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Synthesis of Heterocycles via Metal-Catalyzed Domino/One-Pot Reactions That Generate a C−N or C−O Bond

Juliane Keilitz, Hasnain A. Malik, and Mark Lautens

Abstract This chapter focuses on transition metal-catalyzed domino (cascade) or one-pot syntheses of heterocycles via the formation of a carbon–nitrogen, –oxygen, or –sulfur bond. A precise classification of domino, one-pot, and tandem reactions is given. However, despite that rather strict definition, the chapter includes a variety of processes that are important from a mechanistic and synthetic point of view. These are methods which showcase both ingenious and efficient reaction design while simultaneously aiming to minimize deleterious byproduct formation as well as uneconomical workup and purification steps. While there are several types of protocols highlighted within this section, there is a larger emphasis on transition metal-catalyzed cycloisomerization methods, the utility of *gem*-dihaloolefins, and C−H functionalization protocols within the framework of domino catalysis.

Keywords C−H functionalization · Cycloisomerization · *gem*-Dihaloolefins · Green chemistry · Heterocycles · Transition metal catalysis

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1 Introduction

Transition metal-catalyzed reactions have gained increasing importance in synthetic organic chemistry over the past few decades. There has been a heightened focus on the ability to perform multiple chemical transformations utilizing one or more catalysts in a single reaction vessel. While the ability to achieve several chemical reactions in a one-pot fashion is obviously attractive from the perspective of synthetic efficiency, the potential for cost-savings and positive environmental impact that result from the elimination of time-consuming workup and purification protocols cannot be understated. Indeed, it is highly advantageous for the continued development of chemical processes to be even more effective and robust while resulting in an overall low environmental footprint.

It should be noted that while there has been an effort by some to rigorously classify and define the many types of cascade/domino/tandem transformations [1–4], there remains a lack of consensus in literature. As a consequence, the terms "cascade," "domino," "tandem," "one-pot," "sequential," among many others, are at times routinely and casually interchanged. For the purposes of this review we will take an inclusive view to highlight and illustrate processes that we believe to be important from a mechanistic and synthetic point of view. As a result, while some processes we may describe will not fall within the strictest definition of cascade, domino, or tandem reactions, we did not exclude any processes that display creative reaction design.

There have been early efforts to put forth a clear and unified means to define the variety of reactions that involve multiple sequential chemical transformations that occur in a single vessel. One effective descriptor has been developed by Fogg and dos Santos (Fig. 1) [3].

The content of this chapter will be organized in the following manner:

Section 2: Metal-Catalyzed Cascade Reactions That Result in the Generation of a C−N or C−O Bond

- Section 2.1: Synthesis of Heterocycles via Domino/One-Pot Cycloisomerization Sequences
- Section 2.2: Synthesis of Heterocycles via Use of *gem*-Dihaloolefins
- Section 2.3: Synthesis of Heterocycles via C−H Functionalization
- Section 2.4: Miscellaneous Domino Methods for the Synthesis of Heterocycles

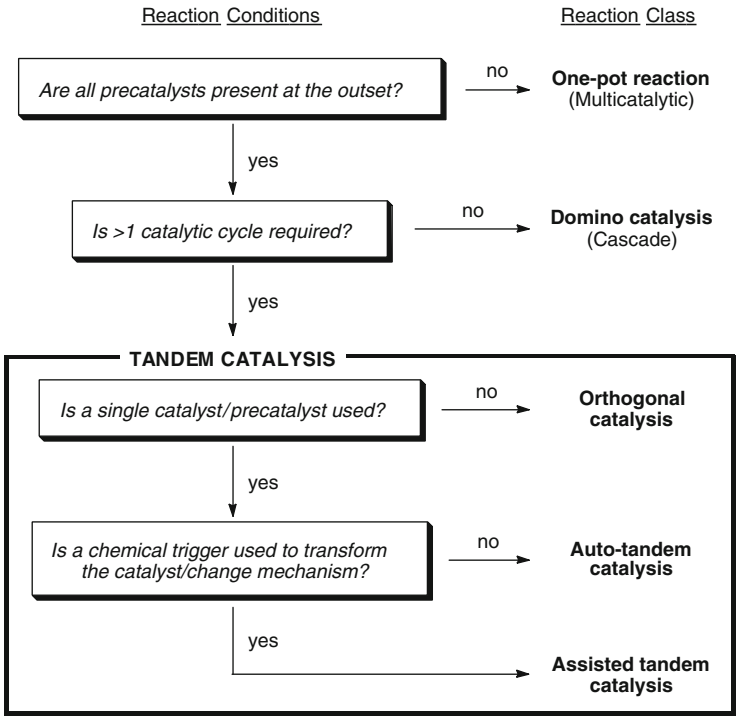


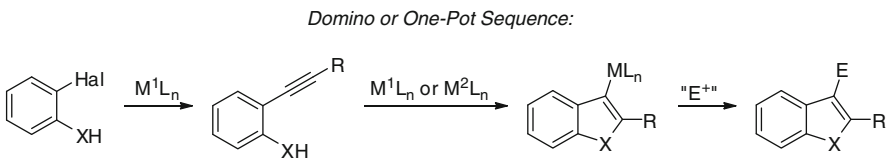
Fig. 1 Flowchart for classification of one-pot processes involving sequential elaboration of an organic substrate via multiple catalytic transformations

2 Metal-Catalyzed Cascade Reactions That Result in the Generation of a C−N or C−O Bond

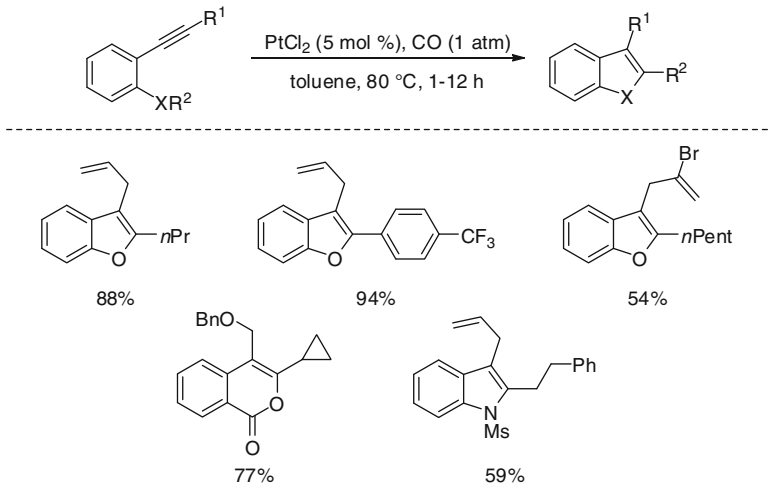
2.1 Synthesis of Heterocycles via Domino/One-Pot Cycloisomerization Sequences

The importance of indole and benzofuran scaffolds as intermediates, natural products, and pharmaceuticals cannot be understated [5–14]. While benzofurans are a common motif in many natural and pharmaceutically relevant compounds, indoles are even more ubiquitous. The most common synthetic approach to these types of structures is illustrated below – usually involving the cycloisomerization of an *ortho*-alkynyl phenol or aniline starting material to the corresponding benzofuran or indole, respectively (Scheme 1). In this section, we will attempt to highlight a variety of approaches to this cycloisomerization in a domino (cascade) or one-pot fashion.

Fürstner and coworkers reported a platinum-catalyzed cycloisomerization/formal allyl transfer method of the synthesis of benzofurans, indoles, and isochromene-1-ones (Scheme 2) [12]. Reaction times vary from 1 to 12 h for complete conversion of starting



Scheme 1 The general synthetic approach to the domino or one-pot synthesis of benzofuran and indole heteroaromatics

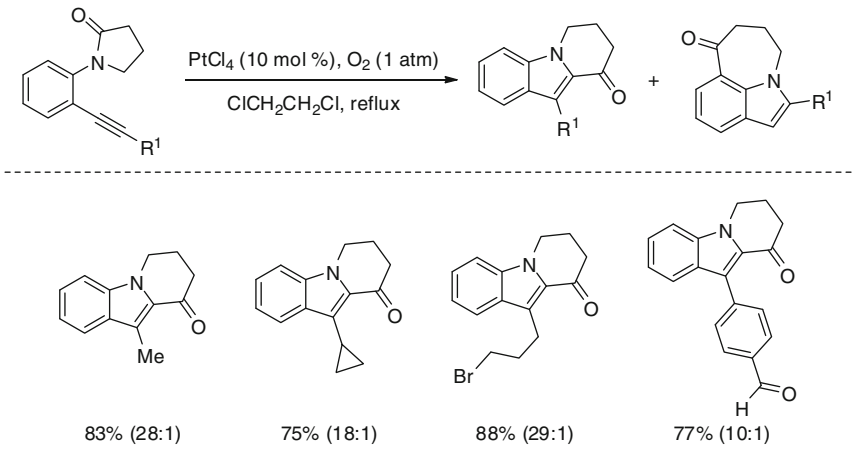


Scheme 2 Platinum-catalyzed domino synthesis of heteroaromatic compounds through a cyclization/allyl transfer pathway

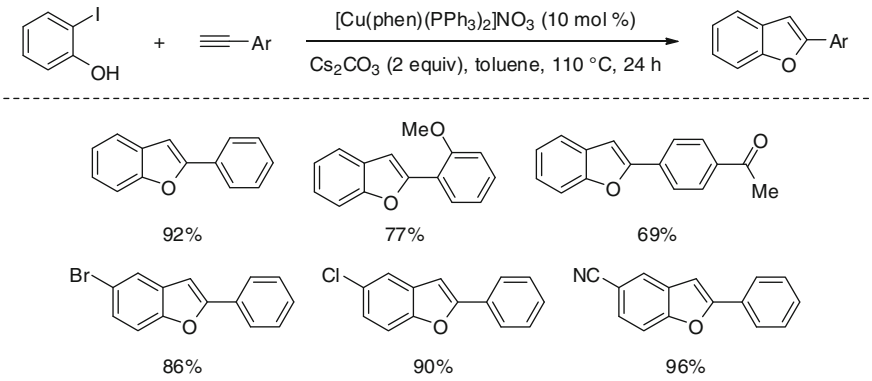
materials. The reaction undergoes a domino sequence and is completely atom-economical, save the requirement of carbon monoxide gas, which is necessary and has been empirically found to accelerate Pt-catalyzed rearrangement reactions. It is noteworthy that vinyl halides are tolerated under the reaction conditions. A closely related transformation was independently discovered and reported by Yamamoto and coworkers whereby the use of cyclooctadiene as a ligand offsets the requirement of CO gas [15].

Zhang and coworkers later expanded and diversified the utility of this type of platinum-catalyzed strategy by employing *N*-(2-alkynylphenyl)lactams as substrates for the synthesis of fused indole products (Scheme 3) [16]. The putative mechanism involves cycloisomerization, ring-expansion/rearrangement, and a 1,2-shift. Levels of selectivity range from good to excellent for the rearrangement product.

Venkataraman and coworkers reported the copper-catalyzed domino Sonogashira/cycloisomerization reaction for the synthesis of a variety of benzofurans (Scheme 4) [17]. Yields are generally good to excellent and the method displays high functional group tolerance. It is worth mentioning that aryl bromides and chlorides remain untouched throughout the catalytic cycle. The reaction also has the added benefit of



Scheme 3 Platinum-catalyzed domino cycloisomerization/ring-expansion/alkyl transfer reactions to form cyclic-ketone-fused indoles

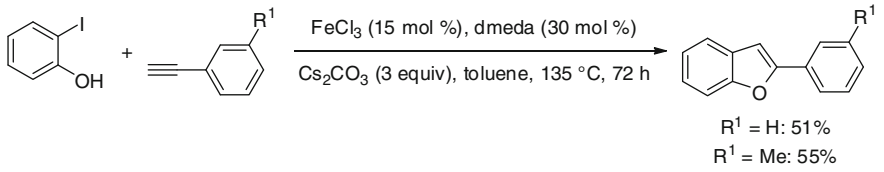


Scheme 4 Copper-catalyzed domino Sonogashira/cycloisomerization sequence for the synthesis of 2-substituted benzofurans

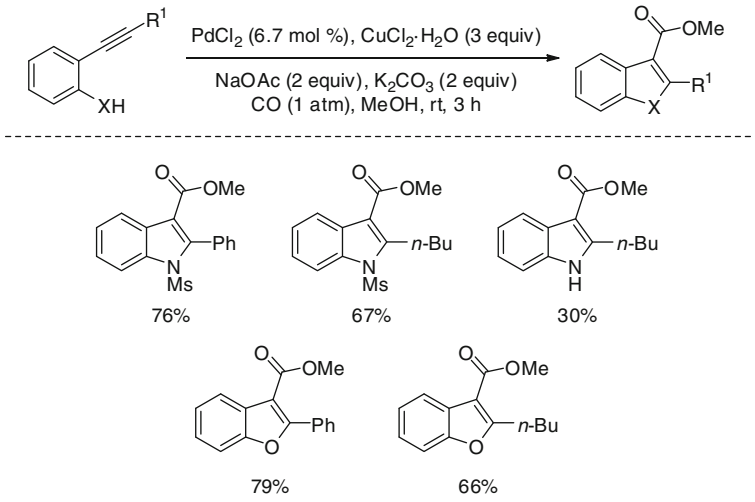
being palladium-free which renders the method more attractive for scale-up with respect to cost.

The iron-catalyzed Sonogashira reaction of 2-iodophenol with terminal aromatic alkynes results in the formation of benzofuran products (Scheme 5) [18–20].[1] Interestingly, the simple Sonogashira product, namely the newly formed internal alkyne, is obtained when *N*-benzyl 2-substituted iodoanilines are employed. The use of an inexpensive and environmentally benign iron catalyst is noteworthy.

[1] There have been recorded instances in literature by Bolm, Buchwald, and others where it has been determined that trace metal impurities are the catalytically active species in transition metal-catalyzed reactions. This is especially relevant in many iron-catalyzed methods.



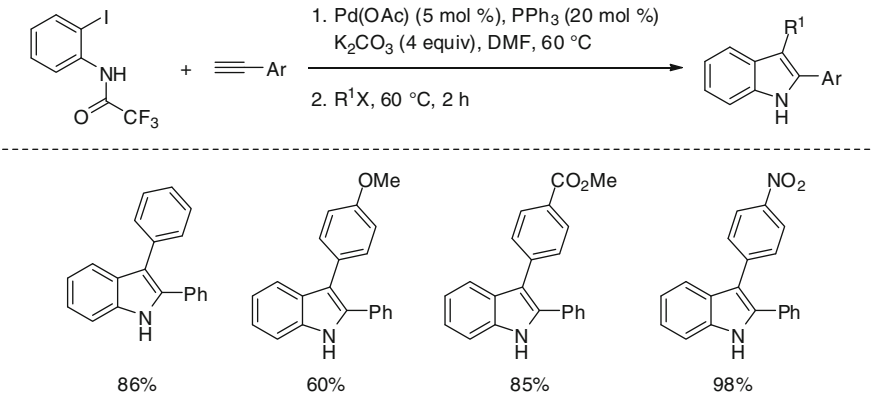
Scheme 5 Iron-catalyzed domino Sonogashira/cycloisomerization for the synthesis of 2-substituted benzofurans



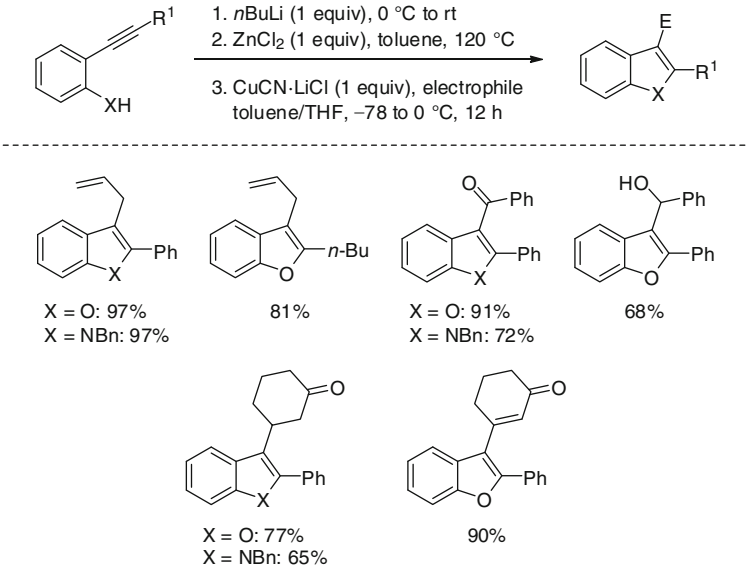
Scheme 6 Palladium-catalyzed domino carbonylative cycloisomerization for the synthesis of heteroaromatics

Sakamoto and coworkers reported a palladium-catalyzed domino carbonylative cyclization for the synthesis of a variety of heteroaromatic compounds (Scheme 6) [21]. Under an atmosphere of carbon monoxide gas in methanol, 2,3-disubstituted indoles and benzofurans could be furnished. Unprotected aniline starting materials were poor substrates and yields were considerably lower than the mesyl-protected variants.

Lu and coworkers disclosed a useful means to synthesize unprotected 2,3-disubstituted indoles in one-pot reaction sequence (Scheme 7) [22]. This palladium-catalyzed reaction incorporates a sequential Sonogashira reaction followed by cycloisomerization and deprotection to afford a variety of 2,3-disubstituted indole scaffolds. While there are currently a limited number of examples that could be carried out in a domino fashion (where all starting materials are present at the beginning of the reaction), high yields can be obtained when the aryl halide is added portionwise at the completion of the Sonogashira coupling step.

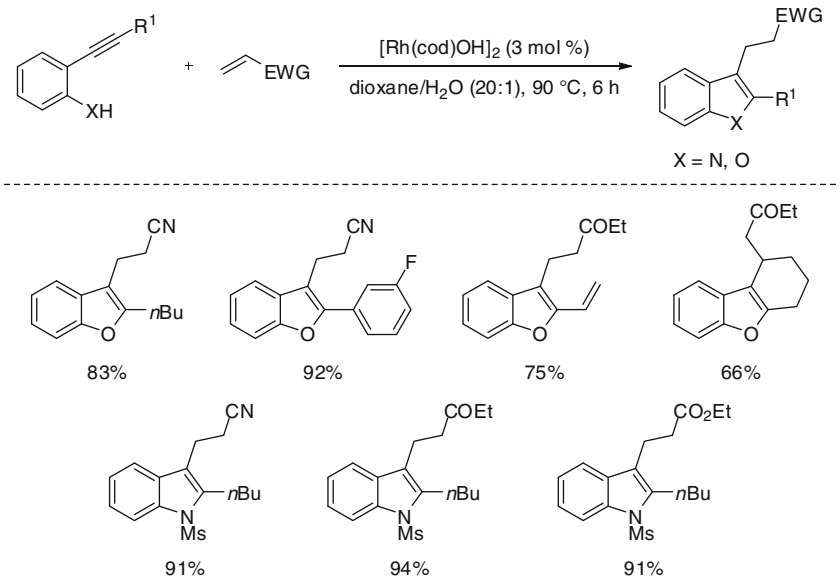


Scheme 7 One-pot palladium-catalyzed Sonogashira/cyclization sequence for the synthesis of 2,3-disubstituted indoles



Scheme 8 One-pot synthesis of 2,3-disubstituted indoles and benzofurans

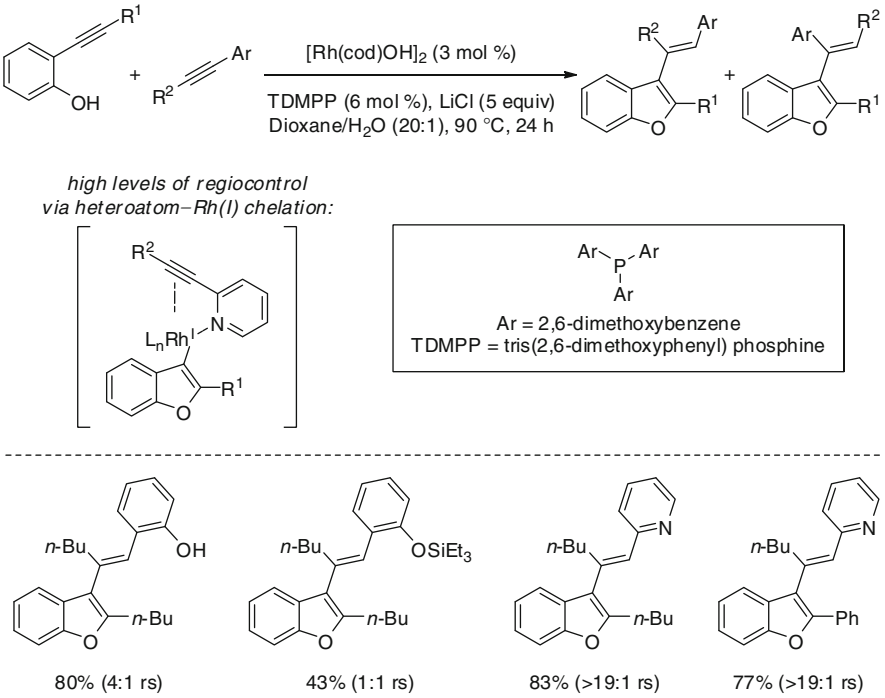
Nakamura and coworkers have reported a one-pot method for the synthesis of a diverse array of 2,3-disubstituted indoles and benzofurans (Scheme 8) [23]. Although the reaction is not catalytic in nature, it has several advantages over similar catalytic methods. Specifically, this method represents one of the rare examples of this type of transformation where allyl halides, acyl chlorides, aldehydes, α,β-unsaturated carbonyls, and vinyl halides are all shown to be competent electrophile partners and yields range from moderate to excellent in all the cases described.



Scheme 9 Rhodium-catalyzed domino cycloisomerization/1-4-addition to afford 2,3-disubstituted benzofurans and indoles

Our own group's interest in tandem and domino processes has led us to develop the rhodium-catalyzed cycloisomerization of *ortho*-alkynyl phenols and anilines followed by electrophile trapping to afford benzofuran and indole products (Scheme 9) [24]. We were able to capitalize on the stability of a rhodium(I)-intermediate that could undergo facile migratory insertion reactions with a variety of π-electrophiles. Deleterious β-hydride elimination by-product formation (usually a minor by-product in this transformation) can be minimized and in many cases completely eliminated through the use of BINAP as a ligand. This method provides an efficient and expedient route to a variety of heteroaromatic compounds under relatively mild conditions. If this domino process is engineered to undergo two intramolecular steps (cycloisomerization followed by intramolecular 1,4-addition), tricyclic compounds can be synthesized in synthetically useful yields.

The scope of this rhodium-catalyzed domino process was later expanded to include reactions with internal alkynes as electrophiles (Scheme 10) [25]. The regioselectivity for alkyne insertion varies from low to high, where the highest levels of regiocontrol are hypothesized to be dependent on a putative heteroatom chelation to the rhodium(I) intermediate (see Scheme 10). Indeed, there seems to be some experimental support for this phenomenon as *ortho*-alkynyl phenols provide a ca. 80:20 mixture of regioisomers and protected *ortho*-alkynyl phenols result in a complete loss of regioselectivity.

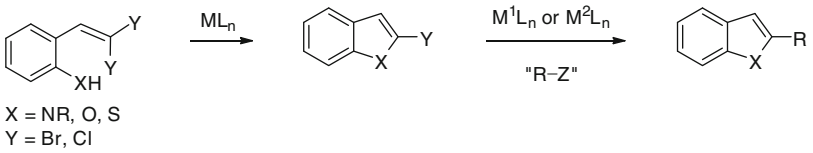


Scheme 10 Rhodium-catalyzed domino cycloisomerization/alkyne migratory insertion to afford 2,3-disubstituted benzofurans

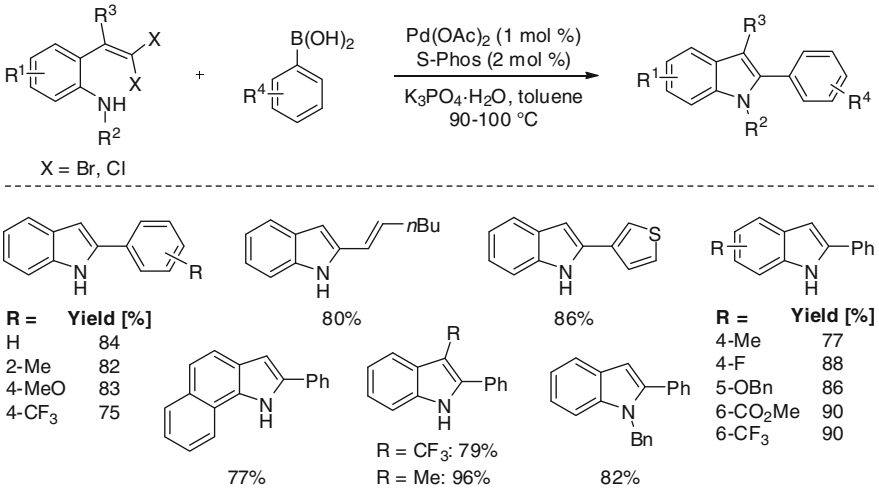
2.2 *Synthesis of Benzofurans and Indoles via Use of* gem-*Dihaloolefins*

In recent years, *gem*-dihaloolefins have attracted attention as versatile substrates for the synthesis of heterocycles via tandem sequences [26–33]. They can be readily obtained through a Ramirez olefination [34–37] of a suitably *ortho*-substituted aniline, phenol, or thiophenol which allows for modular syntheses of indoles, benzofurans, or benzothiophenes, respectively. Our group was the first to employ *ortho-gem*-dihalo vinyl substrates in transition metal-catalyzed tandem reactions [37–44]. While there is uncertainty as to which step occurs first as the substrate is varied, it is generally the case that an initial C–N, C–O, or C–S coupling leads to a 2-bromoindole, -benzofuran, or -benzothiophene [45] moiety which can further react in a separate but tandem transition metal-catalyzed coupling reaction (Scheme 11).

The palladium-catalyzed intramolecular C–N bond formation and intermolecular Suzuki–Miyaura cross-coupling of *ortho-gem*-dibromoolefins with organoboron reagents was first reported by Bisseret with limited substrates [46] and fully developed by our group (Scheme 12) [38]. Specifically, we showed that $Pd(OAc)_2$, with the use



Scheme 11 General approach toward the synthesis of indoles, benzofurans, or benzothiophenes using *ortho-gem*-dihaloolefins



Scheme 12 Tandem Buchwald–Hartwig amination/Suzuki–Miyaura cross-coupling of *ortho-gem*-dihalovinylanilines with organoboron reagents

of Buchwald's SPhos ligand, provides access to a variety of 2- and 2,3-substituted indoles [38, 39]. Substitution at a variety of positions on the indole heterocycle is tolerated and the products are obtained in good to excellent yields (72–96%) within 1–14 h. Interestingly, the use of *ortho-gem*-dichlorovinylanilines provides almost quantitative yields, which is hypothesized to occur due to a higher level of chemoselectivity.

Mechanistic investigations revealed that, in the parent substrate, the Buchwald–Hartwig coupling occurs first. What is not known is if selective insertion into the (*Z*)-C–X bond is responsible or if isomerization of the (*E*)-inserted product to the more reactive (*Z*)-isomer can occur [39]. The generality and practicality of this tandem Buchwald–Hartwig amination/Suzuki–Miyaura cross-coupling sequence were demonstrated through the synthesis of four different KDR kinase inhibitors which are potential therapeutics (Fig. 2) [37] and with the synthesis of various azaindoles and thienopyrroles which were previously not accessible by such a modular and general approach [41].

Alper and coworkers extended the reaction by developing a tandem C–N coupling followed by a carbonylation (Scheme 13) [47]. The reaction is performed

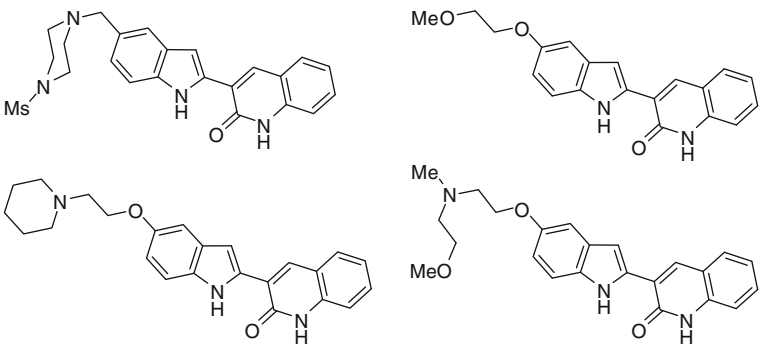
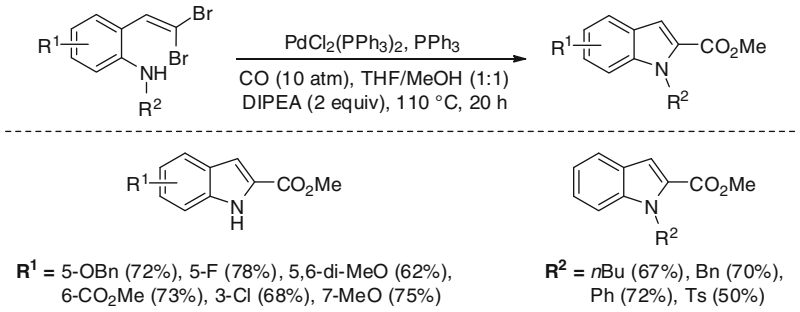


Fig. 2 Targets synthesized via tandem Buchwald–Hartwig amination/Suzuki–Miyaura cross-coupling sequence

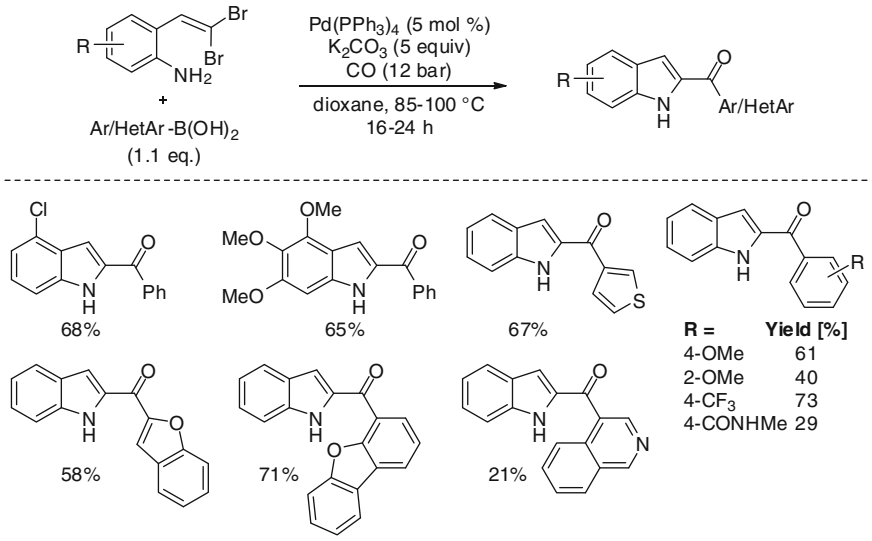


Scheme 13 Palladium-catalyzed tandem intramolecular amination/carbonylation sequence

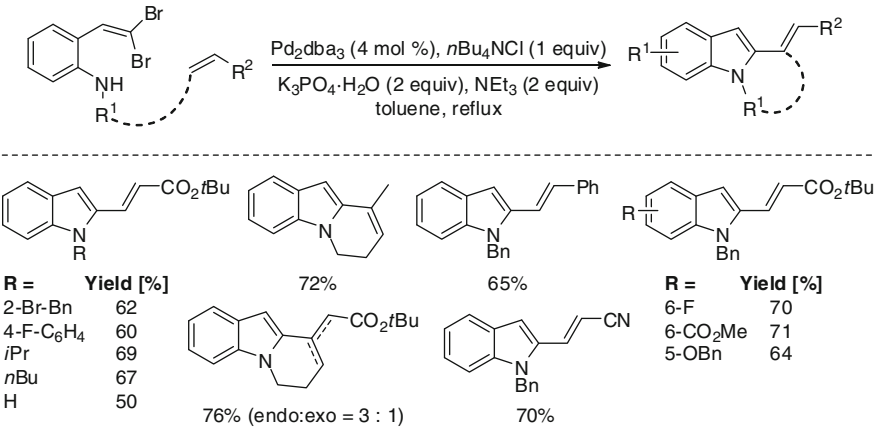
under a CO atmosphere (10 atm) in a THF/MeOH mixture. Various functional groups are tolerated both at the amine moiety and on the aryl ring, including halogens such as chlorine or fluorine. However, when bromine atoms are present on the aromatic ring, a second carbonylation reaction takes place at this position.

In 2009, the group of Pontikis and Florent reported a tandem C–N coupling/carbonylation/C–C coupling sequence employing *gem*-dibromoolefins that furnish the synthesis of 2-aroyl- or 2-heteroaroyl indoles, respectively (Scheme 14) [48]. A range of substituents is tolerated on the aromatic ring of the *gem*-dibromovinyl substrates, but no substitution in the 3-position of the indole has been reported. Sterically demanding substituents at the boronic acid reduce overall reactivity; the use of 2-methoxyphenylboronic acid delivers the corresponding product in a modest yield of 40%, while 2,6-di-methylphenylboronic acid provides no observable product formation.

2-Vinylic indoles and their tricyclic derivatives can be obtained through a tandem Buchwald–Hartwig coupling followed by a Heck–Mizoroki cross-coupling sequence (Scheme 15) [40]. The only limitation of this reaction is in the formation of 3-substituted derivatives, where poor yields were observed when the corresponding



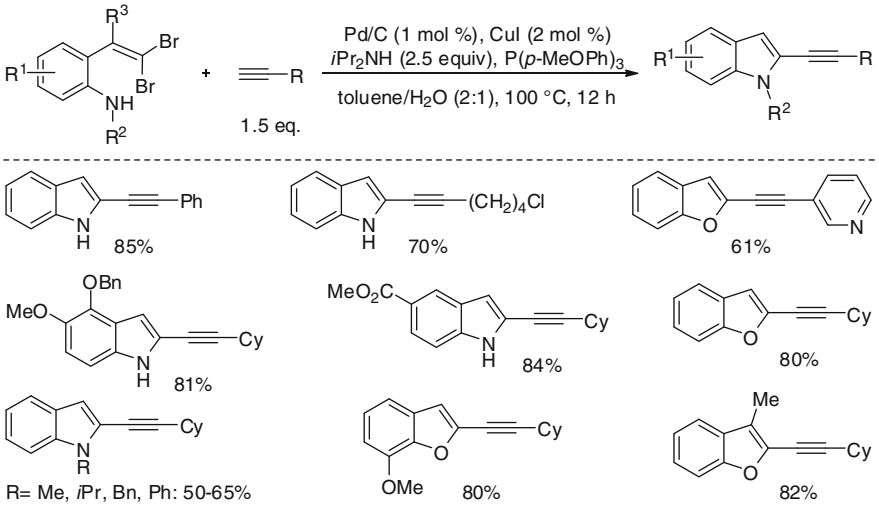
Scheme 14 Palladium-catalyzed C–N coupling/carbonylation/C–C coupling sequence



Scheme 15 Palladium-catalyzed tandem Buchwald–Hartwig/Heck–Mizoroki reaction

substituted dibromovinylanilines are utilized. An intramolecular variant of this method was realized by tethering the alkene moiety to the nitrogen atom of *ortho-gem*-dibromovinylaniline. The tandem reaction yields the corresponding tricyclic adducts as mixtures of two easily separable isomers and even a non-activated alkene could be employed.

For the synthesis of 2-alkynyl indoles and benzofurans, a tandem copper- and palladium-catalyzed cross-coupling reaction was developed involving an Ullmann-type reaction and a Sonogashira cross-coupling tandem reaction [43]. Interestingly, heterogeneous Pd/C (2 mol%) in conjunction with 4 mol% CuI was found to be the

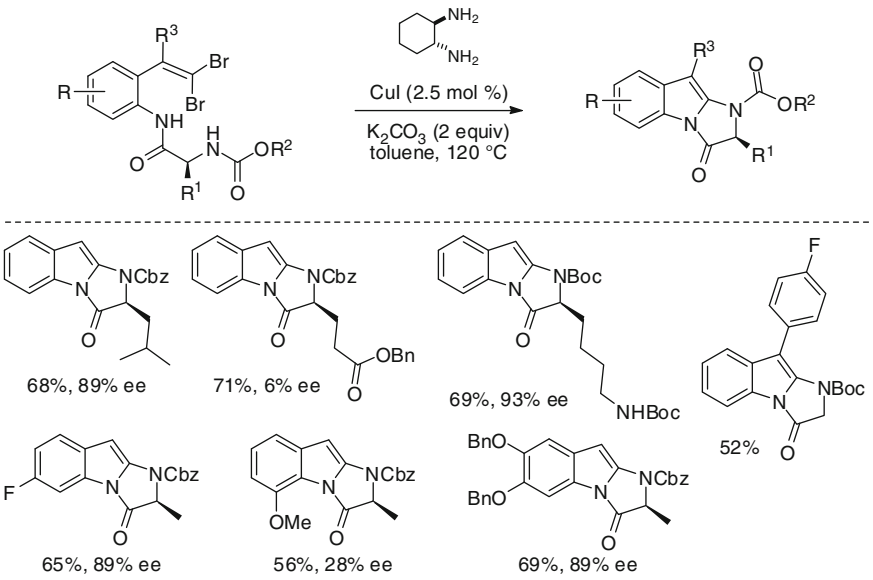


Scheme 16 Sequence of Ullmann-type reaction and Sonogashira cross-coupling for the synthesis of 2-alkynyl indoles and benzofurans

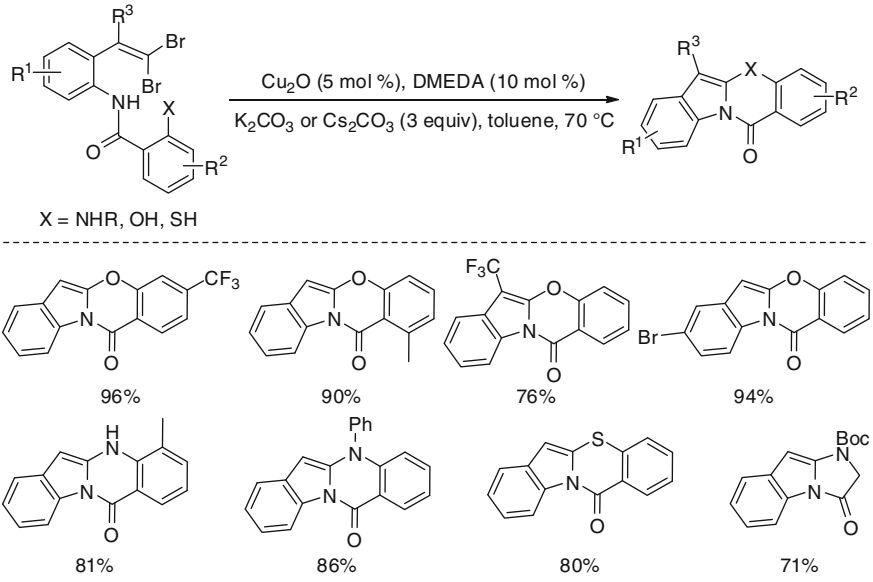
best co-catalyst combination (Scheme 16). However, since the solid support did not negatively affect the efficacy of the catalytic system, it was assumed that the reaction itself occurs in the homogeneous organic phase with trace amounts of leached palladium(0). Different aromatic and aliphatic alkynes as well as a variety of substituted *ortho-gem*-dibromovinyl derivatives could be utilized and the corresponding anilines and benzofurans were obtained in moderate to good yields (40–98%). Substitution on the aniline nitrogen atom generally lowers the yield and the synthesis of 3-substituted indoles has not been reported.

ortho-gem-Dibromoolefins tethered to amino acids were utilized for the synthesis of imidazoindolones via a double amidation reaction (Scheme 17) [42]. The reactions require 12–49 h for completion and a range of substituents is tolerated. However, in case of the 3-substituted *gem*-dibromoolefin, the catalyst loading had to be increased to obtain the corresponding imidazoindolone in a reasonable yield. The preservation of the chiral center originating from the amino acid was highly variable and the extent of epimerization was assumed to depend on a variety of factors. The rate of conversion of the 2-bromoindole intermediate to the product is vital as the proton at the stereocenter is much more acidic than in the starting *gem*-dibromoolefin and therefore much more susceptible to epimerization under the reaction conditions. Thus the extent of epimerization is highly dependent on the rate of the second amidation step.

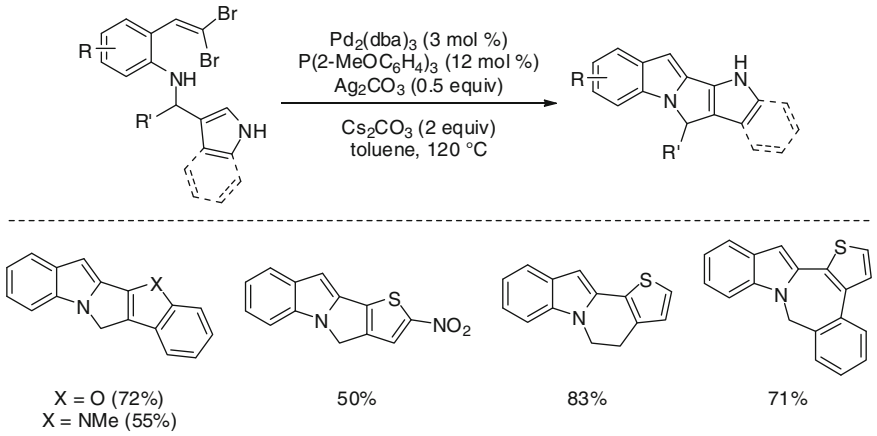
In 2012, Wang, Lv, and coworkers reported a Cu_2O-catalyzed C–N/C–X (X = N, O, S) coupling for the formation of oxazino[3,2-*a*]indole, thiazino[3,2-*a*]indole, and indolo[2,1-*b*]quinazoline derivatives (Scheme 18) [49]. This transformation operates under ambient conditions and it was shown that the copper catalyst is necessary for both steps to occur. Although substitution is possible at most positions, when strongly



Scheme 17 Copper-catalyzed tandem intramolecular amidation for the synthesis of imidazoindolones



Scheme 18 Copper-catalyzed tandem C–N/C–X (X = N, O, S) coupling for the formation of polycyclic indole derivatives



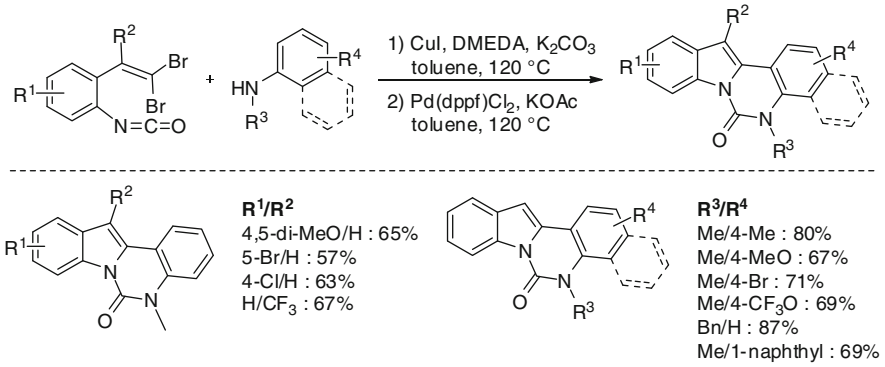
Scheme 19 Palladium-catalyzed Buchwald–Hartwig amination/direct arylation sequence toward tetra- and pentacyclic indole derivatives

electron-withdrawing substituents are present on the aromatic ring of the *gem*-dibromovinyl aniline moiety, only trace amounts of product formation are observed. In order to obtain the corresponding indolo[2,1-*b*]quinazolines, a change of base selection from K_2CO_3 to Cs_2CO_3 was required.

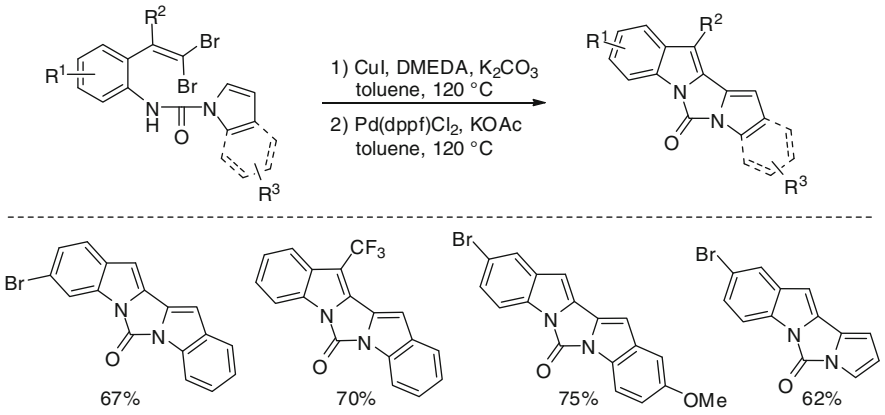
Our group was also able to combine a tandem Buchwald–Hartwig cross-coupling followed by a direct arylation reaction yielding tetracyclic and pentacyclic indole derivatives (Scheme 19) [44]. A variety of indoles with substituents of different electron character are easily accessible and by using a higher catalyst loading even seven-membered rings can be obtained. An apparent limitation is found to be substitution in the 3-position of the indole, which completely inhibits product formation.

Bao and coworkers employed isocyanates as nucleophilic acceptors by introducing them *ortho* on *gem*-dibromovinylbenzene (Scheme 20) [30]. Those *ortho*-*gem*-dibromovinyl isocyanates were reacted with *N*-alkylanilines to provide pyrimido[1,2-*a*]indol-1(2*H*)-one derivatives through a sequence of nucleophilic addition of the aniline group to the isocyanate moiety, copper-catalyzed *N*-arylation, and palladium-catalyzed C–H functionalization. Although this sequence is only a one-pot process (requiring sequential addition of transition metal catalysts) it is a rare example of this type of sequences involving a C–H functionalization step. The scope with regard to substitution is broad and even 3-substituted indoles could be obtained from the corresponding isocyanate substrates. A limitation of the method is that anilines with strongly electron-withdrawing groups on the phenyl ring fail to display reactivity. Additionally, high steric hindrance on the amine prevents addition onto the isocyanate and unprotected amines only furnish urea intermediates where the subsequent Cu-catalyzed *N*-arylation step does not occur.

Bao and coworkers then applied the same method to the synthesis of unsymmetrical 1,1′-carbonyl-2,2′-biindolyls, but their initial experiments proved unsuccessful.



Scheme 20 One-pot synthesis of pyrimido[1,2-*a*]indol-1(2*H*)-ones via nucleophilic addition/copper-catalyzed *N*-arylation/palladium-catalyzed C–H functionalization

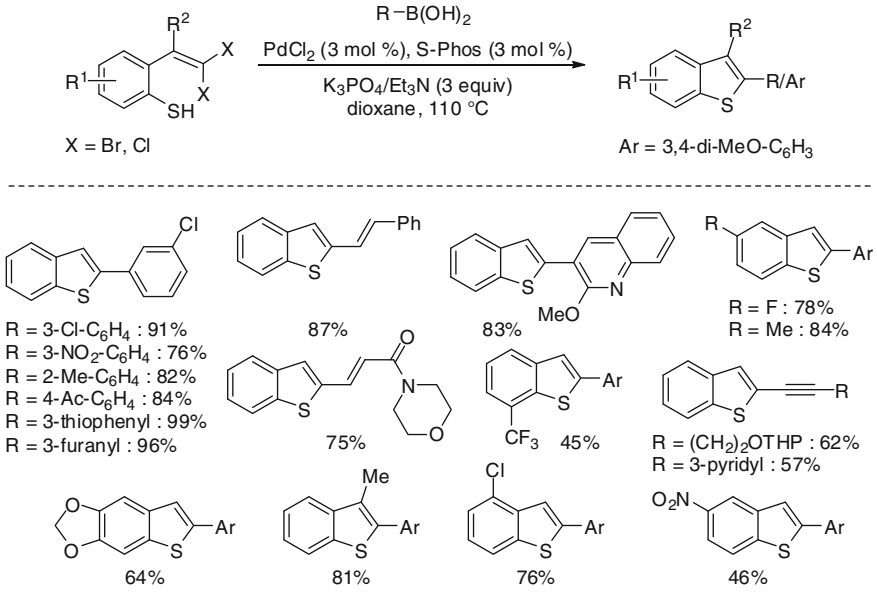


Scheme 21 One-pot sequence for the copper- and palladium-catalyzed formation of unsymmetrical 1,1′-carbonyl-2,2′-biindolyl derivatives

Therefore, indole-1-carboxylic acid and *ortho-gem*-dibromovinyl aniline were coupled and under the established reaction conditions led to the formation of the desired products (Scheme 21) [50]. The method efficiently provides moderate to good yields. A limitation was found to be that the synthesis of unsymmetrical products bearing electron-deficient groups on both indole rings was unsuccessful. Attempts to employ only one metal catalyst and one base failed.

Bao's most recent contribution in this area is a two component sequence where an aromatic acid chloride and the well-studied *ortho-gem*-dibromovinyl aniline react via amide formation/Cu-catalyzed intramolecular C–N coupling/C–H activation to form 6*H*-isoindolo[2,1-*a*]indol-6-ones [51].

In 2009, our group published a tandem process for the synthesis of benzothiophenes consisting of an intramolecular *S*-vinylation followed by intermolecular carbon–carbon bond formation either through a Suzuki–Miyaura, Heck, or Sonogashira reaction (Scheme 22) [52]. Although sulfur has a long-standing

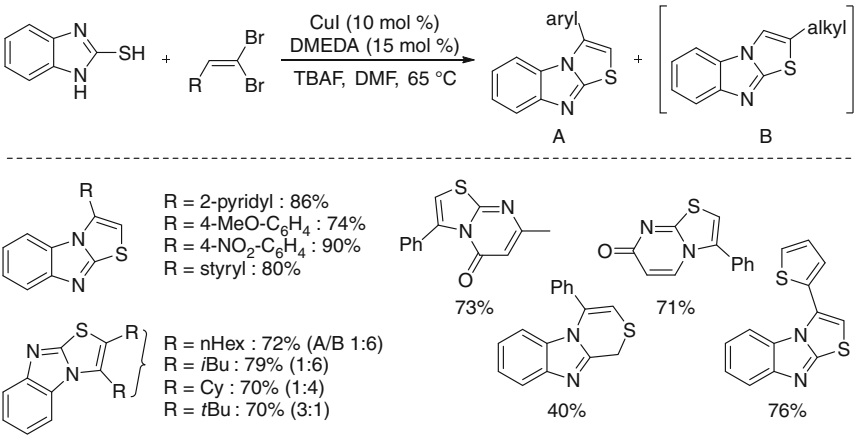


Scheme 22 Synthesis of substituted benzothiophenes via intramolecular *S*-vinylation and intermolecular carbon–carbon cross-coupling

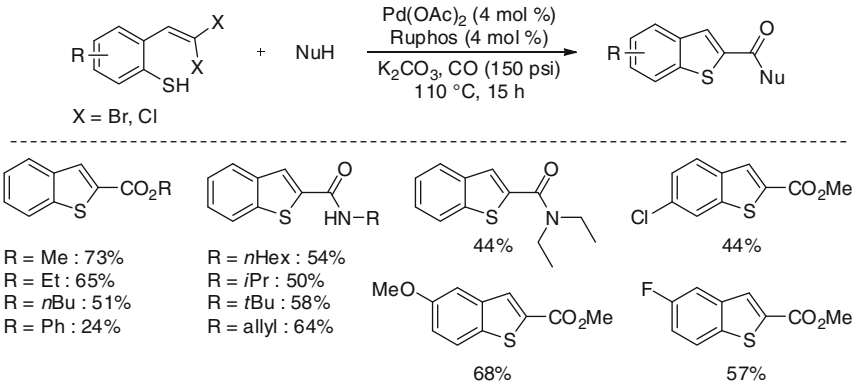
reputation as a catalyst poison, various substituted benzothiophenes can be obtained in good to excellent yields via the *S*-vinylation/Suzuki–Miyaura sequence. A variety of boronic acids and different boron nucleophiles (e.g., boronic esters, trifluoroborate salts, and trialkylboranes) are compatible with this process. In contrast, the nature of the thiophenol fragment has significant influence and the presence of strongly electron-withdrawing substituents provides low yields or the failure of the tandem reaction. The method was also extended to Heck- and Sonogashira-coupling reactions. It is noteworthy that the Sonogashira sequence can be catalyzed by Pd/C.

In 2010, Chen and coworkers utilized aryl- and alkyl-substituted *gem*-dibromovinyl derivatives for the preparation of imidazo[2,1-*b*]-thiazoles and related *N*-fused heterocycles via copper-catalyzed 1,2-aminothiolation (Scheme 23) [31]. For aryl-substituted *gem*-dibromovinyl compounds the 3-substituted imidazo[2,1-*b*]-thiazoles are obtained exclusively while for alkyl-substituted *gem*-dibromovinyl compounds a mixture of the 2- and 3-substituted products are obtained of which the 2-substituted one is the major isomer. The method was also applicable to the aminothiolation of unsubstituted and substituted 2-mercaptoimidazole, perimidine, and pyrimidine derivatives.

Alper and coworkers reported the synthesis of 2-carbonylbenzo[*b*]thiophene derivatives via a selective palladium-catalyzed tandem procedure (Scheme 24) [33]. An intramolecular C–S coupling/intermolecular carbonylation sequence yields various highly functionalized benzo[*b*]thiophenes in moderate yields. The strategy was also applicable for *gem*-dichlorovinyl derivatives, although the desired product was obtained in a lower yield.



Scheme 23 Synthesis of imidazo[2,1-*b*]-thiazoles via copper-catalyzed 1,2-aminothiolation

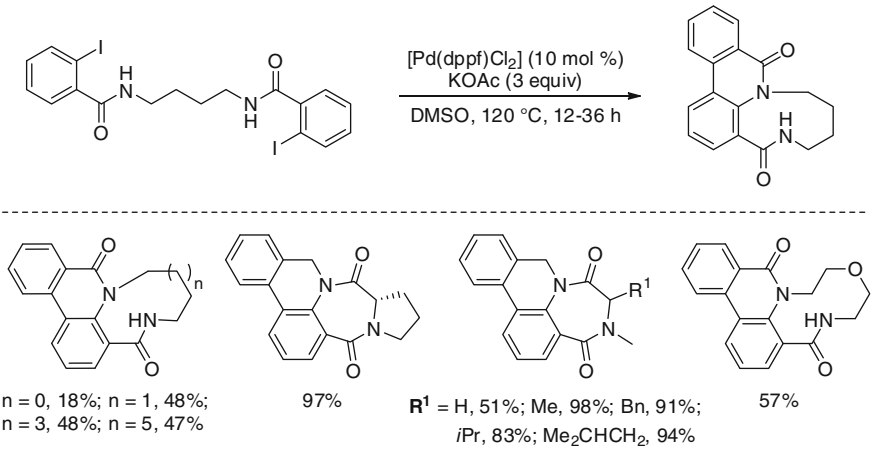


Scheme 24 Tandem palladium-catalyzed intramolecular C–S coupling/intermolecular carbonylation for the synthesis of 2-carbonylbenzo[*b*]thiophenes

2.3 Synthesis of Heterocycles via C–H Functionalization

Direct arylation (or C–H functionalization) offers several advantages such as the use of simplified/unfunctionalized starting materials and a higher degree of atom economy when compared to "traditional" cross-coupling methods [53, 54].

In 2003, Zhu and coworkers reported the synthesis of polyheterocycles by a palladium-catalyzed intramolecular *N*-arylation/C–H functionalization/aryl–aryl bond forming tandem process (Scheme 25) [55, 56]. Interestingly, the authors were able to access medium-sized and even macrocyclic ring systems by their method which was applied to the synthesis of azaphenanthrenes fused with an 8-, 10-, 11-, and 13-membered lactam. The reaction temperature was found to be important, with higher temperatures providing higher yields. It was assumed that



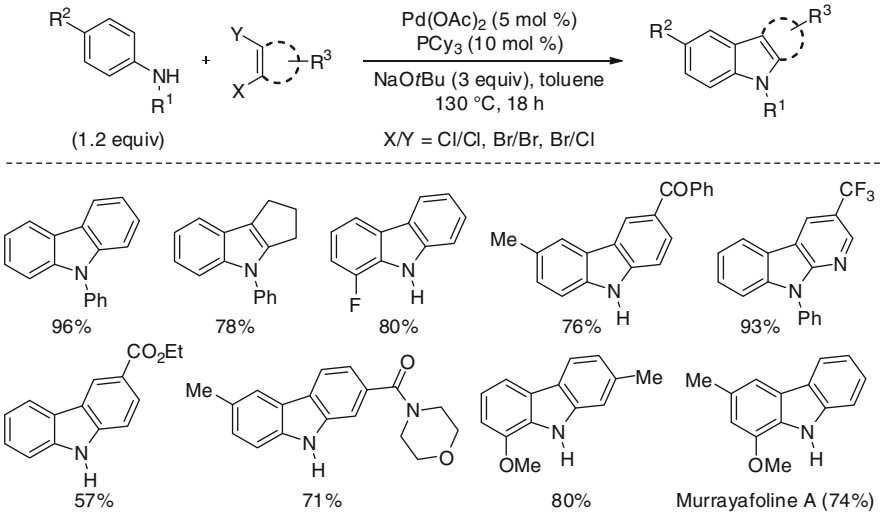
Scheme 25 Palladium-catalyzed intramolecular *N*-arylation/C–H functionalization/aryl–aryl bond forming tandem reaction toward polyheterocycles

a template effect, due to chelation of the transition metal to the two amido groups, leads to conformational pre-orientation which might be the reason for the high efficiency of this method.

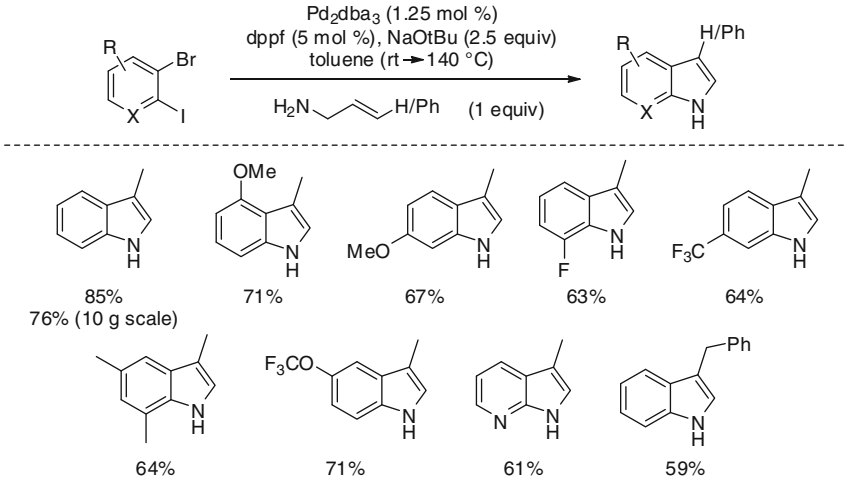
The approach of Ackermann and coworkers for the synthesis of annulated heterocycles involves an amination step and a direct arylation sequence by using anilines and 1,2-dihalo-(hetero)aryls (Scheme 26) [57]. It is noteworthy that easily available and inexpensive chloro-substituted starting materials can be employed. Additionally, primary anilines are applicable for the synthesis of carbazoles which avoids complex protection/deprotection procedures. The authors also demonstrated the efficiency of their approach to the synthesis of naturally occurring murrayafoline A [58].

A route to 3-substituted indoles from *ortho*-dihalobenzenes and allylic amines via intermolecular aryl amination and Heck cyclization was reported by Jørgensen and coworkers in 2008 (Scheme 27) [59]. In consideration of previous results, it was postulated that aryl amination is the first step in the sequence. The regiochemistry of the final product is controlled by the chemoselective amination of the aryl iodide position, and therefore the preparation of functionalized products is limited by the availability of the corresponding 1,2-dihaloarene starting materials. Substituents other than a methyl or benzyl at the 3-position have not been yet reported. Conveniently, the addition of an aryl bromide or aryl iodide after completion of the first two steps generates the corresponding *N*-arylated indole product.

An intermolecular *N*-arylation/intermolecular carbopalladation/C–H functionalization/C–C bond formation sequence was realized by Neuville, Zhu, and coworkers for the synthesis of 3-(diarylmethylene)oxindoles (Scheme 28) [60]. This procedure allows for the formation of one C–N and two C–C bonds by way of three different catalytic cycles in a one-pot fashion. The procedure requires addition of the aryl iodide after the *N*-arylation step is completed, and it is important to use an excess quantity of

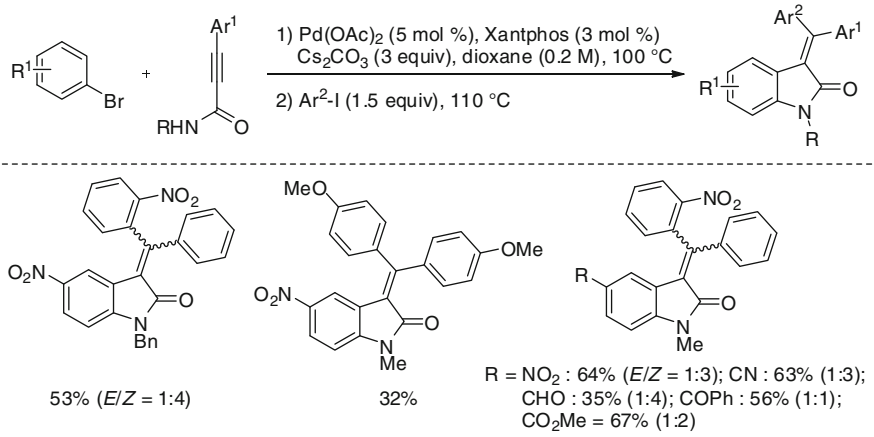


Scheme 26 Palladium-catalyzed synthesis of annulated heterocycles by an amination/direct arylation sequence



Scheme 27 Palladium-catalyzed synthesis of 3-substituted indoles via intermolecular aryl amination and Heck cyclization

palladium relative to the ligand, as Xantphos is necessary for the initial step while it serves to later inhibit the carbopalladation sequence. The scope of this transformation is somewhat limited since the *N*-arylating agent requires an electron-withdrawing group in the *para*-position (*ortho*- or *meta*-substituted aryl bromides were unsuitable) and yields are reduced when the aryl iodide bears an electron-donating group.



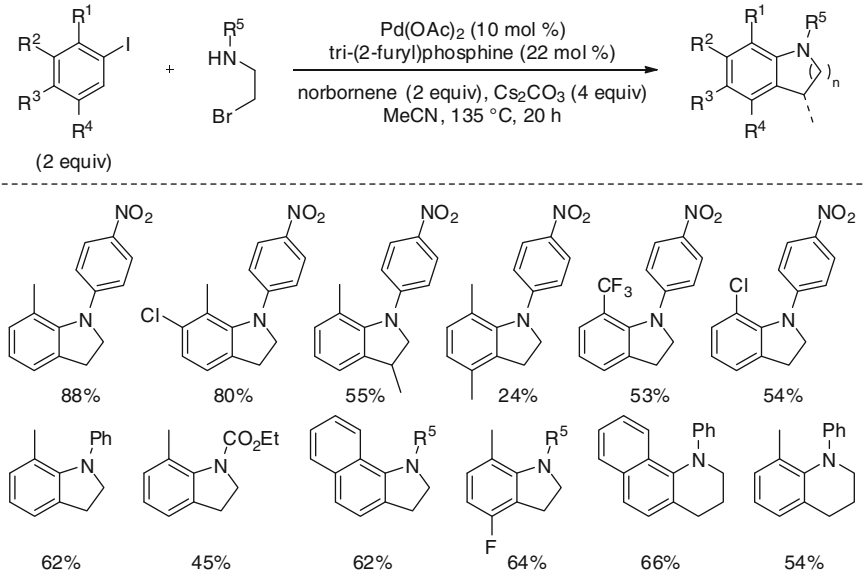
Scheme 28 Synthesis of 3-(diarylmethylene)oxindoles by an intermolecular *N*-arylation/intermolecular carbopalladation/C–H functionalization/C–C bond formation sequence

A powerful example of C–H functionalization in a domino process was reported by Catellani and coworkers who used norbornene as an organic co-catalyst and accomplished a sequence of domino *ortho*-functionalization terminated by cross-coupling [61–64]. Our group successfully implemented this norbornene-mediated C–H functionalization process in domino reactions for the synthesis of various substituted heterocycles [65–69].

The efficiency of this methodology is illustrated by a domino reaction developed by our group in 2007 (Scheme 29) [65]. An intermolecular alkylation at the *ortho*-position of an aryl iodide is followed by an intramolecular amination to afford functionalized indolines and tetrahydroquinolines from simple precursors. The protecting group on nitrogen proved to be important since Boc, Bz, and Ts functional groups only led to decomposition of the starting material. Ethyl carbamate, phenyl, or 4-nitrophenyl protected anilines provided the corresponding functionalized indolines in moderate to good yields. Strongly electron-donating groups at the 2-position are not generally tolerated. However, the use of 2-chloroiodobenzene is possible and the Cl-substituent can be easily converted into electron-rich alcohols, amines, or thiols. Extension of this methodology to the synthesis of tetrahydroquinolines was also shown.

A major drawback of this norbornene-mediated methodology is the requirement of a substituent in the second *ortho*-position of the starting aryl halide, which is necessary to exert regiocontrol over the C–H functionalization step and to avoid double alkylation.

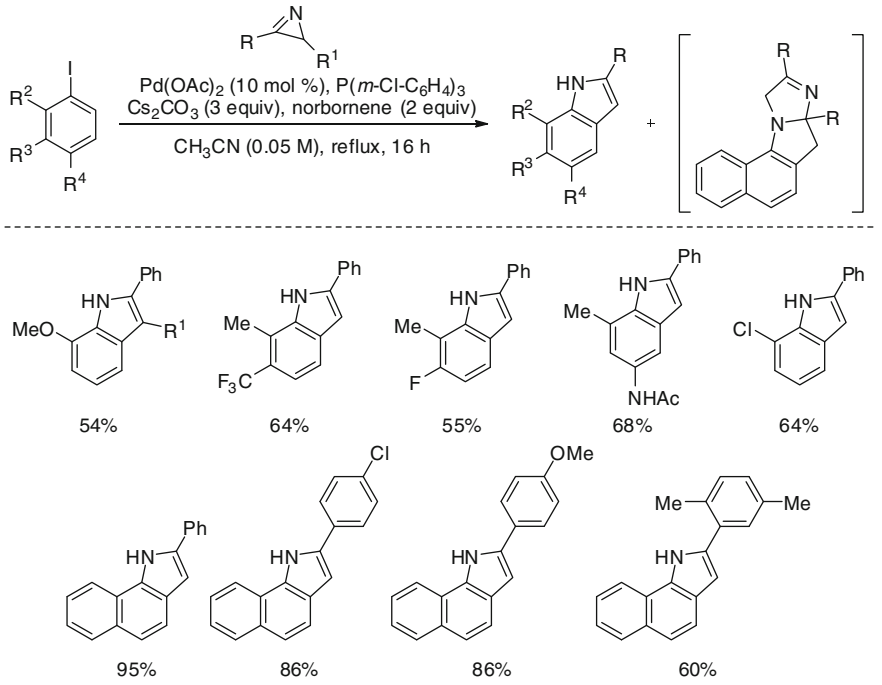
For the synthesis of indoles, our group utilized azirines as the coupling partner in a domino C–H activation/*N*-arylation reaction [66]. Initially, the use of α-haloimines as coupling partners was intended, but during our studies it became apparent that



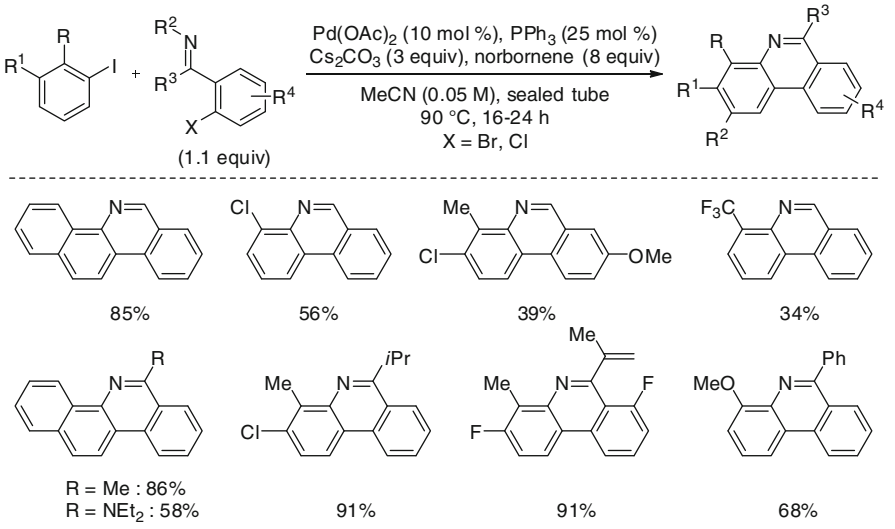
Scheme 29 Palladium-catalyzed domino C–C/C–N coupling of bromoalkylamines for the synthesis of benzannulated *N*-heterocycles

their synthesis is low yielding and often accompanied by decomposition. Therefore, we turned to strained 2*H*-azirines as the 1,3-dipole (Scheme 30). Most substituted indoles are obtained in moderate to excellent yields, except when substituents are placed at the 2-position or when an alkyl or carbonyl group is present at the 3-position of the azirine ring system, which leads to azirine decomposition. During optimization, an unusual tetracyclic by-product was observed that contains two equivalents of the azirine and can be avoided or produced selectively by adjusting the reaction conditions (see Scheme 30).

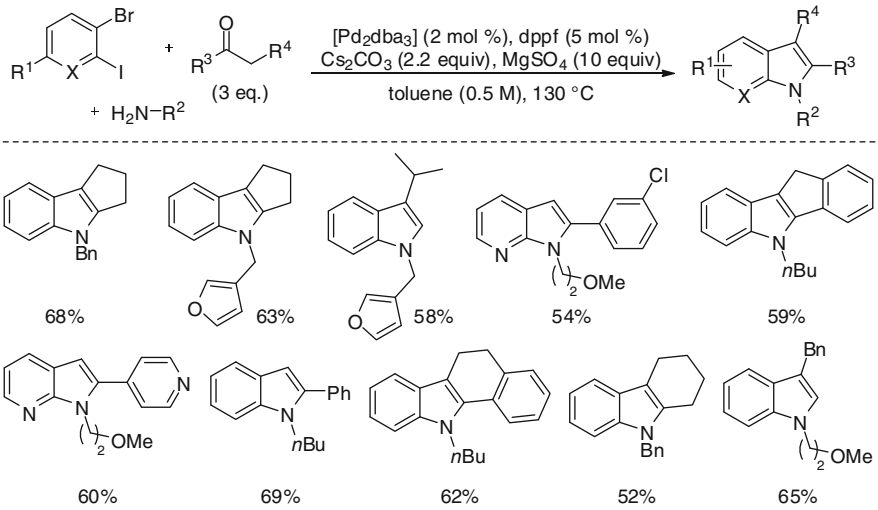
A similar methodology was used for the synthesis of phenanthridines from aryl iodides and *N*-unsubstituted or *N*-silylimines (Scheme 31) [67]. The key step in this transformation is the cleavage of the N–H or N–Si bond in the catalytic cycle which is necessary for the formation of a palladium–imido intermediate which releases the product upon reductive elimination. A mechanistic constraint is that the imine derivative must carry a group on the nitrogen atom which can be cleaved in the catalytic cycle. Another requirement is the presence of an *ortho*-substituent on the aryl iodide. The reaction tolerates a number of substituents on aryl iodide and the azirine, and our group later also showed that instead of aryl iodides the corresponding aryl triflates can be used which are more easily accessible [68]. We were able to demonstrate the applicability of this methodology in the formal syntheses of nitidine and NK190 starting from the corresponding aryl triflates.



Scheme 30 Palladium-catalyzed domino reaction of azirines with aryl iodides



Scheme 31 Palladium-catalyzed domino direct arylation/N-arylation for the synthesis of phenanthridines

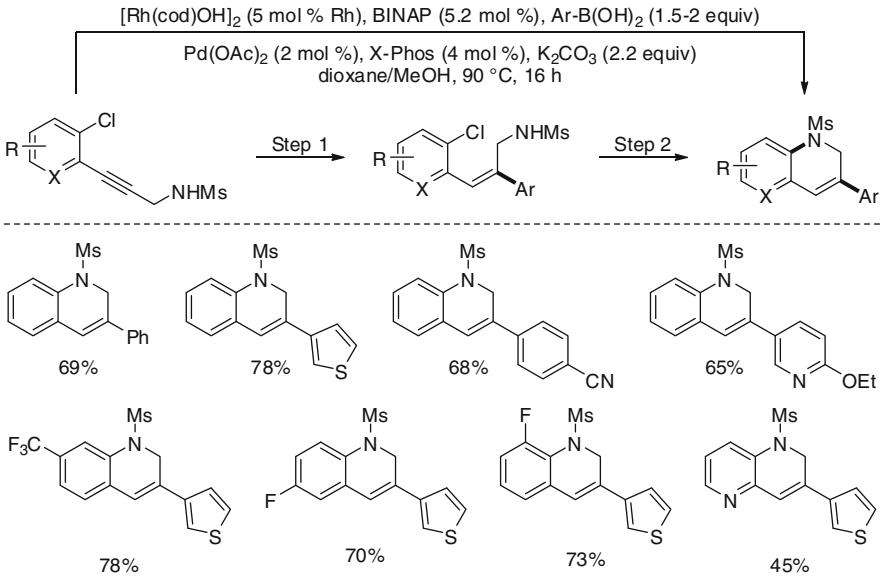


Scheme 32 Palladium-catalyzed tandem synthesis of substituted indoles via Buchwald–Hartwig amination/condensation/arene−alkene coupling

2.4 Miscellaneous Domino Methods for the Synthesis of Heterocycles

A recent example of a domino indole synthesis is a three-component palladium-catalyzed process reported by Kurth and coworkers (Scheme 32) [70]. This three-step process involves a Buchwald–Hartwig reaction, a condensation, and an arene–alkene coupling. A variety of primary amines, carbocycles, an anisole, or a pyridine can be used as the aryl compound, and the carbonyl compounds can be cyclic and acyclic ketones as well as aldehydes. Several experiments were undertaken to determine the sequence of events, and it was concluded that Buchwald–Hartwig coupling initiates the catalytic cycle. The postulated mechanism was supported by quantum chemical calculations.

An example of an orthogonal tandem catalysis is the rhodium-catalyzed alkyne arylation/palladium-catalyzed *N*-arylation that was presented by our group in 2011 (Scheme 33) [71]. We reported the successful implementation of a catalyst system consisting of two different metals with two different phosphine ligands in which both catalysts coexist and preferentially promote two out of three possible reactions to produce 1,2-dihydroquinoline derivatives in moderate to good yields. An initial optimization of the individual steps led to conditions that yielded the final product in 69% yield (versus 71% yield over two steps) by using preformed catalysts. An extensive investigation of the reactivity of the possible metal–ligand combinations showed that [Rh(BINAP)] does not reversibly bind XPhos, while palladium can reversibly bind to both ligands. Since [Pd(BINAP)] is catalytically inactive in the

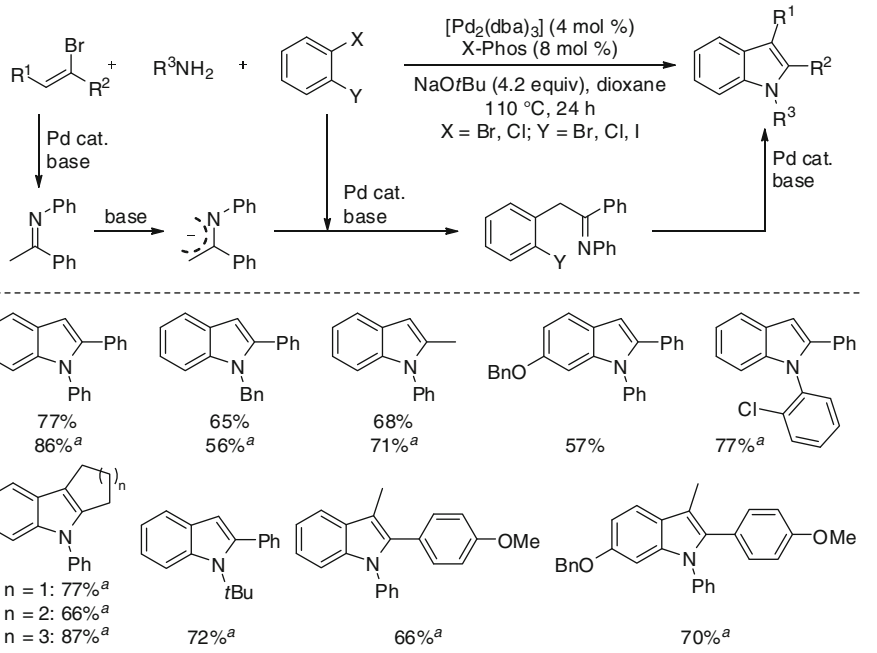


Scheme 33 Orthogonal tandem catalysis for the synthesis of 1,2-dihydroquinoline derivatives

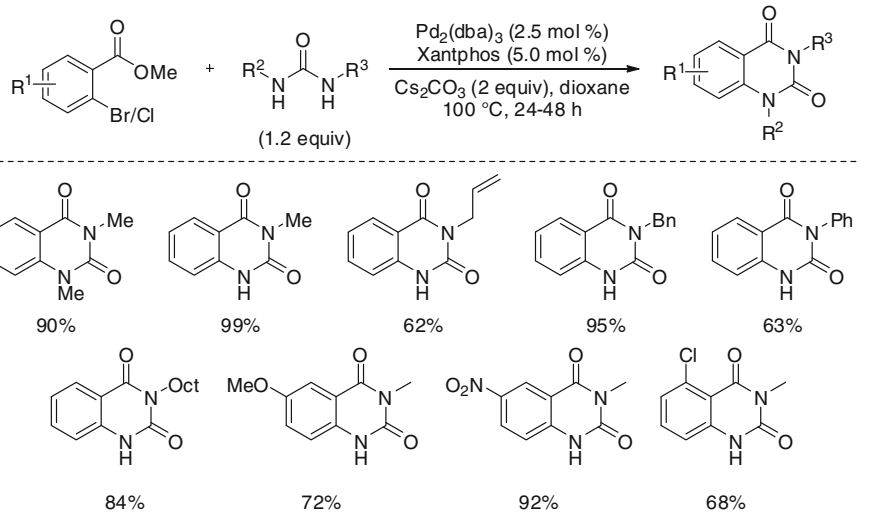
C–N coupling, the amount of BINAP or [Rh(BINAP)], which is a source of trace amounts of free BINAP, had to be carefully adjusted in order to avoid inhibition of the C–N coupling step.

Barluenga and coworkers utilized the bidentate nature of the azaallylic anion as a synthon for palladium-catalyzed construction of various substituted indoles (Scheme 34) [72]. An azaallylic anion can be easily generated in situ through the deprotonation of an imine with α-hydrogen atoms which can then participate in an intermolecular α-arylation reaction. The authors developed a sequence which includes the imine formation, thereby achieving a three-component reaction where the same palladium catalyst promotes three different and independent reactions: (1) the formation of the imine by alkenyl amination, (2) α-arylation of the (deprotonated) imine, and (3) intramolecular *N*-arylation. The reaction conditions of the imine formation are very similar to those of the tandem *C*-arylation/*N*-arylation process, and a couple of successful examples with moderate to good yields were reported. While two different regioisomeric indoles can theoretically be obtained when unsymmetrical 1-bromo-2-chlorobenzene derivatives are employed, only one isomer is ever observed. This regioselectivity may be explained through the different rates of oxidative addition of the palladium catalyst into aryl bromides versus aryl chlorides.

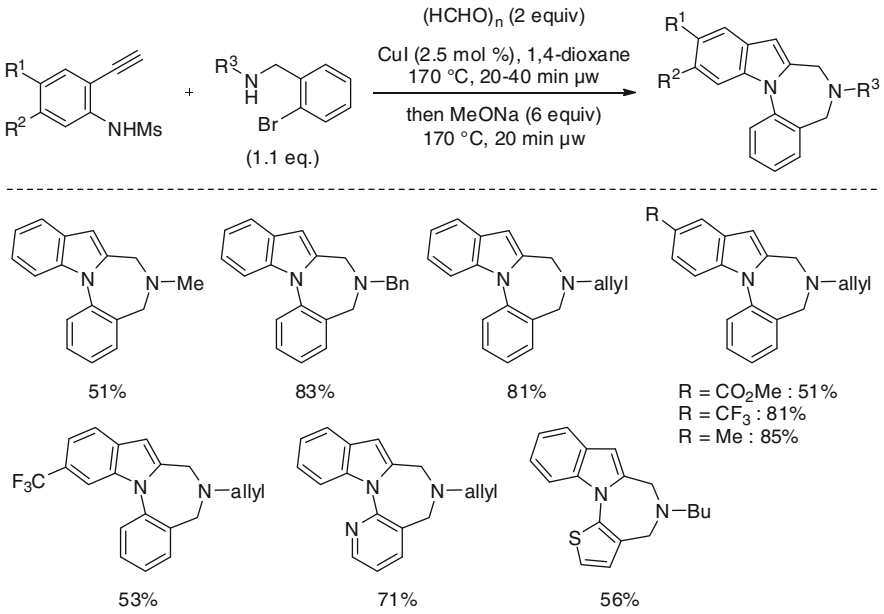
The group of Willis combined the palladium-catalyzed urea arylation with a base-promoted ester amidation to synthesize 3-alkylated 2,4-quinazolinediones (Scheme 35) [73]. This transformation requires relatively high amounts of catalyst loading and long reaction times. An interesting aspect is the fact that for all unsymmetrical urea derivatives studied, the 3-alkyl regioisomer was obtained selectively. This regioselectivity is assumed to arise from the fact that the initial



Scheme 34 Use of the azaallylic anion as synthon in palladium-catalyzed tandem reactions ([a]products obtained directly from the preformed imine)



Scheme 35 Tandem palladium-catalyzed urea arylation/intramolecular ester amidation for the regioselective synthesis of 3-alkylated 2,4-quinazolinediones

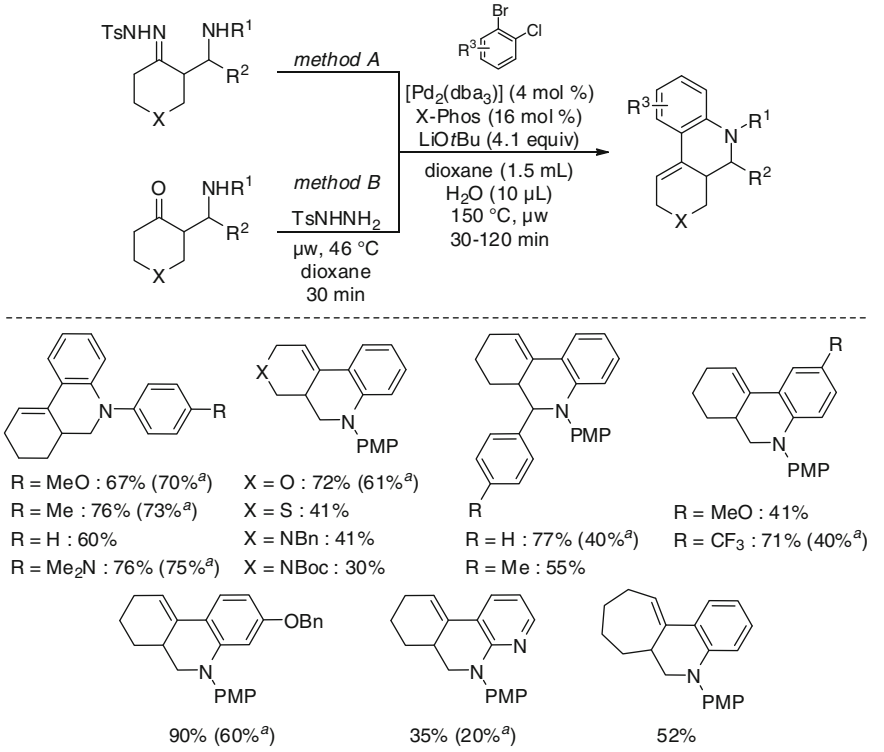


Scheme 36 Synthesis of indole-fused 1,4-diazepines via a ligand-free copper-catalyzed three-component coupling/cyclization/*N*-arylation sequence

arylation reaction occurs on the least hindered, unsubstituted *N*-atom of the urea and is then followed by the ring-closing amidation.

In 2008, Fujii, Ohno, and coworkers reported a ligand-free copper-catalyzed three-component coupling sequence during which four bonds and two rings are formed (Scheme 36) [74]. The sequence is initiated by a Mannich-type reaction followed by intramolecular indole formation. After indole formation is complete, addition of base initiates amine deprotection and the final *N*-arylation can proceed to form indole-fused 1,4-diazepines. The addition of base at a later stage is necessary to avoid decomposition of the starting material. Various *N*-substituted *ortho*-bromobenzylamines and 2-ethynylanilines (with electron-donating or electron-withdrawing groups) as well as heterocyclic secondary amines can be employed to produce the corresponding products in moderate to good yields.

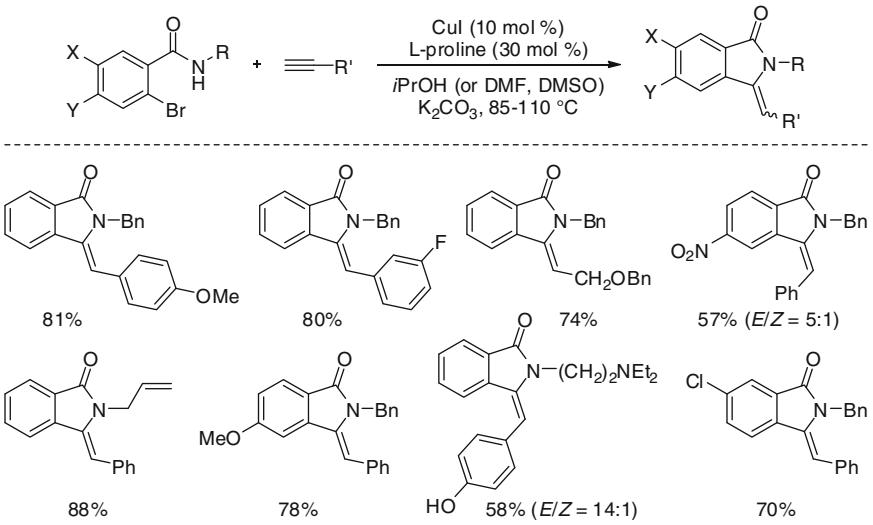
Barluenga, Valdés, and coworkers utilized *N*-tosylhydrazones in a new type of cross-coupling process (Scheme 37) [75]. An intermolecular arylation between tosylhydrazone and a 1-bromo-2-chlorobenzene derivative followed by an intramolecular amination yields substituted tetrahydroquinolines in moderate to good yields. Microwave heating promoted the reaction in one pot, and the tosylhydrazone can be generated in situ from the corresponding carbonyl compound and tosylhydrazine, making the overall process an efficient three-component coupling sequence. A limitation is the failure of the cyclization step when electron-withdrawing substituents are present on the nitrogen atom. The authors were also able to show that chiral substrates can be transformed without loss of enantiomeric excess.



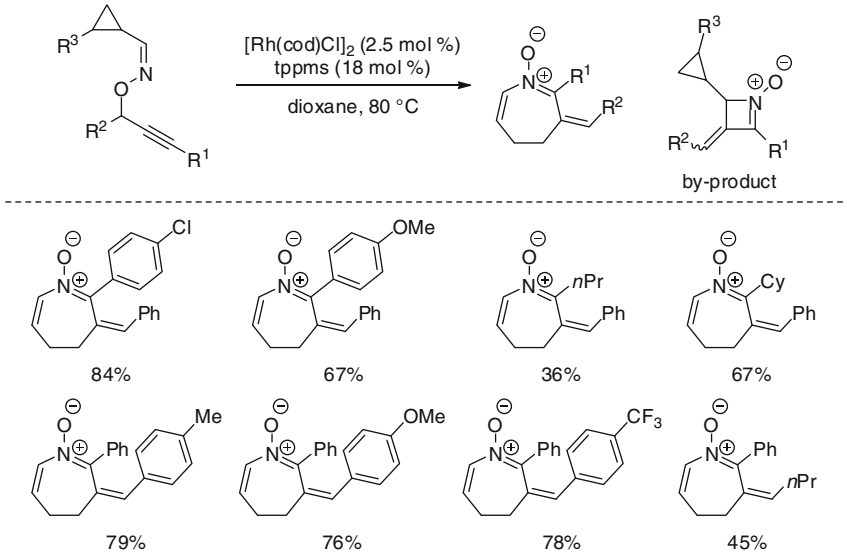
Scheme 37 Tosylhydrazide-promoted palladium-catalyzed synthesis of tetrahydroquinolines via intermolecular arylation/intramolecular amination ([a]results obtained with method B)

Jiang, Ma, and coworkers developed a CuI/L-proline-catalyzed tandem process that generates 3-methyleneisoindolin-1-ones from readily available 2-bromobenzamides and terminal alkynes (Scheme 38) [76]. A variety of functionalized arylacetylenes, aliphatic alkynes, substituted aryl bromides, and a wide range of *N*-substituents were tolerated. In most cases, only the *Z*-isomer was observed. The authors hypothesize that the Sonogashira coupling of aryl bromides with 1-alkynes occurs first. After deprotonation of the amide moiety, the CuI-mediated additive cyclization takes place in a 5-*exo* manner exclusively, which is different for base- or Lewis acid-mediated cyclizations.

Very recently, Nakamura and coworkers utilized in situ generated *N*-allenylimines for the construction of azepine derivatives (Scheme 39) [77]. Starting from *ortho*-propargylic cyclopropylcarbaldoximes, a rhodium catalyst, and TPPMS (sodium diphenylphosphinobenzene-3-sulfonate) the corresponding azepine oxide derivatives are obtained in good yields through a tandem 2,3-rearrangement/heterocyclization reaction. The rhodium catalyst serves a dual role as both π-acidic and redox catalyst. All products are obtained with a *Z*-configuration at the alkylidene moiety, regardless of the configuration of the starting material. For the

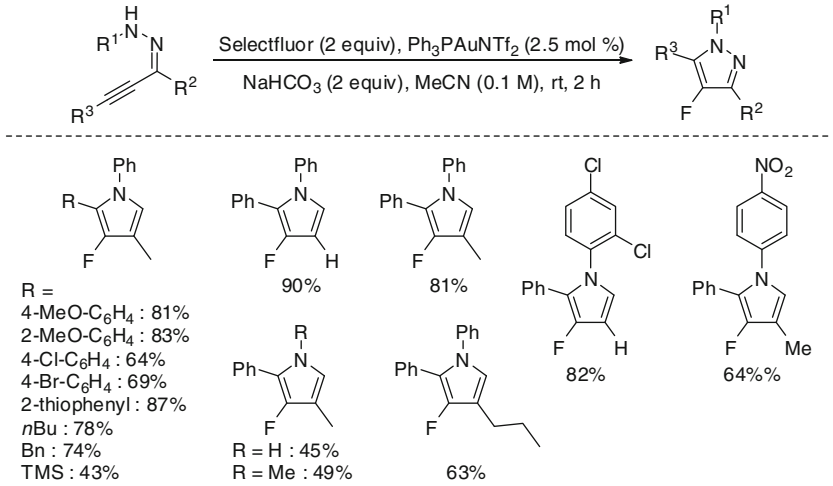


Scheme 38 CuI/L-proline-catalyzed tandem approach toward 3-methyleneisoindol-1-ones



Scheme 39 Rhodium-catalyzed tandem 2,3-rearrangement/heterocyclization for the synthesis of azepine derivatives

(*E*)-isomer of the starting material, reaction conditions had to be re-optimized. In some cases the four-membered cyclic nitrone was obtained as a by-product (see Scheme 39). It was shown to be stable under the reaction conditions and is not converted to the product.



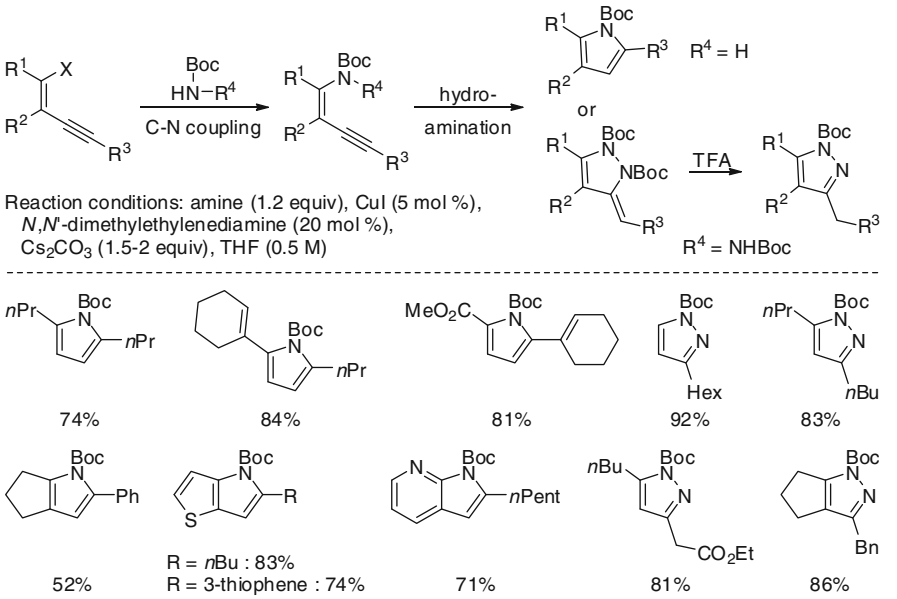
Scheme 40 Gold-catalyzed tandem aminofluorination of alkynes for the synthesis of fluorinated pyrazoles

In 2011, Liu, Xu, and coworkers reported a novel synthesis of fluorinated pyrazoles via a gold-catalyzed tandem aminofluorination of alkynes in the presence of Selectfluor [78]. This methodology was designed to overcome limitations of known approaches to fluoropyrazoles among which are low yields, multiple steps, harsh reaction conditions, or the use of dangerous reagents. The method works at room temperature and has broad scope (Scheme 40). The authors proposed the coordination of an Au^{I} or Au^{III} salt to the alkyne as the key mechanistic step. It is unclear at which step Selectfluor participates in transferring a fluorine atom to the final product. Under the reaction conditions, when a non-fluorinated analogue is obtained as a by-product of the reaction, it can be readily converted to the final fluorine-containing product.

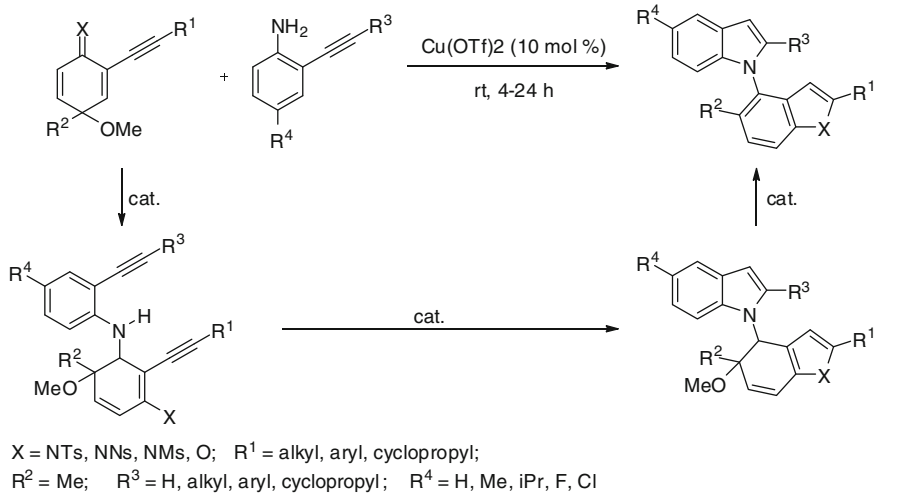
Buchwald and coworkers reported the tandem synthesis of pyrroles and pyrazoles from haloenynes by reaction of either a Boc-protected amine or a bis(Boc)hydrazide (Scheme 41) [79]. The sequence of copper-catalyzed amidation and hydroamidation yields various substituted pyrroles and pyrazoles in good yields. Mechanistic investigations showed that the reaction most likely proceeds via an initial C–N coupling followed by hydroamidation.

Tang, Fan, and coworkers developed a copper-catalyzed tandem reaction for the synthesis of *N*-heteroarylated indoles and benzimidazoles which involves a conjugate addition, two cyclizations, and an aromatization (Scheme 42) [80].

Willis and coworkers reported the synthesis of 2-quinolones via a palladium-catalyzed alkenyl aminocarbonylation followed by intramolecular amidation (Scheme 43) [81]. For the 2-quinolone synthesis it is important at which site the initial reaction takes place (aryl halide versus alkenyl halide, see Scheme 43) and which of the two catalytic reactions occurs first (amination or carbonylation). It is postulated that the alkenyl halide is the first site of reaction and carbonylation is

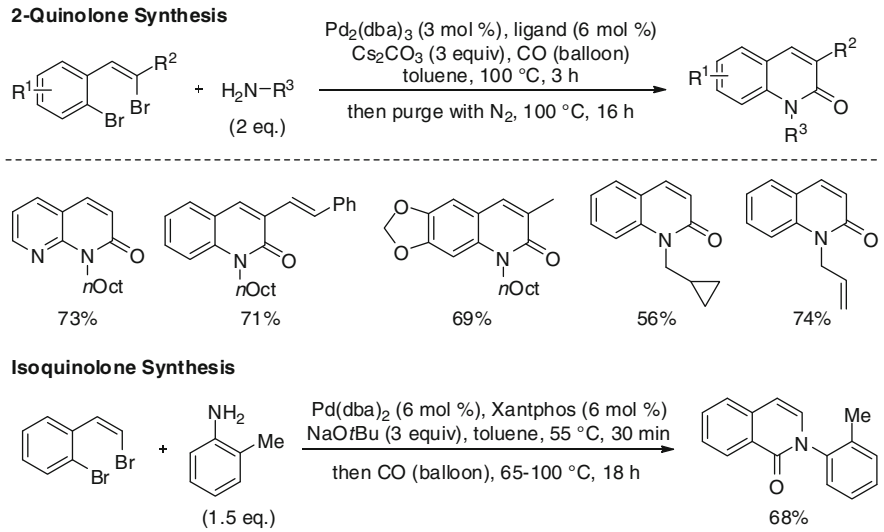


Scheme 41 Tandem synthesis of pyrroles and pyrazoles by copper-catalyzed amidation/hydroamidation of haloenynes



Scheme 42 Copper-catalyzed tandem reaction for the synthesis of *N*-heteroarylated indoles and benzimidazoles

the faster of the two processes. In some cases it was beneficial to remove the CO atmosphere after 3 h. In order to obtain the corresponding isoquinolone, it was necessary to change the order of reagent addition which was done by applying the CO atmosphere at a later stage in the reaction. A limitation of this approach is the



Scheme 43 Palladium-catalyzed alkenyl aminocarbonylation/intramolecular aryl amidation for the synthesis of 2-quinolones

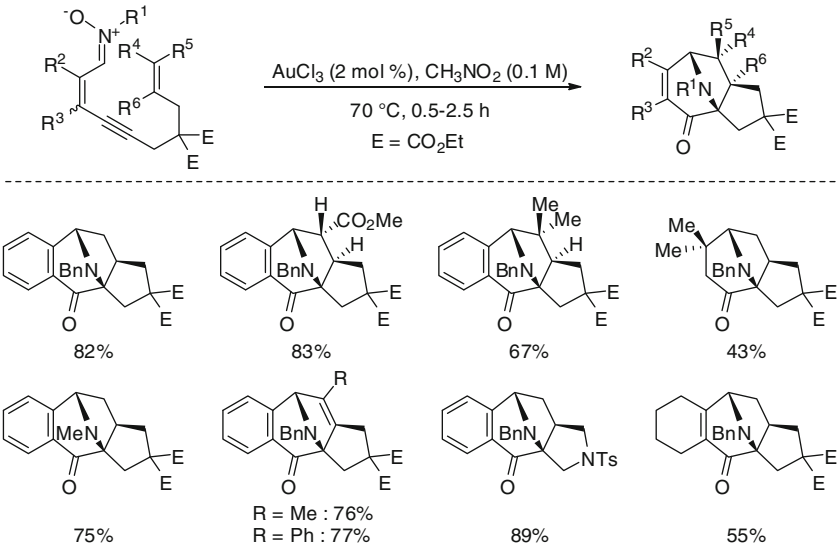
requirement for a sterically demanding *N*-nucleophile since less hindered amines lead to competing indole formation.

In 2008, Shin and coworkers reported a gold-catalyzed generation of an azomethine ylide via an internal redox reaction between a tethered nitrone and an alkyne. The ylide then undergoes an efficient diastereoselective cycloaddition cascade (Scheme 44) [82]. Various platinum(II), silver(I), and gold(III) salts were found to be effective catalysts, while $AuCl_3$ provided the best results. This methodology is particularly attractive because it avoids the use of explosive diazo derivatives and is 100% atom economic. Metal-catalyzed cycloaddition reactions that result in the generation of a C−N or C−O bond will be discussed in length in another chapter of this book and consequently will not be visited further in this section.

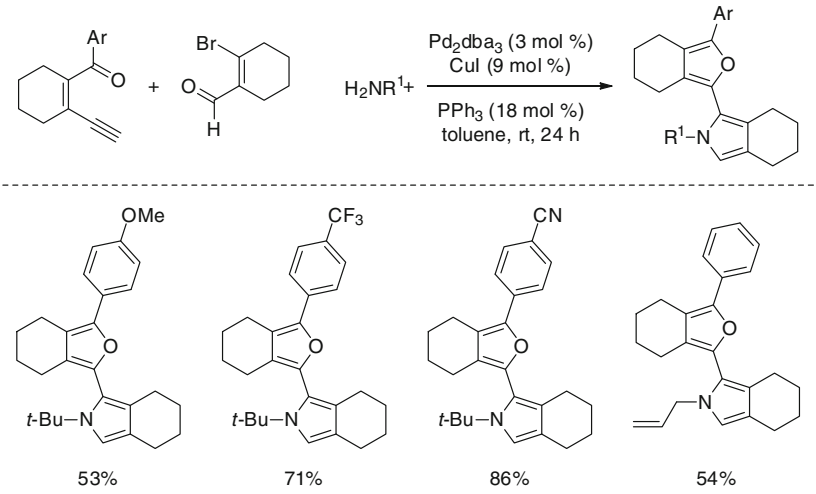
The versatility of incorporating the Sonogashira reaction has been exploited by Ohe and coworkers for the synthesis of hetero α,α′-dimers of heteroaromatic compounds (Scheme 45) [83]. By utilizing bimetallic palladium/copper catalysis, a tandem process can be achieved for the synthesis of a variety of dimeric compounds. Due to the fact that this is a three-component coupling process, chemical diversity can be established very quickly under mild reaction conditions.

Wang and coworkers recently reported an elegant illustration of a copper-catalyzed domino coupling of a diverse array of *N*-tosylhydrazones and a series of terminal alkynes for the synthesis of 2-substituted benzofurans and indole heterocycles (Scheme 46) [84].

Glorius and coworkers published a report that describes the copper-catalyzed domino reaction of 1,2-dihalo carbo- and heterocycles with primary amides for the



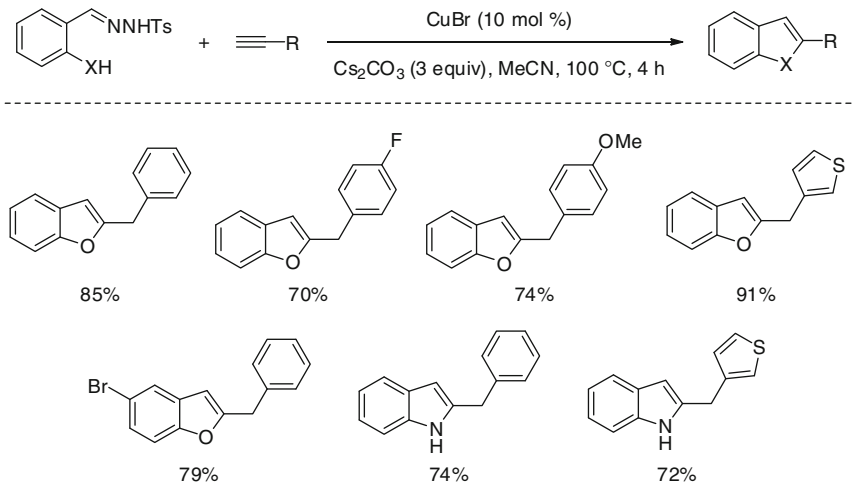
Scheme 44 Gold-catalyzed internal redox/dipolar cycloaddition cascade



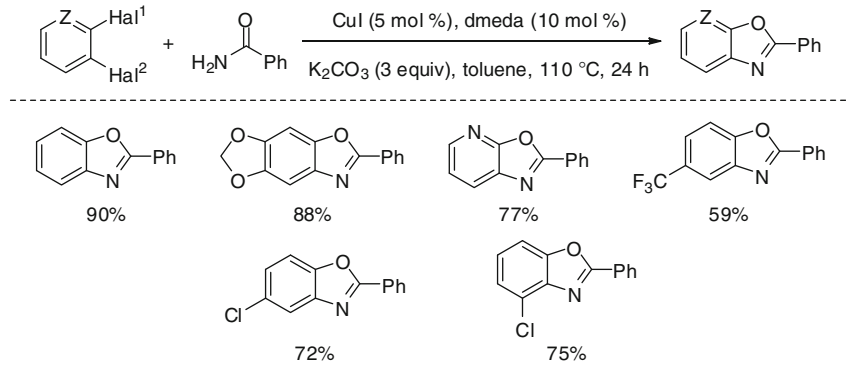
Scheme 45 Palladium/copper-catalyzed tandem multicomponent coupling for the synthesis of α,α′-heteroaromatic dimers

synthesis of benzoxazole products (Scheme 47) [85]. A variety of chloro-, bromo-, and iodo-containing 1,2-dihaloarene starting materials are shown to be competent coupling partners in this methodology.

The Tsuji−Trost reaction has been utilized in a variety of transformations to achieve complex target structures and intermediates [86]. To this end, the



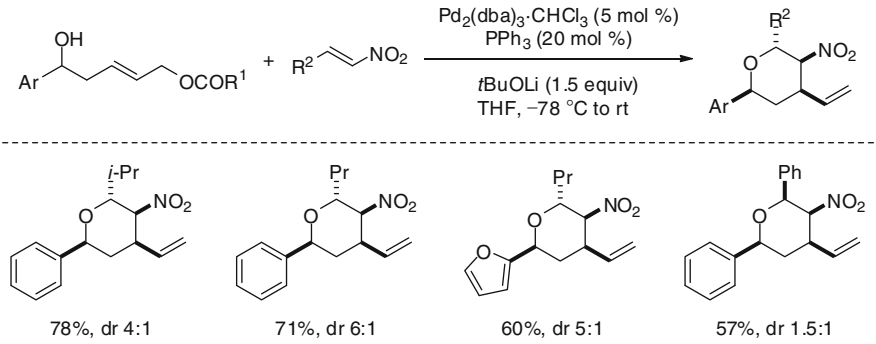
Scheme 46 Copper-catalyzed domino coupling of *N*-tosylhydrazones and terminal alkynes for the synthesis of 2-substituted benzofurans and indoles



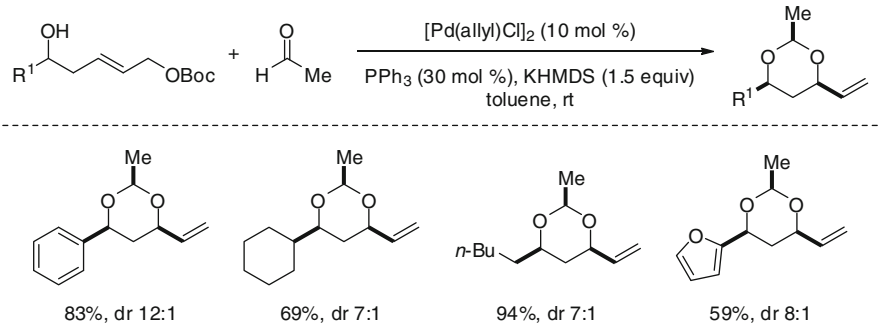
Scheme 47 Copper-catalyzed domino synthesis of benzoxazole heterocycles

Tsuji–Trost reaction has been successfully coupled in tandem or domino processes for the synthesis of heterocycles [87]. Menche and coworkers reported in 2010 the concise Pd-catalyzed diastereoselective domino synthesis of tetrahydropyran heterocycles via an oxa-Michael addition/Tsuji–Trost reaction (Scheme 48) [88]. By employing a chiral alcohol with a pendant allyl carbonate moiety, tetrahydropyrans could be constructed with up to four non-contiguous stereocenters. Yields were generally moderate and level of diastereoselectivity ranged from low to high, dependent on the substrate combination.

Menche and coworkers recently disclosed an expansion of their previous method for the synthesis of masked 1,3-diols via a domino Pd-catalyzed diastereoselective hemiacetal formation/Tsuji–Trost reaction sequence (Scheme 49) [89]. The scope



Scheme 48 Domino synthesis of tetrahydropyrans via an oxa-Michael addition/Tsuji–Trost reaction



Scheme 49 Domino synthesis of protected 1,3-diols via hemiacetal formation/Tsuji–Trost reaction

of the transformation is quite broad and yields range from moderate to excellent with generally high levels of diastereoselectivity.

3 Conclusion

While this particular chapter was specifically focused on the synthesis of heterocycles via metal-catalyzed domino reactions that result in the generation of a C–N or C–O bond, the general field of these types of "domino" transformations represents one of the most efficient, elegant, and atom-economical means to construct complex target structures. It can be expected that efficiencies in these transformations will only increase in the coming years. The ability to reduce the environmental impact represents a potential advantage of this approach. Indeed, the reduction of numerous workup steps such as extractions, purifications (chromatography, recrystallization, distillation, etc.), and the lessening/elimination of the requirement of toxic reagents is an attractive and important goal. It is to be expected that research groups will continue to pursue advances in the field of domino catalysis.

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