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Diverse Strategies for the Synthesis of the Indoline Scaffold

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Because indoline is an important intermediate of angiotensin-converting enzyme (ACE) inhibitor and the antihypertensive drug "pentopril", and also because it is a ubiquitous scaffold found in the structures of several naturally bioactive alkaloids such as vinblastine, strychnine, (–)-physostigmine, ajmaline, and (+)-aspidospermidine, the synthesis of this "privileged structure" is meaningful in the design of new biologically active medicines. This microreview describes the recent advances in the synthesis of indoline derivatives, including Cu- and Pd-catalyzed reactions, metal-free approaches (radical reaction), as well as other types of reactions.

1. Introduction

The indoline scaffold is ubiquitously present in many naturally bioactive alkaloids, such as vinblastine, strychnine, (–)-physostigmine, ajmaline, and (+)-aspidospermidine (Figure 1),[1–5] and it is also the structural component of several important pharmaceutically active compounds, such as angiotensin-converting enzyme (ACE) inhibitor and the antihypertensive drug "pentopril" (Figure 1).[6] In 2005, we isolated indoline derivatives oleracein A–D (Figure 1) from the edible plant *Portulaca oleracea* used in Chinese traditional medicine.[7] Their structures were similar to betanidin, a member of the betalain natural product. Preliminary bioactive screening[8] revealed the interesting structures of these compounds along with many possible diverse derivatives, and because it is difficult to obtain a large quantity of these compounds from the natural origin for further pharmacological research, we are focusing on the approaches for the synthesis of indoline and its derivatives. To date, a large number of approaches have been designed for the synthesis of indolines. One of the key steps in synthesizing indoline is the cyclization of the indoline ring through aryl amination. The Cu-catalyzed Ullmann–Goldberg reaction is a well-known classical approach for aryl amination. However, there are several drawbacks involved in this reaction. Severe reaction conditions, such as, heating

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in the presence of a copper salt at high temperature without solvent or the lack of broad functional group compatibility, limit its utility for the synthesis of complex molecules.[9] During the past two decades, Pd/ligand-catalyzed aryl aminations have been shown to overcome the shortcomings of stoichiometric Cu-mediated reactions. The method was introduced by Buchwald and Hartwig and become a classical method for C–N coupling between an aryl halide and an amine. Tremendous improvements for the construction of indolines have been made based on this method. However, Pd catalysts are more expensive than Cu catalysts. Since 2000, improvements to the Cu^{I}/Cu^{II}-catalyzed aryl amination reaction have resulted in mild reaction conditions and in broad substrate compatibility. In several cases it was proven that this is an efficient and economic method to prepare indolines. Besides these two kinds of catalytic reactions, a metal-free radical reaction and other catalyzed reactions were employed as new ways for constructing the indoline ring. As enantiopure indolines may serve as potential promising pharmaceutical candidates, several routes towards their synthesis have been invented. Synthetic routes towards enantiopure 2-substituted indolines have been thoroughly reviewed in 2009,[10a] without touching upon enantioselective ways to other substituted indolines, which has recently become an area of interest. Besides this, synthetic reviews on other complex indolines, such as spirocyclic indolines and pyrrolidino[2,3-*b*]indolines, have been published recently.[10b,10c] This microreview mainly focuses on the past 10 years and shows the recent advances and improvements in the synthesis of indolines and the asymmetric synthesis of substituted indolines.

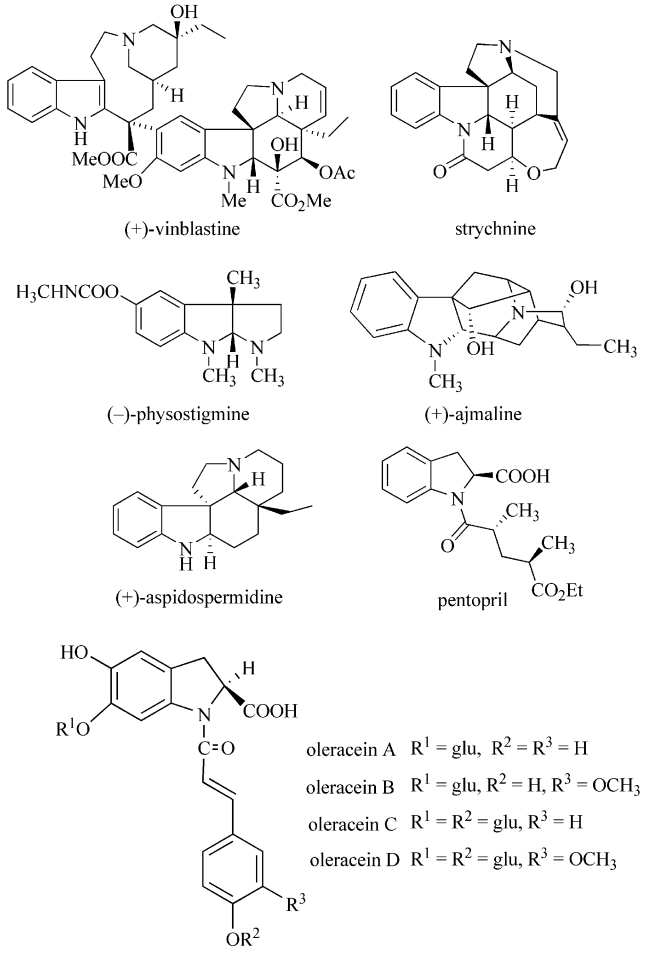


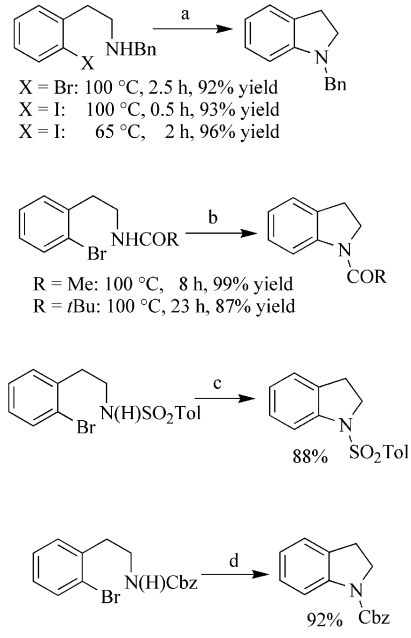
Figure 1. Representative bioactive indolines and its derivatives.

2. Transition-Metal-Catalyzed Reactions

2.1 Pd-Catalyzed Reactions

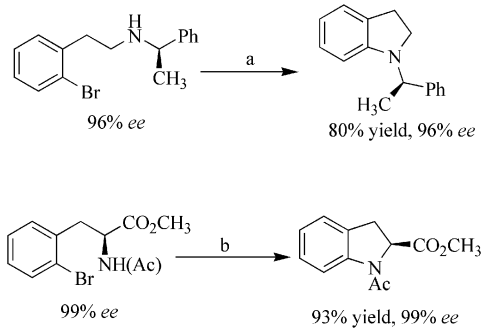
2.1.1 Pd-Catalyzed Intramolecular Aryl Amination

The Pd/ligand-catalyzed Buchwald–Hartwig carboamination reaction between an aryl halide and an amine together with related improved methods have been shown to be a mild and efficient way for the construction of indolines and their analogues. Buchwald reported the Pd-catalyzed intramolecular amination and amidation reactions, which allow efficient access to a variety of indolines (Scheme 1)[11,12] through optimization of the Pd catalyst, ligand, and base. The advantage of this reaction is that the cyclization reaction occurred under mild condition and displayed good functional group tolerance.



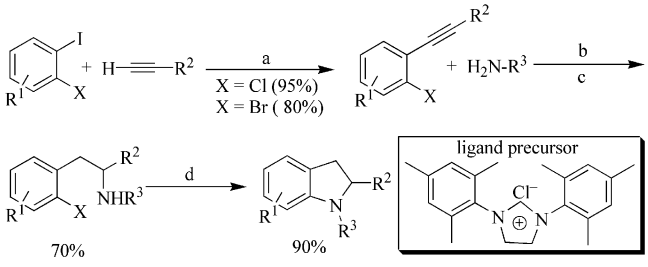
Scheme 1. Pd-catalyzed intramolecular amination or amidation reaction to afford indolines. Reagents and conditions: (a) $Pd(PPh_3)_4$ (1.0 mol-%), *t*BuONa/K_2CO_3; (b) $Pd_2(dba)_3$ (5 mol-%), P(2-furyl)$_3$ (20 mol-%), Cs_2CO_3; (c) $Pd_2(dba)_3$ (2 mol-%), P(*o*-tolyl)$_3$ (8 mol-%), K_2CO_3, 100 °C, 5 h; (d) $Pd(OAc)_2$ (3.3 mol-%), DPEphos (5 mol-%), Cs_2CO_3, 100 °C, 22 h.

This Pd-catalyzed aryl amination reaction has also been extended by Buchwald to construct enantiomerically enriched indolines through the coupling of enantiopure amines with aryl bromide.[13] It is noteworthy the (*S*)-*N*-acetylindoline-2-carboxylate methyl ester as a key intermediate can be used in the synthesis of the ACE inhibitor pentopril (Scheme 2).



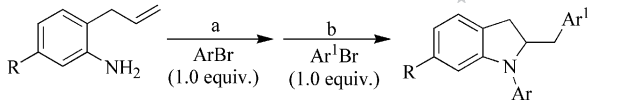
Scheme 2. Construction of enantiopure indolines by Pd-catalyzed aryl amination. Reagents and conditions: (a) $Pd_2(dba)_3$ (4 mol-%), P(*o*-tolyl)$_3$ (8 mol-%), *t*BuONa, 100 °C; (b) $Pd_2(dba)_3$ (10 mol-%), P(*o*-tolyl)$_3$ (20 mol-%), Cs_2CO_3, 100 °C.

Besides this, a variety of methods are available for the construction of indolines through a combination of the intramolecular aryl amination reaction with other reactions. In 2003, Doye et al.[14] developed a flexible and efficient protocol for the synthesis of a variety of indolines and other alkaloids by using cheap and readily available raw materials. Through this protocol, the target indolines can be synthesized from three building blocks (*ortho*-bromo- or *ortho*-chloroiodobenzenes, terminal alkynes, and primary amines) by Sonogashira coupling, one-pot hydroamination reduction, and a final Pd-catalyzed intramolecular amination of aryl halides (Scheme 3).

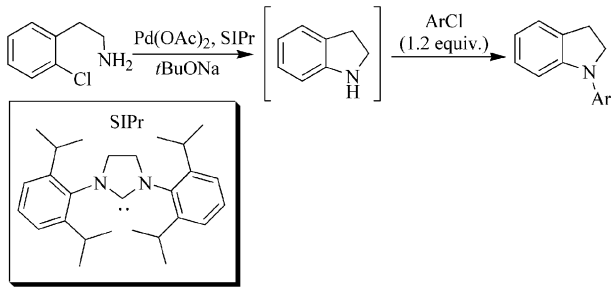


Scheme 3. Flexible synthesis of indolines from aryl halides, terminal alkynes, and primary amines. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$ (2.0 mol-%), CuI (4.0 mol-%), PPh_3 (4.0 mol-%), HN(*i*Pr)$_2$, 84 °C, 6 h; (b) Cp_2TiMe_2 (5.0 mol-%), 110 °C, 24 h; (c) $NaBH_3CN$, $ZnCl_2$·Et_2O, 25 °C, 12 h; (d) $Pd_2(dba)_3$ (5.0 mol-%), ligand precursor (10.0 mol-%), *t*BuOK, 110 °C, 12 h.

Pd-catalyzed amination as part of a sequential or domino process has been developed for the modular construction of indoline in a very simple and convenient way. In 2004, Wolfe et al. described a Pd-catalyzed sequential *N*-arylation/cyclization/*C*-arylation reaction[15] between 2-allylaniline and two different aryl halides, which involves two distinct sequential metal-catalyzed reactions while facilitating a one-pot synthesis of a diverse variety of indoline derivatives, with yields up to 88%. This reaction is accomplished by in situ modification of the Pd catalyst through ligand exchange (Scheme 4). Fort et al.[16] described a novel Pd-catalyzed methodology for sequential intra- and intermolecular amination reactions that use *N*,*N*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr) as a ligand and *t*BuONa as the base (Scheme 5).

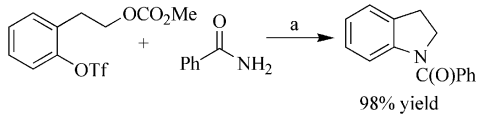


Scheme 4. One-pot, sequential *N*-arylation/cyclization/*C*-arylation to afford indolines. Reagents and conditions: (a) $Pd_2(dba)_3$ (0.5 mol-%), (*t*Bu)$_2$P(*o*-biphenyl) (1.0 mol-%), *t*BuONa (2.1 equiv.), 80 °C; (b) DPEphos (2 mol-%), 105 °C.



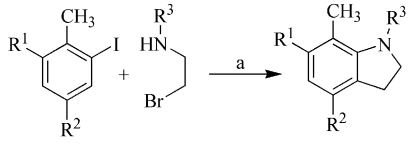
Scheme 5. Sequential intra- and intermolecular *N*-arylation to afford indoline derivatives.

In 2005, Kerr et al.[17] explored a one-pot, sp^2–sp^3 amidation for the formation of indolines from the reaction of *o*-triflyloxyphenethyl carbonates with amides (Scheme 6). This convenient route involved Pd-catalyzed *N*-arylation and sequential intramolecular *N*-alkylation, and it has been successfully applied in synthesis of some pyrrolophenanthridone natural alkaloids such as anhydrolycorinone, hippadine, oxoassoanine, and pratosine.



Scheme 6. Domino sp^2–sp^3 amidation for the formation of indolines. Reagents and conditions: (a) $Pd_2(dba)_3$ (5 mol-%), XANTPHOS (10 mol-%), Cs_2CO_3, 1,4-dioxane, 110 °C.

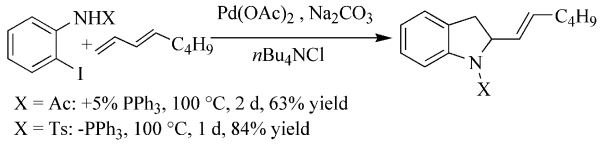
Recently, Lautens et al.[18] developed a convenient strategy involving Pd-catalyzed domino intermolecular alkylation/intramolecular amination of functionalized aryliodides, which affords a new route for the one-step synthesis of highly functionalized indolines in moderate yield from simple precursors (Scheme 7).



Scheme 7. Synthesis of indoline by Pd-catalyzed C–C/C–N coupling of bromoalkylamines. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol-%), tri-(2-furyl)phosphane (22 mol-%), norbornene (2 equiv.), Cs_2CO_3 (4 equiv.), 135 °C, 20 h.

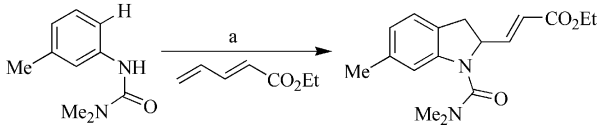
2.1.2 Pd-Catalyzed 1,2-Carboamination of Dienes

The assembly of the indoline ring through Pd-catalyzed 1,2-carboamination of dienes has been performed for many decades. In 1990, Larock et al.[19] invented a Pd-catalyzed heteroannulation of 1,3-dienes by functionally combining nitrogen-containing aryl halides, which could be used for the synthesis of the indoline ring. A substrate such as *o*-iodoaniline tosyl amide facilitates the annulation with excellent yield (Scheme 8).



Scheme 8. Pd-catalyzed synthesis of indoline from 1,3-dienes and nitrogen-substituted aryl iodides.

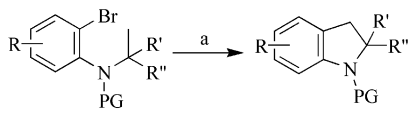
Recently, Booker-Milburm et al.[20] reported an efficient Pd^{II}-catalyzed 1,2-carboamination of dienes that proceeds under milder reaction conditions and facilitates the synthesis of indolines from *N*-aryl ureas by activation of aryl C–H bonds; yields up to 85% were achieved (Scheme 9). It was found in this experiment that the $(MeCN)_2Pd(OTs)_2$ catalyst showed unique reactivity compared to ubiquitously used $Pd(OAc)_2$. The presence of urea moiety is more important than other amides in attaining efficient C–H insertion.



Scheme 9. Pd^{II}-catalyzed 1,2-carboamination of dienes. Reagents and conditions: (a) $(MeCN)_2Pd(OTs)_2$ (10%), BQ (1 equiv.), Ac_2O (1 equiv.), 50 °C, 2–4 h.

2.1.3 Pd-Catalyzed sp^3 C–H Activation

Recently, Ohno et al.[21] described a novel and convenient strategy for the Pd^0-catalyzed sp^3 C–H activation of simple alkyl groups from functionalized *N*-alkyl-2-bromoanilines and subsequent intramolecular cyclization to afford various indoline derivatives (Scheme 10). The highest yield reached 99%. It is striking that the assistance of pyridine or a quaternary carbon moiety in the substrates is not always necessary for the activation of sp^3 C–H bonds. However, the activation of sp^3 C–H bonds is more difficult than activation



R = Me, F, CF_3, CO_2Me, NO_2
R', R" = H, Me, Et, etc.
PG = CO_2Me, $COCF_3$

Scheme 10. Pd-catalyzed cyclization of functionalized *N*-alkyl-2-bromoaniline derivatives through sp^3 C–H activation. Reagents and conditions: (a) $Pd(OAc)_2$ (3 mol-%), PCy_3HBF_4 (6 mol-%), Cs_2CO_3 (1.4 equiv.), *t*$BuCO_2H$ (30 mol-%), 140 °C, 2 h.

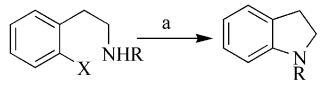
of sp^2 C–H bonds, and this is one of the current challenges in organic chemistry. This method seems quite promising in constructing indoline-based heterocycles.

2.2 Cu-Catalyzed Reactions

2.2.1 Cu^I-Catalyzed Aryl Amination

In recent decades, considerable attention has been paid to inexpensive Cu-catalyzed aryl aminations,[22] and tremendous improvements in the classical Buchwald–Hartwig reaction for the synthesis of indolines and their derivatives have been observed.

At the beginning of 2001, Fukuyama et al. found a unique combination of stoichiometric copper iodide and cesium acetate to mediate the intramolecular amination of aryl halides under mild conditions to construct an indoline core. Remarkably, this reaction can proceed at room temperature and halogens at the *meta* position can be retained, providing a definitive advantage over conventional Pd-catalyzed systems.[23] This approach was successfully applied in the synthesis of naturally occurring antitumor antibiotics duocamycins[24] and gram-scale (+)-yatakemycin.[25] Systematic research on this reaction (Scheme 11)[26] revealed that copper(I) species including CuI, CuBr, CuOAc, and Cu(2-thienylcarboxylate) were all effective. In addition, cesium acetate was the best base, and the acetate anion was essential. The Ns(*o*-nitrobenzenesulfonyl) and benzyl groups served as the best suitable nitrogen protecting groups for the substrate, and aryl iodides were, in general, slightly superior to aryl bromides. The highest rate of production reached 96%.

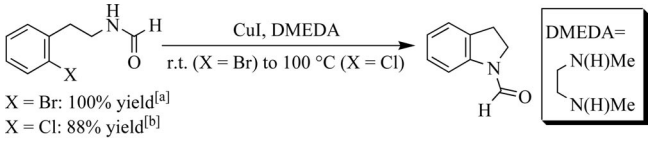


X = Br, I; R = H, Bn, Ns, Ac, Boc, Cbz, Alloc

Scheme 11. The CuI/CsOAc-catalyzed synthesis of indolines. Reagents and conditions: (a) Copper reagent (2 equiv.), CsOAc (5 equiv.), r.t. to 90 °C.

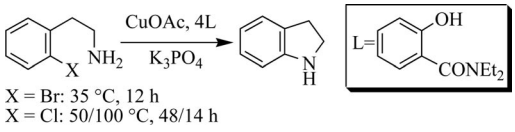
With the aid of a ligand, the quantity of the previously required stoichiometric amount of copper salt will be significantly reduced. Bolm[27] showed that even the use of a submolar percent of Cu could make Ullmann-type reactions happen with the aid of a high concentration of the ligand. Several ligands were introduced to promote the Cu-catalyzed amination reaction, which was fully described by Monnier et al.[28] In 2001, Buchwald et al.[29] found that the formation of indolines through intramolecular amidation of an aryl bromide in the presence of the ligand DMEDA (*N*,*N*′-dimethylethylenediamine) could be performed at room temperature in excellent yield (Scheme 12). In 2003, this group developed an efficient Cu^I-catalyzed amination reaction by using commercially available diethylsalicylamide as the ligand.[9] Intramolecular amination of aryl halides, bromides, or even chlorides afforded nonsubstituted indolines under quite mild reaction conditions (Scheme 13). The highest yield of product that was obtained was 80%.

Besides this, Ma et al.[30] found that many amino acids could be used as the ligands to promote the Ullmann-type C–N bond formation reaction. In 2005, Ma et al.[31] reported an intramolecular amination of aryl chlorides catalyzed by CuI and proline facilitated the production of nonsubstituted indolines in 70% yield (Scheme 14). Recently, the Buchwald group[32] found that an isobutyrylcyclohexanone ligand helped to promote the CuI-catalyzed intramolecular aryl amination of aryl bromides and aryl chlorides to transform the indoline scaffold (Scheme 15).

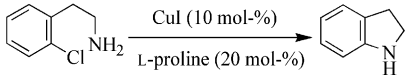


[a] Performed with Cs_2CO_3 (1.5 equiv.) as base and water (1 equiv.) in THF at 25 °C for 4 h.
[b] Performed with K_2CO_3 (2 equiv.) as base in toluene at 100 °C for 23 h.

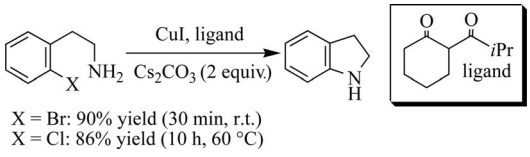
Scheme 12. The CuI-catalyzed synthesis of indolines with DMEDA as the ligand.



Scheme 13. The CuOAc-catalyzed synthesis of indolines with diethylsalicylamide as the ligand.

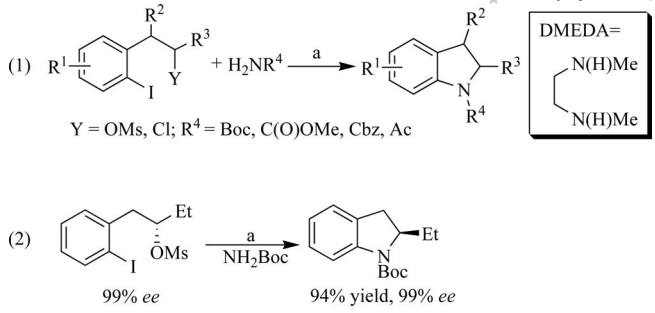


Scheme 14. The CuI-catalyzed synthesis of indolines with L-proline as the ligand.



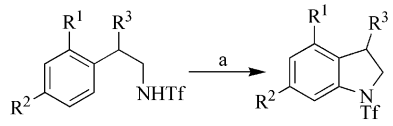
Scheme 15. The CuI-catalyzed synthesis of indolines with isobutyrylcyclohexanone as the ligand.

The above experiment only allows access to nonsubstituted indolines. The Buchwald group[33] invented a highly efficient one-pot procedure to assemble substituted indolines based on a domino amidation/nucleophilic substitution reaction catalyzed by CuI and Cs_2CO_3 with DMEDA as the ligand (Scheme 16, Equation 1). Substituted 2-iodophenethyl mesylates and related substrates afforded the products in excellent yields. The mild reaction conditions and broad substrate scope make this method attractive and complementary to existing methods for the synthesis of substituted indolines. The most striking point is that this protocol can also be applied to the synthesis of enantiomerically pure indolines (Scheme 16, Equation 2).



Scheme 16. The CuI-catalyzed synthesis of substituted indolines with DMEDA as the ligand. Reagents and conditions: (a) CuI (5 mol-%), DMEDA (20 mol-%), Cs_2CO_3 (3 equiv.), THF, 80 °C, 16 h.

More recently, the incorporation of iodination through Pd^{II}-catalyzed C–H activation and sequential Cu^{I}-induced intramolecular aryl amination in a one-step synthesis of functionalized indolines was developed by Yu (Scheme 17).[34] Easily obtainable phenylethylamine derivatives were used as the substrates. Although the production yield is not high, it provided a very convenient way to construct a variety of substituted indolines.



A: $R^1 = R^3 = H$, $R^2 = Me$: 59% yield
B: $R^1 = R^2 = R^3 = H$: 58% yield
C: $R^1 = R^3 = H$, $R^2 = Cl$: 50% yield
D: $R^1 = R^2 = H$, $R^3 = OMe$: 49% yield
E*: $R^1 = Me$, $R^2 = R^3 = H$: 81% yield
F*: $R^1 = Cl$, $R^2 = R^3 = H$: 82% yield

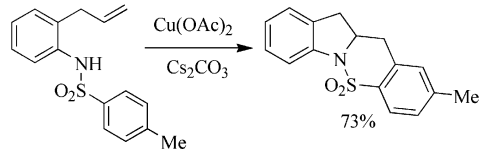
*: CuI (0.5 equiv.)

Scheme 17. One-pot iodination–amination of C–H bonds. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol-%), CuI (1 equiv.), $PhI(OAc)_2$ (2 equiv.), I_2 (2 equiv.), Cs_2CO_3 (1 equiv.), 130 °C.

2.2.2 Cu^{II}-Catalyzed Amination of Olefins

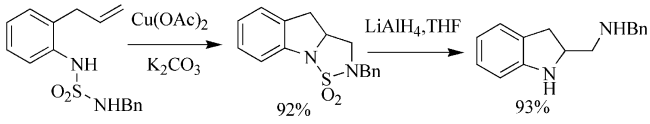
Oxidative cyclization reaction of olefins provides another way for constructing indolines. Cu^{II} oxidants are themselves capable of promoting additions of nitrogen to double bonds. The Sherman group found a new method by employing Cu^{II} salt as the catalyst for rapid assembly of the indoline system through a simple oxidative cyclization procedure.[35,36] They found that *N*-tosyl-*o*-allylaniline underwent efficient oxidative cyclization when treated with $Cu(OAc)_2$ and Cs_2CO_3 in CH_3CN or DMF at 120 °C to afford indoline derivatives in moderate yields (Scheme 18).[35]

Later on, they developed the intramolecular diamination reaction of olefins to afford indoline derivatives. Treatment of *N*-(2-allylphenyl)-*N*′-benzylsulfamide with $Cu(OAc)_2$ in



Scheme 18. Assembly of indolines through Cu^{II}-induced oxidative cyclization of olefins.

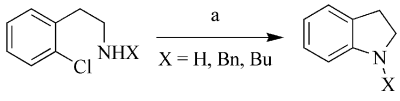
K_2CO_3 at elevated temperature produced the desired diamination adduct with a yield up to 92% (Scheme 19).[37] The free amine was obtained through the reduction of the sulfamide with $LiAlH_4$. $Cu(OAc)_2$ was proven to be the best promoter for this reaction, and the necessary base was K_2CO_3, which was slightly superior to Cs_2CO_3. Sulfamide was the best substrate. It is noteworthy that substrate-based asymmetric induction of indolines could also be achieved.



Scheme 19. Synthesis of indolines by Cu^{II}-catalyzed intramolecular diamination of olefins.

2.3 Ni-Catalyzed Intramolecular Aryl Amination

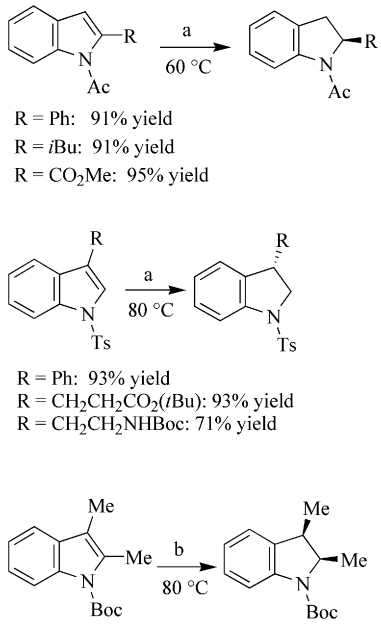
Despite the significant improvements in the intramolecular cyclization of aryl iodides or bromides, few studies have focused on the use of aryl chlorides with pendant amines to construct indolines. In 2003, Fort el al.[38] developed the Ni/ligand-mediated intramolecular amination of aryl chlorides. A variety of aryl chlorides with pendant amino groups was catalyzed by in situ generated Ni^0 combined with the ligand 2,2′-bipyridine or *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr). The presence of *t*BuONa as the base afforded the indolines in high yield (82–98%; Scheme 20).



Scheme 20. Synthesis of indolines by Ni^0-mediated aryl amination. Reagents and conditions: (a) Ni^0/bipyridine (5 mol-%, 3 equiv.) or Ni^0/SIPr (2 mol-%, 1 equiv.), *t*BuONa, 5 h.

2.4 Rh/(Ru)-PhTRAP Complex Catalyzed Asymmetric Hydrogenation of Indole

In 2000, Ito et al. first reported[39] a highly enantioselective hydrogenation of *N*-acetyl-substituted indoles to form 2-substituted indolines with enantiomeric excesses up to 95% by using a chiral catalyst that was generated in situ from $[Rh(nbd)_2]SbF_6$, (*S*,*S*′)-(*R*,*R*′)-PhTRAP, and a base (Scheme 21). Addition of a base, such as Et_3N or Cs_2CO_3, is necessary for achievement of high enantioselectivity and high catalytic activity. Later on, this chiral catalyst was applied again by this research group to synthesize 3-substituted indolines from *N*-tosyl-substituted indoles with high enantioselectivity (95–98% *ee*;[40] Scheme 21). As the Boc group is more easily attached to an indole substrate and detached from an indoline product, Kuwano[41] developed a new chiral ruthenium-PhTRAP catalyst for the hydrogenation of *N*-Boc protected indoles, which form 2- or 3-substituted chiral indolines with enantiomeric excesses up to 95%. This chiral catalyst can also promote the hydrogenation of 2,3-dimethylindoles, providing *cis*-2,3-dimethylindoline with 72% *ee* (Scheme 21).



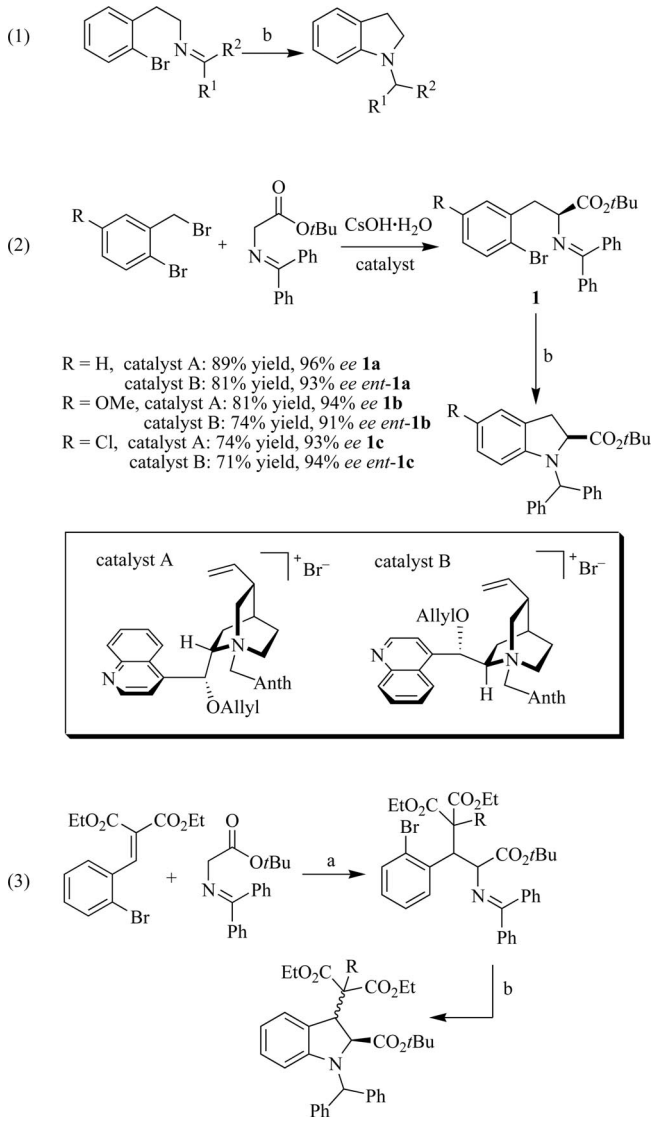
Scheme 21. Rh/(Ru)-PhTRAP chiral catalyst promoted enantioselective hydrogenation of *N*-protected 2- or 3-, or 2,3-substituted indoles. Reagents and conditions: (a) $[Rh(nbd)_2]SbF_6$ (1.0 mol-%), (*S*,*S*′)-(*R*,*R*′)-PhTRAP (1.05 mol-%), Cs_2CO_3 (10 mol-%), *i*PrOH, H_2 (5.0 MPa); (b) $Ru(\eta^3\text{-}2\text{-methylallyl})_2(cod)$ (1.0 mol-%), (*S*,*S*′)-(*R*,*R*′)-PhTRAP (1.1 mol-%), Et_3N (10 mol-%), *i*PrOH, H_2 (50 atm).

3. Radical-Mediated Reactions

3.1 Radical-Mediated Aryl Amination

In 2001, a new radical-mediated aryl amination reaction to synthesize indolines was presented by Johnston et al.[42] This method to construct C–N bonds was conceptually and operationally distinct. Ketimines derived from *o*-bromophenethylamines cyclize to *N*-substituted indolines when treated with tributylstannane (nBu_3SnH) and a radical initiator such as azobisisobutyronitrile (AIBN; Scheme 22, Equation 1). Intensive study demonstrated that aryl, trifluoromethyl alkyl, and α,β-unsaturated ketimines are all able to form an aryl–nitrogen bond through 5-*exo* cyclizations of an aryl radical to an azomethine nitrogen atom; α-ketoimines are a promising new class of aryl radical acceptors because no competitive aryl radical reduction is observed. Unlike basic conditions, which is the requisite in

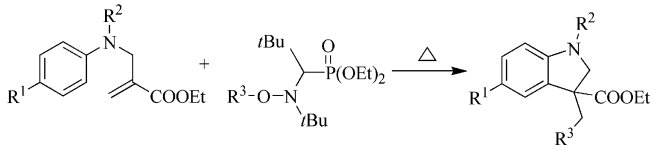
transition-metal-catalyzed aryl aminations, the pH-neutral conditions used in radical-mediated reactions allows base- and acid-sensitive functionalities to be present in the substrate. Later on, the same research group developed this idea in the construction of enantioenriched indolines. This method involves enantioselective phase-transfer-catalyzed glycine Schiff base alkylation with *ortho*-bromobenzyl bromides followed by free radical mediated aryl amination, which ultimately yields enantiopure indolines with high *ee* values. As substrates electronically neutral, rich, and deficient aryl halides (Scheme 22, Equation 2) are tolerated.[43] A phase-transfer-catalyzed Michal addition reaction and subsequent free radical mediated aryl amination can also produce various enantiopure indolines (Scheme 22, Equation 3).[44]



Scheme 22. Radical-mediated aryl amination for the construction of indolines. Reagents and conditions: (a) RX (20 mol-%), $BnEt_3N^+Cl^-$ (20 mol-%), 50% aq. NaOH; (b) nBu$_3$SnH, AIBN, 80 °C.

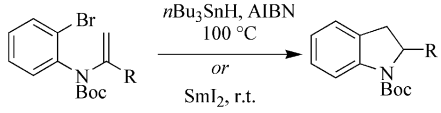
3.2 Radical-Mediated Aryl Alkylation

In 2003, Ciufolini et al.[45] discovered that thermal reaction of *N*-allylaniline derivatives with Tordo-type alkoxyamines resulted in the formation of indolines with moderate yield through radical-mediated C–C bond formation (40–60%; Scheme 23). This technique did not need halogenated substrates and Sn/Si hydrides to promote the C–C bond formation in the radical regime, providing a relatively environmentally benign alternative to traditional radical methodology.



Scheme 23. Radical-induced thermal reaction of *N*-allylaniline derivatives to synthesize indolines.

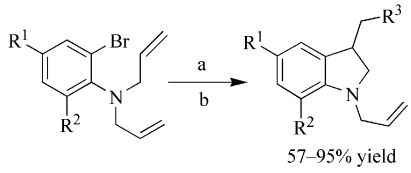
In 2007, Sasaki et al.[46] found that various *N*-(*o*-bromophenyl) enecarbamates derived from acyclic α-phosphoryloxy enecarbamates can undergo 5-*endo*-*trig* radical cyclization and provide a series of 2-substituted indolines. This reaction occurred in the presence of nBu$_3$SnH and a catalytic amount of AIBN at 100 °C, or in the presence of *t*BuOH in THF/HMPA at room temperature with yields up to 90% (Scheme 24).



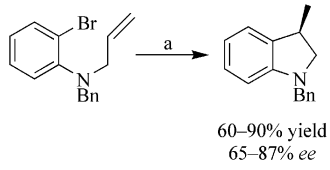
Scheme 24. Synthesis of indolines by 5-*endo*-*trig* aryl radical cyclization.

4. Intramolecular Carbolithiation

In 1996, two groups[47,48] reported a new versatile way to construct 3-substituted indolines through a cyclolithiation process (Scheme 25). Continuous research on this strategy



Scheme 25. Construction of 3-substituted indolines by cyclolithiation. Reagents and conditions: (a) *t*BuLi (2 equiv.), *t*BuOMe, –78 °C to room temp.; (b) electrophile.

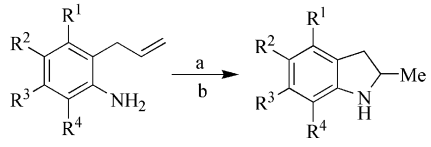


Scheme 26. Enantioselective synthesis of 3-substituted indolines by (–)-sparteine-mediated asymmetric intramolecular carbolithiation. Reagents and conditions: (a) *t*BuLi (2.2 equiv.), (–)-sparteine (1.5 equiv.), –78 or –90 °C to r.t.

has led to highly enantioselective routes to synthesize 3-substituted indolines[49,50] through a (–)-sparteine-mediated asymmetric intramolecular carbolithiation reaction (Scheme 26).

5. Solid-Phase Synthesis

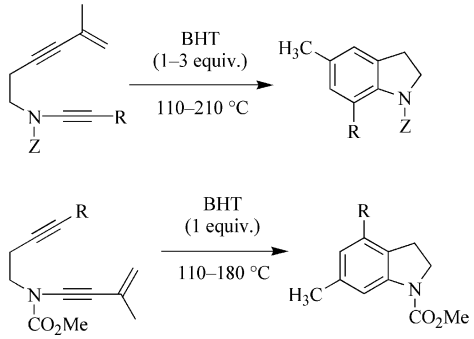
In 2000, Nicolaou[51] developed a novel solid-phase synthesis of indoline derivatives. Substituted *o*-allyl anilines could be loaded onto a polystyrene-based selenenyl bromide resin through a 5-*exo*-*trig* cyclization to afford resin-bound indoline scaffolds, which could then be cleaved through treatment of the resin with nBu$_3$SnH and AIBN to afford indoline derivatives (Scheme 27).



Scheme 27. Solid-phase synthesis of highly functionalized indolines. Reagents and conditions: (a) resin-SeBr (1.0 equiv., 0.75 mmol g^{-1}), $SnCl_4$ (3.0 equiv.), CH_2Cl_2, –20 °C, 0.5 h; (b) nBu$_3$SnH, AIBN, 90 °C.

6. Intramolecular Cycloaddition of Ynamides and Conjugated Enynes

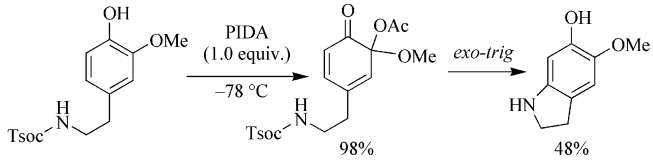
In 2005, Danheiser et al.[52] developed a new intramolecular [4+2] cycloaddition strategy to construct indolines bearing multiple substituents on the six-membered ring. Acyclic precursors, substituted ynamides, and conjugated enynes underwent intramolecular cyclization in toluene at temperatures ranging from 110 to 210 °C to afford highly substituted indolines in yields of 50–96% (Scheme 28).



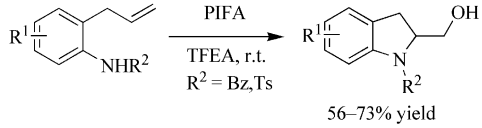
Scheme 28. [4+2] cycloaddition of conjugated enynes with ynamides.

7. Phenyliodine(III)-Mediated Reactions

In 2002, Pouysegu et al.[53] found that oxygenated indolines and their derivatives could be prepared from nitrogen-tethered 2-methoxyphenols by a phenyliodine(III) diacetate (PIDA) mediated oxidative reaction, followed by a fluoride- or base-induced intramolecular nucleophilic addition reaction (Scheme 29). In 2006, Dominguez et al.[54] reported a novel, straightforward approach to synthesize 2-substituted indolines, which involved an olefin amidation reaction mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA; Scheme 30). The key step of this method relied on the ability of PIFA to generate *N*-acylnitrenium intermediates and its succeeding intramolecular trapping by the olefin fragment, which provided the formation of a novel C–N bond as well as the introduction of a hydroxy group in the final product. Mild conditions, clean transformation, low toxicity, easy handling, and low price, in contrast to expensive transition metals, make this method a promising approach for the preparation of heterocycles.



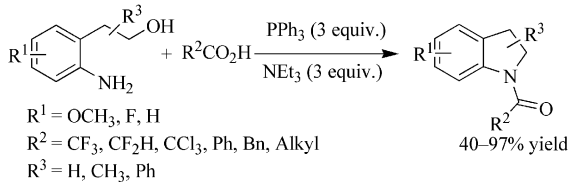
Scheme 29. Synthesis of oxygenated indolines by a PIDA-mediated reaction.



Scheme 30. Synthesis of indolines by a PIFA-mediated olefin amidation reaction.

8. Other Reactions

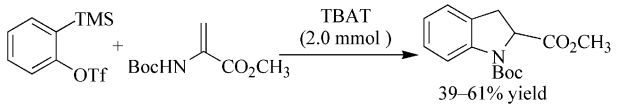
A distinctive one-pot cyclization of 2-aminophenethylethanols with common carboxylic acids to form *N*-acyl indolines (Scheme 31) in the presence of PPh_3, CCl_4, and NEt_3 has been recently discovered by Hao et al.[55] The reaction provides the products in good to excellent yield. This synthetic strategy provides a convenient and scalable approach for the direct construction of *N*-acylindolines.



Scheme 31. One-pot synthesis of indolines from 2-aminophenethylethanols and carboxylic acids.

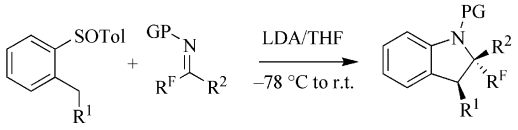
In 2008, Stoltz et al.[56] reported a coupling reaction of readily available *N*-acyl dehydroamino esters with aryne precursors to produce indolines. *N*-Carbamoyl dehydroalanine esters, when reacted with silylaryl triflates in the presence of fluoride sources, produced functionalized indolines through a formal [3+2] cycloaddition (Scheme 32) in modest yield. Optimization of the reaction conditions

identified $Bu_4NPh_3SiF_2$ (TBAT) and THF as the best fluoride source and solvent, respectively. It is notable that a dehydrophenylalanine derivative as the substrate afforded the corresponding 1,2,3-trisubstituted indoline as a single isolated diastereomer.



Scheme 32. Synthesis of indolines by reaction of aryne precursors with *N*-carbamoyl dehydroalanine esters.

Recently, Gracía Ruano et al.[57] developed an asymmetric tandem reaction to facilitate the one-pot synthesis of optically pure fluorinated indolines. The first step involved nucleophilic addition of 2-(*p*-tolylsulfinyl)benzylcarbanions to an electrophilic reagent such as an imine, and subsequent intramolecular aromatic substitution of a sulfinyl group by the nitrogen center. This reaction occurred in the presence of lithium diisopropylamide and produced the optically active indolines in moderate yields ranging from 41 to 75% (Scheme 33).



Scheme 33. One-pot synthesis of optically pure fluorinated indolines ($R^F = CF_3$ or CF_2Cl, PG = protecting group, Tol = tolyl).

9. Conclusion

Researchers strive for efficient, scalable, and direct access to indolines and their derivatives. As illustrated in this paper, a number of methodologies have been exploited for the synthesis of indolines. Pd-catalyzed reactions are efficient to synthesize indolines; however, because of the expensiveness of the catalyst and relatively less mild reaction conditions, as well as some requirements for the substrates, its extensive application is limited. The improved Cu/ligand-catalyzed reactions are superior to the Pd-catalyzed reactions, as reactions can take place with inexpensive copper salts under mild conditions. Expensive chiral catalysts and the danger induced by the presence of hydrogen limit the widespread application of the hydrogenation of indoles to the large-scale production of optically active indolines. Besides this, there are many other disadvantages that limit the extensive application of some reactions, such as the high cost of the chiral ligands, harsh reaction conditions, stoichiometric quantities of the catalyst, narrow substrate scope, low production yield, and inconvenient operation; these processes also tend to be environmentally unfriendly. The synthesis of the indoline scaffold, which is an important structural component in many bioactive alkaloids and pharmaceutical compounds, remains a challenge and deserves in-depth investigation so that a new, economic, efficient, and scalable method can be found.

Acknowledgments

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