Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ChemCommun

FEATURE ARTICLE

Copper-mediated aromatic amination reaction and its application to the total synthesis of natural products

Kentaro Okano,[b] Hidetoshi Tokuyama[b,*] and Tohru Fukuyama[a,*]

Herein, we review copper-mediated aromatic amination reactions including the classical Ullmann coupling and the recently developed mild aryl amination with an effective ligand as well as the C–H amination reaction. Several applications of intramolecular aryl amination to the syntheses of natural products demonstrate the general applicability of the reaction.

1. Introduction

Because a wide variety of pharmacologically important natural products such as duocarmycins and other compounds **1**-**13** contain aromatic C(sp^2)–N bonds, the introduction of nitrogen functionalities onto aromatic rings has been one of the main topics in organic synthesis (Figure 1). Standard methods for the introduction of an amino functionality are illustrated in Scheme 1. One of the most fundamental methods for preparation of anilines is a nitration of aromatic compounds **14** followed by reduction of the nitro group. Because of the harsh reaction conditions used for conventional nitration, the procedures are not always compatible with many sensitive functional groups (Route A). Amination via a benzyne intermediate **15** accompanies a regiochemical problem, giving rise in general to regioisomeric mixtures when using unsymmetrical substrates. Furthermore, a typical generation of reactive benzyne species, for instance, β-elimination of aryl halides, requires a strong base such as $NaNH_2$ (Route B).[1] Nucleophilic aromatic substitution (S_NAr) via a Meisenheimer complex **16** requires high reaction temperature or aryl halides activated by strong electron-withdrawing groups such as a nitro group at the *para* or *ortho* position,[2] thereby diminishing the substrate generality (Route C). Another method for the synthesis of aniline derivatives is halogenation followed by transition metal-catalyzed aryl amination. This route is superior to the above methods because halogenation on an aromatic ring generally proceeds under milder conditions compared to those required for nitration (Route D). In this review, we focus on the historical overview of copper-mediated aromatic amination and its synthetic utility of the intramolecular amination in the total syntheses of natural products with nitrogen heterocycles, because tremendous intermolecular aminations have been reported compared to intramolecular aminations.
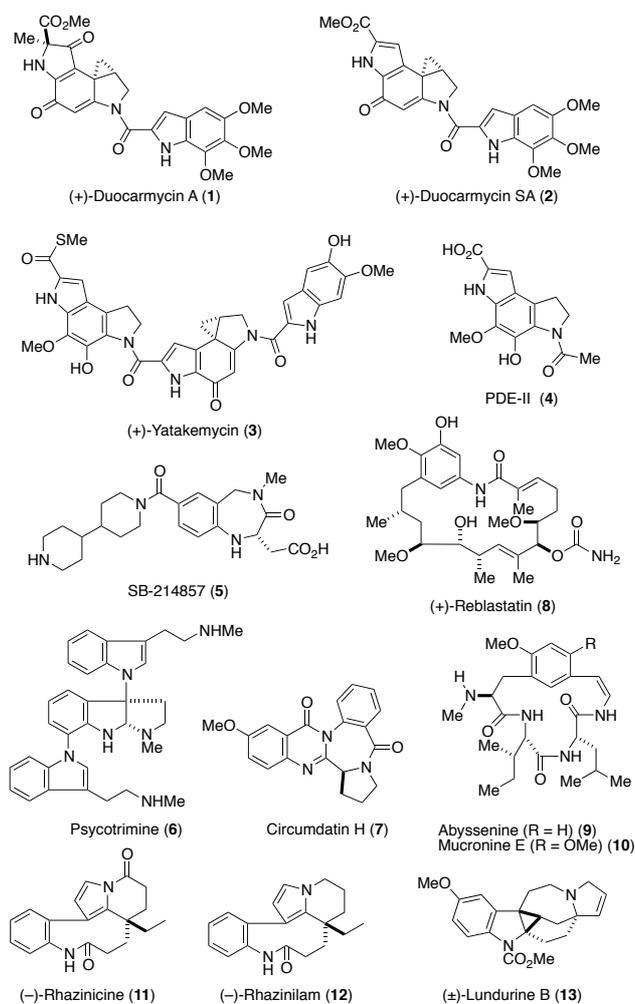
**Figure 1** Natural Products having C(sp^2)–N bonds.
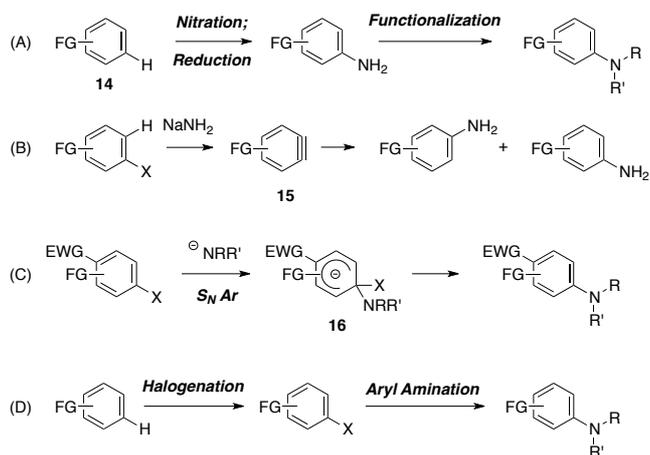
Scheme 1 Approaches to N-arylamines.

Among the transition metal-catalyzed N-arylations, the copper-catalyzed Ullmann[3]–Goldberg[4] reaction is known to be one of the most classical methods (Scheme 2). However, this reaction is not always useful because of harsh conditions, such as high reaction temperature and/or neat conditions. Therefore, the reaction lacks broad functional group compatibility, which is required for the synthesis of highly functionalized, complex molecules.
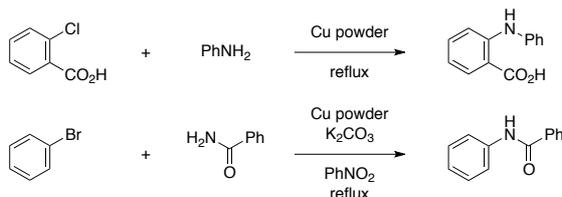

Scheme 2 Copper-mediated Ullmann-Goldberg reaction.

In 1983, Kosugi and Migita reported an aryl amination reaction of aryl bromides using tributyltin amides **17**, catalyzed by PdCl$_2$[P(*o*-tolyl)$_3$]$_2$ (Scheme 3). [5] Reaction of *N,N*-dialkyl tinamides and aryl bromides such as *m*- or *p*-tolyl bromides provided the corresponding coupling products in good yields, although reactions using aryl bromides with methoxy, acetyl, nitro, and dimethylamino substituents resulted in low to moderate yields of the products. In 1994, Guram and Buchwald extended the chemistry beyond electron-neutral aryl bromides.[6] They reported that the use of tin amides prepared from lithium amides and *n*-Bu$_3$SnCl in diethyl ether was ineffective, due to the deactivation of the active species by LiCl, residual BuLi, or diethyl ether. They overcame this problem by in situ generation of tin amides from *n*-Bu$_3$SnNEt$_2$ (**18**) and amines under heating conditions with the removal of volatile Et$_2$NH. The modified amination proceeded in high yield with limited tin amides that could be derived from secondary amines.
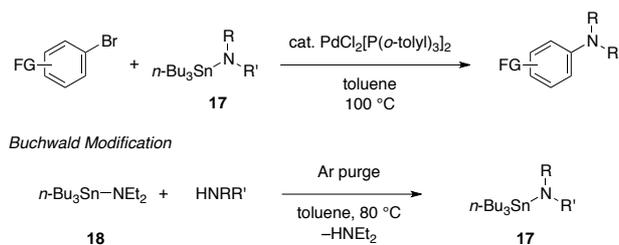

Scheme 3 Synthesis of aniline by coupling of aryl bromide and tin amide.

In 1995, the research groups of Buchwald and Hartwig concurrently published their results on the tin-free amination of aryl halides. They carried out the amination reactions at 65–100 °C using amines and either NaO*t*-Bu or LiN(SiMe$_3$)$_2$ as a base. The catalysts used initially were PdCl$_2$[P(*o*-tolyl)$_3$]$_2$, Pd[P(*o*-tolyl)$_3$]$_2$, or a combination of Pd$_2$(dba)$_3$ and P(*o*-tolyl)$_3$ (Scheme 4). Palladium complexes with monodentate ligands, such as P(*o*-tolyl)$_3$, were effective catalysts for the amination of aryl bromides or aryl iodides; however, these catalysts cannot be applied to aryl triflates. Buchwald and Hartwig reported on the amination of aryl triflates **19** using palladium complexes with the bidentate phosphine ligands BINAP and DPPF as effective catalysts (Scheme 5).[7] Electron-poor aryl halides were susceptible to cleavage under the basic reaction conditions, because the electron-withdrawing groups stabilized the generated phenolate. The use of K$_3$PO$_4$ as the base was effective for suppressing the undesired cleavage of the triflate.[8]
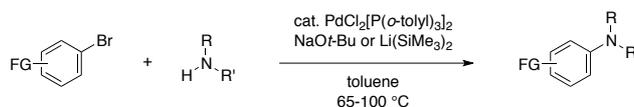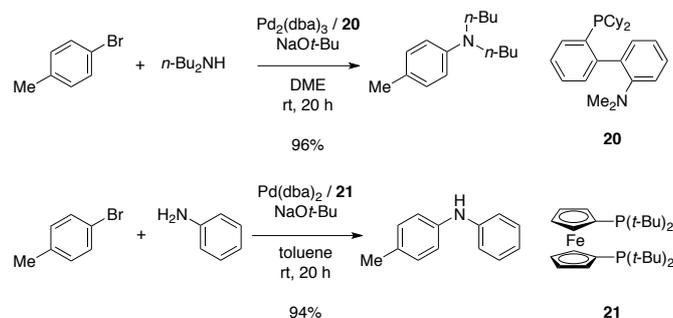

**Scheme 4** Palladium-catalyzed tin-free aryl amination.
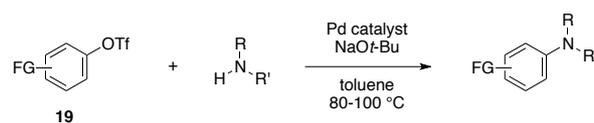
Scheme 5 Palladium-catalyzed aryl amination of aryl triflates.

In 1998, Buchwald reported a highly active catalyst for palladium-catalyzed aryl amination. The reaction proceeds at room temperature utilizing bidentate ligand **20**.[9] Hartwig also published a room temperature aryl amination using modified DPPF-type ligand **21**.[10] Hartwig described that the use of sterically hindered phosphine **21** increases the rates of both oxidative addition and reductive elimination (Scheme 6).

Scheme 6 Mild palladium-catalyzed aryl amination.

Although triarylbismuths,[11] aryllead triacetates,[12] arylboronic acids,[13] and hypervalent aryl siloxanes[14] were excellent transmetalating agents for mild copper-catalyzed aminations, the preparation of densely functionalized substrates often requires multistep sequences, and thus their synthetic utilities are limited (Scheme 7).
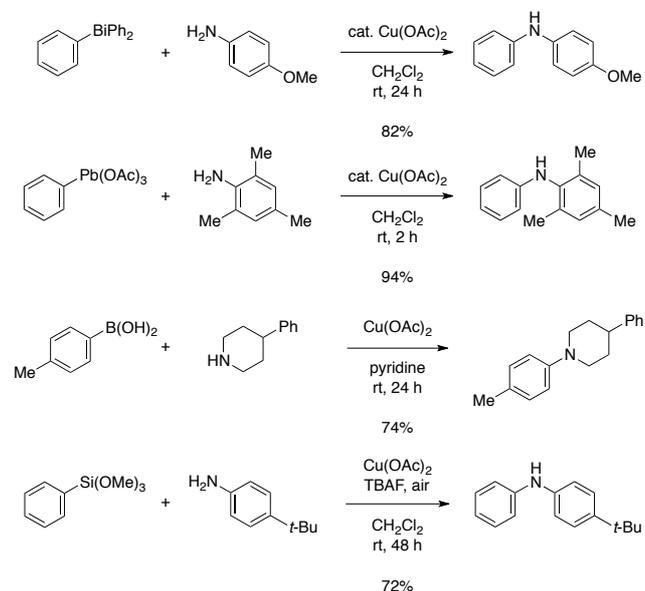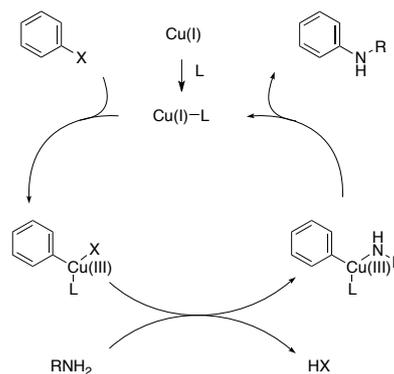

Scheme 7 Copper-catalyzed amination with arylmetal species.

2. Recently developed copper-mediated aromatic amination

### 2.1 Ligand-promoted aromatic amination

Several different reaction mechanisms have been proposed for the Ullmann coupling, but the broadly accepted reaction mechanism is a Cu(I)/Cu(III) catalytic cycle that was initiated by an oxidative addition of an aryl C–X bond to Cu(I) to generate Cu(III) species (Scheme 8).[15] Subsequent ligand exchange followed by reductive elimination provides the N-arylated product with the regeneration of Cu(I) species. In contrast to the classical Ullmann and Goldberg aromatic amination requiring harsh reaction conditions, N-arylation conditions involving a combination of copper(I) salt and

ligand/Brønsted base are milder and have been widely used since the late 1990s.[16]

Scheme 8 Plausible mechanism for a copper-catalyzed amination.

Mechanistic support to promote the reaction was not provided at the beginning of the breakthrough regarding the mild copper-catalyzed amination reaction around 2000. Recent research has revealed that an appropriate choice of ligands is necessary to conduct the animation processes under mild conditions. In 1998, Ma and co-workers first reported that an amino acid acts as an effective ligand (Scheme 9).[17] Notably, protection of either a hydroxyl group or an amino group resulted in significant decrease in chemical yield of the product, which supports the necessity of the appropriate coordination of the unprotected amino acid to the copper center to stabilize the Cu(III) active species to promote the reaction.
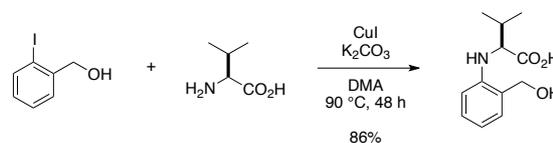
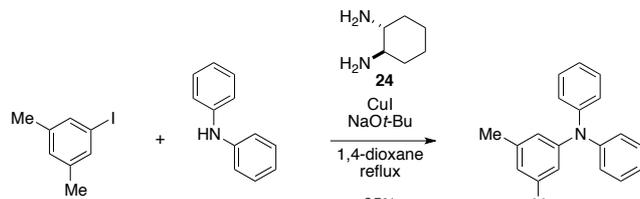**Scheme 9** Aryl amination using valine as a ligand.

Goodbrand and Hu reported that a combination of CuCl–phenanthrine (**22**) was also effective for aryl amination to provide triaryl amine **23** with low catalyst loading (Scheme 10).[18] The bidentate nature of the phenanthroline skeleton promoted the formation of the active copper catalyst.
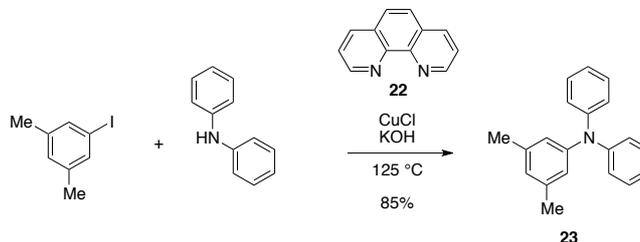

Scheme 10 Aryl amination using 1,10-phenanthroline as a ligand.

Buchwald and co-workers reported 1,2-diaminocyclohexane (**24**) as an effective ligand (Scheme 11).[19] A combination of *trans*-1,2-diaminocyclohexane and sodium *tert*-butoxide was effective for the aryl amination, which provides a wide variety of heterocycles.


Scheme 11 Aryl amination using 1,2-diaminocyclohexane as a ligand.

In 2003, Buchwald and co-workers introduced *N,N'*-diethylsalicylamide (**25**) as an effective ligand to conduct mild copper-catalyzed amination (Scheme 12).[20] The amination reaction were carried out at 90 °C to provide corresponding anilines in excellent yields with high functional group compatibility.
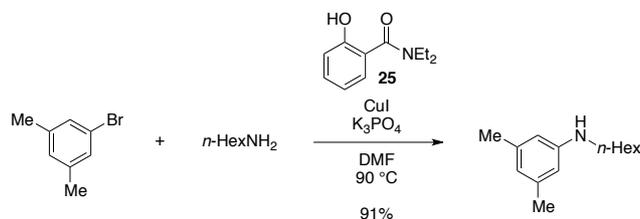

Scheme 12 Aryl amination using *N,N'*-diethylsalicylamide as a ligand.

Buchwald and co-workers developed a method for the copper-catalyzed amination of aryl iodides, which was catalyzed by a combination of copper iodide and ethylene glycol (**26**) in 2-propanol (Scheme 13).[21] The amination procedure is not moisture sensitive and can be carried out under atmospheric conditions.
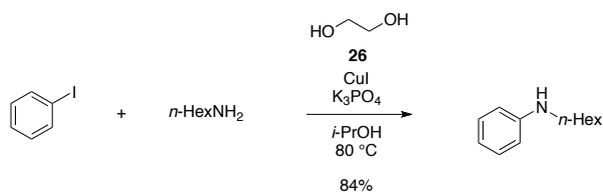

Scheme 13 Aryl amination using ethylene glycol as a ligand.

In addition to ethylene glycol, triol **27** was also effective for the introduction of amine functionality on aryl iodides/bromides, which was reported by Chen and co-workers (Scheme 14).[22] They also applied the reaction conditions to introduce oxygen/sulfur to the aryl halides, which should be useful for the synthesis of heteroatom-containing compounds.
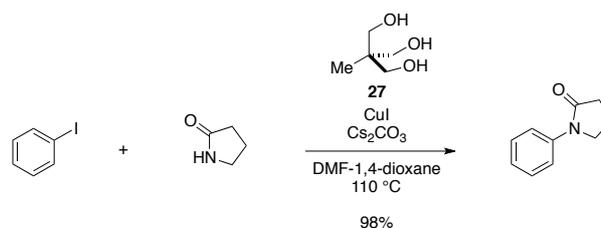

Scheme 14 Aryl amination using triol as a ligand.

Despite the recent progress in this field, longer reaction times and inefficient compatibility of functional groups on substrates remain serious limitations. Buchwald and co-workers reported that the catalyst is occasionally deactivated by competitive *N*- or *O*- arylation of the ligand (Scheme 15). They directed their attention to β-diketones, which would be less prone to arylation. After the optimization of the process, β-diketone **28** was found to be superior to salicylamide **25**. The aryl amination reaction proceeded even at room temperature when 5-iodo-1,3-dimethylbenzene was used as a starting material.[23]
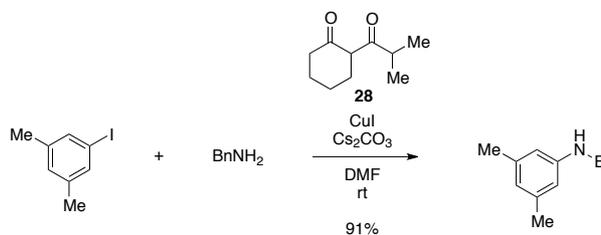
Scheme 15 Aryl amination using β-diketone as a ligand.

Diiminodipyridine **29** also promotes amidation reaction as a tetradentate ligand (Scheme 16).[24] In addition, several aryl bromides and iodides were converted to the corresponding amides, carbamates, pyridazin-2-one, azoles, diethyl malonate, ethyl cyanoacetate, and malononitrile using the combination of CuI and ligand **29**.
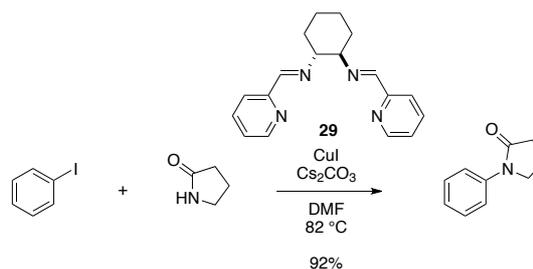
Scheme 16 Aryl amidation using diiminodipyridine as a ligand.

In 2012, Fu and Peters reported a photoinduced Ullmann coupling that proceeds even at −40 °C (Scheme 17).[25] They proposed that the unusually mild reaction proceeded via a single-electron transfer mechanism that is initiated by the activation of copper complex **30**.
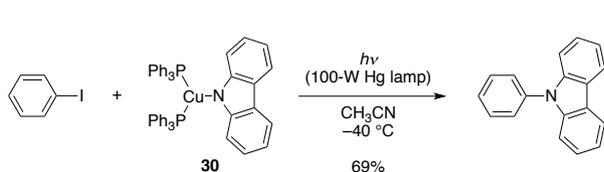
Scheme 17 A mild photoinduced Ullmann coupling reaction.

2.2 Different modes of reactions by switching Pd/Cu or ligands [26]

In contrast to palladium catalysts, copper catalysts possess different reactivities. In addition, even with the same copper precatalysts, the choice of an appropriate ligand sometimes affects reaction pathways to provide dissimilar products, which provides the versatility of the copper-mediated aryl amination. In this section, we present several examples of aminations with different modes of reaction via switching catalysts or ligands.
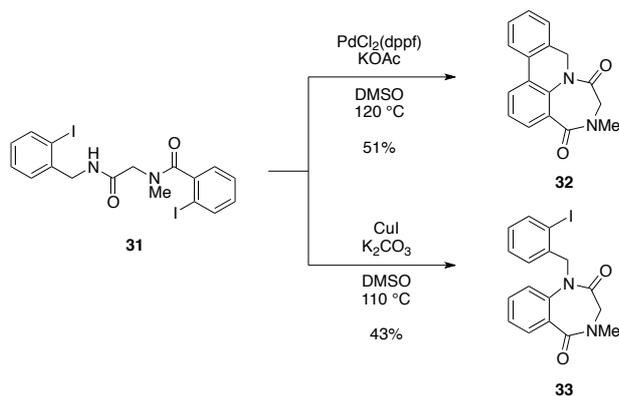
Zhu and co-workers reported a palladium-catalyzed one-pot construction of tetracyclic compound **32** from amide **31** via N-arylation and subsequent biaryl coupling (Scheme 18). [27] Conversely, copper-catalyzed amination conditions provided diazepine **33**. Notably, they also reported that an additional ligand was ineffective at promoting the reaction, suggesting that the amination proceeded via the coordination of the nitrogen/oxygen of the substrate to copper.


Scheme 18 Complementary reactivity of palladium- and copper-mediated aryl amination.

Buchwald and co-workers reported the C/N arylation of oxindole (**34**) utilizing a palladium/copper catalyst (Scheme 19). [28] Although palladium-catalyzed conditions chemoselectively provide C-arylated oxindole **35**, copper-catalyzed conditions give N-arylated oxindole **36**. Computational studies suggest that the reactions proceed via C–Pd/N–Cu reactive species, which provides mechanistic insight into the arylation of unprotected indolines.
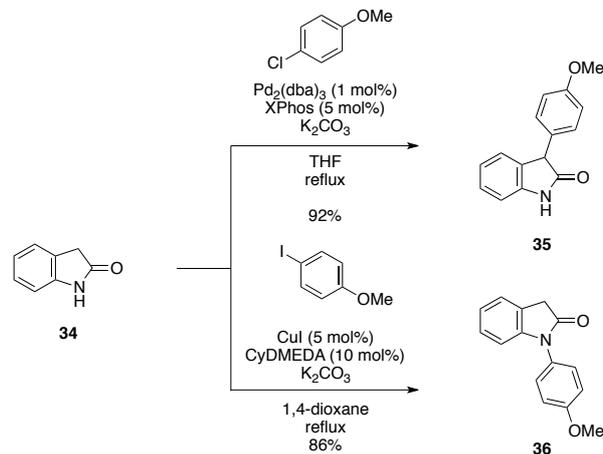
Scheme 19 Orthogonal chemoselectivity of palladium- and copper-mediated aryl amination.

In addition to the metal species that is replaced, an appropriate choice of ligand is necessary for the chemoselective N/O arylation (Scheme 20). [29] The complementary copper-catalyzed N/O arylation of 5-aminopentyl alcohol proceeds simply by switching a ligand, which should be useful for the synthesis of several aniline/phenol derivatives. It was proposed that the coordination of the enolate from diketone **28** to copper generates a less electrophilic Cu(III) species, which predominates N-arylation. Contrarily, the use of 3,4,7,8-tetramethylphenanthroline (**38**) provides O-arylated compound **39**. The bromine atom remains untouched in the copper-catalyzed reaction system, which allows for further functionalization.
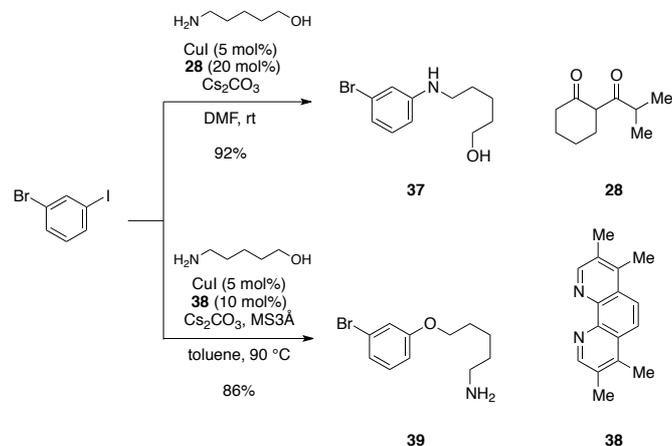
**Scheme 20** Ligand-controlled chemoselective N/O-arylation.

2.3 Mild aromatic amination through the coordination of copper species and nitrogen atom

As discussed above, an intermolecular aryl amination has been extensively investigated and several reaction conditions have been developed to date. Conversely, intramolecular reactions that generate N-heterocyclic compounds, which are often found

in biologically active natural products or medicines, have been rarely reported. In the amination reactions, more catalytic loading (10%~stoichiometric) of copper species[16] is generally required than that in the palladium-catalyzed aryl aminations[30]; however, in some cases, heteroatoms in a substrate remarkably accelerate the reaction rate by the coordination of these atoms and copper species, thus providing the corresponding heterocyclic compounds under mild conditions.

Fukuyama and co-workers independently developed an intramolecular aryl amination during the course of synthetic studies of duocarmycins.[31] They examined the selectivity of the intramolecular amination using substrate **40** with an iodo group introduced at a *meta* position to aminopropyl chain (Scheme 21). Notably, unlike the conventional palladium-catalyzed systems, most of the iodo group survived under the reaction conditions. An acceptable explanation for the bromo selective reaction in the presence of an iodo group, which would be a preferred position for the oxidative addition of palladium catalysts, is that the reaction would be initiated by the coordination of amine to copper species followed by oxidative addition to the proximal C(sp²)–Br bond (Scheme 22).
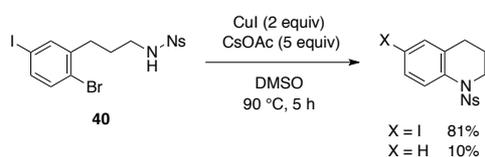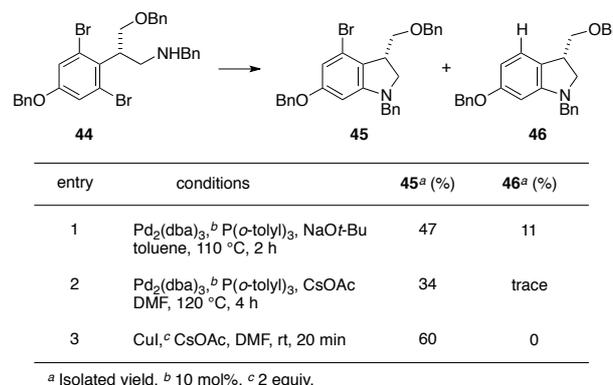

Scheme 21 Intramolecular aryl amination using CuI and CsOAc.

The expected mechanism of this intramolecular amination is shown below (Scheme 22). Preliminary experiments indicated that both Cu(I) and carboxylate ions or CuOAc (**41**) are essential for the smooth conversion. Addition of CsOAc spontaneously turned the suspension of CuI in DMF to a clear solution in which the conversion started strongly indicates that the active species is CuOAc generated from CuI and CsOAc. Then, CuOAc coordinates to the nitrogen, oxidatively adding to the C–X bond to form Cu(III) complex **42**, which finally undergoes reductive elimination to yield the corresponding cyclic amine **43** with the regeneration of the Cu(I) species.
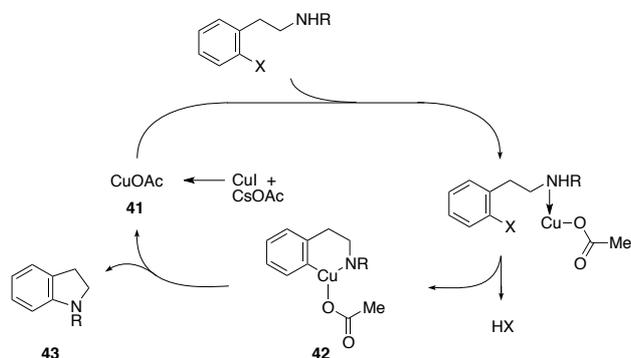
Scheme 22 Plausible reaction mechanism for the aryl amination.

Different from the conventional palladium-catalyzed aryl amination reaction, the copper-mediated aryl amination reaction is useful, because an undesired reduction of the halogen atom is suppressed and the remaining halogen group of indoline **45** is useful for further functionalization (Scheme 23).

entry	conditions	45[a] (%)	46[a] (%)
1	Pd₂(dba)₃,[b] P(*o*-tolyl)₃, NaO*t*-Bu toluene, 110 °C, 2 h	47	11
2	Pd₂(dba)₃,[b] P(*o*-tolyl)₃, CsOAc DMF, 120 °C, 4 h	34	trace
3	CuI,[c] CsOAc, DMF, rt, 20 min	60	0

[a] Isolated yield. [b] 10 mol%. [c] 2 equiv.

Scheme 23 Mild combination of CuI and CsOAc.

2.4 Recent progress on the spectroscopic analysis of active Cu(III) species

Recently, despite the mechanistic debate, there was no report on the observation or isolation of active Cu(III) species in aryl aminations. Ribas and co-workers first described the direct observation of aryl carbon-Cu(III)-X species (Scheme 24).[32] They utilized a macrocyclic tridentate ligand **47** to stabilize the planar Cu(III) species[33] and isolated the copper complex **48** as a red crystal for which the structure was confirmed by X-ray crystallographic analysis. These results indicate that an appropriate ligand decreases the activation energy for the formation of the Cu(III) species.
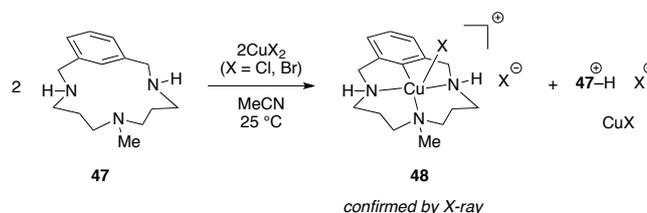
Scheme 24 Formation of copper(III) complex.

This protocol for generating the tridentate ligand stabilized Cu(III) species at the unactivated aromatic C–H bond provides an opportunity to realize direct aromatic C–H amination (Scheme 25). Thus, treatment of the Cu(III) complex **48** with triflic acid provides the corresponding aryl bromide **49** and Cu(I) species, which catalyzes amidation with pyridone (**50**) to provide amide **51** even at room temperature.

TfOH

MeCN
25 °C

+ [Cu(CH₃CN)₄](OTf)

48   **49**

[Cu(CH₃CN)₄](OTf)
(3 mol%)

49   **50**   **51**
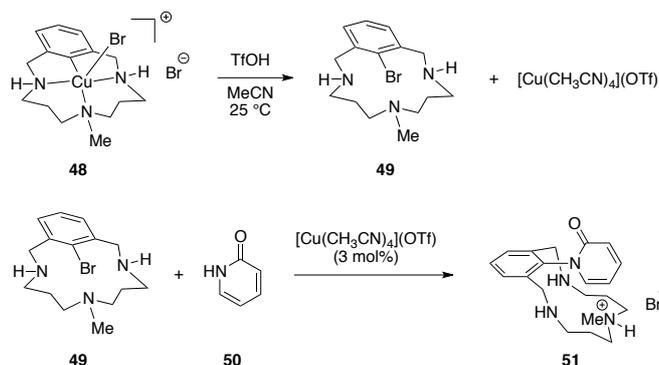
Scheme 25   Copper-mediated C–H functionalization.

and PhI(OAc)₂ at 50 °C. The authors proposed that the amination reaction proceeded through radical intermediates because the addition of a radical inhibitor, such as BHT, significantly decreasing the yield of the carbazole.

cat. Cu(OTf)₂
PhI(OAc)₂
CF₃CO₂H

ClCH₂CH₂Cl
50 °C

93%

56   **57**

Scheme 28   Synthesis of carbazole by directed C–H amination.

2.5 Directed aromatic C–H amination

In addition to the extensive research on the directed amination of aromatic C–H bonds using palladium- or platinum-based catalysts in the 2000s,[34] copper-catalyzed reactions have also been vigorously studied owing to the lower cost and toxicity of copper. In 2008, Buchwald and co-workers reported a Cu(OAc)₂-catalyzed synthesis of benzimidazole **53** from arylamidine **52** via C–H functionalization (Scheme 26).[35] In the reaction, molecular oxygen is used as the reoxidant to generate water as waste. Thus, this process should be environmentally benign and an example of a next-generation chemical transformation.

Cu(OAc)₂
propionic acid

DMSO
100 °C

68%

52   **53**
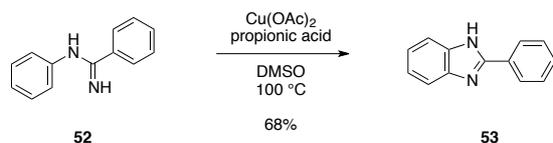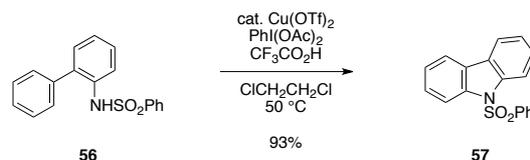
Scheme 26   Directed amination to form benzimidazole.

Zhang and Zhu reported a copper-catalyzed synthesis of pyrido [1,2-*a*]benzimidazole **55** by the amination of the aromatic C–H bond of N-phenyl-2-aminopyridine **54**, utilizing a combination of Cu(OAc)₂ and Fe(NO₃)₃·9H₂O (Scheme 27).[36] They also conducted mechanistic studies based on the kinetic isotope effect, which suggested that the reaction proceeds via a Cu(III)-catalyzed electrophilic aromatic substitution (SEAr) pathway.

Cu(OAc)₂
Fe(NO₃)₃·9H₂O
PivOH, O₂

DMF
130 °C

88%

54   **55**
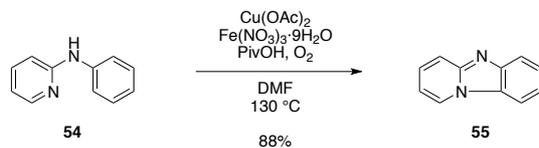
**Scheme 27**   Directed aryl amination of N-phenyl-2-aminopyridine.

Chang reported an intramolecular oxidative formation of C–N bond to provide carbazole **57** from **56** (Scheme 28).[37] Various carbazoles were efficiently synthesized from the corresponding 2-aminobiphenyl derivatives using a combination of Cu(OTf)₂

Deng and Zhou reported a copper-catalyzed synthesis of N-aryl acridones via sp² C–H amination under aerobic conditions (Scheme 29).[38] The reaction conditions are quite simple, and several functional groups are tolerable.

cat. CuI

DMSO
120 °C, 48 h

78%

under air

58   **59**
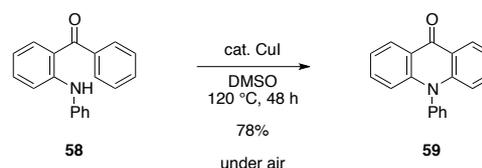
Scheme 29   Synthesis of N-arylacridone by direct C–H amination.

An intermolecular aryl C–H amination was first reported by Yu and co-workers in 2006 utilizing a pyridyl group as a directing group (Scheme 30).[39] After the report, several research groups also demonstrated the effectiveness of the pyridyl group in the same aryl C–H amination.[40] Recently, Daugulis and co-workers reported the intermolecular aryl C–H amination utilizing a quinolylamide moiety as an effective directing group (Scheme 31).[41,42] The directing group on compound **63** was converted to carboxylic acid by basic hydrolysis.

Cu(OAc)₂
TsNH₂

MeCN
reflux
(under air)

74%

60   **61**
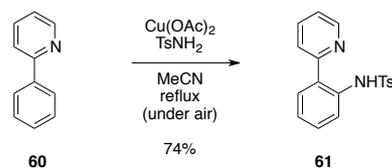
Scheme 30   Intermolecular directed C–H amination using pyridyl group.

cat. Cu(OAc)₂
cat. Ag₂CO₃
NMO

NMP
110 °C

81%

NaOH

EtOH
reflux

91%

t-Bu   *t*-Bu   *t*-Bu

62   **63**   **64**
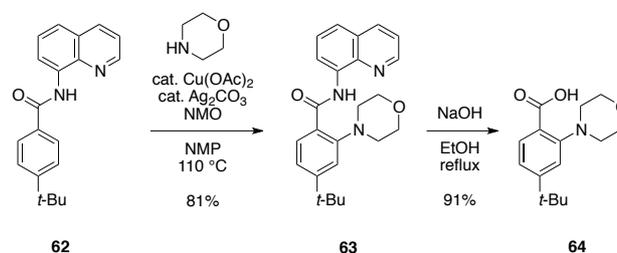
Scheme 31   Intermolecular directed C–H amination using quinolylamide.

3. Application to natural product synthesis

The utility of copper-mediated aryl amination has been demonstrated by the application of the reaction to the syntheses of several bioactive natural products. Because the total synthesis of natural products using intermolecular aryl amination reaction was fully summarized in recent reviews,[43] we herein focus on examples featuring intramolecular aryl aminations.

3.1 Fukuyama's synthesis of pyrroloindole alkaloids

3.1.1 Total synthesis of duocarmycins A and SA[44]

In 2003, Fukuyama reported the total synthesis of antitumor antibiotics (+)-duocarmycins A (**1**) and SA (**2**) involving a mild copper-mediated aryl amination reaction to construct all of the aryl C-N bonds in these natural products. The synthesis starts with the preparation of the common indole segment **65** (Scheme 32). Treatment of a bromobenzaldehyde with phosphonate **67** and TMG (*N*,*N*,*N'*,*N'*-tetramethylguanidine) exclusively provides (*Z*)-dehydroamino acid derivative **68** in a stereoselective manner. Expected intramolecular amination using a combination of CuI and CsOAc proceeds successfully even at the congested reaction site and provides the corresponding indole **69** in almost quantitative yield, which is converted to acid chloride **65** for the condensation reaction at a later stage in the synthesis.
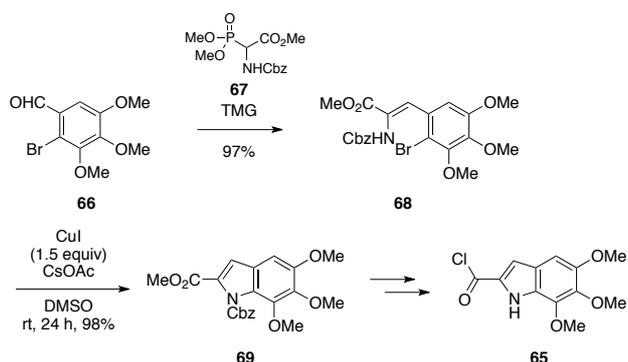
**Scheme 32** Synthesis of the common indole segment.

The synthesis of the left-hand segment of duocarmycin A (**1**) starts with the iodine-selective lithiation of trihalobenzene **70** and subsequent Michael addition to chiral nitroalkene **71** (Scheme 33). After conversion to benzylamine **73**, the aryl amination using a combination of CuI and CsOAc was then conducted to form indoline with the other bromo group retained. The conventional palladium-catalyzed amination reactions, however, provided the desired product in low yields. After the protection of the primary alcohol with *tert*-butyldimethylsilyl ether, a side chain bearing the chiral tetrasubstituted carbon center was constructed by the regioselective addition of the aryl lithium to azlactone **75**. A bromo group was then introduced at the *para* position to the nitrogen. The second intramolecular aryl amination reaction proceeded smoothly at room

temperature with stoichiometric copper iodide to provide the indolinone **78** in quantitative yield. Finally, assembly of two segments and the formation of the cyclopropane ring were successfully achieved to obtain (+)-duocarmycin A (**1**).
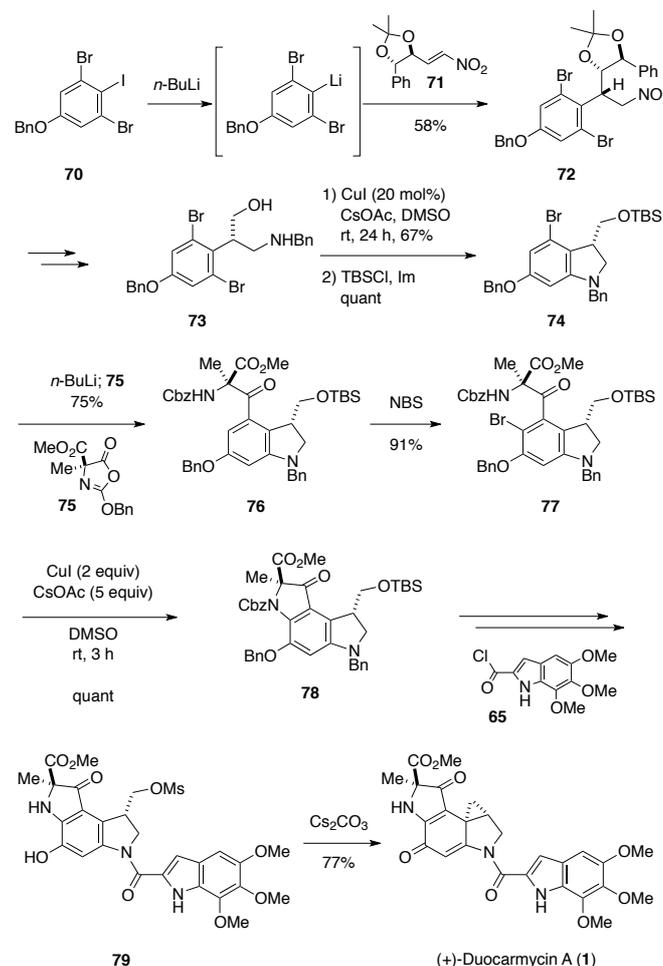
Scheme 33 Synthesis of (+)-duocarmycin A.

The synthesis of duocarmycin SA (**2**), which has an indole ester moiety, begins with Mizoroki–Heck reaction of the iodoindoline **80** that was derived from common intermediate **74** (Scheme 34). Regioselective bromination provided **82**, which was subjected to the amination conditions to obtain the tricyclic dihydropyrroloindole **83**. Finally, the total synthesis of duocarmycin SA (**2**) was accomplished in a similar manner to that developed for (+)-duocarmycin A (**1**).
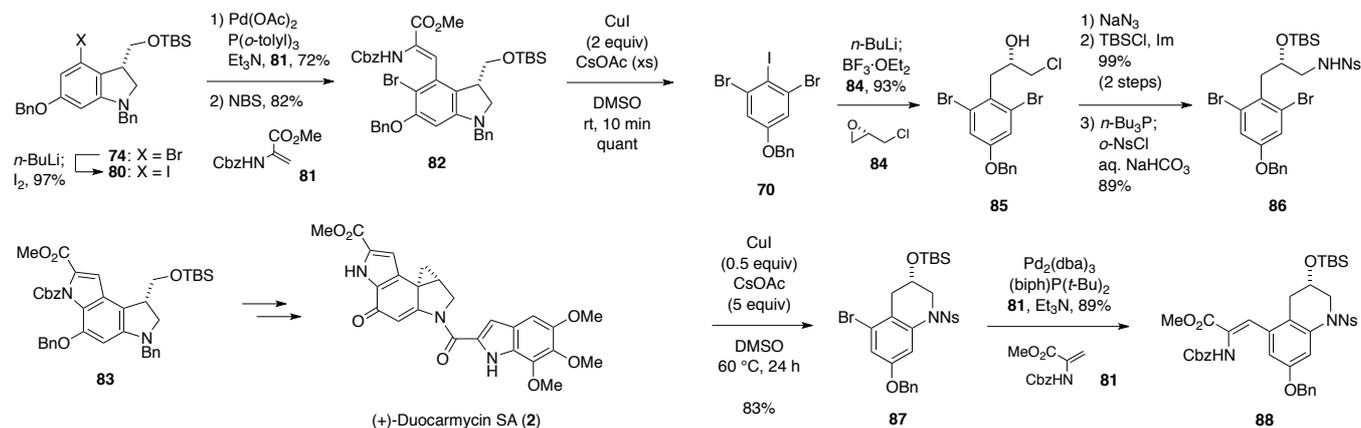
Scheme 34 Synthesis of (+)-duocarmycin SA.

3.1.2 Yatakemycin[45]

Fukuyama and co-workers also applied their intramolecular amination strategy to the total synthesis of a related compound, yatakemycin (**3**). The middle segment of **90** corresponds to the left segment of duocarmycin SA (**2**), except for the ester moiety. They accomplished a more efficient synthetic route for the middle segment by utilizing the tetrahydroquinoline derivative as a key intermediate (Scheme 35). The stereochemistry was controlled by the regioselective ring opening of optically active epichlorohydrin (**84**) with a 2,6-dibromophenyl lithium species that was generated by the iodine-selective halogen–lithium exchange of **70**. The chlorohydrin **85** was then converted to nosylamide **86** in a three-step sequence. The key intramolecular aryl amination proceeded smoothly to provide the desired tetrahydroquinoline **87** with the other bromo group left untouched. Then, the pyrrole ring was constructed through a Heck reaction with a dehydroalanine derivative **81**, a regioselective bromination, and an intramolecular aryl amination at the congested position. The use of a stoichiometric amount of CuI provided the tricyclic middle segment **90** quantitatively even at ambient temperature.
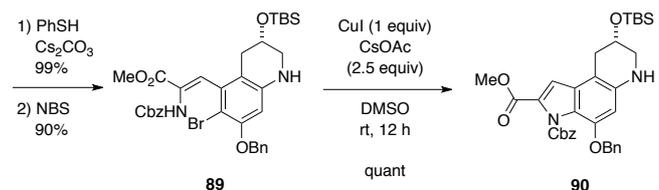
Scheme 35 Synthesis of the middle segment.

The copper-mediated aryl amination was also effective for the facile construction of the dihydropyrroloindole skeleton of the left-hand segment **98** (Scheme 36). Bromoindoline **93** was synthesized by the intramolecular amination of persubstituted phenylethylamine derivative **92** that was prepared from commercially available homoveratrylamine (**91**) via dibromination. Benzyl alcohol **93** was then converted to dehydroamino acid derivative **95** by TPAP oxidation and Horner–Wadsworth–Emmons reaction. The tricyclic pyrroloindole was constructed by the intramolecular amination reaction to provide dihydropyrroloindole **96**. Finally, the manipulation of functional groups including a regioselective demethylation of **97** provided left-hand segment **98**.
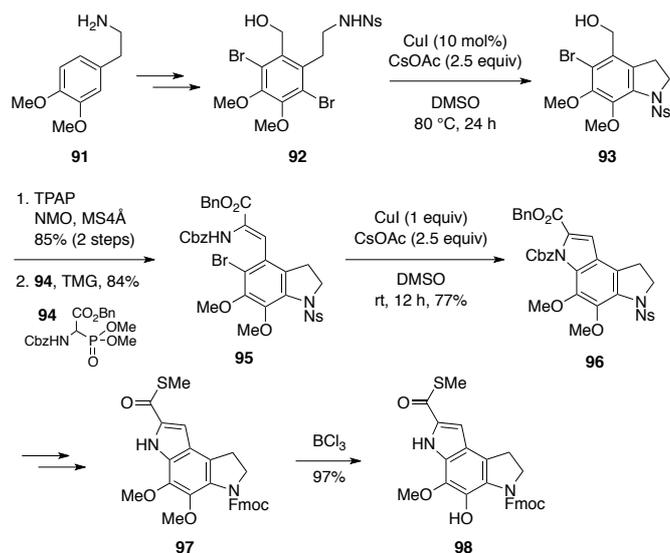
Scheme 36 Synthesis of the left segment.

The amination strategy allows a multigram-scale preparation of the three segments, which leads to the gram-scale total synthesis of yatakemycin (**3**) via the construction of the five aryl carbon–nitrogen bonds (Scheme 37). One of the most important features of this ligand free protocol is that the reaction is applicable to construct an aryl carbon–nitrogen bond at congested reaction sites.
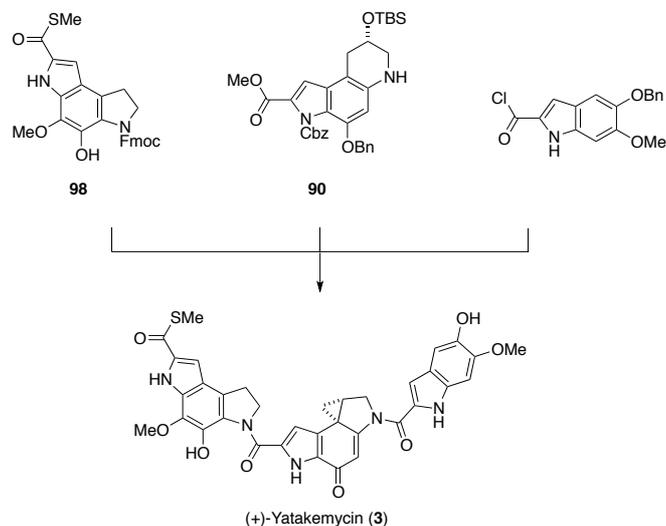
Scheme 37   Synthesis of (+)-yatakemycin by assembly of three segments.

3.1.2 PDE-II[46,47]

In 2010, Tokuyama reported the total synthesis of PDE-II (**4**), a subunit of CC-1065 and yatakemycin (**3**), featuring a double intramolecular amination to construct the characteristic tricyclic di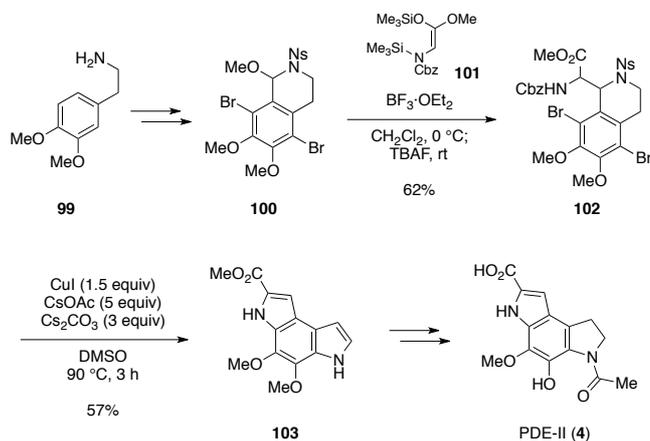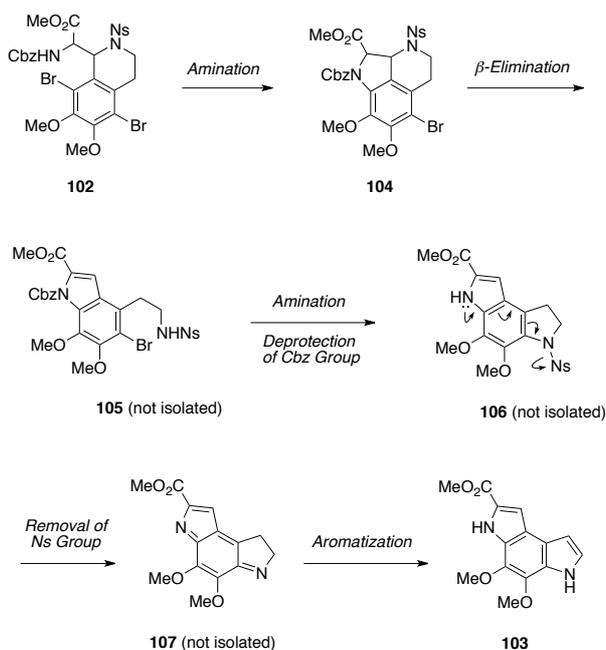hydropyrroloindole skeleton (Scheme 38). The substrate **102** for the amination reaction was synthesized by BF$_3$·OEt$_2$-mediated Mannich reaction of ketene silyl acetal **101** and hemiaminal **100**, which was readily prepared from commercially available homoveratryl amine (**99**) using a seven-step sequence established in our synthetic studies on yatakemycin. The key double amination was effected by the additional base, cesium carbonate, to complete the reaction. The resultant pyrroloindole **103** was transformed to PDE-II (**4**) in three steps.

Scheme 38   Total synthesis of PDE-II (**4**).

An outline of the formation of the pyrroloindole skeleton is shown in Scheme 39. After the first intramolecular amination to form tricyclic intermediate **104**, β-elimination, the second amination of nosyl amide **105**, and base assisted-deprotection of the Cbz group furnished dihydropyrroloindole **106**. Finally, the nosyl group was removed to obtain pyrroloindole **103** through compound **107**.

Scheme 39   Outline of the formation of the pyrroloindole skeleton.

3.2 Ma's synthesis of SB-214857

In 2001, Ma and Xia reported an intramolecular CuI-catalyzed amination of aryl halides with α-amino acids (Scheme 40).[48] In the amination reaction, the use of an unprotected amino acid **109** is necessary for the smooth Ullmann-type aryl amination reaction, which provides the corresponding cyclized product without racemization of the α-position of the amino acid.

Acidic removal of the tertiary butyl group and subsequent condensation with bispiperidine derivative **112** give compound **113**, which is subjected to basic conditions followed by acid treatment to obtain SB-214857 (**5**), a potent GPIIb/IIIa receptor antagonist.
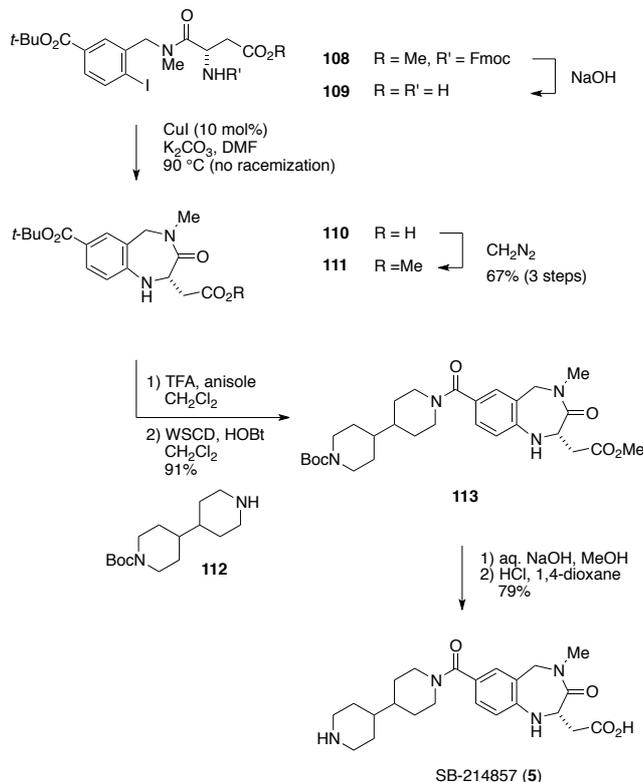
Scheme 40 Total synthesis of SB-214857 (**5**).

Scheme 41 Total synthesis of (±)-psychotrimine (**6**).

3.3 Takayama's synthesis of psychotrimine

In 2008, Takayama and co-workers reported the first total synthesis of (±)-psychotrimine (**6**) utilizing copper-mediated aminations (Scheme 41).[49] The synthesis began with the formation of α-aminonitrile **115** from indoline and *o*-bromobenzaldehyde (**114**) in the presence of hydrogen cyanide. Construction of cyclic amidine was conducted via the installation of nitroalkane followed by the reduction of the nitro group. Subsequent Boc protection resulted in the isomerization of the double bond of amidine to produce the substrate **118** for the key amination reaction. The Buchwald's conditions using palladium catalyst resulted in low yield of the desired compound. Their extensive optimization revealed that the reaction proceeded smoothly using a stoichiometric cop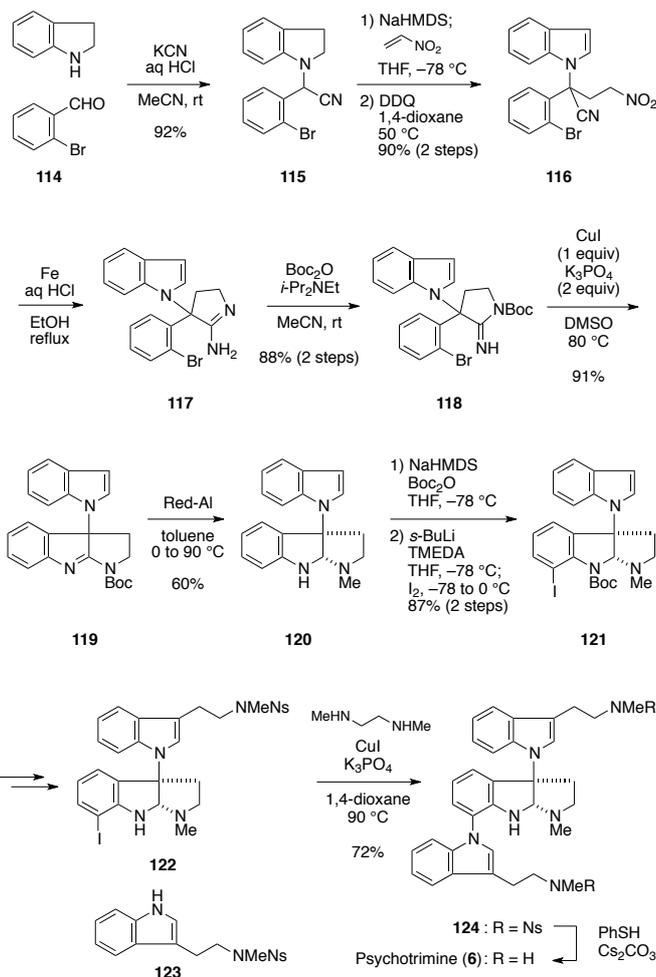per salt. Treatment of **119** with Red-Al provided the desired aminal skeleton, which corresponded to that of psychotrimine (**6**). The regioselective installation of an iodine atom and subsequent introduction of tryptamine unit **123** followed by removal of the nosyl group proceeded to give (±)-psychotrimine (**6**).

3.4 Argade and Kshirsagar's synthesis of (–)-Circumdatins H and J

In 2010, Argade and Kshirsagar demonstrated the utility of a copper-catalyzed intramolecular aryl amination of a quinazolinone to generate the benzodiazepine moiety in their efficient and convergent synthesis of (–)-circumdatins H (**7**) and J (Scheme 42).[50] They first examined the palladium-catalyzed amination of quinazolinone **126a**; however, they only recovered starting material **126a**. The palladium-catalyzed amination using the congested substrate did not proceed probably because of the prevention of the palladium species accessing the reaction site. Notably, the reaction occurred in the presence of copper catalyst and a ligand. The optimal reaction conditions using L-proline and sodium hydride in DMF at 120 °C exclusively produced demethoxy-circumdatin H in 84% yield. The enantiomeric excess was decreased to 73% during the amination reaction. Application of the optimal conditions to compound **126** led to total synthesis of circumdatin H (**7**).
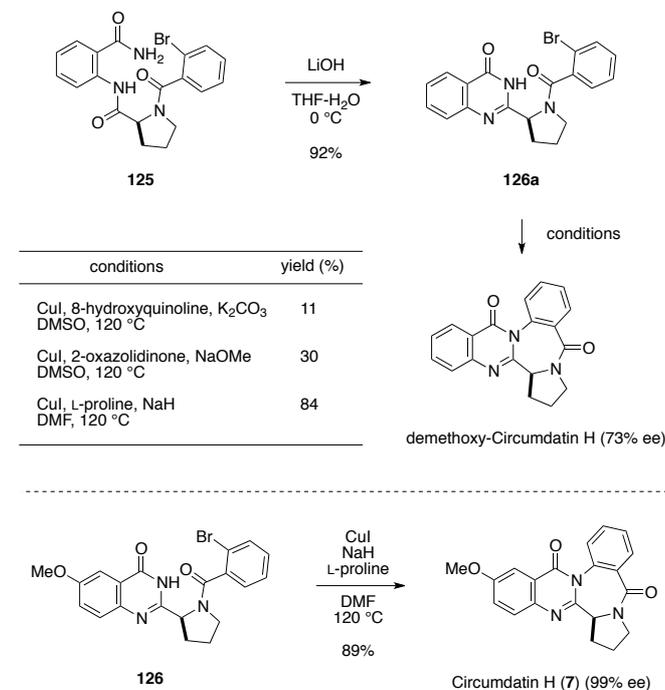
Scheme 42 Total synthesis of circumdatin H (**7**).

Scheme 43 Total synthesis of reblastatin (**8**).

3.5 Panek and Evano's synthesis of macrocyclic compounds

In 2005, Panek and Evano reported the total synthesis of (+)-reblastatin (**8**)[51] based on an intramolecular aryl amidation using a combination of dimethylethylenediamine and CuI (Scheme 43). Regioselective hydrozirconation of acetylene **127** and subsequent nucleophilic addition to aldehyde **129** exclusively produced allylic alcohol **130**. After the transformation of the ester to amide, the resultant **131** was subjected to Buchwald amidation conditions to provide 19-membered lactam **132** in 83% yield. Evano also applied the amidation reaction to the *cis*-styryl iodide **133** for the synthesis of abyssenine (**9**) and mucronine E (**10**) (Scheme 44). They constructed the 15-membered lactam under the same reaction conditions in good yield and achieved the total synthesis of abyssenine (**9**)[52] and mucronine E (**10**)[53] by the deprotection of the Boc group. Similarly, they utilized this amination strategy to synthesize paliurine F (**135**),[54] Ziziphines N (**136**),[55] and Q (**137**),[56] which demonstrated the utility of this reaction for the formation of macrolactam skeletons.

Scheme 44 Total synthesis of natural products having macrolactam moiety.

3.6 Tokuyama's synthesis of rhazinicine and rhazinilam

Tokuyama and co-workers reported an enantiocontrolled total synthesis of rhazinicine (**11**) and rhazinilam (**12**) utilizing a copper-mediated introduction of nitrogen onto an aromatic ring (Scheme 45). [57] They constructed the highly elaborated indolizinone derivative **140** by their original gold-catalyzed double cyclization using a linear substrate **139** bearing aryl acetylene, amide, and acetal functionalities from optically active acetylene **138** in two steps. After the conversion of ester **140** to amide **141**, the amide was subjected to the modified amidation conditions and produced (–)-rhazinicine (**11**). Conversely, the total synthesis of rhazinilam (**12**) was achieved via an intermolecular amination of indolidine **142** using sodium azide as a nitrogen source[58] under milder conditions to produce aniline **143**, which was transformed to (–)-rhazinilam (**12**) by the formation of nine-membered lactam.
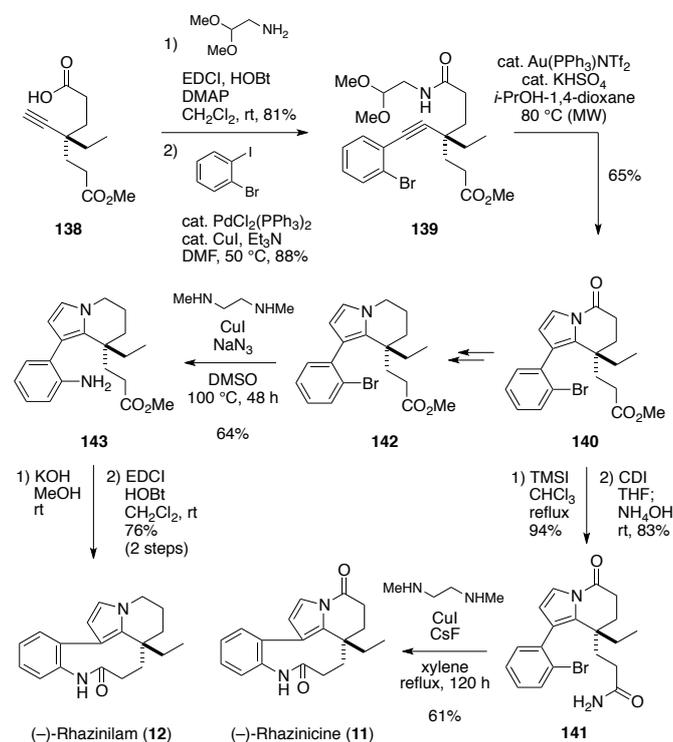

Scheme 45 Total synthesis of rhazinicine (**11**) and rhazinilam (**12**).

3.7 Nishida's synthesis of lundurine B

Recently, Nishida and co-workers utilized a copper-mediated intramolecular aryl amination to form cyclopropane-fused indoline in the total synthesis of (±)-lundurine B (**13**) (Scheme 46). [59] Stereoselective formation of the lactone-fused cyclopropane was achieved by treatment of the trisubstituted olefin **144** with iodine. The methyl ester **145** was converted to the corresponding Boc carbamate via saponification followed by Curtius rearrangement. Regioselective bromination at the *para* position of the methoxy group gave the substrate **146** for the aryl amination. The key amination proceeded smoothly with

TMEDA as a ligand to provide the desired cyclopropane-fused indoline **147** in excellent yield, which led to the total synthesis of (±)-lundurine B (**13**).
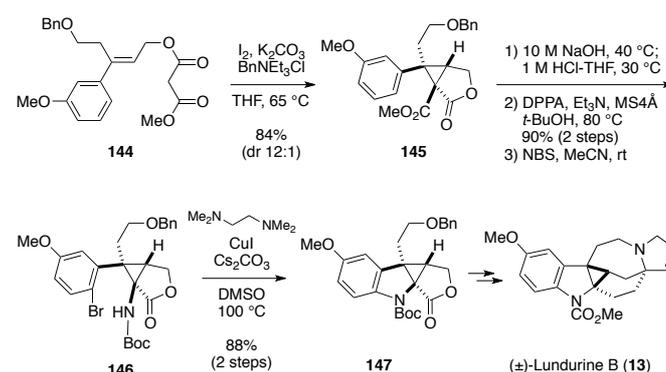
Scheme 46 Total synthesis of lundurine B (**13**).

4. Conclusion

The classical copper-mediated Ullmann coupling had been considered an impractical reaction, although the importance of the formation of $C(sp^2)$–N bonds had been recognized. This situation was dramatically changed by the discovery of palladium-catalyzed aryl amination of aryl halides in the mid-1990s. Several years later, a mild copper-mediated aryl amination was revisited based on the use of fine-tuned ligands. A number of reaction conditions established by several research groups have been utilized for the construction of $C(sp^2)$–N bonds in the syntheses of biologically important natural products and medicines. The copper-mediated aryl aminations described in this review are complementary methods to the palladium-catalyzed aminations. Because there are still lack of copper-mediated $C(sp^2)$–N bond formation of pseudohalides such as sulfonates compared to the palladium-catalyzed aryl amination,[7, 60] further investigation is strongly required for expanding the scope. Recently, several examples of palladium- or copper-catalyzed aryl C–H amination were reported for more direct synthesis of aniline derivatives. Although aryl C–H aminations remain immature and plenty of room for improvement remains, such as the scope of possible substrates and reaction temperatures, these C–H aminations using inexpensive copper catalysts could become a practical method for the conversion of an aromatic C–H bond to a C–N bond.

Author Profiles

a Graduate School of Pharmaceutical Sciences, Nagoya University Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan. Fax: +81-52-747-6817; Tel: +81-52-747-6799; E-mail: fukuyama@ps.nagoya-u.ac.jp
b Graduate School of Pharmaceutical Sciences, Tohoku University Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan.

Kentaro Okano was born in Tokyo in 1979. He received his B.S. in 2003 from Kyoto University, where he conducted undergraduate research under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at the University of Tokyo and started his Ph.D. research on synthetic studies toward antitumor antibiotic yatakemycin using the copper-mediated aryl amination strategy. In 2007, he joined the faculty at Tohoku University, where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. His current research interest is natural product synthesis based on the development of new synthetic methodologies.

Hidetoshi Tokuyama was born in Yokohama in 1967. He received his Ph.D. in 1994 from Tokyo Institute of Technology under the direction of Professor Ei-ichi Nakamura. He spent 1 year (1994–1995) at the University of Pennsylvania as a postdoc with Professor Amos B. Smith. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed associate professor in 2003. In 2006, he was moved to Tohoku University, where he is currently a professor of Pharmaceutical Sciences. His research interests are the development of synthetic methodologies and total synthesis of natural products.

Tohru Fukuyama received his Ph.D. in 1977 from Harvard University with Professor Yoshito Kishi. He remained in Professor Kishi's group as a postdoctoral fellow until 1978 when he was appointed as an assistant professor of Chemistry at Rice University. After 17 years as the faculty at Rice, he returned to his home country and joined the faculty of the University of Tokyo in 1995, where he is currently a professor of Pharmaceutical Sciences. In 2012, he moved to Nagoya University and continued developing practical synthetic methodologies for total synthesis. He has primarily been involved in the total syntheses of complex natural products of biological and medicinal importance. He often chooses target molecules that require the development of new concepts in synthetic design and/or new methodology for their total synthesis.

Notes and references

1   J. D. Roberts, D. A. Semenow, H. E. Simmons and L. A. Carlsmith, *J. Am. Chem. Soc.*, 1956, **78**, 601–611; J. D. Roberts, C. W. Vaughan, L. A. Carlsmith and D. A. Semenow, *J. Am. Chem. Soc.*, 1956, **78**, 611–614; R. S. Berry, G. N. Spokes and R. M. Stiles, *J. Am. Chem. Soc.*, 1960, **82**, 5240–5241; R. S. Berry, M. Stiles and G. N. Spokes, *J. Am. Chem. Soc.*, 1962, **84**, 3570–3577; F. Gavina, S. V. Luis, A. M. Costero and P. Gil, *Tetrahedron*, 1986, **42**, 155–166; H. H. Wenk, M. Winkler and W. Sander, *Angew. Chem. Int. Ed.*, 2003, **42**, 502–528; T. Kitamura, *Aust. J. Chem.*, 2010, **63**, 987–1001; A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140–3152; C. M. Gampe and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2012, **51**, 3766–3778.

2   J. Meisenheimer, *Liebigs Ann.*, 1902, **323**, 205–246; J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273–412; J. Sauer and R. Huisgen, *Angew. Chem.*, 1960, **72**, 294–315; P. Buck, *Angew. Chem. Int. Ed.*, 1969, **8**, 120–131; E. Buncel, J. M. Dust and F. Terrier, *Chem. Rev.*,

1995, **95**, 2261–2280; B. P. Hay and V. S. Bryantsev, *Chem. Commun.*, 2008, 2417–2428.

3   F. Ullmann, *Chem. Dtsch. Ber. Ges.*, 1903, **36**, 2382–2384; F. Ullmann, *Chem. Dtsch. Ber. Ges.*, 1904, **37**, 853–854.

4   I. Goldberg, *Chem. Dtsch. Ber. Ges.*, 1906, **39**, 1691–1692.

5   M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, 927–928; M. Kosugi, M. Kameyama, H. Sano and T. Migita, *Nippon Kagaku Kaishi*, 1985, **1985**, 547–551.

6   A. S. Guram and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 7901–7902; A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 1348–1350.

7   F. Paul, J. Patt and J. F. Hartwig, *J. Am. Chem. Soc.*, 1994, **116**, 5969–5970; J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1264–1267; J. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1997, **62**, 1268–1273.

8   J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158–1174.

9   D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722–9723.

10   B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369–7370.

11   R. J. Sorenson, *J. Org. Chem.*, 2000, **65**, 7747–7749.

12   A. A. Kelkar, N. M. Patil and R. V. Chaudhari, *Tetrahedron Lett.*, 2002, **43**, 7143–7146.

13   P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon and P. K. Jadhav, *Tetrahedron Lett.*, 2001, **42**, 3415–3418; J. C. Antilla and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 2077–2079.

14   P. Y. S. Lam, S. Deudon, K. M. Averill, R. Li, M. Y. He, P. DeShong and C. G. Clark, *J. Am. Chem. Soc.*, 2000, **122**, 7600–7601.

15   H. Weingarten, *J. Org. Chem.*, 1964, **29**, 3624–3626; T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, 1976, **98**, 748–753; W. R. Bowman, H. Heaney and P. H. G. Smith, *Tetrahedron Lett.*, 1984, **25**, 5821–5824; A. J. Paine, *J. Am. Chem. Soc.*, 1987, **109**, 1496–1502; H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem. Eur. J.*, 2004, **10**, 5607–5622; A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl and X. Ribas, *Chem. Sci.*, 2010, **1**, 326–330.

16   S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400–5449; F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.*, 2009, **48**, 6954–6971.

17   D. Ma, Y. Zhang, J. Yao, S. Wu and F. Tao, *J. Am. Chem. Soc.*, 1998, **120**, 12459–12467: H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164–5173; D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450–1460.

18   H. B. Goodbrand and N.-X. Hu, *J. Org. Chem.*, 1999, **64**, 670–674; R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2006, **8**, 2779–2782; G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802–1808.

19   A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727–7729.

20   F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793–796.

21   F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581–584.

22   Y.-J. Chen and H.-H. Chen, *Org. Lett.*, 2006, **8**, 5609–5612.

23   A. Shafir and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 8742–8743.

24 H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem. Eur. J.*, 2004, **10**, 5607–5622.

25 S. E. Creutz, K. J. Lotito, G. C. Fu and J. C. Peters, *Science*, 2012, **338**, 647–651.

26 I. P. Beletskaya and A. V. Cheprakov, *Organometallics*, 2012, **31**, 7753–7808.

27 G. Cuny, M. Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, 2004, **126**, 14475–14484.

28 R. A. Altman, A. M. Hyde, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 9613–9620.

29 A. Shafir, P. A. Lichtor and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3490–3491; G. E. Job and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3703–3706.

30 J. P. Wolfe, S. Wagaw, J.-F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805–818; J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852–860; J. F. Hartwig, *Angew. Chem. Int. Ed.*, 1998, **37**, 2046–2067; B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125–146; J. F. Hartwig, *Synlett*, 2006, 1283–1294; S. L. Buchwald, C. Mauger, G. Mignani and U. Scholz, *Adv. Synth. Catal.*, 2006, **348**, 23–39; J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534–1544.

31 K. Yamada, T. Kubo, H. Tokuyama and T. Fukuyama, *Synlett*, 2002, 231–234; K. Okano, H. Tokuyama and T. Fukuyama, *Org. Lett.*, 2003, **5**, 4987–4990; T. Kubo, C. Katoh, K. Yamada, K. Okano, H. Tokuyama and T. Fukuyama, *Tetrahedron*, 2008, **64**, 11230–11236; T. Komori, N. Satoh, S. Yokoshima and T. Fukuyama, *Synlett* **2011**, 1859–1862.

32 X. Ribas, B. Donnadieu, D. Jackson, K. O. Hodgson, B. Hedman, T. D. P. Stack and A. Llobet, *J. Inorg. Biochem.*, 2001, **86**, 399; X. Ribas, D. A. Jackson, B. Donnadieu, J. Mahía, T. Parella, R. Xifra, B. Hedman, K. O. Hodgson, A. Llobet and T. D. P. Stack, *Angew. Chem. Int. Ed.*, 2002, **41**, 2991–2994; R. Xifra, X. Ribas, A. Llobet, A. Poater, M. Duran, M. Solà, T. D. P. Stack, J. Benet-Buchholz, B. Donnadieu, J. Mahía and T. Parella, *Chem. Eur. J.*, 2005, **11**, 5146–5156; A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl and X. Ribas, *Chem. Sci.*, 2010, **1**, 326–330.

33 B. J. Hathaway, Comprehensive Coordination Chemistry; G.Wilkinson, Ed.; Pergamon: Oxford, 1987, **5**, 745–749.

34 W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560–14561; H.-Y. Thu, W.-Y. Yu and C.-M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 9048–9049; K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto and K. Hiroya, *Org. Lett.*, 2007, **9**, 2931–2934; M. Yamamoto and S. Matsubara, *Chem. Lett.*, 2007, **36**, 172–173; J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 16184–16186; M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14058–14059; T.-S. Mei, X. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 10806–10807; J. J. Neumann, S. Rakshit, T. Droege and F. Glorius, *Angew. Chem. Int. Ed.*, 2009, **48**, 6892–6895; K.-H. Ng, A. S. C. Chan and W.-Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862–12864; Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677; B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1466–1474; K. Sun, Y. Li, T. Xiong, J. Zhang and Q. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 1694–1697; E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7652–7655;

35 G. Brasche and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 1932–1934.

36 H. Wang, Y. Wang, C. Peng, J. Zhang and Q. Zhu, *J. Am. Chem. Soc.*, 2010, **132**, 13217–13219.

37 S. H. Cho, J. Yoon and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996–6005.

38 W. Zhou, Y. Liu, Y. Yanga and G.-J. Deng, *Chem. Commun.*, 2012, **48**, 10678–10680.

39 X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791.

40 T. Uemura, S. Imoto and N. Chatani, *Chem. Lett.*, 2006, **35**, 842–843; A. John and K. M. Nicholas, *J. Org. Chem.*, 2011, **76**, 4158–4162; Q. Shuai, G. Deng, Z. Chua, D. S. Bohle and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 632–636.

41 L. D. Tran, J. Roane and O. Daugulis, *Angew. Chem. Int. Ed.*, 2013, **52**, 6043–6046.

42 Very recently, related aromatic C–H aminations have been reported: Q. Li, S.-Y. Zhang, G. He, Z. Ai, W. A. Nack and G. Chen, *Org. Lett.*, 2014, **16**, 1764–1767; M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 3354–3357.

43 J. R. Dehli, J. Legros and C. Bolm, *Chem. Commun.*, 2005, 973–986; R. M. de Figueiredo, J. M. Campagne and D. Prim, Modern Tools for the Synthesis of Complex Bioactive Molecules; J. Cossy and S. Arseniyadis, Eds.; Wiley: New Jersey, 2012, 77–109; G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131.

44 K. Yamada, T. Kurokawa, H. Tokuyama and T. Fukuyama, *J. Am. Chem. Soc.*, 2003, **125**, 6630–6631.

45 K. Okano, H. Tokuyama and T. Fukuyama, *J. Am. Chem. Soc.*, 2006, **128**, 7136–7137; K. Okano, H. Tokuyama and T. Fukuyama, *Chem. Asian J.*, 2008, **3**, 296–309.

46 K. Okano, N. Mitsuhashi and H. Tokuyama, *Chem. Commun.*, 2010, **46**, 2641–2643.

47 K. Okano, N. Mitsuhashi and H. Tokuyama, *Tetrahedron*, 2013, **69**, 10946–10954.

48 D. Ma and C. Xia, *Org. Lett.*, 2001, **3**, 2583–2586.

49 Y. Matsuda, M. Kitajima and H. Takayama, *Org. Lett.*, 2008, **10**, 125–128.

50 U. A. Kshirsagar and N. P. Argade, *Org. Lett.*, 2010, **12**, 3716–3719.

51 I. E. Wrona, A. E. Gabarda, G. Evano and J. S. Panek, *J. Am. Chem. Soc.*, 2005, **127**, 15026–15027.

52 M. Toumi, F. Couty and G. Evano, *J. Org. Chem.*, 2007, **72**, 9003–9009.

53 M. Toumi, F. Couty and G. Evano, *Synlett*, 2008, 29–32.

54 M. Toumi, F. Couty and G. Evano, *Angew. Chem. Int. Ed.*, 2007, **46**, 572–575.

55 G. He, J. Wang and D. Ma, *Org. Lett.*, 2007, **9**, 1367–1369.

56 M. Toumi, V. Rincheval, A. Young, D. Gergeres, E. Turos, F. Couty, B. Mignotte and G. Evano, *Eur. J. Org. Chem.*, 2009, 3368–3386.

57 K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda and H. Tokuyama, *Angew. Chem. Int. Ed.*, 2013, **52**, 7168–7171

58 J. T. Markiewicz, O. Wiest and P. Helquist, *J. Org. Chem.*, 2010, **75**, 4887–4890.

59 M. Hoshi, O. Kaneko, M. Nakajima, S. Arai and A. Nishida, *Org. Lett.*, 2014, **16**, 768–771; S. Arai, M. Nakajima and A. Nishida, *Angew. Chem. Int. Ed.*, 2014, **53**, 5569–5572.

60 A. H. Roy and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 8704–8705.