Carbon-nitrogen bond formation through cross-dehydrogenative coupling reactions

Carbon-Nitrogen Bond Formation Through Cross Dehydrogenative Coupling Reactions

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Abstract

There are many methods available in the synthetic toolbox to construct carbon nitrogen bonds but these standardly require pre-activation of the substrate. These involve classical, non-metal catalyzed methods (e.g. nucleophilic substitutions) and catalytic methods (e.g. the Ullmann condensation reaction) as well as modern metal-catalyzed approaches with wide scope (Buchwald-Hartwig reaction, hydrogen borrowing reactions). Cross Dehydrogenative Couplings (CDCs) couple a C-H with an N-H bond and do not require any pre-activation and are therefore considered the “nec plus ultra” in amination chemistry. Based on the ubiquitous nature of C-H bonds in substrates and the wide availability of amines as reactants they inherently show great application potential. Especially from a sustainable chemistry point of view it holds great promise, provided green oxidants can be used in a safe manner. However, though major advances have been made in the field, this last addition to the carbon-nitrogen bond forming toolbox is still in its infancy. The major investigations and advances dealing with CDCs for C-N bond formation since 2014 are summarized in this review. Intra- and intermolecular direct oxidative amination reactions on C(sp^2)-H as well as C(sp^3)-H bonds are included. Both metal catalyzed and metal-free approaches are covered, as well as the corresponding mechanistic proposals.

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1. Introduction

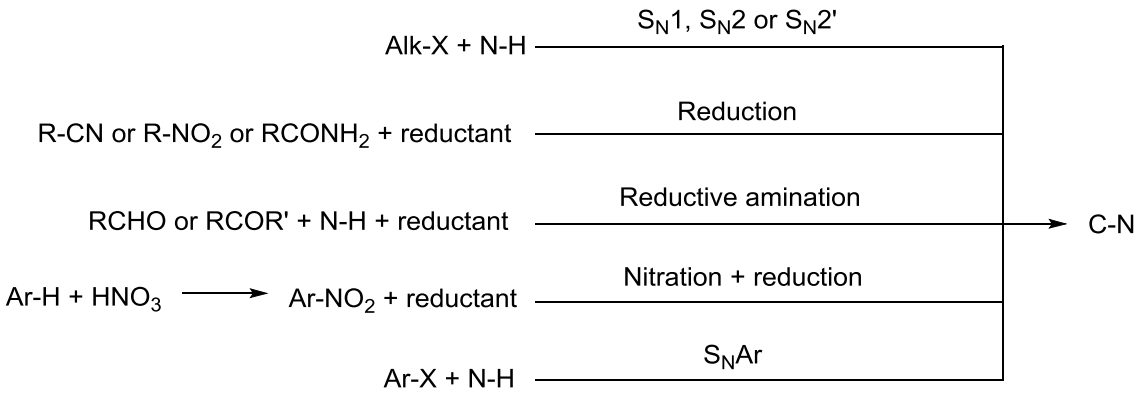
1.1 The importance of nitrogen containing compounds

The carbon-nitrogen bond is ubiquitous in nature. It is present in amino acids, DNA bases and many other important biological compounds as exemplified by neurotransmitters and alkaloids such as (semi synthetic) opiates.[1] Not surprisingly, most active ingredients (AI) of pharmaceuticals and agrochemicals also contain nitrogen.[2] This can be illustrated by the top 150 API sales list of 2013 and the in 2015 new FDA approved drugs.[3] In both lists 93% of the representatives feature one or more nitrogen atoms as an amine, imine, amide, amidine or guanidine functional group or as part of a heteroaromatic system. Introducing an amine functionality in a bioactive compound can greatly enhance the oral bioavailability. This is because the pKa of many amines is similar to the physiological pH[4] and therefore can carry a positive charge at this pH. The dual hydrogen bonding character (donor and acceptor) in primary and secondary amines also contributes to their biological relevance. In material science, nitrogen based compounds also play a notable role.[5] The introduction of nitrogen not only introduces different intermolecular interactions, it also influences HOMO and LUMO levels and changes the molecular geometry, and can therefore alter the (electronic) properties of the material. Diketopyrrolopyrroles (DPPs) for instance, have been used frequently as high quality pigments in inks, plastics and paints.[6] Recently, they gained attention in the field of organic photovoltaic functional materials.[7]

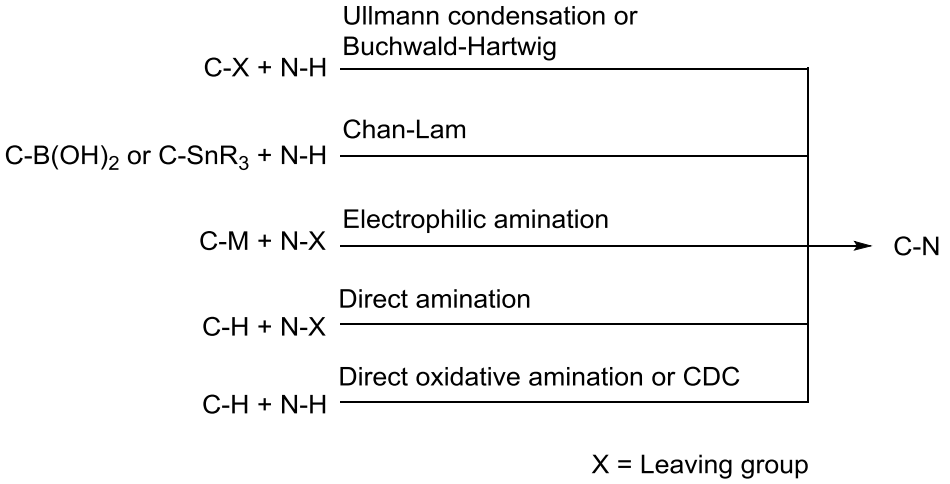
1.2 Amine synthesis: from classical to state-of-the-art methods

The most straightforward way for the formation of a C(sp^3)-N bond is via a simple nucleophilic substitution reaction with an amine as a nucleophile. (

Classical approaches



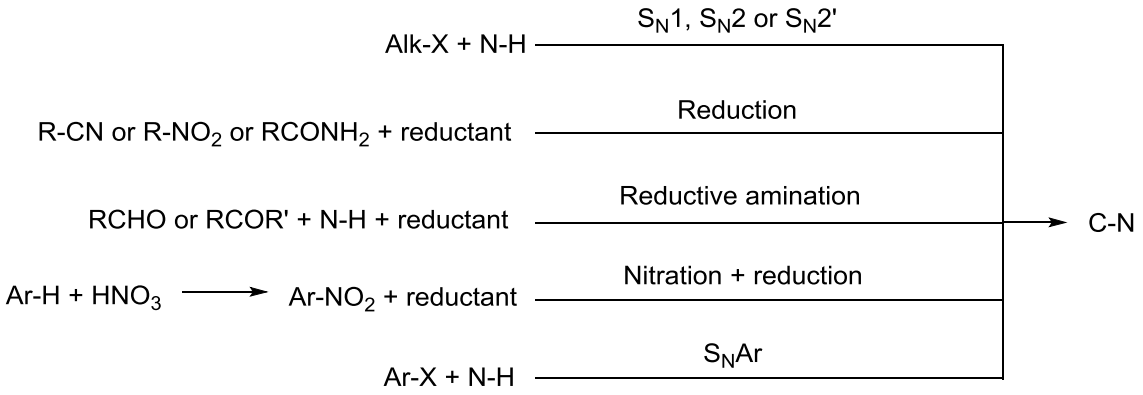
Modern approaches



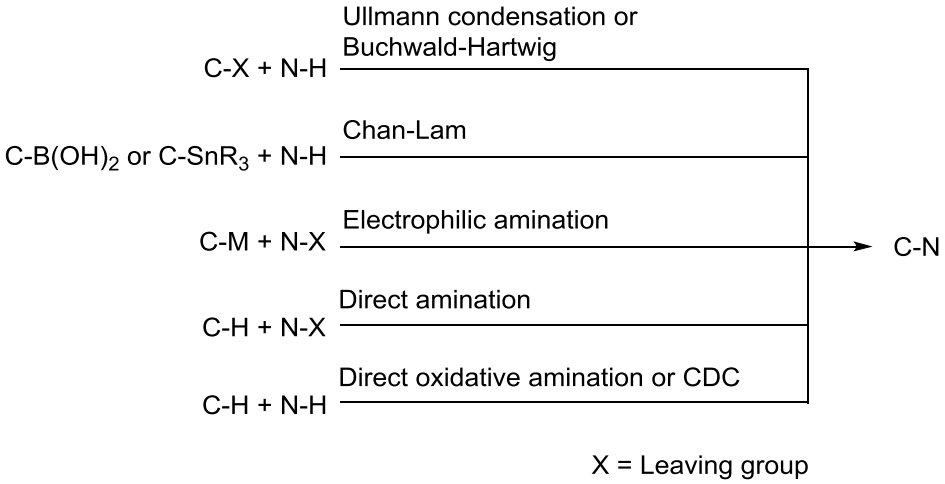
Scheme **1**).[8] However, overalkylation is a typical problem for which specific solutions have been developed such as the Gabriel synthesis.[9] Other classical methods for the synthesis of amines include the reduction of nitriles, amides and nitro compounds, and the reductive

amination of aldehydes and ketones (

Classical approaches



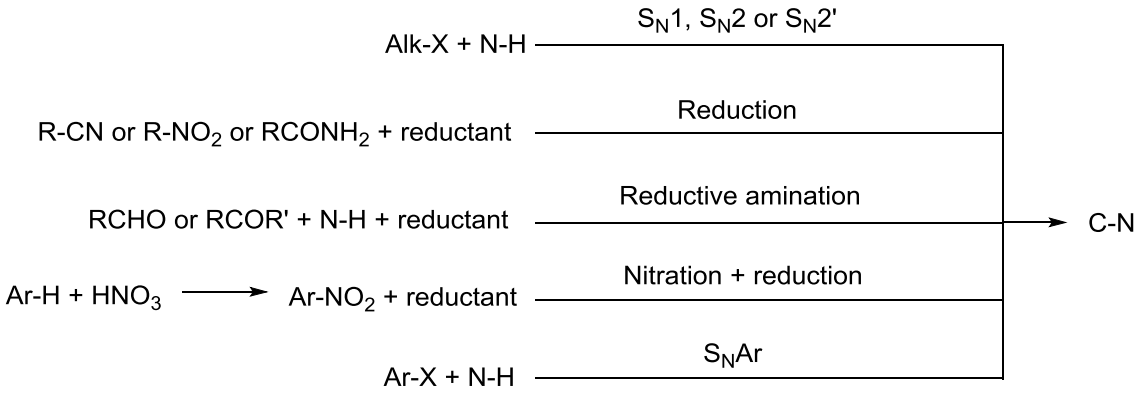
Modern approaches



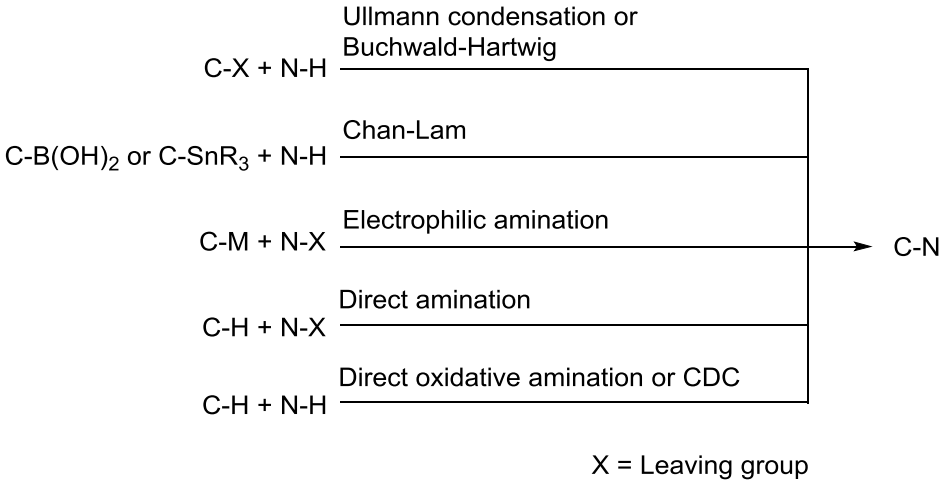
Scheme **1**). A modern and more sustainable approach is the alkylation of amines with alcohols using transition metal catalyzed hydrogen borrowing strategies, which allows selective mono alkylation.[2a, 10]

Aromatic amines are typically made via nitration followed by reduction (

Classical approaches



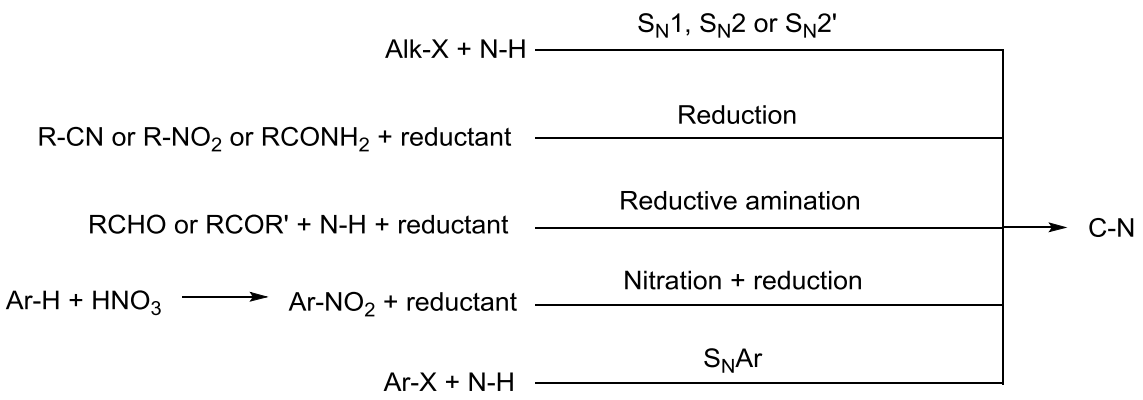
Modern approaches



Scheme **1**). Although arene nitration with nitric acid is a common (industrial) process, it is not hazard-free, and serious accidents have been reported.[11, 12] Nitric acid is not only very corrosive, but also toxic and a strong oxidant,[13] Because of its high oxidizing power, nitric acid reacts violently with various organic compounds, leading to the formation of NO and NO_2, both toxic gases.[11] Not surprisingly, besides its large scale use for the production of fertilizers (ammonium nitrate), the synthesis of explosives is one of the main other applications of nitric acid. A safer alternative reagent for nitration reactions is nitronium tetrafluoroborate.[14] The nitrated organic compound itself, however, can also be shock sensitive or thermally instable and therefore not an ideal intermediate for aniline synthesis.[15] Furthermore, from a synthetic point of view, although nitration of arenes is usually straightforward and efficient, the corresponding reaction on heteroaromatics is often not so. Nitration of pyridine, for example, is very low-yielding under classical conditions, resulting in the development of alternative reactions, for example with N_2O_5.[16] S_NAr with ammonia on haloheteroarenes, is usually a better approach

towards aminoheteroarenes (

Classical approaches



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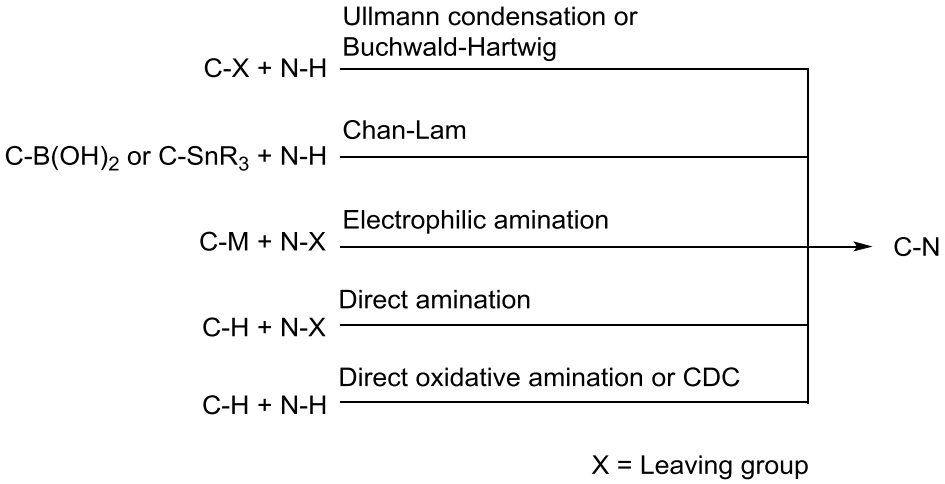
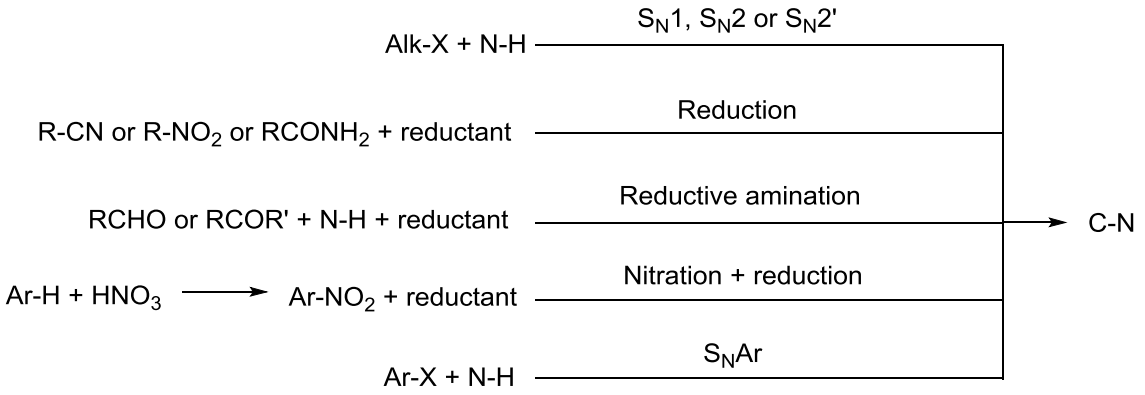


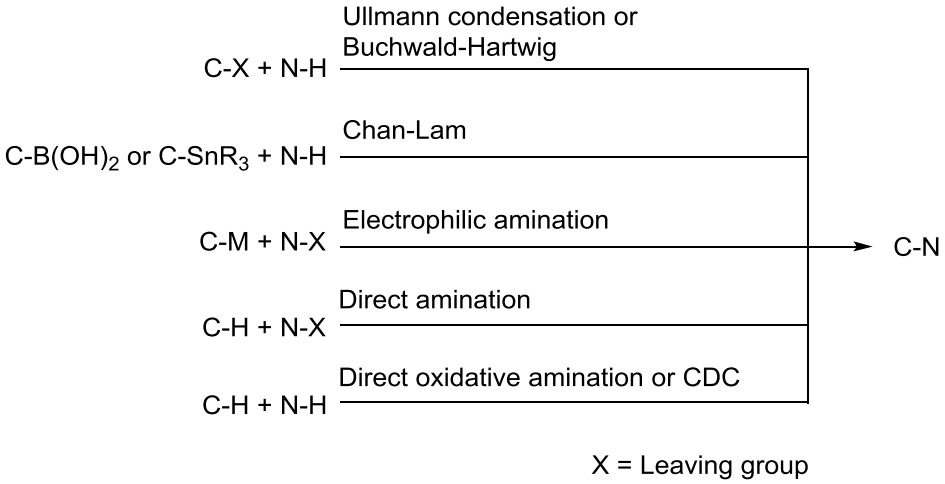
Scheme **1**). This approach requires the same number of steps as through nitration when introducing an amino group, but allows to immediately instal N-substituted derivatives via reaction with an amine, rather than ammonia. The required haloheteroarenes can be accessed either by S_EAr or by dehydroxyhalogenations of readily accessible hydroxyheteroarenes,[17a] A major limitation of the S_NAr amination, however, is the requirement of low LUMO orbitals in the aryl halide, in order to allow formation of the negatively charged intermediate Meisenheimer complex.[8] Electron-poor aryl halides are therefore typically required for this reaction, considerably limiting its scope.[17a]

It was only with the discovery of the Ullmann condensation (Goldberg reaction) in 1906 (

Classical approaches



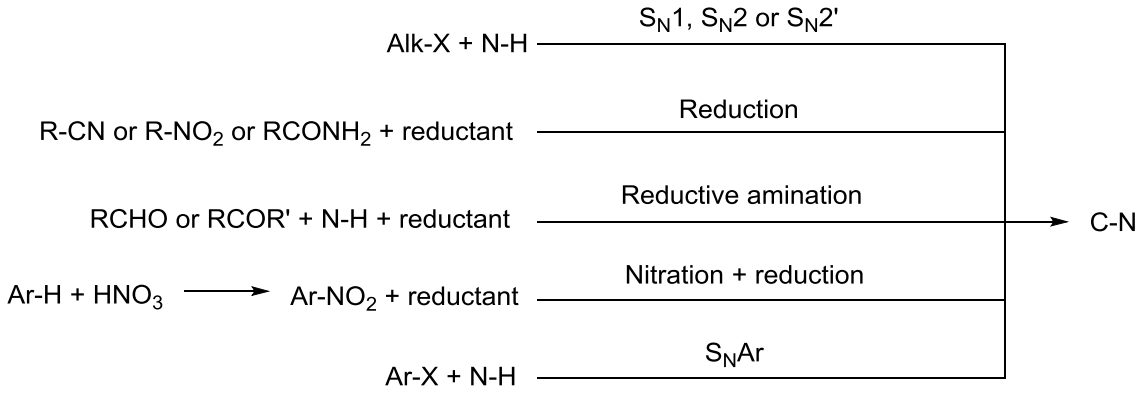
Modern approaches



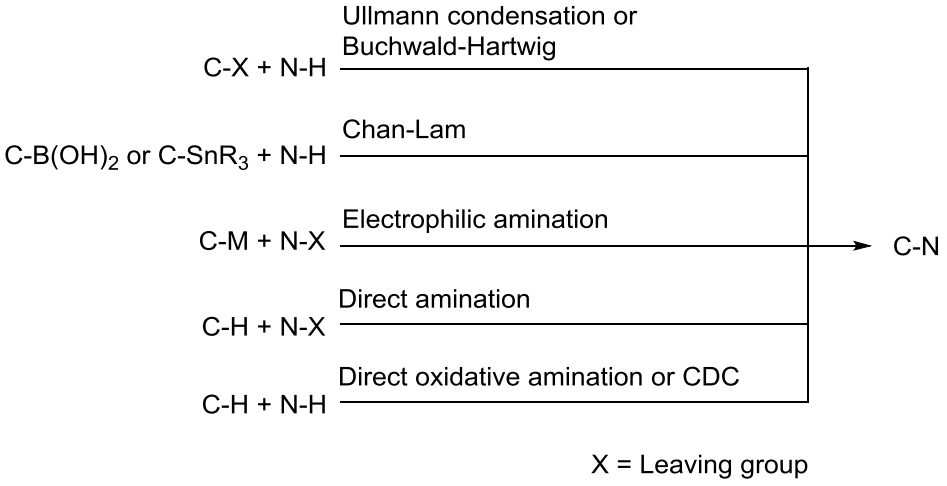
Scheme **1**) that a broadly applicable protocol for the substitution of C(sp^2)-X bonds was established, including substrates with higher LUMO energy values.[18] In this reaction, a copper catalyst enables reaction between an aryl (pseudo)halide and an amine. This has more recently been brought to a next level of performance, “Ullmann condensation 1”, by the introduction of specific ligands containing 1,2-ethylenediamine and 1,3-dicarbonyl entities.[19] Indeed, while classical conditions for Ullmann condensation couplings were very harsh, often requiring reaction temperatures of 150-200 °C, and stoichiometric amounts of metal, the introduction of ligands allowed for much milder reaction conditions. Reactions often proceed at temperatures between 80 °C and 100 °C, although even couplings at room temperature have been reported. Furthermore, catalytic amounts of metal can be used in combination with weak bases. The Chan-Lam reaction introduced in 1998 couples organometals, mostly (hetero)arylboronic acids,

with amines and is mediated by copper. To make it catalytic a stoichiometric oxidant is required

Classical approaches



Modern approaches

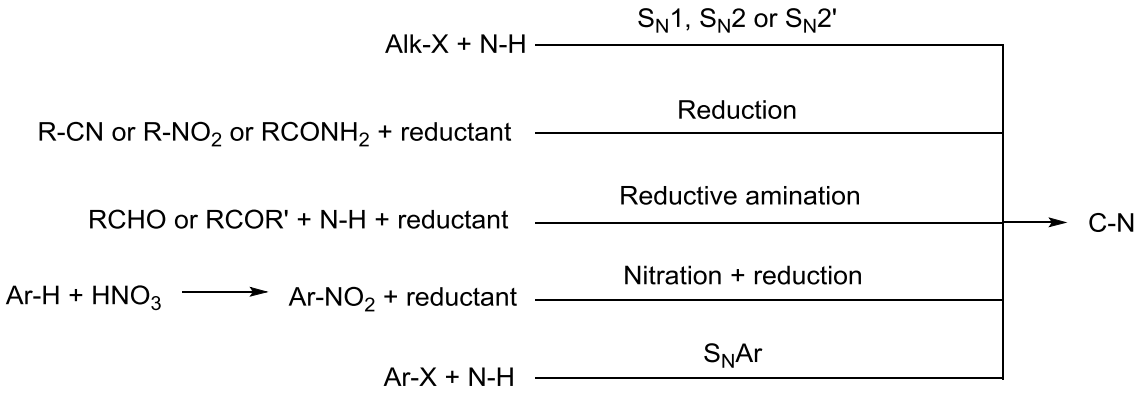


(

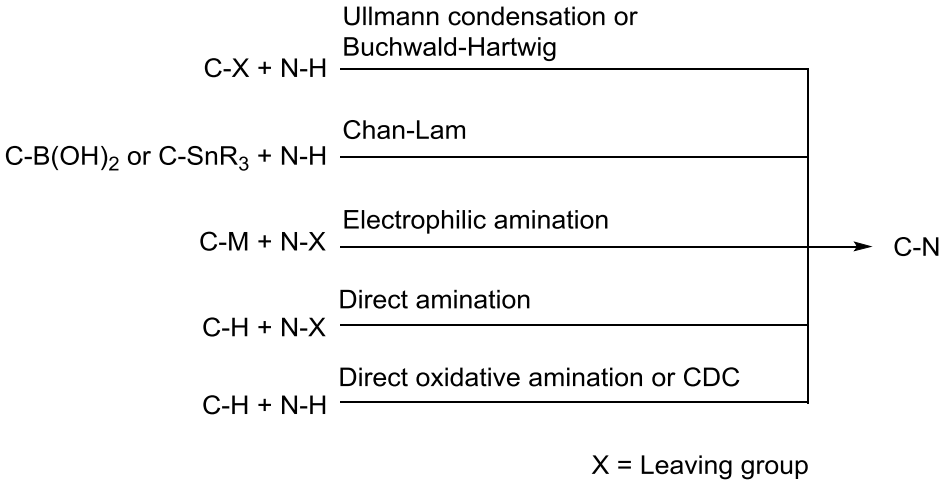
Scheme **1**).[20] This reaction is an interesting alternative when aryl halides do not provide sufficient results. In the mid-90s, the discovery of the Buchwald-Hartwig reaction offered the

starting point of a major breakthrough for the efficient construction of C(sp^2)-N bonds (

Classical approaches



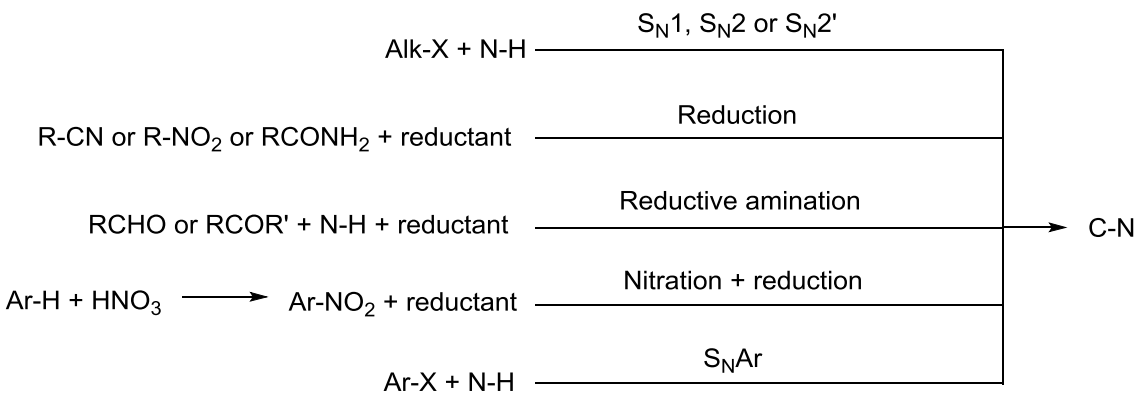
Modern approaches



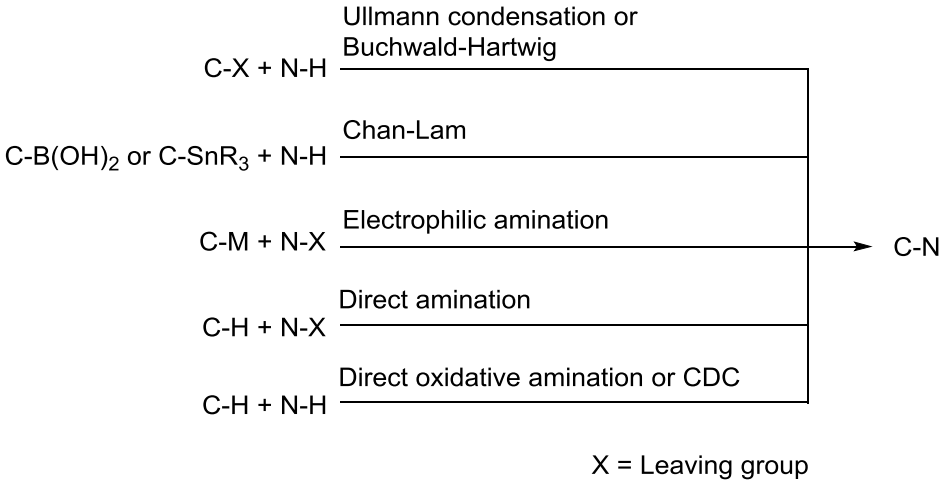
Scheme **1**).[21] The development of this reaction was a huge step forward towards a broadly applicable amination protocol. Currently, a wide variety of (pseudo)halogen leaving groups can be used in the (hetero)arene partner with virtually all classes of nitrogen nucleophiles, thanks to careful ligand design over the years. Based on interesting chemoselectivities in nitrogen (hetero)arylation observed between copper (Ullmann condensation) and palladium (Buchwald-Hartwig) catalysis, an “Ullmann condensation 1” might actually be the preferred reaction.[21a, 22, 23] The Buchwald-Hartwig amination has matured over the years and currently definitely features the broadest scope for C(sp^2)-N bond formation available.

Another approach for the construction of C-N bonds is electrophilic amination (

Classical approaches



Modern approaches

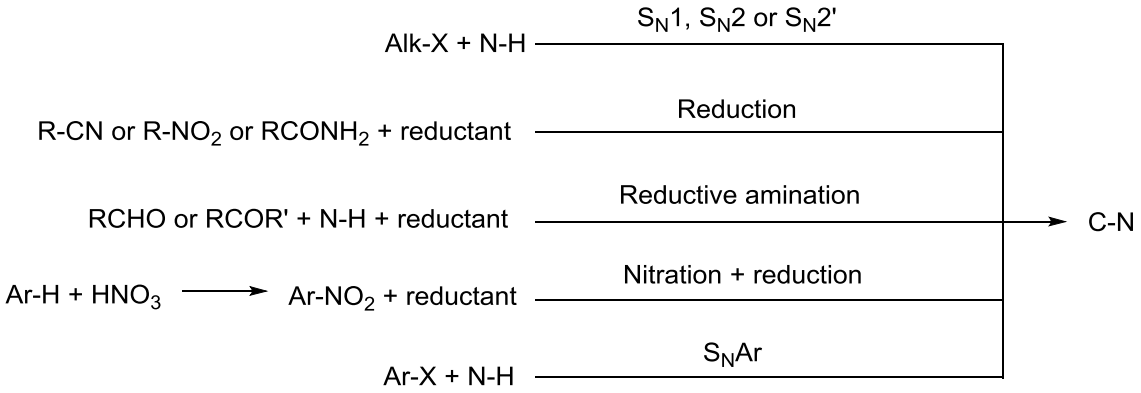


Scheme **1**).[24] This reaction requires the use of organometallic reactants and an electrophilic nitrogen source. Typically these aminating reactants carry a leaving group on nitrogen, often with an additional electron-withdrawing group attached to stabilize the reactant.

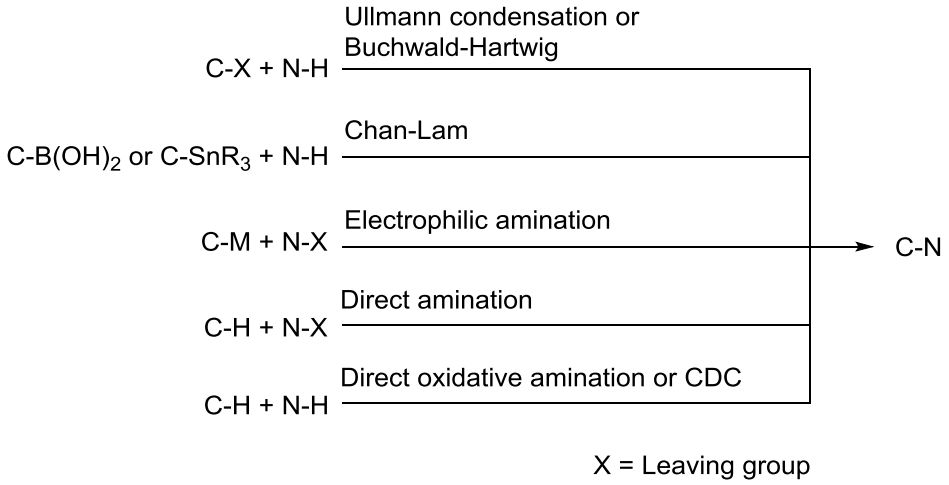
All the reactions described above have one thing in common: they require some kind of pre-activation. This can either be on carbon, under the form of a C-X bond (Ullmann condensation, Buchwald-Hartwig) or a C-M bond (Chan-Lam, electrophilic amination), or on nitrogen involving N-X reactants (direct amination). It is also possible that both C and N are pre-activated as exemplified by the electrophilic amination using organometals and N-X compounds. Pre-activation of any kind, means that one or more synthetic steps are required to obtain the starting materials for amination. More synthetic steps will normally produce more waste and consequently contribute negatively to the process mass intensity (PMI) of a process, and cause a higher production cost.[25] So ecological and resource aspects as well as economic driving forces foster chemistry innovations here.

Cross coupling reactions which directly couple C-H bonds and N-H bonds avoid pre-activation of any kind, and are considered the “nec plus ultra” in amination chemistry. They show a lot of potential with respect to green chemistry. As formally hydrogen gas is being formed, besides a transition metal a stoichiometric oxidant is required to obtain a catalytic cycle. This is reflected in the frequently used name for these reactions; cross dehydrogenative coupling (CDC). The process is also labelled as direct oxidative amination. As amines are also oxidation sensitive competitive oxidation is one of the main challenges of CDCs. However, the border between CDCs and direct amination reactions involving N-X reactants is thin, as CDCs might actually involve initial in-situ nitrogen pre-activation with the oxidant used, as will be shown in this review. So, what’s in a name! Labelling in this review is therefore solely done on whether the reactant used is pre-activated upfront or not.

Classical approaches



Modern approaches



Scheme 1: Classical and modern approaches towards C-N bond formation.

CDCs do not necessarily require a transition metal catalyst, and a stoichiometric oxidant can be sufficient. Nucleophilic aromatic substitutions of hydrogen (S_NH) are the earliest examples which

belong to this category.[26] S_NHs are limited to (hetero)arene substrates with a low LUMO, obtained by introducing both *meta* directing substituents and heteroatoms in the arene, as the formation of a σ^H adduct is required. This is similar to the σ^X adduct in the Meisenheimer intermediate of an S_NAr reaction. The σ^H adduct can be neutral or negatively charged depending on the charge of the amine nucleophile (amine or amide). Amides are not compatible with all types of oxidants and therefore limited in practical use. In principle the adduct can also lose a hydride, as exemplified by the famous Chichibabin 2-aminopyridine synthesis.[27] However, this adduct will not easily lose a hydride to restore aromaticity, since it has a very high basicity, and the number of successful examples is very limited. Therefore oxidants removing two electrons and a proton are normally used. Typical oxidants for oxidative amination are $KMnO_4$, $AgPy_2MnO_4$ or Br_2.[28]

Non-toxic, sustainable and cheap oxidants are required in CDCs, irrespective of whether a transition metal catalyst is used or not, as otherwise the advantage of the avoidance of pre-activation can just be counter balanced. In general for scale-up purposes, oxidants which are cheap, low in mass, have a high O content, only produce “innocent” by-products which can be safely disposed are preferred, such as O_2, H_2O_2, NaOCl, AcOOH, and *t*-BuOOH.[29] Prices of these oxidants, together with prices of other commonly used oxidants are compared in Table 1.[30]

Table 1: Prices of typical oxidants used in CDCs.

Oxidant	Price (€/kg)	Price (€/mol)	Scale[a]
O_2	0.07	0.02	1-10 tons
NaOCl	1.0[b]	0.6	1-10 tons[b]
t-BuOOH	4.5	0.41	1-10 tons
AcOOH	0.9	0.07	1.5 tons
$PhI(OAc)_2$	390	125	1.5 kg
$Cu(OAc)_2$	20	3.63	25 kg
$K_2S_2O_8$	1.6	0.43	20 ton
DDQ	80	18.16	120 kg
Selectfluor	175	62.0	16 kg
$AgBF_4$	1900	370	5 kg
AgOAc	700	117	3 kg
$Ce(SO_4)_2$	32	10.6	10 kg
N-methylmorpholine oxide	95	11.13	20 kg
Oxone	2.0	0.30	16 tons
$NaIO_4$	24	5.13	3 tons

[a] Prices are calculated based on a purchase of the indicated amount (October 2016).
[b] as 12% solution.

The inherent safety (stability) of the oxidant and the type and amount of stoichiometric waste produced in CDCs will be determining for its applicability on a large scale. Ideally, oxygen can be used as oxidant as it has the highest O content and only produces water as the by-product, though the flammability of organic solvents requires solvents with a high flash point and concentrations of oxygen of less than 5-10%. This makes the scale-up in batch, typically used in pharmaceutical and fine chemicals industry, less straightforward.[10a] However, through the

development of appropriate continuous flow processing systems even pure oxygen can be used safely to produce larger quantities.[31] In fact, the production of 6 commodity chemicals involve an oxidation reaction with pure oxygen.[31d] Protocols with oxidants which do not fulfill certain safety and stability criteria are not applicable in chemical development, but are still highly interesting for R&D purposes. To speed up R&D, where reactions are typically run on mg to gram scale, efficient chemical library synthesis is required to explore new chemical space.[32] This involves step efficient chemistry featuring a broad scope based on readily available building blocks, such as amines and C-H substrates. Obviously, the ubiquitous nature of C-Hs in organic molecules introduces a new challenge, one of selectivity. A type of reagents which recently gained popularity in academic R&D are the hypervalent iodine compounds.[33] These oxidants possess several benefits. They are non-toxic, stable and easy to handle and store.[34] They have the added benefit that they can display a very high selectivity and activity depending on their (easily modified) structure. Therefore, reactions using hypervalent iodine reagents often proceed at ambient temperature. The only drawback is that they have to be used in stoichiometric amount. Based on the price and the mass of the iodoarenes by-products, a recovery process is required when one would consider these reagents for development purposes. Hypervalent iodines can be modified so that recovery of by-product is more convenient; this is exemplified by polymer supported[35], ion tailed[36] or fluorine tagged[37] hypervalent iodine compounds. This is however not always straightforward. Polymer supported hypervalent iodine compounds for example have the drawback that the polymer is degrading during reoxidation. Reuse is therefore limited since the performance of the hypervalent iodine compound is decreasing after 4 to 5 recovery steps. Examples of the use of catalytic amounts of iodoarene in combination with a stoichiometric cheap oxidant with high O content, for *in situ* creation of the active hypervalent iodine compound, is a better approach for scale-up as it avoids the use of high molecular weight reagents.[38] Several CDCs for C-N bond formation using catalytic amounts of iodoarene have already been described.[39-44] Another approach is the design of hypervalent iodine compounds to be insoluble in certain solvents to facilitate recovery.[45] Depending on the polarity of the reaction product synthesized, very simple techniques such as extraction with a non-polar solvent can sometimes also be efficiently applied.[46]

1.3 Scope of the review

The main focus in C-H functionalization still lies in C-C bond formation[47], but considering the importance of amines in fine chemicals, the analogous creation of C-N bonds is an emerging field. Direct, including oxidative, amination reactions have been reviewed by Patureau and covered C(sp^2)-H activation.[48] Itami also summarized CDCs for (hetero)aromatic C-H amination involving metal catalysis.[49] In the current review direct oxidative aminations involving all types of C-H bonds are covered. Both transition metal catalyzed as well as metal free procedures are included. We prefer to use the terms direct functionalization, direct oxidative amination and direct amination in this review describing the overall process. After all, those procedures which do not involve a transition metal do not involve a formal C-H activation step. Moreover, even if a transition metal is used, it is not necessarily involved in the C-H bond cleavage step.[50]

Therefore a detailed insight into the reaction mechanism is required to conclude whether it involves the cleavage of an unreactive C-H bond by a transition metal complex to form a product featuring an M-C bond. The review is mainly organized by the hybridization of the carbon atom of the C-H bond involved, with the literature published from 2014 to 2016.

2. Direct oxidative amination

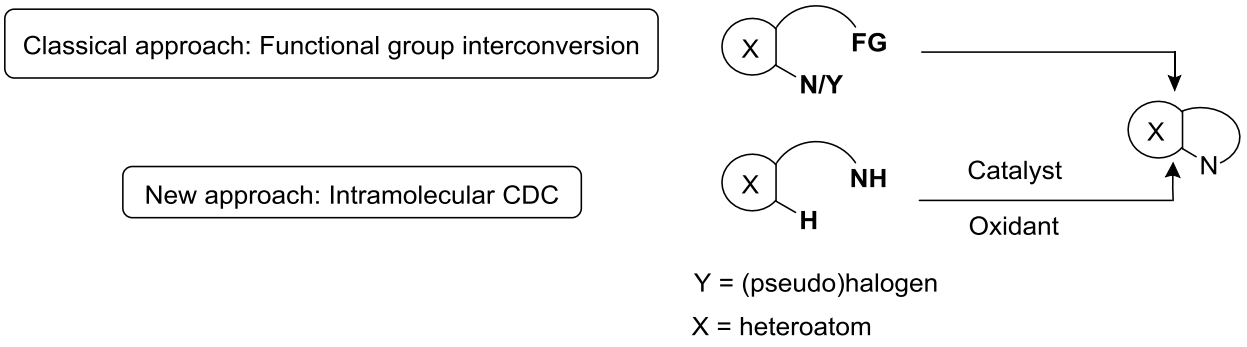
2.1 Intramolecular C(sp^2)-N bond formation

2.1.1 C-H bonds of (hetero)arenes

A new approach for nitrogen containing bicyclic heterocycles:

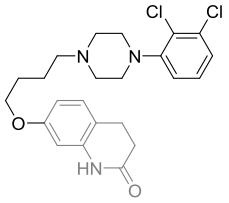
The formation of nitrogen containing bicyclic heterocycles (and their annulated derivatives), both fully aromatic and partly saturated, is one of the main current applications of direct oxidative C-N bond formation.[51] The development of new reactions applicable in the syntheses of heterocycles is important taking into account that ca. 20% of the top 150 best-selling drugs have a nitrogen containing bicyclic heterocycle as a structural element. Heterocycle formation via direct oxidative amination has the benefit that the directing group (DG) which is often required when a transition metal is involved, to direct the catalyst to a specific C-H bond, is incorporated in the reaction product itself. Therefore it does not need to be removed which avoids extra DG removal steps and therefore inherently scores better from a green chemistry point of view (waste, step efficiency and atom economy). [25b]

When direct oxidative amination is used for the synthesis of bicyclic heterocycles one can start from a mono substituted (hetero)arene. This substituent contains the nitrogen atom involved in the actual bond formation (

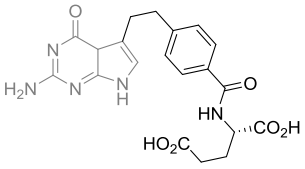


Scheme **3**). Intramolecular CDC gives access to scaffolds which feature a nitrogen atom next to the bridgehead position of which many representatives are considered to be privileged for medicinal chemistry and agrochemistry.[52] Some examples of launched drugs and

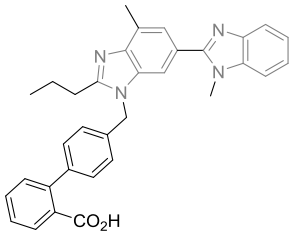
agrochemicals containing such a scaffold are represented in



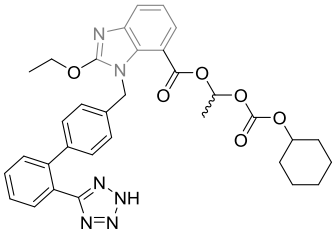
Apriprazole
Brystol-Myers Squibb, Otsuka
Atypical antipsychotic



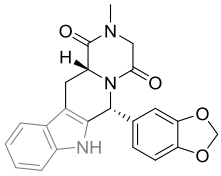
Pemetrexed
Lilly
Folate antimetabolite



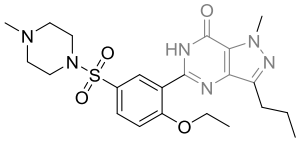
Telmisartan
Boehringer Ingelheim, Astellas
Angiotensin II receptor antagonist



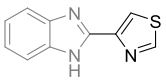
Candesartan Cilexetil
AstraZeneca, Takeda
Angiotensin II receptor antagonist



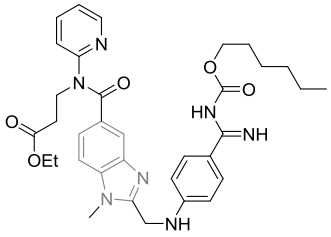
Tadalafil
Lilly
cGMP-specific phospho-diesterase type 5 inhibitor



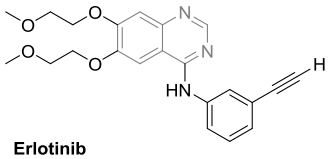
Sildenafil
Pfizer
cGMP-specific phospho-diesterase type 5 inhibitor



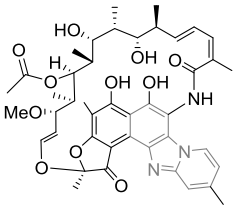
Thiabendazole
Merck
Biocide



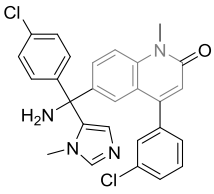
Dabigatran
Boehringer Ingelheim
Direct thrombin inhibitor



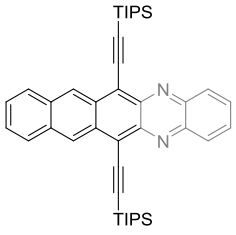
Erlotinib
Genentech, OSI Pharmaceuticals, Roche
Receptor tyrosine kinase inhibitor



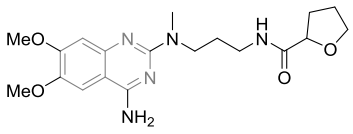
Rifaximin
Salix Pharmaceuticals
Antidiarrhoeal



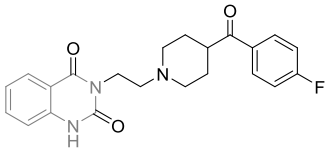
Tipifarnib
Johnson & Johnson
Farnesyltransferase inhibitor



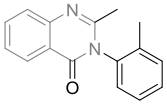
Azapentacene analogue
organic semi-conductor



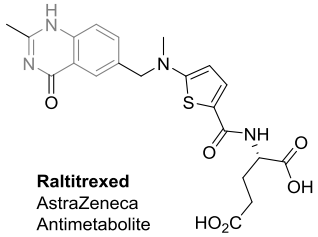
Alfuzosin
Sanofi-Aventis
α_1-receptor antagonist



Ketanserin
Janssen Pharmaceutica
Antihypertensive

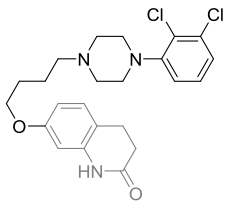


Methaqualone
Roussel Laboratories
Sedative-hypnotic

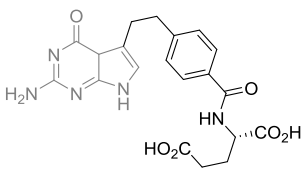


Raltitrexed
AstraZeneca
Antimetabolite

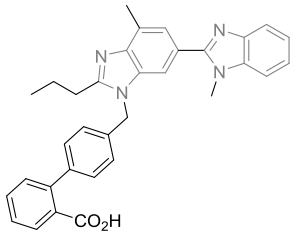
Scheme **2**. Applications of these types of scaffolds are not limited to pharmaceuticals and agrochemistry. In material science, *N*-heteroarenes for instance have applications as organic field-effect transistors or as organic light emitting diodes (OLEDs).[53]



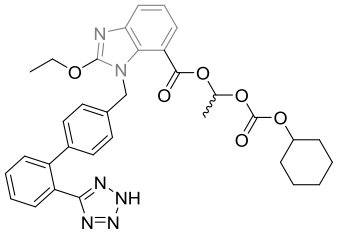
Apriprazole
Brystol-Myers Squibb, Otsuka
Atypical antipsychotic



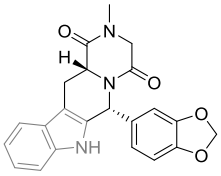
Pemetrexed
Lilly
Folate antimetabolite



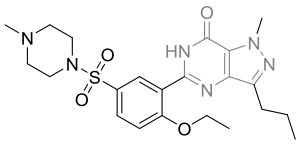
Telmisartan
Boehringer Ingelheim, Astellas
Angiotensin II receptor antagonist



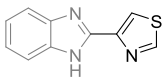
Candesartan Cilexetil
AstraZeneca, Takeda
Angiotensin II receptor antagonist



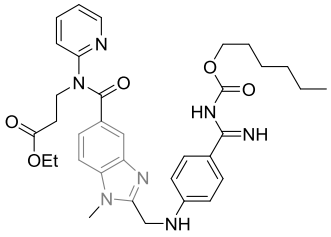
Tadalafil
Lilly
cGMP-specific phospho-diesterase type 5 inhibitor



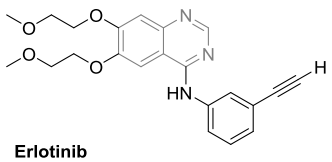
Sildenafil
Pfizer
cGMP-specific phospho-diesterase type 5 inhibitor



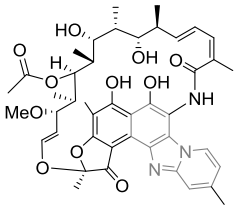
Thiabendazole
Merck
Biocide



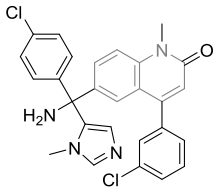
Dabigatran
Boehringer Ingelheim
Direct thrombin inhibitor



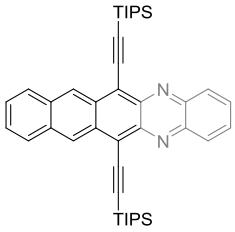
Erlotinib
Genentech, OSI Pharmaceuticals, Roche
Receptor tyrosine kinase inhibitor



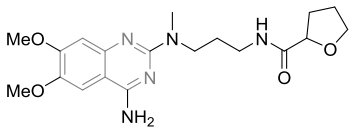
Rifaximin
Salix Pharmaceuticals
Antidiarrhoeal



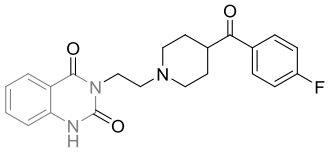
Tipifarnib
Johnson & Johnson
Farnesyltransferase inhibitor



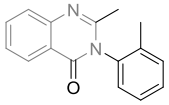
Azapentacene analogue
organic semi-conductor



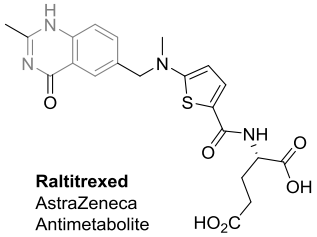
Alfuzosin
Sanofi-Aventis
α_1-receptor antagonist



Ketanserin
Janssen Pharmaceutica
Antihypertensive



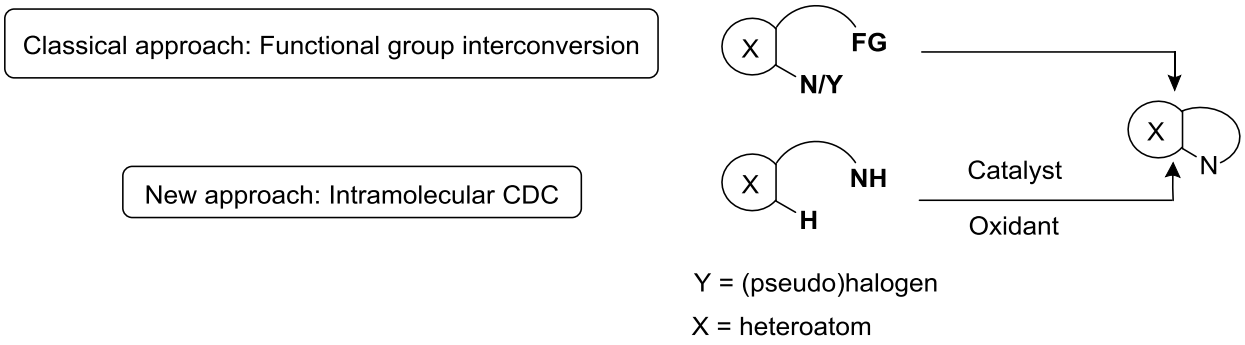
Methaqualone
Roussel Laboratories
Sedative-hypnotic



Raltitrexed
AstraZeneca
Antimetabolite

Scheme 2: Examples of active ingredients and materials containing a bicyclic (privileged) scaffold featuring a nitrogen atom next to a bridgehead position. The scaffold is indicated in grey.

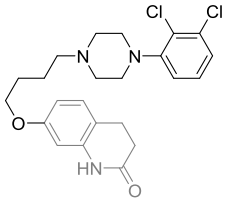
Classical methods for the synthesis of those bicyclic heterocycles start from *ortho* substituted (hetero)aromatic amines which are far less readily available, both commercially and synthetically (Scheme 3). Especially when additional substitution or ring annulation in the arene part of the bicyclic heterocycle is targeted this approach becomes prohibitive. After all, the more substituted the substrate needs to be, the more difficult, lengthy and low yielding the overall synthesis becomes. For heteroarene substrates the necessary minimal *ortho* disubstitution in the building block to build up the unsubstituted scaffold might even already be difficult to access. The nitrogen substituent will be typically introduced directly by nitration or indirectly by halogenation. For both approaches the general drawbacks have been discussed in section 1.2. Not surprisingly, direct oxidative amination has a huge potential as alternative approach for efficient library synthesis as typically (poly)substituted scaffolds are aimed for as target compounds and the higher the number of synthesis steps required for their build up, the less feasible it becomes to practically implement it.[48] For a specific substituted bicyclic heterocycle the approach might also offer access to the molecule in a more sustainable manner creating interesting opportunities for chemical development but this will require careful route analysis involving green metrics to compare with the classical approach(es).[25] Such analysis is very important to objectively determine the greenness of a new process and should already be started in a reaction discovery stage. When the synthetic method is under development it can steer the optimization process and make future implementation in chemical development easier.[54] Importantly, the green metrics also has to incorporate upstream (synthesis of substrate) and downstream (towards the final product) reactions to get a realistic view on the credentials of the whole process. Unfortunately, this has not yet been well adopted in academia. Though in chemical development divisions of fine chemicals industry, such analysis has become a standard item there is unfortunately no unique metrics system, making comparison between data difficult. Fortunately, major European initiatives such as Chem21, focusing on API (Active Pharmaceutical Ingredient) synthesis, try to align activities in specific sectors in this respect.[55]



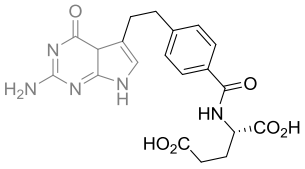
Scheme 3: Nitrogen containing bicyclic heterocycle formation: classical and new approach.

Recent examples:

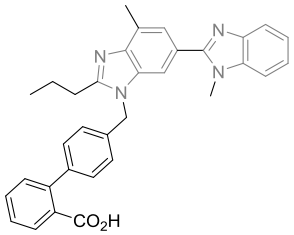
Inspired by the semi synthetic antibiotic Rafixamin (



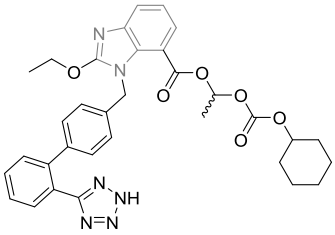
Apriprazole
Brystol-Myers Squibb, Otsuka
Atypical antipsychotic



Pemetrexed
Lilly
Folate antimetabolite



Telmisartan
Boehringer Ingelheim, Astellas
Angiotensin II receptor antagonist



Candesartan Cilexetil
AstraZeneca, Takeda
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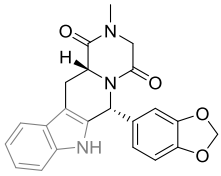
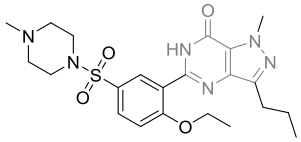
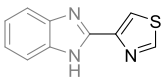


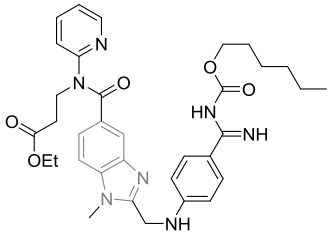
Tadalafil
Lilly
cGMP-specific phospho-diesterase type 5 inhibitor



Sildenafil
Pfizer
cGMP-specific phospho-diesterase type 5 inhibitor



Thiabendazole
Merck
Biocide



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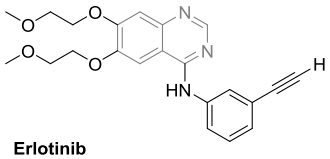
Direct thrombin inhibitor



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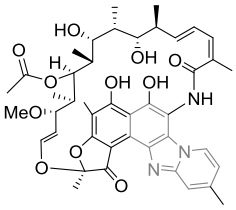
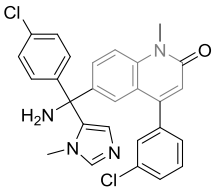
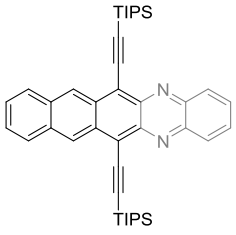
Genentech, OSI Pharmaceuticals, Roche
Receptor tyrosine kinase inhibitor



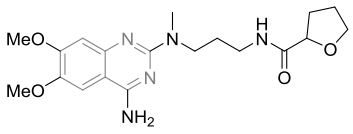
Rifaximin
Salix Pharmaceuticals
Antidiarrhoeal



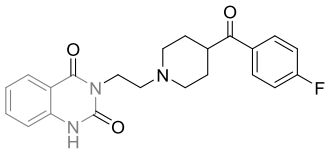
Tipifarnib
Johnson & Johnson
Farnesyltransferase inhibitor



Azapentacene analogue
organic semi-conductor



Alfuzosin
Sanofi-Aventis
α_1-receptor antagonist



Ketanserin
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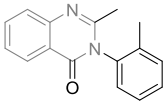
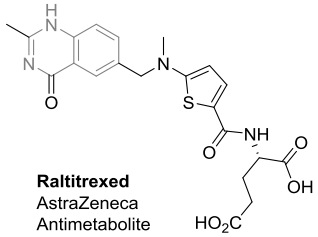
Antihypertensive

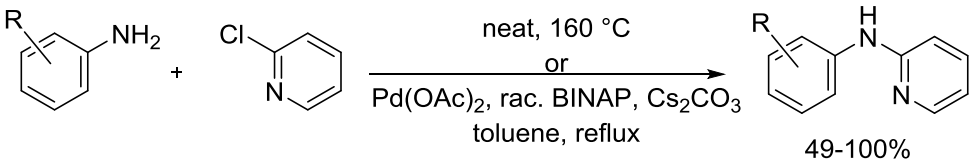


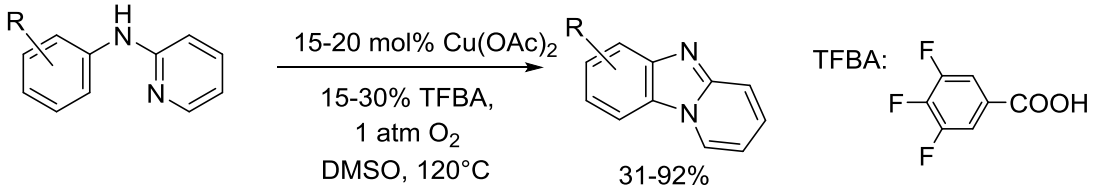
Methaqualone
Roussel Laboratories
Sedative-hypnotic



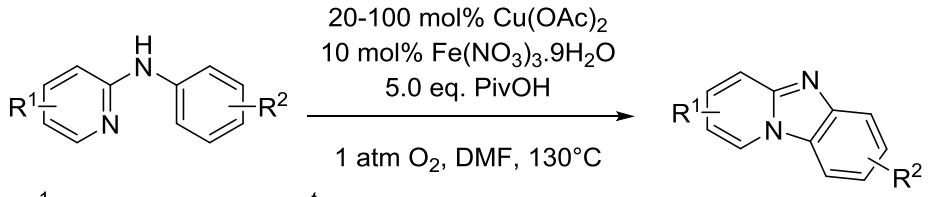
Raltitrexed
AstraZeneca
Antimetabolite

Scheme **2**) a new method to synthesize pyrido[1,2-*a*]benzimidazoles by direct oxidative amination of 2-anilinopyridines was independently reported by the groups of Maes[56] and Zhu (



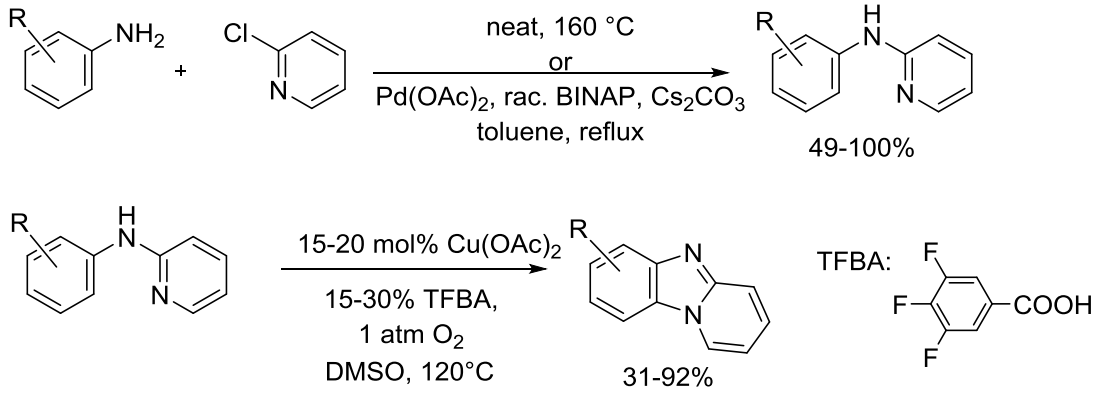


R = 4-CF_3, 6-F, 7-F, 9-F, 8-F, 6-OMe, 7-OMe, 9-OMe, 8-OMe, 8-Cl, 8-CO_2Et, 7-CO_2Et, 8-CF_3, 6-Cl, (2-Cl, 5-OMe), 2-Cl, 2,6-diCl, (2-Cl, 3-F)



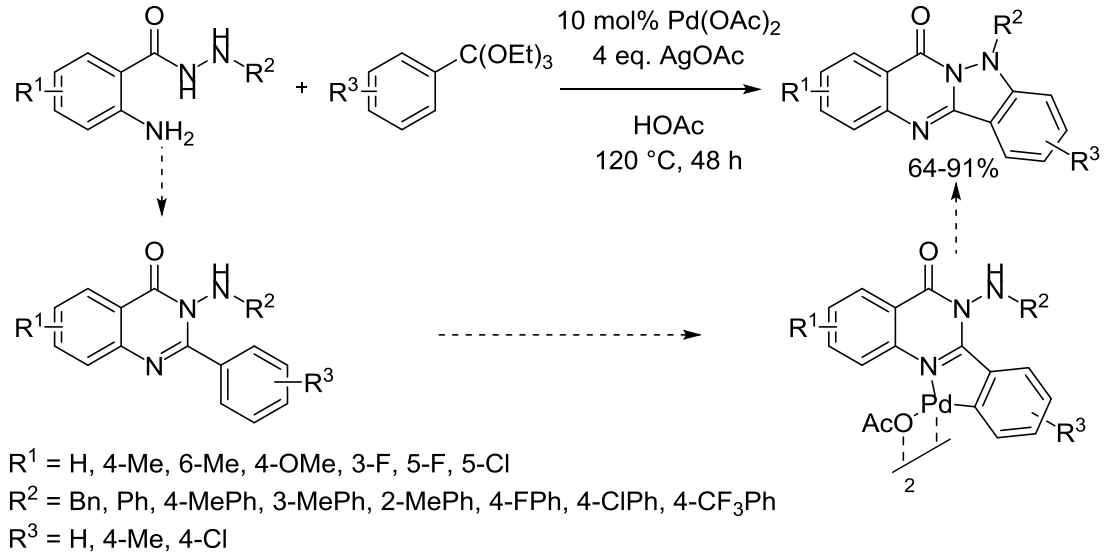
R^1 = H, 4-Me, 4-OMe, 4-^{t}Bu, 4-F, 4-Cl, 4-Br, 2-Me, 2-OMe, 2-F
R^2 = H, 3-Me, 3-OMe, 3-Cl, 3-F, 4-Me

Scheme **4**).[57] Zhu used a Cu^{II}/Fe^{III} catalytic system where $Fe(NO_3)_3.9H_2O$ was used as co-catalyst and oxygen as stoichiometric oxidant. The Fe(III) co-catalyst is believed to oxidize the Cu(II) adduct to a more electrophilic Cu(III) intermediate. This intermediate undergoes subsequent electrophilic substitution more readily. The Maes group reported a Cu(II) reaction with an acid additive. By using catalytic TFBA (3,4,5-trifluorobenzoic acid) it was possible to synthesize the target compounds without the need for an Fe^{III} co-catalyst. Furthermore it was possible to cyclize electron-deficient substrates or substrates with a sterically hindered pyridine nitrogen atom as in *N*-phenylquinoline-2-amine. Those substrates required stoichiometric amounts of $Cu(OAc)_2$ in the Zhu procedure. Moreover, the method using TFBA generally allowed a lower copper catalyst loading, less homo coupling of substrate and a shorter reaction time. Meta substituted anilines gave C7 regioisomers as the major compounds. The Maes group did KIE (kinetic isotope effect) experiments, revealing intramolecular and intermolecular KIE values of respectively 3.5 and 3.1, showing that the breaking of the C-H bond is a kinetically relevant process and involved in the rate-limiting step. A Cu(II)/Cu(0) catalytic cycle was proposed with a $(RCO_2)_2$Cu(II) catalytic species. A Cu(I)/Cu(III) mechanism was ruled out based on an experiment in the absence of oxygen, where an equal amount of product versus the copper loading applied was obtained. This also revealed the role of oxygen as the final electron acceptor of the catalytic cycle. TFBA is assumed to generate a more electrophilic $(RCO_2)_2$Cu(II) catalytic species.



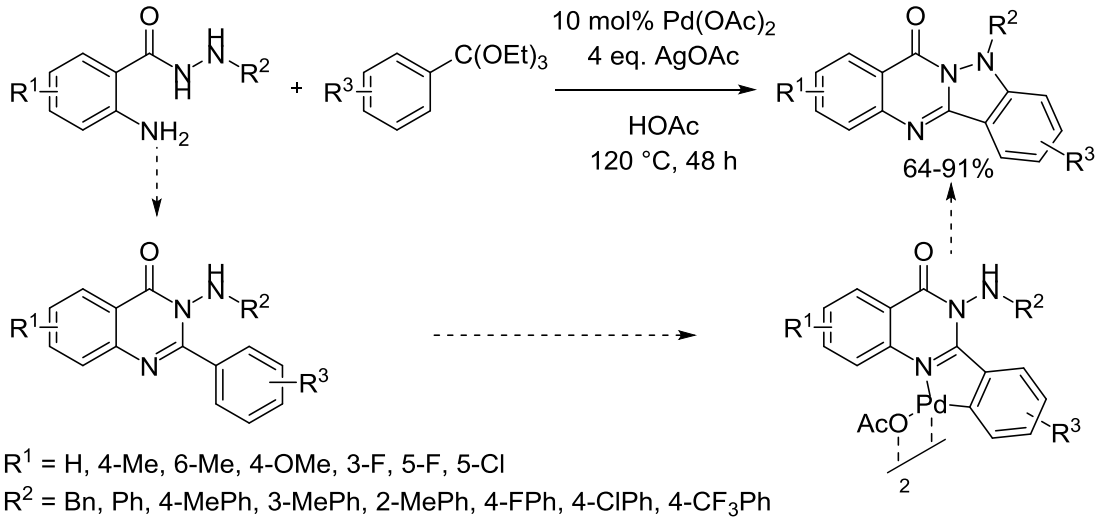
Scheme 4: Synthesis of pyrido[1,2-*a*]benzimidazoles.

Wu reported the synthesis of indazolo[3,2-*b*]quinazolines by a palladium-catalyzed cascade reaction of 2-amino-*N'*-arylbenzohydrazides with triethyl orthobenzoates (



Scheme **5**).[58] This reaction involves two key intermediates which could both be isolated. The first one is a substituted 3-amino-2-arylquinazolinone, formed by condensation reaction of the substrate with triethyl orthobenzoate. On this *in situ* formed product C-H activation occurs via the formation of a palladacycle with $Pd(OAc)_2$ directed by the N1 quinazolinone nitrogen. 4

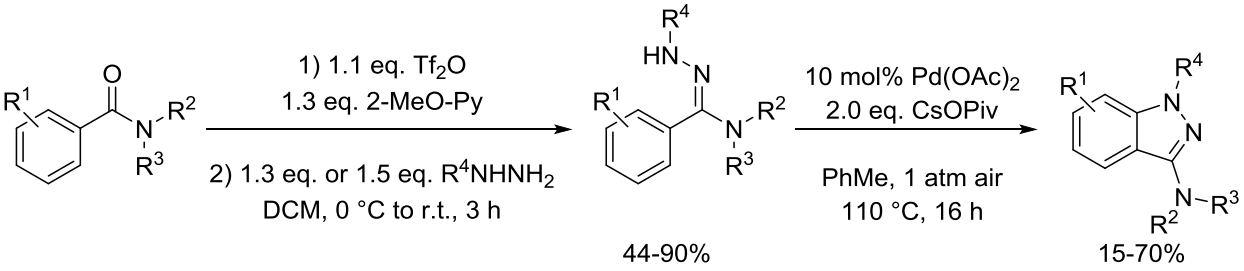
Equivalents of AgOAc were required as oxidant. The authors propose a Pd(0)/Pd(II) catalytic cycle although a Pd(II)/Pd(IV) mechanism cannot be ruled out. Further mechanistic studies are needed to give a more detailed reaction mechanism.



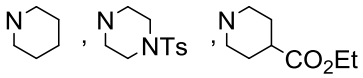
R^1 = H, 4-Me, 6-Me, 4-OMe, 3-F, 5-F, 5-Cl
R^2 = Bn, Ph, 4-MePh, 3-MePh, 2-MePh, 4-FPh, 4-ClPh, 4-CF_3Ph
R^3 = H, 4-Me, 4-Cl

Scheme 5: Synthesis of indazolo[3,2-*b*]quinazolines.

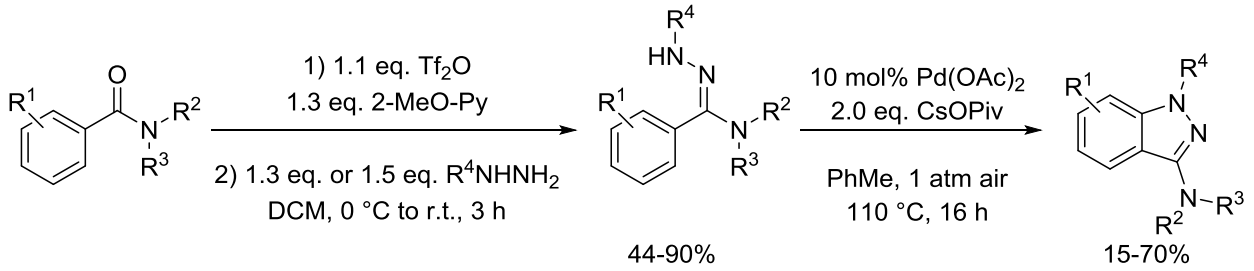
Charette described the synthesis of 3-aminoindazoles, starting from *N*-substituted amidrazones (



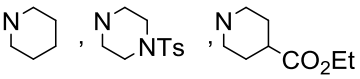
R^1 = H, 4-Me, 2-Me, 4-F, 4-Cl, 4-CO_2Me, 2-thiophenyl, 4-OMe, 3-OMe

R^2R^3N = Et_2N, EtNCy, CyNH, 
R^4 = Ts, Ms, CO_2Et

Scheme 6).[59] Also in this case a hydrazine is involved in the C-N bond forming process. $Pd(OAc)_2$ is used as the catalyst in the presence of CsOPiv and air is used as oxidant. Other oxidants and/or a catalytic amount of ligands were detrimental for the reaction. The substrates could be easily made starting from the corresponding *N*-substituted amides through reaction with triflic anhydride and substituted hydrazine. Based on the absence of an intramolecular KIE it was concluded that the C-H bond cleavage was not related to the rate-determining step. No further mechanistic studies were performed.

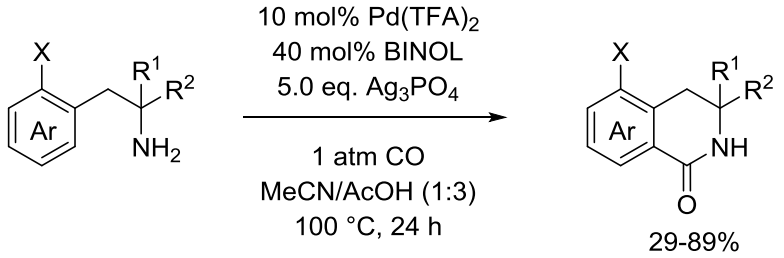


R^1 = H, 4-Me, 2-Me, 4-F, 4-Cl, 4-CO_2Me, 2-thiophenyl, 4-OMe, 3-OMe

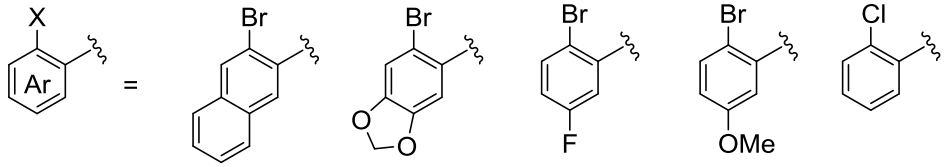
R^2R^3N = Et_2N, EtNCy, CyNH, 
R^4 = Ts, Ms, CO_2Et

Scheme 6: Synthesis of 3-aminoindazoles.

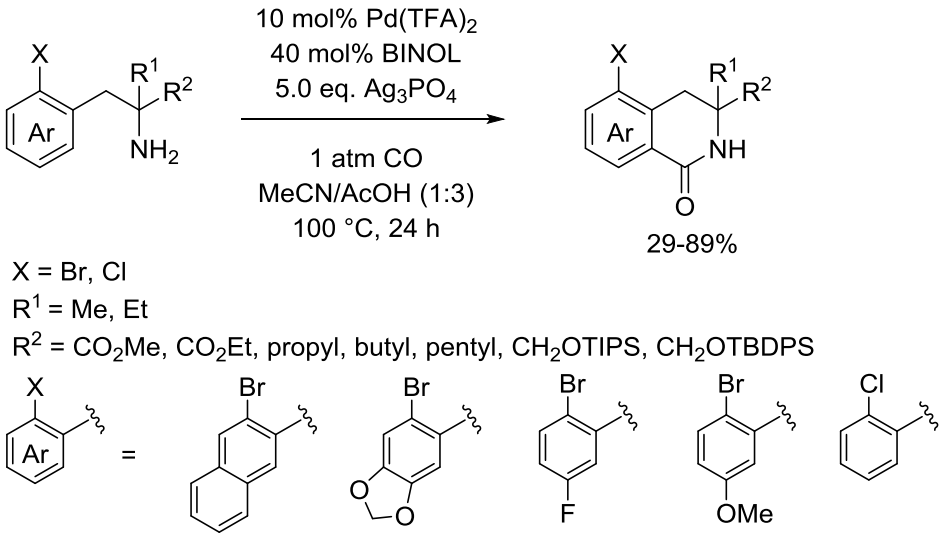
Kondo described the $Pd(TFA)_2$/BINOL catalytic system for the synthesis of benzolactams using a CDC under CO atmosphere (



X = Br, Cl
R^1 = Me, Et
R^2 = CO_2Me, CO_2Et, propyl, butyl, pentyl, CH_2OTIPS, CH_2OTBDPS

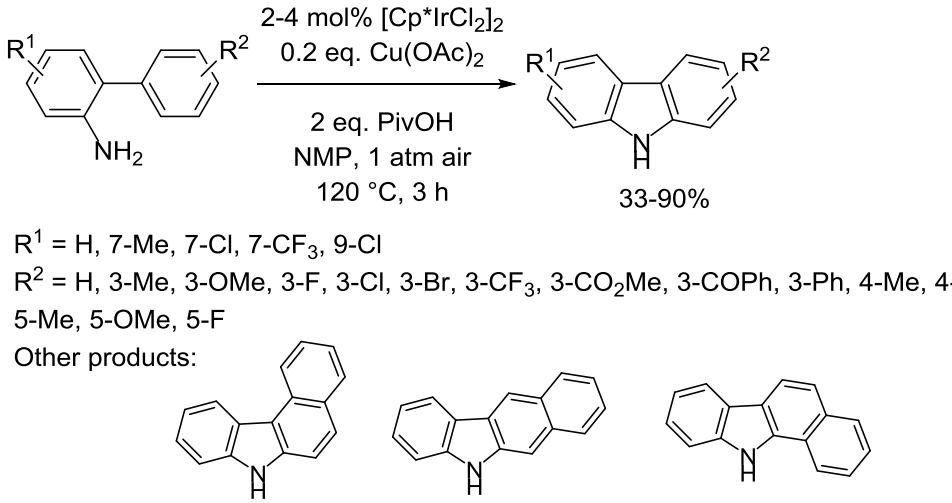


Scheme 7).[60] Ag_3PO_4 was used as oxidant. The more sterically hindered the R^1 and R^2 substituents were, the more efficiently the C-H cyclization proceeded, pointing towards a Thorpe Ingold effect. No experiments towards elucidation of the reaction mechanism were performed. Interestingly, the halogen on the benzene ring of the substrate remained untouched during the aminocarbonylation reaction. It was therefore available for further follow-up cross coupling reactions as demonstrated with a Buchwald-Hartwig, Stille and Suzuki reaction.

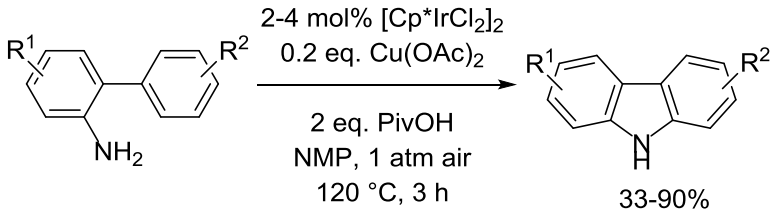


Scheme 7: Synthesis of benzolactams.

Miura reported the synthesis of *N*-H carbazoles via iridium-catalyzed intramolecular oxidative C-H amination (

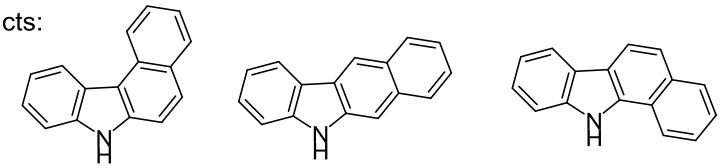


Scheme 8).[61] The [Cp*-Ir(III)Cl_2]$_2$ dimer precatalyst can form an iridacycle intermediate from 2-phenylaniline which undergoes C-N reductive elimination yielding the carbazole. The Cp*Ir(I) species obtained in this process can be reoxidized by the Cu(II) co-catalyst yielding a process which is catalytic in iridium. Copper does not need to be used stoichiometrically as by performing the reaction in air, Cu(I) can be reoxidized to Cu(II) which is similar as in the Wacker process in which a Cu/air system is used to reoxidize Pd(0).[62] The intermolecular KIE was determined as 1.1, suggesting that the C-H bond cleavage step could be irreversible and is not involved in the rate-determining step.



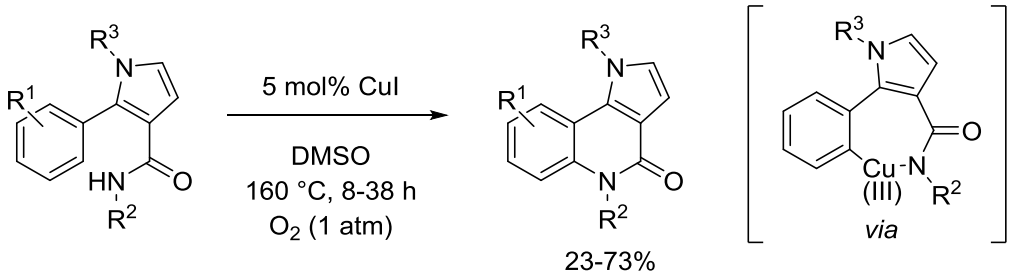
R^1 = H, 7-Me, 7-Cl, 7-CF_3, 9-Cl
R^2 = H, 3-Me, 3-OMe, 3-F, 3-Cl, 3-Br, 3-CF_3, 3-CO_2Me, 3-COPh, 3-Ph, 4-Me, 4-OMe, 4-CF_3, 5-Me, 5-OMe, 5-F

Other products:



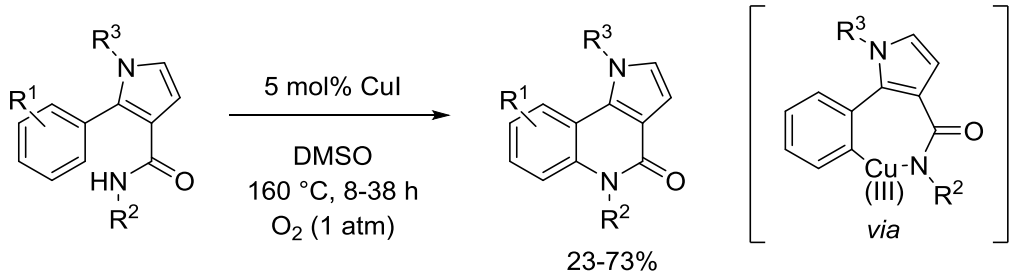
Scheme 8: Synthesis of *N*-H carbazoles.

The CuI catalyzed synthesis of pyrrolo[3,2-*c*]quinolinone derivatives has been described by Zhang involving intramolecular amination of an arene with a carboxamide (



R^1 = H, 4-OMe, 3-OMe, 4-Cl
R^2 = Ph, 4-ClPh, 3-ClPh, 2-ClPh, 4-CO_2EtPh, 4-MeOPh, 3-MeOPh, 2-MeOPh
R^3 = Ph, 4-ClPh, 4-CO_2EtPh, 2-MeOPh, Bn

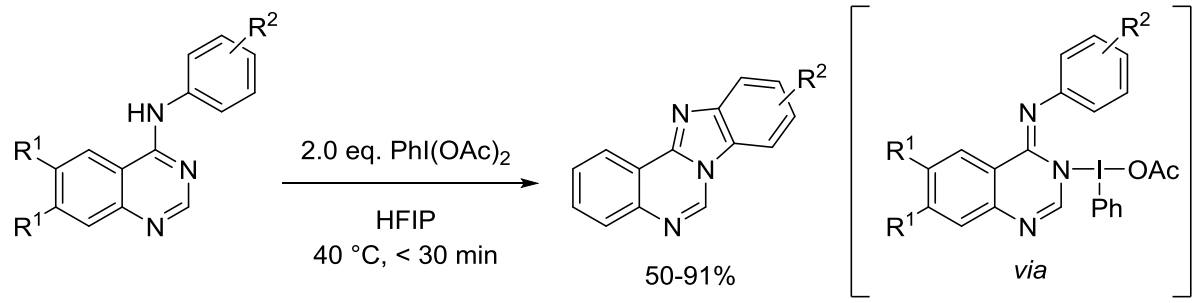
Scheme **9**).[63] Based on control experiments, a radical mechanism was excluded. The proposed mechanism goes over a Cu(III) intermediate which is formed by reaction of the substrate with the Cu(I) catalyst and oxygen. The exact mechanism of this C-H activation step remains unclear. After reductive elimination Cu(I) is formed which can be reoxidized by oxygen.



R^1 = H, 4-OMe, 3-OMe, 4-Cl
R^2 = Ph, 4-ClPh, 3-ClPh, 2-ClPh, 4-CO_2EtPh, 4-MeOPh, 3-MeOPh, 2-MeOPh
R^3 = Ph, 4-ClPh, 4-CO_2EtPh, 2-MeOPh, Bn

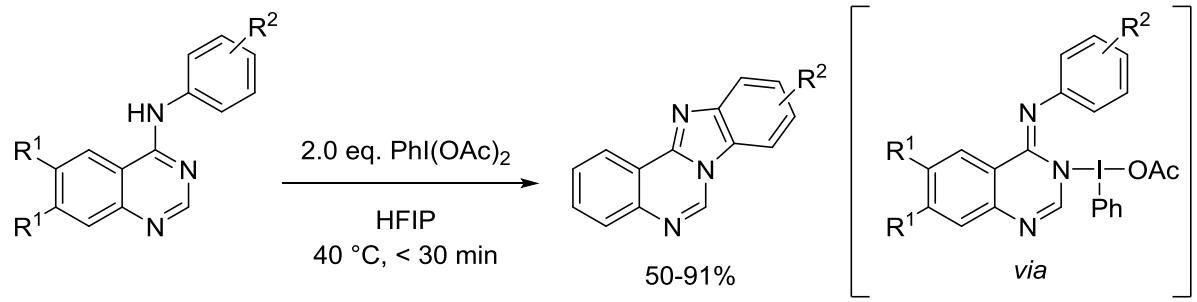
Scheme 9: Synthesis of pyrrolo[3,2-*c*]quinolinones.

A series of benzimidazo[1,2-*c*]quinazolines were synthesized by using a metal-free, $PhI(OAc)_2$ mediated direct oxidative amination reaction (



R^1 = H, $MeOCH_2CH_2O$
R^2 = H,4-Me, 4-MeO, 4-EtO,4-F,4-Br, 4-I, 4-CF_3, 4-Ac, 3-Cl, 3-MeO, 3-ethynyl, 2,5-diMeO

Scheme **10**).[64] The protocol was used for the synthesis of bioactive Erlotinib analogues. The proposed reaction mechanism starts by nucleophilic attack of the pyrimidine nitrogen on the iodine of $PhI(OAc)_2$, yielding an *N*-activated species. Subsequent electrophilic substitution yields the reaction products.



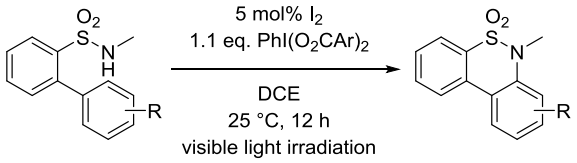
R^1 = H, $MeOCH_2CH_2O$
R^2 = H,4-Me, 4-MeO, 4-EtO,4-F,4-Br, 4-I, 4-CF_3, 4-Ac, 3-Cl, 3-MeO, 3-ethynyl, 2,5-diMeO

Scheme 10: Synthesis of benzimidazo[1,2-*c*]quinazolines.

Muñiz described an interesting iodine catalyzed direct oxidative C-H amination protocol involving stoichiometric $PhI(O_2CAr)_2$ which proceeds at room temperature under visible light

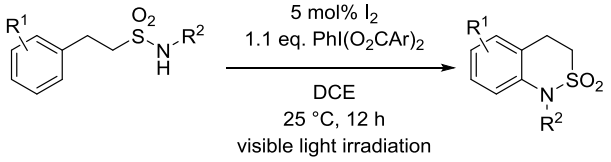
irradiation.[65] Besides the synthesis of benzoannulated thiazines (

A



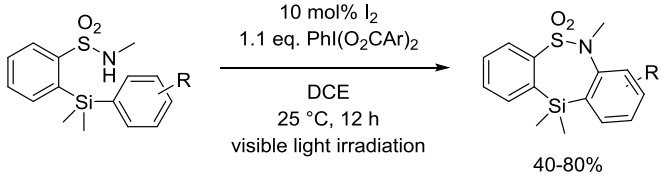
R = H, 4-Me, 4-*t*-Bu, 4-Ph, 4-OMe, 4-OPh, 4-OEt, 4-Cl, 4-F, 4-CF_3, 4-CH_2Br, 2-Me
Ar = 3-ClC_6H_4

B



R^1 = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-Ph
R^2 = Me, Bn, Et
Ar = 3-ClC_6H_4

C

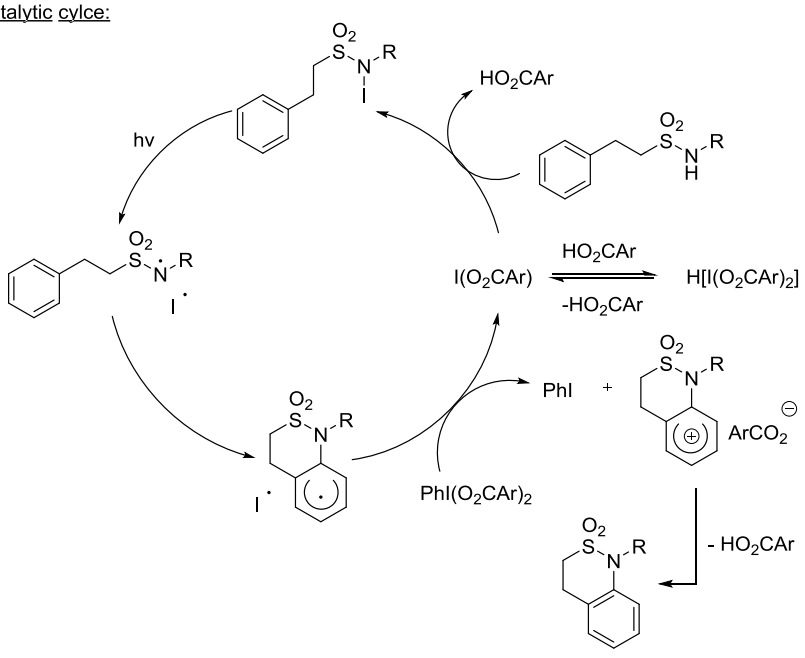


R = H, 4-Me, 4-OMe, 4-F, 4-Cl
Ar = 3-ClC_6H_4

Catalyst formation:

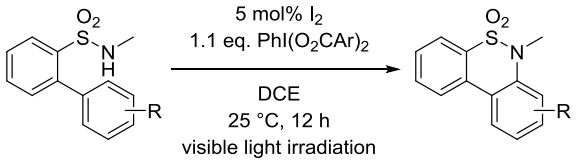
$I_2 + PhI(O_2CAr)_2 \longrightarrow 2\ I(O_2CAr) + PhI$

Catalytic cylce:



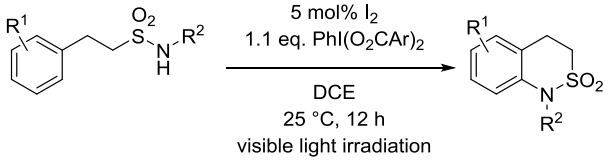
Scheme **11**, A and B), the reaction scope could be extended to silicon-tethered arenes (

A



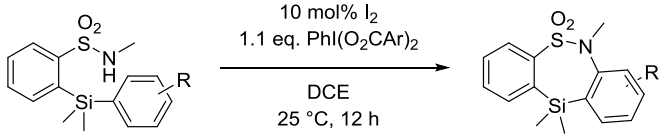
R = H, 4-Me, 4-*t*-Bu, 4-Ph, 4-OMe, 4-OPh, 4-OEt, 4-Cl, 4-F, 4-CF_3, 4-CH_2Br, 2-Me
Ar = 3-ClC_6H_4

B



R^1 = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-Ph
R^2 = Me, Bn, Et
Ar = 3-ClC_6H_4

C

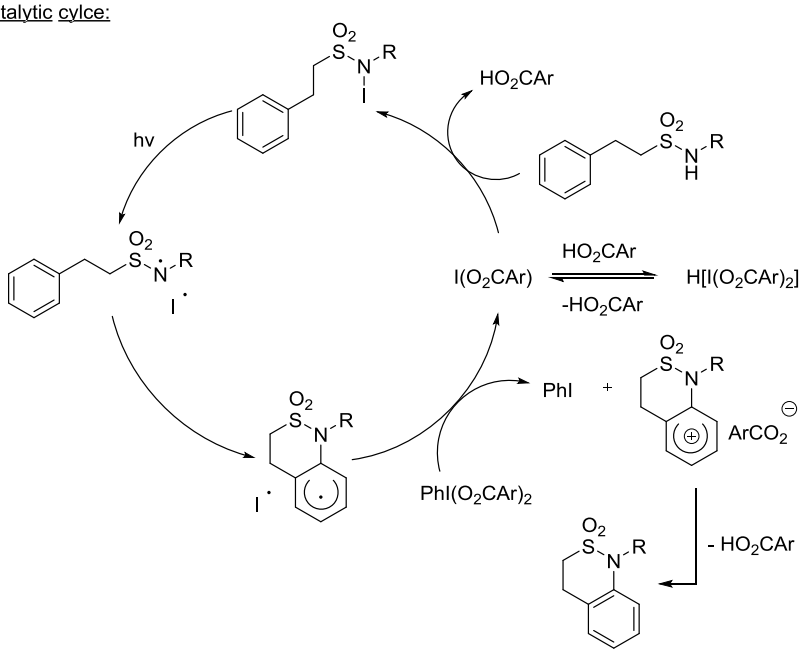


R = H, 4-Me, 4-OMe, 4-F, 4-Cl
Ar = 3-ClC_6H_4

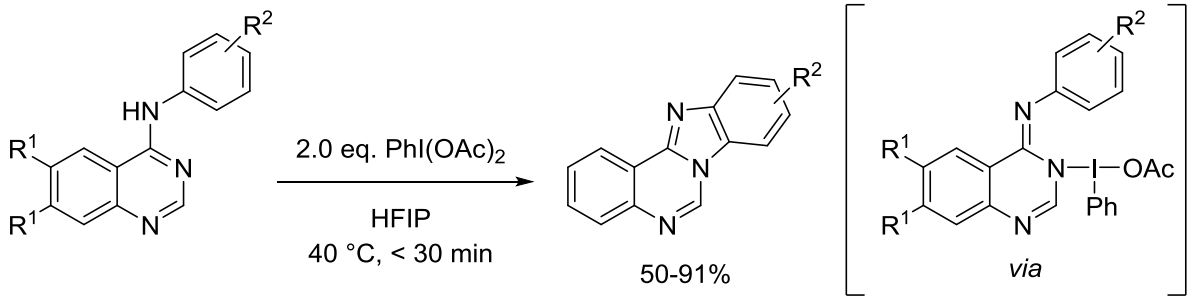
Catalyst formation:

$I_2 + PhI(O_2CAr)_2 \longrightarrow 2\ I(O_2CAr) + PhI$

Catalytic cylce:



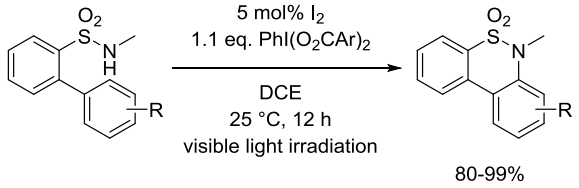
Scheme **11**, C). By increasing the catalyst loading to 10%, formation of a 7-membered ring was possible. The reaction starts by formation of the catalytic species. I_2 reacts with $PhI(O_2CAr)_2$ to form 2 equivalents of $I(O_2CAr)$ and iodobenzene. The catalytic species iodinates the substrate on nitrogen to form an activated N-I bond. Visible light irradiation causes homolytic cleavage of this bond resulting in a nitrogen centered radical. This radical rapidly adds to the aromatic ring with formation of a cyclohexadienyl radical. Oxidation by $PhI(O_2CAr)_2$ leads to a cation which aromatizes upon deprotonation. The mechanism is supported by independent synthesis of intermediates, KIE and competition experiments with substrates featuring different electronics. Interestingly the hypervalent iodine reagent has a clearly distinct role here as it does not react directly with the nitrogen atom of the substrate as is usually the case in direct oxidative aminations (



R^1 = H, $MeOCH_2CH_2O$

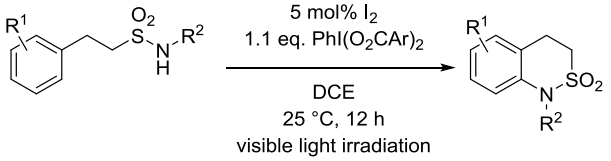
R^2 = H,4-Me, 4-MeO, 4-EtO,4-F,4-Br, 4-I, 4-CF_3, 4-Ac, 3-Cl, 3-MeO, 3-ethynyl, 2,5-diMeO

A



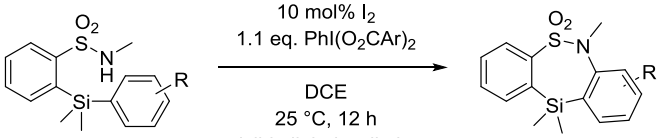
R = H, 4-Me, 4-*t*-Bu, 4-Ph, 4-OMe, 4-OPh, 4-OEt, 4-Cl, 4-F, 4-CF_3, 4-CH_2Br, 2-Me
Ar = 3-ClC_6H_4

B



R^1 = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-Ph
R^2 = Me, Bn, Et
Ar = 3-ClC_6H_4

C

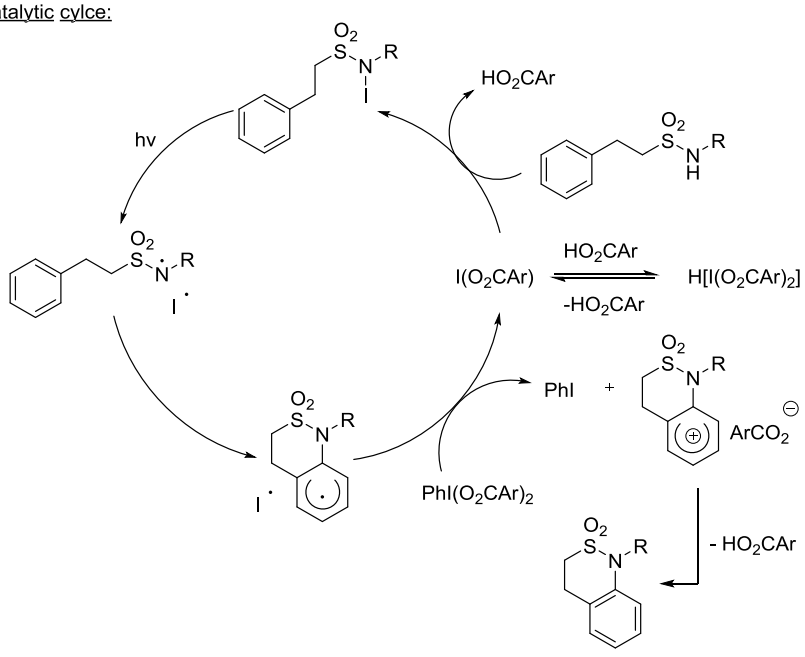


R = H, 4-Me, 4-OMe, 4-F, 4-Cl
Ar = 3-ClC_6H_4

Catalyst formation:

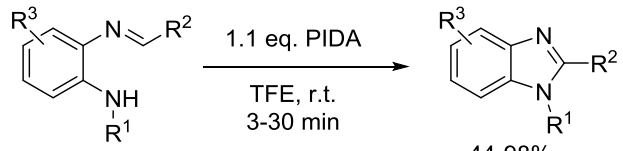
$I_2 + PhI(O_2CAr)_2 \longrightarrow 2\ I(O_2CAr) + PhI$

Catalytic cylce:



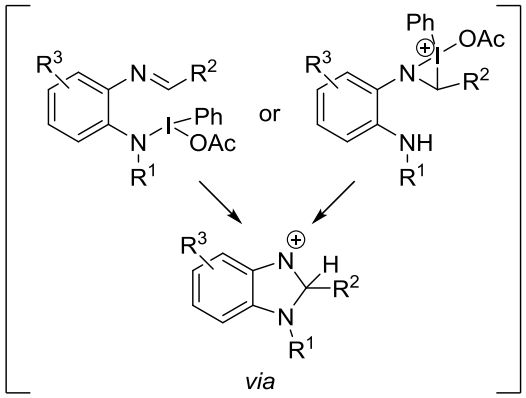
Scheme **10**,

Scheme **11**,



R^1 = Ts, SO_2Ph, Bz

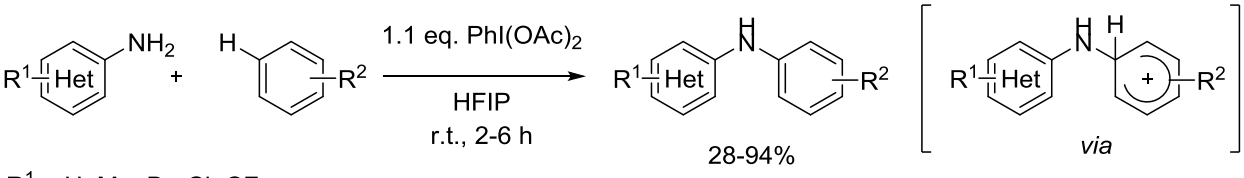
Scheme 12



R^2 = 2-bromophenyl, 2-methylphenyl, 4-isopropylphenyl, 3-bromo, 4-methoxyphenyl, 4-fluorophenyl, (3-bromo-5-cyano-2,4,6-trimethylphenyl), (3,5-dicyano-2,4,6-trimethylphenyl), 4-methoxyphenyl, 2,4,6-trimethylphenyl, 2-bromo-5-fluorophenyl, 2,4-dimethoxy-6-methylphenyl, 4-cyanophenyl, 2,3,4,5,6-pentafluorophenyl, 3-chlorophenyl, 9-anthracenyl, 2-pyridyl, 1-naphthyl, 1-pyrenyl, 2-chloro-6-methoxyquinolin-2-yl, 5-nitrofuran-2-yl, cyclohexyl, H, $CH_2CH(CH_3)Ph$, Me, 4-ethylphenyl, 2-nitrophenyl, 2-fluorophenyl, 4-bromophenyl, 2-thiophenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl

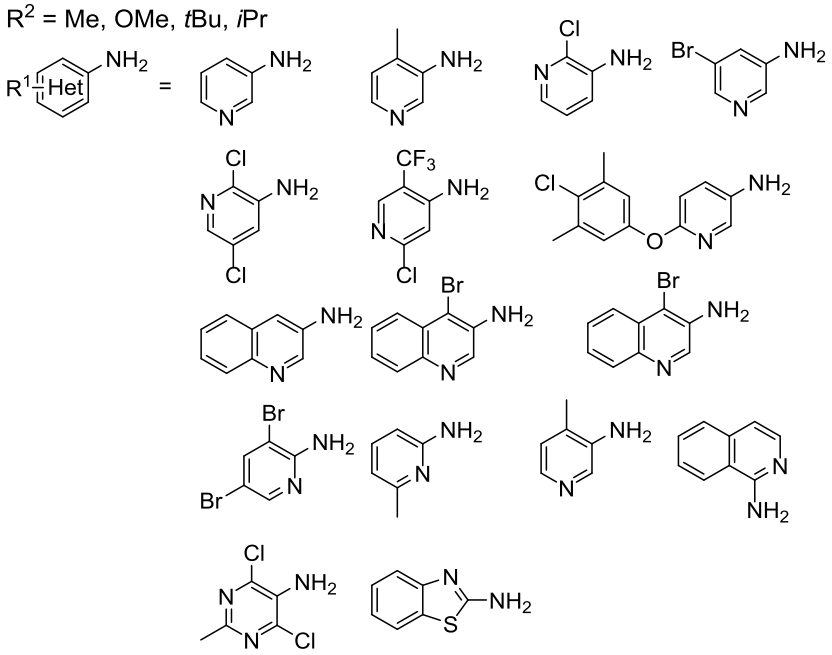
R^3 = H, 5-NO_2, 5-CO_2H, 4,5-diBr, 4,5-diCl, 4,5-diMe

Scheme **16**,

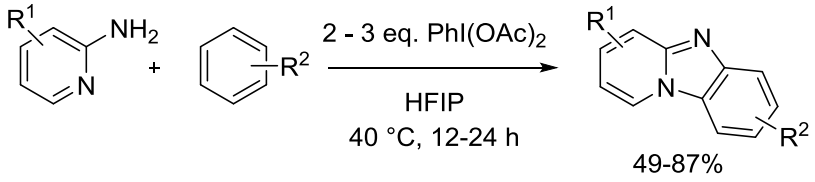


R^1 = H, Me, Br, Cl, CF_3

R^2 = Me, OMe, *t*Bu, *i*Pr



Scheme **40**,



R^1 = H, 2-Br, 4-Br, 5-Br, 6-Br, 2-Me, 4-Me, 5-Me, 6-Me, 5-F, 4-OAc
ArR^2 = anisole, diphenylether, *m*-xylene, *p*-xylene, 1-methylnapthalene, 2,3-diisopropylbenzene, 1-ethyl-3-methylbenzene, toluene, 1,2,3,4-tetrahydronapthalene, iodobenzene, 2-(3-methoxyphenyl)acetonitrile

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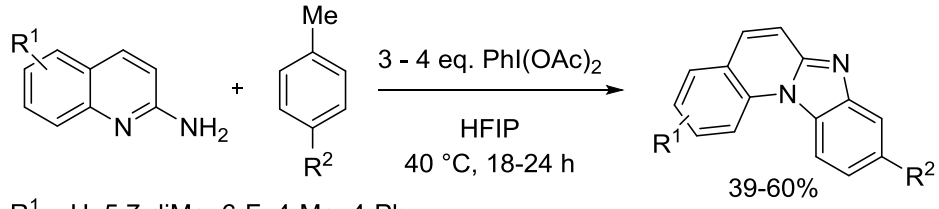
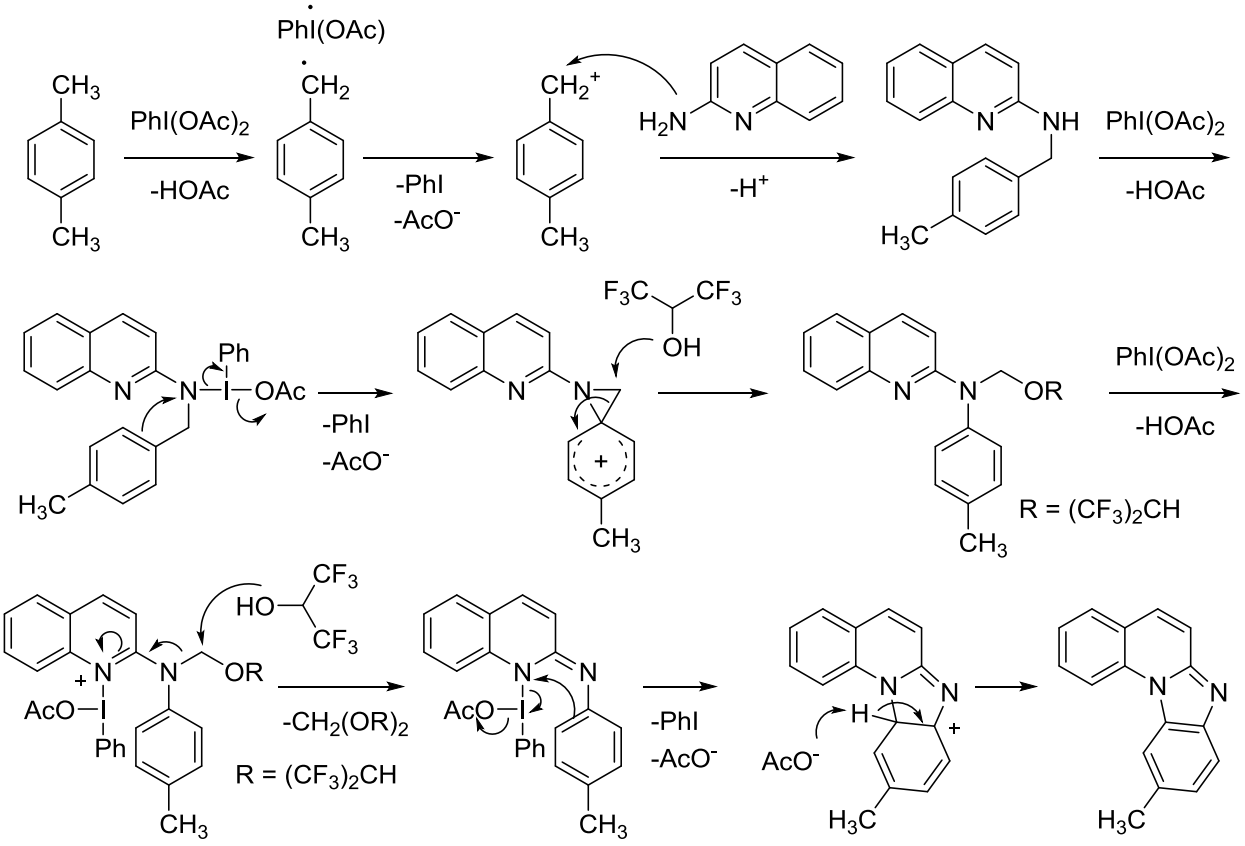
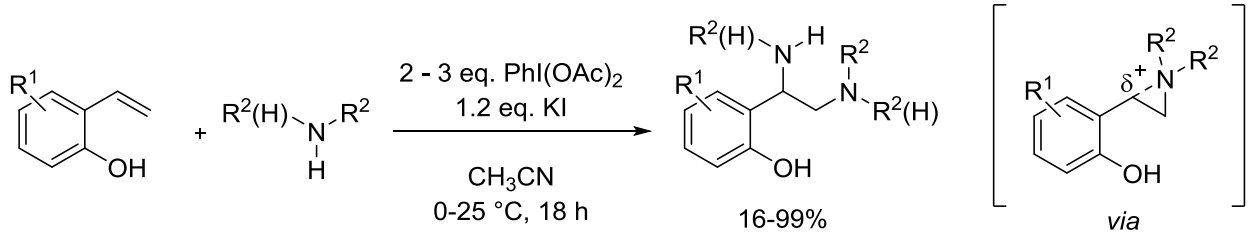


R^1 = H, 5,7-diMe, 6-F, 4-Me, 4-Ph
R^2 = Me, I

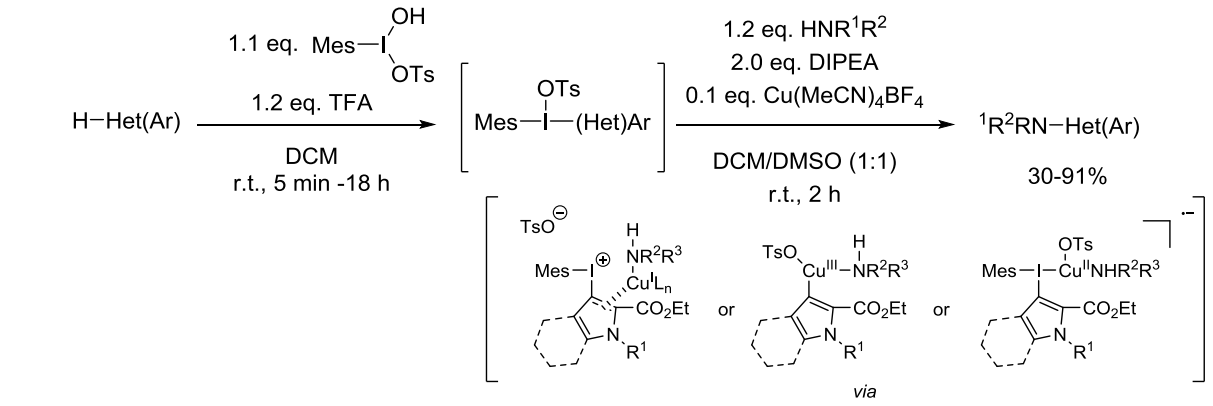


Scheme **41**,

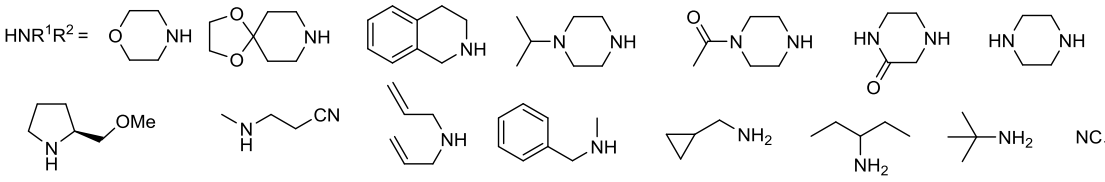


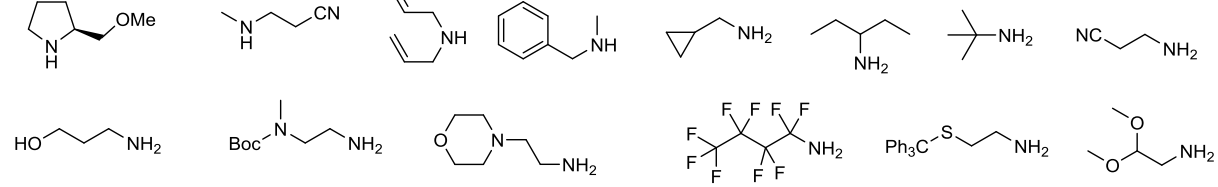
R^1 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OMe, 4-OH, 5-OMe, 6-OMe
$R^2(H)R^2NH$ = thiomorpholine, morpholine, piperidine, isoindole, *N*-Cbz-piperidine, *N*-Boc-piperidine, *N*-CO_2Et-piperidine, *N*-(4-methoxyphenyl)piperidine, *N*-cinnamylpiperazine, dibenzylamine, *N*-methylbenzylamine, aniline, 4-fluoroaniline, 4-*t*Bu-aniline, 3,5-dimethylaniline

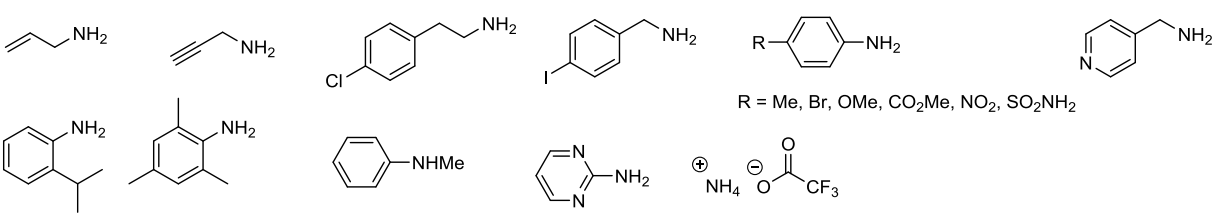
Scheme **42**,



HNR^{1}R^2 =

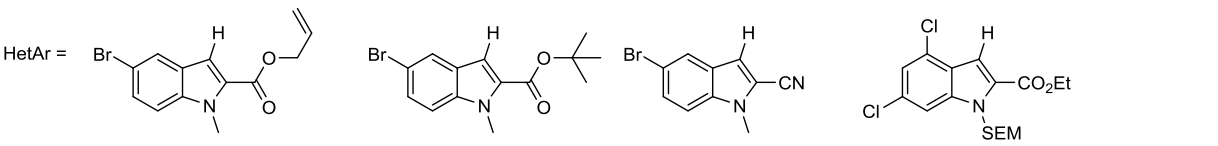


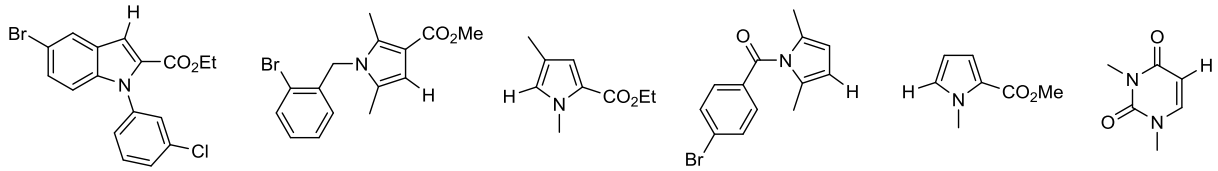


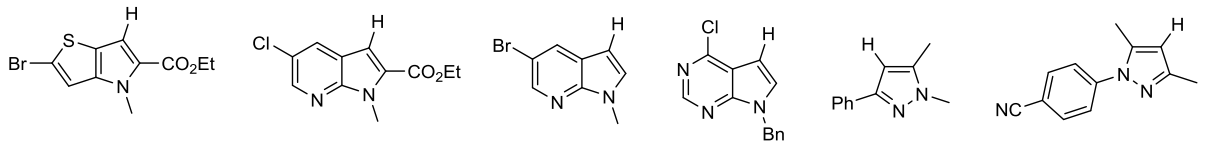


R = Me, Br, OMe, CO_2Me, NO_2, SO_2NH_2

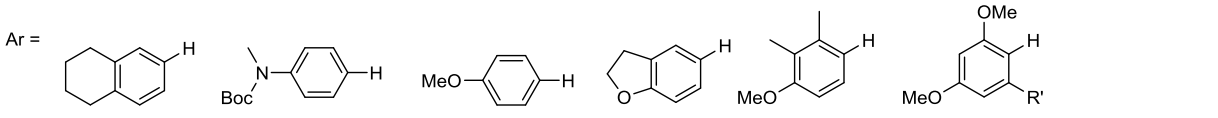
HetAr =



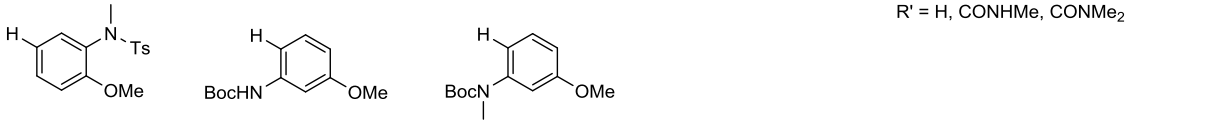




Ar =

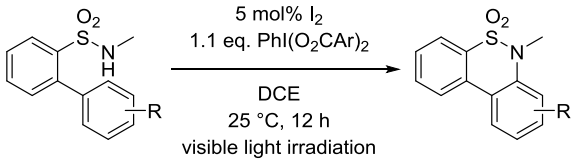


R' = H, CONHMe, $CONMe_2$



Scheme **43**).

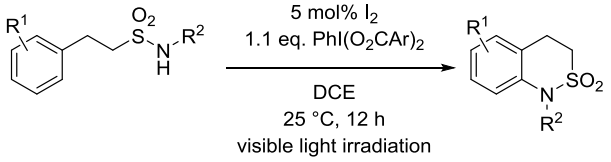
A



80-99%

R = H, 4-Me, 4-*t*-Bu, 4-Ph, 4-OMe, 4-OPh, 4-OEt, 4-Cl, 4-F, 4-CF_3, 4-CH_2Br, 2-Me
Ar = 3-ClC_6H_4

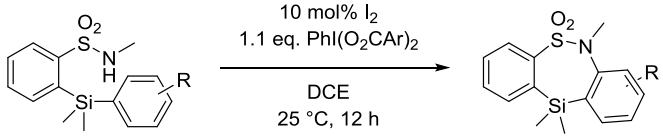
B



51-99%

R^1 = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-Ph
R^2 = Me, Bn, Et
Ar = 3-ClC_6H_4

C



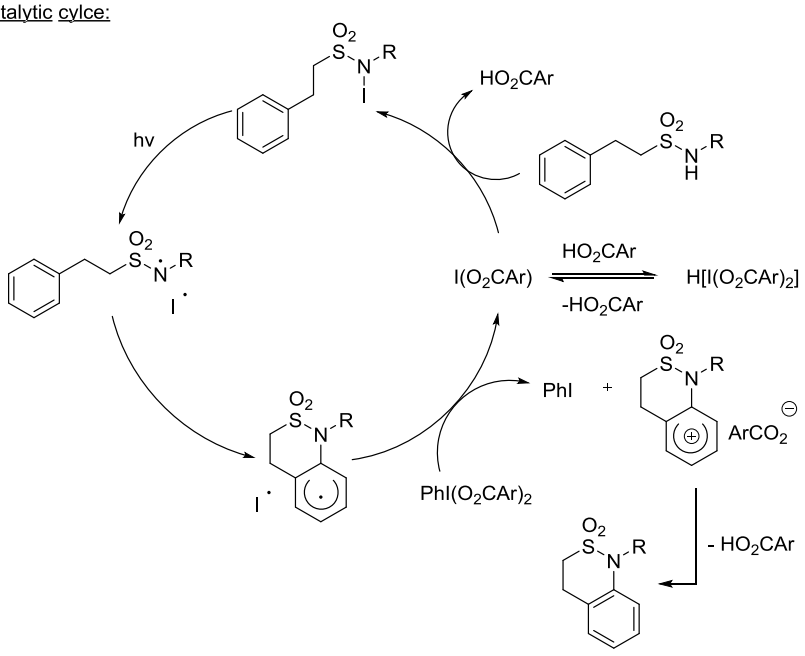
40-80%

R = H, 4-Me, 4-OMe, 4-F, 4-Cl
Ar = 3-ClC_6H_4

Catalyst formation:

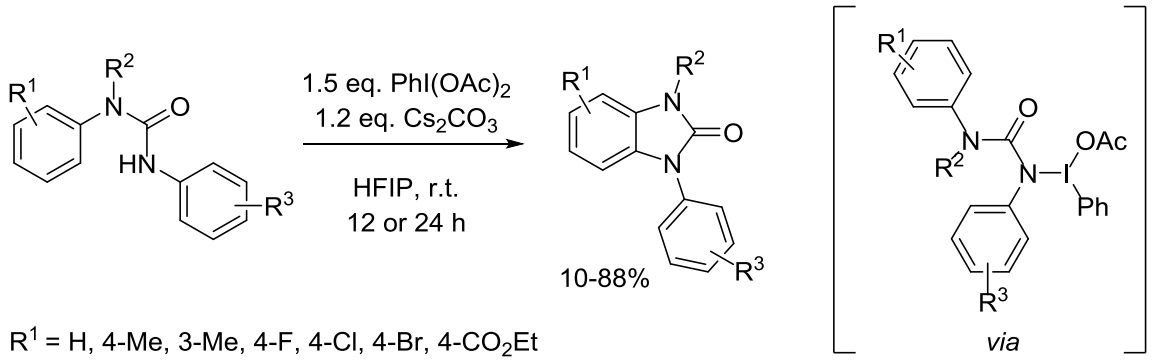
$I_2 + PhI(O_2CAr)_2 \longrightarrow 2\ I(O_2CAr) + PhI$

Catalytic cylce:



Scheme 11: Iodine catalyzed direct oxidative C-H amination under visible light.

A recent example of the use of $PhI(OAc)_2$ in direct oxidative amination is the synthesis of 1,3-dihydro-2*H*-benzimidazol-2-one derivatives from *N*,*N*´-diarylurea (Scheme 12).[66] Although the product was formed in a variety of solvents (DCM, ACN, TFA), the reaction proceeded better in fluorinated solvents such as TFE and HFIP. A higher reactivity was observed with electron donating substituents in the arenes. Mechanistically, the authors propose that the reaction proceeds via reaction of the urea NH with $PhI(OAc)_2$, replacing an acetate with concomitant loss of acetic acid, to give an *N*-activated species. Intramolecular electrophilic substitution leads to the reaction product.



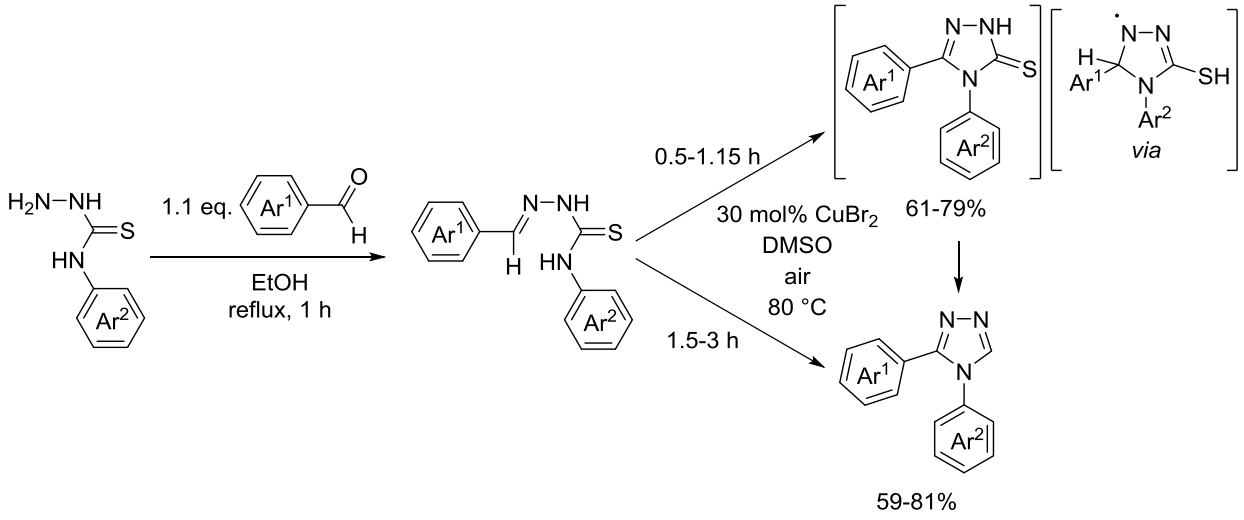
R^1 = H, 4-Me, 3-Me, 4-F, 4-Cl, 4-Br, 4-CO_2Et
R^2 = Me, Et, iPr, *n*-Bu, *n*-pentyl, Cy, allyl, Bn, Ph
R^3 = H, 4-Me, 3-Me, 2-Me, 4-F, 4-Cl, 3-Cl, 2-Cl, 4-Br, 4-CF_3, 3-CO_2Et

Scheme 12: Synthesis of 1,3-dihydro-2*H*-benzimidazol-2-ones.

2.1.2 C-H bonds of imines and alkenes

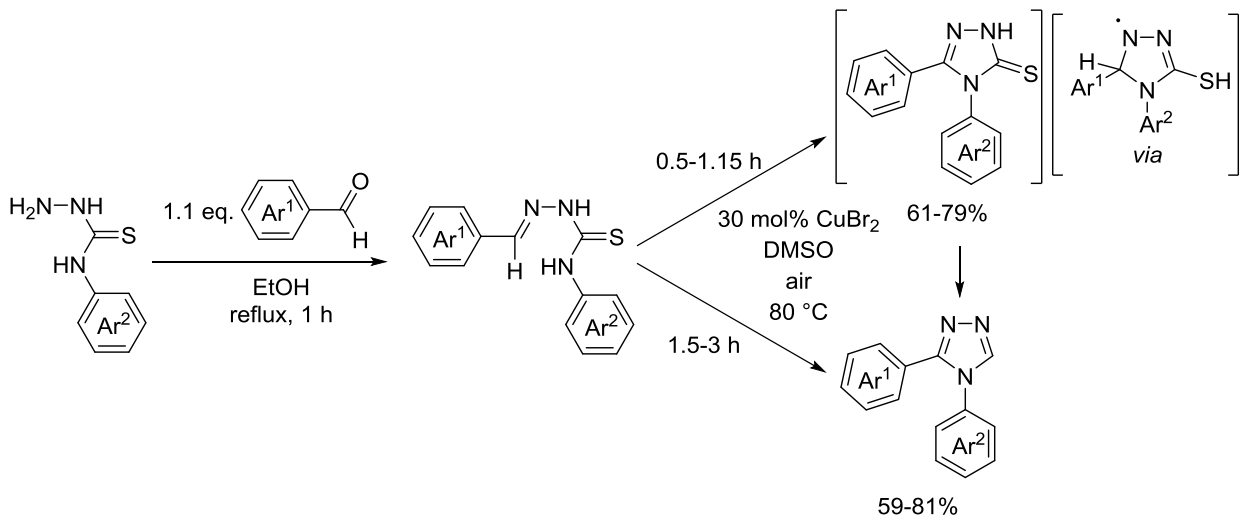
The target heterocycle does not need to be a bicyclic system as an acyclic molecule can also cyclize making use of such technology. Although many disconnections towards azine and azole type systems are known in classical heterocyclic chemistry the integration of this new synthetic methodology lags behind. Patel reported the synthesis of 1,2,4-triazoles starting from

arylidenearylthiosemicarbazides (



Ar^1 = Ph, 4-MeOPh, 4-MePh, 3-BrPh, 4-ClPh, 3,4-diMeOPh, 4-FPh, 4-*n*-BuOPh, 3-ClPh, 4-BrPh, 2-furanyl
Ar^2 = Ph, 4-MePh, 2-MeOPh, 4-*n*-BuPh, 3,4-diMePh, 4-BrPh, 4-ClPh

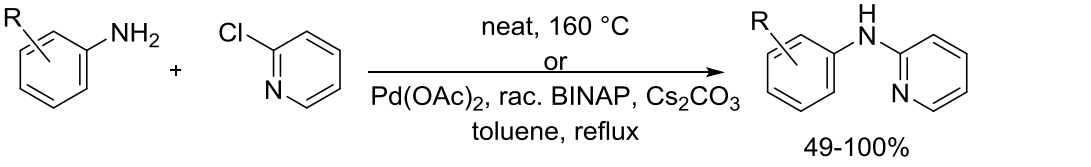
Scheme **13**).[67] The reaction is believed to go via a Cu^{I}/Cu^{II} catalytic cycle. The mechanism proceeds via a five-membered bidentate complex of Cu(II) with the imine nitrogen and the thiourea sulphur. A single electron transfer from the imine nitrogen reduces copper to Cu(I). Cyclization of the resulting radical iminium cation liberates Cu(I) which is re-oxidized to Cu(II) by air. The intermediate loses a hydrogen radical with formation of the cyclized thiosemicarbazone. Interestingly, the direct oxidative amination was followed by *in situ* desulfurization of initially formed 4,5-diaryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione when using a longer reaction time. The exact mechanism of the loss of sulphur is not clear but the hydrogen is not originating from the solvent. Interestingly, the reaction favors C-N bond formation over C-S bond formation. Only for sterically encumbered substrates 1,3,4-thiadiazole formation occurred. This was the case when any one of the aryl rings was *ortho*-disubstituted (Cl or Me group). Another possibility is 2-hydrazinobenzothiazole formation which has not been discussed in the article.

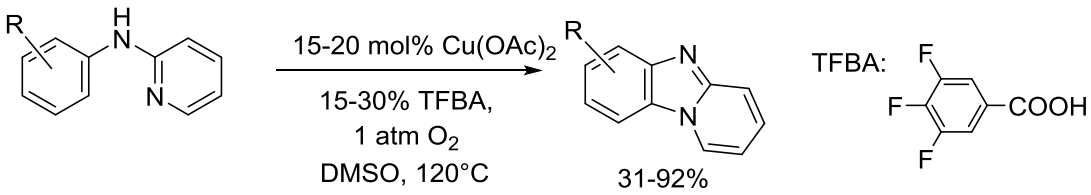


Ar^1 = Ph, 4-MeOPh, 4-MePh, 3-BrPh, 4-ClPh, 3,4-diMeOPh, 4-FPh, 4-*n*-BuOPh, 3-ClPh, 4-BrPh, 2-furanyl
Ar^2 = Ph, 4-MePh, 2-MeOPh, 4-*n*-BuPh, 3,4-diMePh, 4-BrPh, 4-ClPh

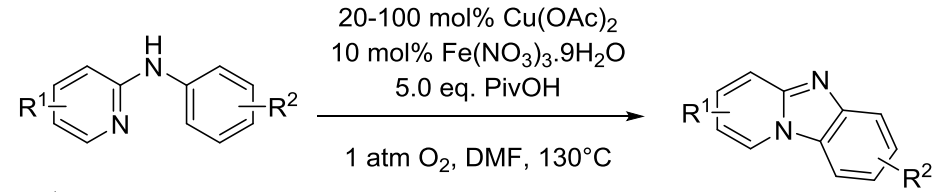
Scheme 13: Synthesis of 1,2,4-triazoles.

Two years after Maes reported the pyrido[1,2-*a*]benzimidazole synthesis (





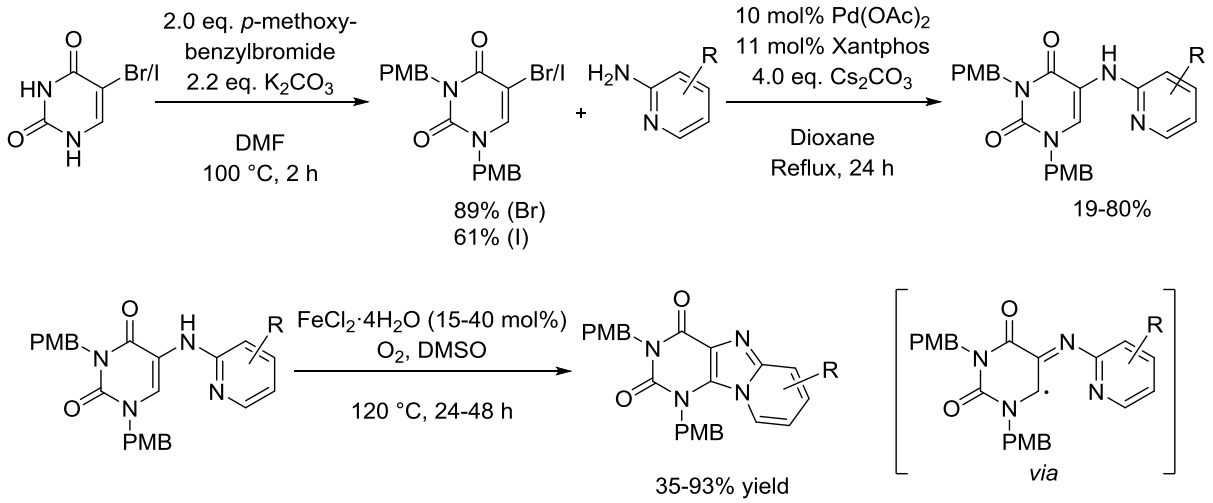
R = 4-CF_3, 6-F, 7-F, 9-F, 8-F, 6-OMe, 7-OMe, 9-OMe, 8-OMe, 8-Cl, 8-CO_2Et, 7-CO_2Et, 8-CF_3, 6-Cl, (2-Cl, 5-OMe), 2-Cl, 2,6-diCl, (2-Cl, 3-F)



R^1 = H, 4-Me, 4-OMe, 4-^{t}Bu, 4-F, 4-Cl, 4-Br, 2-Me, 2-OMe, 2-F
R^2 = H, 3-Me, 3-OMe, 3-Cl, 3-F, 4-Me

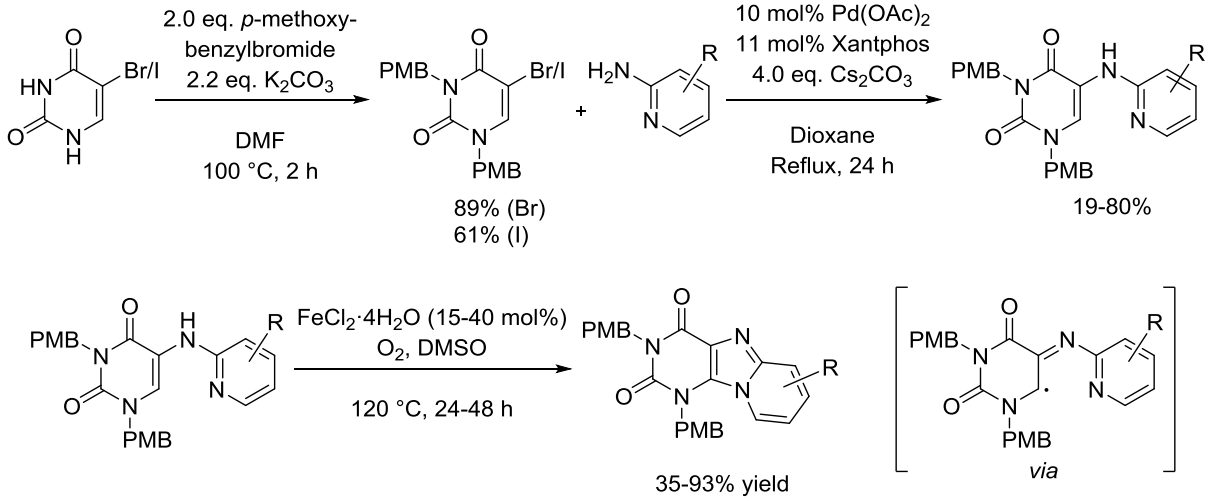
Scheme **4**), a similar ring closure reaction on the alkene moiety of a heterocyclic core rather than on an arene was published. In this way C8-N9 pyrido annulated purines could be obtained

using $FeCl_2.4H_2O$ as a catalyst (



R = 3-Me, 4-Me, 5-Me, 6-Me, 3-OMe, 4-OMe, 5-OMe, 3-Br, 4-Br, 5-Br, 6-Br, 4-Cl, 5-Cl, 5-CF_3, 4-CO_2Me, 5-CO_2Me, 3-Et, 3-Ph, isoquinolin-1-yl

Scheme **14**) Oxygen could again be used as the sole oxidant.



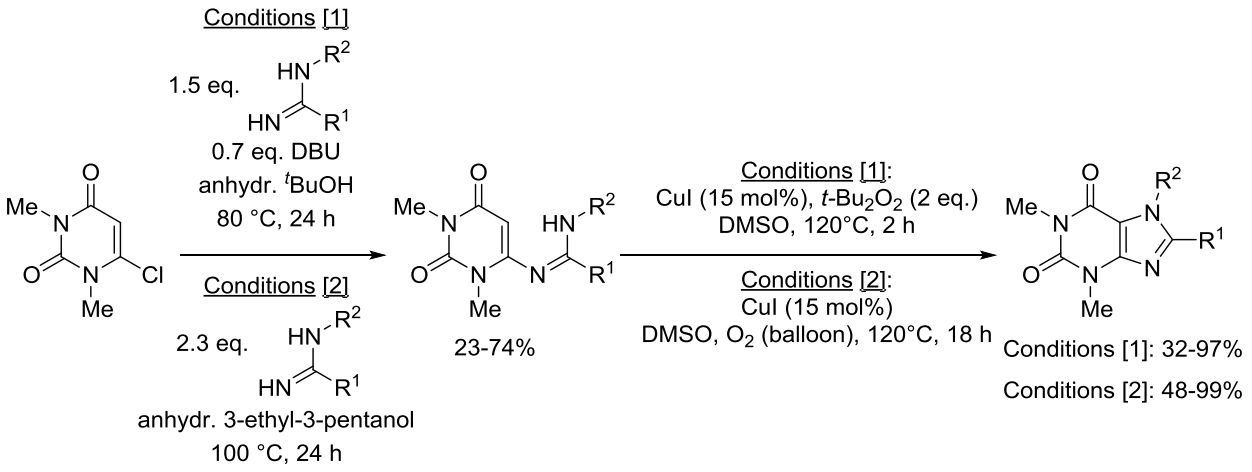
R = 3-Me, 4-Me, 5-Me, 6-Me, 3-OMe, 4-OMe, 5-OMe, 3-Br, 4-Br, 5-Br, 6-Br, 4-Cl, 5-Cl, 5-CF_3, 4-CO_2Me, 5-CO_2Me, 3-Et, 3-Ph, isoquinolin-1-yl

Scheme 14: Synthesis of C8-N9 pyrido annulated purines.

For this reaction, a radical mechanism was suggested based on KIE, effect of radical inhibitors on the reaction rate and experiments in the absence of oxygen revealing the number of iron atoms involved in the catalytic cycle. Loss of a proton on nitrogen and oxidation by Fe(III) leads to a free radical species which can be converted into a cation by a second one electron oxidation using Fe(III). This cation can undergo ring closure via nitrogen addition and

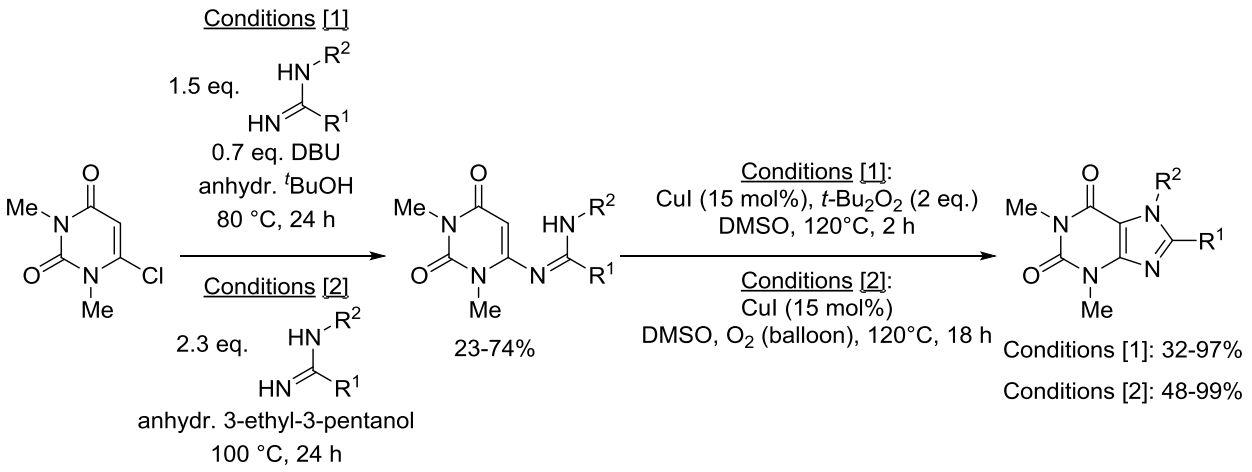
subsequent aromatization by the loss of a proton. The formed Fe(II) can be reoxidized to Fe(III) by oxygen.

The nitrogen atom involved in the cyclization does not need to belong to a heteroaromatic system as disclosed by the same group. Cu-catalyzed direct oxidative amination of *N*-uracil amidines for instance yielded xanthines (



R^1 = Ph, 4-MePh, 2-MePh, 3-MePh, 4-MeOPh, 4-IPh, 4-CF_3Ph, 3-thiophenyl, Cy, ^{n}Pr, Bn, Et, ^{t}Bu
R^2 = Bn, ^{n}Pr, ^{i}Pr, Cy, H

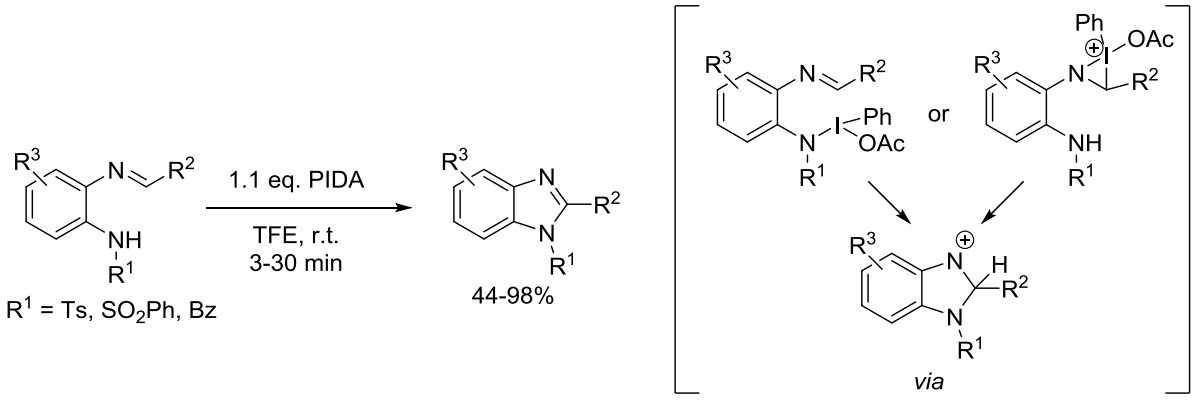
Scheme 15).[68] *t*-Bu_2O_2 was found to give the fastest reactions. Although O_2 gave substantially slower reactions it usually gave a higher yield. The substrates could be made via a S_NAE using readily available 6-chlorouracils and *N*-substituted amidines delivering a concise approach towards this biologically important scaffold, classically obtained via Traube synthesis. Mechanistic studies have not been disclosed yet. Interestingly, it was demonstrated that the catalyst does not degrade, but instead can be reused several times which further contributes to the sustainability of the process. When at the end of the reaction new substrate and oxidant were added the new substrate fully converted. This procedure was repeated up to 4 times without decline in yield and was possible with both oxidants. Both the use of sustainable oxidants as well as the reuse of catalyst make this process very interesting from a green chemistry point of view.



R^1 = Ph, 4-MePh, 2-MePh, 3-MePh, 4-MeOPh, 4-IPh, 4-CF_3Ph, 3-thiophenyl, Cy, ^{n}Pr, Bn, Et, ^{t}Bu
R^2 = Bn, ^{n}Pr, ^{i}Pr, Cy, H

Scheme 15: Synthesis of xanthines.

The direct oxidative amination can also occur in between two ortho positioned substituents placed on the core. It then does not really possess obvious advantages to classical synthetic approaches. 1*H*-Benzimidazole synthesis starting from the imine of an *N*-substituted phenylenediamine is such a reported example based on stoichiometric oxidant only (

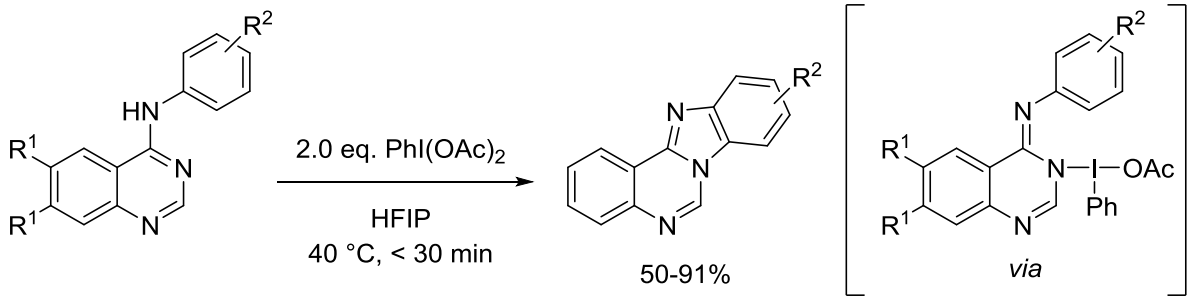


R^1 = Ts, SO_2Ph, Bz

R^2 = 2-bromophenyl, 2-methylphenyl, 4-isopropylphenyl, 3-bromo, 4-methoxyphenyl, 4-fluorophenyl, (3-bromo-5-cyano-2,4,6-trimethylphenyl), (3,5-dicyano-2,4,6-trimethylphenyl), 4-methoxyphenyl, 2,4,6-trimethylphenyl, 2-bromo-5-fluorophenyl, 2,4-dimethoxy-6-methylphenyl, 4-cyanophenyl, 2,3,4,5,6-pentafluorophenyl, 3-chlorophenyl, 9-anthracenyl, 2-pyridyl, 1-naphthyl, 1-pyrenyl, 2-chloro-6-methoxyquinolin-2-yl, 5-nitrofuran-2-yl, cyclohexyl, H, $CH_2CH(CH_3)$Ph, Me, 4-ethylphenyl, 2-nitrophenyl, 2-fluorophenyl, 4-bromophenyl, 2-thiophenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl
R^3 = H, 5-NO_2, 5-CO_2H, 4,5-diBr, 4,5-diCl, 4,5-diMe

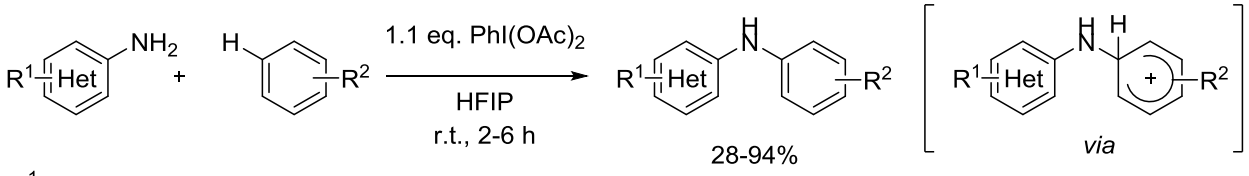
Scheme **16**).[69] TFE, which is a polar and non-nucleophilic solvent was found to be the best solvent for the reaction. Because of their unique properties, fluorinated alcohols are often used as solvent in reactions involving hypervalent iodine compounds as also reveals from other

reactions with PIDA described in this review (

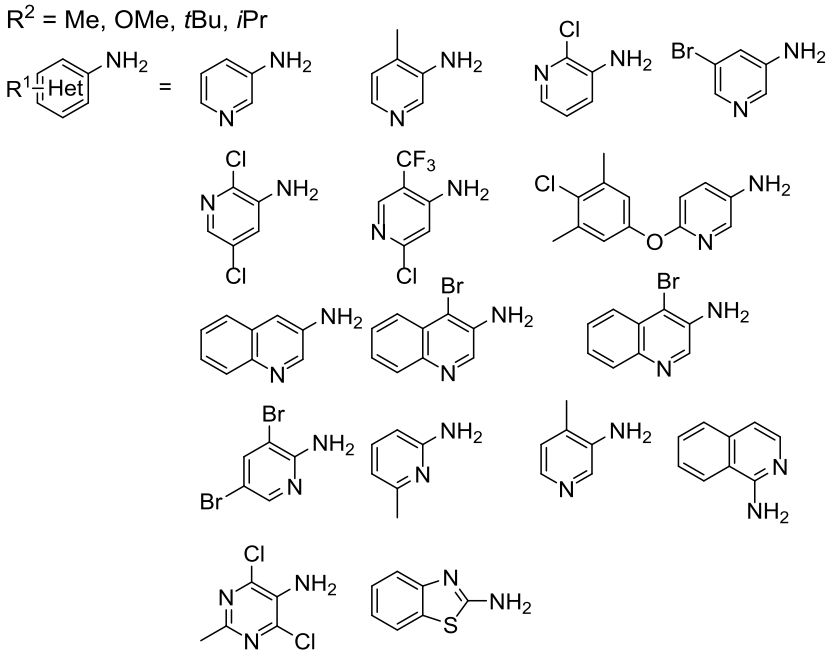


R^1 = H, $MeOCH_2CH_2O$
R^2 = H,4-Me, 4-MeO, 4-EtO,4-F,4-Br, 4-I, 4-CF_3, 4-Ac, 3-Cl, 3-MeO, 3-ethynyl, 2,5-diMeO

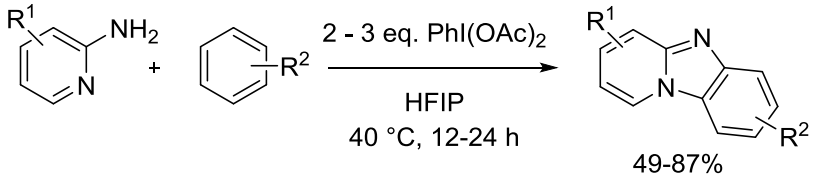
Scheme **10**,



R^1 = H, Me, Br, Cl, CF_3
R^2 = Me, OMe, *t*Bu, *i*Pr



Scheme **40**,



R^1 = H, 2-Br, 4-Br, 5-Br, 6-Br, 2-Me, 4-Me, 5-Me, 6-Me, 5-F, 4-OAc
ArR^2 = anisole, diphenylether, *m*-xylene, *p*-xylene, 1-methylnapthalene, 2,3-diisopropylbenzene, 1-ethyl-3-methylbenzene, toluene, 1,2,3,4-tetrahydronapthalene, iodobenzene, 2-(3-methoxyphenyl)acetonitrile

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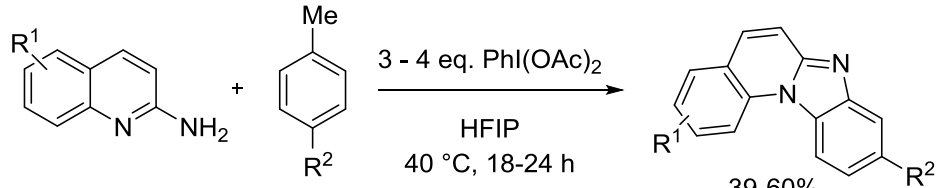
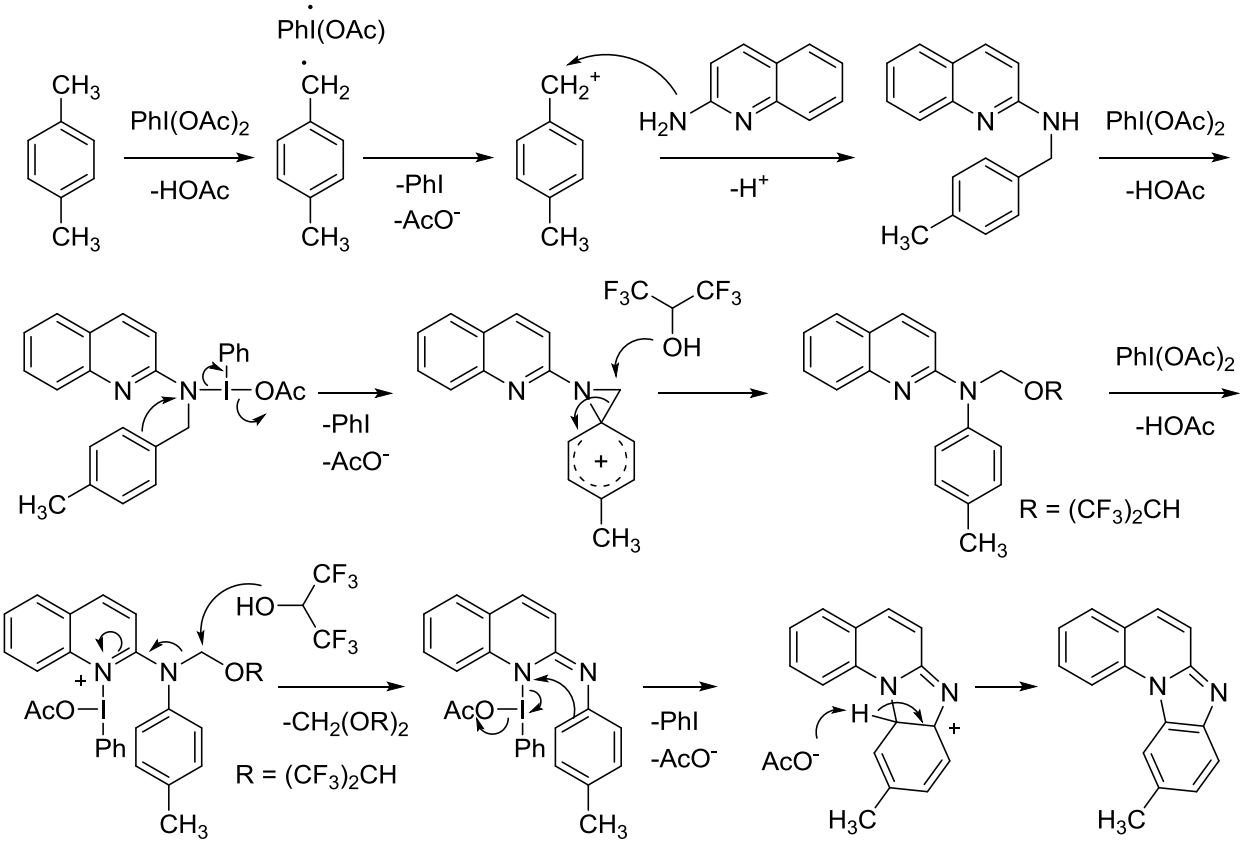
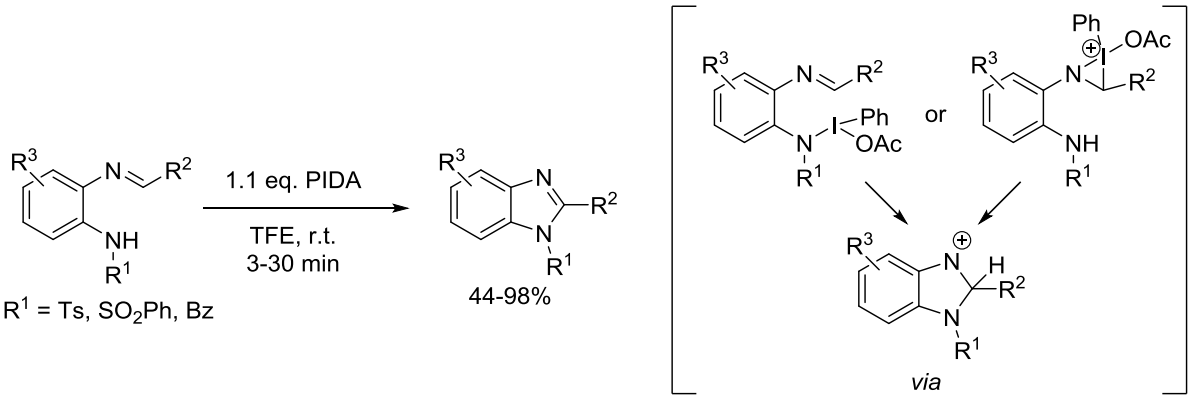


R^1 = H, 5,7-diMe, 6-F, 4-Me, 4-Ph
R^2 = Me, I



Scheme **41**).[70] Two different reaction pathways were proposed, depending whether $PhI(OAc)_2$ reacts with the amine or imine functional group. In case of reaction with the amine group, a N-I species is formed. Nucleophilic attack of the imine on the nitrogen of the N-I species leads to a

partly saturated cyclized cation which aromatizes upon deprotonation. When PhI(OAc) reacts first with the imine, a tricyclic iodonium cation is formed. Ring opening via intramolecular nucleophilic attack of the amine leads to the same cyclized cation.



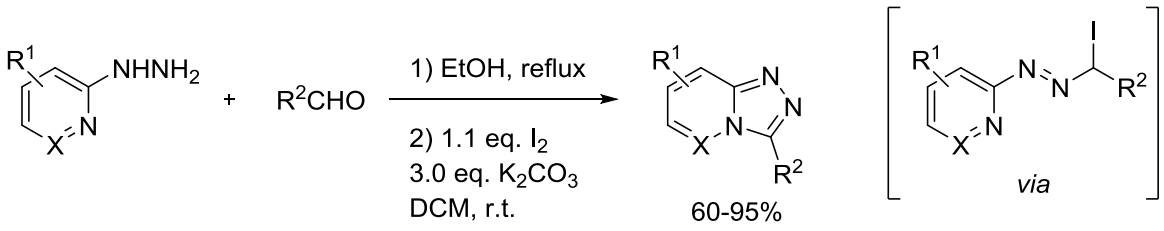
R^1 = Ts, SO_2Ph, Bz

R^2 = 2-bromophenyl, 2-methylphenyl, 4-isopropylphenyl, 3-bromo, 4-methoxyphenyl, 4-fluorophenyl, (3-bromo-5-cyano-2,4,6-trimethylphenyl), (3,5-dicyano-2,4,6-trimethylphenyl), 4-methoxyphenyl, 2,4,6-trimethylphenyl, 2-bromo-5-fluorophenyl, 2,4-dimethoxy-6-methylphenyl, 4-cyanophenyl, 2,3,4,5,6-pentafluorophenyl, 3-chlorophenyl, 9-anthracenyl, 2-pyridyl, 1-naphthyl, 1-pyrenyl, 2-chloro-6-methoxyquinolin-2-yl, 5-nitrofuran-2-yl, cyclohexyl, H, $CH_2CH(CH_3)Ph$, Me, 4-ethylphenyl, 2-nitrophenyl, 2-fluorophenyl, 4-bromophenyl, 2-thiophenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl

R^3 = H, 5-NO_2, 5-CO_2H, 4,5-diBr, 4,5-diCl, 4,5-diMe

Scheme 16: Synthesis of 1*H*-benzimidazoles.

Chang developed the synthesis of 1,2,4-triazolo[4,3-*a*]pyridines based on the iodine mediated ring closure of the hydrazones of 2-pyridinehydrazines and benzaldehydes (

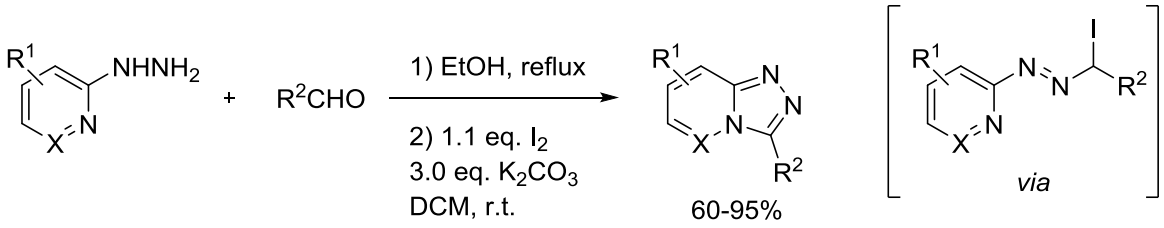


R^1 = H, 5-Me, 3-Cl, 5-CN, 5-CF_3, 6-SMe

R^2 = Aromatic: Ph, 4-MePh, 4-MeOPh, 4-HOPh, 2-FPh, 2-ClPh, 4-ClPh, 3-F_3CPh, 4-CNPh, 4-NO_2Ph, (3,4-diMeOPh), (2,4-diClPh), (2,4,6-triMePh), 1-naphthyl, 2-pyridinyl, 2-furanyl
Aliphatic: Pr, *i*-Pr, *t*-Bu, H, *trans* CH=CHPh, *trans* CH=CHMe

X = CH, N

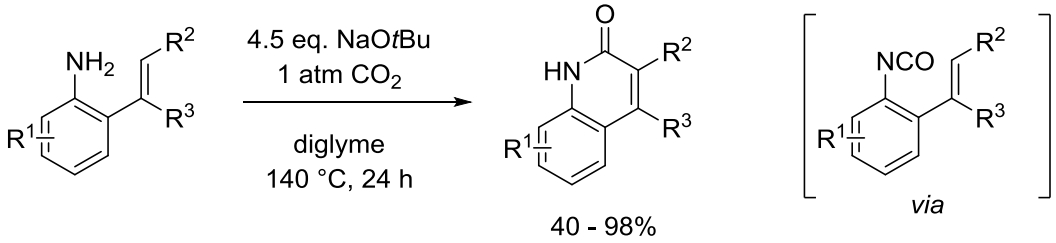
Scheme **17**).[71] The proposed mechanism goes via base promoted iodination of the hydrazonic carbon followed by a SN_2 cyclization.



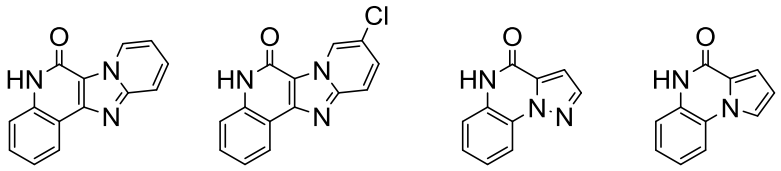
R^1 = H, 5-Me, 3-Cl, 5-CN, 5-CF_3, 6-SMe
R^2 = Aromatic: Ph, 4-MePh, 4-MeOPh, 4-HOPh, 2-FPh, 2-ClPh, 4-ClPh, 3-F_3CPh, 4-CNPh, 4-NO_2Ph, (3,4-diMeOPh), (2,4-diClPh), (2,4,6-triMePh), 1-naphthyl, 2-pyridinyl, 2-furanyl
Aliphatic: Pr, *i*-Pr, *t*-Bu, H, *trans* CH=CHPh, *trans* CH=CHMe
X = CH, N

Scheme 17: Synthesis of 1,2,4-triazolo[4,3-*a*]pyridines.

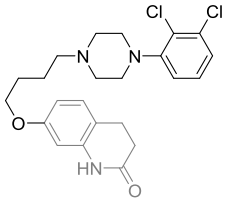
A transition metal free lactamization protocol starting from 2-alkenyl and 2-iminoylanilines using carbon dioxide was published by Yu (



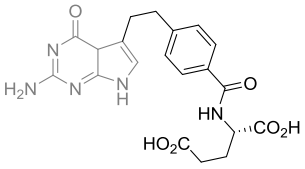
R^1 = H, 6-Me, 4-OMe, 4-CF_3, 4-Cl, 4-Me, 5-Me, 5-OMe, 5-CF_3, 5-Cl, 5-Br
R^2 = H, Me, Et, Ph, 4-MeOPh, 4-FPh, 4-F_3CPh, 4-BrPh, 2-ClPh, 2-FPh
R^3 = H, Me, Ph
Lactamization products of 2-heteroarylanilines:



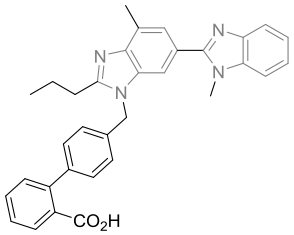
Scheme **18**).[72] They used their method for the synthesis of a key intermediate of Tipifarnib (



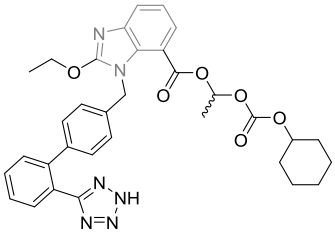
Apriprazole
Brystol-Myers Squibb, Otsuka
Atypical antipsychotic



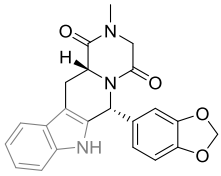
Pemetrexed
Lilly
Folate antimetabolite



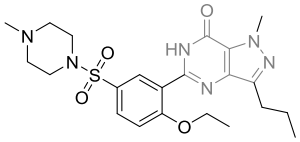
Telmisartan
Boehringer Ingelheim, Astellas
Angiotensin II receptor antagonist



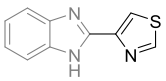
Candesartan Cilexetil
AstraZeneca, Takeda
Angiotensin II receptor antagonist



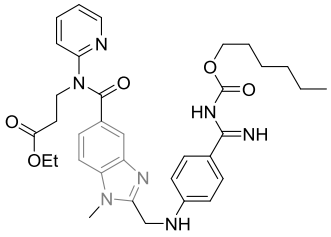
Tadalafil
Lilly
cGMP-specific phospho-diesterase type 5 inhibitor



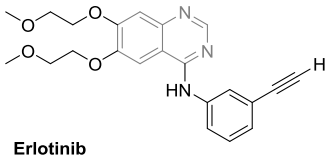
Sildenafil
Pfizer
cGMP-specific phospho-diesterase type 5 inhibitor



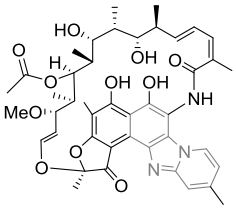
Thiabendazole
Merck
Biocide



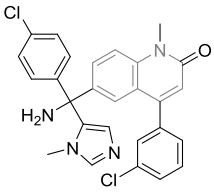
Dabigatran
Boehringer Ingelheim
Direct thrombin inhibitor



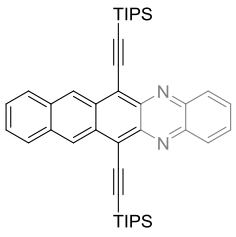
Erlotinib
Genentech, OSI Pharmaceuticals, Roche
Receptor tyrosine kinase inhibitor



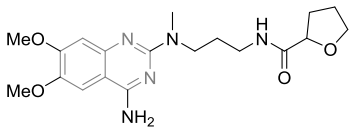
Rifaximin
Salix Pharmaceuticals
Antidiarrhoeal



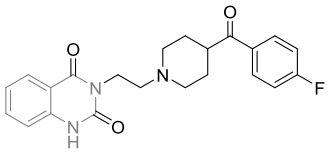
Tipifarnib
Johnson & Johnson
Farnesyltransferase inhibitor



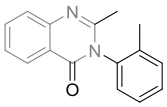
Azapentacene analogue
organic semi-conductor



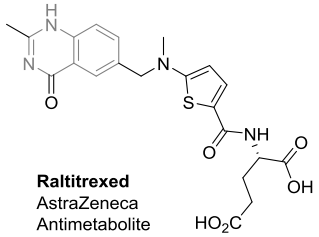
Alfuzosin
Sanofi-Aventis
α_1-receptor antagonist



Ketanserin
Janssen Pharmaceutica
Antihypertensive

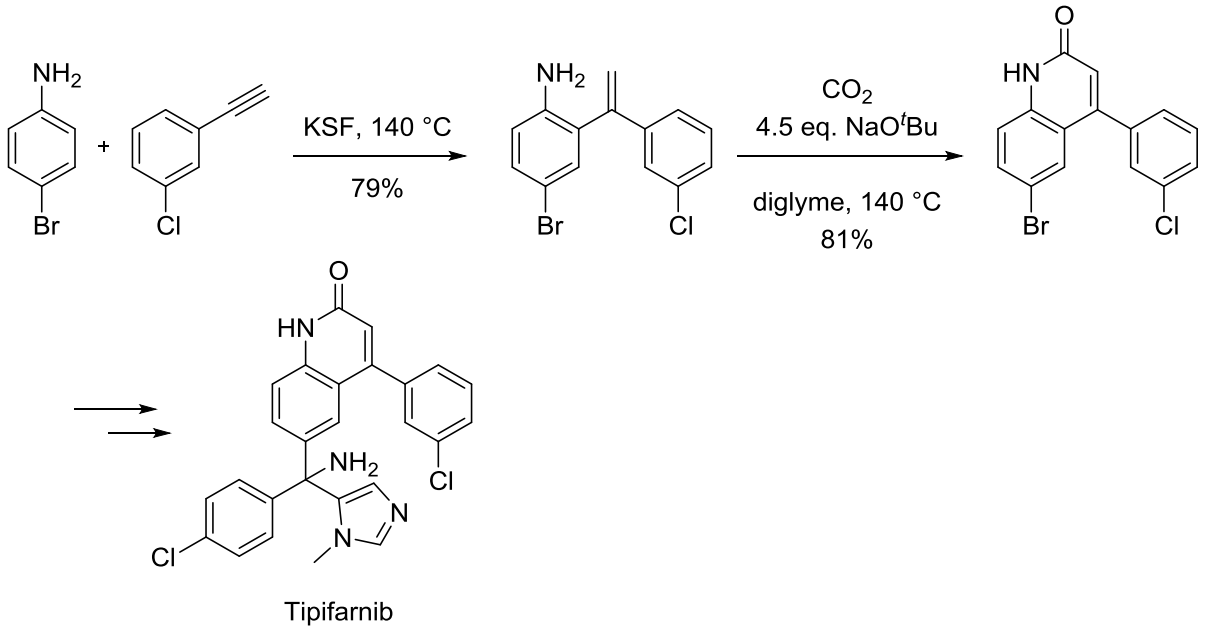


Methaqualone
Roussel Laboratories
Sedative-hypnotic



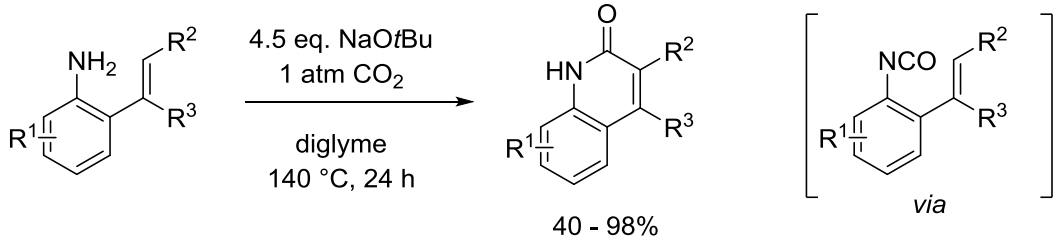
Raltitrexed
AstraZeneca
Antimetabolite

Scheme **2**), a farnesyltransferase inhibitor with activity against leukemia (



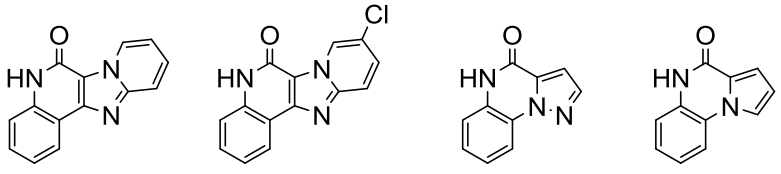
Tipifarnib

Scheme 19). The reaction mechanism proposed goes via an isocyanate which cyclizes irreversibly with formation of the reaction product. This reaction is one of the rare cases in which no oxidant is required to remove 'H_2' from the substrate.

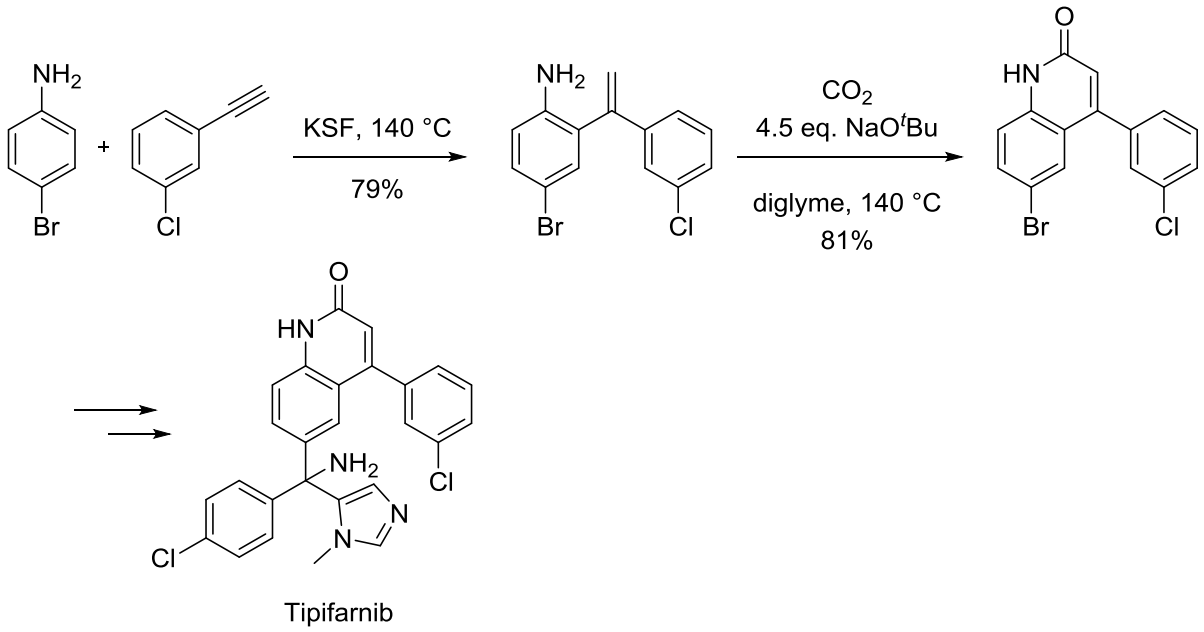


R^1 = H, 6-Me, 4-OMe, 4-CF_3, 4-Cl, 4-Me, 5-Me, 5-OMe, 5-CF_3, 5-Cl, 5-Br
R^2 = H, Me, Et, Ph, 4-MeOPh, 4-FPh, 4-F_3CPh, 4-BrPh, 2-ClPh, 2-FPh
R^3 = H, Me, Ph

Lactamization products of 2-heteroarylanilines:

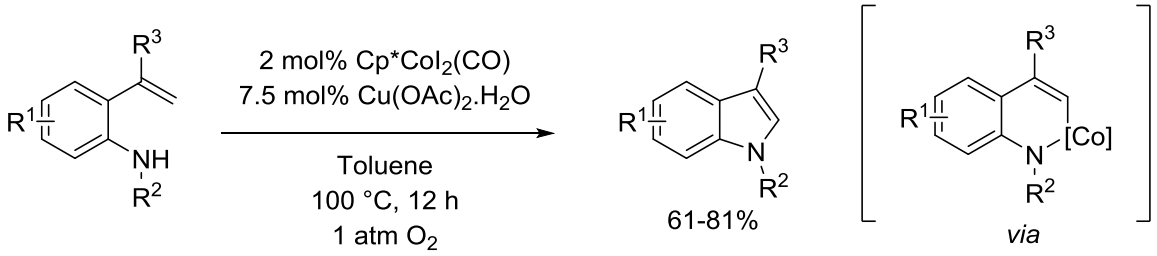


Scheme 18: Synthesis of annulated quinolin-2(1*H*)-ones and quinoxalin-2(1*H*)-one.



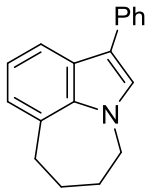
Scheme 19: Synthesis of Tipifarnib.

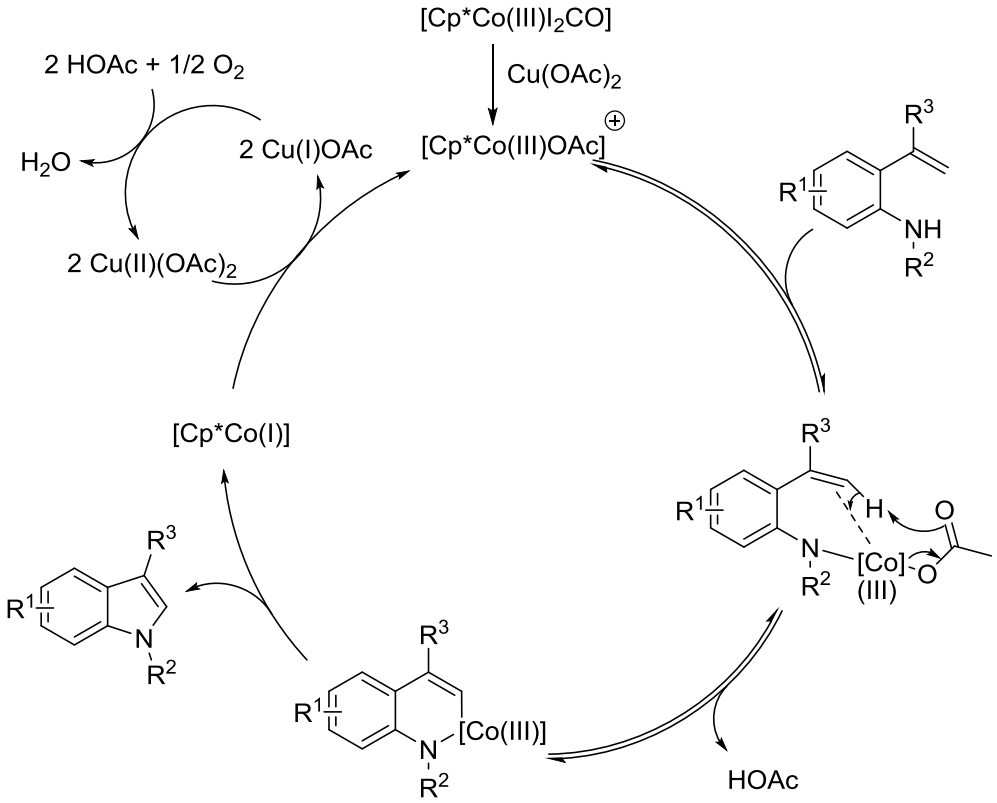
The Co(III) catalyzed synthesis of indoles from *ortho*-alkenylanilines was described by Anbarasan (



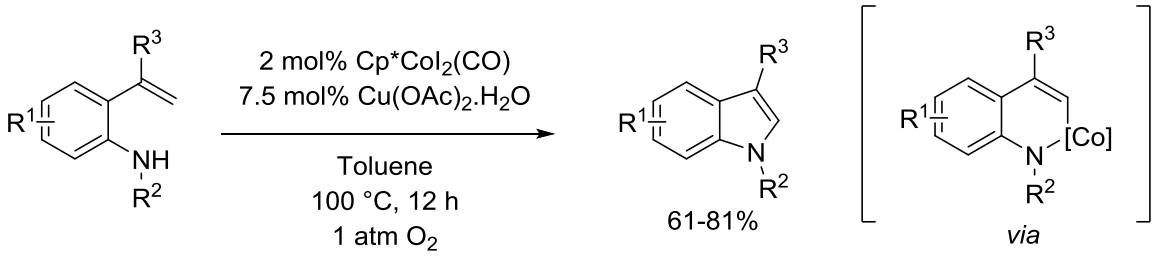
R^1 = H, 4-Me, 4-*t*-Bu, 3,5-diMe, 4-OMe, 4-OBn, 4-OAc, 4-OSi*t*-BuMe_2, 4-F, 4-OTs, 4-CO_2Et
R^2 = Bn, 4-MePh, 4-MeBn, 4-MeOBn, 4-NCBn, $CH_2CH{=}CHPh$ (*E*), CH_2(2-furanyl), CH_2(2-thiophenyl), Me, Et, *i*-Pr, cyclopentyl, cyclohexyl, cycloheptyl
R^3 = Ph, 4-*t*-BuPh, 4-FPh

Other products:



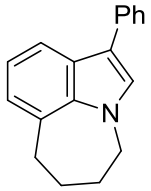


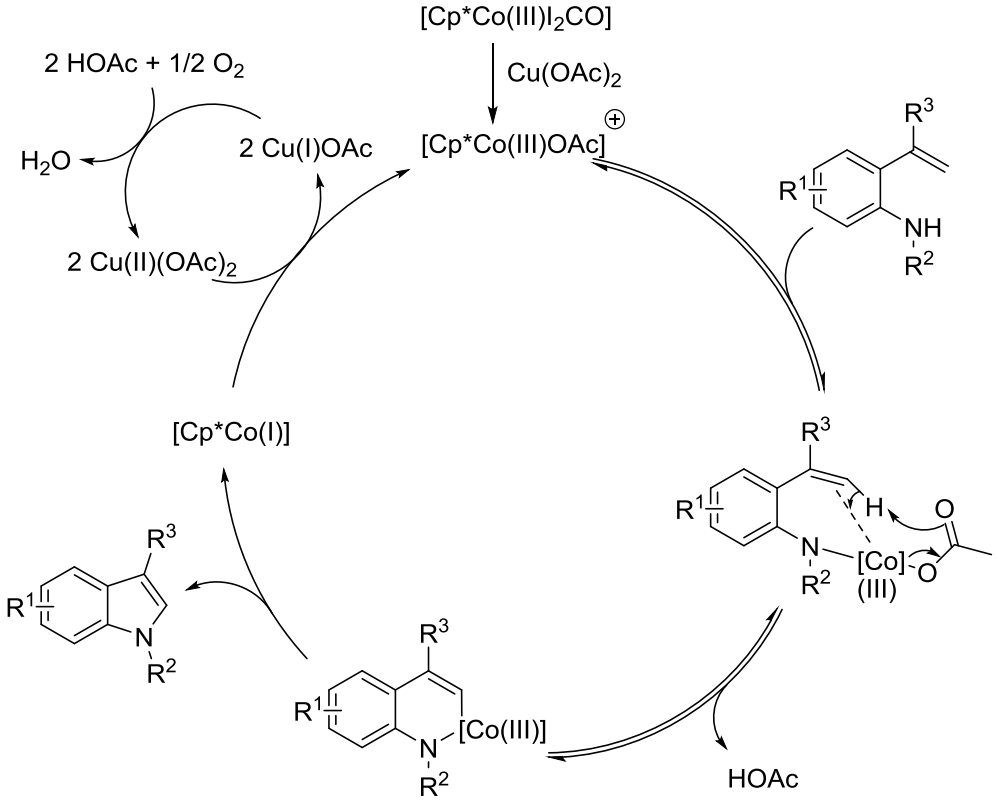
Scheme 20).[73] The mechanism proposed starts with the formation of the catalytically active species. The cobalt atom of this species bounds to the nitrogen of the substrate which is facilitated by a coordination of the vinyl double bond with the metal. Deprotonation of the vinylic proton forms a cyclocobaltated species and acetic acid. Reductive elimination of the cyclocobaltated species leads to the indole. The cobalt catalyst can be reoxidized by 2 equivalents of $Cu(OAc)_2$. The formed CuOAc in turn is reoxidized with oxygen.



R^1 = H, 4-Me, 4-*t*-Bu, 3,5-diMe, 4-OMe, 4-OBn, 4-OAc, 4-OSi*t*-BuMe_2, 4-F, 4-OTs, 4-CO_2Et
R^2 = Bn, 4-MePh, 4-MeBn, 4-MeOBn, 4-NCBn, $CH_2CH{=}CHPh$ (*E*), CH_2(2-furanyl), CH_2(2-thiophenyl), Me, Et, *i*-Pr, cyclopentyl, cyclohexyl, cycloheptyl
R^3 = Ph, 4-*t*-BuPh, 4-FPh

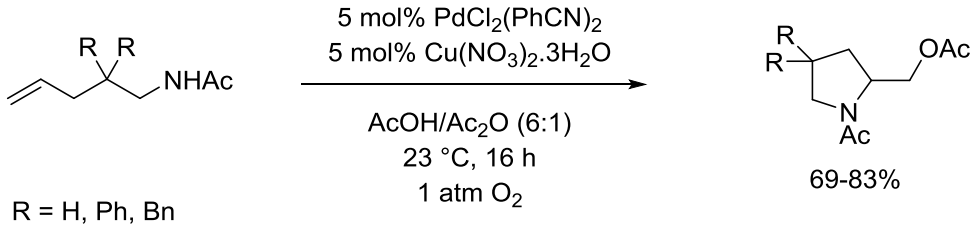
Other products:

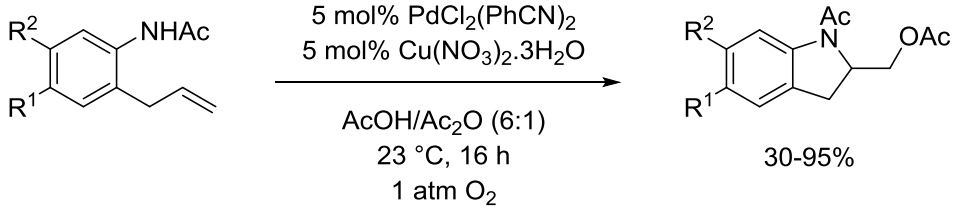




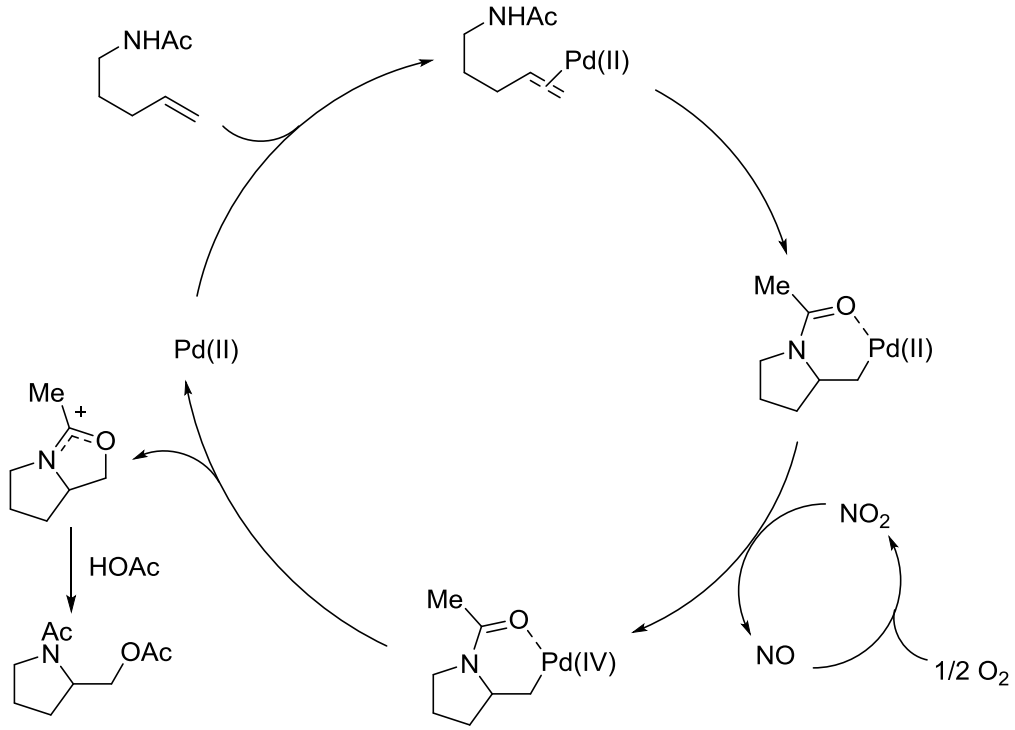
Scheme 20: Synthesis of indoles.

Pyrrolidines and indolines were synthesized using a palladium-catalyzed aminoacetoxylation reaction as described by Stoltz and Grubbs (



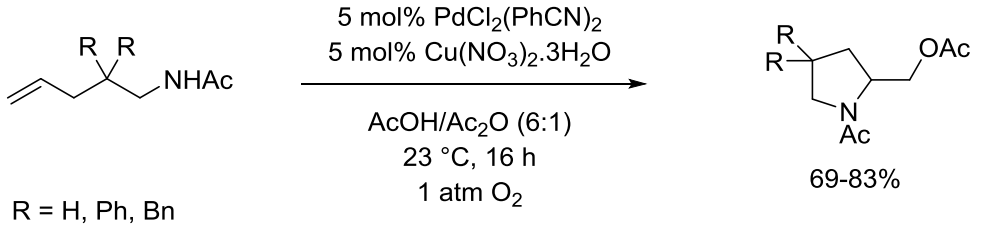


R^1 = H, Me, F, Cl, CO_2Me, CF_3, NO_2, CN
R^2 = H, Me

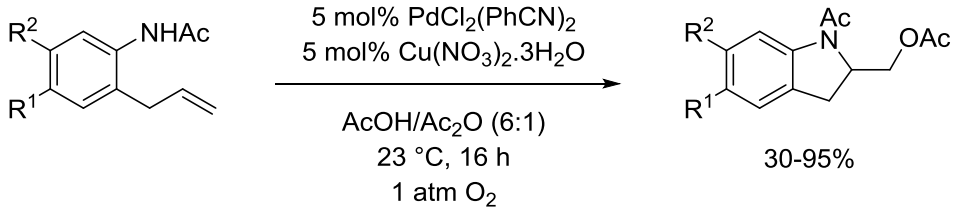


Scheme **21**).[74] Catalytic copper nitrate in combination with oxygen was used to oxidize Pd(II) to Pd(IV). This approach avoids the use of other oxidants such as $PhI(OAc)_2$ or NFSI (*N*-fluorobenzenesulfonimide). The proposed catalytic cycle starts with coordination of the Pd catalyst with the double bond of the alkene. Aminopalladation followed by oxidation of palladium

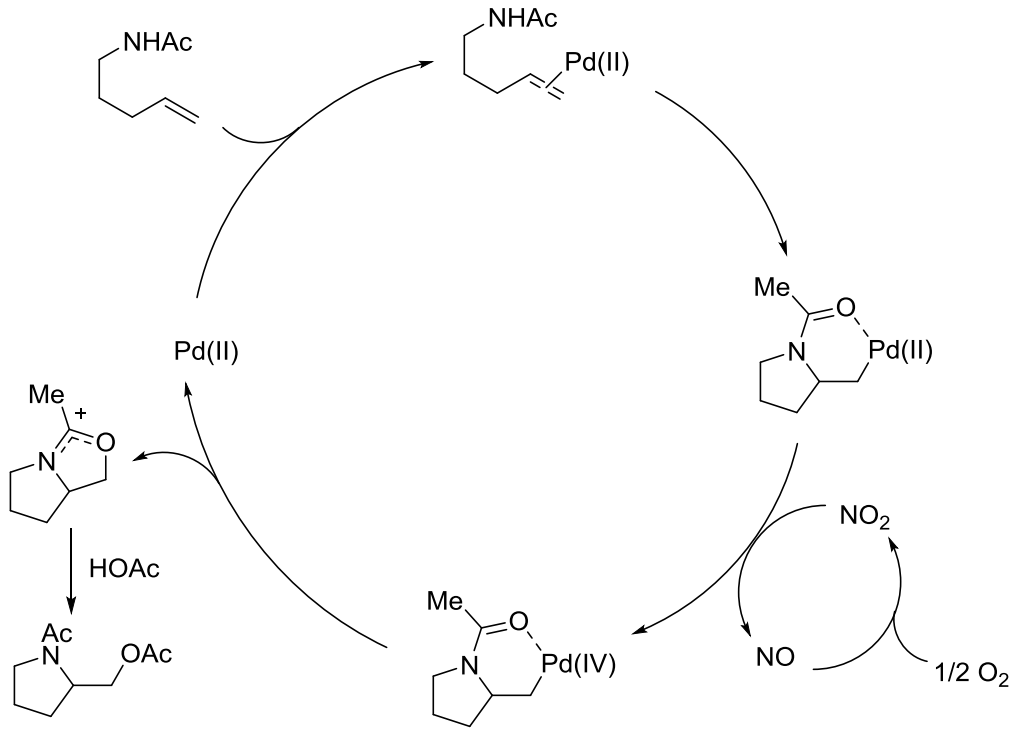
by NO_2 yields a Pd(IV) intermediate. The formed NO can be reoxidized to NO_2 by oxygen. Reductive elimination with C-O bond formation releases a cationic intermediate which forms the reaction product upon acetolysis.



R = H, Ph, Bn



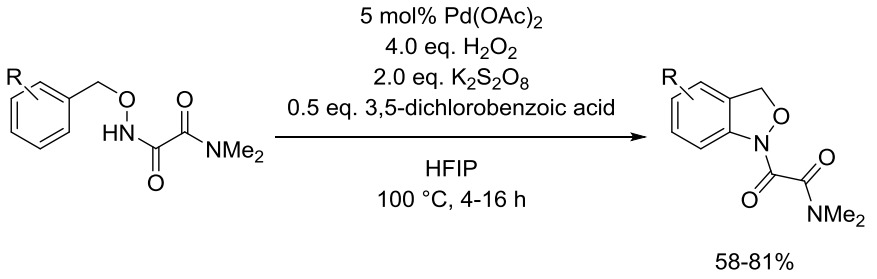
R^1 = H, Me, F, Cl, CO_2Me, CF_3, NO_2, CN
R^2 = H, Me



Scheme 21: Synthesis of pyrrolidines and indolines

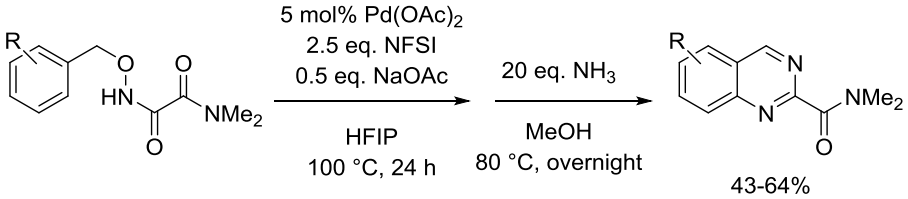
The Pd-catalyzed synthesis of 1,3-dihydrobenzo[*c*]isoxazole derivatives is described by Zhao

A Synthesis of 1,3-dihydrobenzo[*c*]isoxazole derivatives



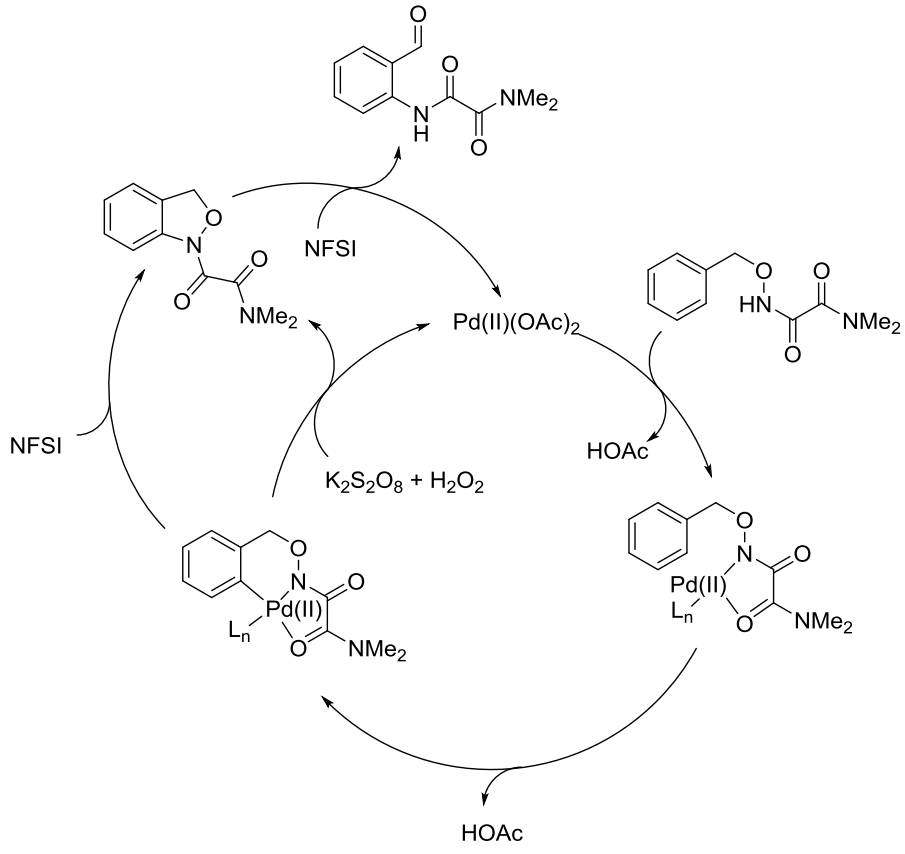
R = 2-F, 2-Cl, 2-Br, 2-Me, 3-Cl, 3-Br, 3-CF_3, 4-Me, 4-F, 4-Cl, 4-Br

B One pot synthesis of quinazolines



R = H, 6-OMe, 7-Cl, 7-Br, 6,7-diCl, 6-Cl

C Proposed catalytic cycle

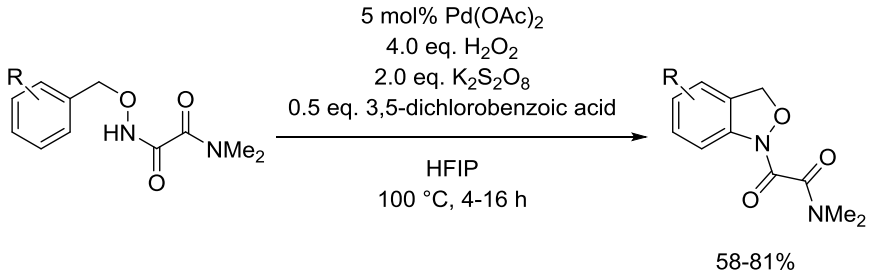


and Zhang (

Scheme **22**, A).[75] Intramolecular Pd-catalyzed amination takes place using a *N*,*N*-dimethyl)oxamoyl amide directing group. Interestingly, the F^+ oxidant NFSI (*N*-fluorobenzenesulfonimide) used could further react with the initial 1,3-dihydrobenzo[*c*]isoxazole reaction product, forming the corresponding 2-aminobenzaldehydes. These can react with

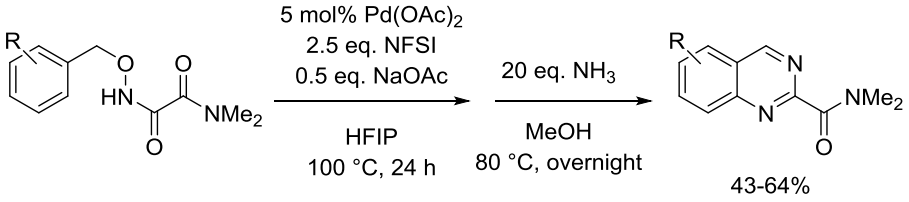
ammonia to form quinazolines in a one-pot reaction (

A Synthesis of 1,3-dihydrobenzo[*c*]isoxazole derivatives



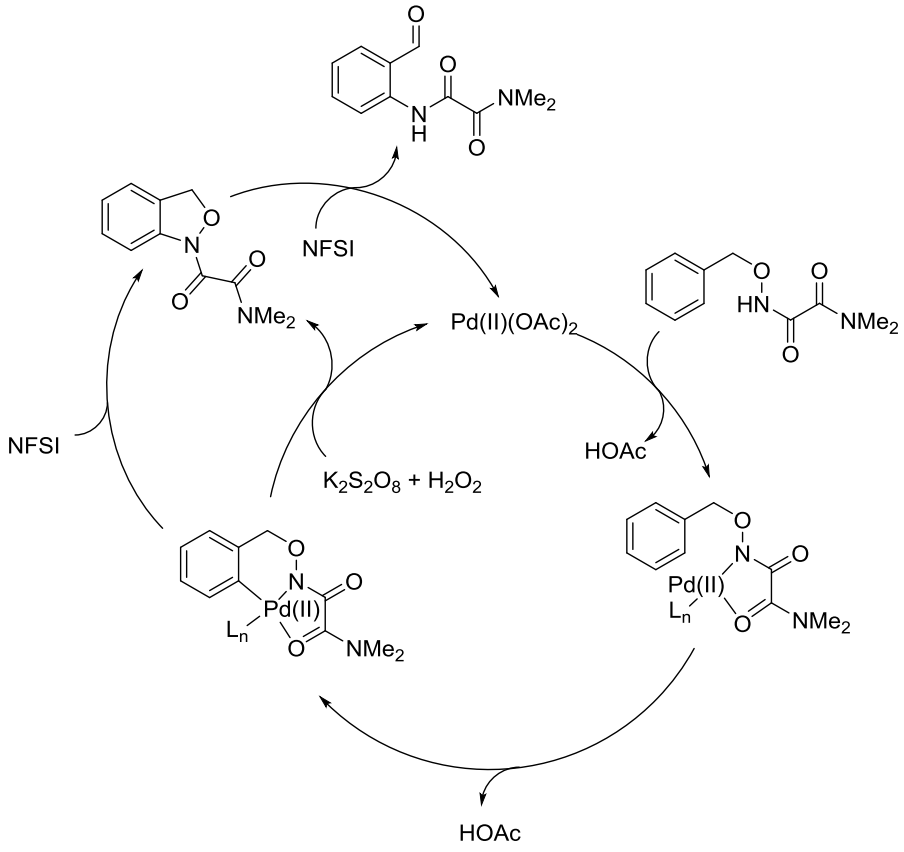
R = 2-F, 2-Cl, 2-Br, 2-Me, 3-Cl, 3-Br, 3-CF_3, 4-Me, 4-F, 4-Cl, 4-Br

B One pot synthesis of quinazolines



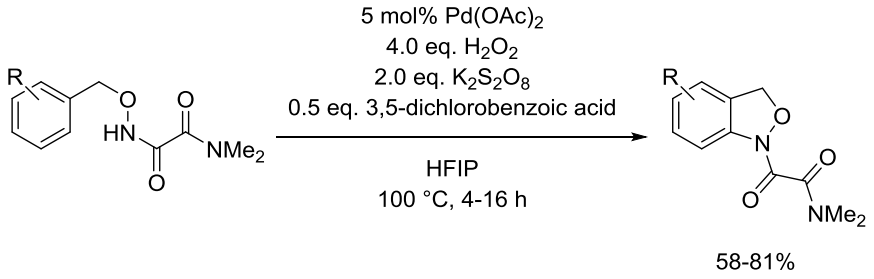
R = H, 6-OMe, 7-Cl, 7-Br, 6,7-diCl, 6-Cl

C Proposed catalytic cycle



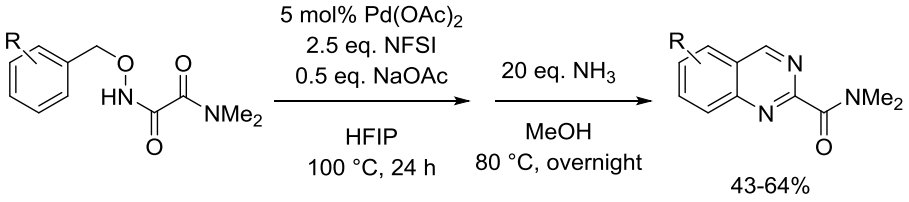
Scheme **22**, B). Reaction of $Pd(OAc)_2$ with the nitrogen of the carboxamide forms a Pd-N bond with loss of acetic acid. No comments were made on the exact mechanism of the C-H activation. Subsequent loss of acetic acid yields the intermediate palladacycle which can either undergo reductive elimination with formation of the heterocyclic reaction product – in this case potassium peroxodisulfate and hydrogen peroxide reoxidize Pd(0) – or, when NFSI is present, Pd(II) can be oxidized to Pd(IV) and after reductive elimination form the dihydrobenzoisoxazole which concomitantly liberates Pd(II). Subsequent oxidation reaction with NFSI opens the ring yielding 2-aminobenzaldehydes.

A Synthesis of 1,3-dihydrobenzo[*c*]isoxazole derivatives



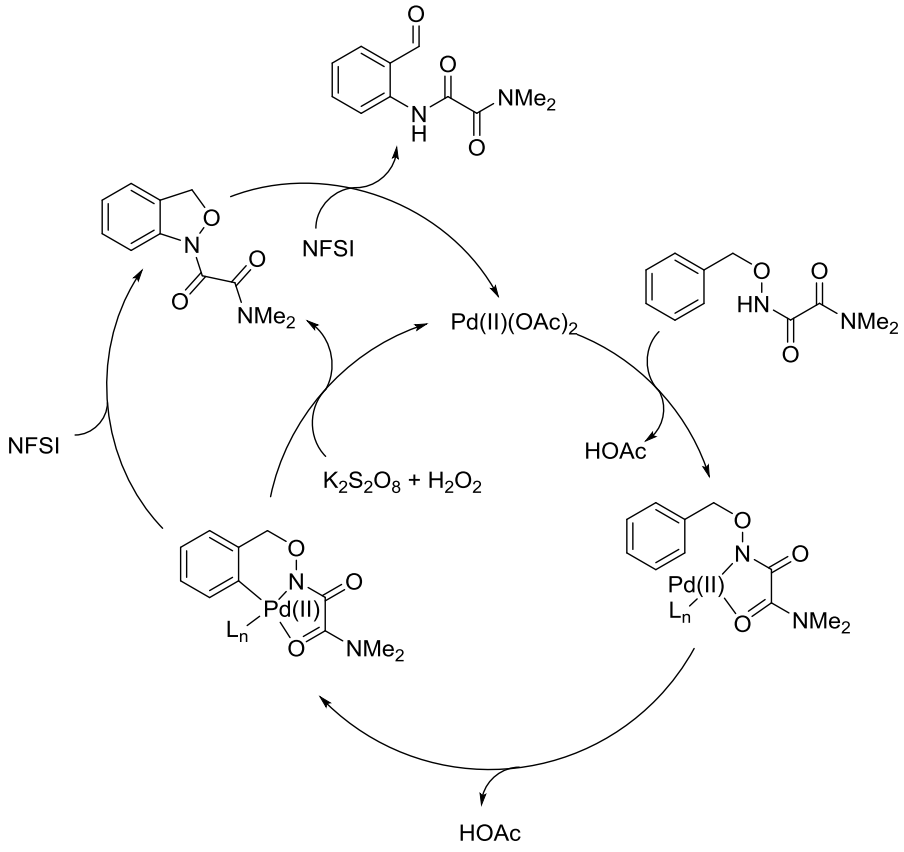
R = 2-F, 2-Cl, 2-Br, 2-Me, 3-Cl, 3-Br, 3-CF_3, 4-Me, 4-F, 4-Cl, 4-Br

B One pot synthesis of quinazolines



R = H, 6-OMe, 7-Cl, 7-Br, 6,7-diCl, 6-Cl

C Proposed catalytic cycle

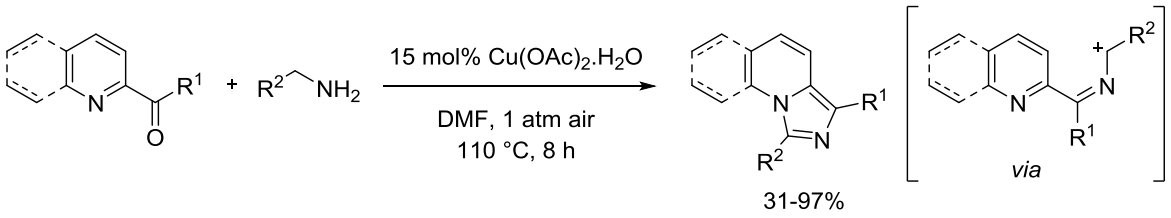


Scheme 22: Synthesis of 1,3-dihydrobenzo[*c*]isoxazole derivatives and one pot synthesis of quinazolines.

2.2 Intramolecular C(sp^3)-N bond formation

The cyclization does not need to occur on a C(sp^2) hybridized carbon atom. This is exemplified by the synthesis of 1,3-diarylated imidazo[1,5-*a*]pyridines which was described by Xu (

A

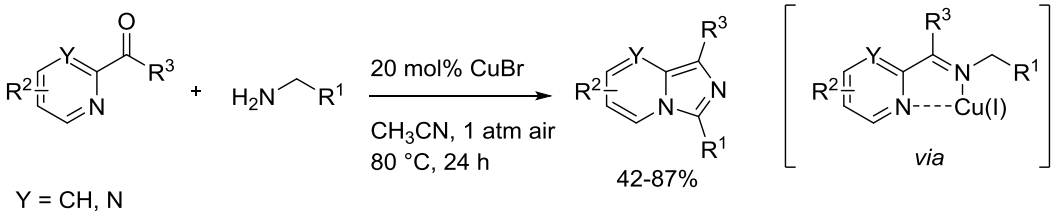


31-97%

R^1 = 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 3,5-dimethoxyphenyl, 1-naphthyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, phenyl

R^2 = phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-furanyl, 2-pyridyl

B



42-87%

Y = CH, N

R^1 = phenyl, 4-bromophenyl 4-trifluoromethylphenyl, benzyl, ethyl, methyl, isopropyl, cyano, 2-pyridyl, 2-furanyl, 2-thiophenyl

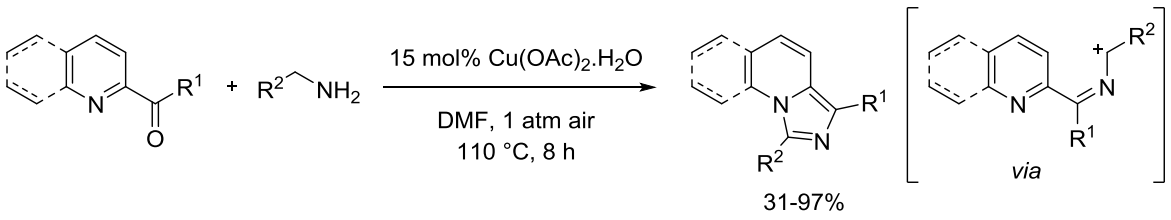
R^2 = H, 4-Me, 4-CO_2Et, 4-Cl, 4-Br

R^3 = H, Ph

Scheme **23**, A).[76] Condensation of benzylamine or a heteroaromatic analogue with a 2-aroylazine gives the corresponding *N*-benzylimine. Subsequently, $Cu(OAc)_2$ oxidation leads to a benzylic carbocation which is stabilized by resonance. A subsequent nucleophilic attack by the azine nitrogen followed by loss of a proton finally leads to the the imidazo[1,5-*a*]pyridine

skeleton. Air functions as the stoichiometric oxidant. A similar protocol was reported by Zeng (

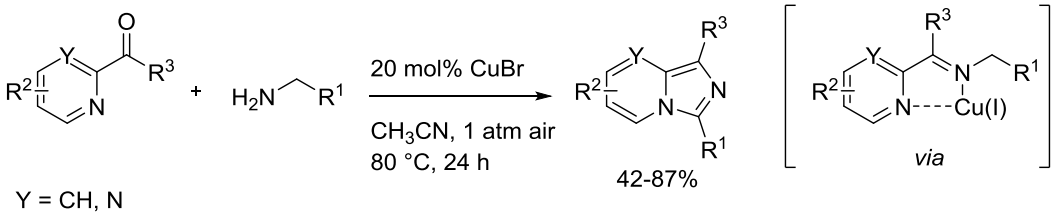
A



R^1 = 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 3,5-dimethoxyphenyl, 1-naphthyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, phenyl

R^2 = phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-furanyl, 2-pyridyl

B



Y = CH, N

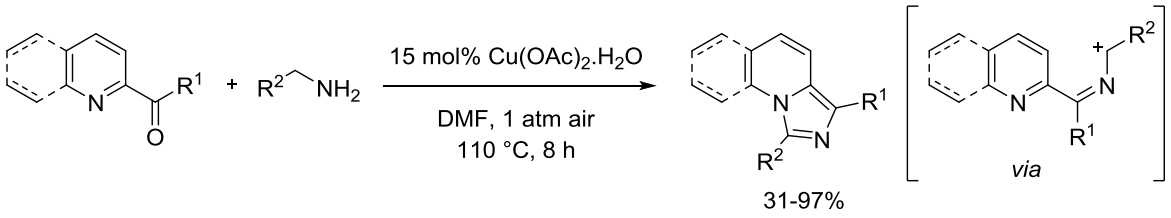
R^1 = phenyl, 4-bromophenyl 4-trifluoromethylphenyl, benzyl, ethyl, methyl, isopropyl, cyano, 2-pyridyl, 2-furanyl, 2-thiophenyl

R^2 = H, 4-Me, 4-CO_2Et, 4-Cl, 4-Br

R^3 = H, Ph

Scheme **23**, B).[77] By using CuBr as catalyst a lower reaction temperature could be used. The intramolecular KIE (1.10) indicated that the C(sp^3)-H bond breaking was not rate limiting. The protocol also features examples with aliphatic amines.

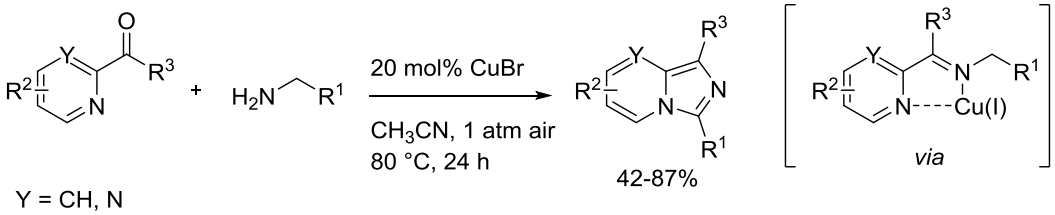
A



R^1 = 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 3,5-dimethoxyphenyl, 1-naphthyl, 3-chlorophenyl, 4-trifluoromethylphenyl, 3,5-ditrifluoromethylphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, phenyl

R^2 = phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 1-naphthyl, 2-furanyl, 2-pyridyl

B



Y = CH, N

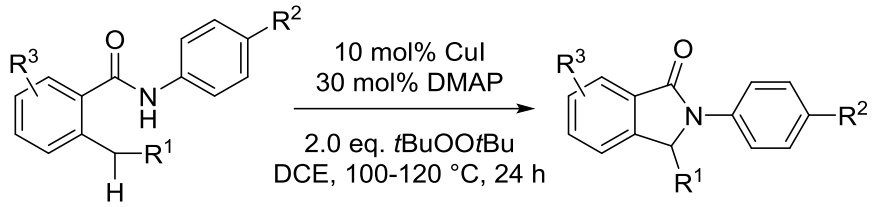
R^1 = phenyl, 4-bromophenyl 4-trifluoromethylphenyl, benzyl, ethyl, methyl, isopropyl, cyano, 2-pyridyl, 2-furanyl, 2-thiophenyl

R^2 = H, 4-Me, 4-CO_2Et, 4-Cl, 4-Br

R^3 = H, Ph

Scheme 23: Synthesis of imidazo[1,5-*a*]pyridines.

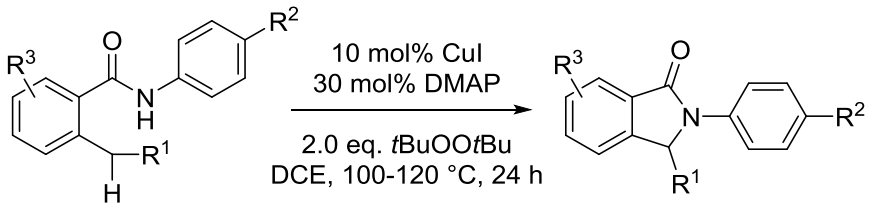
Most examples based on intramolecular C(sp^3)-H amination build up a ring between two substituents. Kondo reported a method for the cyclization of 2-alkyl-*N*-arylbenzamides via a CuI



R^1 = H, Me
R^2 = H, Me, OMe, F, Cl, Br, I, CO_2Me
R^3 = H, Me, OMe, Cl, Br, I

10-100%

catalyzed CDC (Scheme **24**).[78] *t*BuOO*t*Bu was used for the oxidation of copper. The reaction presumably proceeds via a radical pathway as addition of 2 equivalents of TEMPO completely prevented the formation of reaction product.

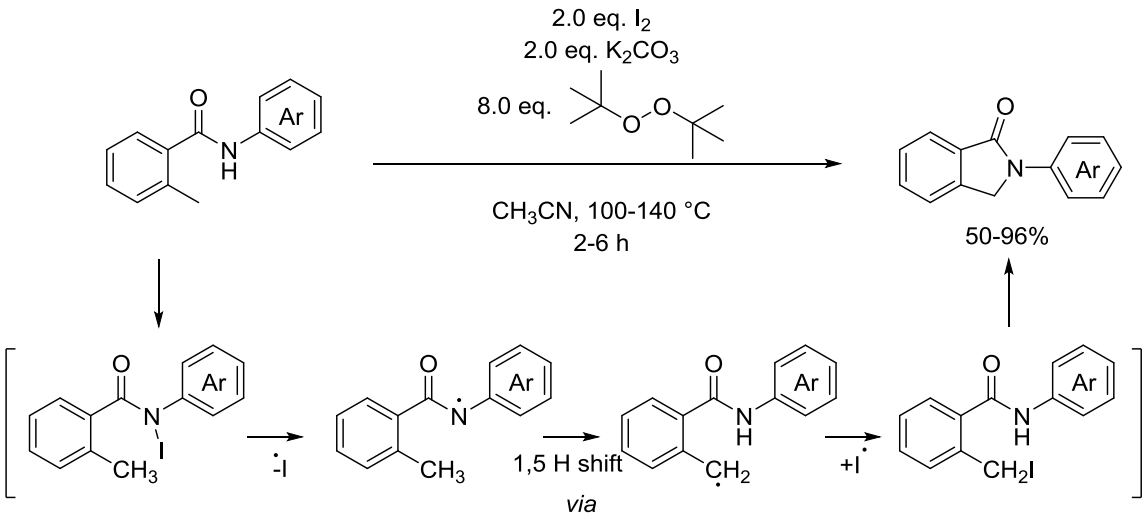


R^1 = H, Me
R^2 = H, Me, OMe, F, Cl, Br, I, CO_2Me
R^3 = H, Me, OMe, Cl, Br, I

10-100%

Scheme 24: Kondo synthesis of 2-arylisoindolin-1-ones.

Another method for the synthesis of the same product class from the same substrates uses a combination of iodine and *t*BuOO*t*Bu (

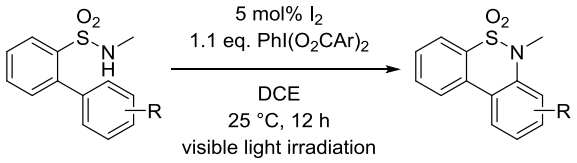


Ar = phenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-fluorophenyl, 3-chlorophenyl, 2,4,5-trichlorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-bromo-2-methylphenyl, 3-bromophenyl, 4-iodophenyl, 4-methylphenyl, 2-methylphenyl, 2,5-dimethylphenyl, 2,4,6-trimethylphenyl, 2,3-dihydro-1*H*-inden-1-yl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methylthiophenyl, 2,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl, 3,4,5-trimethoxyphenyl, 4-biphenyl, 1-naphthyl

Scheme **25**).[79] Kumar also proposes a radical mechanism as addition of TEMPO inhibited the formation of the isoindolinone. The authors proposed a mechanism where first, the nitrogen of the amide was iodinated. This N-iodo intermediate reacts with *t*BuOO*t*Bu with formation of an

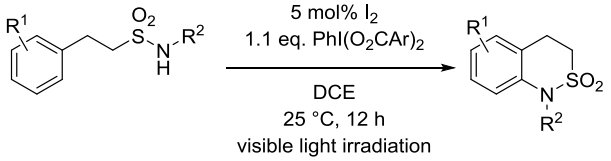
amide radical. This has some resemblance with the Muñiz C(sp^2)-H amination presented in

A



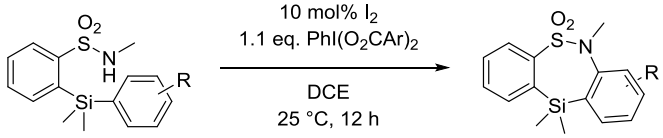
R = H, 4-Me, 4-*t*-Bu, 4-Ph, 4-OMe, 4-OPh, 4-OEt, 4-Cl, 4-F, 4-CF_3, 4-CH_2Br, 2-Me
Ar = 3-ClC_6H_4

B



R^1 = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-Ph
R^2 = Me, Bn, Et
Ar = 3-ClC_6H_4

C

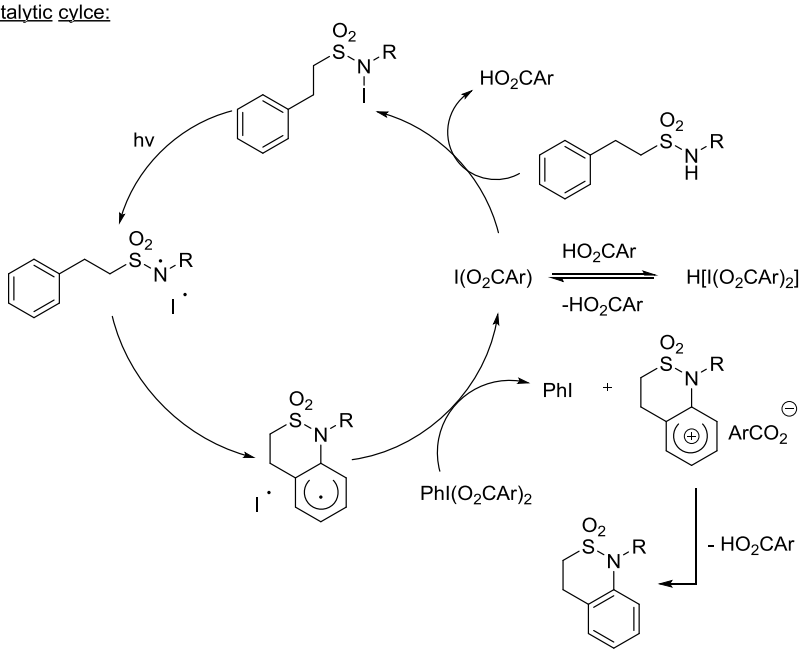


R = H, 4-Me, 4-OMe, 4-F, 4-Cl
Ar = 3-ClC_6H_4

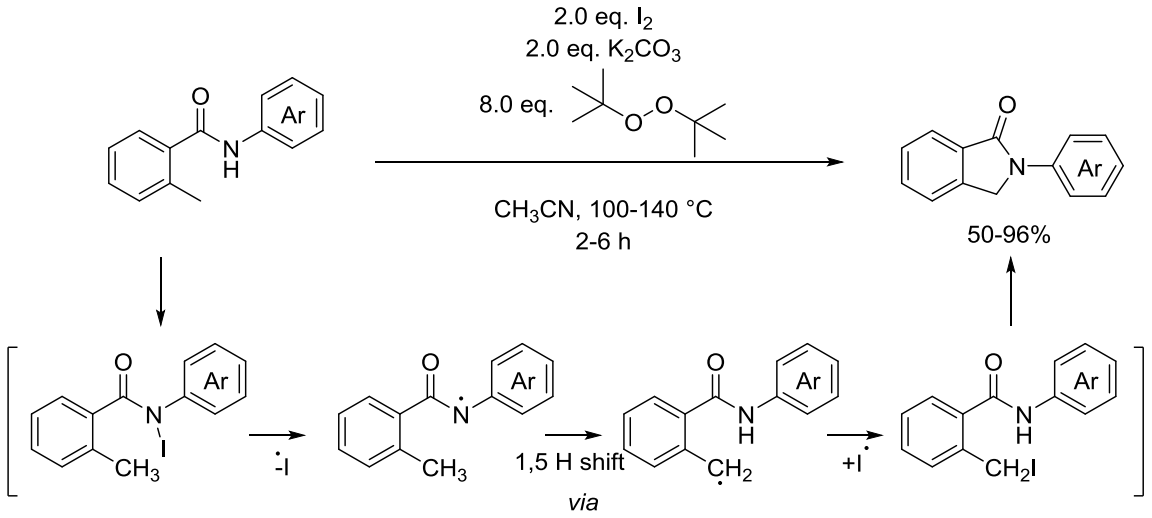
Catalyst formation:

$I_2 + PhI(O_2CAr)_2 \longrightarrow 2\ I(O_2CAr) + PhI$

Catalytic cylce:



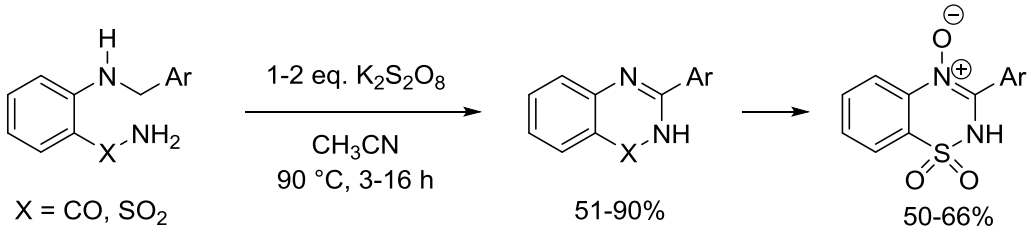
Scheme **11** though both the N-I and N centered radical are generated in a different manner. A 1,5 H shift generates a benzyl radical. Subsequently this radical is iodinated on the benzylic position yielding a benzyl iodide which cyclizes under the basic reaction conditions with formation of the 2-arylisoindolin-1-one and iodide.



Ar = phenyl, 3-fluorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-bromophenyl, 2-fluorophenyl, 3-chlorophenyl, 2,4,5-trichlorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-bromo-2-methylphenyl, 3-bromophenyl, 4-iodophenyl, 4-methylphenyl, 2-methylphenyl, 2,5-dimethylphenyl, 2,4,6-trimethylphenyl, 2,3-dihydro-1*H*-inden-1-yl, 2-methoxyphenyl, 3-methoxyphenyl, 3-methylthiophenyl, 2,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl, 3,4,5-trimethoxyphenyl, 4-biphenyl, 1-naphthyl

Scheme 25: Kumar synthesis of 2-arylisoindolin-1-ones.

Also the following ring closure is an example of a transition metal free CDC (



Ar = Ph, 3-CF3Ph, 3-MePh, 3-MeOPh, 4-MePh, 4-MeOPh, 2-BrPh, 4-CO_2MePh

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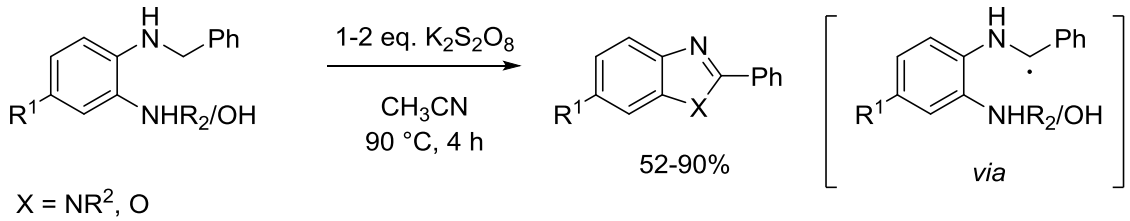
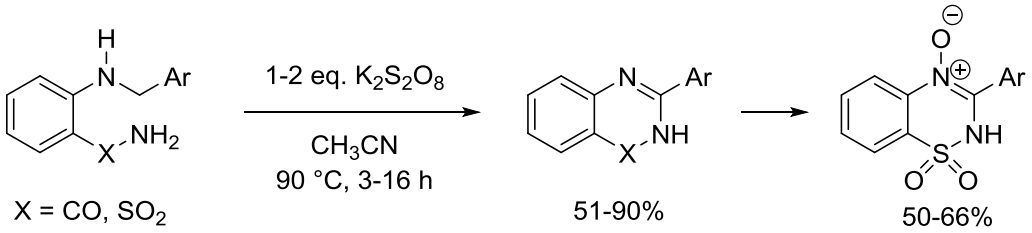


X = NR^2, O

R^1 = H, Me, F

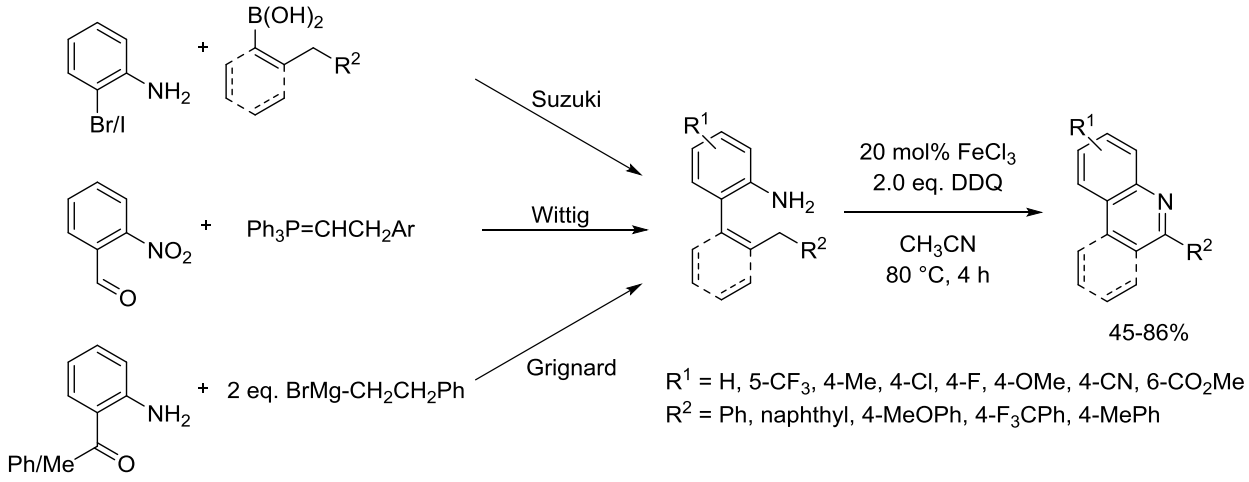
R^2 = H, Ph, 3-NO_2Ph, 3-FPh, 3,5-diMePh

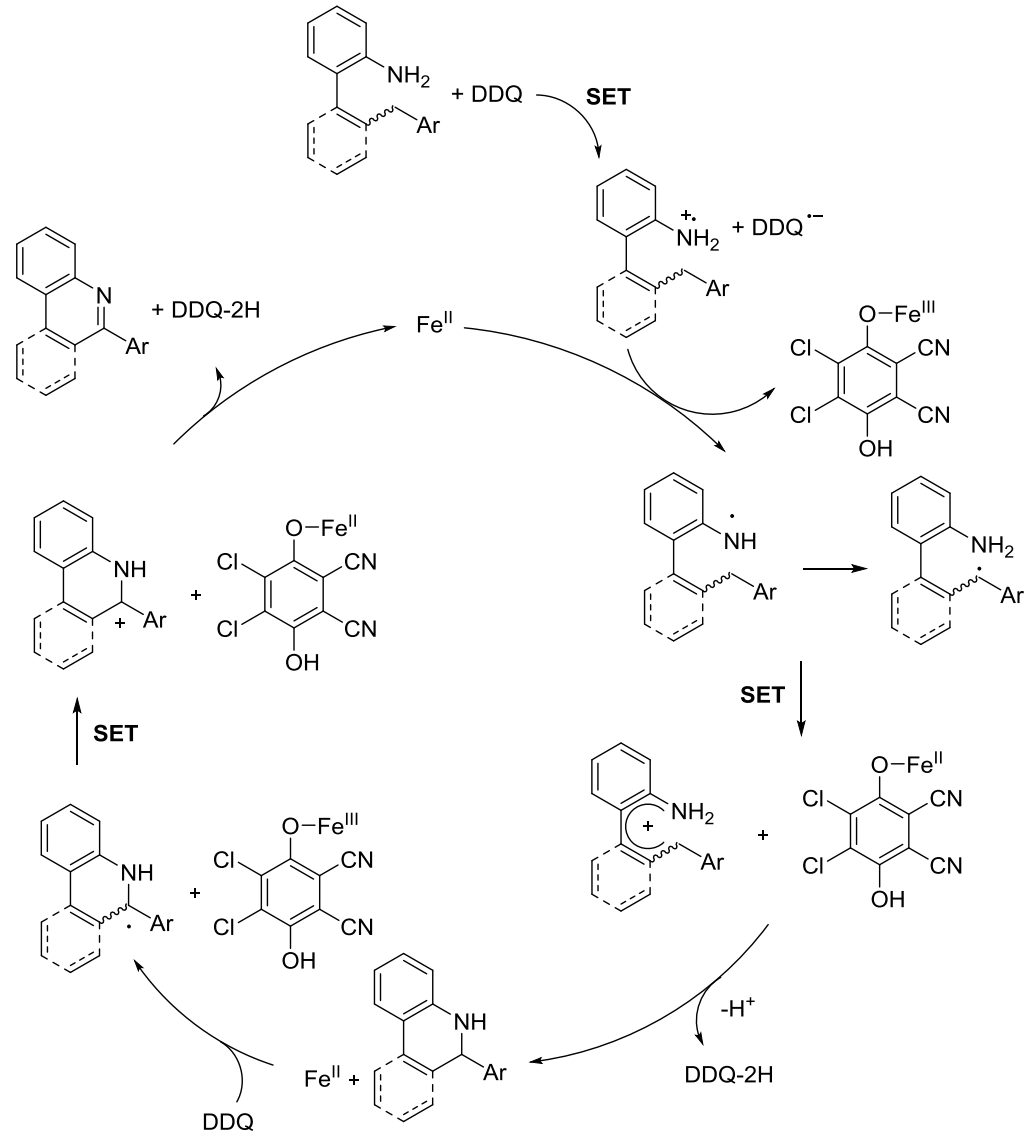
Scheme **26**).[80] Benzamidine containing heterocycles could be made using a sulfate radical anion formed thermally from peroxydisulphate. Depending on the usage of either 1,2-benzenediamines or 2-aminophenols, benzimidazoles or benzoxazoles could be synthesized respectively. Also, 2-aminobenzamides and benzenesulfonamides have been used. In some cases N-oxides were formed due to rapid oxidation of, for example, the cyclized benzosultams (X = SO_2). Initially, a sulphate radical anion is formed by homolytic thermolysis of the peroxide bond in $K_2S_2O_8$. The sulphate radical reacts with the substrate creating a benzyl radical. Further oxidation leads to an iminium cation. Possibly subsequent intramolecular addition yields dihydroquinazolinone which forms the reaction product upon further oxidation.



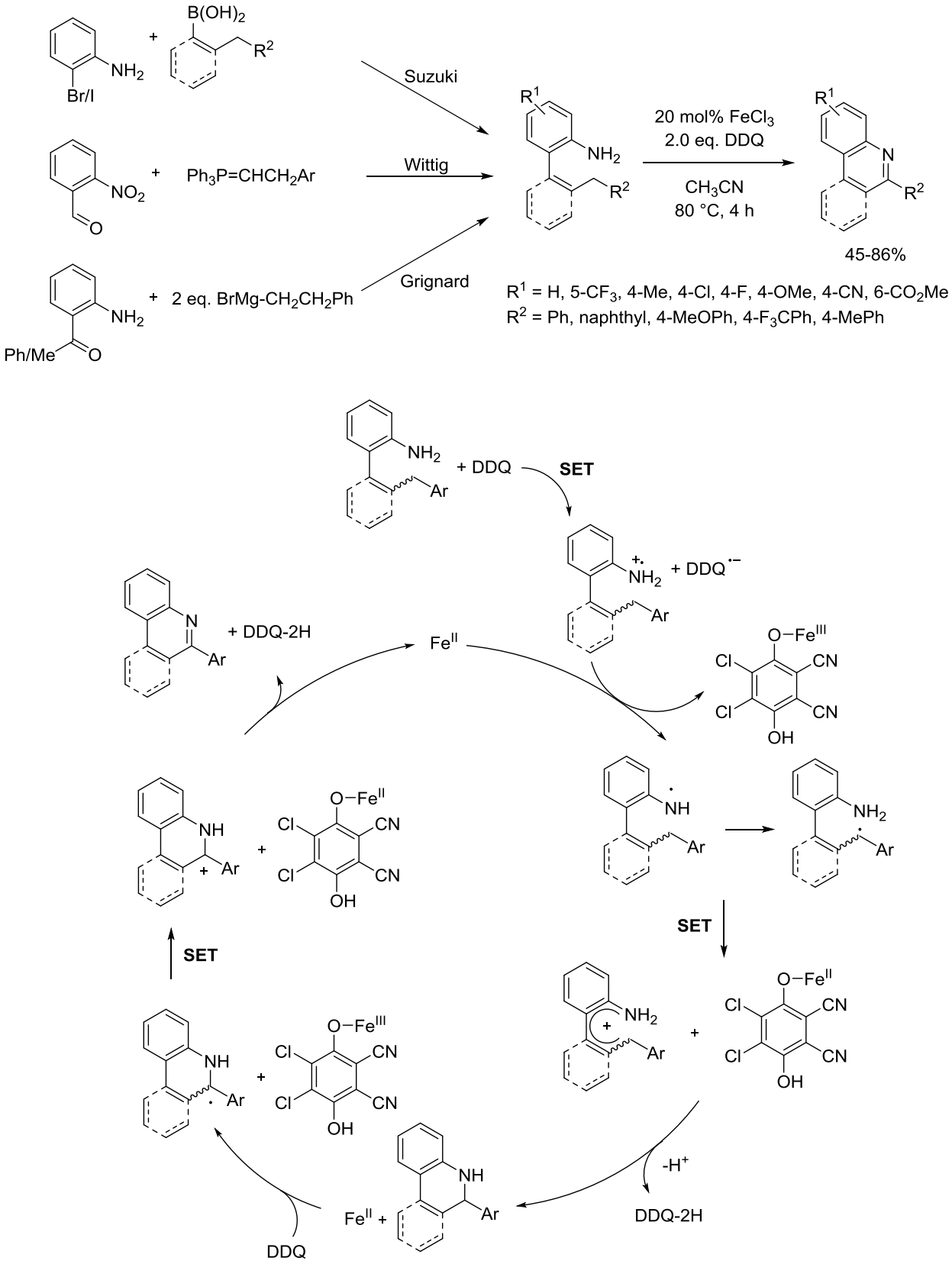
Scheme 26: Synthesis of quinazolinones and its sulfonyl analogues, benzimidazoles and benzoxazoles .

A double iron catalyzed C-H amination reaction of C(sp^3)-H bonds was developed by Alabugin (





Scheme **27**).[81] The substrate could be easily made either *via* a Suzuki coupling with the corresponding haloaniline and arylboronic acid, *via* a Wittig reaction on 2-nitrobenzaldehydes or *via* a Grignard reaction on 2-aminoacetophenones or benzophenones. The substrate undergoes SET oxidation by DDQ with formation of a radical cationic amine species which is deprotonated by the DDQ radical anion. Intramolecular H transfer leads to the benzylic radical. Again, SET oxidation takes place and a benzylic carbocation is formed which undergoes cyclization and subsequent nitrogen deprotonation with formation of a dihydroquinoline. This compound is unstable for isolation under the reaction conditions and will react further. Oxidation with DDQ leads to another benzylic radical which is again further oxidized towards the cation yielding an iminium moiety. Deprotonation forms the imine, hence the name double C-N bond formation.



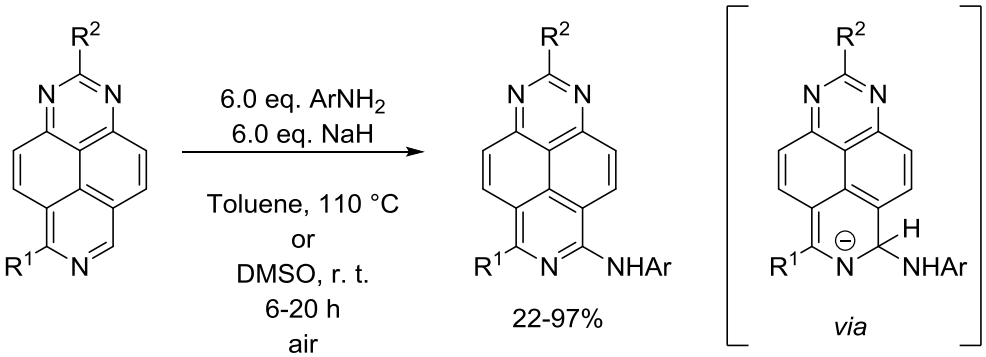
Scheme 27: Synthesis of quinolines and benzoquinolines.

2.3 Intermolecular cross dehydrogenative couplings

When heterocycles are synthesized via an intramolecular CDC, the amino group itself can act as a directing group. An intermolecular CDC often requires a directing group which has to be removed afterwards when it is not desired. Generally, examples of intermolecular CDCs are less abundant.

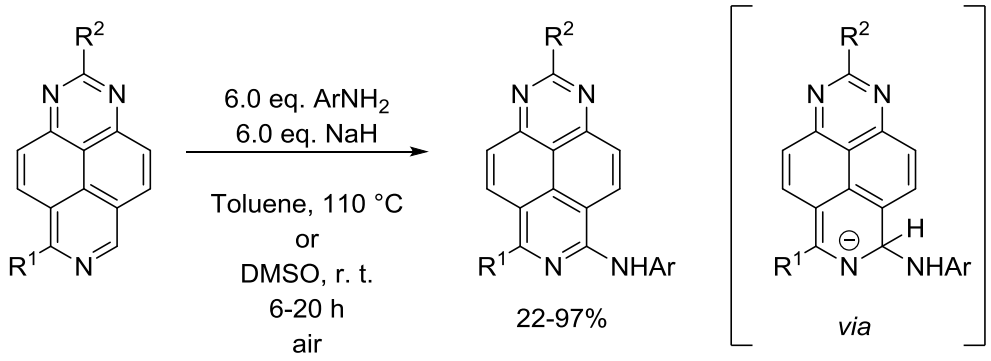
2.3.1 Intermolecular C(sp^2)-N bond formation

Direct oxidative arylamination of 1,3,7-triazapyrenes delivers compounds with electronic applications such as organic light-emitting diodes (OLEDs) (



R^1 = H, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, Me_2N, pyrrolidino
R^2 = H, Me
$ArNH_2$ = Aniline, *p*-toluidine, 2-aminopyridine, 4-aminopyridine, 4-methoxyaniline, 4-fluoroaniline, 4-nitroaniline, 2-chloroaniline

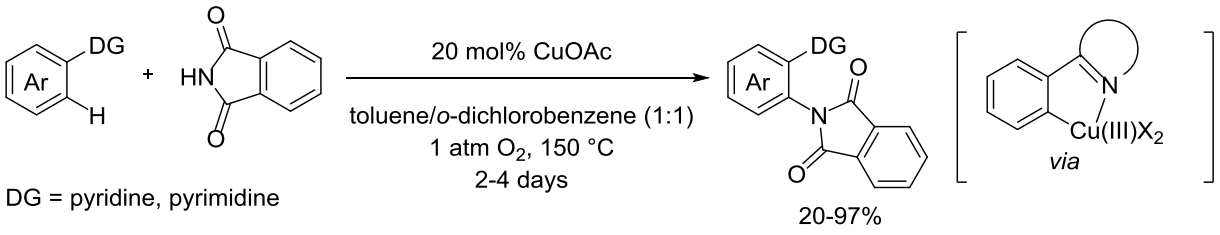
Scheme **28**).[82] When the reaction was performed under argon, only traces of the reaction product could be detected. Therefore it was concluded that air oxygen was crucial for rearomatization. The reaction is an example of an S_NH and goes via a negatively charged σ^H adduct. Subsequent oxidative aromatization and protonation by adding water in the work up leads to the desired aminated 1,3,7-triazapyrenes.



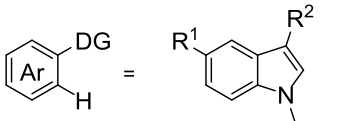
R^1 = H, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, Me_2N, pyrrolidino
R^2 = H, Me
$ArNH_2$ = Aniline, *p*-toluidine, 2-aminopyridine, 4-aminopyridine, 4-methoxyaniline, 4-fluoroaniline, 4-nitroaniline, 2-chloroaniline

Scheme 28: Synthesis of 6-arylamino-1,3,7-triazapyrenes.

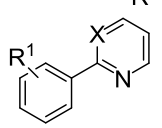
Shen reported an easy access to succinimide protected arylamines via a Cu-catalyzed direct oxidative amidation of arenes (



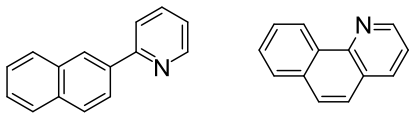
DG = pyridine, pyrimidine



X = N, CH
R^1 = H, Me, OMe, F, Cl, Br, CN, NO_2, CHO
R^2 = H, Me
R^3 = H, Me

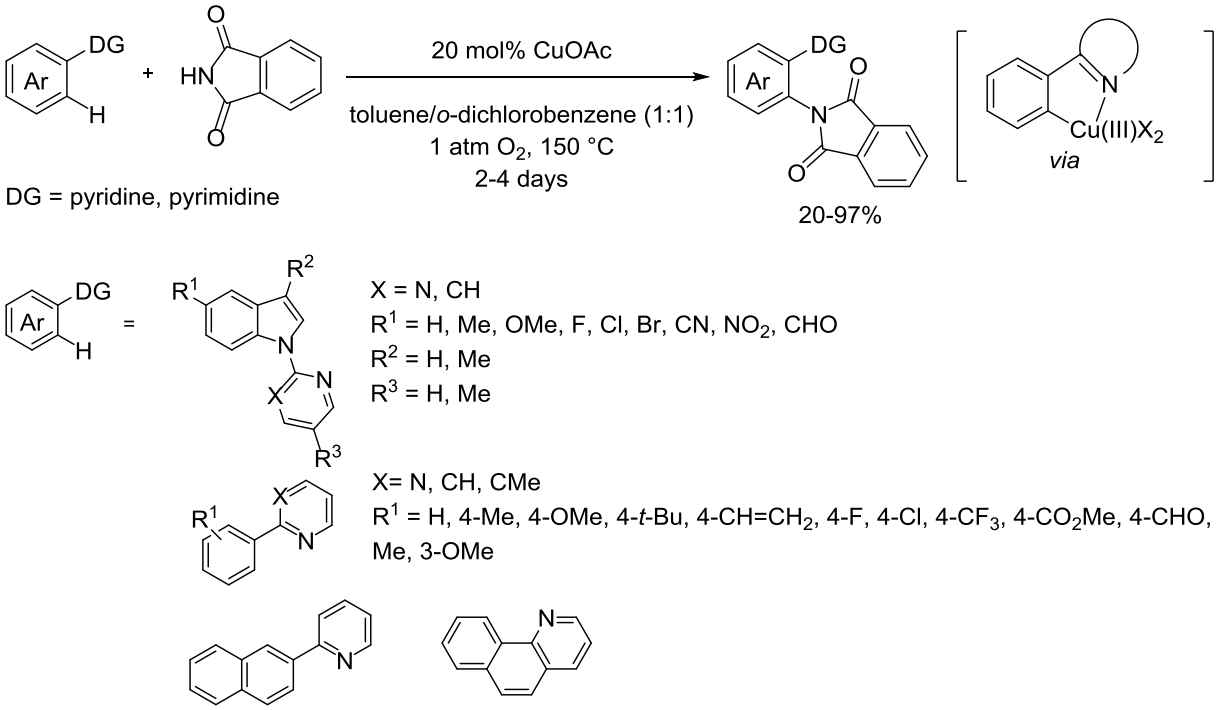


X= N, CH, CMe
R^1 = H, 4-Me, 4-OMe, 4-*t*-Bu, 4-CH=CH_2, 4-F, 4-Cl, 4-CF_3, 4-CO_2Me, 4-CHO, 3-Me, 3-OMe



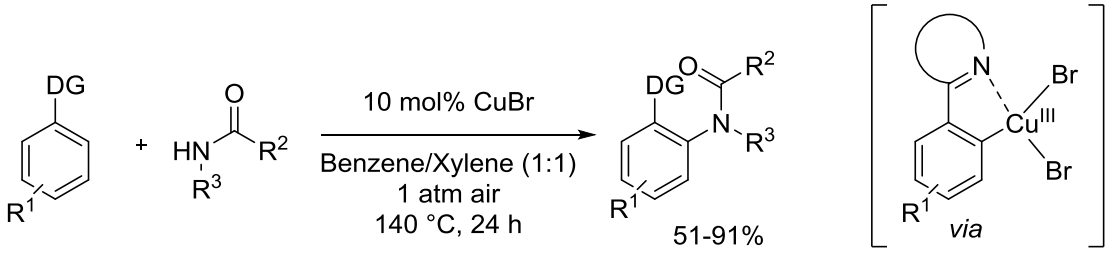
Scheme **29**).[83] In this transformation, a pyridyl or a pyrimidyl group is used to direct the copper catalyst to the ortho C-H bond of the arene. The DGs are irremovable, though the C-N bond connected as present in the indole substrates, might be cleavable.[84] Reoxidation is performed by oxygen. Besides the use of isoindoline-1,3-dione as amine, saccharin and benzamide could

also be used, although in lower yields. The reaction did not give a significant yield drop when radical scavengers such as TEMPO, BHT and 1,4-dinitrobenzene were added. Therefore, a radical mechanism is unlikely. Inter-and intramolecular kinetic isotope effects were determined, 3.7 and 2.1 respectively, indicating that the breaking of the C-H bond occurs in the rate determining step. The mechanism proposed by the authors starts with oxidation of Cu(I) to the active Cu(II) species with oxygen. Then, coordination of copper with the nitrogen atom of the directing group precedes the disproportionative C-H activation involving another Cu(II) species, resulting in an aryl-Cu(III) intermediate and a Cu(I) species. Coordination with phthalimide followed by reductive elimination yields the product. Oxygen reoxidizes the Cu(I) formed. The authors could not rule out a SET pathway.

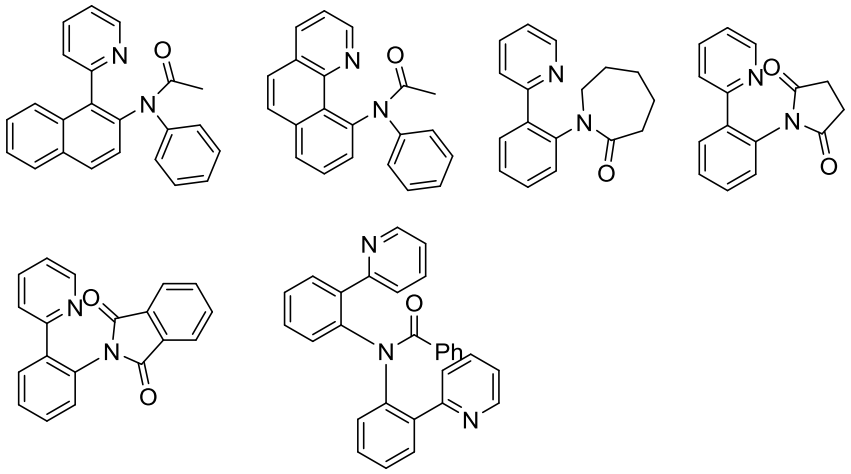


Scheme 29: Synthesis of *N*-arylisoindoline-1,3-diones.

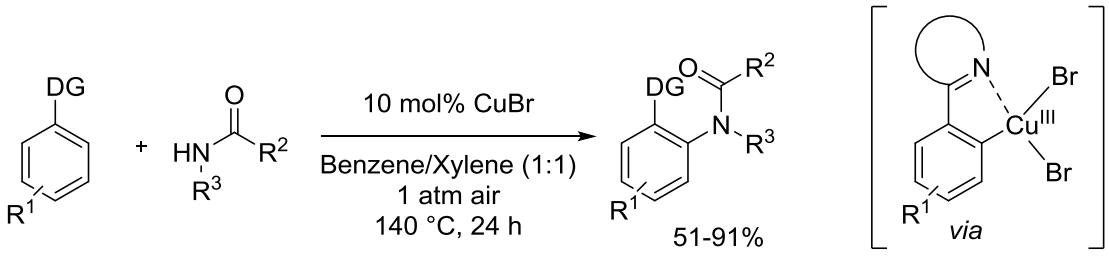
A similar Cu-catalyzed amidation protocol with *N*-acylanilines was developed by Chen (



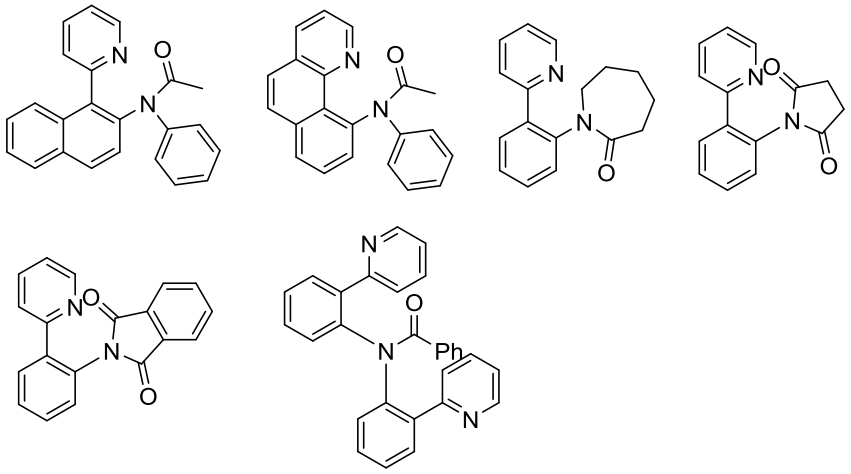
DG = pyridine, imidazole, pyrazole
R^1 = H, 4-Me, 4,6-diMe, 5-OMe, 5-OCF_3, 5-CF_3
R^2 = Me, Et, Ph
R^3 = H, Ph, 4-MePh, 2-MePh, 2,6-diMePh, 4-MeOPH, 4-CF_3Ph, 3-NO_2Ph, 4-ClPh
Other products:



Scheme **30**).[85] Cu(I)Br was used as the catalyst and the authors propose a mechanism which involves a Cu(I)-Cu(III) catalytic cycle supported by the observation that no product was formed in the absence of air. An intermolecular KIE of 2 indicates C-H cleavage occurs in the rate limiting step. Coordination of Cu(I) with the pyridine nitrogen leads to C-H activation with HBr formation. The Cu(I) species is oxidized to Cu(III) by air. One of the bromine atoms attached to copper is subsequently substituted by the amine. Reductive elimination leads to the aniline and regeneration of the Cu(I) catalyst. THF, DMF, DMSO, CH_3CN and 1,4-dioxane were not suitable as solvents. A mixture of benzene and xylene was found optimal.

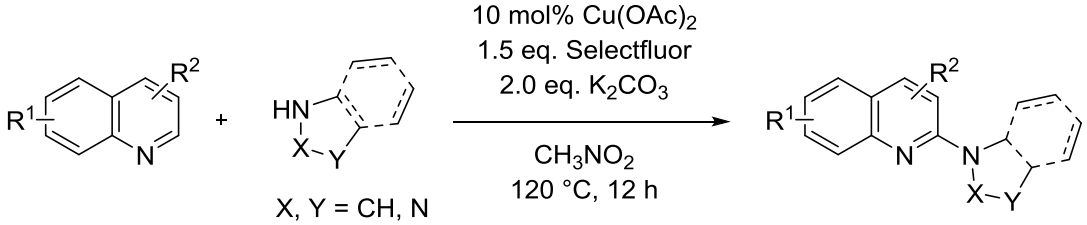


DG = pyridine, imidazole, pyrazole
R^1 = H, 4-Me, 4,6-diMe, 5-OMe, 5-OCF_3, 5-CF_3
R^2 = Me, Et, Ph
R^3 = H, Ph, 4-MePh, 2-MePh, 2,6-diMePh, 4-MeOPH, 4-CF_3Ph, 3-NO_2Ph, 4-ClPh
Other products:



Scheme 30: Synthesis of *N*-aryl *N*-acylanilines.

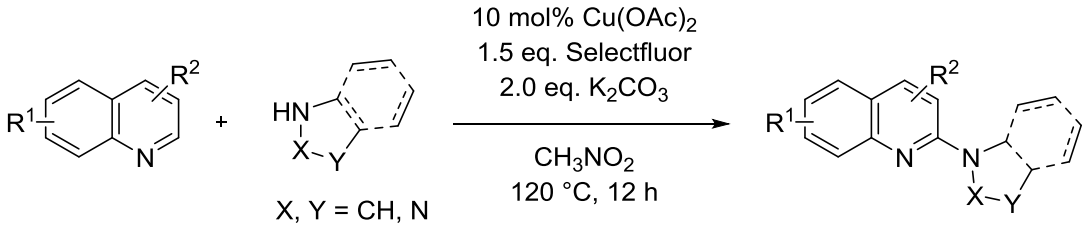
The Cu-catalyzed coupling of azines with azoles has been described by Zhang and Sun (



R_1 = H, 5-Me, 6-Me, 7-Me, 8-Me, 5-Br, 6-Br, 6-Cl, 7-Cl, 6-F, 6-CO_2Me
R_2 = H, 3-Me, 3-Br, 4-Cl

Scheme 31).[86] For this transformation, $Cu(OAc)_2$ is used as catalyst in combination with stoichiometric amounts of selectfluor as the oxidant. When TEMPO was added as a radical trapping agent, no significant loss in yield was observed. Therefore the reaction does not seem to proceed via a radical mechanism. A small intermolecular KIE of 1.31 was measured. In a control experiment where quinazoline was brought under the reaction conditions without any azole nucleophile, no 2-fluoroquinazoline was observed, ruling out the involvement of a classical

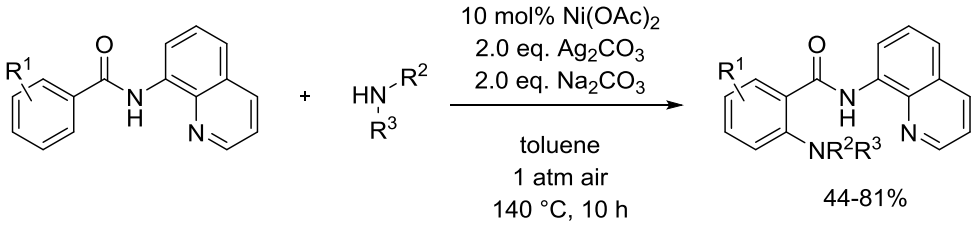
nucleophilic aromatic substitution mechanism. Therefore, a reductive elimination pathway through a Cu(III) complexes was suggested but no catalytic cycle was proposed. In nitromethane good yields were obtained, therefore it was selected as the solvent. Besides coupling with quinazolines as substrate, also coupling with pyridines, pyrroles, furan and thiophene were described.



R_1 = H, 5-Me, 6-Me, 7-Me, 8-Me, 5-Br, 6-Br, 6-Cl, 7-Cl, 6-F, 6-CO_2Me
R_2 = H, 3-Me, 3-Br, 4-Cl

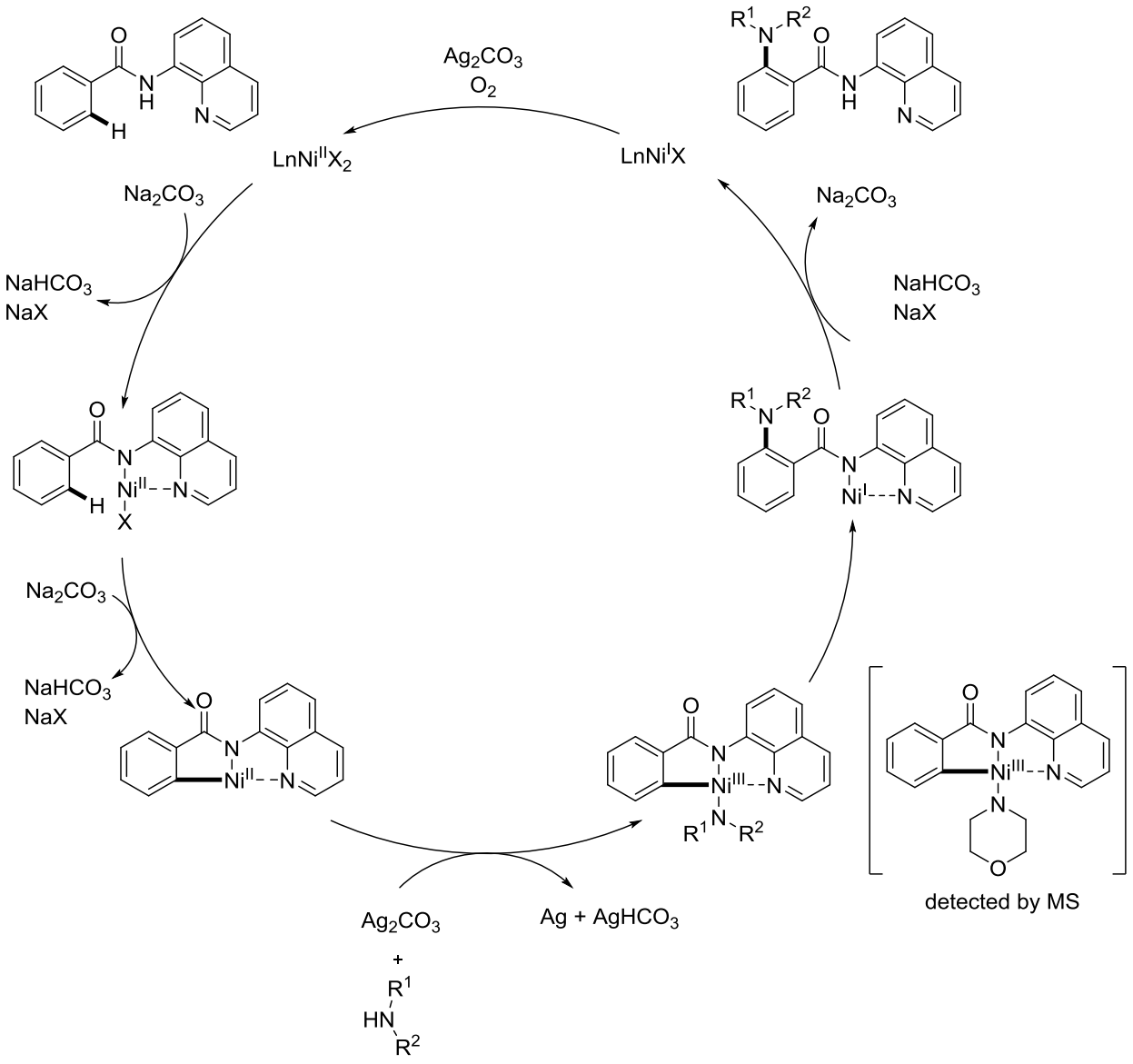
Scheme 31: Synthesis of 2-azoloquinolines.

Nickel has been frequently used for C-H activation reactions.[87] A recent example of a nickel-catalyzed direct oxidative amination is described by Zhang and presented in

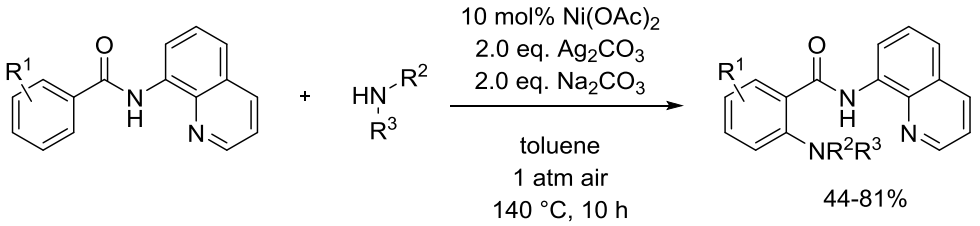


R^1 = H,4-Me, 3-Me, 2-Me, 4-OMe, 3-OMe, 4-*t*-Bu, 4-Ph, 3-NMe_2, 3,4-methylenedioxy, 2,4-diMe, 4-F, 3-F, 4-Cl, 3-Cl, 4-Br, 4-CF_3

R^2R^3NH = morpholine, 4-methylpiperidine, ethyl piperidine-4-carboxylate, 1,4-dioxa-8-azaspiro[4.5]decane, *tert*-butyl piperidin-4-ylcarbamate, *N*-methylbenzylamine, *N*-butylbutanamine, *N*-methylpropylamine, *tert*-butyl piperazine-1-carboxylate, 2,6-dimethylmorpholine

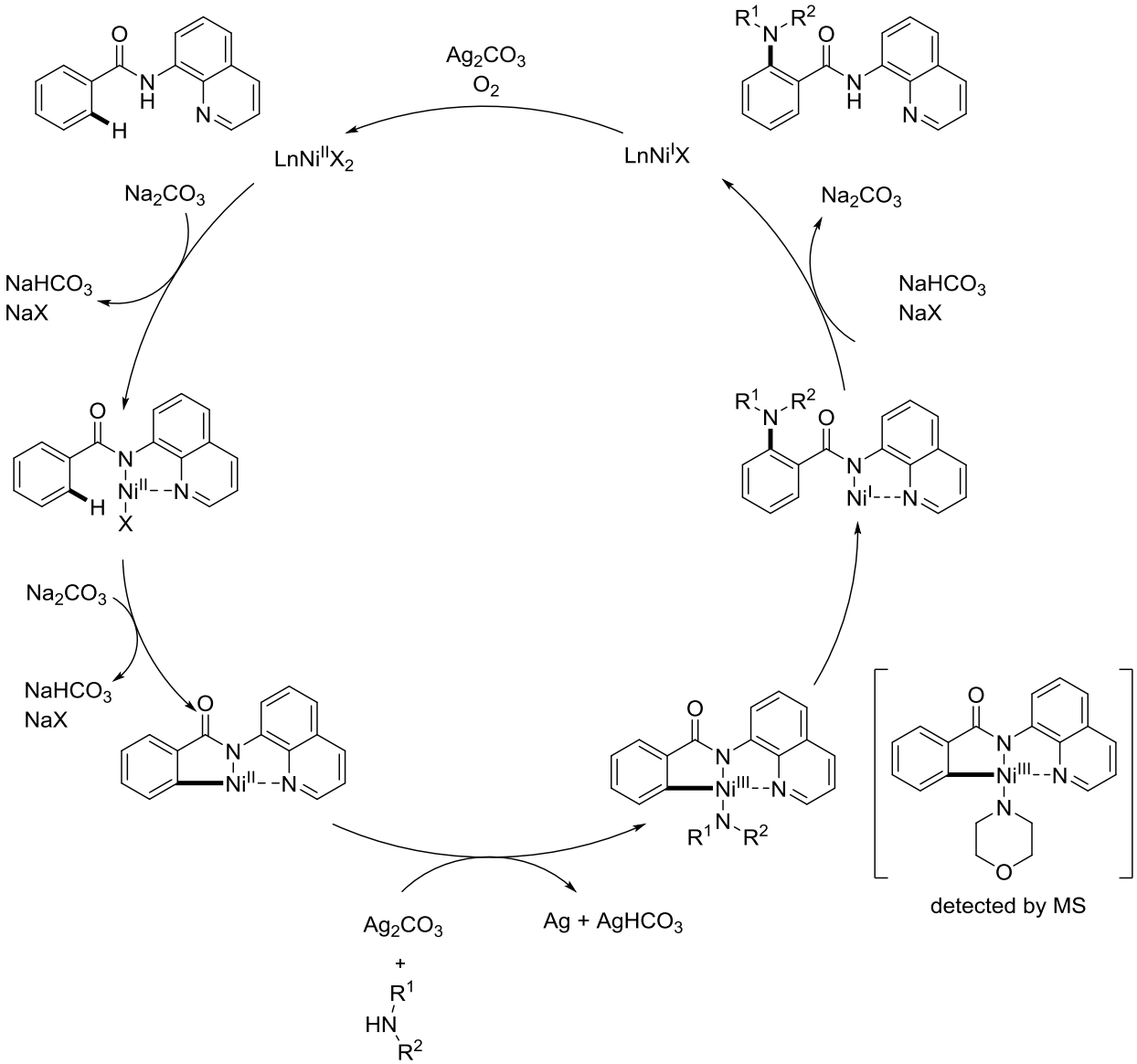


Scheme **32**. [88] In this case an 8-aminoquinolyl group[89] is used as bidentate directing group for the intermolecular amination. This group could be easily removed afterwards by hydrolysis with NaOH in EtOH, yielding *N*-substituted anthranilic acids. Secondary cyclic amines generally work very well and some acyclic ones can also be used. Primary amines are not compatible. An intermolecular KIE of 4.9 showed possible cleavage of the C-H bond in the rate determining step. Addition of a radical scavenger (TEMPO or BHT) seriously decreased the reaction yield, implying that a SET might be involved in the reaction pathway. A Ni^{I}/Ni^{III} catalytic cycle was proposed for the reaction in which Ag^{+} (and air) perform two one electron oxidations (SET) (Ni^{I} to Ni^{II} and Ni^{II} to Ni^{III}). Proof for a Ni^{III} intermediate was generated by MALDI-TOF.



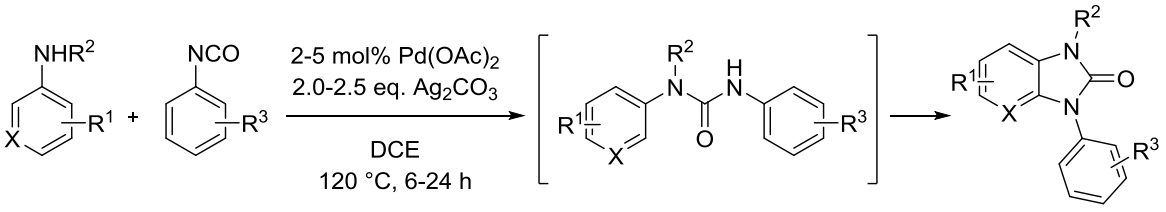
R^1 = H,4-Me, 3-Me, 2-Me, 4-OMe, 3-OMe, 4-*t*-Bu, 4-Ph, 3-NMe_2, 3,4-methylenedioxy, 2,4-diMe, 4-F, 3-F, 4-Cl, 3-Cl, 4-Br, 4-CF_3

R^2R^3NH = morpholine, 4-methylpiperidine, ethyl piperidine-4-carboxylate, 1,4-dioxa-8-azaspiro[4.5]decane, *tert*-butyl piperidin-4-ylcarbamate, *N*-methylbenzylamine, *N*-butylbutanamine, *N*-methylpropylamine, *tert*-butyl piperazine-1-carboxylate, 2,6-dimethylmorpholine



Scheme 32: Synthesis of substituted 2-amino-*N*-(quinolin-8-yl)benzamides.

Youn described the Pd/Ag promoted synthesis of cyclic ureas starting from amino(hetero)arenes and arylisocyanates (



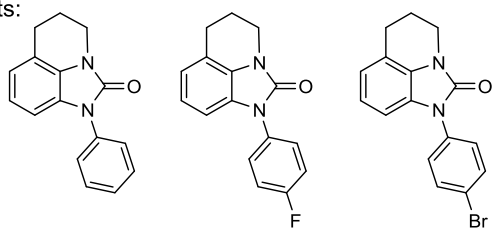
X = CH, N

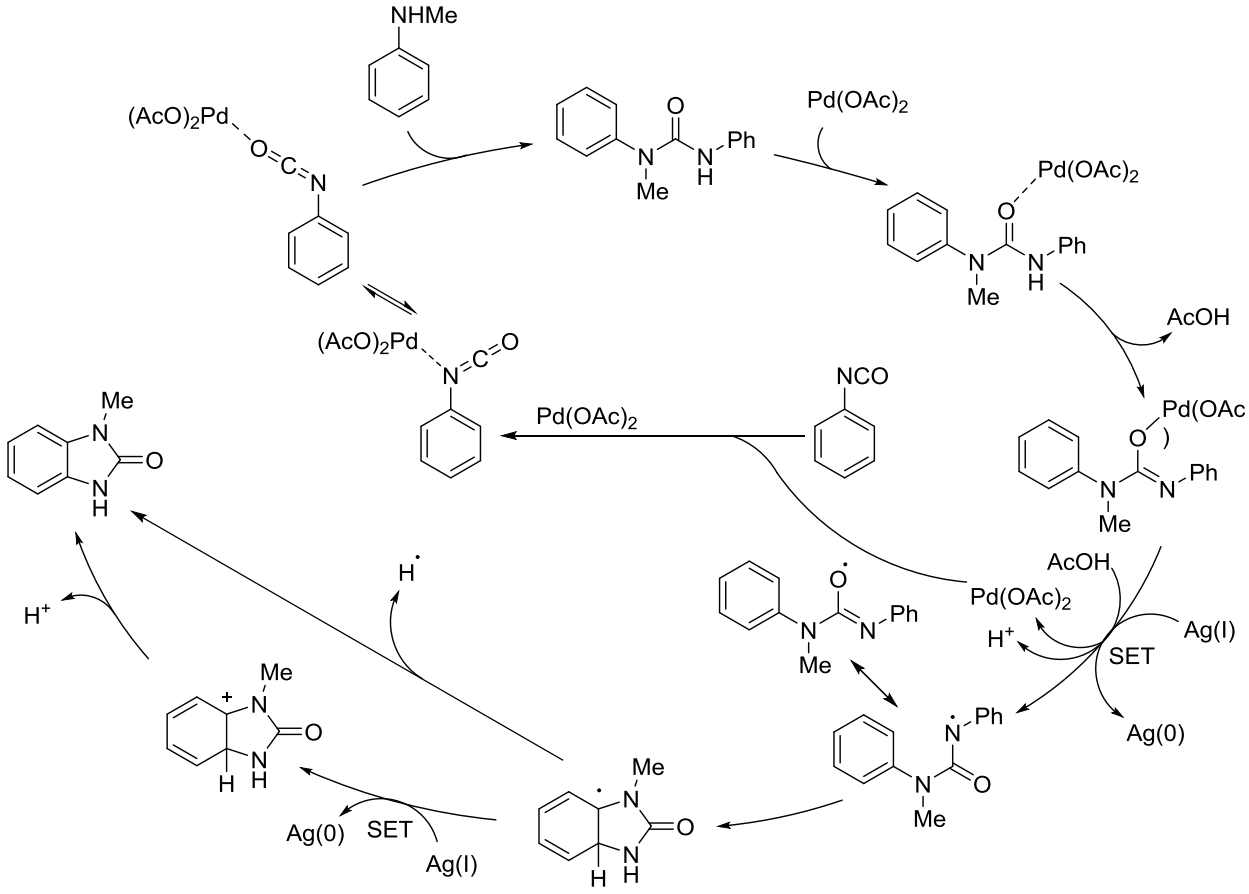
R^1 = H, 4-OMe, 4-Me, 4-Cl, 4-NO_2, 3-Me, 3,5-diMe

R^2 = Me, Et, C_2H_4Ph, $C_2H_4CO_2Me$, C_2H_4CN

R^3 = H, 4-OMe, 4-Et, 4-F, 4-Cl, 4-Br, 4-Ac, 4-NO_2

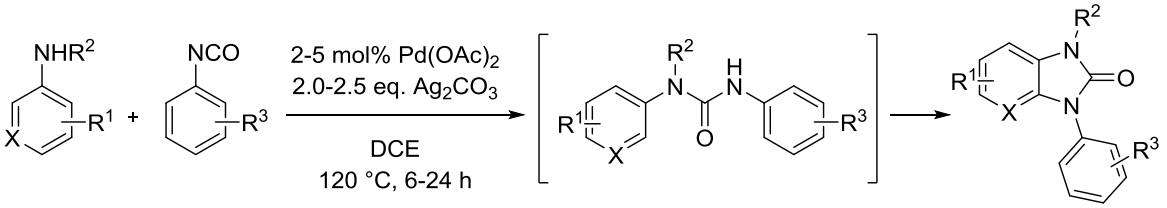
Other products:





Scheme **33**).[90] Coordination of $Pd(OAc)_2$ with the oxygen atom of the *in situ* formed urea induces deprotonation with formation of an isourea. SET from Ag leads to a urea radical which

undergoes cyclization. Then, either another SET leads to the cation which rearomatizes with formation of the product, or the urea radical loses a hydrogen atom directly which also forms the product. Based on the mechanistic proposal, direct oxidative amination occurs in the cyclization step, after intermolecular urea formation. Therefore, this work involving two C–N bond formations can be categorized in Section 2.1 as well.



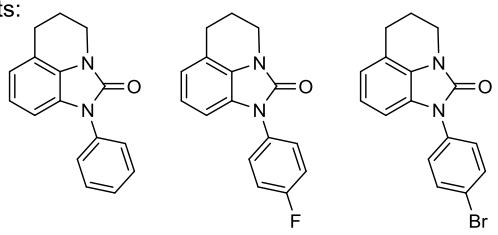
X = CH, N

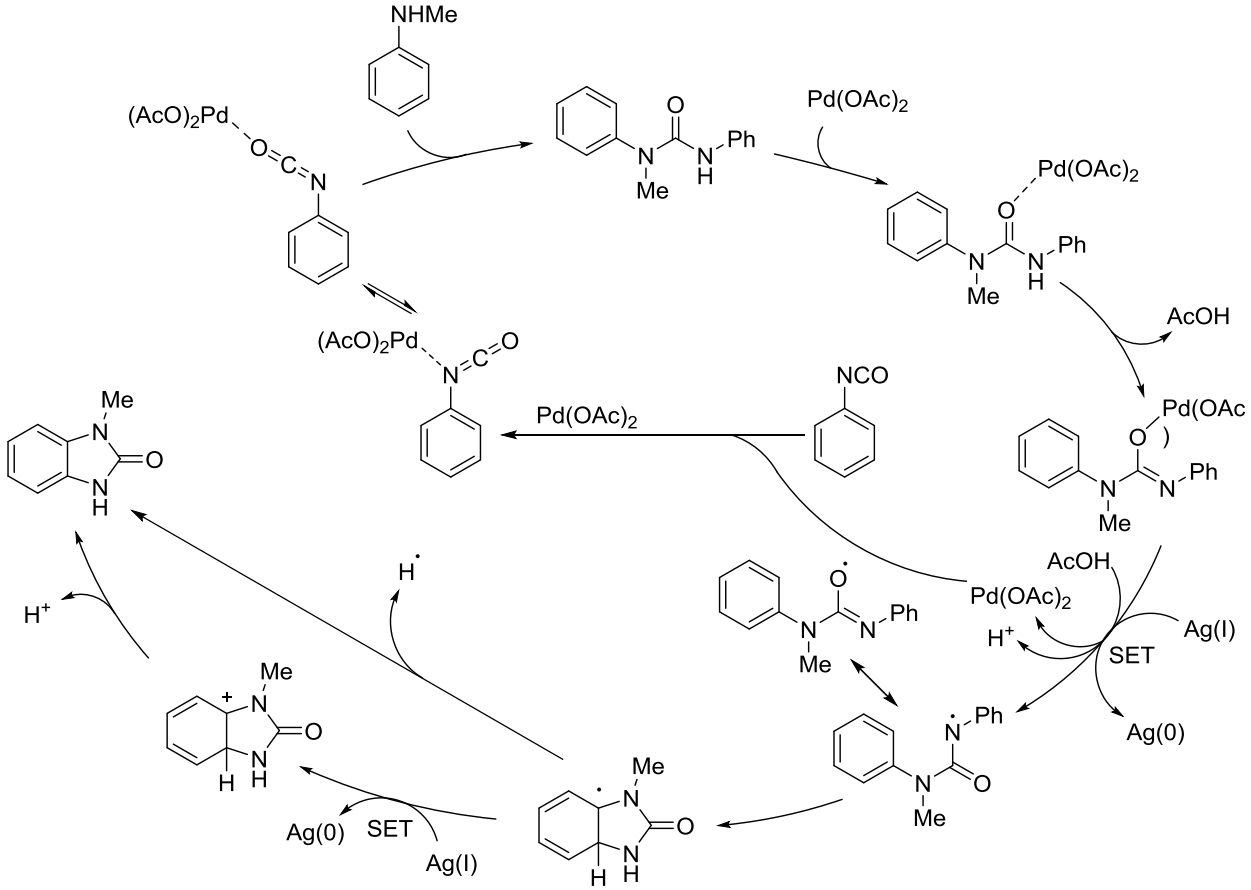
R^1 = H, 4-OMe, 4-Me, 4-Cl, 4-NO_2, 3-Me, 3,5-diMe

R^2 = Me, Et, C_2H_4Ph, $C_2H_4CO_2Me$, C_2H_4CN

R^3 = H, 4-OMe, 4-Et, 4-F, 4-Cl, 4-Br, 4-Ac, 4-NO_2

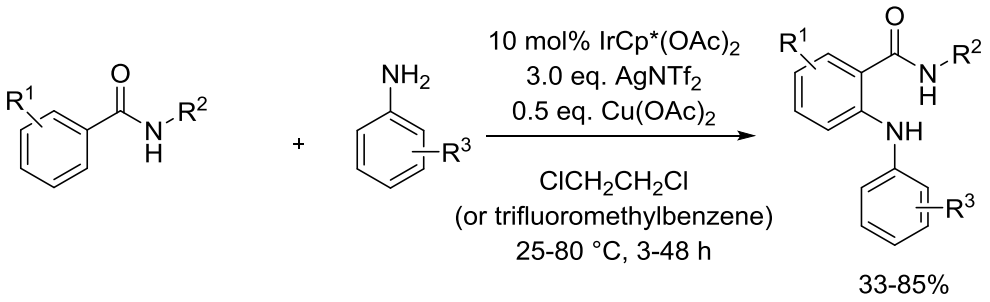
Other products:



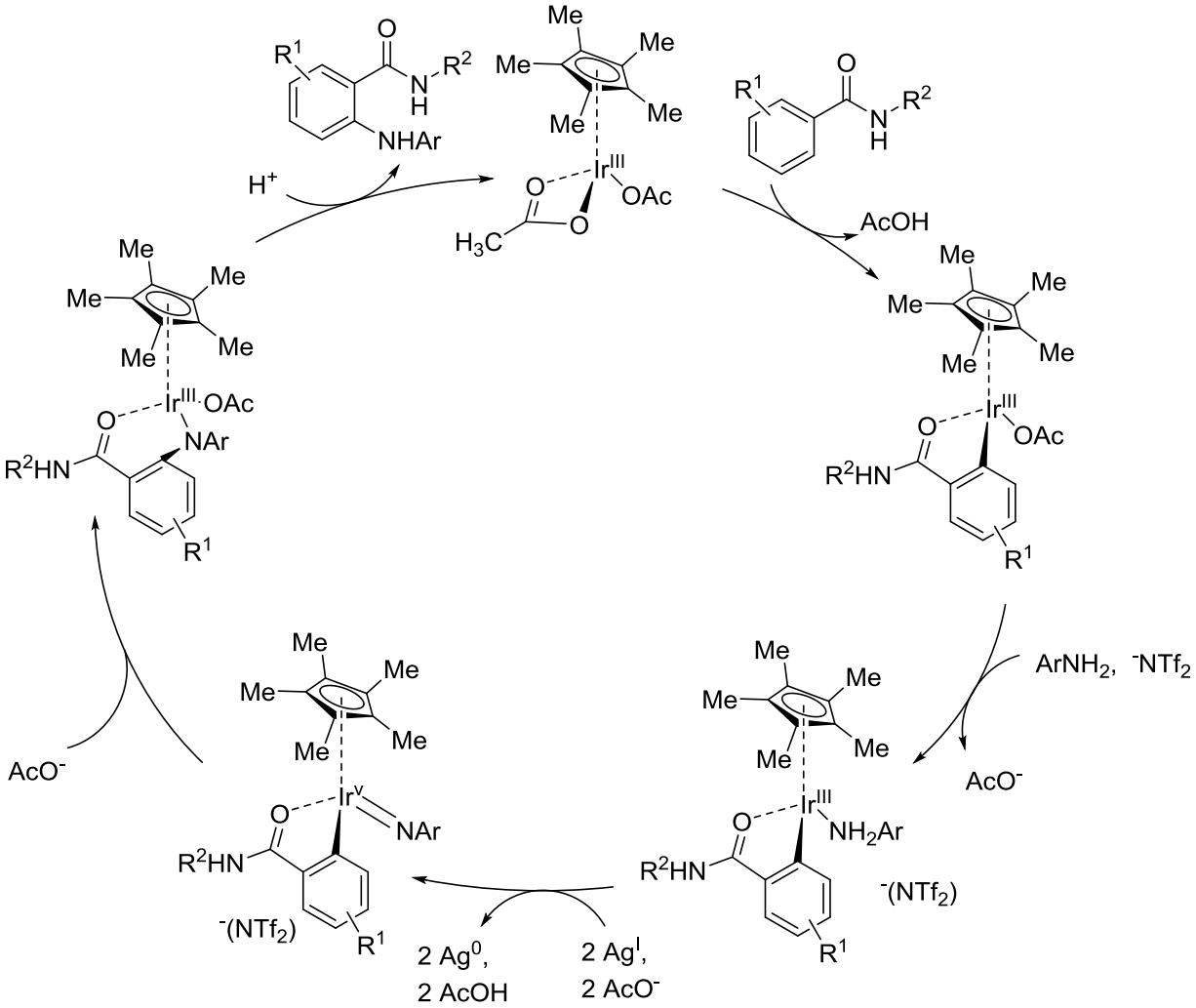


Scheme 33: Synthesis of 1*H*-benzo[*d*]imidazol-2(3*H*)-ones and 1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-ones.

Chang reported the Ir-catalyzed oxidative arylamination of *N*-substituted benzamides (

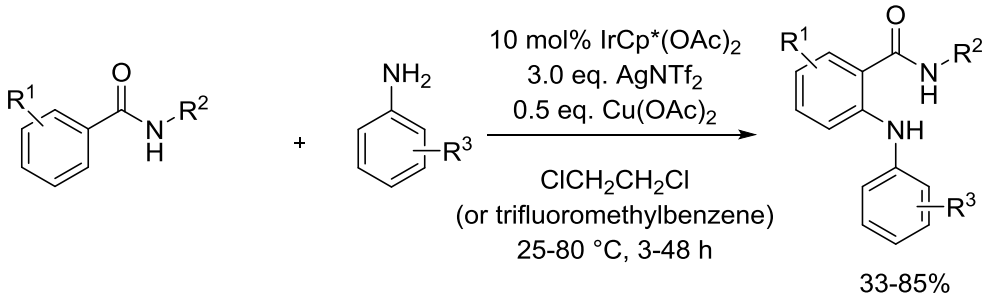


R^1 = H, 4-Me, 3-Me 4-*t*Bu,4-Ph,4-OMe, 4-CF_3,4-CH_2OH, 4-CH_2OAc
R^2 = Adamantyl, cyclohexyl, *t*Bu, CH(Me)Cy, CH(*i*Bu)CO_2Me
R^3 = 4-CF_3, 4-SCF_3, 4-SO_2NMe_2,4-SO_2OPh, 4-SO_2Me, 4-OTf, 3-NO_2, 3-CF_3, (2-OMe, 4-NO_2), (2-OMe, 5-NO_2), (2-Me, 4-CF_3), (3-F, 5-CF_3), 3,4-diCl, (2-Br, 4-Cl)

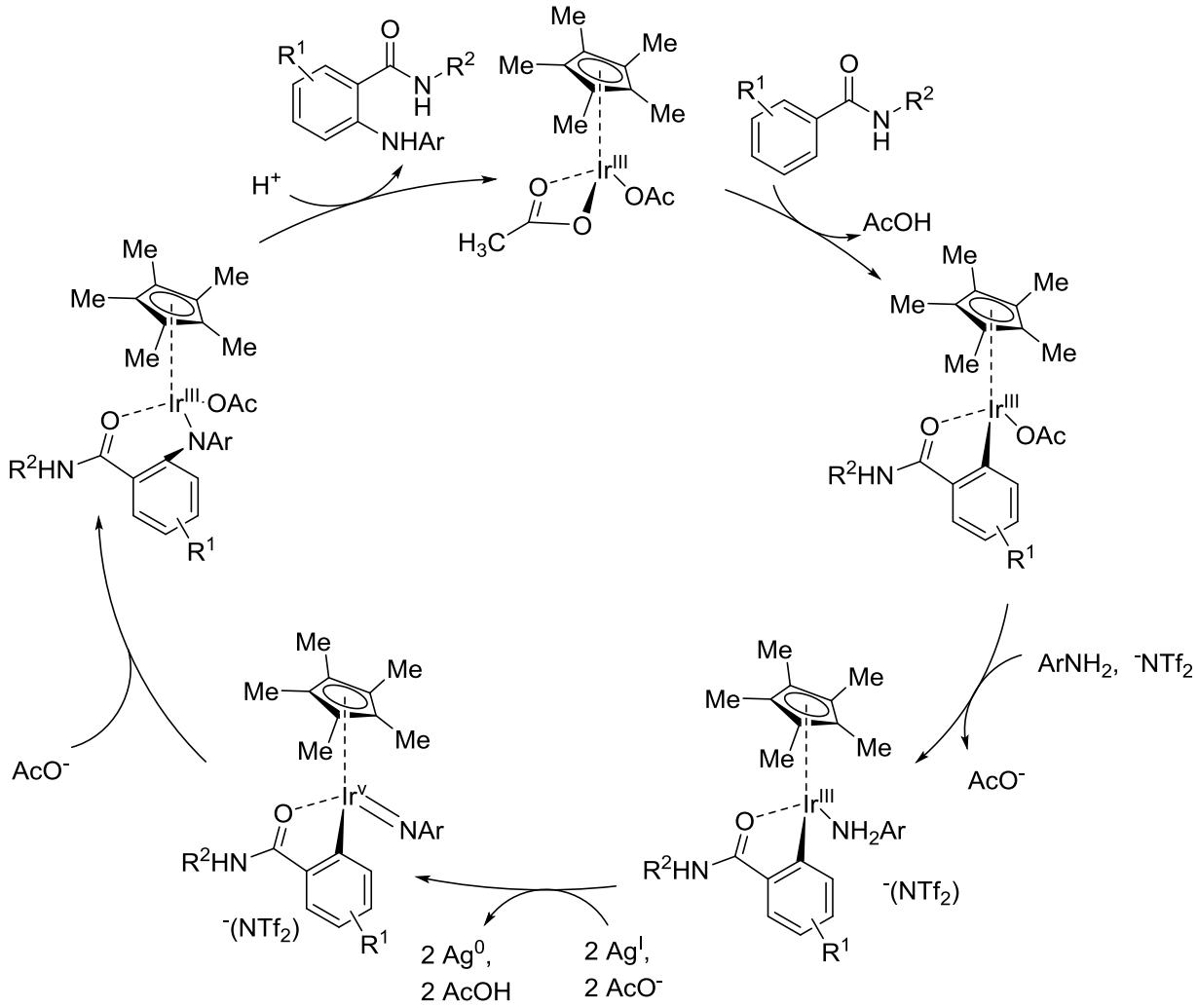


Scheme **34**).[91] $AgNTf_2$ in combination with $Cu(OAc)_2$ were added as oxidant. A variety of electronically different anilines were tolerated. Remarkably the reaction was still effective at

room temperature. As different *N*-substituents can be used for the amide DG no removal afterwards is required. The proposed mechanism starts by irreversible C-H cleavage of the benzamide on the basis of kinetic isotope effect studies. This produces a cyclometalated Ir(III) species and believed to be the RDS (rate determining step). One of the acetate ligands of the Ir(III) complex is then exchanged for aniline which creates an isolable aniline complex. Subsequently this complex is oxidized by 2 equivalents of Ag(I) to produce an Ir(V) nitrenoid species. When the anilino group migrates towards carbon and a free acetate ligand binds again to Ir, an Ir(III) complex is formed from which the reaction product is obtained by proto-demetalation. The catalyst is also regenerated during this last step.

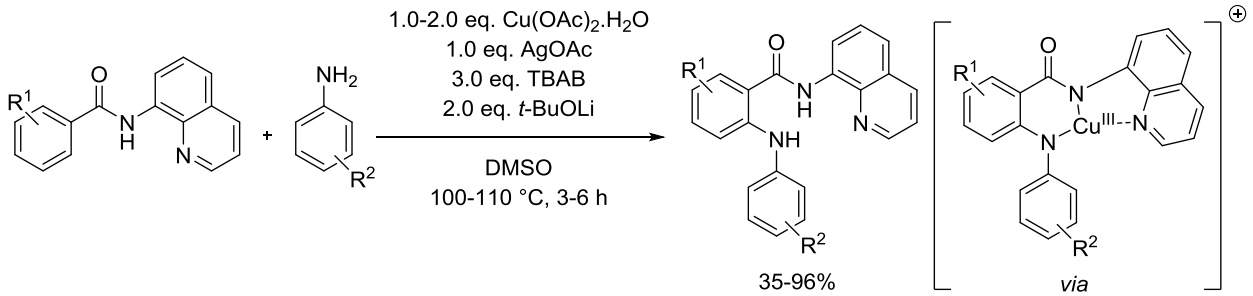


R^1 = H, 4-Me, 3-Me 4-*t*Bu,4-Ph,4-OMe, 4-CF_3,4-CH_2OH, 4-CH_2OAc
R^2 = Adamantyl, cyclohexyl, *t*Bu, CH(Me)Cy, CH(*i*Bu)CO_2Me
R^3 = 4-CF_3, 4-SCF_3, 4-SO_2NMe_2,4-SO_2OPh, 4-SO_2Me, 4-OTf, 3-NO_2, 3-CF_3, (2-OMe, 4-NO_2), (2-OMe, 5-NO_2), (2-Me, 4-CF_3), (3-F, 5-CF_3), 3,4-diCl, (2-Br, 4-Cl)



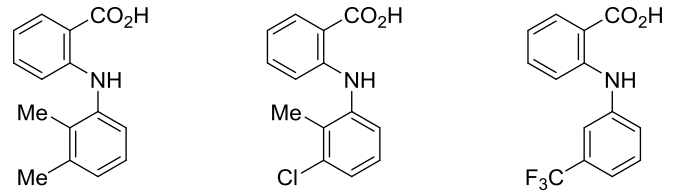
Scheme 34: Synthesis of *N*-substituted-2-(arylamino)benzamides.

A similar reaction was developed by Jana using $Cu(OAc)_2.H_2O$ (



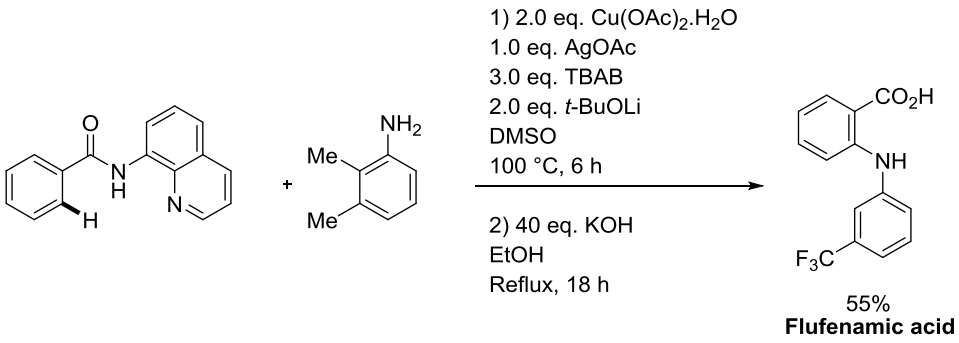
R^1 = H, 4-CF_3, 4-Br, 4-Et, 4-Ac, 2-CF_3, 3-CF_3, 3-*p*-tol, 4-F, 3-Br, 4-Me, 4-CN, 4-*n*-pentO
R^2 = H, 4-OMe, 4-Me, 4-*t*-Bu, 2,4-diOMe, 2,4-diMe, 2,3-diMe, (2-Me, 3-Cl), (2-Me, 3-CF_3), 2,4-diOMe, 4-F, 4-Br, 4-I, 3-CF_3, (2-NO_2, 4-OMe), 3-OMe, 3-Me, 4-NO_2, 4-CN, 3,5-diCF_3

NSAIDs synthesized:



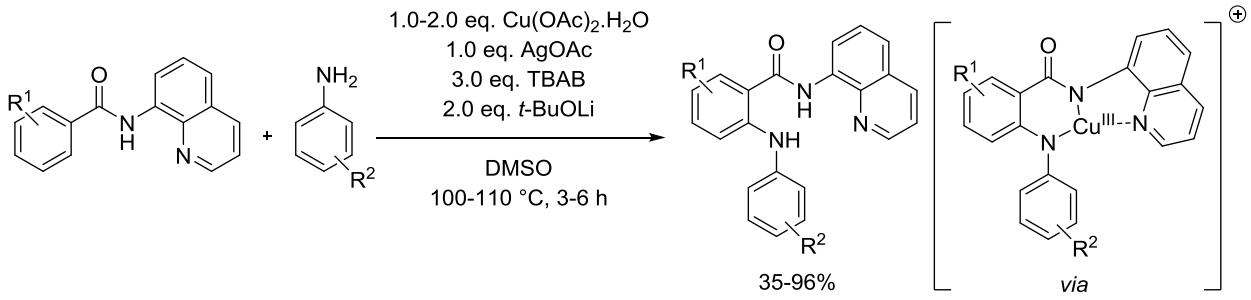
Mefenamic acid **Tolfenamic acid** **Flufenamic acid**

Gram scale synthesis of Flufenamic acid:



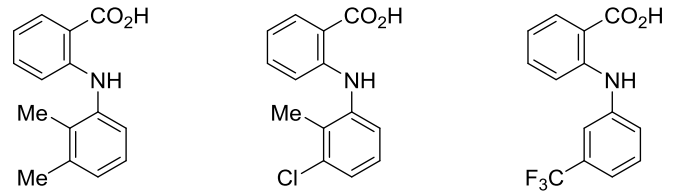
Flufenamic acid

Scheme **35**).[92] In this case an 8-aminoquinoline group was used as removable bidentate directing group. This reaction showed a broader scope and demonstrated that aminations using electron neutral or electron rich anilines are also possible. The method was used to synthesize a series of amide protected variants of nonsteroidal anti-inflammatory drugs (NSAIDs): mefenamic acid, tolfenamic acid and flufenamic acid. Mefenamic acid was synthesized on gram scale in 55% overall yield. The intermolecular KIE was determined as 4.3. This means that C-H activation could occur via a concerted metalation deprotonation type mechanism.



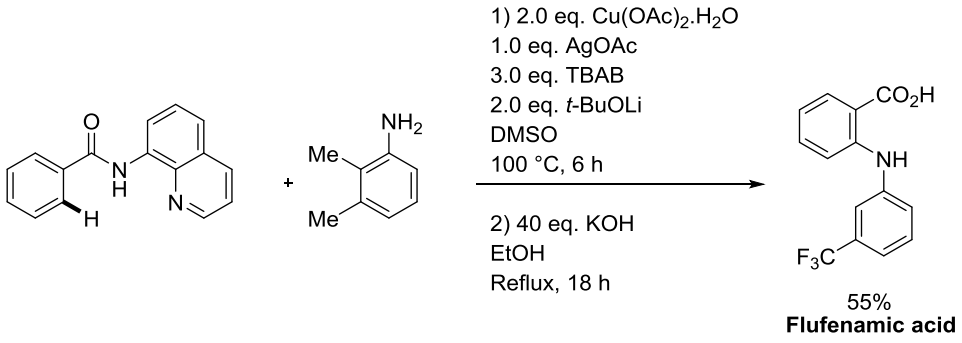
R^1 = H, 4-CF_3, 4-Br, 4-Et, 4-Ac, 2-CF_3, 3-CF_3, 3-*p*-tol, 4-F, 3-Br, 4-Me, 4-CN, 4-*n*-pentO
R^2 = H, 4-OMe, 4-Me, 4-*t*-Bu, 2,4-diOMe, 2,4-diMe, 2,3-diMe, (2-Me, 3-Cl), (2-Me, 3-CF_3), 2,4-diOMe, 4-F, 4-Br, 4-I, 3-CF_3, (2-NO_2, 4-OMe), 3-OMe, 3-Me, 4-NO_2, 4-CN, 3,5-diCF_3

NSAIDs synthesized:



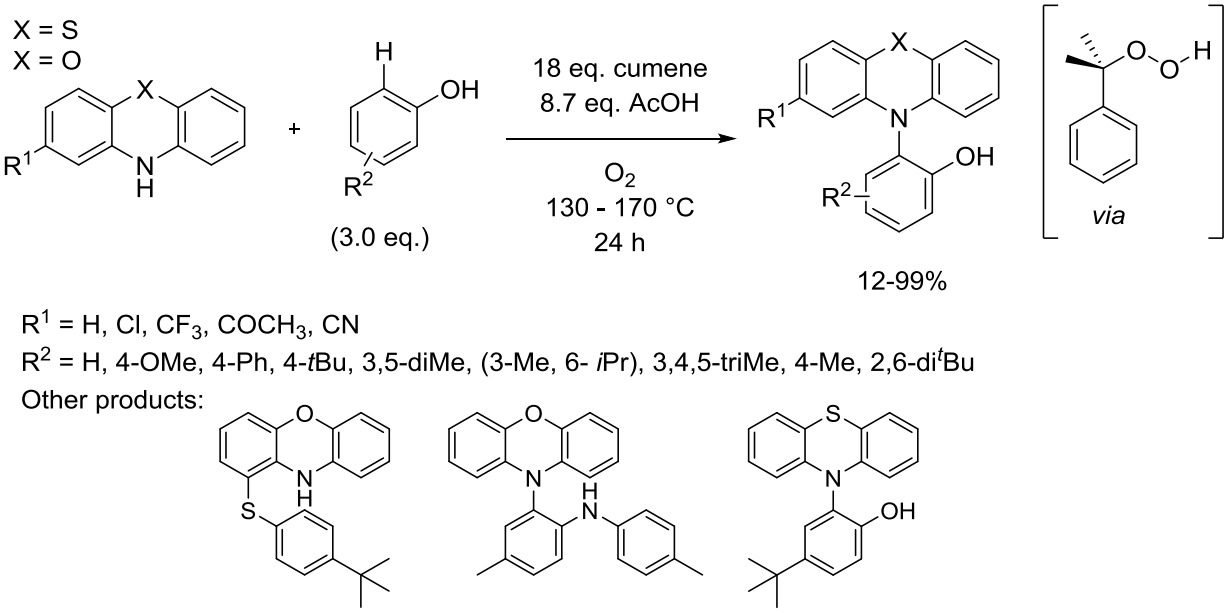
Mefenamic acid **Tolfenamic acid** **Flufenamic acid**

Gram scale synthesis of Flufenamic acid:



Scheme 35: Synthesis of 2-(arylamino)-*N*-(quinolin-8-yl)benzamides.

Patureau reported the O_2-mediated cross dehydrogenative amination of phenols which does not require a transition metal catalyst (

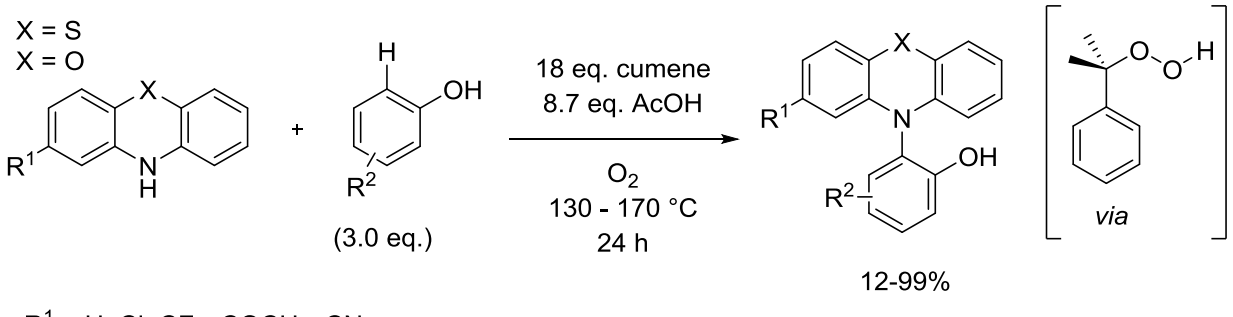


R^1 = H, Cl, CF_3, $COCH_3$, CN

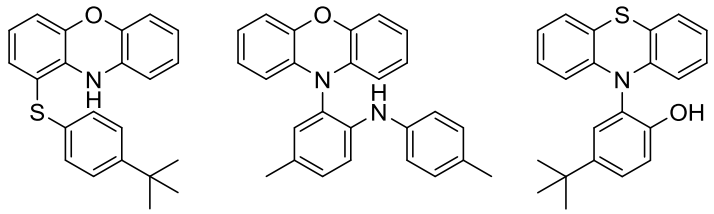
R^2 = H, 4-OMe, 4-Ph, 4-*t*Bu, 3,5-diMe, (3-Me, 6- *i*Pr), 3,4,5-triMe, 4-Me, 2,6-di*t*Bu

Other products:

Scheme **36**). [93] The actual oxidant is generated *in situ* by reaction between cumene and oxygen. Involvement of an α-hydroxycumene was supported by GC-MS and NMR analysis. The C-N bond formation may occur via a homolytic aromatic substitution (HAS) mechanism although an electrophilic amination pathway cannot be ruled out at present. Conceptually it is an interesting study as other oxidants can be *in situ* formed from oxygen and a sacrificial reagent opening new synthetic opportunities. When the phenothiazine or phenoxazine substrate was substituted for a diphenylamine, carbazole or morpholine substrate, unfortunately, no reaction product was formed. The butterfly-shaped structure of the phenothiazine or phenoxazine seems important for the reaction.

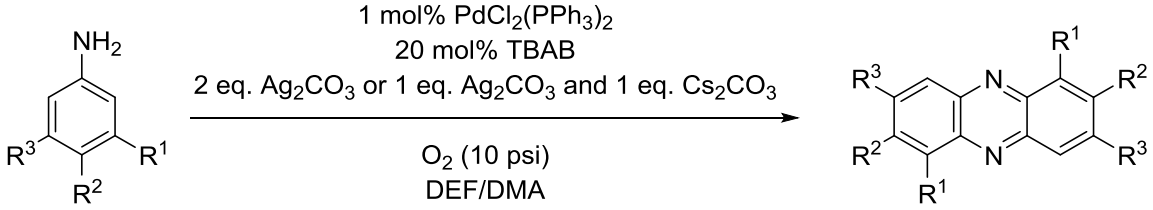


R^1 = H, Cl, CF_3, $COCH_3$, CN
R^2 = H, 4-OMe, 4-Ph, 4-*t*Bu, 3,5-diMe, (3-Me, 6- *i*Pr), 3,4,5-triMe, 4-Me, 2,6-di*t*Bu
Other products:



Scheme 36: Synthesis of 2-(10*H*-phenothiazin-10-yl) and 2-(10*H*-phenoxazin-10-yl) phenols.

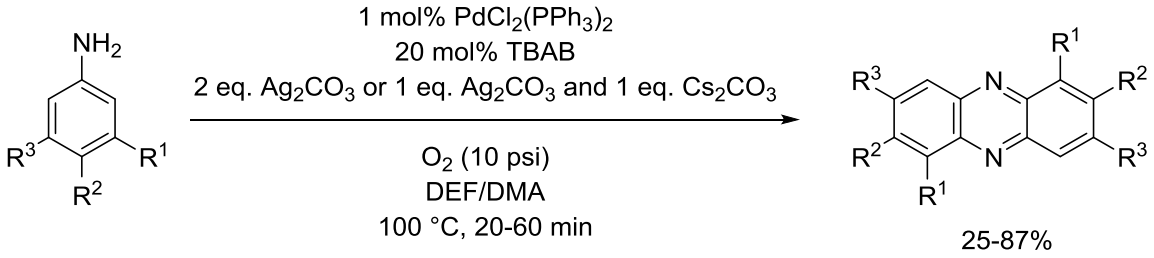
Chakraborti described the synchronous formation of phenazines via homodimerization of anilines based on a synchronous double direct oxidative amination reaction (



R^1 = H, OMe
R^2 = H, Me, OBn, OMe, F, SMe
R^3 = H, OMe

Scheme 37).[94] Tetrabutylammonium bromide (TBAB) is used as stabilizer for the palladium nanoparticles preventing aggregation. A radical reaction was ruled out by addition of TEMPO which had no effect on the reaction rate. The catalytic species is believed to be a Pd-Ag binary nanocluster. Oxygen is capable of oxidizing the Ag(0) atoms to Ag(I) which are situated at the surface of the nanocluster. Ag(I) coordinates with the anilide anion, formed by deprotonation of the aniline substrate by carbonate base. The silver is still bound to palladium via metal metal bonding to which it transfers electron density. Direct ortho palladation by the electron rich Pd forms an intermediate which is converted to a Pd(II) containing metallacycle by oxidative insertion. Another equivalent of this metallacycle reacts with the first one creating a dimeric Pd(IV) species under the influence of Ag_2CO_3 and O_2. Mutual reductive elimination delivers a dihydrophenazine which is converted to the reaction product by Ag(I)/O_2. Oxygen is essential as

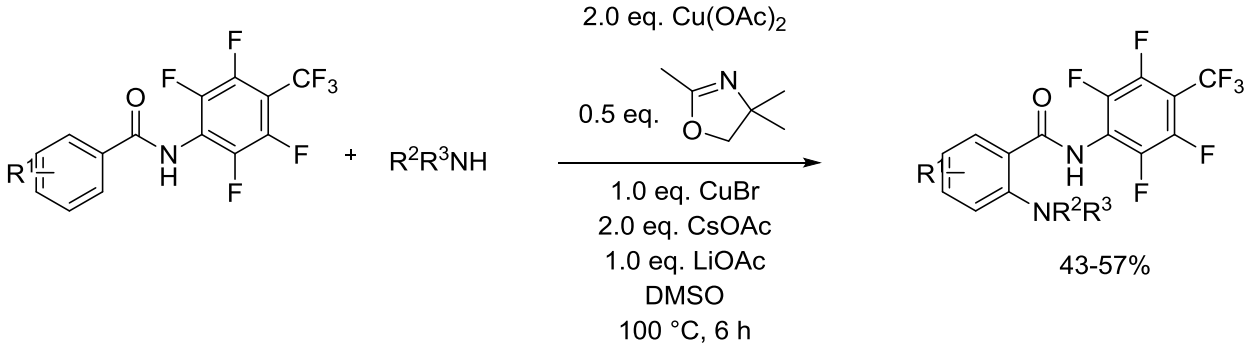
co-oxidant to achieve high yields. A mixture of dimethylacetamide (DMA) and diethylformamide (DEF) was used as solvent.



R^1 = H, OMe
R^2 = H, Me, OBn, OMe, F, SMe
R^3 = H, OMe

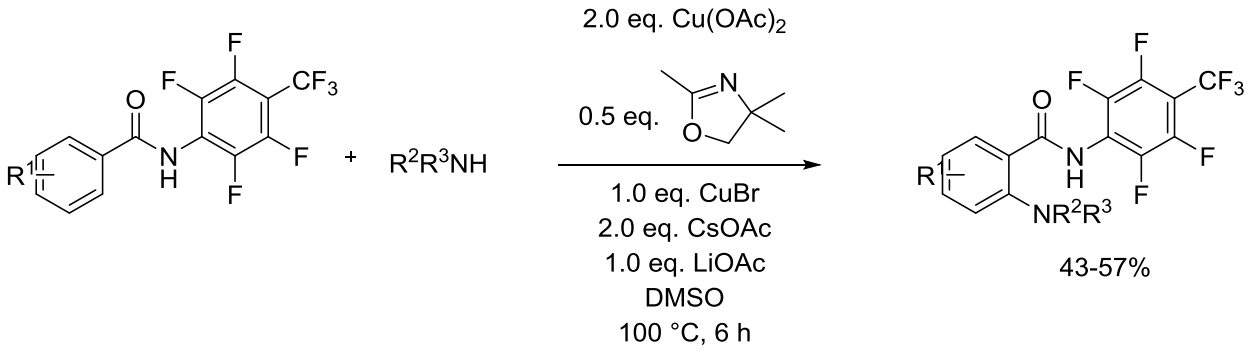
Scheme 37: Synthesis of phenazines.

Yu developed a protocol for direct *ortho* C-H amination using an oxazoline as a ligand for a Cu mediated reaction (



R^1 = H, 4-Me, 4-F, 4-Cl, 4-CF_3, 4-vinyl, 4-PhCO
R^2R^3NH = morpholine, piperidine, 4-methylpiperidine, 4-Boc-piperazine, ethyl piperidine-4-carboxylate

Scheme **38**).[95] A weakly directing coordinating group based on an electron deficient aromatic amide is used which creates a less thermodynamically stable metallacycle upon C-H activation which kinetically facilitates subsequent amine functionalization.



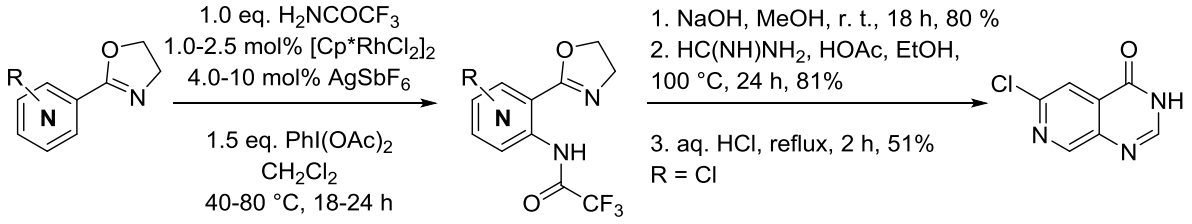
R^1 = H, 4-Me, 4-F, 4-Cl, 4-CF_3, 4-vinyl, 4-PhCO

R^2R^3NH = morpholine, piperidine, 4-methylpiperidine, 4-Boc-piperazine, ethyl piperidine-4-carboxylate

Scheme 38: Synthesis of 2-aminated *N*-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl]benzamides.

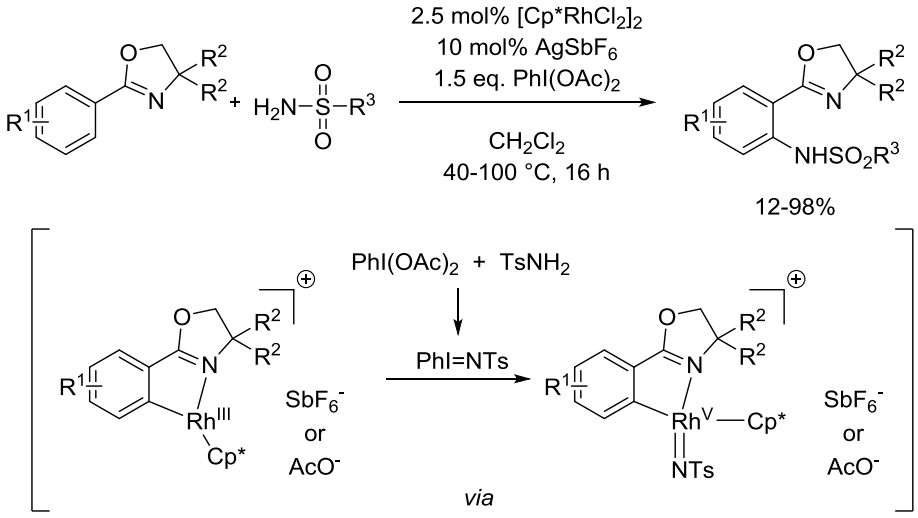
A specific amidation reaction was developed using an oxazoline as directing group (

A Synthesis of *N*-[(4,5-dihydrooxazol-2-yl)-pyridinyl]-2,2,2-trifluoroacetamides.



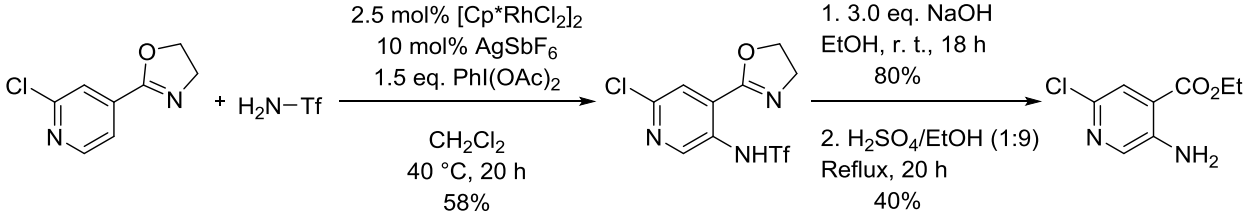
For *2*-substituted pyridine: R = 6-F, 6-Cl, 6-F, 6-Cl, 6-Br, 6-CF_3, 6-SO_2Ph, 6-OMe, 6-NMe_2, 6-Me, 6-*t*-Bu, 6-Ph, 6-(2,6-diMePh)
For 4-subsituted pyridine: R = 2-F, 2-Cl, 2-CF_3, 2-Me, 2-(2,6-diMePh)

B Synthesis of *N*-[2-(4,5-dihydrooxazol-2-yl)phenyl](sulfon)amides.



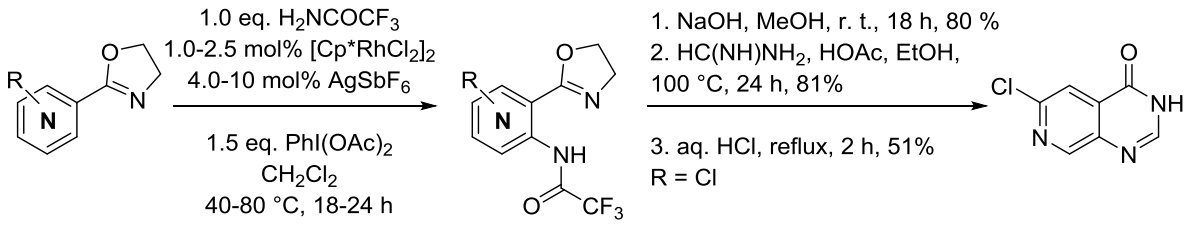
R^1 = H, 3-OMe, 4-OMe, 4-Me_2N, 4-Me, 4-CO_2Me, 4-F, 3-F
R^2 = H, Me
R^3 = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, Me
Other amides: CF_3CONH_2

C Synthesis of ethyl 2-chloro-5 (trifluoromethylsulfonamido)isonicotinate.



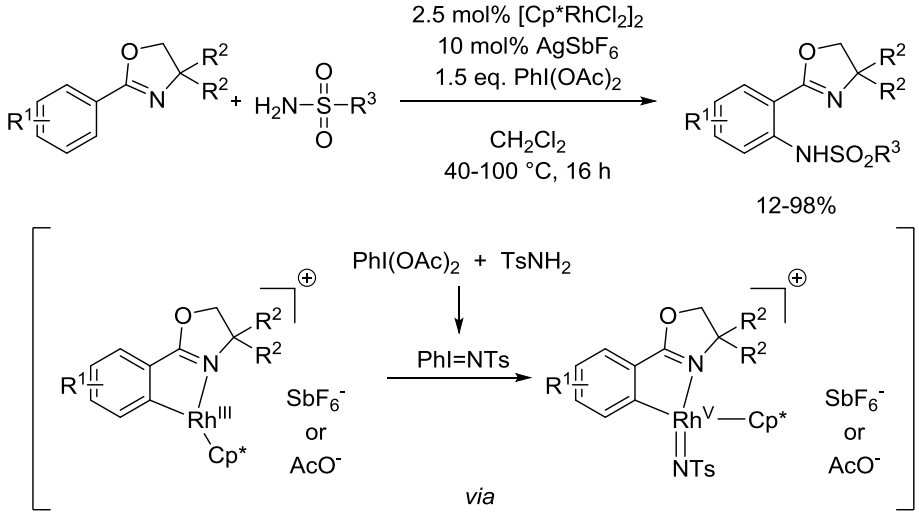
Scheme **39**).[96] Using a rhodium complex as catalyst, trifluoroacetamide could be coupled to either 6- or 2-substituted pyridines featuring the DG in position 2 or 4. PIDA functions as the stoichiometric oxidant but no further mechanistic details were disclosed and therefore the role of $AgSbF_6$ is unclear. Interestingly, the trifluoroacetyl group could be easily removed afterwards by hydrolysis using sodium hydroxide in methanol, yielding the corresponding aminopyridines. The scope included halogenated pyridines, so that after amidation follow-up reactions such as Suzuki cross couplings or nucleophilic aromatic substitutions were possible. The formation of azaquinazolinones was also possible. This was realized by performing three consecutive reactions. The first one involved the deprotection of the trifluoroacetyl group, yielding a free amino group. This amino group was subsequently allowed to react with formamidine. In the last step, acid hydrolysis of the oxazoline group and condensation of the *in situ* formed carboxylic acid with the formamidine group yields azaquinazolinones.

A Synthesis of *N*-[(4,5-dihydrooxazol-2-yl)-pyridinyl]-2,2,2-trifluoroacetamides.



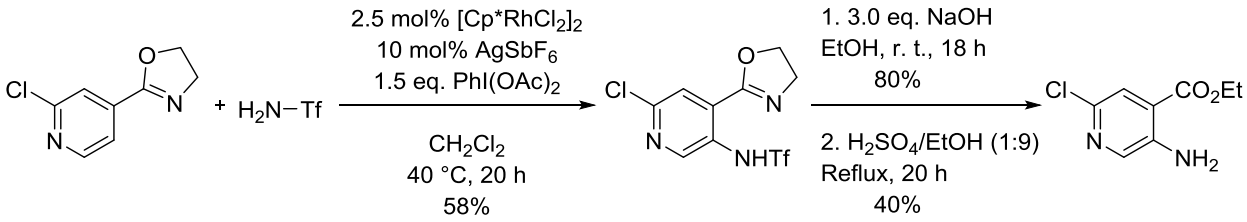
For *2*-substituted pyridine: R = 6-F, 6-Cl, 6-F, 6-Cl, 6-Br, 6-CF_3, 6-SO_2Ph, 6-OMe, 6-NMe_2, 6-Me, 6-*t*-Bu, 6-Ph, 6-(2,6-diMePh)
For 4-subsituted pyridine: R = 2-F, 2-Cl, 2-CF_3, 2-Me, 2-(2,6-diMePh)

B Synthesis of *N*-[2-(4,5-dihydrooxazol-2-yl)phenyl](sulfon)amides.



R^1 = H, 3-OMe, 4-OMe, 4-Me_2N, 4-Me, 4-CO_2Me, 4-F, 3-F
R^2 = H, Me
R^3 = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, Me
Other amides: CF_3CONH_2

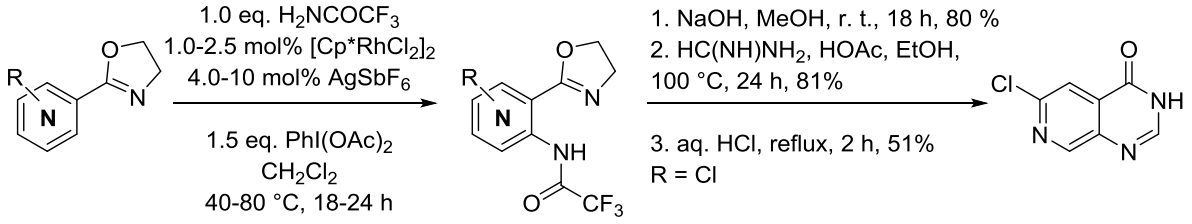
C Synthesis of ethyl 2-chloro-5 (trifluoromethylsulfonamido)isonicotinate.



Scheme 39: Synthesis of *N*-[(4,5-dihydrooxazol-2-yl)-pyridinyl]-2,2,2-trifluoroacetamides and -sulfonamides.

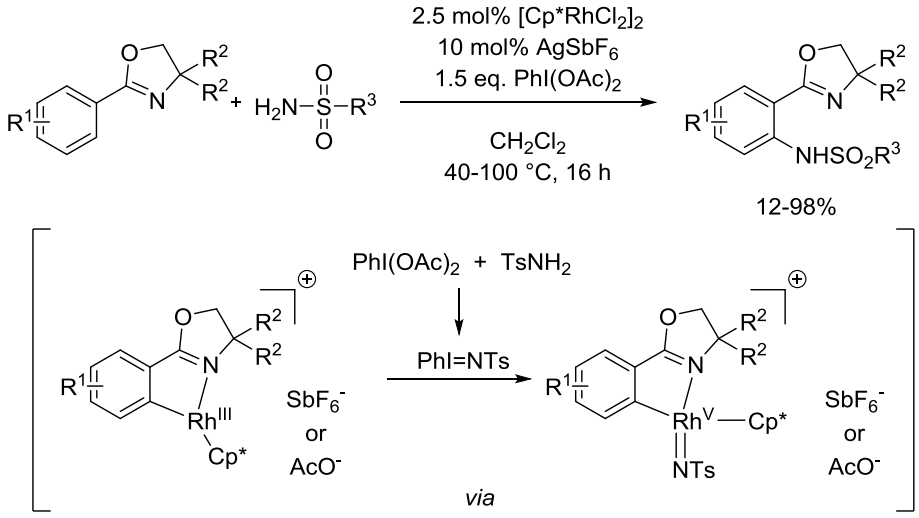
In a follow-up publication, the scope is extended to amidation using sulfonamides (

A Synthesis of *N*-[(4,5-dihydrooxazol-2-yl)-pyridinyl]-2,2,2-trifluoroacetamides.



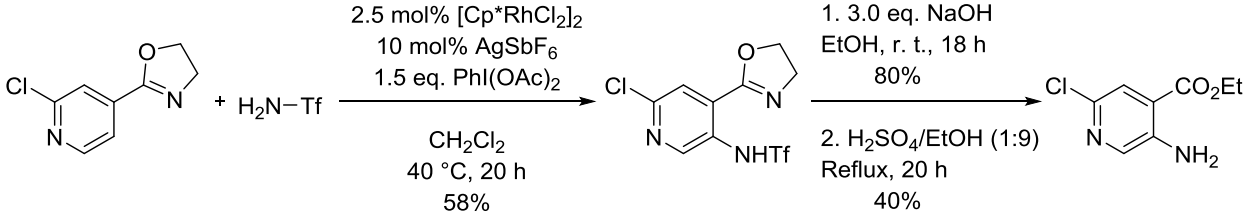
For *2*-substituted pyridine: R = 6-F, 6-Cl, 6-F, 6-Cl, 6-Br, 6-CF_3, 6-SO_2Ph, 6-OMe, 6-NMe_2, 6-Me, 6-*t*-Bu, 6-Ph, 6-(2,6-diMePh)
For 4-subsituted pyridine: R = 2-F, 2-Cl, 2-CF_3, 2-Me, 2-(2,6-diMePh)

B Synthesis of *N*-[2-(4,5-dihydrooxazol-2-yl)phenyl](sulfon)amides.



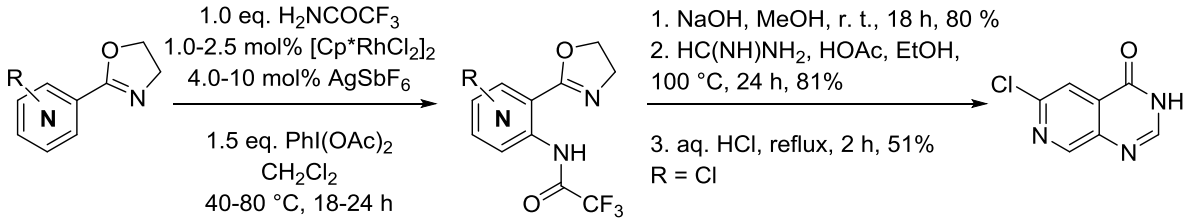
R^1 = H, 3-OMe, 4-OMe, 4-Me_2N, 4-Me, 4-CO_2Me, 4-F, 3-F
R^2 = H, Me
R^3 = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, Me
Other amides: CF_3CONH_2

C Synthesis of ethyl 2-chloro-5 (trifluoromethylsulfonamido)isonicotinate.



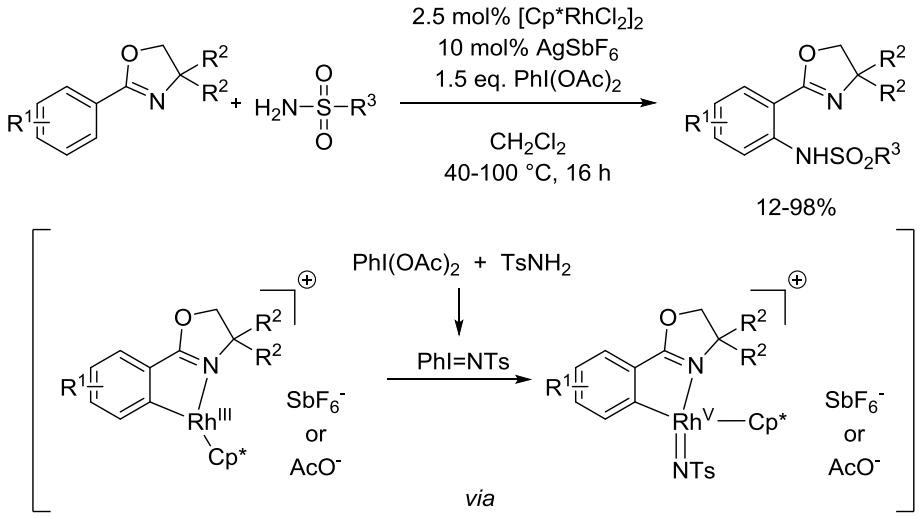
Scheme **39**, B).[97] To demonstrate the potential of the method to synthesize multisubstituted heterocycles, a trisubstituted pyridine was prepared using the newly developed reaction protocol (

A Synthesis of *N*-[(4,5-dihydrooxazol-2-yl)-pyridinyl]-2,2,2-trifluoroacetamides.



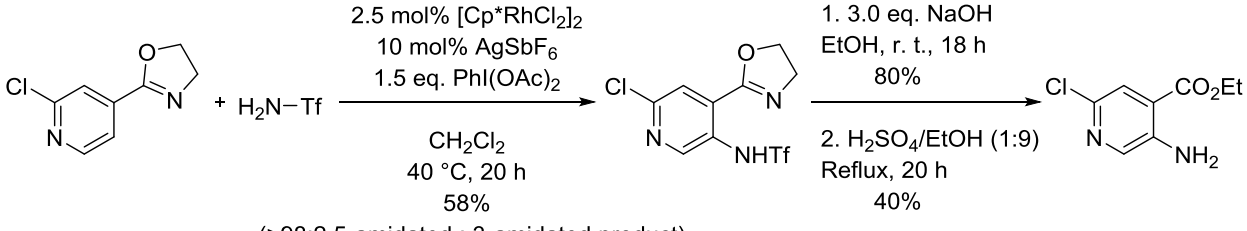
For *2*-substituted pyridine: R = 6-F, 6-Cl, 6-F, 6-Cl, 6-Br, 6-CF_3, 6-SO_2Ph, 6-OMe, 6-NMe_2, 6-Me, 6-*t*-Bu, 6-Ph, 6-(2,6-diMePh)
For 4-subsituted pyridine: R = 2-F, 2-Cl, 2-CF_3, 2-Me, 2-(2,6-diMePh)

B Synthesis of *N*-[2-(4,5-dihydrooxazol-2-yl)phenyl](sulfon)amides.



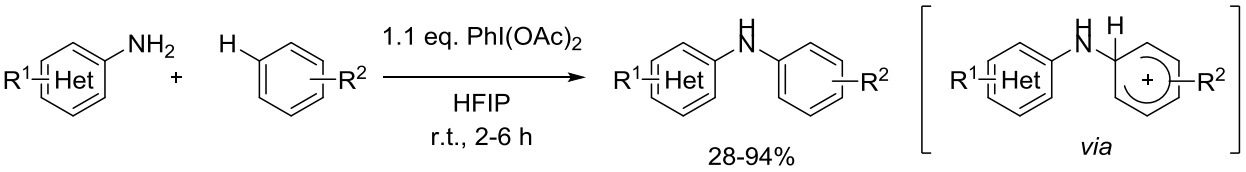
R^1 = H, 3-OMe, 4-OMe, 4-Me_2N, 4-Me, 4-CO_2Me, 4-F, 3-F
R^2 = H, Me
R^3 = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, Me
Other amides: CF_3CONH_2

C Synthesis of ethyl 2-chloro-5 (trifluoromethylsulfonamido)isonicotinate.

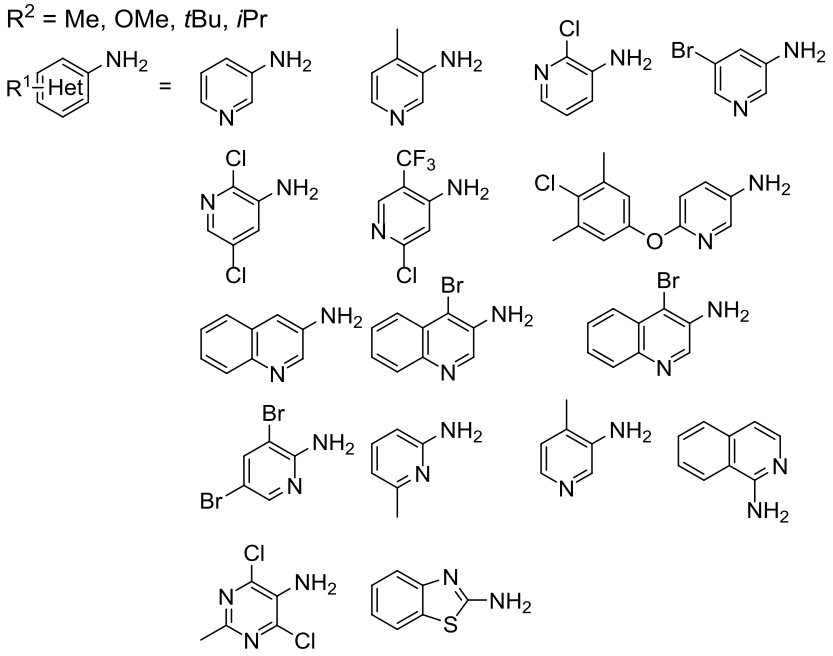


Scheme **39**, C). The oxazoline group could be transformed into an ethyl carboxylate group by subsequent hydrolysis and esterification. C-H activation by the Rh-catalyst produces a rhodacycle which can be transformed into a Rh(IV) nitrenoid species by reaction with PhINTs. The PhINTs is formed *in situ* from reaction of PIDA with $TsNH_2$.

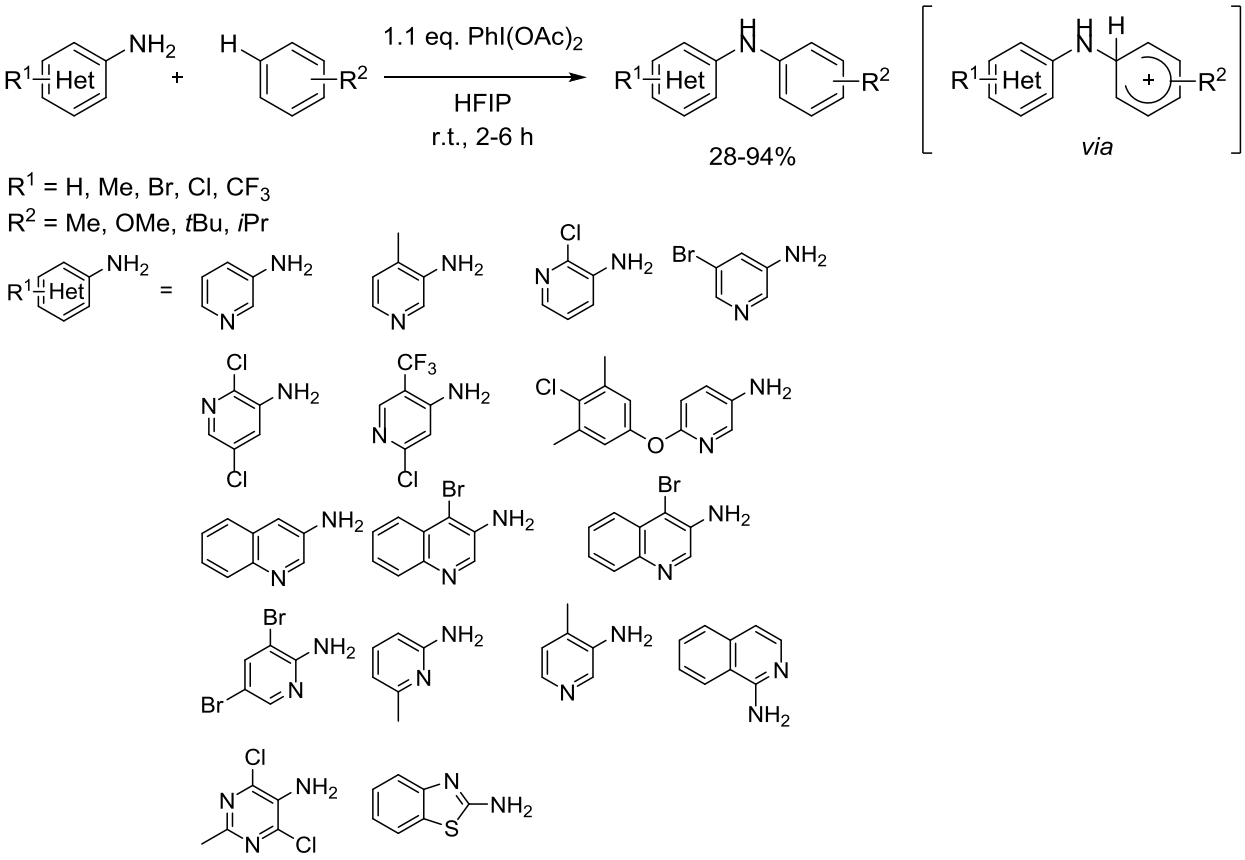
Chupakhin and Antonchick recently reported the use of hypervalent iodine (III) for the cross hydrogenative amination of arenes (



R^1 = H, Me, Br, Cl, CF_3
R^2 = Me, OMe, *t*Bu, *i*Pr

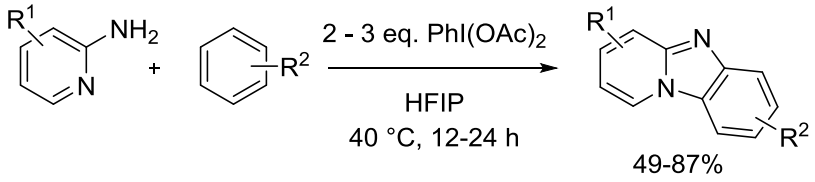


Scheme **40**).[98] This approach allows coupling of electron-poor heterocyclic amines with electron rich arenes without the assistance of metal catalysts. Again a perfluorinated alcohol as solvent is superior. Interestingly, it is also demonstrated that iodobenzene can be used catalytically (0.25 mol%.) when AcOOH is added as the stoichiometric oxidant. A plausible mechanism consists of nucleophilic attack of the aminogroup to the phenyl iodosyl acetate with loss of acetic acid. Subsequently, electrophilic aromatic substitution by attack of the aryl ring to the nitrogen with loss of acetate and iodobenzene gives the cationic intermediate. Deprotonation by acetate leads to rearomatization. This is in agreement with the absence of an intermolecular KIE.

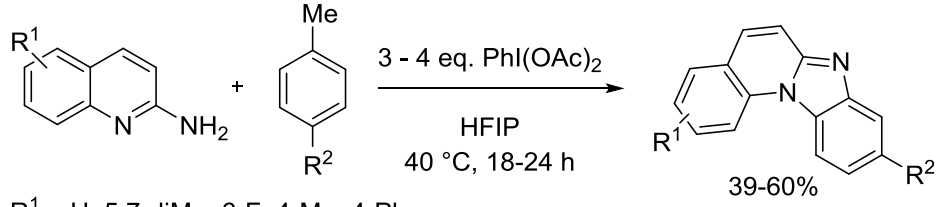


Scheme 40: Synthesis of *N*-(hetero)arylanilines.

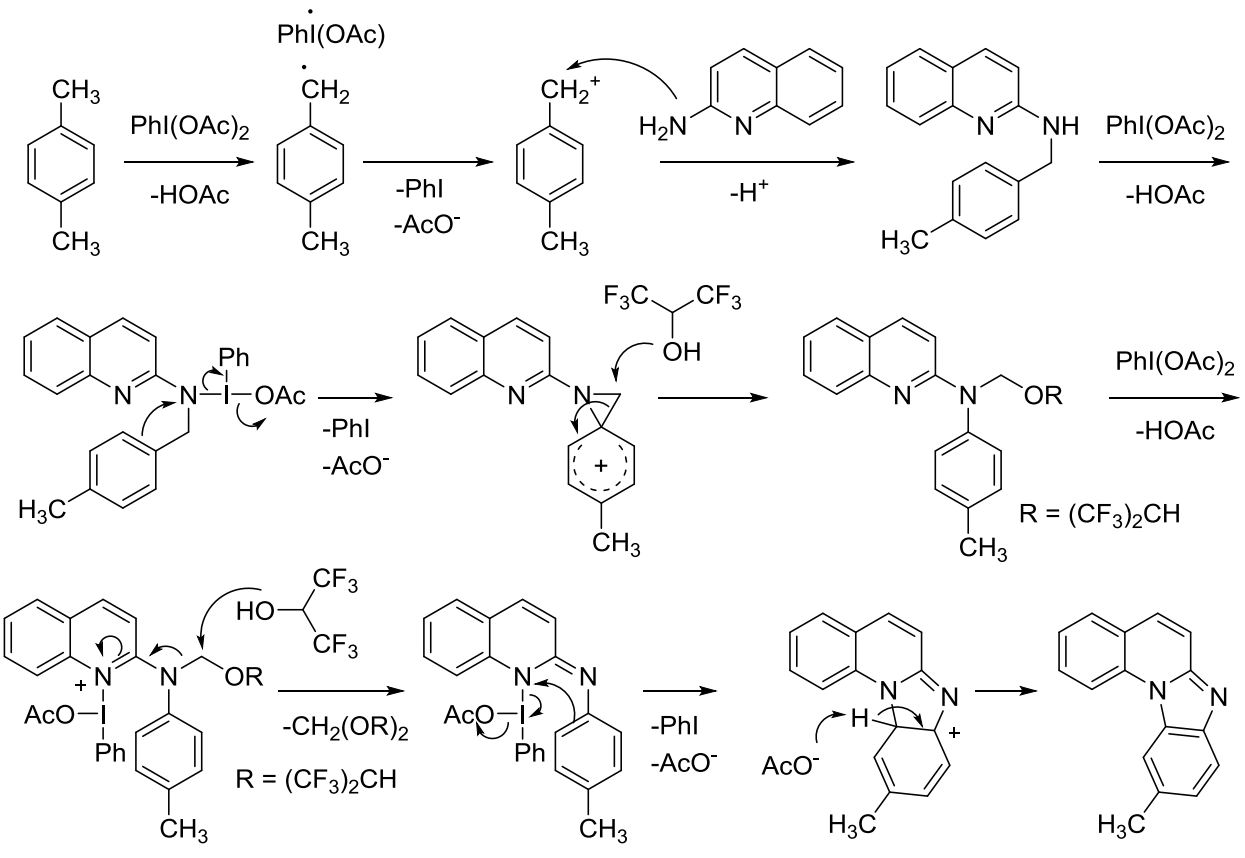
Previously, Antonchick already reported the use of $PhI(OAc)_2$ for the annulation of arenes with 2-aminopyridine derivatives (



R^1 = H, 2-Br, 4-Br, 5-Br, 6-Br, 2-Me, 4-Me, 5-Me, 6-Me, 5-F, 4-OAc
ArR^2 = anisole, diphenylether, *m*-xylene, *p*-xylene, 1-methylnapthalene, 2,3-diisopropylbenzene, 1-ethyl-3-methylbenzene, toluene, 1,2,3,4-tetrahydronapthalene, iodobenzene, 2-(3-methoxyphenyl)acetonitrile

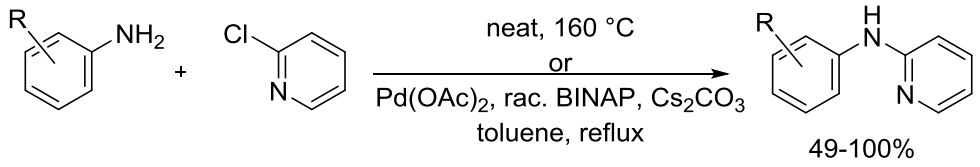


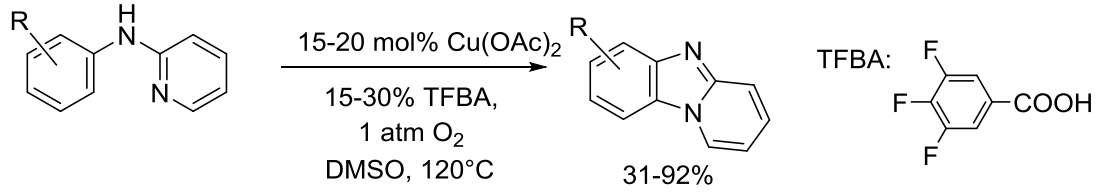
R^1 = H, 5,7-diMe, 6-F, 4-Me, 4-Ph
R^2 = Me, I



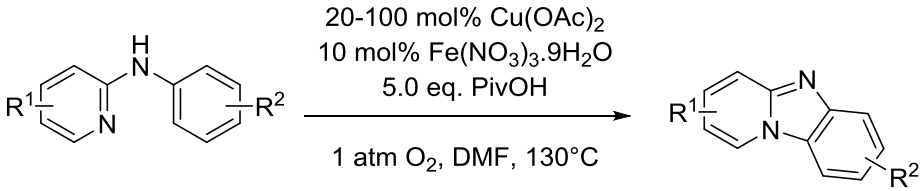
Scheme **41**).[99] This yielded the same products as obtained by Maes and Zhu using a base metal and oxygen as the stoichiometric oxidant, but via a double C-H functionalization in a

tandem fashion (



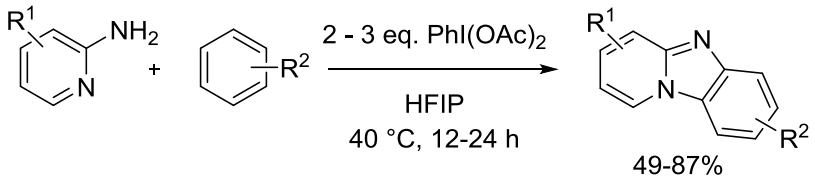


R = 4-CF_3, 6-F, 7-F, 9-F, 8-F, 6-OMe, 7-OMe, 9-OMe, 8-OMe, 8-Cl, 8-CO_2Et, 7-CO_2Et, 8-CF_3, 6-Cl, (2-Cl, 5-OMe), 2-Cl, 2,6-diCl, (2-Cl, 3-F)

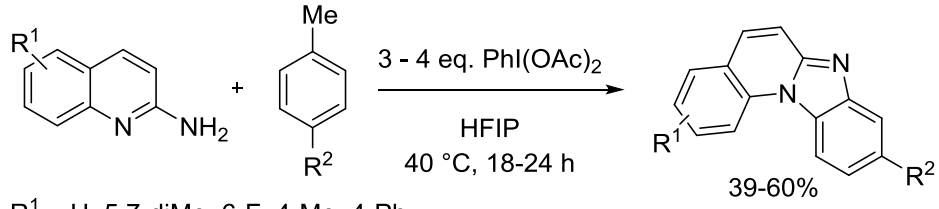


R^1 = H, 4-Me, 4-OMe, 4-^{t}Bu, 4-F, 4-Cl, 4-Br, 2-Me, 2-OMe, 2-F
R^2 = H, 3-Me, 3-OMe, 3-Cl, 3-F, 4-Me

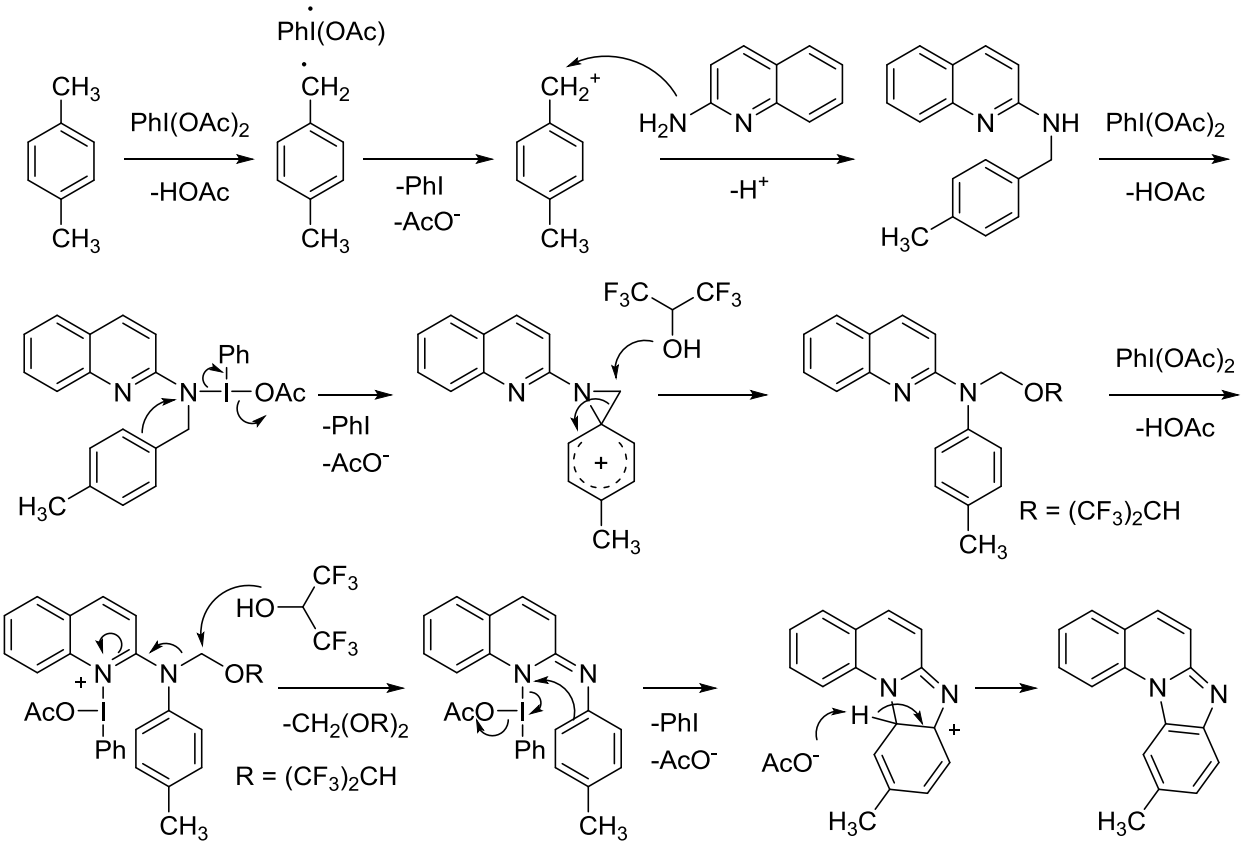
Scheme **4**). In the same article they also describe the use of the methyl group as a traceless, non-chelating directing group when 2-aminoquinolines were used. This is a remarkable demethylative process.



R^1 = H, 2-Br, 4-Br, 5-Br, 6-Br, 2-Me, 4-Me, 5-Me, 6-Me, 5-F, 4-OAc
ArR^2 = anisole, diphenylether, *m*-xylene, *p*-xylene, 1-methylnapthalene, 2,3-diisopropylbenzene, 1-ethyl-3-methylbenzene, toluene, 1,2,3,4-tetrahydronapthalene, iodobenzene, 2-(3-methoxyphenyl)acetonitrile



R^1 = H, 5,7-diMe, 6-F, 4-Me, 4-Ph
R^2 = Me, I

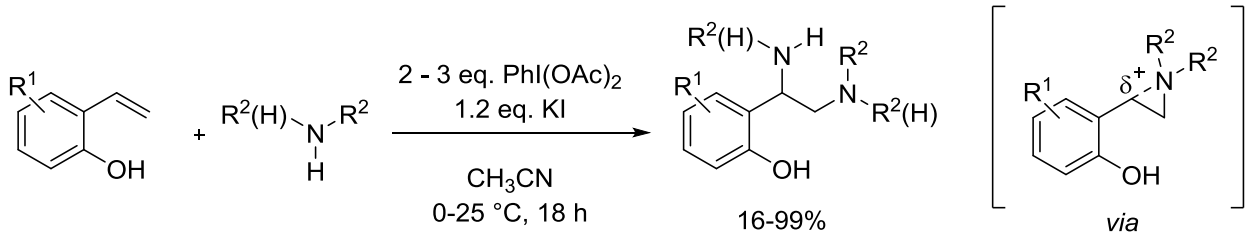


Scheme 41: Synthesis of pyrido[1,2-*a*]benzimidazoles and benzo annulated derivatives.

With 2-aminopyridines, the proposed mechanism is a rather classic C-H functionalization with hypervalent iodine compounds. It starts by nucleophilic attack of the amino group to the

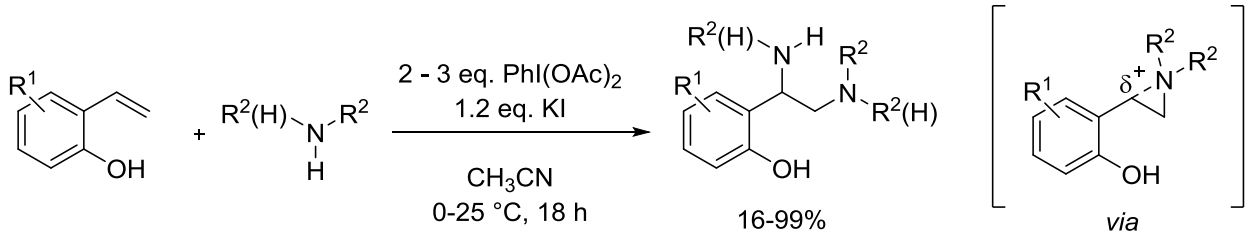
hypervalent iodine compound with loss of acetic acid. Subsequent attack of the aryl group to the formed N activated species followed by deprotonation gives the reaction product and iodobenzene as by-product. When 2-aminoquinolines are used as substrate, the reaction pathway is different. This is most probably due to the lower reactivity of 2-aminoquinolines towards $PhI(OAc)_2$ than 2-aminopyridines. During the reaction, the methyl group is eventually removed as the methylene acetal of the solvent: $CH_2[OCH(CF_3)_2]_2$. Based on the mechanistic proposal a direct oxidative C(sp^3)–H amination is occurring first in this case, representing then an example of Section 2.3.2.

Johnston described the diamination of hydroxystyrenes with electron-rich amines applying a $PhI(OAc)_2$/KI system (



R^1 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OMe, 4-OH, 5-OMe, 6-OMe
$R^2(H)R^2NH$ = thiomorpholine, morpholine, piperidine, isoindole, *N*-Cbz-piperidine, *N*-Boc-piperidine, *N*-CO_2Et-piperidine, *N*-(4-methoxyphenyl)piperidine, *N*-cinnamylpiperazine, dibenzylamine, *N*-methylbenzylamine, aniline, 4-fluoroaniline, 4-*t*Bu-aniline, 3,5-dimethylaniline

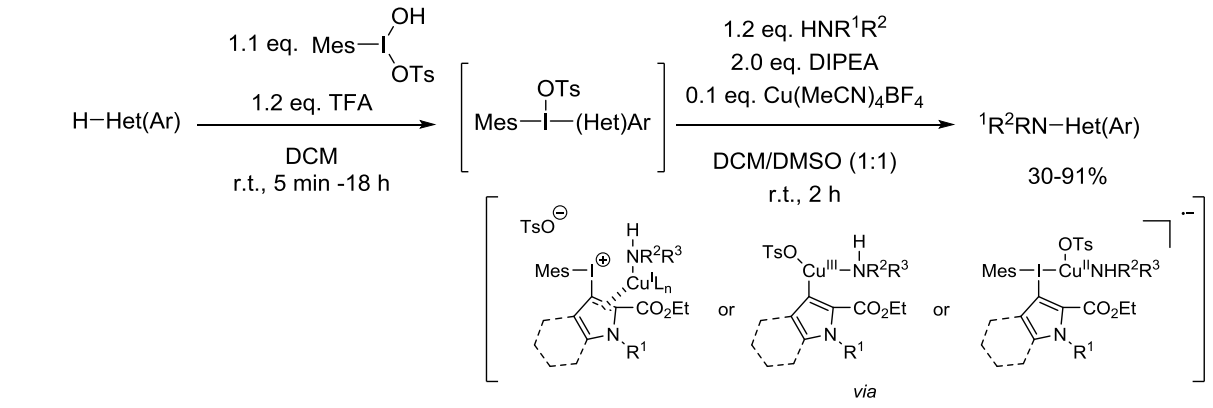
Scheme **42**).[100] Reaction of the amine with the hypervalent iodine compound and KI generates an *N*-iodinated amine R_2NI. Nucleophilic attack of the double bond onto the nitrogen atom of this N-iodo amine gives a benzylic cationic intermediate. Attack of the nitrogen atom on the cation benzylic group leads to stabilization and distribution of the positive charge on nitrogen. Formation of an *ortho*-quinone methide, although not essential, can also lead to cation stabilization. A second equivalent amine can attack the benzylic position with formation of a diaminated product. Similar work was reported before by Muñiz for electron-deficient amines involving a palladium catalyst.[101]

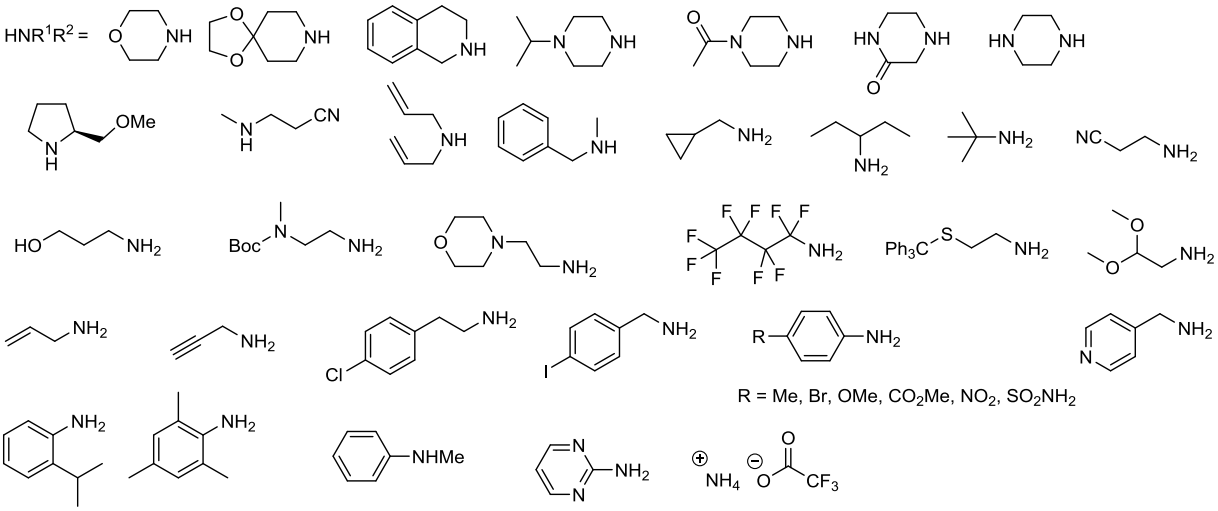


R^1 = H, 4-F, 4-Cl, 4-Br, 4-NO_2, 4-OMe, 4-OH, 5-OMe, 6-OMe
$R^2(H)R^2NH$ = thiomorpholine, morpholine, piperidine, isoindole, *N*-Cbz-piperidine, *N*-Boc-piperidine, *N*-CO_2Et-piperidine, *N*-(4-methoxyphenyl)piperidine, *N*-cinnamylpiperazine, dibenzylamine, *N*-methylbenzylamine, aniline, 4-fluoroaniline, 4-*t*Bu-aniline, 3,5-dimethylaniline

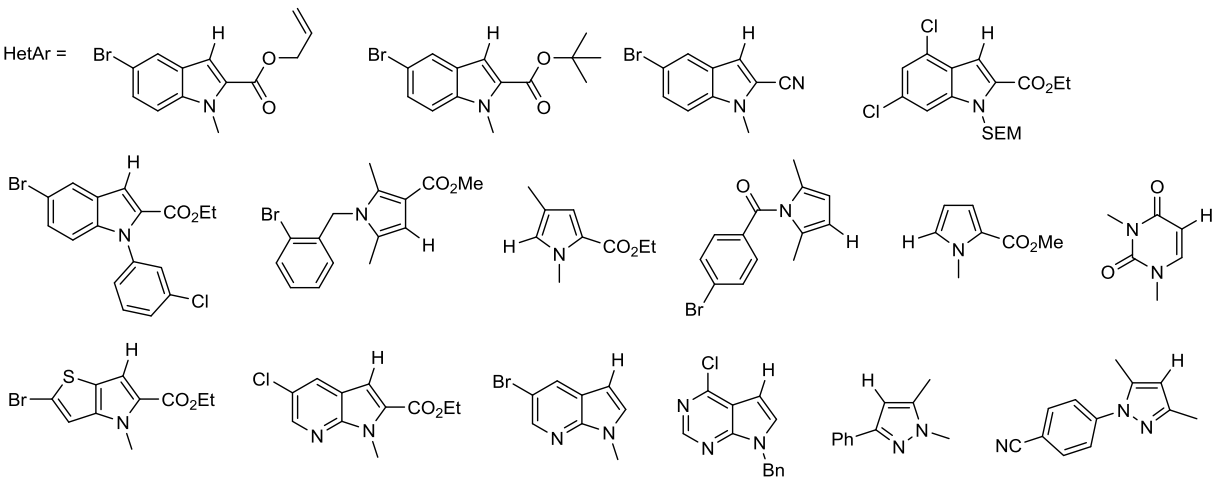
Scheme 42: Synthesis of 2-[1,2-bis(aryl- or alkylamino)ethyl]phenols.

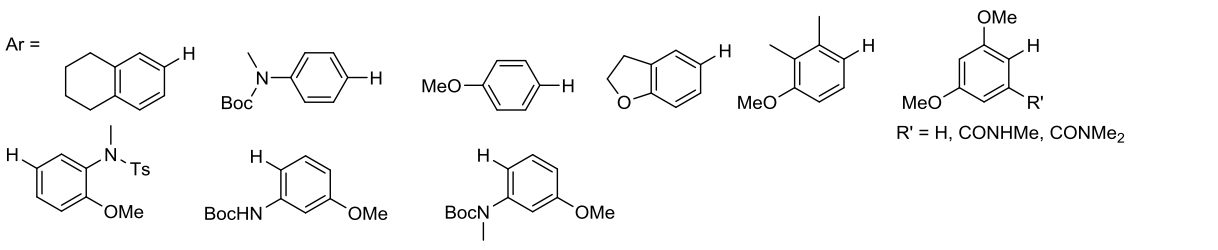
Another example of the use of hypervalent iodine compounds in C-H aminations is the copper-catalyzed amination of various (hetero)arenes using MesI(OH)OTs (





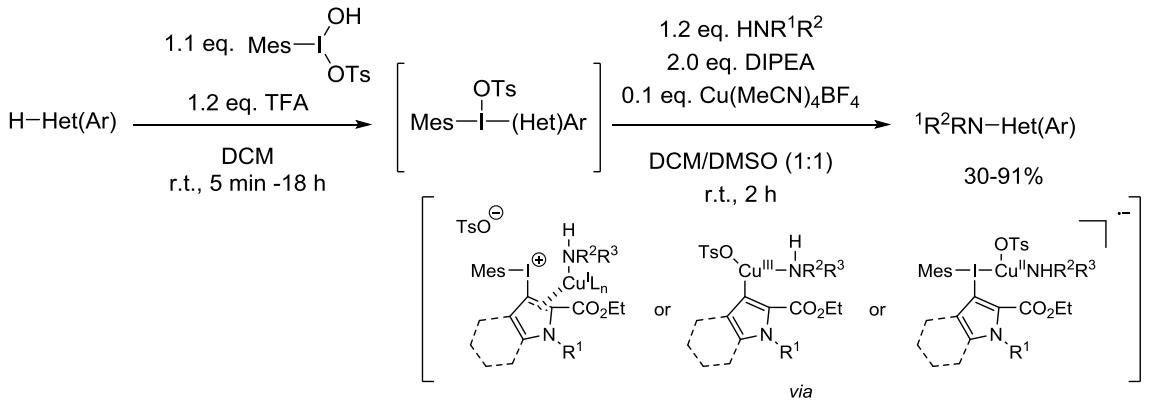
R = Me, Br, OMe, CO_2Me, NO_2, SO_2NH_2

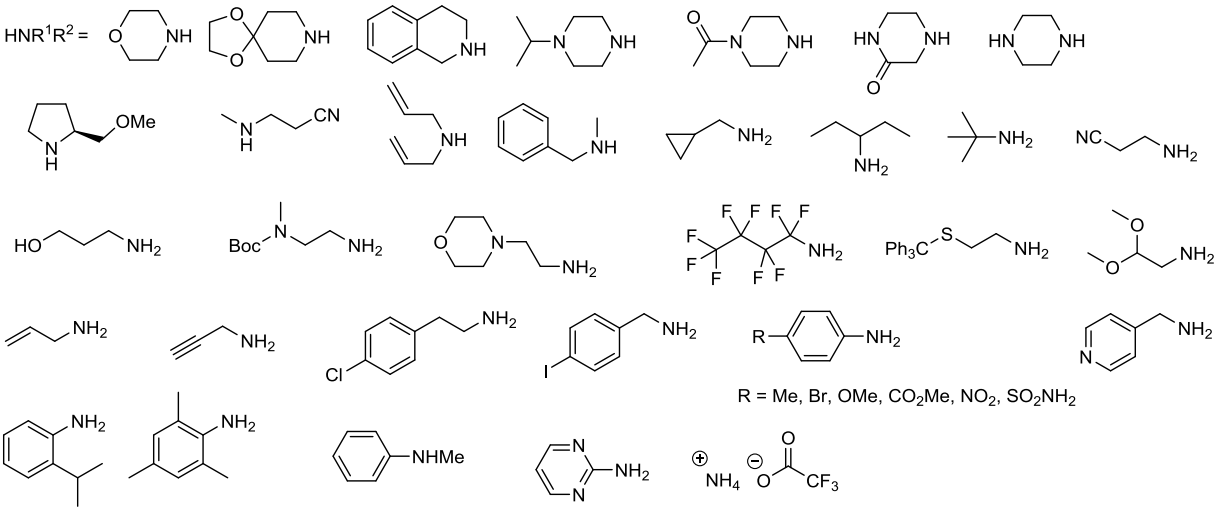


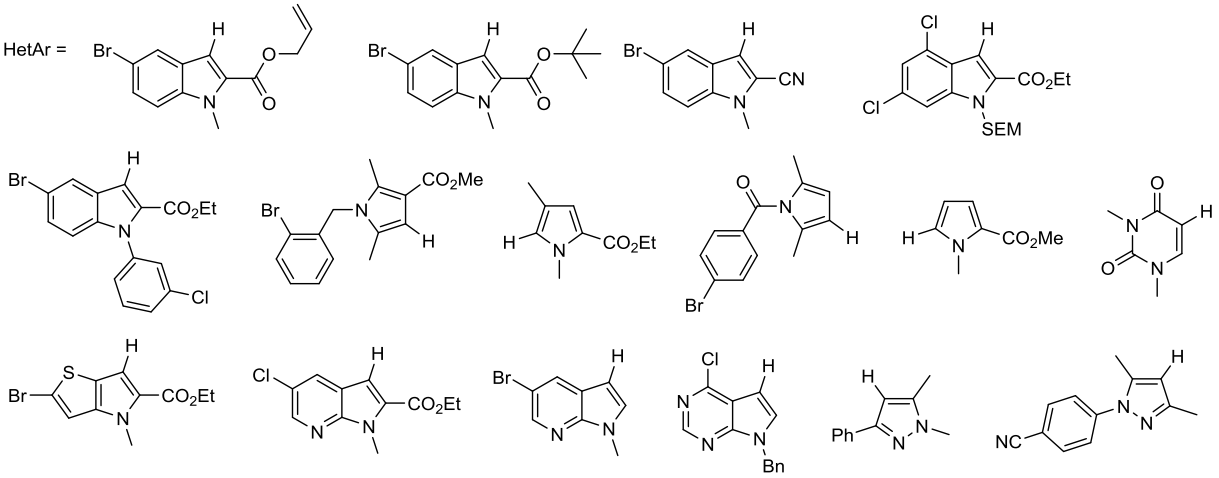


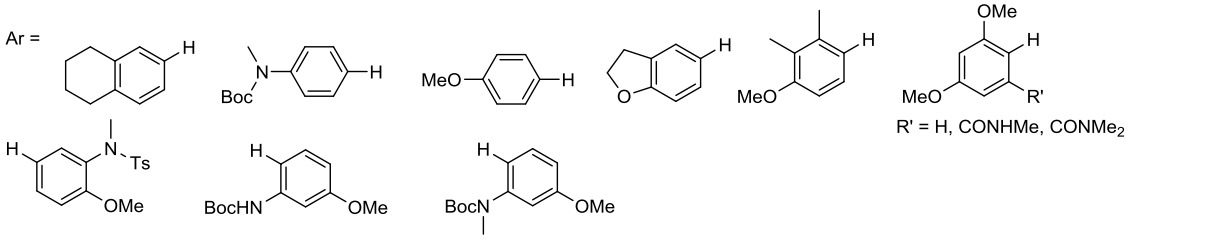
R' = H, CONHMe, $CONMe_2$

Scheme **43**).[102] The reaction is a one-pot protocol in which the (hetero)aryl-λ^3-iodane is first formed. The (hetero)arene needs to be sufficiently electron-rich in order to be able to react with MesI(OH)OTs. Subsequent addition of the amine and copper catalyst leads to the aminated product. The reaction is compatible with a wide range of aliphatic amines as well as anilines. The authors proposed several possible mechanistic pathways for the amination in which $L_nCu(I)NHR^1R^2$ is the catalytic species. In the first possibility, coordination of the Cu(I) catalytic species with the indole of the λ^3-iodine leads to formation of an η^2-coordinated species. Substitution of the tosylate by the amine and subsequent reductive elimination leads to the aminated product. A second possibility starts with a direct oxidative addition of the λ^3-iodine to the Cu(I) catalyst. N-H deprotonation by DIPEA of the formed Cu(III) intermediate complex followed by reductive elimination gives the reaction product. A final alternative is a radical pathway containing a Cu(I)/Cu(II) catalytic cycle. A SET from the Cu(I) species to the λ^3-iodine yields an intimate radical anion Cu(II) complex containing a Cu-I bond. Fragmentation of this complex yields an (hetero)aryl radical which can bond with the amine in a second SET. The regioselectivity is determined by substituents in the heterocycles and arenes and was found to be consistent with electrophilic aromatic substitution (S_EAr) reactions.


1.1 eq. Mes–I(OH)OTs
1.2 eq. TFA
DCM
r.t., 5 min -18 h
H–Het(Ar)
Mes–I(OTs)–(Het)Ar
1.2 eq. HNR1R2
2.0 eq. DIPEA
0.1 eq. Cu(MeCN)4BF4
DCM/DMSO (1:1)
r.t., 2 h
1R2RN–Het(Ar)
30-91%
or
or
via


HNR1R2 =
R = Me, Br, OMe, CO2Me, NO2, SO2NH2

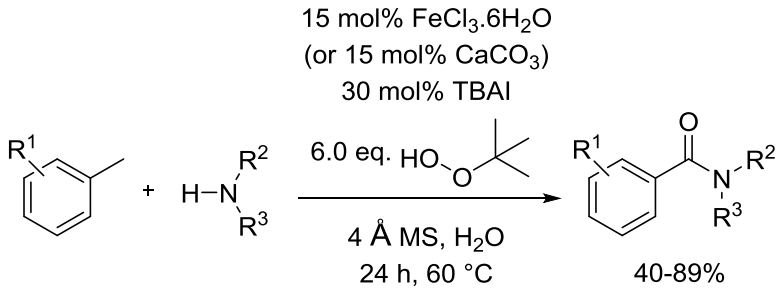

HetAr =


Ar =
R' = H, CONHMe, CONMe2

Scheme 43: Synthesis of heteroarylamines and arylamines.

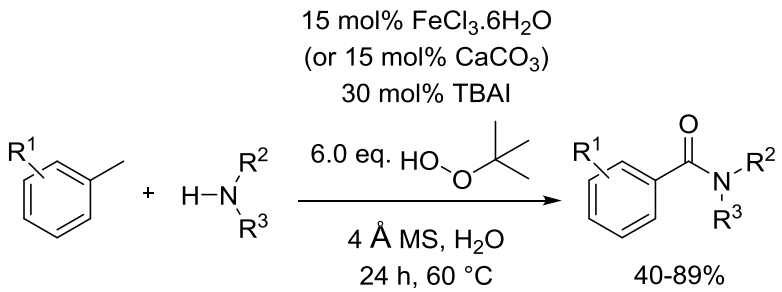
2.3.2 Intermolecular C(sp^3)-N bond formation

Zhao reported the direct oxidative amidation between toluenes and amines in water (



R_1 = 4-Me, 3-Me, 2-Me, 2,4-diMe, 4-OMe, 4-Cl, 3-Cl, 2-Cl, 4-I, 3-I, 4-Br, 4-CN
R_2 = H, R^3 = Bu, Me, Et, Pr, pentyl, CH_2CH_2Ph, $CH_2CH_2CO_2Et$,
$CH(CH_3)CH_2CH_3$, cyclohexyl, cyclohexyl, *t*-Bu, $CH(CH_3)CO_2Me$,
$CH[CH_2CH(CH_3)_2]CO_2Me$, $CH(CH_2Ph)CONHCH_2CO_2Me$
HNR_2R_3 = Morpholine

Scheme **44**).[103] This is a sustainable way for the synthesis of *N*-substituted benzamides. TBHP is used as the stoichiometric oxidant together with TBAI and $FeCl_3$ catalyst. Reaction of the iodide of TBAI with TBHP generates either IO^- or IO_2^-. In combination with $FeCl_3$, the toluene is converted to a benzylic alcohol. Oxidation of this benzylalcohol by either IO^- or IO_2^- forms benzaldehyde. Nucleophilic addition of the amine to the aldehyde carbonyl leads to a hemiaminal which is oxidized again by either IO^- or IO_2^- to amide. Benzyl alcohol and aldehyde have been confirmed as intermediates. When molecular sieves were used, a slight increase in yield was observed. Interestingly, in the presence of TEMPO, the reaction of toluene and benzyl alcohol was completely inhibited while the reaction of benzaldehyde was kept intact which suggest that the oxidation of toluene and benzyl alcohol might involve a radical process.

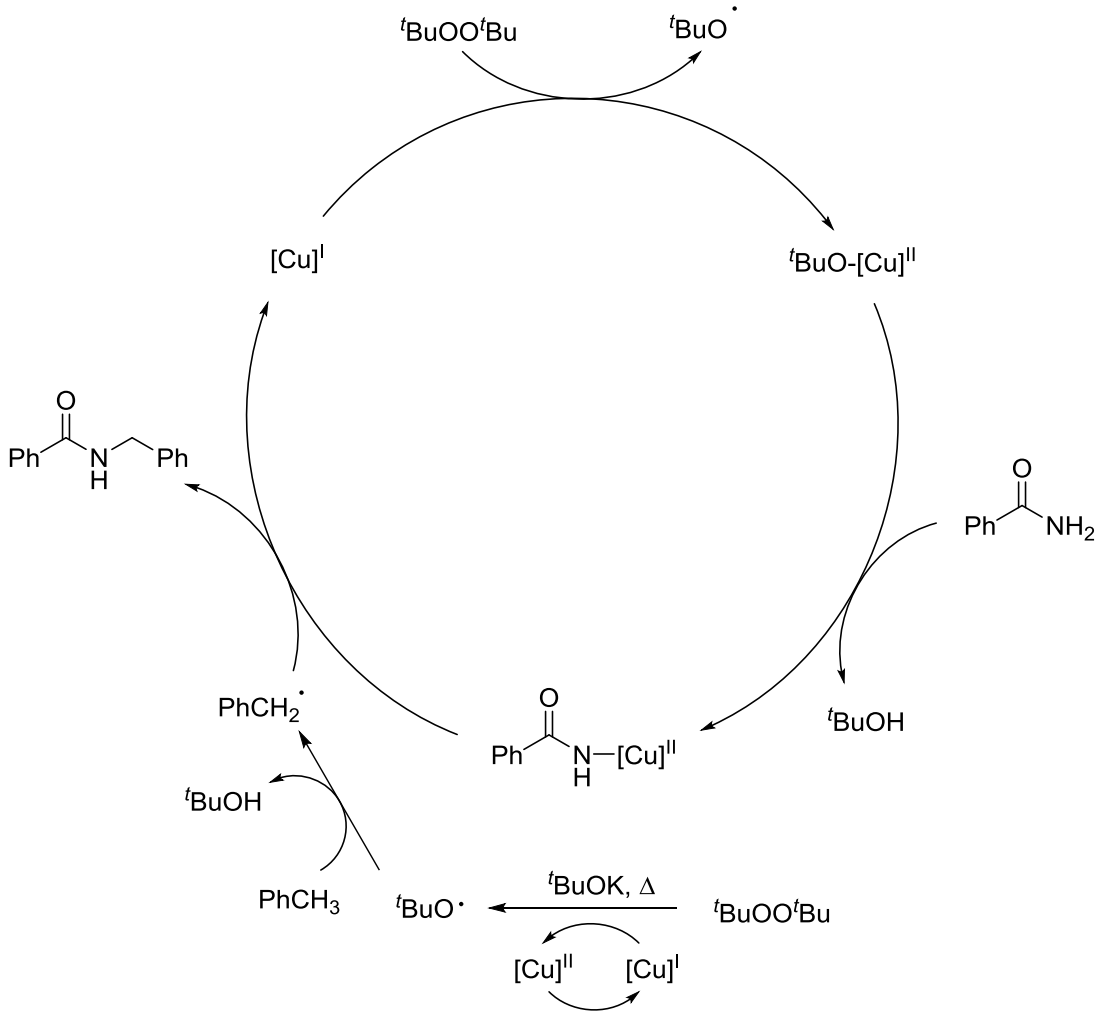


R_1 = 4-Me, 3-Me, 2-Me, 2,4-diMe, 4-OMe, 4-Cl, 3-Cl, 2-Cl, 4-I, 3-I, 4-Br, 4-CN
R_2 = H, R^3 = Bu, Me, Et, Pr, pentyl, CH_2CH_2Ph, $CH_2CH_2CO_2Et$,
$CH(CH_3)CH_2CH_3$, cyclohexyl, cyclohexyl, *t*-Bu, $CH(CH_3)CO_2Me$,
$CH[CH_2CH(CH_3)_2]CO_2Me$, $CH(CH_2Ph)CONHCH_2CO_2Me$
HNR_2R_3 = Morpholine

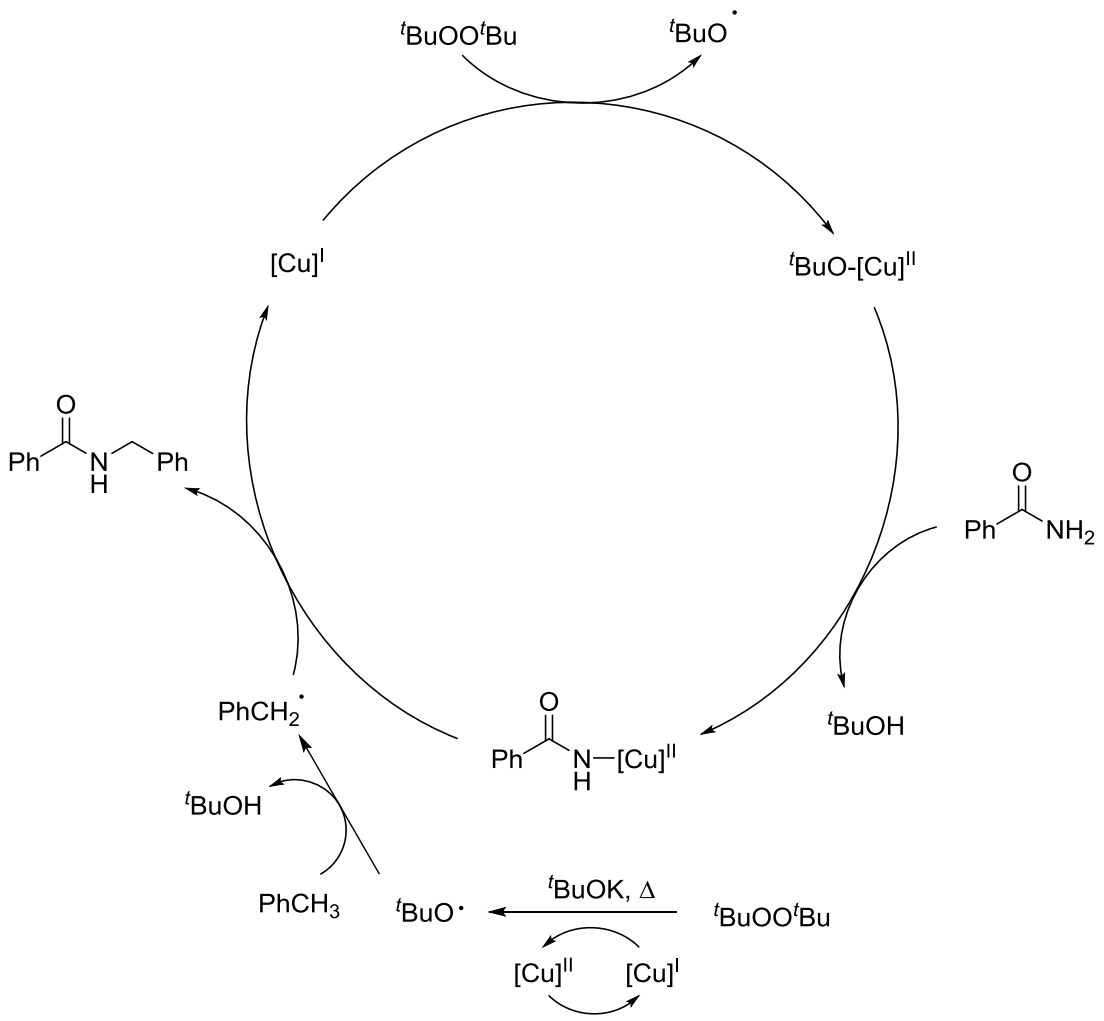
Scheme 44: Synthesis of *N*-substituted benzamides.

A similar protocol using CuCl in combination with DTBP for the synthesis of *N*-substituted benzamides was developed by Huang.[104] Remarkably, also aliphatic substrates could be used, as demonstrated by cyclohexane. Addition of TEMPO completely suppressed the reaction implying a radical process was involved in the coupling and a TEMPO adduct of C-H substrate

could be identified. Formation of a radical and a Cu(I)/Cu(II) catalytic cycle was put forward (

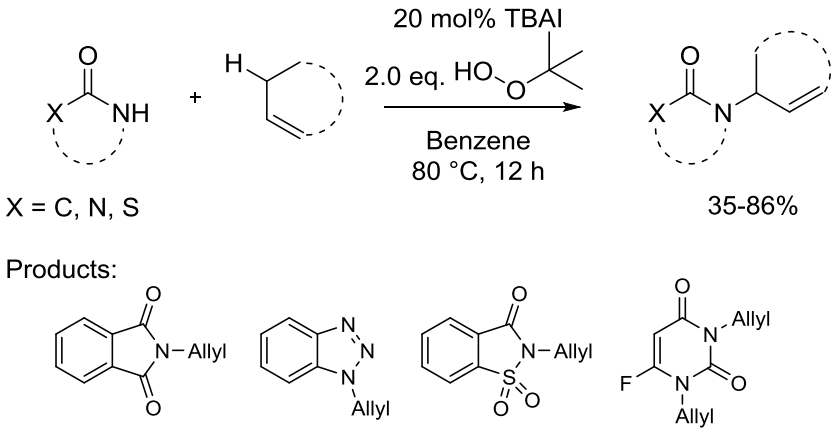


Scheme **45**).



Scheme 45: Proposed catalytic cycle for the synthesis of *N*-substituted benzamides.

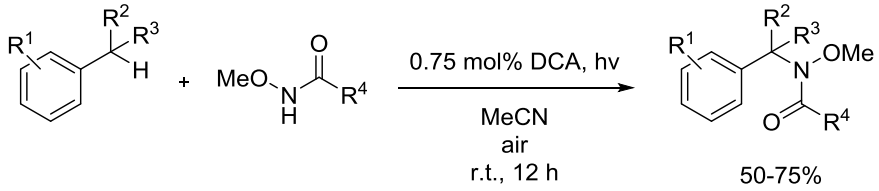
Pan disclosed coupling of *N*-acidic heterocycles with cyclic compounds containing an allylic C-H bond (Scheme 46).[105] Catalytic amounts of TBAI are combined with TBHP as the stoichiometric oxidant. A radical mechanism is suspected as inhibition occurred when the radical scavenger TEMPO was added. Either the active hypoiodite (n-$Bu_4N)^+(IO^-$) or iodite (n-$Bu_4N)^+(IO_2^-$) is believed to be a crucial intermediate. Both compounds are obtained by reaction of TBAI with TBHP. Homolysis of the allylic C-H bond with one of the active species gives an allylic radical which can be oxidized further to an allylic cation. Subsequent nucleophilic attack of the amine to the allylic cation produces the desired aminated product.



Scheme 46: Synthesis of *N*-allyl-isoindolin-1,3-dione, -benzotriazoles, -(isothiazolone 1,1-dioxide) and -uracil.

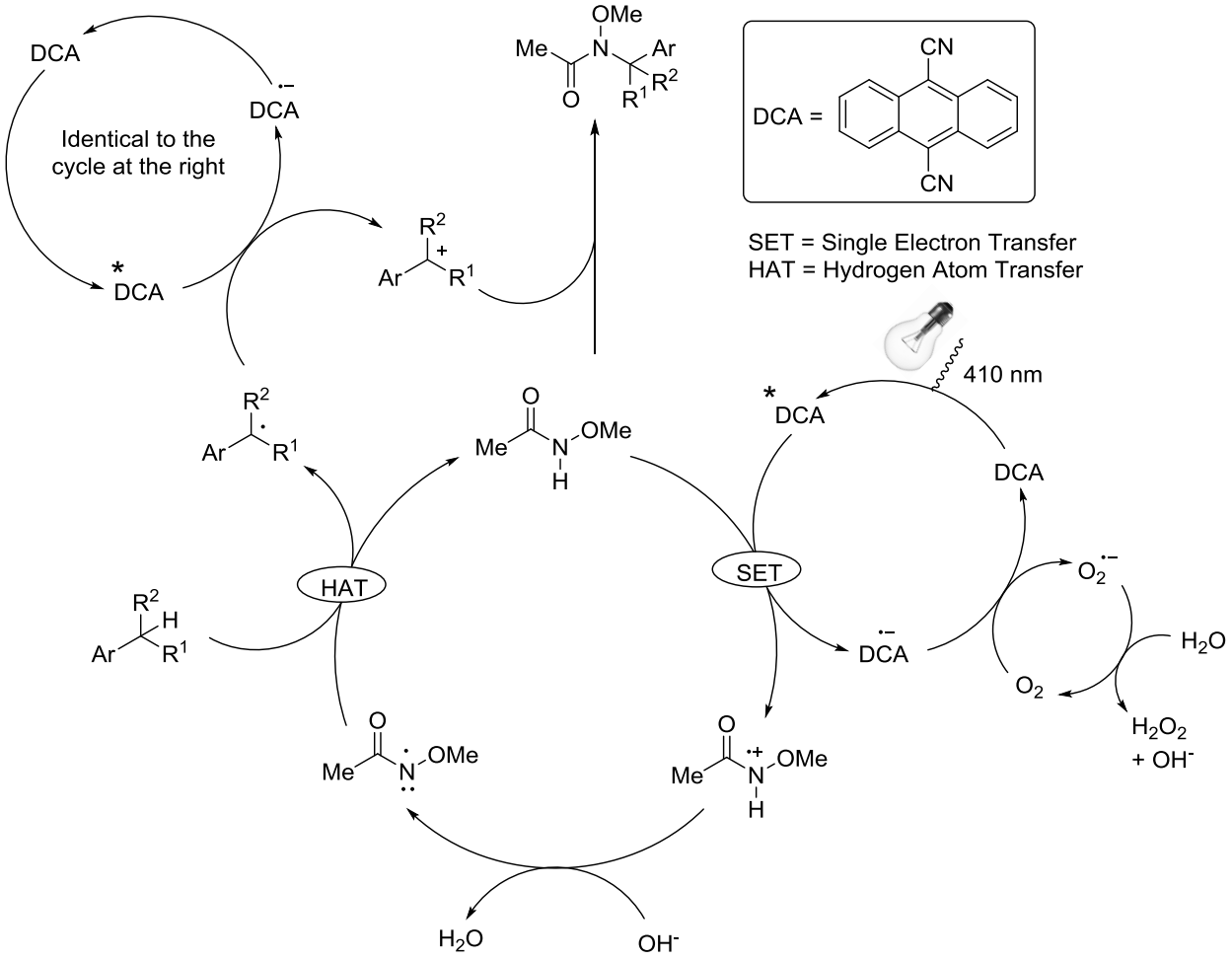
Recently, Pandey reported a new protocol for the amination of benzylic carbons using *N*-methoxyamides.[106] Because the N-O bond of the amide is not broken during the reaction, it does not act as an internal oxidant.[107] Oxidation in this case is carried out by a photoredox catalysis using 9,10-dicyanoanthracene (DCA) as the photoredox catalyst and visible light (410

nm) irradiation. The mechanism of the benzylic amidation is depicted in



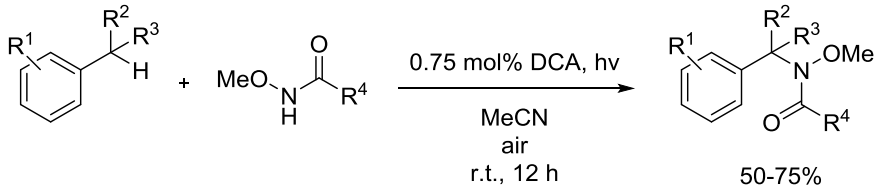
 = ethylbenzene, propylbenzene, methylenediphenyl, isopropylbenzene, *p*-xylene, *m*-xylene, 1,3,5-trimethylbenzene, 2,3-dihydro-1*H*-indene, 1,2,3,4-tetrahydronaphthalene, 1-methylanthracene, 2-methylanthracene, 4-methyl-1,1'-biphenyl, 9*H*-fluorene, *p*-fluorotoluene, *p*-chlorotoluene, *p*-bromotoluene, *p*-tolyl acetate, *p*-anisidine, allylbenzene, methyl 2-(4-methoxyphenyl)acetate, methyl 2-phenylacetate, methyl 4-phenylbutanoate

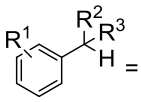
R^4 = Me, Ph, *t*Bu



Scheme **47**. Photolysis of DCA converts it to its excited state DCA*. Reaction of DCA* with the amide produces a cationic amide radical via a single electron transfer of the amide to DCA*. Deprotonation of this cationic amide radical gives a captodative amide radical. Hydrogen atom transfer from the alkylarene substrate to this captodative radical produces a benzylic radical. Another SET with DCA then leads to a benzylic carbocation which reacts with the amide

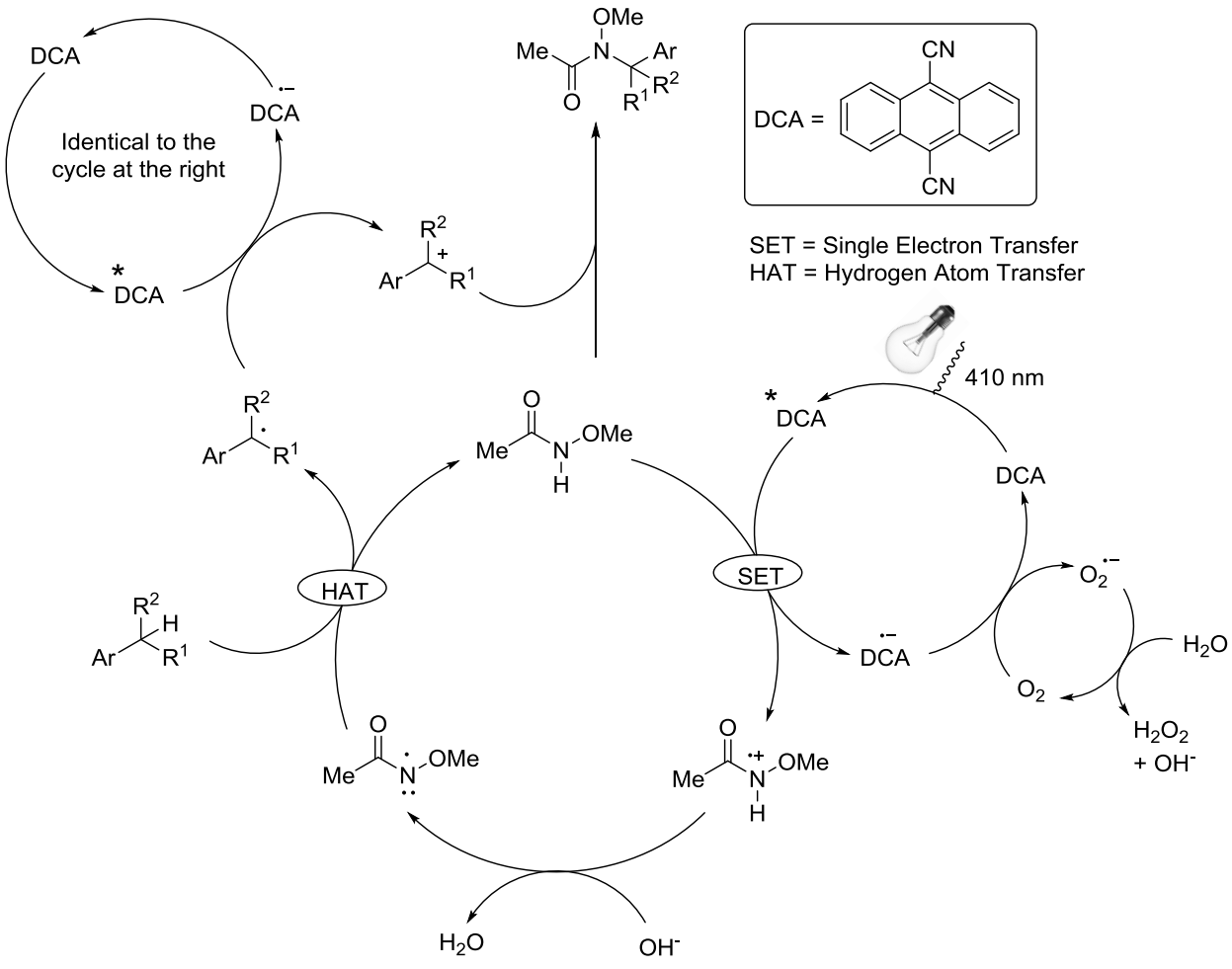
nitrogen to form the amidated product. The formation of the benzylic radical could be demonstrated by formation of the TEMPO-adduct (isolated in 35% yield). When nonanomeric amides were tested no reaction product was formed.





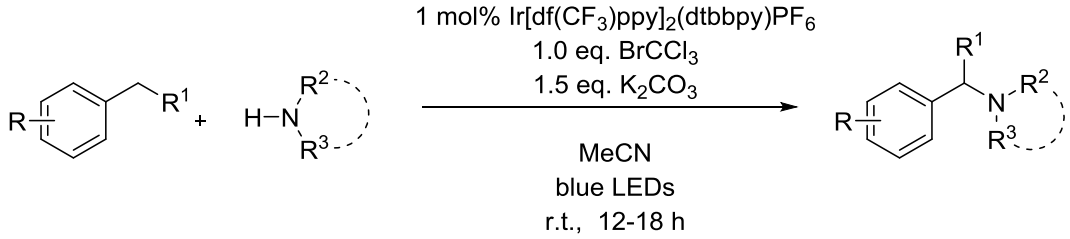
= ethylbenzene, propylbenzene, methylenediphenyl, isopropylbenzene, *p*-xylene, *m*-xylene, 1,3,5-trimethylbenzene, 2,3-dihydro-1*H*-indene, 1,2,3,4-tetrahydronaphthalene, 1-methylanthracene, 2-methylanthracene, 4-methyl-1,1'-biphenyl, 9*H*-fluorene, *p*-fluorotoluene, *p*-chlorotoluene, *p*-bromotoluene, *p*-tolyl acetate, *p*-anisidine, allylbenzene, methyl 2-(4-methoxyphenyl)acetate, methyl 2-phenylacetate, methyl 4-phenylbutanoate

R^4 = Me, Ph, *t*Bu

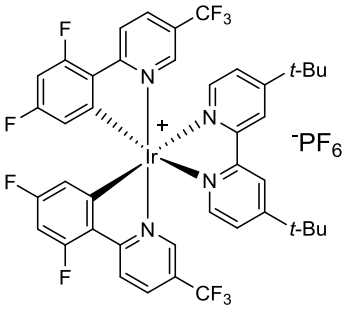


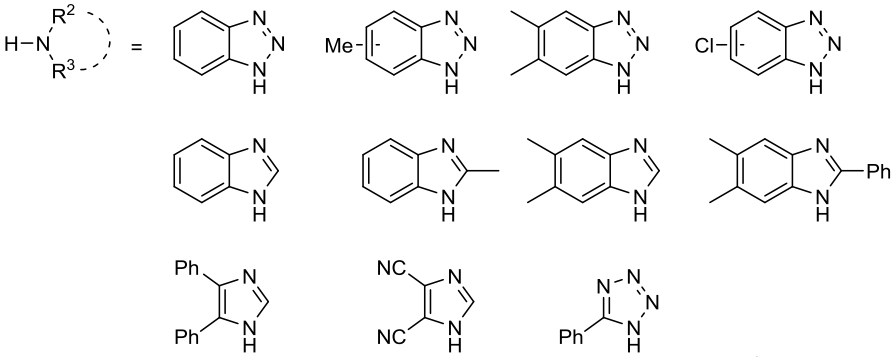
Scheme 47: Synthesis of *N*-arylmethyl-*N*-methoxyamides.

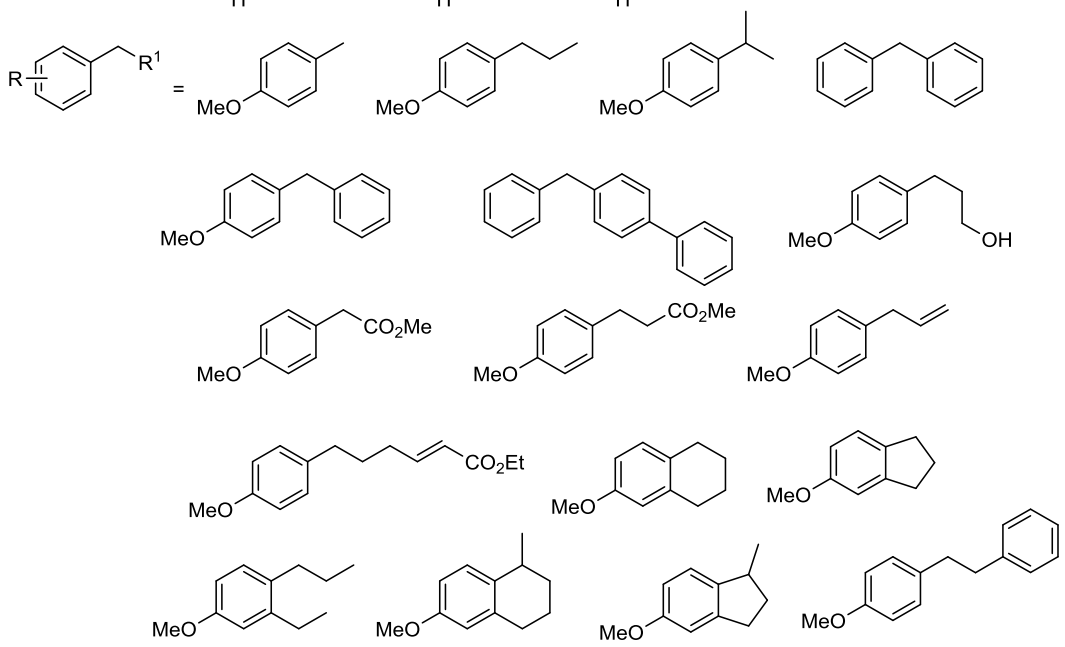
Not much later the same group published the amination of benzylic carbons by blue LED light-mediated photoredox catalysis using an iridium catalyst (



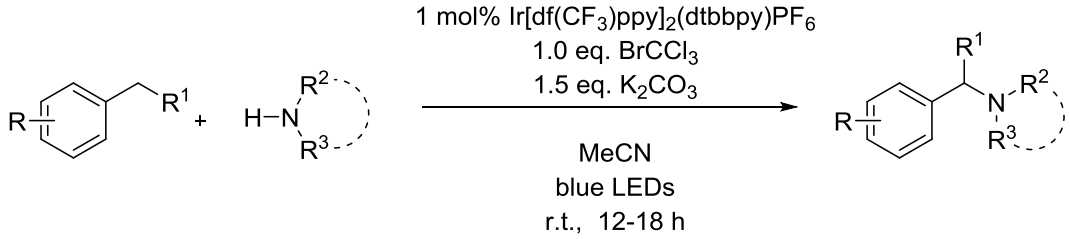
$Ir[df(CF_3)ppy]_2(dtbbpy)PF_6$ =



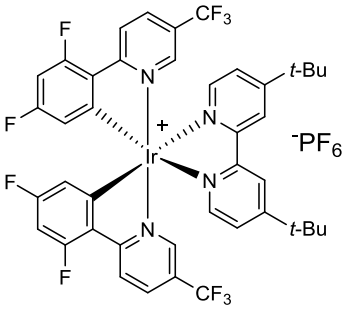


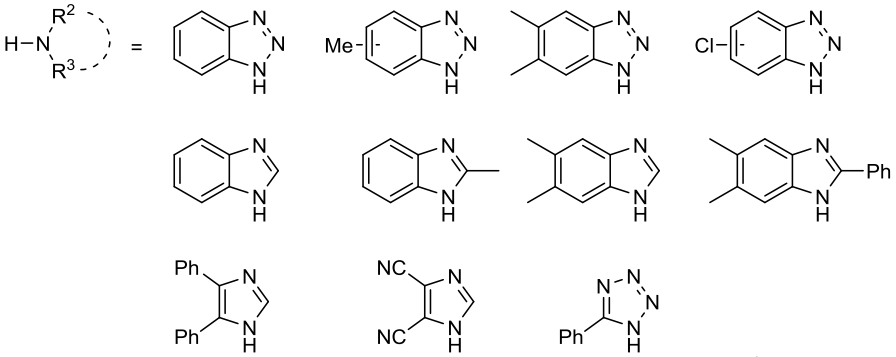


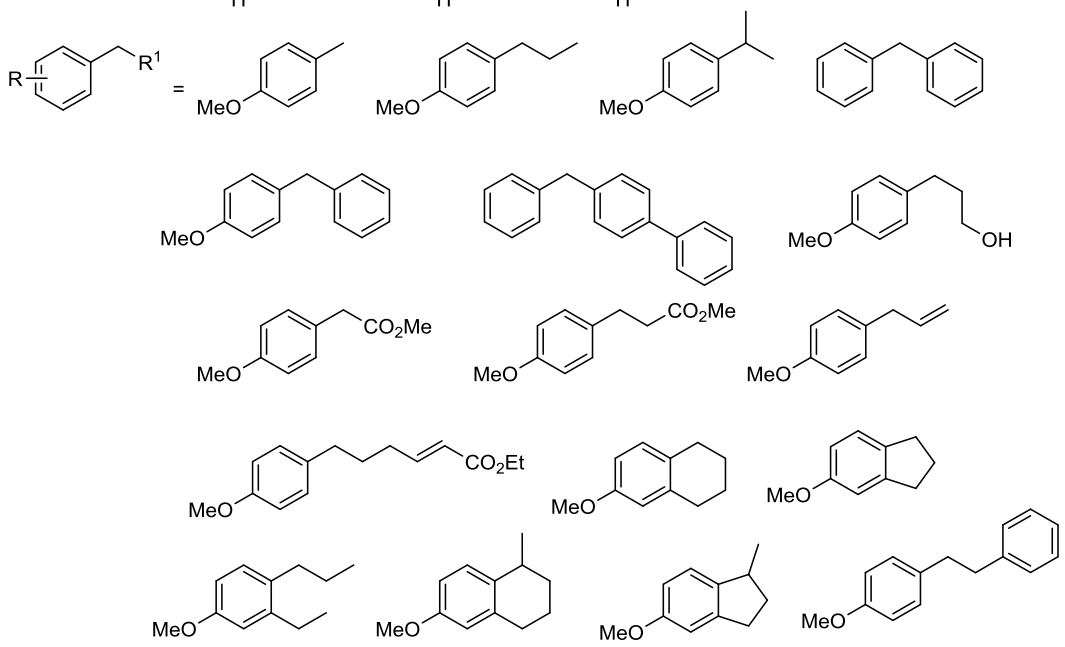
Scheme **48**).[108] Benzotriazoles, tetrazoles and (benz)imidazoles were used as the nucleophiles. Here, it is the Ir(III) catalyst which is irradiated by the LED and gets excited to Ir(III)*. This species can convert $BrCCl_3$ to bromide and a CCl_3 radical. Ir(III)* is simultaneously converted to Ir(IV). This Ir(IV) excepts an electron by a SET from the substrate, regenerating the Ir(III) catalyst and transforming the substrate into a radical cation (arene). Hydrogen atom transfer from this radical cation to the CCl_3 radical forms a benzylic cation which reacts with the amine, producing the benzylic aminated product.



$Ir[df(CF_3)ppy]_2(dtbbpy)PF_6$ =

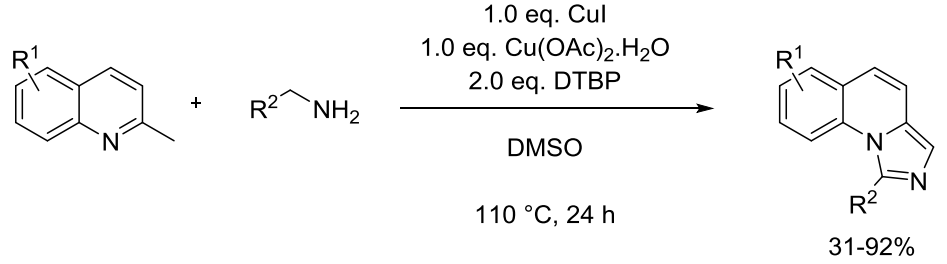




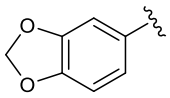


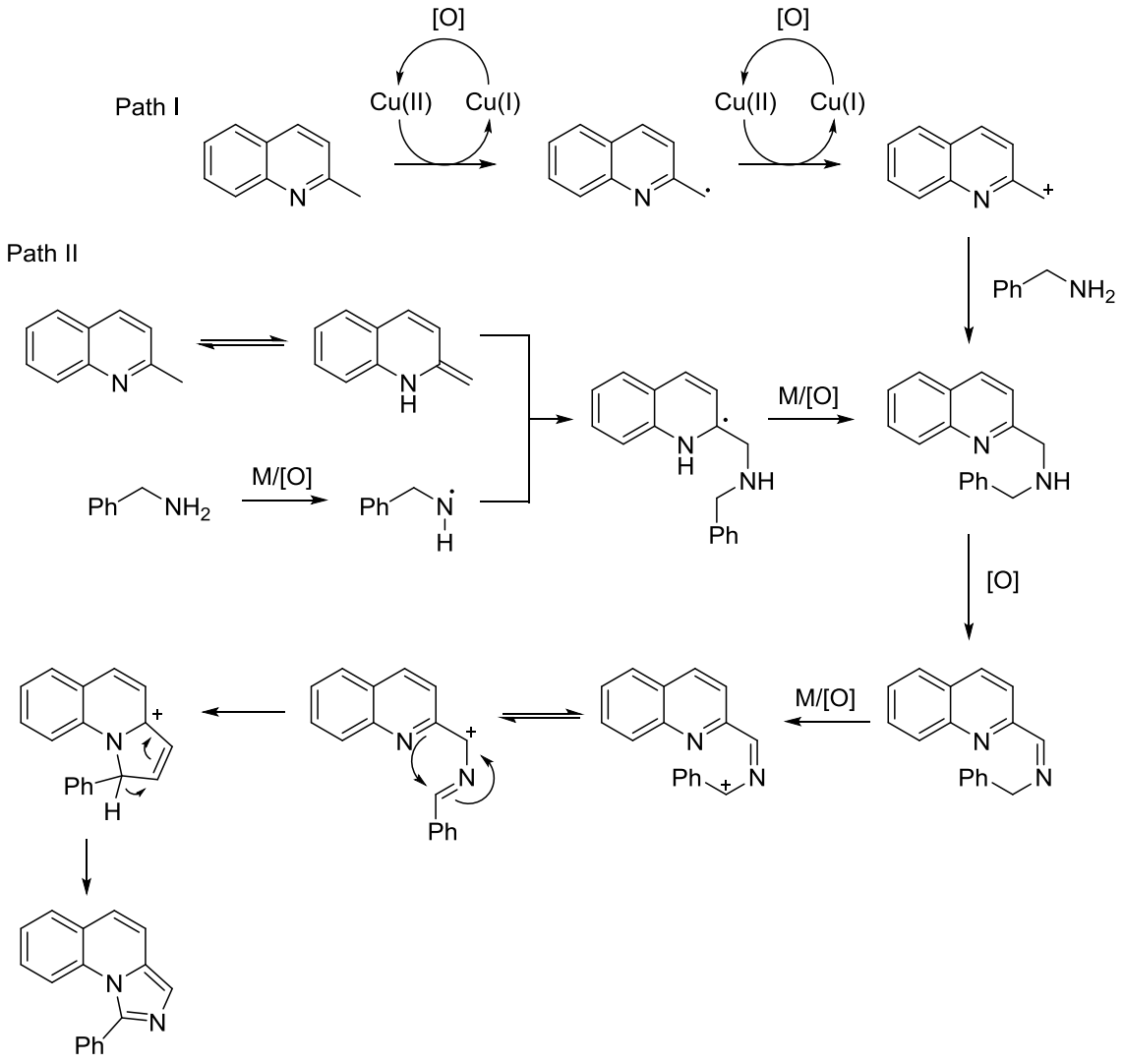
Scheme 48: Benzylic amination using benzotriazoles, (benz)imidazoles and tetrazoles.

A copper-promoted double C-H direct oxidative amination for the synthesis of imidazo[1,5-*a*]quinolines was developed by Feng and Ma (



R^1 = H, 6-Me, 6,8-diMe, 6-OMe, 6-OEt, 9-OMe, 4-Ph, 6-Cl, 6-Br, 6-F, 6-NO_2

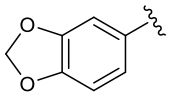
R^2 = Ph, 4-MePh, 3-MePh, 2-MePh, 4-MeOPh, 2-MeOPh, 4-F_3CPh, 4-ClPh, 3-ClPh, 2-ClPh, 3-FPh, 2-FPh, 4-BrPh, 1-napthyl, 2-furanyl, ethyl, 

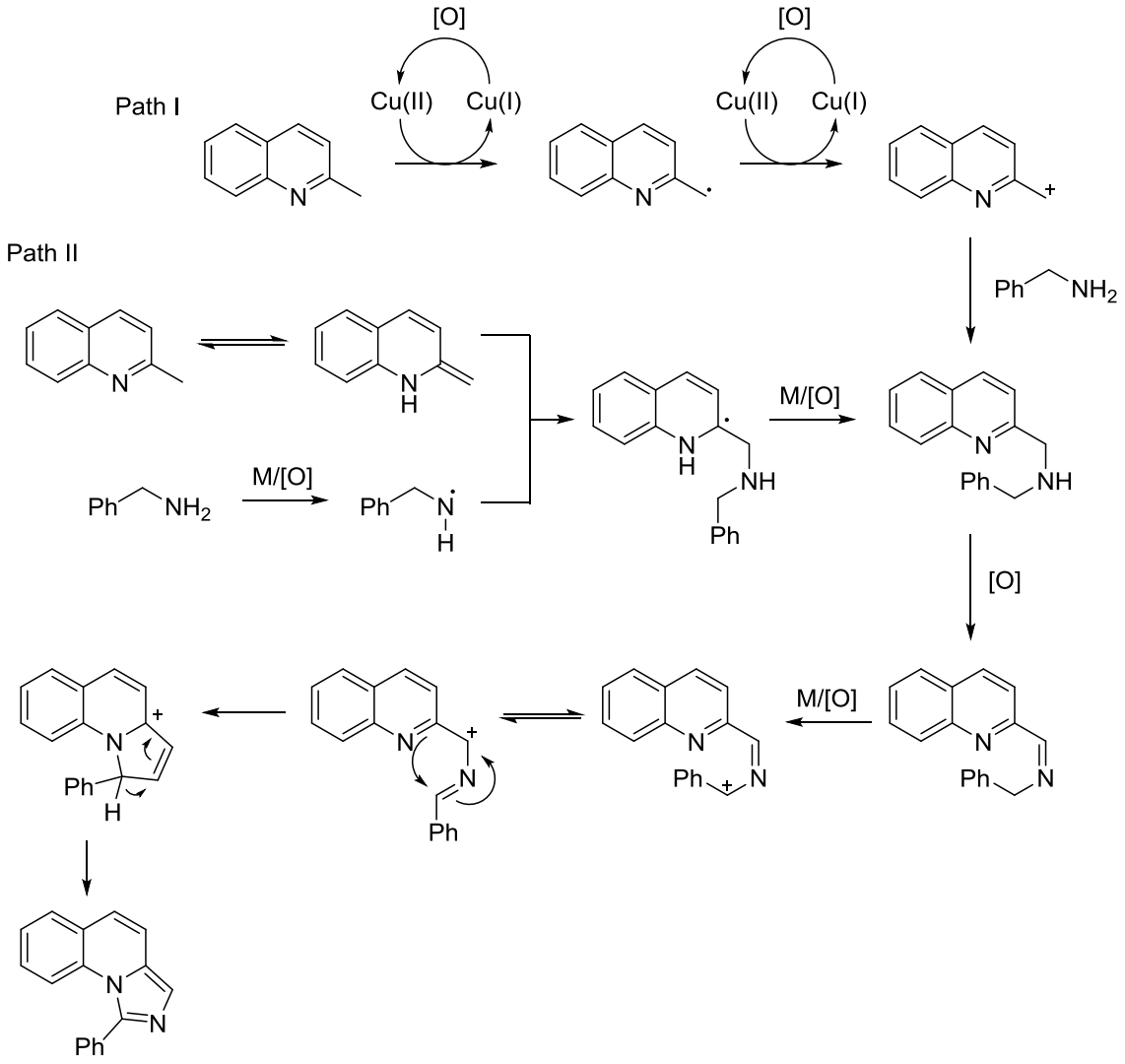


Scheme **49**).[109] The reaction involves two sequential oxidative C(sp^3)-H aminations. Besides 2-methylquinoline also one successful example with a 4-methylquinazoline was demonstrated. The reaction offers an alternative for syntheses which make use of Vilsmeier-type cyclizations for which formylated substrates are required but requires two different copper salts in stoichiometric amount. A radical pathway was put forward based on experiments with radical scavenger TEMPO. Hydrogen abstraction of 2-methylquinoline forms a benzylic radical, which is converted to a benzylic cation by Cu(II) (path I). Nucleophilic addition of the benzylamine followed by oxidation gives an intermediate imine. Another oxidation leads to a new benzylic cation. This cation is delocalized on both benzylic positions. Ring closure and deprotonation leads to the final reaction product. Alternatively, hydrogen abstraction of the benzylamine leads to a nitrogen radical which reacts directly with the 2-methylquinoline in its enamine tautomeric form (path II). Oxidation leads to the same intermediate amine.

R^1 = H, 6-Me, 6,8-diMe, 6-OMe, 6-OEt, 9-OMe, 4-Ph, 6-Cl, 6-Br, 6-F, 6-NO_2

R^2 = Ph, 4-MePh, 3-MePh, 2-MePh, 4-MeOPh, 2-MeOPh, 4-F_3CPh, 4-ClPh, 3-ClPh, 2-ClPh, 3-FPh, 2-FPh, 4-BrPh, 1-napthyl, 2-furanyl, ethyl,

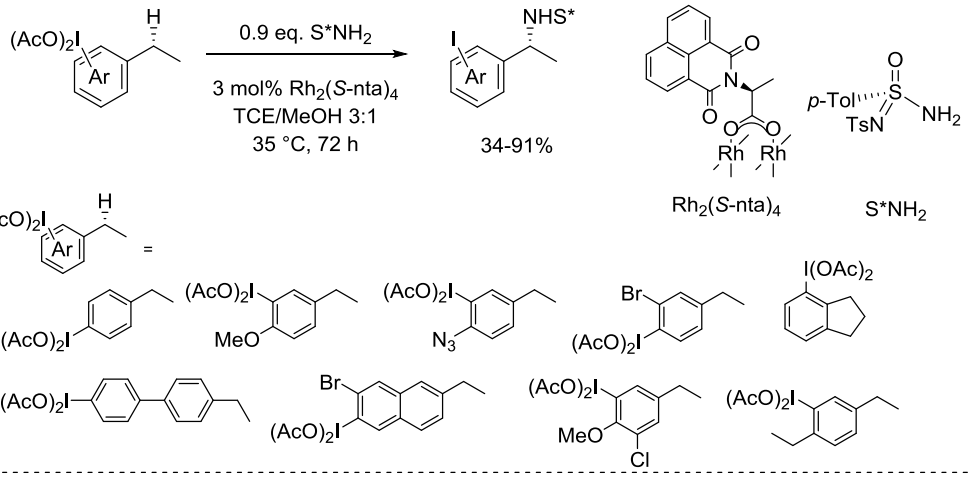




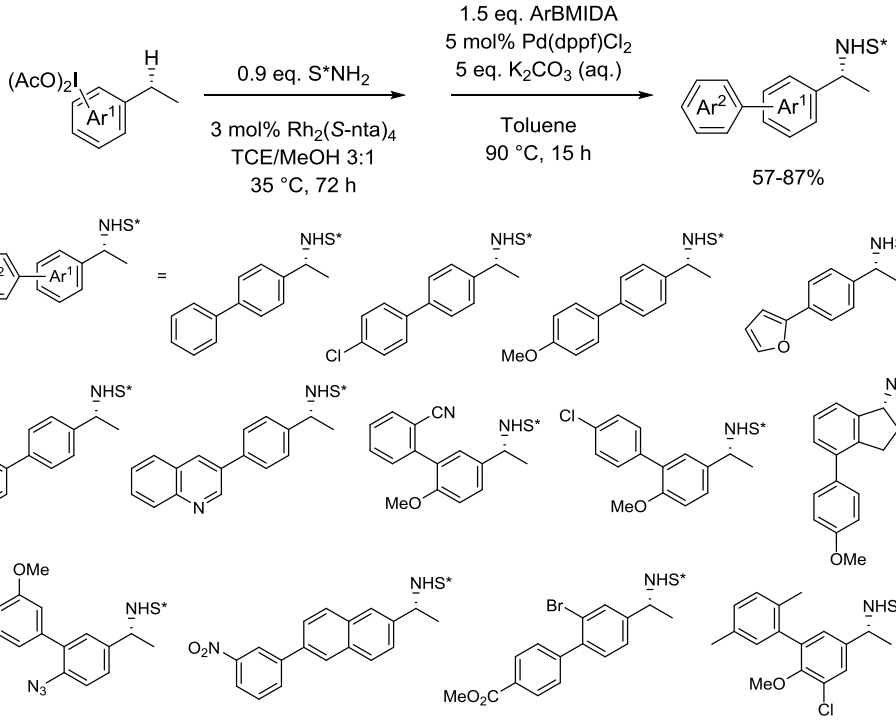
Scheme 49: Synthesis of imidazo[1,5-*a*]quinolines.

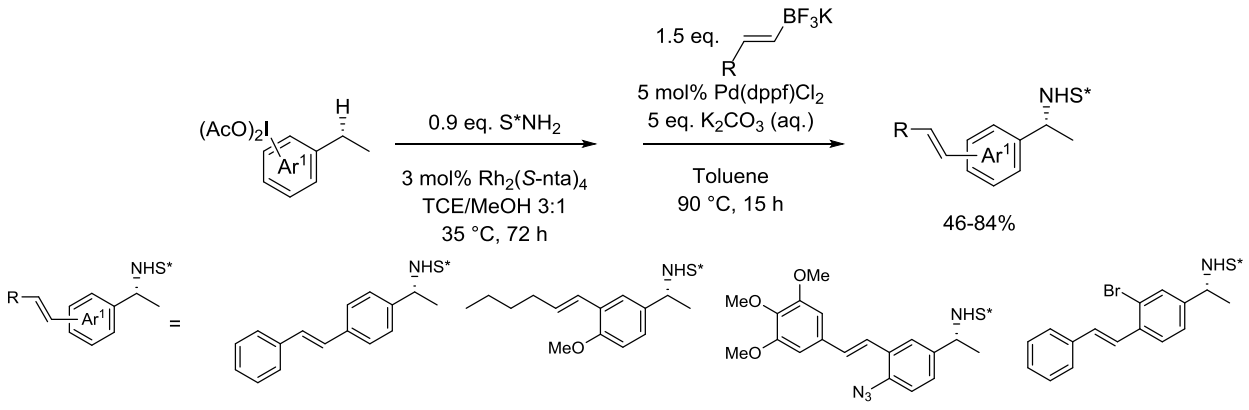
A remarkable procedure for the synthesis of chiral amines makes use of auto-amination (

A: Amination



B: Suzuki follow-up reactions:

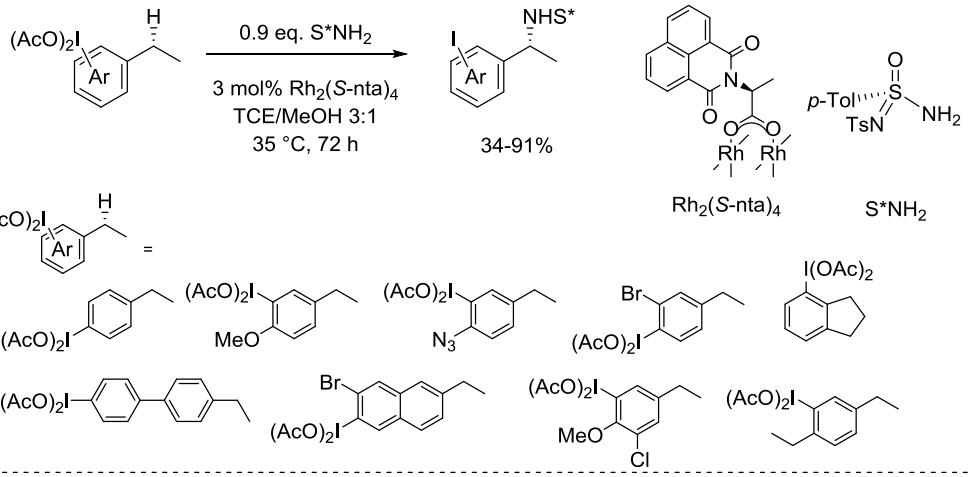




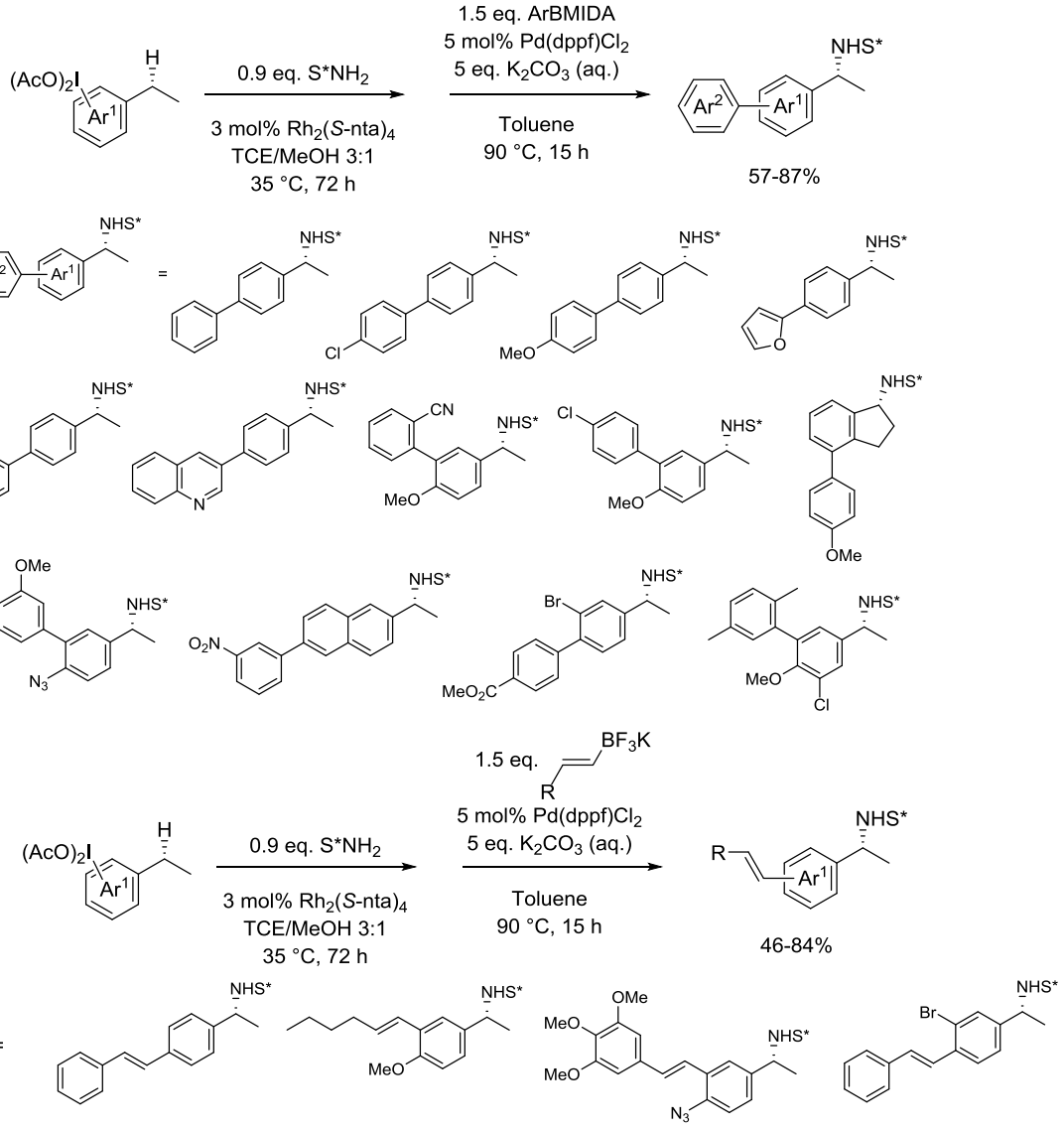
Scheme **50**, A).[110] In this reaction, the oxidant is part of the substrate itself. The hypervalent iodine moiety mediates amination under rhodium catalysis with *S*-sulfonimidamide and is reduced to the corresponding iodide. The iodine "by-product" on the substrate can be used for successive cross-coupling reactions. This was realized in a one pot fashion as demonstrated

with Suzuki (

A: Amination

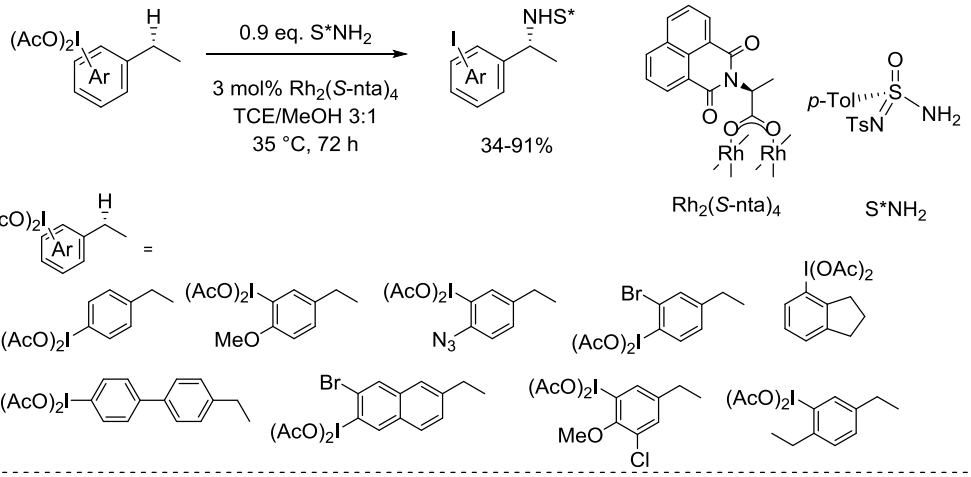


B: Suzuki follow-up reactions:

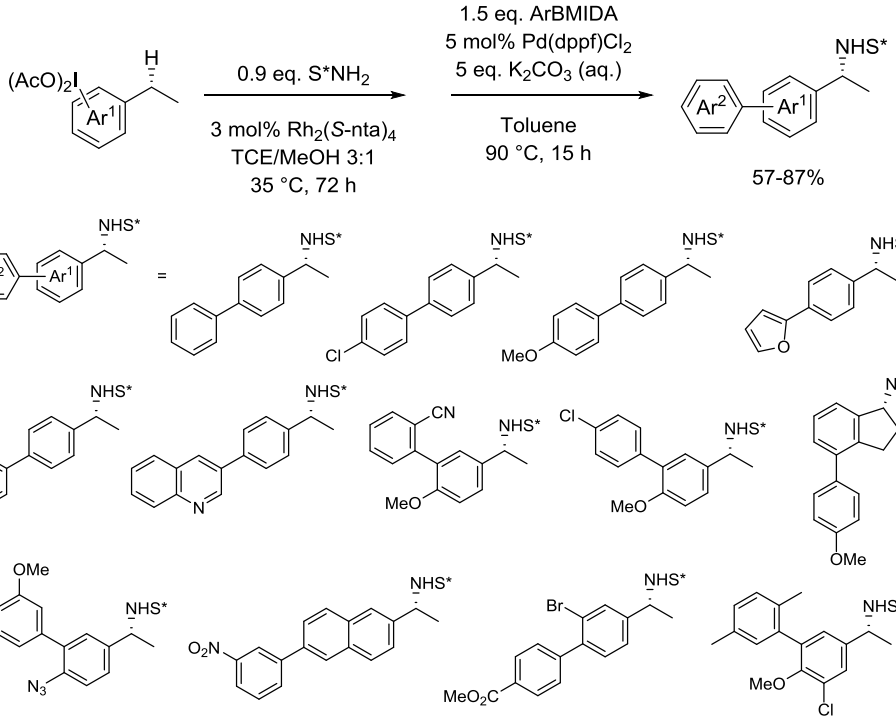


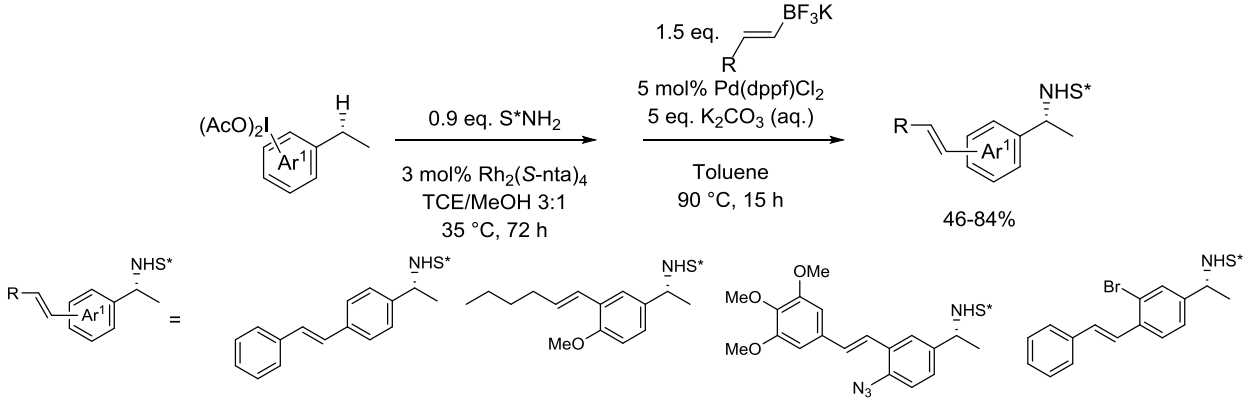
Scheme **50**, B), Sonogashira (Scheme 51, C) and Heck (Scheme 51, D) reactions.

A: Amination



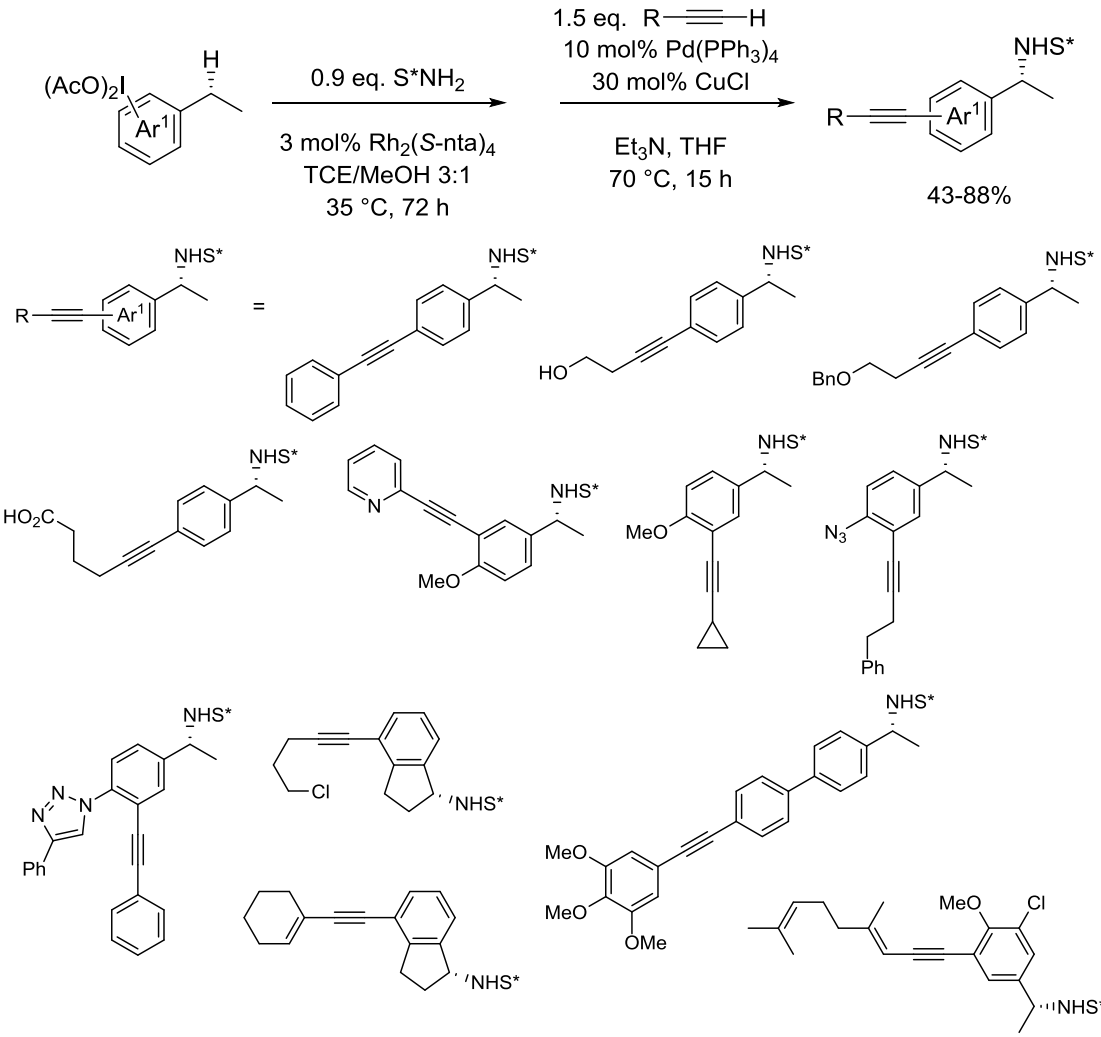
B: Suzuki follow-up reactions:



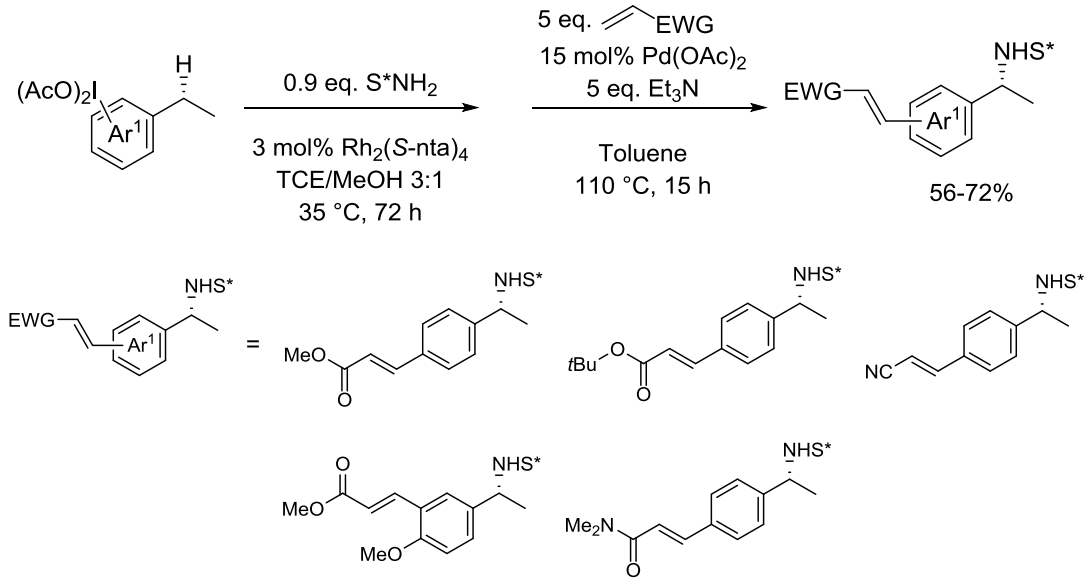


Scheme 50: Synthesis of chiral benzylic aminated ethyliodobenzenes.

C: Sonogashira follow-up reaction

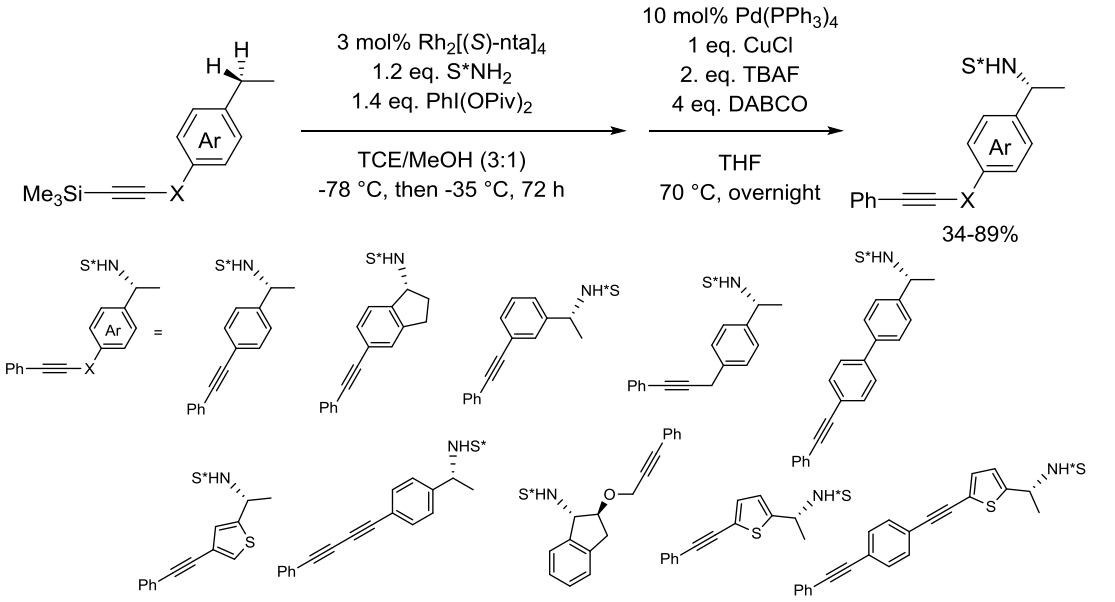


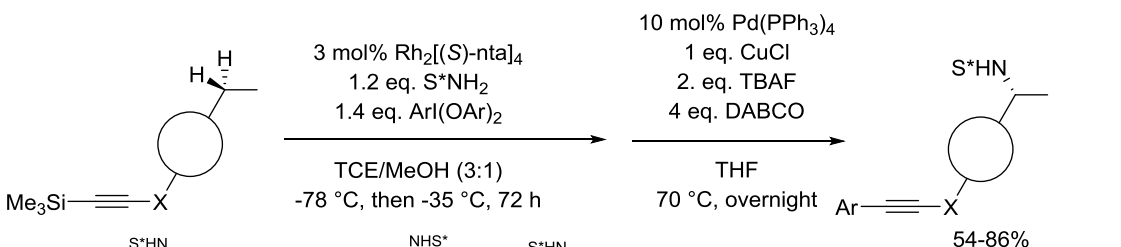
D: Heck follow-up reaction



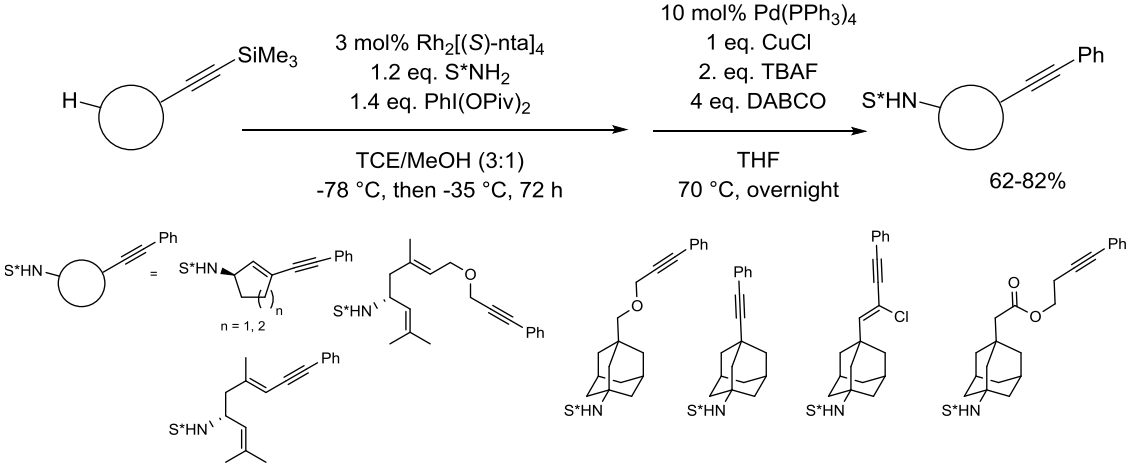
Scheme 51: Sonogashira and Heck follow-up reactions.

This reaction was based on previous work from the same group in which a catalytic C(sp^3)-H amination/Sila-Sonogashira-Hagihara coupling reaction with respectively *S*-sulfonimidamide and ArI *in situ* obtained from $ArI(OR)_2$ is described (Scheme 52).[111]


3 mol% Rh2[(S)-nta]4
1.2 eq. S*NH2
1.4 eq. PhI(OPiv)2
TCE/MeOH (3:1)
-78 °C, then -35 °C, 72 h
10 mol% Pd(PPh3)4
1 eq. CuCl
2. eq. TBAF
4 eq. DABCO
THF
70 °C, overnight
34-89%

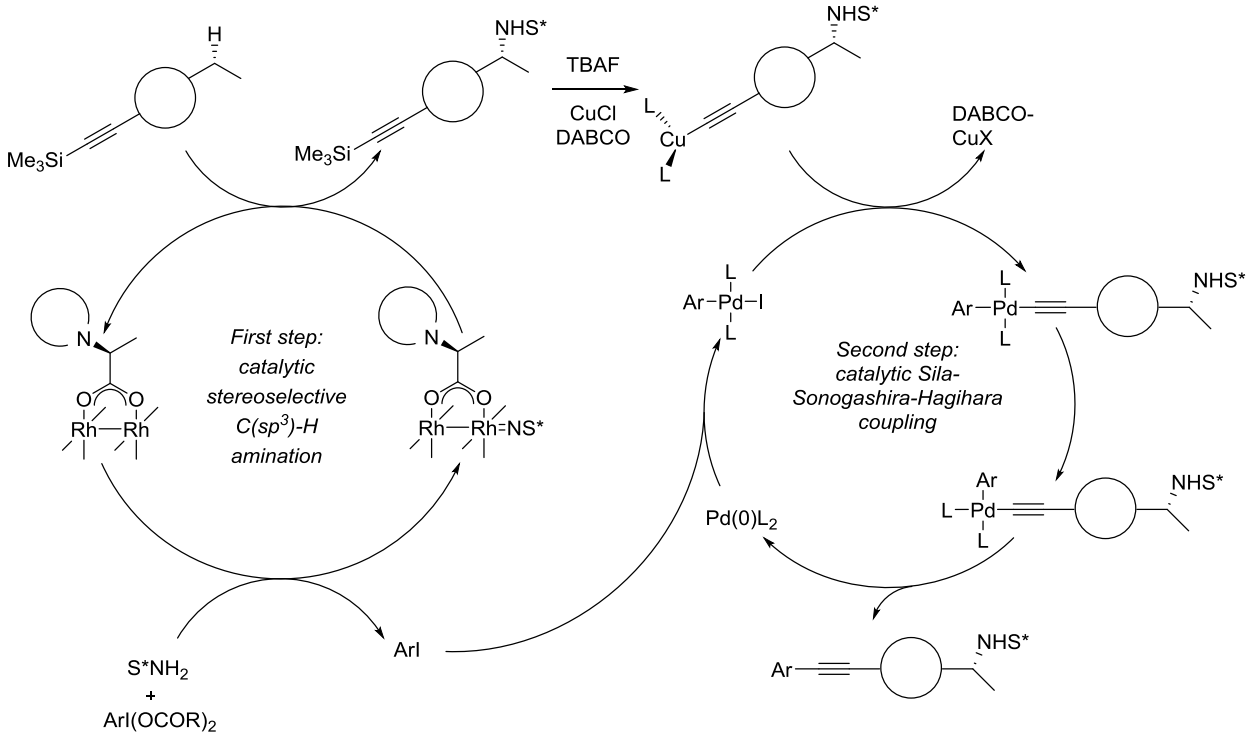


3 mol% Rh2[(S)-nta]4
1.2 eq. S*NH2
1.4 eq. ArI(OAr)2
TCE/MeOH (3:1)
-78 °C, then -35 °C, 72 h
10 mol% Pd(PPh3)4
1 eq. CuCl
2. eq. TBAF
4 eq. DABCO
THF
70 °C, overnight
54-86%
R = Me, Cl
n = 1, 2
R1 = H, Cl
R2 = H, OMe, CF3

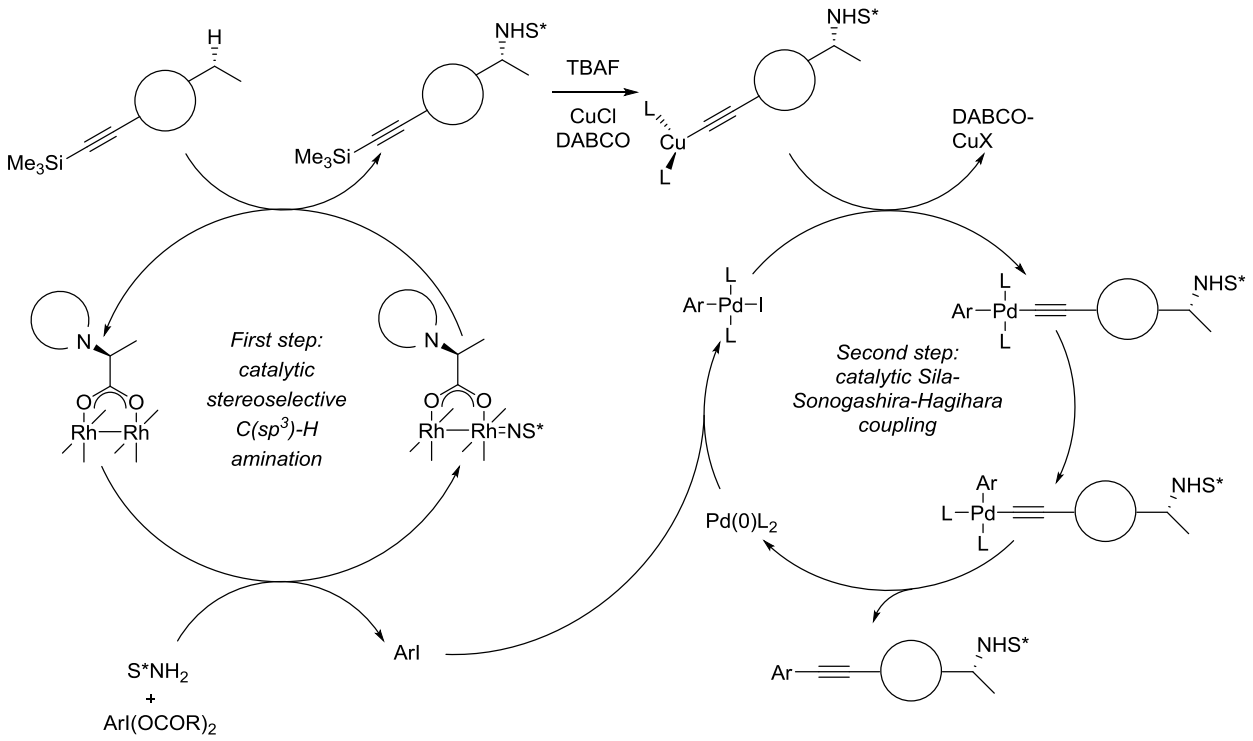

3 mol% Rh2[(S)-nta]4
1.2 eq. S*NH2
1.4 eq. PhI(OPiv)2
TCE/MeOH (3:1)
-78 °C, then -35 °C, 72 h
10 mol% Pd(PPh3)4
1 eq. CuCl
2. eq. TBAF
4 eq. DABCO
THF
70 °C, overnight
62-82%
n = 1, 2

Scheme 52: Synthesis of chiral trimethylsilylalkynylated benzylamines, allyl- and alkylamines via direct oxidative amination followed by Sila-Sonogashira-Hagihara reaction with *in situ* formed ArI.

The mechanism of the tandem reactions are described in



Scheme **53**. Reaction of the sulfonimidamide with the hypervalent iodine reagent in the presence of the Rh catalyst creates a metallanitrene. Nitrene C(sp^3)-H insertion produces the aminated compound. This compound contains a trimethylsilyl group which can be desilylated by TBAF which in the presence of CuCl and DABCO results in the formation of an organocopper compound. This organocopper species undergoes transmetalation with the oxidative addition product of ArI with Pd catalyst. Subsequent reductive elimination yields the cross-coupled product.



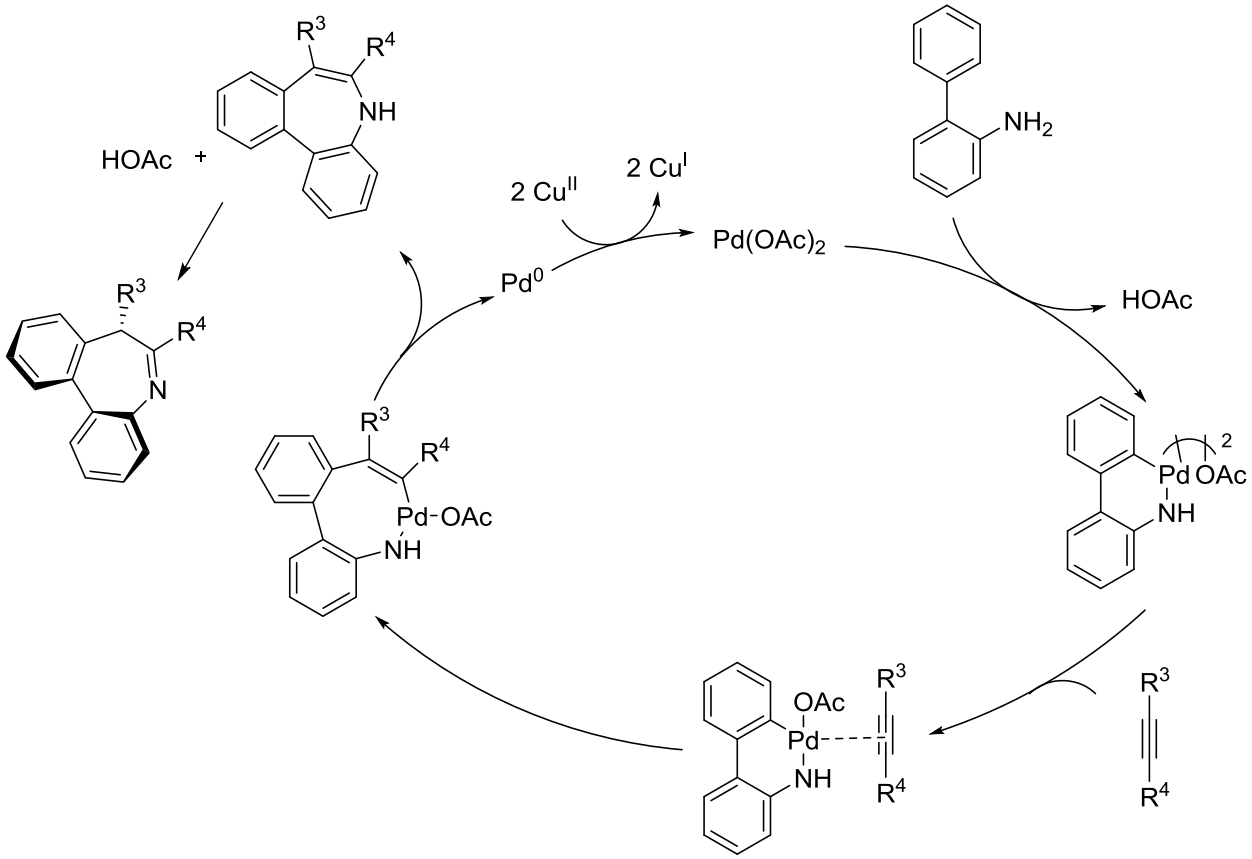
Scheme 53: Mechanism of the oxidative amination followed by Sila-Sonogashira-Hagihara reaction.

2.4 Direct oxidative amination with insertion

When alkynes are used as additional reactant, ring annulation can be achieved in intramolecular direct oxidative amination reactions. Both a C-C and a C-N bond are formed then. The palladium(II)-catalyzed [5+2] oxidative annulation of *o*-arylanilines with alkynes is such an

example (

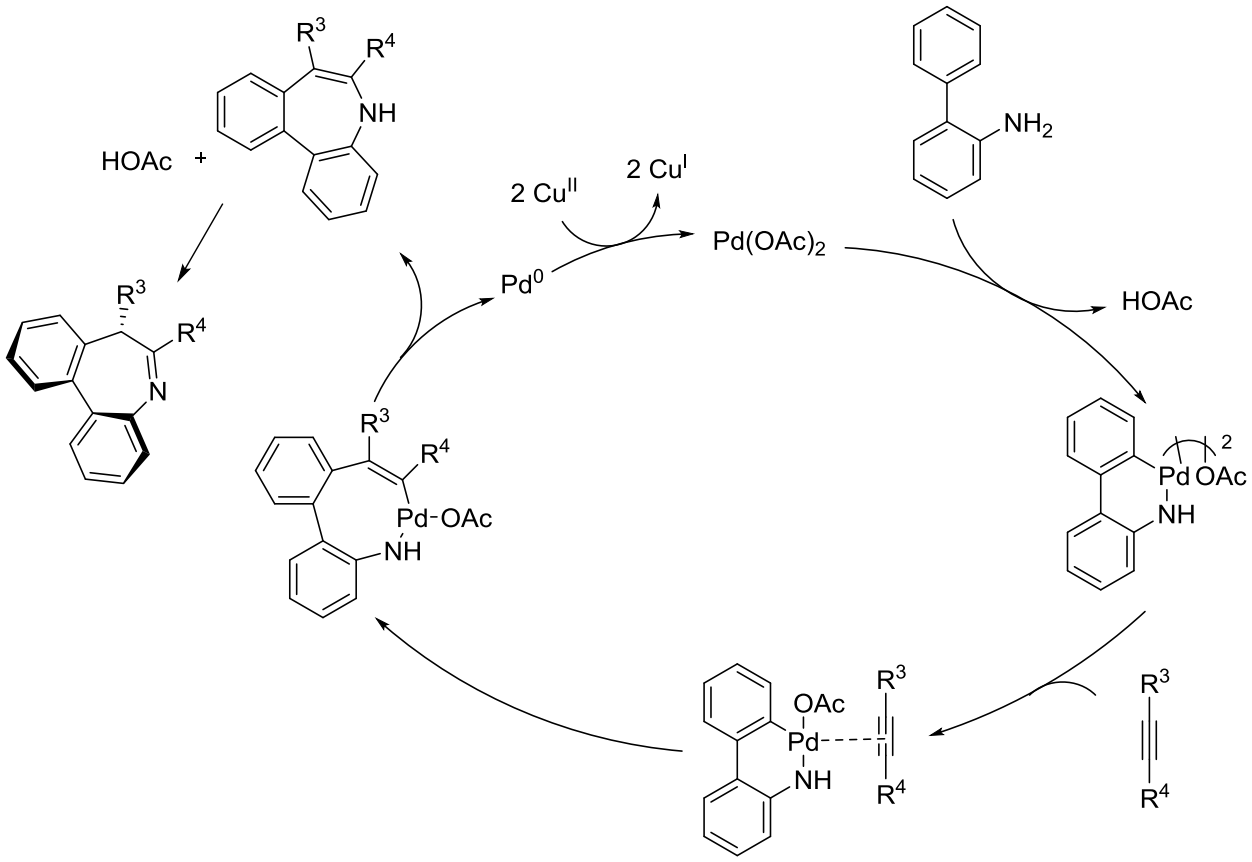
R^1 = H, 4-Me, 4-*t*Bu, 4-Ph, 4-CF_3, 4-NO_2, 4-Ac, 4-CO_2Et, 4-CN, 4-OMe, 4,6-diMe, 5-Me, 3-Me
R^2 = H, 3-OMe, 3,5-diMe, 4-OMe, 4-CF_3, 4-CO_2Me, 2-OMe
R^3 = Ph, 4-$CF_3C_6H_4$, 3-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*Bu, Me, Et, CO_2Et
R^4 = Ph, 4-$CF_3C_6H_4$, 3-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*Bu, *t*Bu,



Scheme **54**).[112] Dibenzo[*b*,*d*]azepines could be synthesized in a highly diastereoselective manner. $Cu(OAc)_2$ was used as oxidant. The reaction had only moderate yields in other solvents than DMSO. C(sp^2)-H bond cleavage of the substrate is initiated by $Pd(OAc)_2$ to give a dimeric palladacycle. An intermolecular KIE of 3.2 suggests that the C-H activation is involved in the rate-determining step. Subsequently, the alkyne breaks the dimer and coordinates to palladium. Migratory insertion of the alkyne forms an 8-membered palladacycle which upon reductive

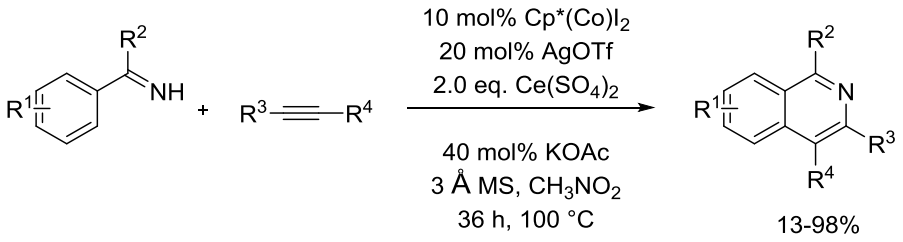
elimination and subsequent enamine-imine tautomerization finally leads to the thermodynamically more stable product.

R^1 = H, 4-Me, 4-*t*Bu, 4-Ph, 4-CF_3, 4-NO_2, 4-Ac, 4-CO_2Et, 4-CN, 4-OMe, 4,6-diMe, 5-Me, 3-Me
R^2 = H, 3-OMe, 3,5-diMe, 4-OMe, 4-CF_3, 4-CO_2Me, 2-OMe
R^3 = Ph, 4-$CF_3C_6H_4$, 3-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*Bu, Me, Et, CO_2Et
R^4 = Ph, 4-$CF_3C_6H_4$, 3-FC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*Bu, *t*Bu,



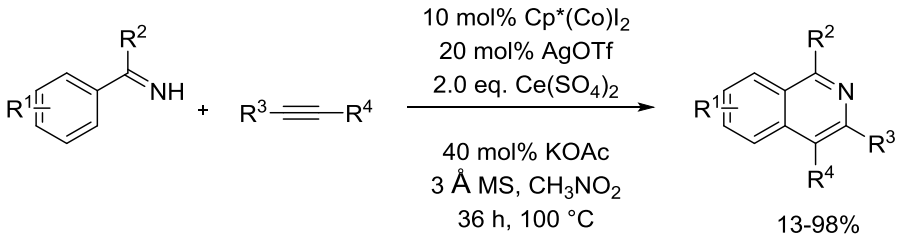
Scheme 54: Synthesis of dibenzo[*b*,*d*]azepines.

Wang published a reaction starting from imines of aromatic ketones rather than *o*-arylanilines yielding isoquinolines (



R^1 = H, 4-OMe, 4-F
R^2 = Ph, 3-CF_3Ph, 4-OMePh, 4-FPh, 2-MePh, Bu, *sec*-Bu, *t*Bu
R^3 = Ph, 4-FPh, 4-BrPh, 4-CNPh, 4-CO_2MePh, 4-BuPh, 3-FPh, 4-CF_3Ph, 3-MeOPh, 2-FPh, 2-BrPh, 2-MeOPh, 2-thiophenyl, ethylenedioxophenyl, ethyl, propyl, Bu, $CH_2OCH_2OCH_3$, CH_2OAc, CO_2Et, Me, CH_2OMe, isopropyl
R^4 = H, Ph, 4-FPh, 4-BrPh, 4-CNPh, 4-CO_2MePh, 4-BuPh, 3-FPh, 3-CF_3Ph, 3-MeOPh, 2-FPh, 2-BrPh, 2-MeOPh, 2-thiophenyl, ethylenedioxophenyl, ethyl, propyl, Bu, $CH_2OCH_2OCH_3$, CH_2OAc, CO_2Et, Me, CH_2OMe, H

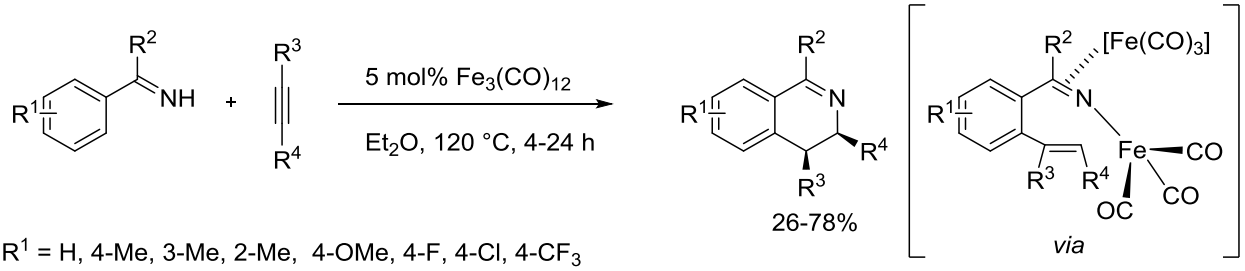
Scheme 55).[113] The reaction proceeds via a Co(I)-Co(III) catalytic cycle. In the case of terminal alkynes, the 4-position of the isoquinoline ring was preferentially unsubstituted (R^4 = H). When unsymmetrical internal alkynes were used, both regioisomers were formed. A small KIE of 1.2 was observed, indicating that the C-H bond cleavage is not involved in the turnover-limiting step. Reaction of the Cp*Co(CO)I_2 catalyst with AgOTf and KOAc leads to formation of the catalytically active cationic $[Cp^*Co^{III}OAc]^+$ species. The imine coordinates with this species and upon deprotonation a N-Co bond is formed. From here, two possible mechanistic pathways are possible. The first pathway is a direct C-H activation pathway in which a cobalt metallacycle is formed. Coordination of the alkyne followed by migratory insertion and reductive elimination gives the isoquinoline reaction product. Alternatively, a SET from the aryl ring to Co^{III} gives a radical cationic intermediate. Also this species can undergo migratory insertion of the alkyne species, to generate a cationic intermediate. Deprotonation by acetate of the cationic intermediate leads to rearomatization. Again, reductive elimination yields the reaction product.



R^1 = H, 4-OMe, 4-F
R^2 = Ph, 3-CF_3Ph, 4-OMePh, 4-FPh, 2-MePh, Bu, *sec*-Bu, *t*Bu
R^3 = Ph, 4-FPh, 4-BrPh, 4-CNPh, 4-CO_2MePh, 4-BuPh, 3-FPh, 4-CF_3Ph, 3-MeOPh, 2-FPh, 2-BrPh, 2-MeOPh, 2-thiophenyl, ethylenedioxophenyl, ethyl, propyl, Bu, $CH_2OCH_2OCH_3$, CH_2OAc, CO_2Et, Me, CH_2OMe, isopropyl
R^4 = H, Ph, 4-FPh, 4-BrPh, 4-CNPh, 4-CO_2MePh, 4-BuPh, 3-FPh, 3-CF_3Ph, 3-MeOPh, 2-FPh, 2-BrPh, 2-MeOPh, 2-thiophenyl, ethylenedioxophenyl, ethyl, propyl, Bu, $CH_2OCH_2OCH_3$, CH_2OAc, CO_2Et, Me, CH_2OMe, H

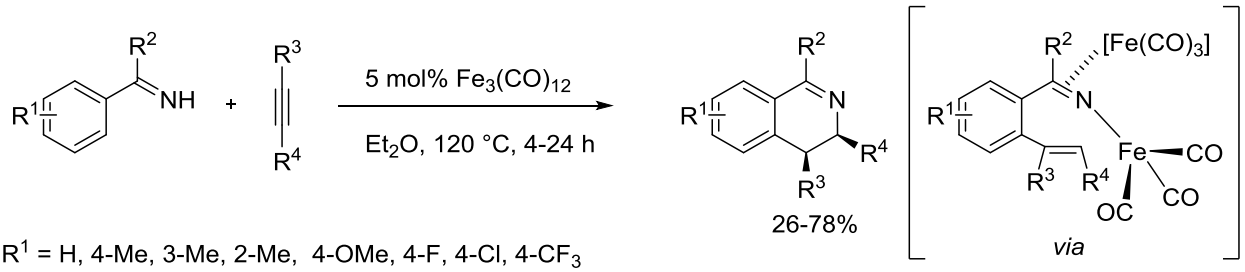
Scheme 55: Synthesis of isoquinolines.

Interestingly, when an iron carbonyl catalyst is used, *cis*-3,4-dihydroisoquinolines are formed rather than isoquinolines (



R^1 = H, 4-Me, 3-Me, 2-Me, 4-OMe, 4-F, 4-Cl, 4-CF_3
R^2 = Ph, 4-MePh, 4-MeOPh, 4-FPh, 3-Me, 1-naphthyl, 3,5-diMe, Bu, *i*Pr
R^3, R^4 = Ph, 4-MePh, 4-EtPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 2-FPh, 3-Me, 3-Cl, 3-Br

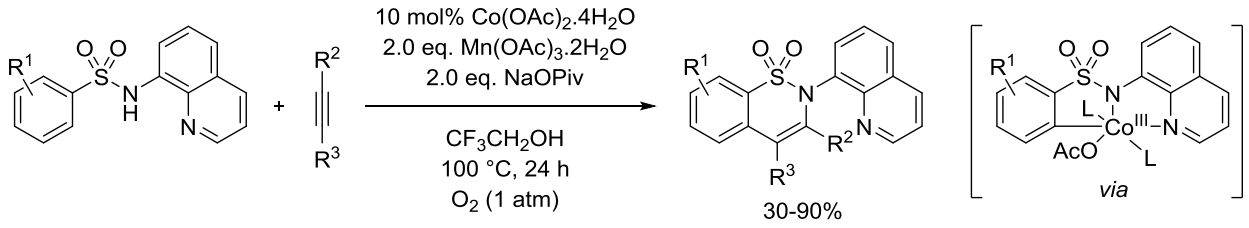
Scheme **56**).[114] The reaction showed complete cis diastereoselectivity. The reaction is compatible with different substituents, both on the imine and alkyne. When unsymmetrical alkynes were used, regioisomers were formed which could be separated using conventional chromatographic techniques. The authors performed several experiments to elucidate the reaction mechanism. Based on these reactions (including determination of KIE) and DFT-calculations, they proposed an oxidative addition mechanism for the C-H activation with a dinuclear iron carbonyl species. Test reactions also revealed that the species with the alkyne attached to the *ortho* position is probably an intermediate. Electrocyclization of this 1-alkenyl-2-iminobenzene gives the reaction product.



R^1 = H, 4-Me, 3-Me, 2-Me, 4-OMe, 4-F, 4-Cl, 4-CF_3
R^2 = Ph, 4-MePh, 4-MeOPh, 4-FPh, 3-Me, 1-naphthyl, 3,5-diMe, Bu, *i*Pr
R^3, R^4 = Ph, 4-MePh, 4-EtPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 2-FPh, 3-Me, 3-Cl, 3-Br

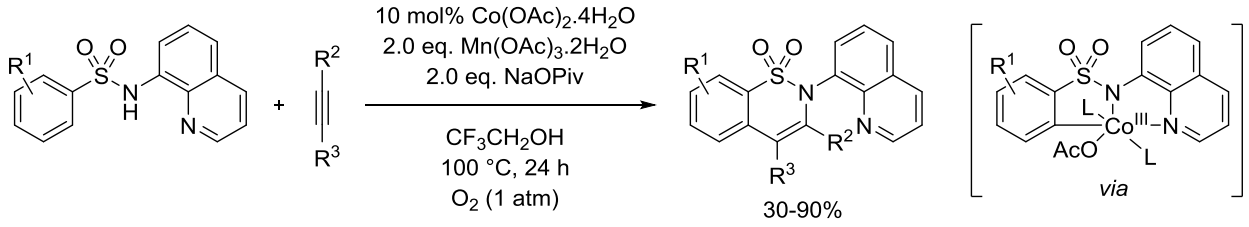
Scheme 56: Synthesis of 3,4-dihydroquinolines.

Another recent example is the cobalt catalyzed reaction of sulfonamides featuring an 8-aminoquinoline bidentate DG with alkynes (



R^1 = H, 4-*t*Bu, 4-OMe, 4-CF_3, 4AcNH, 3-OMe, 3,4$(OMe)_2$
R^2 = Ph, 3-MeC_6H_5, 4-MeC_6H_5, 4-*t*BuC_6H_5, 4-FC_6H_5, hexyl, $CH_2CH_2CH_2CN$, cyclopentyl, cyclopropyl, TMS, CO_2Et, *n*Pr
R^3 = H, Me, Ph, *n*Pr

Scheme **57**).[115] Terminal alkynes with a phenyl or larger substituent gave single regioisomers whereas smaller substituents gave mixtures of two different isomers. Mechanistic studies have not been performed but the authors hypothesize that coordination of the 8-aminoquinoline to the $Co(OAc)_2$ catalyst followed by base-assisted C-H bond functionalization leads to a cobalt metallacyle. Insertion of the alkyne and subsequent reductive elimination gives the reaction product and Co(I). The Co(I) species can be reoxidized to Co(II) using Mn(III). The formed Mn(II) can be reoxidized using oxygen.

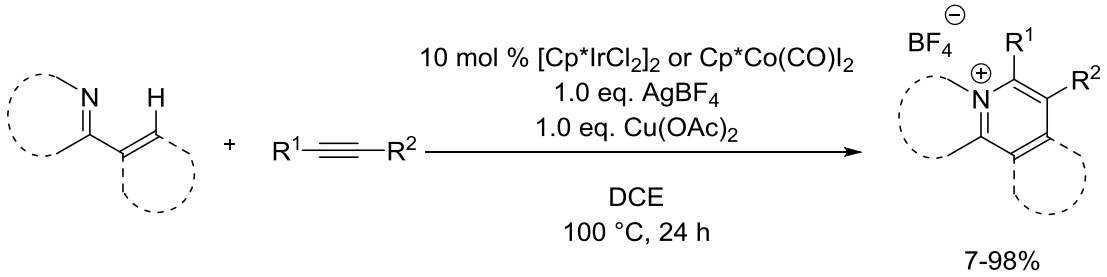


R^1 = H, 4-*t*Bu, 4-OMe, 4-CF_3, 4AcNH, 3-OMe, 3,4$(OMe)_2$
R^2 = Ph, 3-MeC_6H_5, 4-MeC_6H_5, 4-*t*BuC_6H_5, 4-FC_6H_5, hexyl, $CH_2CH_2CH_2CN$, cyclopentyl, cyclopropyl, TMS, CO_2Et, *n*Pr
R^3 = H, Me, Ph, *n*Pr

Scheme 57: Synthesis of 3,4-disubstituted 2-(quinolin-8-yl)-2*H*-benzo[*e*][1,2]thiazine 1,1-dioxides.

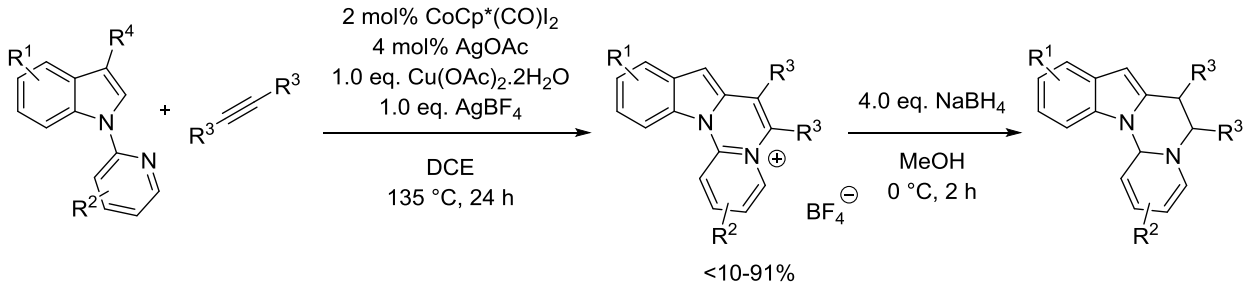
The products synthesized by direct oxidative aminations are not limited to uncharged nitrogen. Recently, Wang reported the synthesis of heteroaromatic quaternary ammonium salts by annulation reactions using alkynes (Scheme 58).[116] Many natural compounds feature a heterocyclic quaternary ammonium core and they have diverse biological activities.[117] Based on mechanistic studies (H/D scrambling, observation of inverse KIE, no effect on the rate of TEMPO addition), the authors propose a reversible electrophilic metalation mechanism rather than a concerted metalation-deprotonation (CMD) or single electron transfer (SET) process for the C-H activation. $Cu(OAc)_2$ was used as stoichiometric oxidant. The mechanism proposed is based on a $[Cp^*Co(III)]^{2+}$ catalytic complex. This species coordinates with the nitrogen of the heterocycle. Subsequent electrophilic metalation and deprotonation leads to a cyclocobaltated

species. The alkyne can insert in the Co-C bond of this species. Finally, reductive elimination yields the reaction product and the Cp*Co(I) catalyst which can be reoxidized using Ag(I) or Cu(II), regenerating the $[Cp^*Co(III)]^{2+}$ catalytic species. Pentamethylcyclopentadienyliridium(III)dichloride dimer was also found to be effective as a precatalyst.



Scheme 58: Synthesis of heteroaromatic quaternary ammonium salts.

Another insertion reaction using alkynes is described by Li (



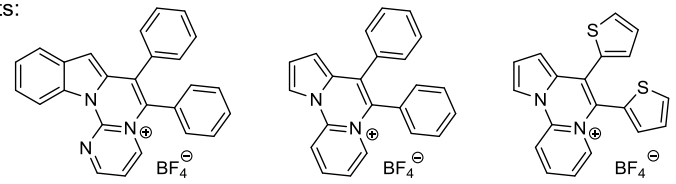
<10-91%

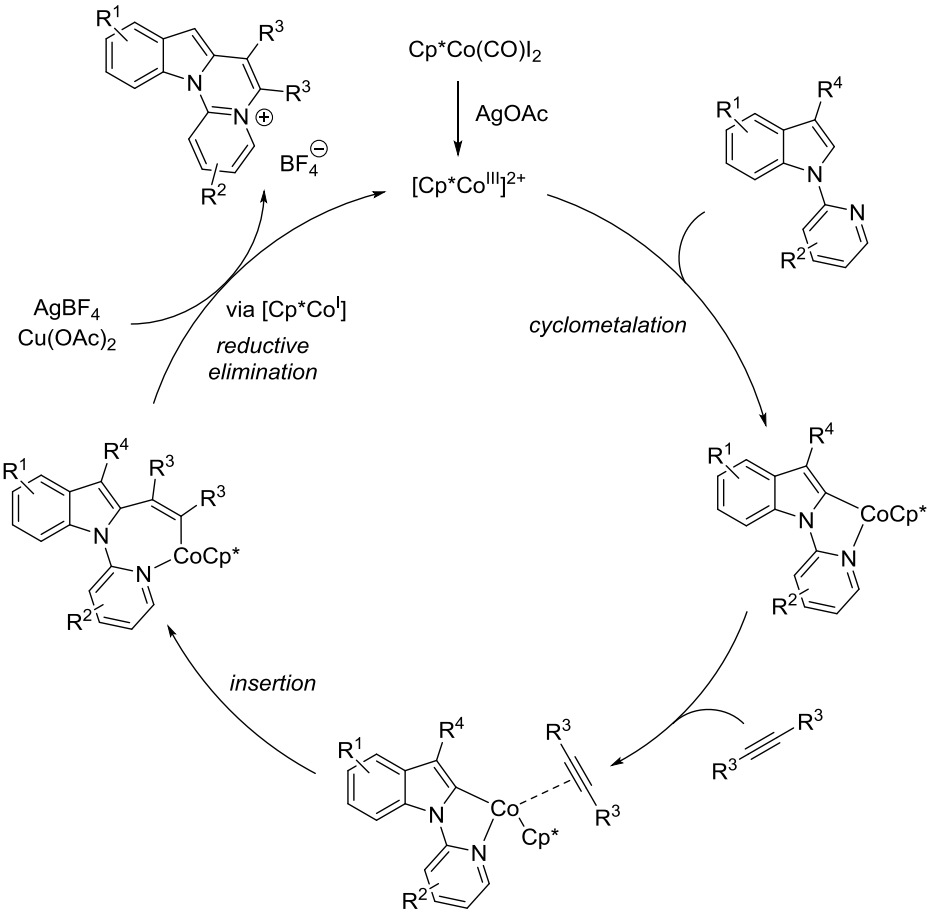
R^1 = H, 3-Me, 4-Me, 5-Me, 6-Me, 5-Cl, 4-Cl, 4-Br, 4-I, 4-NO_2, 4-OMe, 4-F, F-CO_2Me, 4-CN

R^2 = H, 2-Me, 3-Me, 4-Me, 5-Me

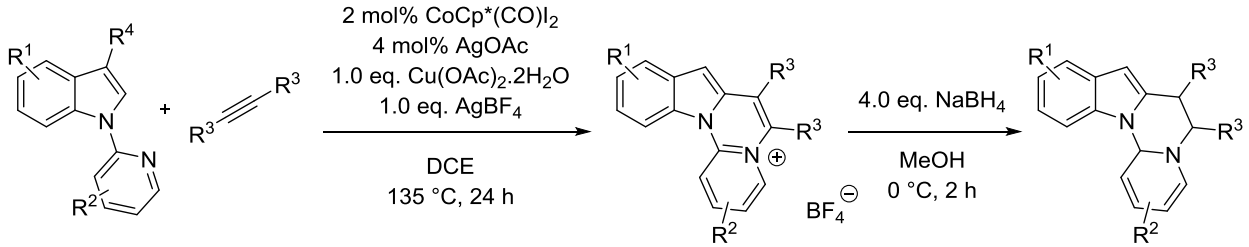
R^3 = H, 4-Me, 3-Me, 2-Me, 4-Cl, 4-NO_2, thiophen-2-yl, Et

Other products:



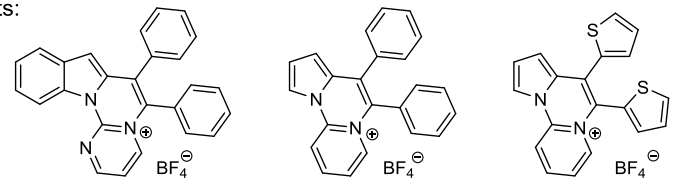


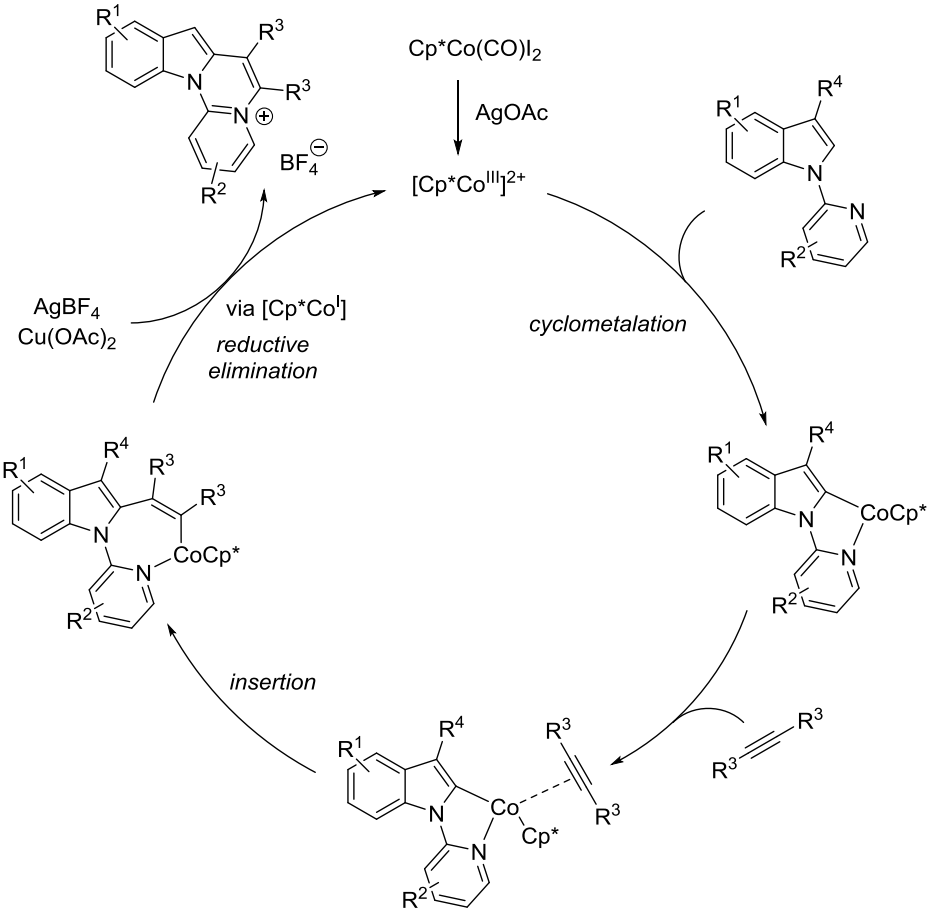
Scheme **59**).[118] Pyrido[2',1':2,3]pyrimido[1,6-*a*]indol-5-ium tetrafluoroborate salts could be synthesized using a Co catalyzed direct oxidative amination. After reduction with $NaBH_4$, a new indole fused heterocycle core could be synthesized. Reaction of $CoCp^*(CO)I_2$ with AgOAc leads to the catalytically active $(Cp^*Co)^{2+}$ species. This species coordinates with the substrate which then undergoes cyclometalation. The resulting cobaltated species coordinates with the alkyne which inserts in the N-Co bond. Reductive elimination forms the reaction product and Co(I) is reoxidized using $AgBF_4/Cu(OAc)_2$.



R^1 = H, 3-Me, 4-Me, 5-Me, 6-Me, 5-Cl, 4-Cl, 4-Br, 4-I, 4-NO_2, 4-OMe, 4-F, F-CO_2Me, 4-CN
R^2 = H, 2-Me, 3-Me, 4-Me, 5-Me
R^3 = H, 4-Me, 3-Me, 2-Me, 4-Cl, 4-NO_2, thiophen-2-yl, Et

Other products:

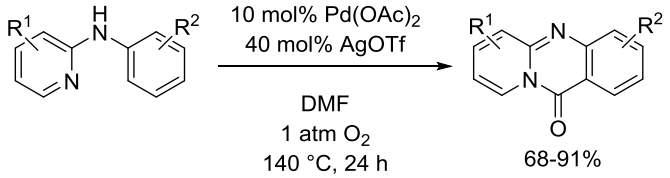




Scheme 59: Synthesis of pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium tetrafluoroborates.

Besides the use of alkynes for insertion reactions, other functionalities can also undergo insertion as demonstrated by the synthesis of pyrido-fused quinazolinones (

A

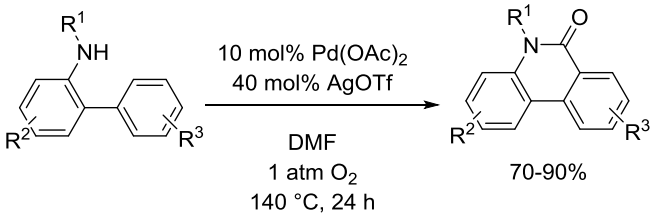


R^1 = H, 4-Me, 4-OMe, 4-Br, 3-Me, 4-I

R^2 = H, 4-Me, 4-OMe, 4-Br, 4-F, 4-CF_3, 4-OCF_3, 3-Cl-3-CF_3, (3-Me, 4-NO_2), 3-Me, 3,4-diCl, 2-Me

---

B

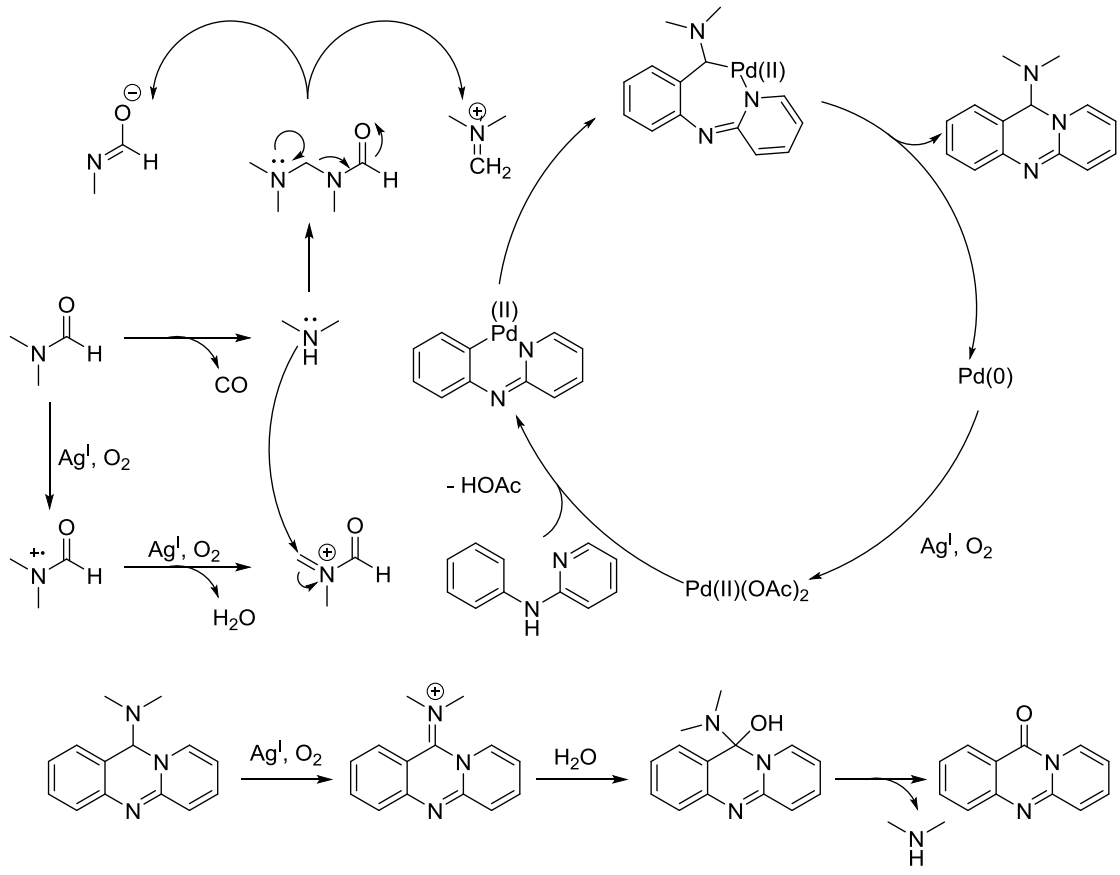


R^1 = Me, H

R^2 = H, 4-Me, 4-MeO, 4-F

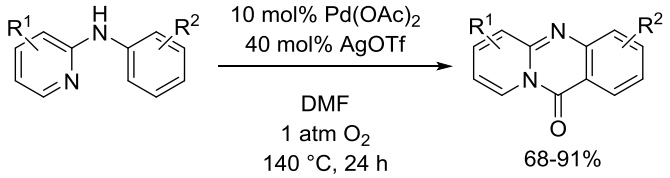
R^3 = H, 4-CO_2Me, 4-Me

C



Scheme 60, A) and phenanthridinones (

A

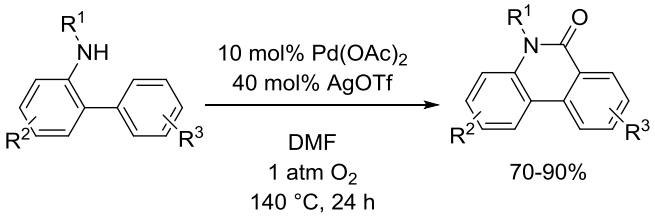


R^1 = H, 4-Me, 4-OMe, 4-Br, 3-Me, 4-I

R^2 = H, 4-Me, 4-OMe, 4-Br, 4-F, 4-CF_3, 4-OCF_3, 3-Cl-3-CF_3, (3-Me, 4-NO_2), 3-Me, 3,4-diCl, 2-Me

---

B

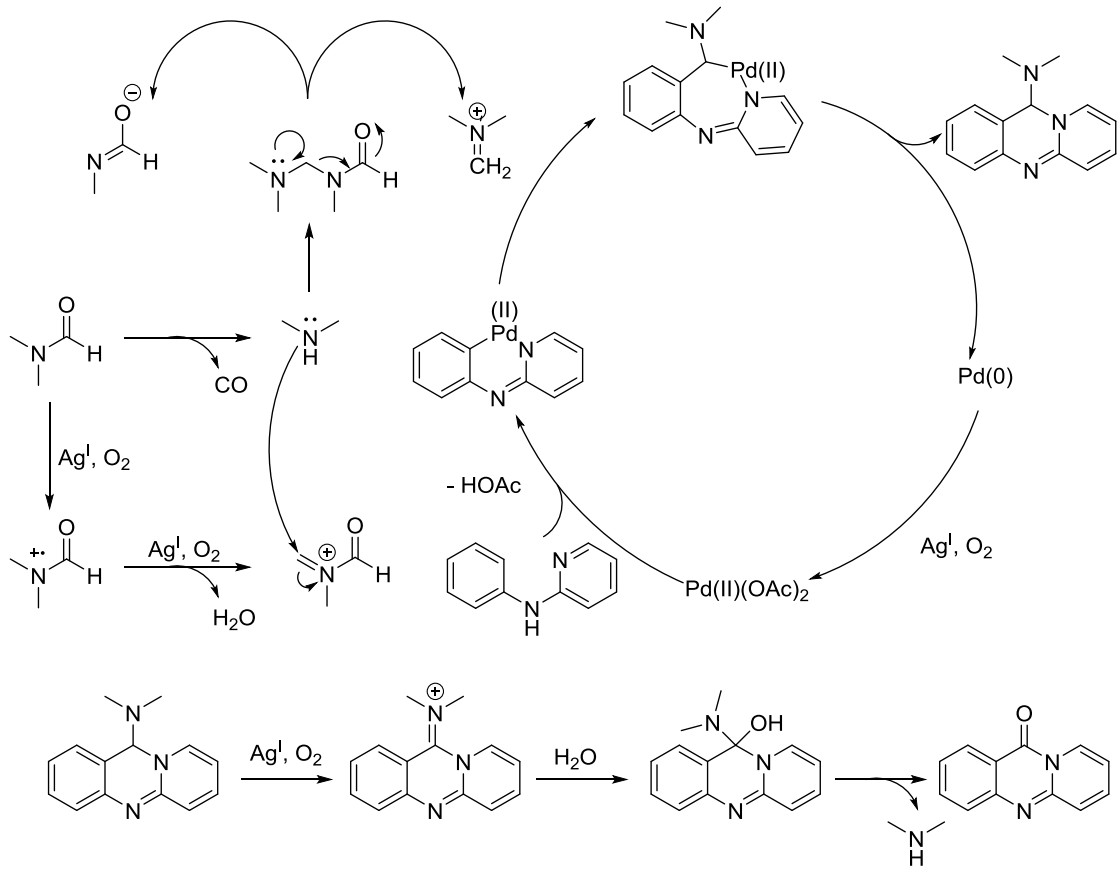


R^1 = Me, H

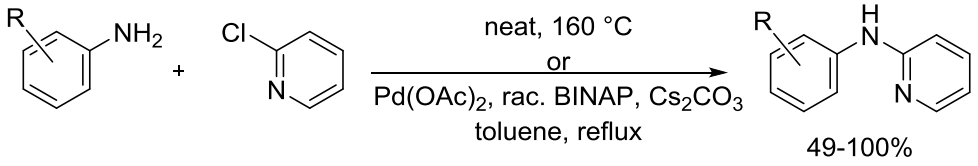
R^2 = H, 4-Me, 4-MeO, 4-F

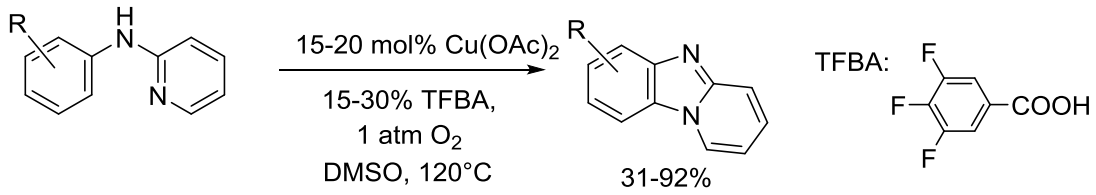
R^3 = H, 4-CO_2Me, 4-Me

C

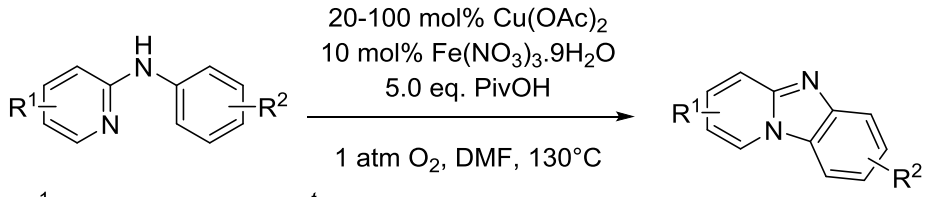


Scheme 60, B) via direct oxidative carbonylation, described by Das.[119] For the former the same substrate types as reported by Zhu and Maes were used (





R = 4-CF_3, 6-F, 7-F, 9-F, 8-F, 6-OMe, 7-OMe, 9-OMe, 8-OMe, 8-Cl, 8-CO_2Et, 7-CO_2Et, 8-CF_3, 6-Cl, (2-Cl, 5-OMe), 2-Cl, 2,6-diCl, (2-Cl, 3-F)

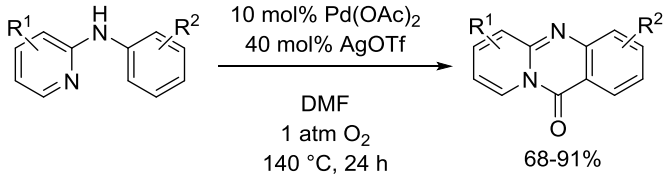


R^1 = H, 4-Me, 4-OMe, 4-^{t}Bu, 4-F, 4-Cl, 4-Br, 2-Me, 2-OMe, 2-F
R^2 = H, 3-Me, 3-OMe, 3-Cl, 3-F, 4-Me

Scheme **4**). A Pd/Ag catalytic system was used for this transformation. Oxygen is the stoichiometric oxidant. The carbon atom of the carbonyl group is coming from DMF, which acts both as a solvent and a reactant. This was confirmed by isotope labeling experiments. A

plausible mechanism for the reaction is displayed in

A

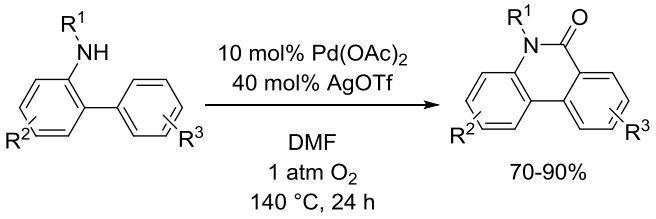


R^1 = H, 4-Me, 4-OMe, 4-Br, 3-Me, 4-I

R^2 = H, 4-Me, 4-OMe, 4-Br, 4-F, 4-CF_3, 4-OCF_3, 3-Cl-3-CF_3, (3-Me, 4-NO_2), 3-Me, 3,4-diCl, 2-Me

---

B

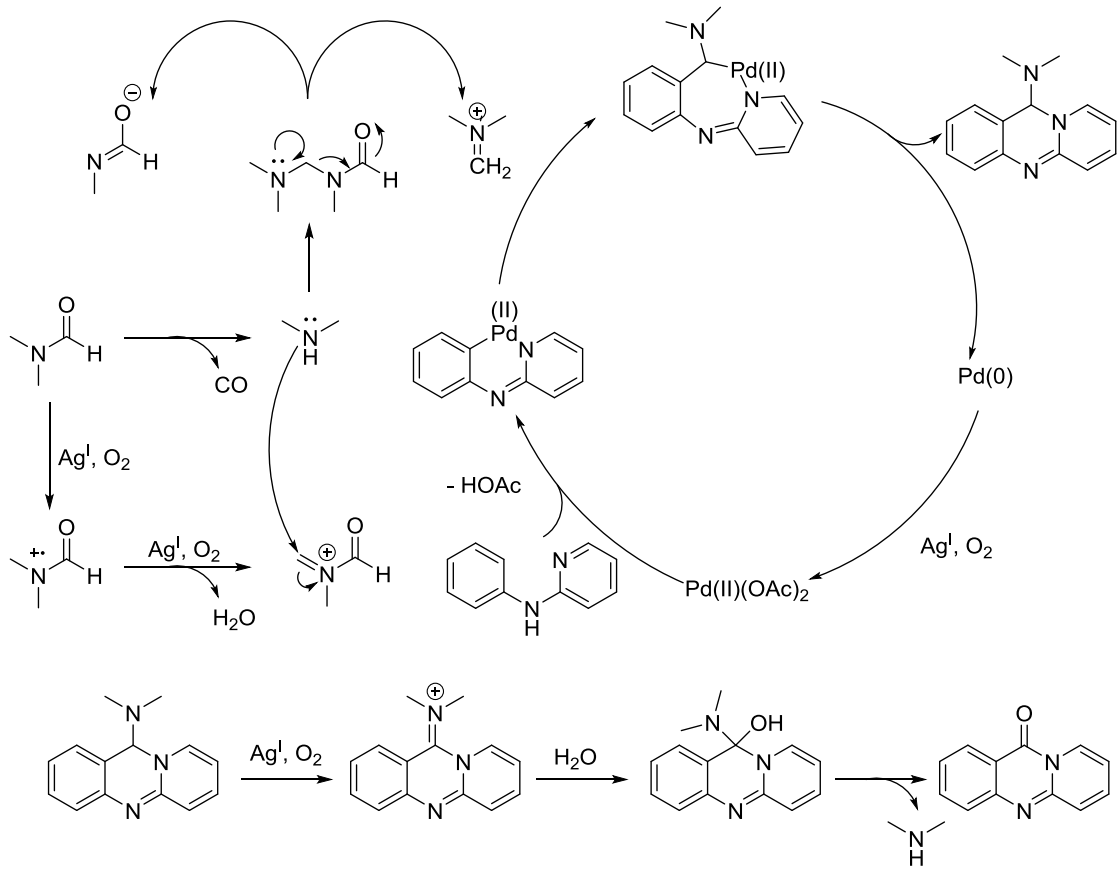


R^1 = Me, H

R^2 = H, 4-Me, 4-MeO, 4-F

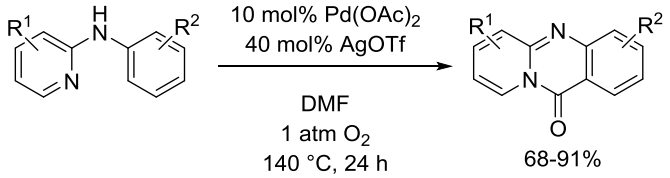
R^3 = H, 4-CO_2Me, 4-Me

C



Scheme 60, C. Coordination of the Pd(II) catalyst with the nitrogen of the substrate leads to C-H activation and formation of a cyclopalladated species. This species can react with a formaldehyde derived dimethyl iminium species, resulting from DMF. This is obtained by decarbonylation of DMF producing dimethylamine which acts as a nucleophile and adds to the unstable *N*-formyl-*N*-methyl formaldehyde iminium species formed by oxidation of DMF by Ag(I) and O_2. Release of CO from DMF at increased temperature has been reported.[120] Isotope labelling experiments demonstrated that the carbonyl in the reaction product came from the dimethyliminium species and not from the CO. The resulting aminal product can release the formaldehyde derived dimethyl iminium species. Nucleophilic addition of the carbopalladated species to this species, followed by reductive elimination leads to a cyclic aminal. Oxidation by Ag(I) and O_2 leads to an *N*,*N*-dimethylamidinium species which can be hydrolysed to the final reaction product with concomitant release of dimethylamine.

A

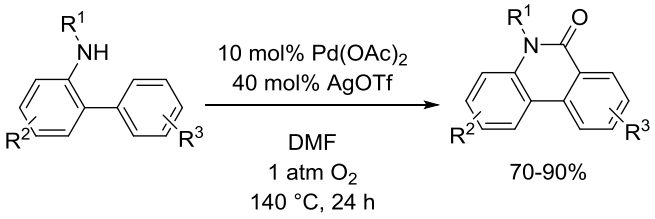


R^1 = H, 4-Me, 4-OMe, 4-Br, 3-Me, 4-I

R^2 = H, 4-Me, 4-OMe, 4-Br, 4-F, 4-CF_3, 4-OCF_3, 3-Cl-3-CF_3, (3-Me, 4-NO_2), 3-Me, 3,4-diCl, 2-Me

---

B

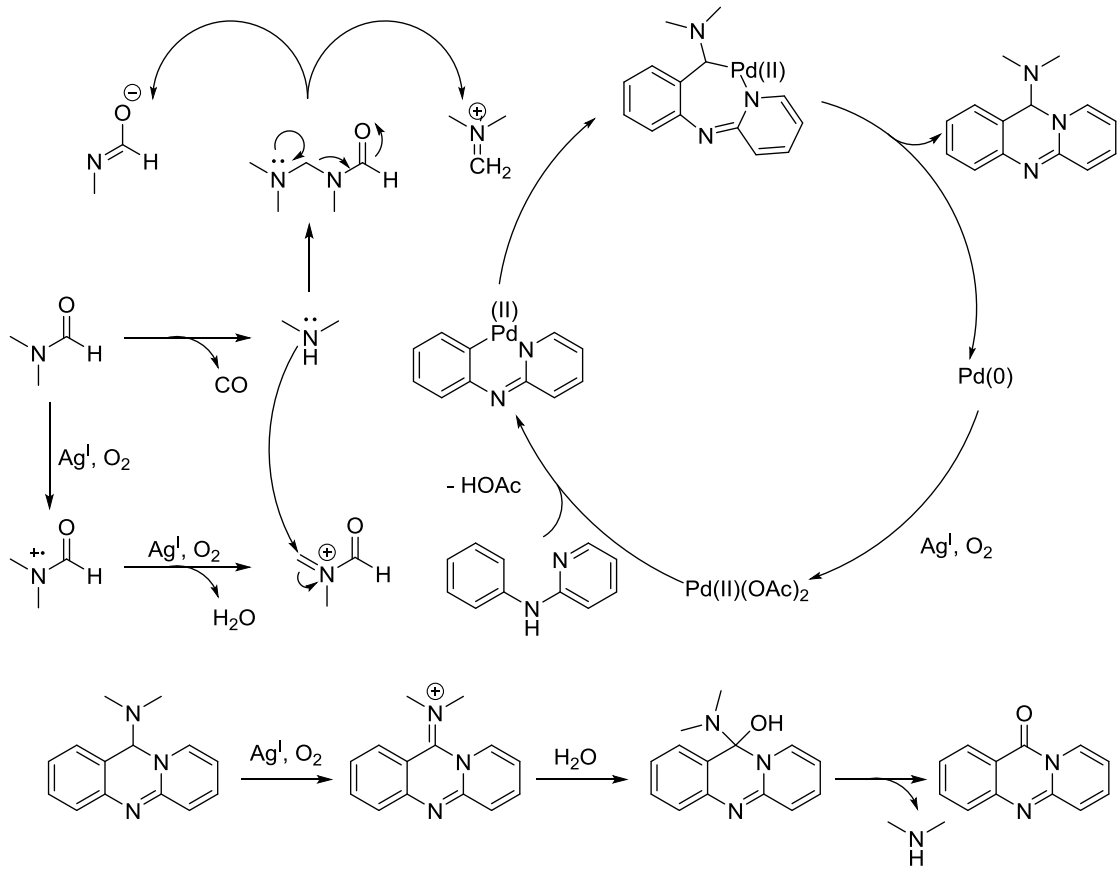


R^1 = Me, H

R^2 = H, 4-Me, 4-MeO, 4-F

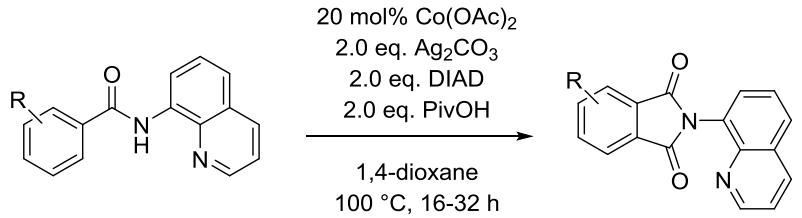
R^3 = H, 4-CO_2Me, 4-Me

C



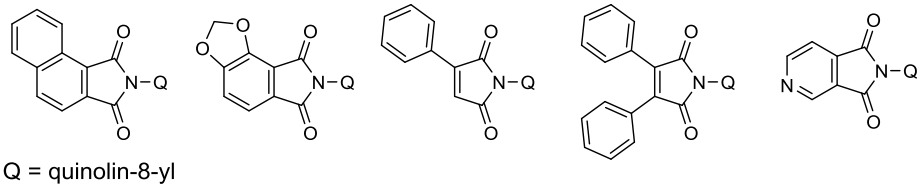
Scheme 60: Synthesis of pyrido-fused quinazolinones and phenanthridinones.

A cobalt-catalyzed oxidative carbonylation reaction using DIAD (diisopropyl azodicarboxylate) as the carbonyl source is described by Zhang (Scheme 61).[121] The catalytic Co^{III} species is produced via oxidation of Co^{II}. This species coordinates with the benzamide substrate and subsequently forms a cobaltated species. Upon heating, DIAD can lose N_2 with formation of an isopropyloxycarbonyl radical. This radical can either react directly with the cobaltated species to form a Co^{IV} intermediate (path a) or it can first further decompose with formation of carbon monoxide and then insert in the cobaltated species (path b). Reductive elimination from the Co^{III} or Co^{IV} species gives the phthalimide either directly (Co^{III}) or via metal-catalyzed amidolysis of the intermediate ester with loss of isopropanol (Co^{IV}). Both pathways are working simultaneously as both the production of CO gas and the formation of the intermediate ester formed by reductive elimination of the Co^{IV} intermediate could be demonstrated. Attempted ring closure of the intermediate ester without any metals present failed. Either the presence of $Co(OAc)_2.4H_2O$ or Ag_2CO_3 was required, indicating that the cyclization (lactamization) might be catalyzed by Lewis-acids.

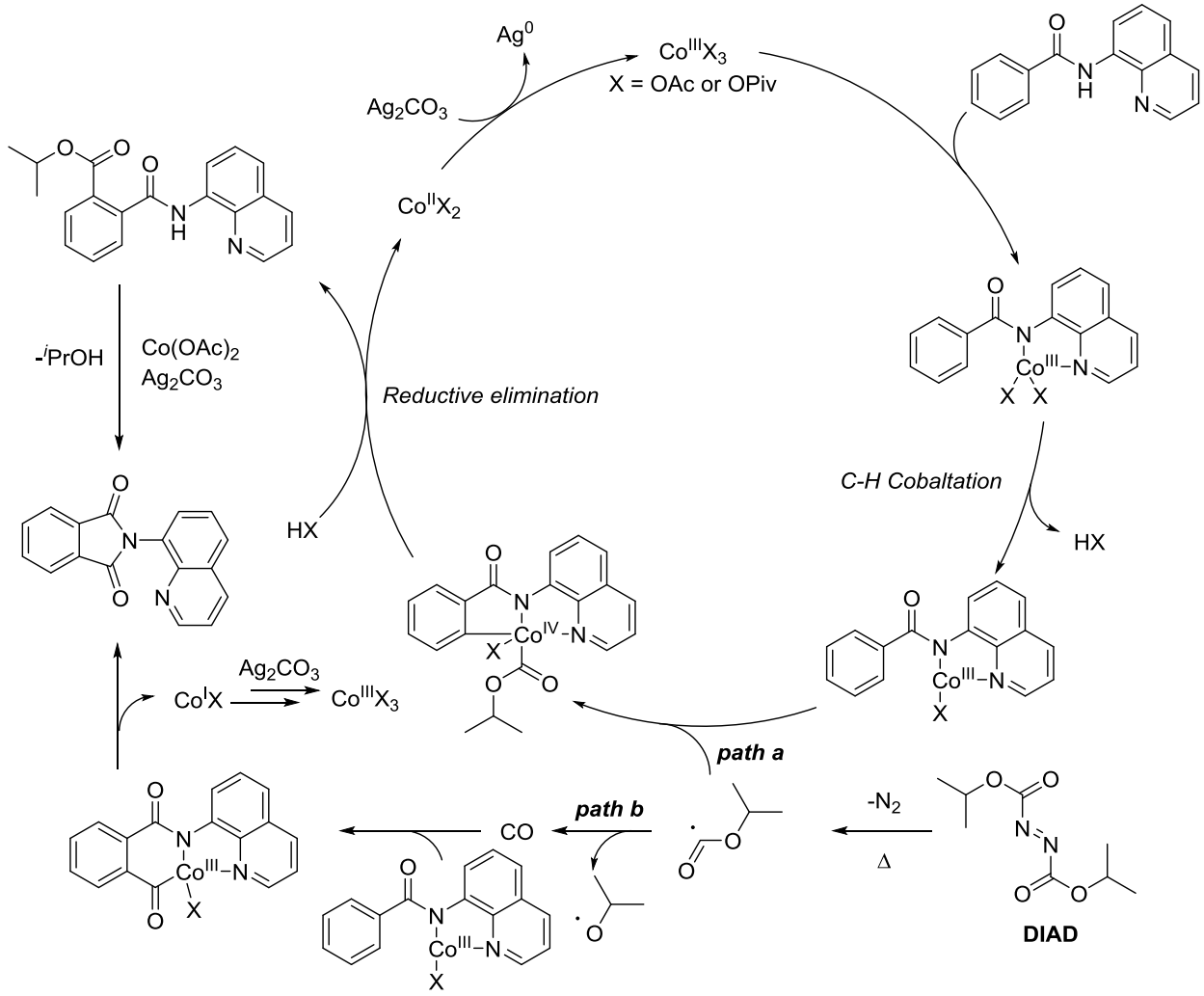


R = H, 4-Me, 4-*t*-Bu, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-Ac, 4-NO_2, 4-CN, 3-Me, 3-F, 3-Cl, 3-Br, 3,5-diMe, 3,5-diCl, 3,6-diMe, 3,5-diMe

Other products:

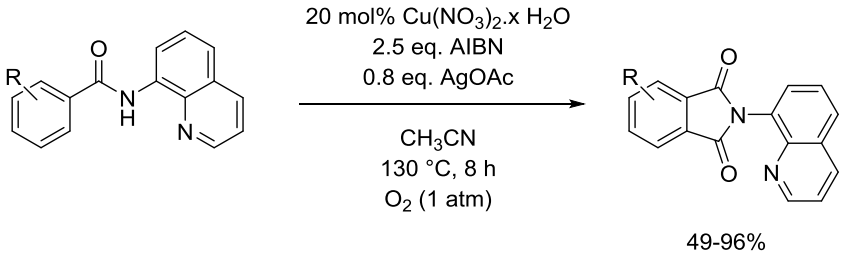


Q = quinolin-8-yl



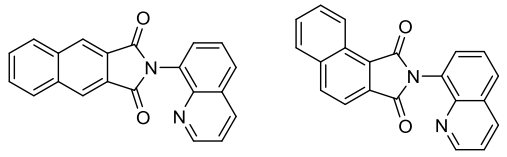
Scheme 61: Synthesis of *N*-(2-quinolin-8-yl)phthalimides and succinimides.

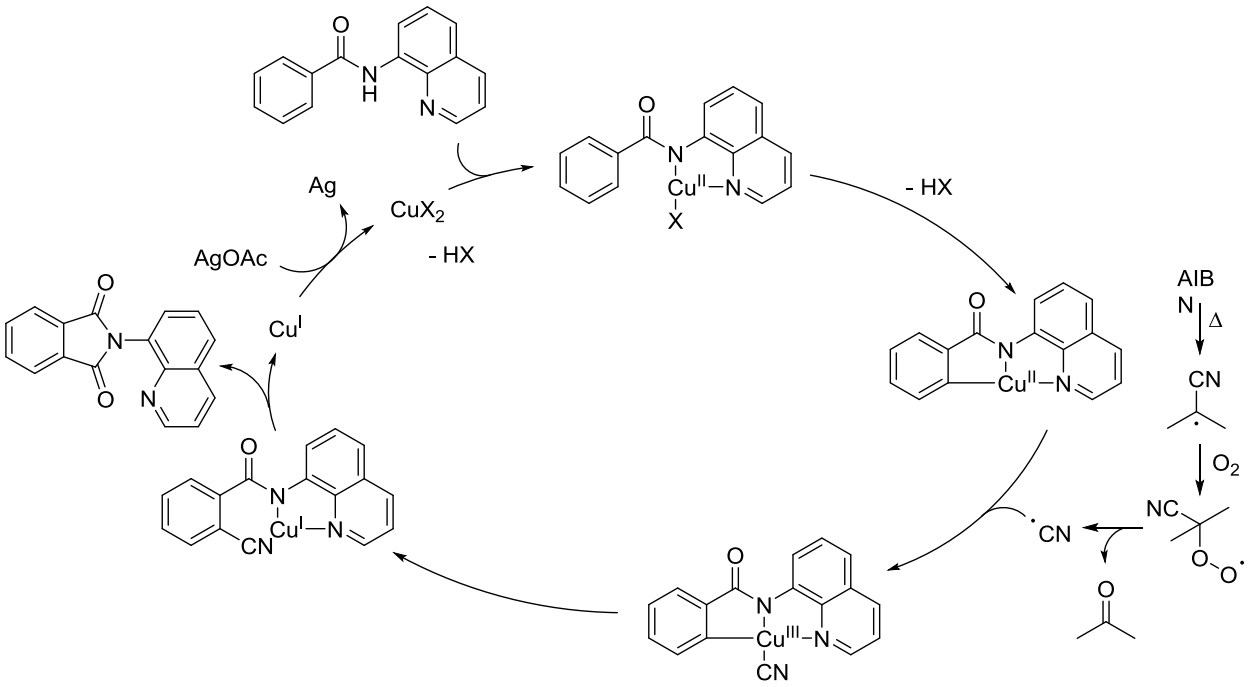
The same compounds can be formed by a copper catalyzed reaction, described by Koley (



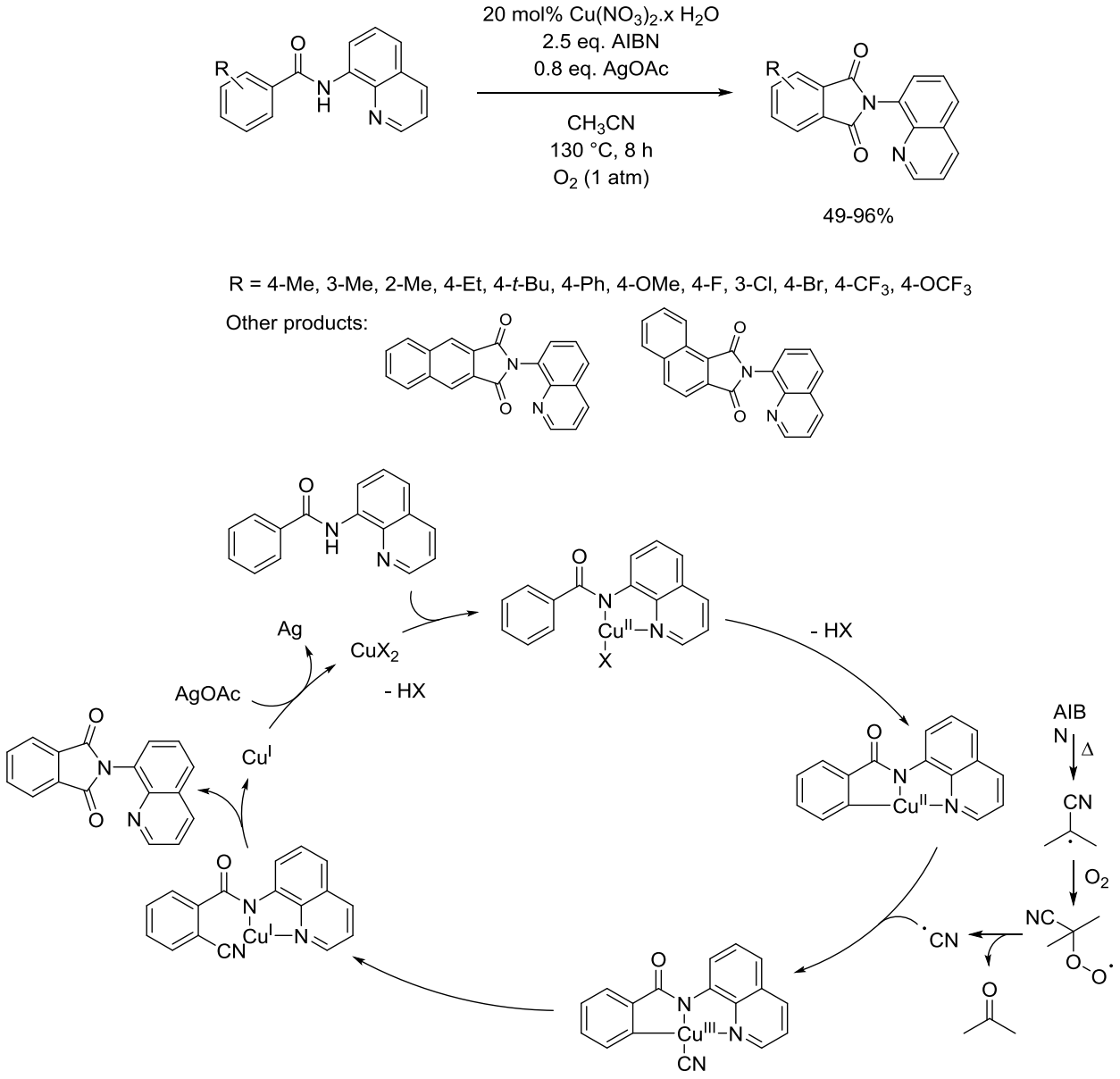
R = 4-Me, 3-Me, 2-Me, 4-Et, 4-*t*-Bu, 4-Ph, 4-OMe, 4-F, 3-Cl, 4-Br, 4-CF_3, 4-OCF_3

Other products:



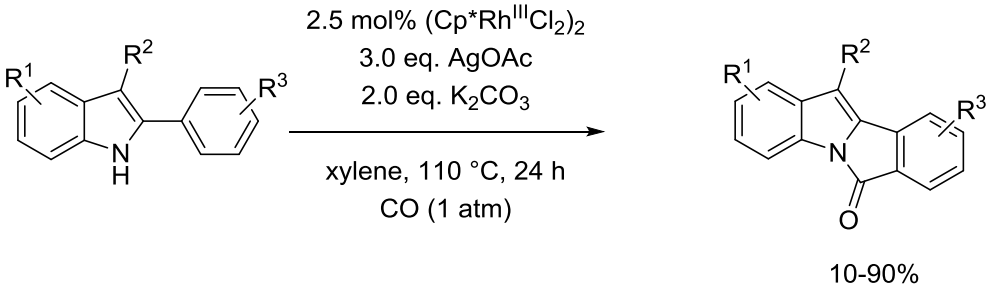


Scheme **62**).[122] In this case AIBN is used as a source of cyanide radicals. A double coordinated species is formed by reaction of Cu^{II} with the substrate. In the C-H activation step, loss of HX creates the copper pincer intermediate. Heating of AIBN induces homolytic cleavage with generation of a 2-cyanoprop-2-yl radical. Reaction of this radical with oxygen generates a peroxide radical which loses acetone and creates a cyanide radical which oxidizes Cu^{II} to Cu^{III}. Cyanation via reductive elimination, followed by intramolecular condensation and hydrolysis of the formed amidine leads to the reaction product. The Cu^{I} obtained in the reductive elimination can be reoxidized using AgOAc. When the reaction was performed under nitrogen atmosphere or in the presence of TEMPO, none or just traces of product was formed supporting the involvement of radicals.



Scheme 62: Synthesis of *N*-(2-quinolin-8-yl)phthalimides.

The carbonyl can also come from carbon monoxide gas as used in the synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones from 2-phenylindoles (

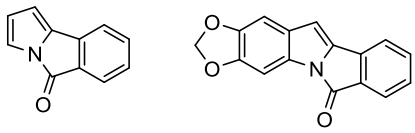


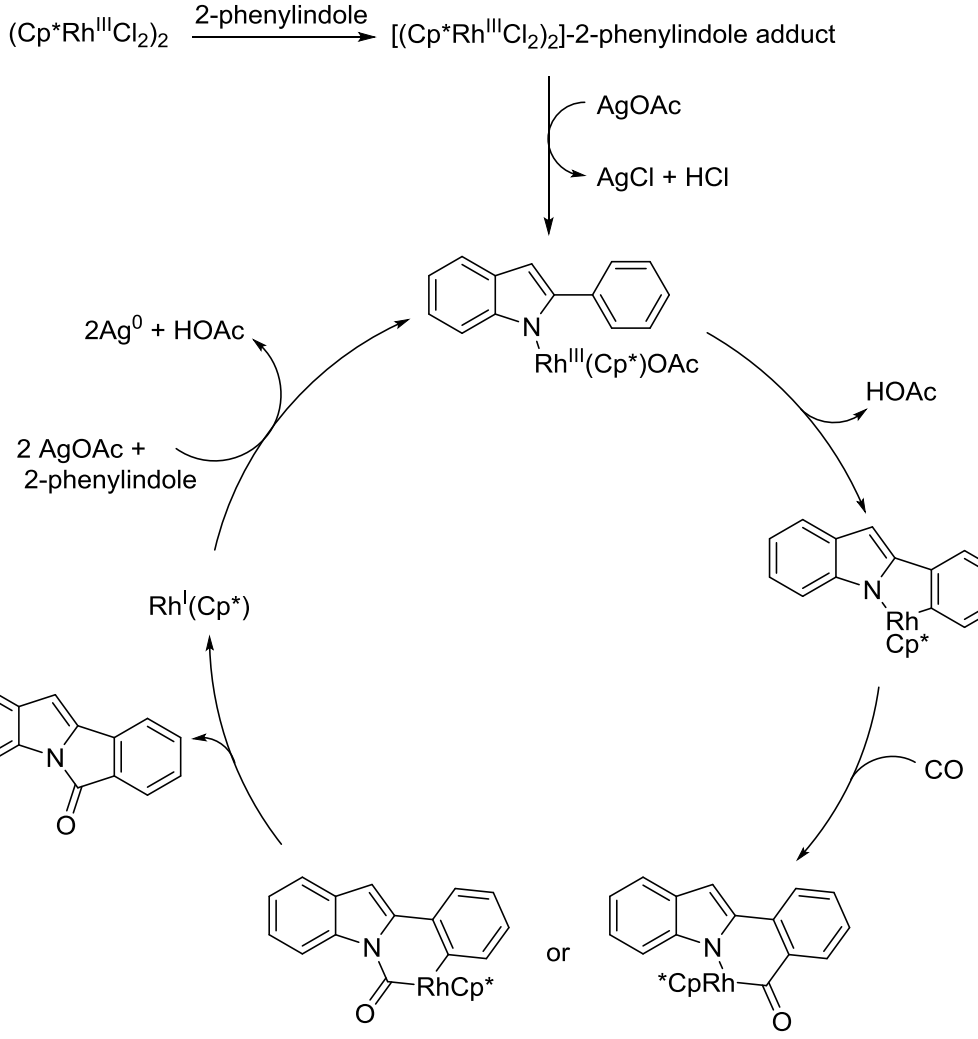
R^1 = H, 4,5-diMe, 5-Me, 6-Me, 5,6-diMe, 7-Me, 5-F, 5-Br, 5-Cl, 5-CN, 5-NO_2

R^2 = H, Me, CHO

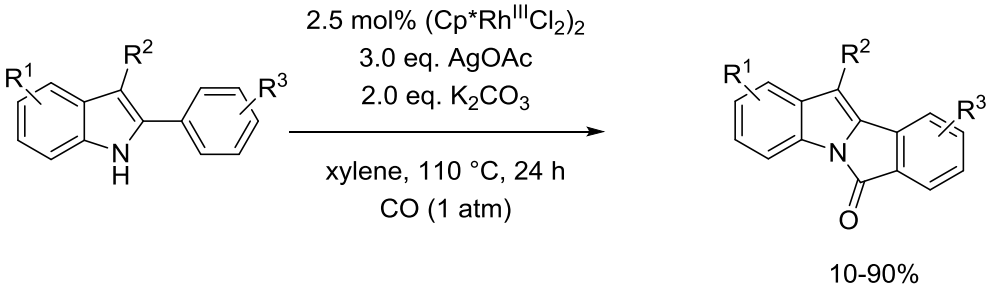
R^3 = H, 2-Me, 3-Me, 4-Me, 2,4-diMe, 3,4-diMe, 4-*i*-Pr, 4-*t*-Bu, 4-Ph, 4-F, 4-Cl, 4-Br, 2-Cl, 2-Br, 2-I, 4-COMe, 4-CO_2Me

Other products:





Scheme **63**).[123] The catalytically active species is a [(Cp*$Rh^{III}Cl_2)_2$]-2-phenylindole adduct, which is formed by reaction of the catalyst with the substrate. By reaction with AgOAc, a N-Rh bond is formed. Further reaction via loss of acetic acid yields a rhodacycle which can undergo CO insertion. This can occur in the Rh-N or in the Rh-C bond. Subsequently, reductive elimination yields the final reaction product. Rh^{I} can be reoxidized to Rh^{III} by 2 SET oxidations with AgOAc closing the catalytic cycle. Although no detailed mechanism of the C-H activation step was put forward, intermolecular KIE studies revealed that the breaking of the C-H bond might be the RDS. Other examples are the synthesis of dihydroisoquinolin-1(2*H*)-ones (Scheme 7).



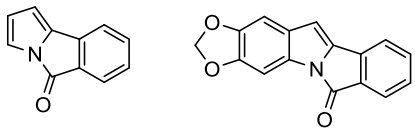
10-90%

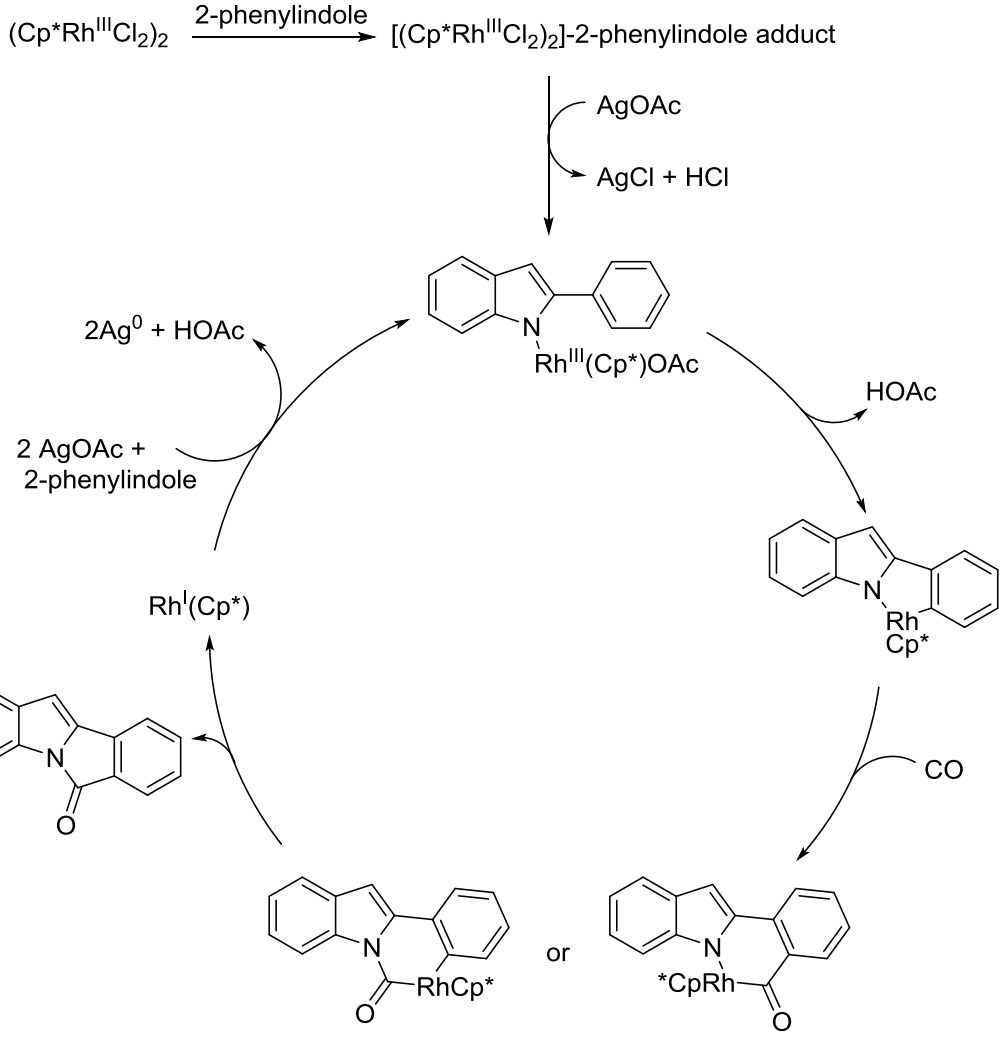
R^1 = H, 4,5-diMe, 5-Me, 6-Me, 5,6-diMe, 7-Me, 5-F, 5-Br, 5-Cl, 5-CN, 5-NO$_2$

R^2 = H, Me, CHO

R^3 = H, 2-Me, 3-Me, 4-Me, 2,4-diMe, 3,4-diMe, 4-*i*-Pr, 4-*t*-Bu, 4-Ph, 4-F, 4-Cl, 4-Br, 2-Cl, 2-Br, 2-I, 4-COMe, 4-CO$_2$Me

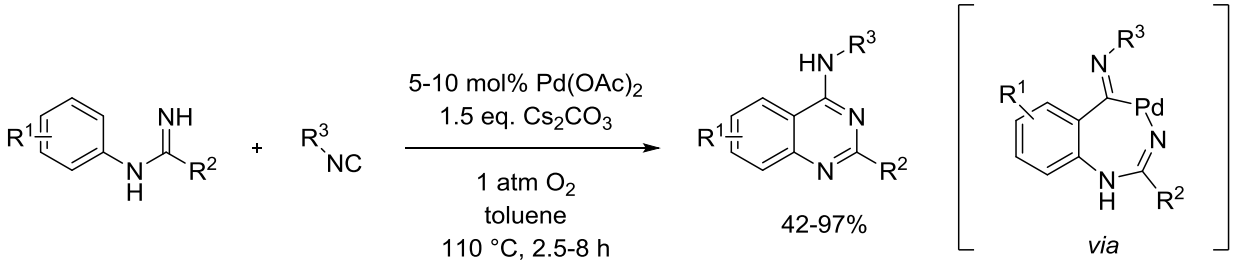
Other products:





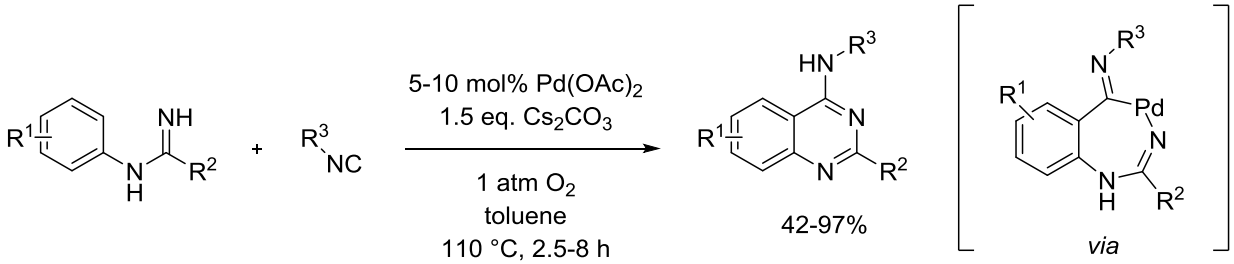
Scheme 63: Synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones.

A third type of molecules which are often used for insertions are isocyanides. Their use is certainly not limited to Buchwald-Hartwig aminations alone[124], also in direct oxidative aminations they can be used as demonstrated by Zhu for 4-aminoquinazoline synthesis from *N*-arylamidines and isocyanides (



R^1 = 5-Me, 5-OMe, 5-F, 5-Cl, 6-Me, 6-OMe, 6-Cl, 8-Me, 8-*t*-Bu, 8-F, 6,8-diMe, 5,7-diMe
R^2 = Ph, 4-MeOPh, 4-MePh, 3-MePh, 3,4-diMePh, 2-MePh, 4-ClPh, 2-ClPh, 4-BrPh, *t*-Bu, Cy, *i*-Pr
R^3 = *t*-Bu, *i*-Pr, Cy, 2,6-diMePh, 2-*t*-BuPh, 2,4-diMePh, 3,5-diMePh

Scheme **64**).[125]

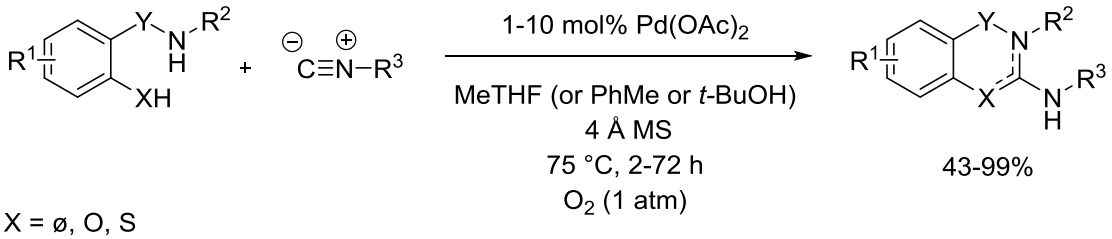


R^1 = 5-Me, 5-OMe, 5-F, 5-Cl, 6-Me, 6-OMe, 6-Cl, 8-Me, 8-*t*-Bu, 8-F, 6,8-diMe, 5,7-diMe
R^2 = Ph, 4-MeOPh, 4-MePh, 3-MePh, 3,4-diMePh, 2-MePh, 4-ClPh, 2-ClPh, 4-BrPh, *t*-Bu, Cy, *i*-Pr
R^3 = *t*-Bu, *i*-Pr, Cy, 2,6-diMePh, 2-*t*-BuPh, 2,4-diMePh, 3,5-diMePh

Scheme 64: Synthesis of 4-aminoquinazolines.

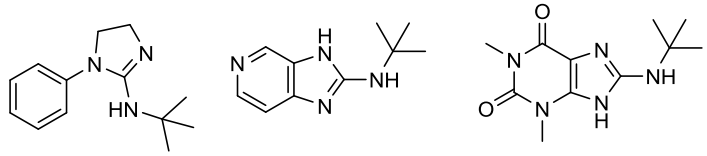
Orru and Maes showed that various privileged scaffolds can be obtained by using a palladium catalyzed direct oxidative amination involving a bisnucleophile (with at least one nitrogen) and

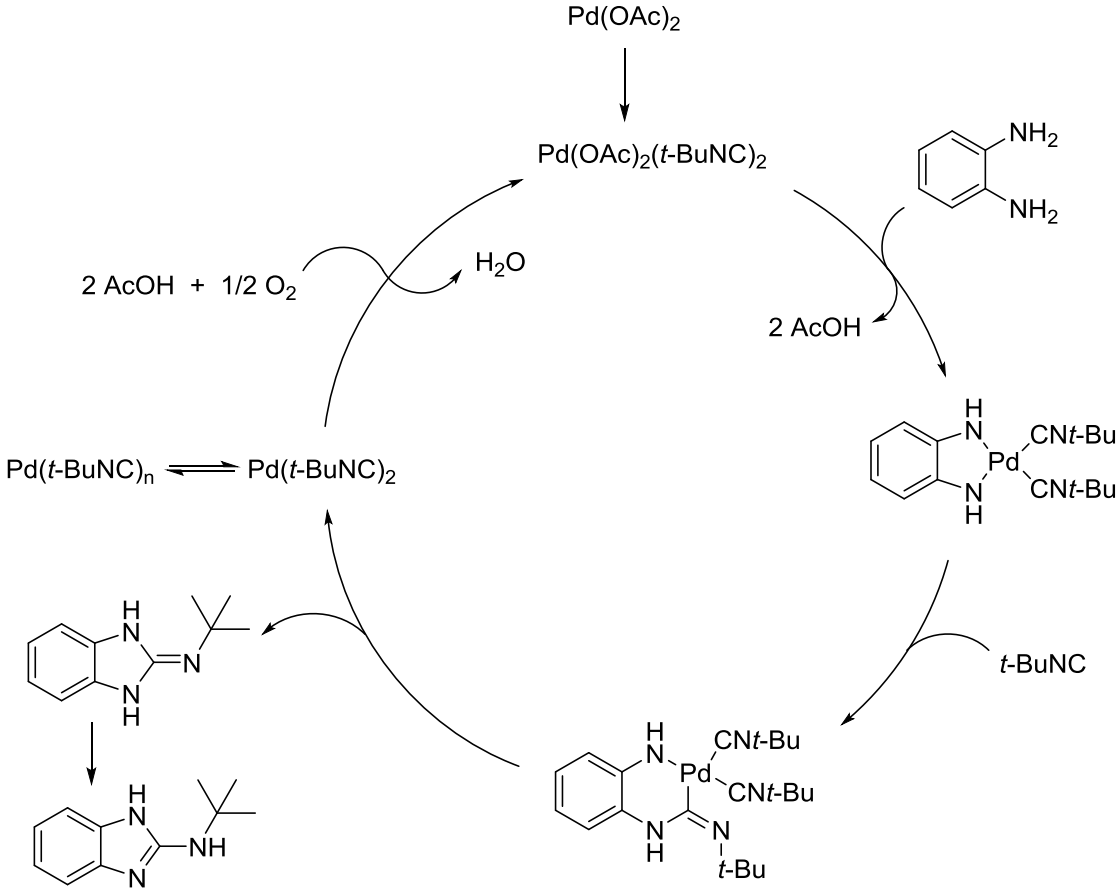
an isocyanide (



X = ø, O, S
Y = ø, CO, SO_2, CH_2
R^1 = H, 4-Me, 3-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CO_2Me, 4-CN, 4-CF_3, 4-NO_2
R^2 = H, Me, PMB
R^3 = *t*-Bu, *i*-Pr, pentyl, Cy

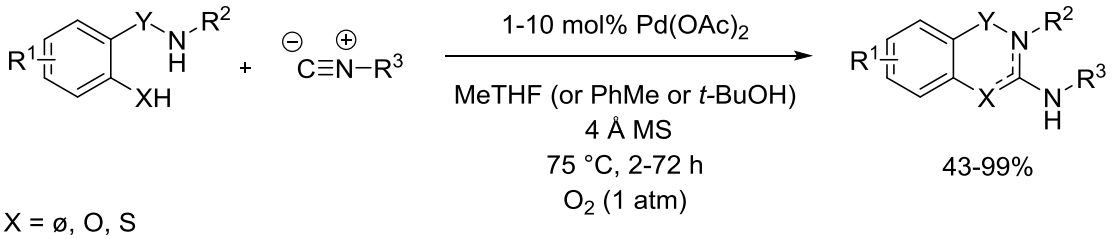
Other products:





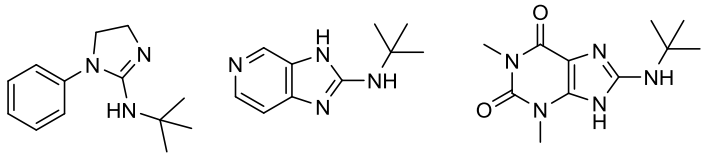
Scheme **65**).[126]. In this case, the two hydrogen atoms that are removed during the dehydrogenative coupling are coming from a heteroatom. Coordination of the isocyanide with the palladium catalyst forms the catalytically active species as exemplified for the synthesis of 2-(*t*-butylamino)-1*H*-benzimidazole in Scheme 65. Reaction with the two heteroatoms of the

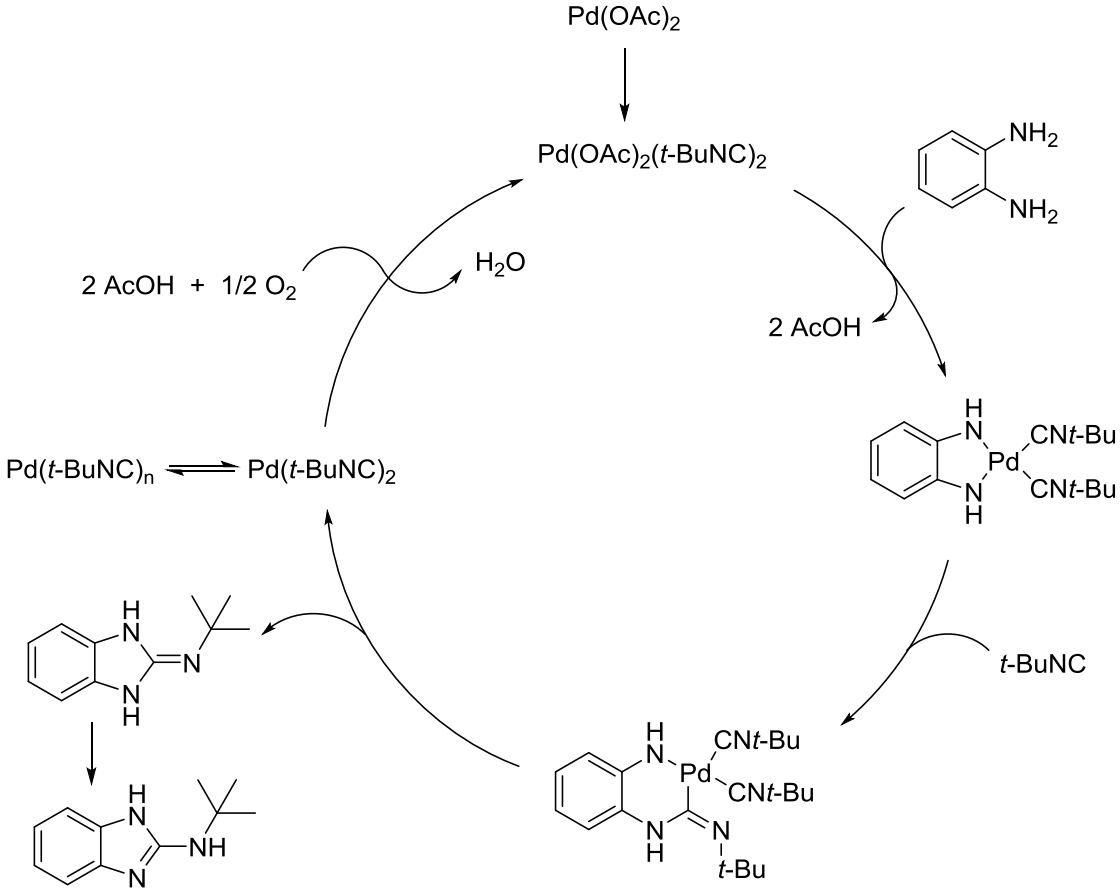
substrate with loss of acetic acid leads to the cyclopalladated intermediate. Insertion of the isocyanide and subsequent reductive elimination leads to the reaction product. Reoxidation of palladium by oxygen regenerates the active species.



X = ø, O, S
Y = ø, CO, SO_2, CH_2
R^1 = H, 4-Me, 3-Me, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CO_2Me, 4-CN, 4-CF_3, 4-NO_2
R^2 = H, Me, PMB
R^3 = *t*-Bu, *i*-Pr, pentyl, Cy

Other products:





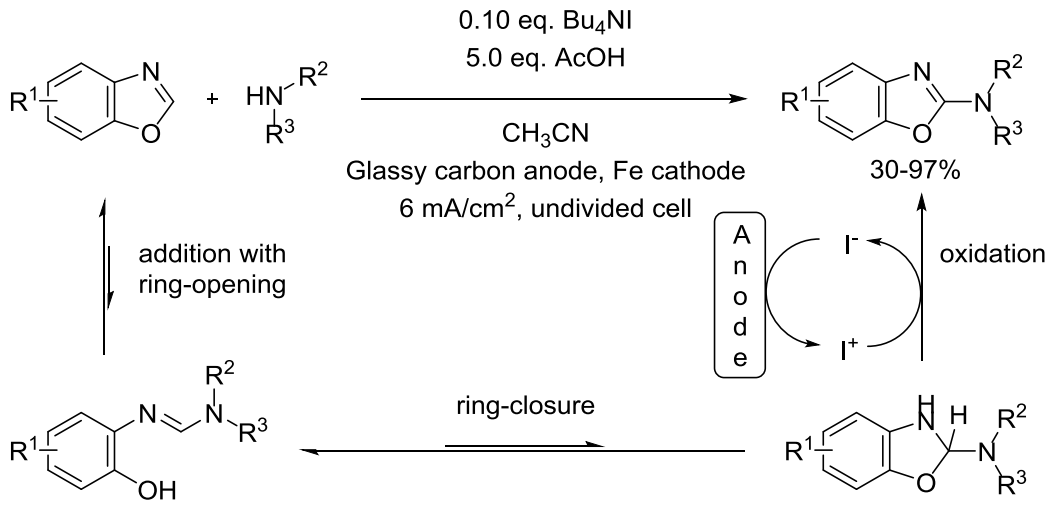
Scheme 65: Synthesis of guanidine, isourea, and isothiourea containing heterocycles.

The use of isocyanides has been reported in the cobalt catalyzed synthesis of 2-aminoquinolines, starting from 2-vinylanilines.[127] Other examples involving isocyanide insertion starting from bisfunctionalized arenes have been described, such as the synthesis of azolo[*c*]quinazolines[128] and 2-aminobenzoxazinones[129].

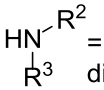
2.5 Electrochemical cross dehydrogenative couplings

Recently, examples of direct oxidative aminations using electrochemical oxidation are appearing. Oxidation with electricity is an interesting way of oxidation as it avoids the use of chemical oxidants and its concomitant waste.[130] Moreover, electrochemical oxidation is considered green as electricity can be generated from sustainable and renewable sources. There are two types of electrochemical oxidation. Direct electrolysis when there is a direct electron transfer between the electrode and the substrate and indirect electrolysis with a redox catalyst fulfilling the role of transfer agent.

An example of indirect electrolysis is the C2 direct oxidative amination of benzoxazoles with secondary amines using a tetraalkylammonium halide as redox catalyst (

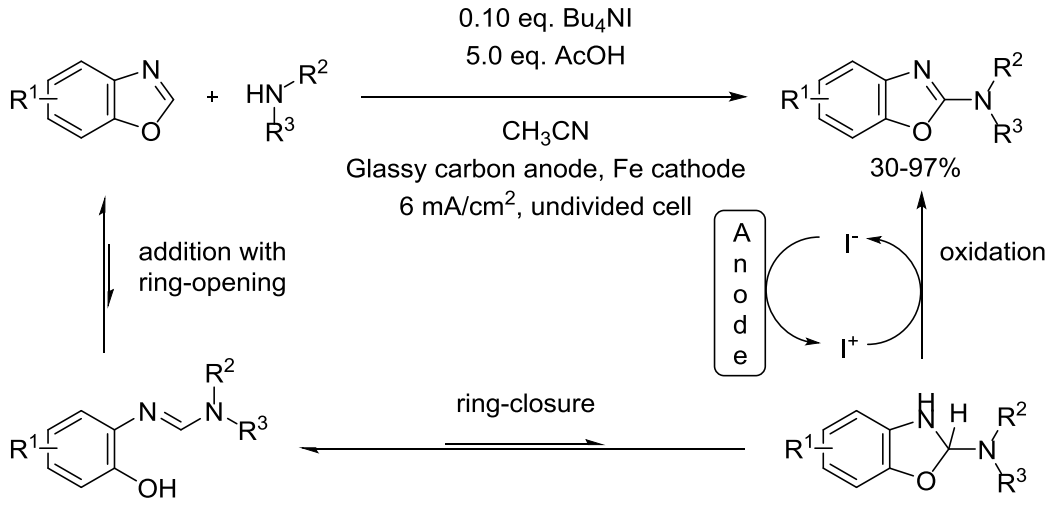


R^1 = H, 5-Me, 5-Cl, 6-Me, 6-Cl, 5-NO_2

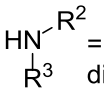

= pyrrolidine, piperidine, morpholine, tetrahydroisoquinoline, 5,6-dimethoxytetrahydroisoquinoline, dibenzylamine

Scheme 66).[131] In this reaction amine adds to the C2 of benzoxazole which is activated by protonation with acetic acid. This σ^H adduct is in equilibrium with ring opened *N*-(2-

hydroxyphenyl)formamidine. σ^H adduct can be oxidized to 2-aminobenzoxazole by ring nitrogen iodination with iodine cation followed by hydrogen iodide elimination. This is generated from iodide by electrochemical oxidation of tetraalkylammonium iodide. Unfortunately, when primary amines were used, complex reaction mixtures were obtained.

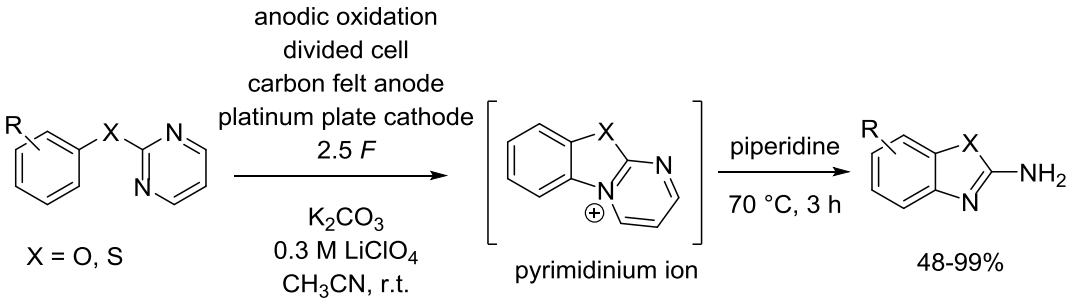


R^1 = H, 5-Me, 5-Cl, 6-Me, 6-Cl, 5-NO_2

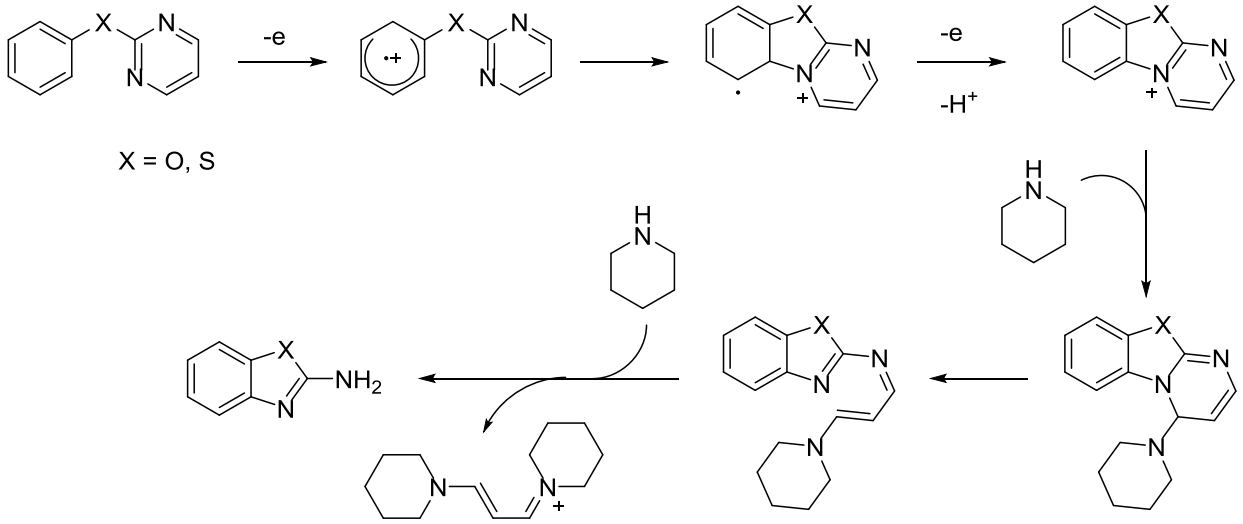
 = pyrrolidine, piperidine, morpholine, tetrahydroisoquinoline, 5,6-dimethoxytetrahydroisoquinoline, dibenzylamine

Scheme 66: Synthesis of 2-aminobenzoxazoles.

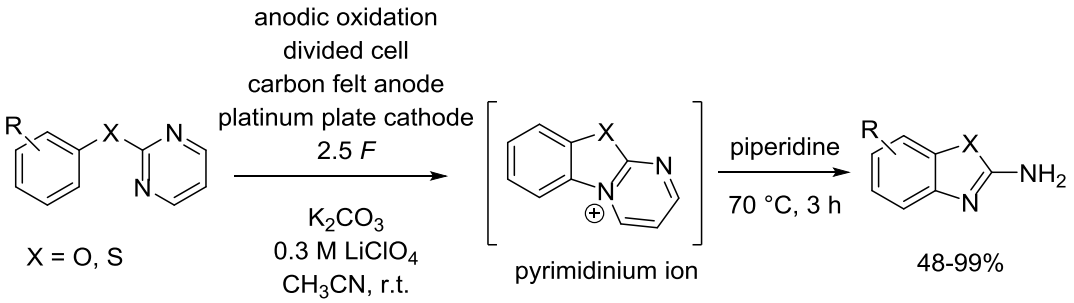
Direct electrolysis can be illustrated by the synthesis of 2-aminobenzoxazoles and -benzothiazoles by cyclization of respectively 2-phenyloxy- and 2-phenylthiopyrimidine (



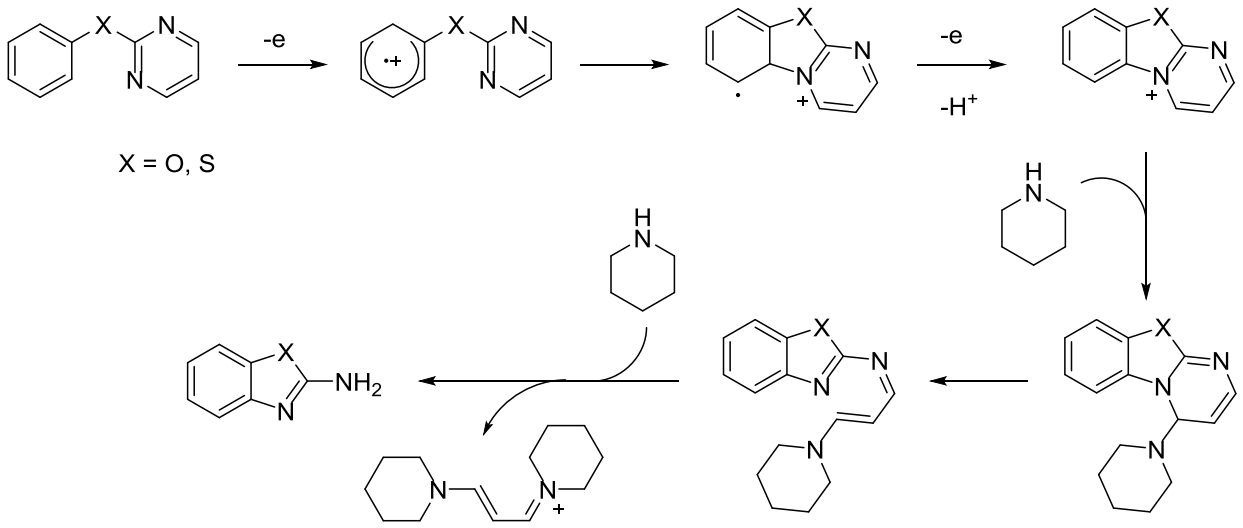
R = H, 2-CO_2Et, 4-CO_2Et, 2-CO_2Me, 4-CO_2Me, 2-Me, 4-F, F-Cl, 4-Br, 4-CF_3, 4-CN, 4-COMe, 4-COPh



Scheme **67**).[132] Electrochemical oxidation leads to a cyclized pyrimidinium ion which can be converted into the target molecules by reaction with piperidine. The reaction is believed to go via a one electron oxidation of the phenoxy/thiophenoxy ring to give a radical cation. Intramolecular addition of the pyrimidine nitrogen followed by a one electron oxidation and extrusion of a proton gives the cyclized pyrimidinium ion. Attack of piperidine at the carbon atom next to the positively charged nitrogen, followed by ring opening and attack of another piperidine on the imine moiety finally gives the target ring system.

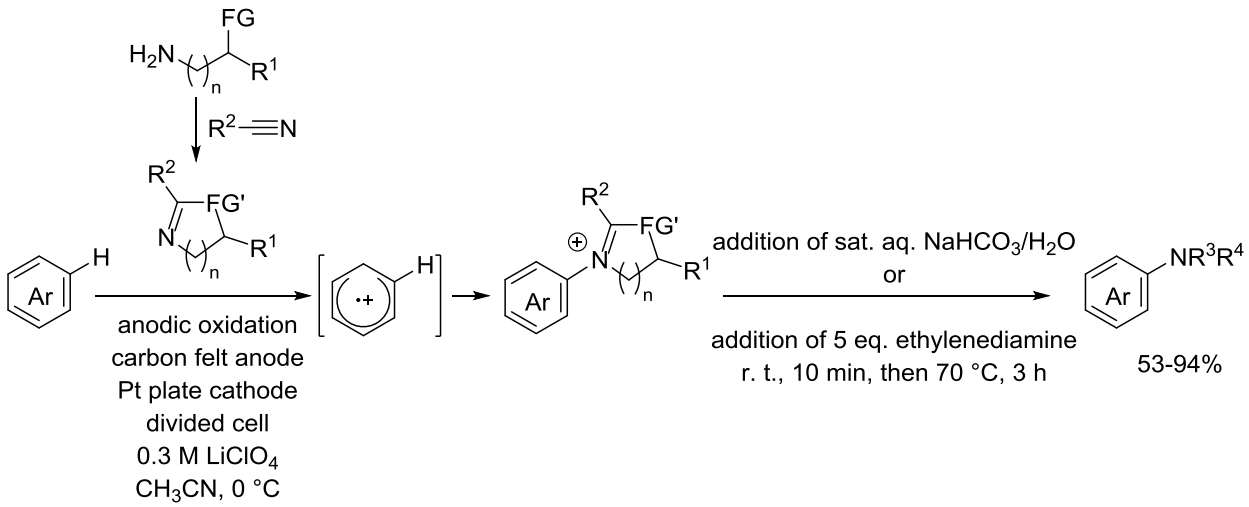


R = H, 2-CO_2Et, 4-CO_2Et, 2-CO_2Me, 4-CO_2Me, 2-Me, 4-F, F-Cl, 4-Br, 4-CF_3, 4-CN, 4-COMe, 4-COPh

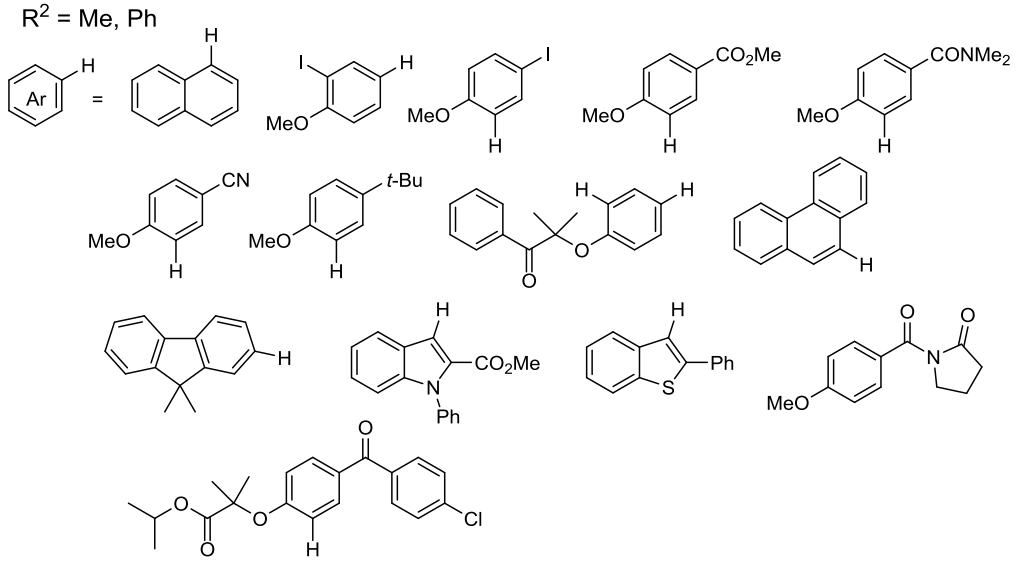


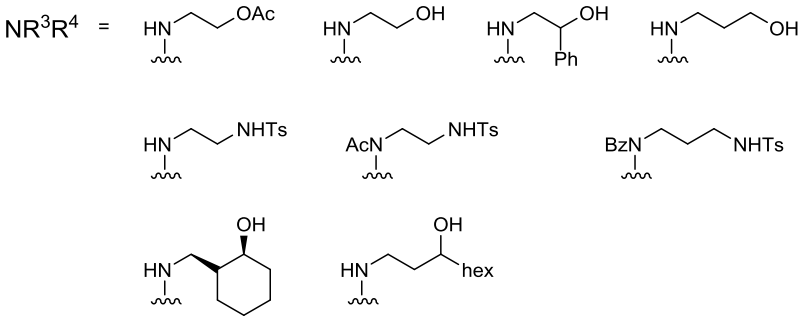
Scheme 67: Synthesis of 2-aminobenzoxazoles and -benzothiazoles.

An example of intermolecular oxidative direct amination via direct electrochemical oxidation is the coupling of arenes with primary alkylamines (



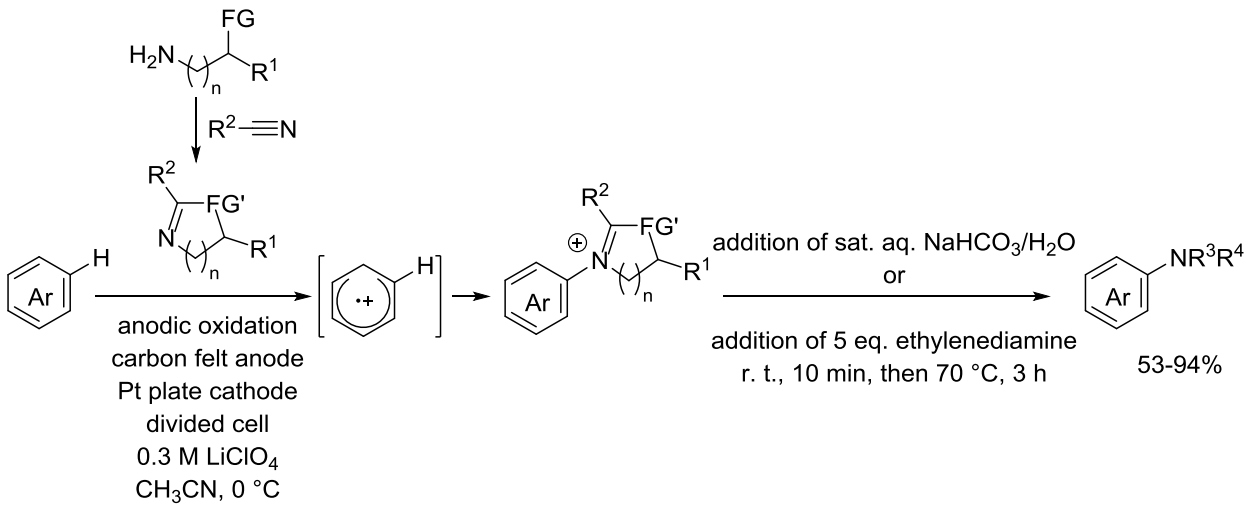
n = 1, 2
FG' = O, NTs
R^1 = H, Ph, hex
R^2 = Me, Ph



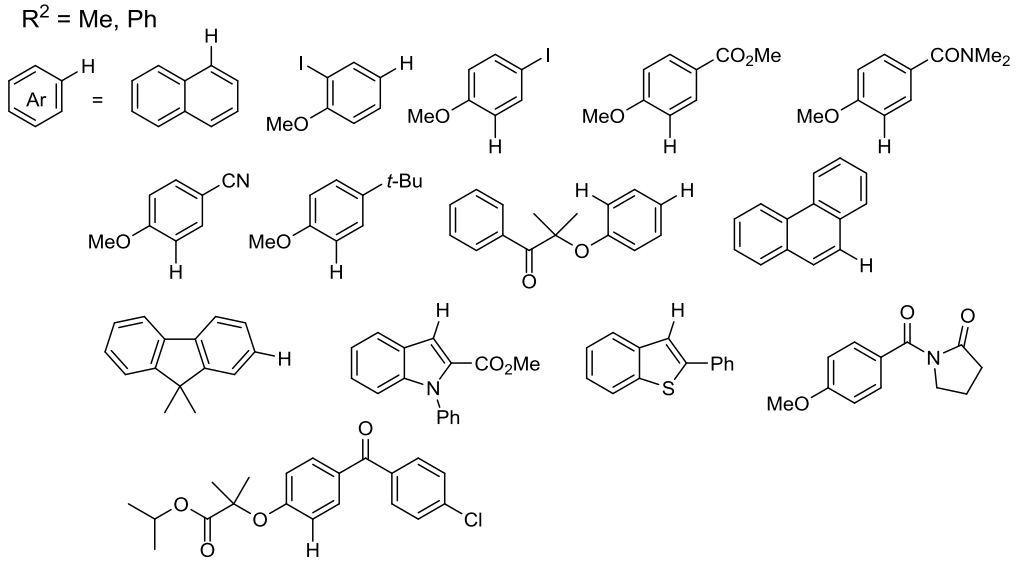


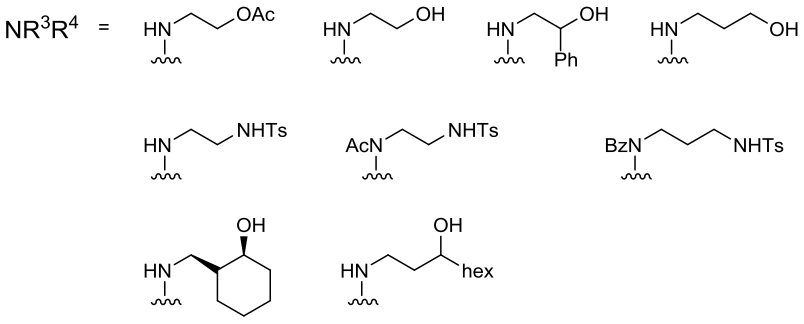
Scheme 68).[133]. The amine needs to be protected first as an imidate or amidine containing heterocycle (5 or 6 membered ring). The direct use of alkylamines is unfortunately not possible as they will be oxidized prior to the aromatic substrates. *N*-protected (electron withdrawing)

alkylamines can suppress this undesired oxidation but it will also reduce the nucleophilicity towards the radical cation. Even if nucleophilic attack is successful, overoxidation of the product will also be inevitable in this case. Oxidation of the arene at the anode gives a cationic aryl radical which subsequently reacts with the cyclic imine nitrogen to finally form a cationic intermediate. This stable cationic intermediate can subsequently be deprotected yielding the target *N*-alkylanilines. This is realized either by hydrolysis using a saturated aqueous bicarbonate mixture or by aminolysis using ethylenediamine.



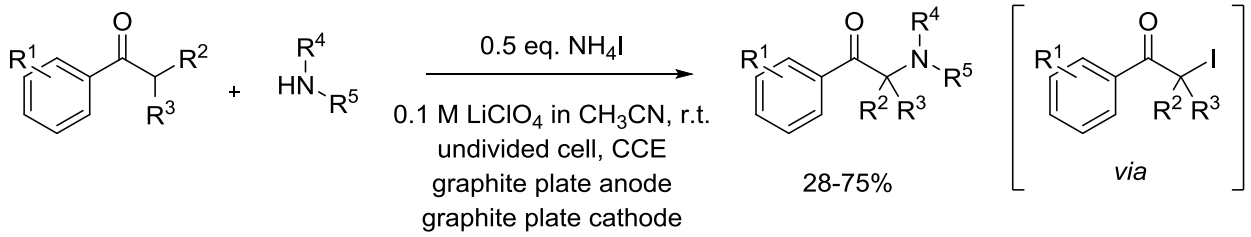
n = 1, 2
FG' = O, NTs
R^1 = H, Ph, hex
R^2 = Me, Ph





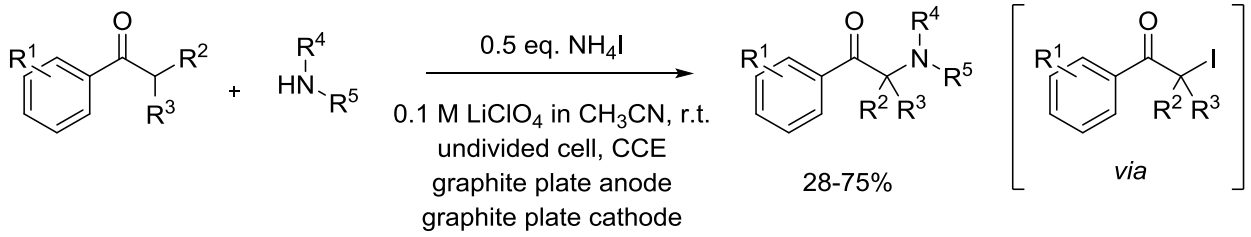
Scheme 68: Synthesis of *N*-alkylanilines.

Another example is the α-amination of phenones (



R^1 = H, 4-Cl, 3-Cl, 4-F, 4-Me, 3-Me, 4-OMe
R^2, R^3 = H, Me, cyclopropyl
R^4R^5NH = piperidine, 4-methylpiperidine, 3-methylpiperidine, 2-methylpiperidine, morpholine, 1,2,3,4-tetrahydroisoquinoline, *N*-methylbenzylamine, *N*-ethylbenzylamine, *n*-$BuNH_2$, $CyNH_2$

Scheme 69).[134] I_2 is generated in-situ by oxidation of I^- at the anode. The mechanism goes over an α-iodinated ketone. This was proposed on the basis of several control experiments: 1) Reaction of α-iodinated ketone with amine gave 90% aminated product. 2) Reaction of phenone substrate with amine in the presence of 1.0 eq. I_2 yielded 50% target compound. 3) Only traces of the product could be detected when ketone was treated with an *N*-iodinated amine.



R^1 = H, 4-Cl, 3-Cl, 4-F, 4-Me, 3-Me, 4-OMe
R^2, R^3 = H, Me, cyclopropyl
R^4R^5NH = piperidine, 4-methylpiperidine, 3-methylpiperidine, 2-methylpiperidine, morpholine, 1,2,3,4-tetrahydroisoquinoline, *N*-methylbenzylamine, *N*-ethylbenzylamine, *n*-$BuNH_2$, $CyNH_2$

Scheme 69: Synthesis of α-amino phenones.

3. Conclusions and outlook

Although many direct oxidative amination reactions have been published in the last couple of years, greatly expanding the type of molecules that can now be made via this methodology, some challenges still remain. Protocols based on metal catalysts, especially involving base metals, often require a high catalyst loading and are frequently executed at a high reaction temperature. Catalysts showing higher productivity and activity are therefore required to allow application of direct oxidative amination in chemical development projects. Generally, the most active catalysts are still based on rare earth metals, palladium, ruthenium, rhodium and iridium.

The limited abundance and reserves of these noble metals on earth have a significant impact on the fine chemicals produced with catalysts based on them. Even when predicted reserves are sufficient for another 100 years, the stability in the price is by no means certain based on current rates of extraction. Geopolitical uncertainty in areas currently mining precious metals, as well as potential market manipulation to limit the amount exported can easily cause global shortages on the international market. This actually represents a more acute threat to the chemical industry than world reserve depletion and obviously goes beyond direct oxidative aminations but is a challenge for contemporary metal catalysis in general. Making the switch from catalysts based on rare earths to base metal catalysts is certainly not a straightforward task. This is especially the case considering the molecular complexity of certain target molecules featuring multiple functional groups which can potentially pose selectivity issues. For these reactions, selectivity is paramount. Even if a suitable base metal alternative could be found with a suitable selectivity, the stability, safety and toxicity issues also have to be taken into account. Fortunately, most base metals feature a low toxicity. Interestingly, direct oxidative aminations using iron, copper, nickel and cobalt catalysts have been described in the preceding five years. However, using a base metal is not a sufficient requirement as the stoichiometric oxidants required in direct oxidative aminations needs to be safe to work with, cheap and deliver waste which is not toxic and can be easily disposed (e.g. incineration). While stoichiometric manganese, cerium, copper and silver salts or selectfluor and DDQ do not fulfill these criteria, oxygen and (di) *t*-butylperoxide for instance might, if special safety precautions are taken. After all, though these oxidants only produce water or alcohols as by-product the LOC of organic solvents[10a] and inherent stability problem of peroxides[135] require special precautions from a safety perspective. Nowadays, recent technological advantages allow safely performing reactions which such oxidants in continuous flow reactors.[31] By scale-up (larger volume and channel dimensions), scale-out (longer operation time) and numbering up (parallelization of reactors), scales suitable for chemical development and/or production of fine chemicals can be achieved.[31c] Though such examples of amine synthesis via direct oxidative amination have not been disclosed yet in the scientific literature, they are expected to appear in due course. The recent finding that oxygen, the most sustainable oxidant available on earth, can be used to create an oxidant *in situ* as exemplified by cumene hydroperoxide formation from cumene and oxygen is an attractive handle to create a variety of peroxide oxidants in small concentration, potentially delivering a tunable catalyst system with respect to activity and selectivity.[93] Similarly, reaction of hydrogen peroxide, produced from O_2 by the anthraquinone process, with organoiodide species acting as catalysts can deliver small amounts of hypervalent iodine oxidants *in situ*.[39] A second area with a huge potential is the use of electricity to perform the oxidation, considering power can be produced in a sustainable manner (wind, sun).[136] While procedures only requiring a stoichiometric oxidant (less is more) or a non-metal based catalyst are definitely preferred most of these systems are currently relying on hypervalent iodine reagents.[34] Though these are very powerful reagents due to their easy tunability, recyclability of the organoiodide by-product is mandatory to reduce cost and waste on scale. At first, direct oxidative aminations have been focusing on C(sp^2)-H bond functionalizations, but more and more recent examples of C(sp^3)

aminations are starting to appear. Though in the majority of the cases, the C(sp^3) carbons are still of the more reactive type, such as benzylic and allylic positions, non-activated C(sp^3)-H bonds will come in focus based on the current knowledge. Finally, stereoselectivity, for example by the use of chiral ligands, has only received minor attention and is a field where major advances are still required.[110] So far, the use of ligands in general (chiral or not) in direct amination reactions has received little attention.

4. Acknowledgments

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