Palladium catalyzed alkenyl amination: from enamines to heterocyclic synthesis

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The most recent advances in the Pd catalyzed amination of alkenyl halides directed towards the synthesis of imines and enamines are reviewed. The application of this cross-coupling reaction in the synthesis of heterocycles appears to be a potentially powerful methodology. The few examples already available are also discussed.

Introduction

The nitrogen atom is present in most natural products, biologically relevant molecules, pharmaceuticals and dyes.[1] For this reason, the development of new and more efficient methodologies to introduce nitrogenated moieties in a synthetic sequence will always be a major issue of interest. In this context, enamines and imines are versatile synthetic intermediates, which have been extensively employed for the introduction of a nitrogen atom in a organic structure, especially in heterocyclic chemistry.[2]

The main strategy to obtain an enamine or an imine is the acid catalyzed condensation of the corresponding amine with a carbonyl compound (path *a* in Fig. 1). However, this general approach may present some limitations, like harsh reaction conditions, low functional group tolerance, and a lack of chemoselectivity and stereoselectivity. Consequently, over the years several different approaches to enamine and imine functionalities have been developed.[3]

Highly desirable transformations leading to imines and enamines are the hydroamination of alkynes,[4] and the oxidative amination of alkenes (path *b* in Fig. 1).[5] These atom economical approaches have attracted enormous interest in recent years and, in fact, several catalytic systems have been devised to achieve successfully the hydroamination of alkynes with primary amines, and to a lesser extent with secondary amines. Moreover, enamines have also been obtained from olefins through Rh catalyzed hydroformylations in the presence of amines (path *c* in Fig. 1), another example of a highly atom economical transformation.[6]

In the recent years, another new powerful synthetic alternative has emerged: the cross-coupling reaction of amines with alkenyl halides and pseudohalides, catalyzed by palladium and copper complexes (path *d* in Fig. 1).[7] This transformation, which is certainly inspired by the well developed Buchwald–Hartwig aryl amination,[8] has enjoyed growing attention since the pioneer publications in 2002.[9]

On the other hand, for many years, our research group has been interested in the synthesis and applications of enamines

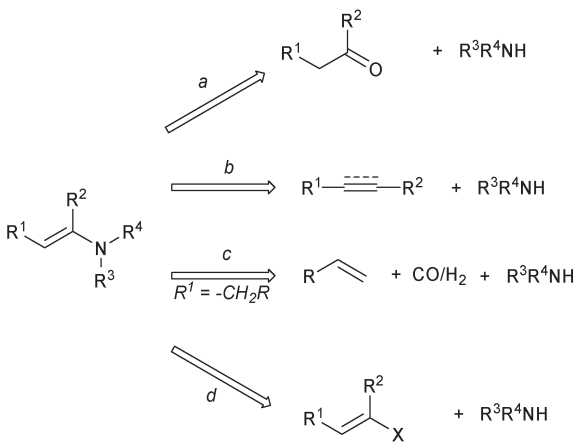

Fig. 1 Main methodologies for the synthesis of enamines

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Carlos Valdés was born in Gijón, Spain in 1964. He studied chemistry in the University of Oviedo, where he received his BS degree in 1987 and his PhD degree in 1992. Then, he spent two years as a Fulbright postdoctoral fellow at the Massachusetts Institute of Technology, (1993–1995) under the supervision of Professor Julius Rebek, Jr., working in the field of tennis-ball self-assembly. He returned to the University of Oviedo where he was appointed Assistant Professor in 1995 and promoted to Associate Professor in 2000. Currently, his main research interests are related to the development of new transition metal catalyzed reactions and cascade processes, and their application in heterocyclic synthesis.

and imines. Back in 1980, we published a novel method for the synthesis of enamines by mercury catalyzed hydroamination of terminal alkynes,[10] a reaction that was further applied in the preparation of 2-amino-1,3-butadienes from 3-buten-1-ynes.[11] Studies of the synthetic applications of these types of aminodiene have been the subject of intense research in our group. In fact, we have shown that these systems are very useful synthetic intermediates due to their versatile reactivity in cycloaddition reactions, to provide heterocycles, and six- and seven-membered ring carbocycles.[12]

Initially motivated by the search for new methodologies to synthesize enamines, and in particular aminodienes, we decided to apply the concept of Pd catalyzed aryl amination to vinyl halides.

In this article, we wish to account our own achievements, and also the most recent advances by other research groups, in the field of Pd catalyzed amination of alkenyl halides. Moreover, the incorporation of vinyl amination reactions in Pd catalyzed tandem processes, appears to be a new powerful approach for the synthesis of nitrogen heterocycles. The promising examples recently published by our group and others in this area will be also discussed.

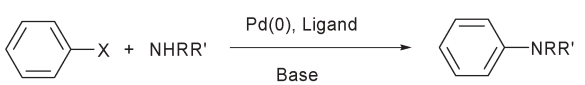
Pd catalyzed amination reactions

The Pd catalyzed cross-coupling reaction of amines with aryl halides, generally known as the Buchwald–Hartwig amination (Scheme 1), has been one of the last transformations to be incorporated in the cross-coupling repertoire.[13] Nevertheless, since the early parallel reports by the Buchwald and Hartwig groups back in 1995,[14] this reaction has prompted enormous experimental development.

In the Buchwald–Hartwig amination, an aniline derivative is obtained by reaction of an amine with an aryl halide. To carry out this transformation, a Pd(0) source, a supporting ligand for the metal, and a base which must deprotonate the amine at some point in the catalytic cycle are required.

One major issue in the development of efficient catalytic systems for Pd catalyzed cross-coupling reactions, and in particular for Pd catalyzed aryl aminations, has been the design and election of proper supporting ligands for the Pd center. In their seminal papers,[14] both Buchwald *et al.* and Louie and Hartwig employed P(*o*-Tol)$_3$ as a ligand, which was soon replaced by several chelating diphosphines, such as dppf, BINAP and XantPhos (Fig. 2), so called second generation ligands. Among these, the Pd(0)–BINAP system can be regarded nowadays as the standard catalyst for the amination of aryl bromides.[15]

The amination of aryl chlorides requires the development of more active catalysts.[16] Bulky and electron-rich ligands are required to achieve cross-couplings with aryl chlorides



X = Br, Cl, OTf, ONf, OTs

R, R' = alkyl, aryl, COR, COOR, SO_2R, azole, $=CPh_2$, $=SO_2$

Scheme 1 General scheme of the Buchwald–Hartwig amination.

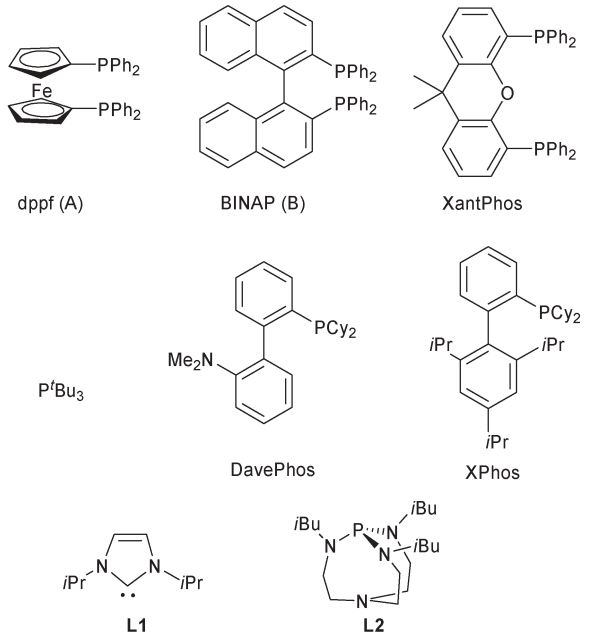


Fig. 2 Some common ligands for Pd catalyzed C–N bond forming reactions.

successfully. In this regard, bulky alkyl substituted phosphines such as P*t*Bu$_3$, and the family of biphenyl ligands developed by Buchwald *et al.* (such as DavePhos[17] and XPhos[18]), are the most popular ligands for aryl aminations.[19] Moreover, imidazolium derived *N*-heterocyclic carbenes **L1**,[20] proazaphosphatranes **L2**,[21] and also palladacyclic catalysts[22] have been employed successfully in aryl aminations with aryl chlorides.

The Pd catalyzed aryl amination is a very general reaction, which has been applied to aromatic and heteroaromatic bromides, chlorides, and also triflates, nonaflates and even tosylates. Regarding the amino partner, almost all N–H containing species have been employed in this cross-coupling process.

The mechanism of this transformation appears to be a point of some debate in the literature, and in fact, several different catalytic cycles have been proposed for the Pd catalyzed aryl amination, depending on the nature of the ligand, and the base involved.[23] Regardless of the particular model, it is generally accepted that the following events must take place (Fig. 3): (i) oxidative addition of the aryl halide to the Pd(0) center to produce the Pd(II) complex **I**; (ii) coordination of the amine to the Pd center, followed by deprotonation to produce the amido Pd complex **II**; (iii) reductive elimination, which releases the coupling product and regenerates the Pd(0) catalyst.

A similar mechanism should also operate for the analogous reaction with vinyl halides. However, the first examples of Pd catalyzed alkenyl aminations had to wait until 2002, when several groups independently reported their progress in this field.[9]

Amination of alkenyl halides

The first example of a Pd catalyzed C–N bond forming reaction involving an alkenyl halide was reported by Voskoboynikov *et al.*,[9a] which studied the alkenylation

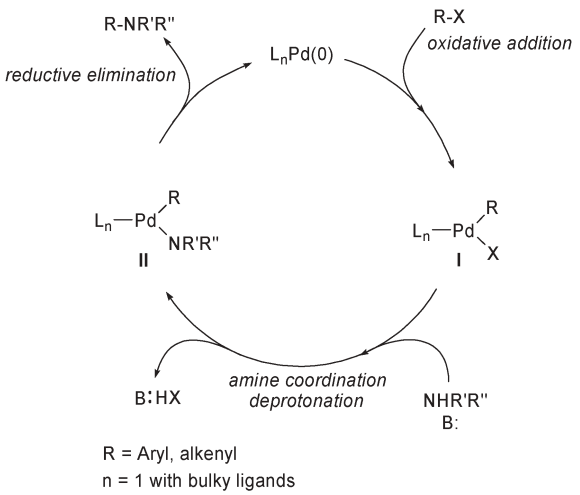
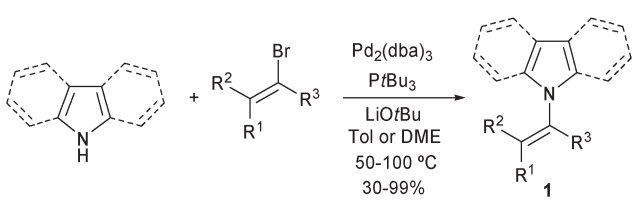


Fig. 3 Outline of the catalytic cycle of the Pd catalyzed C–N bond forming reactions.

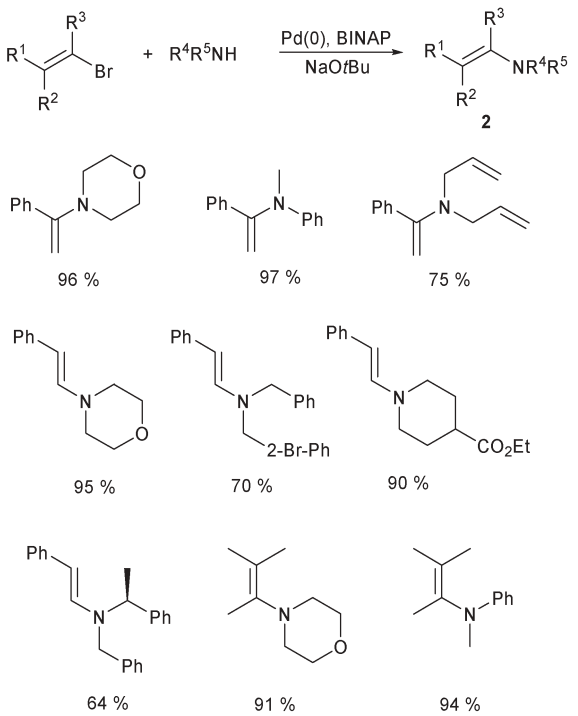
reaction of N–H azoles (Scheme 2). After screening of the ligands and reaction conditions, 2,2′-bis(di-*t*-butylphosphino)-biphenyl and P*t*Bu$_3$ were identified as the most active ligands for this transformation, and LiO*t*Bu as the most effective basic reagent. Under those reaction conditions, pyrrole, indole and carbazole derivatives were coupled with several alkenyl bromides to obtain the corresponding *N*-alkenylazoles **1** with yields ranging from moderate to quantitative. The coupling reaction was achieved successfully with geminal bromolefins such as α-bromostyrene and 2-bromopropene and with β-bromostyrene. It was also possible to perform the reaction with CH_2=CHBr, although it required careful tuning of the conditions to avoid polymerization of the resulting vinyl azoles.

Shortly after Voskoboynikov's contribution, we disclosed the first Pd catalyzed cross-coupling reactions of amines with alkenyl bromides to produce enamines (Scheme 3).[9c,24] After some optimization, we found the Pd(0)–BINAP catalytic system in the presence of NaO*t*Bu to be the most convenient reaction conditions to carry out this transformation.

The coupling reaction proceeded with 2-substituted bromides, geminal bromides, and even with a trisubstituted bromoalkene such as trimethylbromoethylene to provide the corresponding enamines **2** (Scheme 3). Aromatic amines, cyclic and acyclic secondary aliphatic amines, were coupled usually with nearly quantitative yields. In most of the cases, no further purification of the enamines was required, an important advantage of this reaction, since the water sensitivity of the enamine functionality prevents the employment of conventional purification techniques.



Scheme 2 Pd catalyzed vinylation of azoles.

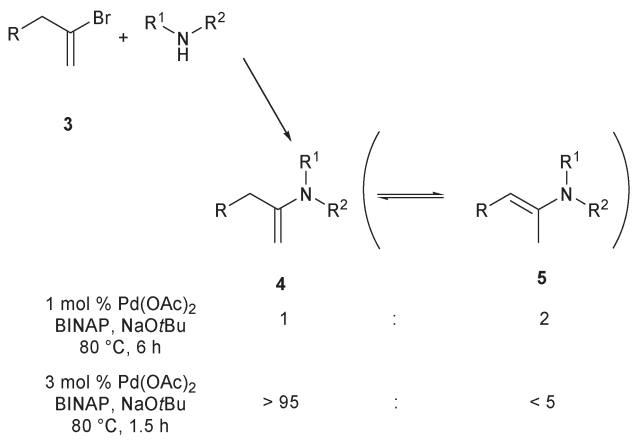


Scheme 3 Pd catalyzed amination of vinyl bromides with secondary amines. Synthesis of enamines **2**.

Very interestingly, it was possible to synthesize the unstable (and previously unavailable) terminal and isomerizable enamines **4** when the coupling reaction was conducted with substituted bromopropenes **3** (Scheme 4). For this purpose, it was necessary to increase the catalyst loading, in order to reduce the reaction time, avoiding isomerization *via* tautomerization, into the more stable trisubstituted internal enamine **5**.

Under these reaction conditions structurally diverse isomerizable enamines **4** could be prepared with nearly quantitative yields (Fig. 4).

The cross-coupling reaction of primary amines under similar reaction conditions affords imines **6**, after enamino–imino tautomerization (Scheme 5). Several Pd–ligand combinations are able to catalyze this process, among them the Pd–BINAP



Scheme 4 Influence of the reaction conditions on the synthesis of terminal isomerizable enamines.

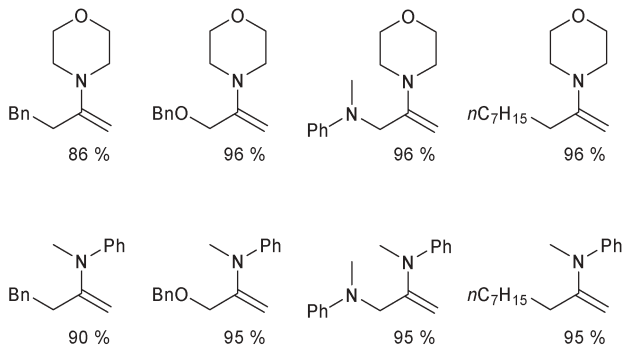
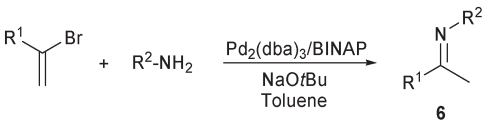


Fig. 4 Terminal enamines **4** synthesized.



Scheme 5 Synthesis of imines **6** by cross-coupling of primary amines with bromoalkenes.

and Pd–DavePhos combinations were found to be the most efficient. Therefore, under reaction conditions similar to those used for the synthesis of enamines, geminal alkenyl bromides are converted into imines with very high yields. The reaction is very general regarding the structure of both coupling partners.

Electron-rich and electron-poor, *ortho*- *meta*- and *para*-substituted, aromatic amines, and also linear and branched aliphatic amines have been coupled with a variety of alkenyl bromides to provide the corresponding imines. Some representative structures are presented in Fig. 5.

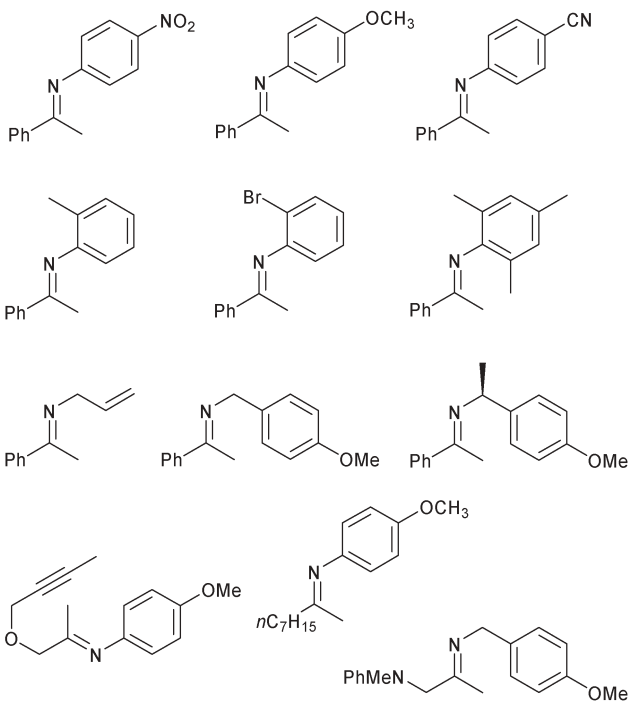
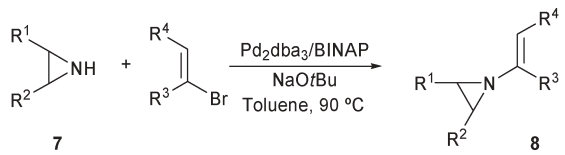


Fig. 5 Some selected imines prepared by amination of vinyl bromides with primary amines.



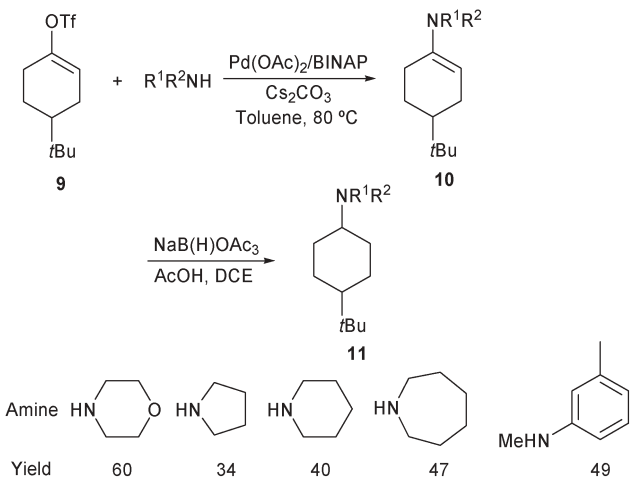
Scheme 6 Vinylation of aziridines through a Pd catalyzed cross-coupling.

An interesting application of the amination of vinyl bromides has been recently reported by Dalili and Yudin, who employed aziridines **7** as the amino partner in the coupling reaction.[25] Under the same catalytic conditions described above, the reaction of α- and β-bromostyrene with aziridines afforded the corresponding *N*-alkenylaziridines **8** (Scheme 6). It is noteworthy that aziridines are not good nucleophiles for condensation reactions with carbonyls, therefore this methodology represents an excellent solution for the synthesis of this particular type of enamine.

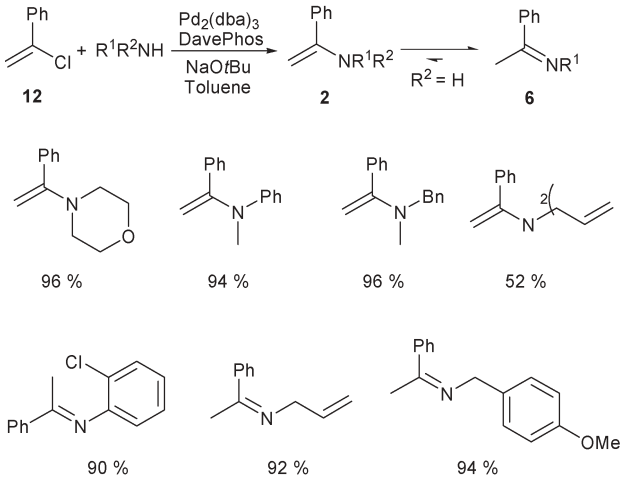
Also in the year 2002, Willis and Brace showed that enol triflates **9** can be coupled with secondary amines to obtain the corresponding enamines **10**.[9d] The Pd–BINAP combination, in the presence of the milder base Cs_2CO_3, was employed to couple the enol triflate with a variety of secondary amines. Reduction of the crude enamines afforded the corresponding amines **11** with moderate yields for the two step process (Scheme 7).

Alkenyl chlorides are expected to be less reactive that the analogous bromides, due to their lower tendency to participate in oxidative addition to metals.[26] In fact, when we investigated the coupling reaction of α-chlorostyrene **12** with morpholine, new catalytic conditions had to be developed. Although many Pd–ligand combinations promoted the reaction to some extent, the catalytic system Pd(0) (2 mol%)–DavePhos (4 mol%) at 90 °C resulted in the best reaction conditions for this coupling, giving rise to a nearly quantitative yield of enamine **2**. The optimized procedure was tested with a variety of primary and secondary amines, to obtain the corresponding imines **6** and enamines **2** with excellent yields (Scheme 8).[27]

The Pd–BINAP catalytic system has been also employed by Hesse and Kirsch to achieve the amination of



Scheme 7 Amination of enol triflates **9**.

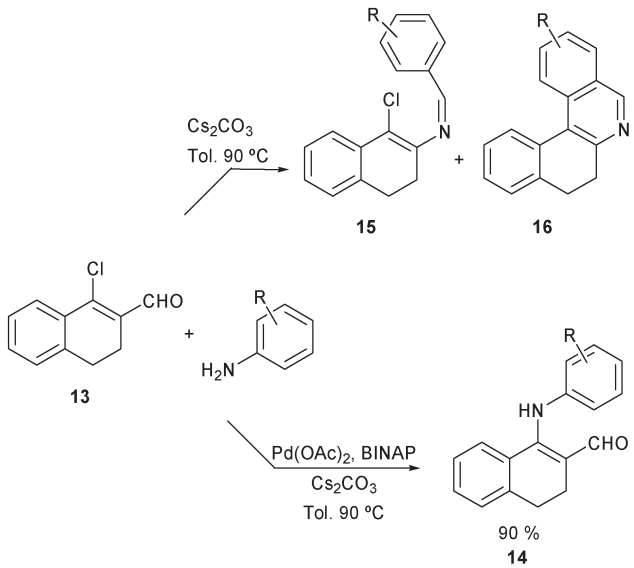


Scheme 8 Synthesis of enamines **2** and imines **6** by the cross-coupling of α-chlorostyrene **12** with secondary and primary amines respectively.

β-chloroacroleins **13**.[28] Interestingly, in the presence of the Pd catalyst, selective amination on the chlorine position occurs, to give the β-aminoacrolein **14**. However, in the absence of the catalyst, under the same conditions, the condensation reaction of the amine with the aldehyde takes place,[29] to afford a mixture of imine **15** and the coumarin derived from the intramolecular cyclization of imine **16** (Scheme 9).

Synthesis of conjugated dienamines

Conjugated dienamines **A** and **B** (Fig. 6) are particularly interesting types of enamines. These electron-rich dienes are very useful in [4 + 2] cycloaddition reactions, due to their high reactivity with activated dienophiles.[30] However, their usefulness has been limited due to the lack of versatile methods for their preparation, since classical condensation protocols are not efficient approaches in many cases.[31] We envisioned that



Scheme 9 Chemoselective aminations of β-chloroacroleins **13** in the presence and absence of a Pd catalyst.

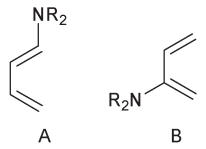


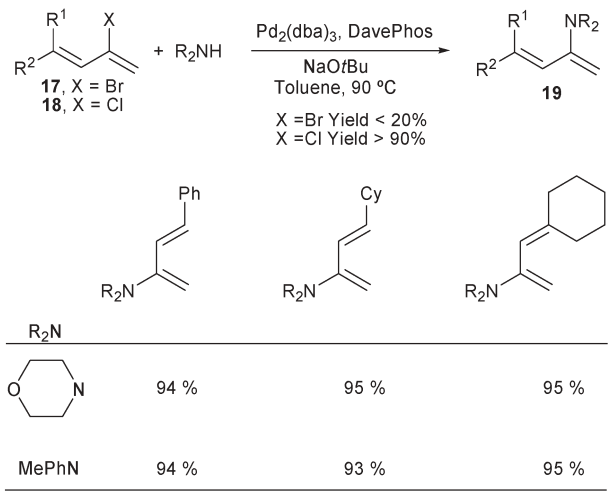
Fig. 6 1-Amino-1,3-butadienes **A** (linear dienamines) and 2-amino-1,3-butadienes **B** (cross-conjugated dienamines).

the cross-coupling strategy might result in a very attractive alternative to the existing methods.

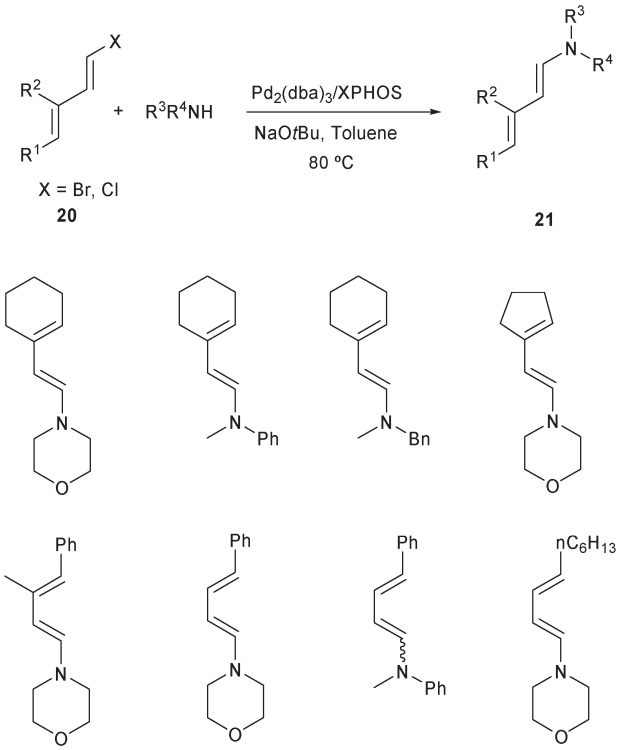
We investigated first the coupling reaction of 2-bromo-1,3-butadienes **17** with amines, which would lead to 2-amino-1,3-butadienes **19** (Scheme 10).[27] However, it soon became clear that 2-bromo-1,3-butadienes were not appropriate coupling partners, since they tend to decompose upon heating, giving rise to 2-aminodienes with very low yields. This observation prompted us to investigate the same reaction with the analogous chlorodienes **18**. Under the reaction conditions developed for the amination of chloroalkenes, the 2-amino-1,3-butadienes **19** were obtained with nearly quantitative yields (Scheme 10). It is remarkable that for this reaction the less reactive chlorides were much better coupling partners than the analogous bromides, in a rare example of the benefits of lower reactivity in a cross-coupling process.

The synthesis of 1-amino-1,3-butadienes **21** could be effected using a similar strategy, starting from either 1-bromo- or 1-chloro-1,3-butadienes **20**.[32] For both types of halide, the Pd–Xphos combination gave the best results. The 1-amino-1,3-butadienes were obtained with very high yields, and like in most of the Pd catalyzed amination reactions, no further purification was required other than filtration through a celite pad. Some representative examples are depicted in Scheme 11.

The amine alkenylation reaction described above represents a novel entry to structurally diverse 2-amino-1,3-butadienes **19** and 1-amino-1,3-butadienes **21**, provided that the corresponding 2-chloro-1,3-butadienes **18** and 1-halo-1,3-butadienes **20** are accessible. At the outset of our research, very few methods were available for the preparation of chlorodienes, and most of



Scheme 10 Synthesis of 2-amino-1,3-butadienes **19** by Pd catalyzed amination of halodienes.



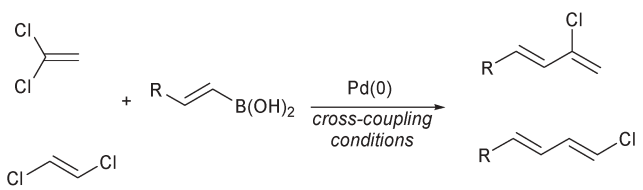
Scheme 11 Synthesis of 1-amino-1,3-butadienes **21** from 1-chloro- and 1-bromo-1,3-butadienes **20**.

them required several steps from commercial sources.[33,34] For this reason, and in order to expand the applicability of this reaction, we have devised a very straightforward method for the preparation of the required 1- and 2-chlorodienes by selective Suzuki cross-couplings of alkenylboronic acids with commercially available 1,1- and 1,2-dichloroethylene respectively (Scheme 12). Full details on this methodology will be published elsewhere.[35]

Thus, the combination of both methodologies, the Suzuki reaction of chloroethylenes followed by the alkenyl amination of the chlorodienes, represents a very efficient entry to diverse 1- and 2-amino-1,3-butadienes, and therefore to their application as intermediates in organic synthesis

Cross-coupling reactions with other nitrogenated species

Amides are excellent coupling partners for metal catalyzed arylations.[36] Moreover, many examples have been published of the copper catalyzed cross-couplings of amides with alkenyl iodides and bromides,[37] a powerful synthetic transformation that affords enamides, a substructure which is present in a



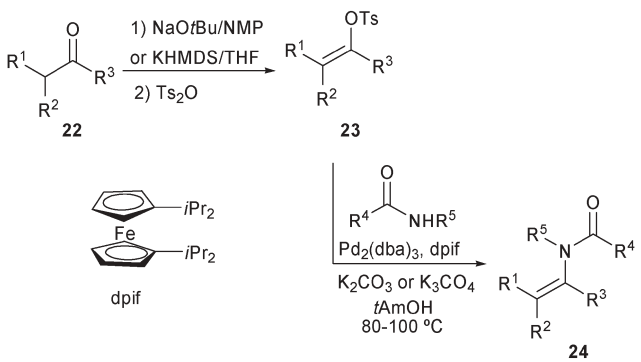
Scheme 12 A very straightforward synthesis of 1-chloro-1,3-butadienes and 2-chloro-1,3-butadienes from commercial sources.

number of natural products. The first example of an alkenyl amidation promoted by Pd was described by Mori's group, who studied the intramolecular amidation reaction of vinyl iodides and bromides as key step in the synthesis of carbapenem antibiotics.[9b,38]

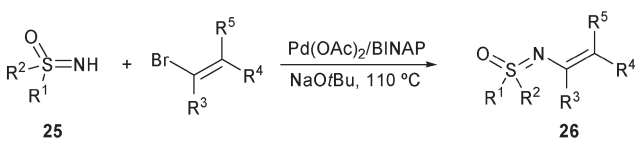
Intermolecular Pd catalyzed amidations have been studied by a research group at Merck using enol sulfonates as coupling partners. The cross-coupling of enol triflates with amides was achieved with the Pd(0)–XantPhos catalyst, and using Cs_2CO_3 as a base.[39] The same research group reported recently the amidation of enol tosylates **23**,[40] which are obtained by enolization of a ketone **22**, followed by treatment with *p*-toluenesulfonic anhydride. After a wide ligand screening, 1,1′-diisopropylphosphino ferrocene (dpif), was identified as the best supporting ligand for this transformation. Under the reaction conditions represented in Scheme 13, primary amides and secondary cyclic amides were coupled with several enol tosylates **23** to provide enamides **24** with high yields. The incorporation of enol tosylates as partners in cross-coupling reactions represents an important advance, as they are more conveniently prepared than the analogous triflates. However, at the present, the reaction seems to be limited to aryl or electron-withdrawing substituted enol tosylates.

Delhi and Bolm have recently disclosed the alkenylation of N–H sulfoximines **25** promoted by the Pd–BINAP catalytic system.[41,42] The reaction has been effected with vinyl bromides and triflates. Moreover, this novel reaction has allowed preparation of the previously unknown *N*-vinyl sulfoximines **26** (Scheme 14).

The direct synthesis of aldimines **28** by a Pd catalyzed cross-coupling reaction had not been possible due to the instability of the required N–H aldimines. To overcome this limitation we introduced *N*-trialkylsilylimines **27** as partners in metal catalyzed cross-coupling reactions.[43] For this reaction to occur, a nucleophilic additive is required, in order to activate the silyl group and cleave the Si–N bond, much like in the



Scheme 13 Pd catalyzed amidation of alkenyl tosylates.



Scheme 14 Synthesis of the previously unknown vinyl sulfoximines by Pd catalyzed coupling of vinyl bromides with N–H sulfoximines.

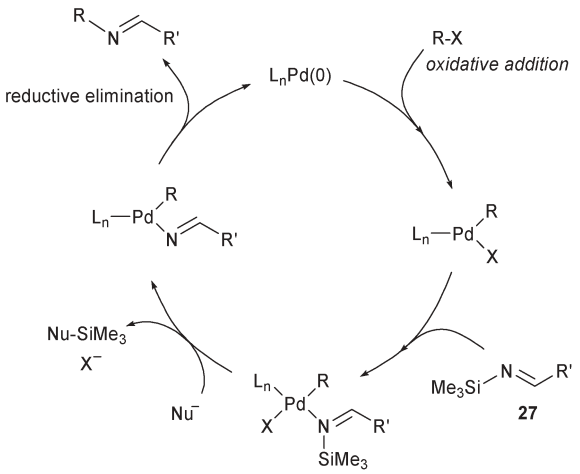
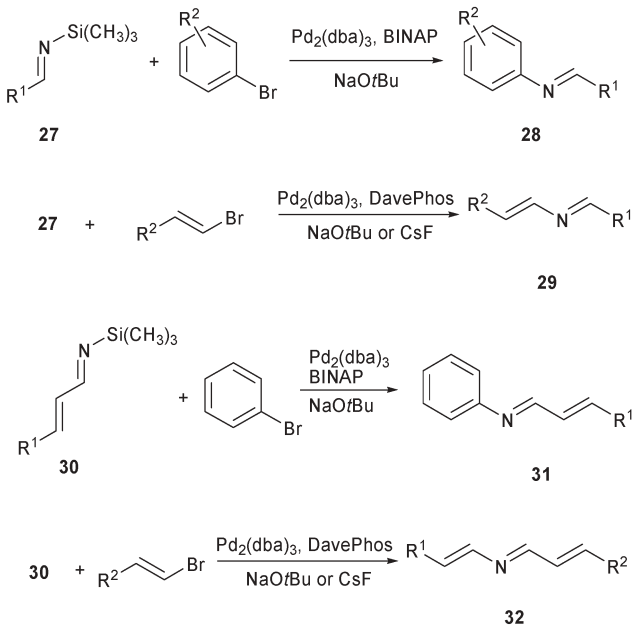


Fig. 7 Proposed catalytic cycle for Pd catalyzed cross-couplings with *N*-methylsilylimines.

transmetallation step of a C–C bond forming process, such as Suzuki or Stille couplings. A simplified sketch of the proposed catalytic cycle is represented in Fig. 7.

The best results were obtained when NaO*t*Bu was used as additive, although in some examples good results were obtained also with CsF. The Pd–BINAP system was the catalyst chosen for the couplings with aryl bromides, while the reaction with vinyl bromides proceeded smoothly with Pd–DavePhos.

The coupling reaction of *N*-silylimines **27** with vinyl bromides gives rise to 2-azadienes **29**, interesting intermediates which are highly reactive in hetero-Diels–Alder cycloadditions.[44] Moreover, if the coupling reaction is conducted with α,β-unsaturated silylimines **30**, 1-azadienes **31** are obtained from the reaction with aryl halides and 2-aza-1,3,5-trienes **32**



Scheme 15 Synthesis of imines **28**, 2-azadienes **29**, 1-azadienes **31** and 2-azatrienes **32** by coupling of *N*-methylsilylimines **27** and **30** with aryl and alkenyl bromides.

from the reaction with vinyl bromides (Scheme 15). These reactions are the first examples of the employment of silylmines in metal catalyzed couplings. We are currently developing further applications of these reagents.

Application of the Pd catalyzed alkenyl amination in heterocyclic synthesis

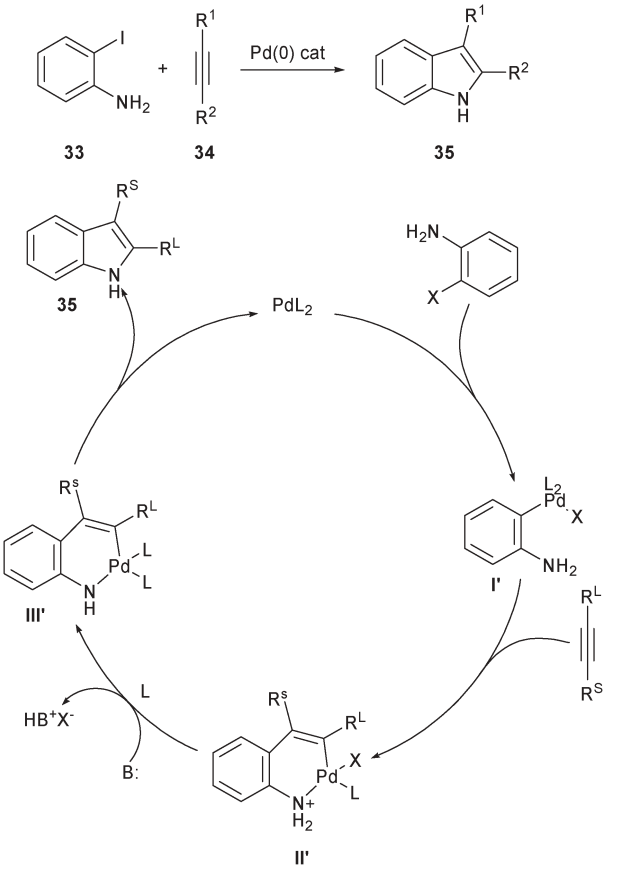
Palladium chemistry has found enormous application in the synthesis of heterocycles, and many examples exist of the construction of different types of heterocyles through a Pd catalyzed cyclization.[45] However, few examples exist of the employment of the amination of an alkenyl halide as a key step in a heterocyclization.[38]

The incorporation of Pd catalyzed alkenyl amination reactions in intramolecular processes should be of great interest in heterocyclic synthesis. Interestingly, the same Pd systems which catalyze the amination reactions also promote other C–C and C–heteroatom forming reactions. Therefore, it should be possible to include the Pd catalyzed alkenyl amination in tandem or cascade processes, which would finally lead to heterocycles.[46] Some examples of this approximation have appeared in very recent literature. Although these methodologies are very promising tools for the preparation of several different classes of heterocycles, the few examples published up until the present have been restricted to the synthesis of the indole ring.

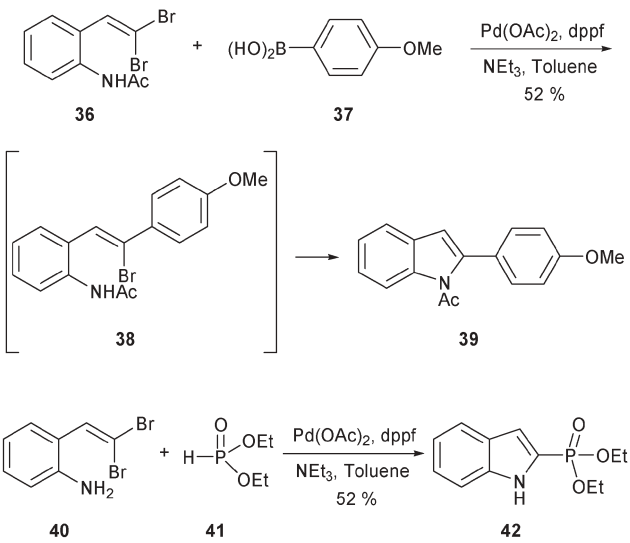
The well-known Pd catalyzed synthesis of indoles by reaction of *o*-haloanilines **33** with internal alkynes **34**—the Larock indole synthesis (Scheme 16)—might be formally regarded as an early example of an intramolecular alkenyl amination reaction applied to heterocyclic chemistry. The textbook mechanism for the Larock indole synthesis involves the following key steps: (i) oxidative addition of the alkenyl halide to the Pd(0) to give arylpalladium complex **I′**. (ii) Alkyne insertion, with formation of a C–C bond, to produce alkenylpalladium complex **II′**. (iii) Deprotonation of the complexed amine by use of base, to furnish paladacycle **III′**. (iv) Reductive elimination, with formation of the C–N bond, to yield indole **35** and regenerate the Pd(0) catalyst. It is noteworthy, that the intermediate **III′** is analogous to the Pd complex **III** (Fig. 2) postulated in the mechanism of the alkenyl amination reactions.

Usually, the Larock indole synthesis is carried out under ligandless conditions. However, the process has been limited to *o*-iodoanilines. In a very recent contribution by Senanayake *et al.*,[47] the scope of the reaction has been extended to *o*-bromo- and *o*-chloroanilines, by using an appropriate supporting ligand for the Pd, that enhances its reactivity towards oxidative addition.

In a process that shares some mechanistic features with the last step of the Larock indole synthesis, *o*-(2,2-dibromovinyl)-aniline **36** has been converted into a 2-substituted indole **39**.[48] The tandem process takes advantage of the different reactivity of the two C–Br bonds towards oxidative addition.[49] Thus, in a first step, Suzuki coupling with substitution of the more reactive *trans*-bromine atom, gives the bromovinyl aniline **38** which undergoes Pd catalyzed intramolecular C–N bond formation (Scheme 17). A similar approach was applied also



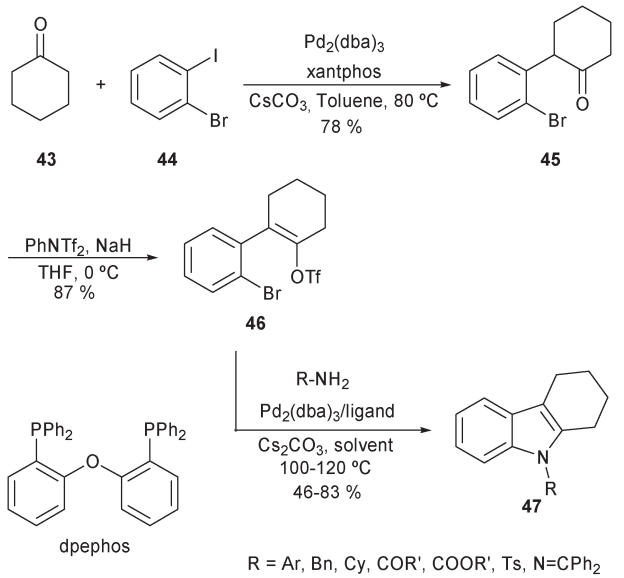
Scheme 16 Larock indole synthesis: mechanistic outline.



Scheme 17 Indole synthesis through a Pd catalyzed tandem "Suzuki reaction–intramolecular alkenyl amination" process.

for the synthesis of phosphonylated 2-indolyl derivative **42**. Moreover, in the same publication, benzofurans were obtained by the same reaction replacing the aniline derivative with a phenol.

An optimization of this strategy for the synthesis of indoles has just been reported by Fang and Lautens.[50] The employment of SPhos as supporting ligand has broadened the scope



Scheme 18 Indole synthesis through a Pd catalyzed tandem "alkenyl amination–aryl amination" sequence.

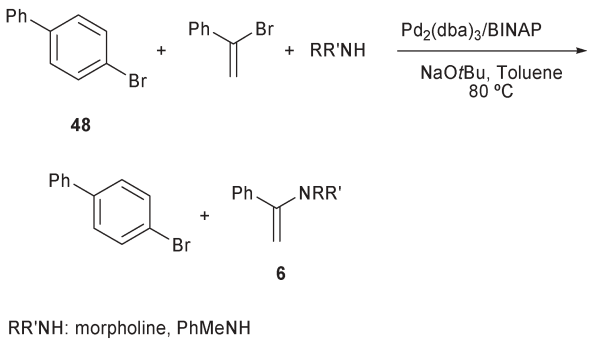
of the tandem process, providing a very general route to the preparation of NH-2-substituted indoles.

Willis *et al.* have uncovered a novel synthesis of the indole ring in a cascade process that involves two Pd catalyzed aminations, an alkenyl amination and an aryl amination.[51] The required bifunctional precursors **46** were prepared from 1-bromo-2-iodobenzene **44** in a two step procedure which included a Pd catalyzed arylation of ketone **43**,[52] followed by formation of an enol triflate using standard procedures (Scheme 18). Under the proper reaction conditions the consecutive amination reactions could be effected to afford the *N*-substituted indoles **47**. The process is very general with respect to the *N*-substituent: aliphatic and aromatic amines, amides, carbamates, sulfonamides, and hydrazones were successfully incorporated.

The $Pd_2(dba)_3$–dpephos catalytic combination provided the best results when the reaction was carried out with amines, while $Pd_2(dba)_3$–XantPhos was identified as the best catalytic system to effect the cyclization with less nucleophilic reagents, such as amides, and carbamates. Structural variations in the bifunctional aromatic precursor led, under the same reaction conditions, to different *N*,2,3-trisubstituted indoles with good yields.

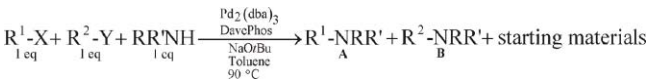
In the course of our studies on the Pd catalyzed amination of alkenyl halides, we observed a remarkable chemoselectivity when various different aryl and alkenyl halides were present. For instance, when an equimolar amount of 1-bromobiphenyl **48** and α-bromostyrene were reacted with one equivalent of an amine, the reaction afforded the corresponding enamine **6** and the unreacted arylbromide (Scheme 19).

Analogous competition experiments were conducted with several alkenyl chlorides and bromides to establish the following reactivity order: alkenyl bromide > aryl bromide > alkenyl chloride > aryl chloride. Interestingly, in every experiment, the reaction proceeded exclusively through the more reactive species (Table 1).[53]



Scheme 19 Selectivity in the alkenyl amination vs the aryl amination.

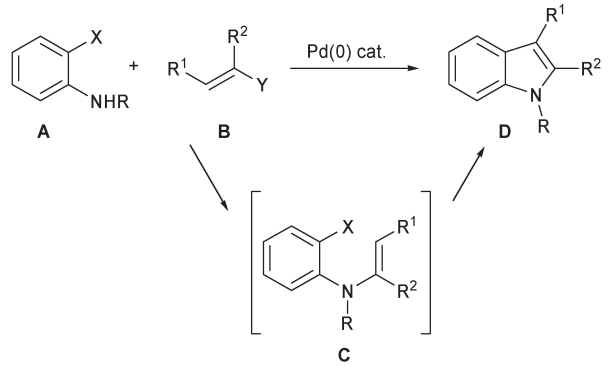
Table 1 Competition experiments in the amination reaction between aryl and alkenyl bromides and chlorides



R^1-X	R^2-Y	Amine	A : B
Ph, Br	Ph, Br	O, NH	>95 : 5
		PhMeNH	>95 : 5
		p-MeO-Bn-NH_2	>95 : 5
Ph, Br	Ph, Cl	O, NH	>95 : 5
		PhMeNH	>95 : 5
		p-MeO-Bn-NH_2	>95 : 5
Ph, Br	Ph, Cl	O, NH	>95 : 5
		PhMeNH	>95 : 5
		p-MeO-Bn-NH_2	>95 : 5
Ph, Cl	Cl	O, NH	>95 : 5
		PhMeNH	>95 : 5
		p-MeO-Bn-NH_2	>95 : 5

The higher reactivity of alkenyl halides when compared with aryl halides towards oxidative addition to Pd(0) centers is a well established fact.[54] Nevertheless, the selectivity observed in our experiments is indeed remarkable. We envisioned that this interesting characteristic of Pd catalyzed aminations could be used to program several cascade Pd catalyzed events, and eventually produce heterocycles.

As a model system to investigate the feasibility of this idea (Scheme 20), we chose the reaction of *o*-haloanilines **A** with alkenyl halides **B**. We anticipated that the initially formed enamine **C** might participate in an intramolecular Heck reaction,[55–58] promoted by the same Pd catalyst, to directly provide a substituted indole **D**.



Scheme 20 Strategy for the synthesis of indoles through a tandem alkenyl aminaton–Heck indolizidation.

Preliminary experiments on the reaction of *o*-bromoaniline **49** with α-bromostyrene were carried out to develop proper conditions for the indolization (Scheme 21). It was observed that the reaction in the presence of BINAP, the ligand of choice for the amination of vinyl bromides, always afforded the imine **50**, with no indole being formed.

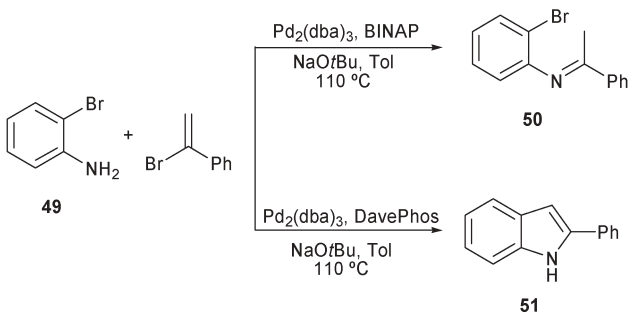
Interestingly, the employment of a more active ligand, such as the bulky electron-rich phosphine DavePhos promoted the indolization with good yield.

The scope of the indolization reaction includes the participation of aryl, alkyl and functionalized geminal bromoalkenes. The employment of *o*-chloroanilines required a new optimization. The tandem process could be achieved only when XPhos was employed as supporting ligand. Under those conditions the indoles **51** are obtained with similar yields to those obtained with *o*-bromoanilines. Selected examples are represented in Scheme 22.

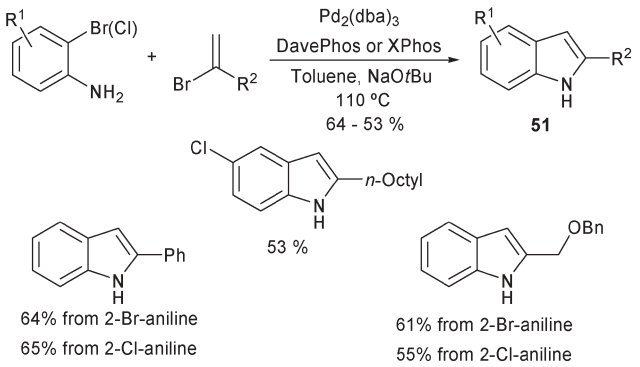
The synthesis of 3-substituted indoles **53** by reaction of 2-substituted bromoalkenes was also possible using the same strategy. However it required the employment of *N*-substituted-*o*-haloanilines **52**. Thus, under similar reaction conditions, the corresponding *N*-alkyl-3-substituted indoles **53** were obtained with yields slightly higher than for the reactions discussed above (Scheme 23).

Summary and outlook

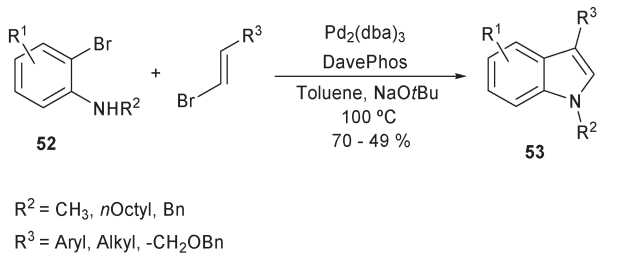
The amination reaction of alkenyl halides and pseudohalides has developed into a very efficient method for the preparation of enamine and imine derivatives. Moreover, the coupling



Scheme 21 Influence of the ligand on the indolization reaction.



Scheme 22 Synthesis of 2-substituted indoles **51** through a tandem alkenyl amination–Heck indolization process.



Scheme 23 Synthesis of *N*,3-disubstituted indoles **53** through a tandem alkenyl amination–Heck indolization process.

products are interesting synthetic intermediates which can participate in further chemical reactions. In this regard, 1-aminodienes, 2-aminodienes and 2-azadienes, versatile reagents for cycloaddition reactions, can be prepared by novel, advantageous and straightforward procedures.

Moreover, particularly interesting results are obtained by the introduction of the alkenyl amination reaction in Pd catalyzed cascade processes, or as a part of a sequence of reactions promoted by a multifunctional catalyst. This approach had not been exploited until very recently. Although few examples are currently known, we believe that strategies based on this principle hold great synthetic potential and further applications will be soon developed.

Acknowledgements

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