 2. Although the scope of azides and isocyanides is limited, the authors nicely demonstrate the use of high valent early transition metals for catalytic nitrene transfer, which is inherently more difficult than with low valent late TM's. This is due to the increased stability of the TM-nitrene fragment with early TM's, compared to late TM's. The stronger bonding interactions between the nitrene fragment and early TM's in a high oxidation state are due to the availability of empty metal d-orbitals and strong σ- and π-coordination of the imido group.[80]

In 2020 the same research group reported the use of dichromium complex **167** with chelating bis(alkoxide) ligands in the context of catalytic synthesis of carbodiimides (**165**) from azides (**130**) and isocyanides (**5**) (Scheme 43).[81] The authors observed that only sterically encumbered azides were able to participate in the nitrene transfer reaction. Based on their previous work (Scheme 42) the authors postulate that

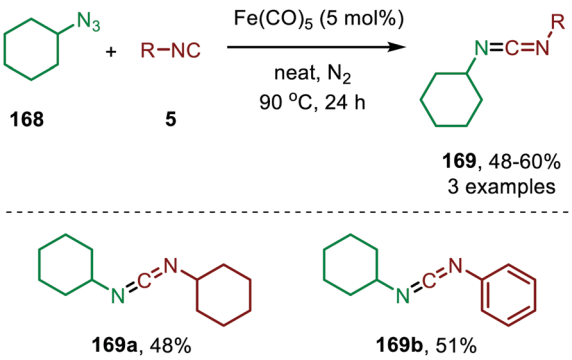


Scheme 43 Cr^{II}-Catalysed coupling of azides (**130**) and isocyanides (**5**) forming carbodiimides (**165**).

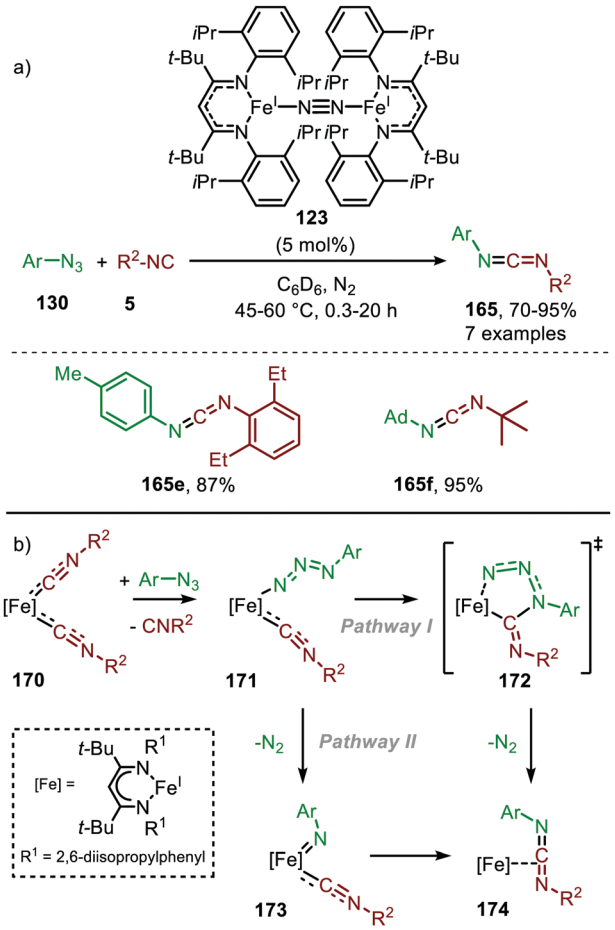
non-bulky azides form a saturated catalytically inactive Cr^{IV}-bis(imido) complex. The tolerated isocyanides also beared sterically demanding electron-rich aromatic, secondary aliphatic or tertiary aliphatic substituents. The proposed mechanism by the authors is in accordance with route II of our general mechanism in Scheme 2.

Iron. The use of late TM low-valent Fe-species for nitrene transfer to isocyanides was already discovered in 1970 by Saegusa *et al.* (Scheme 44).[82] $Fe(CO)_5$ turned out to be a suitable catalyst. The nitrene coupling reaction was investigated with cyclohexyl azide (**168**) as nitrene source and several isocyanides. The corresponding non-symmetrical *N*-cyclohexyl aryl/alkylcarbodiimides (**169**) were obtained in moderate isolated yields. The authors did not comment on a plausible mechanism for this transformation.

It took until 2013 to follow-up on this early iron-based nitrene transfer. Holland and co-workers developed a bimetallic β-ketiminate ligand supported Fe^{I} complex **123** (Scheme 45a) to achieve a catalytic nitrene transfer to isocyanides providing carbodiimides **165**.[83] A brief scope study of the reaction under optimal reaction conditions indicates that the

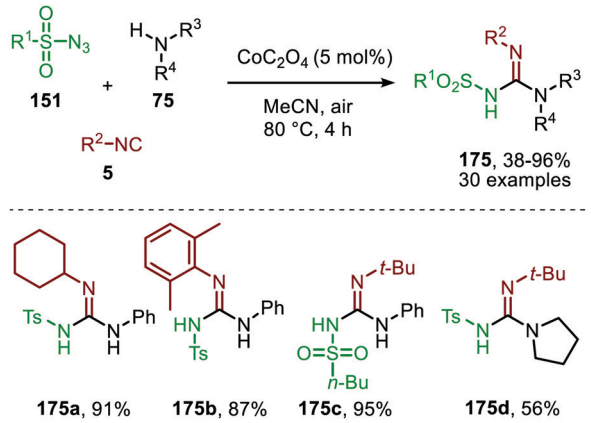


Scheme 44 Fe^{0}-catalysed synthesis of unsymmetrical carbodiimides (**169**) from isocyanides (**5**) and cyclohexyl azide (**168**).



Scheme 45 (a) Fe^{I}-Catalysed carbodiimide (**165**) synthesis *via* nitrene transfer to isocyanides. (b) Postulated pathways towards Fe-carbodiimide (**174**).

bulky tertiary aliphatic and sterically demanding aromatic azides and isocyanides perform well in the reaction (70–95%). The authors state that sterically hindered isocyanides are crucial to prevent the formation of a saturated and inactive tris-isocyanide Fe^{I}-complex. The mechanism of the desired Fe^{I}-catalysed transformation was elucidated through control experiments, EPR and NMR spectroscopy and complemented with DFT calculations. The proposed mechanism complies for the greater part with route I of our general cycle (Scheme 2). The Fe^{I}-based cycle commences with the formation of mononuclear bis-isocyano Fe^{I}-complex (**170**) (Scheme 45b). Subsequently, one isocyanide moiety is displaced by an aryl azide (**130**) to form intermediate **171**. Interestingly, the authors propose that from this intermediate (**171**) the metallated carbodiimide (**174**) can be obtained directly *via* nitrogen extrusion involving a five-membered transition state **172** (Route I). Alternatively, formation of metallated carbodiimide (**174**) from Fe-complex **171** can occur in a stepwise fashion (Route II), which involves nitrogen extrusion to furnish nitrene intermediate **173** followed by 1,1-migratory insertion of isocyanide to provide metallated carbodiimide **174**. 1,1-Migratory insertion in nitrene complex **173** proceeds *via* a 3-membered transition state (**13**)



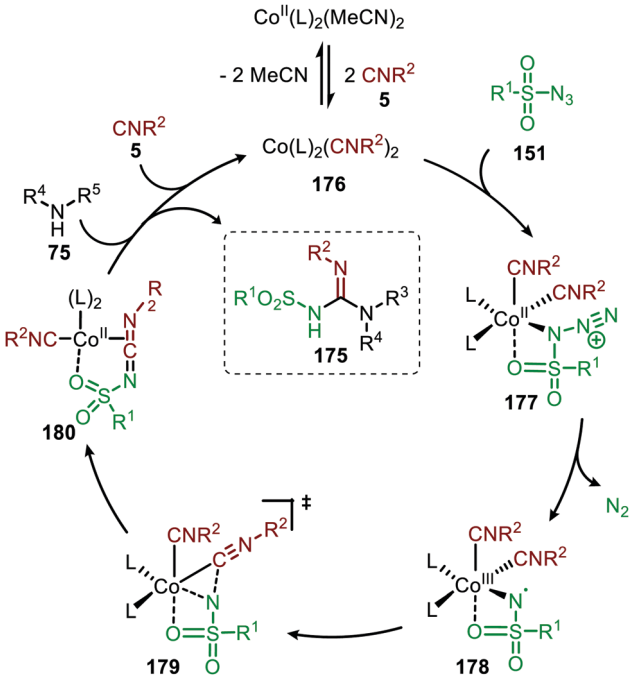
Scheme 46 Cobalt oxalate-catalysed *N*-sulfonyl guanidine (**175**) formation.

(Scheme 3a). Based on the provided data the authors could not discriminate between the two pathways.

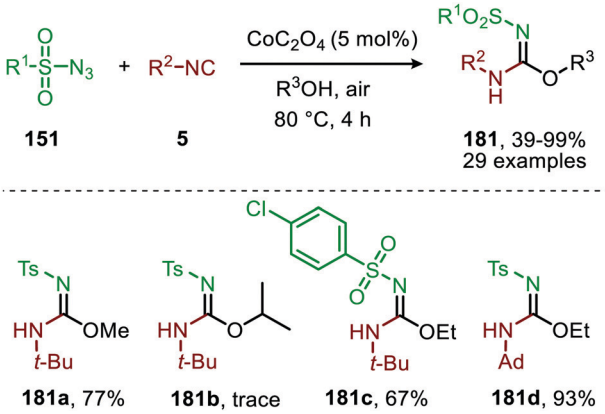
Cobalt. Although several base-metals can catalyse the nitrene transfer to isocyanides, the presented catalytic systems until this stage did not show *in situ* transformation of the carbodiimide (**9**). However, in 2017 Ji *et al.* developed a three-component reaction between isocyanides (**5**), amines (**75**) and sulfonyl azides (**151**) under Co^{II}-catalysis to afford *N*-sulfonyl guanidines (**175**) (Scheme 46).[84] In contrast to previous base-metal catalysed nitrene transfer reactions, this transformation did not require specific ligands and the reaction could even be performed under air atmosphere. The transformation tolerates a wide variety of isocyanides with primary aliphatic- and α-acidic isocyanides as the only exceptions. Both aromatic- and aliphatic sulfonyl azides furnished the corresponding *N*-sulfonyl guanidines **175** in good to excellent yields. However, the yield decreased when electron poor aromatic amines or sterically encumbered cyclic secondary amines were employed.

The proposed mechanism for this Co^{II}-catalysed nitrene transfer to isocyanides was based on experimental observations, EPR spectroscopy and detailed DFT-calculations (Scheme 47). Initial ligand exchange of MeCN with an isocyanide results in bis-isocyanide complex **176**. This is followed by coordination of the azide (**151**) and extrusion of N_2, furnishing the Co^{III}-radical nitrene intermediate **178**. Subsequent 1,1-migratory insertion proceeding through a η^2-transition state (**179**), generates Co^{II}-carbodiimide complex **180**. The structure of the proposed transition state (**179**) is in accordance with metallacycle **13** in Scheme 3a. The metallated carbodiimide is subsequently attacked by a nucleophile furnishing the desired product and Co^{II}-species **176**, thereby closing the catalytic cycle. The proposed cycle is in line with route I (Scheme 2) involving a Co^{III}-radical nitrene intermediate **178**.

The applicability of this three-component reaction was further extended by using alcohols as input instead of amines. This furnished interesting *N*-sulfonyl isoureas (**181**) (Scheme 48) as the products.[85] Notably, for this reaction all types of isocyanides could be used except for primary aliphatic isocyanides, which were not compatible. In addition, a broad range of arenesulfonyl azides



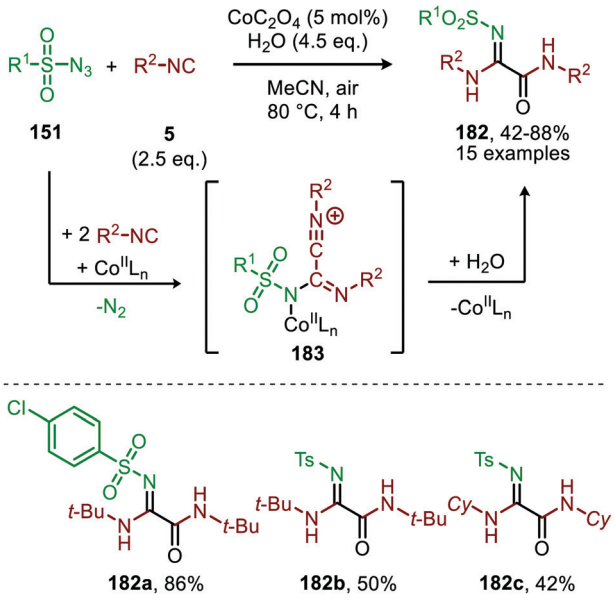
Scheme 47 Proposed catalytic cycle of the Co^{II}-catalysed nitrene transfer to isocyanides (**5**) *via* Co^{III}–carbene radical nitrene intermediate **178**.



Scheme 48 Co^{II}-Catalysed imidoylation of nitrenes for the synthesis of *N*-sulfonyl isoureas (**181**).

(**151**) with different electronic characteristics were well tolerated. Unfortunately, the method is limited to only primary alcohols, while secondary- and tertiary alcohols performed less efficient. Most likely this can be attributed to increased steric demand for these inputs reducing nucleophilicity.

The same group reported the synthesis of sulfonylamidyl amides (**182**) from sulfonyl azides (**151**) and two equivalents of isocyanide *via* a similar Co^{II}-catalysed approach in the presence of water (Scheme 49).[86] The nitrene transfer proceeds *via* Co^{III}-nitrene radical intermediate (**178**) and furnishes metallated carbodiimide (**180**) after 1,1-migratory insertion (Scheme 47). Subsequently, Co^{II}-carbodiimide complex (**180**) (Scheme 47) is attacked by an additional isocyanide molecule (**5**) to furnish nitrilium ion intermediate (**183**) (Scheme 49). This cationic



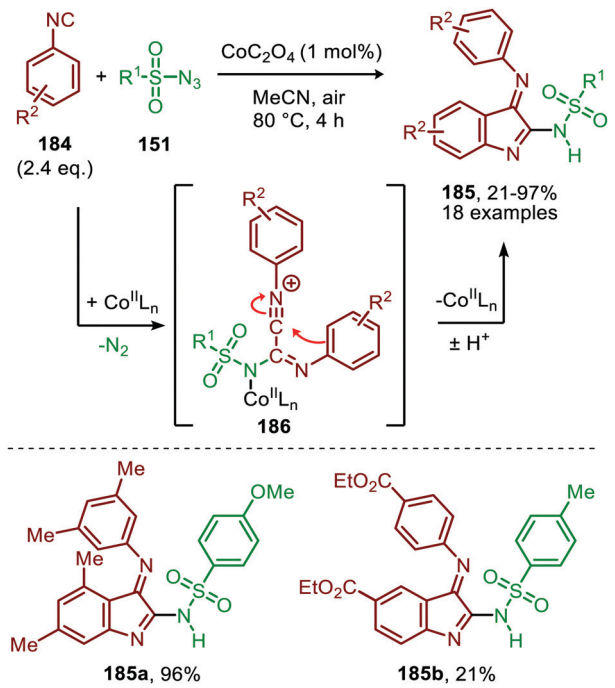
Scheme 49 Co^{II}-Catalysed nitrene transfer to isocyanides (**5**) in the synthesis of sulfonylamidinyl amides (**182**).

intermediate is then trapped by water, which after tautomerisation result in the sulfonylamidyl amides (**182**). The reaction tolerated a broad range of substituted aromatic- and aliphatic isocyanides to afford sulfonylamidinyl amides (**182**) in moderate to good yield.

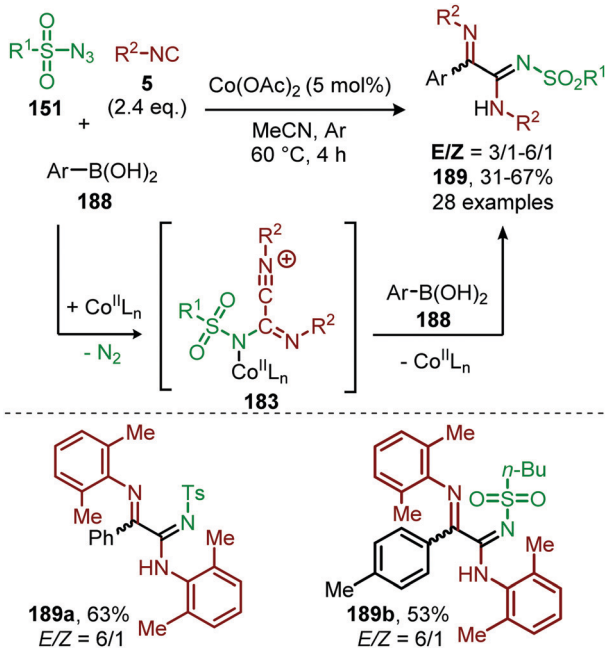
Interestingly, when aromatic isocyanides are used in the absence of water, a completely different reaction product was obtained (Scheme 50).[86] The reaction between sulfonyl azide (**151**) and aromatic isocyanides (**184**) results in Co^{II}-carbodiimide complex (**180**) (Scheme 47), which in turn is attacked by a second isocyanide to furnish nitrilium ion **186** (Scheme 50). Subsequent intramolecular electrophilic aromatic substitution affords 3-imino-3*H*-indole derivatives **185** in low to excellent yields. Electron poor aryl isocyanides drastically lower the yield due to their poor performance in the electrophilic aromatic substitution step from nitrillium intermediate **186**.

In 2018, Ji and co-workers developed a similar Co^{II}-catalysed strategy to arrive at amidinyl imine derivatives (**189**) in low to moderate yields. For this they combined sulfonyl azides (**151**), isocyanides (**5**) and boronic acids (**188**) in one-pot (Scheme 51).[87] The transformation commences with carbodiimide formation according to the mechanism in Scheme 47 and complies with route I of our general mechanism (Scheme 2). Again, the metallated carbodiimide (**180**) (Scheme 47) is attacked by a second isocyanide to furnish nitrillium intermediate (**183**) (Scheme 51). **183** is then trapped with boronic acids (**188**) to arrive at amidinyl imine **189**. Bis-*o*-substituted aromatic isocyanides were tolerated in the reaction (51–67%), however, aliphatic isocyanides did not show any conversion. Only aryl boronic acids (**188**) served effectively as coupling partner determining the observed *E*/*Z*-ratio. The selectivity of the reaction depends on the position of the substituent on the aryl ring of boronic acid. Typically, *ortho*-groups achieve an *E*/*Z* selectivity of 3/1, whereas *para*- or *meta*-substituents afforded a better *E*/*Z* selectivity of 6/1.

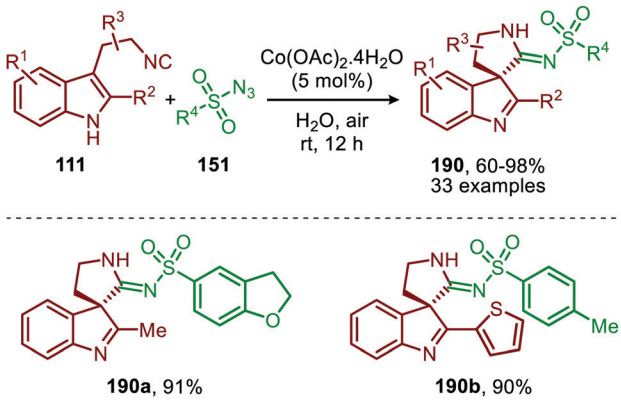
Spiroindolenines (**190**) could also be synthesized from sulfonyl azides (**151**) and functionalized tryptamine-derived isocyanides (**111**) in good to excellent yield (Scheme 52).[88] A major advantage is that the reaction could be performed in water.



Scheme 50 Co^{II}-Catalysed nitrene transfer to aryl isocyanides (**184**) in the synthesis of 3-imino-3*H*-indole scaffolds **185**.



Scheme 51 Co^{II}-Catalysed four-component coupling between isocyanides (**5**), sulfonyl azides (**151**) and aryl boronic acids (**188**) towards amidinyl imines (**189**).



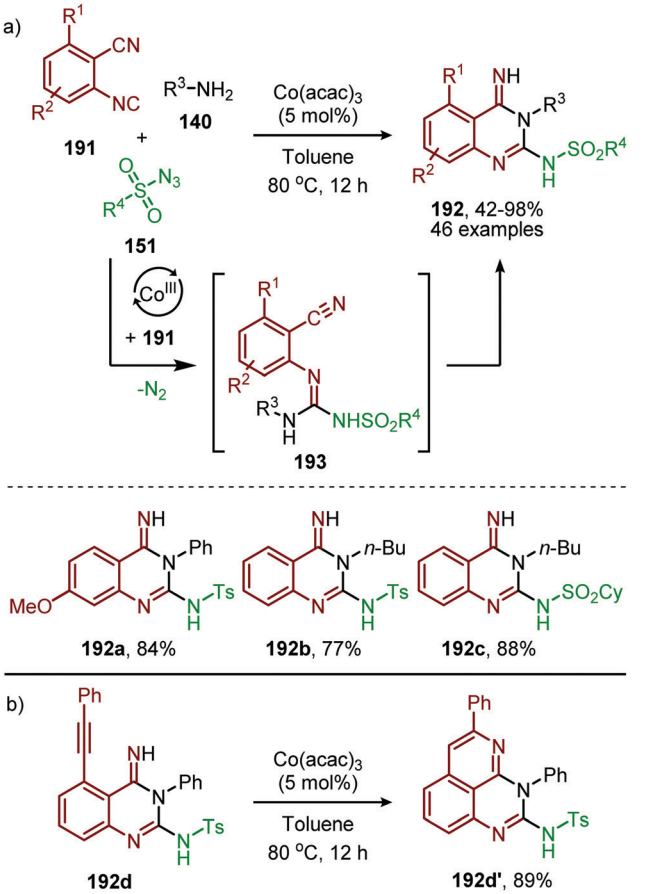
Scheme 52 Co^{II}-Catalysed nitrene transfer of sulfonyl azides (**151**) to tryptamine derived isocyanides (**111**).

Arguably, this makes the reaction attractive from a sustainable point of view. Noteworthy is that a substituent on the C2-position of the indole is essential in order to isolate the desired product **190**. However, when a hydrogen is present at this position the corresponding indoline was isolated, as a result of *in situ* imine reduction with $NaBH_4$ of the obtained indolenine (**190**). Arene- as well as alkanesulfonyl azides (**151**) were suitable nitrene precursors. The authors propose the reaction to proceed *via* Co^{III}/nitrene radical species (**178**) (Scheme 47), where bis-isocyanide Co^{II}-complex (**176**) initiates the formation of the Co^{III}-nitrene intermediate (Scheme 47).

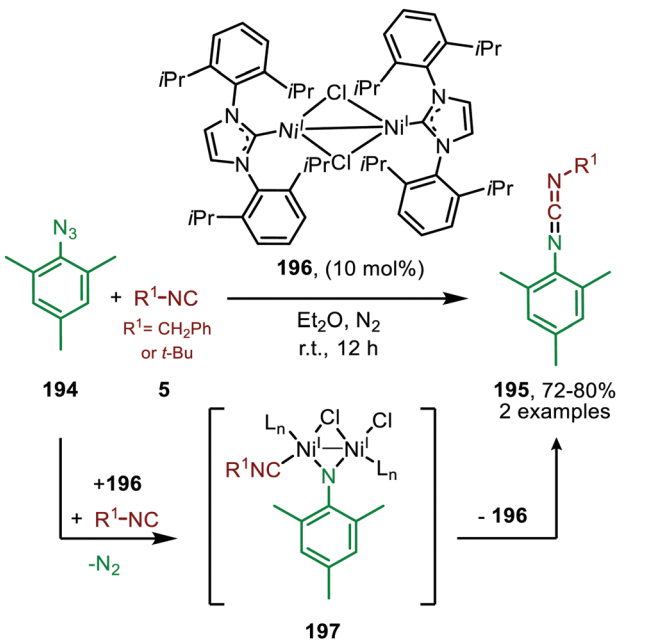
In recent work of this group, the Co^{II}-catalysed nitrene transfer of sulfonyl azides (**151**) to cyanoarylisocyanides was applied for the formation of quinazolin-4(3*H*)-imines (**192**) (Scheme 53a).[89] The cascade process commences with Co^{II}-catalysed formation of the corresponding carbodiimide following the mechanism illustrated in Scheme 47. Subsequent nucleophilic addition of aromatic as well as aliphatic amines (**140**) furnished the corresponding *N*-sulfonyl guanidines (**193**). Finally, ring closure on the aromatic nitrile results in quinazolin-4(3*H*)-imines (**192**) in moderate to excellent yields. Interestingly, when an alkyne as R^1-substitutent is present on substrate **191**, a second cyclisation could occur to obtain product **192d′** (Scheme 53b).

Nickel. Also, nickel received some attention though only to form carbodiimides but not involving *in situ* post transformations with nucleophiles. The di-nickel^{II} bridged complex **196** featuring IPr ligands was developed by Hillhouse and co-workers for the synthesis of unsymmetrical carbodiimides **195** (Scheme 54).[90] The scope of the reaction was not extensively studied and solely benzyl isocyanide and *tert*-butyl isocyanide were employed as input examples. The proposed mechanism follows either route I or II of the cycle presented in Scheme 2. One notable rare aspect is that the active intermediate is considered to be di-Ni^{I}-μ-imido species **197** rather than a monometallic one. The authors do not demonstrate the use of additional azides beyond mesityl azide or *in situ* post transformation of the carbodiimide obtained.

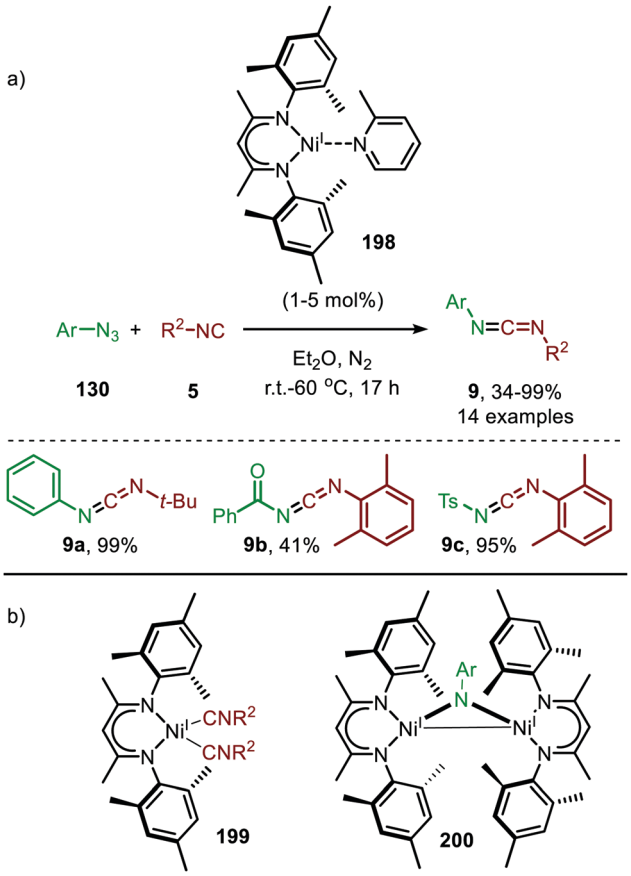
Warren and co-workers developed another Ni^{I}-catalyst (**198**) for the nitrene transfer reaction to isocyanides (Scheme 55).[91]



Scheme 53 (a) Co^{III}-Catalysed three-component coupling between 2-cyanoarylisocyanides (**191**), sulfonyl azides (**151**), and amines (**140**) towards quinazolin-4(3*H*)-imines (**192**). (b) When R^1 is an alkyne *in situ* cyclization occurs forming a fused quinazoline derivative **192d′**.



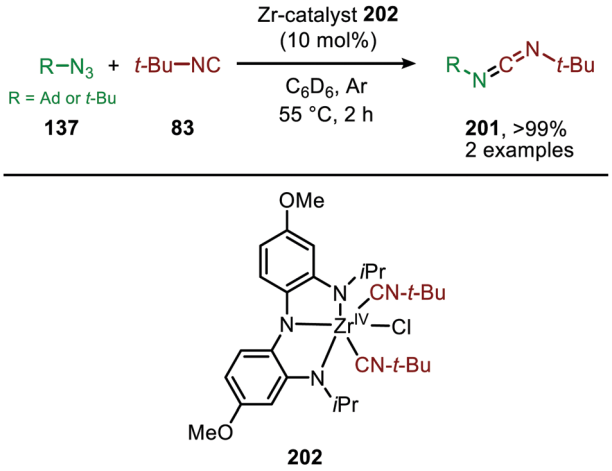
Scheme 54 Ni^{I}-Catalysed imidoylation of nitrene derived from mesityl azide *via* bridged-di-nickel imido species **197**.



Scheme 55 (a) Ni^{I}-Catalysed imidoylation of aromatic azides, and (b) proposed active species in the nitrene transfer to isocyanides.

This β-diketiminato Ni^{I}-catalyst with picoline spectator ligand (**198**) proved highly active at relatively low catalyst loading. Under optimal conditions the reaction of aryl azides (**130**) afforded carbodiimides (**9**) in good yields. However, reaction with electron poor azides such as tosyl azide, furnished the product **9** in lower yield. The authors assume that the lower electron density of these organoazides hampers entering the coordination sphere of the metal centre as it competes with the more electron-rich isocyanide. In addition to aromatic azides, homobenzylic azide and benzoyl azide were successfully employed. Turning attention to the isocyanide substrate scope, only *tert*-butyl isocyanide and 2,6-dimethylphenyl isocyanide were tested. Moreover, the carbodiimides (**9**) were not always isolated and the reaction was carried out in a glove box. Notably, the authors synthesized β-diketiminato bis-(isocyanide)-Ni^{I} complex **199** (Scheme 55b) and imido bridged di-Ni^{I}-imido complex (**200**) derived from β-diketiminato Ni^{I}-catalyst (Scheme 55b). Stoichiometric experiments with complex **199** and azide (**130**), and with complex **200** and isocyanide (**5**), both afforded the carbodiimide (**9**), indicating that both Ni-species **199** and **200** could be active intermediates within the catalytic cycle. Unfortunately, the authors do not further comment on the exact mechanism of carbodiimide formation.

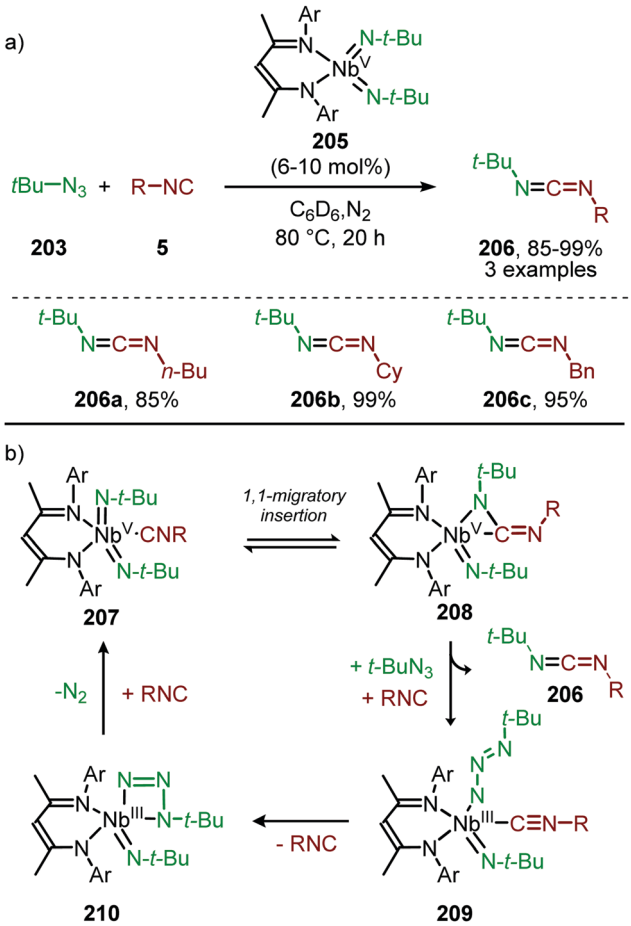
Zirconium. Arriving at the early row V transition metals, Heyduk *et al.* described a rare Zr^{IV}-catalysed nitrene transfer to



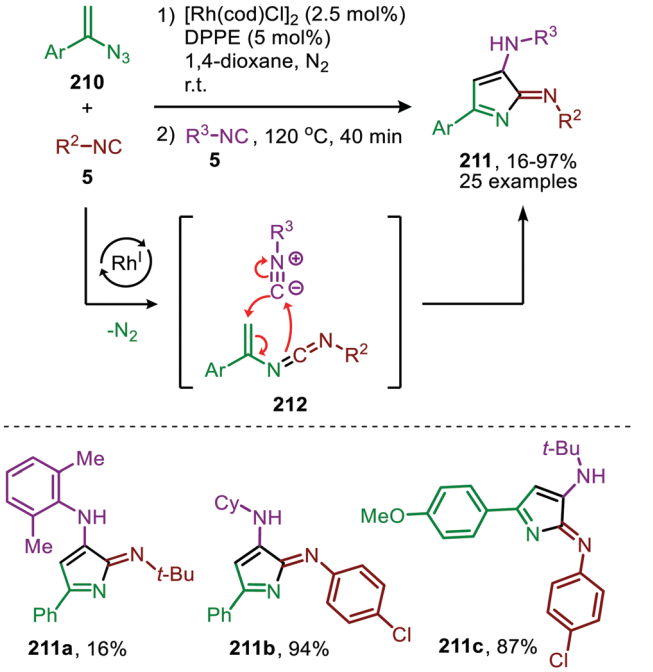
Scheme 56 Zr^{IV}-Catalysed nitrene transfer to *t*-BuNC using a redox active ligand.

isocyanides using a pincer complex **202**. The bis(2-isopropylamido-4-methoxyphenyl)amide ($[NNN^{cat}]^{3-}$) acting as a redox-active ligand is key here (Scheme 56).[92] The redox activity of this ligand, cycling between the catecholate and quinonate form, allows the zirconium metal centre to remain in its more stable d^0 – oxidation state. According to their scope studies the reaction with *tert*-butyl isocyanide tolerates bulky adamantyl azide and *tert*-butyl azide, furnishing carbodiimides **201** quantitatively. An inert Zr^{IV}-imido dimer is observed when aromatic azides are employed. The proposed mechanism is generally in accordance with route I (Scheme 2), however there are important differences when zooming in as the ligand is actively involved here. Zr imido complex is formed *via* reaction with azide. Two electrons of the ligand are used for this process providing the quinonate ligand form. 1,1-Migratory insertion of coordinated isocyanide affords an η^2- coordinated metallacycle similar to **13** (Scheme 3a). Subsequently, carbodiimide **201** is formed *via* a reductive elimination of the corresponding η^2-carbodiimide Zr-complex, involving a two electron reduction of the quinonate form of the redox-active ligand into its catecholate rather than the metal centre. In principle, the nitrene fragment in early-transition-metal complexes is considered nucleophilic. Therefore, nitrene transfer to an isocyanide, which is intrinsically nucleophilic, can only occur after it is activated by the electrophilic metal centre.[92] This in contrast with mid- to late TM processes where the nitrene fragment is considered to be electrophilic.[92] Therefore, depending on the substrates and TM employed, different type of reactivity can be observed.

Niobium. Neighboring to Zr in row V is middle transition metal Nb. It can catalyse the nitrene transfer to isocyanides as is demonstrated by Arnold *et al.* (Scheme 57a).[93] They report the use of bis-imido Nb-complex **205** in the nitrene transfer to cyclohexyl isocyanide or *tert*-butyl isocyanide in good to excellent yield. An extensive scope study, however, was not provided. The proposed mechanism is similar to route II of the general cycle in Scheme 2. Nb cycles in between oxidation state V and III in the catalytic cycle. First the isocyanide fragment



Scheme 57 (a) Nb^{V}-Catalysed imidoylation of nitrenes towards carbodiimides (**206**). (b) Postulated intermediates involved in the reaction mechanism.

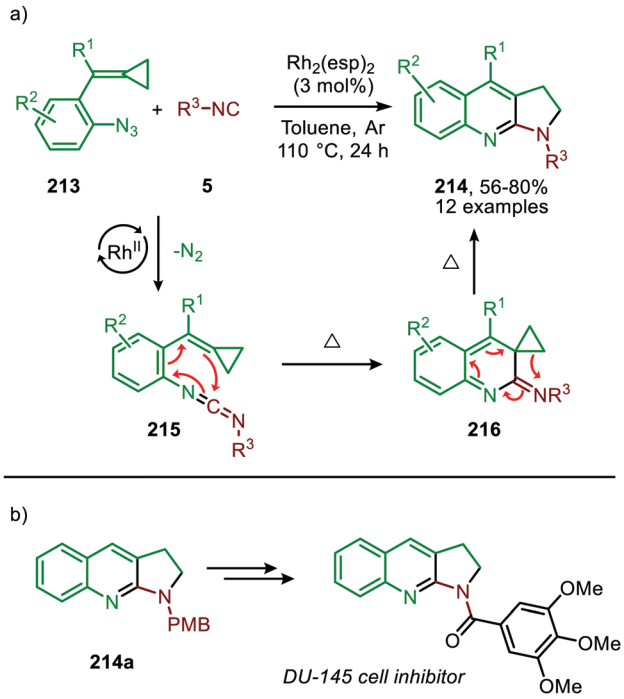


Scheme 58 One-pot Rh^{I}-catalysed nitrene transfer to isocyanide (**5**) followed by a [4+1]-cycloaddition furnishing 3-amino-2*H*-pyrrol-2-imines (**211**).

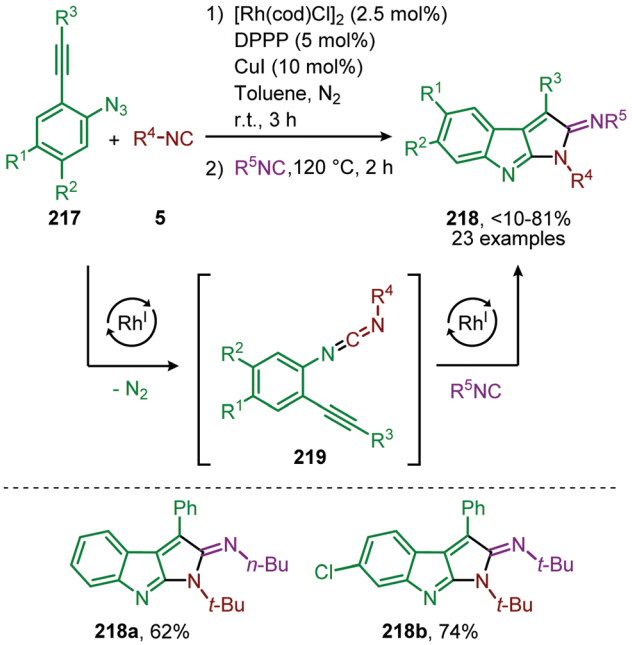
coordinates to bis-imido complex **205**, affording Nb-complex **207** (Scheme 57b), which is in equilibrium with η^2- coordinated metallacycle **208**. The latter undergoes reductive elimination and releases the carbodiimide **206**, concomitantly coordinating azide and isocyanide forming Nb complex **209**. In this step the oxidation state reduces from V to III. This is followed by dissociation of the isocyanide and formation of four-center intermediate **210**. Subsequently, bis-imido complex **207** is regenerated with the release of N_2 and coordination of the isocyanide. The authors observed that the use of aromatic isocyanides resulted in a nitrene metathesis instead of affording the corresponding carbodiimide. This *scrambling* process resembles the earlier described metathesis process in the Ti-catalysed nitrene transfer to isocyanides (Scheme 41).

Rhodium. Rhodium is a reoccurring catalyst for the imidoylation and carbonylation of carbenes as well as in the imidoylation of nitrenes. This is often followed by *in situ* transformation of the resulting corresponding carbodiimide (**9**) making it especially powerful for organic synthesis. Zhang *et al.* demonstrated this *via* a Rh^{I}-catalysed nitrene transfer to isocyanides followed by a [4+1]-cycloaddition with an additional isocyanide. This one-pot operation affords 3-amino-2*H*-pyrrol-2-imines (**211**) (Scheme 58).[94] The reaction is receptive to an array of aryl substituted vinyl azides (**210**) (69–96%). In addition, aromatic isocyanides as well as aliphatic isocyanides were accepted in the formation of carbodiimide **212** and the subsequent [4+1]-cycloaddition. However, using aliphatic isocyanides in the first step (carbodiimide formation) furnished the product either in trace amount or low yields, indicating that aromatic isocyanides tend to work better for the nitrene transfer. A similar trend was observed in the Rh-catalysed carbene transfer to isocyanides, where aromatic isocyanides were superior to aliphatic isocyanides (*vide supra*). The presumed mechanism is initiated by generating a carbodiimide according to either route I or II of the general catalytic cycle (Scheme 2). Subsequently, by adding another isocyanide and heating to 120 °C the carbodiimide undergoes a thermal [4+1]-cycloaddition forming 3-amino-2*H*-pyrrol-2-imines (**211**).

Additionally, Shi *et al.* reported a Rh^{II}-catalysed cascade process towards 2,3-dihydropyrrolo[2,3-*b*]quinolines (**214**) based on isocyanides and functionalised aromatic azides (**213**) (Scheme 59).[95] The reaction proceeds *via* carbodiimide **215**, which undergoes a 6π-electrocyclisation. The thus formed intermediate **216** furnishes, upon thermal rearrangement, the desired product **214**. Both aromatic-, benzylic and secondary- or tertiary aliphatic isocyanides were tolerated in the tandem reaction. The authors propose a mechanism, which is in accordance with either route I or II of the mechanism depicted in Scheme 2. Although this Rh^{II} catalyst is known to participate in radical reactions involving distinct nitrene species,[96] a radical mechanism was ruled out based on radical trapping experiments using TEMPO as radical scavenger. Noteworthy,



Scheme 59 (a) Rh^{II}-Catalysed nitrene transfer/electrocyclisation/thermal rearrangement cascade forming 2,3-dihydropyrrolo[2,3-*b*]-quinolines (**214**). esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid. (b) Access to DU-145 cell inhibitor from product **214a**.



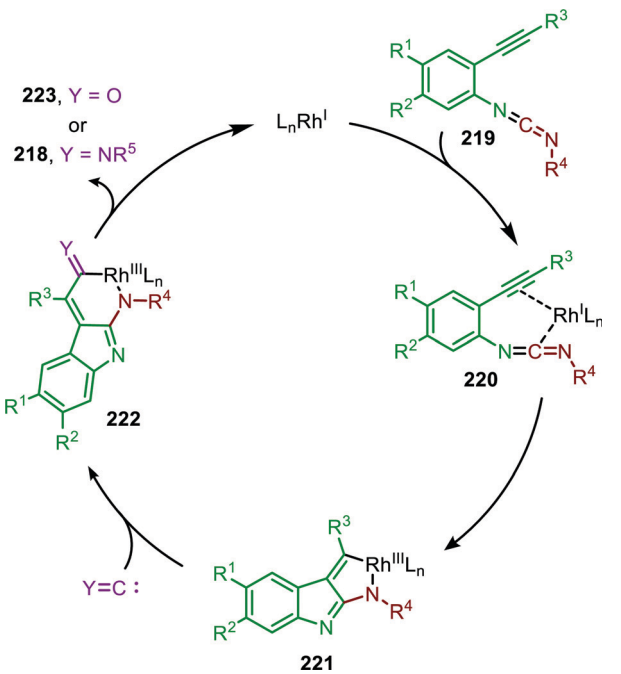
Scheme 60 One-pot Rh^{I}-catalysed nitrene transfer to isocyanides followed by isocyanide addition and aza-Pauson-Khand type cyclisation on carbodiimide **219**.

the authors provided a facile method to synthesise a DU-145 cell inhibitor, starting from product **214a** (Scheme 59b).

Additionally, a self-relay[97] Rh^{I}-catalysed transformation towards pyrrolo[2,3-*b*]indol-2(1*H*)-imine scaffolds **218** was developed by Zhang and co-workers (Scheme 60).[98] The reaction proceeds *via* a Rh^{I}-catalysed nitrene transfer to isocyanides furnishing carbodiimide **219**. By addition of isocyanide to the same reaction vessel and heating to 120 °C an aza-Pauson-Khand type cyclisation occurs yielding pyrroloindoles **218**. In general, for the nitrene transfer step, linear primary-, cyclic secondary and tertiary aliphatic isocyanides were able to form the product **218** in good yields. When aromatic isocyanides were employed in the carbodiimide formation product formation occurs, albeit less efficiently (47–66%).

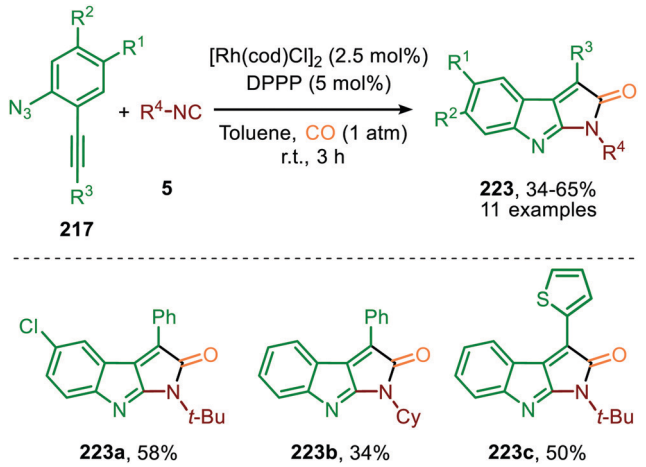
Based on the provided mechanistic data the formation of carbodiimide **219** presumably proceeds according to either route I or II in the general mechanism in Scheme 2. The cyclisation commences with coordination of intermediate **219** to a Rh^{I}-species (Scheme 61). After formation of π-complex **220** an oxidative cyclisation occurs, furnishing cyclometallated Rh^{III}-species **221**. Subsequently, an isocyanide can insert into the Rh-C bond, forming metallacycle **222**, followed by reductive elimination to afford product **218**. The authors observe that the addition of $Cu^{I}I$ improved the yield of the reaction. However, in their proposed mechanism they do not consider its catalytic role in either the nitrene transfer or the aza-Pauson-Khand type cyclisation.

Instead of utilizing an isocyanide in the aza-Pauson-Khand reaction, CO could be used and present at the start of the reaction (reaction atmosphere) selectively forming scaffolds



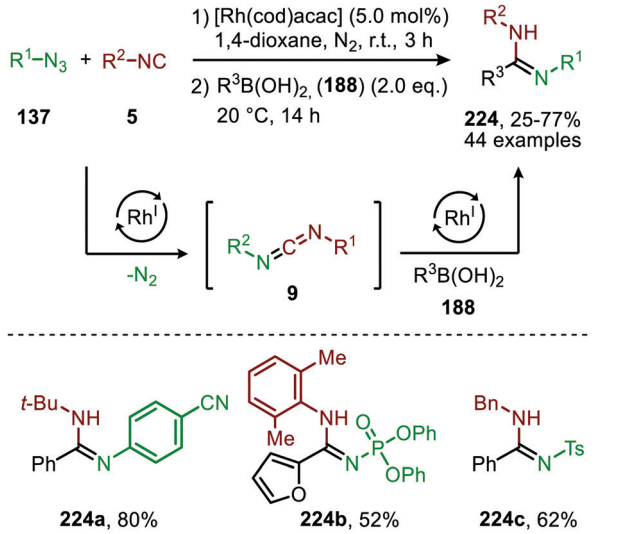
Scheme 61 Mechanism of the Rh^{I}-catalysed relay-cycle involving oxidative cyclometallation of carbodiimide **219** into **221**.

223 in moderate yields (Scheme 62).[98] Presence of both isocyanide and CO at the same time implies that in this catalytic system, the isocyanide reacts faster in the carbodiimide formation step than its isoelectronic counterpart CO. Noteworthy is that the Cu^{I}-salt was omitted in this case.



Scheme 62 Tandem Rh^{I}-catalysed nitrene transfer to isocyanides and Pauson-Khand type cyclisation on carbodiimide **219**.

An additional self-relay Rh^{I}-catalysed cross-coupling of azides (**137**), isocyanides (**5**) and aryl- or alkenyl boronic acids (**188**) to access highly functionalized amidines (**224**) (Scheme 63) was reported by the group of Zhang.[99] The reaction accepted a variety of electron poor nitrene precursors, such as sulfonyl-, phosphoryl-, and acyl azides (**137**). On the other hand, the isocyanide scope was limited to *tert*-butyl isocyanide, cyclohexyl isocyanide, benzyl isocyanide and 2,6-xylyl isocyanide. Presumably, the mechanism for *in situ* carbodiimide (**9**) formation operates *via* either route I or II of the generalized mechanism (Scheme 2). The second catalytic cycle is initiated by addition of boronic acid **188** providing transmetallation of the aryl or alkenyl moiety to the Rh-centre, followed by insertion in the C=N of the *in situ* generated carbodiimide. This generates a *N*-bound Rh^{I}-complex, which undergoes protonolysis with another boronic acid to furnish a rhodium boronate complex accompanied by release of the desired amidine **224**.



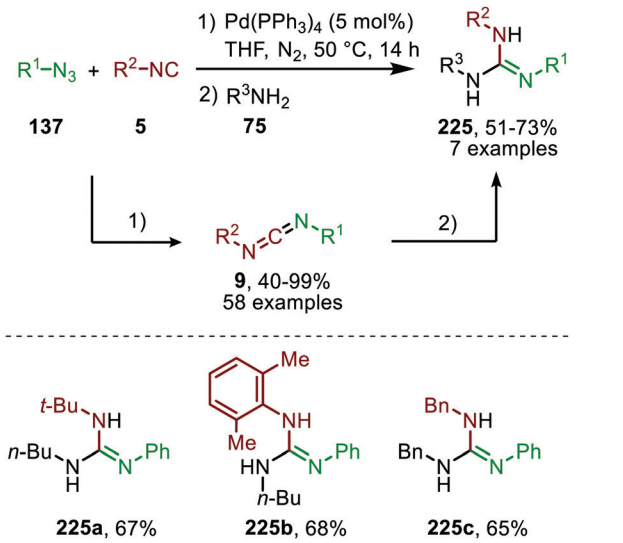
Scheme 63 Self-relay Rh^{I}-catalysed formation of amidines **224** from azides (**137**), isocyanides (**5**) and aryl- or alkenyl boronic acids (**188**).

The rhodium boronate complex regenerates an aryl or alkenyl rhodium complex through β-elimination to close the catalytic cycle.

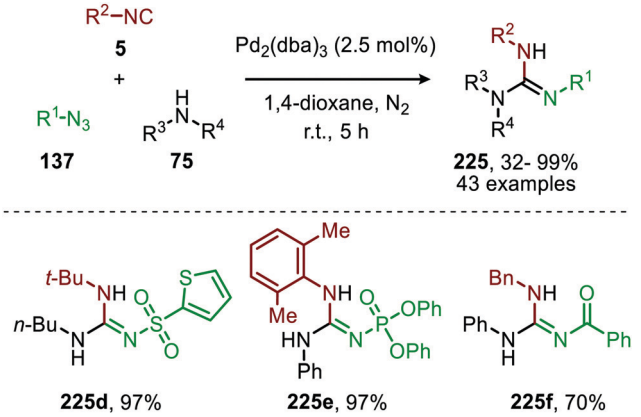
Palladium. Pd-Catalysis holds a pivotal position in the imidoylation reaction of both carbenes and nitrenes. Although the Pd-catalysed imidoylation of nitrenes was covered in our broader review of 2020 on Pd-catalysed cross-coupling reactions with isocyanide insertion[11b] here the focus is on the mechanistic implications.

Zhang and co-workers demonstrated the use of Pd^{0} as catalyst in the nitrene transfer to isocyanides and isolated numerous non-symmetrical carbodiimides (**9**) in moderate to excellent yield (Scheme 64).[100] In addition, they extended their method to the one-pot synthesis of guanidines (**225**) by trapping the carbodiimides (**9**) with primary aromatic- and aliphatic amines. The reaction of aromatic azides in combination with a range of aliphatic and aromatic isocyanides was successful, however the carbodiimide yield dropped when benzylic- or aliphatic azides were evaluated. The authors postulate a mechanism, which is in accordance with either route I or II in Scheme 2. Unfortunately, no in depth mechanistic studies were provided to support their proposed mechanism.

In continuation of their work, they also developed a Pd-catalysed three-component coupling of acyl-, sulfonyl- or phosphoryl azides (**137**), isocyanides (**5**), and primary- and secondary amines (**75**) towards guanidines (**225**) (Scheme 65).[101] Electron poor azides were transformed towards the corresponding *N*-sulfonyl-, *N*-acyl-, and *N*-phosphoryl guanidines (**225**) in moderate to excellent yield. However, lower yields were obtained when benzyl isocyanide or aromatic isocyanides were employed. The amine scope proved to be broad and overall the reaction displayed a high functional group tolerance. The proposed mechanism is in accordance with route I or II of general catalytic cycle (Scheme 2). However, the authors did not



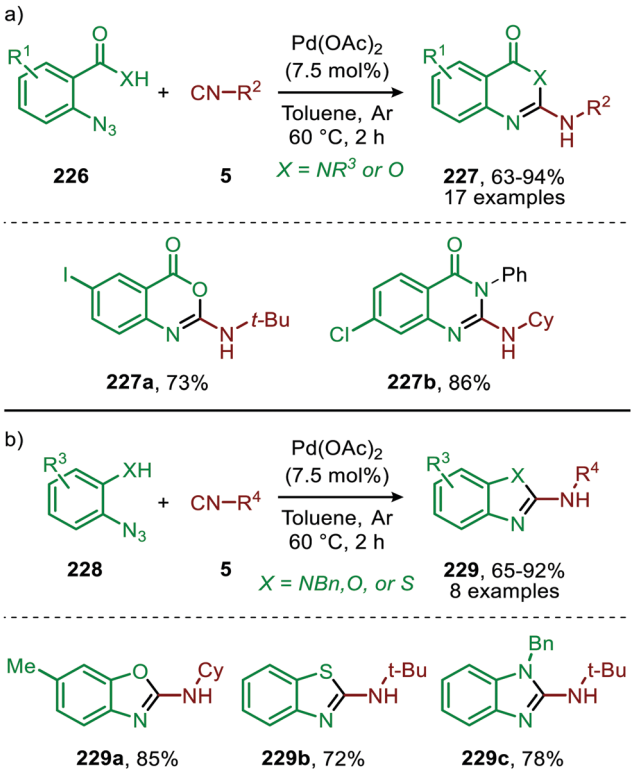
Scheme 64 One-pot Pd^{0}-catalysed synthesis of carbodiimides (**9**) *via* imidoylation of azides (**137**) followed by addition reaction of amines (**75**) providing guanidines (**225**).



Scheme 65 Tandem Pd^0-catalysed synthesis of carbodiimides *via* imidoylation of azides (**136**) followed by addition reaction of amines (**75**) forming guanidines (**225**).

perform any mechanistic or computational studies to provide support.

In addition to the synthesis of guanidines (**225**) *via* initial Pd-catalysed nitrene transfer to isocyanides, Pardansani and co-workers extended the Pd-catalysed transformation to the synthesis of numerous *N*-heterocycles *via* combination with an intra- rather than an intermolecular addition reaction on carbodiimides (Scheme 66).[25] They studied the nitrene transfer



Scheme 66 Tandem Pd^{II}-catalysed synthesis of carbodiimides *via* nitrene transfer to isocyanides followed by intramolecular addition on the *in situ* formed carbodiimide providing (a) benzoxazinones (**227**, X = O), quinazolinones (**227**, X = NR) and (b) benzimidazoles (**229**, X = NR), benzoxazoles (**229**, X = O), and benzothiazoles (**229**, X = S).

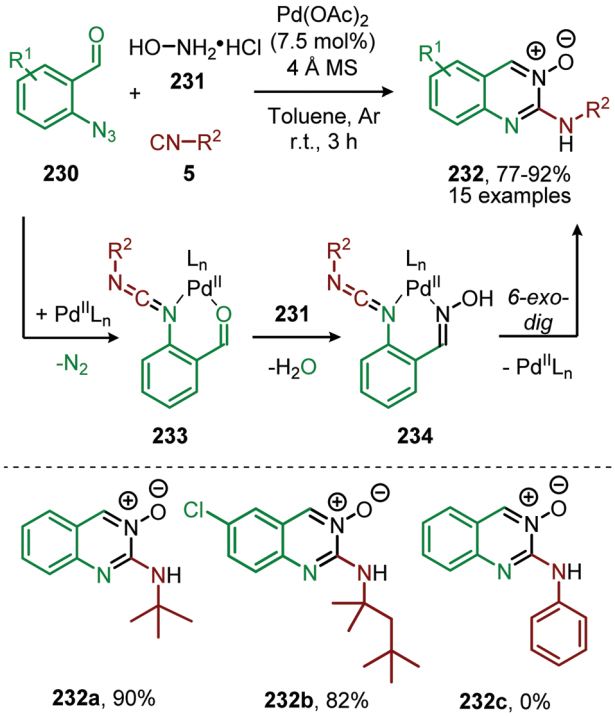
of aryl azides (**226, 228**) (Schemes 66a and b) to isocyanides (**5**) followed by an intramolecular nucleophilic addition on the *in situ* formed carbodiimide moiety to arrive at benzoxazinones (X = O), quinazolinones (X = NR) (**227**) (Scheme 66a), benzimidazoles (X = NR), benzoxazoles (X = O), and benzothiazoles (X = S) (**229**) (Scheme 66b), which could be obtained in good to excellent yield.

The authors conduct an extensive study to determine the substrate scope and both transformations display a high tolerance with respect to the azide **226** and **228** used. Moreover, the reactions with secondary- and tertiary aliphatic isocyanides, benzyl isocyanide, and α-isocyano esters furnished the products in good yield. Even notoriously unstable phenyl isocyanide reacted smoothly in the synthesis, affording the corresponding benzoxazole **229** in 65% yield. Unfortunately, aromatic isocyanides were not tolerated in the synthesis of benzoxazinones (**227**, X = O) and quinazolinones (**227**, X = NR). The authors provided some mechanistic insights for the synthesis of diverse *N*-heterocycles *via* experimental observations and extensive DFT studies. The postulated order of events for carbodiimide formation is in accordance with route I of the general mechanism in Scheme 2, with nitrogen extrusion as the rate-determining step. Interestingly, the authors could not find an energy minimum on the potential energy surface (PES) for the η^2-metallaaziridine intermediate (**13**) (Scheme 3a), which is a commonly proposed intermediate after 1,1-migratory insertion of the isocyanide to the nitrene fragment. Instead, the authors found a transition state resembling the η^2-metallaaziridine intermediate (**13**) (Scheme 3a), indicating that 1,1-migratory insertion towards the η^2-metallated carbodiimide (**12**, Scheme 3a) can proceed in an asynchronous concerted fashion. It is reported in literature that metallaziridines can be stable intermediates for early TMs.[102–104] However, such a metallaaziridine intermediate has not been isolated in the case of Pd.

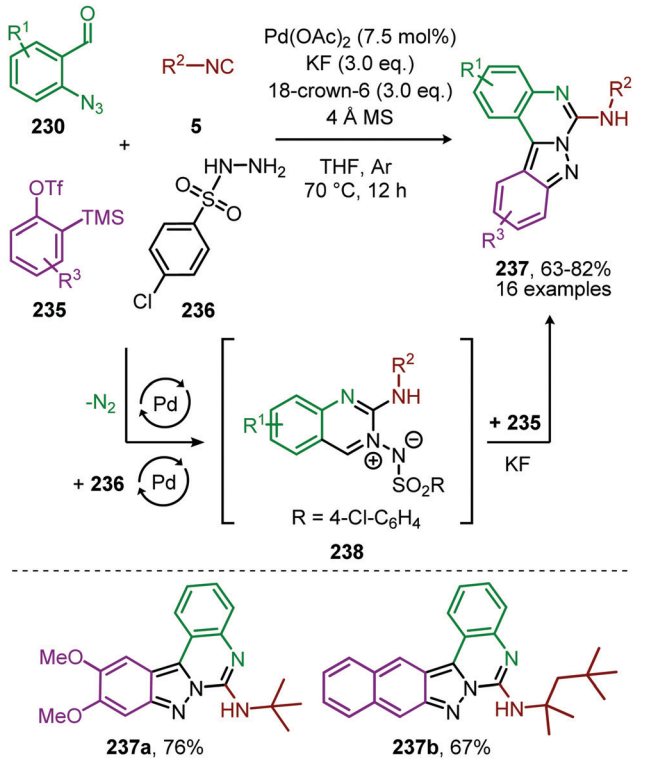
Sawant *et al.* extended the redox neutral Pd^{II}-catalysed nitrene transfer to a three-component reaction of 2-azidobenzaldehydes (**230**), isocyanides (**5**) and hydroxylamine hydrochloride (**231**) for the synthesis of quinazoline-3-oxides (**232**) in good to excellent yields (Scheme 67).[105]

Within this tandem catalytic process, the isocyanide scope is limited towards tertiary aliphatic isocyanides, such as in scaffolds **232a and b** (Scheme 67). It is noteworthy to mention that the reaction operates under relatively mild conditions. Based on control experiments and literature precedents the authors postulate that after nitrene transfer carbodiimide chelated Pd^{II}-complex (**233**) (Scheme 67) is formed. Subsequent condensation of hydroxylamine (**231**) with the benzaldehyde of **233** furnishes Pd-oxime complex **234**, which after Pd-facilitated 6-exo-dig cyclization delivers quinazoline-3-oxides (**232**). The proposed mechanism of carbodiimide formation follows route I of our mechanism depicted in Scheme 2.

This concept of self-relay Pd^{II}-catalysed nitrene transfer followed by 6-exo-dig annulation was also applied by these authors in a four-component coupling towards fluorescent indazolo[2,3-*c*]quinazolin-6-amines (**237**) (Scheme 68).[106] The transformation combines 2-azidobenzaldehydes (**230**),



Scheme 67 Three-component synthesis of quinazoline-3-oxides (**232**) *via* self-relay Pd^{II}-catalysis involving initial nitrene transfer to isocyanides followed by Pd-catalysed *6-exo-dig* cyclisation.



Scheme 68 Four-component synthesis of indazolo[2,3-*c*]quinazolin-6-amines (**237**) *via* self-relay Pd^{II}-catalysis involving initial nitrene transfer to isocyanides followed by Pd-catalysed *6-exo-dig* cyclisation.

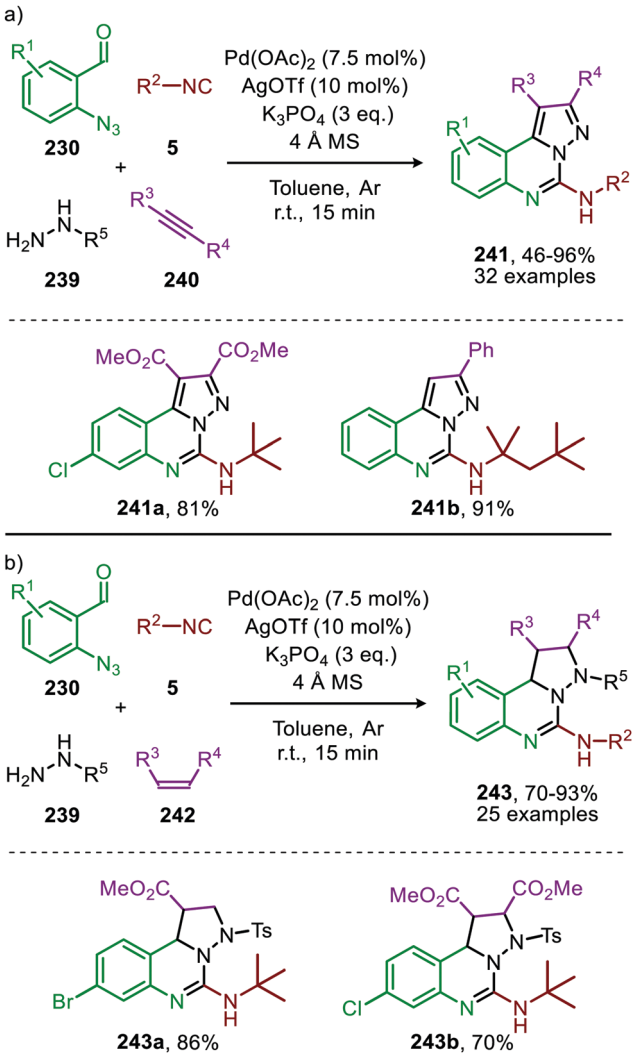
isocyanides (**5**) and *N*-tosylhydrazine (**236**) providing azomethine imine intermediate **238** *via* carbodiimide intermediate **233** as described in Scheme 68. In this case *N*-sulfonylhydrazone rather than oxime is formed from benzaldehyde, which adds in an intramolecular fashion to the carbodiimide. Subsequent dipolar cycloaddition of **238** with an *in situ* generated benzynes derived from 2-trimethylsilylaryl triflates (**235**) and KF,[107] results in products **237**. The reaction tolerates various halogenated 2-azidobenzaldehydes **230**, but the isocyanide scope was limited to tertiary isocyanides. Cycloadditions of benzyne precursors **235** were performed with electron-rich precursors and no 2-trimethylsilylaryl triflates (**235**) with electron-withdrawing substituents were included in this study.

The authors demonstrate the synthetic applicability in the formation of a high quantum yielding organic dye (**237b**). The dye has been used for life cell imaging of the mitochondria and cytoplasm. The authors propose a mechanism based on literature precedents and the carbodiimide is generated according to route I in the general proposed cycle of Scheme 2. Instead of benzynes also alkynes (**240**) (Scheme 69a) or alkenes (**242**) (Scheme 69b) could be used as fourth coupling partner in the cascade sequence between 2-azidobenzaldehydes (**230**), isocyanides (**5**) and *N*-tosylhydrazines (**239**).[108]

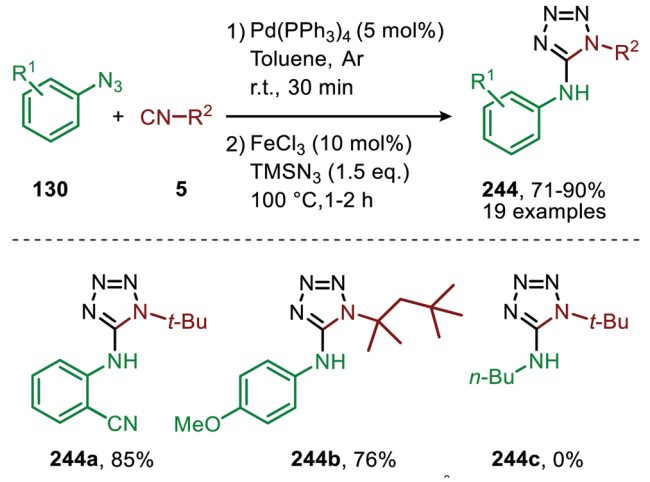
The transformation relies on an orthogonal relay Pd^{II}/Ag^{I}-catalytic process, in which Ag^{I} activates the alkyne or alkene moiety for the [3+2]-cycloaddition with azomethine imine intermediate **238** (Scheme 68), delivering pyrazolo[1,5-*c*]quinazolin-5-amines (**241**) (Scheme 69a) or tetrahydropyrazolo[1,5-*c*]quinazolin-5-amines (**243**) (Scheme 69b). Halogen- or -trifluoromethyl substituted 2-azidobenzaldehydes (**230**) reacted smoothly to afford product **241** or **243** in good to excellent yield. In accordance with previous methodology, the isocyanide scope was limited to tertiary aliphatic isocyanides. In addition, numerous *N*-sulfonyl hydrazines **239** were accepted a well as acyl hydrazines (**239**). Notable is that electron-deficient alkynes or alkenes allow for a successful [3+2]-cycloaddition with azomethine imine intermediate **238** (Scheme 68). The Pd-catalysed formation of carbodiimide intermediate **9** complies with route I (Scheme 2). Noteworthy is that various products (**241**) display anti-cancer activity with derivative **241a** as the most effective according to the essay of the authors.

Finally, these authors also developed a sequential Pd^{0}-catalysed azide-isocyanide coupling into carbodiimide followed by a Fe^{III}-catalysed formal [3+2]-cycloaddition with trimethylsilylazide yielding 5-arylaminotetrazoles (**244**) in good to excellent yield (Scheme 70).[109] This one-pot transformation accepts a variety of diversely substituted aromatic azides (**130**). Aliphatic azides on the other hand did not lead to any product formation. Tertiary and secondary isocyanides were predominantly used throughout the scope study. However, a few examples demonstrate the use of aromatic isocyanides, which also furnished tetrazoles **244** in good yields. The authors propose a catalytic cycle for the nitrene transfer step, which is in agreement with either route I or II of our proposed mechanism (Scheme 2).

In conclusion, compared to the other heteroallenes, carbodiimide synthesis *via* nitrene transfer to isocyanides and *in situ*



Scheme 69 Orthogonal-relay Pd^{II}/Ag^{I}-catalysed four-component synthesis of (a) pyrazolo[1,5-*c*]quinazolin-5-amine (**241**) and; (b) tetrahydropyrazolo[1,5-*c*]quinazolin-5-amines (**243**).



Scheme 70 Tetrazole (**244**) synthesis *via* one-pot Pd^{0}-catalysed formation of carbodiimides followed by an $FeCl_3$-catalysed azide addition to carbodiimide.

transformation thereof holds a pivotal position. This is also reflected in the amount of base-metal catalysed processes that are already reported, of which cobalt is most often encountered. The use of simple Co^{II}-salts as base-metal catalyst is more prominent than for the carbene transfer to isocyanides (Section 2.2) and multiple nitrene transfer-based cascades have been reported. However, these cascade processes are limited to solely sulfonylazides as the nitrene precursor. Mechanistic studies[84] reveal that the isocyano-Co^{II}-complex is the active species as was also observed for the Co^{II}-catalysed carbene transfer to isocyanides (Scheme 17). Co^{II} seems to tolerate both aliphatic- and aromatic isocyanides. However, in transformations where both aliphatic and aromatic isocyanides were used as input, there is typically a preference for either one of the two. As for the Iron-catalysed examples both aliphatic and aromatic isocyanides seem to be both equally well accepted in the synthesis of carbodiimides, indicating that iron has the potential to allow for the use of both type of isocyanides in a cascade process. However, to date noble metal catalysis still allows for accessing a more divers set of functionalities. In addition, the scope for nitrene precursors is typically more diverse. Unfortunately, rationalizing the acceptance of either aliphatic or aromatic isocyanides in different transformations with different TM's remains troublesome with the available experimental data. In the nitrene transfer to isocyanides, Rh typically performs well for tertiary aliphatic and aromatic isocyanides, whereas Pd holds a strong preference for tertiary- and secondary aliphatic isocyanides. Although aromatic isocyanides do work for Pd, they typically perform less in the reaction. With regards to the transformations accepting aliphatic isocyanides, tertiary aliphatic isocyanides generally work best whereas primary aliphatic isocyanides and α-acidic isocyanides typically do not afford the desired product. Aromatic isocyanides standardly require sterically hinderance, such as commonly encountered 2,6-dimethylphenyl isocyanide.

With respect to the preferred mechanism for the noble-metal catalysed transformations, in the case of Pd computational data supports the formation of a Pd-isocyano species prior to nitrene formation, thereby favoring route I.[25] However, route II cannot be fully ruled out in most reports due to a lack of experimental supporting data. The same holds for the Rh-catalysed examples.

4 Summary and outlook

This review highlights the current synthetic utility and mechanistic considerations of the transition metal (TM)-catalysed synthesis of heteroallenes (*i.e.* ketenes, ketenimines, isocyanates and carbodiimides) *via* carbene- and nitrene transfer reactions towards carbon monoxide and isocyanides offering a lot of opportunities to create chemical diversity.

From the reviewed literature it is evident that *in situ* manipulation of these reactive heteroallenes is preferred and provides a powerful tool in the synthesis of a variety of functional groups

and organic molecules, including numerous heterocycles. Typical follow up reactions can be executed in a one-pot or even more challenging tandem process. These follow up reactions can be catalysed by the metal involved in the group transfer (relay-catalysis). Sometimes an additional transition metal is required (orthogonal relay-catalysis). Of course also a non-transition metal-catalysed follow up process is possible, indicating the huge potential for organic synthesis. The tandem processes are often multicomponent reactions ideally suited to maximize diversity for molecular library synthesis in a step-efficient manner. Different reaction types with the double bond of the heteroallenes have been exemplified such as nucleophilic addition, (formal) cycloaddition and electrocyclisation reactions. In comparison to carbon monoxide, an isocyanide provides an additional point of diversity. It can both end up in or as amino substituent of the azaheterocyclic ring itself. This certainly does not make carbon monoxide less attractive, it just creates other opportunities. After all, it is a very important building block in contemporary chemical industry and more readily accessible in comparison to isocyanides. In heteroallene synthesis it fulfils a powerful role, as both isocyanates (transfer to nitrene) and ketenes (transfer to carbenes) can be accessed with important applications, *i.e.* monomers for polyurethanes and privileged β-lactams *via* [2+2]-cycloaddition with imines, respectively.

Palladium and rhodium are to date the most widely employed transition metals to catalyse the carbene or nitrene transfer to carbon monoxide and isocyanides. Pleasingly, a handful of base-metal catalysed processes have already been developed, but these generally do not include *in situ* transformation of the generated heteroallenes. However, cobalt proves to be a promising candidate in this respect, both in the carbonylation of carbenes as well as in the imidoylation of nitrenes it has been accompanied with *in situ* further transformations. Further research in other base-metal systems, such as iron and nickel is required to replace the best in class noble-metal catalysed processes in accordance with sustainable developments. A deeper understanding of the mechanism will certainly play a pivotal role in future developments of such novel catalytic systems that allow for both efficient formation and manipulation of the linear intermediates. The use of redox-active ligands is expected to even allow to use early transition metals and are therefore appealing. Only one example is currently available and more research is certainly needed here. Its combination with *in situ* further transformations is not explored yet, providing interesting opportunities.

We set out to provide general mechanisms for heteroallene formation (route I–III) in the introduction section of this review, based on the proposals found throughout the literature. These generalised mechanistic pathways hold merit for a wide variety of TMs in both group transfer reactions to CO and isocyanides. Deviations or more detailed aspects of the general mechanisms have been discussed at the place where the specific transformations are shown in the review. The key step in the catalytic cycle is the reaction of the C1-isocyanide/carbon monoxide fragment with the metal-carbene/nitrene species, where route I and II both involve a 1,1-migratory insertion step to arrive at the corresponding η^2-metallacycle. This is proposed to be an intermediate for low valent early transition metals. However, for late transition metals this could best be considered a transition state, relying on the computational work available. The difference between route I and II is just the order of CO/isocyanide coordination, which is specific for each catalytic system. Outer sphere addition of the C1-fragment to the metal-carbene/nitrene species (route III) is less encountered, but can be observed with complexes lacking a vacant TM coordination site to allow 1,1-migratory insertion, such as in Co^{II}-porphyrin-based systems. Further detailed mechanistic studies and generation of more information with relation to the transition metal employed will be of great importance in the development of additional cascade processes, especially with base metals. Ligand design is expected to play a major role in advancing this field further.

All in all, we hope this review will induce further research into the transition metal-catalysed group transfer reaction of carbenes and nitrenes to CO and isocyanides. Research is required to expand the range of accessible organic compounds *via* further transformation of *in situ* generated heteroallenes in one-pot or tandem fashion. Acquiring a deeper mechanistic understanding will be essential to advance heteroallene synthesis with base metal catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

T. R. R. and R. V. A. O. acknowledge financial support of Nederlandse Organisatie voor Wetenschappelijk Onderzoek (N. W. O.) (ECHO-grant). B. U. W. M. and R. V. A. O. acknowledge financial support of Fund for Scientific Research Flanders (FWO) (Senior Research Project G0D1921N). B. U. W. M. thanks the Francqui Foundation for an appointment as Collen Francqui Research Professor.

Notes and references

1 (*a*) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091–1160; (*b*) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. N. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981–10080.

2 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Rev. Soc.*, 2016, **45**, 546–576.

3 (*a*) F. Kuijpers, J. I. van der Vlugt, S. Schneider and B. de Bruin, *Chem. – Eur. J.*, 2017, **23**, 13819–13829; (*b*) L. W. Ye, X. Q. Zhu, R. L. Sahani, Y. Xu, P. C. Qian and R. S. Liu, *Chem. Rev.*, 2021, **121**, 9039–9112; (*c*) Y. Wang, X. Lai, K. Huang, S. Yadav, G. Qiu, L. Zhang and H. Zhou, *Org. Chem. Front.*, 2021, **8**, 1677–1693.

4 (*a*) X. Qi and Y. Lan, *Acc. Chem. Res.*, 2021, **54**, 2905–2915; (*b*) D. G. Ene and M. P. Doyle, *Chim. Oggi*, 1998, **16**, 37–39; (*c*) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810–13889; (*d*) M. Jia and S. Ma, *Angew. Chem., Int. Ed.*, 2016, **55**, 9134–9166.
5 (*a*) A. H. Li, L. X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341–2372; (*b*) G. T. Gurmessa and G. S. Singh, *Res. Chem. Intermed.*, 2017, **43**, 6447–6504.
6 (*a*) H. Pellissier, *Adv. Synth. Catal.*, 2014, **356**, 1899–1935; (*b*) N. Jung and S. Bräse, *Angew. Chem., Int. Ed.*, 2012, **51**, 5538–5540.
7 (*a*) A. H. Li, L. X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341–2372; (*b*) S. Jana, Y. Guo and R. M. Koenigs, *Chem. – Eur. J.*, 2021, **27**, 1270–1281.
8 Carbene insertion into X–H bonds: (*a*) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2903; (*b*) D. Gillingham and N. Fei, *Chem. Soc. Rev.*, 2013, **42**, 4918–4931; (*c*) B. Wang, D. Qiu, Y. Zhang and J. Wang, *Beilstein J. Org. Chem.*, 2016, **12**, 796–804.
9 Nitrene insertion into C–H bonds: (*a*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061–5074; (*b*) B. Plietker and A. Röske, *Catal. Sci. Technol.*, 2019, **9**, 4188–4197.
10 (*a*) X. Wu, H. Neumann and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 4986–5009; (*b*) J. B. Peng, F. P. Wu and X. F. Wu, *Chem. Rev.*, 2019, **119**, 2090–2127; (*c*) J. Pospech, I. Fleischer, R. Franke, S. Buchholz and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 2852–2872; (*d*) A. Brennfuhrer, H. Neumann and M. Beller, *ChemCatChem*, 2009, **1**, 28–41.
11 (*a*) T. Vlaar, E. Ruijter, B. U. W. Maes and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2013, **52**, 7084–7097; (*b*) J. W. Collet, T. R. Roose, B. Weijers, B. U. W. Maes, E. Ruijter and R. V. A. Orru, *Molecules*, 2020, **25**, 4906; (*c*) J. W. Collet, T. R. Roose, E. Ruijter, B. U. W. Maes and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2020, **59**, 540–558.
12 (*a*) J. Dupont and M. Pfeffer, *J. Chem. Soc., Dalton Trans.*, 1990, 3193–3198; (*b*) J. Vicente, J. A. Abad, A. D. Frankland, J. López-Serrano, M. C. Ramírez de Arellano and P. G. Jones, *Organometallics*, 2002, **21**, 272–282; (*c*) J. Vicente, I. Saura-Llamas, C. Grünwald, C. Alcaraz, P. G. Jones and D. Bautista, *Organometallics*, 2002, **21**, 3587–3595; (*d*) H. M. F. Viart, A. Bachmann, W. Kayitare and R. Sarpong, *J. Am. Chem. Soc.*, 2017, **139**, 1325–1329; (*e*) K. Usui, B. E. Haines, D. G. Musaev and R. Sarpong, *ACS Catal.*, 2018, **8**, 4516–4527.
13 (*a*) M. Tobisu and N. Chatani, *Chem. Lett.*, 2011, **40**, 330–340; (*b*) M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron and J. Zhu, *Chem. Soc. Rev.*, 2017, **46**, 1295–1357; (*c*) T. Kaur, P. Wadhwa and A. Sharma, *RSC Adv.*, 2015, **5**, 52769–52787.
14 A. Domling, *Chem. Rev.*, 2006, **106**, 17–89.
15 (*a*) X. F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1–35; (*b*) S. Perrone, L. Troisi and A. Salomone, *Eur. J. Org. Chem.*, 2019, 4626–4643.
16 A. V. Lygin and A. De Meijere, *Angew. Chem., Int. Ed.*, 2010, **49**, 9094–9124.
17 (*a*) P. Lu and Y. Wang, *Chem. Soc. Rev.*, 2012, **41**, 5687–5705; (*b*) M. Alajarin, M. Marin-Luna and A. Vidal, *Eur. J. Org. Chem.*, 2012, 5637–5653.
18 (*a*) A. Williams and I. T. Ibrahim, *Chem. Rev.*, 1981, **81**, 589–636; (*b*) Y. Wang, W. X. Zhang and Z. Xi, *Chem. Soc. Rev.*, 2020, **49**, 5810–5849.
19 (*a*) T. T. Tidwell, *Angew. Chem., Int. Ed.*, 2005, **44**, 5778–5785; (*b*) A. D. Allen and T. T. Tidwell, *Chem. Rev.*, 2013, **113**, 7287–7342.
20 (*a*) S. Ozaki, *Chem. Rev.*, 1972, **72**, 17–40; (*b*) O. Kreye, H. Mutlu and M. A. R. Meier, *Green Chem.*, 2013, **15**, 1431–1455.
21 C. R. Pitts and T. Leckta, *Chem. Rev.*, 2014, **114**, 7930–7953.
22 C. Liang, U. R. Gracida-Alvarez, E. T. Gallant, P. A. Gillis, Y. A. Marques, G. P. Abramo, T. R. Hawkins and J. B. Dunn, *Environ. Sci. Technol.*, 2021, **55**, 14215–14224.
23 V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin and V. Y. Kukushkin, *Chem. Rev.*, 2015, **115**, 2698–2779.
24 M. Elian and R. Hoffmann, *Inorg. Chem.*, 1975, **14**, 1058–1076.
25 A. J. Ansari, R. S. Pathare, A. K. Maurya, V. K. Agnihotri, S. Khan, T. K. Roy, D. M. Sawant and R. T. Pardasani, *Adv. Synth. Catal.*, 2018, **360**, 290–297.
26 R. Aumann, *Angew. Chem., Int. Ed. Engl.*, 1988, 1456–1467.
27 K. J. Cavell, *Coord. Chem. Rev.*, 1996, **155**, 209–243.
28 I. Fernández, F. P. Cossío and M. A. Sierra, *Organometallics*, 2007, **26**, 3010–3017.
29 Z. Zhang, Y. Zhang and J. Wang, *ACS Catal.*, 2011, **1**, 1621–1630.
30 N. Ungvári, T. Kégl and F. Ungváry, *J. Mol. Catal., A*, 2004, **219**, 7–11.
31 R. Tuba and E. F. Ungváry, *J. Mol. Catal. A: Chem.*, 2003, **206**, 59–67.
32 T. Kegl and F. Ungvary, *Lett. Org. Chem.*, 2010, **7**, 634–644.
33 J. Balogh, T. Kégl, F. Ungváry and R. Skoda-Földes, *Tetrahedron Lett.*, 2009, **50**, 4727–4730.
34 I. Ojima and X. Qiu, *J. Am. Chem. Soc.*, 1987, **109**, 6538–6540.
35 (*a*) J. Baloch, Z. Csók, L. Párkányi, F. Ungváry, L. Kollár and R. Skoda-Földes, *J. Organomet. Chem.*, 2012, **718**, 131–138; (*b*) Ethyl diazoacetate **18** & imine **25** were mixed in a 1 : 1 molar ratio.
36 Y. Baek, S. Kim, B. Jeon and P. H. Lee, *Org. Lett.*, 2016, **18**, 104–107.
37 A. Chirila, K. M. van Vliet, N. D. Paul and B. de Bruin, *Eur. J. Inorg. Chem.*, 2018, 2251–2258.
38 N. D. Paul, A. Chirila, H. Lu, X. P. Zhang and B. de Bruin, *Chem. – Eur. J.*, 2013, **19**, 12953–12958.
39 Z. Tang, S. Mandal, N. D. Paul, M. Lutz, P. Li, J. I. Van Der Vlugt and B. De Bruin, *Org. Chem. Front.*, 2015, **2**, 1561–1577.
40 C. Brancour, T. Fukuyama, Y. Ohta, I. Ryu, A. L. Dhimane, L. Fensterbank and M. Malacria, *Chem. Commun.*, 2010, **46**, 5470–5472.
41 T. Fukuyama, Y. Ohta, C. Brancour, K. Miyagawa, I. Ryu, A. L. Dhimane, L. Fensterbank and M. Malacria, *Chem. – Eur. J.*, 2012, **18**, 7243–7247.
42 W. Song, X. Li, K. Yang, X. L. Zhao, D. A. Glazier, B. M. Xi and W. Tang, *J. Org. Chem.*, 2016, **81**, 2930–2942.

43 Z. Zhang, Y. Liu, L. Ling, Y. Li, Y. Dong, M. Gong, X. Zhao, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 4330–4341.
44 J. Volkman and P. Kalck, Carbon Monoxide in Organic Synthesis: Carbonylation Chemistry, in *Cobalt-Catalyzed Carbonylations*, ed. B. Gabriele, WILEY-VCH, Weinheim, 1st edn, 2021, ch. 2, pp. 15–41.
45 H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635–646.
46 A. Grass, N. S. Dewey, R. L. Lord and S. Groysman, *Organometallics*, 2019, **38**, 962–972.
47 Z.-Y. Gu, H. Han, Z.-Y. Li, S.-J. Ji and J.-B. Xia, *Org. Chem. Front.*, 2021, **8**, 1544–1550.
48 (*a*) A. K. Maity, M. Zeller and C. Uyeda, *Organometallics*, 2018, **37**, 2437–2441; (*b*) Y. Zhou, D. R. Hartline, T. J. Steiman, P. E. Fanwick and C. Uyeda, *Inorg. Chem.*, 2014, **53**, 11770–11777.
49 X. Bin, Bu, Z. Wang, X. Di Wang, X. H. Meng and Y. L. Zhao, *Adv. Synth. Catal.*, 2018, **360**, 2945–2951.
50 Y. Yu, Y. Zhang, Z. Wang, Y. X. Liang and Y. L. Zhao, *Org. Chem. Front.*, 2019, **6**, 3657–3662.
51 L. Zhang, T. Liu, Y. M. Wang, J. Chen and Y. L. Zhao, *Org. Lett.*, 2019, **21**, 2973–2977.
52 F. Zhou, K. Ding and Q. Cai, *Chem. – Eur. J.*, 2011, **17**, 12268–12271.
53 Q. Dai, Y. Jiang, J. T. Yu and J. Cheng, *Chem. Commun.*, 2015, **51**, 16645–16647.
54 X. Yan, J. Liao, Y. Lu, J. Liu, Y. Zeng and Q. Cai, *Org. Lett.*, 2013, **15**, 2478–2481.
55 G. S. Chen, S. J. Chen, J. Luo, X. Y. Mao, A. S. C. Chan, R. W. Y. Sun and Y. L. Liu, *Angew. Chem., Int. Ed.*, 2020, **59**, 614–621.
56 Z. Liu, S. Cao, J. Wu, G. Zanoni, P. Sivaguru and X. Bi, *ACS Catal.*, 2020, **10**, 12881–12887.
57 X. Zhang, Z. Liu, X. Yang, Y. Dong, M. Virelli, G. Zanoni, E. A. Anderson and X. Bi, *Nat. Commun.*, 2019, **10**, 1–9.
58 J. Huang, F. Li, L. Cui, S. Su, X. Jia and J. Li, *Chem. Commun.*, 2020, **56**, 4555–4558.
59 (*a*) T. W. Hudnall, A. G. Tennyson and C. W. Bielawski, *Organometallics*, 2010, **29**, 4569–4578; (*b*) T. W. Hudnall, E. J. Moorhead, D. G. Gusev and C. W. Bielawski, *J. Org. Chem.*, 2010, **75**, 2763–2766; (*c*) D. Martin, Y. Canac, V. Lavallo and G. Bertrand, *J. Am. Chem. Soc.*, 2014, **136**, 5023–5030.
60 (*a*) I. D. Jurberg and H. M. L. Davies, *Chem. Sci.*, 2018, **9**, 5112–5118; (*b*) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2018, **58**, 1203–1207.
61 P. A. Sakharov, M. S. Novikov, T. K. Nguyen, M. A. Kinzhalov, A. F. Khlebnikov and N. V. Rostovskii, *ACS Omega*, 2022, **7**, 9071–9079.
62 A. Wurtz, *Justus Liebigs Ann. Chem.*, 1849, **71**, 326.
63 S. Jana, D. Samanta, M. M. Fahad, S. N. Jaisankar and H. Kim, *Polymers*, 2021, **13**, 2875.
64 P. Kaur and V. Tyagi, *Adv. Synth. Catal.*, 2021, **363**, 877–905.
65 R. E. Cowley, N. A. Eckert, J. Elhaïk and P. L. Holland, *Chem. Commun.*, 2009, 1760–1762.
66 B. L. Yonke, J. P. Reeds, P. P. Fontaine, P. Y. Zavalij and L. R. Sita, *Organometallics*, 2014, **33**, 3239–3242.
67 L. Ren and N. Jiao, *Chem. Commun.*, 2014, **50**, 3706–3709.
68 Z. Li, S. Xu, B. Huang, C. Yuan, W. Chang, B. Fu, L. Jiao, P. Wang and Z. Zhang, *J. Org. Chem.*, 2019, **84**, 9497–9508.
69 J. Zhao, Z. Li, S. Yan, S. Xu, M. A. Wang, B. Fu and Z. Zhang, *Org. Lett.*, 2016, **18**, 1736–1739.
70 J. P. Simeone and J. R. Sowa, *Tetrahedron*, 2007, **63**, 12646–12654.
71 Y. Zhang, Z. Yin, H. Wang and X. F. Wu, *Org. Lett.*, 2019, **21**, 3242–3246.
72 J. Zhao, Z. Li, S. Song, M. A. Wang, B. Fu and Z. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 5545–5549.
73 S. Y. Chow, M. Y. Stevens and L. R. Odell, *J. Org. Chem.*, 2016, **81**, 2681–2691.
74 T. Peddarao, A. Baishya, M. K. Barman, A. Kumar and S. Nembenna, *New J. Chem.*, 2016, **40**, 7627–7636.
75 (*a*) P. Debnath, M. Baeten, N. Lefevre, S. Van Daele and B. U. W. Maes, *Adv. Synth. Catal.*, 2015, **357**, 197–209; (*b*) M. Baeten and B. U. W. Maes, *Adv. Synth. Catal.*, 2016, **358**, 826–833.
76 W. P. Fehlhammer and W. Beck, *Z. Anorg. Allg. Chem.*, 2015, **641**, 1599–1678.
77 E. P. Beaumier, M. E. McGreal, A. R. Pancoast, R. H. Wilson, J. T. Moore, B. J. Graziano, J. D. Goodpaster and I. A. Tonks, *ACS Catal.*, 2019, **9**, 11753–11762.
78 Z. W. Davis-Gilbert, X. Wen, J. D. Goodpaster and I. A. Tonks, *J. Am. Chem. Soc.*, 2018, **140**, 7267–7281.
79 E. D. Glendening, C. R. Landis and F. Weinhold, *J. Comput. Chem.*, 2013, **34**, 1429–1437.
80 M. Yousif, D. J. Tjapkes, R. L. Lord and S. Groysman, *Organometallics*, 2015, **34**, 5119–5128.
81 S. S. Kurup, R. J. Staples, R. L. Lord and S. Groysman, *Molecules*, 2020, **25**, 273.
82 T. Saegusa, Y. Ito and T. Shimizu, *J. Org. Chem.*, 1970, **11**, 3995–3996.
83 R. E. Cowley, M. R. Golder, N. A. Eckert, M. H. Al-Afyouni and P. L. Holland, *Organometallics*, 2013, **32**, 5289–5298.
84 Z. Y. Gu, Y. Liu, F. Wang, X. Bao, S. Y. Wang and S.-J. Ji, *ACS Catal.*, 2017, **7**, 3893–3899.
85 T. Jiang, Z. Y. Gu, L. Yin, S. Y. Wang and S.-J. Ji, *J. Org. Chem.*, 2017, **82**, 7913–7919.
86 Z. Y. Gu, J. H. Li, S. Y. Wang and S.-J. Ji, *Chem. Commun.*, 2017, **53**, 11173–11176.
87 Z. Y. Gu, R. Zhang, S. Y. Wang and S.-J. Ji, *Chin. J. Chem.*, 2018, **36**, 1011–1016.
88 S. Jiang, W.-B. Cao, H.-Y. Li, X.-P. Xu and S.-J. Ji, *Green Chem.*, 2021, **23**, 2619–2623.
89 S. Jiang, W.-B. Cao, X.-P. Xu and S.-J. Ji, *Org. Lett.*, 2021, **23**, 6740–6744.
90 C. A. Laskowski and G. L. Hillhouse, *Organometallics*, 2009, **28**, 6114–6120.
91 S. Wiese, M. J. B. Aguila, E. Kogut and T. H. Warren, *Organometallics*, 2013, **32**, 2300–2308.
92 A. I. Nguyen, R. A. Zarkesh, D. C. Lacy, M. K. Thorson and A. F. Heyduk, *Chem. Sci.*, 2011, **2**, 166–189.

93 B. M. Kriegel, R. G. Bergman and J. Arnold, *J. Am. Chem. Soc.*, 2016, **138**, 52–55.
94 Y. Wang, Z. Li, H. Zhao and Z. Zhang, *Synthesis*, 2019, 3250–3258.
95 K. Chen, X. Y. Tang and M. Shi, *Chem. Commun.*, 2016, **52**, 1967–1970.
96 K. Chen, Z. Z. Zhu, J. X. Liu, X. Y. Tang, Y. Wei and M. Shi, *Chem. Commun.*, 2016, **52**, 350–353.
97 N. T. Patil, V. S. Shinde and B. Gajula, *Org. Biomol. Chem.*, 2012, **10**, 211–224.
98 Z. Zhang, F. Xiao, B. Huang, J. Hu, B. Fu and Z. Zhang, *Org. Lett.*, 2016, **18**, 908–911.
99 Z. Zhang, B. Huang, G. Qiao, L. Zhu, F. Xiao, F. Chen, B. Fu and Z. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 4320–4323.
100 Z. Zhang, Z. Li, B. Fu and Z. Zhang, *Chem. Commun.*, 2015, **51**, 16312–16315.
101 G. Qiao, Z. Zhang, B. Huang, L. Zhu, F. Xiao and Z. Zhang, *Synthesis*, 2018, 330–340.
102 L. Li, K. E. Kristian, A. Han, J. R. Norton and W. Sattler, *Organometallics*, 2012, **31**, 8218–8224.
103 J. A. Bexrud, P. Eisenberger, D. C. Leitch, P. R. Payne and L. L. Schafer, *J. Am. Chem. Soc.*, 2009, **131**, 2116–2118.
104 P. Bazinet, G. P. A. Yap and D. S. Richeson, *Organometallics*, 2001, **20**, 4129–4131.
105 R. S. Pathare, A. K. Maurya, A. Kumari, V. K. Agnihotri, V. P. Verma and D. M. Sawant, *Org. Biomol. Chem.*, 2019, **17**, 363–368.
106 A. J. Ansari, G. Joshi, P. Sharma, A. K. Maurya, R. K. Metre, V. K. Agnihotri, C. G. Chandaluri, R. Kumar, S. Singh and D. M. Sawant, *J. Org. Chem.*, 2019, **84**, 3817–3825.
107 S. Yoshida, Y. Hazama, Y. Sumida, T. Yano and T. Hosoya, *Molecules*, 2015, **20**, 10131–10140.
108 D. M. Sawant, S. Sharma, R. S. Pathare, G. Joshi, S. Kalra, S. Sukanya, A. K. Maurya, R. K. Metre, V. K. Agnihotri, S. Khan, R. Kumar and R. T. Pardasani, *Chem. Commun.*, 2018, **54**, 11530–11533.
109 R. S. Pathare, A. J. Ansari, S. Verma, A. Maurya, A. K. Maurya, V. K. Agnihotri, A. Sharon, R. T. Pardasani and D. M. Sawant, *J. Org. Chem.*, 2018, **83**, 9530–9537.