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Synthesis of Benz-fused Azoles via C-Heteroatom Coupling Reactions Catalysed by Cu(I) in presence of Glycosyltriazole Ligands

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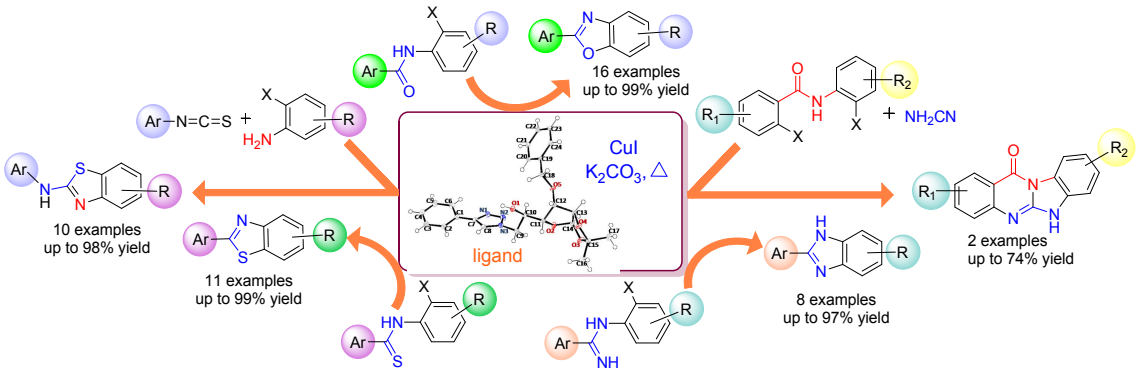
Abstract:



Glycosyl triazoles are conveniently accessible and contain multiple metal-binding units that may assist in metal-mediated catalysis. Azide derivatives of D-glucose have been converted to their respective aryltriazoles and screened as ligands for the synthesis of 2-substituted benz-fuzed azoles and benzimidazoquinazolinones by Cu-catalyzed intramolecular Ullmann type C-heteroatom coupling. Good to excellent yields for a variety of benz-fused heterocyles were obtained for this readily accessible catalytic system.

Key words: Benzazole; Catalysis; Click Chemistry; Cross-coupling; Glycosyl triazole; Ligand

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INTRODUCTION

Benz-fused azole derivatives show a broad range of biological activities and constitute the core structures of a number of marketed drugs (**Figure 1**).[1] Biological and medicinal significance of benz-fused azoles amplifies the importance of new modified approaches for the synthesis of these derivatives.[2] One of the most efficient and convenient methods for the synthesis of these derivatives is ligand promoted intramolecular Cu-catalyzed *C*-heteroatom cross-coupling of (2-halophenyl)aryl amides/ thioamides/ amidines. A number of conventional ligands,[3] as well as new ligands,[4] have been utilized for this purpose, but all ligands are not useful for all the three types (i.e. *C*-*O*, *C*-*N,* and *C*-*S*) of cross-couplings. Moreover, most of the catalytic systems applied for these reactions require high loading of a ligand as well as Cu-source (10-30 mol%).

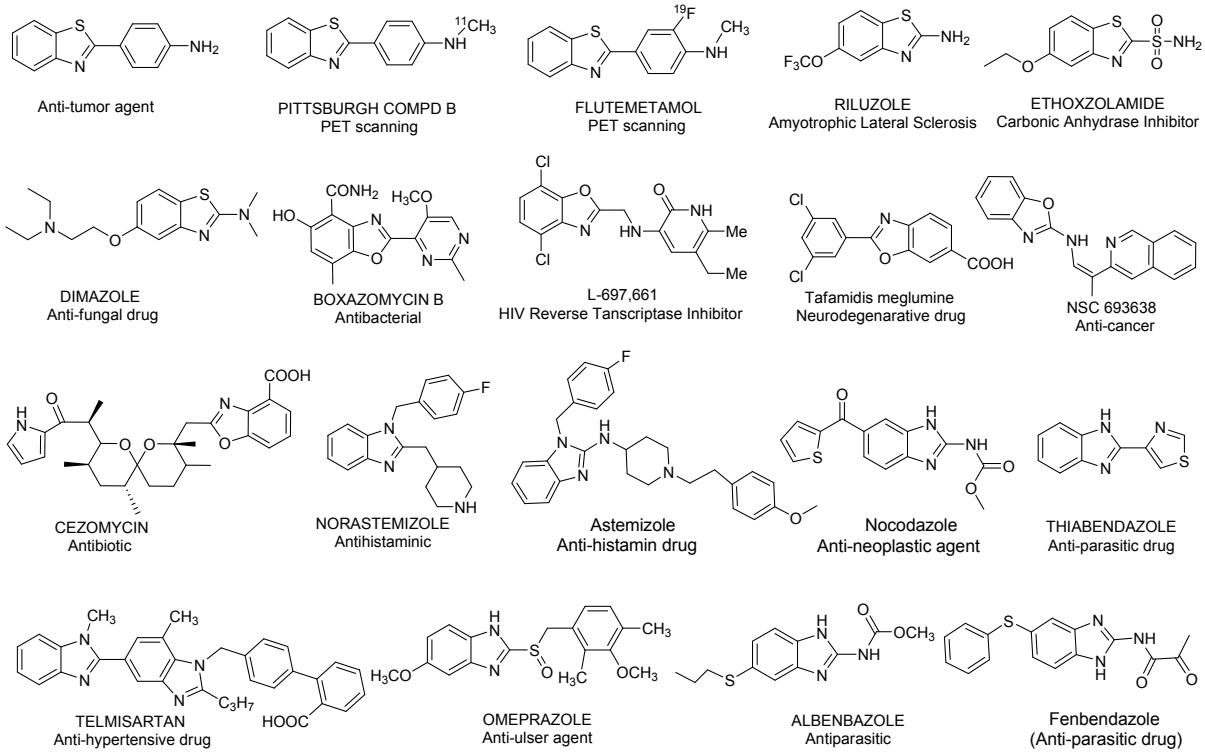


Figure 1: Structures of some biologically relevant benzothiazoles, benzoxazoles and benzimidazoles skeletons.

Carbohydrates provide a suitable skeleton to develop new synthetic tools counting a number of organocatalysts and ligands.[5-8] The spatial arrangement of multiple free hydroxy groups attached to rigid pyranose and furanose structures of carbohydrate moiety and easy transformation of these hydroxy groups to various functionalities, offer prospects to modify these molecules into suitable ligands. Moreover, easy availability and low cost of carbohydrates make it a convenient source for development of the ligands. A large number of synthetically modified carbohydrate derivatives have been used as ligands in a broad range of metal-catalyzed reactions.[7,8] Along with other carbohydrate derivatives, glycosylated triazoles have shown tremendous utility in form of metal-ion ligands and exhibited their efficacy in terms of asymmetric induction, low catalyst loading, and drug synthesis.[6] The success of these ligands lies in the structural benefits associated with carbohydrate moiety as well as presence of triazole ring which offers an efficient coordinating site for metal ions and promotes catalysis in many reactions.[9] Despite the promising features of carbohydrate-derived ligands, no such ligand has been used so far for efficient catalysis of Ullmann-type *C-O*, *C-S,* and *C-N* cross-coupling reactions.

Here, we have developed triazolyl derivatives of D-glucose as potential ligands for Cu(I)-catalyzed cross-coupling and employed them for the synthesis of 2-aryl benzoxazoles, 2-arylbenzothiazoles, 2-arylbenzimidazoles, 2-aminobenzothiazoles, and benzimidazo[2,1-b]quinazolin-12(6*H*)-ones.

RESULTS AND DISCUSSION

Keeping in mind the easy remarkable coordination ability of 1,2,3-triazoles with various metal ions[9] and their easy accessibility through high yielding synthetic protocols[10], we tended to modify the structure of D-glucose in such a way that it contains at least one

triazolyl ring along with its skeletal oxygen atoms either in the form of free hydroxy group or with protection. Accordingly, we designed three glycoconjugates **L1**, **L2** and **L4** containing one 1,2,3-triazolyl ring and at least one free hydroxy group. Ligands **L3** and **L7** were designed in a manner that they contain one triazole ring with protected hydroxy groups of sugar skeleton whereas, **L5** contains two triazolyl rings with one free hydroxy group. Ligand **L6** was designed without any triazole ring to compare the effect of triazole ring in ligands. Another ligand **L8**, containing benzotriazole ring and a free phenolic group, was used in the reaction to compare with the sugar-containing ligands and estimate the role of sugar skeleton in coordination (**Figure 2**).

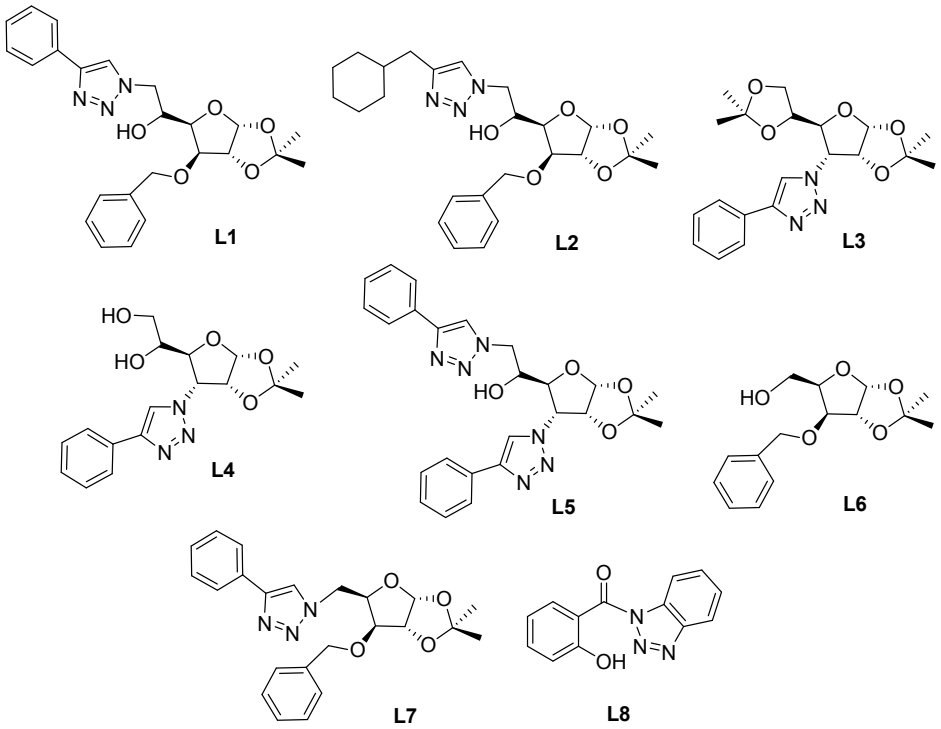
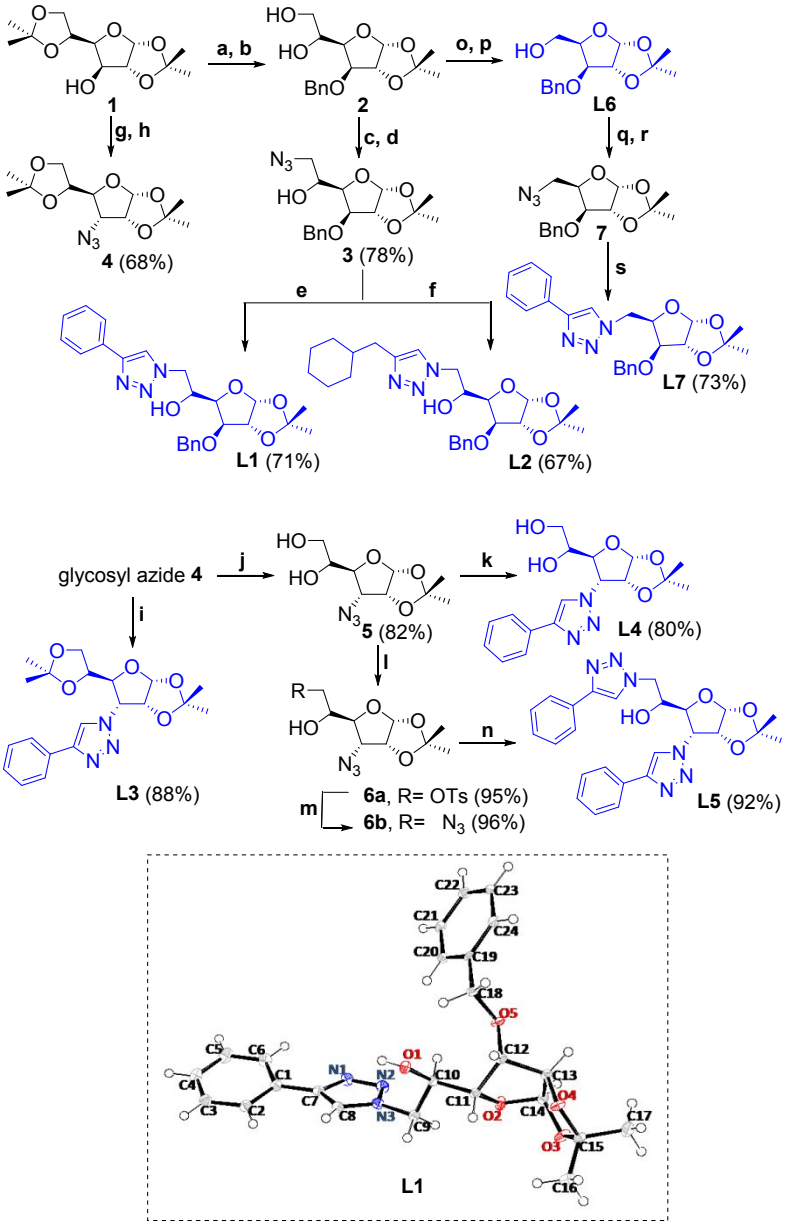


Figure 2. Structure of ligands designed and investigated for the intramolecular *C*-*O* cross-coupling.

We instigated strategic synthesis of triazolyl glycoconjugates with classical acetonide protection of readily available D-glucose resulting into 1,2,5,6-di-*O*-isopropylidene-*α*-D-glucofuranose **1**

(**Scheme 1**).[11] 3-*O*-Benzyl protection of diacetonide glucose **1** followed by selective deprotection of 5,6-isopropylidene group gave glycosyl diol **2**.[12] Selective tosylation of 6-OH of diol **2** followed by reaction with NaN_3 afforded glycosyl azide **3**.[13] Azide-alkyne cycloaddition of compound **3** with phenyl acetylene (1.2 equiv.) in presence of $CuSO_4.5H_2O$ (0.3 equiv.) and sodium ascorbate (0.6 equiv.) in DCM-water (1:1) at room temperature afforded triazolyl glycoconjugate **L1** in good yields. In a similar pattern, reaction of azido alcohol **3** with 3-cyclohexylpropyne-1 in presence of Cu-catalyst afforded **L2**. On the other hand, reaction of diacetonide glucose **1** with triflic anhydride in presence of pyridine furnished 3-*O*-triflate derivative which could be easily converted to 3-azido derivative **4** with inversion at C-3 by heating with sodium azide in DMF.[14] Cu(I)-catalyzed cycloaddition of glycosyl azide **4** with phenyl acetylene afforded **L3** in high yields. Selective isopropylidene deprotection of compound **4** afforded diol **5**[15] which on cycloaddition with phenyl acetylene furnished **L4**. Similarly, selective tosylation of diol **5** followed by azidation afforded 3,6-diazido derivative **6** which on cycloaddition with two equivalents of phenyl acetylene produced a bis-triazolyl glycoconjugate ligand **L5**. Oxidation of 5,6-diol of **2** into the corresponding aldehyde followed by reduction furnished compound **L6**[16] with a free alcohol group which was easily converted into corresponding azide **7** on successive tosylation and azidation.[17] Synthesis of **L7** was achieved by Cu-catalyzed reaction of azide **7** with phenylacetylene. Ligand **L8** was synthesized by *N*-acylation of 1*H*-benzotriazole by the standard procedure described in literature.[18] All the synthesized ligands were characterized using NMR, IR and mass spectroscopy. Ligand **L1** was also characterized by single crystal X-ray crystallography.

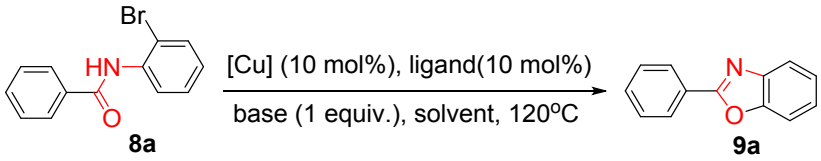


Scheme 1. Synthesis of ligands **L1-L7** starting from D-glucose and ORTEP diagram of **L1** crystal. (a) BnBr, NaH, rt; (b) AcOH/H_2O, rt; (C) TsCl, Et_3N, DCM, rt; (d) NaN_3,DMF, 90 ^oC; (e) Phenyl acetylene, $CuSO_4.5H_2O$, sodium ascorbate, DCM/water (1:1), rt; (f) 3-Cyclohexyl propyne-1, $CuSO_4.5H_2O$, sodium ascorbate, DCM/water (1:1), rt; (g) Tf_2O, pyridine, DCM, 0 ^oC; (h) NaN_3, DMF, 90 ^oC; (i) Phenyl acetylene, $CuSO_4.5H_2O$, sodium ascorbate, DCM/water (1:1), rt; (j) AcOH/H_2O, heat; (k) Phenyl acetylene, $CuSO_4.5H_2O$, sodium ascorbate, DCM/water (1:1), rt; (l) TsCl, Et_3N, DCM, rt; (m) NaN_3, DMF, 90 ^oC; (n) Phenyl acetylene, $CuSO_4.5H_2O$,

sodium ascorbate, DCM/water (1:1), rt; (o) $NaIO_4$, $NaHCO_3$, MeOH, rt; (p) $NaBH_4$, MeOH, rt; (q) TsCl, Et_3N, DCM, rt; (r) NaN_3,DMF, 90 ^oC; (s) Phenyl acetylene, $CuSO_4.5H_2O$, sodium ascorbate, DCM/water (1:1), rt.

Having ligands of our choice in hands, we moved forward for their application in intramolecular *C*-heteroatom coupling reaction. For the optimization of reaction conditions and identification of best ligand and most suitable Cu-source, base and solvent, a prototype reaction was set for the intramolecular *C-O* cross-coupling of *N*-(2-bromophenyl)benzamide **8a** to afford 2-phenyl benzoxazole **9a**. Results are summarized in **Table 1**. For the catalytic screening of ligands, initially 1 equiv. of *N*-(2-bromo phenyl)benzamide **8a** was heated with 10 mol% of ligand,10 mol% of CuI as Cu-source and 1 equiv. of KOH as a base in dry DMF at 120^{o}C for 10 hours. The best result in form of product yields was obtained with ligand **L1** (Table 1, entry 1). Only 17% yield was obtained when no ligand was used (Table 1, entry 9), whereas no product was formed in absence of Cu-source (Table 1, entry 10). The formation of the product **9a** was confirmed on the basis of ^1H and ^{13}C NMR spectra analysis which was found in agreement with the literature.[4a]

Table 1. Screening of ligands **L1-L8** for intramolecular *C-O* cross-coupling and optimization of the reaction conditions

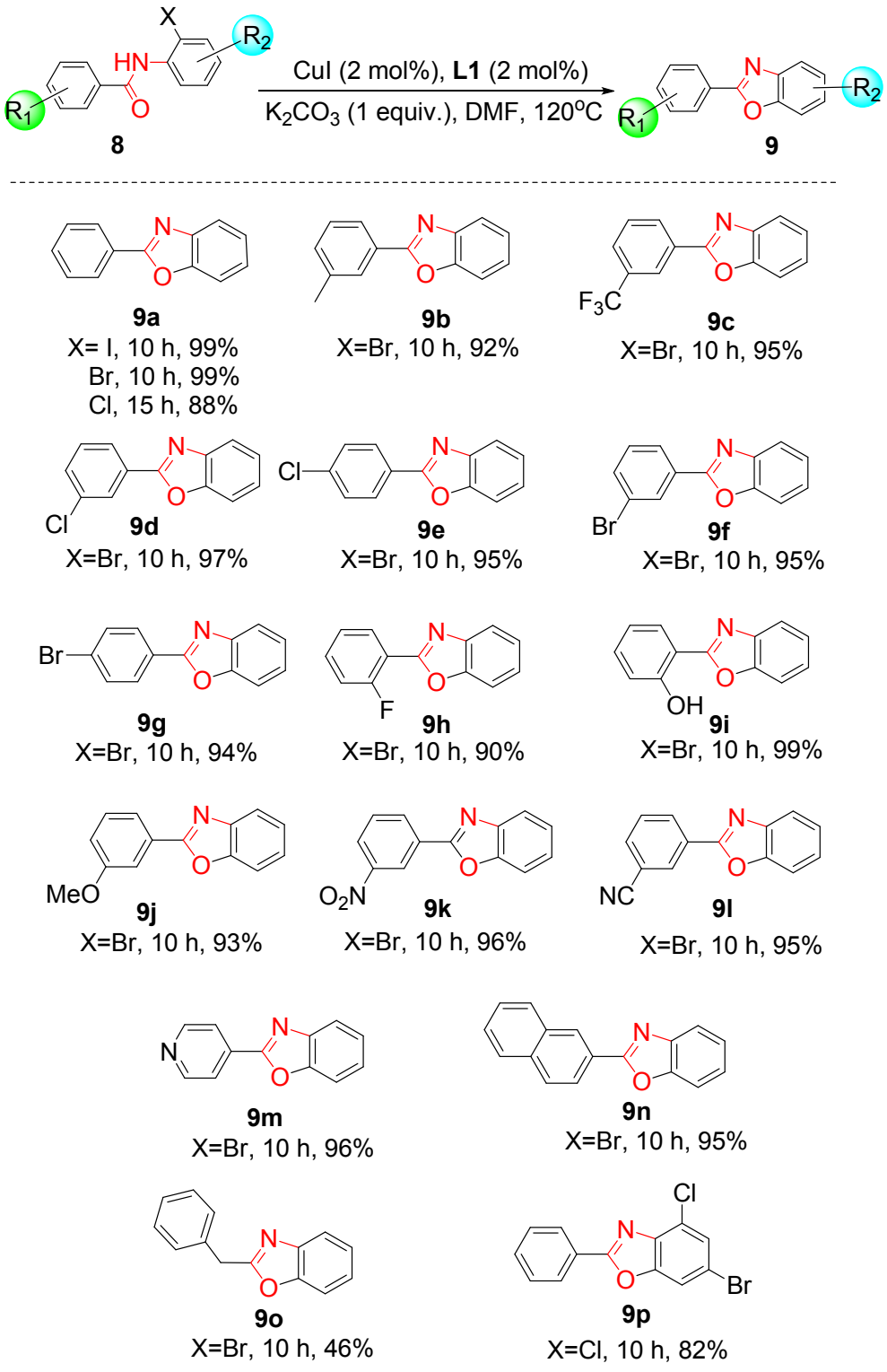


Entry	Ligand	[Cu]	Base	Solvent	Yield[a]
1	L1	CuI	KOH	DMF	83%
2	L2	CuI	KOH	DMF	82%
3	L3	CuI	KOH	DMF	50%

4	L4	CuI	KOH	DMF	55%
5	L5	CuI	KOH	DMF	80%
6	L6	CuI	KOH	DMF	30%
7	L7	CuI	KOH	DMF	40%
8	L8	CuI	KOH	DMF	32%
9	-	CuI	KOH	DMF	17%
10	L1	-	KOH	DMF	00
11	L1	CuI	K_2CO_3	DMF	99%
12	L1	CuI	Cs_2CO_3	DMF	65%
13	L1	CuI	K_3PO_4	DMF	27%
14	L1	CuI	$KOBu^t$	DMF	82%
15	L1	CuI	$NaHCO_3$	DMF	80%
16	L1	CuI	Na_2CO_3	DMF	20%
17	L1	CuI	DIPEA	DMF	00
18	L1	CuI	Et_3N	DMF	00
19	L1	CuI	K_2CO_3	THF	10%
20	L1	CuI	K_2CO_3	Toluene	00
21	L1	CuI	K_2CO_3	DMSO	96%
22	L1	CuI	K_2CO_3	MeOH	70%
23	L1	CuI	K_2CO_3	CH_3CN	43%
24	L1	CuCl	K_2CO_3	DMF	42%
25	L1	Cu_2O	K_2CO_3	DMF	76%
26	L1	CuOAc	K_2CO_3	DMF	84%
27	L1	$CuSO_4$	K_2CO_3	DMF	40%
28[b]	L1	CuI	K_2CO_3	DMF	99%
29[c]	**L1**	**CuI**	**K_2CO_3**	**DMF**	**99%**
30[d]	L1	CuI	K_2CO_3	DMF	43%
31[e]	L1	CuI	K_2CO_3	DMF	45%
32[f]	L1	CuI	K_2CO_3	DMF	00
33[g]	L1	CuI	K_2CO_3	DMF	38%

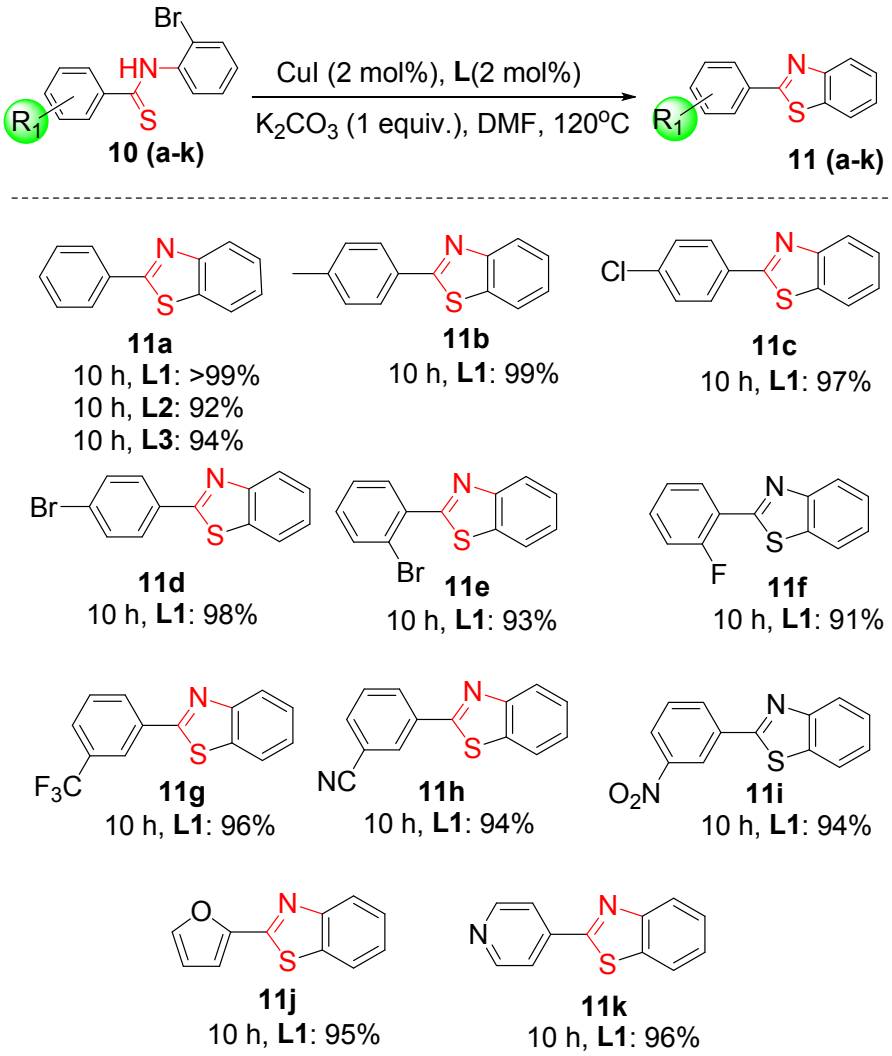
Molar ratios: *N*-(2-bromophenyl) benzamide (1.0 equiv.), ligands (10 mol%), Cu-source (10 mol%), base (1.0 equiv.), solvent (2 mL), temperature 120 ^{o}C, reaction time 10h. [a]Yields reported after purification by column chromatography (SiO_2). [b]**L1** (5 mol%), CuI (5 mol%). [c]**L1** (2 mol%), CuI (2 mol%). [d]**L1** (1 mol%), CuI (1 mol%). [e]K_2CO_3 (0.5 equiv). [f]Reaction at room temperature for 24 h. [g] Temperature 100 ^{o}C for 15 h.

The optimized reaction conditions for preparation of 2-phenyl benzoxazole **9a** from *N*-(2-bromophenyl)benzamide **8a** involving 2 mol% CuI, 2 mol% of ligand **L1**, 1 equiv. of K_2CO_3 and 120^{o}C temperature were investigated with a variety of *N*-(2-haloaryl)benzamides containing different aromatic rings with different substitutions (**Scheme 2**). Comparatively slower reaction and slightly lower yield was obtained in case of *N*-(2-chlorophenyl)benzamide than that of respective bromo and iodo analogues (**Scheme 2**, **9a**). No remarkable variation in yields were observed with different substitutions i.e. electron releasing (**Scheme 2**, **9b**, **9i**, **9j**) or electron withdrawing groups (**Scheme 2**, **9c**, **9e**, **9g**, **9h**, **9k**, **9l**) at different positions of phenyl ring attached to C=O group. Reactions with other aromatic rings, such as, pyridyl and naphthyl in place of phenyl ring were also good yielding (**Scheme 2**, **9m**, **9n**), however low yield was observed in case of benzyl group (**Scheme 2**, **9p**). Also, the substitution at phenyl ring attached to nitrogen atom of amide did not alter the expected yield (**Scheme 2**, **9o**).



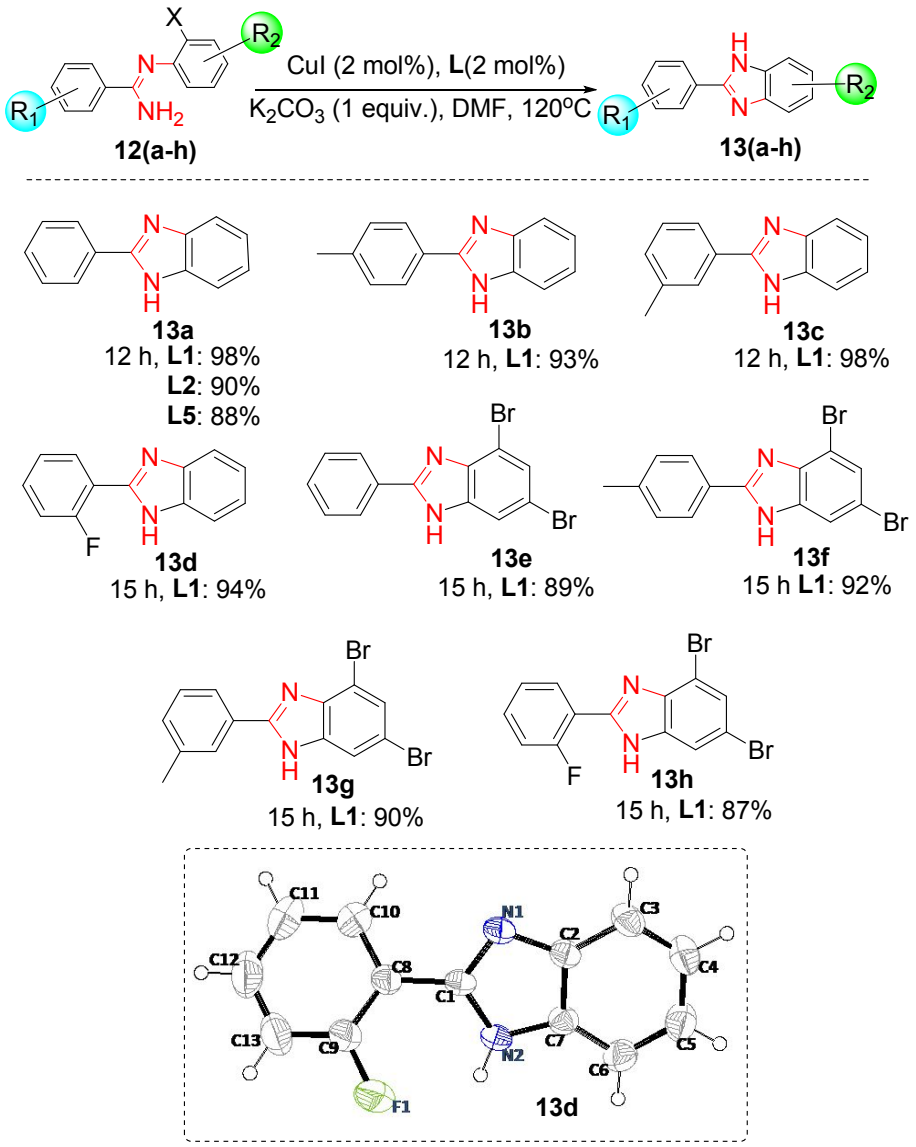
Scheme 2. Synthesis of 2-aryl benzoxazoles *via* optimized reaction conditions. Yields in % reported after purification by column chromatography (SiO_2).

After success of glycosyl triazole ligands in the catalysis of intramolecular *C*-*O* coupling of *N*-(2-haloaryl)benzamide, we further investigated ligands **L1**, **L2** and **L5** for intramolecular *C*-*S* and *C*-*N* coupling with optimized reaction conditions and molar ratios. In the initial investigations for the intramolecular *C*-*S* coupling of *N*-(2-bromophenyl)benz-thioamide, all the three ligands **L1**, **L2** and **L5** showed good results for the formation of the respective product 2-aryl benzothiazole **11a** which was characterized by its spectral analysis (MS, ^{1}H and ^{13}C NMR spectra) and found in agreement with the literature.[20] Likewise, in the investigation for the intramolecular *C*-*N* coupling of *N*-(2-bromophenyl) benzamidine, all the three ligands **L1**, **L2** and **L5** again showed good results for the formation of the product **13a.** The respective compound **13a** was characterized by its spectral analysis (MS, ^{1}H and ^{13}C NMR spectra) and found in agreement with the literature.[21] However, for the both intramolecular *C*-*S* coupling of *N*-(2-bromophenyl)benz-thioamide and intramolecular *C*-*N* coupling of *N*-(2-bromophenyl) benzamidine, we noticed that ligand **L1** again outperform **L2** and **L3** and produced best yields of coupling products (**Scheme 3** and **Scheme 4**). We moved forward with **L1** for intramolecular *C*-*S* coupling of differently substituted *N*-(2-haloaryl)benz-thioamides **10**(**a-k**) and achieved excellent yields (91-99%) of 2-arylbenzothiazoles **11**(**a-k**) (**Scheme 3**).



Scheme 3. Synthesis of 2-aryl benzothiazoles *via* optimized reaction conditions with ligand **L1**. Yields in % reported after purification by column chromatography (SiO_2).

On the other hand, the application of ligand **L1** in Cu-catalyzed intramoleculer *C-N* coupling of *N*-(2-haloaryl) benzamidines **12(a-h)** with optimized reaction conditions and molar ratios resulted into formation of 2-arylbenzimidazoles **13**(**a-h**) in high yields (88-97%) (**Scheme 4**). High product yields in intramolecular *C-O*, *C-S* and *C-N* couplings proved **L1** to be a versatile ligand for Ullmann-type coupling.



Scheme 4. Synthesis of 2-aryl benzimidazoles *via* optimized reaction conditions and ORTEP diagram of **13d** crystal. Yields in % reported after purification by column chromatography (SiO_2).

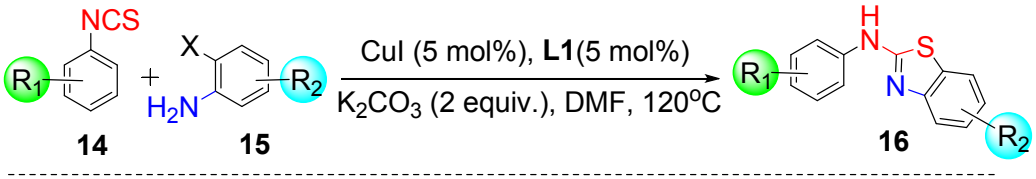
We further assessed the effectiveness of ligand **L1** in cascade synthesis of 2-phenyl benzoxazoles from reaction of benzamide and 1,2-dibromobenzene *via* intermolecular *C-N* coupling followed by intramolecular *C-O* coupling in presence of CuI and K_2CO_3. Optimization of the reaction conditions with respect to molar ratios of **L1**, CuI and K_2CO_3, temperature and

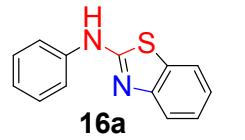
reaction time has been summarized in **Table S1 (**See, supporting information). Best results were obtained when reaction was catalyzed with 10 mol% **L1** and 10 mol% CuI in presence of 2 equiv. K_2CO_3 in DMF solvent at 130°C temperature and 24 h reaction time (Table S1, entry 5). Spectral data of developed compound **9a** using tandem one-pot reaction of 1,2-dibromobenzene and benzamide was exactly matched with the compound obtained by intramolecular *C*-*O* cross coupling of *N*-*(*2-haloaryl) benzamide **8a.** Due to low product yield (up to 45%) in tandem approach with our ligand, we did not further explore the optimized conditions with other derivatives.

To check the efficacy of glycosyl triazole ligands for Cu-catalyzed cascade synthesis of *N*-phenyl-2-aminobenzothiazole from reaction of phenyl isothiocyanate **14a** and 2-iodoaniline **15a**, we optimized the reaction with respect to molar ratios of **L1**, CuI and K_2CO_3 and for temperature and solvent (See, supporting information, **Table S2**). 5 Mol% **L1** with 5 mol% CuI catalyzed the reaction most effectively in presence of 1.0 equiv. K_2CO_3 (Table S2, entry 6). Maximum reaction yield (98%) was obtained at 120 °C in 20 h reaction time (Table S2, entry 6). Ligands **L2** and **L5** also showed good results for the coupling of phenyl isothiocyanate and 2-iodoaniline under same reaction conditions but produced slightly lower yields than ligand **L1**(Table S2, entry 9, 10). Formation of product **16a** was confirmed by the analysis of MS, NMR (^{1}H and ^{13}C NMR) spectra which were found in agreement with the literature data.[22]

We applied the optimized reaction conditions to coupling of various commercially available aryl isothiocyanates and 2-halo anilines to develop a series of *N*-aryl-2-aminobenzothiazoles (**Scheme 5**). Among 2-haloanilines, chloroaniline took more time to react and gave lesser yield as compared to bromo and iodo derivatives (**Scheme 5**, **16a**). Nature of other substitutions at phenyl ring of isothiocyanate unit did not affect the product yield remarkably. On the other hand,

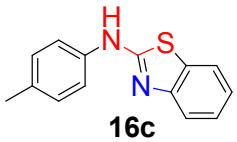
halo group substitution on the aryl ring of 2-haloaniline reduced the product yield a little (**Scheme 5**, **16g-j**) probably due to deactivation of the aromatic ring which restricts its attack on isothiocyanate to form phenylthiourea intermediate.





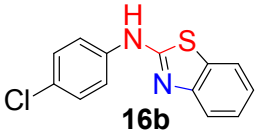
16a

X= I, 20 h, 98%
Br, 20 h, 91%
Cl, 25 h, 80%



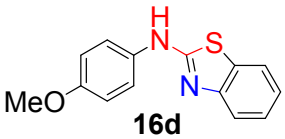
16c

X= Br, 20 h, 93%



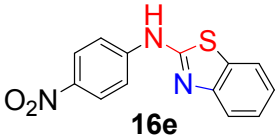
16b

X= Br, 20 h, 92%



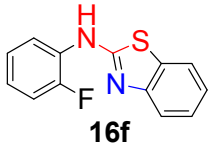
16d

X= Br, 20 h, 92%



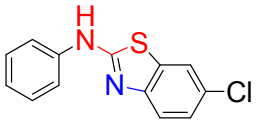
16e

X= Br, 20 h, 89%



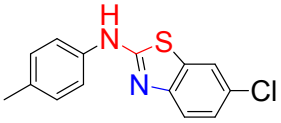
16f

X= Br, 20 h, 95%



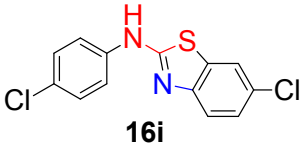
16g

X= Br, 20 h, 86%



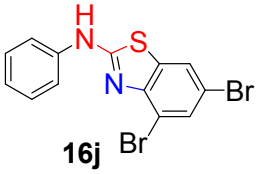
16h

X= Br, 20 h, 87%



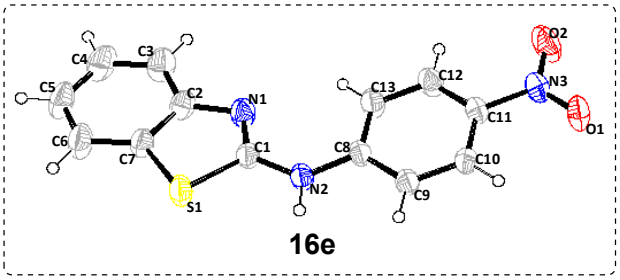
16i

X= Br, 20 h, 84%



16j

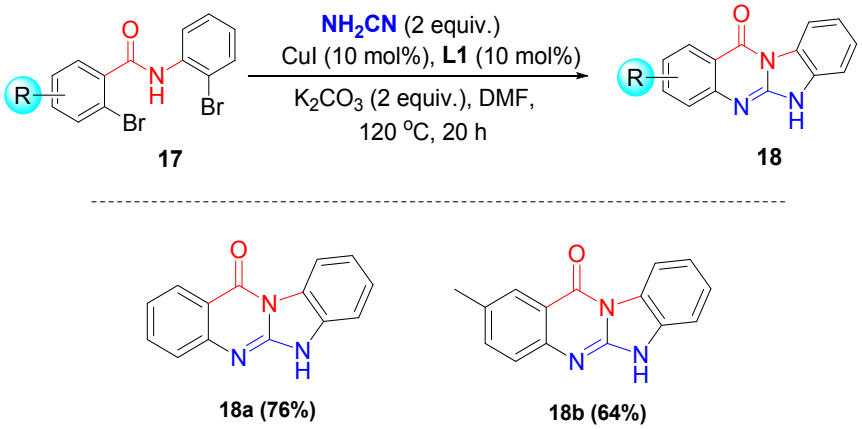
X= Br, 20 h, 81%



16e

Scheme 5. Synthesis of 2-(*N*-arylamino) benzothiazoles *via* optimized reaction conditions and ORTEP diagram of **16e** crystal. Yields in % are reported after purification by column chromatography (SiO_2).

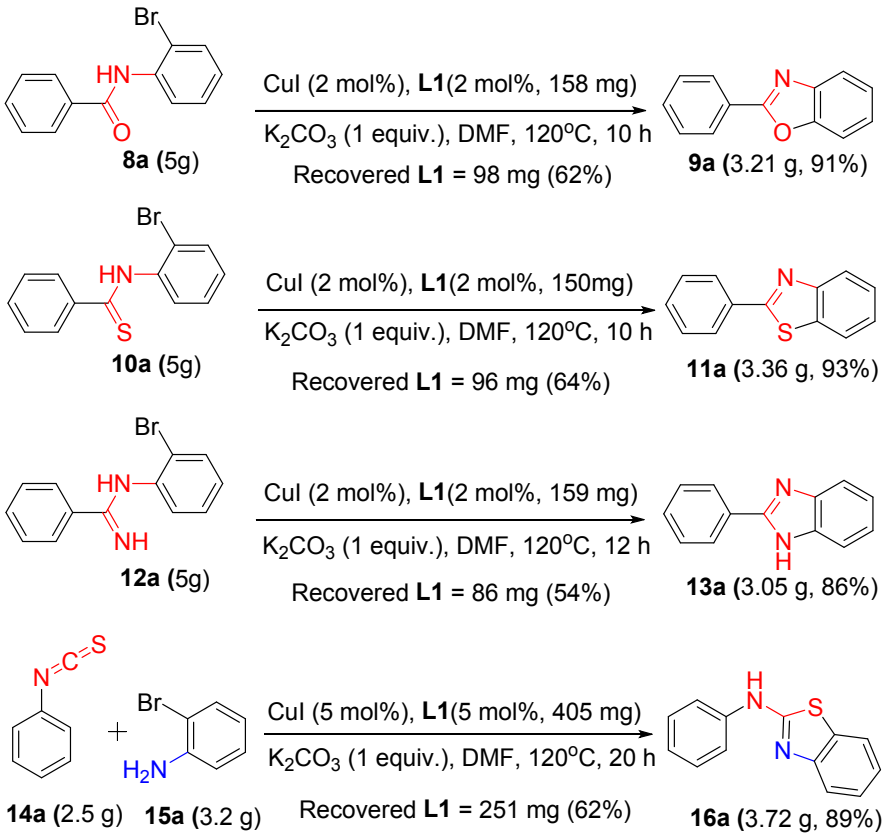
Moving towards some more complex reactions, we considered to employ **L1**-CuI catalytic system for the synthesis of benzimidazo[2,1-b]quinazolin-12(6*H*)-ones from reaction of *N*-(2-bromoaryl)-2-bromobenzamide with cyanamide.[19] 10 Mol% **L1** with 10 mol% CuI gave best catalyzing results for reaction of *N*-(2-bromophenyl)-2-bromobenzamide **17a** with 2 equiv. cyanamide resulting into benzo[4,5]imidazo[2,1-b]quinazolin-12(6*H*)-one **18a** with 76% product yield at 120°C temperature and in 20 h reaction time while taking 2.0 equivalent K_2CO_3 as base (See, supporting information, Table S3, entry 4). Optimized reaction conditions also gave good yield (64%) for synthesis of 2-methylbenzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one **18b** **(Scheme 6**).



Scheme 6. Application of **L1** in tandem synthesis of benzimidazo[2,1-b]quinazolin-12(6*H*)-ones

For quantitative generalization of the reactions catalyzed with the assistance of ligand **L1**, we carried out reactions in gram scale and found good yields of 2-phenylbenzoxazole, 2-

phenylbenzothiazole, 2-phenylbenzimidazole and 2-(*N*-phenylamino)benzothiazole (**Scheme 7**). Moreover we successfully recovered ligand **L1** from reaction mixture through column chromatography (SiO_2), in up to 64% recovered yield.



Scheme 7. Gram scale reactions with ligand **L1** and recovery of ligand.

To postulate the most favorable coordination sites of the ligand **L1**, we did a comparative analysis of yields obtained with 2 mol% loading of ligands **L1**, **L2**, **L5**, **L6**, **L7** and **L8** in Cu-catalyzed intramolecular *C-O* crosscoupling of 2-phenylbenzamide in presence of K_2CO_3 (**Figure 3**). Ligand **L2** which structurally differs with **L1** by aliphatic substituent instead of phenyl ring at position-4 of triazole ring, gave comparable yield to that obtained with **L1**. This suggests that the phenyl ring attached to triazole ring has no major contribution in coordination with Cu(I). Similarly **L5** which differs with **L1** by the moiety attached at *C*-3 with inversion of

stereochemistry at *C*-3 of sugar skeleton, also furnished high yields of coupling product, which suggests that the benzyloxy moiety attached to *C*-3 of glycosyl part of **L1** does not play considerable role in coordination. On the other hand, **L6** and **L7** which structurally differ with **L1** by lacking free hydroxy group and triazole ring respectively, afforded much lesser yield of final product in comparison to that obtained with **L1**, which suggests that the most plausible effective coordination sites of **L1** are triazole ring attached at *C*-6 and free hydroxy group at *C*-5 of sugar skeleton. Although ligand **L8** which contains a triazole moiety as well as a free hydroxy group in the proximity of triazole ring, produced poor yield of product which advocates the role of sugar skeleton in providing most favorable spatial arrangement of triazole ring and hydroxy group to offer suitable coordination with Cu(I).

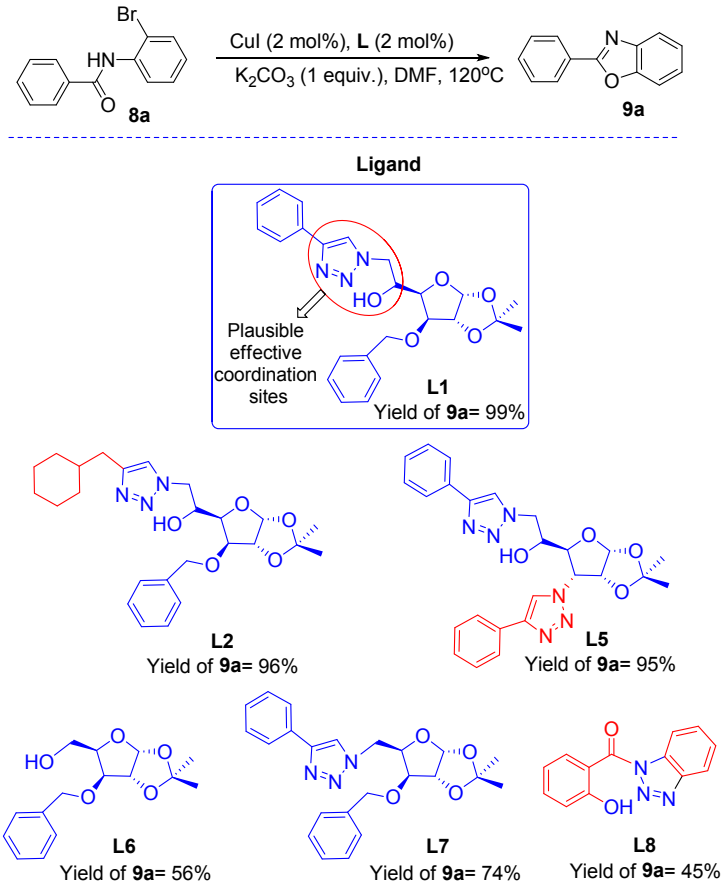
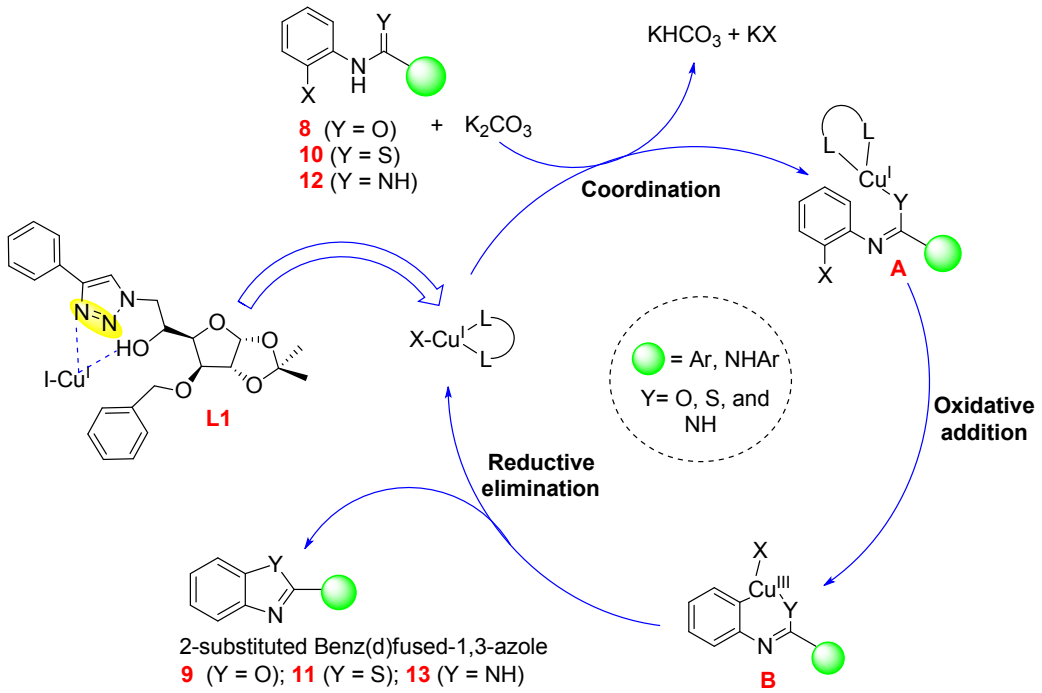


Figure 3. Comparative analysis to estimate the effective coordination sites of ligand **L1**.

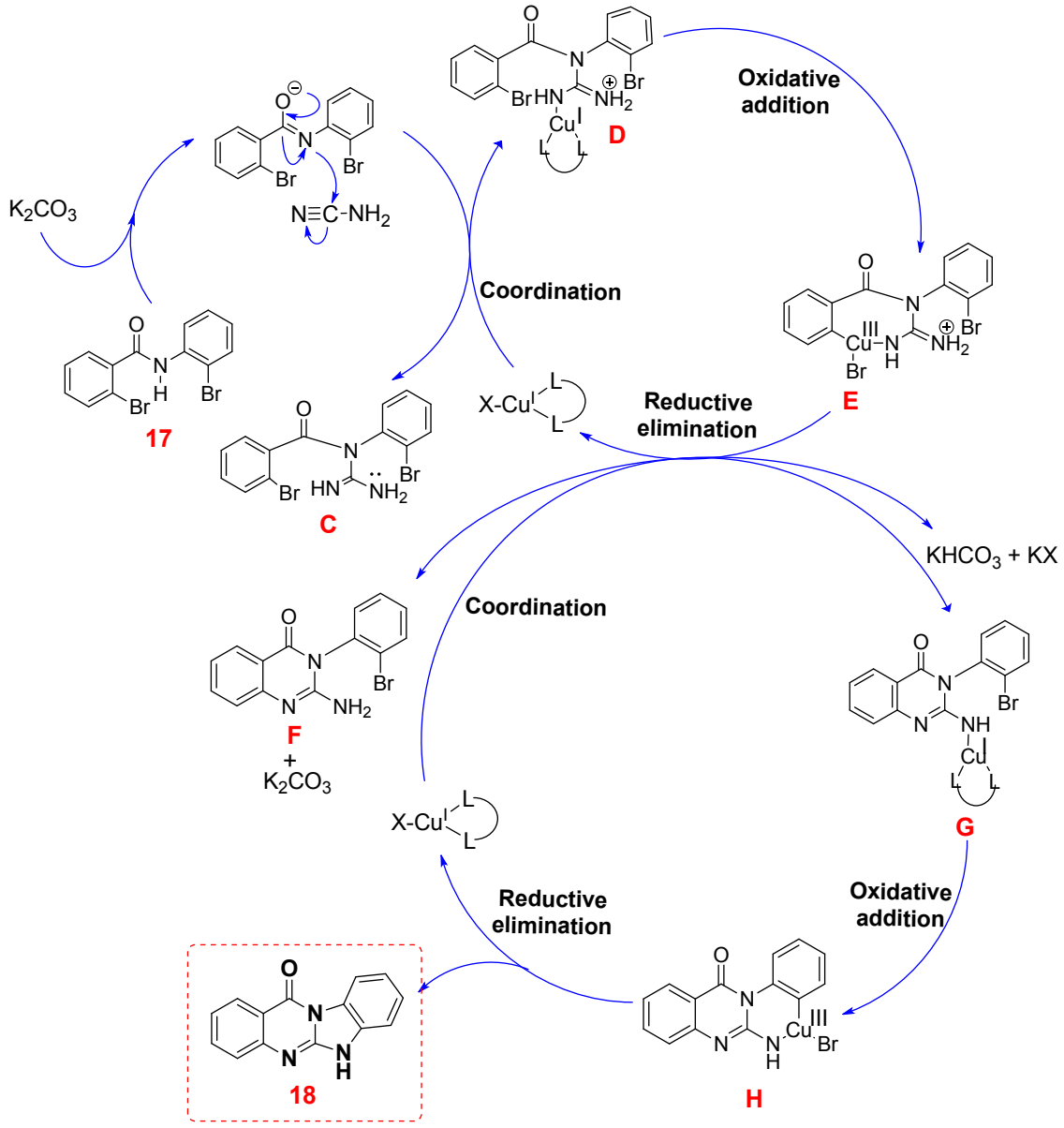
A plausible mechanism for the synthesis of benz-fused azoles (**9**, **11**, **13**, **13** and **16**) and benzimidazoquinazolinones (**18**) using **L1**-Cu(I) catalytic system has been depicted in **Scheme 8** and **Scheme 9**. According to our postulations, our ligand coordinates with Cu(I) as a bi-dentate ligand through triazole ring and free hydroxy group as probable coordination sites. Ligand-coordinated Cu(I) reacts with substrate (for example amides **8** or thioamides **10** or benzamidines **12)** in presence of base (K_2CO_3) to form respective coordinated intermediate **A.** Oxidative addition converts **A** into intermediate **B** which on reductive elimination produces corresponding 2-substituted benz-fused azoles (amides **9** or thioamides **11** or benzamidines **13**) as the final product regenerating the ligand-coordinated Cu(I) (**Scheme 8**).



Scheme 8: Plausible mechanism for Cu-**L1** catalyzed synthesis of benz-fuzed azoles (**9, 11,** and **13**).

On the other hand, the synthetic route for benzimidazoquinazolinones (**18**) start from the reaction of cyanamide with substrate **17** in presence of base which affords intermediate **C**. Coordination

of **C** with Cu(I)-**L1** in presence of base produces intermediate **D** which furnishes adduct **E** through catalytic steps of oxidative addition and reductive elimination. Adduct **F** again coordinates with ligand coordinated Cu(I) in presence of base to produce intermediate **G** which at last gets converted into final product **18** through oxidative addition (*via* intermediate **H)** and reductive elimination (**Scheme 9**).



Scheme 9: Plausible mechanism for Cu-**L1** catalyzed synthesis of benzimidazoquinazolinones **18.**

CONCLUSIONS

Conclusively, we have developed glycosyl triazoles as efficient ligands for Cu-catalyzed Ullmann-type intramolecular cross-coupling to synthesize benz-fuzed azoles. Out of eight ligands (seven derived from D-glucose and one benzotriazole derivative) screened for the synthesis of 2-phenyl benzoxazole, ligands **L1**, **L2** and **L5** exhibited highest efficacy and produced excellent yields with as low as 2 mol% loading. Ligand **L1** was also employed in synthesis of a series of 2-substituted benzothiazoles, benzothiazoles and benzimidazoles in high yields by optimized reaction conditions. A tandem approach for 2-aminobenzothiazoles was also achieved in high yields with CuI-**L1** catalytic system. A tandem approach for synthesis of benzoxazole from benzamide was also achieved with **L1** in moderate yield. Ligand **L1** successfully catalyzed Cu-catalyzed tandem synthesis of benzimidazo[2,1-b]quinazolin-12(6*H*)-ones also and produced good yields. A comparative analysis of ligand structures and product yields produced by them inferred that the triazole moiety and hydroxy group of **L1** are the most probable coordination sites which acquire appropriate spatial arrangement due to suitable sugar skeleton.

EXPERIMENTAL

General

All the reactions were performed under argon atmosphere using anhydrous solvents except for those in which water was used as solvent. All the reagents and solvents used were of analytical grade. Glasswares were dried in an oven at 100 °C for one hour and cooled in a desiccator before

use. 60 F254 Silica gel pre-coated aluminum plates were used for thin layer chromatography (TLC) and spots were located either under a UV lamp (λmax = 254 nm) or by charring after 5% H_2SO_4-MeOH solution spray. ^1H and ^{13}C NMR were recorded at 500 MHz and 125 MHz, respectively. Chemical shifts given in ppm are relative to that of TMS as internal standard; *J* values are given in Hz. Mass spectra were recorded by electron spray ionization mass spectrometry (ESI-MS). IR spectra were recorded as Nujol mulls in KBr pellets. C, H, N Analyzer was used for elemental analysis and results were found to be within 0.4% of the calculated values. Single-crystal X-ray data collected on CCD-diffractometer.

General experimental procedure for the synthesis of glycosylated triazole ligands

4-Phenyl-1-(3-O-benzyl-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranos-6-yl)-1H-1,2,3 triazole **(L1):**

Glycosyl azide **3** (1.0 g, 2.98 mmol) was taken in 50 ml 1:1 mixture of dichloromethane and water. 1 Equiv. of phenyl acetylene (304 mg, 2.98 mmol, 327 µl) was added to this mixture followed by an addition of 0.3 equiv. of $CuSO_4.5H_2O$ (223 mg, 0.89 mmol) and 0.6 equiv. of sodium ascorbate (354 mg, 1.79 mmol). The resultant suspension was stirred at room temperature for 10 hours. The completion of reaction was confirmed by TLC using 5% H_2SO_4-MeOH solution spray as locating agent followed by charring. The reaction mixture was filtered through a sintered funnel and the filtrate was extracted three times with dichloromethane. The collected organic layer was given brine wash, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude compound. Purification of the crude by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (7:3) afforded pure compound **L1** in 71% yield (930 mg).

White solid, yield 71%; R_f = 0.4 (30% ethyl acetate/n-hexane); m.p. = 146-148°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.28-7.24 (m, 6H), 5.97 (d, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 13.5 Hz, 2H), 4.70-4.63 (m, 4H), 4.32-4.28 (m, 1H), 4.15 (s, 1H), 4.02 (d, *J* = 6.5 Hz, 1H), 1.42 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 137.4, 130.1, 128.7, 128.6, 128.1, 128.0, 125.3, 121.6, 112.0, 105.3, 82.5, 81.3, 80.9, 72.6, 67.3, 54.6, 26.8 and 26.3 ppm; HRMS m/z $[M+H]^+$ calculated for $C_{24}H_{27}N_3O_5Na^+$ 460.1843, found 460.1841.

General procedure for the synthesis of 2-substituted benzoxazoles (9) by intramolecular *C-O* cross coupling of *N-(*2-haloaryl) benzamides (8)

*N-(*2-bromophenyl) benzamide **8a** (500 mg, 1.81 mmol) was taken in 1.5 ml of dry DMF and ligand **L1** (2 mol%, 16 mg, 0.036 mmol), CuI (2 mol%, 7 mg 0.036 mmol) and K_2CO_3 (1.0 equiv., 250 mg, 1.81 mmol) were added to it. The mixture was heated at 120°C in a sealed vessel under argon atmosphere for 10-15 hrs. Completion of reaction was confirmed by TLC and the reaction mass was cooled to room temperature followed by evaporation of DMF under reduced pressure. Crude was purified by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (50:1) to afford pure compound **9a** (350 mg, 99%).

2-Phenylbenzo[*d*]oxazole (9a):[4a] White solid, yield 99%; R_f = 0.6 (2% ethyl acetate/*n*-hexane); m.p. = 103-104°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.24 (m, 2H), 7.79-7.76 (m, 1H), 7.58-7.55 (m, 1H), 7.52-7.49 (m, 3H), 7.35-7.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 150.8, 142.2, 131.5, 128.9, 127.7, 127.2, 125.1, 124.6, 120.1 and 110.6 ppm.

General procedure for synthesis of 2-substituted benzothiazoles (11a-i) by intramolecular *C-S* cross coupling of *N-(*2-haloaryl) benzthiamides (10a-i)

N-(2-Haloaryl) benzthiaamide **10a** (500 mg, 1.71 mmol) was taken in 1.5 ml of dry DMF and ligand **L1** (2 mol%, 15 mg, 0.034 mmol), CuI (2 mol%, 7 mg, 0.034 mmol) and K_2CO_3 (1 equiv., 236 mg, 1.71 mmol) were added to it. The mixture was heated at 120°C in a sealed vessel under argon atmosphere for 10 hrs. Completion of reaction was confirmed by TLC and the reaction mass was cooled to room temperature followed by evaporation of DMF under reduced pressure. Crude was purified by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (30:1) to afford pure compound **11a** (359 mg, >99%).

2-Phenylbenzo[*d*]thiazole (11a)[20]: White solid, yield >99%; R_f = 0.5 (2% ethyl acetate/n-hexane); m.p. = 100-104°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-8.08 (m, 3H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.50-7.47 (m, 4H), 7.37 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 154.2, 135.1, 133.7, 131.0, 129.1, 127.6, 126.4, 125.2, 123.3 and 121.7 ppm.

General procedure for synthesis of 2-substituted benzimidazoles (13a-h) by intramolecular *C-N* cross coupling of *N-(*2-haloaryl) benzamidines (12a-h)

N-(2-Haloaryl) benzamidine **12a** (500 mg, 1.81 mmol) was taken in minimum 1.5 ml of dry DMF and ligand **L1** (2 mol%, 16 mg, 0.036 mmol), CuI (2 mol%, 7 mg, 0.036 mmol) and K_2CO_3 (1 equiv., 251 mg, 1.81 mmol) were added to it. The mixture was heated at 120°C in a sealed vessel under argon atmosphere for 15 hrs. Completion of reaction was confirmed by TLC and the reaction mass was cooled to room temperature followed by evaporation of DMF under reduced pressure. Crude was purified by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (7:1) to afford pure compound **13a** (346 mg, 98%).

2-Phenyl-1*H*-benzo[*d*]imidazole (13a)[21]: White solid, yield 98%; R_f = 0.5 (30% ethyl acetate/*n*-hexane); m.p. = 292-294°C; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 12.7 (s, 1H), 8.19 (d, *J* =

7.5 Hz, 2H), 7.59-7.42 (m, 5H), 7.19 (t, *J* = 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$+DMSO-d_6): δ 151.9, 135.7, 130.5, 129.9, 128.9, 126.8, 122.4, 118.9 and 111.7 ppm.

General procedure for synthesis of *N*-aryl-2-aminobenzothiazoles (16a-j) by tandem reaction of aryl isothiocyanate (14) and 2-haloaniline (15)

Phenyl isothiocyanate **14a** (200 mg, 1.48 mmol, 177 µl) and 2-iodoaniline **15a** (1 equiv., 324 mg, 1.48 mmol) were taken in 1.5 ml of dry DMF and ligand **L1** (5 mol%, 32 mg, 0.074 mmol), CuI (5 mol%, 14 mg, 0.074 mg) and K_2CO_3 (1.0 equiv., 204 mg, 1.48 mmol) were added to it. The mixture was heated at 120°C in a sealed vessel under argon atmosphere for 20 hrs. Completion of reaction was confirmed by TLC and the reaction mass was cooled to room temperature followed by evaporation of DMF under reduced pressure. Crude was purified by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (6:1) to afford pure compound **16a** (328 mg, 98%)

***N*-Phenylbenzo[*d*]thiazol-2-amine (16a)**[22]: White solid, yield 98%; R_f = 0.7 (30% ethyl acetate/*n*-hexane); m.p. = 156-158°C; ^{1}H NMR (500 MHz, DMSO d_6+CD_3OD): δ 10.34 (s, 1H), 7.71-7.69 (m, 3H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.30-7.24 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.97-6.94 (m, 1H); ^{13}C NMR (125 MHz, DMSO d_6+CD_3OD): δ 162.3, 152.5, 141.0, 140.9, 130.4, 129.4, 126.3, 122.7, 122.6, 121.3 119.6 and 118.2 ppm.

General procedure for tandem synthesis of benzimidazo[2,1-b]quinazolin-12(6*H*)-ones (18a,b)

Compound **17a** (150 mg, 0.42 mmol) was dissolved in 1.5 ml dry DMF and cyanamide (2 equiv., 35 mg, 0.84 mmol), ligand **L1** (10 mol%, 18 mg, 0.04 mmol), CuI (10 mol%, 8 mg, 0.04 mmol) and K_2CO_3 (2 equiv., 116 mg, 0.84 mmol) were added to it. The mixture was heated at 120°C in

a sealed vessel under argon atmosphere for 20 hours. Completion of reaction was confirmed by TLC and the reaction mass was cooled to room temperature followed by evaporation of DMF under reduced pressure. Crude was purified by silica gel (230-400 mesh) column chromatography using gradient mixtures of *n*-hexane/ethylacetate (3:2) to afford pure compound **18a** (100 mg, 76%).

Benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (18a)[19]**:** White solid, yield 76%; R_f = 0.4 (80% ethyl acetate/*n*-hexane); m.p. >300° C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.42 (s, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.51-7.40 (m, 3H), 7.33-7.26 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 174.5, 160.0, 159.0, 147.0, 134.6, 128.1, 127.1, 126.7, 125.7, 122.1, 121.0, 114.9 and 113.0 ppm.

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Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all compounds and X-ray crystallographic data for **L1**, **13d** and **16e** (CIF) are given. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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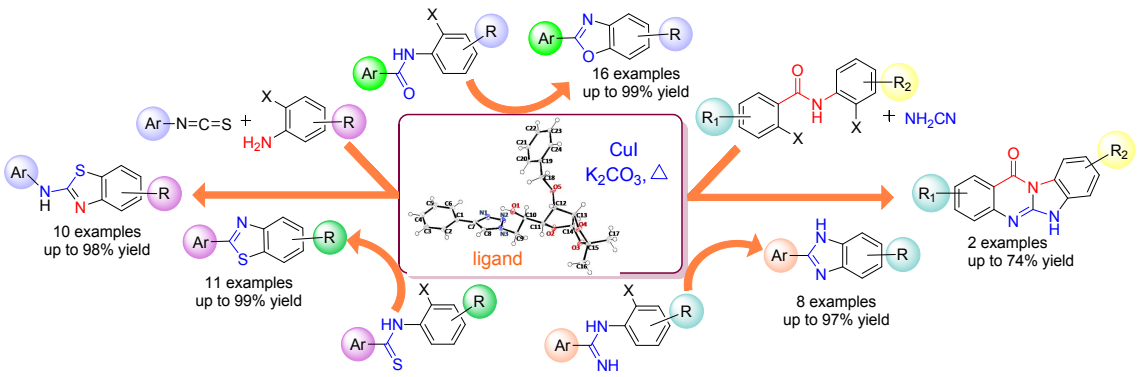

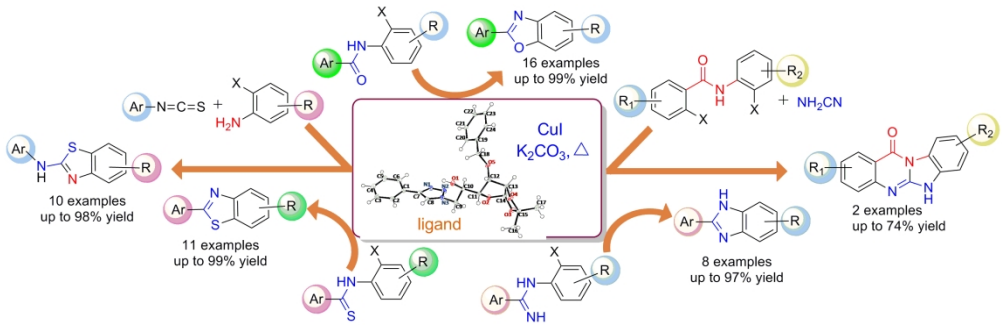

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