Tetrahedron xxx (2014) 1–11

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of 3,5-diaryl-1,2,4-triazoles via copper-catalyzed domino nucleophilic substitution/oxidative cyclization using amidines or imidates as substrates

Kavitha Sudheendran [a], Dietmar Schmidt [a], Wolfgang Frey [b], Jürgen Conrad [a], Uwe Beifuss [a,*]

[a] Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, D-70599 Stuttgart, Germany
[b] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form 8 January 2014
Accepted 11 January 2014
Available online xxx

Keywords:
Amidine
Imidate
Catalysis
Copper
1,2,4-Triazole

ABSTRACT

Two methods for the synthesis of 3,5-diaryl-1,2,4-triazoles, both domino reactions, are reported. The first procedure, the $Cu(OTf)_2$-catalyzed reaction between two amidines using $NaHCO_3$ as a base, 1,10-phenanthroline as an additive and $K_3[Fe(CN)_6]$/atmospheric oxygen as the oxidant, delivers 3,5-diaryl-1,2,4-triazoles with yields up to 68%. The second procedure for the synthesis of 3,5-diaryl-1,2,4-triazoles with yields up to 64% rests on the $Cu(OTf)_2$-catalyzed reaction between two imidates and ammonium carbonate. This method features the formation of three bonds in a single synthetic step.

1. Introduction

Currently, the synthesis of heterocycles is receiving a strong impetus from copper-catalysis.[1,2] The main reasons are that copper-catalyzed cross couplings, such as the arylation between aryl halides and different nucleophiles, can be successfully performed under relatively mild reaction conditions, are highly selective, tolerate a wide range of functional groups and use cheap reagents.[3] Another advantage is that copper-catalyzed cross couplings can be coupled with numerous other transformations to new domino processes. In particular, the combination of copper-catalyzed C-, N-, O- and S-arylations with copper-catalyzed oxidations[4] opens up new prospects for the selective and efficient synthesis of heterocycles in one pot.

1,2,4-Triazoles are important heterocycles since they exhibit a wide range of significant biological activities, including antifungal, antibacterial, anticancer, antimicrobial and anticonvulsant activities.[5,6] More recently, it has been reported that symmetrical triazoles like the trisubstituted compound **A** are effective in inhibiting the replication of the hepatitis C virus (Fig. 1).[7a] Trisubstituted 1*H*-1,2,4-triazoles **B** are compounds with promising antimycobacterial and antimicrobial activities.[7b] 3,5-Disubstituted 1,2,4-triazoles act as A_{2A} receptor antagonists[7c] and 3,5-diaryl-1,2,4-triazoles, such as **C** have been identified as selective inhibitors of 11β-hydroxysteroid dehydrogenases type 1.[7d] Of particular interest are compounds like 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1*H*-1,2,4-triazole (DL111-IT) (Fig. 1, **D**) that has been identified as a non-hormonal antifertility agent.[8] It was demonstrated that DL111-IT inhibits the synthesis of progesterone by inactivation of 3β-hydroxysteroid dehydrogenase that it induces apoptosis in corpus luteum, and inhibits the growth of embryos. In addition, there are also a number of natural products with a 1,2,4-triazole skeleton. Typical examples include the cytotoxic penipanoid A (Fig. 1, **E**), which has been isolated from the marine sediment derived fungus *Penicillium paneum* SD-44,[9] and 1-(β-D-ribofuranosyl)-1,2,4-triazole from the sea urchin *Glyptocidaris crenularis*.[10] 1,2,4-Triazoles and their derivatives also play an important role as ligands in organometallic compounds, as precursors for *N*-heterocyclic carbenes, as ionic liquids and as corrosion inhibitors.[11] This is why the synthesis of 1,2,4-triazoles is a topic receiving much attention.

Over the years, a number of general synthetic methods have been developed for the preparation of the 1,2,4-triazoles.[12] Many of them are based on the intramolecular condensation of acylamidrazones,[13] which can be obtained from amides or thioamides and

* Corresponding author. Fax: +49 711 459 22951; e-mail address: ubeifuss@uni-hohenheim.de (U. Beifuss).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.01.019

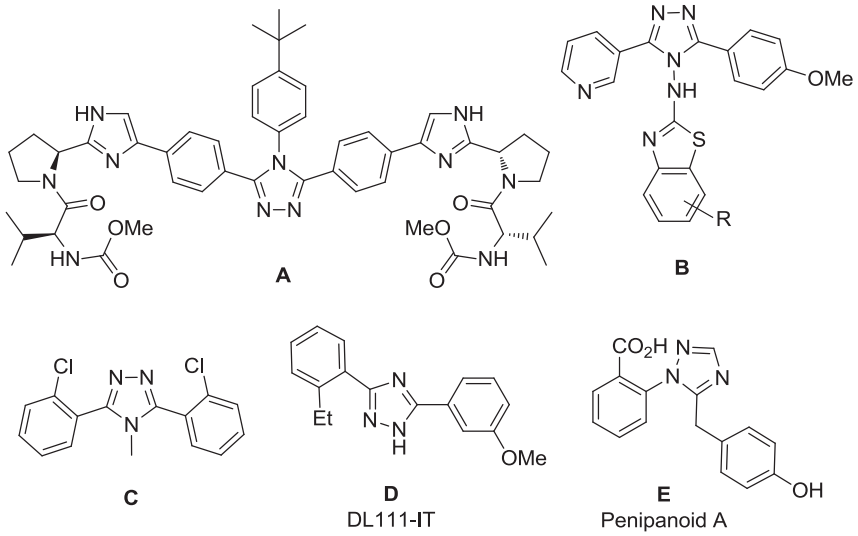


Fig. 1. Selected biologically active compounds with a 1,2,4-triazole core.

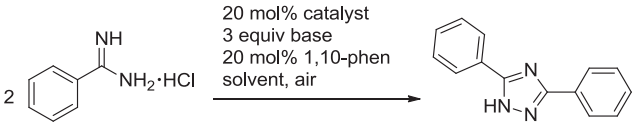
hydrazides (Pellizzari reaction),[14] from diacylamines and hydrazines (Einhorn–Brunner reaction),[15] from 1,2-diacylhydrazines and ammonia,[12e] or the acylation of amidrazones.[16] Recently, 1,2,4-triazoles have been obtained by in situ generation of primary acylamidines and their reaction with hydrazines.[17] More specific, the synthesis of 3,5-diaryl-1,2,4-triazoles can be achieved by Pellizzari reaction,[12–14,18] the reaction between a hydrazide and a nitrile,[19a,b] an imidate,[19c] or an amidine.[19d] Other methods for the synthesis of 3,5-diaryl-1,2,4-triazoles include the reaction between 3,6-diaryl-1,2,4,5-tetrazines with acetonitrile derivatives under basic conditions,[20] the 1,3-dipolar cycloaddition between azodicarboxylates and münchnones, which is accompanied by elimination of carbon dioxide,[21] and the photolysis of 1,3,4-oxadiazoles in alcohols.[22]

In an early study T. Kauffmann et al. reported that 3,5-diphenyl-1,2,4-triazole can be prepared by dimerization of sodium benzamidine with equimolar amounts of CuCl or $CuCl_2$ in 1,2-dimethoxyethane in the presence of oxygen.[23a] However, so far only a few methods are known, which allow for the copper-catalyzed synthesis of 3,5-diaryl-1,2,4-triazoles. Among them is the CuBr-catalyzed one pot reaction between 1.5 equiv of an amidine and 1 equiv of a nitrile using 3 equiv Cs_2CO_3 as the base and aerial oxygen as the oxidant.[23b] Recently, Fu et al. reported on the intramolecular oxidative cyclization of 2,4-diaryl-1,3,5-triazapenta-1,3-dienes to the corresponding 3,5-diaryl-1,2,4-triazoles using elemental copper as the catalyst and oxygen as the oxidant for 48 h at 120 °C.[23c] The 2,4-diaryl-1,3,5-triazapenta-1,3-dienes, which were not isolated were obtained by the copper-catalyzed reaction of two amidines using Cs_2CO_3 as the base under an atmosphere of nitrogen for 24 h at 120 °C. Here, we report a) that both the intermolecular nucleophilic substitution and the copper-catalyzed intramolecular oxidative ring closure to the 3,5-diaryl-1,2,4-triazoles can be performed as a domino reaction under identical reaction conditions and b) that 3,5-diaryl-1,2,4-triazoles can be obtained by a copper-catalyzed domino reaction between two imidates and an ammonium source in a single synthetic operation.

2. Results and discussion

For the transformation between two amidines, the reaction of two molecules benzamidine hydrochloride (**1a**) was chosen as a model. When 1 mmol **1a** was reacted in the presence of 20 mol % CuBr as the catalyst and 3 equiv K_2CO_3 in DMF at 110 °C for 20 h in a sealed vial the required 3,5-diphenyl-1,2,4-triazole (**2a**) was isolated with 17% yield (Table 1, entry 1). The yield of **2a** could be improved slightly to 24% and 27%, respectively, when the model reaction was performed in the presence of 20 mol % 1,10-phenanthroline (1,10-phen) as an additive at 130 °C for 24 h in DMF and *o*-dichlorobenzene, respectively (Table 1, entries 2 and 3). Interestingly, the yield of **2a** could be almost doubled to 53% when CuBr was replaced with $Cu(OTf)_2$ (Table 1, entry 4). A similar yield was observed with $NaHCO_3$ as the base (Table 1, entry 5).

Table 1
Initial experiments for the copper-catalyzed synthesis of 3,5-diphenyl-1,2,4-triazole (**2a**) from benzamidine hydrochloride (**1a**)[a]



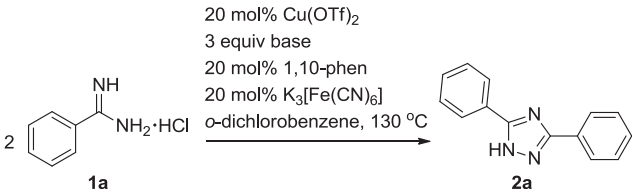
1a **2a**

Entry	Catalyst	Base	Solvent	*T* (°C)	Time (h)	Yield (%)
1[b]	CuBr	K_2CO_3	DMF	110	20	17
2	CuBr	K_2CO_3	DMF	130	24	24
3	CuBr	K_2CO_3	*o*-Dichlorobenzene	130	24	27
4	$Cu(OTf)_2$	K_2CO_3	*o*-Dichlorobenzene	130	24	53
5	$Cu(OTf)_2$	$NaHCO_3$	*o*-Dichlorobenzene	130	24	50

[a] All reactions were performed using 1 mmol of **1a** in 3 mL solvent in a sealed vial. The temperatures given refer to oil bath temperatures.
[b] The reaction was performed in the absence of 1,10-phenanthroline.

We assumed that the yield of the intramolecular oxidative coupling could be improved by running the reaction with a more suitable oxidant. J. D. Bower and G. R. Ramage have reported that the oxidative ring closure of 2-(2-aminoethyl)pyridine to 1,7a-diazaindene via intramolecular oxidative *N*,*N*-coupling can be achieved by using an aqueous alkaline solution of $K_3[Fe(CN)_6]$ as the oxidant.[24] When benzamidine hydrochloride (**1a**) was reacted with 20 mol % $Cu(OTf)_2$ as the catalyst, 3 equiv $NaHCO_3$ as a base, 20 mol % 1,10-phenanthroline as an additive and 20 mol % $K_3[Fe(CN)_6]$ as the oxidant in *o*-dichlorobenzene at 130 °C for 44 h under air the desired 3,5-diphenyl-1,2,4-triazole (**2a**) was obtained in 59% (Table 2, entry 1). The yield of **2a** was further increased to 63% by shortening the reaction time to 24 h (Table 2, entry 2). The yield failed to improve with K_2CO_3 as the base (Table 2, entry 3). It

Table 2
Optimization of the copper-catalyzed synthesis of **2a** from **1a** and control experiments[a]



Entry	Catalyst	Base	Additive	Atmosphere	Time (h)	Yield (%)
1	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	Air[a]	44	59
2	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	Air[a]	24	63
3	$Cu(OTf)_2$	K_2CO_3	1,10-Phen	Air[a]	24	50
4	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	Air[b]	24	23
5	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	O_2[b]	24	23
6	—	$NaHCO_3$	1,10-Phen	Air[a]	24	5
7	$Cu(OTf)_2$	—	1,10-Phen	Air[a]	24	—
8	$Cu(OTf)_2$	$NaHCO_3$	—	Air[a]	24	37
9	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	Ar[a]	24	41

[a] The reactions were performed with 1 mmol of **1a** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.
[b] The reactions were performed with 1 mmol of **1a** in 3 mL *o*-dichlorobenzene in a round-bottomed flask equipped with a reflux condenser.

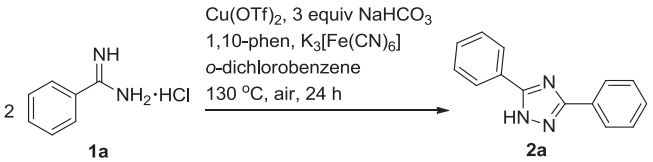
was demonstrated that the reaction could also be run in an open round-bottomed flask; however, the yield of **2a** dropped to 23% (Table 2, entries 4 and 5).

Then, some control experiments were performed. For this purpose, the model reaction was run in the absence of a) a copper source, b) any base, c) 1,10-phenanthroline and d) aerial oxygen. These experiments clearly established that the reaction cannot be run successfully in the absence of a copper source or in the absence of a base. Without a copper source, **2a** was isolated in only 5% (Table 2, entry 6). When the reaction was run without a base, not even a trace of **2a** could be detected (Table 2, entry 7). Interestingly, the reaction takes place in the absence of an additive (Table 2, entry 8) or in the absence of aerial oxygen (Table 2, entry 9). However, in both cases the yields of **2a** were considerably lower than under the conditions given in Table 2, entry 2.

In the next set of experiments the influence of different amounts of $Cu(OTf)_2$, 1,10-phenanthroline and $K_3[Fe(CN)_6]$ on the outcome of the model reaction was studied. With 20 mol % $Cu(OTf)_2$ and 20 mol % $K_3[Fe(CN)_6]$, the amount of 1,10-phenanthroline was gradually reduced from 20 mol % to 15 mol % and 10 mol %. Since the yields of **2a** dropped from 63% to 52% and 38%, respectively (Table 3, entries 1–3) all further experiments were performed with 20 mol % 1,10-phenanthroline. Remarkably, a reduction of the amount of $Cu(OTf)_2$ from 20 to 15 mol % had only little influence on the outcome of the model reaction; the yields of **2a** were nearly identical (Table 3, entry 4). However, neither an increase of the amount of $K_3[Fe(CN)_6]$ to 40 mol % nor a decrease to 15 mol % had a positive effect on the yield of **2a** (Table 3, entries 5 and 6). More significantly, the amount of $Cu(OTf)_2$ could be lowered from 15 to 10 and 5 mol %, respectively, without a drastic loss in yield (Table 3, entries 7 and 8): with only 5 mol % $Cu(OTf)_2$, the yield of 3,5-diphenyl-1,2,4-triazole (**2a**) still amounted to 52% (Table 3, entry 8). Gratifyingly, the yield of **2a** could be improved to 60%, when the amount of $K_3[Fe(CN)_6]$ was increased to 30 mol % (Table 3, entry 9). As a result of these experiments, all further reactions were run with 5 mol % of a copper catalyst, 3 equiv of a base, 20 mol % of an additive and 30 mol % of $K_3[Fe(CN)_6]$ in *o*-dichlorobenzene at 130 °C for 24 h.

The experiments performed so far revealed that the copper catalyst has a decisive influence on the successful formation of **2a**. This is why the influence of different copper sources on the outcome of the reaction was studied in more detail. For this purpose,

Table 3
Influence of the amounts of $Cu(OTf)_2$, 1,10-phenanthroline and $K_3[Fe(CN)_6]$ on the yields of **2a**[a]

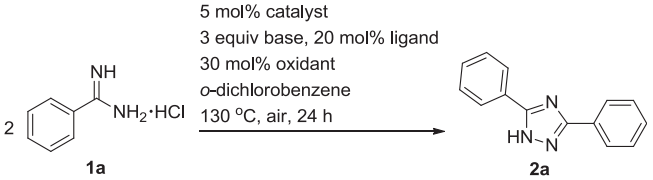


Entry	$Cu(OTf)_2$ (mol %)	1,10-Phen (mol %)	$K_3[Fe(CN)_6]$ (mol %)	Yield (%)
1	20	20	20	63
2	20	15	20	52
3	20	10	20	38
4	15	20	20	62
5	15	20	40	55
6	15	20	15	48
7	10	20	20	57
8	5	20	20	52
9	5	20	30	60

[a] The reactions were performed with 1 mmol of **1a** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.

the reaction was performed with a number of Cu(II)- and Cu(I) salts as well as with elemental copper under the conditions of Table 3, entry 9 (Table 4). It was found that the reaction can not only be run with other Cu(II) salts, such as $Cu(OAc)_2$, $CuCl_2$ and $CuSO_4$ (Table 4, entries 1–3), but also with Cu(I) salts like CuI, CuBr and CuCN (Table 4, entries 4–6). Even with elemental copper the formation of **2a** was achieved (Table 4, entry 7). However, with none of these catalysts the yield exceeds the yield observed with $Cu(OTf)_2$. In summary, the experiments clearly demonstrated that $Cu(OTf)_2$ is the most suitable catalyst for the conversion of **1a** into **2a**. Next, the influence of a number of bases, including Cs_2CO_3, K_3PO_4 and NaOEt,

Table 4
Influence of different copper sources, bases, additives and oxidants on the synthesis of **2a** from **1a**[a]



Entry	Catalyst	Base	Additive	Oxidant	Yield (%)
1	$Cu(OAc)_2$	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	49
2	$CuCl_2$	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	48
3	$CuSO_4$	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	39
4	CuI	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	50
5	CuBr	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	53
6	CuCN	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	36
7	Cu	$NaHCO_3$	1,10-Phen	$K_3[Fe(CN)_6]$	41
8	$Cu(OTf)_2$	Cs_2CO_3	1,10-Phen	$K_3[Fe(CN)_6]$	5
9	$Cu(OTf)_2$	K_3PO_4	1,10-Phen	$K_3[Fe(CN)_6]$	13
10	$Cu(OTf)_2$	NaOEt	1,10-Phen	$K_3[Fe(CN)_6]$	14
11	$Cu(OTf)_2$	NaOH	1,10-Phen	$K_3[Fe(CN)_6]$	34
12	$Cu(OTf)_2$	DBU	1,10-Phen	$K_3[Fe(CN)_6]$	—
13	$Cu(OTf)_2$	$NaHCO_3$	Pivalic acid	$K_3[Fe(CN)_6]$	53
14	$Cu(OTf)_2$	$NaHCO_3$	DMEDA	$K_3[Fe(CN)_6]$	50
15	$Cu(OTf)_2$	$NaHCO_3$	2-Aminopyridine	$K_3[Fe(CN)_6]$	54
16	$Cu(OTf)_2$	$NaHCO_3$	8-Hydroxy quinoline	$K_3[Fe(CN)_6]$	26
17	$Cu(OTf)_2$	$NaHCO_3$	L-Proline	$K_3[Fe(CN)_6]$	12
18	$Cu(OTf)_2$	$NaHCO_3$	Picolinic acid	$K_3[Fe(CN)_6]$	59
19	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	Ag_2CO_3	53
20	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	$K_2S_2O_8$	33
21	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	$PhI(OAc)_2$	31
22	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	TEMPO	23
23	$Cu(OTf)_2$	$NaHCO_3$	1,10-Phen	$FeCl_3$	13

[a] The reactions were performed with 1 mmol of **1a** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.

Please cite this article in press as: Sudheendran, K.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.01.019

NaOH and DBU was studied (Table 4, entries 8–12). Surprisingly, none of those was suitable for the transformation of **1a** into **2a**.

Even if the model reaction could be performed in the absence of any additive, it was clear from the experiments with 1,10-phenanthroline that the yield of **2a** can be improved significantly by using an additive. This is why the influence of several other additives on the outcome of the transformation was investigated. It was shown that the reaction can be conducted in the presence of a number of additives, including pivalic acid, DMEDA, 2-aminopyridine, 8-hydroxy quinoline, L-proline and picolinic acid (Table 4, entries 13–18). With pivalic acid, DMEDA and 2-aminopyridine the yields were in the range between 50 and 54%. Picolinic acid proved to be a particularly valuable alternative to 1,10-phenanthroline, since the yield observed with this additive nearly matches the yield obtained with 1,10-phenanthroline (Table 4, entry 18).

Finally, the influence of the oxidant on the domino reaction of **1a** was briefly examined. When $K_3[Fe(CN)_6]$ was replaced by Ag_2CO_3, the yield dropped to 53% and there was a further decrease to 33% and 31%, when $K_2S_2O_8$ and $PhI(OAc)_2$, respectively, were used as oxidants (Table 4, entries 19–21). In the case of TEMPO, the yield obtained was 23% (Table 4, entry 22). With $FeCl_3$ the yield decreased significantly to 13% (Table 4, entry 23).

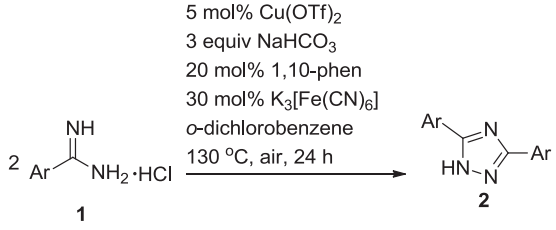
The optimization of the model reaction of **1a** to **2a** with regard to the copper source, the base, the additive, the oxidant, the solvent and the reaction conditions clearly demonstrated that the highest yield of **2a** was obtained when 1 equiv of **1a** was reacted in the presence of 5 mol % $Cu(OTf)_2$, 3 equiv $NaHCO_3$, 20 mol % 1,10-phenanthroline and 30 mol % $K_3[Fe(CN)_6]$ in *o*-dichlorobenzene at 130 °C under air for 24 h (Table 3, entry 9).

With the optimized conditions in hand, the substrate scope of the copper-catalyzed domino reaction was evaluated. It could be demonstrated that in addition to **1a**, numerous substituted amidine hydrochlorides **1b**–**l** carrying different substituents on the phenyl ring could be employed as substrates to produce the corresponding substituted 3,5-diaryl-1,2,4-triazoles **2b**–**l** with yields ranging from 41 to 68% as the sole products (Table 5, entries 2–12). Apart from the phenyl compounds **1a**–**l** the reaction could also be performed with the naphthyl derivative **1m** as the substrate (Table 5, entry 13). Remarkably, the substituents on the phenyl ring of the amidine exert a strong influence on the triazole formation. It was found that +I- or +M substituents in *para*-position have a positive influence on the yields. As an example, the *p*-methoxy derivative **1e** delivered the triazole **2e** in 68% yield while with the *m*-methoxy derivative **1d** the yield of the corresponding triazole **2d** didn't exceed 54% (Table 5, entries 4 and 5). It should be mentioned that aliphatic amidines, such as acetamidine hydrochloride and cyclopropaneamidine hydrochloride, did not react under the reaction conditions reported in Table 3, entry 9.

Some of the amidine hydrochlorides **1a**–**c**,**i**,**k**,**l** employed in this study are commercially available, some others **1d**–**h**,**j**,**m** had to be synthesized. Amidine hydrochlorides **1d**–**h**,**j**,**m** were prepared by reaction of the corresponding imidate hydrochlorides **4d**–**h**,**j**,**m** with ammonia in methanol with yields ranging between 67 and 91% (Scheme 1).[25a] The required imidate hydrochlorides **4b**–**h**,**j**,**m** could be obtained by treatment of the corresponding nitriles **3b**–**h**,**j**,**m** with ethanol and acetyl chloride.[25b] Using this method the imidate hydrochlorides **4b**–**h**,**j**,**m** were obtained with yields between 73 and 95%.

The high-yielding and simple to perform access to imidates prompted us to consider developing a new method for the synthesis of 3,5-diaryl-1,2,4-triazoles **2**, that is, based on a domino reaction between two imidates and an ammonia source (Scheme 2). It was suggested that in the first step an imidate **A** would react with the ammonia source **B** to give the corresponding amidine **C** as an intermediate. Reaction of **C** with a second imidate **A** would

Table 5
Synthesis of 3,5-diaryl-1,2,4-triazoles **2a**–**m** from amidine hydrochlorides **1a**–**m**[a]



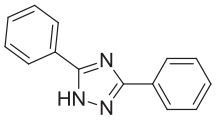
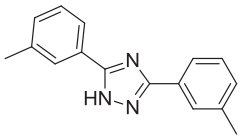
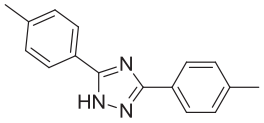
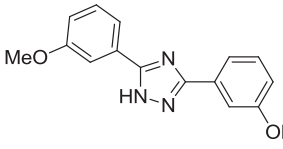
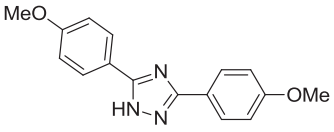
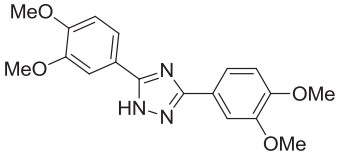
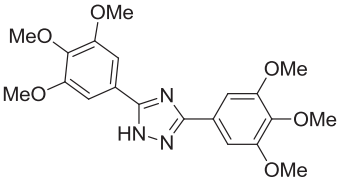
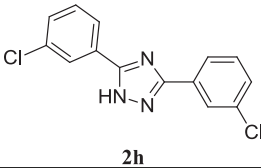
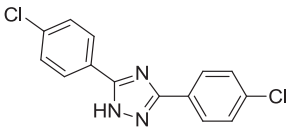
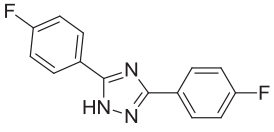
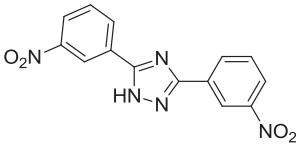
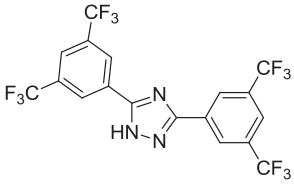
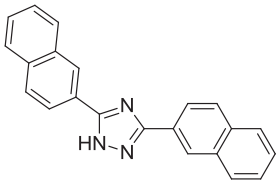
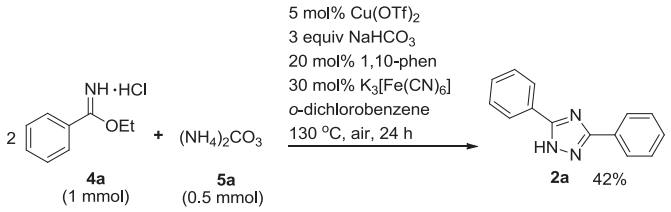
Entry	Product	Yield (%)
1	 **2a**	60
2	 **2b**	54
3	 **2c**	58
4	 **2d**	54
5	 **2e**	68
6	 **2f**	67
7	 **2g**	67
8	 **2h**	48

Table 5 (*continued*)

Entry	Product	Yield (%)
9	 **2i**	53
10	 **2j**	55
11	 **2k**	41
12	 **2l**	41
13	 **2m**	52

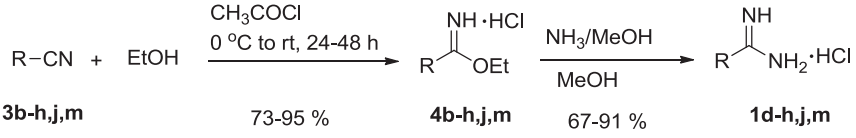
[a] The reactions were performed with 1 mmol of **1** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.

amidine hydrochlorides **1a**–**m**, i.e., with 5 mol % $Cu(OTf)_2$, 3 equiv $NaHCO_3$, 20 mol % 1,10-phenanthroline and 30 mol % $K_3[Fe(CN)_6]$ in *o*-dichlorobenzene at 130 °C under air for 24 h. Gratifyingly, 3,5-diphenyl-1,2,4-triazole (**2a**) was formed with 42% yield as the sole product under these conditions (Scheme 3).

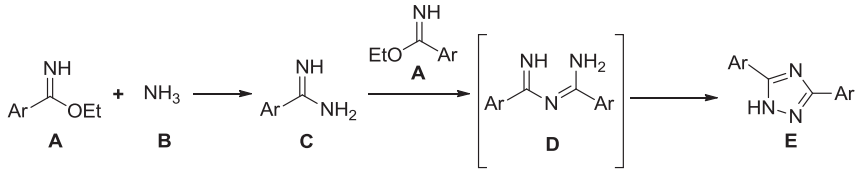


Scheme 3. Initial experiment for the copper-catalyzed synthesis of **2a** from two ethyl benzimidate hydrochloride (**4a**) and ammonium carbonate (**5a**).

This result clearly demonstrated that the triazole formation can also be achieved by using two imidates and an ammonia source as the substrates. To increase the yield of the triazole, a number of experiments were performed (Table 6). First, the influence of the ratio of ethyl benzimidate hydrochloride (**4a**) and ammonium carbonate (**5a**) was studied. It was found that the yield of **2a** could be raised from 42 to 52% when the molar ratio of **4a** and **5a** was changed from 2:1 to 1:1 (Table 6, entry 1). A further increase of the amount of **5a** didn't pay off (Table 6, entry 2). However, the yield of **2a** could be improved to 60% when the amount of $Cu(OTf)_2$ was doubled from 5 mol % to 10 mol % (Table 6, entry 3). Finally, we focused on the role of different ammonia sources. For this purpose, the model reaction was run with several ammonium salts (Table 6, entries 4–7). It was found that **2a** was formed with ammonium carbamate (**5b**), ammonium acetate (**5c**), ammonium formate (**5d**) and ammonium chloride (**5e**), but in all cases the yields were inferior compared to ammonium carbonate (**5a**). To sum up, the highest yield of **2a** was obtained when 1 equiv of ethyl benzimidate hydrochloride (**4a**) and 1 equiv of ammonium carbonate (**5a**) were reacted in the presence of 10 mol % $Cu(OTf)_2$, 3 equiv $NaHCO_3$, 20 mol % 1,10-phenanthroline and 30 mol % $K_3[Fe(CN)_6]$ in *o*-dichlorobenzene at 130 °C under air for 24 h.



Scheme 1. Synthesis of imidate hydrochlorides **4b**–**h**,**j**,**m** and amidine hydrochlorides **1d**–**h**,**j**,**m** from nitriles **3b**–**h**,**j**,**m**.[25]



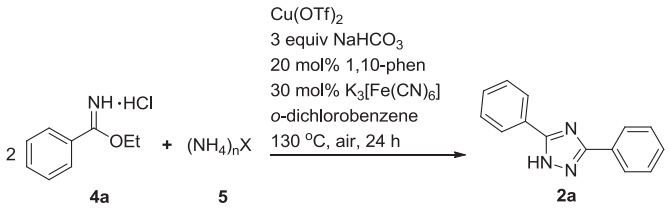
Scheme 2. Proposed synthesis of 3,5-diaryl-1,2,4-triazoles from imidates **A** and an ammonia source **B**.

result in the formation of an 2,4-diaryl-1,3,5-triazapenta-1,3-diene **D**, which could undergo oxidative ring closure to the triazole **E**. However, it is also possible that two molecules of **C** react under formation of **D** and ammonia.

To test the feasibility of this approach, 1 mmol of ethyl benzimidate hydrochloride (**4a**) and 0.5 mmol of ammonium carbonate (**5a**) were reacted under the conditions that had proven successful for the preparation of 3,5-diaryl-1,2,4-triazoles **2a**–**m** from

After optimizing the model reaction, we focused on the substrate scope of the new triazole synthesis. For this purpose, a number of imidate hydrochlorides **4a**–**h**,**j** carrying different substituents on the phenyl ring were synthesized from the corresponding nitriles and reacted with ammonium carbonate (**5a**) under the conditions given in Table 6, entry 3. It was found that a number of substituents, such as methyl-, methoxy-, chloro- and fluoro, were tolerated (Table 7, entries 2–9). The yields of the

Table 6
Optimization of the synthesis of **2a** from ethyl benzimidate hydrochloride (**4a**) and different ammonium salts **5**[a]

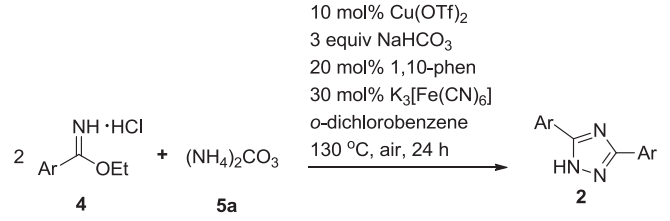


4a 5 2a

Entry	Ammonia source	Ammonia source (mmol)	$Cu(OTf)_2$ (mol %)	Yield (%)
1	$(NH_4)_2CO_3$ (**5a**)	1	5	52
2	$(NH_4)_2CO_3$ (**5a**)	2	5	53
3	$(NH_4)_2CO_3$ (**5a**)	1	10	60
4	$NH_2CO_2NH_4$ (**5b**)	2	10	49
5	$CH_3CO_2NH_4$ (**5c**)	2	10	29
6	HCO_2NH_4 (**5d**)	2	10	45
7	NH_4Cl (**5e**)	2	10	46

[a] The reactions were performed with 1 mmol of **4a** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.

Table 7
Copper-catalyzed synthesis of 3,5-diaryl-1,2,4-triazoles **2a**–**h**,**j**,**m** from imidate hydrochlorides **4a**–**h**,**j**,**m** and ammonium carbonate (**5a**)[a]



4 5a 2

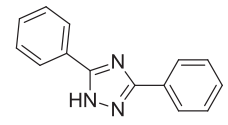
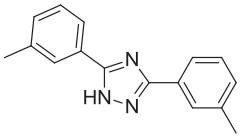
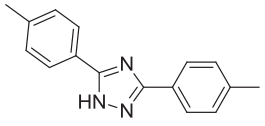
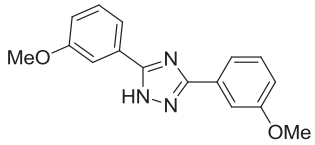
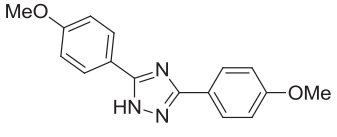
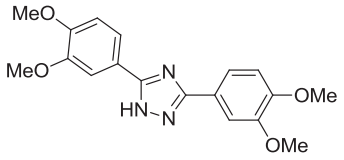
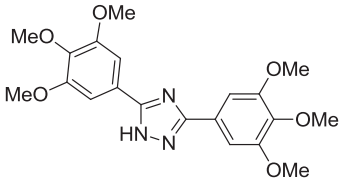
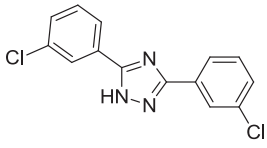
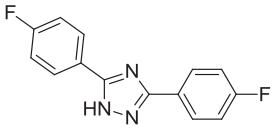
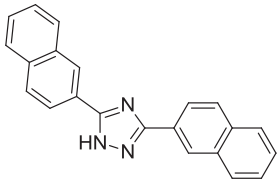
Entry	Product	Yield (%)
1	 **2a**	60
2	 **2b**	60
3	 **2c**	62
4	 **2d**	57
5	 **2e**	61

Table 7 (*continued*)

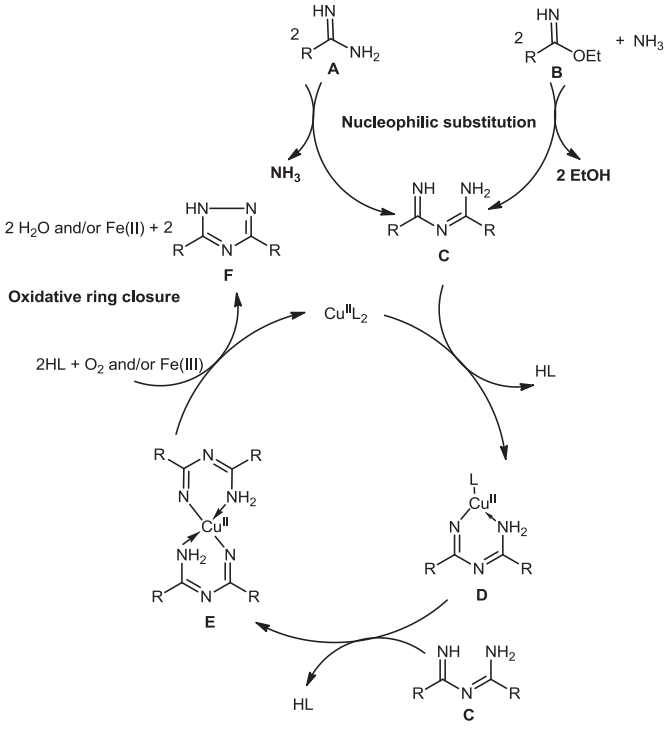
Entry	Product	Yield (%)
6	 **2f**	64
7	 **2g**	62
8	 **2h**	40
9	 **2j**	56
10	 **2m**	54

[a] The reactions were performed with 1 mmol of **4** in 3 mL *o*-dichlorobenzene in a sealed vial. The temperature given refers to oil bath temperature.

corresponding 3,5-diaryl-1,2,4-triazoles **2** were in the range between 40 and 64%. In addition to the phenyl compounds **4a**–**h**,**j** the reaction could also be performed with the naphthyl derivative **4m** (Table 7, entry 10).

With respect to the mechanism of the two methods presented here[23c,26] it is assumed that **C** is a common intermediate (Scheme 4). It can either be formed by reaction of two amidines **A** or by reaction of two imidates **B** and ammonia. Coordination of **C**[23c,26c,g,h] with a Cu^{2+} ion delivers **D**,[26g] which reacts with a second molecule **C** to furnish the copper complex **E**.[26a,c,f] Oxidative cyclization using O_2 as the oxidant gives two triazoles **F** and H_2O. Alternatively, $K_3[Fe(CN)_6]$ can act as the oxidant for the *N*,*N*-bond formation. In accordance with earlier reports[4a,23c,26] it is assumed that the *N*,*N* bond formation is initiated by a copper-catalyzed one electron oxidation to form the corresponding radical, which undergoes *N*,*N* coupling. After the oxidative ring closure a second copper-catalyzed one electron oxidation occurs, which delivers the triazole.

The structures of all triazoles **2** were elucidated by mass spectrometry and NMR spectroscopy. In case of the already known compounds **2a**–**e**,**i**,**k** the structural confirmation was also done by comparison with the literature data. Full assignment of the ^1H and ^{13}C chemical shifts of the unknown compounds **2f**–**h**,**j**,**l**,**m** was achieved by evaluating their gCOSY, gHSQC and gHMBC spectra. As an example, four singlets in the ^1H NMR spectrum represent the



Scheme 4. Plausible mechanism for the $Cu(OTf)_2$-catalyzed oxidative cyclization for the synthesis of 1,2,4-triazoles.

symmetrical compound **2g**, i.e., δ=14.37 (NH), δ=7.39 (2′-H/6′-H), δ=3.89 (1″-H and 3″-H), δ=3.73 ppm (2″-H). The ^3J-gHMBC correlation between 2′-H/6′-H with C-5/C-3 provides evidence for the connection of both aromatic ring systems to the triazole moiety. The chemical shift of C-4′ at δ=138.7 ppm was unambiguous by the strong ^3J-gHMBC correlation between C-4′ and 2′-H/6′-H. The remaining quaternary carbons C-1′ (δ=124.9 ppm) and C-3′/C-5′ (δ=153.2 ppm) were assigned on the basis of weak ^2J–^{1}H–^{13}C long range couplings with the adjacent aromatic protons 2′-H/6′-H as shown in Fig. 2.

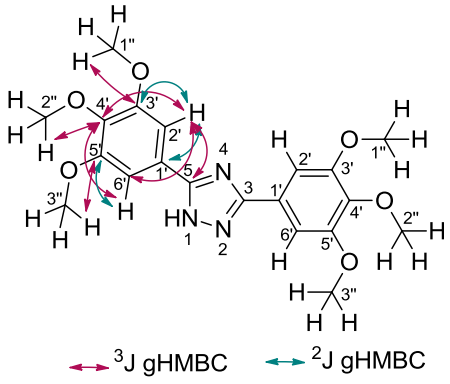


Fig. 2. Important gHMBC correlations of compound **2g**.

Unambiguous evidence for the structure of the **2a** was produced by X-ray structure analysis. For this purpose the crystals of **2a** were studied by X-ray crystal structure analysis (see Supplementary data).[27]

3. Conclusion

In summary, two easy to perform and efficient methods for the synthesis of 3,5-diaryl-1,2,4-triazoles **2** in a single preparative step have been developed. The first approach is based on a copper-catalyzed domino intermolecular nucleophilic substitution/oxidative ring closure between two molecules of an amidine hydrochloride in a single pot. Here two bonds are formed in one-step. Best results were achieved when 1 equiv of the amidine hydrochloride **1** was reacted in the presence of 5 mol % $Cu(OTf)_2$, 3 equiv $NaHCO_3$, 20 mol % 1,10-phenanthroline and 30 mol % $K_3[Fe(CN)_6]$ in 3 mL *o*-dichlorobenzene at 130 °C under air for 24 h. Using this protocol, the 3,5-diaryl-1,2,4-triazoles **2** were obtained exclusively with yields ranging from 41 to 68%. The 3,5-diaryl-1,2,4-triazoles can also be obtained in one pot by a copper-catalyzed domino reaction between two molecules of an imidate hydrochloride **4** and an ammonium source **5**. The reaction of 1 equiv of an imidate hydrochloride **4** and 1 equiv of ammonium carbonate (**5a**) in the presence of 10 mol % $Cu(OTf)_2$, 3 equiv $NaHCO_3$, 20 mol % 1,10-phenanthroline and 30 mol % $K_3[Fe(CN)_6]$ in 3 mL *o*-dichlorobenzene at 130 °C under air for 24 h allows for the exclusive formation of the 3,5-diaryl-1,2,4-triazoles **2** with yields up to 64%. Using this method, two C,N bonds and one *N*,*N* bond are formed in a single synthetic step.

4. Experimental section

4.1. General

All chemicals were purchased from commercial suppliers. Solvents used in extraction and purification were distilled prior to use. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F245 aluminium plates (Merck) with visualization under UV light and by immersion in ethanolic vanillin solution followed by heating. Flash chromatography was carried out on silica gel MN 60, 0.04–0.053 mm (Macherey & Nagel). Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were measured on a Perkin–Elmer Spectrum One (FT-IR spectrometer). ^{1}H and ^{13}C NMR spectra were recorded at 300 (75) MHz on a Varian Unity Inova instrument using $CDCl_3$, CD_3OD and DMSO-d_6 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.00 ($CDCl_3$), 3.31/49.10 (CD_3OD) and 2.50/39.50 (DMSO-d_6) relative to TMS as internal standard. HSQC-, HMBC- and COSY-spectra were recorded on an NMR spectrometer at 300 MHz. Coupling constants *J* [Hertz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Low resolution electron spray ionisation mass spectra (ESI-LRMS) and exact electron spray ionisation mass spectra (HRMS) were recorded on a Bruker Daltonics (micro TOFQ) instrument. The intensities are reported as percentages relative to the base peak (*I*=100%).

4.2. General procedure I for the synthesis of imidate hydrochlorides 4b–h,j,m[25b]

The benzonitrile **3** (15 mmol) was dissolved in ethanol (180 mmol) and cooled to 0 °C. Acetyl chloride (120 mmol) was added drop wise to the reaction mixture. The reaction mixture was stirred at room temperature for 24–48 h. Then, the reaction mixture was evaporated in vacuo. The crude product was washed with diethyl ether (3×20 mL) and petroleum ether (3×20 mL). Recrystallization from ethanol afforded the imidate hydrochloride **4**.

*4.2.1. Ethyl-3-methylbenzimidate hydrochloride (**4b**).* Compound **3b** (1.76 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-3-methylbenzimidate hydrochloride (**4b**) as a white solid in 93% yield (2.80 g, 14.0 mmol): mp 131–133 °C; R_f 0.63 (EtOAc/CH_3OH=4:1); IR (ATR) $\tilde{\nu}$ 2997, 2777,

1633, 1591, 1461, 1436, 1381, 1356, 1121, 1072, 875, 857, 729, 670 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 248 nm (4.02); ^1H NMR (300 MHz, CD_3OD) δ 1.62 (t, ^3J=6.9 Hz, 3H, 4′-H), 2.47 (s, 1″-H), 4.67 (q, ^3J=6.9 Hz, 2H, 3′-H), 7.53 (t-like, ^3J (4-H, 5-H), (5-H, 6-H)=7.8 Hz, 1H, 5-H), 7.65 (d, ^3J (4-H, 5-H)=7.8 Hz, 1H, 4-H), 7.88 (overlapped, 2H, 2-H and 6-H); ^{13}C NMR (75 MHz, CD_3OD) δ 13.9 (C-4′), 21.2 (C-1″), 71.3 (C-3′), 127.1 (C-1), 127.2 (C-2), 130.3 (C-6), 130.4 (C-5), 137.6 (C-4), 141.0 (C-3), 174.5 (C-1′); MS (ESI) *m*/*z* (%) 186 (10) $[M-HCl+Na]^+$, 164 (55) $[M-HCl+1]^+$, 136 (100), 119 (8); HRMS (ESI) calcd for $C_{10}H_{14}NO$ 164.1075, found 164.1064.

*4.2.2. Ethyl-4-methylbenzimidate hydrochloride (**4c**).*[28c,31] Compound **3c** (1.76 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-4-methylbenzimidate hydrochloride (**4c**) as a white solid in 95% yield (2.85 g, 14.0 mmol).

*4.2.3. Ethyl-3-methoxybenzimidate hydrochloride (**4d**).*[28b,31] Compound **3d** (2.00 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-3-methoxybenzimidate hydrochloride (**4d**) as a white solid in 82% yield (2.65 g, 12.3 mmol).

*4.2.4. Ethyl-4-methoxybenzimidate hydrochloride (**4e**).*[28b,31] Compound **3e** (2.00 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-4-methoxybenzimidate hydrochloride (**4e**) as a white solid in 78% yield (2.52 g, 11.7 mmol).

*4.2.5. Ethyl-3,4-dimethoxybenzimidate hydrochloride (**4f**).*[28a,31] Compound **3f** (2.45 g, 15 mmol) was reacted under the conditions of general procedure I for 48 h to deliver ethyl-3,4-dimethoxybenzimidate hydrochloride (**4f**) as a white solid in 83% yield (3.06 g, 12.5 mmol).

*4.2.6. Ethyl-3,4,5-trimethoxybenzimidate hydrochloride (**4g**).* Compound **3g** (2.9 g, 15 mmol) was reacted under the conditions of general procedure I for 48 h to deliver ethyl-3,4,5-trimethoxybenzimidate hydrochloride (**4g**) as a white solid in 79% yield (3.27 g, 11.9 mmol): mp 165–167 °C; R_f 0.58 (EtOAc/CH_3OH=4:1); IR (ATR) $\tilde{\nu}$ 2839, 1624, 1587, 1469, 1427, 1357, 1315, 1243, 1121, 1071, 998, 856, 735, 704 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 217 (4.43), 295 nm (3.97); ^1H NMR (300 MHz, CD_3OD) δ 1.63 (t, ^3J (3′-H, 4′-H)=6.9 Hz, 3H, 4′-H), 3.88 (s, 3H, 2″-H), 3.93 (s, 6H, 1″-H and 3′-H), 4.66 (q, ^3J (3′-H, 4′-H)=6.9 Hz, 2H, 3′-H), 7.39 (s, 2H, 2-H and 6-H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.0 (C-4′), 57.2 (C-1″ and C-3″), 61.5 (C-2″), 71.3 (C-3′), 108.0 (C-2 and C-6), 121.6 (C-1), 146.0 (C-4), 155.0 (C-3 and C-5), 173.6 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 239 (20) $[M-HCl]^+$, 211 (10), 193 (24), 178 (12), 150 (4); HRMS (EI, M^+) calcd for $C_{12}H_{17}NO_4$ 239.1158, found 239.1161.

*4.2.7. Ethyl-3-chlorobenzimidate hydrochloride (**4h**).* Compound **3h** (2.06 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-3-chlorobenzimidate hydrochloride (**4h**) as a white solid in 73% yield (2.41 g, 11.0 mmol): mp 107–108 °C; R_f 0.63 (EtOAc/CH_3OH=4:1); IR (ATR) $\tilde{\nu}$ 1720, 1623, 1569, 1426, 1382, 1365, 1291, 1279, 1254, 1122, 1072, 1012, 747, 674 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 204 (4.73), 276 nm (2.92); ^1H NMR (300 MHz, CD_3OD) δ 1.63 (t, ^3J (3′-H, 4′-H)=7.2 Hz, 3H, CH_3), 4.69 (q, ^3J=7.2 Hz, 2H, CH_2), 7.66 (t, ^3J (4-H, 5-H), (5-H, 6-H)=7.8 Hz, 1H, 5-H), 7.79–7.88 (m, 1H, 4-H), 8.01 (dd, ^3J (5-H, 6-H)=7.8 Hz, 1H, 6-H), 8.08 (ddd, ^4J (2-H, 4-H), ^4J (2-H, 6-H)=1.8 Hz, 1H, 2-H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.0 (CH_3), 71.9 (CH_2), 128.6 (C-6), 129.4 (C-1), 130.0 (C-2), 132.3 (C-5), 136.5 (C-3), 136.6 (C-4), 173.4 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 182 (2) $[M-HCl+1]^+$, 155 (9), 139 (25), 111 (8), 75 (4); HRMS (EI, M^+) calcd for $C_9H_{10}ClNO$ 183.0451, found 183.0464.

*4.2.8. Ethyl-4-fluorobenzimidate hydrochloride (**4j**).*[28b,31] Compound **3j** (1.82 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-4-fluorobenzimidate hydrochloride (**4j**) as a white solid in 92% yield (2.81 g, 13.8 mmol).

*4.2.9. Ethyl-2-naphthimidate hydrochloride (**4m**).* Compound **3m** (2.30 g, 15 mmol) was reacted under the conditions of general procedure I for 24 h to deliver ethyl-2-naphthimidate hydrochloride (**4m**) as a white solid in 85% yield (3.54 g, 12.7 mmol): mp 193–195 °C; R_f 0.64 (EtOAc/CH_3OH=4:1); IR (ATR) $\tilde{\nu}$ 2979, 2807, 1616, 1599, 1482, 1439, 1384, 1342, 1281, 1119, 1068, 1001, 924, 846, 816, 770, 752, 718 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 288 (3.37), 250 (4.06), 241 nm (4.07); ^1H NMR (300 MHz, CD_3OD) δ 1.66 (t, ^3J (3′-H, 4′-H)=7.2 Hz, 3H, CH_3), 4.71 (q, ^3J (3′-H, 4′-H)=7.2 Hz, 2H, CH_2), 7.64–7.77 (m, 2H, 6-H and 7-H), 7.98 (overlapped, 2H, 3-H and 5-H), 8.10 (overlapped, 2H, 4-H and 8-H), 8.69 (d-like, ^4J (1-H, 3-H)= 1.5 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.05 (CH_3), 71.46 (CH_2), 124.19 (C-3), 124.22 (C-2), 129.05 (C-7), 129.14 (C-5), 130.57 (C-4), 130.93 (C-8), 131.35 (C-6), 132.84 (C-1), 133.61 (C-8a), 137.90 (C-4a), 174.38 (C-1′); MS (ESI) *m*/*z* (%) 222 (10) $[M-HCl+Na]^+$, 200 (73) $[M-HCl+1]^+$, 172 (100), 129 (42); HRMS (ESI) calcd for $C_{13}H_{14}NO$ 200.1075, found 200.1050.

4.3. General procedure II for the synthesis of amidine hydrochlorides 1d-h,j,m[25a]

The ethyl imidate hydrochloride **4** (10 mmol) was dissolved in ethanol (10 mL) and placed in a round-bottomed flask equipped with a magnetic stir bar. After sealing the flask with a rubber septum ammonia in methanol (10 mL) was added to the reaction mixture using a syringe. The reaction mixture was stirred at room temperature for 24 h. After evaporation in vacuo, the crude product was purified by flash column chromatography over silica gel (EtOAc/methanol=4:1) to afford the amidine hydrochloride **1**.

*4.3.1. 3-Methoxybenzenecarboximidamide hydrochloride (**1d**).*[29d,31] Compound **4d** (2.16 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 3-methoxybenzenecarboximidamide hydrochloride (**1d**) as a white solid in 74% yield (1.38 g, 7.4 mmol).

*4.3.2. 4-Methoxybenzenecarboximidamide hydrochloride (**1e**).*[29a,31] Compound **4e** (2.16 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 4-methoxybenzenecarboximidamide hydrochloride (**1e**) as a white solid in 67% yield (1.25 g, 6.7 mmol).

*4.3.3. 3,4-Dimethoxybenzenecarboximidamide hydrochloride (**1f**).*[29e,31] Compound **4f** (2.46 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 3,4-dimethoxybenzenecarboximidamide hydrochloride (**1f**) as a white solid in 91% yield (1.97 g, 9.1 mmol).

*4.3.4. 3,4,5-Trimethoxybenzenecarboximidamide hydrochloride (**1g**).*[29b,31] Compound **4g** (2.76 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 3,4,5-trimethoxybenzenecarboximidamide hydrochloride (**1g**) as a white solid in 78% yield (1.93 g, 7.8 mmol).

*4.3.5. 3-Chlorobenzenecarboximidamide hydrochloride (**1h**).* Compound **4h** (2.20 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 3-chlorobenzenecarboximidamide hydrochloride (**1h**) as a white solid in 69% yield (1.32 g, 6.9 mmol): mp 121–123 °C; R_f 0.45 (EtOAc/methanol=5:3); IR (ATR) $\tilde{\nu}$ 1656, 1525, 1466, 1088, 799, 713 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 203 (4.55), 231 (3.93), 280 nm (2.79); ^1H NMR (300 MHz, DMSO-d_6) δ 7.64 (t, ^3J (5-H, 6-H)=7.8 Hz, ^3J (4-H, 5-H)=8.1 Hz, 1H, 5-H), 7.78–7.85 (m, 2H, 4-H and 6-H), 7.97 (s, 1H, 2-H), 9.52 (br s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 126.9 (C-6), 128.0 (C-2), 130.0 (C-1), 130.9 (C-5), 133.5 (C-3), 133.6 (C-4), 164.6 (C-1′); MS (EI, 70 eV) *m*/*z* (%) 154 (28) $[M-HCl]^+$,

138 (31), 111 (5), 75 (6); HRMS (EI, M^+) calcd for $C_7H_7ClN_2$ 154.0298, found 154.0299.

*4.3.6. 4-Fluorobenzenecarboximidamide hydrochloride (**1j**).*[29c,31] Compound **4j** (2.04 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 4-fluorobenzenecarboximidamide hydrochloride (**1j**) as a white solid in 87% yield (1.52 g, 8.7 mmol).

*4.3.7. 2-Naphthimidamide hydrochloride (**1m**).* Compound **4m** (2.36 g, 10 mmol) was reacted under the conditions of general procedure II to deliver 2-naphthimidamide hydrochloride (**1m**) as a white solid in 86% yield (1.77 g, 8.6 mmol): mp 228–230 °C; R_f 0.37 (EtOAc/methanol=5:3); IR (ATR) $\tilde{\nu}$ 3256, 3094, 2734, 1670, 1651, 1632, 1521, 1496, 1282, 1081, 913, 764, 654, 619 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 331 (2.47), 283 (3.67), 240 (4.58), 207 nm (4.33); ^1H NMR (300 MHz, DMSO-d_6) δ 7.64–7.74 (m, 2H, 6-H and 7-H), 7.89 (dd, ^3J (3-H, 4-H)=8.7 Hz, ^4J (1-H, 3-H)=1.8 Hz, 1H, 3-H), 8.07 (ddd, ^3J (5-H, 6-H), (7-H, 8-H)=7.5 Hz, 2H, 5-H and 8-H), 8.13 (dd, ^3J (3-H, 4-H)=8.7 Hz, 1H, 4-H), 8.59 (d-like, ^4J (1-H, 3-H)=1.2 Hz, 1H, 1-H), 9.57 (br s, 4H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.6 (C-3), 125.2 (C-2), 127.5 (C-6), 127.8 (C-5), 128.7 (C-4), 129.0 (C-7), 129.1 (C-8), 129.6 (C-1), 131.7 (C-8a), 135.0 (C-4a), 165.8 (C-1′); MS (ESI) *m*/*z* (%) 171 (100) $[M-HCl+1]^+$, 154 (14) $[171-NH_2]^+$; HRMS (ESI) calcd for $C_{11}H_{11}N_2$ 171.0922, found 171.0915.

4.4. General procedure III for the $Cu(OTf)_2$-catalyzed dimerization of amidine hydrochlorides 1a–m

A dry 10 mL vial was equipped with a magnetic stir bar and charged with amidine hydrochloride **1** (1.0 mmol), $Cu(OTf)_2$ (18 mg, 0.05 mmol), $NaHCO_3$ (252 mg, 3.0 mmol), 1,10-phenanthroline (36 mg, 0.20 mmol), $K_3[Fe(CN)_6]$ (99 mg, 0.30 mmol) and sealed under air. Then, freshly distilled *o*-dichlorobenzene (3 mL) was added using a syringe and the reaction mixture was stirred at 130 °C for 24 h. After cooling to room temperature the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The crude product was subjected to flash column chromatography over silica gel to yield the product **2**.

*4.4.1. 3,5-Diphenyl-1H-1,2,4-triazole (**2a**).*[23b,31] Compound **1a** (157 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-diphenyl-1*H*-1,2,4-triazole (**2a**) as a white solid in 60% yield (66 mg, 0.30 mmol).

*4.4.2. 3,5-Bis(3-methylphenyl)-1H-1,2,4-triazole (**2b**).*[30c,31] Compound **1b** (171 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-methylphenyl)-1*H*-1,2,4-triazole (**2b**) as a white solid in 54% yield (67 mg, 0.27 mmol).

*4.4.3. 3,5-Bis(4-methylphenyl)-1H-1,2,4-triazole (**2c**).*[23c,31] Compound **1c** (171 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole (**2c**) as a white solid in 58% yield (72 mg, 0.29 mmol).

*4.4.4. 3,5-Bis(3-methoxyphenyl)-1H-1,2,4-triazole (**2d**).*[30a,31] Compound **1d** (187 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-methoxyphenyl)-1*H*-1,2,4-triazole (**2d**) as a white solid in 54% yield (76 mg, 0.27 mmol).

*4.4.5. 3,5-Bis(4-methoxyphenyl)-1H-1,2,4-triazole (**2e**).*[30a,31] Compound **1e** (187 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:2) afforded 3,5-bis(4-methoxyphenyl)-1*H*-1,2,4-triazole (**2e**) as a white solid in 68% yield (96 mg, 0.34 mmol).

*4.4.6. 3,5-Bis(3,4-dimethoxyphenyl)-1H-1,2,4-triazole (**2f**).* Compound **1f** (217 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=1:3) afforded 3,5-bis(3,4-dimethoxyphenyl)-1*H*-1,2,4-triazole (**2f**) as a white solid in 67% yield (114 mg, 0.34 mmol): mp 179–180 °C; R_f 0.08 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 1608, 1511, 1446, 1428, 1259, 1231, 1136, 1018, 884, 864, 761 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 215 (4.62), 219 (4.61), 265 (4.43), 294 nm (4.30); ^1H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 6H, 1″-H), 3.86 (s, 6H, 2″-H), 7.09 (d, ^3J (5′-H, 6′-H)=8.4 Hz, 2H, 5′-H), 7.65 (dd, ^3J (5′-H, 6′-H)=8.4 Hz, ^4J (2′-H, 6′-H)=1.8 Hz, 4H, 2′-H and 6′-H), 14.17 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.5 (C-1″and C-2″), 109.3 (C-6′), 111.8 (C-5′), 118.9 (C-2′), 123.3 (C-1′), 148.8 (C-4′), 149.9 (C-3′), 158.8 (C-3 and C-5); MS (ESI) *m*/*z* (%) 364.1 (100) $[M+Na]^+$; HRMS (ESI) calcd for $C_{18}H_{19}N_3NaO_4$ 364.1273, found 364.1267.

*4.4.7. 3,5-Bis(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (**2g**).* Compound **1g** (247 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=1:3) afforded 3,5-bis(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole (**2g**) as a white solid in 67% yield (134 mg, 0.33 mmol): mp 151–153 °C; R_f 0.09 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 1591, 1471, 1421, 1380, 1233, 1119, 999, 846, 757 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 224 (4.63), 278 nm (4.44); ^1H NMR (300 MHz, DMSO-d_6) δ 3.73 (s, 6H, 3″-H), 3.89 (s, 12H, 1″-H and 2″-H), 7.39 (s, 4H, 2′-H and 6′-H), 14.37 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.0 (C-1″ and C-3″), 60.1 (C-2″), 103.5 (C-2′ and C-6′), 124.9 (C-1′), 138.7 (C-4′), 153.2 (C-3′ and C-5′), 158.8 (C-3 and C-5); MS (ESI) *m*/*z* (%) 424.1 (100) $[M+Na]^+$; HRMS (ESI) calcd for $C_{20}H_{23}N_3NaO_6$ 424.1485, found 424.1461.

*4.4.8. 3,5-Bis(3-chlorophenyl)-1H-1,2,4-triazole (**2h**).* Compound **1h** (191 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-chlorophenyl)-1*H*-1,2,4-triazole (**2h**) as a white solid in 48% yield (70 mg, 0.24 mmol): mp 233–234 °C; R_f 0.55 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 1582, 1458, 1404, 1077, 1008, 998, 888, 859, 797, 788, 742, 678 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 210 (4.57), 237 (4.16), 258 nm (4.17); ^1H NMR (300 MHz, C_6D_6) δ 7.45–7.47 (m, 4H, 4′-H and 5′-H), 8.32–8.34 (m, 2H, 6′-H), 8.50 (s, 2H, 2′-H); ^{13}C NMR (75 MHz, C_6D_6) δ 125.6 (C-6′), 127.4 (C-2′), 132.8 (C-1′), 130.3 (C-4′), 131.4 (C-5′), 135.5 (C-3′), 159.2 (C-3 and C-5); MS (EI, 70 eV) *m*/*z* (%) 289 (12) $[M]^+$, 152 (6); HRMS (EI, M^+) calcd for $C_{14}H_9N_3Cl_2$ 289.0174, found 289.0156.

*4.4.9. 3,5-Bis(4-chlorophenyl)-1H-1,2,4-triazole (**2i**).*[30b,31] Compound **1i** (191 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(4-chlorophenyl)-1*H*-1,2,4-triazole (**2i**) as a white solid in 53% yield (77 mg, 0.27 mmol).

*4.4.10. 3,5-Bis(4-flouorophenyl)-1H-1,2,4-triazole (**2j**).* Compound **1j** (175 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(4-flouorophenyl)-1*H*-1,2,4-

triazole (**2j**) as a white solid in 55% yield (71 mg, 0.28 mmol): mp 257–259 °C; R_f 0.50 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 1606, 1500, 1421, 1220, 1158, 1000, 842, 814, 757 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 235 (4.31), 253 nm (4.30); ^1H NMR (300 MHz, DMSO-d_6) δ 7.36 (t, ^3J (2′-H, 3′-H) and ^3J (5′-H, 6′-H)=8.7 Hz, 4H, 3′-H and 5′-H), 8.09–8.13 (m, 4H, 2′-H and 6′-H), 14.55 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 115.9 (d, ^2J (C–F)=21.8 Hz, C-3′ and C-5′), 125.8 (C-1′), 128.3 (d, ^3J (C–F)=8.5 Hz, C-2′ and C-6′), 157.8 (C-3 and C-5), 162.9 (d, ^1J (C–F)=245.5 Hz, C-4′); MS (EI, 70 eV) *m*/*z* (%) 257 (63) $[M]^+$, 136 (29), 109 (8); HRMS (EI, M^+) calcd for $C_{14}H_9N_3F_2$ 257.0765, found 257.0748.

*4.4.11. 3,5-Bis(3-nitrophenyl)-1H-1,2,4-triazole (**2k**).*[23c,31] Compound **1k** (202 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-nitrophenyl)-1*H*-1,2,4-triazole (**2k**) as a white solid in 41% yield (63 mg, 0.20 mmol).

*4.4.12. 3,5-Bis[3,5-bis(trifluoromethyl)phenyl]-1H-1,2,4-triazole (**2l**).* Compound **1l** (293 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=9:1) afforded 3,5-bis[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazole (**2l**) as a white solid in 41% yield (101 mg, 0.20 mmol): mp 185–186 °C; R_f 0.72 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 1400, 1339, 1320, 1172, 1134, 1021, 904, 824, 714, 700, 680 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 203 (4.55), 206 (4.54), 259 nm (4.27); ^1H NMR (300 MHz, CD_3OD) δ 8.03 (s, 2H, 4′-H), 8.60 (s, 4H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, CD_3OD) δ 124.3 (m, ^3J (C–F)=6 Hz, C-4′), 124.7 (q, ^1J (C–F)=271 Hz, C-1″ and 2″), 127.7 (d, ^3J (C–F)=3 Hz, C-2′ and 6′), 132.7 (C-1′), 133.6 (q, ^2J (C–F)=33 Hz, C-3′ and 5′), 158.5 (C-3 and C-5); MS (EI, 70 eV) *m*/*z* (%) 493 (35) $[M]^+$, 474 (6) $[493-F]^+$, 254 (22); HRMS (EI, M^+) calcd for $C_{18}H_7N_3F_{12}$ 493.0448, found 493.0426.

*4.4.13. 3,5-Di(naphthalen-2-yl)-1H-1,2,4-triazole (**2m**).* Compound **1m** (207 mg, 1.0 mmol) was reacted under the conditions of general procedure III. Column chromatography over silica gel (petroleum ether/EtOAc=9:1) afforded 3,5-di(naphthalen-2-yl)-1*H*-1,2,4-triazole (**2m**) as a white solid in 52% yield (83 mg, 0.26 mmol): mp 221–222 °C; R_f 0.44 (petroleum ether/EtOAc=1:1); IR (ATR) $\tilde{\nu}$ 3181, 3050, 1557, 1508, 1494, 1393, 1269, 1106, 1006, 856, 817, 761, 732, 687 cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 333 (3.20), 290 (4.38), 250 (4.78), 248 (4.77), 243 (4.77), 231 (4.73), 229 nm (4.73); ^1H NMR (300 MHz, DMSO-d_6) δ 7.58–7.62 (m, 4H, 6′-H and 7′-H), 7.99 (ddd, ^3J (5′-H, 6′-H)=6.6 Hz, 2H, 5′-H), 8.07–8.12 (overlapped, 4H, 4′-H and 8′-H), 8.26 (dd, ^3J (3′-H, 4′-H)=8.7 Hz, ^4J (1′-H, 3′-H)=1.5 Hz, 2H, 3′-H), 8.71 (s, 2H, 1′-H), 14.74 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.6 (C-3′), 125.4 (C-1′ and C-2′), 126.8 (C-6′), 127.0 (C-7′), 127.8 (C-5′), 128.5 (C-8′), 128.6 (C-4′), 132.9 (C-8′a), 133.4 (C-4′a), 158.8 (C-3 and C-5); MS (ESI) *m*/*z* (%) 344 (46) $[M+Na]^+$, 322 (100) $[M+1]^+$, 200 (6); HRMS (ESI) calcd for $C_{22}H_{16}N_3$ 322.1344, found 322.1330.

4.5. General procedure IV for the $Cu(OTf)_2$-catalyzed reaction between imidate hydrochlorides 4a–h,j,m and ammonium carbonate (5a)

A dry 10 mL vial was equipped with a magnetic stir bar and charged with imidate hydrochloride **4** (1.0 mmol), $Cu(OTf)_2$ (36 mg, 0.1 mmol), $NaHCO_3$ (252 mg, 3.0 mmol), 1,10-phenanthroline (36 mg, 0.20 mmol), $K_3[Fe(CN)_6]$ (99 mg, 0.30 mmol), $(NH_4)_2CO_3$ (96 mg, 1.0 mmol) and sealed under air. Then, freshly distilled *o*-dichlorobenzene (3 mL) was added using a syringe and the reaction mixture was stirred at 130 °C for 24 h. After cooling to room temperature the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The crude product was subjected to flash column chromatography over silica gel to yield the product **2**.

*4.5.1. 3,5-Diphenyl-1H-1,2,4-triazole (**2a**).* Compound **4a** (186 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-diphenyl-1*H*-1,2,4-triazole (**2a**) as a white solid in 60% yield (66 mg, 0.30 mmol).

*4.5.2. 3,5-Bis(3-methylphenyl)-1H-1,2,4-triazole (**2b**).* Compound **4b** (200 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-methylphenyl)-1*H*-1,2,4-triazole (**2b**) as a white solid in 60% yield (75 mg, 0.30 mmol).

*4.5.3. 3,5-Bis(4-methylphenyl)-1H-1,2,4-triazole (**2c**).* Compound **4c** (200 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(4-methylphenyl)-1*H*-1,2,4-triazole (**2c**) as a white solid in 62% yield (77 mg, 0.31 mmol).

*4.5.4. 3,5-Bis(3-methoxyphenyl)-1H-1,2,4-triazole (**2d**).* Compound **4d** (216 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(3-methoxyphenyl)-1*H*-1,2,4-triazole (**2d**) as a white solid in 57% yield (80 mg, 0.28 mmol).

*4.5.5. 3,5-Bis(4-methoxyphenyl)-1H-1,2,4-triazole (**2e**).* Compound **4e** (216 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:2) afforded 3,5-bis(4-methoxyphenyl)-1*H*-1,2,4-triazole (**2e**) as a white solid in 61% yield (86 mg, 0.31 mmol).

*4.5.6. 3,5-Bis(3,4-dimethoxyphenyl)-1H-1,2,4-triazole (**2f**).* Compound **4f** (246 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=1:3) afforded 3,5-bis(3,4-dimethoxyphenyl)-1*H*-1,2,4-triazole (**2f**) as a white solid in 64% yield (109 mg, 0.32 mmol).

*4.5.7. 3,5-Bis(3,4,5-trimethoxyphenyl)-1H-1,2,4-triazole (**2g**).* Compound **4g** (276 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=1:3) afforded 3,5-bis(3,4,5-trimethoxyphenyl)-1*H*-1,2,4-triazole (**2g**) as a white solid in 62% yield (124 mg, 0.31 mmol).

*4.5.8. 3,5-Bis(3-chlorophenyl)-1H-1,2,4-triazole (**2h**).* Compound **4h** (220 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=1:3) afforded 3,5-bis(3-chlorophenyl)-1*H*-1,2,4-triazole (**2h**) as a white solid in 40% yield (58 mg, 0.20 mmol).

*4.5.9. 3,5-Bis(4-fluorophenyl)-1H-1,2,4-triazole (**2j**).* Compound **4j** (204 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum ether/EtOAc=3:1) afforded 3,5-bis(4-fluorophenyl)-1H-1,2,4-triazole (**2j**) as a white solid in 56% yield (72 mg, 0.28 mmol).

*4.5.10. 3,5-Di(naphthalen-2-yl)-1H-1,2,4-triazole (**2m**).* Compound **4m** (236 mg, 1.0 mmol) was reacted under the conditions of general procedure IV. Column chromatography over silica gel (petroleum

ether/EtOAc=1:3) afforded 3,5-di(naphthalen-2-yl)-1*H*-1,2,4-triazole (**2m**) as a white solid in 54% yield (87 mg, 0.27 mmol).

Acknowledgements

We thank Ms. Sabine Mika for recording of NMR spectra, Dipl.-Chem. Hans-Georg Imrich, Dr. Alevtina Baskakova and Ms. Katrin Wohlbold (Institut für Organische Chemie der Universität Stuttgart) for recording of mass spectra.

Supplementary data

Analytical and spectroscopic data of selected known compounds; ^{1}H NMR and ^{13}C NMR spectra of selected starting materials and all products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.01.019.

References and notes

1. For reviews on copper-catalyzed reaction for the synthesis of heterocycles, see: (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084; (b) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805; (c) Liu, Y.; Wan, J.-P. *Org. Biomol. Chem.* **2011**, *9*, 6873.
2. Selected examples on the copper-catalyzed reaction for the synthesis of *N*-heterocyclic compounds see: (a) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem.—Eur. J.* **2012**, *18*, 8882; (b) Zhou, W.; Liu, Y.; Yang, Y.; Deng, G.-J. *Chem. Commun.* **2012**, 10678; (c) Sakai, N.; Tamura, K.; Shimamura, K.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2012**, *14*, 836; (d) Suri, M.; Jousseaume, T.; Neumann, J. J.; Glorius, F. *Green Chem.* **2012**, *14*, 2193; (e) Ma, D.; Lu, X.; Shi, L.; Zhang, H.; Jiang, Y.; Liu, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 1118; (f) Kumar, M. R.; Park, A.; Park, N.; Lee, S. *Org. Lett.* **2011**, *13*, 3542; (g) Guin, S.; Ghosh, T.; Rout, S. K.; Banerjee, A.; Patel, B. K. *Org. Lett.* **2011**, *13*, 5976; (h) Lu, J.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 3694; (i) Hirano, K.; Biju, A. T.; Glorius, F. *J. Org. Chem.* **2009**, *74*, 9570.
3. For reviews on copper-catalyzed cross couplings, see: (a) Liu, Y.; Wan, J.-P. *Chem.—Asian J.* **2012**, *7*, 1488; (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054; (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450; (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
4. For reviews on copper-catalyzed oxidations, see: (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234; (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062.
5. For reviews on the biological activity of 1,2,4-triazoles, see: (a) Kumar, S. S.; Kavitha, H. P. *Mini-Rev. Org. Chem.* **2013**, *10*, 40; (b) Kathiravan, M. K.; Salake, A. B.; Chothe, A. S.; Dudhe, P. B.; Watode, R. P.; Mukta, M. S.; Gadhwe, S. *Bioorg. Med. Chem.* **2012**, *20*, 5678; (c) Sahoo, S.; Veliyath, S. K.; Kumar, M. C. B. *Int. J. Res. Pharm. Sci.* **2012**, *3*, 326; (d) Lass-Flörl, C. *Drugs* **2011**, *71*, 2405; (e) Wahi, A. K.; Singh, A. *Asian J. Biochem. Pharm. Res.* **2011**, *1*, 193.
6. For selected examples of 1,2,4-triazoles with biological activities, see: (a) Plech, T.; Luszczki, J. J.; Wujec, M.; Flieger, J.; Pizoń, M. *Eur. J. Med. Chem.* **2013**, *60*, 208; (b) Desai, S.; Laddi, U.; Bennur, R.; Bennur, S. *Indian J. Chem.* **2013**, *52B*, 1176; (c) Singh, R. J. *Der. Pharma Chem.* **2009**, *1*, 141; (d) Chu, Y.; Xu, M. X.; Lu, D. *Chin. Chem. Lett.* **2004**, *15*, 1011; (e) Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem.* **2002**, *37*, 511.
7. (a) Yasger, P. D. et al. U.S. Patent 43066241, June 10, 2010. (b) Patel, N. B.; Khan, I. H.; Rajani, S. D. *Arch. Pharm. Chem. Life Sci.* **2010**, *10*, 692; (c) Alanine, A.; Anselm, L.; Steward, L.; Thomi, S.; Vifian, W.; Groaning, M. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 817; (d) Aster, S. D.; Graham, D. W.; Kharbanda, D.; Patel, G.; Ponpipom, M.; Santorelli, G. M.; Szymonifka, M. J.; Mundt, S. S.; Shah, K.; Springer, M. S.; Thieringer, R.; Hermanowski-Vosatka, A.; Wright, S. D.; Xiao, J.; Zokian, H.; Balkovec, J. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2799.
8. (a) He, Q.; Yang, B.; Wang, W.; Wu, H.-H.; Fang, R. *Contraception* **2003**, *68*, 289; (b) Bo, Y.; Lin, C.; Ruiying, F.; Zhiping, G. *Eur. J. Pharmacol.* **1999**, *380*, 145; (c) Yang, B.; Fang, R. *Acta Pharm. Sin.* **1996**, *17*, 361; (d) Galliani, G.; Luzzani, F.; Colombo, G.; Conz, A.; Mistrello, L.; Barone, D.; Lancini, G. C.; Assandri, A. *Contraception* **1986**, *33*, 263.
9. Li, C.-S.; An, C.-Y.; Li, X.-M.; Gao, S.-S.; Cui, C.-M.; Sun, H.-F.; Wang, B.-G. *J. Nat. Prod.* **2011**, *74*, 1331.
10. Zhou, X.; Xu, T.; Wen, K.; Yang, X.-W.; Xu, S.-H.; Liu, Y. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 1089.
11. (a) Sudheer; Quraishi, M. A. *Corros. Sci.* **2013**, *70*, 161; (b) Meyer, D.; Strassner, T. *J. Org. Chem.* **2011**, *76*, 305; (c) Dash, C.; Shaikh, M. M.; Ghosh, P. *J. Chem. Sci.* **2011**, *123*, 97; (d) Papini, G.; Pellei, M.; Lobbia, G. G.; Burini, A.; Santini, C. *Dalton Trans.* **2009**, 6985; (e) Klingele, M. H.; Brooker, S. *Coord. Chem. Rev.* **2003**, *241*, 119; (f) Haasnoot, J. G. *Coord. Chem. Rev.* **2000**, *200–202*, 131; (g) Fox, P. G.; Bradley, P. A. *Corros. Sci.* **1980**, *20*, 643.
12. For reviews on the synthesis of 1,2,4-triazoles, see: (a) Holm, S. C.; Straub, B. F. *Org. Prep. Proced. Int.* **2011**, *43*, 319; (b) Moulin, A.; Bibian, M.; Blayo, A.-L.; Habnouni, S. E.; Martinez, J.; Fehrentz, J.-A. *Chem. Rev.* **2010**, *110*, 1809; (c) Garratt, P. J. In *Comprehensive Heterocyclic Chemistry II*; Storr, R. C., Ed.; Elsevier: Oxford, UK, 1996; Vol. 4, pp 127–163; (d) Al-Masoudi, A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 1377; (e) Potts, K. T. *Chem. Rev.* **1961**, *61*, 87.
13. Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1969**, 151.
14. Pellizzari, G. *Gazz. Chim. Ital.* **1911**, *41*, 20.
15. (a) Brunner, K. *Monatsh. Chem.* **1915**, *36*, 509; (b) Brunner, K. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 2671; (c) Einhorn, A.; Bischkopff, E.; Ladisch, C.; Mauermayer, T.; Schupp, G.; Spröngerts, E.; Szelinski, B. *Liebigs Ann. Chem.* **1905**, *343*, 207.
16. Larsen, S. D.; DiPaolo, B. A. *Org. Lett.* **2001**, *3*, 3341.
17. (a) Castanedo, G. M.; Seng, P. S.; Blaquiere, N.; Trapp, S.; Staben, S. T. *J. Org. Chem.* **2011**, *76*, 1177; (b) Staben, S. T.; Blaquiere, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325.
18. Wang, X.-C.; Wang, J.-K.; Wu, D.-Q.; Zong, Y.-X. *Synlett* **2005**, 2595.
19. (a) Potts, K. T. *J. Chem. Soc.* **1954**, 3461; (b) Yeung, K.-S.; Farkas, M. E.; Kadow, J. F.; Meanwell, N. A. *Tetrahedron Lett.* **2005**, *46*, 3429; (c) Omodei-Salé, A.; Consonni, P.; Galliani, G. *J. Med. Chem.* **1983**, *26*, 1187; (d) Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. *Tetrahedron Lett.* **1987**, *28*, 5133.
20. Haddadin, M. J.; Zadeh, E. H. G. *Tetrahedron Lett.* **2010**, *51*, 1654.
21. (a) Samanta, S. K.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2005**, *7*, 142; (b) Wang, J.-K.; Zong, Y.-X.; Yue, G.-R. *Synlett* **2005**, 1135; (c) Brunn, E.; Funke, E.; Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1971**, *104*, 1562.
22. Tsuge, O.; Oe, K.; Tashiro, M. *Chem. Lett.* **1977**, 1207.
23. (a) Kauffmann, T.; Albrecht, J.; Berger, D.; Legler, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 633; (b) Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080; (c) Xu, H.; Jiang, Y.; Fu, H. *Synlett* **2013**, 125.
24. Bower, J. D.; Ramage, G. R. *J. Chem. Soc.* **1957**, 4506.
25. (a) Boehringer, M.; Loeffler, B. M.; Peters, J.-U.; Steger, M.; Weiss, P. Patent 068757 A1, August 21, 2003. (b) Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, 452.
26. (a) Shixaliyev, N. Q.; Maharramov, A. M.; Gurbanov, A. V.; Gurbanova, N. V.; Nenajdenko, V. G.; Muzalevskiy, V. M.; Mahmudov, K. T.; Kopylovich, M. N. *J. Mol. Struct.* **2013**, *1041*, 213; (b) Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2; (c) Kopylovich, M. N.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **2011**, *255*, 339; (d) Häger, I.; Fröhlich, R.; Würthwein, E.-U. *Eur. J. Inorg. Chem.* **2009**, 2415; (e) Tzeng, B.-C.; Chang, T.-Y. *Cryst. Growth Des.* **2009**, *9*, 5343; (f) Zhang, J.-P.; Lin, Y.-Y.; Huang, X.-C.; Chen, X.-M. *Cryst. Growth Des.* **2006**, *6*, 519; (g) Zhang, J.-P.; Lin, Y.-Y.; Huang, X.-C.; Chen, X.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5495; (h) Heβe, N.; Fröhlich, R.; Humelnicu, I.; Würthwein, E.-U. *Eur. J. Inorg. Chem.* **2005**, 2189; (i) Mineo, S.; Kawamura, S.; Nakagawa, K. *Synth. Commun.* **1976**, *6*, 69.
27. CCDC-962488 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge crystallographic data center via www.ccdc.cam.ac.uk/data_request/cif.
28. (a) Berger, O.; Wein, S.; Duckert, J.-F.; Maynadier, M.; Fangour, S. E.; Escale, R.; Durand, T.; Vial, H.; Vo-Hoang, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5815; (b) Giorgio, T.; Pierfranco, S.; Dominga, S.; Duccio, F.; Sergio, C. *Eur. J. Med. Chem.* **1976**, *11*, 263; (c) Dewolfe, R. H.; Augustine, F. B. *J. Org. Chem.* **1965**, *30*, 699.
29. (a) Wang, B. L.; Li, Y. H.; Wang, J. G.; Ma, Y.; Li, Z. M. *Chin. Chem. Lett.* **2008**, *19*, 651; (b) Schmitt, J.-L.; Stadler, A.-M.; Kyritsakas, N.; Lehn, J.-M. *Helv. Chim. Acta* **2003**, *86*, 1598; (c) Girreser, U.; König, M.; Clement, B. *Magn. Reson. Chem.* **2002**, *40*, 202; (d) Curd, F. H. S.; Rose, F. L. *J. Chem. Soc.* **1946**, 343; (e) Easson, A. P. T.; Pyman, F. L. *J. Chem. Soc.* **1931**, 2991.
30. (a) Bentiss, F.; Lagrenée, M.; Vezin, H.; Bouanis, M.; Mernari, B. *J. Heterocycl. Chem.* **2002**, *39*, 93; (b) O'Rourke, M.; Lang, S. A.; Cohen, E. *J. Med. Chem.* **1977**, *20*, 723; (c) Weidinger, H.; Kranz, J. *Chem. Ber.* **1963**, 2070.
31. For further analytical and spectroscopic data, see the Supplementary data.