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Copper immobilized on nano-silica triazine dendrimer (Cu(II)-TD@nSiO₂) catalyzed synthesis of symmetrical and unsymmetrical 1,3-diynes under aerobic conditions and ambient temperature

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A highly efficient route for the synthesis of symmetrical and unsymmetrical 1,3-diynes has been developed by Cu(II)-TD@nSiO₂/DBU catalyzed homocoupling/heterocoupling of aromatic as well as aliphatic terminal alkynes under aerobic conditions and ambient temperature. The catalyst could be easily recovered and reused several times without significant loss of its activity.

Since the discovery of Glaser homocoupling reaction of terminal alkynes in 1869,[1] 1,3-diynes has been found wide applications in the synthesis of natural products and analogues,[2] construction of linear π-conjugated acetylenic oligomers and polymers,[3] molecular electronic devices,[4] optical materials,[5] supramolecular switches,[6] as well as in the synthesis of a variety of heterocyclic compounds.[7] In addition, 1,3-diynes are common structural motifs found in pharmaceutically and biologically active compounds, which have shown antifungal,[8] anti-HIV,[9] antibacterial[10] and anticancer properties.[11]

The homocoupling of terminal alkynes leading to symmetrical 1,3-diynes are commonly catalyzed by Pd[12] and Cu[13] salts, and/or Pd in combination with Cu(I) salts as co-catalyst.[14] It is well known that the Pd-catalyzed homocoupling of terminal alkynes is a very important and powerful strategy for the formation of symmetrical 1,3-diynes owing to its mildness, selectivity and efficiency. However, their major drawbacks are that palladium catalysts are expensive and often require phosphine ligands which are air- and moisture-sensitive, expensive and toxic.[15] Also, some of these protocols need oxidants such as O₂[14c,d,16] and iodine[17] for the reoxidation of Pd(0) to Pd(II).

In order to circumvent the use of expensive palladium catalysts, and due to easy availability as well as economical, and environmental concerns, several copper-based catalysts have been introduced in recent years for the homocoupling of terminal alkynes.[18,19] Although these copper catalysts are highly efficient for the homocoupling of terminal alkynes to symmetrical 1,3-diynes, the use of stoichiometric amounts of copper salts,[19c] high temperature,[18d-f,19a] long reaction times,[19a,b] and low to moderate yields for aliphatic alkynes[13b,13c,19a] are limitations of some of these catalytic systems. Another disadvantage of some of these methods is that the catalysts cannot be recovered and reused[18e,f,19a] which limit their usefulness, specially in large scale operations. Consequently, there is enormous interest in the further development of copper-based catalysts with high activity and excellent reusability for the homocoupling of terminal alkynes.

The most imperative route for synthesis of unsymmetrical 1,3-diynes is Cu-catalyzed Cadiot–Chodkiewicz coupling between 1-haloalkynes and terminal alkynes.[20] Palladium-catalyzed heterocoupling of 1-haloalkynes and terminal alkynes have been also reported for the preparation of unsymmetrical 1,3-diynes.[21] Since, 1-haloalkynes are generally prepared by halogenation of terminal alkynes, so, coupling of two different terminal alkynes is a more straightforward approach to gain unsymmetrical 1,3-diynes. Recently, different Cu-based catalysts have been examined for heterocoupling of terminal alkynes.[13b,18h-k,22] However, most of these reported protocols suffered from prolonged reaction times and low yields. Therefore, there is still crucially needed to develop a more convenient and efficient procedure for the synthesis of these compounds.

Nowadays, dendrimers have been widely used not only in nanomedicine and material science, but also as ligands in modern organometallic chemistry.[23] Dendrimers, due to their highly branched and three-dimensional structures with many cavities, have been used for encapsulation of a variety of ions and molecules.[24] Among the known applications of metal encapsulated-dendritic compounds, catalysis is an important field.[25] In addition, the immobilization of metal encapsulated-dendrimers on different insoluble solid supports, with the advantages of easy separation, recovery and reusability, is of

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great importance from economical and environmental point of views.[26,27]

Recently, we reported the Cu (II) immobilized on nano-silica triazine dendrimer, Cu(II)-TD@nSiO$_2$ as an efficient and reusable catalyst for the synthesis of benzimidazoles, benzothiazoles, *bis*-benzimidazoles, and *bis*-benzothiazoles.[28] For the preparation of the catalyst, CuCl$_2$·2H$_2$O was used as the source of copper(II) species. In continuation of our efforts on the new application of Cu(II)-TD@nSiO$_2$ catalytic system, herein we report a Pd-free expedient protocol for the synthesis of symmetrical and unsymmetrical conjugated 1,3-diynes in excellent yields through a Glaser oxidative coupling of terminal alkynes using Cu(II)-TD@nSiO$_2$ as a highly recoverable catalyst under aerobic conditions at room temperature (Scheme 1). As far as we know, this is the first report on the use of heterogeneous Cu-based dendritic catalyst for the synthesis 1,3-diynes.
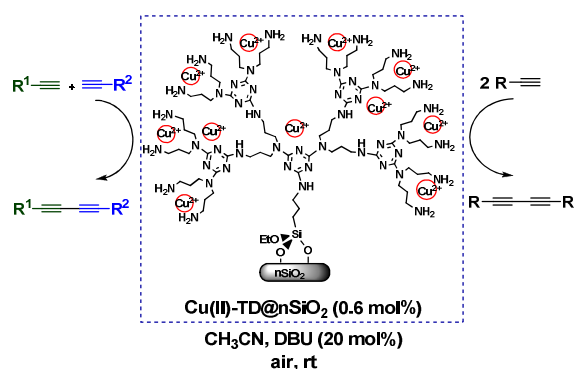
Scheme 1 Synthesis of symmetrical and unsymmetrical 1,3-diynes catalyzed by Cu(II)-TD@nSiO$_2$

We initiated our investigations by using phenylacetylene (**1a**) as a model for screening the reaction conditions (Table 1). At first, 20 mol% of a variety of bases such as K$_2$CO$_3$, ^{t}BuOK, NEt$_3$, DABCO (1,4-diazabicyclo[2.2.2]octane) and DBU (1,8-
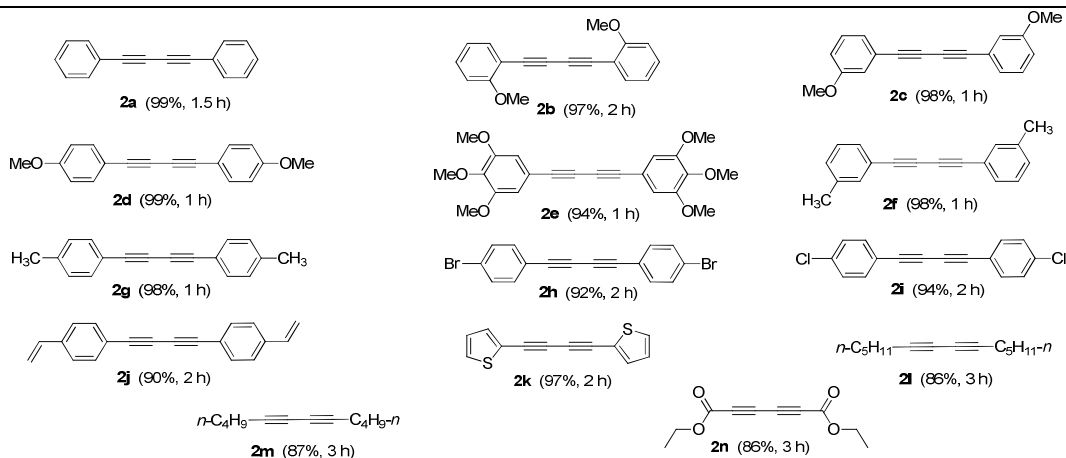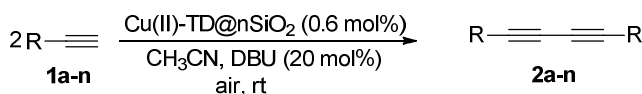
Table 1 Optimization of alkyne homocoupling catalyzed by Cu(II)-TD@nSiO$_2$[a]

Entry	Cat (mol%)	Base (20 mol%)	Solvent	Time (h)	Yield (%)[b]
1	0.6	K$_2$CO$_3$	CH$_3$CN	6	-
2	0.6	^{t}BuOK	CH$_3$CN	6	-
3	0.6	NEt$_3$	CH$_3$CN	6	15
4	0.6	DABCO	CH$_3$CN	6	60
5	0.6	DBU	CH$_3$CN	1.5	99
6	0.6	DBU	EtOH	6	-
7	0.6	DBU	DMF	6	78
8	0.6	DBU	Dioxane	6	45
9	0.6	DBU	Toluene	6	-
10	0.4	DBU	CH$_3$CN	6	70
11[c]	-	DBU	CH$_3$CN	6	-
12	CuCl$_2$ (10 mol%)	DBU	CH$_3$CN	6	15

[a] Containing 0.34 mmol Cu(II) per gram Cu(II)-TD@nSiO$_2$, determined by ICP analysis. [b] Isolated yield. [c] Without Cu(II)-TD@nSiO$_2$ catalyst.

diazabicyclo[5.4.0]undec-7-ene) were tested (Table 1, entries 1-5). Of these, DBU was found to be superior in terms of conversion (Table 1, entry 5). NEt$_3$ and DABCO gave only low to moderate yields, while no reaction was observed in the presence of K$_2$CO$_3$ and ^{t}BuOK. The function of different solvents such as EtOH, DMF, dioxane, toluene, and CH$_3$CN was also checked (Table 1, entries 5-9). Among these, only CH$_3$CN was found to be the best medium for attaining optimum yield (Table 1, entry 5). The variation in the catalyst loading also affected the yield of **2a**. When 0.4 and 0.6 mol% of Cu(II)-TD@nSiO$_2$ were used for the model reaction under the identical reaction conditions, it resulted in 70%, and 99% yields. of **2a** (Table 1, entries 5, 10), respectively. It is worthy to mention that only 15% of **2a** was obtained in the presence of CuCl$_2$·2H$_2$O (10 mol%) as a catalyst (Table 1, entry 12), and no conversion was observed when the reaction was performed

Table 2 Synthesis of symmetrical 1,3-diynes catalyzed by Cu(II)-TD@nSiO$_2$[a]

2a (99%, 1.5 h) 2b (97%, 2 h) 2c (98%, 1 h)
2d (99%, 1 h) 2e (94%, 1 h) 2f (98%, 1 h)
2g (98%, 1 h) 2h (92%, 2 h) 2i (94%, 2 h)
2j (90%, 2 h) 2k (97%, 2 h) 2l (86%, 3 h)
2m (87%, 3 h) 2n (86%, 3 h)

[a] Isolated yield

in the absence Cu(II)-TD@nSiO$_2$ catalyst (Table 1, entry 11). These results clearly exhibited the crucial role of this catalyst during the coupling reaction.

Encouraged by the efficiency of the above mentioned reaction protocol, we examined the substrate scope to generalize the versatility of this methodology. As shown in Table 2, the homocoupling of aromatic terminal alkynes with electron-donating as well as electron-withdrawing groups (**1a-1i**) was performed efficiently in the presence of Cu(II)-TD@nSiO$_2$/DBU catalytic system to afford the corresponding 1,3-diyne derivatives (**2a-2i**) in excellent yields (92-99%) under aerobic conditions at room temperature. 4-Ethenylphenylacetylene (**1j**), as an example of enyne, was found to be efficient and provided excellent yield of the desired 1,3-diyne (**2j**). Heteroaromatic alkyne such as 2-ethynylthiophene (**1k**) also provided the corresponding 1,3-diyne (**2k**) in excellent yield. Moreover, the present catalytic system could be applied successfully for the homocoupling of aliphatic terminal alkynes. Accordingly, the homocoupling of 1-heptyne (**1l**), 1-hexyne (**1m**) and ethyl propiolate (**2n**) proceeded effectively to afford the corresponding 1,3-diyne derivatives (**2l-2n**) in 86-87% yields.

In order to further widen the application of this protocol, the Cu(II)-TD@nSiO$_2$/DBU catalytic system was applied to the synthesis of unsymmetrical 1,3-diynes via heterocoupling of two different terminal alkynes. First, the reaction between phenylacetylene **1a** and ethyl propiolate **1n** was selected as a model. The reaction was carried out in the presence Cu(II)-TD@nSiO$_2$ (0.6 mol%) and DBU (20 mol%) in acetonitrile under aerobic conditions at room temperature for 2 h (Table 3). When the reaction was performed using 1:1 molar ratio of **1a** to **1n**, 43% heterocoupled product **3an** was obtained along with 50% and 15% homocoupled products **2a** and **2n**, respectively (Table 3, entry 1). Using a molar ratio of 2:1 of **1n** to **1a** or increasing the amount of base up to 30 mol%, did not improve the yield of the heterocoupled product significantly (Table 3, entries 2 and 3). Wherase, the yield of the heterocoupled

Table 3 Optimization of heterocoupling of alkynes catazyed by Cu(II)-TD@nSiO$_2$

Entry	1a (mmol)	1n (mmol)	DBU (mol%)	3an Yield (%)[a]	2a Yield (%)[b]	2n Yield (%)[c]
1	1	1	20	43	50	15
2	1	1	30	45	51	15
3	1	2	20	61	25	20
4	2	1	20	89	55	5

[a] Isolated yield based on 1.0 mmol of the reactant. [b] Yield based on **1a**. [c] Yield based on **1n**

product was increased to 89%, when the molar ratio of **1a** to **1n** changed to 2:1 (Table 3, entry 4). According to the results presented in Table 3, it seems that the best yield of the heterocoupled product could be achieved using excess amount of electron-rich alkyne. Under these conditions, the heterocoupling of different terminal alkynes was investigated and the results are summarized in Table 4. The heterocoupling of phenylacetylene **1a** with 4-ethynylanisole **1d** proceeded efficiently to provide the corresponding unsymmetrical 1,3-diyne **3ad** in 95% (Table 4, entry 2). 3-Ethynylanisole **1c** underwent smooth coupling with 1-ethynyl-4-chlorobenzene **1i** and 1-hexyne **1m** to furnish the corresponding heterocoupled products **3ci** and **3cm** in 93% and 78% yields, respectively (Table 4, entries 3, 4). In addition, the coupling between 4-ethynylanisole **1d** and 2-ethynylthiophene **1k** furnished the desired product **3dk** in 88% yield (Table 4, entry 5). It is also noteworthy that in comparison to the reported methods for the preparation of unsymmetrical 1,3-diynes,[13b,18h-k,22] the yields are higher, the reaction times are remarkably shorter, and the required amount of the catalyst for successful reaction is lesser

Table 4 Synthesis of unsymmetrical 1,3-diynes catalyzed by Cu(II)-TD@nSiO$_2$

Entry	R^1≡	R^2-≡	R^1≡-≡-R^2	Time (h)	Yield (%)[a]
1	1a	1n	3an	2	89
2	1a	1d	3ad	1.5	95
3	1c	1i	3ci	1.5	93
4	1c	1m	3cm	2	78
5	1d	1k	3dk	1.5	88

[a] Isolated yield.

using this method.

A plausible mechanism for the synthesis of 1,3-diynes is shown in Scheme 2. The Cu(II) catalyst is first reduced by DBU[29] to give the Cu(I) species which upon reaction with a terminal alkyne in the presence of DBU generates Cu-acetylide. The oxidative coupling of the resulting Cu-acetylide in the presence of oxygen affords the desired 1,3-diyne and releases the catalyst for the next catalytic cycle. To verify the proposed mechanism, the model reaction was carried out under argon atmosphere; no desired product was obtained under these conditions. On the other hand, bubbling of oxygen into the mixture accelerated the reaction considerably. All These observations indicated that the presence of oxygen is essential for the reaction and the proposed mechanism is reasonable.
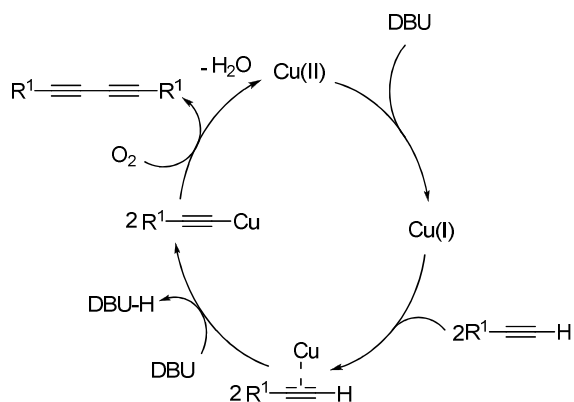
Scheme 2 Proposed mechanism

The structures of the products were deduced from their IR, mass, ^{1}H NMR and ^{13}CNMR spectra, and from their elemental analysis data. The structure **3ad** was also confirmed by X-ray crystallographic analysis (Figure 1, CCDC 972614).
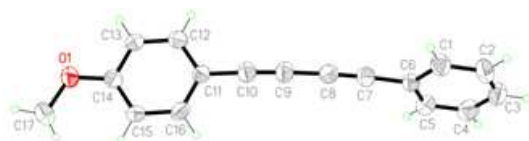

Figure 1 X-ray crystal structure of compound **3ad**. Thermal ellipsoids are drawn at the 30% probability level, while the hydrogen size is arbitrary

Finally, we turned our attention to the Cu(II)-TD@nSiO$_2$ catalyst reusability. The recovery of the catalyst was checked in the homocoupling of phenylacetylene **1a**. After completion of the reaction, the mixture was diluted with acetonitrile and the catalyst was separated by centrifugation. The catalyst was washed with acetonitrile, dried and reused for subsequent reactions. As shown in Table 5, the Cu(II)-TD@nSiO$_2$ could be recycled and reused at least eight times without any obvious loss of activity. Moreover, copper leaching in Cu(II)-TD@nSiO$_2$ catalyst, measured by inductively coupled plasma analysis (ICP-OES), indicated that very restricted leaching of copper (less than 0.1 ppm) has taken place throughout the reaction.

Table 5 Reusability of Cu(II)-TD@nSiO$_2$ catalyst in the synthesis of **2a**[a]

Run	1	2	3	4	5	6	7	8
Yield (%)[b]	99	99	97	98	97	96	95	92

[a] Reaction conditions: Phenylacetylene (1 mmol) Cu(II)-TD@nSiO$_2$ (0.6 mol%), rt, 1.5 h. [b] Isolated yield.

Conclusions

In summary, we have developed a highly efficient method for the synthesis of a variety of symmetrical and unsymmetrical 1,3-diynes via coupling of aromatic as well as aliphatic terminal alkynes in the presence of Cu(II)-TD@nSiO$_2$/DBU catalytic system under very mild reaction conditions; aerobic conditions and room temperature, without any oxidant. The outstanding features of the present method are excellent yields, very short reaction times, operational simplicity and reusability of the catalyst which make it a useful and attractive process for the synthesis of symmetrical and unsymmetrical 1,4-disubstituted 1,3-diynes.

Acknowledgements

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Copper immobilized on nano-silica triazine dendrimer (Cu(II)-TD@nSiO$_2$) catalyzed synthesis of symmetrical and unsymmetrical 1,3-diynes under aerobic conditions and ambient temperature

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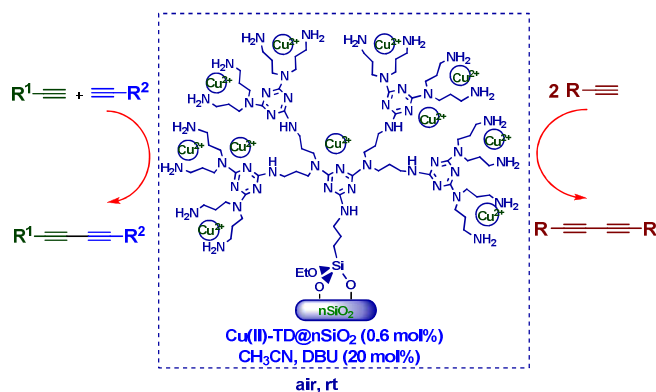
Highly efficient synthesis of symmetrical and unsymmetrical 1,3-diynes catalyzed by Cu(II)-TD@nSiO$_2$/DBU under aerobic conditions and ambient temperature is reported.