Isocyanide Insertion

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Palladium-Catalyzed Migratory Insertion of Isocyanides: An Emerging Platform in Cross-Coupling Chemistry

Tjøstil Vlaar, Eelco Ruijter, Bert U. W. Maes,* and Romano V. A. Orru**

heterocycles · homogeneous catalysis · isocyanides · palladium · synthetic methods

Isocyanides have been important building blocks in organic synthesis since the discovery of the Ugi reaction and related isocyanide-based multicomponent reactions. In the past decade isocyanides have found a new application as versatile C_1 building blocks in palladium catalysis. Palladium-catalyzed reactions involving isocyanide insertion offer a vast potential for the synthesis of nitrogen-containing fine chemicals. This Minireview discusses all the achievements in this emerging field.

1. Introduction

Palladium catalysis is of undisputed importance in organic synthesis for the formation of C–C, C–O, and C–N bonds,[1] and its impact on contemporary synthetic method development in the production of fine chemicals is enormous.[2] It is therefore not surprising that Heck, Negishi, and Suzuki were awarded the Nobel Prize in Chemistry 2010 for their groundbreaking contribution to this chemistry. In addition to the well-known single-bond-forming reactions, carbon monoxide (CO) has emerged as a valuable C_1 building block in palladium-catalyzed processes and has been used for the construction of important carbonyl functionalities (Figure 1 a).[3] CO is often used in palladium-catalyzed cascade reactions to increase molecular complexity of the products by incorporating carbonyl groups and many important heterocycles can be prepared atom economically in this manner.[4]

Isocyanides are highly versatile reagents which have found widespread application in organic, medicinal, and combinatorial chemistry (e.g. multicomponent reactions, heterocycle synthesis, and cycloadditions).[5] Since isocyanides are isoelectronic with CO (Figure 1 b), they show similar reactivity towards palladium and undergo the same fundamental transformations. However, their use in palladium catalysis is much less explored. Palladium pincer complexes have been used to activate α-acidic isocyanides for [3+2] cycloadditions,[6] but isocyanide insertive (or imidoylative) palladium-catalyzed reactions similar to carbonylative cross-couplings are scarce. This scarcity is surprising considering the significant advantages of isocyanides. Isocyanides are easily handled liquids or solids and can therefore be used in stoichiometric quantities, whereas CO is a toxic gas typically used in excess and under high pressures. Most importantly, however, isocyanides have a diversity point, which makes them more flexible. Consequently, palladium-catalyzed reactions utilizing isocyanide insertion offer tremendous opportunities for the synthesis of fine chemicals containing a nitrogen functionality. It is therefore not surprising that this type of chemistry has seen a surge of interest in recent years (Figure 2).

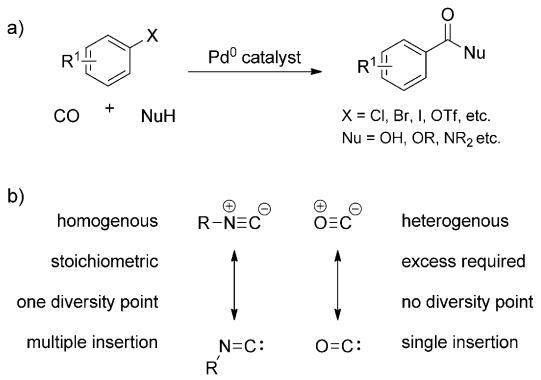

Figure 1. a) Typical CO insertion reactions. b) isoelectronic isocyanides.

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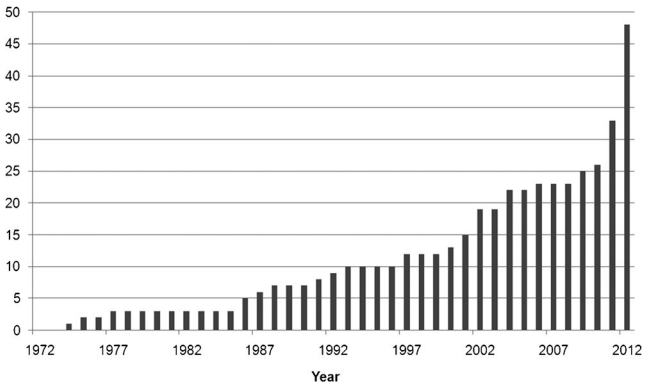


Figure 2. Cumulative number of publications on palladium-catalyzed reactions involving isocyanide insertion.

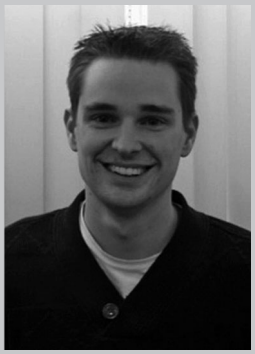
A possible explanation for the scarcity of imidoylative palladium-catalyzed processes is the tendency of isocyanides to undergo multiple consecutive insertions. The insertion of two or three molecules of isocyanide is commonly described and depends on a variety of factors, including ligand, solvent, and type of isocyanide used.[7] Triple isocyanide insertion leads to a stable palladium species by coordination of the nitrogen atom from the first inserted isocyanide, which often prevents more isocyanide insertions.[8] However, polymerization of isocyanides by palladium catalysts is also known.[9] Detailed studies into the mechanism of isocyanide insertion into palladium–aryl, palladium–alkyl, and palladium–allyl bonds have been reported.[10] An important recent observation is that electronically and sterically different isocyanides have the same coordinating ability towards Pd^{II}, but a different rate of migratory insertion.[11]

Many excellent reviews are available that describe the reactivity of isocyanides and their use in organic synthesis in great detail.[5] In this Minireview we exclusively focus on palladium-catalyzed reactions involving migratory insertion of isocyanides into Pd–C or Pd–heteroatom bonds. Stoichiometric insertions of isocyanides and reactions catalyzed by other metals are beyond the scope of this text. To the best of our knowledge, all known palladium-catalyzed isocyanide insertion reactions reported at the time of writing this review are discussed. The current major limitation of this type of transformation is often the limited variability of the isocyanide. Therefore, the scope with regard to the isocyanide is discussed in all cases and creative solutions are highlighted. We hope to illustrate the versatility and potential of this intriguing type of transformation.

2. Palladium-Catalyzed Redox-Neutral Isocyanide Insertion Reactions

2.1. Palladium-Catalyzed Synthesis of Amidines and (thio)Imidates

The palladium-catalyzed synthesis of amidines or imidates from aryl halides, isocyanides, and oxygen or nitrogen nucleophiles is one of the most important applications of imidoylative palladium catalysis to date. A general catalytic

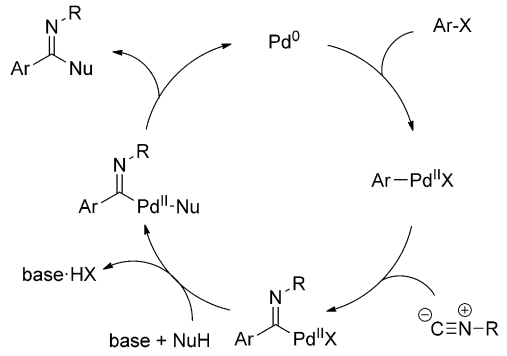


Tjøstil Vlaar was born in 1987 in Alkmaar, Netherlands. He studied chemistry at the VU University Amsterdam, where he received his B. Sc. degree in 2008 and his M. Sc. degree (cum laude) in 2010. In 2010 he started his Ph.D. studies with Prof. R. V. A. Orru at the VU University Amsterdam working on palladium-catalyzed isocyanide insertion reactions. His research interests include organocatalysis and palladium catalysis.

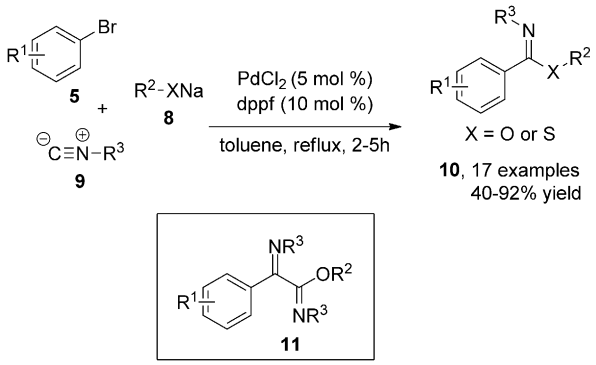
Bert U. W. Maes obtained his Ph.D. in chemistry in 2001 from the University of Antwerp. He was a Post-Doctoral Fellow of the National Science Foundation (FWO) in Belgium. In 2002 he held a postdoctoral position at the Hungarian Academy of Sciences. In 2003 he was appointed Assistant, and then in 2008 Associate Professor in the Department of Chemistry at the University of Antwerp. He received a prestigious Research Professorship in 2009. His research focuses on homogeneous catalysis and heterocyclic chemistry.

Eelco Ruijter studied chemistry at the VU University Amsterdam. He obtained his Ph.D. from L. A. Wessjohann at the VU University Amsterdam and the Institute of Plant Biochemistry in Halle (Saale), Germany. In 2004, he joined the group of R. M. J. Liskamp at Utrecht University as a postdoctoral fellow, and in 2006, he was appointed Assistant Professor at the VU University Amsterdam. His research interests include the use of multicomponent, cascade, and new catalytic reactions for the efficient construction of complex small molecules.

Romano V. A. Orru studied molecular sciences at the Agricultural University in Wageningen, where he obtained his Ph.D. in 1994. From 1996–2000 he worked with K. Faber at the Technical and Karl-Franzens Universities (Graz, Austria). In 2000 he was appointed Assistant Professor and later Associate Professor at the VU University Amsterdam. In 2007 he became a full professor of synthetic and bioorganic chemistry. His research focuses on the development of novel diversity-oriented synthetic methodology for the synthesis of pharmaceutically relevant compounds and natural products.



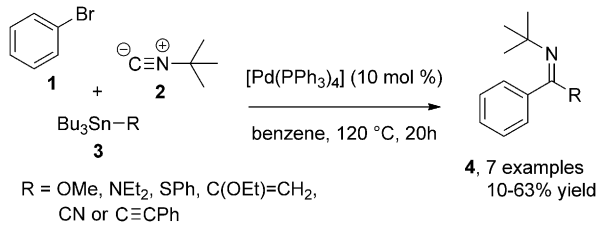
Scheme 1. Catalytic cycle of amidine or (thio)imidate synthesis.



Scheme 4. Imidate/thioimidate synthesis.

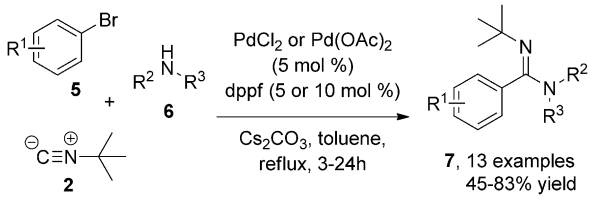
cycle for these reactions is depicted in Scheme 1 and is similar to typical carbonylative catalysis.

In 1986, the first contribution to this area was made by Kosugi and Migita et al., who reported the coupling of bromobenzene (**1**), *tert*-butyl isocyanide (**2**), and organotin reagents (**3**; Scheme 2).[12] Whitby et al. further developed



Scheme 2. First example of amidine, (thio)imidate and imine formation.

this system and reported a tin-free version for the amidination of bromobenzenes (**5**; Scheme 3).[13] Simple amines (**6**) can be employed as coupling partners instead of organotin reagents, thus making the reaction more versatile and more benign.



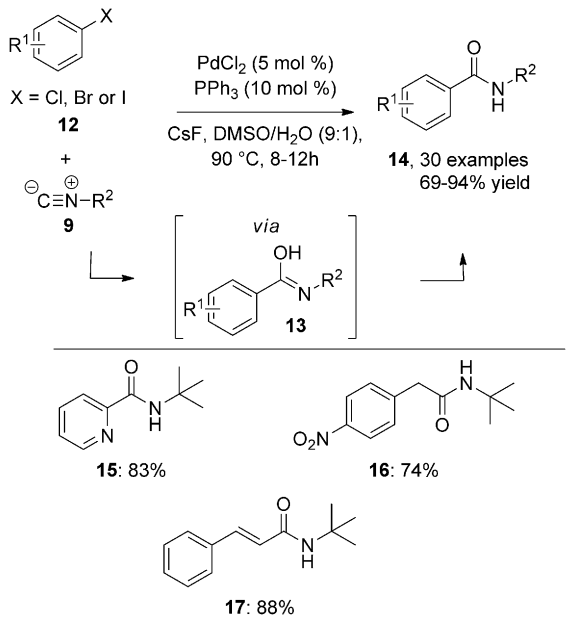
Scheme 3. Amidine synthesis. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Unfortunately, only *tert*-butyl isocyanide was tolerated well in this system. To overcome this limitation, the authors developed a one-pot dealkylation strategy which removes the *tert*-butyl group under acidic conditions.

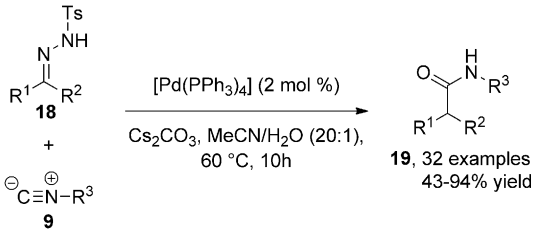
The same group established a related procedure for the synthesis of imidates and thioimidates (**10**) using sodium salts of alcohols and thiols (**8**), respectively (Scheme 4).[14] Surprisingly, other isocyanides could be used in this case although occasionally the double insertion product **11** was isolated in significant quantities when secondary or primary isocyanides were used. The reaction could be optimized to selectively afford double insertion products (**11**), while only trace amounts of triple insertion product were observed.[15]

The authors later showed that alkenyl bromides are viable inputs for these reactions to furnish α,β-unsaturated amidines and imidates.[16] In addition, cyclic amidines and imidates are accessible by this strategy.[17] In all cases amidine formation was limited to *tert*-butyl isocyanide, whereas imidate formation allowed the use of primary, secondary, and tertiary aliphatic isocyanides.

Jiang et al. showed that water, instead of amines or alcohols, can be used as nucleophile in this type of chemistry. With this strategy, amides (**14**) are obtained in an efficient manner (Scheme 5).[18] The reaction is closely related to the well-known approach to amides from CO and amines,[3] but avoids the handling of pressurized toxic CO gas. The reaction tolerates a variety of tertiary and secondary aliphatic isocyanides, as well as aromatic isocyanides. Ding and Cai et al. also developed a strategy towards amides (**19**) starting from *N*-tosylhydrazones (**18**; Scheme 6).[19] *N*-tosylhydra-

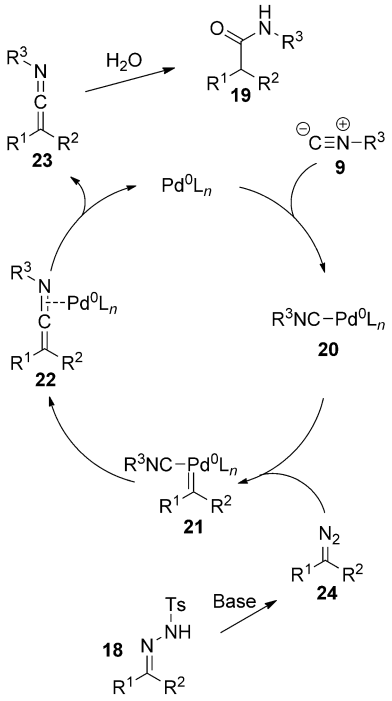


Scheme 5. Amide synthesis. DMSO = dimethylsulfoxide.



Scheme 6. Amidation of *N*-tosylhydrazones with isocyanides. Ts = 4-toluenesulfonyl.

zones (**18**) are converted into diazo compounds (**24**) under basic conditions, and react with palladium to form the carbene complex **21** (Scheme 7). This carbene complex can react with coordinated isocyanide to form a ketenimine product that is hydrolyzed under the reaction conditions to ultimately form

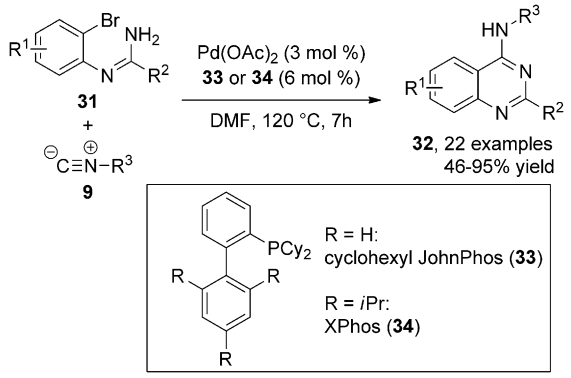


Scheme 7. Proposed mechanism.

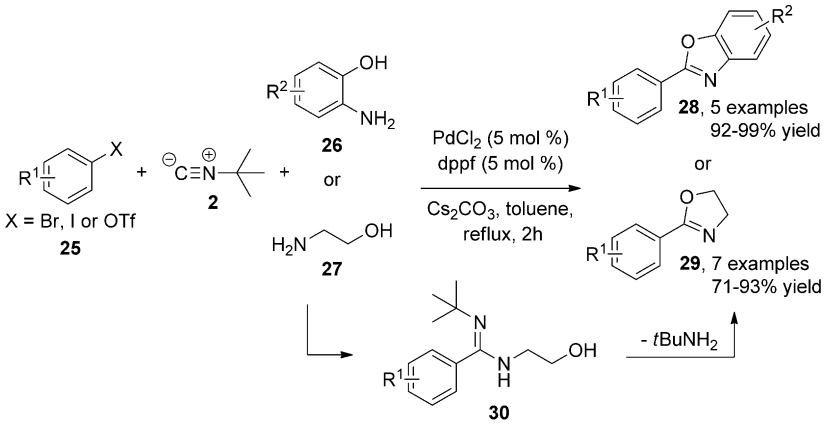
amides. Several primary, secondary, and tertiary aliphatic isocyanides are tolerated in this reaction.

Lang et al. introduced a clever solution to avoid the typically limited isocyanide scope of imidoylative amidine synthesis. An additional cyclization step is induced by employing amines linked to a second nucleophile, thus eliminating *tert*-butylamine.[20] The strategy was successfully applied in the synthesis of benzoxazoles (**28**) and oxazolines (**29**) by using 2-aminophenols (**26**) and ethanolamine (**27**), respectively, as the nucleophile (Scheme 8).[20a] The reaction did not work with 2-aminothiophenol under these reaction conditions; instead unsubstituted benzothiazole was obtained. A one-pot formation and C2-arylation of benzothiazole was realized by C–H activation using a copper cocatalyst under modified reaction conditions (DMF, 120 °C).[20b]

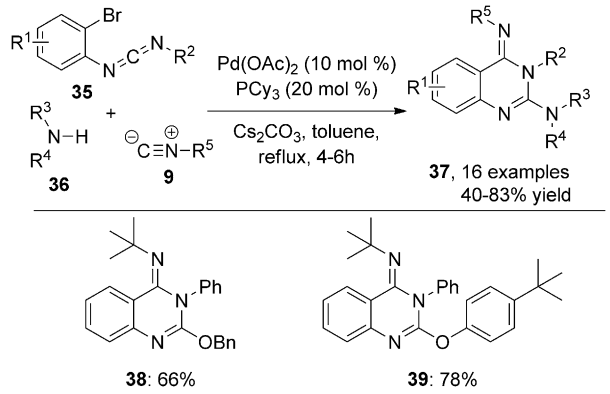
The palladium-catalyzed amidination of aryl halides by isocyanide insertion has been used in several synthetic methods towards nitrogen heterocycles. Our group has contributed to this area by a novel approach to 4-aminoquinazolines (**32**) from *N*-(2-*b*romoaryl)amidines (**31**) (Scheme 9).[21] Primary, secondary, and tertiary aliphatic isocyanides all afford the heterocyclic products in good yields. Cyclohexyl JohnPhos (**33**) was a good ligand for *tert*-butyl isocyanide and cyclohexyl isocyanide, but XPhos (**34**) was essential for good reactivity of primary aliphatic isocyanides.



Scheme 9. Synthesis of 4-aminoquinazolines. DMF = *N*,*N*′-dimethylformamide.



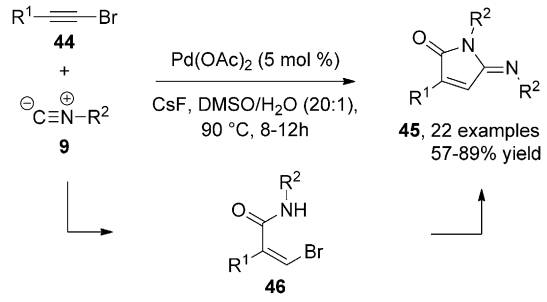
Scheme 8. Synthesis of oxazolines and benzoxazoles. Tf = trifluoromethanesulfonyl.



Scheme 10. Synthesis of quinazolin-4(3*H*)-imines.

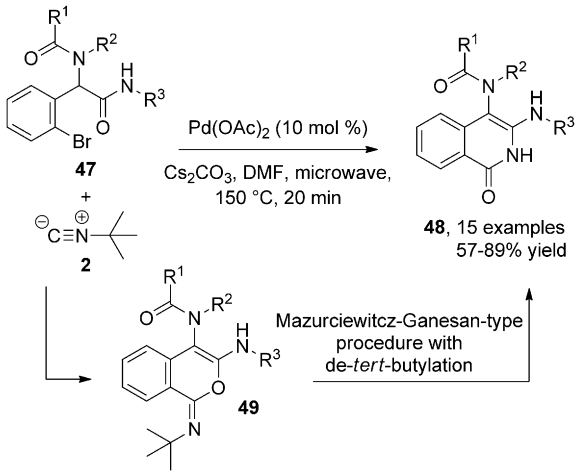
Pu and Wu et al. reported a palladium-catalyzed imidoylative cascade towards quinazolin-4(3*H*)-imines (**37**; Scheme 10).[22] *N*-(2-*B*romoaryl)carbodiimides (**35**) were used in combination with secondary amines (**36**) to produce, in situ, a guanidine which can then undergo the typical intramolecular palladium-catalyzed amidine synthesis. Both primary and tertiary aliphatic isocyanides can be used and alcohol nucleophiles were also viable. In additional work the authors show phosphites can be used as nucleophiles.[23] Furthermore, the procedure could be extended to include a second cyclization event by employing symmetric carbodiimides (**40**) containing two aryl iodide moieties (Scheme 11).[24] The tetracyclic products **42** contain two isocyanide fragments when three equivalents of *tert*-butyl isocyanide are used, but products (**43**) incorporating one molecule of isocyanide can be obtained by using 1.1 equivalents of **2** in the presence of P*t*Bu$_3$.

Jiang et al. showed that bromoalkynes (**44**) and two equivalents of isocyanide (**9**) can be coupled selectively to provide 5-iminopyrrolones (**45**) with excellent to modest *E*/*Z* selectivity of the exocyclic imine (Scheme 12).[25] Secondary and tertiary aliphatic isocyanide were used, as well as 2,6-dimethylphenyl isocyanide. *cis*-Bromoacrylamides (**46**) are formed first under the reaction conditions and subsequently undergo intramolecular palladium-catalyzed imidoylation.



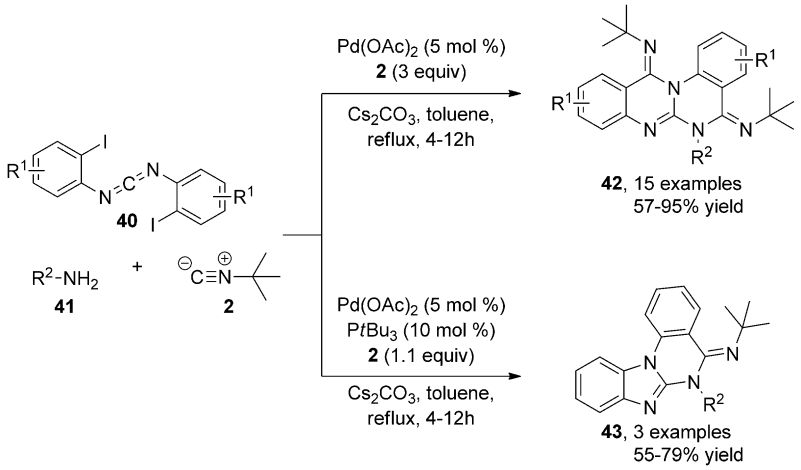
Scheme 12. Synthesis of 5-iminopyrrolones.

Chauhan et al. reported a protocol for the conversion of amide precursors **47** into isoquinolin-1(2*H*)-one derivatives (**48**), which presumably proceeds through imidate intermediate **49** (Scheme 13).[26] The starting materials are conviently accessible by an Ugi reaction, making this an efficient approach.

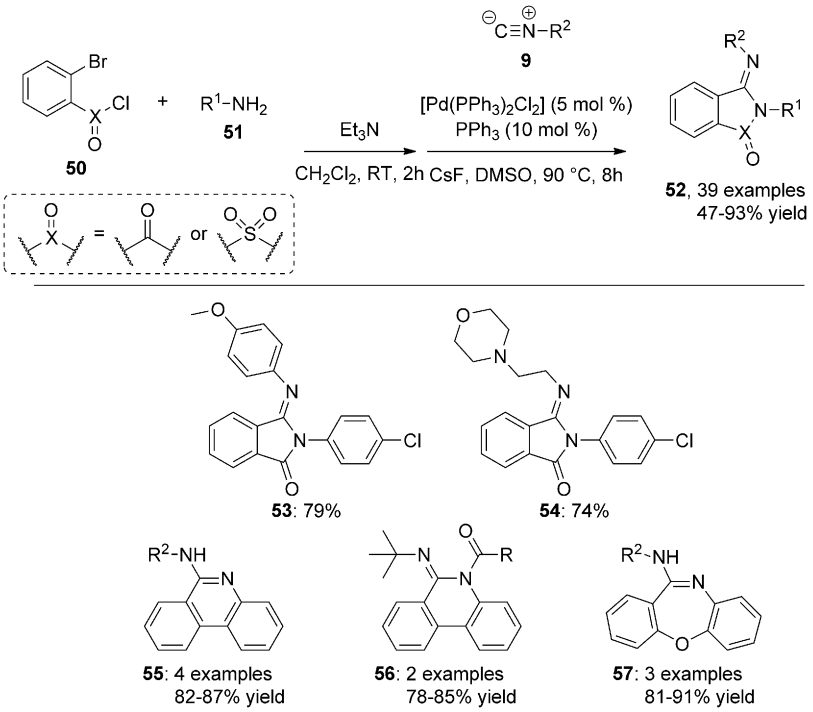


Scheme 13. Synthesis of isoquinolin-1(2*H*)-one derivatives.

Jiang et al. recently reported effective reaction conditions for the intramolecular palladium-catalyzed imidoylative ami-



Scheme 11. Cascade reaction with isocyanide insertion.

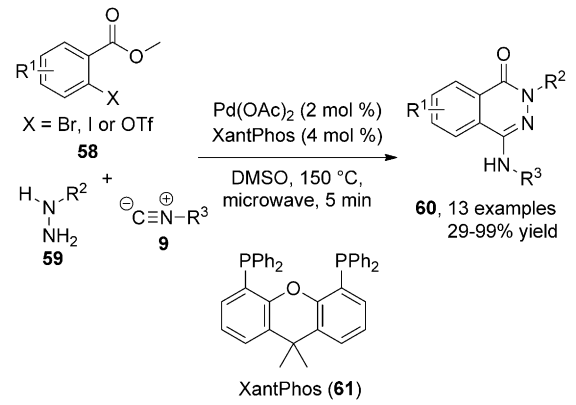


Scheme 14. Heterocyclic amidine synthesis.

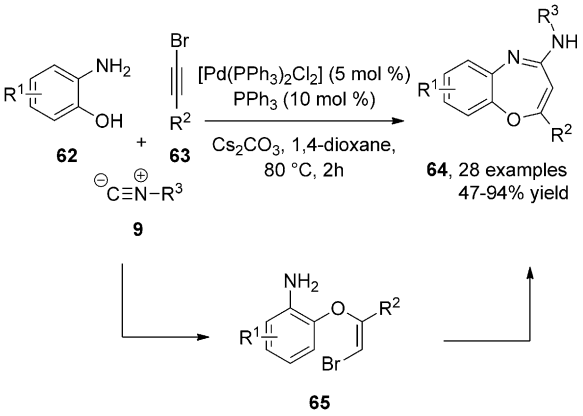
dination that are applicable to a wide range of heteroaromatic products (Scheme 14).[27] Reaction between **50** and amines (**51**) cleanly affords amides, which are used without purification for the amidination by isocyanide insertion. Almost all isocyanides are easily inserted under the same reaction conditions, and even challenging isocyanides provide high yields of the respective products (**53** and **54**). Interestingly, (isocyanomethyl)trimethylsilane is a compatible isocyanide, and the trimethylsilyl group is removed under the reaction conditions to afford the corresponding methyl substituted product **52** ($R^2 = Me$). The potential of these reaction conditions is illustrated by the synthesis of a variety of amidine-containing heterocycles (**55**–**57**) involving an aniline nucleophile.

Our group has found that 2-halobenzoates (**58**), isocyanides (**9**), and hydrazines (**59**) undergo a cascade reaction which leads to formation of 4-aminophthalazin-1(2*H*)-ones (**60**) by palladium-catalyzed amidine formation and subsequent cyclization (Scheme 15).[28] The reaction is extremely fast and is completed within five minutes under microwave irradiation. The 4-aminophthalazin-1(2*H*)-ones (**60**) are isolated in excellent yield in most cases, although only tertiary isocyanides were successfully used. A simple dealkylation procedure provides the unsubstituted products, which can be further derivatized.

Jiang et al. reported a cascade reaction with amidination to give seven-membered rings. *o*-Aminophenols (**62**), bromoalkynes (**63**), and secondary or tertiary aliphatic isocyanides (**9**) afford 4-aminobenzo[*b*][1,4]oxazepine derivatives (**64**) in high yields (Scheme 16).[29] The reaction proceeds through **65** as demonstrated by reaction of isolated **65** with *tert*-butyl isocyanide under the standard catalytic conditions.

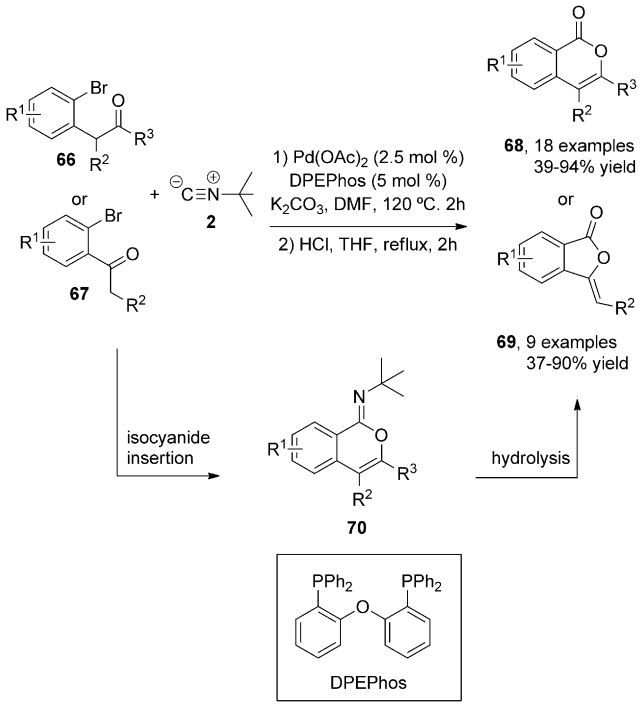


Scheme 15. Synthesis of 4-aminophthalazin-1(2*H*)-ones.



Scheme 16. Cascade reaction towards seven-membered heterocycles.

Isocyanides are potential replacements for carbon monoxide when hydrolysis of the product leads to the carbonyl functionality otherwise obtained from CO. Although this is not advantageous from an environmental or economical perspective, it avoids the handling of this toxic gas under high pressures. Zhu and Ji et al. recently provided an example and used *tert*-butyl isocyanide as a carbon monoxide surrogate to synthesize valuable lactones (**68** and **69**; Scheme 17).[30]

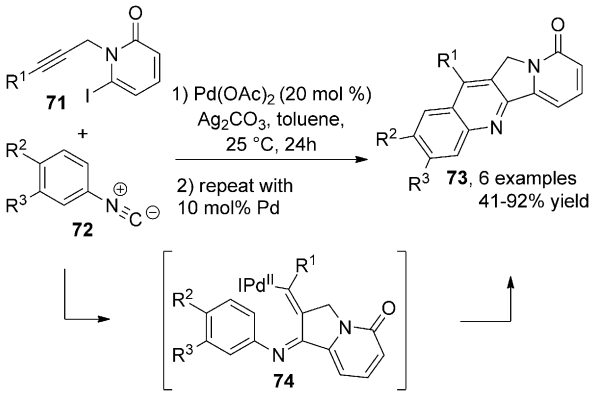


Scheme 17. Synthesis of lactones using *t*BuNC as CO surrogate.

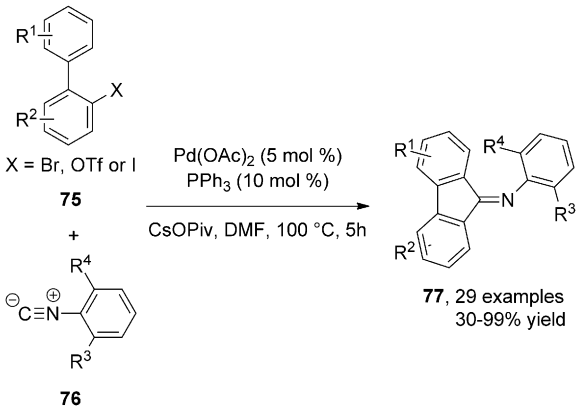
2.2. Palladium-Catalyzed Isocyanide Insertion Reactions with C–H Activation

The selective catalytic activation of C–H bonds, rather than preactivation of substrates as halides or metallated reagents, currently is an important and popular research topic in organic chemistry.[31] Direct C–H functionalization offers substantially improved atom and step economy compared to traditional preactivation, but also creates new possibilities when activated substrates are difficult to access. In 2002, Curran and Du were the first to combine isocyanide insertion chemistry with C–H arylation in an impressive cascade process (Scheme 18).[32] They coupled electron-rich aromatic isocyanides (**72**) and 6-iodo-*N*-propargylpyridin-2(1*H*)-ones (**71**), which affords tetracyclic compounds (**73**) in reasonable to high yields.

In 2010, the group of Chatani further demonstrated the potential of isocyanides in catalytic C–H bond activation reactions (Scheme 19).[33] 2-Halobiaryls (**75**) are readily coupled with 2,6-disubstituted aryl isocyanides (**76**) using a simple palladium catalyst to furnish fluorenylidene imines (**77**) in high yields.

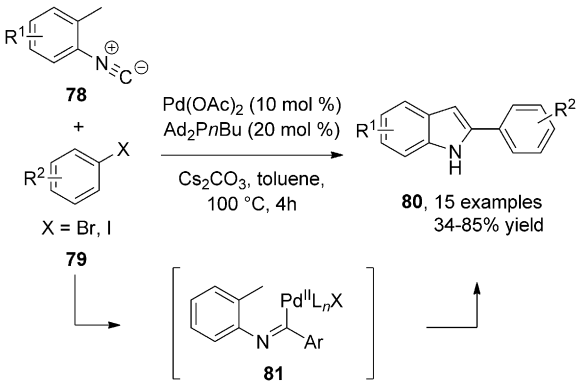


Scheme 18. First example of C–H bond activation with isocyanide insertion.



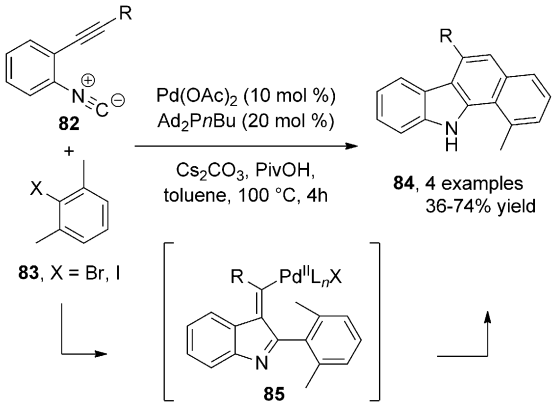
Scheme 19. Synthesis of fluorenylidene imines. Piv = pivaloyl.

Very recently Takemoto et al. combined isocyanide insertion with C(sp^3)–H activation (Scheme 20).[34] In their system, aryl halides (**79**) undergo oxidative addition to palladium and subsequent insertion of 2-methylphenyl isocyanides (**78**) to give the intermediates **81**. C(sp^3)–H activation then results in formation of 2-arylindoles (**80**). The isocyanide has to be added slowly over a period of three hours to allow lower catalyst loadings. Most likely, the presence of



Scheme 20. Synthesis of 2-arylindoles involving benzylic C(sp^3)–H bond activation and isocyanide insertion.

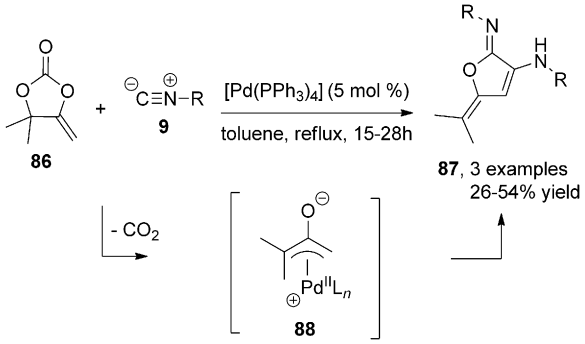
excess isocyanide leads to coordinatively saturated palladium species which inhibits catalysis. The procedure was extended to a cascade reaction involving an additional alkyne insertion yielding benzo[α]carbazoles (**84**; Scheme 21).



Scheme 21. Synthesis of benzo[α]carbazoles.

2.3. Palladium-Catalyzed Isocyanide Insertion Reactions with Extrusion of Small Molecules

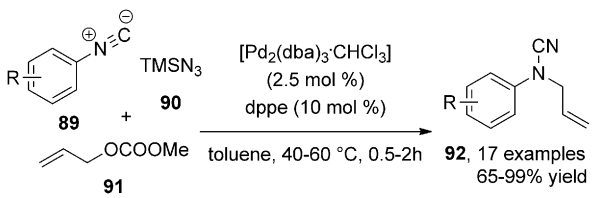
In 1993, Murai et al. reported a decarboxylative process combined with double isocyanide insertion (Scheme 22).[35] The reaction involves a cyclic carbonate (**86**) and is believed to proceed by oxidative addition of palladium and subsequent



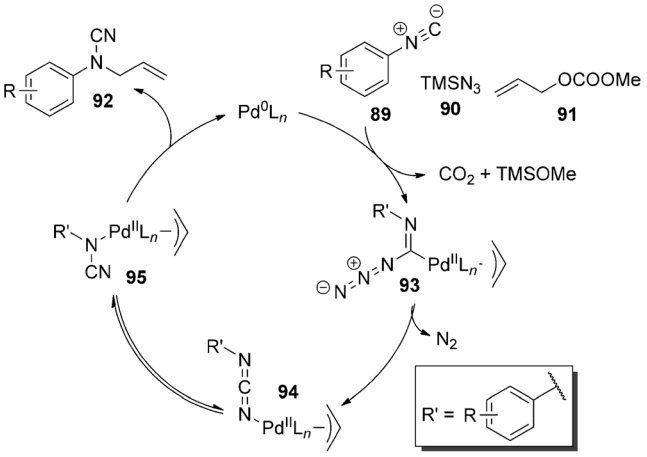
Scheme 22. Decarboxylative process with isocyanide insertion.

decarboxylation to yield the π-allyl palladium species **88**. A double isocyanide insertion most likely occurs next to form the product (**87**). Aromatic isocyanides and *tert*-butyl isocyanide could be used in this system, which is surprising considering that catalytic double insertion of *tert*-butyl isocyanide is quite uncommon.

An elegant decarboxylative synthesis of *N*-allylcyanamides (**92**) from aromatic isocyanides (**89**), allyl methyl carbonate (**91**), and trimethylsilyl azide (**90**) was discovered by Yamamoto et al. (Scheme 23).[36] The mechanism proposed by the authors starts with the formation of species **93**, which eliminates N_2 and undergoes a 1,2-migration of the π-allylpalladium to form **94** (Scheme 24). Reductive elimination of Pd^0 from the intermediate **95** results in formation of the

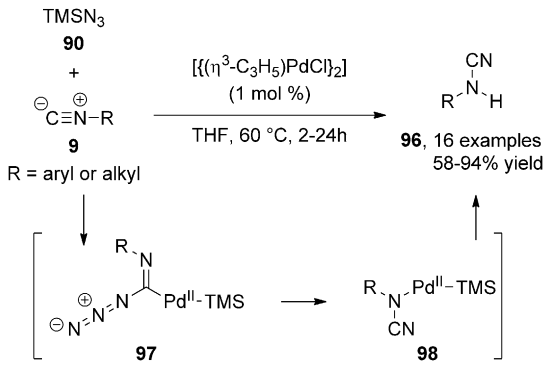


Scheme 23. Palladium-catalyzed synthesis of *N*-allylcyanamides. dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphino)ethane, TMS = trimethylsilyl.



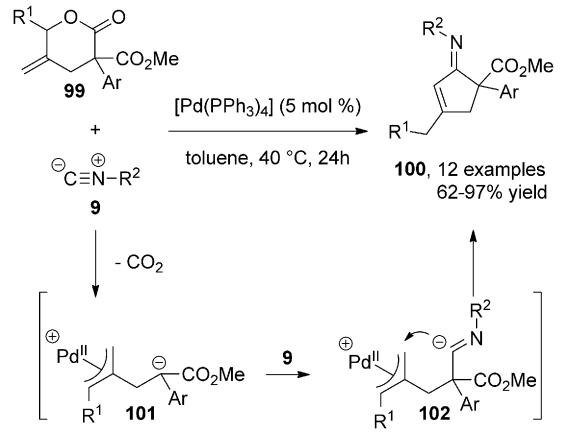
Scheme 24. Proposed mechanism.

product. The reaction was also used for the synthesis of *N*-cyanoindoles by employing 2-alkynylisocyanobenzenes under modified reaction conditions, where an additional alkyne insertion is involved (not shown).[37] In a later study the authors showed monosubstituted cyanamides (**96**) are accessible by a similar strategy through direct coupling of isocyanides (**9**) and trimethylsilyl azide (**90**; Scheme 25).[38] Aliphatic isocyanides are also tolerated in this system.



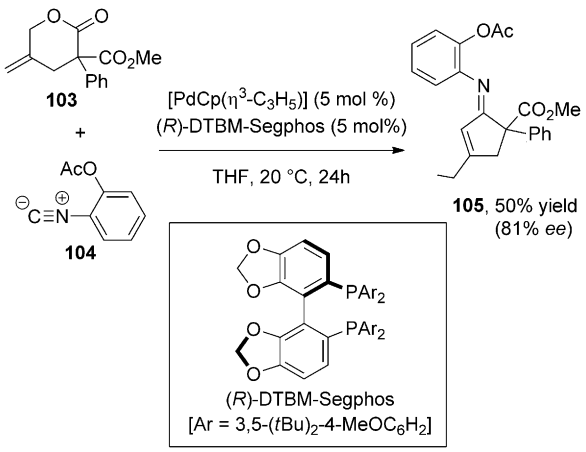
Scheme 25. Palladium-catalyzed synthesis of cyanamides. THF = tetrahydrofuran.

A decarboxylative cyclization with isocyanide insertion towards cyclopentenimines (**100**) was reported by Shintani and Hayashi et al. (Scheme 26).[39] Aromatic isocyanides work best, although benzyl isocyanide could also be used. The mechanism proposed by the authors involves formation of the π-allyl palladium intermediate **101** and nucleophilic addition



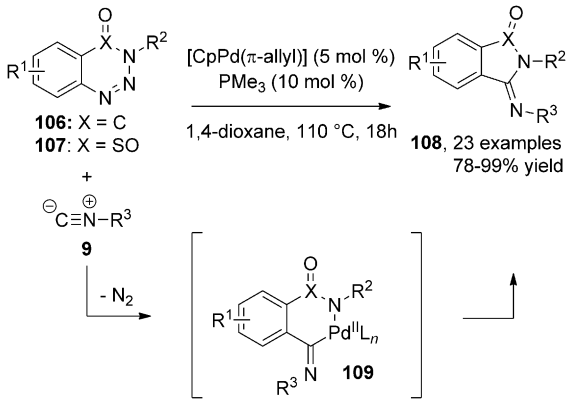
Scheme 26. Decarboxylative synthesis of cyclopentenimines.

of the stabilized anion to the isocyanide to form the intermediate **102**, which then cyclizes. Alternatively, migratory insertion of the isocyanide could be involved, since insertion of isocyanides in Pd–C bonds is extremely facile. In line with this rationale is that isocyanides generally react as nucleophiles instead of electrophiles, unlike that which is proposed here. Preliminary results towards the development of an asymmetric version were reported and very promising results (81 % *ee*) were obtained (Scheme 27).



Scheme 27. Asymmetric decarboxylative synthesis of cyclopentenimines. Cp = cyclopentadienyl.

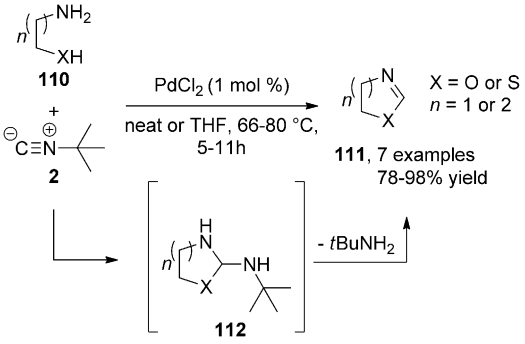
Murakami et al. reported a reaction involving extrusion of molecular nitrogen from benzotriazinones (**106**), or the sulphur analogue **107**, and subsequent isocyanide insertion (Scheme 28). The process yields 3-(imino)isoindolin-1-ones (**108**, X = C) or the related 3-(imino)thiaisoindoline 1,1-dioxides (**108**, X = SO) in excellent yields.[40] Primary, secondary and tertiary aliphatic isocyanides and several aromatic isocyanides could be used.



Scheme 28. Palladium-catalyzed denitrogenation reaction.

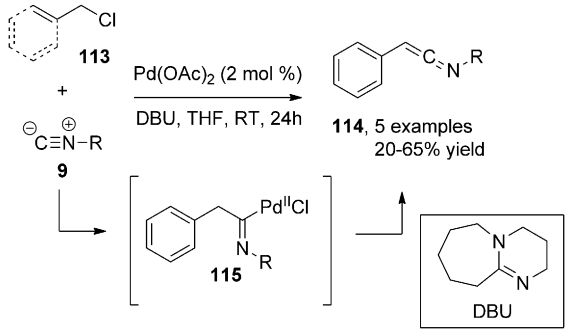
2.4. Miscellaneous Palladium-Catalyzed Isocyanide Insertion Reactions

The first palladium-catalyzed reaction involving isocyanide insertion was reported by Saegusa et al. in 1974.[41] Their work involves a cyclization reaction of amino alcohols or thiols (**110**) with *tert*-butyl isocyanide insertion to form cyclic (thio)imidates (**111**; Scheme 29). A mechanism involving the formation of **112** was proposed by the authors.



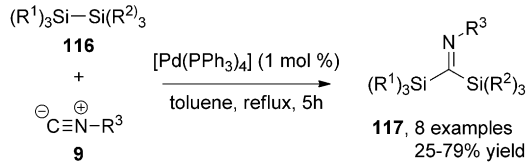
Scheme 29. Palladium-catalyzed synthesis of cyclic (thio)imidates.

In 1977 the same group reported the coupling of tertiary aliphatic isocyanides (**9**) and allylic or benzylic chlorides (**113**) to furnish ketenimines (**114**; Scheme 30).[42] The reaction is believed to proceed via imidoyl palladium species **115**, which undergoes β-hydride elimination.



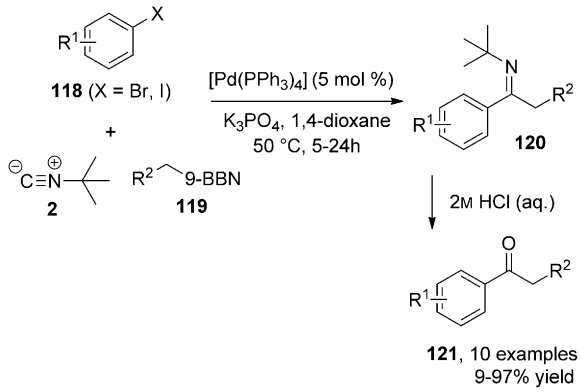
Scheme 30. Palladium-catalyzed synthesis of ketenimines.

The group of Ito later developed a protocol for the catalytic insertion of isocyanides into Si–Si bonds in which both *o*-tolyl and cyclohexyl isocyanide could be used (Scheme 31).[43] The reaction could be extended to oligosilanes, wherein isocyanides are inserted in all Si–Si bonds to yield oligo(silylimine) derivatives.[44] In addition, the authors also showed isocyanide insertion in silicon–tin bonds is possible.[45] The palladium-catalyzed insertion of isocyanides into S–S bonds has also been studied in detail by Kurosawa et al., who showed that isocyanide insertion into Pd–S bonds is reversible.[46]



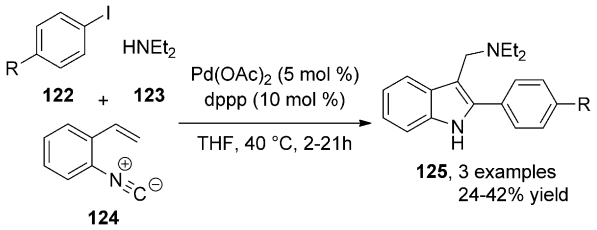
Scheme 31. Isocyanide insertion into Si–Si bonds.

The Suzuki coupling can be extended with isocyanide insertion as reported by Suzuki et al. (Scheme 32).[47] The required 9-alkyl-BBN derivatives (**119**) were prepared in situ and used directly. The reaction is very sensitive to the stoichiometry between *tert*-butyl isocyanide (**2**) and the 9-BBN species (**119**): if more than one equivalent of isocyanide is used the yield drops drastically. Complex formation of *tert*-butyl isocyanide and **119** is proposed, and effectively lowers the isocyanide concentration in solution. However, it is not clear why excess isocyanide inhibits catalysis. Presumably saturation of palladium by isocyanide ligands prevents catalysis. The imines (**120**) obtained by this approach were hydrolized to the corresponding ketones (**121**) before isolation.



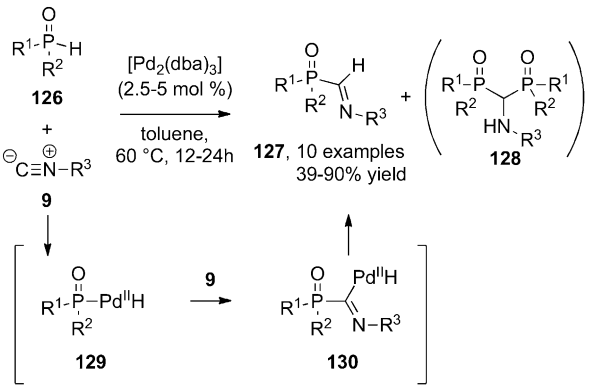
Scheme 32. Suzuki coupling combined with isocyanide insertion. 9-BBN = 9-borabicyclo[3.3.1]nonane.

A Heck-type reaction has also successfully been combined with isocyanide insertion by Takahashi et al. in their synthesis of 2,3-disubstituted indoles (**125**; Scheme 33).[48] The reaction demonstrates the possibility to combine an isocyanide insertion process with alkene insertion. More importantly, the regioselectivity in the product shows isocyanide insertion precedes alkene insertion, and indicates that isocyanide insertion into aryl–palladium bonds is more facile than alkene insertion.



Scheme 33. Palladium-catalyzed synthesis of indoles. dppp = 1,3-bis(diphenylphosphino)propane.

Han et al. reported a palladium-catalyzed isocyanide insertion into P–H bonds of phosphine oxides (**126**) to furnish α-iminophosphine oxides (**127**) in good yields (Scheme 34).[49] Both aromatic and aliphatic isocyanides were used, including cyclohexyl isocyanide. Bisphosphinoylaminomethanes (**128**) were observed in trace amounts as side products in this reaction. A rhodium catalyst allows the selective synthesis of **128** instead of **127**.

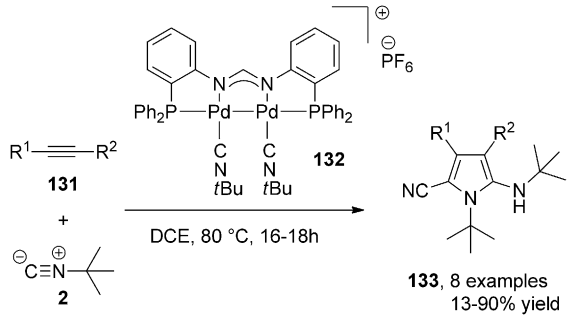


Scheme 34. Palladium-catalyzed synthesis of phosphinoyl imines.

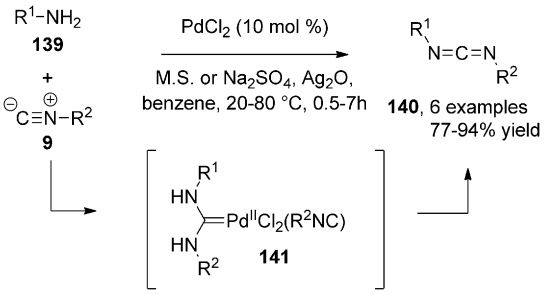
Tsukada and Inoue et al. used a novel dinuclear palladium catalyst (**132**) containing two coordinated isocyanides as catalyst for the formation of pyrroles (**133**; Scheme 35).[50] The reaction involves insertion of three isocyanides and loss of 2-methyl-1-propene, and has only been applied to *tert*-butyl isocyanide (**2**).

3. Oxidative Isocyanide Insertion Reactions

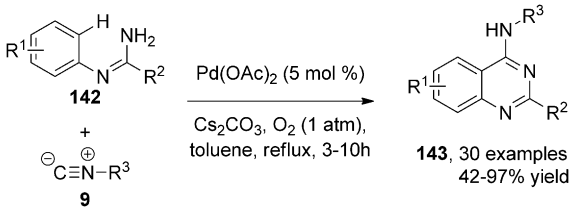
Palladium(II)-catalyzed oxidative reactions have emerged as important tools to tackle the limitations of classical cross-coupling reactions by avoiding prefunctionalization of the coupling partners.[31] A stoichiometric oxidant is required to reoxidize Pd^0. In the ideal case molecular oxygen fulfills this role, as it is the most abundant and environmentally benign oxidant available. In addition, it avoids waste production as



Scheme 35. Dinuclear palladium catalyst for pyrrole formation. DCE = 1,2-dichloroethane.



Scheme 37. Palladium-catalyzed oxidative coupling of isocyanides and amines. M.S. = molecular sieves.



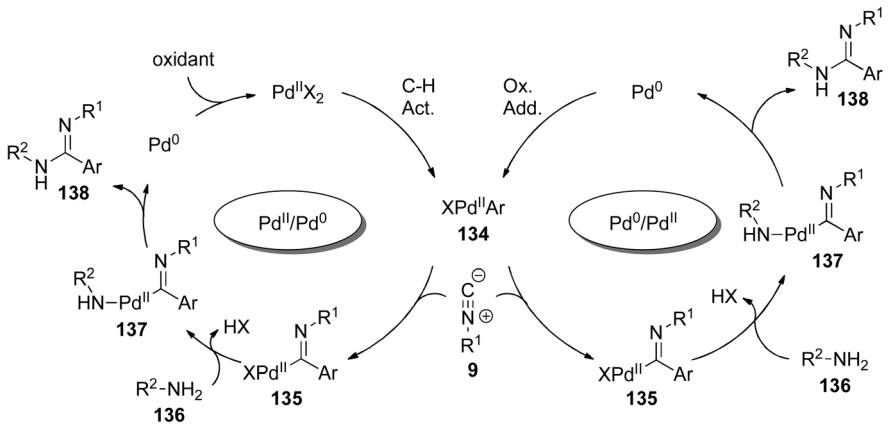
Scheme 38. Palladium-catalyzed oxidative synthesis of 4-aminoquinazolines.

the only waste product is H_2O when molecular oxygen is used.[51] Oxidative palladium catalysis has successfully been combined with isocyanide insertion and indeed leads to a more sustainable synthesis of heterocyclic products. The general mechanism of these transformations is very similar to Pd^0 catalysis (Scheme 36).

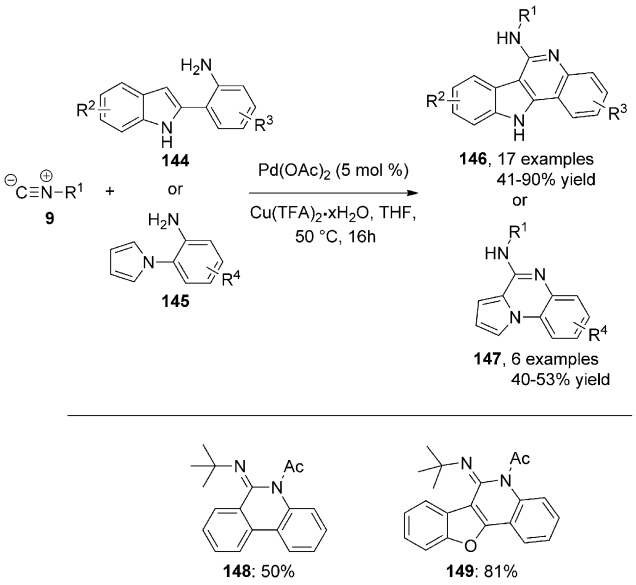
The first oxidative palladium-catalyzed reaction involving isocyanides was reported in 1975 by Saegusa et al., who discovered the oxidative coupling of isocyanides with amines through the carbene complex **141** using Ag_2O as the oxidant (Scheme 37).[52] In 1997, Schwartz et al. reported improved reaction conditionsthat use molecular oxygen as the stoichiometric oxidant in combination with catalytic iodine.[53]

The group of Zhu has pioneered the palladium-catalyzed oxidative formation of amidines and reported the first example in 2011 (Scheme 38).[54] The strategy relies on the use of *N*-arylamidines (**142**), which serve both as an intramolecular nucleophile and a directing group for C–H activation. The stoichiometric oxidant is molecular oxygen. Tertiary and secondary aliphatic isocyanides were used, although secondary isocyanides provide lower yields of **143**. Aromatic isocyanides are also viable coupling partners in this reaction.

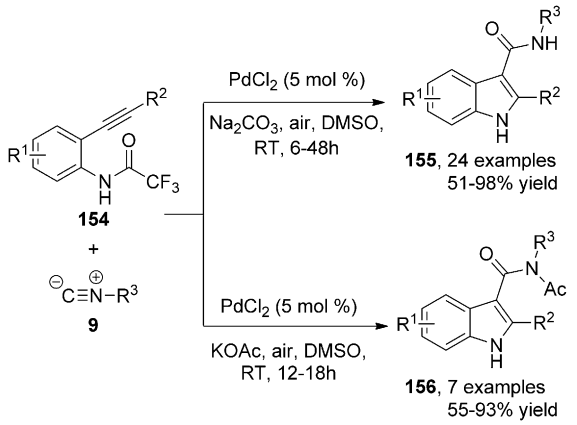
The same group later reported an amidination of 2-(2-aminophenyl)indoles (**144**) by C–H activation (Scheme 39).[55] The reaction has a remarkably broad substrate scope and almost any isocyanide could be used, including ethyl isocyanoacetate. Zhu and co-workers also developed the direct carboxamidation of indoles by C–H activation and isocyanide insertion (Scheme 40).[56] The carboxamidation occurs regioselectively on the C3-position to yield indole-3-carboxamides (**152**). Tertiary and secondary aliphatic isocyanide are both inserted, but secondary isocyanides require more catalyst and a prolonged reaction time. In addition, 2,6-dimethylphenyl isocyanide was successfully used. Interestingly, N-acetylated carboxamides (**153**) are obtained if water and trifluoroacetic acid are omitted from the reaction conditions. The same indole products (**155** and **156**) can be obtained by 5-*exo*-dig cyclization of *o*-alkynyl trifluoroanilides (**154**) and subsequent carboxamidation (Scheme 41).[57] The carbonyl oxygen atom originates from residual moisture in the reaction mixture, as demonstrated by a control experiment with $H_2{}^{18}O$. Several isocyanides could be used in this transformation as well.



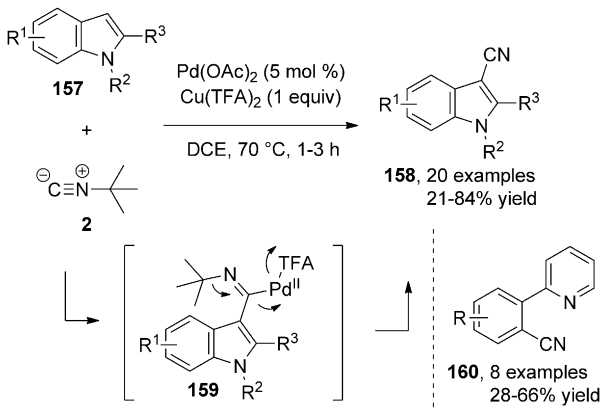
Scheme 36. Amidine formation through Pd^{II}/Pd^0 (left) and Pd^0/Pd^{II} (right) catalysis (ligands omitted for clarity).



Scheme 39. Palladium-catalyzed oxidative amidination by C–H activation. TFA = trifluoroacetate.



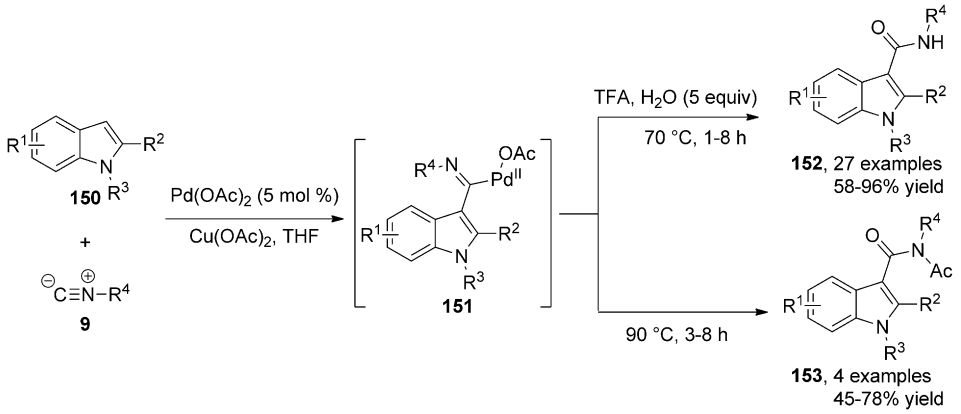
Scheme 41. Palladium-catalyzed oxidative synthesis of (*N*-acetyl) indole-3-carboxamides.



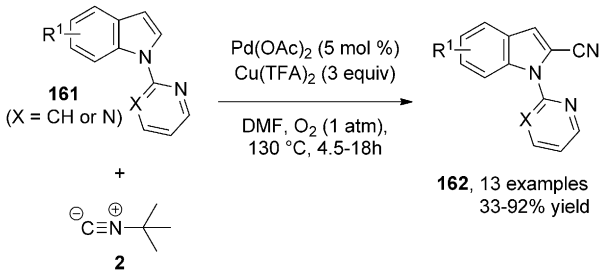
Scheme 42. Palladium-catalyzed oxidative C3 cyanation of indoles and arylpyridines.

The groups of Zhu and Xu independently reported palladium-catalyzed oxidative cyanation reactions using *tert*-butyl isocyanide as the cyanide source. Zhu and co-workers found mild reaction conditions for the C3 cyanation of indoles, and it proceeds by β-*tert*-butyl elimination of **159** (Scheme 42).[58] $Cu(TFA)_2$ was the only viable stoichiometric reoxidant for this reaction. The procedure was also applied in a regioselective cyanation of arenes using pyridine as a directing group, thus leading to benzonitrile derivatives (**160**). The group of Xu also studied the C3 cyanation of indoles, but developed a complementary pyridine directed C2 cyanation by attaching a directing group on the N1-position of the indole moiety (Scheme 43).[59] In this case a combination of $Cu(TFA)_2$ and O_2 was used as oxidant.

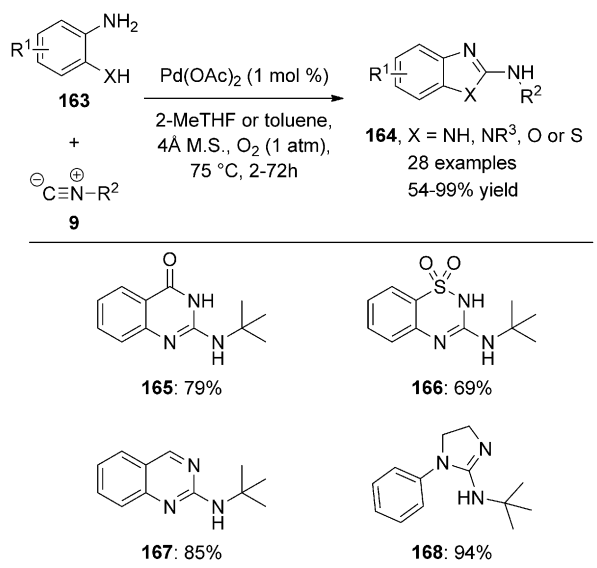
We have developed a broadly applicable synthesis of guanidine-containing heterocycles using aerobic oxidative palladium catalysis (Scheme 44).[60] Isocyanides (**9**) and *o*-phenylenediamines (**163**, X = NH or NR^3) are cleanly coupled under oxidative conditions to provide 2-aminobenzimidazoles in excellent yields. Primary, secondary, and tertiary aliphatic isocyanides are viable, although N-substitution of the *o*-phenylenediamines (**163**, X = NR^3) is important for high yields in case of primary and secondary isocyanides. A one-pot acid-mediated dealkylation of the *tert*-butyl guanidines in the crude reaction mixture allows straightforward access to N-



Scheme 40. Palladium-catalyzed oxidative synthesis of (*N*-acetyl) indole-3-carboxamides. TFA = trifluoroacetic acid.



Scheme 43. Palladium-catalyzed oxidative C2 cyanation of indoles.

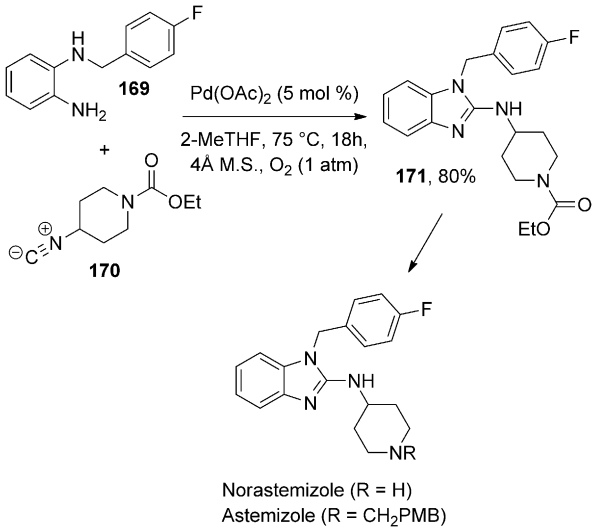


Scheme 44. Palladium-catalyzed oxidative synthesis of guanidine-containing heterocycles.

unsubstituted 2-aminobenzimidazoles (**164**, $R^2 = H$). A wide range of privileged heterocyles (**164**–**168**), containing a guanidine functionality, was readily accessible by varying the bis(nucleophile) substrate with only subtle changes in the reaction conditions. As an illustration of the potential of this novel methodology we completed a formal synthesis of the antihistamines norastemizole and astemizole (Scheme 45).[61] This demonstration is the first example of a palladium-catalyzed reaction involving isocyanide insertion that has been applied in the synthesis of a drug.

4. Summary and Outlook

The migratory insertion of isocyanide into Pd–C bonds is well established and a few catalytic applications of this phenomenon have been known for decades. Nevertheless, the widespread use of palladium-catalyzed isocyanide insertions in organic synthesis has thus far remained elusive and only in 2011 did it garner much attention. The recent advances discussed herein illustrate the potential of this chemistry, as shown by the synthesis of various valuable fine chemicals. The current limitation is the substrate tolerance with respect to the isocyanide, although several elegant solutions have been



Scheme 45. Synthesis of norastemizole and astemizole. PMB = *para*-methoxybenzyl.

reported. It is important to note that many of the more recently developed reactions in this field are applicable to various isocyanides, and even some functionalized isocyanides have been used. The rapid development of palladium-catalyzed oxidative isocyanide insertive processes is noteworthy and has resulted in several highly efficient novel reactions. Molecular oxygen is often a suitable stoichiometric oxidant in these reactions, thus resulting in high atom efficiency and only water as the by-product. The use of O_2 is an important new development in this field considering the drive for sustainability in modern society. We strongly believe this field is in its infancy and there is substantial room for further development. The increasing knowledge about the reactivity of different isocyanides towards palladium catalysts will lead to a better mechanistic understanding and subsequently, most likely, to broader substrate scopes. The development of novel reactions, including more sophisticated cascade reactions and applications in total synthesis, will further establish this field as it matures in the decade to come.

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[1] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**; b) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**; c) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.
[2] C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *353*, 1825.
[3] A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114.

[4] a) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1.
[5] a) I. Ugi, *Isonitrile Chemistry*, Academic Press, New York, **1971**; b) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; c) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; d) A. V. Lygin, A. de Meijere, *Angew. Chem.* **2010**, *122*, 9280; *Angew. Chem. Int. Ed.* **2010**, *49*, 9094; e) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235; f) V. G. Nenajdenko, *Isocyanide Chemistry*, Wiley-VCH, Weinheim, **2012**.
[6] N. Selander, K. J. Szabó, *Chem. Rev.* **2011**, *111*, 2048.
[7] a) Y. Yamamoto, H. Yamazaki, *Inorg. Chem.* **1974**, *13*, 438; b) G. R. Owen, R. Vilar, A. J. P. White, D. J. Williams, *Organometallics* **2002**, *21*, 4799.
[8] a) Y. Yamamoto, T. Tanase, T. Yanai, T. Asano, K. Kobayashi, *J. Organomet. Chem.* **1993**, *456*, 287; b) T. Tanase, T. Ohizumi, K. Kobayashi, Y. Yamamoto, *Organometallics* **1996**, *15*, 3404.
[9] a) Y. Ito, E. Ihara, M. Murakami, M. Shiro, *J. Am. Chem. Soc.* **1990**, *112*, 6446; b) K. Onitsuka, T. Joh, S. Takahashi, *Angew. Chem.* **1992**, *104*, 893; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 851; c) K. Onitsuka, K. Yanai, F. Takei, T. Joh, S. Takahashi, *Organometallics* **1994**, *13*, 3862; d) F. Takei, K. Yanai, K. Onitsuka, S. Takahashi, *Chem. Eur. J.* **2000**, *6*, 983.
[10] a) J. G. P. Delis, P. G. Aubel, K. Vrieze, P. W. N. M. van Leeuwen, N. Veldman, A. L. Spek, F. J. R. van Neer, *Organometallics* **1997**, *16*, 2948; b) L. Canovese, F. Visentin, C. Santo, C. Levi, A. Dolmella, *Organometallics* **2007**, *26*, 5590; c) L. Canovese, F. Visentin, C. Santo, C. Levi, *Organometallics* **2009**, *28*, 6762.
[11] L. Canovese, G. Chessa, F. Visentin, *Inorg. Chim. Acta* **2010**, *363*, 3426.
[12] M. Kosugi, T. Ogata, H. Tamura, H. Sano, T. Migita, *Chem. Lett.* **1986**, *15*, 1197.
[13] C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem.* **2000**, *112*, 4326; *Angew. Chem. Int. Ed.* **2000**, *39*, 4156.
[14] C. G. Saluste, R. J. Whitby, M. Furber, *Tetrahedron Lett.* **2001**, *42*, 6191.
[15] R. J. Whitby, C. G. Saluste, M. Furber, *Org. Biomol. Chem.* **2004**, *2*, 1974.
[16] K. K. R. Tetala, R. J. Whitby, M. E. Light, M. B. Hurtshouse, *Tetrahedron Lett.* **2004**, *45*, 6991.
[17] C. G. Saluste, S. Crumpler, M. Furber, R. J. Whitby, *Tetrahedron Lett.* **2004**, *45*, 6995.
[18] H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org. Lett.* **2011**, *13*, 1028.
[19] F. Zhou, K. Ding, Q. Cai, *Chem. Eur. J.* **2011**, *17*, 12268.
[20] a) P. J. Boissarie, Z. E. Hamilton, S. Lang, J. A. Murphy, C. J. Suckling, *Org. Lett.* **2011**, *13*, 6256; b) V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, S. Lang, *J. Org. Chem.* **2013**, *78*, 1471.
[21] G. van Baelen, S. Kuijer, L. Rýček, S. Sergeyev, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2011**, *17*, 15039.
[22] G. Qiu, G. Liu, S. Pu, J. Wu, *Chem. Commun.* **2012**, *48*, 2903.
[23] G. Qiu, Y. Lu, J. Wu, *Org. Biomol. Chem.* **2013**, *11*, 798.
[24] G. Qiu, Y. He, J. Wu, *Chem. Commun.* **2012**, *48*, 3836.
[25] Y. Li, J. Zhao, H. Chen, B. Liu, H. Jiang, *Chem. Commun.* **2012**, *48*, 3545.
[26] V. Tyagi, S. Khan, A. Giri, H. M. Gauniyal, B. Sridhar, P. M. S. Chauhan, *Org. Lett.* **2012**, *14*, 3126.
[27] B. Liu, Y. Li, H. Jiang, M. Yin, H. Huang, *Adv. Synth. Catal.* **2012**, *354*, 2288.
[28] T. Vlaar, E. Ruijter, A. Znabet, E. Janssen, F. J. J. de Kanter, B. U. W. Maes, R. V. A. Orru, *Org. Lett.* **2011**, *13*, 6496.
[29] B. Liu, Y. Li, M. Yin, W. Wu, H. Jiang, *Chem. Commun.* **2012**, *48*, 11446.
[30] X.-D. Fei, Z.-Y. Ge, T. Tang, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem.* **2012**, *77*, 10321.
[31] a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; b) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; c) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.
[32] D. P. Curran, W. Du, *Org. Lett.* **2002**, *4*, 3215.
[33] M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835.
[34] T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270.
[35] K. Ohe, H. Matsuda, T. Ishihara, S. Ogoshi, N. Chatani, S. Murai, *J. Org. Chem.* **1993**, *58*, 1173.
[36] S. Kamijo, T. Jin, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 9453.
[37] S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 11940.
[38] S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem.* **2002**, *114*, 1858; *Angew. Chem. Int. Ed.* **2002**, *41*, 1780.
[39] S. Park, R. Shintani, T. Hayashi, *Chem. Lett.* **2009**, *38*, 204.
[40] T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi, M. Murakami, *Org. Lett.* **2011**, *13*, 1429.
[41] Y. Ito, I. Ito, T. Hirao, T. Saegusa, *Synth. Commun.* **1974**, *4*, 97.
[42] Y. Ito, T. Hirao, N. Ohta, T. Saegusa, *Tetrahedron Lett.* **1977**, *18*, 1009.
[43] Y. Ito, S. Nishimura, M. Ishikawa, *Tetrahedron Lett.* **1987**, *28*, 1293.
[44] a) Y. Ito, T. Matsuura, M. Murakami, *J. Am. Chem. Soc.* **1988**, *110*, 3692; b) Y. Ito, M. Suginome, T. Matsuura, M. Murakami, *J. Am. Chem. Soc.* **1991**, *113*, 8899.
[45] Y. Ito, T. Bando, T. Matsuura, M. Ishikawa, *J. Chem. Soc. Chem. Commun.* **1986**, 980.
[46] H. Kuniyasu, K. Sugoh, M. S. Su, H. Kurosawa, *J. Am. Chem. Soc.* **1997**, *119*, 4669.
[47] T. Ishiyama, T. Oh-e, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1992**, *33*, 4465.
[48] K. Onitsuka, S. Suzuki, S. Takahashi, *Tetrahedron Lett.* **2002**, *43*, 6197.
[49] T. Hirai, L.-B. Han, *J. Am. Chem. Soc.* **2006**, *128*, 7422.
[50] N. Tsukada, M. Wada, N. Takahashi, Y. Inoue, *J. Organomet. Chem.* **2009**, *694*, 1333.
[51] a) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400; b) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851.
[52] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1975**, *40*, 2981.
[53] I. Pri-Bar, J. Schwartz, *Chem. Commun.* **1997**, 347.
[54] Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett.* **2011**, *13*, 4604.
[55] Y. Wang, Q. Zhu, *Adv. Synth. Catal.* **2012**, *354*, 1902.
[56] J. Peng, L. Liu, Z. Hu, J. Huang, Q. Zhu, *Chem. Commun.* **2012**, *48*, 3772.
[57] Z. Hu, D. Liang, J. Zhao, J. Huang, Q. Zhu, *Chem. Commun.* **2012**, *48*, 7371.
[58] J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang, Q. Zhu, *Org. Lett.* **2012**, *14*, 4966.
[59] S. Xu, X. Huang, X. Hong, B. Xu, *Org. Lett.* **2012**, *14*, 4614.
[60] T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem.* **2012**, *124*, 13235; *Angew. Chem. Int. Ed.* **2012**, *51*, 13058.
[61] F. Janssens, J. Torremans, M. Janssen, R. A. Stokbroekx, M. Luyckx, P. A. J. Janssen, *J. Med. Chem.* **1985**, *28*, 1934.

