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A Review: SYNTHESIS OF 5- AND 6-MEMBER NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS

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ABSTRACT

There are a great number of biological and commercial applications for heterocyclic compounds that include nitrogen, particularly those with five- or six-membered rings. These compounds are plentiful in nature and have a wide range of applications, including biomedicine, agrochemicals, and functional materials. The focus of this study is on the most recent advancements in the synthesis of these heterocycles, with a particular emphasis on approaches that are selective and efficient. Including pyrroles, pyrrolidines, indoles, oxindoles, isoindoles, indolizines, and carbazoles, the article provides a current description of synthetic techniques for creating rings with five or six members. These methods are mostly based on reactions that are catalysed by transition metals. In addition, we discuss a few of the mechanistic results that have been uncovered in order to acquire a deeper comprehension of the chemical pathways and the methods that might be used to construct synthetic heterocycles.

Keywords: *Nitrogen heterocycles, Five-membered rings, Six-membered rings, Transition metal catalysis, Carbon-nitrogen bond formation, Pyrroles, Pyridines, Indoles, Quinolines, Isoquinolines, Heterocyclic synthesis*

INTRODUCTION

The nitrogen-containing heterocyclic compounds family of organic molecules is of critical significance in a number of fields, including medicinal chemistry, agrochemicals, and materials research, amongst others. As a result of the prevalence of nitrogen heterocycles in natural products, pharmaceuticals, and bioactive substances, a substantial amount of research has been carried out in order to develop synthetic methods that are both effective and diversified. Nitrogen heterocycles that have five or six members stand out from the rest of the pack due to the fact that they are versatile, stable, and easy to build. These ring structures serve as the core framework for a wide variety of physiologically active substances, including alkaloids, antibiotics, anti-inflammatory pharmaceuticals, and anticancer therapies, amongst others.

Five-membered nitrogen heterocycles, which include pyrroles, indoles, imidazoles, and carbazoles, are well-known for the medicinal and organic material activities that they perform. In a similar vein, pyridines, piperidines, quinolines, and isoquinolines are significant structural motifs that may be found in bioactive compounds that are found in nature as well as in molecules that have been synthesised. As a result of the biological and pharmacological relevance of these compounds, there is an urgent need for synthesis processes that are both environmentally benign and efficient.

Over the course of the last several decades, heterocyclic synthesis has made significant progress as a result of advancements in microwave-assisted procedures, green chemistry tactics, and reactions catalysed by transition metals. There is a high atom economy, simplicity of operation, and selective formation of C-N bonds under mild conditions that can be achieved by the use of these approaches. The addition of multi-step transformations into single-pot procedures has made heterocycle synthesis much more practical and scalable. This is because of the increased efficiency of the process.

The purpose of this work is to provide a comprehensive overview of the many methods that are currently being used for the synthesis of nitrogen-containing heterocycles that include either five or six carbon atoms. A number of cutting-edge techniques, such as carbon-nitrogen bond-forming processes, transition metal catalysis, and others, are emphasised in the book. For the purpose of developing nitrogen heterocycles that have special applications in the fields of health, agriculture, and high-tech materials, research into these synthetic advancements will be of great assistance.

OBJECTIVES

1. To investigate and evaluate contemporary synthetic techniques for creating heterocyclic compounds with nitrogen that have five or six members.
2. To assess the effectiveness and suitability of ecologically friendly, transition metal-catalyzed methods for heterocyclic synthesis

SYNTHESIS OF FIVE-MEMBERED RING HETEROCYCLES

1. Synthesis of Pyrrole and Pyrrolidine Derivatives

Given its prevalence in naturally occurring compounds with biological activity, the pyrrole ring piques the curiosity of synthetic organic chemists. The synthesis of pyrrole and related compounds is facilitated by a wide variety of synthetic routes.

Synthesis from the Reaction of Amines with Alkenes

Hydroamination of unactivated olefin is a problem in organic synthesis. He et al. observed that gold catalysts made sulfonamides efficient in inter- and intramolecular hydroamination. PPh3AuOTf (5 mol %), synthesised in situ from Ph3PAuCl and AgOTf in equal quantities at 85 ° C., catalysed the intramolecular hydroamination of N-tosylated -amino olefins 1 to generate several pyrrolidine derivatives 2. In contrast, anilines and free amines did not react.

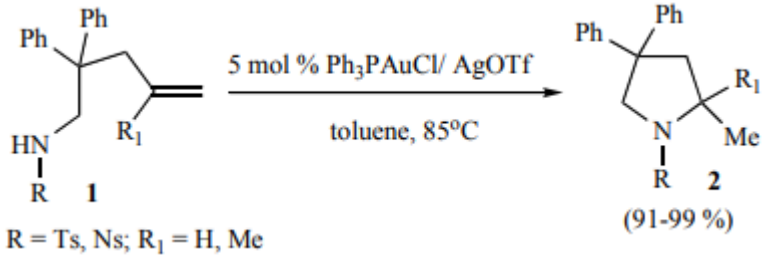
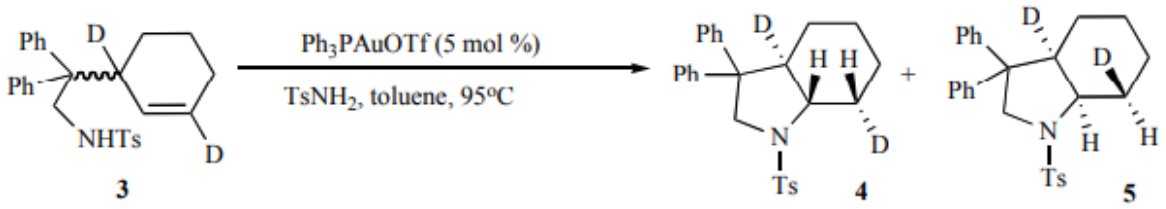


Figure 1.



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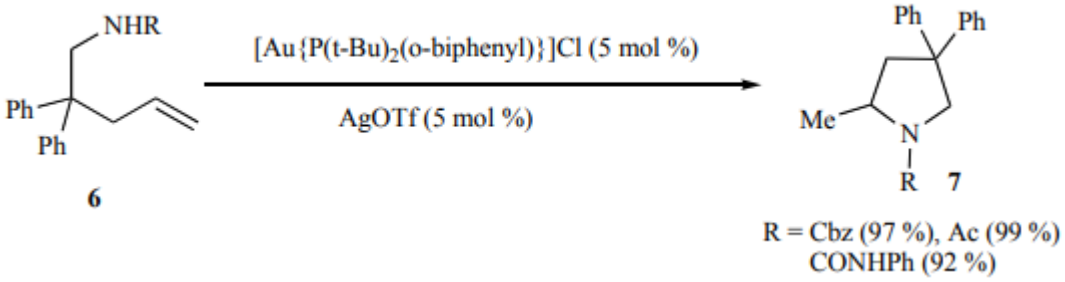

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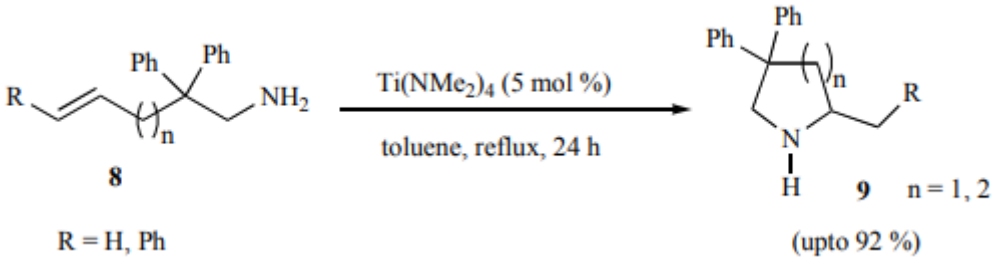


Figure 4.

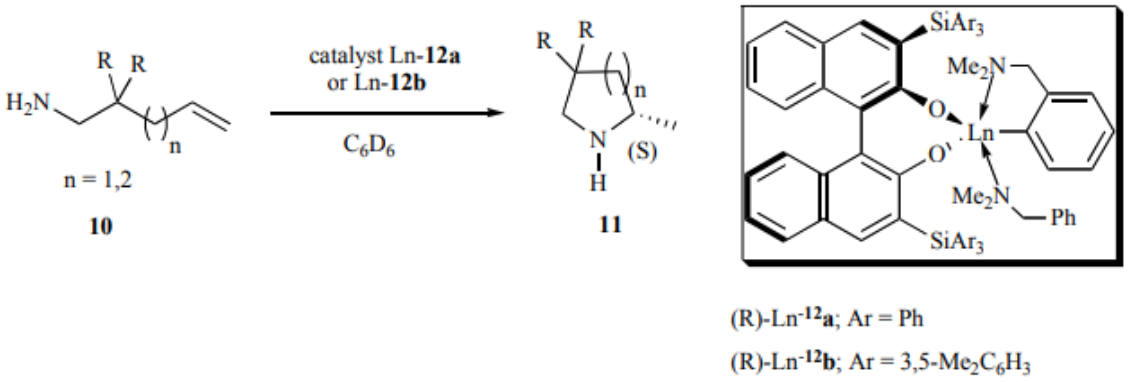


Figure 5.

Figure 2 implies the nucleophile approaches the gold(I)-alkene complex from the opposite side as d2-labeled molecule 3 formed products 4 and 5. GOLD-catalyzed intramolecular hydroamination of carbamates and amides yielded nitrogen heterocycles. Widenhoefer et al. described a room-temperature hydroamination reaction of N-alkenyl ureas using a gold complex and a large, electron-rich N-heterocyclic carbene ligand. Next, density functional theory and polarisable continuum models elucidated alkene hydroamination's mechanistic characteristics, emphasising the counterion-assisted proton shuttling process. Platinum-catalyzed intramolecular hydroamination of unactivated olefins with secondary alkyl amines was developed by Widenhoefer et al. A 1:1 mixture of Au[P(tBu)2(o-biphenyl)]Cl and AgOTf catalysed the intramolecular exo-hydroamination of N-alkenyl carbamates (Figure 3 6. Figure 4 shows that commercially available Ti(NMe2)4-catalyzed intramolecular hydroamination of free aminoalkenes 8 yielded several pyrrolidine and piperidine derivatives. 9. Alkenes with geminate substituents responded most. Hydroamination of activated internal alkenes is another precatalyst specialisation. Secondary amines did not cyclize despite increasing temperature and reaction time. Titanium-imido species production in situ seems to catalyse the process. Hultzsch et al. synthesised 3,3/-bis(tris-arylsilyl)-substituted binaphtholate utilising rare earth metal complexes (Figure 5). Asymmetric aminoalkene hydroamination/cyclization was possible with these catalytic complexes. All binaphtholate complexes hydroaminated/cyclized aminopentenes at room temperature, whereas aminohexenes needed higher temperatures. As the metal's ionic radius decreased, pyrrolidine products became more enantioselective, and achiral aminopentene cyclisation reached 95% ee Che et al. used a sterically bulky phosphine ligand, [Au{P(t-Bu)2(o-biphenyl)}]Cl., to catalyse the addition of a dicarbonyl molecule to an unactivated alkene. Highly diastereoselective lactam ketoamide 13. In Figure 6, cis-12 or trans-12 olefin may generate 15. The original Claisen rearrangement yields the identical intermediate, which produces the product. Product of gold-catalyzed hydroamination.

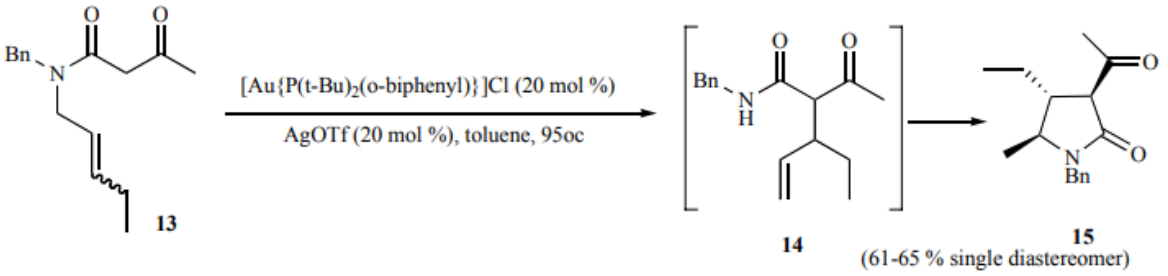
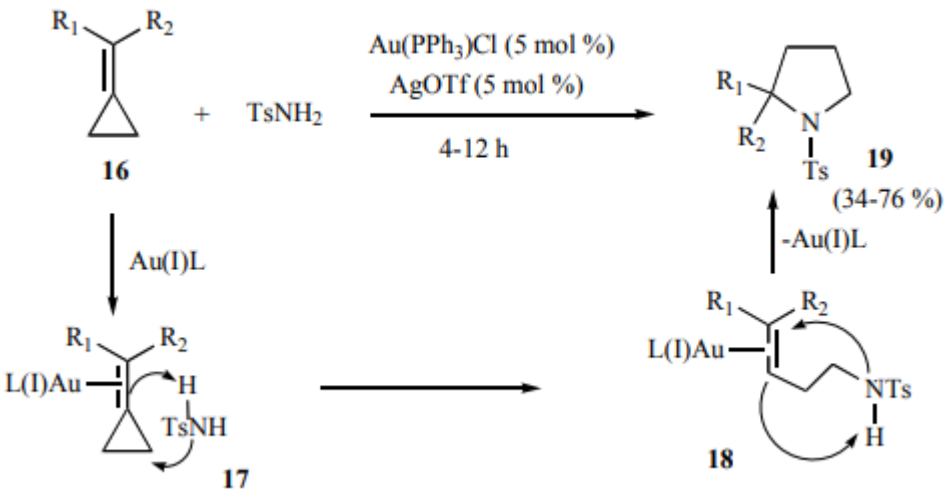


Figure 6.



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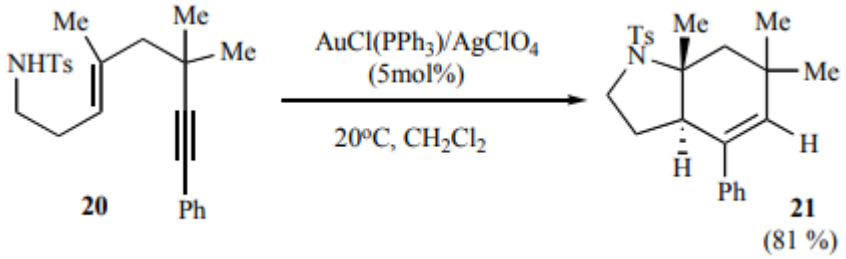
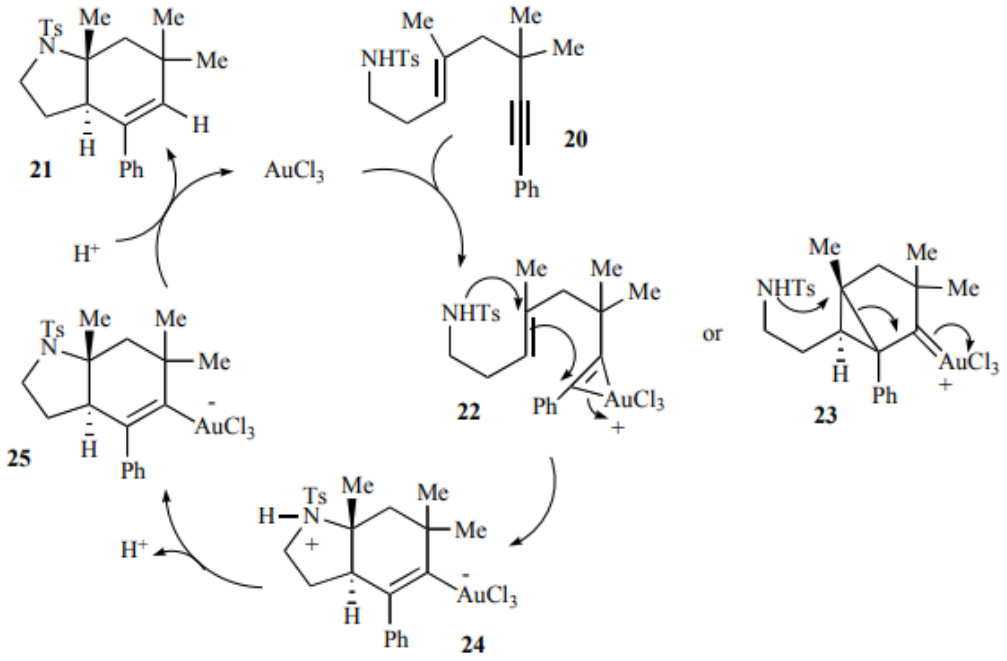


Figure 8.

Gold (I)-activated methylenecyclopropanes 16 may be hydroaminated with sulfonamides to create pyrrolidine derivatives 19 (Figure 7). A domino ring-opening and hydroamination ring-closing reaction cascade produces the product, likely with gold activation. Kozmin et al. used gold-catalyzed double cyclisation of simple 1,5-enynes hydroamination with oxygen or nitrogen nucleophiles. Treating enyne 20 with 5 mol% AuCl(PPh3)/AgClO4 in dichloromethane generated 81% 6-azabicyclo[3.2.1]octene 21 (Figure 8). Whether the product was generated by a concerted process via 22 or step-wise employing the nucleophilic opening of the cyclopropyl gold carbine intermediate 23, the diastereospecific double cyclisation could be observed. Figure 9 shows proton release from 24 and protodemetalation of the alkenyl gold complex 25 to produce the bicyclic product 21. Figure 10 depicts a straightforward and efficient pyrrole 28 synthesis utilising readily available amino acids. This procedure relies on Pd(II)/Cu(OTf)2 as an aza-Wacker oxidation-cyclization catalyst.

Synthesis from the Reaction of Amines with Alkynes

Transition metals catalyse the inter- and intramolecular addition of nitrogen nucleophiles to acetylenic triple bonds to produce pyrrole derivatives. Terminal alkynes and sulfonyl azides may be transformed to amidines imidates and amides via Cu-catalyzed three-component coupling. The intramolecular hydroamination reactions of 1,n-aminoalkynes with sulfonyl azides, catalysed by the Ru-carbonyl complex Ru3(CO)12, were used to synthesise amidines to expand these coupling mechanisms. The catalyst produced very efficient cyclic amidines from a range of aminoalkynes 29 and electron-deficient azides 30 (Figure 11). The majority of 1, 4-aminoalkynes treated with azides produced 5-membered amidines (31), whereas 1,5-aminoalkynes produced six-membered amidines (32), which contained a Me group on the ring. Figure 12 demonstrates that intramolecular hydroamination with a Ru-catalyst produces the 5-exo-methylene pyrrolidine adduct 33, indicating that the reaction began at n = 1. After releasing diazomethane, the pyrrolidine adduct 29 preferentially azide cyclizes to a spiro triazoline 34, which reorganises to cycloamidine 31a. In contrast, endo-adduct 35 reacts quickly with azides to make triazoline 36; rearrangement, 1,2-Me migration, and nitrogen release produce 32a.



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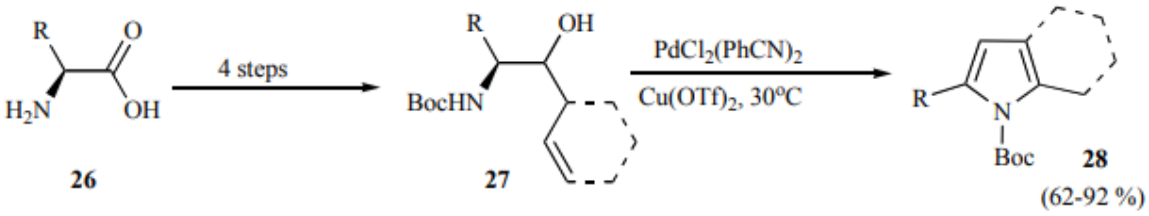

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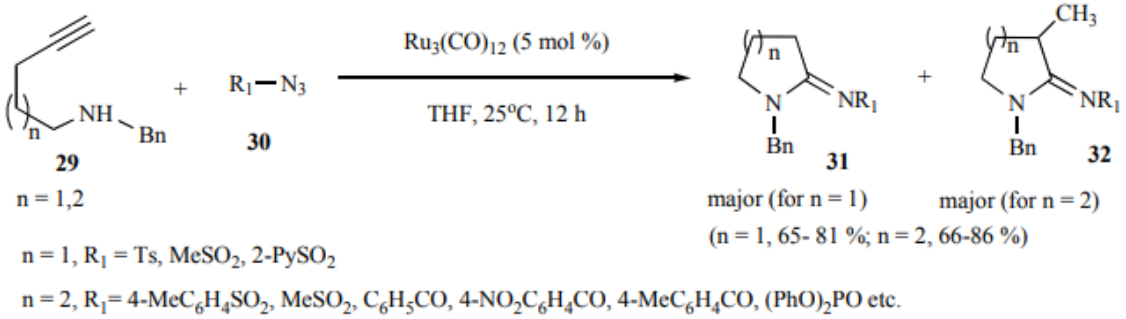


Figure 11.

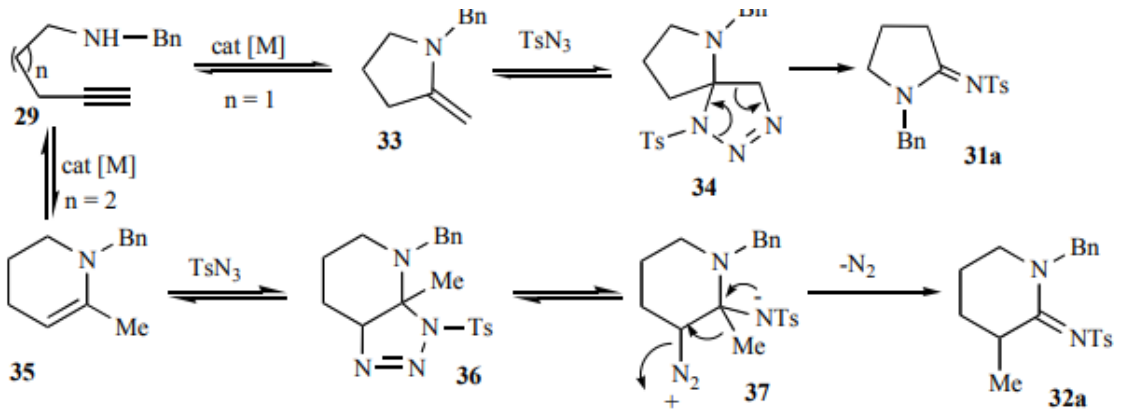
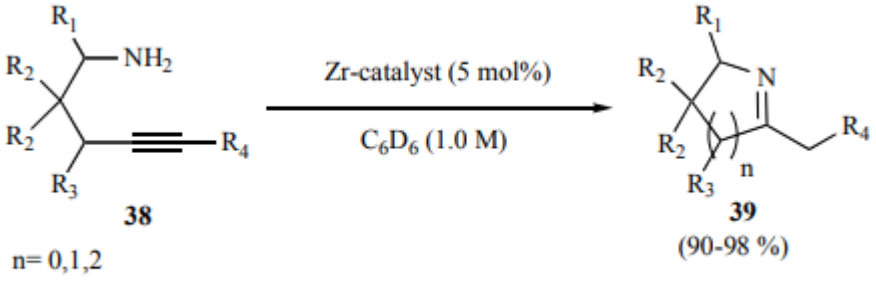


Figure 12

Neutral zirconium(IV) complexes are good pre-catalysts for intramolecular hydroamination of aminoalkenes and aminoallenes. The neutral zirconium(IV) bis(thiophosphinic amidate) complex catalyses 5-, 6-, and 7-exo-dig intramolecular hydroamination of aminoalkynes to cyclic imines 39. Titanium or yittrium complexes yielded high-yield cyclic imines while taking longer to react. Helquist et al. hydroaminated aminoalkynes using a silver-phenanthroline complex.



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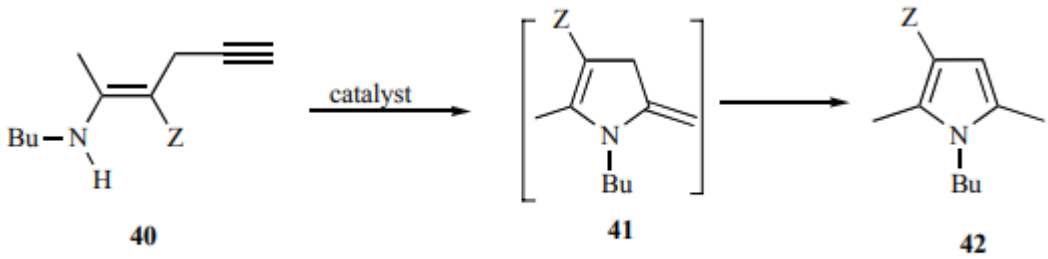

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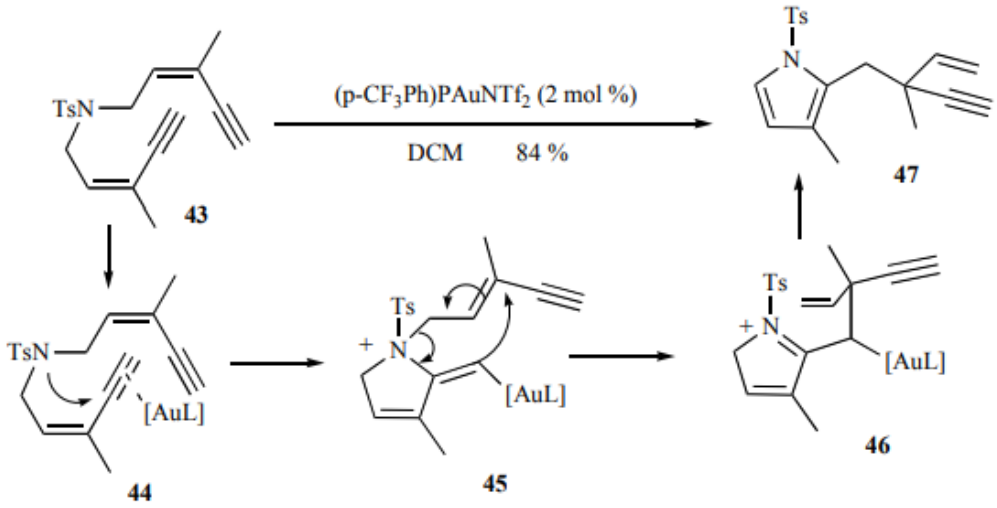

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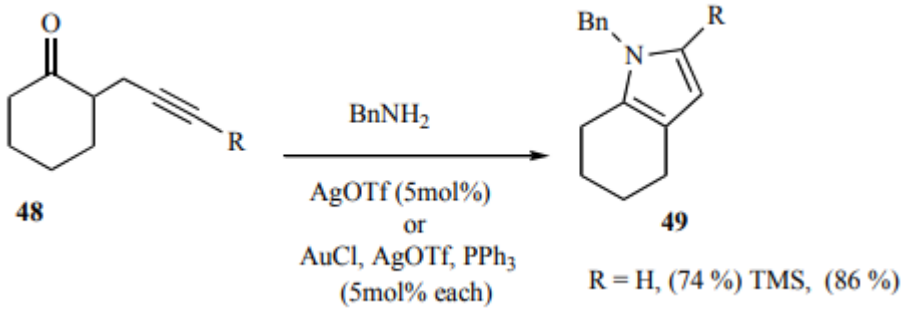
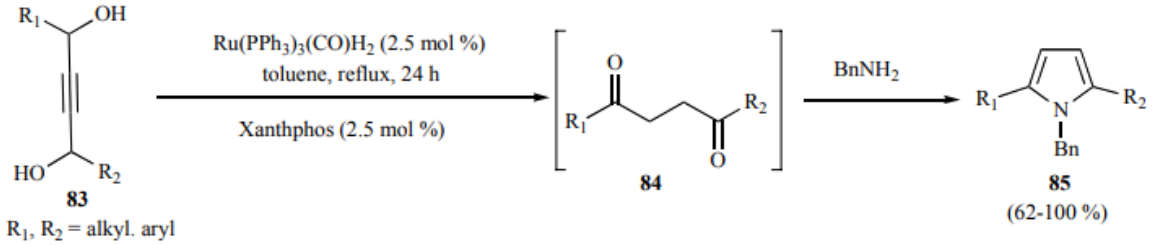


Figure 16

Using n-BuLi and propargyl bromide to propargylate secondary enaminones and silver nitrate for intramolecular hydroamination creates functionalised pyrroles. Robinson et al. reported that late transition metal salts may hydroaminate C-propargyl vinylogous amides into pyrroles under microwave conditions (Figure 14). Cu(II), Ag(I), Zn(II), Cd(II), and Hg(II) oxide, acetate, nitrate, and chloride derivatives of group 11 and 12 metals were utilised as hydroamination catalysts. Except for ZnO, Zn(II) catalysts such ZnAc2, Zn(NO3)2, and ZnCl2 yielded the most product. The substituted pyrrole 47 is formed from pentenynyl allyl tosylamide 43 by a gold(I)-catalyzed nucleophilic addition of its nitrogen to alkynes via an azaClaisen-type rearrangement and aromatisation, resulting in cationic vinyl gold intermediate 45. The [3,3]-sigmatropic rearrangement may produce a quaternary carbon, as seen in Figure 15. Silver trifluoromethanesulfonate (AgOTf) or a combination of gold(I) chloride, AgOTf, and triphenylphosphine can catalyse the intramolecular interaction between alkynes and imines, which are generated in situ from -alkynyl ketones and amines, and functionalised pyrroles (Figure 16).

Synthesis from Diketones

Ru(PPh3)3(CO)H2 catalyses 1,4-alkynediol isomerisation and N-heterocyclization into pyrroles. Figure 17 demonstrates that nitrogen heterocyclization was affected by the production of diketone 84 in the reaction of alkynediol 83 with benzylamine in refluxing toluene with a Ru catalyst (2.5 mol%) and Xanthphos (2.5 mol%) ligand. Langer et al. synthesised functionalised 1-aminopyrroles and 1-amino-4,5,6,7-tetrahydroindoles using 1,3-bis(silyl enol ethers) and 1,2-diazo-1,3-butadienes in a ZnCl2-catalyzed one-pot conjugate addition/cycl In Figure 18, the mild-condition, bismuth nitrate-catalyzed modified Paal Knorr reaction-based synthesis of highly substituted pyrroles is reported. Less basic aromatic amines take slower to react than more basic amino compounds, although yields are equal. TiCl4/Sm (1:1; 4 equiv) was used to react 1,3-diketones 87 with imines 88 to yield 1,2,3,4-tetrasubstituted pyrroles 89 (Figure 28). Symmetrical 1,3-diketones and imines treated with low-valent titanium yielded excellent coupler cyclisation products. Imine would self-couple if 1,3-diketones weren't 1,3-diaroylmethane. Unsymmetrical 1,3-diketones formed one coupling cyclisation product regioselectively.



Scheme 17.

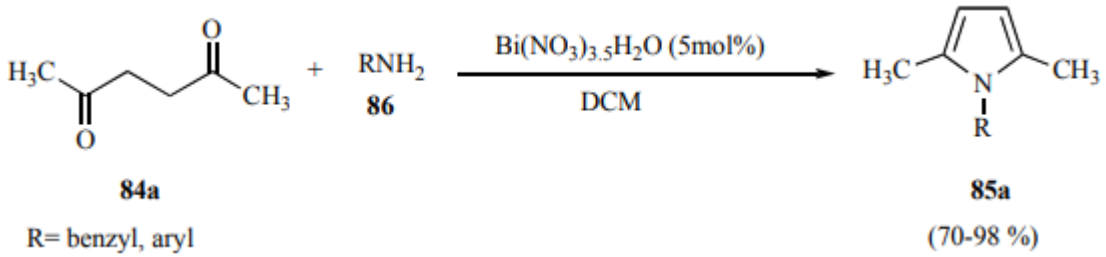


Figure 18.

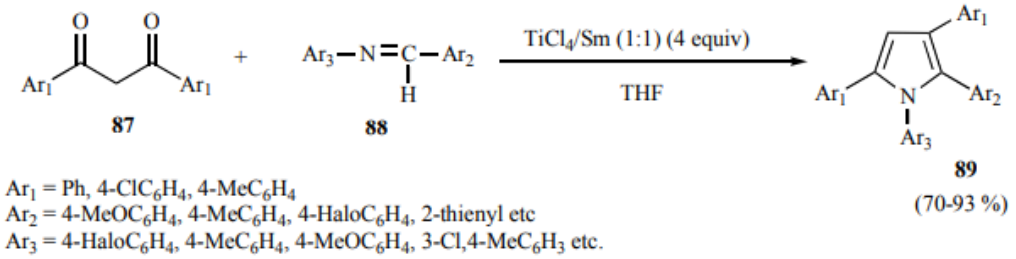


Figure19.

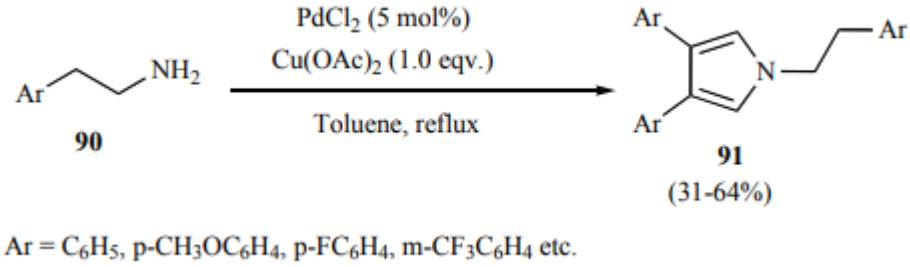


Figure 20.

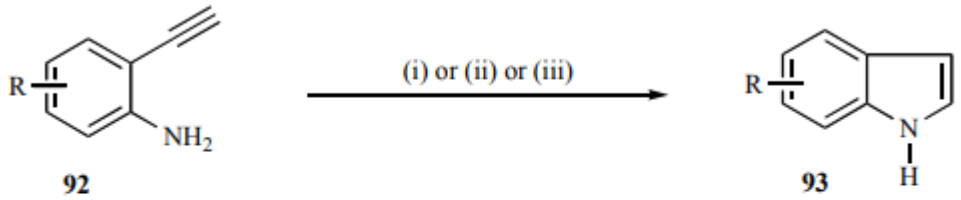
2. Synthesis of Indoles, Oxindoles and Isoindoles

Key structural motifs seen in many naturally occurring chemicals include indole, oxindole, and isoindole. One of the most recent methods for synthesising them involves catalytic transformation using a transition metal catalyst, among other synthetic methodologies.

Synthesis of Indoles

Various substrates and catalytic systems have been employed to synthesise indoles via intramolecular nitrogen nucleophile addition to alkynes. A few recent reports are summarised below. Trost et al. found useful yields of indole derivatives 93 utilising [{Rh(cod)Cl}2] as a catalyst and phosphine as a ligand. Tris(4-flurophenyl)phosphine ligand yielded more indole than other ligands. A catalyst, InBr3, cyclized 2-ethynylanilines 94 with an alkyl or aryl group on the terminal alkynes to form polysubstituted indoles 95. A gold catalyst annulated 2-alkynylanilines 96, according to Arcadi et al. Hg(OTf)2 was used to regioselectively synthesise 2-substituted indole derivatives 99 by Nishizawa et al. Zhao et al. hydroaminted alkynyl

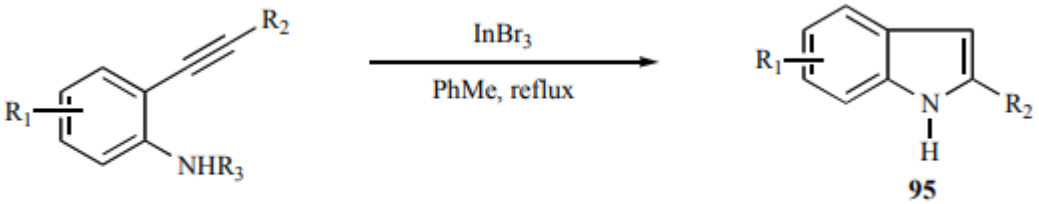
sulphonamides 98 intramolecularly with Et2Zn. Fujii et al. synthesised 2-(aminomethyl)indoles 101 utilising a novel CuBr-catalyzed domino three-component coupling technique. For 2-(aminomethyl)indole derivatives, yields were 61% to 79%. Piperidine, pyrrolidine, diethylamine, and bulky diisopropylamine also reacted with compound 100 (R = H) to create indole derivatives in yields of 78% to 89%, as shown in Figure 21. We also generated pyrrolopyridines and 2-substituted indoles by intramolecularly cyclizing acetylenic amines 102 with AuCl3. Cycloisomerization of acetylenic amines required no acid or N-protecting group (Figure 22). Pd(OAc)2, PPh3, and piperidine hydrolysed p-iodoanisole with ethyl 3-(o-trifluoroacetamidophenyl)-1-propargyl carbonate 104 to yield 2-Methyl Indole and 2-(piperidin-1-ylmethyl)Indole (Figure 23). However, compound 104 yielded 2-(piperazin-1-ylmethyl) indoles with N-substituted piperazine and Pd(PPh3)4. However, reacting 3-(o-trifluoroacetamidophenyl)-1-propargyl carbonates 108 with formate anions and Et3N in acetonitrile with Pd(PPh3)4 generated 2-alkylindoles 109 with good to excellent yield



92 **93**

R = CH_3,Cl, NO_2, $COCH_3$, CO_2Et etc.

(i) 1 % [{Rh(cod)Cl}$_2$], 4 % PPh_3, DMF, 85 oC, 2 h, (52^{-90} %).
(ii) 5 % {Rh(cod)Cl}$_2$], 60 % (4-$FC_6H_4)_3P$, DMF, 85 oC, 2 h (79^{-98} %).
(iii) 1 % [{Rh(cod)Cl}$_2$], 4 % (4-$FC_6H_4)_3P$, DMF, 85 oC, 2 h, 72^{-92} %.



94 **95**
(48-98 %)

R_1=H, Me, NO_2, F, CN; R_2=Ph, C_6H_{13}, t-Bu; R_3=H, Bn, Ac

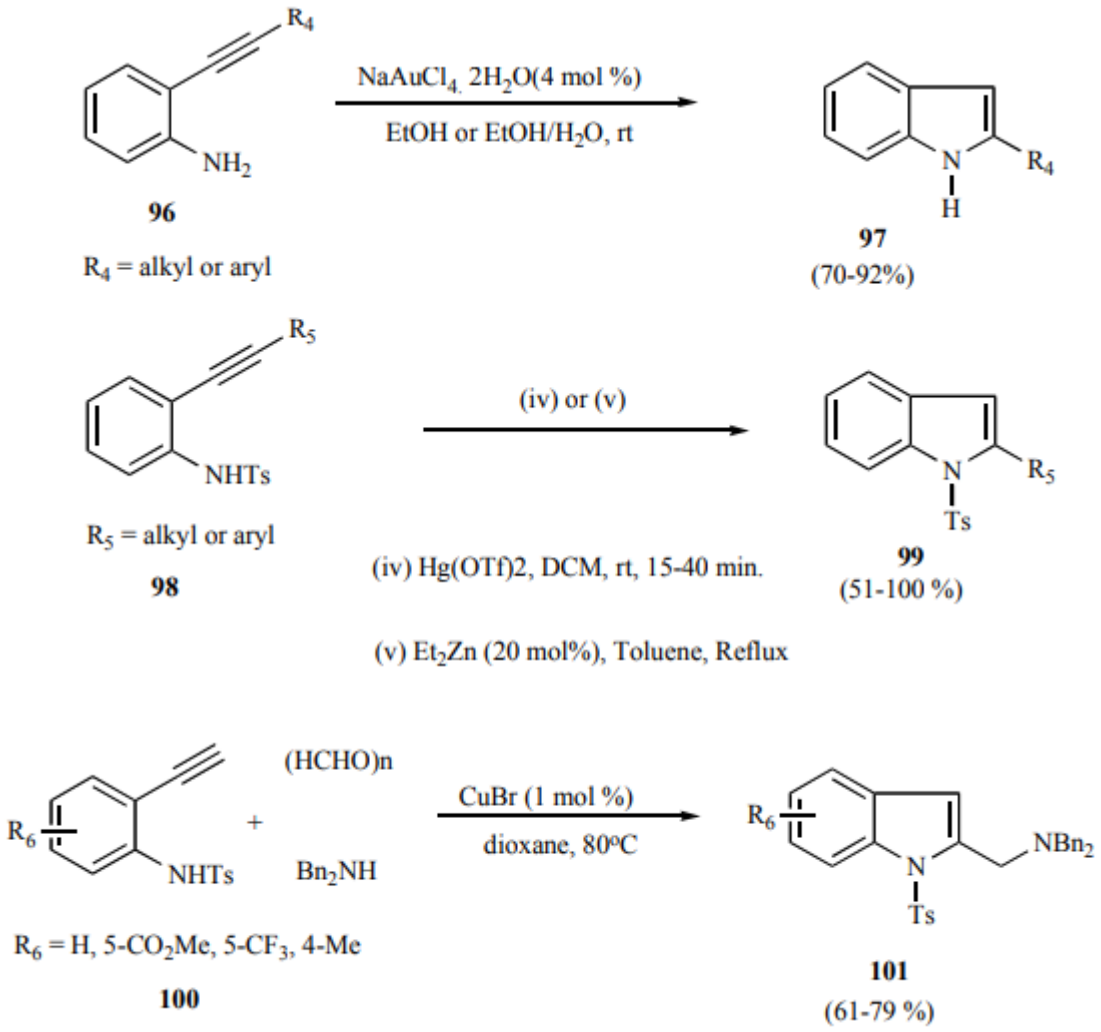


Figure 21.

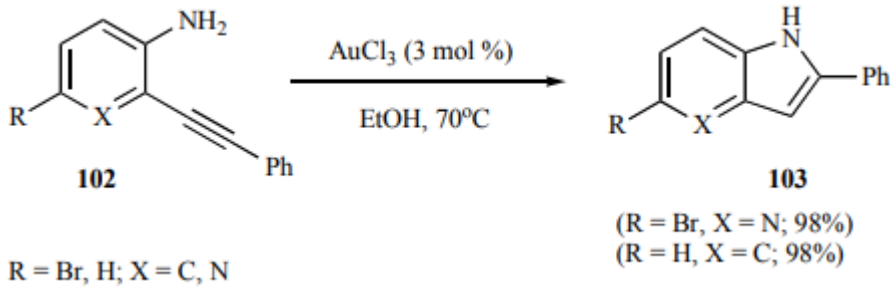


Figure 22.

Wang et al. established a selective method for synthesis of 2-substituted 3-halo-1H-indoles. This technique annuls 2-ethynylbenzeneamines using PdX2/CuX2 (X = Cl, Br). Figure 24 demonstrates that annulation reactions with a variety of 2'-ethynylacetanilides 94a in the presence of PdX2 and CuX2 yielded moderate to good yields of 2-substituted 3-haloindoles 110. Lack of CuBr2 produced 2-substituted indole as the main product.

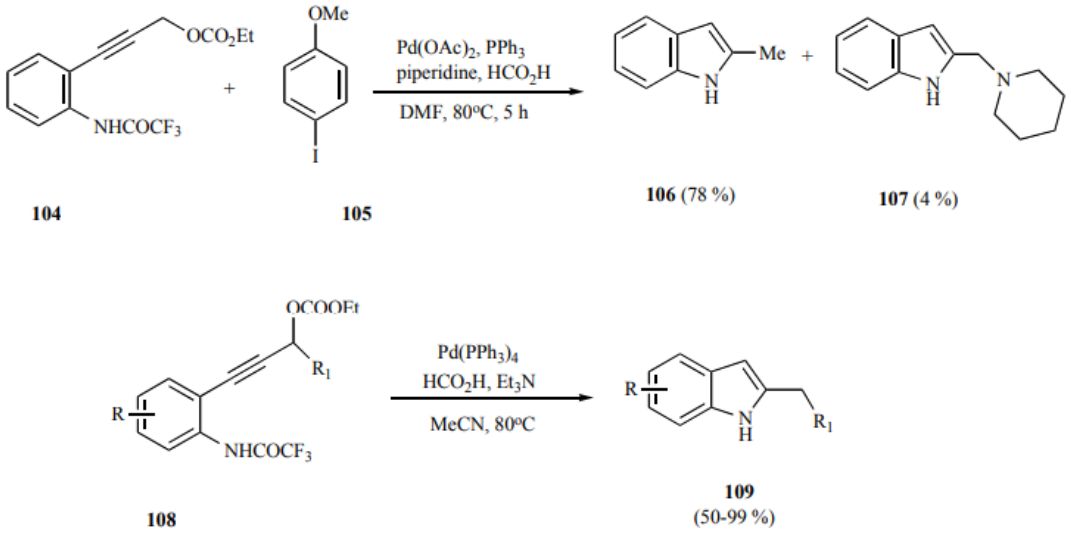
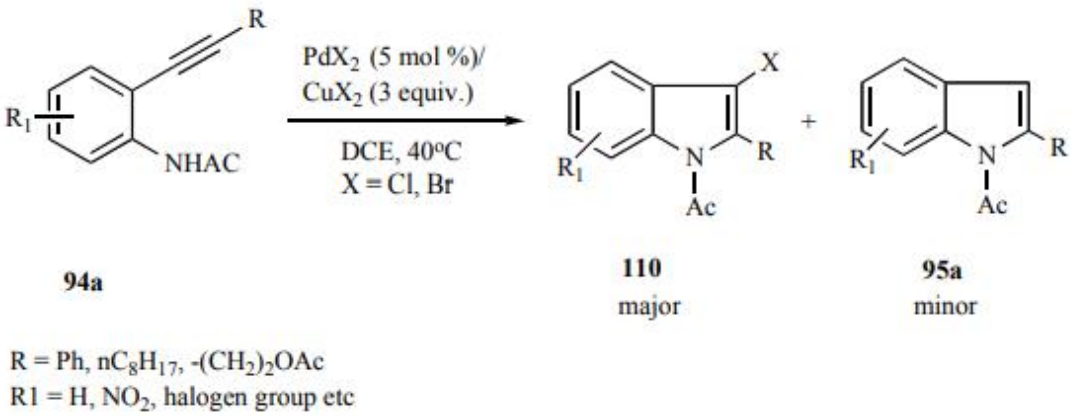


Figure 23.



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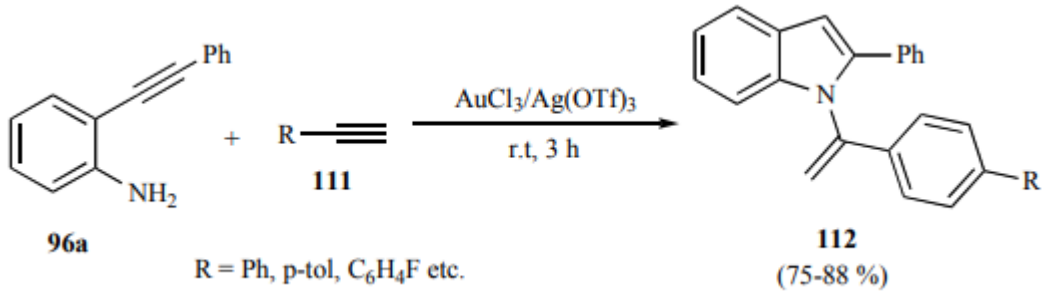


Figure 25.

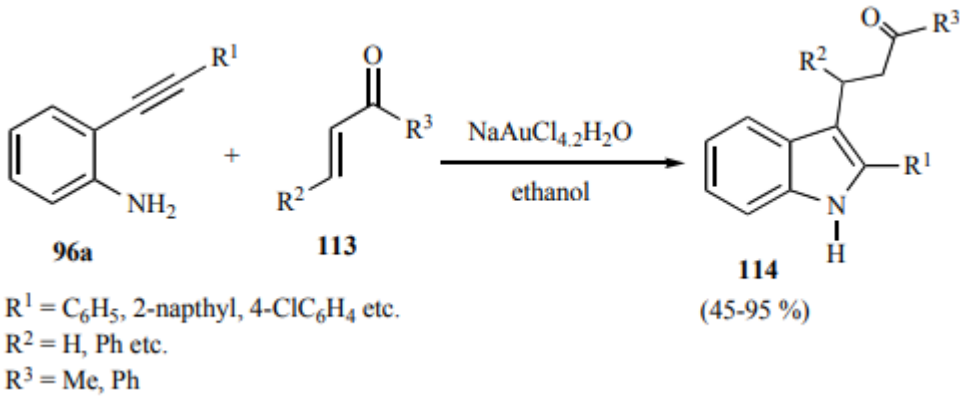


Figure 26.

A two-step hydroamination procedure from o-alkynylaniline 96a to N-alkenylindoles 112 was produced using gold(III) as a catalyst in a clean environment. Figure 25 demonstrates that 75%–88% of the necessary indoles were generated at room temperature. This cyclisation revealed that In(OTf)3, Y(OTf), and Sn(OTf)3 catalysts failed. Figure 26 indicates that gold salts may catalyse the cyclization/conjugate addition of o-alkynylaniline with,-enones 112 to produce 3-alkylindoles 114 in moderate to high yields [70, 71]. Gold-catalyzed annulations of 2-substituted indoles to o-alkynylaniline were also examined in ionic liquid. Figure 27 illustrates that microwave irradiation greatly reduced reaction time.

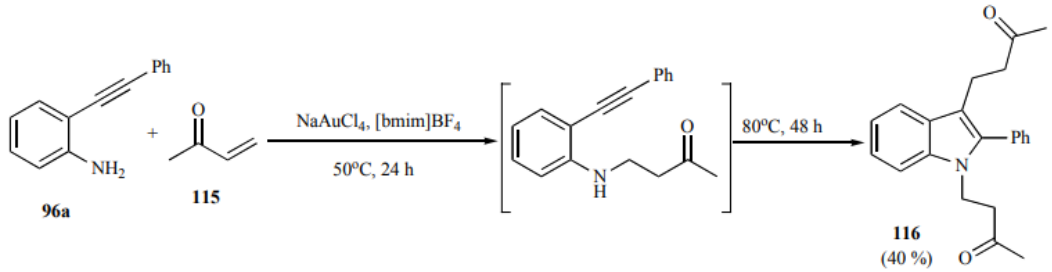
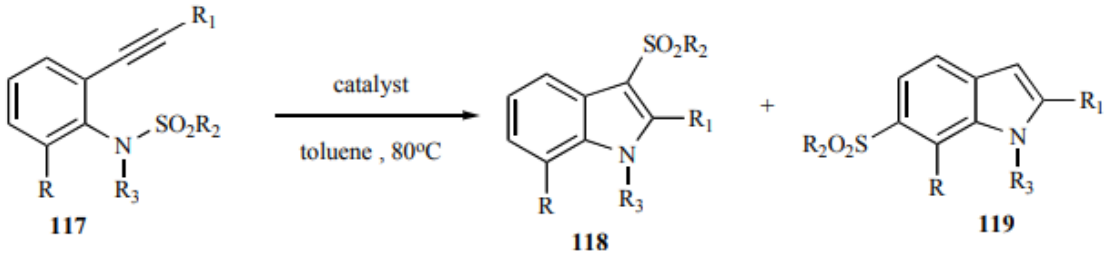


Figure 27.



Major product **118** when R = H and catalyst $AuBr_3$ (10 mol %)
Major product **119** when R = OMe and catalyst $InBr_3$ (5 mol %)

Figure 28.

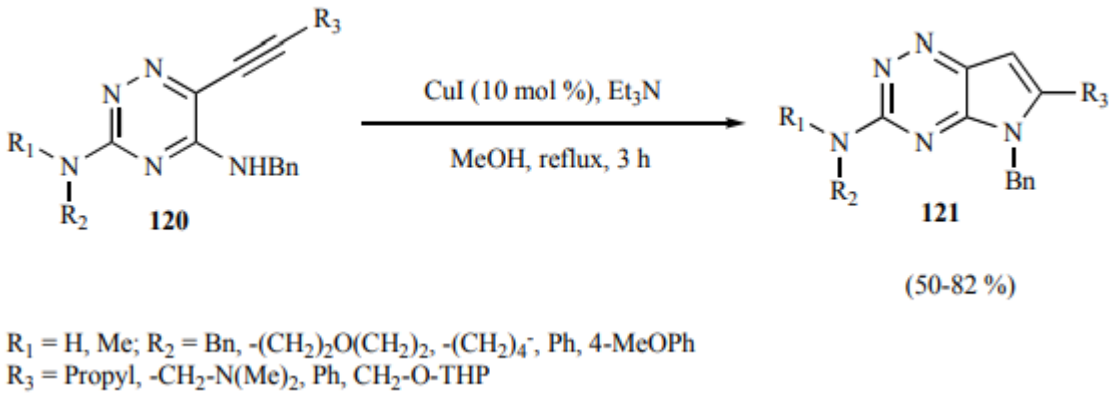


Figure 29.

Physiologically active sulfonylindole substances include RO4368554 and L-737126. Nakamura et al. established a novel method to synthesise 3-sulfonylindoles 118 from o-alkynyl-N-sulfonylanilines 117 by migrating the sulfonyl group during amination. AuBr3 is the preferred catalyst for 3-sulfonylindole production. However, an InBr3 catalyst caused a 1,7-miration of the sulfonyl group, resulting in 6-sulfonylindoles 119 (Figure 28). Sonogashira/Cu(I)-catalyzed heteroannulation of 3,5-diamino-6-chloro-1,2,4-triazines 120 produced 3-amino-5H-pyrrolo[2,3-e]-1,2,4-triazine derivatives 121 (Figure 29). Indole 123 containing cyclic ketone functional groups was generated via Au/Pt-catalyzed cyclisation, 1,2-acyl migration, and 1,2-migration of substrate 122's n-butyl group. As illustrated in Figure 30, the tricyclic compound 124 was generated via an intramolecular Friedel-Crafts reaction followed by an Au/Pt-catalyzed cyclisation (route b) without n-butyl group migration. The transformation yield and selectivity increase using PtCl4 as a catalyst. Gold catalysts with heterocyclic carbene ligands can do both. Lu et al. presented a Pd-catalyzed one-pot three-component method for 2,3-disubstituted indoles 130. Sonogashira coupling and aminopalladation have similar reaction conditions (Figure 31). Selective indole derivatives may be synthesised utilising unsymmetrically substituted alkynes and primary 2-bromo- or 2-chloroanilines in a one-pot annulation method. TiCl4 catalyses regioselective intramolecular hydroamination. Palladium catalyses an intramolecular aza-Heck reaction. Indoles with predominantly 3-aryl substituents were made from unsymmetrically substituted aryl alkynes. A heterocyclization procedure using N-(3-chloropyrazin-2-yl)-methanesulfonamide 131 and internal alkynes 132 in microwave-irradiated Pd(dppf)Cl2 and LiCl yielded 6-substituted-5Hpyrrolo[2,3-b]pyrazines 133 (Figure 32). 2-Substituted indole 97a was synthesised in high yield by Sonogashira coupling-5-endo-dig cyclisation without ligands, copper, or amines. Both ultrasonic and conventional stirring conditions were used to react 2-iodoaniline 134a and phenyl acetylene with Pd(OAc)2. Figure 33 indicates that ultrasonic irradiation considerably increased rate.

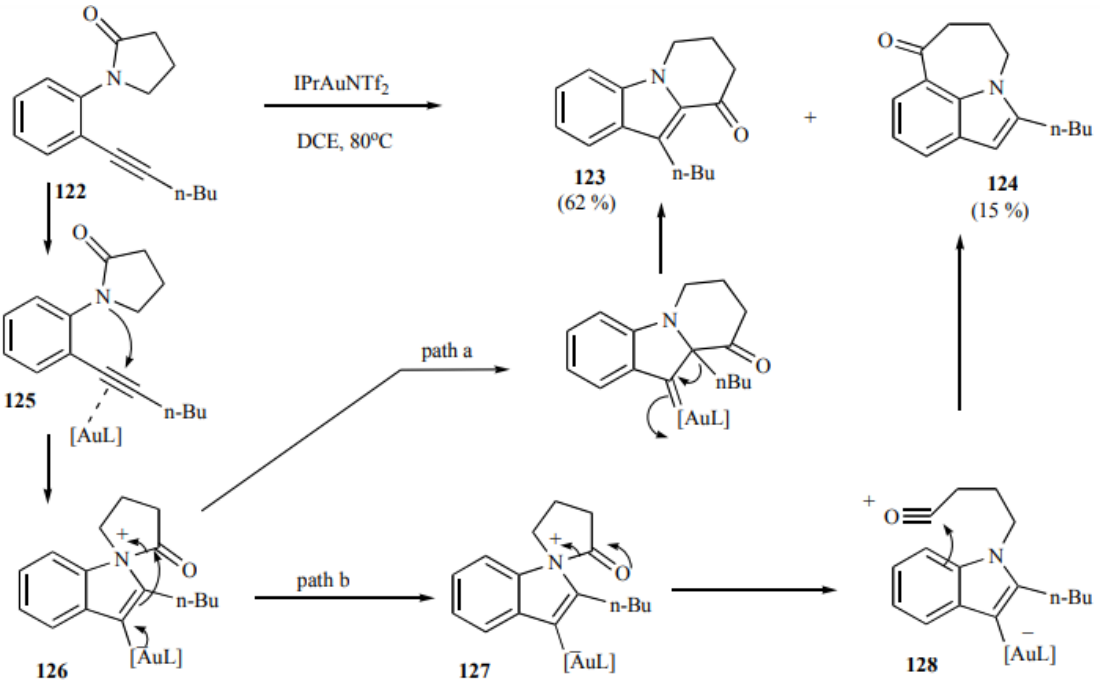


Figure 30.

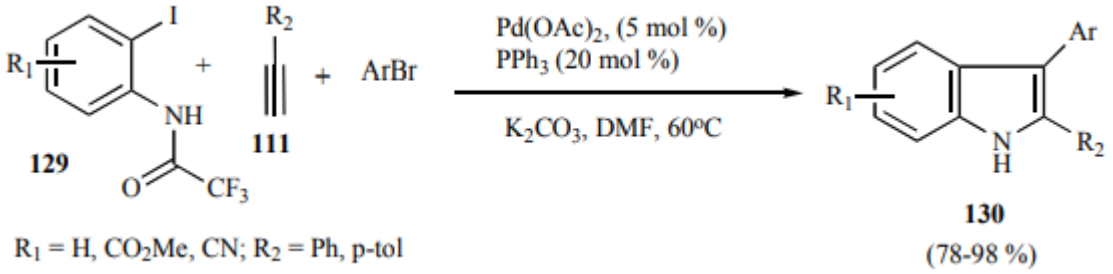


Figure 31.

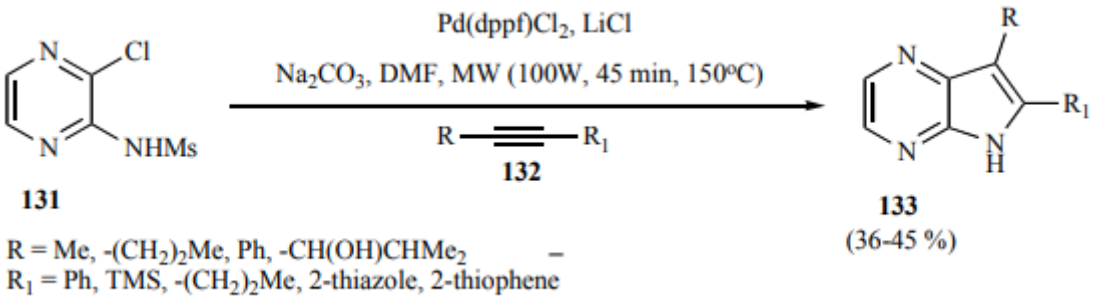


Figure 32.

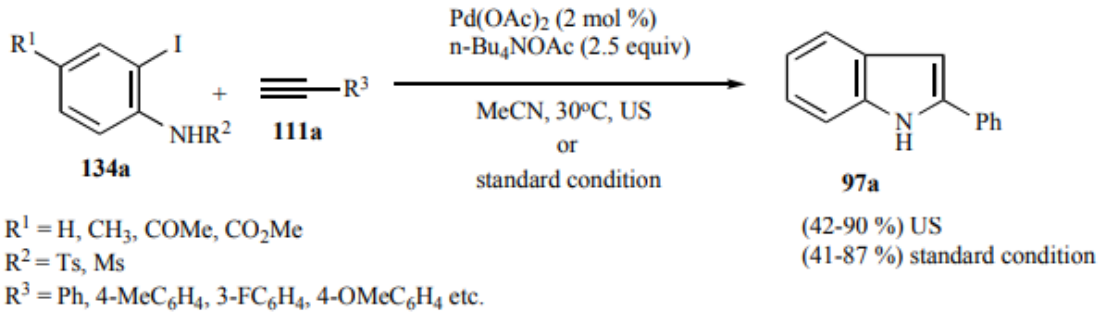


Figure 33.

Without phosphine, 2-bromonilines may be indolized with internal alkynes using Pd as a catalyst. Phenylurea was found to be the best ligand for synthesis of 2,3-disubstituted indole with high yield and regioselectivity (Figure 34). Figure 35 demonstrates the one-pot synthesis of 2-aryl- and 2-vinyl indoles using 2-chloroaniline 136 as a precursor, palladium-catalyzed intramolecular Heck reaction, and ruthenium-catalyzed hydroxyamination. A unique method for synthesising functionalised indoles is palladium-catalyzed reductive N-heteroannulation of 1-(2- nitroaryl)-1-alkenes. Carbon monoxide reduces palladium. The palladium-phenanthroline complex-catalyzed intermolecular cyclisation of unfunctionalized nitroarenes 138 and alkynes to produce 3-arylindoles 139 was fully studied. With [Pd(Phen)2][BF4]2 as a catalyst and carbon monoxide in DMF at 170 °C, indole synthesis was selective (Figure 36).

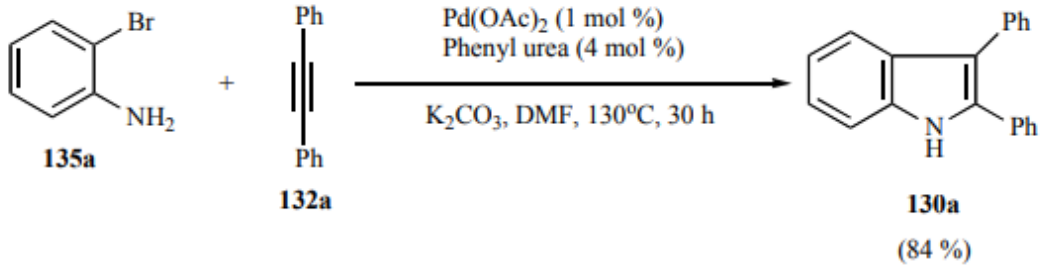


Figure 34.

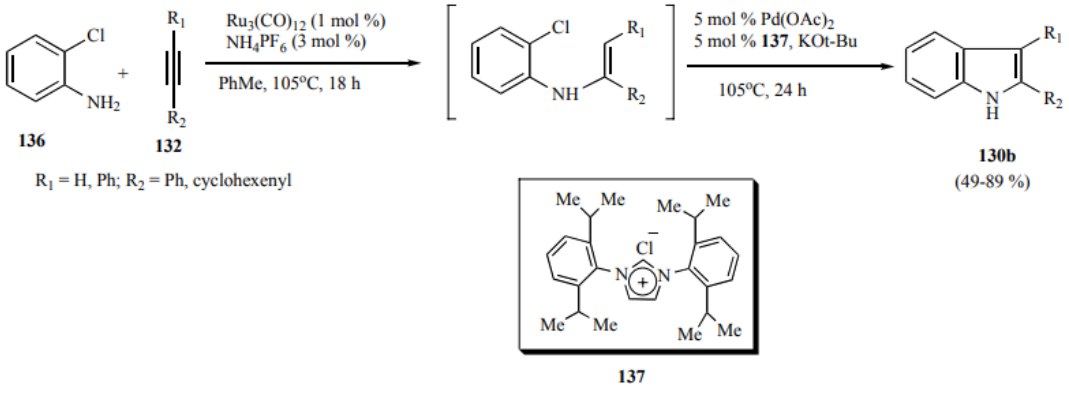


Figure 35.

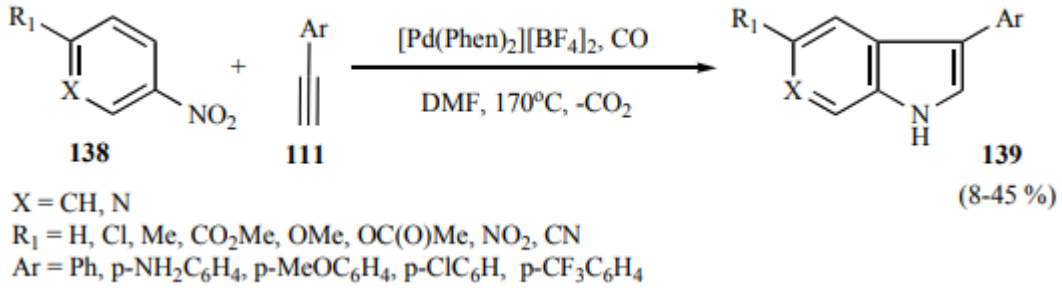


Figure 36.

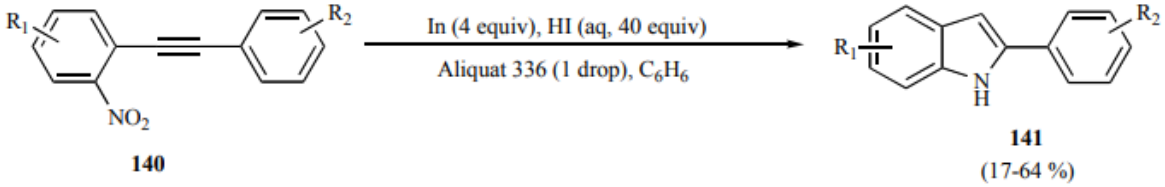


Figure 37.

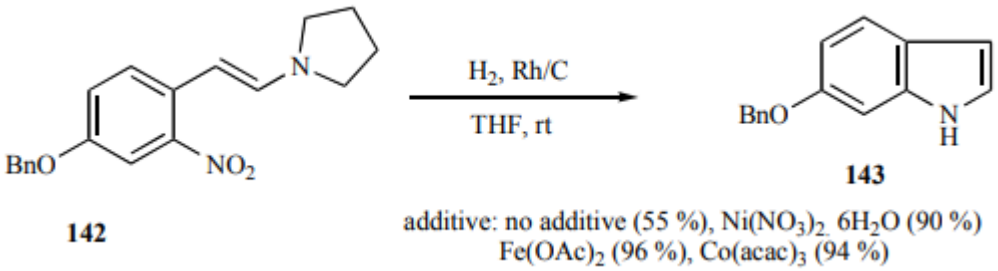


Figure 38.

Kim et al. synthesised 2-arylindoles using indium-promoted reductive heterocyclization. In benzene refluxing with indium metal, aqueous HI, and aliquat 336 (1 drop), 1-(2-arylethynyl)-2-nitroarenes 140 were converted to 2-anilines. However, 2-(2-arylethynyl)anilines reductively cyclized to 2-arylindoles 141 with excellent yields (Figure 37). Catalytic hydrogenation of (E)-2-nitropyrrolidinostyrene 142 generated indole 143 effectively at 5% Rh/C (Figure 38). Rh/C and Ni(NO3)2.6H2O, Fe(OAc)2, or Co(acac)3 additive combinations with significant chemo selectivity provided the necessary indoles in high yields. Without additives, product yield decreased.

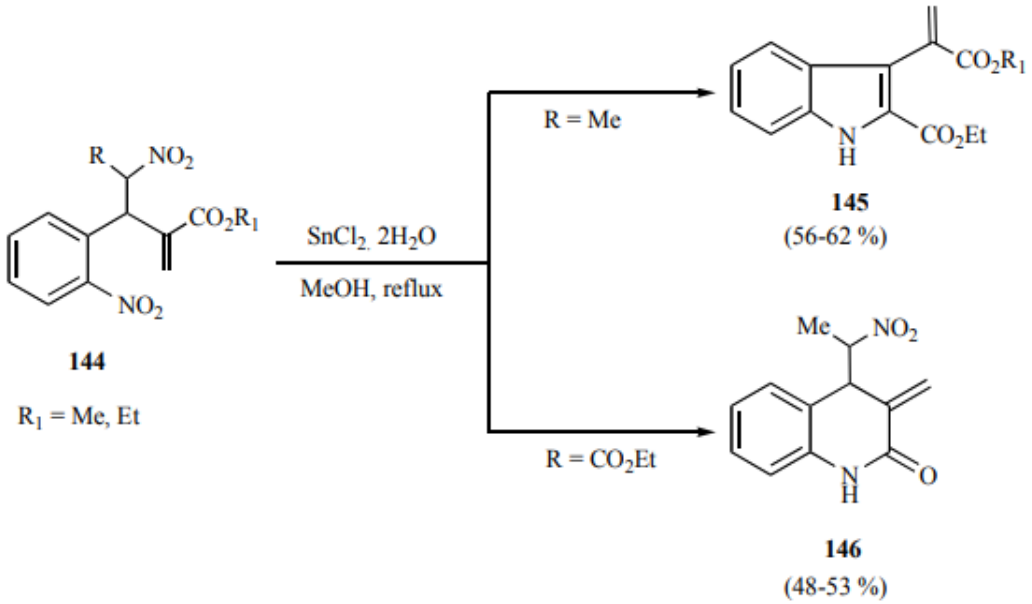


Figure 39.

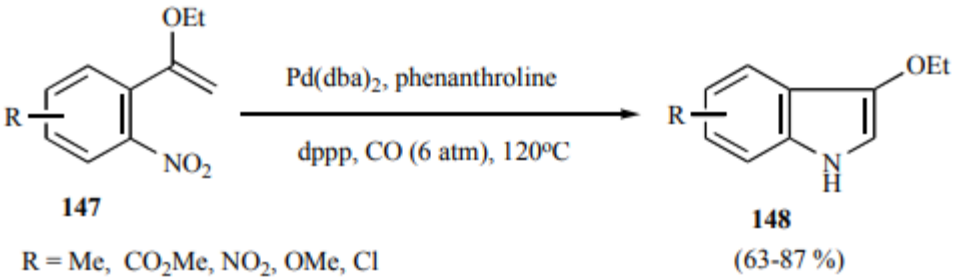


Figure 40.

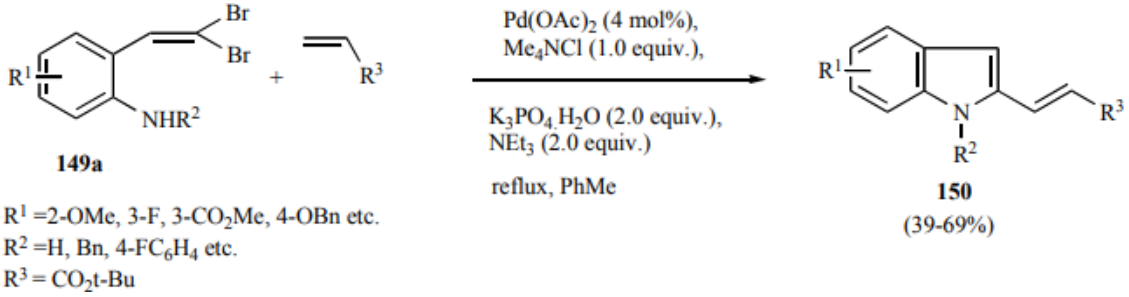


Figure 41.

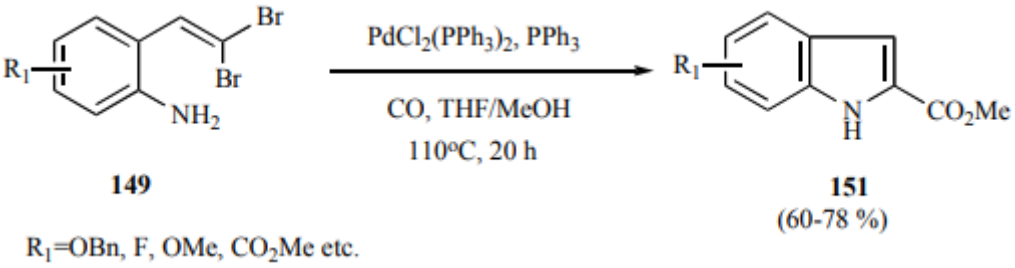


Figure 42.

The secondary nitro group of 3-aryl-2-methylene-4-nitroalkanoates may be reduced to produce substituted 2-pyrrolidinones and indoles. Figure 39 shows that SnCl2.2H2O reductively cyclized 144 to form 3-(1-alkoxycarbonylvinyl)-1H-indole-2-carboxylates 145 and 4-alkyl-3-methylene-2-quinolones 146. N-heterocyclization of 3-alkoxy indole derivatives was another noteworthy example [88a]. A Pd(dba)2/phenanthroline/dppp catalytic system converted 1-(2-nitrophenyl)-1-alkoxyalkenes 147 to the indole derivative 148 at a lower temperature (Figure 40). The agreement is that palladacycles decrease the NO2 group to a nitroso group, which is cyclized and reduced with CO to yield the desired product. The same method has also produced indole-3-carboxylic acid derivatives. The Domino Buchwald-Hartwig amination / Heck method produced 2-vinylic indoles 150 from gemdibromovinylanilines 149a (Figure 41). Silver salts increased Pd-catalyst reaction reactivity and selectivity. Pd-catalyzed tandem intramolecular amination and intermolecular Suzuki coupling with organoboron reagents and gem-dibromovinylaniline substrates produces 1,2-Diarylindole. 2-(2,2- dibromovinyl)phenylamines 149 were tandem Pd-catalyzed N,Ccoupling/carbonylation under 10 atm CO at 110 °C to create 2-carbomethoxyindoles 151 (Figure 42). Catalytic systems can tolerate several functional groups, and indole yields were high.

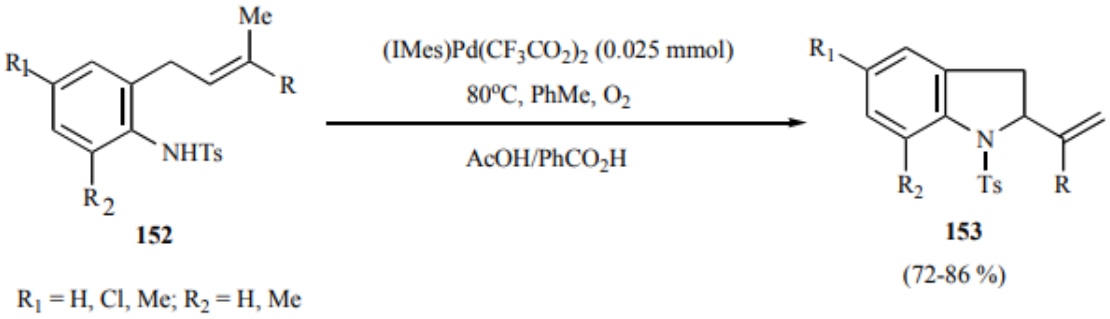


Figure 43.

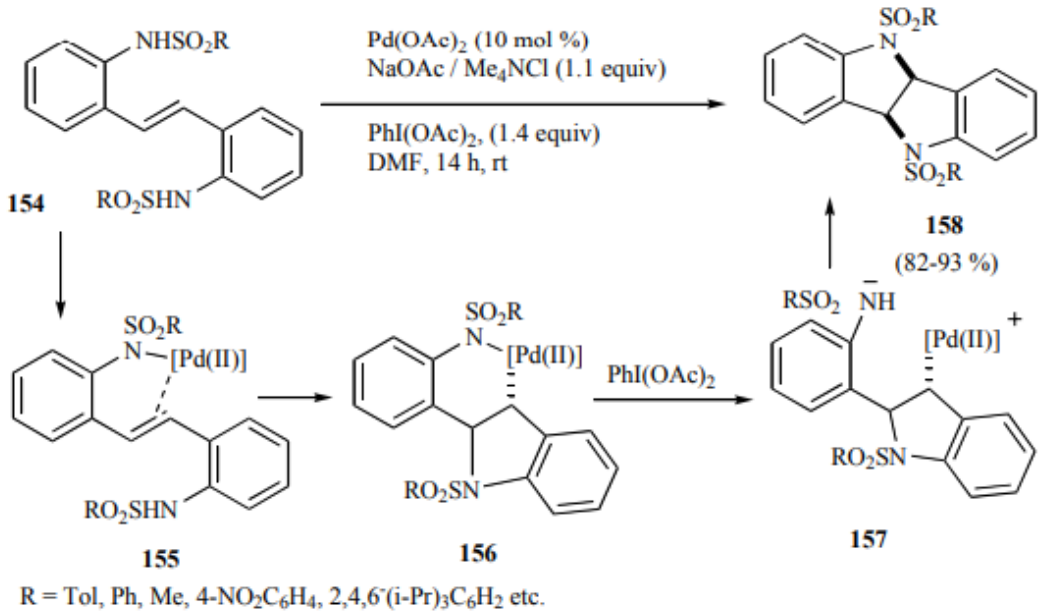


Figure 44.

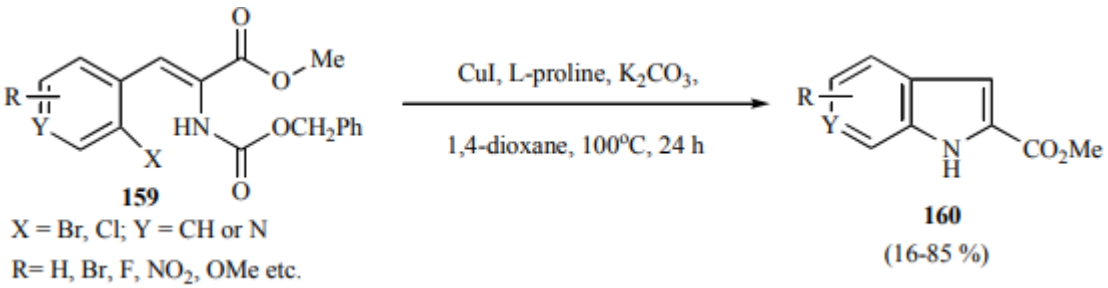


Figure 45.

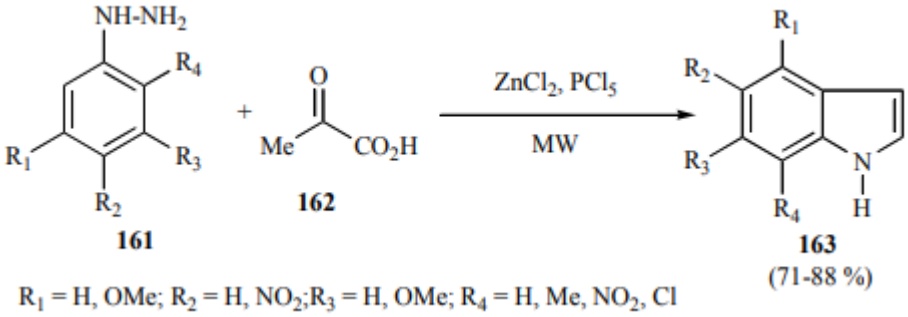


Figure 46.

Figure 43 shows the indole derivatives 153 produced by aerobic intramolecular oxidative amination of olefinic tosyl amines 152 with an N-heterocyclic carbene (NHC)-coordinated Pd(II) complex, (IMes)Pd(CF3CO2)2, air or pure oxygen gas as the oxidant and a carboxylic acid, such as PhCO2H or AcOH, as the co-catalyst. Two sulfonamides may be effectively transformed to bisindoline by successive catalytic transfer to internal alkenes. A domino oxidative diamination reaction of component 154 with Pd(OAc)2 and NaOAc yielded bisindoline derivatives 158. Palladium-tosyl amide pre-coordination and endo-selective anti-aminopalladation switch the reaction to chelation. Oxidation to palladium(IV), amide dissociation, and selective antiamination/depalladation convert compound 156 to bisindoles 158 (Figure 44). Two-substituted indoles 160 (Figure 45) and pyrrolo[2,3-c]pyridines were generated by intramolecular cyclisation of ene-carbamates 159 using CuI/L-proline catalysts. Combining the Horner-Wadsworth-Emmons condensation with the proper phenyl or pyridyl carboxyldehyde generated ene-carbamates, precursors to cyclisation. Microwave irradiation with the Lewis acids ZnCl2 and PCl5 may generate indoles from phenylhydrazines and pyruvic acid in high yields. Figure 46 depicts microwave-induced decarboxylation. Moderate intramolecular heterocyclization of 3-alkoxyimino-2-arylalkylnitriles 164 produces functionalised N-alkoxyindole-3-carbonitrile 165 derivatives (Figure 47).

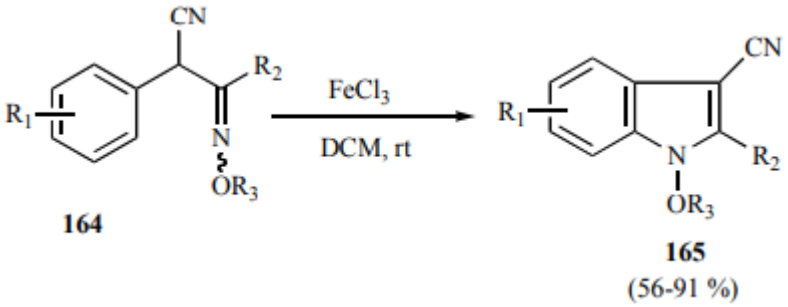


Figure 47.

They used palladium-catalyzed direct annulation of electron-poor o-chloro/bromoanilines and o-chloropyridines with aldehydes to synthesise 2-substituted indoles and azaindoles. Catalysed reaction of 2-(3,4,5-trimethoxyphenyl)propanal 167 and 2-chloro-5-nitroaniline 166 with t-Bu3P. HBF4 and KOAc in DMA yielded 43% indole (Figure 48). A domino-heterocyclization reaction with o-iodoanilines 134 and 2-N,N-di-t-butoxycarbonylamino-5-oxopentanoate 169 produced ring-A substituted tryptophan derivatives 170 (Figure 49). A new method for synthesising indole derivatives employing successive Pd-catalyzed C-C and C-N bond-forming processes using imine aza-allylic anions has been devised. Indoles 173 were synthesised utilising o-dihalobenzenes 171 and imine 172, x-phos as a ligand, and sodium tertiary butoxide as a

base (Figure 50). C-H activation with dirhodium(II) nitrenoids produces stereoselective heterocycles. Diazo compounds are often broken down using a rhodium(II)-catalyst to yield reactive intermediates. Driver and colleagues recently described rhodium(II)-assisted synthesis of substituted indoles from vinyl azides to activate C-H bonds. Dirhodium(II) perfluorobutyrate was the most reactive catalyst for vinyl azides 174 to rhodium nitrenoid intermediate 175 and nitrogen removal and regioselective C-N bond formation to indole derivatives 177 (Figure 51).

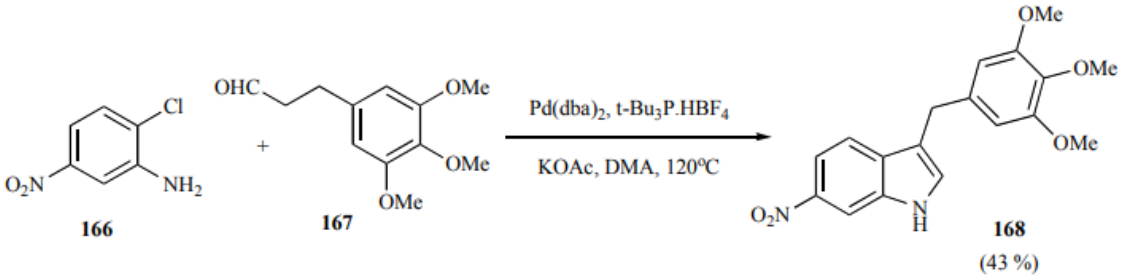


Figure 48.

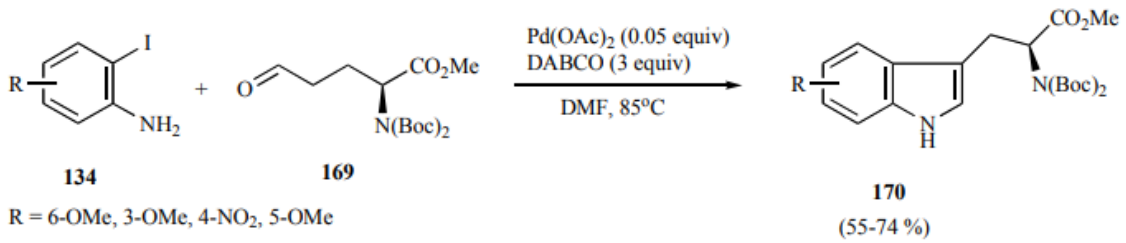


Figure 49.

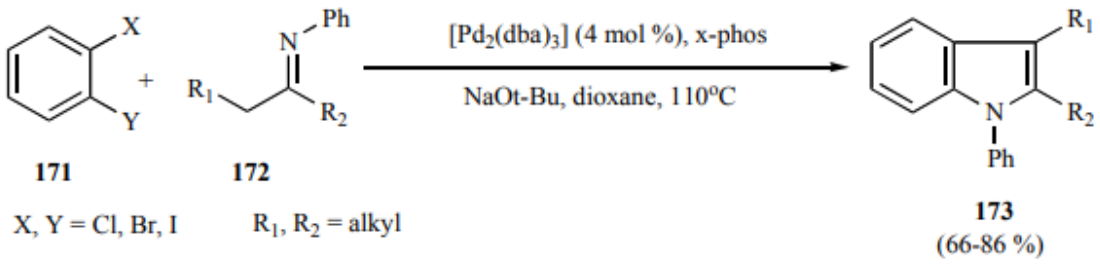


Figure 50.

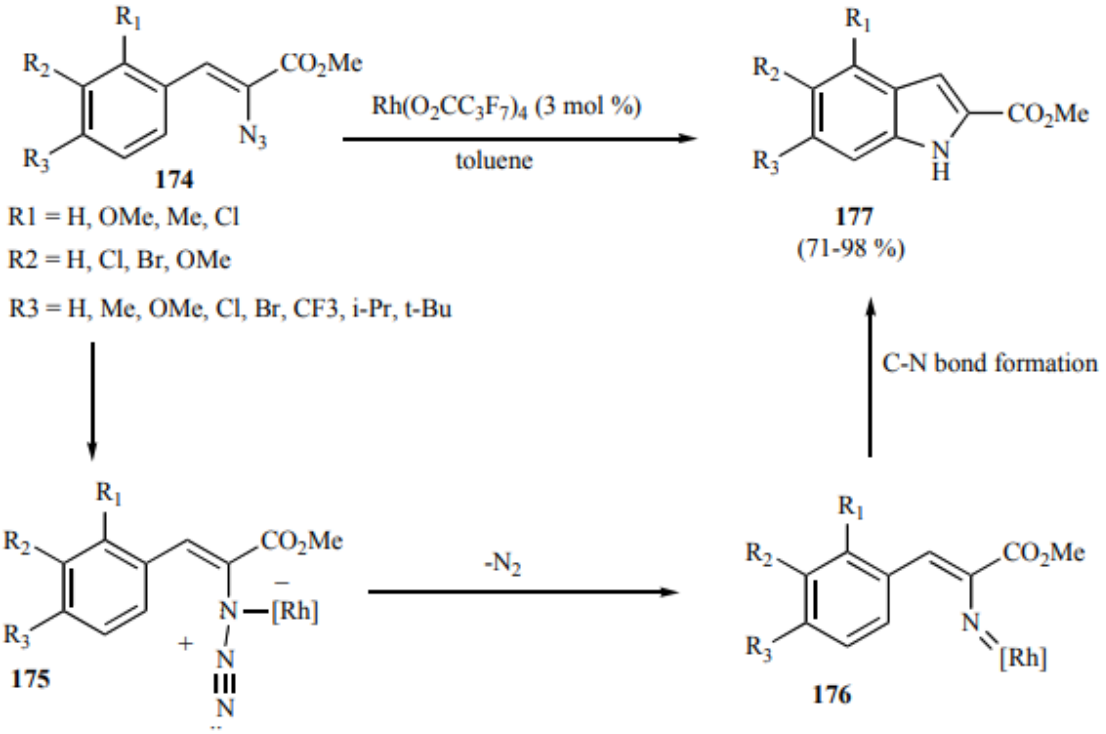


Figure 51.

Synthesis of Oxindoles

Copper-catalyzed intramolecular amidation of N-substituted 2,6-dibromophenylacetamides produces 4-Bromo-N-substituted oxindoles. Figure 52 indicates that N-substituted 2,6-dibromophenylacetamides 178 treated with 10 mol% CuCl, 0.5 equiv. K2CO3, and 25 mol% acetylacetone yielded 5-8% 4-bromooxindoles 179. Importantly, solvent and ligand strongly alter the effectiveness of Pd(dba)2-catalyzed intramolecular Buchwald-Hartwig amination of amide 180. The necessary oxindole was not generated efficiently by Pd(OAc)2. Amination in a microwave oven with Pd(dba)2 as the catalyst yielded 82% oxindole 181 (Figure 53).

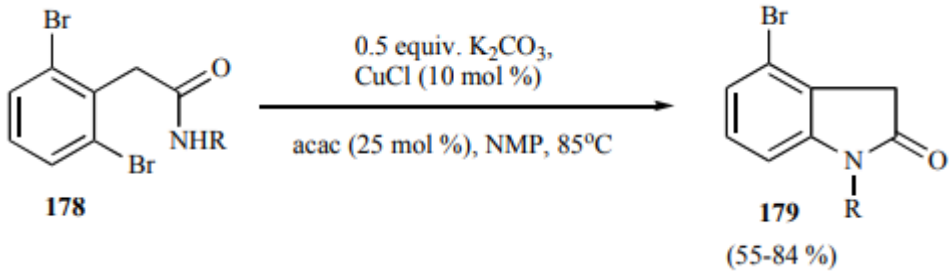


Figure 52

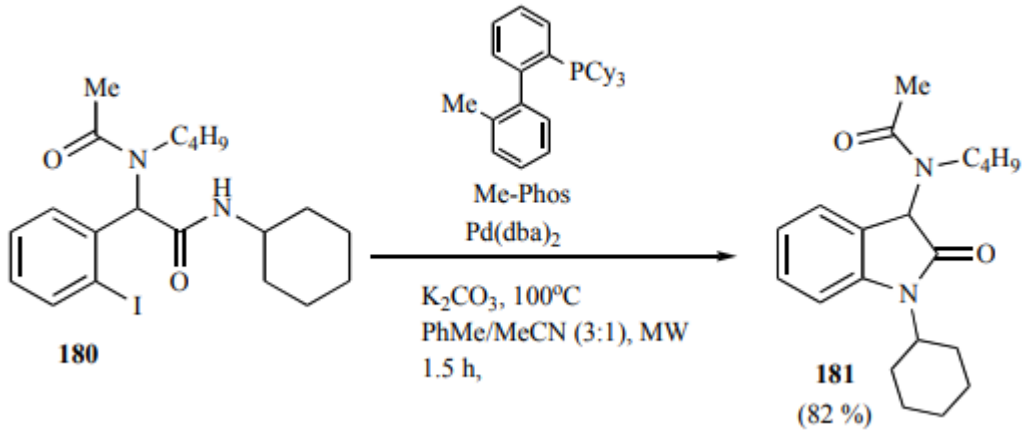


Figure 53

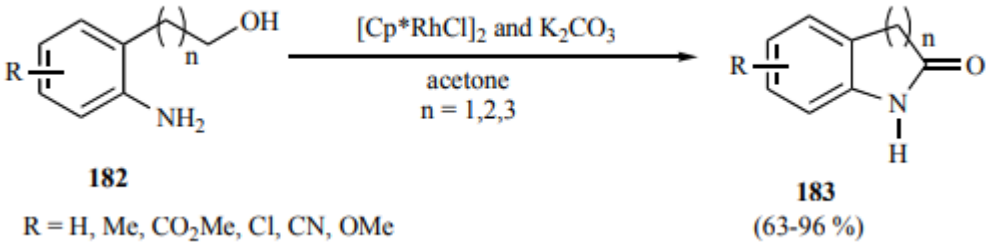


Figure 54.

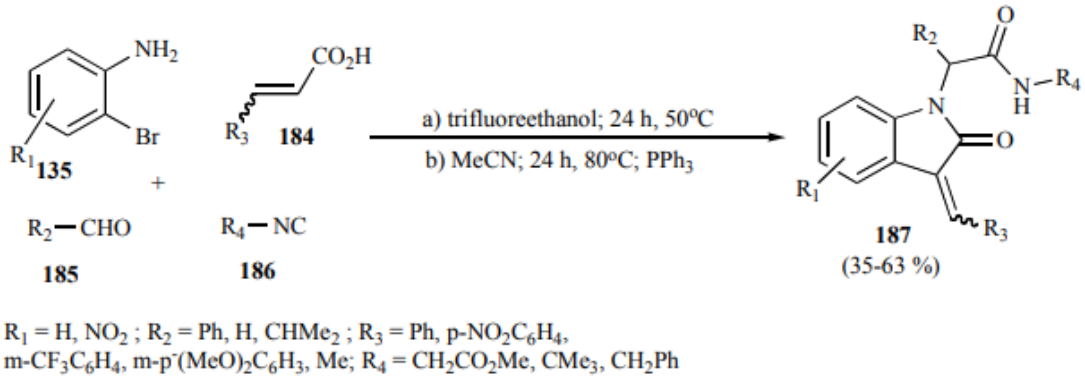


Figure 55.

Yamaguchi et al. designed a [Cp*RhCl]2/K2CO3 catalytic system for amino alcohol lactamization. The reaction of 3-(2-aminophenyl)-1-propanols in acetone with [Cp*RhCl]2 (5 mol%) and K2CO3 (10 mol%) yielded 3,4-dihydro-2(1H)-quinolinones in 63-96%. 2-aminophenylethyl alcohols 182 treated with [Cp*RhCl]2 (3 mol %) and K2CO3 in acetone under reflux for 8 h yielded 46–80% oxindoles 183 (Figure 54). Indol-2-ones may be prepared using a unique one-pot solution phase Ugi-Heck reaction (Ugi-4CRHeck). The intermediate Ugi product undergoes intramolecular Heck reaction to provide the indol-2-one derivatives 187 (Figure 55).

3. Synthesis of Indolizine Derivatives

Pyridinyl propargylic alcohol, a nitrogen nucleophile, may be used for metal-catalyzed cycloisomerization to access nitrogen-containing heterocycles. Sarpong and colleagues employed tandem cyclisation/1,2-migration or Pt(II)-catalyzed cycloisomerization to synthesise indolizine, pyrrolone, and indolizinone heterocycles from propargyl alcohol. Treating propargyl alcohols 198 with 5 mol% PtCl2 and 10 mol% of the electron-rich phosphine ligand 2-(ditert-butylphosphino)biphenyl in benzene yielded 40-70% indolizines 199 (Figure 56). Gevorgyan et al. synthesised N-fused

heterocycles by intramolecularly adding aromatic compounds with Sp2 nitrogen atoms to alkynes using Ag-catalyst, AgBF4, or AgPF6. In the presence of an Au(I) or Au(III)-catalyst, propargylic derivatives of N-containing heterocycles cascade cyclizoisomerize into indolizine and other fused pyrrole heterocycles, according to Gevorgyan et al. Many fused pyrrole heterocycles (204) have been synthesised utilising gold vinylidene intermediates by 1,2-migration of propargyl silyl ether 200's trialkyl silicon, tin, and germanium groups. By adding nitrogen to gold vinylidene (201), Zwitterion 202 was created. Deuterium-labeling experiments demonstrate that Zwitterion 202 produces commodities via 1,2-hydride shifts (Figure 57). Silver catalyst cycloisomerization of propargyl-containing heterocycles produced indolizines and other N-fused heterocycles by the same group.

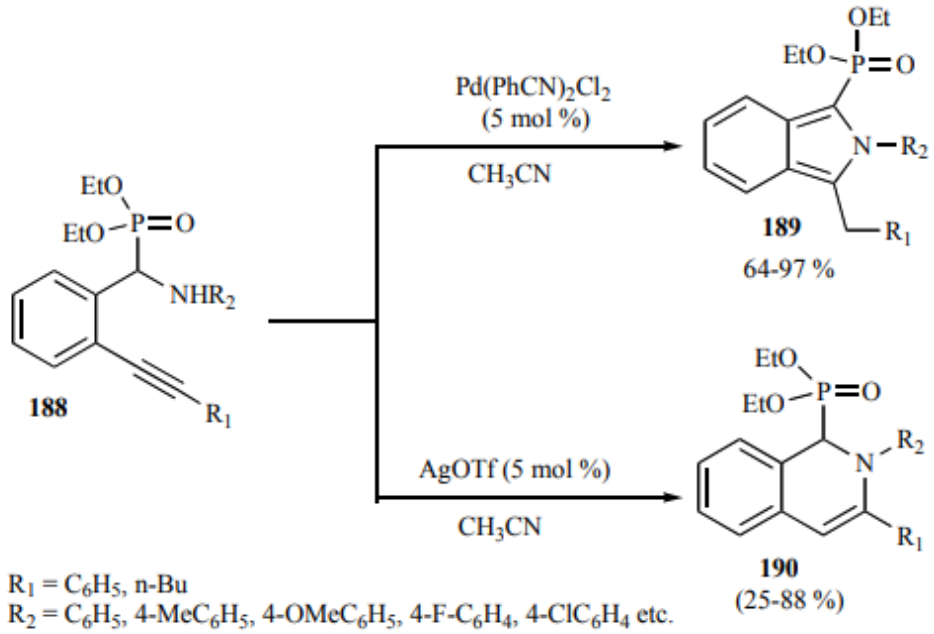


Figure 56

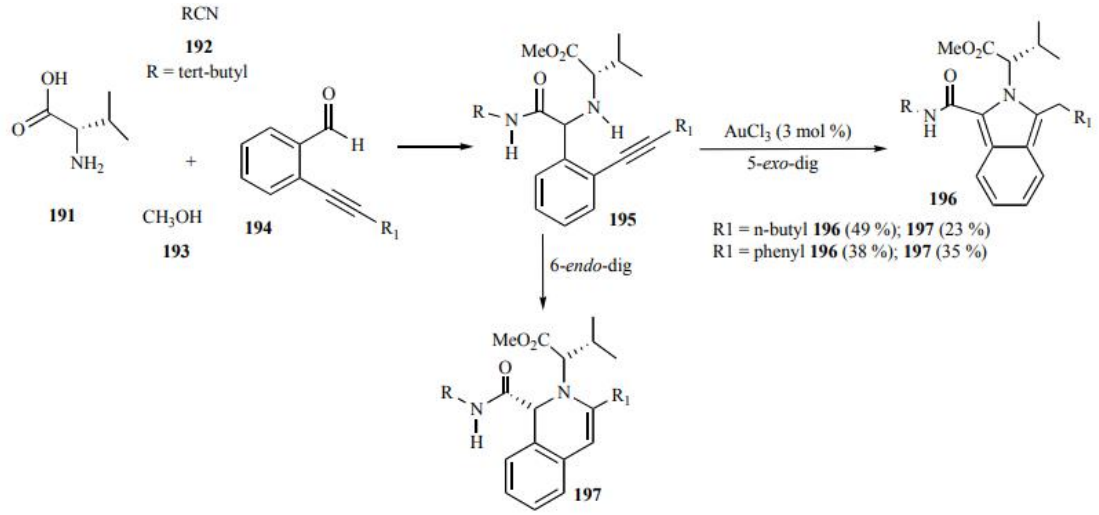


Figure 57.

4. Synthesis of Carbazoles

Ackermann et al. synthesised carbazole compounds utilising palladium-catalyzed domino reaction. The procedure used readily available anilines and 1,2-dichloroarenes for amination and direct arylation. Optimisation experiments indicated that Pd(OAc)2 catalyst, PCy3 ligand, and sodium tertiary butoxide base yielded N-substituted carbazole derivatives. NH-free carbazoles were synthesised using NMP as solvent, K3PO4 as base, and PCy3 as ligand (Figure 58). The tandem Suzuki-Miyaura coupling and amination methods synthesised carbazole from two aromatic rings in one pot. Figure 59

indicates that the phosphine ligand aided intermolecular biaryl formation and ring-closing amination. Intermolecular reaction with microwaves created carbazole derivatives 226 from 2-chloroaniline derivative 224, different arylbromides, Pd(OAc)2 as catalyst, and P(t-Bu)3 as ligand (Figure 60). Buchwald-Hartwig amination and intramolecular ring closure by C-H activation are possible domino reaction steps.

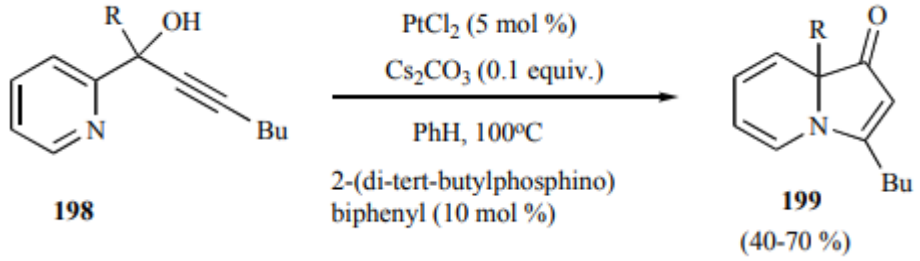


Figure 58.

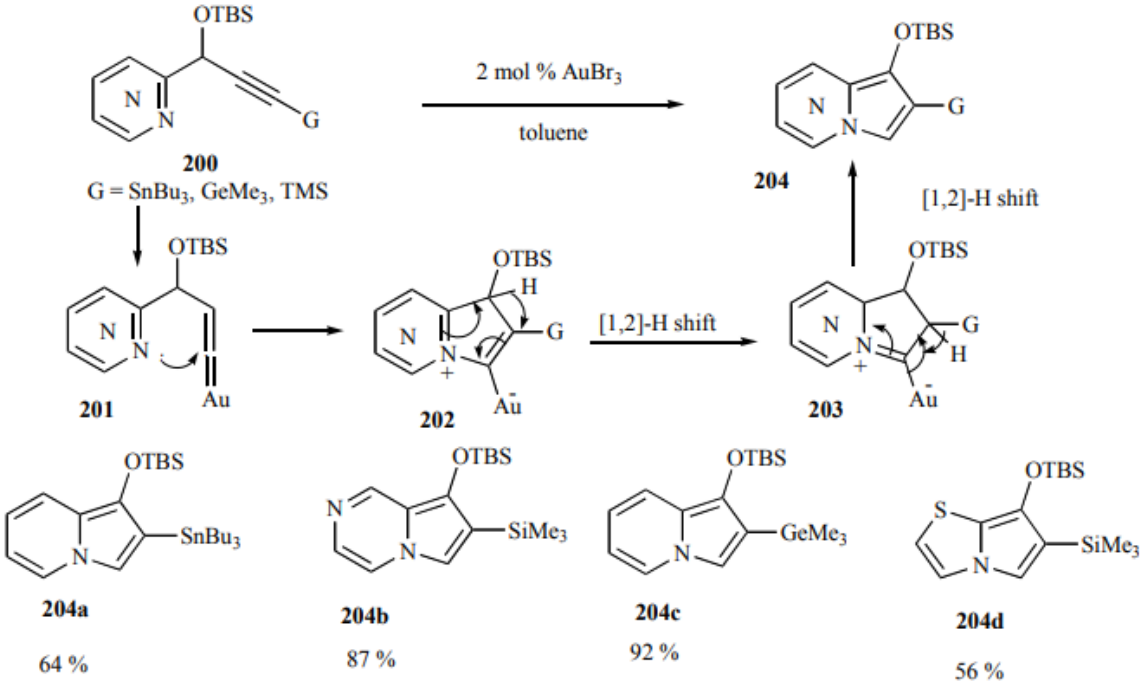


Figure 59.

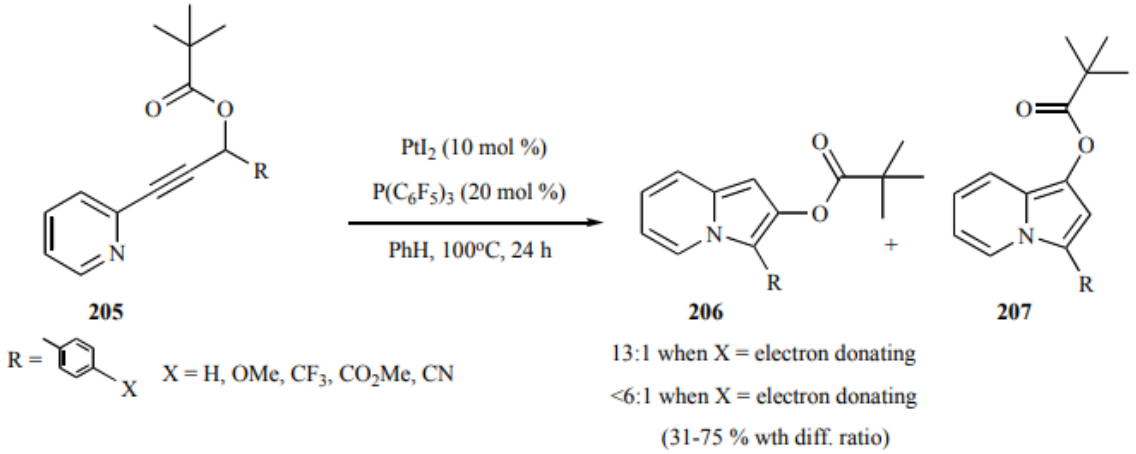
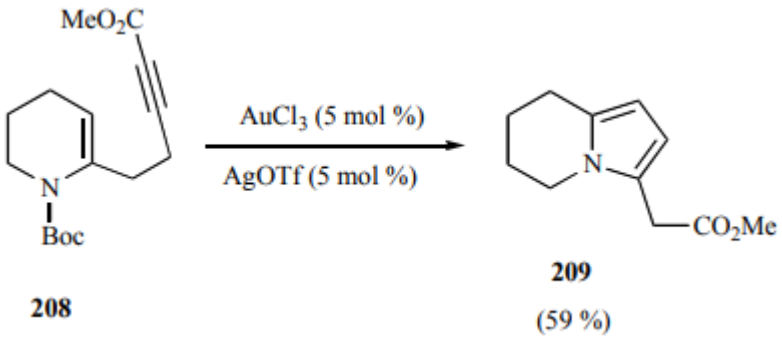


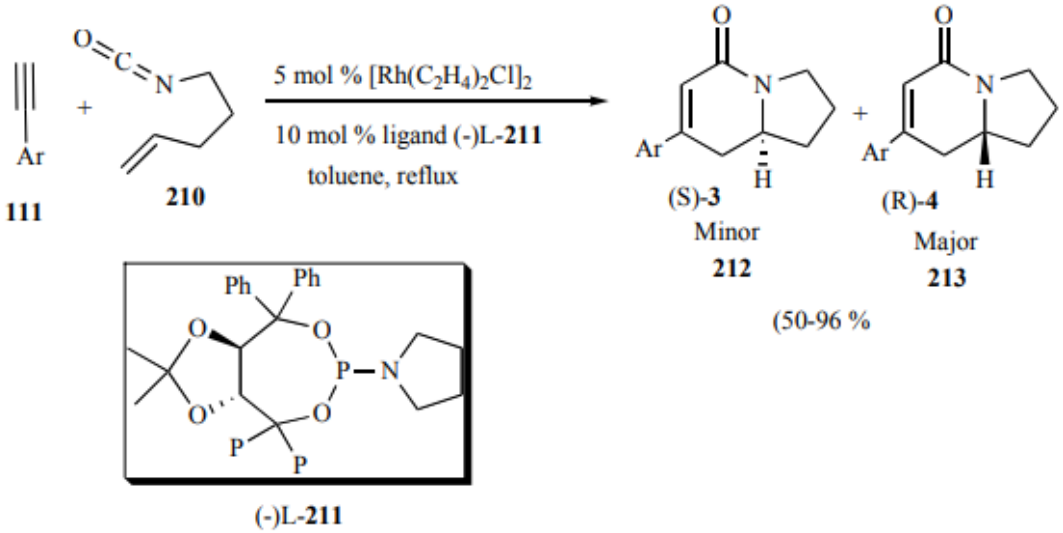
Figure 60.



208 **209**

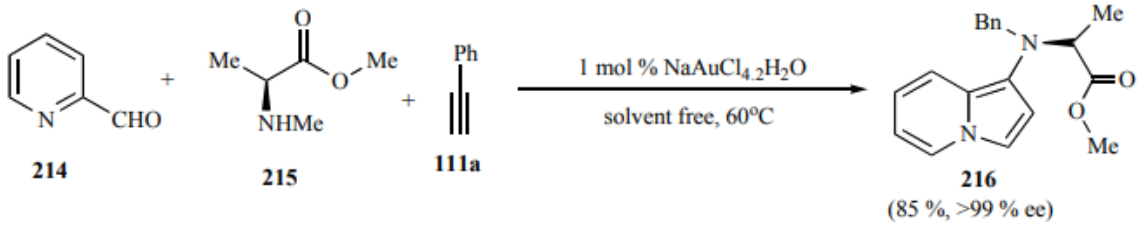
(59 %)

Figure 61.



111 **210** (-)L-**211**

Figure 62.



214 **215** **111a** **216**

(85 %, >99 % ee)

Figure 63.

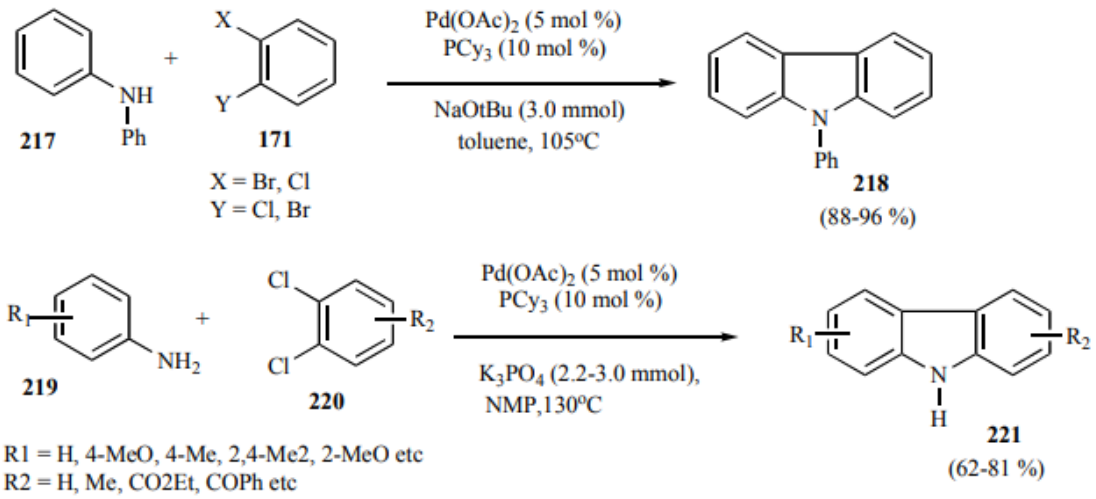


Figure 64

A one-pot carbazole synthesis involving numerous C-H activations was reported by Shi et al. The figure (61). Pd(OAc)2-catalyzed double N-arylation of 230 with ligand-232 and 2,6-di-tert-butyl-4-methylphenol (BHT) produced the 231-indolo[3,2-b]carbazole ring. Figure 62 shows how the ligand altered aniline diamination to yield compounds 231. Palladium-catalyzed intermolecular coupling of odibromobenzene 171 and 5-methylanthranillic acid 233 yields a carbazole derivative in one process. Figure 63 demonstrates that intramolecular reductive elimination produced carbazole derivative 234 instead of o-diarylaminobenzene, which would have generated by a second nucleophilic attack. Söderberg et al. used Pd(dba)2/dppe/1,10-phenanthroline to reductively Nheterocyclize 3-(2-nitrophenyl)-2-cycloalkene-1-one 235 to synthesise tetrahydrocarbazolone derivative 236 as an advanced step to carbazole alkaloids (Figure 64). The natural carbazole alkaloid Murrayquinone-A 239 has been effectively synthesised. The carbazolone intermediate 238 was also generated in high yield from its nitroarene precursor 237 using Pd(dba)2/dppe/1,10-phenanthroline-catalyzed reductive N-heterocyclization [128,129]. Figure 65 demonstrates the simplest way to make Murrayquinone-A 239 from 238.

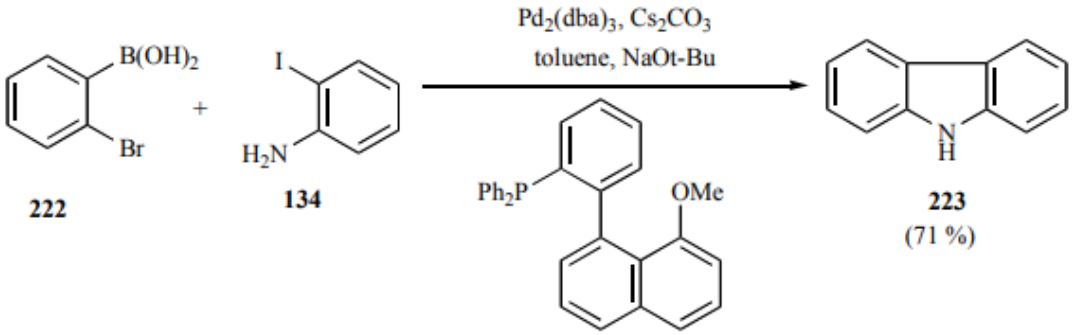


Figure 65

SYNTHESIS OF SIX-MEMBERED HETEROCYCLES

1. Synthesis of Pyridines and Piperidines

Organic synthesis requires metal-catalyzed nucleophile addition to alkenic or allenic double bonds, activated or not, to create functionalised heterocycles. An AgNO3-catalyzed cyclisation of allenic amino acids allowed Mitasev and Brummond to synthesise highly functionalised 3-pyrrolidines by transferring chiral information from the original allene to the result. Ellman et al. produced dihydropyridine and pyridine derivatives by C-H alkenylation, electrocyclization, and aromatisation of,-unsaturated imines and alkynes. Using toluene at 100 °C and a [RhCl(coe)2]2 (2.5 mol%) catalyst, imines 240 were treated with alkynes to create dihydropyridines. Moderate to fair yields of pyridines 243 were obtained by oxidising these dihydropyridines (Figure 66). Use a precise molar ratio of ligand and rhodium for optimal results.

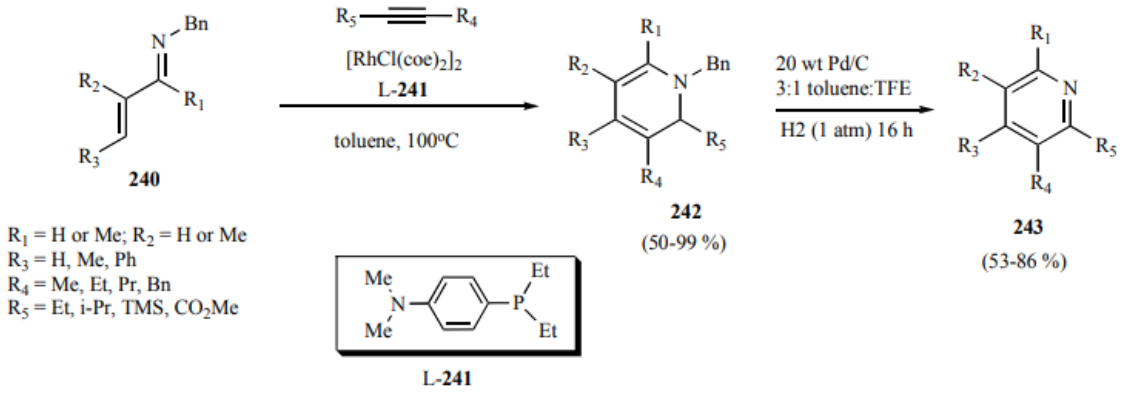


Figure 66.

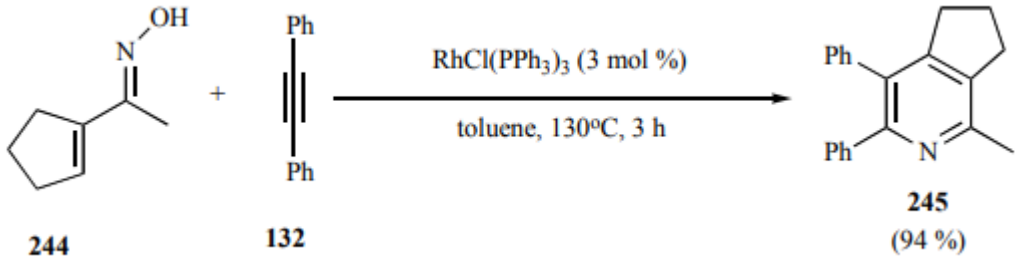


Figure 67

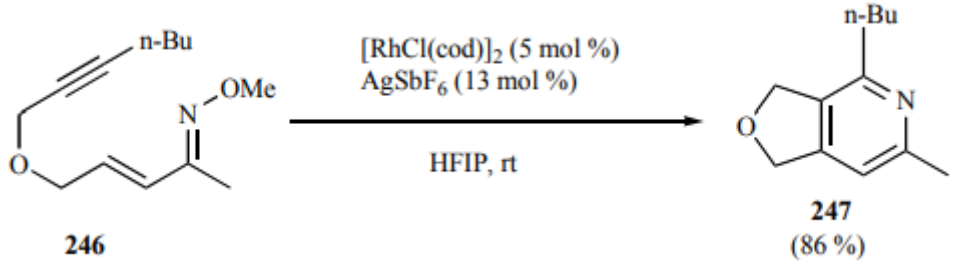


Figure 68.

Using rhodium to C-H activate,-unsaturated oximes 244 and alkynes 132, a unique method was developed for producing highly substituted pyridines (Figure 67). Isoquinoline derivative synthesis is another successful use. Bicyclic pyridine derivatives 247 were catalysed using a cationic rhodium(I)-catalyst made from [RhCl(cod)]2 (5 mol %) and AgSbF6 (13 mol %) in hexafluoroisopropanol (HFIP) via the intramolecular hetero-[4+2] cycloaddition of -alkynylvinyl oximes 2 Sarpong et al. cycloisomerized aziridinyl propargylic esters to 1,2-dihydropyridines in moderate to good yields with configuration preservation via PtCl2-catalyzed processes. When treating enantiopure aziridinyl propargylic ester 248 with 10 mol % PtCl2 in 0.2 M toluene for 3 hours at 100 0 C, 1,2-dihydropyridine 249 lost some enantiomeric excess (Figure 69).

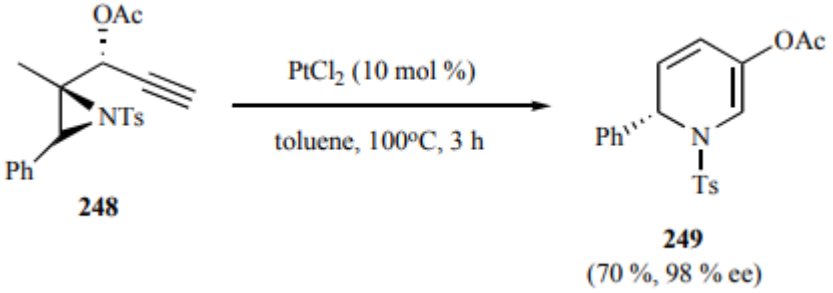


Figure 69.

Six-membered azacycles were generated via Fe(III)-promoted aza-Prins cyclisation of,-unsaturated tosylamines with aldehydes. Figure 70 shows that the alkyne aza-Prins cyclisation reaction involving homopropargyl tosylamine 253 and aldehydes 250 produced 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines 254 and trans-2-alkyl-4-halo-1-tosylpiperidines 252. A nucleophilic unsaturated C-C bond attacks progressively created -unsaturated-iminium ions to complete cyclisation. A similar method yielded 4-iodopiperidines with high selectivity by moderately aza-Prins-cyclizing homoallylic amine and benzaldehyde with 10 mol % GaI3 and stoichiometric iodine.

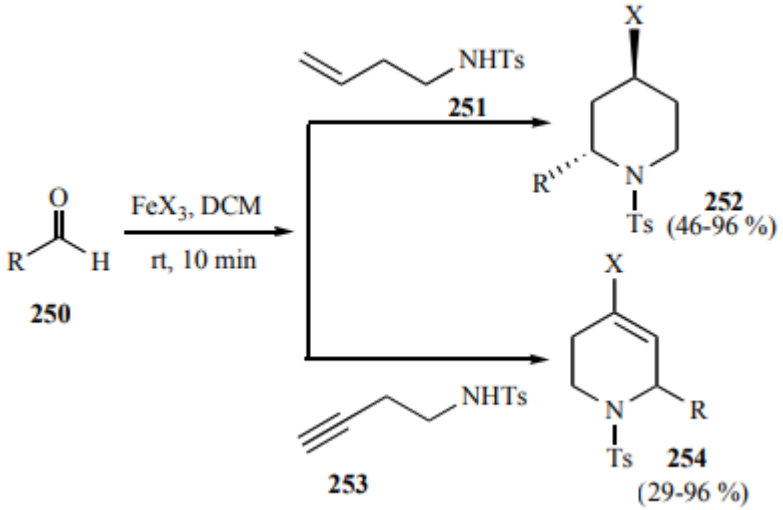
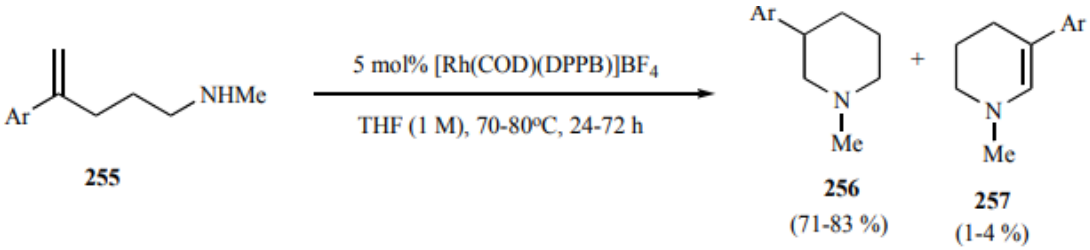


Figure 70.



Ar = Ph, 4-OMeC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$, 3,4-di-OMeC$_6$H$_3$, 3,4-di-FC$_6$H$_4$

Figure 71.

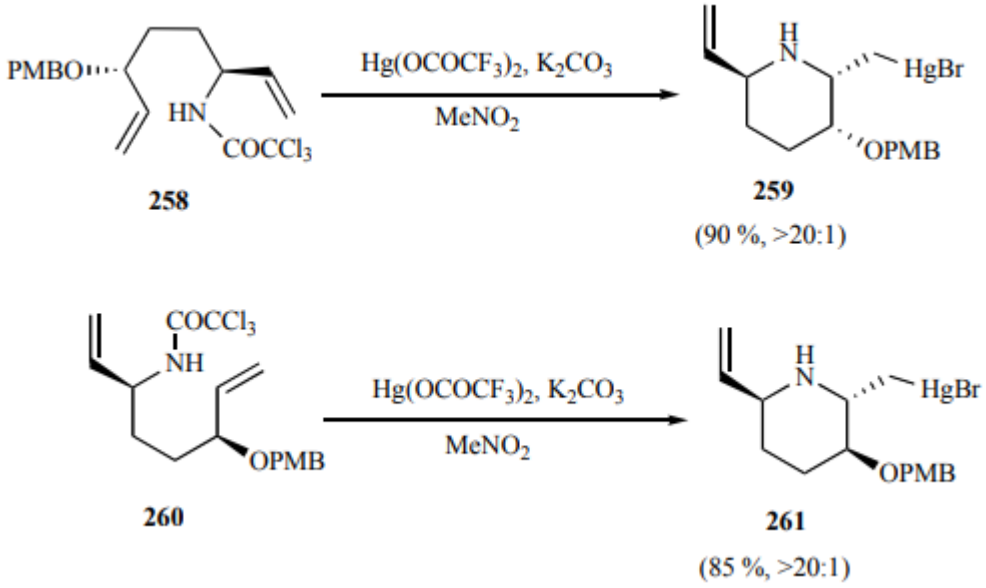


Figure 72.

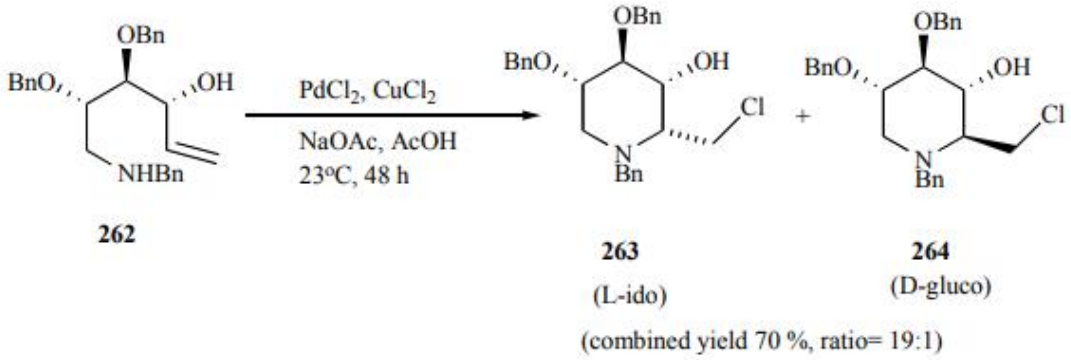


Figure 73.

Anti-Markonikov intramolecular hydroamination reactions were performed on 255 and its derivatives using [Rh(COD)2]BF4 (5 mol %) and a 5 mol % DPPB ligand in 1M THF at 70–80 °C. In 71%–83% yields, 256 3-arylpiperidines were produced (Figure 70). Aminoolefins with substituents at or to the amino group did not cyclize to create the desired product, while those with alkyl or alkoxy substituents produced diastereoselectively cis products. Figure 71 shows that diastereoisomers 258 and 260 were N-heterocyclized using Hg(OCOCF3)2 in nitromethane and K2CO3 to create 2,6-trans diastereomers 259 and 261. The reaction produced >20:1 diastereoselectivity. The intramolecular amidomercuration method was used to asymmetrically synthesise (+)-iso-6-cassine. Aminoalkenitol 262 chlorocyclizes to L-ido configured C-6 chlorinated azasugar 263 and its minor D-gluco diasteromer 264. The procedure uses a PdCl2/CuCl2 catalyst and NaOAc as a base in AcOH to produce 70% and had strong diastereoselectivity (Figure 72). In DMF, DCM, THF, MeOH, and PhMe, the procedure yielded low yield and diastereoselectivity. A Ph3PAuCl/AgSbF6 hydration, methanol -elimination, and gold-encouraged 1,4-addition sequence produced a six-membered nitrogen heterocycle from homopropargylic amines. Piperidine synthesis yields and diastereoselectivity are excellent. This method successfully synthesised (+)-andrachcinidine 268 (Figure 73). Krause et al. found that gold cycloisomerized -amino, -thio, and -hydroxyallenes. The allene systems gave the tetrahydro pyridine derivative chiral information throughout these processes. Figure 74 depicts how an AuCl catalyst cycloisomerized -aminoallenes 269 to tetrahydropyridines 270.

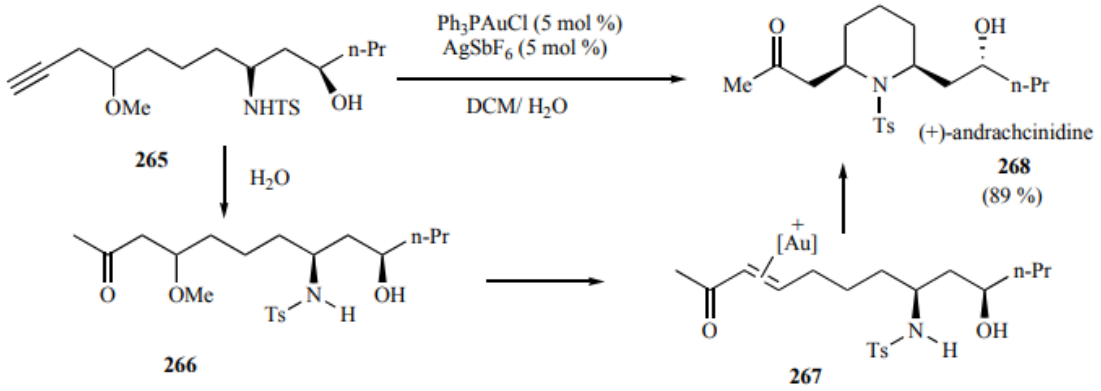


Figure 74

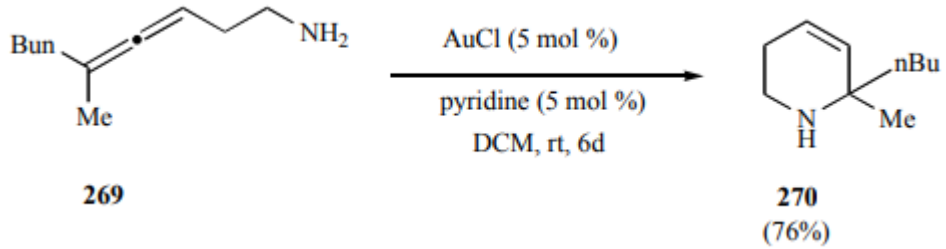


Figure 75

The pot, atom, and step procedure by Clarke et al. produced highly functionalised piperidines inexpensively. The reaction used two parts methyl acetoacetate, one part aldehyde, and one part aniline and one part inorganic salt. Imine and enamine may arise in situ. Piperidines 273 may be made by condensing aldehyde, imine, and enamine after cyclisation (Figure 76).

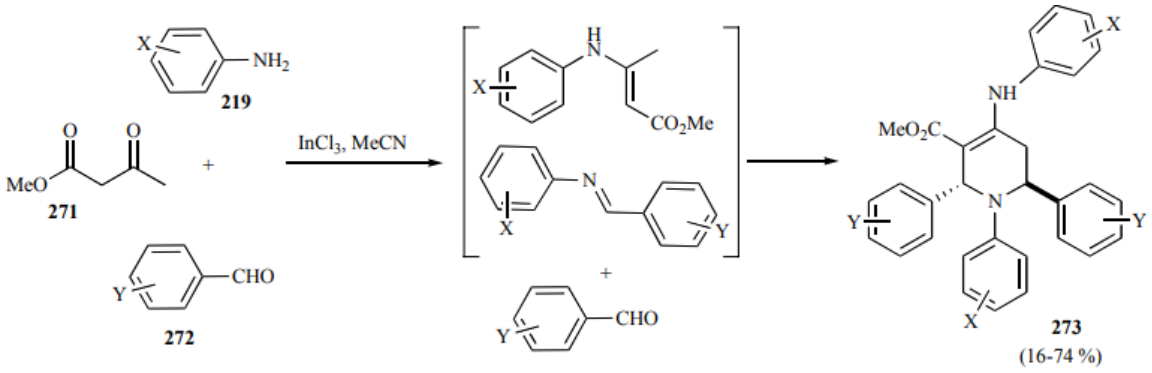


Figure 76

2. Synthesis of Quinolines

Quinolines and their derivatives are important in medicinal chemistry since they are found in natural and pharmaceutical goods. Skraup's technique is one of various synthesis alternatives. An intriguing and atom-economical technique for synthesising functionalised heterocycles is the intramolecular attack of the coordinated alkynyl moiety by the nearest nucleophilic substituent catalysed by a transition metal. An Au(I) complex catalyses tandem hydroaminationhydroarylation of aromatic alkynes and amines to synthesise substituted quinolines. Some reactions are accelerated by microwaves. Using the catalyst 275/AgOTf to combine alkynes with primary arylamines 274 containing o-alkylcarbonyl or o-arylcarbonyl groups yielded 2,4-disubstituted quinolines 276 in 63% to 94% yields in 30 minutes (Figure 77).

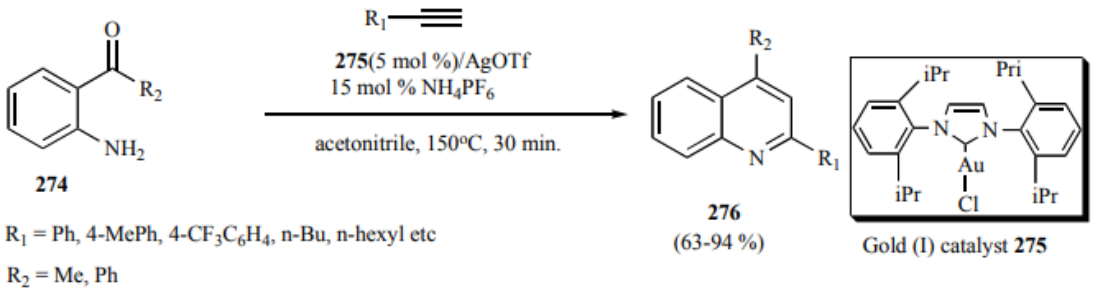


Figure 77.

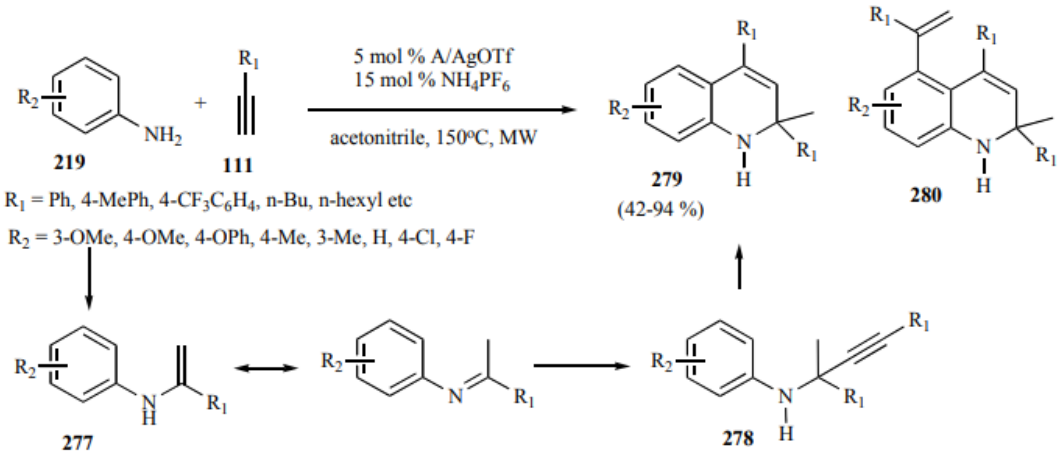


Figure 78.

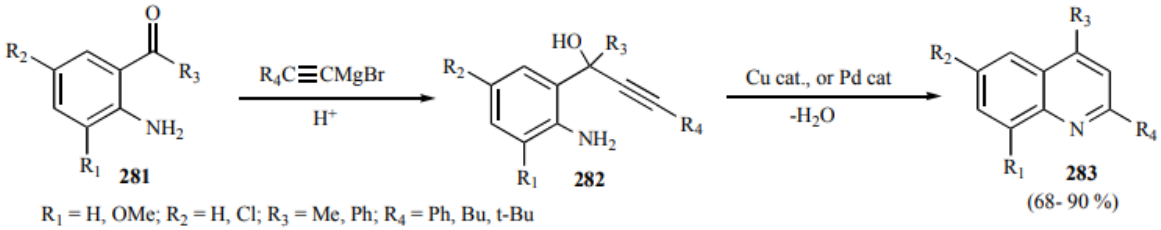


Figure 79.

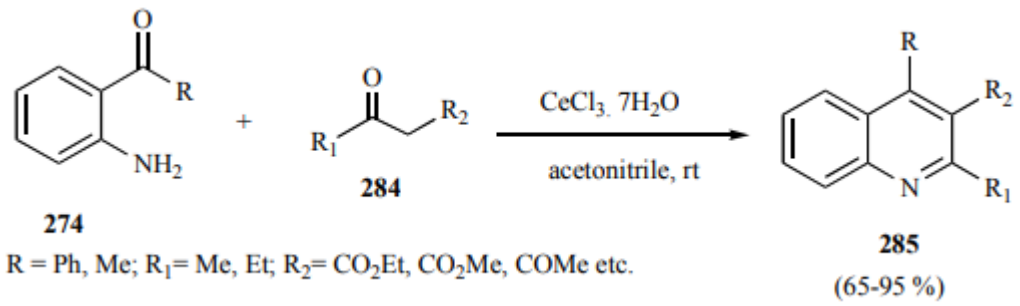


Figure 80.

Like circumstances produce substituted 1,2-dihydroquinolines. Gold-catalyzed alkyne hydroamination creates an enamine intermediate. The intermediate tautomerises to a ketimine, interacts with an alkyne molecule to form a propargylic amine, then hydrolyses intramolecularly to produce the final product (Figure A comparable reaction was found at 140–190 °C using AgBF4 alone as the catalyst. Gabriele and colleagues synthesised 2,4-disubstituted quinolines from 1-(2-aminoaryl)-2-yn-1-ols 282 utilising copper or palladium-catalyzed 6-endo-trig heteroannulation-dehydration (Figure 79 A PdI2-KI catalytic system 6-endo-dig cyclized 1-(2-Aminoaryl)-2-yn-1-ols, which have an aromatic group and a primary amino

group at the triple bond's terminal, with fair to good yields (45-70%) under oxidative conditions (80 atm of a 4:1 mixture of CO-O2 in MeOH at 100 0 C). In a nonoxidative environment (90 atm CO in MeOH at 100 °C), a PdI2-KI catalytic system selectively synthesised indol-2-acetic esters in 42–88% yields. Under moderate reaction conditions, condensing 2-aminoarylketones 274 with -methylene ketones 284 at ambient temperature with reusable catalyst CeCl3.7H2O yielded poly-substituted quinolines 285 in high yields (Figure With little reaction time, this technique works on various substrates. Two-quinolones were synthesised solvent-free using microwaves and ester molecules containing reactive methylene moiety, such as -ketoesters, ethylcyanoacetate, and diethyl malonate. Gold catalyses Friedlander condensation of 2-aminoarylketones with various -keto-esters, -diketones, -keto-amides, and -keto-sulfones to create several 2,3,4-trisubstiuted quinolines. The recyclable water-tolerant heteropolyacid Ag3PW12O40 may produce quinolines. Recent investigations show effective production of 2,4-disubstituted quinoline molecules. Figure 81 depicts a simple alkylation-cyclization reaction of 2-aminoaryl ketones 286 with phenylacetylenes and 1 mol % Indium(III) trifluoromethanesulfonate, In(OTf)3, to create 2,4-disubstituted quinoline derivatives 287 in Solvent-free microwave-irradiated reaction. The catalyst may be reused after the reaction. Cho et al. found quinoline derivatives in a ruthenium-catalyzed modified Friedlander reaction with 2-aminobenzyl alcohol, ketones, or secondary alcohols and 1-dodecene, a hydrogen acceptor. Research shows RuCl2(=CHPh)(PCy3)2 is a potent quinoline catalyst. Figure 82 shows that 2-aminobenzyl alcohol 288 treated with CuCl2 and KOH in dioxane under O2 produced moderate to excellent yields of 2-substituted quinolines 289. The mixture was agitated under argon after adding ketones. Kaneda and coworkers synthesised 2-aminobenzyl alcohols and ketones in toluene using Ru-grafted hydrotalcite and dioxygen as hydrogen acceptors. In a solvent-free environment, Ishii et al. reported that 2 equiv. of ketones reacts with [IrCl(cod)]2 or IrCl3 and KOH to convert 2-aminobenzyl alcohol to 290 quinoline derivatives in 74% to 91% Modified Frieldlander procedure worked with [IrCl(coe)2]2, [IrCO(PPh3)2], and [CpIrCl2].

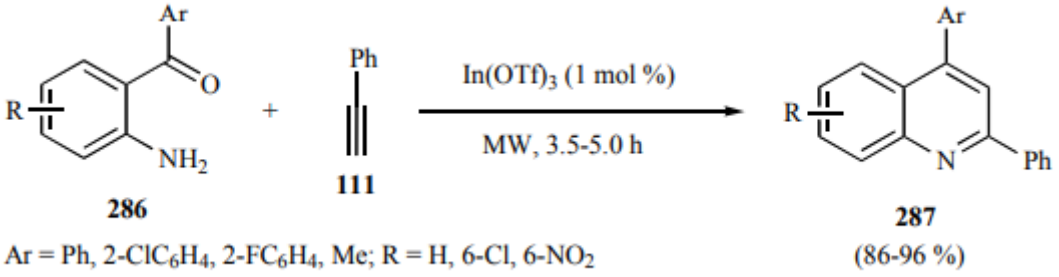


Figure 81.

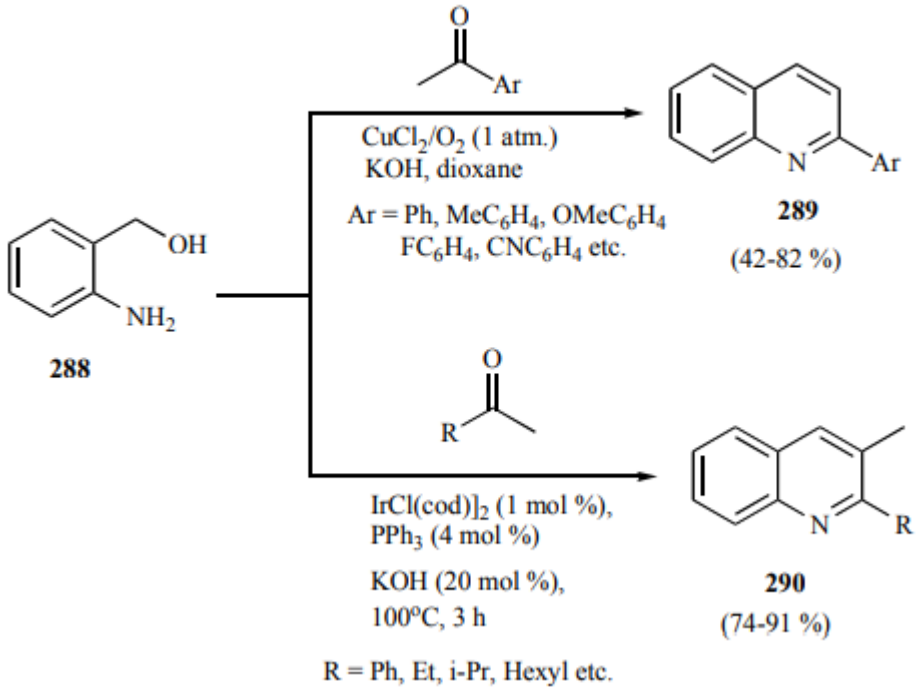


Figure 82.

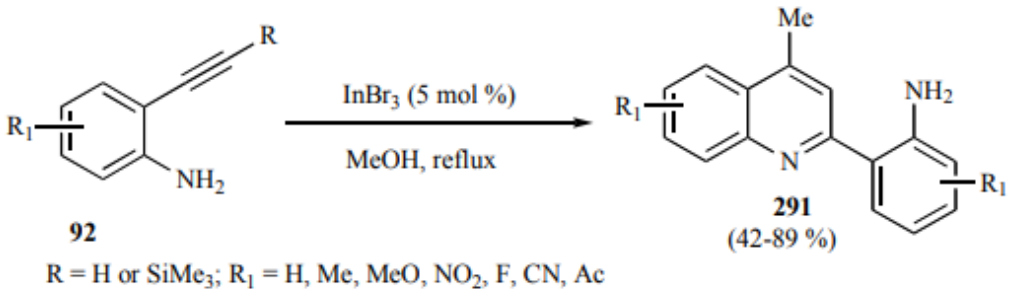


Figure 83.

Similar circumstances produce substituted 1,2-dihydroquinolines. Gold-catalyzed alkyne hydroamination produces enamine intermediates. Figure depicts how the intermediate tautomerises to a ketimine, interacts with an alkyne molecule to generate a propargylic amine, and hydrolyses intramolecularly. AgBF4 alone catalysed a comparable reaction at 140-190 °C. Gabriele headed a team that synthesised 2,4-disubstituted quinolines utilising 1-(2-aminoaryl) 6-endo-trig heteroannulation-dehydration with palladium or copper (Figure 79) yields 282 -2-yn-1-ols. 2-Aminoaryl 6-endo-dig PdI2-KI catalysis Oxidative conditions (80 atm, 4:1 CO_2/MeOH, 100 0 C) produced medium to excellent yields (45-70%), with aromatic and primary amino groups at the triple bond terminal. A PdI2-KI catalytic system selectively synthesised indol-2-acetic esters in 42-88% yields in a nonoxidative condition (90 atm CO in MeOH at 100 °C). Under moderate reaction conditions, 2-aminoarylketones 274 and -methylene ketones 284 were condensed to create poly-substituted quinolines 285 in excellent yields at room temperature using a reusable catalyst CeCl3.7H2O. This approach works on many substrates and reacts quickly. Two-quinolones were synthesised solvent-free using microwaves and ester molecules having reactive methylene groups such -ketoesters, ethylcyanoacetate, and diethyl malonate. Gold enhances Friedlander condensation of 2-aminoarylketones with various -keto-esters, -diketones, -keto-amides, and -keto-sulfones to create numerous 2,3,4-trisubstiuted quinolines. Quinolines may be made from recyclable, water-tolerant heteropolyacid Ag3PW12O40. New study shows effective 2,4-disubstituted quinoline production. Figure 81 shows how 2-aminoaryl ketones 286 are coupled with phenylacetylenes and 1 mole % Indium(III) trifluoromethanesulfonate, In(OTf)3, to make 2,4-disubstituted quinoline derivatives 287 in a solvent-free microwave-irradiated procedure. The catalyst may be reused after the reaction. Cho et al. found quinoline derivatives in a modified Friedlander reaction using 2-aminobenzyl alcohol, ketones, or secondary alcohols and 1-dodecene, a hydrogen acceptor. Ruthenium triggered it. Research suggests RuCl2(=CHPh)(PCy3)2 is a potent quinoline catalyst. Figure 82 shows that 2-aminobenzyl alcohol 288 treated with CuCl2 and KOH in dioxane under O2 produced 2-substituted quinolines 289 in moderate to excellent yields. The ketones were added and mixed under argon. Kaneda and coworkers synthesised 2-aminobenzyl alcohols and ketones in toluene using dioxygen and Ru-grafted hydrotalcite. Ishii et al. found that two ketones react with [IrCl(cod)]2 or IrCl3 and KOH in a solvent-free environment to generate 290 quinoline derivatives from 2-aminobenzyl alcohol with a yield of 74% to 91%. With [IrCl(coe)2]2, [IrCO(PPh3)2], and [CpIrCl2], the modified Frieldlander technique worked.

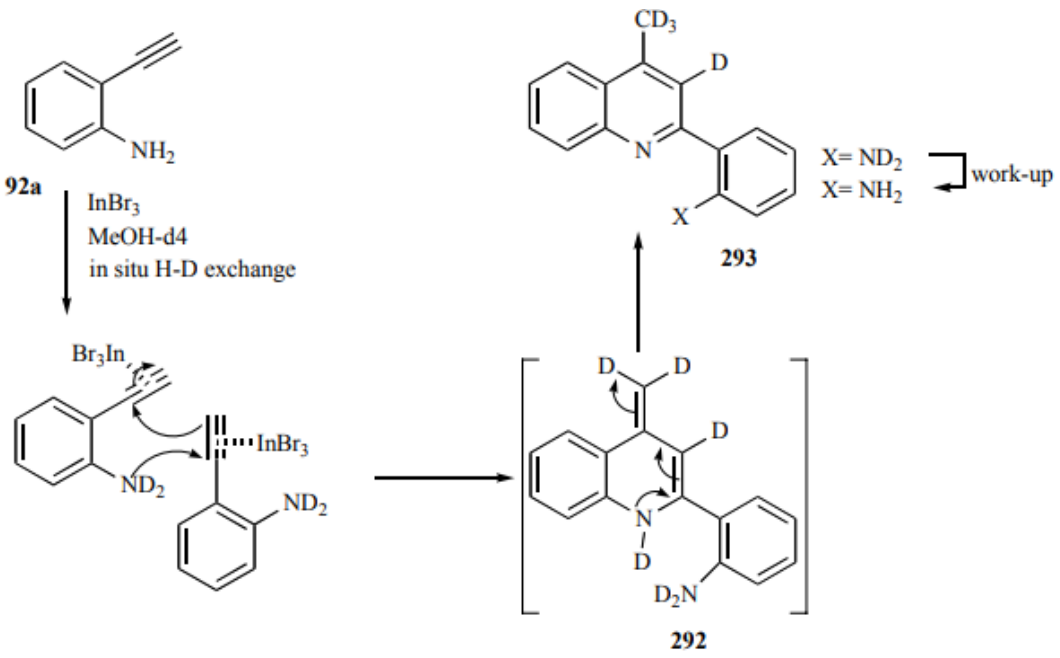


Figure 84.

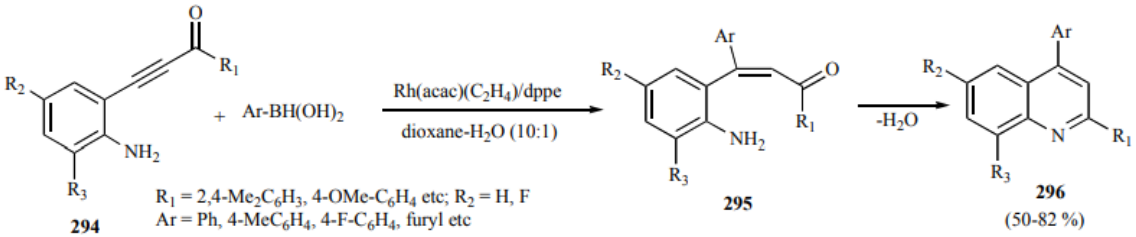


Figure 85.

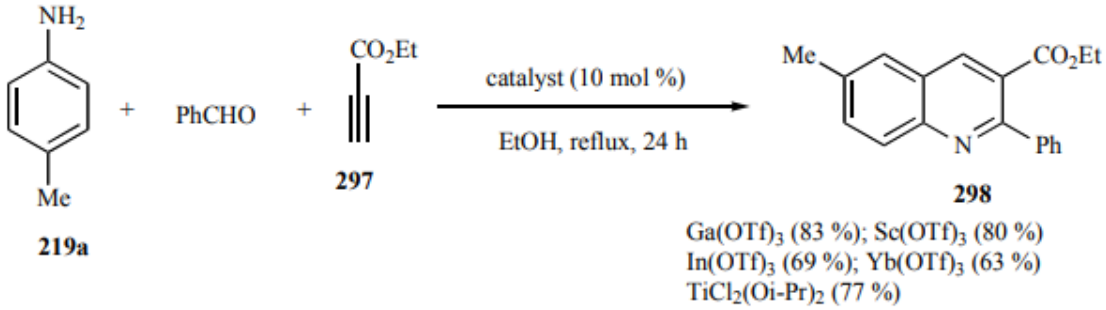


Figure 86.

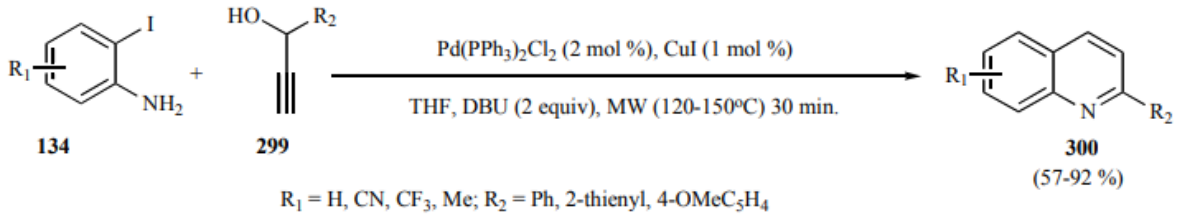


Figure 87.

Figure 87 shows the one-pot microwave-assisted Pd(PPh3)2Cl2 couplingisomerization of 2-aminoaryl halides 134 and propargyl alcohol 299 to 2-substituted quinolines 300. Under microwave irradiation, intramolecular condensation and base-mediated trans-cis isomerisation equilibrium may yield quinoline cores. Alkynyl arylketones 301 and 2-iodoanilines 134 in acetonitrile with NiBr2(dppe) and Zn metal powder at 80 °C generated 48-91% 2,4-disubstitutedquinoline 302 (Figure 88). Zinc metal presumably reduces Ni(II) to NI(0) to start the catalytic cycle. The o-metalated aniline complex from oxidatively adding 2-iodoaniline to Ni(0) species may be combined with an alkyne to produce 303 (Figure 89). Protonation with water yields amino chalcone 304 and Ni(II) spy. Amino chalcone cis condensation yields 302. A innovative method analysed isoflavanones and azaisoflavanones, which may have biological effects. Aryl-substituted alkynes 306 and 2-tosylaminobenzaldehyde 305 formed atom-efficient heterocycles 307 in toluene with AuCN and PBu3. Azaisoflavanone was not generated by 2-aminobenzaldehyde. The same conditions fail for alkyl-substituted terminal alkynes. Substituted quinoline was synthesised from benzaldehydes, aniline, and alkynes using AuCl3/CuBr. An N-substituted phenyl ring linked to nitrogen may intramolecularly assault 308's triple bond in AuCl3 (Figure 91). This creates dihydroquinoline intermediates that air or O2 may oxidise to quinoline 309. Silica gel-supported-TaBr5 solvent-free isomerises 2-aminochalcones to 2-aryl-2,3-dihydroquinolin-4(1H)-ones. Figure 92 shows that silica and alumina-supported CeCl3.7H2O-NaI is an affordable intramolecular azaMichael cyclisation catalyst for aminochalcones 310 to flavanones 311. The starting material deteriorated, therefore alumina-supported-KF could not make the essential products. Using Pd(OAc)2 in air, Wang et al. suggested the aza-Wacker cyclisation of anilines to synthesise quinoline derivatives. 2-homoallylaniline derivatives 312 formed substantial quantities of 2-methylquinoline 313 with 10 mol% Pd(OAc)2 in MeOH and 10 mol% phenanthroline ligand at 25 0 C in air (Figure 93). Quinolines may be directly synthesised from o-aminophenylboronic acid derivatives 314 and,-unsaturated ketones 315 using Rh as a catalyst (Figure 94). Under basic circumstances, the reaction is regiocomplementary to the Skraup-Doebner-Von Miller synthesis. Catalytic FeCl3 tandem benzylation-cyclization from 2-amino-aryl alcohols and -ketoesters yielded 3-quinolinecarboxylic esters in excellent to high yields. Figure 95 depicts the process. The process now incorporates propargylation-cyclization. Reacting 2-nitrophenyl propargyl alcohols with -ketoesters in FeCl3 and SnCl2 produced 4-alkyne-3-quinoline carboxylic esters.

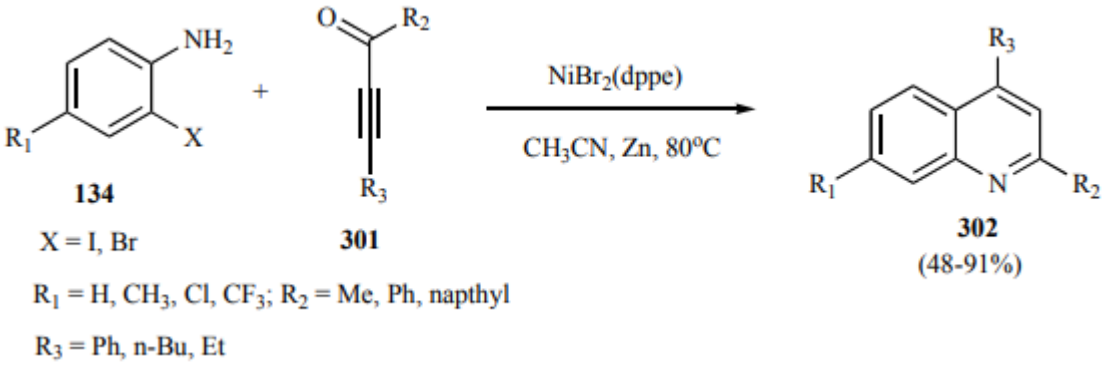


Figure 88.

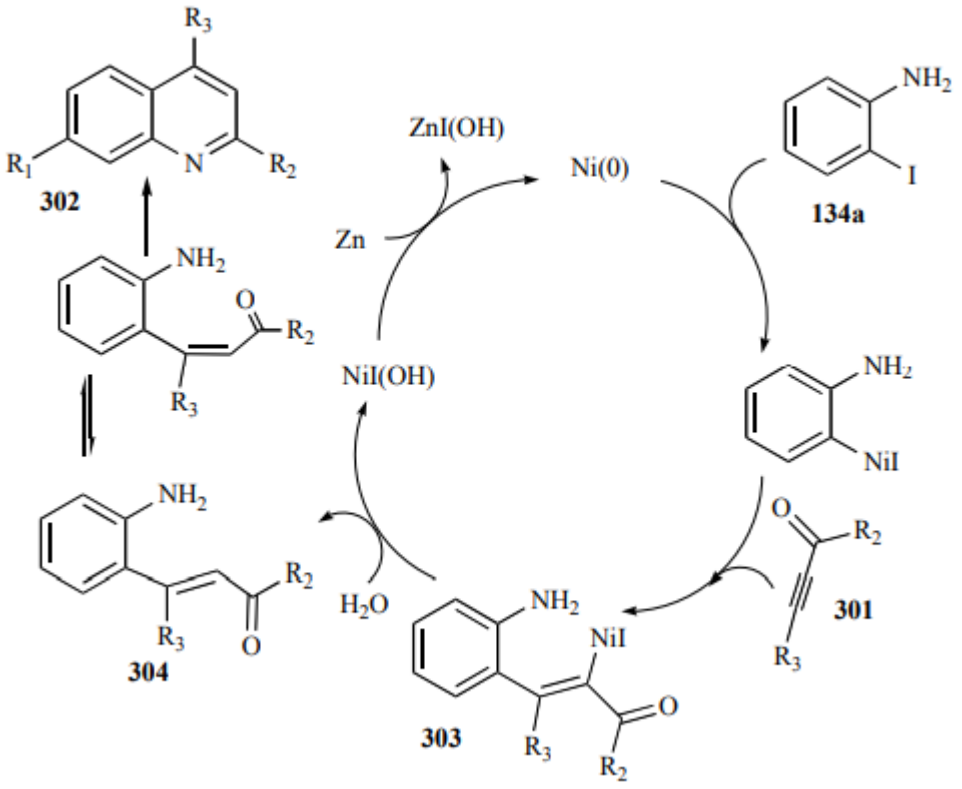


Figure 89.

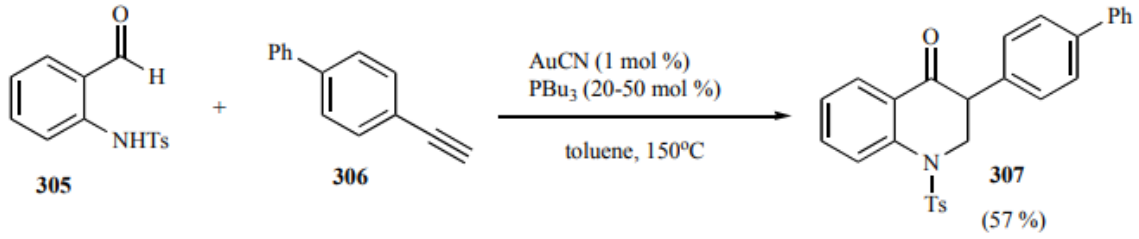


Figure 90.

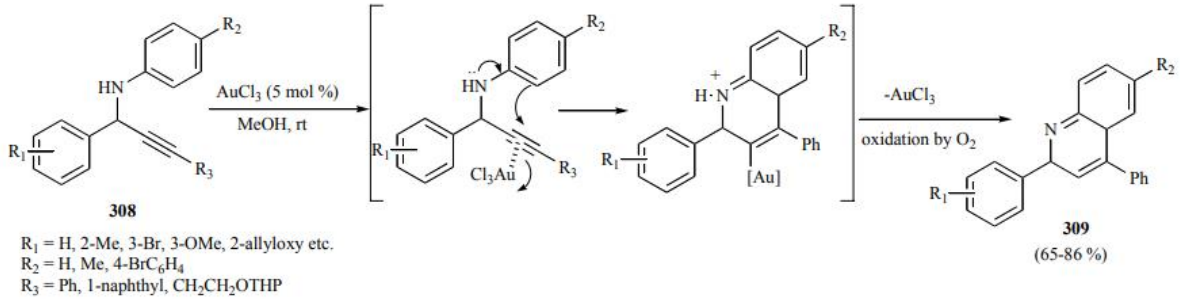
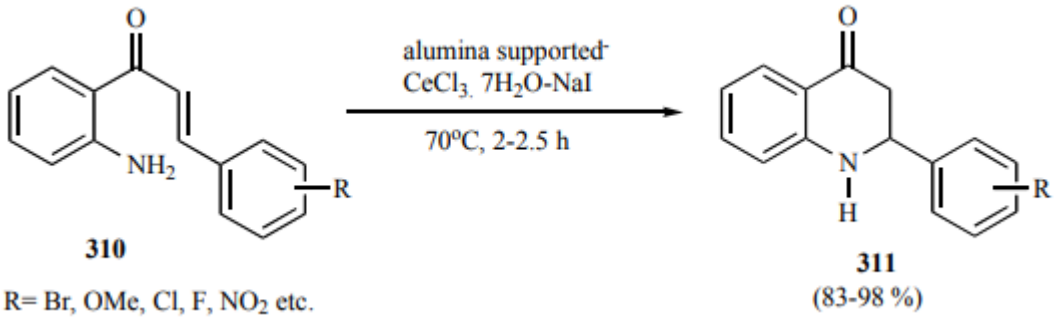


Figure 91.



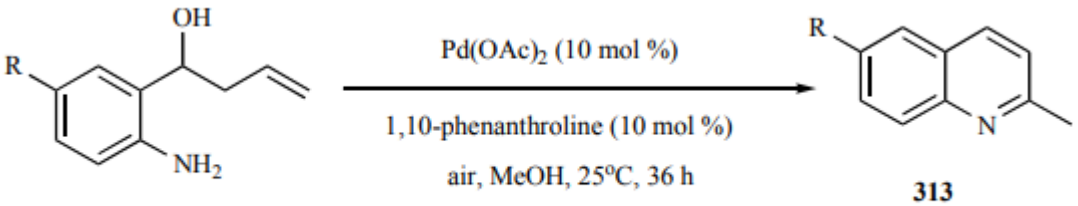
310

R= Br, OMe, Cl, F, NO_2 etc.

311

(83-98 %)

Figure 92.

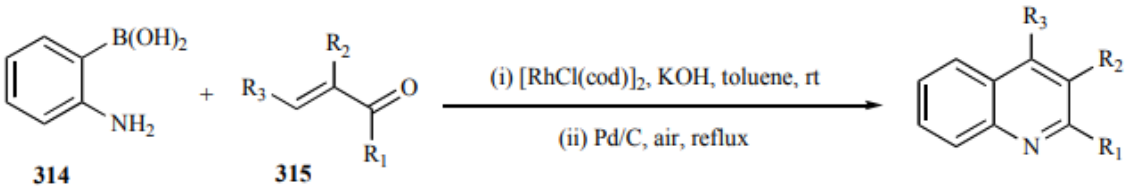


312

313

R = H (87 %)
R = Cl (90%)

Figure 93.



314 **315**

316

(42-96%)

R_1= Me, Ph, 4-$MeOC_6H_4$, 1-naphthyl, 3-thienyl, 2-pyridyl
R_2= M, Me
R_3= C_5H_{11}, 4-$MeOC_6H_4$, Ph, C_9H_{19}, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Figure 94.

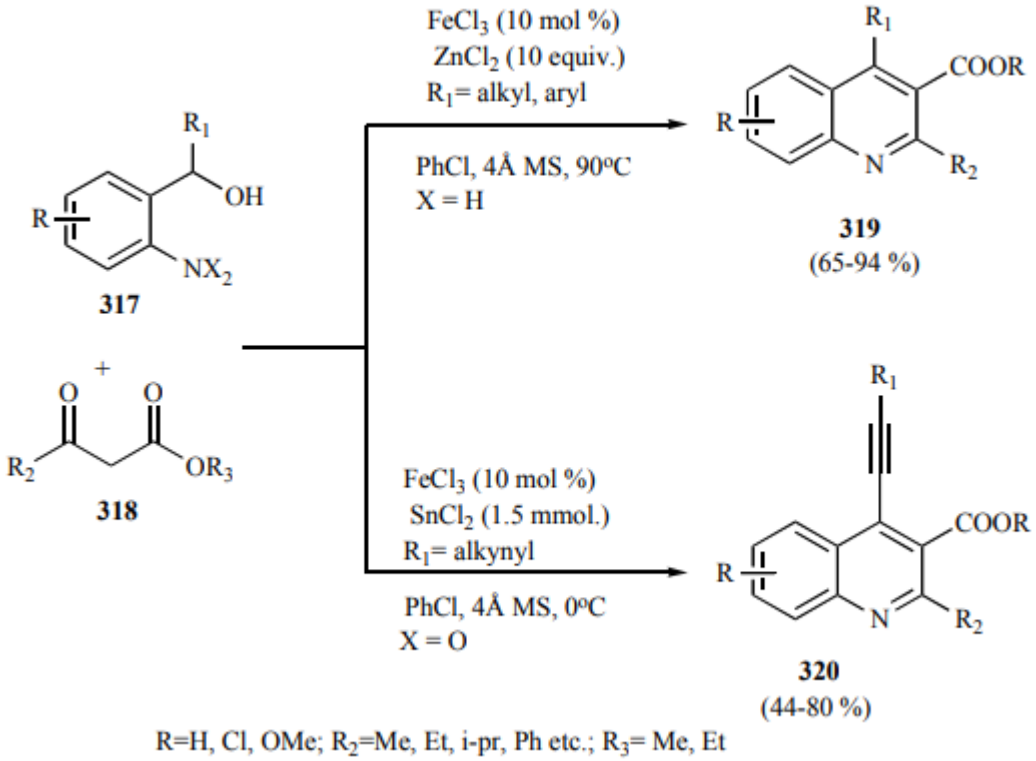


Figure 95.

3. Synthesis of Isoquinoline

Transition metals catalysed the 6-endo cyclisation of 2-(1- alkynyl)arylaldimines to produce isoquinolines and 1,2-dihydroisoquinolines. Takemoto et al. observed that an In(III) catalyst activated the C=N and C-C triple bonds, enabling intramolecular nucleophilic addition to an imine and alkyne cyclisation of the amide to produce 1,3-disubstituted 1,2-dihydroisoquinolines. Takemoto et al. recently synthesised 1,2-dihydroisoquinolines using Lewis acid-catalyzed tandem nucleophilic addition and cyclisation of 2-(1-alkynyl)arylaldimines. The most efficient carbophilic Lewis acids for this cyclisation are In(OTf)3, NiCl2, and AuCl(PPh3)/AgNTf2. Water, CF3CH2OH, or 2,6-di-tert-butyl-4-methoxyphenol must be provided as a proton source to allow tandem reactions with organometallic reagents. Cheng et al. synthesised isoquinolines by reacting 2-iodobenzaldimines 321 with alkynes and using a nickel catalyst. Figure 96 demonstrates high yields of 3,4-disubstitutedisoquinolines 322 from acetonitrile at 80 °C using NiBr2(dppe)2 as the catalyst and Zn powder.

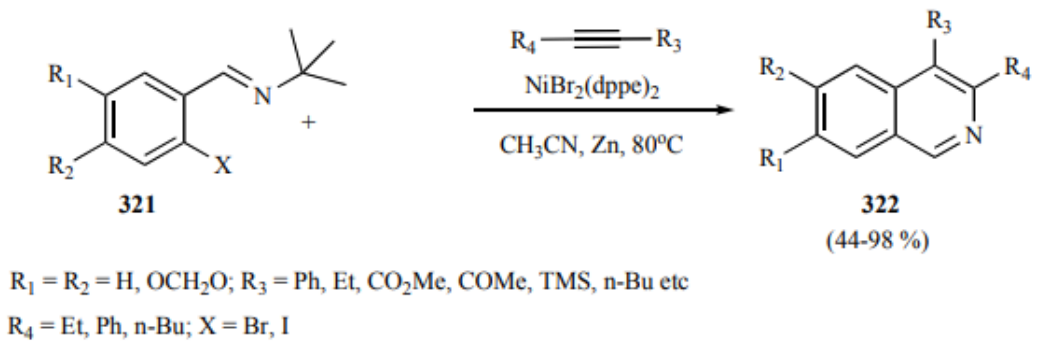


Figure 96.

During the cyclisation of 2-alkynylbenzaldoxime derivatives 323, Au(IMes)Cl or Silver trifluoromethanesulfonate may catalyse stereospecific isoquinoline-N-oxides 324 (Figure 97). It is chemo selective (N- vs. O nucleophile) and regio- (6-endo-dig) selective and synthesises a variety of isoquinoline-N-oxides easily.

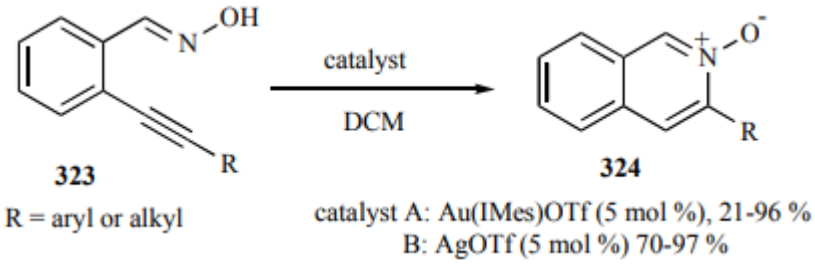


Figure 97.

Recently, palladium(0)-catalyzed addition-cyclization of chloroform to ortho-alkynylaldimines in PdCl2(PPh3)2/dppe produced 1,2-dihydroisoquinolines. Figure 98 shows good yields of 1,2-dihydroisoquinolines 326 at 100 °C. Palladium inserted C-H into chloroform. The alkynyl carbamates were hydroaminated by cationic gold(I)-complexes to produce 1,2-dihydroisoquinolines 328 and 1, alkylidenyl-1,2,3,4-tetrahydroisoquinolines 330 (Figure 99).

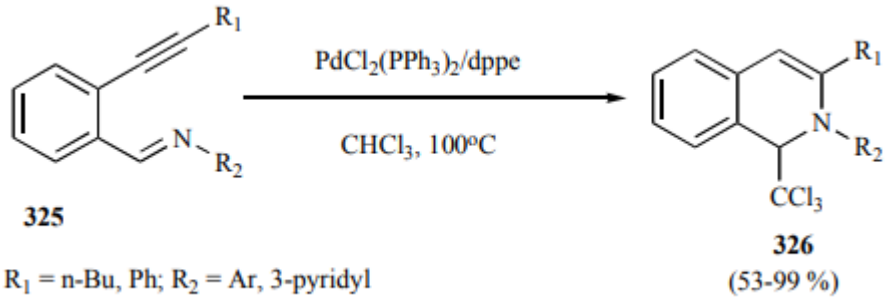


Figure 98.

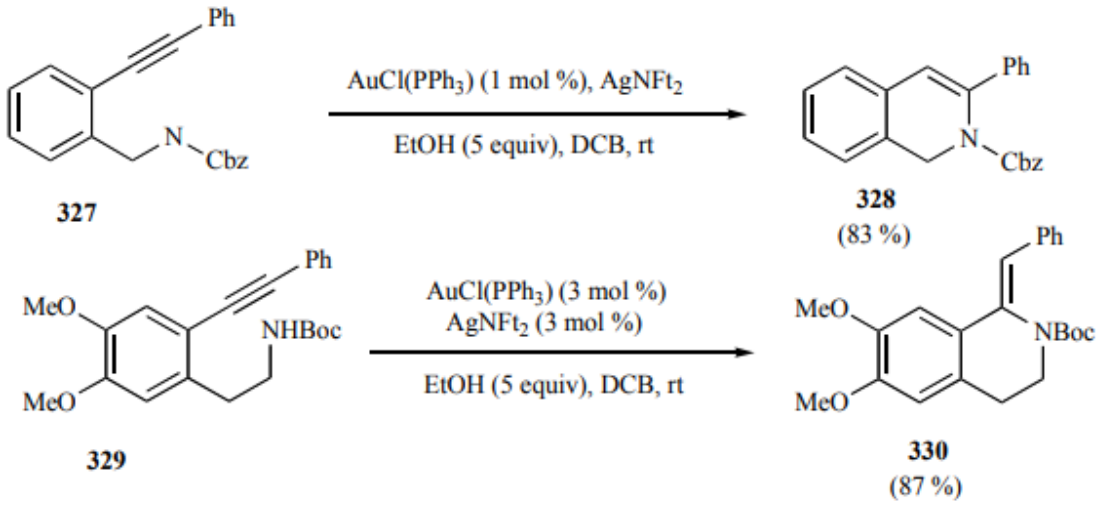
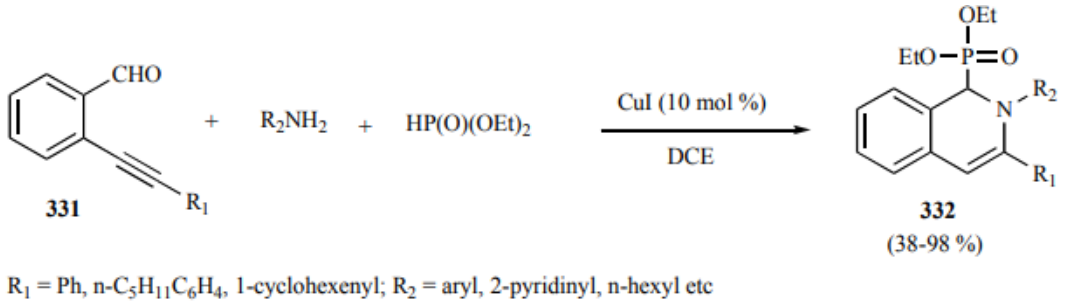


Figure 99.

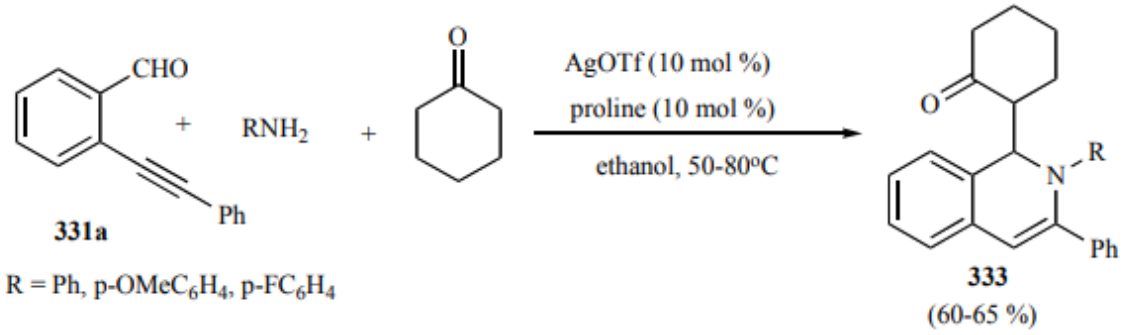
Copper iodide, 2-alkynyl benzaldehydes 331, amines, and diethyl phosphate easily produce 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates 332, as shown in Figure 100. Many aniline derivatives with electron-donating or electron-removing groups work. Like PdCl2, findings were comparable. The Lewis acid-surfactant catalyst C12H25SO3Na/CuSO4 catalysed ultrasonic water cyclisation. Wu et al. synthesised 1,2-dihydroisoquinoline compounds from 2-alkynlbenzaldehydes, amines, and ketones using AgOTf and proline. Cyclohexanone, 2-alkynlbenzaldehyde 331a, 1 mol % AgOTf, and 10 mol % proline react smoothly in ethanol at 50-60 °C to form 1,2-dihydroisoquinolines 333 (Figure 116). NaBH4 cyclized 2-(1-alkynyl)benzaldehydes and amines in one pot. Similar group synthesised 1,2-dihydroisoquinolines 334 using Mg(ClO4)2 (10 mol%) / Cu(OTf)2 multicomponent process of 2-alkynylbenzaldehydes. Figure 101 depicts allylic bromides, zinc dust, amines, and 331. This reaction worked best with THF/DCE (1:20). Figure

102 shows that Ca[OCH(CF3)2] catalysed the Pictet-Spengler reaction with mtyramine 335 and aldehydes to produce tetrahydroisoquinolines. 2. Regioselective tetrahydroisoquinolines are produced from aryl, heteroaryl, and alkyl aldehydes.



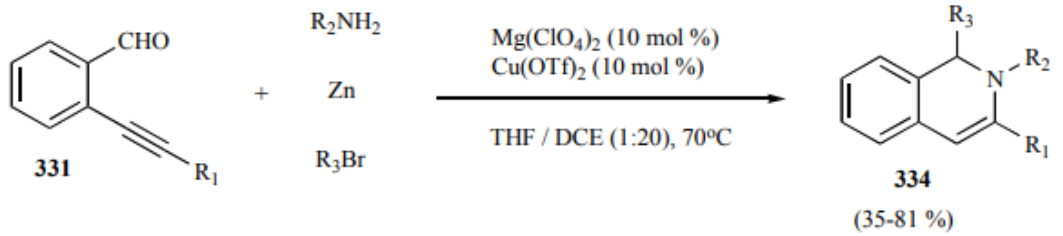
R_1 = Ph, n-$C_5H_{11}C_6H_4$, 1-cyclohexenyl; R_2 = aryl, 2-pyridinyl, n-hexyl etc

Figure 100.



R = Ph, p-$OMeC_6H_4$, p-FC_6H_4

Figure 101.



R_1 = C_6H_5, p-$MeOC_6H_4$; R_2 = C_6H_5, p-MeC_6H_4, p-$MeOC_6H_4$, p-ClC_6H_4, p-FC_6H_4

Figure 102.

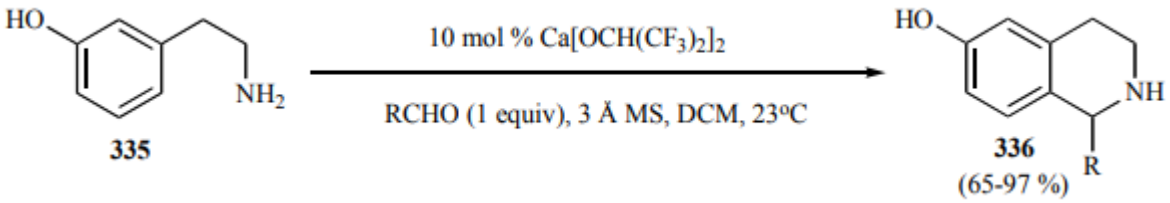


Figure 103.

4. Synthesis of Quinazolin and Quinazolinone Derivatives

Quinazolin and quinazolinone derivatives are fused heterocyclic compounds made of benzene rings and pyrimidine nuclei. These structures have anti-inflammatory, antibacterial, anticancer, and anticonvulsant properties and are found in bioactive chemicals and pharmaceuticals. Due of their relevance, effective and environmentally acceptable synthetic techniques to these compounds have been sought. In classic quinazolinone derivative synthesis, 2-aminobenzamide or anthranilic acid byproducts are cyclized with carbonyl compounds like formamide or aldehydes. Standard procedure: reflux 2-

aminobenzamide with formic acid or formamide to make quinazolin-4(3H)-one. The simplicity and high yields of this method assure its widespread use. The reaction is commonly done in ethanol or glacial acetic acid-free environment, however this depends on functional group tolerance. In recent years, several ecologically friendly and catalyst-assisted efficiency increase methods have been studied. Microwave-assisted synthesis improves reaction times and yields. Use of ionic liquids, water, and solvent-free processes has also reduced environmental impact. Transition metals including copper, zinc, and iron salts have also helped quinazolinone skeletons create C-N and C-C bonds. One-pot synthesis of highly substituted quinazolinones utilising 2-aminobenzamides, aldehydes, and isocyanides or nitriles is another quick and atom-economical method. These methods make bioactive analogues with superior pharmacological properties easier to synthesise.

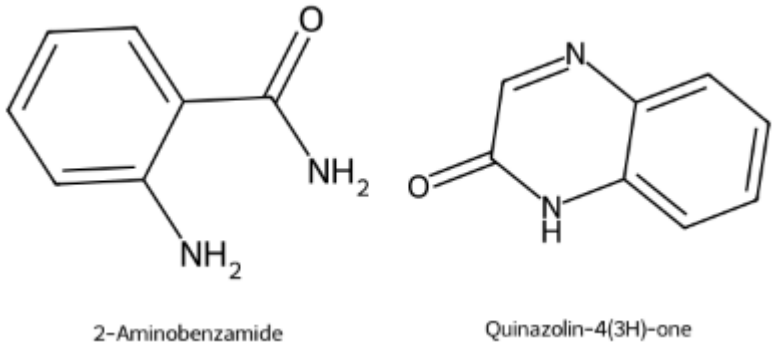


Figure 104 .

5. Synthesis of Napthopyranopyrimidine Derivatives

Naphthopyrimidine derivatives are fused naphthalene-pyranopyrimidine frameworks with nitrogen. These compounds are promising medicinal chemistry targets due to their anticancer, antibacterial, anti-inflammatory, and antiviral properties. Chromone derivatives and aminopyrimidines are commonly reacted in a controlled setting to make napthopyranopyrimidines. This method creates a fused tricyclic system with the chromone ring as the electrophilic centre and the aminopyrimidine as the nucleophile. Usually, 2- or 4-aminopyrimidine derivatives nucleophilically attack chromone or its substituted counterparts. The napthopyranopyrimidine core is formed via cyclisation and aromatisation. As catalysts, acids, piperidine, or triethylamine may speed the process, while heating or microwave irradiation can boost yields and decrease reaction times. Recent developments in green methods using water or ethanol as solvents or without solvent grinding have improved environmental compatibility. Adding functional groups to fused ring structures allows for wide structural changes, which may improve their pharmacological potential. Thus, napthopyranopyrimidine derivative synthesis is emphasised to develop novel drugs.

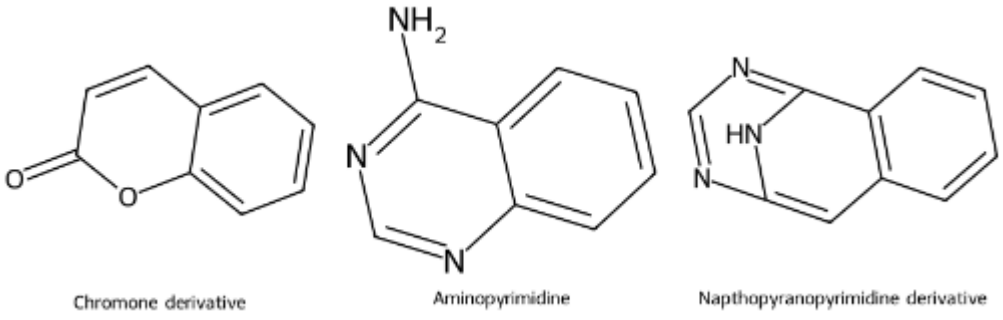


Figure 105.

DISCUSSION

Nitrogen-containing heterocycles, particularly five- and six-membered ring systems, continue to be at the forefront of organic and medicinal chemistry. This is primarily due to the structural diversity and profound biological significance of these heterocycles. The purpose of this research was to investigate the synthesis of significant heterocyclic scaffolds such as pyrroles, indoles, carbazoles, pyridines, quinolines, isoquinolines, quinazolinones, and napthopyranopyrimidines. The study focused on synthetic methodologies, mechanistic insights, and the importance of application.

The synthesis of five-membered nitrogen heterocycles, such as indoles and pyrroles, by the reactions of amines with carbonyl derivatives, which include alkenes, alkynes, diketones, and other compounds, is an important area of study. The access to essential intermediates and bioactive molecules is possible via the use of these specific methods. Along the same lines, heteroaromatic fusion procedures are an essential component in the process of raising the level of molecular complexity that occurs during the manufacture of indolizines and carbazoles. The use of these compounds as possible medications has been shown, and they are also prevalent in natural products.

The six-membered ring systems and the continued advances in the synthesis of pyridine, quinoline, and isoquinoline utilising classical and transition metal-catalyzed methods were the primary topics of discussion in this study. A further enhancement of the variety is achieved by the incorporation of 2-amino-3-cyano pyridine derivatives. These derivatives are helpful in the field of medicinal chemistry due to the fact that they are functionalised and rich in electrons. The cyclisation of anthranilamide with either aldehyde or formic acid is a common method for producing quinazolinone and quinazolin derivatives, which are another category that deserves special attention. These heterocycles are key to a variety of pharmaceutical substances and serve an important function as pharmacophores in addition to their other contributions.

The synthesis of napthopyranopyrimidine derivatives, which is a significant area of research, demonstrates the effectiveness of multicomponent and fused ring assembly. There are many applications for these types of assemblies. The condensation of chromones and aminopyrimidines results in the formation of a complex tricyclic structure that has a significant potential for bioactivity. It is possible to construct molecules with great functional and pharmacological potency by carefully joining simpler heterocycles, as shown by these fused systems.

Through the whole of the approaches that have been provided, a focus has also been placed on green chemistry techniques. These techniques include reactions that are facilitated by microwaves, processes that do not need solvents, and the use of catalysts that are kind to the environment. The objective of these findings is to develop a heterocyclic synthesis that is both sustainable and scalable, with applications in both the industrial and therapeutic fields.

It is an area that is both active and vital to conduct research into the invention of synthetic techniques for nitrogen-containing heterocycles that are efficient, selective, and favourable to the environment. Compounds that have been evaluated not only serve as the structural foundation for a number of bioactive chemicals, but they also give significant information that can be used to optimise reaction pathways and construct rational heterocycles, which may be of great assistance in future discovery attempts.

CONCLUSION

Synthesis of nitrogen-containing heterocyclic compounds with five or six members is crucial to medicinal, pharmaceutical, and materials science. This review covers ancient and modern synthesis techniques for heterocycles such pyrroles, indoles, carbazoles, pyridines, quinolines, isoquinolines, quinazolinones, and napthopyranopyrimidines. These compounds are essential structures in many bioactive substances and provide a basis for structural changes and functional diversity. Modern technologies including multicomponent reactions, microwave irradiation, solvent-free conditions, and transition metal catalysis make heterocyclic synthesis more efficient, selective, and ecologically benign. Napthopyranopyrimidines and quinazolinone derivatives show how nitrogen heterocycles may be fused to generate complex frameworks with therapeutic promise. Synthetic methodological advances are making nitrogen heterocycles more accessible and adaptable, enabling drug discovery, agrochemical development, and revolutionary material uses. Freshly synthesised derivatives should undergo biological evaluation and research should concentrate on sustainable and scalable methods to exploit their potential.

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