

NITROGEN-CONTAINING HETEROCYCLES VIA PALLADIUM-CATALYZED REACTION OF ALKYNES WITH ORGANIC HALIDES OR TRIFLATES

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Abstract – The construction of nitrogen-containing heterocycles promoted by the reaction of alkynes with organic halides or triflates in the presence of palladium catalysts is reviewed.

Introduction

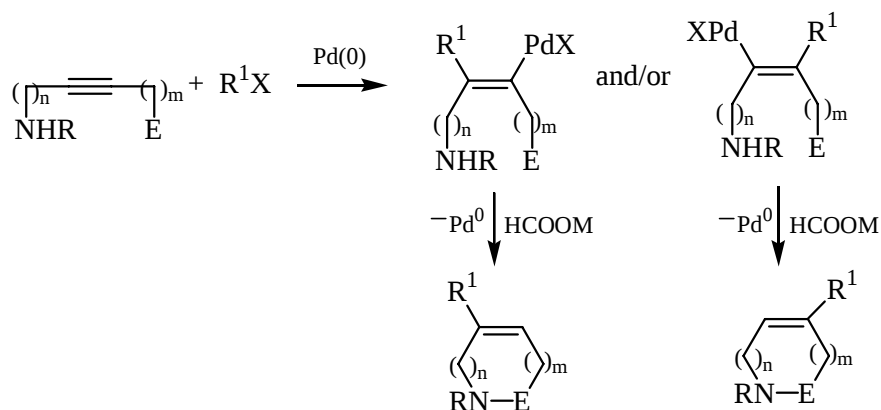
Organopalladium chemistry is presently one of the most powerful and versatile tool for the functionalization of organic molecules.¹ It is utilized in vast areas of the organic synthesis and a great number of applications deal with heterocyclic synthesis. As for the synthesis of heterocyclic compounds, palladium catalysis has been primarily employed to develop two basic approaches: the functionalization of pre-existing heterocycles and the construction of heterocyclic rings through the formation of the carbon-heteroatom bond. This review is focused on the latter type of reactions, particularly on the procedures leading to the construction of nitrogen-containing heterocycles which involve the following general classes of reactions: carbopalladation-cyclization, aminopalladation-reductive elimination and coupling-cyclization.

All these procedures are based on the palladium-catalyzed reaction of alkynes with aryl and vinylic halides or triflates and the formation of carbon-nitrogen bond at the key step of the heterocyclic ring construction.

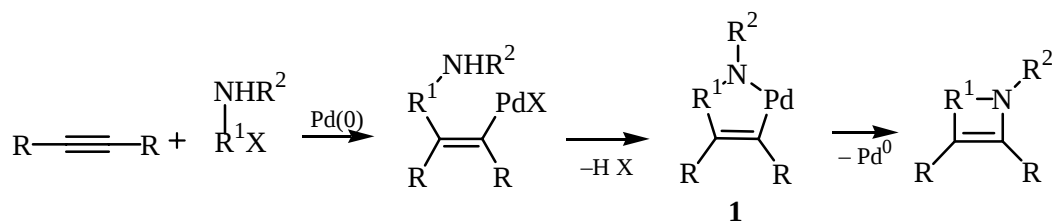
Carbopalladation-Cyclization

The carbopalladation-cyclization process involves the conversion of the alkyne to a carbopalladation adduct whose fate depends on the nature of the starting alkyne and the aryl or vinylic halide or triflate: with starting alkynes containing a proximate nitrogen nucleophile on one side and an electrophilic center on the other side, heterocycles can be obtained through the hydroarylation(hydrovinylation)/cyclization

pathway outlined in Scheme 1; when the aryl or vinylic halide contains a nitrogen nucleophile in a location that allows it to attack the palladium atom once the carbopalladation adduct is formed (Scheme 2), intramolecular halide displacement from the palladium can occur to form a nitrogen-containing palladacycle **1** which subsequently affords the cyclization product *via* a reductive elimination step.



Scheme 1

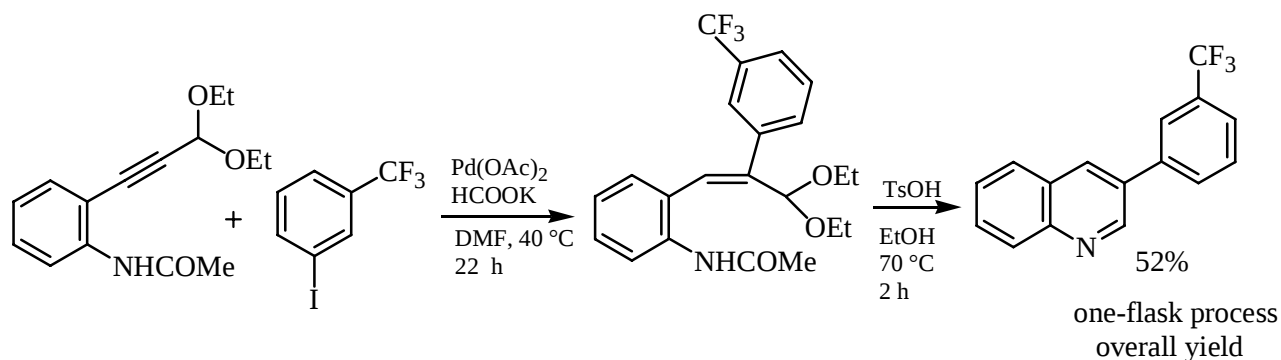


Scheme 2

The carbopalladation step is crucial to the stereo- and regiochemical outcome of these reactions. As for the stereochemistry, the formation of cyclic derivatives argues in favor of a *syn* addition mechanism. Furthermore, a general predominance of *cis* addition products following the carbopalladation step has been observed when carbopalladation adducts have been trapped with external nucleophiles such as hydrogen donors (formate anions),² organometals,³ carbon monoxide and oxygen^{4,5} or nitrogen⁵ nucleophiles. The formation of *trans* addition products has been in some cases observed. However, their formation is more likely due to a *cis-trans* isomerization of the initially formed *cis* adducts rather than a direct *trans* addition paralleling the *cis* addition pathway.⁶ The regiochemistry of the carbopalladation step appears to be primarily controlled by steric and coordinating effects. Steric effects control the carbopalladation step in such a way that the palladium moiety ends up close to the more hindered end of the carbon-carbon triple bond and the organic residue to the less hindered end.^{6f,g,7} Coordinating effects tend to favor the formation of carbopalladation adducts with the added palladium close to the coordinating group.^{2e,6g,7e,f,7i-k,8} In general, electronic effects appear to play a minor role, though there are indications that in some cases they can control the carbopalladation step.⁹

The hydroarylation(hydrovinylation)/cyclization methodology has been applied to the regioselective synthesis of 3-aryl- and 3-vinylquinolines^{6f} (Scheme 3). The new carbon-carbon bond is formed

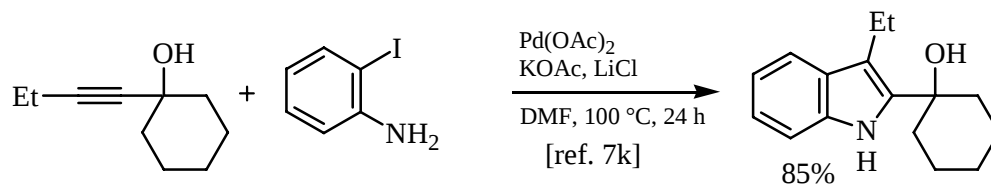
preferentially at the carbon close to the acetal group. Regioisomeric 4-substituted quinolines have been isolated in minor amounts. The reaction can be best carried out as a one-flask process, omitting the isolation of hydroarylation or hydrovinylation products.



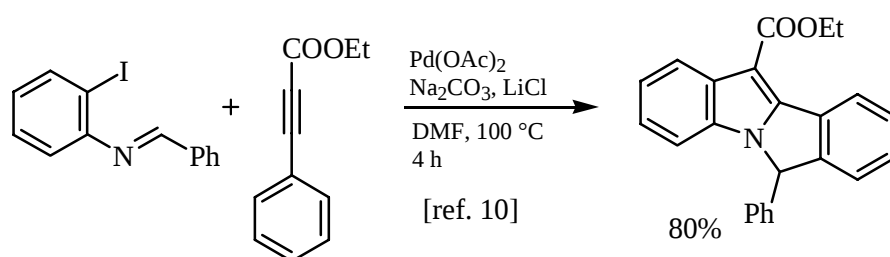
Scheme 3

The second methodology has been developed by employing internal alkynes and aryl or vinylic halides containing proximate nitrogen nucleophiles to provide access to 2,3-disubstituted indoles,^{7e,k,8c-g} 5-, 6-, and 7-azaindoles,^{8i,j} isoindolo[2,1-*a*]indoles,¹⁰ substituted β - and γ -carbolines,¹¹ isoquinolines,¹² pyridines,¹² pyrrolo[3,2-*c*]pyridines,^{8c,i} 1,2-dihydroisoquinolines,¹³ alkylidene-dihydropyrroles,¹⁴ thieno[3,2-*b*]pyrroles,^{8c} pyrrolo[3,2-*c*]pyrimidines.^{8c} The methodology has been adapted to solid phase syntheses of indole derivatives.¹⁵ Some examples of this chemistry are shown in Schemes 4-8.

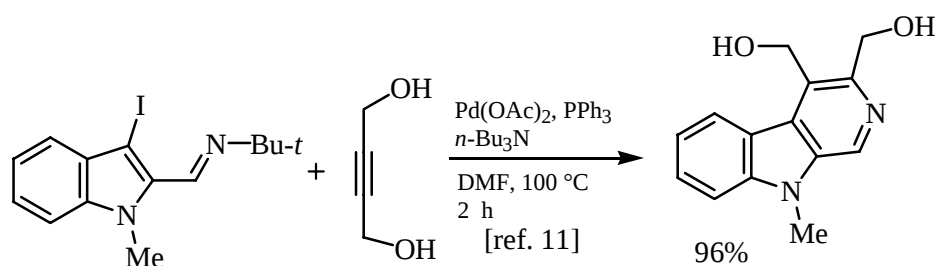
The carbopalladation-cyclization mechanism has been suggested to be operating even with terminal alkynes. Particularly, it has been invoked to account for the formation of 6-imino-substituted pyrrolo[3,2,1-*ij*]quinolines from 8-iodoquinoline derivatives and propargyl alcohol in the presence of iodo(phenyl)bis(triphenylphosphine) and copper(I) iodide¹⁶ (Scheme 9).



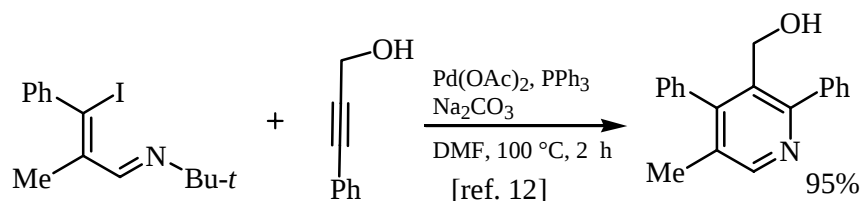
Scheme 4



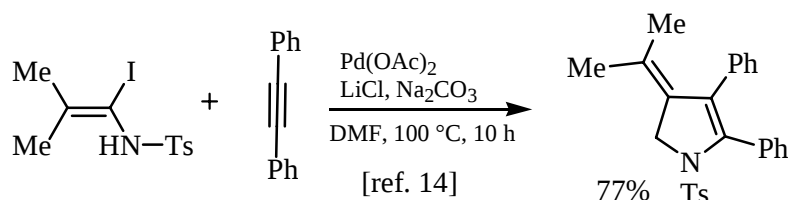
Scheme 5



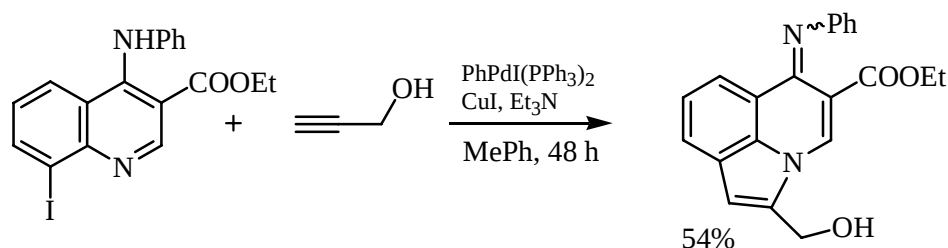
Scheme 6



Scheme 7



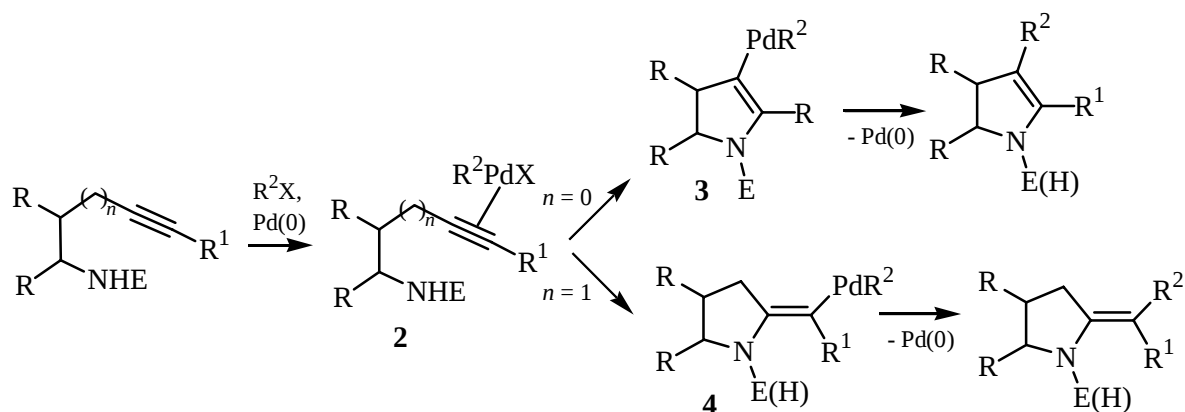
Scheme 8



Scheme 9

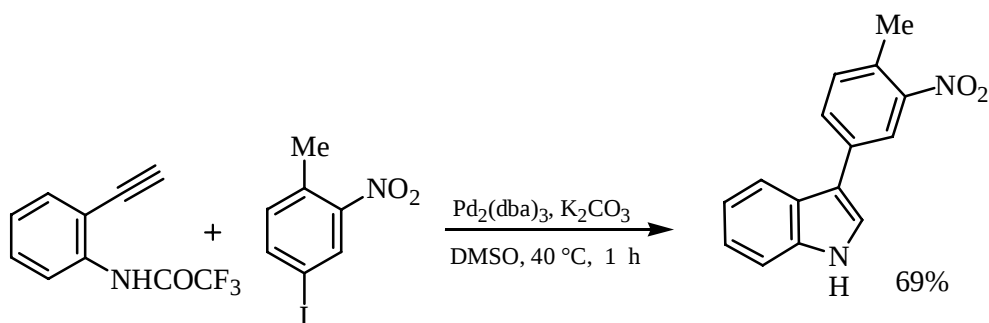
Aminopalladation-Reductive Elimination Domino Reaction

The aminopalladation-reductive elimination domino reaction has been suggested to proceed through the intermediacy of an η^2 -alkyne-organopalladium complex (**2**) that undergoes an intramolecular nucleophilic attack by the nitrogen atom across the carbon-carbon triple bond. Subsequently, the resultant *endo-dig* aminopalladation adduct (**3**) or *exo-dig* aminopalladation adduct (**4**) affords the heterocyclic product *via* a reductive elimination step (Scheme 10). *Exo* cyclization products normally contain the organic fragment transferred onto the carbon-carbon triple bond *trans* with respect to the nitrogen nucleophile. The course of this reaction is strongly influenced by a number of reaction parameters such as the absence or the presence – as well as the nature – of phosphine ligands, the solvents, the substitution pattern of the alkyne, the presence of added salts, and the nucleophilic strength of the nitrogen.

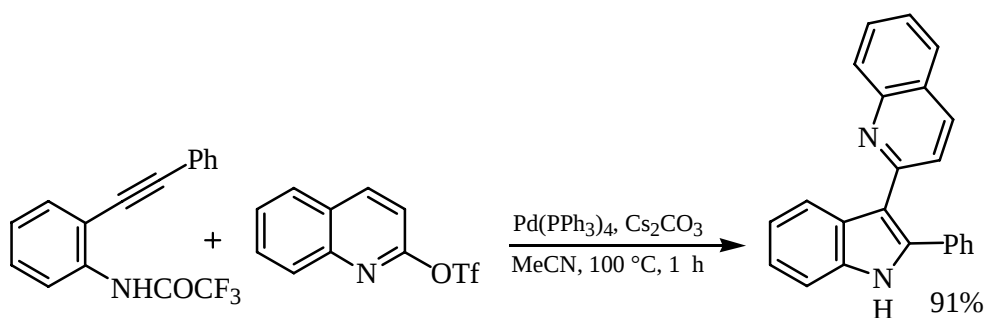


Scheme 10

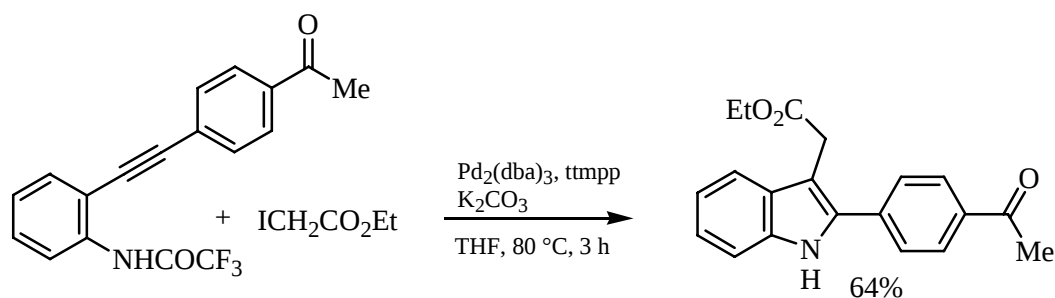
This chemistry has been widely employed in the synthesis of substituted indoles: 2-unsubstituted 3-arylinroles¹⁷ (Scheme 11), 2,3-disubstituted indoles¹⁸ (Scheme 12), 2-substituted 3-alkylindoles¹⁹ (Scheme 13), 2-substituted 3-allylinroles²⁰ (Schemes 14) have been prepared from *o*-alkynyltrifluoroacetanilides and aryl and vinylic iodides, bromides, triflates, alkyl halides, allylic carbonates. Employment of alkynes containing free amino groups and acetamido groups met with failure. The trifluoroacetamido group was proved to be the nitrogen derivative of choice, suggesting that the success of the reaction is strongly dependent on the acidity of the nitrogen-hydrogen bond. The trifluoroacetamido group exhibits the additional advantage of being readily removable under reaction conditions, leading to the isolation of *N*-unprotected indoles.



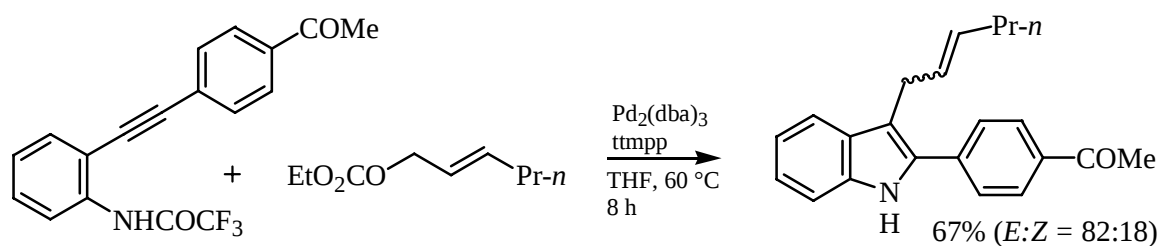
Scheme 11



Scheme 12

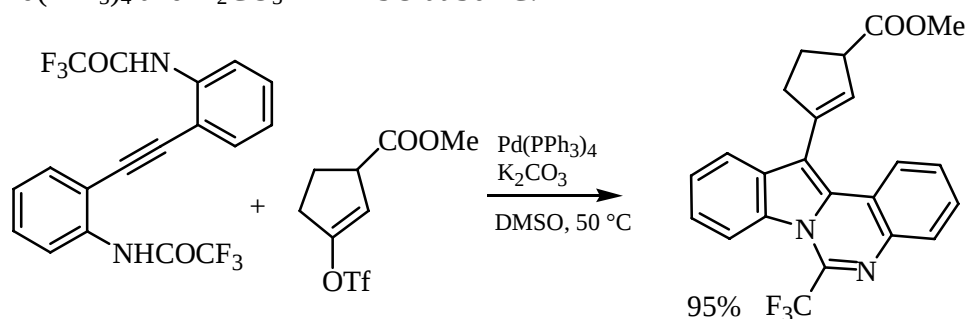


Scheme 13



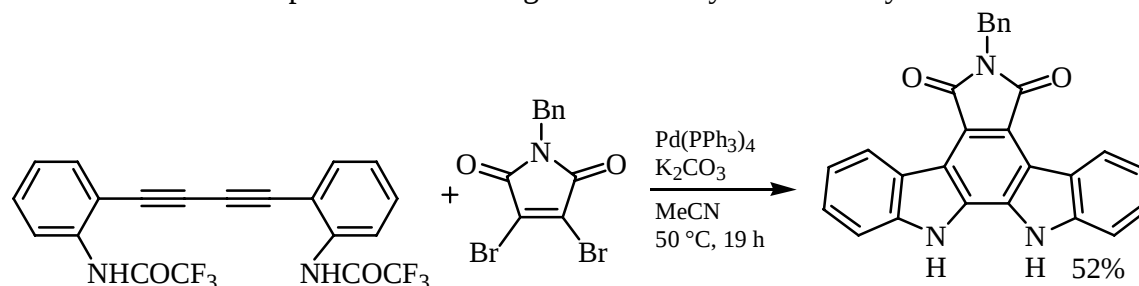
Scheme 14

Extension to bis(*o*-trifluoroacetamidophenyl)acetylene as the starting alkyne allowed the development of a straightforward approach to 12-aryl(vinyl)indolo[1,2-*c*]quinazolines²¹ (Scheme 15), whose skeleton is present in the unusual marine alkaloid hinckdentine A.²² The best conditions developed employ $\text{Pd}(\text{PPh}_3)_4$ and K_2CO_3 in DMSO at 50°C .



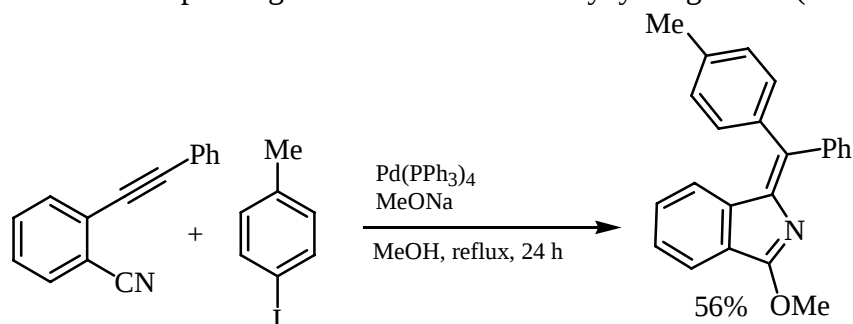
Scheme 15

The methodology has been adapted to a solid-supported synthesis, to afford indoles with three independently variable components,²³ and employed to develop an elegant synthesis of the indolo[2,3-*a*]carbazole alkaloid ring system²⁴ (Scheme 16), a common functionality of several biologically active molecules such as the potent antitumor agent rebeccamycin²⁵ and arcyliaflavin A.²⁶

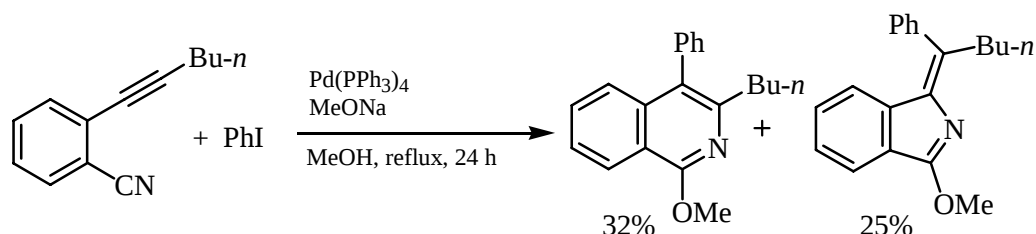


Scheme 16

The tendency of the cyano group to add strong bases generating anionic species has been exploited to involve *o*-alkynylbenzonitriles in this type of chemistry. Indeed, subjection of *o*-alkynylbenzonitriles to aryl iodides in the presence of Pd(PPh₃)₄ and sodium methoxide gives isoquinoline and/or isoindole derivatives depending on the nature of the alkynyl fragment²⁷ (Schemes 17 and 18).

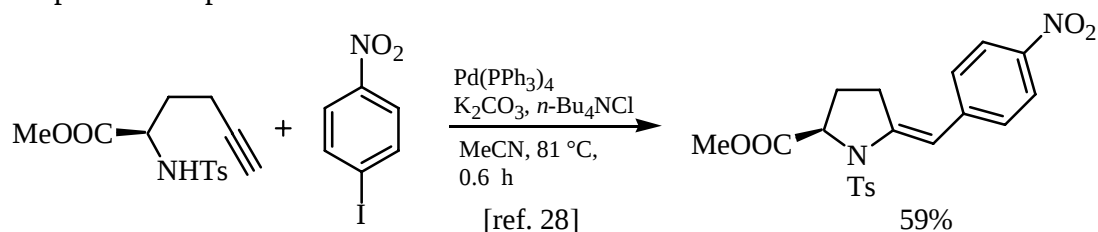


Scheme 17

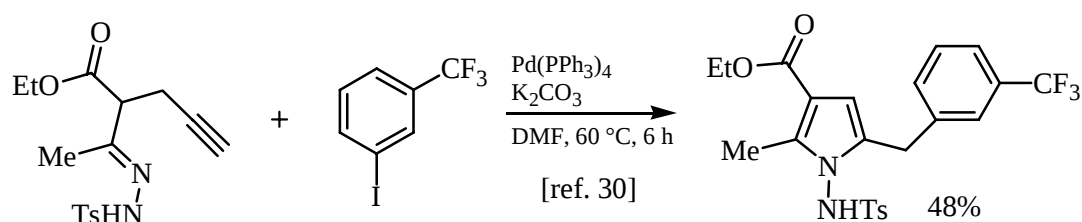


Scheme 18

This cyclization strategy has also been applied to alkynes with non-aromatic amino groups close to the carbon-carbon triple bond to prepare a variety of five- and six-membered ring heterocycles: acetylenic tosylamides have been used as building blocks in the synthesis of α -alkylidenepyrrolidines²⁸ and α -alkylidenepiperidines;²⁹ ethyl 2-acetyl-4-pentynoate tosylhydrazone has been treated with aryl iodides to give 1,2,3,5-tetrasubstituted pyrroles;³⁰ propargylic tosylcarbamates have been subjected to aryl iodides or vinylic triflates to afford regio- and stereoselectively (*E*)-4-alkylidene-3-tosyloxazolidin-2-ones.³¹ A couple of examples are shown in Schemes 19 and 20.

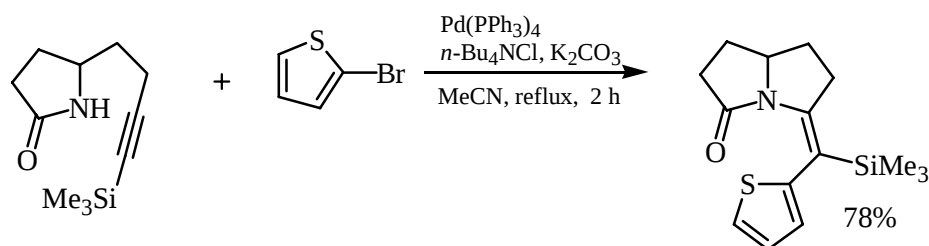


Scheme 19



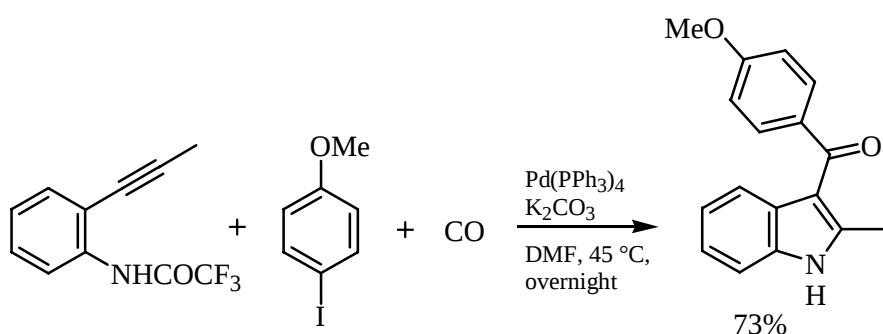
Scheme 20

The related reaction of acetylenic lactames with aryl, heteroaryl and vinylic halides yields bicyclic enamides in which aryl, heteroaryl and vinylic moieties are incorporated (Scheme 21).³² However, the double bond geometry is opposite of what is normally observed³³ and this appears to be the result of a different cyclization mechanism that most probably involves coordination of the nitrogen nucleophile to the aryl(heteroaryl, vinylic)palladium complex before the carbopalladation step.

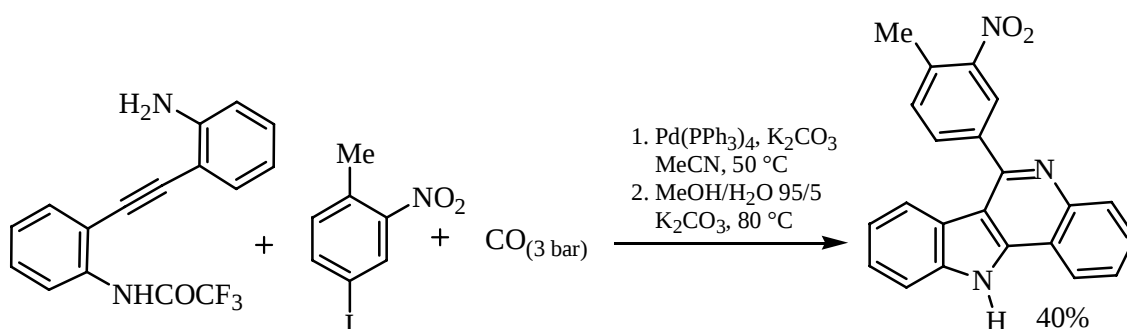


Scheme 21

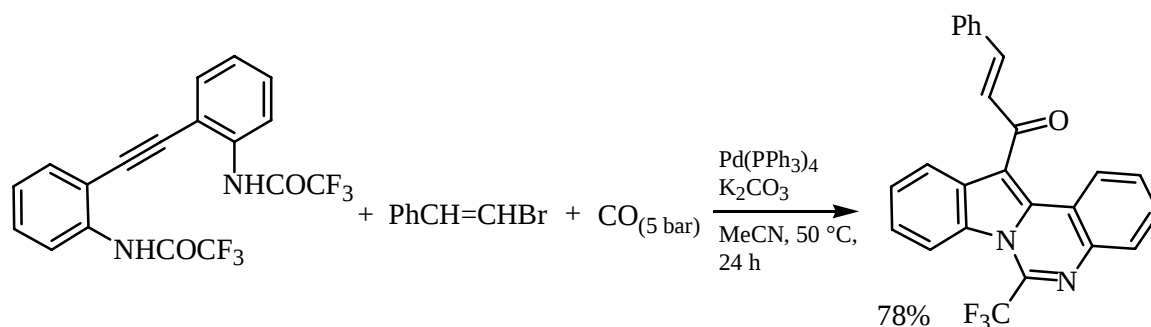
Under an atmosphere of carbon monoxide, the aminopalladation-reductive elimination domino reaction can form nitrogen-containing heterocycles incorporating a molecule of carbon monoxide. This three component approach to the preparation of heterocyclic rings has been employed to develop new routes to 2-substituted 3-acylindoles³⁴ (Scheme 22), functionalized indolo[3,2-*c*]quinolines³⁵ (Scheme 23), 12-acylindolo[1,2-*c*]quinazolines³⁶ (Scheme 24) and 1,2,3,5-tetrasubstituted pyrroles³⁰ (Scheme 25).



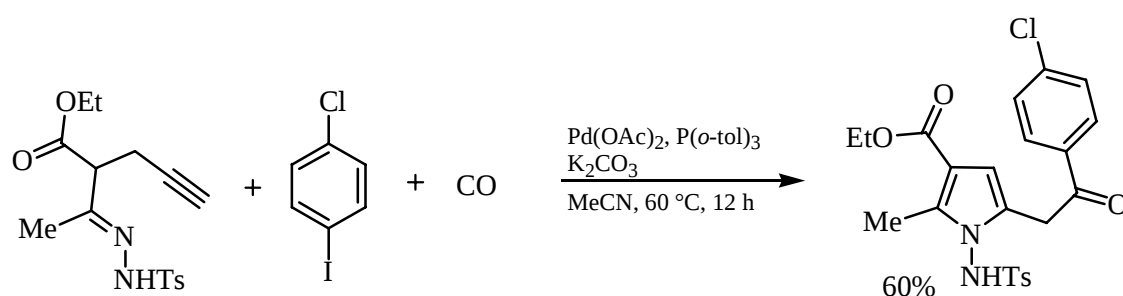
Scheme 22



Scheme 23



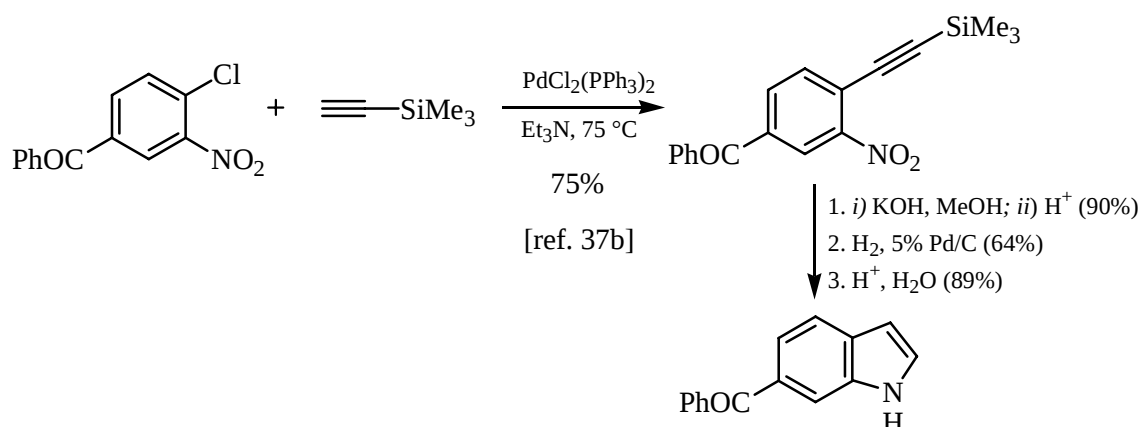
Scheme 24



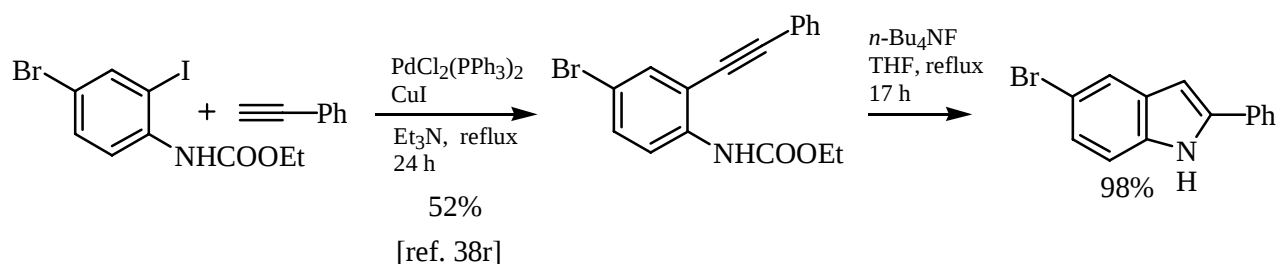
Scheme 25

Coupling-Cyclization

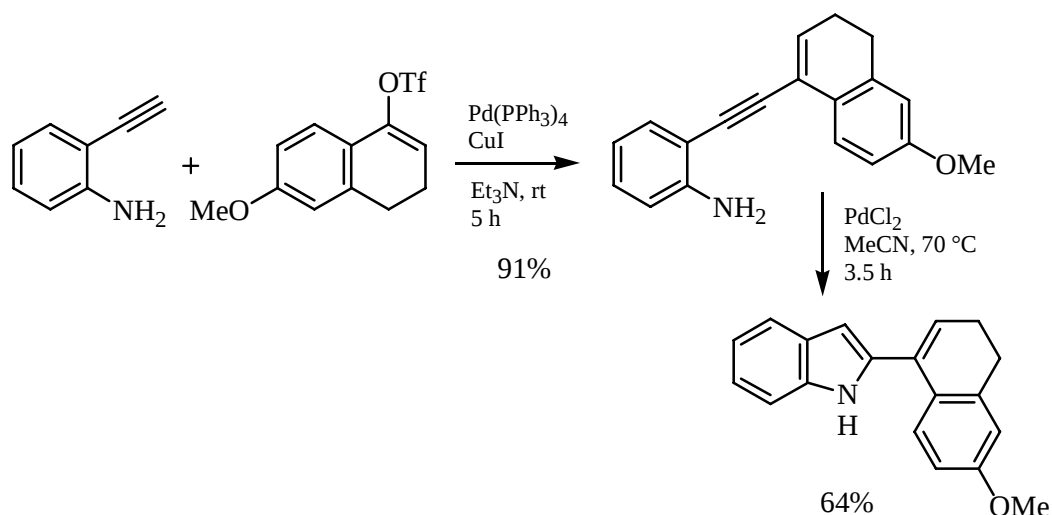
The coupling-cyclization methodology usually involves the coupling of 1-alkynes with *o*-halonitrobenzenes³⁷ (Scheme 26) or *o*-haloanilines(anilides)³⁸ (Scheme 27) or the coupling of 1-alkynes containing a nitrogen nucleophile close to the carbon-carbon triple bond with organic halides or triflates³⁹ (Scheme 28), followed by cyclization through the formation of the carbon-nitrogen bond. The coupling reaction is best carried out in the presence of a palladium catalyst under Sonogashira conditions.⁴⁰ Depending on the nature of the nitrogen group and the acetylenic fragment, the cyclization step may or may not involve palladium catalysis and, in many cases, occurs under coupling conditions. Adaptation of the coupling-cyclization methodology to solid phase synthesis has also been described.⁴¹



Scheme 26

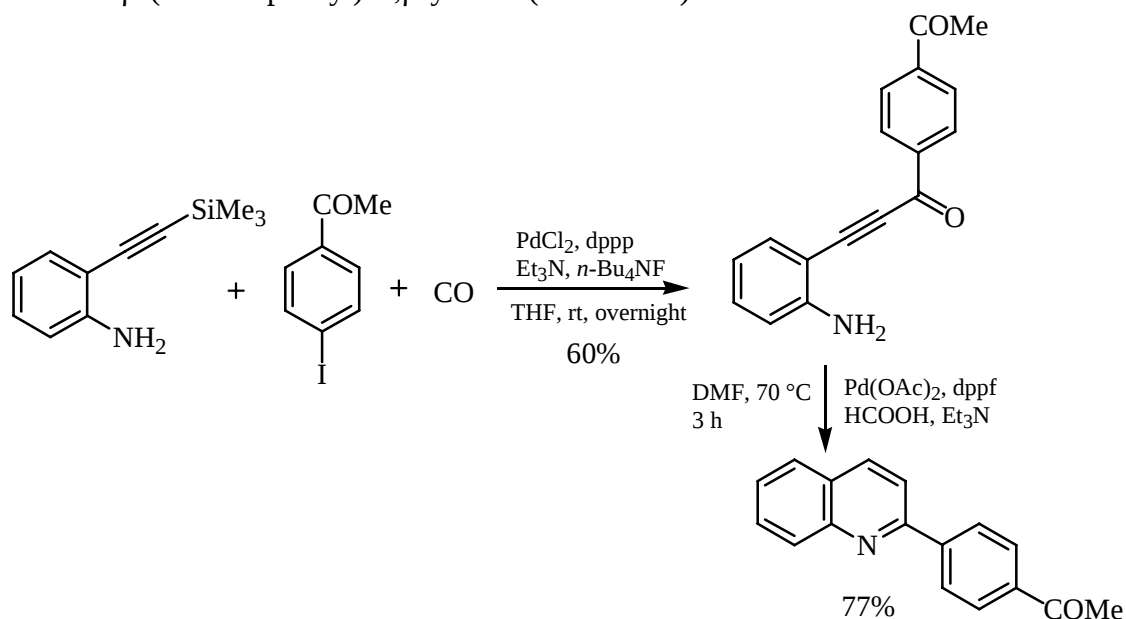


Scheme 27



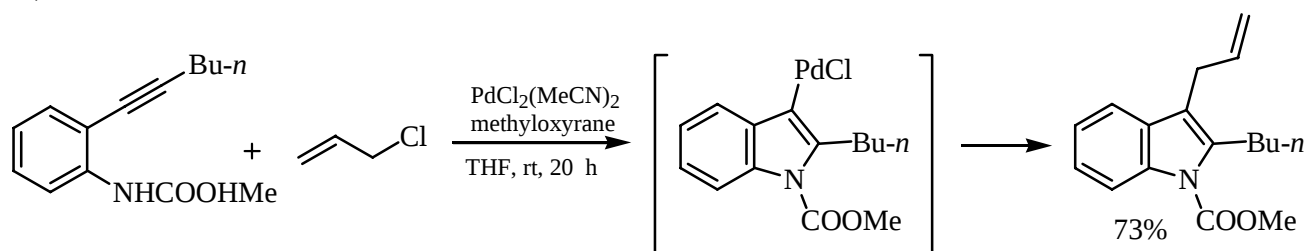
Scheme 28

Carbonylative coupling-cyclization has been employed to develop new routes to heterocycles. This approach has been used in the synthesis of 2-aryl- and 2-vinylquinolines,⁴² which have been prepared through the palladium-catalyzed carbonylative coupling of *o*-trimethylsilylaniline and aryl iodides or vinylic triflates, followed by the palladium-catalyzed transfer hydrogenation/heterocyclization of the resultant β -(2-aminophenyl)- α,β -ynones (Scheme 29).

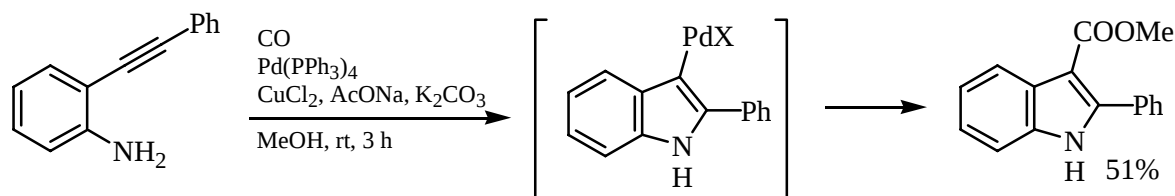


Scheme 29

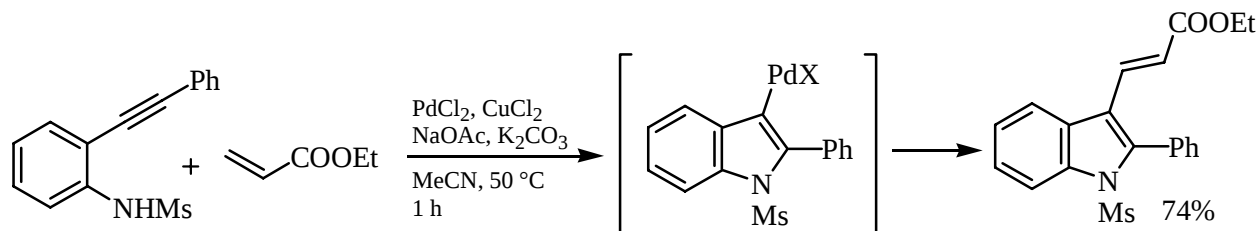
Cyclization of coupling products *via* palladium-catalyzed reactions can provide a powerful tool for increasing molecular complexity of the indole derivative by trapping indolylpalladium intermediates that are initially formed with suitable reagents. This synthetic strategy has been employed to combine the cyclization step with allylation^{38d} (Scheme 30), carbonylation⁴³ (Scheme 31) and vinylation⁴⁴ (Scheme 32) reactions.



Scheme 30

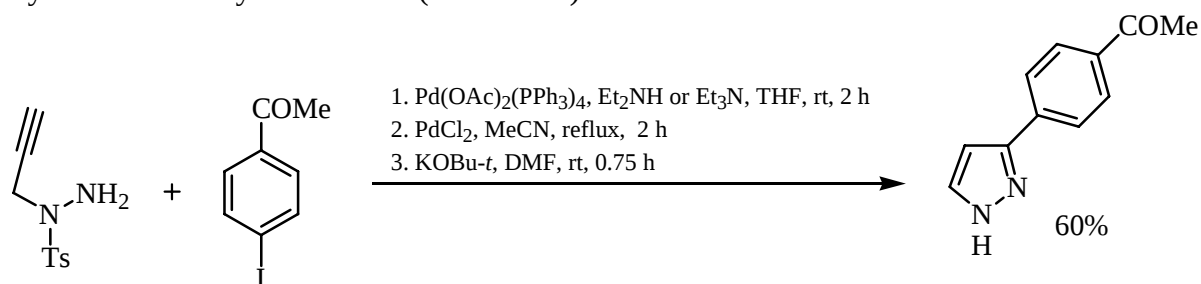


Scheme 31



Scheme 32

As it has been shown, most of the coupling-cyclization chemistry has been employed for the preparation of indole derivatives. However, some applications to the synthesis of other nitrogen-containing heterocycles have been reported. For example, functionalized pyrazoles have been prepared in good overall yield through a coupling-cyclization one-pot procedure from *N*-tosyl-*N*-propargylhydrazine and aryl iodides or vinylic triflates⁴⁵ (Scheme 33).



Scheme 33

ACKNOWLEDGEMENTS

We are most indebted to the Ministero dell'Università e della Ricerca Scientifica (MURST; National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni"), the Consiglio Nazionale delle Ricerche (CNR), and the Università degli Studi "La Sapienza", Rome, for their continuing financial support of the work done in our laboratories.

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