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# Copper-Catalyzed Chelation Assisted *ortho*-Nitration of 2-Aryls with Pharmacophoric Benzo-thiazoles and -oxazoles as Directing Groups.

Botla Vinayak,‡ Akudari Ashok‡ and Malapaka Chandrasekharam*

**Abstract:** Copper-catalyzed chelation assisted *ortho*-nitration of aryls with benzazoles as efficient directing group has been achieved. The reaction is general and efficient for electronically differentiated aryls and pharmacophorically important directing groups i.e., benzoxazoles, benzthiazoles and benzimidazoles. This class of nitro-products have significance as fluorogenic and potential nitroreductase substrates for the detection of clinically important microorganisms. The nitration reaction proceeds with inexpensive copper catalyst and mild, cheap and environmentally friendly nitro source, $Fe(NO_3)_3.9H_2O$. This operationally simple and functional group tolerant protocol highlights the high regioselectivity for the nitration of 2-aryl benzazoles without the exclusion of air or moisture.

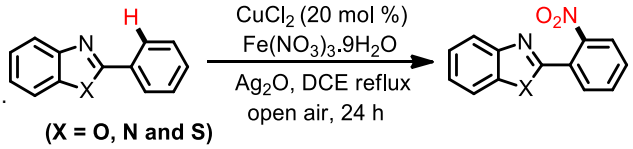
## Introduction

Introduction of nitrogen atoms into organic molecules is the subject of intense interest. Nitroarenes are versatile aromatic building blocks in organic synthesis due to their wide usage as chemical feedstock in industry, for the synthesis of drugs, dyes, perfumes, fertilizers, plastics and explosives.[1] Nitroarenes not only serve as versatile substrates for sulfonamidation and Barans hydroamination but also are excellent electrophilic coupling partners in Suzuki-Miyaura coupling reactions to access a wide range of functionalized biaryls.[2] Classical methods of nitroarene synthesis involve Friedel-Crafts type nitration to obtain predominantly the *para*-nitro compounds. These reactions suffer from the use of strong acids, intolerance of diverse functional groups, and low *ortho/meta* site-selectivitiy.[3] The direct transformation of C-H bonds to C-C and C-X (heteroatom) offers easy access to many natural and synthetic complex molecules. Particularly directing group (DG) assisted reactions forge new bonds selectively at one C-H bond in a molecule among several other reactive C-H bonds in a single step overriding the innate reactivity of the substrate and eliminating the additional prefunctionalization step.[4] In recent times, transition metal-catalyzed DG-assisted C-H functionalizations received increased attention as powerful C-C, C-N, and C-O bond-forming reactions and in this context regioselective aryl nitration is an important transformation.[5] Further traceless, easily removable and transient DG-assisted C-H functionalizations are gaining tremendous importance in order to prevent additional steps in the reaction sequence. However pharmacophorically significant DGs, provide value addition to the product and therefore does not necessarily warrant removal at the end.[6]

On the other hand Benzazole scaffolds are found in natural products, pharmaceuticals and agrochemicals.[7] Particularly aryl benzazoles are important pharmacophores with biological activities, such as anti-HIV, antibiotic, anti-microbial, anti-inflammatory and anti-tumor properties.[8] Further detection, enumeration and identification of harmful bacteria are connected to our day to day life particularly in the basic areas of health, food and environment.[9] In this context 2-(2'-nitro)aryl-benzo-thiazole and -oxazole derivatives are known to be fluorogenic and potential nitroreductase substrates for the detection of clinically important microorganisms[10] and hence synthesis and biological study of these compounds attracted increased attention. In addition to the biological significance, benzazoles are versatile biorelevant heterocyclic DGs. Although N- donor atom as the DG has been widely employed in direct *o*-arylation, -acetoxylation, -alkylation, -alkenylation, -fluorination -hydroxylation and recently *o*-nitration, most of these transformations required precious Rh and Pd metal catalysts.[11,12] Further less expensive and environmentally benign methods surrogates the traditional use of expensive and noble transition metals such as rhodium, ruthenium, palladium etc.[13a] Despite of the above, forging of the Nitro group, an important functionality at the *ortho*- position on 2-aryl benzazoles has not been adequately addressed in the chemical literature.

Recently Leng & Wu group reported chelation assisted *ortho*-nitration employing precious Pd metal and $AgNO_2$ under difficult to operate, external oxygen and energy intensive, drastic reaction conditions with the substrate scope limited to 2-arylbenzoxazoles.[12j] Therefore we assumed that the developement of a general reaction protocol for the *ortho*-nitration of 2-aryl benzo-oxazole and -thiazole scaffolds with less expensive and earth abundant catalyst, under easy to operate reaction conditions is warranted.

**Scheme 1.** *Ortho*-Nitration **of** 2-aryl Benzazole.




In our laboratory we have been engaged in the transitional metal mediated C-H functionalization (C-C, C-O and C-N) and condensation reactions with particular emphasis on green technologies.[13] Further we recently reported two efficient regioselective aryl nitration protocols involving 1. Concomitant azidation-oxidation chemistry with TMS azide, TBHP and copper catalyst [13g] 2. $Fe(NO_3)_3.9H_2O$ with dual role as catalyst and nitro source.[13a] Both of these strategies are effective under aerobic conditions. Our above studies on aryl nitration combined with the

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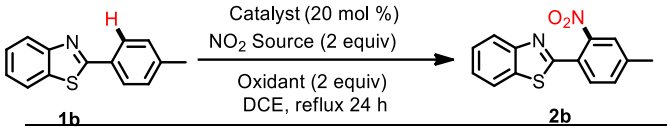
biological importance of 2-(2'-nitro)aryl benzazoles prompted us to investigate further on DG-assisted aryl nitrations and we herein, report our new findings wherein copper-catalyzed chelation assisted *ortho*-nitration on aryls is effected with biorelevant 2-aryl-benzthiazoles and -benzoxazoles as DGs that proceed without the exclusion of air or moisture.

## Results and Discussion

**Table 1.** Optimization of *Ortho*-Nitration of 2-aryl bezothiazoles.[a]



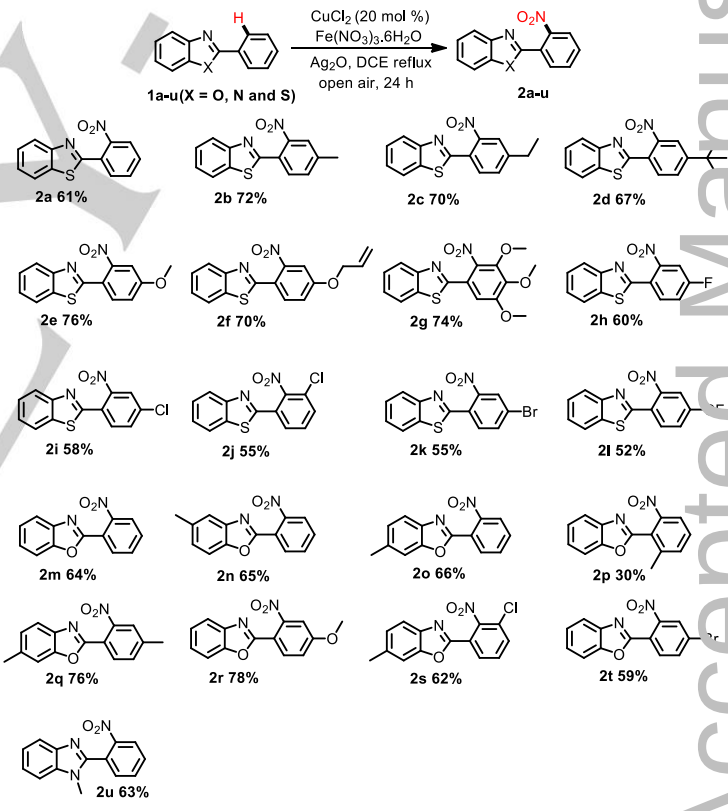

1b 2b

| S.No | Catalyst | Nitro source(equiv) | Additive | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(1.0) | - | - |
| 2 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | - | 28 |
| 3 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | DTBP | 42 |
| 4 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | BP | 51 |
| 5 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $K_2S_2O8$ | 69 |
| 6 | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 83 |
| 7 | $CuCl_2$ | $Cu(NO_3)_2{\cdot}3H_2O$(2.0) | $Ag_2O$ | 21 |
| 8 | $CuCl_2$ | $AgNO_3$(2.0) | $Ag_2O$ | - |
| 9 | $CuCl_2$ | $AgNO_2$(2.0) | $Ag_2O$ | - |
| 10 | $CuCl_2$ | $Bi(NO_3)_3{\cdot}5H_2O$(2.0) | $Ag_2O$ | - |
| 11 | $CuCl_2$ | $Co(NO_3)_3.6H_2O$(2.0) | $Ag_2O$ | - |
| 12 | $CuCl_2$ | $NaNO_2$(2.0) | $Ag_2O$ | - |
| 13 | $CuCl_2$ | $KNO_2$(2.0) | $Ag_2O$ | - |
| 14 | $CuBr_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 34 |
| 15 | $Cu(OAc)_2{\cdot}H_2O$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 42 |
| 16 | CuI | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 35 |
| 17 | $FeCl_3$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | - |
| 18 | $FeBr_3$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | - |
| 19 | $Pd(OAc)_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 13 |
| 20 | $CuCl_2.2H_2O$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 72 |
| 21 | - | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | - |
| 22[c] | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 71 |
| 23[d] | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 71 |
| 24[e] | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 69 |
| 25[f] | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 74 |
| 26[g] | $CuCl_2$ | $Fe(NO_3)_3{\cdot}9H_2O$(2.0) | $Ag_2O$ | 71 |

[a] The Reaction was performed with 1b (1.0 mmol), catalyst (20 mmol %), nitro source (2.0 mmol), oxidant (2.0 mmol) in 1,2 DCE solvent, reflux 24 h in an open air atmosphere unless otherwise noted. [b] Isolated yields, [c] catalyst (10 mmol %), [d] catalyst (40 mmol %), [e] under Oxygen atmosphere [f] Nitrogen atmosphere, [g] 4 Å molecular sieves.

We initiated our investigation with 2-(*p*-tolyl)benzo[d]thiazole **1b** as a model substrate to examine various nitrating agents, solvents and catalysts for the optimization of reaction conditions (Table 1). The nitration reaction conducted at room temperature with $CuCl_2$ (20 mol %) and $Fe(NO_3)_3{\cdot}9H_2O$ (1.0 equiv) in DCE for 24 h produced no desired product, However the reaction conducted with $CuCl_2$ (20 mol %) and $Fe(NO_3)_3{\cdot}9H_2O$ (2.0 equiv) at reflux (83 °C) resulted in poor yields (28%) of the product (**2b)** and significant quantity of starting material (**1b)** was recovered. To examine the advantage of additive, the nitration reaction was carried out in presence of DTBP (2.0 equiv) and found that the yield of nitro product **2b** was increased to 42% (Entry 3, Table 1). Among various other additives (Benzoyl peroxide, $K_2S_2O_8$ and $Ag_2O$) tested $Ag_2O$ proved to be the most efficient affording 83%

**Scheme 2.** Substrate Scope of *Ortho*-Nitration of 2-aryl benzazoles. [a]

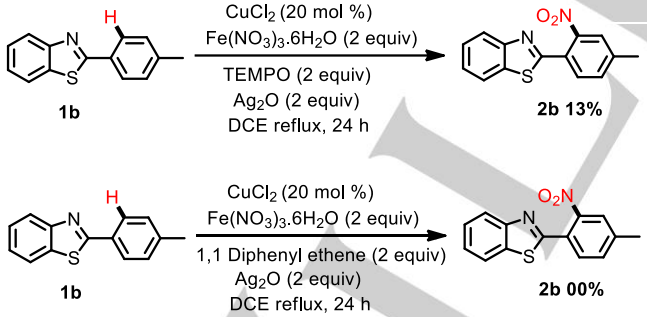



[a] The Reaction was performed with 1 (1.0 mmol), $CuCl_2$ (20 mmol %), $Fe(NO_3)_3.9H_2O$ (2.0 mmol), $Ag_2O$ (2.0 mmol) in 1,2 DCE solvent, reflux 24 h in an open air atmosphere unless otherwise noted. [b] Isolated yields.

yield of the product (Entries **4-6**, Table 1). $Fe(NO_3)_2{\cdot}9H_2O$ was found to be the most effective nitro source (Entry 6, Table 1), while other nitrating agents including $Cu(NO_3)_2.3H_2O$ are deleterious for this reaction (Entries **7-13**, Table 1). Other transition metal catalysts i.e., iron, palladium salts were tested (Entries **14-20**, Table 1) and in the absence of catalyst, the reaction did not proceed (Entry **21**, Table 1). The copper chloride is found to be the most suitable and efficient catalyst for

this chelation assisted *ortho*-nitration. Further 10 mol% of catalyst loading decreased the product yield dramatically, while increasing to 40 mol% did not significantly change the outcome of the reaction (Entries **22**, **23**, Table 1). The reaction outcome was not significantly changed in the presence of oxygen or nitrogen atmosphere (Entry **24**, **25**, Table 1). Neither the product yield improved when reaction was conducted in the presence of ~~additive,~~ 4 Å molecular sieves. (Entry **26**, Table 1), with the optimized conditions in hand, the scope of the reaction was investigated with various electronically differentiated substrates (Table 2). Good yields were often achieved when electron-donating moieties including 4-methyl, 4-ethyl, 4-*tert*-butyl, 4-methoxy and 4-allyloxy groups were present on the phenyl ring of 2-arylbenzothiazoles under the standard reaction conditions (Table 2, **2b**–**2f**). 3,4,5-Trimethoxy phenyl substituted benzthiazole also found to be a good substrate for this nitration reaction producing 74% yield of the product. (Table 2, **2g**) Moderate to good yields of the corresponding products were obtained with 4-fluoro, 4-chloro, 3-chloro, 4-bromo and 4-trifluoromethyl phenyl benzothiazole. (Table 2, **2h**-**2l**). Then the substrate scope was expanded to 2-aryl benzoxazoles where benzoxazole serving as DG. The unsubstituted substrate as well as the substrates with e-donating alkyl/alkoxy substitutions on either of the aryl rings of the benzoxazoles are effective for this chelation assisted nitration reaction (Table 2, **2m**-**2r**). 3-chloro and 4-bromo phenyl benzoxazoles also underwent nitration affording the corresponding products in 62% and 59% yields respectively under the optimized reaction conditions. (Table 2, **2s**-**2t**). These halogen subistitutions on the aryl ring would allow further decoration of the nitro benzazoles to produce value added products.[14] Moreover the *ortho*-nitration protocol is further extended to the substrate 2-aryl- *N*-methyl benzimidazole and produced product **2v** in 63% yield demonstrating that benzimidazole is also an effective DG for the nitration reaction. All the new compounds have been fully characterized with $^{1}H$ and $^{13}C$ NMR, Mass and HRMS.

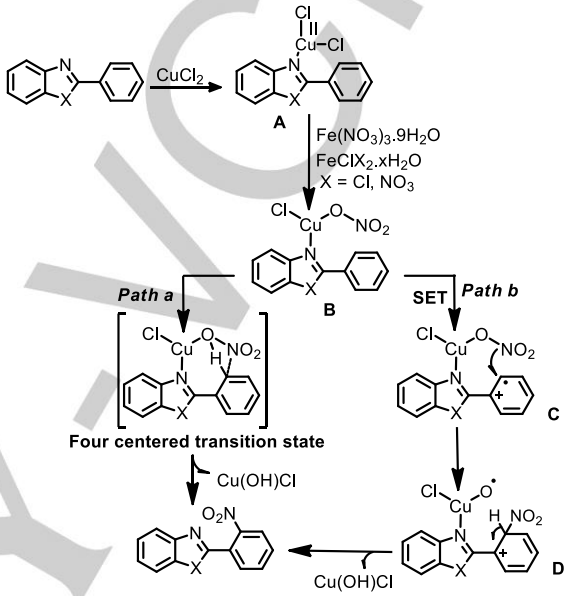
**Scheme 3.** Mechanistic Insights.




To understand the mechanism, **1b** was subjected to the standard reaction conditions in the presence of the radical scavenger TEMPO, which led to a diminished yield (13%) of the product **2b** demonstrating that a radical species may be involved in the reaction process. When 1,1-diphenylethylene was employed as a radical acceptor, formation of neither **2b** nor radical intercepted product was detected. These experiments demonstrate that the *ortho*-nitration reaction may proceed via a radical mechanism.

Although the reaction mechanism is not clear yet, from the above observations and prior literature,[15] a plausible mechanism has been proposed for the copper-catalyzed chelation-assisted *ortho*-nitration of 2-aryl benzazoles (Scheme 4). Initially, copper chloride is coordinated with nitrogen of the 2-aryl benzazole to give intermediate **A**. Subsequently the nitrate ion-containing copper (II) complex **B** was formed by anion exchange. We propose two pathways for the formation of *ortho*-nitro product from complex **B**. The intermediate **B** undergoes a single electron transfer (SET) event from the aryl ring to the coordinated Cu(II) leading to the formation of a radical cation intermediate **C**.

**Scheme 4.** Proposed Mechanism.




Subsequently the radical cation is trapped with the nitro group present in the proximity forming the cationic species **D**. Finally deprotonation of intermediate **D** generates the desired product.[15b] Following path **a**, a four centered bridged transition state is presumed to operate wherein cleavage of C-H and N-O bonds and simultaneous formation of O-H and C-N bonds occurred through a concerted mechanism delivering the *ortho*-nitro product.[15a] Overall the regioselectivity of the chelation assisted nitration is controlled by DG assisted proximity effect.

## Conclusions

In conclusion we have achieved the copper-catalyzed chelation assisted *ortho*-nitration of aryls with bio-relevant 2-aryl benzazoles serving as efficient directing groups. The reaction proceeds well with wide substrate scope (benzo-oxazoles, -thiazoles and -imidazoles) and high functional group tolerance in presence of iron(III) nitrate as a mild nitro source without the exclusion of air or moisture. The halo appended nitro products could be used as handles for further functional group transformation. Employment of non toxic, inexpensive and readily available copper catalyst and iron nitro source combined with operational simplicity highlights the efficiency of this reaction. Further mechanistic investigations and testing of these nitro products as fluorogenic and potential nitroreductase substrates for the detection of clinically important microorganisms are underway in our laboratory.

## Experimental Section

General Considerations: All commercially available chemicals were used as received. Thin-layer chromatography plates were visualized by exposure to UV or Iodine, and/or by immersion in an acidic staining solution of phosphomolybdic acid followed by heating on a hot plate. 1H NMR spectra were obtained with 400 and 500 MHz spectrometers, 13C NMR spectra were obtained with 100 and 125 MHz spectrometers in CDCl3 at 298 K with tetramethylsilane and CDCl3 as the internal standard. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 ppm for 1H NMR and δ = 77.0 ppm for 13C NMR). Data for 1H NMR are reported as follows: chemical shift (multiplicity, coupling constant, number of hydrogen atoms). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were carried out with a Quattro LC triple-quadrupole mass spectrometer (Micromass, Manchester, UK). High-resolution mass spectra were determined with a Quadrupole time-of-flight (Q-TOF) mass spectrometer (QSTARXL, Applied Biosystems/MDS Sciex, Foster city, USA).

**General Procedure for *ortho*-Nitration of 2-aryl benzazoles:**

A 10 mL round-bottomed flask was charged with 2-Aryl benzothiazole or benzoxazole (1a-u) (1.0 mmol), were dissolved in 1, 2 DCE (3 mL) and copper(II)chloride (20 mol %), $Fe(NO_3)_3.9H_2O$ (2.0 mmol) and $Ag_2O$ (2.0 mmol), were sequentially added and the reaction mixture was stirred at reflux 83 °C and reaction progress was observed by TLC (24 h). After completion of the reaction the crude compound obtained was washed with a saturated aqueous solution of brine (aq NaCl) and then extracted with ethyl acetate. The combined organic layers were dried with $Na_2SO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (60–120 mesh; hexane/ ethyl acetate) to obtain the desired product.

**Characterization Data**

**2-(2-nitrophenyl)benzo[d]thiazole (2a):** [12j] Pale yellow solid, mp. 116-118 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.12-8.08 (m, 2H), 7.92 (d, *J* = 8.15 Hz, 1H), 7.52-7.47 (m, 4H), 7.41-7.36 (m, 1H), $^{13}$CNMR (125 MHz, $CDCl_3$) δ: 168.0, 154.0, 135.0, 133.5, 130.9, 128.9, 127.5, 126.2, 125.1, 123.1, 121.5; ESI-MS: m/z 257 (M+H)+

**2-(4-methyl-2nitrophenyl)benzo[d]thiazole (2b);** Pale yellow solid, mp. 86-88 ˚C, $^1$HNMR (400 MHz, $CDCl_3$) δ: 8.85-8.80 (m, 1H), 8.37-8.34 (m, 1H), 8.12-8.09 (m, *J* = 8.85 Hz, 1H), 8.03-7.99 (d, *J* = 8.19 Hz, 2H), 7.36-7.32 (d, *J* = 8.06 Hz, 2H), 2.48 (m, 3H) $^{13}$C NMR (125 MHz, $CDCl_3$), 173.9, 157.9, 144.7, 142.9, 135.1, 129.9, 127.8, 123.0, 121.8, 118.1, 21.6; ESI-MS: m/z 271 (M+H)+,

**2-(4-ethyl-2-nitrophenyl)benzo[d]thiazole (2c):** Pale yellow solid, mp. 164-166 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 2.20 Hz, 1H), 8.378.34 (m, 1H), 8.12-8.10 (m, 1H), 8.04 (d, *J* = 8.34 Hz, 2H), 7.36 (d, *J* = 8.34 Hz, 2H), 2.78-2.71 (m, 2H), 1.32-1.27 (m, 3H), $^{13}$CNMR (100 MHz, $CDCl_3$) δ: 173.9, 157.9, 149.2, 144.7, 135.1, 130.2, 128.7, 127.9, 123.0, 121.8, 118.1, 28.9, 15.1, ESI-MS: m/z 285 (M+H)+

**2-(4-(*tert*-butyl)-2-nitrophenyl)benzo[d]thiazole (2d);** Pale yellow solid, mp. 144-146 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.84-8.82 (m, 1H), 8.38-8.35 (m, 1H), 8.12 (d, *J* = 8.92 1H), 8.06 (d, *J* = 8.31 2H), 7.56 (d, *J* = 8.43 2H), 1.59-1.53 (s, 9H), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 157.9, 156.0, 135.2, 130.0, 127.7, 126.1, 123.1, 121.8, 118.1, 31.1, 29.6; ESI-MS: m/z 313 $(M+H)^+$, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}O_2N_2S$ = 313.10053 found 313.10047.

**2-(4-methoxy-2-nitrophenyl)benzo[d]thiazole (2e):** Pale yellow solid, mp. 178-180 ˚C, $^1$HNMR (500 MHz, $CDCl_3$) δ: 8.80 (d, *J* = 2.28 Hz, 1H), 8.36-8.33 (m, 1H), 8.08-8.05 (m, 3H), 7.03 (d, *J* = 9.00 Hz, 2H), 3.91 (s, 3H), $^{13}$C NMR(100 MHz, $CDCl_3$) 173.5, 162.7, 158.0, 144.5, 135.1, 129.6, 125.5, 122.7, 121.8, 118.0, 114.6, 55.5, ESI-MS: m/z 287 $(M+H)^+$, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{11}O_3N_2S$ = 287.04849, found 287.04908.

**2-(4-(allyloxy)-2-nitrophenyl)benzo[d]thiazole (2f);** Pale yellow solid, mp. 172-174 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.93-8.72 (m, 1H), 8.41-8.28 (m, 1H),8.19-7.95 (m, 3H), 7.14-6.99 (m, 2H), 6.18-5.97 (m, 1H), 5.51-5.39 (m, 1H), 5.38-5.28 (m, 1H), 4.72-4.56 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 173.4, 161.9, 158.0, 144.5, 133.0, 129.6, 125.5, 122.7, 121.8, 118.2, 118.0, 115.3, 68.9, ESI-MS: m/z 313 $(M+H)^+$

**2-(3,4,5-trimethoxy-2-nitrophenyl)benzo[d]thiazole (2g);** Pale yellow solid, mp. 110-112 ˚C, $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.24 Hz, 1H), 7.90 (d, *J* = 7.93 Hz,, 1H), 7.53-748 (m, 1H), 7.45-7.39 (m, 1H) 7.12-7.10 (m, 1H), 4.034-4.02 (s, 3H), 4.00 (s, 3H), 3.98 (s, 3H), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.1, 154.5, 153.3, 146.5, 144.3, 135.3, 126.5, 125.8, 124.0, 121.4, 108.0, 62.6, 61.2, 56.5; HRMS (ESI) m/z [M + H]+ calcd for $C_{16}H_{15}O_5N_2S$ = 347.06962 found 347.06949.

**2-(4-fluoro-2-nitrophenyl)benzo[d]thiazole (2h);** Pale yellow solid, mp. 90-92 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 8.31 Hz, 1H), 7.94 (d, *J* = 7.45 Hz, 1H), 7.85-7.79 (m, 1H), 7.70-7.64 (m, 1H), 7.56-7.52 (m, 1H), 7.48-7.41 (m, 2H), $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 164.1, 161.5, 161.2, 153.4, 135.7, 133.5, 126.6, 125.9, 123.9, 121.5, 119.7, 119.5, 112.7, 117.4; ESI-MS: m/z 275 $(M+H)^+$

**2-(4-chloro-2-nitrophenyl)benzo[d]thiazole (2i);** Pale yellow solid, mp. 230-232 ˚C, $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.88-8.84 (m, 1H), 8.41-8.36 (m, 1H), 8.16-8.12 (m, 1H), 8.09-8.06 (m, 2H), $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 129.6, 129.0, 123.4, 122.0, 118.262; ESI-MS: m/z 291 $(M+H)^+$.

**2-(3-chloro-2-nitrophenyl)benzo[d]thiazole (2j);** Pale yellow solid, mp. 225-227 ˚C, $^1$H NMR (400 MHz ,$CDCl_3$) δ: 8.13-8.07 (m, 1H), 7.98-7.90 (m, 2H), 7.80-7.79 (m, 1H), 7.63-7.60 (m, 1H), 7.57-7.45 (m, 2H), $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 138.4, 131.2, 129.09, 123.4, 122.0, 118.262; HRMS (ESI) m/z $[M^+]$ calcd for $C_{13}H_8O_2N_2ClS$ = 290.99895 found 290.99858.

**2-(4-bromo-2-nitrophenyl)benzo[d]thiazole (2k);** Pale yellow solid, mp. 110-112 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.13-8.01 (m, 2H), 7.95 (d, *J* = 7.82, 1H), 7.87-7.81 (m, 1H), 7.70 (d, *J* = 8.19, 1H), 7.56-7.51 (m, 1H),7.49-7.43 (m, 1H), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 161.0, 153.5, 149.0, 135.7, 135.3, 132.8, 127.5, 126.7, 126.0, 124.5, 124.0, 121.5; ESI-MS: m/z 335 $(M)^{+\cdot}$ HRMS (ESI) m/z $[M-H]^{+\cdot}$ calcd for $C_{13}H_8O_2N_2BrS$ = 334.94844 found 334.94829.

**2-(2-nitro-4-(trifluoromethyl)phenyl)benzo[d]thiazole (2l);** Pale yellow solid, mp. 156-158 ˚C, $^1$H NMR (500 MHz, $CDCl_3$) δ: 8.43-8.38 (m, 1H), 8.26 (d, *J* = 8.08 Hz, 2H), 8.22-8.17 (m, 1H), 7.81 (d, *J* = 8.08 Hz, 2H), $^{13}$C NMR (100 MHz, $CDCl_3$), 171.6, 157.5, 145.3, 135.7, 135.4, 128.2, 126.2, 123.8, 122.1,118.3; ESI-MS: m/z 325 (M+H)+,

**2-(2-nitrophenyl)benzo[d]oxazole (2m):**[12j] Yellow solid, mp.104-106 ˚C $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 8.17-8.14 (m, 1H), 7.91 (d, *J* = 7.51 Hz, 1H), 7.83-7.81 (m, 1H), 7.78-7.63 (m, 2H), 7.59-7.57 (m, 1H), 7.43-7.38 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 158.80, 151.00, 149.18, 141.52, 132.37, 131.86, 131.41, 126.05, 124.95, 124.22, 121.48, 120.70, 110.94.

**5-methyl-2-(2-nitrophenyl)benzo[d]oxazole (2n):** [16a] Pale yellow solid, mp. 134-136 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.32-8.23 (m, 3H), 7.70-7.65 (m, 1H), 7.63-7.54 (m, 3H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 166.2, 154.2, 145.3, 143.4,129.8, 128.0, 123.1, 120.9, 116.0, 110.5, 21.7; ESI-MS: m/z 255 $(M+H)^+$, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{11}O_3N_2$ = 255.07642 found 255.07608.

**6-methyl-2-(2-nitrophenyl)benzo[d]oxazole (2o):** [16b] Pale yellow solid, mp. 103-105 ˚C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.40 (s, 1H), 8.26-8.22 (m,

2H), 7.60-7.50 (m, 4H), 2.74 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ: 165.3, 152.9, 146.7, 132.3, 131.6, 129.0, 127.9, 126.150, 116.9, 113.4, 21.3; ESI-MS: m/z 255 $(M+H)^+$ HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{11}O_3N_2$ = 255.07642 found 255.07606.

**2-(2-methyl-6-nitrophenyl)benzo[d]oxazole (2p):** [12j] Yellow solid, mp. 59-61 °C, $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.01 (d, *J* = 7.51 Hz, 1H), 7.84-7.81 (m, 1H), 7.64-7.60 (m, 3H), 7.42-7.40 (m, 2H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 158.6, 150.8, 149.5, 141.5, 141.4, 135.4, 131.0, 125.6, 124.7, 122.9, 122.3, 120.5, 110.9, 20.0.

**6-methyl-2-(4-methyl-2-nitrophenyl)benzo[d]oxazole (2q);** Pale yellow solid, mp. 178-180 °C $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 8.18-8.13 (m, 2H), 7.62-7.50 (m, 4H). $^{13}$C NMR (100MHz, CDCl3) δ: 167.4, 148.1, 146.1, 145.7, 143.5, 131.1, 129.8, 128.1, 123.2, 122.4, 107.8, 21.7, 21.3; ESI-MS: m/z 269 $(M+H)^+$, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{13}O_3N_2$ = 269.09207 found 269.09161.

**2-(4-methoxy-2-nitrophenyl)benzo[d]oxazole (2r):** [12j] Yellow solid, mp. 110-112 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.84 Hz, 1H), 7.79- 7.77 (m, 1H), 7.56-7.53 (m, 1H), 7.38-7.34 (m, 3H), 7.21 (d, *J* = 8.81 Hz, 1H), 3.94 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 162.0, 158.9, 150.9, 150.3, 141.6, 132.5, 125.6, 124.7, 120.4, 117.8, 113.3, 110.7, 109.7, 56.2.

**2-(3-chloro-2-nitrophenyl)-6-methylbenzo[d]oxazole (2s);** Pale yellow solid, mp. 150-152 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.30-8.26 (m, 2H), 8.17-8.14 (m, 1H), 7.69 (s, 1H) 7.59-7.56 (m, 1H), 7.53-7.48 (m. 1H); $^{13}$C NMR (125 MHz, CDCl3) δ: 165.6, 148.2, 146.3, 145.6, 135.3, 132.6, 131.2, 130.4, 128.0, 127.7, 126.1, 122.9, 108.0, 21.2; ESI-MS: m/z 289 $(M+H)^+$, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{10}O_3N_2Cl$ = 289.03745 found 289.03727.

**2-(4-bromo-2-nitrophenyl)benzo[d]oxazole (2t):** [16a] Yellow solid, mp. 158-159 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 8.42 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 8.43 Hz, 1H), 7.83-7.80 (m, 1H), 7.59 - 7.57 (m, 1H), 7.44 -7.38 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 157.8, 150.9, 149.3, 141.5, 135.4, 132.3, 127.2, 126.3, 125.6, 125.1, 120.8, 120.0, 110.1.

**1-Methyl-2-(2-nitrophenyl)-1H-benzo[d]imidazole (2u):** [12j] Yellow solid, mp. 125-126 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, *J* = 4.73 Hz, 1H), 7.78 (m, 2H), 7.72 (m, 1H), 7.65 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 4.6 Hz, 1H), 7.31 (m, 2H), 3.61 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 149.7, 148.6, 142.7, 135.6, 133.5, 131.1, 125.9, 124.7, 123.2, 122.5, 120.1, 109.6, 30.5.

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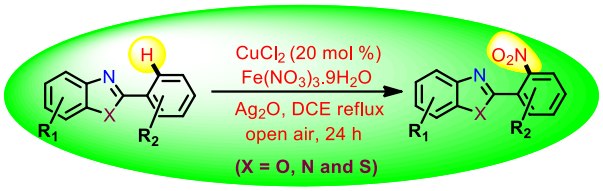


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**Key Topic***

*Botla Vinayak, Akudari Ashok and Malapaka Chandrasekharam**

***Page No. – Page No.***

**Copper-Catalyzed Chelation Assisted *ortho*-Nitration of 2- Aryls with Pharmacophoric Benzo-thiazoles and -oxazoles as Directing Groups.**

A Copper-catalyzed chelation assisted *ortho*-nitration of aryls with benzazoles i.e., benzoxazoles, benzthiazoles and benzimidazoles as efficient pharmacophorically important directing groups has been achieved. This nitration protocol employs inexpensive and environmentally friendly reagents and highlights the operational simplicity, functional group tolerance and high regioselectivity.