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Copper(I) chloride catalysed room temperature C_{sp}–C_{sp} homocoupling of terminal alkynes mediated by visible light†

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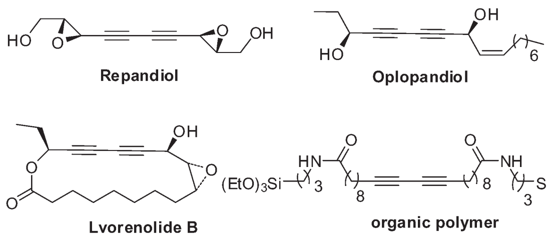
We developed a technique mediated by visible light for the aerobic homocoupling of terminal alkynes to synthesize 1,3-conjugated diynes using a copper(I) chloride catalyst at room temperature. Compared with previously reported thermal processes, this photochemical method is simple, uses only mild reaction conditions, produces high yields and works well for substrates with electron-withdrawing groups without the need for bases/ligands, oxidants or palladium catalysts.

The discovery of mild and highly efficient methods for the construction of 1,3-conjugated diynes and polyynes is a central objective in organic synthesis.[1] The 1,3-conjugated diynes are important building blocks in numerous natural products, pharmaceuticals and medicinally important molecules, including anti-inflammatory, anticancer, anti-HIV and antifungal drugs.[1a,2] Conjugated diynes play an essential part in the synthesis of functional organic molecules, such as acetylenic oligomers, polymers and supramolecular materials (Scheme 1).[3]

Glaser–Hay coupling was one of the earliest techniques of synthesizing conjugated diynes through the homocoupling of terminal alkynes[4] and is still considered to be the classical method.[5] Many other processes have been developed, including the use of Cu, Pd and bimetallic Pd/Cu, Ni/Cu catalyst systems.[6–10] Jia *et al.*[11] reported the oxidative homocoupling of terminal alkynes using Cu(I) or Cu(II) salts without any palladium or base. A dimethylsulfoxide solvent is necessary in the homocoupling reaction (Scheme 2). However, this reaction does not work at room temperature and is limited to electron-rich terminal acetylenes. Despite the utility of such processes, the development of an eco-friendly and green method for the oxidative C_{sp}–C_{sp} homocoupling of terminal alkynes at room temperature using an inexpensive catalyst (*e.g.* Cu) with the exclusion of palladium and bases/ligands remains challenging.

Transition metal/organic dye based photoredox catalysis initiated by visible light is now recognized as a powerful alternative to metal-catalysed "thermal" reactions.[12] This is because most of the reactions mediated by visible light are performed at room temperature in the absence of ligands or bases.[12a] Visible light is easier to handle than high-energy UV light and complex organic molecules are more stable under low-energy visible light irradiation. Photoredox Cu catalysts have been used as an inexpensive catalytic system for C–C coupling, atom transfer radical addition reactions,[13] alkyne–azide cycloaddition click reactions[14] and Ullmann-type C–N coupling reactions.[15] We recently reported a copper(I)-catalysed Sonogashira C–C cross-coupling reaction[16] and oxidative C_{sp}–N cross-coupling reactions of terminal acetylenes with anilines at room temperature mediated by visible light,[17] in which the key photocatalyst was copper(I)-phenylacetylide. We report here that copper(I)-phenylacetylide catalytically generated *in situ* can also catalyse the aerobic C_{sp}–C_{sp} homocoupling reaction of terminal alkynes at room temperature on irradiation with light from blue LEDs (see Scheme 2). The unique features of our current work include: (a) no base or ligand/additive is required; (b) the reaction proceeds cleanly at room temperature; (c) there is a high reactivity towards electron-withdrawing substituted aryl acetylenes and aliphatic alkynes; and (d) this protocol also



Scheme 1 1,3-Diynes in natural and organic products.

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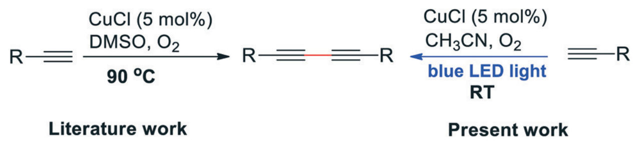
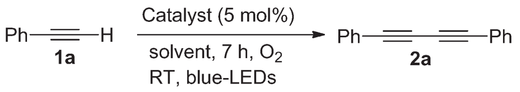


Scheme 2 Comparison of previously reported thermal process and the current CuCl-catalysed homocoupling of terminal alkynes mediated by visible light.

provides a practical and mild synthetic approach to prepare 1,3-conjugated diynes under visible light irradiation.

We observed in an initial study that the presence of atmospheric oxygen leads to the formation of the homocoupling product exclusively through a Glaser–Hay coupling reaction.[16] Based on this preliminary result, we further optimized the reaction conditions using 5 mol% copper(I) chloride without any base in the presence of O_2 under visible light irradiation. The reaction yielded 55% of the desired homocoupling product (Table 1, entry 1), indicating that a base is not required for the observed reaction. CH_3CN was found to be the most efficient solvent in the solvent screening, providing the desired product at 74% yield after 7 h of irradiation (Table 1, entry 2). This might be because the polarity of CH_3CN matches well with that of the products and thus drives the reaction forwards more efficiently. We observed a dramatic increase in the homocoupling product yield to 98% on increasing the concentration of terminal alkynes (Table 1, entry 3). This result indicated that the concentration of terminal alkynes is crucial in the homocoupling reaction.

Table 1 Optimization studies for the homocoupling reaction of phenylacetylene (**1a**)[a]



Entry	Catalyst (mol%)	Solvent	Yield[b]
1	CuCl	CH_3CN–MeOH	55
2[c]	CuCl	CH_3CN	74
3	CuCl	CH_3CN	98
4	CuCl (2)	CH_3CN	80
5	CuBr	CH_3CN	98
6	CuI	CH_3CN	98
7	$CuCl_2$	CH_3CN	Trace
8	$Cu(OAc)_2$	CH_3CN	nr
9	CuCl	MeOH	74
10	CuCl	THF	23
11	CuCl	DMSO	22
12	CuCl	DMF	45
13	CuCl	Neat	Trace
14[d]	CuCl	CH_3CN	Trace
15[e]	CuCl	CH_3CN	n.r
16[f]	CuCl	CH_3CN	Trace
17[g]	CuCl	CH_3CN	92
18[h]	CuCl	CH_3CN	73

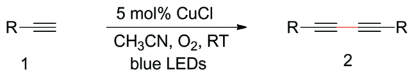
[a] Reaction conditions: 1 M (**1a**) and 5 mol% catalyst in solvent. The solution was irradiated with blue LEDs for 7 h in the presence of 1 atm O_2 atmosphere (in balloon). [b] Isolated yield (note: entry 4, 2 mol% catalyst used). [c] 0.5 M of **1a** was used in the reaction. [d] Reaction was conducted in the dark at RT. [e] In the absence of CuCl catalyst. [f] In the absence of O_2. [g] 1 atm air (in balloon) was used in the reaction. [h] Phenylacetylene-d_1 was used as a substrate.

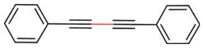
We also examined many other solvents, including methanol, THF, dimethylsulfoxide and DMF. These solvents afforded the homocoupling product, but did not give a complete conversion (Table 1, entries 9–12). No reaction was observed under solvent-free conditions (Table 1, entry 13). In the screening of metal salts, CuX (X: Cl, Br, I) gave the highest yield (98%) of desired product **2a** (Table 1, entries 3, 5 and 6). When 2 mol% CuCl was used, the yield of product **2a** decreased slightly to 80% (Table 1, entry 1). By contrast, the Cu(II) salt did not catalyse the formation of the product in any appreciable yield (Table 1, entries 7 and 8). Therefore the key catalyst responsible for this reaction is most probably the copper(I)-related species. Control experiments showed that with the exclusion of light, CuCl or O_2, no (or only a trace amount of) product was obtained (Table 1, entries 14–16). We examined the reaction of various substituted aromatic terminal alkynes under the optimized conditions. Excellent yields were generally observed for substrates bearing electron-donating and electron-neutral groups in a short period of time (Table 2, **2a–2g**). Alkynes containing the naphthalene moiety (**1h**) were also well tolerated in the reaction and afforded product **2h** in good yield.

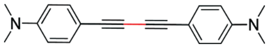
The homocoupling reactions of electron-deficient aromatic terminal alkynes are generally very difficult to accomplish because these groups have less π-basicity on the C≡C triple bond and do not easily react when using a soft Lewis acid such as Cu(I).[18] However, the system reported here was more effective for these substrates (**1m–1t**). The use of 5 mol% CuCl was sufficient to promote the homocoupling reactions and provided 1,3-diynes in good yields (82–93%) over a period of 12–15 h (Table 2, **2m–2t**). For halo-substituted aryl acetylenes, F, Br and I afforded the corresponding products in good to excellent yields (82–94%, Table 2, **2i–2l**). Heteroarylalkynes (**1u**) and anisole-substituted aliphatic alkynes (**1v**) can also effectively undergo homocoupling reactions to generate their corresponding products (**2u** and **2v**) in very good yields. Cyclohexylacetylene (**1w**) and 1-cyclohexenylacetylene (**1x**) were also well tolerated in the reaction and produced their corresponding products (**2w** and **2x**) in good yields. The homocoupling reaction of linear aliphatic alkynes was also completed with 8 h of photoirradiation and a good yield was obtained (**2y–2dd**). The current homocoupling reaction of a broad range of electron-deficient phenylacetylenes/aliphatic linear chain terminal alkynes provides a powerful method for the synthesis of 1,3-conjugated diynes through a homocoupling reaction, which is either very difficult or not achievable by previously reported thermal processes.[11]

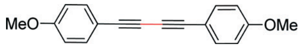
We also evaluated the green chemistry metrics[11c] of the synthesis of the 1,3-diynes-(**2g**) on a preparative scale (see ESI†). The green metrics values (*E* factor = 5.76, atom economy = 94%, atom efficiency = 82%, carbon efficiency = 100% and reaction mass efficiency = 87%), the turnover number of *c.* 17.6–20 and the turnover frequency of 2.8 h^{-1} indicated that the current photochemical process is a very simple,

Table 2 Results of CuCl-catalysed homocoupling reaction of terminal acetylene (**2a**) mediated by visible light[a]



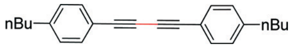

2a (98%, 7 h)


2b (99%, 7 h)

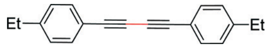


2c (98%, 7 h)

2d (98%, 7 h)

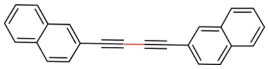


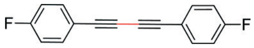
2e (95%, 7 h)

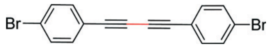


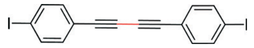
2f (94%, 7 h)


2g (95%, 7 h)

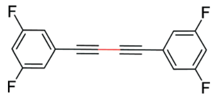

2h (94%, 7 h)


2i (92%, 8 h)

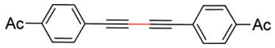

2j (84%, 12 h)


2k (76%, 15 h)

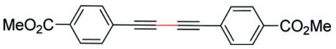
2l (85%, 12 h)



2m (93%, 12 h)



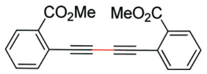
2n (82%, 15 h)



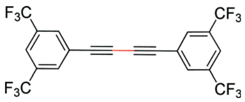
2o (88%, 15 h)

2p (86%, 15 h)

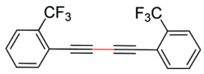
2q (82%, 15 h)



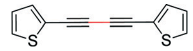
2r (88%, 15 h)



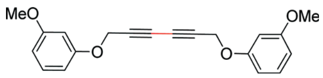
2s (87%, 12 h)



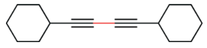
2t (85%, 12 h)

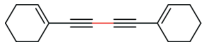


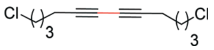
2u (88%, 10 h)



2v (86%, 10 h)


2w (88%, 8 h)

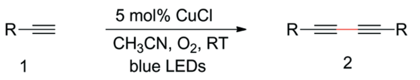

2x (84%, 8 h)

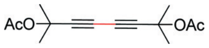


2y (90%, 8 h)

2z (88%, 8 h)

Table 2 *(continued)*

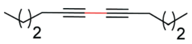




2aa (91%, 8 h)

2bb (85%, 8 h)

2cc (85%, 8 h)

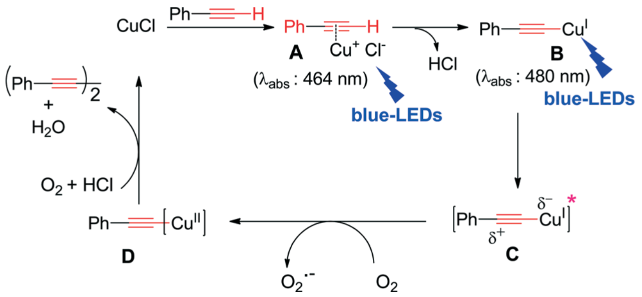


2dd (86%, 8 h)

[a] Isolated yield after purification by column chromatography on SiO_2.

practical and eco-friendly method for the preparation of 1,3-diynes, which makes this process a greener alternative to existing thermal methodologies.[6–11]

A possible reaction mechanism for the CuCl-catalysed homocoupling reaction mediated by visible light (λ_{max} = 460 nm) is proposed in Scheme 3. The first step involves the formation of the π–alkyne complex **A**, which makes the terminal H of alkynes more acidic.[18] In the next step, the irradiation of the π–alkyne complex with visible light (λ_{abs} = 464 nm, see Fig. 1) resulted in the *in situ* formation of copper(I) phenylacetylide **B**, as evidenced by the increase in the 480 nm absorption in the UV–visible absorption spectra (see Fig. 1 and S1†). Thus irradiation of the π–alkyne complex with visible light (λ_{abs} = 464 nm) is probably the key step in the formation of the key catalyst, copper(I)-phenylacetylide in the absence of a base. Without photoirradiation, copper(I)-phenylacetylide could not be formed in the dark (thermal process) and in the absence of base.[17d] Direct visible light excitation of copper(I)-phenylacetylide (λ_{max} = 480 nm) leads to the formation of a partial positive charge on the acetylene ligand and a partial negative charge on the metal centre *via* ligand to metal charge transfer.[19] It is thought that the excited state of copper(I)-phenylacetylides undergoes facile intersystem crossing[16b,17,19] and hence **C** probably undergoes single electron transfer to molecular oxygen to generate the superoxide[17b,20] and electron-deficient Cu(II)-phenylacetylide **D** (see EPR spectra in Fig. S1†). The dissociation of complex D leads to the formation C_{sp}–C_{sp} homocoupling products and the



Scheme 3 Proposed mechanism for the CuCl-catalysed homocoupling of terminal alkynes mediated by visible light.

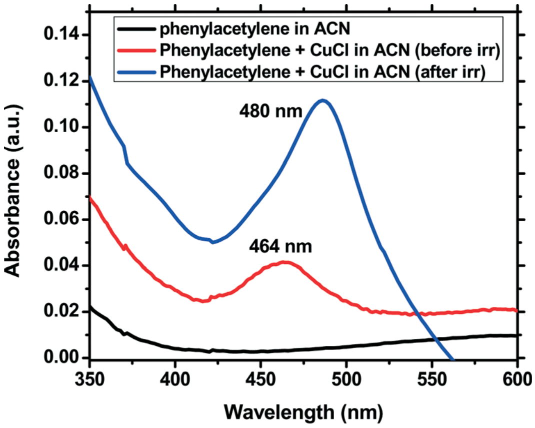


Fig. 1 UV–visible absorption spectra of *in situ* generated Cu(I)-phenylacetylide (**B**) in CH_3CN.

regeneration of CuCl. The proposed mechanism is supported by the experimental results given in Table 2, the UV absorption of the π–alkyne complex **A** and the *in situ* formation of copper(I)-phenylacetylide **B** (see Fig. 1).

Conclusions

We have successfully developed a novel homocoupling method for terminal alkynes (including substrates with electron-withdrawing groups) using CuCl as a catalyst and mediated by visible light. This method can be used for the preparation of 1,3-conjugated diynes. This is the first example of the use of visible light to initiate the Glasser homocoupling reaction of terminal alkynes to synthesize 1,3-conjugated diynes at room temperature using a CuCl catalyst in the absence of base/ligands and expensive palladium catalysts. This mechanistic study illustrates that the π–alkyne complex **A** and copper(I)-acetylides (alkyl and aryl, λ_{max} = 425–490 nm) are the key light-absorbing species and are responsible for the visible light-induced C_{sp}–C_{sp} homocoupling of terminal alkynes. The cost-effective nature of the catalyst, the absence of bases/ligands, the wide tolerance of different functional groups (electron-withdrawing groups) and the high reaction efficiency under low-energy visible light irradiation make this process a green alternative to existing thermal methodologies.

Acknowledgements

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