C-H FUNCTIONALIZATION OF INDOLES AND OXINDOLES THROUGH CDC REACTIONS

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Abstract. *Cross-dehydrogenative-coupling (CDC) reactions have emerged as highly efficient and atom-economical methods for the direct C–C bond formations via C–H functionalization. Indole and oxindole frameworks are important structural units in many bioactive molecules, natural products and functional materials. Various CDC reactions have been developed to construct C–C and C–X bonds for the modification of indole and oxindole molecules. By designing new catalyst systems and using directing group strategy, the site-selective C–H bond functionalization of indoles can be achieved at either C3-C2 positions or less-reactive C4-C7 positions of indoles.*

Contents

1. Introduction

Cross-Dehydrogenation-Coupling (CDC) reaction is a type of reaction that does not require pre-functionalizations and directly couples two molecules *via* activation of C–H bonds.[1] It has the advantages of simple synthesis, high atomic economy, and waste minimizations. As indole and oxindole frameworks are widely present in natural products and biologically active molecules, the C–H functionalization of indoles **1** and oxindoles **2** through CDC reaction provides a highly efficient and enabling tool to construct such compounds (Figure 1).

There are six C–H bonds in an indole with subtle differences in activation barriers (Figure 1). These C–H bonds can be classified into two different classes at C2 to C3 (pyrrole core) and C4 to C7 (benzene core) positions of indole ring. Because of the inherent reactivity of the pyrrole-type ring, the C–H functionalization of the indole framework usually takes place at the C3 position *via* an aromatic electrophilic substitution pathway, or at C2 position when the C3 position has a substituent group. However, the reactivity discrimination of the less reactive benzenoid C–H bonds at indole C4 to C7 positions remains a synthetic challenge. Over the past decades, many synthetic strategies have been developed to facilitate C–H functionalization of indoles in a site-selective manner, such as selective directing-group assisted strategies and remote C–H functionalization techniques.[2] This review highlights the C–H functionalization of indoles and oxindoles through CDC reaction to construct C–C and C–X bonds to access diversely functionalized indoles and oxindoles.

2. Coupling of indole Csp^2–H with Csp–H

The classic alkynylation of indoles is achieved by the transition metal-catalyzed Heck-Cassar-Sonogashira (HCS) coupling of (pseudo)halogenated indoles with alkynes or indoles with (pseudo)halogenated alkynes.[3] In 2010, Li and co-workers reported the first Pd-catalyzed CDC reaction for

the direct alkynylation of indoles **3** with terminal alkynes **4** (Scheme 1).[4] Using O_2 as the terminal oxidant, the alkynylation of indoles takes place at C2 position with 3-methylindole derivatives **3** as the substrates. The mechanism of this Pd-catalyzed oxidative HCS-type coupling is illustrated in Scheme 1. The electrophilic attack of formed alkynylpalladium species **A** at the C2 position of indole **3** generates intermediate **B**. After deprotonation, intermediate **B** yields intermediate **C**, and then reductive elimination of intermediate **C** produces the alkynylated indole product **5**.

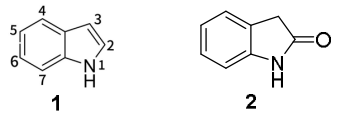
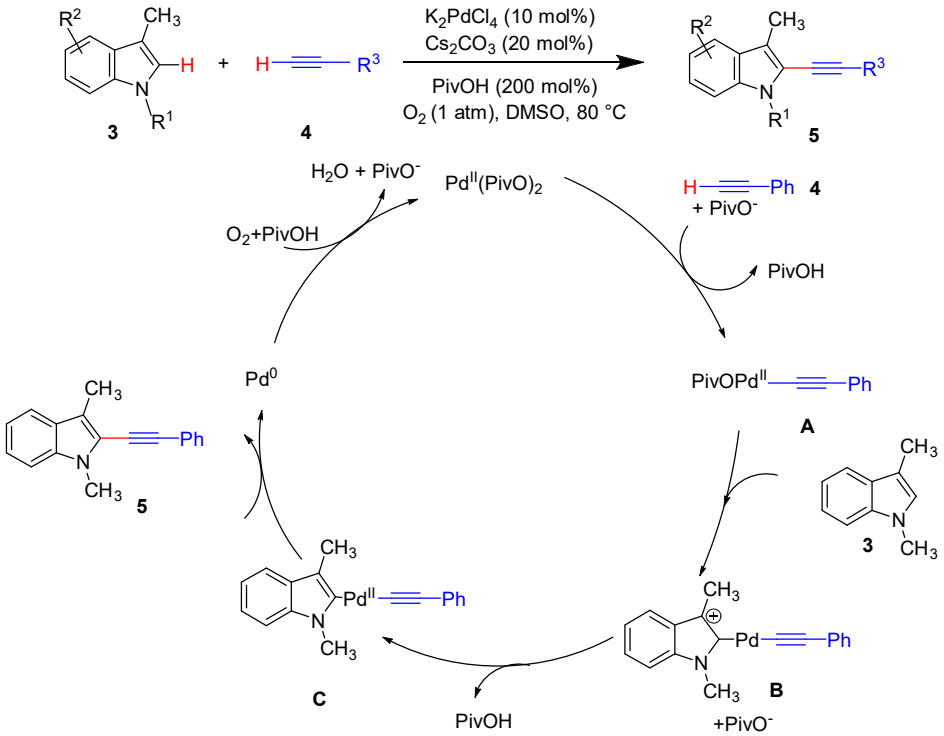


Figure 1. Structure of indole and 2-oxindole.



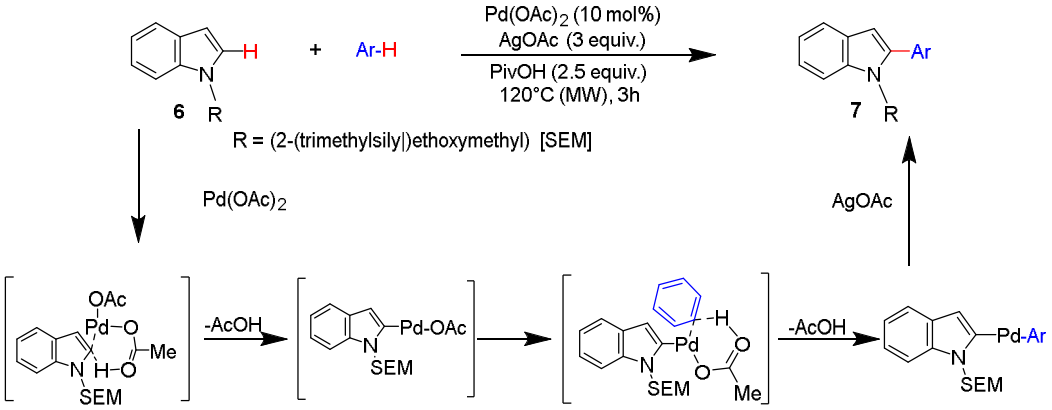
Scheme 1. Pd-catalyzed direct alkynylation of indoles.

Using $PhI(OAc)_2$ as oxidant and gold catalysis, Nevado and co-workers explored the CDC reaction of electron-rich arenes and electron-deficient terminal alkynes. One example of alkynylation of indole was given and propiolate was coupled at the C3 position of indole.[5]

3. Coupling of indole Csp^2–H with Csp^2–H

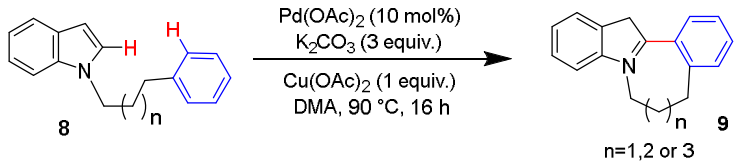
Arylindole and vinylindole derivatives are important indole frameworks and widely exit in bioactive molecules, natural products and optoelectronic materials. The selective and green C–H arylation and alkenylation of indoles have tremendous demands in many research areas such as medicinal chemistry and functional materials.

In 2010, DeBoef and co-workers reported a CDC reaction of indoles **6** with arenes by Pd-catalyzed double C–H activation with AgOAc as a promoter in an acidic medium (Scheme 2).[6] With *N*-alkyl protecting groups such as 2-(trimethylsilyl)-ethoxymethyl (SEM), 2-arylated indoles **7** were obtained. The proposed mechanism proceeds *via* a concerted metalation-deprotonation (CMD) process through a six-membered cyclic transition state.



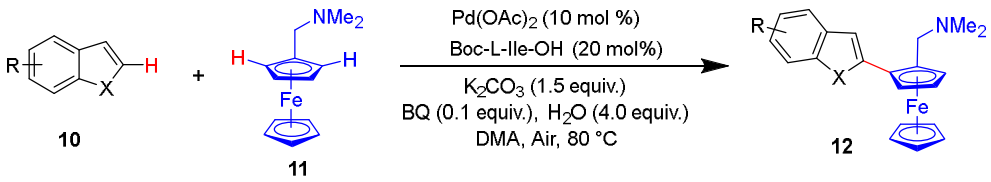
Scheme 2. Pd-catalyzed C-2 arylation of indoles.

The Pd-catalyzed oxidative C–H functionalization at the indole 2-position could be expanded to other *N*-substituted indole substrates.[7] Greaney and co-workers developed an effective strategy for synthesizing medium-sized ring compounds **9** through an intramolecular C2-arylation of indoles **8** (Scheme 3).[8]



Scheme 3. Pd-catalyzed intramolecular oxidative coupling of indoles with arenes.

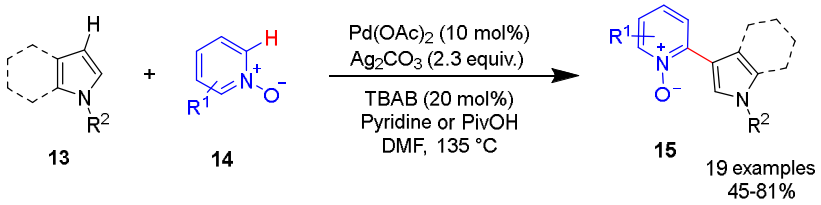
In 2016, You and co-workers developed a Pd-catalyzed enantioselective CDC reaction of ferrocenes **11** with heteroaromatics **10** (Scheme 4).[9] Using an amino acid chiral ligand, the reaction of indole **10** with ferrocene **11** provided a planar chiral ferrocene **12** *via* C-H functionalization at the C2 position of indole **10**. A plausible mechanism was proposed as the oxidative double C−H activations through the preferential formation of Pd-σ-heteroaryl complexes at C2 position of indole.[10]



Scheme 4. Asymmetric Pd-catalyzed 2-arylation of indole with ferrocene.

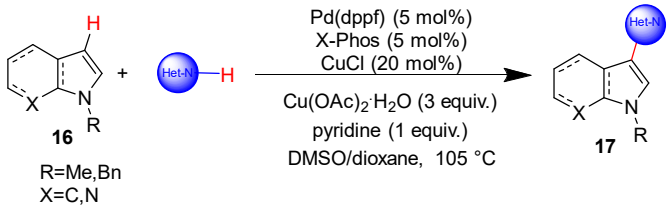
In 2011, Pd-catalyzed C3 selective arylation of *N*-substituted indoles **13** with pyridine *N*-oxides **14** was reported by Li and co-workers (Scheme 5).[11] By the Pd-catalyzed CDC reaction, various *N*-substituted indoles **13** such as *N*-MOM and *N*-Ts indole could react with azine *N*-oxides **14** to give the corresponding product **15**

through the selectively coupling at the C3 position of indoles **13** and the C2 position of pyridine *N*-oxides **14**.[12] Yamaguchi and Itami demonstrated the synthetic application of oxidative C−H/C−H coupling of indoles with azine *N*-oxides in the synthesis of Eudistomin U.[12]



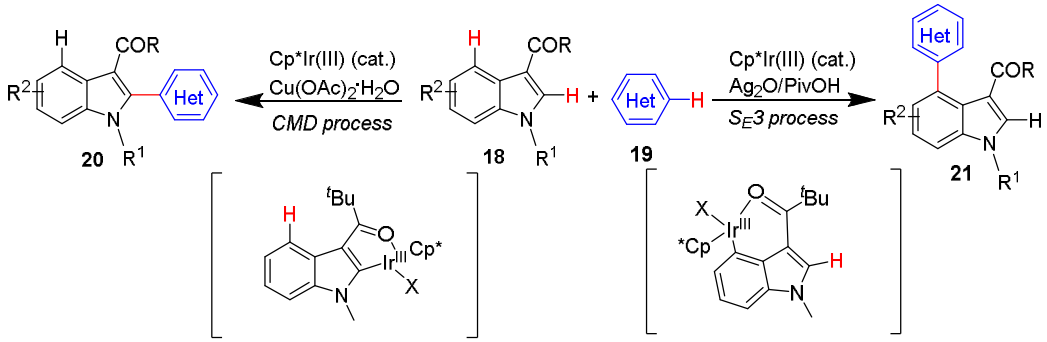
Scheme 5. Pd-catalyzed C3 heteroarylation of indoles with pyridine *N*-oxides.

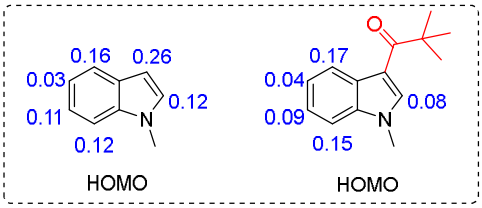
In the same year, You and co-workers reported a Pd/Cu bimetallic co-catalytic system that allowed selective C3 heteroarylation of indoles and pyrroles **16** (Scheme 6).[13] Various π-electron-poor *N*-heteroarene or *N*-oxides (*e.g.* pyridine *N*-oxide, quinoline *N*-oxide, quinoxaline *N*-oxide, pyrazine *N*-oxide, *etc.*) smoothly underwent the dehydrogenative couplings with the *N*-alkylated indoles **16** to provide the corresponding products **17** in good yields.



Scheme 6. Pd-catalyzed C3 heteroarylation of indoles.

In addition, You, Yang and co-workers disclosed an Ir-catalyzed C2/C4 regioselective C−H heteroarylation of indoles **18** with the assistance of a pivaloyl group as a directing group at the C3 position (Scheme 7).[14] Various heteroarenes **19**, including thiophenes, furans, benzo[*b*]thiophene and benzo[*b*]furans, could react with indoles **18** to provide the CDC products. Based on DFT calculations, the introduction of a carbonyl group at the C3 position as a directing group enlarges the difference of the electron density (HOMO) between C2 and C4 positions. The C−H heteroarylation takes place at the C2 position of the indole **18** to provide the product **20** through a CMD pathway with $Cu(OAc)_2$ serving as oxidant; whereas the C4 heteroarylation of the indole **18** forms the product **21** proceeding *via* the trimolecular electrophilic substitution pathway (S_E3) utilizing Ag_2O as the oxidizing agent.

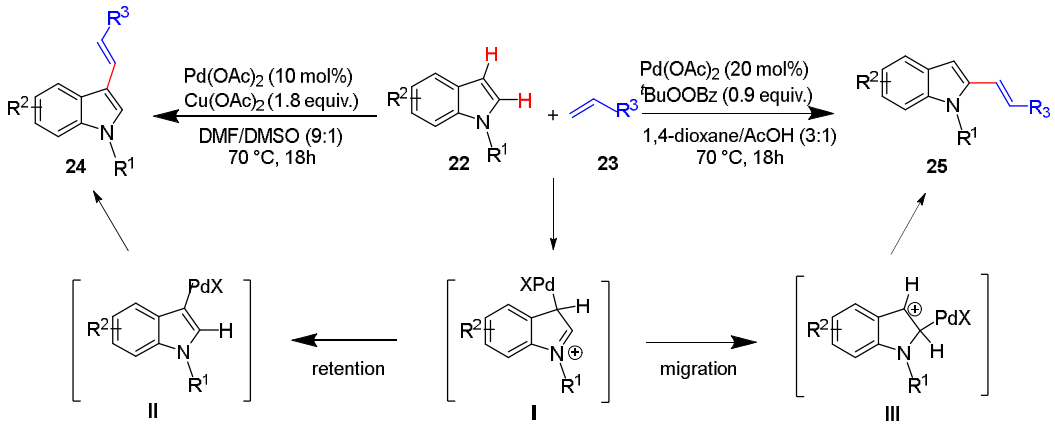




Scheme 7. Ir-catalysed C4 heteroarylation of indoles.

Direct C–H alkenylations of arenes and heteroarenes by CDC reaction under the catalysis of transition metal have emerged as an important atom-economical alternative of the Heck reaction, also known as the Fujiwara-Moritani reaction.[15]

In 2005, Gaunt and co-workers reported a Pd-catalyzed regioselective C2 or C3 alkenylation of indoles **22** with alkenes **23** (Scheme 8).[16] The solvent plays an important role in the regioselective control. C3-vinylated indoles **24** were observed exclusively when DMF/DMSO was used as solvent with $Cu(OAc)_2$ as the oxidant. By contrast, C2-vinylated indoles **25** were obtained when the reaction was performed in dioxane/AcOH with *t*-BuOOBz as the oxidant. A plausible mechanism may involve initial palladation at the C3-position of indole (intermediate **I**), and then follow a Heck-type reaction after depronation (intermediate **II**) to provide the C3-vinylation product **24**. When the reaction was performed in an acidic medium, Pd-migration from C3 to C2-position (intermediate **III**) could occur due to slow depronation and finally resulted in C2-vinylation product **25**.

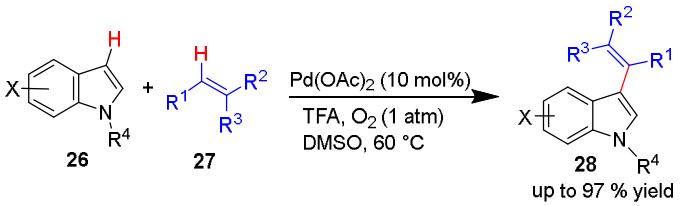


Scheme 8. Pd-catalyzed C2/C3 alkenylation of indoles with alkenes.

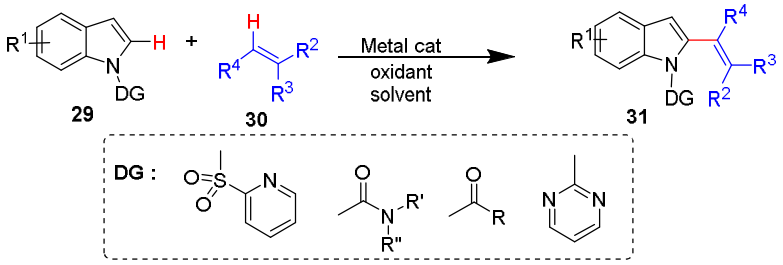
In 2012, Wang and co-workers reported a Pd-catalyzed C3 alkenylation of indoles **26** with alkenes **27** using oxygen as an oxidizing agent (Scheme 9).[17] $Pd(CF_3CO_2)^+$ as an active catalyst affords the C3-palladated species through electrophilic addition of indole **26**. The reaction works well without Cu(II) and provides an economical and environmentally benign process to provide the C3 alkenylated indoles **28**. In 2017, Carrow and co-workers disclosed that a thioether-based ligand could accelerate the Pd-catalyzed CDC reaction for C–H alkenylation such as C3 alkenylation of indoles with acrylate and styrene.[18]

The installation of a directing group at the N atom of indole would help the alkenylation occur at the less nucleophilic 2-position. To date, a series of DG auxiliaries at the 1-position of indole have been successfully employed for the C2-alkenylation of indoles. For example, in 2009, Carretero and co-workers reported a Pd-catalyzed C-2 alkenylation of indoles **29** by using the *N*-(2-pyridyl)sulfonyl group as directing group (Scheme 10).[19] Under Pd(II)-catalysis with $Cu(OAc)_2$ as oxidant, the CDC reaction of *N*-protected indoles **29** with alkenes **30** in DMA could proceed regioselective at the C2-position of indoles to generate the

product **31**. Several Ru and Rh catalytic systems have also been reported using amide, ketone and 2-pyrimidyl group at the N atom as the directing group.[20] Various alkenes, including active and unactive alkenes, could react with these *N*-protected indoles to provide the coupling products at the C2-position of indoles.

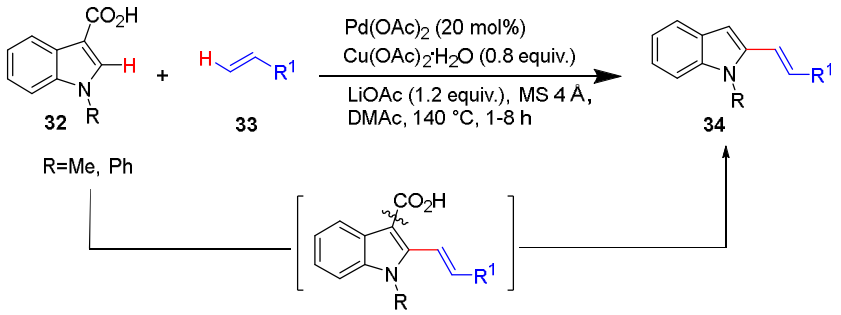


Scheme 9. Pd-catalyzed C3 alkenylation of indoles with olefines.



Scheme 10. Directing group strategy for metal-catalyzed C2 alkenylation of indoles with alkenes.

Miura and co-workers developed a Pd-catalyzed C2 alkenylation of indoles **32** using carboxylic acid as a traceless directing group (Scheme 11).[21] The reaction of indole-3-carboxylic acids **32** with alkenes **33** underwent an oxidative coupling and decarboxylation to produce 2-vinylated indoles **34** exclusively.

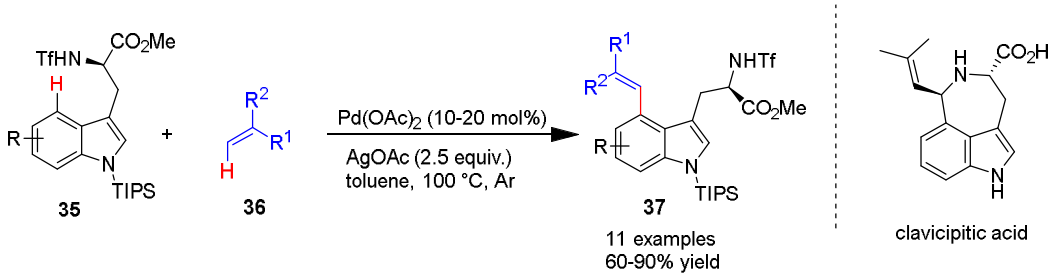


Scheme 11. Pd-catalyzed C2 alkenylation of indole-3-carboxylic acids.

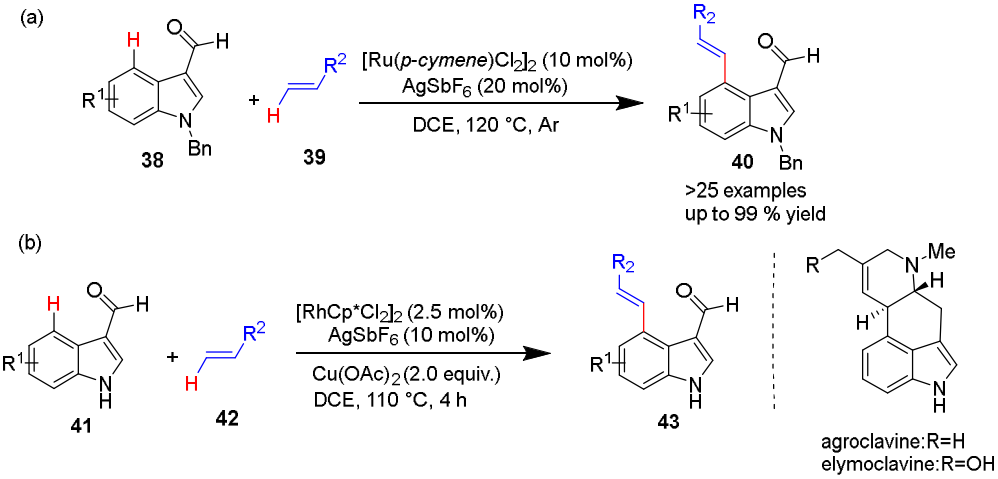
In 2013, Jia and co-workers developed the first Pd-catalyzed C4 alkenylation of tryptophan derivatives **35** (Scheme 12).[22] With the bulky TIPS group for the *N*-protection of the indole and TfNH as the directing group, the CDC reaction of tryptophan derivatives **35** with alkenes **36** demonstrated high site selectivity at the C4 position to provide the corresponding products **37**. This method can be used for the biomimetic synthesis of clavicic acid quickly and efficiently.

In the same year, Prabhu and co-workers reported a Ru-catalyzed CDC reaction at the C4 position of indole **38** with alkenes **39** using an aldehyde as a directing group at the C3 position (Scheme 13a).[23] Various olefins, such as acrylates, vinyl ketones, acrylonitrile as well as styrenes, could react with indoles **38** to afford the C4 alkenylation products **40** which could serve as precursors for ergot alkaloids and related heterocyclic compounds. Using C3 substituted aldehyde as a directing group, in 2017, Jia and co-workers developed a low

catalyst loading Rh-catalyzed (2.5 mol%) reaction of indoles **41** with alkenes **42** to provide the C4 alkenylated indoles **43** (Scheme 13b).[24] The application of this methodology has been elegantly demonstrated in the total synthesis of (−)-agroclavine and (−)-elymoclavine. The directing group strategy by employing various substituents at the C3 position, such as aldehyde, ketone, ester, carboxylic acid and thioether, could make the CDC reaction of indoles with alkenes under the catalysis of Pd, Ru and Rh to selectively generate C4 or C2 alkenylation products.[25]



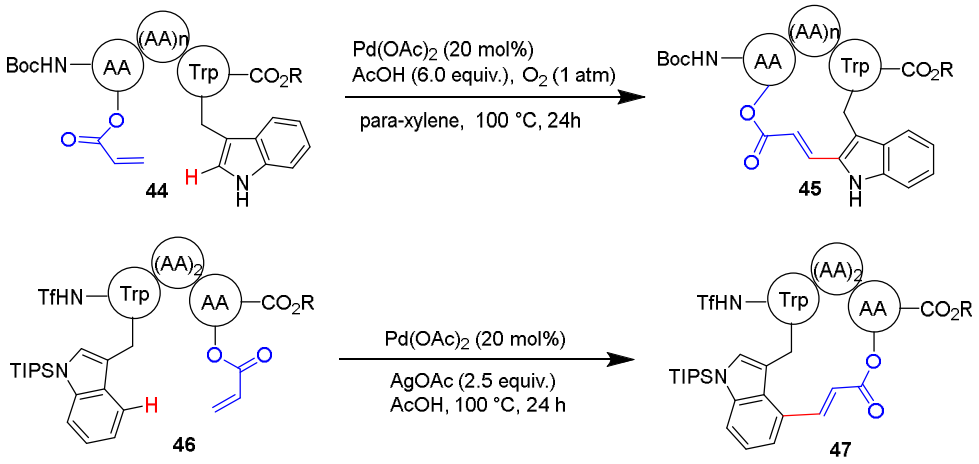
Scheme 12. Pd-catalysed C4 alkenylation of tryptophan derivatives.



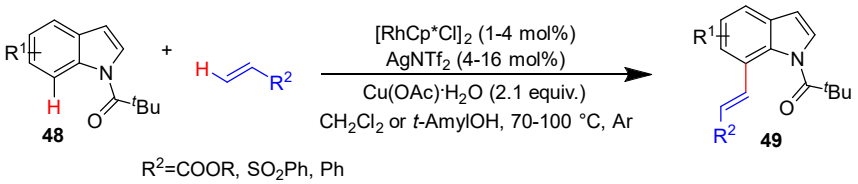
Scheme 13. The C4-alkenylation of indoles using the C3 substituted aldehyde as a directing group.

In 2020, Wang and co-workers developed the Pd-catalyzed CDC reaction for functionalization and macrocyclization of peptides chains **44** and **46**, which allows the regioselective olefination at C2 or C4 position of tryptophan indole residues to give the corresponding macrocyclization products **45** and **47** (Scheme 14).[26] The endogenous peptide backbone can serve as the directing group for the C2 alkenylation of tryptophan residues **44**, whereas the TfNH directing group was utilized to facilitate the alkenylation at the C4 position of the *N*-terminal tryptophan residue **46**. This method is very effective in peptide modification and has great potential in generating peptide macrocycles with complex topological structures and biological correlations.

When 1-position of indoles has been installed a directing group, C–H functionalization of indoles can be site-selectively controlled at C7 position. In 2016, Ma and co-workers developed an efficient method for the Rh-catalyzed C7-alkenylation of indoles **48** using the easily removable *N*-pivaloyl group as a directing group to provide the product **49** (Scheme 15).[27a] The main reason for achieving C7 rather than C2 functionalization is attributed to the formation of a six-membered intermediate over a five-membered intermediate owing to the bulkiness of the *tert*-butyl group.[27b]

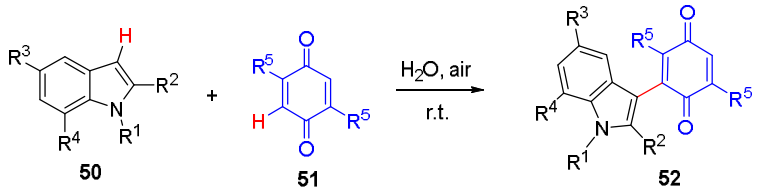


Scheme 14. Pd-catalysed alkenylation of Tryptophan for macrocyclization of peptides chains.



Scheme 15. Catalytic C7-alkenylation of indoles with various olefins.

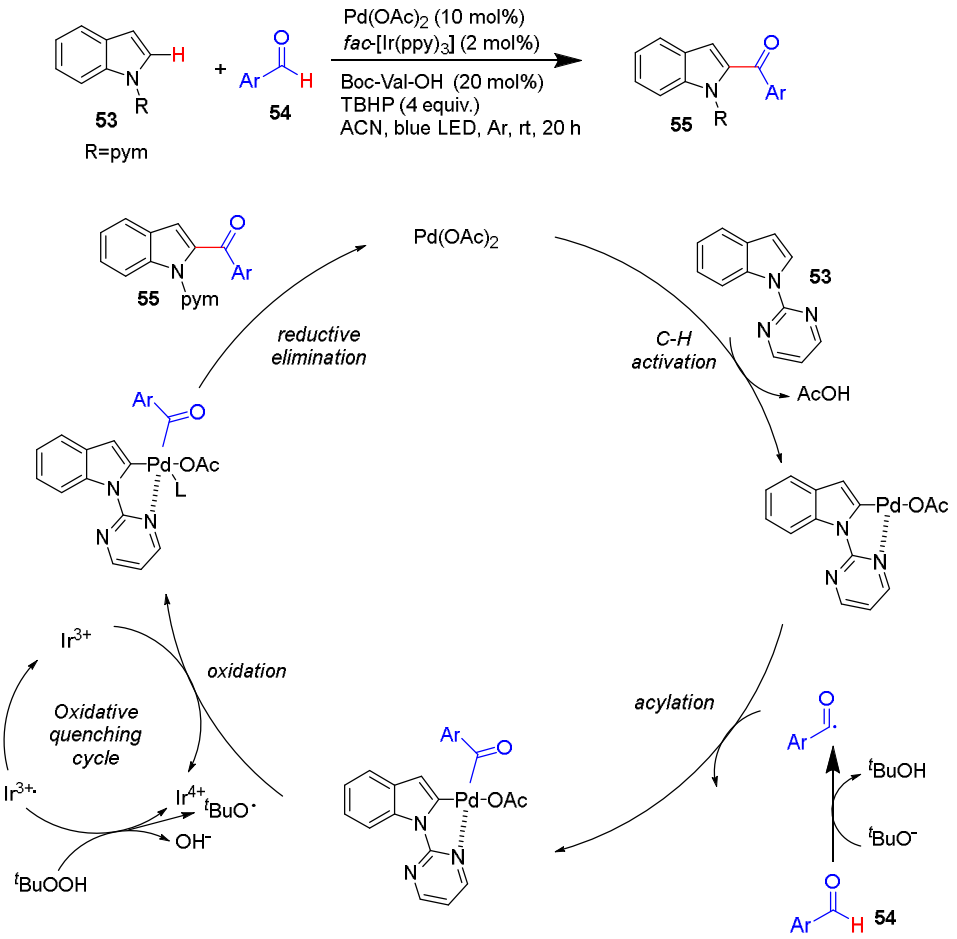
3-Indolylquinone, especially bis(indolyl)quinone, compounds such as asterriquinone A1 and demethylasterriquinone B1 as important structural units widely exist in many natural products and bioactive molecules. The dehydrogenative coupling of indole compounds with 1,4-benzoquinones under the catalysis of Lewis acids or protic acids in the presence of oxidant provided the most direct approach to 3-indolylquinones.[28a-c] In 2006, Wang, Li and co-workers developed a highly efficient direct coupling between indoles **50** and 1,4-benzoquinones **51** in pure water to give 3-indolylquinones **52** (Scheme 16).[28d] This reaction did not require any catalyst, organic cosolvent, or additive, and a notable "on water" acceleration was observed, which provided an efficient method for the synthesis of bis(indolyl)-1,4-quinones.



Scheme 16 Coupling of indoles with 1,4-benzoquinones "on water".

The acylations of indoles at C3 position are well known through the Friedel-Crafts acylation and Vilsmeier-Haack reaction in the literature. By installing amide, pyridine or pym at 1-position as the directing auxiliary, C2 acylation of indoles with aldehydes *via* CDC reaction could be achieved under the catalysis of transition metal such as Pd or Rh.[29] In 2017, Eycken and co-workers reported a dual photoredox/transition-metal-catalyzed C2-acylation of *N*-pyrimidylindoles **53** in batch and flow (Scheme 17).[30] By the Pd(II) and Pd(IV) catalytic cycle and Ir-catalyzed photoredox with TBHP in acetonitrile, the

reaction of *N*-pyrimidylindoles **53** with a series of aldehydes **54** could provide the C2-acylated indoles **55** under mild reaction conditions.



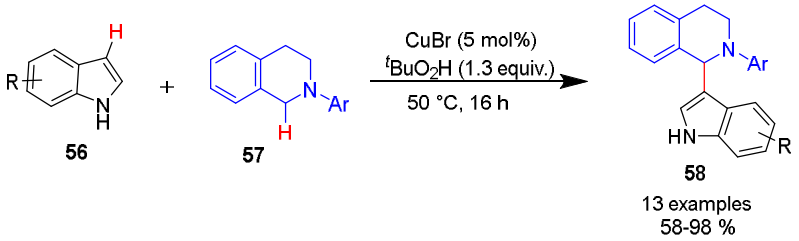
Scheme 17. Pd-catalyzed direct C2-acylation of indoles with aldehydes.

4. Coupling of indole C*sp*^{2}–H with C*sp*^{3}–H

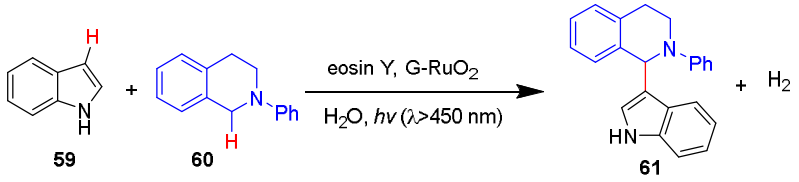
Although the C3 alkylation of indoles has long been achieved through Friedel-Crafts alkylations, allylic alkylations, and conjugate additions, the first catalytic coupling of C*sp*^{3}–H bond with indoles C–H bond *via* the CDC reaction was reported by Li and co-workers in 2005 (Scheme 18).[31] Under the catalysis of CuBr with TBHP as the oxidant, a series of *N*-aryl tetrahydroisoquinolines **57** could react with unprotected indoles **56** to provide the alkylation product of indoles at C3 **58**. If C3 was blocked, the C2 alkylation of indoles could occur. The plausible mechanism involves the Cu-catalyzed generation of tetrahydroisoquinoline imine cations which subsequently react with the indoles **56** in an electrophilic aromatic substitution. Based on this research, the scope of cross-dehydrogenative Friedel-Crafts-type arylation was significantly expanded to various proelectrophiles including *N,N*-dialkylanilines and *N*-alkyl amides or amino acids.[32]

In the following years, the scope of CDC reactions of indoles with amino ortho C*sp*^{3}–H was significantly improved by the development of various highly efficient metal or metal-free catalyst systems, recyclable catalysts as well as photochemical and electrochemical catalytic systems.[33] For example, Wu and co-workers developed a photocatalytic cross-coupling hydrogen evolution (CCHE) reaction of *N*-aryl

tetrahydroisoquinolines **60** with indoles **59** in water (Scheme 19).[34] Under visible light irradiation with eosin Y as a photosensitizer and a graphene-supported RuO_2 nanocomposite (G-RuO_2) as a catalyst, the desired cross-coupling products **61** and H_2 were obtained at room temperature.

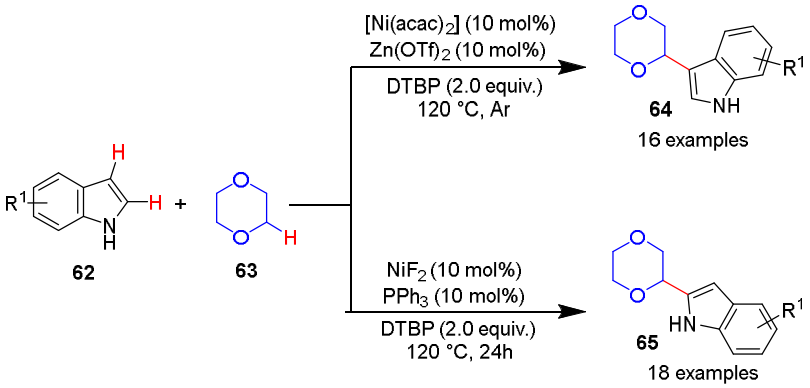


Scheme 18. Cu-catalyzed alkylation of indoles with tetrahydroisoquinolines.



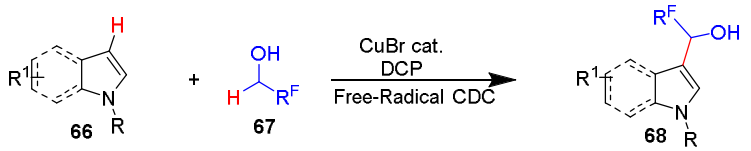
Scheme 19. The alkylation of indoles by the CCHE reaction.

The Csp^3–H bonds adjacent to oxygen atoms usually have relatively lower bond dissociation energy (BDE) and can be functionalized by CDC reaction. In 2015, Cai and co-workers reported a Ni(II)-catalyzed CDC reaction of cyclic ethers **63** with indoles **62** (Scheme 20).[35] Interestingly, when $Ni(acac)_2$ was used as the catalyst and $Zn(OTf)_2$ as an additive, the coupling of indoles **62** with cyclic ether **63** selectively occurred at C3 position of indole **64**. By contrast, when NiF_2 and triphenylphosphine were used, the C2 alkylated oindoles **65** were obtained.



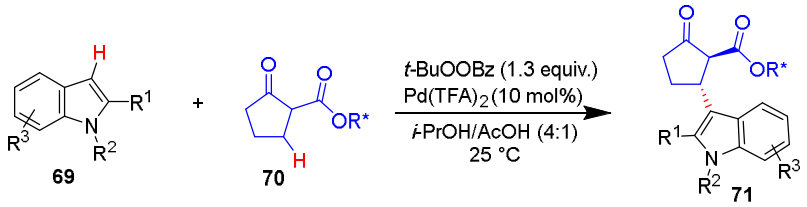
Scheme 20. Ni-catalyzed site-selective alkylation of indoles with cyclic ether.

In 2016, Liu and co-workers developed a CuBr-catalyzed CDE reaction of electron-rich *N*-heteroaromatics **66** with fluorinated alcohols **67** (Scheme 21).[36] The C3 alkylation of indoles **66** with fluorinated alcohols **67** proceeded to give the product **68** through a free-radical-initiated Friedel-Crafts reaction of aldehydes and indoles.



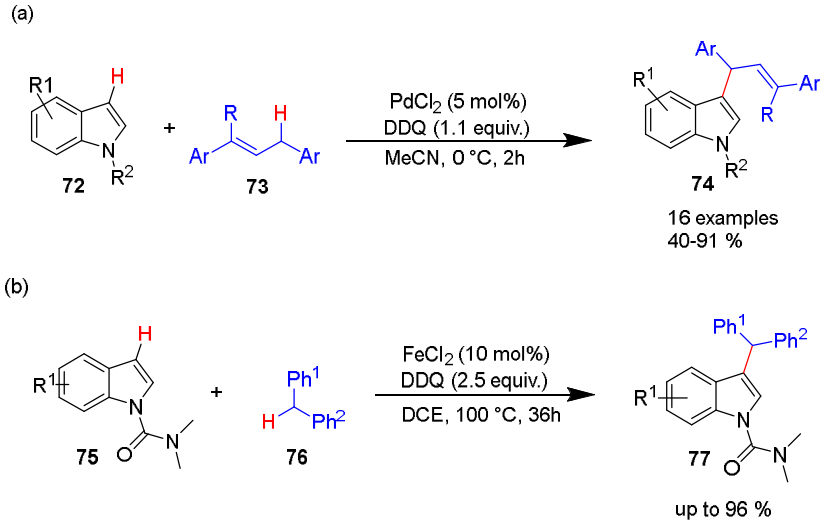
Scheme 21. CuBr-catalyzed alkylation of indoles with fluorinated alcohols.

The alkylation of indoles **69** with β-keto esters **70** could also be achieved by Pd(II)-catalyzed CDC reaction to provide the alkylated indoles **71** (Scheme 22).[37] The mechanistic studies show that this reaction undergoes a Friedel-Crafts-type addition of enone intermediate with indoles.



Scheme 22. Pd-catalyzed alkylation of indoles with β-keto esters.

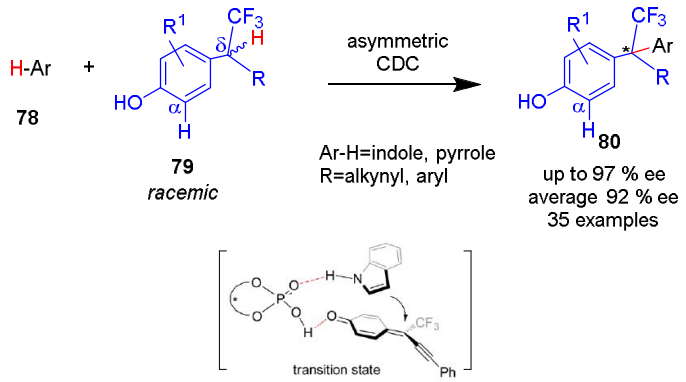
For the alkylation of indoles, allylic compounds as well as diphenylmethanes have been disclosed as proelectrophiles. In 2009, Bao and co-workers reported a $PdCl_2$-catalyzed allylation reaction of indoles **72** (Scheme 23a).[38] Using DDQ as the oxidant, various indole derivatives **72** were successfully coupled with 1,3-diarylpropenes **73** to form the CDC products **74**. For the coupling reaction of *N*-substituted indoles **75** with diphenylmethanes **76**, $FeCl_2$ was found to be a good catalyst in the presence of DDQ for the C3 alkylation of indoles **77** through a Friedel-Crafts reaction of carbocation intermediates with indoles (Scheme 23b).[39]



Scheme 23 The C3 alkylation of indoles with allylic compounds and diphenylmethanes.

In 2020, Liu and co-workers developed an enantioselective CDC reaction for the C3 alkylation of indoles **78** (Scheme 24).[40] By using catalytic DDQ with MnO_2 as an inexpensive terminal oxidant and under the catalysis of chiral phosphoric acid, the asymmetric cross-coupling of racemic *p*-hydroxybenzyl-CF_3 moieties

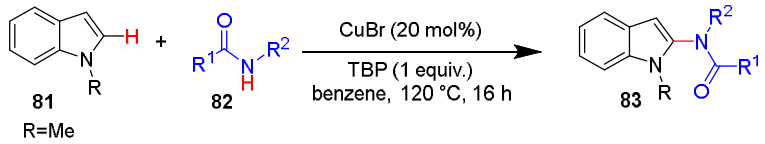
79 with indoles **78** provided the alkylated indoles **80** with CF_3-substituted all-carbon quaternary stereocenter in excellent enantioselectivities. A plausible transition state was proposed for the addition of indoles **78** to *p*-QM intermediates generated in situ through chiral phosphoric acid-catalyzed dehydration of *p*-hydroxybenzyl alcohols **79**.



Scheme 24. Asymmetric alkylation of indoles with *p*-hydroxybenzyl-CF_3 moieties.

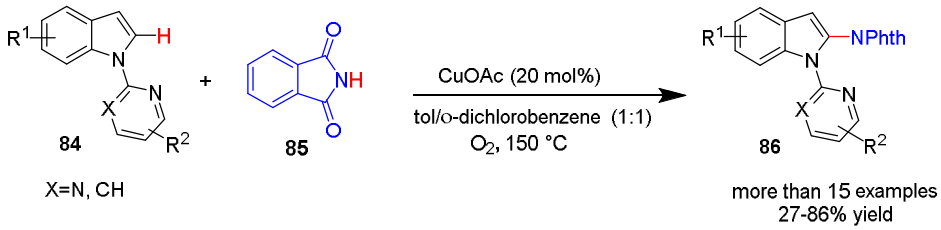
5. Coupling of indole C*sp*^{2}–H with X–H

(Hetero)arylamines are core structures in many natural products, pharmaceuticals, agrochemicals and organic materials. Many synthetic methodologies, including CDC reactions, have been reported for the construction of C–N bonds. In 2010, Li and co-workers reported a Cu-catalyzed CDC reaction of 1-methyl indoles **81** or 2-aryl pyridine with a variety of amides **82** (Scheme 25).[41] By employing *tert*-butyl peroxide (TBP) as an oxidizing agent, the C–N coupling of indoles **81** with *N*-aryl amides **82** provided the C2 amidated indoles **83**.



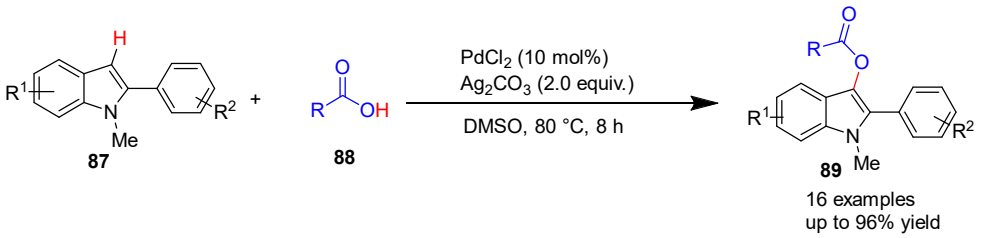
Scheme 25. Cu-catalyzed C–N coupling of indoles with amides.

Later, Shen and co-workers reported a Cu-catalyzed C–N coupling reaction of indoles **84** with phthalimide **85** as the aminating source and oxygen as the oxidant (Scheme 26).[42] With *N*-pyrimidyl or pyridyl group as a directing group, the C−H amination selectively occurred at C2 position of indoles **86**.



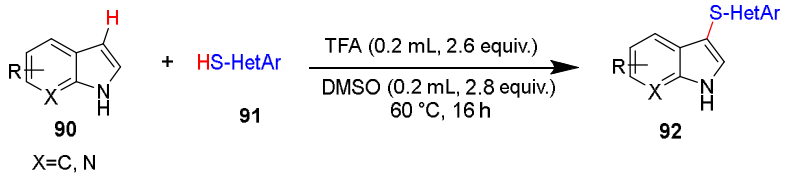
Scheme 26. Cu-catalyzed C–N coupling of indoles with phthalimide.

In 2018, Liu and co-workers reported a Pd-catalyzed CDC reaction of indoles **87** with carboxylic acid **88** (Scheme 27).[43] With an excess of Ag_2CO_3 as the oxidant, the coupling reaction of 2-arylindoles **87** with carboxylic acid **88** provided C3 acetoxylated indoles.**89**.



Scheme 27 Pd-catalyzed acetoxylation of 2-arylindoles.

In 2022, Nguyen and co-workers described a metal-free CDC reaction of indoles **90** with hetaryl thiols **91** (Scheme 28).[44] Under the promotion of TFA/DMSO system, indole derivatives **90** could react with hetaryl thiols **91** to provide C–S bond coupling product **92** at C3 position of indoles. The plausible mechanism involves the dehydrogenation dimerization of heterocyclic thiols **91** with DMSO as an oxidant; then, the disulfide undergoes an acid-catalyzed nucleophilic attack of indole **90** to generate the C3 sulfenylated indoles **92** after deprotonation.



Scheme 28. The C3 sulfenylation of indoles with hetaryl thiols.

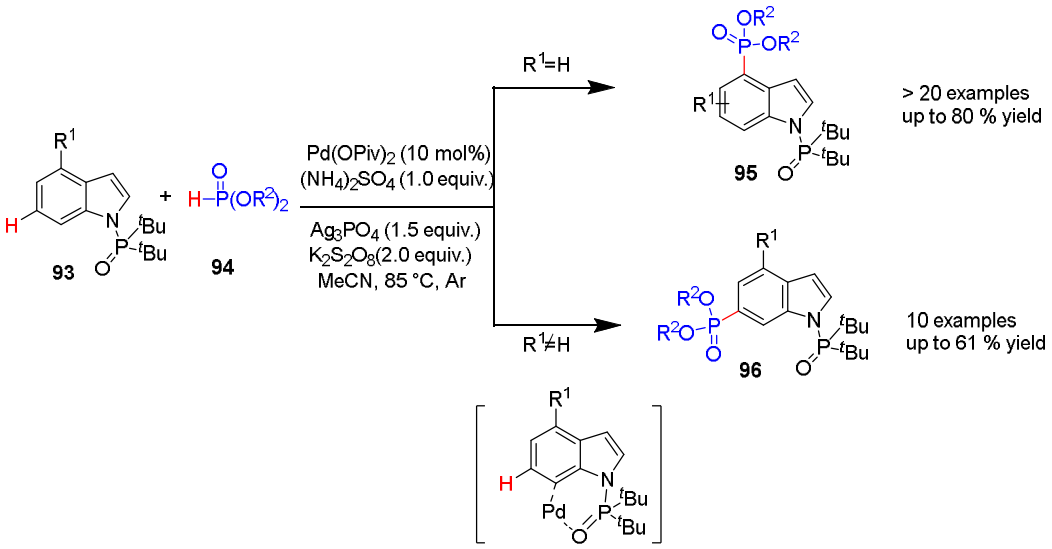
Phosphorous-substituted heterocycles have received much attention in medicinal chemistry and functional materials. In 2021, Shi and co-workers reported a Pd-catalyzed selective C–H phosphonylation of *N*-P(O)^{t}Bu$_2$ (TBPO)-protected indoles **93** at C4 or C6 position by a radical approach to construct C–P bond (Scheme 29).[45] With di-*tert*-butylphosphinoyl at 1-position as an effective directing group, a series of indole derivatives **93** including tryptophan and tryptophan-containing dipeptides could react with phosphites **94** to provide C4-phosphonylated indoles **95**. Notably, the C6-phosphonylated indoles **96** were obtained when the C4 position of indole substrates **93** was blocked. The preliminary mechanistic studies indicated that the reactions might proceed *via* a C7-palladacycle/remote-activation process and the steric/ electronic property of the phophinoyl directing group may play an important role in site-selectivity control.

6. Coupling of oxindole C*sp*^{3}-H with C–H and X–H

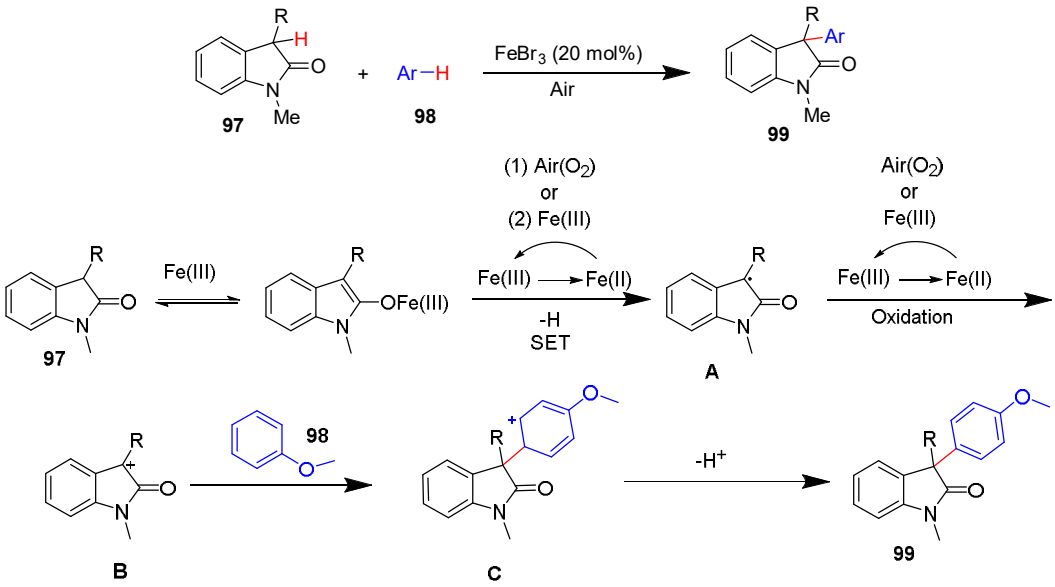
The oxindoles are also core structures of natural products and biologically active pharmaceutical molecules. The functionalization of oxindoles C*sp*^{3}–H bonds through dehydrogenative coupling reaction provides a new approach for green and efficient synthesis methodology. In 2015, Liu, Li and co-workers developed a new and efficient Fe-catalyzed cross-dehydrogenative arylation of 3-substituted oxindoles **97** with electron-rich aromatic and heteroaromatic compounds **98** using aerobic oxygen as an oxidant source (Scheme 30).[46] The proposed mechanism shows that the enol form of oxindole **97** is oxidized by Fe(III) to the corresponding radical **A** *via* a single-electron-transfer (SET). Then radical **A** is further oxidized to the cation species **B** by air or Fe(III). Finally, a Friedel-Crafts type reaction of intermediate **B** with an electron-rich aromatic **98** provides the desired 3-aryloxindole product **99**.

Subsequently, the Fe(III)-mediated strategy was applied to the reaction of 3-benzyl-2-oxindoles **100** with styrene derivatives **101** for the rapid construction of spirocyclohexene oxindoles **102** (Scheme 31).[47] With

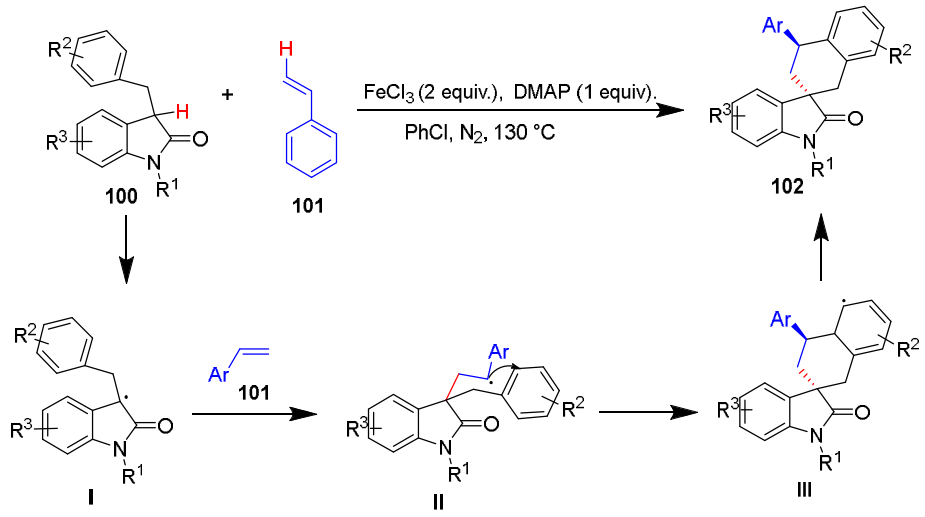
the above similar mechanism, a 3-benzyl-2-oxindole radical **I** adds to styrene to provide radical intermediate **II**, which undergoes an intramolecular cyclization to generate radical **III** with high diastereoselectivity. Finally, an Fe(III)-mediated oxidation of the radical intermediate **III**, followed by the loss of H^+, affords the desired spiro-oxindole product **102**.



Scheme 29 Pd-catalyzed selective C4/C6 phosphonylation of *N*-TBPO protected indoles.

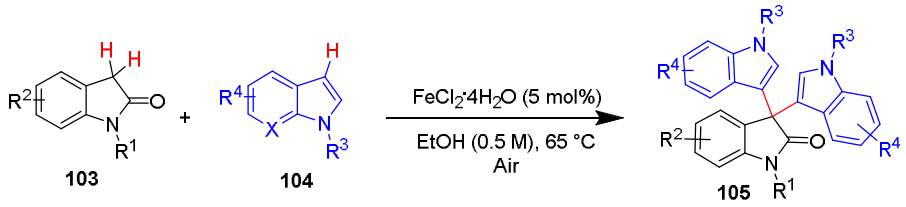


Scheme 30. Fe-catalyzed arylation of 2-oxindoles.



Scheme 31. Fe-catalyzed reaction of 3-benzyl-2-oxindoles with styrene derivatives.

Using $FeCl_2 \cdot 4H_2O$ as the catalyst and employing air (molecular oxygen) as the terminal oxidant, the cross-coupling of oxindoles **103** with indoles **104** could provide bis-arylation products of oxindoles **105** (Scheme 32).[48]



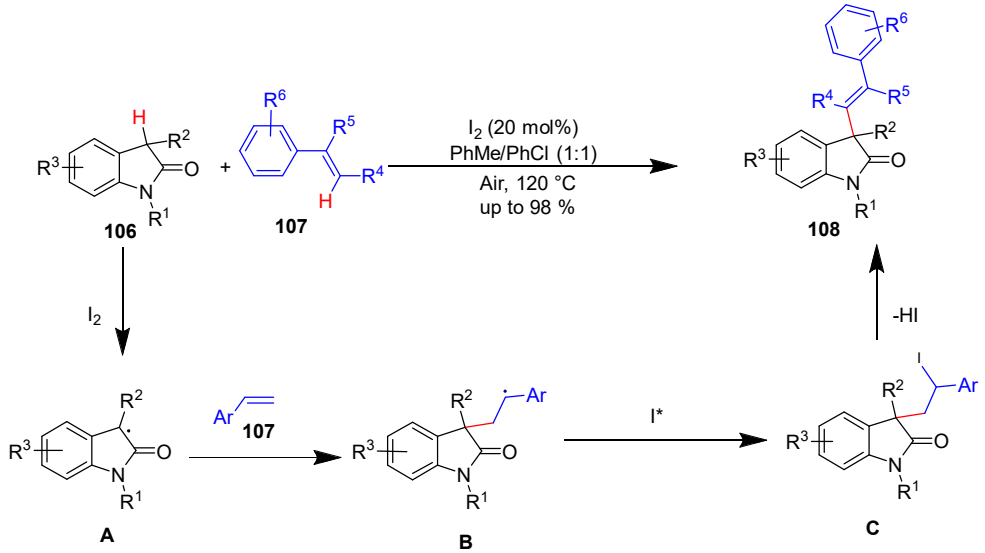
Scheme 32. Fe-catalyzed bis-arylation of 2-oxindoles.

Besides using Fe(III) to promote the CDC reaction of oxindoles with styrenes, Liu and co-workers reported an iodine-catalyzed direct olefination of 2-oxindoles **106** and alkenes **107** *via* CDC in air (Scheme 33).[49] The reaction has a wide substrate adaptability, and 3-alkyl or aryl substituted oxindoles **106** could react with styrene derivatives **107** to provide 3-alkenyl-2-oxindoles **108**. In a possible mechanism, an oxindole radical **A** formed by iodine oxidation was captured by styrene **107** to generate a benzyl radical **B**. Subsequently, the intermediate **B** was quenched by iodine radical to provide intermediate **C**, which eliminated a HI to give the olefination product of 2-oxindole **108**.

In many CDC reactions of 2-oxindoles, oxidative dimerization of 2-oxindoles was observed. Actually, 3-substituted oxindole radicals are known as persistent tertiary carbon radicals and accessible from both monomer and the homolytic of dimer.[50] Sohtome, Sodeoka and co-workers developed a regioselective arylation of oxindoles **109** with 4-substituted catechols **110** (Scheme 34).[51] Oxindole monomer is less reactive than its dimer under aerobic conditions. The oxidative cross-coupling reaction of oxindole dimers **109** with catechols **110** gave the C5-selective coupling products **112** under the catalysis of binuclear (±)-Pd(II)-BINAP complex, while the C6 products **111** were obtained under catalyst-free conditions. Based on the studies of reaction mechanism, the persistent radical generated from the homolytic of oxindole dimers **109** reacting directly with catechols **110** or Pd(II)-catecholates is the regio-determining step.

In 2019, Kozlowski and co-workers reported a Pd-catalyzed dehydrogenative coupling of nucleophilic C−H with benzylic C−H to construct Csp^3−Csp^3 bond.[52] According to this strategy, oxindoles and

benzofuranones **113** could react with aromatic hydrocarbons **114** to provide the alkylation products **115** under Pd-catalysis and $K_2S_2O_8$ as oxidant (Scheme 35).[52] Mechanistic studies show that the process is the catalytic activation of the terminal position Csp^3–H bond of the tolyl analogs **114** under oxidizing conditions and the key intermediate reacts with the generated oxindole dimer to form hindered quaternary centers at the 3-position of oxindoles. The available substrates for the CDC reactions have the C–H bond dissociation energy (BDE) in the range of 60-70 kcal/mol which are smaller than that of toluene (90 kcal/mol).



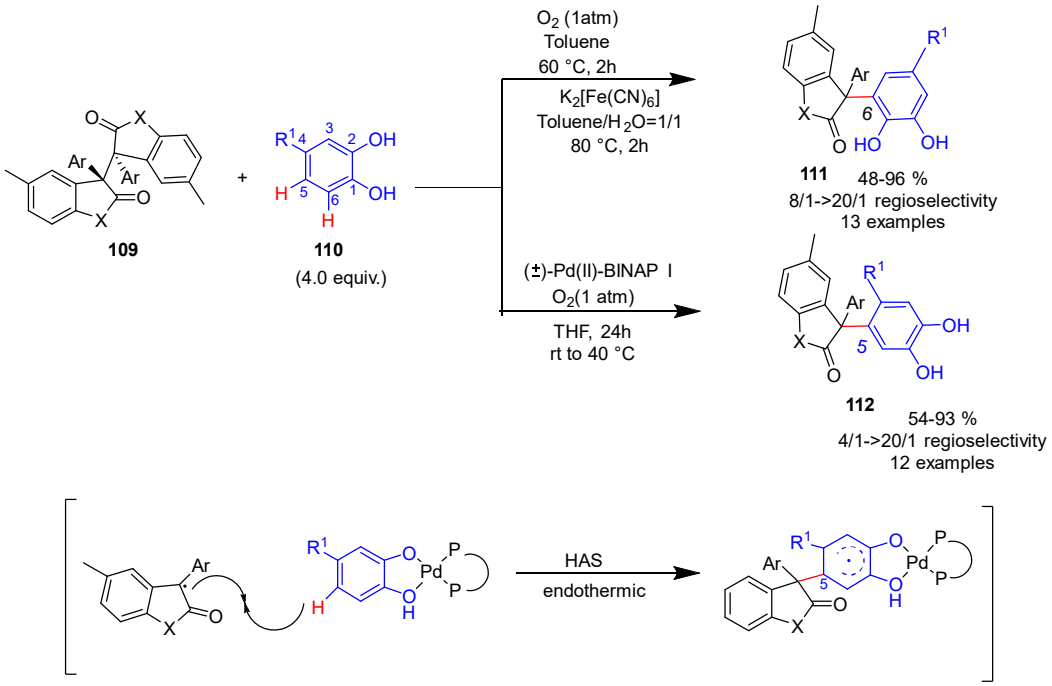
Scheme 33. Iodine-catalyzed alkenylation of 2-oxindoles with styrene derivatives.

Later, the authors realized a metal-free CDC reaction of oxindoles **116** with acetonitrile **117** under the promoter of di-*tert*-butyl peroxide (DTBP), giving the corresponding product alkylation products **118** through radical-radical cross-coupling (Scheme 36).[53]

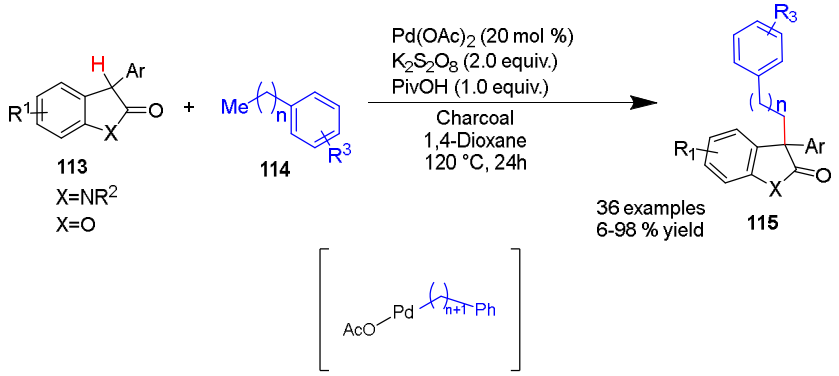
Peroxide bond (C–O–O) is a key pharmacological motif that is widely present in various biologically active molecules. In 2016, Liu and co-workers reported peroxidation reactions of oxindoles **119** using *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP) under the catalysis of Co(salen) in water (Scheme 37).[54] 3-Peroxyoxindoles **120** were obtained under mild conditions through radical-radical cross-coupling. Subsequently, more methods for peroxidation of 2-oxindoles were developed, such as by metal-free onditions or in continuous flow CDC reactions.[55]

The C3-functionalized oxindoles bearing heteroatoms were currently explored as privileged structures in medicinal chemistry. The development of efficient and sustainable approaches for C–X bonds formation of oxindoles has always been of particular interest. Liu and co-workers reported a TBAI/H_2O_2-catalyzed intramolecular dehydrogenative coupling reaction of 3-aminoalkyl-2-oxindoles **121** (Scheme 38).[56] 3,2'-Pyrrolidinyl-spirooxindoles and their 6/7-membered analogs **122** were obtained *via* direct oxidative C–H/N–H coupling.

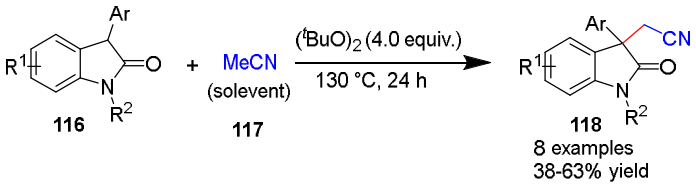
In 2019, Xu and co-workers successfully developed an Fe-catalyzed CDC reaction of oxindoles **123** with aromatic and aliphatic **124** thiols as well as selenols to effectively construct Csp^3–S(Se) bonds (Scheme 39).[57] All these operations are carried out under mild conditions with molecular oxygen as an oxidant and 3-sulfenylated oxindoles were obtained in good yields. In 2020, Loh and co-workers achieved 3-arylation and 3-thiolation of oxindoles **125** through CDC catalyzed by graphene-oxide. This non-metallic strategy has a wide substrate range and good functional group tolerance.[58]



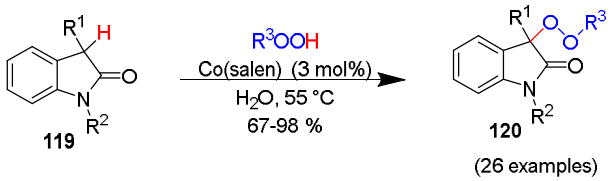
Scheme 34. The regioselective arylation of oxindoles with 4-substituted catechols.



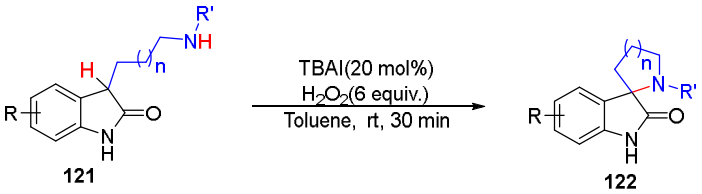
Scheme 35. Pd-catalyzed alkylation of 2-oxindoles with tolyl analogs.



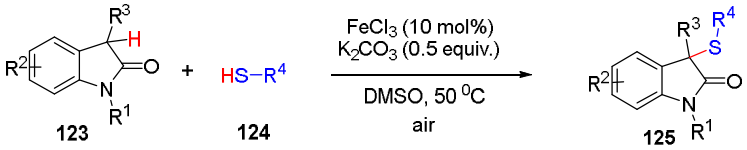
Scheme 36. The alkylation of 2-oxindoles with acetonitrile.



Scheme 37. The peroxidation of oxindoles with TBHP.



Scheme 38. The intramolecular amination of 2-oxindoles.



Scheme 39. The 3-thiolation of oxindoles through CDC.

Conclusions

In summary, the C−H functionalization of indole skeleton and 2-oxindoles by CDC reaction to form C−C or C−X bonds can be accomplished through the mediation of transition metal catalysis or *via* oxidative reactions. Moreover, such conversions can be facilitated or initiated by means of photocatalytic and electrocatalytic processes. By introducing directing groups containing nitrogen, oxygen or sulfur atom into the backbones of indole, site-selective functionalization at the less accessible positions (C4 to C7) of the indole framework can be achieved. This C−H functionalization methodology has witnessed the development of various CDC reactions for a broad application in the modifications of indole molecules. Although CDC reaction has made significant progress in the C−H functionalization of indole derivatives, there are still several challenges, especially in designing new catalyst systems or directing groups for the selective C−H activation at difficult-to-approach positions of aromatic ring, applying oxygen or air as a broadly available and green terminal oxidant, and establishing enantioselective catalytic systems. In addition, developing efficient and green catalytic reactions to achieve large-scale industrial applications is a future research goal.

Acknowledgement

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