Larock Reaction in the Synthesis of Heterocyclic Compounds

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Abstract:

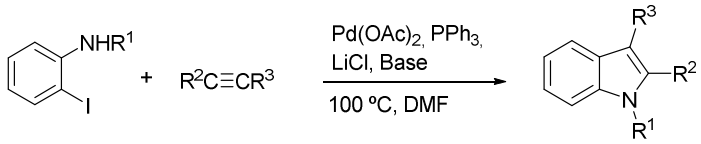
The indole ring is one of the most common features in natural products and small molecules with important bioactivity. Larock reported a new methodology for the synthesis of the indole ring system based on the palladium-catalyzed heteroannulation of 2-iodoaniline and substituted alkyne moieties. This procedure was subsequently extended to the preparation of other nitrogen- and oxygen-containing heterocycles. This is the process of choice for the synthesis of a large number of heterocyclic derivatives, as it provides outstanding regioselectivity and good to excellent yields.

Keywords: Heteroannulation, Heterocycles, Alkynes, Palladium Catalyst, Natural Compounds

1. INTRODUCTION

Larock indole synthesis, also known as Larock heteroannulation, is a one-pot palladium-catalyzed heteroannulation of *o*-iodoaniline and internal alkynes for the

synthesis of 2,3-disubstituted indoles. The original Larock reaction was performed with $Pd(OAc)_2$ using carbonate or acetate bases with or without catalytic amounts of triphenyl phosphine and *n*-Bu_4NCl. However, it was subsequently observed that LiCl was often more effective and reproducible (Scheme 1) (1991JA6689). The reaction was shown to be a high regioselective process giving the bulky substituent of the alkyne in position two of the resulting indole ring.



R^1 = H, Me, Ac, Ts

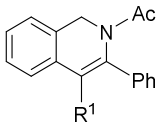
R^2 = *n*-Pr, *t*-Bu, *c*-C_6H_{11}, 1-OH-*c*-C_6H_{11}, CMe_2OH, $SiMe_3$, Ph, CH_2OH

R^3 = *n*-Pr, Me, $CMe{=}CH_2$, CH_2OH, Ph

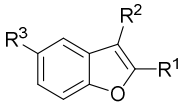
Scheme 1. Palladium-catalyzed heteroannulation of alkynes

Larock modified the annulation process to access 3-substituted indoles by employing silyl-substituted alkynes. In this case, the bulky silyl group dominates the regioselectivity of the annulation and thus serves as a phantom-directing group in the heteroannulation step. Silylated alkynes provide 2-silyl-3-substituted indoles with excellent regioselectivity. Subsequent desilylation affords 3-substituted indoles in good yield.

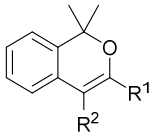
In 1995, Larock and co-workers reported that this chemistry provides a valuable route for the synthesis of benzofurans, benzopyrans, and isocoumarins in good to excellent yields (Figure 1) (1995JOC3270).



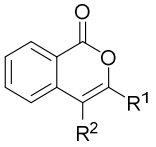
R^1 = CO_2Et, Ph
Me, CHO



R^1 = *t*-Bu, Ph, TIPS
R^2 = Me, CO_2Me, Ph
R^3 = H, Ac



R^1 = *t*-Bu, Ph, TIPS,
CMe_2OH
R^2 = Me, CO_2Me, Ph



R^1 = *t*-Bu, TMS
1-OH-C_6H_{11}
R^2 = Me, Et, Ph

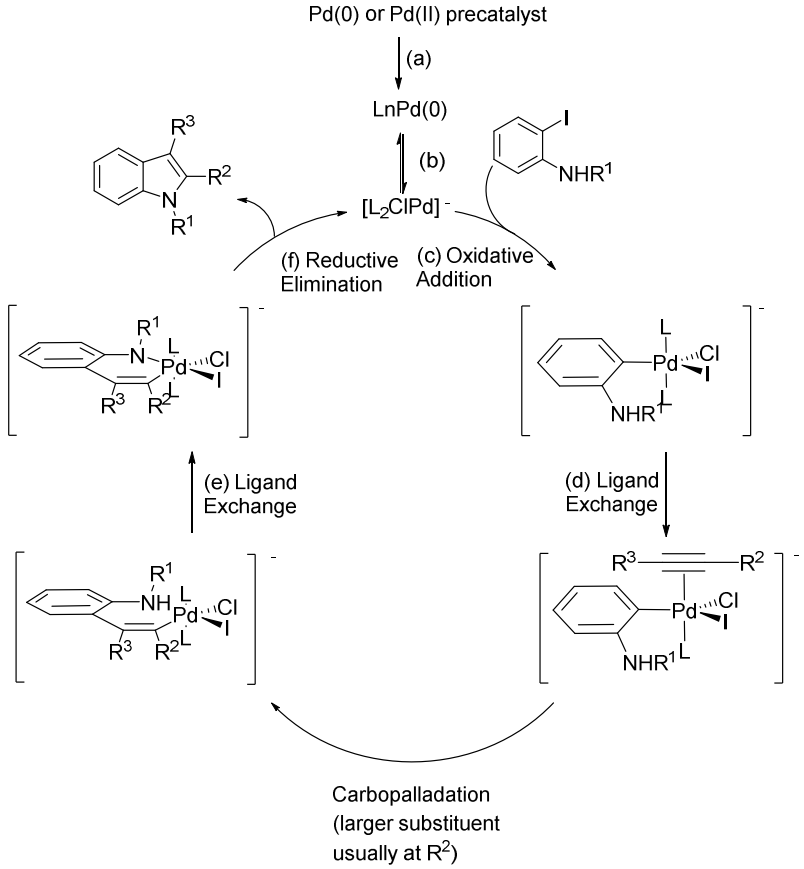
Figure 1. Benzoheterocycles synthetized by Larock heteroannulation

Several reviews about synthesis of heterocycles via palladium-catalyzed reactions containing revisions of Larock procedures were made until the end of 2014 (2005CR2873, 2006CR2875, 2006CR4644). This chapter provides a review and update of the Larock reaction. It will be implemented not only for the preparation of indole and its derivatives but also in other heterocyclic systems, natural compounds and derivatives.

2. MECHANISM OF LAROCK HETEROANNULATION

The scope and mechanism of palladium-catalyzed annulation of internal alkynes to give 2,3-disubstituted indoles, the effect of substituents on the aniline nitrogen or on the alkynes, as well as, the effect of the salts such as LiCl or *n*-Bu_4NCl was studied by Larock and co-workers (1998JOC7652). The mechanism they propose for indole synthesis is carried out as follows: (a) reduction of the $Pd(OAc)_2$ to Pd(0), (b) coordination of the chloride to form a chloride-ligated zerovalent palladium species, (c) oxidative addition of the aryl iodide to Pd(0), (d) coordination of the alkyne to the palladium atom of the resulting arylpalladium intermediate and subsequent regioselective *syn*-insertion into the arylpalladium bond, (e) nitrogen displacement of the halide in the resulting vinyl palladium intermediate to form a six-membered, heteroatom-containing palladacycle, and (f) reductive elimination to form the indole and to regenerate Pd(0) (Scheme 2) (1993JA9531).

These first and third steps are well known and integral to a wide variety of Pd(0)-catalyzed processes. Less hindered alkynes are known to insert more readily than more hindered alkynes (1993T5471). *syn*-Addition of the arylpalladium compound to the alkyne has been established for the analogous palladium-catalyzed hydroarylation process (1986G725, 2004JOM4642) and implemented in many other alkyne insertion processes (1989JA3454, 1989JOC2507, 1990JA8590, 1990TL4393, 1991JOC6487, 1991SL777, 1991TL4167, 1992JA791, 1992JA10091, 1992CC390, 1992PAC3323, 1992TL3253, 1992TL8039, 1993JOC560, 1993T5471, 1994JA7923, 1995TL1771).



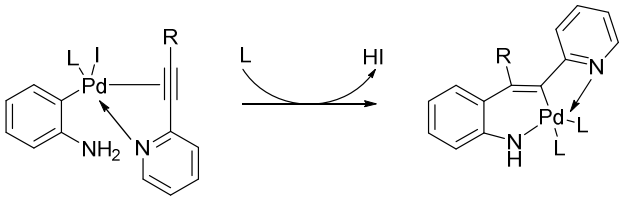
Scheme 2. Proposed mechanism for Larock heteroannulation

The Larock annulation process is highly regioselective, and, generally, significantly higher than the related palladium catalyzed hydroarylation process, which often produces regioisomers mixtures (1984TL3137, 1985T5121, 1986G725, 1986TL6397, 1988T481, 1989TL3465). The regioselectivity is perhaps due to chelation of the palladium in the arylpalladium intermediates by the neighboring nitrogen, which reduces the overall reactivity and increases the steric hindrance of these intermediates towards alkyne insertion.

The controlling factor in the insertion processes may be the steric hindrance present in the developing carbon-carbon bond or the orientation of the

alkyne immediately prior to *syn*-insertion of the alkyne into the aryl palladium bond. Alkyne insertion occurs to generate the least steric strain near the developing carbon-carbon bond rather than the longer carbon-palladium bond. The alkyne may adopt an orientation in which the more steric demanding group is located away from the sterically encumbered aryl group. The result of that orientation is the regioselectivity of the reaction in which the aryl group of the aniline is located at the less sterically hindered end of the triple bond and the nitrogen moiety at the more sterically hindered end.

The regioselectivity of Larock indole annulation with 2-alkynylpyridines and *o*-iodoaniline to give 3-substituted-2-pyridin-2-ylindoles was also rationalized by a combination of steric and electronic coordinative effects (2008TL363) (Scheme 3). A coordination of the pyridine nitrogen during the catalytic cycle was postulated to justify the different regioisomeric ratios 94:6, 68:32 and 72:28 of the Larock reaction obtained with cyclopentyl 2-, 3- and 4-pyridyl acetylenes, respectively.



Scheme 3. Proposed coordinative effect in Larock indolization with 2-alkynylpyridines

The same work but using *tert*-butyl 2-pyridyl acetylene showed the importance of steric factor in the regioselectivity of the Larock indolization. The large steric bulk of the *tert*-butyl group overrides the electronic effect of the pyridin-2-yl group favoring production of 2-(*tert*-butyl)indole **1** over 3-(*tert*-butyl)indole **2** in a ratio of 69:31 (Figure 2).

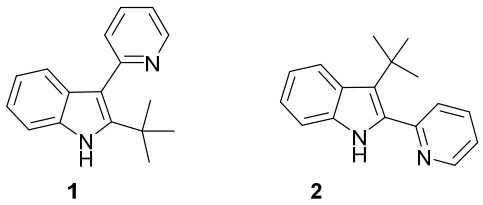
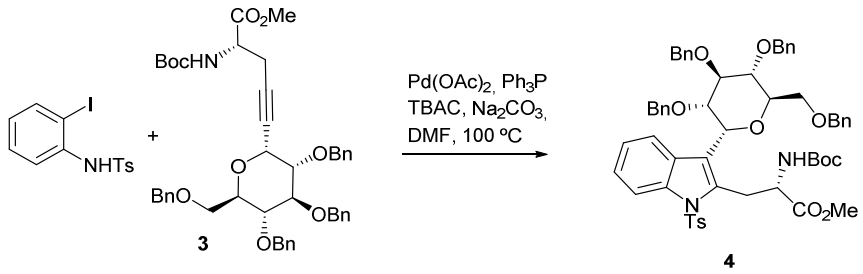


Figure 2. Structures of indole derivatives **1** and **2**

Reversed regioselectivity was described by Isobe and co-workers in the reaction between an *N*-protected iodoaniline and the α-*C*-glucosylpropargyl glycine **3** (2002MI2273). Excellent yield of 3-substituted isotryptophan **4** was obtained with a *N*-tosyl protecting group. Isobe and co-workers could not identify the motif of reversed regioselectivity after systematic studies on the Larock reaction using *N*-tosyliodoaniline (2008MI2092) (Scheme 4).



Scheme 4. Reversed regioselectivity in the Larock heteroannulation

2.1. Homogeneous catalyst

The ligand-free conditions of the Larock reaction work well with iodoanilines but not with the more economic and accessible 2-bromo or 2-chloroanilines. Lu, Senanayake and co-workers were the first group to test the preparation of indole from chloroaniline or bromoanilines in combination with highly active phosphine ligands such as trialkylphosphines (Cy_3P, *t*-Bu_3P) (2004OL4129). Ferrocenyl phosphines (**5**-**7**) and biaryl phosphines (**8**-**11**) were examined (Figure 3). Among

these phosphines, 1,1'-bis(di-*tert*-butylphosphino)ferrocene (**7**) was the most active. Several bases were also tested to ascertain their effect on the reaction rate and regioselectivity.

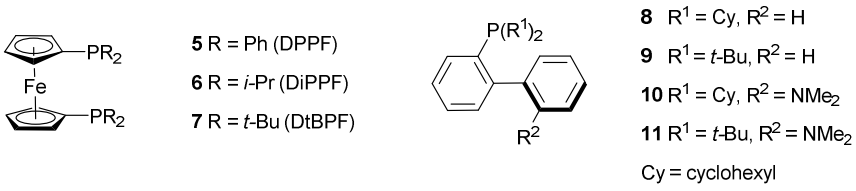


Figure 3. Structures of ferrocenyl **5**-**7** and biaryl phosphines **8**-**11**

To avoid using bulky electron-rich phosphine ligands, the Pd-catalyzed indolization of 2-bromoanilines with internal alkynes was examined by Liu, Guo and co-workers (2008TL3458). A large number of ligands with different functionalities were tested. Phenylurea was the ligand that gave better yields and high regioselectivities when the reaction was performed in DMF with K_2CO_3.

2.2. Heterogeneous catalyst

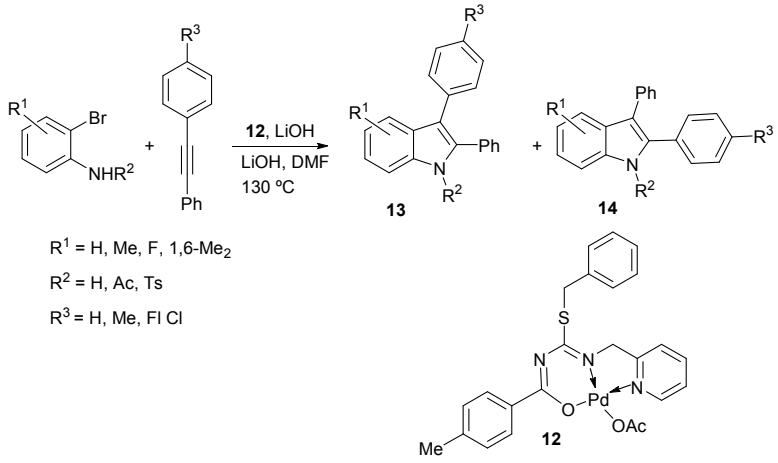
Heterogeneous palladium catalysts, $[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15, for the synthesis of 2-substituted indoles gave high progress and selectivities (2006MI715). Change of iodoaniline into *N*-tosyl-2-iodoaniline produced significantly increased reaction times for full conversion. The heteroannulation of phenylacetylene with sulfonamide requires 6 days and only 1 day with the free aniline.

Heterogeneous catalysis of the Larock heteroannulation via coupling of internal alkynes with 2-bromoanilines using ligand free Pd/C in DMF gave good yields of 2,3-disubstituted indoles (2009MI2055; 2010MI3338; 2011TL1916; 2011MI2).

2.3 Phosphine-free thiopseudourea-Pd(II)

The phosphine-free thiopseudourea palladium(II) complex **12** was found to be an efficient catalyst for heteroannulation of internal alkynes with 2-bromoanilines and substituted *N*-tosyl-2-bromoanilines (Scheme 5). A variety of 2-bromoanilines

and *N*-tosyl substituted 2-bromoanilines afforded the corresponding products as a mixture of regioisomers in good to high yields (2013JOM162). This is an example in which the two substituents in the internal alkyne had a similar hindrance and the two regioisomers **13** and **14** were obtained in the same proportion.



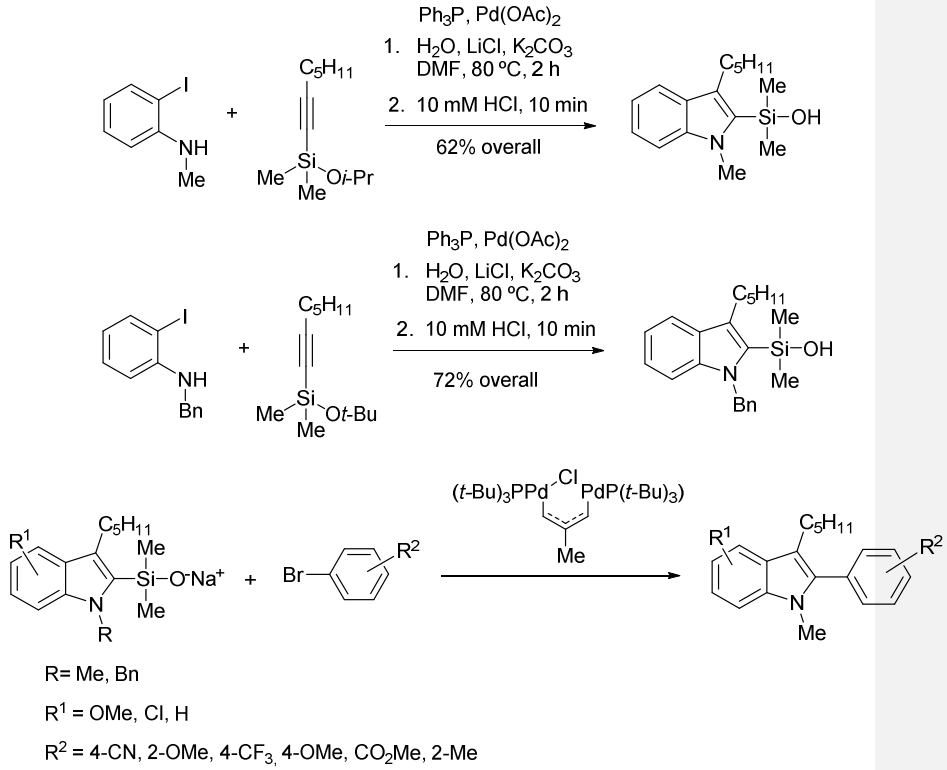
Scheme 5. Larock reaction with thiopseudourea-Pd(II) complex **12**

2.4. Stabilized palladium colloid

Palladium nanoparticles stabilized in micelles formed by polystyrene-*co*-poly(ethylene oxide) copolymer (PS-PEO) and acetylpyridinium chloride (CPC) as a surfactant were used to catalyze heterocyclization of *N*-methylsulfonyl-*o*-iodoaniline with phenylacetylene leading to formation of substituted indole. The activity of the colloidal palladium catalytic system is comparable to that of the low-molecular-weight palladium complexes, whereas the stability of the colloidal palladium system is much higher. The reuse of the catalyst PS-PEO-CPC was demonstrated in the experiments with fresh starts as well as by thermomorphous separation of the catalyst from products (2006OM154).

2.5 Silicon-based cross-coupling reactions

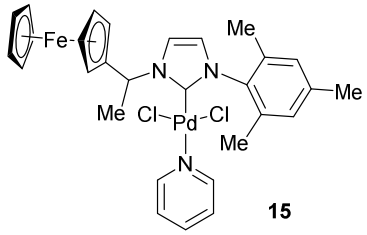
A sequential Larock and cross-coupling strategy may solve the problem of regioselectivity that appears by using alkynes with two similar bulky substituents (2009T3120). Larock heteroannulation of substituted 2-iodoanilines and alkynyldimethylsilyl *tert*-butyl ether afforded 3-substituted indole-2-silanols after hydrolysis. The cross-coupling between sodium 2-indolylsilanolate salts with aryl bromides and chlorides successfully afforded multi-substituted indoles (Scheme 6). The development of an alkynyldimethylsilyl *tert*-butyl ether as a masked silanol equivalent enabled a smooth heteroannulation process and an easy cross-coupling reaction with the suitable catalyst and ligand combination.



Scheme 6. Synthesis of 1,2,3-trisubstituted indoles

2.6. *N*-Heterocyclic carbene-Pd complexes

N-heterocyclic carbenes (NHC) have been used in Larock heteroannulation as ligands for the Pd catalyst giving good yields and high regioselectivity. As an extension of the previous work developed by Cao, Shi and co-workers published an efficient regioselective synthesis of 2,3-disubstituted indole derivatives catalyzed by the ferrocenyl NHC–Pd–Py complex **15** (Figure 4) (2013MI575, 2013MI18345).



15

Figure 4. Structure of ferrocenyl NHC-Pd-Pyr complex **15**.

The heteroannulation was tested with iodo and bromoaniline using symmetrical and unsymmetrically substituted alkynes. The electronic effect of the aniline substituents as well the reactivity of aromatic alkynes were tested. The proposed mechanism is agreement with that shown in Scheme 2, whereby the insertion of the Pd(II)–aryl bond into the alkyne occurs in a manner in which the bulky group in the alkyne is preferentially located near the smaller Pd(II) side. As a result of the regioselective *syn*-insertion of the alkyne, the bulky substituent in the resulting indole ring is located in position two.

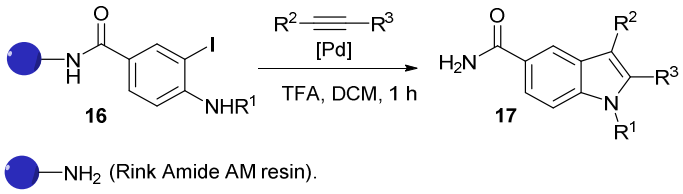
3. LAROCK REACTION IN SOLID PHASE

Reactions in solid phase offer the advantage of easy removal of catalysts, excess reagents and byproducts by washing, which makes the purification of the products much simpler. Two different strategies have been used for Larock solid phase catalyzed reactions. The first strategy is based on linking one reagent to the polymeric support to perform the reaction on solid phase. In that way the reaction product remains linked to the solid support during the washings of the

resin and it is recovered after the cleavage. The second alternative is to anchor the catalyst onto the solid support. This is an important strategy for Pd catalysts that are sometimes difficult to remove.

3.1. Synthesis of trisubstituted indoles on solid phase

Pd-mediated heteroanulation of alkynes with resin-bound *o*-iodoanilines **16** gave trisubstituted indoles with good yields. Zhang and co-workers used Rink amide AM resin as solid support and the iodoaniline was linked by formation of an amide bond (1997TL2439) (Scheme 7). After the heteroannulation reaction, the cleavage with TFA gave the indoloamide functionalized compounds.



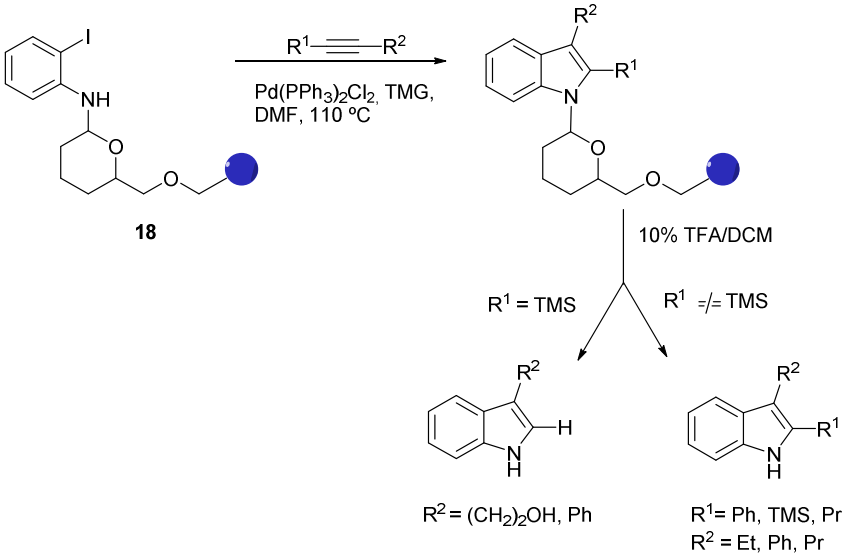
R^1 = H, COMe, $COCHMe_2$

R^2 = Me, Pr, Ph, CO_2Et, $(CH_2)_2OH$, $(CH_2)_2Cl$, $(CH_2)_2C_6H_4$-*m*-OMe, *N*-pyrrolidynmethyl

R^3 = Pr, Ph, *tert*-Bu, $SiMe_3$, *N*-pyrrolidynmethyl

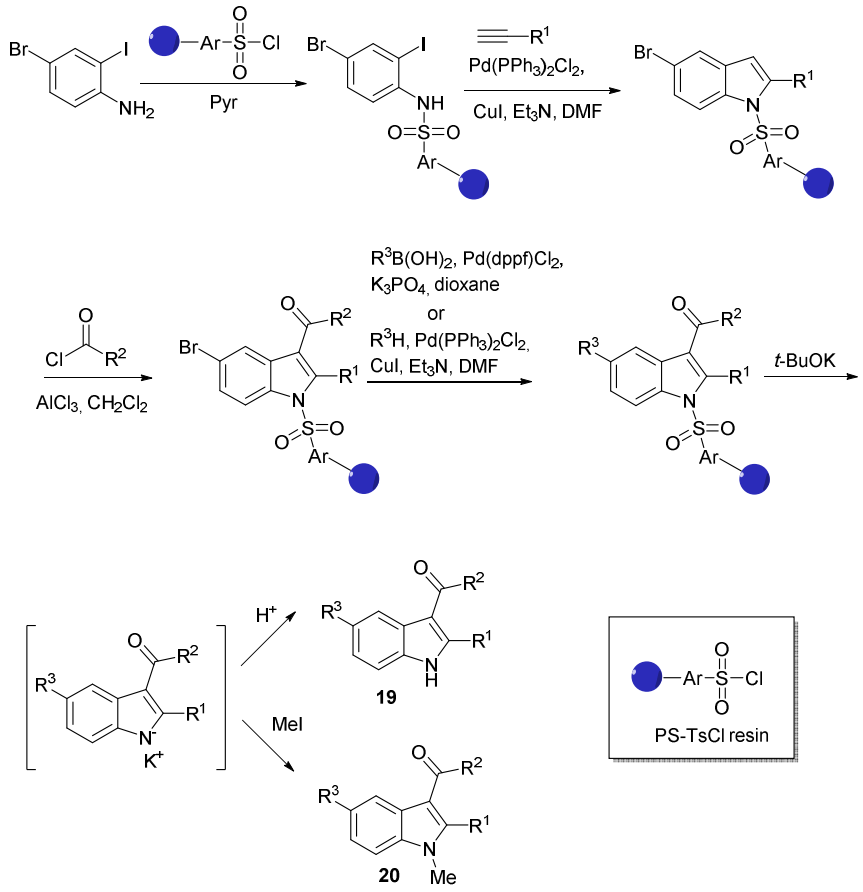
Scheme 7. Heteroanulation of alkynes with resin-bounded *o*-iodoanilines

The traceless solid phase heteroannulation was performed using Elman's THP resin for linking the *o*-iodoaniline by the nitrogen through an aminal functional group such as resin **18** (Scheme 8) (1994TL9333, 1998TL8317). The usual Larock combination of bases and catalyst was not useful. However, replacing the catalyst system with $Pd(PPh_3)_2Cl_2$ and using tetramethylguanidine (TMG) as base gave a good to excellent mass recovery after the acidic cleavage.



Scheme 8. Heteroannulation with the *N*-linked of *o*-iodoaniline to a THP-resin

A small library of 2,3,5-trisubstituted indoles was obtained by Schultz and co-workers starting from a solid supported 3-bromo-2-iodoaniline on commercially available PS-TsCl resin (polystyrene sulfonyl chloride; Argonaut Technologies). A successive Larock heteroannulation, followed by electrophilic substitution on indole position three and final Suzuki or Sonogashira cross coupling reactions, gave excellent results for the preparation of an important number of indole derivatives **19** and **20** (Scheme 9) (2001OL3827).



R^1= Ph, 2-MePh, 4-FPh, 4-MeOPh, 4-MePh, Pr

R^2 = Ph, 2-MePh, 4-FPh, 3-MePh, 3-MeOPh, 4-MeOPh, 4-tBuPh, 4-MeOPh, 4-MePh, Me, 2-Me-1-naphtyl, cyclopropyl, cyclohexyl

R^3 = Ph, 2-MePh, 3,4-Cl_2Ph, 3-MePh, 3-F-4-MePh, 2,3-Me_2Ph, 2-Cl-4-PhOPh, 2-Cl-6-MeOPh, 2-F-Ph-ethynyl, 4-F-Ph-ethynyl, 4-MeO-Ph-ethynyl, 4-tBuPh, 4-MePh-ethynyl, 2-CNPh, 3,4-F_2Ph, Bn-ethynyl, 2-propenyl, Ph-ethynyl, Pr, 2-benzothienyl, 2-naphtyl,

Scheme 9. Schultz synthesis of substituted indoles **19** and **20**

A similar strategy to that explained above was used by Zhang for heteroannulation with a traceless sulfonyl linker which has a dual-activation process. The traceless sulfonyl linker serves as an activating group to facilitate

indole cyclization. After indole formation, it is activated and poised for cleavage under mild conditions (2000OL89). Some time later, the same group described the synthesis of 3-substituted 2-arylindoles by sequential reactions in solid phase based on the use of silylalkyne for heteroannulation, followed by transformation of trimethylsilyl to iodide and then by Suzuki cross-coupling (2001TL4751).

3.2 Larock indole synthesis using immobilized palladium complexes

Heterogeneous palladium catalysts were prepared by covalent immobilization of palladium (II) complexes onto SBA-15 silica. The heteroannulation of 2-iodoaniline with triethyl(phenylethynyl)silane using these preformed palladium complexes gave excellent yields in Larock synthesis of indoles. The palladium catalysts demonstrated to be recyclable through multiple recycling experiments (2010MI179).

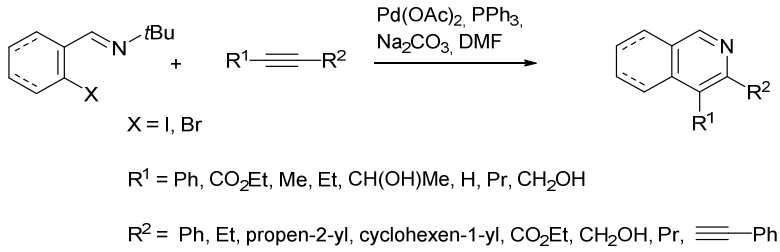
The thiopseudourea palladium(II) complex described by Mandapati and co-workers (Scheme 5) was used by same group on solid phase version. (2013JOM162, 2014JOM31). The polystyrene supported thiopseudourea palladium(II) complex was used for 2,3-disubstitutedindole synthetized by reaction between the iodoaniline and diphenylacetylene. Among the studied bases and solvents, K_2CO_3 and DMF gave the best results.

4. POLYHETEROCYCLIC COMPOUNDS BY LAROCK REACTION

The importance of small molecules containing polycyclic heterocycles as privileged structures for developing new drugs has been demonstrated (2011CC12754, 2014JA14629). This highlights the value of a general synthetic procedure such as the one proposed herein that allows the synthesis of a wide range of different structures. The introduction of this chapter depicts how Larock heteroannulation was used for the synthesis of benzofurans, benzopyrans, and Isocoumarins, giving good to excellent yields (Figure 1) (1995JOC3270). This section describes the further development and application of the same procedure.

4.1. Isoquinolines and pyridines by iminoannulation of internal alkyne

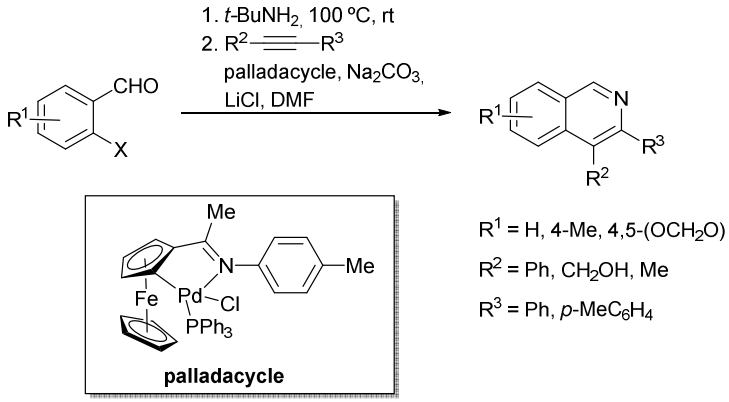
An efficient palladium catalyzed synthesis of nitrogen heterocycles, including isoquinolines, tetrahydroisoquinolines, pyrindines and pyridines, was developed by Larock and co-authors (1998JOC5306). Palladium-catalyzed iminoannulation of internal alkynes with a number of substituents employing the *tert*-butylimine of *o*-iodobenzaldehyde gave good to excellent yields of isoquinolines with high regioselectivity. The procedure was extended to the preparation of other nitrogen-containing heterocycles (2001JOC8042). More than fifty heterocycles were prepared under optimized conditions with substituted quinoline, tetrahydroquinoline, pyridine, cyclopenta[*b*]pyridine and dihydrobenzo[*f*]isoquinoline as principal motifs (Scheme10).



Scheme 10. Synthesis of isoquinolines, tetrahydroisoquinolines and pyridines

4-Fluoroalkylated isoquinolines were obtained by Konno using fluorine containing alkynes, $R^1 = CF_3$, CHF_2 or $C(CHF_2)_3$, and the same procedure as shown before in (Scheme10) (2005JOC10172).

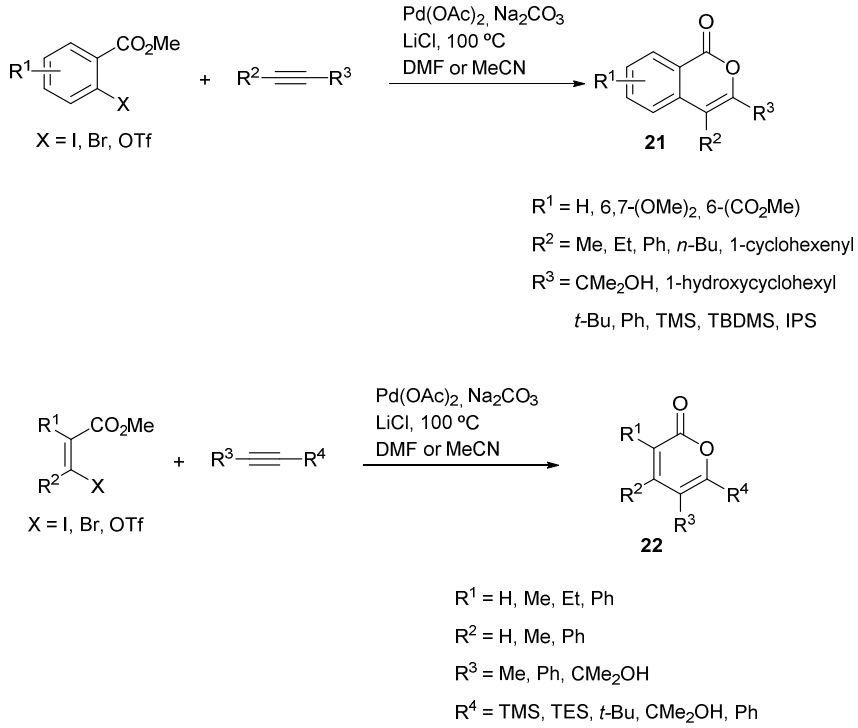
A tandem reaction of imination of *o*-halobenzaldehydes with *tert*-butyl amine and subsequent palladacycle-catalyzed iminoannulation of internal alkynes has been recently developed by Wu el al for the synthesis of isoquinolines (Scheme 11) (2011T2969).



Scheme 11. Palladacycle catalyzed synthesis of isoquinolines

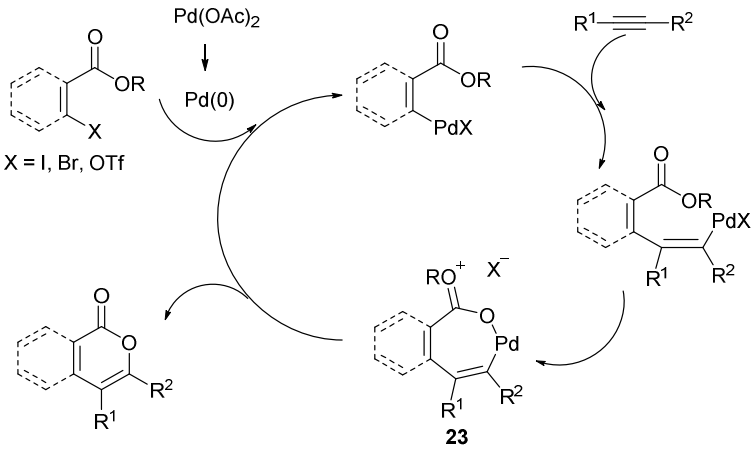
4.2. Isocoumarins and α-pyrones

A regioselective route to isocoumarins **21** and α-pyrones **22** (Scheme 12) containing aryl, silyl, ester, *tert*-alkyl, and other hindered groups were prepared in good yields by treating halogen or triflate containing aromatic and α,β–unsaturated esters, respectively, with internal alkynes in the presence of a palladium catalyst (1999JOC8770).



Scheme 12. Synthesis of isocoumarins **21** and α-pyrones **22**

The proposed mechanism for the oxygen containing heterocycles is based on a seven-membered palladacyclic complex **23** (Scheme 13) in which the regiochemistry of the reaction is controlled by steric factors.

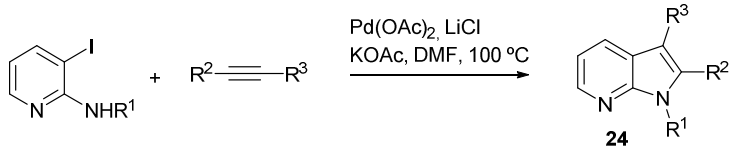


Scheme 13. Proposed mechanism for the synthesis of isocoumarins **21** and α-pyrones **22**

The same reaction for isocoumarin preparation was performed using colloidal catalyst PS-PEO-PC-Pd in dimethylacetamide at 100 °C in the presence of Et_3N and sodium acetate with yields comparable to those of low-molecular-weight palladium complexes (2006OM154). Excellent results were obtained for the substituted isocoumarin preparation, as described for indoles in section 2.4.

4.3. Pyrrolo[2,3-*b*]pyridines

Several 2,3-disubstituted pyrrolo[2,3-*b*]pyridines (7-azaindoles) **24** were obtained by Pd-catalyzed heteroannulation of alkynes with 2-amino-3-iodopyridine derivatives with high regioselectivity under the experimental conditions shown in (Scheme 14) (1998TL627). The easy manipulation of substituents was also demonstrated.



R^1 = H, Me, Bn, *p*-OMeBn

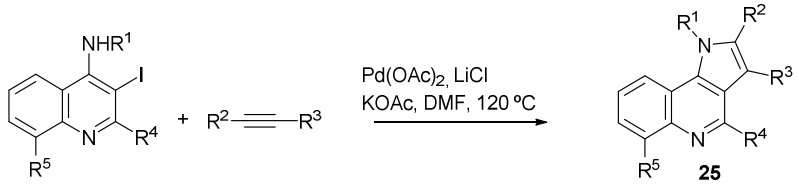
R^2 = TMS, *t*-Bu, Ph

R^3 = CH_2OH, CH_2CH_2OH, *n*-Pr, Me

Scheme 14. Synthesis of 2,3-disubstituted pyrrolo[2,3-*b*]pyridines **24**

4.4. Pyrrolo[3,2-*c*]quinolones

Several substituted pyrrolo[3,2-*c*]quinolines **25** were prepared by heteroannulation of internal alkynes and substituted 3-iodo-4-aminoquinolines using Pd-catalyst with good yields (Scheme 15) (1999TL4379). The obtained compounds were further transformed by desilylation, debenzylation or substitution.



R^1 = 2-MePh, Bn, 2-OMe-4-MePh

R^2 = TMS, Pr, Ph

R^3 = Me, CH_2OH, CH_2CH_2OH, *i*-Pr

R^4 = H, Me

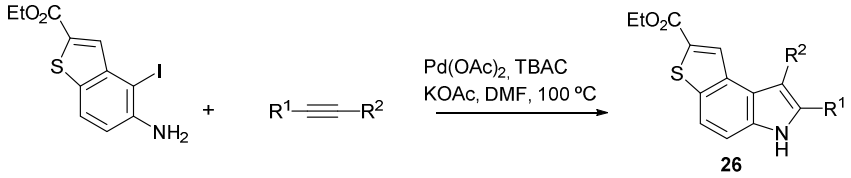
R^5 = OCF_3, OMe

Scheme 15. Synthesis of substituted pyrrolo[3,2-*c*]quinolines **25**

4.5. Thieno[3,2-*e*]indoles

Several thieno[3,2-*e*]indoles **26** were obtained by heteroannulation of 5-amino-4-iodobenzo[*b*]thiophene with internal alkynes (2009T8497). The synthesis of 7,8-

disubstituted thienoindoles was attempted using $Pd(OAc)_2$ with different bases (K_2CO_3, KOAc, Na_2CO_3, NaOAc) with or without PPh_3 as coupling reagent (Scheme 16). An important conclusion was the confirmation that the yield is highly dependent on the choice of base. Regioselectivity was good when the two alkyne substituents were of a different size.



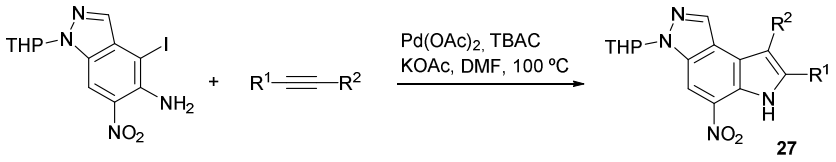
R^1 = TBDMS, Ph, 2-Pyr, TMS

R^2 = CH_2CH_2THP, CH_2CH_2OH, Ph, 3-FPh, CO_2Et

Scheme 16. Synthesis of thieno[3,2-*e*]indoles **26**

4.6. 1,6-Dihydropyrrolo[2,3-*g*]indazoles

The synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives **27** was described. The indolic ring system was constructed via a Larock palladium-catalyzed annulation using terminal and internal alkynes (Scheme 17). A directing effect on regioselectivity mediated by the ester function of alkyl 3-substituted propiolate derivatives used as internal alkynes was demonstrated (2011T7330).



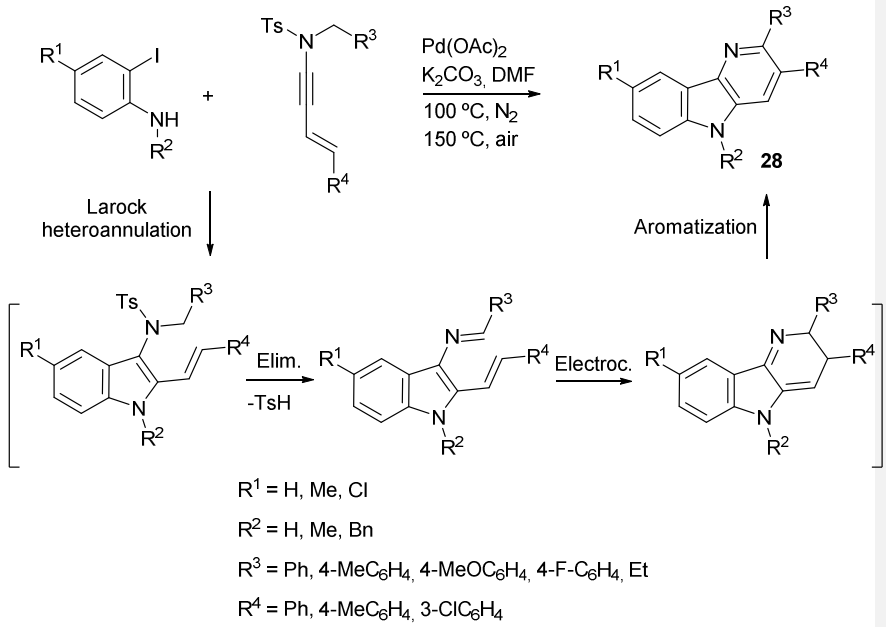
R^1 = TMS, H, Ph, *n*-Pr, $CH(OEt)_2$, CH_2OBn, CH_2OH, CH_2OAc

R^2 = H, TMS, Ph, *n*-Pr, $CH(OEt)_2$, CH_2OBn, CH_2OAc

Scheme 17. Synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole

4.7. δ-Carbolines

An efficient methodology for the synthesis of δ-carbolines **28** was developed by Cao, Lai and co-workers. Such methodology was based on a Pd-catalyzed cascade reaction between 2-iodoanilines and *N*-tosyl-enynamines (2012OL38).



Scheme 18. Synthesis of synthesis of δ-carbolines **28**

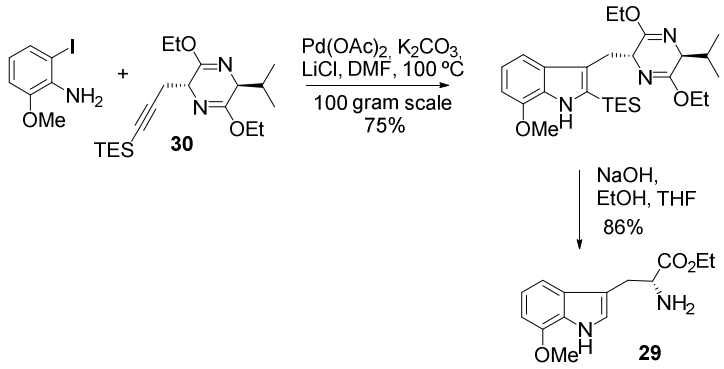
The mechanism was stablished by several experimental control processes and involved Larock heteroannulation, subsequent elimination of a molecule of 4-methylbenzenesulfinic acid, electrocyclization of the resulting dienimine, and, lastly, oxidative aromatization (Scheme 18).

5. SYNTHESIS OF NATURAL COMPOUNDS

5.1. Tryptophan derived alkaloids

An important group of tryptophan-derived alkaloids with oxygenated substituents at the benzene ring was obtained using the same strategy described by Cook and co-workers for stereoselective tryptophan synthesis (2001JOC4525). The enantio-specific synthesis of the 7-methoxy-D-tryptophan ethyl ester **29** was

completed in good yield by a two-step process based on a Larock heteroannulation using a Schollkopf-based chiral auxiliary **30** followed by basic removal of the chiral auxiliary (Scheme 19).



Scheme 19. Larock heteroannulation using a chiral auxiliary

The same procedure was used for the syntheses of other methoxy-substituted indole alkaloids such as sarpagine and other several derivatives of (+)-vellosimine, (+)-affisamine (-)-fuchsiaefoline, mitragynine, geissoschizol and voachalotine (Figure 5) (2004OL249, 2006JOC251, 2007OL3491).

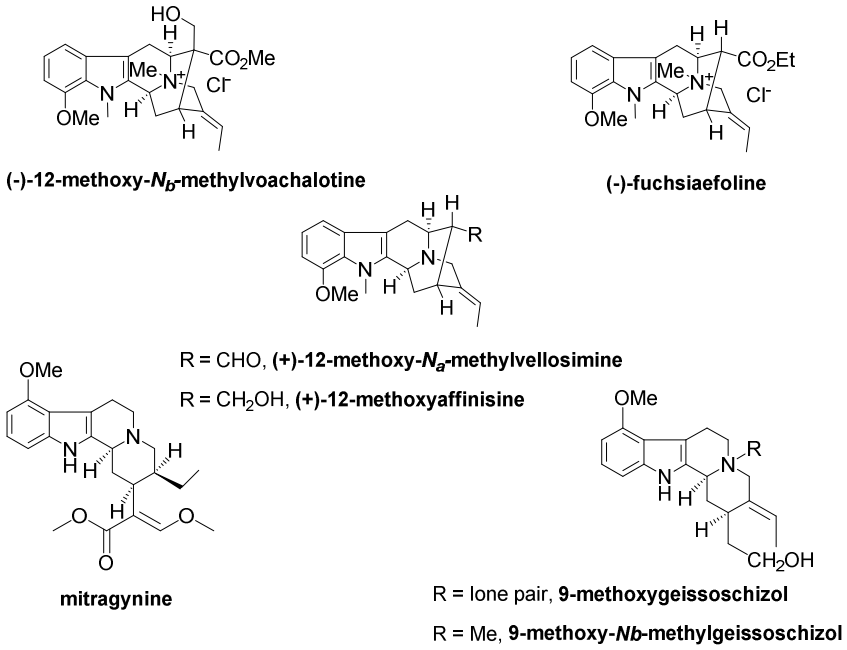


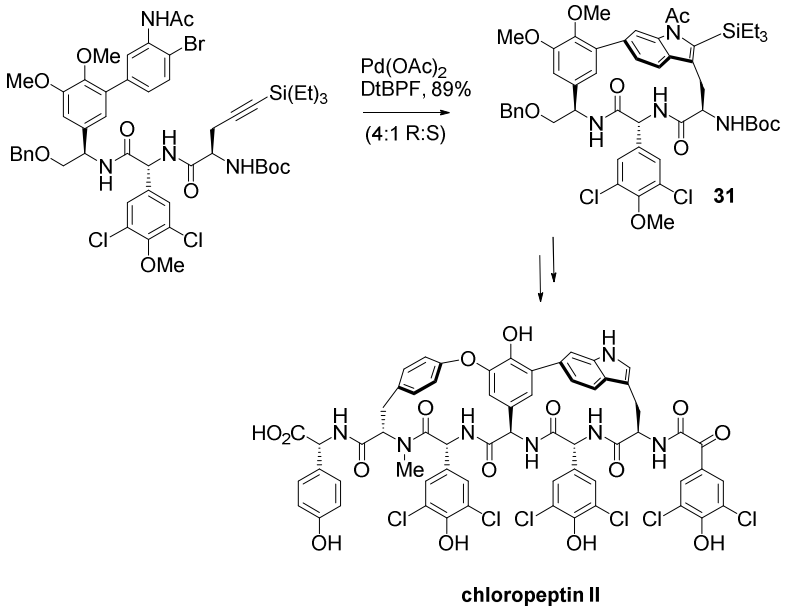
Figure 5. Structures of indole alkaloids with methoxy substituents

5.2. Synthesis of complestatins

Complestatins, named chloropeptin II and chloropeptin I, were isolated from *Streptomyces lavendulae* by Sankyo Co. Ltd in 1989. That same year, Seto and co-workers supplemented this information with the elucidation of the structure of these two chloropeptins, and provided additional details on their biological activity. Later Omura and co-workers reported their isolation from *Streptomyces* sp. WK-3419 (1989MI236, 1989TL4987, 1994MI1173). Important inhibitory activitiy for HIV gp120-CD4 binding were described (1980MI1194, 1994MI1173). Chloropeptins are structurally similar to glycopeptide antibiotics such as vancomycine.

Boger and co-workers reported the first total synthesis of chloropeptin II and later its transformation into chloropeptin I (2009JA16036). The key step to total synthesis was macrocyclization of peptide **31** by an intramolecular Larock indole heteroannulation. An intramolecular reaction between a substituted 2-

bromoaniline with a removable terminal alkyne afforded simultaneous regioselective indole ring formation and macrocyclization. The TES substituent of the alkyne dictates indole cyclization regioselectivity (Scheme 20).



Scheme 20. Larock heteroannulation for the synthesis of chloropeptin II

5.3. Substituted glycines and homotryptophan derivatives

Indolylglycines are a common motif found in 2,5-bis(3'-indolyl)piperazine alkaloids such as dragmacidin and hamacanthin (Figure 6). They have been secluded from Deep-water sponges *Dragmacidon*, *Halicortex*, *Hexadella*, *Spongosorites*, and the tunicate *Didemnum candidum* (2000OL3027, 2005T2309). The interest on these compounds lies on their capability for limiting conformational flexibility in solid phase peptide synthesis to enhance enzymatic stability and bioavailability compared with naturally occurring peptides. They afford a wide range of biological responses, including anticancerous, antifungal, antiviral and anti-inflammatory properties.

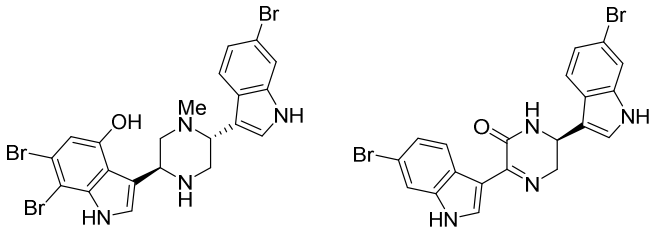
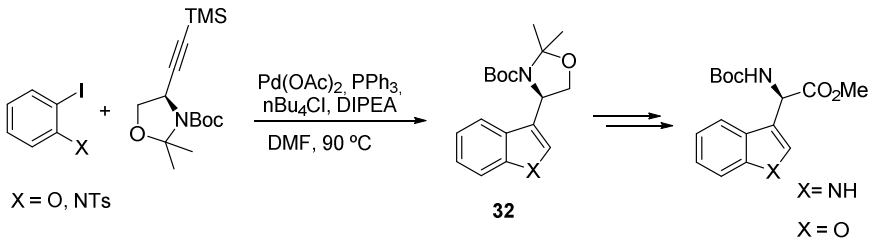


Figure 6. Structures of dragmacidin and hamacanthin A

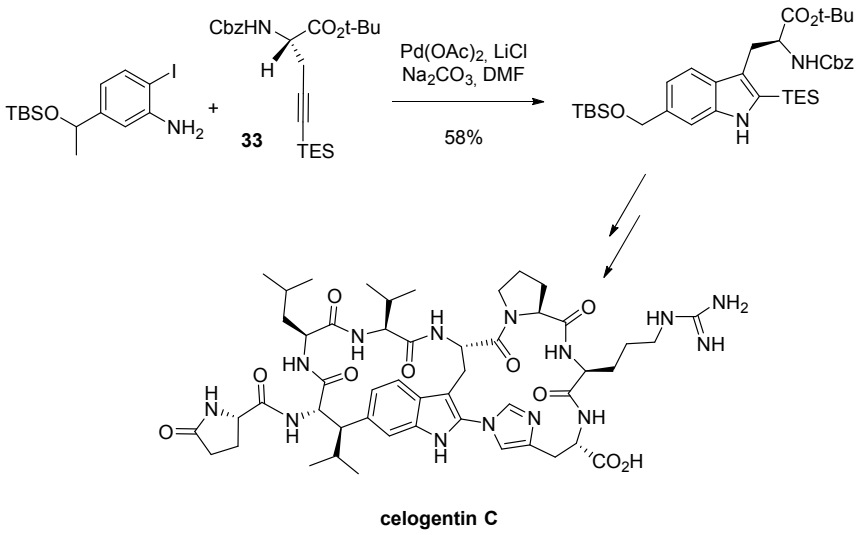
Sinha and co-workers developed a methodology for the synthesis of enantiopure 2- and 3-indolylglycine derivatives and their oxygen analogues. The procedure is based on a Larock heteroannulation using a sylilated chiral alkyne with a *N*-protected oxazolidine as the key reaction step that affords compound **32**, a precursor of substituted glycines (2012JOC7081) (Scheme 21).



Scheme 21. Synthesis of enantiopure 3-indolylglycine and 3-benzofurylglycine

The same synthetic strategy was used for the synthesis of several homotryptophan derivatives (2012T280). Tryptophan analogues constitute a class of indoleamine 2,3-dioxygenase (IDO) inhibitors (1993MI473, 1994MI531). IDO glycoprotein is of great interest as potential substrate for therapeutic purposes (2010JMC1172, 1995CSR401).

An alkyne-substituted glycine **33** was used by Castle and Srikanth for the asymmetric synthesis of the central Trp residue of Celogentin C (Scheme 22) (2003OL3611). Celogentin C is an octapeptide constituted by a bicyclic framework in which a substituted Trp is the central core. Celogentin C shows a strong inhibitory activity in tubulin polymerization.

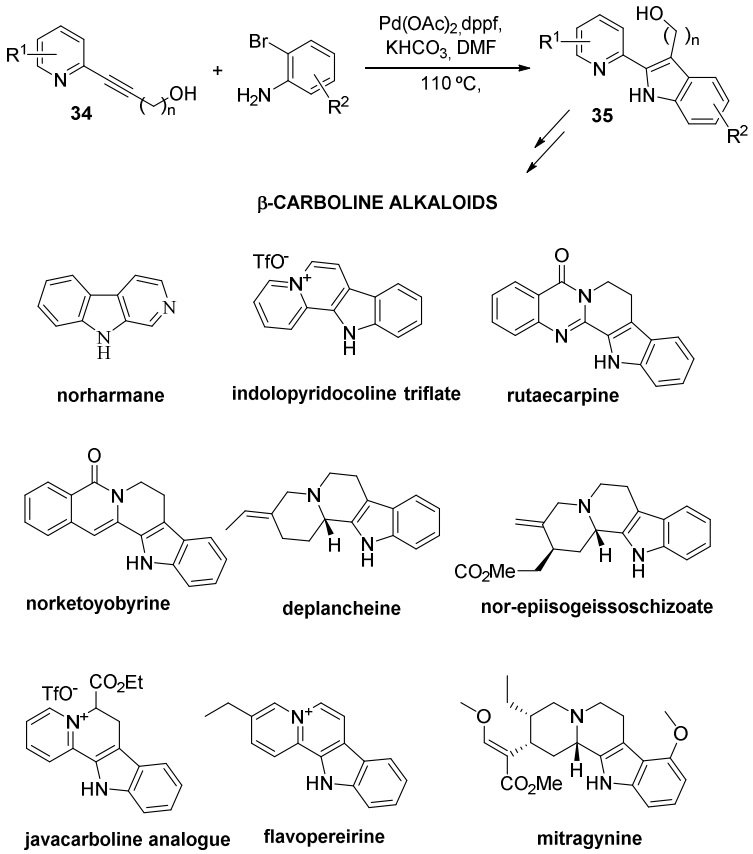


Scheme 22. Structure of celogentin C and synthesis of the central Trp residue

5.4. β-Carboline-containing alkaloids

β-Carboline-containing alkaloids comprise a large family of interesting polycyclic natural products isolated from different sources (Figure 7). These compounds afford a wide range of activities: intercalate into DNA, inhibit CDK, topoisomerase and monoamine oxidase, and interact with benzodiazepine and 5-hydroxy serotonin receptors. In addition, they have shown sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic as well as antimicrobial activity (2007MI14).

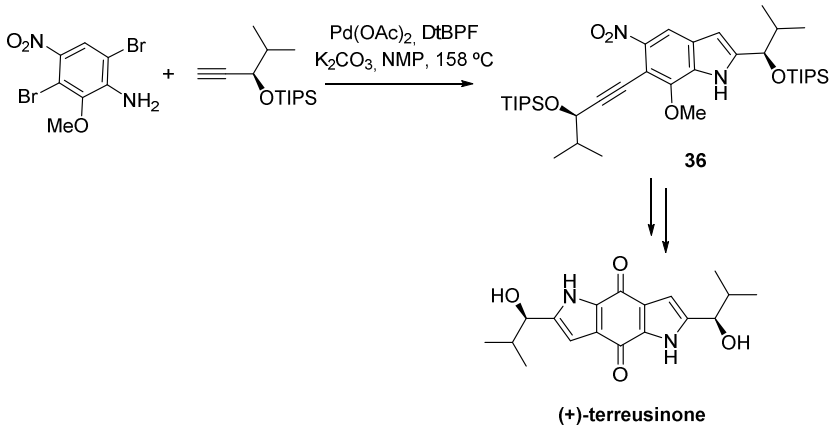
Bannister and co-workers developed a general synthetic approach for the synthesis of tetracyclic and pentacyclic β-carboline-containing alkaloids (2014OL6124). Two consecutive Pd catalyzed reactions are the basis for this synthetic strategy: a Sonagashira coupling for the preparation of the 2-pyridyl alkyne **34** and a Larock indole heteroannulation of alkyne **34** with the proper bromoaniline to give pyridylindole **35** (Scheme 23).



Scheme 23. Synthesis of β-carboline alkaloid precursors

5.5. Synthesis of terreusinone

Terreusinone is a dipyrrolobenzoquinone with a particular a pyrrolo[2,3-*f*]indole-4,8-dione ring system, which is unique among natural products. It was first isolated from the marine algicolous fungus *Aspergillus terreus* (2003TL7707). The first synthesis of (+)-terreusinone and its subsequent revision were described by Wang and Sperry (2011OL6444, 2013T4563). The key transformation includes a one-pot Larock indolization – Sonogashira coupling starting with a highly substituted dibromoaniline to give indole **36**, properly substituted with the new heterocyclic ring formation (Scheme 24).

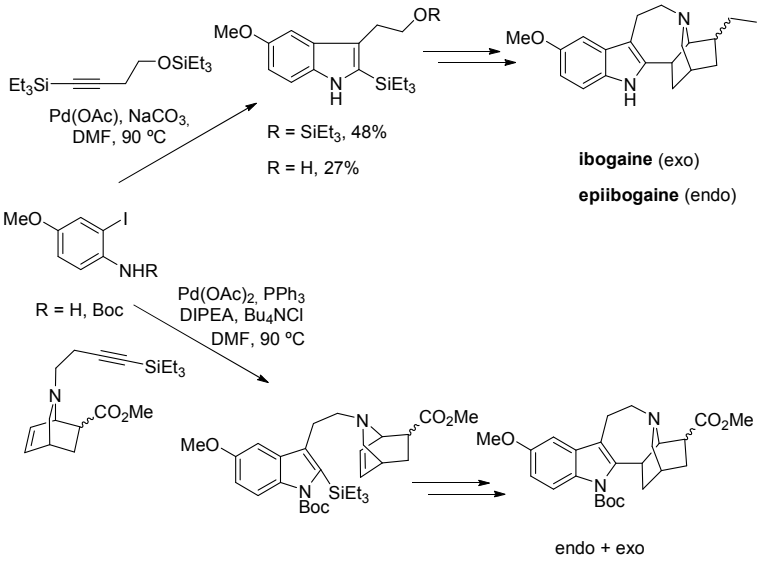


Scheme 24. Synthesis of indole **36,** precursor of (+)-terreusinone

5.6. Synthesis of ibogaine

Ibogaine is a monoterpenoid indole alkaloid belonging to the large family iboga isolated from the *Apocynaceae* plant family (2002MI281, 2011OPP541). A wide range of antifungal, antilipase, anti HIV-1, anticholinesterase or anti-leishmania pharmaceutical properties have been described for (1995MI235, 2005BMC4092, 2002MI2111).

Jana and Sinha have described the total synthesis of ibogaine, epiibogaine and their analogues, utilizing Larock heteroannulation reaction for the creation of the suitably substituted indole (Scheme 25) (2012T7155).

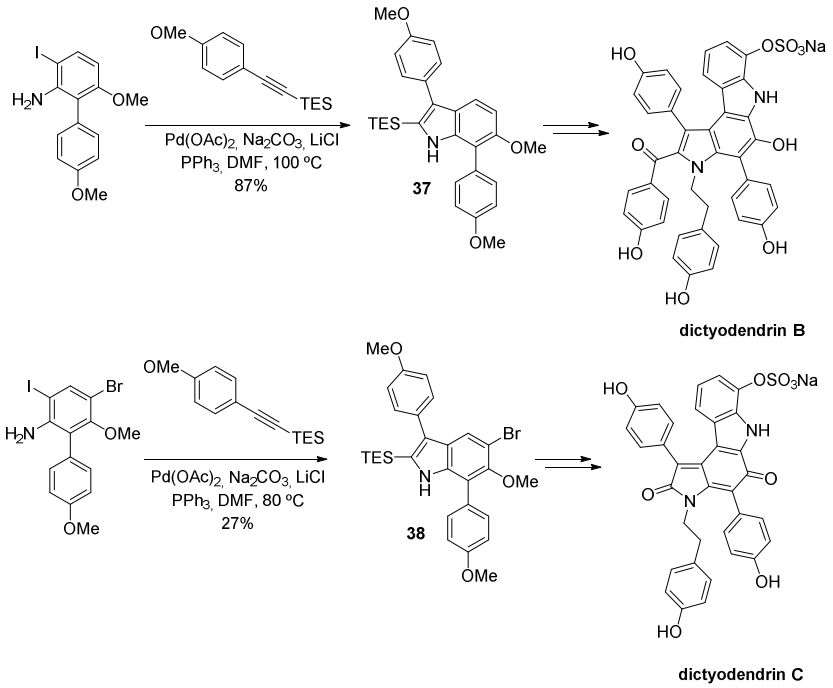


Scheme 25. Total synthesis of ibogaine and analogues

5.7. Synthesis of dictyodendrins

Dictyodendrins A-E are a family of marine products, isolated by Fusetani and Matsunaga from the sponge *Dictyodendrilla verongiformis* (2003JOC2765). Dictyodendrins have a unique pyrrolo[2,3-*c*]carbazole core. They exhibit strong telomerase inhibitory activity and their function exerts an important effect on relevant vital processes such as aging or cancer.

Jia and co-workers have described a concise total synthesis of dictyodendrins B and C, utilizing palladium catalyzed Larock annulation for the construction of the highly substituted indole core of compounds **37** and **38** (2014EJO5735) (Scheme 26).

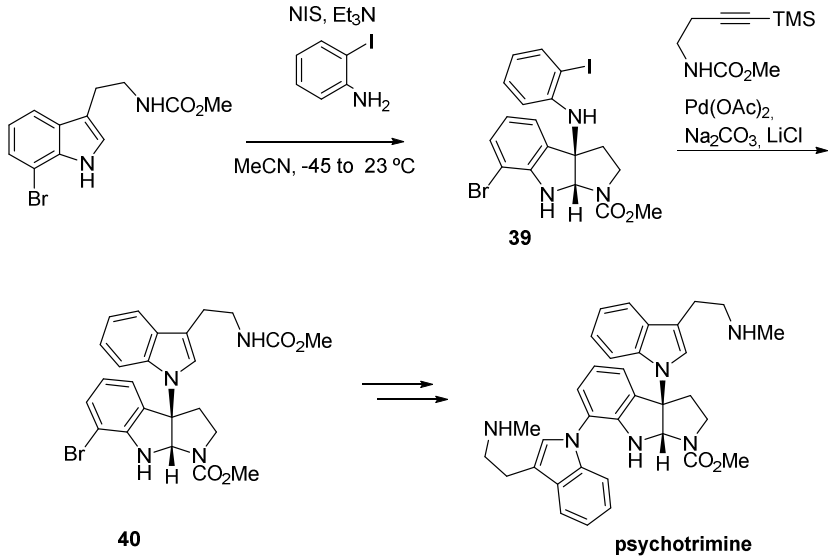


Scheme 26. Synthesis of polysubstituted indoles **37** and **38**, precursors of dictyodendrins B and C

5.8. Synthesis of natural products containing the tryptamine-HPI bond

Psychotrimine and psychotetramine constitute a couple of natural compounds whose biosynthesis seems to take place via tryptophan dimerization (2004OL2945). A differential structural feature of these alkaloids lies in the bond between the *N*-indole of one tryptamine and the carbon 3a of a hexahydropyrroloindole (HPI) coming from de intramolecular cyclization of the second Trp unit. In order to establish the challenging N1-C3a linkage, Baran and co-workers developed a novel methodology for the synthesis of psychotrimine (2008JA10886). The key step in that synthesis is based on the reaction of the *N*-protected bromotryptamine derivative with *o*-iodoaniline and *N*-iodosuccinimide

to afford the coupled product **39** which has resulted in the simultaneous formation of tricyclic pyrroloindole and the bond between C3a and *N*-aniline. A chemoselective Larock annulation between **39** and known alkyne was performed to afford the corresponding indolyl-hexahydropyrroloindole **40** precursor of psychotrimine (Scheme 27). The same methodology was subjected for Baran, Takayama and co-workers for the synthesis of psychotetramine (2008JA10886).



Scheme 27. Synthesis of indolyl-hexahydropyrroloindole **40**, a precursor of psychotrimine

Later the same group described the total synthesis of psychotrimine and more complex peptides containing the same bond between two Trp units such as kapakahines B and F using a Larock heteroannulation as key step (Figure 7) (2009JA6360, 2010JA7119, 2011AG(E)2716).

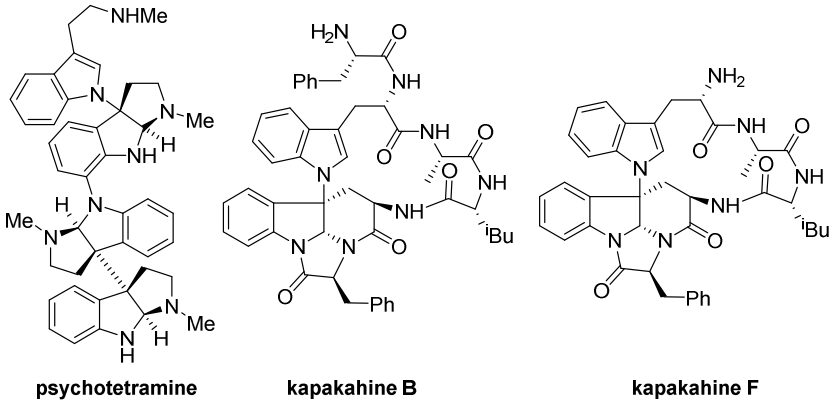


Figure 7. Structures of psychotetramine, kapakahine B and kapakahine F

5.9. Larock reactions in drug discovery

Larock reaction has been used in the pharmaceutical industry because of ease of manipulation, high regioselectivity, good to excellent yields and scaling capacity to multigram. The fluoro-indole ring system of a glucagon receptor antagonist drug candidate **41** for the treatment of type 2 diabetes in the multikilogram scale afforded by means of a Larock-type indole synthesis was described by Scott and co-workers Figure 8 (2012MI1832). *N,N*-dialkyltryptamine derivatives have been studied as 5-hydroxytryptamine (serotonin) receptor 1D agonists for the treatment of migraine. MK-0462 receptor agonist was synthesized using Larock heteroannulation for the synthesis of the indole system (Figure 8) (1994TL6981).

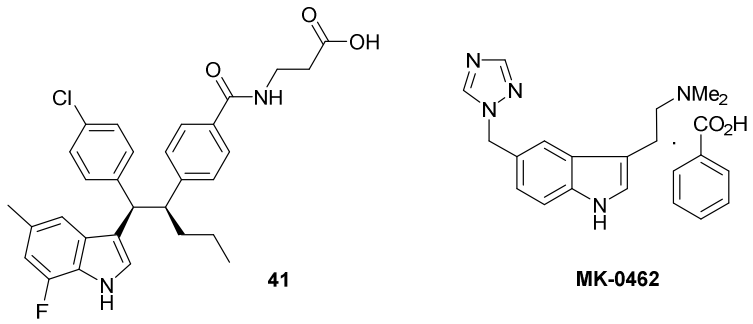
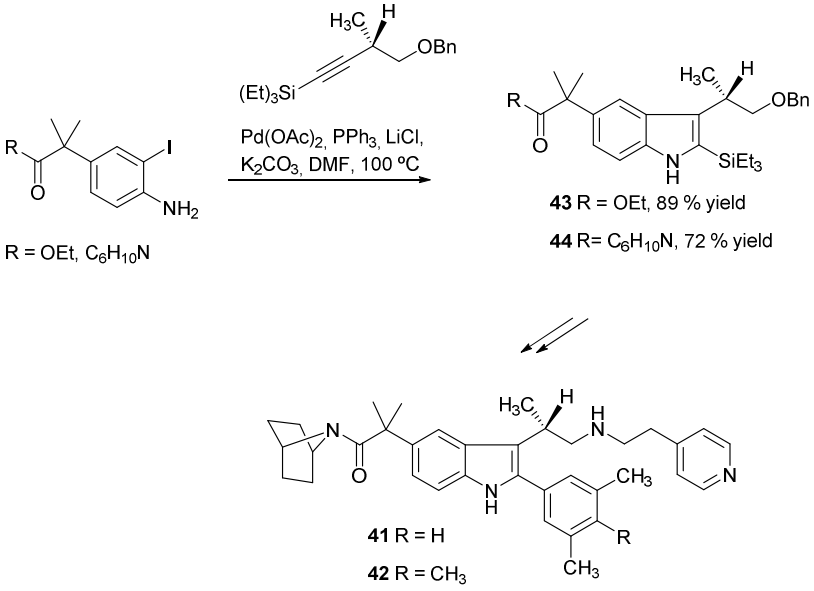


Figure 8. Structures of glucagon receptor antagonist **41** and MK-0462

Gonadotropin Releasing Hormone (GnRH) is a decapeptide synthesized and produced by the neurons of the hypothalamus. GnRH stimulates the synthesis and secretion of hormones involved in male and female gonad function. Researchers from Merck Lab. working in the synthesis of gonadotropin antagonists **41** and **42** found that Larock heteroannulation for the synthesis of indole derivatives **43** and **44** improved reaction yields compared to procedures of indole nucleus formation (2001T5233) (Scheme 28).



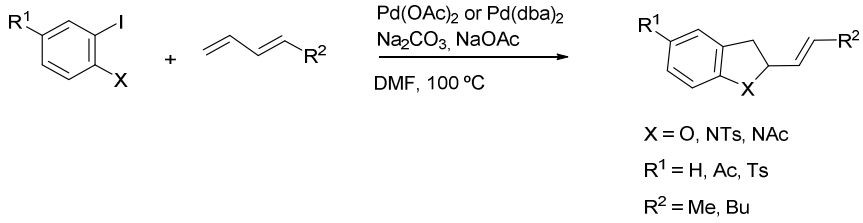
Scheme 28. Larock heteroannulation for the synthesis of gonadotropin antagonists **42** and **43**

6. HETEROANNULATION WITH SUBSTRATES OTHER THAN ALKYNES

Extension of heteroannulation procedure performed by Larock to other unsaturated compounds such as dienes and allenes permitted the synthesis of an important range of different heterocyclic compounds.

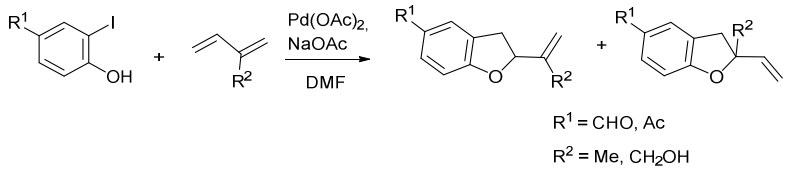
6.1. Heteroannulation of 1,3-dienes

Heteroatom-containing aryl iodides react with 1,3-dienes in the presence of a palladium catalyst and an appropriate base to afford a variety of oxygen and nitrogen heterocycles. Mechanistically, heteroannulation proceeds via aryl- and π-allylpalladium intermediates. Similar results were obtained using either $Pd(OAc)_2$ or $Pd(dba)_2$ as catalysts (Scheme 29). The yield of heterocycle can vary depending on the base, with the best results being obtained with either NaOAc or Na2CO3 (1990JOC3447).



Scheme 29. Heteroannulation of 1,3-Dienes

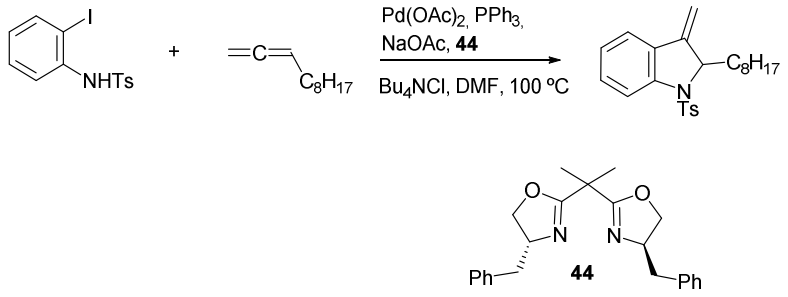
A mixture of regioisomers was obtained using only 2-substituted 1,3-dienes (Scheme 30).



Scheme 30. Heteroannulation of 2-substituted-1,3-Dienes

6.2. Heteroannulation of allenes

Asymmetric hetero- and carboannulation of allenes and aryl or vinyl iodides with a nucleophilic heteroatom substituent in the ortho or allylic position has been achieved in moderate to high levels of enantiomeric excess in the presence of a palladium catalyst and a chiral bisoxazoline ligand, such as **44** (1999JOC7312). Optimization of the process was performed testing several different ligands, catalysts and reaction conditions. The generality of this process has been demonstrated by the use of several nucleophilic substituents as different as tosylamides, alcohols, phenols, carboxylic acids, and stabilized carbanions (Scheme 31).



Scheme 31. Allene heteroannulation

Various chiral ligands were tested with the reaction between *N*-tosyl-2-iodoaniline and 1,2-undecadiene. When coordinated to Pd, these ligands form a six-membered ring that produces products with higher enantiomeric excess than those obtained from a five-membered ring. More electron-rich ligands tend to give higher asymmetric induction. The best results were obtained using bisoxazoline ligands. Several heterocycles with the structures shown in Figure 9 were obtained with good to excellent yields and ee.

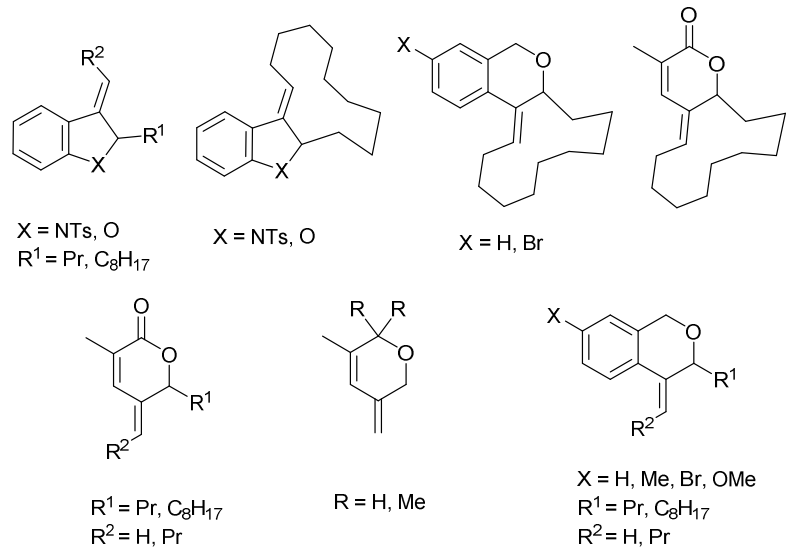


Figure 9. Heterocycles obtained by heteroannulation of allenes

7. CONCLUSIONS

Since the Larock heteroannulation was first described, the mechanism of the process has been established and different synthetic procedures in solution and solid phase have been developed. The ease of reaction handling, the absence of toxic waste and its overall high performance make it the procedure of choice for the preparation of both small molecules such as intermediate synthetic complexes. Elegant routes to a variety of alkaloid and polyoxygenated natural products have resulted from basic methodology research on these heteroannulation reactions. New advances in regioselective constructions of polysubstituted nitrogen- and oxygen-containing heterocycles will continue to drive new applications for this reaction.

ACKNOWLEDGMENTS

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