# A copper-benzotriazole based coordination polymer catalyzes the efficient one-pot synthesis of (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines from azines

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**Abstract.** A series of new (*N*'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines were successfully synthesized via a facile one-pot catalytic pathway utilizing azines and propiolate esters as starting materials and 1D Cu benzotriazoles based coordination polymer as catalyst. In the absence of catalyst, the corresponding 5-substituted 4,5-dihydro pyrazoles were formed in moderate to high yields. Fine-tuning the catalysts allowed us to gain more insights regarding the plausible reaction mechanism.

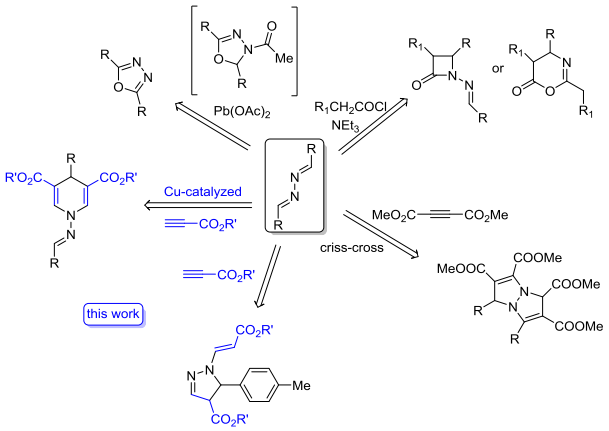
**Keywords:** catalysis; copper; azine;1,4-dihydropyridines; coordination polymer

## Introduction

Azines (aldazines and ketazines),[1] are a class of compounds with interesting chemical properties that undergo a wide variety of chemical processes (i.e. redox, cycloadditions, criss-cross reactions)[2–4] to yield hydrazones, pyrazoles, purines or pyrimidines (Scheme 1). Aldazines, as conjugated diene, undergo [1,3]-cycloaddition with electron poor unsaturated molecules, providing an efficient route towards 1,5-diazabicyclooctanes through the known criss-cross reaction.[2] In view of the importance of the synthesis of 1,4-dihydropyridines (1,4-DHPs), the metal-catalyzed process has received considerable attention.[5,6] 1,4-DHPs and their derivatives, are an important class of biologically active organic compounds, i.e. the calcium channel blocker, amlodipine.[7–9] Moreover, symmetrical *N*'-substituted-hydrazo-4-aryl-1,4-DHPs (HA-1,4-DHPs), are new heterocycles in nature with probably wide-ranging biological activity.[10,11] Methodologies including Hantzsch,[12] multicomponent,[5,6,13] cycloaddition,[14–16] or C-C coupling reactions,[17] are used for the synthesis of 1,4-DHPs derivatives (see Supporting Information, Scheme S1). A series of organocatalytic procedures have been used for such reaction,[18–21] these however exhibit major drawbacks such as the high cost of the reagents, the high temperature and tedious work up.

Coordination polymers (CPs) are a class of compounds containing repeating coordination entities extending in 1, 2 or 3 dimensions.[22] that have received considerable attention due to their applications in gas adsorption, catalysis, drug delivery, separation, and imaging.[23] Especially in catalysis, in contrast to the porous well-structured three dimensional CPs (known as metal organic frameworks MOFs), that retain their structural integrity during a catalytic reaction, one dimensional (1D) CPs have been far less studied.[24–26] However, their easy synthesis and the possibility for tuning make them very promising candidates for catalysis.

Combining our research interests on the synthesis of simple biologically active compounds,[27–29] and the coordination chemistry of benzotriazole based organic ligands,[30,31] we report herein a new one-pot synthesis, under mild conditions, of a series of HA-1,4-DHPs based on Cu-catalyzed reactions between symmetrical electron rich aldrazines and alkylpropiolate (Scheme 1). To the best of our knowledge, the synthesis of substituted symmetrical HA-1,4-DHPs using aryl aldazines and propiolates as starting materials, is an unknown chemical transformation.




**Scheme 1.** Synthetic scheme for known reactions that aldrazines undergo. Retrosynthetic methodology towards HA-1,4-DHP derivatives *vs* 5-aryl-pyrazoles (highlighted in blue).

## Results and Discussion

The present catalytic protocol arose during the study of the title reaction using 1,2-bis ((*E*)-4-methylbenzylidene) hydrazine (**1**) and ethyl propiolate, in the presence of different copper salts $Cu(ClO_4)_2$, $Cu(NO_3)_2$, $Cu(OAc)_2$, $CuCl_2$, $CuSO_4$, $[Cu(PPh_3)_2(MeCN)_2]ClO_4$ (see Supporting Information for synthesis) and the following $[Cu^{II}(L)_2(MeCN)_2]\cdot 2(ClO_4)\cdot 2MeCN$ (**2**), $[Cu^{II}(L)_2(NO_3)_2]$ (**3**) and $[Zn(L)_2(H_2O)_2]\cdot 2(ClO_4)\cdot 2MeCN$ (**4**) CPs, where L is 1-(2-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)benzyl) -1H-benzo[d][1,2,3]tri-azole). Metal salts were used with no further purification, whereas compounds **2** – **4** were characterized with IR, NMR, UV-Vis, ESI-MS, TGA (see Supporting Information) and single crystal X-Ray diffraction. Compound **2** consists of a $Cu^{II}$ center, possessing a slightly distorted octahedral geometry, coordinated to four nitrogen atoms belonging to four different organic ligands (equatorial positions) and two acetonitrile solvent molecules (axial positions). The structure extends to one dimension along the *a* axis, forming a 1D CP (Figure 1). Compound **4** is isostructural to **2**; the two coordinating acetonitrile moieties are replaced by $H_2O$ molecules (see Supporting Information, Figure S2). In compound **3**, the asymmetric unit consists of a $Cu^{II}$ center, one organic ligand molecule, two nitrate anions and one acetonitrile solvent molecule (see Supporting Information, Figure S3). The $Cu^{II}$ center has a coordination environment of $\{N_2O_5\}$ and possesses a pseudo octahedral geometry. A dimeric $Cu^{II}_2$ unit is formed via the chelating and bridging nitrate moieties and the structure extends in two dimensions along the *b* plane. The relevant N-Cu-O bond angles range from 85.32(4)° to 95.66(4)°. As for the relevant bond lengths, the mean Cu-N distances are 1.9849(6) and 1.9916(6) Å, while the Cu-O distances range from 1.9813(6) to 2.6587(6) Å.

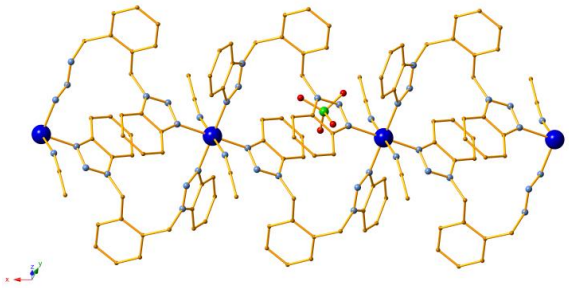


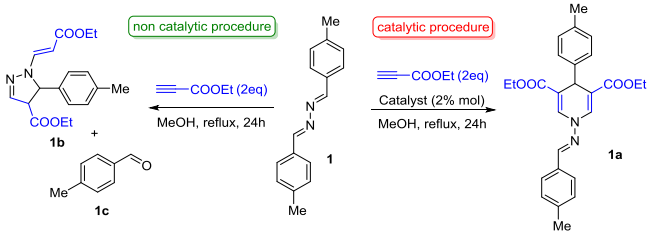
**Figure 1.** Molecular structure of **2**.Color code: Cu, blue; C, black; N, light blue; O, red, Cl, green. H-atoms are omitted for clarity.

The initial experiments with copper salts, 0.1 mmol of **1**, ethyl propiolate (2 eq. based on the amount of **1**) in MeOH under reflux for 24h (Table 1, entries 1 - 6), show almost quantitative consumption of **1** with the corresponding 4-methylbenzaldehyde (**1c**) to produced as the major or only product, along with a mixture of unidentified products. Aldehyde is the product formed through a hydrolysis pathway or an oxidation reaction between the starting aldazine with molecular oxygen. Indeed, aldehyde **1c** was formed as the only product, when oxygen saturated methanolic solution of **1** was used under the same catalytic conditions (result not shown). In the absence of catalyst, except aldehyde **1c** that was formed in 35% relative yield, a significant amount (30%) of the 5-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-4-carboxylate derivative (**1b**) was isolated (Table 1, entry 8). To the best of our knowledge, this transformation has never been reported before under the present reaction conditions, however, the average relative pyrazole yields are in the range of 5-30% (see Supporting Information, Table S1). When we employed L as catalyst, formation of **1b** with lower conversion and yield was observed (Table 1, entry 9). Astonishingly, incorporating **2** (2 mol%) as the catalyst under similar conditions, the corresponding **1a** was formed in 65% yield, determined by $^1$H NMR (Table 1, entry 10). On the contrary, the use of **3** gives no conversion (Table 1, entry 11), whereas the use of **4** yields **1b** (Table 1, entry 12). These results clearly indicate that a clean and selective transformation of **1** to **1a** takes place only in the presence of **2**. For comparison, a mixture of $Cu(ClO_4)_2$ (2 mol%) and L (4mol%) was found to catalyze the formation of **1a** in lower yield 14% (Table 1, entry 7), however, in the absence of L no formation of **1a** was observed (Table 1, entry 1). The latter indicates a significant ligand-effect that probably plays a crucial role to the catalytic reaction mechanism (see below in the mechanistic part).

Among the solvents studied, high conversion of **1** was observed using methanol and less in EtOH, however, in non protic polar solvents, such as DMF, $CH_3CN$, acetone, DCE or THF, the C-C coupling product, diethyl hexa-2,4-diynedioate, was only observed (see Supporting Information, Table S2). In contrary, using $H_2O$ as reaction solvent or co-solvent,

no formation of **1a** was observed. However, under dry methanolic solution (over 3A molecular sieves) no significant increase of the relative yield of **1a** was observed (see Supporting Information, Table S2). In addition, using higher loadings of **2** or the ethyl propiolate, the corresponding hydrolakoxylation product ethyl (*Z*)-3-methoxyacrylate was observed as the major product (see Supporting Information, Table S3). When a similar reaction is performed at room temperature, then **1** remains intact, however under microwave irradiation the formation of the ethyl (*Z*)-3-methoxyacrylate is only observed (see Supporting Information, Table S3). Finally, in the presence of several other alkyl or aryl alkynes (i.e. DMAD, phenyl acetylene, propargyl bromide, propargyl alcohol and crotyl ester), no formation of the corresponding HA-1,4-DHP derivative was observed (see Supporting Information, Table S4).

**Table 1.** Transformation of aldazine (**1**) in HA-1,4-DHPs derivative (**1a**) using various catalyst.




| Entry | Catalyst[a] | Conv.[b] | 1a[c] | 1b[c] | 1c[c] |
|---|---|---|---|---|---|
| 1[d] | $Cu(ClO_4)_2$ | 98% | - | - | - |
| 2[d] | $Cu(NO_3)_2$ | 54% | - | - | 31% |
| 3[d] | $Cu(OAc)_2$ | 42% | - | - | 32% |
| 4 | $CuCl_2$ | >99% | - | - | >99% |
| 5 | $CuSO_4$ | >99% | - | - | >99% |
| 6 | $Cu(PPh_3)_2(MeCN)_2]ClO_4$ | N.r.[f] | - | - | - |
| 7[d] | $Cu(ClO_4)_2$[e] | 99% | 14% | - | - |
| 8 | No catalyst | 65% | - | 30% | 35% |
| 9 | L | 25% | - | 12% | 13% |
| 10 | **2** | >99% | 65% | 13% | 22% |
| 11 | **3** | N.r.[f] | - | - | - |
| 12 | **4** | 52% | - | 25 | 27% |

[a] **1** (0.1 mmol), ethyl propiolate (0.2 mmol) and 3 mg of the solid catalysts. [b] Based on the consumption of 1 determined by $^1$H NMR. [c] Relative yields based on $^1$H NMR analysis from the integration of the corresponding proton shifts. [d] A mixture of unidentified products was observed by $^1$H NMR. [e]Five equivalents of benzotriazole (3mg) was added into the reaction mixture. [f] No reaction.

To study the limitation of the above catalytic procedure, a series of substituted azines (**1** and **5-13**) were examined. Figure 2 summarizes the results obtained using catalyst **2** as catalyst. In all cases the corresponding HA-1,4-DHPs derivatives (**1a** and **5a-13a** (R=Et) and **14a-18a** (R=Me)) were formed with good isolated yields (ca. 44-68%). It is worth noting that electron rich aromatic azines (**1** and **5-8**) are transformed to the corresponding HA-1,4-DHPs derivatives (**1a** and **5a-8a**), with higher yields (44%-68%) within 24h, compared to the electron deficient azine (**11**, X=$CF_3$) in which negligible yield (<5%) was observed within 48 h. Remarkably, no reaction w as observed when *para*-nitrosubstituted azine **12** was used as substrate. In addition, the use of methyl propiolate instead of ethyl propiolate gave similar conversions and isolated yields of the corresponding HA-1,4-DHPs derivatives compared to the corresponding ethyl propiolate (Figure 2, **14a** – **18a**). It is worthnoting that, heterocyclic substituted azines **20** (2-thiophenyl) and **21** (2-furyl), under the present catalytic conditions gives the corresponding dihydropyridines **20a** and **21a** in ca.10% and 67% isolated yield, repsectively. Subsequently, naphthyl subtituted azine **22a** shows lower activity, with the corresponding product formed in negligible yield (<5%), see Figure 2. All the products were determined by $^1$H NMR spectroscopy, whereas **7a**, **8a**, **9a** and **16a** were additionally characterized with single X-Ray diffraction (see Supporting Information, Figure S11).

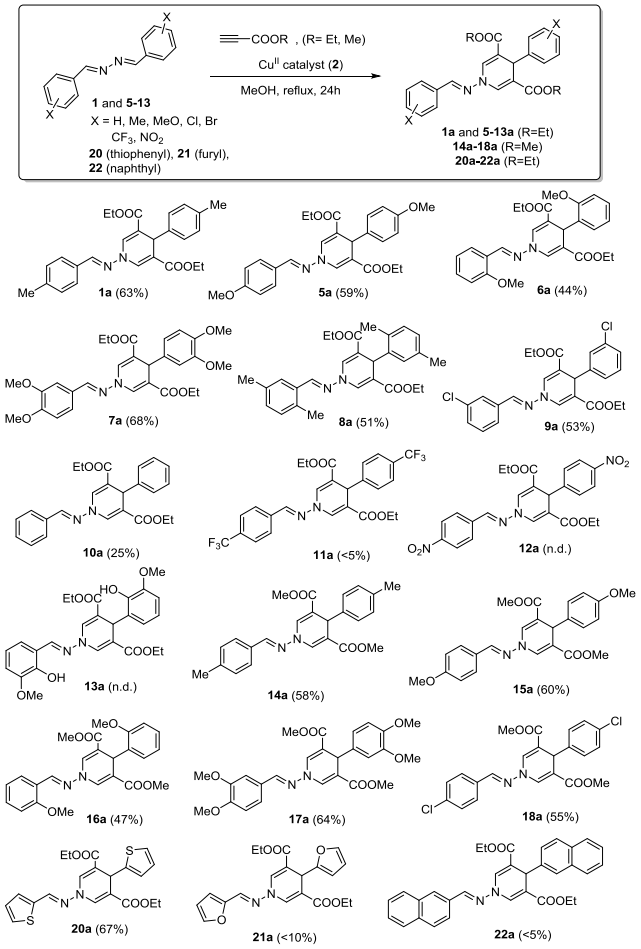



**Figure 2.** Various (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines synthesized by Cu-catalyzed reaction. The percentages correspond to the yields of isolated products. n.d. = not detected.

Regarding the mechanism of the title reaction, we observed the following:

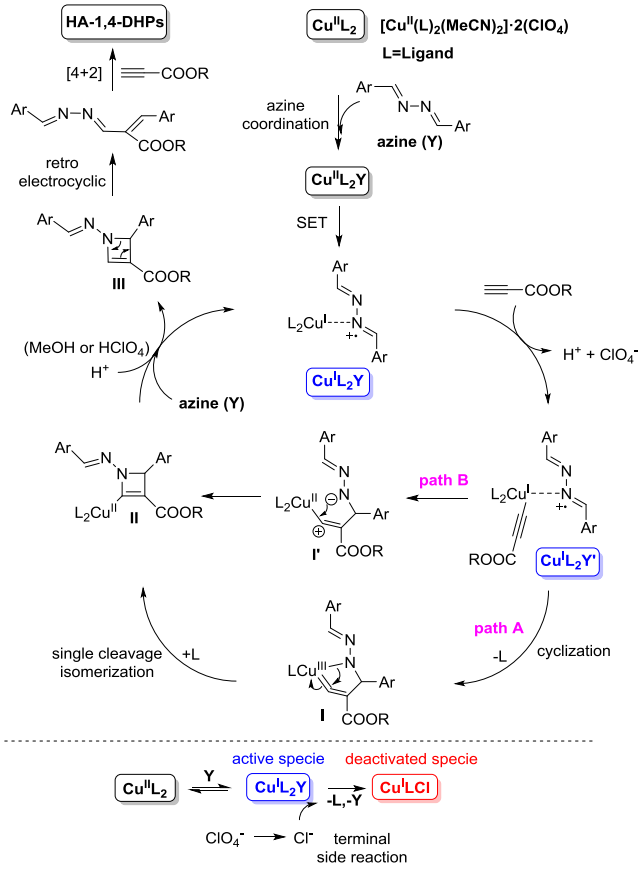
a) For azines bearing electron donating groups such as **1** (4-Me), **5** (4-MeO), **6** (3-MeO), **7** (3,4-diMeO) and **8** (2,5-diMe) a five times faster reaction was observed than the corresponding reaction of azine **10** (4-H). On the other hand, azines **11** (4-$CF_3$) bearing an electron-withdrawing substituent in the *para* position reacted with a slower manner, however **12** (4-$NO_2$) remain intact. This first observation implies that an initial complex between the azine and the $Cu^{II}$-catalyst is formed, followed by a single electron transfer (SET)[32] process forming the active species $Cu^{I}L_2Y$ (Scheme 2). In the same context, addition of a small amount (10 mol%, based on **1**) of an electron donor molecule (e.g. trimethoxybenzene, TMB) with oxidation potential less than that of azines ($E_{1/2}$ox *vs* SCE 1.12 V),[33] retards the reaction process (see Supporting Information, Table S3).

b) Based on the azines ability to donate electrons via lone pairs of the N atom or the C=N p-orbital electrons,[1] it is know that they show versatile properties of coordination in binding to metal centers, such as $Cu^{II}$ or $Fe^{II}$, especially when the aromatic ring of the azine contains a hydroxyl group in the ortho position.[34] Indeed, under our catalytic conditions, azine **13** (2-OH, 3-MeO), shows no reactivity towards the synthesis of **13a**, probably through the *in-situ* azine-$Cu^{II}$-catalyst coordination effect (see Figure 2 and Figure S12 in Supporting Information).

c) The reaction of 4-methylbenzaldehyde (**1c**), ethyl propiolate and **2** in methanol yielded a mixture of unidentified products as confirmed by $^1$H NMR (see Supporting Information, Figure S13). In the case of the hetero-azine **19**, which bears two different substituent's in the *para*-positions of the aromatic rings (MeO and Cl), both HA-1,4-DHP derivatives **19a** and **19a'** were formed in a ratio of 2/1, as determined by $^1$H NMR and LC-MS (see Supporting Information, Figures S14-S16). These results indicate that the azines does not dissociate during our catalytic reactions. Therefore, our catalytic procedure follows probably a different mechanistic pathway compared to the common proposed multi component reaction (MCR) or Lewis-acid catalyzed processes.[5,6] In addition, using the (*Z*)-3-methoxyacrylate (a common starting material for the above literature studies) instead of the propiolate ester, and under the same catalytic conditions, the desired 1,4-dihydropyridine product was not observed (see Supporting Information, Table S4).

d) In our attempts to recover the catalyst we isolated and characterized via single crystal X-Ray crystallography a yellow solid material formulated [$Cu^{I}$LCl] (**2i**) corresponding to a 1D CP (see Supporting Information, Figure S4). This indicates that $ClO_4^-$ converts to $Cl^-$ and $Cu^{II}$ to $Cu^{I}$.[35] Therefore, we envisage that at a certain point, transformation of perchlorate to chlorine occurs, which in turn starts to coordinate to $Cu^{I}$ centres, transforming the catalyst to **2i** (Scheme 2). In addition, under new catalytic cyclic **2i** was found to be inactive. This result indicates a low value of tern over number (TON) of the present catalytic system **2**, with a max number of ca. 55).

Based on the above experimental results we propose a possible reaction mechanism (Scheme 2). Azine (**Y**) initially coordinates to the catalyst $\mathbf{Cu^{II}L_2}$ forming a new catalytic intermediate $\mathbf{Cu^{II}L_2Y}$ (Scheme 2). ESI-MS and UV-Vis studies in methanolic solutions indicate that $Cu^{II}$ in **2** retains the octahedral geometry and coordinates to four N atoms of four different L ligands; a similar pattern was observed for the isostructural Zn analogue **4**. In addition, $Cu^{II}$, in the catalytically inactive compound **3**, retains its geometry but coordinates to two N atoms belonging to two ligands L.[36] In sequence, a single electron transfer (SET) occurs from the electron rich azine to the $\mathbf{Cu^{II}L_2Y}$, yielding the active reduced form; $\mathbf{Cu^{I}L_2Y}$. This active specie is responsible for the first catalytic pathway which contains the simultaneously propiolate complexes and the proton release by the presence of the perchlorate anion forming the corresponding $Cu^{I}$-acetylide intermediate ($\mathbf{Cu^{I}L_2Y'}$). Then, $\mathbf{Cu^{I}L_2Y'}$ undergoes a cyclization process, forming the unusual five-membered $Cu^{III}$-metallacycle intermediate **I** (**path A**, Scheme 2). Similar intermediate is been supported by previous theoretical study on the copper-catalyzed synthesis of azoles.[37] This hypothesis found support from related literature on Cu-benzotriazole catalyzed electrophilic cyclization of *N*-arylamines,[38] as well as Cu-catalyzed synthesis of isoquinoline derivatives or other heteroarenes.[39–41]



**Scheme 2.** Plausible mechanism for the synthesis of the (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines through the hydrazine and propiolate Cu-catalyzed coupling.

Subsequently, a reductive single cleavage (ring contraction)[42] leads to the common intermediate **II**, which after proteolysis releases the cyclo-compound dihydroazete **III**, followed by simultaneously conrotatory ring opening, yielding the corresponding diene which in turn reacts *in situ* with a second molecule of propiolate via a [4+2], giving the desired product dihydopyridine derivative (**HA-1,4-DHPs**). Pathway A requires a ligand (L) replacement by the azine material that coordinates to Cu center (Scheme 2).[37] In contrast, pathway B that contains the cyclization process without any ligand replacement or azine binding effect cannot be excluded (**path B**, Scheme 2). It is worth noting that during the catalytic process a white powder was formed, that was found to be ligand L (confirmed by IR and NMR). In addition, a possible reductive elimination pathway from intermediate **I**, leads to the $Cu^{I}L$ which react with $Cl^{-}$ to form the inactive specie $Cu^{I}LCl$ (Scheme 2).

In parallel and under non catalytic conditions, only pyrazole products were formed, through a stepwise mechanism contains a known criss-cross reaction ([3+2] cycloaddition) between the azine and the triple bond of propiolate, at a first step.[1,2] After that, a nucleophilic addition and hydrolysis take place simultaneously (or with the opposite turn) forming the corresponding 5-substituted-4,5-dihydro pyrazoles, as shown in Figure S17 of the Supporting Information, accompanying with an equimolar amount of the corresponding X-substituted benzaldehydes as the product from the hydrolysis pathway. It is worth noting that X-substituted benzylaldehydes were also formed through an oxidative pathway form the initial azine (result not shown). Indeed, using molecular oxygen ($O_2$) saturated methanolic solution and under the present catalytic conditions (**1**, ethylpropiolate and **2** as catalyst) the corresponding aldehyde **1c** was observed as the only product (see Supporting Information, Table S3).

## Conclusion

In conclusion, the current work exemplifies the unique nature of the Cu-benzotriazole one-dimensional coordination polymer as a catalyst in the efficient synthesis of (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines (HA-1,4-DHPs). A series of substituted HA-1,4-DHPs we formed in good isolated yields; however, fine tuning the catalyst we were able to obtain useful information about the mechanism. From the mechanistic point of view, a hydrazine coordination initial step following by a SET pathway and a cyclization process forming a five-membered $Cu^{III}$-metallacycle intermediate, constitutes the basic catalytic procedures in the title reaction. The herein Cu-catalyzed process is advantageous because of its possible wide use towards the synthesis of different heterocyclic organic molecules and because of its unique mechanistic understanding. Future efforts of our groups will concentrate on improving the catalytic behavior of **2** and its application towards other chemical transformations.

## Experimental Section

### General

The aromatic aldehydes used as starting materials for the synthesis of aryl hydrazines were of high purity and commercially available from Aldrich. Aryl hydrazines were synthesized via the reaction between the corresponding aldehydes and hydrazine. $Cu(ClO_4)_2$, $Cu(NO_3)_2$, $Cu(OAc)_2$, $CuCl_2$, $CuSO_4$ and all the solvents were purchased from Sigma-Aldrich.

### Cu-Catalyst (2) preparation

Synthetic Protocol.0.24 mmol (0.082 g) of L were dissolved in 10 ml MeCN while stirring to produce a colorless solution. A solution containing 0.48 mmol (0.178 g) of $Cu(ClO_4)_2 \cdot 6H_2O$ in MeCN (7.5 ml) was slowly added. The resulting green solution was filtered, then stored atroom temperature. High quality green crystals were obtained after 3 days. Yield: 49% (based on Cu). For $C_{46}H_{41}Cl_2CuN_{14.5}O_8$ ($M$ =1059.37 g/mol) crystal data see Supporting Information.

### General Cu-Catalyzed Reactions

Into a sealed tube containing the azine (0.2 mmol) and methanol (1 mL), 0.4 mmol of ethylpropiolate and 3 mg of the corresponding catalyst (2 mol% Cu) were added. The reaction mixture was vigorously stirred at 70 °C for selected time and then reaction process was monitored by thin layer chromatography (TLC). After completion, the slurry was filtered and the filtrate was then evaporated under vacuum to give a mixture containing the corresponding HA-1,4-DHPs. Further purification with column chromatography afforded the HA-1,4-DHPs in pure form (see Supporting Information). Product analysis was conducted by $^{1}H$ NMR and $^{13}C$ NMR spectroscopy (Bruker AM 300 and Agilent AM 500). Identification of the products was realized by comparing the NMR spectra data with those of the commercially available pure substances. Mass spectra were determined on an LCMS-2010 EV Instrument (Shimadzu) under Electrospray Ionization (ESI) conditions.

CCDC 1482180-1482186, 1482276. contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## Acknowledgements

*Financial support by the A.U.TH Research Committee (KA 89309) is kindly acknowledged. I.N.L. and M.K. acknowledged the sponsorship of the Short Term Scientific Mission from COST action CM1201.We thank Dr. Nikolaos Tsoureas (University of Sussex) for preliminary CV data of compound 2. We thank the EPSRC UK National Crystallography Service at the University of Southampton for the collection of the crystallographic data for compounds 2a, 7a and 16a.*[43]

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A copper-benzotriazole based coordination polymer catalyzes the efficient one-pot synthesis of (N'-substituted)-hydrazo-4-aryl-1,4-dihydropyridines from azines

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

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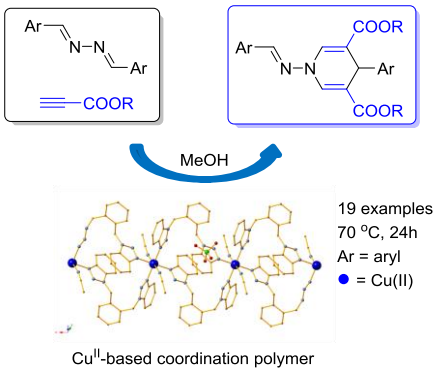


$Cu^{II}$-based coordination polymer