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Metal-catalyzed synthesis of five-membered ring N-heterocycles. A recent update

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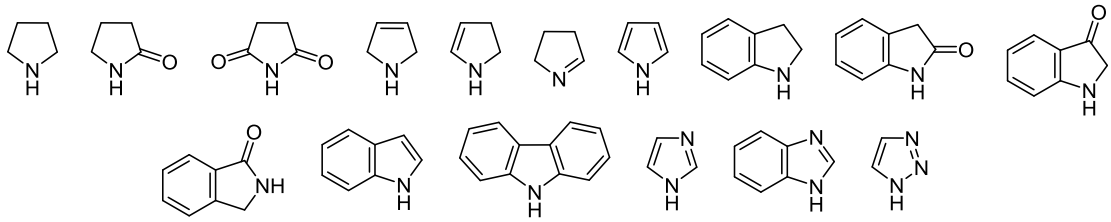


The review deals with the metal-catalyzed synthetic methods used for the construction of 5-membered nitrogen-containing aromatic and nonaromatic heterocycles with one to three nitrogen atoms, published in the years 2008–2017. The methodology is based on the metal-catalyzed activation of the alkyl C(sp^3)–H, alkenyl C(sp^2)–H, and terminal alkyne C(sp)–H bonds of appropriate precursors in order to perform intermolecular and intramolecular reactions. These bond forming reactions include C(sp^3)–C(sp^2), C(sp^2)–C(sp^2), and C(sp^2)–C(sp) coupling, hydroamination at C(sp^2)–H and C(sp)–H bonds, and oxidative amination of alkyl C(sp^3)–H, alkenyl and arene C(sp^2)–H, and terminal alkyne C(sp)–H bonds. Two further bond forming methods are intramolecular nitrenoid–arene C(sp^2) coupling and cycloaddition reactions. Transition metals are systematically used in these synthetic methods, and only in a few cases Lewis acids are used as catalysts. In general, the metal-catalyzed cyclizations leading to five-membered heterocycles are very efficient and particularly useful in the synthesis of natural and unnatural biologically active products.

Keywords: five-membered N-heterocycles, C–H bond activation, C–H bond hydroamination, C–H bond oxidative amination, metal-catalyzed synthesis.

Five-membered nitrogen-containing heterocycles, fused to carbocyclic rings or as monocyclic entities, aromatic or nonaromatic, are important structural subunits that occur in bioactive natural products, pharmaceuticals, agrochemicals, cosmetics, dyes, and functional materials.[1] The present review is organized according to the number of nitrogen atoms, one, two, or three, in the five-membered heterocyclic ring, the size and number of carbocyclic rings, one or two, fused to the heterocycle, and the degree of unsaturation in each ring. It covers the literature on the metal-catalyzed synthesis of five-membered nitrogen heterocycles published from 2008 till 2017. Since during this period there has been no review exclusively dealing with this subject, the current work intends to fill this gap. At the beginning of each ring system coverage, a brief account of the metal-catalyzed synthetic reactions found in review articles, is presented.

1. PYRROLIDINES

Substituted pyrrolidines are significant biologically active molecules, either as single units or part of other structural frameworks.[2] The transition metal-catalyzed synthesis of pyrrolidines *via* C–N bond forming reactions is described in a review articles by Majumdar[3] and Zhang.[4] Here, the most widely used method of synthesizing pyrrolidines is intramolecular hydroamination of amino olefins with Ph_3PAuCl and AgOTf or [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl and AgOTf catalysts.

Several review articles survey other reaction types. Liu and Fu[5] describe an efficient $CuBr_2$-catalyzed one-pot tandem hydroamination–alkynylation of alkynes under microwave heating and also the coupling reaction of aldehydes, glycylsultam, and alkenes using $Cu(MeCN)_4PF_6$ or CuOAc as catalysts, and 1,2-bis(diphenylphosphino)butane (dppb) or 1,1'-bis(diphenylphosphino)ferrocene (dppf) as ligands. Wu et al.[6] describe a Pd(II)-catalyzed intramolecular aminocarbonylation of olefins bearing many types of nitrogen nucleophiles using among others $PdCl_2(MeCN)_2$/CO/O_2, $Pd(CF_3CO)_2CO$/ligand, or $Pd(PhCN)_2Cl_2$/$In(OTf)_3$/CuCl/CO as catalysts. In another article, Majumdar et al.[7] refer to the $FeCl_3$-catalyzed, domino aza-Cope–Mannich rearrangements between 2-hydroxy homoallyl or propargyl tosylamines and aldehydes and intramolecular hydroamination of amino olefins. Nandakumar et al.[8] describe

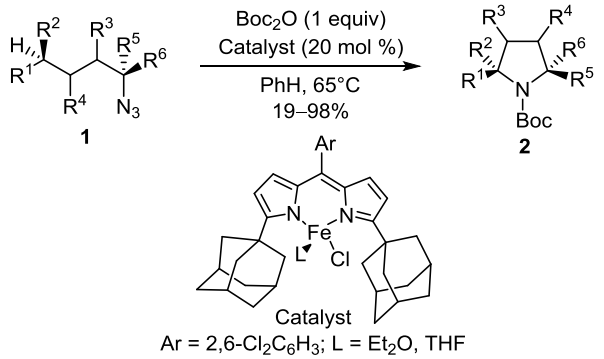
the transition metal-catalyzed hydrogen-transfer strategy in the *N*-alkylation of amino alcohols, diols, and amines with dienes using [$RhH(PPh_3)_4$], [{$Ru(p$-cymene)Cl_2}$_2$], or [$HClRu(CO)(PPh_3)_3$] as catalysts. Liu and coworkers[9] mention pyrrolidine formation *via* the C–H/N–H coupling of butylamines where AgOAc together with 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) were the catalysts and $PhI(OTFA)_2$ served as the oxidant.

Among the most important methods for assembling pyrrolidines is 1,3-dipolar cycloaddition. A good example is the Fesulphos/$Cu(MeCN)_4ClO_4$-catalyzed enantioselective 1,3-dipolar cycloaddition of azomethine ylides to 2-methylpropenal.[10] Another efficient method is the combining of organocatalysis and $Au(PPh_3)Cl/AgBF_4$ catalysis in the addition of a nitroallene to *N*-acylimines followed by cyclization or the enantioselective $Pd(dba)_2$-catalyzed reaction of *N*-acylimines with an allyl acetate in the presence of chiral phosphoramidite ligand.[2] In the review by Chen and Xu,[11] the majority of pyrrolidine syntheses refer to the Rh(I)-catalyzed, asymmetric ene-type cyclization of nitrogen atom-bridged 1,6-enynes, cyclization of alkynals and alkynones, and the intramolecular hydroacylation of ketones and alkenes.

1.1. {CCCCN} cyclization

Hennessy and Betley[12] have developed an iron dipyrrinato catalyst (Scheme 1) that can selectively aminate sp^3 C–H bonds. It is postulated that oxidation of the Fe(II) by the alkyl azide produces an Fe(III)-bound imido radical after elimination of nitrogen. Intramolecular H atom abstraction generates an alkyl radical followed by radical recombination to form the pyrrolidine which reacts with Boc_2O. From aliphatic azides **1**, a large number of polysubstituted *N*-Boc pyrrolidines **2** were synthesized in poor to excellent yields.

Scheme 1

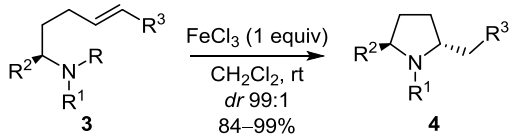


Ar = 2,6-$Cl_2C_6H_3$; L = Et_2O, THF

R^1 = Me, CH_2HC, Et, EtO_2C, $(CH_2)_5$, Ph; R^2 = H, Me, $(CH_2)_5$, Ph
R^3 = H, Et; R^4 = H, Me, TMSO, Ph; R^5 = H, Me; R^6 = H, Me, Ph

Hydroamination is a process that involves metal-catalyzed direct addition of nitrogen and hydrogen atoms to carbon–carbon multiple bonds. Olefins **3** were subjected to a diastereoselective, $FeCl_3$-catalyzed intramolecular hydroamination and cyclization reaction to afford enantiopure *trans*-2,5-disubstituted pyrrolidines **4** in excellent yields (Scheme 2).[13] It was found that high yields depended on using a stoichiometric amount of the catalyst.

Scheme 2

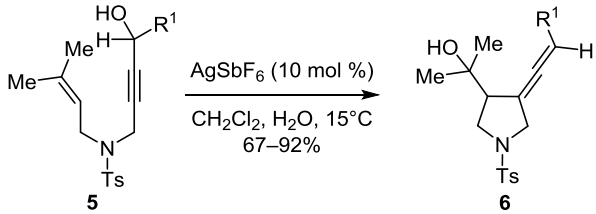


R = H, Boc; R^1 = Ms, Ts
R^2 = Me, Me_2CHCH_2, Et(Me)CH, *n*-Bu, Bn, CO_2Me
R^3 = H, *n*-Pr, *n*-Bu, CO_2Me

1.2. {CCNCC} cyclization

C–C bond forming transition metal-catalyzed cyclization reactions between alkene and alkyne groups in compounds bridged by a heteroatom is an efficient and simple methodology for the synthesis of, among others, 5-membered heterocycles. Liang and coworkers[14] introduced a novel direct intramolecular $AgSbF_6$-catalyzed process for C–C bond formation between the electrophilic propargylic alcohol and nucleophilic olefin moieties of compounds **5** leading to pyrrolidines **6**. The reaction requires trace amounts of water and gives good to excellent yields (Scheme 3).

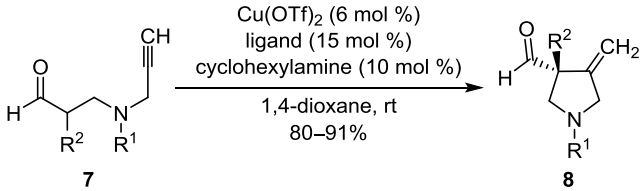
Scheme 3

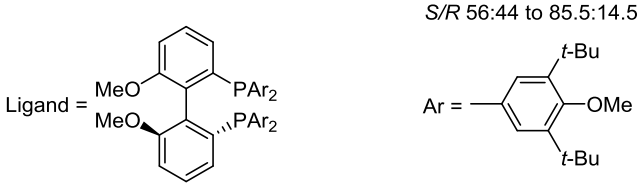


R^1 = Et, Ph, 3-MeC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 2-FC_6H_4, 2-Fur

Vidal, Michelet, and coworkers[15] studied in detail the use of a copper(I)-based metallo-organocatalytic system for the cyclization of *N*-bridged alkynyl aldehydes **7** to produce enantioenriched pyrrolidines **8** (Scheme 4). They demonstrated the superiority of the $Cu(OTf)_2$ catalyst over the $InCl_3$ catalyst. The catalytic synergy between the (*R*)-phosphane ligand copper(I) complex and cyclohexylamine is responsible for the moderate enantioselectivities (by chiral HPLC) and very good to excellent yields of the heterocycles.

Scheme 4



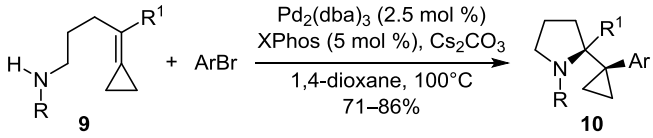


R^1 = Ts, 4-$O_2NC_6H_4SO_2$, 2,3,5-$Me_3C_6H_4SO_2$, 2,3,5-(*i*-Pr)$_3C_6H_4SO_2$
R^2 = Me, *n*-Bu, Bn, 4-$MeOC_6H_4CH_2$, $BnO(CH_2)_2$

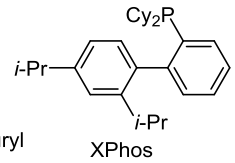
1.3. {CCCCN} cyclization and {C} addition

Eichman et al.[16] introduced an intramolecular carboamination of *N*-(4-cyclopropylidenebutan-1-yl)amides **9** in the presence of aryl bromides for the synthesis of 2-cyclopropylpyrrolidines **10**, using the catalyst system Pd(0)/XPhos (Scheme 5). The important feature of this reaction is the insertion of a cyclopropyl group in position 2 of the pyrrolidine ring, which can be utilized for subsequent reactions.

Scheme 5

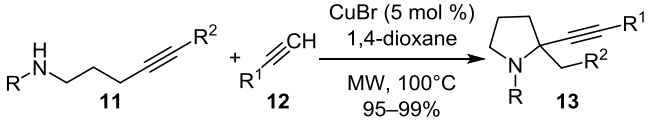


R = *i*-PrO$_2$C, Boc
R^1 = Me, Et, Me(CH$_2$)$_5$
Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-*t*-BuC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 6-MeO-2-naphthyl, 3-furyl



An efficient route to 2-ethynylpyrrolidines **13** is provided by a CuBr-catalyzed, microwave assisted, tandem hydroamination/alkynylation reaction (Scheme 6).[17] The reaction likely involves an intramolecular 5-*endo-dig* hydroamination of inactive terminal ynylamines **11** followed by an intermolecular 5-*exo-dig* addition to the 2-methylenepyrrolidine intermediates by alkyne **12**.

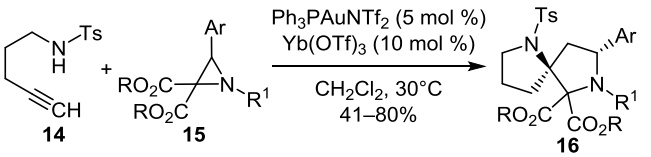
Scheme 6



R = Bn, Ph(Me)CH; R^1 = H, *n*-Bu, MeOCH$_2$, Cl(CH$_2$)$_3$, Ph, Et$_3$Si
R^2 = H, Me, *n*-Bu

Aziridines are useful organic synthons that have been used as masked 1,3-dipoles in cycloaddition reactions. In particular, aziridine-2,2-dicarboxylic acid diesters are known to undergo ring opening to azomethine ylides in the presence of Lewis acids *via* heterolytic C−C bond cleavage. Combining this concept with that of the metal-catalyzed intramolecular 5-*endo-dig* hydroamination of inactive terminal ynylamines (see Scheme 6), Jia, Xu, and coworkers[18] utilized activated azomethine ylides, generated from aziridines **15** in the presence of Yb(OTf)$_3$ (Scheme 7), for the 1,3-dipolar cycloaddition reaction to the 2-methylidene-pyrrolidine intermediate produced by the Ph$_3$PAuNTf$_2$-catalyzed 5-*exo-dig* hydroamination/cyclization of ynylamine **14**. Spiropyrrolidines **16** were obtained in fair to good yields.

Scheme 7

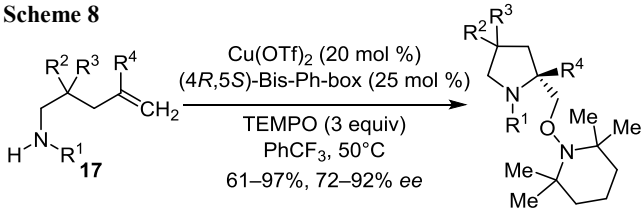


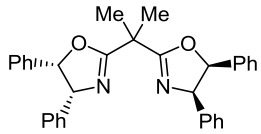
R = Me, Et; R^1 = Ms, Ts
Ar = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-BrC$_6$H$_4$, 2-Naphth

1.4. {CCCCN} cyclization and {O} addition

In 2008, Chemler and coworkers[19] reported a novel Cu(OTf)$_2$-catalyzed enantioselective intramolecular aminooxygenation of olefins **17** that provided chiral pyrrolidines **18** in very good yield and high enantioselectivity (Scheme 8). The (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO) was used to facilitate the Cu(I) to Cu(II) turnover and to trap the methyl radical which is supposedly produced after the Cu(II)-promoted and catalyzed intramolecular C–N bond forming reaction between the amine and alkene groups of the substrate.

Scheme 8

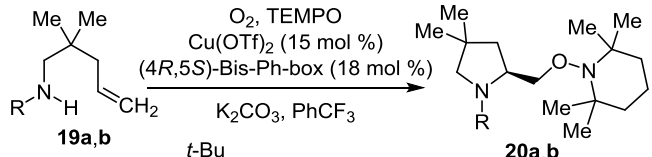




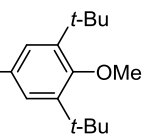
R^1 = Ts, 4-O$_2$NC$_6$H$_4$SO$_2$
R^2, R^3 = H, Me, Ph, CH$_2$O(CH$_2$)$_2$OCH$_2$, CH$_2$OSi(*t*-Bu)$_2$OCH$_2$
R^4 = H, Me

Five years later, Chemler and coworkers[20] performed scale-up experiments on the synthesis of pyrroles **20a**,**b** from substrates **19a**,**b** by varying the protective group and the amount of substrate used (Scheme 9). It became possible to improve the enantioselectivity of this intramolecular aminooxygenation reaction (up to 97% *ee*) with

Scheme 9



a R = Ts
b R = O$_2$S



Amine (load, mmol)	TEMPO (load, equiv)	*T*, °C	Pyrrole (yield, % / *ee*, %)
19a (0.19)	1.5	110	**20a** (97/88)
19a (0.93)	3.0	120	**20a** (19/85)*
19a (0.93)	3.0	110	**20a** (88/86)**
19a (0.93)	1.5	110	**20a** (95/90)
19b (0.76)	1.5	110	**20b** (89/95)
19b (2.53)	1.5	110	**20a** (88/97)

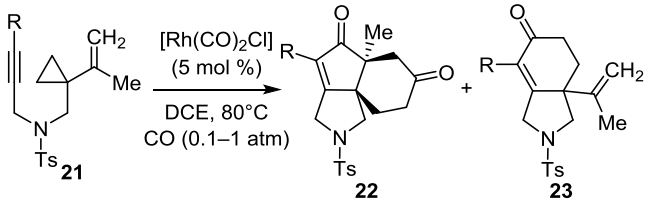
* 80% of the starting alkene **19a** was recovered.
** 9% of the starting alkene **19a** was recovered.

the use of a bulky *N*-substituent in amines **19b**. The optimal ligand for the reaction was (4*R*,5*S*)-Bis-Ph-box while optimal loadings for ligand, catalyst, and TEMPO were 18 mol %, 15 mol %, and 1.5 equiv, respectively. Environmentally benign O_2 was used as the stoichiometric oxidant and the reaction worked efficiently on a gram scale.

1.5. {CCNCC} cyclization and {C} addition

Many angular tricyclic 5,5,6-systems are biologically active natural products making them lucrative targets for synthesis. Yu and coworkers[21] have presented (Scheme 10) a novel [$Rh(CO)_2Cl$]-catalyzed formal [5+1]/[2+2+1] cycloaddition reaction of 1-[(propargylamino)methyl]-1-vinylcyclopropanes **21** and 2 equiv of CO to synthesize 2,3,5a,6,8,9-hexahydro-1*H*-indeno[1,7a-*c*]pyrrole-5,7-diones **22** together with 2,3,7,7a-tetrahydro-1*H*-isoindol-5(6*H*)-ones **23** in varying mediocre yields.

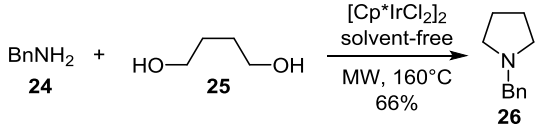
Scheme 10



1.6. {CCCC + N} cyclization

Mono-, di-, and trialkylation of aliphatic amines by aliphatic alcohols has been achieved under solvent-free microwave conditions and [Cp*$IrCl_2$]$_2$ catalysis (Cp* = pentamethylcyclopentadienyl). The additional advantages of this method, compared with other iridium catalysts, are the absence of base and short reaction time (1 h). Among the several secondary and tertiary amines synthesized, 1-benzylpyrrolidine (**26**) was obtained from benzylamine (**24**) and butane-1,4-diol (**25**), in 66% yield (Scheme 11).[22]

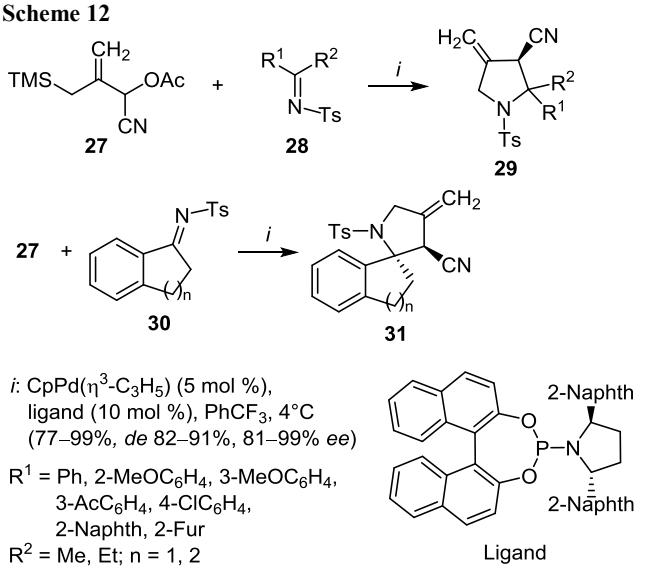
Scheme 11



1.7. {CCC + CN} cyclization

The CpPd(η^3-C_3H_5)-catalyzed asymmetric [3+2] cycloaddition reaction of cyano-substituted trimethylenemethane, delivered in the form of 1-cyano-2-[(trimethylsilyl)methyl]allyl acetate (**27**), with variably substituted ketimines **28** (Scheme 12) in the presence of the bis-(2-naphthyl)phosphoramidite ligand provided 4-methylidenepyrrolidine-3-carbonitriles **29** in good to excellent enantio- and diastereoselectivities. In an analogous manner, spiropyrrolidines **31** were obtained from compound **27** and cyclic imines **30**.[23]

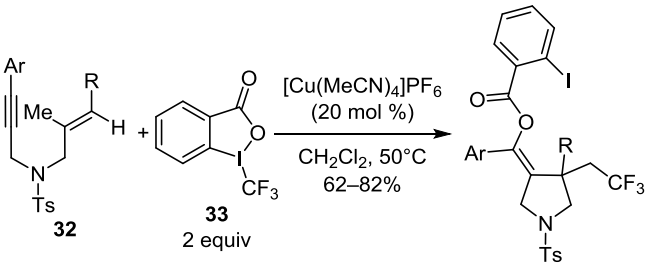
Scheme 12



1.8. {CCC + CN} cyclization

A copper-catalyzed trifluoromethylation–cyclization of enynes **32** by Togni's reagent (**33**) was reported to provide 3-methyl-3-(2,2,2-trifluoroethyl)pyrrolidines **34** in very good yields (Scheme 13).[24] Among the catalysts (CuI, CuCl, CuOAc, $Cu(OTf)_2$, [$CuBr(PPh_3)_3$], $FeCl_2$, and [$Cu(MeCN)_4$]PF_6) and solvents (MeOH, THF, PhMe, DCE, $CHCl_3$, and CH_2Cl_2) used in optimization reactions, the combination of [$Cu(MeCN)_4$]PF_6 and CH_2Cl_2 proved to be the most efficient.

Scheme 13



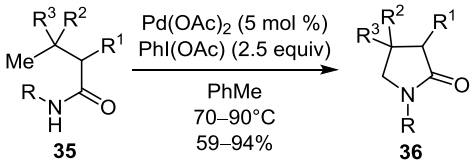
2. PYRROLIDIN-2-ONES

Pyrrolidin-2-ones are widespread motifs in bioactive molecules of both natural and nonnatural origin.[25] Recent syntheses of pyrrolidin-2-ones include the use of three different types of strongly donating N-heterocyclic carbenes complexed with ruthenium catalysts for the intramolecular hydrogen-transfer annulation of 1,4-amino alcohols,[8] Au(I)-catalyzed intramolecular hydroamination of *N*-substituted pent-4-enamides under microwave irradiation,[26] cycloisomerization of *N*-allylpropiolamides with [$Rh(COD)Cl]_2$ and BINAP in the presence of $AgSbF_6$,[11] and the metal (Cu(I), Cu(II), Ru(II), Mn(VI), Fe(II) or Ag(I))-promoted atom transfer radical cyclization of *N*-substituted *N*-allyltrichloroacetamides.[27]

2.1. {CCCCN} cyclization

A new reaction was developed for the synthesis of 3-substituted and 4-mono- or disubstituted pyrrolidin-2-ones **36** from carboxamides **35** (Scheme 14).[28] The reaction proceeds through the $Pd(OAc)_2$-catalyzed intramolecular amination of nonactivated γ-C(sp^3)–H bond of the amide in the presence of $PhI(OAc)_2$ as oxidant.

Scheme 14

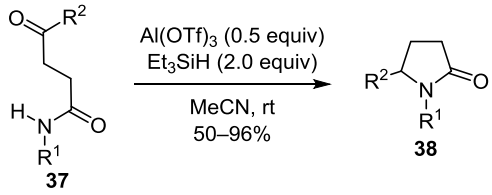


35 **36**

R = 2-Py, 8-quinolyl; R^1 = H, F, 2-phthalyl
R^2 = H, Me, *t*-BuO; R^3 = H, Me

An efficient synthesis of 1-substituted 5-methyl- or phenyl-substituted pyrrolidin-2-ones **38** was discovered by Yin, Wang, and coworkers (Scheme 15).[29] The procedure involves the $Al(OTf)_3$-catalyzed cascade cyclization and ionic hydrogenation reaction of *N*-substituted 4-oxobutanamides or -pentanamides **37**. The reaction is applicable to a wide range of alkyl, aryl, and heterocyclic substituents at position 1 of the pyrrolidinone.

Scheme 15



37 **38**

R^1 = Bn, *n*-pentyl, cyclohexyl, 4-NCC_6H_4, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3-ClC_6H_4, 2-FC_6H_4, $CH_3CO_2CH_2$, 3-thienyl, 1,3-benzodioxol-5-yl, 5-quinolyl; R^2 = Me, Ph

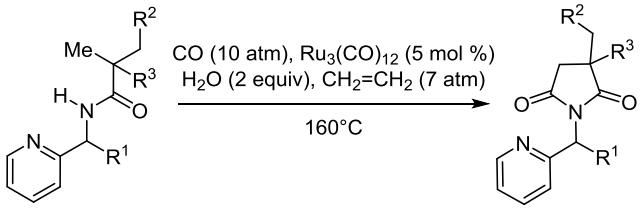
3. PYRROLIDINE-2,5-DIONES

Pyrrolidine-2,5-diones have important applications in organic synthesis as well as in medicinal chemistry. For example, certain compounds of this class exhibit anticonvulsant[30] and tyrosinase inhibitory[31] activities. 1,3,4-Trisubstituted pyrrolidine-2,5-diones were prepared by $Fe_3(CO)_{12}$-catalyzed carbonylation/amination reactions of alkynes in the presence of CO (12 bar) and excess of primary amines at 120°C.[7] The synthesis of 1-aryl-3,3-disubstituted pyrrolidine-2,5-diones was achieved by $Pd(OAc)_2$-catalyzed intramolecular C(sp^3)–H activation and carbonylation of *N*-arylpropanamides using CO in the presence of AgOAc as oxidant and TEMPO as cooxidant. The aryl group in this reaction is *N*-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl].[32]

3.1. {CCCN + C} cyclization

Chatani et al.[33] approached the synthesis of 3,3-disubstituted 1-(2-pyridinylmethyl)pyrrolidine-2,5-diones **40** through a $Ru_3(CO)_{12}$-catalyzed regioselective carbonylation of the inactivated C(sp^3)–H bonds of aliphatic amides **39** (Scheme 16). It was found that the reaction did not proceed when the nitrogen atom in the pyridine ring was in the *meta* or *para* position or if pyridine was substituted by a phenyl group. These observations indicate that coordination of the pyridine nitrogen to the catalyst is essential for reaction to proceed.[34]

Scheme 16



39 **40**

R^1 = H; R^3 = Me; R^2 = H, Et, *n*-Bu, $MeOCH_2$, Bn, $Me_5C_6CH_2$, 4-$MeOC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 2-$BrC_6H_4CH_2$, 3-$BrC_6H_4CH_2$, 4-$CF_3C_6H_4CH_2$, 4-$NCC_6H_4CH_2$ (59–87%)
R^1 = R^3 = H; R^2 = *i*-Pr (68%)
R^1 = H; R^2 + R^3 = cyclohexyl (74%)
R^1 = Ph; R^2 = H; R^3 = Me (59%, *dr* 1:1)

4. DIHYDRO-1*H*-PYRROLES

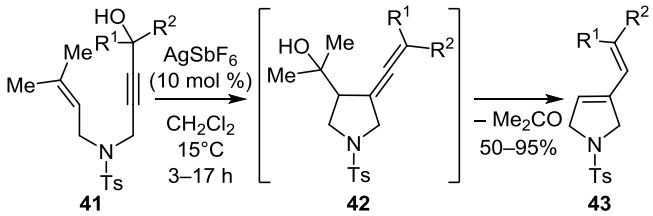
2,3-Dihydro-1*H*-pyrroles (2-pyrrolines) are by far less described in the literature than 2,5-dihydro-1*H*-pyrroles (3-pyrrolines).[35] Some 3-pyrroline derivatives exhibit biological activity[36] and are useful intermediates in the synthesis of heterocyclic compounds.[37] The following reactions refer to the synthesis of 2,5-dihydro-1*H*-pyrroles. *N*,*N*-Diallyl-4-methylbenzenesulfonamide underwent Ru-catalyzed cyclization to afford 1-tosylpyrrole in excellent yield.[26,38] A stereoselective synthesis of 5-alkyl-1-tosylpyrrole-3-carbaldehyde was achieved based on $FeCl_3$-catalyzed domino aza-Cope–Mannich rearrangement reaction between 2-hydroxypropargyltosylamines and aldehydes.[7] Chiral 2,4,5-trisubstituted 1-tosylpyrrole-3-carbaldehydes were synthesized by an unprecedented domino aza-Michael/carbocyclization reaction between α,β-unsaturated aldehydes and *N*-tosylpropargylamines using a novel chiral diphenylprolinol triethylsilyl ether/$PdCl_2$ catalytic system.[10] 3,5-Diaryl-1-tosyl-2,3-dihydro-1*H*-pyrroles could be synthesized *via* $FeCl_3$-catalyzed reaction of 2-aryl-1-tosylaziridines with terminal arylalkynes.[7] The following reactions refer to the synthesis of 2,3-dihydro-1*H*-pyrroles. Thus, 2,3-disubstituted methyl 2,3-dihydro-1*H*-pyrrole-1-sulfonates could be synthesized from α,β-unsaturated aldehydes, terminal alkynes, and methanesulfonyl azide under Rh catalysis.[10] Optically active 2,5-disubstituted *tert*-butyl 3,3-dicyanopyrrole-1-carboxylates were synthesized from *N*-acylimines and 2-propargylmalononitrile derivatives using PPh_3AuNTf_2 as a catalyst. The reaction requires the presence of a quinidine ligand.[2]

4.1. {CCNCC} cyclization

By the reaction of the propargylic alcohol with olefin under anhydrous conditions and silver catalysis, Liang and coworkers[14] synthesized a series of 2,5-dihydropyrroles **43**

(Scheme 17). It was postulated that in the absence of water, allene alcohol intermediate **42**, resulting from the $AgSbF_6$-catalyzed intramolecular cyclization of compound **41**, eliminates acetone to form a 1,3-diene complex with $AgSbF_4$. Protonation of this complex regenerates the catalyst and produces 3-pyrroline **43**.

Scheme 17

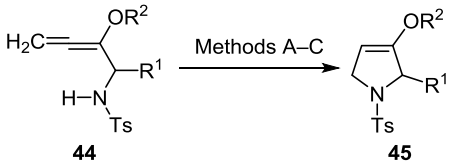


R^1 = H, Me, Ph; R^2 = Ph, CH=CHPh, C≡CPh, C≡CCH$_2$N(Bn)Ts or R^1+ R^2 = Cy, tetrahydronaphthalenyl

4.2. {CCCCN} cyclization

Allenyl *N*-tosylamines **44** were subjected to 5-*endo*-*trig* cyclization with either Ag(I) or Au(I) catalysis to afford 2,5-dihydropyrrole derivatives **45** in good to excellent yields (Scheme 18).[39] A comparison of the following reaction conditions took place: $AgNO_3$ in acetone, $AgNO_3$ in acetonitrile, and AuCl in pyridine while altering the equivalents of the catalyst used. In general, AuCl-catalyzed reactions proceeded with the lowest catalyst loadings and produced the best yields.

Scheme 18

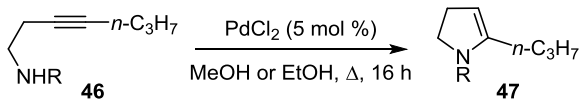


Method A: $AgNO_3$ (0.24–0.27 equiv), Me_2CO, rt, 1–3 h
Method B: $AgNO_3$ (0.27 equiv), MeCN, rt, 16 h
Method C: AuCl (0.05 equiv), Py, CH_2Cl_2, rt, 12 h

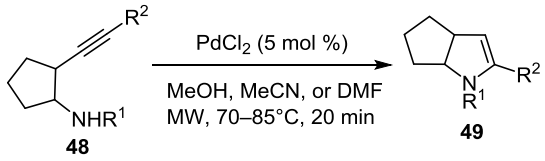
R^1 = Ph, R^2 = Me (93%, Method A)
R^1 = 2-Py, R^2 = Me (80%, Method A)
R^1 = PhCH=CH, R^2 = Me (35%, Method A)
R^1 = *t*-Bu, R^2 = Me (51%, Method A)
R^1 = Ph, R^2 = Bn (82%, Method B)
R^1 = *n*-Hex, R^2 = Bn (51%, Method B)
R^1 = Ph, R^2 = Me (94%, Method C)
R^1 = 2-thienyl, R^2 = Me (100%, Method C)
R^1 = 3-thienyl, R^2 = Me (95%, Method C)
R^1 = 3-thienyl, R^2 = Bn (100%, Method C)
R^1 = 3-thienyl, R^2 = $Me_3Si(CH_2)_2$ (100%, Method C)

Under conventional heating using either MeOH or EtOH as a solvent, $PdCl_2$-catalyzed intramolecular cyclization of *N*-(3-alkynyl)sulfonamides **46** afforded 2,3-dihydropyrroles **47** (Scheme 19).[40] Tosyl derivative in MeOH produced the best yield of the corresponding pyrrole **47**. This reaction has limited applicability because 1-aminoheptan-4-one is a competitive product. However, when cyclopentane derivatives **48** were subjected to microwave irradiation in MeOH, acetonitrile, or DMF, $PdCl_2$-catalyzed intramolecular cyclization afforded dihydropyrroles **49** in low to excellent

Scheme 19



R = Ms (36% in MeOH), Ts (61% in MeOH), Ts (27% in EtOH)

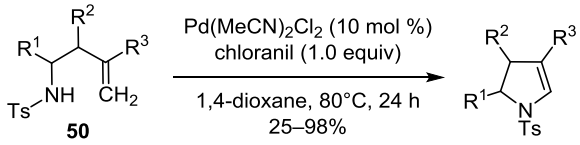


R^1 = Ts, R^2 = Ph (48% in MeOH, 77% in MeCN, 67% in DMF)
R^1 = Ms, R^2 = Ph (27% in MeOH, 71% in MeCN)
R^1 = Ts, R^2 = *n*-Bu (53% in MeCN)
R^1 = Ms, R^2 = *n*-Bu (37% in MeCN)
R^1 = Ts, R^2 = 4-$O_2NC_6H_4$ (87%), 3-ClC_6H_4 (92%), 2-ClC_6H_4 (83%), 2-FC_6H_4 (74%) in MeCN
R^1 = Ms, R^2 = 4-$O_2NC_6H_4$ (84%), 4-$MeO_2CC_6H_4$ (76%), 4-ClC_6H_4 (70%), 4-*t*-BuC_6H_4 (78%), 4-$MeOC_6H_4$ (65%) in MeCN

yields, depending on the solvent and the substitution on the pyrrole ring.

Loh, Xu, and coworkers[41] showed that Pd-catalyzed oxidative intramolecular 5-*endo*-*trig* cyclization of tosyl-protected aminoalkenes **50** provides dihydropyrrole derivatives **51** in poor to excellent yields (Scheme 20). High yields for the majority of products were obtained using $Pd(MeCN)_2Cl_2$ as a catalyst and chloranil as oxidant. An important feature of this reaction is retention of the alkene group functionalization.

Scheme 20



R^1 = *n*-Bu, *t*-Bu, Cy, $BnOCH_2$, Ph, PhCHCH, 4-NCC_6H_4, 2-HOC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 2-Naphth, 2-Fur
R^2 = H, Me; R^3 = Me, $Me(CH_2)_8$, Ph, CF_3, CO_2Et, CO_2n-Bu, CO_2t-Bu, 4-MeC_6H_4, 3-$F_3CC_6H_4$, 2-Naphth

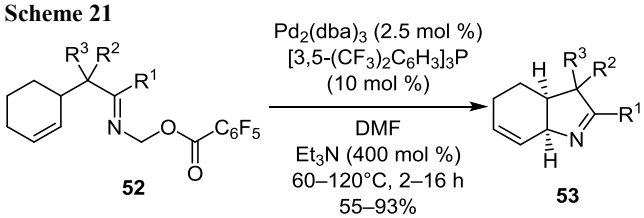
5. 3,4-DIHYDRO-2*H*-PYRROLES

3,4-Dihydro-2*H*-pyrroles (1-pyrrolines) are part of important natural products such as hemes, chlorophyll, alkaloids, etc. They have also been used as scaffolds in drug development.[35] The neutral zirconium(IV) bis-(thiophosphinic amidate) complex is an effective catalyst for 5-*exo*-*dig* intramolecular hydroamination of pent-4-yn-1-amines to give 3,4-dihydro-2*H*-pyrroles.[3]

5.1. {CCCCN} cyclization

The highly efficient $Pd_2(dba)_3$-catalyzed Narasaka–Heck cyclization of cyclic alkene-tethered oxime esters **52** to pyrrole derivatives **53** in good to excellent yields was reported by Bower and Faulkner[42] (Scheme 21). It is postulated that the mechanistic requirements for intramolecular C(sp^3)–N bond formation are *syn*-iminopallada-

Scheme 21



R^1 = Me, *i*-Pr, cyclopropyl, *n*-Bu, *t*-Bu, Ph, 2-Naphth, 4-Py
R^2 = H, Me; R^3 = H, Me, Et, Bn

tion and *syn*-β-hydride elimination. Ligand $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ is necessary for the C(sp^3)–N bond formation, but the reason of its high efficiency remains to be determined.

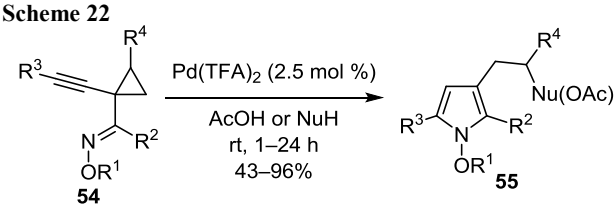
6. 1*H*-PYRROLES

Synthesis of pyrroles by metal-catalyzed cyclization of aliphatic substrates is widely described in the literature. Synthetic methods include trimerization of phenethylamine to 1-phenylethyl-3,4-diarylpyrroles using $PdCl_2$ catalysis and $Cu(OAc)_2$ as oxidant;[43] coupling of a carbonyl compound, an amine, and an α,β-unsaturated nitroalkene on the surface of alumina[38] or catalyzed by $FeCl_3$;[7] cycloisomerization of PhS-substituted allenyl aldehydes and anilines using AuCl or AgOTf catalysis;[44] one-pot multicomponent domino reactions (MDR) of 1,3-diketones, aldehydes, and amines promoted by $TiCl_4$;[45] MDR of carbonyl compounds and 1,2-hydroxylamines or carbonyl compounds, 1,2-diols, and amines catalyzed by $[Ru_3(CO)_{12}]$[46] or a Ir-containing tridentate ligand;[8] and MDR of 1,3-diketones, aldehydes, amines, and nitromethanes catalyzed by $FeCl_3$.[7] Five different syntheses of pyrroles were described in the review by Fu,[5] including the C–N bond forming reaction of 1,4-dihalo-1,3-dienes with *tert*-butyl carbamate catalyzed by CuI and coupling of α-diazooxime ethers with 3-aminoalkenoates, in the presence of a catalytic amount of $Cu(hfac)_2$; three-component CuOTf-catalyzed reaction of α-diazoketones, nitroalkenes, and amines under aerobic conditions;[47] Michael addition of β-enamino ketones or esters with dialkyl ethylenecarboxylates followed by oxidative cyclization catalyzed by CuI under O_2; and cycloaddition of *N*-(allyl or prop-2-yne)-*N*-enamine carboxylates under O_2. There are several reactions where alkynes are one of the two or more components of a reaction. Those are reactions between enamines and alkynes in the presence of $(Cp{\cdot}RhCl_2)_2$ or $[RuCl_2(p\text{-cymene})]_2$ catalysts,[48] 4-acetylenic ketones or pent-2-en-4-yn-1-yl acetates with primary amines and $FeCl_3$ and $PdCl_2$ catalysts, respectively,[7] dimethyl acetylenedicarboxylate and acylated ketoximes under CuCl catalysis,[49] terminal alkynes and 2,2-dimethoxyethanamines catalyzed by PrAuCl,[50] alkynes and enamides with $Pd(OAc)_2$ catalysis,[34] and 2-methylenebut-3-ynals and primary amines with AgOTf as a catalyst.[10] A four-component system comprising of alkynes, imines, acid chlorides, and CO coupled under $PdCl_2$ catalysis was used to produce polysubstituted pyrroles.[6] The alkyne group can also be a substituent of a single intermediate that undergoes metal-catalyzed intramolecular cyclization to the pyrrole ring. Examples are the MW-assisted cyclization of but-3-yn-1-yl azides using $ZnCl_2$ etherate catalyst,[51] $PPh_3PauOTs$-catalyzed ring expansion of aryl-substituted *N*-tosylalkynylaziridines,[50] and the MW-assisted 5-*endo-dig* cyclization of 4-azidobut-1-ynes in the presence of $ZnCl_2$ catalyst.[52] Other important reactions are the PPh_3AuOTf-catalyzed cyclization of β-allenyl hydrazones,[26] the $TiCl_4$-catalyzed condensation of β-amido-α,β-unsaturated aldehydes with α-diaza ketones and esters,[10] and $Pd(OAc)_2$-catalyzed cyclization of disubstituted *N*-allylimines.[32]

6.1. {CCCCN} cyclization and {C}, {O}, or {N} addition

Shi and coworkers[53] (Scheme 22) found that 1-(1-alkynyl)-cyclopropyloxime derivatives **54** underwent $Pd(TFA)_2$-catalyzed tandem heterocyclization in the presence of a nucleophile. The reaction proceeds *via* an intramolecular nucleophilic attack/ring opening followed by another intramolecular nucleophilic attack and protonation to afford highly functionalized pyrroles **55**.

Scheme 22

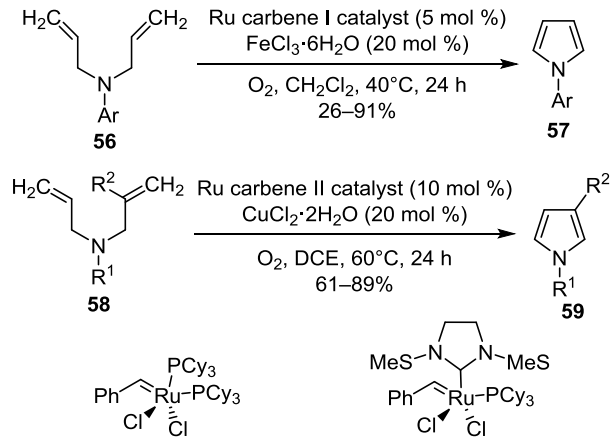


R^1 = H, Me, Ac; R^2 = H, Me, Ph, Bn, 2-$HOCH_2C_6H_4$, 4-MeC_6H_4, 4-PhC_6H_4, 3-$MeOC_6H_4$, 2-FC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 2-$MeO_2CC_6H_4$, 1-Naphth, 2-Fur, 2-thienyl; R^3 = Ph, 4-MeC_6H_4, 4-PhC_6H_4, 3-$MeOC_6H_4$, 2-FC_6H_4, 1-Naphth, 2-Fur, 2-thienyl
R^4 = H, Ph
NuH = MeOH, *i*-PrOH, BnOH, Boc(Ts)NH, $EtO_2C(CN)CH_2$

6.2. {CCNCC} cyclization

Wang and Chen[54] studied the two-phase, Ru carbene I/$FeCl_3{\cdot}6H_2O$-catalyzed ring-closing metathesis reaction and *in situ* oxidative dehydrogenation reaction of diallylamines **56** under an O_2 atmosphere, leading to a series of 1-arylpyrroles **57** (Scheme 23). Substituted diallylamines **58** reacted similarly under Ru carbene II/$CuCl_2{\cdot}2H_2O$

Scheme 23



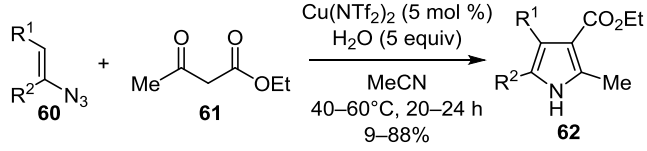
R^1 = 2-MeC_6H_4, 4-$MeC(O)C_6H_4$, 4-$EtO_2CC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 1-Naphth
R^2 = H, Me, Ph

catalysis and O_2 atmosphere to afford 1-substituted or 1,3-disubstituted pyrroles **59**. The yields of the pyrroles in $CuCl_2 \cdot 2H_2O$-assisted metathesis reaction were overall better.

6.3. {CCN + CC} cyclization

Chiba et al.[55] demonstrated the Cu(II)-catalyzed synthesis of substituted pyrroles **62** through the 1,4-addition of ethyl acetoacetate **61** to vinyl azides **60** (Scheme 24).

Scheme 24

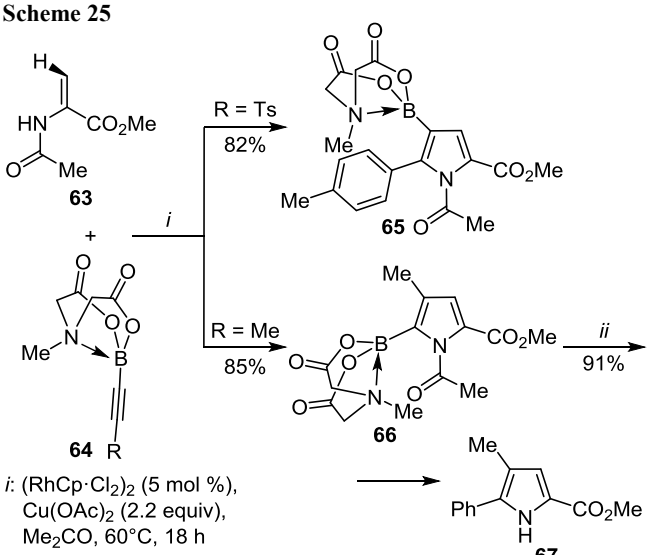


60 **61** **62**

R^1 = H, Bn, 4-MeC_6H_4, 3-$O_2NC_6H_4$, 4-NCC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4; R^2 = H, CO_2Et, CO_2Bn, Ph

Glorius and coworkers[56] found that coupling of methyl 2-acetamidoacrylate **63** with ethynyl MIDA (*N*-methyliminodiacetic acid) boronate **64** (Scheme 25) using a C–H activation/alkyne MIDA boronate annulation strategy, under Rh(III) catalysis, produced pyrrole MIDA boronate **65** when R = Ts and boronate **66** when R = Me. The Suzuki−Miyaura coupling of compound **66** with bromobenzene produced pyrrole **67** in excellent yield.

Scheme 25



63 **64** **65** **66** **67**

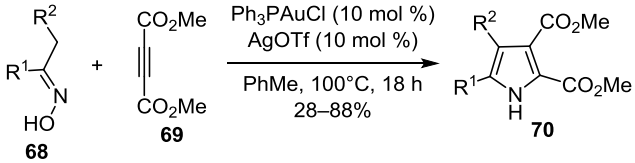
i: $(RhCp \cdot Cl_2)_2$ (5 mol %), $Cu(OAc)_2$ (2.2 equiv), Me_2CO, 60°C, 18 h

ii: PhBr, $Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), K_3PO_4, THF, H_2O, 60°C, 18 h

A study of the Au(I)-catalyzed regioselective synthesis of substituted pyrroles **70** directly from oximes **68** and dimethyl but-2-ynedioate (**69**) revealed that reaction occurs as a multiple-step process (Scheme 26).[57] Au(I) promotes addition of the oxime oxygen to the activated alkyne to form *in situ* an *O*-vinyloxime, followed by Au(I)-catalyzed tautomerization, [3,3] sigmatropic rearrangement, and cyclodehydration. Pyrrole derivatives **71** and **72** were also synthesized by this method.

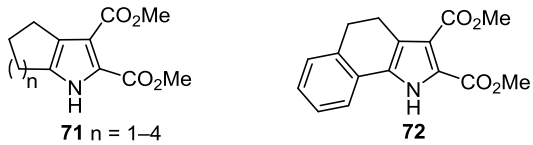
A Rh(III)-catalyzed oxidative cycloaddition of *N*-*tert*-butoxycarbonyl hydrazones **73** to internal alkynes **74** to

Scheme 26



68 **69** **70**

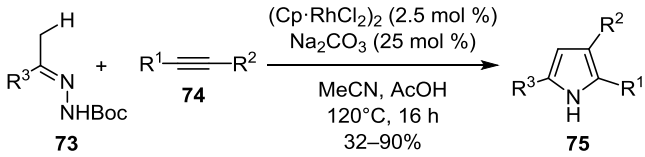
R^1 = *n*-C_3H_7, cyclohexenyl, Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$ 4-$MeOC_6H_4$, 4-FC_6H_4, 2-Br-3-FC_6H_3, 3-Py
R^2 = H, Me, *n*-C_6H_{13}, Ph, Cl



71 n = 1–4 **72**

give functionalized pyrroles **75** was presented by Yu and coworkers (Scheme 27).[58] Experiments with deuterium-labelled compounds show that *N*-Boc group could play a key role in directing the kinetically competitive C(sp^3)–H bond functionalization.

Scheme 27



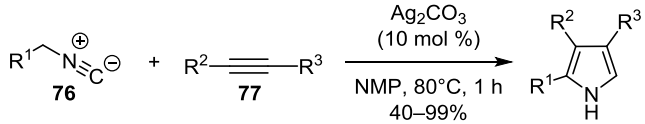
73 **74** **75**

R^1, R^2 = H, Et, *n*-Pr, *n*-Bu, Ph,
R^3 = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-EtC_6H_4, 4-$EtOC_6H_4$, 4-$MeSC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-BrC_6H_4, 3-ClC_6H_4, 2-MeC_6H_4, 2,4,6-$(MeO)_3C_6H_2$, 3-Cl-4-$MeOC_6H_3$, 2-Naphth, 2,3-dihydro-1,4-benzodioxinyl

6.4. {CNC + CC} cyclization

The first cycloaddition reaction of isocyanides **76** to alkynes **77** with Ag_2CO_3 as a catalyst was realized by Lei and coworkers (Scheme 28).[59]

Scheme 28



76 **77** **78**

R^1 = H, MeO_2C, EtO_2C, P(O)(OEt)$_2$
R^2, R^3 = H, Ph, PhC_6H_4, 4-MeC_6H_4, 4-AcC_6H_4, 4-$MeSC_6H_4$, 4-$MeSO_2C_6H_4$, 4-$CH{\equiv}CC_6H_4$, 3-$EtO_2CC_6H_4$, 2-$MeO_2CC_6H_4$, 2-$MeOC_6H_4$, cyclopropyl, *n*-C_4H_9, *n*-C_5H_{11}, CH_2OH, *n*-BuO_2C, MeO_2C

7. INDOLINES

The cytotoxic activity of *N*-substituted indolines has been the subject of a recent publication,[60] although various biological activities have been recorded for the molecule in the past.[61]

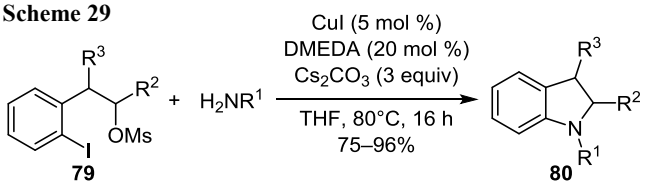
Intramolecular chelation-assisted C(sp^2)–H aryl–alkenyl coupling of *N*-allyl-*N*-substituted anilines catalyzed by $Rh(PPh_3)_3Cl$ affords 1-substituted 3-methylindolines in moderate yields.[43] When the reaction of *N*-allyl-*N*-Boc-protected anilines is catalyzed by CuI in the presence of

Togni's reagent, carbotrifluoromethylation occurs and 3-(2,2,2-trifluoroethyl)pyrrolidines are produced.[47,62] Several transition metals and oxidants are suitable to promote the intramolecular aryl C–H bond amination of *N*-protected β-arylethylamines to indolines. With triflate as a protecting group and $Pd(OAc)_2$ as a catalyst the oxidant can be either 2,4,6-trimethyl-*N*-fluoropyridinium triflate,[63] or $PhI(OAc)_2$.[9] With 2-pyridylsulfonyl or 2-pyridylbenzoyl protecting groups the oxidants are $AgOAc$[9] and $PhI(OAc)_2$,[32] respectively. *N*-Protected ethyl-*N*-(2-bromoanilines) underwent $Pd(Pcy_3)_2$ intramolecular arylation of their terminal primary C–H bond in the presence of a chiral base to afford pyrrolidines bearing tri- and tetrasubstituted stereocenters,[64] while *N*-protected allyl-*N*-(2-bromoanilines) were cyclized to 3-cyanomethylpyrrolidines by C(sp^2)–H activation using $Pd(OAc)_2$ and K_4FeCN_6.[65] In the presence of MnO_2 and Rh_2(R-PTAD)$_4$, 2-hydrazinylidenemethyl-*N*-substituted anilines produced 1-substituted 2,3-dihydro-1*H*-indoles in very good yields.[11]

7.1. {CCCCN} cyclization

An efficient domino CuI-catalyzed amidation/cyclization reaction of 2-iodophenethyl mesylates **79**, provided 1,2,3-trisubstituted indolines **80** in excellent yields (Scheme 29).[61] Three distinct mechanistic pathways have been proposed for this domino process. The most probable mechanism is initial intermolecular Cu-catalyzed amidation of the aryl iodide followed by intramolecular displacement of the mesylate group by the carbamate or amide group.

Scheme 29



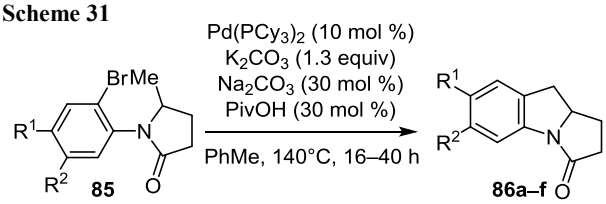
R^1 = Ac, Cbz, Boc, CO_2Me; R^2 = H, Me, $TBSOCH_2$, PhO_2CCH_2
R^3 = H, Me, $Ph(CH_2)_2$

Tetrahydropyrroloindoles **84** were synthesized stereoselectively through cascade Pd-catalyzed coupling reactions between aryl chlorides and 1-(2-bromophenyl)hex-5-en-2-amines **81** (Scheme 30).[66] The results using two catalytic systems – $Pd(OAc)_2$/Cy_4Dpe-Phos and $Pd_2(dba)_3$/$PCy_3 \cdot HBF_4$, are compared. $Pd(OAc)_2$ was effective for transformations of electron-rich or electron-neutral aryl chlorides, whereas $Pd_2(dba)_3$ gave best results in transformations of chlorinated aromatic N-heterocycles. It is postulated that the first step is a chemoselective intramolecular *N*-arylation reaction of amine **81** to give intermediate indoline **82**, followed by a stereoselective intermolecular carboamination reaction with an exogenous aryl or heteroaryl chloride to a chair-like transition state **83** that cyclizes into product **84**.

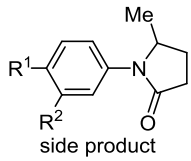
7.2. {CCNCC} cyclization

$Pd(PCy_3)_2$-catalyzed intramolecular C(sp^3)–H arylation of 1-(2-bromophenyl)-5-methylpyrrolidin-2-ones **85** furnished fused indolines **86** in moderate to very good yields (Scheme 31).[67] In previous studies[68] of the related reactions it has been shown that C(sp^3)–H activation occurs through the base-induced, concerted metalation-deprotonation (CMD) mechanism. Combination of two bases, K_2CO_3 and Na_2CO_3, allows selective formation of the desired product **86**; debromination side product is formed in 1.4:1 to 3:1 ratio.

Scheme 31



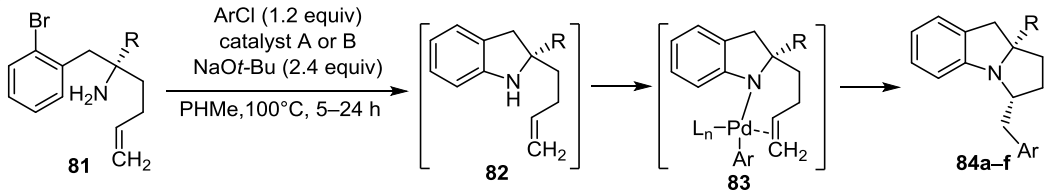
a R^1 = CN, R^2 = H (59%); **b** R^1 = CF_3, R^2 = H (61%); **c** R^1 = CO_2Me, R^2 = H (84%, 1.4:1, inseparable mixture of **86c** : side product); **d** R^1 = NO_2, R^2 = H (82%); **e** R^1 = F, R^2 = H (56%); **f** R^1 = CO_2Me, R^2 = OMe (86%, 3:1, inseparable mixture of **86f** : side product)



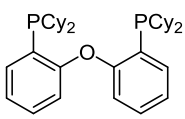
7.3. {CCCCN} cyclization and {C} addition

Due to the significance of the CF_2 and CF_3 groups in the synthetic and medicinal chemistry fields Wu and Jiang[69] decided to incorporate them, as a single or a multiple functionality, at the C-2 position of the indoline framework. They performed an oxidative Pd-catalyzed fluoroalkylative cyclization of *N*-(2-allylphenyl)benzenesulfon-

Scheme 30



Catalyst A = $Pd(OAc)_2$ (4 mol %), Cy_4Dpe-Phos (4 mol %)
Catalyst B = $Pd_2(dba)_3$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %)

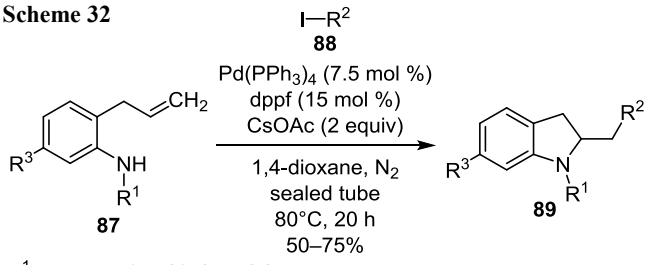


Cy_4Dpe-Phos

a R = H, Ar = 4-MeC_6H_4 (76%, *dr* >25:1, catalyst A)
b R = H, Ar = 3-FC_6H_4 (42%, *dr* >25:1, catalyst B)
c R = H, Ar = 1-Naphth (78%, *dr* 8:1, catalyst A)
d R = H, Ar = 2-pyrazinyl (58%, *dr* >8:1, catalyst B)
e R = Me, Ar = 3-$MeOC_6H_4$ (75%, *dr* >25:1, catalyst B)
f R = Me, Ar = 1-isoquinolinyl (60%, *dr* 14:1, catalyst B)

amides **87** (Scheme 32) with readily available iodoperfluoro reagents **88** that led to 2-fluoroalkylated indolines **89**. The novelty of this reaction is that both C(sp^3)−CF_2 and C−N bonds are formed in a single step.

Scheme 32

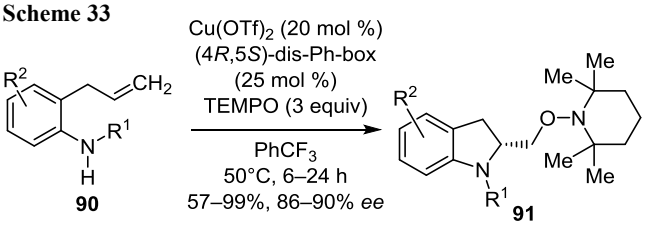


R^1 = Ts, 3,4-$(MeO)_2C_6H_3SO_2$
R^2 = EtO_2CCF_2, $F_3C(CF_2)_2$, $F_3C(CF_2)_3$, $F_3C(CF_2)_7$; R^3 = H, MeO, Cl

7.4. {CCCCN} cyclization and {O} addition

Enantioselective $Cu(OTf)_2$-catalyzed aminooxygenation of *N*-sulfonyl-2-allylaniline substrates **90** with the (4*R*,5*S*)-di-Ph-box ligand in the presence of TEMPO radical provided pyrrolidines **91** in good to excellent yields and high *ee* (Scheme 33).[19] In the case of R^1 = Ts and R^2 = 4-F in substrate **90**, the reaction was carried out in toluene at 110°C in the presence of O_2 (1 atm), giving the corresponding pyrrolidine **91** (R^1 = Ts, R^2 = 5-F) in 89–96% yield (in several experiments with different reagent ratio and reaction times) and >98% *ee* after recrystallization.[70]

Scheme 33

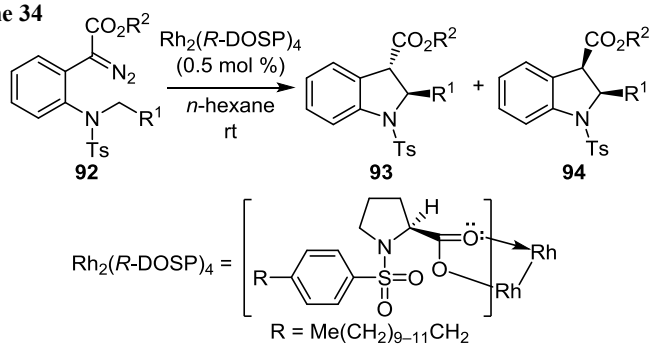


R^1 = $MeSO_2$, Ts, 4-$O_2NC_6H_4SO_2$
R^2 = H, 4-Me, 4-CN, 4-MeO, 4-F, 4-Cl

7.4. {CCCN + C} cyclization

trans- and *cis*-2,3-Disubstituted indolines **93**, **94** were obtained with high diastereomeric excesses (up to 94% *de*) and enantioselectivities (up to 94% *ee*) from α-diazocarbonyl compounds **92** using Rh_2(R-DOSP)$_4$ as the chiral catalyst for the intramolecular C–H insertion reaction (Scheme 34).[71] A highly stereoselective Cu-catalyzed synthesis of *cis*-2,3-disubstituted indolines from *N*-substituted benzylidene-2-vinylanilines was reported by Ascic and Buchwald.[72]

Scheme 34

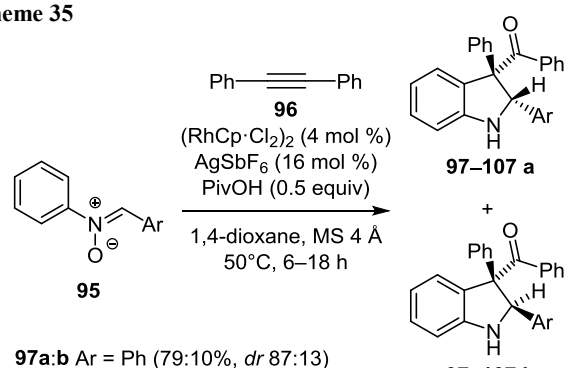


93, **94 a** R^1 = Ph, R^2 = Me (82%, *dr* 11:1, 86% *ee*)
b R^1 = Ph, R^2 = *i*-Pr (62%, *dr* 2.2:1, 35% *ee*)
c R^1 = 4-$MeOC_6H_4$, R^2 = Me (80%, *dr* 35:1, 66% *ee*)
d R^1 = 4-$F_3CC_6H_4$, R^2 = Me (82%, *dr* 5:1, 80% *ee*)
e R^1 = 2-PhC_6H_4, R^2 = Me (94%, *dr* 13:1, 94% *ee*)
f R^1 = 2-MeC_6H_4, R^2 = Me (86%, *dr* 8:1, 64% *ee*)
g R^1 = 3- MeC_6H_4, R^2 = Me (73%, *dr* 8:1, 71% *ee*)
h R^1 = 4-MeC_6H_4 R^2 = Me (92%, *dr* 14:1, 42% *ee*)
i R^1 = 1-Br-2-naphthyl, R^2 = Me (48%, *dr* 6:1, 75% *ee*)
j R^1 = PhCH=CH, R^2 = Me (53%, *dr* 7:1, 33% *ee*)
k R^1 = $Me(CH_2)_4$, R^2 = Me (64%, *dr* 99:1, 48% *ee*)

7.5. {CCNC + C} cyclization

Chang and Dateer,[73] have presented a result of an extensive study – the first intermolecular coupling of arylnitrones with internal alkynes to give diastereomeric mixtures of indolines in the presence of $RhCp{\cdot}Cl_2$ as a catalyst, $AgSbF_6$ salt, and pivalic acid under an O_2-free atmosphere. The catalyst seems to mediate both the C−H bond activation and O atom transfer. The reactions of arylnitrones **95** with diphenylacetylene (**96**) provided indoline derivatives **97**–**107 a**,**b** with yields and diastereoselectivity from moderate to high (Scheme 35). In general, high stereoselectivity of indolines was observed when the aryl substituent of the nitrone contained electron-withdrawing groups. Examples of the reactions of nitrones **95** with different alkyl-, aryl-, and heteroaryl-substituted internal alkynes are also given.

Scheme 35



97a:**b** Ar = Ph (79:10%, *dr* 87:13)
98a Ar = 4-*t*-BuC_6H_4 (44%, *dr* 84:16)
99a:**b** Ar = 4-$MeOC_6H_4$, (67:18%, *dr* 76:24)
100a:**b** Ar = 4-$MeOC_6H_4$ (63:14%, *dr* 79:21)
101a Ar = 4-ClC_6H_4 (81%, *dr* 94:6)
102a Ar = 4-FC_6H_4 (78%, *dr* 90:10)
103a Ar = 4-$CF_3C_6H_4$ (82%, *dr* 90:10)
104a Ar = 2-Naphth (32%, *dr* 81:19)
105a Ar = 1,3-benzodioxol-5-yl (35%, *dr* 76:24)
106a:**b** Ar = 2-thienyl (51:42%, *dr* 55:45)
107a:**b** Ar = Ph (51:35%, *dr* 58:42)

8. INDOLIN-2-ONES

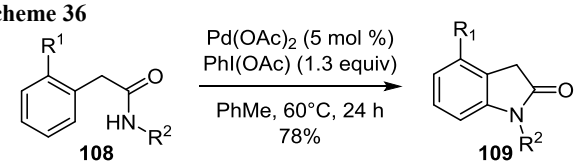
Indolin-2-one (2-oxindole) moiety is found in a large number of biologically active natural products and pharmaceuticals.[74,75]

3-Alkylideneindolin-2-ones were synthesized by Rh-catalyzed cyclization reactions of 2-alkynylaryl isocyanates with organoboron compounds.[76] Indolin-2-ones with mono- or disubstitution at the C-3 position have been prepared by the oxidative Pd(II)-catalyzed lactamization of aryl C–H bonds of *N*-alkoxy-2-(aryl)acetamides,[9,43,63] intramolecular Cu-catalyzed amidation of *N*-substituted 2,6-dibromophenylacetamides,[3] Pd(II)-catalyzed cyclization of *N*-(2-iodophenyl)alkylamides,[51] carbotrifluoromethylation of *N*-phenylacrylamides using CuI/Togni's reagent,[62] $Cu(NO_3)_2/CF_3SO_2Na$,[47] or $Pd(OAc)_2/Me_3SiCF_3$[32] reagent systems and also by $RhCp{\cdot}Cl_2$-catalyzed intramolecular dehydrogenation of 2-(2-aminophenyl)ethanols.[8] *N*-Phenylacrylamides can also be carboacetoxylated or carbomethylcyanated using $Pd(OAc)_2/PhI(OAc)_2$ and $Pd(OAc)_2$/RCN (R = alkyl), respectively.[65]

8.1. {CCCCN} cyclization

The synthesis of indolin-2-ones **109** was achieved by the Pd(II)-catalyzed carboxamide-directed intramolecular amination of inactivated C(sp^2)–H bond at the γ-position of secondary amide precursors **108** (Scheme 36).[28] The 2-pyridylmethyl or 8-quinolyl auxiliaries are essential for this reaction, since it is postulated that they form a five-membered Pd(II) palladacycle intermediate that facilitates the oxidative cyclization process.

Scheme 36

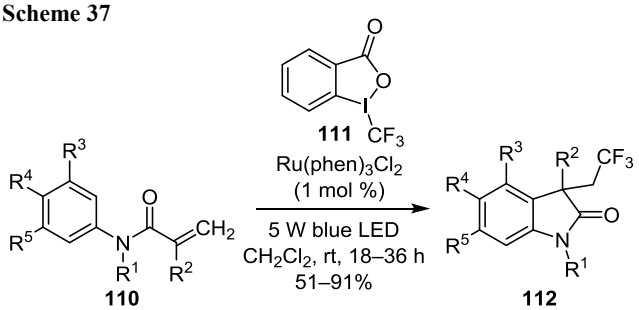


R^1 = H, F; R^2 = 2-pyridylmethyl, 8-quinolyl

8.2. {CCNCC} cyclization and {C} addition

Zhu and coworkers reported another method of *N*-phenylacrylamide **110** carbotrifluoromethylation using Togni's reagent **111** (Scheme 37).[77] The trifluoromethyl group was coupled to alkenes through a visible light-induced radical addition using $Ru(phen)_3Cl_2$ catalyst. The method offers the advantage to synthesize a variety of CF_3-containing 2-oxindoles **112** bearing a quaternary C-3 center at room temperature with a low catalyst loading and without additives.

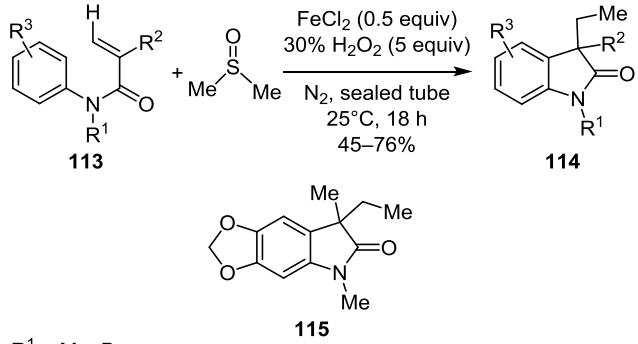
Scheme 37



R^1 = Me, Et, *i* - Pr, Bn, Ph
R^2 = H, Me, CH_2OH, CH_2CHCH_2, CH_2Ac, Bn, Ph, CH_2NPhth
R^3 = H, Me; R^4 = H, Me, MeO, Cl, Br, I; R^5 = H, Me

Li, Yan, and coworkers[78] published the first example of a free radical cascade methylation of *N*-arylacrylamides **113** to afford 3,3-disubstituted pyrrolidin-2-ones **114** in moderate to very good yields (Scheme 38). The reaction utilizes dimethyl sulfoxide, which is the methyl group donor, $FeCl_2$ as the catalyst, and the source of atomic chlorine and hydrogen peroxide as the oxidant. Derivative **115** was also synthesized by this method. The authors consider that the reaction is analogous to the Fenton reaction.

Scheme 38

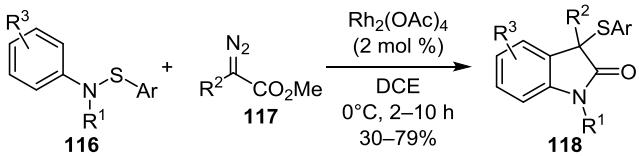


R^1 = Me, Bn
R^2 = Me, $AcOCH_2$, (1,3-dioxoisoindol-2-yl)methyl
R^3 = H, 7-MeO, 4,6-Me_2, 5-Ph, 5-Cl, 5-Br, 5-I

8.3. {CCN + CC} cyclization

3-Arylsulfanil-1,3-disubstituted indolin-2-ones **118** were synthesized, in moderate to high yields, by the $Rh_2(OAc)_4$-catalyzed reaction of sulfenamides **116** and diazoacetates **117** (Scheme 39).[79] It was postulated that in the first step of the reaction, an intermediate sulfonium ylide is formed, which then undergoes thia-Sommelet–Hauser rearrangement leading to an exocyclic imine. The latter aromatizes by tautomerism to a 2-substituted aniline derivative, whose amino group interacts with the ester group by intramolecular acyl substitution. An important feature of the reaction is that it shows excellent functional group tolerance.

Scheme 39



R^1 = Me, C_3H_5, *i*-Pr, Bn; R^2 = Me, *i*-Pr, CF_3, Cy
R^3 = H, 5-F, 5-Cl, 5-O_2N, 5-MeO, 3,4-Cl_2, 4,5-Cl_2
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

9. INDOLIN-3-ONES

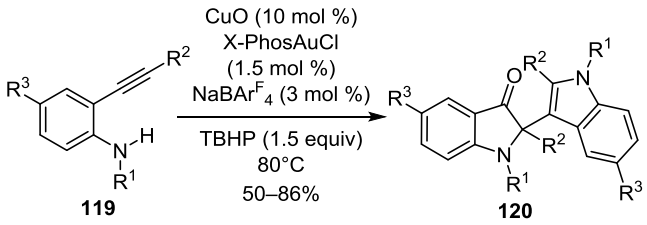
Indolin-3-one derivatives, especially those disubstituted at position 2, are found in many natural products with interesting biological activities.[79]

9.1. {CCNCC} cyclization and {C} and {O} addition

For the period covered by this review, the only reference found on indolin-3-ones was the new one-pot synthesis of 2,2-disubstituted indolin-3-ones **120** from simple 2-alkynyl-

anilines **119** (Scheme 40).[80] The reaction occurred *via* Au/Cu-co-catalyzed tandem reactions employing TBHP as terminal oxidant and oxygen atom source. The novel features of this tandem process are intermolecular nucleophilic addition, intramolecular cyclization/oxidative cross-dehydrogenative-coupling steps where four new bonds and two indole rings were formed.

Scheme 40



R^1 = H, Me, EtO_2CCH_2, PhN(Me)$COCH_2$, 4-$HNCOCH_2C_6H_4$, 4-$MeOC_6H_4CH_2$, 4-$ClC_6H_4CH_2$
R^2 = H, *n*-Pr, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-thienyl
R^3 = H, Me, Cl

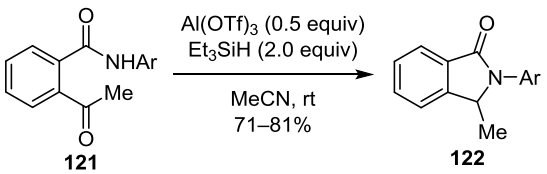
10. ISOINDOLINONES

The isoindolinone (phthalimidine) ring system is a popular scaffold due to its wide range of applications and pharmacological properties.[81] Various 2-aryl-3-*tert*-butylaminoisoindolinones were synthesized from benzyl imines and aryl isocyanates by what seems to be a rare case of rhenium-catalyzed C(sp^2)–H bond activation.[43] 3,3-Disubstituted isoindolinones were obtained from the oxidative, Rh(III)-catalyzed C(sp^2)–H activation of benzhydroxamates, with diazo compounds contributing as one-carbon component coupling partners.[49] *N*-Tosylbenzamides were used, due to their directing group properties, in a $Pd(OAc)_2$-catalyzed tandem C(sp^2)–H olefination/annulation reaction with various aliphatic or conjugated alkenes to afford a wide range of 3-substituted 2-tosyl methylisoindolinones.[34] In the presence of $Pd(OAc)_2$ with O_2/1,4-benzoquinone/AcOH, *N*-methoxybenzamides underwent the Heck and aza-Wacker reactions to afford 2-methoxy-3-alkylideneisoindolinone.[32]

10.1. {CCCCN} cyclization

The same methodology used to synthesize pyrrolidin-2-ones **38** (Scheme 15) served to transform arylketoamides **121** to 2-aryl-3-methylisoindolinones **122** in very good yields (Scheme 41).[29]

Scheme 41

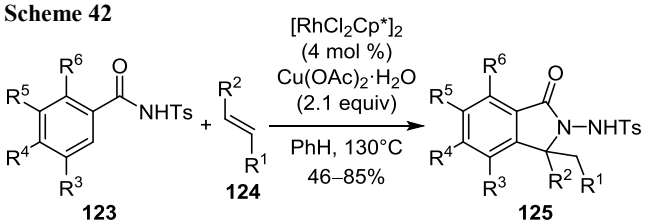


Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

10.2. {CCCN + C} cyclization

Zhu and Falck described[82] the tandem annulation of *N*-benzoylsulfonamides with alkenes that provided efficient access to a series of 3,3-disubstituted 2-tosylisoindolinones **125** (Scheme 42). The reaction proceeded by Rh-catalyzed C(sp^2)–H olefination of *N*-benzoylsulfonamides **123** with internal alkenes **124**, followed by C–N bond formation.

Scheme 42

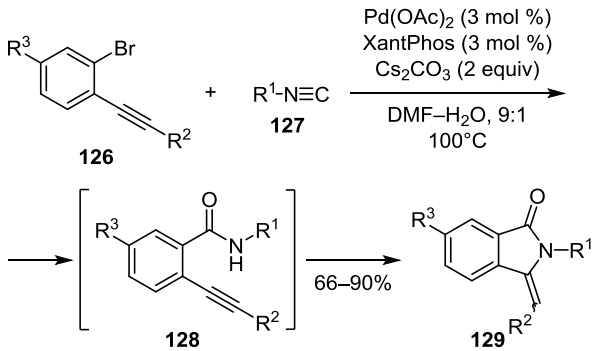


R^1 = CN, EtO_2C; R^2 = EtO_2C; R^3 = H, MeO
R^4 = H, Me, MeO, F, Br, CF_3; R^5 = H, MeO; R^6 = H, F

10.3. {CCC + CN} cyclization

Sawant, Khan, Pardasani, and coworkers[83] studied the application of isocyanides as amide surrogates in one-pot regio- and stereoselective synthesis of isoindolinones (Scheme 43). Thus, (*E*/*Z*)-2-(alkyl or aryl)-3-alkylideneisoindolinones **129** with the *E*/*Z* diastereomer ratio from 69:31 to 95:5 were obtained from the following proposed sequence of reactions of 2-bromo-1-ethynylbenzene derivatives **126** with isocyanides **127**, involving Pd-catalyzed isocyanide insertion (C–C bond formation) and imine hydration (C–O bond formation) to form intermediate **128**, followed by a 5-*exo*-*dig* cycloisomerization (C–N bond formation).

Scheme 43



R^1 = *t*-Bu, Ph, 3-Cl-4-FC_6H_3, 2-$MeOC_6H_3$, 3-$MeOC_6H_3$, 3-ClC_6H_3, 4-NCC_6H_3, 4-FC_6H_3, 4-$MeOC_6H_3$, 2-thienyl, 2-Py
R^2 = Ph, *t*-$BuCH_2C(Me)_2$, 4-MeC_6H_3, 4-NCC_6H_3, 2-Naphth, 4-$F_3CC_6H_3$, 2-Py; R^3 = H, Me

11. 1*H*-INDOLES

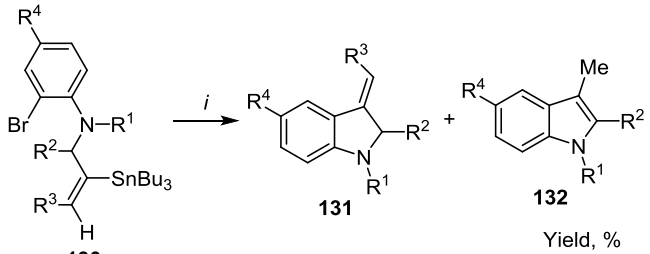
Although there is no review article dealing exclusively with metal-catalyzed syntheses of 1*H*-indoles, the sheer number of these reactions found in 19 review articles for the period of 2008–2017 has compelled the authors to categorize these reactions according to the metal catalyst employed. Thus, the metal catalysts used to synthesize 1*H*-indoles are as follows: $Pd(OAc)_2$,[5,9,32,43,48,63,65] $Pd(dba)_2$,[32,48,49] $Pd_2(dba)_3$,[9] $PdCl_2$,[48] $PdCl_2(PPh_3)_2$,[6,51] $Pd(PPh_3)_4$,[6] PdI_2,[6] $PdCl_2(MeCN)_2$,[9] $PdCl_2/CuCl_2$,[6] $PdCl_2/(PhCN)_2$,[63] $PdCl_2$, $PdBr_2$,[6] $FeBr_2$, $FeCl_2$, $FeBr_3$, $FeCl_3/PdCl_2$, $Fe(OTf)_2$, $Fe(F_{20}TPP)Cl$, FeI_2,[7] $FeCl_3$,[7,48] CuOAc,[5,84] $Cu(OTf)_2$,[5,9] CuI,[5,47,48,51] CuBr,[5,47] $AlCl_3$,[84] $AuBr_3$,[44]

$HSnBu_3$,[84] $ZnCl_2$,[52] $[Cp^*RhCl_2]_2$,[34,43] $[Cp^*RhCl_2]_2AgSbF_6$,[7,34] $[Cp^*Rh(MeCN)_3]_2[SbF_6]_2$,[7] $[Ru(bpz)_3](PF_6)_2$,[9] $[RuCl_2(p\text{-cymene})]_2$,[7] $Rh_2(O_2CC_3F_7)_4$,[7,43,63] $Rh_2(O_2CC_7F_{15})_4$,[85] $Rh_2(esp)_2$,[7,85] $[\{Cp^*IrCl_2\}I_2]$, $[\{Cp^*IrCl_2\}_2]$,[8] $[Au(PPh_3)]Cl$,[50,52] and $IPrAuNTf_2$.[50,49]

11.1. {CCNCC} cyclization

Kazmaier and Lin[86] presented Pd-catalyzed intramolecular Stille coupling of α-stannylated allylic amines **130** to afford either 3-methylideneindole derivatives **131** or 3-methylindoles **132** and in some cases, mixtures of both compounds (Scheme 44). Although there is no clear-cut explanation for these results, the tendency is for indoles **131** to isomerize to indoles **132** very slowly when the substituent on the pyrrole nitrogen atom is electron-withdrawing. The opposite was observed when the substituent on the pyrrole nitrogen atom had either no effect or a weak electron-donating effect. In that case, the double bond migration to indole **132** was fast.

Scheme 44



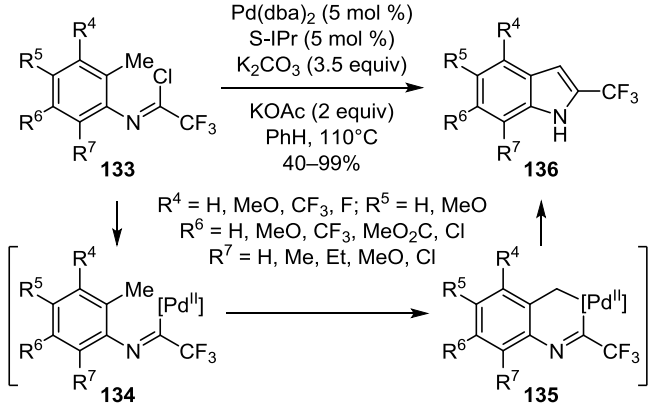
i: [(allyl)$PdCl_2$] (2 mol %), Ph_3P (4 mol %), THF, 60°C

R^1	R^2	R^3	R^4	Yield, % 131	132
CO_2Et	H	H	H	84	0
Ac	H	H	Me	86	7
Ac	H	H	Br	56	26
CO_2Et	H	Me	H	58	0
H	*i*-Pr	H	H	0	<10
H	Me	H	H	0	<10
Bn	Me	H	H	0	65

11.2. {CCCN + C} cyclization

A convenient synthesis of 3-trifluoromethyl-1*H*-pyrroles from trifluoroacetimidoyl chlorides, derived from widely available 2-methylanilines, was introduced by Cramer and Pedroni (Scheme 45).[87] The reaction is thought to proceed by the oxidation of trifluoroacetimidoyl chloride **133** with the Pd(0) catalyst to give palladated intermediate **134**, followed by Pd-catalyzed C(sp^3)−H functionalization of the methyl group to form the cyclic palladated intermediate **135** and then reductive elimination and tautomerization to 2-(trifluoromethyl)indoles **136**.

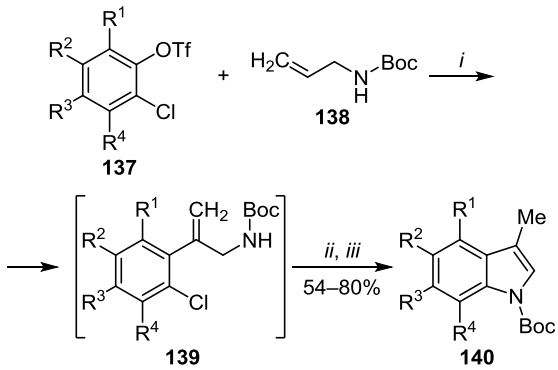
Scheme 45



11.3. {CCN + CC} cyclization

Baxter, Cleator, et al.[88] applied a novel three-step one-pot reaction for the synthesis of 3-methylindoles **140** from chloroaryl triflates **137** and *N*-Boc-allylamine (**138**) (Scheme 46). All three reaction steps were relatively clean, allowing a successful outcome. In the first step, 2-aryl-substituted allyl carbamates **139** were formed through the Heck reaction of compounds **137** and **138** in the presence of $Pd(OAc)_2$ catalyst. A solvent switch to DMF, followed by the addition of more $Pd(OAc)_2$ catalyst, the XPhos ligand, and a stronger base triggered an intramolecular carbamate/aryl chloride coupling of compound **139** to afford the 3-methylinepyrrole intermediate. Isomerization by the addition of camphorsulfonic acid (CSA) yielded indoles **140** in fair to very good yields.

Scheme 46

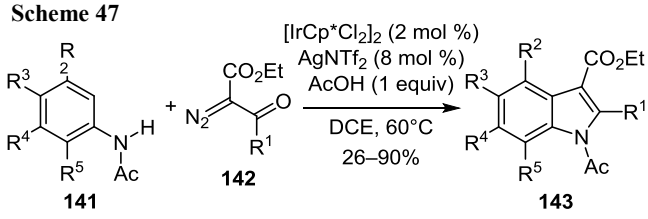


i: *N*-Boc-allylamine (1.2 equiv), $Pd(OAc)_2$, (3 mol %), dppf (10 mol %), NaOAc (1.2 equiv), MeCN, 80°C
ii: $Pd(OAc)_2$ (3 mol %), XPhos (10 mol %), K_2CO_3 (1.5 equiv), DMF, 80°C
iii: CSA (20 mol %), CH_2Cl_2, 25°C

R^1 = H, MeO; R^2 = H, F, Me
R^3 = H, Me, MeO, EtO_2C, F; R^4 = H, CF_3

Patel and Borah[89] reported an Ir(III)-catalyzed carbenoid functionalization of *N*-arylacetamides **141** by employing ethyl 2-diazo-3-oxobutanoate and ethyl 3-aryl-2-diazo-3-oxopropanoates **142** for the synthesis of polysubstituted 1*H*-indole derivatives **143** (Scheme 47). The reaction gave

Scheme 47



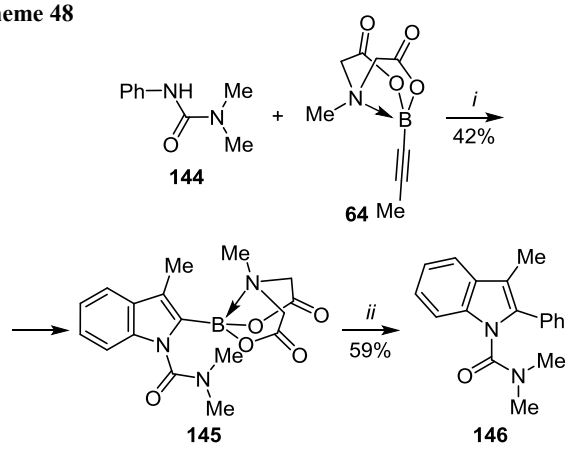
R^1 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^2, R^4 = H, Me, MeO
R^3 = H, Me, *i*-Pr, MeO, Ac, MeO_2C, CF_3, F, Cl, Br
R^5 = H, MeO

1*H*-indoles in low to high yields with *N*-substituents such as acetyl, pivaloyl, or benzoyl groups.

11.4. {CCN + CC} cyclization and {C} addition

The 1*H*-indole derivative **146** was synthesized from urea **144** through intermediate complex **145** (Scheme 48)[56] by a method analogous to the one previously described for 1*H*-pyrrole **67** (Scheme 25).

Scheme 48



i: $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (10 mol %), $Cu(OAc)_2$ (2.2 equiv), Me_2CO, 80°C
ii: $Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), PhBr, K_3PO_4, THF, H_2O, 60°C

12. CARBAZOLES

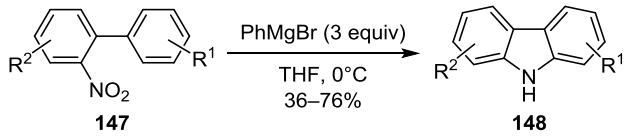
The carbazole structural unit is commonly found in many biologically active natural and unnatural compounds. For example, murrayaquinone A is a carbazole alkaloid isolated from the root bark of *Murraya euchrestifolia* that exhibits cytotoxic properties against human tumor cells. A review article by Knölker et al. deals with the occurrence, biogenesis, and synthesis of biologically active carbazole alkaloids.[90]

Among the metal catalysts used for cyclizations leading to carbazoles, $Pd(OAc)_2$ is one of the most popular choices. The substrates in these reactions are *N*-([1,1'-biphenyl]-2-yl)acetamides,[3,9,43,48,63] *N*-([1,1'-biphenyl]-2-yl)-4-methylbenzenesulfonamides,[9,48] 2-nitro-1,1'-biphenyls,[43] diphenylamines,[48,91] aryl triflates and anilines,[43] 1,2-dihalobenzenes and anilines,[3,43,90,91] iodobenzenes and *N*-(2-bromophenyl)acetamides,[91] *N*-(3-iodophenyl)anilines and alkynes,[48,91] 2-chloroanilines and bromobenzenes,[3,48] and biphenyl-2,2'-diyl bistriflates or the corresponding 2,2'-dihalobiphenyls with primary amines or ammonia.[90] 1,2-Dihalobenzenes and anilines have also been cyclized with $Cu(OTf)_2$[47] while $PdCl_2$(dppf) worked as well for the cyclization of 1,2-dihalobenzenes and anilines.[90] Carbazoles have been synthesized with various other catalysts by cyclization of (2-bromophenyl)boronic acids and 2-iodoanilines with $Pd_2(dba)_3$,[3] 2-azido-1,1'-biphenyls with $AlCl_3$, $Rh_2(O_2CC_3F_7)_4$ or $Rh_2(O_2CC_7F_{15})_4$,[63] and 1-ethynyl-2-(1-tosylprop-2-yn-1-yl)benzenes and alkynes with $RhCl(PPh_3)_3$.[89] The alkaloid karapinchamine A has been synthesized from the appropriately 1-substituted 4-(benzyloxy)-1-(1-methyl-1*H*-indol-2-yl)but-2-yn-1-ol in the presence of catalytic IprAuCl–$AgSbF_6$ system.[47] Finally, the review article by Kaur[92] covers most of the syntheses of carbazoles mentioned so far.

12.1. {CCCCN} cyclization

The intramolecular amination reaction of 2-nitrobiaryls usually proceeds by a formal electrophilic nitrene insertion, which was first studied six decades ago by Cadogan.[93] It requires high temperatures and the use of either excess aryl phosphines or trialkyl phosphites. Later studies demonstrated the effectiveness of transition metal catalysts in the presence of pressurized CO. Recently, Ess, Kürti et al.[94] found that PhMgBr catalyzed the intramolecular amination reaction of *ortho*-arylated nitroarenes **147** to give mono- and disubstituted carbazoles **148** in high regioselectivity and moderate to very good yields (Scheme 49).

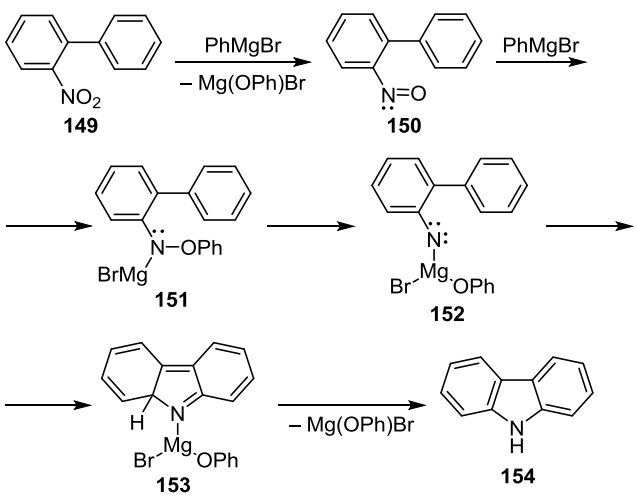
Scheme 49



R^1 = 2-Me, 4-Me, 6-Me, 3-MeO, 4-MeO, 2-F, 2-Cl, CN, 2-CF_3, MeO_2C, 2-*t*-Bu; R^2 = H, 7-MeO

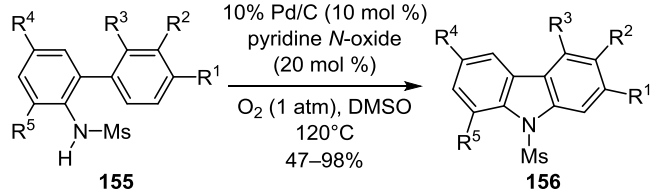
With the aid of density functional theory calculations probing the likely cyclization mechanisms under reducing conditions, stepwise electrophilic aromatic cyclization/tautomerization mechanism was postulated (Scheme 50). Thus, deoxygenation of nitroarene **149** occurred by reaction with PhMgBr, providing nitrosoarene **150**, followed by nitroso *O*-addition to PhMgBr to form intermediate **151**. The latter underwent MgBr-mediated N–O bond cleavage (TS1, $\Delta H^{\ddagger}$ 15.7) to yield nitrenoid **152** (ΔH 6.4), followed by aromatic addition/pseudo-electrocyclization to give carbazole **153** (ΔH –24.6) (TS2, $\Delta H^{\ddagger}$ 17.1) and then hydrogen migration or tautomerization ($\Delta H^{\ddagger}$ –13.3) to produce carbazole **154** (ΔH –45.1) (ΔH values are in kcal·mol^{-1}).[94]

Scheme 50



Monguchi and Sajiki[95] presented a Pd-catalyzed intramolecular C(sp^2)–H amination of substituted *N*-mesylated 2-aminobiphenyls **155** to the corresponding *N*-mesylcarbazoles **156** (Scheme 51). This reaction required a catalytic amount of pyridine *N*-oxide while heating in DMSO under oxygen atmosphere. Optimization studies revealed that pyridine *N*-oxide significantly enhanced the generation of carbazole and that the large surface area of 10% Pd/C was essential for effective catalytic activity.

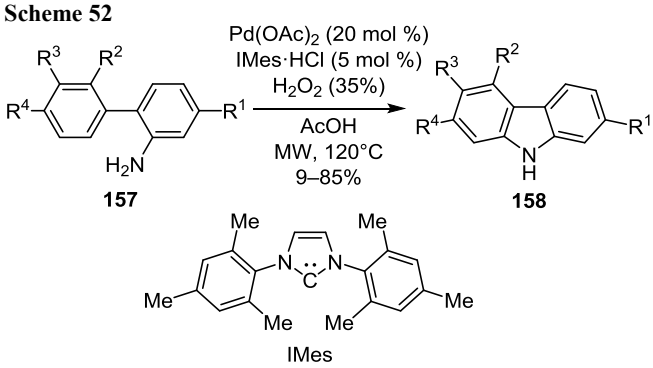
Scheme 51



R^1 = H, Me, CF_3, MeO, NO_2, CO_2Et; R^2 = H, MeO
R^3 = H, MeO, F_3C, Cl; R^4 = H, Me, F_3C, Cl; R^5 = H, Me

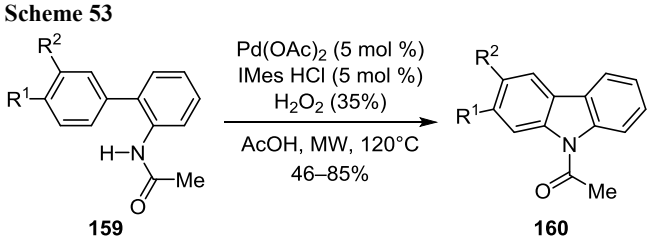
Bjørsvik et al.[96] performed ring closure of unprotected 2-aminobiphenyls **157** by applying the N-heterocyclic carbine ligand IMes with $Pd(OAc)_2$ as metal source to afford mono- and disubstituted carbazoles **158** in poor to excellent yields (Scheme 52). The reaction is believed to proceed by intramolecular tandem C(sp^2)–H activation and C–N bond formation. Although either electron-withdrawing and electron-donating groups can be generally tolerated on one or both of the two aromatic rings of substrate molecule, *C*-monosubstituted 3- and 4-methoxycarbazoles **160** were obtained in higher yields than the corresponding 3- and 4-methoxycarbazoles **158**, showing the advantage of using an auxiliary acetyl group in this case. A further advantage of the reactions with biphenylacetamides **159** is the much lower catalyst load of both

Scheme 52



R^1 = H, Me, CO_2H, Ac; R^2 = H, Me, CF_3, MeO, Cl
R^3 = H, MeO; R^4 = H, Me, Et, MeO, *t*-Bu(Me)$_2$SiO, Cl

Scheme 53

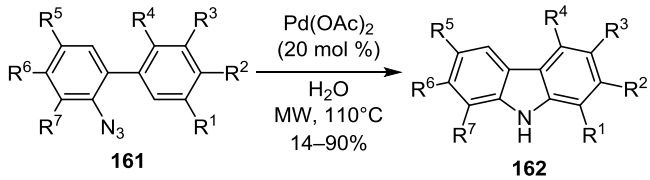


R^1 = H, Me, Et, MeO, Ac; R^2 = H, MeO, Ac

$Pd(OAc)_2$ and IMes and the fact that the cyclization reactions generally did not produce disubstituted by-products. In addition to product **160** (R^1 = H, R^2 = MeO, yield 61%) a minor quantity (12%) of the isomeric 9-acetyl-1-methoxy-9*H*-carbazole was also isolated (Scheme 53).

Lu et al.[97] introduced for the first time the intramolecular C(sp^2)–H amination of 2-azidobiphenyls **161** in water, that is believed to occur *via* a metallonitrene intermediate. The method requires microwave irradiation, works best with $Pd(OAc)_2$ as catalyst, and various carbazoles **162** with electron-withdrawing and electron-donating substituents are tolerated. The method was used to synthesize four natural alkaloids, glycoborine and clauzines C, L, and H in 68–82% yields (Scheme 54).

Scheme 54

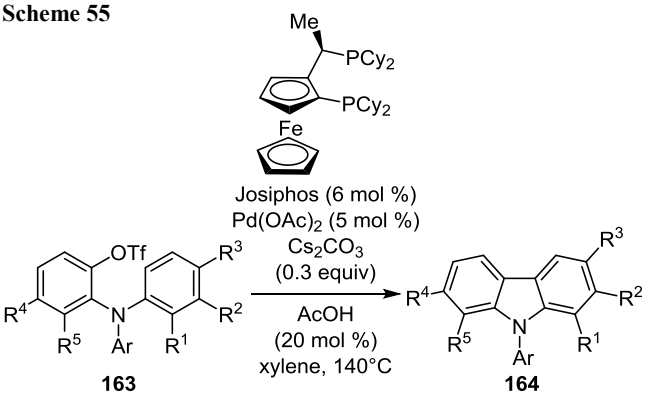


R^1 = H, Me; R^2 = H, MeO, CHO, CO_2Et, Ph, F; R^3 = H, Me
R^4 = H, *i*-Pr, MeO, Br; R^5 = F, MeO, CHO, Ac, EtO_2C, Ph, Cl
R^6 = H, CF_3; R^7 = H, Br, 4-$MeOC_6H_4$

12.2. {CCNCC} cyclization

Following up earlier work by by Larock[98] and Ackermann[99] who independently synthesized *N*-phenylcarbazoles by Pd-catalyzed direct C–H arylation of 2-halophenyldiphenylamines, Kamikawa and coworkers[100] studied direct Pd-catalyzed arylation of 2-(diarylamino)phenyl triflates **163** for the synthesis of *N*-arylcarbazoles **164** (Scheme 55). The participation of the Josiphos ligand in the reaction was essential for obtaining high yields of the products.

Scheme 55



R^1, R^3 = H, Me, MeO; R^2, R^5 = H, Me; R^4 = H, Me, *t*-Bu, Cl
Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4,
2-EtC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$

13. IMIDAZOLES

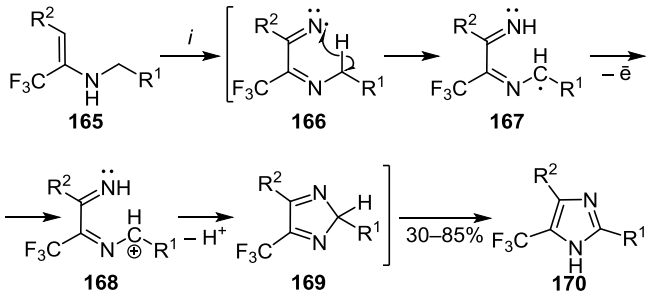
Imidazoles are present in certain molecules found in the human body that play crucial roles in biochemical processes. They are also found in a large number of natural products and synthetic drug molecules.[101,102]

Ethyl 1-aryl-1*H*-imidazole-4-carboxylates have been synthesized *via* Cu_2O-catalyzed cross cycloaddition between aryl isocyanides and ethyl 2-isocyanoacetate. 1,10-Phenanthroline was used as the ligand, while products were obtained in very good to excellent yields. The reaction worked also by converting *N*-arylformamides and ethyl 2-formamidoacetate with $POCl_3$ and Et_3N into the respective crude aryl isocyanides and ethyl 2-isocyanoacetate, followed by Cu_2O-catalyzed cross-cycloaddition reaction. The yields of ethyl 1-aryl-1*H*-imidazole-4-carboxylates were comparable to the direct method, except when *N*-[2- or 3-nitrophenyl]formamides were used. In that case, the product yields dropped to 10–20%.[5] The reaction of (*E*)-(2-nitrovinyl)benzene or terminal alkynes with *N*-arylbenzamidines under the conditions of $FeCl_3$[7] and $CuCl_2$[47] catalysis, respectively, produced very good yields of 1,2,4-triaryl-substituted 1*H*-imidazoles. The reaction is thought to proceed *via* a stepwise [3+2] cycloaddition mechanism. The CuI-catalyzed reaction of 1-(unsubstituted- or substituted phenyl)ethanones and 4-unsubstituted- or 4-substituted benzylamines led to 1,2,4-triaryl-substituted 1*H*-imidazoles in moderate to good yields.[47] Three types of substituted *N*-phenylbenzamidines were studied in Cu-catalyzed syntheses of trisubstituted 1*H*-imidazoles.[103] *N*-Allyl-*N*-benzylbenzamidines and *N*-alkyl-*N*-propargylbenzamidines underwent $Cu(OTf)_2$- and $Cu(OAc)_2$-catalyzed aerobic amine oxidation, providing 1-benzyl-2-phenyl-1*H*-imidazole-4-carbaldehyde and 1,2,4-trisubstituted 1*H*-imidazoles, respectively. Using CuI as catalyst, DABCO as ligand, and MnO_2 as oxidant, coupling of α,β-unsaturated aldehydes with *N*-arylbenzamidines provided 1,2,4-trisubstituted 1*H*-imidazole-5-carbaldehydes in low to very good yields.

13.1. {CCNC + N} cyclization

Yu et al.[104] developed a strategy toward the synthesis of 5-trifluoromethyl-1*H*-imidazoles **170** (Scheme 56). *N*-Alkylenamine **165** was predicted to undergo C(sp^2)–H azidation with $TMSN_3$ in the presence of $Cu(OAc)_2$ catalyst, resulting in iminyl radical **166**. This radical abstracted a hydrogen atom from the methylene group adjacent to the other nitrogen atom, with this C(sp^3)–H amination providing

Scheme 56



i: $PhI(OAc)_2$ (3.0 equiv), $TMSN_3$ (3.0 equiv), $Cu(OAc)_2$ (10 mol %), TBAI (2 equiv), DMF

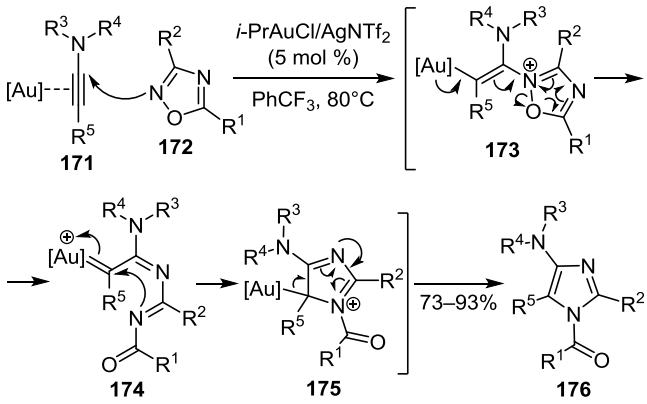
R^1 = Et, Bn, CH_2=CH, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-NCC_6H_4, 4-$MeOC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-Py, 3-Py, 1-Naphth; R^2 = CO_2Me

α-imino radical **167**. Radical **167** was oxidized by $PhI(OAc)_2$ to carbocation **168**, which was then trapped intramolecularly by its imine nitrogen atom, forming cyclized intermediate **169** that tautomerized to 5-trifluoromethyl-1*H*-imidazole derivatives **170**.

13.2. {NCN + CC} cyclization

Hashmi et al.[105] presented a novel and atom-economical synthesis of 1,4,5-trisubstituted 1*H*-imidazoles **176** by gold-catalyzed selective [3+2] annulation of 1,2,4-oxadiazoles **172** with ynamides **171**. According to the proposed mechanism (Scheme 57), the reaction proceeded by regioselective addition of 1,2,4-oxadiazoles **172** (as formal nitrene equivalents) to gold-activated ynamides **171** *via* gold carbene intermediates **173** and **174**. Because of the high electrophilicity of the latter, subsequent intramolecular chemoselective trapping *via* intermediate **175** completed the [3+2] annulation, affording 1-acyl-4-amino-2,5-disubstituted 1*H*-imidazoles **176** in very good to excellent yields.

Scheme 57



R^1 = Me, Ph, 4-$MeO_2CC_6H_4$, 4-FC_6H_4; R^2 = Et, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4; R^3 = Ms, Bs, Ts; R^4 = Me, Bn, Ph
R^5 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-thienyl

14. BENZIMIDAZOLES

The benzimidazole nucleus is an important core structure in many categories of therapeutic agents. The most biologically active benzimidazoles are substituted at positions 1, 2, and/or 5 (or 6).[106–108]

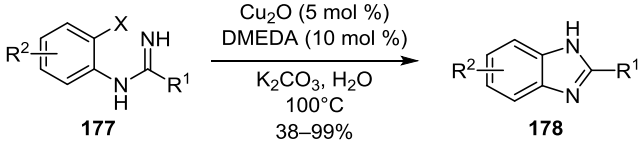
A popular method providing access to 2-phenyl(aryl)-benzimidazoles is the intramolecular oxidative amination of aryl C(sp^2)–H bonds in *N*-arylbenzimidamides using $Cu(OAc)_2$ or $Cu(OAc)_2$ and $PdCl_2(PhCN)_2$ catalysts in *N*-methyl-2-pyrrolidone (NMP) and DMSO at 100°C.[5,9,47,51,63,103,109] All of these reactions required the addition of a few equivalents of acetic acid, except when $Cu(OAc)_2$ and $PdCl_2(PhCN)_2$ were used as catalysts,[9,63] and the reactions proceeded under oxygen atmosphere. 3-Substituted 1-(2-bromo(iodo)phenyl)thioureas were alkylated to *S*,*N*'-substituted *N*-(2-bromophenyl)carbamidothioate intermediates and then subjected to CuI-catalyzed intramolecular *N*-arylation to afford 1-substituted 2-sulfanyl-

1*H*-benzimidazoles in good to excellent yields.[5] Using the same catalytic system and mode of cyclization, *N*-(2-bromo-(iodo)phenyl)-*N*'-substituted formimidamide provided 1-substituted 1*H*-benzimidazoles, whereas the addition of nitrogen or oxygen nucleophiles to 2-(bromo(iodo))-arylcarbodiimides gave the corresponding substituted guanidine or isourea intermediates that cyclized to afford the respective 1-substituted 2-(heteroalkyl(aryl))-1*H*-benzimidazoles in comparable yields.[5] The latter reaction also proceeded with $Cu(OAc)_2$ as catalyst, albeit in lower yield.[47] A reductive intramolecular cyclization of benzylidene(2-nitroaryl)amines was accomplished *via* the insertion of nitrenoid group into the C(sp^2)–H bond of imine to produce 2-aryl-1*H*-benzimidazoles. Reductive deoxygenation of the nitro group to a nitrenoid group took place by selenium-assisted carbonylation with Se and CO.[109] A similar outcome was achieved by a one-pot synthesis using 2-azidoaniline and aryl aldehydes with $FeBr_2$ as catalyst.[63,109] An alternative method for the preparation of 2-aryl-1*H*-benzimidazoles is the $CuBr_2$-catalyzed oxidative dehydrogenation of *o*-phenylenediamine with various benzylamines,[47] while *o*-phenylenediamine and benzaldehyde were reported to give 2-phenyl-1*H*-benzimidazole in the presence of an organic Cu(II) catalyst.[109] CuBr catalyzed the addition of primary amines to the isocyano group of 1-bromo-2-isocyanobenzene and the intramolecular arylation of the thus formed amidine to provide 1-substituted 1*H*-benzimidazoles in moderate to good yields. Bromodifluoro- or trifluoromethyl-*N*-(2-iodophenyl)acetimidoyl chlorides reacted with various primary amines in the presence of CuI, providing 1-substituted 2-(bromodifluoromethyl)- or 2-(trifluoromethyl)-1*H*-benzimidazoles in poor to very good yields.[5] Two equally efficient reactions have been reported to give 1,2-disubstituted 1*H*-benzimidazoles bearing substituents in the phenyl ring. These processes are CuI- and L-proline-catalyzed amination of *N*-(2-iodophenyl)alkyl(aryl)amides with primary amines or ammonia followed by intramolecular condensation and $Cu(OAc)_2$-catalyzed one-pot reaction of benzamidines with arylboronic acids entailing an intermolecular C–N bond formation and an intramolecular aryl C(sp^2)–H functionalization/C–N bond forming procedure.[5,47] The CuBr-catalyzed reaction of *N*-(2-iodo(bromo)phenyl)acetamide derivatives with amidine hydrochlorides provided 1*H*-benzimidazoles substituted at position 2, but not at position 1. The reaction cascade may involve an Ullmann coupling, hydrolysis of the amide group, intramolecular nucleophilic attack of amino group onto the carbon atom in the amidine moiety, and aromatization by elimination of ammonia.[5,107]

14.1. {CCNCN} cyclization

Peng and Chen[110] selected an environmentally benign and affordable copper catalyst instead of palladium or nickel complexes for intramolecular C–N cross-coupling reactions of (*o*-haloaryl)amidines **177** to benzimidazoles **178** (Scheme 58). The reaction utilized Cu_2O as the catalyst, *N*,*N*'-dimethylethylenediamine as the ligand, K_2CO_3 as the base, and water as the solvent.

Scheme 58

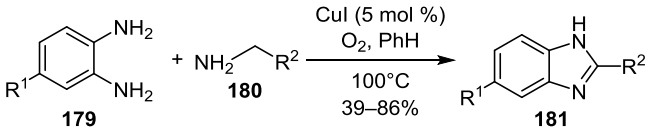


R^1 = Me, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-NCC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4
R^2 = H, 4-Me, 4-Cl, 4-NO_2, 4-$MeOC_6H_4$; X = Cl, Br, I

14.2. {NCCN + C} cyclization

Liu and Xu[111] reported that the reaction of a large variety of arylmethylamines, benzylamine, or 2-(aminomethyl)furan **180** with benzene-1,2-diamine, 4-chlorobenzene-1,2-diamine, or 4-methylbenzene-1,2-diamine **179** catalyzed by CuI under oxygen atmosphere at reflux in benzene afforded 2,5-disubstituted 1*H*-benzimidazoles **181** in good overall yields (Scheme 59).

Scheme 59

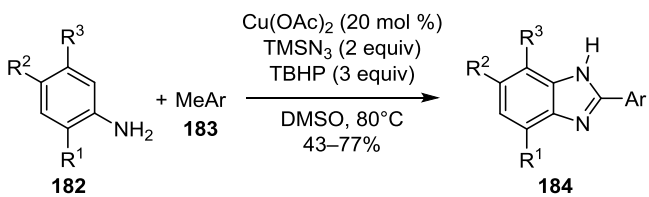


R^1 = H, Me, Cl; R^2 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-Fur

14.3. {CCN + C + N} cyclization

Punniyamurthy et al.[112] presented $Cu(OAc)_2$-promoted coupling of methyl arene **183** with anilines **182** in the presence of *tert*-butylhydroperoxide (Scheme 60) to produce an intermediate *N*-benzylaniline that reacted *in situ* with $TMSN_3$ to afford 2-aryl-4,6,7-trisubstituted 1*H*-benzimidazoles **184** at moderate temperature and in overall good yields. The reaction proceeded by a tandem C(sp^3/sp^2)–H functionalization and C–N bond formation.

Scheme 60



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3,5-$(Me)_2C_6H_3$, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-IC_6H_4, 3-I,4-BrC_6H_3, 2-Naphth
R^1 = H, Me; R^2 = H, Me, F, Cl, Br, MeO, MeS, NO_2; R^3 = H, Me

15. 1,2,3-TRIAZOLES

The 1,2,3-triazoles are important compounds because of their wide spectrum of biological activities and their representation in a number of important pharmaceutical drugs and agrochemicals.[113,114] One of the most successful "click reactions" to date is the catalyzed variant of the thermal Huisgen 1,3-dipolar cycloaddition reaction to

afford 1,2,3-triazoles. Sharpless and coworkers[115] improved on this reaction by applying a Cu(I)-catalyzed azide-alkyne [3+2] cycloaddition for the synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles. Another important metal-catalyzed synthesis of 1,2,3-triazoles is the $Cu(OAc)_2$-catalyzed reaction of *N*-tosyl hydrazones, derived from *N*-tosyl-hydrazines and aryl ethanones with anilines to provide 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles.[116] Many variations of these reactions exist. The *N*,*N*'-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) ligand together with CuBr was evaluated as the most efficient catalytic system for the formation of 1,4-disubstituted 1*H*-1,2,3-triazoles by the [3+2] cyclo-addition of *in situ* generated azides and monosubstituted alkynes in water and in contact with air. This high yielding 1,2,3-triazole synthesis worked efficiently also with disub-stituted alkynes.[38] 1,4-Disubstituted 1*H*-1,2,3-triazoles have been synthesized using microwave irradiation from azides and terminal alkynes with heterogeneous catalysis using either charcoal-supported elemental copper or elemental Cu and Mn.[117] Another synthesis of 1,4-disub-stituted 1*H*-1,2,3-triazoles under microwave irradiation is the $CuO/CuSO_4$-catalyzed reaction of alkyl halides and sodium azide to generate alkyl azides that couple with terminal alkynes.[118] The introduction of a dialkyl-aminomethyl group at position 4 and an arylalkyl group at position 1 of 1*H*-1,2,3-triazole occurs *via* the reaction of dialkylamines with propargyl bromide or iodide and arylalkyl azides under CuI-catalysis. Reactions take place in water under an atmosphere of air and the yields of products are from very good to excellent.[38]

$CuSO_4 \cdot 5H_2O$ and sodium ascorbate have been used to catalyze the reaction of formaldehyde, sodium azide, and terminal alkynes to provide 4-substituted 2-hydroxymethyl-2*H*-1,2,3-triazoles[45] and the reaction of 2-azido-2-phenyl-ethanol, derived *in situ* from styrene epoxide and sodium azide, with phenylacetylene to afford 2-phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol in 92% yield.[107] 1-Substituted 5-hydroxymethyl-4-trifluoromethyl-1*H*-1,2,3-triazoles were synthesized in high regioselectivity by Rh(II)-catalyzed cycloaddition of trifluoromethyl alkynols with azides.[109] The introduction of an aryl group at position 5 of 1,4-disub-stituted 1*H*-1,2,3-triazoles was accomplished by a four-component reaction using alkyl halides and sodium azide, to generate *in situ* alkyl azides, alkyl- or aryl-substituted alkynes, and aryl iodides catalyzed by CuI.[45]

In their review article, Chen, Ren et al.[119] describe a multi-component synthesis of 1,4,5-trisubstituted 1*H*-1,2,3-tri-azoles. The review focuses on the synthesis of 5-halo-, 5-hydrocarbyl-, and 5-heteryl-1,2,3-triazoles. In the synthe-ses of (5-bromo- or iodo)-1,4-disubstituted 1*H*-1,2,3-triazoles, azides and terminal alkynes were used as the [3+2] cycloaddition components. For the introduction of the iodine atom, CuI/ICl, CuI/NBS, NaI/$Cu(ClO_4)_2$, or CuI/*t*-$BuMe_2SiCl$ have been used, whereas CuBr/NCS or CuBr/TBDMSCl were used for bromination. 1,4-Substituted amino-5-(allyl or propargyl)-1*H*-1,2,3-triazoles were synthe-sized from ynamides, azides, allyl iodide or propargyl iodide. A regioselective approach to 4-substituted 5-alkynyl-1-aryl-1*H*-1,2,3-triazoles was achieved by using $CuI/CuSO_4$-cata-lyzed tandem 1,3-dipolar cycloaddition of terminal alkynes, arylboronic acids, and sodium azide at room temperature. By essentially replacing arylboronic acids by substituted methyl bromides or iodides and $CuI/CuSO_4 \cdot 5H_2O$ by Cu_2O in the previous cycloaddition reaction, 4-substituted 1-alkyl-5-alkynyl-1*H*-1,2,3-triazoles were obtained under equally mild conditions, but with higher efficiency, since only a low loading (1 mol %) of Cu_2O catalyst was required. Further reactions of interest are the CuI-catalyzed multicomponent synthesis of 1,4-disubstituted 1*H*-1,2,3-triazolyl-5-phospho-nates from terminal alkynes, azides, and dialkyl phosphites and the CuI-catalyzed interrupted click reaction of azides and terminal alkynes followed by reaction with a hetero-atom electrophile such as *O*-benzoyl-*N*,*N*-dibenzylhydroxyl-amine or *S*-methyl benzenesulfonothioate to provide 1,4-disub-stituted 5-amino- or methylsulfanyl-1*H*-1,2,3- triazoles.[118]

15.1. {NNN + CC} cyclization

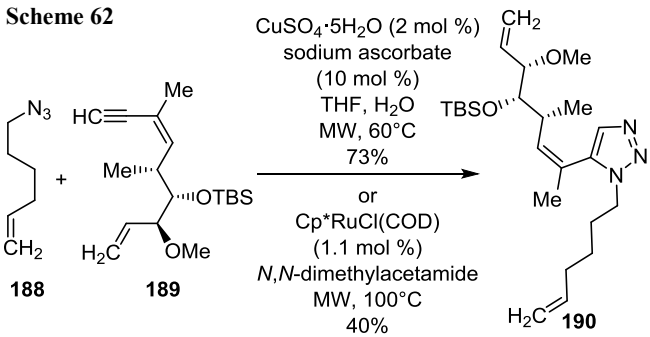
Tiwari and coworkers[120] developed a useful one-pot tandem nano Cu(0)/Fe_3O_4-catalyzed synthesis of 4-methoxy-1-[(methylsulfanyl)methyl]-1*H*-1,2,3-triazoles **187** from alkyl, aryl, heteroaryl, or polyaromatic terminal alkynes **185**, trimethylsilyl azide ($TMSN_3$), and DMSO (Scheme 61). The nitrogen and sulfur atoms are derived from the latter two reagents, respectively. A possible reaction pathway is the *in situ* generation of (azidomethyl)(methyl)sulfane from $TMSN_3$ (**186**) and DMSO followed by [3+2] cycloaddition with the appropriate *in situ* formed copper acetylide species. The important feature of this reaction is the magnetic recovery of the catalyst and its reuse up to six times virtually without loss of activity.

Scheme 61

R = MeO, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu, Cy, Ph, $Me(CH_2)_4$, $Me(CH_2)_4O$, 2-MeC_6H_4, 4-EtC_6H_4, 3-$F_3CC_6H_4$, 2-thiophenyl, 3-pyridyl, 1-Ts-3-pyrrolyl, pyren-1-yl, phenathren-9-yl, 6-MeO-2-naphthyl

As part of a route toward the synthesis of three macro-triazole analogs of migrastatin, Murphy, Passarella, and coworkers[121] reported the cycloaddition of 6-azidohex-1-ene (**188**) with terminal alkyne **189** catalyzed by $CuSO_4 \cdot 5H_2O$ and sodium ascorbate that gave 1,5-disubstituted 1*H*-triazole derivative **190** in 73% yield (Scheme 62).

Scheme 62



The metal-catalyzed synthesis of five-membered nitrogen-containing heterocycles has been exemplified by numerous methods entailing a spectacular variety of predominantly transition metal catalysts. The hallmarks of these reactions are their convenience and efficiency.

No doubt this area of research will continue developing, since pyrroles, indoles, carbazoles, as well as their saturated and unsaturated analogs are useful precursors in the construction of natural and nonnatural products with significant biological activity, finding useful applications in the pharmaceutical and organic materials science industries.

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