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COMPREHENSIVE REVIEW

Synthetic applications and methodology development of Chan–Lam coupling: a review

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Abstract
Chan–Lam coupling is one of the most popular and easy methods to perform arylation of amines (*N*-arylations). This cross-coupling is generally performed by reacting aryl boronate derivatives with a variety of substrates involving nitrogen containing functional groups such as amines, amides, ureas, hydrazine, carbamates. This article summarizes the synthetic applications of this reaction and the efforts of scientists to develop novel and efficient methodologies for this reaction.

Keywords Chan–Lam coupling · Cross-coupling reactions · Boronic acids · *N*-heterocycles · *N*-Arylation

Introduction

Compounds with carbon-heteroatom bonds find tremendous importance in organic synthesis and pharmaceutical chemistry. Specially, C–N-containing compounds have great contribution toward synthesis of dyes, agrochemicals and drugs [1]. Until now, several methods have been discovered and applied to generate carbon-heteroatom bonds; however, each method has its own merits and demerits. In 1998, Chan, Evans and Lam independently worked on C–N bond construction [2]. This classical protocol involved the use of aryl boronic acids with amines under mild reaction conditions and offers many advantages over the others such as inexpensive catalyst, normal temperature, good functional group tolerance, use of air and variety of substrates including amines, amides, ureas, hydrazine, carbamates and different heterocycles (imidazole, pyrazole, indole) which are used for the arylation [3].

In the last decade, a lot of effort has been made by the researchers on Chan–Lam coupling and still efforts are ongoing to develop new methodologies as well as its applications such as use of cellulose-supported catalyst [4]. Chan–Lam coupling has found application in the synthesis of *N*-arylated pyridine-2(1*H*)-one analogues which paved the path toward formation of an anti-epileptic drug, named Perampanel [5] (Fig. 1).

Structurally modified nucleosides such as inosine (**2**) and guanosine (**3**) (responsible for having antiviral and anticancer activities) can also be accessed by *N*-arylation of purine nucleosides using Chan–Lam coupling [6] (Fig. 2).

Another important application of Chan–Lam coupling involves its use for functionalization of the surface of silica gel [7] and formation of porous aromatic framework [8]. The obtained material can be modified for further applications and use. Similarly, Chan–Lam coupling can also be used to prepare polymer coated microelectrode array by adding amino acid to it [9] which can be helpful in electrochemical signaling.

Review of the literature

Amine and ether formation via Chan–Lam coupling

The reaction involving the formation of C–N and C–O bonds is of significant importance in organic and medicinal chemistry. This importance is largely due to the occurrence of amine and ether linkages in many molecules of biological importance. Chan–Lam coupling reactions have appeared as an important synthetic tool for the development of such bonds.

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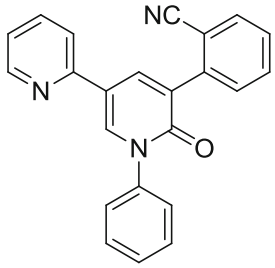
Fig. 1 Structure of Perampanel **1**



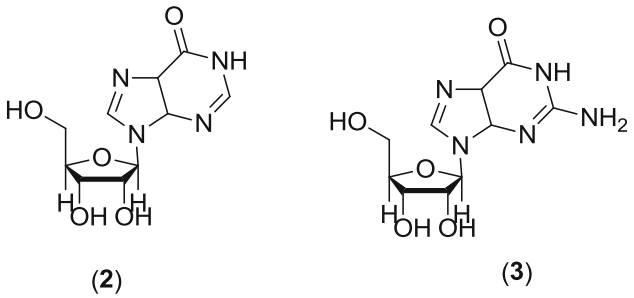


Fig. 2 Structure of inosine (**2**) and guanosine (**3**)

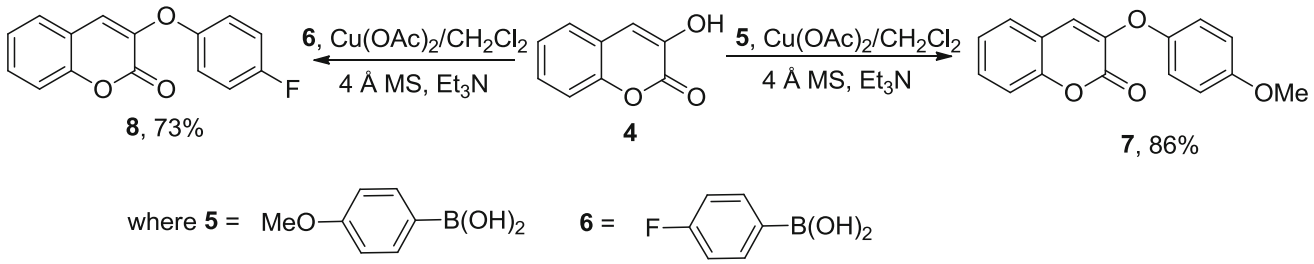
Coumarin moiety is the one of the important structure having great contribution in pharmaceutical industry. Keeping in view its biological importance, Medda et al. [10] reported the first Cu-catalyzed coupling of hydroxycoumarins with aryl boronic acid by applying Chan–Lam coupling. The reaction of 3-hydroxycoumarin was performed with aryl boronic acid having electron-donating groups such as –OMe, –Me, *t*-Bu and electron-withdrawing groups –F, –Br, –Cl. It was observed that electron-donating groups showed higher yield (56–86%) as compared to electron-withdrawing groups (63–73%). The reaction of 3-hydroxycoumarin **4** with 4-methoxyphenyl boronic acid **5** and 4-flourophenyl boronic acid **6** afforded 86% and 73% yield of product **7** and **8**, respectively (Scheme 1).

Reactions of 4-hydroxycoumarin **9** were performed with phenyl boronic acid **10** and 4-chlorophenyl boronic acid **11** to afford 70% and 66% yield of the corresponding products **12–13**, respectively (Scheme 2).

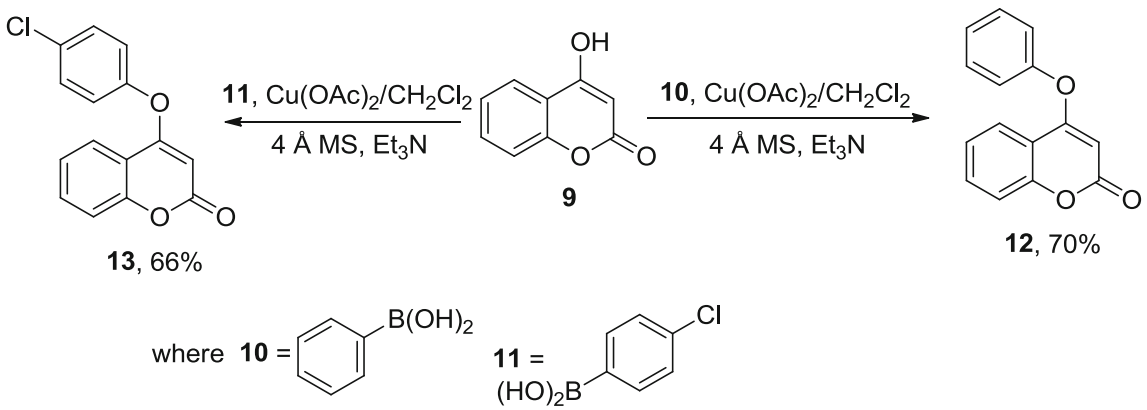
Similarly, reaction of 7-hydroxy-4-methylcoumarin with different aryl boronic acid gave good yields (54–82%). Reaction of 7-hydroxy-4-methylcoumarin **14** with 4-methoxyphenyl boronic acid **5** resulted in 82% yield of corresponding product **15** (Scheme 3).

O-Arylation of (hydroxyamino)ethylcoumarin resulted in 55–75% yield on reacting with different boronic acid. (Phenoxyimino)ethyl-7-methoxycoumarin **17** was obtained in 75% yield when phenyl boronic acid **10** was allowed to react with (hydroxyamino)ethylcoumarin **16** (Scheme 4).

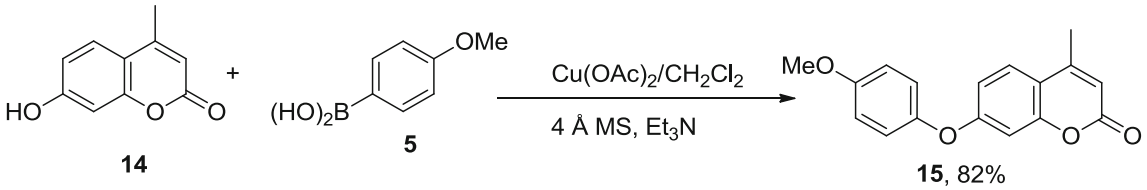
Sueki and Kuninobu [11] reported the synthesis of alkylated amine and alkyl aryl ethers via Chan–Lam coupling reaction. For example, reaction of benzyl boronic acid pinacol ester **18** with *N*-methyl-substituted amine **19** and tyrosine derivative **20** resulted in alkylated amine **21** (>99%) and alkyl aryl ether **22** (91%) (Scheme 5).



Scheme 1 Synthesis of *O*-arylated 3-hydroxycoumarin **7–8**

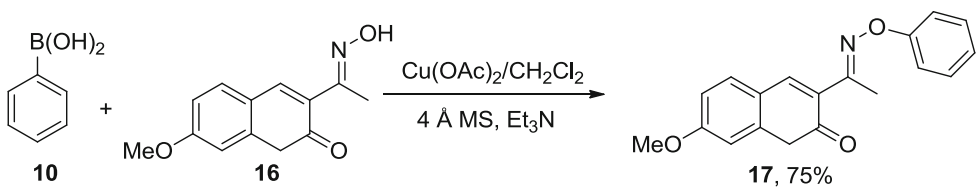


Scheme 2 Arylation of 4-hydroxy coumarin **9**

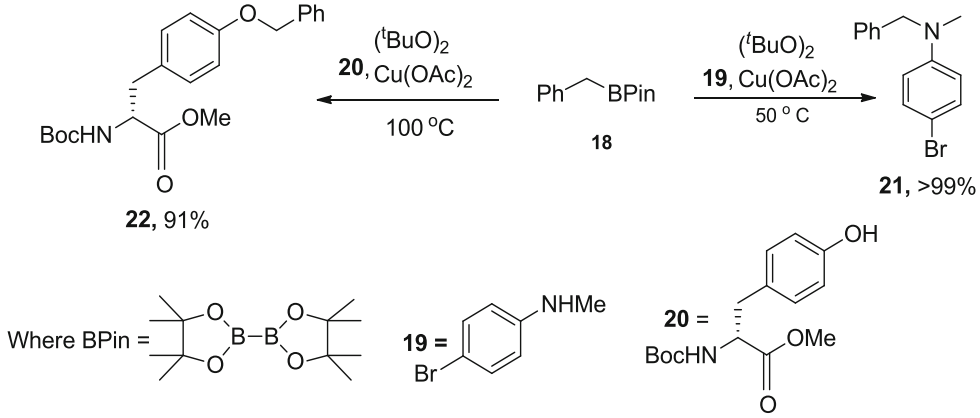


Scheme 3 Synthesis of ether **15** from 7-hydroxy-4-methylcoumarin **14**

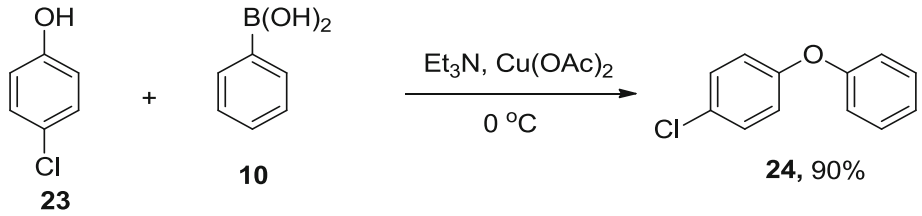
Scheme 4 Synthesis of (phenoxyimino)ethyl-7-methoxycoumarin **17**



Scheme 5 Synthesis of alkylated amine **21** and alkyl aryl ether **22** through Chan–Lam coupling



Scheme 6 Synthesis of chlorinated ether **24**



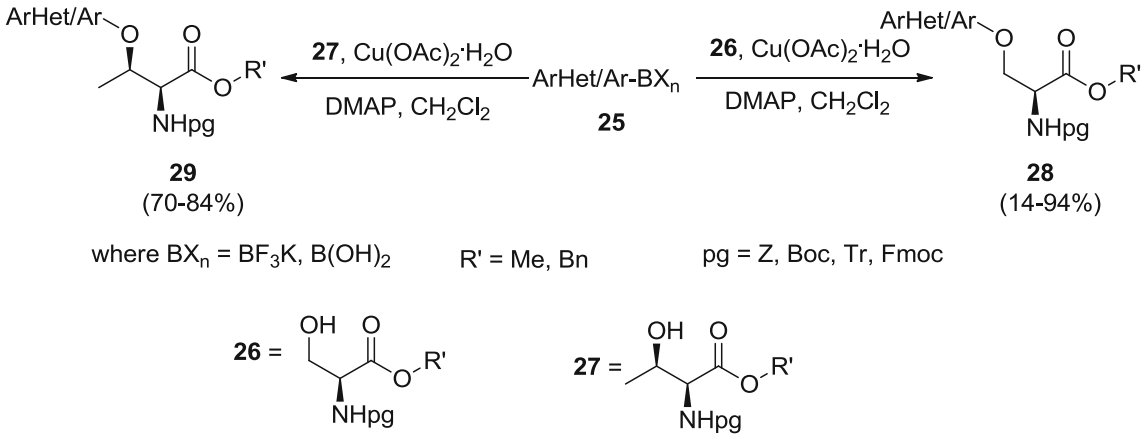
Formation of mono/polychlorinated diphenyl ethers was reported by Cermak and Cirkva [12] using Chan–Lam coupling. Monochlorinated biphenyl ethers were obtained in 86–90% yield, and polychlorinated biphenyl ethers were obtained in 8–84% yield. Chlorinated phenol **23** reacted with phenyl boronic acid **10** to give the chlorinated diaryl ether **24** with 90% yield (Scheme 6).

El Khatib and Molander [13] discovered the protocol for synthesis of alkyl aryl ethers through Chan–Lam coupling of β-hydroxy-α-amino acid derivatives. In their approach, protected L-serine and L-threonine derivatives **26**–**27** were allowed to react with aryl boronic acids/trifluoroborates, and corresponding products **28** and **29** were obtained in good-to-excellent yields (14–94%) and (70–84%), respectively (Scheme 7)

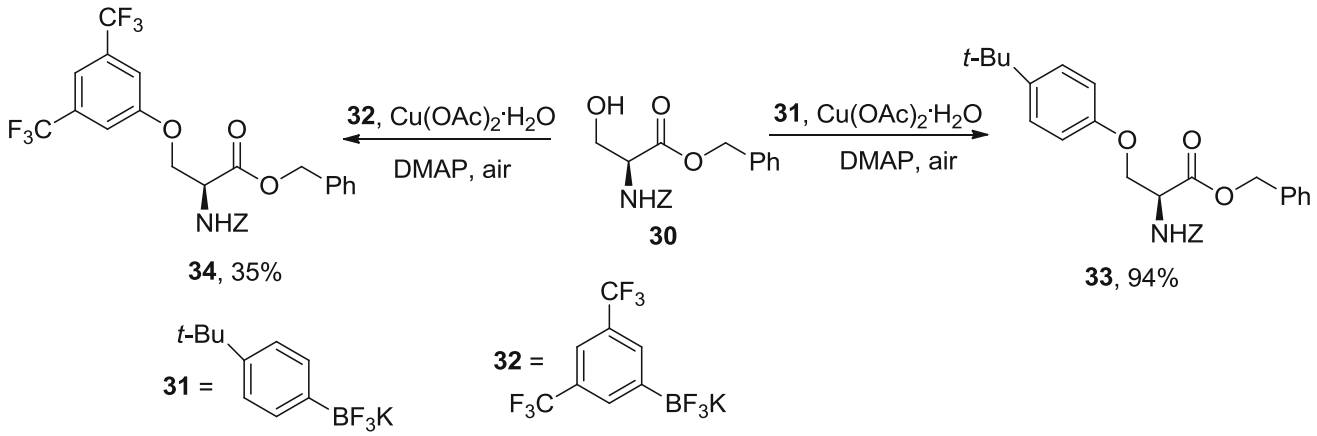
However, in case of L-serine derivatives, study of substitution pattern revealed that electron-donating groups gave higher yield. For example, protected L-serine derivative **30** was allowed to react with *t*-butyl-substituted potassium triflouroborate **31** and 3,5-trifluoromethyl-substituted trifluorobortate **32**. Results showed that *t*-butyl-substituted potassium triflouroborate **31** gave higher yield (94%) of the corresponding product **33** (Scheme 8).

Under same reaction conditions, *O*-arylation of L-threonine derivatives was performed. Maximum yield (84%) of the product **36** was obtained as single diastereomer when protected L-threonine derivative **35** was treated with *t*-butyl-substituted potassium trifluoroborate (Scheme 9).

The methodology was further applied to the synthesis of *O*-arylated dipeptide. In this case, dipetide **37** was allowed to react with potassium phenyl triflouroborate **38** and product **39** was formed (22%), showing that the arylation occurred selectively at the L-serine moiety (Scheme 10).

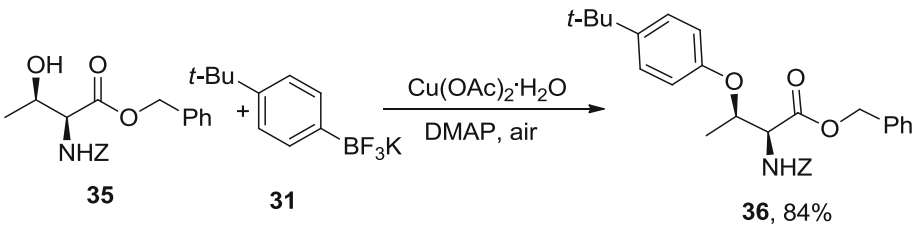


Scheme 7 *O*-Arylation of L-serine and L-threonine derivatives **26**–**27**

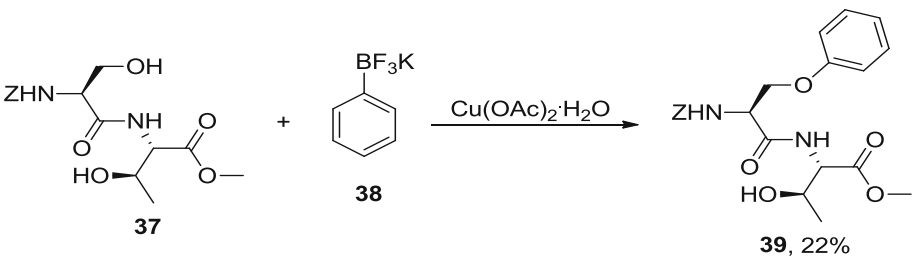


Scheme 8 Synthesis of *O*-arylated L-serine derivative **33**–**34**

Scheme 9 Synthesis of *O*-arylated L-threonine derivative **36**



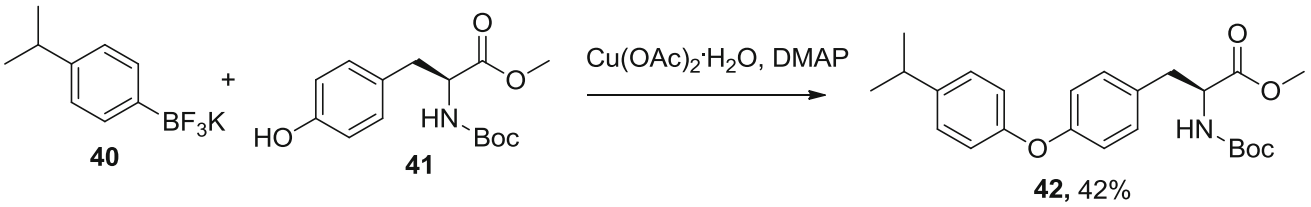
Scheme 10 Synthesis of *O*-arylated dipeptide **39** by Chan–Lam coupling



Same methodology was applied to synthesize tyrosine *O*-arylated tyrosine **42**, by the reaction of (4-isopropyl phenyl)trifluoro borate **40** with Boc-*L*-Try-OMe **41** and product **42** was obtained in 42% yield (Scheme 11).

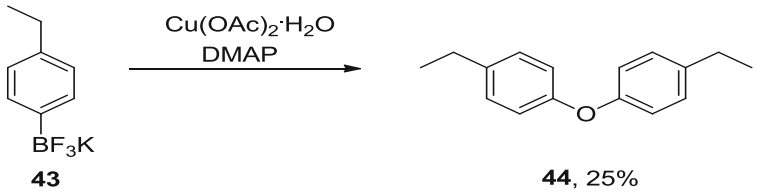
They also investigated the formation of side product and concluded that in absence of amino acid, organoboron reagents with electron-donating group resulted in ether **44** (25%) of corresponding boron reagents. It was postulated that this transformation occurred due to copper promoted oxidation of $ArBF_3K$ (Scheme 12).

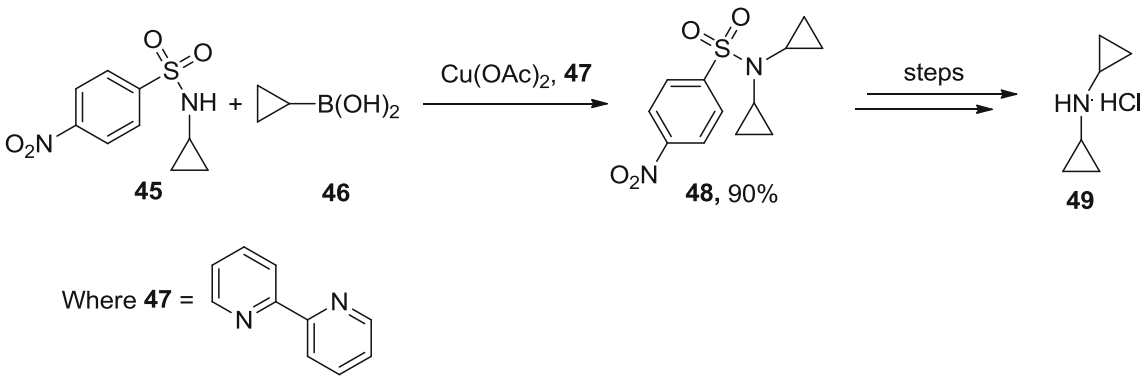
A new process for the preparation of dicyclopropylamine hydrochloride by using Chan–Lam coupling was developed



Scheme 11 Synthesis of *O*-arylated tyrosine **42**

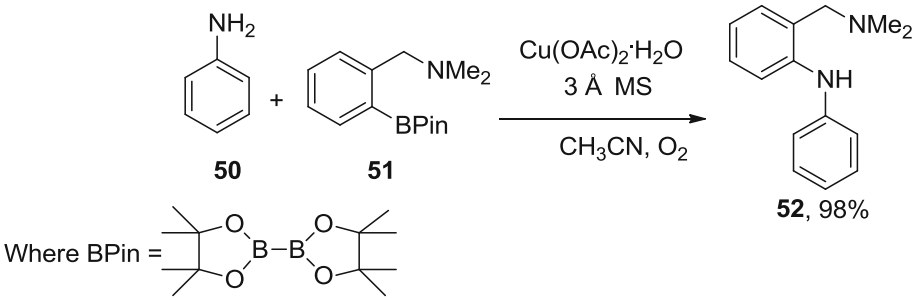
Scheme 12 Formation of ether **44** as side product





Scheme 13 Synthesis of dicyclopropylamine hydrochloride **49** by using Chan–Lam coupling

Scheme 14 *N*-arylation of aniline **50** using Chan–Lam coupling

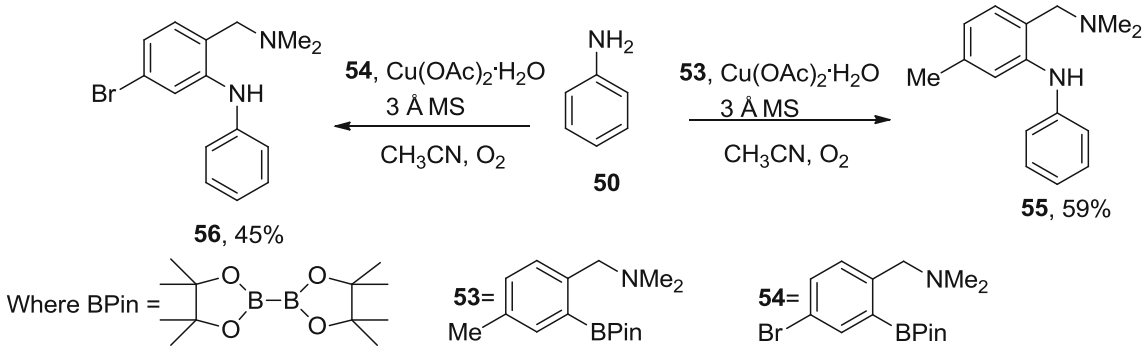


by Mudryk et al. [14]. The key step involved the reaction of sulfonamide **45** with cyclopropyl boronic acid **46** to synthesize dicyclopropyl sulfonamide **48** which was subjected to different reactions continuously to give final product dicyclopropylamine hydrochloride **49** (Scheme 13).

McGarry et al. [15] applied Chan–Lam coupling strategy on boronate esters and aniline. Studies showed that benzylamine moiety enhanced the reactivity of boronate ester. Effect of electron-deficient and electron-rich substituents on both reactants was studied and good functional group tolerance was observed, whereas the major side product was formed via homocoupling of aryl boronate ester. Maximum yield (98%) of corresponding product **52** was obtained when simple aniline **50** was treated with boronate ester having benzylamine moiety **51** (Scheme 14).

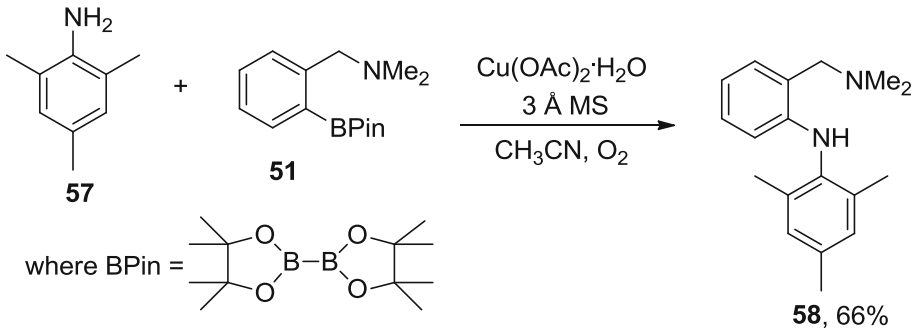
Effect of substituents on aryl ring of boronate ester showed that electron-donating groups resulted in higher yield as compared to electron-withdrawing groups. Aniline **50** was allowed to react with methyl-substituted boronate ester **53** and bromine-substituted boronate ester **54**. Results proved that methyl-substituted boronate ester gave higher yield (59%) of the product **55** (Scheme 15).

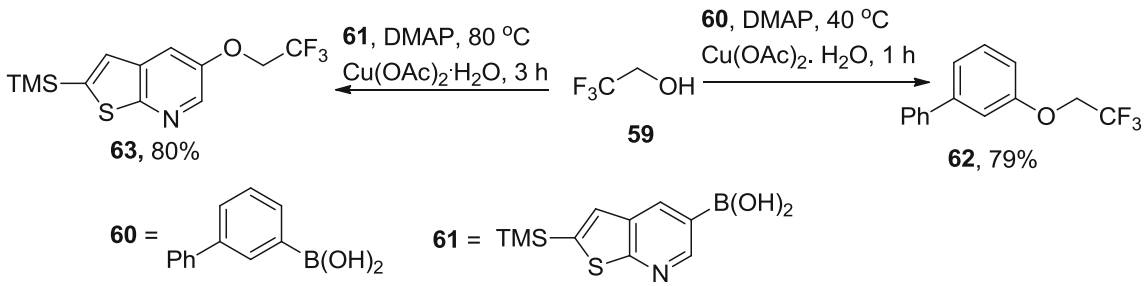
Similarly, 2,4,6-methyl aniline **57** was reacted with boronate ester **51** to yield the corresponding product **58** (66%) (Scheme 16).



Scheme 15 Effect of substituents on *N*-arylation of aniline **50**

Scheme 16 Synthesis of *N*-arylated product **58** by using substituted aniline



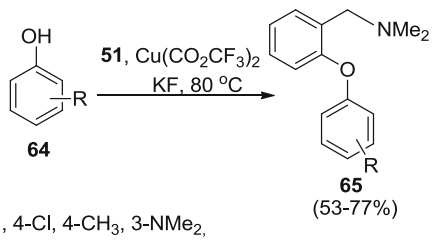


Scheme 17 Synthesis of trifolouro aryl ether **62** and trifolouro heteroaryl ether **63**

Chan–Lam coupling has also found application in the synthesis of trifluoroethyl aryl/heteroaryl ethers via copper mediated coupling of trifluoro ethanol and aryl/heteroaryl boronic acids as reported by Wang et al. [16]. For example, 2,2,2-trifluoroethanol **59** was allowed to react with substituted aryl boronic acid **60** and substituted heteroaryl boronic acid **61** to provide trifluoroethyl aryl ether **62** in 79% yield and trifluoro heteroaryl ether **63** in 80% yield (Scheme 17).

Synthesis of biologically important biaryl ethers via Chan–Lam coupling was described by Marcum et al. [17]. Etherification was achieved by the reaction of benzylic amine boronate esters **51** with substituted phenols **64** to afford the biaryl ethers **65** (53–77%) (Scheme 18).

Further, the effect of various electron-donating groups (–Me, –OMe) and electron-withdrawing groups (–F, –COOEt) on benzylic amine boronate ester was examined,



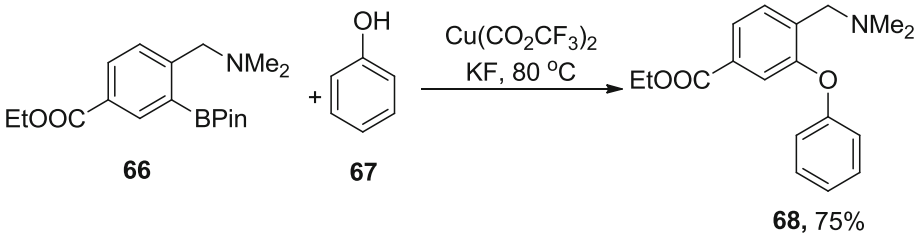
Where R = 2-Cl, 3-Cl, 4-Cl, 4-CH_3, 3-NMe_2, 4-CF_3, 3-NO_2, 2-OEt-5-CH=CHMe

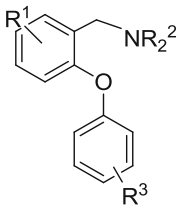
Scheme 18 Synthesis of biaryl ethers **65** by using substituted phenol **64**

and the best results were achieved in case of electron-withdrawing substituents (Scheme 19).

Under same reaction conditions, multi-substituted biaryl ethers were also synthesized in moderate yields (42–55%) (Fig. 3).

Scheme 19 Formation of biaryl ether **68** by using substituted benzylic boronate amine ester **66**





69

R^1 = 5-Me, NR_2^2 = NMe_2, R^3 = 4-CF_3, 55%

R^1 = H, NR_2^2 =  , R^3 = 3-NMe_2, 42%

R^1 = 6-F, NR_2^2 = NMe_2, R^3 = 2-OEt, 5-CH=CHMe, 44%

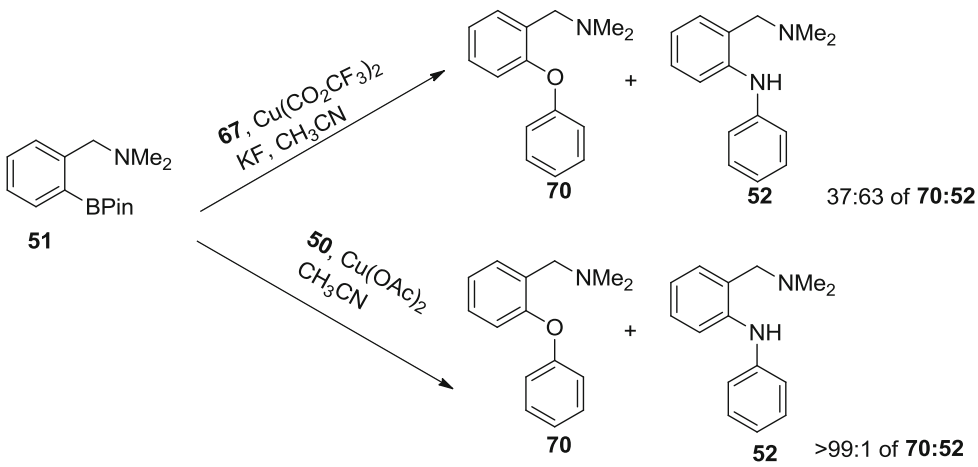
Fig. 3 General structure of multi-substituted biaryl ethers **69**

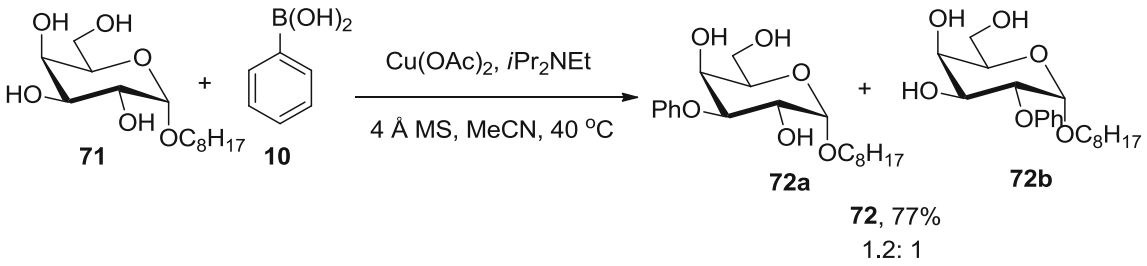
In order to evaluate the reactivity of phenols and anilines, a competition reaction was carried out with parent boronate ester using two sets of reaction conditions. For aniline **50**, $Cu(OAc)_2$ was used in the absence of base while for phenol **67**, $Cu(CO_2CF_3)_2$ was used with KF as base. However, phenols showed higher selectivity to synthesize the desired product (Scheme 20).

Considering the importance of glycobiology, Dimakos et al. [18] applied Chan–Lam coupling for *O*-arylation of carbohydrates and satisfactory results were obtained. The synthesis afforded the target compounds in 38–77% yield. The highest yield 77% was recorded when α-D-glactopyranoside **71** reacted with phenyl boronic acid **10** (Scheme 21).

Further, to evaluate the substrate scope of aryl boronic acids, methyl α-L-rhamnopyranoside **73** was chosen as model substrate. Both electron-withdrawing and electron-donating groups on boronic acid showed good results (35–76%), but the best result was obtained when methyl α-L-rhamnopyranoside was allowed to react with 4-methoxyphenyl boronic acid **5** and 76% yield of product **74** was obtained (Scheme 22).

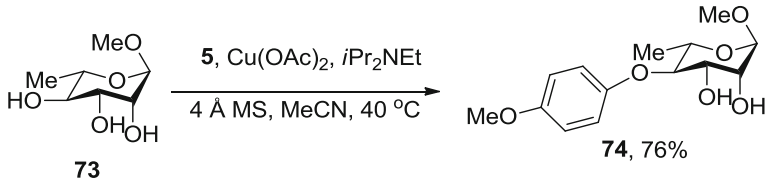
Scheme 20 Competition experiment between phenol and aniline

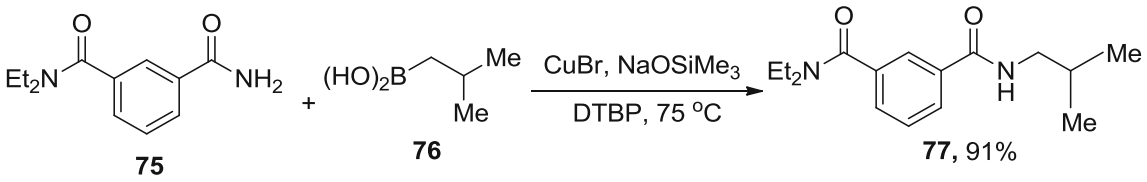




Scheme 21 Synthesis of sugar-derived aryl ether **72**

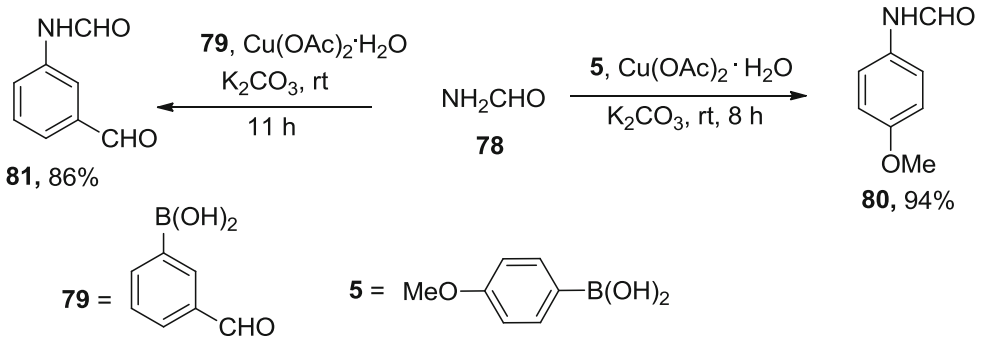
Scheme 22 Synthesis of sugar-derived aryl ether **74**



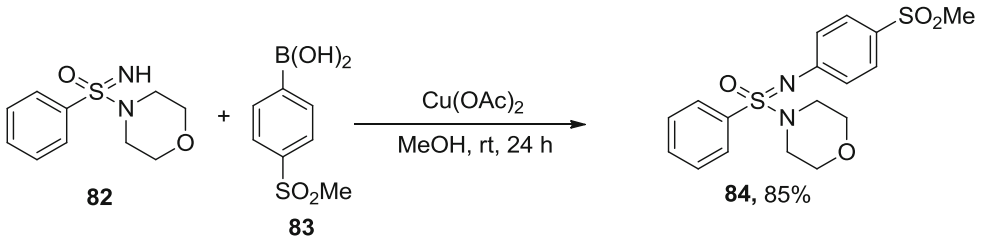


Scheme 23 Synthesis of secondary amide **77** via copper-catalyzed reaction

Scheme 24 Synthesis of formanilide **80** and **81**



Scheme 25 *N*-arylation of unprotected sulfonimidamides **84**



Synthesis of amides and their derivatives

Until 2013, few alkyl Chan–Lam coupling reactions were reported and most of them were limited to the use of methyl or cyclopropyl boronates. Rossi et al. [19] carried out the copper-catalyzed reaction to synthesize secondary amides using alkyl boronic acids, and products were obtained in moderate-to-high yields (40–91%). The best result was obtained when primary amide **75** was allowed to react with isobutyl boronic acid **76** to afford secondary amide **77** in 91% yield (Scheme 23).

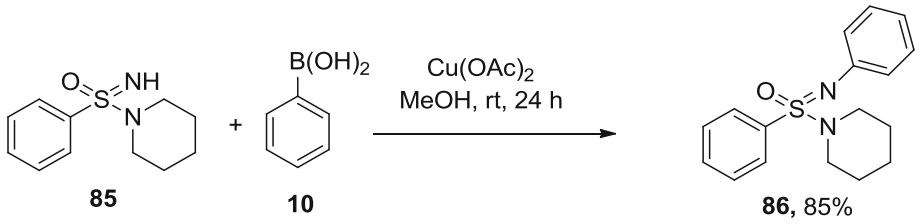
Srivastava et al. [20] reported the very first synthesis of copper-catalyzed formanilides. A number of aryl boronic acids having electronically diverse substitution pattern was subjected to Chan–Lam coupling under the optimized reaction conditions. Results revealed that aryl boronic acids having electron-donating groups resulted in higher yields. *p*-Methoxyphenyl boronic acid **5** was allowed to react with formamide **78**, and corresponding formanilide **80** was obtained in 94% yield. In case of electron-withdrawing substituted phenyl boronic acids, boronic acid having aldehyde group **79** gave the best yield (Scheme 24).

N-Arylation of unprotected sulfonimidamides in presence of anhydrous $Cu(OAc)_2$ was achieved by Battula et al. [21]. Previously, this reaction was performed in the presence of palladium catalyst. Reaction of 4-(phenylsulfonimidoyl)morpholine was conducted with different substituted heteroaryl systems and alkyl boronic acids, resulting in good yield of products. Maximum yield was reported for 4-SO_2Me phenyl boronic acid **83** when it was treated with 4-(phenyl sulfonimidoyl morpholine) **82,** and *N*-arylated product **84** was obtained in 85% yield (Scheme 25).

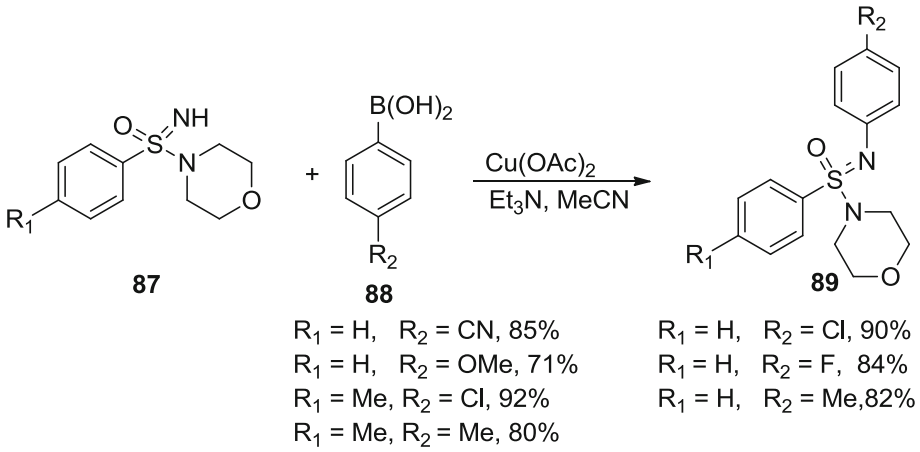
Similarly, piperidine-based sulfonimidamide **85** underwent *N*-arylation with phenyl boronic acid **10** under same reaction conditions and resulted in 85% yield of desired product **86** (Scheme 26).

Nandi et al. [22] described another route for *N*-arylation of *N*-protected and *N*′-deprotected sulfonimidamides. It

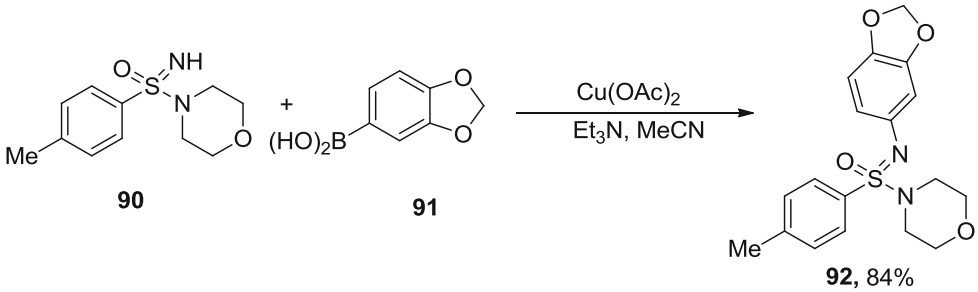
Scheme 26 Synthesis of *N*-arylated sulfonimidamides **86** by using Chan–Lam coupling



Scheme 27 Synthesis of *N*-arylated sulfonamides **89**



Scheme 28 Synthesis of *N*-arylated sulfonamide **92**



was observed that both electron-withdrawing and electron-donating groups on aryl boronic acid gave good-to-excellent yields. Substituted sulfonamide **87** reacted with substituted boronic acids **88** and corresponding products **89** were obtained (Scheme 27).

Under same reaction conditions, fused aryl boronic acids were treated with sulfonamides, and products were obtained in excellent yields. Reaction of fused aryl boronic acid **91** with sulfonamide gave 81% yield while methyl-substituted sulfonamide **90** was treated with fused boronic acid **91** and corresponding product **92** was obtained in 84% yield (Scheme 28).

Furthermore, morpholine moiety of sulfonamides was replaced by pyrrolidine **93** and treated with substituted aryl boronic acid **88** to give corresponding product in good-to-excellent yield (87–94%) (Scheme 29).

Reaction of 2-thienylboronic acid with sulfonamide resulted the product **95** in 38% yield. It was observed that addition of Et_3N resulted in complex reaction. Therefore, only $Cu(OAc)_2$ was used to carry out these reactions, and longer reaction time (13 h) for completion was required (Fig. 4).

Their research group also worked on *N*-arylation of protected sulfonimidamides by applying the same methodology to afford the products in good-to-excellent yields (82–93%) (Scheme 30).

The reaction between protected sulfonamide **98** and benzofused boronic acid **91** gave rise to the product **99** in 82% yield (Scheme 31).

Green synthesis of medicinally important *N*-arylated sulfonamides was presented by Nasrollahzadeh et al. [23]. It was observed that this methodology has wide scope of substrate when a variety of aryl boronic acids with electron-donating (Me, OMe) and electron-withdrawing (CF_3) substituents was used. Same methodology was applicable for heteroaryl boronic acid as well (65–89%). The best results were observed when sulfonamide **100** was reacted with phenyl boronic acid **10** and heteroaryl boronic acid **101**, corresponding products **102** and **103** were obtained in 95% and 89% yield (Scheme 32).

Scheme 29 Synthesis of *N*-arylated sulfonamides **94**

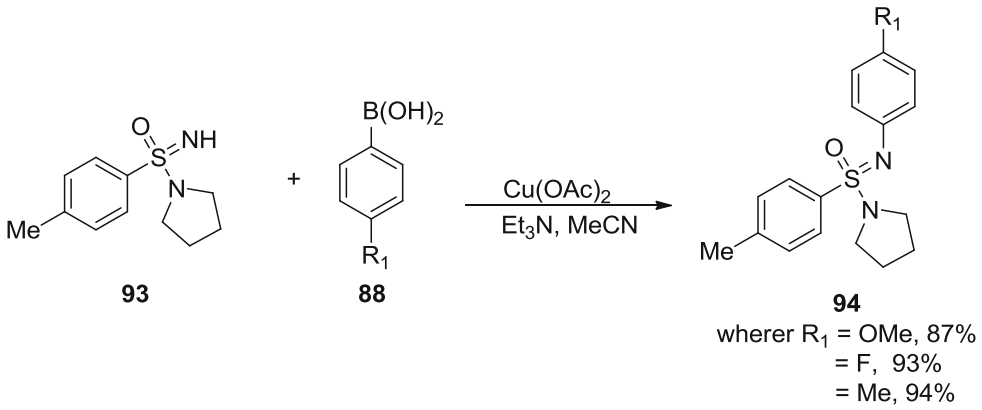
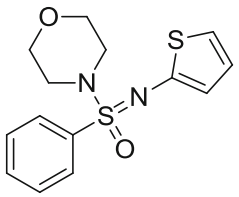


Fig. 4 Structure of *N*-arylated sulfonamide **95**



N-Arylation of benzamides was performed by Alapati et al. [24]. The *N*-arylation of different benzamides was done with substituted aryl boronic acid and 80–91% yield of desired compounds was obtained. The best result was obtained when 4-nitrobenzamide **104** was treated with phenyl boronic acid **10** and 91% yield was obtained (Scheme 33).

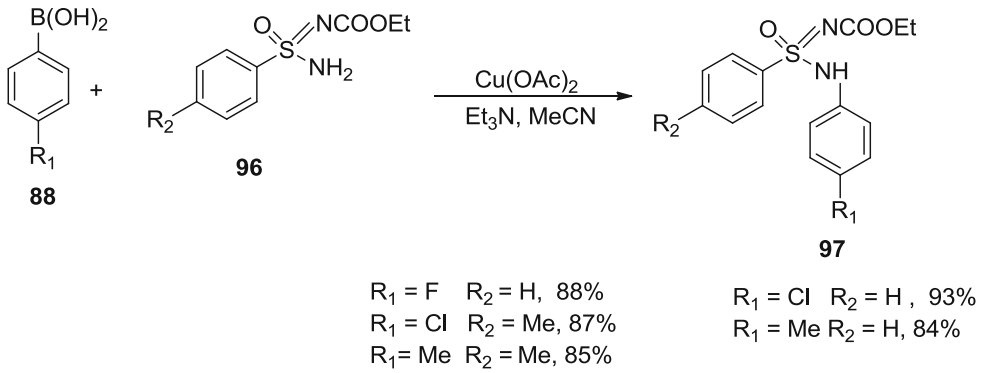
Scope of substrates was also evaluated by treating benzamide with different substituted boronic acids. Maximum yield of 89% was obtained when benzamide **106** was treated with 4-nitrophenyl boronic acid **107** (Scheme 34).

Sahoo et al. [25] described C–N coupling between boronic acid and various amides and 54–93% yield of products was obtained. The best result was obtained when *N*-(4-bromo-3-methylphenyl)picolinamide **109** was treated with phenyl boronic acid **10** and furnished the required product in 93% yield (Scheme 35).

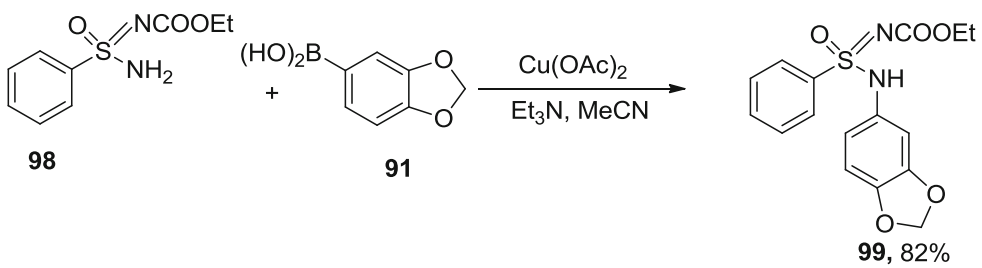
Similarly, heterocyclic-substituted amide also underwent this reaction and 70% yield was obtained when *N*-(2-(1*H*-indol-3-yl)ethyl)picolinamide **112** was treated with 4-bromophenyl boronic acid **111** (Scheme 36).

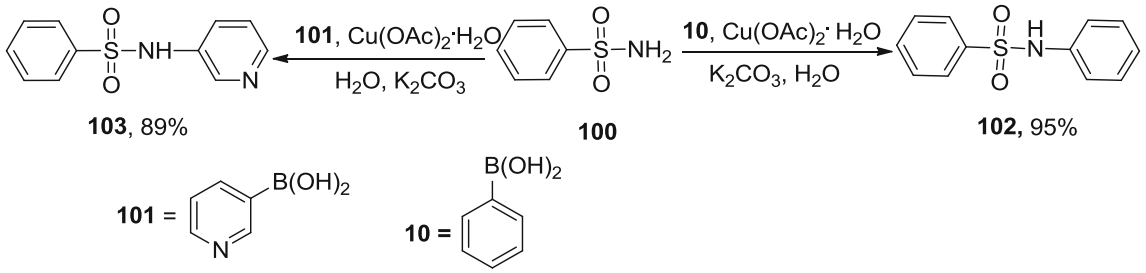
Xu et al. [26] extended the scope of Chan–Lam coupling by applying it on phosphonic/phosphinic amides. The phosphonamides having electron-donating and electron-withdrawing groups demonstrated good results. Maximum yield of 88% of product **116** was obtained when phosphonamide having unsaturated carbon–carbon triple bond containing substituent **114** was treated with *p*-Tol-B(OH)$_2$ **115** (Scheme 37).

Scheme 30 Synthesis of *N*-arylated protected sulfonamides **97**



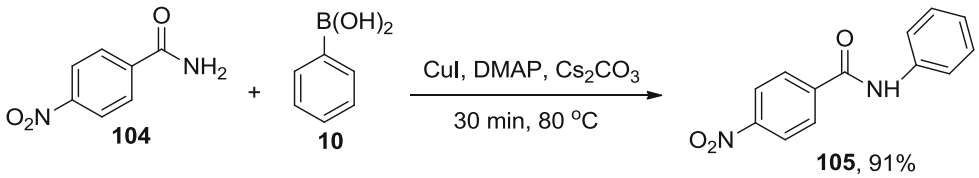
Scheme 31 Synthesis of *N*-arylated protected sulfonamide **99**



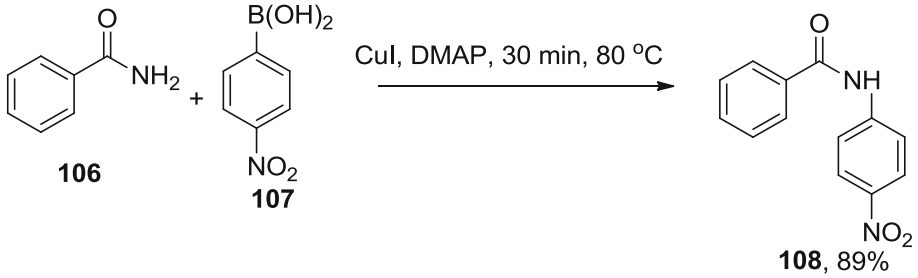


Scheme 32 Synthesis of *N*-arylated sulfonamide **102** and **103**

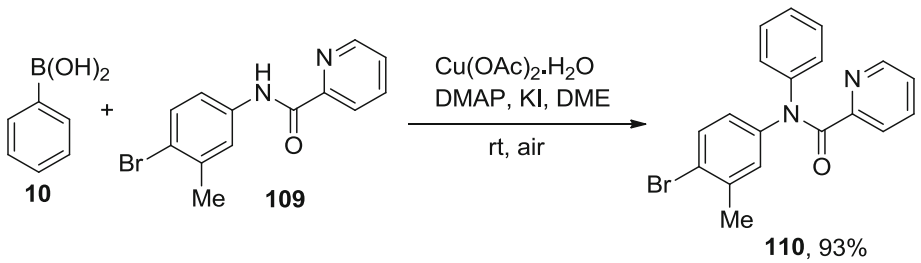
Scheme 33 Formation of *N*-arylated amides **105**

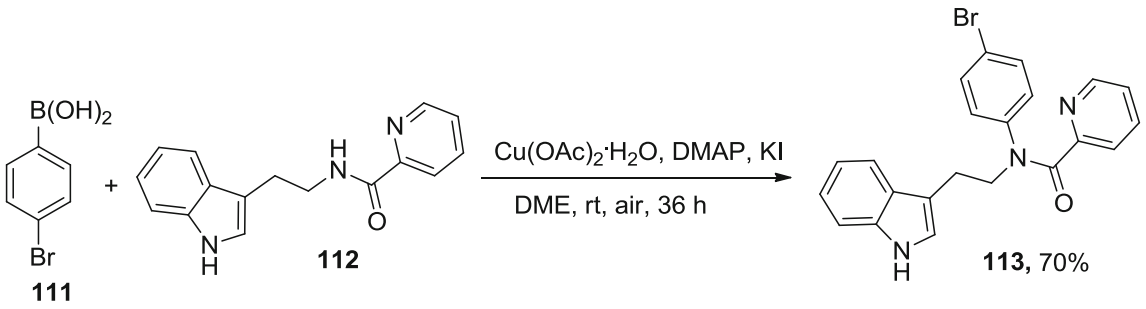


Scheme 34 Formation of *N*-arylated amides **108** by using substituted boronic acid



Scheme 35 Synthesis of *N*-arylated amide **110** through Chan–Lam coupling



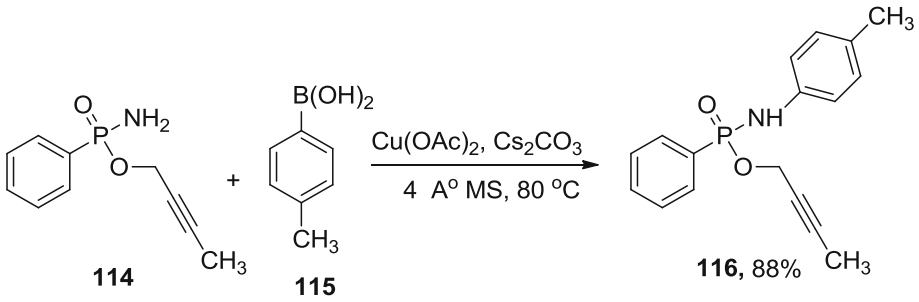


Scheme 36 Synthesis of *N*-arylated amide **113**

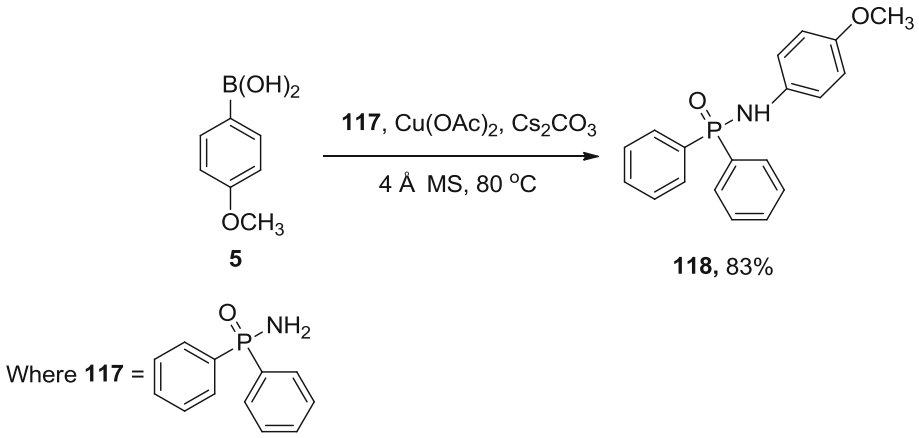
Afterward, scope of substituents on aryl boronic acid was investigated. Encouraging results were obtained showing good yield of products. The best results were seen in case of 4-methoxy phenyl boronic acid **5** when it was treated with *P*,*P*-diphenyl phosphinamide **117** and 83% yield of *N*-arylated *P*,*P*-diphenyl phosphinamide **118** was obtained (Scheme 38).

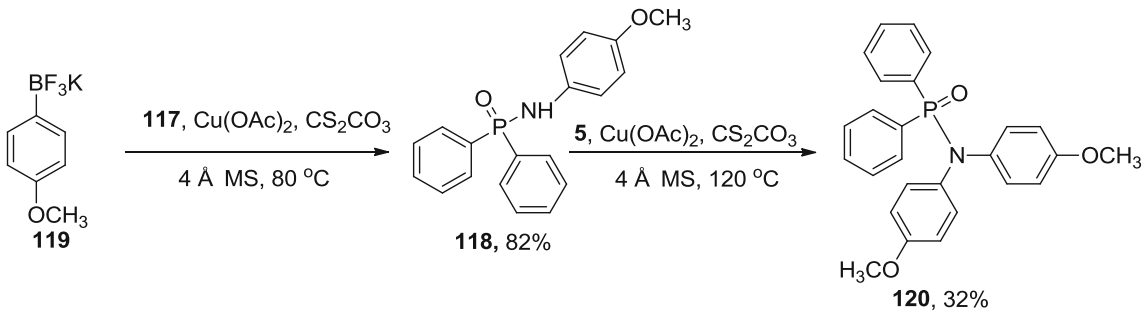
A controlled experiment was conducted in which *P*,*P*-phosphinamide **117** was treated with potassium trifluoro *p*-totyl borate **119** to afford the arylated product **118** in 82% yield. Further, arylation attempts to form diarylated product

Scheme 37 Synthesis of *N*-arylated phosphonamide **116**



Scheme 38 Formation of *N*-arylated *P*,*P*-diphenyl phosphinamide **118**





Scheme 39 Controlled experiment to form diarylated product **120**

were tried. It was observed that at 80 °C and 100 °C, no traceable product was formed; however, at 120 °C, diarylated product **120** could be accessed in only 32% yield (Scheme 39).

Formation of pyridine and purine derivatives

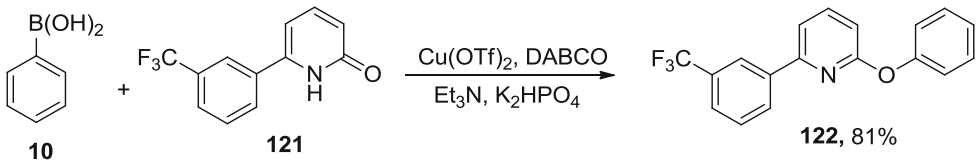
Chen et al. [27] developed the methodology for *O*-arylation of C-6-substituted pyridine-2-ones by using a number of arylboronic acids. A study of different groups as C-6 substituents showed that electron-withdrawing groups gave higher yield. For example, phenyl boronic acid **10** was allowed to react with 6-(3-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one **121** in the presence of $Cu(OTf)_2$, DABCO, Et_3N, and K_2HPO_4 to attain the product **122** in 81% yield (Scheme 40).

Similarly, effect of different substituents on phenyl boronic acid was investigated. It was observed that electron-donating groups on phenyl boronic acid facilitated the coupling reaction. For example, 6-methyl-pyridine-2-one **123** was allowed to react with 3-methoxyphenyl boronic acid **124** under same reaction conditions and corresponding product **125** was obtained in 56% yield (Scheme 41).

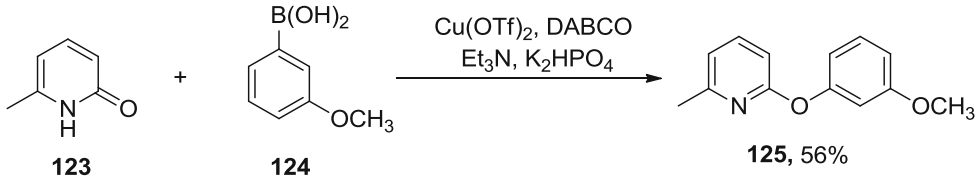
It was also postulated that steric hindrance of DABCO catalyst system and C-6 substituents contributed to regioselectivity.

Considering the importance of antitumor agents, a novel route to synthesize these biologically important compounds was designed by Chen et al. [28] through applying a consecutive Chan–Lam coupling and Suzuki coupling. The target compounds were synthesized in two subseries. In

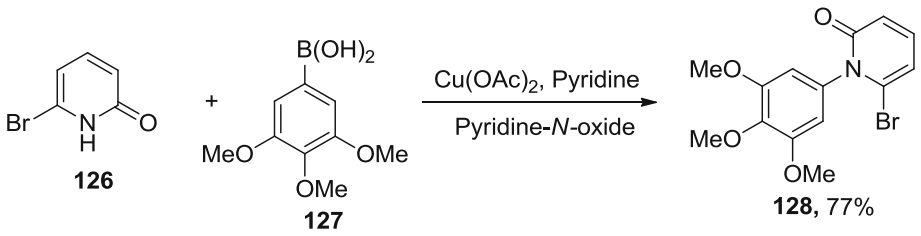
Scheme 40 Formation of 2-phenoxy-6-(3-(trifluoromethyl)phenyl)pyridin **122**

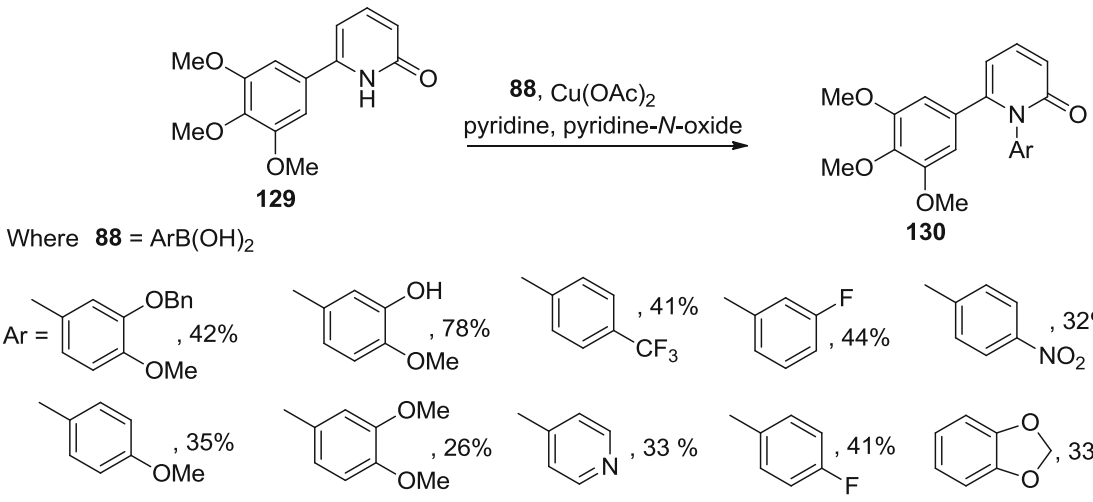


Scheme 41 Synthesis of *O*-arylated pyridine-2-ones **125** using substituted phenyl boronic acid



Scheme 42 Synthesis of 1,6-diaryl pyridine-2(1*H*)-one analogs **128** by using Chan–Lam coupling





Scheme 43 Synthesis of 1,6-diaryl pyridine-2(1*H*)-one analogs **130** by using Chan–Lam coupling

first subseries, *N*-arylation was performed by treating 6-bromopyridine-2(*H*)-one **126** with 3,4,5 trimethoxyphenyl boronic acid **127**, resulting product **128** was subjected to Suzuki coupling to synthesize the final product (Scheme 42).

For second subseries, Suzuki coupling was applied on 6-bromopyridine-2(*H*)-one **126** and resulting product **129** was subjected to Chan–Lam coupling to get target compounds **130** (Scheme 43).

Anti-proliferative activity of both the subseries of pyridine-2(1*H*)-one was investigated for human ovarian carcinoma cell line (SKOV-3) and human hepatoma cell line (HepG2). First subseries showed more potent anti-proliferative activity. Compounds **131** and **132** (Fig. 5) were found equally effective for both cell lines with IC_{50} <0.01 μM/mL. In vivo antitumor activity of these compounds was also investigated against H22 cell line and moderate activities were observed.

Chen et al. [29] described the synthesis of *N*-(3,4,5-trimethoxyphenyl)pyridine-2(1*H*)-one derivatives via consecutive Chan–Lam and Buchwald–Hartwig couplings. 6-Bromopyridine-2(1*H*)-one **126** was allowed to react with (3,4,5-trimethoxyphenyl)boronic acid **127** and product **128** was obtained (77%), which was further subjected to a Buchwald–Hartwig coupling. Two subseries of compounds were prepared by coupling of **128** with substituted anilines **133** and benzyl amines **134**, respectively (Scheme 44).

Antitumor activity of all the synthesized compounds was tested against human colon carcinoma HCT-116. All com-

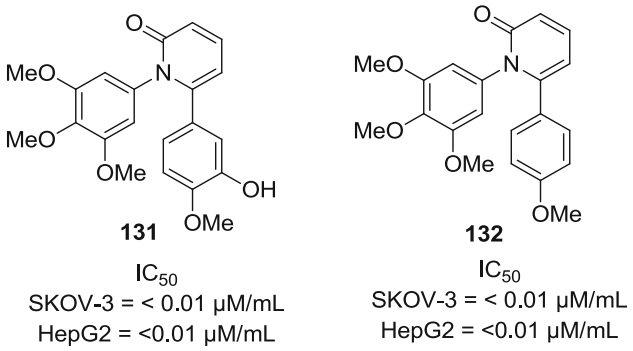


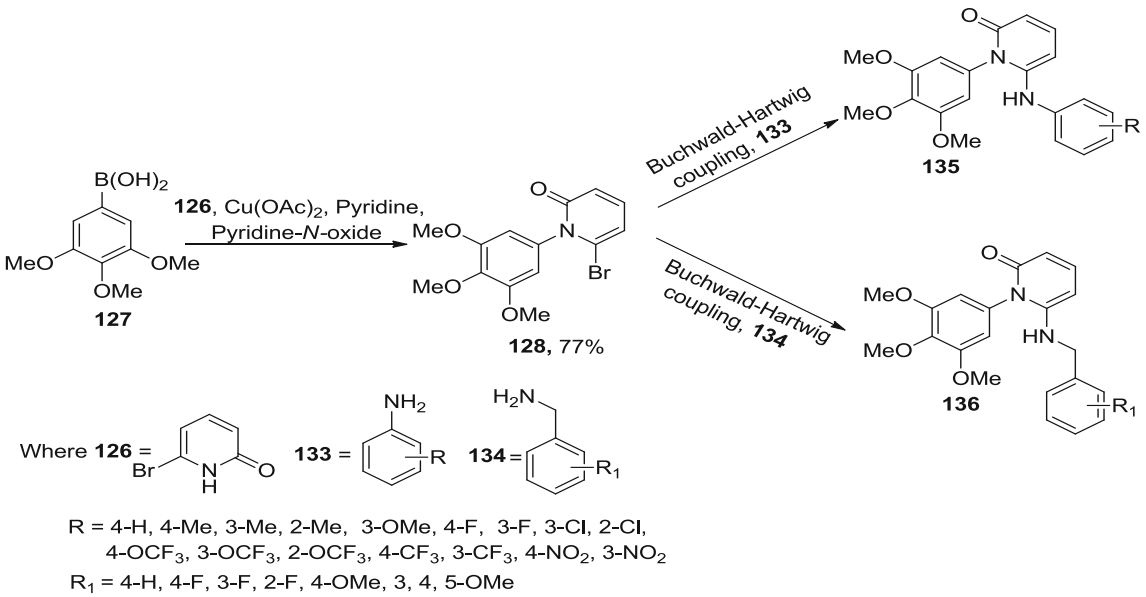
Fig. 5 Structure of anti-proliferative compounds

pounds of the first subseries showed moderate cytotoxic activity. The most potent compounds **137** and **138** of this series showed activity IC_{50} = 0.96 and 0.40 μg/mL, respectively. However, the second subseries did not show good anti-proliferative activity except a single compound **139** which showed activity 7.53 μg/mL (Fig. 6).

Activity of conformation restricted compound **140** was compared to a flexible compound **141**. Results showed that rigidity of conformation contributed positively to the antitumor activity (Fig. 7).

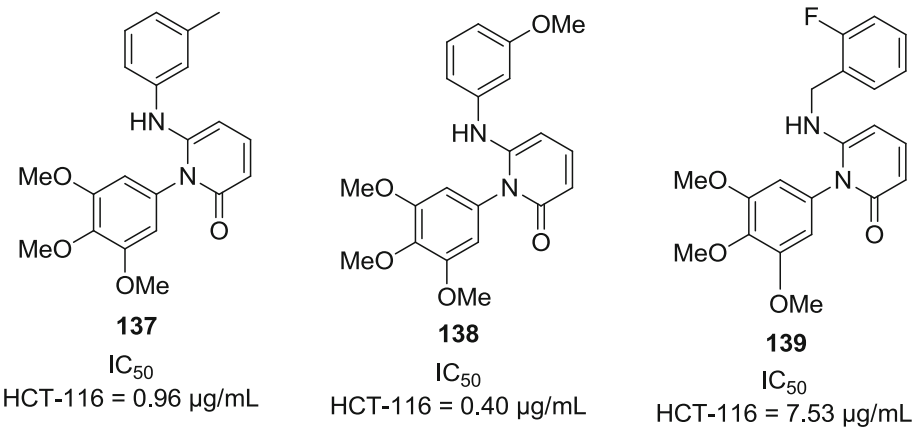
Morellato et al. [30] performed a Chan–Lam coupling to synthesize the series of 9-hetero aryl purine derivatives. For example, 6-chloropurine **142** was treated with 3-bromo boronic acid **143** and hetero aryl boronic acid **144**, products **145** (90%) and **146** (69%) were obtained. The products were treated with ammonia in the presence of methanol to yield target compounds (Scheme 45).

Chen et al. [31] reported the synthesis of *N*-arylpyridin-2-amines using the Chan–Lam coupling. A variety of phenyl boronic acids with electron-donating (–Me, –OMe) and electron-withdrawing groups (–F, –Cl, $–CF_3$) were used, and good results were obtained. For example, 2-amino pyri-



Scheme 44 Synthesis of *N*-(3,4,5-trimethoxyphenyl)pyridine-2(1*H*)-one derivatives **135**–**136** by using Chan–Lam and Buchwald–Hartwig coupling

Fig. 6 Structure of antitumor compounds **137**, **138**, and **139**



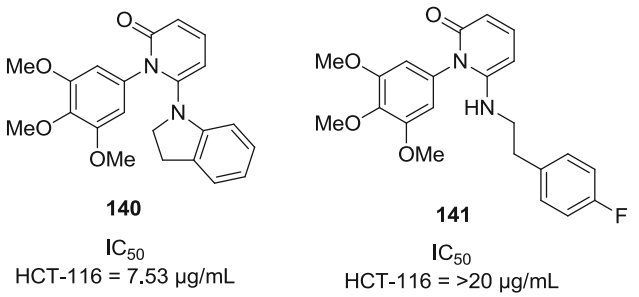


Fig. 7 Structure of compounds **140** and **141** showing effect of conformation

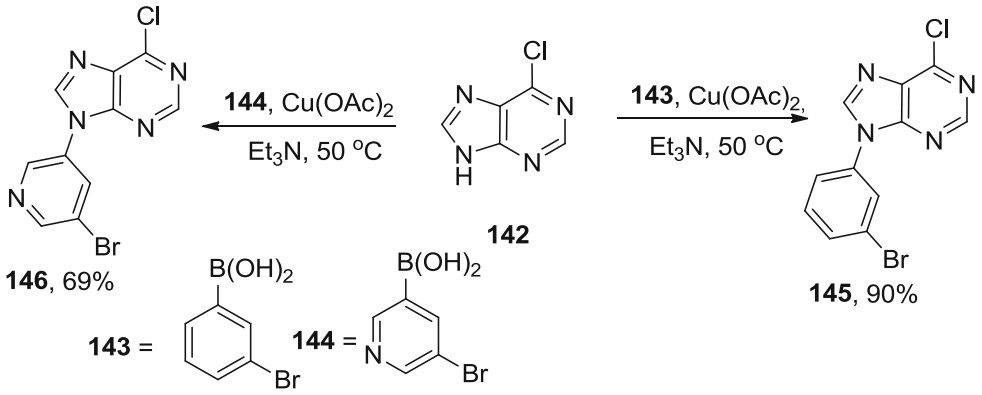
dine **147** was treated with substituted boronic acid **148** and resulted in product **150** (88%). Similarly, pyridine-3-boronic acid **149** reacted with 2-aminopyridine **147,** and product **151** (52%) was obtained at 40 °C (Scheme 46).

Formation of arylated thiocyanates

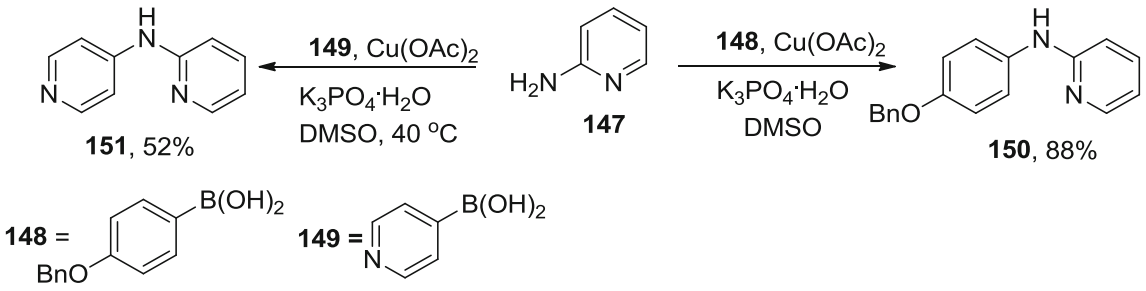
Organic thiocyanates are used as intermediates for the formation of different sulfur-containing compounds such as thioethers, thiocarbamates, disulfides, and heterocycles. It is also observed that aryl thiocyanates are biologically active compounds. Sun et al. [32] reported the first construction scheme for aryl thiocyanates by direct C–S bond formation. The effect of different substitution patterns was observed which reflected the suitability of this protocol for electron-donating and moderate electron-withdrawing groups. However, strong electron-withdrawing groups resulted in lesser yield. This protocol was also applicable to fused aryl boronic acids. The best results were obtained when KSCN **152** was treated with substituted phenyl boronic acid **153** and naphthyl boronic acid **154**, desired products **155** (91%) and **156** (80%) were obtained (Scheme 47).

Arylation of thiophene

Rizwan et al. [33] studied the *N*-arylation of methyl 2-aminothiophene-3-carboxylate through Chan–Lam coupling. It was observed that longer reaction time (24 h) led to formation of diaryl products. To overcome this problem, reaction concentration was decreased to 0.03 M. The reaction yields were not significantly influenced by the electronic nature of different substituents on boron substrates. Aryl boronic acids having electron-withdrawing groups such as fluoro, cyano, formyl, and acetyl groups resulted in formation of desired compounds. The best results were obtained in case of acetyl group where methyl 2-aminothiophene-3-carboxylate **157** was allowed to react with 4-acetylphenyl boronic acid **158** which resulted in formation of corresponding arylated product **160** in 73% yield. Same reaction was carried out at gram-scale level and 69% yield of desired product was obtained. Different electron-donationg groups were also tried such as 4-isopropyl, 4-*tert*-butyl, 4-ethyl phenyl boronic acid and 2,4-dimethyl phenyl boronic acid. The best result was obtained when the reaction was done

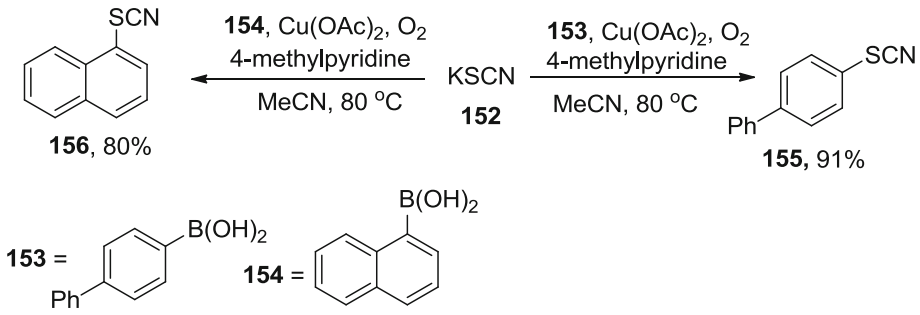


Scheme 45 Synthesis of aryl purine using Chan–Lam coupling

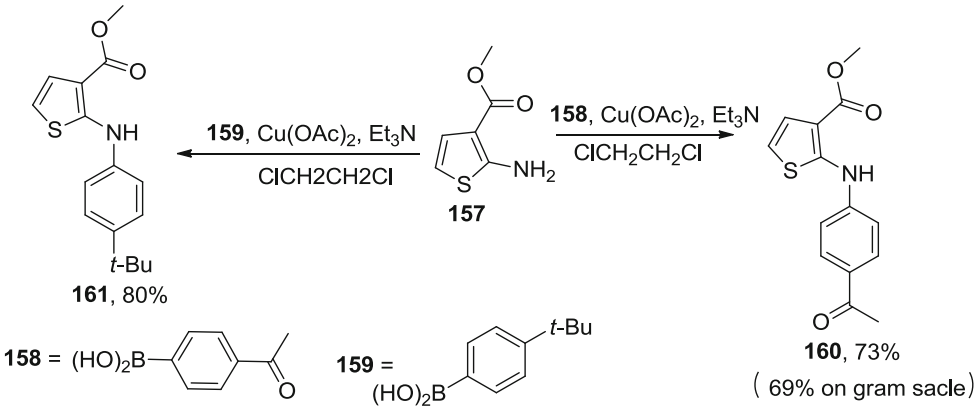


Scheme 46 Synthesis of *N*-arylpyridine-2-amines **150** and **151**

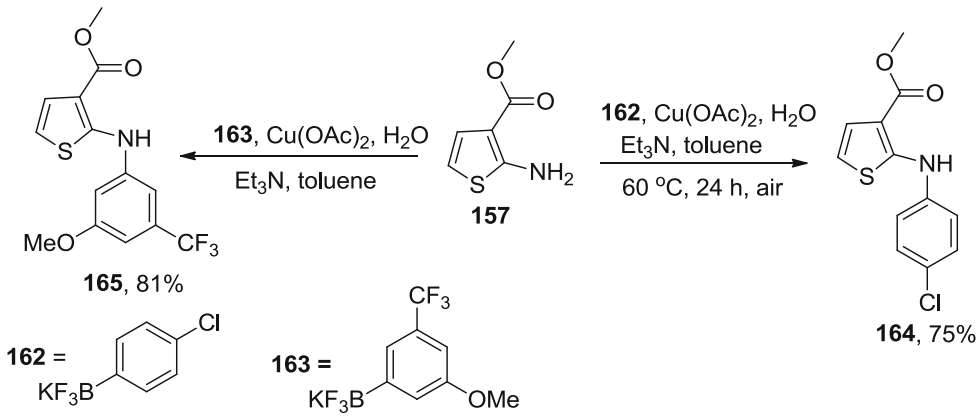
Scheme 47 Synthesis of aryl thiocyanates **155** and **156** using Chan–Lam coupling



Scheme 48 Synthesis of *N*-arylated thiophene **160** and **161**



Scheme 49 Synthesis of *N*-arylated 2-aminothiophene-3-carboxylate **164** and **165**



by 4-*tert*-butyl phenyl boronic acid **159**, and *N*-arylated 2-aminothiophene-3-carboxylate **161** (80%) was obtained (Scheme 48).

Some modifications were made in reaction conditions by replacing DCM with toluene having few drops of water and conducting the reaction at 60 °C in air made possible the coupling of 2-aminothiophene-3-carboxylate with potassium aryltrifluoroborate. Electron-donating groups on potassium trifluoroborates resulted in good yield (such as 3-methyl, 2-methyl, 4-*t*-butyl, 4-ethoxy, 3-methoxy). Similarly, electron-withdrawing groups substituted potassium triflouro borates were well tolerated such as 4-chloro potassium triflouroborate **162**. However, excellent yield was observed when 3-methoxy-5-trifluoromethyl trifluoroborate **163** was allowed to react with 2-amino-3-thiophene-caroxylate **157** giving product **165** (81%) (Scheme 49).

Furthermore, it was observed that the position of substituent strongly effected the yield. For example, good yield of **166** (50%) was obtained which was derived from 3-methyl-substituted potassium trifluoro borate and it was higher as compared to the derivative of 2-methyl-substituted potassium triflouro borate **167** (35%). Same effect was also observed in case of 4-chloro- and 3-chloro-substituted derivatives (Fig. 8).

Arylation of thiols

C–S bond formation through Chan–Lam coupling was demonstrated by Pulakhandam et al. [34]. The methodol-

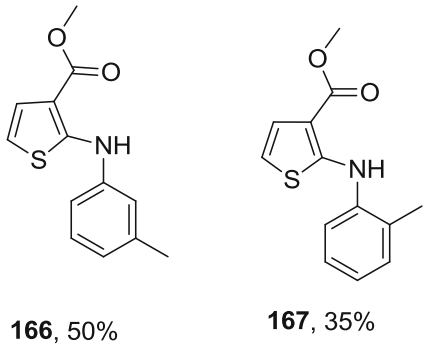


Fig. 8 Structure of compounds **166** and **167** showing effect of position of substituent

ogy involved the reaction of 1,4-dihydroquinazoline with different aryl/heteroaryl boronic acid and good-to-excellent yield was obtained (72–90%). The best result was obtained when 1,4-dihydroquinazoline-2-thiol **168** reacted with (5-formylthiophen-2-yl)boronic acid **169** to give corresponding product **170** in 92% yield (Scheme 50).

Preparation of indoles/oxindoles

Until 2014, different methods were being used to prepare the 1,2-disubstituted indoles and most of the methods involved the use of toxic and expensive catalysts. Gao et al. [35] reported the first one-pot method for the formation of 1,2-disubstituted indoles using Chan–Lam coupling. The synthesis was done by using 2-alkenylanilines and boronic acids.

The synthesis of 1,2-disubstituted indoles was carried out by treating 2-phenylethynyl-aniline with a number of aryl/alkyl boronic acid. The best results were seen when 2-(phenylethynyl)-aniline **171** was treated with 4-methylphenyl boronic acid **115** and cyclopropyl boronic acid **46** and corresponding products **172** (91%) and **173** (55%) were formed (Scheme 51).

Scope of this reaction for substituted 2-alkenylanilines was also investigated. Results showed that electron-donating as well as electron-withdrawing groups are well tolerated. However, strong electron-withdrawing groups, such as cyano, led to lower yields. The best results were obtained when methyl-substituted alkenylaniline **174** was treated with 4-methylphenyl boronic acid **115,** and corresponding product **175** was obtained in 90% yield (Scheme 52).

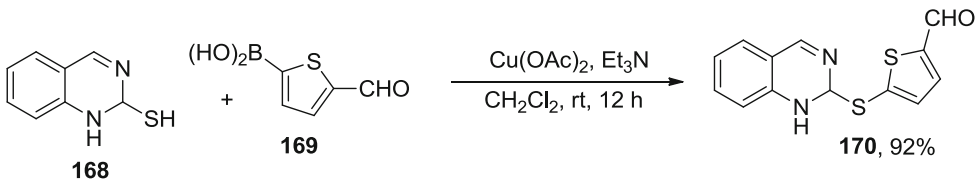
Effect of various substituents on ethynyl chain of 2-alkenylaniline was also investigated, and results indicated that reaction was equally feasible for the reactants with substituted aryl and alkyl groups and moderate-to-good yields were obtained (48–85%). The best results were obtained for aryl-substituted 2-alkenylanilines **176** when it was treated with phenyl boronic acid **10,** and 1,2 disubstituted indole **177** was synthesized in 85% yield (Scheme 53).

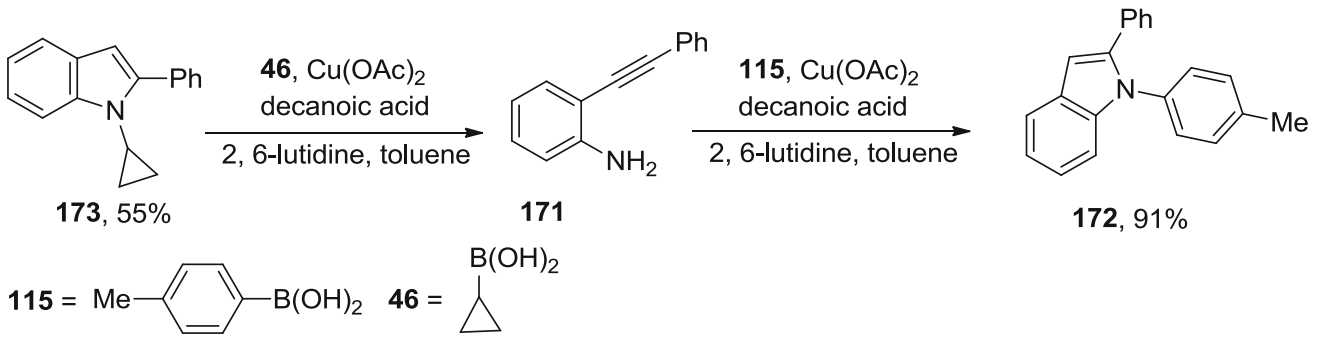
The synthesized compounds were further allowed to undergo the Pd-catalyzed intramolecular arylation to produce the polycyclic indole derivatives.

Chan–Lam coupling was successfully applied on 3-(hydroxyimino)indoline-2-ones to perform *N*-vinylation by Chen et al. [36]. Substituted vinyl boronic acid and substituted 3-(hydroxyimino)indolin-2-one were reacted to form products in (5–98%) yield. Best results were obtained when (*Z*)-3-(hydroxyimino)indolin-2-one **178** was allowed to react with boronic acid **179** and resulted in 98% product **180** (Scheme 54).

The double *N*-vinylated product was formed by using 2 equivalents of $Cu(OAc)_2$, keeping the other conditions same.

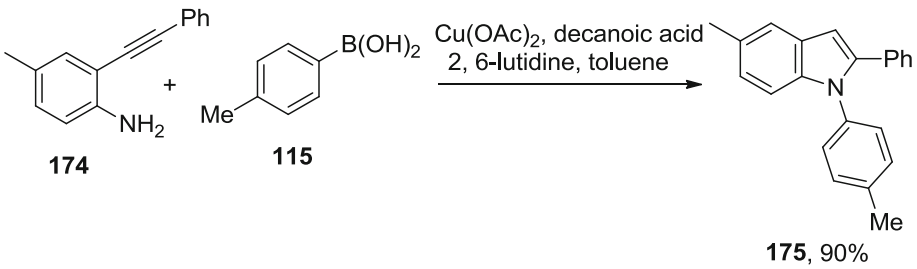
Scheme 50 Construction of C–S bond in **170** through Chan–Lam coupling



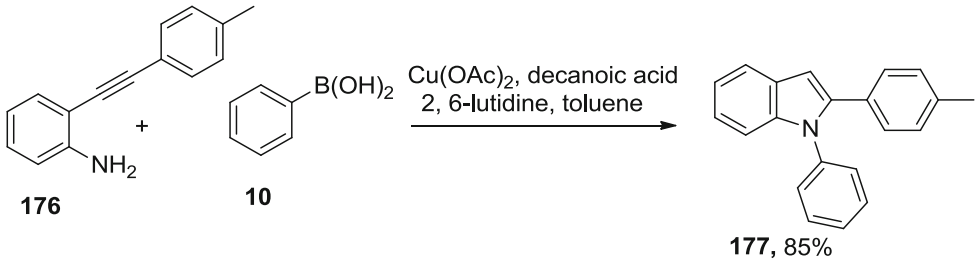


Scheme 51 Synthesis of 1, 2 disubstituted indoles **172** and **173**

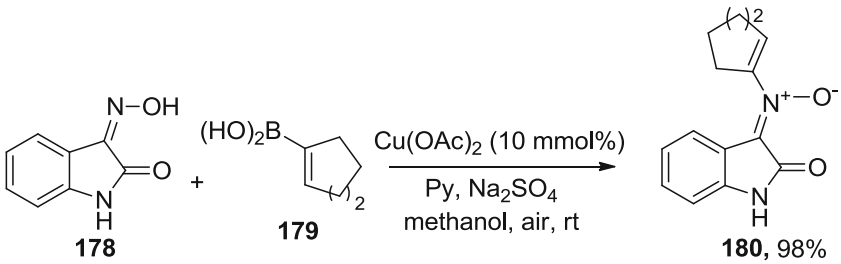
Scheme 52 Synthesis of 1, 2 disubstituted indoles **175** by using substituted alkenylaniline **174**



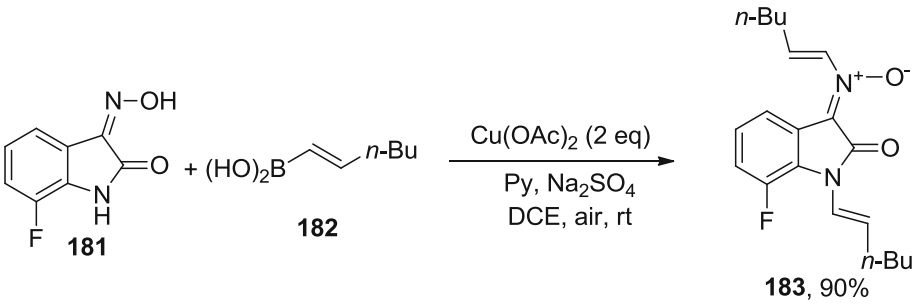
Scheme 53 Synthesis of indoles **177** by using substituents on alkenyl chain



Scheme 54 Synthesis of nitrone **180**



Scheme 55 Synthesis of divinylated indole **183**



(*E*)-Hex-1-en-1-ylboronic acid **182** was treated with (*Z*)-7-fluoro-3-(hydroxyimino)indolin-2-one **181**, which resulted in 90% yield of double vinylated product **183** (Scheme 55). The resulting compound underwent thermal reaction to form final product spirooxindole.

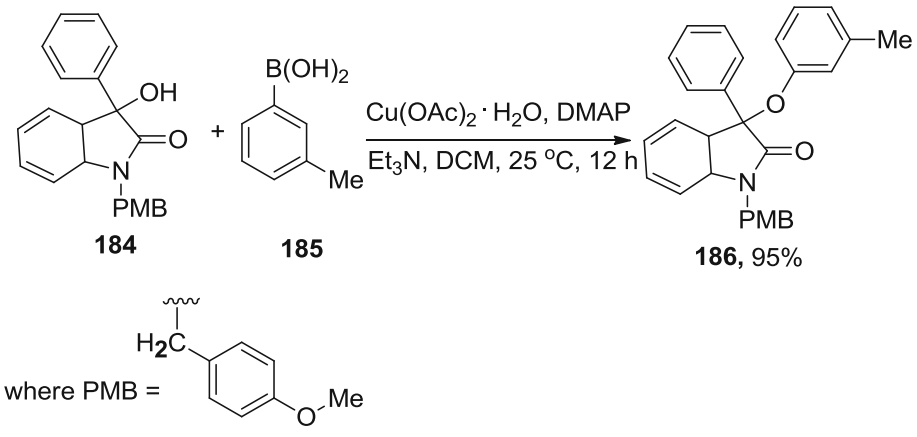
3-Aryloxy-2-oxindoles are considered pharmaceutically important compounds due to their diverse biological properties. Li et al. [37] described the copper(II) catalyzed formation of 3-aryloxy-2-oxindole. A number of aryl boronic acids were allowed to react with 3-hydroxy-2-oxindoles, but the best yield was observed when 3-hydroxy-2-oxindole **184** was reacted with 3-methylphenyl boronic acid **185** and resulted in 95% yield of desired product **186** (Scheme 56).

In case of substituted 3-hydroxy 2-oxindoles, the best results were obtained when chloro-substituted 3-hydroxy-2-oxindol **187** was reacted with phenyl boronic acid **10** to form the desired product **188** in 91% yield. This reaction was also performed at gram-scale level to check its applicability, and 95% of product was obtained (Scheme 57).

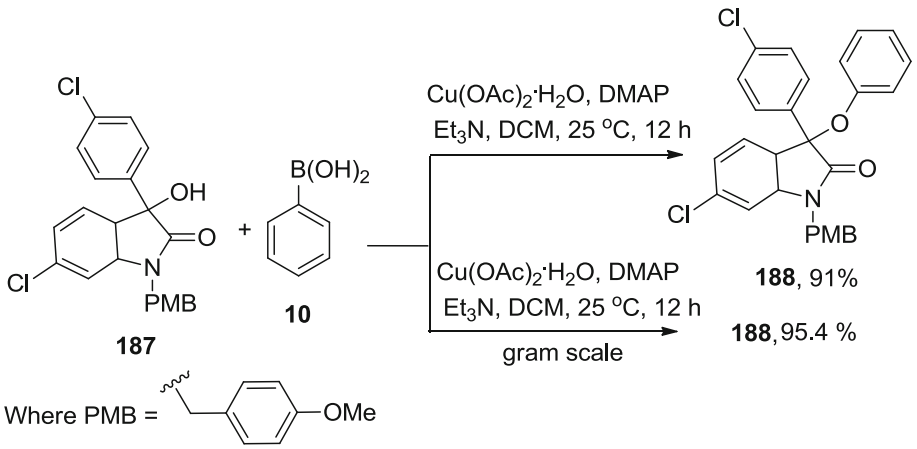
Arylation of benzimidazole and 3-amino pyrazole

One-pot N^1,N^2-diarylation of 3-amino pyrazole was described by Beyer et al. [38]. The first *N*-arylation was performed under Ullman conditions and 46–94% yield of resulted compounds, as mixture of regioisomers, was obtained. Monoarylated pyrazole **189** was selected to perform second *N*-arylation under Chan–Lam conditions. The products were obtained in up to 88% yield, and the results proved the efficiency for electron-rich and electron-neutral substrates, while electron-withdrawing groups resulted in less yield due to lack of reactivity such as para-nitro boronic

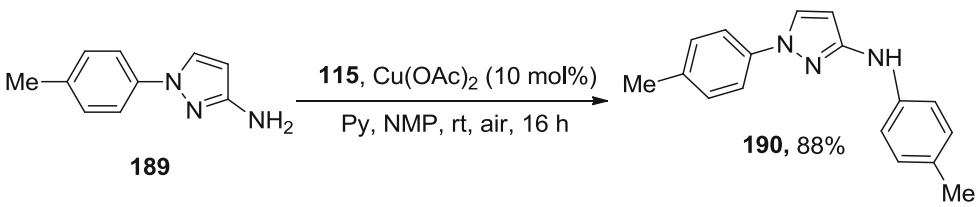
Scheme 56 Synthesis of *O*-arylated oxindole **186**



Scheme 57 Synthesis of *O*-arylated substituted oxindole **188**



Scheme 58 *N*-Arylation of substituted pyrazole **189**



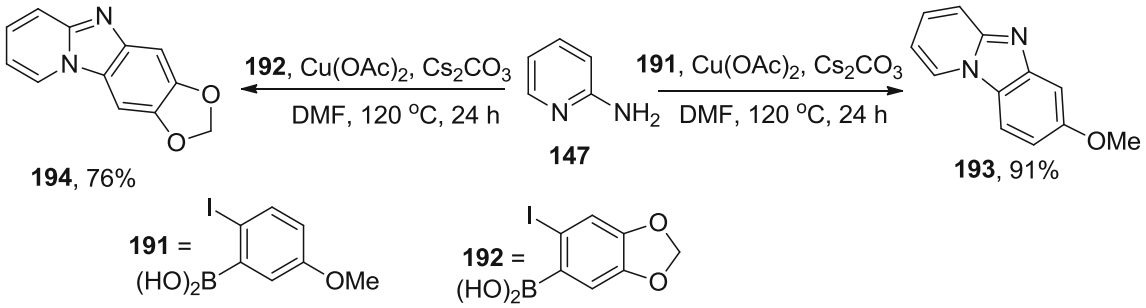
acid where no product formation (0%) was observed except para-iodo boronic acid. Maximum yield of 88% was obtained in case of 4-methylphenyl boronic acid **115** when it was treated with **189** (Scheme 58).

Rasheed et al. [39] described the preparation of benzimidazole-fused heterocycles by applying Chan–Lam coupling followed by Ullmann-*type reaction. The synthesis involved the one-pot reaction of 2-iodoarylboronic acid and 2-aminoheteroarenes. During the reaction, intermolecular C–N bond formation was done by Chan–Lam coupling and intra molecular cyclization was done by Ullmann type reaction. 2-Aminopyridine **147** was allowed to react with different substituted phenyl boronic acid having electron-donating as well as electron-withdrawing groups and corresponding products were obtained in good yields (75–91%). The best results were obtained when 2-aminopyridine **147** was allowed to react with (2-iodo-5-methoxyphenyl)boronic acid **191** and benzo[*d*][1,3]dioxo 1-5-yl boronic acid **192** and corresponding products **193** (91%) and **194** (76%) were obtained (Scheme 59).

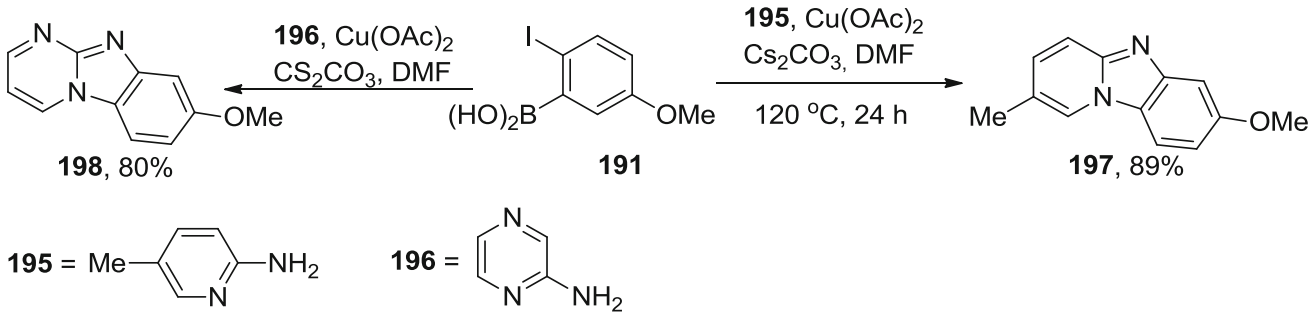
This methodology was also applied on substituted 2-aminopyridine derivatives (75–89%) and benzimidazo [1,2-a]pyrazine. Maximum yields were obtained when (2-iodo-5-methoxyphenyl)boronic acid **191** was treated with methyl-substituted amino pyridine **195** and 2-amino pyrazine **196** (Scheme 60).

It was also observed that steric hindrance did not play any role, and different products were formed in good yield. For example, 6-methyl-substituted 2-amino pyridine **199** was allowed to react with dimethoxy-substituted phenyl boronic acid **200,** and this highly substituted compound furnished the product **201** in 80% yield (Scheme 61).

This methodology also proved helpful for synthesis of fused heterocylces **202**–**203** (Fig. 9).

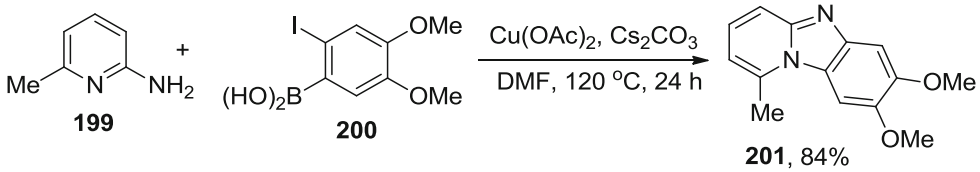


Scheme 59 Synthesis of benzimidazole-fused heterocycles **193** and **194**



Scheme 60 Synthesis of benzimidazole-fused heterocycle **197** and **198**

Scheme 61 Synthesis of benzimidazole based heterocycle **201**



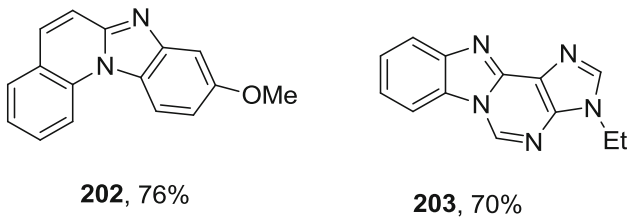
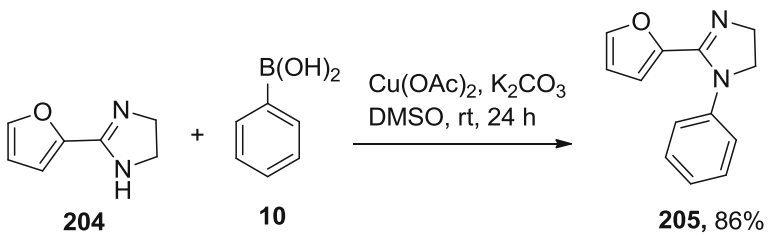


Fig. 9 Structures of heterocyclic compounds **202** and **203** prepared by Chan–Lam coupling

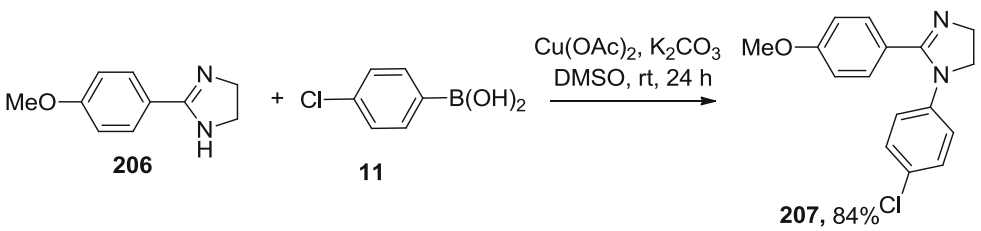
N-(Hetero)aryl-substituted 2-imidazolines are widely applied as an important motif in medicinal chemistry. Different inhibitors and anti-tubercular agents are based on this important moiety. Previously reported methods involved the use of palladium and copper catalyst at higher temperature (100–150 °C). Darin and Krasavin [40] successfully disclosed the application of Chan–Lam coupling for *N*-arylation of 2-imidazolines with little modification which was made by replacing pyridine (base) with K_2CO_3. This research group created a library of *N*-arylated-2-imidazolines which fall in range of good yields. Maximum yield of 86% of **205** was reported for phenyl boronic acid **10** and heteroaryl-substituted 2-imidazoline **204** (Scheme 62).

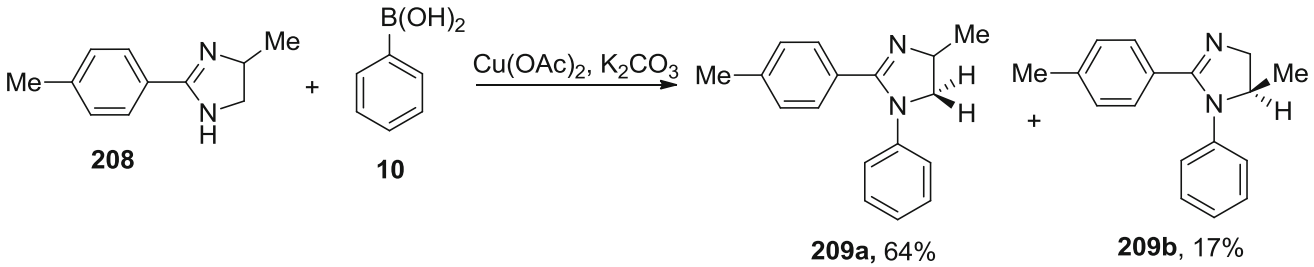
Moreover, the reaction with electron-donating substituent 4-methoxyphenyl 2-imidazoline **206** with 4-chlorophenyl boronic acid **11** resulted in desired product **207** in 84% yield (Scheme 63).

Scheme 62 Formation of 2-(furan-2-yl)-1-phenyl-4,5-dihydro-1*H*-imidazole **205**

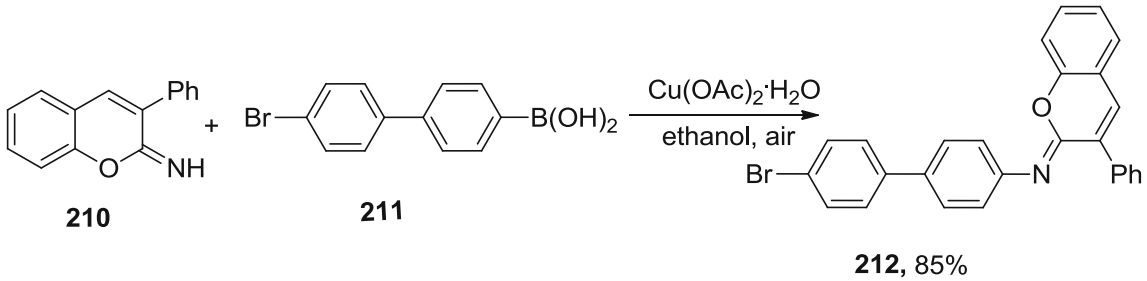


Scheme 63 Synthesis of *N*-arylated 2-imidazoline **207** using substituted substrates





Scheme 64 Regioselective *N*-arylation of 4-methyl-4, 5-dihydro-1*H*-imidazole **208**



Scheme 65 Synthesis of arylated iminochromenes **212**

Regioselective *N*-arylation of 4-methyl-4, 5-dihydro-1*H*-imidazole **208** was achieved by treating it with phenyl boronic acid **10** which resulted in 3.6:1 ratio of regioisomers **209a** and **209b** (Scheme 64).

Formation of arylated iminochromenes

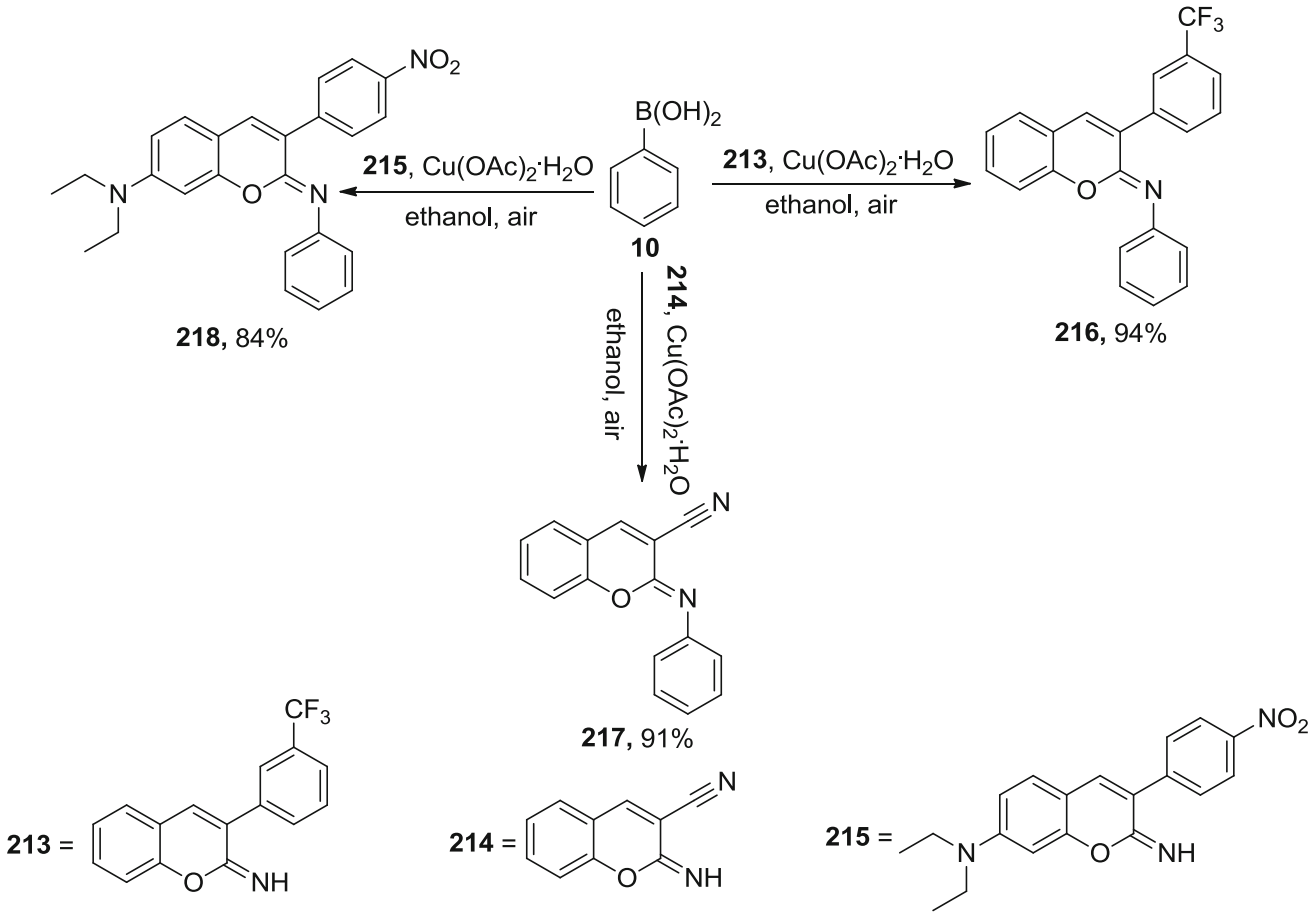
Mandal et al. [41] reported the synthesis of arylated iminochromenes. The reaction was performed with various substituted aryl boronic acids with 3-phenyl iminochromene, and products were obtained in 42–85% yield. For example, 3-phenyl iminochromene **210** was allowed to react with 4-bromo aryl boroic acid **211** producing arylated iminochrome **212** in 85% yield (Scheme 65).

Similarly, substituted iminochromenes were allowed to react with simple phenyl boronic acid and products were formed in good yield (77–94%). For example, phenyl boronic acid **10** was reacted with 3-(3-(trifluoromethyl)phenyl)-2H-chromen-2-imine **213**, 3-cynao iminochromene **214**, 7-(diethylamine)-3-(4-nitrophenyl) iminochromene **215,** and desired produtcs **216** (94%), **217** (91%), and **218** (84%) were formed (Scheme 66).

Their research group tried a one-pot synthesis of *N*-arylated iminochromene by using a Knoevenagel reaction of salicylaldehyde **219** and malononitrile **220** in the presence of piperidine (old method) by replacing it with DABCO due to low yield. Addition of $Cu(OAc)_2 \cdot H_2O$ and phenyl boronic acid into the reaction mixture led to the formation of *N*-arylated iminochromene **221** in 89% yield (Scheme 67).

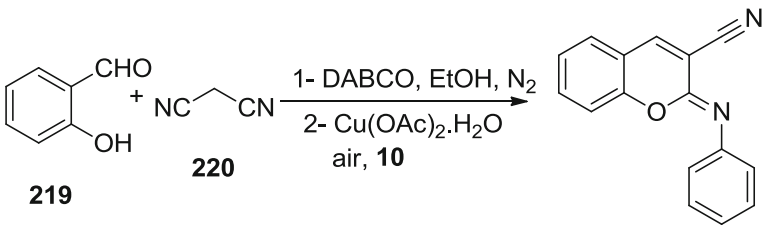
Synthesis of arylated aminomethyl acetylene

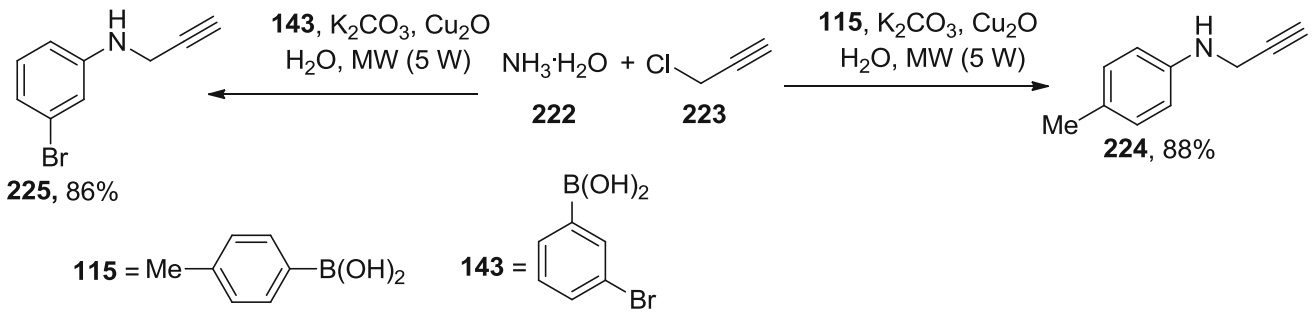
Jiang and Huang [42] described the formation of aryl aminomethyl acetylenes. The target was achieved by treating substituted phenyl boronic acid with aqueous ammonia and propargyl halide. A variety of aromatic boronic acids having electron-donating groups and electron-withdrawing groups was used. Electron-donating groups such as methyl and methoxy gave better results. The best results were obtained when 4-methylphenyl boronic acid **115** was treated with aqueous ammonia **222** and propargyl chloride **223,** and 88% yield of the corresponding product **224** was obtained (Scheme 68).



Scheme 66 Synthesis of arylated iminochromene **216**–**218**

Scheme 67 One-pot synthesis and arylation of iminochromene **221**





Scheme 68 Synthesis of aryl aminomethyl acetylene **224**–**225**

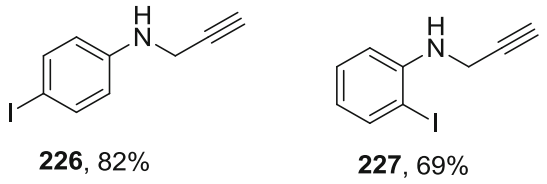


Fig. 10 Structure of different positional isomer

It was also observed that para-substituted substrates gave higher yields as compared to ortho-substituted substrates (Fig. 10).

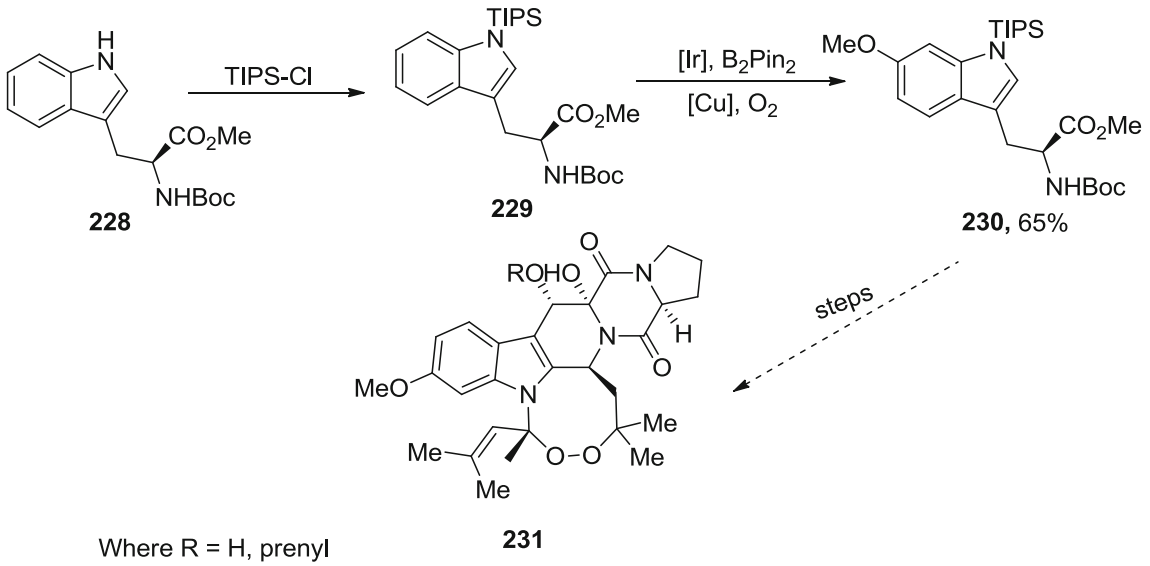
Preparation of alkaloids

Feng et al. [43] worked on the synthesis of biologically active alkaloids Verruculogen and Fumitremorgin A. A series of steps was involved where Chan–Lam coupling was applied as an intermediate step. The synthesis was started with easily available Boc-*L*-Trp-OMe **228** which was protected with TIPS-Cl. Afterward, Boc-*L*-Trp(TIPS)-OMe **229** was borylated at the C6 position and then immediately subjected to Chan–Lam coupling with methanol to generate the corresponding product **230** in 65% yield which further underwent a series of chemical reactions to yield the target compound **231** (Scheme 69).

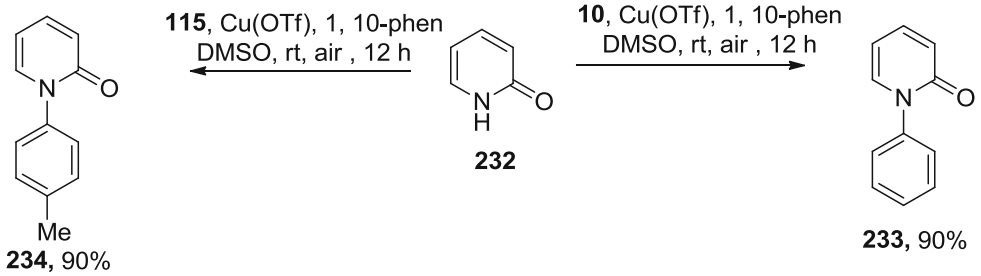
Kumar et al. [44] described the *N*-arylation of different tautomerizable heterocycles such as quinoline-2(1*H*)-one, bicyclic,6,7-dimethoxy isoquinoline-1(2*H*)-one, bromoquinazoline-4(3*H*)-one, and 7-bromoqunioxalin-2(1*H*)-one, and different products were obtained in good yield (60–90%). The best results were observed when pyridine2(1*H*)-one **232** was treated with phenyl boronic acid **10** and 4-methylphenyl boronic acid **115**; both reactant afforded 90% yield in 12 h (Scheme 70).

The same reaction conditions were applied on benzo[*d*] oxazole-2(3*H*)-ones **235** to yield *N*-arylated benzooxazolone. The best results were obtained on treating it with phenyl boronic acid **10** and 4-methoxyphenyl boronic acid **5** (Scheme 71).

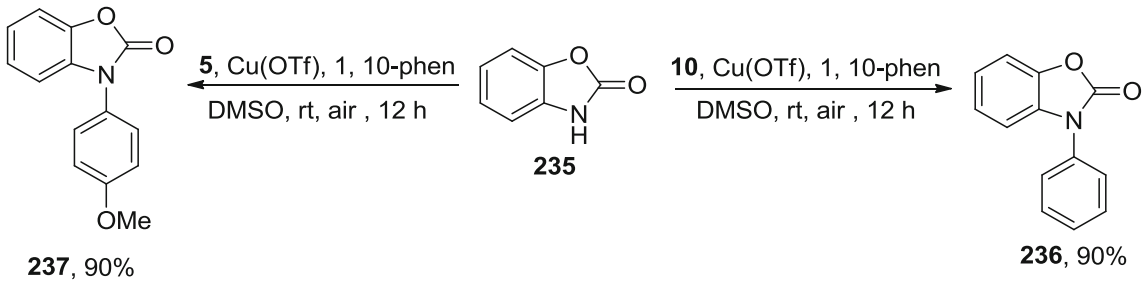
N-Arylated benzoxazolone were further subjected to different reactions to synthesize oxygenated carbazole alkaloids.



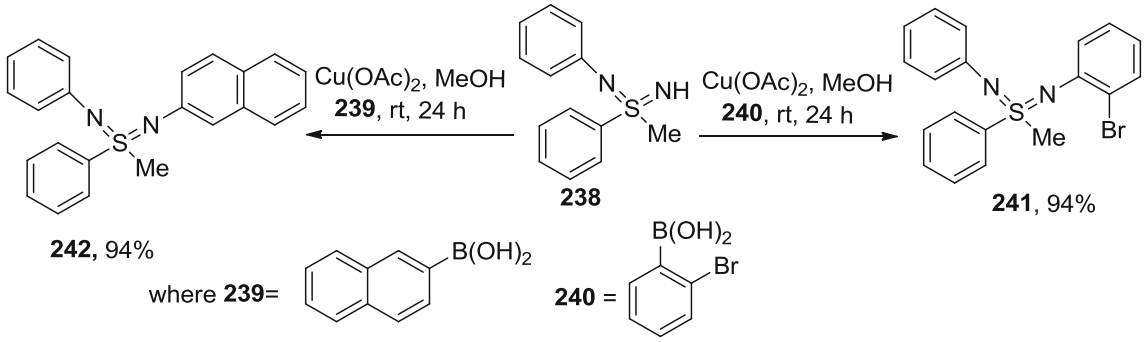
Scheme 69 Synthesis of biologically active alkaloids **231**



Scheme 70 Synthesis of *N*-arylated pyridine2(1*H*)-ones **233** and **234**



Scheme 71 Formation of *N*-arylated benzo[d] oxazole-2(3*H*)-ones **236**–**237**



Scheme 72 *N*-arylation of sulfondiimines **238**

Formation of sulfondiimines

Bohmann and Bolm [45] described the route to synthesize the *N*–*N*′-disubstituted sulfondiimines. Sulfondiimine was treated with variety of boronic acids having electronically diverse substitution pattern. Results demonstrated the fact that this reaction was equally feasible for electron-donating as well as electron-withdrawing groups and corresponding products were formed in good yields (51–85%). The best results were obtained in case of 2-naphthyl-boronic acid **239** and 2-bromo phenyl boronic acid **240** when these reactants were allowed to react with sulfondiimine **238** under optimum conditions, in both cases corresponding products were obtained in 94% yield (Scheme 72).

It was observed that steric effect strongly influenced the yield of the products. Para- and meta-substituted boronic acids gave higher yields compared to ortho-substituted boronic acids, while 2,4,6-trimethylphenyl-substituted boronic acid led to the failure of reaction.

Moreover, reaction of hetero aromatic boronic acid was also tested, and moderate-to-good results were observed. The best results were given when sulfondiimines **238** was allowed to react with 6-chloro-pyridine-3-yl-boronic acid **243** and resulted in product **245** (84%). Sulfondiimine **238** was also treated with (*E*)-styryl boronic acid **244**. This reaction paved the path for the synthesis of new class of *N*–*N*′-disubstituted sulfondiimines (Scheme 73).

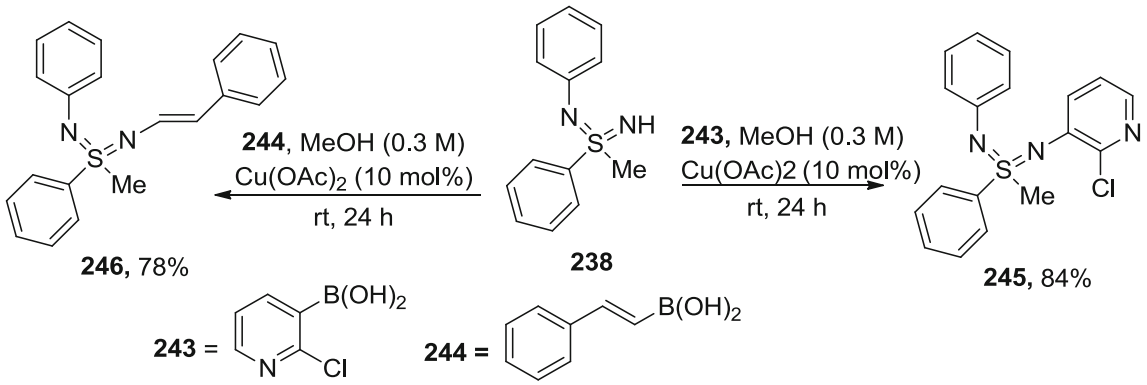
The reaction was further extended to *S*-aryl-*S*-alkyl sulfondiimines to get the phenylated products. Reaction of sulfondiimine **238** with 4-methoxyphenyl boronic acid **5** resulted in 72% yield while same product **248** was formed in higher yield (90%) by phenylation of *N*-(4-methoxyphenyl)-NH-sulfondiimine **247** (Scheme 74).

However, sulfondiimines having strong electron-withdrawing groups such as tosyl, benzyl, and tetrahydrothiophene resulted in failure of reaction, and no product was obtained.

Synthesis of functionalized aldehyde/ketone

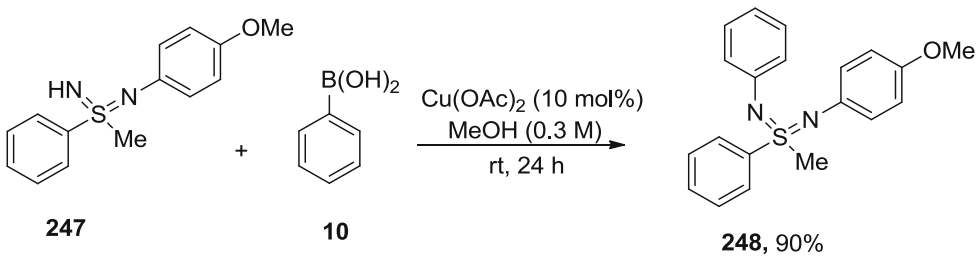
Konstokosa et al. [46] worked on the synthesis of α-imino aldehydes. The target was achieved by applying Chan–Lam coupling on benzophenone oxime and alkenyl boronic acids to generate the *O*-alkenyl oximes which underwent [1,3] rearrangement followed by olefination to get the target compound ϒ-imino-α, β-unsaturated esters. A number of trans-alkenyl boronic acids were treated with benzophenone oxime **249**. The best results were obtained in case of *n*-hexane and $-(CH_2)_3CN$ containing acid **250,** and 96% yield of corresponding product **251** was obtained in both cases which underwent [1,3] rearrangement to produce the corresponding aldehyde **252** in 62% and 58% yield, respectively. The synthesized aldehydes were further subjected to olefination to get the desired product (Scheme 75).

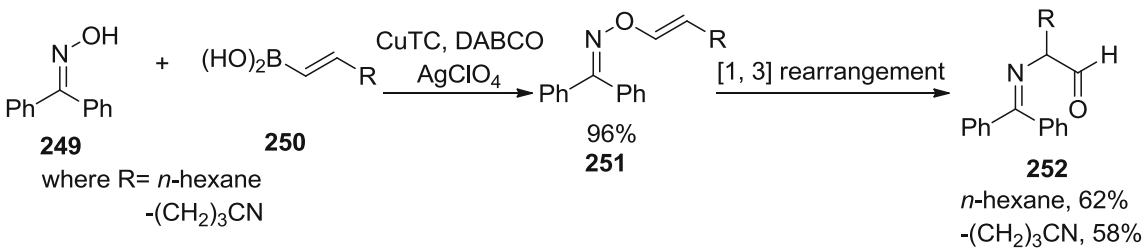
Kroc et al. [47] synthesized α-oxygenated ketones and substituted catechols by rearrangement of *N*-enoxy- and *N*-aryloxyphthalimides. These precursors were generated by applying Chan–Lam coupling. The synthesis



Scheme 73 Synthesis of arylated sulfoniimides **245** and **246**

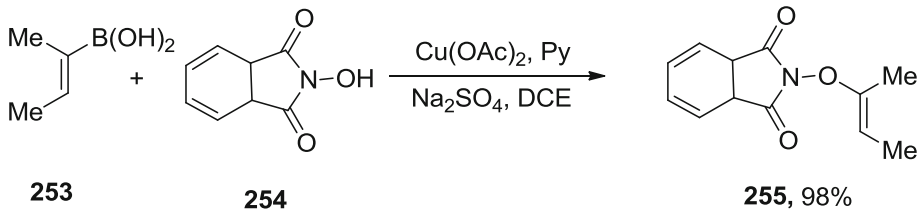
Scheme 74 Synthesis of arylated sulfoniimides **248**





Scheme 75 Synthesis of α-imino aldehyde **252**

Scheme 76 Synthesis of *N*-enoxyphthalimide **255**



of *N*-enoxyphthalimides was achieved by reaction of *N*-hydroxypthalimide with alkenyl boronic acid under typical Chan–Lam conditions. Maximum yield of 98% of product **255** was observed when methyl-substituted alkenyl boronic acid **253** was allowed to react with *N*-hydroxy phthalimide **254** under optimum conditions (Scheme 76).

Carbamate formation through Chan–Lam coupling

Until 2014, no reaction was reported between azido formate/acyclic carbamate with boronic acids at room temperature. Moon et al. [48] got the credit for reporting the first synthesis of *N*-aryl carbamate at room temperature by applying Chan–Lam coupling. The synthesis was performed by reaction of azido formate/acyclic carbamates with electronically diverse boronic acids. Electronically neutral and electron-donating groups on boronic acids resulted in higher yields (23–95%) as compared to electron-withdrawing groups (13–75%). The best results in both cases were obtained when benzyl azidoformate was allowed to react with 3,5-dimethyl phenyl boronic acid and 4-fluoro aryl boronic acid, desired product **256** (95%) and **257** (75%) was obtained. The reaction was extended to naphthalene and methylene dioxy substituted aryl/non-aryl/heteroaryl boronic acids. The best results

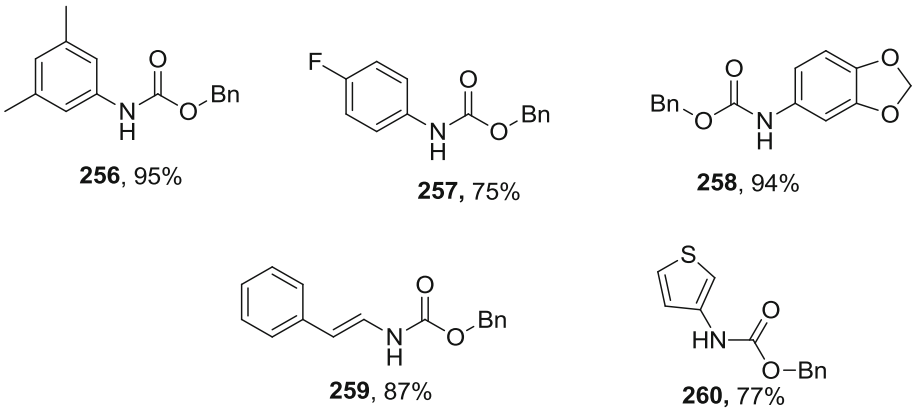
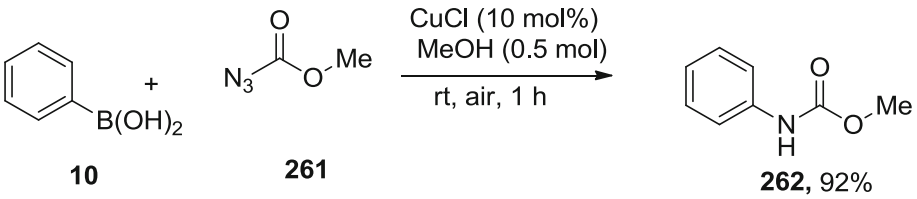


Fig. 11 Synthesis of carbamates **256–260**

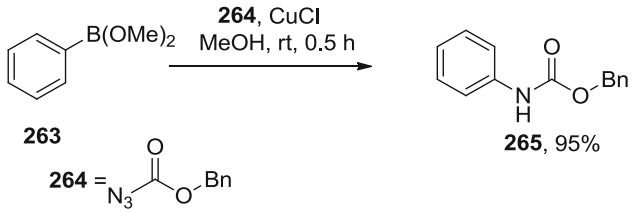


Scheme 77 Synthesis of carbamate **262** by methyl azido formate **261**

were given by bicyclic aryl boronic acid, (*E*)-styrylboronic acid, 3-thienylboronic acid on reacting with benzyl azidoformate in different time, and corresponding products **258–260** were obtained (Fig. 11).

Moreover, a number of different substituted azido formates were allowed to react with phenyl boronic acid. Maximum yield was obtained when methyl azido formate **261** was allowed to react with phenyl boronic acid **10** to yield methyl-*N*-arylcarbamate **262** in 92% under same reaction conditions (Scheme 77).

Two-step, one-pot synthesis of urea derivatives was also performed. Addition of aluminum–amine complex, to the *N*-arylcarbamates prepared through Chan–Lam coupling, resulted in multicomponent products (70–95%). Scope of Chan–Lam coupling was investigated for phenyl boronic acid derivatives such as pinacol phenyl borate, potassium trifluoroborate, and dimethyl phenyl borate to react with benzyl azidoformate **264**. Maximum product formation was observed in case of dimethyl phenyl boronate **263** (Scheme 78).



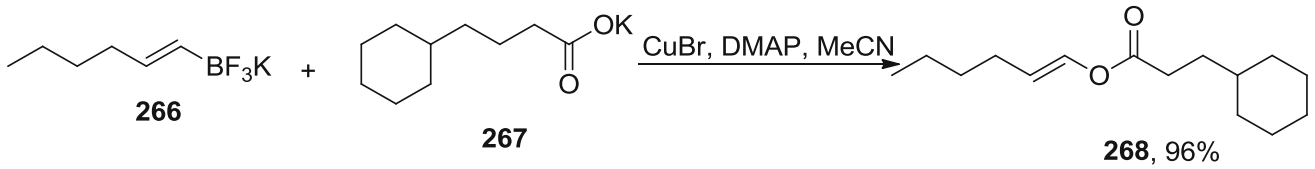
Scheme 78 Investigation of the reactive boronic acid derivative **263**

Arylation of esters

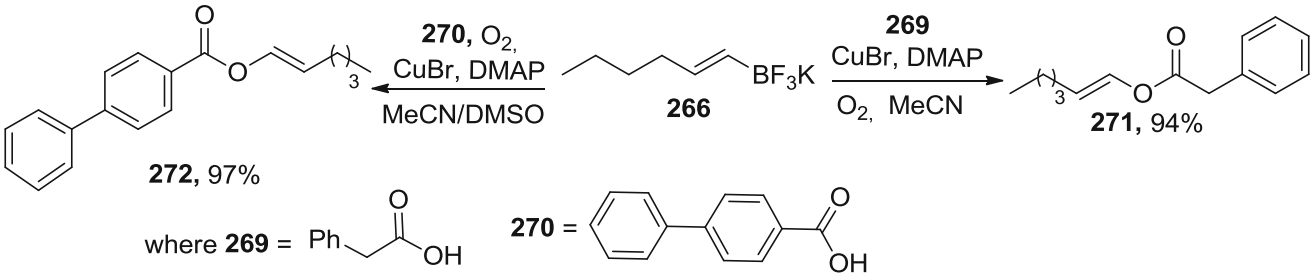
Huang et al. [49] explored the use of Chan–Lam coupling for synthesis of enol esters. The reaction was found to be regioselective and stereospecific to prepare (*E*) or (*Z*)-enol esters. A trial experiment was performed by using potassium (*E*)-triflourohexenyl borate with four different carboxylic acids and maximum yield was obtained when potassium (*E*)-triflourohexenyl borate **266** was treated with potassium 4-cyclohexylbutanoate **267** (Scheme 79).

A number of substituted carboxylic acids were allowed to react with potassium (*E*) triflouroborates Studies showed that both electron-deficient and electron-rich benzoic acid/carboxylate salts resulted in *cis*-selectivty of products. Experiments revealed that different solvent systems could be used for this transformation, for example, one system involved the use of MeCN (Method 1) and other involved the mixture of MeCN/DMSO (4:1) (Method 2). Potassium (*E*) triflourohexenyl borate **266** was allowed to react with phenyl-substituted carboxylic acid **269** under method 1, and corresponding product **271** was obtained in 94% yield. Application of method 2 gave the highest yield of 97% of product **272** when potassium (*E*) triflourohexenyl borate **266** was treated with biphenyl-substituted carboxylic acid **280** (Scheme 80).

Jacobson et al. [50] applied the Chan–Lam coupling for the methylation of carboxylic acids by using methyl boronic acid in the presence of $CuCO_3{\cdot}Cu(OH)_2$, pyridine, DCM at 90 °C. Before this work, only cyclopropylation of indoles was reported. Aromatic carboxylic acids with electron-donating and electron-withdrawing groups were well tolerated. Fused carboxylic acid and heterocyclic carboxylic acids also showed good results. The best example was provided by



Scheme 79 Cross-coupling reaction between potassium carboxylate **267** and potassium (*E*) hexenyl borate **266**



Scheme 80 Synthesis of enol ester **271** and **272** through cross-coupling

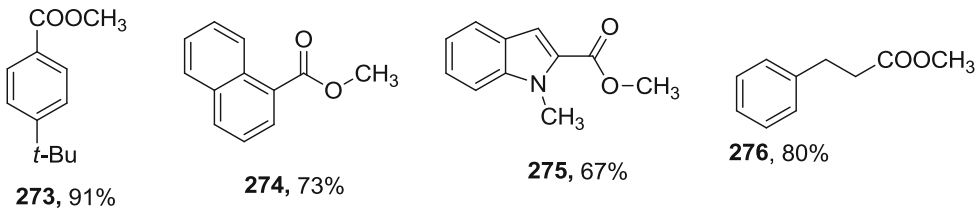


Fig. 12 Synthesis of ester **273**–**276** by using Chan–Lam coupling

4-(*tert*-butyl)benzoic acid, 2-naphthalene carboxylic acid, 1-methyl-1*H*-indole-2-carboxylic acid when these substrates were allowed to react with methyl boronic acid and resulted in corresponding products **273**–**275**. The reaction was extended to aliphatic and alkenyl acid which were allowed to react with methyl boronic acid, and products were obtained in 60–80% yield. Hydrocinnamic acid provided the best yield (80%) of the ester **276** (Fig. 12).

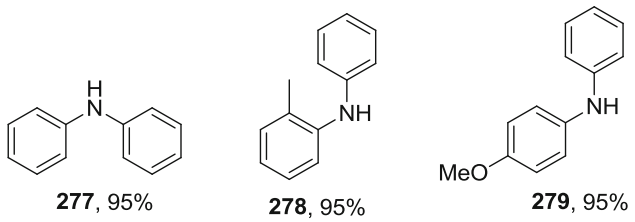


Fig. 13 Synthesis of *N*-arylated anilines **277**–**279** by using bimetallic catalyst

Methodology development

This section of the paper covers all the developments for the new/novel methodologies reported by different research groups to cater the research needs in this field.

Use of bimetallic catalyst in Chan–Lam coupling

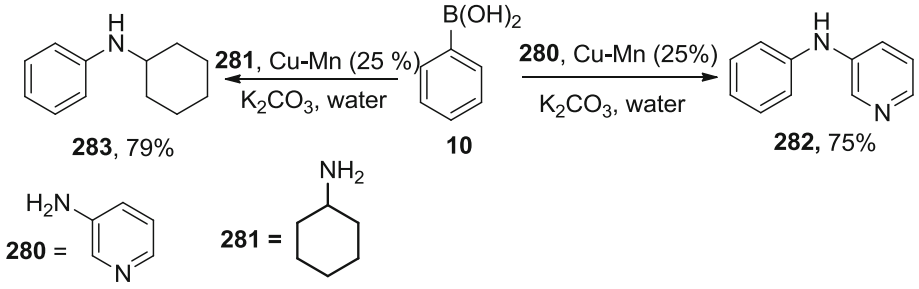
A novel reusable bimetallic catalyst consisting of Cu-Mn was introduced by Sawant et al. [51]. In this heterogeneous and reusable catalyst, Mn stabilizes the copper and avoids the need of expensive catalyst. This catalyst was tested for *N*-arylation of anilines, and good-to-excellent yields (70–95%) of desired products were obtained. Screening for optimum conditions suggested that use of 2 equivalents of K_2CO_3 in water with this bimetallic catalyst made the reaction feasible. The *N*-arylation of aryl/alkyl and heteroaryl amines was done and results showed that aryl amines exhibited higher yields as compared to alkyl and heteroaryl amines. The best result was obtained when phenyl boronic acid **10** was allowed to react with aniline, 2-methylaniline, and 4-methoxyaniline under given conditions, and corresponding products **277**–**279** were obtained in 95% yield each (Fig. 13).

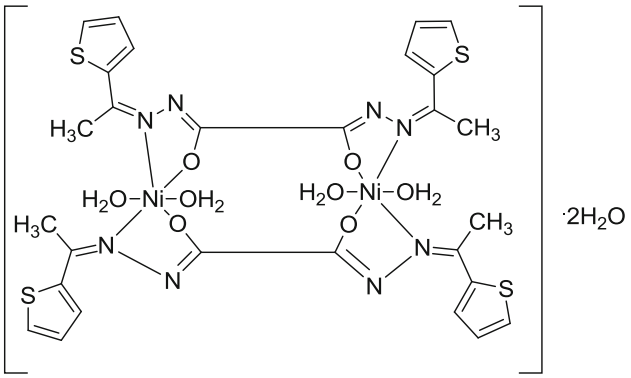
In case of heterocyclic compounds and alkyl amines, 3-amino pyridine **280** and cyclo hexanamine **281** gave the maximum yield on reacting with phenyl boronic acid **10** (Scheme 81).

Role of metal complexes in C–N bond formation

Singh et al. [52] succeeded in developing a series of complex catalyst and evaluated their activity for C–N bond construction. The synthesis of complex was achieved by treating bis-(2-acetylthiophene)oxalyldihydrazone with dif-

Scheme 81 *N*-Arylation of 3-amino pyridine **280** and cyclohexanamine **281** using bimetallic catalyst





284

Fig. 14 Structure of Ni(II) complex **284**

ferent transition metal ions. Different metals such as Co(II), Ni(II), Cu(II) and Zn(II) were employed. Among synthesized complexes, Ni(II) **284** was the most efficient catalyst giving the products in good yield (Fig. 14).

Use of Ni complex (15 mol%) with 2 equivalents 1,8-Diazabicyclo[5.4.0]undec-7ene (DBU) in acetonitrile at 40 °C gave maximum results. Different electron-deficient and electron-rich anilines were treated with phenyl boronic acid and 4-methylphenyl boronic acid to find the catalytic activity of this complex. Maximum results were obtained when 4-methylaniline **285** was allowed to react with phenyl boronic acid **10** and *N*-arylated product **286** was formed in 82% yield (Scheme 82).

Application of Chan–Lam coupling on a new substrate

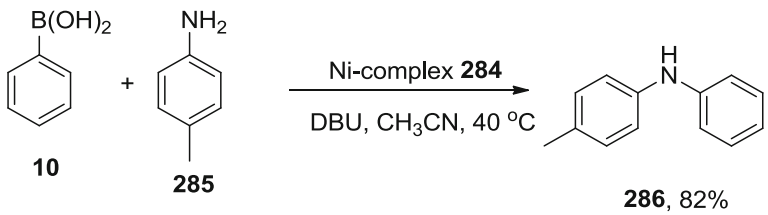
Until 2013, Chan–Lam coupling was applied on a number of substrates such as phenols, amines, sulfonamides. In 2013, Zhou et al. [53] extended the scope of Chan–Lam coupling by application of aminal reactants for the first time. Use of $Cu(acac)_2$ as catalyst with $phCO_2H$, CH_3CN at 50 °C was the best set of conditions for this new substrate. A variety of aryl boronic acids was allowed to react with aminal. Aryl boronic acids having electron-donating groups such as CH_3, CH_3O, F_3CO at para and meta position furnished the products in moderate yields. Maximum yield was obtained when 3,5-methyl-substituted aryl boronic acid **288** was allowed to react with aminal **287** and afforded the corresponding product **290** in 57% yield. It was also observed that ortho-substituted aryl boronic acid lead to significant decrease in yield. This transformation was also done with meta and para F and CF_3 groups. The best results were observed when meta-flouro boronic acid **289** was treated with aminal. Further, the reaction was extended to 1-naphthalene boronic acid and 2-naphthalene boronic acid, but reaction was more feasible with 2-naphthalene boronic acid **239** (Scheme 83).

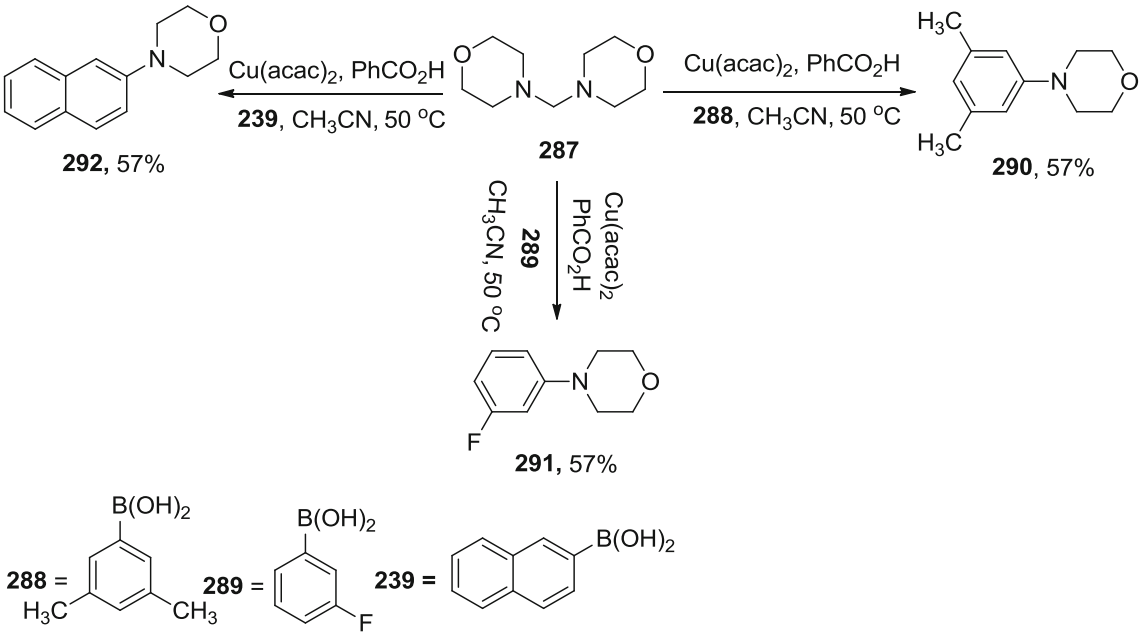
Reactivity of different aminals toward this cross-coupling reaction was investigated. Results showed that piperidine-derived aminal gave the maximum yield of product (45%), on reacting with phenyl boronic acid as compared to the other substrates such as pyrroline-derived aminal and unsymmetrical aminal.

Use of copper-based heterogeneous catalyst in Chan–Lam coupling

A new heterogeneous catalyst was developed by Debreczeni et al. [54] which was prepared by impregnating Cu(II)chloride in the presence of deionized water. The catalyst proved to be sensitive to atmospheric oxygen. The reaction conditions were screened and results showed the replacing the Cu^{+2}/4A with Cu°/4 A leads to higher yields. A number of reactions were performed using dif-

Scheme 82 Synthesis of *N*-arylated product by appling newly generated Ni(II) complex **284**





Scheme 83 Use of aminal **287** as substrate in Chan–Lam coupling

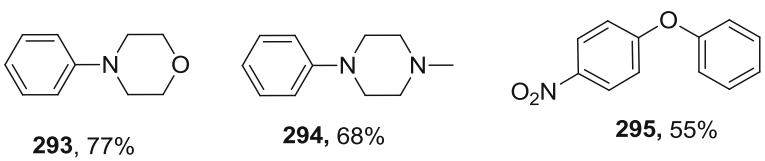


Fig. 15 Effect of new catalyst in Chan–Lam coupling of phenyl boronic acid **10** with different substrates

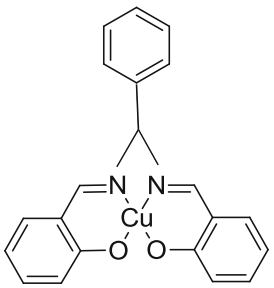
ferent amines such as *N*,*N*-dibutyl amine, morpholine, and *N*-methyl piperazine and different substituted aryl boronic acids, and corresponding products were obtained in good yield (43–77%). The best yields of products **293**–**295** were observed when phenyl boronic acid **10** was treated with morpholine, *N*-methyl piperazine, 4-nitrophenol in the presence of Cu catalyst, dichloromethane and pyridine (Fig. 15).

Copper–salen complex for arylation

Gogoi et al. [55] explored the effect of newly prepared copper–salen complex **296** as catalyst on arylation of anilines and imidazole. Three types of complexes were generated, and their activity was determined in water. Results showed that Cu complex **296** (Fig. 16) was the most effective among the synthesized complexes.

After finding the most efficient catalyst, other conditions were screened and optimum conditions were established which involved the use of Cu complex **296**, K_2CO_3, H_2O at room temperature in the presence of air. Previously reported catalysts were not selective due to OH-containing substrate resulting in competitive C–O coupling. But this catalytic system was selective and resulted in only C–N coupling. Maximum yields were observed when phenyl boronic acid **10**

Fig. 16 Structure of newly prepared copper–salen complex **296**



296

was allowed to react with 4-methylaniline, imidazole, benzimidazole and gave the corresponding products **286**, **297**, and **298**. However, solvent was replaced with 1:1 aqueous *iso*-propanol in case of imidazole (Fig. 17).

Coupling reaction by polymer-anchored copper catalyst

Islam et al. [56] reported the use of new polymer-anchored Cu-catalyst for coupling reaction which was prepared by furfural functionalization followed by grafting with copper (Fig. 18). Characterization of this newly generated catalyst was done by UV–Vis spectroscopy, scanning electron microscope and Fourier transform infrared spectroscopy. It was

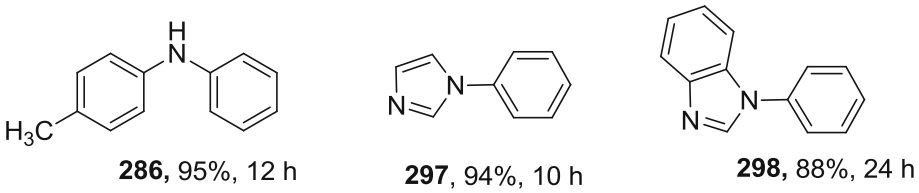
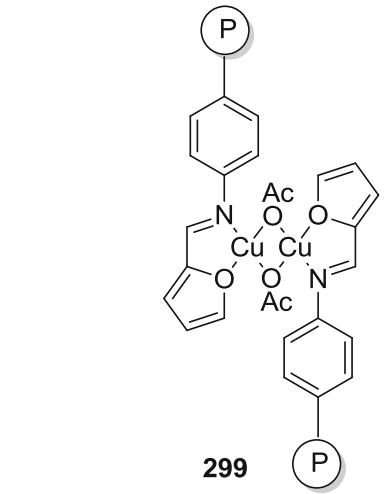


Fig. 17 Use of copper–salen complex **296** in Chan–Lam coupling



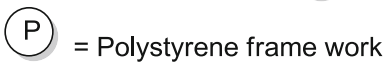
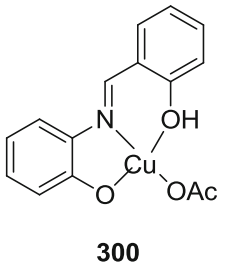


Fig. 18 Structure of new polymer-anchored copper catalyst **299**



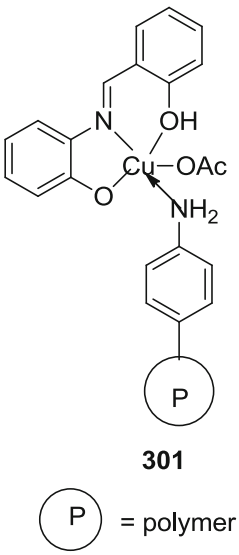
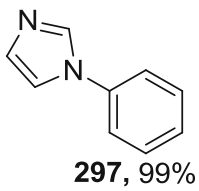


Fig. 20 Structure of homogenous and heterogeneous Schiff base catalyst **300** and **301**

Fig. 19 *N*-Arylation of imidazole using polymer-anchored copper catalyst **297**



also observed that developed catalyst can be reused five times without any lose in catalytic activity.

N-Arylation was carried out by treating imidazole with a number of aryl boronic acids using this catalyst in presence of MeOH, without using any base. It was observed that aryl boronic acid having electron-donating groups such as *o/p* Me and OMe gave higher yields as compared to aryl boronic acid containing electron-withdrawing groups such as F, Cl, NO, COMe. It was stated that *o/p* position did not affect the yield. However, the best results were obtained in case of electronically neutral phenyl boronic acid **10** with imidazole which resulted in product **297** (99%) (Fig. 19).

Use of Cu(II) Schiff base complex catalyst

N-Arylation of different heterocyles was described by Islam et al. [57] by using copper(II) Schiff base complex catalyst. The copper(II) Schiff base complex [Cu(amp)(OAc)] **300** and heterogeneous polymer-anchored Cu(II) Schiff base

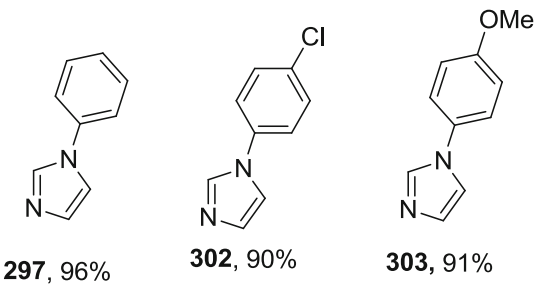
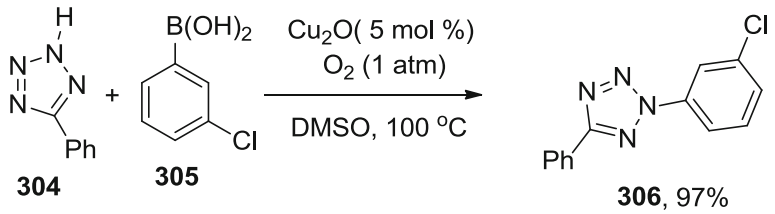


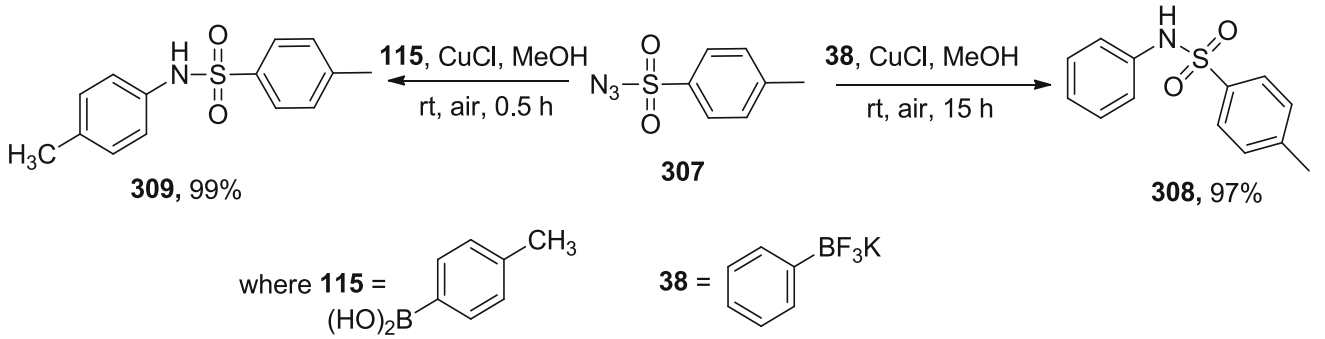
Fig. 21 Formation of *N*-arylated imidazole using homogenous Schiff base catalyst **300**

catalyst PS-Cu-amp-OAc **301** were employed for the *N*-arylation of different heterocycles (Fig. 20).

N-Arylation of imidazole, benzimidazole, phthalimide, succinamide, and sulfonamide was done in presence of new catalyst and methanol at 40 °C for 6 h. Phenyl boronic acid **10**, 4-methoxy boronic acid **5,** and 4-chloroboronic acid **11** gave the best yields with imidazole when a number of substituted aryl bornic acid were tried in presence of Cu(amp)-OAc. Results showed that homogeneous catalyst (96%) gave slightly higher yield as compared to heterogeneous catalyst (92%) in case of phenyl boronic acid (Fig. 21).

Scheme 84 *N*-arylation of tetrazole **304** under simple conditions





Scheme 85 Formation of *N*-arylated tosyl azide **308**–**309** at room temperature

Use of simplified conditions for Chan–Lam coupling

A simple set of conditions was suggested by Liu et al. [58] for *N*-arylation of *H*-tetrazoles. The synthesis of *N*-arylated tetrazole was carried out in the presence of Cu_2O (5 mol%), O_2 (1 atm), DMSO at 100 °C. The positive aspect of this method was the prevention of metalated tetrazoles. Moreover, additives, ligands, and other external bases were not required as in classical Chan–Lam coupling. A variety of substituted aryl-*H*-tetrazoles and aryl boronic acids having diverse substitution pattern were allowed to react, and a library of compounds was synthesized in low-to-excellent yields (14–97%). Maximum yield of 97% was observed when 3-chlorophenyl boronic acid **305** and tetrazole **304** were allowed to react under optimum conditions (Scheme 84).

Ligand/base/additive method for arylation

Moon et al. [59] discovered base, ligand, and additive-free Chan–Lam coupling reaction conditions. Positive aspect was that this reaction proceeded at room temperature while no reaction at room temperature between sulfonyl azides and borocnic acid had been reported earlier. Reaction proceeded well at room temperature in open air, using CuCl as catalyst and MeOH as solvent. A variety of aryl boronic acids was treated with tosyl azide to furnish the desired product under optimum conditions. It was demonstrated that electron-donating and electron-withdrawing groups on aryl boronic acid were well tolerated. Excellent yield of *N*-arylated tosyl azide **309** (99%) was obtained when 4-methylphenyl boronic acid **115** was treated with tosyl azide. Pinacol phenyl boronate and potassium phenyl trifluoro boronate were also treated with tosyl azide **307** to evaluate their efficiencies and the best result was observed in case of potassium phenyl triflouro boronate **38** in 15 h when it was treated with tosyl azide (Scheme 85).

Furthermore, substituted aryl boronic acids and hetero aryl boronic acid were allowed to react with mesyl azide under same reaction conditions. Maximum yield of 99% and 94% of products **312** and **313** was obtained when 3-methoxyphenyl boronic acid **124** and thiophen-3-ylboronic acid **311** was allowed to react with mesyl azide **310** (Scheme 86).

In case of aryl boronic acids, excellent yield (92–98%) was obtained. For example, phenyl boronic acid **10** was treated with 2,4,6-methylphenyl sulfonyl azide **314** to get the product **315** in 98% yield (Scheme 87).

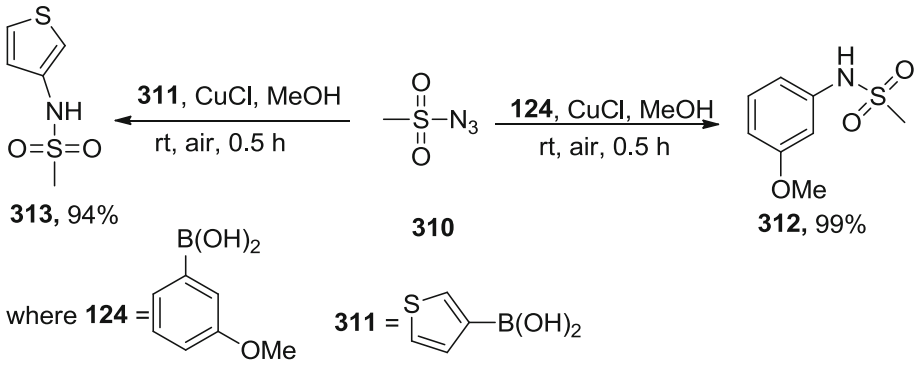
Use of triazine based mesoporous material

Synthesis of biologically important *N*-aryl flavones was reported by Puthiaraj and Pitchumani [60] by using triazine-based mesoporous material as support in the reaction (Fig. 22).

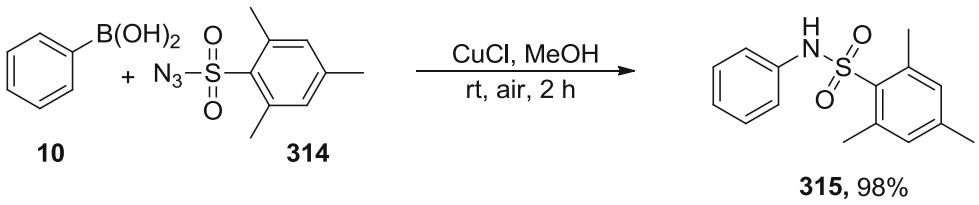
N-Arylation of 7-aminoflavone, 6-aminoflavone, and 8-aminoquinoline was done with a variety of substituted aryl boronic acid. Synthesis of *N*-arylated 7-aminoflavone with substituted aryl boronic acids resulted in corresponding products in good-to-excellent yield (78–93%). Maximum yield (93%) was observed when 7-aminoflavone **317** was treated with 4-ethylphenyl boronic acid **318** (Scheme 88).

Under same reaction conditions, *N*-arylation of 6-aminoflavone **320** and 8-aminoquinoline **321** was done with

Scheme 86 *N*-arylation of mesyl azide under base-free conditions



Scheme 87 Formation of *N*-arylated sufonyl azide **315**



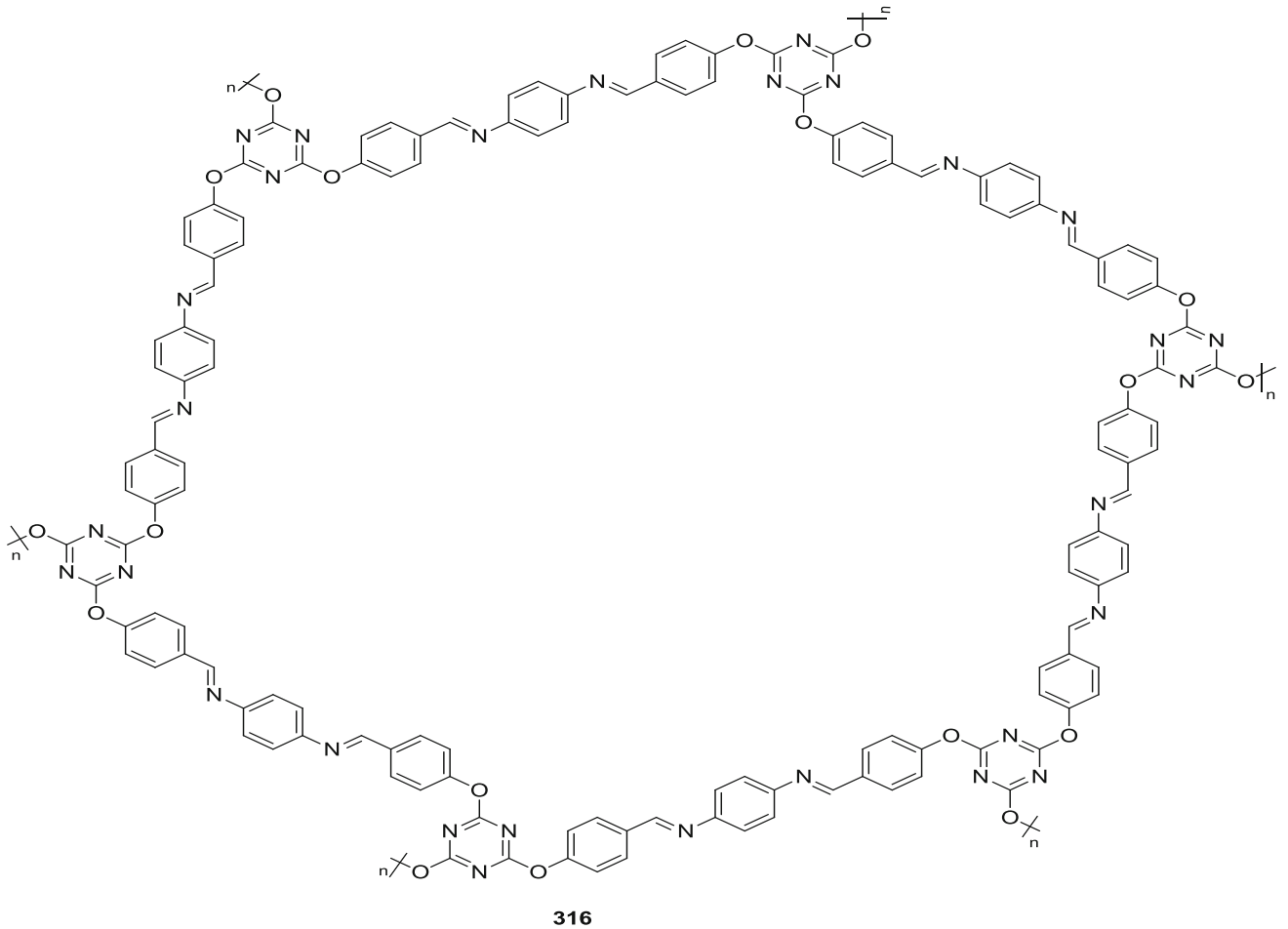


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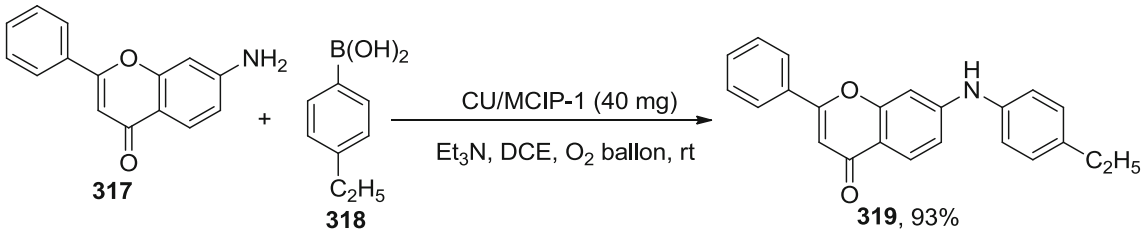
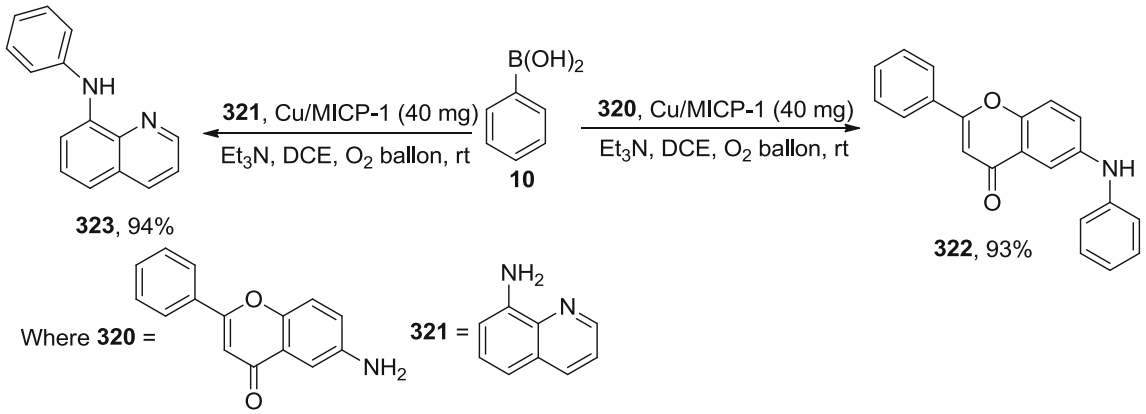
Fig. 22 Structure of triazine based mesoporous material **316**



Scheme 88 Synthesis of *N*-arylated 7-aminoflavone **319**



Scheme 89 Synthesis of *N*-arylated flavone and quinoline **322**–**323**

phenyl boronic acid **10** which resulted in formation of desired products **322** (93%) and **323** (94%), respectively (Scheme 89).

C–N bond formation by using Ni(II) thiolates

Shi et al. [61] reported the synthesis of Ni(II) thiolates and tested their effect on coupling reactions involving the C–N bond construction. These complexes were prepared through transmetallation of Ni(II) ions with $[Zn(Tab)_4](PF)_6$ using different ligands. Three complexes were generated and catalytic activity was investigated for Chan–Lam protocol, which involved the reaction of aryl boronic acid with amines to synthesize the *N*-arylated products in good yield. The complex **324** showed the most amazing and promising results for this reaction (Fig. 23).

A number of substituted anilines and substituted phenyl boronic acids were used to find the scope of this catalyst and reaction as well. Maximum yield was obtained in case of benzyl amine **325** when it was reacted with phenyl boronic acid **10** to yield the desired product **326** in 80% (Scheme 90).

It was observed that electron-withdrawing groups on phenyl boronic acids led to the formation of products in lower yields as compared to electron-rich aryl boronic acids. For example, when aniline **50** underwent the reaction with 4-methylphenyl boronic acid **115**, it resulted in 71% of product **286**, while on reaction with 4-nitroboronic acid **107** gave 59% of product **327** (Scheme 91).

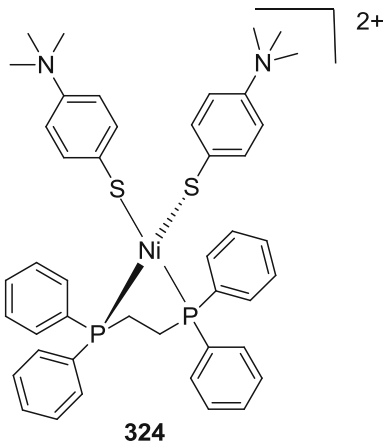


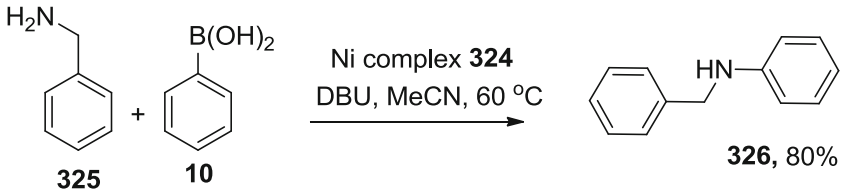
Fig. 23 Structure of Ni(II) thiolate complex **324**

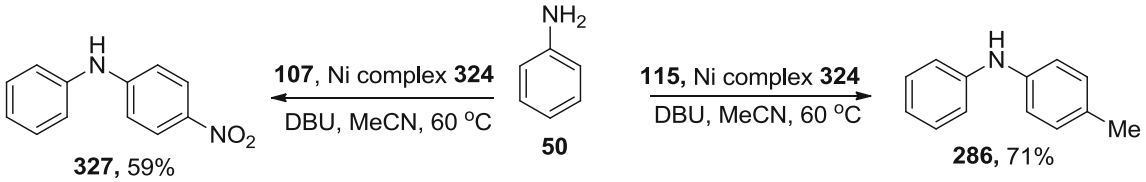
Similar trend was seen for anilines where *p*-methyl aniline **285** gave out 75% of arylated product **286** on reacting with phenyl boronic acid **10** while *p*-nitro aniline **328** resulted in 35% yield of the product **327** (Scheme 92).

Use of chitosan-anchored copper complex

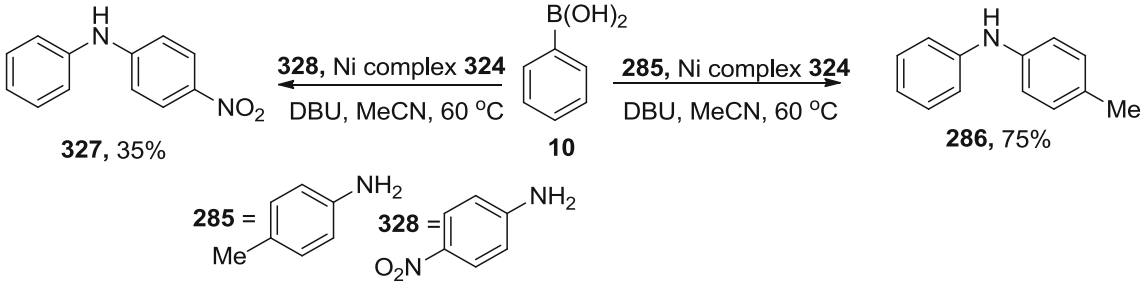
Anuradha et al. [62] worked on the preparation of new chitosan-anchored copper complex having Schiff base ligands and employed it for the *N*-arylation of amines. Chitosan provided support for this catalyst, and these easily separable heterogeneous catalysts were generated (Fig. 24). Studies

Scheme 90 Formation of *N*-arylated aniline using Ni(II) thiolate complex **324**





Scheme 91 Synthesis of *N*-arylated anilines **286** and **327** by using Ni complex **324**



Scheme 92 Synthesis of *N*-arylated anilines **286** and **327** by using substituted anilines

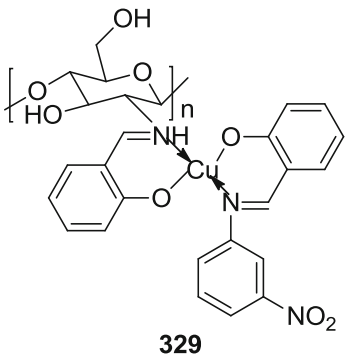


Fig. 24 Structure of chitosan-based copper complex **329**

showed that copper complex having nitro group was the most efficient as compared to other two catalysts. It was postulated that electron-withdrawing effect of nitro group was the reason of good performance of catalyst because it increased the Lewis acidity of the complex, and it was found effective for five cycles.

Aromatic as well as aliphatic amines were used for Chan–Lam coupling; however, aromatic amines easily undergo the transformation in lesser time as compared to aliphatic amines. Aromatic amines having electron-withdrawing groups were more reactive than electron-donating substituted amines. For example, 82% yield of *N*-arylated product **331** was obtained on reacting the 3-nitro aniline **330** with phenyl boronic acid **10** (Scheme 93).

Meta- and para-substituted amines gave slightly higher yields as compared to ortho-substituted amines. For example, *o*-Cl-substituted anilines gave product **332** in 72% yield, whereas *p*-Cl aniline produced the product **333** in 74% yield (Fig. 25).

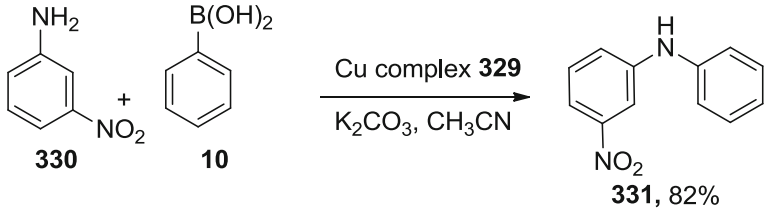
Here, electron-donating groups increased the activity of boronic acid and resulted in higher yield of desired products. 4-Methylphenyl boronic acid **115** was the best example which gave 81% of desired product **286** on reacting with aniline **50** (Scheme 94).

Novel nickel-catalyzed Chan–Lam coupling

Keesara [63] described the novel nickel-catalyzed Chan–Lam coupling in which *N*-(pyridine-2-yl)benzamide ligand **334** was used with $Ni(OAc)_2{\cdot}4H_2O$ in the presence of 1,1,3,3-tetramethyl guanidine (TMG base). Substituted anilines were allowed to react with substituted aryl boronic acids and good-to-excellent yields (68–84%) were obtained. Similarly, *N*-phenyl piperazine **335** was allowed to react with substituted boronic acids. The best yield was observed for the phenyl boronic acid **10** on treating with *N*-phenyl piperazine **335** and aniline **50** (Scheme 95).

Under same reaction conditions, naphthyl boronic acid was allowed to react with piperidine, morpholine, and pyrro-

Scheme 93 *N*-arylation of substituted anilines by using new copper complex **329** as catalyst



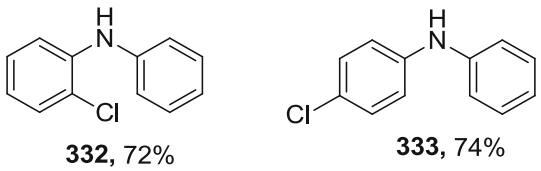


Fig. 25 Structure of different isomers of *N*-arylated aniline **332**–**333**

lidine derivatives. Maximum yield was obtained in case of piperidine **337** when it was allowed to react with 2-naphthyl boronic acid **239** and product **338** was obtained in 66% yield. Reaction between 2-naphthyl boronic acid **239** and cyclohexyl amine **281** was also performed which resulted in 70% yield of **339** (Scheme 96).

S-Arylation under ligand/base-free conditions

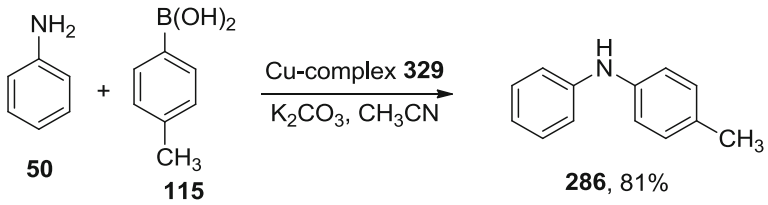
S-Arylation of α-enolic thioesters was performed under ligand and base-free conditions by Koley et al. [64]. A library of compounds under mild reaction conditions were synthesized in excellent yields (71–92%) by the reaction of substituted α-enolic dithioester aryl boronic acid **340**. Maximum yield was obtained when 4-acetyl-substituted phenyl boronic acid **158** was reacted with α-enolic thioesters **340** under standard conditions and 92% yield of *S*-arylated product **342** was recorded. Similar results were observed for pyridine-based dithioester. The methodology could also be applied to heterocyclic dithioethers such as furan-based dithioesters **341** (Scheme 97).

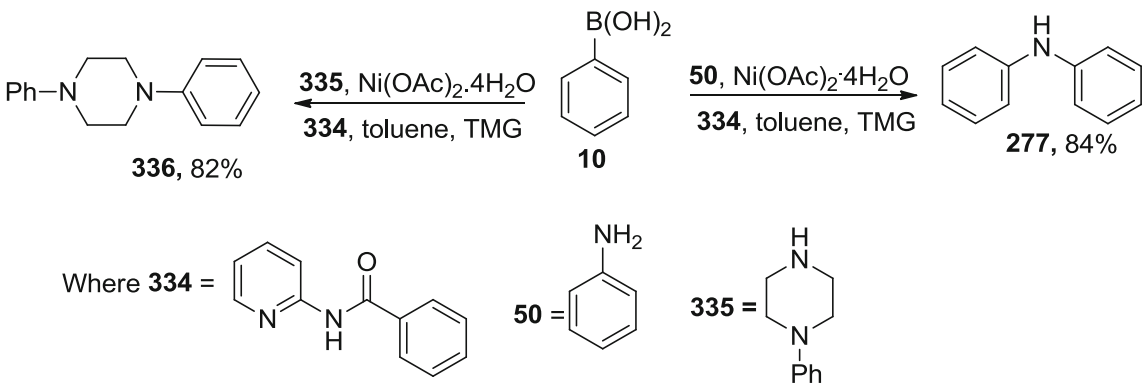
Similarly, naphthalene-based dithioester **344** was treated with phenyl boronic acid **10** and 4-fluorophenyl boronic acid **6**, separately; however, phenyl boronic acid resulted in higher yield (90%) of the product **345** (Scheme 98).

Use of metal organic frame work for Chan–Lam coupling

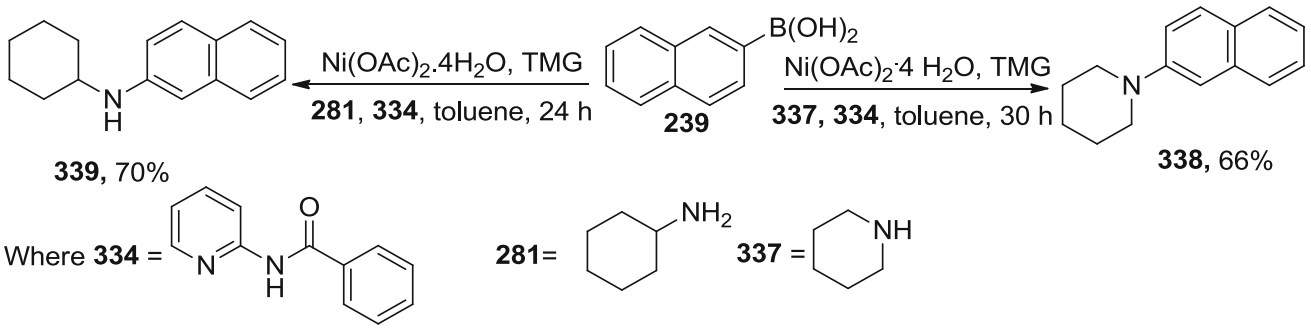
Wang et al. [65] reported the use of a metal–organic frame work {[Cu(4-tba)](solvent)}$_n$ in Chan–Lam coupling. The aforementioned catalyst was synthesized by the reaction of 4-(1*H*-1,2,4-triazole-1-yl)benzoic acid (Htba) and Cu(II) nodes and was employed for different C–N bond forming reaction. Maximum yield (98%) of the product **297** was obtained when phenyl boronic acid was treated with imidazole in the presence of this metal–organic framework and

Scheme 94 Synthesis of *N*-arylated aniline **286** using Cu complex **329**

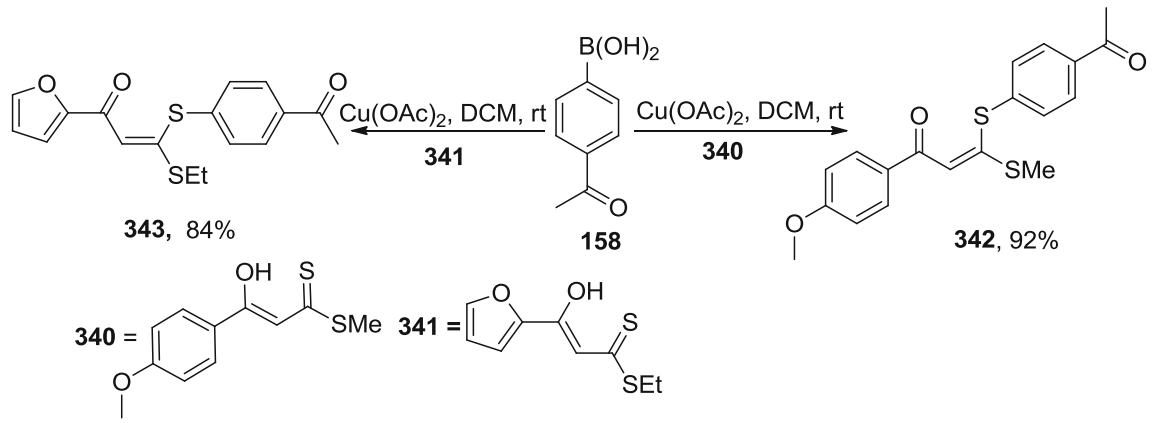




Scheme 95 Nickel-catalyzed Chan–Lam coupling of anilines **50** and piperazine **335**



Scheme 96 Synthesis of *N*-arylated piperadine **338** and *N*-arylated cyclohexyl amine **339**



Scheme 97 *S*-arylation of α-enolic thioesters **340** and furan-based dithioester **341**

Scheme 98 *S*-arylation of naphthalene-based α-enolic thioesters **344**

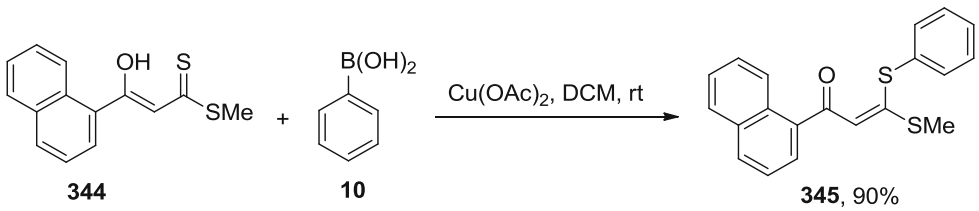
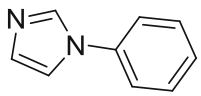


Fig. 26 Formation of *N*-arylated imidazole **297** using metal–organic framework



297, 98%

methanol at 40 °C. It was observed that this catalyst retains its activity till six cycles (Fig. 26).

Chan–Lam coupling under visible light

Modification in Chan–Lam coupling was made by Yoo et al. [66] by conducting it in the presence of visible light. $Cu(OAc)_2$ was used with iridium-based photocatalyst irradiated with blue light-emitting diode while other parameters included 2,6-lutidine, toluene/MeCN (1:1), myristic acid at 35 °C in open air for 20 h. A number of compounds were synthesized by treating substituted aryl amines with substituted aryl boronic acids. Maximum yield of respective products **346**–**348** (100%) was obtained when 4-chlorophenyl boronic acid **11** was allowed to react with 2-methylaniline, 4-methylaniline, and 4-chloroaniline (Fig. 27).

Results showed that electron-withdrawing and electron-donating groups are well tolerated. Similarly, reaction of aniline **50** with phenyl boronic acid **10** resulted in 100% yield of the product **277** (Scheme 99).

Use of solid copper reactor as catalyst

Bao and Tranmer [67] developed a novel method for generating C–N bond by using simple alkyl and aryl boronic acids. Use of solid copper reactor was the novelty in the history of catalyst. Optimum conditions included the catalyst, H: TEMPO (1:1.5) in MeCN and 2 equivalents of CH_3CO_2H. Applying this catalyst, a number of compounds were synthesized by using phenyl boronic acid **10** and 4-methoxyphenyl boronic acid with morpholine and substituted aniline. 79%

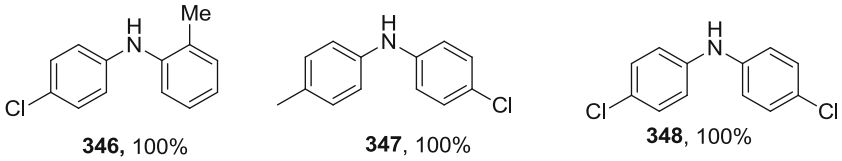
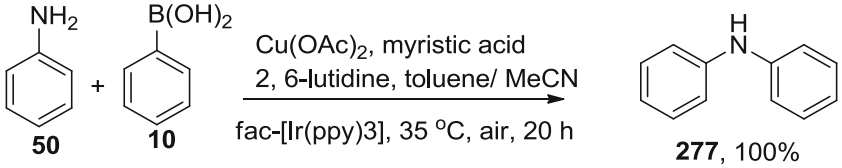


Fig. 27 Synthesis of *N*-arylated substituted anilines **346**–**348**



Scheme 99 *N*-arylation of aniline **50** with phenyl boronic acid

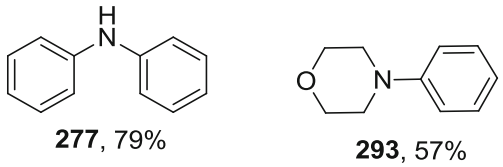


Fig. 28 Formation of *N*-arylated aniline **277** and *N*-arylated norpholine **293** using Cu-column

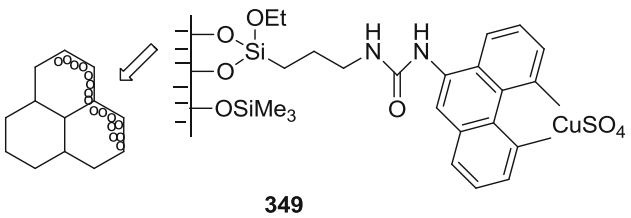


Fig. 29 Structure of mesoporous heterogeneous copper catalyst **349**

yield of *N*-arylated product **277** was obtained on treating the phenyl boronic acid **10** with aniline **50**. In case of morpholine, simple phenyl boronic acid **10** gave higher yield (57%) of the product **293** as compared to when 4-chlorophenyl boronic acid was used (25%) (Fig. 28).

Heterogeneous copper catalyst for arylation of C–S bond

A novel heterogeneous copper catalyst was developed by Lin et al. [68] to prepare diaryl sulfides. Other previously reported Chan–Lam coupling transformation involved the use of homogenous catalyst which led to the contamination of products by copper and limited their use in biomedicine and electronics. To overcome this problem, heterogeneous catalyst was suggested. For this purpose, mesoporous MCM-41 material was used as support to the copper catalyst. The synthesis of catalyst involved the reaction of immobile material MCM-41 with 1-(1,10-phenanthroline) and complex formation was done by treating it with $CuSO_4$ (Fig. 29).

A number of bases and solvent were tried, and results demonstrated that *n*-Bu_4NOH as base and EtOH as solvent were the best choice to make this transformation effective. After establishing the reaction conditions, this protocol was applied for *S*-arylation. For this purpose, phenyl boronic acid was allowed to react with substituted thiols. Maximum yield of 89% was obtained when phenyl boronic acid **10** was allowed to react with 4-*iso* propyl-substituted thiols **350** (Scheme 100).

Same reaction conditions were applied on substituted aryl boronic acids and substituted benzene thiol. Both the reactants were substituted with electron-donating and electron-withdrawing groups and resulted in good-to-excellent yield. Reaction of 4-chlorophenyl boronic acid **11** with 4-fluorobenzenethiol **352** was performed and 92% yield of the product **353** was obtained (Scheme 101).

New catalyst system based on diketimine ligands

Mori-Quiroz et al. [69] developed the new catalyst system which was based on diketimine (NacNac) ligands **354** and **355**. These catalysts were tested for their catalytic activity to form amide through Chan–Lam coupling (Fig. 30).

A variety of amides and boronic esters were used to synthesize the corresponding products in moderate-to-good yields (36–86%). Maximum yield was obtained when 2-ethoxybenzamide **356** was allowed to react with alkyl boronic ester **357** and resulted in desired product **358** (86%) (Scheme 102).

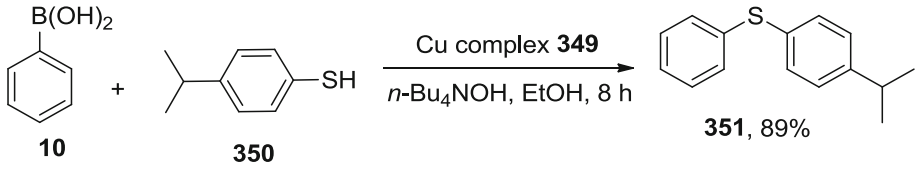
Under same reaction conditions, scope of acetamide and trifluoroacetamide was evaluated for different esters and result demonstrated that acetamide resulted in higher yield as compared to trifluoro acetamide (Scheme 103).

Scope of secondary boronic acid for *N*-alkylation of amides was also investigated by using ligand **355.** Different substrates with different substituents were tried and moderate-to-good yields were obtained. Maximum yield (82%) was obtained when 4-flourobenzamide **362** was allowed to react with alkyl boronic ester **363** under optimum conditions (Scheme 104).

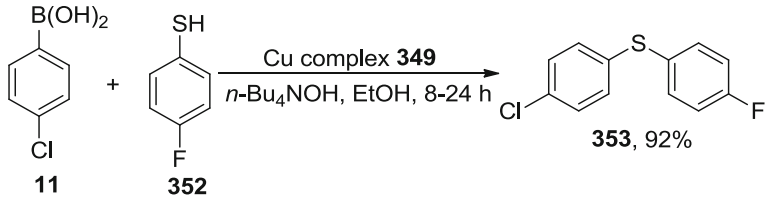
Use of MeCN/EtOH as solvent system

Vantourout et al. [70] elaborated the set of reaction conditions for Chan–Lam coupling of aryl BPin with aryl and alkyl

Scheme 100 Synthesis of *S*-arylated thiol **351** using Cu complex **349**



Scheme 101 Crosscoupling of substituted thiol **352** and 4-chloroboronic acid **11**



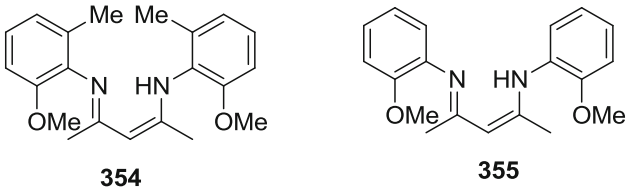
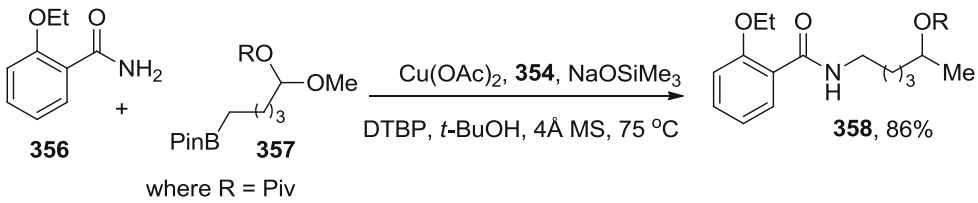


Fig. 30 Structure of diketimine ligands **354–355**

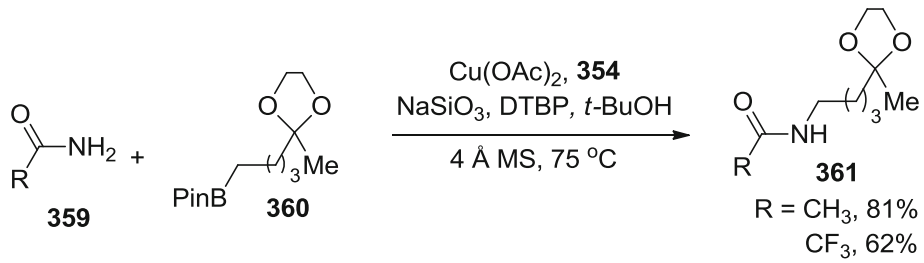
amines. The reaction conditions were modified by switching to MeCN (in case of alkyl amines) and MeCN/EtOH (in case of aryl amines) from typical solvent system, keeping other conditions same such as $Cu(OAc)_2$, Et_3N at 80 °C for 24 h. Application of these reaction conditions on aryl amine and variety of substituted aryl BPin, resulted in good-to-high yields. It was observed that electron-donating groups such as MeO and MeO_2C and electron-withdrawing groups such as Br, Cl, NC, CF_3, F were well tolerated. Maximum yield of 84% product **367** was obtained in case of 3-CN substituted aryl BPin **365** when it was allowed to react with aniline **50**. Application of this protocol on fused ring system was also evaluated; for example, naphthalene-based BPin **366** gave 77% yield of product **368** upon treatment with aniline **50** (Scheme 105).

Same reaction conditions were applied on different aryl amine substrates and moderate-to-good yields were obtained. The best results were obtained when phenyl BPin **369** was allowed to react with 4-methoxyphenyl amine **370** and product **279** was obtained in 87% yield. Similarly, a number of substituted alkyl amine were tried for this transformation. The reaction was conducted by the reaction of alkyl amines with Ph-BPin demonstrating good yields. Optimum yield was formed when (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine **371** allowed to react with phenyl-BPin **369** and afforded the product **372** in 91% yield (Scheme 106).

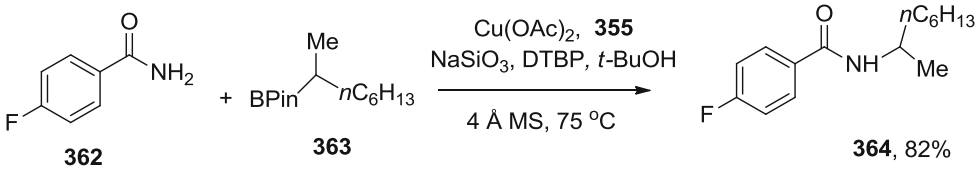
Scheme 102 Synthesis of *N*-arylated amide **358** by using alkyl ester

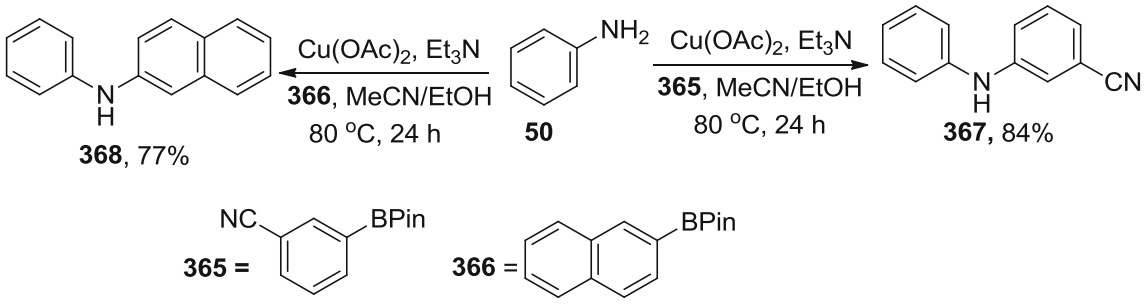


Scheme 103 Synthesis of *N*-arylated amide **361**

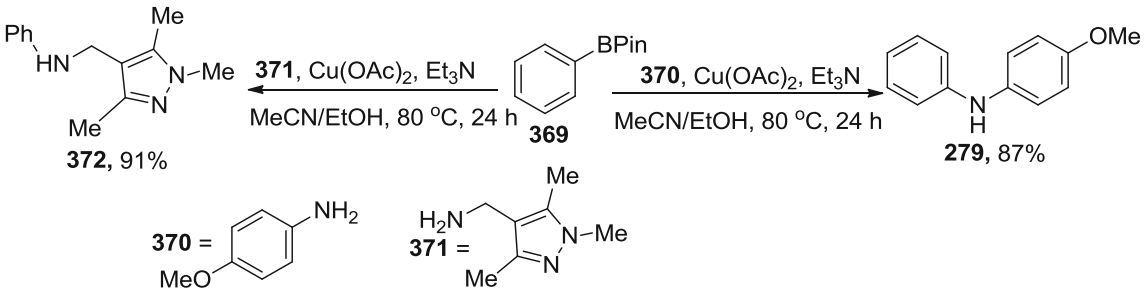


Scheme 104 Synthesis of *N*-alkylated amide **362** using diketiimine **355**

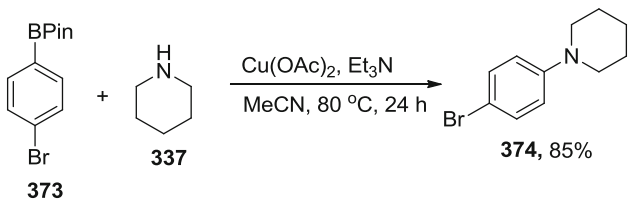




Scheme 105 Chan–Lam coupling of aniline **50** with aryl boronate ester



Scheme 106 Chan–Lam coupling of substituted aniline **370** and methanamine **371** with boronate ester **369**



Scheme 107 Cross-coupling reaction of boronate ester **373**

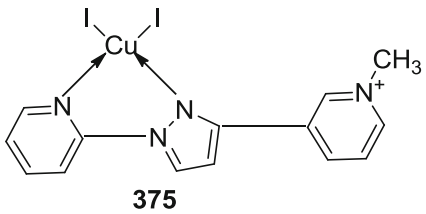


Fig. 31 Structure of Cu complex **375**

Results encouraged their research group to apply these conditions on alkyl amines. Little modification was done by replacing EtOH/MeCN with MeCN. Firstly, this experiment was tried with different substituted Ar-BPin. Different electron-donating (OMe, Me) and electron-withdrawing (Br, Cl, CF_3O, NC) groups were employed and resulted in good-to-excellent yields. The best results were observed when 4-bromophenyl BPin **373** was allowed to react with **337,** and corresponding product **374** was formed in 85% yield (Scheme 107).

New copper complexes catalyzed Chan–Lam coupling

Xue et al. [71] described the effect of newly synthesized copper complexes **375** on Chan–Lam strategy. Ligands were synthesized according to already reported method and further treated with CuI to generate the respective complex (Fig. 31). Studies proved that complex was found compatible with H_2O/MeCN (2:1) system at 60 °C to perform the reaction between 1*H*-imidazole and phenyl boronic acid.

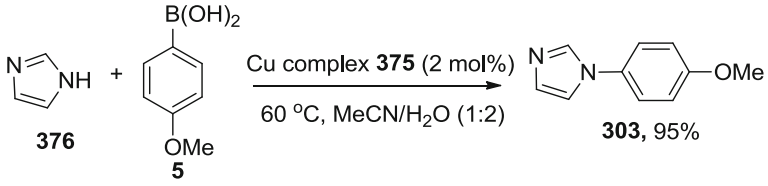
Electron-rich *p*-substituted aryl boronic acids proved to be more reactive and resulted in higher yields as compared to electron-deficient phenyl boronic acid. 4-Methoxyphenyl boronic acid **5** was reacted with 1*H*-imidazole **376** and afforded the corresponding *N*-arylated product **303** in 95% yield (Scheme 108).

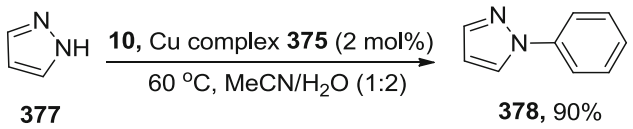
Scope of this reaction was also investigated by treating phenyl boronic acid **10** with pyrazole, aniline, benzamide. Maximum yield (90%) was obtained when phenyl boronic acid **10** was treated with pyrazole **377** (Scheme 109).

Use of copper–salen complex in Chan–Lam coupling

Azam et al. [72] studied the catalytic activity of different Cu(II)–salen complexes in Chan–Lam coupling. The Cu(II) complex **379** was found the most effective to perform this coupling (Fig. 32).

Scheme 108 *N*-Arylation of imidazole **376** by substituted boronic acid





Scheme 109 Cross-coupling of pyrazole **377** and boronic acid **10** through Chan–Lam coupling

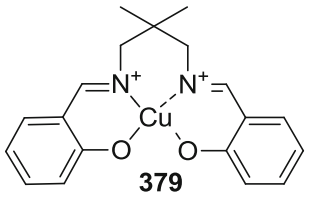


Fig. 32 Structure of copper(II)–salen complex **379**

DNA-binding study and antimicrobial, anticancer activities of Cu(II)–salen complexes were also studied. The Cu(II)–Salen complex **379** (40 mol%) was used along with Et_3N in the presence of DCM at room temperature and 83% yield of *O*-arylated product **380** of phenol **67** with phenyl boronic acid **10** was observed (Scheme 110).

Chan–Lam coupling through sulfonate diketimine copper(II) complex

Duprac and Schaper [73] prepared the sulfonate diketimine copper(II) complex **381** and applied it on the Chan–Lam coupling of amines and anilines (Fig. 33). This system was used without adding any base, ligand, and molecular sieves.

Using this system, relative reactivity of different amines and anilines was determined by treating them with phenyl boronic acid **10,** and it was observed that some substituted anilines showed good reactivity up to 100% among the tested compounds.

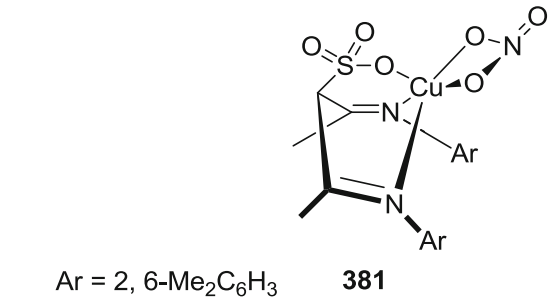
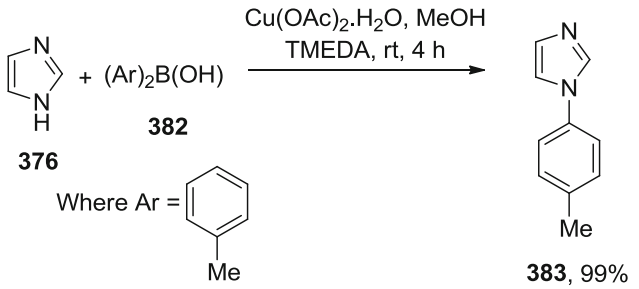


Fig. 33 Structure of copper(II) complex **381**



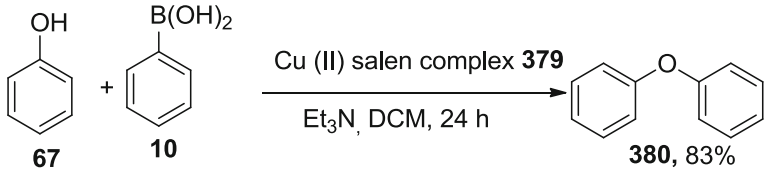
Scheme 111 Synthesis of *N*-arylated imidazole **383**

Use of diaryl boronic acid for *N*-arylation of (benz)imidazole

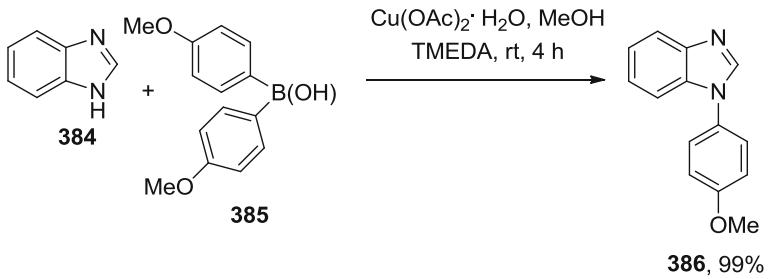
Use of diaryl boronic acid **382** for *N*-arylation of (benz)imidazole was reported by Guan et al. [74]. This protocol involved the use of $Cu(OAc)_2{\cdot}H_2O$, MeOH, tetramethylethylenediamine (TMEDA) at room temperature. Reaction of diaryl boric acid with (benz)imidazole resulted in corresponding product in low-to-good yields (10–99%). Maximum yield (99%) was observed with 1*H*-imidazole **376** when it was allowed to react with 4-methyl diphenyl boronic acid **382** (Scheme 111).

Similarly, in case of benzimidazole **384,** the best yield (99%) of *N*-arylated benzimidazole **386** was obtained when

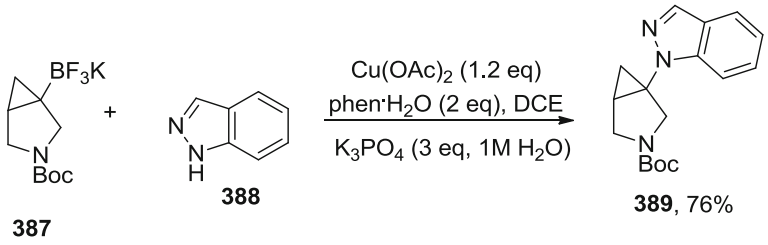
Scheme 110 Synthesis of biaryl ether **380** using Cu(II)–Salen complex **379**



Scheme 112 Synthesis of *N*-arylated benzimidazole **386**



Scheme 113 *N*-Arylation of 1*H*-indazole **388**



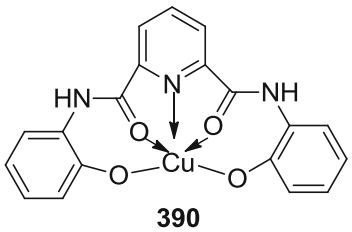


Fig. 34 Structure of pyridine-based catalyst **390**

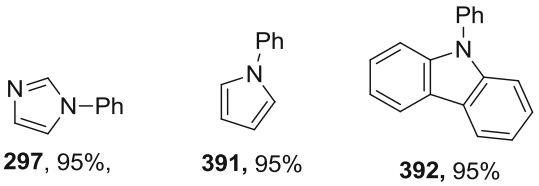


Fig. 35 Synthesis of *N*-arylated heterocycles using Cu complex **390**

it was allowed to react with 4-OMe diphenyl boronic acid **385** (Scheme 112).

Use of tertiary trifluoroborates

Harris et al. [75] presented the Chan–Lam coupling of tertiary trifluoroborates. This conversion was done in the presence of 1.2 equivalent of $Cu(OAc)_2$, 2 equivalents of phenanthroline monohydrate ligand and three equivalents of K_3PO_4 (1 M H_2O, 3 eq) in presence of DCE at 80 °C for 18 h. The reaction resulted in successful formation of corresponding products in good range (37–76%). Maximum yield was observed when *tert*-butyl bicyclo[3.1.0] **387** was treated with indazole **388** under these reaction conditions and resulted in 76% yield (Scheme 113).

Use of pyridine-based polydentate Cu(11) complex

A novel pyridine-based polydentate Cu(II) complex **390** (Fig. 34) was found helpful in cross-coupling reactions by Sharghi et al. [76]. This new catalyst was economical, efficient with the ability to catalyze a variety of reactions.

Its applications in Chan–Lam coupling was proved very effective by observing that the desired products were formed in good yields (65–95%). The reaction of phenyl boronic acid **10** with 1*H*-imidazole, 1*H*-pyrrole and 9*H*-carbazole resulted in 95% yield of corresponding products **297**, **391**, and **392** (Fig. 35).

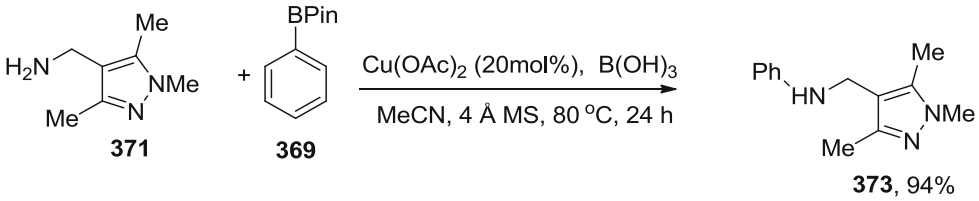
Role of boric acid in Chan–Lam coupling

During the spectroscopic studies of Chan–Lam coupling amination, Vantourout et al. [77] identified the synergistic promotive role of boric acid. The investigation proved the success of the non basic conditions for Chan–Lam coupling. Aryl boronic esters on reacting with different groups of substrates gave good-to-high yields, i.e., alkyl amines (36–94%), aryl amine (52–90%), sulphonamide and azole nucleophile (53–74%) and *O*-and *S*-nucelophile (53–74%). Classical conditions were modified by replacing the organic base Et_3N with $B(OH)_3$. Maximum yield of 94% of aryl amine was observed when (1,3,5-trimethyl-1*H*-pyrazol-4-yl)methanamine **371** was treated with phenyl boronate ester **369** (Scheme 114).

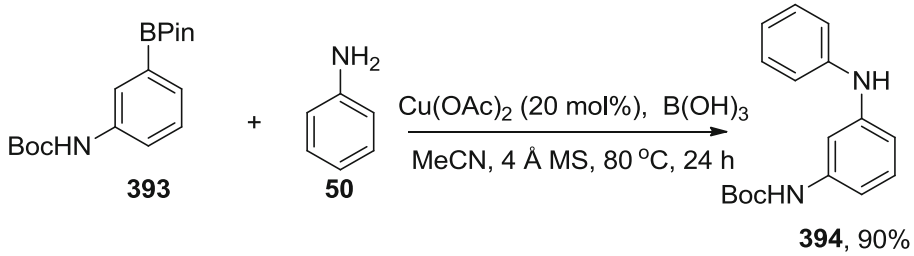
In case of aryl boronic acid, maximum yield of 90% was recorded when Chan–Lam coupling was performed by treating aniline **50** with substituted aryl boronic ester **393** (Scheme 115).

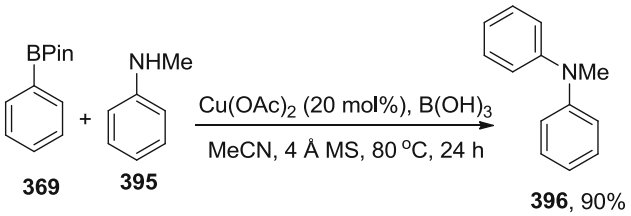
Same result was also observed on *N*-arylation of *N*-methylaniline **395** with phenyl boronic ester **369** under same reaction conditions (Scheme 116).

Scheme 114 *N*-arylation of heterocyclic compound **371**



Scheme 115 *N*-arylation of aniline through substituted boronic ester **393**





Scheme 116 *N*-arylation of *N*-substituted aniline through boronic ester **369**

Triflouoromethylation with trifluoroethanol

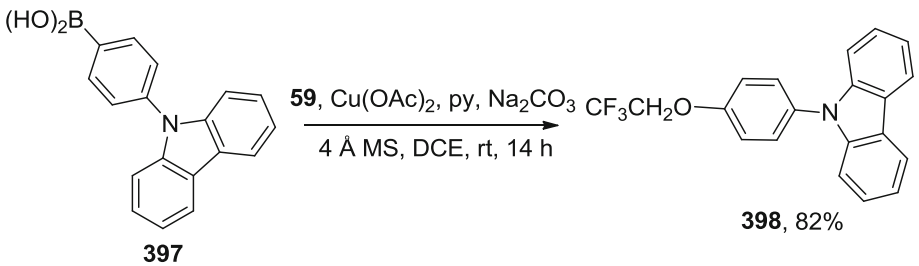
Zhang et al. [78] described the triflouoromethylation of aryl boronic acid by using only 2 equilvalents of 2,2,2-trifluoroethanol. Reactions were conducted in presence of $Cu(OAc)_2$, pyridine, Na_2CO_3, $Cl(CH_2)_2Cl$ and these condition were found suitable for this transformation. A variety of aryl and heteroaryl boronic acid having different functional groups such as ether, amide, vinyl, ester, thioester, nitro, cyano, bromo, iodo, chloro, ketones and aldehyde were well tolerated in this coupling reaction giving moderate-to-good yields (35–82%). Maximum yield was observed when phenyl boronic acid having carbazole group **397** was allowed to undergo the Chan–Lam coupling reaction with 2 equivalents of 2,2,2-trifluoroethanol **59** in the optimum conditions and corresponding product **398** was obtained in 82% yield (Scheme 117).

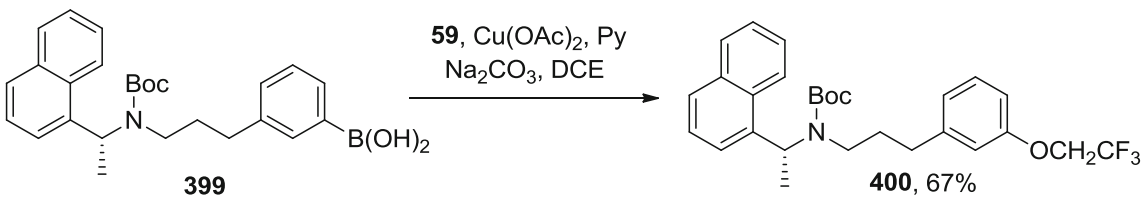
Their research group also attempted to prepare the medicinally important cinacalcet (calcimimetic drug) analogues by trifluoromethylation of substituted phenyl boronic acid **399** which resulted in 67% yield of desired product **400** (Scheme 118).

Conclusion

In this study, a range of strategies have been discussed so as to provide a comprehensive insight into the methodolog-

Scheme 117 Chan–Lam coupling by using carbazole based boronic acid





Scheme 118 Synthesis of cinacalcet analogue **400** through Chan–Lam coupling

ical routes to synthesize the new and biologically important compounds using Chan–Lam coupling. During recent years, a lot of work in organic synthesis has been carried out leading to synthesis of novel and more active drugs to achieve the targets with regard to pharmaceutical needs. In this connection, a number of substrates were employed to meet these requirements of synthesizing different moieties, having great contributions in the activity of compounds. Furthermore, new developments regarding methodologies have also been described to show the pathways for researchers' fraternity to prepare the desired compounds in more efficient and economical ways. The plethora of research substantiated in this review will provide a detailed outlook on synthetic applications of this coupling and will open new horizons to extend the methodology development.

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