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Palladium-Catalyzed Imidoylative Cross-Coupling Reactions

Tjøstil Vlaar

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Isocyanides' Latest Trick:

Palladium-Catalyzed Imidoylative Cross-Coupling Reactions

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. F.A. van der Duyn Schouten,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Exacte Wetenschappen
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door
Tjøstil Vlaar
geboren te Alkmaar

promotor: prof.dr.ir. R.V.A. Orru

copromotor: dr. E. Ruijter

“Vertrouwen is goed,

controle is beter”

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List of Abbreviations

9-BBN	9-borabicyclo(3.3.1)nonane	ee	enantiomeric excess
Ac	acetyl	ESI	electrospray ionization
Ad	adamantyl	EWG	electron withdrawing group
APO	4-aminophthalazin-1(2*H*)-one	*et al.*	*et alii* (and others)
Ar	aryl	GC	gas chromatography
atm	atmosphere	h	hour
aq.	aqueous	*i.e.*	*id est* (that is)
Bn	benzyl	IR	infrared (spectroscopy)
br	broad	HRMS	high resolution mass
conc.	concentrated		spectroscopy
Cp	cyclopentadienyl	Hz	hertz
Cy	cyclohexyl	L	ligand
d	doublet	m	multiplet (NMR) or medium
dba	dibenzylideneacetone		(IR)
DBU	1,8-diazabicycloundec-7-ene	m.p.	melting point
DCE	1,2-dichloroethane	MCR	multicomponent reaction
DCM	dichloromethane	MeTHF	2-methyltetrahydrofuran
DIPEA	*N,N*-diisopropylethylamine	min	minutes
DME	dimethoxyethane	MS	molecular sieves
DMF	dimethylformamide	Mts	2,4,6-trimethylphenylsulfonyl
DMSO	dimethylsulfoxide	NMM	*N*-methylmorpholine
DPEphos	(oxydi-2,1-phenylene)-	NMR	nuclear magnetic resonance
	bis(diphenyl-phosphine)	NMP	*N*-methylpyrrolidone
dppe	1,2-bis(diphenylphosphino)-	MOM	methoxymethyl
	ethane	NHC	N-heterocyclic carbene
dppf	1,1'-bis(diphenylphosphino)-	Ns	nosyl, 2- or 4-nitrobenzene-
	ferrocene		sulfonyl
dppp	1,3-bis(diphenylphosphino)-	Nu	nucleophile
	propane	PG	protecting group
e.g.	*exempli gratia* (for example)	Piv	pivaloyl

PMB	*para*-methoxybenzyl	THF	tetrahydrofuran
ppm	parts per million	TLC	thin layer chromatography
q	quartet	TMS	trimethylsilyl
rt	room temperature	tol	tolyl
SAR	structure-activity relationship	Ts	tosyl
SM	starting material	s	singlet (NMR) or strong (IR)
t	triplet	UV	ultraviolet
TBS	*tert*-butyldimethylsilyl	vs.	versus
Tf	triflyl, trifluoromethane-sulfonyl	w	weak
		XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
TFA	trifluoroacetic acid *or* trifluoroacetate	µW	microwave

Preface

Isocyanides are isoelectronic with carbon monoxide and show similar reactivity in the presence of palladium catalysts. They are, however, underexplored as C_1 building block despite their obvious advantages compared to CO, such as easier handling and the presence of a variable group. This thesis describes our efforts to further utilize isocyanides as powerful C_1 building block in palladium catalysis. **Chapter 1** will provide an overview of selected Pd-catalyzed cascade cyclizations in order to get acquainted with palladium catalysis and appreciate the range of opportunities it offers. In **Chapter 2** all Pd-catalyzed reactions involving isocyanide insertion known at the time of writing are summarized to illustrate both the opportunities and current limitations of this chemistry. The most common class of compounds obtained *via* this chemistry are (cyclic) amidines or related functionalities. We therefore focused on obtaining other type of products during the course of our work to broaden the synthetic utility of this field. **Chapter 3 and 4** show that hydrazines can be used in Pd-catalyzed amidination reactions of aryl halides by isocyanide insertion. Hydrazines are very challenging cross-coupling reagents since they are able to reduce key Pd^{II} intermediates and thereby disrupt the catalytic cycle. **Chapter 3** focuses on the reaction optimization and substrate scope of the Pd-catalyzed reaction between 2-halobenzoates, hydrazines and isocyanides that furnishes 4-aminophthalazin-1(2*H*)-ones. **Chapter 4** provides solutions to the shortcomings in the substrate scope that were encountered. A one-pot dealkylation protocol overcomes the limitation to *tert*-butyl isocyanide and highly selective N2-funtionalizations obviate the need for poorly available mono-substituted hydrazines. **Chapter 5** describes the development of the Pd-catalyzed oxidative coupling of diamines and isocyanides using molecular oxygen as the stoichiometric oxidant. This novel concept allows for the sustainable synthesis of a diverse range of cyclic guanidines, which are of considerable importance in medicinal chemistry. **Chapter 6** demonstrates azoles are suitable nucleophiles in this oxidative coupling as well, thus allowing the synthesis of various azolo[*c*]quinazolines in a convergent manner. This substrate class is particularly challenging for our reaction because of the many coordinating heteroatoms in the product. **Chapter 7** illustrates the oxidative coupling of diamines and isocyanides is more broadly

applicable and also anthranilic acid derivatives can be used as bisnucleophiles. The oxidative coupling of anthranilic acids and isocyanides affords medicinally valuable 2-aminobenzoxazinones. In **Chapter 8** our efforts towards an imidoylative double C-H activation cascade are presented. Such a reaction would yield enamine/imine-containing products in an atom-efficient manner if molecular oxygen can be used as the oxidant. We have realized this transformation by imidoylative cyclization of *N*-aryl imines, although the 4-aminoquinoline products were obtained in modest yield. Finally, **Chapter 9** is a summary of less successful as well as ongoing projects. It also provides a further outlook on possible future directions of Pd-catalyzed imidoylative reactions.

Chapter 1

Introduction:

Recent Advances in Palladium-Catalyzed Cascade Cyclizations

***Abstract**: The importance of Pd-catalyzed cross-coupling reactions in contemporary organic synthesis is undisputed and underlined by the Nobel Prize for Chemistry in 2010. In addition to the highly efficient cross-coupling reactions for single C-C bond construction, Pd-catalyzed cascade processes involving multiple bond formations have emerged in recent years as valuable tools for the rapid synthesis of complex molecular scaffolds. This Chapter presents an overview of the developments in this field, with a focus on the generation of diverse poly- and heterocyclic scaffolds.*

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1.1 Introduction

Chemical synthesis is an advanced science capable of synthesizing most of the complex compounds found in nature by linear total synthesis. The main challenge for the future therefore lies in producing these complex molecules in a more efficient and economical manner, which will enable the use of more sophisticated structures in industry and academia. In this respect, especially step economy is an important factor, since accessibility highly depends on the amount of steps required to reach the desired compounds.[1] Other important aspects currently challenging organic chemistry are nicely summarized in the ideal synthesis proposed by Wender *et al.* in 1997 (Figure 1).[2] Improvements to this end are of high importance, although the ideal synthesis will most likely remain a utopia.

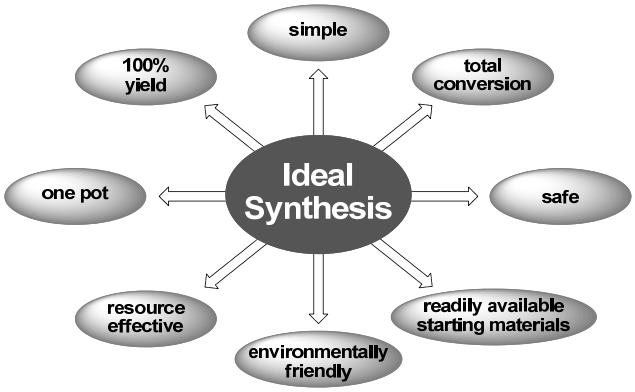


Figure 1. The ideal synthesis as proposed by Wender.[2]

Cascade reactions are important tools to meet these challenges currently facing synthetic chemists and are therefore drawing considerable attention.[3] Cascade reactions are sequences of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process repeats until a product stable under the reaction conditions is formed. The intrinsic advantage of such cascade reactions is the step economy. Multiple bond formations are combined in one pot, which lowers the amount of steps required to reach the same product. As a result, an increase of molecular complexity in economically feasible compounds is realized. Cascade reactions are also considered to contribute to green chemistry because of the reduced waste production and increased atom efficiency. In addition, in some cases new synthetic possibilities open up by producing and utilizing reactive intermediates *in*

situ that are otherwise difficult or impossible to isolate and use. Cascade reactions require a combination of highly selective transformations compatible with different functional groups, which can be challenging to engineer. Consequently, a good understanding of the combined processes is required in order to develop such combinations. Nevertheless, there is significant interest in the field and important cascade reactions have been developed.

Palladium is a versatile transition metal showing useful reactivity with various functional groups.[4] Consequently, Pd-catalyzed cross-couplings nowadays are essential tools for the construction of carbon-carbon bonds. In addition, the important chemistry of π-allylpalladium species has been widely studied and applied in chemical synthesis. The significance of palladium catalysis and the cross-couplings in particular has recently been illustrated by the Nobel Prize for Chemistry in 2010, which was awarded to Heck, Negishi and Suzuki for the development of their Pd-catalyzed cross-coupling reactions.

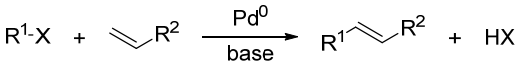
The chemistry of palladium is well understood and versatile, which means there is a huge potential for Pd-catalyzed cascade reactions. Chemists have exploited this potential and many interesting Pd-catalyzed cascade reactions have been reported.[5] This Chapter presents an overview of recent advances in Pd-catalyzed cascade reactions with a focus on cascades involving ring formation(s), although the cyclization step is not necessarily Pd-catalyzed in all cases. The aim of this Chapter is to introduce the plethora of possibilities palladium catalysis offers and to get familiarized with the basic knowledge of this important field. Rather than an exhaustive or more focused overview, we aim to present inspiring examples covering a broad scope of the topic. Section 1.2 will deal with cascades involving the reactivity of classical cross-coupling reactions (*i.e.* Mizoroki-Heck reaction, Suzuki coupling, Stille coupling and Sonogashira coupling). There are, of course, various important reactions involving other organometallic coupling reagents (*e.g.* Negishi coupling, Kumada coupling), but those are not included here since they are not as widely used in cascade reactions and/or are similar to cascades involving boron or tin species. Most Pd-catalyzed cascades, however, are not easily categorized according to the traditional cross-couplings. Therefore, section 1.3 will deal with frequently encountered building blocks in Pd-catalyzed cascade reactions. Section 1.4 will be devoted to the synthesis of indoles. Indoles exhibit important biological activity and are therefore often found in pharmaceuticals. Accordingly, cascade reactions towards substituted indoles are a popular field of chemistry and several Pd-catalyzed processes have been reported.

1.2 Cross-couplings in Pd-catalyzed cascade reactions

Pd-catalyzed cross-couplings are reactions in which two different hydrocarbon fragments are coupled with the aid of a palladium catalyst. These cross-couplings have emerged as one of the most important ways to construct C-C bonds and can be combined with other transformations to develop Pd-catalyzed cascade cyclization reactions. This section will describe the use of one or more of these cross-couplings in cascade cyclization reactions.

1.2.1 The Mizoroki-Heck reaction

The Mizoroki-Heck reaction involves the Pd-catalyzed coupling of an unsaturated halide and an alkene to form a 1,2-disubstituted alkene (Scheme 1). The reaction, often referred to simply as the Heck reaction, was independently discovered by Mizoroki and Heck in 1971 and 1972, respectively.[6] The unsaturated halide (Br, I, Cl or triflate) is an aryl, benzyl or vinyl halide and the palladium catalyst can come from various palladium sources, including $Pd(PPh_3)_4$, $PdCl_2$ and $Pd(OAc)_2$. Phosphine ligands are required to generate the active species by reducing Pd^{II} to Pd^0 and to stabilize the Pd^0 catalyst. A base is necessary to neutralize the accumulating hydrogen halide, which otherwise has a detrimental effect on the yield.

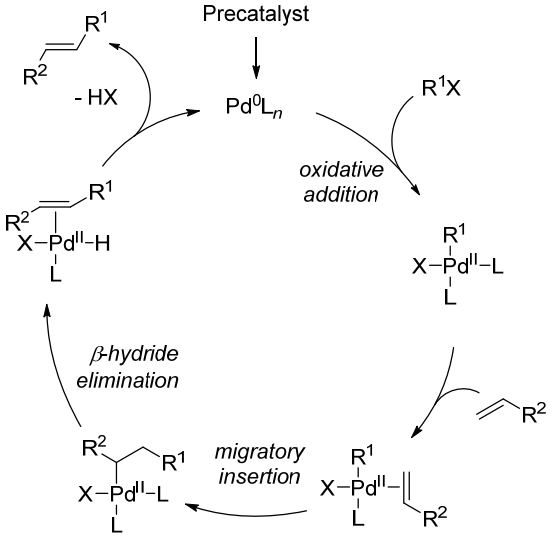


Scheme 1. The Mizoroki-Heck reaction.

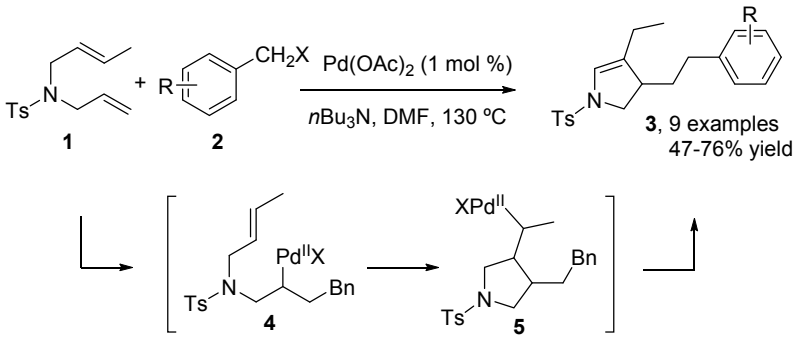
The mechanism of the reaction is described in great detail in the literature and starts by preactivation of the palladium source to form the active species (Scheme 2).[7] Then, oxidative addition of the unsaturated halide occurs, followed by coordination of the alkene to form a π-complex. Migratory insertion results in the formation of a palladium-alkyl bond and β-hydride elimination subsequently leads to the formation of the product. The hydrogen halide is removed from the catalyst by base-mediated reductive elimination forming a salt as the by-product.

In 2003, Pan *et al.* reported a cascade reaction with two alkene insertions affording dihydropyrroles (**3**, Scheme 3).[8] Oxidative addition of the benzyl halides is followed by insertion of the less sterically hindered terminal alkene, leading to formation of intermediate **4**. Intramolecular insertion of the second alkene is preferred over β-hydride elimination and accomplishes ring formation in a cascade

fashion. Then, β-hydride elimination takes place and the newly formed double bond rearranges to form the more stable endocyclic enamine.



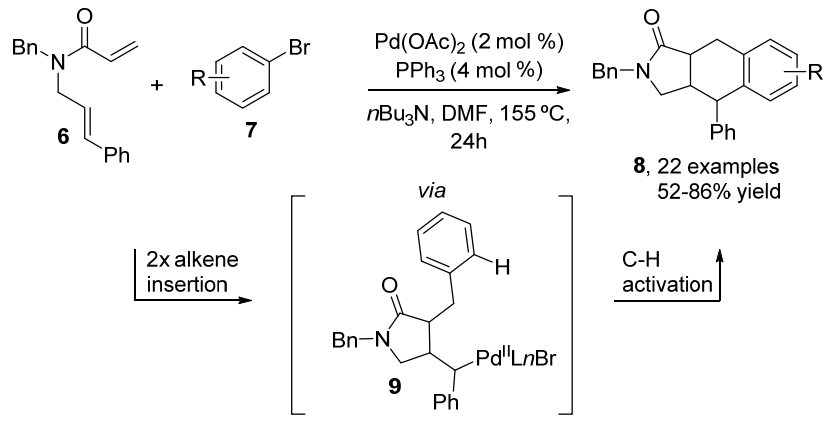
Scheme 2. Mechanism of the Heck reaction.



Scheme 3. Heck reaction with double alkene insertion.

Hu *et al.* also used a diene for a Heck-type reaction with double alkene insertion, but finish the catalytic cycle with C-H activation instead of β-hydride elimination (Scheme 4).[9] *N*-benzyl-*N*-cinnamylacrylamide (**6**) reacts with electron-deficient aryl bromides to construct various tri- and tetracyclic compounds (**8**). In 2009, they reported two more substrate classes that undergo the same transformation. Evidently, also cycloalkenes can be used for this cascade reaction,

generating hydronaphthoindolones (**10**, Scheme 5).[10] Furthermore, tosylated allylic amines instead of amides also react smoothly to afford polycyclic structures as **11**.[11]

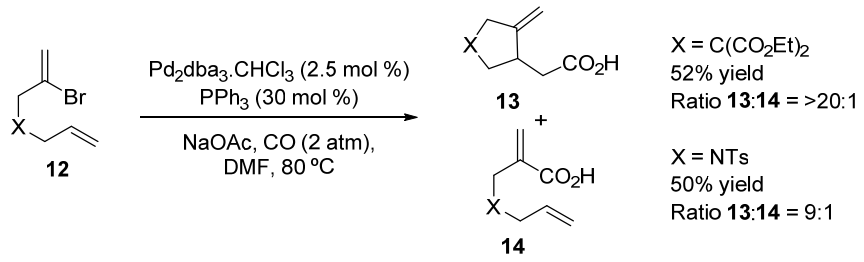


Scheme 4. Heck reaction/C-H activation cascade.

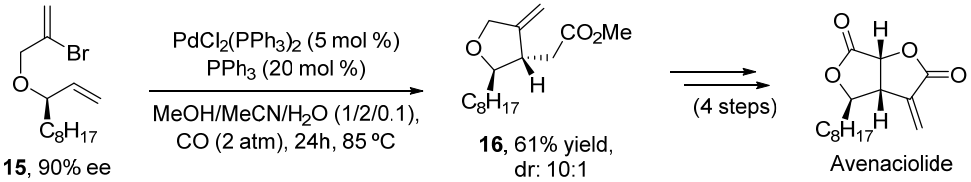
Scheme 5. Heck reaction/C-H activation cascade.

Aggarwal *et al.* reported a Heck cyclization/carbonylation cascade of vinylic bromide **12** with the aim of obtaining unsaturated carboxylic acid **13** (Scheme 6).[12] The intrinsic difficulty of this transformation is the possible formation of linear carboxylic acid **14** and the standard Heck product, which is obtained if β-hydride elimination proceeds faster then carbonylation. The authors argued that the reactivity could be tuned by choosing the appropriate phosphine ligand and intensive optimization eventually provided moderate yields for this reaction.

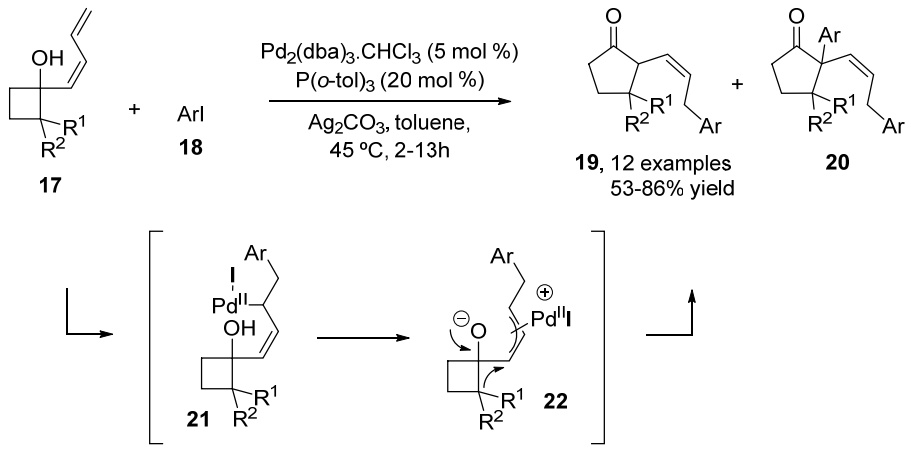
Two years later, Aggarwal and coworkers showed the utility of their work by completing the total synthesis of avenaciolide using their Heck cyclization/carbonylation cascade (Scheme 7).[13] The reaction was shown to be highly diastereoselective and provided the desired building block (**16**) required for the synthesis of avenaciolide in a high diastereomeric ratio and good yield. Slightly modified conditions were used and methanol was added to the solvent mixture to produce methyl esters instead of carboxylic acids.



Scheme 6. Cyclization/carbonylation cascade.



Scheme 7. Cyclization/carbonylation cascade.

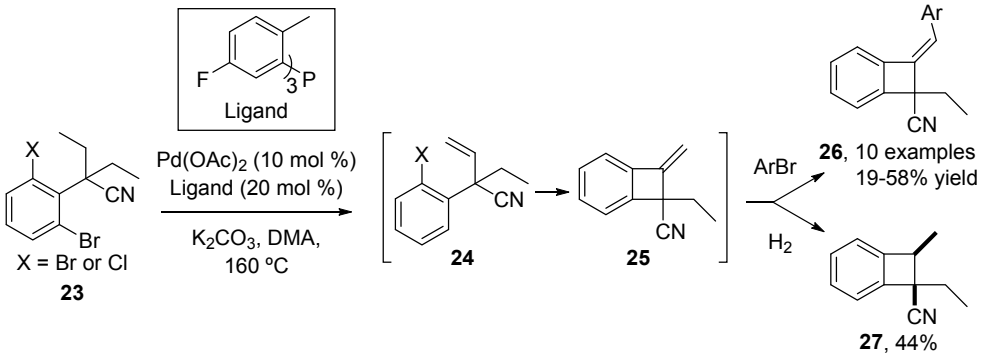


Scheme 8. Ring expansion by Heck-type cascade.

Yoshida and Ihara *et al*. developed a cascade involving a Heck-type process for the ring expansion of (*Z*)-1-(1,3-butadienyl)cyclobutanols (**17**) by Pd-catalyzed reaction with aryl iodides (Scheme 8).[14] The reaction stereospecifically produces only (*Z*)-2-(3-aryl-1-propenyl)cyclopentanones (**19**). In some cases, the *α*-arylated product **20** is formed regioselectively under the reaction conditions in minor quantities. It is worth noting that cascade ring expansion reactions of cyclobutanols bearing isopropenyl,[15] allenyl,[16] alkynyl[17] and propargyl[18] groups have also been

developed by the same authors and others. A mechanism involving Heck intermediate **21** is proposed. Intermediate **21** reacts with silver carbonate to form zwitterionic π-allylpalladium intermediate **22**, which undergoes ring expansion to form the product and regenerate Pd^0. The authors also provide an explanation for the (*Z*)-selectivity of the reaction and the low reactivity of the (*E*)-isomer of the substrate (**17**).

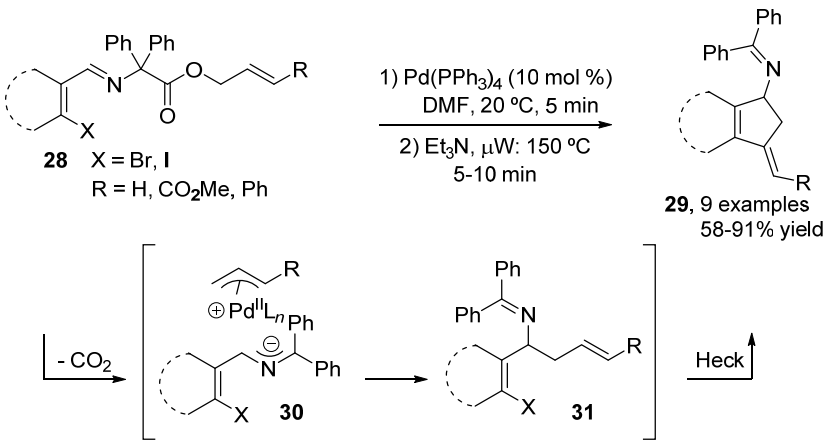
In 2007, Hitce and Baudoin reported an elegant three-step one-pot cascade procedure catalyzed by a single palladium catalyst (Scheme 9).[19] The first step in their cascade involves a C(*sp*³)-H activation of **23** leading to the dehydrogenated product **24**, which they published earlier in separate work.[20] In this work they efficiently combine this C(*sp*³)-H activation with an unusual 4-*exo*-*trig* Heck-cyclization forming an *exo*-methylenebenzocyclobutene (**25**). The final step of their one-pot sequence is then either a Heck arylation to afford (*E*)-trisubstituted olefins (**26**) or a hydrogenation to obtain benzocyclobutane **27** as a single diastereoisomer.



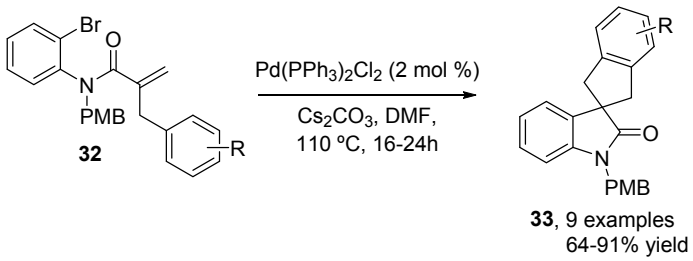
Scheme 9. C(*sp*³)-H activation/Heck cyclization/Heck arylation cascade.

Chruma *et al.* combined the Heck reaction with a Pd-catalyzed decarboxylative allylation in a one-pot synthesis of 1-aminoindanes (**29**, Scheme 10).[21] A variety of allyl diphenylglycinate imines (**28**) undergo decarboxylative allylation in the presence of $Pd(PPh_3)_4$ to form **31**, which then cyclizes in an intramolecular Heck reaction to afford 1-aminoindanes (**29**).

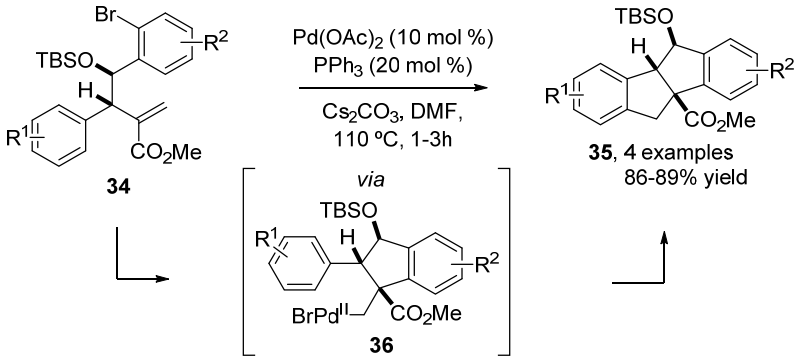
Ruck *et al.* reported a cascade where C-H activation is preceded by the Heck reaction leading to spiro-fused indane-oxindoles (**33**, Scheme 11).[22] Oxindoles are common structural motifs in natural products and especially 3,3-disubstituted oxindoles have shown promising biological activity.[23] Both electron-rich and electron-deficient aromatics are tolerated and the isolated yields are good to excellent. The authors sought to achieve an enantioselective version of their reaction by probing different chiral phosphine ligands, but no enantiomeric excess was observed.



Scheme 10. Decarboxylative allylation/Heck cascade.



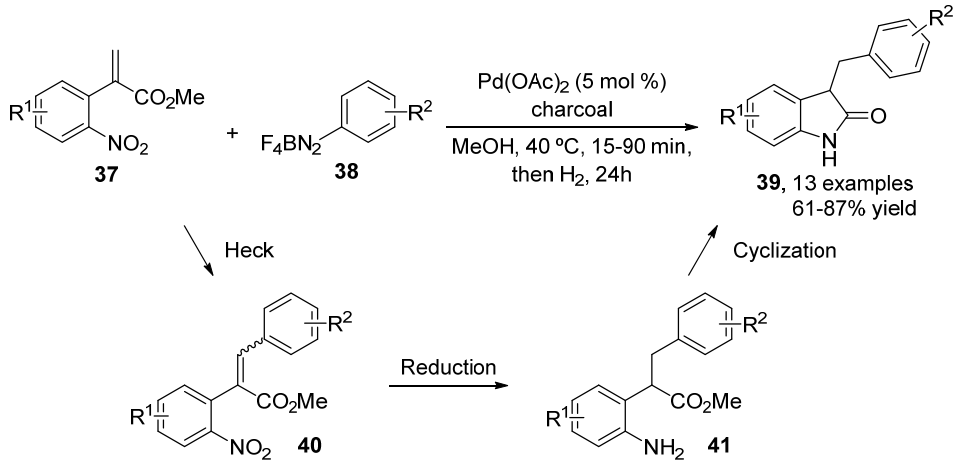
Scheme 11. Tandem Heck reaction/C-H functionalization.



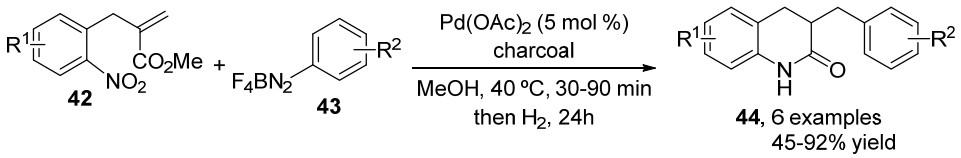
Scheme 12. Heck reaction/C-H functionalization cascade.

Kim *et al.* reported another Heck reaction/C-H activation cascade starting from γ-silyloxy ester **34** furnishing fused tetracycles (**35**, Scheme 12).[24] The alcohol needs to be TBS-protected, as other protection groups favor 6-*endo*-*trig* carbo-palladation

and predominantly furnish naphthalene derivatives. Furthermore, the ester is essential, presumably due to the steric size, since a nitrile group on the same position also leads to naphthalene compounds.

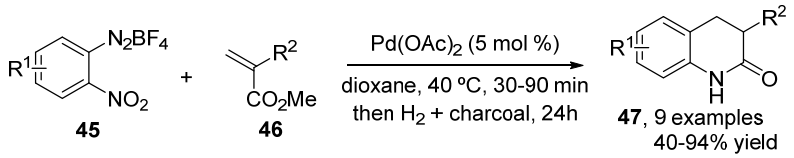


Scheme 13. Heck reaction/reduction/cyclization cascade.



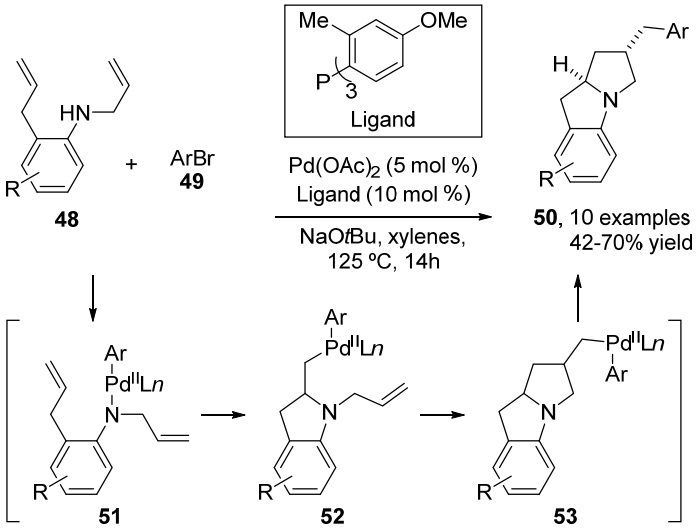
Scheme 14. Heck reaction/reduction/cyclization cascade.

Felpin *et al.* introduced a tandem Heck reaction/reduction/cyclization synthesis of oxindoles (**39**) using an *in situ* prepared heterogeneous palladium catalyst (Scheme 13).[25] Different 2-(2-nitrophenyl)acrylates (**37**) and aryl diazonium salts (**38**) were coupled to form Heck products (**40**) without base or ligand present. The Heck products are reduced by the same catalyst and subsequently cyclize. Dihydroquinolones (**44**) are also accessible using the same procedure (Scheme 14).[26] Simply combining 2-(2-nitrobenzyl)acrylates (**42**) and aryl diazonium salts (**43**) under the same reaction conditions furnished benzylated quinolones (**44**). A complementary approach using diazonium salts **45** and substituted acrylates (**46**) was developed in order to access a larger substitution pattern on the C3 position (Scheme 15). A different solvent was required in this case and the charcoal had to be added after the Heck reaction, but with this approach C3-unsubstituted, arylated and alkylated dihydroquinolones (**47**) can be obtained.



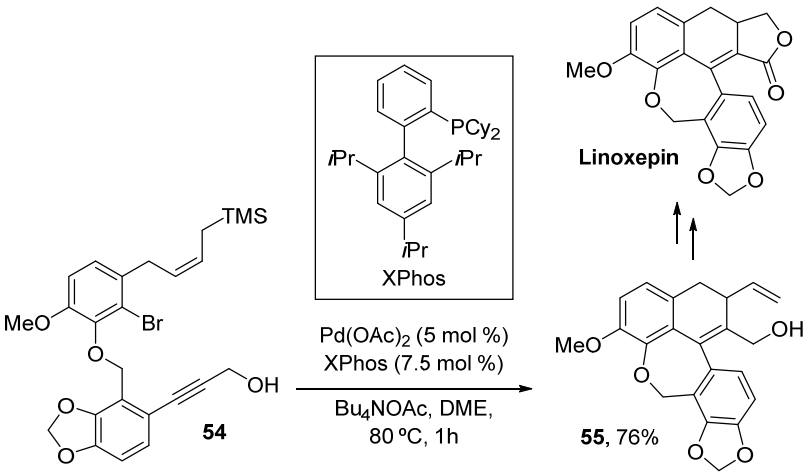
Scheme 15. Heck reaction/reduction/cyclization cascade.

Wolfe *et al*. reported a Pd-catalyzed aminopalladation/carbopalladation cascade cyclization of *N*,2-diallylaniline derivatives (**48**, Scheme 16).[27] Initially a palladium(aryl)(amido) complex (**51**) is formed, which undergoes two consecutive alkene insertions. The diastereomeric ratios vary from reasonable (3:1) to excellent (>20:1). The main challenge was to avoid reductive elimination of **51** or **52**, which can form thermodynamically favored C-C or C-N bonds. Bulky triarylphosphines eventually gave acceptable results, although the yields remain moderate.



Scheme 16. Aminopalladation/carbopalladation cascade.

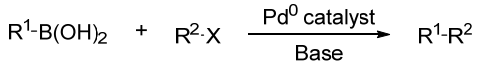
In 2013, Tietze *et al*. showed the potential of cascade cyclizations in total synthesis by using the Heck reaction in a cascade process towards linoxepin (Scheme 17).[28] This cascade involves an intramolecular Heck reaction with an additional carbopalladation step of the alkyne moiety. The alkyne in **54** is introduced by a Sonogashira reaction, but higher yields were obtained if the Sonogashira coupling was performed separately instead of in a cascade fashion. The main reason for this is the inhibiting effect of CuI on the carbopalladation/Heck cascade.



Scheme 17. Cascade reaction applied in total synthesis of linoxepin.

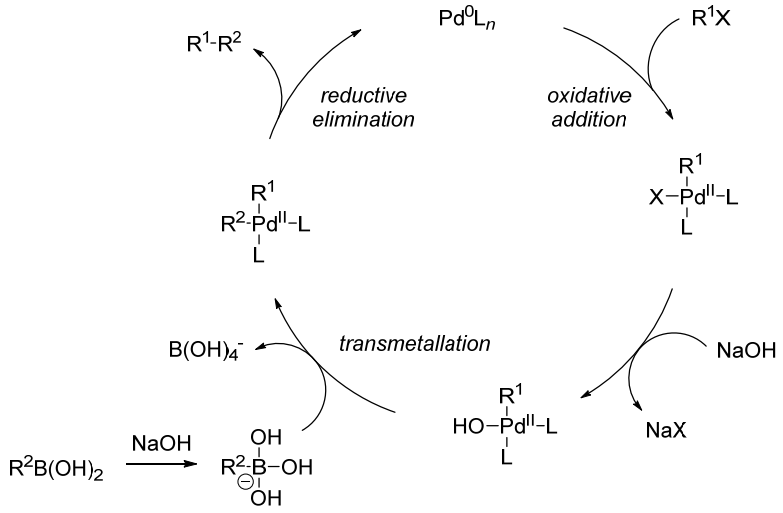
1.2.2 The Suzuki Coupling

The Suzuki coupling is another Pd-catalyzed process of great importance for the construction of C-C bonds discovered by Suzuki *et al.* in 1979.[29] Originally, aryl- or vinylboronic acids were coupled with aryl or vinyl halides by a Pd^0 catalyst to yield polyolefins, styrenes or biphenyls (Scheme 18). Nowadays, significant improvements have been made to the substrate scope and also alkyl, alkenyl and alkynyl coupling partners can also be used.[30] Boronic esters can be used instead of boronic acids and some pseudohalides (*e.g.* triflates) can be used instead of halides.



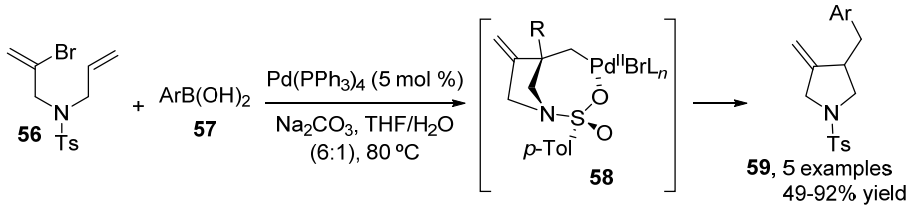
Scheme 18. The Suzuki coupling.

A major advantage of the Suzuki coupling over similar transformations, such as the Stille coupling (see section 1.2.3), is the stability, ease of preparation and low toxicity of boronic acids compared to other coupling reagents. Consequently, there is enormous interest in the further development of the Suzuki coupling, resulting in a broader range of suitable coupling partners, better catalysts, and lower catalyst loadings. Catalyst loadings as low as 0.001 mol % have been reported, making this reaction extremely economical and viable in industry.[31]



Scheme 19. Mechanism of the Suzuki coupling.

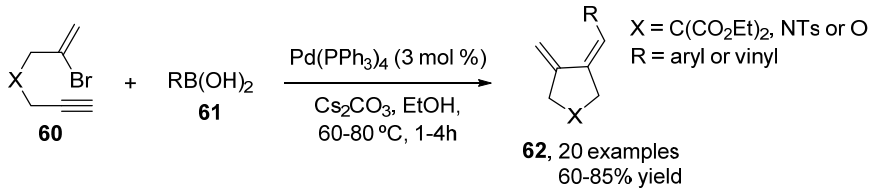
The mechanism of the Suzuki coupling starts by oxidative addition of the organic halide to Pd^0 and the coordinated halide is then exchanged with hydroxide (Scheme 19). The boronic acid has to be activated *in situ* to facilitate transmetallation, which can be achieved by hydroxide. Transmetallation with the activated boron species can then occur and leads to formation of the product after reductive elimination.



Scheme 20. Heck reaction/Suzuki coupling cascade.

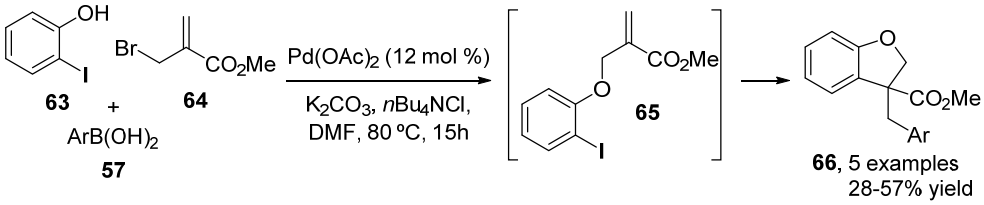
The Suzuki coupling can be combined with the Heck reaction as illustrated by Ahn *et al.* (Scheme 20).[32] The Suzuki coupling is preceded by an intramolecular Heck reaction of vinylic bromide **56** to yield 4-methylene-3-arylmethyl-pyrrolidines (**59**). The direct Suzuki coupling of **56** was not observed, indicating that intramolecular Heck reaction is preferred. Interestingly, no β-hydride elimination occurs after double bond insertion. Instead, the organopalladium species is sufficiently stable for the subsequent Suzuki coupling. This is intriguing, since normally the reversed preference is observed. The authors propose a neighboring group participation of one of the

oxygen atoms of the tosyl group as in **58**, where the donation of electron density to palladium disfavors β-hydride elimination. Several analogues of **56** with other groups on nitrogen did not show similar reactivity, which supports an intermediate as **58**. A diastereoselective domino Heck/Suzuki cascade was reported by Braun *et al.*[33] Similar work was reported in 2003 by Oh *et al.*, who used 2-bromo-1,6-enynes (**60**) in a cascade to obtain exocyclic dienes (**62**) (Scheme 21).[34] In this case no β-hydride elimination can take place, since the intermediate vinylpalladium species does not contain any β-hydrides.

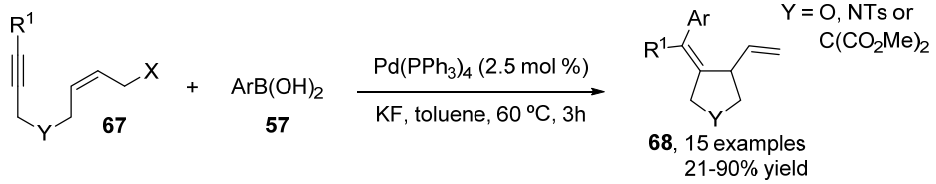


Scheme 21. Alkyne insertion/Suzuki coupling cascade.

Lamaty *et al.* discovered a three-component reaction between 2-iodophenol (**63**), methyl bromomethylacrylate (**64**) and arylboronic acids (Scheme 22).[35] Initial O-allylation of 2-iodophenol (**63**) leads to aryl iodide **65**. Subsequently, a Heck cyclization/Suzuki coupling cascade occurs, again feasible due to the lack of β-hydrides after double bond insertion. The same authors later elaborated on this work and used automated synthesis to prepare more examples.[36] Furthermore, they also used the Stille coupling (section 1.2.3) as the terminating reaction in this cascade.

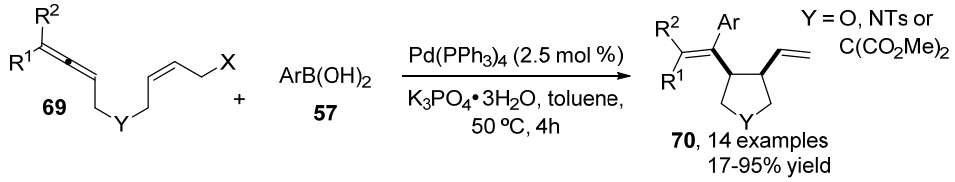


Scheme 22. O-allylation/Heck reaction/Suzuki coupling cascade.

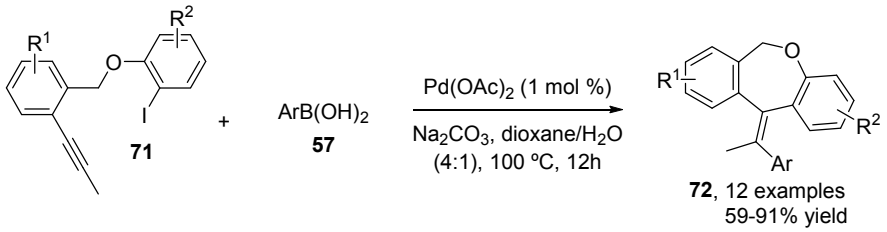


Scheme 23. Cyclization/arylation cascade.

In 2003, Zhang *et al.* developed a cyclization/arylation cascade reaction of enynes (**67**) leading to cyclic products with a stereodefined exocyclic double bond (**68**, Scheme 23).[37] The yields are generally very good, except when terminal alkynes or NBn tethered enynes are used. The authors propose a few plausible mechanistic pathways and are unsure which is predominant. Most likely, a π-allylpalladium complex is formed from the allylic halide. Subsequent insertion of the triple bond followed by Suzuki coupling would then lead to the product. The same group later extended this strategy to the cyclization/arylation of 1,2,7-trienes (**69**) using nearly identical conditions (Scheme 24).[38] Aryl substituted allenes (R^1 or R^2 = aryl) do not show any conversion, which the authors attribute to polymerization of the substrate due to activation of the allene by conjugation. The mechanism of this reaction is proposed to be similar to their previous work.



Scheme 24. Cyclization/arylation cascade of 1,2,7-trienes.

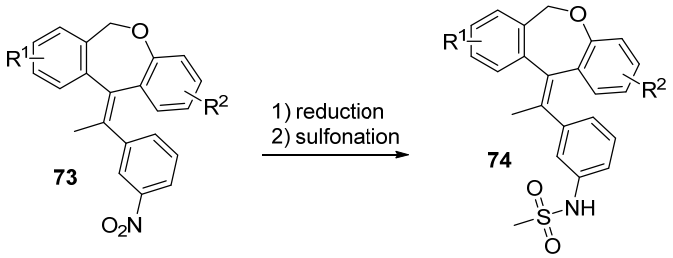


Scheme 25. Carbopalladation/Suzuki coupling of alkynes.

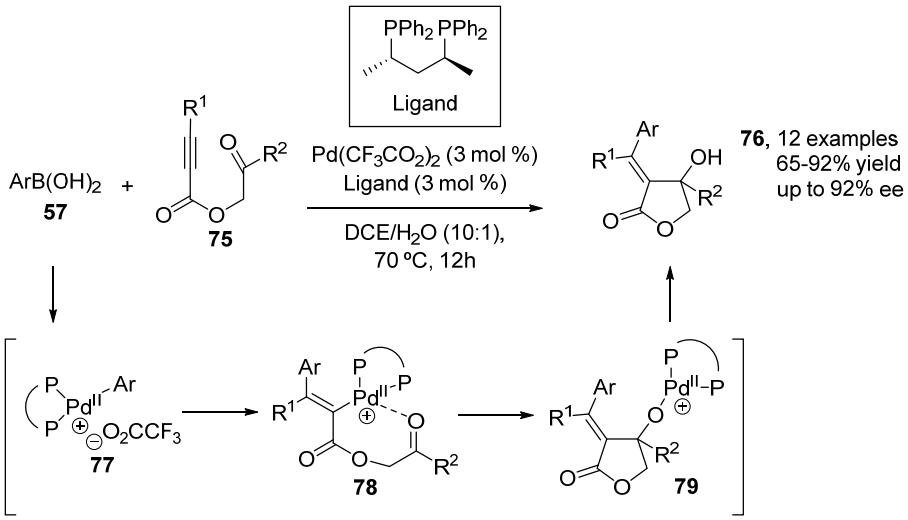
Yu *et al.* combined the Suzuki coupling with an alkyne insertion into aryl iodides (**71**, Scheme 25).[39] Various aryl iodides (**71**) underwent intramolecular alkyne insertion followed by Suzuki coupling to form seven-membered rings (**72**). The use of *m*-nitrophenylboronic acid leads to products like **73**, which can easily be converted into dibenzoxapines **74** (Scheme 26). Dibenzoxapine derivatives have been studied as nuclear hormone receptor modulators.[40]

Sheni *et al.* reported an elegant cascade involving carbopalladation of alkynoates (**75**) and enantioselective intramolecular addition of the resulting vinylpalladium species to ketones, all catalyzed by a cationic Pd^{II} complex (Scheme

27).[41] Unlike the insertion of alkenes into carbon-palladium bonds, the insertion of ketones is uncommon. The authors achieved this interesting transformation by using a cationic Pd^{II} complex to activate the ketone as in **78**. Unfortunately, it was not reported which enantiomer of the product is formed.

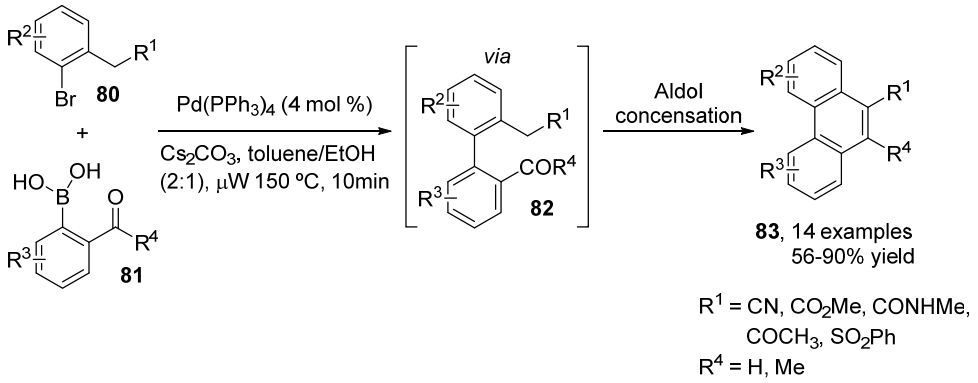


Scheme 26. Synthesis of dibenzoxapine derivatives.

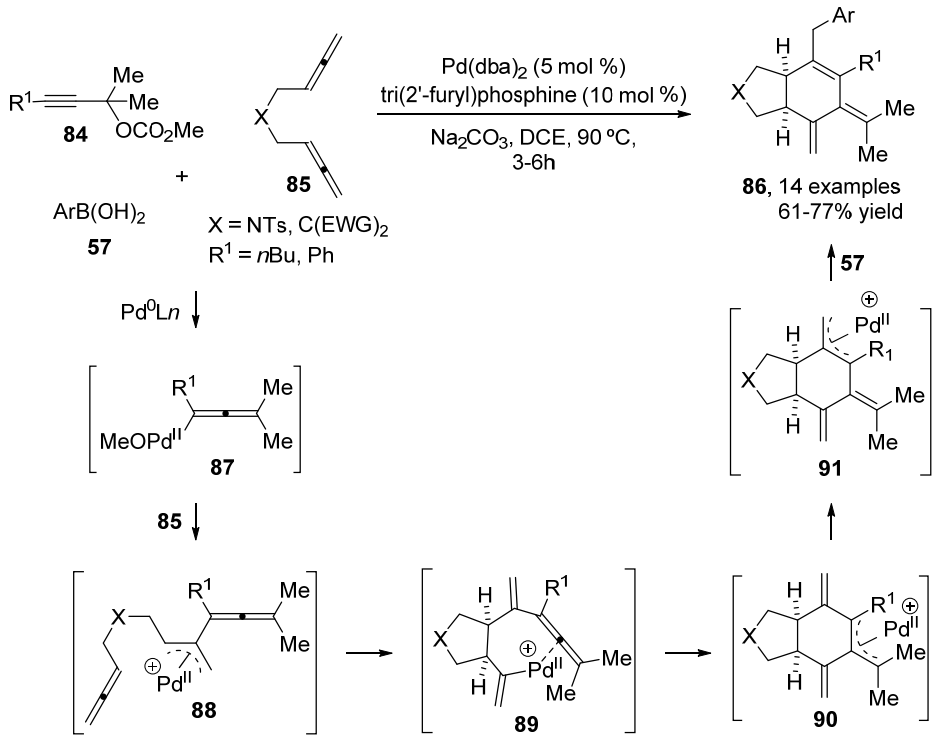


Scheme 27. Enantioselective cascade with ketone insertion.

The Suzuki coupling can also be combined with an intramolecular aldol condensation, as demonstrated by Heo *et al.* (Scheme 28).[42] The product of the Suzuki coupling (**82**) is an excellent precursor for aldol condensation, which is accomplished *in situ* to provide a general cascade route towards highly substituted phenanthrenes (**83**).



Scheme 28. Suzuki coupling/Aldol condensation cascade.

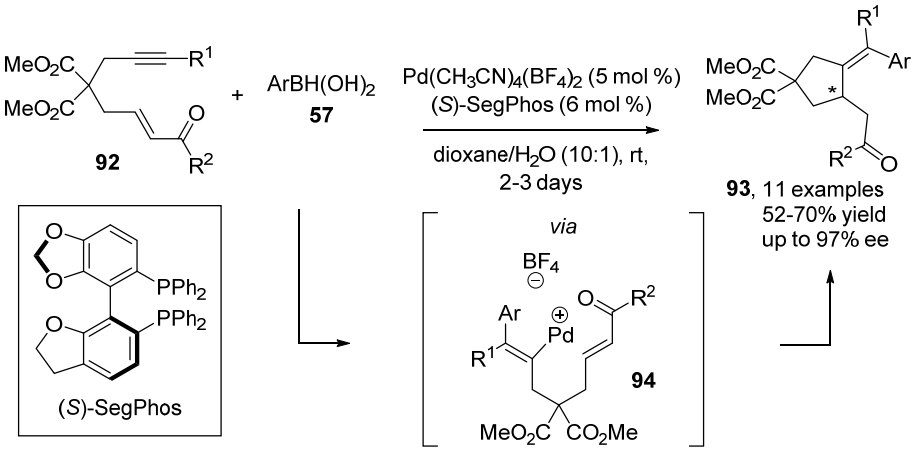


Scheme 29. Multicomponent reaction involving Suzuki coupling.

An impressive multicomponent reaction involving a Suzuki coupling was reported in 2009 by Ma *et al.* (Scheme 29).[43] The reaction between 2-alkynyl carbonates (**84**), symmetric bisallenes (**85**) and arylboronic acids affords *cis*-fused

bicyclic trienes (**86**). The authors propose a plausible mechanism initiated by formation of allenylpalladium species **87** from the propargylic carbonate (**84**). Carbopalladation of bisallene **85** then leads to π-allylic palladium species **88**, which undergoes an intramolecular carbopalladation to selectively obtain cyclic compound **89** in excellent diastereoselectivity. A third and final carbopalladation provides bicycle **90**, that is isomerized to the more stable **91**. The final step is the coupling of the arylboronic acid to generate the product.

In recent work Lu *et al.* show that cationic palladium catalysts can realize an enantioselective arylative cyclization of enals or enones (**92**) using boronic acids as aryl source (Scheme 30).[44] The authors postulate an arylpalladium species is formed first by transmetalation, after which carbopalladation of the alkyne affords vinylpalladium intermediate **94**. Insertion of the C-C double bond and protonolysis affords the products. It was not reported which enantiomer of the product is formed.

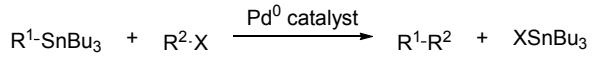


Scheme 30. Asymmetric arylative cyclization using boronic acids.

1.2.3 The Stille Coupling

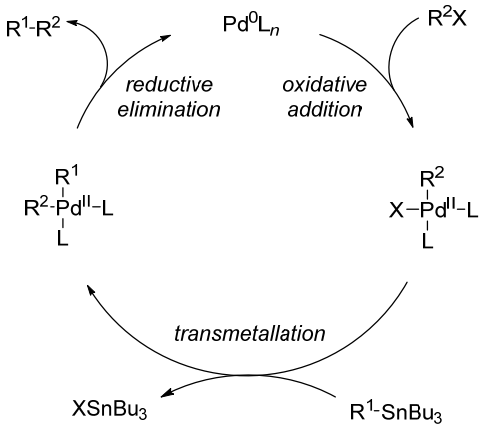
The Stille coupling is a versatile coupling reaction between stannanes and halides that was first described by Stille in 1978 (Scheme 31).[45] The reaction has an extremely high substrate scope and is consequently of high importance for chemical synthesis. However, stannanes are highly toxic and therefore the Suzuki coupling is preferred where possible. There is hardly a limit to the stannanes that can be used; alkyl, aryl, benzyl, vinyl and allyl stannanes are all tolerated. Usually, tributyl stannanes are used since they are less toxic than the more reactive trimethyl stannanes. The organic

halide can be an aryl, benzyl, vinyl, allyl or acyl halide and, as in the Suzuki coupling, pseudohalides (*e.g.* triflates) can be used.

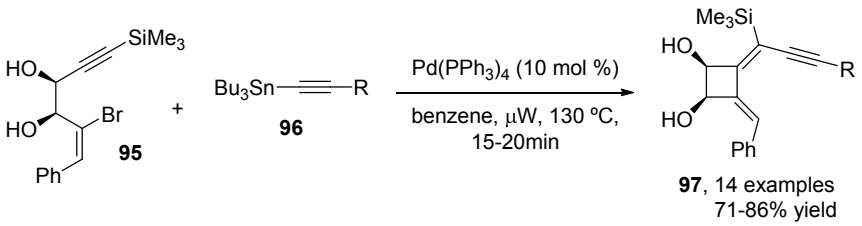


Scheme 31. The Stille coupling.

The mechanism of the Stille coupling is somewhat simpler then the Suzuki reaction because activation of stannanes is not required for reactivity (Scheme 32). Oxidative addition of the organic halide to Pd^0 is followed by transmetallation. Reductive elimination then furnishes the product and regenerates the catalyst. No base is needed for the Stille coupling, making the use of base-sensitive substrates possible. The reaction mixture has to be anhydrous and degassed, otherwise homocoupling of stannanes can lower the yield.



Scheme 32. Mechanism of the Stille coupling.

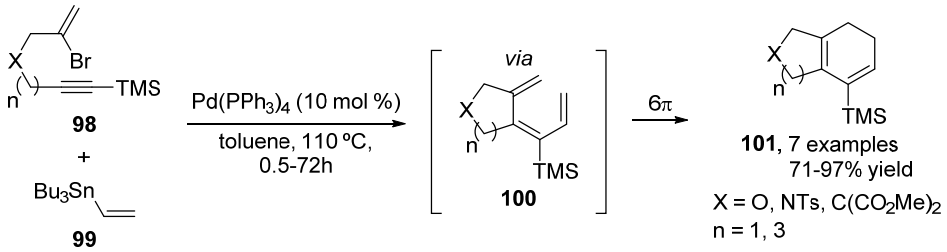


Scheme 33. Alkyne insertion/Stille reaction cascade.

The Stille coupling can be combined with a preceding intramolecular alkyne insertion into vinylic bromides (Scheme 33), as demonstrated by Suffert *et al.*[46] γ-

Bromopropargylic diols (**95**) undergo 4-*exo-dig* cyclocarbopalladation and subsequent coupling with alkynyl stannanes (**96**) to furnish strained cyclobutanediol derivatives (**97**). Microwave conditions proved to be superior to conventional heating for this reaction. Vinyl stannanes can also be used for this cascade and results in an *in situ* 6π-electrocylization to afford fused bicycles. The authors summarized this and their related work in a short review.[47]

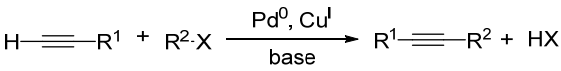
A similar strategy was employed by Anderson *et al.* to obtain various fused bi- and tricycles (Scheme 34).[48] In this case carbon-, nitrogen-, or oxygen-tethered bromoenynes (**98**) were used to furnish triene **100**. *In situ* 6π-electrocyclization affords the products (**101**) in high yields. The strategy was also be used to form 8-membered rings by coupling dienylstannanes and 8π-electrocyclization (not shown). The reaction was later extended to afford various azabicycles using organoboron species instead of stannanes.[49]



Scheme 34. Alkyne insertion/Stille/6π-electrocyclization cascade.

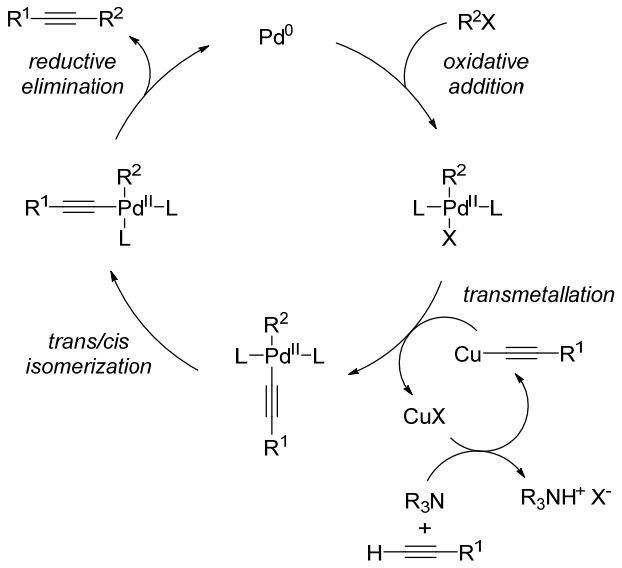
1.2.4 The Sonogashira Coupling

The Sonogashira reaction is an important tool for the synthesis of alkynes by cross-coupling of terminal alkynes and aryl or vinyl (pseudo)halides, and was first described by Sonogashira in 1975.[50] The reaction is catalyzed by Pd^0 and requires a Cu^I cocatalyst and the presence of base (Scheme 35).[51] Typical conditions include the use of $Pd(PPh_3)_4$ as palladium source combined with cuprous halides and secondary or tertiary amine bases. Degassed and anhydrous solvents are required for high yields, since otherwise oxidative homocoupling of the terminal alkyne occurs.



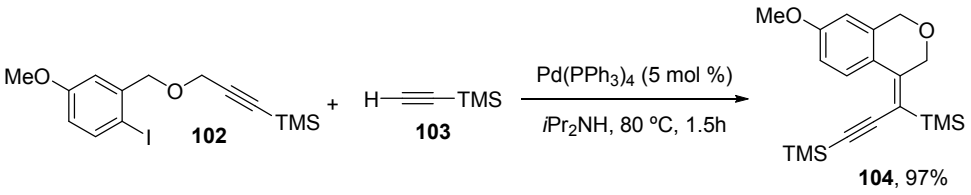
Scheme 35. The Sonogashira coupling.

The mechanism of the Sonogashira coupling again starts with oxidative addition of Pd^0 to the aryl or vinyl halide (Scheme 36). A second catalytic cycle results in a copper acetylide species, which displaces a ligand on palladium. *Cis*/*trans* isomerization then has to occur in order to align the organic ligands correctly for reductive elimination.

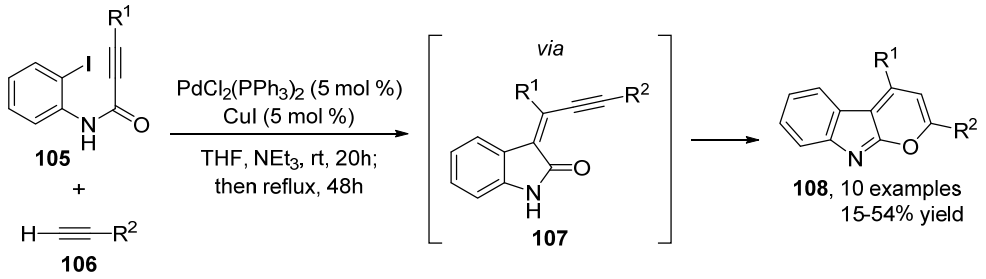


Scheme 36. Mechanism of the Sonogashira Coupling.

Teplý *et al*. combined the Sonogashira coupling with an alkyne insertion (Scheme 37).[52] Evidently, if the copper cocatalyst is removed the Sonogashira coupling is very slow, opening the way for a preceding alkyne insertion. This reaction, however, appears to be far from general and only some substrates show this reactivity. In some cases, some of the product cyclizes by C-H activation to give complicated reaction mixtures. If a copper halide is added to the reaction mixture the standard Sonogashira coupling product predominates, which demonstrates the sophisticated kinetic balance required for this reaction.



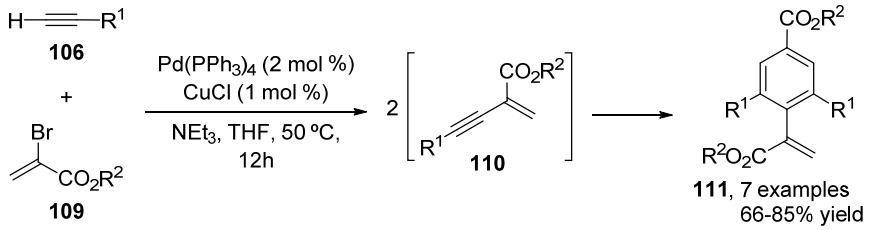
Scheme 37. Alkyne insertion/Sonogashira coupling.



Scheme 38. Sonogashira coupling cascade.

Related work has been reported by the group of Müller (Scheme 38).[53] Alkynoyl *o*-iodoanilides (**105**) react with terminal arylacetylenes under standard Sonogashira conditions to furnish novel 2,4-diarylpyrano[2,3*b*]indoles (**108**). Also in this case, the Sonogashira reaction is preceded by alkyne insertion into an organopalladium species. Subsequent heating to reflux conditions induces a second cyclization. The products display unique photophysical properties; as a free base no fluorescence is observed, but after protonation, methylation or complexation halochromic green fluorescence is displayed.

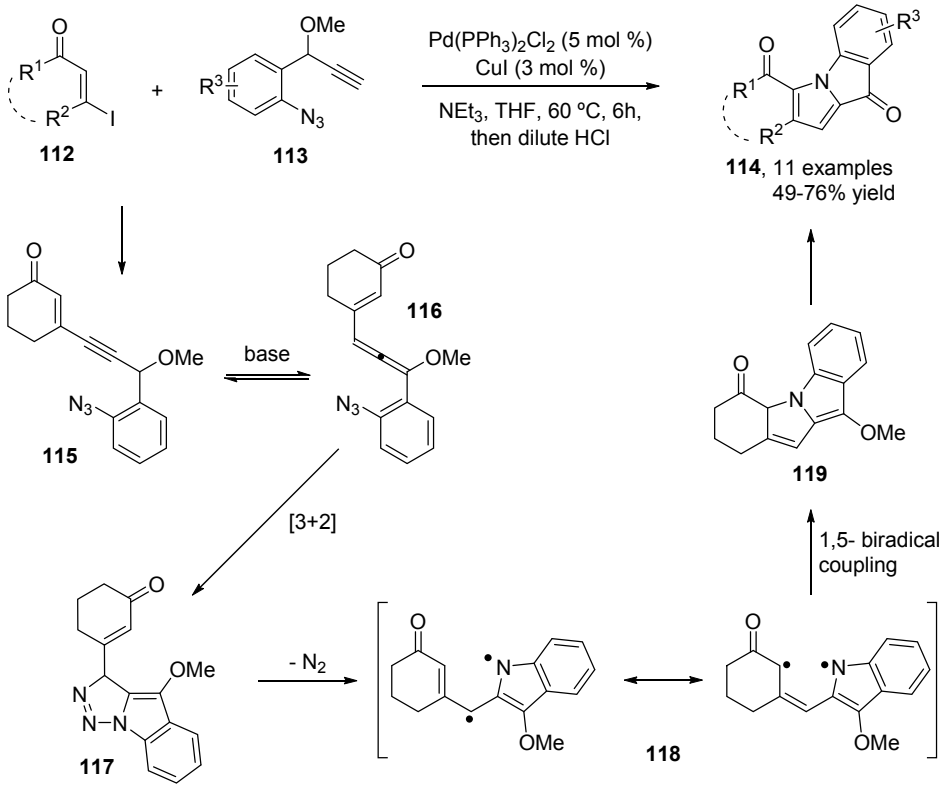
Densely substituted benzene derivatives are widely used in industry and academia, but transition metal catalyzed processes towards benzenes are scarce due to significant regioselectivity issues in [2+2+2] and related processes. In 2005, Xi *et al*. reported a regioselective reaction towards tetrasubstituted symmetric benzenes by a Pd-catalyzed process (Scheme 39).[54] Sonogashira coupling of α-bromoacrylates (**109**) and terminal alkynes provides **110**, which dimerizes by benzannulation to give benzenes. The authors do not elaborate whether this benzannulation is spontaneous or catalyzed by palladium.



Scheme 39. Sonogashira coupling/benzannulation cascade.

An intriguing cascade reaction between 3-iodo-enones (**112**) and *o*-azidobenzyl alkynes (**113**) towards various tri- and tetracycles (**114**) has been established by

Huang *et al*. (Scheme 40).[55] Typical Sonogashira conditions were used, followed by an acidic work-up. The mechanism of this compelling reaction is not obvious, but the authors provide a plausible mechanism. Sonogashira product **115** is formed first, which then isomerizes under the basic reaction conditions to the thermodynamically more stable doubly conjugated allene (**116**). Then, an intramolecular [3+2] cycloaddition furnishes a triazoline intermediate (**117**). Nitrogen is eliminated to form a delocalized diradical (**118**) that undergoes a regioselective 1,5-biradical coupling to obtain **119**. Finally, the acidic work-up results in the polycyclic pyrroles (**114**) by hydrolysis and aromatization.



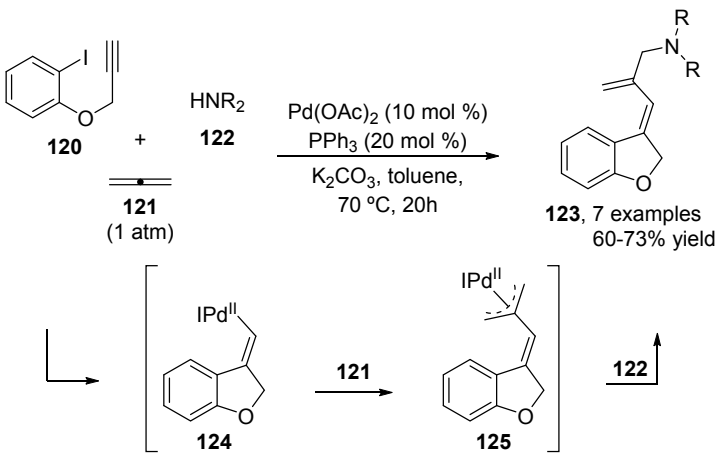
Scheme 40. Sonogashira coupling in a cascade towards polycycles.

1.3 Versatile building blocks in Pd-catalyzed cascades

Many Pd-catalyzed cascade reactions can be classified by the classical coupling reactions (section 1.2). However, other cascades do not involve any of the classical reactivity, but are isolated examples or less known reaction types. Therefore, these cascade reactions are better categorized by the building blocks used. For example, allenes are frequently encountered in cascades, although they do not belong to any of the reactions discussed in section 1.2. This section will deal with such frequently encountered versatile building blocks in Pd-catalyzed cascade reactions.

1.3.1 Allenes

Allenes represent an important class of compounds in Pd-catalyzed cascades, where they are predominantly used for the formation of π-allylpalladium species or carbopalladations. Allenes are more reactive towards insertion into organopalladium species than alkenes, as shown by Negishi *et al*. in their studies on intramolecular cyclocarbopalladation of ω-haloallenes towards five- through twelve-membered ring products.[56] Eight- or nine-membered rings are accessible by allene insertion in reasonable yields, but the corresponding alkene insertion only results in side products.

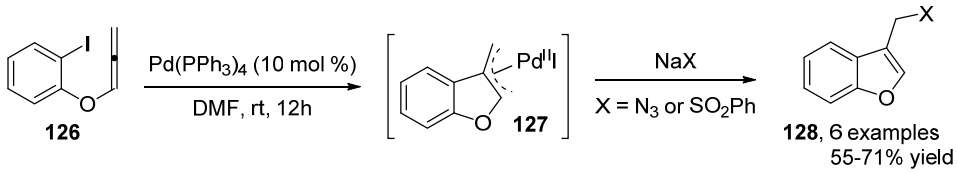


Scheme 41. Allene insertion cascade (selected example).

Allene gas (**121**) can be used in cascades, as shown by the work of Grigg *et al*. (Scheme 41).[57] They combined an intramolecular alkyne insertion of **120** with π-allyl

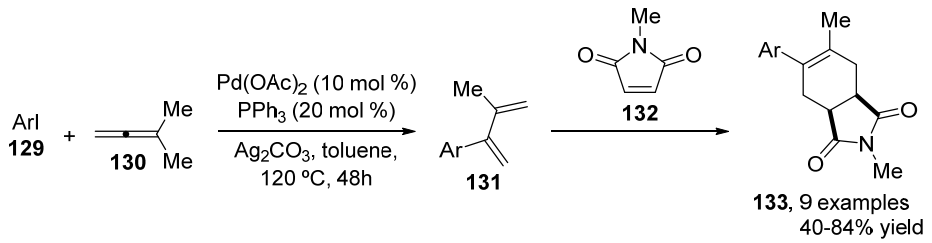
formation to yield intermediate **125**, which is then captured by a secondary amine to furnish five- to eight-membered heterocycles in decent yields. The results demonstrate that intramolecular *exo-dig* cyclization to form five- to seven-membered rings is significantly faster then allene insertion into aryl palladium species, making the two processes suitable for combination. The formation of eight-membered rings, however, was shown to be problematic since the rates of *exo-dig* cyclization and allene insertion are comparable.

The same group later used aryl iodides bearing a tethered allene (**126**) for an intramolecular allene insertion (Scheme 42).[58] This strategy leads to π-allylpalladium species (**127**), which can be captured by nucleophiles (NaX) to produce benzofurans (**128**). A few years later the authors published a more thorough study including an intermolecular version of this reaction.[59]



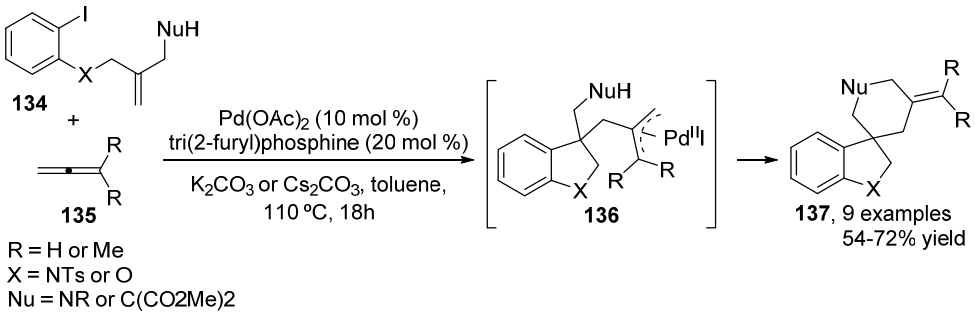
Scheme 42. Intramolecular allene insertion cascade.

An intermolecular allene insertion followed by Diels-Alder reaction was reported by the Grigg group in 1998 (Scheme 43).[60] Aryl iodides (**129**) react with 1,1-dimethylallene (**130**) to form a π-allylpalladium species that undergoes β-hydride elimination and provides diene **131**. *In situ* Diels-Alder reaction with *N*-methylmaleimide (**132**) affords the *cis*-fused products (**133**) in a one-pot procedure. The authors later reported more extensive work on the same reaction, including an increased substrate scope.[61] For example, vinylidenecyclohexane can be used as allene input in this reaction, generating a fused tricyclic product. Furthermore, more detailed studies towards the diastereoselectivity of this reaction using allenes with longer alkyl chains were reported.

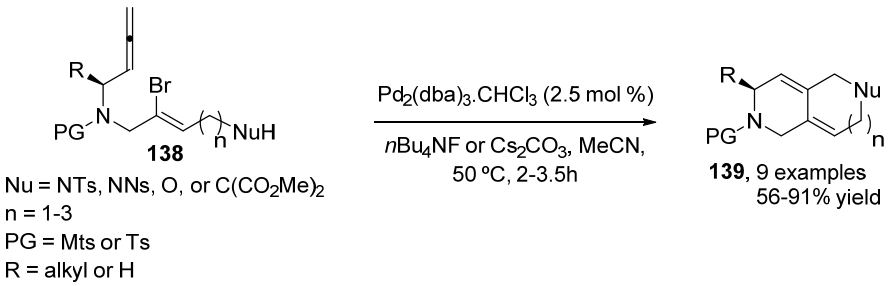


Scheme 43. Intermolecular allene insertion cascade.

Allene chemistry was also used to obtain spirocycles from aryl iodides with a tethered nucleophile (**134**, Scheme 44).[62] Intramolecular alkene insertion is followed by formation of π-allylpalladium species **136**, which subsequently is attacked by the tethered nucleophile to obtain spirocycles **137**. Allene or dimethylallene can be used and the nucleophile can be an amine or a malonate. The allene moiety can also be integrated in the substrate to provide a completely intramolecular process leading to fused tricycles.



Scheme 44. Allene insertion cascade towards spirocycles.

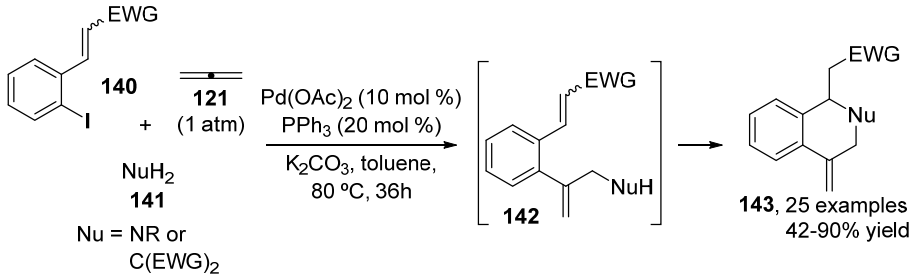


Scheme 45. Cascade cyclization of allenic bromoalkenes.

A similar procedure using allenic bromoalkenes (**138**) leading to fused bicycles (**139**) has been reported by Fujii *et al.* (Scheme 45).[63] Different ring sizes can be obtained, including eight-membered rings. Furthermore, nitrogen, oxygen, and carbon nucleophiles are tolerated, although oxygen nucleophiles require Cs_2CO_3 as a base instead of TBAF. The protecting groups on the secondary amines in the product can be varied (Nu = NTs or NNs), allowing straightforward desymmetrization of otherwise symmetric products (R = H).

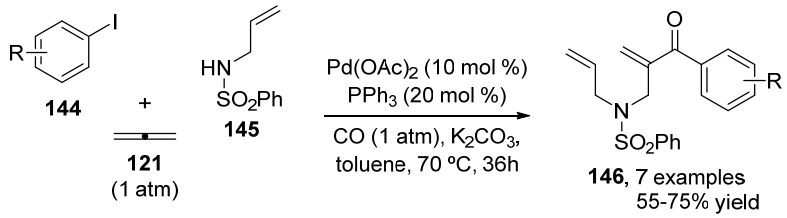
Later, the Grigg group introduced a fully intermolecular version of this type of caacde and combined it with intramolecular Michael reaction (Scheme 46).[64] Aryl iodides, allene and nucleophiles react to form **142**, which then undergoes a Michael

reaction to furnish fused bicycles **143**. A more detailed description of this reaction was later published.[65] Furthermore, similar work excluding the intramolecular Michael reaction was also reported.[66]



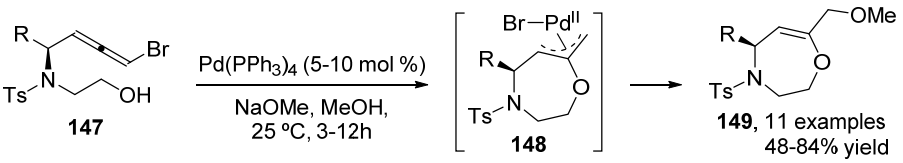
Scheme 46. Allene insertion/Michael addition cascade.

A four-component reaction catalyzed by palladium exploiting allene reactivity was reported by Grigg *et al*. in 2003.[67] Carbonylation of aryl iodides is followed by allenylation and the resulting π-allylpalladium species is intercepted by a nitrogen nucleophile (**145**, Scheme 47). The authors did not mention any direct allenylation of the aryl iodides (**144**), which could be envisioned as a potential side reaction. Several more examples were reported later in a more thorough study.[68]



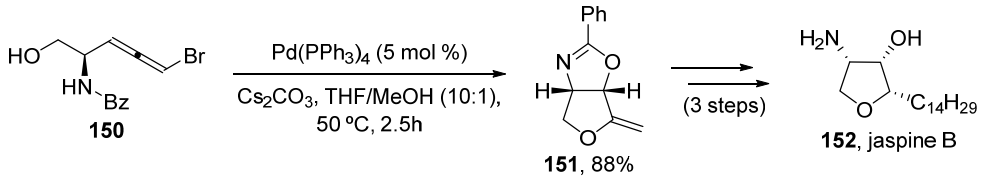
Scheme 47. Four-component reaction using allene.

An interesting Pd-catalyzed cascade leading to medium sized heterocycles (**149**) starting from bromoallenes with a tethered nucleophile (**147**) has been developed by Tanaka *et al*. (Scheme 48).[69] Bromoallenes (**147**) act as allyl dication equivalents and are consequently attacked by nucleophiles twice. Intramolecular attack by the alcohol leads to π-allylpalladium species **148**, which is then intercepted by the solvent to form the product. Although the intramolecular attack always occurs at the central carbon atom of the π-allylpalladium species, two regioisomers can be formed depending on the carbon atom that is attacked by the solvent. Bulky substituents (R) increase the selectivity and usually only traces of the undesired isomer are found.



Scheme 48. Bromoallenes in Pd-catalyzed cascade.

Ohno *et al*. used a similar cascade for an elegant enantioselective synthesis of jaspine B (**152**, Scheme 49).[70] Their approach consists of a fully intramolecular system that furnishes fused bicycle **151** diastereoselectively in 88% yield as a single enantiomer. This product can easily be converted into jaspine B by a three-step sequence. Jaspine B exhibits cytotoxic activity against various tumor cell lines at the nanomolar level and therefore attracts interest from synthetic chemists.[71] Various pachastrissamine derivatives were prepared and reported in separate work.[72] Furthermore, propargylic chlorides could be used for the same transformation.

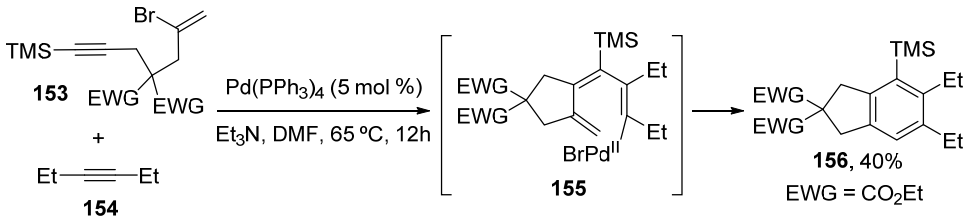


Scheme 49. Bromoallenes in Pd-catalyzed cascade towards jaspine B.

1.3.2 Alkynes

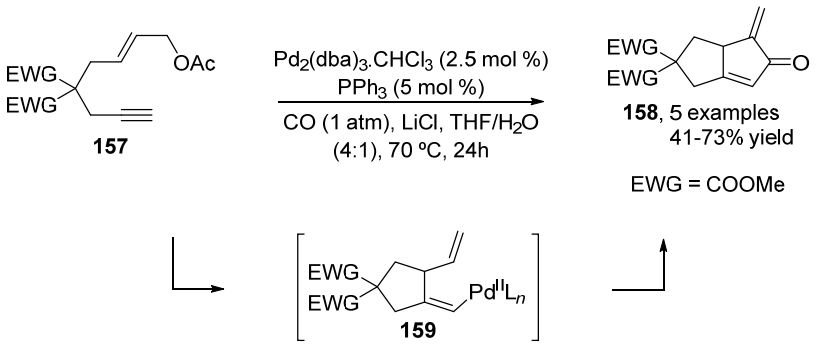
Alkynes, like allenes, represent an important class of versatile reagents for Pd-catalyzed processes. For example, terminal alkynes are used in the Sonogashira reaction (section 1.2.4) and alkyne insertion into aryl-palladium bonds is a commonly encountered phenomenon. This section will deal with Pd-catalyzed cascade cyclizations in which an alkyne is used.

In 1992, Negishi *et al*. used alkynes in a Pd-catalyzed cascade towards benzene derivatives (Scheme 50).[73] The authors reported only one example and are unsure about the mechanism. Most likely, intermediate **155** is formed first by two consecutive carbopalladations. Conversion of **155** to the product may then occur via carbopalladation or an electrocyclic reaction, but the authors were not able to rule out either of the two at the time of writing. Other Pd-catalyzed carbopalladation approaches towards benzene derivatives with varying degrees of intermolecularity were described.



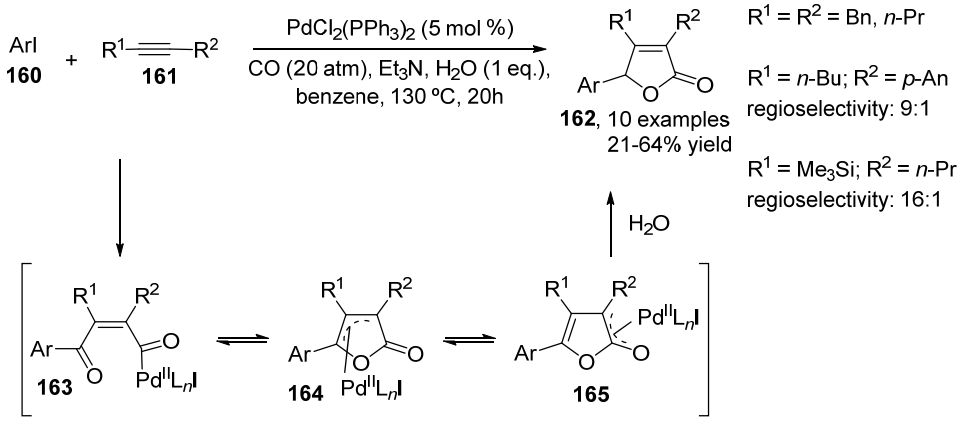
Scheme 50. Pd-catalyzed cascade towards benzenes.

Heathcock *et al*. used allylic acetates (**157**) to generate π-allylpalladium species that subsequently undergo intramolecular alkyne insertion to form **159** (Scheme 51).[74] Then, carbonylation takes place, followed by an intramolecular Heck-type reaction to afford α-methylenecyclopentenones (**158**) in moderate yield. The product is unstable and presumably partly decomposes during purification, thereby lowering the yield.



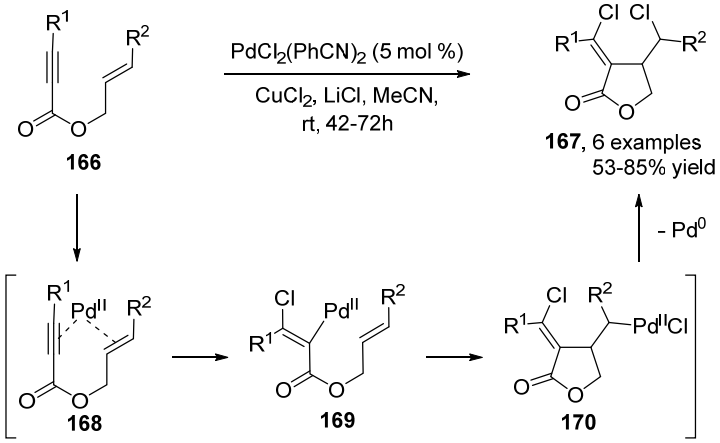
Scheme 51. Intramolecular alkyne/carbon monoxide/alkene insertion cascade.

Negishi *et al*. reported a complex cascade involving alkyne insertion and two carbonylations to furnish *γ*-butyrolactones (**162**, Scheme 52).[75] They assume that oxidative addition of aryl iodides to palladium is followed by a sequence of carbonylation/alkyne insertion/carbonylation to yield palladium species **163**. Intermediate **163** is converted into a cyclic π-allylpalladium species (**164**), which undergoes migration of palladium to give **165.** Hydrolysis then results in formation of the products. Remarkably, the proposed catalytic cycle regenerates Pd^{II}, while Pd^{0} is required for oxidative addition. Since no reducing agent is present in the reaction mixture it is proposed that carbon monoxide acts as the reducing agent. Water is essential for reactivity and is therefore deliberately added. If unsymmetrical alkynes are used a good regioselectivity is generally observed.



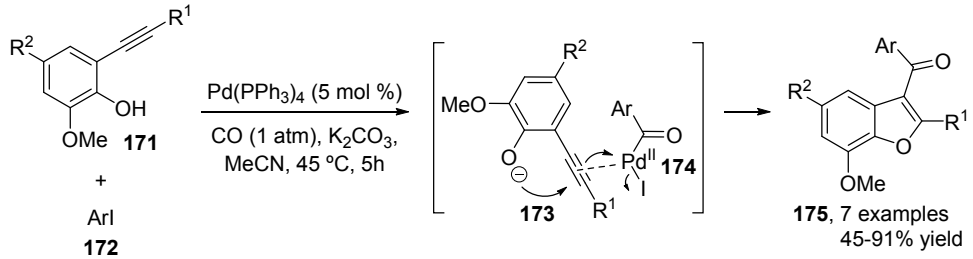
Scheme 52. Pd-catalyzed cascade towards γ-butyrolactones.

Lu *et al*. also developed a cascade reaction towards γ-butyrolactones starting from allylic alkynoates (**166**, Scheme 53).[76] The authors propose a mechanism starting with coordination of Pd^{II} as in metal-enyne complex **168**. Then, stereoselective chloropalladation leads to intermediate **169**, which can undergo intramolecular alkene insertion to form palladium species **170**. Finally, formation of the last carbon-chlorine bond leads to the product and Pd^0, which is oxidized to Pd^{II} by cupric chloride. Terminal alkynes selectively afford *E*-exocyclic alkenes, while internal alkynes furnish *Z*-exocyclic alkenes in good selectivity. Two years later, the same group extended this strategy to produce brominated γ-butyrolactones.[77]



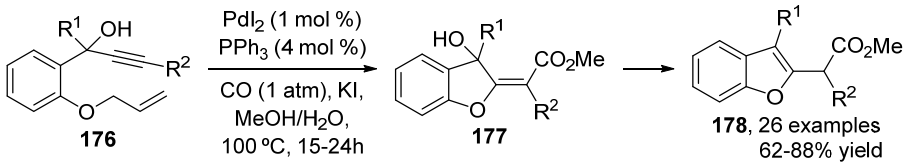
Scheme 53. Cascade towards γ-butyrolactone.

Yang *et al*. discovered the Pd-catalyzed carbonylative annulation of *o*-alkynylphenols (**171**) leading to 2-substituted-3-aroyl-benzo[*b*]furans (**175**, Scheme 54).[78] Oxidative addition followed by carbonylation results in σ-acyl-palladium species **174**. The acylpalladium species then coordinates to the triple bond, rendering it sufficiently electrophilic for attack by the deprotonated phenol. The methoxy group on the 2-alkynyl-6-methoxyphenols (**171**) is essential to provide the product.



Scheme 54. Pd-catalyzed carbonylative annulation.

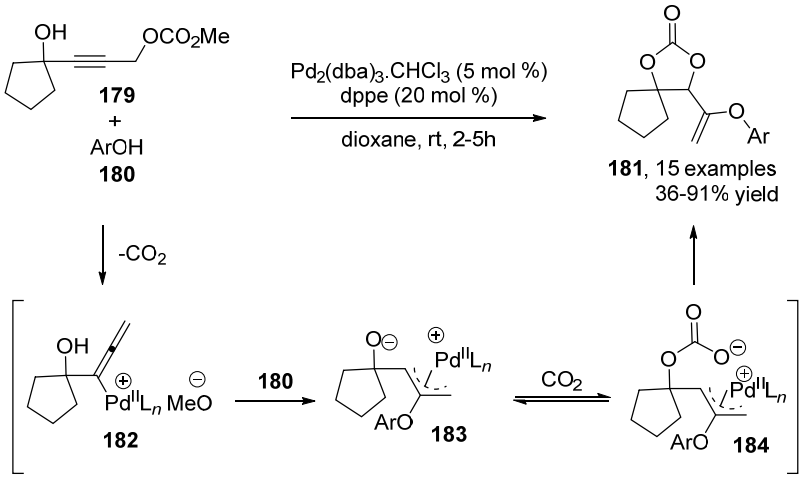
Gabriele *et al*. communicated a novel sequential homobimetallic Pd-catalyzed cascade also yielding benzofurans (Scheme 55).[79] Sequential homobimetallic catalysis involves two different active catalysts of the same transition metal, but with different oxidation states. In the work of Gabriele *et al*. an *in situ* generated Pd^0 catalyst deallylates **176**. Subsequently, Pd^{II} catalyzes a 5-*exo*-*dig* type cyclization by activating the triple bond towards nucleophilic attack of the alcohol function. Carbonylation and capture by methanol results in intermediate **177**, which is reduced by formation of a π-allyl complex and elimination of water. Finally, protonolysis leads to the product. It is also possible to synthesize 2-benzofuran-2-ylacetamides by adding an amine to the reaction mixture.[80]



Scheme 55. Sequential homobimetallic catalysis.

Tsuji *et al.* found that propargylic carbonates form allenylpalladium complexes by decarboxylation under appropriate conditions.[81] Propargylic carbonates are now widely used in palladium catalysis and the resulting allenylpalladium species can be used for a variety of transformations, including cascade cyclization reactions.[82] A

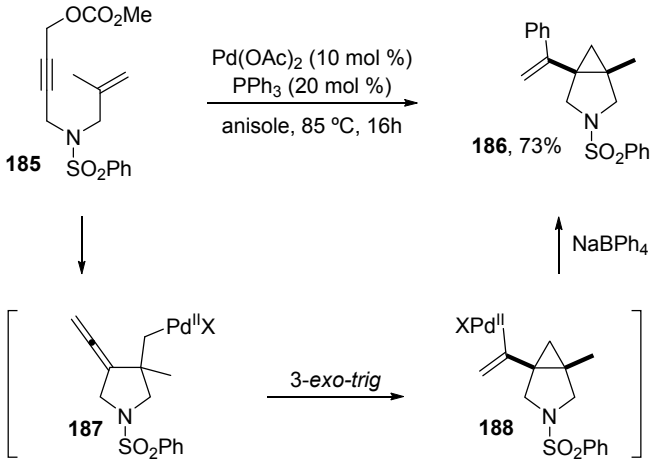
very elegant example has been reported in 2001 by Ihara *et al*., who describe the use of propargylic carbonates (**179**) in a carbon dioxide recycling synthesis of cyclic carbonates (**181**, Scheme 56).[83] A plausible mechanism starts with formation of allenylpalladium methoxide **182**, which is attacked by the phenol (**180**) to form π-allyl species **183**. Carbon dioxide is then recycled by attack of the alcohol and a cyclization completes the catalytic cycle. Proof for the dissociation of carbon dioxide is given. If CO_2 pressure is applied the yields increase dramatically (>95%) for the low yielding substrates. Meanwhile, if argon is bubbled through the reaction mixture to remove CO_2 the yields decrease. An enantioselective variant of this transformation was reported later.[84] The reaction proceeds in a highly enantiospecific manner when propargylic carbonates bearing a chiral centre at the propargylic position are used.[85] Furthermore, the (*E*)- and (*Z*)-selectivity can be controlled by the choice of ligand.



Scheme 56. Recycling of carbon dioxide in a cascade towards cyclic carbonates.

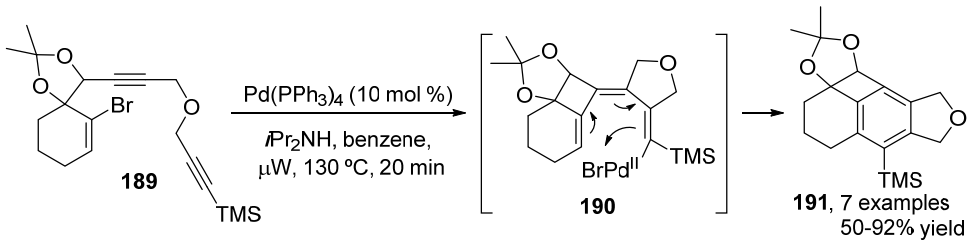
Grigg *et al*. used propargylic carbonates (**185**) in a bicyclization/anion capture cascade reaction (Scheme 57).[86] Treatment of propargylic carbonate (**185**) with Pd^0 generates an allenylpalladium species and is followed by 5-*exo*-*trig* cyclization to furnish intermediate **187**. An unusual 3-*exo*-*trig* cyclization results in vinylpalladium species **188**, which undergoes anion capture to form the bicyclic product **186**. The anion capture can be accomplished with sodium tetraphenylborate, but CO/MeOH can also be used to afford acrylates. Furthermore, organotin reagents can be used as capturing agents, although a different catalytic system is required. The reaction was detailed further by the group of Oppolzer shortly after Grigg's report.[87] De Meijere *et al*. optimized the reaction for a large scale process because the acrylates obtained

using CO/MeOH are of possible interest as monomers for low-shrinkage polymers.[88] A related approach to similar products using a $Pd^{II/IV}$ catalyst was reported in 2009 by Sanford *et al*.[89]



Scheme 57. Biscyclization/anion capture cascade.

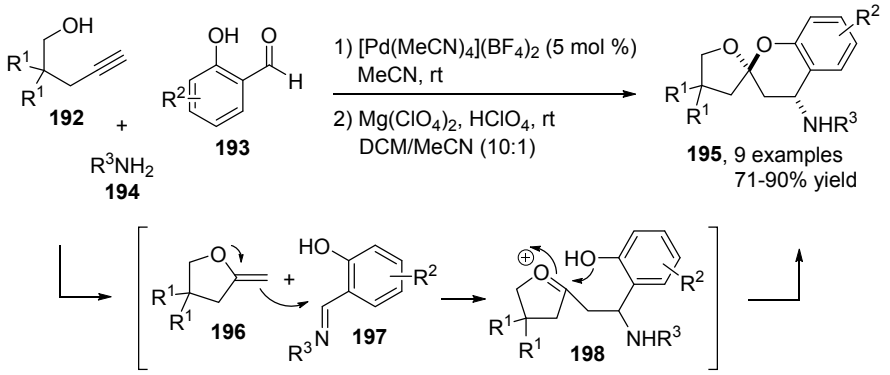
Suffert *et al*. discovered a Pd-catalyzed cascade reaction towards highly strained aromatic polycycles (**191**, Scheme 58).[90] Bromoenediynes (**189**) undergo 4-*exo-dig* cyclocarbopalladation and subsequent 5-*exo-dig* cyclization to furnish intermediate **190**, which possibly undergoes a concerted 6π-electrocyclization. A *syn* dehydropalladation would then yield the observed products. A Heck-type cyclization is also possible, although then an unusual but not unprecedented *anti* dehydropalladation elimination is required. The authors are unsure which of the possible mechanistic pathways is predominant.



Scheme 58. Synthesis of highly strained polycycles.

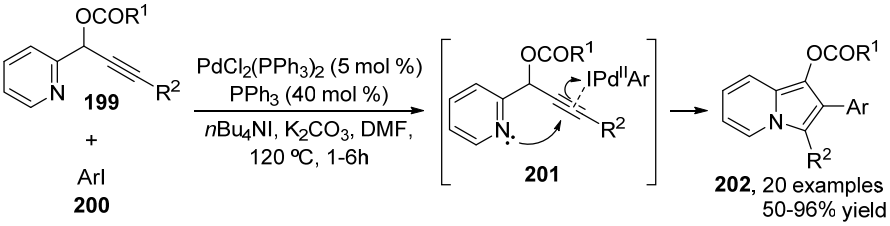
An ingenious Pd-catalyzed multicomponent reaction towards spiroacetals (**195**) was developed by Barluenga *et al*. (Scheme 59).[91] Hydroalkoxylation of

alkynols (**192**) catalyzed by palladium leads to formation of exocyclic enol ethers (**196**). Meanwhile, condensation of the amine (**194**) and aldehyde (**193**) produces imine **197**. A Mannich-type reaction, presumably mediated by Pd^{II}, results in oxonium ion **198** which cyclizes by nucleophilic attack of the phenol to furnish spiroacetals. The product was found as a mixture of diastereoisomers, but can be equilibrated to diastereomerically pure material by treating the crude mixture with $Mg(ClO_4)_2$ and $HClO_4$. Oxygen-substituted chroman spiroacetals are also accessible by employing orthoesters instead of amines (9 examples, 72-96% yield). In this case the products were found as a single diastereoisomer, eliminating the requirement for equilibration.

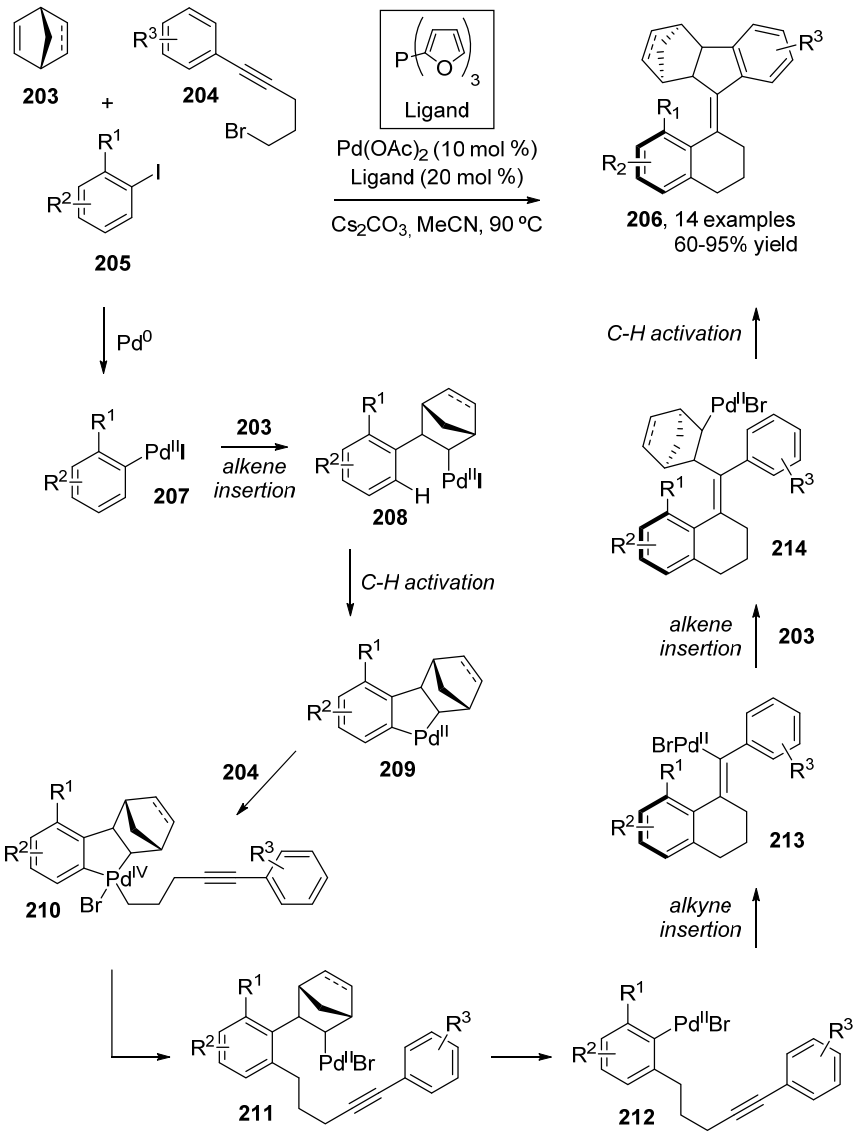


Scheme 59. Pd-catalyzed three-component reaction towards spiroacetals.

Gevorgyan *et al*. reported an arylation/cyclization cascade towards 2-arylindolizines (**202**, Scheme 60).[92] Presumably, the aryl iodide oxidatively adds to palladium first and the resulting acylpalladium species coordinates to the triple bond, which triggers attack by the pyridyl nitrogen (**201**). Deprotonation, tautomerization and subsequent reductive elimination furnishes the product. In 2012, the same group developed a carbonylative version that affords 2-aroylindolizines.[93]



Scheme 60. Pd-catalyzed arylation/cyclization cascade.



Scheme 61. Pd-catalyzed synthesis of helical alkenes.

Lautens and co-workers developed an intriguing Pd-catalyzed multicomponent cascade synthesis of helical alkenes (**206**, Scheme 61).[94] Similar compounds have proven useful as chiroptical molecular switches or light-driven molecular motors.[95] The mechanism of the cascade cyclization to **206** starting from aryl iodides, norborn(adi)ene (**203**), and 5-bromo-1-pentynylbenzenes (**204**) is far from obvious.

The authors propose that arylpalladium species **207** is formed first and then undergoes alkene insertion to give **208**. C-H activation furnishes palladacycle **209** and reductive elimination is not favored at this stage as it would lead to a highly strained benzocyclobutane. Instead, **209** undergoes a second oxidative addition of **204** leading to Pd^{IV} species **210**. Reductive elimination affords Pd^{II} species **211**, which undergoes a retro-carbopalladation to give **212**. Subsequently, intramolecular alkyne insertion is followed by alkene insertion of **203** and C-H activation to furnish the final product.

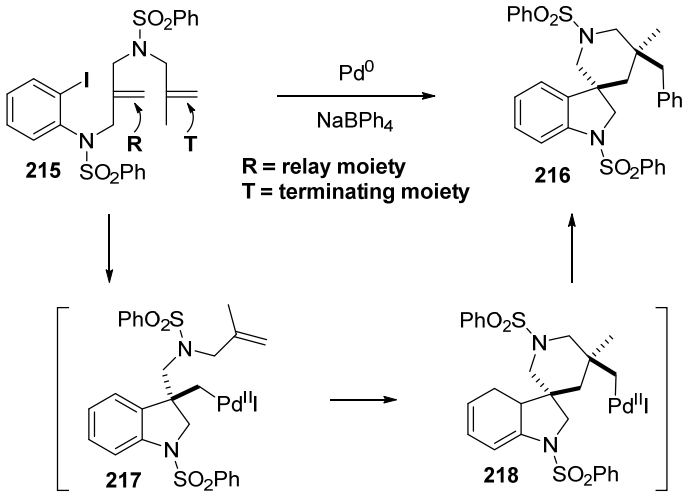
In summary, alkynes are widely used in Pd-catalyzed processes and show three distinct important reactivities. First, simple alkyne insertions are commonly used in Pd-catalyzed cascades. Second, alkynes can be activated towards nucleophilic attack by coordination of Pd^{II}, which removes electron density from the triple bond and renders it sufficiently electrophilic for reaction with nucleophiles. Third, propargylic carbonates form allenylpalladium complexes by decarboxylation when treated with an appropriate palladium catalyst.

1.3.3 'Zipper'-type

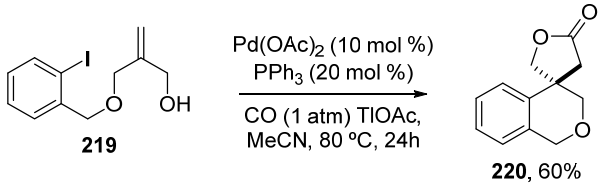
The group of Grigg thoroughly investigated the general concept of an intramolecular Heck-type reaction lacking a suitable β-hydride in the alkylpalladium intermediate, which leads to formation of a relatively stable palladium species.[96] The concept is illustrated by Scheme 62. Oxidative addition to an aryl or vinyl halide (**215**) is followed by 5-*exo*-*dig* carbopalladation of the relay moiety to yield palladium species **217**. No β-hydride is present, so species **217** is sufficiently stable to undergo a second cyclocarbapalladation with the terminating moiety. Intermediate **218** has no β-hydrides and no intramolecular options, therefore anion transfer and reductive elimination happen next to finish the catalytic cycle. The phrase "zipper reaction" was first coined by Negishi[97] and refers to a "zipper-like" series of cyclizations and a terminating event. Although the above conditions were not explicitly stated by Negishi, they have proven hard requirements for Pd-catalyzed zipper sequences to complete.

In the example above two cyclizations were accomplished, but the relay phase can, in principle, incorporate several successive cyclizations or just one. The starting moiety can be an allylic[98], aryl[99], benzylic[98] or vinyl[99] halide, but propargylic carbonates can also be used to induce allenyl palladium species as starting point (Scheme 57).[86] The relay moiety is not limited to alkenes[100], but alkynes[100], allenes and 1,3-dienes can be used as well. Moreover, the terminating species can be an alkene, an alkyne[99], a allene,[99] or a 1,3-diene. In addition, the anion transfer reagent

can be varied extensively: hydride sources[96], organotin reagents[101], organozinc and organoboron species[98-99], carbon-, nitrogen- or oxygen-centred nucleophiles[102], CO/MeOH[103] and cyanide[104] can all be used. A C-H activation of tethered (hetero)aromatics is also feasible as terminating step in these queuing processes, which leads to the formation of fused tetracycles.[105] The use of carbon monoxide and intramolecular nucleophiles as anion transfer reagents can be used for the synthesis of lactones or lactams. (Scheme 63).[106] A similar procedure using alkynes instead of alkenes as relaying moiety was reported by the group of Negishi.[107]



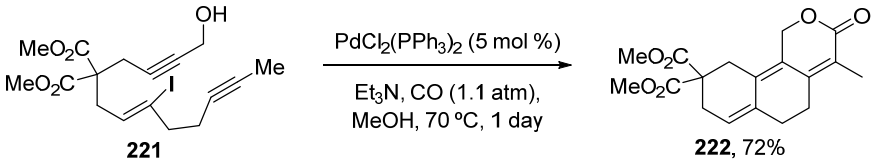
Scheme 62. Illustration of zipper-type cyclization/anion capture process.



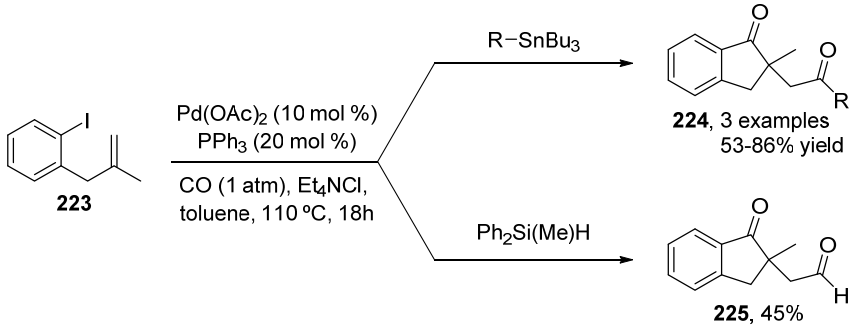
Scheme 63. Pd-catalyzed synthesis of lactones.

Negishi *et al*. also studied polycyclizations with carbonylation as terminating step, either by external nucleophiles (*e.g.* MeOH) or intramolecular alcohols.[108] They describe the relative rates of cyclocarbopalladation and carbonylation in detail and show that selective polycyclizations can be realized when internal alkynes are placed strategically. Important factors are the ring size produced by carbocyclopalladation and the pressure of carbon monoxide that is applied. An illustrative example is

depicted in Scheme 64. Since 6-*exo-dig* cyclization is faster than carbonylation followed by 7-*exo-dig* cyclization, the desired tricycle **222**, without premature incorporation of CO, can be obtained in 72% yield.



Scheme 64. Pd-catalyzed polycyclization.

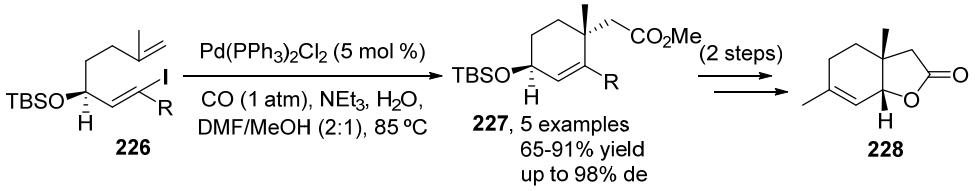


Scheme 65. Double CO insertion cascades.

A novel three-component reaction was realized when CO is combined with an organometallic reagent for anion transfer.[109] Moreover, it is even possible to extend this strategy to a formal four-component reaction where carbonyl insertion precedes the insertion step (**224**, Scheme 65).[110] This can only be realized when carbonylation is faster than cyclization, which is generally not the case. However, when direct cyclization leads to a four membered ring, a sequence of carbonylation/5-*exo-trig* cyclization is favored. Aldehydes (**225**) are obtained instead of ketones (**224**) under identical catalytic conditions by using $Ph_2Si(Me)H$ as a hydride source.[111] Moreover, it was found that vinyl organostannanes can be produced *in situ* by hydrostannylation of the appropriate alkynes and subsequently act as terminating anions after CO insertion to obtain enones.[112] The *in situ* prepared vinyl stannanes can also be used without carbon monoxide present in a 'standard' zipper-type cascade.[113]

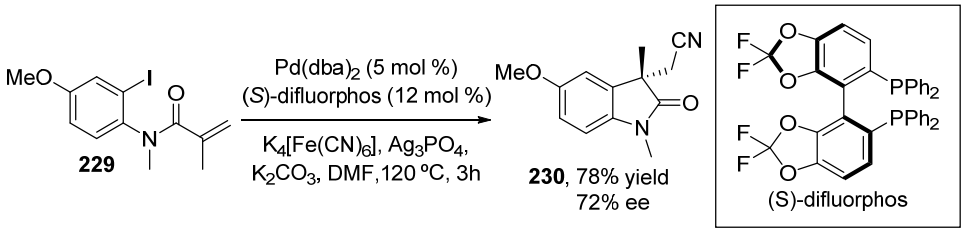
Negishi *et al*. reported a diastereoselective zipper-type process starting from iododienes (**226**) using CO/MeOH as anion transfer reagent (Scheme 66).[114] The products (**227**) are isolated in high yield with excellent diastereoselectivity. The bulky TBS protecting group was essential for efficient chiral induction and a less bulky MOM

group resulted in a 1:1 diastereomeric mixture. The products are highly functionalized and can be used for the enantioselective synthesis of cyclic natural compounds, which is illustrated by the conversion of **227** to Colvin-Raphael's lactone (**228**) in two known steps. Colvin-Raphael's lactone has served as an intermediate in the synthesis of the natural products trichodermin[115] and trichodiene[116].

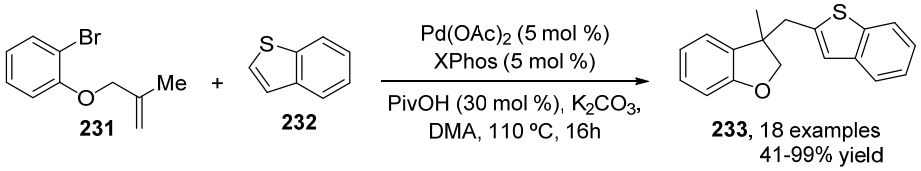


Scheme 66. Diastereoselective zipper process.

Zhu *et al*. studied the use of potassium ferrocyanide as a cyanide source for a Heck reaction/cyanation cascade of aryl iodides **229** (Scheme 67).[117] They also studied an asymmetric variant of this zipper-type process. A variety of conditions and chiral ligands were screened, eventually leading to an optimized enantiomeric excess of 72%. Although the enantioselectivity is modest, this result is encouraging and demonstrates that an enantioselective cascade is viable.



Scheme 67. Enantioselective zipper-type process.



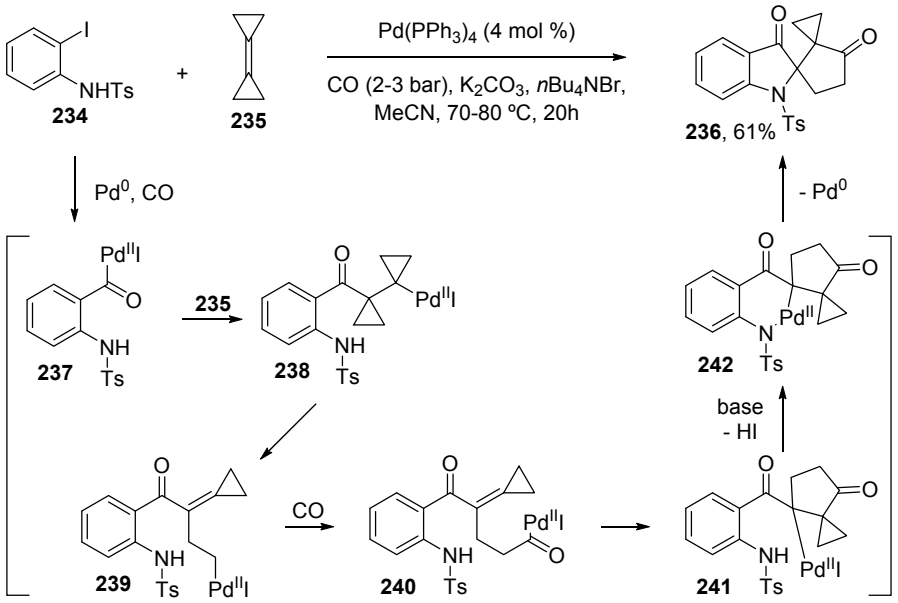
Scheme 68. Zipper-type cascade with C-H activation.

In 2009 the group of Fagnou reported a zipper-type cascade with a direct arylation of the alkylpalladium intermediate by C-H activation (Scheme 68).[118] Sulfur-containing heterocycles (**232**) were required, but the substrate scope is

impressive. Various substituents on the heterocycle are allowed, including aldehydes, esters and chlorides. Pivalic acid has a significant beneficial effect on the yield and is added in substochiometric amounts.

1.3.4 Bicyclopropylidene

Bicyclopropylidene (**235**) has emerged as a highly versatile building block in Pd-catalyzed queuing cascades. The double bond in bicyclepropylidene is electron-rich due to the electron-donating character of the cyclopropyl groups and therefore highly reactive. Although bicyclopropylidene is not frequently encountered in the literature, the interesting chemistry it displays is noteworthy.

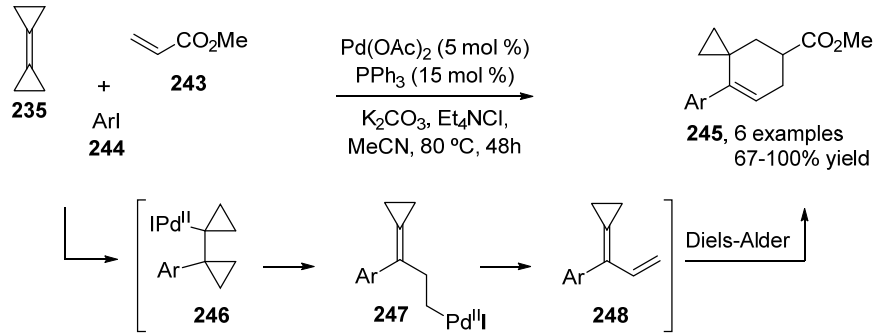


Scheme 69. Bicyclopropylidene in a Pd-catalyzed cascade.

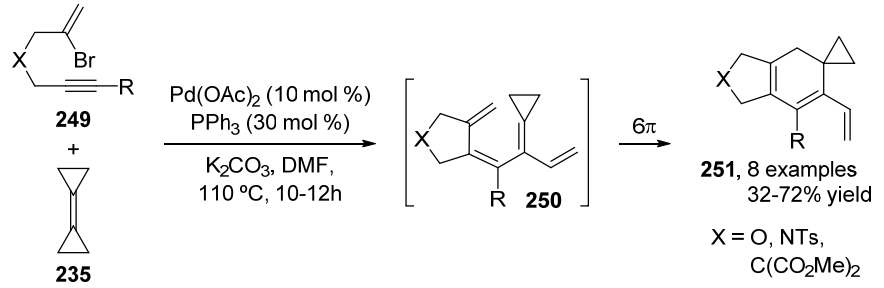
De Meijere and Grigg reported an intriguing cascade using *N*-tosyl-*o*-iodoaniline (**234**), carbon monoxide and bicyclopropylidene (Scheme 69).[119] The yield is reasonable and only one example was shown to work, but the increase in molecular complexity is astonishing. The authors propose a mechanism starting with oxidative addition of the aryl iodide and subsequent carbonyl insertion to form **237**. Insertion of bicyclopropylidene then results in formation of intermediate **238** and is followed by cyclopropylcarbinyl-homoallyl rearrangement to give **239**. Carbon

monoxide insertion and 5-*exo*-*trig* cyclization results in **241**, which cyclizes by base-mediated nucleophilic attack of the amine.

A three-component reaction involving bicyclopropylidene was reported by the de Meijere group in 2002 (Scheme 70).[120] Following the general reactivity of bicyclopropylidene intermediate **247** is obtained. In this case, however, no intramolecular options exist and β-hydride elimination is predominant. The dienophile present in solution reacts with the generated diene in a Diels-Alder reaction to furnish spirocycle **245** in good yields. A functional group can be present on the cyclopropane ring, furnishing cyclopropane-substituted products as a mixture of two isomers.[121]



Scheme 70. Bicyclopropylidene in a Pd-catalyzed three-component reaction.

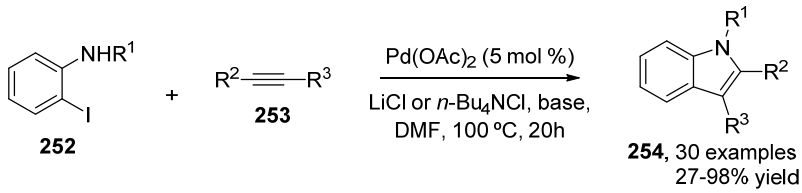


Scheme 71. Zipper-type process using bicyclopropylidene.

Bicyclopropylidene was used in a zipper-type process by de Meijere *et al*. in 2005 (Scheme 71).[122] A sequence of oxidative addition, intramolecular alkyne insertion and bicyclopropylidene insertion results in intermediate **250** after the previously mentioned rearrangement. At a reaction temperature of 80 °C these reasonably stable tetraenes can be isolated and stored in solution for days at -20 °C, but at 110 °C a 6π-electrocyclization occurs to furnish tricyclic compounds (**251**).

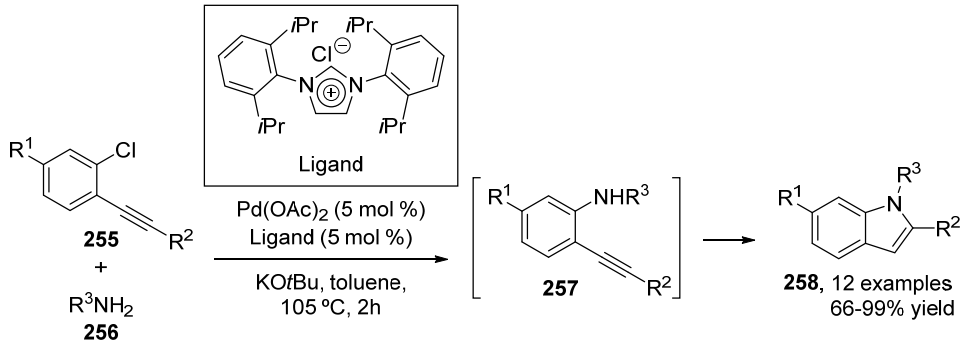
1.4. Synthesis of indoles by Pd-catalyzed cascades

The indole scaffold is a privileged core structure often found in pharmaceuticals and natural products. Accordingly, indoles attract considerable attention of synthetic chemists and efficient processes towards indoles have been developed.[123] The rise of palladium catalysis has led to a tremendous increase in synthetic possibilities, which have been exploited in various Pd-catalyzed cascade cyclizations towards indoles.



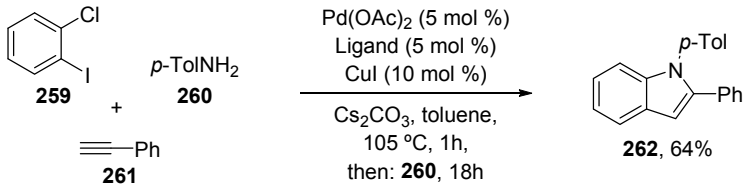
Scheme 72. Indole synthesis by Larock *et al.*

Larock communicated his pioneering work in 1991,[124] which was explored and described in more detail in 1998.[125] Coupling of 2-iodoaniline derivatives (**252**) with various internal alkynes (**253**) leads to 2,3-disubstituted indoles (**254**) in good to excellent yield (Scheme 72). A considerable number of examples is provided, demonstrating the high substrate scope, and much effort was invested in the optimization of the reaction. Either LiCl or nBu$_4$NCl is added, although later studies showed LiCl to be superior. Furthermore, several bases were screened and the optimal base is substrate dependant. Mechanistically, the reaction starts with oxidative addition of the aryl iodide. Alkyne insertion and intramolecular amination results in ring closure. The regioselectivity depends on the alkyne employed and is generally high, although it can be problematic in some cases.



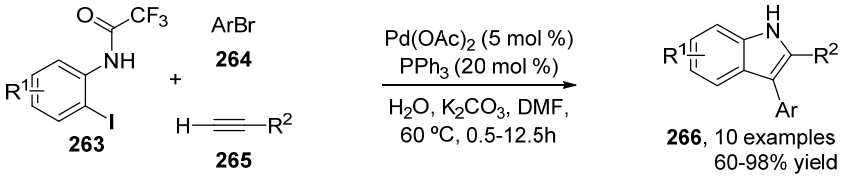
Scheme 73. Indole synthesis by Ackermann.

Ackermann reported a different approach towards indoles avoiding regioselectivity issues, but eliminating the possibility of C3-substitution (Scheme 73).[126] Potassium *tert*-butoxide is used as a base, but the milder base potassium carbonate in combination with copper iodide is also viable. The reaction is assumed to start with amination of the aryl chloride (**255**) followed by Pd-catalyzed cyclization. Interestingly, the amination/cyclization sequence can also be combined with the Sonogashira coupling used to obtain the *o*-alkynyl-chloroarenes (**255**). This is demonstrated by the one-pot procedure starting from *o*-chloroiodobenzene (**259**) towards indole **262** in 64% yield, although no further examples were provided (Scheme 74).



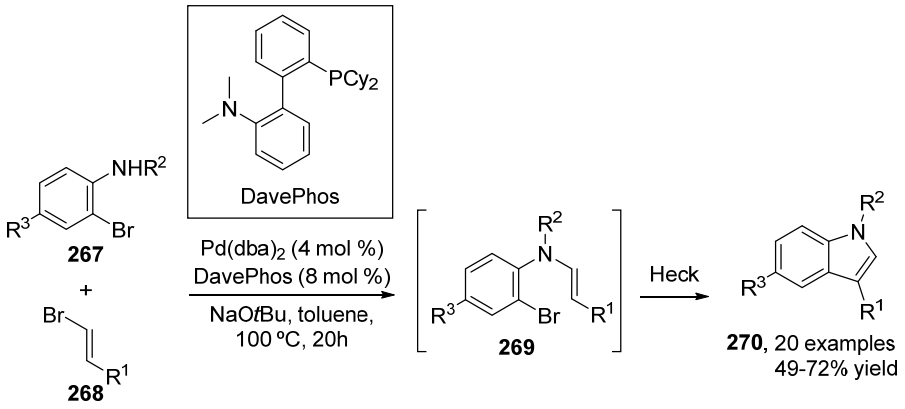
Scheme 74. Three-component indole synthesis.

Another approach involving the Sonogashira coupling was reported by Lu *et al*. in 2006 (Scheme 75).[127] In this case, however, the C3-position is also substituted by combining the Sonogashira coupling with cyclization and arylation. *In situ* deprotection of the trifluoroacetyl group is realized by deliberately adding 1-6 equivalents of H_2O. All starting materials can be combined simultaneously and no Sonogashira coupling between the aryl bromide and the acetylene is observed.



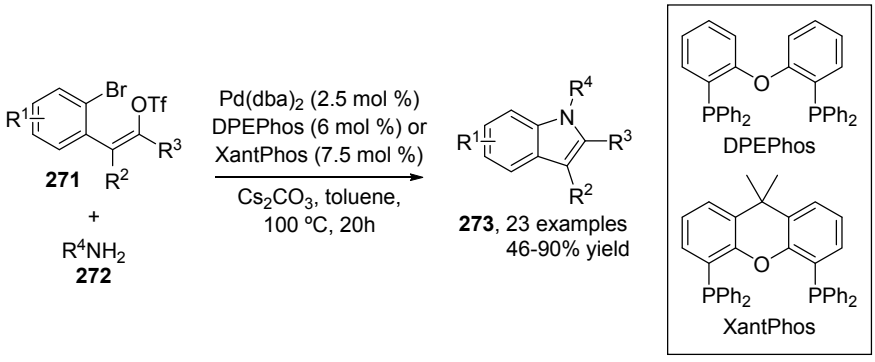
Scheme 75. Sonogashira coupling/amination cascade.

Barluenga *et al*. used an amination/Heck reaction cascade between alkenyl bromides (**268**) and *o*-bromoanilines (**267**) (Scheme 76).[128] Selective amination of alkenyl bromides leads to **269**, which then cyclizes by an intramolecular Heck reaction to furnish *N*-substituted indoles in good yields. The amination rates of aryl bromides and alkenyl bromides were compared in competition experiments to prove this order of events.



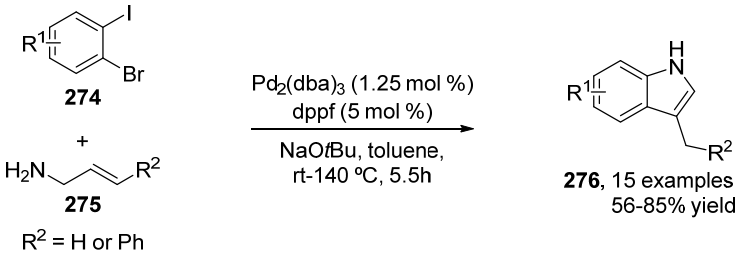
Scheme 76. Indole synthesis by amination/Heck cyclization cascade.

Willis *et al*. developed a Pd-catalyzed synthesis of *N*-substituted indoles (**273**) in which the N-fragment is introduced last (Scheme 77).[129] The carbon framework (**271**) is combined with primary amines to furnish indoles by a cascade of alkenyl C-N and aryl C-N formation. Advantageous to this approach is the ability to systematically vary the *N*-substituent without relying on functionalization of the relatively non-nucleophilic N-H indole group. The ligand choice depends on the substrate; DPEPhos is used for aryl-, alkyl-, or benzylamines while XantPhos is superior for electron-deficient nucleophiles, such as carbamates, sulfonamides, and amides. Chloroindoles with the chloro substituent on the 4-, 5-, 6- or 7-positions of the indole were obtained in later work.[130] Furthermore, the same group later developed a similar procedure towards azaindoles.[131]



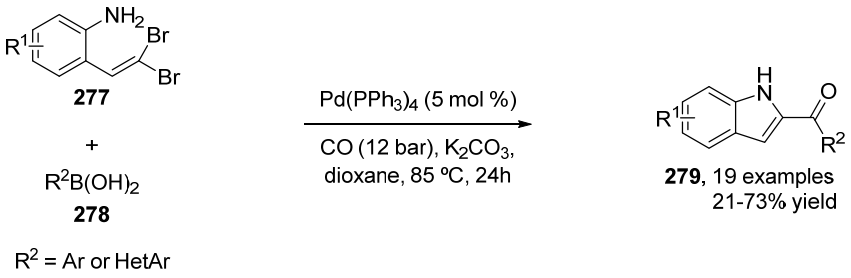
Scheme 77. Indole synthesis by aryl and alkenyl C-N bond formation.

A novel Pd-catalyzed indole synthesis using an aryl amination/Heck cyclization cascade was developed by Jørgensen and coworkers (Scheme 78).[132] *o*-Iodobromobenzenes (**274**) selectively undergo a Pd-catalyzed amination (with allylic amines **275**) on the position of the iodide, which ensures regioselectivity in the products. Subsequently, a 5-*exo*-*trig* cyclization affords the C3-substituted indoles.



Scheme 78. Indole synthesis by aryl amination/Heck cyclization cascade.

Pontikis *et al*. used a C-N coupling/carbonylation/Suzuki coupling cascade to produce 2-(hetero)aroylindoles (**279**) from 2-*gem*-dibromovinylanilines (**277**) in the presence of carbon monoxide and (hetero)arylboronic acids (Scheme 79).[133] Carbon monoxide only inserts once and does not interfere with the intramolecular Buchwald-Hartwig amination.



Scheme 79. C-N coupling/carbonylation/Suzuki coupling cascade.

1.5. Conclusion

Palladium catalysts offer a wealth of opportunities for organic synthesis as illustrated by the various important cross-coupling reactions described in this Chapter. The mechanisms of many of these reactions are well studied and the reactivity of palladium is well understood. Synthetic chemists are therefore able to predict many aspects of palladium catalysis, thereby making the union of several transformations in a one-pot or cascade fashion possible. Many highly efficient one-pot cascade reactions are known and can afford products with a tremendous increase in molecular complexity. Cheap and readily available starting materials can be converted to valuable pharmaceutical intermediates or fine chemicals in a single step using a catalytic amount of palladium. The number of Pd-catalyzed cascade cyclizations in the literature is constantly growing and the majority of the work presented in this Chapter is from the 21st century. New ligands and reactions are still being developed, which in turn opens up new possibilities for cascade reactions.

The overview of Pd-catalyzed cascade reactions in this Chapter is far from complete and is merely a collection of illustrative and interesting examples. This Chapter mainly serves to introduce the plethora of possibilities palladium catalysis offers and to get acquainted with the basic knowledge of this important field. Many examples are included were carbon monoxide serves as a C_1 building block to introduce carbonyl functionality. Isocyanides, which are isoelectronic with carbon monoxide, show similar reactivity but are much less explored. The next Chapter will introduce the use of isocyanides as a C_1 building block in palladium catalysis and will set the stage for the rest of this thesis.

1.6 References

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Chapter 2

Introduction:

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

***Abstract**: 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 Chapter summarizes all the achievements in this emerging field.*

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2.1 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 Heck, Negishi and Suzuki were awarded the Nobel Prize in Chemistry 2010 for their ground-breaking 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 Pd-catalyzed processes and has been used for the construction of important carbonyl functionalities (Figure 1a).[3] CO is often used in Pd-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 (see Chapter 1).[4]

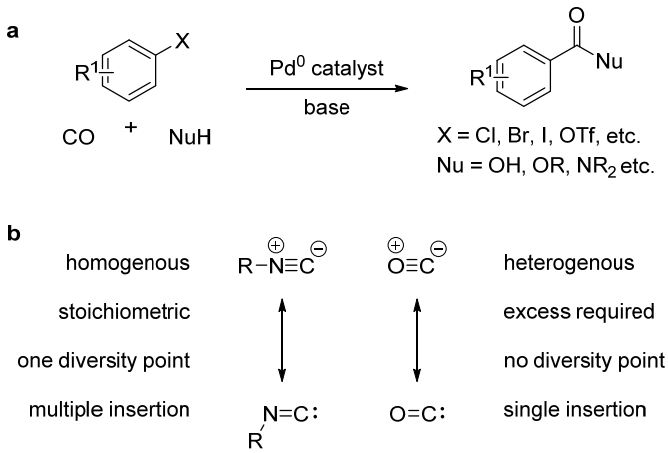


Figure 1. **a.** Typical CO insertion reactions. **b.** isoelectronic isocyanides.

Isocyanides are highly versatile reagents that 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 1b), 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) Pd-catalyzed reactions similar to carbonylative cross-couplings are scarce. This is surprising considering the significant advantages of isocyanides. Isocyanides are easily handled liquids or solids and can therefore be used in

stoichiometric quantities, while 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 versatile. Consequently, Pd-catalyzed reactions utilizing isocyanide insertion therefore offer tremendous opportunities for the synthesis of fine chemicals containing nitrogen functionality. It is therefore not surprising that this type of chemistry has seen a surge of interest in the last years (Figure 2).

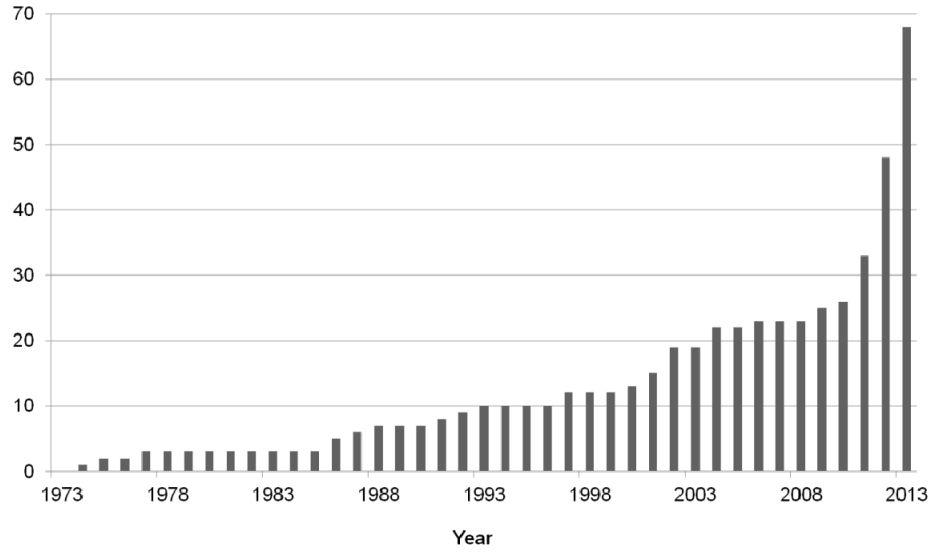


Figure 2. Cumulative number of publications on Pd-catalyzed reactions involving isocyanide insertion.

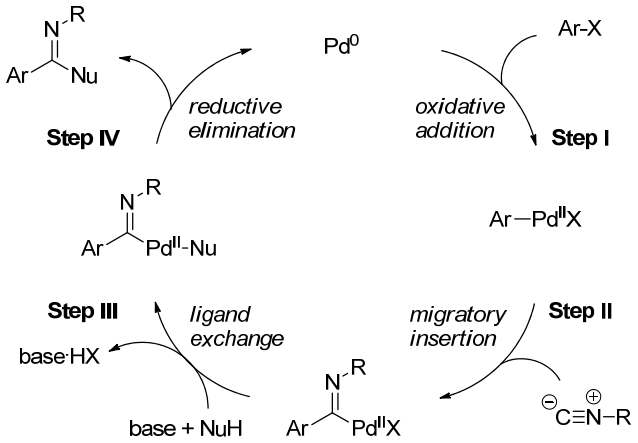
A possible explanation for the scarcity of imidoylative Pd-catalyzed processes is the tendency of isocyanides to undergo multiple consecutive insertions. The insertion of two or three molecules of isocyanide is commonly described and depends on a variety of factors, including ligand, solvent and type of isocyanide used.[7] Triple isocyanide insertion leads to a stable palladium species by coordination of the nitrogen 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 in Pd-aryl, Pd-alkyl and Pd-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]

The purpose of this Chapter is to provide an overview of *all* the Pd-catalyzed imidoylative cross-coupling reactions known at the time of writing in order to place this thesis in context.[12] The current major limitation of this type of transformation is the often limited variability of the isocyanide input. Therefore, the scope with regard to the isocyanide is discussed in all cases and creative solutions are highlighted throughout this Chapter. Section 2.2 will deal with redox neutral reaction, *i.e.* those based on typical Pd^0/Pd^{II} chemistry, while section 2.3 describes the advances of oxidative processes. The sections are mostly ordered chronologically and therefore give an historic overview of the development of this field.

2.2 Pd-Catalyzed Redox Neutral Isocyanide Insertion Reactions

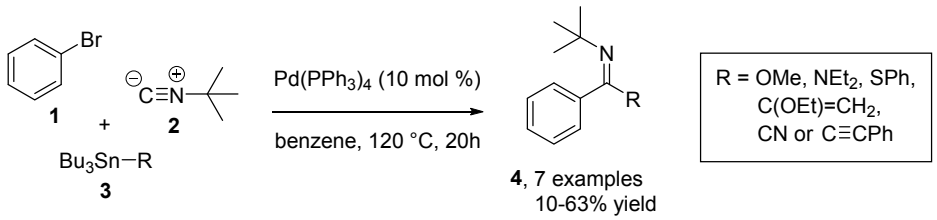
2.2.1 Pd-catalyzed synthesis of amidines and (thio)imidates

The Pd-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 cycle for these reactions is depicted in Scheme 1 and is similar to typical carbonylative catalysis. The catalytic cycle starts with oxidative addition of an aryl (pseudo)halide to the Pd^0 catalyst (Step I), after which the isocyanide inserts in the aryl-Pd bond (Step II). The halide ligand present on palladium (from the aryl halide) is displaced by a nucleophile (most commonly an amine or alcohol) in Step III. In the last step reductive elimination occurs to yield the desired product and to regenerate the Pd^0 catalyst.

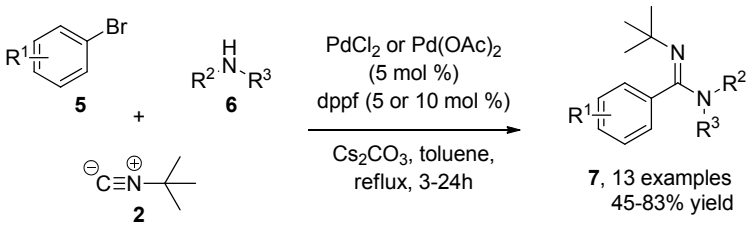


Scheme 1. Catalytic cycle of amidine or (thio)imidate synthesis. Ligands omitted for clarity.

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).[13] Whitby *et al*. further developed this system 14 years later and reported a tin-free version for the amidination of bromobenzenes (**5**, Scheme 3).[14] Simple amines (**6**) can be employed as coupling partners instead of organotin reagents, making the reaction more versatile and more benign. Unfortunately, only *tert*-butyl isocyanide was tolerated well in this system. To overcome this limitation, the authors developed a one-pot dealkylation strategy that removes the *tert*-butyl group under acidic conditions.

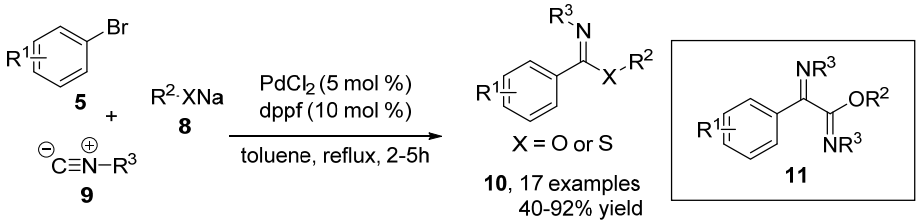


Scheme 2. First example of amidine, (thio)imidate and imine formation.



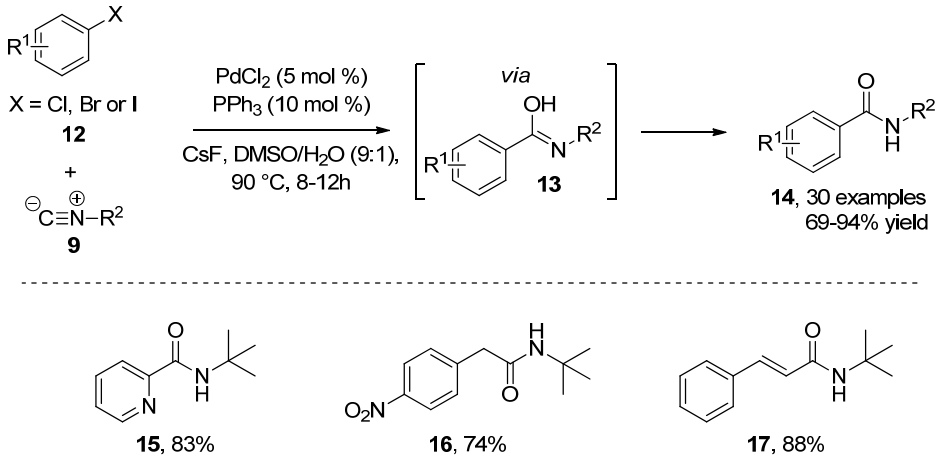
Scheme 3. Amidine synthesis.

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).[15] Surprisingly, other isocyanides could be used in this case although occasionally 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.[16] The synthesis of double insertion product **11** is restricted to primary or secondary isocyanides. These results highlight one of the major challenges in using different isocyanides and provides an explanation why *tert*-butyl isocyanide commonly is the best substrate. Preferred multiple consecutive insertions or polymerization of less bulky isocyanides can interfere with the desired pathway and prevent selectivity.

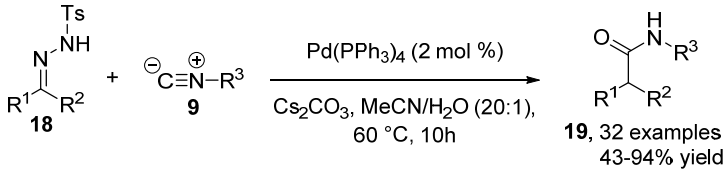


Scheme 4. (Thio)imidate synthesis.

The authors later showed that alkenyl bromides are viable inputs for these reactions to furnish α,β-unsaturated amidines and imidates.[17] In addition, cyclic amidines and imidates are accessible *via* this strategy.[18] In all cases amidine formation was limited to *tert*-butyl isocyanide, while imidate formation allowed the use of primary, secondary and tertiary aliphatic isocyanides.



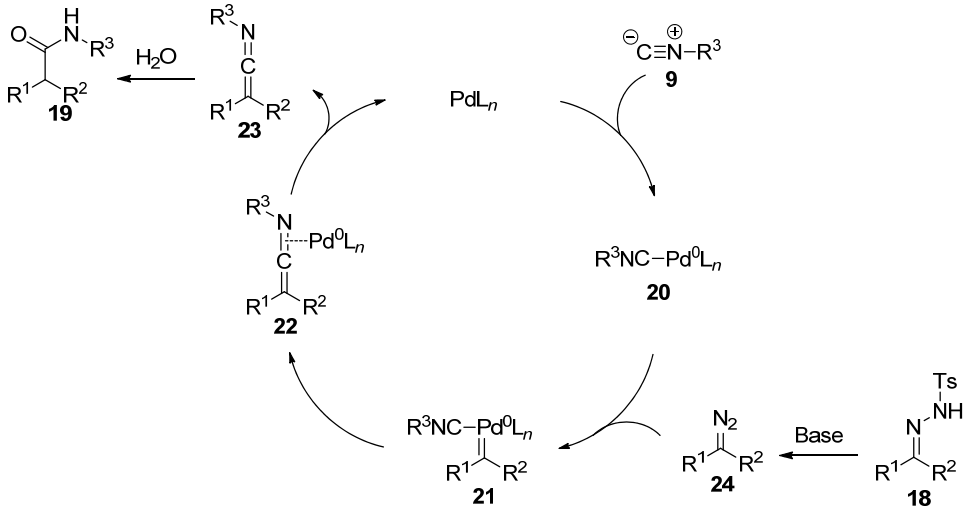
Scheme 5. Amide synthesis.



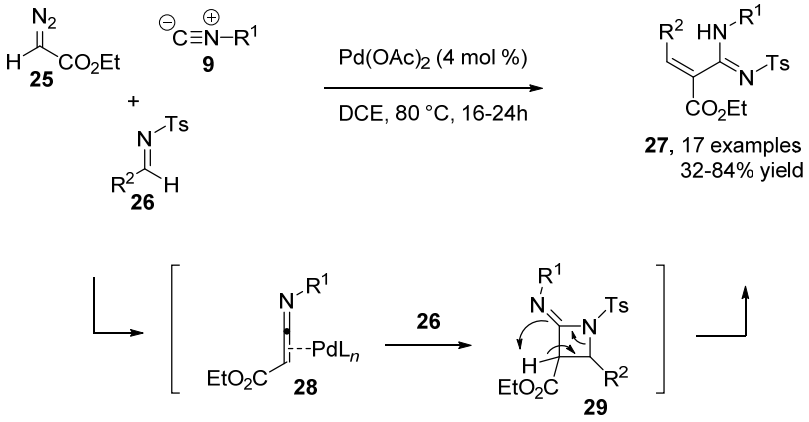
Scheme 6. Amidation of *N*-tosylhydrazones with isocyanides. ***Scheme 5.*** Amide synthesis.

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).[19] The reaction is closely related to the well-known approach to amides from carbon monoxide 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).[20] *N*-tosylhydrazones (**18**) are converted into diazo compounds (**24**) under basic conditions, which react with palladium to form a carbene complex (**21**, Scheme 7). This carbene complex can react with coordinated isocyanide to form a ketenimine product, which is hydrolyzed under the reaction conditions to ultimately

form amides. Several primary, secondary, and tertiary aliphatic isocyanides are tolerated in this reaction. In later work Zeng and Cai *et al*. showed that the ketenimine intermediates (**28**) can also be trapped with *N*-tosylimines (**26**) *via* a [2+2] cycloaddition to furnish acrylamidines (**27**, Scheme 8).[21]



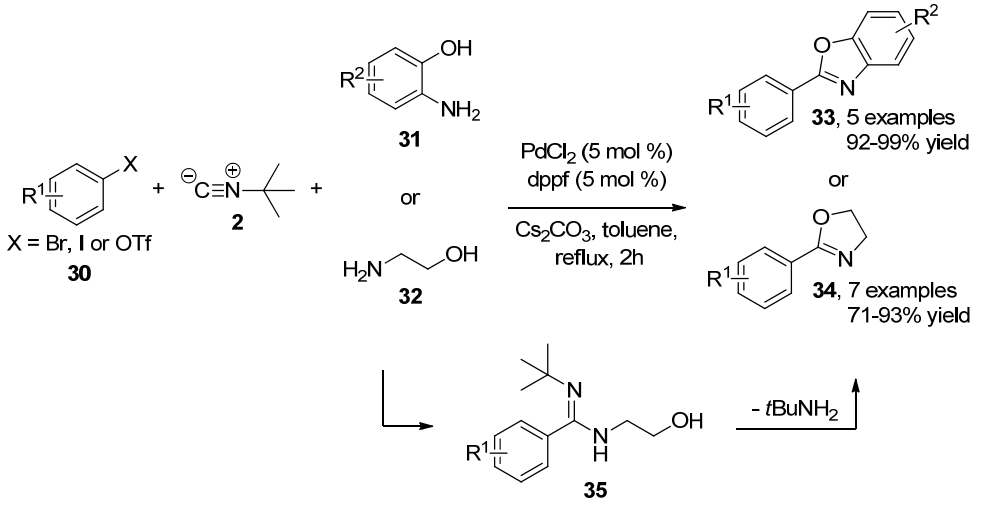
Scheme 7. Proposed mechanism.



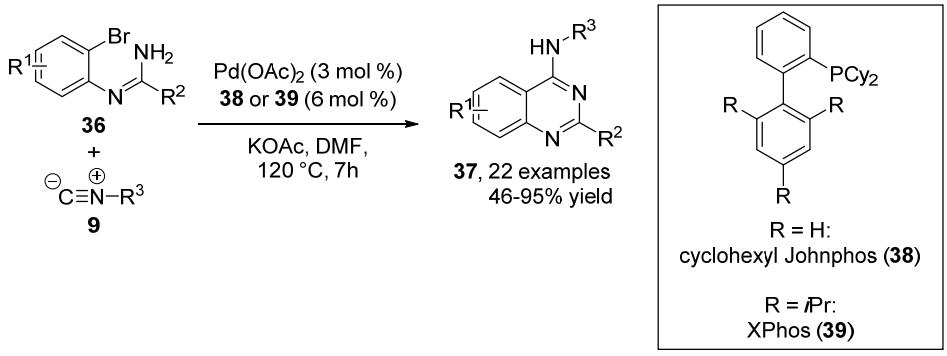
Scheme 8. Cycloaddition of ketenimines with *N*-tosylimines.

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, eliminating *tert*-butylamine. The

strategy was successfully applied in the synthesis of benzoxazoles (**33**) and oxazolines (**34**) by using 2-aminophenols (**31**) or ethanolamine (**32**) respectively as the nucleophile (Scheme 9).[22] The group of Shipman later showed that diamines can also be used as bisnucleophiles to obtain 2-aryl-2-imidazolines and related heterocyclic products in a similar manner.[23]



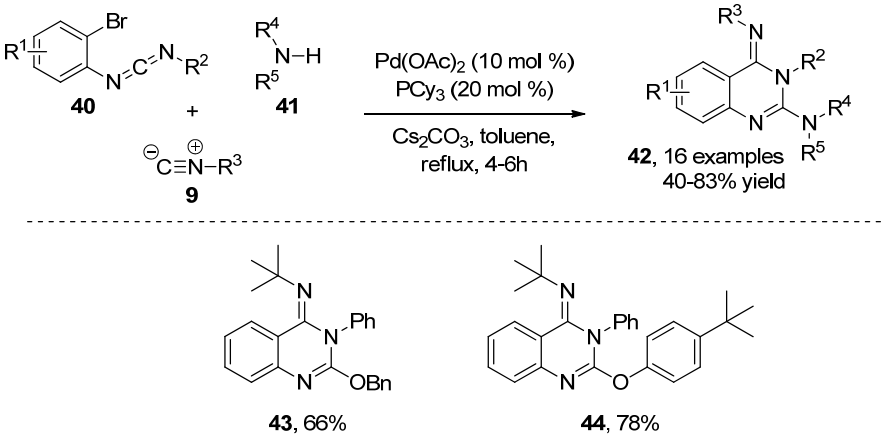
Scheme 9. Synthesis of oxazolines and benzoxazoles.



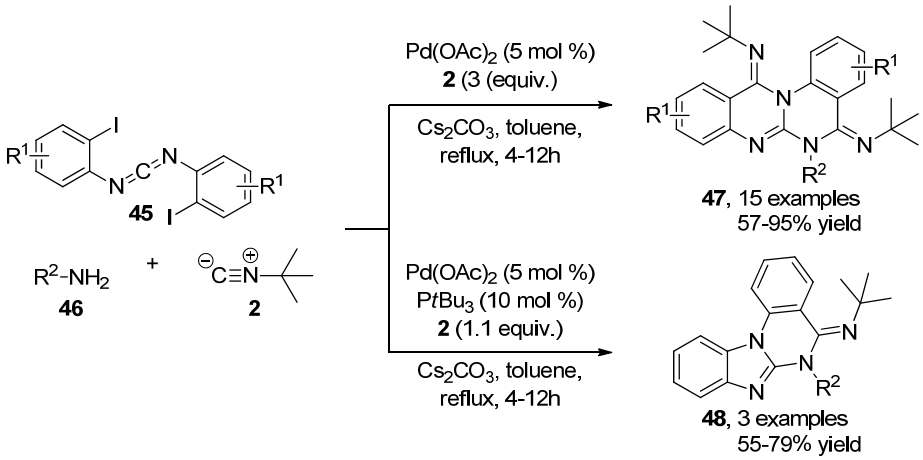
Scheme 10. Synthesis of 4-aminoquinazolines.

The Pd-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 (**37**) from *N*-(2-bromoaryl)amidines (**36**, Scheme 10).[24] Primary, secondary and tertiary aliphatic isocyanides all afford the heterocyclic products in good yields. Cyclohexyl JohnPhos

(**38**) was a good ligand for *tert*-butyl isocyanide and cyclohexyl isocyanide, but XPhos (**39**) was essential for good reactivity of primary aliphatic isocyanides.



Scheme 11. Synthesis of quinazolin-4(3*H*)-imines.

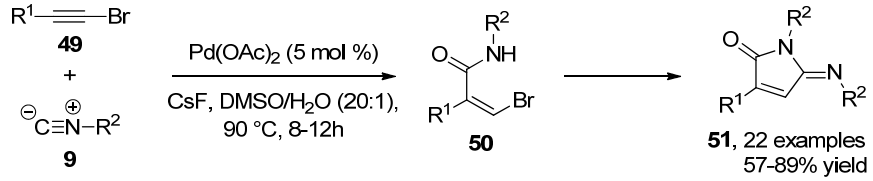


Scheme 12. Cascade reaction with isocyanide insertion.

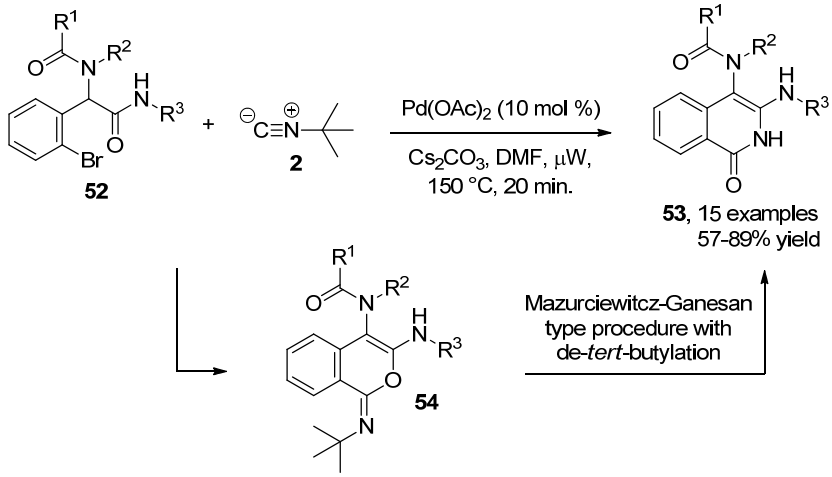
Pu and Wu *et al.* reported a Pd-catalyzed imidoylative cascade towards quinazolin-4(3*H*)-imines (**42**) (Scheme 11).[25] *N*-(2-Bromoaryl)carbodiimides (**40**) were used in combination with secondary amines (**41**) to produce a guanidine *in situ*, which can then undergo the typical intramolecular Pd-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.[26] Furthermore, the procedure could be extended with a second

cyclization event by employing symmetric carbodiimides (**45**) containing two aryl iodide moieties (Scheme 12).[27] The tetracyclic products contain two isocyanide fragments when three equivalents of *tert*-butyl isocyanide are used (**47**), but products incorporating one molecule of isocyanide (**48**) can be obtained by using 1.1 equivalents of **2** in the presence of P*t*Bu$_3$.

Jiang *et al*. showed that bromoalkynes (**49**) and two equivalents of isocyanide (**9**) can be coupled selectively to provide 5-iminopyrrolones (**51**) with modest to excellent E/Z selectivity of the exocyclic imine (Scheme 13).[28]. Secondary and tertiary aliphatic isocyanides were used, as well as 2,6-dimethylphenyl isocyanide. *cis*-Bromoacrylamides (**50**) are formed first under the reaction conditions and subsequently undergo intramolecular Pd-catalyzed imidoylation.



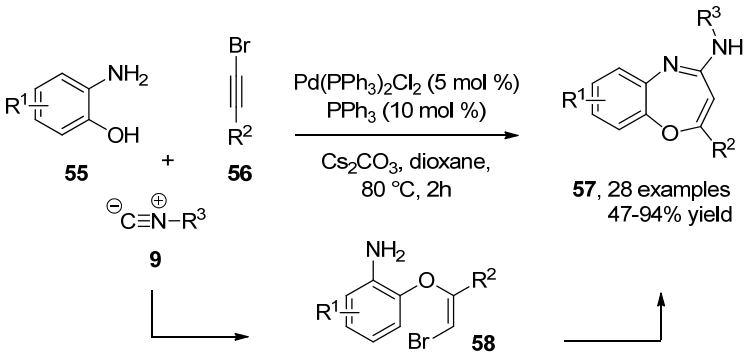
Scheme 13. Synthesis of 5-iminopyrrolones.



Scheme 14. Synthesis of isoquinolin-1(2*H*)-one derivatives.

Chauhan *et al*. reported a protocol for the conversion of amide precursors **52** into isoquinolin-1(2*H*)-one derivatives (**53**), which the authors presume proceeds through imidate intermediate **54** (Scheme 14).[29] The starting materials are

conveniently accessible *via* an Ugi reaction, making this an efficient approach towards this highly functionalized scaffold.

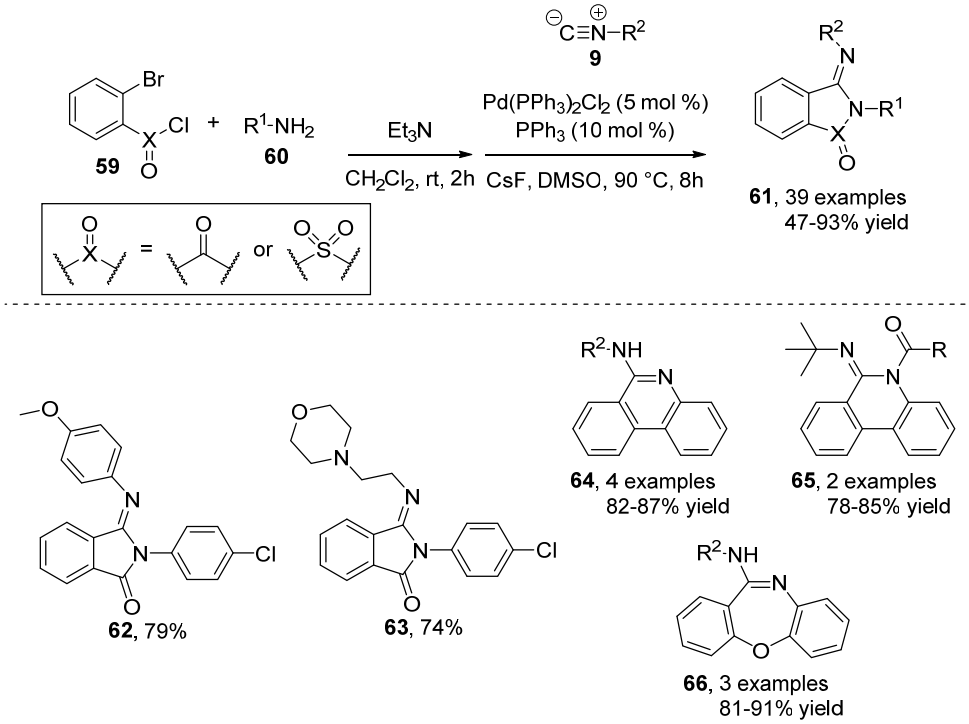


Scheme 15. Cascade reaction towards 7-membered heterocycles.

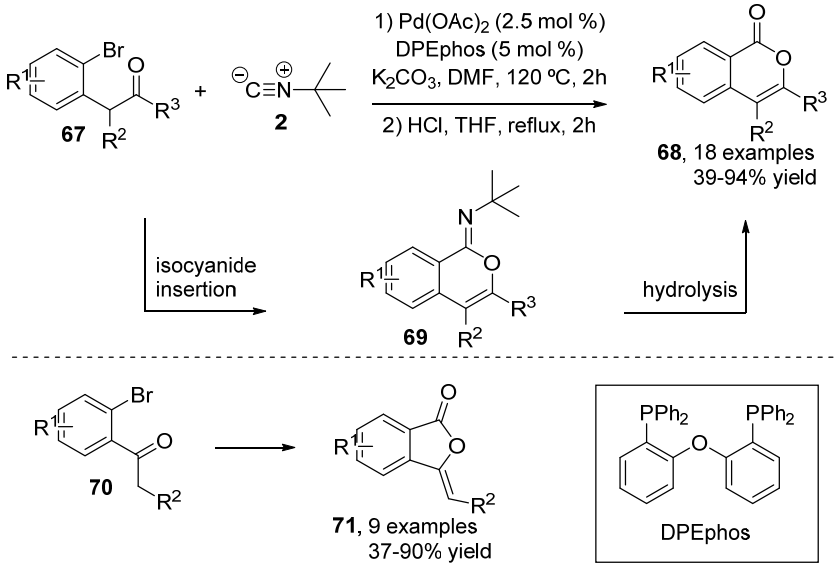
Jiang *et al.* reported a cascade reaction with amidination to give seven-membered rings. *o*-Aminophenols (**55**), bromoalkynes (**56**) and secondary or tertiary aliphatic isocyanides (**9**) afford 4-aminobenzo[*b*][1,4]oxazepine derivatives (**57**) in high yields (Scheme 15).[30] The reaction proceeds *via* **58**, which is cyclized by an intramolecular imidoylative amidination. The authors validated this order of events by converting isolated **58** to product **57** under the standard catalytic conditions.

Jiang *et al*. recently reported effective conditions for the intramolecular Pd-catalyzed imidoylative amidination, which are applicable to a wide range of heteroaromatic products (Scheme 16).[31] Reaction between **59** and amines 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 (**62** and **63**). Interestingly, (isocyanomethyl)trimethylsilane is a compatible isocyanide and the trimethylsilyl group is cleaved under the reaction conditions to afford the corresponding methyl substituted product (**61**, R^2 = Me). The potential of these conditions is illustrated by the synthesis of diverse amidine-containing heterocycles (**64**-**66**) involving an aniline nitrogen.

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 carbon monoxide surrogate to synthesize valuable lactones (**68** and **71**, Scheme 17).[32]



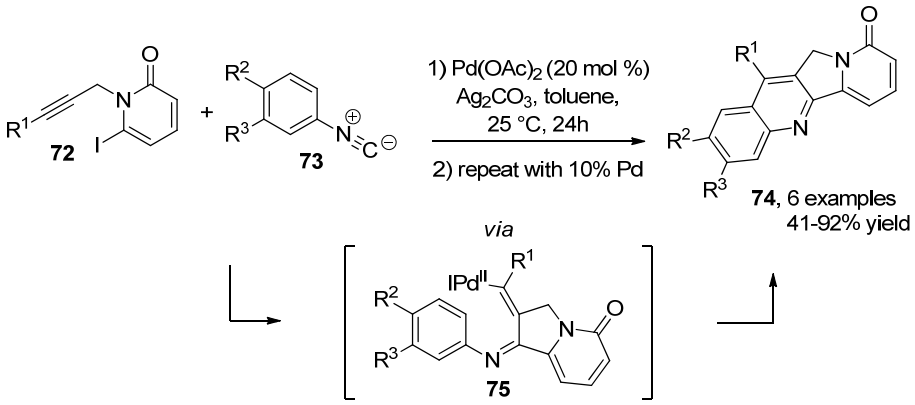
Scheme 16. Heterocyclic amidine synthesis.



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

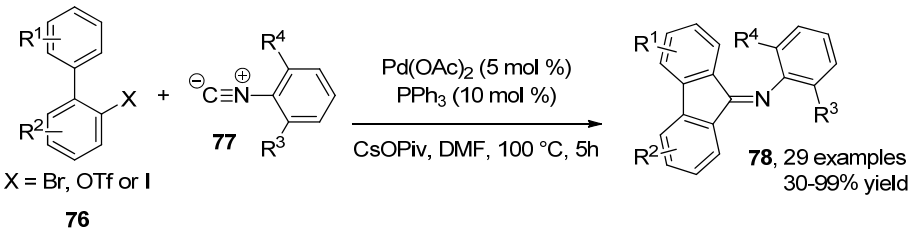
2.2.2 Pd-catalyzed isocyanide insertion reactions with C-H activation

The selective catalytic activation of C-H bonds, rather than preactivation of substrates as halides or metallated reagents, is an important and popular research topic in current organic chemistry.[33] 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 activation in an impressive cascade process (Scheme 18).[34] They coupled 6-iodo-*N*-propargylpyridin-2(1*H*)-ones (**72**) and electron-rich aromatic isocyanides (**73**), which affords tetracyclic compounds (**74**) in reasonable to high yields.

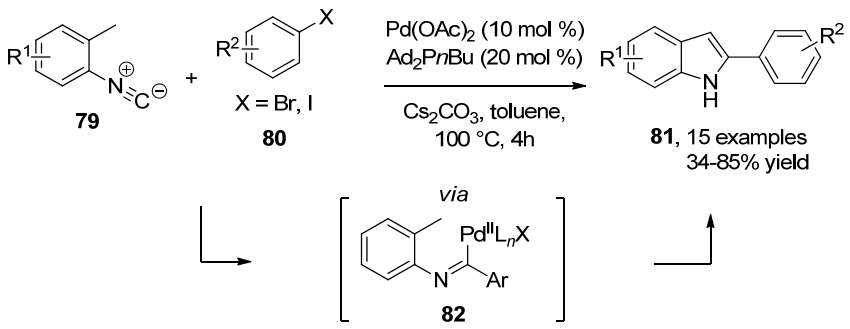


Scheme 18. First example of C-H bond activation with isocyanide insertion.

In 2010, the group of Chatani further demonstrated the potential of isocyanides in catalytic C-H bond activation reactions (Scheme 19).[35] 2-Halobiaryls (**76**) are readily coupled with 2,6-disubstituted aryl isocyanides (**77**) with a simple palladium catalyst to furnish fluorenylidene imines (**78**) in high yields.

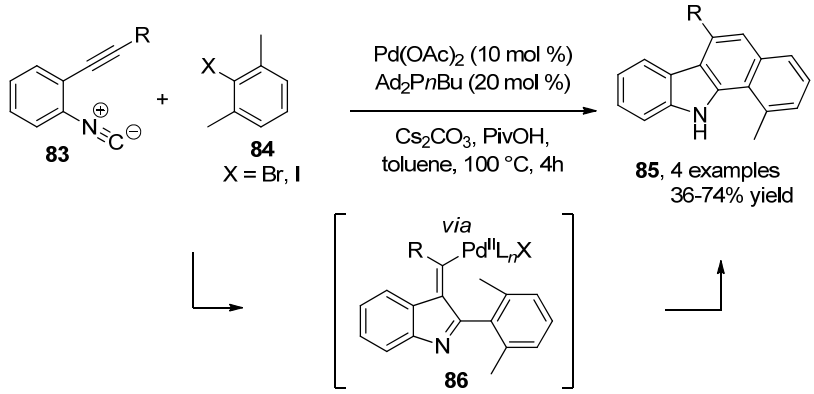


Scheme 19. Synthesis of fluorenylidene imines.



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

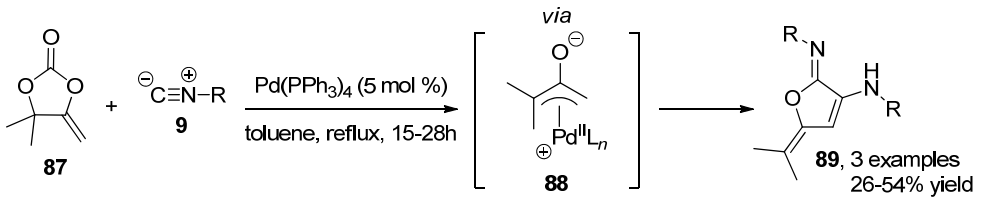
Very recently Takemoto *et al*. combined isocyanide insertion with C(sp^3)-H activation (Scheme 20).[36] In their system, aryl halides (**80**) undergo oxidative addition to palladium followed by insertion of 2-methylphenyl isocyanides (**79**) to give intermediates **82**. C(sp^3)-H activation then results in the formation of 2-arylindoles (**81**). The isocyanide has to be added slowly over a period of three hours to allow lower catalyst loadings. Most likely, the presence of 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 (**85**, Scheme 21). In later work the same group showed that intermediate **86** can also be trapped with H_2O to furnish 3-acyl-2-arylindoles (not shown).[37]



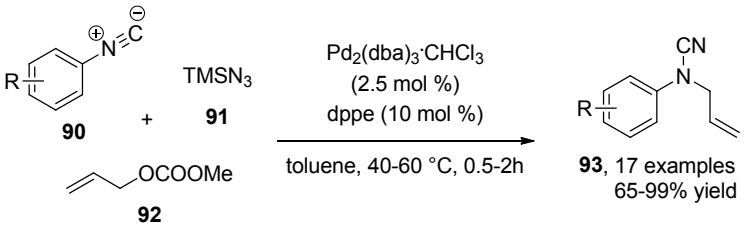
Scheme 21. Synthesis of benzo[α]carbazoles.

2.2.3 Pd-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).[38] The reaction involves a cyclic carbonate (**87**) and is believed to proceed *via* oxidative addition of palladium and subsequent decarboxylation to yield π-allylpalladium species **88**. A double isocyanide insertion most likely occurs next to form the product. 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.



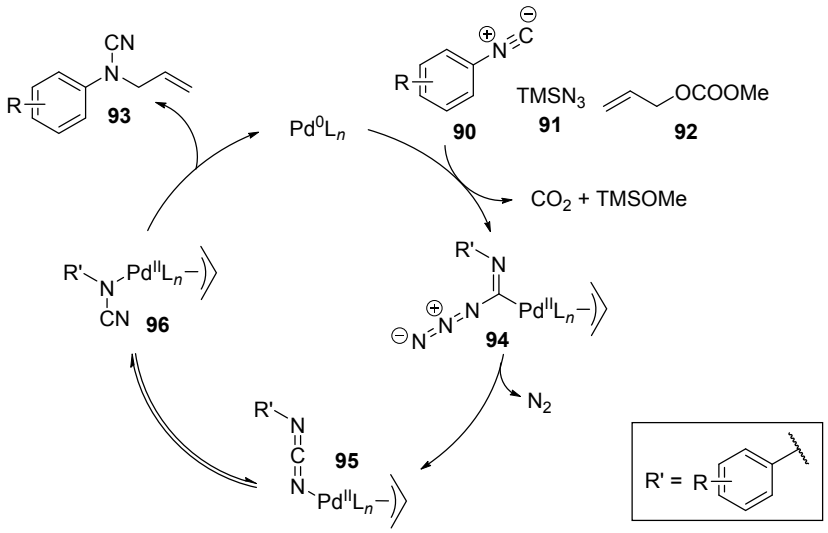
Scheme 22. Decarboxylative process with isocyanide insertion.



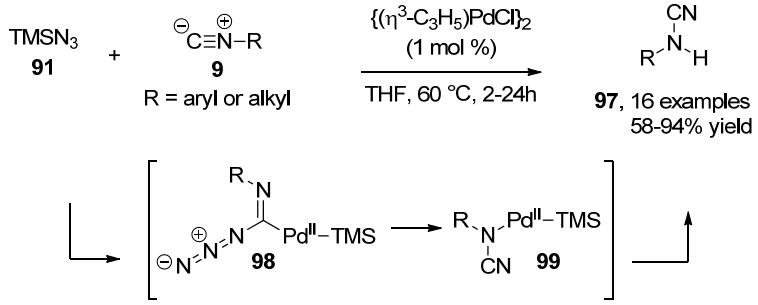
Scheme 23. Pd-catalyzed synthesis of *N*-allylcyanamides.

An elegant decarboxylative synthesis of *N*-allylcyanamides (**93**) from aromatic isocyanides (**90**), allyl methyl carbonate (**92**) and trimethylsilyl azide (**91**) was discovered by Yamamoto *et al*. (Scheme 23).[39] The mechanism proposed by the authors starts with the formation of species **94**, which eliminates N_2 and undergoes a 1,2-migration of the π-allylpalladium forming **95** (Scheme 24). Reductive elimination of Pd^0 from intermediate **96** results in formation of the product. The reaction was also used for the synthesis of *N*-cyanoindoles by employing 2-alkynylisocyanobenzenes under modified conditions, where an additional alkyne insertion is involved (not shown).[40] In a later study the authors showed monosubstituted cyanamides (**97**) are accessible *via* a similar strategy by direct coupling of isocyanides (**9**) and

trimethylsilyl azide (**91**) (Scheme 25).[41] Aliphatic isocyanides are also tolerated in this system.



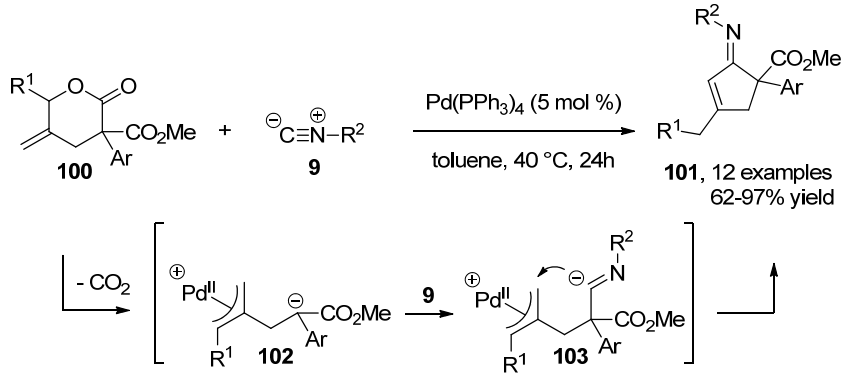
Scheme 24. Proposed mechanism.



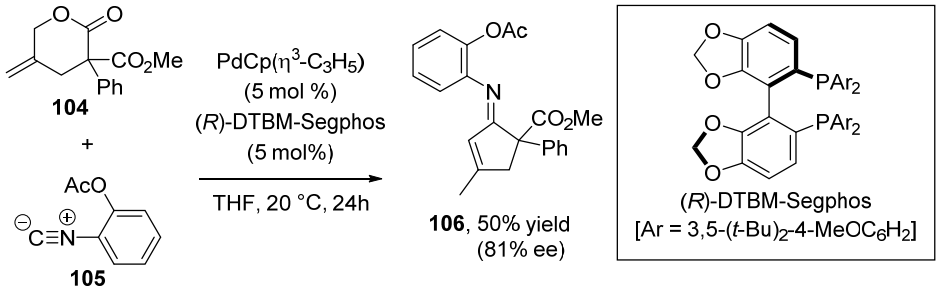
Scheme 25. Pd-catalyzed synthesis of cyanamides.

A decarboxylative cyclization with isocyanide insertion towards cyclopentenimines (**101**) was reported by Shintani and Hayashi *et al*. (Scheme 26).[42] Aromatic isocyanides work best, although benzyl isocyanide could also be used. The mechanism proposed by the authors involves formation of π-allylpalladium intermediate **102** and nucleophilic addition of the stabilized anion to the isocyanide to form intermediate **103**, 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

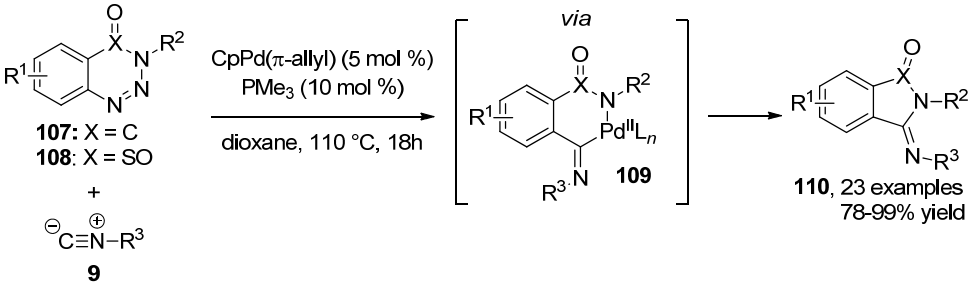
instead of electrophiles, unlike proposed here. Preliminary results towards the development of an asymmetric version were reported and very promising results (81% ee) were obtained (Scheme 27).



Scheme 26. Decarboxylative synthesis of cyclopentenimines.



Scheme 27. Asymmetric decarboxylative synthesis of cyclopentenimines.



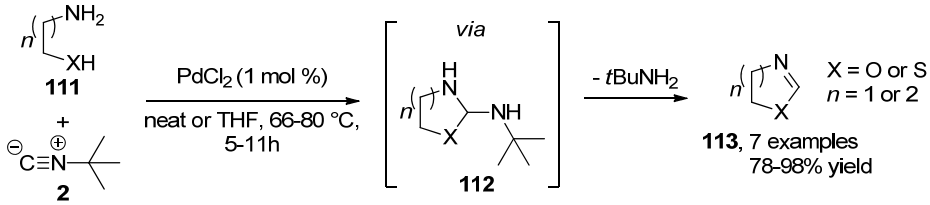
Scheme 28. Pd-catalyzed denitrogenation reaction.

Murakami *et al*. reported a reaction involving extrusion of molecular nitrogen from benzotriazinones (**107**), or its sulfur analogs **108**, and subsequent isocyanide

insertion. The process yields 3-(imino)isoindolin-1-ones (**110**, X = C) or the related 3-(imino)thiaisoindoline 1,1-dioxides (**110**, X = SO) in excellent yields. (Scheme 28).[43] Primary, secondary and tertiary aliphatic isocyanides and several aromatic isocyanides could be used.

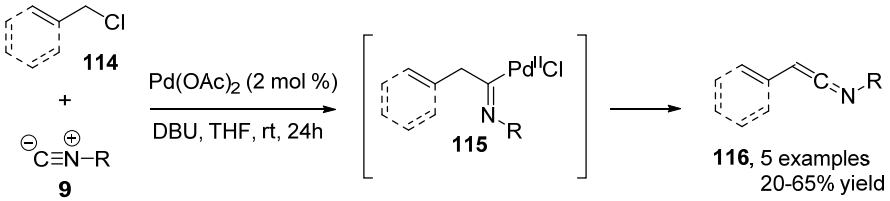
2.2.4 Miscellaneous Pd-catalyzed isocyanide insertion reactions

The first Pd-catalyzed reaction involving isocyanide insertion was reported by Saegusa *et al.* in 1974.[44] Their work involves a cyclization reaction of amino alcohols (**111**) with *tert*-butyl isocyanide insertion to form cyclic (thio)imidates (**113**) (Scheme 29). A mechanism involving the formation of **112**, which can eliminate *tert*-butyl amine, was proposed by the authors.



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

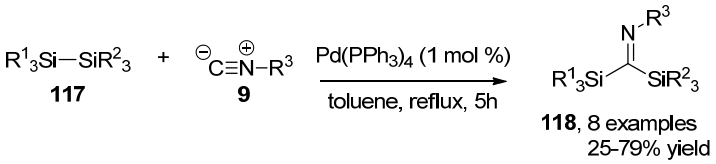
In 1977 the same group reported the coupling of tertiary aliphatic isocyanides (**9**) and allylic or benzylic chlorides (**114**) to furnish ketenimines (**116**, Scheme 30).[45] The reaction is believed to proceed *via* imidoyl palladium species **115**, which undergoes β-hydride elimination.



Scheme 30. Pd-catalyzed synthesis of ketenimines.

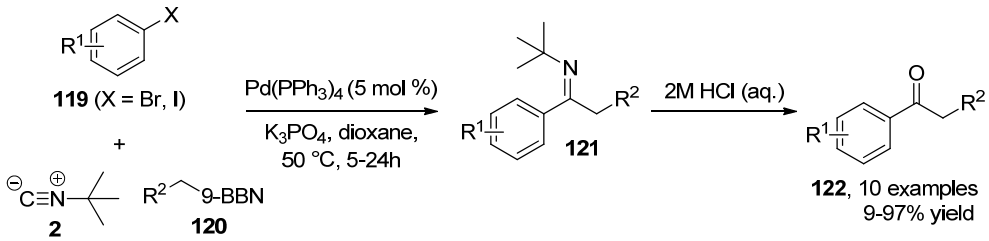
The group of Ito later developed a protocol for the catalytic insertion of isocyanides in Si-Si bonds in which both *o*-tolyl and cyclohexyl isocyanide could be used (Scheme 31).[46] The reaction could be extended to oligosilanes, where isocyanides are inserted in all Si-Si bonds to yield oligo(silylimine) derivatives.[47] In addition, the authors also showed isocyanide insertion in silicon-tin bonds is

possible.[48] The Pd-catalyzed insertion of isocyanides in S-S bonds has also been studied in detail by Kurosawa *et al.,* who showed that isocyanide insertion in Pd-S bonds is reversible.[49]



Scheme 31. Isocyanide insertion in Si-Si bonds.

The Suzuki coupling can be extended with isocyanide insertion as reported by Suzuki *et al.* (Scheme 32).[50] The required 9-alkyl-BBN derivatives (**120**) 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 (**120**): if more than one equivalent of isocyanide is used the yield drops drastically. Complex formation of *tert*-butyl isocyanide and **120** is proposed, which 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 (**121**) obtained by this approach were hydrolyzed to the corresponding ketones (**122**) before isolation.

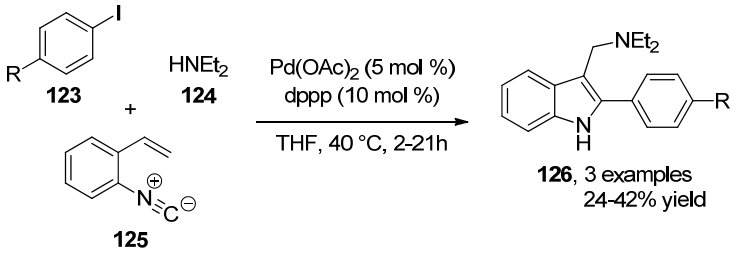


Scheme 32. Suzuki coupling combined with isocyanide insertion.

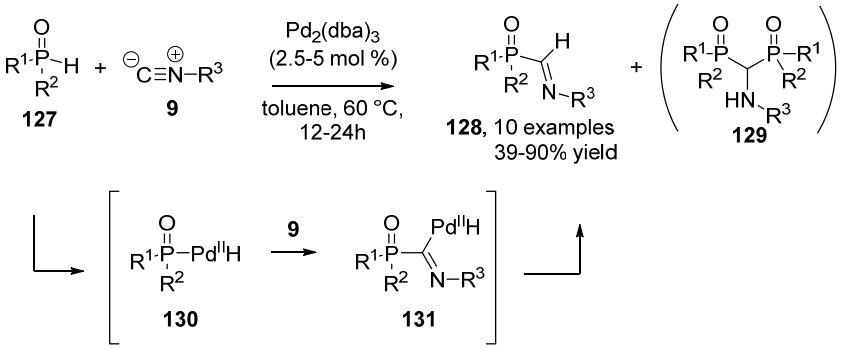
A Heck type reaction has also been combined successfully with isocyanide insertion by Takahashi *et al*. in their synthesis of 2,3-disubstituted indoles (**126**) (Scheme 33).[51] The reaction demonstrates the possibility to combine an isocyanide insertion process with alkene insertion. More importantly, the regioselectivity in the product shows isocyanide insertion precedes alkene insertion, which indicates that isocyanide insertion in aryl-palladium bonds is more facile than alkene insertion.

Han *et al*. reported a Pd-catalyzed isocyanide insertion into P-H bonds of phosphine oxides (**127**) to furnish α-iminophosphine oxides (**128**) in good yields

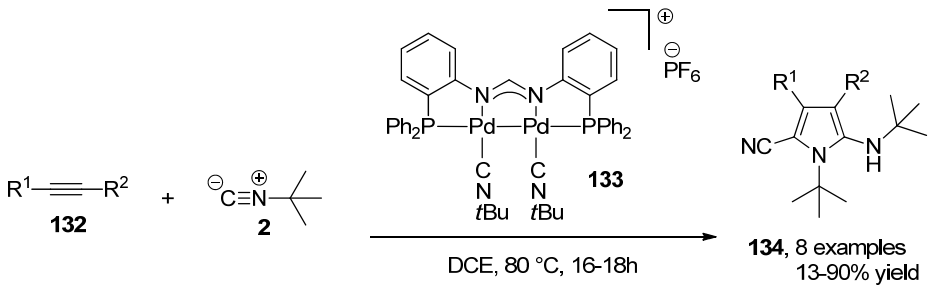
(Scheme 34).[52] Both aromatic and aliphatic isocyanides were used, including cyclohexyl isocyanide. Bisphosphinoylaminomethanes (**129**) were observed as trace side products in this reaction. A rhodium catalyst allows the selective synthesis of **129** instead of **128**.



Scheme 33. Pd-catalyzed synthesis of indoles.



Scheme 34. Pd-catalyzed synthesis of phosphinoyl imines.

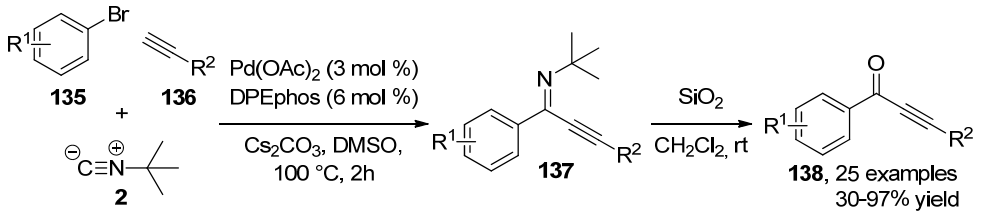


Scheme 35. Dinuclear palladium catalyst for pyrrole formation.

Tsukada and Inoue *et al*. used a novel dinuclear palladium catalyst (**133**) containing two coordinated isocyanides as catalyst for the formation of pyrroles (**134**)

(Scheme 35).[53] The reaction involves insertion of three isocyanides and loss of isobutene and has only been applied to *tert*-butyl isocyanide (**2**).

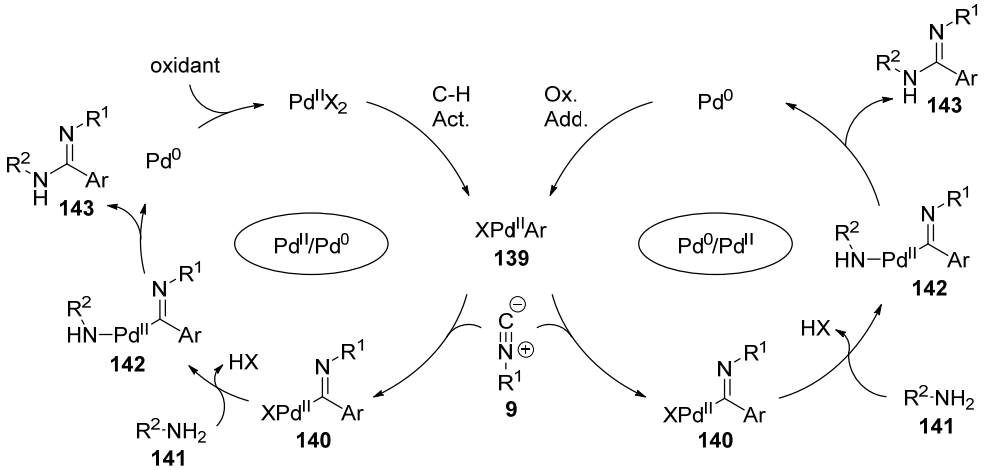
Very recently, the first imidoylative Sonogashira coupling was reported by Zhu and Ji *et al*. (Scheme 36).[54] A variety of (hetero)aryl bromides (**135**) was tolerated and both aliphatic and aromatic alkynes (**136**) were used successfully. The resulting alkynyl imines (**137**) were hydrolyzed with silica gel to afford the final alkynone products (**138**) in high yields.



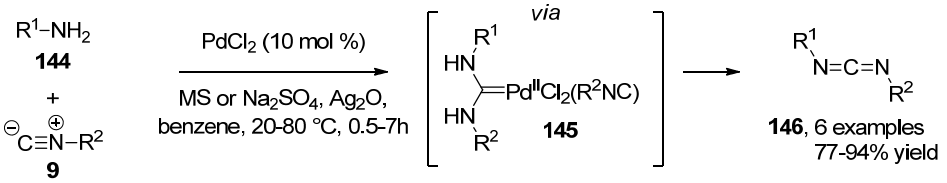
Scheme 36. Imidoylative Sonogashira coupling.

2.3. Oxidative Isocyanide Insertion Reactions

Pd^{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.[33] In these reactions, a stoichiometric oxidant is required to reoxidize Pd^0 to Pd^{II}. In the ideal case, molecular oxygen fulfills this role, being the most abundant and environmentally benign oxidant available. In addition, it avoids waste production as the only waste product is H_2O.[55] Oxidative palladium catalysis has been successfully combined with isocyanide insertion and indeed leads to a more sustainable synthesis of heterocyclic compounds. The general mechanism of these transformations is very similar to Pd^0 catalysis (Scheme 37).



Scheme 37. Amidine formation via Pd^{II}/Pd^0 (left) and Pd^0/Pd^{II} (right) catalysis (ligands omitted for clarity).

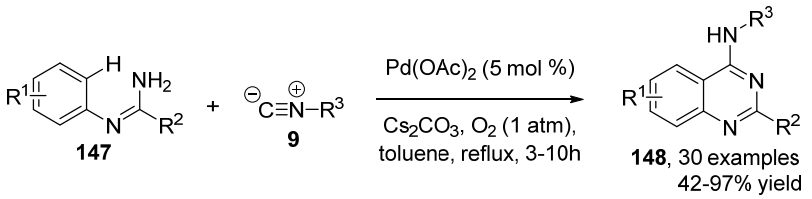


Scheme 38. Pd-catalyzed oxidative coupling of isocyanides and amines.

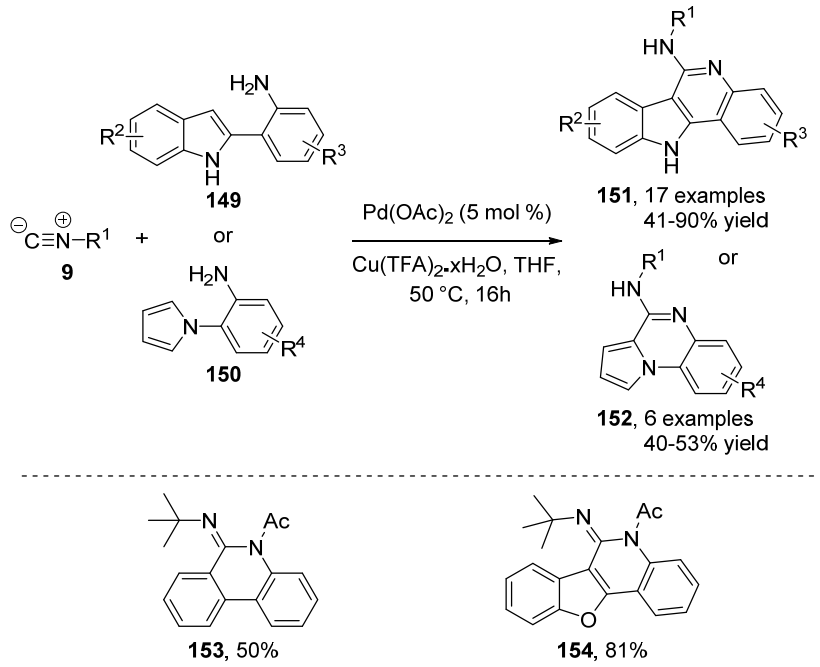
The first oxidative Pd-catalyzed reaction involving isocyanides was reported in 1975 by Saegusa *et al.*, who discovered the oxidative coupling of isocyanides with amines *via* carbene complex **145** to give carbodiimides (**146**) using Ag_2O as the

oxidant (Scheme 38).[56] In 1997, Schwartz *et al*. reported improved reaction conditions that use molecular oxygen as the stoichiometric oxidant in combination with catalytic iodine.[57]

The group of Zhu has pioneered the Pd-catalyzed oxidative formation of amidines and reported the first example in 2011 (Scheme 39).[58] The strategy relies on the use of *N*-arylamidines (**147**), which serve both as intramolecular nucleophiles and directing groups for C-H activation. The stoichiometric oxidant is molecular oxygen. Tertiary and secondary aliphatic isocyanides were used, although secondary isocyanides provided lower yields of **148**. Aromatic isocyanides are also viable coupling partners in this reaction.

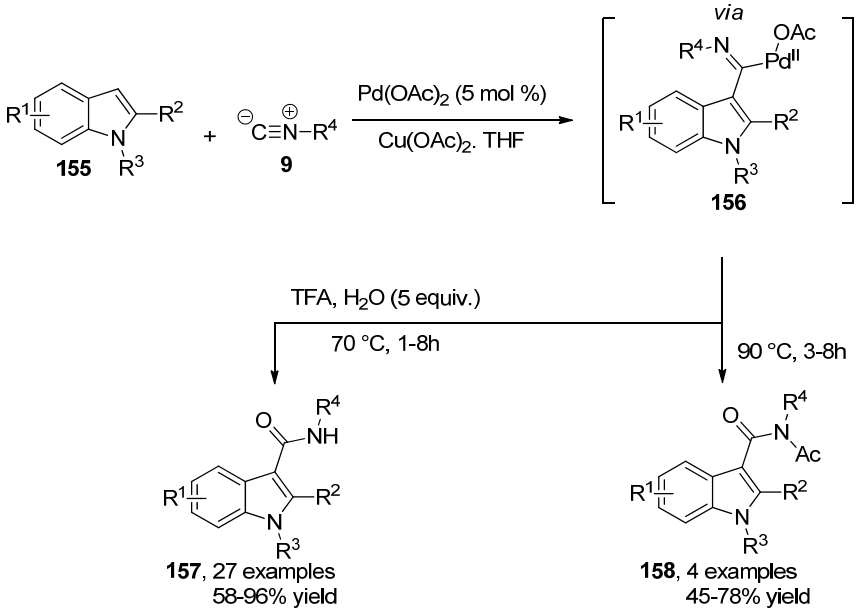


Scheme 39. Pd-catalyzed oxidative synthesis of 4-aminoquinazolines.

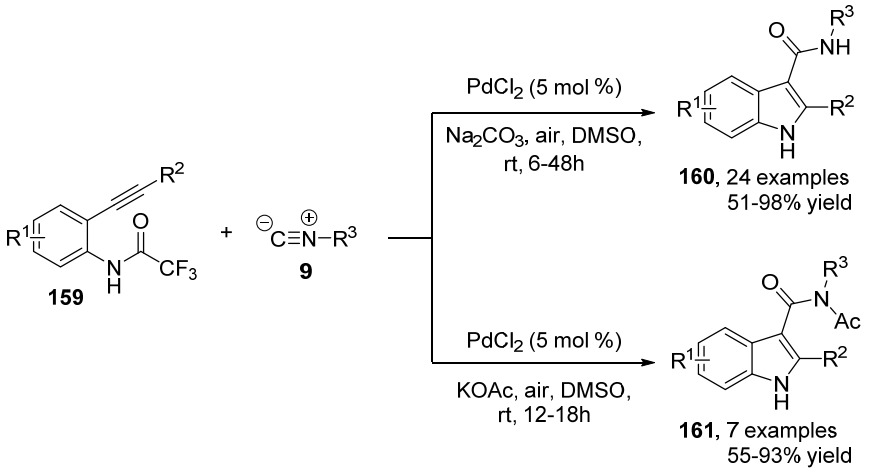


Scheme 40. Pd-catalyzed oxidative amidination *via* C-H activation.

The same group later reported an amidination of 2-(2-aminophenyl)indoles (**149**) *via* C-H activation (Scheme 40).[59] The reaction has a remarkably broad substrate scope and almost any isocyanide could be used, including ethyl isocyanoacetate. Zhu and coworkers also developed the direct carboxamidation of indoles *via* C-H activation and isocyanide insertion (Scheme 41).[60] The carboxamidation occurs regioselectively on the C3-position to yield indole-3-carboxamides (**157**). Tertiary and secondary aliphatic isocyanides are both inserted, although secondary isocyanides require more catalyst and prolonged reaction time. In addition, 2,6-dimethylphenyl isocyanide was successfully used. Interestingly, *N*-acetylated carboxamides (**158**) are obtained when water and trifluoroacetic acid are omitted from the reaction conditions. The same indole products (**160** and **161**) can be obtained by 5-*exo*-*dig* cyclization of *o*-alkynyl trifluoroacetanilides (**159**) and subsequent carboxamidation (Scheme 42).[61] The carbonyl oxygen 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.

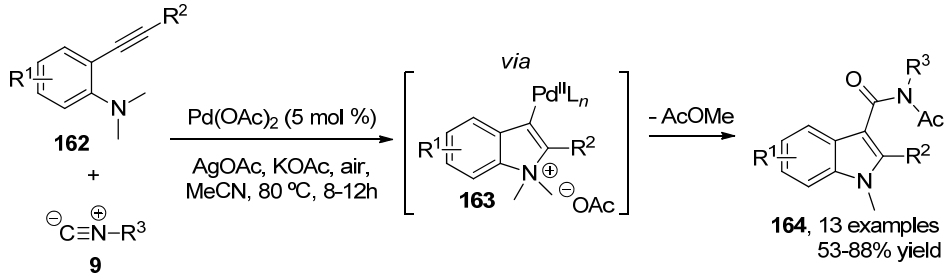


Scheme 41. Pd-catalyzed oxidative synthesis of (*N*-acetyl) indole-3-carboxamides.



Scheme 42. Pd-catalyzed oxidative synthesis of (*N*-acetyl) indole-3-carboxamides.

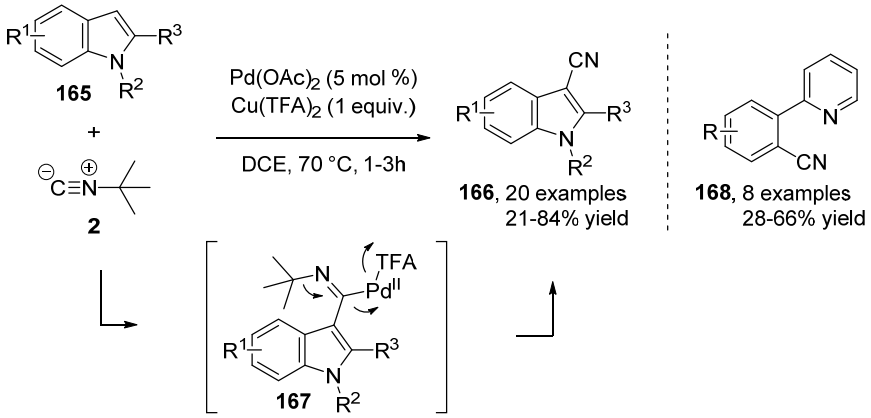
Yao and Wu *et al*. developed another imidoylative synthesis of *N*-acetyl indole-3-carboxamides (**164**) starting from *N,N*-dimethyl-2-alkynylanilines (**162**) using silver acetate as both the acetyl source and stoichiometric oxidant (Scheme 43).[62] Intermediate **163** is presumably formed first under the reaction conditions and an isolated sample was indeed converted to the product (**164**) under the standard reaction conditions. Notably, primary, secondary and tertiary aliphatic isocyanides could be used in this reaction.



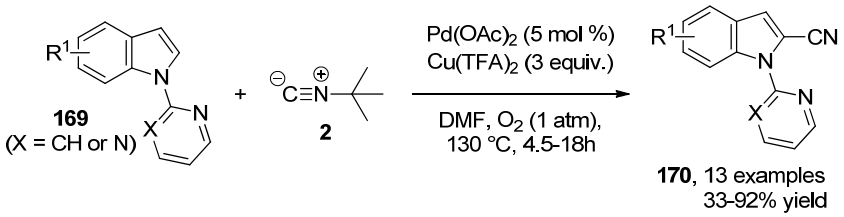
Scheme 43. Pd-catalyzed oxidative synthesis of *N*-acetyl indole-3-carboxamides.

The groups of Zhu and Xu independently reported Pd-catalyzed oxidative cyanation reactions using *tert*-butyl isocyanide as the cyanide source. Zhu and coworkers found mild conditions for the C3 cyanation of indoles, which proceeds by β-*tert*-butyl elimination of **167** (Scheme 44).[63] $Cu(TFA)_2$ was the only viable stoichiometric oxidant for this reaction. The procedure was also applied in the

regioselective cyanation of arenes using pyridine as directing group, leading to benzonitrile derivatives (**168**). The group of Xu also studied the C3 cyanation of indoles, but developed a complementary pyridine-directed C2 cyanation by attaching a directing group to the N1-position of the indole moiety (Scheme 45).[64] In this case, a combination of $Cu(TFA)_2$ and O_2 was used as the oxidant.



Scheme 44. Pd-catalyzed oxidative C3 cyanation of indoles and arylpyridines.



Scheme 45. Pd-catalyzed oxidative C2 cyanation of indoles.

2.4. Conclusions

The migratory insertion of isocyanide in Pd-C bonds is well established and scattered catalytic applications of this phenomenon are known for decades. Nevertheless, the widespread use of Pd-catalyzed isocyanide insertions in organic synthesis has thus far remained elusive and only in 2011 has its popularity seen an upsurge. The recent advances discussed in this Chapter illustrate the potential of this chemistry, as shown by the synthesis of various valuable fine chemicals. The main current limitation is the substrate tolerance with respect to the isocyanide, although several elegant solutions have been 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 Pd-catalyzed oxidative isocyanide insertion processes is noteworthy and has resulted in several highly efficient novel reactions. Molecular oxygen is often a suitable stoichiometric oxidant in these reactions, resulting in high atom efficiency and only water as the by-product. This is an important new development in this field considering the drive for sustainability in modern society. We strongly believe this field is still in its infancy and there is ample room for further development. The increasing knowledge about the reactivity of different isocyanides towards palladium catalysts will lead to a better mechanistic understanding and consequently 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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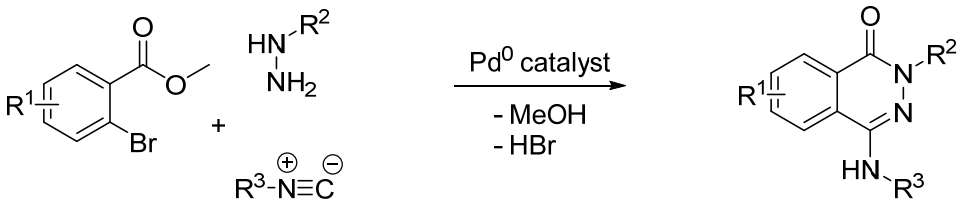
Chapter 3

4-Aminophthalazin-1(2*H*)-ones:

Reaction Optimization and Substrate Scope



***Abstract**: The Pd-catalyzed imidoylative cross-coupling of a wide range of substituted o-(pseudo)halobenzoates and hydrazines efficiently affords 4-aminophthalazin-1(2H)-ones after lactamization. These products are difficult to obtain regioselectively by classical methods.*

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3.1 Introduction

Efficient access to libraries of functionalized heterocycles for lead discovery and optimization is essential for drug development and relies heavily on combinatorial chemistry and high-speed synthesis. In this respect, cascade reactions (see Chapter 1) and multicomponent reactions (MCRs) are of high importance, since they allow rapid generation of complex and structurally diverse heterocycles. MCRs[1] are defined as reactions between three or more different compounds in a single reaction vessel. Since multiple bond forming processes are combined in one pot, there are typically fewer synthetic steps required to obtain the target compounds using MCRs (Figure 1). An additional benefit is the high atom economy often associated with MCRs, which makes them attractive from an environmental point of view. Furthermore, since fewer purification steps are needed a lot of time and chemicals can be saved. MCRs can also open up new synthetic possibilities by producing and utilizing reactive intermediates *in situ* that are otherwise difficult or impossible to isolate and use.

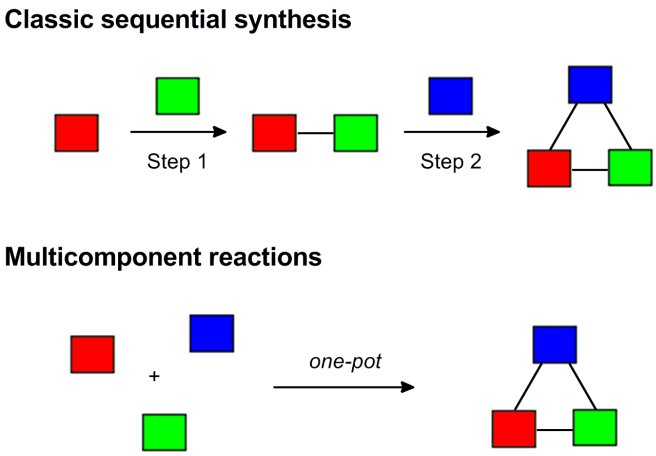
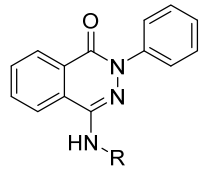


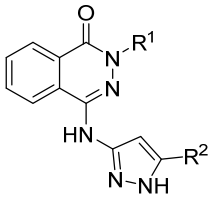
Figure 1. Sequential synthesis versus multicomponent reactions.

The discovery of novel or underexplored scaffolds that exhibit valuable biological activity is important to meet the contemporary demand for new and better pharmaceuticals. It is essential to have efficient synthetic approaches toward these scaffolds to make quick synthesis and evaluation possible. In this respect, novel MCRs towards underexplored scaffolds with promising biological activity are an ideal starting point for high throughput screenings to identify potential new pharmaceuticals. 4-Aminophthalazin-1(2*H*)-ones (APOs) have recently shown

promising activity as Aurora-A kinase inhibitors and human A3 adenosine receptor antagonists (Scheme 1).[2] In addition, they have shown potential as PARP (poly ADP ribose polymerase) inhibitors, associated with cancer treatment, and for the treatment of inflammatory and auto-immune diseases.[3] However, despite this promising precedence, APOs have remained rather unexplored.



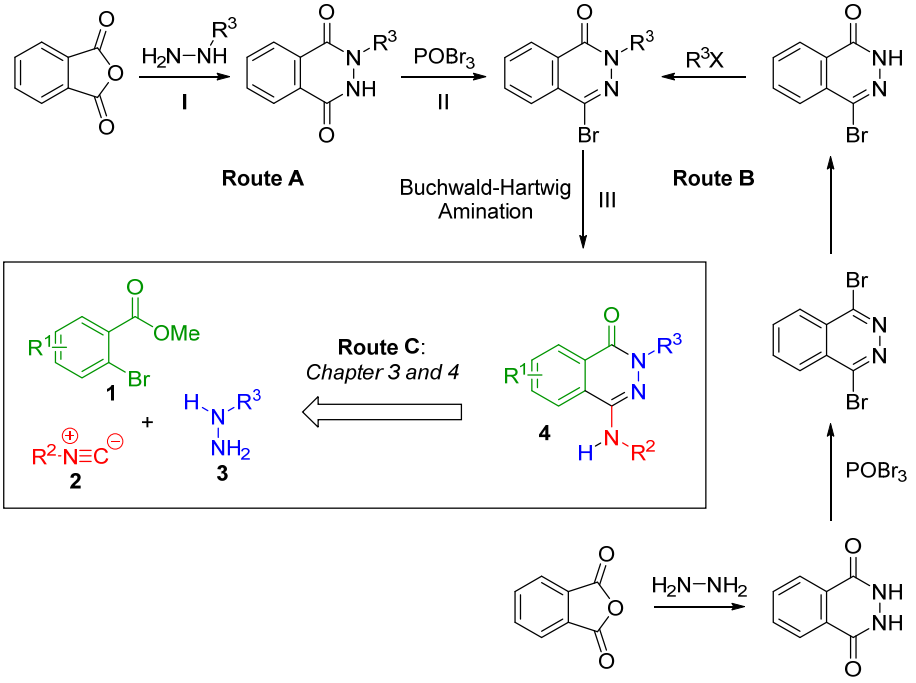
Human A3 Adenosine Receptor Antagonists



Aurora-A Kinase Inhibitors

Scheme 1. Examples of biologically active 4-aminophthalazin-1(2*H*)-ones.

We believe this might be explained by the tedious linear synthesis of APOs and the lack of regioselective approaches towards core-substituted APOs (Scheme 2, **4**, $R^1 \neq H$).[2a, 4] The typical synthesis starts from phthalic anhydride and is a multistep process that consists of *(I)* condensation with hydrazine, *(II)* dehydroxyhalogenation and *(III)* Buchwald-Hartwig amination (Scheme 2, route A).[2a] This sequence is highly inefficient for variation of the N2-position (**4**, R^3) due to the poor commercial availability of substituted hydrazines and early incorporation of this group in the synthesis. To circumvent this, unsubstituted hydrazine ($R^3 = H$) can be employed and the resulting N2-position functionalized later on, thereby extending the sequence to 5 steps (Scheme 2, route B). In addition, selective introduction of substituents on the phenyl ring (**4**, R^1) is difficult in both routes since condensation with substituted hydrazine and monodehydroxyhalogenation both proceed with very poor regioselectivity. We envisioned a much more efficient approach toward APOs starting from *o*-bromobenzoates (**1**), isocyanides (**2**) and hydrazines (**3**) using Pd-catalyzed isocyanide insertion chemistry (Scheme 2, Route C). This MCR approach would also control regioselectivity and thus make substitution of the APO scaffold possible. It is, however, particularly challenging since hydrazine is a difficult coupling partner that has only recently successfully been used in the Buchwald-Hartwig reaction.[5]

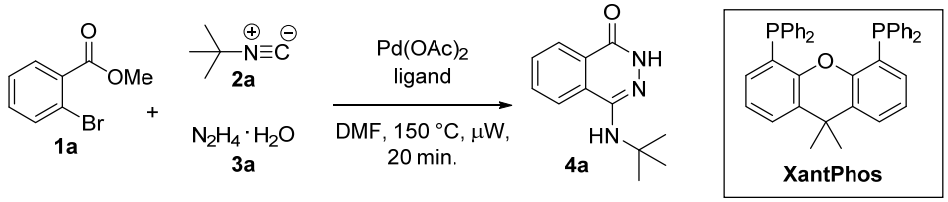


Scheme 2. Synthetic routes towards 4-aminophthalazin-1(2*H*)-ones.

3.2 Results and Discussion

We started our investigations by studying the reaction between methyl *o*-bromobenzoate (**1a**), *tert*-butyl isocyanide (**2a**) and hydrazine monohydrate (**3a**) as benchmark reaction (Table 1). We initially chose $Pd(OAc)_2$ (10 mol %) in combination with the ligand XPhos (20 mol %) as the catalytic system, using DMF as the solvent and potassium acetate as the base. However, these conditions did not result in any product formation under conventional heating. Initial screenings indicated that employing hydrazine as both a reagent and a convenient and cheap base under microwave irradiation did furnish **4a** in 30% yield (Table 1, entry 1). Delighted by this result, we set out to further optimize the reaction conditions. We were pleased to find that dppf is a much better ligand than XPhos (entry 2), providing the product in 55% yield with only 2 mol % of $Pd(OAc)_2$ (entry 3). We tried to lower the palladium/ligand ratio to 1 : 1.1, but the yield was reduced significantly (entry 4). A screening of several different ligands indicating that bidentate ligands are essential (entries 5-7). XantPhos was the most effective ligand during these studies (entry 7). A control experiment validated that a palladium catalyst is indeed required for this reaction (entry 8).

Table 1. Catalyst optimization.[a]

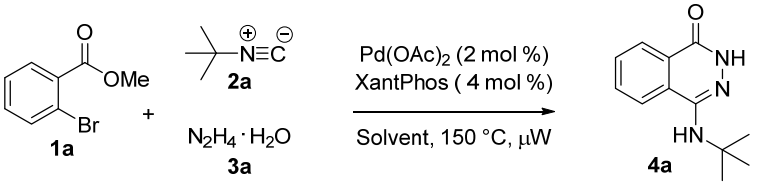


Entry	Ligand	$Pd(OAc)_2$ (mol %)	Conversion of **1a**[b]	Yield of **4a**[b]
1	X-Phos	10	>99%	30%
2	dppf	10	>99%	81%
3	dppf	2	>99%	55%
4[c]	dppf	2	>99%	31%
5	PPh_3	2	41%	5%
6	dppp	2	70%	21%
7	XantPhos	2	>99%	64%
8	---	0	39%	0%

[a] Standard reaction conditions: $Pd(OAc)_2$/ligand (1:2), methyl o-bromobenzoate (**1a**, 0.50 mmol), *tert*-butyl isocyanide (**2a**, 0.75 mmol), hydrazine monohydrate (**3a**, 1.05 mmol) in DMF (2.5 mL), 20 min at 150 °C (μW). [b] Determined by GC analysis using dodecane as internal standard. [c] $Pd(OAc)_2$/ligand ratio 1 : 1.1.

A variety of common solvents were examined next (Table 2). Polar aprotic solvents are essential for high yields and particularly DMSO proved to be a highly effective solvent affording the product in quantitative yield (entry 5). The reaction was equally efficient when the reaction time was reduced to just 5 minutes in the microwave (entry 6). Microwave irradiation proved clearly superior to conventional heating (entry 7, preheated oil bath), although we cannot exclude the actual temperature in the microwave vessel was higher.[6] Nevertheless, we choose microwave irradiation as heat source to continue our studies because of convenience.

Table 2. Solvent screening.[a]



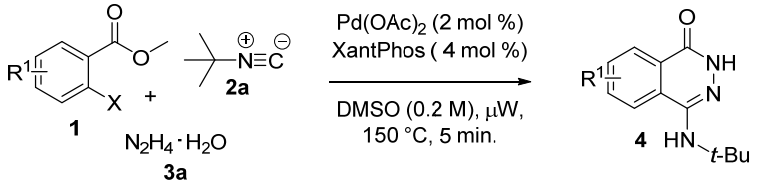
Entry	Solvent	Time (min.)	Conversion of **1a**[b]	Yield of **4a**[b]
1	MeCN	20	50%	31%
2	Toluene	20	23%	2%
3	THF	20	23%	5%
4	NMP	20	58%	40%
5	DMSO	20	>99%	>99%
6	DMSO	5	>99%	99%
7[c]	DMSO	5	86%	78%

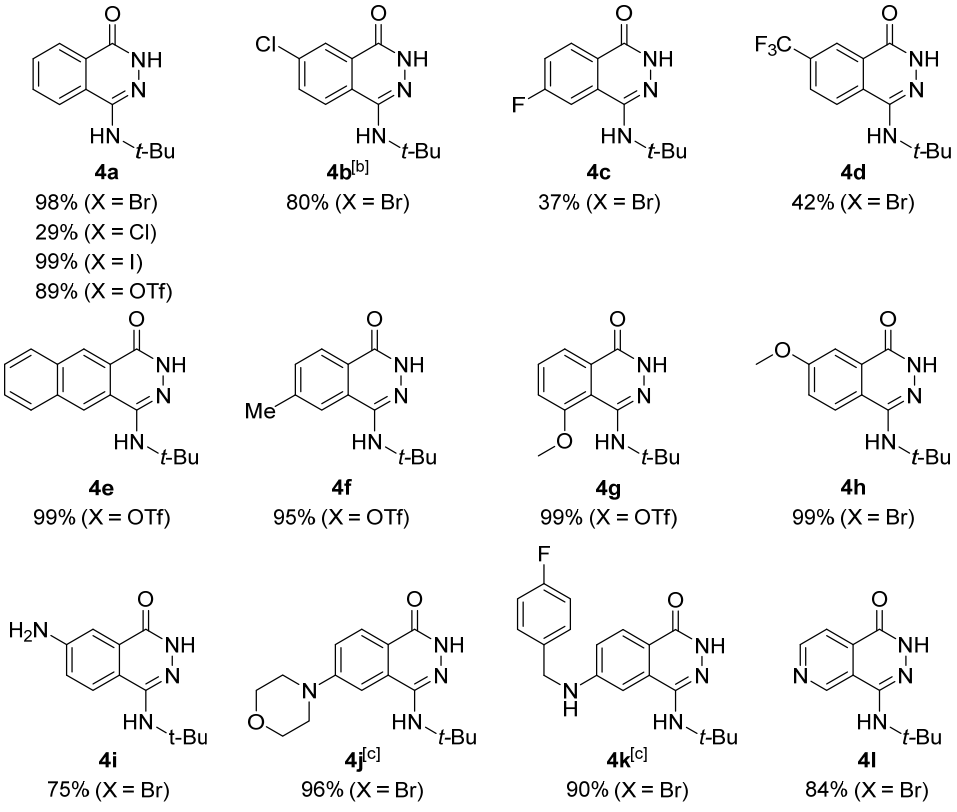
[a] Standard reaction conditions: $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %), methyl o-bromobenzoate (**1a**, 0.50 mmol), *tert*-butyl isocyanide (**2a**, 0.75 mmol), hydrazine monohydrate (**3a**, 1.05 mmol) in 2.5 mL solvent at 150 °C (μW). [b] Determined by GC analysis using dodecane as internal standard. [c] Conventional heating (preheated oil bath).

After having defined the optimal catalytic system and reaction conditions, we explored the substrate scope of the reaction starting with the aryl bromide input (Table 3). The reaction was easily extendable to the corresponding aryl iodide and aryl triflate, but the aryl chloride was much less reactive and provides **4a** in only 29% yield. Diverse substitution (*e.g.* Cl, CF_3, NH_2, F, OMe) on the methyl *o*-halobenzoate (**1**) was well tolerated on diverse positions and led to the isolation of the corresponding products **4b**-**4k** in moderate to excellent yields. Electron-poor methyl benzoates (**1**) are typically converted in moderate yield (**4b**-**4d**). We assume this is due to compatibility issues; aryl chloride **1b** might undergo competitive oxidative addition and methyl 2-bromo-4-fluorobenzoate (**1c**) is an excellent substrate for nucleophilic aromatic substitution by hydrazine. Interestingly, the yield of **4b** increased

significantly (from 62% to 80%) when the reaction time was reduced to just 2 minutes, suggesting undesired Pd-catalyzed reactions of the aryl chloride occur on the reaction product. It is important to note that the medicinally important fluoro and trifluoromethyl substituents could be smoothly incorporated,[7] although the yields were modest (**4c** and **4d**).

Table 3. Substrate scope of the methyl 2-(pseudo)halidebenzoate input.[a]





[a] Conditions: $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %), ArX (**1**, 0.50 mmol), *tert*-butyl isocyanide (**2a**, 0.75 mmol), hydrazine monohydrate (**3a**, 1.05 mmol) in DMSO (2.5 mL), 5 min at 150 °C (μW). Yields refer to isolated products. [b] Reaction time 2 min. [c] Reaction time 15 minutes.

A naphthalene-fused derivative (**4e**) and methyl substituted APO **4f** were both obtained in excellent yield (99% and 95%, respectively). Electron-rich methyl *o*-halobenzoates undergo the desired reaction extremely well, affording the corresponding APOs **4g**-**4k** in excellent yields. The reactions are sometimes slower for electron-rich substrates and can require 15 minutes of reaction time (*e.g.*, for **4j**). Substrate **1i**, containing a free amino group, was not fully consumed under the reaction conditions. The products containing a free amino group (**4i** and **4k**) are notable examples. They are obviously very challenging substrates, but they also allow further functionalization on the typically unsubstituted side of the product. The reaction tolerates heterocyclic substrates, as exemplified by the conversion of pyridine analog **1l** to aza-APO **4l** in 84% yield. Azaphthalazinones lacking the 4-amino group very recently received attention as human histamine H_1 receptor antagonists.[8] The structure of compound **4b** was unambiguously established by X-ray crystallography (Figure 2).

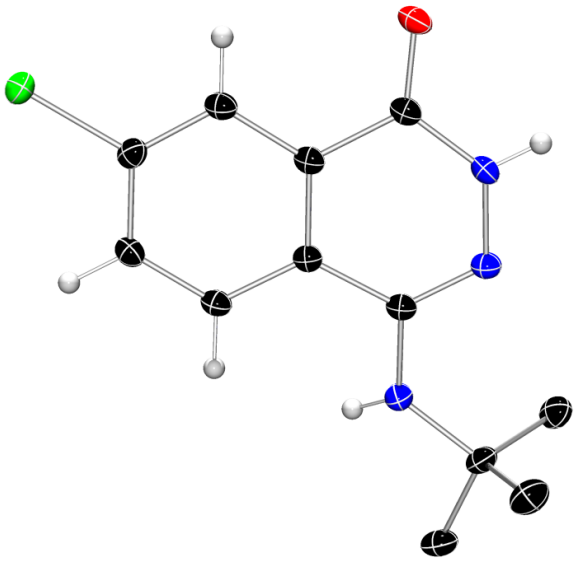
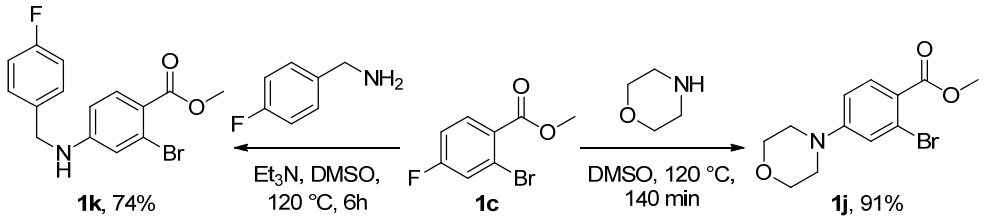


Figure 2. X-ray structure of compound **4b.** Displacement ellipsoids are drawn at 50% probability level. Protons of the *tert*-butyl group are omitted for clarity.

The main limitation in scope with respect to the benzoate (**1**) is the availability or straightforward access to this building block. We were therefore pleased to find that methyl 2-bromo-4-fluorobenzoate (**1c**), which can be obtained in one step from the commercially available corresponding carboxylic acid, is an excellent substrate for nucleophilic aromatic substitution reactions with amines. In the event, benzoates **1j** and **1k** were readily obtained in this manner (Scheme 3). Considering the prevalence of amines in biologically active molecules, this is an important handle for introducing additional functionality.



Scheme 3. Synthesis of substrates **1j** and **1k**.

The substrate tolerance of the isocyanide was examined next, which unfortunately revealed that the reaction is highly specific for tertiary aliphatic isocyanides. Although Walborsky's reagent provided product **4m** in 64% yield (Figure 3), neither primary and secondary aliphatic nor aromatic isocyanides gave the desired product. We do not yet have a satisfactory explanation for this high sensitivity. A possibility could be the tendency of less bulky isocyanides to form stable fully ligated palladium complexes, thereby inhibiting catalysis.[9] An alternative explanation is oligomerisation or polymerization of the isocyanide by consecutive insertions, which is more facile with less bulky isocyanides (see Chapter 2).

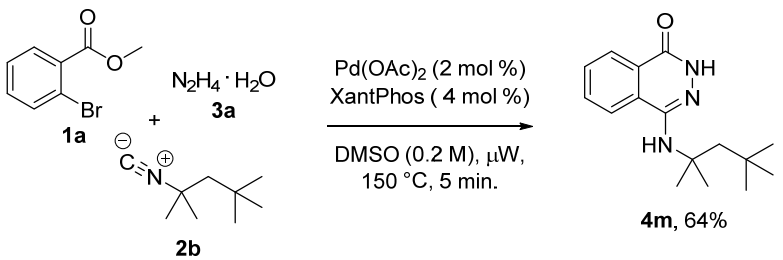
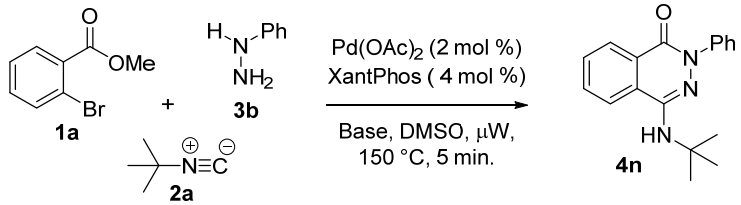


Figure 3. Insertion of Walborsky's reagent.

The use of substituted hydrazines also proved to be difficult. Replacing hydrazine monohydrate with phenylhydrazine under the standard reaction conditions

did not lead to product formation. We argued that, since hydrazine is both a reagent and base in this reaction, the difference in basicity might be responsible for the observed results. Accordingly, we examined the use of an additional base (Table 4). A promising first result was obtained using triethylamine as a base (entry 1), affording product **4n** in 24% yield. Typical inorganic bases, such as cesium carbonate or sodium *tert*-butoxide, led to complex reaction mixtures (entry 2 and 3). A range of different organic bases was evaluated and surprisingly the presence of a free N-H group seems to be important for better yields (entry 4-10). The best results were obtained with diisopropylamine (entry 9) and increasing the amount of base slightly improved the yield further (entry 10). It was possible to obtain a synthetically useful yield of **4n** by using more equivalents of phenylhydrazine (entry 11).

Table 4. Base screening with phenylhydrazine as reagent.[a]



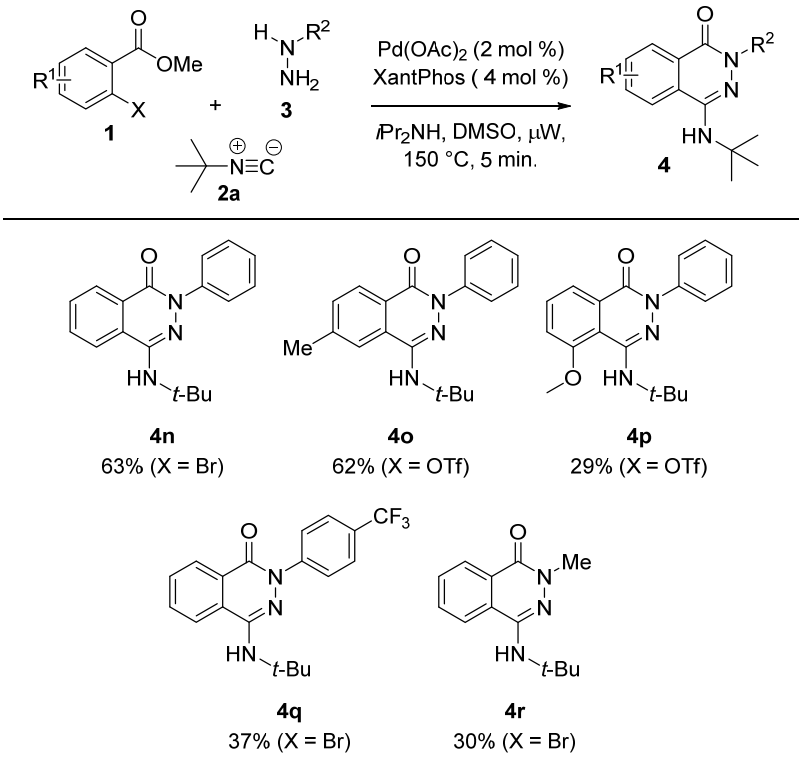
Entry	Base (eq.)	Comment	Conversion of **1a**[b]	Yield of **4n**[b]
1	Et_3N (1.5)	-	50%	24%
2	Cs_2CO_3 (1.5)	-	88%	3%
3	NaO*t*Bu (1.5)	-	>99%	0%
4	DBU (1.5)	-	>99%	30%
5	DIPEA (1.5)	-	44%	22%
6	NMM (1.5)	-	27%	9%
7	Pyridine (1.5)	-	18%	4%
8	*t*BuNH_2 (1.5)	-	94%	43%
9	*i*Pr_2NH (1.5)	-	84%	41%
10	*i*Pr_2NH (3)	-	>99%	46%
11	*i*Pr_2NH (3)	2.5 eq. **3b**	>99%	64%

[a] Standard reaction conditions: $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %), methyl o-bromobenzoate (**1a**, 0.50 mmol), *tert*-butyl isocyanide (**2a**, 0.75 mmol), phenylhydrazine (**3b**, 0.65 mmol) in DMSO (2.5 mL), 5 min at 150 °C (μW). [b] Determined by GC analysis using dodecane as internal standard.

With these optimized modified reaction conditions we obtained **4n** in 63% isolated yield (Table 5). Pleasingly, substitution on the methyl benzoate is still tolerated (**4o** and **4p**), although a strongly electron-donating methoxy group in the ortho position decreases the yield. Interestingly, a change in the electronic character

of the aryl hydrazine has a pronounced effect. Electron-poor *para*-trifluoromethylphenylhydrazine gives **4q** in 37% yield, whereas *para*-methoxyphenylhydrazine gave only trace amounts of product. Methylhydrazine can be used, but product **4r** was obtained in poor yield (30%).

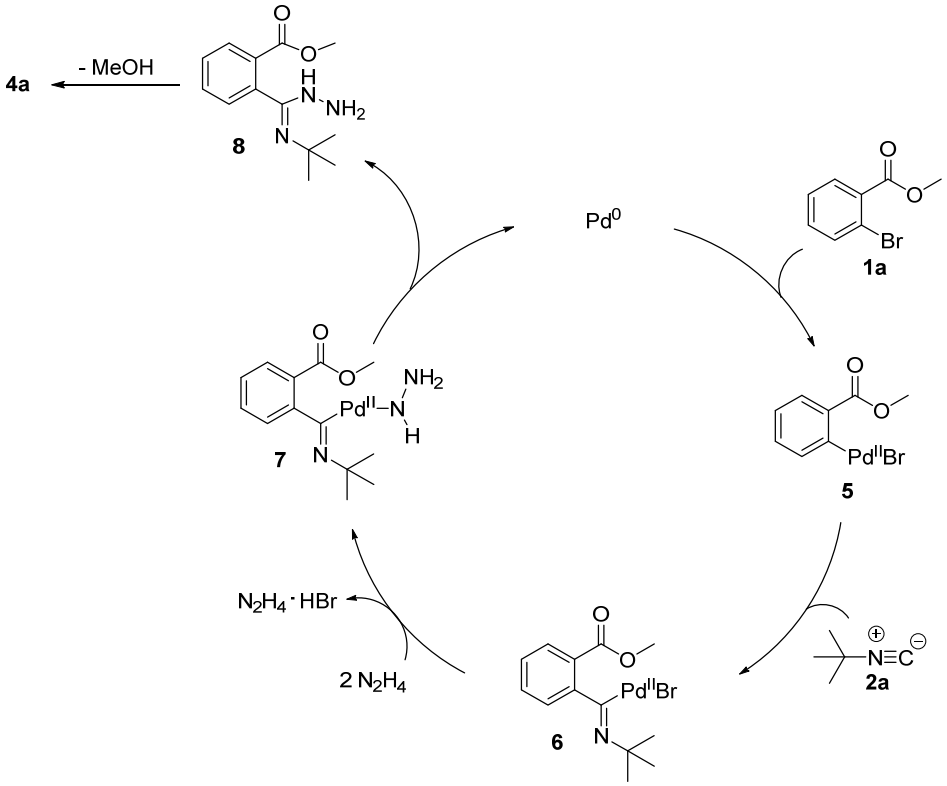
Table 5. Substrate scope with different hydrazines.[a]



[a] Conditions: $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %), *i*Pr_2NH (1.5 mmol), ArX (**1**, 0.50 mmol), *tert*-butyl isocyanide (**2a**, 0.75 mmol), hydrazine derivative (**3**, 1.25 mmol) in DMSO (2.5 mL), 5 min at 150 °C (μW). Yields refer to isolated products.

A plausible mechanism for the three-component reaction toward APOs is depicted in Scheme 3. Oxidative addition of **1a** to the Pd^0 catalyst followed by isocyanide insertion leads to palladium species **6**. Coordination of hydrazine to Pd^{II} and subsequent deprotonation followed by reductive elimination provides intermediate **8**, which cyclizes and tautomerizes under the reaction conditions to form product **4a**. Alternatively, hydrazide formation by hydrazinolysis of the ester functional group may occur first. This is, however, not in accordance with the

observed reaction products when phenylhydrazines are used as reactants. Furthermore, only trace amounts of the hydrazide are formed in the absence of a palladium catalyst (Table 1, entry 8). It is therefore highly unlikely that hydrazide formation occurs prior to the isocyanide insertion reaction.



Scheme 3. Proposed mechanism of the reaction (ligands on Pd are omitted for clarity).

3.3 Conclusion

We have developed a fast and efficient palladium-catalyzed MCR towards 4-aminophthalazin-1(*2H*)-ones using a simple commercially available catalyst. A wide range of methyl 2-(pseudo)halidebenzoates are readily converted, among which are important groups for medicinal applications (*e.g.* CF_3, F and morpholino) and substituents that allow further functionalization (*e.g.* Cl and NH_2). The work described in this Chapter is the first synthetic method that allows straightforward regioselective introduction of substituents on the phenyl ring of APOs. It should therefore find applications in medicinal chemistry when substituent patterns are required that were previously inaccessible. Our method represents the first example of a multicomponent reaction combining isocyanides and free hydrazines as well as one of the few palladium-catalyzed reactions using unprotected hydrazines as reactants. The scope with regard to the hydrazine and isocyanide inputs is unfortunately limited. Chapter 4 will provide an overview of our efforts to overcome these limitations by follow-up chemistry that allows diversification of the APO scaffold.

3.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as received. Palladium acetate and XantPhos were obtained from Sigma Aldrich or Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled before use. Diisopropylamine was distilled before use and stored in a Schlenk under inert atmosphere. All other compounds were stored under normal atmosphere. THF and toluene were distilled from appropriate drying agents before use, other anhydrous solvents were obtained from Sigma Aldrich. Non-commercial starting materials were prepared as described below or according to literature procedures: compound **1i** was prepared from the corresponding nitro compound[10] and triflates **1a** (X = OTf), **1g** (**1p**), **1f** (**1o**) and **1e** were synthesized from the corresponding phenols.[11] The microwave reactions were performed in a sealed vessel using either a CEM Discover or a Biotage Initiator Plus and the reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature. GC yield and conversion analysis was performed using a Supelco Equity capillary column (30m x 0.25 mm). Melting points were measured using a Stuart Scientific SMP3 or a Büchi M-565 melting point apparatus. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 400 or 500 (100.62 or 125.78 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, $^{13}C\{^{1}H\}$: δ 77.16 ppm for $CDCl_3$ and ^{1}H: δ 2.50 ppm, $^{13}C\{^{1}H\}$: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz. Electrospray Ionisation (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 or 366 nm).

X-ray data

The crystallographic information file (CIF) for compound **4b** is available free of charge via the internet at http://pubs.acs.org. We thank Dr. Madeleine Helliwell (University of Manschester) for the X-ray crystal structure determination.

Synthesis of substrates

methyl 2-bromo-4-fluorobenzoate (1c):
2-Bromo-4-fluorobenzoic acid (4.38 g, 20 mmol, 1 eq.) and dry MeOH (60 mL) were added to a three-necked flask under N_2 atmosphere. The solution was cooled to 0 °C and $SOCl_2$ (2.9 mL, 40 mmol, 2 eq.) was added. The mixture was refluxed for 100 min. and then concentrated *in vacuo*. The residue was dissolved in DCM and washed twice with $NaHCO_3$ (aq. sat.). The organic layer

was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 4.30 g of a colorless oil. (92%). TLC (cyclohexane/EtOAc, 20:1 v/v): R_f = 0.31; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, J = 8.8, 6.0 Hz, 1H), 7.41 (dd, J = 8.3, 2.5 Hz, 1H), 7.08 (m, 1H), 3.92 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7 (C), 164.0 (d, *J* = 257 Hz, C), 133.5 (d, *J* = 9.3 Hz, CH), 128.1 (d, *J* = 3.5 Hz, C), 123.3 (d, *J* = 10 Hz, C), 122.0 (d, *J* = 24.6 Hz, CH), 114.7 (d, *J* = 21.4 Hz, CH), 52.7 (CH_3) ppm. IR (neat) : νmax (cm^{-1}) = 1732 (m), 1595 (m), 1433 (m), 1286 (m), 1109 (s).

methyl 2-bromo-5-(trifluoromethyl)benzoate (1d):

A solution of 2-bromo-5-(trifluoromethyl)benzoic acid[12] (1.93 g, 7.1 mmol, 1 eq.) in dry MeOH (22.5 mL) under N_2 atmosphere was cooled to 0 °C**.** $SOCl_2$ (1.09 mL, 15 mmol, 2.1 eq.) was slowly added and then the mixture was refluxed for 5 hours. The reaction mixture was concentrated *in vacuo*, dissolved in DCM, washed twice with $NaHCO_3$ (aq. sat.) and dried (Na_2SO_4). Purification by flash chromatography using cyclohexane/EtOAc (50:1 > 1:9) afforded 1.88 g of a yellow oil (93%). TLC (cyclohexane/EtOAc, 50:1 v/v): R_f = 0.20; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.05 (d, *J* = 2.1 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 2.3, 8.4 Hz, 1H), 3.89 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.9 (C), 135.2 (CH), 133.3 (C), 129.3 (q, J = 3.4 Hz, CH), 128.5 (q, J = 32.9 Hz, C), 127.4 (q, J = 3.7 Hz, CH), 124.9 (C), 123.3 (q, J = 273 Hz, C), 52.9 (CH_3) ppm; IR (neat) : νmax (cm^{-1}) =1735 (s), 1334 (s), 1245 (s), 1172 (s), 1122 (s), 1080 (s) 1029 (s), 968 (s) 833(s) 779 (m).

methyl 2-bromo-4-morpholinobenzoate (1j):

Methyl 2-bromo-4-fluorobenzoate (**1c**, 2.32 g, 10 mmol, 1 eq.) and morpholine (4.37 mL, 50 mmol, 5 eq.) were dissolved in DMSO (10 mL) and the solution was stirred at 120 °C for 140 minutes. Subsequently, the reaction mixture was partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography using EtOAc/cyclohexane (1:3) afforded 2.73 g of an off-white solid (91%). TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.38; m.p.: 75.5-76.5 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.87 (s, 3H), 3.84 (t, *J* = 5.0 Hz, 4H), 3.27 (t, *J* = 5.0 Hz, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0 (CH), 153.7 (CH), 133.4 (C), 124.4 (CH), 120.5 (CH), 119.8 (C), 112.5 (C), 66.6 (CH_2), 52.1 (CH_3), 47.6 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 1693 (s), 1599 (s), 1433 (m), 1302 (s), 1236 (s), 1111 (s), 760 (s). HRMS (ESI): m/z calculated for $C_{12}H_{14}NO_3BrNa$ (M+Na) 322.0049, found 322.0035.

methyl 2-bromo-4-((4-fluorobenzyl)amino)benzoate (1k):

Methyl 2-bromo-4-fluorobenzoate (**1c**, 1.16 g, 5 mmol, 1 eq.), 4-fluorobenzylamine (0.86 mL, 7.5 mmol, 1.5 eq.) and triethylamine (1.4 mL, 10 mmol, 2 eq.) were dissolved in dry DMSO (10 mL). The reaction mixture was stirred at 120 °C for 5 hours, then cooled and partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography using EtOAc/cyclohexane (1:9 > 1:1) gave 1.15 g of an off-white solid (74%). TLC (EtOAc/cyclohexane, 1:3 v/v): R_f = 0.59; m.p.: 73.6-74.9 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65 (d, *J* = 8.8 Hz, 1H), 7.39-7.35 (m, 2H), 7.27 (t, *J* = 6.0 Hz, 1H), 7.19-7.14 (m, 2H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.61 (dd, *J* = 2.3, 8.8 Hz, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.72 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.1 (C), 161.3 (d, *J* = 243 Hz, C), 152.4 (C), 135.0 (d, *J* =

2.7 Hz, C), 133.3 (CH), 129.2 (d, *J* = 8.2 Hz, CH), 123.3 (C), 116.8 (CH), 116.1 (C), 115.2 (d, *J* = 21.5 Hz, CH), 110.6 (CH), 51.6 (CH_3), 44.9 (CH_2) ppm; IR (neat) : νmax (cm^{-1}) = 3354 (m), 1678 (s), 1585 (m), 1508 (s), 1433 (s), 1290 (m), 1217 (s), 1026 (m), 819 (s), 764 (m), 690 (s); HRMS (ESI): m/z calculated for $C_{15}H_{14}BrFNO_2$ (M+H) 338.0186, found 338.0180.

General synthetic procedures

Optimization of the MCR towards 4-(*tert*-butylamino)phthalazin-1(*2H*)-one (4a):
A microwave tube was flame dried under a flow of argon before addition of the palladium source and ligand. Dry solvent (2.5 mL) was added to the catalyst and the resulting mixture was stirred. Subsequently, *tert*-butyl isocyanide (85 µL, 0.75 mmol, 1.5 eq.), methyl *o*-bromobenzoate (70 µL, 0.5 mmol, 1 eq.) and hydrazine monohydrate (51 µL, 1.05 mmol, 2.1 eq.) were added in this order. The tube was then placed in the microwave reactor and heated at 150 °C for the indicated time. Afterwards, the reaction mixture was diluted with EtOAc (2.5 mL) to ensure complete solution of product and dodecane (114 µL, 1 eq.) was added. A sample of the mixture was filtered and subjected to GC analysis to determine yield and conversion.

Base screening for the Pd-catalyzed MCR towards 4-(*tert*-butylamino)-2-phenylphthalazin-1(*2H*)-one (4n):
A microwave tube charged with the base (if solid) was flame dried under a flow of argon before addition of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 2 mol %) and XantPhos (11.6 mg, 0.02 mmol, 4 mol %). Dry DMSO (2.5 mL) was added to the catalyst, followed by the base (if liquid), and the resulting mixture was stirred. Subsequently, *tert*-butyl isocyanide (85 µL, 0.75 mmol, 1.5 eq.), methyl *o*-bromobenzoate (70 µL, 0.5 mmol, 1 eq.) and phenylhydrazine (63 µL, 0.65 mmol, 1.3 eq.) were added in this order. The tube was then placed in the microwave reactor and heated at 150 °C for 5 minutes. Afterwards, the reaction mixture was diluted with EtOAc (2.5 mL) to ensure complete solution of the product and then dodecane (114 µL, 1eq.) was added. A sample of the mixture was filtered and subjected to GC analysis to determine yield and conversion.

General procedure 1: the Pd-catalyzed MCR towards 4-aminophthalazin-1(2*H*)-ones with hydrazine monohydrate:
A microwave tube was flame dried under a flow of argon before addition of Pd(OAc)2 (2.2 mg, 0.01 mmol, 2 mol %) and XantPhos (11.6 mg, 0.02 mmol, 4 mol %). Dry DMSO (2.5 mL) was added to the catalyst and the resulting mixture was stirred. Subsequently, isocyanide (0.75 mmol, 1.5 eq.), methyl benzoate (0.5 mmol, 1 eq.) and hydrazine monohydrate (51 µL, 1.05 mmol, 2.1 eq.) were added in this order. The tube was then placed in the microwave reactor and heated at 150 °C for 5 minutes. The crude reaction mixture was filtered through a short plug of silica (EtOAc) and then concentrated *in vacuo*. Remaining DMSO was removed by freeze drying. The crude product was purified by flash chromatography using the eluent specified below.

General procedure 2: the Pd-catalyzed MCR towards 4-aminophthalazin-1(2*H*)-ones using substituted hydrazines:
A microwave tube was flame dried under a flow of argon before addition of Pd(OAc)2 (2.2 mg, 0.01 mmol, 2 mo l%) and XantPhos (11.6 mg, 0.02 mmol, 4 mol %). Dry DMSO (2.5 mL) was

added to the catalyst, followed by *i*Pr$_2$NH (210 µL, 1.5 mmol, 3 eq.). The resulting mixture was stirred and subsequently *tert*-butyl isocyanide (85 µL, 0.75 mmol, 1.5 eq.), methyl benzoate (0.5 mmol, 1 eq.) and the hydrazine derivative (1.25 mmol, 2.5 eq.) were added in this order. The tube was then placed in the microwave reactor and heated to 150 °C for 5 minutes. The crude reaction mixture was filtered through a short plug of silica (EtOAc) and then concentrated *in vacuo*. Remaining DMSO was removed by freeze drying. The crude product was purified by flash chromatography using the eluent specified below.

Spectral data

4-(*tert*-butylamino)phthalazin-1(*2H*)-one (4a):

Prepared from methyl *o*-bromobenzoate according to general procedure 1. Purification: EtOAc/cyclohexane (2:1) + 2% Et$_3$N. Isolated as an off-white solid. Yield: 107 mg, 98%.

Alternatively methyl 2-(trifluoromethylsulfonyloxy)benzoate (134 mg; yield: 89%), methyl *o*-iodobenzoate (76 µL; yield: 99%) or methyl *o*-chlorobenzoate (72 µL; yield: 29%) were used instead of methyl *o*-bromobenzoate. TLC (EtOAc/cyclohexane, 2:1 v/v): R_f = 0.42; m.p.: 182.2-185.6 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.45 (d, *J* = 7.3 Hz, 1H), 7.74 (t, *J* = 6.9 Hz, 1H), 7.69 (t, *J* = 7.1 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 4.36 (br, 1H), 1.47 (s, 9H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.3 (C), 144.1 (C), 132.9 (CH), 130.8 (CH), 128.7 (C), 127.5 (CH), 126.0 (C), 121.4 (CH), 51.7 (C), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2916 (m), 1632 (m), 1585 (s), 1524 (s), 1446 (m), 1346 (m), 1219 (s), 764 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{16}N_3O$ (M+H) 218.1288, found 218.1279.

4-(*tert*-butylamino)-7-chlorophthalazin-1(*2H*)-one (4b):

Prepared from methyl 2-bromo-5-chlorobenzoate according to general procedure 1 but only 2 minutes reaction time. Purification: EtOAc/cyclohexane (1:2 to 1:1) + 2% Et$_3$N. Isolated as an off-white solid. Yield: 101 mg, 80%. TLC (EtOAc/cyclohexane, 1:2 v/v): R_f = 0.26; m.p.: 193.7-199.5 °C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.88 (dd, *J* = 2.4, 8.7 Hz, 1H), 5.84 (br, 1H), 1.40 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 156.4 (C), 143.6 (C), 135.9 (C), 132.6 (CH), 130.0 (C), 126.3 (CH), 125.3 (CH), 124.5 (C), 51.0 (C), 28.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3155 (m), 2962 (m), 2901 (m), 1655 (s), 1585 (s), 1516 (m), 1219 (s), 818 (s), 660 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{15}ClN_3O$ (M+H) 252.0898, found 252.0893.

4-(*tert*-butylamino)-6-fluorophthalazin-1(2*H*)-one (4c):

Prepared from methyl 2-bromo-4-fluorobenzoate (**1c**) according to general procedure 1. Purification: EtOAc/cyclohexane (1:2 to 1:1). Isolated as a yellow solid. Yield: 44 mg, 37%. TLC (EtOAc/cyclohexane, 1:2 v/v): R_f = 0.19; m.p.: 210.2-212.2 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.63 (s, 1H), 8.26 (dd, *J* = 6.0, 9.0 Hz, 1H), 8.06 (dd, *J* = 2.0, 10.5 Hz, 1H), 7.64 (dt, *J* = 2.5, 9.0 Hz, 1H), 5.78 (s, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.6 (d, *J* = 250 Hz, C), 156.8 (C), 143.3 (d, *J* = 2.5 Hz, C), 129.8 (d, *J* = 8.8 Hz, CH), 128.1 (d, *J* = 8.8 Hz, C), 125.3 (d, *J* = 1.3 Hz, C), 119.1 (d, *J* = 22.6 Hz, CH), 109.5 (d, *J* = 23.9 Hz, CH), 51.0 (C), 28.6 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 1620 (m), 1585 (s), 1528 (s), 1443 (m), 1346 (m), 1215 (m),

1142 (s), 841 (s), 771 (s); HRMS (ESI): m/z calculated for $C_{12}H_{15}FN_3O$ (M+H) 236.1194, found 236.1192.

4-(*tert*-butylamino)-7-(trifluoromethyl)phthalazin-1(2*H*)-one (4d):
Prepared from methyl 2-bromo-5-(trifluoromethyl)benzoate (**1d**) according to general procedure 1. Purification: EtOAc/cyclohexane/Et_3N (10:90:2 > 33:66:2). Isolated as a yellow solid. Yield: 61 mg, 42%. TLC (EtOAc/cyclohexane/Et_3N, 25:75:2 v/v/v): R_f = 0.42; m.p.: 200.0-202.2 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.88 (s, 1H), 8.44-8.40 (m, 2H), 8.22 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.00 (s, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.6 (C), 143.3 (C), 130.7 (q, *J* = 32.8 Hz, C), 128.8 (C), 128.7 (q, *J* = 3.5 Hz, CH), 128.5 (C), 125.6 (CH), 123.6 (q, *J* = 273 Hz, C), 123.1 (q, *J* = 4.0 Hz, CH), 51.1 (C), 28.5 (CH_3) ppm; IR (neat): ν_{max} (cm^{-1}) = 1659 (s), 1593 (s), 1528 (s), 1319 (s), 1126 (m), 926 (s), 829 (s), 725 (m), 652 (s); HRMS (ESI): m/z calculated for $C_{13}H_{14}F_3N_3NaO$ (M+Na) 308.0981, found 308.0954.

4-(*tert*-butylamino)benzo[*g*]phthalazin-1(*2H*)-one (4e):
Prepared from 3-carbomethoxy-2-naphthyl trifluoromethanesulfonate according to general procedure 1. Purification: EtOAc/cyclohexane (1:2 > 1:1) + 2% Et_3N. Isolated as a neon yellow solid. Yield: 132 mg, 99%. TLC (EtOAc/cyclohexane/Et_3N, 50:50:1 v/v/v): R_f = 0.31; m.p.: 281.0-282.8 °C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.42 (s, 1H), 8.87 (s, 1H), 8.78 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.75 (dt, *J* = 1.4, 8.3 Hz, 1H), 7.71 (dt, *J* = 1.3, 8.2 Hz, 1H), 5.92 (s, 1H), 1.49 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 157.7 (C), 143.9 (C), 134.3 (C), 133.0 (C), 129.1 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.1 (CH), 125.2 (C), 123.5 (CH), 122.6 (C), 51.0 (C), 28.8 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3198 (w), 2924 (m), 1628 (s), 1531 (s), 1223 (s), 744 (s), 471 (s); HRMS (ESI): *m/z* calculated for $C_{16}H_{18}N_3O$ (M+H) 268.1444, found 268.1431.

4-(*tert*-butylamino)-6-methylphthalazin-1(*2H*)-one (4f):
Prepared from methyl 2-trifluoromethanesulphonyloxy-4-methylbenzoate according to general procedure 1. Purification: EtOAc/cyclohexane (1:1) + 2% Et_3N. Isolated as an off-white solid. Yield: 110 mg, 95%. TLC (EtOAc/cyclohexane, 1:1 v/v): R_f = 0.31; m.p.: 222.4-223.4 °C (decomposed); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.31 (s, 1H), 4.22 (br, 1H), 2.55 (s, 3H), 1.48 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 157.6 (C), 143.8 (C), 142.9 (C), 131.9 (CH), 126.1 (CH), 126.1 (C), 125.8 (C), 123.2 (CH), 50.8 (C), 28.7 (CH_3), 21.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3155 (m), 3001 (m), 2897 (m), 1643 (s), 1582 (s), 1512 (m), 1450 (m), 690 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O$ (M+H) 232.1444, found 232.1437.

4-(*tert*-butylamino)-5-methoxyphthalazin-1(*2H*)-one (4g):
Prepared from methyl 2-trifluoromethanesulphonyloxy-3-methoxybenzoate according to general procedure 1. Purification: EtOAc/cyclohexane (3:1) + 2% Et_3N. Yield: 123 mg, 99%. TLC (EtOAc/cyclohexane, 3:1 v/v): R_f = 0.32; m.p.: 238.8-240.2 °C (decomposed); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.85 (d, *J* = 7.3 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 4.00 (s, 3H), 1.41 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 156.5 (C), 155.5 (C), 143.6 (C), 131.9 (CH), 130.5 (C), 118.8 (CH), 115.4 (CH), 114.9 (C), 56.9 (CH_3), 50.4 (C), 28.6

(CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3437 (m), 2912 (m), 1647 (s), 1589 (s), 1520 (s), 1045 (m), 760 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O_2$ (M+H) 248.1394, found 248.1389.

4-(*tert*-butylamino)-7-methoxyphthalazin-1(*2H*)-one (4h):
Prepared from methyl 2-bromo-5-methoxybenzoate according to general procedure 1. Purification: EtOAc/cyclohexane (2:1 > 9:1) + 2% Et_3N. Isolated as an off-white solid. Yield: 123 mg, 99%. TLC (EtOAc/cyclohexane/Et_3N, 66:33:2 v/v/v): R_f = 0.33; m.p.: 153.4-155.4 °C (decomposed); ^1H NMR (500 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.27 (dd, *J* = 2.8, 8.9 Hz, 1H), 4.27 (br, 1H), 3.90 (s, 3H), 1.45 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.5 (C), 159.2 (C), 144.4 (C), 130.5 (C), 123.4 (CH), 122.7 (CH), 119.7 (C), 107.6 (CH), 55.9 (CH_3), 51.7 (C), 29.1 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2920 (m), 1647 (m), 1593 (m), 1489 (s), 1366 (s), 1215 (s), 1030 (m), 694 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O_2$ (M+H) 248.1394, found 248.1373.

7-amino-4-(*tert*-butylamino)phthalazin-1(*2H*)-one (4i):
Prepared from methyl 2-bromo-5-aminobenzoate according to general procedure 1. Silica filtration using EtOAc/MeOH (4:1). Purification: EtOAc + 2% Et_3N. Isolated as a yellow solid. Yield: 87 mg, 75%. TLC (EtOAc): R_f = 0.21; m.p.: 266.8-268.5 °C (decomposed); ^1H NMR (500 MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 2.5, 8.7 Hz, 1H), 5.95 (s, 2H), 5.33 (s, 1H), 1.40 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 157.8 (C), 151.1 (C), 144.5 (C), 130.0 (C), 124.9 (CH), 119.0 (CH), 114.9 (C), 107.1 (CH), 50.6 (C), 28.9 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3348 (m), 3236 (m), 2966 (m), 1655 (m), 1589 (s), 1551 (s), 1447 (s), 1223 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{17}N_4O$ (M+H) 233.1397, found 233.1390.

4-(*tert*-butylamino)-6-morpholinophthalazin-1(2*H*)-one (4j):
Prepared from methyl 2-bromo-4-morpholinobenzoate (**1j**) according to general procedure 1 but with 15 minutes reaction time. Purification: EtOAc/MeoH (19:1). Isolated as an off-white solid. Yield: 145 mg, 96%. TLC (EtOAc/MeOH, 95:5 v/v): R_f = 0.44; m.p.: >230 °C (decomposition); ^1H NMR (500 MHz, DMSO-d_6): δ 11.24 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.37 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 5.62 (s, 1H), 3.78 (t, *J* = 4.5 Hz, 4H), 3.37 (t, *J* = 4.5 Hz, 4H), 1.43 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.6 (C), 153.7 (C), 143.6 (C), 127.6 (CH), 127.2 (C), 119.4 (C), 117.6 (CH), 105.6 (CH), 65.9 (CH_2), 50.8 (C), 47.2 (CH_2), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3375 (m), 3140 (m), 2955 (m), 2851 (m), 1636 (s), 1528 (s), 1238 (s), 1041 (s); HRMS (ESI): m/z calculated for C16H23N4O2 (M+H) 303.1816, found 303.1801.

4-(*tert*-butylamino)-6-((4-fluorobenzyl)amino)-phthalazin-1(2*H*)-one (4k):
Prepared from methyl 2-bromo-4-((4-fluorobenzyl)amino)benzoate (**1k**) according to general procedure 1 but with 15 minutes reaction time. Purification: EtOAc/cyclohexane/MeOH/Et_3N (2:1:0:0 > 93:0:5:3). Isolated as an off-white solid. Yield: 153 mg, 90%. TLC (EtOAc/cyclohexane, 2:1 v/v): R_f = 0.11; m.p.: 181.2-185.2 °C (decomposition); ^1H NMR (400 MHz, DMSO-d_6): δ 11.05 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 5.6, 8.4 Hz, 2H), 7.16 (t, *J* = 8.8 Hz, 2H) 7.08 (t, *J* = 5.6 Hz, 1H), 7.00 (dd, *J* = 2.0, 8.8 Hz , 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 5.23 (s, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 1.41 (s, 9H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.3 (d, *J* = 243

Hz, C), 157.8 (C), 152.0 (C), 143.4 (C), 135.4 (d, *J* = 2.5 Hz, C), 129.5 (d, *J* = 8.8 Hz, CH), 127.7 (C), 127.4 (CH), 117.4 (C), 117.2 (CH), 115.1 (d, *J* = 20.1 Hz, CH), 101.6 (CH), 50.7 (C), 45.3 (CH_2), 28.8 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2961 (w), 2922 (w), 1636 (m), 1610 (s), 1589 (s), 1529 (s), 1506 (s), 1448 (s), 1385 (m), 1346 (m), 1296 (w), 1261 (s), 1213 (s), 1155 (m), 1107 (w), 1028 (w), 1014 (w), 822 (s), 708 (m); HRMS (ESI): m/z calculated for $C_{19}H_{22}FN_4O$ (M+H) 341.1772, found 341.1753.

4-(*tert*-butylamino)pyrido[4,3-*d*]pyridazin-1(2*H*)-one (4l):

Prepared from 3-bromopyridine-4-carboxylic acid methyl ester. Purification: EtOAc/cyclohexane (1:2). isolated as an off-white solid. Yield: 91 mg, 84%. TLC (EtOAc/cyclohexane, 2:1 v/v): R_f = 0.21; m.p.: 218.0-220.2 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.86 (s, 1H), 9.50 (s, 1H), 8.94 (d, *J* = 4.8 Hz, 1H), 8.02 (t, *J* = 4.8 Hz, 2H), 6.07 (s, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.1 (C), 150.5 (CH), 147.2 (CH), 143.0 (C), 133.6 (C), 120.1 (C), 118.3 (CH), 51.1 (C), 28.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3321 (w), 2968 (w), 2907 (w), 1653 (s), 1616 (m), 1580 (s), 1553 (s), 1528 (s), 1448 (s), 1421 (m), 1387 (w), 1358 (w), 1333 (m), 1219 (s), 1178 (m), 1038 (m), 851 (s), 771 (m); HRMS (ESI): m/z calculated for $C_{11}H_{15}N_4O$ (M+H) 219.1240, found 219.1254.

4-((2,4,4-trimethylpentan-2-yl)amino)phthalazin-1(2*H*)-one (4m):

Prepared from methyl *o*-bromobenzoate according to general procedure 1. Purification: EtOAc/cyclohexane (1:1) + 2% Et_3N. Isolated as a light yellow solid. Yield: 87 mg, 64%. TLC (EtOAc/cyclohexane/Et_3N, 50:50:2 v/v/v): R_f = 0.45; m.p.: 157.4-159.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.46 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 4.35 (s, 1H), 1.87 (s, 2H), 1.52 (s, 6H), 1.00 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.1 (C), 144.0 (C), 133.0 (CH), 130.8 (CH), 128.8 (C), 127.7 (CH), 126.1 (C), 121.2 (CH), 55.7 (C), 51.5 (C), 31.9 (CH_2), 31.7 (CH_3), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2947 (m), 1647 (s), 1585 (s), 1528 (s), 1474 (s), 1350 (m), 1227 (s), 775 (s), 683 (s), 633 (s); HRMS (ESI): *m/z* calculated for $C_{16}H_{24}N_3O$ (M+H) 274.1914, found 274.1909.

4-(*tert*-butylamino)-2-phenylphthalazin-1(2*H*)-one (4n):

Prepared from methyl *o*-bromobenzoate according to general procedure 2. Purification: EtOAc/cyclohexane (1:3) + 2% Et_3N. Isolated as an off-white solid. Yield: 93 mg, 63%. TLC (EtOAc/cyclohexane, 1:3 v/v): R_f = 0.23; m.p.: 169.6-171.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.4 Hz, 1H), 7.79-7.74 (m, 4H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 4.36 (br, 1H), 1.51 (s, 9H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.6 (C), 143.3 (C), 142.8 (C), 132.8 (CH), 131.2 (CH), 129.6 (C), 128.6 (CH), 128.5 (CH), 126.7 (CH), 125.4 (CH), 125.4 (C), 121.0 (CH), 51.9 (C), 29.2 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3526 (m), 3348 (w), 1620 (w), 1535 (s), 1350 (s), 1223 (s), 687 (s); HRMS (ESI): *m/z* calculated for $C_{18}H_{20}N_3O$ (M+H) 294.1601, found 294.1591.

4-(*tert*-butylamino)-6-methyl-2-phenylphthalazin-1(2*H*)-one (4o):

Prepared from methyl 2-trifluoromethanesulphonyloxy-4-methylbenzoate according to general procedure 2. Purification: DCM/cyclohexane (4:1) + 2% Et_3N. The resulting solid was further purified by trituration (Et_2O). Isolated as an off-white solid. Yield: 96 mg, 62%. TLC (DCM/cyclohexane/Et_3N, 80:20:2 v/v/v): R_f = 0.34; m.p.: 239.4-240.6 °C (decomposed); ^{1}H

NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.34 (s, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 4.34 (s, 1H), 2.54 (s, 3H), 1.51 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6 (C), 143.6 (C), 143.2 (C), 142.8 (C), 132.4 (CH), 128.5 (CH), 128.4 (CH), 127.3 (C), 126.5 (CH), 125.5 (C), 125.3 (CH), 121.0 (CH), 51.8 (C), 29.2 (CH_3), 22.2 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3306 (s), 1632 (s), 1556 (s), 1531 (s), 1489 (m), 1447 (m), 1342 (s), 1227 (s); HRMS (ESI): *m/z* calculated for $C_{19}H_{22}N_3O$ (M+H) 308.1757, found 308.1735.

4-(*tert*-butylamino)-5-methoxy-2-phenylphthalazin-1(*2H*)-one (4p):

Prepared from methyl 2-trifluoromethanesulphonyloxy-3-methoxybenzoate according to general procedure 2. Purification: EtOAc/cyclohexane (1:2 > 3:1) + 2% Et_3N. Additional flash chromatography using DCM/cyclohexane/EtOAc (2:1:0 > 4:1:0 > 4:0:1) + 2% Et_3N as eluent was required. Isolated as a yellow solid. Yield: 47 mg, 29%. TLC (EtOAc/cyclohexane/Et_3N, 33:66:2 v/v/v): R_f = 0.29; m.p.: 169.9-171.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 4.01 (s, 3H), 1.48 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 156.5 (C), 155.7 (C), 143.9 (C), 142.9 (C), 131.9 (C), 131.6 (CH), 128.3 (CH), 126.4 (CH), 125.2 (CH), 121.0 (CH), 115.5 (C), 114.5 (CH), 56.6 (CH_3), 51.2 (C), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3414 (s), 2962 (m), 1659 (m), 1585 (s), 1524 (s), 1312 (m), 1261 (s), 1223 (m), 1041 (s), 750 (s), 690 (s); HRMS (ESI): *m/z* calculated for $C_{19}H_{22}N_3O_2$ (M+H) 324.1707, found 324.1689.

4-(*tert*-butylamino)-2-(4-(trifluoromethyl)phenyl)phthalazin-1(*2H*)-one (4q):

Prepared from methyl *o*-bromobenzoate according to general procedure 2. Purification: DCM/cyclohexane (9:1) + 2% Et_3N. The product was additionally purified by recrystallization from toluene. Isolated as a yellow/green solid. Yield: 67 mg, 37%. TLC (DCM/cyclohexane/Et_3N, 90:10:2 v/v/v): R_f = 0.56; m.p.: 159.4-162.7 °C (decomposed); ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 1.3, 7.7 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.83-7.76 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 4.42 (s, 1H), 1.52 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.7 (C), 145.6 (C), 143.6 (C), 133.2 (CH), 131.4 (CH), 129.5 (C), 128.7 (CH), 128.2 (q, *J* = 32.6 Hz, C), 125.6 (q, *J* = 3.8 Hz, CH), 125.4 (C), 125.5 (CH), 124.3 (q, *J* = 272.8 Hz, C), 121.1 (CH), 51.9 (C), 29.2 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2959 (m), 2924 (m), 1647 (m), 1582 (m), 1531 (m), 1319 (s), 1122 (s), 833 (m), 687 (s); m.p.: 159.4-162.7 °C (decomposed); HRMS (ESI): *m/z* calculated for $C_{19}H_{19}F_3N_3O$ (M+H) 362.1475, found 362.1478.

4-(*tert*-butylamino)-2-methylphthalazin-1(*2H*)-one (4r):

Prepared from methyl *o*-bromobenzoate according to general procedure 2. Purification: EtOAc/cyclohexane (1:2) + 2% Et_3N. Isolated as an off-white solid. Yield: 35 mg, 30%. TLC (EtOAc/cyclohexane, 1:2 v/v): R_f = 0.24; m.p.: 154.9-155.9 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.47-8.46 (m, 1H), 7.73-7.70 (m, 2H), 7.53-7.52 (m, 1H), 4.25 (br, 1H), 3.73 (s, 3H), 1.50 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6 (C), 143.0 (C), 132.2 (CH), 130.9 (CH), 128.9 (C), 127.8 (CH), 125.4 (C), 121.0 (CH), 51.8 (C), 39.2 (CH_3), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3475 (m), 3356 (m), 2885 (m), 1620 (m), 1528 (s), 1358 (s), 1223 (s), 683 (m); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O$ (M+H) 232.1444, found 232.1441.

3.5 References

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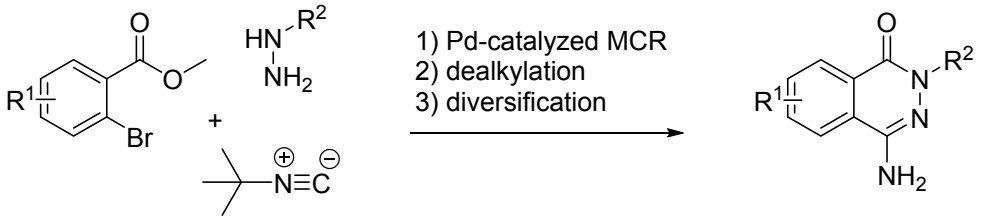
Chapter 4

4-Aminophthalazin-1(2*H*)-ones:

Follow-up Chemistry and Scaffold Diversification



***Abstract**: The limitations in the substrate scope of the Pd-catalyzed imidoylative synthesis of APOs can be overcome by acidic removal of the tert-butyl group and subsequent regioselective diversification of the product. In addition, a novel heterocyclic scaffold can be accessed by using the dealkylated APOs in the Groebke-Bienaymé-Blackburn reaction.*

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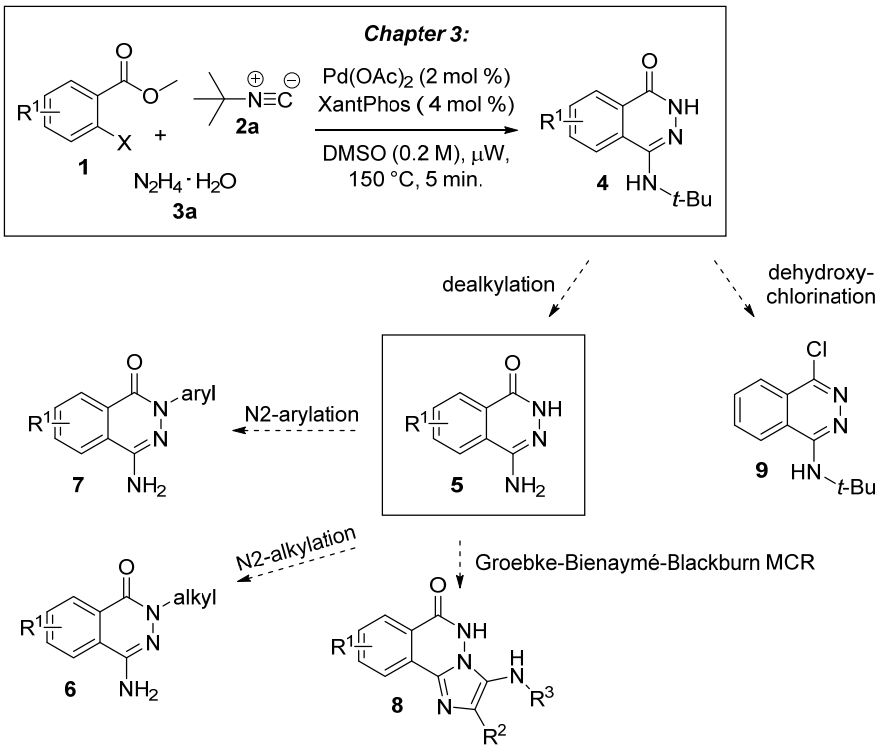
4.1 Introduction

A novel MCR towards 4-aminophthalazin-1(2*H*)-ones (APOs, **4**) using a Pd-catalyzed isocyanide insertion was presented in Chapter 3 (Scheme 1). Unfortunately, the reaction was limited to tertiary aliphatic isocyanides and substituted hydrazines only gave low yields under modified reaction conditions. In order to overcome these limitations we wondered if the *tert*-butyl group could be removed from the product to form the corresponding free amines (**5**). Essentially, *tert*-butyl isocyanide then serves as a convertible CN source and potentially as a transient protective group for the exocyclic amino group. We expected the unfunctionalized products (**5**) can be selectively decorated on the N2-position as it is much more acidic than the C4-amino group. A two- or three-step sequence that selectively introduces substituents on *all* positions of the APO scaffold is thereby attained. Furthermore, we explored additional follow-up chemistry on the APO scaffold, such as dehydroxychlorination to obtain **9** and a Groebke-Bienaymé-Blackburn MCR furnishing an hitherto unexplored scaffold (**8**) in just two steps from commercially available compounds.

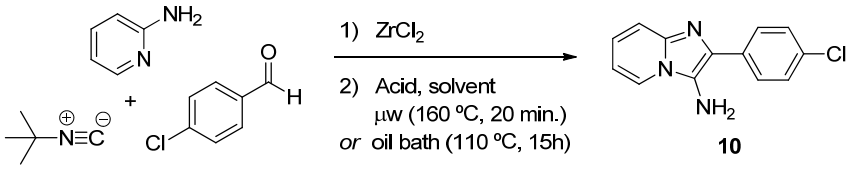


Scheme 1. Follow-up chemistry on the APO scaffold.

4.2 Results and Discussion

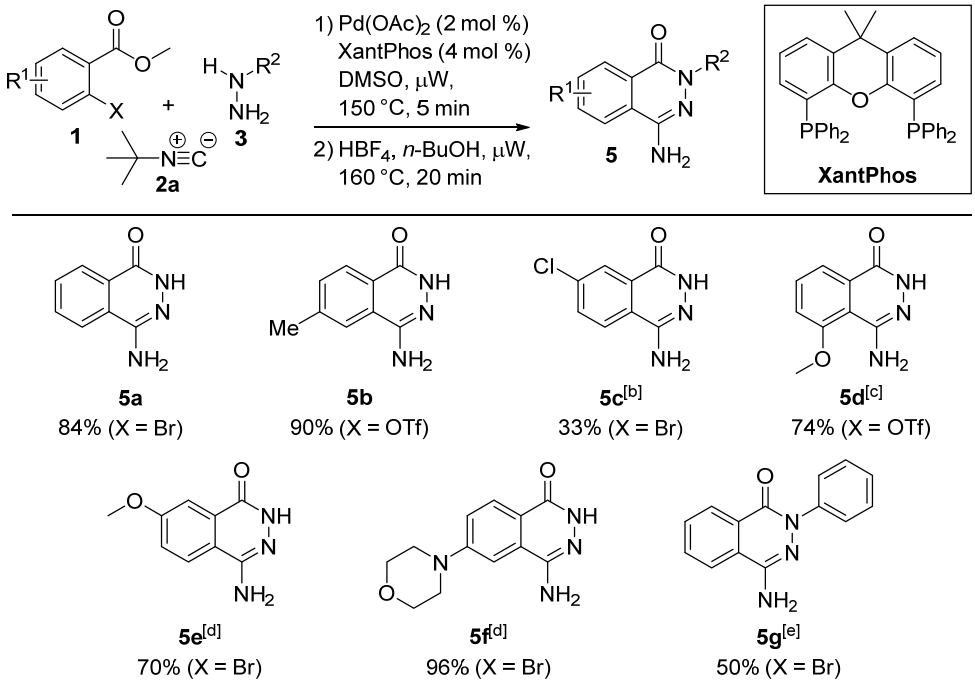
The group of Guchhait has studied the removal of *tert*-butyl groups from aromatic amines using various Brønsted acids (Table 1).[1] In their studies, they combined the Groebke-Bienaymé-Blackburn MCR with dealkylation in a one-pot fashion affording imidazo[1,2-*a*]pyridin-3-amines (**10**). Inorganic acids performed better than organic acids (entries 1-5) and tetrafluoroboric acid provided optimal results (entry 5). Notably, the dealkylation proceeds better under microwave irradiation compared to conventional heating (entry 5 vs. 6) and DMSO is an acceptable solvent. Considering that the MCR towards APOs proceeds best in DMSO and under microwave irradiation, we attempted a one-pot removal of the *tert*-butyl group by simply adding one equivalent HBF_4 to the crude reaction mixture. However, a complex dark colored mixture apparently containing significant quantities of dimethyl sulfide was obtained. Evidently, DMSO is not the appropriate solvent for our case. Pleasingly, the HBF_4-mediated removal of the *tert*-butyl group is straightforward after a solvent switch to *n*-butanol and could be performed without intermediate purification of the 4-(*tert*-butylamino)phthalazin-1(2*H*)-one (**5a**, Table 2).

Table 1. Dealkylation studies by Guchhait *et al.*[1]



Entry	Acid	Solvent	Heating step 2	Yield
1	TFA	*n*-BuOH	μW	0%
2	CH_3SO_3H	*n*-BuOH	μW	60%
3	HBr	*n*-BuOH	μW	76%
4	HCl	*n*-BuOH	μW	81%
5	HBF_4	*n*-BuOH	μW	90%
6	HBF_4	*n*-BuOH	Conventional	35%
7	HBF_4	DMSO	μW	72%

Table 2. Substrate scope of the one-pot MCR and de-*tert*-butylation strategy.[a]



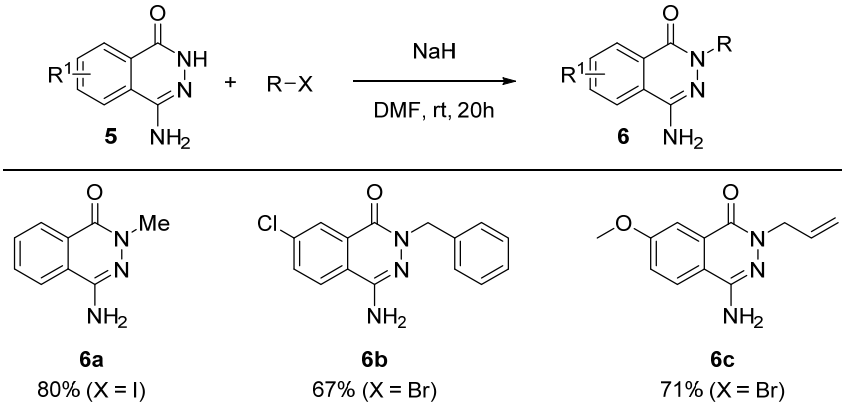
[a] Conditions: Step 1: $Pd(OAc)_2$ (2 mol %), XantPhos (4 mol %), ArX (4.0 mmol), *tert*-butyl isocyanide (**2a**, 6.0 mmol), hydrazine monohydrate (8.4 mmol) in DMSO (2.5 mL), 5 min at 150 °C (μW). Step 2: HBF_4 (48 wt% in H_2O, 4.0 mmol), *n*-BuOH (16 mL), 20 min at 160 °C (μW). Yields refer to isolated products. [b] Reaction time step 1: 2 min. Purification was necessary after step 1. [c] Reaction time step 1: 15 min. [d] Reaction time step 1: 30 min. [e] Conditions as under [a], but using phenylhydrazine (10 mmol) and *i*-Pr_2NH (12 mmol).

We increased the scale for this one-pot two-stage procedure to 4 mmol to evaluate if practical quantities can be obtained *via* this approach. In the event, a variety of 2-(pseudo)halobenzoates (**1**) were readily converted to the corresponding products (**5**) on this scale (Table 2). The required reaction times for the multicomponent reaction are typically longer compared to the reactions on a smaller scale (Chapter 3). For example, while 7-methoxy substituted APO **4h** (Chapter 3) was obtained within 5 minutes on a 0.5 mmol scale, 30 minutes were required for high yields on a 4 mmol scale (Step 1, **5e**, Table 2). A possible explanation for this observation is the lower amount of microwaves per reaction volume and reduced efficiency of heating in case of the larger reaction quantity. In general, electron-rich methyl 2-(pseudo)halobenzoates (**1**) need prolonged reaction times to allow full conversion and proceed in excellent yield (**5d**-**5f**). The chloro-substituted APO **5c** was obtained in optimal yield after just 2 minutes and required intermediate purification

before dealkylation due to formation of side products (see also Chapter 3). Finally, N2-substituted APOs, as exemplified by the synthesis of **5g**, could also be obtained *via* this one-pot two-stage procedure using phenylhydrazine as reagent in the presence of *i*-Pr_2NH as base. The difference in yield between the examples in Table 2 is predominantly caused by varying efficiency of the MCR (step 1), while the dealkylation appears to proceed in excellent yield in all cases.

With the dealkylated 4-aminophthalazin-1(2*H*)-ones (**5a**-**5g**) in hand, we set out to develop a strategy to access a broad range of decorated APOs by further functionalization. Two difficulties were apparent: *(1)* the APOs (**5a**-**5g**) are very polar and only dissolve well in DMSO or DMF, and *(2)* differentiation between the N2-position and the C4-amino group is necessary. We argued that stoichiometric deprotonation of the more acidic N2-position with a strong base and subsequent quenching with an electrophile should provide N2-alkylated products selectively. Indeed, 4-aminophthalazin-1(2*H*)-one **5a** was readily N2-methylated by treatment with sodium hydride followed by addition of methyl iodide delivering **6a** in 80% yield (Table 3). The selective alkylation was further applied by benzylation and allylation of **5c** and **5e** yielding APOs **6b** and **6c**, respectively, illustrating that the electronic nature of the APO has no pronounced effect on the yield.

Table 3. Substrate scope of the N2-alkylation of APOs.[a]

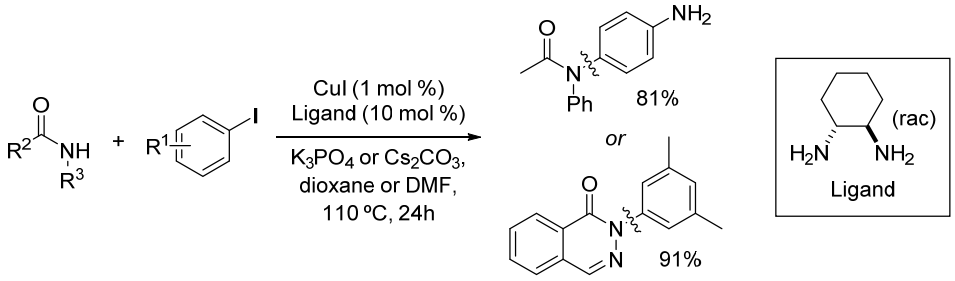


[a] Conditions: 4-aminophthalazin-1(2*H*)-one (**5**, 0.5 mmol), alkyl halide (0.5 mmol), NaH (60% in oil, 0.5 mmol) in dry DMF (3.5 mL) stirred at room temperature for 20h. Yields refer to isolated products.

APOs with an aryl group at the N2-position are the most studied class of 4-aminophthalazin-1(2*H*)-ones in medicinal chemistry and typically show better biological activity than N2-alkylated APOs.[2] They are, however, difficult to access with traditional methods that rely on aryl hydrazines owing to the poor commercial

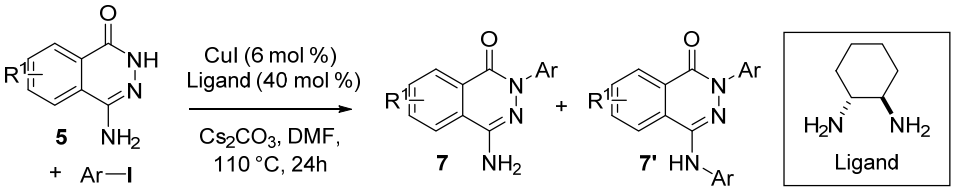
availability of substituted hydrazines. Although our MCR approach tolerates arylhydrazines, the yields are significantly lower than observed with unsubstituted hydrazine. We therefore explored a selective N2-arylation with readily available aryl iodides under transition metal catalysis.

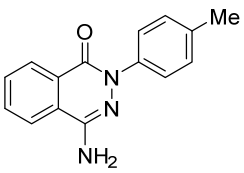
In 2001, Buchwald *et al.* reported an efficient copper-catalyzed arylation of amides and various *N*-heterocycles using aryl halides.[3] In their work, amides were selectively arylated with aryl iodides containing a free NH_2 group in high yield (Scheme 2). The phthalazinone scaffold was also readily N2-arylated under the same conditions, although for this specific substrate a stronger base (Cs_2CO_3) and more catalyst was required. Based on these observations, we surmised Buchwald's conditions might be applicable to our challenge as well. We found that a copper catalyst is indeed able to differentiate between the N2 and C4-amino positions to furnish 2-arylated APOs after subtle modifications to the reaction conditions (Table 4). APO **5a** was readily arylated with *p*-iodotoluene to yield **7a** in 72% yield, while only 7% of the double arylation product (**7a'**) was isolated (Table 4). Several electronically diverse aryl iodides were coupled in good yield and similar selectivities (**7b**-**7d**) and even 4-iodopyridine worked well (**7e**). We did not optimize the reaction for each substrate specifically, but rather focused on one robust set of conditions that allows the smooth conversion of a broad scope of APOs and aryl iodides. We tested a range of substituted APOs and found good yields in most cases. For example, a 7-methoxy or 6-methyl group had no pronounced effect on the yield (**7f** and **7g**). In contrast, a chloro substituent decreased the yield significantly (**7h**), presumably due to competing reaction of copper catalyst with the aryl chloride. A 5-methoxy group resulted in low conversion and only 16% of product **7i** was isolated. We speculate that bidentate coordination of copper to the methoxy and amino groups inhibits catalysis. Finally, a 6-morpholino group was tolerated and product **7j** was obtained in 58% yield. Surprisingly, in this specific case a significant amount (27%) of double arylation product was found.



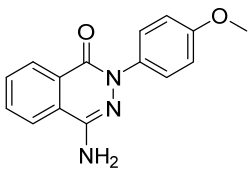
Scheme 2. *N*-arylation of amides and nitrogen heterocycles.

Table 4. Substrate scope of the N2-arylation of APOs.[a]

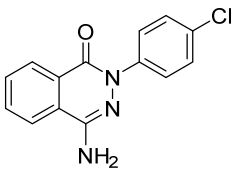




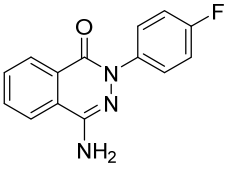
7a
72%[a]



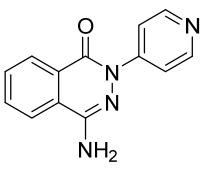
7b
74%



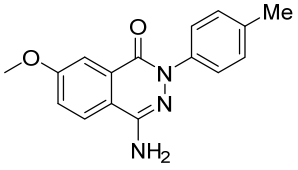
7c
80%



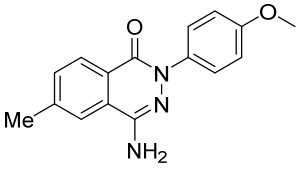
7d
73%



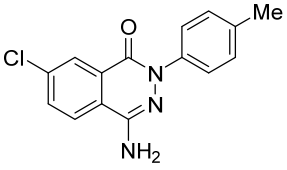
7e
59%



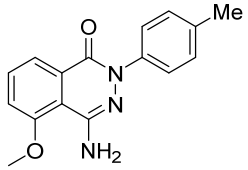
7f
62%



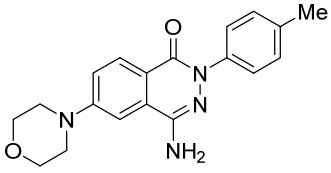
7g
68%



7h
37%



7i
16%

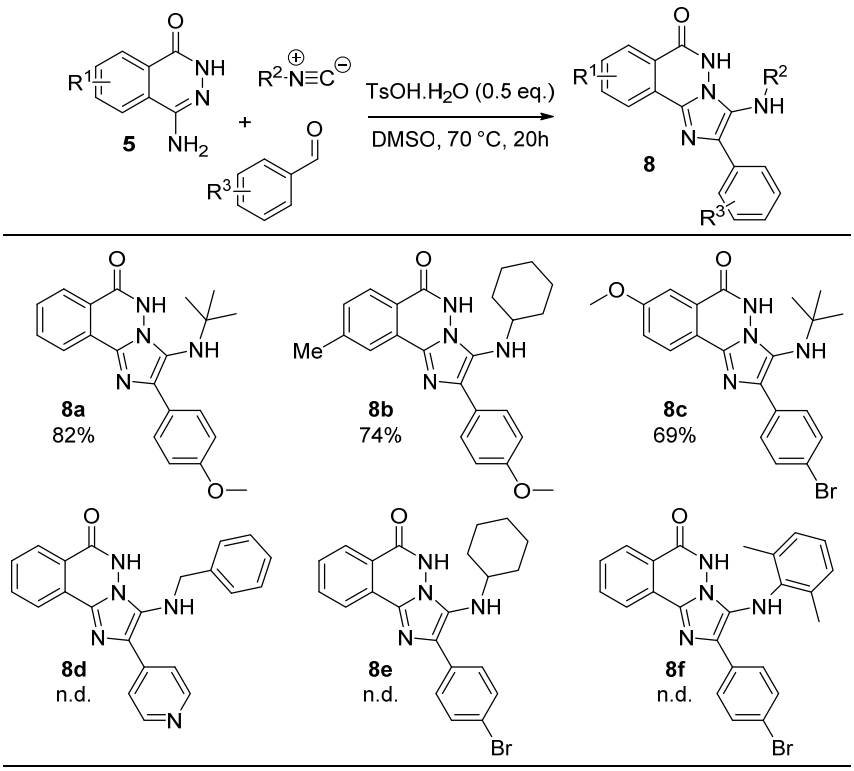


7j
58%[c]

[a] Conditions: 4-aminophthalazin-1(2*H*)-one (**5**, 0.50 mmol), aryl iodide (0.75 mmol), Cs_2CO_3 (1.25 mmol), CuI (6 mol %), (±)-*trans*-1,2-diaminocyclohexane (40 mol %) in dry DMF (1 mL) at 110 °C for 20h. Yields refer to isolated products. [b] 7% of double arylation product was isolated. [c] 27% of double arylation product was isolated.

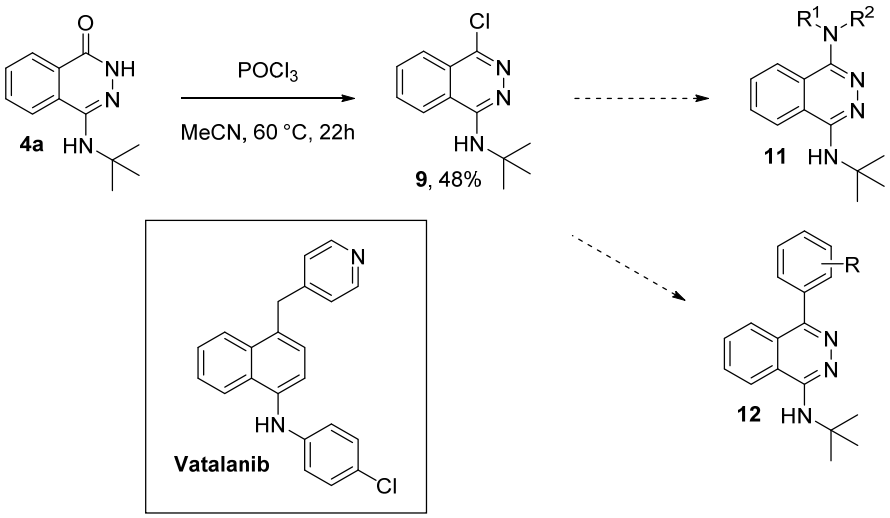
Considering that the discovery of new molecular scaffolds is essential to meet the contemporary demand for improved materials and pharmaceuticals, we used the dealkylated APOs (**5**) as inputs in the complexity-generating Groebke-Bienaymé-Blackburn MCR (Table 5).[4] The resulting imidazo-[2,1*a*]phthalazin-6-ones (**8**) are unexplored scaffolds and accessible in just two steps by this double MCR approach. Ammonium chloride and *p*-toluenesulfonic acid can both be used as acidic mediators, but *p*-toluenesulfonic acid proved to be superior (64% vs. 82% yield of **8a**). A quick scope evaluation revealed several APOs can be used as substrates and both electron-rich and -deficient aldehydes are tolerated (**8a**-**8c**). A peculiar result was obtained for examples **8d**-**8f.** Although the Groebke-Bienaymé-Blackburn MCR most likely worked in these cases, a precipitate was formed that is not soluble in any common laboratory solvent. This effect does not seem to be specific for a certain input, since, for example, all inputs used for **8e** are successfully converted to products **8a**-**8c**.

Table 5. Substrate scope of the Groebke-Bienaymé-Blackburn MCR with APOs.[a]



[a] Conditions: 4-aminophthalazin-1(2*H*)-one (**5**, 0.50 mmol), *p*-toluenesulfonic acid monohydrate (0.25 mmol), aldehyde (0.60 mmol), and isocyanide (0.55 mmol) in dry dry DMSO (2.5 mL) at 70 °C for 20h. Yields refer to isolated products.

We explored dehydroxychlorination of APOs and found that *N*-(*tert*-butyl)-4-chlorophthalazin-1-amine (**9**) can be prepared in a modest 48% yield using phosphoryl chloride in acetonitrile (Scheme 3). In this case the *tert*-butyl group serves as a protecting group to prevent homo-coupling of the reaction product. In fact, the dealkylated APOs (**5**) cannot be used for this transformation due to polymerization issues. Traditionally, 4-chlorophthalazin-1-amines are obtained from 1,4-dichlorophthalazines suffering from the same regioselectivity problems as APOs (for discussion see Chapter 3). They are, however, very useful precursors and readily undergo nucleophilic aromatic substitution by amines to furnish 1,4-diaminophthalazines (**11**).[5] Our route allows regioselective amine introduction when substituents are present on the phenyl ring and therefore avoids tedious separation of regioisomers. Furthermore, 4-chlorophthalazin-1-amines have also been used as substrates for Pd-catalyzed cross-coupling reactions as exemplified by Suzuki reactions furnishing medicinally interesting arylphthalazines (**12**).[6] Vatalanib, a promising drug candidate in clinical trials for the treatment of several types of cancer,[7] might also be prepared from APOs using this strategy.



Scheme 3. Dehydroxychlorination of **4a**.

4.3 Conclusion

We have developed a multicomponent reaction towards 4-aminophthalazin-1(2*H*)-ones that, unlike other methods, allows the regioselective introduction of functional groups on the C5-C8 positions (see Chapter 3). A one-pot MCR/dealkylation strategy overcomes the limited scope with respect to the isocyanide input and provides opportunities for scaffold post-diversification. The poor commercial availability of mono-substituted hydrazines prompted us to develop procedures for regioselective N2-functionalization that avoid the use of these reagents and allow straightforward access to both *N*-arylated and *N*-alkylated APOs. A selective N2-alkylation is realized by treatment with sodium hydride and subsequent quenching with various alkyl halides. The N2-arylation of APOs was achieved using a copper catalyst and high selectivity over the C4-amino group was observed. Additionally, we used APOs as inputs in Groebke-Bienaymé-Blackburn MCRs to obtain new and highly functionalized scaffolds in just two synthetic steps. Finally, we have shown that 4-aminophthalazin-1(2*H*)-ones can be converted to 4-chlorophthalazin-1-amines, which are interesting intermediates towards medicinally relevant products.

4.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as received. Palladium acetate and XantPhos were obtained from Sigma Aldrich or Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled before use. Diisopropylamine was distilled before use and stored in a Schlenk under inert atmosphere. All other compounds were stored under normal atmosphere. Anhydrous MeCN, DMF and DMSO were obtained from Sigma Aldrich. The synthesis of methyl 2-(pseudo)halidebenzoates (**1**) is described in Chapter 3. The microwave reactions were performed in a sealed vessel using a Biotage Initiator Plus and the reaction temperatures were measured using IR. Reaction times refer to the hold time at the desired set temperature. Melting points were measured using a Büchi M-565 melting point apparatus. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 400 or 500 (100.62 or 125.78 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, $^{13}C\{^{1}H\}$ δ 77.16 ppm for $CDCl_3$ and ^{1}H: δ 2.50 ppm, $^{13}C\{^{1}H\}$: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz. Electrospray Ionisation (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 or 366 nm).

General synthetic procedures

General Procedure 1: the one-pot MCR/dealkylation sequence towards 4-aminophthalazin-1(2*H*)-ones (5):

A microwave tube was flame dried under a flow of argon before addition of $Pd(OAc)_2$ (18.0 mg, 0.08 mmol, 2 mol %) en Xantphos (92.6 mg, 0.16 mmol, 4 mol %). Dry DMSO (20 mL) was added to the catalyst and the resulting mixture was stirred. Subsequently, *tert*-butyl isocyanide (0.68 mL, 6.0 mmol, 1.5 eq.), methyl benzoate (4.0 mmol, 1 eq.) and hydrazine monohydrate (0.41 mL, 8.4 mmol, 2.1 eq.) were added in this order. The tube was sealed, placed in the microwave reactor and heated at 150 °C for 5 minutes unless indicated otherwise. The reaction mixture was then concentrated *in vacuo* and the remaining DMSO was removed by freeze drying. (NOTE: traces of DMSO lead to an unpleasant smell along with lower yields during dealkylation. We found co-freeze drying with H_2O helpful to remove all traces of DMSO.) The resulting solid was suspended in *n*-BuOH (16 mL) and HBF_4 (48 wt.% in H_2O, 0.52 mL, 4 mmol, 1 eq.) was added subsequently. The reaction mixture was heated in the microwave reactor at 160 °C for 20 minutes, resulting in a suspension of the product as HBF_4 salt and palladium black. This product was dissolved in DMSO and applied to 30 grams of activated DOWEX 50W X2 (50-100 mesh). HBF_4 was washed off with H_2O (wash until pH = 7) and impurities were removed by

eluting with MeOH. Then, the product was removed from the column by washing in succession with NH_3 (25 % in H_2O) and MeOH. The solution was concentrated *in vacuo* and the resulting solid was further purified by trituration to yield analytically pure product.

General Procedure 2: the N2-alkylation of 4-aminophthalazin-1(2*H*)-ones:
A flamedried Schlenk tube under N_2 atmosphere was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 eq.) and dry DMF (3.5 mL). Subsequently, NaH (60% in mineral oil, 20 mg, 0.5 mmol, 1 eq.) was added and the reaction mixture was stirred for 1h at room temperature. Then, the alkyl halide (0.5 mmol, 1 eq.) was added. After stirring for 20h at room temperature the reaction mixture was concentrated *in vacuo*. The residu was portioned between H_2O/EtOAc, and the layers were separated. The water layer was extracted with EtOAc (3x) and the combined organic layers were dried (Na_2SO_4). The product was purified using flash chromatography with the eluent specified below.

General Procedure 3: the N2-arylation of 4-aminophthalazin-1(2*H*)-ones:
A Schlenk tube was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 eq.), CuI (5.7 mg, 6 mol %), Cs_2CO_3 (411 mg, 1.25 mmol, 2.5 eq.) and aryl iodide (0.75 mmol, 1.5 eq.). The Schlenk tube was put under vacuum and backfilled with argon (3x). Subsequently, a stock solution of (±) *trans*-1,2-cyclohexanediamine in DMF (0.2 mM, 1 mL, 0.20 mmol, 40 mol %) was added. The tube was sealed and placed in an oil bath for 24 hours at 110 °C. The crude reaction mixture was filtered through a short plug of silica (EtOAc) and then concentrated *in vacuo*. The crude product was purified by flash chromatography using the eluent specified below.

General Procedure 4: the Groebke-Bienaymé-Blackburn MCR with 4-aminophthalazin-1(2*H*)-ones:
A flamedried Schlenk tube was charged with 4-aminophthalazin-1(2*H*)-one (0.5 mmol, 1 eq.) and *p*-toluenesulfonic acid monohydrate (48 mg, 0.25 mmol, 0.5 eq.) and then purged with N_2 (3x). Dry DMSO (2.5 mL) was added, followed by aldehyde (0.6 mmol, 1.2 eq.) and isocyanide (0.55 mmol, 1.1 eq.) The reaction mixture was stirred at 70 °C for 20 hours. Subsequently, the reaction mixture was concentrated and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified using flash chromatography with the eluent specified below.

Spectral data

4-aminophthalazin-1(2*H*)-one (5a):
Prepared from methyl 2-bromobenzoate according to general procedure 1. Trituration: DCM. Isolated as an off-white solid. Yield: 556 mg , 86%. TLC (EtOAc/Et_3N, 98:2 v/v): R_f = 0.21; m.p.: 266.6-268.9 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.50 (s, 1H), 8.21 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 7.88 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 5.98 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.1 (C), 146.1 (C), 132.9 (CH), 131.6 (CH), 128.4 (C), 126.1 (CH), 125.0 (C), 123.9 (CH) ppm; IR (neat): νmax (cm^{-1}) = 3244 (m), 3155 (m), 1639

(s), 1593 (s), 1404 (m), 1350 (s), 1161 (m), 1022 (s), 744 (s), 675 (s), 586 (s); HRMS (ESI): m/z calculated for $C_8H_7N_3ONa$ (M+Na) 184.0481, found 184.0484.

4-amino-6-methylphthalazin-1(2*H*)-one (5b):

Prepared from methyl 2-trifluoromethanesulphonyloxy-4-methylbenzoate according to general procedure 1. Trituration: Et_2O. Isolated as a light yellow solid. Yield: 629 mg, 90%. TLC (EtOAc/MeOH/Et_3N, 95:5:2 v/v/v): R_f = 0.48; m.p.: 285.8-289.5 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.41 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 7.62 (dd, *J* = 1.0, 8.0 Hz, 1H*)*, 5.89 (s, 2H), 2.49 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.1 (C), 146.0 (C), 143.0 (C), 132.1 (CH), 126.1 (C), 126.1 (CH), 125.0 (C), 123.7 (CH), 21.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3229 (m), 3171 (m), 1639 (s), 1400 (m), 1346 (s), 1037 (s), 748 (s), 582 (s); HRMS (ESI): m/z calculated for $C_9H_9N_3ONa$ (M+Na) 198.0638, found 198.0635.

4-amino-7-chlorophthalazin-1(2*H*)-one (5c):

Prepared from methyl 2-bromo-5-chlorobenzoate according to general procedure 1. Reaction time for MCR step: 2 minutes. The intermediate 4-(*tert*-butylamino)-7-chlorophthalazin-1(2*H*)-one was purified by flash chromatography using EtOAc/cyclohexane (1:2) to yield 468 mg of solid product, which was then subjected to the standard dealkylation conditions. Trituration: DCM. isolated as a yellow solid. Yield (over 2 steps): 257 mg, 33%. TLC (EtOAc/MeOH/Et_3N, 95:5:2 v/v/v): R_f = 0.65; m.p.: 301.0-304.6 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H*)*, 7.97 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.07 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.0 (C), 145.8 (C), 136.2 (C), 133.0 (CH), 130.0 (C), 126.6 (CH), 125.4 (CH), 123.6 (C) ppm; IR (neat): νmax (cm^{-1}) = 3171 (m), 1643 (s), 1404 (s), 1157 (s), 1034 (s), 737 (m), 582 (s); HRMS (ESI): m/z calculated for C8H6ClN3ONa (M+Na) 218.0092, found 218.0090.

4-amino-5-methoxyphthalazin-1(2*H*)-one (5d):

Prepared from methyl 2-trifluoromethanesulphonyloxy-3-methoxybenzoate according to general procedure 1. Reaction time for the MCR step: 15 minutes. Trituration: DCM. Isolated as an off-white solid. Yield: 563 mg, 74%. TLC (EtOAc/cyclohexane, 1:2 v/v): R_f = 0.34; m.p.: >240 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 7.81 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 1.2, 8.0 Hz, 1H*)*, 6.07 (s, 2H), 3.99 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.2 (C), 156.1 (C), 145.3 (C), 132.2 (CH), 130.4 (C), 118.3 (CH), 114.9 (CH), 114.3 (C), 56.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3460 (s), 3271 (m), 1655 (s), 1585 (s), 1481 (m), 1365 (s), 1265 (s), 1061 (s), 1026 (s), 845 (s); HRMS (ESI): m/z calculated for $C_9H_9N_3O_2Na$ (M+Na) 214.0587, found 214.0583.

4-amino-7-methoxyphthalazin-1(2*H*)-one (5e):

Prepared from methyl 2-bromo-5-methoxybenzoate according to general procedure 1. Reaction time for the MCR step: 30 minutes. isolated as an off-white solid. Yield: 537 mg, 70%. TLC (EtOAc/MeOH, 95:5 v/v): R_f = 0.43; m.p.: >230 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 3.0 Hz, 1H), 7.44 (dd, *J* = 2.5, 9.0 Hz, 1H), 5.88 (s, 2H), 3.91 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.2 (C), 158.0 (C), 146.1 (C), 130.3 (C), 126.0 (CH), 121.5 (CH), 118.7 (C), 107.2 (CH), 55.7 (CH_3) ppm; IR (neat): νmax (cm^{-1})

= 3298 (m), 3213 (m), 1593 (m), 1250 (s), 1022 (s), 663 (m), 606 (m); HRMS (ESI): m/z calculated for $C_9H_9N_3O_2Na$ (M+Na) 214.0587, found 214.0583.

4-amino-6-morpholinophthalazin-1(2*H*)-one (5f):

Prepared from methyl 2-bromo-4-morpholinobenzoate according to general procedure 1. Reaction time for the MCR step: 30 minutes. Trituration: Et_2O. Isolated as an off-white solid. Yield: 946 mg, 96%. TLC (EtOAc/cyclohexane, 1:20 v/v): R_f = 0.31; m.p.: >250 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.15 (s, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 5.84 (s, 2H), 3.77 (t, *J* = 4.5 Hz, 4H), 3.36 (m, 4H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 158.2 (C), 153.7 (C), 145.9 (C), 127.5 (CH), 126.4 (C), 119.3 (C), 118.0 (CH), 106.0 (CH), 65.9 (CH_2), 47.2 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 3352(s), 3339 (s), 3202(m), 1610 (s), 1570 (s), 1499 (s), 1447 (s), 1244 (s), 1113 (s), 1032 (s), 950 (m), 829 (s), 669 (s), 611 (s); HRMS (ESI): m/z calculated for $C_{12}H_{15}N_4O_2$ (M+H) 247.1190, found 247.1192.

4-amino-2-phenylphthalazin-1(2*H*)-one (5g):

A microwave tube was flame dried under a flow of argon before addition of $Pd(OAc)_2$ (18.0 mg, 0.08 mmol, 2 mol %) en XantPhos (92.6 mg, 0.16 mmol, 4 mol %). Dry DMSO (20 mL) was added to the catalyst, followed by *i*Pr_2NH (1.69 mL, 12 mmol, 3 eq.) and the resulting mixture was stirred. Subsequently *tert*-butyl isocyanide (0.68 mL, 6 mmol, 1.5 eq.), methyl 2-bromobenzoate (0.56 mL, 4 mmol, 1 eq.) and phenyl hydrazine (0.98 mL, 10 mmol, 2.5 eq.) were added in this order. The tube was sealed, placed in the microwave reactor and heated at 150 °C for 5 minutes. The reaction mixture was concentrated *in vacuo* and the remaining DMSO was removed by freeze drying. The resulting solid was suspended in *n*-BuOH (16 mL) and HBF_4 (48 wt.% in H_2O, 0.52 mL, 4 mmol, 1 eq.) was added subsequently. The reaction mixture was heated in the microwave reactor at 160 °C for 20 minutes. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed with 1M NaOH. Subsequently, the water layer was extracted with EtOAc (3x) and the combined organic extracts were dried (Na_2SO_4). Flash chromatography using EtOAc/cyclohexane/NEt_3 (33:66:2 > 50:50:2) afforded 470 mg of an off-white solid (50%). TLC (EtOAc:cyclohexane, 1:2 v/v): R_f = 0.18; m.p.: >160 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 7.2 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.64 (dd, *J* = 1.2, 8.8 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.30 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.8 (C), 146.3 (C), 142.3 (C), 133.1 (CH), 131.8 (CH), 128.5 (C), 128.2 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 124.6 (C), 124.0 (CH) ppm; IR (neat): νmax (cm^{-1}) = 3421 (s), 3317 (s), 1562 (m), 1493 (s) 1338 (s), 760 (s), 683 (s); HRMS (ESI): m/z calculated for $C_{14}H_{11}N_3ONa$ (M+Na) 260.0794, found 260.0790.

2-methyl-4-aminophthalazin-1(2*H*)-one (6a):

Prepared from methyl iodide according to general procedure 2. Purification: EtOAc/cyclohexane/NEt_3 (80:20:2). Isolated as a white solid. Yield: 70 mg, 80%. TLC (EtOAc/DCM/Et_3N, 80:20:2 v/v/v): R_f = 0.59; m.p.: 161.1-163.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.23 (dd, *J* = 1.0, 7.5 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.85 (m, 1H), 7.81 (m, 1H), 6.17 (s, 2H), 3.53 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.8 (C), 145.9 (C), 132.5 (CH), 131.5 (CH), 128.1 (C), 126.4 (CH), 124.5 (C), 123.7 (CH), 38.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) =

3369 (m), 3203 (m), 1616 (s), 1555 (m), 1364 (s), 1263 (s), 781 (s), 687 (s); HRMS (ESI): m/z calculated for $C_9H_{10}N_3O$ (M+H) 176.0818, found 176.0822.

2-benzyl-4-amino-7-chlorophthalazin-1(2*H*)-one (6b):

Prepared from benzyl bromide according to general procedure 2. Purification: EtOAc/DCM/Et_3N (50:50:2 > 80:20:2). Isolated as a white solid. Yield: 96 mg, 67%. TLC (EtOAc/DCM/Et_3N, 80:20:2 v/v/v): R_f = 0.59; m.p.: 207.0 - 207.6 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.21 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 7.98 (dd, *J* = 2.5, 8.5 Hz , 1H), 7.33-7.24 (m, 5H), 6.31 (s, 2H), 5.14 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 155.8 (C), 145.8 (C), 137.7 (C), 136.6 (C), 133.0 (CH), 129.6 (C), 128.4 (CH), 127.6 (CH), 127.2 (CH), 126.5 (CH), 125.9 (CH), 123.2 (C), 53.0 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 3394 (s), 3292 (m), 3196 (m), 1616 (s), 1562 (s), 1489 (s), 1406 (s), 1365 (m), 1090 (s), 851 (s), 708 (s); HRMS (ESI): m/z calculated for $C_{15}H_{13}ClN_3O$ (M+H) 286.0742, found 286.0740.

2-allyl-4-amino-7-methoxyphthalazin-1(2*H*)-one (6c):

Prepared from allyl bromide according to general procedure 2. Purification: EtOAc/DCM/Et_3N (50:50:2 > 66:33:2). Isolated as an off-white solid. Yield: 82 mg, 71%. TLC (EtOAc/DCM/NEt_3, 80:20:2 v/v/v): R_f = 0.59; m.p.: 138.5-141.3 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.02 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 3.0 Hz, 1H), 7.45 (dd, *J* = 2.5, 9.0 Hz , 1H), 6.09 (s, 2H), 5.93 (m, 1H), 5.11 (m, 2H), 4.55 (d, *J* = 5.5 Hz, 2H), 3.92 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.5 (C), 156.3 (C), 146.0 (C), 133.6 (CH), 130.0 (C), 126.1 (CH), 121.4 (CH), 118.1 (C), 116.7 (CH_2), 107.6 (CH), 55.7 (CH), 52.0 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 3344 (m), 3213 (s), 2928 (m), 1616 (s), 1574 (m), 1510 (s), 1379 (m), 1290 (s), 1235 (s), 1113 (m), 827 (m), 698 (m); HRMS (ESI): m/z calculated for $C_{12}H_{14}N_3O_2$ (M+H) 232.1081, found 232.1083.

2-(*p*-tolyl)-4-aminophthalazin-1(2*H*)-one (7a):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:2 > 2:1). isolated as an off-white solid. Yield **7a**: 91 mg, 72%. Yield **7a'**: 13 mg, 7%. Data **7a**: TLC (EtOAc/cyclohexane, 1:1 v/v): R_f = 0.46; m.p.: 209.8-210.4 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.31 (dd, *J* = 0.5, 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.93 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.87 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 2H*J*), 7.25 (d, *J* = 8.5 Hz, 2H), 6.28 (s, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.7 (C), 146.2 (C), 139.9 (C), 135.9 (C), 133.1 (CH), 131.7 (CH), 129.0 (CH), 128.6 (C), 127.0 (CH), 125.6 (CH), 124.5 (C), 124.0 (CH), 20.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3398 (s), 3294 (s), 3194 (s), 1624 (s), 1574 (m), 1493 (m), 1354 (m), 1026 (s), 683 (m); HRMS (ESI): m/z calculated for $C_{15}H_{13}N_3ONa$ (M+Na) 274.0951, found 274.0945. Data **7a'**: TLC (EtOAc/cyclohexane, 1:1 v/v): R_f = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70-8.68 (m, 1H), 7.91-7.87 (m, 3H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 4.0 Hz, 3H*J*), 7.20 (d, *J* = 8.4 Hz, 2H), 6.52 (s, 1H), 2.49 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1 (C), 141.8 (C), 139.9 (C), 138.4 (C), 137.0 (C), 133.1 (CH), 132.0 (C), 131.8 (CH), 129.8 (C), 129.7 (CH), 129.3 (CH), 128.7 (CH), 125.4 (C), 125.3 (CH), 122.1 (CH), 119.4 (CH), 21.3 (CH_3), 20.9 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{22}H_{20}N_3O$ (M+H) 342.1601, found 342.1599.

2-(4-methoxyphenyl)-4-aminophthalazin-1(2*H*)-one (7b):
Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:2 > 2:1). Isolated as an off-white solid. Yield: 99 mg, 74%. TLC (EtOAc/cyclohexane, 1:1 v/v): R_f = 0.28; m.p.: 208.6-209.6 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.30 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.93 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.86 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.53 (dd, *J* = 2.0, 7.0 Hz, 2H), 7.00 (dd, *J* = 2.0, 7.0 Hz, 2H), 6.27 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.7 (C), 156.7 (C), 146.1 (C), 135.4 (C), 133.0 (CH), 131.7 (CH), 128.6 (C), 127.0 (CH), 126.9 (CH), 124.5 (C), 124.0 (CH), 113.7 (CH), 55.3 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3429 (s), 3340 (s), 1620 (s), 1570 (s), 1512 (s), 1362 (s), 1242 (s), 1014 (m), 822 (s), 690 (s); HRMS (ESI): m/z calculated for $C_{15}H_{13}N_3O_2Na$ (M+Na) 290.0900, found 290.0900.

2-(4-chlorophenyl)-4-aminophthalazin-1(2*H*)-one (7c):
Prepared according to general procedure 3. Purification: EtOAc/cyclohexane/Et_3N (25:75:2 > 50:50:2). Isolated as an off-white solid. Yield: 109 mg, 80%. TLC (EtOAc/cyclohexane/Et_3N, 50:50:2 v/v/v): R_f = 0.29; m.p.: 216.3-217.3 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.32 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 6.38 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.8 (C), 146.5 (C), 141.0 (C), 133.3 (CH), 131.9 (CH), 130.7 (C), 128.4 (C), 128.2 (CH), 127.2 (CH), 127.1 (CH), 124.6 (C), 124.0 (CH) ppm; IR (neat): νmax (cm^{-1}) = 3429 (s), 3348 (s), 1614 (s), 1580 (s), 1493 (m), 1342 (s), 1088 (s), 1018 (m), 820 (s), 773 (s) 683 (s); HRMS (ESI): m/z calculated for $C_{14}H_{11}ClN_3O$ (M+H) 272.0585, found 272.0584.

2-(4-fluorophenyl)-4-amino-phthalazin-1(2*H*)-one (7d):
Prepared according to general procedure 3. Purification: EtOAc/cyclohexane/Et_3N (50:50:2 > 66:33:2). Isolated as an off-white solid. Yield: 93 mg, 73%. TLC (EtOAc/cyclohexane/Et_3N, 66:33:2 v/v/v): R_f = 0.49; m.p.: >225 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.31 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 7.0 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.69-7.66 (m, 2H), 7.29-7.27 (m, 2H), 6.34 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 160.3 (d, *J* = 244 Hz, C), 156.8 (C), 146.4 (C), 138.6 (d, *J* = 2.5 Hz, C), 133.2(CH), 131.8 (CH), 128.4 (C), 127.8 (d, *J* = 8.8 Hz, CH), 127.0 (CH), 124.6 (C), 124.0 (CH), 115.0 (d, *J* = 22.6 Hz, CH) ppm; IR (neat): νmax (cm^{-1}) = 3475 (s), 3356 (s), 1618 (s), 1582 (s), 1497 (m), 1435 (s), 1339 (s), 1204 (s), 1026 (m), 824 (s), 771 (s), 683 (s); HRMS (ESI): m/z calculated for $C_{14}H_{11}FN_3O$ (M+H) 256.0881, found 256.0880.

2-(4-pyridinyl)-4-amino-phthalazin-1(2*H*)-one (7e):
Prepared according to general procedure 3. Purification: EtOAc/MeOH (9:1). Isolated as an off-white solid. Yield: 70 mg, 59%. TLC (EtOAc/MeOH, 9:1 v/v): R_f = 0.49; m.p.: >240 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.63 (dd, *J* = 1.5, 5.0 Hz, 2H), 8.36 (dd, *J* = 1.0, 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.99-7.88 (m, 4H), 6.52 (s, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.5 (C), 150.0 (CH), 148.6 (C), 146.9 (C), 133.8 (CH), 132.1 (CH), 128.4 (C), 127.3 (CH), 124.5 (C), 124.1 (CH), 118.2 (CH) ppm; IR (neat): νmax (cm^{-1}) = 3418 (s), 3337 (s), 1666 (s), 1635 (s), 1582 (s), 1431(s), 1319 (s), 1211 (s), 1026 (s), 818 (s), 775 (s), 687 (s); HRMS (ESI): m/z calculated for $C_{13}H_{11}N_4O$ (M+H) 239.0927, found 239.0912.

2-(*p*-tolyl)-4-amino-7-methoxyphthalazin-1(2*H*)-one (7f):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:2 > 2:1). Isolated as an off-white solid. Yield: 86 mg, 62%. TLC (EtOAc/cyclohexane, 2:1 v/v): R_f = 0.42; m.p.: >210 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 2.8 Hz, 1H), 7.51-7.48 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.16 (s, 2H), 3.94 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 162.1 (C), 157.0 (C), 146.6 (C), 140.4 (C), 136.3 (C), 131.0 (C), 129.1 (CH), 126.7 (CH), 126.0 (CH), 122.2 (CH), 118.6 (C), 108.6 (CH), 56.2 (CH_3), 21.1 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3402 (s), 3298 (s), 3198 (s), 1616 (s), 1574 (m), 1512 (s), 1366 (s), 1288 (s), 1022 (s), 825 (m), 694 (m), 617 (s); HRMS (ESI): m/z calculated for $C_{16}H_{15}N_3O_2Na$ (M+Na) 304.1056, found 304.1046.

2-(4-methoxyphenyl)-4-amino-6-methylphthalazin-1(2*H*)-one (7g):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:1 > 2:1). Isolated as an off-white solid. Yield: 96 mg, 68%. TLC (EtOAc/cyclohexane, 2:1 v/v): R_f = 0.42; m.p.: 239.4-241.2 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.19 (s, 2H), 3.79 (s, 3H), 2.52 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.6 (C), 156.8 (C), 146.0 (C), 143.3 (C), 135.4 (C), 132.8 (CH), 126.7 (CH), 126.3 (C), 124.6 (C), 123.7 (CH), 113.4 (CH), 56.3 (CH_3), 21.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3406 (s), 3310 (s), 1609 (s), 1558 (m), 1512 (s), 1346 (s), 1246 (m), 1030 (s), 833 (s), 702 (s); HRMS (ESI): m/z calculated for $C_{16}H_{16}N_3O_2$ (M+H) 282.1237, found 282.1219.

2-(*p*-tolyl)-4-amino-7-chlorophthalazin-1(2*H*)-one (7h):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:2). Isolated as an off-white solid. Yield: 53 mg, 37%. TLC (EtOAc/cyclohexane, 1:1 v/v): R_f = 0.59; m.p.: >230 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.23 (d, *J* = 2.0 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.02 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.37 (s, 2H), 3.94 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 155.6 (C), 145.8 (C), 139.6 (C), 136.7 (C), 136.2 (C), 133.2 (CH), 130.2 (C), 128.7 (CH), 126.5 (CH), 126.2 (CH), 125.5 (CH), 123.2 (C), 20.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3306 (s), 3194 (s), 1620 (s), 1566 (s), 1404 (s), 1343 (s), 1107 (s), 899 (s), 822 (s), 706 (s); HRMS (ESI): m/z calculated for $C_{15}H_{12}ClN_3ONa$ (M+Na) 308.0561, found 308.0557.

2-(*p*-tolyl)-4-amino-5-methoxyphthalazin-1(2*H*)-one (7i):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane (1:2 > 2:1). Isolated as an off-white solid. Yield: 23 mg, 16%. TLC (EtOAc/cyclohexane/Et_3N, 66:33:2 v/v/v): R_f = 0.19; m.p.: >200 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.54-7.52 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.35 (s, 2H), 4.02 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.2 (C), 155.9 (C), 145.3 (C), 139.7 (C), 135.9 (C), 132.8 (CH), 130.7 (C), 128.7 (CH), 125.3 (CH), 119.1 (CH), 115.3 (CH), 113.7 (C), 56.7 (CH_3), 20.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3487 (s), 3317 (s), 1618 (s), 1578 (m), 1512 (s), 1356 (s), 1273 (s), 1067 (s), 1035 (s), 866 (s), 762 (s), 723 (s); HRMS (ESI): m/z calculated for $C_{16}H_{16}N_3O_2$ (M+H) 282.1237, found 282.1233.

2-(*p*-tolyl)-4-amino-6-morpholinophthalazin-1(2*H*)-one (7j):

Prepared according to general procedure 3. Purification: EtOAc/cyclohexane/Et_3N (80:20:2). Isolated as an off-white solid. Yield **7j**: 97 mg, 58%. Yield **7j'**: 58 mg, 27%. Data **7j**: TLC (EtOAc/cyclohexane/Et_3N, 80:20:2 v/v/v): R_f = 0.26; m.p.: >220 °C (decomposition); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.44 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.15 (s, 2H), 3.78 (t, *J* = 4.5 Hz, 4H), 3.40 (t, *J* = 4.5 Hz, 4H), 2.34 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ 156.8 (C), 153.9 (C), 146.0 (C), 140.0 (C), 135.3 (C), 128.7 (CH), 128.4 (CH) 126.0 (C), 125.3 (CH), 119.1 (C), 118.2 (CH), 105.9 (CH), 65.8 (CH_2), 47.1 (CH_2), 20.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3439 (s), 3321 (s), 3213 (m), 2833 (m) 1612 (s), 1553 (s), 1510 (s), 1452 (s), 1340 (s), 1229 (s), 1117 (s), 1045 (s), 959 (s), 818 (s), 673 (s); HRMS (ESI): m/z calculated for $C_{19}H_{21}N_4O_2$ (M+H) 337.1659, found 337.1672. Data **7j'**: TLC (EtOAc/cyclohexane/Et_3N, 80:20:2 v/v/v): R_f = 0.46; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.31-7.29 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 2.0 Hz,1H), 6.40 (br, 1H), 3.86 (t, *J* = 4.5 Hz, 4H), 3.33 (t, *J* = 4.5 Hz, 4H), 2.37 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.2 (C), 154.2 (C), 141.7 (C), 139.9 (C), 138.8 (C), 136.6 (C), 131.7 (C), 129.9 (CH), 129.6 (CH), 129.2 (CH), 127.2 (C), 125.2 (CH), 121.2 (C), 119.5 (CH), 119.1 (CH), 104.9 (CH), 67.1 (CH_2), 47.9 (CH_2), 21.2 (CH_3), 20.9 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{26}H_{27}N_4O_2$ (M+H) 427.2129, found 427.2133.

3-(*tert*-butylamino)-2-(4-methoxyphenyl)imidazo[2,1-*a*]phthalazin-6(5*H*)-one (8a):

Prepared according to general procedure 4. Purification: EtOAc/heptane (1:2 > 2:1). Isolated as an off-white solid. Yield: 149 mg, 82%. TLC (EtOAc/heptane, 2:1 v/v): R_f = 0.54; m.p.: > 210 °C (decomposes); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (br, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.89 (td, *J* = 1.0, 8.1 Hz, 1H), 7.67 (td, *J* = 1.0, 8.1 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.94 (s, 1H), 3.79 (s, 3H), 1.09 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.9 (C), 156.1 (C), 133.3 (C), 132.9 (CH), 130.9 (C), 128.1 (C), 128.0 (CH), 128.0 (CH), 127.1 (C), 126.6 (C), 125.1 (CH), 121.1 (CH), 117.5 (C), 113.3 (CH), 55.7 (C), 54.9 (CH_3), 30.1 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2970 (w), 1736 (w), 1614 (w), 1572 (w), 1514 (m), 1452 (m), 1358 (m), 1296 (m), 1244 (s), 1177 (m), 1032 (m), 827 (m), 758 (w); HRMS (ESI): m/z calculated for $C_{21}H_{23}N_4O_2$ (M+H) 363.1816, found 363.1795.

3-(cyclohexylamino)-2-(4-methoxyphenyl)-9-methylimidazo[2,1-*a*]phthalazin-6(5*H*)-one (8b):

Prepared according to general procedure 4. Purification: EtOAc/heptane (1:2 > 2:1). Isolated as a white solid. Yield: 149 mg, 74%. TLC (EtOAc/heptane, 2:1 v/v): R_f = 0.26; m.p.: >170 °C (decomposes); ^{1}H NMR (400 MHz, DMSO-d_6): 12.15 (br, 1H), 8.12-8.09 (m, 3H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.48 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 4.13 (d, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 3.17-3.13 (m, 1H), 2.55 (s, 3H), 1.80-1.14 (m, 11H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.8 (C), 156.5 (C), 143.5 (C), 130.2 (C), 129.3 (CH), 128.8 (C), 128.6 (C), 127.4 (C), 127.0 (CH), 126.5 (C), 125.2 (CH), 120.6 (CH), 115.1 (C), 113.6, (CH), 55.1 (CH), 55.0 (CH_3), 33.3 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 21.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2926 (m), 2851 (w), 1616 (w), 1570 (w), 1518 (m), 1448 (s), 1300 (m) 1244 (s), 1184 (m), 1038 (s), 891 (w), 827 (m); HRMS (ESI): m/z calculated for $C_{24}H_{27}N_4O_2$ (M+H) 403.2129, found 403.2106.

2-(4-bromophenyl)-3-(*tert*-butylamino)-8-methoxyimidazo[2,1-*a*]phthalazin-6(5*H*)-one (8c):

Prepared according to general procedure 4. Purification: EtOAc/heptane (1:2 > 2:1). Isolated as a white solid. Yield: 152 mg, 69%. TLC (EtOAc/heptane, 1:1 v/v): R_f = 0.38; m.p.: 231.1-233.6 °C (decomposition); ^{1}H NMR (400 MHz, DMSO-d_6): 12.26 (br, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 2H), 7.57-7.50 (m, 4H), 4.00 (s, 1H), 3.92 (s, 3H), 1.10 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 159.3 (C), 155.8 (C), 134.9 (C), 131.8 (C), 131.5 (C), 130.7 (CH), 128.5 (CH), 127.6 (C), 123.2 (CH), 122.4 (CH), 120.6 (C), 119.3 (C), 119.0 (C), 106.3 (CH), 55.9 (C), 55.6 (CH_3), 30.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2968 (w), 1562 (w), 1489 (s), 1391 (m), 1366 (m), 1281 (w), 1223 (s), 1070 (m), 1032 (m), 1011 (s), 870 (m), 831 (m); HRMS (ESI): m/z calculated for $C_{21}H_{22}BrN_4O_2$ (M+H) 441.0921, found 441.0902.

***N*-(*tert*-butyl)-4-chlorophthalazin-1-amine (9):**

4-(*tert*-butylamino)phthalazin-1(2*H*)one (**4a**, 108.6 mg, 0.5 mmol, 1 eq.) was suspended in dry MeCN (1 mL) under N_2 atmosphere. $POCl_3$ (140 µL, 1.5 mmol, 3 eq.) was added and the mixture was stirred at 60 °C for 22h. Then, the reaction mixture was cooled, diluted with EtOAc, washed with $NaHCO_3$ (aq. sat.), H_2O and brine and dried (Na_2SO_4). The product was purified with flash chromatography (cyclohexane/EtOAc (3:1)) to furnish 57 mg of a white solid (48%). TLC (EtOAc/cyclohexane, 1:3 v/v): R_f = 0.38; m.p.: 176.2-177.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 8.48-8.44 (m, 1H), 8.06-7.92 (m, 3H), 6.75 (s, 1H), 1.54 (s, 9H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 153.8 (C), 144.0 (C), 132.7 (CH), 132.2 (CH), 125.3 (C), 124.4 (CH), 123.5 (CH), 120.5 (C), 52.9 (C), 28.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3279 (m), 2961 (w), 2922 (w), 1560 (m), 1518 (s), 1420 (s), 1364 (m), 1356 (m), 1294 (w), 1229 (s), 1171 (s), 1132 (m), 1067 (m), 1030 (m), 989 (m), 868 (m), 762 (s); HRMS (ESI): m/z calculated for $C_{12}H_{15}N_3Cl$ (M+H) 236.0949, found 236.0940.

4.5 References

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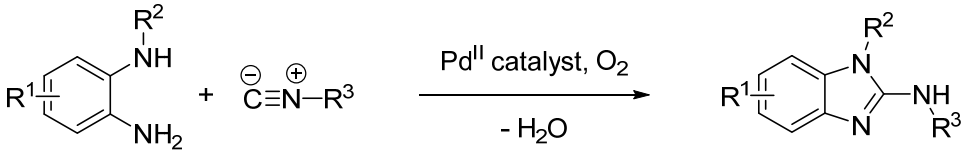
Chapter 5

Heterocyclic Guanidines:

Aerobic Oxidative Coupling of Diamines and Isocyanides



***Abstract**: Various diamines and related bisnucleophiles readily undergo oxidative coupling with isocyanides using 1 mol% $Pd(OAc)_2$ as catalyst and O_2 as terminal oxidant to give a diverse array of medicinally relevant N-heterocycles. The utility of this highly sustainable method is demonstrated by a formal synthesis of the antihistamines astemizole and norastemizole.*

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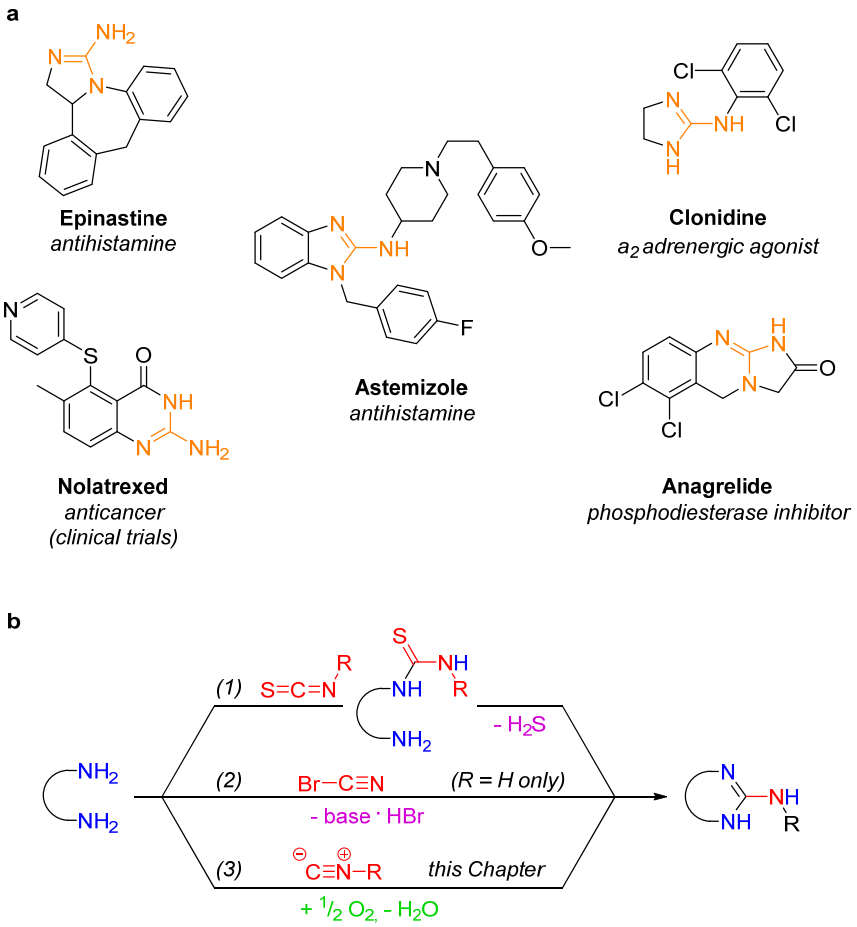
5.1 Introduction

Straightforward access to functional small molecules for contemporary chemical biology and medicinal research, but also for catalysis and material science, relies heavily on novel synthetic methodologies that focus on innovative bond construction and functional group compatibility. These methods are key to both the exploration of chemical space and the more efficient and sustainable production of current high added value fine chemicals such as pharmaceuticals. The guanidine functionality is commonly encountered in a variety of natural products, drugs and organocatalysts and is therefore of importance in both the pharmaceutical industry and organic synthesis.[1] In particular, (aromatic) heterocycles containing a guanidine moiety (such as 2-amino-benzimidazoles, -imidazolines and -quinazolin(on)es) are of great importance in medicinal chemistry and many of them are found in pharmaceuticals (see Scheme 1a for diverse examples). As a result, there is significant interest in the development of synthetic methodologies towards these 'privileged scaffolds' and several methods have been reported in the literature.[2] The classical approaches include *(1)* addition of diamines to isothiocyanates followed by condensation, which typically requires a stoichiometric desulfurizing agent, and *(2)* coupling of diamines with cyanogen bromide (Scheme 1b).[3] However, these methods share some clear limitations, such as the availability or toxicity of reagents, and narrow substrate scope and/or product range. Moreover, these procedures suffer from poor atom and/or step efficiency, making them unattractive from a sustainability point of view.[4] We therefore set out to develop a green and robust synthetic methodology that is applicable to a wide range of guanidine-containing heterocyclic scaffolds. We envisioned the aerobic oxidative coupling of diamines and isocyanides using palladium catalysis would fulfill these criteria. This conceptually novel approach would provide guanidine-containing heterocycles in a single step with water as the sole by-product (Scheme 1b, route *(3)*). The oxidation sensitivity of *e.g. o*-phenylenediamines —which forms the basis for most permanent hair dyes— makes this approach particularly challenging.

Oxidative palladium catalysis has drawn considerable attention because of its mild and environmentally benign character, especially when molecular oxygen is used as the terminal oxidant.[5] Recently developed oxidation reactions employing palladium as catalytic oxidant, such as the oxidative diamination of alkenes, demonstrate the potential of this novel reaction type.[6] Interestingly, bicyclic 2-aminoimidazolines are accessible *via* this method by employing a guanidine derivative as the nitrogen source.[7] We argued that isocyanides might also be coupled with

diamines under oxidative conditions to afford cyclic guanidines. Reactions involving Pd-catalyzed isocyanide insertion with two carbon-heteroatom bond formations are hitherto unknown and offer the potential to synthesize a range of structurally diverse guanidine-based heterocyclic scaffolds. It would also significantly expand the utility of imidoylative cross-coupling chemistry, which is now mainly used for amidine synthesis, by enabling the synthesis of a new structural feature (see Chapter 2 for an overview of the literature on imidoylative cross-coupling chemistry).

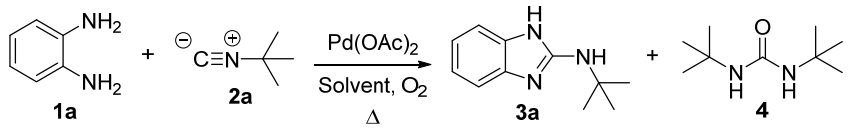


Scheme 1. **a.** Structures of clinically used guanidine-containing heterocycles. **b.** Routes to guanidine-containing heterocycles starting from diamines: *(1)* condensation with isothiocyanates followed by desulfurization; *(2)* Reaction with cyanogen bromide (for R = H only); *(3)* Oxidative insertion of isocyanides (this Chapter).

5.2 Results and Discussion

We started our investigations with the benchmark reaction between *o*-phenylenediamine (**1a**) and *tert*-butyl isocyanide (**2a**, 3 eq.) under an atmosphere of molecular oxygen (1 atm) in the presence of $Pd(OAc)_2$ (5 mol %) and KOAc (150 mol %) in toluene (Table 1, entry 1). We were delighted to find clean conversion towards 2-(*tert*-butylamino)benzimidazole (**3a**) in 82% yield along with the unexpected formation of *N,N'*-di-*tert*-butyl urea (**4**) in an appreciable 53% yield (with respect to **1a**). We found that a base is unnecessary (entry 2) and a solvent screen indicated THF is the best solvent (entry 10). It is noteworthy that the reaction proceeds in any solvent we evaluated in comparable yield; THF only slightly outperforms other common solvents (entries 3-10). We reduced the catalyst loading to just 0.5 mol % to allow further optimization (entry 11). Such a low catalyst loading is exceptional in Pd-catalyzed aerobic oxidations, which typically require at least 5 mol % of palladium, especially in the absence of an external ligand or cocatalyst.[5] It is possible coordination of isocyanides stabilizes the Pd^0 species before oxidation, thereby preventing aggregation to palladium black. Control experiments revealed that an air atmosphere is viable, but less effective than O_2, and that palladium is indeed required for this transformation (entries 12 and 13). Interestingly, we found an increase in yield when the stoichiometry of *tert*-butyl isocyanide was lowered to only 1.2 equivalents (entry 14), which also prevents excessive formation of urea **4**. Other Pd salts such as $PdCl_2$, $Pd(MeCN)_2Cl_2$ or $Pd(O_2CF_3)_2$ did not lead to improved rates or yields (not shown). We also tried $CuCl_2$ and $Cu(OAc)_2$ as catalyst, but no product nor urea formation was observed even with 5 mol % copper. A catalyst loading of 1 mol % $Pd(OAc)_2$ provided nearly quantitative conversion in a convenient reaction time of 20 hours (entry 15). Molecular sieves (4Å) had a small beneficial effect on the reaction performance (entry 16). We experienced irreproducible results during scale-up, which we could attribute to the formation of gaseous THF (boiling point 66°C) which presumably prevents transfer of O_2 to the liquid phase. Mass transfer of O_2 to the liquid phase can be rate-limiting in Pd-catalyzed aerobic oxidation reactions in some cases.[8] We resolved this issue by switching to solvents with a higher boiling point. Toluene and 2-methyltetrahydrofuran (MeTHF) both provide the product in almost quantitative yield on a 1 mmol scale at 75 °C (entries 17 and 18). We thus decided to evaluate the substrate scope of the reaction using the environmentally friendly and renewable solvent MeTHF.[9]

Table 1. Optimization of the aerobic oxidative coupling of *o*-phenylenediamine and *tert*-butyl isocyanide[a]



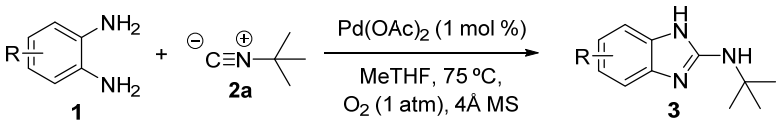
Entry	Solvent	Pd(OAc) (mol %)	SM (**1a**)[b]	Urea (**4**)[b]	Product (**3a**)[b]
1[c]	Toluene	5 mol %	<1%	53%	82%
2	Toluene	5 mol %	<1%	48%	83%
3	DMSO	5 mol %	21%	1%	56%
4	DMF	5 mol %	6%	30%	75%
5	MeCN	5 mol %	16%	29%	68%
6	Dioxane	5 mol %	<1%	67%	74%
7	DME	5 mol %	<1%	69%	78%
8	DCE	5 mol %	1%	19%	78%
9	*t*BuOH	5 mol %	<1%	36%	82%
10	THF	5 mol %	<1%	38%	86%
11	THF	0.5 mol %	38%	6%	43%
12[d]	THF	0.5 mol %	48%	5%	28%
13	THF	--	100%	0%	0%
14[e]	THF	0.5 mol %	24%	5%	60%
15[e]	THF	1,0 mol %	4%	7%	84%
16[e, f]	THF	1,0 mol %	2%	3%	86%
17[e, f, g]	Toluene	1,0 mol %	<1%	4%	97%
18[e, f, g]	MeTHF	1,0 mol %	<1%	4%	99%

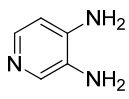
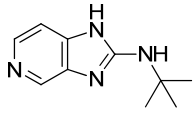
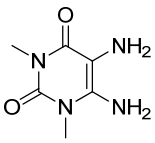
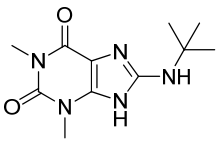
[a] Standard conditions: *o*-phenylenediamine (**1a**, 0.5 mmol), *tert*-butyl isocyanide (**2a**, 3 eq.) and $Pd(OAc)_2$ in solvent (2.5 mL) were stirred for 20h at 70 °C under O_2 atmosphere (1 atm, balloon). [b] Determined by GC analysis using dodecane as internal standard. [c] KOAc (150 mol %) added. [d] Air atmosphere. [e] 1.2 eq. *tert*-butyl isocyanide used. [f] 4Å molecular sieves used. [g] 1 mmol scale and 75 °C.

We then evaluated the reactivity of electronically diverse *o*-phenylenediamines in the aerobic oxidative coupling with *tert*-butyl isocyanide (Table 2). Pleasingly, all examined substrates underwent clean conversion to the desired 2-aminobenzimidazoles **3a-k** in excellent yields (83-99%) and the only noticeable difference was observed in the reaction rate. Electron-donating groups (OMe, Me), or weakly and moderately electron-withdrawing groups (F, Cl, COOMe) give full conversion under the standard conditions, whereas strongly electron-withdrawing groups (CN, CF_3, NO_2) require more catalyst and longer reaction times. Bromo-substituted *o*-phenylenediamine is an exception in the trend and also shows a slower

reaction, although the corresponding product **3g** was obtained in good yield (83%, entry 7). Aza analogue **1l** also underwent clean, albeit slower, conversion to product **3l** in 65% yield (entry 12). Finally, an interesting theophylline analog (**3m**) could be prepared in 43% yield from diaminouracil substrate **1m**, further illustrating the broad substrate scope. Importantly, the reaction is amenable to scale-up with negligible loss of yield (entry 1).

Table 2. Substrate scope of the aerobic oxidative coupling of *o*-phenylenediamines and isocyanides[a]



Entry	Diamine	Product	Time	Yield
1	**1a** (R = H)	**3a** (R = H)	20h	99% (97%)[b]
2	**1b** (R = 4-Me)	**3b** (R = 5-Me)	20h	95%
3	**1c** (R = 3-Me)	**3c** (R = 4-Me)	20h	90%
4	**1d** (R = 4-OMe)	**3d** (R = 5-OMe)	20h	93%
5	**1e** (R = 4-F)	**3e** (R = 5-F)	20h	99%
6	**1f** (R = 4-Cl)	**3f** (R = 5-Cl)	20h	92%
7[c]	**1g** (R = 4-Br)	**3g** (R = 5-Br)	72h	83%
8	**1h** (R = 4-CO_2Me)	**3h** (R = 5-CO_2Me)	20h	99%
9[c]	**1i** (R = 4-CN)	**3i** (R = 5-CN)	72h	95%
10[c]	**1j** (R = 4-CF_3)	**3j** (R = 5-CF_3)	66h	95%
11[c]	**1k** (R = 4-NO_2)	**3k** (R = 5-NO_2)	72h	98%
12[c]	 **1l**	 **3l**	72h	65%
13[c]	 **1m**	 **3m**	20h	43%

[a] Standard conditions: diamine (**1**, 1.0 mmol), *tert*-butyl isocyanide (**2a**, 1.2 mmol), $Pd(OAc)_2$ (1 mol %) and 4Å MS (300 mg) in MeTHF (5 mL) at 75 °C under O_2 atmosphere (1 atm, balloon). Yields refer to isolated material. [b] 10 mmol scale. [c] 5 mol % $Pd(OAc)_2$.

The substrate scope of isocyanides in Pd-catalyzed processes is often limited and occasionally only *tert*-butyl isocyanide is viable (see Chapter 2). A general understanding why different isocyanides show such striking different reactivity in Pd-catalyzed reactions is, to the best of our knowledge, still lacking. We believe two factors could be responsible: *(1)* coordination of multiple less bulky isocyanides to the palladium catalyst, blocking vacant sites for catalysis, and *(2)* insertion of multiple less bulky isocyanides hampering or slowing down the desired reductive elimination. A selective double insertion of primary and secondary aliphatic isocyanides has indeed been reported, suggesting oligomerization or polymerization could be the predominant problem.[10]

We were therefore not surprised that isopropyl isocyanide (**2b**) was a poor reactant in the aerobic oxidation towards 2-(isopropylamino)benzimidazole (**3n**) under the standard conditions (Table 3, entry 1; next page). It was, however, surprising to find a selective reaction towards a compound incorporating three isocyanide molecules (**6**). It proved very difficult to corroborate the structure of compound **6** by NMR experiments, but an X-ray structure unambiguously validated our proposed structure (Figure 1). Compound **6** is most likely formed from the desired product (**3n**) and a control experiment validated that conversion of **3n** to **6** under the standard conditions indeed occurs.

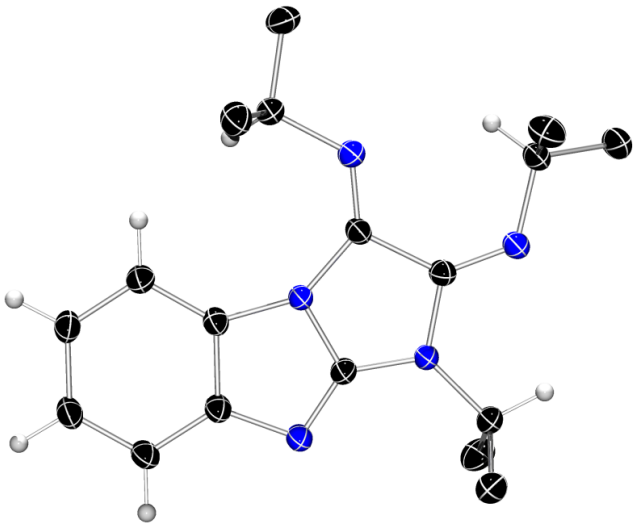
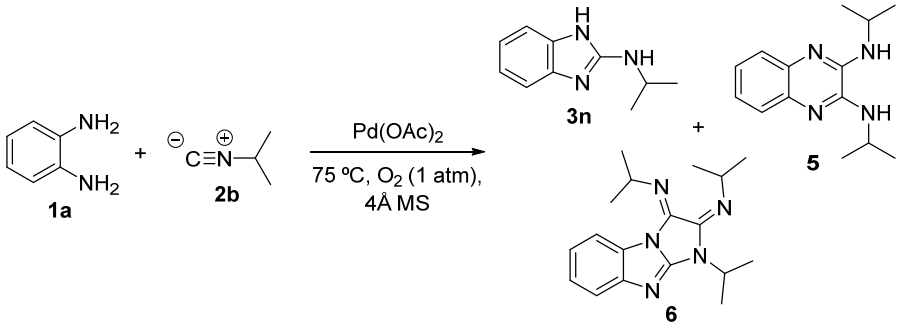


Figure 1. X-ray structure of compound **6.** Displacement ellipsoids are drawn at 50% probability level. Protons of the methyl groups are omitted for clarity.

Table 3. Optimization of the aerobic oxidative coupling of *o*-phenylenediamine and isopropyl isocyanide[a]



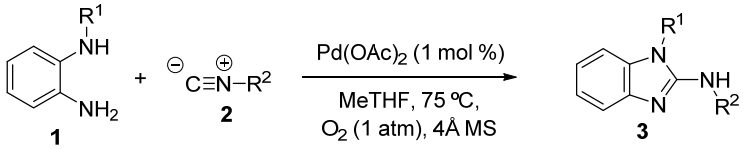
Entry	Solvent	*i*PrNC eq.	Pd(OAc) (mol %)	Time / Slow Add.	**1a**[b]	**3n**[b]	**5**[b]	**6**[b]
1	MeTHF	1.2	1	20h / no	72%	-	-	20%
2	MeTHF	1.2	10	20h / no	25%	21%	9%	15%
3	*t*BuOH	1.2	10	20h / no	14%	31%	21%	-
4[c]	*t*BuOH	1.2	10	5 / yes	27%	46%	8%	3%
5[c]	*t*BuOH	1.5	10	5 / yes	15%	55% (54%)[d]	10%	2%
6[c]	*t*BuOH	1.8	10	5 / yes	15%	55%	11%	9%
7[c]	*t*BuOH	1.8	10	21 /yes	9%	53%	14%	7%
8[c]	*t*BuOH	1.5	5	5 / yes	37%	43%	7%	7%

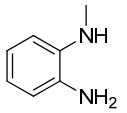
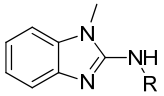
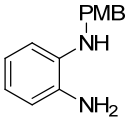
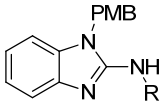
[a] Standard conditions: *o*-phenylenediamine (**1a**, 0.5 mmol), isopropyl isocyanide (**2b**), $Pd(OAc)_2$ and 4Å MS (150 mg) in solvent (2.5 mL) were stirred at 75 °C under O_2 atmosphere (1 atm, balloon). [b] Determined by GC analysis using dodecane as internal standard. [c] Performed on 1 mmol scale for convience. [d] Isolated yields between brackets.

An increased catalyst loading of 10 mol % for the oxidative coupling of **1a** with isopropyl isocyanide resulted in a complex reaction mixture, containing the starting material (**1a**), double insertion product **5**, triple insertion product **6** and the desired product (**3n**, Table 3, entry 2). Encouraged by this result, we optimized the reaction conditions and found *tert*-butanol to be a superior solvent in this case, which efficiently suppresses the formation of **6** (entry 3). Furthermore, slow addition of isocyanide by syringe pump was helpful to obtain a better ratio between single and double insertion and addition of more isocyanide provided product **3n** in a synthetically useful 54% isolated yield (entry 5). Addition of more equivalents of isocyanide did not further increase this yield, but leads to more formation of **6** (entry 6). Slower addition over 21h did not improve the ratio of products either (entry 7). We also tried to reduce the catalyst loading to 5 mol %, but inferior results were

obtained (entry 8). Based on the sideproducts formed, it seems that, at least in our reaction system, consecutive insertion of multiple isocyanides is the main hurdle to overcome in the use of different isocyanides. We reasoned that this is more pronounced for isopropyl isocyanide compared to *tert*-butyl isocyanide because of steric effects, since: *(1)* steric repulsion between *tert*-butyl groups should thermodynamically disfavor (reversible) double insertion, and *(2)* reductive elimination is favored by steric bulk at the palladium center.

Table 4. Substrate scope of the aerobic oxidative coupling of N-substituted *o*-phenylenediamines and various isocyanides[a]



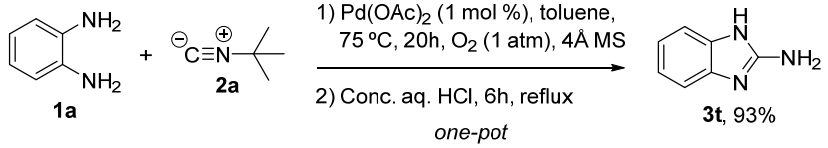
Entry	Diamine	Product	Time	Yield
				
1	**1n**	**3o** (R = *i*Pr)	22h	88%
2	**1n**	**3p** (R = *t*Bu)	2h	97%
3[b]	**1n**	**3q** (R = *n*Pent)	20h	87%
				
4	**1o**	**3r** (R = *t*Bu)	4h	92%
5[b]	**1o**	**3s** (R = cyclohexyl)	18h	94%

[a] Standard conditions: diamine (**1**, 1.0 mmol), isocyanide (**2**, 1.2 mmol), $Pd(OAc)_2$ (1 mol %) and 4Å MS (300 mg) in MeTHF (5 mL) at 75 °C under O_2 atmosphere (1 atm, balloon). Yields refer to isolated material. [b] 5 mol % $Pd(OAc)_2$.

We reasoned that N1-substituted substrates lack the possibility to form products like **6**, since no second N*H* would be present for an additional oxidative isocyanide insertion. In addition, double insertion would not lead to a favorable aromatic system like **5**. Accordingly, we tested oxidative coupling of commercially available *N*-methyl-*o*-phenylenediamine (**1n**) with isopropyl isocyanide (**2b**) under the standard reaction conditions (1 mol % $Pd(OAc)_2$, 22h). Gratifyingly, we obtained the desired 2-aminobenzimidazole **3o** in 88% isolated yield (Table 4, entry 1). The reaction of isopropyl isocyanide (22h, entry 1) is much slower than that of *tert*-butyl

isocyanide (2h, entry 2) under otherwise identical conditions. In addition, *n*-pentyl isocyanide coupled selectively with **1n** in very good yield, although, as expected, the reaction rate further decreased (entry 3). *N*-*p*-Methoxybenzyl-*o*-phenylenediamine (**1o**) is a suitable substrate for aerobic oxidative coupling with *tert*-butyl isocyanide and cyclohexyl isocyanide and provides **3r** and **3s** in 92% and 94% yield, respectively (entries 4 and 5). N1-Benzylated 2-aminobenzimidazoles often display unique biological activity (*e.g.* astemizole, see Scheme 1a).

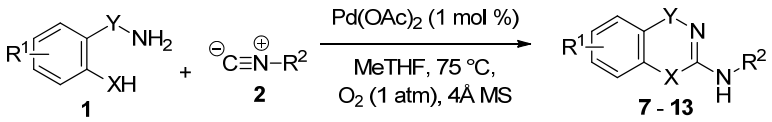
We were also able to access N-unsubstituted 2-aminobenzimidazoles by a one-pot acid-promoted dealkylation sequence. Addition of concentrated aqueous hydrochloric acid to the crude reaction mixture followed by heating under reflux furnished 2-aminobenzimidazole (**3t**) in an excellent 93% yield (Scheme 2). This procedure provides a valuable alternative to highly toxic cyanogen bromide that typically is typically used to obtain these products (Scheme 1b), especially since *tert*-butyl isocyanide is an easily accessible and stable isocyanide.



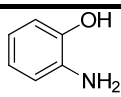
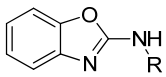
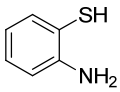
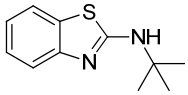
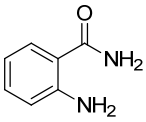
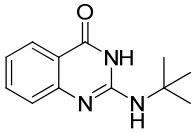
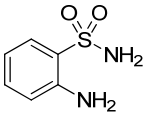
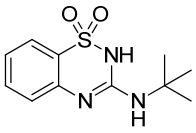
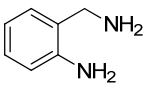
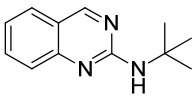
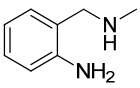
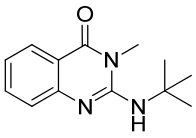
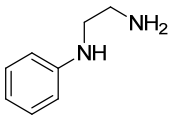
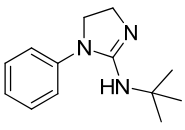
Scheme 2. One-pot oxidative coupling and dealkylation.

Most importantly, the aerobic oxidative coupling proves to be a general, reliable and broadly applicable reaction for the synthesis of various other aminoheterocycles with only subtle changes in the reaction conditions. We first tested oxygen and sulfur analogs of **1a**, which are also oxidation sensitive substrates. 2-Aminophenol (**1p**) is an excellent substrate and smoothly coupled with *tert*-butyl isocyanide and isopropyl isocyanide to yield 2-aminobenzoxazoles **7a** and 7**b** in 99% yield in both cases (Table 5, entries 1 and 2). Notably, the group of Jiang also reported the Pd-catalyzed aerobic oxidative coupling of 2-aminophenols and isocyanides shortly after appearance of our work in the literature.[11] They used slightly different conditions (compared to ours) that were specifically optimized for this substrate and showed a wide range of different isocyanides could be used. Wang and Ji *et al.* reported a cobalt-catalyzed oxidative coupling of bisnucleophiles and isocyanides using potassium persulfate as stoichiometric oxidant,[12] also shortly after appearance of our work in the literature. They showed 2-amino(thio)phenol and *o*-phenylenediamine are viable substrates and can be coupled with a range of isocyanides.

Table 5. Substrate scope of the oxidative coupling of various bisnucleophiles and isocyanides[a]



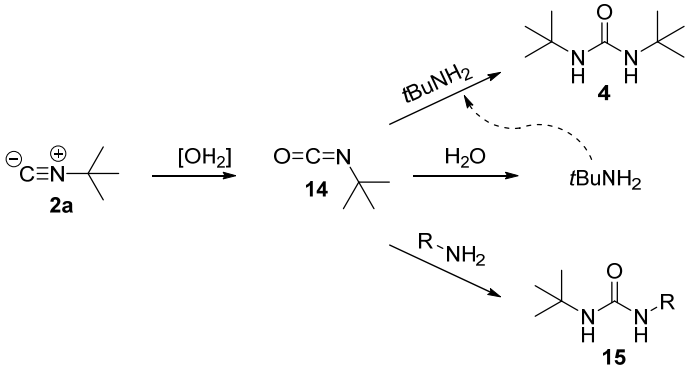
1 + **2** → **7 - 13**

Entry	Diamine	Product	Time	Yield
1[b]	 **1p**	 **7a** (R = *t*Bu)	2h	99%
2	**1p**	**7b** (R = *i*Pr)	6h	99%
3[b, c]	 **1q**	 **8**	72h	69%
4[b]	 **1r**	 **9**	20h	79%
5[b, d]	 **1s**	 **10**	72%	69%
6	 **1t**	 **11**	20h	85%
7	 **1u**	 **12**	20h	77%
8	 **1v**	 **13**	20h	94%

[a] Standard conditions: bisnucleophile (**1**, 1.0 mmol), isocyanide (**2**, 1.2 mmol), $Pd(OAc)_2$ (1 mol %) and 4Å MS (300 mg) in MeTHF (5 mL) at 75 °C under O_2 atmosphere (1 atm, balloon). Yields refer to isolated material. [b] Toluene as solvent. [c] 10 mol % $Pd(OAc)_2$. [d] 5 mol % $Pd(OAc)_2$.

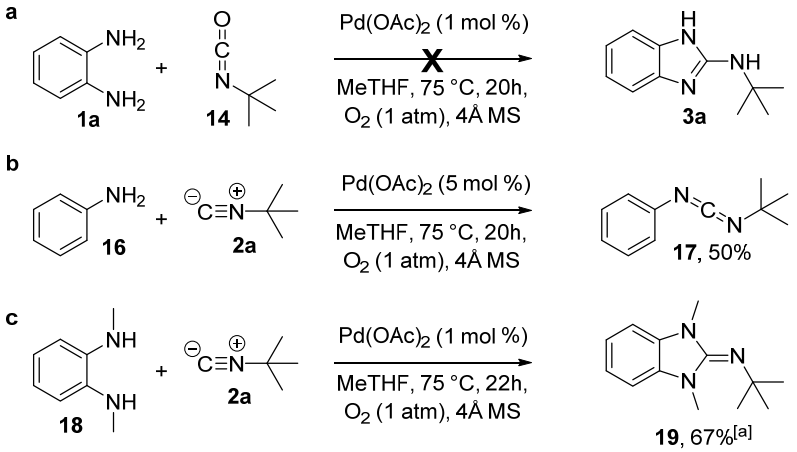
Also in our system 2-aminothiophenol (**1q**) furnished 2-(*tert*-butylamino)-benzothiazole (**8**) selectively in 69% yield (entry 3), although it reacted much slower than 2-aminophenol and starting material remained even after 72 hours of reaction time with 10 mol % of catalyst. Substantially different bisnucleophiles such as anthranilamide (**1r**) and 2-aminobenzenesulfonamide (**1s**) also coupled successfully without significant modification to the reaction conditions to afford products **9** and **10** in good yield (entries 4 and 5). Importantly, 2-aminoquinazolinones are valuable scaffolds in medicinal chemistry as illustrated by nolatrexed (Scheme 1a). In some cases we observed formation of high boiling point impurities derived from MeTHF under the reaction conditions, which made isolation more difficult. We resolved this issue by simply switching to toluene as the solvent in these cases (entries 1, 3, 4 and 5).

The reaction is extendable to aliphatic amines, as shown by the conversion of 2-aminobenzylamine (**1t**) to 2-(*tert*-butylamino)quinazoline (**11**) in 85% (entry 6). Evidently, the product has undergone an additional oxidation under the reaction conditions to aromatize. Methyl substitution of the benzylic amine surprisingly led to the formation of a 2-aminoquinazolinone (**12**, entry 7). Apparently, the benzylic position is very prone to oxidation under the reaction conditions. The origin of the oxygen atom in **12** remains unclear. The presence of molecular sieves makes it unlikely that it is derived from water which is formed during the reaction. Alternatively, the oxygen atom may be derived directly from O_2.[13] Finally, *N*-phenyl ethylenediamine (**1v**) was readily converted to the corresponding 2-aminoimidazoline **13** in 94% yield (entry 8). Interestingly, further oxidation to the corresponding imidazole was not observed in this case.



Scheme 3. Tentatively proposed mechanism for formation of ureas.

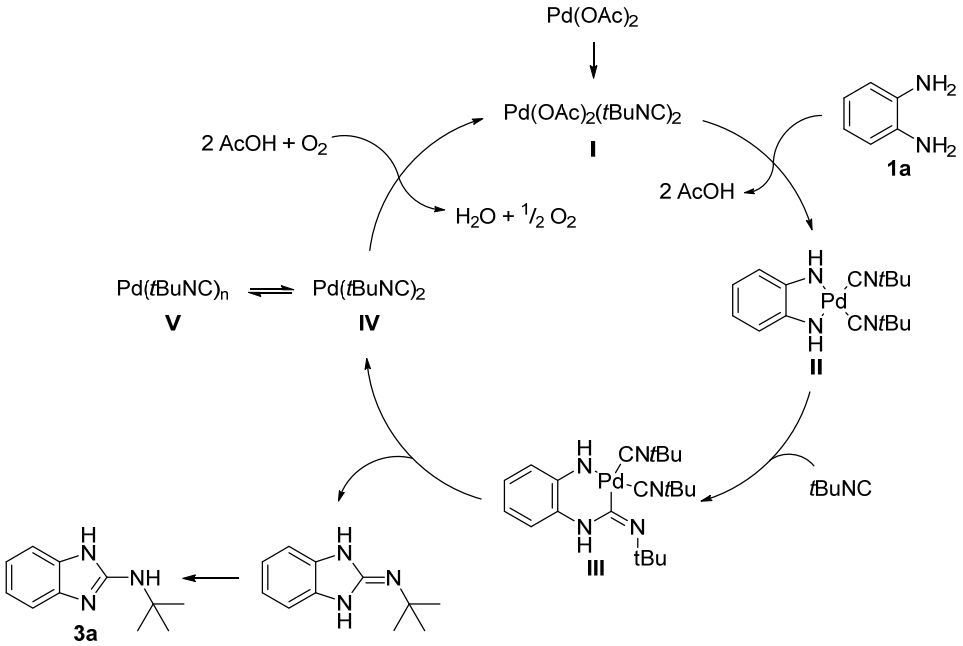
The only noticeable side products we occasionally observed in these reactions were nonsymmetric *tert*-butyl ureas (**15**) and *N,N'*-di-*tert*-butyl urea (**4**, Scheme 3), or the corresponding analogs if a different isocyanide was used. Although we have no proof for a mechanism that would lead to these sideproducts, we imagine that *tert*-butyl isocyanate (**14**) might be formed by oxidation of the isocyanide under the reaction conditions.[14] The nonsymmetric *tert*-butyl ureas can then be formed by nucleophilic addition of the amine substrate to *tert*-butyl isocyanate. Likewise, hydrolysis of *tert*-butyl isocyanate would liberate *tert*-butylamine, which could add to the isocyanate in the absence of an alternative nucleophile in the substrate. This would imply hydrolysis of **14** is very rapid considering molecular sieves are present to capture the water produced by reduction of O_2. The fact that addition of molecular sieves to the reaction mixture reduces formation of **4** by approximately 50% seems to be in correspondence with our proposed pathway involving water.



Scheme 4. Control experiments. [a] Yield determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

To study the mechanism of the oxidative coupling of *o*-phenylenediamine and *tert*-butyl isocyanide in more detail we conducted a series of control experiments. First, we replaced *tert*-butyl isocyanide (**2a**) by *tert*-butyl isocyanate (**14**) under the standard catalytic conditions and observed no product formation (Scheme 4a). This excludes oxidation of isocyanide to isocyanate and subsequent condensation with the diamine as a possible mechanism. Second, we found that aniline (**16**) is converted to carbodiimide **17** under the catalytic conditions in 50% isolated yield (Scheme 4b).[15] Although this suggests carbodiimides might be intermediates in these reactions, we successfully demonstrated this is not necessarily the case (in contrast to the

analogous carbonylative reaction)[16] by converting *N,N'*-dimethyl-*o*-phenylenediamine (**18**), which cannot form a carbodiimide, to the corresponding guanidine **19** (Scheme 4c).

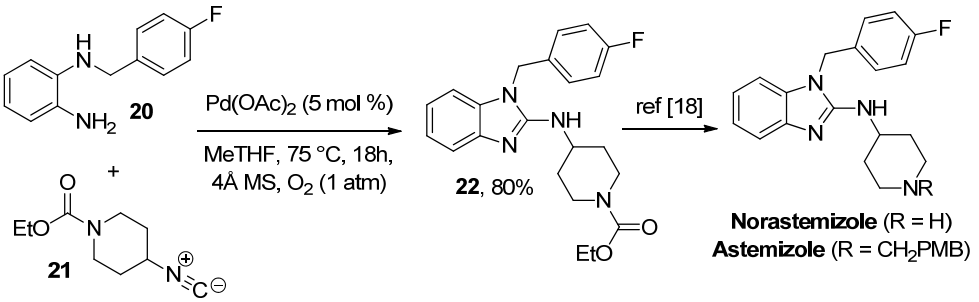


Scheme 5. Proposed mechanism.

Based on the control experiments, we propose the mechanism shown in Scheme 5. Catalyst **I** reacts with the diamine to form intermediate **II**. Then, isocyanide insertion occurs, resulting in species **III** or, in the case of less bulky isocyanides, multiple insertion might take place. Intermediate **III** subsequently undergoes reductive elimination to afford the product. Pd^0 species **IV** is then possibly stabilized by coordination of multiple isocyanides (**IV** > **V**) and oxidized by molecular oxygen to regenerate the catalyst.[13] We cannot exclude an alternative pathway to species **III** involving outer sphere attack of amine to coordinated (and thereby activated) isocyanide.

To further illustrate the utility of our method we completed a formal synthesis of the antihistamines norastemizole and astemizole (Scheme 6). Astemizole has been withdrawn from the market in Europe and the United States due to potentially lethal side effects, but has recently been identified as a potential anti-malaria agent.[17] Diamine **20** was synthesized from 2-nitrofluorobenzene in 65% yield by nucleophilic

aromatic substitution followed by nitro reduction in one pot. Isocyanide **21** was readily obtained in a two step procedure with a single work-up and purification step by formylation and subsequent dehydration of the corresponding amine. The aerobic oxidative coupling of **20** and **21** proceeded smoothly in the presence of 5 mol % $Pd(OAc)_2$ to afford 2-aminobenzimidazole **22** in 80% yield (Scheme 6). Acidic hydrolysis of **22** is known to furnish norastemizole, which can then be functionalized to yield astemizole.[18] To the best of our knowledge, this is the first example of a Pd-catalyzed cross-coupling with insertion of a functionalized isocyanide to synthesize a drug.

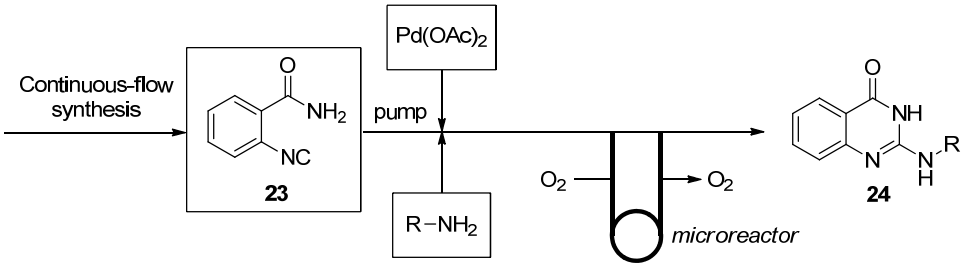


Scheme 6. Formal synthesis of astemizole and norastemizole.

5.3 Conclusion

We have developed a novel Pd-catalyzed aerobic oxidation reaction that produces guanidine-containing and related heterocycles from bisnucleophiles and aliphatic isocyanides. The reaction is applicable to a wide variety of pharmaceutically relevant heterocyclic systems and thus will find application in medicinal chemistry, as illustrated by a formal synthesis of the antihistamines astemizole and norastemizole. Easily handled and relatively low-cost palladium acetate is used as the catalyst and molecular oxygen —the most sustainable oxidant available— as the stoichiometric oxidant. The procedure is operationally simple, since bench solvents and atmospheric pressure are used, and environmentally benign due to the low catalyst loading, renewable solvent and high atom efficiency. A remarkable feature of our methodology is that even though it uses an oxidant and a transition metal at elevated temperature, the oxidation sensitive bisnucleophiles did not undergo oxidative side reactions and were cleanly converted to the desired products.

We investigated the isocyanide substrate scope and found that primary and secondary aliphatic isocyanides can also be used in many cases. The predominant problem in using isocyanides other than *tert*-butyl isocyanide is the tendency for multiple consecutive insertions. This knowledge may prove helpful for the further development of imidoylative cross-coupling reactions. Noteworthy is also that the reaction appeals to other chemists. For example, the group of Jiang also reported the Pd-catalyzed aerobic oxidative coupling of 2-aminophenols and isocyanides, while Wang and Ji *et al.* reported the cobalt-catalyzed coupling of bisnucleophiles and isocyanides using potassium persulfate as oxidant.[11-12] Both of these reports appeared in the literature shortly after our initial report. Furthermore, Kim *et al*. implemented our methodology in continuous-flow chemistry. Unstable 2-isocyanobenzamide (**23**) can be produced in continuous flow and is then directly coupled to amines to furnish 2-aminoquinazolines (**24**, Scheme 7).[19]



Scheme 7. Continuous-flow synthesis of 2-aminoquinazolines.

5.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Palladium acetate was obtained from Sigma Aldrich or Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled prior to use. Other solvents were used as purchased. THF and DCM were distilled from appropriate drying agents before use, anhydrous DMF was obtained from Sigma Aldrich. Powdered 4Å molecular sieves were purchased from Sigma Aldrich and activated before use. GC yield and conversion analysis was performed using a Shimadzu GC2010 equipped with a Zebron ZB-1 capillary column (30m x 0.25 mm) with dodecane as internal standard. GC/MS analysis was performed with a Shimadzu GCMS-QP2010 plus equipped with the same column. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 500 (125.78 MHz for ^{13}C) or Bruker Avance 400 (100.62 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, $^{13}C\{^{1}H\}$: δ 77.16 ppm for $CDCl_3$, ^{1}H: δ 2.50 ppm, $^{13}C\{^{1}H\}$: δ 39.52 ppm for DMSO-d_6 and ^{1}H: δ 3.31 ppm, $^{13}C\{^{1}H\}$: δ 49.00 ppm for MeOD-d_4). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Melting points were recorded on a Büchi M-565 melting point apparatus. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 µm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm) unless mentioned otherwise.

X-ray data

The crystallographic information file (CIF) for compound **6** is available upon request per e-mail (t.vlaar@vu.nl). We thank Dr. Christophe van Vande Velde (University of Antwerp) for X-ray structure determination and Dr. Christopher S. Frampton (SAFC Pharmorphix) for the collection of the X-ray data set.

Synthesis of substrates

***N*-(*p*-methoxybenzyl)-*o*-phenylenediamine (1o)[20]:**
A solution of 2-fluoronitrobenzene (2.11 mL, 20 mmol, 1 eq.) in dry THF (25 mL) was added to a solution of *p*-methoxybenzylamine (2.61 mL, 20 mmol, 1 eq.) in dry THF (25 mL). Triethylamine (5.6 mL, 40 mmol, 2 eq.) was added to the mixture, which was then refluxed for 21 hours. After that, the mixture was cooled to room temperature and concentrated *in vacuo*. EtOH/H_2O (1:1, 100 mL) was added, followed by sodium dithionite (13.9 g, 80 mmol, 4 eq.). The mixture was stirred at 70 °C for 2.5 hours, and then the product was extracted with DCM. The organic phase

was washed with H_2O, dried (Na_2SO_4) and concentrated. Purification by flash chromatography using EtOAc/cyclohexane (1:3 > 1:2) afforded 2.71 g of an off-white solid (59%). TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.27; m.p.: 96-97 °C (lit.[21] 97 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.55-6.51 (m, 1H), 6.42-6.32 (m, 3H), 4.97 (t, *J* = 5.8 Hz, 1H), 4.52 (br, 2H), 4.20 (d, *J* = 5.8 Hz, 2H), 3.72 (s, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 158.1 (C), 135.6 (C), 135.2 (C), 132.2 (C), 128.4 (CH), 117.4 (CH), 116.9 (CH), 114.1 (CH), 113.6 (CH), 110.3 (CH), 55.0 (CH_2), 46.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3396 (w), 3308 (w), 3258 (w), 1585 (w), 1508 (s), 1450 (m), 1267 (m), 1236 (s), 1028 (m), 820 (s), 737 (s), 449 (s); HRMS (ESI): *m/z* calculated for $C_{14}H_{17}N_2O$ (M+H) 229.1335, found 229.1334.

***N*-methyl-2-nitrobenzylamine[22]:**

A solution of 2-nitrobenzylchloride (858 mg, 5 mmol, 1 eq.) in EtOH (5 mL) was added over 10 minutes to a solution of methylamine (8M, 3.1 mL, 25 mmol, 5 eq.) in EtOH. After 2 hours of reflux, the reaction was stopped and EtOH was removed *in vacuo*. Purification by flash chromatography using $CHCl_3$/MeOH/Et_3N (95:5:0.3) afforded 715 mg of a yellow oil (86%). TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.27; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.57-7.51 (m, 2H), 7.36 (dt, *J* = 7.6 Hz, 1.8 Hz, 1H), 3.94 (s, 2H), 2.40 (s, 3H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 149.1 (C), 135.3 (C), 133.2 (CH), 131.3 (CH), 128.0 (CH), 124.7 (CH), 52.7 (CH_2), 36.1 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_8H_{11}N_2O_2$ (M+H) 167.0815, found 167.0827.

***N*-methyl-2-amino-benzylamine (1u)[22]:**

N-methyl-2-nitrobenzylamine (300 mg, 1.8 mmol, 1 eq.) was dissolved in AcOH (5 mL) and 10% Pd/C (150 mg) was added. The mixture was stirred under H_2 pressure (4 bar) for 1.5 hours. The catalyst was removed by filtration over Celite and the filtrate was concentrated *in vacuo*. Next, the crude product was dissolved in Et_2O, washed with 2 M NaOH (aq.) (2x), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography using $CHCl_3$/MeOH (1:0 > 9:1) afforded 210 mg of a yellow oil (85%). TLC ($CHCl_3$/MeOH, 9:1 v/v): R_f = 0.27; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.00-6.92 (m, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.50 (t, *J* = 7.0 Hz, 1H), 3.58 (s, 2H), 2.27 (s, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz): δ 147.5 (C), 129.3 (CH), 127.6 (CH), 123.0 (C), 115.8 (CH), 114.6 (CH), 53.5 (CH_2), 35.5 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_8H_{13}N_2$ (M+H) 137.1073, found 137.1072.

***N,N'*-dimethyl-*N,N'*-ditosyl-*o*-phenylenediamine:**

NaH (50% in mineral oil, 1.44 g, 30 mmol, 3 eq.) and dry DMF (20 mL) were added to an oven-dried 3-neck flask. The mixture was cooled to 0 °C and then *N,N'*-ditosyl-*o*-phenylenediamine[23] (4.16 g, 10 mmol, 1 eq.) was added. After stirring for 15 min, MeI (80 mmol, 5.0 mL, 8 eq.) was added dropwise. The ice bath was removed and the mixture was stirred for 6 hours at room temperature. The reaction was then quenched with water and the product precipitated, was filtered off, washed with water and dried under vacuum. The product was isolated as an off-white solid (4.22 g, 95%) and used without further purification. m.p.: 173-176 °C (lit.[24] 175 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.60 (d, *J* = 8.2 Hz, 4H), 7.45 (d, *J* = 8.2 Hz, 4H), 7.32-7.28 (m, 2H), 6.82-6.77 (m, 2H), 3.12 (s, 6H), 2.43 (s, 6H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 143.7 (C), 140.5 (C), 134.2 (C), 129.8 (CH), 129.1 (CH), 128.0 (CH), 127.8 (CH), 38.6 (CH_3), 21.1

(CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2920 (w), 1593 (w), 1493 (w), 1450 (w), 1346 (s), 1285 (w), 1153 (s), 1053 (m), 906 (s), 818 (m), 760 (m), 725 (s), 648 (s), 540 (s), 505 (m); HRMS (ESI): *m/z* calculated for $C_{22}H_{24}N_2O_4S_2Na$ (M+Na) 467.1070, found 467.1071.

_N,N'_-dimethyl-_o_-phenylenediamine (18):

N,N'-dimethyl-*N,N'*-ditosyl-*o*-phenylenediamine (889 mg, 2 mmol, 1 eq.) was dissolved in 90% aq. H_2SO_4 (5.5 mL) and the mixture was stirred at 100 °C for 8 hours. Next, the solution was poured into ice and solid NaOH was added until pH ~ 11 was reached. After stirring for 1 hour, the product was extracted with Et_2O. The organic phase was dried (Na_2SO_4) and concentration *in vacuo* gave the desired product in satisfactory purity as a brown oil (270 mg, 99%). ^1H NMR (DMSO-d_6, 400 MHz): δ 6.63-6.55 (m, 2H), 6.46-6.39 (m, 2H), 4.54 (q, *J* = 4.5 Hz, 2H), 2.73 (d, *J* = 4.5 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 101 MHz): δ 137.3 (C), 117.1 (CH), 108.4 (CH), 30.3 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_8H_{13}N_2$ (M+H) 137.1073, found 137.1075.

***N*-(*p*-fluorobenzyl)-*o*-phenylenediamine (20)[20]:**

To a solution of 2-fluoronitrobenzene (1.05 mL, 10 mmol, 1 eq.) in dry THF (25 mL) was added *p*-fluorobenzylamine (1.14 mL, 10 mmol, 1 eq.) and triethylamine (2.8 mL, 20 mmol, 2 eq.). The mixture was refluxed for 24 hours, and then concentrated *in vacuo*. EtOH/H_2O (1:1, 50 mL) was added, followed by sodium dithionite (6.96 g, 40 mmol, 4 eq.). The mixture was stirred at 70 °C for 3 hours, and then the product was extracted with DCM. The organic phase was washed with H_2O, dried (Na_2SO_4) and concentrated. The product was immediately purified by flash chromatography using cyclohexane/EtOAc (3:1) as eluent to yield a yellow solid (1.42 g, 66%). TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.32; m.p.: 79-82 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 7.39 (dd, *J* = 8.5 Hz, 5.7 Hz, 2H), 7.16-7.11 (m, 2H), 6.57-6.52 (m, 1H), 6.42-6.37 (m, 2H), 6.34-6.29 (m, 1H), 5.10 (t, *J* = 5.8 Hz, 1H), 4.54 (br, 2H), 4.26 (d, *J* = 5.8 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 161.1 (d, *J* = 241.8 Hz, C), 136.6 (d, *J* = 2.7 Hz, C), 135.4 (C), 135.3 (C) 129.0 (d, *J* = 7.9 Hz, CH), 117.4 (CH), 117.1 (CH), 114.9 (d, *J* = 21.4 Hz, CH), 114.2 (CH), 110.4 (CH), 46.1 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 3400 (w), 3327 (w), 2851 (w), 1595 (m), 1504 (s), 1452 (m), 1267 (m), 1215 (s), 1155 (s), 1094 (m), 820 (s), 735 (s), 501 (s), 447 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{14}FN_2$ (M+H) 217.1136, found 217.217.1139.

ethyl 4-isocyanopiperidine-1-carboxylate (21):

Ethyl 4-aminopiperidine-1-carboxylate (1.72 mL, 10 mmol, 1 eq.) was dissolved in dry DCM (25 mL). Then, freshly prepared and unpurified acetic formic anhydride (44 mmol, 4.4 eq.) was added at 0 °C. The mixture was stirred at room temperature for 5 hours and then all volatiles were removed *in vacuo*. The resulting formamide was dissolved in dry DCM (50 mL) and *N*-methylmorpholine (3.3 mL, 30 mmol, 3 eq.) was added. The solution was cooled to -78 °C before addition of triphosgene (1.04 g, 3.5 mmol, 0.35 eq.). The reaction mixture was stirred at -78 °C for 5 minutes, slowly warmed to -30 °C and then stirred at -30 °C for 3 hours. The reaction was quenched with H_2O and the product extracted with EtOAc (2x). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and then purified by flash chromatography using cyclohexane/EtOac/Et_3N (66:33:1) as eluent. The product was dissolved in DCM, washed with H_2O and dried (Na_2SO_4) to remove Et_3N traces and provide the product as a colorless oil (1.52 g, 84%). TLC (cyclohexane/EtOac/Et_3N, 66:33:1 v/v/v): R_f = 0.32; ^1H NMR (DMSO-d_6, 500 MHz): δ 4.03 (q, *J* = 7.1 Hz, 2H), 4.06-3.96 (m, 1H), 3.56-3.46 (m, 2H), 3.34-3.25 (m, 2H), 1.92-1.82 (m,

2H), 1.67-1.58 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 155.7 (C, split in 3 signals), 154.4 (C), 60.8 (CH_2), 48.9 (CH, split in 3 signals), 40.1 (CH_2), 30.9 (CH_2), 14.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2935 (w), 2139 (m), 1690 (s), 1427 (s), 1381 (w), 1273 (m), 1225 (s), 1126 (m), 1030 (m), 768 (m); HRMS (ESI): *m/z* calculated for $C_9H_{14}N_2O_2Na$ (M+Na) 205.0947, found 205.0954.

Note 1: acetic formic anhydride (44 mmol) was prepared by heating a mixture of formic acid (1.8 mL, 48.4 mmol, 1.1 eq.) and acetic anhydride (4.2 mL, 44 mmol, 1 eq.) at 60 °C for 2 hours.

Note 2: the product was visualized on TLC with p-*anisaldehyde stain.*

Note 3: two ^{13}C NMR signals are split in three signals with equal intensity, which is common for isocyanides.[25]

General synthetic procedures

Optimization of the oxidative coupling of *o*-phenylenediamine and *tert*-butyl isocyanide:

A Radleys parallel synthesis unit was used to simultaneously run multiple reactions. A Radleys tube was charged with *o*-phenylenediamine (**1a**), catalyst, 4Å MS (if applicable) and KOAc (if applicable). Subsequently, the vessel was placed under vacuum and backfilled with O_2 (3x). Then, solvent (2.5 mL) and *tert*-butyl isocyanide were added and the resulting mixture was stirred at the indicated temperature for 20 hours under a reflux condenser. Afterwards, the crude reaction mixture was diluted with EtOAc (4 mL) and dodecane (114 µL, 0.5 mmol, 1 eq.) was added as internal standard. A sample was filtered and subjected to GC analysis to determine conversion of **1a** and yield of urea side product **4** and 2-aminobenzimidazole **3a**.

Optimization of the oxidative coupling of *o*-phenylenediamine and isopropyl isocyanide:

A Radleys parallel synthesis unit was used to simultaneously run multiple reactions. A Radleys tube equipped with a reflux condenser was charged with *o*-phenylenediamine (**1a**,), $Pd(OAc)_2$ and 4Å MS. Subsequently, the vessel was placed under vacuum and backfilled with O_2 (3x). Then, solvent (2.5 mL) and isopropyl isocyanide were added and the resulting mixture was stirred at 75 °C for 20 hours. Afterwards, the crude reaction mixture was diluted with EtOAc (4 mL) and dodecane (114 µL, 0.5 mmol, 1 eq.) was added as internal standard. A sample was filtered and subjected to GC analysis to determine conversion of **1a** and yield of products **3n**, **5** and **6**.

Note: for reactions with slow addition of isopropyl isocyanide a syringe pump was used and a solution of isopropyl isocyanide in MeTHF (1 mL) was slowly added during the indicated time, while the reaction mixture was stirred at 75 °C. A 3-neck flask was used as reaction vessel. The reaction time is the same as the addition time in all these cases. Furthermore, a constant flow of O_2 was used since the system otherwise leaked and balloons deflated.

General procedure for the aerobic oxidative coupling of bisnucleophiles with isocyanides:

$Pd(OAc)_2$ (if > 1 mol % catalyst loading), solid bisnucelophile (1.0 mmol, 1 eq.) and 4Å molecular sieves (300 mg, powdered) were added to a 25 mL round-bottom flask equipped with a reflux condenser. Vacuum was applied and the flask was backfilled with O_2 (3x). After that, solvent (5 mL) or a stock solution (5 mL) containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol

%) was added. Liquid bisnucleophile (1.0 mmol, 1 eq.) was added at this stage, followed by isocyanide (1.2 mmol, 1.2 eq.). The reaction mixture was stirred at 75 °C under O_2 atmosphere (balloon) for the indicated time and conversion was monitored by GC analysis. The crude reaction mixture was filtered through Celite with thorough washing (EtOAc or MeOH for highly polar products) and concentrated *in vacuo*. The product was purified by flash chromatography using the eluent indicated below.

Note: reaction solvent is toluene or MeTHF depending on the substrate, see below.

Spectral data

2-(*tert*-butylamino)-benzimidazole (3a):

Prepared from *o*-phenylenediamine (108 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: EtOAc/cyclohexane/Et_3N (66:33:2). Isolated as a white solid. Yield: 188 mg, 99%. TLC (EtOAc/cyclohexane/Et_3N, 66:33:2 v/v/v): R_f = 0.31; m.p.: 227-228 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.15 (br, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.14 (s, 1H), 1.41 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 154.1 (C), 144.0 (C), 132.9 (C), 119.6 (CH), 118.2 (CH), 114.8 (CH), 108.4 (CH), 50.6 (C), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3427 (w), 1632 (w), 1572 (s), 1553 (s), 1464 (m), 1456 (m), 1414 (m), 1265 (m), 1204 (s), 1068 (w), 725 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{16}N_3$ (M+H) 190.1339, found 190.1337.

2-(*tert*-butylamino)-5-methyl-benzimidazole (3b):

Prepared from 4-methylbenzene-1,2-diamine (122 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/EtOAc/MeOH (70:20:10). Isolated as an off-white solid. Yield: 193 mg, 95%. TLC ($CHCl_3$/EtOAc/MeOH, 70:20:10 v/v/v): R_f = 0.25; m.p.: 151-155 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.20 (br, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.15 (br, 1H), 2.30 (s, 3H), 1.41 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 154.1 (C), 137.5 (C), 135.4 (C), 130.4 (C), 121.7 (CH), 112.5 (CH), 111.8 (CH), 51.7 (C), 29.7 (CH_3), 21.6 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3410 (w), 2962 (w), 1635 (m), 1573 (s), 1488 (m), 1458 (m), 1361 (m), 1272 (m), 1215 (s), 956 (m), 798 (s), 598 (m), 428 (w); HRMS (ESI): *m/z* calculated for $C_{12}H_{18}N_3$ (M+H) 204.1495, found 204.1494.

2-(*tert*-butylamino)-4-methyl-benzimidazole (3c):

Prepared from 3-methylbenzene-1,2-diamine (122 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/MeOH/Et_3N (95:5:0.3). Isolated as a brown solid. Yield: 183 mg, 90%. TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.10; m.p.: 164-170 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.29 (br, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.68 (t, *J* = 7.5 Hz, 1H), 5.92 (br, 1H), 2.36 (s, 3H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 154.3 (C), 140.1 (C), 134.2 (C), 121.4 (CH), 120.8 (CH), 120.5 (C), 111.4 (CH), 51.6 (C), 29.7 (CH_3), 17.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3310 (w), 1608 (w), 1569

(s), 1531 (m), 1454 (m), 1388 (m), 1353 (m), 1269 (m), 1215 (s), 949 (w), 775 (m), 740 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{18}N_3$ (M+H) 204.1495, found 204.1498.

2-(*tert*-butylamino)-5-methoxy-benzimidazole (3d):

Prepared from 4-methoxybenzene-1,2-diamine (138 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/EtOAc/MeOH (70:20:10). Isolated as a brown solid. Yield: 203 mg, 93%. TLC ($CHCl_3$/EtOAc/MeOH, 70:20:10 v/v/v): R_f = 0.20; m.p.: 55-63 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.02 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.47 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.18 (br, 1H), 3.70 (s, 3H), 1.40 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 155.1 (C), 154.3 (C), 138.5 (C), 131.5 (C), 112.0 (CH), 107.9 (CH), 97.9 (CH), 56.1 (CH_3), 51.7 (C), 29.6 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3250 (br), 2962 (m), 1635 (m), 1566 (s), 1485 (s), 1442 (s), 1365 (m), 1191 (s), 1149 (s), 1110 (m), 1026 (m), 956 (m), 787 (m), 555 (w); HRMS (ESI): *m/z* calculated for $C_{12}H_{18}N_3O$ (M+H) 220.1444, found 220.1444.

2-(*tert*-butylamino)-5-fluoro-benzimidazole (3e):

Prepared from 4-fluorobenzene-1,2-diamine (126 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/MeOH/Et_3N (96:4:0.3). Isolated as a light-brown solid. Yield: 205 mg, 99%. TLC ($CHCl_3$/MeOH/Et_3N, 96:4:0.3 v/v/v): R_f = 0.23; m.p.: 212-213 °C (decomposition); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.24 (br, 1H), 7.08 (dd, *J* = 8.4 Hz, 5.0 Hz, 1H), 6.96 (dd, *J* = 9.8 Hz, 2.5 Hz, 1H), 6.64 (ddd, *J* = 10.3 Hz, 9.3 Hz, 2.5 Hz), 6.32 (br, 1H), 1.41 (9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$-MeOD-d_4, 126 MHz): δ 158.6 (d, *J* = 234 Hz, C), 154.9 (C), 139.0 (d, *J* = 13 Hz, C), 132.9 (C), 111.1 (d, *J* = 10 Hz, CH), 107.1 (d, *J* = 25 Hz, CH), 99.6 (d, *J* = 27 Hz, CH), 51.4 (C), 29.3 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3437 (w), 2974 (w), 2923 (w), 1635 (m), 1562 (s), 1485 (s), 1450 (s), 1400 (s), 1350 (m), 1207 (m), 1137 (s), 1064 (m), 945 (m), 837 (m), 791 (s), 605 (m); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}FN_3$ (M+H) 208.1245, found 208.1239.

2-(*tert*-butylamino)-5-chloro-benzimidazole (3f):

Prepared from 4-chlorobenzene-1,2-diamine (143 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/MeOH/Et_3N (95:5:0.3). Isolated as a brown solid. Yield: 206 mg, 92%. TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.27; m.p.: 193-197 °C (decomposition); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.29 (br, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.84 (dd, *J* = 8.3 Hz, 2.2 Hz, 1H), 6.41 (br, 1H), 1.41 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$-MeOD-d_4, 126 MHz): δ 154.8 (C), 139.2 (C), 135.8 (C), 125.9 (C), 120.6 (CH), 112.4 (CH), 112.2 (CH), 51.6 (C), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3440 (m), 2955 (m), 1635 (m), 1558 (s), 1469 (m), 1438 (s), 1404 (s), 1365 (w), 1269 (m), 1215 (s), 1060 (s), 953 (m), 926 (m), 860 (m), 791 (s), 694 (m), 597 (m); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}ClN_3$ (M+H) 224.0949, found 224.0947.

2-(*tert*-butylamino)-5-bromo-benzimidazole (3g):

Prepared from 4-bromobenzene-1,2-diamine (187 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 72 hours). Purification: $CHCl_3$/MeOH/Et_3N (95:5:0.3). Isolated as a brown solid. Yield:

222 mg, 83%. TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.19; m.p.: 187-190 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.32 (br, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.97 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H), 6.44 (br, 1H), 1.40 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 154.4 (C), 139.4 (C), 136.3 (C), 123.6 (CH), 115.5 (CH), 113.5 (C), 113.1 (CH), 52.0 (C), 29.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3440 (w), 2963 (w), 1631 (m), 1562 (s), 1442 (s), 1392 (m), 1365 (m), 1265 (m), 1211 (s), 953 (m), 910 (m), 790 (s), 675 (m), 590 (m); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}BrN_3$ (M+H) 268.0444, found 268.0436.

methyl 2-(*tert*-butylamino)-benzimidazole-5-carboxylate (3h):
Prepared from methyl 3,4-diaminobenzoate (166 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$/MeOH/Et_3N (95:5:0.3). Isolated as an orange solid. Yield: 244 mg, 99%. TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.20; m.p.: 73-78 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.43 (br, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 7.58 (dd, *J* = 8.2 Hz, 1.5 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.66 (br, 1H), 3.80 (s, 3H), 1.42 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 168.6 (COOMe), 155.8 (C), 143.5 (C), 136.4 (C), 123.1 (CH), 121.6 (C), 112.8 (CH), 112.1 (CH), 52.0 (CH_3), 51.7 (C), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3352 (w), 2962 (w), 1689 (s), 1627 (s), 1566 (s), 1434 (s), 1280 (s), 1195 (s), 1087 (s), 949 (m), 771 (m), 744 (m), 590 (w); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O_2$ (M+H) 248.1394, found 248.1391.

2-(*tert*-butylamino)-5-cyano-benzimidazole (3i):
Prepared from 3,4-diaminobenzonitrile (133 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 72 hours). Purification: $CHCl_3$/MeOH/Et_3N (96:4:0.3). Isolated as an off-white solid. Yield: 203 mg, 95%. TLC ($CHCl_3$/MeOH/Et_3N, 96:4:0.3 v/v/v): R_f = 0.17; m.p.: 203-205 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.59 (br, 1H), 7.52 (s, 1H), 7.27 (s, 2H), 6.78 (br, 1H), 1.41 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$-MeOD-d_4, 126 MHz): δ 155.7 (C), 142.2 (C), 137.2 (C), 124.9 (CH), 120.9 (C), 115.0 (CH), 112.4 (CH), 101.5 (C), 51.4 (C), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3336 (m), 2970 (w), 2221 (s), 1627 (s), 1577 (s), 1469 (m), 1442 (m), 1261 (m), 1218 (s), 960 (m), 867 (m), 831 (m), 624 (s), 462 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{15}N_4$ (M+H) 215.1291, found 215.1281.

2-(*tert*-butylamino)-5-(trifluoromethyl)-benzimidazole (3j):
Prepared from 4-trifluoromethylbenzene-1,2-diamine (176 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 66 hours). Purification: $CHCl_3$/MeOH/Et_3N (95:5:0.3). Isolated as an off-white solid. Yield: 244 mg, 95%. TLC ($CHCl_3$/MeOH/Et_3N, 95:5:0.3 v/v/v): R_f = 0.23; m.p.: 157-159 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.48 (br, 1H), 7.45 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.64 (br, 1H), 1.43 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 155.8 (C), 140.1 (C), 137.8 (C), 125.2 (q, *J* = 275 Hz, CF_3), 123.0 (q, *J* = 32 Hz, C), 118.1 (q, *J* = 3 Hz, CH), 111.7 (CH), 109.4 (CH), 51.9 (C), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3325 (w), 2977 (w), 1581 (s), 1531 (m), 1446 (m), 1323 (s), 1222 (m), 1161 (s), 1110 (s), 1050 (s), 948 (s), 871 (m), 810 (m), 663 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{15}F_3N_3$ (M+H) 258.1213, found 258.1200.

2-(*tert*-butylamino)-5-nitro-benzimidazole (3k):
Prepared from 4-nitrobenzene-1,2-diamine (153 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 72 hours). Purification: $CHCl_3$/MeOH/Et_3N (96:4:0.3). Isolated as an off-white solid. Yield: 229 mg, 98%. TLC ($CHCl_3$/MeOH/Et_3N, 96:4:0.3 v/v/v): R_f = 0.16; m.p.: 149-152 °C (decomposition); ^1H NMR ($CDCl_3$-MeOD-d_4, 500 MHz): δ 7.97 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.70 (br, 1H), 1.40 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$-MeOD-d_4, 126 MHz): δ 156.8 (C), 145.1 (C), 141.0 (C), 136.1 (C), 117.6 (CH), 111.4 (CH), 106.9 (CH), 51.5 (C), 29.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3363 (w), 2966 (w), 1631 (m), 1569 (s), 1508 (m), 1462 (s), 1319 (s), 1276 (s), 1207 (s), 1068 (m), 937 (m), 871 (m), 737 (m), 590 (w); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_4O_2$ (M+H) 235.1190, found 235.1180.
Note: the ^{13}C signals at 145.1 and 136.1 ppm were not observed in regular APT measurements. A ^1H, ^{13}C-HMBC experiment was used to identify these chemical shifts.

2-(*tert*-butylamino)-imidazo[4,5-*c*]pyridine (3l):
Prepared from pyridine-3,4-diamine (109 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 72 hours). Celite filter washed with MeOH. Purification: $CHCl_3$/MeOH (4:1). Isolated as an off-white solid. Yield: 123 mg, 65%. TLC ($CHCl_3$/MeOH, 4:1 v/v): R_f = 0.16; m.p.: 219-225 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 8.37 (s, 1H), 8.00 (d, *J* = 5.5 Hz, 1H), 7.18 (d, *J* = 5.3 Hz, 1H), 6.85 (br, 1H), 1.42 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (MeOD-d_4, 126 MHz): δ 158.4 (C), 148.0 (C), 139.3 (CH), 137.5 (C), 130.8 (CH), 108.8 (CH), 52.4 (C), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3247 (w), 3043 (w), 2966 (m), 1631 (m), 1593 (s), 1573 (s), 1520 (m), 1469 (s), 1361 (s), 1215 (s), 1161 (m), 1029 (m), 952 (m), 914 (m), 813 (s), 702 (w), 605 (m); HRMS (ESI): *m/z* calculated for $C_{10}H_{15}N_4$ (M+H) 191.1291, found 191.1282.

8-(*tert*-butylamino)-1,3-dimethyl-1*H*-purine-2,6(3*H*,9*H*)-dione (3m):
Prepared from 5,6-diamino-1,3-dimethyl uracil hydrate (170 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Celite filter washed with MeOH. Purification: EtOAc/cyclohexane, (4:1 > 9:1). Isolated as a light yellow solid. Yield: 107 mg, 43%. TLC (EtOAc/cyclohexane, 4:1 v/v): R_f = 0.36; m.p.: 256-266 °C; ^1H NMR (DMSO-d_6, 400 MHz): δ 10.83 (s, 1H), 6.28 (s, 1H), 3.37 (s, 3H), 3.18 (s, 3H), 1.37 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 154.8 (C), 154.4 (C), 151.7 (C), 151.2 (C), 101.4 (C), 52.1 (C), 30.3 (CH_3), 29.4 (CH_3), 28.1 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3310 (m), 2962 (w), 1690 (m), 1639 (s), 1614 (s), 1560 (s), 1491 (s), 1452 (s), 1383 (m), 1281 (m), 1213 (s), 1059 (m), 980 (m), 941 (m), 754 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{18}N_5O_2$ (M+H) 252.1455, found 252.1447.

2-(isopropylamino)-benzimidazole (3n):
$Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 10 mol %), *o*-phenylenediamine (108 mg, 1.0 mmol, 1 eq.) and 4Å MS (300 mg, powdered) were added to a 50 mL 3-neck flask equipped with a reflux condenser. Vacuum was applied and the flask was backfilled with O_2 (3x). After that, *t*-BuOH (4 mL) was added and the mixture was heated to 75 °C. Isopropyl isocyanide (141 µL, 1.5 mmol, 1.5 eq.) dissolved in MeTHF (1 mL) was added by syringe pump over a period of 5 hours during which the reaction was heated to 75 °C under a constant flow of O_2. Then, the crude reaction mixture

was filtered through Celite with thorough washing (EtOAc) and concentrated *in vacuo*. The product was purified by flash chromatography using $CHCl_3$/MeOH/Et_3N (95:3:2) as the eluent. The product (**3n**) was isolated as an off-white solid (95 mg, 54%) along with double insertion product **5** (11%) and triple insertion product **6** (2%). Spectral data of **3n**: TLC ($CHCl_3$/MeOH/Et_3N, 97:3:2 v/v/v): R_f = 0.21; m.p.: 182-190 °C (decomposition); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.05 (br, s), 7.29-7.24 (m, 2H), 7.06-7.02 (m, 2H), 5.49 (br, s), 4.04 (septet, *J* = 6.4 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 154.6 (C), 137.0 (C), 121.0 (CH), 112.1 (CH), 45.4 (CH), 23.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3418 (w), 2922 (w), 2870 (w), 1568 (s), 1512 (m), 1462 (s), 1367 (m) 1342 (m), 1256 (s), 1175 (s), 1072 (m) 1011 (m), 743 (s), 727 (s); HRMS (ESI): *m/z* calculated for $C_{10}H_{14}N_3$ (M+H) 176.1182, found 176.1191. Spectral data of **5**: m.p.: 198-199 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 7.38-7.34 (m, 2H), 7.14-7.10 (m, 2H), 6.66 (d, *J* = 6.9 Hz, 2H), 4.35 (octet, *J* = 6.6 Hz, 2H), 1.25 (d, *J* = 6.5 Hz, 12H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 142.7 (C), 136.4 (C), 124.5 (CH), 123.0 (CH), 41.8 (CH), 22.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3344 (m), 2972 (w), 1599 (w), 1556 (s), 1491 (s), 1460 (s), 1366 (m), 1298 (m), 1211 (s), 1165 (m), 1126 (m), 935 (w), 746 (s), 604 (s); HRMS (ESI): *m/z* calculated for $C_{14}H_{21}N_4$ (M+H) 245.1761, found 245.1761. Spectral data of **6**: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (d, *J* = 7.5 Hz 1H), 7.38 (d, *J* = 7.5 Hz 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.31-5.19 (m, 1H), 4.74 (br, 1H), 4.39 (septet, *J* = 6.0 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 6H), 1.38 (d, *J* = 6.5 Hz, 6H), 1.20 (d, *J* = 6.0 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 155.7 (C), 146.8 (C), 142.8 (C), 132.1 (C), 129.4 (C), 123.9 (CH), 121.4 (CH), 118.5 (CH), 112.4 (CH), 52.2 (CH), 47.5 (CH), 44.6 (CH), 24.8 (CH_3), 24.1 (CH_3), 19.3 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{18}H_{26}N_5$ (M+H) 312.2183, found 312.2180.

2-(isopropylamino)-1-methyl-benzimidazole (3o):

Prepared from *N*-methyl-*o*-phenylenediamine (114 µL, 1.0 mmol, 1 eq.) and isopropyl isocyanide (113 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 22 hours). Purification: EtOAc/cyclohexane/Et_3N (80:20:2). Isolated as a beige solid. Yield: 167 mg, 88%. TLC (EtOAc/cyclohexane/Et_3N, 80:20:2 v/v/v): R_f = 0.39; m.p.: 145-149 °C (decomposition); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.17 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.92 (dt, *J* = 7.4, 1.2 Hz, 1H), 6.88 (dt, *J* = 7.4, 1.2 Hz, 1H), 6.32 (d, *J* = 7.6 Hz, 1H), 4.08-3.98 (m, 1H), 3.47 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 154.5 (C), 142.7 (C), 135.1 (C), 120.1 (CH), 118.1 (CH), 114.8 (CH), 107.1 (CH), 44.1 (CH), 28.2 (CH_3), 22.8 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3410 (w), 2962 (w), 1635 (m), 1573 (s), 1488 (m), 1458 (m), 1361 (m), 1272 (m), 1215 (s), 956 (m), 798 (s), 598 (m), 428 (w); HRMS (ESI): *m/z* calculated for $C_{11}H_{16}N_3$ (M+H) 190.1339, found 190.1339.

2-(*tert*-butylamino)-1-methyl-benzimidazole (3p):

Prepared from *N*-methyl-*o*-phenylenediamine (114 µL, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 2 hours). Purification: $CHCl_3$/MeOH (95:5). Isolated as an off-white solid. Yield: 197 mg, 097%. TLC ($CHCl_3$/MeOH, 95:5 v/v): R_f = 0.22; m.p.: 142-145 °C (decomposition) (lit.[26] 150-151 °C); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.22 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.89 (br, 1H), 3.48 (s, 3H), 1.47 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 153.6 (C), 142.7 (C), 134.5 (C), 120.0 (CH), 118.2 (CH), 115.1 (CH), 107.1 (CH), 51.2 (C), 28.9 (CH_3), 28.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3290 (m), 2966 (w),

1601 (m), 1550 (s), 1523 (s), 1461 (s), 1356 (s), 1280 (s), 1211 (s), 1130 (m), 1010 (m), 910 (m), 737 (s), 570 (w), 435 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{18}N_3$ (M+H) 204.1495, found 204.1493.

2-(*n*-pentylamino)-1-methyl-benzimidazole (3q):
Prepared from *N*-methyl-*o*-phenylenediamine (114 µL, 1.0 mmol, 1 eq.) and *n*-pentyl isocyanide (151 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: EtOAc/cyclohexane/Et_3N (66:33:2). Isolated as an off-white solid. Yield: 189 mg, 87%. TLC (EtOAc/cyclohexane/Et_3N, 66:33:2 v/v/v): R_f = 0.40; m.p.: 102-107 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.16 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.92 (dt, *J* = 7.4, 1.3 Hz, 1H), 6.88 (dt, *J* = 7.5 Hz, 1.3 Hz, 1H), 3.47 (s, 3H), 3.35-3.30 (m, 2H), 1.65-1.57 (m, 2H), 1.37-1.30 (m, 4H), 0.91-0.86 (m, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 155.2 (C), 142.7 (C), 135.2 (C), 120.0 (CH), 118.0 (CH), 114.8 (CH), 107.0 (CH), 42.5 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.1 (CH_3), 22.0 (CH_2), 14.0 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3329 (br), 2949 (w), 2868 (w), 1609 (s), 1580 (s), 1524 (m), 1477 (s), 1447 (m), 1375 (m), 1279 (s), 1236 (s), 1124 (m), 1007 (m), 733 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{20}N_3$ (M+H) 218.1652, found 218.1651.

2-(*tert*-butylamino)-1-(*p*-methoxybenzyl)-benzimidazole (3r):
Prepared from *N*-*p*-methoxybenzyl-*o*-phenylenediamine (**1o**) (228 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 4 hours). Purification: $CHCl_3$. Isolated as an off-white solid. Yield: 285 mg, 92%. TLC ($CHCl_3$): R_f = 0.19; m.p.: 130-133 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (d, *J* = 7.9, 1H), 7.14-7.01 (m, 5H), 6.87, (d, *J* = 8.6 Hz, 2H), 5.00 (s, 2H), 3.89 (br, 1H), 3.79 (s, 3H), 1.42 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 159.6 (C), 152.8 (C), 142.6 (C), 134.2 (C), 128.0 (CH), 127.6 (C), 121.2 (CH), 119.7 (CH), 116.8 (CH), 114.6 (CH), 107.1 (CH), 55.5 (CH_3), 52.3 (C), 45.5 (CH_2), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3420 (w), 2957 (w), 1614 (m), 1593 (m), 1545 (s), 1508 (s), 1464 (s), 1360 (m), 1352 (m), 1288 (m), 1242 (s), 1207 (s), 1175 (s), 1150 (m), 1030 (s), 1009 (m), 810 (s), 750 (s); HRMS (ESI): *m/z* calculated for $C_{19}H_{24}N_3O$ (M+H) 310.1914, found 310.1908.

2-(cyclohexylamino)-1-(*p*-methoxybenzyl)-benzimidazole (3s):
Prepared from *N*-*p*-methoxybenzyl-*o*-phenylenediamine (**1o**) (228 mg, 1.0 mmol, 1 eq.) and cyclohexyl isocyanide (2d) (149 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 18 hours). Purification: $CHCl_3$/MeOH (99:1). Isolated as an off-white solid. Yield: 315 mg, 94%. TLC ($CHCl_3$/MeOH, 99:1 v/v): R_f = 0.15; m.p.: 55-71 °C (decomposition); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.17 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 5.19 (s, 2H), 3.80-3.71 (m, 1H), 3.69 (s, 3H), 2.04-1.96 (m, 2H), 1.81-1.71 (m, 2H), 1.66-1.57 (m, 1H), 1.39-1.09 (m, 5H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 158.5 (C), 154.1 (C), 142.9 (C), 134.3 (C), 129.2 (C), 128.4 (CH), 120.3 (CH), 118.1 (CH), 114.8 (CH), 113.9 (CH), 107.8 (CH), 55.0 (CH_3), 51.5 (CH), 43.8 (CH_2), 32.9 (CH_2), 25.5 (CH_2), 25.0 (CH_2) ppm; IR (neat): νmax (cm^{-1}) = 2927 (m), 2851 (w), 1601 (m), 1553 (s), 1508 (s), 1462 (s), 1348 (m), 1281 (m), 1247 (s), 1175 (m), 1111 (m), 1092 (m), 1030 (m), 818 (m), 735 (s); HRMS (ESI): *m/z* calculated for $C_{21}H_{26}N_3O$ (M+H) 336.2070, found 336.2052.

2-aminobenzimidazole (3t):

o-Phenylenediamine (108 mg, 1.0 mmol, 1 eq.) and 4Å MS (300 mg, powdered) were added to a 25 mL round-bottom flask equipped with a reflux condenser. Vacuum was applied and the flask was backfilled with O_2 (3x). After that, a stock solution (PhMe, 5 mL) containing $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol %) was added, followed by *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.). The reaction mixture was stirred at 75 °C under O_2 atmosphere (balloon) for 20 hours. After completion of the reaction (as confirmed by GC analysis), the reaction mixture was cooled to room temperature and concentrated HCl (5 mL) was added. The mixture was refluxed for 6 hours and then basified with aq. NaOH (3M). The mixture was filtered to remove molecular sieves and the product was extracted with EtOAc (3x) and dried (Na_2SO_4). The product was purified by flash chromatography using EtOAc/MeOH/Et_3N (90:10:1) as eluent to yield an off-white solid (124 mg, 93%). TLC (EtOAc/MeOH/Et_3N, 90:10:1 v/v/v): R_f = 0.18; m.p.: 213-223 °C (decomposition) (lit.[27] 222-224 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.67 (br, 1H), 7.10-7.06 (m, 2H), 6.86-6.81 (m, 2H), 6.10 (br, 2H) ppm; ^{13}C{^{1}H} NMR (MeOD-d_4, 126 MHz): δ 156.6 (C), 138.9 (C), 121.4 (CH), 112.8(CH) ppm; IR (neat): νmax (cm^{-1}) = 3371 (w), 3047 (br), 1647 (m), 1535 (m), 1479 (m), 1452 (s), 1406 (s), 1313 (m), 1242 (m), 1105 (m), 1032 (m), 897 (m), 741 (s), 723 (s); HRMS (ESI): *m/z* calculated for $C_7H_8N_3$ (M+H) 134.0713, found 134.0711.

2-(*tert*-butylamino)-benzoxazole (7a):

Prepared from 2-aminophenol (109 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, toluene, 2 hours). Purification: $CHCl_3$/MeOH (100:0 > 95:5). Isolated as a light-yellow solid. Yield: 188 mg, 99%. TLC ($CHCl_3$): R_f = 0.23; m.p.: 93-95 °C (lit.[28] 100-102 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.70 (br, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.09 (dt, *J* = 7.5 Hz, 0.4 Hz, 1H), 6.96 (dt, *J* = 7.6 Hz, 0.9 Hz, 1H), 1.40 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 160.7 (C), 147.3 (C), 143.5 (C), 123.4 (CH), 120.0 (CH), 115.5 (CH), 108.2 (CH), 50.9 (C), 28.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3290 (w), 2966 (m), 1650 (s), 1581 (s), 1481 (m), 1458 (s), 1346 (m), 1207 (s), 1010 (m), 918 (m), 848 (m), 737 (s), 686 (m), 582 (m); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_2O$ (M+H) 191.1179, found 191.1169.

2-(isopropylamino)-benzoxazole (7b):

Prepared from 2-aminophenol (109 mg, 1.0 mmol, 1 eq.) and isopropyl isocyanide (113 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 6 hours). Purification: $CHCl_3$/MeOH (98:2). Isolated as an off-white solid. Yield: 175 mg, 99%. TLC ($CHCl_3$/MeOH, 98:2 v/v): R_f = 0.33; m.p.: 69-71 °C (lit.[28] 82-84 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.92-3.81 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.6 (C), 147.9 (C), 143.4 (C), 123.5 (CH), 120.0 (CH), 115.3 (CH), 108.4 (CH), 44.5 (CH), 22.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3034 (w), 2970 (m), 1639 (s), 1585 (s), 1460 (s), 1352 (m), 1275 (m), 1240 (s), 1165 (m), 1153 (m), 1130 (m), 1020 (m), 829 (m), 721 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_2O$ (M+H) 191.1179, found 191.1169.

2-(*tert*-butylamino)-benzothiazole (8):

Prepared from 2-aminothiophenol (107 µL, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (10 mol % $Pd(OAc)_2$, toluene, 72 hours).

Purification: EtOAc/cyclohexane (1:9). Isolated as an off-white solid. Yield: 142 mg, 69%. TLC (EtOAc/cyclohexane, 1:9 v/v): R_f = 0.23; m.p.: 90-93 °C (lit.[29] 91-95 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.76 (br, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 1.43 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 163.9 (C), 153.0 (C), 130.0 (C), 125.3 (CH), 120.8 (CH), 120.5 (CH), 118.0 (CH), 52.9 (C), 28.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3236 (w), 2966 (w), 1593 (m), 1527 (s), 1446 (s), 1361 (m), 1253 (m), 1211 (m), 1188 (s), 910 (w), 748 (s), 725 (m), 590 (w), 428 (w); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_2S$ (M+H) 207.0950, found 207.0952.

2-(*tert*-butylamino)-quinazolin-4(*3H*)-one (9):
Prepared from 2-aminobenzamide (136 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, toluene, 20 hours). Purification: $CHCl_3$/MeOH (99:1 > 96:4). Isolated as a light-yellow solid. Yield: 171 mg, 79%. TLC ($CHCl_3$/MeOH, 99:1 v/v): R_f = 0.24; m.p.: 203-210 °C (decomposition) (lit.[30] 218-220 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.45 (br, 1H), 7.87 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.57-7.52 (m, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.01 (br, 1H), 1.43 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.8 (C), 150.9 (C), 149.3 (C), 134.1 (CH), 125.8 (CH), 125.0 (CH), 121.6 (CH), 117.3 (C), 50.9 (C), 28.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3363 (m), 3150-3050 (br), 2966 (w), 1678 (m), 1604 (s), 1569 (s), 1473 (m), 1280 (s), 1211 (s), 1145 (m), 1014 (w), 760 (s), 621 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{16}N_3O$ (M+H) 218.1288, found 218.1278.

3-(*tert*-butylamino)-*2H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (10):
Prepared from 2-aminobenzenesulfonamide (172 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, toluene, 72 hours). Celite filter is washed with MeOH, solvent is evaporated and then trituration with small amounts of EtOAc removes most of the unreacted starting material. Purification: $CHCl_3$/MeOH (9:1). Isolated as a white solid. Yield: 175 mg, 69%. TLC ($CHCl_3$/MeOH, 96:4 v/v): R_f = 0.25; m.p.: 277-279 °C (decomposition); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.16 (br, 1H), 7.66 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.25-7.21 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.69 (br, 1H), 1.39 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 150.3 (C), 135.6 (C), 132.4 (CH), 123.6 (CH), 122.8 (CH), 122.3 (C), 116.3 (CH), 51.6 (C), 28.6 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3321 (m), 3124 (w), 2977 (w), 1620 (s), 1573 (s), 1477 (m), 1427 (m), 1342 (m), 1254 (s), 1215 (m), 1137 (s), 1103 (s), 1064 (s), 972 (m), 856 (m), 752 (s), 671 (m), 574 (s), 520 (s), 482 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_3O_2SNa$ (M+Na) 276.0777, found 276.0788.

2-(*tert*-butylamino)-quinazoline (11):
Prepared from 2-aminobenzylamine (122 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: $CHCl_3$. Isolated as a yellow solid. Yield: 172 mg, 85%. TLC ($CHCl_3$): R_f = 0.22; m.p.: 77-83 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.07 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 0.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.92 (br, 1H), 1.45 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.5 (CH), 159.0 (C), 151.3 (C), 133.9 (CH), 127.8 (CH), 125.1 (CH), 121.8 (CH), 119.3 (C), 50.3 (C), 28.5 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3359 (w), 3301 (m), 2960 (m), 1620 (m), 1593 (s), 1535 (s), 1450 (m), 1404 (m), 1357 (m), 1215 (s), 1087 (m),

860 (w), 794 (m), 752 (s), 717 (s), 636 (m), 540 (m), 455 (m); HRMS (ESI): *m/z* calculated for $C_{12}H_{16}N_3$ (M+H) 202.1339, found 202.1332.

2-(*tert*-butylamino)-3-methylquinazolin-4(3*H*)-one (12):
Prepared from *N*-methyl-2-aminobenzylamine (**1u**) (136 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: EtOAc/cyclohexane (1:4). Isolated as a pink solid. Yield: 179 mg, 77%. TLC (EtOAc/cyclohexane, 1:4 v/v): R_f = 0.19; m.p.: 129-131 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.92 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 7.58-7.54 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.80 (br, 1H), 3.43 (s, 3H), 1.50 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.8 (C), 149.4 (C), 148.5 (C), 133.9 (CH), 126.3 (CH), 124.7 (CH), 121.7 (CH), 116.1 (C), 52.1 (C), 28.7 (CH_3), 28.1 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3375 (s), 2959 (w), 1659 (s), 1558 (s), 1535 (s), 1473 (s), 1319 (m), 1211 (s), 1168 (m), 1141 (m), 867 (m), 737 (s). 698 (m), 513 (m); HRMS (ESI): *m/z* calculated for $C_{13}H_{18}N_3O$ (M+H) 232.1444, found 232.1444.

2-(*tert*-butylamino)-1-phenyl-imidazoline (13):
Prepared from *N*-phenyl-ethylenediamine (131 µL, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: EtOAc/Et_3N, (95:5). Isolated as a light yellow oil. Yield: 205 mg, 94%. TLC (EtOAc/Et_3N, 95:5 v/v): R_f = 0.28; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (t, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 3.86 (br, 1H), 3.77-3.73 (m, 2H), 3.70-3.65 (m, 2H), 1.37 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 155.4 (C), 142.0 (C), 129.8 (CH), 124.2 (CH), 122.6 (CH), 51.5 (C), 51.4 (CH_2), 50.2 (CH_2), 29.4 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2958 (w), 2862 (w), 1627 (s), 1596 (s), 1497 (s), 1454 (m), 1358 (s), 1311 (w), 1269 (s), 1215 (s), 1060 (w), 756 (s), 698 (s), 563 (m), 505 (m); HRMS (ESI): *m/z* calculated for $C_{13}H_{20}N_3$ (M+H) 218.1652, found 218.1644.

***N*-phenyl-*N'*-(*tert*-butyl)-carbodiimide (17):**
Prepared from aniline (91 µL, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 20 hours). Purification: EtOAc/cyclohexane (9:91). Isolated as a yellow oil. Yield: 88 mg, 50%. TLC (EtOAc/cyclohexane, 9:99 v/v): R_f = 0.78; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.33 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 1.36 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 140.4 (C), 135.7 (C), 129.7 (CH), 124.8 (CH), 123.0 (CH), 57.3 (C), 31.2 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 2970 (m), 2106 (s), 1593 (s), 1496 (s), 1365 (m), 1234 (s), 1184 (s), 1137 (m), 856 (m), 756 (s), 690 (s), 632 (s), 594 (s), 516 (m); HRMS (ESI): *m/z* calculated for $C_{11}H_{15}N_2$ (M+H) 175.1230, found 175.1236.

1,3-dimethyl-2-(*tert*-butylimino)-benzimidazole (19):
Prepared from *N,N'*-dimethyl-*o*-phenylenediamine (17) (136 mg, 1.0 mmol, 1 eq.) and *tert*-butyl isocyanide (136 µL, 1.2 mmol, 1.2 eq.) according to the general procedure (1 mol % $Pd(OAc)_2$, MeTHF, 22 hours). Yield: 67%, calculated by crude ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Hydrolysis towards 1,3-dimethyl-1*H*-benzo[d]imidazol-2(*3H*)-one was observed and complicated purification efforts. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97-6.89 (m, 2H), 6.77-6.68 (m, 2H), 3.39 (s, 6H), 1.44 (s, 9H) ppm; ^{13}C{^{1}H} NMR

($CDCl_3$, 101 MHz): δ 144.0 (C), 134.3 (C), 120.0 (CH), 105.8 (CH), 51.1 (C), 33.8 (CH_3), 31.2 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{13}H_{20}N_3$ (M+H) 218.1652, found 218.1667.

ethyl 4-((1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)amino)piperidine-1-carboxylate (22):

Prepared from *N*-(*p*-fluorobenzyl)-*o*-phenylenediamine (**13**) (216 mg, 1.0 mmol, 1 eq.) and ethyl 4-isocyanopiperidine-1-carboxylate (**14**) (219 mg, 1.2 mmol, 1.2 eq.) according to the general procedure (5 mol % $Pd(OAc)_2$, MeTHF, 18 hours). Purification: EtOAc/cyclohexane/Et_3 (80:20:2). Isolated as a red/brown solid. Yield: 317 mg, 80%. TLC (EtOAc/cyclohexae/Et_3N, 80:20:2 v/v/v): R_f = 0.38; m.p.: 172-179 °C (decomposition) (lit.[31] 181 °C); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.23-7.18 (m, 3H), 7.17-7.12 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.93 (dt, *J* = 7.6, 0.7 Hz, 1H), 6.84 (dt, 7.7, 0.7 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 5.26 (s, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 4.00-3.90 (m, 3H), 2.95 (br, 2H), 1.99 (dd, *J* = 12.8, 2.8, 2H), 1.41 (dq, *J* = 11.6, 3.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 161.4 (d, *J* = 242 Hz, C), 154.7 (C), 153.8 (C), 142.8 (C), 134.3 (C), 133.3 (d, *J* = 3 Hz, C), 129.0 (d, *J* = 8 Hz, CH), 120.6 (CH), 118.5 (CH), 115.4 (d, *J* = 22 Hz, CH), 115.1 (CH), 107.9 (CH), 60.7 (CH_2), 49.6 (CH), 43.7 (CH_2), 42.7 (CH_2), 31.6 (CH_2), 14.7 (CH_3) ppm; IR (neat): νmax (cm^{-1}) = 3333 (w), 1672 (m), 1601 (m), 1560 (s), 1508 (s), 1466 (s), 1450 (s), 1273 (m), 1221 (s), 1142 (s), 1113 (m), 1086 (s), 1030 (m), 829 (m), 814 (m), 733 (s); HRMS (ESI): *m/z* calculated for $C_{22}H_{26}FN_4O_2$ (M+H) 397.2034, found 397.2016.

5.5 References

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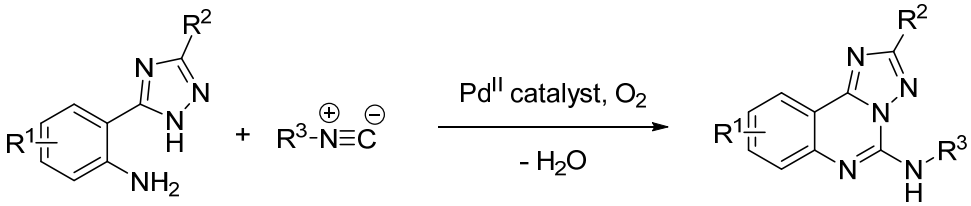
Chapter 6

Heterocyclic Guanidines:

Synthesis of Diverse Azolo[*c*]quinazolines



***Abstract**: Azoles are suitable nucleophiles in the Pd-catalyzed aerobic oxidative coupling of bisnucleophiles and isocyanides, thus allowing the convergent synthesis of valuable azolo[c]quinazolines. The use of azoles poses new challenges to our chemistry because of to the many available unproductive coordination sites and the potential formation of regioisomers.*

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6.1 Introduction

The adenosine A_{2A} receptor is widely recognized for the numerous therapeutic possibilities it offers and selective antagonists for this receptor are highly desired as potential drugs against Parkinson's disease.[1] CGS-15943 was discovered in 1987 and is the first highly potent non-xanthine adenosine receptor antagonist with modest A_{2A} selectivity (Figure 1).[2] Non-xanthine antagonists are preferred over xanthine derived antagonists because of the poor pharmacological properties of xanthines, such as poor water solubility and instability.[1] As a result, the structural motif of CGS-15943 has received significant attention in the last decades, leading to the discovery of SCH-58261 and preladenant (Figure 1). Preladenant very recently successfully completed phase II clinical trials for the treatment of Parkinson's disease,[3] but unfortunately failed phase III trials because it was not more effective than a placebo.

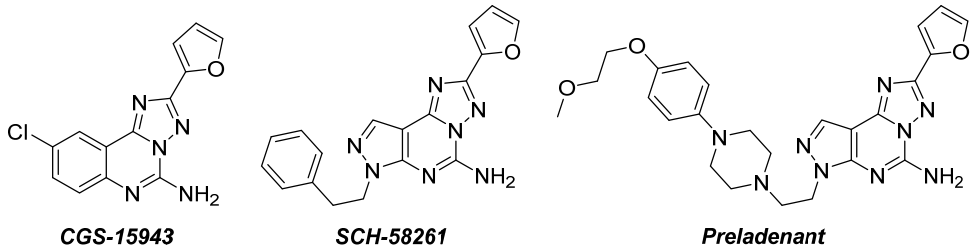
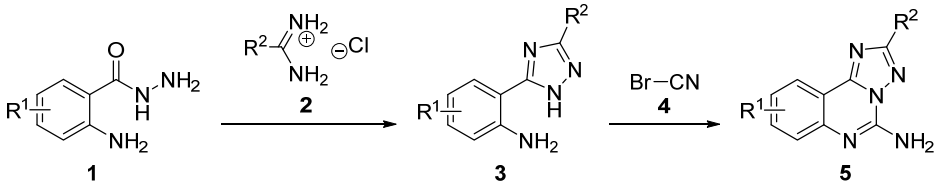


Figure 1. A_{2A} selective adenosine receptor antagonists.

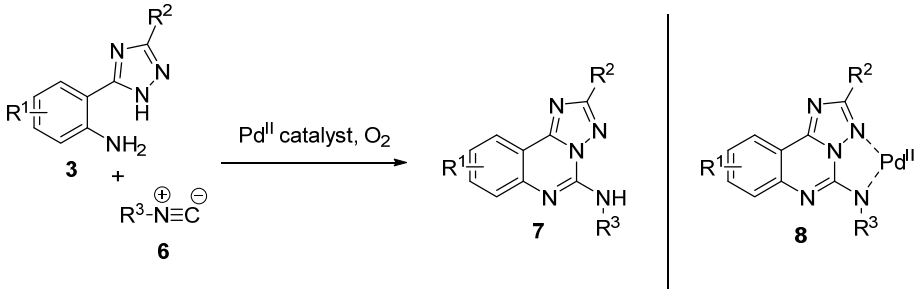


Scheme 1. Synthesis of azolo[*c*]quinazolines.

CGS-15943 and preladenant never made it to the clinic, but it is likely that derivatives will be more successful or other applications for this class of compounds might arise. It is therefore important to have a convenient and convergent synthetic route that makes straightforward and quick library synthesis possible. A recent approach to CGS-15943 (and related) compounds is based on the coupling of readily accessible triazoles (**3**) and cyanogen bromide (**4**, Scheme 1).[4] Triazolo[*c*]quinazolines containing a free 5-amino group (**5**) are easily obtained in this manner, but direct substitution of the exocyclic amino group is not possible *via* this

non-convergent approach. In contrast, mono-alkylated amino groups are typically installed by nucleophilic aromatic substitution of an appropriate leaving group by amines and requires more synthetic steps.[2c] Both approaches are not complementary because they require different precursors and library synthesis is therefore tedious.

We envisioned the use of 2-(2-aminophenyl)-triazoles (**3**) as substrates in our oxidative guanidine synthesis (Chapter 5) to access a broad range of triazolo[*c*]quinazolines (**7**) in a more convergent manner from a single precursor (Scheme 2). There are several new challenges that this substrate class poses to our reaction. For examples, two regioisomers can be formed in this case, potentially leading to lower yields of the desired products. In addition, we have not used an azole as one of the nucleophiles before, which can be challenging due to the reduced nucleophilicity compared to amines. Furthermore, the presence of many heteroatoms in the heterocyclic core provides several unproductive coordination sites for Pd^{II} on both the starting material and the product. Complex **8** seems especially favourable and could potentially result in product inhibition. Owing to the importance of triazolo[*c*]quinazolines in medicinal chemistry, we decided to explore this challenging substrate class in our guanidine synthesis.

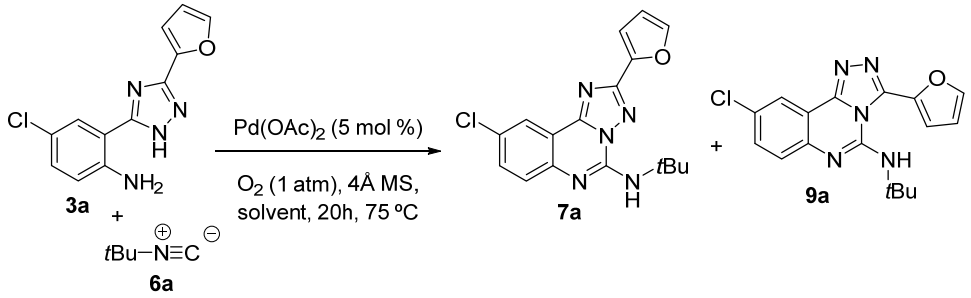


Scheme 2. Our proposed approach and potential product inhibition.

6.2 Results and Discussion

We started our investigations by the conversion of triazole **3a** to product **7a** using our previously established conditions (toluene, 5 mol % $Pd(OAc)_2$, 4Å MS, 75 °C, 20h). A good yield of the desired product was obtained, along with regioisomeric product **9a** (Table 1, entry 1). The formation of significant amounts of **9a** is rather surprising considering the less nucleophilic nitrogen is coupled and the more sterically encumbered product is formed. Fortunately, the two regioisomers are readily separated by flash chromatography. Intensive NMR studies did not provide conclusive evidence for our assigned regioisomers, but an X-ray crystal structure unambiguously confirms the identity of the major isomer **7a** (Figure 2).

Table 1. Reaction optimization.[a]



Entry	Solvent	Conversion of **3a**[b]	Yield of **7a**[b]	Yield of **9a**[b]
1	Toluene	>95%	65%	15%
2	MeCN	>95%	80%	-
3	*t*BuOH	>95%	74%	6%
4	Dioxane	>95%	58%	16%
5	DMF	50%	21%	6%
6	MeTHF	>95%	83%	2%
7[c]	MeTHF	77%	43%	7%
8[d]	MeTHF	>95%	72%	7%
9[d, e]	MeTHF	>95%	81%	4%

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol %), **3a** (0.50 mmol), **6a** (0.6 mmol) and 4Å MS in solvent (5 mL) were stirred for 20h at 75 °C under O_2 atmosphere (1 atm.). [b] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. [c] No 4Å MS used. [d] $Pd(OAc)_2$ (2 mol %) and 2.5 mL MeTHF used [e] Air atmosphere.

A solvent screen revealed the selectivity and yield are highly dependent on the solvent (entry 2-6). MeTHF and acetonitrile give the desired product in high yields and good selectivity, while none of the evaluated solvents gave better selectivity for **9a**. We chose the renewable MeTHF as solvent for further studies.[5] A control experiment revealed that molecular sieves are essential for good yield and selectivity (entry 7). Pleasingly, the catalyst loading and amount of solvent could readily be lowered with only a minor loss in selectivity (entry 8). We performed the reaction under air atmosphere as control experiment and were surprised to find a higher yield and selectivity compared to molecular oxygen atmosphere (entry 9). This result is in stark contrast with our previous work (Chapter 5), where oxygen atmosphere was important for good results. The use of air atmosphere is much more convenient and should make our protocol more accessible and appealing to other chemists.

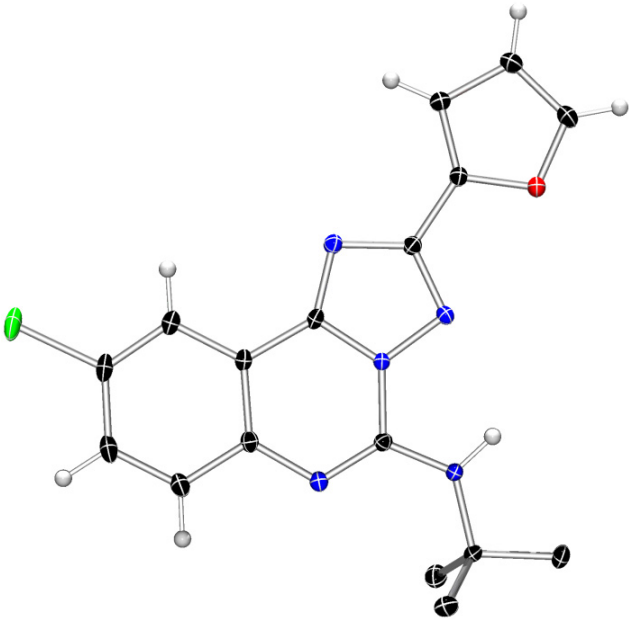
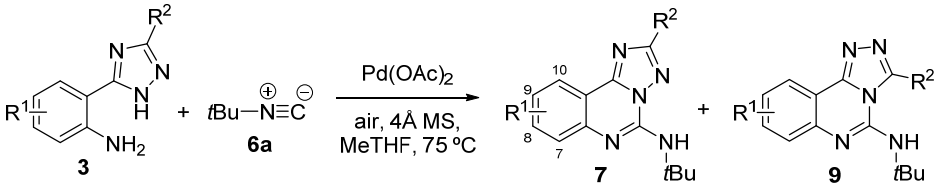
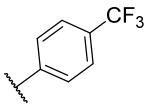
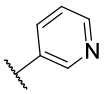
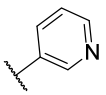
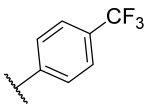


Figure 2. X-ray structure of compound **7a.** Displacement ellipsoids are drawn at 50% probability level. Protons of the *tert*-butyl group are omitted for clarity.

Table 2. Substrate scope.[a]

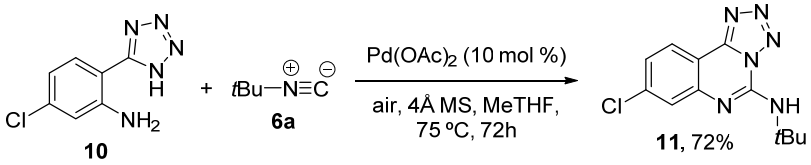


Entry	$Pd(OAc)_2$	Time	R^1[b]	R^2	Product (**7**)	Isomer (**9**)
1	2 mol %	20h	9-Cl		81% (**7a**)	4% (**9a**)
2	4 mol %	20h	9-Cl	Ph	78% (**7b**)	6% (**9b**)
3	5 mol %	44h	9-Cl		83% (**7c**)	<5% (**9c**)[c]
4	10 mol%	44h	9-Cl		65% (**7d**)	-
5	2 mol %	20h	9-F		71% (**7e**)	-
6	4 mol %	20h	H	Ph	75% (**7f**)	9% (**9f**)
7	4 mol %	20h	H		74% (**7g**)	13% (**9g**)
8	2 mol %	20h	7-Me		80% (**7h**)	-
9	6 mol %	20h	7-Me		72% (**7i**)	-
10	5 mol %	44h	8,9-$(OMe)_2$	Ph	74% (**7j**)	-

[a] Standard conditions: **3** (0.5 mmol), **6a** (0.6 mmol), $Pd(OAc)_2$ and 4Å MS (150 mg) in MeTHF (2.5 mL) at 75 °C under air. Yields refer to isolated material. [b] Position is indicated for the case of product **7**, see scheme for numbering. [c] Obtained as mixture with **7c**.

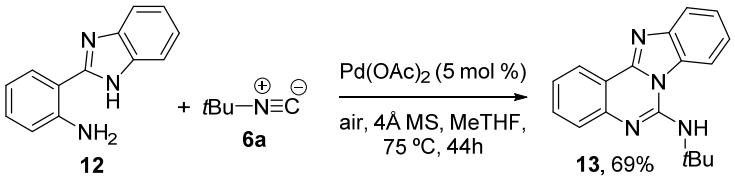
We next evaluated the substrate scope with respect to the triazole (**3**) in the Pd-catalyzed coupling with *tert*-butyl isocyanide (**6a**) using the optimized reaction conditions (Table 2). Pleasingly, a wide range of (hetero)aromatic groups are tolerated on the triazole (R^2 position) after minor tuning of the catalyst loading and reaction time (Table 2, entries 1-4). A remarkably strong effect on the reaction rate of

this group was found, considering the group is far away from the reaction site. In the case of the 3-pyridyl group (entry 4) a catalyst loading as high as 10 mol % was required to obtain an acceptable conversion to the desired product (65%). It is possible the pyridine nitrogen competes as ligand for Pd^{II} and thereby retards the reaction (*vide supra*). In contrast, product **7h** containing the same 3-pyridyl group could be obtained with a much lower catalyst loading (2 mol %). We have no explanation for this surprising result. Various electron-withdrawing and –donating groups are tolerated at the R^1 position and afford the corresponding products in good yields (Table 2, entries 5-10). The use of sterically more congested substrates is tolerated and does not deteriorate the yield or rate of the reaction (entries 8 and 9). Notably, a highly electron-rich substrate possessing two methoxy groups is readily converted to the tricyclic guanidine product (**7j**, 74%).



Scheme 3. Synthesis of 5-aminotetrazolo[1,5-*c*]quinazoline **11**.

Excited by the diverse range of triazoles that could successfully be used, we explored other azoles as coupling partners as well. Tetrazole **10** coupled with *tert*-butyl isocyanide in the presence of 10 mol % $Pd(OAc)_2$ to afford **11** in 72% yield (Scheme 3). To the best of our knowledge, this is the first example of a 5-aminotetrazolo[1,5-*c*]quinazolines containing a monosubstituted 5-amino group. A benzimidazole can also be employed as nucleophile as illustrated by the conversion of commercially available **12** to benzimidazoquinazoline **13** in 69% yield (Scheme 4).

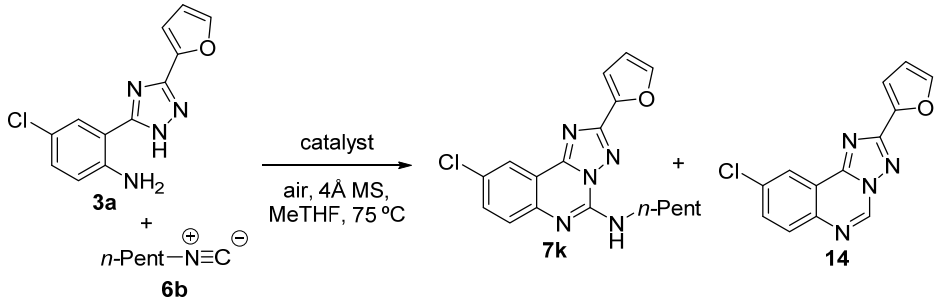


Scheme 4. Synthesis of benzimidazoquinazoline **13**.

After having established the generality with respect to the bisnucleophile, we turned our attention to the compatibility of the reaction with other isocyanides. We hypothesized, based on our previous work described in Chapter 5, that other isocyanides than *tert*-butyl isocyanide might be viable for this substrate class. The

double insertion of isocyanides should be less pronounced in this case because it would result in unfavorable seven-membered rings. Furthermore, there are no opportunities for a second oxidative coupling in these products. In the event, *n*-pentyl isocyanide (**6b**) was readily coupled with 3**a** under the standard reaction conditions with a slightly higher catalyst loading (Table 3, entry 1), albeit in moderate yield (39%). Compound **14**, lacking the 5-amino group, was isolated as a side-product in this reaction. There is literature precedence for such a transformation,[6] but we do not understand why it only occurs if *n*-pentyl isocyanide is used. Perhaps non-catalyzed nucleophilic addition of amine to the isocyanide is more pronounced in this case because *n*-pentyl isocyanide is less electron-rich and thus more electrophilic. The efficiency of the oxidative coupling of **3a** and **6b** could be improved by employing more catalyst, which surprisingly also reduced the formation of **14** (entry 2). This suggests the formation of **14** is indeed not catalyzed by palladium. Palladium pivalate is a slightly better catalyst than palladium acetate and affords the product in 62% isolated yield (entry 3). Addition of more isocyanide (2 eq.) increased the yield (entry 4), but the product was more difficult to purify and was isolated along with trace impurities.

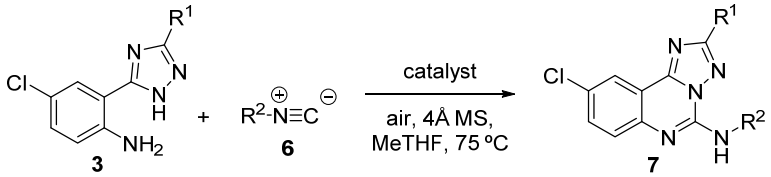
Table 3. Optimization of the reaction conditions with *n*-pentyl isocyanide.[a]

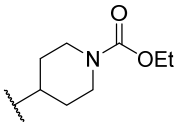
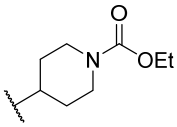


Entry	Catalyst	Time	Yield of **7k**	Yield of **14**
1	$Pd(OAc)_2$ (10 mol %)	44h	39%	18%
2	$Pd(OAc)_2$ (15 mol %)	72h	54%	5%
3	$Pd(OPiv)_2$ (15 mol %)	72h	62%	8%
4[b]	$Pd(OPiv)_2$ (15 mol %)	72h	71%[c]	11%

[a] Reaction conditions: catalyst, **3a** (0.50 mmol), **6b** (0.6 mmol) and 4Å MS (150 mg) in MeTHF (2.5 mL) were stirred at 75 °C under air. Yields refer to isolated material. [b] 2 equivalents **6b** were used. [c] Contains impurities, actual yield is lower.

Table 4. Isocyanide scope.[a]



Entry	Catalyst	Time	R^1	R^2	Yield
1	$Pd(OPiv)_2$ (15 mol %)	72h	2-furyl	*n*Pent	62% (**7k**)
2	$Pd(OPiv)_2$ (15 mol %)	72h	2-furyl	Bn	11% (**7l**)
3	$Pd(OPiv)_2$ (10 mol %)	72h	2-furyl	*i*Pr	43% (**7m**)
4	$Pd(OAc)_2$ (7.5 mol %)	20h	2-furyl	cHex	50% (**7n**)
5	$Pd(OPiv)_2$ (15 mol %)	72h	2-furyl		43% (**7o**)
6	$Pd(OPiv)_2$ (15 mol %)	72h	Ph	*n*Pent	51% (**7p**)
7	$Pd(OAc)_2$ (10 mol %)	72h	Ph	*i*Pr	45% (**7q**)
8	$Pd(OAc)_2$ (10 mol %)	72h	Ph	cHex	57% (**7r**)
9	$Pd(OAc)_2$ (10 mol %)	72h	Ph		38% (**7s**)

[a] Reaction conditions: catalyst, **3** (0.50 mmol), **6** (0.6 mmol) and 4Å MS in MeTHF (2.5 mL) were stirred at 75 °C under air. Yields refer to isolated material.

We next evaluated the isocyanide scope of this transformation (Table 4). Benzyl isocyanide is sterically and electronically similar to pentyl isocyanide, but only a trace amount of the *N*-benzyl product was formed (entry 2). The only sideproduct we could identify was again compound **14**. The most plausible explanation for the poor reactivity of benzyl isocyanide is an undesired reaction on the more activated α-position compared to pentyl isocyanide. We next evaluated isopropyl isocyanide as coupling partner in the presence of 10 mol % catalyst and found a yield of 43% (entry 3). We anticipated a higher yield considering secondary aliphatic isocyanides generally perform better than primary isocyanides. A possible explanation is the volatility of isopropyl isocyanide, and cyclohexyl isocyanide indeed performs slightly better under less forcing conditions (entry 4). Pleasingly, an isocyanide containing a protected amine was readily coupled and provides **7o** in 43% isolated yield (entry 5). Unfortunately, commercially available 2,6-dimethylphenyl isocyanide did not provide an appreciable amount of product (not shown). A less reactive triazole (**3b**)

possessing a phenyl group at the R^1 position also reacted with various isocyanides under the standard conditions (entries 6-9). We chose to use 10 mol % $Pd(OAc)_2$ as catalyst with a long reaction time (72h) as standard conditions for the reactions with secondary isocyanides for convenience and to illustrate generality. It is likely that lower catalyst loadings and/or reaction times are possible after additional optimization.

6.3 Conclusion

We have shown that azoles are suitable nucleophiles in the Pd^{II}-catalyzed aerobic oxidative coupling of bisnucleophiles and isocyanides. Various medicinally important azolo[*c*]quinazolines were readily obtained by coupling of 2-(2-aminophenyl)-azoles with isocyanides using air as the stoichiometric oxidant. In most of these reactions two regioisomeric products could potentially be formed, but high selectivity is obtained if renewable 2-MeTHF is used as the solvent. The high number of heteroatoms present in the products is challenging for this chemistry because it offers several unproductive coordination sites for Pd^{II}, which possibly explains the higher catalyst loading required for some substrates. The relative ease with which the aerobic oxidative guanidine synthesis could be applied to these difficult substrates is indicative of the broad utility of this chemistry.

6.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Carboxamidine hydrochloride salts were prepared according to literature or obtained commercially.[7] Palladium acetate and palladium pivalate were obtained from Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled prior to use. Other solvents were used as purchased. 4Å molecular sieves were purchased from Sigma Aldrich and activated before use. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 400 or 500 (100.62 or 125.78 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, $^{13}C\{^{1}H\}$: δ 77.16 ppm for $CDCl_3$, ^{1}H: δ 2.50 ppm, $^{13}C\{^{1}H\}$: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Melting points were recorded on a Büchi M-565 melting point apparatus. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm).

X-ray data

The crystallographic information file (CIF) for compound **7a** is available upon request per e-mail (t.vlaar@vu.nl). We thank Dr. Christophe van Vande Velde (University of Antwerp) for X-ray structure determination and Prof. Dr. Matthias Zeller (Youngstown State University) for the collection of the X-ray data set. The diffractometer was funded by NSF grant 0087210, Ohio Board of Regents grant CAP-491, and YSU.

Synthesis of substrates

Synthesis of 2-aminobenzhydrazides (1):
Method A (from isatoic anhydrides): An aqueous 18% hydrazine solution (13 eq.) was added to the corresponding isatoic anhydride (1 eq.) and the mixture was stirred at room temperature. After 4.5 h the product was filtered off, washed with H_2O, dried *in vacuo* and used without further purification. **Method B (from methyl 2-aminobenzoates):** Hydrazine monohydrate (8 eq.) was added to the corresponding methyl 2-aminobenzoate derivative (1 eq.) and the mixture was refluxed for 3h. The mixture was cooled to room temperature and the product was filtered off, washed with H_2O and used without further purification unless mentioned otherwise below.

2-Amino-5-chlorobenzhydrazide:

Prepared from 5-chloroisatoic anhydride (9.88 g, 50 mmol) according to method A. Isolated as a white solid. Yield: 7.70 g, 83%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.27; m.p.: 139-140 °C (Lit.[8] 129-134 °C); ^{1}H NMR (DMSO-d_6, 500 MHz,): δ 9.59 (s, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.15 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.45 (s, 2H), 4.40 (br s, 2H); ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 167.3 (C), 148.3 (C), 131.3 (CH), 127.0 (CH), 117.8 (CH),117.8 (C), 114.6 (C); IR (neat) νmax (cm^{-1}) = 3283 (m), 1610 (s), 1578 (m), 1512 (m), 1479 (s), 1298 (s), 1254 (s), 1157 (m), 891 (s), 827 (s); HRMS (ESI): *m/z* calculated for $C_7H_9N_3OCl$ (M+H) 186.0429, found 186.0429.

2-Aminobenzhydrazide:

Prepared from isatoic anhydride (8.16 g, 50 mmol) according to method A. Isolated as a beige solid. Yield: 5.08 g, 67%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.23; m.p.: 118-120 °C (decomposition) (Lit.[9] 122-124 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): *δ* 9.46 (s, 1H), 7.41 (dd, *J* = 8.0, 1.5Hz, 1H), 7.15-7.07 (m, 1H), 6.68 (dd, (*J* = 8.0, 1.0 Hz, 1H), 6.51-6.44 (m, 1H), 6.31 (s, 2H), 4,38 (br s, 2H); ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): *δ* 168.6 (C), 149.4 (C), 131.6 (CH), 127.7 (CH), 116.3 (CH), 114.7 (CH), 113.7 (C); IR (neat) νmax (cm^{-1}) = 3443 (s), 3323 (s), 3175 (br), 1616 (s), 1576 (s), 1560 (s), 1504 (s), 1479 (s), 1448 (s), 1215 (m), 1261 (s), 1150 (s), 957 (s), 743 (s); HRMS (ESI): *m/z* calculated for $C_7H_{10}N_3O$ (M+H) 152.0818, found 152.0817.

2-Amino-4,5-dimethoxybenzhydrazide:

Prepared from methyl 2-amino-4,5-dimethoxybenzoate (6.33 g, 30 mmol) according to method B. Isolated as an off white solid. Yield: 6.11 g, 96%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.20; m.p.: 175-177 °C (Lit.[10] 178-179 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.28 (s, 1H), 7.05 (s, 1H), 6.30 (s, 1H), 6.25 (s, 2H), 4.29 (br s, 2H), 3.70 (s, 3H), 3.65 (s, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz): δ 168.9 (C), 153.0 (C), 146.3 (C), 139.5 (C), 111.9 (CH), 104.3 (C), 100.3 (CH), 56.8 (CH_3), 55.5 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3304 (m), 3267 (br), 1630 (m), 1591 (m), 1506 (s), 1468 (m), 1263 (m), 1211 (s), 1150 (s), 1086 (s), 957 (m), 868 (s); HRMS (ESI): *m/z* calculated for $C_9H_{14}N_3O_3$ (M+H) 212.1030, found 212.1023.

2-Amino-5-fluorobenzhydrazide:

Prepared from methyl 2-amino-5-fluorobenzoate (3.72 g, 22 mmol) according to method B. Isolated as a white solid. Yield: 2.59 g, 70%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.20; m.p.: 130-131 °C (Lit.[10] 128-130 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.54 (s, 1H), 7.26 (dd, *J* = 10.0, 3.0 Hz, 1H), 7.06-6.98 (m, 1H), 6.70 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.23 (s, 2H), 4.40 (s, 2H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 167.5 (d, *J* = 2.5 Hz, C), 152.7 (d, *J* = 229 Hz, C), 146.1 (C), 119.0 (d, *J* = 23 Hz, CH), 117.4 (d, *J* = 6.3 Hz, CH), 113.4 (d, *J* = 5 Hz, C), 113.2 (d, *J* = 23 Hz, CH) ppm; IR (neat): vmax (cm^{-1}) = 3325 (m), 1589 (m), 1568 (s), 1508 (s), 1481 (s), 1221 (s), 1144 (m), 972 (s), 881 (s), 820 (s); HRMS (ESI): *m/z* calculated for $C_7H_9FN_3O$ (M+H) 170.0724, found 170.0724.

2-Amino-3-methylbenzhydrazide:

Prepared from methyl 2-amino-3-methylbenzoate (3.30 g, 20 mmol) according to method B. Additional purification by recrystallization from EtOH was required. Isolated as a white solid. Yield: 1.78 g, 54%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.25; m.p.: 161-162 °C (Lit.[11] 155-158 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.47 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H),

6.45 (t, *J* = 7.5 Hz, 1H), 6.14 (s, 2H), 4.38 (s, 2H), 2.08 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 126 MHz): δ 168.9 (C), 147.3 (C), 132.4 (CH), 125.5 (CH), 122.9 (C), 114.6 (CH), 113.7 (C), 17.6 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3446 (m), 3340 (m), 3284 (m), 1614 (s), 1571 (s), 1510 (s), 1288 (m), 1259 (m), 962 (m), 750 (s); HRMS (ESI): *m/z* calculated for $C_8H_{12}N_3O$ (M+H) 166.0975, found 166.0971.

Synthesis of triazoles (3):

Method A:[2c] A solution of carboxamidine hydrochloride salt (10 mmol, 1 eq.) in EtOH (30 mL) was added to a solution of sodium methoxide (11 mmol, 1.1 eq.) in EtOH (25 mL) and stirred for 15 minutes. Subsequently a solution of 2-aminobenzhydrazide (11 mmol, 1.1 eq.) in chlorobenzene (100 mL) was added to the white suspension. A Dean-Stark trap was placed and the temperature was raised to 130 °C. Once distillation ceased, the Dean Stark trap was removed and an addition funnel with activated 4Å molecular sieves was placed between the flask and the condenser. The mixture was refluxed for 22h. The mixture was cooled down to room temperature and filtered. The residue was partitioned between EtOAc/H_2O and the two layers were separated. The water layer was extracted with EtOAc (2x) and the combined organic extracts were washed with brine and dried (Na_2SO_4). If necessary, the product was further purified by flash chromatography (see below). **Method B:**[12] The corresponding carboxamidine hydrochloride (1.5 eq.) was added to a solution of sodium methoxide (2 eq.) in dry EtOH and the mixture was stirred for 3h under nitrogen. The mixture was filtered, concentrated and dissolved in dry chlorobenzene. The 2-aminobenzhydrazide derivative (1 eq.) was added and the solution was refluxed for 46 h. The mixture was cooled to room temperature, concentrated and triturated with water. If necessary, the product was further purified by trituration with cyclohexane and/or flash chromatography (see below).

*Note: the presence of two rotamers or tautomers in the ^{1}H NMR spectrum makes analysis difficult, but the purity is readily established. For some compounds two rotamers or tautomers were observed in ^{1}H NMR and both are described for these cases. In other cases peak broadening was observed. Complete and clear ^{13}C NMR spectra could not be obtained for most triazoles (**6**) because of problems associated with these rotamers or tautomers, which might explain the lack of ^{13}C NMR spectra for such compounds in the literature.[4] High temperature (130 °C) NMR experiments did in some cases help to verify the identity and purity of these compounds.*

3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (3a):

Prepared from furan-2-carboxamidine hydrochloride (15 mmol) and 2-amino-5-chlorobenzhydrazide (10 mmol) according to method B (40 mL dry EtOH, 40 mL dry chlorobenzene). Also triturated with cyclohexane. Isolated as an off-white solid. Yield: 2.32 g, 89%. TLC (MeOH/$CHCl_3$, 1:24 v/v): R_f = 0.38; m.p.: 251-252 °C (decomposition) (Lit.[2c] 246-249 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 14.71 (s, 1H, isomer A), 14.40 (br s, 1H, isomer B), 7.96 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 15 Hz, 1H), 7.20-6.60 (m, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 126 MHz): δ 145.8 (C), 126.5 (CH), 118.5 (C), 117.7 (CH), 112.0 (CH) ppm, *the rest of the carbon signals were not observed*; IR (neat) νmax (cm^{-1}) = 3464 (m), 3344 (m), 3130 (m), 1740 (w), 1612 (s), 1549 (s), 1493 (s), 1418 (m), 1369 (s), 1317 (s), 1296 (s), 1186 (m), 1157 (s), 1099 (s), 1020 (s), 991 (s), 905 (s), 876 (s), 808 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{10}ClN_4O$ (M+H) 261.0538, found 261.0539.

3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (3b):
Prepared from benzamidine hydrochloride (15 mmol) and 2-amino-5-chlorobenzhydrazide (10 mmol) according to method B (40 mL dry ethanol, 40 mL dry chlorobenzene). Purified by flash chromatography using EtOAc/MeOH (9:1) as eluent. Isolated as an off white solid. Yield: 1.84 g, 68%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.36; m.p.: >256 °C (decomposition) (Lit.[8] 254-255 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.66 (br s, 1H, isomer A), 14.36 (br s, 1H, isomer B), 8.10 (d, *J* = 7.6 Hz, 2H), 8.00 (s, 1H, isomer A), 7.86 (s, 1H, Isomer B), 7.55-7.45 (m, 3H), 7.22-6.56 (m, 4H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.0 (C, isomer A), 160.4 (C, isomer B), 154.2 (C, isomer B), 153.9 (C, isomer A), 146.1 (C, isomer A), 145.6 (C, isomer B), 130.9 (C, isomer probably overlaps with CH signals), 130.6 (CH, isomer A), 130.4 (CH, isomer B), 129.1 (CH), 128.8 (CH), 126.9 (CH, isomer A), 126.3 (CH, isomer B), 126.0 (CH, isomer B), 125.9 (CH, isomer A), 118.5 (C), 118.0 (CH, isomer A), 117.4 (CH, isomer B), 113.7 (C, isomer A), 108.8 (C, isomer B) ppm; IR (neat): vmax (cm^{-1}) = 3475 (s), 3302 (s), 3055 (m), 1589 (s), 1553 (m), 1492 (s), 1443 (s), 1387 (m), 1315 (s), 1161 (s), 1101 (m), 1072 (m), 1003 (s), 879 (s), 808 (s); HRMS (ESI): *m/z* calculated for $C_{14}H_{12}ClN_4$ (M+H) 271.0745, found 271.0727.

3-(4-trifluoromethylphenyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (3c):
Prepared from 4-trifluoromethylphenylcarboxamidine hydrochloride (2 mmol) and 2-amino-5-chlorobenzhydrazide (1.33 mmol) according to method B (5.3 mL dry ethanol, 5.3 mL dry chlorobenzene). Purified by flash chromatography using cyclohexane/EtOAc (2: 1 → 1:1) as eluent. Isolated as a yellow solid. Yield: 294 mg, 65%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.42; m.p.: 242.3-245.0 °C (decomposition); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.65 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 2H), 7.92-7.86 (m, 3H), 7.19 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.04-6.71 (br s, 2H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz): δ 146.0 (C) 130.3 (CH), 129.5 (C, q, *J* = 31.2 Hz), 126.7 (CH), 126.3 (CH), 125.9 (CH, q, *J* = 4.0 Hz), 124.1 (C, q, *J* = 270 Hz), 118.5 (C), 117.9 (CH) ppm, *four quaternary carbon signals were not observed*; IR (neat): vmax (cm^{-1}) = 3491 (m), 3329 (m), 3132 (w), 3065 (w), 2972 (w), 1624 (m), 1603 (m), 1551 (m), 1495 (s), 1448 (w), 1423 (s), 1379 (w), 1319 (s), 1261 (w), 1175 (m), 1151 (s), 1097 (s), 1061 (s), 1016 (s), 1001 (s), 987 (s), 879 (m), 847 (s), 812 (s), 762 (s); HRMS (ESI): *m/z* calculated for $C_{15}H_{11}ClF_3N_4$ (M+H) 339.0619, found 339.0622.

3-(3-pyridyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (3d):
Prepared from 3-pyridinecarboxamidine hydrochloride (3 mmol) and 2-amino-5-chlorobenzhydrazide (2 mmol) according to method B (5.3 mL dry ethanol, 5.3 mL dry chlorobenzene) with longer reaction time (68 hours). Also triturated with cyclohexane. Purified by flash chromatography using cyclohexane/EtOAc/MeOH (1:1:0 → 0:10:1 gradient) as eluent. Isolated as a yellow solid. Yield: 374 mg, 68%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.34; m.p.: >290 °C (decomposition); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.61 (br s, 1H), 9.28 (s, 1H), 8.67 (d, *J* = 4.8 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 7.56 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.19 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.04-6.67 (br s, 2H), 6.88 (d, *J* = 8.8 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 161.3 (C, isomer A), 158.3 (C, isomer B), 154.5 (C, isomer B), 151.8 (C, isomer A), 151.2 (CH, isomer A), 150.1 (CH, isomer B), 147.3 (CH, isomer A), 147.0 (CH, isomer B), 146.2 (C, isomer B), 145.6 (C, isomer A), 133.9 (CH, isomer A), 133.3 (CH, isomer B), 130.8 (CH, isomer B), 129.4 (CH, isomer A), 126.9 (CH, isomer A), 126.7 (C, isomer B), 126.0 (CH, isomer B), 124.2 (CH, isomer A), 124.0 (CH, isomer B), 123.1 (C, isomer A), 118.5 (C, isomer A), 118.4 (C, isomer B),

118.1 (CH, isomer B), 117.5 (CH, isomer A), 113.3 (C, isomer A), 108.4 (C, isomer B) ppm; IR (neat): vmax (cm^{-1}) = 3450 (m), 3317 (m), 2777 (br), 1601 (m), 1558 (s), 1495 (s), 1448 (m), 1375 (m), 1306 (m), 1263 (w), 1248 (w), 1176 (w), 1155 (m), 1097 (m), 1043 (m), 1030 (m), 984 (s), 879 (m), 818 (s), 806 (s), 756 (s), 706 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{11}ClN_5$ (M+H) 272.0697, found 272.0693.

3-(2-furyl)-5-(2-amino-5-fluorophenyl)-1,2,4-triazole (3e):

Prepared from furan-2-carboxamidine hydrochloride (15 mmol) and 2-amino-5-fluorobenzhydrazide (10 mmol) according to method B. Purified by flash chromatography using cyclohexane/EtOAc (2:1 > 0:1) as eluent and recrystallization from toluene. Isolated as a yellow solid. Yield: 1.68 g, 69%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.33; m.p.: 235-236 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.66 (br s, 1H), 7.89 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.10 (s, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 8.8, 5.2 Hz, 1H), 6.69 (s, 1H), 6.47 (br s, 2H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 154.3 (C), 152.4 (C), 143.7 (C, br), 128.9 (CH), 128.2 (CH), 125.3 (CH), 117.4 (CH, br), 112.6 (CH, br), 112.0 (CH) ppm, *three quaternary carbon signals were not observed*; IR (neat): vmax (cm^{-1}) = 3466 (w), 3362 (w), 3134 (w), 3063 (w), 2970 (w), 2895 (w), 2827 (w), 1553 (m), 1508 (s), 1418 (s), 1312 (m), 1254 (m), 1211 (m), 1182 (m), 1146 (m), 1117 (m), 1022 (w), 999 (s), 906 (s), 866 (m), 810 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{10}FN_4O$ (M+H) 245.0833, found 245.0835.

3-phenyl-5-(2-aminophenyl)-1,2,4-triazole (3f):

Prepared from benzamidine hydrochloride and 2-aminobenzhydrazide according to method A. Isolated as an off white solid. Yield: 1.25 g, 53%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.36; m.p.: 187-188 °C (decomposition) (Lit.[13] 189-190 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.44 (br, 1H, isomer A), 14.29 (br, 1H, isomer B), 8.09 (d, *J* = 7.6 Hz, 2H), 7.77 (br s, 1H), 7.59-7.41 (m, 3H), 7.15 (br s, 1H), 6.95-6.35 (m, 4H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz): δ 147.0 (C), 130.4 (CH), 129.5 (CH), 128.9 (CH), 127.3 (CH), 126.0 (CH), 116.1 (CH), 115.3 (CH) ppm, *four quaternary carbon signals were not observed* ; IR (neat): vmax (cm^{-1}) = 3061 (m), 2922 (m), 1610 (s), 1599 (s),1556 (s), 1470 (s), 1443 (s), 1394 (s), 1333 (s), 1153 (s), 1134 (s), 1068 (m), 1038 (m), 993 (s), 786 (s); HRMS (ESI): *m/z* calculated for $C_{14}H_{13}N_4$ (M + H) 237.1135, found 237.1136.

3-(2-furyl)-5-(2-aminophenyl)-1,2,4-triazole (3g):

Prepared from furan-2-carboxamidine hydrochloride and 2-aminobenzhydrazide according to method A. Purification using flash chromatography with EtOAc/cyclohexane (1:1 → 9:1) as eluent was required. Isolated as an off white solid. Yield: 1.24 g, 55%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.38; m.p.: 204.9-206.5 °C (decomposition) (Lit.[4] 234-236 °C); ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 14.43 (br, 1H), 7.87-7.70 (m, 2H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.06 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.66-6.62 (m, 2H), 6.90-6.30 (br, 2H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz, 130 °C): δ 146.3 (C), 143.1 (CH), 129.6 (CH), 127.0 (CH), 115.7 (CH), 114.9 (CH), 110.9 (CH), 108.9 (CH) ppm, *four quaternary carbon signals were not observed*; IR (neat): vmax (cm^{-1}) = 1616 (s), 1551 (s), 1504 (s), 1339 (s), 1296 (m), 1157 (s), 1016 (s), 905 (s); HRMS (ESI): m/z calculated for $C_{12}H_{11}N_4O$ (M+H) 227.0927, found 227.0926.

3-(3-pyridyl)-5-(2-amino-3-methylphenyl)-1,2,4-triazole (3h):

Prepared from 3-pyridinecarboxamidine hydrochloride (3 mmol) and 2-amino-3-methylbenzhydrazide (2 mmol) according to method B (5.3 mL dry ethanol, 5.3 mL dry chlorobenzene) with longer reaction time (68 hours). Also triturated with cyclohexane. Isolated as a yellow solid. Yield: 448 mg, 89%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.49; m.p.: 217.2-218.5 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.66 (s, 1H), 9.27 (s, 1H), 8.65 (d, *J* = 4.8 Hz, 1H), 8.40 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.68 – 6.47 (br s, 2H), 2.18 (s, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 165.7 (CH), 157.4 (C), 156.5 (C), 150.1 (CH), 147.0 (CH), 145.1 (C), 133.2 (CH), 131.5 (CH), 126.2 (C), 125.2 (CH), 124.0 (CH), 123.0 (C), 115.3 (CH), 108.7 (C), 17.9 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3393 (m), 3312 (w), 3117 (w), 3063 (w), 2984 (w), 2912 (w), 2804 (w), 2359 (w), 1636 (m), 1607 (s), 1578 (m), 1551 (m), 1475 (m), 1464 (m), 1404 (s), 1329 (m), 1286 (m), 1256 (w), 1173 (m), 1122 (m), 1088 (w), 1018 (m), 987 (m), 945 (w), 920 (w), 837 (w), 806 (m), 775 (w), 743 (s), 725 (s), 696 (s), 633 (m); HRMS (ESI): *m/z* calculated for $C_{14}H_{14}N_5$ (M+H) 252.1244, found 252.1243.

3-(4-trifluoromethylphenyl)-5-(2-amino-3-methylphenyl)-1,2,4-triazole (3i):

Prepared from 4-trifluoromethylphenylcarboxamidine hydrochloride (2 mmol) and 2-amino-3-methylbenzhydrazide (1.33 mmol) according to method B (5.3 mL dry ethanol, 5.3 mL dry chlorobenzene). Purified by flash chromatography using cyclohexane/EtOAc (2:1) as eluent. Isolated as a yellow solid. Yield: 265 mg, 62%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.42; m.p.: 248.7 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.52 (br s, 1H), 8.29 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.72 (br s, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.62 (t, *J* = 7.6 Hz, 1H), 6.78-6.40 (br s, 2H), 2.18 (s, 3H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 162.7 (C, isomer A), 159.0 (C, isomer B), 156.0 (C, isomer B), 152.3 (C, isomer A), 145.3 (C, isomer B), 144.7 (C, isomer A), 134.9 (C, isomer B), 131.9 (CH, isomer B), 130.8 (C, isomer A), 130.7 (CH, isomer A), 129.1 (C, q, *J* = 31.5 Hz), 127.0 (CH, isomer A), 126.4 (CH, isomer B), 126.2 (CH, isomer A), 125.8 (CH, q, *J* = 3.8 Hz), 124.9 (CH, isomer B), 124.3 (C, q, *J* = 272 Hz), 123.3 (C, isomer B), 122.5 (C, isomer A), 115.3 (CH), 112.2 (C, isomer A), 107.5 (C, isomer B), 17.9 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3398 (w), 3308 (w), 3211 (w), 2345 (w), 1624 (m), 1541 (w), 1481 (m), 1421 (w), 1323 (s), 1252 (w), 1171 (m), 1155 (m), 1115 (s), 1103 (s), 1065 (s), 1014 (s), 993 (m), 849 (s), 789 (w); HRMS (ESI): *m/z* calculated for $C_{16}H_{14}F_3N_4$ (M+H) 319.1165, found 319.1162.

3-phenyl-5-(2-amino-4,5-dimethoxyphenyl)-1,2,4-triazole (3j):

Prepared from benzamidine hydrochloride (3 mmol) and 2-amino-4,5-dimethoxybenzhydrazide (2 mmol) according to method B (5.3 mL dry ethanol, 5.3 mL dry chlorobenzene). Purified by flash chromatography using cyclohexane/EtOAc/MeOH (2:1:0 → 0:10:1 gradient) as eluent. Isolated as a yellow solid. Yield: 307 mg, 52%. TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.46; m.p.: >80 °C (decomposition); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.32 (s, 1H isomer A), 14.03 (s, 1H, isomer B), 8.08 (d, *J* = 8.1 Hz, 2H), 7.61-7.28 (m, 4H), 6.47 (s, 1H), 6.80-6.10 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H) ppm; IR (neat): vmax (cm^{-1}) = 3369 (w), 3265 (m), 3001 (w), 2941 (w), 2841 (w), 2357 (w), 1628 (m), 1601 (m), 1551 (w), 1508 (s), 1466 (s), 1458 (s), 1439 (s), 1396 (m), 1258 (s), 1223 (s), 1209 (s), 1167 (s), 1094 (m), 1070 (s), 1014 (w), 987 (m), 964 (m), 930 (w), 837 (s), 816 (s), 791 (m), 756 (w), 721 (w); HRMS (ESI): *m/z* calculated for $C_{16}H_{17}N_4O_2$ (M+H) 297.1346, found 297.1356.

5-(2-amino-4-chlorophenyl)-tetrazole (10):
Sodium azide (845 mg, 13 mmol, 1.3 eq.) was added to a mixture of triethylamine hydrochloride (1.79 g, 13 mmol, 1.3 eq.) and 2-amino-4-chlorobenzonitrile (1.53 g, 10 mmol, 1 eq.) in toluene (23 mL). The mixture was stirred for 17h at 100 °C, then cooled to room temperature and washed with H_2O (3x). The combined aqueous layers were acidified with aq. 3M HCl (3.2 mL) and the product was filtered off as a beige solid and dried (1.53 g, 78%). TLC ($CHCl_3$/MeOH, 24:1 v/v): R_f = 0.49; m.p.: >180 °C (decomposition) (Lit.[14] 192-194 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): *δ* 7.73 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H) ppm, *NH protons were not observed*; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 154.4 (C), 148.6 (C), 136.4 (C), 129.8 (CH), 115.4 (CH), 115.2 (CH), 103.9 (C) ppm; IR (neat): vmax (cm^{-1}) = 3479 (m), 3346 (m), 3067 (w), 3022 (w), 2976 (w), 2912 (w), 2772 (w), 1622 (s), 1609 (s), 1560 (s), 1551 (m), 1485 (s), 1447 (m), 1406 (w), 1360 (w), 1327 (w), 1288 (w), 1256 (s), 1155 (w), 1113 (m), 1090 (w), 1057 (m), 991 (w), 908 (m), 843 (m), 800 (w), 748 (s); HRMS (ESI): *m/z* calculated for $C_7H_7ClN_5$ (M+H) 196.0384, found 196.0383.

General synthetic procedures

Optimization of the oxidative coupling of triazole 3a and *tert*-butyl isocyanide:
A Radleys parallel synthesis unit was used to simultaneously run multiple reactions. A Radleys tube was charged with 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg, 0.5 mmol, 1 eq.), $Pd(OAc)_2$ and 4Å MS (150 mg). If O_2 atmosphere was used, the reaction vessel was placed under vacuum and backfilled with O_2 (3x) at this point. Then, the indicated solvent and *tert*-butyl isocyanide (68 µL, 0.6 mmol, 1.2 eq.) were added and the resulting mixture was stirred at 75 °C for 20 hours under a reflux condenser. A balloon was used for reactions under O_2 atmosphere. Afterwards, the crude reaction mixture was filtered through Celite with thorough washing (EtOAc) and concentrated. The conversion of **3a** and yield of **7a** and **9a** were determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard.

General procedure for the synthesis of azolo[*c*]quinazolines by aerobic oxidative coupling of (2-aminophenyl)-azoles and isocyanides:
A 10 mL round-bottom flask equipped with a reflux condenser was charged with the corresponding (2-aminophenyl)-azole (0.5 mmol, 1 eq.), Pd catalyst and 4Å molecular sieves (150 mg). Next, 2-methyltetrahydrofuran (2.5 mL) and the isocyanide (0.6 mmol, 1.2 eq.) were added and the reaction mixture was stirred at 75 °C for the indicated time under air atmosphere. The mixture was cooled to room temperature, filtered through Celite (DCM) and concentrated. The residue was purified by flash chromatography (SiO_2) using the indicated eluent.
Note: it is likely some of the solvent evaporated during the course of the reaction, especially in the case of longer reaction times. It is possible this has sped up or otherwise had an effect on the reaction outcome.

Spectral data

2-(2-furyl)-5-(*tert*-butylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7a):
Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (2 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). The product (7**a**) was isolated as a white solid (139 mg, 81%) and regioisomer **9a** as a white solid (6.4 mg, 4%). **Spectral data of 7a**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v): R_f = 0.67; m.p.: 198-199 °C (Lit.[2c] 193-195 °C); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.37 (d, *J* = 2 Hz, 1H), 7.66-7.62 (m, 2H), 7.60-7.56 (m, 1H), 7.27 (s, 1H), 6.61 (s, 1H), 6.18 (s, 1H), 1.66 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 156.1 (C), 151.1 (C), 145.8 (C), 144.6 (CH), 143.4 (C), 141.8 (C), 132.6 (CH), 129.0 (C), 127.8 (CH), 123.2 (CH), 114.6 (C), 112.4 (CH), 112.1 (CH), 52.9 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3414 (m), 3117 (w), 2974 (w), 1618 (s), 1556 (s), 1529 (s), 1508 (s), 1475 (s), 1431 (s), 1225 (s), 1192 (s), 1121 (m), 1074 (m), 1008 (s), 982 (m), 820 (s); HRMS (ESI): *m/z* calculated for $C_{17}H_{17}ClN_5O$ (M+H) 342.1116, found 342.1099. **Spectral data of 9a**: TLC (cyclohexane/EtOAc/Et_3N, 10:10:0.5 v/v/v): R_f = 0.67; m.p.: 202.4-204.2 °C (decomposition); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.47 (s, 1H), 7.74 (s, 1H), 7.54 (s, 2H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.73 (s, 1H), 5.93 (s, 1H), 1.49 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$,126 MHz): δ 150.6 (C), 145.0 (CH), 141.8 (C), 140.4 (C), 139.4 (C), 138.4 (C), 132.5 (CH), 129.7 (C), 127.0 (CH), 123.0 (CH), 117.0 (CH), 113.9 (C), 113.0 (CH), 53.1 (C), 28.7 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3423 (m), 3402 (m), 1634 (s), 1558 (m), 1524 (m), 1474 (s), 1427 (w), 1360 (m), 1310 (m), 1202 (s), 1180 (m), 1072 (w), 1034 (m), 1011 (m), 899 (s), 883 (s), 820 (s); HRMS (ESI): m/z calculated for $C_{17}H_{17}ClN_5O$ (M+H) 342.1116, found 342.1114.

2-phenyl-5-(*tert*-butylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7b):
Prepared from 3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3b**) (135 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (4 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (80:10:0.5 → 10:10:0.5). The product (**7b**) was isolated as a white solid (137 mg, 78%) and regioisomer **9b** as a yellow solid (10 mg, 6%). **Spectral data of 7b**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.75; m.p.: 174.5-175.8 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.37 (d, *J* = 2.0 Hz, 1H), 8.33 (d, *J* = 6.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.55-7.48 (m, 3H), 6.22 (s, 1H), 1.67 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): *δ* 163.5 (C), 151.2 (C), 143.3 (C), 141.9 (C), 132.3 (CH), 130.6 (CH), 130.3 (C), 128.9 (CH), 128.9 (C), 127.8 (CH), 127.6 (CH), 123.1 (CH), 114.9 (C), 52.7 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3396 (m), 2964 (w), 2928 (w), 2870 (w), 1632 (s), 1620 (s), 1560 (s), 1533 (s), 1522 (s), 1479 (s), 1443 (s), 1393 (m), 1358 (s), 1350 (m), 1327 (w), 1285 (m), 1246 (m), 1213 (s), 1173 (m), 1128 (w), 1149 (w), 1074 (m), 1024 (m), 928 (w), 872 (m), 820 (s), 779 (w), 764 (m), 725 (s); HRMS (ESI): *m/z* calculated for $C_{19}H_{19}ClN_5$ (M+H) 352.1323, found 352.1323. **Spectral data of 9b**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.07; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.47 (t, *J* = 1.4 Hz, 1H), 7.71-7.58 (m, 5H), 7.53 (d, *J* = 1.5 Hz, 2H), 4.83 (s, 1H), 1.29 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): *δ* 150.0 (C), 146.4 (C), 141.8 (C), 139.6 (C), 132.1 (CH), 131.6 (CH), 131.0 (CH), 129.6 (C), 129.2 (CH), 127.4 (C), 127.1 (CH), 122.9 (CH), 114.5 (C), 53.0 (C), 28.6 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{19}H_{19}ClN_5$ (M+H) 352.1323, found 352.1332.

2-(4-trifluoromethylphenyl)-5-(*tert*-butylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7c):

Prepared from 3-(4-trifluoromethylphenyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3c**) (170 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (5 mol % $Pd(OAc)_2$, 44 hours). Purification: cyclohexane/EtOAc/Et_3N (100:10:0.5 → 50:50:0.5). Isolated as a white solid. Yield: 175 mg, 83%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.74; m.p.: 203.5-204.8 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.43 (d, *J* = 8.1 Hz, 2H), 8.33 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.56 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.17 (s, 1H), 1.66 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 162.1 (C), 151.3 (C), 143.3 (C), 141.7 (C), 133.7 (C), 132.6 (CH), 132.2 (q, *J* = 32.6 Hz, C), 129.1 (C), 127.9 (CH), 127.9 (CH), 125.8 (q, *J* = 3.8 Hz, CH), 124.2 (q, *J* = 272 Hz, C), 123.1 (CH), 114.8 (C), 52.8 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3391 (m), 2968 (w), 2935 (w), 1632 (s), 1560 (s), 1533 (m), 1483 (m), 1458 (m), 1414 (w), 1393 (w), 1366 (m), 1321 (s), 1283 (m), 1250 (m), 1213 (m), 1188 (w), 1159 (s), 1115 (s), 1103 (s), 1078 (m), 1063 (s), 1016 (s), 972 (w), 916 (w), 879 (m), 851 (s), 824 (s), 771 (m), 756 (m), 719 (m), 694 (m), 681 (m), 621 (s), 594 (m), 515 (w), 488 (w), 463 (s), 420 (w); HRMS (ESI): *m/z* calculated for $C_{20}H_{18}ClF_3N_5$ (M+H) 420.1197, found 420.1190.

2-(3-pyridyl)-5-(*tert*-butylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7d):

Prepared from 3-(3-pyridyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3d**) (135 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (10 mol % $Pd(OAc)_2$, 44 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). Isolated as a yellow solid. Yield: 114 mg, 65%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.20; m.p. 183.9-185.8 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.51 (s, 1H), 8.71 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.56 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.17 (s, 1H), 1.66 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 161.2 (C), 151.3 (CH), 151.3 (C), 148.9 (CH), 143.3 (C), 141.7 (C), 134.9 (CH), 132.6 (CH), 129.1 (C), 127.9 (CH), 126.4 (C), 123.7 (CH), 123.1 (CH), 114.7 (C), 52.8 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3402 (w), 2972 (w), 1630 (s), 1599 (w), 1560 (s), 1529 (m), 1475 (m), 1412 (s), 1356 (m), 1300 (w), 1283 (w), 1213 (m), 1128 (m), 1074 (w), 1024 (m), 876 (m), 831 (s), 702 (s); HRMS (ESI): *m/z* calculated for $C_{18}H_{18}ClN_6$ (M+H) 353.1276, found 353.1259.

2-(2-furyl)-5-(*tert*-butylamino)-9-fluoro[1,2,4]triazolo[1,5-*c*]quinazoline (7e):

Prepared from 3-(2-furyl)-5-(2-amino-5-fluorophenyl)-1,2,4-triazole (**3e**) (122 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (2 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). Isolated as a white solid. Yield: 116 mg, 71%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.36; m.p.: 162.6-163.5 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.03 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.69 (dd, *J* = 9.1, 4.9 Hz, 1H), 7.66-7.63 (m, 1H), 7.39 (td, *J* = 8.6, 2.8 Hz, 1H), 7.27-7.26 (m, 1H), 6.61 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.12 (s, 1H), 1.66 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 158.8 (d, *J* = 244 Hz, C), 156.1 (C), 151.5 (d, *J* = 4.2 Hz, C), 145.9 (C), 144.6 (CH), 141.6 (C), 141.3 (C), 128.3 (d, *J* = 8.3 Hz, CH), 120.9 (d, *J* = 25.2 Hz, CH), 114.2 (d, *J* = 10.1 Hz, C), 112.3 (CH), 112.1 (CH), 108.7 (d, *J* = 24.4 Hz, CH), 52.7 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3398 (w), 3146 (w), 2957 (w), 1618 (s), 1570 (m), 1547 (s), 1514 (m), 1491 (s), 1460 (m), 1427 (s), 1315 (m), 1286 (w), 1256 (s), 1215 (m), 1180 (s), 1153 (m), 1124 (m), 1107 (m), 1072 (w), 1032 (w), 1009 (m), 982 (m), 941 (w), 901 (m), 862

(s), 835 (s), 825 (m), 758 (s), 743 (s), 710 (w); HRMS (ESI): *m/z* calculated for $C_{17}H_{17}FN_5O$ (M+H) 326.1412, found 326.1423.

2-phenyl-5-(*tert*-butylamino)-[1,2,4]triazolo[1,5-*c*]quinazoline (7f):

Prepared from 3-phenyl-5-(2-aminophenyl)-1,2,4-triazole (**3f**) (118 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (4 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (50:5:0.5 → 20:10:0.5). The product (**7f**) was isolated as a white solid (119 mg, 75%) and regioisomer **9f** as a white solid (14 mg, 9%). **Spectral data of 7f**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.28; m.p.: 93.0-95.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.41 (d, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.56-7.47 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 1H), 6.20 (s, 1H), 1.69 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 163.3 (C), 152.1 (C), 144.9 (C), 141.9 (C), 132.0 (CH), 130.6 (C), 130.4 (CH), 128.9 (CH), 127.6 (CH), 126.4 (CH), 123.9 (CH), 123.6 (CH), 114.1 (C), 52.6 (C), 29.2 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3402 (w), 2976 (w), 2926 (w), 1626 (s), 1562 (s), 1539 (s), 1520 (m), 1483 (m), 1458 (w), 1443 (s), 1389 (w), 1360 (m), 1321 (m), 1258 (m), 1246 (m), 1215 (m), 1175 (m), 1153 (w), 1122 (m), 1109 (m), 1072 (m), 1020 (m), 1013 (m), 922 (w), 868 (w), 802 (w), 789 (m), 758 (s), 721 (s); HRMS (ESI): *m/z* calculated for $C_{19}H_{20}N_5$ (M+H) 318.1713, found 318.1710. **Spectral data of 9f**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.08; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.48 (d, *J* = 7.9 Hz, 1H), 7.68-7.56 (m, 7H), 7.38-7.32 (m, 1H), 4.75 (s, 1H), 1.28 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 150.9 (C), 146.1 (C), 143.3 (C), 139.5 (C), 131.7 (CH), 131.4 (CH), 131.0 (CH), 129.1 (CH), 127.7 (C), 125.6 (CH), 124.3 (CH), 123.5 (CH), 113.5 (C), 52.8 (C), 28.6 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{19}H_{20}N_5$ (M + H) 318.1713, found 318.1727.

2-(2-furyl)-5-(*tert*-butylamino)-[1,2,4]triazolo[1,5-*c*]quinazoline (7g):

Prepared from 3-(2-furyl)-5-(2-aminophenyl)-1,2,4-triazole (**3g**) (113 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (4 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (100:10:0.5 → 50:50:0.5). The product (**7g**) was isolated as a white solid (113 mg, 74%) and regioisomer **9g** as a yellow solid (20 mg, 13%). **Spectral data of 7g**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.45; m.p.: 138.8-139.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.68-7.63 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.27-7.26 (m, 1H), 6.60 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.15 (s, 1H), 1.66 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 156.0 (C), 152.1 (C), 146.1 (C), 145.0 (C), 144.5 (CH), 141.7 (C), 132.2 (CH), 126.4 (CH), 124.0 (CH), 123.7 (CH), 113.8 (C), 112.1 (CH), 112.1 (CH), 52.7 (C), 29.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3317 (w), 1618 (m), 1603 (m), 1562 (s), 1535 (s), 1508 (m), 1479 (m), 1450 (w), 1423 (w), 1391 (w), 1354 (m), 1312 (m), 1288 (w), 1242 (w), 1213 (m), 1184 (m), 1150 (w), 1124 (w), 1109 (w), 1076 (w), 1011 (w), 982 (w), 924 (w), 901 (w), 885 (w), 758 (m), 743 (w), 712 (m); HRMS (ESI): *m/z* calculated for $C_{17}H_{18}N_5O$ (M+H) 308.1506, found 326.1509. **Spectral data of 9g**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.07; ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 8.47 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 4.2 Hz, 2H), 7.38-7.33 (m, 1H), 7.13 (d, *J* = 3.3 Hz, 1H), 6.69 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.79 (s, 1H), 1.48 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 151.6 (C), 144.8 (CH), 143.3 (C), 140.7 (C) 139.2 (C), 138.1 (C), 132.1 (CH), 125.6 (CH), 124.4 (CH), 123.6 (CH), 116.7 (CH), 113.0 (C), 112.8 (CH), 52.9 (C), 28.8 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{17}H_{18}N_5O$ (M + H) 308.1506, found 326.1513.

2-(3-pyridyl)-5-(*tert*-butylamino)-7-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline (7h):
Prepared from 3-(3-pyridyl)-5-(2-amino-3-methylphenyl)-1,2,4-triazole (**3h**) (126 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (2 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (60:10:0.5). Isolated as a white solid. Yield: 133 mg, 80%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.10; m.p.: 178.4-179.3 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.53 (s, 1H), 8.70 (d, *J* = 4.6 Hz, 1H), 8.58 (dt, *J* = 7.9, 1.6 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.1 Hz, 1H), 7.42 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 2.66 (s, 3H), 1.69 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 161.0 (C), 152.6 (C), 151.2 (CH), 149.0 (CH), 143.5 (C), 140.8 (C), 134.9 (CH), 134.5 (C), 132.7 (CH), 126.8 (C), 123.7 (CH), 123.4 (CH), 121.6 (CH), 113.7 (C), 52.6 (C), 28.9 (CH_3), 18.6 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3410 (w), 2962 (w), 1628 (s), 1595 (m), 1578 (s), 1535 (s), 1508 (m), 1483 (m), 1445 (s), 1418 (m), 1389 (w), 1358 (m), 1327 (m), 1294 (m), 1240 (m), 1213 (m), 1177 (m), 1157 (w), 1134 (w), 1088 (w), 1063 (w), 1020 (w), 995 (w), 972 (w), 933 (w), 860 (w), 829 (m), 762 (s), 744 (s), 706 (m); HRMS (ESI): *m/z* calculated for $C_{19}H_{21}N_6$ (M+H) 333.1822, found 333.1822.

2-(4-trifluoromethylphenyl)-5-(*tert*-butylamino)-7-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline (7i):
Prepared from 3-(4-trifluoromethylphenyl)-5-(2-amino-3-methylphenyl)-1,2,4-triazole (**3i**) (159 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (6 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (100:10:0.5). Isolated as a white solid. Yield: 143 mg, 72%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.68; m.p.: 183.0-183.9 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.45 (d, *J* = 8.0 Hz, 2H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 2.66 (s, 3H), 1.69 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 161.9 (C), 152.7 (C), 143.5 (C), 140.8 (C), 134.5 (C), 134.1 (C), 132.7 (CH), 132.0 (q, *J* = 32.5 Hz, C), 127.9 (CH), 125.8 (q, *J* = 3.6 Hz, CH), 124.2 (q, *J* = 272 Hz, C), 123.4 (CH), 121.6 (CH), 113.7 (C), 52.6 (C), 28.8 (CH_3), 18.6 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3410 (w), 2962 (w), 2928 (w), 1634 (s), 1580 (w), 1533 (m), 1493 (s), 1452 (w), 1418 (m), 1393 (w), 1371 (w), 1319 (s), 1259 (w), 1246 (m), 1213 (m), 1157 (m), 1115 (s), 1099 (s), 1063 (s), 1016 (s), 928 (w), 851 (m), 800 (m), 758 (m), 712 (w); HRMS (ESI): *m/z* calculated for $C_{21}H_{21}F_3N_5$ (M+H) 400.1744, found 400.1740.

2-phenyl-5-(*tert*-butylamino)-8,9-dimethoxy-[1,2,4]triazolo[1,5-*c*]quinazoline (7j):
Prepared from 3-phenyl-5-(2-amino-4,5-dimethoxyphenyl)-1,2,4-triazole (**3j**) (148 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (5 mol % $Pd(OAc)_2$, 44 hours). Purification: cyclohexane/EtOAc/Et_3N (80:10:0.5). Isolated as a white solid. Yield: 139 mg, 74%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.24; m.p.: 194.5-195.6 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.33 (dd, *J* = 7.8, 2.0 Hz, 2H), 7.73 (s, 1H), 7.54-7.46 (m, 3H), 7.15 (s, 1H), 6.08 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 1.67 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 163.1 (C), 153.5 (C), 151.8 (C), 147.0 (C), 141.4 (C), 141.0 (C), 130.7 (C), 130.3 (CH), 128.9 (CH), 127.6 (CH), 107.3 (CH), 107.0 (C), 103.5 (CH), 56.5 (CH_3), 56.3 (CH_3), 52.4 (C), 29.2 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3404 (w), 2964 (w), 1643 (m), 1626 (m), 1572 (w), 1497 (s), 1475 (m), 1443 (w), 1388 (w), 1375 (m), 1360 (m), 1275 (m), 1246 (m), 1213 (m), 1194 (w), 1177 (w), 1030 (m), 1003 (m), 847 (m), 797 (w), 762 (m), 721 (m); HRMS (ESI): *m/z* calculated for $C_{21}H_{24}N_5O_2$ (M+H) 378.1925, found 378.1921.

2-(2-furyl)-5-(*n*-pentylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7k):
Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and *n*-pentyl isocyanide (76 µL) according to the general procedure (15 mol % $Pd(OPiv)_2$, 72 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). The product (**7k**) was isolated as a white solid (110 mg, 62%) and side-product **14** as a yellow solid (11 mg, 8%). **Spectral data of 7k**: TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.48; m.p.: 109.2-112.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.34 (d, *J* = 2.5 Hz, 1H), 7.65-7.59 (m, 2H), 7.56 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.25 (s, 1H), 6.60-6.58 (m, 1H), 6.20 (t, *J* = 5.0 Hz, 1H), 3.68 (q, *J* = 6.7 Hz, 2H), 1.76 (pentet, *J* = 7.3 Hz, 2H), 1.48-1.36 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 156.6 (C), 151.3 (C), 145.8 (C), 144.7 (CH), 143.7 (C), 143.2 (C), 132.8 (CH), 129.1 (C), 127.5 (CH), 123.3 (CH), 114.6 (C), 112.5 (CH), 112.1 (CH), 41.4 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 22.5 (CH_2), 14.1 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3406 (m), 3103 (w), 2959 (w), 2937 (w), 2853 (w), 1636 (s), 1608 (s), 1562 (s), 1533 (s), 1508 (s), 1475 (s), 1450 (m), 1375 (w), 1315 (w), 1229 (w), 1192 (m), 1175 (m), 1128 (w), 1076 (m), 1011 (s), 822 (s), 766 (s), 735 (s); HRMS (ESI): *m/z* calculated for $C_{18}H_{19}ClN_5O$ (M+H) 356.1273, found 356.1266. **Spectral data of 14**:[4] TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.23; m.p.: >230 °C decomposition; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.19 (s, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.65 (s, 1H), 7.28 (d, *J* = 3.4 Hz, 1H), 6.62-6.60 (m, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 158.0 (C), 150.5 (C), 145.5 (C), 145.1 (CH), 141.5 (C), 136.8 (CH, *only detected by HSQC measurement*), 135.4 (C), 133.0 (CH), 130.6 (CH), 123.4 (CH), 119.0 (C), 113.0 (CH), 112.1 (CH) ppm; HRMS (ESI): *m/z* calculated for $C_{13}H_8ClN_4O$ (M+H) 271.0381, found 271.0383.

2-(2-furyl)-5-(benzylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7l):
Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and benzyl isocyanide (73 µL) according to the general procedure (15 mol % $Pd(OPiv)_2$, 72 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). Isolated as a yellow solid. Yield: 21 mg, 11%. TLC (cyclohexane/EtOAc, 7:1 v/v): R_f = 0.33; m.p.: 181.3-184.4 °C (Lit.[15] 184-185 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.30 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.56-7.50 (m, 2H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.20-7.15 (m, 1H), 6.52 (s, 1H), 6.47 (t, *J* = 5.2 Hz, 1H), 4.82 (d, *J* = 5.5 Hz, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 156.6 (C), 151.4 (C), 145.7 (C), 144.7 (CH), 143.5 (C), 143.0 (C), 137.5 (C), 132.8 (CH), 129.4 (C), 129.0 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 123.3 (CH), 114.8 (C), 112.6 (CH), 112.1 (CH), 45.4 (CH_2) ppm; IR (neat): vmax (cm^{-1}) = 3391 (m), 3109 (w), 2922 (w), 1618 (s), 1560 (s), 1531 (s), 1510 (s), 1475 (m), 1421 (s), 1375 (m), 1321 (m), 1283 (m), 1227 (m), 1188 (m), 1121 (w), 1024 (m), 976 (m), 881 (m), 827 (s), 748 (s), 700 (m); HRMS (ESI): *m/z* calculated for $C_{20}H_{15}ClN_5O$ (M+H) 376.0960, found 376.0977.

2-(2-furyl)-5-(isopropylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7m):
Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and isopropyl isocyanide (57 µL) according to the general procedure (10 mol % $Pd(OPiv)_2$, 72 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). Isolated as a white solid. Yield: 70 mg, 43%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.26; m.p.: 139.9-141.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.33 (d, *J* = 2.0 Hz, 1H), 7.63- 7.58 (m, 2H), 7.55 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.26-7.23 (m, 1H), 6.60-6.58 (m, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 4.49 (octet, *J* = 6.6 Hz, 1H), 1.39 (d, *J* = 6.5 Hz, 6H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 156.6 (C), 151.4 (C), 145.9 (C),

144.7 (CH), 143.9 (C), 142.5 (C), 132.8 (CH), 129.1 (C), 127.6 (CH), 123.3 (CH), 114.7 (C), 112.6 (CH), 112.2 (CH), 43.7 (CH), 23.0 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3404 (m), 2968 (w), 1620 (s), 1560 (s), 1529 (s), 1508 (s), 1477 (s), 1425 (s), 1366 (s), 1321 (m), 1296 (m), 1283 (m), 1225 (m), 1198 (s), 1180 (s), 1121 (m), 1074 (m), 1014 (m), 978 (m), 820 (s), 744 (s); HRMS (ESI): *m/z* calculated for $C_{16}H_{15}ClN_5O$ (M+H) 328.0960, found 328.0974.

2-(2-furyl)-5-(cyclohexylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7n):

Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and cyclohexyl isocyanide (75 µL) according to the general procedure (7.5 mol % $Pd(OAc)_2$, 20 hours). Purification: cyclohexane/EtOAc/Et_3N (80:10:0.5). Isolated as a yellow solid. Yield: 92 mg, 50%. TLC (cyclohexane/EtOAc/Et_3N, 40:10:0.5 v/v/v): R_f = 0.42; m.p.: >150 °C (decomposition); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.34 (d, *J* = 2.2 Hz, 1H), 7.64-7.60 (m, 2H), 7.56 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.26-7.23 (m, 1H), 6.60-6.58 (m, 1H), 6.10 (d, *J* = 8.2 Hz, 1H), 4.21-4.12 (m, 1H), 2.20-1.20 (m, 10H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 156.5 (C), 151.3 (C), 145.8 (C), 144.6 (CH), 143.8 (C), 142.4 (C), 132.7 (CH), 128.9 (C), 127.4 (CH), 123.2 (CH), 114.6 (C), 112.5 (CH), 112.1 (CH), 50.3 (CH), 33.3 (CH_2), 25.7 (CH_2), 25.1 (CH_2) ppm; IR (neat): vmax (cm^{-1}) = 3391 (w), 2928 (w), 2845 (w), 1614 (s), 1560 (s), 1531 (m), 1508 (m), 1474 (s), 1448 (w), 1421 (m), 1375 (w), 1350 (w), 1319 (m), 1310 (m), 1219 (w), 1200 (w), 1182 (m), 1171 (m), 1121 (m), 1097 (w), 1070 (m), 1012 (m), 978 (w), 903 (w), 885 (m), 822 (s), 746 (s), 735 (s), 708 (w); HRMS (ESI): *m/z* calculated for $C_{19}H_{19}ClN_5O$ (M+H) 368.1273, found 368.1285.

ethyl 4-((9-chloro-2-(furan-2-yl)-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)amino)piperidine-1-carboxylate (7o):

Prepared from 3-(2-furyl)-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3a**) (130 mg) and ethyl 4-isocyanopiperidine-1-carboxylate (109 mg) according to the general procedure (10 mol % $Pd(OPiv)_2$, 72 hours). Purification: cyclohexane/EtOAc/Et_3N (20:10:0.5). Isolated as a white solid. Yield: 95 mg, 43%. TLC (cyclohexane/EtOAc, 2:1 v/v): R_f = 0.37; m.p.: 212.4-213.9 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.32 (s, 1H), 7.65- 7.59 (m, 3H), 7.24 (d, *J* = 2.8 Hz, 1H), 6.59 (s, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.38-4.11 (m, 3H) 4.16 (q, *J* = 7.0 Hz, 2H), 3.11-2.98 (m, 2H), 2.20 (d, *J* = 12.2 Hz, 2H), 1.64-1.53 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 156.5 (C), 155.6 (C), 151.3 (C), 145.6 (C), 144.7 (CH), 143.4 (C), 142.1 (C), 132.7 (CH), 129.3 (C), 127.4 (CH), 123.2 (CH), 114.7 (C), 112.7 (CH), 112.1 (CH), 61.6 (CH_2), 48.7 (CH), 42.9 (CH_2), 32.0 (CH_2). 14.8 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3420 (w), 2858 (w), 1701 (s), 1616 (s), 1566 (m), 1533 (m), 1510 (w), 1473 (w), 1431 (m), 1373 (w), 1273 (w), 1227 (s), 1173 (m), 1136 (m), 1094 (m), 1036 (w), 820 (s), 768 (s); HRMS (ESI): *m/z* calculated for $C_{21}H_{22}ClN_6O_3$ (M+H) 441.1436, found 441.1455.

2-phenyl-5-(*n*-pentylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7p):

Prepared from 3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3b**) (135 mg) and *n*-pentyl isocyanide (76 µL) according to the general procedure (15 mol % $Pd(OPiv)_2$, 72 hours). Purification: cyclohexane/EtOAc (7:1). Isolated as an off-white solid. Yield: 94 mg, 51%. TLC (cyclohexane/EtOAc, 7:1 v/v): R_f = 0.50; m.p.: 95.7-99.3 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.34 (d, *J* = 2.3 Hz, 1H), 8.32-8.28 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.55 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.54-7.46 (m, 3H), 6.20 (t, *J* = 5.4 Hz, 1H), 3.69 (q, *J* = 6.9 Hz, 2H), 1.83-1.75 (m, 2H), 1.50-1.38 (m, 4H), 0.95 (t, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 163.8 (C), 151.2 (C), 143.5

(C), 143.3 (C), 132.4 (CH), 130.6 (CH), 130.2 (C), 128.9 (C), 128.9 (CH), 127.6 (CH), 127.4 (CH), 123.2 (CH), 114.9 (C), 41.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.5 (CH_2), 14.1(CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3292 (w), 2928 (w), 2856 (w), 1628 (s), 1556 (s), 1529 (s), 1518 (s), 1479 (s), 1443 (s), 1364 (m), 1327 (m), 1281 (m), 1126 (w), 1084 (w), 1072 (w), 1026 (w), 908 (w), 824 (s), 770 (s), 723 (s), 689 (s); HRMS (ESI): *m/z* calculated for $C_{20}H_{21}ClN_5$ (M+H) 366.1480, found 366.1476.

2-phenyl-5-(isopropylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7q):

Prepared from 3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3b**) (135 mg) and isopropyl isocyanide (57 µL) according to the general procedure (10 mol % $Pd(OAc)_2$, 72 hours). Purification: cyclohexane/EtOAc (7:1). Isolated as a white solid. Yield: 76 mg, 45%. TLC (cyclohexane/EtOAc, 7:1 v/v): R_f = 0.50; m.p.: 159.8-161.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 (d, *J* = 2.2 Hz, 1H), 8.34-8.30 (m, 2H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.56 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.54-7.47 (m, 3H), 6.07 (d, *J* = 7.8 Hz, 1H), 4.56-4.46 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 163.8 (C), 151.3 (C), 143.6 (C), 142.5 (C), 132.4 (CH), 130.6 (CH), 130.3 (C), 128.9 (C), 128.9 (CH), 127.6 (CH), 127.5 (CH), 123.2 (CH), 114.9 (C), 43.5 (CH), 23.0 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3394 (w), 2968 (w), 1622 (s), 1560 (s), 1531 (s), 1520 (s), 1479 (s), 1443 (s), 1366 (m), 1327 (w), 1283 (m), 1234 (w), 1194 (m), 1124 (m), 1072 (m), 1024 (m), 920 (w), 881 (w), 820 (s), 723 (s), 689 (s); HRMS (ESI): *m/z* calculated for $C_{18}H_{17}ClN_5$ (M+H) 338.1167, found 338.1158.

2-phenyl-5-(cyclohexylamino)-9-chloro[1,2,4]triazolo[1,5-*c*]quinazoline (7r):

Prepared from 3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3b**) (135 mg) and cyclohexyl isocyanide (75 µL) according to the general procedure (10 mol % $Pd(OAc)_2$, 72 hours). Purification: cyclohexane/EtOAc (9:1). Isolated as a white solid. Yield: 108 mg, 57%. TLC (cyclohexane/EtOAc, 9:1 v/v): R_f = 0.48; m.p.: 175.4-177.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 (d, *J* = 2.1 Hz, 1H), 8.34-8.31 (m, 2H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.54-7.46 (m, 3H), 6.13 (d, *J* = 8.1 Hz, 1H), 4.24-4.15 (m, 1H), 2.29-2.17 (m, 2H), 1.91-1.68 (m, 3H), 1.59-1.25 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): *δ* 163.8 (C), 151.3 (C), 143.6 (C), 142.5 (C), 132.4 (CH), 130.6 (CH), 130.3 (C), 128.9 (CH), 128.8 (C), 127.6 (CH), 127.4 (CH), 123.2 (CH), 114.9 (C), 50.1 (CH), 33.3 (CH_2), 25.8 (CH_2), 25.1 (CH_2) ppm; IR (neat): vmax (cm^{-1}) = 3315 (m), 2932 (m), 2849 (m), 1628 (s), 1560 (s), 1535 (m), 1520 (m), 1477 (m), 1441 (s), 1352 (w), 1327 (m), 1281 (m), 1175 (m), 1122 (m), 1068 (m), 1024 (w), 883 (w), 827 (s), 768 (m), 725 (s), 692 (s); HRMS (ESI): *m/z* calculated for $C_{21}H_{21}ClN_5$ (M+H) 378.1480, found 378.1468.

ethyl 4-((9-chloro-2-phenyl-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)amino)piperidine-1-carboxylate (7s):

Prepared from 3-phenyl-5-(2-amino-5-chlorophenyl)-1,2,4-triazole (**3b**) (135 mg) and ethyl 4-isocyanopiperidine-1-carboxylate (109 mg) according to the general procedure (10 mol % $Pd(OAc)_2$, 72 hours). Purification: cyclohexane/EtOAc (3:1), then second column with $CHCl_3$/MeOH (200:1). Isolated as an off-white solid. Yield: 85 mg, 38%. TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.31; m.p.: 180.2-182.2 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.36 (d, *J* = 2.1 Hz, 1H), 8.33-8.28 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.55-7.47 (m, 3H), 6.12 (d, *J* = 7.9 Hz, 1H), 4.41-4.14 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.14-3.04 (m,

2H), 2.29-2.20 (m, 2H), 1.70-1.58 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz): δ 164.0 (C), 155.6 (C), 151.3 (C), 143.3 (C), 142.3 (C), 132.5 (CH), 130.7 (CH), 130.1 (C), 129.2 (C), 128.9 (CH), 127.6 (CH), 127.5 (CH), 123.2 (CH), 115.0 (C), 61.6 (CH_2), 48.5 (CH), 42.9 (CH_2), 32.1 (CH_2), 14.9 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3396 (w), 3560 (w), 2968 (w), 2930 (w), 2862 (w), 1618 (s), 1560 (s), 1531 (s), 1520 (m), 1477 (m), 1441 (s), 1327 (m), 1281 (m), 1236 (m), 1175 (m), 1124 (m), 1070 (m), 1026 (m), 820 (s), 768 (s), 721 (s), 689 (s); HRMS (ESI): *m/z* calculated for $C_{23}H_{24}ClN_6O_2$ (M+H) 451.1644, found 451.1647.

5-(*tert*-butylamino)-8-chlorotetrazolo[1,5-*c*]quinazoline (11)

Prepared from 5-(2-amino-4-chlorophenyl)-tetrazole (**10**) (98 mg) and *tert*-butyl isocyanide (68 µL) according to the general procedure (10 mol % $Pd(OAc)_2$, 72 hours). Purification: cyclohexane/EtOAc/Et_3N (80:10:0.5). Isolated as a yellow solid. Yield: 99 mg, 72%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.31; m.p.: 198.0-201.1 °C (decomposition); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.31 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.20 (s, 1H), 1.64 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz): δ 149.4 (C), 146.0 (C), 139.6 (C), 139.6 (C), 126.0 (CH), 125.8 (CH), 125.4 (CH), 109.7 (C), 53.7 (C), 28.8 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3225 (w), 2966 (w), 2932 (w), 1632 (s), 1618 (s), 1555 (s), 1537 (s), 1508 (m), 1443 (m), 1362 (m), 1331 (m), 1283 (w), 1242 (w), 1207 (s), 1175 (m), 1150 (m), 1070 (m), 987 (w), 949 (m), 876 (s), 816 (m), 768 (m), 717 (w); HRMS (ESI): *m/z* calculated for $C_{12}H_{13}ClN_6Na$ (M+Na) 299.0782, found 299.0786.

6-(*tert*-butylamino)-benzo[4,5]imidazo[1,2-*c*]quinazoline (13)

Prepared from 2-(2-aminophenyl)benzimidazole (**12**) (104 mg) and tert-butyl isocyanide (68 µL) according to the general procedure (5 mol % $Pd(OAc)_2$, 44 hours). Purification: cyclohexane/EtOAc/Et_3N (70:10:0.5). Isolated as a white solid. Yield: 100 mg, 69%. TLC (cyclohexane/EtOAc/Et_3N, 70:10:0.5 v/v/v): R_f = 0.33; m.p. 121-131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.53 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.67-7.59 (m, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.41 -7.34 (m, 2H), 5.29 (s, 1H), 1.72 (s, 9H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 126 MHz): δ 149.5 (C), 144.6 (C), 144.3 (C), 143.6 (C), 131.9 (CH), 128.1 (C), 125.8 (CH), 125.2 (CH) 124.3 (CH) 123.8 (CH), 122.6 (CH), 120.4 (CH), 115.3 (C), 112.1 (CH), 53.3 (C), 29.3 (CH_3) ppm; IR (neat): vmax (cm^{-1}) = 3443 (w), 2966 (w), 1626 (s), 1601 (s), 1566 (s), 1529 (s), 1475 (s), 1447 (s), 1391 (m), 1339 (s), 1246 (m), 1219 (m), 1198 (s), 762 (s); HRMS (ESI): m/z calculated for $C_{18}H_{19}N_4$ (M+H) 291.1604, found 291.1592.

6.5 References

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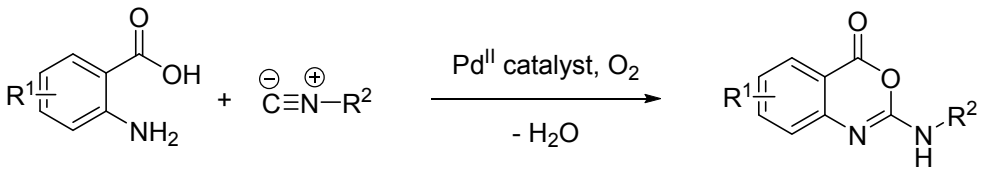
Chapter 7

2-Aminobenzoxazinones:

Aerobic Oxidative Coupling of Anthranilic Acids and Isocyanides



***Abstract**: Anthranilic acids are also oxidatively coupled with isocyanides in the presence of Pd^{II}, thus affording medicinally relevant 2-aminobenzoxazinones. The possibility of undesired decarboxylative pathways and the susceptibly of the products to nucleophilic attack make this is a particularly challenging substrate class. This work therefore underlines the generality and broad potential of the oxidative coupling of bisnucleophiles and isocyanides.*

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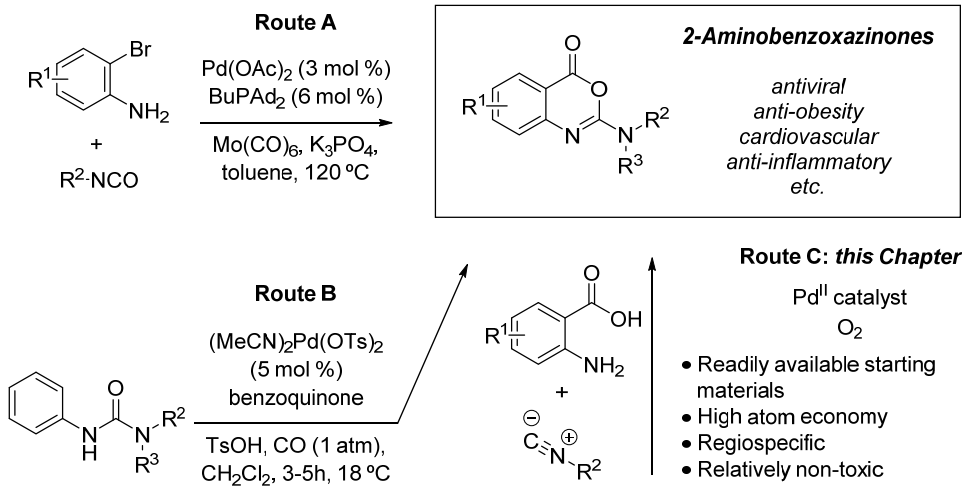
7.1 Introduction

Benzoxazinones are valuable nitrogen-containing heterocycles that exhibit a wide variety of biological activities.[1] Especially 2-amino substituted benzoxazinones (Scheme 1) have frequently been studied during the past decades because of their pharmacological potential that covers a range of possible applications (*e.g.* antiviral, anti-obesity, cardiovascular and anti-inflammatory activities).[2] In the last decade several Pd-catalyzed carbonylative approaches towards benzoxazinones have been developed,[3] but only a limited arsenal of synthetic methodologies is available for the synthesis of 2-aminobenzoxazinones.[4] Wu and Beller *et al.* developed a Pd^0-catalyzed carbonylative synthesis of 2-aminobenzoxazoles from 2-bromoanilines and isocyanates (Scheme 1, Route A),[5] while Lloyd-Jones and Booker-Milburn *et al.* developed a carbonylative Pd^{II}-catalyzed procedure involving *ortho* C-H activation of *N*-arylureas (Scheme 1, Route B).[6] However, both methods suffer from limitations, such as relatively poor atom economy, lack of regiocontrol in the product, limited substrate scope and/or handling of toxic CO gas.



Scheme 1. Recent approaches towards 2-aminobenzoxazinones.

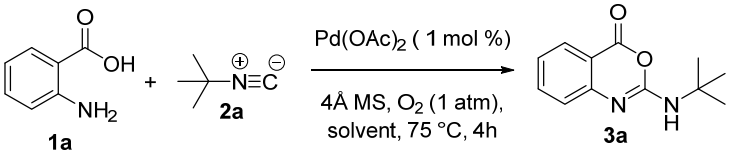
The potential of Pd-catalyzed imidoylative cross-coupling chemistry has so far predominantly been used in the synthesis of amidines, imidates and amides (Chapter 2, 3 and 4). We have recently addressed this limitation by introducing the Pd^{II}-catalyzed synthesis of cyclic guanidines by oxidative coupling of diamines and isocyanides using molecular oxygen as the stoichiometric oxidant (Chapter 5 and 6).[7] Indeed, this novel reaction provides a sustainable approach towards various

medicinally important heterocyclic scaffolds and has already been implemented in flow chemistry.[8] We have previously shown that 2-aminophenols also oxidatively couple with isocyanides under the same reaction conditions and in line with this work we envisioned an attractive approach towards 2-aminobenzoxazinones by aerobic oxidative coupling of anthranilic acids and isocyanides (Scheme 1, Route C). This approach would entail important advantages such as control over regioselectivity, readily available substrates and a high atom economy. It is, however, also a particularly challenging expansion of our guanidine synthesis due to the sensitivity of the benzoxazinone products to nucleophilic attack[4] and, most importantly, the tendency of benzoic acids to undergo decarboxylative processes in the presence of Pd^{II}.[9] In addition, benzoic acid derivatives may undergo Pd-catalyzed decarbonylative coupling with isocyanides at temperatures as low as 70 °C.[10] Moreover, isocyanides have also been reported to react with anthranilic acids to produce 4-quinazolinones.[11] We hope that by extending our oxidative coupling of bisnucleophiles and isocyanides to such a challenging substrate class we further illustrate the general applicability of this chemistry.

7.2 Results and Discussion

We were not surprised that our previously established optimal conditions for the synthesis of cyclic guanidines (Chapter 5)[7] gave rise to the formation of complex mixtures with only trace amounts of the desired product **3a** (Table 1, entry 1). The reaction worked better in MeTHF (entry 2), although the reaction was significantly less 'clean' than the guanidine synthesis. We tested the requisite for 4Å MS and O_2 atmosphere and found they are beneficial to the reaction (entry 3 and 4). A solvent screening indicated the reaction only performs well in ethereal solvents (entry 4-11). Dioxane performed particularly well and resulted in 82% conversion and 52% yield of **3a** after 4h (entry 11). No purification or drying of the solvent is necessary, thus making the procedure as operationally simple and convenient as the guanidine synthesis.

Table 1. Optimization of the reaction conditions.[a]



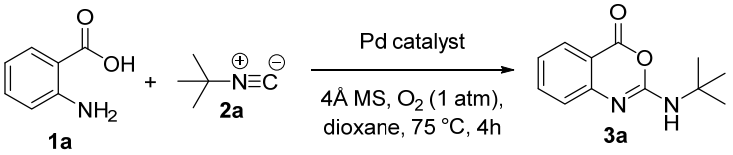
Entry	Solvent	Conversion of **1a** (GC)[b]	Yield of **3a** (GC)[b]
1	Toluene	88%	2%
2	MeTHF	68%	24%
3[c]	MeTHF	58%	10%
4[d]	MeTHF	55%	4%
5	tBuOH	68%	2%
6	DMF	50%	2%
7	DMSO	32%	1%
8	MeCN	67%	0%
9	DCE	82%	1%
10	DME	61%	24%
11	Dioxane	82%	52%

[a] Standard conditions: $Pd(OAc)_2$ (1 mol %), anthranilic acid (**1a**, 0.5 mmol), *tert*-butyl isocyanide (**2a**, 0.6 mmol), 4Å MS (150 mg) in the indicated solvent (2.5 mL) at 75 °C for 4h in O_2 atmosphere (1 atm). [b] Yields and conversions were determined by GC analysis using dodecane as internal standard. [c] No MS added. [d] Air atmosphere. [e] Reaction time 20h.

Remarkably, the reaction does not proceed further if the reaction time is increased and only more side products are formed (Table 2, entry 1). These results

indicate catalyst decomposition occurs, which is in stark contrast with our guanidine synthesis where only low reaction rates warranted higher catalyst loadings. Various palladium salts gave comparable yields and selectivities (entries 2-6), so we selected readily available and inexpensive palladium acetate to further our investigations. Increasing the catalyst loading to just 5 mol % resulted in an excellent 92% yield of **3a** (entry 6). Although this is a higher catalyst loading than we used for the guanidine synthesis, it is still a relatively low catalyst loading for Pd-catalyzed oxidizations using molecular oxygen as stoichiometric oxidant.[12]

Table 2. Optimization of the reaction conditions.[a]

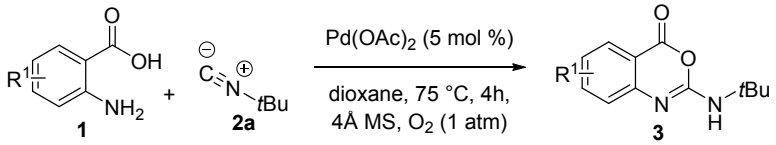


Entry	Solvent	Conversion of **1a** (GC)[b]	Yield of **3a** (GC)[b]
1[c]	$Pd(OAc)_2$ (1 mol %)	97%	48%
2	$Pd(OPiv)_2$ (1 mol %)	79%	48%
3	$Pd(O_2CCF_3)_2$ (1 mol %)	61%	22%
4	$PdCl_2(MeCN)_2$ (1 mol %)	79%	54%
5	$Pd(PPh3)_4$ (1 mol %)	81%	53%
6	$Pd(OAc)_2$ (5 mol %)	99%	92%

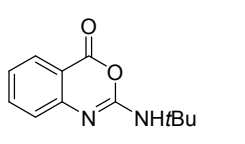
[a] Standard conditions: Pd catalyst, anthranilic acid (**1a**, 0.5 mmol), *tert*-butyl isocyanide (**2a**, 0.6 mmol), 4Å MS (150 mg) in the indicated solvent (2.5 mL) at 75 °C for 4h in O_2 atmosphere (1 atm). [b] Yields and conversions were determined by GC analysis using dodecane as internal standard. [c] Reaction time 20h.

We evaluated the substrate scope of this novel transformation with a catalyst loading of 5 mol % and a reaction time of 4 hours. We deliberately chose not to minimize the catalyst loading and reaction time for each specific example to underline the generality of this reaction. Electron-rich substrates perform very well (**3b**-**3j**) and even product **3h** containing three methoxy groups was readily obtained in 92% yield (Table 3). Remarkably, substrates bearing challenging substituents such as acetamido (**3i**, 68%) or trifluoromethoxy (**3j**, 62%) groups are also efficiently converted. The reaction is amenable to scale-up (10 mmol of **1a**) with negligible loss of yield furnishing 1.97 grams (90%) of product **3a**. An anthranilic acid derivative bearing an hydroxyl group only afforded trace amounts of products and was not isolated.

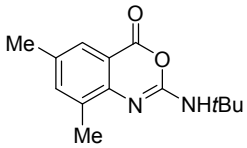
Table 3. Oxidative coupling of electron-rich anthranilic acids with *tert*-butyl isocyanide.[a]



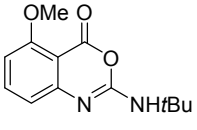
1 + **2a** → **3**



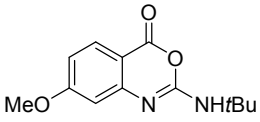
3a, 92% (90%)[b]



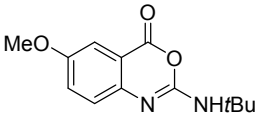
3b, 93%



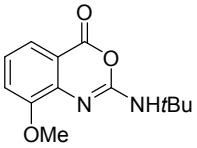
3c, 83%



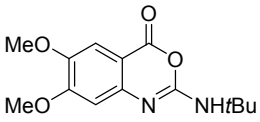
3d, 85%



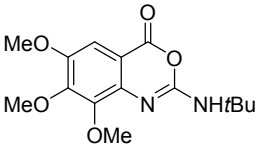
3e, 73%



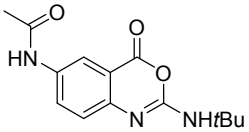
3f, 89%



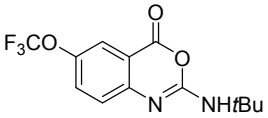
3g, 93%



3h, 92%



3i, 68%



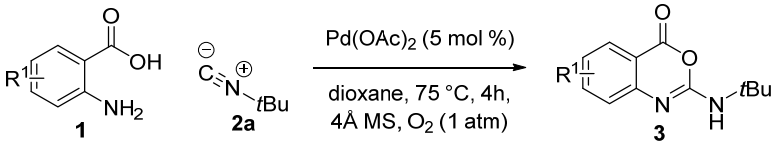
3j, 62%

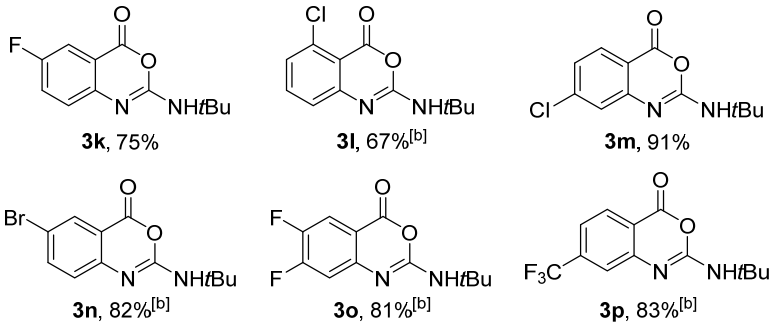
[a] Standard conditions: $Pd(OAc)_2$ (5 mol %), anthranilic acid derivative (1.0 mmol), *tert*-butyl isocyanide (1.2 mmol), 4Å MS (300 mg) in dioxane (5 mL) at 75 °C for 4h in O_2 atmosphere (1 atm). Yields refer to isolated material. [b] Reaction between brackets performed on 10 mmol scale.

Electron-withdrawing groups, such as the medicinally important fluoro (**3k** and **3o**) and trifluoromethyl (**3p**) groups,[13] were also easily incorporated under the same reaction conditions (**3k**-**3p**), although in some cases a higher catalyst loading was required to achieve high yields (Table 4). Furthermore, 5-bromoanthranilic acid is converted to **3n** in 82% yield, which provides a plethora of opportunities for Pd^0-catalyzed functionalization of the product. The position of a chloro substituent seems to have a pronounced effect on the yield (compare **3l** and **3m**). Considering steric effects are not observed in other substrates (compare **3c** and **3d**), a possible explanation for the lower yield of product **3l** is a carboxylic acid-directed reaction of

palladium with the aryl chloride. We also tested substrates with -NO_2, -I or –COOH substituents, but only traces of product were found.

Table 4. Oxidative coupling of electron-poor anthranilic acids with *tert*-butyl isocyanide.[a]





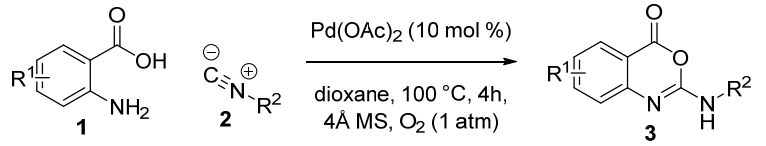
[a] Standard conditions: $Pd(OAc)_2$ (5 mol %), anthranilic acid derivative (1.0 mmol), *tert*-butyl isocyanide (1.2 mmol), 4Å MS (300 mg) in dioxane (5 mL) at 75 °C for 4h in O_2 atmosphere (1 atm). Yields refer to isolated material. [b] 10 mol % $Pd(OAc)_2$ used.

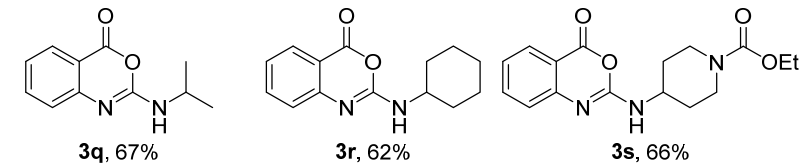
Isocyanides bearing other groups than *tert*-butyl unfortunately gave low yields of desired product under the standard conditions. Indeed, this is a well-known issue with Pd-catalyzed insertion reactions of isocyanides that typically limits the scope and applicability significantly (see previous Chapters). We were therefore delighted to find that after modest adjustments to the reaction conditions (10 mol % $Pd(OAc)_2$, 100 °C, 2 eq. isocyanide) good yields were obtained with various isocyanides (Table 5). Secondary aliphatic isocyanides are readily inserted independent of the electronic nature of the anthranilic acid used and give very useful products in 60-70% yield (**3q**-**3u**). Product **3s** derived from an isocyanide containing additional functionality is especially noteworthy and uncommon in imidoylative Pd-catalysis. A primary aliphatic isocyanide is viable, although **3v** was only obtained in moderate yield. The use of an aromatic isocyanide (2,6-dimethylphenyl isocyanide) did not afford an appreciable amount of product under the current conditions.

In analogy with the guanidine synthesis we propose the plausible mechanism depicted in Scheme 2 for the oxidative coupling of anthranilic acids and isocyanides. Intermediate **II** is formed by substitution of the acetate ligands by the substrate and

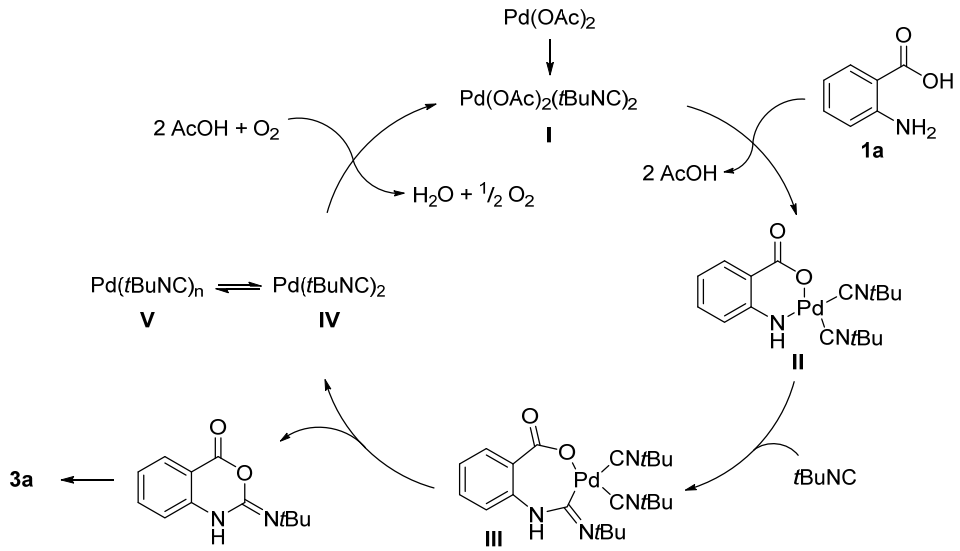
subsequently undergoes migratory insertion of coordinated isocyanide. The resulting complex **III** then undergoes reductive elimination to afford the product and Pd^0, which is reoxidized by molecular oxygen.[14]

Table 5. Aerobic oxidative coupling of anthranilic acids with various isocyanides.[a]





[a] Standard conditions: $Pd(OAc)_2$ (10 mol %), anthranilic acid (1.0 mmol), isocyanide (2.0 mmol), 4Å MS (300 mg) in dioxane (5 mL) at 100 °C for 4h in O_2 atmosphere (1 atm). Yields refer to isolated material.



Scheme 2. Proposed mechanism.

7.3 Conclusion

We have developed a Pd^{II}-catalyzed aerobic oxidative synthesis of 2-aminobenzoxazinones from readily available and relatively non-toxic starting materials. The reaction provides these medicinally valuable products in high atom economy and thereby prevents waste production. The procedure is operationally simple and does not require the handling of toxic carbon monoxide. Furthermore, this transformation is particularly challenging extension of our guanidine synthesis due to the instability of the products and the possibility of undesired decarboxylative reactions of the anthranilic acid. It therefore further illustrates the broad utility of the oxidative coupling of bisnucleophiles and isocyanides as a general approach towards this type of heterocyclic products, which will be imperative for the further implementation of this chemistry.

7.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. The synthesis of ethyl 4-isocyanopiperidine-1-carboxylate is described in Chapter 5. Palladium acetate was obtained from Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled prior to use. Other solvents were used as purchased. Powdered 4Å molecular sieves were purchased from Sigma Aldrich and activated before use. GC yield and conversion analysis was performed using a Shimadzu GC2010 equipped with a Zebron ZB-1 capillary column (30m x 0.25 mm) with dodecane as internal standard. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 500 (125.78 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, ^{13}C: δ 77.16 ppm for $CDCl_3$, ^{1}H: δ 2.50 ppm, ^{13}C: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Melting points were recorded on a Büchi M-565 melting point apparatus. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm).

General synthetic procedures

Optimization of the oxidative coupling of anthranilic acid (1a) and *tert*-butyl isocyanide:
A Radleys parallel synthesis unit was used to simultaneously run multiple reactions. A reaction vessel was charged with the appropriate Pd salt, anthranilic acid (**1a**, 69 mg, 0.5 mmol) and powdered 4Å MS (150 mg). The system was then put under vacuum and backfilled with O_2 (3x). Solvent (2.5 mL) and *tert*-butyl isocyanide (**2a**, 68 μL, 0.6 mmol) were added and the mixture was stirred at 75 °C for the indicated time in O_2 atmosphere (1 atm, balloon) with reflux condenser. Subsequently, the reaction mixture was cooled to room temperature, diluted with EtOAc (4 mL) and dodecane (114 μL, 0.5 mmol) was added as internal standard. A sample was filtered and subjected to GC analysis to determine conversion of **1a** and yield of **3a**.
Note: in a few cases GC peaks of product or starting material overlapped with impurities so an estimated conversion or yield is given.

General procedure 1: the aerobic oxidative coupling of anthranilic acid derivatives with with *tert*-butyl isocyanide:
A 25mL round-bottom flask was charged with $Pd(OAc)_2$ (11.2 mg, 5 mol % or 22.5 mg, 10 mol %), anthranilic acid derivative (**1**, 1.0 mmol) and powdered 4Å molecular sieves (300 mg). The flask was connected to a reflux condenser and the system was then put under vacuum and backfilled with O_2 (3x). Dioxane (5 mL) and *tert*-butyl isocyanide (**2a**, 136 μL, 1.2 mmol) were

added and the mixture was stirred at 75 °C for 4h in O_2 atmosphere (1 atm, balloon). Subsequently, the reaction mixture was cooled to room temperature, filtered over Celite and purified by flash chromatography with cyclohexane/ethyl acetate as eluent.

General procedure 2: the aerobic oxidative coupling of anthranilic acid derivatives with with other isocyanides:

A 25mL round-bottom flask was charged with $Pd(OAc)_2$ (22.5 mg, 10 mol%), anthranilic acid derivative (**1**, 1.0 mmol) and powdered 4Å molecular sieves (300 mg). The flask was connected to a reflux condenser and the system was then put under vacuum and backfilled with O_2 (3x). Dioxane (5 mL) and isocyanide (**2**, 2.0 mmol) were added and the mixture was stirred at 100 °C for 4h in O_2 atmosphere (1 atm, balloon). Subsequently, the reaction mixture was cooled to room temperature, filtered over Celite and purified by flash chromatography with cyclohexane/ethyl acetate as eluent. In some cases a second column using a different solvent system (DCM/cyclohexane) was required to obtain high purity material.

Spectral data

2-(*tert*-butylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3a):

Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 201 mg, 92% (1 mmol scale) or 1.97 g, 90% (10 mmol scale). TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.29; m.p.: 128.5-129.7 °C (Lit.[6] 127-128 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.15 (dt, *J* = 7.6, 0.8 Hz, 1H), 4.85 (s, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.3, 152.2, 150.5, 136.6, 128.7, 124.7, 123.6, 113.5, 52.1, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3296 (m), 2972 (w), 1736 (s), 1626 (s), 1603 (s), 1568 (s), 1474 (s), 1361 (m), 1277 (s), 1198 (s), 1150 (s), 1070 (s), 758 (s); HRMS (ESI): m/z calculated for $C_{12}H_{15}N_2O_2$ (M+H) 219.1128, found 219.1130.

2-(*tert*-butylamino)-6,8-dimethyl-4*H*-benzo[*d*][1,3]oxazin-4-one (3b):

Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 230 mg, 93%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.33; m.p.: 172.2-173.1 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 (s, 1H), 7.31 (s, 1H), 4.73 (s, 1H), 2.39 (s, 3H), 2.32 (s, 3H), 1.49 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.0, 150.7, 146.8, 138.5, 132.9, 132.7, 125.6, 112.9, 51.9, 28.7, 20.9, 17.3 ppm; IR (neat): νmax (cm^{-1}) = 3296 (w), 3246 (m), 2970 (w), 1740 (m), 1720 (s), 1632 (s), 1614 (s), 1541 (m), 1483 (s), 1283 (m), 1211 (m), 1041 (m), 785 (s); HRMS (ESI): m/z calculated for $C_{14}H_{19}N_2O_2$ (M+H) 247.1441, found 247.1437.

2-(*tert*-butylamino)-5-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3c):

Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 205 mg, 83%. TLC (cyclohexane/EtOAc, 4:1 v/v): R_f = 0.19; m.p.: 154.1-154.9 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (t, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 4.80 (br, 1H), 3.93 (s, 3H), 1.44 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 161.4, 156.9, 153.0, 152.7, 137.0, 116.9, 105.0, 103.0, 56.3, 51.9, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3285 (m), 2962 (w), 1730 (s), 1632 (s), 1599 (s), 1566 (s), 1481 (s), 1454 (m), 1356 (m), 1304 (m), 1256 (m),

1119 (s), 1043 (m), 1009 (s), 800 (s); HRMS (ESI): m/z calculated for $C_{13}H_{17}N_2O_3$ (M+H) 249.1234, found 249.1228.

2-(*tert*-butylamino)-7-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3d):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 210 mg, 85%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.19; m.p.: 177.0-177.7 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, *J* = 8.8 Hz, 1H), 6.71 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 4.86 (br, 1H), 3.87 (s, 3H), 1.47 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.6, 159.9, 153.1, 152.9, 130.4, 113.2, 106.4, 106.1, 55.7, 52.0, 29.0 ppm; IR (neat): νmax (cm^{-1}) = 3285 (m), 1713 (m), 1601 (s), 1568 (s), 1447 (s), 1360 (m), 1288 (s), 1213 (s), 1171 (s), 1063 (m), 962 (m), 839 (s), 770 (s); HRMS (ESI): m/z calculated for $C_{13}H_{17}N_2O_3$ (M+H) 249.1234, found 249.1226.

2-(*tert*-butylamino)-6-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3e):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a yellow solid. Yield: 182 mg, 73%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.24; m.p.: 134.0-135.2 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, *J* = 2.7 Hz, 1H), 7.23 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.20(d, *J* = 8.8 Hz, 1H), 4.71 (s, 1H), 3.83 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.5, 155.9, 151.2, 144.9, 126.6, 126.1, 113.5, 108.4, 55.9, 51.9, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3292 (m), 1736 (s), 1630 (s), 1491 (s), 1437 (m), 1360 (w), 1319 (w), 1259 (m), 1205 (m), 1074 (m), 1038 (m), 1011 (m), 883 (m), 829 (s), 779 (m); HRMS (ESI): m/z calculated for $C_{13}H_{17}N_2O_3$ (M+H) 249.1234, found 249.1232.

2-(*tert*-butylamino)-8-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3f):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as an off-white solid. Yield: 220 mg, 89%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.12; m.p.: 165.4-167.9 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.11-7.05 (m, 2H), 5.17 (s, 1H), 3.92 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.8, 153.9, 152.4, 141.5, 123.2, 120.2, 116.9, 113.7, 56.5, 52.4, 29.4 ppm; IR (neat): νmax (cm^{-1}) = 3281 (m), 1732 (s), 1626 (s), 1601 (s), 1574 (s), 1541 (m), 1493 (s), 1447 (m), 1391 (w), 1348 (m), 1261 (s), 1217 (s), 1200 (s), 1107 (m), 1053 (s), 1013 (s), 744 (s); HRMS (ESI): m/z calculated for $C_{13}H_{17}N_2O_3$ (M+H) 249.1234, found 249.1238.

2-(*tert*-butylamino)-6,7-dimethoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3g):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as an off-white solid. Yield: 258 mg, 93%. TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.34; m.p.: 131.6-138.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (s, 1H), 6.69 (s, 1H), 4.73 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.0, 157.0, 152.2, 147.3, 146.5, 107.8, 105.9, 105.2, 56.4, 56.3, 51.9 29.0 ppm; IR (neat): νmax (cm^{-1}) = 3281 (m), 1720 (s), 1609 (s), 1578 (m), 1489 (s), 1452 (m), 1389 (m), 1294 (s), 1240 (s), 1205 (s), 1136 (m), 1065 (m), 1009 (w), 932 (w), 858 (m), 839 (m), 809 (w), 768 (m); HRMS (ESI): m/z calculated for $C_{14}H_{19}N_2O_4$ (M+H) 279.1339, found 279.1333.

2-(*tert*-butylamino)-6,7,8-trimethoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3h):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 285 mg, 92%. TLC (cyclohexane/EtOAc, 3:1 v/v): R_f = 0.44; m.p.: 144.6-146.0 °C; ^{1}H NMR

($CDCl_3$, 500 MHz): δ 7.22 (s, 1H), 4.85 (br, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.0, 151.4, 150.1, 149.8, 145.7, 140.5, 108.2, 104.1, 62.0, 61.5, 56.3, 52.0, 29.0 ppm; IR (neat): νmax (cm^{-1}) = 3300 (m), 2935 (w), 1718 (m), 1628 (s), 1533 (w), 1470 (s), 1427 (s), 1393 (w), 1366 (s), 1306 (m), 1286 (m), 1207 (m), 1111 (s), 1078 (s), 1041 (s), 1013 (m), 984 (s), 937 (m), 849 (m), 760 (m); HRMS (ESI): m/z calculated for $C_{15}H_{21}N_2O_5$ (M+H) 309.1445, found 309.1440.

_N_-(2-(_tert_-butylamino)-4-oxo-4_H_-benzo[_d_][1,3]oxazin-6-yl)acetamide (3i):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as an off-white solid. Yield: 186 mg, 68%. TLC (cyclohexane/EtOAc, 1:1 v/v): R_f = 0.34; m.p.: 240.6-242.5 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 10.07 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.61 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 2.05 (s, 3H), 1.38 (s, 9H) ppm; ^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.2, 159.7, 151.7, 146.0, 134.6, 128.3, 124.5, 116.5, 112.5, 50.8, 28.3, 23.9 ppm; IR (neat): νmax (cm^{-1}) = 3327 (m), 2978 (w), 1738 (s), 1676 (m), 1637 (s), 1616 (s), 1545 (s), 1495 (s), 1421 (w), 1360 (m), 1269 (s), 1256 (s), 1202 (s), 1065 (m), 903 (w), 839 (s), 777 (m); HRMS (ESI): m/z calculated for $C_{14}H_{18}N_3O_3$ (M+H) 276.1343, found 276.1331.

2-(_tert_-butylamino)-6-(trifluoromethoxy)-4_H_-benzo[_d_][1,3]oxazin-4-one (3j):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 188 mg, 62%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.30; m.p.: 129.6-130.7 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.29 (d, *J* = 8.9 Hz, 1H), 4.95 (s, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.3, 152.3, 149.3, 144.5 (q, *J* = 1.7 Hz), 130.2, 126.5, 120.6 (q, *J* = 258 Hz), 120.4, 113.9, 52.3, 28.8 ppm; IR (neat): νmax (cm^{-1}) = 3288 (m), 2978 (w), 1751 (s), 1634 (s), 1609 (s), 1541 (w), 1487 (s), 1394 (w), 1364 (w), 1254 (s), 1209 (s), 1198 (s), 1161 (s), 1063 (m), 1014 (m), 897 (m), 831 (m), 779 (m); HRMS (ESI): m/z calculated for $C_{13}H_{14}F_3N_2O_3$ (M+H) 303.0951, found 303.0943.

2-(_tert_-butylamino)-6-fluoro-4_H_-benzo[_d_][1,3]oxazin-4-one (3k):
Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 178 mg, 75%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.33; m.p.: 131.9-133.0 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.65 (dd, *J* = 8.1, 2.9 Hz, 1H), 7.33 (dt, *J* = 8.5, 2.9 Hz, 1H), 7.25 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.87 (s, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6 (d, *J* = 3.5 Hz), 158.6 (d, *J* = 244 Hz), 151.7, 147.1 (d, *J* = 1.4 Hz), 126.6 (d, *J* = 7.5 Hz), 124.9 (d, *J* = 23.8 Hz), 114.0 (d, *J* = 8.7 Hz), 113.4 (d, *J* = 23.7 Hz), 52.1, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3312 (m), 2978 (w), 1744 (s), 1636 (s), 1610 (s), 1576 (m), 1529 (m), 1487 (s), 1475 (s), 1460 (s), 1393 (m), 1358 (m), 1339 (m), 1271 (s), 1246 (m), 1198 (s), 1115 (m), 1057 (m), 1013 (w), 916 (w), 879 (m), 849 (m), 829 (s), 777 (s); HRMS (ESI): m/z calculated for $C_{12}H_{14}FN_2O_2$ (M+H) 237.1034, found 237.1031.

2-(_tert_-butylamino)-5-chloro-4_H_-benzo[_d_][1,3]oxazin-4-one (3l):
Prepared according to general procedure 1 (10 mol % $Pd(OAc)_2$). Isolated as an off-white solid. Yield: 170 mg, 67%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.29; m.p.: 159.8-161.8 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.17-7.13 (m, 2H), 4.94 (s, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.9, 153.1, 152.5, 135.9, 135.8, 126.0, 123.8, 111.2, 52.2, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3269 (m), 1747 (s), 1630 (s), 1591 (s), 1553 (s), 1423 (m), 1393 (w),

1366 (m), 1279 (m), 1207 (s), 1167 (m), 1049 (m), 947 (s), 800 (s), 771 (w); HRMS (ESI): m/*z* calculated for $C_{12}H_{14}ClN_2O_2$ (M+H) 253.0738, found 253.0755.

2-(*tert*-butylamino)-7-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one (3m):

Prepared according to general procedure 1 (5 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 229 mg, 91%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.30; m.p.: 174.5-175.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.09 (dd, *J* = 8.5, 1.9 Hz, 1H), 5.00 (s, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.6, 152.8, 151.6, 142.9, 130.0, 124.4, 124.1, 111.9, 52.3, 28.8 ppm; IR (neat): νmax (cm^{-1}) = 3298 (m), 1736 (s), 1630 (s), 1589 (s), 1560 (s), 1456 (s), 1441 (s), 1393 (w), 1362 (m), 1327 (m), 1306 (w), 1275 (m), 1209 (s), 1078 (m), 1059 (s), 943 (s), 912 (w), 820 (w), 795 (w), 768 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{14}ClN_2O_2$ (M+H) 253.0738, found 253.0735.

2-(*tert*-butylamino)-6-bromo-4*H*-benzo[*d*][1,3]oxazin-4-one (3n):

Prepared according to general procedure 1 (10 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 244 mg, 82%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.30; m.p.: 180.5-181.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (d, *J* = 2.3 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 4.96 (s, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.1, 152.3, 149.5, 139.6, 130.9, 126.5, 115.8, 114.9, 52.3, 28.9 ppm; IR (neat): νmax (cm^{-1}) = 3290 (m); 2978 (w), 1742 (s), 1624 (s), 1593 (s), 1556 (m), 1470 (s), 1391 (m), 1362 (m), 1321 (m), 1273 (s), 1230 (m), 1209 (s), 1132 (m), 1064 (s), 1013 (m), 906 (m), 833 (s), 779 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{14}BrN_2O_2$ (M+H) 297.0233, found 297.0219.

2-(*tert*-butylamino)-6,7-defluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (3o):

Prepared according to general procedure 1 (10 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 207 mg, 81%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.28; m.p.: 163.8-164.6 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77 (t, *J* = 9.1 Hz, 1H), 7.04 (dd, *J* = 11.2, 6.9 Hz, 1H), 4.95 (br, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.7, 156.6 (dd, *J* = 259, 14.4 Hz), 152.5, 148.7 (d, *J* = 12.5 Hz), 147.3 (dd, *J* = 248, 14.3 Hz), 116.0 (dd, *J* = 19.2, 2.7 Hz), 112.6 (d, *J* = 18.5 Hz), 109.5 (d, *J* = 5.2 Hz), 52.4, 28.8 ppm; IR (neat): νmax (cm^{-1}) = 3279 (m), 2970 (w), 1745 (s), 1639 (s), 1618 (s), 1580 (m), 1549 (m), 1489 (s), 1393 (w), 1362 (m), 1286 (s), 1242 (m), 1207 (s), 1171 (s), 1132 (w), 1057 (s), 1011 (w), 897 (s), 856 (s), 798 (m), 775 (s); HRMS (ESI): *m/z* calculated for $C_{12}H_{13}F_2N_2O_2$ (M+H) 255.0940, found 255.0930.

2-(*tert*-butylamino)-7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (3p):

Prepared according to general procedure 1 (10 mol % $Pd(OAc)_2$). Isolated as a white solid. Yield: 238 mg, 83%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.28; m.p.: 166.0-168.2 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 5.11 (br, 1H), 1.49 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.3, 152.7, 150.8, 137.9 (q, *J* = 32.6 Hz), 129.7, 123.4 (q, *J* = 274 Hz), 122.1, 119.5 (q, *J* = 3.4 Hz), 115.9, 52.4, 28.8 ppm; IR (neat): νmax (cm^{-1}) = 3298 (m), 1742 (s), 1639 (m), 1609 (s), 1572 (s), 1541 (m), 1455 (s), 1396 (w), 1348 (m), 1308 (s), 1267 (m), 1256 (m), 1211 (m), 1200 (m), 1167 (s), 1128 (s), 1057 (s), 1045 (m), 947 (s), 897 (s), 829 (m), 781 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{14}F_3N_2O_2$ (M+H) 287.1002, found 287.0994.

2-(isopropylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3q):

Prepared according to general procedure 2. Isolated as a white solid. Yield: 137 mg, 67%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.18; m.p.: 150.5-151.0 °C (Lit.[6] 150-151 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63-7.59 (m, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 4.90 (br, 1H), 4.13 (octet, *J* = 6.7 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.2, 153.2, 150.7, 136.8, 128.8, 124.4, 123.6, 113.3, 43.8, 22.8 ppm; IR (neat): νmax (cm^{-1}) = 3294 (m), 2982 (w), 1736 (s), 1628 (s), 1599 (s), 1566 (s), 1535 (m), 1472 (s), 1385 (w), 1367 (w), 1348 (m), 1329 (w), 1313 (m), 1269 (s), 1238 (s), 1171 (m), 1148 (m), 1134 (m), 1107 (w), 1055 (s), 1030 (w), 1007 (m), 941 (m), 874 (w), 760 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{13}N_2O_2$ (M+H) 205.0972, found 205.096.

2-(cyclohexylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3r):

Prepared according to general procedure 2. Isolated as a white solid. Yield: 151 mg, 62%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.22; m.p.: 209.6-210.7 °C (Lit.[15] 208-210 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.63-7.59 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 4.82 (br, 1H), 3.86-3.77 (m, 1H), 2.11-2.01 (m, 2H), 1.82-1.70 (m, 2H), 1.68-1.60 (m, 1H), 1.49-1.38 (m, 2H), 1.32-1.19 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.2, 153.2, 150.8, 136.8, 128.9, 124.3, 123.6, 113.3, 50.3, 33.1, 25.6, 24.8 ppm; IR (neat): νmax (cm^{-1}) = 3286 (m), 2920 (m), 2853 (m), 1734 (s), 1630 (s), 1601 (s), 1568 (s), 1541 (m), 1474 (s), 1344 (w), 1341 (w), 1313 (m), 1279 (m), 1250 (m), 1231 (m), 1153 (m), 1119 (w), 1047 (m), 1020 (s), 957 (m), 891 (m), 870 (w), 758 (s); HRMS (ESI): *m/z* calculated for $C_{14}H_{17}N_2O_2$ (M+H) 245.1285, found 245.1279.

ethyl 4-((4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)amino)piperidine-1-carboxylate (3s):

Prepared according to general procedure 2. Isolated as a white solid. Yield: 210 mg, 66%. TLC (cyclohexane/EtOAc, 2:1 v/v): R_f = 0.21; m.p.: 198.9-201.3 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.64-7.60 (m, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.19-7.15 (m, 1H), 5.24 (d, *J* = 7.4 Hz, 1H), 4.23-4.04 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.04-3.94 (m, 1H), 3.06-2.97 (m, 2H), 2.12-2.05 (m, 2H), 1.53-1.43 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.1, 155.6, 153.0, 150.4, 136.9, 128.9, 124.4, 123.9, 113.4, 61.6, 48.7, 42.7, 31.9, 14.8 ppm; IR (neat): νmax (cm^{-1}) = 3269 (m), 1742 (m), 1693 (s), 1628 (s), 1605 (s), 1570 (w), 1541 (w), 1475 (m), 1433 (m), 1373 (m), 1302 (m), 1271 (m), 1225 (s), 1142 (s), 1086 (m), 1049 (m), 1024 (m), 872 (w), 762 (s); HRMS (ESI): *m/z* calculated for $C_{16}H_{20}N_3O_4$ (M+H) 318.1454, found 318.1468.

2-(isopropylamino)-7-chloro-4*H*-benzo[*d*][1,3]oxazin-4-one (3t):

Prepared according to general procedure 2. Isolated as a white solid. Yield: 145 mg, 61%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.20; m.p.: 153.3-153.9 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 1H), 7.09 (dd, *J* = 8.5, 1.9 Hz, 1H), 4.99 (br, 1H), 4.16-4.06 (m, 1H), 1.28 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.5, 153.8, 151.9, 143.1, 130.1, 124.1, 111.7, 44.0, 22.7 ppm; IR (neat): νmax (cm^{-1}) = 3298 (m), 1736 (s), 1632 (s), 1589 (s), 1556 (s), 1454 (s), 1439 (s), 1387 (w), 1369 (w), 1333 (m), 1271 (m), 1259 (m), 1227 (m), 1161 (m), 1132 (m), 1074 (m), 1047 (s), 945 (m), 924 (s), 868 (s), 820 (m), 766 (s); HRMS (ESI): *m/z* calculated for $C_{11}H_{12}ClN_2O_2$ (M+H) 239.0582, found 238.0576.

Note: Two ^{13}C signals overlap at 124.1 ppm as confirmed by a ^{1}H, ^{13}C-HSQC measurement.

2-(isopropylamino)-6,7-dimethoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (3u):
Prepared according to general procedure 2. Isolated as an off-white solid. Yield: 184 mg, 70%. TLC (cyclohexane/EtOAc, 2:1 v/v): R_f = 0.28; m.p.: 194.0-196.4 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (s, 1H), 6.69 (s, 1H), 4.80 (br, 1H), 4.12-4.04 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.8, 157.1, 153.2, 147.4, 146.5, 107.9, 105.5, 105.0, 56.4, 56.3, 43.7, 22.8 ppm; IR (neat): νmax (cm^{-1}) = 3281 (m), 1715 (s), 1610 (s), 1574 (m), 1493 (s), 1479 (m), 1454 (m), 1435 (s), 1383 (m), 1281 (m), 1231 (m), 1213 (s), 1167 (m), 1134 (s), 1055 (m), 1043 (m), 999 (m), 945 (w), 858 (s), 841 (s), 798 (s), 770 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{17}N_2O_4$ (M+H) 265.1183, found 265.1179.

2-(pentylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (3v):
Prepared according to general procedure 2. Recrystallized from cyclohexane and isolated as an off-white solid. Yield: 74 mg, 32%. TLC (cyclohexane/EtOAc, 8:1 v/v): R_f = 0.18; m.p.: 124.7-126.8 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.64-7.60 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 5.02 (br, 1H), 3.43 (t, *J* = 7.0 Hz, 2H), 1.67-1.60 (m, 2H), 1.40-1.34 (m, 4H), 0.94-0.90 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz): δ 160.0, 154.0, 150.5, 136.9, 128.9, 124.3, 123.7, 113.3, 41.7, 29.1, 29.0, 22.4, 14.1 ppm; IR (neat): νmax (cm^{-1}) = 3302 (m), 2951 (w), 2928 (m), 2862 (w), 1742 (s), 1634 (s), 1601 (s), 1568 (m), 1474 (s), 1377 (w), 1271 (m), 1238 (m), 1153 (m), 1045 (m), 1013 (m), 957 (w), 878 (w), 760 (s); HRMS (ESI): *m/z* calculated for $C_{13}H_{17}N_2O_2$ (M+H) 233.1285, found 233.1288.

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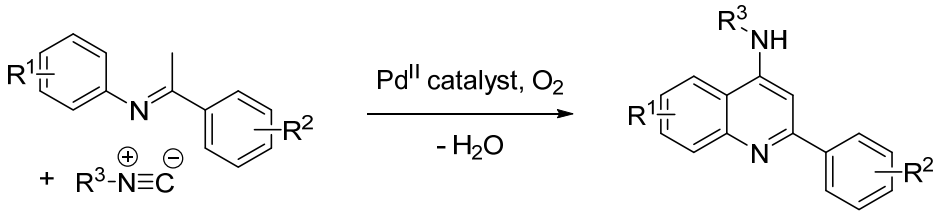
Chapter 8

4-Aminoquinolines:

Imidoylative Oxidative Pd-Catalyzed Double C-H Activation



***Abstract**: The first example of a Pd-catalyzed imidoylative coupling of two C-H fragments is described. The reaction produces medicinally valuable 4-aminoquinolines from readily available starting materials and proceeds with O_2 as stoichiometric oxidant, but yields are still modest and further optimization is required. We believe imidoylative C-H activation offers various opportunities for the efficient synthesis of fine chemicals with nitrogen functionality, as illustrated by this preliminary work.*

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8.1 Introduction

Isocyanides were recently identified as versatile C_1 building blocks in palladium catalysis and readily undergo 1,1-migratory insertion similar to carbon monoxide (see previous Chapters).[1] This strategy has been applied in amidination reactions of aryl halides by imidoylative cross-coupling with amines, which has found various applications in the synthesis of important functional groups and heterocycles (see Chapter 2 for an overview). The amidine motif is a recurring theme of this field and we believe the horizons should be broadened to allure more interest for this chemistry. To this end, we developed the oxidative coupling of bisnucleophiles and isocyanides using molecular oxygen as oxidant (see Chapters 5, 6 and 7). We also became intrigued by the potential of an imidoylative double C-H activation cascade that would yield valuable imine/enamine-containing products in a highly sustainable manner. The selective catalytic activation of C-H bonds, rather than preactivation as halides, offers substantial advantages, like improved atom and step economy, and is therefore a more environmentally benign alternative.[2] Indeed, C-H activation has already been combined with isocyanide insertion in the synthesis of amidine-containing heterocycles,[3] but also imine/enamine-containing heterocycles are accessible by imidoylative cross-coupling of aryl halides and C-H fragments.[4] An imidoylative coupling of two C-H fragments is, however, still elusive. An inherent difficulty of such a transformation is differentiation between the various C-H bonds present in a typical organic molecule.

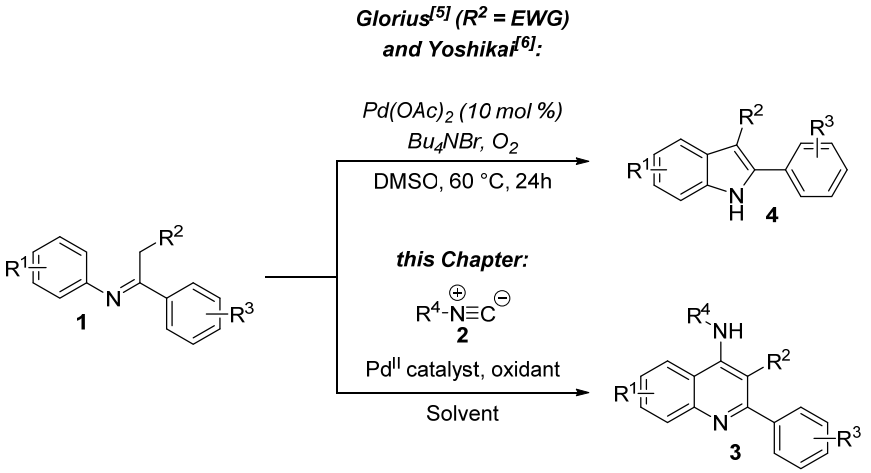
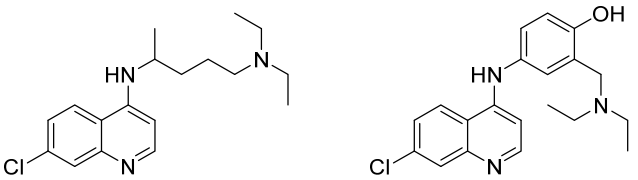


Figure 1. Indole synthesis by Glorius and Yoshikai and outline of this Chapter.

Glorius *et al*. recently reported an elegant synthesis of indoles (**4**) by Pd-catalyzed oxidative cyclization of *N*-aryl imines (**1**) that overcomes this difficulty by using an activated enamine/imine C-H bond (Figure 1).[5] An activating electron-withdrawing group was required on the R^2 position of the *N*-aryl imines (**1**) to increase the acidity of the α-proton. However, Yoshikai *et al*. subsequently reported modified conditions that overcame this limitation.[6] We chose to evaluate the potential use of our envisioned imidoylative double C-H activation reaction with this system. An imidoylative Pd-catalyzed oxidative cyclization of *N*-aryl imines (**1**) provides straightforward access to 4-aminoquinolines (**3**). These products are valuable in medicinal chemistry, as illustrated by the important antimalarial drugs chloroquine and amodiaquine (Figure 2).



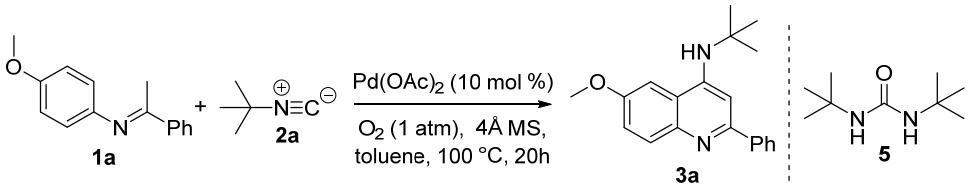
Chloroquine ***Amodiaquine***

Figure 2. Antimalarial agents with 4-aminoquinoline motif.

8.2 Results and Discussion

We started our investigations by studying the reaction between *N*-aryl imine **1a** and *tert*-butyl isocyanide (**2a**, Table 1). We first tested the conditions developed by Yoshikai *et al.*, but no detectable amount of the desired product **3a** was formed.[6] We then tried our conditions for the oxidative guanidine synthesis (Chapter 5) and were pleased to find conversion to 4-aminoquinoline **3a** using $Pd(OAc)_2$ (10 mol %) in the presence of molecular sieves in toluene at 100 °C under oxygen atmosphere, although the conversion was poor (Table 1, entry 1). The black reaction mixture, which was observed after a few hours, indicated formation of palladium black. We screened several other oxidants ($CuCl_2$, $Cu(OAc)_2$, $Cu(TFA)_2$, AgOAc, benzoquinone, $K_2S_2O_8$), solvents (THF, DMSO, DMF, MeCN, *t*BuOH, dioxane, DCE, DME), palladium catalysts ($PdCl_2$, $Pd(O_2CCF_3)_2$, $Pd(MeCN)_2Cl_2$) and additives (CsF, NBu_4Br) but no improvements were achieved.

Table 1. Optimization of the reaction conditions.[a]



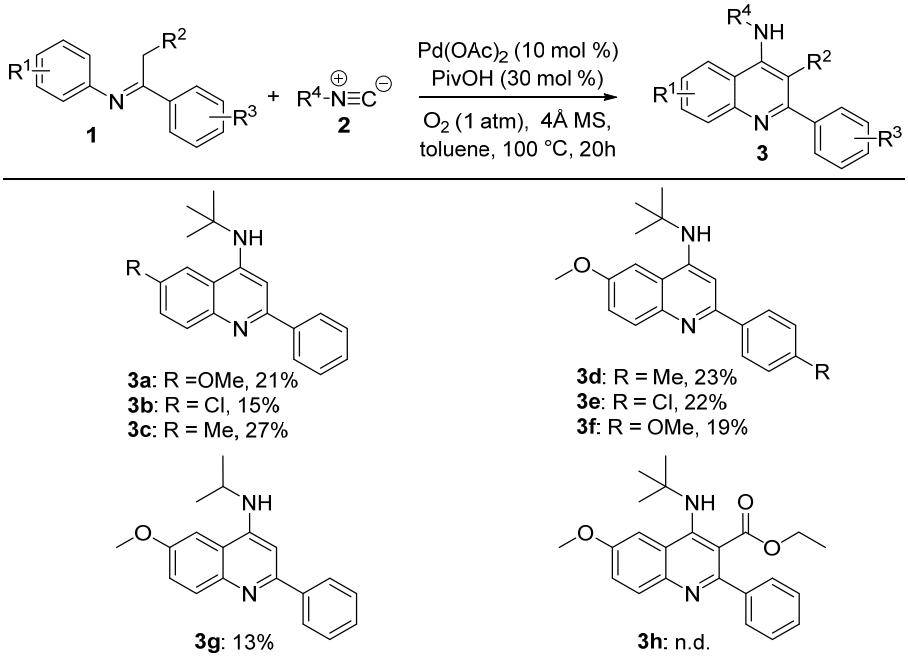
Entry	Equivalents **2a**	Additive	Conversion[b]	Yield[b]
1	1.5	none	20%	8%
2	3	none	31%	15%
3	3	1,10-phenanthroline (20 mol %)	30%	12%
4	3	Pyridine (1 eq.)	31%	12%
5	3	PivOH (10 mol %)	40%	24%
6	3	PivOH (20 mol %)	42%	25%
7	3	PivOH (30 mol %)	64%	46%
8	3	PivOH (40 mol %)	48%	19%
9	3	PivOH (60 mol %)	40%	6%

[a] Standard conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), 4Å MS (150 mg), toluene (2.5 mL) at 100 °C under O_2 atmosphere for 20h. [b] Determined by GC analysis using dodecane as internal standard.

We argued that palladium black formation could be retarded by addition of more *tert*-butyl isocyanide, which coordinates to Pd^0 species. Indeed, a higher yield was obtained when three equivalents of **2a** were used (entry 2). Coordinating

additives, such as 1,10-phananthroline and pyridine, gave no further improvement (entry 3 and 4) and varying the temperature did also not improve the yield. Finally, we found that a catalytic amount of pivalic acid is beneficial to the reaction (entry 5-9). The reaction is highly sensitive to the amount of pivalic acid used, with 30 mol % giving the optimal result. It is, however, important to note that the yields varied between individual experiments using 'identical' reaction conditions and the reaction is apparently very sensitive to minor changes in the conditions. Therefore, only the relative trend shown in Table 1 is of value and the absolute numbers should be disregarded. Surprisingly, the unreacted starting material (**1a**) remained intact under the optimal conditions (entry 7), suggesting only catalyst deactivation hampers the reaction. Other carboxylic acids, such as 2,4,6-trimethylbenzoic acid and Boc-L-Valine did not work better than pivalic acid. We were unfortunately not able to further improve the conversion of this transformation. The only side product we identified was *N,N'*-di-*tert*-butyl urea (**5**), which we have also encountered in other aerobic oxidative Pd-catalyzed imidoylation reactions (Chapters 5 and 7).

Table 2. Scope of the reaction towards 4-aminoquinolines.[a]



[a] Standard conditions: **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), PivOH (30 mol %), 4Å MS (150 mg), toluene (2.5 mL) at 100 °C under O_2 atmosphere for 20h. Yields refer to isolated material and are corrected for contamination with $(t\text{BuNH})_2CO$ (**5**).

We evaluated the scope of the Pd-catalyzed coupling of various *N*-aryl imines (**1**) and isocyanides (**2**) hoping to find a more suitable substrate (Table 2, previous page). In the event, electron-withdrawing and -donating substituents on both aromatic rings had only a minor influence on the course of the reaction. In all cases a similar isolated yield (15-27%) was observed. In some cases removal of urea **5** was problematic and the product was isolated as a mixture. Remarkably, isopropyl isocyanide was readily converted to 4-aminoquinoline **3g** under the same conditions. We also installed an electron-withdrawing ester group on the *N*-aryl imine to activate the methylene group for C-H activation, but surprisingly in this case product **3h** was not observed in an appreciable quantity.

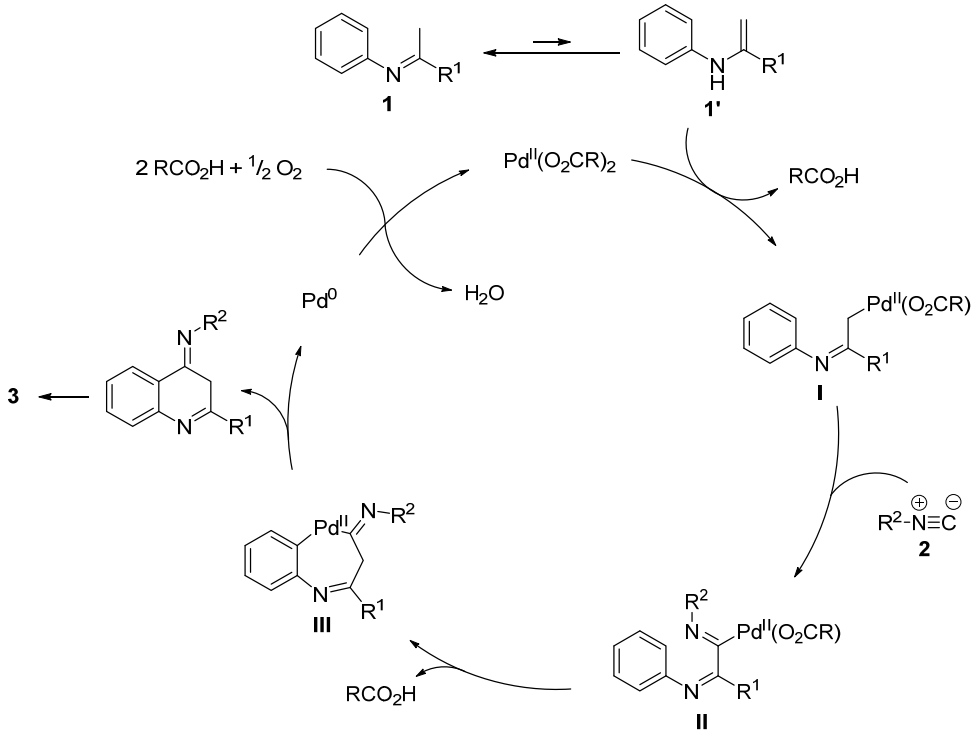


Figure 3. Proposed mechanism. Possible additional ligands on palladium are omitted for clarity. R = *t*-butyl or methyl.

A plausible mechanism, based on previous literature reports,[5-6] is depicted in Figure 3. Nucleophilic attack of enamine **1'** on palladium and elimination of carboxylic acid leads to α-palladated imine **I**. Migratory insertion of isocyanide followed by intramolecular C-H activation provides palladium species **III**, which undergoes

reductive elimination to afford the product and Pd^0. Alternatively, the second C-H activation event could occur prior to isocyanide insertion. Finally, palladium is reoxidized by molecular oxygen.

8.3 Conclusion

The first Pd-catalyzed imidoylative coupling of two C-H fragments is described in this Chapter. This type of transformation is a valuable expansion of the product scope of imidoylative cross-coupling chemistry and enables the imidoylative synthesis of imine/enamine containing products. In the reaction discussed in this Chapter, medicinally valuable 4-aminoquinolines are produced from readily available starting materials. Molecular oxygen can be used as stoichiometric oxidant, which makes the reaction highly atom efficient. The yields are, however, still modest and further optimization is a necessity. We believe imidoylative C-H activation offers various opportunities for the efficient synthesis of fine chemicals with nitrogen functionality, as illustrated by this preliminary work.

8.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Palladium acetate was obtained from Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Solvents were used as purchased. Powdered 4Å molecular sieves were purchased from Sigma Aldrich and activated before use. GC yield and conversion analysis was performed using a Shimadzu GC2010 equipped with a Zebron ZB-1 capillary column (30m x 0.25 mm) with dodecane as internal standard. NMR spectra were recorded on a Bruker Avance 500 (125.78 MHz for ^{13}C) spectrometer using the residual solvent as internal standard (^{1}H: δ 2.50 ppm, $^{13}C\{^{1}H\}$: δ 39.52 ppm for DMSO-d_6). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz. Melting points were recorded on a Büchi M-565 melting point apparatus. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO_2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm).

Synthesis of substrates

N-aryl imines (**1**) were prepared by condensation of the corresponding aniline and acetophenone derivatives according to literature procedure and purified by vacuum distillation or crystallization from EtOH, Et_2O or EtOAc.[7] ^{1}H NMR spectra of all imines were in good agreement with literature data: **1a**[8], **1b**[9], **1c**[10], **1d**[11], **1e**[10], **1f**[7], **1g**[7], **1h**[12].

General synthetic procedures

Optimization of the oxidative coupling of *o*-phenylenediamine and *tert*-butyl isocyanide:
A Radleys parallel synthesis unit was used to simultaneously run multiple reactions. *N*-aryl imine **1a** (0.5 mmol), catalyst and all other solid reagents or additives were added to a Radley tube. Vacuum was applied and the vessel was backfilled with O_2 (3x). Solvent (2.5 mL) was added, followed by *tert*-butyl isocyanide and any other liquid reagents or additives. The resulting mixture was stirred vigorously for 20h under O_2 atmosphere (balloon). Afterwards, the crude reaction mixture was diluted with EtOAc (4 mL) and dodecane (114 μL, 0.5 mmol, 1 eq.) was added as internal standard. A sample was filtered and subjected to GC analysis to determine conversion of **1a** and yield of the product (**3a**).

General procedure for the synthesis of 4-aminoquinolines (3):
N-aryl imine (**1**, 0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 10 mol %), pivalic acid (15.3 mg, 30 mol %) and activated powdered molecular sieves (4Å, 150 mg) were added to a Schlenk tube. Vacuum was

applied and the vessel was backfilled with O_2 (3x). Toluene (2.5 mL) was added, followed by isocyanide (**2**, 1.5 mmol). The resulting mixture was stirred vigorously at 100 °C for 20h under O_2 atmosphere (balloon). Then, the mixture was cooled, filtered over Celite, concentrated and purified by flash chromatography (eluent: $CHCl_3$/MeOH gradient). Products were isolated in reasonable purity (>90% by ^1H NMR), or along with *N,N'*-di-*tert*-butyl urea (**5**) in some cases (indicated below).

Spectral data

_N_-(tert-butyl)-6-methoxy-2-phenylquinolin-4-amine (3a):
Prepared according to the general procedure. Isolated as a brownish oil Yield: 32 mg, 21% yield. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.18; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.32 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.09 (s, 1H), 6.30 (br, 1H), 3.93 (s, 3H), 1.57 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 156.2 (C), 153.5 (C), 148.6 (C), 143.2 (C), 139.7 (C), 130.3 (CH), 128.9 (CH), 128.7 (CH), 126.9 (CH), 120.8 (CH), 119.3 (C), 101.5 (CH), 98.2 (CH), 55.9 (CH_3), 51.4 (C), 29.0 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{20}H_{23}N_2O$ (M+H) 307.1805, found 307.1812.

_N_-(*tert*-butyl)-6-chloro-2-phenylquinolin-4-amine (3b):
Prepared according to the general procedure. Isolated as mixture with *N,N'*-di-*tert*-butyl urea (**5**) in a 1:1.6 ratio (**3b**:**5**, determined by ^1H NMR) as a yellow/brown solid. Yield: 15% after correction for impurities. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.48; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.52 (d, *J* = 1.9 Hz, 1H), 8.09 (d, *J* = 7.3 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.64 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.12 (s, 1H), 6.61 (br, 1H), 1.55 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 156.2 (C), 148.9 (C), 146.5 (C), 139.4 (C), 130.9 (CH), 129.8 (CH), 129.3 (CH), 128.7 (CH), 128.6 (C), 127.1 (CH), 121.4 (CH), 119.5 (C), 98.5 (CH), 51.6 (C), 28.8 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{19}H_{20}ClN_2$ (M+H) 311.1310, found 311.1320.

_N_-(*tert*-butyl)-6-methyl-2-phenylquinolin-4-amine (3c):
Prepared according to the general procedure. Isolated as an off-white solid. Yield: 39 mg, 27%. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.27; m.p.: 128.3-131.6 °C; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.11-8.05 (m, 3H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.53-7.42 (m, 4H), 7.05 (s, 1H), 6.34 (br, 1H), 2.47 (s, 3H), 1.53 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 158.8 (C), 149.0 (C), 146.0 (C), 139.7 (C), 133.5 (C), 131.3 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.0 (CH), 120.8 (CH), 118.4 (C), 97.9 (CH), 51.4 (C), 28.9 (CH_3), 21.2 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{20}H_{23}N_2$ (M+H) 291.1856, found 291.1867.

_N_-(*tert*-butyl)-6-methoxy-2-(*p*-tolyl)quinolin-4-amine (3d):
Prepared according to the general procedure. Isolated as an off-white oil. Yield: 37 mg, 23%. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.23; ^1H NMR (DMSO-d_6, 500 MHz): δ 7.07 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.34-7.29 (m, 3H), 7.07 (s, 1H), 6.28 (br, 1H), 3.93 (s, 3H), 2.37 (s, 3H), 1.56 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6, 126 MHz): δ 156.1 (C), 153.4 (C), 148.6 (C), 143.1 (C), 138.4 (C), 136.8 (C), 130.2 (CH), 129.3 (CH), 126.8 (CH), 120.7 (CH), 119.2

(C), 101.5 (CH), 98.0 (CH), 55.9 (CH_3), 51.4 (C), 29.0 (CH_3), 20.9 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{21}H_{25}N_2O$ (M+H) 321.1961, found 321.1976.

***N*-(*tert*-butyl)-2-(4-chlorophenyl)-6-methoxyquinolin-4-amine (3e):**

Prepared according to the general procedure. Isolated as mixture with *N,N'*-di-*tert*-butyl urea (**5**) in a 4:1 ratio (**3e**:**5**, determined by ^{1}H NMR) as a yellowish oil. Yield: 22%, yield after correction for impurities. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.28; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.32 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.08 (s, 1H), 6.31 (br, 1H), 3.93 (s, 3H), 1.56 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 156.3 (C), 152.2 (C), 148.7 (C), 143.3 (C), 138.5 (C), 133.6 (C), 130.4 (CH), 128.6 (CH), 128.6 (CH), 120.9 (CH), 119.3 (C), 101.5 (CH), 97.9 (CH), 55.9 (CH_3), 51.4 (C), 29.0 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{20}H_{22}ClN_2O$ (M+H) 341.1415, found 341.1428.

***N*-(*tert*-butyl)-6-methoxy-2-(4-methoxyphenyl)quinolin-4-amine (3f):**

Prepared according to the general procedure. Isolated as an off white solid. Yield: 32 mg, 19%. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.14; m.p.: 67.2-81.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.03 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 9.1 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.04 (s, 1H), 6.32 (br, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 160.1 (C), 156.0 (C), 153.0 (C), 148.7 (C), 142.8 (C), 131.7 (C), 129.8 (CH), 128.3 (CH), 120.8 (CH), 119.0 (C), 114.1 (CH), 101.6 (CH), 97.7 (CH), 55.9 (CH_3), 55.3 (CH_3), 51.5 (C), 29.0 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{21}H_{25}N_2O_2$ (M+H) 337.1911, found 337.1925.

***N*-isopropyl-6-methoxy-2-phenylquinolin-4-amine (3g):**

Prepared according to the general procedure. Isolated as a brown oil. Yield: 19 mg, 13%. TLC ($CHCl_3$/MeOH, 97:3 v/v): R_f = 0.16; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.13 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.32 (dd, *J* = 9.1, 2.4 Hz, 1H), 6.96 (s, 1H), 6.88 (br, 1H), 4.12 (octet, *J* = 6.6 Hz, 1H), 3.93 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (DMSO-d_6, 126 MHz): δ 156.2 (C), 153.9 (C), 149.7 (C), 143.0 (C, only observed in ^{1}H, ^{13}C-HMBC), 139.4 (C), 129.8 (CH), 128.9 (CH), 128.5 (CH), 127.1 (CH), 121.1 (CH), 118.4 (C), 101.3 (CH), 95.7 (CH), 55.9 (CH_3), 43.5 (CH), 22.0 (CH_3) ppm; HRMS (ESI): m/z calculated for $C_{19}H_{21}N_2O$ (M+H) 293.1648, found 293.1661.

8.5 References

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Chapter 9

Reflections and Future Directions

9.1 Introduction

The work described in this thesis hopefully provokes the interest of chemists in imidoylative cross-coupling reactions and could thereby stimulate further developments in this field. Indeed, a lot of progress has been realized in the past decade as is summarized in the comprehensive overview of the literature provided in Chapter 2. This overview also makes two aspects of imidoylative cross-couplings clear:

(1) they are mainly used for the synthesis of amidines and related products, and

(2) every isocyanide has a unique reactivity which severely hampers generality.

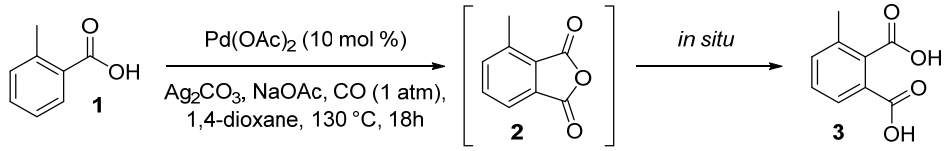
At the outset of our work we particularly aimed to tackle aspect *(1)*, to which we contributed by the development of the aerobic oxidative coupling of bisnucleophiles and isocyanides described in Chapters 5, 6 and 7. In addition, we have developed a sustainable approach towards imine/enamine-containing products by an imidoylative double C-H activation cascade, although yields were disappointing (Chapter 8). In doing so, we hoped to learn more about aspect *(2)* and explain the strong effect of the isocyanide on the selectivity of insertion reactions. By studying the sideproducts of the oxidative coupling of *o*-phenylenediamine and isopropyl isocyanide, we learned firsthand that multiple consecutive insertions of isocyanides is a possible explanation for the problems in isocyanide scope. In more complex intermolecular reactions, such as the MCR towards 4-aminophthalazin-1(2*H*)-ones (Chapter 3 and 4), this could lead to a variety of oligomers that make analysis difficult. Although there is still no solution to this issue, this knowledge could prove useful in future research endeavors. Further (theoretical) mechanistic studies on the oxidative coupling of *o*-phenylenediamines and isocyanides are recommended. If the reason for more pronounced double insertion of less bulky isocyanides is known, it is perhaps possible to rationally design catalysts that can counter-effect this.

This Chapter will provide an overview of other novel transformations using isocyanides that either were unsuccessful in our hands, are still ongoing, or have not been tried yet.

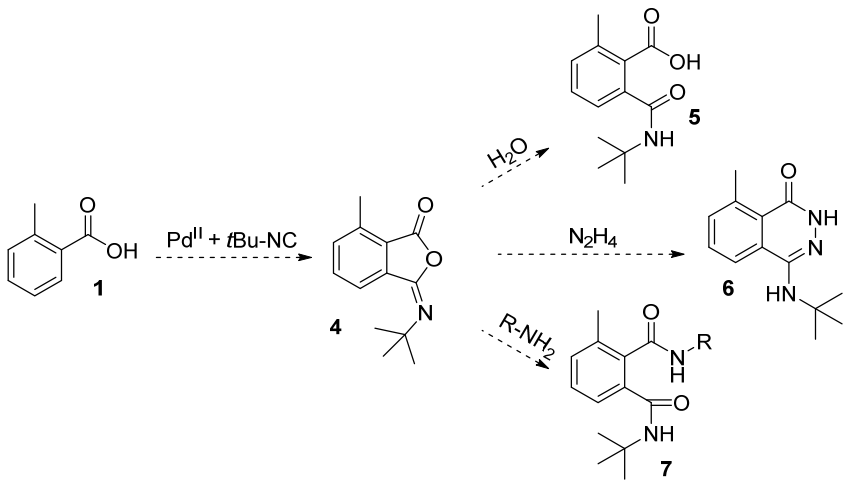
9.2 Future Directions

9.2.1 Directed ortho C-H activation

The catalytic activation of C-H bonds is a popular research topic that offers significant improvements, such as improved atom and step economy, over the more traditional preactivation of coupling partners as halides or organometallic reagents.[1] Selective C3-amidination and C3-carboxamidation reactions of indoles *via* C-H activation and isocyanide insertion have recently been developed (Chapter 2).[2] In these examples the electronic bias of the heterocyclic indole core is responsible for the regioselectivity. We became interested in a more general directing group driven C-H activation of benzene derivatives. The pioneering work by the group of Yu, aimed at utilizing 'useful' directing groups such as carboxylic acids, is especially appealing.[3]



Scheme 1. Carboxylic acid directed *ortho* C-H activation and CO insertion.

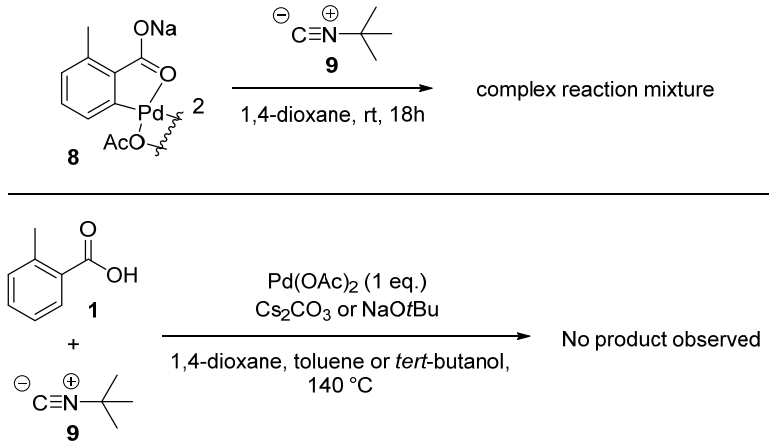


Scheme 2. Imidoylative *ortho* C-H activation.

In 2008, Yu *et al*. reported a Pd^{II}-catalyzed *ortho*-carboxylation of benzoic acids to form dicarboxylic acids (Scheme 1).[4] The initially formed anhydride **2** is

hydrolyzed under the reaction conditions in their case. We wondered if it is possible to replace carbon monoxide with an isocyanide in this transformation to furnish products like **4**, which can serve as precursor for densely functionalized benzene derivatives like **5** and **7** (Scheme 2). It might also be possible to convert them to 4-aminophthalazin-1(2*H*)-ones (**6**, see also Chapter 3 and 4).

We first tried to simply replace carbon monoxide by *tert*-butyl isocyanide under otherwise identical conditions to Yu's work. Unfortunately, no product formation could be observed and mainly starting material remained. Next, we prepared cyclopalladated intermediate **8**, which was also prepared by Yu *et al*. and is readily converted to anhydride **2** under CO atmosphere at room temperature. In our hands, however, compound **8** did not provide a clean reaction when treated with *tert*-butyl isocyanide (**9**, Scheme 3). In a final effort, we treated 2-methylbenzoic acid (**1**) with a stoichiometric amount of $Pd(OAc)_2$ in the presence of Cs_2CO_3 or NaO*t*Bu in either dioxane, toluene or *tert*-butanol. However in none of our experiments we saw any trace of products derived from **4** and complicated mixtures were found.

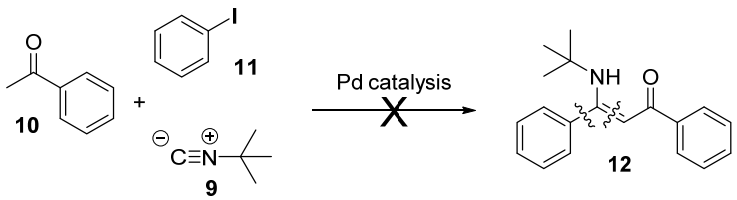


Scheme 3. Synthetic attempts for selective imidoylative *ortho* C-H activation.

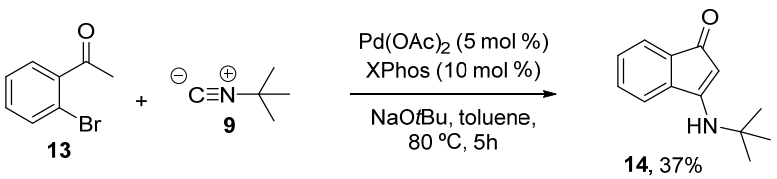
Despite the disappointing results obtained thus far, more effort directed towards imidoylative *ortho* C-H activation is warranted. Many more directing groups are known and could potentially be used for such a transformation. For example, *N*-aryl-*N',N'*-dialkylureas were used by Lloyd-Jones and Booker-Milburn *et al*. and also readily undergo *ortho* C-H activation and carbonylation to afford methyl esters.[5]

9.2.2 Imidoylative α-arylation of ketones

The Pd-catalyzed α-arylation of ketones (or aldehydes/esters) has been a fruitful area of research and nowadays is a convenient method for the synthesis of benzylic carbonyl compounds.[6] In fact, very recently a Pd-catalyzed carbonylative α-arylation of ketones leading to 1,3-diketones was reported by the group of Skrydstrup.[7] At the beginning of our study of imidoylative palladium catalysis we briefly explored the imidoylative α-arylation of ketones. The intermolecular coupling of acetophenone (**10**), iodobenzene (**11**), and *tert*-butyl isocyanide (**9**) was not successful (Scheme 4), but the intramolecular version was more promising and we obtained enaminone **14** in 37% isolated yield in our first attempt (Scheme 5). The reaction, however, proved to be irreproducible and yields varying between 29% and 52% yield (determined by ^{1}H NMR) were observed. Also, modifications to the reaction in terms of solvent, base, temperature and catalyst resulted in lower yield. Although full conversion was typically achieved, it was not possible to isolate or identify any sideproducts. The abovementioned reasons led us to suspend the pursuit of this interesting transformation. However, it is important to note that not much optimization work was done because our focus shifted to the other projects described in this thesis. It is very well possible higher yielding conditions can be found and further research is recommended, especially since this novel disconnection could find application in the synthesis of diverse heterocycles. Furthermore, enaminones are widely used as synthetic building blocks and have pharmaceutical potential.[8]



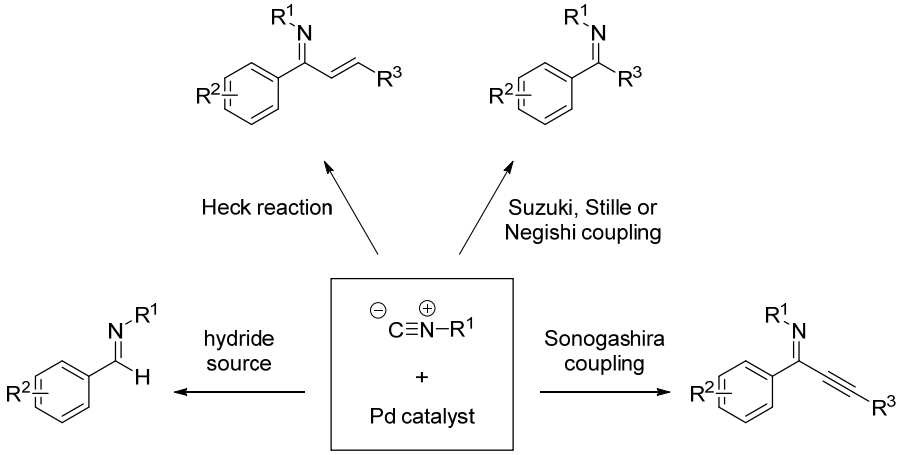
Scheme 4. Imidoylative α-arylation of ketones.



Scheme 5. Intramolecular imidoylative α-arylation of ketones.

9.2.3 Imidoylative cross-coupling chemistry

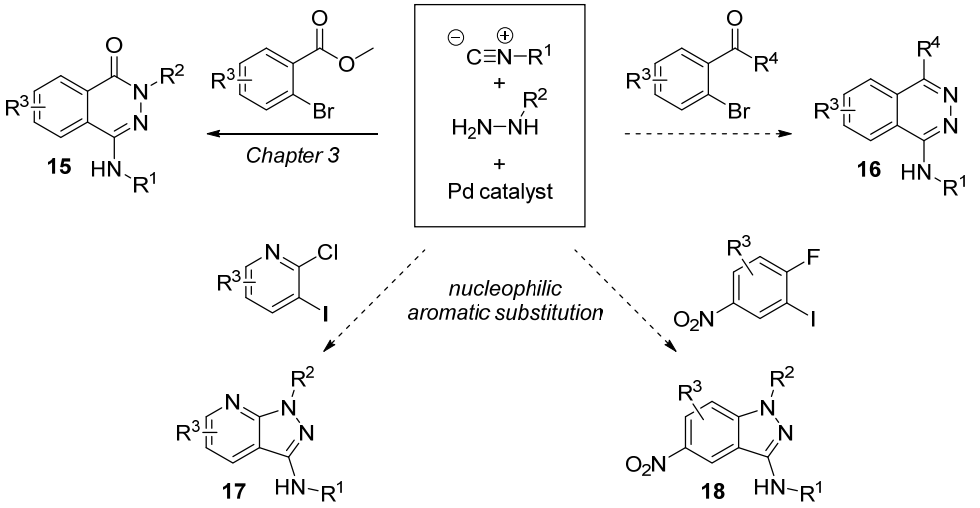
In the past decade significant progress has been made in the field of Pd-catalyzed reactions involving the insertion of isocyanides (see Chapter 2). However, there is no general imidoylative version of many of the well-known cross-coupling reactions (*i.e.* Heck, Suzuki, Negishi, Stille, and others). The group of Suzuki briefly studied the imidoylative Suzuki coupling in 1992 and found a system were *tert*-butyl isocyanide can be inserted.[9] No other isocyanides were used and a general imidoylative Suzuki coupling is still lacking. Very recently the first imidoylative Sonogashira coupling was reported by Zhu and Ji *et al*.[10] In both of these reactions, *tert*-butyl isocyanide was used as carbon monoxide equivalent and the resulting imine species were hydrolyzed. Although these accomplishments are important contributions and offer a very convenient alternative to carbon monoxide, we believe general and practical approaches towards imines based on traditional cross-coupling reactions could offer useful building blocks for a variety of follow-up chemistry (Scheme 6). Imines are commonly encountered in multicomponent reactions as they are readily prepared *in situ* from carbonyl compounds and amines.[11] An imidoylative Pd-catalyzed approach towards imines might be combined with such MCRs to obtain atom-efficient routes to valuable functionalized products. A possible advantage over conventional imine synthesis is the tolerance of different functional groups that are not compatible with condensation, such as ketones or aldehydes. Additionally, these products might be used in Pd-catalyzed cascade reactions (Chapter 1) or be valuable in their own right.



Scheme 6. Imidoylative imine synthesis.

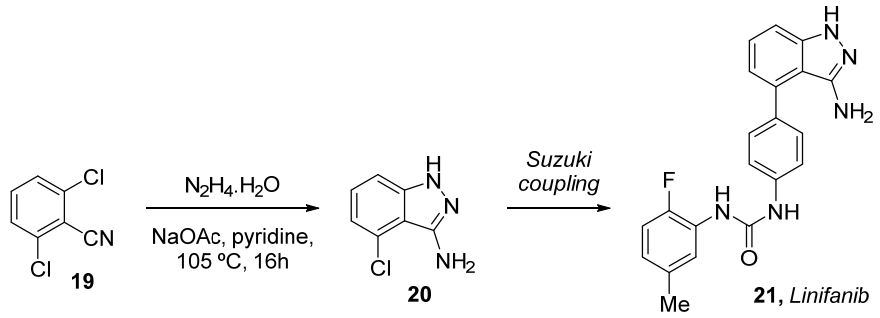
9.2.4 Pd-catalyzed MCRs with hydrazines and isocyanides

We have developed a novel approach towards 4-aminopthalazin-1(2*H*)-ones (APOs, **22**) by a Pd-catalyzed coupling of hydrazines, isocyanides and methyl 2-bromobenzoates (Scheme 7, see Chapter 3 for details). It is likely this strategy can be applied to various other heterocyclic systems be employing other aryl halides with pendant electrophilic positions. For example, the ester functionality might be replaced by a ketone to afford aminophthalazines (**16**), which are commonly studied for their medicinal potential.[12] Aminophthalazinones are typically prepared from 1,4-dichlorophthalazines by amination and subsequent substitution or Suzuki coupling. This approach is similar to the usual synthesis of APOs (**15**) discussed in Chapter 3 and consequently suffers from the same limitation; nonsymmetrical substitution on the phenyl ring (**16**, $R^3 \neq H$) will lead to regioisomers during the amination and therefore low yields and difficult separation are expected. The strategy based on isocyanide insertion eliminates this limitation and would allow straightforward access to diverse aminophthalazines. Interestingly, Beller *et al.* very recently used the same concept to obtain phthalazinones by inserting carbon monoxide instead of isocyanides.[13] We briefly explored the proposed route towards **16** (Scheme 7) using the optimal conditions established for the synthesis of APOs (Chapter 3) and indeed found formation of product, but a low yield was obtained and further optimization is required.



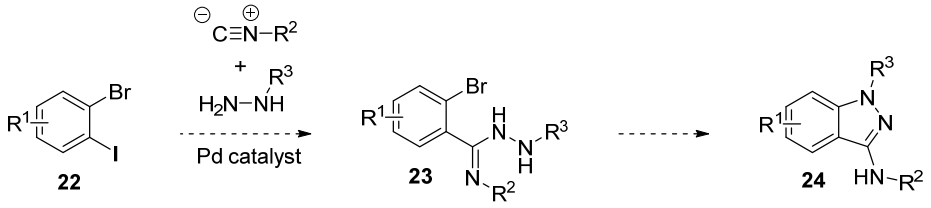
Scheme 7. MCRs with hydrazines and isocyanides.

Indazoles and their aza analogs (**17** and **18**, Scheme 7) are valuable compounds and their chemistry and pharmacological properties are well-studied.[14] For example, Linifanib (**21**, Scheme 8) is a potent and selective inhibitor of vascular endothelial growth factor receptor (VEGFR)-related and platelet-derived growth factor receptor (PDGFR)-related tyrosine kinases. Inihibition of these kinases is associated with the treatment of hepatocellular carcinoma (HCC), the most common type of liver cancer. Linifanib very recently successfully went through phase 2 clinical trials.[15] Although linifanib is easily synthesized on industrial scale (Scheme 8),[16] it is an illustrative example of the importance of 3-aminoindazoles.



Scheme 8. Linifanib and its synthesis.

We imagine that our imidoylative cross-coupling with hydrazine strategy can also be used to obtain this type of products by introducing nucleophilic aromatic substitution as cyclization step (Scheme 7). Alternatively, the nucleophilic aromatic substitution might be replaced by Pd-catalyzed amination if two different halides are present to allow selectivity (Scheme 9). Imidoylative Buchwald-Hartwig amination of the more reactive aryl iodide might afford product **23**, which can cyclize under the reaction conditions by intramolecular amination of the less reactive aryl bromide. We have not yet explored any of these approaches towards indazoles.



Scheme 9. Imidoylative approach towards 3-aminoindazoles.

9.3 Conclusion

The use of isocyanides in palladium catalysis has flourished in the past decade and especially the past two years, after occasional examples were reported in the 20th century. The wide variety of applications developed by us and others in recent years has established isocyanides as useful C_1 building block and will stimulate further developments. The work described in this thesis was focused at using imidoylative palladium catalysis to obtain other functionalities than amidines or imidates, which are the most common products. We hope that this broadened horizon will further catch the attention of synthetic chemists and lead to new developments in the near future. The ideas presented in this Chapter are just some of the possibilities we envision and might pursue ourselves, but many more complex cascades involving isocyanide insertion can be imagined. In order to achieve this, a better mechanistic understanding is required to rationalize the behavior of isocyanides in palladium catalysis. We strongly feel the field of imidoylative palladium catalysis is still in its infancy and there is ample room for additional progress.

9.4 Experimental Section

General comments

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Palladium acetate was obtained from Strem Chemicals and stored in a desiccator from which small portions (+/- 200 mg) were taken periodically. Cyclohexane was distilled prior to use. Other solvents were used as purchased. IR spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance 500 (125.78 MHz for ^{13}C) using the residual solvent as internal standard (^{1}H: δ 7.26 ppm, $^{13}C\{^{1}H\}$: δ 77.16 ppm for $CDCl_3$). Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Melting points were recorded on a Büchi M-565 melting point apparatus. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO2, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm).

Synthetic procedures and spectral data

3-(*tert*-butylamino)-1*H*-inden-1-one (20):

NaO*t*Bu (62 mg, 0.65 mmol, 1.3 eq.) was added to a flamedried Schlenk. $Pd(OAc)_2$ (5.6 mg, 5 mol %) and XPhos (23.8 mg, 10 mol %) were added, followed by, *tert*-butyl isocyanide (85 μL, 0.75 mmol, 1.5 eq.), 2'-bromoacetophenone (67 μL, 0.5 mmol, 1 eq.) and toluene (1 mL). The mixture was stirred at 80 °C for 5h and then cooled to room temperature. The crude mixture was filtered over a small plug of silica, washed with water and brine, and dried (Na_2SO_4). The product was purified by flash chromatography using cyclohexane/EtOAc (3:2) as eluent to yield yellow solid (37 mg, 37%). TLC (EtOAc/cyclohexane, 2:3, v/v): R_f = 0.29; NMR (500 MHz, $CDCl_3$): δ 7.47-7.44 (m, 1H), 7.37-7.30 (m, 2H), 7.07-7.06 (m, 1H), 5.30 (br, 1H), 5.05 (s, 1H), 1.47 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.8 (C), 161.3 (C), 139.4 (C), 134.8 (C), 130.3 (CH), 130.2 (CH), 120.5 (CH), 115.6 (CH), 94.1 (CH), 53.1 (C), 28.9 (CH_3) ppm; HRMS (ESI): *m/z* calculated for $C_{13}H_{16}NO$ (M+H) 202.1226, found 202.1223.

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Summary

Isocyanides' Latest Trick:

Palladium-Catalyzed Imidoylative Cross-Coupling Reactions

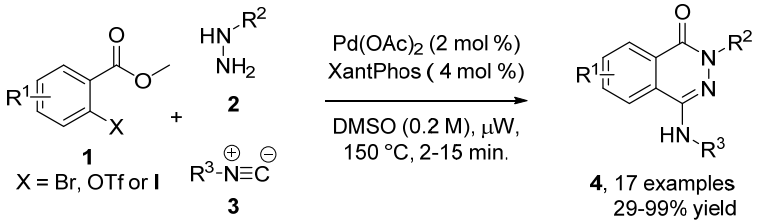
Chemical synthesis is an advanced science capable of synthesizing most of the complex compounds found in nature by a linear total synthesis. The main challenge for the future therefore lies in producing these complex molecules in a more efficient and economical manner, which will enable the use of more sophisticated compounds in industry and academia. In this respect especially step economy is an important factor, since accessibility highly depends on the amount of steps required to reach the desired compounds. In addition, reducing the number of synthetic steps towards valuable fine chemicals also reduces the amount of solvents and energy required and thus helps save the environment. Cascade reactions are important tools to meet these challenges synthetic chemists are currently facing. Cascade reactions are sequences of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process is repeated until a product stable under the reaction conditions is formed. The intrinsic advantage of such cascade reactions is the step economy, since multiple bond formations are combined in one pot.

Palladium is a versatile transition metal showing useful reactivity with various functional groups. Consequently, the various Pd-catalyzed cross-couplings nowadays are essential tools for the construction of carbon-carbon bonds. The significance of palladium catalysis and the cross-couplings in particular has recently been illustrated by the Nobel Prize for Chemistry in 2010, which was awarded to Heck, Negishi and Suzuki for the development of their Pd-catalyzed cross-coupling reactions.

The chemistry of palladium is generally quite well understood and versatile, which means there is a huge potential for Pd-catalyzed cascade reactions. Chemists have exploited this potential and many interesting Pd-catalyzed cascade reactions have been reported (**Chapter 1**). We became interested in using isocyanides as C_1

building blocks in palladium catalysis and have developed several new transformations based on the insertion of isocyanides between two coupling fragments. In the timeframe of our studies this topic has received increasing attention and many other groups have started using isocyanides in palladium catalysis (**Chapter 2**).

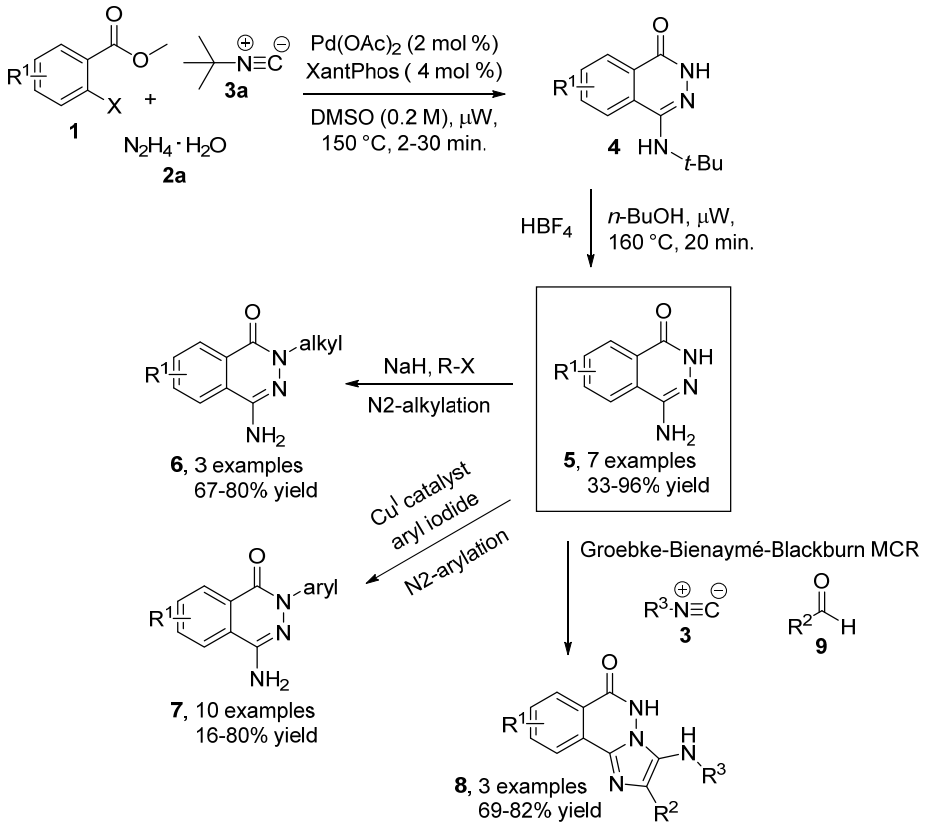
The most common type of reaction in this field involves amidination of aryl halides by imidoylative cross-coupling with amines, but in 2011 only a few examples had been reported. We envisioned a useful application of this chemistry in the synthesis of heterocycles by combining the amidination event with a cyclization step in a cascade fashion. **Chapter 3** describes how we realized this concept by using hydrazines, which are difficult coupling patterns, as amine inputs in amidination reactions of 2-(pseudo)halobenzoates (Scheme 1). The cyclization event occurs in a cascade fashion by lactamization and furnishes 4-aminophthalazin-1(2*H*)-ones (APOs, **4**) in a single reaction step in just five minutes. APOs are valuable in medicinal chemistry where they are studied, *e.g.*, for their potential in the treatment of cancer. The classical synthesis of APOs is a lengthy three to five step sequence. Our approach is not only faster it also allows, for the first time, non-symmetric substitution of the phenyl ring ($R^1 \neq H$). The traditional chemistry used to obtain APOs unavoidably leads to regioisomers, severely hampering the yield and simplicity of the synthesis. Our method should therefore prove highly useful in the future by allowing more efficient and diverse structure-activity relationship (SAR) studies.



Scheme 1. Pd-catalyzed imidoylative cascade towards APOs.

There are limitations to our cascade synthesis of APOs, as is the case in most synthetic strategies. Although the benzoate (**1**) can be varied extensively, only tertiary aliphatic isocyanides (**3**) can be used and monosubstituted hydrazines (**2**) are poorly available and could not be varied to the desired degree. We were able to overcome these limitations by developing a semi one-pot removal of the *tert*-butyl group derived from the isocyanide (**Chapter 4**, Scheme 2). This sequence requires a solvent switch, but no purification is necessary after the Pd-catalyzed reaction. The products that are obtained (**5**) contain two different nucleophilic positions, but are readily alkylated or

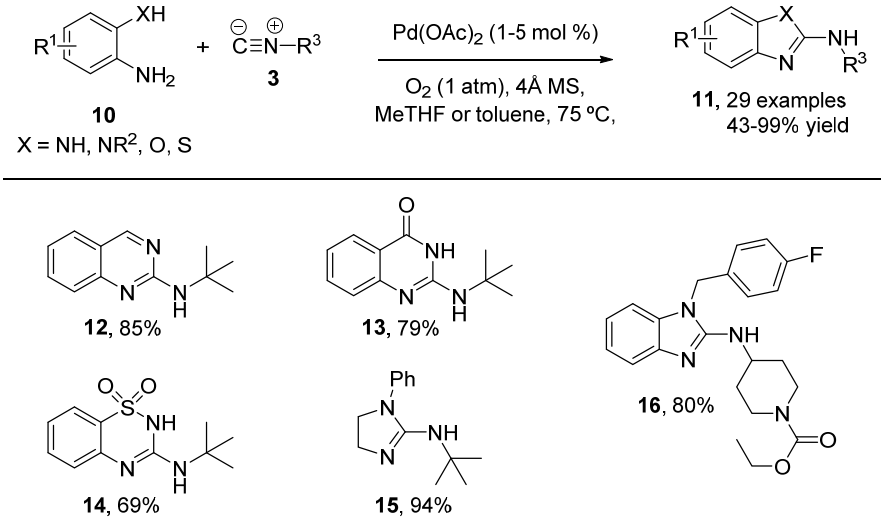
arylated at the more acidic N2-position. In this way, a two step synthesis leads to highly functionalized APOs containing a free 4-amino group (**6** and **7**) that can be derivatized as desired. To demonstrate the power of multicomponent reactions we also showed that **5** can be used in the complexity-generating Groebke-Bienaymé-Blackburn reaction to afford unexplored tricyclic products (**8**) in just two steps from commercial compounds.



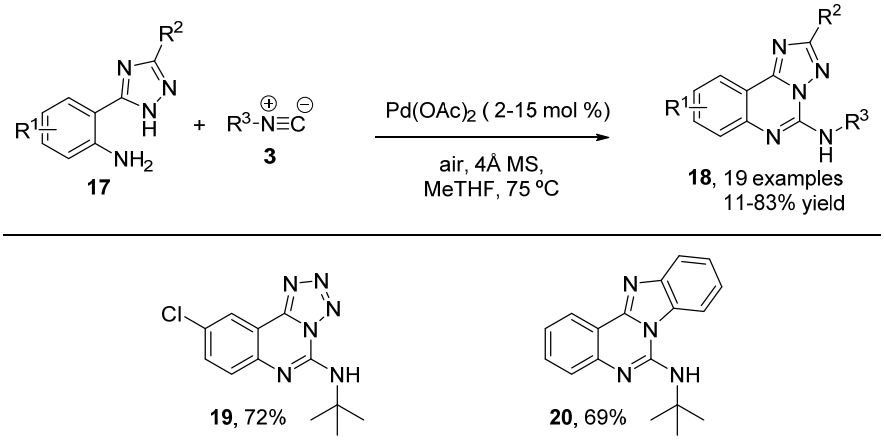
Scheme 2. Follow-up chemistry on the APO scaffold.

The guanidine motif is present in various scaffolds that are frequently found in pharmaceuticals and exhibit a wide range of therapeutic applications. The prevalent synthesis of this type of products has significant drawbacks, such as the availability or toxicity of reagents, and narrow substrate scope and/or product range. Moreover, these procedures suffer from poor atom and/or step efficiency, making them unattractive from a sustainability point of view. In **Chapter 5** a new approach towards guanidine-containing heterocycles, based on Pd-catalyzed isocyanide insertion, is

outlined. A wide range of bisnucleophiles (**10**) are oxidatively coupled with isocyanides in the presence of a simple Pd^{II} catalyst (Scheme 3). Most notably, the conditions are highly sustainable owing to the low catalyst loading, renewable solvent and absence of base. Molecular oxygen, the most abundant and sustainable oxidant available, is used as stoichiometric oxidant and only water is produced as a byproduct. The utility of this method was shown by the synthesis of **16**, which is a known precursor for the antihistamines norastemizole and astemizole.



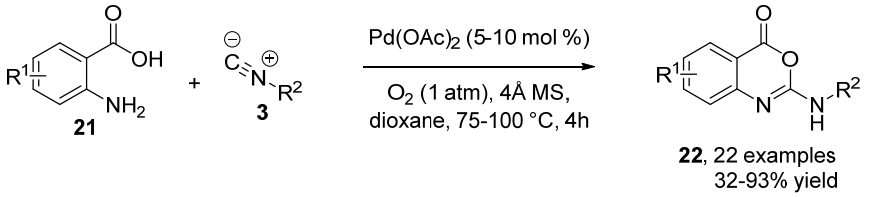
Scheme 3. Aerobic oxidative coupling of bisnucleophiles and isocyanides.



Scheme 4. Azoles as nucleophile in the oxidative coupling of bisnucleophiles and isocyanides.

It is possible to use an azole as one of the nucleophiles in the aerobic oxidative coupling of bisnucleophiles and isocyanides, as is described in **Chapter 6**. The use of azoles as substrates affords valuable azolo[*c*]quinazolines (Scheme 4), which have shown potential in the treatment of Parkinson's disease. An atmosphere of molecular oxygen is not required for this substrate class; a simple air atmosphere provides slightly better results and a much more convenient procedure. The high number of heteroatoms in the products is challenging for this chemistry because it offers several unproductive coordination sites for Pd^{II}. The relative ease with which the aerobic oxidative guanidine synthesis could be applied to these difficult substrates is indicative of the broad utility of this chemistry.

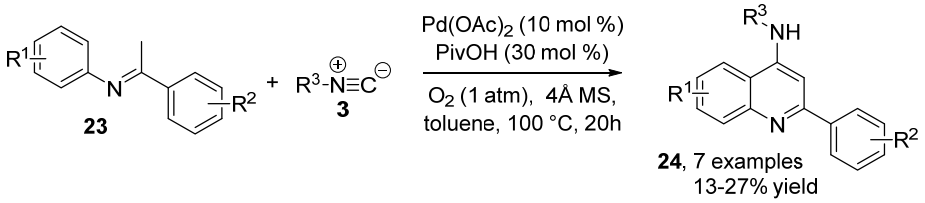
In **Chapter 7** we show that anthranilic acids (**21**) can also be coupled with isocyanides under aerobic oxidative Pd^{II} catalysis (Scheme 5). The resulting 2-aminobenzoxazinones (**22**) are valuable for medicinal chemistry purposes and our synthesis has advantages over other methodologies. It is, however, also another particularly challenging expansion of our guanidine synthesis due to the sensitivity of the benzoxazinone products to nucleophilic attack and the tendency of benzoic acids to undergo decarboxylative processes in the presence of Pd^{II}. In addition, benzoic acid derivatives may undergo Pd-catalyzed decarbonylative coupling with isocyanides at temperatures as low as 70 °C. Moreover, isocyanides have also been reported to react with anthranilic acids to produce 4-quinazolinones. The extension of our oxidative coupling of bisnucleophiles and isocyanides to such a challenging substrate class further illustrate the general applicability of this chemistry.



Scheme 5. Aerobic oxidative synthesis of 2-aminobenzoxazinones.

Chapter 8 describes our efforts to develop an imidoylative double C-H activation cascade reaction that provides products containing an imine/enamine moiety in a highly atom-economical manner. Only a few Pd-catalyzed isocyanide insertion reactions toward this structural motif are known, of which none is based on a double C-H activation cascade. We have realized this type of transformation by converting tautomerizable *N*-arylimines (**23**), that are readily activated at the α-position, to 4-aminoquinolines (**24**, Scheme 6). Unfortunately, the yields were low and

full conversion was not reached, indicating the catalyst is deactivated. Extensive optimization did not improve the catalytic efficiency, but nevertheless a proof-of-concept for the proposed imidoylative double C-H activation cascade is provided.



Scheme 6. Pd-catalyzed imidoylative double C-H activation cascade.

In summary, the results described in this thesis show that isocyanides are highly versatile and useful C_1 building blocks in palladium catalysis. The recent surge of interest in this field will undoubtedly lead to further developments and applications of this chemistry. We have contributed to the advancement of imidoylative palladium catalysis by the synthesis of various important heterocycles, demonstrating the potential for medicinal chemistry purposes, and the discovery of the first oxidative coupling of bisnucleophiles with isocyanides.

Samenvatting

Het Nieuwste Trucje van Isocyanides:

Palladiumgekatalyseerde Imidoylatieve Cross-Koppelingreacties

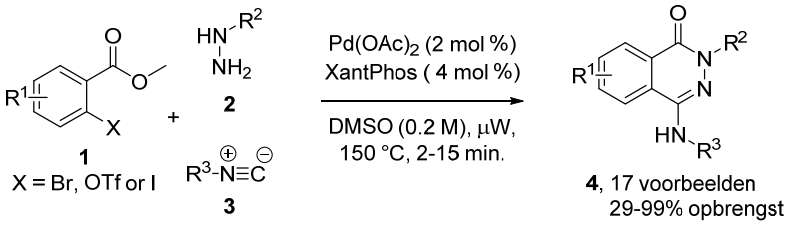
Chemische synthese is een vergevorderde wetenschap die gebruikt kan worden om de meeste complexe verbindingen die in de natuur voorkomen te synthetiseren door middel van een lineaire totaalsynthese. De uitdaging voor de toekomst is om deze complexe verbindingen op een efficiëntere en goedkopere manier te maken. Hierdoor kunnen complexere stoffen gebruikt worden in de industrie en academische wereld. De 'stap-economie' speelt hierbij een belangrijke rol, aangezien de toegankelijkheid van verbindingen sterk afhankelijk is van het aantal benodigde stappen om ze te maken. Daarnaast is er ook minder oplosmiddel en energie nodig om waardevolle fijnchemicaliën te maken als er minder synthetische stappen nodig zijn. Dit helpt het milieu te beschermen. Om deze uitdagingen het hoofd te bieden zijn cascadereacties een belangrijk middel. Cascadereacties zijn sequenties van transformaties waarbij het product van de eerste stap het uitgangsmateriaal vormt van de tweede stap, wiens product weer het substraat is voor de volgende stap en zo verder. Dit proces herhaalt zich tot een product gevormd is dat stabiel is onder de reactiecondities. Het intrinsieke voordeel van zulke cascadereacties is de stap-economie, aangezien meerdere bindingen gevormd worden in één pot.

Palladium is een veelzijdig overgangsmetaal dat met verscheidene functionele groepen nuttige reactiviteit heeft. Als gevolg daarvan zijn Pd-gekatalyseerde cross-koppelingsreacties essentiële methoden om koolstof-koolstofbindingen te maken. De waarde van palladiumkatalyse en vooral de cross-koppelingsreacties is recentelijk gebleken uit de toekenning van de Nobelprijs voor de Scheikunde 2010 aan Heck, Negishi en Suzuki voor de ontwikkeling van hun Pd-gekatalyseerde cross-koppelingsreacties.

Omdat de reactiviteit van palladium goed in kaart is gebracht, is het uitermate geschikt voor cascadereacties. Chemici hebben dan ook veel Pd-gekatalyseerde

cascade reacties ontwikkeld (**Hoofdstuk 1**). Wij zijn geïnteresseerd in het gebruik van isocyanides als C_1 bouwsteen in palladiumkatalyse en hebben enkele nieuwe reacties ontwikkeld gebaseerd op de insertie van isocyanides. Tijdens ons onderzoek is de populariteit van dit onderwerp erg gestegen. Veel andere groepen zijn inmiddels ook begonnen met het gebruiken van isocyanides in palladiumkatalyse (**Hoofdstuk 2**).

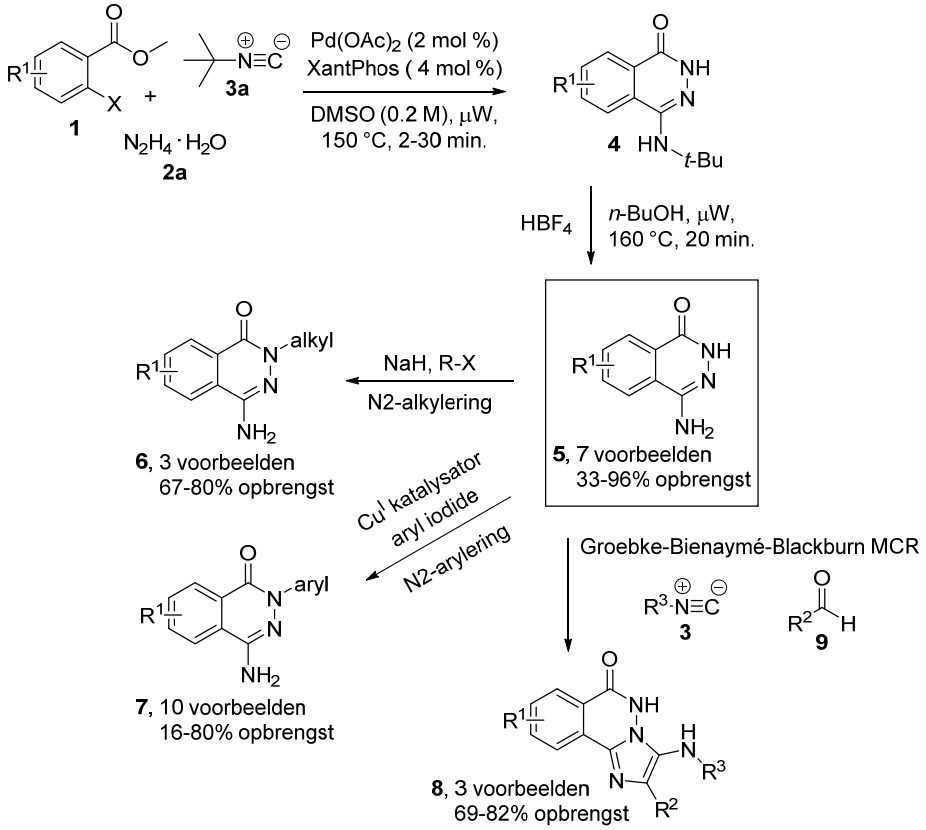
Het meest voorkomende type reactie in dit veld is de amidinering van arylhalides door imidoylatieve cross-koppeling met amines. In 2011 waren er echter pas een paar voorbeelden bekend en wij bedachten een nuttige toepassing van deze chemie in de synthese van heteroaromaten door de amidinering te combineren met een cyclisatiestap. **Hoofdstuk 3** beschrijft hoe we dit concept gerealiseerd hebben door hydrazines, wat erg moeilijke koppelingsreactanten zijn, te gebruiken als aminereactant in de amidinering van 2-halobenzoaten (Schema 1). De ringsluitingsstap vindt plaats door middel van lactamisatie en leidt tot de vorming van 4-aminoftalazin-1(2*H*)-onen (AFOs, **4**) in één enkele reactiestap in slechts vijf minuten. AFOs zijn waardevolle verbindingen in de medicinale chemie en zijn bestudeerd vanwege hun potentie als medicijn tegen onder andere kanker. De klassieke synthese van AFOs is een lange drie- tot vijf-stapssynthese. Onze synthese is niet alleen sneller, maar maakt ook niet symmetrische substitutie van de fenylring mogelijk ($R^1 \neq H$). De traditionele chemie die gebruikt wordt om AFOs te maken leidt onvermijdelijk tot regioisomeren, met als gevolg een lage opbrengst en moeilijke zuivering. Onze methode zou daarom erg nuttig kunnen zijn in de toekomst door efficiëntere en meer diverse structuur-activiteitsstudies mogelijk te maken.



Schema 1. Pd-gekatalyseerde imidoylatieve cascade synthese van AFOs.

Zoals het geval is in de meeste synthetische strategieën zijn er ook beperkingen in onze cascadesynthese van AFOs. Hoewel het benzoaat (**1**) uitgebreid gevarieerd kan worden, is de reactie gelimiteerd tot tertiaire alifatische isocyanides (**3**) en zijn monogesubstitueerde hydrazines (**2**) moeilijk verkrijgbaar. We waren in staat deze beperkingen te overwinnen door de *tert*-butyl group afkomstig van het isocyanide in een quasi één-pots methode te verwijderen (**Hoofdstuk 4**, Schema 2). Het bleek noodzakelijk om een ander oplosmiddel te gebruiken, maar er was geen zuivering

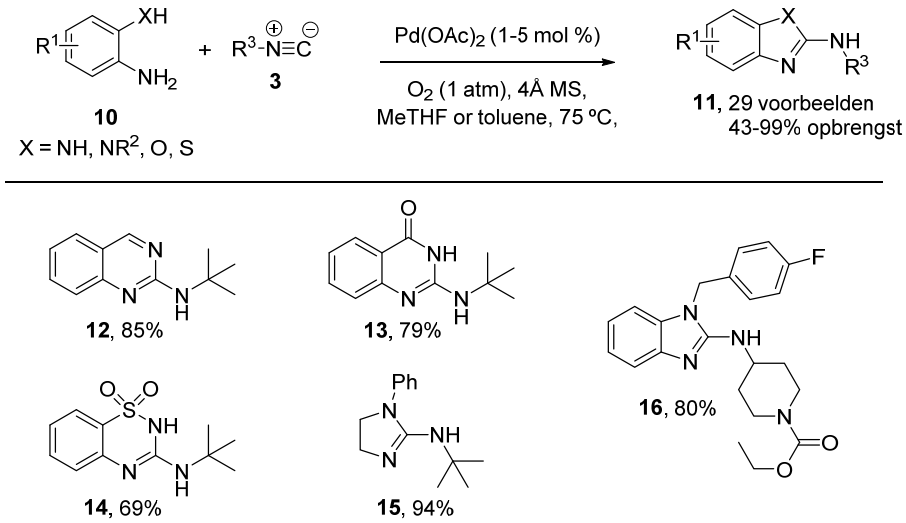
nodig na de Pd-gekatalyseerd reactie. De producten die we op deze manier verkregen (**5**) hebben twee verschillende nucleofiele groepen. Het is gemakkelijk deze selectief te alkyleren of aryleren op de zuurdere N2-positie. Op deze manier is een twee-stapssynthese ontwikkeld die resulteert in sterk gefunctionaliseerde AFOs met een vrij amine op de 4-positie (**6** en **7**), die naar wens gederivatiseerd kan worden. Om de kracht van multicomponentreacties te demonstreren hebben we laten zien dat **5** gebruikt kan worden in de complexiteitgenererende Groebke-Bienaymé-Blackburn reactie om tricyclische producten (**8**) te verkrijgen in slechts twee stappen vanuit commercieel verkrijgbare stoffen.



Schema 2. Vervolgchemie met AFOs.

Cyclische guanidines hebben een grote diversiteit aan biologische activiteit en komen dan ook voor in medicijnen tegen verschillende aandoeningen. De meest toegepaste syntheses van dit type verbindingen hebben behoorlijke nadelen, zoals de verkrijgbaarheid en toxiciteit van reactanten en een slechte scope en/of productrange.

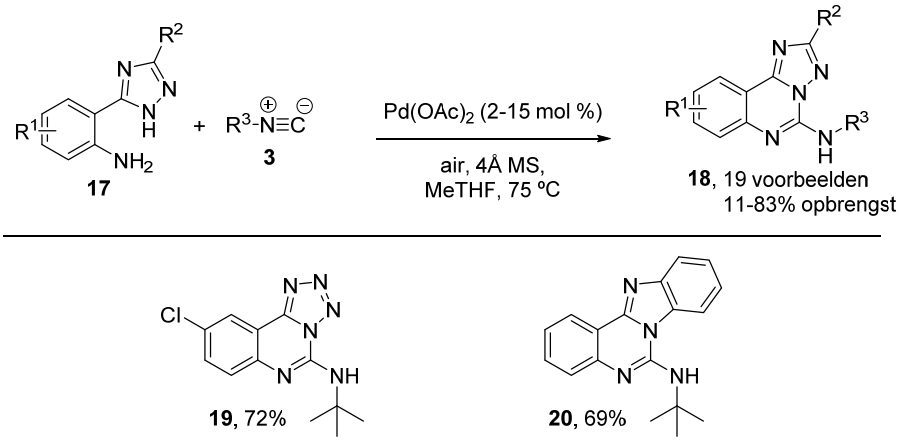
Bovendien hebben deze procedures een slechte atoom- en/of stapefficiëntie, wat ze erg onaantrekkelijk maakt vanuit een duurzaamheidspersepctief. In **Hoofdstuk 5** is een nieuwe methode naar guanidine-bevattende heteroaromaten beschreven, gebaseerd op Pd-gekatalyseerde isocyanide insertie. Een grote variatie bisnucleofielen (**10**) kan oxidatief gekoppeld worden met isocyanides door gebruik te maken van een simpele Pd^{II} katalysator (Schema 3). Het meest opmerkelijke is dat de condities buitengewoon duurzaam zijn door de lage hoeveelheid katalysator, het hernieuwbare oplosmiddel en de afwezigheid van base. Moleculair zuurstof, de meest voorkomende en duurzaamste oxidator, is de stoichiometrische oxidator en alleen water wordt gevormd als bijproduct. Het nut van deze methode is aangetoond door de synthese van **16**, wat een bekend intermediair is voor de productie van de antihistamines norastemizol en astemizol.



Schema 3. Oxidatieve koppeling van bisnucleofielen en isocyanides.

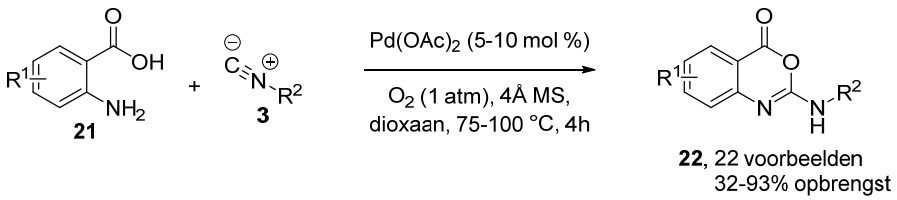
Het is ook mogelijk om een azool als een van de nucleofielen te gebruiken in de oxidatieve koppeling van bisnucleofielen en isocyanides, zoals staat beschreven in **Hoofdstuk 6**. Het gebruik van een azool als nucleofiel in deze reactie resulteert in waardevolle azolo[*c*]quinazolines als product (Schema 4). Deze verbindingen zijn erg interessant als potentiële medicijnen tegen de ziekte van Parkinson. Het is voor deze substraat klasse niet nodig om een zuurstof atmosfeer te gebruiken; een lucht atmosfeer geeft iets betere resultaten en is veel makkelijker uitvoerbaar vanuit praktisch oogpunt. De vele heteroatomen die in deze producten zitten vormen een uidaging voor dit soort chemie omdat het meerdere coördinatie mogelijkheden biedt

voor Pd^{II}. Het feit dat de oxidatieve guanidine synthese toch relatief makkelijk kan worden toegepast op deze lastige substraten geeft aan hoe breed de toepasbaarheid van deze reactie is.



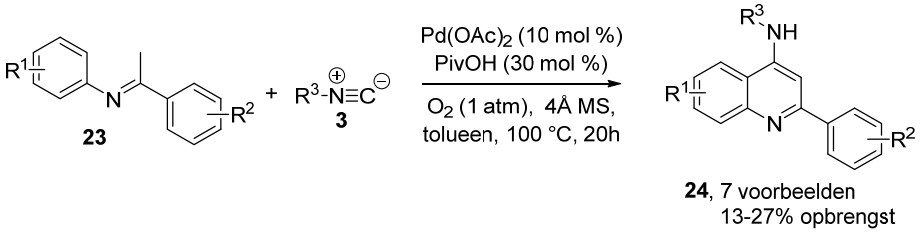
Scheme 4. Azolen als nucleofiel in de oxidatieve koppeling van bisnucleofielen en isocyanides.

In **Hoofdstuk 7** laten we zien dat antranilzuren (**21**) ook gekoppeld kunnen worden met isocyanides door middel van oxidatieve Pd^{II} katalyse (Schema 5). De 2-aminobenzoxazinonen (**22**) die op deze manier verkregen worden zijn waardevol voor medicinale chemie doeleinden en onze synthese biedt voordelen ten opzichte van bestaande alternatieven. Dit is een erg uitdagende reactie vanwege de gevoeligheid van de producten voor nucleofiele aanval en de neiging van benzoëzuren om decarboxylatieve processen te ondergaan in de aanwezigheid van Pd^{II}. Daarnaast is een Pd-gekatalyseerde decarbonylatieve koppeling van benzoëzuren met isocyanides ook een mogelijk probleem. Dit kan zelfs al gebeuren bij 70 °C. Het feit dat de oxidatieve koppeling van bisnucleofielen en isocyanides ook mogelijk is met zulke moeilijke substraten geeft nogmaals aan dat deze chemie breed toepasbaar is.



Schema 5. Oxidatieve synthese van 2-aminobenzoxazinonen.

Hoofdstuk 8 beschrijft onze pogingen om een imidoylatieve dubbele C-H activeringscascade te ontwikkelen. Dit zou leiden tot een atoom-efficiënte synthese van producten met imine/enamine functionaliteit. Ook zou dit het veld van de imidoylatieve palladium katalyse verder uitbreiden door een nieuwe productklasse makkelijk toegankelijk te maken. We hebben dit doel gerealiseerd door tautomeriseerbare *N*-arylimines (**23**), die relatief makkelijk te activeren zijn op de α-positie, om te zetten naar 4-aminoquinolines (**24**, Schema 6). Helaas zijn de opbrengsten laag en wordt het substraat niet volledig omgezet, wat aangeeft dat de katalysator gedeactiveerd wordt onder de reactiecondities. Een uitgebreide optimalisatie leidde uiteindelijk niet tot hogere katalytische efficiëntie.



Schema 6. Pd-gekatalyseerde imidoylatieve dubbele C-H activatie cascade.

Kortom, de resultaten die zijn beschreven in dit proefschrift bewijzen dat isocyanides veelzijdige en nuttige C_1 bouwstenen zijn in de palladiumkatalyse. De recente golf van interesse in dit veld zal ongetwijfeld tot nieuwe ontwikkelingen en toepassingen van deze chemie leiden. Wij hebben bijgedragen aan de ontwikkeling van imidoylatieve palladiumkatalyse door de synthese van verscheidene belangrijke heteroaromaten, wat de potentie van deze reacties voor de medicinale chemie bewijst. We hebben ook de oxidatieve koppeling van bisnucleofielen en isocyanides ontdekt, waarmee guandine-bevattende heteroaromaten op een erg duurzame wijze gesynthetiseerd kunnen worden.

Dankwoord

En dan nu, na drie jaar onderzoek en het schrijven van honderden pagina's, het stuk dat iedereen *wél* leest. Ik heb het altijd erg naar mijn zin gehad in de organische sectie van de VU en ik was dus ook erg blij dat ik hier mijn promotieonderzoek kon doen. Ook tijdens mijn promotie ben ik met veel plezier naar de VU gegaan en daar wil ik iedereen voor bedanken! Zonder de maandelijkse borrels, gezellige sfeer en collegialiteit zou het niet hetzelfde zijn geweest.

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Ik wil graag Prof. Dr. ***Maarten Honing***, Prof. Dr. ***Rob Leurs***, Prof. Dr. ***Floris Rutjes*** en Prof. Dr. ***Bert Maes*** bedanken voor deelnemen aan mijn lees- en/of promotiecommissie. ***Bert***, ik wil jou ook bedanken voor de samenwerking van de afgelopen jaren. Ik hoop dat de voortzetting ervan net zo voortvarend gaat als het begin. I would also like to thank Prof. Dr. ***Alexander Dömling***, Prof. Dr. ***Thomas Müller*** and Prof. Dr. ***Benjamin List*** for reading and correcting this thesis. ***Ben***, I am still very grateful for my internship. The stimulating environment of your group helped me develop as a scientist and thereby had a profound effect on my PhD research.

Ik heb tijdens mijn promotietijd veel hulp gehad van studenten, waar ik erg dankbaar voor ben. ***Anne*** en ***Angela*** jullie waren mijn eerste studenten en kwamen al bij me op het lab toen ik net was begonnen. Ik heb door het begeleiden van jullie een hoop geleerd. ***Nargis***, jij was ook een van mijn eerste studenten en hebt in je lange stage meerdere projecten aangepakt. Een deel van jouw werk staat beschreven in dit

proefschrift. ***Yoran***, jij hebt ook je bachelor stage bij me gedaan en een aantal nuttige verbindingen gesynthetiseerd. ***Jasper***, jij bent begonnen met het CGS-15943 project met als hoogtepunt natuurlijk je kristalstructuur. Jij hebt de basis gelegd voor dit project en de synthese van de startmaterialen geoptimaliseerd. Je rampzalige lovesongs playlist wordt nog steeds zo nu en dan (met tegenzin van iedereen) gedraaid op N374. ***Lisa***, you were here at the very end of my PhD. You continued the project Jasper left behind and really did a great job. You almost managed to finish this work in the mere 3 months you were here! Verder zijn er tijdens mijn promotie veel studenten in N374 geweest die niet onder mijn directe begeleiding stonden. Ik wil ***Lucas***, ***Jasper***, ***Marieke***, ***Lisanne***, ***Ghislaine*** en ***Jurriën*** bedanken voor de aangename sfeer op het lab! Ook alle andere studenten van de afgelopen 3 jaar die niet bij mij op het lab stonden wil ik bedanken voor de gezelligheid.

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mijn promotie heb je me erg geholpen met acute praktische problemen, maar met name de brainstorm sessies waren erg belangrijk voor me. Uiteindelijk is uit zo'n sessie een mooie gezamenlijke publicatie gekomen. ***Gitte***, jij bent begonnen met de palladiumgekatalyseerde isocyanide inserties in onze groep en hebt daarmee het fundament voor mijn promotiewerk gelegd. ***Guido***, bedankt voor de goede samenwerking tussen onze labs en de besprekingen over onze chemie. ***Gydo***, jij bedankt voor het in stand houden van deze prettige samenwerking. ***Sanne***, sinds jouw komst naar N374 is de rust definitief verstoord, op een positieve manier. Er is altijd wat te beleven, wat als het onderzoek even tegenzit erg fijn is. Je staat ook altijd klaar om ergens mee te helpen, van het meten van een HRMS sample tot het praten over de dagelijkse dingen. ***Leon***, ***Jaap, Jeroen*** en ***Jos*** met jullie is er veel energie, haat en gezelligheid de groep binnen gekomen. Ik zal de vele gesprekken niet snel vergeten. ***Leon***, ik heb erg genoten van onze fitness uurtjes en de bijbehorende besprekingen van de dag en het leven. Ook de barbecues waren erg goed. Ik hoop dat je de belofte om exact net zoveel woorden aan mij te besteden in jouw dankwoord als ik aan jou besteed in mijn dankwoord waarmaakt! ***Paul***, heel erg bedankt voor het design van de cover van dit proefschrift. Ik hoop dat het er gedrukt net zo goed uitziet als op het scherm. Prof. Dr. ***Fritz Bickelhaupt***, het is een eer geweest uw kantoorgenoot te mogen zijn de afgelopen jaren.

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Tjøstil

List of Publications

[11] **"Sustainable Synthesis of Isothiourea Based on a Three Component Reaction Involving Isocyanides"**
P. Mampuys, Y. Zhu, T. Vlaar, E. Ruijter, R. V. A. Orru and B. U. W. Maes
Manuscript in preparation.

[10] **"Synthesis of Diverse Azolo[*c*]quinazolines by Pd(II)-Catalyzed Aerobic Oxidative Coupling of Bisnucleophiles and Isocyanides"**
T. Vlaar, L. Bensch, J. Kraakman, C. M. L. Vande Velde, B. U. W. Maes, R. V. A. Orru and E. Ruijter
Adv. Synth. Catal. **2014**, DOI: 10.1002/adsc.201301129.

[9] **"Synthesis of Pyridopyrimidines by Pd-Catalyzed Isocyanide Insertion"**
V. Estévez, G. Baelen, B. Lentferink, T. Vlaar, E. Janssen, B. U. W. Maes, R. V. A. Orru and E. Ruijter
ACS Catal. **2014**, *4*, 40.

[8] **"Palladium-Catalyzed Synthesis of 2-Aminobenzoxazinones by Aerobic Oxidative Coupling of Anthranilic Acids and Isocyanides"**
T. Vlaar, R. V. A. Orru, B. U. W. Maes and E. Ruijter
J. Org. Chem. **2013**, *78*, 10469.

[7] **"Palladium-Catalyzed Migratory Insertion of Isocyanides: An Emerging Platform in Cross-Coupling Chemistry"**
T. Vlaar, E. Ruijter, B. U. W. Maes and R. V. A. Orru
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[6] **"Multicomponent Synthesis of 4-Aminophthalazin-1(2*H*)-ones by Palladium-Catalyzed Isocyanide Insertion"**
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