Study of Copper(II) Based Oxidative C–H Functionalization/C–C/N–N/C–N/C–O Bonds Formation for Synthesis of Substituted Azoles

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated

To

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati
July 2012

Murali Mohan Guru

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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CERTIFICATE

This is to certify that Mr. Murali Mohan Guru has been working under my supervision since February 2010. I am forwarding his thesis entitled "*Study of Copper(II) Based Oxidative C–H Functionalization/C–C/N–N/C–N/C–O Bonds Formation for Synthesis of Substituted Azoles*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
July 2012

Prof. Tharmalingam Punniyamurthy
Supervisor

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Murali Mohan Guru

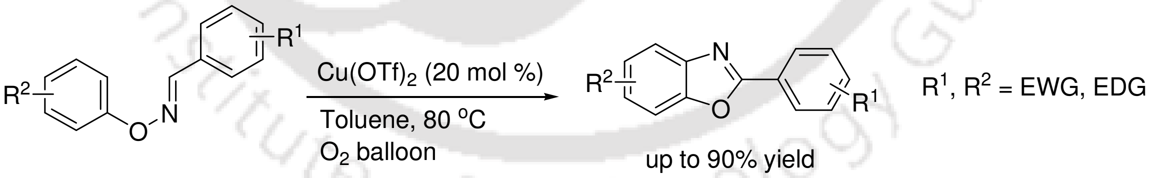
Abstract

The thesis contains four chapters. The first two chapters focus on the copper(II) based synthesis of 2-arylbenzoxazoles and 2-aryl-*N*-benzylbenzimidazoles from bisaryloxime ethers and *N*-benzylbisarylhydrazones via C–H functionalization/C–N/C–O bonds formation. The last two chapters deal with the copper(II)-catalyzed aerobic oxidative synthesis of substituted 1,2,3- and 1,2,4-triazoles from bisarylhydrazones via C–H functionalization/C–C/N–N/C–N bonds formation.

1. Synthesis of 2-Arylbenzoxazoles from Bisaryloxime Ethers via C–H Functionalization/C–N/C–O Bonds Formation

Benzoxazoles are an important class of heterocycles that are encountered in a number of biologically active natural products and medicinally significant compounds. This chapter describes an unprecedented copper(II)-catalyzed conversion of bisaryloxime ethers to 2-arylbenzoxazoles in presence of molecular oxygen at 80 °C under ligand-free condition (Scheme 1). This process involves a cascade C–H functionalization/C–N/C–O bonds formation. The substrates bearing electron-withdrawing or electron-donating groups in the arenes proceeded reaction smoothly to provide the corresponding benzoxazoles in moderate to high yields.

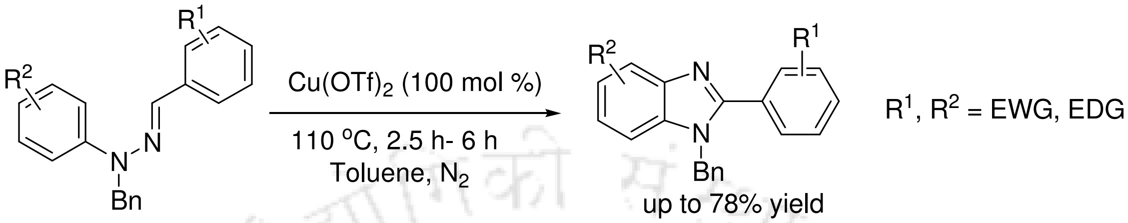
Scheme 1. Synthesis of 2-Arylbenzoxazoles



2. Synthesis of 2-Aryl-*N*-benzylbenzimidazoles from *N*-Benzyl Bisarylhydrazones via C–H Functionalization/C–N Bond Formation

Benzimidazoles are the privileged structural units because of their applications in pharmaceutical and medicinal fields. In this chapter, study of copper(II)-mediated synthesis of 2-aryl-*N*-benzylbenzimidazoles has been described from *N*-benzyl bisarylhydrazones via C–H functionalization/C–N bond formation in toluene solvent at 110 °C under inert atmosphere (Scheme 2). This protocol could be explored to large synthetic scope with readily available substrates.

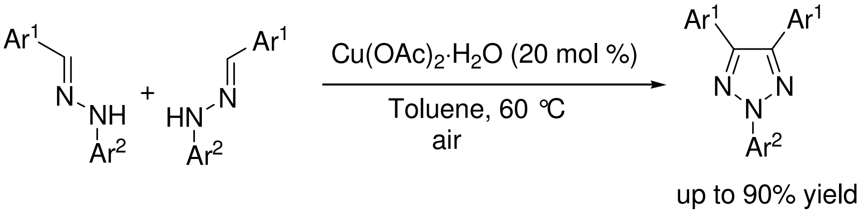
Scheme 2. Synthesis of 2-Aryl-*N*-benzylbenzimidazoles



3. Aerobic Oxidative Synthesis of Substituted 1,2,3-Triazoles from Bisarylhydrazones via C–H Functionalization/C–C/N–N Bonds Formation

1,2,3-Triazoles are important class of heterocycles because of their pharmacological properties like antifungal, antiviral and anticoccidiostatic activities. Moreover, 1,2,3-triazoles are common in pharmaceutical targets and biologically active substances like chemotherapeutic and cardiovascular agents. The present method uses the readily accessible bisarylhydrazones as substrate and offers a new route for the regioselective synthesis of 2,4,5-triaryl-1,2,3-triazoles via a cascade copper(II)-catalyzed aerobic oxidative C–H functionalization/C–C/N–N bonds formation (Scheme 3). The reaction could be performed in presence of aerial oxygen as a readily available oxidant.

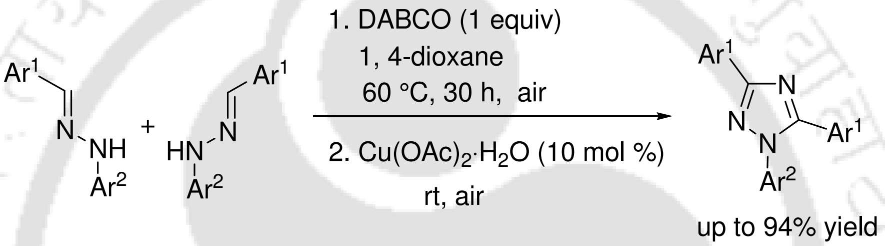
Scheme 3. Aerobic Oxidative Synthesis of Substituted 1,2,3-Triazoles



4. Aerobic Oxidative Synthesis of Substituted 1,2,4-Triazoles from Bisarylhydrazones via C–H Functionalization/C–N Bond Formation

1,2,4-Triazoles have received considerable attention in biological and pharmaceutical fields as they display potent biological properties such as antibacterial and antifungal activities. A regioselective path for the synthesis of 1,3,5-triaryl-1,2,4-triazoles via a cascade copper(II)-catalyzed aerobic oxidative C–H functionalization/C–N bond formation has been described in this chapter (Scheme 4). The reactive intermediates have been isolated to sketch out the mechanism.

Scheme 4. Aerobic Oxidative Synthesis of Substituted 1,2,4-Triazoles



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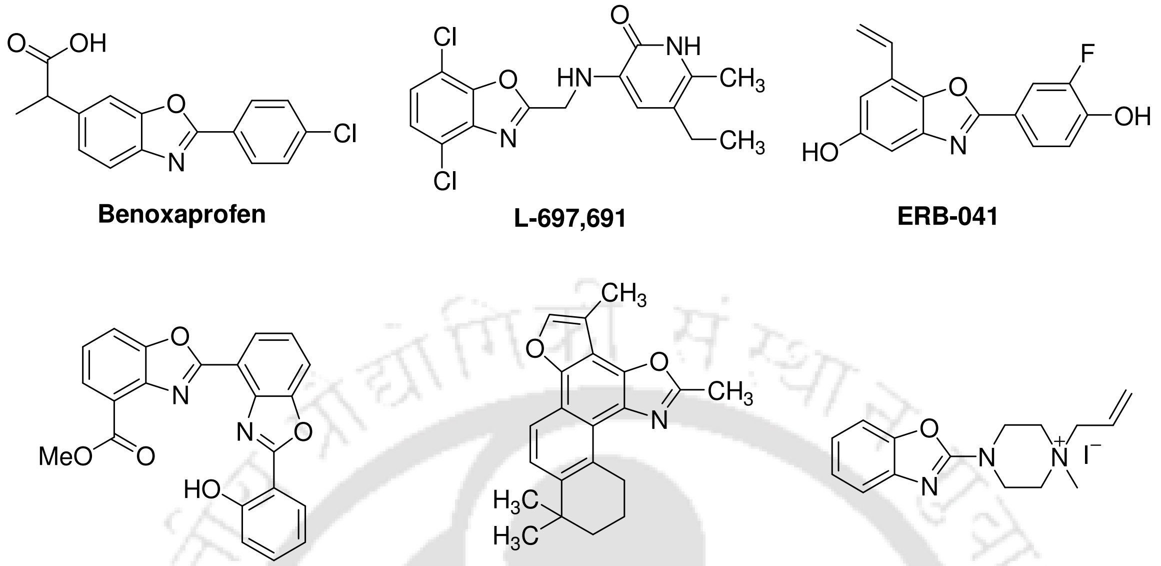
Chapter I

Synthesis of 2-Arylbenzoxazoles from Bisaryloxime Ethers via C–H Functionalization/C–N/C–O Bonds Formation

In recent years, heterocyclic compounds have gained considerable attention as an important skeleton in numerous natural products[1] as well as in pharmaceutical[2] and material sciences.[3] As a consequence, formidable challenges have been committed for constructions of heterocyclic frameworks through carbon-carbon and carbon-heteroatom bonds formation.[4-6] The most notable aspect in this context is the functionalization of traditionally inert C–H bonds, a powerful tool in organic synthesis, improving the overall efficiency of the desired transformation. Inspired by direct C–H bond functionalization, transition-metal catalysis have culminated in pioneering discoveries over the past two decades.[7] The reactions are usually aided by the directing groups that can coordinate to the catalyst to direct *ortho* functionalization *via* a five- or six-membered metallocycle. However, the inherently high bond dissociation energies of C–H bonds often require harsh reaction conditions for the goal, leading to limited substrate scope and wide functional group incompatibilities. To overcome these drawbacks, it has been a central issue to develop mild methods for activation of ubiquitous C–H bonds in organic transformations. In this chapter, a new copper(II)-catalyzed rearrangement of bisaryloxime ethers to 2-arylbenzoxazoles in presence of molecular oxygen under mild conditions has been demonstrated. This process involves a cascade C–H functionalization and C–N/C–O bonds formation.

Benzoxazoles are an important class of heterocycles that are encountered in a number of medicinally significant compounds and biologically active natural products (Figure 1). Recent medicinal chemistry applications of benzoxazole derivatives include the poly(ADP-ribose)polymerase (PARP) inhibitors,[8a] HIV reverse transcriptase inhibitor L-697,661,[8b] estrogen receptor-b agonist ERB-041,[8c] anticancer agent NSC-693638,[8d] 5-HT3 receptor agonist CP 2289,[8e] orexin-1 receptor antagonist SB-334867[8f] and potent anti-inflammatory benoxaprofen.[8g] In addition, a particular class of heterocycle, 2-arylbenzoxazoles could be used as upregulators of utrophin production for the treatment of Duchenne Muscular Dystrophy (DMD).[8h] Benzoxazole heterocore could also be found in a range of cytotoxic natural products such as AJI9561,[9a] salvianen[9b] and UK-1.[9c]

Because of their fluorescent properties, they have wide applications in photoluminescent dyes,[10a] electronic devices[10b] and sensors for metals.[10c]



Benoxaprofen **L-697,691** **ERB-041**

UK-1 **Salvianen** **CP 2289**

Figure 1. Examples of some biologically active and medicinally significant compounds

1.1 Strategies for Synthesis of 2-Arylbenzoxazoles

1.1.1 Classical Methods

The common classical methods used for the construction of the benzoxazole framework start from 2-aminophenols (Figure 2a). Condensation of 2-aminophenols with aromatic carboxylic acid derivatives could generate 2-arylbenzoxazoles catalyzed by strong acid, such as polyphosphoric acid[11] or *p*-toluensulfonic acid.[12] Another approach involves the condensation of aromatic aldehydes with 2-aminophenols followed by oxidative cyclization in presence of stoichiometric amount of oxidant.[13] However, often they are limited due to non-availability of suitably substituted starting precursors and sometimes, the requirement of harsh reaction conditions, such as an involvement of strong acid in combination with elevated temperature. To overcome these limitations, considerable attentions have been focused to develop alternative paths for the synthesis of 2-arylbenzoxazoles.

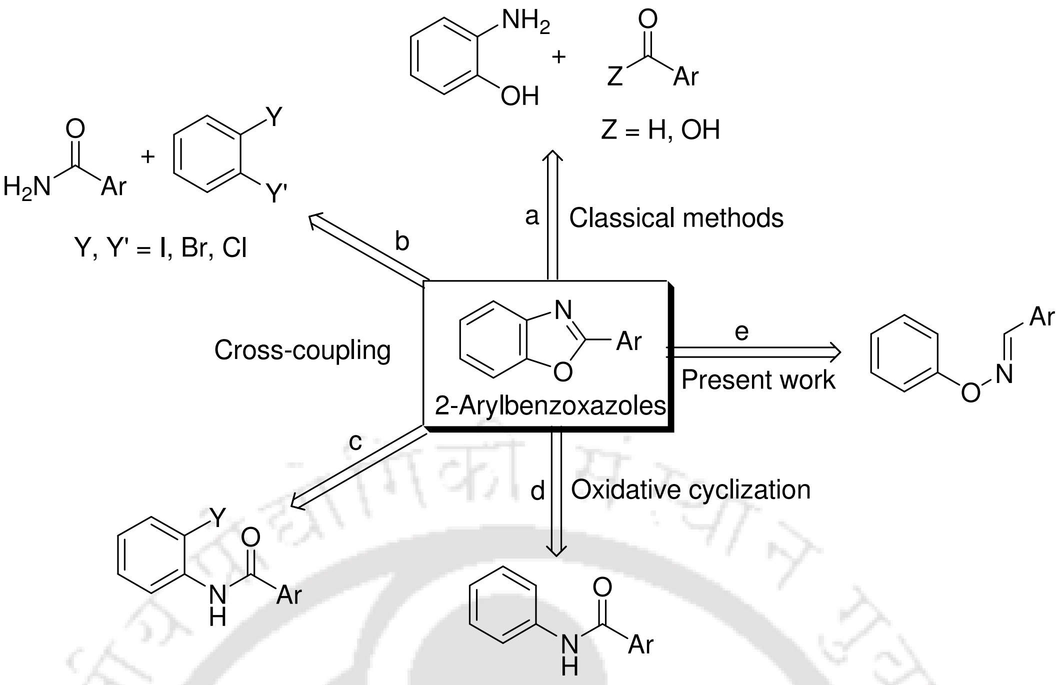


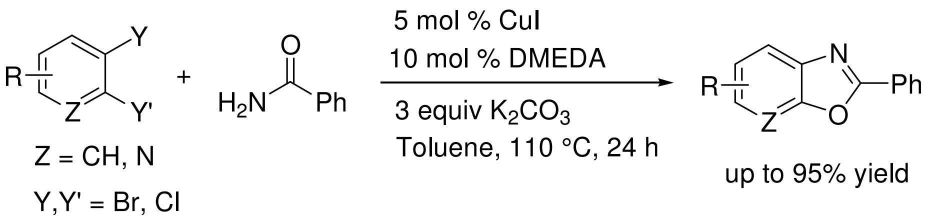
Figure 2. Different approaches for synthesis of 2-arylbenzoxazoles: (a) Classical methods with 2-aminophenols, (b,c) metal-catalyzed cross-coupling reactions and (d,e) C–H functionalization

1.1.2 Cross-Coupling Reactions

Transition-metal-catalyzed C–O cross-coupling is a valuable tool for organic transformations.[14] Some of the drawbacks of classical methods have recently been overcome using metal-catalyzed cross-coupling reactions that allow the construction of the target heterocycles under relatively milder conditions.

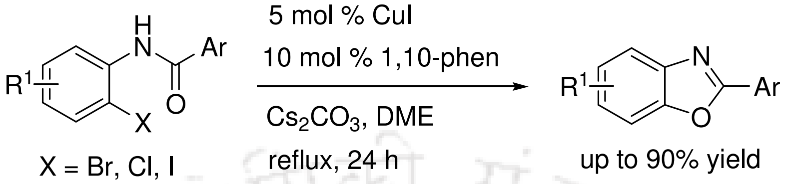
As for example, copper-catalyzed intermolecular domino C–N/C–O cross-coupling reaction has been incorporated for synthesis of 2-arylbenzoxazoles from 1,2-dihaloarene and primary amides (Figure 2b). Catalytic amount of CuI in combination with *N*,*N'*-dimethylethylenediamine could provide target benzoxazoles in good yields (Scheme 1).[15a]

Scheme 1. Copper-Catalyzed Domino Cross-Coupling



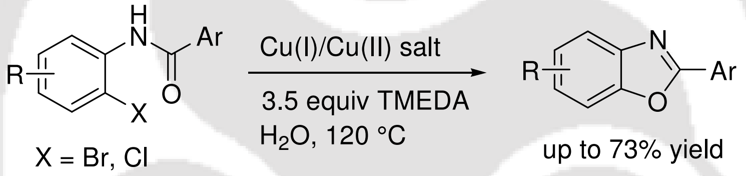
In later stage, copper-catalyzed intramolecular C–O cross-coupling reaction of *o*-halobenzanilides (Figure 2c) has been developed using ligand and base under reflux condition (Scheme 2).[15b-c]

Scheme 2. Copper-Catalyzed Intramolecular Cross-Coupling



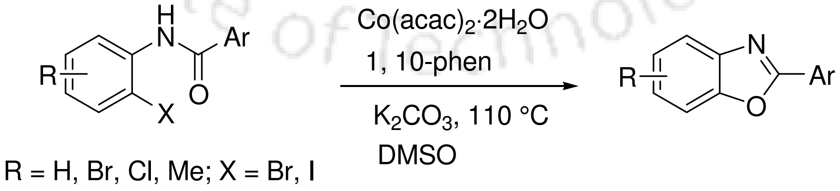
The synthesis of 2-arylbenzoxazoles has also been achieved in water through an intramolecular *O*-arylation of *o*-halobenzanilides in presence of copper catalysts (Scheme 3).[15d]

Scheme 3. Copper-Catalyzed Synthesis of Benzoxazoles in Water



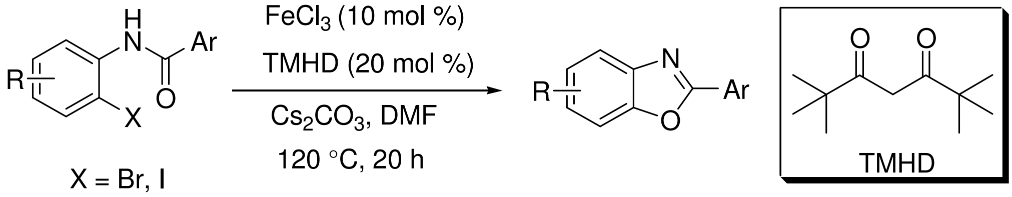
Other metal-salts have also been used for intramolecular cross-coupling of 2-haloarylanilides. In our laboratory, we have developed an efficient cobalt(II)-catalyzed intramolecular C–O cross-coupling reaction for synthesis of 2-arylbenzoxazoles in presence of K_2CO_3 at moderate temperature (Scheme 4).[16]

Scheme 4. Cobalt-Catalyzed Intramolecular Cross-Coupling of 2-Haloarylanilides



Iron-catalyzed intramolecular *O*-arylation of 2-haloanilides has also been presented for synthesis of benzoxazole derivatives (Scheme 5).[17] This cyclization involves the use of $FeCl_3$ and 2,2,6,6-tetramethyl-3,5 heptanedione (TMHD) as the catalytic system.

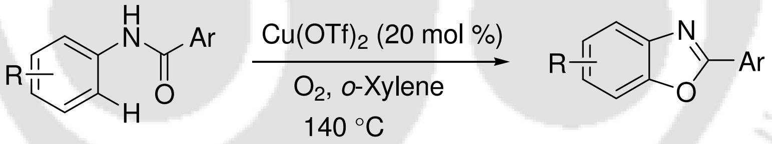
Scheme 5. Iron-Catalyzed Intramolecular *O*-Arylation of 2-Haloanilides



1.1.3 C–H functionalization Reactions

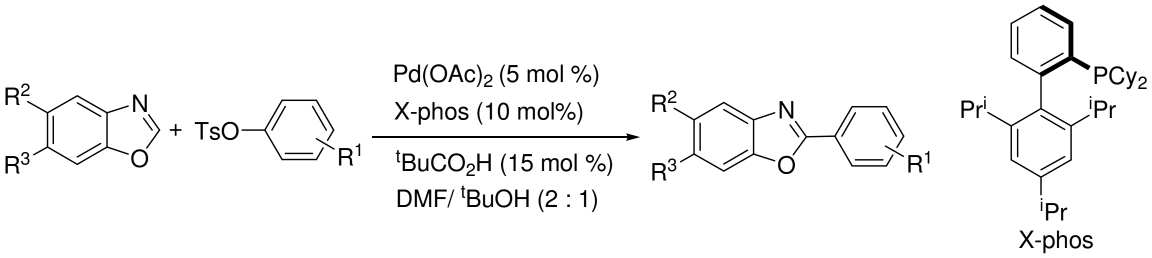
Transition-metal-catalyzed C–H functionalization is now considered as a pioneering strategy for synthesis of substituted benzoxazoles. Copper catalysts are particularly useful for the direct C–H functionalization reactions because of low cost and low toxicity.[6a,18] Recently, a copper(II)-catalyzed intramolecular oxidative C–H functionalization/C–O bond formation of benzanilides has been developed for the synthesis of 2-arylbenzoxazoles (Figure 2d). The protocol shows high functional group tolerance in *o*-xylene solvent at relatively high temperature under molecular oxygen (Scheme 6).[18]

Scheme 6. Copper-Catalyzed C–H Functionalization of Arylanilides



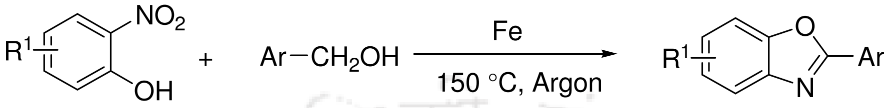
Although palladium-salts are very expensive, it has a crucial role for C–H functionalization reactions. In presence of catalytic amount of palladium(II)-salt and ligand, arylation of heteroarenes has been achieved through direct C–H bond functionalization using tosylates as electrofiles (Scheme 7).[19]

Scheme 7. Palladium-Catalyzed C–H Functionalization of Heteroarenes



Iron-salts have also been introduced for convenient synthesis of 2-arylbenzoxazoles through C–H bond activation. Benzylic alcohols and *o*-nitrophenols in presence of iron-catalyst could form the target heterocycles *via* cascade alcoholic oxidation, nitro reduction, condensation and dehydrogenation (Scheme 8).[20]

Scheme 8. Iron-Catalyzed Synthesis of 2-Arylbenzoxazoles



1.2 Present Study

In this contribution, we present a detailed study of the scope of the synthesis of 2-arylbenzoxazoles from bisaryloxime ethers by copper(II)-catalyzed intramolecular C–H functionalization/C–N/C–O bonds formation. The synthesis of bisaryloxime ether **D** is shown in Scheme 9.[21] The copper-mediated C–O cross-coupling of *N*-hydroxyphthalimide **A** and arylboronic acid provides *N*-aryloxyphthalimide **B** that could be treated with hydrazine to give aryloxyamine **C**. The target bisaryloxime ether **D** could be obtained by the condensation of **C** with aryl aldehydes in the presence of a catalytic amount of acetic acid under ambient conditions.

Scheme 9. Synthesis of Bisaryloxime Ethers

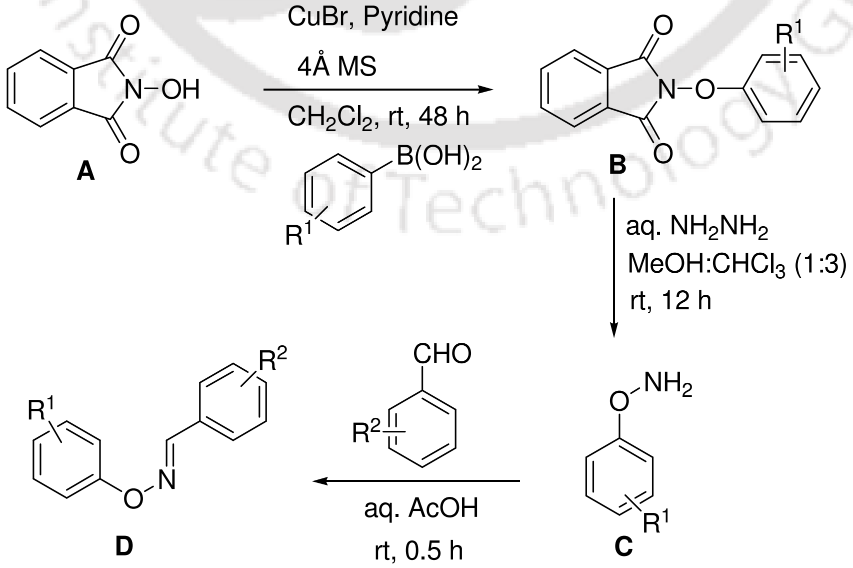
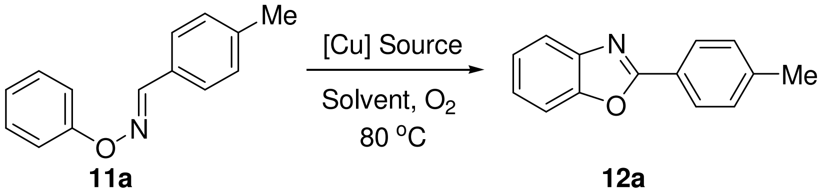


Table 1. Screening of Reaction Conditions[a]



Entry	[Cu] Source	Solvent	Time (h)	Yield (%)[b]
1	**$Cu(OTf)_2$**	**Toluene**	**3.0**	**90**[c]
2	$Cu(OTf)_2$	Xylene	4.0	88[c]
3	$Cu(OTf)_2$	DMSO	0.5	40[d]
4	$Cu(OTf)_2$	DMF	1.5	45[e]
5	$Cu(OTf)_2$	1,4-Dioxane	12	35[f]
6	$Cu(OTf)_2$	THF	12	37[f]
7	$Cu(OAc)_2 \cdot H_2O$	Toluene	24	30[g]
8	$Cu(SO_4)_2 \cdot 5H_2O$	Toluene	24	35[h]
9[i]	$Cu(OTf)_2$	Toluene	8	80[c]
10[j]	$Cu(OTf)_2$	Toluene	4	55[c]
11[k]	$Cu(OTf)_2$	Toluene	3	74[h]
12	-	Toluene	5	n.d.

[a] Reaction conditions: Bisaryloxime ether **1a** (0.5 mmol) and [Cu] (20 mol %) were stirred in solvent (2 mL) at 80 °C under oxygen balloon. [b] Isolated yield. 4-Methylbenzonitrile and phenol ([c]5%, [d]50%, [e]43%, [f]35%, [g]16% and [h]12%) were obtained. [i] $Cu(OTf)_2$ (10 mol %) used. [j] Temperature = 70 °C. [k] Under air. n.d. = not detected.

Optimization of Reaction Conditions. The rearrangement of the aryloxime ethers was optimized using bisaryloxime ether **11a** as a model substrate (Table 1). To our delight, the substrate readily underwent conversion to give 2-arylbenzoxazole **12a** along with a trace of 4-methylbenzonitrile and phenol in presence of 20 mol % copper(II)-salts under oxygen atmosphere. Screening of copper sources revealed $Cu(OTf)_2$ as the most effective catalyst, while other copper sources afforded inferior results (Entries 7-8). With $Cu(OTf)_2$ as the catalyst, we went on to screen other reaction parameters. The reaction was found to proceed more selectively in non-polar solvents than in polar solvents, and toluene was found to be the solvent of choice (Entries 1-6). The reaction in xylene required slightly longer reaction time to afford similar results (Entry 2). The effect of temperature was studied, and 80 °C afforded the best results (Entries 1 and 10). Lower catalyst loading (10 mol %) led to a slower rate of the target reaction along with increase in the yield of the byproducts (Entry 9). A control experiment confirmed that in the absence of the copper catalyst, for 5 h, a trace of nitrile and phenol were obtained along with starting material **11a** (Entry 12).

Synthesis of 2-Arylbenzoxazoles. With the optimized conditions, the scope of the reaction with various bisaryloxime ethers **11b-z** was next explored (Table 2). Monosubstituted bisaryloxime ethers **11b-h** having 2-Br, 2-OMe, 3-Br, 4-Br, 4-Cl, 4-F and 4-OMe groups on the aryl ring proceeded cyclization to give the corresponding 2-arylbenzoxazoles **12b-h** in 57-90% yields. Bisphenyloxime ether **11i** having unsubstituted arenes could cyclize to give the target heterocycle **12i** in 80% yield. Likewise, the cyclization of the disubstituted bisaryloxime ethers **11k-r** with 4-Br, 4-Cl, 4-OMe, 4-Me and 4-vinyl groups on the aryl rings could be accomplished to provide the desired substituted 2-arylbenzoxazoles **12j-q** in 38-88% yields. In acetonitrile solvent, the compound **12q** gave single crystals and it was analyzed by single crystal X-ray analysis (Figure 3). Furthermore, 2,4,5-trimethoxy substituted bisaryloxime ether **11s** underwent reaction to give the corresponding benzoxazole **12r** in 2 h with 80% yield. In addition, aryl furanyloxime ethers **11t-u**, aryl thiophenyloxime ether **11v**, aryl naphthyloxime ethers **11w-x**, aryl 8-methoxyquinolinyloxime ether **11y** and aryl pyrenyloxime ether **11z** proceeded reaction to give the substituted benzoxazoles **12s-y** in <4.0 h with 41-85% yields. In contrast, bisaryloxime ether **11j** having 4-NO_2 group showed no desired cyclization giving a 1:1 mixture of 4-nitrophenol and benzonitrile in quantitative yields due to cleavage of N–O bond. Similar results were obtained with alkyl aryloxime ether **13** and allyl aryloxime ether **14** affording a 1:1 mixture of the respective phenol and nitrile in quantitative yields (Scheme 10).

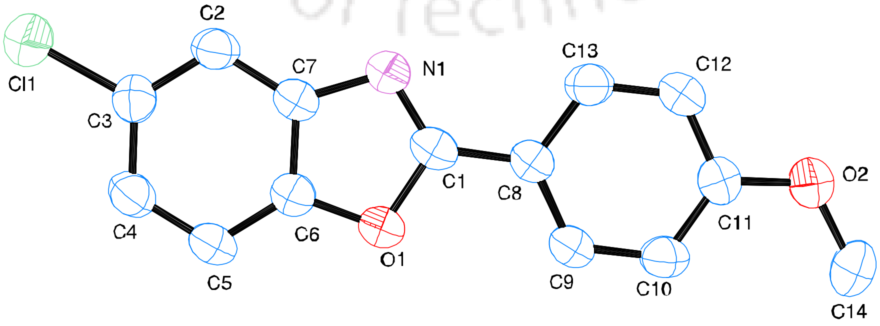
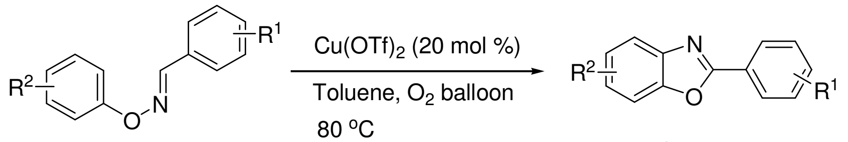


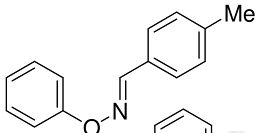
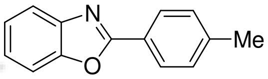
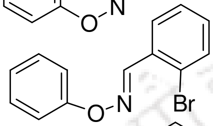
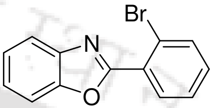
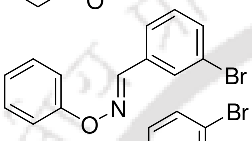
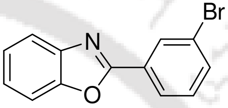
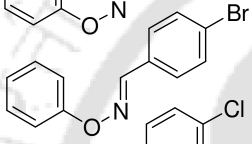
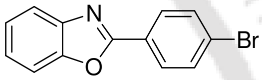
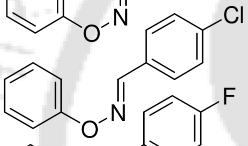
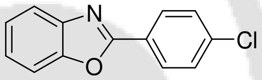
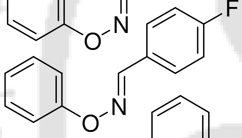
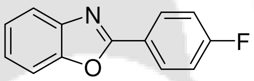
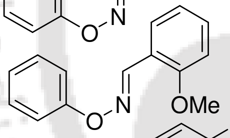
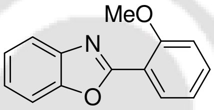
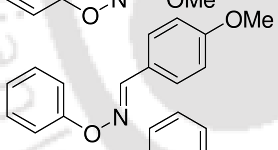
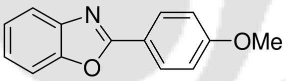
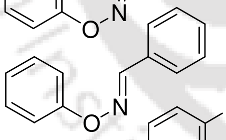
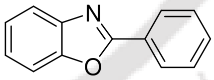
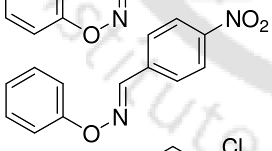
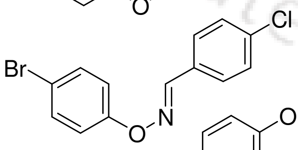
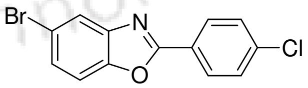
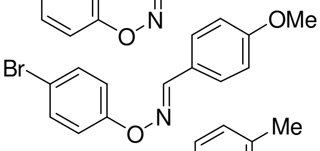
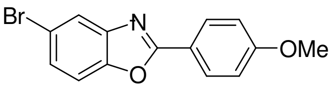
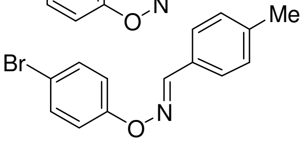
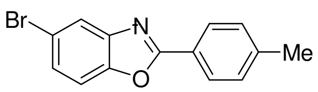
Figure 3. ORTEP diagram of the single-crystal X-ray structure of 5-chloro-2-(4-methoxyphenyl)benzo[*d*]oxazole **12q.** H-Atoms have been omitted for clarity.

Table 2. Scope of Copper(II)-Catalyzed Cyclization of Bisaryloxime Ethers[a]



11a-z **12a-y**

R^1, R^2 = EWG, EDG

Entry	Substrate		Time (h)	Product		Yield(%)[b]
1		**11a**	3.0		**12a**	90
2		**11b**	1.0		**12b**	60
3		**11c**	3.0		**12c**	83
4		**11d**	3.0		**12d**	81
5		**11e**	3.5		**12e**	82
6		**11f**	1.0		**12f**	57
7		**11g**	1.0		**12g**	67
8		**11h**	3.5		**12h**	85
9		**11i**	3.0		**12i**	80
10		**11j**	2.5	n.d.		-
11		**11k**	1.5		**12j**	51
12		**11l**	1.5		**12k**	38
13		**11m**	2.0		**12l**	50

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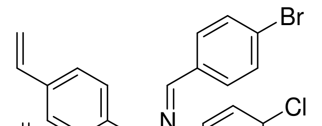
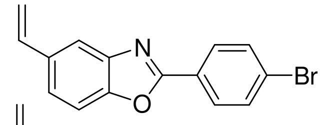
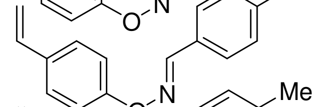
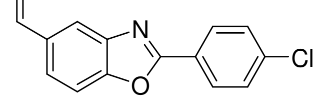
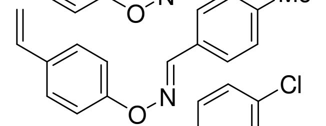
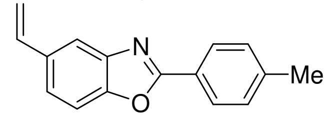
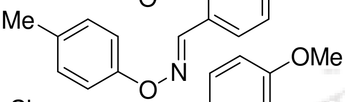
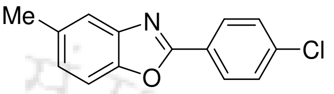
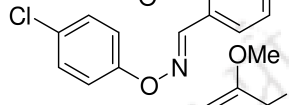
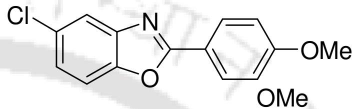
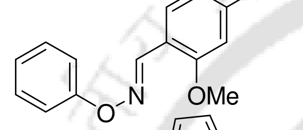
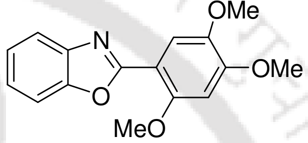
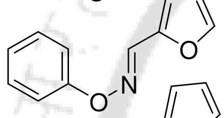
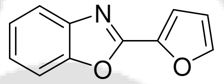
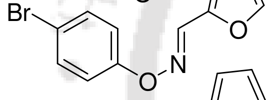
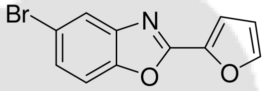
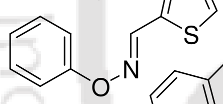
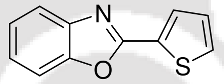
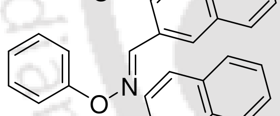
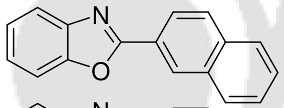
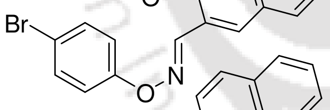
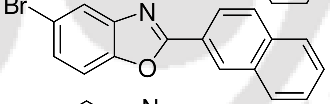
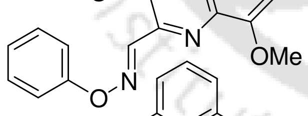
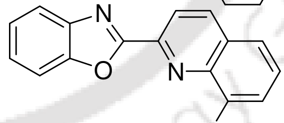
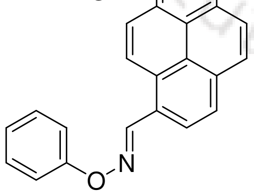
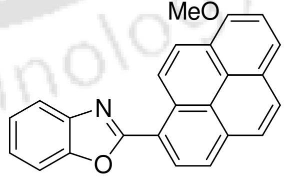
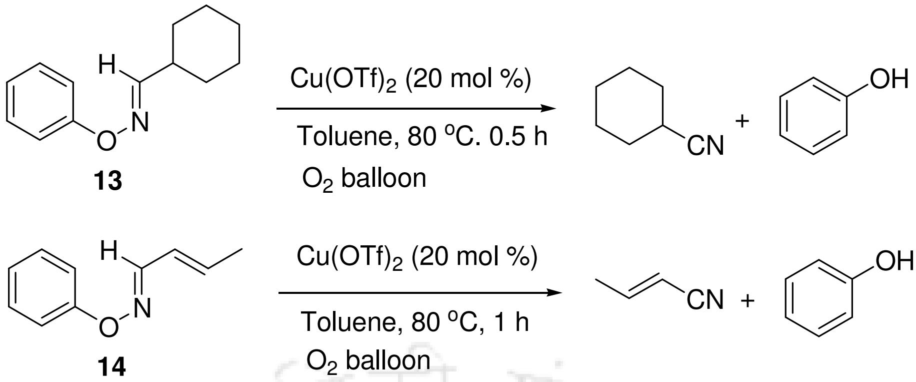
14		**11n**	3.0		**12m**	80
15		**11o**	3.0		**12n**	62
16		**11p**	3.0		**12o**	56
17		**11q**	3.0		**12p**	88
18		**11r**	1.5		**12q**	84
19		**11s**	2.0		**12r**	80
20		**11t**	3.5		**12s**	62
21		**11u**	3.0		**12t**	41
22		**11v**	4.0		**12u**	80
23		**11w**	2.5		**12v**	80
24		**11x**	2.5		**12w**	81
25		**11y**	1.5		**12x**	85
26		**11z**	2.0		**12y**	74

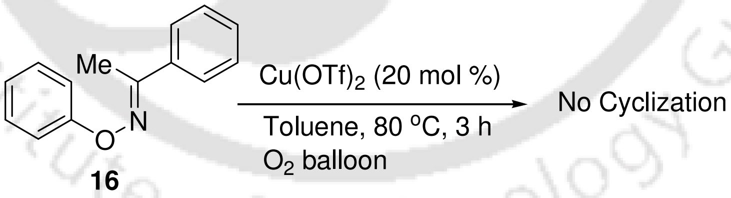
[a] Reaction conditions: Bisaryloxime ethers **11a-z** (0.5 mmol) and $Cu(OTf)_2$ (20 mol %) were stirred in toluene (2 mL) at 80 °C under O_2 balloon. [b] ~5% Phenol and nitrile were obtained. n.d. = not detected.

Scheme 10. Reaction of Alkyl Phenyloxime and Allyl Phenyloxime Ethers

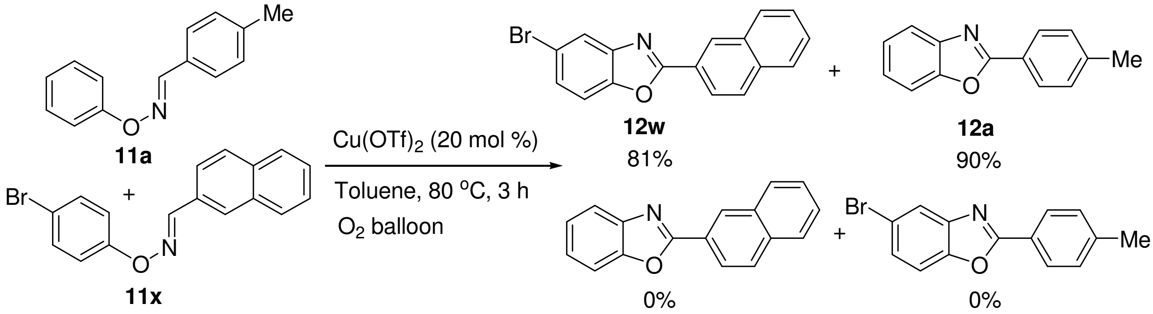


Mechanistic Studies. Bisaryloxime ether **15** having α-methyl group showed no reaction and the starting material was recovered intact, which suggests that the imine C–H is crucial for the cyclization process (Scheme 11). Furthermore, benzonitrile showed no reaction with phenol under similar conditions suggesting that the reaction does not involve an oxonium intermediate.[22] Cross-over experiment with the substrates **11a** and **11x** afforded **12a** and **12w**, respectively, as the only cyclized products (Scheme 12). This result reveals that the reaction involves an intramolecular process. Kinetic isotope studies with **11a** and **11a (D)** showed $k_H/k_D = 0.96$, which suggests that the imine C–H bond cleavage is not involved in the rate determining step (Scheme 13).

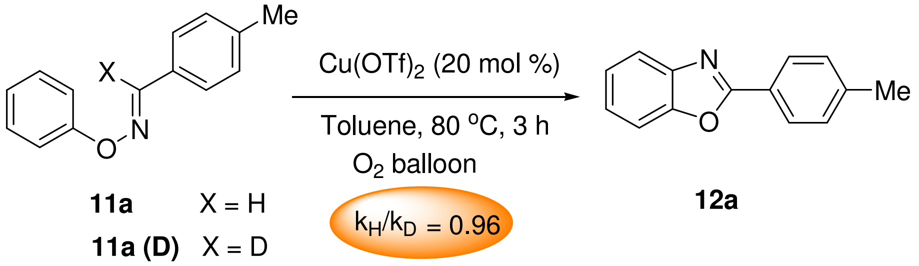
Scheme 11. Reaction of Bisaryloxime Ether without Imine C–H Bond



Scheme 12. Cross-Over Experiment for Intramolecular Cyclization



Scheme 13. Kinetic Isotope Effect



Bisaryloxime ethers having electron-withdrawing substituents showed greater reactivity compare to those bearing electron-donating groups. For example, bisaryloxime ethers **11e** and **11f** having 4-Cl and 4-F groups, respectively, showed enhanced reactivity compared to unsubstituted bisaryloxime ether **11i**, while the substrate **11h** having 4-OMe group exhibited less reactivity (Figure 4). These results suggest that the reaction of bisaryloxime ether bearing electron-withdrawing groups in the imine aryl ring is facilitated compared to that having electron-donating groups.

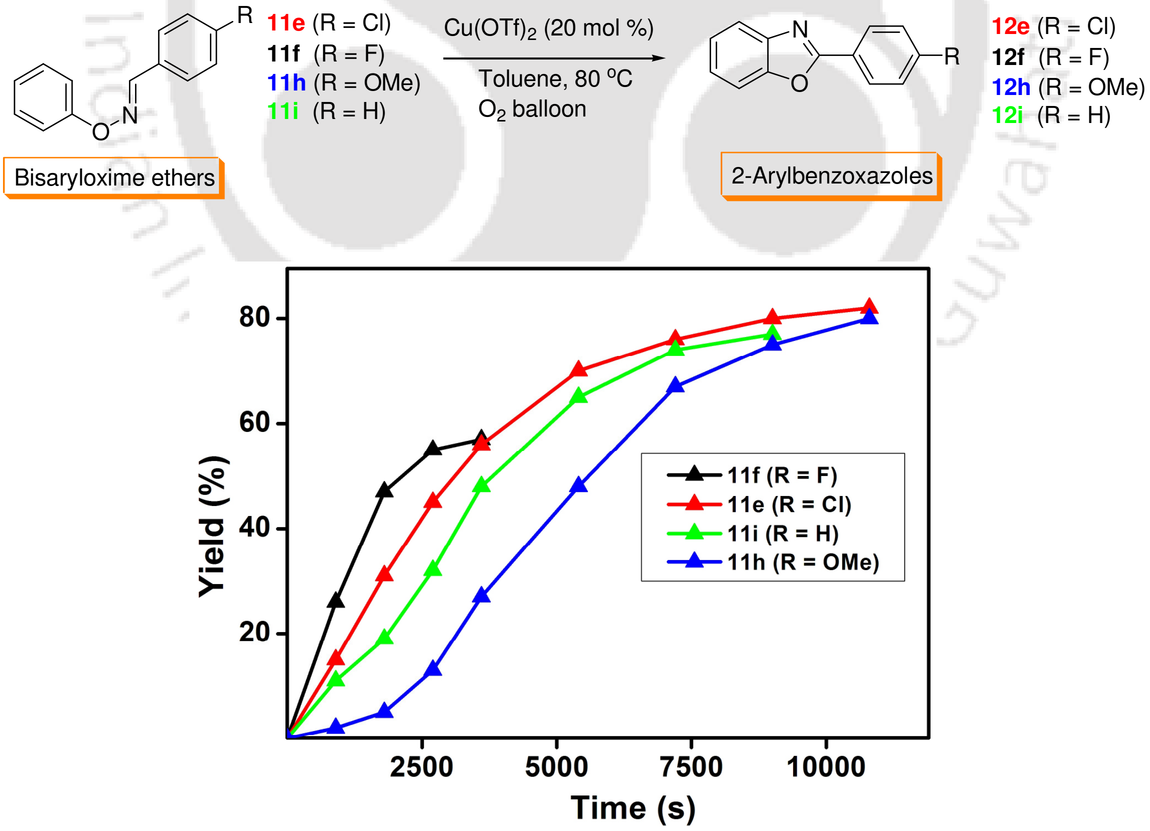
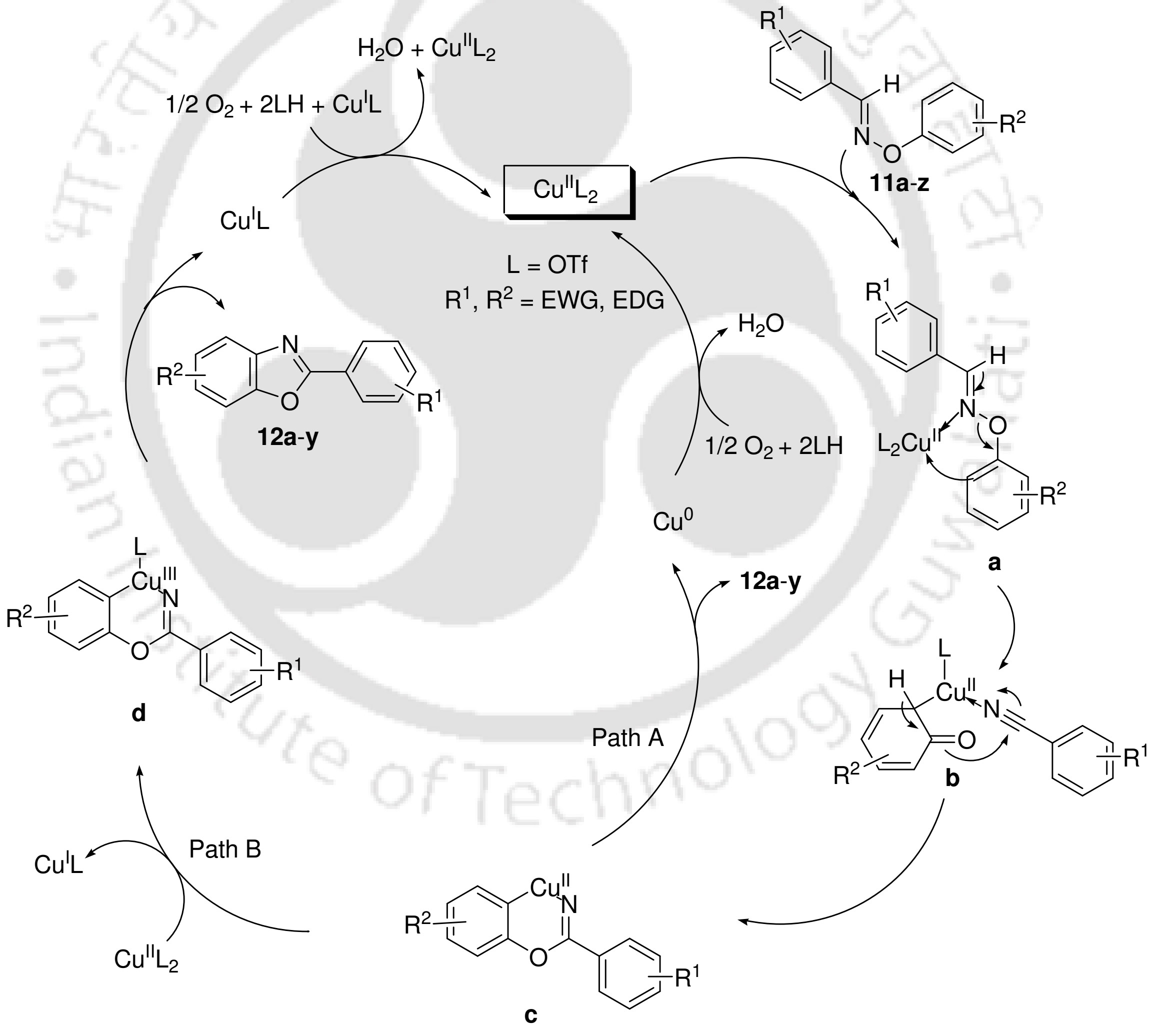


Figure 4. Study of relative rates of bisaryloxime ethers **11e**, **11f**, **11h** and **11**

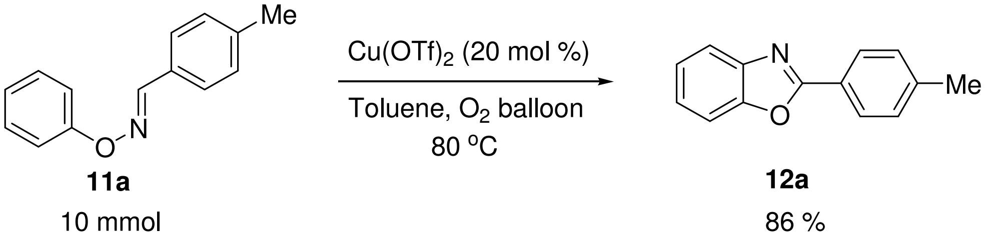
These experimental results reveal that the reaction might involve a Lewis acid catalyzed cascade rearrangement with C–H functionalization and C–N/C–O bonds formation (Scheme 14). Thus, the substrates **11a-z** may undergo chelation with Cu(OTf)$_2$ to give an intermediate **a** that could rearrange to produce **c** *via* **b**. The intermediate **c** could provide the target heterocycles **12a-y** by reductive elimination of metal (Path A).[6a] Alternatively, **c** may be oxidized by another equivalent of Cu(OTf)$_2$, forming a copper(III) intermediate **d** that may undergo reductive elimination to give the target products **12a-y** (Path B).[23] The reduced copper species may be oxidized by molecular oxygen to complete the catalytic cycle.[6a,23]

Scheme 14. Proposed Catalytic Cycle for Synthesis of 2-Arylbenzoxazoles



To reveal the practical utility of the protocol, the reaction of bisaryloxime ether **11a** was studied on a 10 mmol scale and the rearrangement readily occurred to give the desired product **12a** in 86% yield (Scheme 15).

Scheme 15. Bulk Scale Synthesis of 2-Arylbenzoxazole

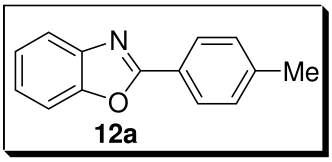


In conclusion, copper(II)-catalyzed conversion of bisaryloxime ethers to 2-arylbenzoxazoles has been achieved *via* cascade C–H functionalization/C–N/C–O bonds formation. The reactions could be performed under molecular oxygen as readily available oxidant. The observed experimental results suggest that the reactions involve an intramolecular process. The substrates having electron-withdrawing groups in the arenes have exhibited greater reactivity in comparison to those bearing electron-donating groups.

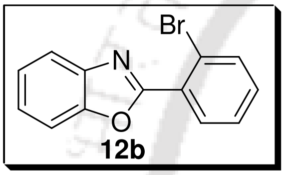
Experimental Section

General Information. Aldehydes, arylboronic acids, *N*-hydroxyphthalimide and CuCl were purchased from commercial sources and were used as received. $Cu(OTf)_2$ (98%) was purchased from Aldrich. Toluene was freshly distilled from sodium under nitrogen prior to use. Purification of reaction products was carried out by column chromatography. Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on NMR spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined by melting point apparatus and are uncorrected. FT-IR spectra were recorded on IR spectrometer. Elemental analyses were recorded on CHNS analyzer. LC-Mass spectra were recorded on a mass spectrometer. HPLC analysis was carried out by C_{18} column using 2% 2-propanol in CH_3CN as eluent. X-Ray data were collected on SMART APEX equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany). Bisaryloxime ethers were prepared according to reported procedure.[21]

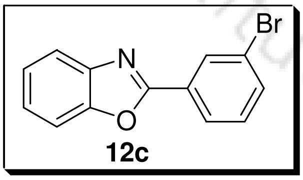
General Procedure for Conversion of Bisaryloxime Ethers to 2-Arylbenzoxazoles. Substrates **11a-z** (0.5 mmol) and $Cu(OTf)_2$ (20 mol %, 0.1 mmol, 36.15 mg) were stirred at 80 °C in toluene (2 mL) under oxygen balloon. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to afford the titled compounds **12a-y** in analytically pure form.


12a

2-(4-Methylphenyl)benzo[*d*]oxazole[13k] **12a.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 90% (94.09 mg); mp 115-116 °C (lit.[13k] mp 114-115 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.75-7.73 (m, 1H), 7.57-7.54 (m, 1H), 7.33-7.31 (m, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.9, 142.4, 142.2, 129.8, 127.8, 125.3, 125.0, 124.7, 120.0, 110.7, 21.8; FT-IR (KBr) 3281, 2964, 2920, 2855, 1651, 1622, 1581, 1530, 1502, 1451, 1435, 1411, 1346, 1262, 1244, 1112, 1019 cm^{-1}; *m/z* (ESI-MS) 210.09 $[M + H]^+$. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.44; H, 5.29; N, 6.64.

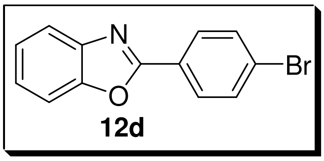

12b

2-(2-Bromophenyl)benzo[*d*]oxazole 12b. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.35; colorless solid; yield 60% (82.23 mg); mp 54-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.85-7.83 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.62-7.60 (m, 1H), 7.47-7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 150.7, 141.7, 134.8, 132.3, 132.1, 127.7, 127.6, 125.7, 124.8, 122.0, 120.6, 110.9; FT-IR (KBr) 2925, 1606, 1565, 1530, 1469, 1450, 1427, 1307, 1262, 1251, 1235, 1081, 1016 cm^{-1}; (ESI-MS) *m/z* 273.99, 275.99 $[M + H]^+$. Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.91; H, 2.96; N, 5.14.


12c

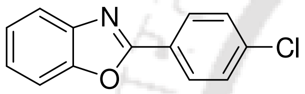
2-(3-Bromophenyl)benzo[*d*]oxazole[24] **12c.** Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.60; white solid; yield 83% (113.76 mg); mp 129-130 °C (lit.[24] mp 128-130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.76-7.74 (m, 1H), 7.64-7.61 (m, 1H), 7.57-7.55 (m, 1H), 7.38-7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 151.0, 142.1, 134.6, 130.7, 130.6, 129.3, 126.3, 125.7, 125.0, 123.2, 120.4, 110.9; FT-IR (KBr) 2925, 2854, 1614, 1570, 1547, 1451, 1429, 1292, 1239, 1195, 1071, 1051 cm^{-1}; *m/z* (ESI-MS) 274.01, 276.01 $[M + H]^+$.

Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.91; H, 2.92; N, 5.16.



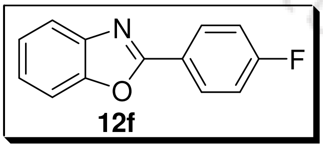
12d

2-(4-Bromophenyl)benzo[*d*]oxazole[18] **12d.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; white solid; yield 81% (111.01mg); mp 156-158 °C (lit.[18] mp 157-158 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10-8.08 (m, 2H), 7.76-7.73 (m, 1H), 7.65-7.62 (m, 2H), 7.56-7.54 (m, 1H), 7.35-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 150.8, 142.1, 132.3, 129.1, 126.3, 126.2, 125.5, 124.9, 120.2, 110.7; FT-IR (KBr) 3057, 2924, 1615, 1592, 1547, 1484, 1452, 1400, 1342, 1294, 1261, 1244, 1176, 1107, 1069, 1052, 1009 cm^{-1}; *m/z* (ESI-MS) 273.99, 275.99 $[M + H]^+$. Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.90; H, 2.93; N, 5.05.



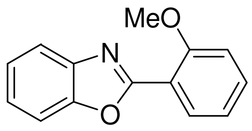
12e

2-(4-Chlorophenyl)benzo[*d*]oxazole[18] **12e.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.65$; white solid; yield 82% (94.16 mg); mp 153-154 °C (lit.[18] mp 152-153 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 2H), 7.76-7.74 (m, 1H), 7.58-7.55 (m, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.37-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 150.5, 141.8, 137.5, 129.0, 128.6, 125.4, 125.2, 124.5, 119.8, 110.5; FT-IR (KBr) 3054, 2961, 1639, 1618, 1596, 1555, 1484, 1453, 1405, 1343, 1274, 1244, 1175, 1091, 1055, 1025, 1012 cm^{-1}; *m/z* (ESI-MS) 230.05 $[M + H]^+$. Anal. Calcd for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 68.06; H, 3.49; N, 6.04.



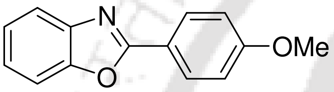
12f

2-(4-Fluorophenyl)benzo[*d*]oxazole[25] **12f.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 57% (60.79 mg); mp 95-96 °C (lit.[25] mp 94-96 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.22 (m, 2H), 7.76-7.73 (m, 1H), 7.57-7.54 (m, 1H), 7.36-7.33 (m, 2H), 7.22-7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (d, J = 252 Hz), 162.4, 151.0, 142.3, 130.1 (d, J = 9 Hz), 125.3, 124.9, 123.7, 120.2, 116.5 (d, J = 22 Hz), 110.8; FT-IR (KBr) 2927, 1622, 1498, 1470, 1454, 1414, 1243, 1231, 1156, 1092, 1055 cm^{-1}; (ESI-MS) *m/z* 214.08 $[M + H]^+$. Anal. Calcd for $C_{13}H_8FNO$: C, 73.23; H, 3.78; N, 6.57. Found: C, 73.28; H, 3.80; N, 6.53.



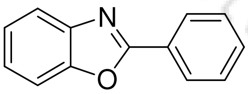
12g

2-(2-Methoxyphenyl)benzo[*d*]oxazole[15b] **12g.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; orange solid; yield 67% (75.46 mg); mp 53-54 °C (lit.[15b] mp 53-55 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.11 (m, 1H), 7.82-7.79 (m, 1H), 7.59-7.56 (m, 1H), 7.51-7.47 (m, 1H), 7.34-7.32 (m, 2H), 7.11-7.07 (m, 2H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 158.7, 150.5, 142.3, 133.0, 131.5, 125.2, 124.5, 120.9, 120.4, 116.3, 112.3, 110.6, 56.3; FT-IR (KBr) 2925, 2853, 1616, 1583, 1548, 1496, 1456, 1432, 1282, 1264, 1243, 1197, 1165, 1055, 1029, 1017 cm^{-1}; (ESI-MS) *m/z* 226.09 $[M + H]^+$. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.71; H, 4.89; N, 6.27.



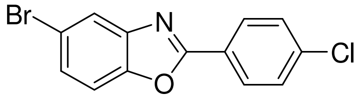
12h

2-(4-Methoxyphenyl)benzo[*d*]oxazole[18] **12h.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; white solid; yield 85% (95.73 mg); mp 103-105 °C (lit.[18] mp 105-106 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.2, 2.0 Hz, 2H), 7.67-7.65 (m, 1H), 7.48-7.46 (m, 1H), 7.26-7.23 (m, 2H), 6.96 (d, J = 9.2 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 162.4, 150.8, 142.4, 129.4, 124.6, 124.5, 119.8, 119.7, 114.4, 110.4, 55.4; FT-IR (KBr) 2960, 2927, 2855, 1619, 1604, 1503, 1455, 1421, 1254, 1245, 1184, 1170, 1102, 1057, 1027 cm^{-1}; *m/z* (ESI-MS) 226.10 $[M + H]^+$. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.73; H, 4.94; N, 6.17.



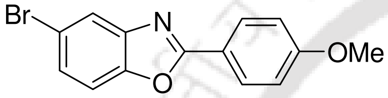
12i

2-Phenylbenzo[*d*]oxazole[18] **12i.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; white solid; yield 80% (78.09 mg); mp 103-104 °C (lit.[18] mp 102-103 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 2H), 7.78-7.75 (m, 1H), 7.58-7.55 (m, 1H), 7.52-7.49 (m, 3H), 7.36-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 150.5, 142.0, 131.2, 128.6, 127.4, 127.0, 124.8, 124.3, 119.8, 110.4; FT-IR (KBr) 3060, 2961, 1616, 1552, 1472, 1447, 1344, 1318, 1241, 1196, 1052, 1022 cm^{-1}; *m/z* (ESI-MS) 196.06 $[M + H]^+$. Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.91; H, 4.67; N, 7.12.



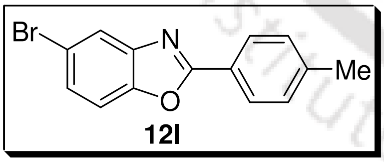
12j

5-Bromo-2-(4-chlorophenyl)benzo[*d*]oxazole 12j. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 51% (78.68 mg); mp 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.88 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.46-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 149.6, 143.5, 133.3, 129.3, 128.9, 128.2, 125.0, 122.9, 117.3, 111.8; FT-IR (KBr) 2862, 1648, 1547, 1480, 1447, 1401, 1273, 1260, 1092, 1080, 1025 cm^{-1}; (ESI-MS) *m/z* 307.95, 309.95 $[M + H]^+$. Anal. Calcd for $C_{13}H_7BrClNO$: C, 50.60; H, 2.29; N, 4.54. Found: C, 50.67; H, 2.31; N, 4.49.



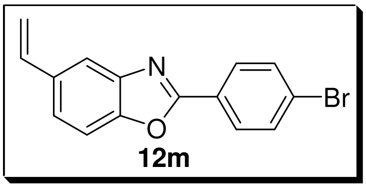
12k

5-Bromo-2-(4-methoxyphenyl)benzo[*d*]oxazole 12k. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.35; colorless solid; yield 38% (57.79 mg); mp 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 1H), 7.40 (s, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.9, 149.9, 144.1, 129.8, 129.0, 127.7, 122.8, 117.3, 114.6, 111.8, 55.7; FT-IR (KBr) 2961, 2927, 1639, 1614, 1601, 1553, 1497, 1464, 1449, 1419, 1305, 1292, 1256, 1199, 1169, 1059, 1042, 1028 cm^{-1}; (ESI-MS) *m/z* 304.01, 306.01 $[M + H]^+$. Anal. Calcd for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.23; H, 3.34; N, 4.65.



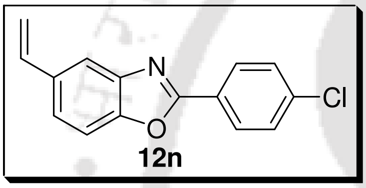
12l

5-Bromo-2-*p*-tolylbenzo[*d*]oxazole 12l. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 50% (72.04 mg); mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.86 (s, 1H), 7.42 (s, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 149.9, 144.0, 142.8, 129.9, 128.0, 127.9, 124.1, 123.0, 117.4, 111.9, 21.9; FT-IR (KBr) 2923, 1620, 1556, 1497, 1447, 1408, 1278, 1259, 1178, 1116, 1059, 1036, 1012 cm^{-1}; (ESI-MS) *m/z* 288.01, 290.01 $[M + H]^+$. Anal. Calcd for $C_{14}H_{10}BrNO$: C, 58.36; H, 3.50; N, 4.86. Found: C, 58.43; H, 3.53; N, 4.82.



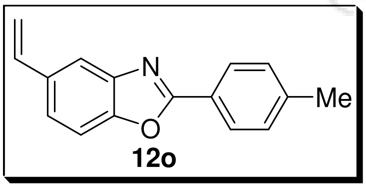
12m

2-(4-Bromophenyl)-5-vinylbenzo[d]oxazole 12m. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.30$; white solid; yield 80% (120.06 mg); mp 159-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.66-7.62 (m, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.4, 1.6 Hz, 1H), 6.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.78 (d, J = 17.2 Hz, 1H), 5.28 (d, J = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 150.7, 142.7, 136.7, 135.2, 132.5, 129.2, 126.5, 126.3, 124.2, 117.7, 114.1, 110.7; FT-IR (KBr) 3057, 2926, 1609, 1556, 1541, 1503, 1456, 1440, 1421, 1362, 1285, 1265, 1231, 1182, 1064, 1044 cm^{-1}; *m/z* (ESI-MS) 300.01, 302.01 $[M + H]^+$. Anal. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67. Found: C, 60.09; H, 3.34; N, 4.62.



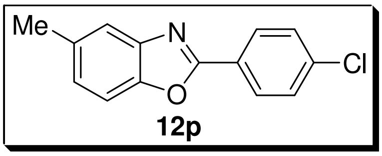
12n

2-(4-Chlorophenyl)-5-vinylbenzo[*d*]oxazole 12n. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 62% (79.27 mg); mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.15 (m, 2H), 7.77 (s, 1H), 7.51-7.48 (m, 3H), 7.43 (dd, J = 8.4, 1.6 Hz, 1H), 6.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.79 (dd, J = 18.4, 0.8 Hz, 1H), 5.29 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.7, 142.7, 136.7, 132.7, 131.1, 129.5, 129.0, 125.8, 124.1, 117.6, 114.1, 110.6; FT-IR (KBr) 2962, 2930, 1600, 1580, 1473, 1402, 1381, 1261, 1202, 1089, 1073, 1052, 1022 cm^{-1}; (ESI-MS) *m/z* 256.07 $[M + H]^+$. Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.40; H, 3.96; N, 5.54.



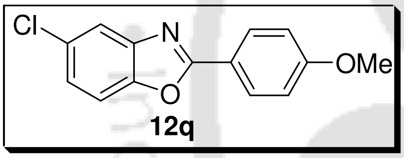
12o

2-*p*-Tolyl-5-vinylbenzo[*d*]oxazole 12o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 56% (65.88 mg); mp 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4, 2.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 10.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 150.7, 142.8, 136.8, 134.9, 129.9, 127.8, 125.2, 124.5, 123.7, 117.4, 113.8, 110.5, 21.9; FT-IR (KBr) 2963, 2922, 1618, 1553, 1499, 1474, 1435, 1407, 1260, 1201, 1177, 1095, 1053, 1018 cm^{-1}; (ESI-MS) *m/z* 236.11 [M + H]$^+$. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.75; H, 5.55; N, 5.89.



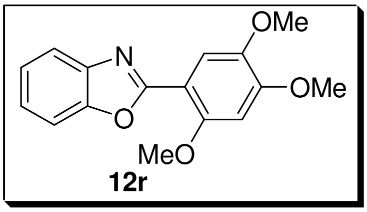
12p

2-(4-Chlorophenyl)-5-methylbenzo[*d*]oxazole[26] 12p. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.55$; colorless solid; yield 88% (107.22 mg); mp 150-151 °C (lit.[26] mp 148-150 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 149.2, 144.3, 142.4, 137.8, 134.8, 129.4, 129.0, 126.7, 120.2, 110.2, 21.7; FT-IR (KBr) 2962, 2925, 2855, 1618, 1598, 1552, 1480, 1458, 1403, 1384, 1334, 1261, 1200, 1090, 1052, 1022 cm^{-1}; *m/z* (ESI-MS) 244.07 [M + H]$^+$. Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.07; H, 4.15; N, 5.69.



12q

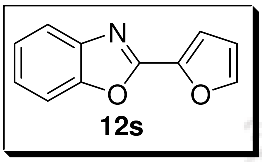
5-Chloro-2-(4-methoxyphenyl)benzo[*d*]oxazole[13k] 12q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 84% (109.07 mg); mp 152-154 °C (lit.[13k] mp 153-155 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2 Hz, 2H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.29-7.26 (m, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.3, 148.9, 143.1, 129.4, 129.2, 124.4, 119.1, 118.7, 114.1, 110.8, 55.2; FT-IR (KBr) 3069, 2995, 2945, 2914, 2837, 1681, 1631, 1602, 1556, 1497, 1470, 1454, 1421, 1334, 1306, 1290, 1256, 1199, 1183, 1115, 1052, 1028 cm^{-1}; *m/z* (ESI-MS) 260.06 [M + H]$^+$. Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.81; H, 3.86; N, 5.34.



12r

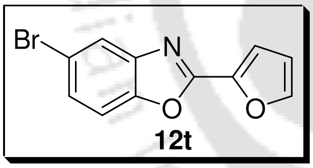
2-(2,4,5-Trimethoxyphenyl)benzo[*d*]oxazole 12r. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.45$; light brown solid; yield

80% (114.12 mg); mp 145-147 °C (lit.[4] mp 146-148 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77-7.75 (m, 1H), 7.66 (s, 1H), 7.56-7.54 (m, 1H), 7.31-7.29 (m, 2H), 6.63 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 154.3, 152.9, 150.4, 143.4, 142.3, 124.7, 124.4, 120.0, 110.5, 107.6, 98.0, 96.7, 57.3, 56.8, 56.3; FT-IR (KBr) 3092, 2991, 2956, 2933, 2851, 1612, 1590, 1556, 1519, 1454, 1438, 1410, 1399, 1382, 1357, 1287, 1217, 1155, 1123, 1027 cm^{-1}; *m/z* (ESI-MS) 286.11 [M + H]$^+$. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.45; H, 5.32; N, 4.85.



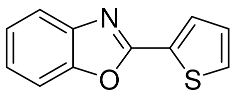
12s

2-(Furan-2-yl)benzo[*d*]oxazole[27a] **12s.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.40; colorless solid; yield 62% (57.41 mg); mp 85-86 °C (lit.[27b] mp 83-85 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75-7.73 (m, 1H), 7.66-7.65 (m, 1H), 7.56-7.54 (m, 1H), 7.35-7.33 (m, 2H), 7.27-7.26 (m, 1H), 6.61-6.60 (dd, *J* = 3.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.6, 150.3, 146.0, 142.8, 141.8, 125.5, 125.1, 120.3, 114.6, 112.5, 110.8; FT-IR (KBr) 2961, 2925, 2854, 1645, 1637, 1591, 1540, 1527, 1451, 1394, 1343, 1299, 1261, 1246, 1157, 1081, 1059, 1019 cm^{-1}; (ESI-MS) *m/z* 186.06 [M + H]$^+$. Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.29; H, 3.83; N, 7.51.

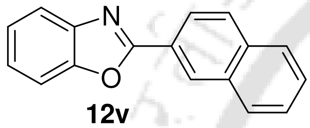


12t

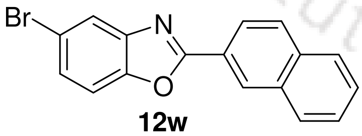
5-Bromo-2-(furan-2-yl)benzo[*d*]oxazole 12t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.50; colorless solid; yield 41% (54.13 mg); mp 91-92 °C (lit.[28b] mp 92-93 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, *J* = 1.6 Hz, 1H), 7.67-7.66 (m, 1H), 7.44-7.42 (m, 2H), 7.29-7.28 (m, 1H), 6.62 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.5, 149.3, 146.4, 143.4, 142.2, 128.5, 123.2, 120.0, 115.3, 112.6, 111.9; FT-IR (KBr) 3095, 2962, 2926, 1642, 1627, 1580, 1531, 1482, 1456, 1442, 1421, 1325, 1293, 1260, 1236, 1156, 1090, 1068, 1039, 1017 cm^{-1}; (ESI-MS) *m/z* 263.97, 265.97 [M + H]$^+$. Anal. Calcd for $C_{11}H_6BrNO_2$: C, 50.03; H, 2.29; N, 5.30. Found: C, 50.09; H, 2.27; N, 5.25.


12u

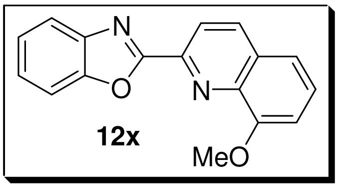
2-(Thiophen-2-yl)benzo[*d*]oxazole[13k] **12u.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 80% (80.50 mg); mp 82-83 °C (lit.[13k] mp 80-82 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 3.6 Hz, 1H), 7.73-7.70 (m, 1H), 7.55-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.19 (t, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 150.6, 142.2, 131.1, 130.4, 130.1, 129.0, 125.2, 124.9, 120.0, 110.6; FT-IR (KBr) 3074, 2961, 2929, 2859, 1615, 1571, 1494, 1452, 1422, 1384, 1344, 1262, 1245, 1228, 1091, 1074, 1045, 1022, 1000 cm^{-1}; *m/z* (ESI-MS) 202.04 [M + H]$^+$. Anal. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96; S, 15.93. Found: C, 65.74; H, 3.49; N, 7.02; S, 15.98.


12v

2-(Naphthalen-2-yl)benzo[*d*]oxazole[18] **12v.** Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.65$; white solid; yield 80% (98.11 mg); mp 115-116 °C (lit.[18] mp 116-118 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.31 (dd, J = 8.8, 1.6 Hz, 1H), 7.98-7.95 (m, 2H), 7.89-7.86 (m, 1H), 7.81-7.78 (m, 1H), 7.62-7.58 (m, 1H), 7.57-7.52 (m, 2H), 7.37-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 151.0, 142.3, 134.8, 133.1, 129.1, 128.9, 128.2, 128.0, 127.9, 127.0, 125.3, 124.8, 124.5, 124.1, 120.1, 110.7; FT-IR (KBr) 3051, 2962, 2923, 1614, 1596, 1542, 1504, 1451, 1390, 1363, 1301, 1244, 1191, 1179, 1128, 1108, 1049, 1000 cm^{-1}; *m/z* (ESI-MS) 246.10 [M + H]$^+$. Anal. Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.34; H, 4.54; N, 5.65.

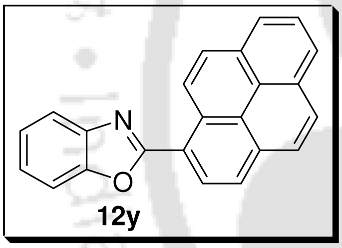

12w

5-Bromo-2-(naphthalen-2-yl)benzo[*d*]oxazole 12w. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; white solid; yield 81% (131.29 mg); mp 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.28 (dd, J = 8.4, 1.6 Hz, 1H), 7.99-7.88 (m, 4H), 7.59-7.56 (m, 2H), 7.48-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.1, 144.1, 135.1, 133.1, 129.2, 129.1, 128.7, 128.4, 128.3, 128.2, 127.2, 124.1, 123.2, 117.6, 112.0, 110.0; FT-IR (KBr) 2963, 2927, 2851, 1628, 1593, 1474, 1397, 1261, 1201, 1095, 1067, 1050, 1024 cm^{-1}; *m/z* (ESI-MS) 324.01, 326.01 [M + H]$^+$. Anal. Calcd for $C_{17}H_{10}BrNO$: C, 62.99; H, 3.11; N, 4.32. Found: C, 63.07; H, 3.13; N, 4.36.



12x

2-(Benzo[*d*]oxazol-2-yl)-8-methoxyquinoline 12x. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f = 0.55$; pale yellow solid; yield 85% (117.42 mg); mp 142-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 7.85-7.83 (m, 1H), 7.71 (d, *J* = 6.4 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.46-7.37 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 156.0, 151.5, 144.8, 142.0, 140.1, 137.3, 131.0, 128.8, 126.3, 125.0, 121.0, 120.8, 119.5, 111.8, 108.5, 56.3; FT-IR (KBr) 2962, 2923, 2851, 1610, 1596, 1562, 1544, 1502, 1464, 1451, 1437, 1426, 1379, 1328, 1260, 1247, 1112, 1103, 1087, 1061, 1020 cm^{-1}; *m/z* (ESI-MS) 277.12 [M + H]$^+$. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.98; H, 4.36; N, 10.20.



12y

2-(Pyren-1-yl)benzo[*d*]oxazole 12y. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; yellow solid; yield 74% (118.16 mg); mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, *J* = 9.2 Hz, 1H), 8.88 (d, *J* = 8.0 Hz, 1H), 8.32-8.04 (m, 7H), 7.94-7.91 (m, 1H), 7.70-7.68 (m, 1H), 7.43-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.6, 142.8, 133.7, 131.4, 130.8, 130.1, 129.7, 129.5, 127.8, 127.4, 126.5, 126.4, 126.3, 125.5, 125.4, 125.2, 124.8, 124.7, 124.5, 120.4, 110.7; FT-IR (KBr) 2962, 2926, 2855, 1595, 1548, 1531, 1455, 1261, 1209, 1095, 1016 cm^{-1}; (ESI-MS) *m/z* 320.12 [M + H]$^+$. Anal. Calcd for $C_{23}H_{13}NO$: C, 86.50; H, 4.10; N, 4.39. Found: C, 86.62; H, 4.08; N, 4.33.

Reaction Rate Experiments of the Cyclization of Bisaryloxime Ethers 11e, 11f, 11h and 11i (Figure 4). Bisaryloxime ethers **11e**, **11f** , **11h** and **11i** (0.5 mmol) and $Cu(OTf)_2$ (20 mol %) were stirred at 80 °C in toluene (2 mL) under oxygen balloon. Progress of the reactions was monitored at 0.25 h interval by taking a portion of the reaction mixture and passing through a short pad of silica gel using ethyl acetate and hexane as eluent to remove toluene and copper salt. The eluent having the product and starting material was evaporated to dryness. The product yield (%) was determined by HPLC with C_{18} column using 2% 2-propanol in CH_3CN as eluent by comparing product-substrate ratio [$\lambda = 254$ nm, flow rate: 0.5 mL/min for all substrates].

Kinetic Isotope Effect Experiments of 11a and 11a (D) (Scheme 13). Bisaryloxime ether **11a** (0.48 mmol, 102 mg) and $Cu(OTf)_2$ (20 mol %, 35.7 mg) were stirred at 80 °C in toluene (2 mL) under oxygen balloon. The product formation was measured at 0.5 h interval by removing 40 µL of the reaction mixture and passing through a short pad of silica gel using hexane followed by hexane/ethyl acetate as eluent, the solvent was evaporated under reduced pressure and the residue containing the starting material **11a** and the product **12a** was dissolved in 3.5 mL of CH_3CN and 20 µL was injected for HPLC analysis.

The reaction of bisaryloxime ether **11a (D)** (0.47 mmol, 100 mg) to **12a** was performed as described for the conversion of **11a** to **12a** in general procedure.

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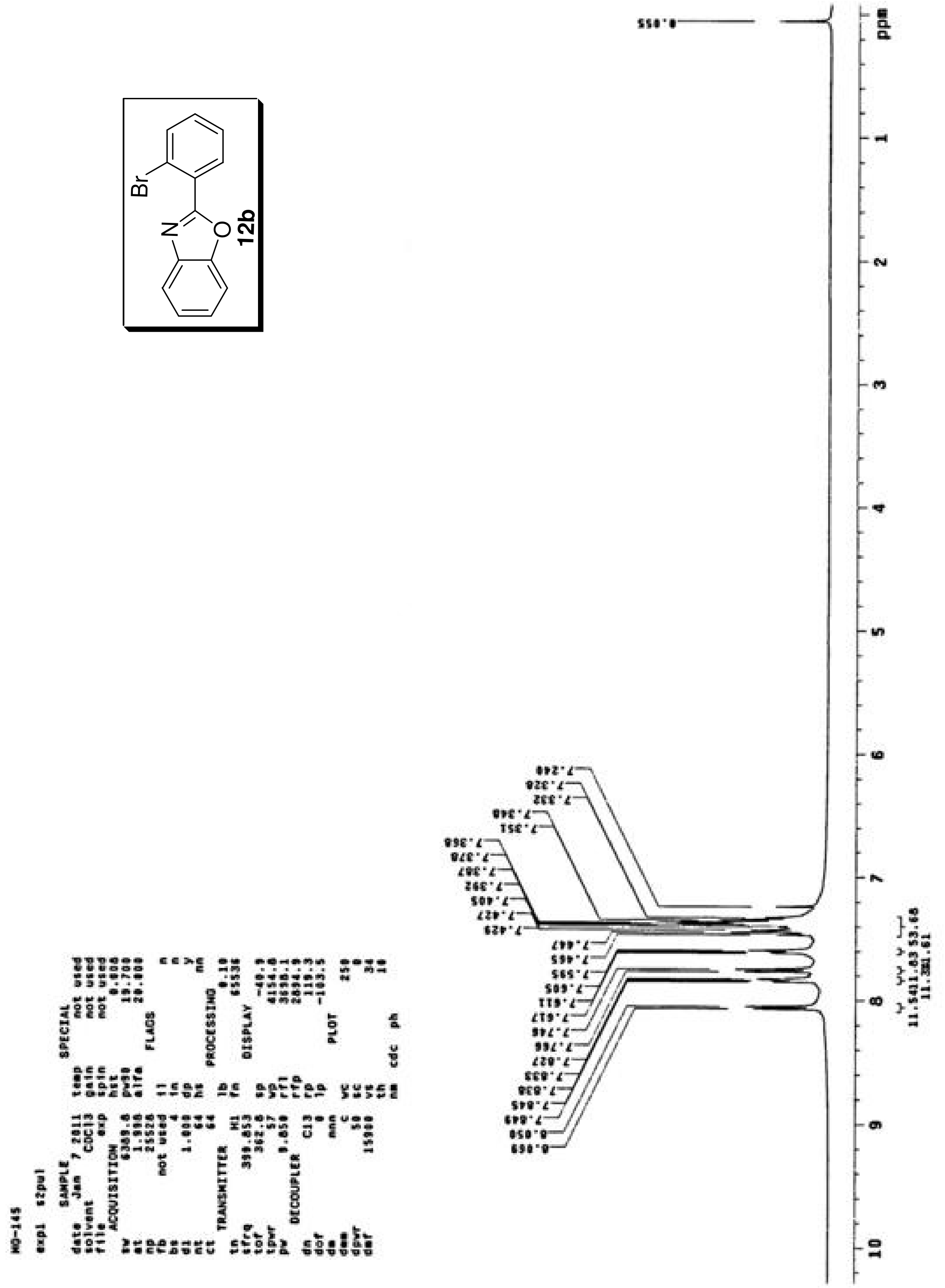
Crystal Data and Structure Refinement for 12q at 298(2) K

Identification code	mg_1	
Empirical formula	$C_{14}H_{10}ClNO_2$	
Formula weight	259.68	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P-1* Loop xyz 'x, y, z' '-x, -y, -z'	
Unit cell dimensions	a = 8.1974(3) Å	α(°)= 97.304(3)
	b = 8.1978(4) Å	β(°)= 108.420(3)
	c = 10.6661(4) Å	γ(°)= 114.655(3)
Volume	589.52(4) $Å^3$	
Z	2	
Density (calculated)	1.463 Mg/m^3	
Absorption coefficient	0.315 mm^{-1}	
F(000)	268.0	
Crystal size	0.34x 0.31 x 0.28 mm	
Theta range for data collection	2.11 to 28.29 °	
Index ranges	-10<=h<=10, -10<=k<=10, -14<=l<=13	
Reflections collected	2910	
Independent reflections	2870 [R (int) = 0.0640]	
Completeness to theta = 28.29°	99.5 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.916 and 0.898	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2708 / 0 /193	
Goodness-of-fit on F^2	0.961	
Final R indices [I>2sigma (I)]	$R1$ = 0.0367, $wR2$ = 0.0596	
R indices (all data)	$R1$ = 0.0779, $wR2$ = 0.0645	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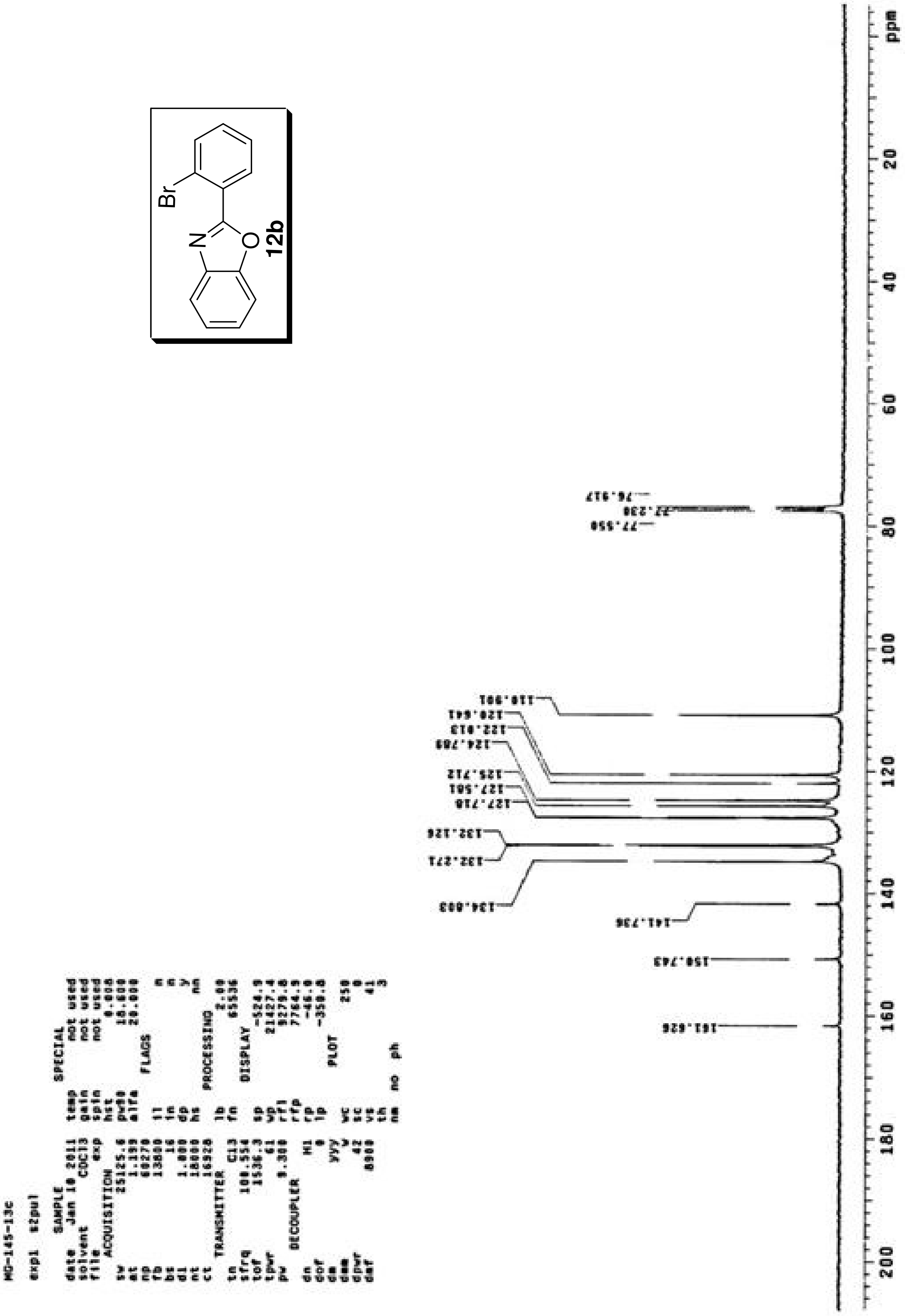
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PROCESSING
DISPLAY
TRANSMITTER
DECOUPLER
PLOT
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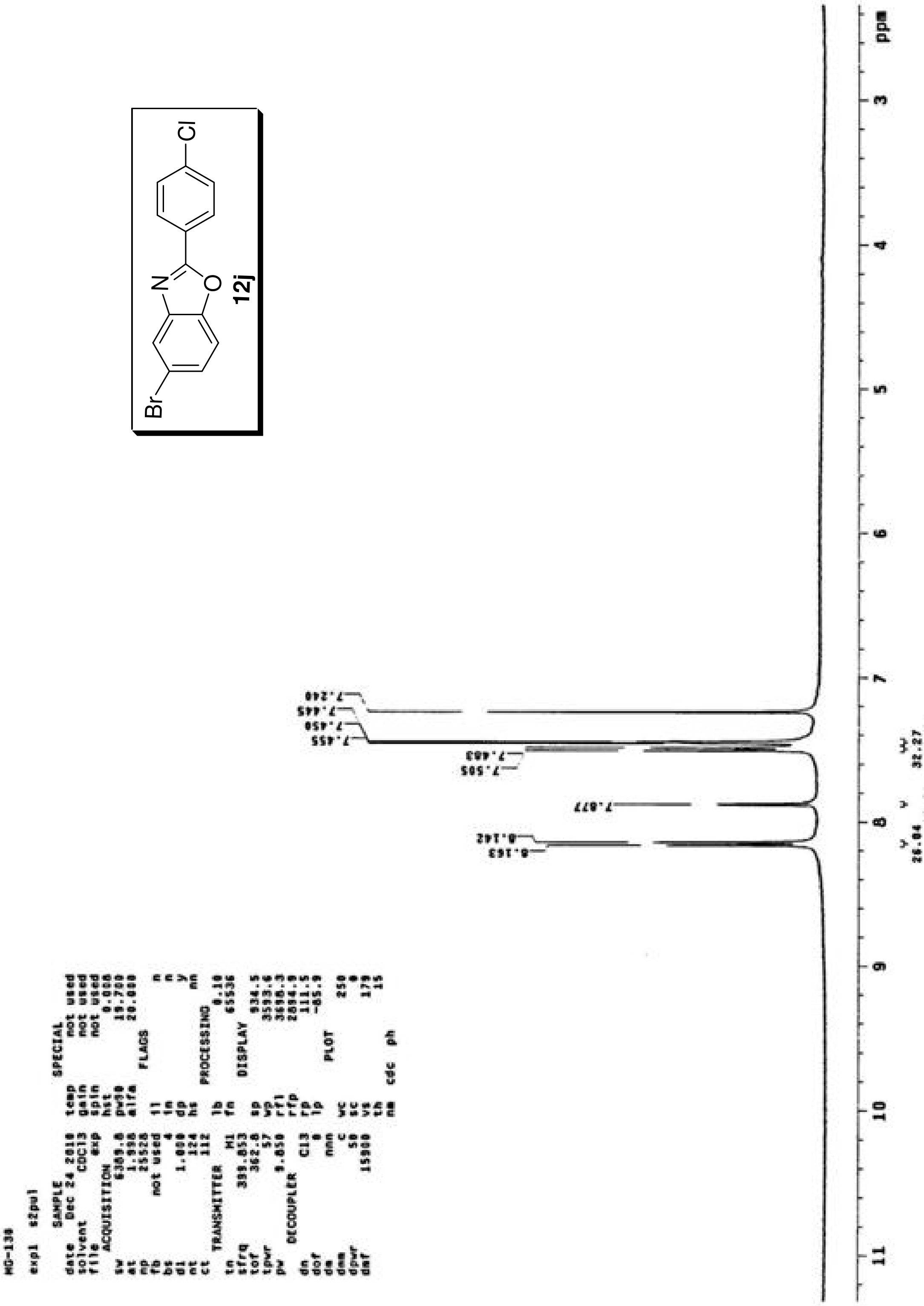
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9
10
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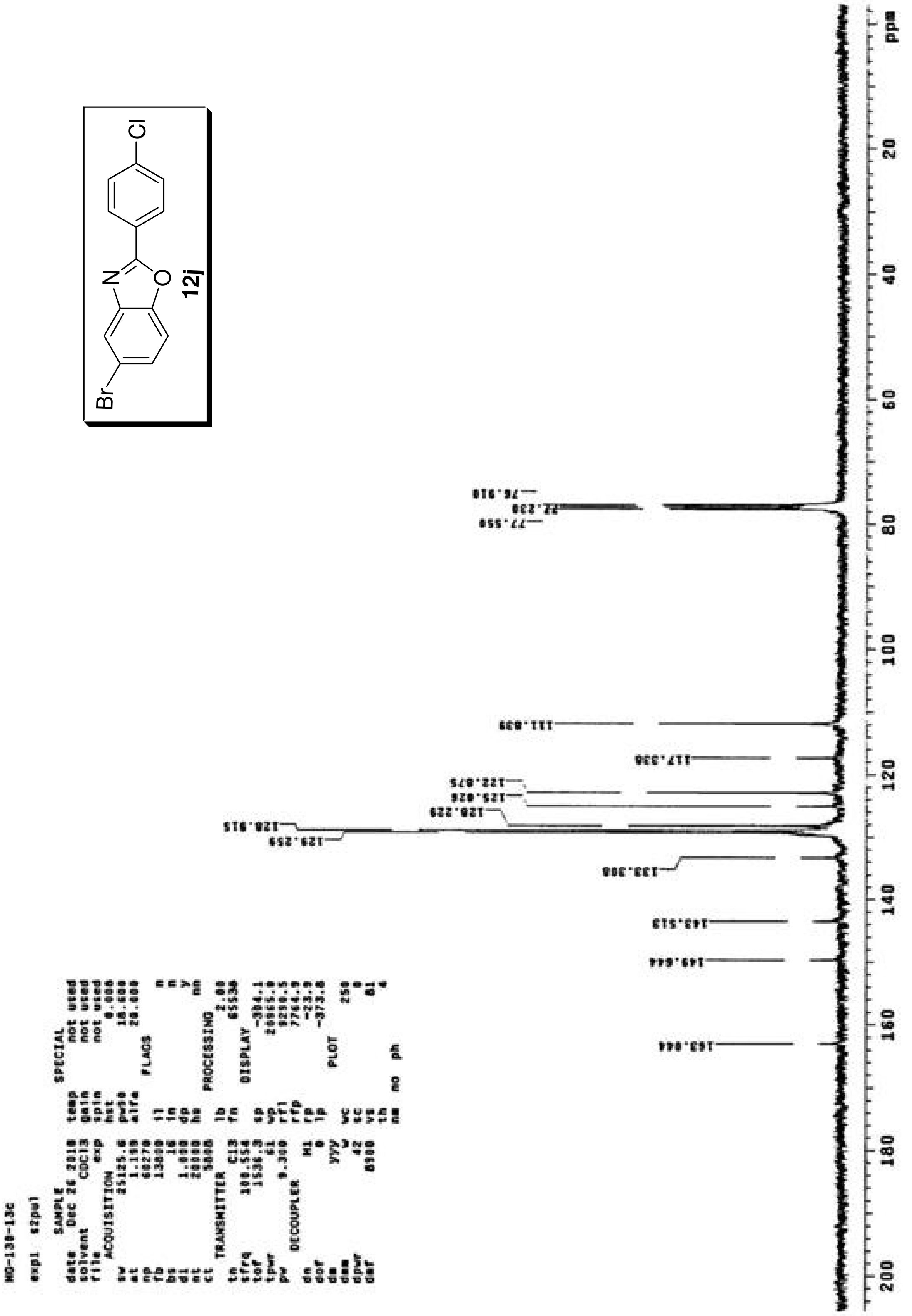

12j

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117.338
111.839
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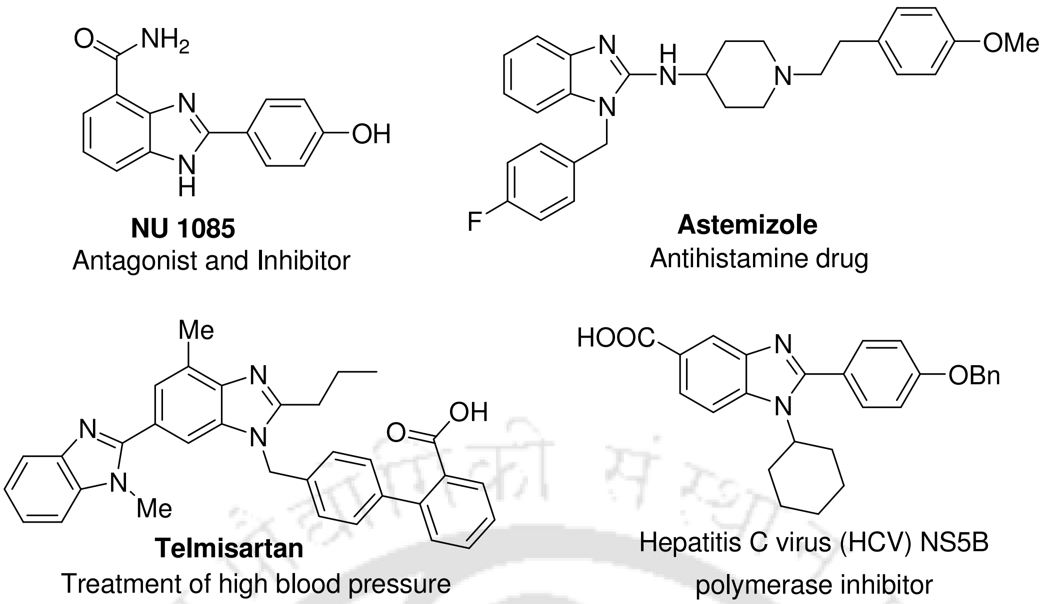
77.230
76.910
200
180
160
140
120
100
80
60
40
20
ppm

Chapter II

Synthesis of 2-Aryl-*N*-benzylbenzimidazoles from *N*-Benzyl Bisarylhydrazones via C–H Functionalization/C–N Bond Formation

In recent decades, carbon-carbon[1] or carbon-heteroatom[2-4] bond formation through C–H functionalization by transition-metal complexes has gained importance because it obviates the need for prior activation steps. These reactions could be considered as a complementary to the classical reactions in organic synthesis and it has become a common protocol for drug discovery as an enabling technology. Intramolecular version of these protocols has been successfully explored for the synthesis of benz-fuzed heterocycles from simple precursors. For example, the synthesis of carbazoles[2b] has been accomplished using palladium-catalyzed C–H activation followed by intramolecular C–N bond formation. Subsequently, the scope of the palladium-catalyzed C–H activation and carbon-heteroatom bond formation has been explored for the access to other classes of benz-fuzed heterocycles such as benzothiazoles,[4] indazoles,[5] indolines,[6] oxindoles,[7] benzothiophenes[8] and benzotriazoles.[9] In addition, copper(II)-catalyzed oxidative cyclization has been explored for the synthesis of benzimidazoles[2a] and benzoxazoles[3a] *via* C–H functionalization followed by carbon-heteroatom bond formation. In this chapter, we wish to report a detailed study of the scope of the synthesis of 2-aryl-*N*-benzylbenzimidazoles from *N*-benzyl bisarylhydrazones through intramolecular C–H functionalization/C–N bond formation. A series of substrates have been cyclized to afford the target heterocycles in short time at moderate temperature.

Benzimidazoles are privileged organic compounds because of their applications in therapeutic[10] and biological sciences (Figure 1).[11] In the field of medicinal chemistry these compounds have been characterized as neuropeptide YY1 receptor antagonist,[12a] *N*-methyl-D-aspartate (NMDA) antagonist,[12b] factor Xa(FXa) inhibitor,[12c] poly(ADP-ribose)polymerase (PARP) inhibitor[12d] and nonpeptide thrombin inhibitor.[12e] These compounds could also show anti-inflammatory, antimicrobial and antibacterial activities.[13] Their applications are not limited to these fields only. They could also be used for the preparation of dyes and high-temperature resistance polymers.[14] Thus enormous efforts have been committed for the development of effective methods for construction of benzimidazole structural frameworks.



NU 1085
Antagonist and Inhibitor

Astemizole
Antihistamine drug

Telmisartan
Treatment of high blood pressure

Hepatitis C virus (HCV) NS5B
polymerase inhibitor

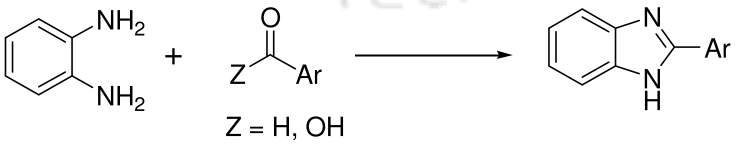
Figure 1. Examples of some biologically active benzimidazoles

2.1 Strategies for Synthesis of Substituted Benzimidazoles

2.1.1 Classical Methods

The common method used for the construction of the benzimidazole heterocores involves the condensation of 2-aminoaniline[15] with either carboxylic acids or aldehyde followed by intramolecular cyclization (Scheme 1). As a substitute of 1,2-diaminoarene derivatives, *o*-nitroanilines could be used under reductive conditions.[16] These reactions are, however, have some limitations because of unavailability of suitably substituted 1,2-diaminoarenes or *o*-nitroanilines, harsh reaction conditions and lack of regioselectivity.

Scheme 1. Common Route to Benzimidazoles



2.1.2 Cross-Coupling Reactions

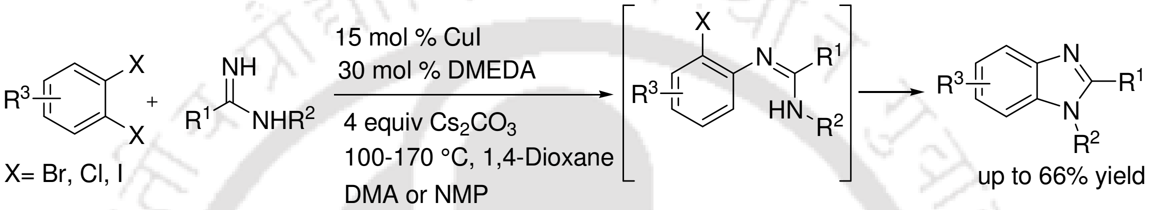
Some of these drawbacks have been overcome by the recent development in the transition-metal-catalyzed cross-coupling reactions that allow the construction of the target heterocyclic frameworks under relatively milder conditions.

2.1.2.1 Copper Catalysts

Copper catalysts, because of its less-toxic nature and low cost, have been extensively used for synthesis of various substituted benzimidazoles *via* C–N cross-coupling reactions.

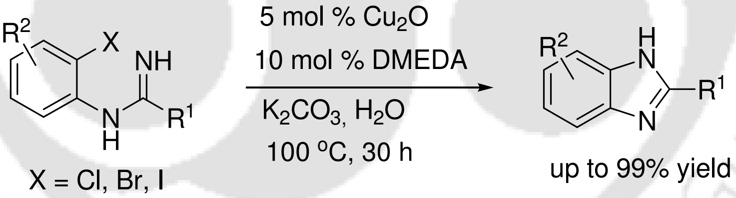
1,2-Dihaloarenes *via* cross-coupling reactions with amidines in presence of copper-salts could form substituted benzimidazoles. CuI in combination with DMEDA as ligand has been used as an efficient catalytic system for this transformation (Scheme 2).[17a]

Scheme 2. Copper-Catalyzed Amination of 1,2-Dihaloarenes



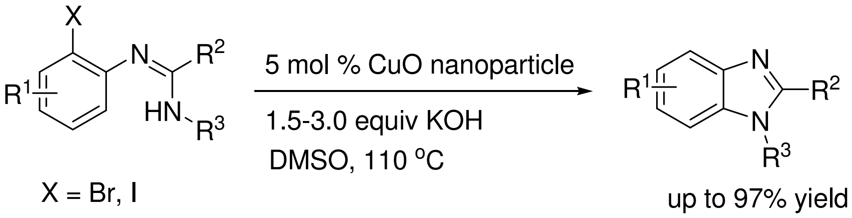
Synthesis of benzimidazoles has also been achieved in water *via* intramolecular C–N bond formation of 2-haloarylamidines using Cu_2O as catalyst, DMEDA as ligand and K_2CO_3 as base (Scheme 3).[17b]

Scheme 3. Copper-Catalyzed Synthesis of Benzimidazoles in Water



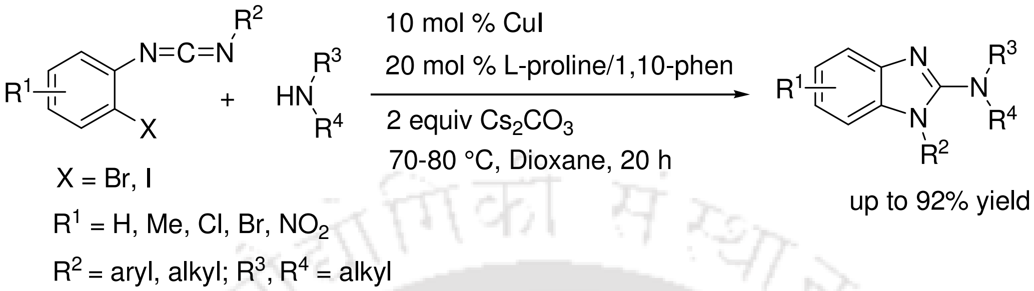
Incorporating CuO nanoparticle, we have also successfully synthesized substituted benzimidazoles through intramolecular C–N cross-coupling reaction of *o*-haloarylamidines with wide substrate scope (Scheme 4).[17c]

Scheme 4. CuO Nanoparticle Catalyzed Cross-Coupling Reaction



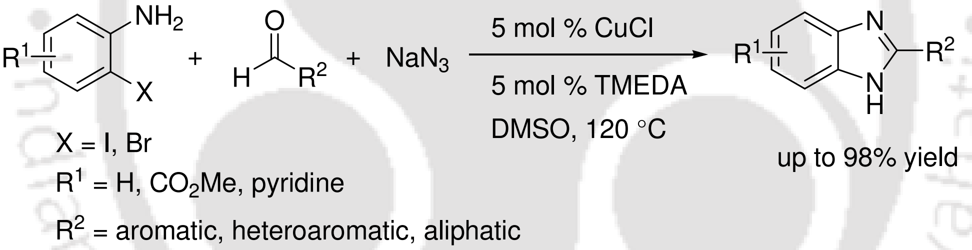
By changing the precursors to *o*-haloarylcarbodiimides and *N*-nucleophiles, *N*-substituted benzimidazoles have been synthesized by copper(I)-catalyzed cascade intermolecular addition/intramolecular C–N cross-coupling reaction (Scheme 5).[17d]

Scheme 5. Cascade Synthesis of *N*-Substituted Benzimidazoles



Recently, a three-component reaction has been carried out with 2-haloanilines, aldehydes and NaN_3 in presence of 5 mol% of CuCl and 5 mol % of TMEDA in DMSO at 120 °C to get benzimidazoles in excellent yields (Scheme 6).[17e]

Scheme 6. Copper-Catalyzed Three-Component Synthesis of Benzimidazoles

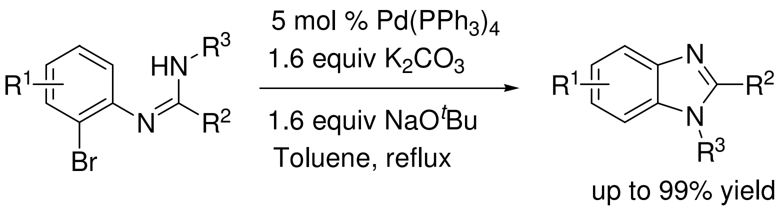


2.1.2.2 Palladium Catalysts

Palladium-catalyzed C–N cross-coupling reactions have emerged as a valuable tool in contemporary heterocyclic synthesis.

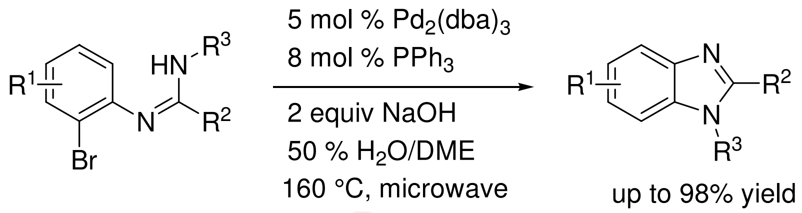
As for example, the synthesis of substituted benzimidazoles has been described *via* palladium-catalyzed intramolecular C–N cross-coupling reaction of 2-haloarylamidines in toluene under reflux condition (Scheme 7).[18a]

Scheme 7. Palladium-Catalyzed C–N Cross-Coupling of 2-Haloarylamidines



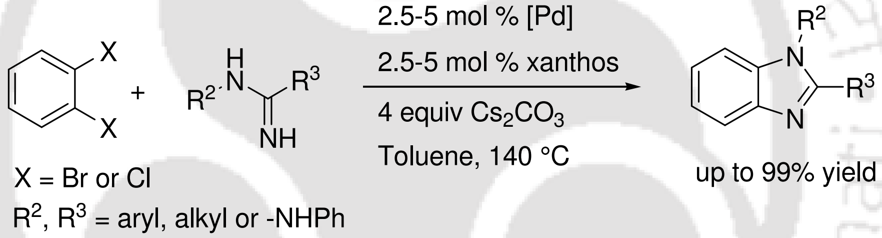
The procedure has been further modified by the same group using palladium complex under microwave conditions in aqueous DME (Scheme 8).[18b]

Scheme 8. Synthesis of Substituted Benzimidazoles under Microwave Conditions



Palladium-catalyzed twofold amination has been developed for the regiospecific synthesis of 1,2-disubstituted benzimidazoles that have been applied as florescent probes in live cell imaging with tunable fluorescence emission (Scheme 9).[18c]

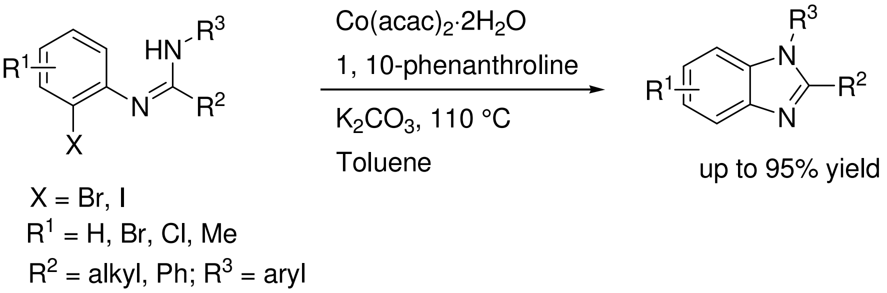
Scheme 9. Palladium-Catalyzed Twofold Amination of 1,2 Dihaloarenes



2.1.2.3 Cobalt Catalysts

Cobalt-salts have also been used for C–N cross-coupling reaction for synthesis of substituted benzimidazoles. As an example, the combination of cobalt(II) acetoacetate and 1,10-phenanthroline have been employed for construction of benzimidazole frameworks *via* intramolecular C–N cross-coupling of *o*-haloarylamidines (Scheme 10).[19]

Scheme 10. Cobalt-Catalyzed Intramolecular Cyclization of 2-Haloarylamidines



2.1.3 C–H Functionalization Reactions

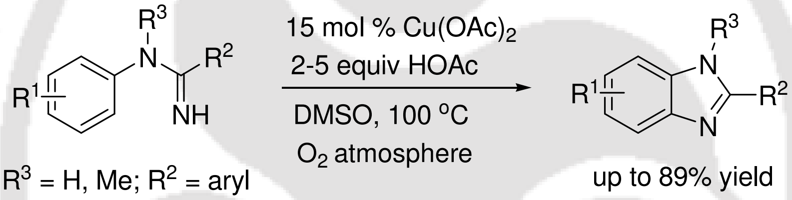
The generation of C–N bonds at the expense of C–H bonds during chemical transformations may be considered as the most spectacular examples of C–H functionalization reactions, basically carried out by transitional elements.

2.1.3.1 Copper Catalysts

Copper-catalyzed C–H functionalization is an excellent strategy for the construction of heterocyclic compounds through intramolecular carbon-heteroatom bond formation.

An immense effort has been made to develop a new Cu(II)-catalyzed synthesis of substituted benzimidazoles *via* C–H functionalization/C–N bond forming protocol from arylamidines using oxygen as the readily available oxidant (Scheme 11).[20]

Scheme 11. Copper-Catalyzed C–H Functionalization of Arylamidines

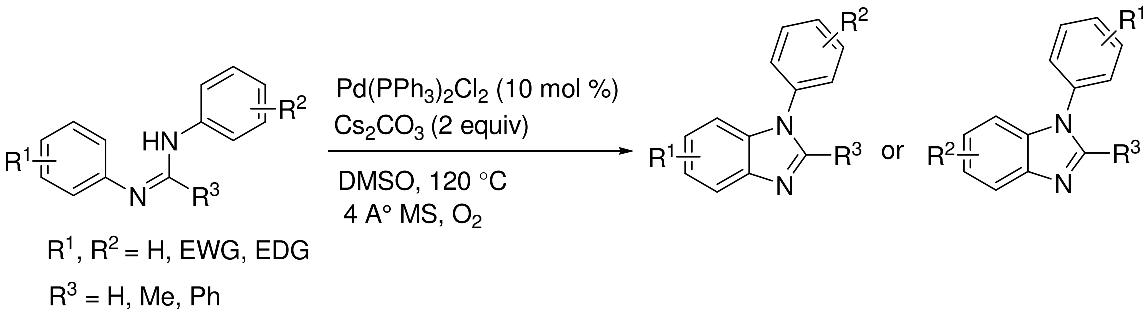


2.1.3.2 Palladium Catalysts

Impressive achievements have been made to enhance the efficiency of direct C–H functionalization using palladium catalysts.

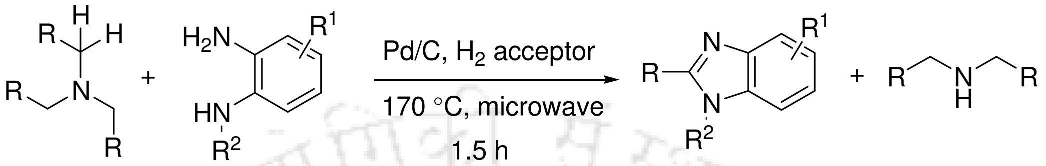
Most recently, a palladium-catalyzed aerobic oxidative C–H amination of *N*,*N'*-bis(aryl)amidines has been studied by our group for synthesis of 2-unsubstituted and 2-substituted *N*-aryl benzimidazoles (Scheme 12).[21a]

Scheme 12. Palladium-Catalyzed C–H Amination of Bis(aryl)amidines



As a substitution of aldehydes or carboxylic acids, tertiary amines could be useful for synthesis of benzimidazoles. Dehydrogenative amine activation in presence of heterogeneous palladium catalyst under microwave has also been described for the direct transformation of tertiary amines into benzimidazoles (Scheme 13).[21b]

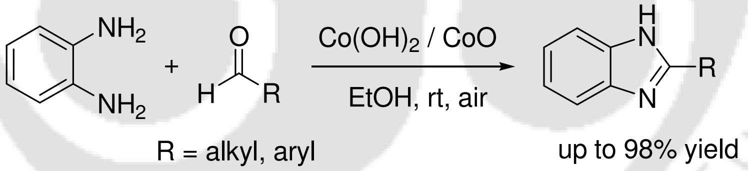
Scheme 13. Dehydrogenative Amine Activation of Tertiary Amines



2.1.3.3 Cobalt-Catalysts

Recently, cobalt(II)-salts have been reported as active catalysts for synthesis of benzimidazoles. The target heterocycles could be synthesized through the coupling of 1,2-phenylenediamine with aldehydes in presence of $Co(OH)_2$ or CoO as efficient solid catalyst in ethanol at room temperature (Scheme 14).[22]

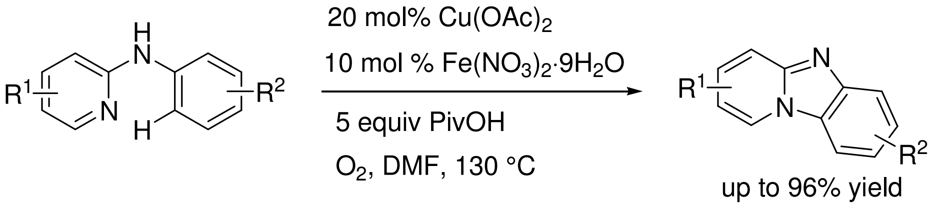
Scheme 14. Cobalt-Catalyzed Synthesis of Benzimidazoles



2.1.3.4 Co-catalysts

Direct intramolecular aromatic C–H amination of *N*-aryl-2-aminopyridines has been developed for efficient synthesis of benzimidazole derivatives catalyzed by $Cu(OAc)_2$ and $Fe(NO_3)_3 \cdot 9H_2O$ in DMF under a dioxygen atmosphere (Scheme 16).[23]

Scheme 16. Intramolecular Aromatic C–H Amination

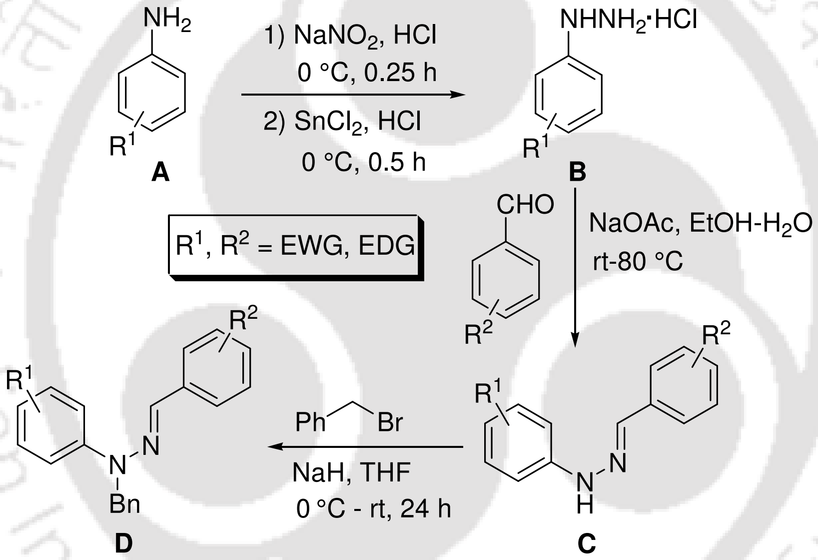


2.2 Present Study

We have studied the synthesis of 2-aryl-*N*-benzylbenzimidazoles from *N*-benzyl bisarylhydrazones via copper(II)-mediated C–H functionalization strategy.

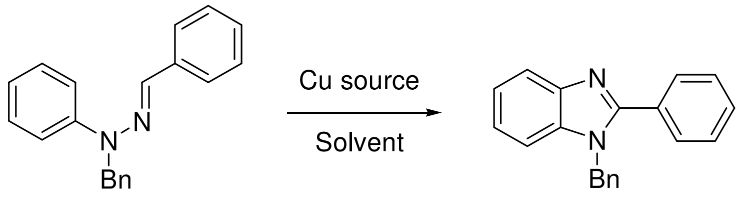
Synthesis of *N*-Benzyl Bisarylhydrazones. The reaction of anilines **A** with $NaNO_2$/HCl gave the corresponding aryl diazonium salts that could be readily converted into aryl hydrazines **B** in the presence of $SnCl_2 \cdot 2H_2O$ and HCl at 0 °C under air.[24] Condensation of **B** with aryl aldehydes provided arylhydrazones[25] **C**, which could be alkylated with benzyl bromide in the presence of NaH to afford the desired *N*-benzyl bisarylhydrazones **D** in high yields (Scheme 17).

Scheme 17. Synthesis of *N*-Benzyl Bisarylhydrazones



Screening of the Reaction Conditions. The cyclization of *N*-benzyl bisarylhydrazone **9a** was investigated as model substrate (Table 1). The reaction of bisarylhydrazone **9a** was found to be effective at 110 °C to afford the desired 2-aryl-*N*-benzylbenzimidazole **10a** in 64% yield along with ~5% of benzaldehyde[26] as byproduct in presence of 100 mol % of $Cu(OTf)_2$ under nitrogen atmosphere (Entry 4) . Either lowering of the reaction temperature (100 °C) or decrease in the amount of $Cu(OTf)_2$ (20 mol %) led to the formation of **10a** in <40% yield (Entry 2 and 13). The reaction was moderately effective under oxygen atmosphere, affording **10a** in 50% yield along with 10% of benzaldehyde[26] as byproduct (Entry 5). The benzylation of N–H of the bisarylhydrazone **C** was essential, as its absence caused the substrate **C** to undergo C=N cleavage to give benzaldehyde in 80% yield.[26]

Table 1. Optimization of the Reaction Conditions[a]



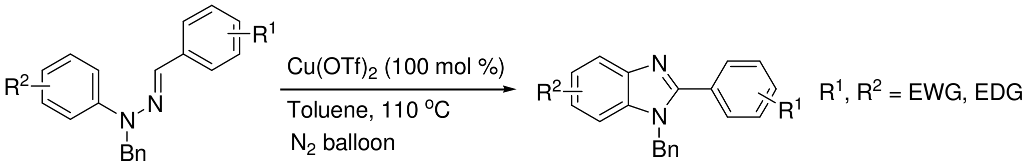
9a **10a**

Entry	[Cu] (mol %)	Temp. (°C)	Solvent	Time (h)	N_2/O_2/air	Yield (%)[b]
1[c]	$Cu(OTf)_2$ (20)	110	Toluene	4	O_2	9
2[d]	$Cu(OTf)_2$ (20)	110	Toluene	4	N_2	14
3[e]	$Cu(OTf)_2$ (20)	110	Toluene	4	air	10
4[d]	**$Cu(OTf)_2$ (100)**	**110**	**Toluene**	**4**	**N_2**	**64**
5[c]	$Cu(OTf)_2$ (100)	110	Toluene	4	O_2	50
6[f]	$Cu(OTf)_2$ (100)	110	Dioxane	7	N_2	21
7	$Cu(OTf)_2$ (100)	110	DMSO	7	N_2	n.d.
8[c]	$Cu(OTf)_2$ (100)	110	Xylene	5	N_2	55
9	CuCl/CuI (100)	110	Toluene	7	N_2	n.d.
10	$Cu(OAc)_2$ (100)	110	Toluene	7	N_2	n.d.
11[g]	$CuCl_2$ (100)	110	Toluene	8	N_2	5
12	$CuSO_4 \cdot 5H_2O$	110	Toluene	8	N_2	n.d.
13[c]	$Cu(OTf)_2$ (100)	100	Toluene	4	N_2	40
14[c]	-	110	Toluene	4	N_2	n.d.

[a] Reaction conditions: Bisarylhydrazone **9a** (0.5 mmol) and copper source (20-100 mol %) were stirred in appropriate solvent (2 mL). [b] Isolated yield. Benzaldehyde ([c]10%, [d]5%, [e]8%, [f]50% and [g]20%) was obtained. n.d. = not detected.

Synthesis of Benzimidazoles. With the optimized conditions in hand, the scope of the protocol was further explored for the reactions of a variety of substituted *N*-benzyl bisarylhydrazones (Table 2). The reactions of the substrates having substituents in both as well as one of the aryl rings were studied. For example, *N*-benzyl bisarylhydrazone **9b** having 4-CO_2Me substituent underwent cyclization to give the desired 2-aryl-*N*-benzylbenzimidazole **10b** in 3.0 h with 54% yield. Similarly, the substrates **9c-l** bearing 2-OMe, 4-Br, 4-Cl, 4-F, 4-OMe and 4-Me substituents in the aryl rings could be transformed to the corresponding 2-aryl-*N*-benzylbenzimidazoles **10c-k** in <5.0 h with

Table 2. Scope of Copper(II)-Mediated Cyclization of *N*-Benzyl Bisarylhyrazones[a]



9b-x **10b-v**

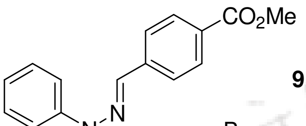
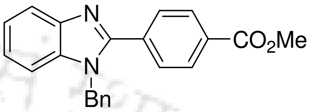
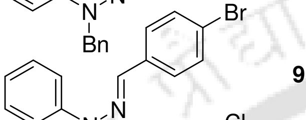
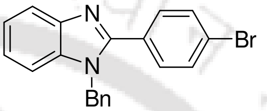
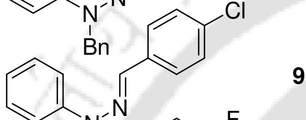
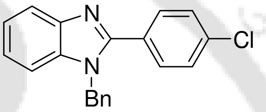
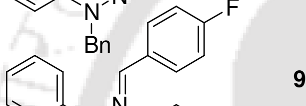
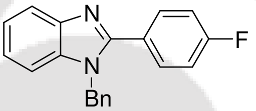
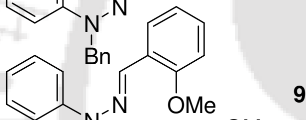
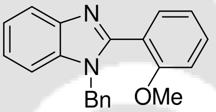
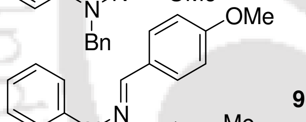
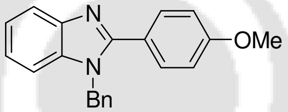
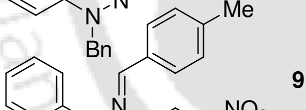
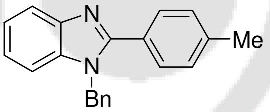
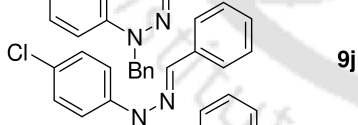
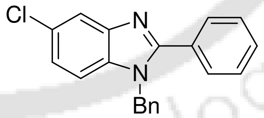
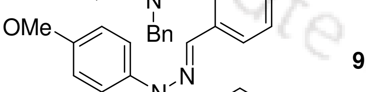
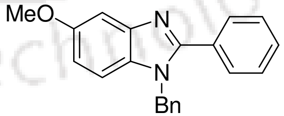
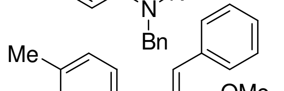
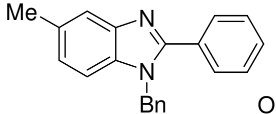
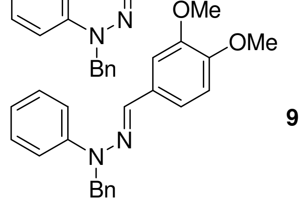
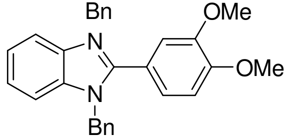
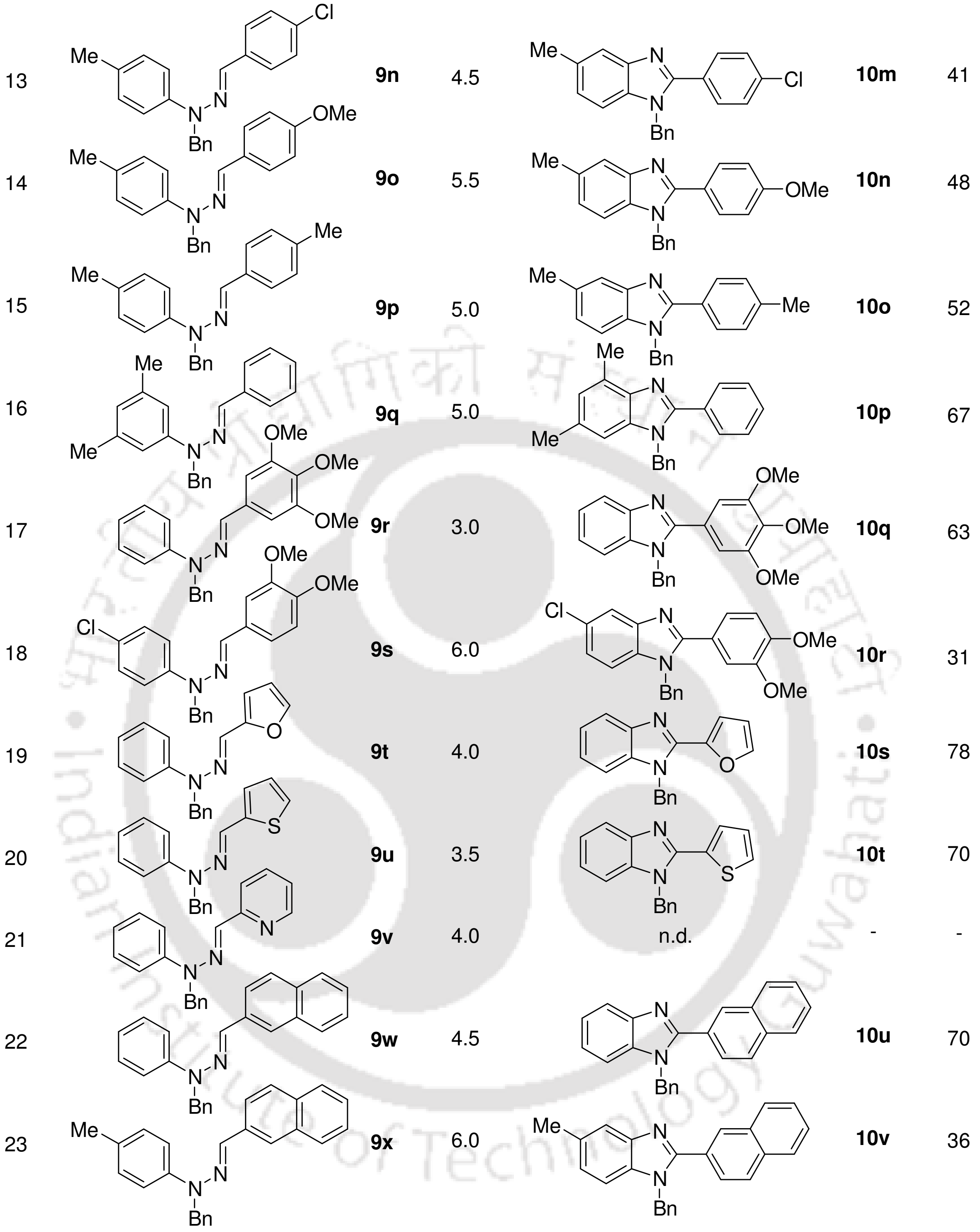
Entry	Substrate	Time (h)	Product	Yield (%)[b-c]
1	 **9b**	3.0	 **10b**	54
2	 **9c**	3.5	 **10c**	72
3	 **9d**	4.0	 **10d**	70
4	 **9e**	2.5	 **10e**	75
5	 **9f**	4.0	 **10f**	62
6	 **9g**	4.0	 **10g**	60
7	 **9h**	3.5	 **10h**	65
8	 **9i**	4.0	n.d.	-
9	 **9j**	5.0	 **10i**	68
10	 **9k**	5.0	 **10j**	70
11	 **9l**	4.0	 **10k**	64
12	 **9m**	3.0	 **10l**	65

Table 2 continues......



13	**9n**	4.5	**10m**	41
14	**9o**	5.5	**10n**	48
15	**9p**	5.0	**10o**	52
16	**9q**	5.0	**10p**	67
17	**9r**	3.0	**10q**	63
18	**9s**	6.0	**10r**	31
19	**9t**	4.0	**10s**	78
20	**9u**	3.5	**10t**	70
21	**9v**	4.0	n.d. -	-
22	**9w**	4.5	**10u**	70
23	**9x**	6.0	**10v**	36

[a] Reaction conditions: Bisarylhydrazones **9a-x** (0.5 mmol) and Cu(OTf)$_2$ (100 mol %) were stirred in toluene (2 mL) at 110 °C under N_2 balloon. [b] Isolated yield. [c] Aldehyde (~5%) was obtained as byproduct. n.d. = not detected.

60-75% yields. Recrystallization of **10i** in CH$_3$CN gave single crystals and the structure was confirmed by single crystal X-ray analysis (Figure 2). Furthermore, *N*-benzyl bisarylhydrazones **9m-s** having 4-Me, 4-Cl, 4-OMe, 3,4-diOMe, 3,5-diMe and 3,4,5-triOMe substituents on one or both of the aryl rings proceeded cyclization to afford benzimidazoles **10l-r** in <6.0 h with 31-67% yields. In addition, *N*-benzyl aryl furanylhydrazone **9t**, *N*-benzyl aryl thiophenylhydrazone **9u** and *N*-benzyl aryl naphthylhydrazones **9w-x** were cyclized to give the benzimidazoles **10s-v** in <6.0 h with 36-78% yields. Under these conditions, *N*-benzyl bisarylhydrazone **9i** having 4-NO_2 group and *N*-benzyl aryl pyridylhydrazone **9v** exhibited no desired cyclization undergoing C=N cleavage to give the corresponding aldehydes in quantitative yields. In case of *N*-benzyl bisarylhydrazone **9y** containing 3-Me substituent, the cyclization proceeded to give a 1:2 mixture of the regioisomers **10w** and **10x** in 37% yield (Scheme 18).

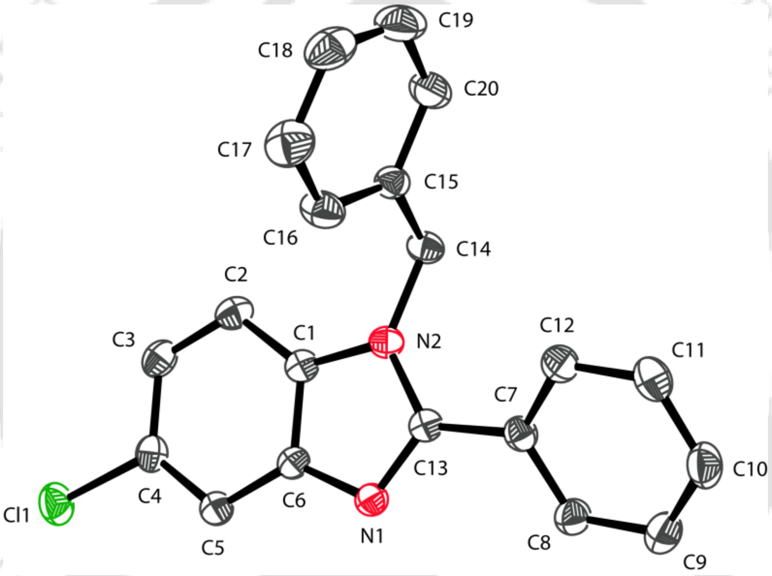
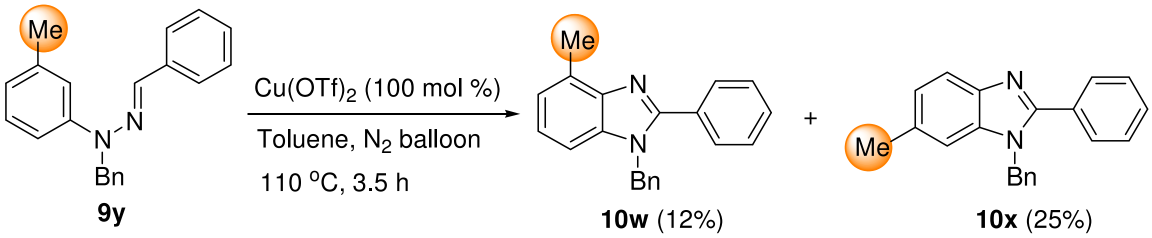


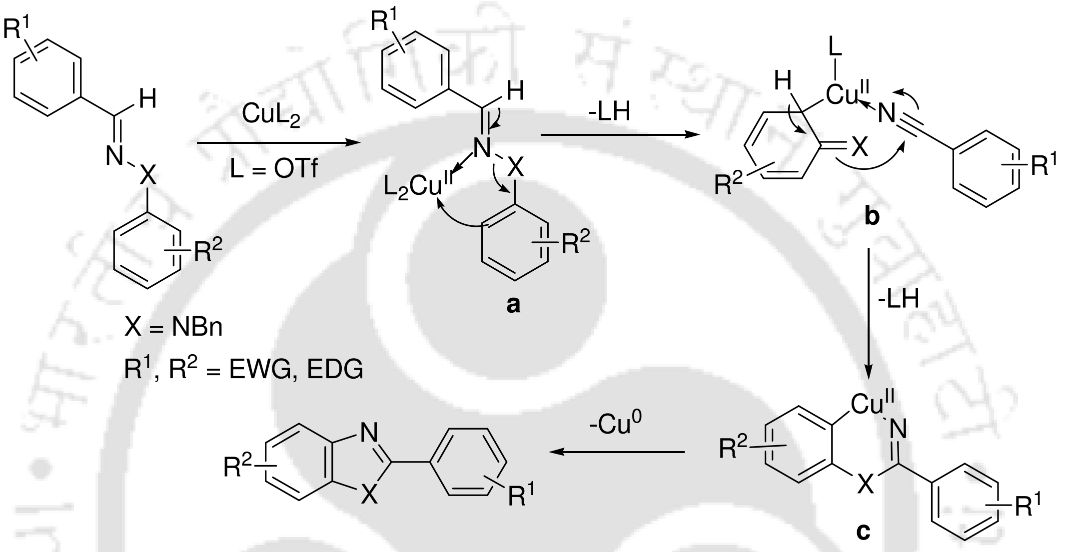
Figure 2. ORTEP diagram of 1-benzyl-5-chloro-2-phenyl-1*H*-benzo[*d*]imidazole **10i**. H-Atoms have been omitted for clarity.

Scheme 18. Reaction of *meta* Substituted *N*-Benzyl Bisarylhydrazone



Proposed Mechanism. Based on the experimental results[27] and observations, the reaction might be involved a Lewis acid assisted C–H functionalization followed by C–N bond formation (Scheme 19). Copper(II) triflate may undergo coordination with the imine nitrogen of the substrates **9a-x** to give the intermediate **a**. The activated intermediate **a** may then lead to the formation of **b** by electrophilic aromatic substitution at the copper center. Intermediate **b** may further rearrange to form six membered metallocycle **c** and the subsequent reductive elimination of elemental copper[28] could give the target heterocycles **10a-v**.

Scheme 19. Plausible Mechanistic Path



In conclusion, copper(II)-mediated conversion of *N*-benzyl bisarylhydrazones into *N*-benzyl 2-arylbenzimidazoles has been developed *via* a cascade C–H functionalization/C–N bond formation. The reactions could be performed under neutral and ligand free conditions. This methodology could be utilized for large scale synthesis of *N*-benzyl-2-arylbenzimidazoles from readily available starting precursors.

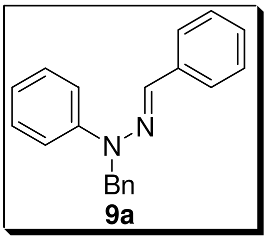
Experimental Section

General Experimental Methods. Aldehydes, anilines, benzyl bromide, NaH, $SnCl_2{\cdot}2H_2O$ and $Cu(OTf)_2$ (98%) were purchased from commercial sources and used as received. Solvents were freshly dried prior to use. Purification of the reaction products was carried out by column chromatography using silica gel (230-400 mesh). Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on 400 MHz spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz.

Melting points were determined using melting point apparatus and are uncorrected. IR spectra were recorded using FT-IR spectrometer. Elemental analyses were recorded using CHNS analyzer. Mass spectra were recorded on mass spectrometer. Single crystal X-ray data were recorded using Mo/Kα radiation equipped with a CCD area detector. The structures were solved by direct method using *SHELLX-97* (Göttingen, Germany). Bisaryhydrazones were prepared according to reported procedure.[25]

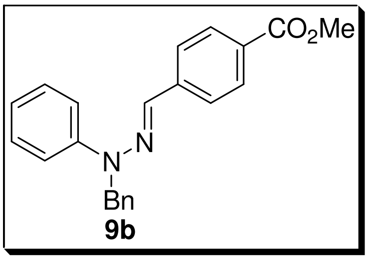
General Procedure for Preparation of Arylhydrazine Hydrochlorides B.[24] To a stirred solution of anilines **A** (6 mmol) in conc. HCl (10.4 mL) at 0 °C, an ice cooled solution of $NaNO_2$ (6.38 mmol, 0.44 g) in distilled water (2.5 mL) was added drop wise for 0.25 h. A solution of $SnCl_2{\cdot}2H_2O$ (13.3 mmol, 3.00 g) in conc. HCl (3.0 mL) was then added drop wise for 0.1 h and the stirring was continued for an additional 0.5 h. The precipitate was filtered and dried under vacuum to give the titled hydrazine hydrochlorides **B** and were used without further purification for the condensation with aldehydes.

General Procedure for *N*-Benzylation of Bisarylhydrazones C. To a stirred suspension NaH (5 mmol, 0.20 g)) in THF (2 mL) at 0 ^{o}C, bisarylhydrazones **C** (5 mmol) in THF (3 mL) were added drop wise under nitrogen atmosphere. After 2 h, the solution was treated with benzyl bromide (5 mmol, 0.86 g) in THF (2 mL) drop wise and the resultant mixture was allowed to stir for 24 h at ambient temperature. Evaporation of the solvent gave a residue that was extracted using ethyl acetate (30 mL). The organic layer was washed with water (2x15 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford the titled compounds **9a-y** those were used for the cyclization reactions.



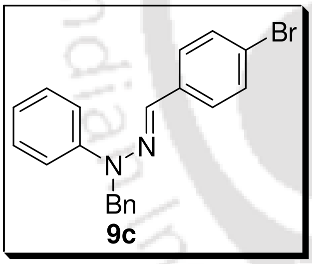
9a

1-Benzyl-2-benzylidene-1-phenylhydrazine 9a. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 88% (1.15 g); mp 111-112 °C (lit.[29a] mp 112 °C); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.42-7.23 (m, 13H), 6.97 (t, *J* =7.2 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 148.0, 136.6, 135.8, 132.6, 129.3, 129.1, 128.6, 128.0, 127.4, 126.3, 126.1, 120.9, 114.9, 50.4; FT-IR (KBr) 3085, 3060, 3024, 3003, 2949, 2922, 1950, 1599, 1589, 1561, 1491, 1462, 1453, 1442, 1393, 1352, 1331, 1312, 1296, 1285, 1248, 1223, 1191, 1157, 1148, 1070, 1046, 1027 cm^{-1}; (ESI-MS) *m/z* 287.17 [M + H]$^+$. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.95; H, 6.31; N, 9.74.



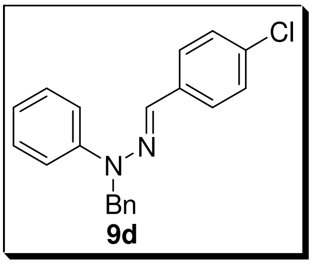
9b

2-(4-Carbomethoxybenzylidene)-1-benzyl-1-phenylhydrazine 9b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.45; light yellow solid; yield 85% (1.46 g); mp 130-132 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.41-7.39 (m, 2H), 7.34-7.26 (m, 6H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.99-6.96 (m, 1H), 5.14 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.0, 147.7, 141.0, 135.3, 131.1, 130.0, 129.4, 129.2, 128.9, 127.6, 126.1, 125.9, 121.6, 115.3, 52.1, 50.7; FT-IR (KBr) 3032, 2948, 2868, 1717, 1596, 1586, 1555, 1495, 1454, 1431, 1410, 1393, 1353, 1331, 1314, 1275, 1242, 1160, 1149, 1110 cm^{-1}; (ESI-MS) *m/z* 345.16 [M + H]$^+$. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.79 H, 5.87; N, 8.07.

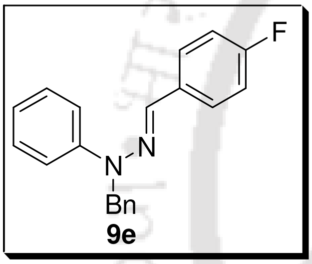


9c

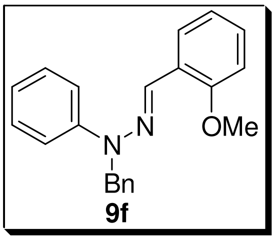
2-(4-Bromobenzylidene)-1-benzyl-1-phenylhydrazine 9c. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R$_f$ = 0.50; colorless solid; yield 92% (1.68 g); mp 150-151 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49-7.24 (m, 14H), 6.98 (t, *J* = 7.2 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.8, 135.7, 135.5, 131.7, 131.2, 129.4, 129.2, 127.7, 127.5, 126.1, 121.6, 121.2, 115.1, 50.7; FT-IR (KBr) 3082, 3059, 3022, 2868, 1590, 1576, 1552, 1496, 1453, 1398, 1352, 1333, 1302, 1245, 1227, 1150, 1099, 1069, 1041, 1028, 1005 cm^{-1}; (ESI-MS) *m/z* 365.08, 367.08 [M + H]$^+$. Anal. Calcd for $C_{20}H_{17}BrN_2$: C, 65.76; H, 4.69; N, 7.67. Found: C, 65.84; H, 4.66; N, 7.61.



2-(4-Chlorobenzylidene)-1-benzyl-1-phenylhydrazine 9d. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 90% (1.44 g); mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.4$ Hz, 2H), 7.40-7.21 (m, 12H), 6.98 (t, $J = 7.2$ Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 135.6, 135.3, 133.5, 131.3, 129.4, 129.2, 128.9, 127.6, 127.5, 126.2, 121.2, 115.1, 50.7; FT-IR (KBr) 3086, 3061, 3023, 1593, 1577, 1555, 1497, 1454, 1401, 1392, 1353, 1331, 1302, 1292, 1245, 1229, 1219, 1192, 1149, 1100, 1086, 1041, 1029, 1008 cm^{-1}; (ESI-MS) *m/z* 321.13 $[M + H]^+$. Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.88; H, 5.34; N, 8.73. Found: C, 74.95; H, 5.32; N, 8.79.

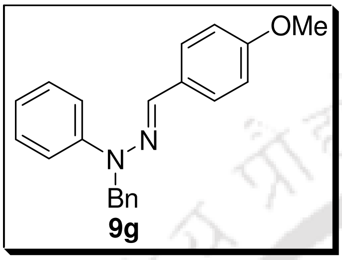


2-(4-Fluorobenzylidene)-1-benzyl-1-phenylhydrazine 9e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.45$; colorless solid; yield 88% (1.34 g); mp 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.40-7.22 (m, 10H), 7.03-6.94 (m, 3H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 147.9, 135.7, 132.9, 131.5, 129.3, 129.2, 127.9, 127.8, 127.5, 126.2, 121.0, 115.7, 115.5, 115.0, 50.7; FT-IR (KBr) 3060, 3024, 2923, 2851, 1654, 1599, 1566, 1489, 1451, 1407, 1394, 1352, 1331, 1290, 1227, 1212, 1192, 1148, 1092, 1075, 1047, 1028 cm^{-1}; (ESI-MS) *m/z* 305.15 $[M + H]^+$. Anal. Calcd for $C_{20}H_{17}FN_2$: C, 78.92; H, 5.63; N, 9.20. Found: C, 78.84; H, 5.60; N, 9.28.



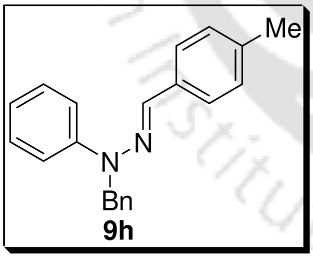
2-(2-Methoxybenzylidene)-1-benzyl-1-phenylhydrazine 9f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 80% (1.27 g); mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, $J = 7.6$ Hz, 1.2

Hz, 1H), 7.81 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.34-7.18 (m, 8H), 6.99-6.90 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 148.1, 136.0, 129.3, 129.0, 128.8, 128.6, 127.3, 126.4, 125.6, 125.3, 121.0, 120.6, 114.8, 111.3, 55.6, 50.2; FT-IR (KBr) 3014, 2967, 2939, 2835, 1597, 1561, 1485, 1462, 1428, 1391, 1350, 1329, 1283, 1239, 1199, 1145, 1105, 1072, 1047, 1025 cm^{-1}; (ESI-MS) *m/z* 317.17 [M + H]$^+$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.78; H, 6.34; N, 8.79.



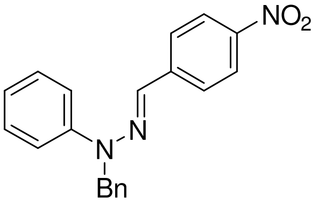
9g

2-(4-Methoxybenzylidene)-1-benzyl-1-phenylhydrazine 9g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; light yellow solid; yield 90% (1.42 g); mp 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 3H), 7.37-7.24 (m, 9H), 6.92-6.86 (m, 3H), 5.15 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 148.1, 136.1, 132.6, 129.5, 129.3, 129.1, 127.6, 127.4, 126.2, 120.5, 114.6, 114.1, 55.4, 50.4; FT-IR (KBr) 3023, 2965, 2926, 2840, 1647, 1604, 1590, 1563, 1496, 1453, 1444, 1415, 1394, 1354, 1331, 1295, 1247, 1220, 1193, 1179, 1160, 1152, 1106, 1075, 1046, 1027, cm^{-1}; (ESI-MS) *m/z* 317.18 [M + H]$^+$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.79; H, 6.39; N, 8.81.



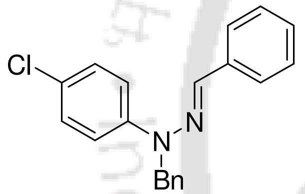
9h

2-(4-Methylbenzylidene)-1-benzyl-1-phenylhydrazine 9h. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.45; colorless solid; yield 81% (1.22 g); mp 136-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.42-7.12 (m, 12H), 6.95-6.93 (m, 1H), 5.17 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 138.0, 136.0, 134.0, 132.8, 129.3, 129.2, 127.4, 126.3, 126.2, 120.7, 114.9, 50.6, 21.5; FT-IR (KBr) 3054, 3024, 2916, 1589, 1578, 1558, 1497, 1453, 1393, 1353, 1331, 1301, 1246, 1190, 1158, 1148, 1109, 1078, 1045, 1027 cm^{-1}; (ESI-MS) *m/z* 301.17 [M + H]$^+$. Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.88; H, 6.73; N, 9.39.



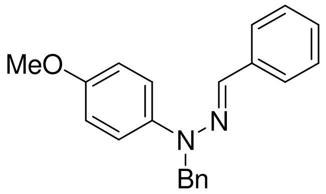
9i

2-(4-Nitrobenzylidene)-1-benzyl-1-phenylhydrazine 9i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.50$; orange solid; yield 83% (1.38 g); mp 119-121 °C (lit.[29a] mp 121-124 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 2H), 7.73-7.71 (m, 2H), 7.45-7.42 (m, 2H), 7.39-7.35 (m, 5H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.26-7.22 (m, 2H), 7.07-7.05 (m, 1H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.5, 142.9, 134.7, 129.5, 129.4, 129.2, 127.7, 126.2, 126.0, 124.0, 122.2, 115.6, 50.9; FT-IR (KBr) 3057, 3029, 2921, 2852, 1596, 1557, 1508, 1495, 1450, 1411, 1397, 1338, 1247, 1181, 1161, 1152, 1108, 1024 cm^{-1}; (ESI-MS) *m/z* 332.15 [M + H]$^+$. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.55; H, 5.15; N, 12.75.



9j

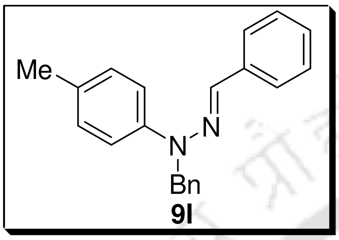
1-Benzyl-2-benzylidene-1-(4-chlorophenyl)hydrazine 9j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.80$; light yellow solid; yield 85% (1.36 g); mp 121-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J = 7.6$ Hz, 2H), 7.39-7.19 (m, 13H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 136.2, 135.2, 133.2, 129.2, 129.1, 128.6, 128.2, 127.5, 126.4, 126.0, 125.6, 115.9, 50.1; FT-IR (KBr) 3063, 3033, 2971, 2916, 2868, 1953, 1589, 1558, 1493, 1454, 1441, 1410, 1394, 1356, 1329, 1312, 1303, 1241, 1221, 1193, 1182, 1148, 1094, 1071, 1026, 1001 cm^{-1}; (ESI-MS) *m/z* 321.12 [M + H]$^+$. Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.88; H, 5.34; N, 8.73. Found: C, 74.82; H, 5.31; N, 8.80.



9k

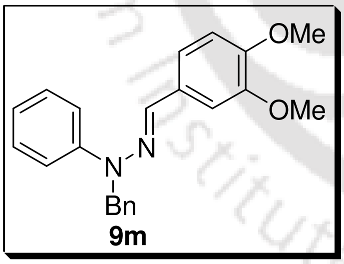
1-Benzyl-2-benzylidene-1-(4-methoxyphenyl)hydrazine 9k. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.30$; light yellow solid;

yield 91% (1.44 g); mp 112-113 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (m, 2H), 7.34-7.18 (m, 11H), 6.88-6.86 (m, 2H), 5.12 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.3, 136.9, 136.2, 131.8, 129.1, 128.6, 127.7, 127.4, 126.3, 126.1, 116.8, 114.7, 55.8, 51.7; FT-IR (KBr) 3029, 2961, 2935, 2853, 1590, 1557, 1509, 1453, 1441, 1423, 1394, 1356, 1326, 1295, 1248, 1177, 1157, 1072, 1044, 1026 cm^{-1}; (ESI-MS) *m/z* 317.18 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.66; H, 6.35; N, 8.91.



9l

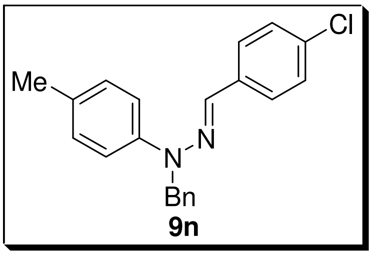
1-Benzyl-2-benzylidene-1-*p*-tolylhydrazine 9l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.45$; yellow solid; yield 88% (1.32 g); mp 137-138 °C (lit.[29b] mp 138 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H), 7.34-7.22 (m, 11H), 7.13-7.11 (m, 2H), 5.15 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 136.8, 136.0, 132.0, 130.2, 129.8, 129.1, 128.6, 127.8, 127.4, 126.2, 115.1, 50.7, 20.7; FT-IR (KBr) 3061, 3026, 2917, 2857, 1611, 1590, 1558, 1510, 1495, 1453, 1442, 1392, 1355, 1329, 1316, 1282, 1245, 1224, 1191, 1151, 1072, 1028 cm^{-1}; (ESI-MS) *m/z* 301.18 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.90; H, 6.68; N, 9.42.



9m

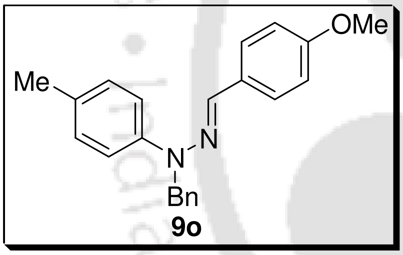
2-(3,4-Dimethoxybenzylidene)-1-benzyl-1-phenylhydrazine 9m. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 92% (1.59 g); mp 117-118 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 11H), 7.01-6.94 (m, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 147.8, 135.8, 132.5, 129.7, 129.1, 128.9, 127.2, 126.0, 120.4, 120.0, 114.5, 110.8, 107.8, 55.8, 50.3; FT-IR (KBr) 3023, 2998, 2966, 2936, 2838, 1594, 1566, 1516, 1497, 1454, 1412, 1394, 1337, 1299, 1266, 1241, 1203, 1191, 1167, 1148, 1138, 1128, 1080, 1023 cm^{-1}; (ESI-MS) *m/z* 347.19 [M +

H]$^+$. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.35; H, 6.37; N, 8.14.



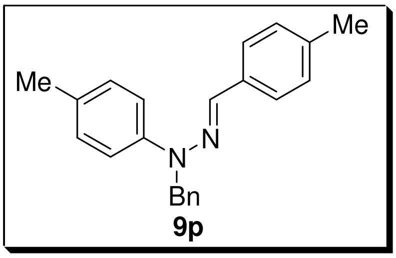
9n

1-(4-Chlorobenzylidene)-2-benzyl-2-*p*-tolylhydrazine 9n. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; light yellow solid; yield 80% (1.34 g); mp 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.36-7.21 (m, 10H), 7.14 (d, *J* = 8.4 Hz, 2H), 5.15 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 135.8, 135.4, 133.3, 130.7, 129.9, 129.2, 128.8, 127.5, 127.3, 126.2, 115.2, 51.0, 20.7; FT-IR (KBr) 3027, 3000, 2917, 1604, 1594, 1553, 1510, 1489, 1455, 1401, 1355, 1329, 1247, 1168, 1152, 1085, 1011 cm^{-1}; (ESI-MS) *m/z* 335.14 [M + H]$^+$. Anal. Calcd for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37. Found: C, 75.41; H, 5.75; N, 8.30.



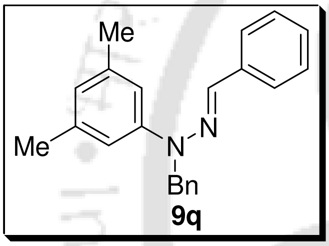
9o

1-(4-Methoxybenzylidene)-2-benzyl-2-*p*-tolylhydrazine 9o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; light brown solid; yield 81% (1.34 g); mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.32-7.22 (m, 8H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.12 (s, 2H), 3.80 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 146.0, 136.2, 132.0, 129.8, 129.1, 127.5, 127.3, 126.2, 114.8, 114.1, 55.4, 50.6, 20.7; FT-IR (KBr) 3060, 3024, 3002, 2934, 2916, 2838, 1608, 1561, 1507, 1453, 1415, 1393, 1345, 1332, 1316, 1256, 1182, 1149, 1104, 1076, 1031 cm^{-1}; (ESI-MS) *m/z* 331.18 [M + H]$^+$. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.05; H, 6.74; N, 8.42.



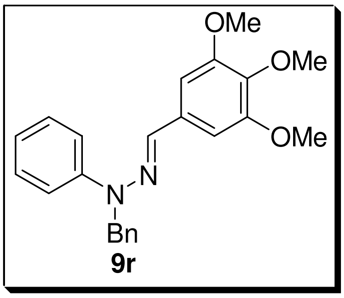
9p

1-(4-Methylbenzylidene)-2-benzyl-2-*p*-tolylhydrazine 9p. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; light yellow solid; yield 80% (1.26 g); mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.32-7.22 (m, 9H), 7.13-7.10 (m, 3H), 5.14 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 137.8, 136.2, 134.1, 132.3, 130.1, 129.8, 129.4, 129.1, 127.4, 126.3, 126.2, 115.0, 50.8, 21.5, 20.7; FT-IR (KBr) 3063, 3023, 2994, 2916, 1611, 1589, 1556, 1508, 1454, 1391, 1355, 1329, 1315, 1301, 1245, 1223, 1193, 1186, 1153, 1108, 1075, 1028 cm^{-1}; (ESI-MS) *m/z* 315.20 $[M + H]^+$. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.11; H, 7.03; N, 8.86.



9q

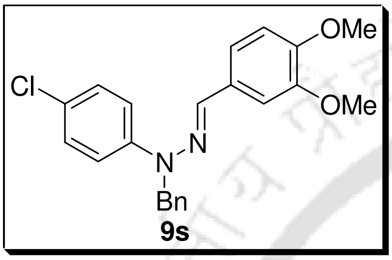
1-Benzyl-2-benzylidene-1-(3,5-dimethylphenyl)hydrazine 9q. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 89% (1.40 g); mp 155-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.34-7.21 (m, 9H), 7.04 (s, 2H), 6.62 (s, 1H), 5.16 (s, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.9, 136.8, 136.0, 132.4, 129.1, 128.6, 127.9, 127.4, 127.3, 126.3, 126.25, 126.20, 123.0, 112.9, 50.8, 21.9; FT-IR (KBr) 3060, 3025, 2969, 2915, 2851, 1598, 1585, 1558, 1494, 1474, 1453, 1440, 1396, 1378, 1355, 1330, 1305, 1294, 1282, 1227, 1207, 1167, 1148, 1072, 1028 cm^{-1}; (ESI-MS) *m/z* 315.20 $[M + H]^+$. Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.09; H, 7.02; N, 8.89.



9r

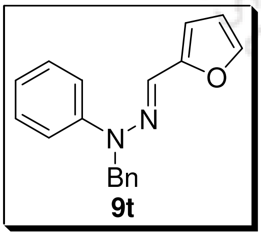
2-(3,4,5-Trimethoxybenzylidene)-1-benzyl-1-phenylhydrazine 9r. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$;

light yellow solid; yield 81% (1.52 g); mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 10H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.87 (s, 2H), 5.18 (s, 2H), 3.89 (s, 6H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 147.8, 138.2, 135.6, 132.3, 132.2, 129.2, 129.1, 127.3, 126.0, 120.8, 114.8, 103.2, 60.9, 56.1, 50.4; FT-IR (KBr) 3088, 3064, 3026, 2998, 2987, 2958, 2926, 2825, 1595, 1565, 1495, 1455, 1430, 1413, 1394, 1351, 1325, 1277, 1238, 1181, 1163, 1130, 1079, 1051, 1040, 1026, 1003 cm^{-1}; (ESI-MS) *m/z* 377.19 [M + H]$^+$. Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.28; H, 6.45; N, 7.37.



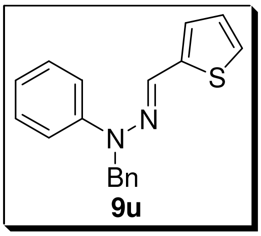
9s

1-(3,4-Dimethoxybenzylidene)-2-benzyl-2-(4-chlorophenyl)hydrazine 9s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; light brown solid; yield 83% (1.58 g); mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 11H), 7.02-7.00 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 2H), 3.95 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 149.3, 146.4, 135.4, 133.3, 129.3, 129.1, 129.0, 127.4, 125.9, 125.2, 120.2, 115.6, 110.9, 107.9, 55.9, 55.8, 50.2; FT-IR (KBr) 3077, 3061, 3021, 3002, 2961, 2936, 2839, 1593, 1563, 1514, 1492, 1455, 1417, 1395, 1340, 1320, 1303, 1240, 1200, 1187, 1165, 1146, 1135, 1119, 1105, 1094, 1073, 1022, 1001 cm^{-1}; (ESI-MS) *m/z* 381.15 [M + H]$^+$. Anal. Calcd for $C_{22}H_{21}ClN_2O_2$: C, 69.38; H, 5.56; N, 7.36. Found: C, 69.31; H, 5.58; N, 7.32.



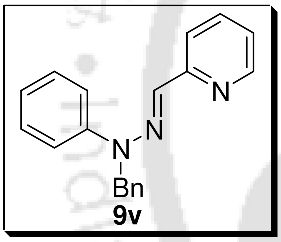
9t

1-Benzyl-2-((furan-2-yl)methylene)-1-phenylhydrazine 9t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 90% (1.24 g); mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 11H), 6.97-6.94 (m, 1H), 6.46-6.40 (m, 2H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 147.6, 142.4, 135.4, 129.3, 129.1, 127.5, 126.1, 123.4, 121.1, 115.1, 111.6, 108.1, 50.6; FT-IR (KBr) 3131, 3109, 3086, 3062, 3029, 3007, 1956, 1867, 1676, 1593, 1544, 1496, 1483, 1452, 1391, 1377, 1357, 1329, 1315, 1301, 1246, 1217, 1191, 1162, 1153, 1142, 1082, 1030, 1013 cm^{-1}; (ESI-MS) *m/z* 277.14 [M + H]$^+$. Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.29; H, 5.82; N, 10.08.



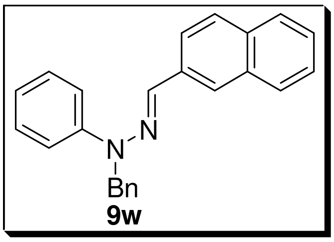
9u

1-Benzyl-1-phenyl-2-((thiophen-2-yl)methylene)hydrazine 9u. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 88% (1.29 g); mp 130-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.36-7.17 (m, 11H), 6.94 (d, *J* = 3.2 Hz, 2H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 142.4, 135.4, 129.2, 129.1, 127.6, 127.4, 127.2, 126.0, 125.9, 125.1, 120.8, 114.7, 50.5; FT-IR (KBr) 3097, 3081, 3062, 3030, 2985, 2923, 2857, 1953, 1650, 1593, 1567, 1520, 1495, 1453, 1436, 1381, 1359, 1346, 1327, 1311, 1299, 1246, 1219, 1194, 1182, 1079, 1041, 1028 cm^{-1}; (ESI-MS) *m/z* 293.12 [M + H]$^+$. Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58; S, 10.97. Found: C, 73.87; H, 5.50; N, 9.61; S, 11.02.



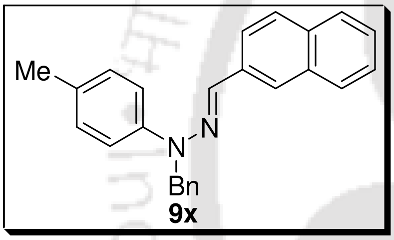
9v

1-Benzyl-1-phenyl-2-((pyridine-2-yl)methylene)hydrazine 9v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; brown solid; yield 90% (1.29 g); mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.44 (m, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.68-7.63 (m, 1H), 7.50 (s, 1H), 7.45-7.42 (m, 2H), 7.37-7.21 (m, 7H), 7.12-7.09 (m, 1H), 7.02-6.98 (m, 1H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 149.0, 147.5, 136.2, 134.9, 133.2, 129.3, 129.0, 127.4, 126.0, 122.1, 121.5, 119.3, 115.2, 50.7; FT-IR (KBr) 3054, 3027, 3000, 1950, 1681, 1593, 1567, 1495, 1473, 1454, 1431, 1388, 1352, 1329, 1283, 1192, 1168, 1154, 1089, 1048, 1029 cm^{-1}; (ESI-MS) *m/z* 288.16 [M + H]$^+$. Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41 H, 5.96; N, 14.62. Found: C, 79.36; H, 5.94; N, 14.70.



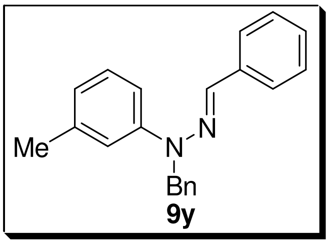
9w

1-Benzyl-2-((naphthalen-2-yl)methylene)-1-phenylhydrazine 9w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.70$; colorless solid; yield 90% (1.51 g); mp 190-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.4$ Hz, 1H), 7.81-7.74 (m, 4H), 7.55 (s, 2H), 7.47-7.25 (m, 10H), 6.99 (t, $J = 6.4$ Hz,1H) 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 135.9, 134.5, 133.7, 133.5, 132.9, 129.4, 129.2, 128.4, 128.1, 128.0, 127.5, 126.7, 126.4, 126.2, 126.1, 123.3, 121.0, 115.1, 50.7; FT-IR (KBr) 3060, 3032, 2981, 1933, 1625, 1595, 1577, 1560, 1496, 1454, 1431, 1400, 1377, 1356, 1327, 1313, 1299, 1272, 1241, 1187, 1180, 1161, 1145, 1076, 1045, 1028 cm^{-1}; (ESI-MS) *m/z* 337.18 $[M + H]^+$. Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.76; H, 5.96; N, 8.28.



9x

2-Benzyl-1-((naphthalen-2-yl)methylene)-2-*p*-tolylhydrazine 9x. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.45$; colorless solid; yield 87% (1.52 g); mp 296-298 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.8$ Hz, 1H), 7.80-7.73 (m, 4H), 7.51-7.14 (m, 12H), 5.21 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.3, 134.0, 133.0, 132.7, 131.5, 129.7, 129.3, 128.6, 127.7, 127.4, 127.3, 126.9, 125.9, 125.8, 125.7, 125.4, 122.6, 114.5, 50.1, 20.1; FT-IR (KBr) 3032, 2928, 2857, 1614, 1560, 1511, 1455, 1430, 1403, 1377, 1357, 1321, 1306, 1242, 1188, 1153, 1028 cm^{-1}; (ESI-MS) *m/z* 351.20 $[M + H]^+$. Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.78; H, 6.29; N, 7.93.

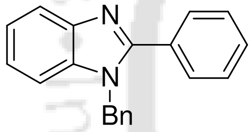


9y

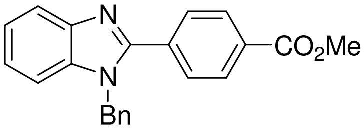
2-Benzyl-1-benzylidene-2-m-tolylhydrazine 9y. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.55$; colorless solid; yield 92% (1.38 g); mp 146-147 °C (lit.[29b] mp 145 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d,

J = 7.2 Hz, 2H), 7.35-7.19 (m, 12H), 6.79-6.77 (m, 1H), 5.16 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 139.1, 136.7, 135.9, 132.5, 129.2, 128.7, 128.0, 127.4, 126.3, 126.2, 121.9, 115.7, 112.2, 50.7, 22.1; FT-IR (KBr) 3054, 3030, 2925, 1637, 1606, 1585, 1560, 1494, 1452, 1442, 1395, 1351, 1329, 1312, 1254, 1225, 1200, 1167, 1148, 1074, 1028 cm^{-1}; (ESI-MS) *m/z* 301.19 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.90; H, 6.73; N, 9.37.

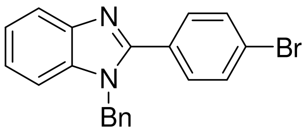
General Procedure for the Cyclization of *N*-Benzyl Bisarylhydrazones 9a-y. Substrates **9a-y** (0.5 mmol) and $Cu(OTf)_2$ (0.5 mmol, 180.75 mg) were stirred at 110 °C in toluene (2 mL) under nitrogen balloon. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and poured into 30% aqueous NH_4OH (5 mL). The solution was extracted with EtOAc (3 x 15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to afford the desired *N*-benzyl 2-arylbenzimidazoles **10a-x** in analytically pure form.


10a

1-Benzyl-2-phenyl-1*H*-benzo[*d*]imidazole[29c] **10a.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.20; colorless solid; yield 64% (90.99 mg); mp 123-124 °C (lit.[29c] mp 132-133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 7.2 Hz, 3H), 7.36-7.30 (m, 4H), 7.26-7.21 (m, 2H), 7.12 (d, J = 6.8 Hz, 2H), 5.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 143.0, 136.5, 136.1, 132.7, 130.2, 129.5, 129.2, 128.9, 128.0, 126.1, 123.3, 123.0, 120.1, 110.7, 48.5; FT-IR (KBr) 3060, 3029, 2962, 2928, 1706, 1600, 1508, 1492, 1469, 1449, 1441, 1392, 1361, 1330, 1314, 1261, 1177, 1163, 1097, 1028, 1002 cm^{-1}; (ESI-MS) *m/z* 285.14 $[M + H]^+$. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.60; H, 5.65; N, 9.75.

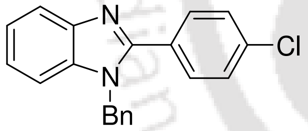

10b

Methyl 4-(1-benzyl-1*H*-benzo[*d*]imidazol-2-yl)benzoate 10b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.20; light yellow solid; yield 54% (92.45 mg); mp 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.11 (m, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.79-7.77 (m, 2H), 7.36-7.26 (m, 6H), 7.11-7.09 (m, 2H), 5.47 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.5, 153.0, 143.2, 136.4, 136.2, 134.4, 131.4, 130.1, 129.4, 129.3, 128.1, 126.0, 123.7, 123.1, 120.3, 110.7, 52.4, 48.5; FT-IR (KBr) 3060, 2950, 2925, 2851, 1713, 1610, 1593, 1518, 1428, 1410, 1310, 1277, 1237, 1157, 1108, 1029, 1015 cm^{-1}; (ESI-MS) *m/z* 343.15 [M + H]$^+$. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.11; H, 5.29; N, 8.23.



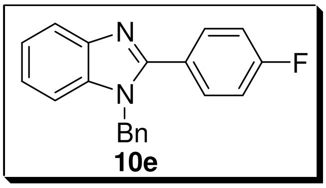
10c

1-Benzyl-2-(4-bromophenyl)-1*H*-benzo[*d*]imidazole 10c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 72% (130.77 mg); mp 130-131 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.60-7.54 (m, 4H), 7.35-7.26 (m, 6H), 7.10 (d, *J* = 6.4 Hz, 2H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.1, 143.0, 136.3, 132.2, 130.9, 129.3, 129.0, 128.4, 128.1, 126.0, 124.8, 123.6, 123.2, 120.2, 110.7, 48.5; FT-IR (KBr) 3058, 2963, 2917, 2855, 1611, 1459, 1446, 1409, 1360, 1328, 1303, 1261, 1162, 1096, 1025 cm^{-1}; (ESI-MS) *m/z* 363.05, 365.05 [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}BrN_2$: C, 66.13; H, 4.16; N, 7.71. Found: C, 66.19; H, 4.14; N, 7.66.



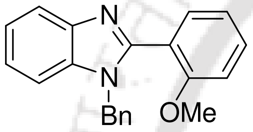
10d

1-Benzyl-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole 10d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.20; colorless solid; yield 70% (111.58 mg); mp 137-138 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.63-7.61 (m, 2H), 7.44-7.42 (m, 2H), 7.34-7.31 (m, 4H), 7.26-7.24 (m, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.0, 142.7, 136.5, 136.2, 136.1, 130.7, 129.3, 129.2, 128.3, 128.1, 126.0, 123.6, 123.2, 120.1, 110.7, 48.5; FT-IR (KBr) 3083, 3059, 3032, 2963, 2855, 1638, 1612, 1601, 1570, 1495, 1459, 1447, 1412, 1390, 1360, 1329, 1303, 1286, 1261, 1180, 1163, 1093, 1027 cm^{-1}; (ESI-MS) *m/z* 319.11 [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}ClN_2$: C, 75.35; H, 4.74; N, 8.79. Found: C, 75.42; H, 4.72; N, 8.85.



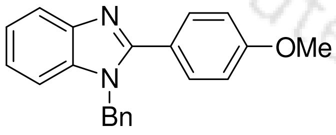
10e

1-Benzyl-2-(4-fluorophenyl)-1*H*-benzo[*d*]imidazole 10e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.20$; colorless solid; yield 75% (113.38 mg); mp 115-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 1H), 7.68-7.65 (m, 2H), 7.34-7.31 (m, 3H), 7.26-7.23 (m, 3H), 7.17-7.09 (m, 4H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.7, 153.3, 142.9, 136.3, 136.1, 131.6, 131.5, 129.3, 128.1, 126.1, 123.5, 123.1, 120.1, 116.2, 116.0, 110.7, 48.5; FT-IR (KBr) 3033, 2926, 2854, 1717, 1607, 1534, 1462, 1450, 1418, 1391, 1361, 1329, 1279, 1258, 1231, 1162, 1102, 1027 cm^{-1}; (ESI-MS) *m/z* 303.14 $[M + H]^+$. Anal. Calcd for $C_{20}H_{15}FN_2$: C, 79.45; H, 5.00; N, 9.27. Found: C, 79.52; H, 4.97; N, 9.23.



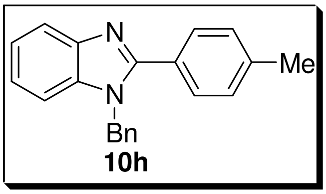
10f

1-Benzyl-2-(2-methoxyphenyl)-1*H*-benzo[*d*]imidazole 10f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.20$; colorless liquid; yield 62% (97.45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 6.0$ Hz, 2H), 7.50-7.45 (m, 1H), 7.27-7.15 (m, 5H), 7.08-7.03 (m, 2H), 6.98 (d, $J = 8.4$ Hz, 2H), 5.23 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 152.3, 143.2, 136.5, 135.3, 132.7, 131.9, 128.7, 127.6, 126.8, 122.9, 122.4, 121.2, 120.0, 119.4, 111.1, 110.8, 55.4, 48.6; FT-IR (KBr) 2962, 2931, 2857, 1608, 1519, 1462, 1455, 1394, 1331, 1287, 1258, 1181, 1162, 1076, 1023 cm^{-1}; (ESI-MS) *m/z* 315.15 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.17; H, 5.79; N, 8.96.



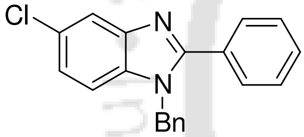
10g

1-Benzyl-2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole 10g. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.20$; colorless liquid; yield 60% (94.31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.34-7.20 (m, 6H), 7.12 (d, $J = 6.0$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 5.44 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 154.3, 143.2, 136.7, 136.2, 130.9, 130.3, 129.3, 127.9, 126.1, 123.0, 122.8, 119.9, 114.4, 110.6, 55.5, 48.6; FT-IR (KBr) 3031, 2997, 2961, 2927, 2854, 1718, 1610, 1575, 1509, 1495, 1453, 1442, 1420, 1389, 1362, 1329, 1302, 1260, 1179, 1163, 1097, 1033 cm^{-1}; (ESI-MS) *m/z* 315.16 [M + H]$^+$. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.28; H, 5.79; N, 8.86.



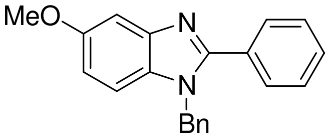
10h

1-Benzyl-2-*p*-tolyl-1*H*-benzo[*d*]imidazole 10h. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 65% (96.97 mg); mp 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.31-7.21 (m, 8H), 7.12 (d, *J* = 6.4 Hz, 2H), 5.45 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.1, 140.3, 136.6, 136.1, 129.6, 129.3, 129.2, 127.9, 127.1, 126.1, 123.1, 122.8, 120.0, 110.6, 48.5, 21.6; FT-IR (KBr) 3032, 2939, 2925, 2855, 1611, 1448, 1416, 1392, 1362, 1331, 1279, 1251, 1190, 1163, 1115, 1027 cm^{-1}; (ESI-MS) *m/z* 299.16 [M + H]$^+$. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.59; H, 6.06; N, 9.35.



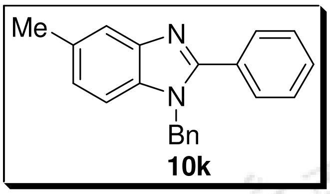
10i

1-Benzyl-5-chloro-2-phenyl-1*H*-benzo[*d*]imidazole 10i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 68% (108.39 mg); mp 145-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.6 Hz, 1H), 7.66-7.64 (m, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.32-7.29 (m, 2H), 7.19-7.16 (m, 2H), 7.10-7.05 (m, 4H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 144.2, 136.1, 134.8, 130.4, 129.8, 129.4, 129.3, 129.0, 128.5, 128.2, 126.1, 123.6, 119.9, 111.5, 48.7; FT-IR (KBr) 3046, 2957, 2928, 1608, 1496, 1470, 1453, 1426, 1390, 1362, 1321, 1312, 1258, 1179, 1162, 1076, 1057, 1027 cm^{-1}; (ESI-MS) *m/z* 319.11 [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}ClN_2$: C, 75.35; H, 4.74; N, 8.79. Found: C, 75.28; H, 4.76; N, 8.74.



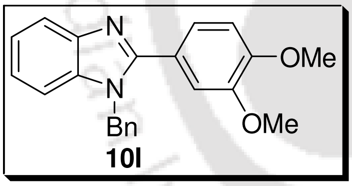
10j

1-Benzyl-5-methoxy-2-phenyl-1*H*-benzo[*d*]imidazole 10j. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.20; colorless liquid; yield 70% (110.03 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.44 (d, *J* = 6.4 Hz, 3H) 7.33-7.27 (m, 4H), 7.09-7.04 (m, 3H), 6.87 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H) 5.41 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 154.5, 144.1, 136.6, 130.9, 130.4, 130.0, 129.4, 129.2, 128.9, 128.0, 126.2, 113.3, 111.1, 102.3, 56.0, 48.7; FT-IR (KBr) 3063, 2933, 2834, 1621, 1514, 1488, 1472, 1453, 1435, 1392, 1342, 1277, 1199, 1154, 1116, 1075, 1028 cm^{-1}; (ESI-MS) *m/z* 315.16 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.30; H, 5.75; N, 8.87.



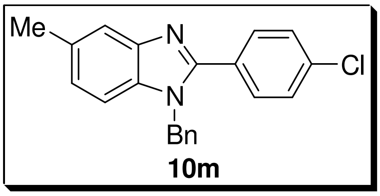
10k

1-Benzyl-5-methyl-2-phenyl-1*H*-benzo[*d*]imidazole[29d] 10k. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.30; colorless solid; yield 64% (95.48 mg); mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 3H), 7.44 (d, *J* = 6.8 Hz, 3H), 7.31-7.27 (m, 3H), 7.09-7.05 (m, 4H), 5.41 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 143.3, 136.6, 134.2, 132.6, 130.1, 130.0, 129.4, 129.1, 128.8, 127.9, 126.1, 124.7, 119.8, 110.2, 48.5, 21.7; FT-IR (KBr) 3029, 2963, 1699, 1603, 1493, 1471, 1449, 1421, 1392, 1364, 1326, 1312, 1261, 1172, 1096, 1027 cm^{-1}; (ESI-MS) *m/z* 299.17 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.46; H, 6.10; N, 9.44.



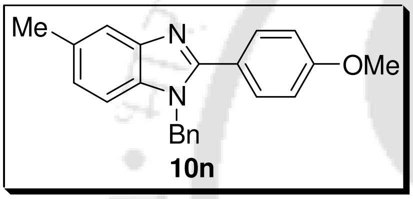
10l

1-Benzyl-2-(3,4-dimethoxyphenyl)-1*H*-benzo[*d*]imidazole 10l. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.20; colorless liquid; yield 65% (11.93 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2 Hz, 1H), 7.45 (s, 1H) 7.35-7.22 (m, 7H), 7.15-7.09 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 3.91 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 150.8, 149.3, 142.7, 136.8, 136.2, 129.6, 129.3, 128.0, 126.0, 123.3, 123.1, 122.1, 119.8, 112.6, 111.3, 110.5, 56.1, 55.9, 48.6; FT-IR (KBr) 2961, 2935, 2034, 1707, 1638, 1605, 1495, 1456, 1439, 1355, 1325, 1266, 1225, 1178, 1140, 1024 cm^{-1}; (ESI-MS) *m/z* 345.17 $[M + H]^+$. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.78 H, 5.87; N, 8.08.



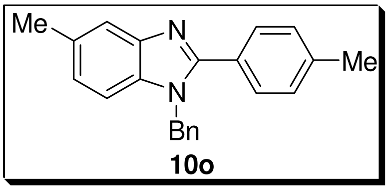
10m

1-Benzyl-2-(4-chlorophenyl)-5-methyl-1*H*-benzo[*d*]imidazole 10m. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 41% (68.23 mg); mp 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.58 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.32-7.28 (m, 4H), 7.08-7.06 (m, 3H), 5.39 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 152.9, 143.5, 136.4, 136.2, 132.7, 130.6, 130.0, 129.2, 129.1, 128.7, 128.0, 126.0, 124.9, 119.9, 110.1, 48.4, 21.7; FT-IR (KBr) 3028, 2922, 2854, 1624, 1599, 1569, 1496, 1489, 1468, 1452, 1430, 1408, 1386, 1359, 1325, 1298, 1279, 1259, 1171, 1143, 1092, 1028, 1012 cm^{-1}; (ESI-MS) *m/z* 333.12 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42. Found: C, 75.70; H, 5.18; N, 8.47.



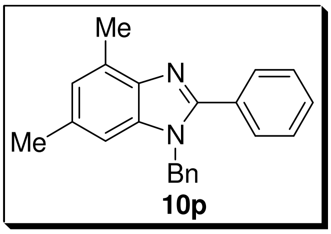
10n

1-Benzyl-2-(4-methoxyphenyl)-5-methyl-1*H*-benzo[*d*]imidazole 10n. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.20$; colorless solid; yield 48% (78.82 mg); mp 73-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 3H), 7.31-7.27 (m, 3H), 7.10-7.03 (m, 4H), 6.94 (d, J = 8.8 Hz, 2H), 5.39 (s, 2H), 3.82 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 154.1, 143.4, 136.7, 134.2, 132.3, 130.7, 129.1, 127.7, 126.0, 124.3, 122.4, 119.5, 114.2, 110.0, 55.4, 48.4, 21.6; FT-IR (KBr) 3028, 2924, 2855, 1610, 1578, 1536, 1479, 1465, 1450, 1417, 1391, 1353, 1324, 1295, 1254, 1175, 1113, 1025 cm^{-1}; (ESI-MS) *m/z* 329.17 $[M + H]^+$. Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.54; H, 6.12; N, 8.48.



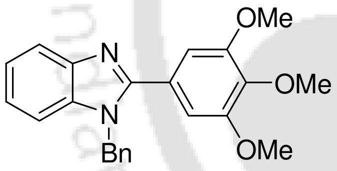
10o

1-Benzyl-5-methyl-2-*p*-tolyl-1*H*-benzo[*d*]imidazole 10o. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 52% (81.23 mg); mp 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.32-7.23 (m, 5H), 7.10-7.04 (m, 4H), 5.41 (s, 2H), 2.49 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 143.5, 140.0, 136.7, 134.3, 132.3, 129.5, 129.2, 129.1, 127.7, 127.3, 126.0, 124.4, 119.7, 110.1, 48.4, 21.7, 21.5; FT-IR (KBr) 3028, 2956, 2923, 2854, 1606, 1503, 1467, 1452, 1416, 1386, 1364, 1323, 1280, 1259, 1171, 1141, 1104, 1027 cm^{-1}; (ESI-MS) *m/z* 313.18 [M + H]$^+$. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.51; H, 6.47; N, 9.02.



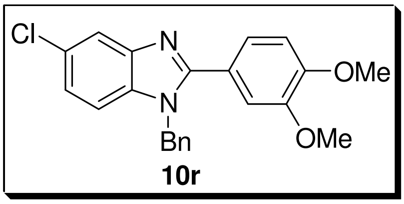
10p

1-Benzyl-4,6-dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole 10p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.30$; colorless liquid; yield 67% (104.66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.41 (d, *J* = 6.4 Hz, 3H), 7.34-7.26 (m, 3H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.93 (s, 1H), 6.81 (s, 1H), 5.35 (s, 2H), 2.68 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 140.8, 136.9, 136.1, 133.1, 130.6, 129.8, 129.5, 129.1, 128.8, 127.8, 126.1, 124.9, 120.2, 120.0, 107.9, 48.3, 21.9, 16.9; FT-IR (KBr) 2919, 2856, 1627, 1495, 1452, 1392, 1359, 1332, 1262, 1230, 1174, 1075, 1027 cm^{-1}; (ESI-MS) *m/z* 313.17 [M + H]$^+$. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.66; H, 6.42; N, 8.92.



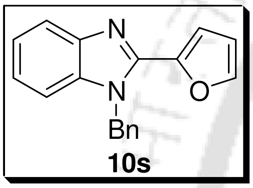
10q

1-Benzyl-2-(3,4,5-trimethoxyphenyl)-1*H*-benzo[*d*]imidazole 10q. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f = 0.25$; colorless liquid; yield 63% (117.95 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.34-7.26 (m, 4H), 7.14 (d, *J* = 7.2 Hz, 2H), 6.85 (s, 2H), 5.46 (s, 2H), 3.85 (s, 3H), 3.62 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.5, 142.7, 139.7, 136.9, 136.4, 131.2, 129.4, 128.0, 125.8, 124.9, 123.5, 123.2, 120.0, 110.4, 106.6, 104.0, 61.1, 56.5, 56.1, 48.6; FT-IR (KBr) 2967, 2933, 2151, 1957, 1635, 1588, 1455, 1416, 1328, 1238, 1177, 1125, 1012 cm^{-1}; (ESI-MS) *m/z* 375.18 [M + H]$^+$. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.86; H, 5.95; N, 7.44.



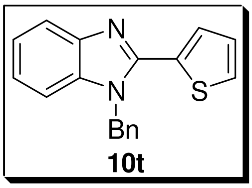
10r

1-Benzyl-5-chloro-2-(3,4-dimethoxyphenyl)-1*H*-benzo[*d*]imidazole 10r. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.50$; colorless liquid; yield 31% (58.72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, $J = 1.6$ Hz, 1H), 7.35-7.29 (m, 3H), 7.20-7.17 (m, 3H), 7.11-7.08 (m, 3H), 6.90 (d, $J = 8.0$ Hz, 1H), 5.43 (s, 2H), 3.89 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 150.8, 149.2, 143.9, 136.3, 135.0, 129.3, 128.3, 128.0, 125.8, 123.4, 122.0, 119.5, 112.2, 111.1, 56.0, 55.8, 48.6; FT-IR (KBr) 2928, 1639, 1491, 1464, 1314, 1265, 1219, 1175, 1136, 1051, 1024 cm^{-1}; (ESI-MS) *m/z* 379.13 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.05; N, 7.39. Found: C, 69.69; H, 5.08; N, 7.45.



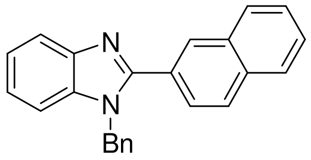
10s

1-Benzyl-2-(furan-2-yl)-1*H*-benzo[*d*]imidazole 10s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.30$; light yellow solid; yield 78% (106.98 mg); mp 126-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J = 8.0$ Hz, 1H), 7.57 (s, 1H), 7.32-7.23 (m, 6H), 7.15 (d, $J = 6.4$ Hz, 2H), 7.09 (d, $J = 2.8$ Hz, 1H), 6.56 (dd, $J = 3.6, 1.6$ Hz, 1H), 5.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.6, 144.3, 143.2, 136.6, 135.9, 129.1, 127.9, 126.5, 123.5, 123.2, 120.1, 113.1, 112.2, 110.2, 48.5; FT-IR (KBr) 3146, 3127, 3030, 2963, 2926, 2854, 1618, 1604, 1514, 1495, 1450, 1424, 1354, 1328, 1283, 1261, 1226, 1173, 1150, 1091, 1071, 1026 cm^{-1}; (ESI-MS) *m/z* 275.12 $[M + H]^+$. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.87; H, 5.16; N, 10.15.



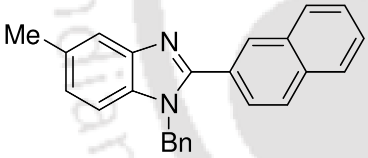
10t

1-Benzyl-2-(thiophen-2-yl)-1*H*-benzo[*d*]imidazole 10t. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.35$; light yellow solid; yield 70% (101.63 mg); mp 136-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 5.2$ Hz, 1H), 7.35-7.25 (m, 7H), 7.14 (d, $J = 6.8$ Hz, 2H), 7.09-7.07 (m, 1H), 5.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 143.2, 136.5, 136.3, 132.2, 131.1, 129.3, 129.0, 128.1, 126.1, 123.5, 123.2, 120.1, 110.2, 48.4; FT-IR (KBr) 2963, 2927, 2855, 2215, 1726, 1638, 1494, 1453, 1421, 1388, 1355, 1324, 1261, 1225, 1095, 1023 cm^{-1}; (ESI-MS) *m/z* 291.10 [M + H]$^+$. Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 74.38; H, 4.84; N, 9.69; S, 11.09.



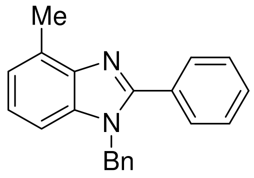
10u

1-Benzyl-2-(naphthalen-2-yl)-1*H*-benzo[*d*]imidazole 10u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.30$; colorless solid; yield 70% (117.04 mg); mp 131-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.92-7.85 (m, 3H), 7.81-7.75 (m, 2H), 7.53-7.49 (m, 2H), 7.35-7.29 (m, 4H), 7.26-7.25 (m, 2H), 7.15 (d, *J* = 6.8 Hz, 2H), 5.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 143.1, 136.6, 136.3, 133.9, 133.1, 129.5, 129.3, 128.7, 128.0, 127.9, 127.4, 127.2, 126.9, 126.3, 126.2, 123.4, 123.0, 120.1, 110.7, 48.7; FT-IR (KBr) 3056, 2963, 2927, 2853, 1693, 1599, 1525, 1494, 1459, 1451, 1436, 1399, 1354, 1328, 1285, 1260, 1229, 1095, 1019 cm^{-1}; (ESI-MS) *m/z* 335.16 [M + H]$^+$. Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.28; H, 5.40; N, 8.32.



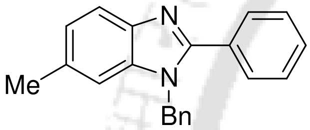
10v

1-Benzyl-5-methyl-2-(naphthalen-3-yl)-1*H*-benzo[*d*]imidazole 10v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.30$; colorless solid; yield 36% (62.72 mg); mp 169-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.90-7.75 (m, 5H), 7.68 (s, 1H), 7.53-7.49 (m, 2H), 7.34-7.30 (m, 3H), 7.14-7.07 (m, 3H), 5.47 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 143.7, 136.7, 134.5, 133.8, 133.0, 132.6, 129.4, 129.2, 129.1, 128.6, 128.3, 127.9, 127.5, 127.3, 126.8, 126.3, 126.1, 124.8, 119.9, 110.1, 48.6, 21.7; FT-IR (KBr) 3019, 2921, 2853, 1601, 1525, 1496, 1487, 1445, 1423, 1390, 1357, 1341, 1321, 1254, 1228, 1196, 1160, 1137, 1075, 1030 cm^{-1}; (ESI-MS) *m/z* 349.18 [M + H]$^+$. Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79; N, 8.04. Found: C, 86.24; H, 5.77; N, 7.99.



10w

1-Benzyl-4-methyl-2-phenyl-1*H*-benzo[*d*]imidazole 10w. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; gummy liquid; yield 12% (17.90 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.45-7.43 (m, 3H), 7.33-7.27 (m, 3H), 7.13-7.03 (m, 5H), 5.40 (s, 2H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 142.7, 136.7, 135.8, 130.5, 130.3, 130.0, 129.6, 129.2, 128.9, 127.9, 126.2, 123.2, 123.1, 108.2, 48.5, 17.0; FT-IR (KBr) 3059, 3029, 2950, 2923, 2854, 1610, 1496, 1470, 1452, 1423, 1384, 1353, 1333, 1264, 1246, 1206, 1153, 1112, 1075, 1029 cm^{-1}; (ESI-MS) *m/z* 299.17 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.59; H, 6.06; N, 9.35.



10x

1-Benzyl-6-methyl-2-phenyl-1*H*-benzo[*d*]imidazole[29e] 10x. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.45$; colorless solid; yield 25% (37.30 mg); mp 196-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $J = 8.0$ Hz, 1H), 7.65-7.63 (m, 2H), 7.44-7.41 (m, 3H), 7.34-7.29 (m, 3H), 7.13-7.08 (m, 3H), 6.98 (s, 1H), 5.41 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 141.4, 136.7, 136.5, 133.3, 130.3, 129.9, 129.4, 129.2, 128.9, 127.9, 126.1, 124.5, 119.6, 110.5, 48.4, 22.0; FT-IR (KBr) 3057, 3029, 2924, 2854, 1615, 1603, 1493, 1470, 1450, 1394, 1367, 1330, 1313, 1276, 1204, 1179, 1142, 1123, 1068, 1029 cm^{-1}; (ESI-MS) *m/z* 299.17 $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.48; H, 6.10; N, 9.42.

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Crystal Data and Structure Refinement for 10i at 298(2) K

Identification code	mg-1	
Empirical formula	$C_{20}H_{15}ClN_2$	
Formula weight	318.79	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
	Loop xyz ‘x, y, z’ ‘-x, y+1/2, -z+1/2’ ‘-x, -y, -z’ ‘x, -y-1/2, z-1/2’	
Unit cell dimensions	*a* = 6.2920(3) Å	α(°)=90.00
	b = 17.3537(9) Å	β(°)=91.041(2)
	c = 14.9263(7) Å	γ(°)=90.00
Volume	1629.53(14)$Å^3$	
Z	4	
Density (calculated)	1.299Mg/m^3	
Absorption coefficient	0.235mm^{-1}	
F(000)	664.0	
Crystal size	0.34x 0.31 x 0.26 mm	
Theta range for data collection	1.80 to 28.43 °	
Index ranges	-8<=h<=8, -22<=k<=21, -17<=l<=19	
Reflections collected	4009	
Independent reflections	2826 [R (int) = 0.0715]	
Completeness to theta = 28.43°	97.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.941and 0 0.923	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4009 / 0 /209	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma (I)]	*R1* = 0.0413, *wR2* = 0.1218	
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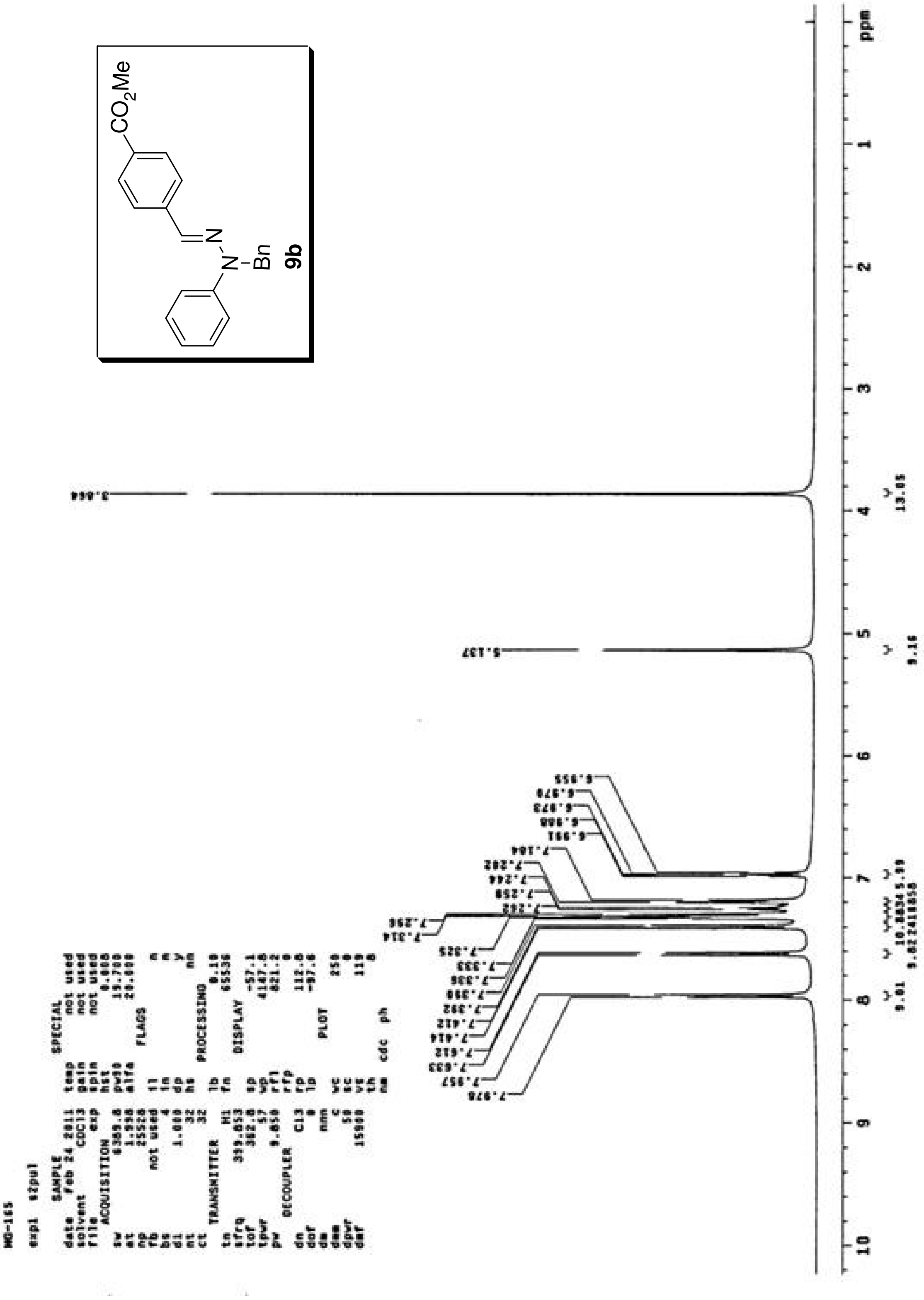
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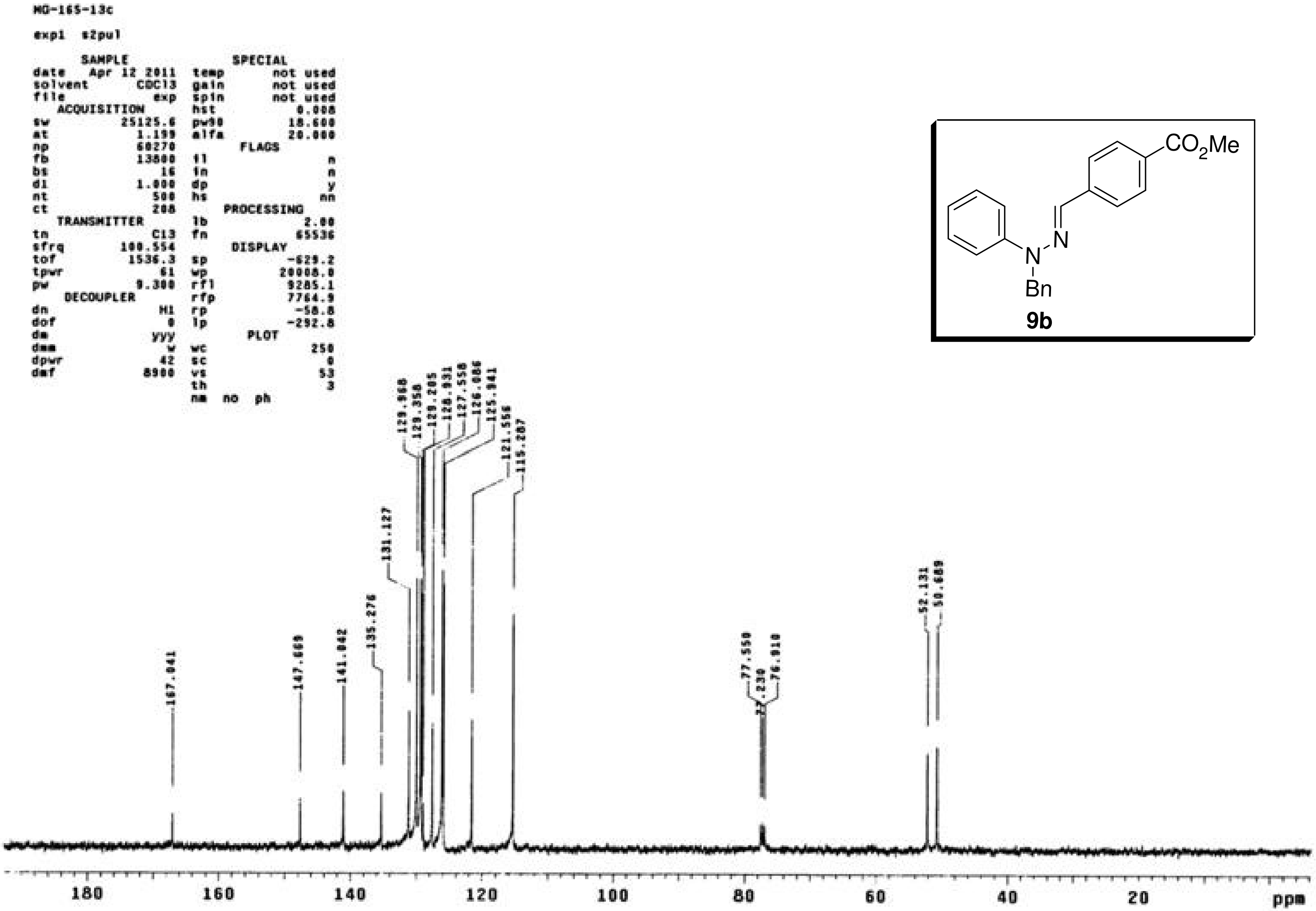
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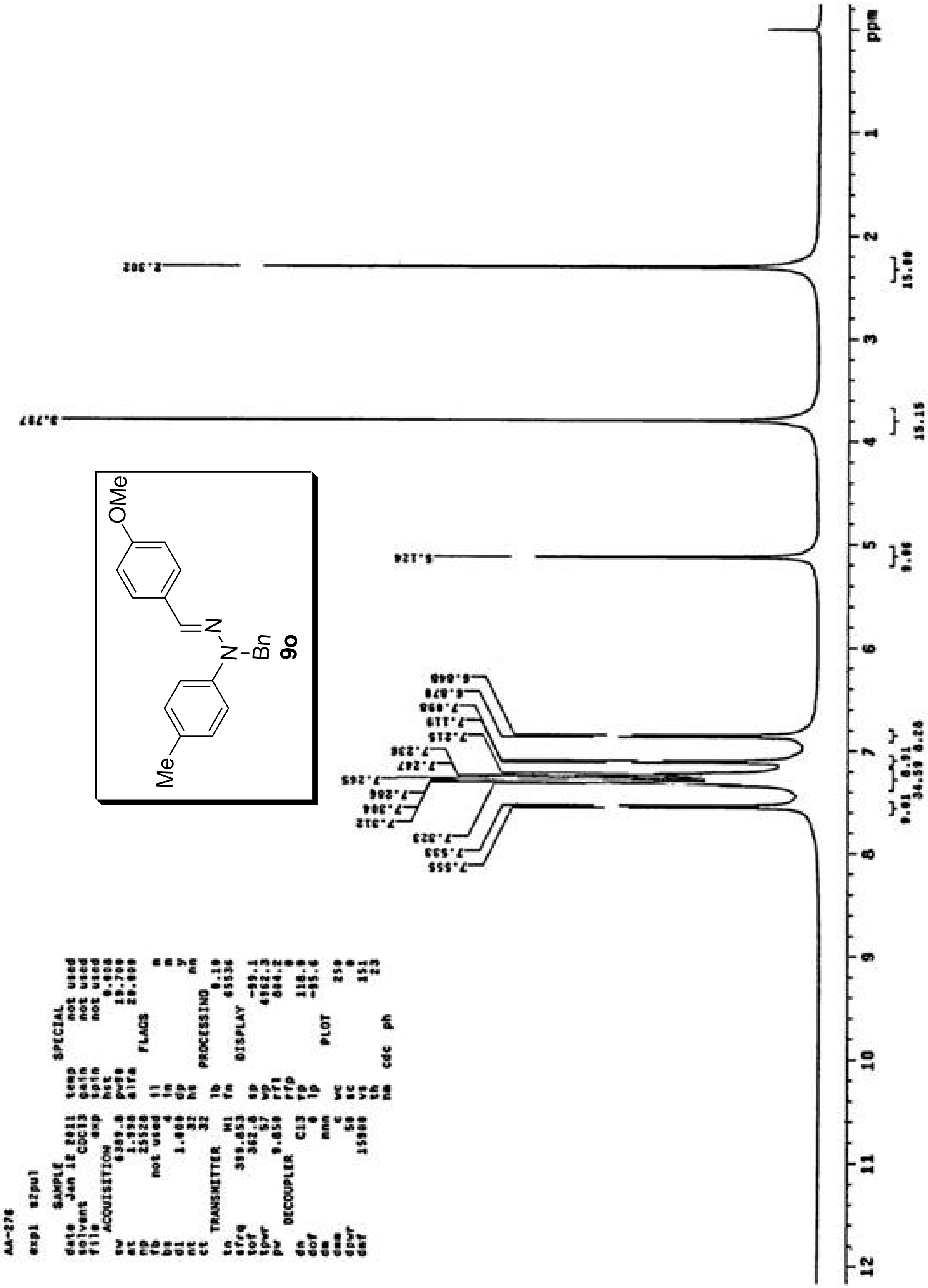
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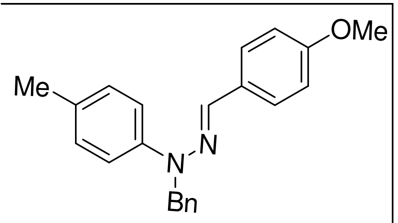

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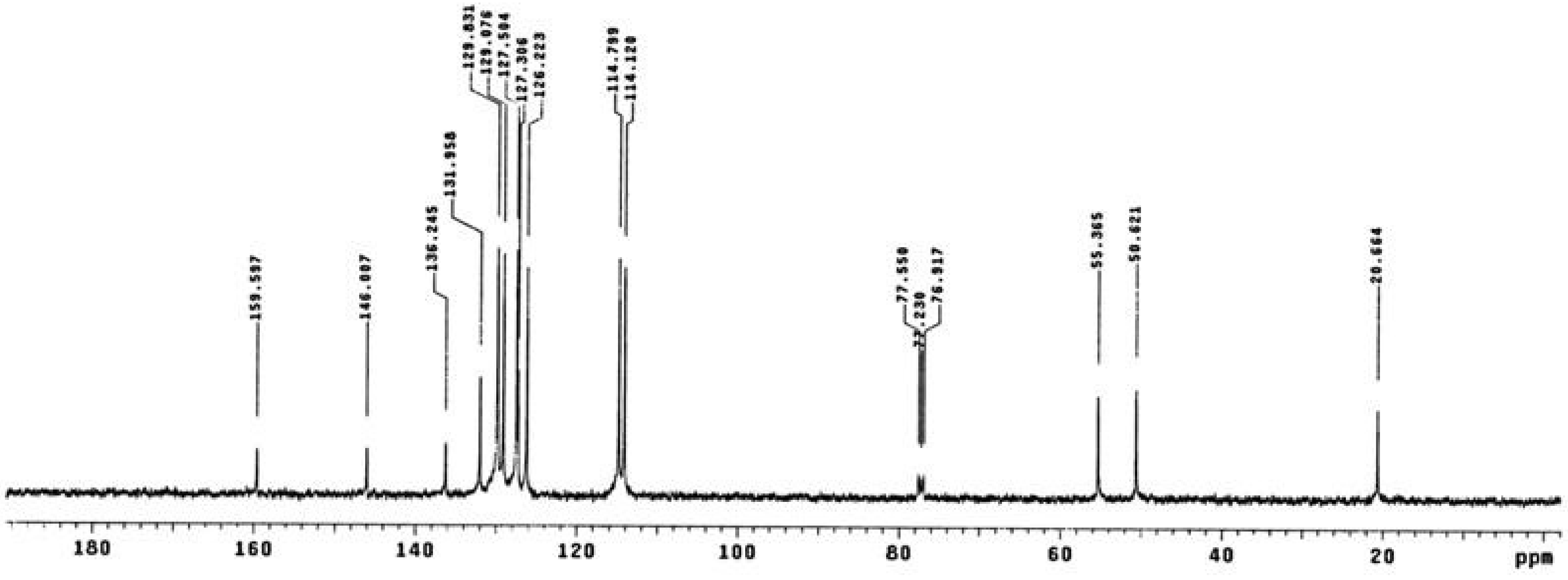

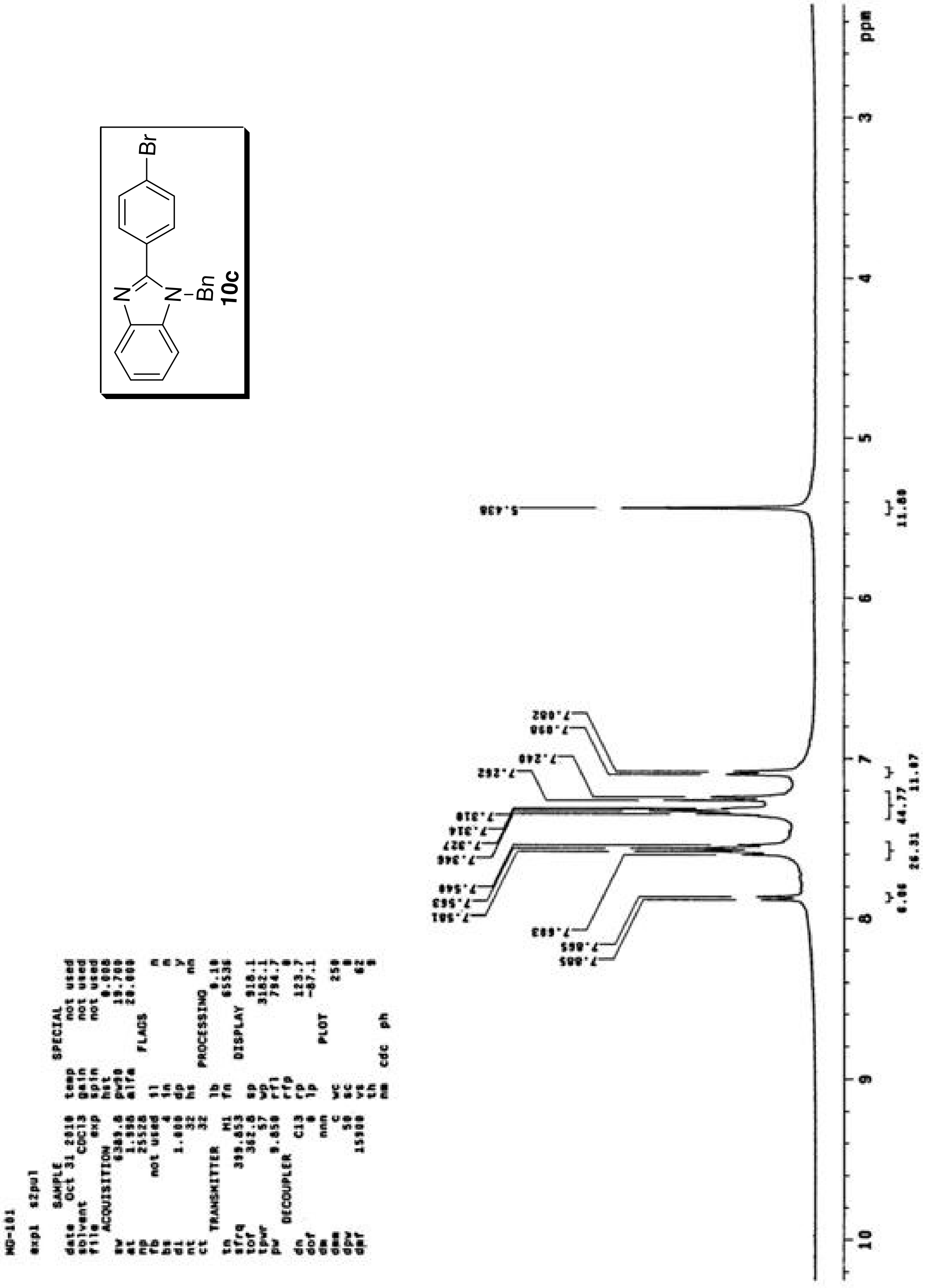
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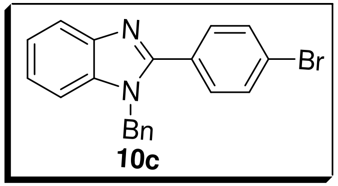

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ct             9104       PROCESSING
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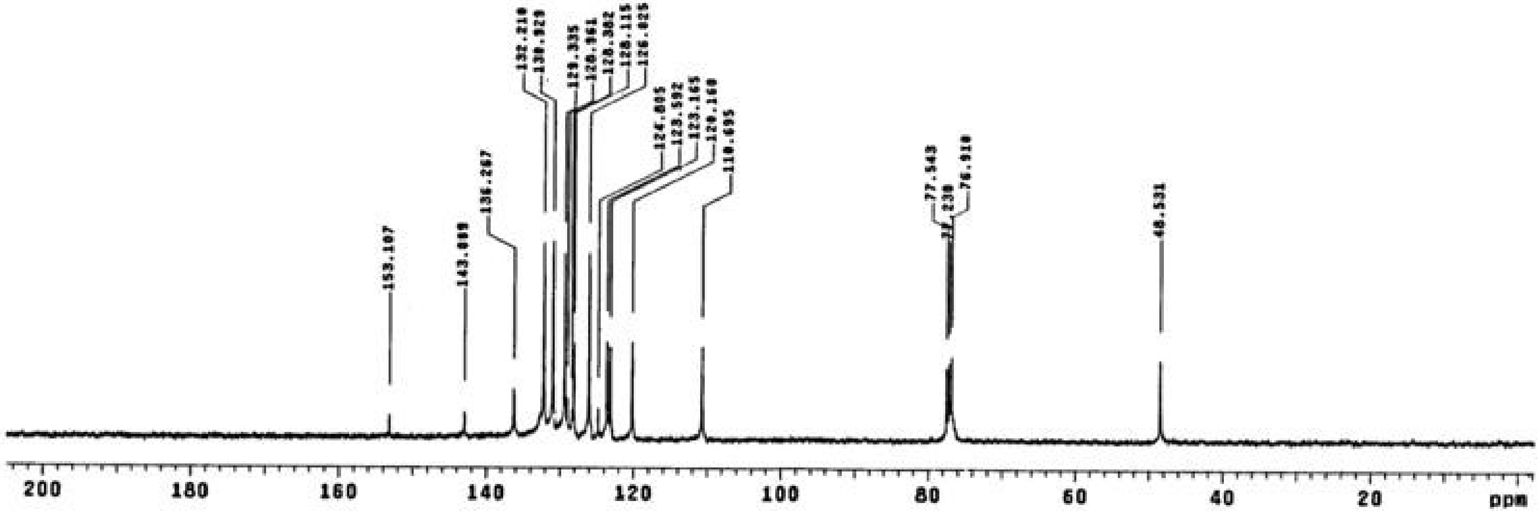

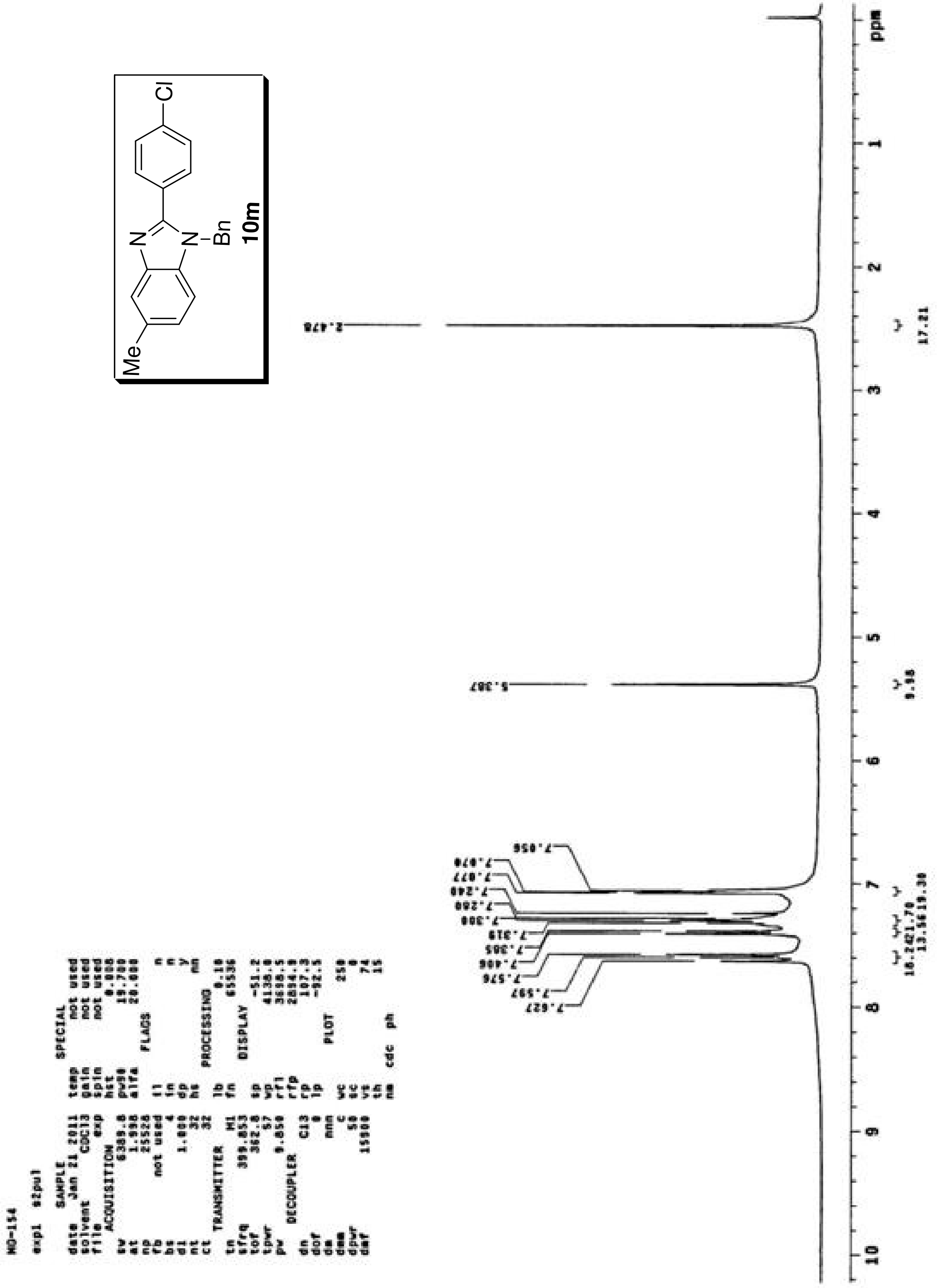

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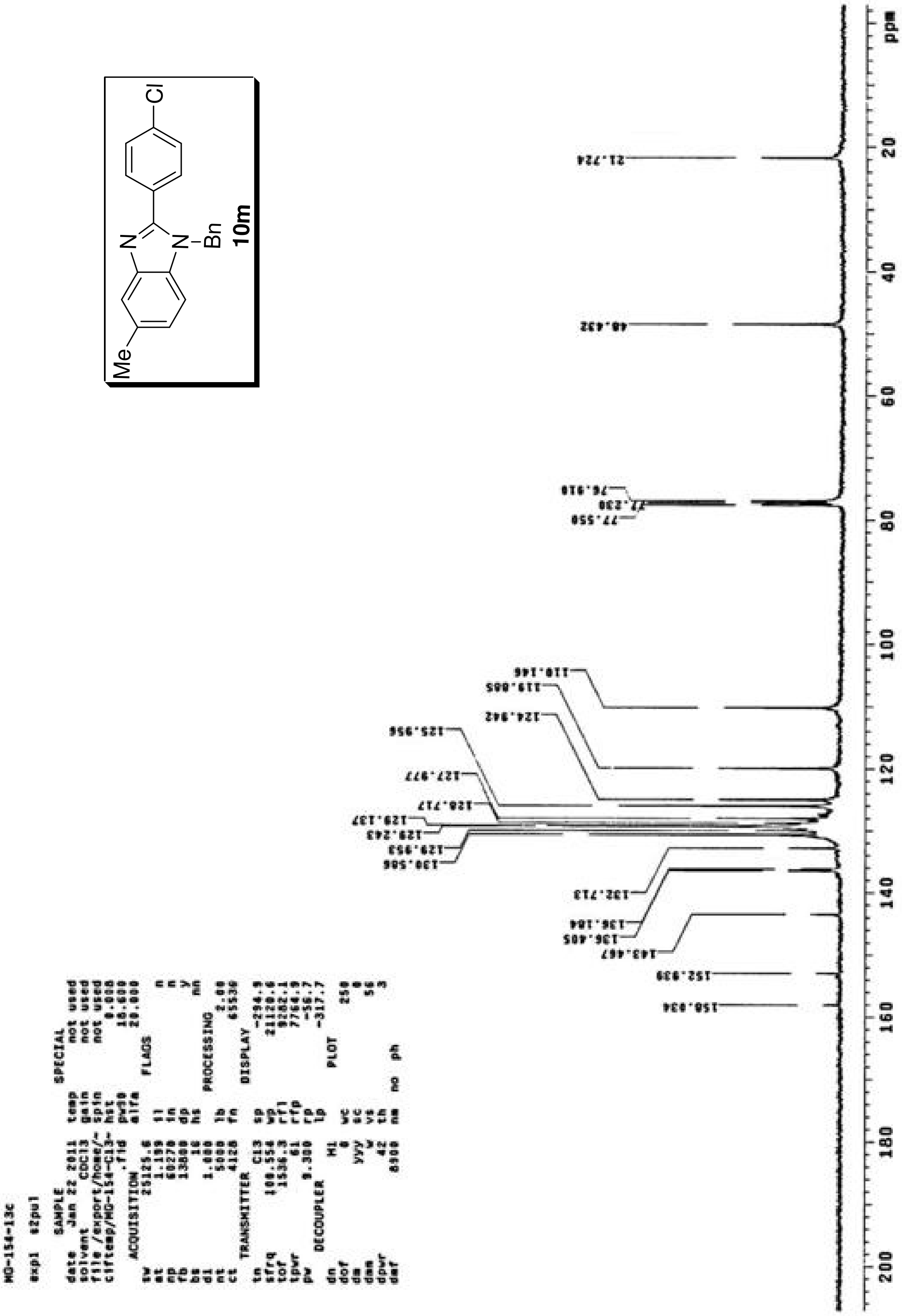
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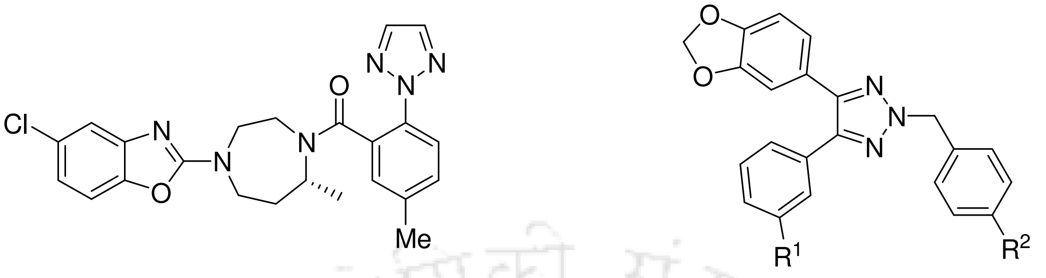
Chapter III

Aerobic Oxidative Synthesis of Substituted 1,2,3-Triazoles from Bisarylhydrazones via C–H Functionalization/C–C/N–N Bonds Formation

The selective oxidation of organic molecules has now become a topic of immense interest to the scientific endeavor for industrial chemical synthesis.[1] The most prominent challenge engross in this protocol is transition-metal-catalyzed oxidative functionalization of C–H bonds[2] using aerial oxygen as an ideal oxidant because of its abundance and lack of toxic byproducts.[3] Although palladium-catalyzed reactions have been widely integrated for oxidative organic transformations,[4] many of the methods are incompatible with the use of molecular oxygen as the stoichiometric oxidant. To achieve catalytic turnover, the latter require other oxidants, such as benzoquinone, phenyl iodoacetate, Cu(II) or Ag(I) to promote reductive elimination of the products from the metal centre through the formation of high-valent intermediate.[5] Free from all of the above drawbacks, there exit a number of copper-catalyzed aerobic oxidation reactions[6] with industrial applications[7] where the aerobic oxidation of Cu(I) to Cu(II) is widely accepted.[8] Despite considerable diversity in oxidation reactions, copper(II) is an effective one-electron oxidant which has been used in a number of oxidative transformations initiated by single-electron transfer (SET) from electron rich organic species.[9] In these reactions, copper(II) is especially an oxidant because under appropriate conditions the reactions could be carried out with catalytic copper using aerial oxygen as the stoichiometric oxidant to form carbon-carbon or carbon-heteroatom bond, a convenient tool for synthesis of important heterocycles. In this chapter, we disclose an unprecedented route for the regioselective synthesis of 2,4,5-triaryl-1,2,3-triazoles from bisaryl hydrazones *via* a cascade copper(II)-catalyzed aerobic oxidative C–H functionalization/C–C/N–N bonds formation.

Azaheterocycles are iconic building blocks of potent pharmaceutical drugs, numerous natural products and synthons for material-based applications. In this connection, 1,2,3-triazoles have attracted significant attention because of their pharmacological properties like antifungal,[10i] antiviral[10j] and anticoccidiostatic activities.[10k] However a subset *N*-2-substituted 1,2,3-triazoles could be used as biologically active compounds such as orexin receptor antagonist (MK-4305),[10d] SYK kinase inhibitors[10l] and ALK5 inhibitors (Figure 1).[10m] 1,2,3-Triazoles have also become increasingly common in pharmaceutical targets and biologically active substances, such as chemotherapeutic and cardiovascular agents.[11] Thus development of effective methods for synthesis of substituted 1,2,3-triazoles have become an important task in heterocyclic chemistry.



MK 4305
Orexin Receptor Antagonist

R^1 = H, Me; R^2 = CN, $CONH_2$
ALK5 Inhibitor

Figure 1. Biologically active *N*-2-substituted 1,2,3-triazoles

3.1 Strategies for Synthesis of *N*-1 Substituted 1,2,3-Triazoles

3.1.1 Azide-Alkyne Cycloaddition (AAC) Reaction

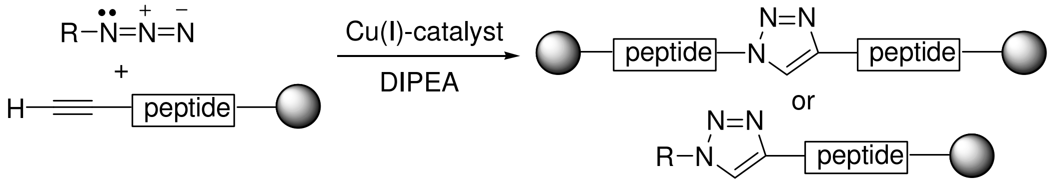
Due to limitations of the traditional Huisgen azide-alkyne dipolar cycloaddition (AAC) processes,[12] metal-catalyzed AAC reactions[13] have enabled the assembly of diversely *N*-1-substituted 1,2,3-triazoles under relatively mild reaction conditions.

3.1.1.1 CuAAC Reactions

To date, the most powerful click reaction is copper-catalyzed azide-alkyne cycloaddition (CuAAC) which has enabled the synthesis of 1,4- or 1,5-disubstituted 1,2,3-triazoles from an unprecedented range of substrates with excellent selectivity.

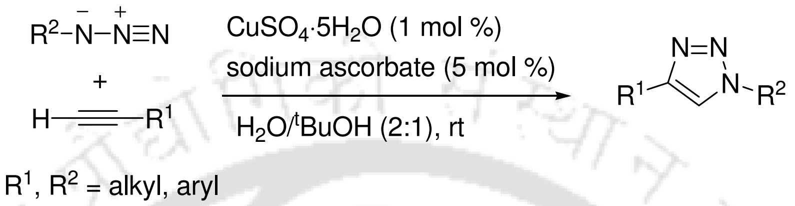
A novel regiospecific copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes to azides on solid-phase has been reported for synthesis of *N*-1-substituted 1,2,3-triazoles where alkyl azides, aryl azides and an azido sugar have been used (Scheme 1).[13a]

Scheme 1. Solid Phase Synthesis of Substituted 1,2,3-Triazoles



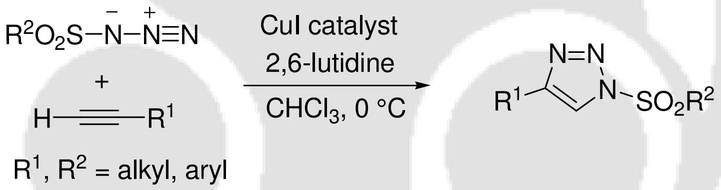
Copper(I)-catalyzed regiospecific synthesis of 1,4-disubstuted 1,2,3-triazoles has also been developed from organic azides and terminal acetylenes at room temperature (Scheme 2).[13b] Copper(I)-catalyst freshly generated from 5 mol % sodium ascorbate and 1 mol % copper(II) sulfate in a 2:1 mixture of water and *tert*-butyl alcohol furnish the desired products with no effort to exclude oxygen.

Scheme 2. Copper-Catalyzed Regiospecific Synthesis of Substuted 1,2,3-Triazoles



Convenient access to 4-substituted 1-(*N*-sulfonyl)-1,2,3-triazoles could be found from sulfonyl azides by the copper(I)-catalyzed azide–alkyne cycloaddition reaction at 0 °C in chloroform in presence of 2,6-lutidine as additive (Scheme 3).[13c]

Scheme 3. Synthesis of *N*-1-Sulfonyl-1,2,3-Triazoles

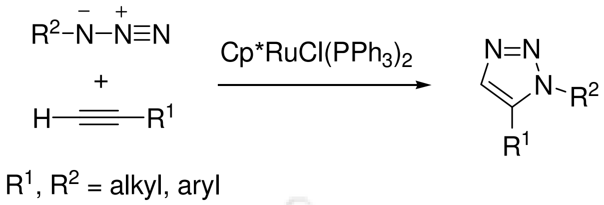


3.1.1.2 RuAAC Reactions

The success of copper-catalyzed azide-alkyne cycloaddition reaction (CuACC) highlights the need of easily accessible methods for synthesis of the other regioisomer, the 1,5-disubstituted 1,2,3-triazoles and also for the 1,4,5-trisubstituted 1,2,3-triazoles. Ruthenium complexes are well known for catalytic transformations of alkynes and there are evidences for the formation of ruthenium(II) acetylide, vinylidene and ruthenametallacyclic complexes as intermediates. With this finding, ruthenium has been a logical choice in search for a new catalyst of azide-alkyne cycloaddition reactions.

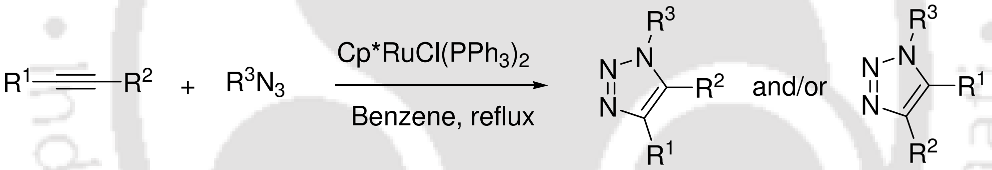
As a result, the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from organic azides and terminal and internal alkynes has been examined by ruthenium-catalyzed azide-alkyne cycloaddition reaction (RuAAC) (Scheme 4).[13d] It is an experimentally convenient catalytic process that could allow the selective preparation of one of the regioisomer of 1,2,3-triazoles.

Scheme 4. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition Reaction



Trisubstituted-1,2,3-triazoles have been synthesized by [3 + 2]-cycloadditions of alkyl azides with various unsymmetrical internal alkynes in presence of Cp*RuCl(PPh_3)$_2$ as catalyst in refluxing benzene (Scheme 5).[13e] In this reaction, alkyl phenyl and dialkyl acetylenes undergo cycloadditions to afford mixtures of regioisomeric 1,2,3-triazoles, whereas acyl-substituted internal alkynes react with complete regioselectivity.

Scheme 5. Ruthenium-Catalyzed Synthesis of Trisubstituted 1,2,3-Triazoles



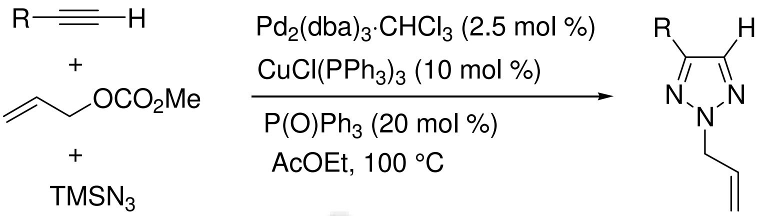
3.2 Strategies for Synthesis of *N*-2 Substituted 1,2,3-Triazoles

3.2.1 Three-Component Coupling (TCC) Reactions

Till now, we have discussed about the regioselective synthesis of *N*-1-substituted 1,2,3-triazoles via copper(I)- or ruthenium (II)-catalyzed AAC reactions. However, the synthesis of another subset *N*-2-substituted 1,2,3-triazoles has remain been a challenging task to the scientific endeavor.[14] Metal-catalyzed three-component coupling (TCC) reaction has proved to be a useful route for the preparation of *N*-2-substituted 1,2,3-triazoles.

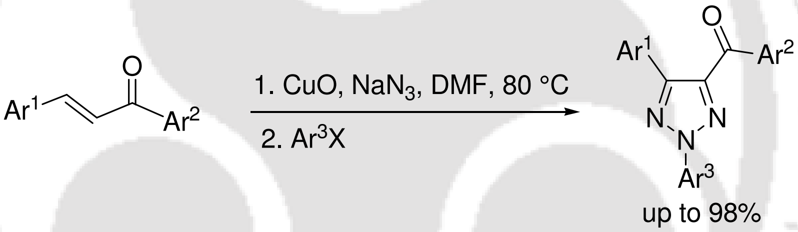
Palladium(0)–copper(I) bimetallic catalyst has been developed for the synthesis of *N*-2-allyl-1,2,3-triazoles via three-component coupling (TCC) reaction of unactivated terminal alkynes, allyl carbonate and trimethylsilyl azide in AcOEt at 100 °C (Scheme 6).[14a] The reaction possibly proceeds via formation of a π-allylpalladium azide complex and a copper-acetylide followed by a successive [3 + 2] cycloaddition.

Scheme 6. Bimetal-Catalyzed Formation of Triazole



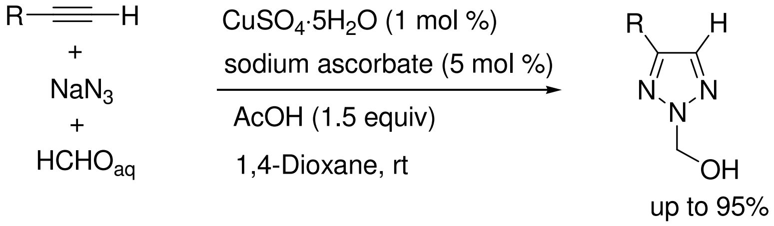
An efficient one-pot three-component synthesis of *N*-2-aryl-substituted 1,2,3-triazoles has also been achieved via CuO promoted azide-chalcone oxidative cycloaddition and post-triazole arylation process (Scheme 7).[14b] A series of *N*-2-aryl-substituted 1,2,3-triazoles could be readily prepared under mild reaction conditions in excellent yields and high regioselectivity by using readily available substrates and catalyst.

Scheme 7. CuO Promoted Azide-Chalcone Oxidative Cycloaddition



Alkynes undergo a copper(I)-catalyzed three-component cycloaddition (TCC) with sodium azide and formaldehyde to yield 2-hydroxymethyl-2*H*-1,2,3-triazoles (Scheme 8).[14c] These compounds could be used as versatile intermediates for the preparation of 2-chloromethyl-2*H*-1,2,3-triazoles and N*H*-1,2,3-triazoles, an important class of heterocycles with pharmacological properties. The reactive copper(I)-catalyst could be accessible in the reaction medium through the reaction of copper(II) sulfate and sodium ascorbate in presence of acetic acid.

Scheme 8. One-Pot Synthesis of *N*-Hydroxymethyl-1,2,3-Triazoles

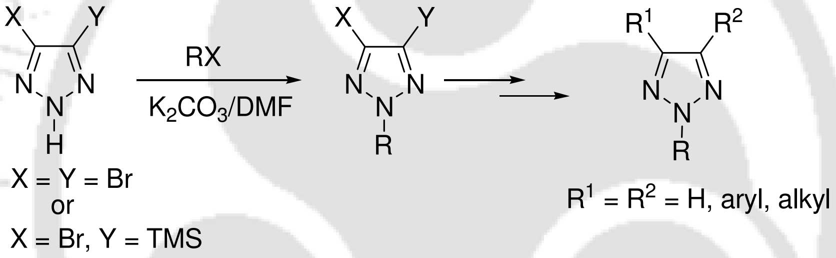


3.2.2 Regioselective Post-Triazole Arylation or Alkylation

N-2 Substitution is one of the major challenges for triazole derivatives. Click-chemistry with substituted azides could give only *N*-1 products. For post-triazole derivatization, the higher electron density on the two terminal nitrogens of the triazole heterocore allow to give only *N*-1 substituted products. Therefore immense efforts have been devoted for *N*-2 selective post-triazole arylation or alkylation in past few years.

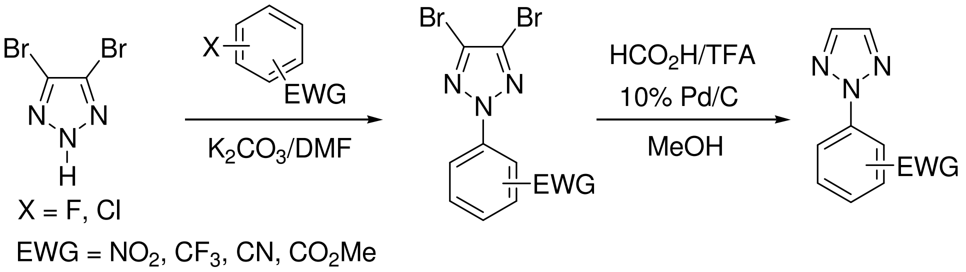
The regioselective *N*-2-alkylation of 4,5-dibromo- and 4-bromo-5-trimethylsilyl-1,2,3-triazoles have been demonstrated via base mediated post-triazole alkylation (Scheme 9).[15a] These building blocks could readily be converted to 2-mono-, 2,4-di-, and 2,4,5-trisubstituted triazoles, providing a general method for the synthesis of *N*-2-substituted triazoles.

Scheme 9. Post-Triazole Alkylation of 1,2,3-Triazoles



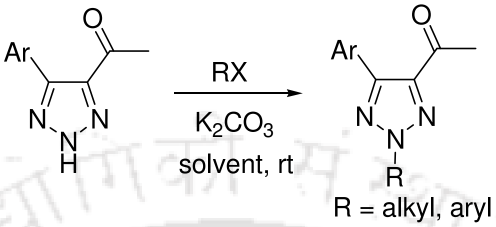
But for *N*-2-arylation, the arene ring of the aryl halides should contains electron-withdrawing substituent to give selectively *N*-2-aryl-1,2,3-triazoles. For example, 4,5-dibromo-1,2,3-triazole with electron-deficient aromatic halides in DMF produces the corresponding 2-aryl-4,5-dibromotriazoles with high regioselectivity in presence of potassium carbonate (Scheme 10).[15b] Subsequent debromination of these triazoles furnishes *N*-2-aryl-1,2,3-triazoles in good yields.

Scheme 10. Post-Triazole *N*-2-Arylation of 1,2,3-Triazoles



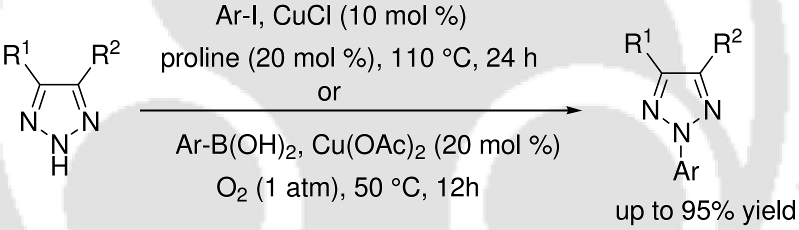
Considering the fact that C-4 and C-5 substituents on the 1,2,3-triazoles could provide the necessary steric hindrance to prevent the nucleophilic substitution on the terminal nitrogens of heteroarenes, N-2 selective post-triazole alkylation and allylation have been done with C-4 and C-5 crowded 1,2,3-triazoles in presence of K_2CO_3 (Scheme 11).[15c]

Scheme 11. Regioselective Synthesis of *N*-2 Substituted 1,2,3-Triazoles



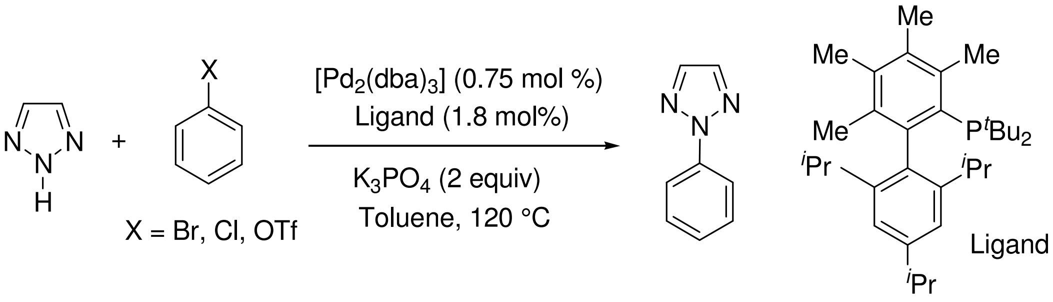
Efficient regioselective post-triazole *N*-2 arylation has also been developed from C-4, C-5 disubstituted-1,2,3-NH-triazoles via copper-catalyzed cross-coupling reactions with aryl halides or aryl boronic acids (Scheme 12).[15d]

Scheme 12. Copper-Catalyzed Post-Triazole Arylation



Recently, instead of using bulky substituents on the heteroaromatic ring of 1,2,3-triazole, bulky ligand has been incorporated for regioselective *N*-2-arylation of 1,2,3-triazoles. For this goal, 4,5-unsubstituted and 4-substituted 1,2,3-triazoles have been treated for the first time by the palladium/ligand catalytic system with aryl bromides, chlorides and triflates with excellent N-2 selectivity (Scheme 13).[15e]

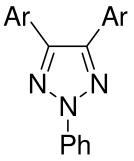
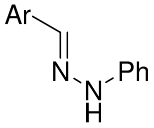
Scheme 13. Post-Triazole Arylation using Bulky Ligand



3.3 Present Study

Optimization of Reaction Conditions. Our recent study[16] and literature reports[17] reveal that bisarylhydrazones are unstable at elevated temperature. With this finding when we initiated our new approach with the reaction of bisarylhydrazone **1a** in presence of 20 mol % $Cu(OAc)_2{\cdot}H_2O$ in toluene at 60 °C under air, gratifyingly, we got 1,2,3-triazole **2a** in 75 % yield after 6 h (Table 1, Entry 1). Other reaction parameters were examined with **1a** as a model substrate (Table 1). Anhydrous $Cu(OAc)_2$ was found to be slightly less efficient than the hydrated one whereas other copper-salts gave inferior results (Entries 5-9). In polar solvents such as dioxane, DMSO and THF, the product **2a** was obtained with

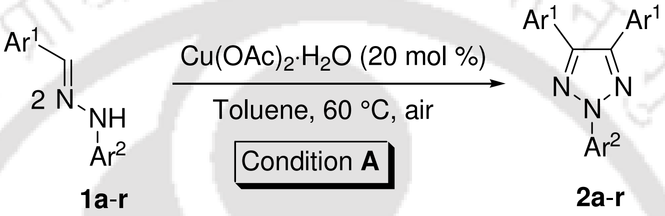
Table 1. Screening of Reaction Parameters for Synthesis of Triaryl-1,2,3-Triazoles[a]

Entry	Substrate	[Cu] Source	Solvent	Time (h)	Product	Yield (%)[b]
1		**$Cu(OAc)_2{\cdot}H_2O$**	**Toluene**	**6**		**75**[c]
2		$Cu(OAc)_2{\cdot}H_2O$	Dioxane	4		65[c]
3		$Cu(OAc)_2{\cdot}H_2O$	DMSO	2	 Ar = (4-OMe)C_6H_4 **2a**	trace[d]
4	 Ar = (4-OMe)C_6H_4 **1a**	$Cu(OAc)_2{\cdot}H_2O$	THF	4		58[e]
5		$Cu(OAc)_2$	Toluene	6		72[c]
6		$Cu(OTf)_2$	Toluene	6		trace[d]
7		$CuSO_4{\cdot}5H_2O$	Toluene	6		n.d.
8		$CuCl_2$	Toluene	6		n.d.
9		CuI	Toluene	6		n.d.
10[f]		$Cu(OAc)_2{\cdot}H_2O$	Toluene	12		30[g]
11[h]		$Cu(OAc)_2{\cdot}H_2O$	Toluene	4		74[c]
12[i]		$Cu(OAc)_2{\cdot}H_2O$	Toluene	10		30[c]
13[j]		$Cu(OAc)_2{\cdot}H_2O$	Toluene	10		45[e]
14[k]		$Cu(OAc)_2{\cdot}H_2O$	Toluene	4		65[l]
15		-	Toluene	24		n.d.

[a] Conditions: Bisarylhydrazone **1a** (0.5 mmol) and Cu source (20 mol %) were stirred in solvent (2 mL) at 60 °C under air. [b] Isolated yield. *p*-Anisaldehyde ([c]5%, [d]66%, [e]23%, [g]43% and [l]15%) was obtained as byproduct. [f] Reaction temperature 40 °C. [h] Under oxygen balloon. [i] Under N_2. [j] Cu source (10 mol %) used. [k] 30% Aqueous H_2O_2 (1 equiv) used. n.d. = not detected.

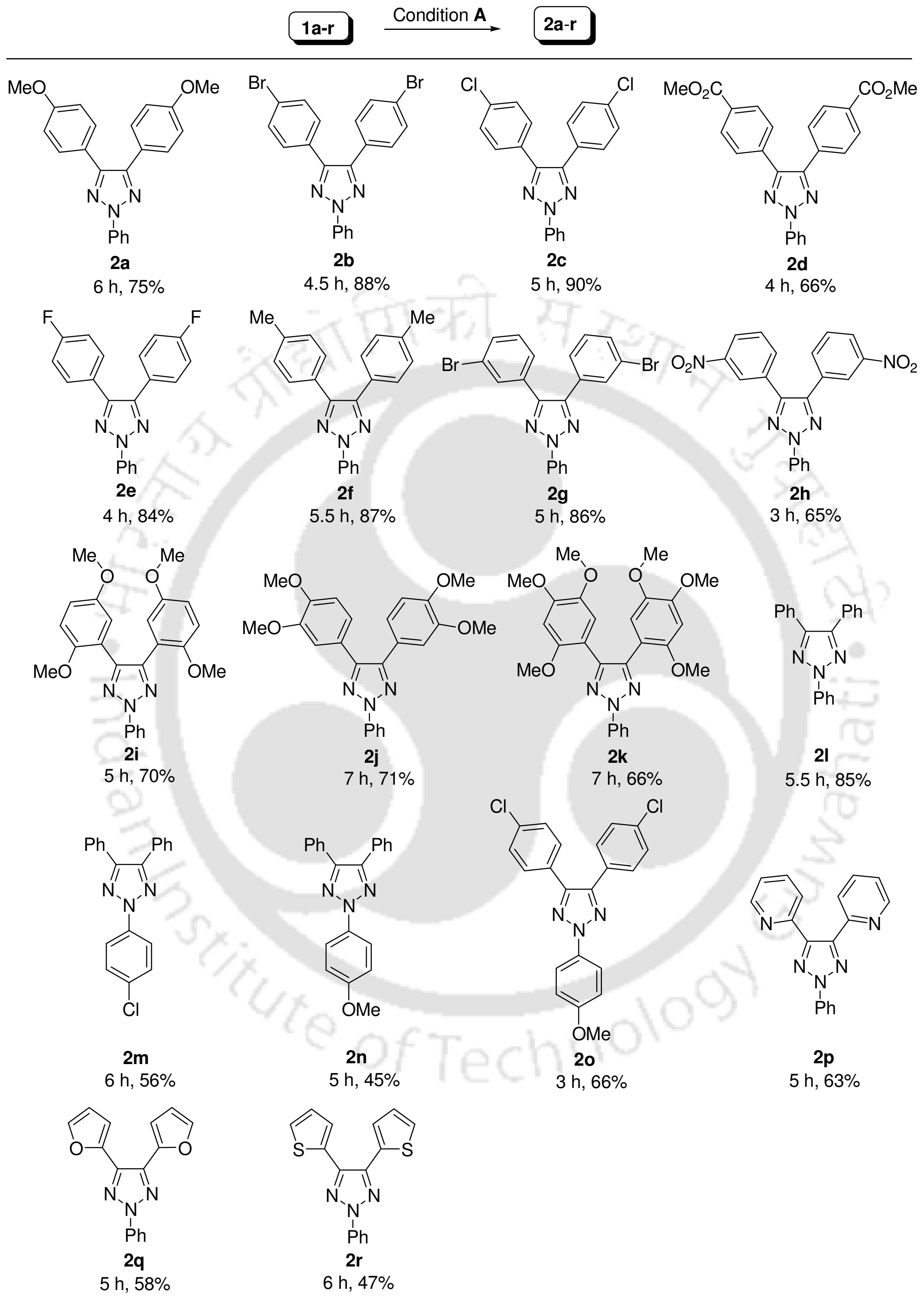
trace to moderate yields (Entries 2-4). Use of molecular oxygen led to the formation of **2a** in 74% yield (Entry 11), while the reaction utilizing aqueous 30% H_2O_2 afforded **2a** in 65% yield (Entry 14). In contrast, under nitrogen atmosphere, the yield of the target compound **2a** was reduced to 30% (Entry 12). A similar result was observed when either the reaction temperature (40 °C) or the amount of the copper source (10 mol %) was reduced (Entries 10 and 13). Control experiment confirmed that without the copper source, the product **2a** was not obtained (Entry 15). In brief, condition **A** provided the best results for the synthesis of 2,4,5-triaryl-1,2,3-triazoles (Scheme 14).

Scheme 14. C–H Functionalization of Bisarylhydrazones



Substrate Scope for the Synthesis of 1,2,3-Triazoles (Condition A). Having the optimal conditions in hand, we set out to explore the scope of the reactions of a wide range of readily accessible bisarylhydrazones by employing condition **A**. For examples, bisarylhydrazones **1a-r** underwent reaction to give the substituted 1,2,3-triazoles **2a-r** in 45-90% yields (Table 2). Bisarylhydrazones **1b-e**, **1g-h** and **1m** bearing electron-withdrawing substituents on the arenes led to give **2b-e**, **2g-h** and **2m** in 56-90% yields. While bisarylhydrazones **1a**, **1f** and **1n** having electron-donating substituents on the aryl rings proceeded cyclization to afford the corresponding heterocycles **2a**, **2f** and **2n** in 45-87% yields. Furthermore, bisarylhydrazone **1o** having both electron-withdrawing and electron-donating substituents on the arenes could afford the target heterocycle **2o** in 66% yield. The substrate **1l** with unsubstituted arenes afforded **2l** in 85% yield. The substrates **1i-k** bearing dimethoxy and trimethoxy substituents on the aryl rings underwent reaction to provide the corresponding 1,2,3-triazoles **2i-k** in 66-71% yields. Arylhydrazones **1p-r** having pyridinyl, furanyl and thiophenyl moieties also proceeded cyclization to provide the target heterocycles **2p-r** in moderate yields. Under this condition, alkyl arylhydrazones were not stable and underwent decomposition to give aldehydes. For structural confirmation the single crystal of the compound **2f**, grown from acetonitrile solvent, was analyzed by single crystal X-ray analysis (Figure 2).

Table 2. Synthesis of 2,4,5-Triaryl-1,2,3-Triazoles[a-b]



2a 6 h, 75%

2b 4.5 h, 88%

2c 5 h, 90%

2d 4 h, 66%

2e 4 h, 84%

2f 5.5 h, 87%

2g 5 h, 86%

2h 3 h, 65%

2i 5 h, 70%

2j 7 h, 71%

2k 7 h, 66%

2l 5.5 h, 85%

2m 6 h, 56%

2n 5 h, 45%

2o 3 h, 66%

2p 5 h, 63%

2q 5 h, 58%

2r 6 h, 47%

[a] Conditions: Substrates **1a-r** (0.5 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mol %) were stirred in toluene (2 mL) at 60 °C under air. [b] Aldehydes (5-10%) were obtained as byproduct.

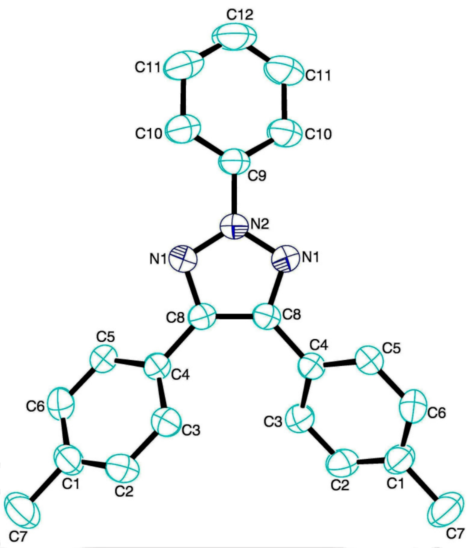
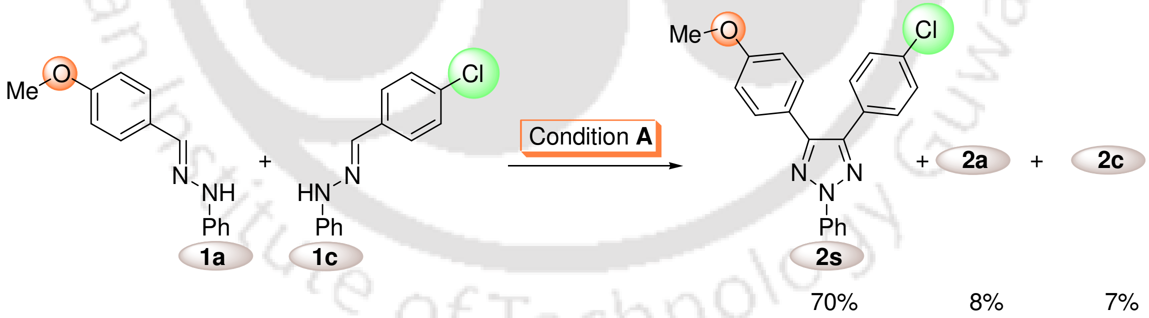


Figure 2. ORTEP representation of substituted 1,2,3-triazole **2f**. H-Atoms have been omitted for clarity

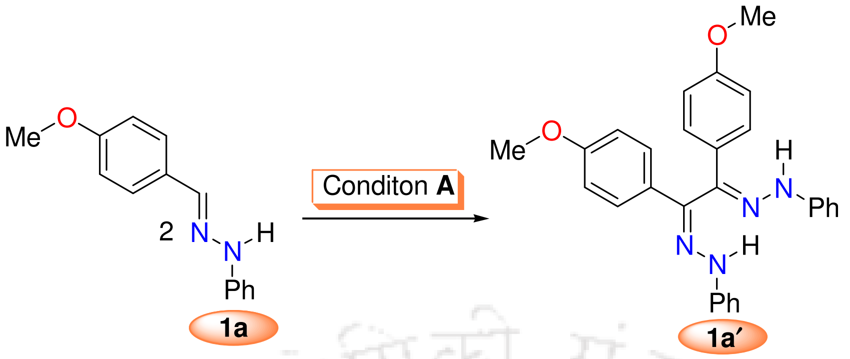
Synthesis of Unsymmetrically Substituted 1,2,3-Triazole. The reaction condition **A** was also compatible for the synthesis of unsymmetrical 2,4,5-triaryl-1,2,3-triazoles. For an example, bisarylhydrazones **1a** and **1c** readily proceeded reaction to give the unsymmetrical 2,4,5-triaryl-1,2,3-triazole **2s** in 70% yield along with the symmetrically substituted 1,2,3-triazoles **2a** and **2c** as minor products (Scheme 15).

Scheme 15. Synthesis of Unsymmetrically Substituted 1,2,3-Triazole



Mechanistic Studies of the Synthesis of 1,2,3-Triazoles 2a-r. During the transformation of bisarylhydrazone **1a** to give the substituted 1,2,3-triazole **2a**, we were able to isolate the intermediate **1a′** (eq 1) as crystals, a dimer of **1a**, whose structure was confirmed by single crystal X-ray analysis (Figure 3). Next, to get insight whether the reaction involves a radical pathway, a radical inhibition test was carried out. When TEMPO, an effective radical scavenger, was added to the reaction mixture, the progress of the reaction was significantly slowed and a mixture of **2a** (7%) and unreacted **1a** (55%)

was isolated (Table 3). This result clearly suggests that the reaction may involve radical intermediate.



(eq 1)

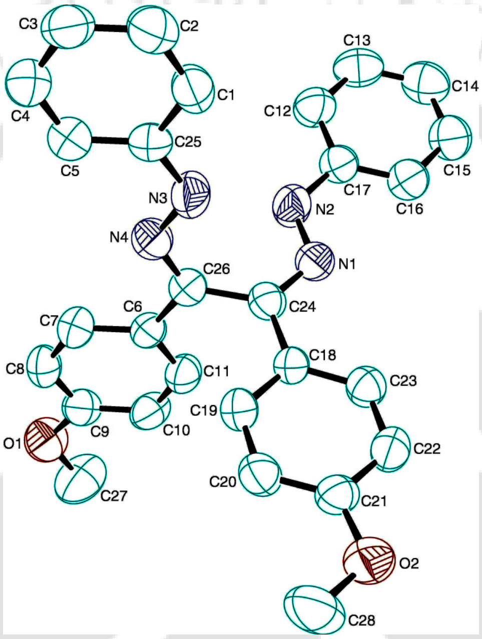
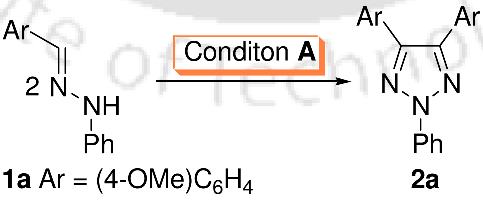


Figure 3. ORTEP representation of the intermediate **1a′**. H-Atoms have been omitted for clarity.

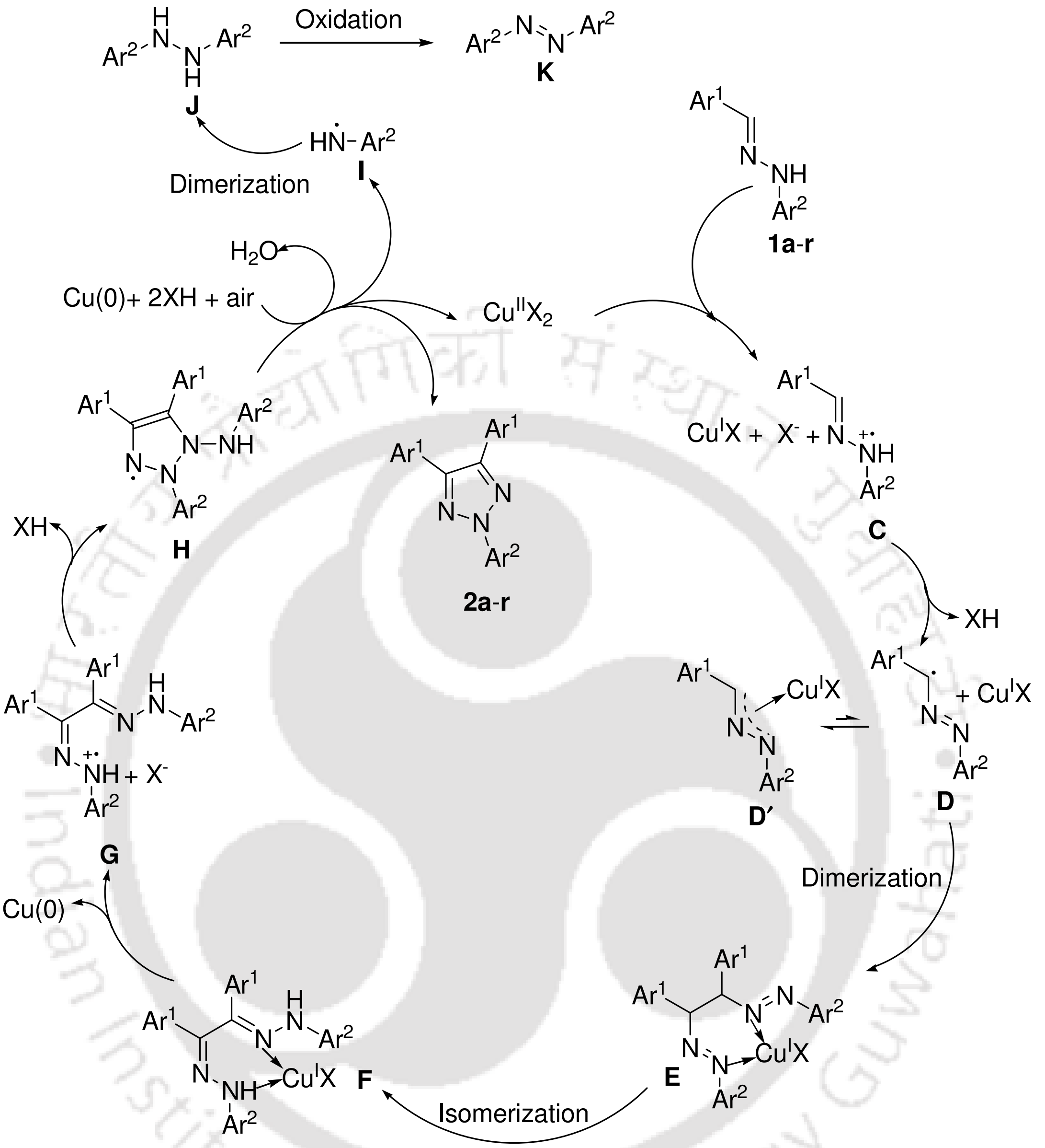
Table 3. Effects of Radical Inhibitor on the Synthesis of Substituted 1,2,3-Triazoles[a]



Entry	Radical Scavenger	Time (h)	Recovered **1a** (%)	**2a** (%)
1	-	6	-	75
2[b]	TEMPO	10	55	7

[a] Bisarylhydrazone **1a** (0.5 mmol) and $Cu(OAC)_2{\cdot}H_2O$ (10 mol %) were stirred in toluene (2 mL) at 60 °C under air. [b] TEMPO (0.5 mmol) used.

Scheme 16. Proposed Catalytic Cycle for the Synthesis of Substituted 1,2,3-Triazoles



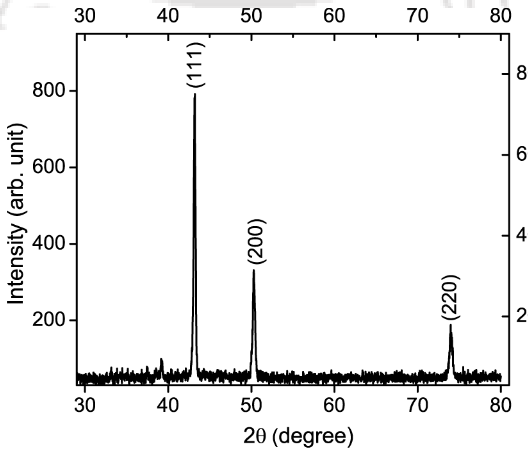
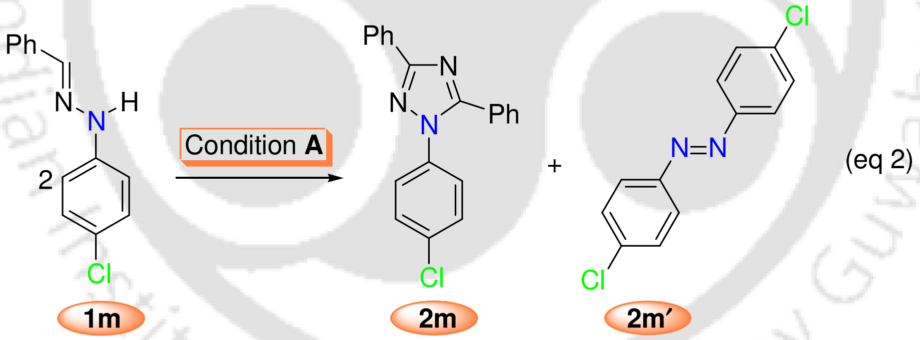


Figure 4. Powder XRD analysis of the recovered copper(0) species.

Based on the above experimental observations and literature reports,[18] a plausible pathway for the synthesis of substituted 1,2,3-triazoles has been proposed (Scheme 16). Thus, bisarylhydrazones **1a-r** may transform into the radical cation **C** via single-electron transfer (SET) to Cu(II)X_2. The intermediate **C** could then transform into **D** by the elimination of HX. Dimerization of **D** could lead to the formation of **E** that could isomerize to afford the intermediate **F**. The latter could form a radical cation **G** by reductive elimination of elemental copper through SET process. The generation of metallic copper(0) was confirmed by powder XRD analysis (Figure 4). The sharp peaks at 43.20°, 50.29° and 73.98° correspond to the (111), (200) and (220) planes of face-centered cubic copper(0) (with space group Fm3m, JCPDS 03-1005).[19] Elimination of HX followed by cyclization of **G** may lead to the formation of **H**, which could afford the target heterocycles **2a-r** via elimination of the radical intermediate **I**. Dimerization of **I** may give **J** that could readily undergo oxidation under air to give the more stable azo compound **K** that was confirmed by single crystal X-ray analysis of **2m′** (Figure 5), a byproduct, formed during the transformation of **1m** to **2m** (eq 2). The reduced copper(0) species may be reoxidized by air to regenerate the active copper(II) species to complete the catalytic cycle.[20]



(eq 2)

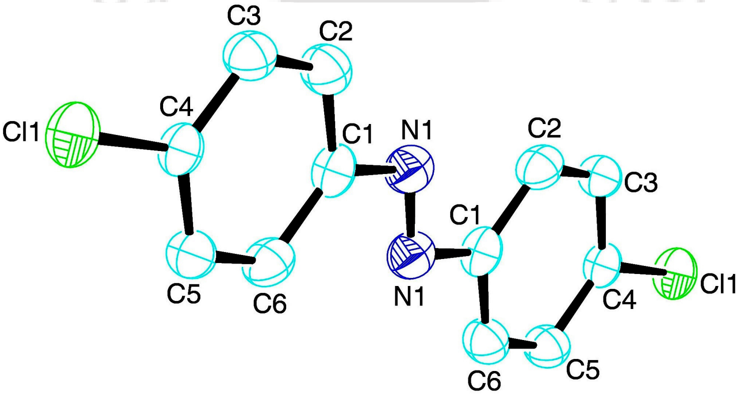
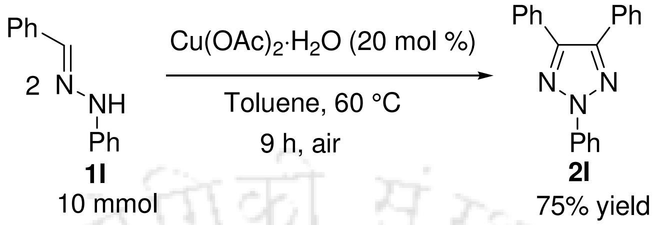


Figure 5. ORTEP representation of byproduct **2m′**. H-Atoms have been omitted for clarity.

Finally, the scale up of the conditions **A** was studied with **1l** as a substrate (Scheme 17). As anticipated, the reaction was efficient to afford the corresponding target heterocycle **2l** in 75% yield, with slightly longer reaction time.

Scheme 17. Gram Scale Synthesis of 2,4,5-Triphenyl-1,2,3-Triazole



In summary, copper(II)-promoted oxidative C–H functionalization of bisarylhydrazones for the regioselective synthesis of 2,4,5-triaryl-1,2,3-triazoles has been achieved through C–H functionalization/C–C/N–N bonds formation strategy. The reaction could be performed under air as environment friendly oxygen source. The reactive intermediate has been isolated to elucidate the mechanistic scenario. This Protocol could be explored to large synthetic scope with wide functional group compatibility from the readily accessible substrates.

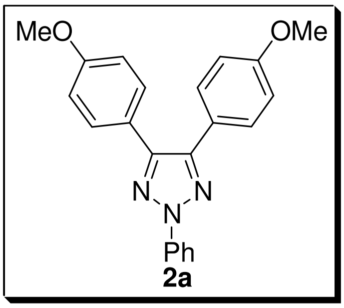
Experimental Section

General Information: Anilines and aldehydes were purchased from commercial sources and were used as received. $Cu(OAc)_2{\cdot}H_2O$ (≥98%) was purchased from Aldrich. Solvents were freshly dried prior to use according to the standard procedure.[21] Product purification was carried out by silica gel column chromatography using silica gel (60-120 mesh). All reactions were monitored by analytical TLC on silica gel G/GF 254 plates. NMR (^{1}H and ^{13}C) spectra were recorded on a NMR spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration).The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by melting point apparatus. FT-IR spectra of air-dried samples were recorded on FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using CHNS analyzer. The electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a liquid chromatography (LC)-MS. Powder X-ray diffraction (XRD) pattern of dried crystalline catalyst was recorded on a X-ray diffractometer with Cu Kα irradiation (λ = 1.54 Å) at 40 kV and 40 mA with a scan rate of 0.1°/s for 2θ in the range of 20-80°. For single crystal X-ray analysis the intensity data were collected using CCD diffractometer, equipped with 1.75 kW sealed-tube Mo Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods and refined with full-matrix least squares on F^2. Arylhydrazines and bisarylhydrazones were prepared according to our recent study.[16]

General Procedure for Copper(II)-Catalyzed Synthesis of 2,4,5-Triaryl-1,2,3-Triazoles. Bisarylhydrazones **1a-r** (0.5 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mol %, 20.0 mg) were stirred at 60 °C in toluene (2 mL) under air. After stirring for appropriate time the reaction mixture was cooled to room temperature and passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to accomplish the target 2,4,5-triaryl-1,2,3-triazoles **2a-r** in analytically pure form.

Typical Procedure for Copper(II)-Catalyzed Synthesis of Unsymmetrical 2,4,5-Triaryl-1,2,3-Triazole 2s. Bisarylhydrazones **1a** (0.25 mmol, 56.6 mg) and **1c** (0.25 mmol, 57.7 mg) with $Cu(OAc)_2 \cdot H_2O$ (20 mol %, 20.0 mg) were stirred at 60 °C in toluene (2 mL) under air. After stirring for 6 h the reaction mixture was cooled to room temperature and passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to accomplish the target 2,4,5-triaryl-1,2,3-triazole **2s** in 70% (63.3 mg) yield along with symmetrical 2,4,5-triaryl-1,2,3-triazoles **2a** and **2c** in 8% (7.1 mg) and 7% (6.4 mg) yields, respectively.

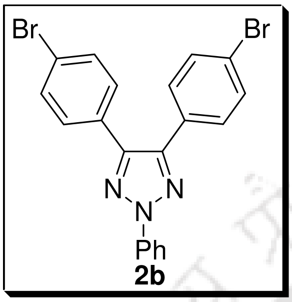
Typical Procedure for Gram Scale Synthesis of 2,4,5-Triphenyl-1,2,3-Triazole 2l. Bisphenylhydrazone **1l** (10 mmol, 1.96 g) and $Cu(OAc)_2 \cdot H_2O$ (20 mol %, 0.40 g) were stirred at 60 °C in toluene (40 mL) under air for 9 h. After cooling to room temperature the reaction mixture was passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to afford the target 2,4,5-tripenyl-1,2,3-triazole **2l** in 75% (1.11 g) yield.



2a

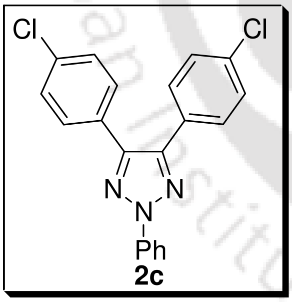
4,5-Bis(4-methoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2a. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 75% (67.0 mg); mp 134-135 °C (lit.[22] mp 133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d,

J = 8.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 4H), 7.50 (t, J = 8.0 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.8 Hz, 4H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 145.6, 139.9, 129.8, 129.3, 127.1, 123.4, 118.6, 114.1, 55.33, 55.27; FT-IR (KBr) 2966, 2934, 1614, 1598, 1526, 1493, 1459, 1443, 1435, 1300, 1274, 1248, 1177, 1027 cm^{-1}; *m/z* (ESI-MS) 358.16 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.86; H, 5.34; N, 11.81.



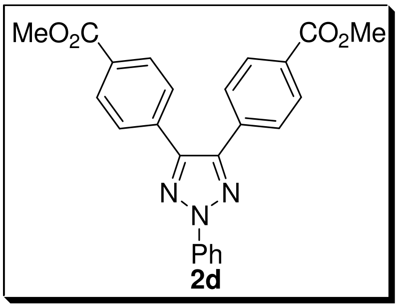
2b

4,5-Bis(4-bromophenyl)-2-phenyl-2*H*-1,2,3-triazole 2b. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 88% (100.0 mg); mp 159-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 2H), 7.55-7.42 (m, 10H), 7.38 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.6, 132.0, 130.0, 129.6, 129.4, 127.8, 123.2, 118.9; FT-IR (KBr) 2917, 1651, 1597, 1497, 1486, 1455, 1392, 1372, 1309, 1284, 1262, 1078, 1072, 1013 cm^{-1}; *m/z* (ESI-MS) 453.96, 455.97, 457.96 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.87; H, 2.87; N, 9.18.



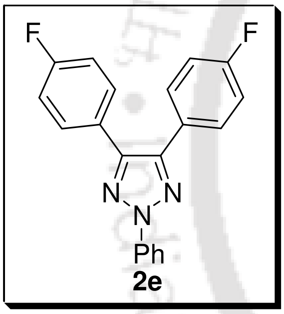
2c

4,5-Bis(4-chlorophenyl)-2-phenyl-2*H*-1,2,3-triazole 2c. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 90% (82.4 mg); mp 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.8 Hz, 4H), 7.50 (t, J = 7.6 Hz, 2H), 7.38-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.6, 135.0, 129.8, 129.4, 129.1, 127.8, 118.9; FT-IR (KBr) 1637, 1598, 1496, 1456, 1396, 1372, 1310, 1285, 1264, 1092, 1071, 1016 cm^{-1}; *m/z* (ESI-MS) 366.06 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47. Found: C, 65.66; H, 3.60; N, 11.42.



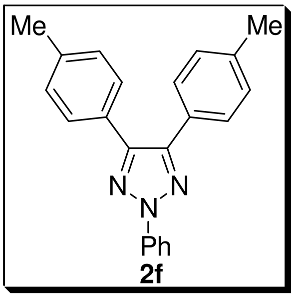
2d

4,5-Bis(4-carbomethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 66% (68.2 mg); mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.0 Hz, 4H), 7.70 (d, J = 8.0 Hz, 4H), 7.53 (t, J = 8.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 3.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.1, 139.3, 134.8, 130.2, 129.9, 129.3, 128.3, 127.9, 118.8, 52.2; FT-IR (KBr) 2945, 2923, 1717, 1614, 1593, 1497, 1432, 1404, 1311, 1277, 1176, 1103, 1015 cm^{-1}; *m/z* (ESI-MS) 414.16 $[M + H]^+$. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.65; H, 4.64; N, 10.19.

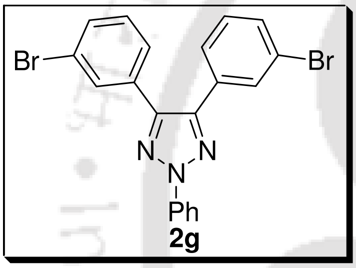


2e

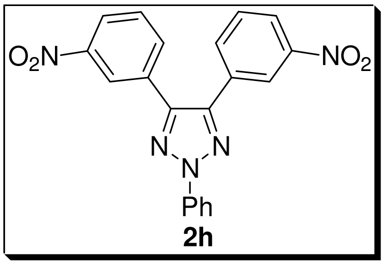
4,5-Bis(4-fluorophenyl)-2-phenyl-2*H*-1,2,3-triazole 2e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 84% (70.0 mg); mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 2H), 7.61-7.57 (m, 4H), 7.51 (t, J = 8.0 Hz, 2H), 7.37-7.33 (m, 1H), 7.11-7.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.0, 145.0, 139.7, 130.4, 130.3, 129.4, 127.7, 126.9, 118.8, 116.0, 115.8; FT-IR (KBr) 3067, 1605, 1594, 1522, 1498, 1456, 1263, 1225, 1156, 1070 cm^{-1}; *m/z* (ESI-MS) 334.14 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}F_2N_3$: C, 72.06; H, 3.93; N, 12.61. Found: C, 72.13; H, 3.92; N, 12.56.


2f

2-Phenyl-4,5-di*p*-tolyl-2*H*-1,2,3-triazole 2f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 87% (70.8 mg); mp 144-145 °C (lit.[23] mp 145-146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.0 Hz, 4H), 7.50 (t, J = 8.0 Hz, 2H), 7.35-7.31 (m, 1H), 7.20 (d, J = 8.4 Hz, 4H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 139.9, 138.5, 129.4, 129.3, 128.5, 128.1, 127.3, 118.8, 21.5; FT-IR (KBr) 3034, 3019, 2912, 1615, 1596, 1496, 1455, 1372, 1288, 1266, 1070 cm^{-1}; *m/z* (ESI-MS) 326.17 [M + H]$^+$. Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.15; H, 5.90; N, 12.95.

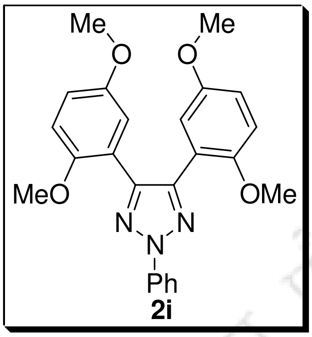

2g

4,5-Bis(3-bromophenyl)-2-phenyl-2*H*-1,2,3-triazole 2g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.70; colorless solid; yield 86% (97.86 mg); mp 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.81-7.80 (m, 2H), 7.44-7.38 (m, 6H), 7.28-7.27 (m, 1H), 7.14 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 139.3, 132.4, 131.8, 131.2, 130.1, 129.3, 127.8, 126.9, 122.8, 118.7; FT-IR (KBr) 1637, 1595, 1564, 1497, 1446, 1400, 1370, 1286, 1273, 1261, 1069, 1008 cm^{-1}; *m/z* (ESI-MS) 453.96, 455.94, 457.97 [M + H]$^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.72; H, 2.89; N, 9.25.


2h

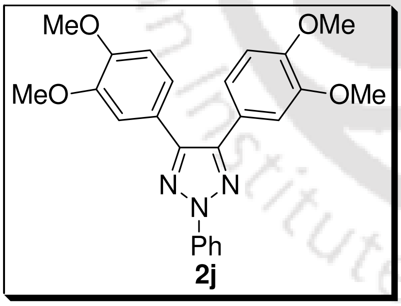
4,5-Bis(3-nitrophenyl)-2-phenyl-2*H*-1,2,3-triazole 2h. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 65% (62.9 mg); mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.54 (m, 2H), 8.29-8.27 (m, 2H), 8.20 (d, J = 8.4 Hz, 2H), 7.92-7.90 (m, 2H), 7.62-7.52 (m, 4H), 7.44 (t, J =

7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 143.9, 139.2, 134.0, 131.9, 130.1, 129.8, 129.6, 128.5, 123.9, 123.3, 119.0; FT-IR (KBr) 1595, 1537, 1509, 1488, 1466, 1374, 1347, 1303, 1262, 1168, 1100, 1072, 1023 cm^{-1}; *m/z* (ESI-MS) 388.12 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08. Found: C, 62.09; H, 3.37; N, 18.05.



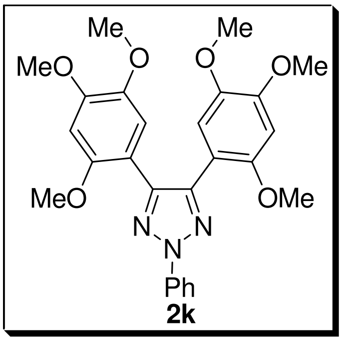
2i

4,5-Bis(2,5-dimethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2i. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.30$; colorless solid; yield 70% (73.06 mg); mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 2H), 7.48 (t, $J = 8.0$ Hz, 2H), 7.33-7.29 (m, 1H), 7.144-7.136 (m, 2H), 6.87-6.84 (m, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 3.77 (s, 6H), 3.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.1, 145.1, 139.6, 128.9, 126.8, 122.0, 118.3, 115.5, 114.4, 111.8, 55.2, 54.9; FT-IR (KBr) 2998, 2934, 2831, 1595, 1519, 1493, 1479, 1461, 1434, 1418, 1366, 1298, 1258, 1236, 1212, 1176, 1062, 1043, 1013 cm^{-1}; *m/z* (ESI-MS) 418.18 $[M + H]^+$. Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.98; H, 5.57; N, 10.09.



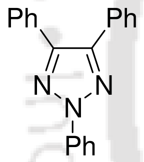
2j

4,5-Bis(3,4-dimethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2j. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 71% (74.10 mg); mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.50 (t, $J = 8.0$ Hz, 2H) 7.34-7.31 (m, 1H), 7.19-7.18 (m, 4H), 6.88-6.86 (m, 2H), 3.90 (s, 6H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 148.4, 145.0, 139.2, 128.7, 126.6, 122.9, 120.7, 117.9, 111.1, 110.6, 55.2; FT-IR (KBr) 2832, 1609, 1598, 1581, 1528, 1498, 1478, 1439, 1335, 1318, 1256, 1230, 1212, 1170, 1137, 1024 cm^{-1}; *m/z* (ESI-MS) 418.15 $[M + H]^+$. Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.13; H, 5.53; N, 10.04.



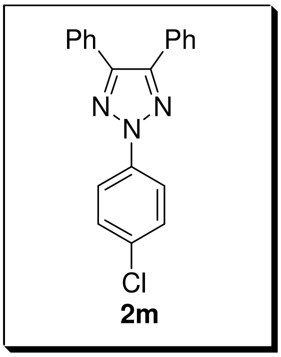
2k

4,5-Bis(2,4,5-trimethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2k. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.60$; brown solid; yield 66% (78.8 mg); mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.4$ Hz, 2H), 7.33-7.29 (m, 2H), 7.16-7.12 (m, 1H), 6.98 (s, 2H), 6.37 (s, 2H), 3.73 (s, 6H), 3.69 (s, 6H), 3.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.7, 144.9, 142.7, 139.6, 128.9, 126.6, 118.3, 113.6, 112.6, 97.4, 56.2, 55.8; FT-IR (KBr) 2935, 2842, 1614, 1596, 1527, 1497, 1461, 1436, 1399, 1379, 1291, 1261, 1210, 1175, 1102, 1029 cm^{-1}; *m/z* (ESI-MS) 478.21 $[M + H]^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.31; H, 5.69; N, 8.85.



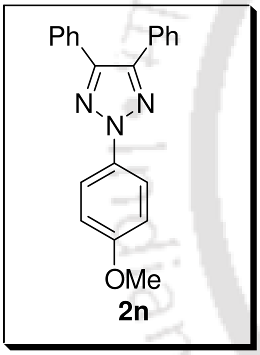
2l

2,4,5-Triphenyl-2*H*-1,2,3-triazole 2l. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.45$; colorless solid; yield 85% (63.2 mg); mp 123-124 °C (lit.[23] mp 124-125 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, $J = 8.4$ Hz, 2H), 7.74-7.72 (m, 4H), 7.55 (t, $J = 8.0$ Hz, 2H), 7.47-7.43 (m, 6H), 7.40 (t, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.9, 130.9, 129.4, 128.7, 128.6, 127.5, 118.8; FT-IR (KBr) 1632, 1597, 1496, 1458, 1441, 1375, 1322, 1289, 1266, 1074 cm^{-1}; *m/z* (ESI-MS) 298.15 $[M + H]^+$. Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.73; H, 5.10; N, 14.17.



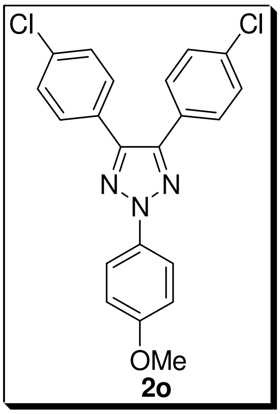
2m

2-(4-Chlorophenyl)-4,5-diphenyl-2*H*-1,2,3-triazole 2m. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.70$; colorless solid; yield 56% (46.5 mg); mp 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, $J = 9.2$ Hz, 2H), 7.66-7.63 (m, 4H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.41-7.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 138.4, 133.1, 130.7, 129.5, 129.0, 128.8, 128.6, 120.1; FT-IR (KBr) 3054, 2917, 1492, 1456, 1439, 1410, 1371, 1286, 1263, 1088, 1067 cm^{-1}; *m/z* (ESI-MS) 332.08 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66. Found: C, 72.49; H, 4.23; N, 12.61.



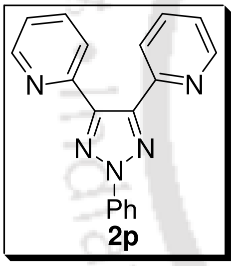
2n

2-(4-Methoxyphenyl)-4,5-diphenyl-2*H*-1,2,3-triazole[24] 2n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.70$; colorless solid; yield 45% (36.8 mg); mp 103-104 °C (lit.[24] mp 101-102 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 8.8$ Hz, 2H), 7.63-7.61 (m, 4H), 7.39-7.37 (m, 6H), 7.00 (d, $J = 9.2$ Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 145.7, 128.8, 128.7, 128.6, 124.5, 120.4, 114.5, 114.3, 55.7; FT-IR (KBr) 2963, 2928, 1603, 1577, 1511, 1459, 1440, 1294, 1260, 1176, 1144, 1102, 1024 cm^{-1}; *m/z* (ESI-MS) 328.15 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.11; H, 5.21; N, 12.81.



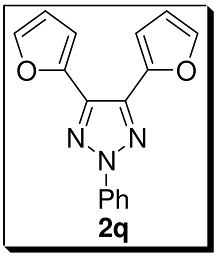
2o

4,5-Bis(4-chlorophenyl)-2-(4-methoxyphenyl)-2*H*-1,2,3-triazole 2o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 66% (65.4 mg); mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.2 Hz, 2H), 7.54-7.52 (m, 4H), 7.37-7.35 (m, 4H), 7.00 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.5, 134.8, 133.5, 129.8, 129.3, 129.1, 120.4, 114.5, 55.7; FT-IR (KBr) 2962, 2923, 1632, 1603, 1510, 1451, 1393, 1297, 1258, 1163, 1093, 1030 cm^{-1}; *m/z* (ESI-MS) 396.09 $[M + H]^+$. Anal. Calcd for $C_{21}H_{15}Cl_2N_3O$: C, 63.65; H, 3.82; N, 10.60. Found: C, 63.74; H, 3.83; N, 10.55.



2p

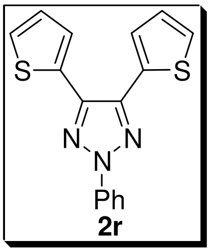
2-(2-Phenyl-5-(pyridin-2-yl)-2*H*-1,2,3-triazol-4-yl)pyridine 2p. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.30$; colorless liquid; yield 63% (47.14 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 4.4 Hz, 2H), 8.24 (d, J = 7.6 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H), 7.77-7.73 (m, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 7.30-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 149.6, 146.5, 139.6, 136.5, 129.3, 128.0, 124.3, 123.5, 119.4; FT-IR (KBr) 1637, 1590, 1566, 1495, 1417, 1372, 1313, 1264, 1148, 1016 cm^{-1}; *m/z* (ESI-MS) 300.14 $[M + H]^+$. Anal. Calcd for $C_{18}H_{13}N_5$: C, 72.23; H, 4.38; N, 23.40. Found: C, 72.14; H, 4.41; N, 23.45.



2q

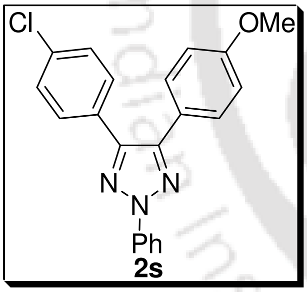
4,5-Di(furan-2-yl)-2-phenyl-2*H*-1,2,3-triazole 2q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.60$; yellow solid; yield 58% (40.2 mg);

mp 75-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 2H), 7.654-7.652 (m, 2H), 7.56-7.44 (m, 2H), 7.43-7.30 (m, 1H), 7.09-7.08 (m, 2H), 6.61-6.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 143.3, 139.5, 137.4, 129.4, 128.0, 119.2, 111.7, 110.8; FT-IR (KBr) 2963, 1594, 1513, 1491, 1425, 1369, 1294, 1261, 1095, 1030 cm^{-1}; *m/z* (ESI-MS) 278.07 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.39; H, 3.98; N, 15.11.



2r

2-Phenyl-4,5-di(thiophen-2-yl)-2*H*-1,2,3-triazole 2r. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.70$; orange solid; yield 47% (36.4 mg); mp 80-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 2H), 7.50-7.40 (m, 5H), 7.37 (d, J = 7.6 Hz, 2H), 7.10-7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 139.5, 131.6, 129.7, 129.4, 127.8, 127.7, 127.1, 119.0; FT-IR (KBr) 2961, 1593, 1494, 1421, 1261, 1093, 1026 cm^{-1}; *m/z* (ESI-MS) 310.05 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3S_2$: C, 62.11; H, 3.58; N, 13.58; S, 20.73. Found: C, 62.02; H, 3.56; N, 13.63; S, 20.79.



2s

4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2s. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 70% (63.3 mg); mp 98-99 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7.40-7.33 (m, 4H), 7.28-7.26 (m, 2H), 7.16-7.11 (m, 3H), 6.73-6.71 (m, 2H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 145.9, 144.5, 139.7, 134.6, 129.8, 129.7, 129.5, 129.3, 128.9, 127.4, 122.9, 118.7, 114.2, 55.3; FT-IR (KBr) 2962, 1614, 1599, 1497, 1458, 1251, 1175, 1092, 1032 cm^{-1}; *m/z* (ESI-MS) 362.12 $[M + H]^+$. Anal. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.80; H, 4.44; N, 11.58.

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Crystal Data and Structure Refinement for 1a′ at 298(2) K

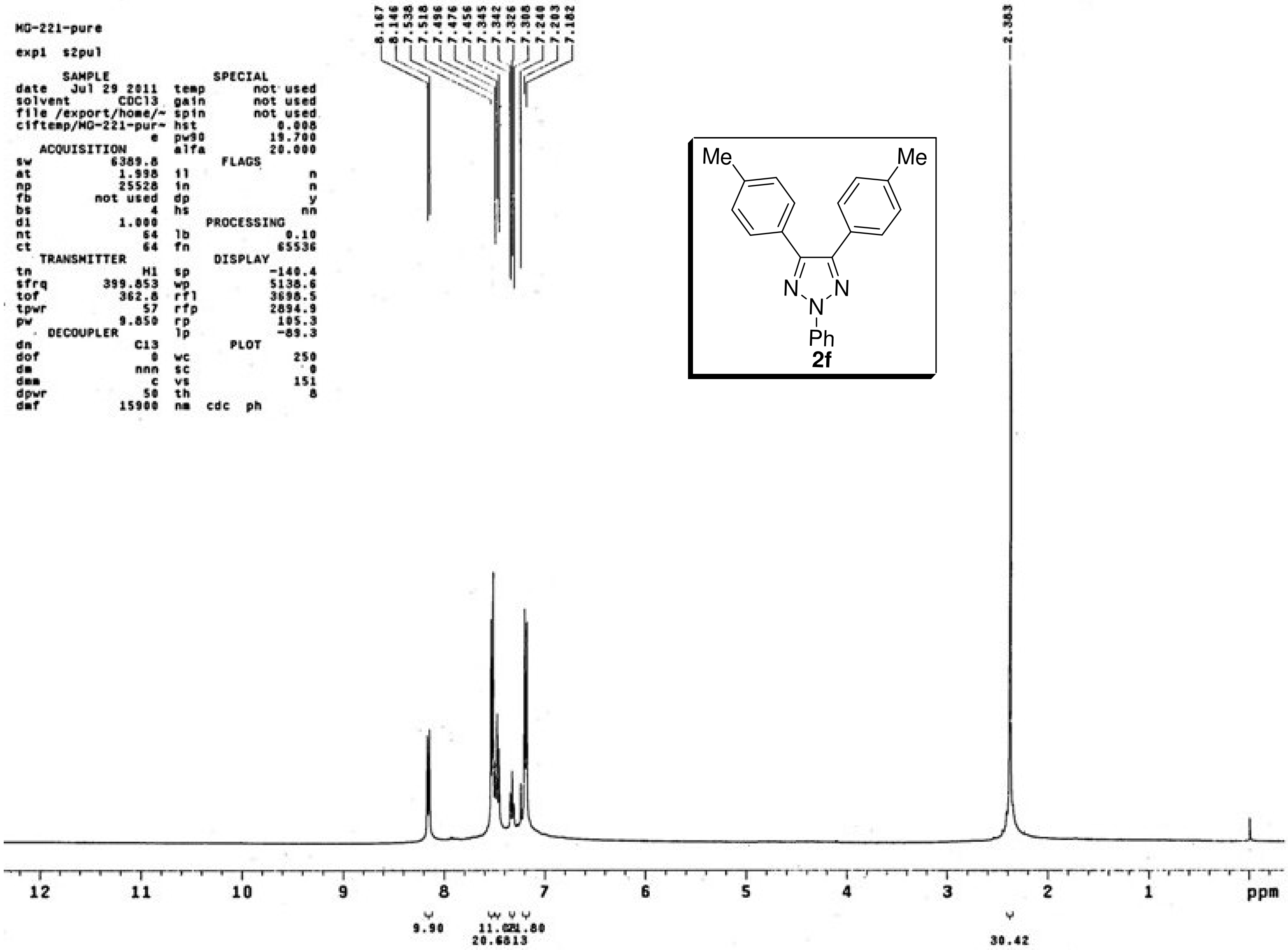
Identification code	**1a′**
Empirical formula	$C_{28}H_{26}N_4O_2$
Formula weight	450.53
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c Loop xyz ‘x, y, z’ ‘-x, y+1/2, -z+1/2’ ‘-x, -y, -z’ ‘x, -y-1/2, z-1/2’
Unit cell dimensions	*a* = 12.7013(16) Å α(°)= 90.00 *b* = 13.3293 (16) Å β(°)= 106.462(7) *c* = 15.6503(19) Å γ(°)= 90.00
Volume	2541.0(5) $Å^3$
Z	4
Density (calculated)	1.172 Mg/m^3
Absorption coefficient	0.076 mm^{-1}
F(000)	952.0
Crystal size	0.38 x 0.34 x 0.26 mm
Theta range for data collection	1.67 to 27.77°
Index ranges	-16<=h<=16, -17<=k<=17, -20<=l<=20
Reflections collected	5980
Independent reflections	5895 [R (int) = 0.0826]
Completeness to theta = 27.77°	99.7 %
Absorption correction	Multi-scan
Max. and min. transmission	0.980 and 0.972
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5512 / 0 /317
Goodness-of-fit on F^2	0.804
Final R indices [I>2sigma (I)]	$R1$ = 0.0628, $wR2$ = 0.1382
R indices (all data)	$R1$ = 0.2668, $wR2$ = 0.2161

Crystal Data and Structure Refinement for 2f at 298(2) K

Identification code	**2f**	
Empirical formula	$C_{22}H_{19}N_3$	
Formula weight	325.40	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c Loop xyz ‘x, y, z’ ‘-x, y, -z+1/2’ ‘x+1/2, y+1/2, z’ ‘-x+1/2, y+1/2, -z+1/2’ ‘-x, -y, -z’ ‘x, -y, z-1/2’ ‘-x+1/2, -y+1/2, -z’ ‘x+1/2, -y+1/2, z-1/2’	
Unit cell dimensions	*a* = 19.1122(16) Å	α(°)= 90.00
	b = 12.5233(10) Å	β(°)= 100.455(4)
	c = 7.4703(6) Å	γ(°)= 90.00
Volume	1758.3(2) $Å^3$	
Z	4	
Density (calculated)	1.229 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	688.0	
Crystal size	0.35 x 0.32 x 0.28 mm	
Theta range for data collection	1.95 to 26.07°	
Index ranges	-23<=h<=23, -12<=k<=15, -9<=l<=6	
Reflections collected	1734	
Independent reflections	1418 [R (int) = 0.0212]	
Completeness to theta = 26.07°	99.6 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.979 and 0.974	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1734 / 0 /118	
Goodness-of-fit on F^2	1.281	
Final R indices [I>2sigma (I)]	*R1* = 0.0512, *wR2* = 0.1541	
R indices (all data)	*R1* = 0.0602, *wR2* = 0.1651	

Crystal Data and Structure Refinement for 2m′ at 298(2) K

Identification code	**2m′**	
Empirical formula	$C_{12}H_8Cl_2N_2$	
Formula weight	251.10	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c Loop xyz 'x, y, z' '-x, y+1/2, -z+1/2' '-x, -y, -z' 'x, -y-1/2, z-1/2'	
Unit cell dimensions	*a* = 9.8369(15) Å	α(°)= 90.00
	b = 4.7221(8) Å	β(°)= 91.268(10)
	c = 11.6470(18) Å	γ(°)= 90.00
Volume	540.88(15) $Å^3$	
Z	2	
Density (calculated)	1.542 Mg/m^3	
Absorption coefficient	0.569 mm^{-1}	
F(000)	256	
Crystal size	0.36 x 0.31 x 0.29 mm	
Theta range for data collection	2.07 to 28.35°	
Index ranges	-13<=h<=12, -6<=k<=6, -15<=l<=15	
Reflections collected	1338	
Independent reflections	1296 [R (int) = 0.0293]	
Completeness to theta = 28.35°	98.8 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.848 and 0.815	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1318 / 0 /74	
Goodness-of-fit on F^2	1.018	
Final R indices [I>2sigma (I)]	$R1$ = 0.0351, $wR2$ = 0.0864	
R indices (all data)	$R1$ = 0.0381, $wR2$ = 0.0887	



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sw           6389.8            FLAGS
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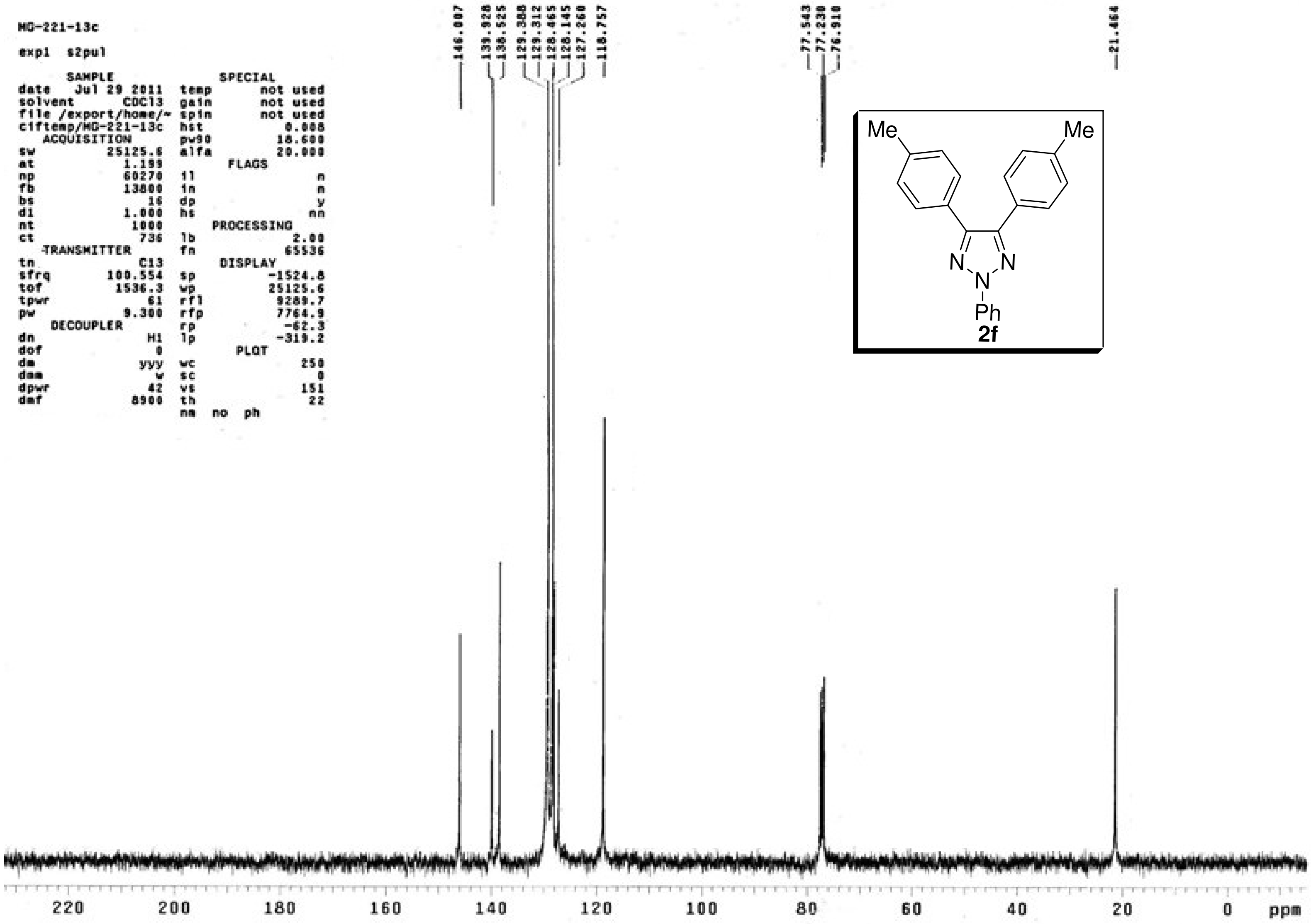

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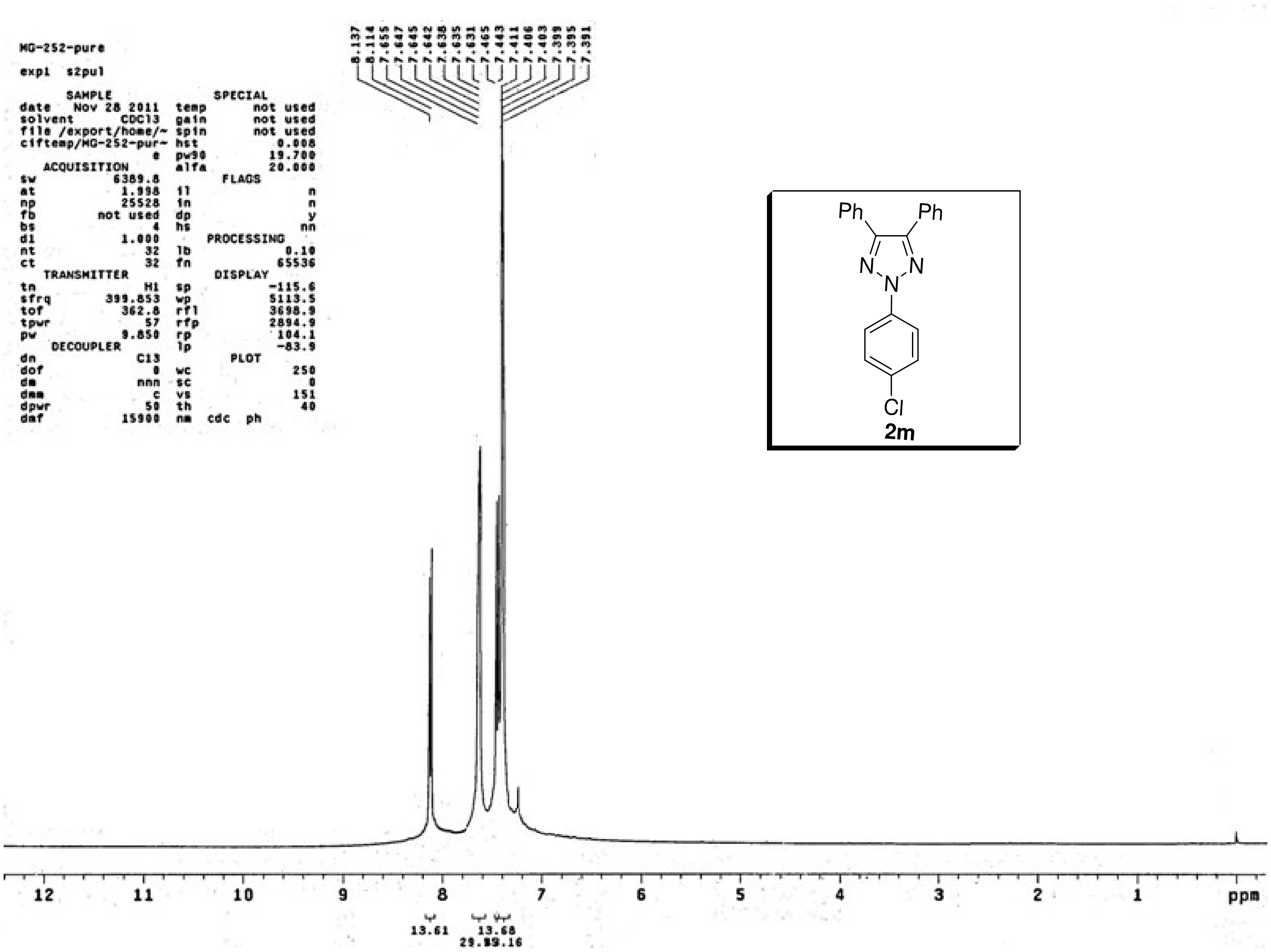

2m

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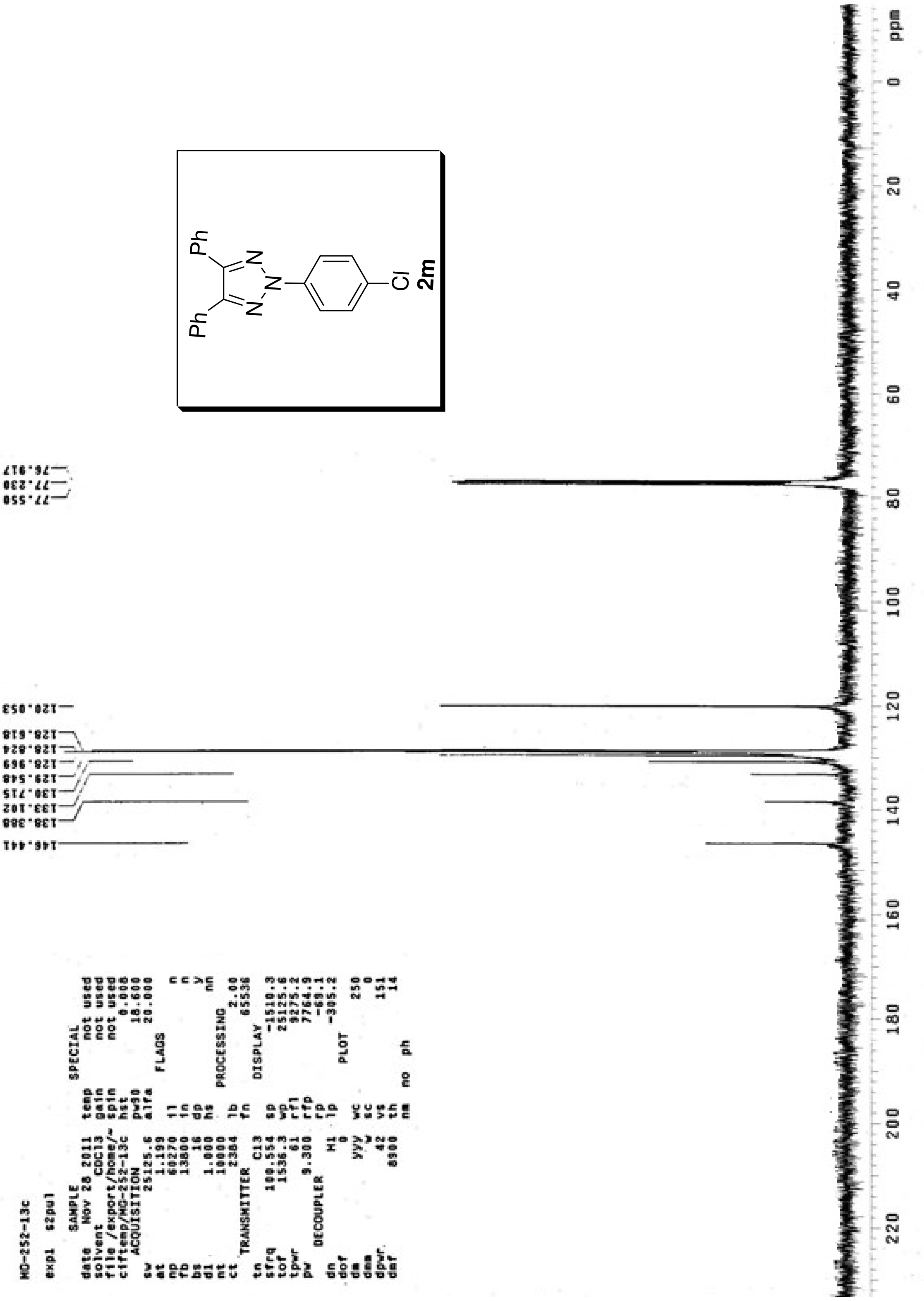
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80
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120
140
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220

Chapter IV

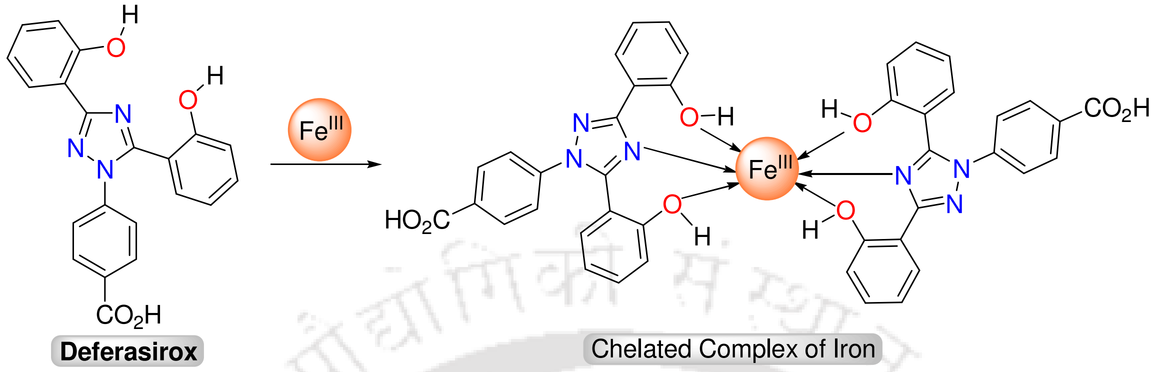
Aerobic Oxidative Synthesis of Substituted 1,2,4-Triazoles from Bisarylhydrazones via C–H Functionalization/C–N Bond Formation

The functionalization of C–H bonds has emerged to be a powerful strategy for its increased efficiency and ideality of new synthetic routes. The most alluring aspect in this context is the construction of the heterocyclic compounds through transition-metal-catalyzed C–H activation.[1] Although for the most parts, rhodium-,[2] ruthenium-[3] and palladium-based[4] catalysts are contributing to the dramatic resurgence of interest in carbon-carbon or carbon-heteroatom bond formation by the cleavage of ubiquitous C–H bonds, the use of copper[5] catalysts can also be beneficial for achieving the same, a pivotal advantage with respect to cost and toxicity.

With regards to sustainable chemistry, molecular oxygen present in air is an ideal oxidant for oxidative C–H bond functionalization, which is one of the most powerful and attractive strategies in organic synthesis. To this aim, the most ideal processes involve the use of dioxygen activation for functionalization reactions.[6] Copper enzymes are widely known for activation of dioxygen in biological oxygenase systems that effect hydroxylation of C–H bonds.[7] Recently, considerable attentions have been focused for copper-catalyzed dioxygen activation in organic transformations.[8] Our contribution in this field has been modest[6d] and our contention was to extend this strategy for the synthesis of heterocycles, such as substituted triazoles, which have found versatile applications in biological, material and medicinal sciences.[9] In this chapter, we demonstrate an unprecedented aerobic oxidative synthesis of substituted 1,2,4-triazoles from bisarylhydrazones via base mediated dimerization followed by copper(II)-catalyzed C–H functionalization/dioxygen activation/C–N bond formation strategy.

1,2,4-Triazoles have received considerable attention in biological and pharmaceutical fields as molecules with these structural features have been found to display potent biological properties such as antihypertensive, antibacterial[9f] and antifungal[9g] activities. Furthermore, *N*-1-aryl-1,2,4-triazoles such as ICL670 (deferasirox), an orally active iron chelator (Scheme 1), is very useful in iron overload therapy.[9e] Therefore development of efficient and convenient procedures to construct the 1,2,4-triazole building blocks have provoked considerable attention.

Scheme 1. Chelation of Iron with Deferasirox



4.1 Strategies for Synthesis of Trisubstituted 1,2,4-Triazoles

Several intermediates could be used for synthesis of two isomeric trisubstituted 1,2,4-triazoles (Figure 1). *N*-Acylamidrazone and dichloroaldazine are the intermediates for preparation of 3,4,5-trisubstituted 1,2,4-triazoles under metal-free conditions (Figure 1a-b)[10] whereas the other isomer, 1,3,5-trisubstituted 1,2,4-triazoles could readily be obtained from acyl amidine, triazene and ketoimine intermediates under metal induced conditions (Figure 1c-e).

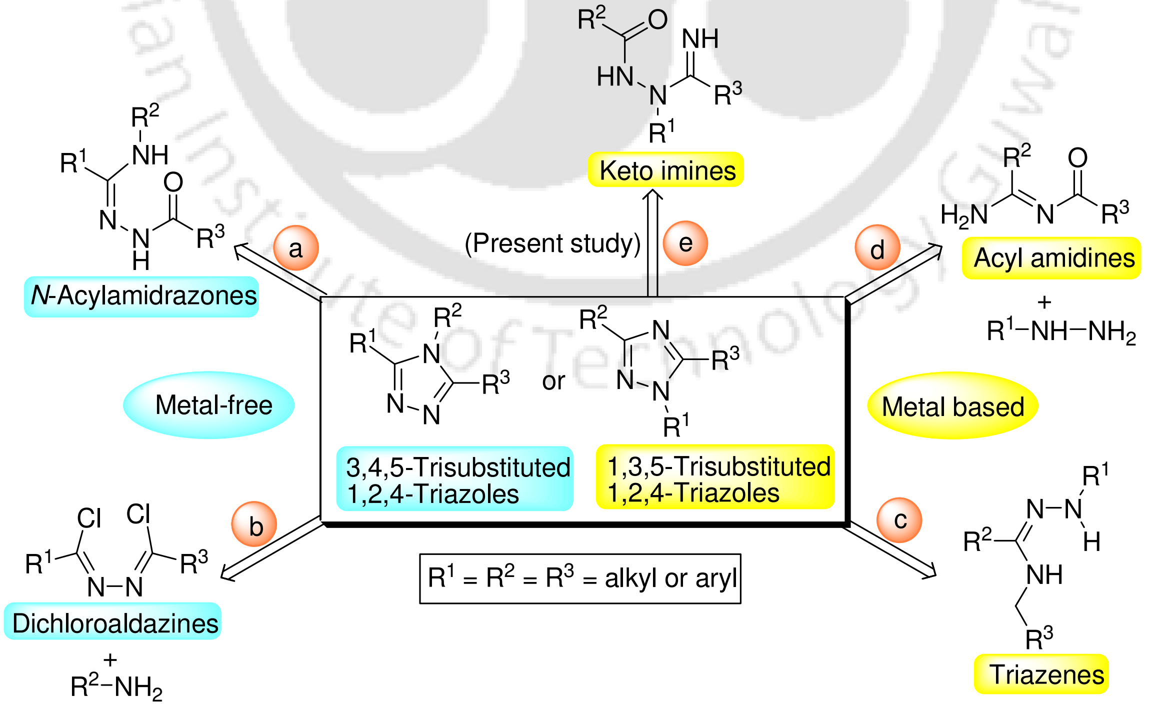


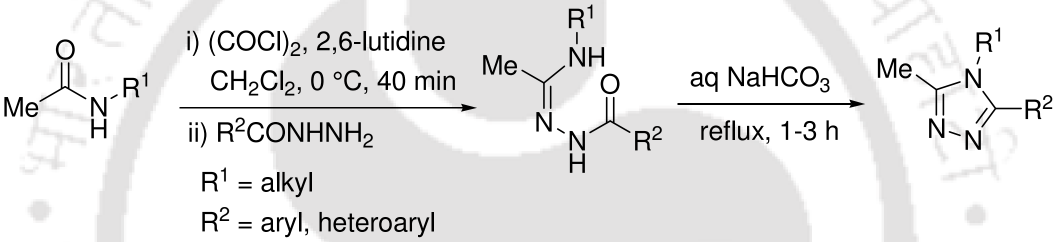
Figure 1. Different intermediates for synthesis of trisubstituted 1,2,4-triazoles

4.1.1 Synthesis of 1,2,4-Triazoles under Metal-Free Conditions

N-Acylamidrazones are the most common intermediates for synthesis of 3,4,5-trisubstituted 1,2,4-triazoles under metal-free conditions (Figure 1a). There are number of precursors (chloromethylene amides, imidates, thioamides, thioimidates, imidoylbenzotriazoles, amidrazones, oxadiazoles, *N*-nitrosoamidines and orarylphosphazoanilides) that could produce *N*-acylamidrazones.

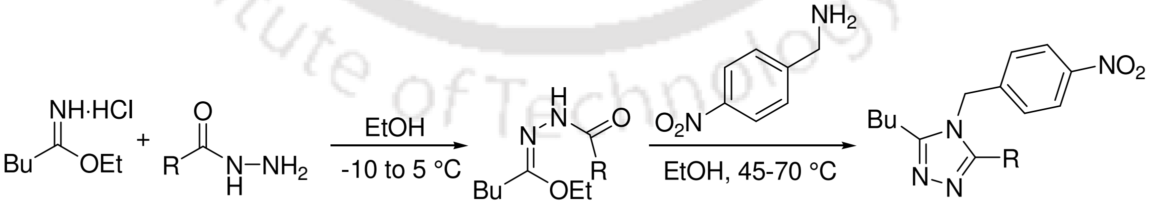
In presence of oxalyl chloride, *N*-alkyl substituted acetamides and aryl or alkyl hydrazides could produce 3,4,5-trisubstituted 1,2,4-triazoles via *N*-acylamidrazone intermediates (Scheme 2).[11a] The reaction could be performed in one-pot without isolation of the intermediates.

Scheme 2. Synthesis of Triazoles from Activated Amide Derivatives



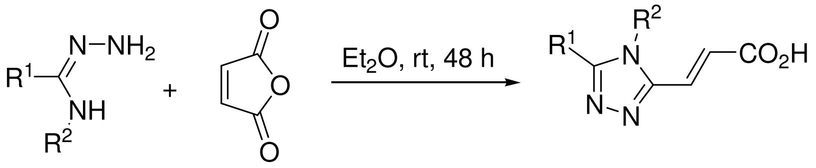
In an another approach, the synthesis of the target trisubstituted 1,2,4-triazoles could be achieved via the same intermediate by the reaction of imidate hydrochlorides with hydrazides followed by cyclization using *p*-nitrobenyl amine (Scheme 3).[11b] This method provides imidates as a suitable precursor to get *N*-acylamidrazone intermediates.

Scheme 3. Synthesis of Triazoles from Imidate Precursosrs



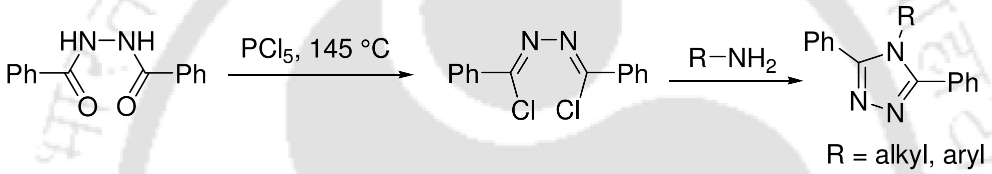
There are also reports where amidrazones have been used as a precursor to get the *N*-acylamidrazone intermediates for synthesis of triazole derivatives. For examples, 3-(3,4-diaryl-1,2,4-triazole-5-yl)propenoic acid derivatives have been isolated by the condensation of *N*-3-subatituted amidrazones and maleic anhydride after precipitation and recrystallization (Scheme 4).[11c-d]

Scheme 4. Synthesis of Triazoles from Amidrazones



Dichloroaldazines are considered as the classical intermediates for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles (Figure 1b). The target intermediates could be synthesized from *N*-acylhydrazides by the treatment of phosphorous pentachloride in heating condition. The corresponding dichloroaldazines, thus obtained, could react with alkyl or aryl amines under reflux conditions to give trisubstituted triazoles (Scheme 5).[11e]

Scheme 5. Classical Approach for Synthesis of Substituted 1,2,4-Triazoles

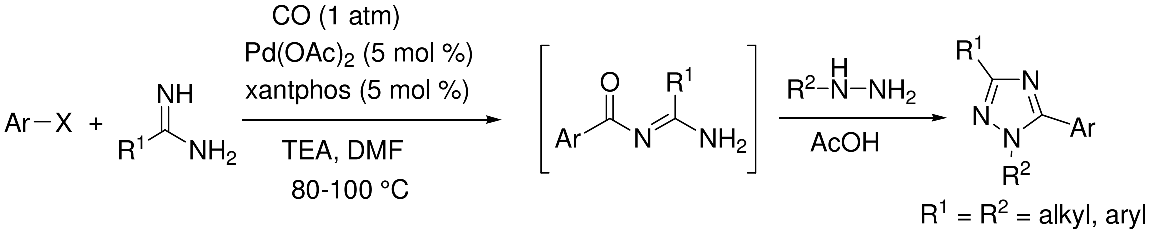


4.1.2 Synthesis of 1,2,4-Triazoles under Metal Based Conditions

Despite the classical methods in organic synthesis, the most reliable and widely used strategy is metal-catalyzed chemical transformations. Transition-metal-catalyzed cross-coupling reactions remain the most prevalent route for synthesis of azaheterocycles.

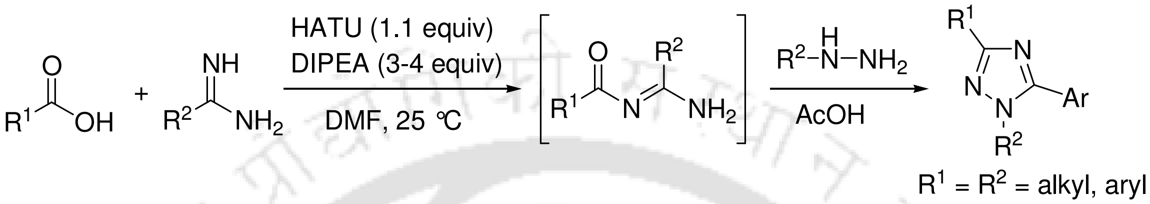
1,3,5-Trisubstituted 1,2,4-triazoles could be synthesized from acyl amidine intermediate via palladium-catalyzed four-component C–C–N coupling strategy (Figure 1d). The reaction takes place through carbonylative coupling of amidines with aryl halides followed by in situ reaction with monosubstituted hydrazines (Scheme 6).[12a]

Scheme 6. Palladium-Catalyzed Carbonylative Access of Acyl Amidines



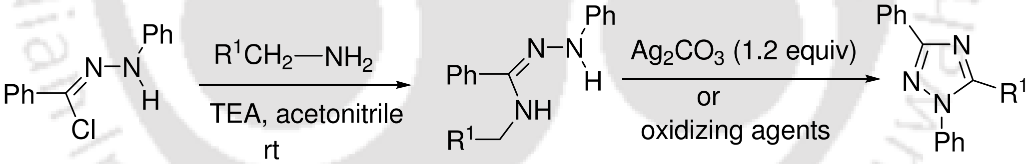
Later, the above strategy has been modified by an alternative and experimentally convenient strategy to get the reactive acyl amidine intermediates. Here, primary amidines with carboxylic acids, that obviate the need of carbon monoxide, could produce the target trisubstituted 1,2,4-triazoles via the same intermediate in presence of a coupling reagent at room temperature (Scheme 7).[12b]

Scheme 7. Noncarbonylative Access to Acyl Amidines



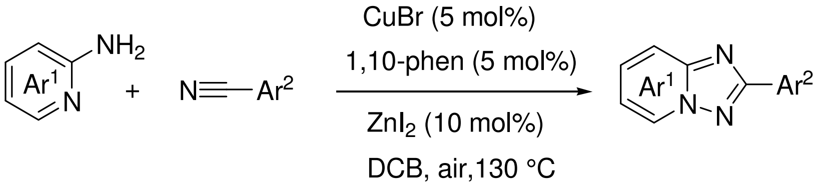
Triazenes are also important intermediates for synthesis of 1,3,5-trisubstituted 1,2,4-triazoles (Figure 1c). The convenient way to get the intermediate is the reaction of hydrazonyl chloride with aliphatic amines in presence of triethyl amine which could undergo cyclization by incorporation of stoichiometric amount of silver salt or oxidizing agents like H_2O_2, NaOCl, $Ca(ClO)_2$, Dess-Martin periodinate etc (Scheme 8).[12c-d]

Scheme 8. Synthesis of Triazoles via Triazenes



Transition-metals are also known to activate nitriles for catalytic oxidative constructions of nitrogen heterocycles. For example, a direct synthesis of 1,2,4-triazole heterocore by reaction of 2-amonopyridines and nitriles have been achieved via copper-catalyzed cascade C–N/N–N bonds formation in presence of catalytic amount of ligand and additive under aerobic conditions (Scheme 9).[12e]

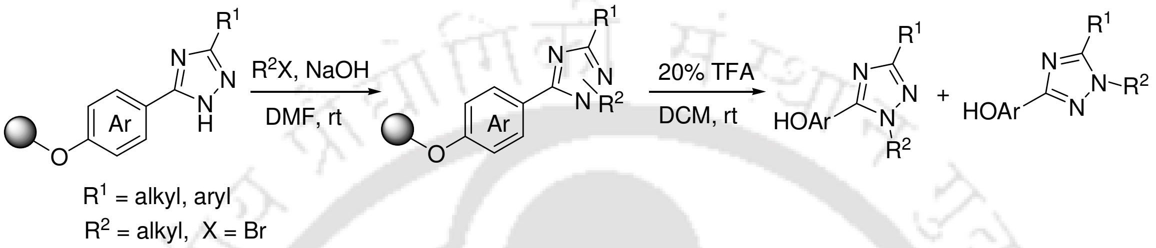
Scheme 9. Copper-Catalyzed Tandem Addition-Oxidative Cyclization



4.1.3 Synthesis of Trisubstituted 1,2,4-Triazoles by Other Methods

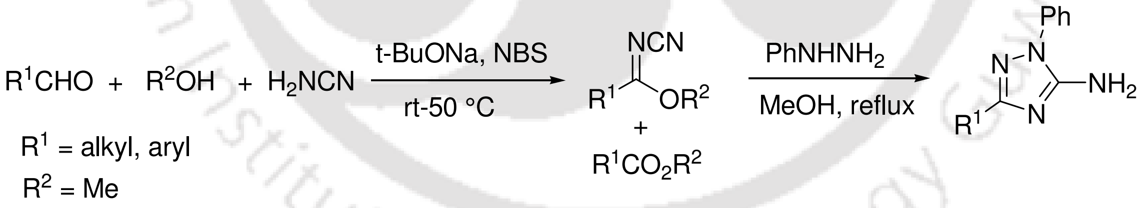
There are several synthetic paths for preparation of substituted 1,2,4-triazoles in the solution phase. But solid phase synthesis of trisubstituted 1,2,4-triazoles has also been established from triazole-functionalized solid support in presence of alkyl halides (Scheme 10).[13a]

Scheme 10. Solid Phase Synthesis of Trisubstituted 1,2,4-Triazoles



A one-pot synthesis of trisubstituted 1,2,4-triazoles has also been described via cyanoamidation of aryl or alkyl aldehydes with cyanamide in presence of methanol followed by intermolecular cyclization with phenylhydrazine under reflux conditions. NBS could act as an oxidizing agent for cyanoamidation giving rise to the formation of intermolecular C–N and C–O bonds without the use of metal catalysts (Scheme 11).[13b]

Scheme 11. Cyanoamidation of Aldehydes for Synthesis of 1,2,4-Triazoles

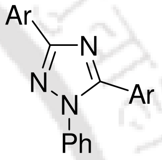
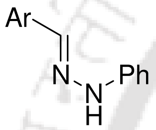


4.2 Present Study

An unprecedented copper(II)-catalyzed aerobic oxidative synthesis of 1,3,5-triaryl-1,2,4-triazoles from bisarylhydrazones as the precursors have been achieved via cascade C–H functionalization/C–N bond formation under mild reaction conditions. This new class of compounds could give prospective luminescence as an iconic component in the area of pharmaceutical and biological sciences.

Screening of Reaction Conditions. During investigation of the reaction conditions, intriguingly, we found that bisarylhydrazone **3a** could readily undergo reaction with an organic base such as Et_3N in toluene at 60 °C for 30 h under air to give an intermediate that could proceed reaction further with 10 mol % $Cu(OAc)_2\cdot H_2O$ at room temperature to afford 1,3,5-triaryl-1,2,4-triazole **4a** in 55% yield (Table 1, Entry 1). Having this

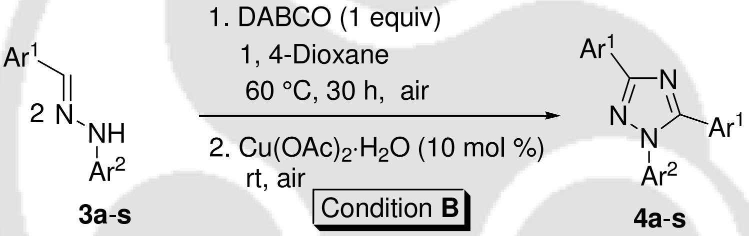
Table 1. Screening of Reaction Conditions for Synthesis of Triaryl-1,2,4-Triazoles[a]

Entry	Substrate	Base	Solvent	[Cu]	Product	Yield(%)[b]
1		Et_3N	Toluene	$Cu(OAC)_2\cdot H_2O$		55[c]
2		Pyridine	Toluene	$Cu(OAC)_2\cdot H_2O$		n.d.
3		DIPA	Toluene	$Cu(OAC)_2\cdot H_2O$		49[c]
4		DABCO	Toluene	$Cu(OAC)_2\cdot H_2O$	 Ar = $(4\text{-}OMe)C_6H_4$ **4a**	62[d]
5	 Ar = $(4\text{-}OMe)C_6H_4$ **3a**	DBU	Toluene	$Cu(OAC)_2\cdot H_2O$		58[d]
6		Pyrrolidine	Toluene	$Cu(OAC)_2\cdot H_2O$		31[e]
7		DMEDA	Toluene	$Cu(OAC)_2\cdot H_2O$		trace[f]
8		TMEDA	Toluene	$Cu(OAC)_2\cdot H_2O$		21[f]
9		Cs_2CO_3	Toluene	$Cu(OAC)_2\cdot H_2O$		n.d.
10		K_2CO_3	Toluene	$Cu(OAC)_2\cdot H_2O$		n.d.
11		**DABCO**	**Dioxane**	$\mathbf{Cu(OAC)_2\cdot H_2O}$		**72[g]**
12		DABCO	THF	$Cu(OAC)_2\cdot H_2O$		66[g]
13		DABCO	DMF	$Cu(OAC)_2\cdot H_2O$		24[f]
14		DABCO	Dioxane	$Cu(OAC)_2$		70[g]
15		DABCO	Dioxane	$CuCl_2$		68[g]
16		DABCO	Dioxane	$Cu(OTf)_2$		65[g]
17		DABCO	Dioxane	CuCl		66[g]
18		DABCO	Dioxane	CuI		62[g]
19[h]		DABCO	Dioxane	$Cu(OAC)_2\cdot H_2O$		58[g]
20[i]		DABCO	Dioxane	$Cu(OAC)_2\cdot H_2O$		62[g]

[a] Conditions: Bisarylhydrazone **3a** (0.5 mmol) and base (1 equiv) were stirred in solvent (2 mL) at 60 °C for 30 h under air and then treated with [Cu] source (10 mol %) at rt under air and the stirring continued for 2 h. [b] Isolated yield. *p*-Anisaldehyde ([c]20%, [d]12%, [e]35%, [f]47% and [g]5%) was obtained as byproduct. [h] [Cu] source (5 mol %) used. [i] Base (0.5 equiv) used. n.d. = not detected.

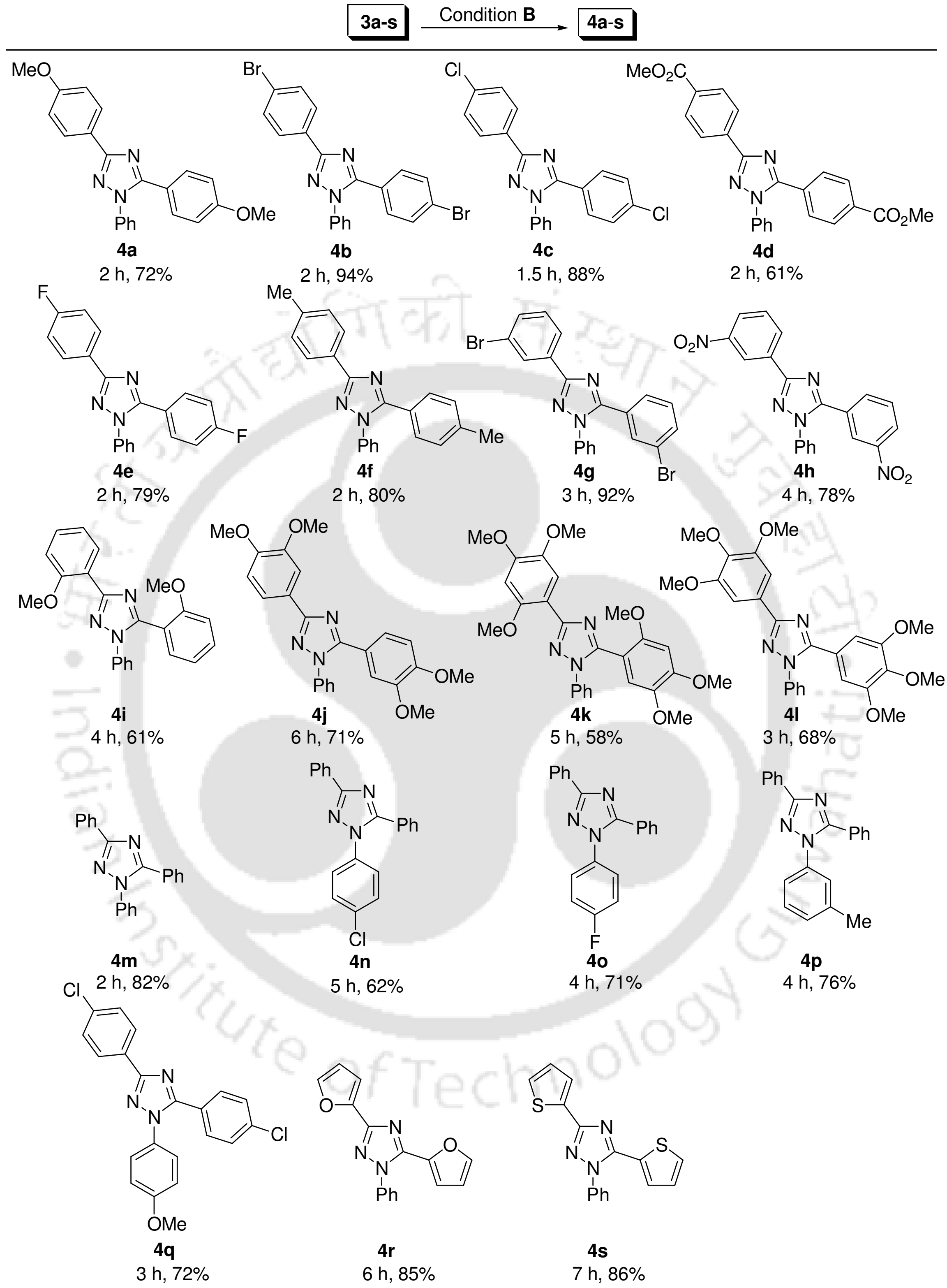
important result in our hand, we went on further to screen the other reaction parameters with **4a** as a model substrate. Employing other organic bases (Entries 1-8) and solvents (Entries 11-13) led to find DABCO and dioxane as the choice of base and solvent (Entries 4 and 11), respectively. In contrast, the reactions with inorganic bases were found to be ineffective (Entries 9-10). The catalytic activity of the other copper sources such as $Cu(OAc)_2$, $CuCl_2$, $Cu(OTf)_2$, CuCl and CuI was examined and Cu(II)-salts were found to be superior to Cu(I)-salts to afford the product **4a** in high yields (Entries 14-18). When the amount of the copper source (5 mol %) or quantity of the base (0.5 equiv) was reduced, the yield of **4a** was significantly dropped (Entries 19 and 20). Control experiment revealed that in the absence of the copper source no cyclization was observed to give the target heterocycle **4a**. As a whole, condition **B** was fascinated to be the best for the synthesis of 1,3,5-triaryl-1,2,4-triazoles (Scheme 12).

Scheme 12. Copper-Catalyzed Oxidative C–H Functionalization



Substrate Scope for the Synthesis of 1,2,4-Triazoles (Condition B). Next, we explored the scope for the synthesis of 1,3,5-triayl-1,2,4-triazoles **4a-s** with optimal condition **B** (Table 2). Bisarylhydrazones **3b-e**, **3g-h** and **3n-o** bearing electron-withdrawing groups on the aryl rings proceeded cyclization to give the corresponding substituted triazoles **4b-e**, **4g-h** and **4n-o** in 61-94% yields. Furthermore, the substrates **3a**, **1f**, **3i**, **3m** and **3p** bearing H or electron-donating substituents on the aryl rings afforded the target heterocycles **4a**, **4f**, **4i**, **4m** and **4p**, respectively, in 61-82% yields. Bisarylhydrazone **3q** with both electron-donating and withdrawing substituents on the aryl rings cyclized to give 1,2,4-triazole **4q** in 72% yield. In addition, bisarylhydrazones **3j-l** having dimethoxy and trimethoxy substituents in the aromatic rings could be converted into the corresponding substituted 1,2,4-triazoles **4j-l** in 58-71% yields. Furthermore, the substrates **3r** and **3s** underwent reaction to give substituted 1,2,4-triazoles **4r** and **4s**, respectively, in 85-86% yields. The single crystal of the compound **4c** obtained from acetonitrile solution was analyzed by X-ray analysis (Figure 2).

Table 2. Cu(II)-Catalyzed Synthesis of 1,3,5-Triaryl-1,2,4-Triazoles[a]



4a 2 h, 72%
4b 2 h, 94%
4c 1.5 h, 88%
4d 2 h, 61%
4e 2 h, 79%
4f 2 h, 80%
4g 3 h, 92%
4h 4 h, 78%
4i 4 h, 61%
4j 6 h, 71%
4k 5 h, 58%
4l 3 h, 68%
4m 2 h, 82%
4n 5 h, 62%
4o 4 h, 71%
4p 4 h, 76%
4q 3 h, 72%
4r 6 h, 85%
4s 7 h, 86%

[a] Conditions: Substrate **3a-s** (0.5 mmol) and DABCO (1 equiv) were stirred in dioxane (2 mL) at 60 °C for 30 h under air and the resulting mixture was treated with $Cu(OAc)_2 \cdot H_2O$ (10 mol %) at rt under air and the stirring continued for the appropriate time.

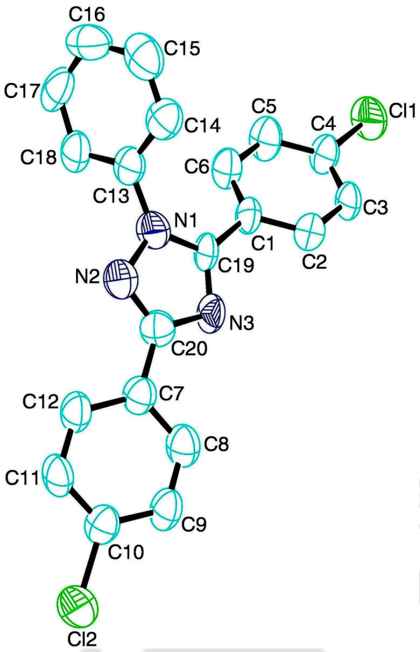
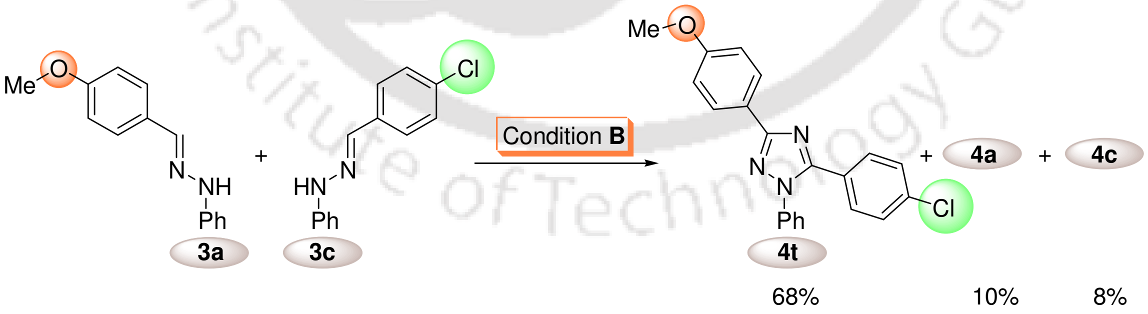


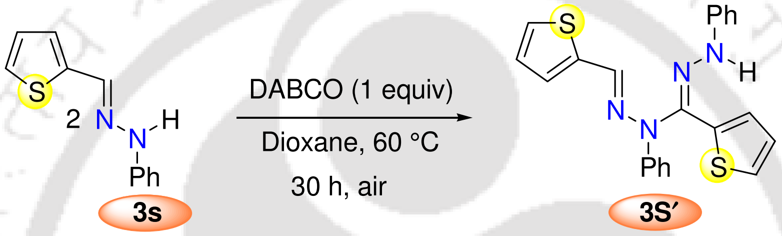
Figure 2. ORTEP diagram of 1,3,5-triaryl-1,2,4-triazole **4c.** H-Atoms have been omitted for clarity.

Synthesis of Unsymmetrically Substituted 1,2,4-Triazole. The reaction condition **B** could also be readily employed for the synthesis of unsymmetrical 1,3,5-triaryl-1,2,4-triazoles. For an example, a 1:1 mixture of hydrazones **3a** and **3c** underwent reaction to give the corresponding unsymmetrical 1,2,4-triazole **4t** in 68% yield along with the symmetrical 1,2,4-triazoles **4a** and **4c** as minor products (Scheme 13).

Scheme 13. Synthesis of Unsymmetrically Substituted 1,2,4-Triazole



Mechanistic Studies of the Synthesis of 1,2,4-Triazoles 4a-s. To demonstrate the mechanism for the synthesis of 1,2,4-triazoles **4a-s**, the intermediate **3S′**, formed from **3s** in presence of organic base (eq 1), was isolated and its structure was confirmed by single crystal X-ray analysis (Figure 3). To our delight, the intermediate **3c″** has also been isolated from **3c** when it was treated with organic base for 30 h followed by the addition of copper catalyst in presence of air (eq 2). Furthermore, the keto imine intermediate **3c″** whose structure was confirmed by X-ray analysis (Figure 4), readily proceeded cyclization to give the substituted 1,2,4-triazole **4c** when the reaction was prolonged. To see whether DABCO has any role in the cyclization step, the reaction of the dimeric intermediate **3S′** was investigated with 10 mol % $Cu(OAC)_2{\cdot}H_2O$ in dioxane at room temperature under air. However, no cyclization was observed and the intermediate **3S′** was isolated intact. In contrast, when DABCO was added, the reaction proceeded efficiently to afford the target heterocycle **4s**. These results clearly suggest that DABCO is not only acting as a base but also playing a crucial role of an effective ligand for the copper(II)-catalyzed oxidative cyclization to give the target heterocycles **4a-s**.



(eq 1)

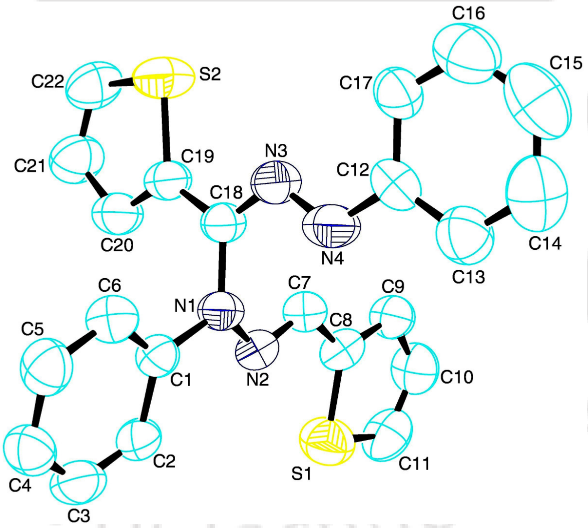
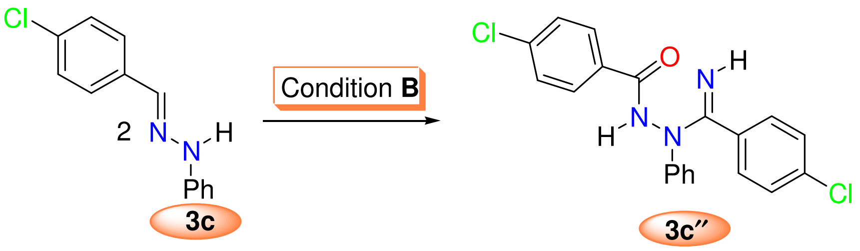


Figure 3. ORTEP representation of the intermediate **3S′**. H-Atoms have been omitted for clarity.



(eq 2)

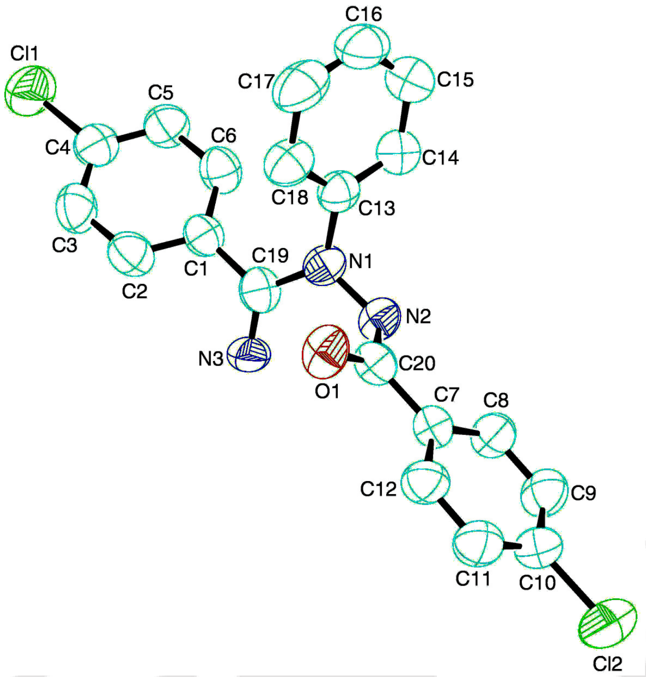
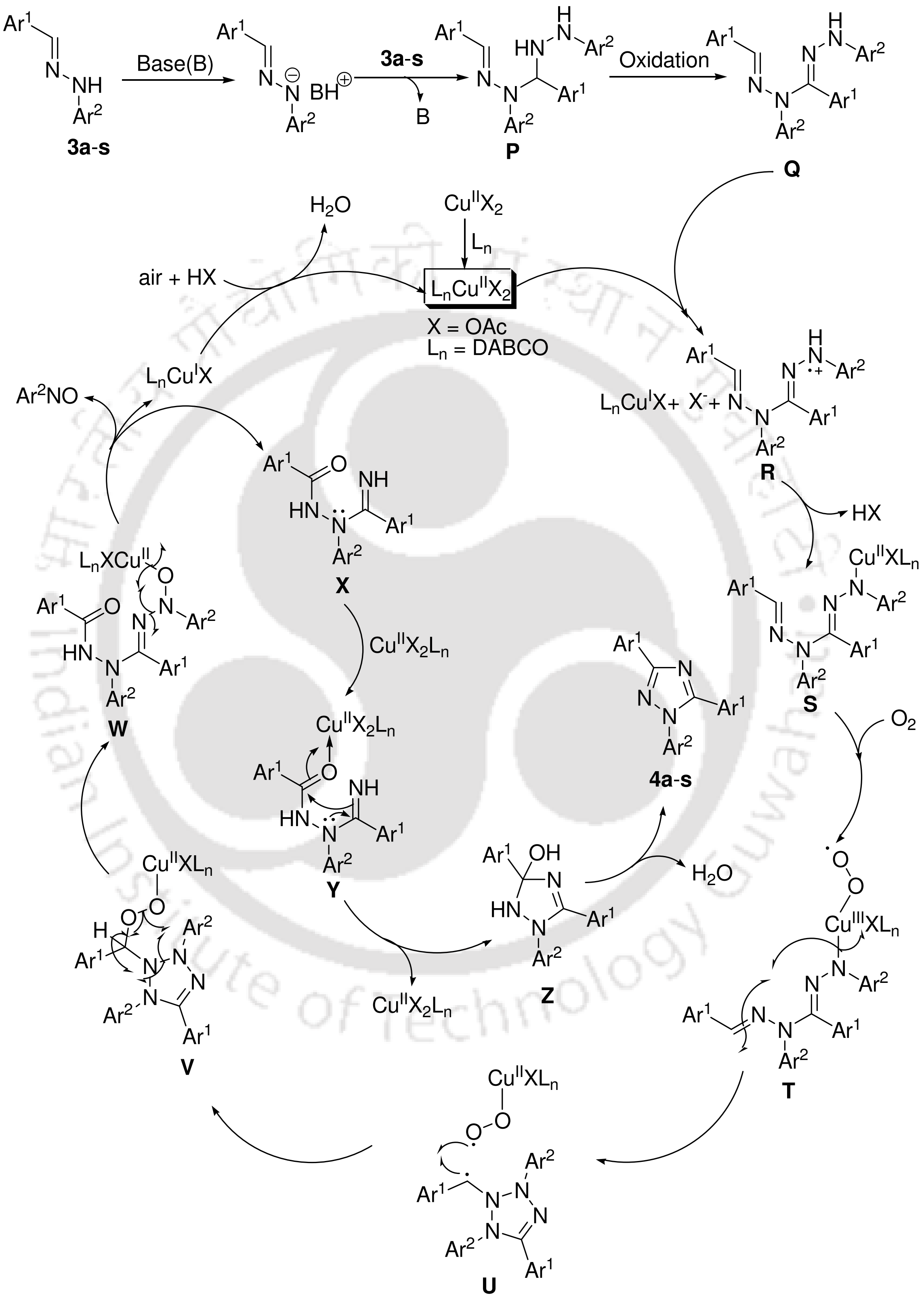


Figure 4. ORTEP representation of the intermediate **3c″**. H-Atoms have been omitted for clarity.

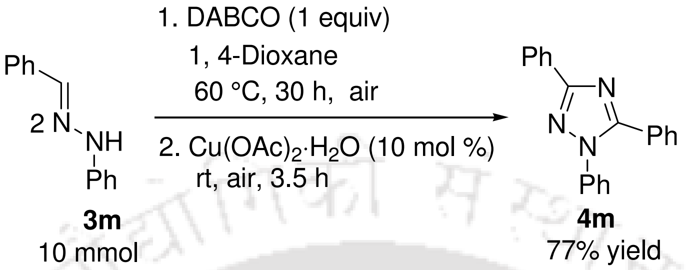
The literature reports on copper-catalyzed aerobic oxidative transformations developed by Chiba[8] and Stahl[14] facilitate to unravel the mechanistic route for the synthesis of substituted 1,2,4-triazoles. Observed experimental results and the literature precedent on copper-catalyzed aerobic oxidative processes[15] suggest that the base may mediate the dimerization of bisarylhydrazones **3a-s** to give **P** via C–N bond formation (Scheme 14). The aerobic oxidation of **P** could give **Q** that may lead to the formation of the radical cation **R** by single-electron transfer to copper(II) complex derived from copper(II)-salt with DABCO. The radical intermediate **R** may react with copper(I) complex to give copper(II) species **S** by elimination of HX. Aerobic oxidation of **S** may provide the copper(III)-superoxo species **T**. Heterocyclization of **T** may lead to the formation of benzylic radical **U** which may further be converted into copper(II)-peroxo species **V**.[8a] Rearrangement of **V** could form the intermediate **W** that with elimination of nirosoarenes[16] and copper(I) complex may afford keto imine intermediate **X** by abstracting hydrogen either from water generating during reaction or from intermediate **Q**. The Lewis acid assisted heterocyclization of **X** may lead to the target azaheterocycles **4a-s** via **Y** and **Z**. The active copper(II) complex could be regenerated by the aerobic oxidation of copper(I) complex in presence of HX.

Scheme 14. Plausible Catalytic Cycle for Synthesis of 1,3,5-Triaryl-1,2,4-Triazoles



Finally, conditions **B** was applied for the scale up of the reaction with **3m** as a substrate (Scheme 15). To our delight, the reactions was convenient and efficient to give the corresponding target azaheterocycles **4m** in 77% yield, with slightly longer reaction time.

Scheme 15. **Gram Scale Synthesis of Substituted Triazoles**



In summary, the intriguing chemistry of copper(II)-catalyzed oxidative C–H functionalization of bisarylhydrazones for the regioselective synthesis of 1,3,5-triaryl-1,2,4-triazoles have been exploited under aerobic conditions. This strategy, carried out under mild reaction conditions, could be explored to large synthetic scope with wide functional group compatibility from the readily accessible substrates. The ground breaking feature with this protocol involves the synthesis of 1,3,5-triaryl-1,2,4-triazoles by copper(II)-catalyzed C–H functionalization at room temperature using aerobic oxygen as an oxidant. This could introduce a new incarnation to the scientific endeavor for copper-catalyzed room temperature C–H functionalization. Although we have isolated the reactive intermediates to unravel the mechanistic ubiquity, the detailed mechanism of each elementary step is still to be illuminated.

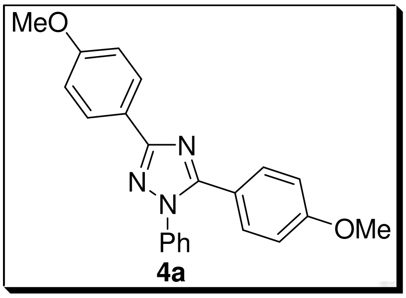
Experimental Section

General Information: Anilines, aldehydes and DABCO (≥99%) were purchased from commercial sources and were used as received. The catalyst $Cu(OAc)_2 \cdot H_2O$ (≥98%) was purchased from Aldrich. Prior to use solvents were freshly dried following standard procedure.[1] Isolation of product was carried out by silica gel column chromatography. All reactions were monitored by analytical TLC on silica gel G/GF 254 plates. NMR (^{1}H and ^{13}C) spectra were recorded on a NMR spectrometer and the data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration).The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet. Melting points were determined by melting point apparatus. FT-IR spectra of air-dried samples were recorded on FT-IR spectrometer using KBr disks and are reported in frequency of absorption (cm^{-1}). Elemental analyses were recorded using CHNS analyzer. The electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a liquid chromatography (LC)-MS. For single crystal X-ray analysis the intensity data were collected using CCD diffractometer, equipped with a sealed-tube Mo Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structures were solved by direct methods and refined with full-matrix least squares on F^2. Arylhydrazines and bisarylhydrazones were prepared according to our previous study.[5i]

General Procedure for Copper(II)-Catalyzed Synthesis of 1,3,5-Triaryl-1,2,4-Triazoles. Bisarylhydrazones **3a-s** (0.5 mmol) with DABCO (1 equiv, 56.1 mg) were stirred in dioxane (2 mL) at 60 °C for 30 h under air. After cooling to room temperature, $Cu(OAc)_2 \cdot H_2O$ (10 mol %, 10.0 mg) was added in the same pot and the stirring was continued for appropriate time at room temperature under air. After completion of the reaction, the solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford the desired heterocycles **4a-s** in analytically pure form.

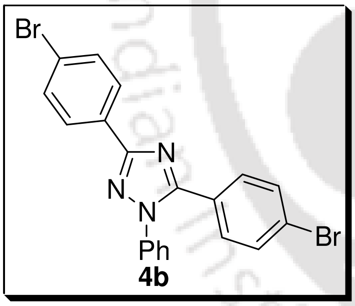
Typical Procedure for Copper(II)-Catalyzed Synthesis of Unsymmetrical 1,3,5-Triaryl-1,2,4-Triazole 4t. Bisarylhydrazones **3a** (0.25 mmol, 56.6 mg) and **3c** (0.25 mmol, 57.7 mg) with DABCO (1 equiv, 56.1 mg) were stirred in dioxane (2 mL) at 60 °C for 30 h under air. After cooling to room temperature, $Cu(OAc)_2 \cdot H_2O$ (10 mol %, 10.0 mg) was added in the same pot and the stirring was continued for 3 h at room temperature under air. After completion of the reaction, the solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford unsymmetrical 1,3,5-triaryl-1,2,4-triazole **4t** in 68% (61.5 mg) yield along with symmetrical 1,3,5-triaryl-1,2,4-triazoles **4a** and **4c** in 10% (8.9 mg) and 8% (7.3 mg) yield, respectively.

Typical Procedure for Gram Scale Synthesis of 1,3,5-Triphenyl-1,2,4-Triazole 4m. Bisphenylhydrazone **3m** (10 mmol, 1.97 g) and DABCO (10 mmol, 1.12 g) were stirred in dioxane (40 mL) at 60 °C for 48 h under air. After cooling to room temperature, $Cu(OAc)_2 \cdot H_2O$ (10 mol %, 0.20 g) was added in the same pot and the stirring was continued for 3.5 h at room temperature under air. The solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford 1,3,5-triphenyl-1,2,4-triazole **4m** in 77% (1.14 g) yield.



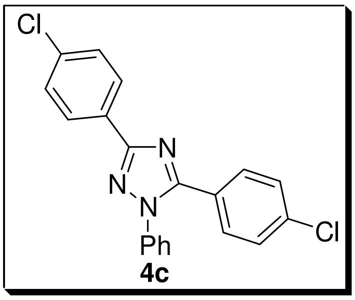
4a

3,5-Bis(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 72% (64.3 mg); mp 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.34-7.31 (m, 5H), 6.94 (d, $J = 8.0$ Hz, 2H), 6.77 (d, $J = 8.0$ Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.7, 160.5, 154.3, 138.4, 130.3, 129.2, 128.5, 127.8, 125.3, 123.5, 120.2, 113.8, 55.0; FT-IR (KBr) 2939, 2837, 1611, 1577, 1531, 1498, 1482, 1465, 1426, 1390, 1345, 1301, 1255, 1172, 1108, 1031 cm^{-1}; *m/z* (ESI-MS) 358.18 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.01; H, 5.35; N, 11.73.



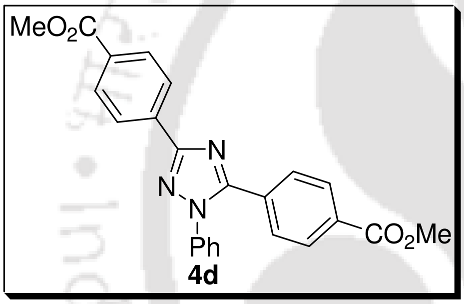
4b

3,5-Bis(4-bromophenyl)-1-phenyl-1*H*-1,2,4-triazole 4b. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; gummy liquid; yield 94% (106.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 8.8$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 2H), 7.49-7.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 153.7, 138.0, 131.81, 131.75, 130.4, 129.6, 129.5, 129.1, 128.1, 126.7, 125.3, 124.7, 123.7; FT-IR (KBr) 2961, 1638, 1597, 1497, 1470, 1456, 1416, 1404, 1339, 1262, 1173, 1139, 1094, 1070, 1012 cm^{-1}; *m/z* (ESI-MS) 453.96, 455.93, 457.95 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.72; H, 2.89; N, 9.25.



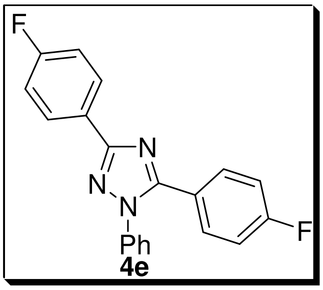
4c

3,5-Bis(4-chlorophenyl)-1-phenyl-1*H*-1,2,4-triazole 4c. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 88% (80.6 mg); mp 133-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.48-7.38 (m, 9H), 7.33 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 153.8, 138.0, 136.3, 135.4, 130.2, 129.6, 129.2, 128.9, 128.7, 127.9, 127.2, 126.2, 125.4, 112.7; FT-IR (KBr) 1644, 1598, 1498, 1471, 1455, 1408, 1337, 1178, 1136, 1086, 1014 cm^{-1}; *m/z* (ESI-MS) 366.07 [M + H]$^+$. Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47. Found: C, 65.68; H, 3.56; N, 11.44.



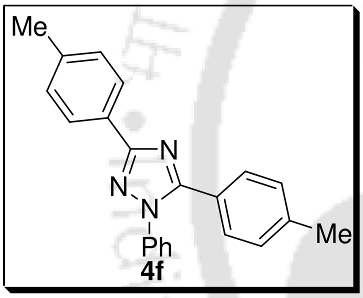
4d

3,5-Bis(4-carbomethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.30$; colorless solid; yield 61% (63.1 mg); mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.46-7.43 (m, 2H), 7.42-7.37 (m, 3H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.3, 161.3, 154.1, 137.9, 134.8, 131.9, 131.5, 130.9, 130.0, 129.8, 129.7, 129.4, 129.0, 126.5, 125.5, 52.4, 52.2; FT-IR (KBr) 2923, 2851, 1719, 1637, 1613, 1497, 1434, 1418, 1341, 1277, 1138, 1108, 1017 cm^{-1}; *m/z* (ESI-MS) 414.17 [M + H]$^+$. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.64; H, 4.61; N, 10.21.



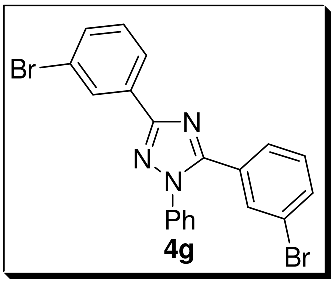
4e

3,5-Bis(4-fluorophenyl)-1-phenyl-1*H*-1,2,4-triazole 4e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.45$; colorless solid; yield 79% (65.8 mg); mp 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.17 (m, 2H), 7.55-7.51 (m, 2H), 7.45-7.38 (m, 5H), 7.15 (t, J = 8.8 Hz, 2H), 7.06 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.8, 160.4, 153.2, 137.5, 130.5, 130.4, 128.9, 128.6, 128.4, 128.0, 127.9, 126.4, 124.8, 123.5, 115.3, 115.12, 115.06, 114.9; FT-IR (KBr) 3061, 1604, 1599, 1529, 1499, 1483, 1462, 1451, 1422, 1385, 1343, 1217, 1159, 1141, 1098 cm^{-1}; *m/z* (ESI-MS) 334.13 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}F_2N_3$: C, 72.06; H, 3.93; N, 12.61. Found: C, 72.13; H, 3.94; N, 12.57.



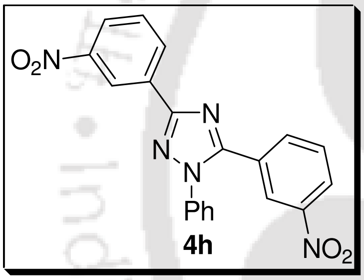
4f

1-Phenyl-3,5-di*p*-tolyl-1*H*-1,2,4-triazole 4f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.40$; colorless solid; yield 80% (65.1 mg); mp 115-116 °C (lit.[17] mp 116.5-117 °C) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 7.46-7.41 (m, 7H), 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 154.4, 139.8, 138.9, 138.2, 129.1, 128.99, 128.96, 128.6, 128.3, 127.9, 126.3, 125.1, 124.9, 21.14, 21.05; FT-IR (KBr) 3025, 2919, 2857, 1613, 1595, 1499, 1478, 1462, 1417, 1389, 1344, 1262, 1178, 1139, 1021 cm^{-1}; *m/z* (ESI-MS) 326.19 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.12; H, 5.92; N, 12.96.



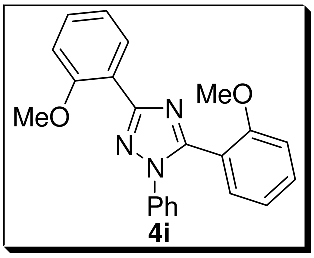
4g

3,5-Bis(3-bromophenyl)-1-phenyl-1*H*-1,2,4-triazole 4g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; gummy liquid; yield 92% (104.68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.38 (m, 1H), 8.15-8.12 (m, 1H), 7.81-7.80 (m, 1H), 7.55-7.52 (m, 2H), 7.48-7.45 (m, 3H), 7.42-7.30 (m, 4H), 7.20 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 152.9, 137.5, 132.8, 132.4, 132.1, 131.6, 130.0, 129.7, 129.3, 129.2, 129.0, 127.0, 125.1, 124.8, 122.6, 122.4; FT-IR (KBr) 1627, 1595, 1569, 1507, 1493, 1468, 1434, 1401, 1334, 1260, 1172, 1069 cm^{-1}; *m/z* (ESI-MS) 453.96, 455.95, 457.94 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.84; H, 2.89; N, 9.21.



4h

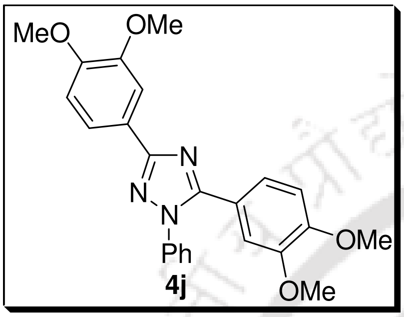
3,5-Bis(3-nitrophenyl)-1-phenyl-1*H*-1,2,4-triazole 4h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow solid; yield 78% (75.53 mg); mp 194-195 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07-9.06 (m, 1H), 8.55 (d, *J* = 7.6 Hz, 1H) 8.454-8.445 (m, 1H), 8.29-8.26 (m, 2H), 7.89-7.87 (m, 1H), 7.67 (t, *J* = 7.6 Hz, 2H), 7.58-7.51 (m, 3H), 7.44-7.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 147.8, 138.7, 136.3, 134.2, 130.9, 130.5, 130.2, 130.0, 129.9, 128.7, 126.2, 126.0, 125.0, 124.2, 123.5, 122.5, 120.6, 120.3; FT-IR (KBr) 2923, 1598, 1531, 1512, 1345, 1264, 1156, 1072 cm^{-1}; *m/z* (ESI-MS) 388.11 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08. Found: C, 62.07; H, 3.37; N, 18.05.



4i

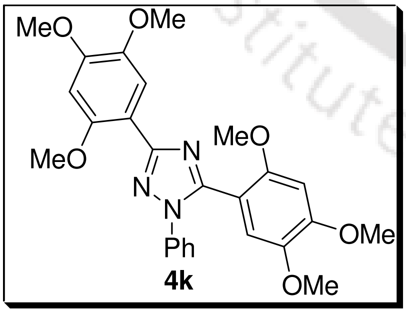
3,5-Bis(2-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4i. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.40; gummy liquid; yield

61% (54.5 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.42-7.26 (m, 7H), 7.06-7.00 (m, 3H), 6.78 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.2, 157.5, 156.5, 151.9, 138.9, 131.8, 131.4, 131.0, 130.4, 128.6, 127.7, 123.2, 120.8, 120.4, 111.9, 111.7, 111.6, 111.2, 55.7, 54.6; FT-IR (KBr) 2923, 1629, 1603, 1583, 1498, 1462, 1250, 1160, 1105, 1023 cm^{-1}; *m/z* (ESI-MS) 358.13 [M + H]$^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.85; H, 5.37; N, 11.81.



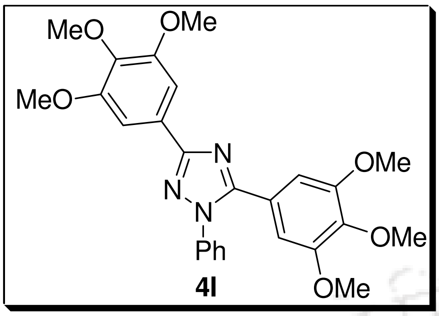
4j

3,5-Bis(3,4-dimethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4j. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 71% (74.10 mg), mp 146-147 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.82-7.79 (m, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.44-7.42 (m, 5H), 7.08-7.05 (m, 2H), 6.94 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.3, 154.3, 150.1, 149.9, 148.7, 148.4, 138.3, 129.1, 128.5, 125.5, 123.5, 121.9, 120.0, 119.3,111.6, 110.8, 110.6, 109.2, 55.8, 55.6, 55.4; FT-IR (KBr) 2837, 1605, 1530, 1503, 1493, 1471, 1440, 1422, 1404, 1350, 1261, 1231, 1177, 1164, 1138, 1125, 1024 cm^{-1}; *m/z* (ESI-MS) 417.18 [M + H]$^+$. Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.11; H, 5.54; N, 10.05.



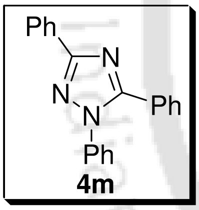
4k

3,5-Bis(2,4,5-trimethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4k. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.20; gummy liquid; yield 58% (69.2 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 1H), 7.35-7.26 (m, 5H), 7.17 (s, 1H), 6.61 (s, 1H), 6.33 (s, 1H), 3.90-3.88 (m, 9H), 3.85 (s, 6H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.6, 159.6, 152.1, 151.4, 151.1, 150.2, 142.9, 142.7, 138.8, 128.3, 127.3, 122.9, 113.7, 113.5, 111.4, 108.3, 98.1, 96.7, 59.9, 56.7, 56.1, 55.6, 54.9, 53.3; FT-IR (KBr) 2933, 2840, 1612, 1504, 1465, 1437, 1375, 1276, 1214, 1171, 1028 cm^{-1}; *m/z* (ESI-MS) 478.18 [M + H]$^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.50; H, 5.68; N, 8.76.



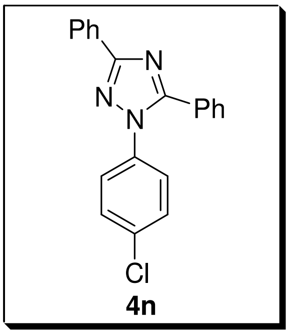
4l

3,5-Bis(3,4,5-trimethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4l. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.40; gummy liquid; yield 68% (81.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 7H), 6.64-6.60 (m, 2H), 3.79-3.66 (m, 12H), 3.52-3.47 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.2, 153.1, 152.7, 139.1, 138.8, 138.0, 129.1, 128.7, 125.8, 125.5, 122.3, 106.0, 103.3, 60.4, 55.8, 55.5; FT-IR (KBr) 2932, 2846, 1590, 1497, 1486, 1463, 1418, 1347, 1234, 1127, 1004 cm^{-1}; *m/z* (ESI-MS) 478.17 [M + H]$^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.48; H, 5.71; N, 8.75.



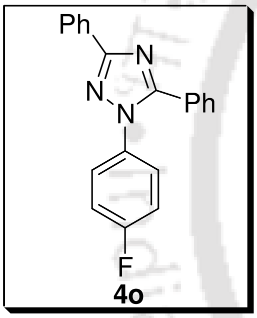
4m

1,3,5-Triphenyl-1*H*-1,2,4-triazole 4m. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.65; colorless solid; yield 82% (61.0 mg); mp 105-106 °C (lit.[18] mp 104-105 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.42-7.20 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 154.5, 138.1, 130.7, 129.8, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 127.8, 126.4, 125.2; FT-IR (KBr) 3062, 2923, 1594, 1517, 1496, 1478, 1442, 1397, 1352, 1272, 1262, 1172, 1138, 1070, 1027 cm^{-1}; *m/z* (ESI-MS) 298.14 [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.85; H, 5.06; N, 14.09.



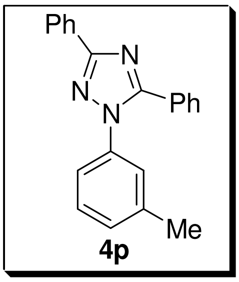
4n

1-(4-Chlorophenyl)-3,5-diphenyl-1*H*-1,2,4-triazole 4n. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.35; colorless solid; yield 62% (51.4 mg); mp 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 6.8 Hz, 2H), 7.45-7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 154.8, 136.8, 134.5, 130.6, 130.2, 129.6, 129.0, 128.8, 128.7, 127.8, 126.6, 126.5; FT-IR (KBr) 3066, 2923, 1519, 1494, 1478, 1443, 1396, 1352, 1171, 1141, 1094, 1016 cm^{-1}; *m/z* (ESI-MS) 332.08 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66. Found: C, 72.31; H, 4.24; N, 12.71.



4o

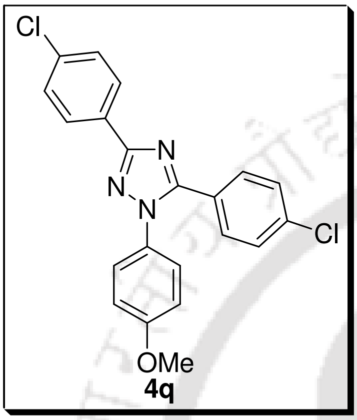
1-(4-Fluorophenyl)-3,5-diphenyl-1*H*-1,2,4-triazole 4o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; orange solid; yield 71% (56.0 mg); mp 100-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.8 Hz, 2H), 7.54-7.47 (m, 2H), 7.46-7.34 (m, 8H), 7.14-7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 162.1, 161.3, 155.0, 134.5, 130.7, 130.3, 129.7, 129.1, 128.81, 128.76, 127.9, 127.5, 127.4, 126.7, 116.7, 116.4; FT-IR (KBr) 2923, 2851, 1637, 1509, 1478, 1440, 1399, 1352, 1219, 1155, 1097, 1067 cm^{-1}; *m/z* (ESI-MS) 316.13 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}FN_3$: C, 76.18; H, 4.47; N, 13.33. Found: C, 76.11; H, 4.45; N, 13.39.



4p

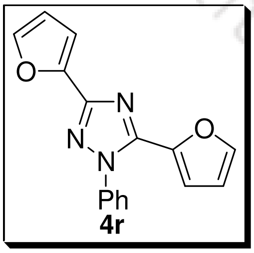
3,5-Diphenyl-1-*m*-tolyl-1*H*-1,2,4-triazole 4p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless liquid; yield 76% (59.2 mg); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.49-7.22 (m, 9H), 7.14 (d, *J* = 8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 154.8, 139.8, 138.3, 130.9, 130.0, 129.7, 129.5, 129.2, 129.1, 128.7, 128.6, 128.2, 126.7, 126.1, 122.7, 21.4; FT-IR (KBr) 3064, 2956, 2917, 1610, 1591, 1517, 1491, 1478, 1443, 1395, 1352, 1262, 1173, 1137, 1071, 1027, 1012 cm^{-1}; *m/z* (ESI-MS) 312.17 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.08; H, 5.48; N, 13.44.



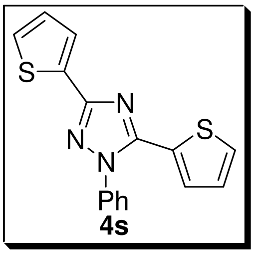
4q

3,5-Bis(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-1,2,4-triazole 4q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 72% (71.3 mg); mp 191-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33-7.28 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.1, 153.9, 136.4, 135.5, 130.6, 130.2, 128.92, 128.86, 128.5, 127.8, 126.9, 125.9, 114.7, 55.5; FT-IR (KBr) 2955, 2928, 1599, 1509, 1469, 1459, 1424, 1406, 1307, 1251, 1170, 1137, 1102, 1087, 1027, 1013 cm^{-1}; *m/z* (ESI-MS) 396.08 $[M + H]^+$. Anal. Calcd for $C_{21}H_{15}Cl_2N_3O$: C, 63.65; H, 3.82; N, 10.60. Found: C, 63.55; H, 3.83; N, 10.64.



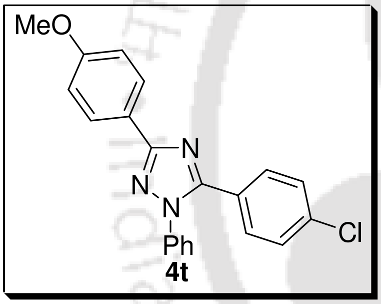
4r

3,5-Di(furan-2-yl)-1-phenyl-1*H*-1,2,4-triazole 4r. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.30; gummy liquid; yield 85% (58.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 1H), 7.53-7.45 (m, 5H), 7.36-7.32 (m, 1H), 7.11-7.10 (m, 1H), 6.52-6.51 (m, 2H), 6.41-6.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.0, 144.3, 144.1, 143.2, 137.4, 129.4, 129.1, 128.7, 125.8, 119.9, 113.1, 111.5, 109.9; FT-IR (KBr) 2963, 1599, 1508, 1497, 1437, 1319, 1261, 1094, 1075, 1016 cm^{-1}; *m/z* (ESI-MS) 278.11 [M + H]$^+$. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.23; H, 4.01; N, 15.19.



4s

1-Phenyl-3,5-di(thiophen-2-yl)-1*H*-1,2,4-triazole 4s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; gummy liquid; yield 86% (66.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 3.6 Hz, 1H), 7.54-7.49 (m, 5H), 7.39-7.36 (m, 2H), 7.12-7.10 (m, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.96-6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 149.0, 136.6, 132.3, 129.1, 128.8, 128.3, 128.0, 126.9, 126.8, 126.0, 125.9; FT-IR (KBr) 3090, 3071, 1594, 1549, 1499, 1469, 1451, 1434, 1393, 1314, 1229, 1107, 1075 cm^{-1}; *m/z* (ESI-MS) 310.02 [M + H]$^+$. Anal. Calcd for $C_{16}H_{11}N_3S_2$: C, 62.11; H, 3.58; N, 13.58; S, 20.73. Found: C, 62.19; H, 3.57; N, 13.54; S, 20.70.



4t

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 4t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 68% (61.5 mg); mp 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.2 Hz, 2H), 7.48-7.40 (m, 7H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 153.4, 138.0, 136.1, 130.2, 129.44, 129.37, 128.9, 128.8, 128.0, 127.8, 125.4, 123.2, 114.0, 55.2; FT-IR (KBr) 2991, 1613, 1596, 1499, 1471, 1440, 1424, 1250, 1169, 1092, 1027 cm^{-1}; *m/z* (ESI-MS) 362.09 [M + H]$^+$. Anal. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.60; H, 4.48; N, 11.64.

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Crystal Data and Structure Refinement for 3S′ at 298(2) K

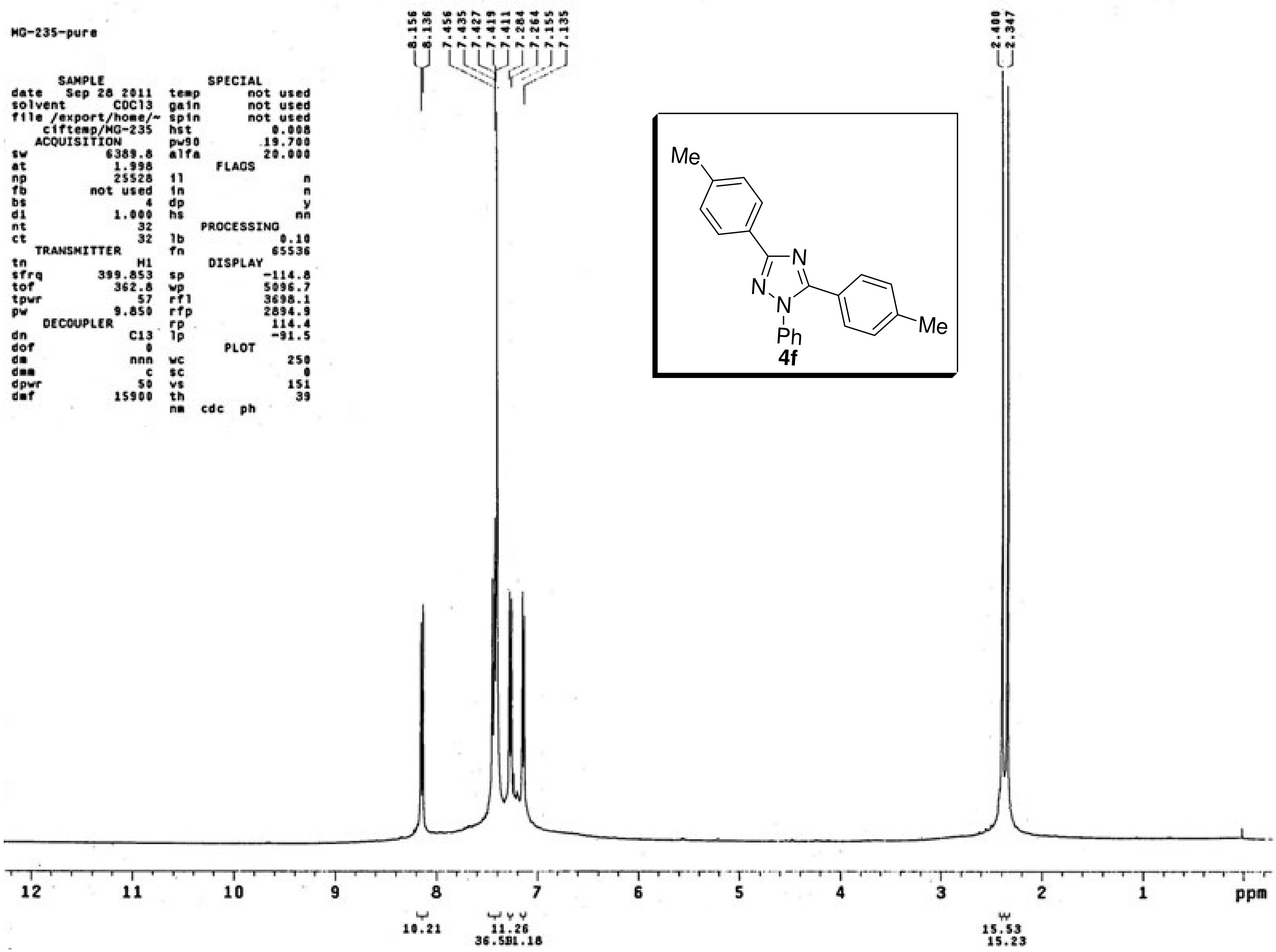
Identification code	**3S′**	
Empirical formula	$C_{22}H_{18}N_4S_2$	
Formula weight	402.54	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P n a 21 Loop xyz 'x, y, z' '-x, -y, z+1/2' '-x+1/2, y+1/2, z+1/2' 'x+1/2, -y+1/2, z'	
Unit cell dimensions	*a* = 9.2005(5) Å	α(°)= 90.00
	b = 12.5030(6) Å	β(°)= 90.00
	c = 17.8158(9) Å	γ(°)= 90.00
Volume	2049.42(18) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.272 mm^{-1}	
F(000)	840.0	
Crystal size	0.38 x 0.32 x 0.29 mm	
Theta range for data collection	1.99 to 28.40°	
Index ranges	-11<=h<=12, -16<=k<=15, -22<=l<=23	
Reflections collected	2635	
Independent reflections	2539 [R (int) = 0.0650]	
Completeness to theta = 28.40°	99.1 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.902 and 0.924	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2439 / 1 /258	
Goodness-of-fit on F^2	0.979	
Final R indices [I>2sigma (I)]	$R1$ = 0.0473, $wR2$ = 0.0884	
R indices (all data)	$R1$ = 0.1198, $wR2$ = 0.1069	

Crystal Data and Structure Refinement for 3c″ at 298(2) K

Identification code	**3c″**	
Empirical formula	$C_{20}H_{15}Cl_2N_3O$	
Formula weight	384.25	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*P* c a 21 Loop xyz ‘x, y, z’ ‘-x, -y, z+1/2’ ‘x+1/2, -y, z’ ‘-x+1/2, y, z+1/2’	
Unit cell dimensions	a = 9.8152(6) Å	α(°)= 90.00
	b = 10.6246(5) Å	β(°)= 90.00
	c = 17.8012(8) Å	γ(°)= 90.00
Volume	1856.36(17) $Å^3$	
Z	4	
Density (calculated)	1.375 Mg/m^3	
Absorption coefficient	0.363 mm^{-1}	
F(000)	792.0	
Crystal size	0.36 x 0.32 x 0.29 mm	
Theta range for data collection	1.92 to 24.84°	
Index ranges	-11<=h<=11, -11<=k<=12, -21<=l<=20	
Reflections collected	3195	
Independent reflections	2075 [R (int) = 0.0431]	
Completeness to theta = 24.84°	99.6 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.900 and 0.877	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3195 / 4 /236	
Goodness-of-fit on F^2	0.836	
Final R indices [I>2sigma (I)]	$R1$ = 0.0452, $wR2$ = 0.1166	
R indices (all data)	$R1$ = 0.0809, $wR2$ = 0.1380	

Crystal Data and Structure Refinement for 4c at 298(2) K

Identification code	**4c**	
Empirical formula	$C_{20}H_{13}Cl_2N_3$	
Formula weight	366.23	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1 Loop xyz 'x, y, z' '-x, -y, -z'	
Unit cell dimensions	*a* = 5.8381(13) Å	α(°)= 106.642(19)
	b = 11.958(3) Å	β(°)= 92.54(2)
	c = 12.782(3) Å	γ(°)= 91.559(19)
Volume	853.3(4) $Å^3$	
Z	2	
Density (calculated)	1.425 Mg/m^3	
Absorption coefficient	0.387 mm^{-1}	
F(000)	324	
Crystal size	0.45 x 0.38 x 0.33 mm	
Theta range for data collection	1.67 to 28.20°	
Index ranges	-7<=h<=7, -15<=k<=15, -16<=l<=16	
Reflections collected	4185	
Independent reflections	4067 [R (int) = 0.0871]	
Completeness to theta = 28.20°	98.4 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.880 and 0.840	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1708 / 0 /227	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma (I)]	*R1* = 0.0811, *wR2* = 0.2055	
R indices (all data)	*R1* = 0.1106, *wR2* = 0.2311	



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MG-235-pure

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solvent      CDCl3   gain        not used
file /export/home/~  spin        not used
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    ACQUISITION      pw90          19.700
sw          6389.8   alfa          20.000
at           1.998           FLAGS
np           25528   il                 n
fb        not used   in                 n
bs               4   dp                 y
d1           1.000   hs                nn
nt              32          PROCESSING
ct              32   lb              0.10
    TRANSMITTER      fn             65536
tn              H1           DISPLAY
sfrq       399.853   sp            -114.8
tof          362.8   wp            5096.7
tpwr            57   rfl           3698.1
pw           9.850   rfp           2894.9
    DECOUPLER        rp             114.4
dn             C13   lp             -91.5
dof              0            PLOT
dm             nnn   wc               250
dmm              c   sc                 0
dpwr            50   vs               151
dmf          15900   th                39
                     nm    cdc  ph
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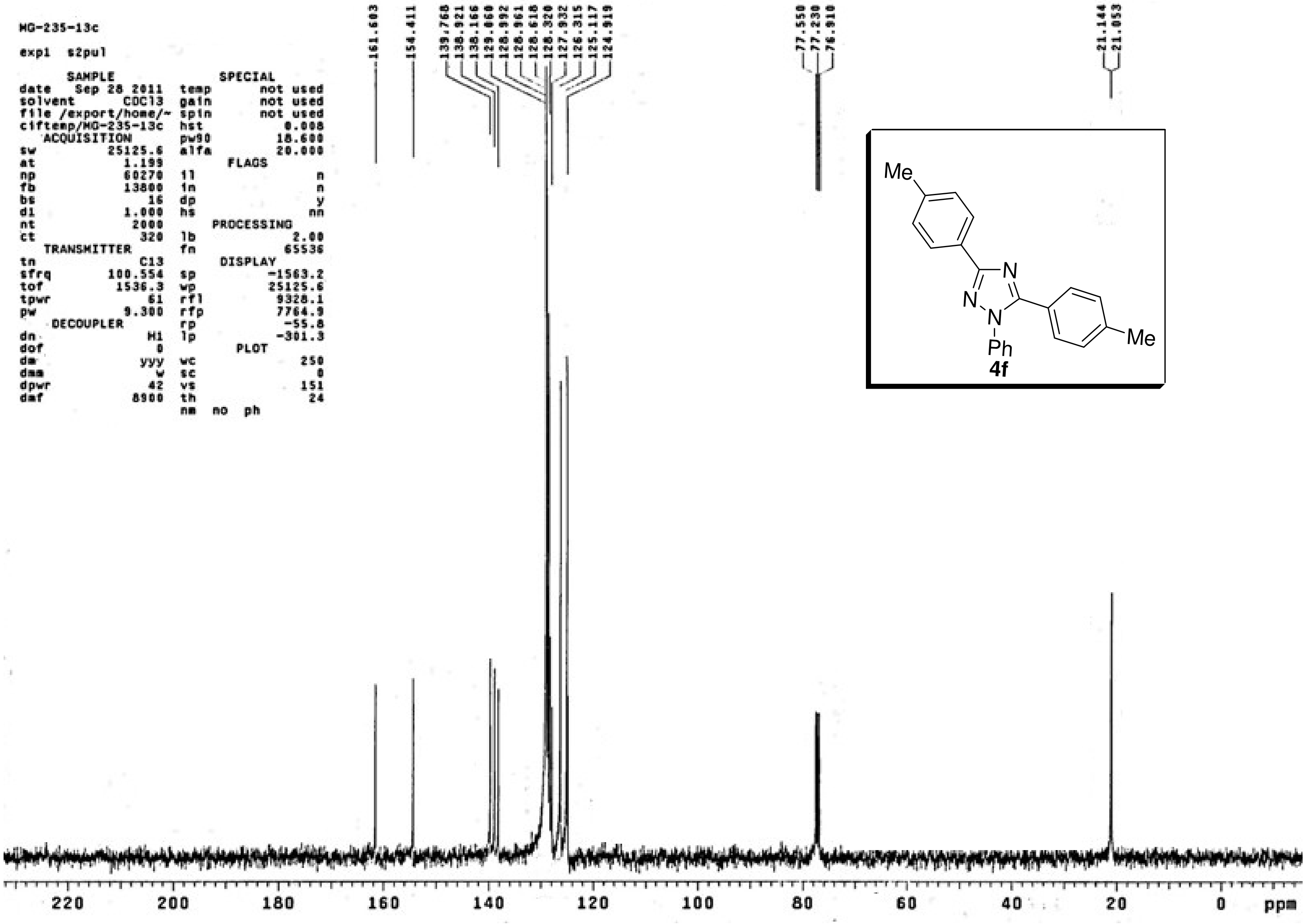

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MG-235-13c

exp1  s2pul

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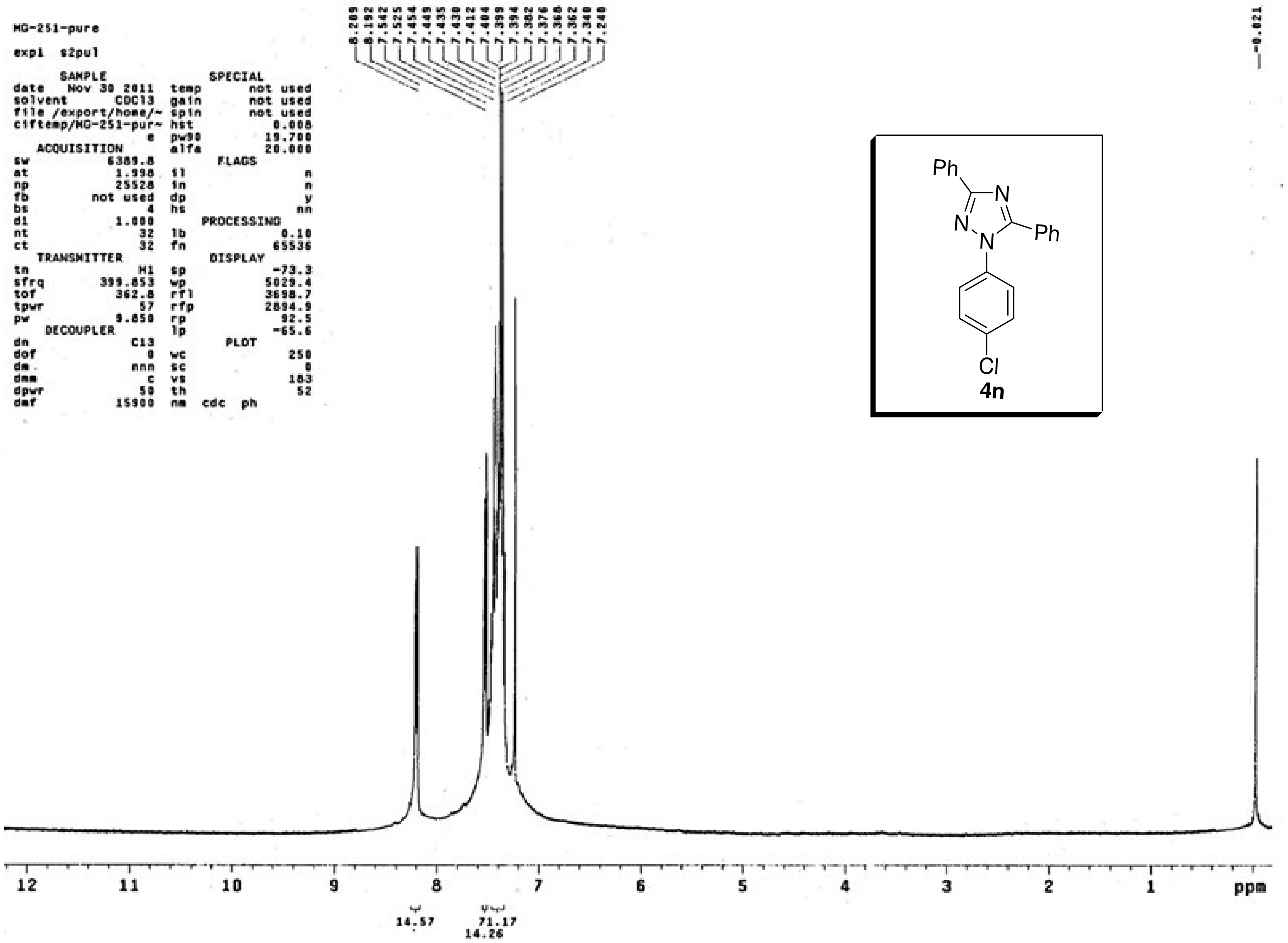
date   Sep 28 2011  temp        not used
solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/MG-235-13c  hst            0.008
   ACQUISITION      pw90          18.600
sw         25125.6  alfa          20.000
at           1.199          FLAGS
np           60270  il                 n
fb           13800  in                 n
bs              16  dp                 y
d1           1.000  hs                nn
nt            2000        PROCESSING
ct             320  lb              2.00
   TRANSMITTER      fn             65536
tn             C13         DISPLAY
sfrq       100.554  sp           -1563.2
tof         1536.3  wp           25125.6
tpwr            61  rfl           9328.1
pw           9.300  rfp           7764.9
    DECOUPLER       rp             -55.8
dn              H1  lp            -301.3
dof              0           PLOT
dm             yyy  wc               250
dmm              w  sc                 0
dpwr            42  vs               151
dmf           8900  th                24
                    nm  no   ph
```

4f



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MG-251-pure

expl  s2pul

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solvent      CDCl3  gain        not used
file /export/home/~ spin        not used
ciftemp/MG-251-pur~ hst            0.008
                 e  pw90          19.700
   ACQUISITION      alfa          20.000
sw          6389.8          FLAGS
at           1.998  il                 n
np           25528  in                 n
fb        not used  dp                 y
bs               4  hs                nn
d1           1.000         PROCESSING
nt              32  lb              0.10
ct              32  fn             65536
   TRANSMITTER              DISPLAY
tn              H1  sp             -73.3
sfrq       399.853  wp            5029.4
tof          362.8  rfl           3698.7
tpwr            57  rfp           2894.9
pw           9.850  rp              92.5
    DECOUPLER       lp             -65.6
dn             C13            PLOT
dof              0  wc               250
dm .           nnn  sc                 0
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dpwr            50  th                52
dmf          15900  nm  cdc  ph
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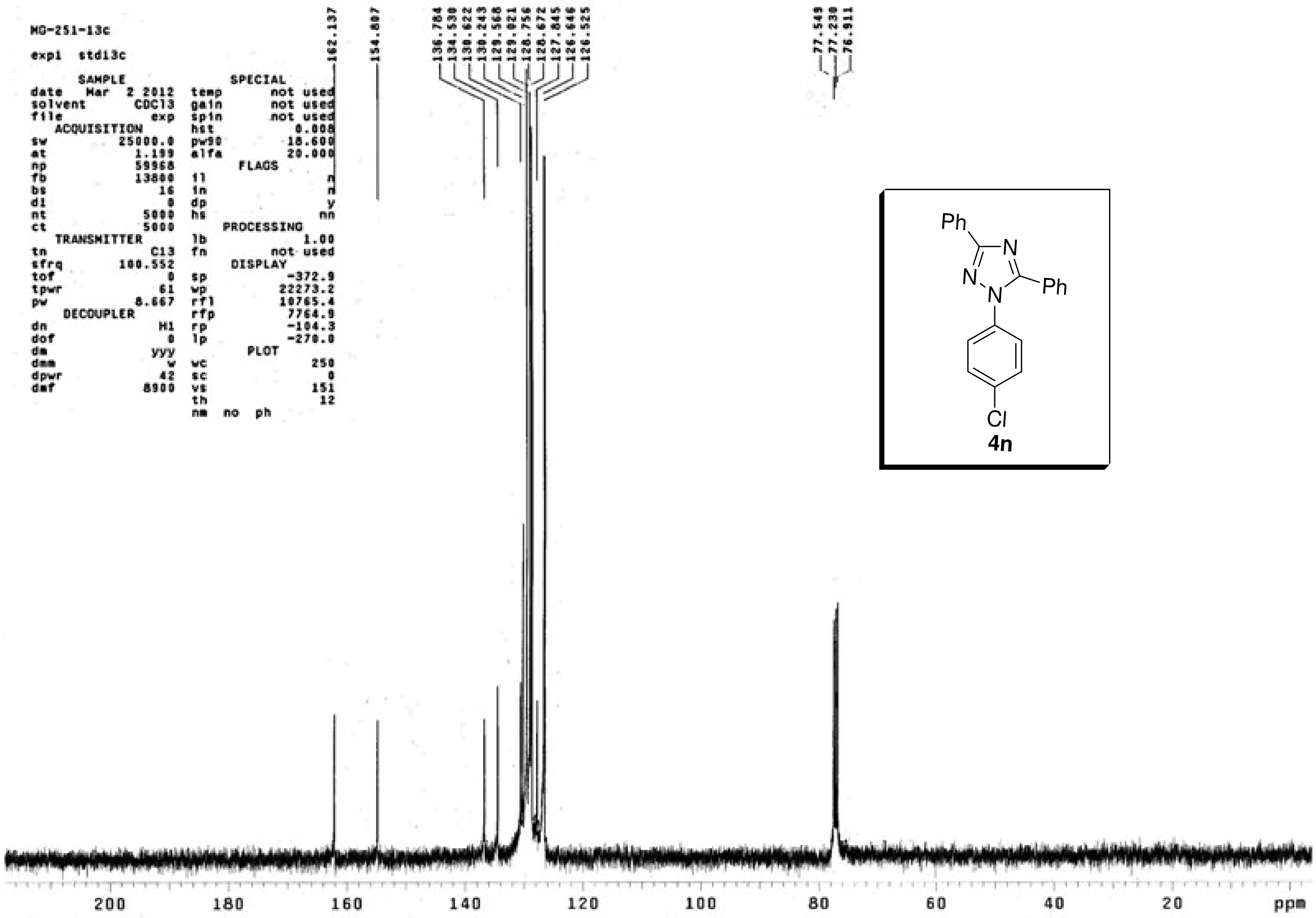
4n



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MG-251-13c

expl  std13c

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solvent        CDCl3 gain       not used
file             exp spin       not used
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sw           25000.0 pw90         18.600
at             1.199 alfa         20.000
np             59968         FLAGS
fb             13800 il               n
bs                16 in               n
d1                 0 dp               y
nt              5000 hs              nn
ct              5000       PROCESSING
    TRANSMITTER      lb            1.00
tn               C13 fn        not used
sfrq         100.552       DISPLAY
tof                0 sp          -372.9
tpwr              61 wp         22273.2
pw             8.667 rfl        10765.4
     DECOUPLER       rfp         7764.9
dn                H1 rp          -104.3
dof                0 lp          -270.0
dm               yyy         PLOT
dmm                w wc             250
dpwr              42 sc               0
dmf             8900 vs             151
                     th              12
                     nm  no  ph
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List of Publications

1. "Copper(II)-Catalyzed Aerobic Oxidative Synthesis of Substituted 1,2,3- and 1,2,4-Triazoles from Bisarylhydrazones via C–H Functionalization/C–C/N–N/C–N Bonds Formation" **Guru, M. M.**; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063.

2. "Copper-Mediated Synthesis of Substituted 2-Aryl-*N*-benzylbenzimidazoles and 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bonds Formation" **Guru, M. M.**; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295 (Highlighted in *ChemInform* **2011**, *42*).

3. "Copper(II)-Catalyzed Conversion of Bisaryloxime Ethers to 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bonds Formation" **Guru, M. M**.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194 (Highlighted in *Synfacts* **2011**, 479).

Conferences

1. "Copper-Mediated Synthesis of Substituted 2-Aryl-*N*-benzylbenzimidazoles and 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bonds Formation" **Guru, M. M.**; Ali, M. A.; Punniyamurthy, T. International Symposium on *Advances in Chemical Science-2012*, January 30, IIT Guwahati, India.

2. "Copper-Mediated Synthesis of Substituted 2-Aryl-N-benzylbenzimidazoles and 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bonds Formation" **Guru, M. M.**; Ali, M. A.; Punniyamurthy, T. *7th J-NOST Conference for Research Scholars 2011*, December 15-17, IISER Mohali, India.