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Mayotlide: synthetic approaches and structural elucidation

Jesús Herraiz Cobo

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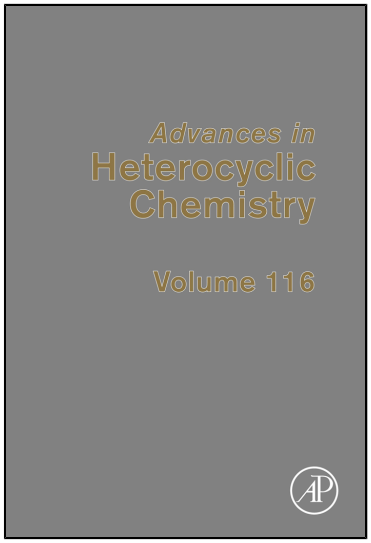

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CHAPTER ONE

The Larock Reaction in the Synthesis of Heterocyclic Compounds

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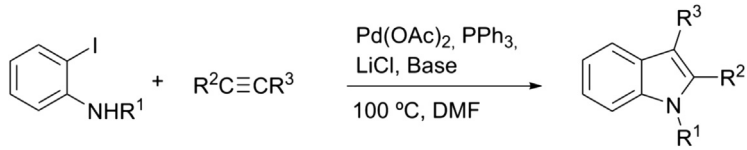
Abstract

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: Alkynes; Heteroannulation; Heterocycles; Natural compounds; Palladium catalyst

1. INTRODUCTION

The Larock indole synthesis, also known as the 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_4NCI. However, it was subsequently observed that LiCl is often more effective and reproducible (Scheme 1; 1991JA6689). The reaction



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.

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was shown to be a high regioselective process giving the bulky substituent of the alkyne in position two of the resulting indole ring.

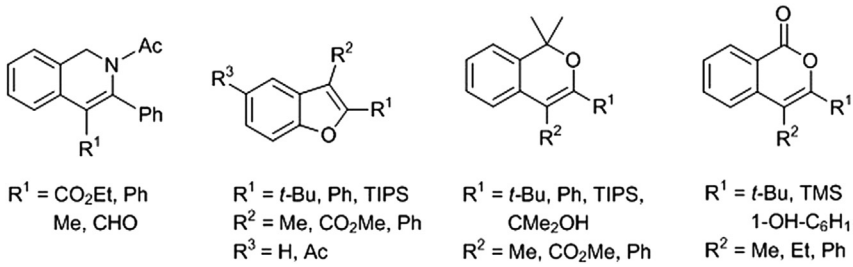
Larock modified the annulation process to access 3-substituted indoles by employing silyl-substituted alkynes. In this case, the bulky silyl group dominates the regioselectivity of the annulation and thus serves as a phantom-directing group in the heteroannulation step. Silylated alkynes provide 2-silyl-3-substituted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

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

Several reviews about the synthesis of heterocycles via palladium-catalyzed reactions containing revisions of Larock procedures have been 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 for 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 were studied by Larock and coworkers (1998JOC7652). The mechanism they propose for indole synthesis proceeds 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



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 synthesized by Larock heteroannulation.

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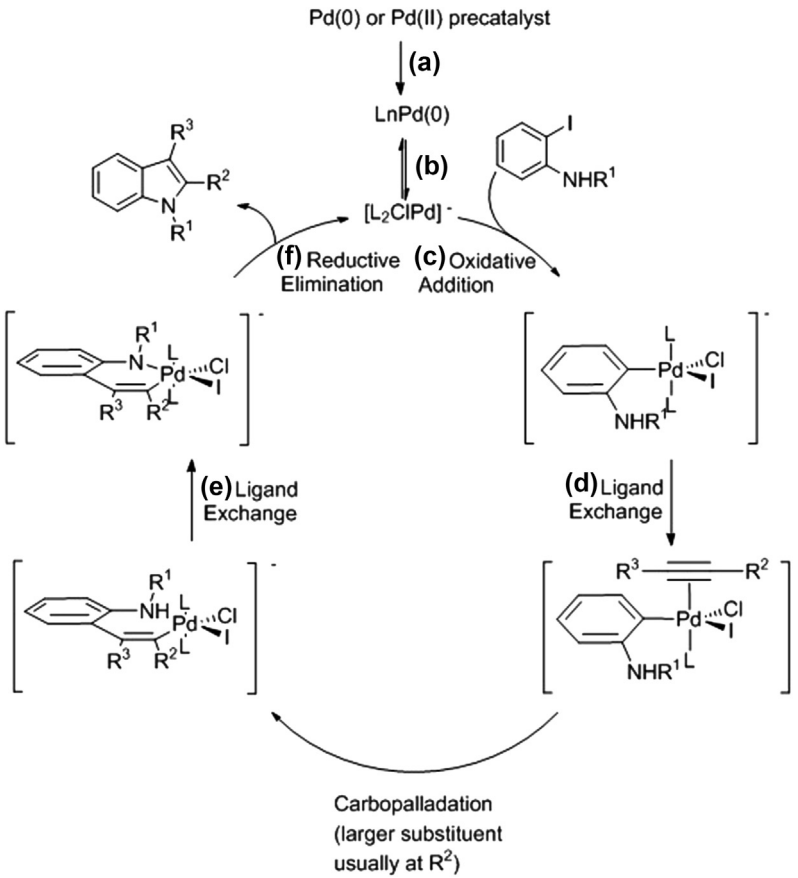
palladium atom of the resulting arylpalladium intermediate and subsequent regioselective syn-insertion into the arylpalladium bond; (e) nitrogen displacement of the halide in the resulting vinyl palladium intermediate to form a six-membered, heteroatom-containing palladacycle; and (f) reductive elimination to form the indole and to regenerate Pd(0) (Scheme 2; 1993JA9531).

The 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,



Scheme 2 Proposed mechanism for Larock heteroannulation.

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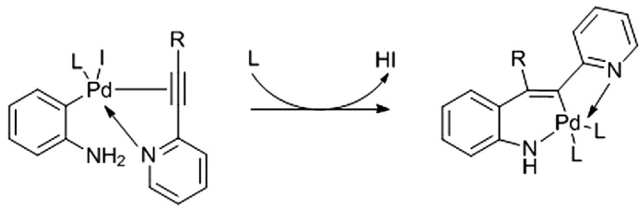
1989JOC2507, 1990JA8590, 1990TL4393, 1991JOC6487, 1991SL777, 1991TL4167, 1992JA791, 1992JA10091, 1992CC390, 1992PAC3323, 1992TL3253, 1992TL8039, 1993JOC560, 1993T5471, 1994JA7923, 1995TL1771).

The Larock annulation process is highly regioselective, and, generally, significantly higher in selectivity than the related palladium-catalyzed hydroarylation process, which often produces regioisomeric 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 has also been 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.

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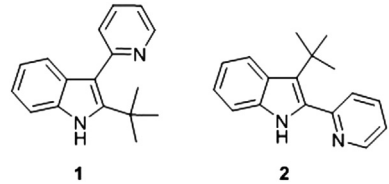


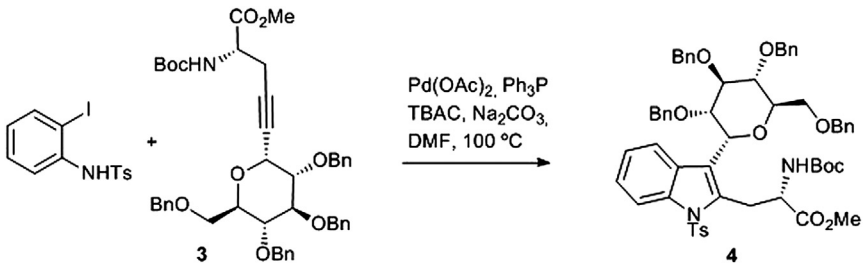
Figure 2 Structures of indole derivatives **1** and **2**.

The same work but using *tert*-butyl-2-pyridylacetylene showed the importance of steric factors 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 the 2-(*tert*-butyl) indole **1** over the 3-(*tert*-butyl)indole **2**, in a ratio of 69:31 (Figure 2).

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

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 coworkers 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 found to be the most active. Several bases



Scheme 4 Reversed regioselectivity in the Larock heteroannulation.

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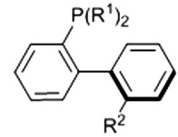
5 R = Ph (DPPF)
6 R = *i*-Pr (DiPPF)
7 R = *t*-Bu (DtBPF)



8 R^1 = Cy, R^2 = H
9 R^1 = *t*-Bu, R^2 = H
10 R^1 = Cy, R^2 = NMe_2
11 R^1 = *t*-Bu, R^2 = NMe_2
Cy = cyclohexyl

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

were also tested to ascertain their effect on the reaction rate and regioselectivity.

To avoid using bulky electron-rich phosphine ligands, the Pd-catalyzed indolization of 2-bromoanilines with internal alkynes was examined by Liu, Guo, and coworkers (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 (dimethylformamide) with K_2CO_3.

2.2 Heterogeneous Catalyst

Use of heterogeneous palladium catalysts, $[Pd(NH_3)_4]^{2+}$/NaY and [Pd]/SBA-15, for the synthesis of 2-substituted indoles gave high conversions and selectivities (2006MI715). Changing iodoaniline to *N*-tosyl-2-iodoaniline produced significantly increased reaction times for full conversion. The heteroannulation of phenylacetylene with sulfonamide requires 6 days but 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 gives good yields of 2,3-disubstituted indoles (2009MI2055; 2010MI3338; 2011TL1916; 2011MI2).

2.3 Phosphine-Free Pseudothiourea Palladium(II)

The phosphine-free pseudothiourea 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 afford the corresponding products as mixtures of regioisomers in good to high yields (2013JOM162). These are examples in which the two substituents in the internal alkyne have a similar hindrance and the regioisomers **13** and **14** are obtained in the same proportion.

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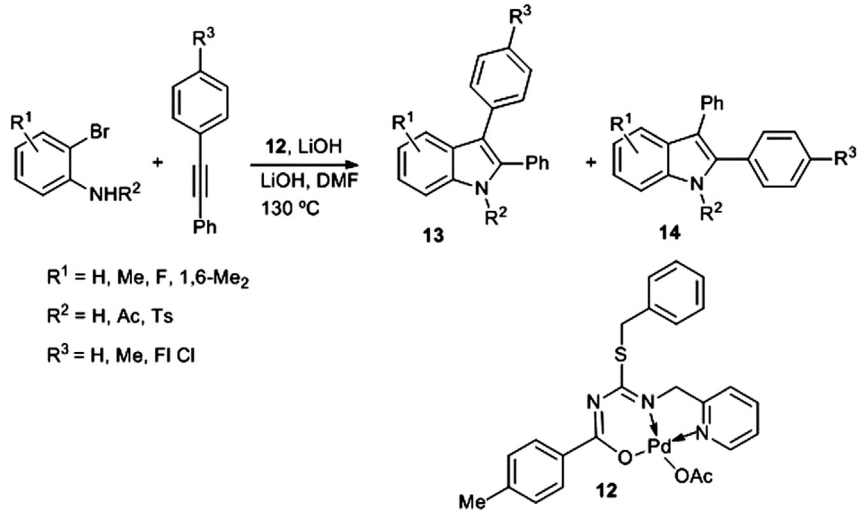

Scheme 5 Larock reaction with pseudothiourea-Pd(II) complex **12**.

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, have been used to catalyze heterocyclization of *N*-methylsulfonyl-*o*-iodoaniline with phenylacetylene leading to formation of a 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 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 afford 3-substituted indole-2-silanols after hydrolysis. The cross-coupling between sodium 2-indolylsilanolate salts with aryl bromides and chlorides successfully afforded multisubstituted indoles (Scheme 6). The development of an alkynyldimethylsilyl *tert*-butyl ether as a masked silanol equivalent enabled a smooth

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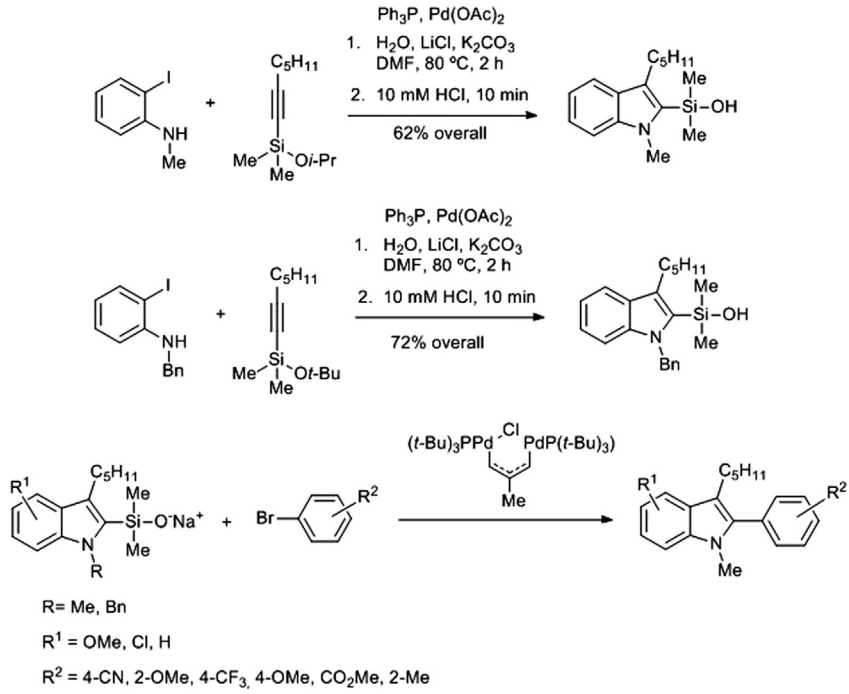

Scheme 6 Synthesis of 1,2,3-trisubstituted indoles.

heteroannulation process and an easy cross-coupling reaction with the suitable catalyst and ligand combination.

2.6 *N*-Heterocyclic Carbene-Pd Complexes

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

These heteroannulations were tested with iodo- and bromoaniline using symmetrical and unsymmetrically substituted alkynes. The electronic effects of the aniline substituents as well the reactivity of aromatic alkynes were tested. The proposed mechanism is in 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

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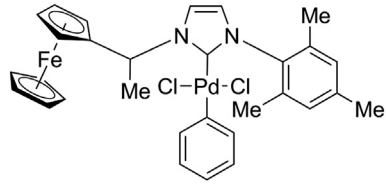

Figure 4 Structure of ferrocenyl NHC-Pd-Py complex **15**.

syn-insertion of the alkyne, the bulky substituent in the resulting indole ring is located in position two.

3. LAROCK REACTIONS IN THE SOLID PHASE

Reactions in the 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 the 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 a Solid Phase

Pd-mediated heteroannulation of alkynes with resin-bound *o*-iodoanilines **16** gives trisubstituted indoles with good yields. Zhang and coworkers have 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, cleavage with trifluoroacetic acid gave the indoloamide functionalized compounds **17**.

Traceless solid-phase heteroannulation has been performed using Elman's tetrahydropyranyl 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 as base gives good to excellent mass recovery after the acidic cleavage.

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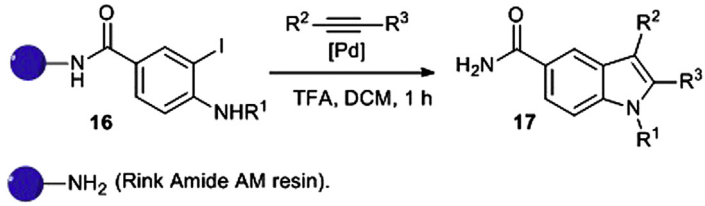


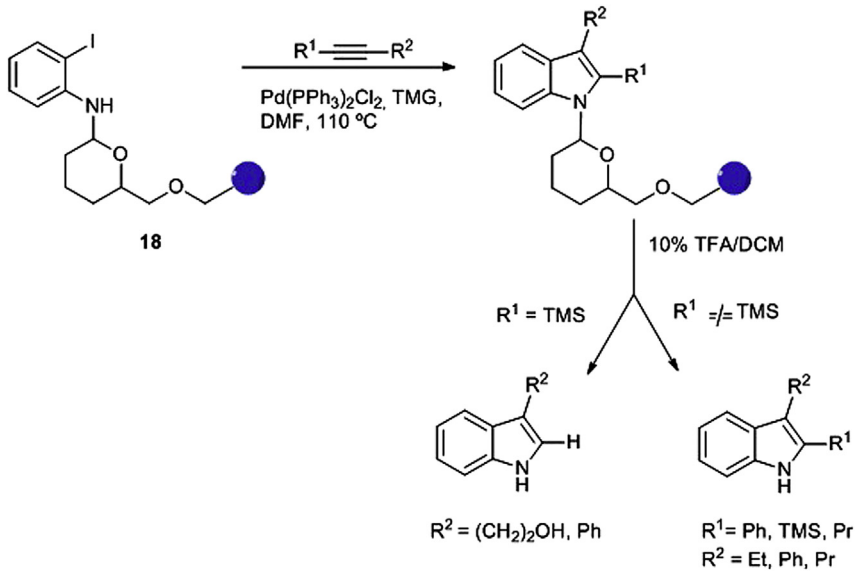
R^1 = H, COMe, $COCHMe_2$

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.

A small library of 2,3,5-trisubstituted indoles was obtained by Schultz and coworkers 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).



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

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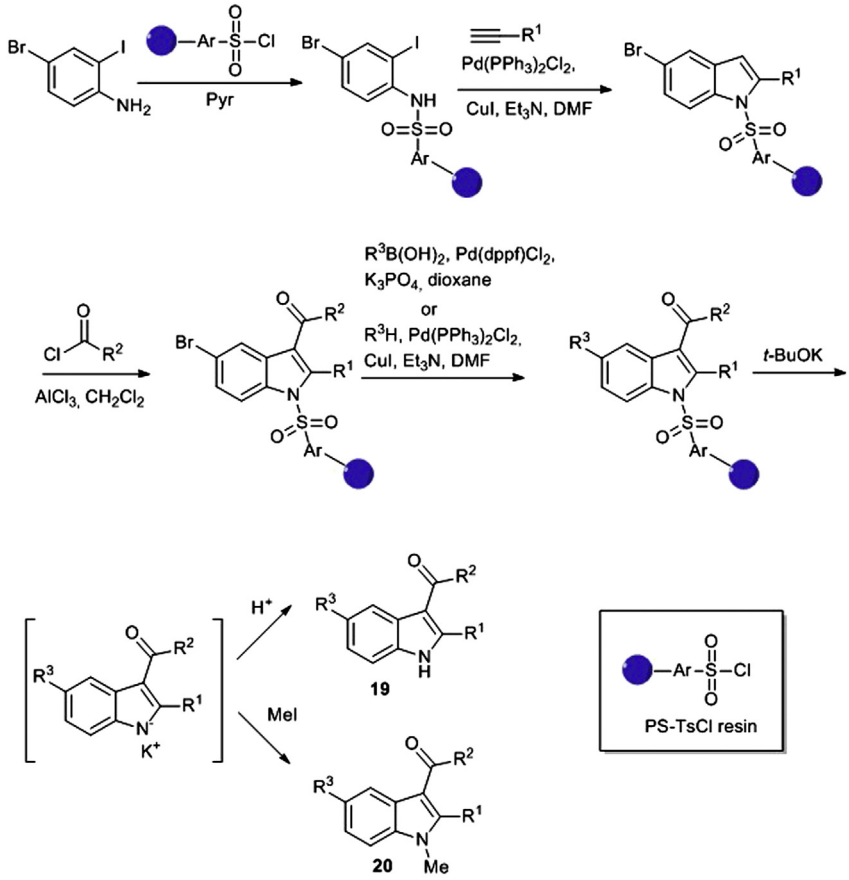

R^1= Ph, 2-MePh, 4-FPh, 4-MeOPh, 4-MePh, Pr

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 described 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). Later, the same group

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described the synthesis of 3-substituted 2-arylindoles by sequential reactions in the solid phase based on the use of silylalkynes 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 have been 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 gives excellent yields in Larock synthesis of indoles. These palladium catalysts have been demonstrated to be recyclable through multiple recycling experiments (2010MI179).

The pseudoisourea palladium(II) complex described by Mandapati and coworkers (Scheme 5) has been used by the same group in a solid-phase version. (2013JOM162, 2014JOM31). The polystyrene-supported pseudoisourea palladium(II) complex was used for 2,3-disubstituted indole synthesis 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 has been 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 (cyclopenta[b] piridines), and pyridines, has been developed by Larock and coauthors

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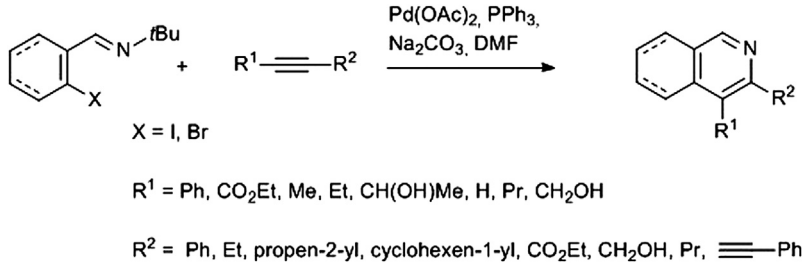

Scheme 10 Synthesis of isoquinolines, tetrahydroisoquinolines, and pyridines.

(1998JOC5306). Palladium-catalyzed iminoannulation of internal alkynes, with a variety of substituents, employing the *tert*-butylimine of *o*-iodobenzaldehyde give good to excellent yields of isoquinolines with high regioselectivity (Scheme 10). The procedure has been extended to the preparation of other nitrogen-containing heterocycles (2001JOC8042). More than 50 heterocycles were prepared under optimized conditions with substituted quinoline, tetrahydroquinoline, pyridine, cyclopenta[b]pyridine, and dihydrobenzo[f]isoquinoline as principal motifs (Scheme 10).

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 in Scheme 10 (2005JOC10172).

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

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 has been described. A number of derivatives **21** and **22** were prepared in good yield by treating halogen or triflate containing aromatic and α,β−unsaturated esters, respectively, with internal alkynes in the presence of a palladium catalyst (1999JOC8770).

The proposed mechanism for the formation of the oxygen-containing heterocycles **21** and **22** is based on a seven-membered palladacyclic complex **23** (Scheme 13) in which the regiochemistry of the reaction is controlled by steric factors.

The same reaction for isocoumarin preparation was performed using colloidal catalyst PS-PEO-PC-Pd in dimethylacetamide at 100 °C in the

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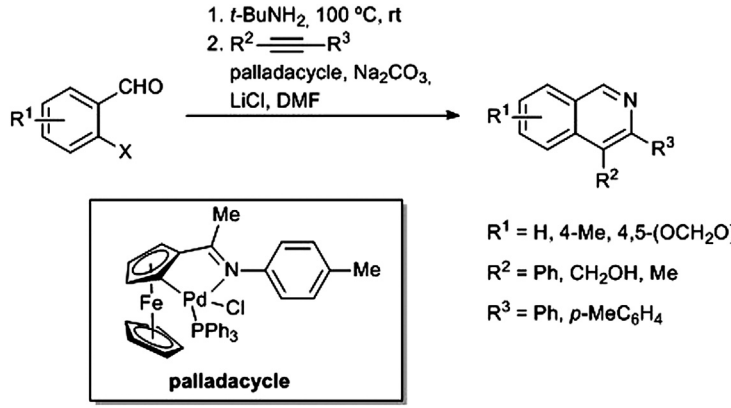
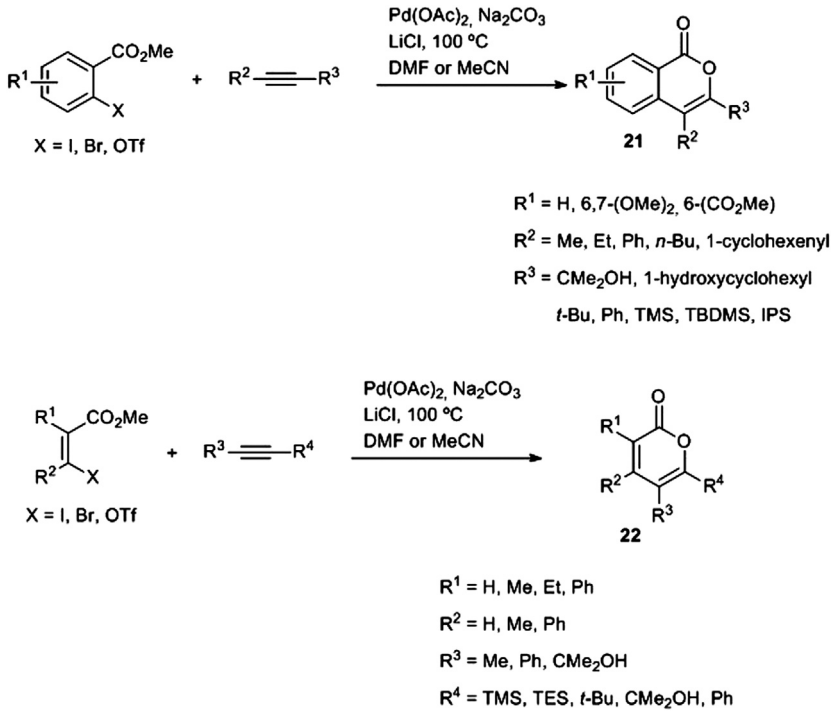


Scheme 11 Palladacycle-catalyzed synthesis of isoquinolines.

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.



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

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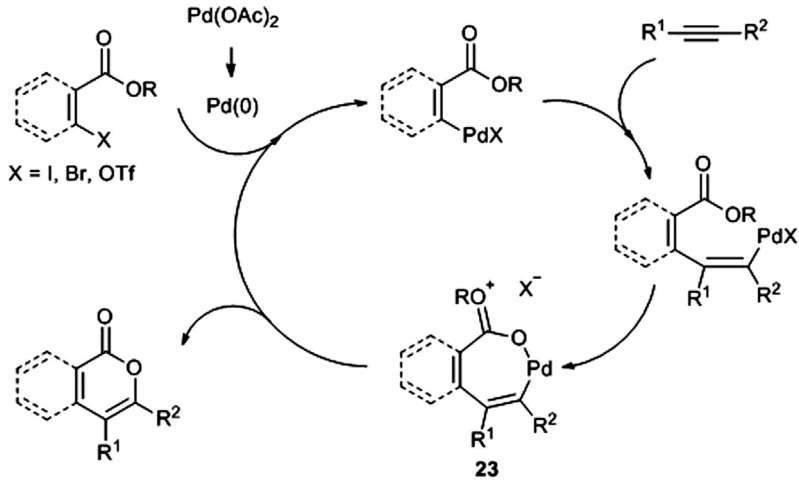


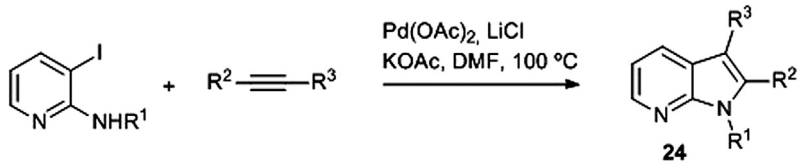
Scheme 13 Proposed mechanism for the synthesis of isocoumarins **21** and α-pyrones **22**.

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

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

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

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



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**.

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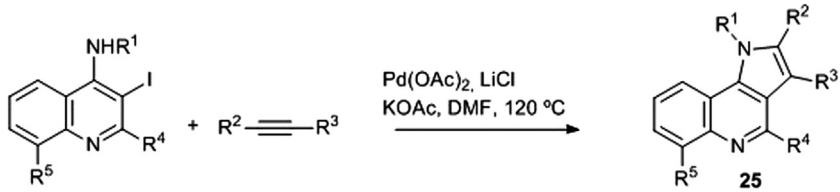


R^1 = 2-MePh, Bn, 2-OMe-4-MePh

R^2 = TMS, Pr, Ph

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

R^4 = H, Me

R^5 = OCF_3, OMe

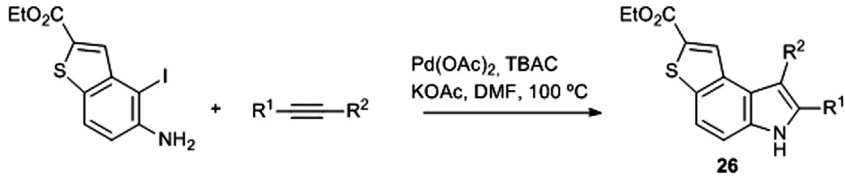
Scheme 15 Synthesis of substituted pyrrolo[3,2-*c*]quinolines **25**.

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

Several thieno[3,2-*e*]indoles **26** have been 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 different sizes.

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

The synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole derivatives **27** has been described. The indolic ring system was constructed via a Larock palladium-catalyzed annulation using terminal and internal alkynes (Scheme 17).



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**.

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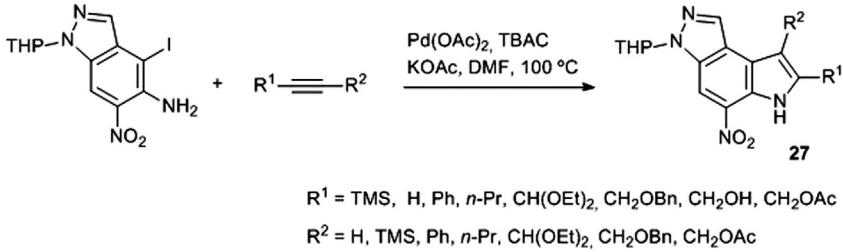

Scheme 17 Synthesis of 1,6-dihydropyrrolo[2,3-*g*]indazole.

A directing effect on regioselectivity, mediated by the ester function of alkyl 3-substituted propiolate derivatives used as internal alkynes, was demonstrated (2011T7330).

4.7 δ-Carbolines

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

The mechanism was established by several experimental control processes and involved Larock heteroannulation, subsequent elimination of a molecule of 4-methylbenzenesulfinic acid, electrocyclization of the resulting dienimine, and, finally, 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 as that described by Cook and coworkers for stereoselective tryptophan synthesis (2001JOC4525). The enantiospecific 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).

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

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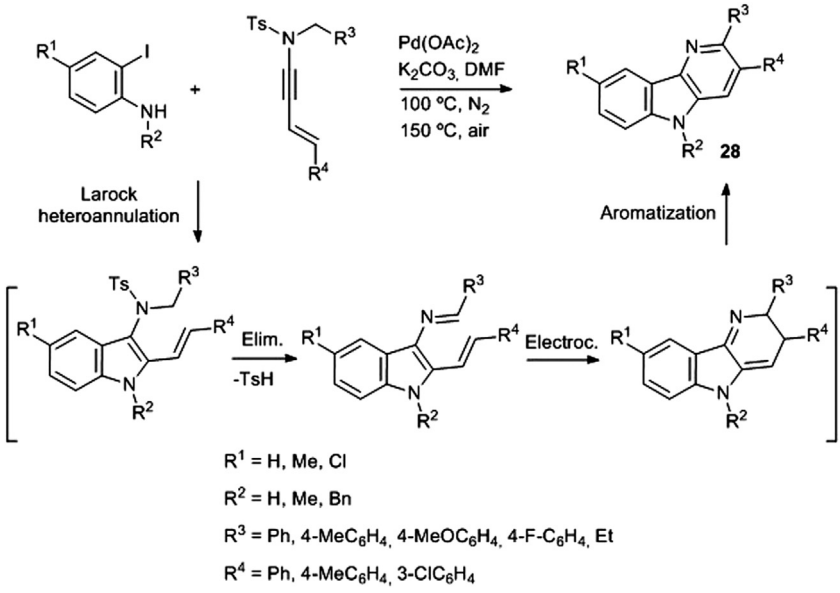
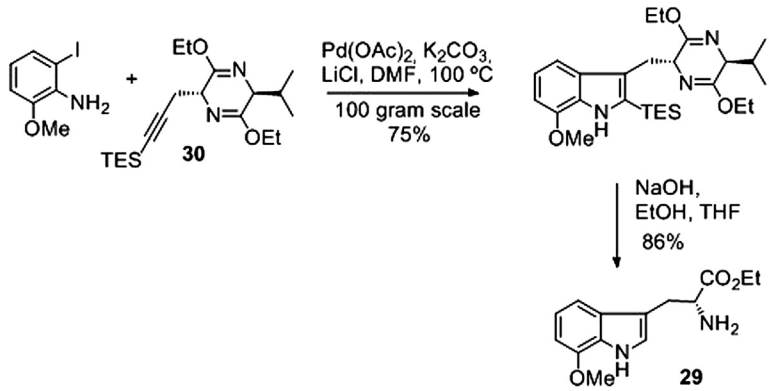


Scheme 18 Synthesis of synthesis of δ-carbolines **28**.

5.2 Synthesis of Complestatins

Complestatins, named chloropeptin I and chloropeptin II, were isolated from *Streptomyces lavendulae* by Sankyo Co. Ltd in 1989. That same year, Seto and coworkers supplemented this information with the elucidation of the structure of these chloropeptins and provided additional details on their biological activity. Later, Omura and coworkers reported their



Scheme 19 Larock heteroannulation using a chiral auxiliary.

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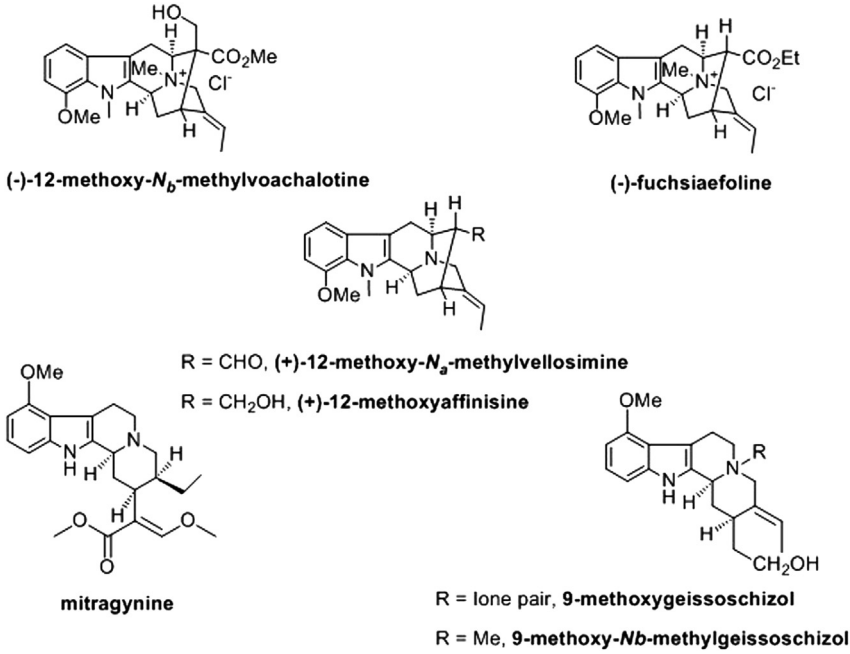

Figure 5 Structures of indole alkaloids with methoxy substituents.

isolation from *Streptomyces* sp. WK-3419 (1989MI236, 1989TL4987, 1994 MI1173). Important inhibitory activity for HIV gp120-CD4 binding was described (1980MI1194, 1994MI1173). Chloropeptins are structurally similar to glycopeptide antibiotics such as vancomycin.

Boger and coworkers reported the first total synthesis of chloropeptin II and later its transformation into chloropeptin I (2009JA16036). The key step to this total synthesis was macrocyclization of peptide **31** by an intramolecular Larock indole heteroannulation. This intramolecular reaction between a substituted 2-bromoaniline with a removable terminal alkyne substituent afforded simultaneous regioselective indole ring formation and macrocyclization. The TES substituent of the alkyne dictates indole cyclization regioselectivity (Scheme 20).

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 A (Figure 6). They have been isolated from deep-water sponges *Dragmacidon*, *Halicortex*, *Hexadella*, *Spongosorites* and the tunicate *Didemnum candidum* (2000OL3027,

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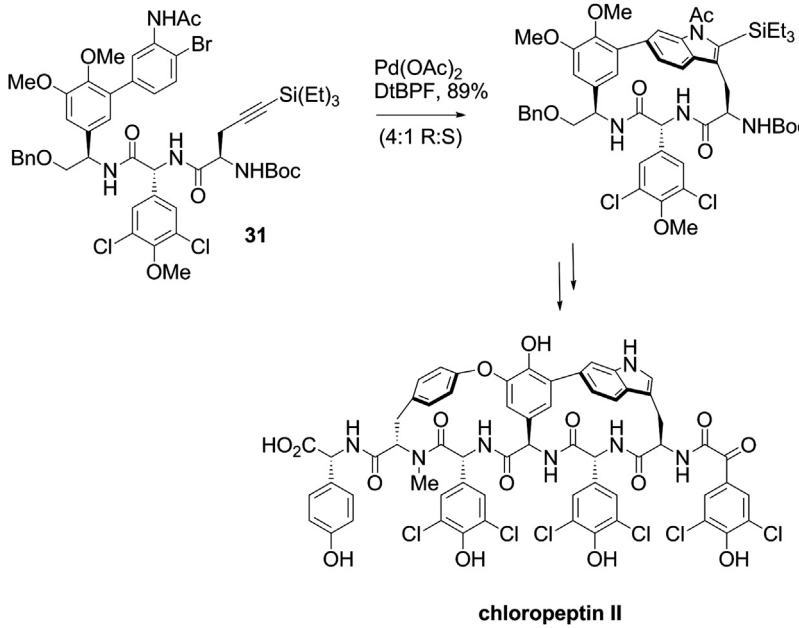
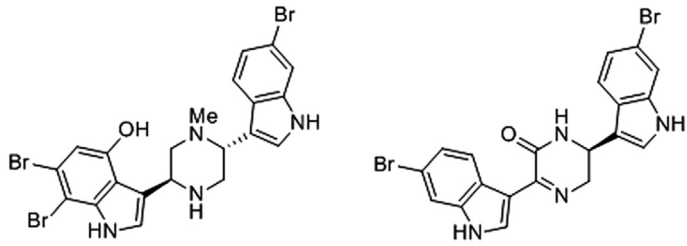


chloropeptin II

Scheme 20 Larock heteroannulation for the synthesis of chloropeptin II.



dragmacidin **hamacanthin A**

Figure 6 Structures of dragmacidin and hamacanthin A.

2005T2309). The interest in these compounds lies in 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 anticancer, antifungal, antiviral, and antiinflammatory properties.

Sinha and coworkers developed a methodology for the synthesis of enantiopure 2- and 3-indolylglycine derivatives and their oxygen analogues.

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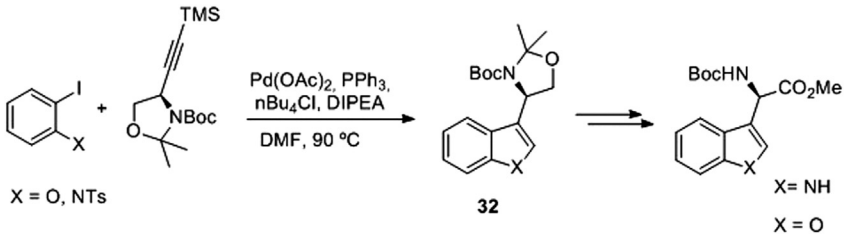
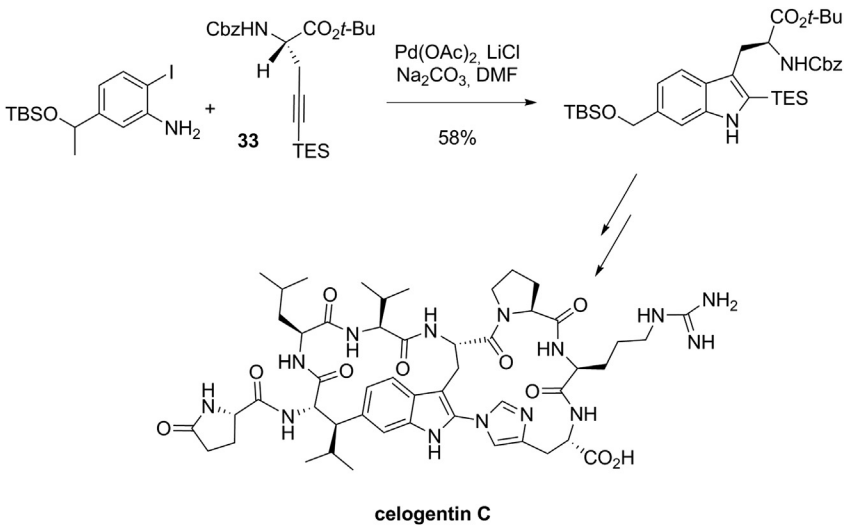


Scheme 21 Synthesis of enantiopure 3-indolylglycine and 3-benzofurylglycine.

The procedure is based on a Larock heteroannulation using a silylated chiral alkyne with an N-protected oxazolidine substituent as the key reaction step that affords compounds **32** (X = O, NTs), which are precursors of substituted glycines (2012JOC7081; Scheme 21).

The same synthetic strategy was used for the synthesis of several homotryptophan derivatives (2012T280). Tryptophan analogs constitute a class of IDO (indoleamine 2,3-dioxygenase) 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 characterized by a bicyclic



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

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framework in which a substituted Trp is the central core. Celogentin C shows a strong inhibitory activity in tubulin polymerization.

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: they intercalate into DNA; they inhibit CDK, topoisomerase, and monoamine oxidase; and they interact with benzodiazepine and 5-hydroxy serotonin receptors. In addition, they have shown sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic, and antimicrobial activity (2007MI14).

Bannister and coworkers 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 2-pyridyl alkynes **34** and a Larock indole heteroannulation of alkynes **34** with the appropriate bromoaniline to give pyridylindoles **35** (Scheme 23).

5.5 Synthesis of Terreusinone

Terreusinone is a dipyrrolobenzoquinone that in particular contains a pyrrolo [2,3-*f*]indole-4,8-dione ring system, which is unique among known 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 the indole **36**, appropriately substituted for formation of the new heterocyclic ring (Scheme 24).

5.6 Synthesis of Ibogaine

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

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

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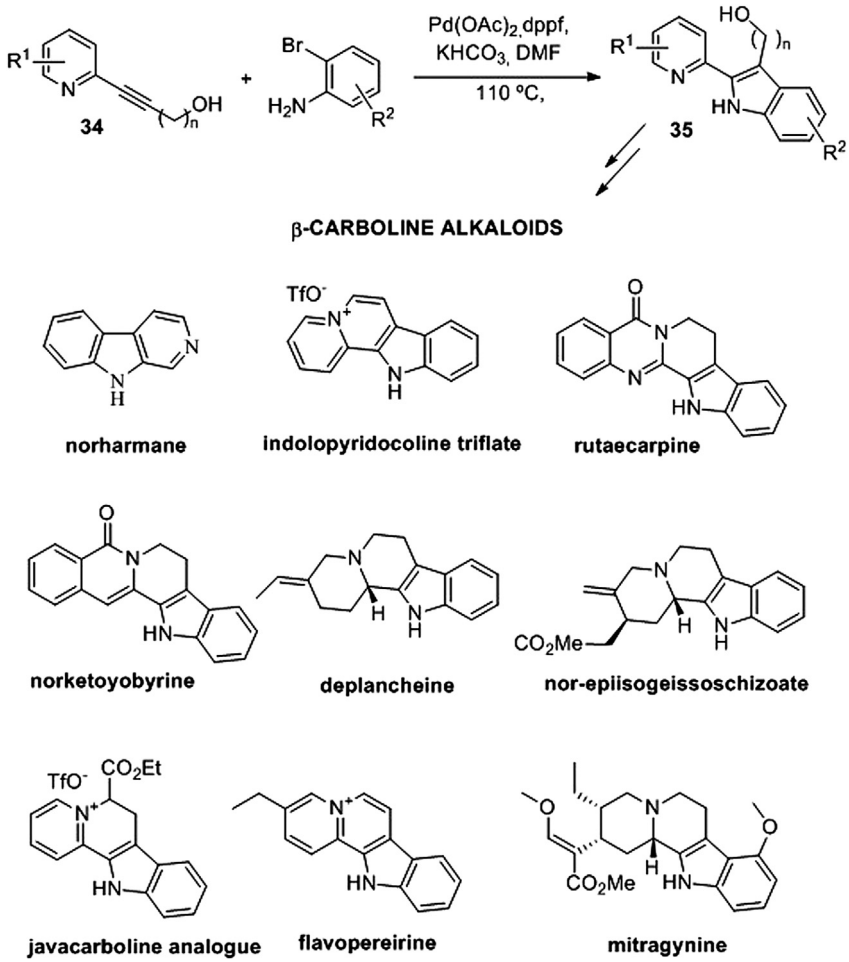

Scheme 23 Synthesis of β-carboline alkaloid precursors.

5.7 Synthesis of Dictyodendrins

Dictyodendrins A–E are a family of marine natural 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 and cancer.

Jia and coworkers 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** (Scheme 26; 2014EJO5735).

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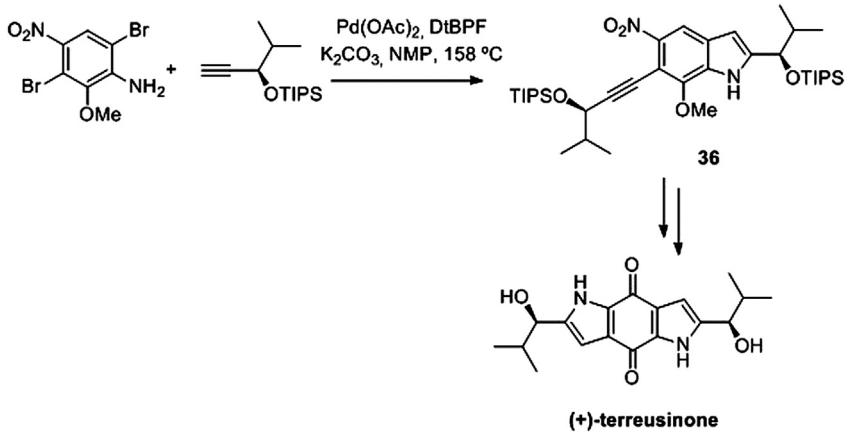
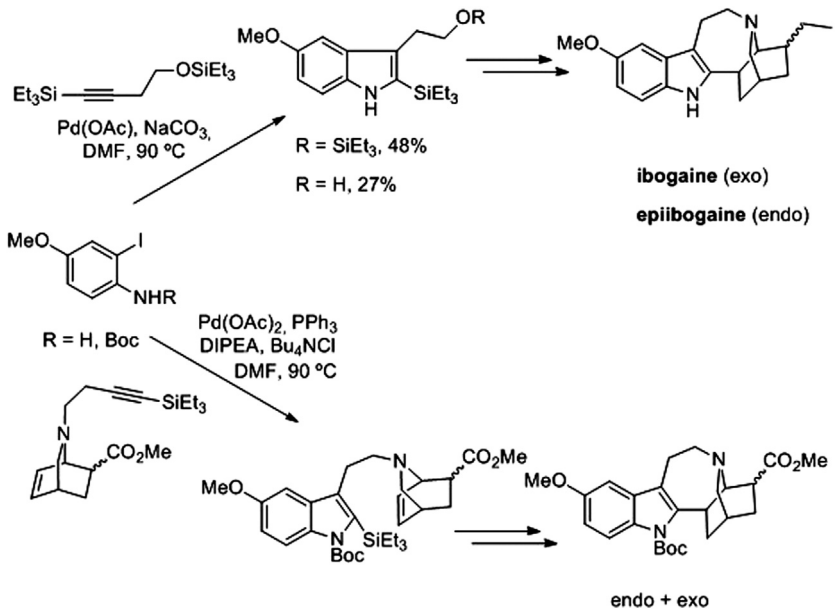


Scheme 24 Synthesis of indole **36**, precursor of (+)-terreusinone.

5.8 Synthesis of Natural Products Containing the Tryptamine-HPI Bond

Psychotrimine and psychotetramine are two natural compounds whose biosynthesis seems to take place via tryptophan dimerization (2004OL2945). A distinguishing structural feature of these alkaloids lies in the bond between



Scheme 25 Total synthesis of ibogaine and analogs.

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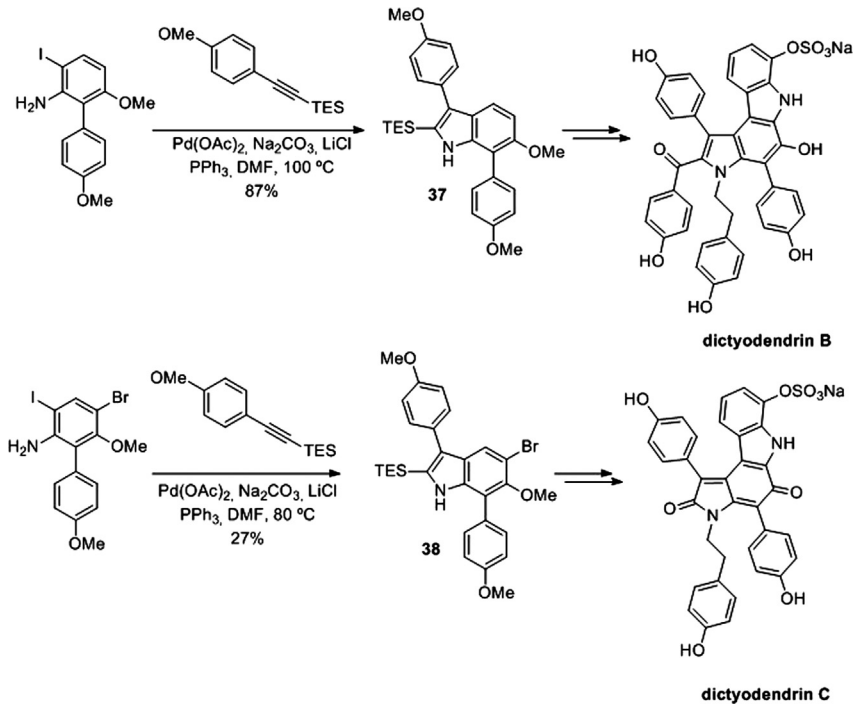

Scheme 26 Synthesis of polysubstituted indoles **37** and **38**, precursors of dictyodendrins B and C.

the indole-N of one tryptamine and the carbon-3a of an hexahydropyrroloindole (HPI) coming from the intramolecular cyclization of the second Trp unit. In order to establish the challenging N1-C3a linkage, Baran and coworkers developed a novel methodology for the synthesis of psychotrimine (2008JA10886). The key step in this 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 a tricyclic pyrroloindole and the bond between C3a and the aniline N. A chemoselective Larock annulation between **39** and a known alkyne was then performed to afford the corresponding indolyl-hexahydropyrroloindole **40**, which is a precursor of psychotrimine (Scheme 27). The same methodology was used by Baran, Takayama, and coworkers for the synthesis of psychotetramine (2008JA10886).

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 the key step (Figure 7; 2009JA6360, 2010JA7119, 2011AG(E)2716).

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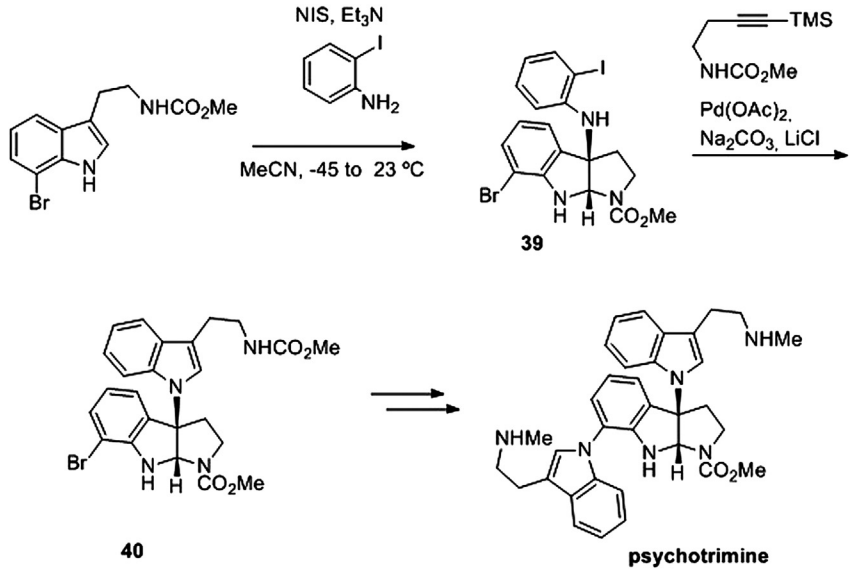

Scheme 27 Synthesis of indolyl-hexahydropyrroloindole **40**, a precursor of psychotrimine.

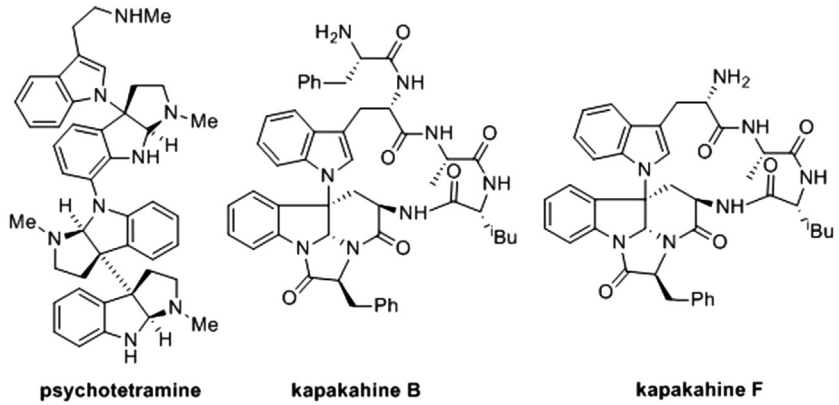

Figure 7 Structures of psychotetramine, kapakahine B, and kapakahine F.

5.9 Larock Reactions in Drug Discovery

The Larock reaction has been used in the pharmaceutical industry because of the ease of manipulation, high regioselectivity, good to excellent yields, and scaling capacity to multigram. The fluoroindole ring system of a glucagon receptor antagonist drug candidate **41** (Figure 8) for the treatment of type 2

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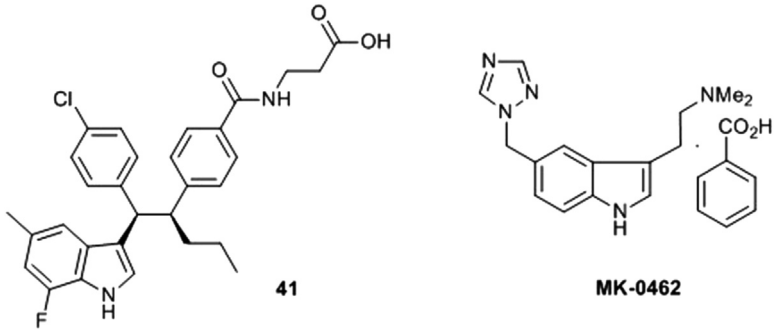
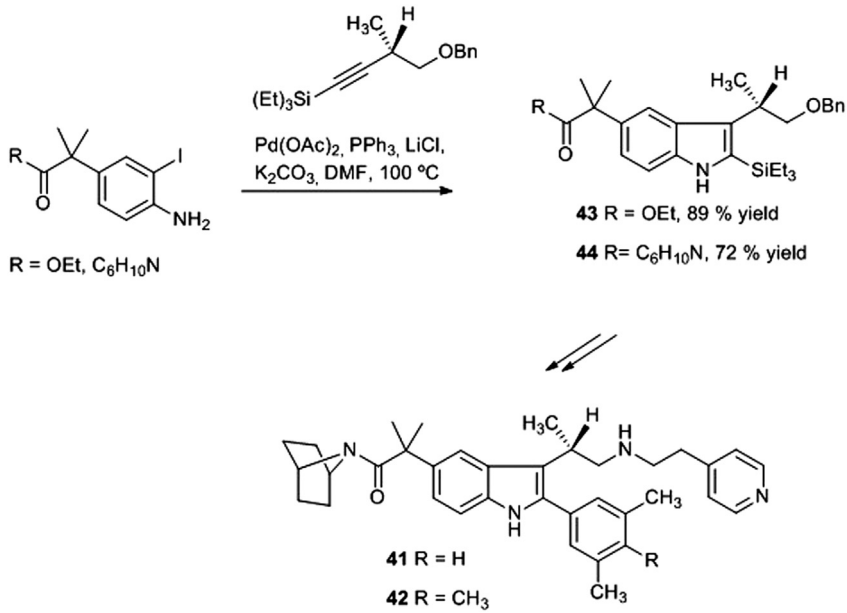


Figure 8 Structures of glucagon receptor antagonist **41** and MK-0462.

diabetes was afforded by means of a Larock-type indole synthesis on a multi-kilogram scale in a procedure described by Scott and coworkers (2012MI1832). *N,N*-Dialkyltryptamine derivatives have been studied as 5-hydroxytryptamine (serotonin) receptor 1D agonists for the treatment of migraine. The receptor agonist MK-0462 was synthesized using Larock heteroannulation for the formation of the indole system (Figure 8; 1994TL6981).



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

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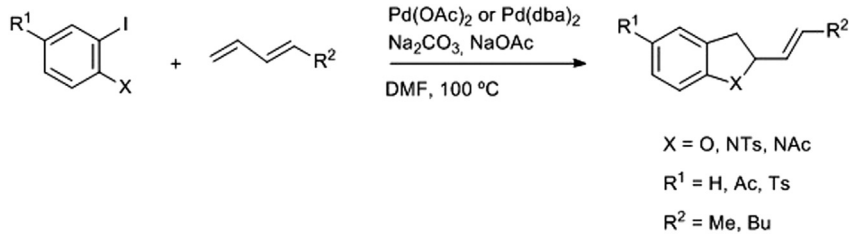


Scheme 29 Heteroannulation of 1,3-dienes.

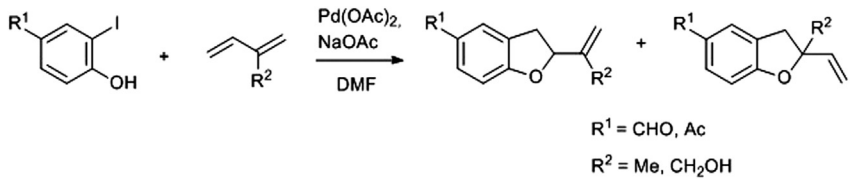
GnRH (gonadotropin releasing hormone) is a decapeptide synthesized and produced by the neurons of the hypothalamus. GnRH stimulates the synthesis and secretion of hormones involved in male and female gonad function. Researchers from Merck Laboratories working on the synthesis of gonadotropin antagonists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

6. HETEROANNULATION WITH SUBSTRATES OTHER THAN ALKYNES

Extension of heteroannulation procedure performed by Larock to other unsaturated compounds such as dienes and allenes has 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 have been obtained using either $Pd(OAc)_2$ or $Pd(dba)_2$ as catalysts (Scheme 29). The yield of



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

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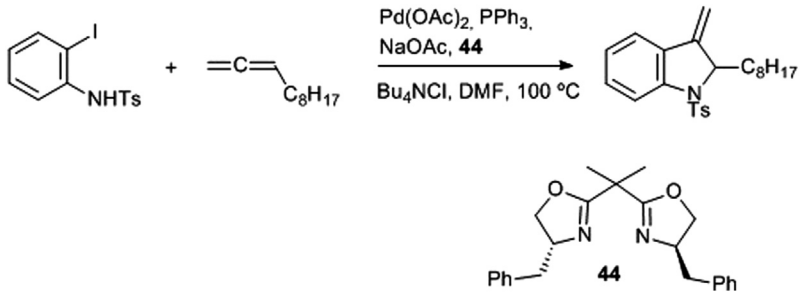

Scheme 31 Allene heteroannulation.

heterocycle can vary depending on the base, with the best results being obtained with either NaOAc or Na_2CO_3 (1990JOC3447).

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

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, e.g.,

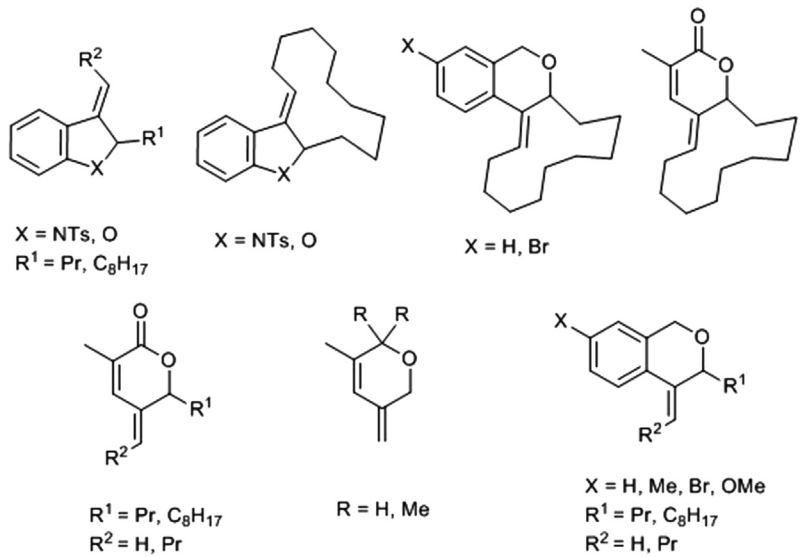

Figure 9 Heterocycles obtained by heteroannulation of allenes.

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44 (1999JOC7312). Optimization of the process was performed by 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).

Various chiral ligands were tested for 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 (1999JOC7312).

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 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.

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