EXPLOITING THE AMBIPHILIC NATURE OF σ-ARYLPALLADIUM SPECIES IN THE SYNTHESIS OF HETEROCYCLES: A PERSONAL ACCOUNT

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Abstract. *Palladium-catalyzed chemistry constitutes an important and growing area of research due to its exceptional synthetic versatility and selectivity. Indeed, no other transition metal acts as the catalyst of such a wide range of transformations. This account describes our efforts toward selectively promoting different palladium-catalyzed carbon-carbon bond-forming reactions for the synthesis of azaheterocycles. We have explored alternative ways of controlling the amphiphilic character of σ-arylpalladium species in intramolecular coupling reactions with carbonyl compounds as well as the development of domino processes based on intramolecular palladium-catalyzed α-arylation reactions. Our results show that the outcome of the reaction with a given aryl halide can be finely tuned by adjusting the type of palladium catalyst and reaction conditions. As a consequence, diverse synthetic methodologies were developed to access high added value azahererocycles.*

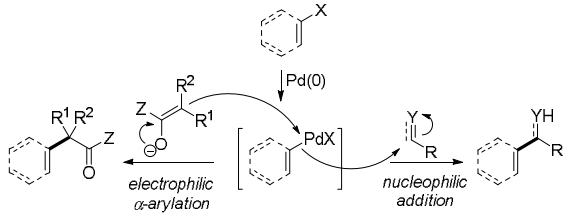
Contents

1. Introduction

The catalytic effectiveness and versatility of palladium have made it a pivotal element in organic synthesis. Indeed, no other transition metal has been used to develop so many reliable carbon-carbon bond-forming reactions.[1] The extremely diverse chemistry of palladium in carbon-carbon bond formation, including the well-known Heck reaction as well as Suzuki and Negishi cross-couplings, is mainly based on the electrophilic nature of transient σ-organopalladium intermediates. Among the different carbon-carbon bond-forming reactions based on the electrophilicity of organopalladium species, the palladium-catalyzed arylation of enolate-type nucleophiles[2-6] has emerged as an extremely powerful tool in organic synthesis. In particular, the intramolecular versions of this reaction have found growing application in the synthesis of complex natural products.[7]

In parallel with the progress in this field, in the last decades it has been demonstrated that the same palladium species can also react with carbon-heteroatom multiple bonds in a nucleophilic manner.[8] In fact, the intramolecular nucleophilic attack of σ-aryl- or σ-vinylpalladium species on the carbonyl group of aldehydes,[9-11] ketones,[12-16] and esters[17] and on the imino,[18-20] cyano,[21] and isocyanate[22] groups has also allowed the development of new reliable catalytic processes.[23]

Our research group has long been interested in finding new ways to increase the versatility of palladium catalysis in carbon-carbon bond-forming reactions,[24] for example, by controlling the amphiphilic character of σ-arylpalladium species in intramolecular coupling reactions with carbonyl compounds (Scheme 1).[25,26] In this account, we review our achievements in the application of different palladium-catalyzed intramolecular coupling reactions of amino-tethered aryl halides developed in our laboratory to the synthesis of azaheterocycles.



Scheme 1. Ambiphilic character of σ-arylpalladium species.

2. Pd-catalyzed intramolecular coupling of amino-tethered aryl halides and ketones

2.1. α-Arylation

About twenty years ago, as part of our ongoing program on the synthesis of natural products, we became interested in exploring the palladium-catalyzed intramolecular coupling of aryl halides and ketone enolates as a methodology for the synthesis of nitrogen heterocycles. Our initial efforts were focused on the synthesis of the hexahydro-2,6-methano-1-benzazocine framework, which is a bridged ring system present in natural products such as aspernomine[27] and strychnochromine (Figure 1).[28]

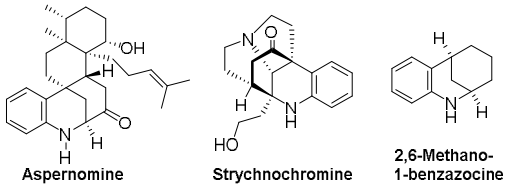


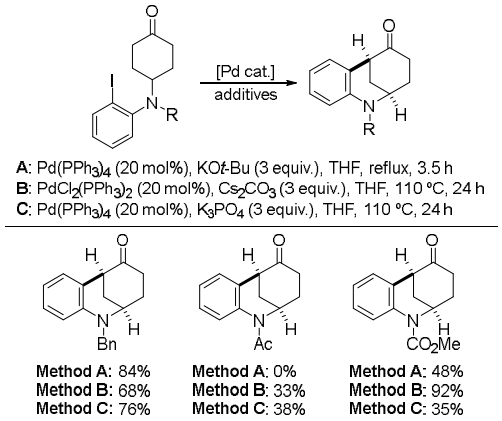
Figure 1. Natural products containing the hexahydro-2,6-methano-1-benzazocine core.

A variety of reactions were run to investigate the synthesis of this bridged tricyclic system. From these studies, we established three general reaction procedures (Methods A, B and C) for the intramolecular α-arylation of 2-iodoanilines, which were based on the use of KO*t*-Bu, Cs_2CO_3 or K_3PO_4 as the base, respectively (Scheme 2).[29-31] Whereas no significant effect was observed when the halide was changed from iodide to bromide, varying the substituent at the nitrogen atom had a marked impact on cyclization. As can be seen, the *N*-benzyl derivative exhibited the highest efficiency in the intramolecular coupling and the least satisfactory results were obtained with the 2-iodoacetanilide.

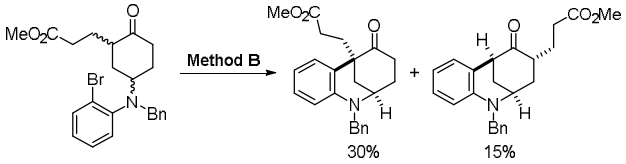
With this information in hand, we decided to investigate the regioselectivity of the palladium-catalyzed α-arylation in a cyclohexanone with both an enolizable methylene and a methine group. Unfortunately, only moderate selectivity towards the α-arylation at the methine position was observed, the best results arising from the reaction conditions of Method B (Scheme 3).

Once we had developed a set of reaction conditions for the intramolecular ketone α-arylation, we planned to extend the carbocyclization process to the construction of other azaheterocyclic systems by

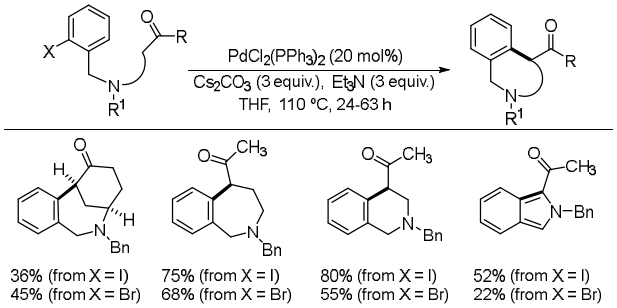
varying the relative position of the (2-haloaryl) moiety and the ketone carbonyl group.[32,33] We began by studying the intramolecular coupling of (2-halobenzyl)amino ketone derivatives (Scheme 4),[33] which under the reaction conditions of Method A, using KO*t*-Bu as the base, failed to give any cyclization product. In contrast, when the palladium-catalyzed reactions were run using Cs_2CO_3 as the base (Method B), either γ-, β- or α-(2-halobenzylamino) ketones successfully afforded the corresponding α-arylation compounds in moderate to good yields, with the respective formation of seven-, six- and five-membered rings. In general, aryl bromides gave less satisfactory results than iodides. Interestingly, the reaction of the α-(2-halobenzylamino) ketones directly afforded the corresponding isoindoles, resulting from the dehydrogenation under the reaction conditions leading to the initially formed α-arylation product. The use of K_3PO_4 as the base (Method C) also resulted in α-arylation, albeit with lower yields.



Scheme 2. Synthesis of hexahydro-2,6-methano-1-benzazocines.



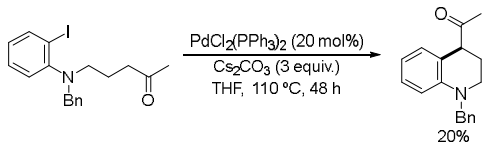
Scheme 3. Synthesis of hexahydro-2,6-methano-1-benzazocines.



Scheme 4. α-Arylation of (2-halobenzyl)amino ketones.

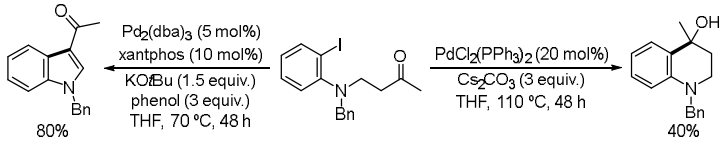
Continuing with our studies on the α-arylation of amino-tethered ketones, we returned to the reaction of 2-iodoaniline derivatives. In sharp contrast with (2-halobenzyl)amino ketones, (2-haloanilino) ketones showed a remarkable structure-dependent reactivity.[32,33] Thus, for example, the palladium-catalyzed reaction

of the linear γ-(2-iodoanilino) ketone in the presence of Cs_2CO_3 afforded the corresponding quinoline, although in low yield (Scheme 5).



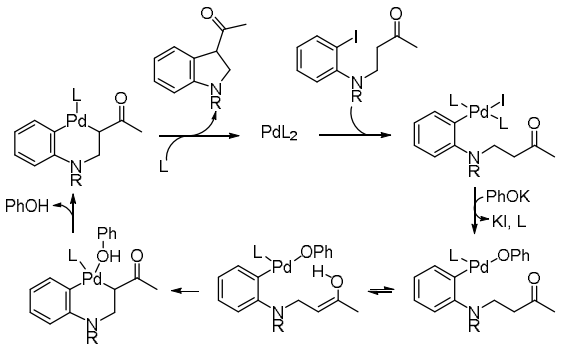
Scheme 5. α-Arylation of γ-(2-iodoanilino) ketones.

By contrast, under the same reaction conditions, the β-(2-iodoanilino) ketone afforded the alcohol arising from the nucleophilic addition of the transient σ-arylpalladium(II) intermediate at the carbonyl group (Scheme 6). However, we were able to overcome the nucleophilic attack at the carbonyl and favor the α-arylation reaction by using xantphos as the ligand and potassium phenoxide as the base, generated *in situ* by reaction of phenol with KO*t*-Bu.[34,35]



Scheme 6. α-Arylation of β-(2-iodoanilino) ketones.

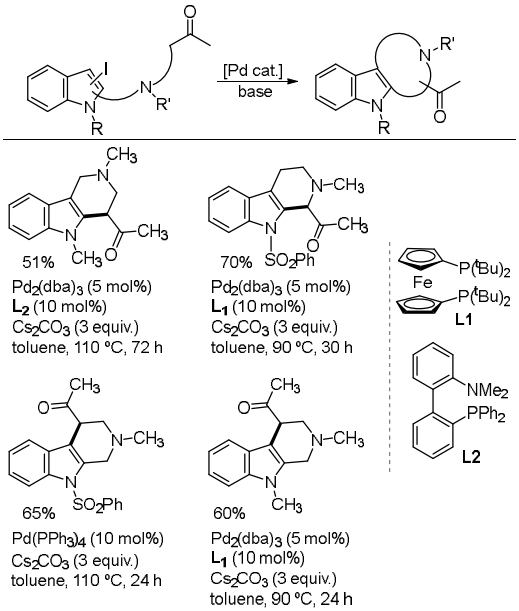
We had already observed the effectiveness of using potassium phenoxide as the base to promote the palladium-catalyzed intramolecular coupling of amino-tethered vinyl halides with enolate-type nucleophiles.[36,37] The role of the PhO^- anion in the α-arylation reaction was suggested by means of computational studies.[25,34] According to our calculations, the reaction would start from the σ-arylpalladium(II) intermediate, initially generated by oxidative addition of the aryl iodide to the Pd(0) catalyst. Replacement of the iodide ligand by the PhO^- anion would afford a σ-arylpalladium(II) phenoxide complex. From this intermediate, base-mediated enolization and subsequent intramolecular proton transfer from the enol moiety to the phenoxy ligand would lead to the formation of a palladium enolate species, which bears PhOH as the ligand. After dissociation of this weakly coordinated ligand, a reductive elimination reaction would give the corresponding indoline and release the active catalytic species (Scheme 7).



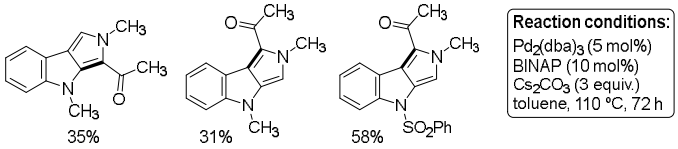
Scheme 7. Mechanism of the α-arylation in the presence of PhOK.

Indole-*b*-fused nitrogen heterocycles are the basic structural units of a variety of natural products and synthetic biologically active compounds.[38] In consequence, although they can be accessed by numerous

methods, the development of new strategies for their synthesis continues to be a very active area of research.[39] Encouraged by the success of our studies with ketones, we were interested to see whether the palladium-catalyzed intramolecular ketone α-arylation of 2- and 3-iodoindole substrates could be used to prepare diversely substituted *b*-annelated indoles. Gratifyingly, by means of this methodology we were able to synthesize tetrahydro-β-carbolines, tetrahydro-γ-carbolines (Scheme 8), and pyrrolo[3,4-*b*]indoles (Scheme 9) with acceptable yields, the latter being formed by a sequential palladium-catalyzed α-arylation-dehydrogenation reaction.[40] As previously observed in the reactions of (2-halobenzyl)amino ketones,[33] Cs_2CO_3 is also the most suitable base for the α-arylation processes of amino-tethered iodoindoles with ketones. Optimization of the solvent revealed that the reaction could be carried out in either toluene or THF, the latter usually giving inferior results. Regarding the ligand, the phosphine of choice for annulation reactions is highly substrate-dependent. Thus, while different phosphines were successfully used in the preparation of tetrahydrocarbolines, BINAP proved to be the most efficient ligand for the synthesis of pyrrolo[3,4-*b*]indoles.



Scheme 8. Synthesis of tetrahydrocarbolines.

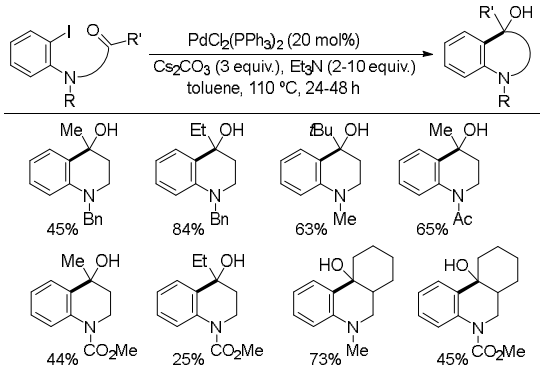


Scheme 9. Synthesis of pyrrolo[3,4-*b*]indoles.

2.2. Carbonyl addition

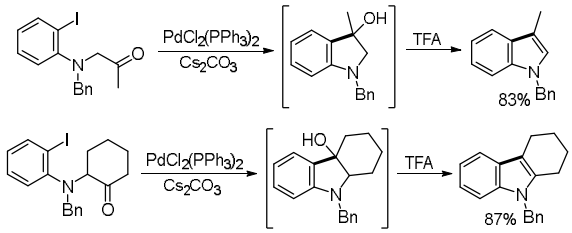
As previously mentioned, during our studies on the palladium-catalyzed α-arylation of amino-tethered ketones we observed that β-(2-iodoanilino) ketones showed an anomalous behavior, as they easily changed the reaction pathway from the expected α-arylation to the addition at the carbonyl group (Scheme 6). We therefore decided to study the palladium-catalyzed nucleophilic addition of aryl halides to ketones in more depth to ascertain its feasibility for the synthesis of azaheterocycles.[41,42]

During the course of the optimization studies, we found that the nucleophilic addition reaction requires a salt rather than a base. Thus, while the use of K_2CO_3 gave similar results to Cs_2CO_3, no reaction took place when Et_3N was used alone. Interestingly, however, the best results were obtained with a combination of Cs_2CO_3 and Et_3N in toluene at high temperature.[33] Under the optimized reaction conditions, the palladium-catalyzed intramolecular addition to the carbonyl proceeded smoothly from a variety of β-(2-iodoanilino) ketones to give the corresponding tetrahydroquinolinols in moderate to good yields (Scheme 10). The presence of electron-withdrawing groups (CO_2Me and Ac) at the aniline nitrogen was tolerated, although the transformation was less efficient.



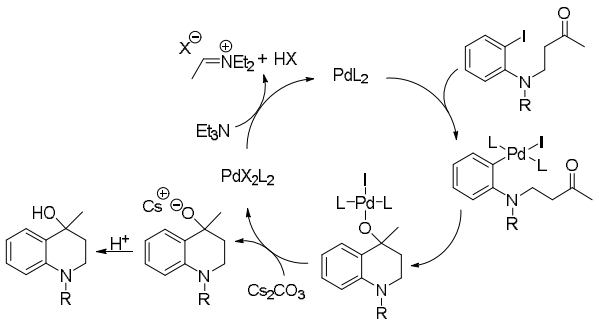
Scheme 10. Synthesis of tetrahydroquinolin-4-ols.

The intramolecular addition to the carbonyl was not limited to β-(2-iodoanilino) ketones, but also proved suitable for α-(2-iodoanilino) ketones. In this case, the resulting alcohols were converted to the corresponding indoles without previous isolation by treatment with TFA (Scheme 11).



Scheme 11. Synthesis of indole derivatives.

These studies also helped to clarify some of the mechanistic steps of the palladium-catalyzed addition to the carbonyl, as shown in Scheme 12. The oxidative addition of the aryl iodide to the Pd(0) catalyst would give a σ-arylpalladium(II) intermediate, which would undergo carbopalladation with the ketone carbonyl to afford a Pd(II) alkoxide. The catalytic cycle requires the presence of a salt (K_2CO_3 or Cs_2CO_3) able to undergo transmetallation with the oxypalladium intermediate to a give a potassium or cesium alkoxide, which would then afford the corresponding alcohol by protonolysis during the workup.[43] Regeneration of the Pd(0) catalyst depends on the reduction of the Pd(II) species obtained in the transmetallation step. The isolation of considerable amounts of γ-butyrolactone when the reaction was carried out in THF proved that a redox process had taken place. Alternatively, in the presence of Et_3N, using either THF or toluene, the tertiary amine would act as the reductant in the regeneration of the Pd(0) catalyst.



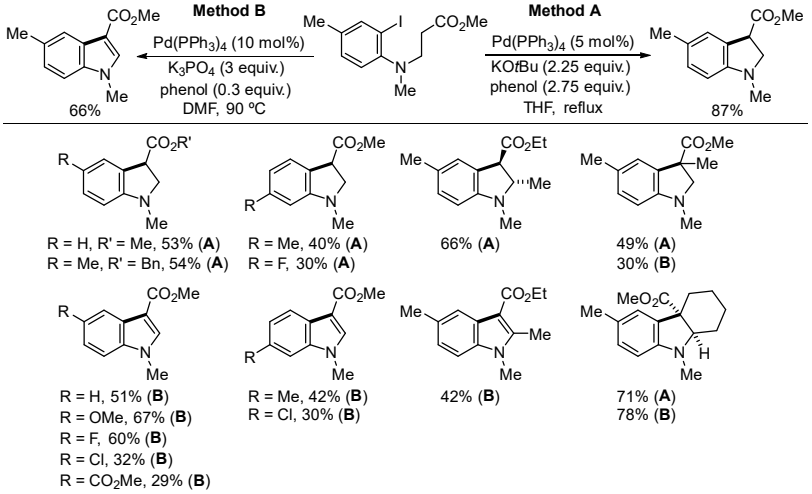
Scheme 12. Mechanism of the palladium-catalyzed nucleophilic addition of aryl halides to ketones.

3. Pd-catalyzed intramolecular coupling of amino-tethered aryl halides and esters

3.1. α-Arylation

The indole nucleus is a ubiquitous motif in bioactive natural products as well as synthetic pharmaceuticals.[44] Accordingly, after a hundred years of intensive research, a variety of well-established methods for elaborating and functionalizing indoles are now available. In particular, recent advances in the area of palladium-catalyzed transformations have led to the development of several reliable methods for the synthesis of indoles from simple starting materials.[45,46]

Continuing our investigations on the intramolecular palladium-catalyzed α-arylation of carbonyl compounds, we turned our attention to the coupling of β-(2-haloanilino) esters[47] with the aim of developing a new methodology for the synthesis of indoles. Starting from these esters, we established two alternative procedures for the α-arylation reaction (Scheme 13).[48] Method A, using PhOK (2.25 equiv.) as the base, generated *in situ* by reaction of phenol with KO*t*-Bu, leads to the formation of indolines. Alternatively, Method B, in which K_3PO_4 is used as the base together with a catalytic amount of phenol, furnishes the corresponding indoles by a sequential palladium-catalyzed α-arylation-dehydrogenation reaction.

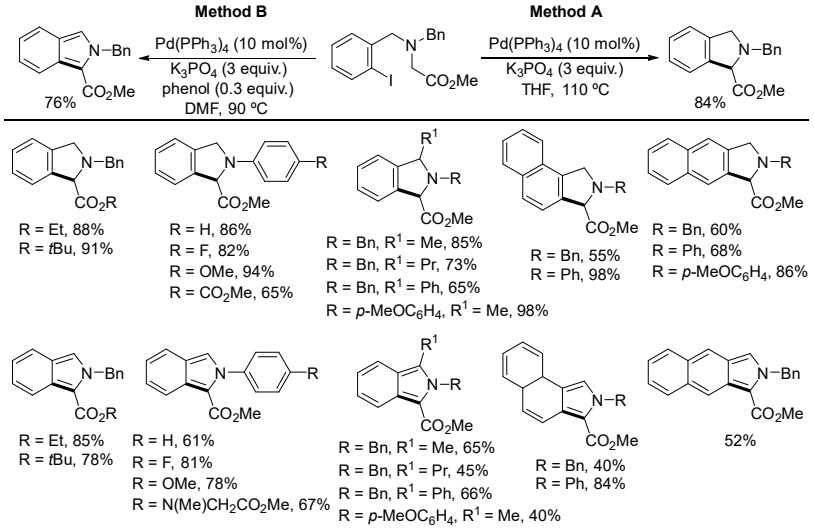


Scheme 13. Synthesis of indole-3-carboxylic acid ester derivatives.

As shown in Scheme 13, both reactions were applied to iodoanilines with different electronic properties on the aromatic ring. It was found that, in general, the substrates with electron-withdrawing groups at the arene ring underwent the α-arylation reaction with lower yields than those obtained from

iodoanilines with electron-neutral or electron-donating groups. A high tendency to undergo aerobic oxidation to the corresponding indoles would explain why 3-monosubstituted indolines were only obtained in moderate yields under the reaction conditions of Method A. Thus, for example, when starting from the aniline with a *para*-MeO substituent, although the proton NMR analysis of the reaction crude indicated an indoline formation of approximately 80% yield, during the purification it was completely oxidized to the corresponding indole. Other substrates, such as the 4-fluoro-2-iodoaniline, directly afforded the indole. In contrast, the reaction conditions of method A were successfully applied for the preparation of 2,3- and 3,3-disubstituted and 2,3,3-trisubstituted indolines. Our computational studies showed that, similarly to the α-arylation of ketones in the presence of PhOK, the formation of a transient σ-arylpalladium(II) phenoxide intermediate is crucial for the α-arylation of β-(2-haloanilino) esters.[34]

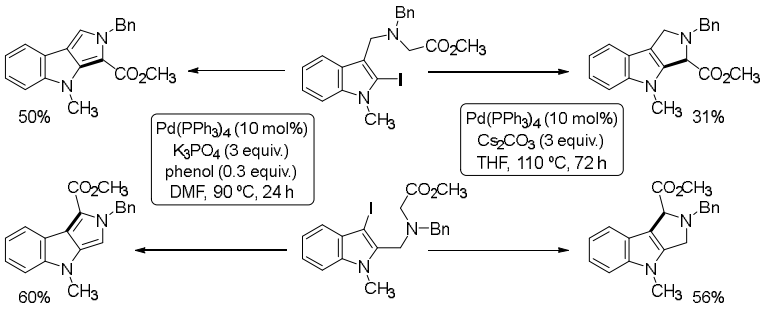
The success of the above α-arylation reactions prompted us to investigate the synthesis of isoindole derivatives using similarly designed reaction conditions. The isoindole moiety and its reduced counterpart isoindoline (2,3-dihydro-1*H*-isoindole) have become attractive targets in organic and medicinal chemistry. These heterocyclic frameworks are an integral part of the structure of some biologically active and naturally occurring compounds. Moreover, isoindoles have been widely used for their high level of reactivity in cycloaddition reactions[49] and their fluorescent and electroluminescent properties,[50,51] which make them suitable candidates for organic light-emitting devices. The optimization studies provided us with two different procedures for the cyclization reactions of α-(2-halobenzylamino) esters (Scheme 14).[52,53] Thus, while the use of $Pd(PPh_3)_4$ (10 mol%) in combination with K_3PO_4 (3 equiv.) in THF at 110 ºC (Method A) gave the isoindoline, the use of $Pd(PPh_3)_4$ and K_3PO_4 together with a catalytic amount of phenol (0.3 equiv.) in DMF at 90 ºC (Method B) afforded the corresponding isoindole, which arises from the *in situ* palladium-catalyzed dehydrogenation of the initially formed isoindoline.



Scheme 14. Synthesis of isoindoles and isoindolines.

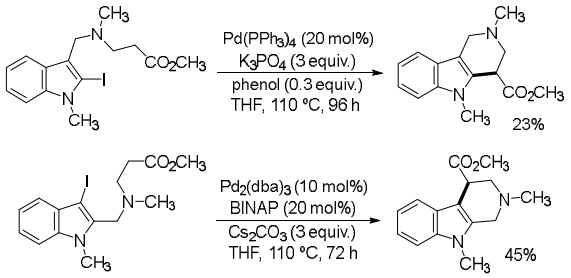
The scope and functional group tolerance of these arylation reactions were demonstrated by preparing a variety of *N*-aryl and *N*-benzyl substituted isoindoles and isoindolines. Methyl, ethyl and *tert*-butyl esters were used as substrates in these reactions. Both cyclization methods were successfully applied not only for the synthesis of isoindole-1-carboxylic acid ester derivatives, but also for the preparation of 1,3-disubstituted substrates and benzo-fused derivatives.

Moreover, both α-arylation protocols were used with iodoindole-derived α-aminoesters, which allowed us to selectively prepare pyrrolo[3,4-*b*]indoles or their dihydro derivatives (Scheme 15).[40]



Scheme 15. Synthesis of pyrrolo[3,4-*b*]indoles.

We also extended the studies on the intramolecular α-arylation of iodoindoles to β-aminoesters in order to prepare tetrahydrocarbolines. However, these esters proved more reluctant to undergo α-arylation and afforded the cyclization products in low yields (Scheme 16).[40]

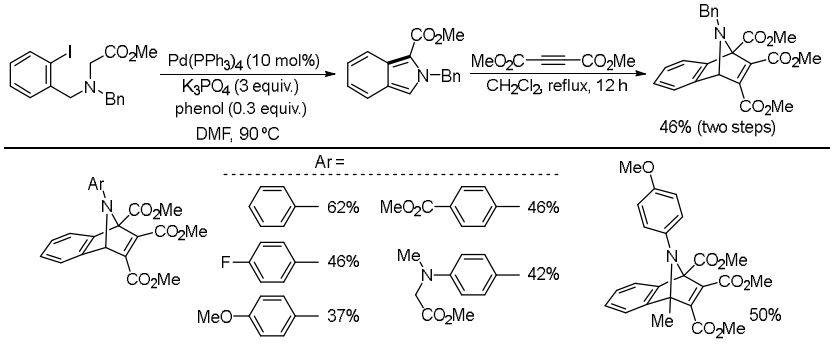


Scheme 16. Synthesis of tetrahydrocarbolines.

3.2. Sequential α-arylation/Diels Alder reaction

Owing to the high level of reactivity of isoindoles in cycloaddition reactions, we also decided to explore the development of a sequential ester-α-arylation/Diels-Alder reaction as a methodology to create more complex and diverse scaffolds starting from the readily accessible α-aminoesters.

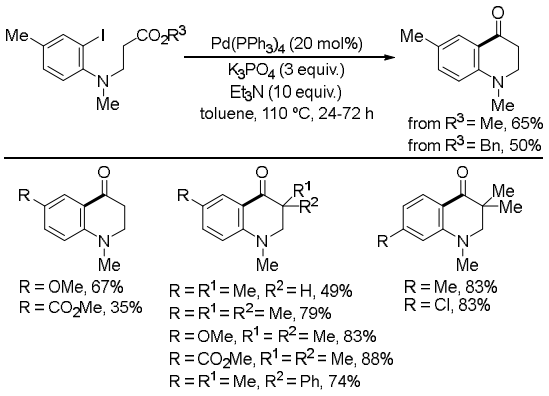
To this end, after α-arylation of the esters under the reaction conditions of Method B, the resulting isoindoles were treated with dimethyl acetylenedicarboxylate. As shown in Scheme 17, both *N*-benzyl and *N*-aryl substituted α-amino esters were successfully used as substrates in this reaction, which afforded the bridged cycloadducts in moderate to good yields.[54]



Scheme 17. Synthesis of bridged heterocycles by sequential α-arylation/Diels-Alder reaction.

3.3. Acylation

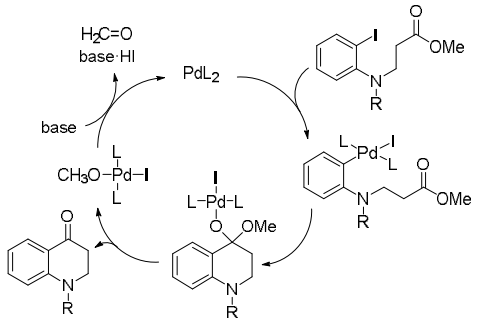
Having successfully controlled the ambiphilic character of σ-arylpalladium species in their intramolecular reactions with ketones, we decided to attempt the same with esters, hoping to force the nucleophilic attack of the σ-arylpalladium intermediates to the ester carbonyl group while overcoming the α-arylation reaction. After optimization studies, we found that the substitution reaction at the alkoxycarbonyl group on β-(2-iodoanilino) esters can be successfully promoted when using $Pd(PPh_3)_4$ as the catalyst and K_3PO_4 as the base in toluene at 110 ºC (Scheme 18).[55] When comparing these reaction conditions with those previously used for the α-arylation of the same β-(2-iodoanilino) esters, the crucial role of the phenoxide anion in the α-arylation reactions is once again evident.



Scheme 18. Synthesis of dihydroquinolin-4-ones by palladium-catalyzed acylation with esters.

A range of differently substituted dihydroquinolin-4-ones were synthesized under the optimized reaction conditions. In general, substituents on the aromatic ring were found to have little effect on the success of the carbopalladation reaction, suggesting that the nucleophilicity of the arylpalladium species is not affected by the electronic properties of the substituent. The reaction of amino esters without hydrogen atoms α to the carbonyl group proceeded smoothly to give the corresponding ketones in high yields.

According to our computational studies, the acylation reaction with esters proceeds through a mechanism involving carbopalladation between the σ-arylpalladium moiety and the alkoxycarbonyl group to give a Pd(II) alkoxide. A subsequent β-alkoxide elimination reaction affords the ketone and a Pd(II) methoxide complex. This species would finally undergo β-hydride elimination to give formaldehyde and regenerate the Pd(0) catalyst (Scheme 19).[34,55]

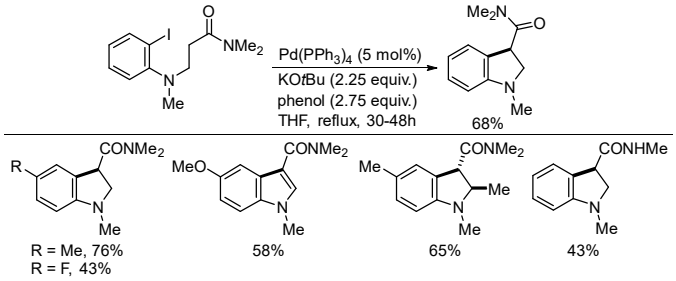


Scheme 19. Mechanism of the palladium-catalyzed acylation with esters.

4. Pd-catalyzed intramolecular coupling of amino-tethered aryl halides and amides

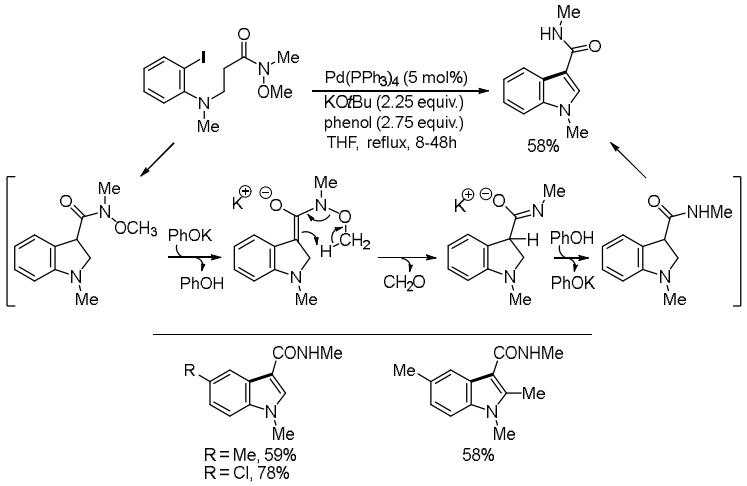
4.1. α-Arylation

The palladium-catalyzed α-arylation of carbonyl compounds was also extended to β-(2-iodoanilino) carboxamides.[56] As shown in Scheme 20, the conditions we previously employed in the intramolecular arylation of amino-tethered esters, using 5 mol% of $Pd(PPh_3)_4$ and 2.25 equivalents of PhOK in refluxing THF, also allowed carboxamides to undergo the α-arylation to afford the corresponding indolines. These indolines could be isolated and characterized, except when bearing a methoxy group, which promoted aerobic oxidation during the purification process to give the corresponding indole.



Scheme 20. Synthesis of indole-3-carboxamides.

Under the same reaction conditions, indoles were obtained by the palladium-catalyzed α-arylation of Weinreb amides through a sequential process of α-arylation, demethoxylation of the Weinreb amide and dehydrogenation (Scheme 21).

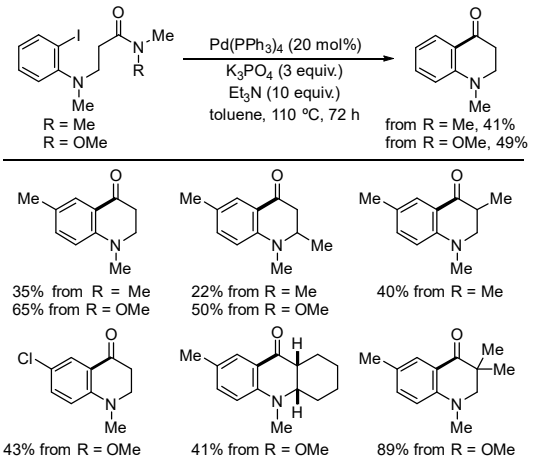


Scheme 21. Synthesis of indole-3-carboxamides.

4.2. Acylation

The carbamoyl group has been traditionally considered inert toward organopalladium reagents. One would therefore expect that the lower electrophilic character of the amide carbonyl group could hinder the nucleophilic attack of the σ-arylpalladium intermediate. However, using the same reaction conditions we had developed for the acylation reactions with esters, it was possible to promote the nucleophilic substitution at the carbamoyl group of both amides and Weinreb amides (Scheme 22).[56] Interestingly, Weinreb amides

afforded better results than *N*,*N*-dimethyl amides in the acylation reaction, which very likely proceeds through a mechanism similar to that proposed for the palladium-catalyzed acylation with esters.

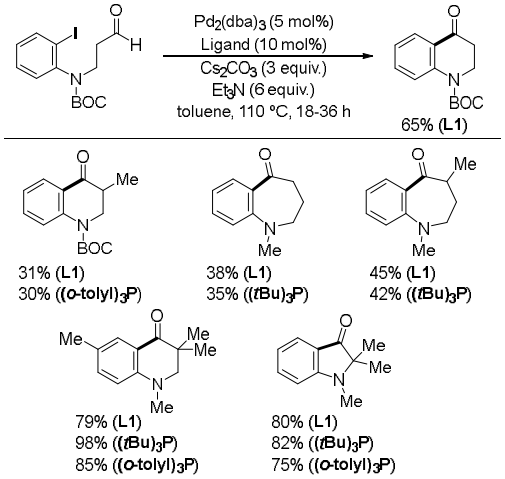


Scheme 22. Synthesis of dihydroquinolin-4-ones by palladium-catalyzed acylation with amides.

5. Pd-catalyzed intramolecular coupling of amino-tethered aryl halides and aldehydes

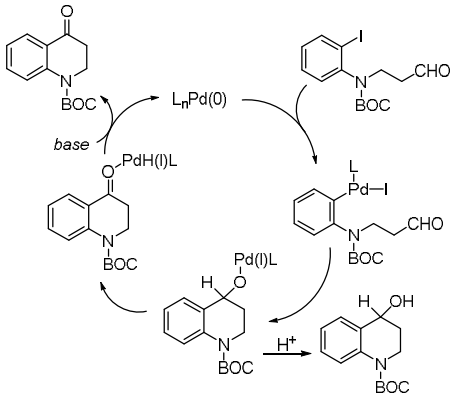
5.1. Acylation

Our work on the versatility of σ-arylpalladium species was also extended to the intramolecular coupling reactions of amino-tethered aryl halides and aldehydes. It was found that the nucleophilic attack to the carbonyl group, which also resulted in an acylation process,[57-59] was the preferred pathway of these substrates when using bulky monodentate phosphines as the ligands (Scheme 23).[60] The acylation with aldehydes was successfully promoted starting from α-, β-, or γ-(anilino)aldehydes to give five-, six-, and seven-membered rings, respectively. The aminoaldehydes without hydrogen atoms α to the carbonyl group smoothly underwent acylation to afford the corresponding ketones in high yields.



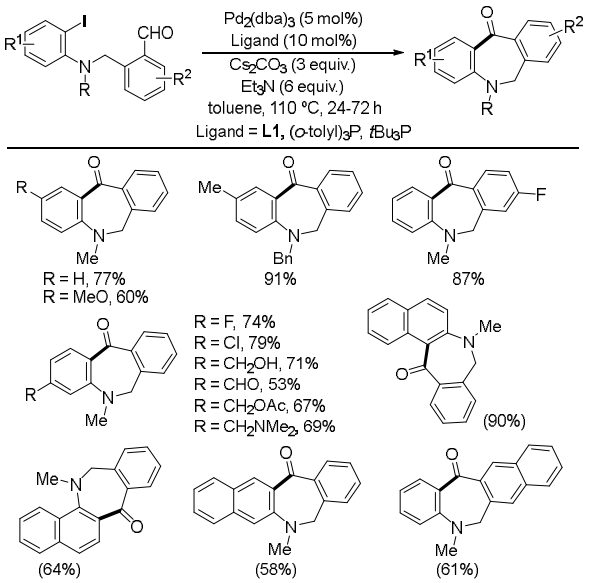
Scheme 23. Palladium-catalyzed acylation with aldehydes.

Our experimental and computational studies allowed us to establish the mechanism of this acylation. The reaction would involve the initial carbopalladation between the σ-arylpalladium(II) species and the carbonyl group to give a Pd(II) alkoxide. β-hydride elimination from the latter would afford the ketone and regenerate the Pd(0) catalyst (Scheme 24). This nucleophilic addition mechanism was supported by the isolation of minor amounts of the alcohol in some of the optimization reactions, which arises from the competitive protonation of the transient palladium(II) alkoxide intermediate. In a recent comparative study of the palladium-catalyzed intramolecular reactions of aryl iodides and aldehydes with N, O and S tethers, we have shown that, regardless of the nature of the heteroatom, the acylation leading to the ketone always follows the same nucleophilic addition mechanism.[61]



Scheme 24. Mechanism of the palladium-catalyzed acylation with aldehydes.

To further demonstrate the potential of the palladium-catalyzed acylation with aldehydes, we explored the reaction as a methodology for the synthesis of polycyclic compounds containing the dibenzo[*b*,*e*]azepine moiety (Scheme 25).[62]

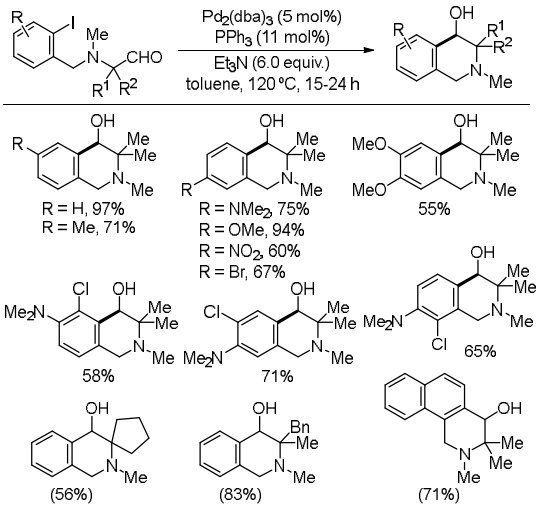


Scheme 25. Synthesis of dibenzo[*b*,*e*]azepin-11-ones by palladium-catalyzed acylation with aldehydes.

The synthesis of dibenzo[*b*,*e*]azepines was successfully accomplished using the previously optimized reaction conditions. In general, the introduction of substituents on the aniline ring had little effect on the success of the acylation reaction. Once again, the nucleophilicity of the aryl palladium intermediate did not appear to be significantly affected by the electronic properties of the substituent on the aromatic ring.

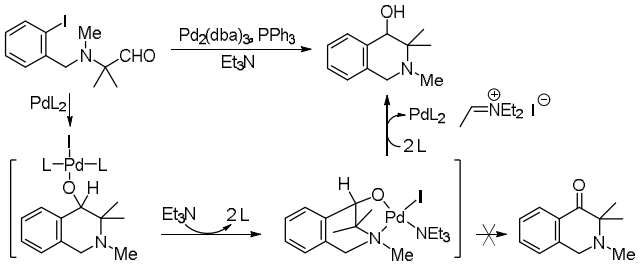
5.2. Nucleophilic addition

We also developed an efficient protocol for the synthesis of tetrahydroisoquinolin-4-ols by means of the palladium-catalyzed intramolecular nucleophilic addition of aryl halides to aldehydes (Scheme 26).[63] The examples presented in Scheme 24 demonstrate the generality and functional group tolerance of the reaction. Overall, the introduction of substituents on the aromatic ring had little influence on the success of the reaction. Thus, aldehydes bearing electron-donating or electron-withdrawing groups, or a combination of both, on the aromatic ring afforded the corresponding nucleophilic addition alcohols in good yields.



Scheme 26. Synthesis of isoquinolin-4-ols by palladium-catalyzed nucleophilic addition to aldehydes.

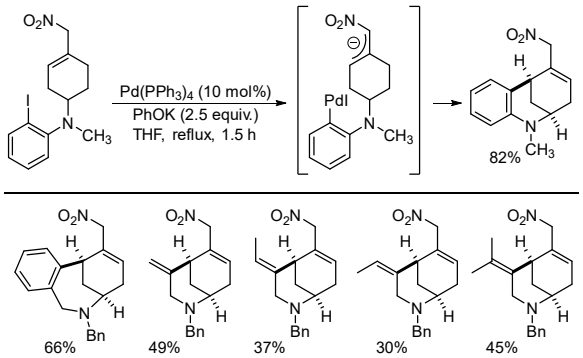
The optimization studies of the reaction demonstrated that the use of Et_3N as the base is essential for the formation of tetrahydroisoquinolinols. Our DFT calculations showed that after the initial oxidative addition and nucleophilic addition at the carbonyl steps, the resulting palladium alkoxide evolves through the coordination of the inner nitrogen atom to the transition metal to give a chelated palladium alkoxide. This intramolecular coordination hinders the β-hydride elimination that would lead to the corresponding ketone. Instead, a reductive protonation process mediated by the weakly coordinated Et_3N ligand renders the corresponding alcohol and regenerates the Pd(0) catalyst (Scheme 27).



Scheme 27. Mechanism of the palladium-catalyzed nucleophilic addition.

6. Pd-catalyzed intramolecular coupling of amino-tethered aryl/vinyl halides and β,γ-unsaturated nitronates

Continuing our search for alternative nucleophiles for the palladium-catalyzed intramolecular α-arylation reaction, we decided to explore the feasibility of using an α,β-unsaturated nitronate, the anion derived from an allylic nitro compound, as the nucleophilic counterpart. As shown in Scheme 28, both aryl and vinyl halides effectively underwent intramolecular coupling with amino-tethered allylic nitro moieties in the presence of $Pd(PPh_3)_4$ and PhOK. The reaction constitutes a useful methodology for the synthesis of bridged nitrogen-containing systems.[64]



Scheme 28. Pd-catalyzed intramolecular coupling with β,γ-unsaturated nitronates.

7. Pd-catalyzed intramolecular α-arylation of amino-tethered aryl halides and sulfonyl derivatives

7.1. Domino reactions leading to tetrahydroisoquinolines

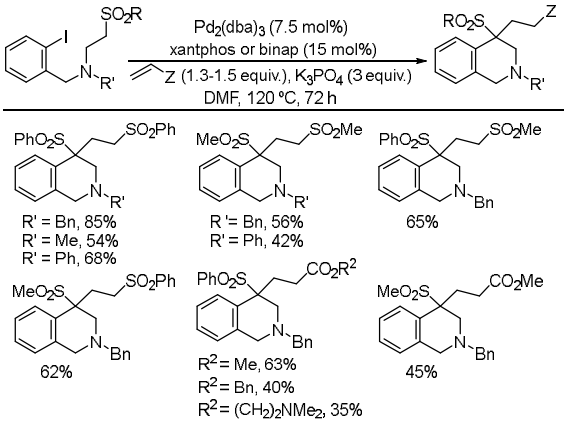
The sulfone is a ubiquitous organic structural motif often used as an auxiliary group in powerful synthetic methodologies, in which the sulfonyl group usually acts as an electron-withdrawing moiety, facilitating the deprotonation of a neighboring carbon atom. Nevertheless, examples of palladium-catalyzed α-arylation of sulfones are scarce, probably due to the higher pK_as of the sulfonyl α-C-H acid, and they are limited to intermolecular processes.[65-67]

To generalize the application of the intramolecular α-arylation reaction to the synthesis of azaheterocycles, we tested the use of sulfones as the nucleophilic counterpart and developed a set of domino processes that combine the intramolecular sulfone α-arylation with Michael addition reactions.

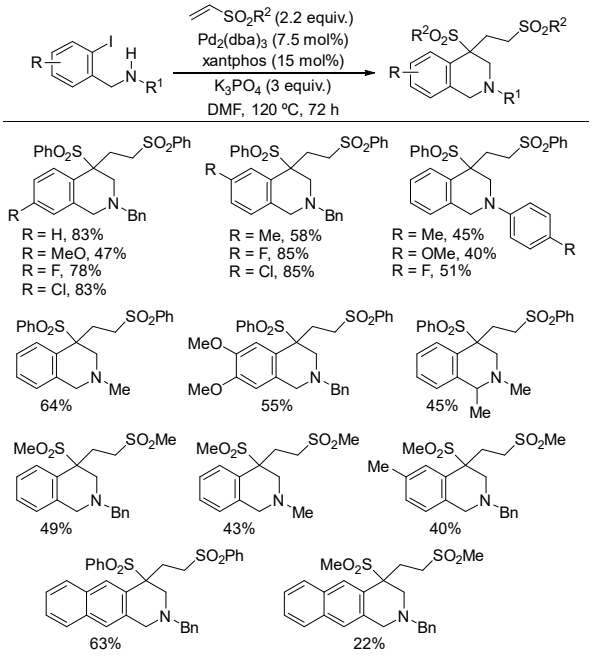
Our first goal was the development of a tandem intramolecular α-arylation/Michael addition reaction to prepare tetrahydroisoquinolines (Scheme 29).[68] We devised an efficient two-step domino reaction in which either phenyl or methyl sulfones were used as nucleophiles and phenyl vinyl sulfone, methyl vinyl sulfone and some acrylic acid esters were successfully employed as Michael acceptors. The best results were obtained when the reaction was performed in DMF, using K_3PO_4 as the base and a combination of $Pd_2(dba)_3$ with either xantphos or binap as the catalyst. The "crossed" tandem processes leading to orthogonally-substituted disulfones and sulfone-containing esters were especially interesting due to the generation of diverse highly functionalized tetrahydroisoquinolines.

In order to simplify the synthesis of disulfones bearing the same substituent at both sulfone moieties, we also developed a three-step domino aza-Michael addition/α-arylation/Michael addition reaction starting from the readily available *N*-alkyl-2-iodobenzylamines (Scheme 30). This process generates a high level of molecular complexity in one operation, minimizing the expenditure of solvents, reagents, time, and energy. The novel domino reaction proceeded smoothly with the use of 2.2 equivalents of vinyl sulfone in the presence of K_3PO_4 and the catalyst $Pd_2(dba)_3$/xantphos. Its scope and functional group tolerance are illustrated by the examples in Scheme 30. Overall, phenyl sulfones afforded better results than methyl sulfones as also observed in the two-step domino processes. The higher acidity of the α-C-H bonds of the phenyl sulfone favors both the α-arylation and the Michael addition, while the higher electrophilicity of phenyl vinyl sulfone benefits the Michael addition reactions. The three-step domino reaction proceeded

smoothly from 2-iodobenzylamines bearing either electron-donating or electron-withdrawing groups on the aromatic ring, the latter affording higher yields.

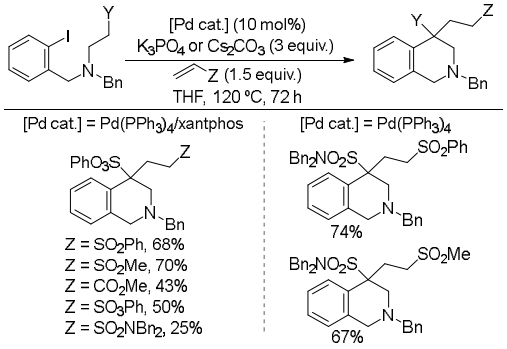


Scheme 29. Synthesis of tetrahydroisoquinolines by two-step domino processes.



Scheme 30. Synthesis of tetrahydroisoquinolines by three-step domino processes.

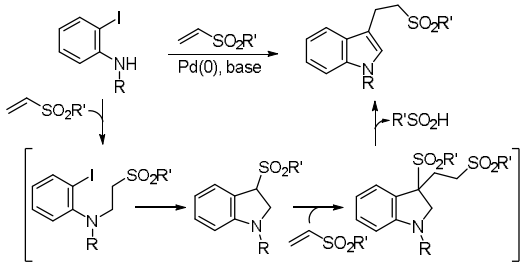
The success of the above domino reactions prompted us to investigate the feasibility of using other sulfonyl derivatives as nucleophiles in the tandem process leading to tetrahydroisoquinolines (Scheme 31).[69] Gratifyingly, we were able to develop new domino reactions by combining the α-arylation of sulfonates with Michael additions to vinyl sulfones, methyl acrylate, phenyl ethenesulfonate and *N*,*N*-dibenzylethenesulfonamide. In contrast, when using a sulfonamide[70-72] as the nucleophile in the initial intramolecular α-arylation reaction only vinyl sulfones could be successfully used as Michael acceptors.



Scheme 31. Synthesis of tetrahydroisoquinolines by two-step domino processes.

7.2. Domino reactions leading to indoles

Continuing these studies, we explored the possibility to synthesize indole derivatives by means of a multistep sequence based on the palladium-catalyzed intramolecular α-arylation of sulfones (Scheme 32). We realized that if the previously developed three-step domino process (aza-Michael addition/α-arylation/Michael addition) was developed from a 2-haloaniline, it should generate a 3-(sulfonyl)indoline intermediate, a type of compound known to undergo β-elimination of sulfinic acid to afford indoles.[73] We therefore postulated that this additional step would allow us to prepare 3-[2-(aryl/alkylsulfonyl)ethyl]indoles in a new four-step domino process from readily available 2-haloanilines.[74]



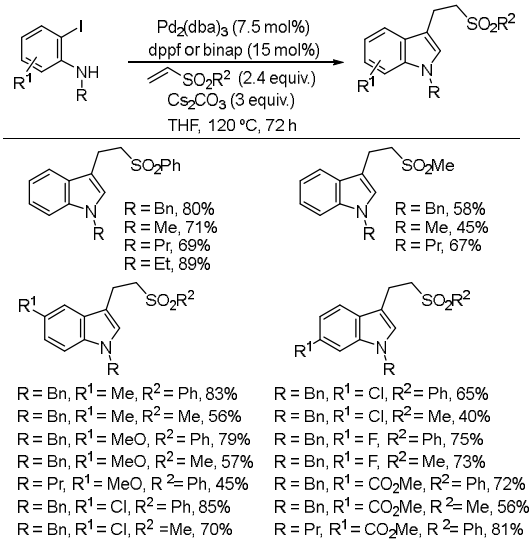
Scheme 32. Synthesis of indoles by four-step domino processes.

After optimization studies, we found that the best results in the four-step domino process were obtained when using a combination of $Pd_2(dba)_3$ with either dppf or binap as the catalyst, and Cs_2CO_3 as the base in THF (Scheme 33). Under these reaction conditions, the domino process tolerated the presence of substituents with different electronic properties on the aniline ring and produced good yields when both phenyl vinyl sulfone and methyl vinyl sulfone were used as the Michael acceptors.

8. Conclusions

This account has summarized our studies on the development of new palladium-catalyzed methodologies for the synthesis of azaheterocycles. We have shown that the properties of σ-arylpalladium intermediates derived from amino-tethered aryl halides can be finely tuned to achieve chemoselective transformations. By controlling the amphiphilic nature of such intermediates through the adequate selection of a suitable catalyst, additives and reaction conditions, the same materials can be selectively promoted to undergo either electrophilic α-arylation or nucleophilic addition reactions to different carbonyl groups. The judicious choice of catalysts and reaction conditions also allowed us to develop a series of domino processes that combine the intramolecular α-arylation of sulfones with Michael addition reactions. Further research in

this field will be aimed at the synthetic applications of these methodologies to access more complex heterocyclic structures of potential interest in fields such as pharmaceutical and material sciences.



Scheme 33. Synthesis of indoles by three-step domino processes.

Acknowledgements

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