Cu–Mn bimetallic catalyst for Huisgen [3+2]-cycloaddition†

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Cu–Mn spinel oxide catalyst has been investigated for the ligand-free Huisgen [3+2] cycloaddition. The copper(I) species required in the cycloaddition reaction has been stabilized in the tetrahedral site of the spinel without the need of a stabilizing agent. The new catalyst is robust and can be reused several times under MW conditions with negligible loss in catalytic activity.

Bimetallic catalysts in which one metal can finetune or modify the catalytic properties of the other metal offer considerable promise in the area of fundamental organic transformations such as C–C bond formation,[1] hydrogenation,[2] and cycloaddition.[3] In a bimetallic catalyst, metal type, oxidation state and concentration can be varied to modulate the catalytic performance.[4] For example, addition of a second metal to a noble metal catalyst alters catalytic performance to an extent not accountable by a simple superposition of monometallic properties.[5] The formation of a bimetallic phase changes the geometry of the available sites either by generation of entirely new spinel structures or by limiting the ensemble of each component metal.[6] Thus, alteration of either the electronic or geometric properties of an active site may change the adsorption energetics of the reactants and the products resulting in higher activity[7] or suppression of side reactions, culminating in improved selectivity. Despite having these qualities, the scope of bimetallic catalysts in organic synthesis has not been studied in detail. Herein, we report the use of a bimetallic catalyst in the Huisgen [3+2] cycloaddition reaction also known as click chemistry.[8]

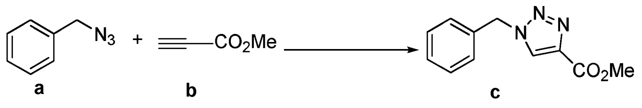
Copper(I) salts are quite prone to redox processes and it is desirable to protect and stabilize the active copper catalysts during the azide–alkyne cycloaddition reaction (CuAAC). Nanopowders,[9] copper nanoclusters,[10] solid supported Cu on titanium oxide or zeolites,[11] porphyrinatocopper nanoparticles[12] as well as Cu(I) salts[13] in the presence of phosphorous or nitrogen bases[14] (ligands) have been used for this purpose. However, all the above mentioned methods suffer from low product yields, low activities, require additives,[15] high reaction temperature[15] and are generally accompanied by the formation of side products like bistriazole, diacetylenes *etc.*[12]

Table 1 Comparative study of the effect of three different catalysts and various solvents on the reaction of **a** and **b** to yield the product **c**

S.No.	Catalyst[a]	Solvent[b]	Time/h	Yield (%)[c]
1	**A**	CH_3CN	8	99
2	**B**	CH_3CN	8	94
3	**C**	CH_3CN	8	73
4	**D**	CH_3CN	15	52[d]
5	**A**	DMF	12	77
6	**A**	THF	12	78
7	**A**	Toluene	12	78
8	**A**	Solvent free (Mw)	0.05	99
9	**B**	Solvent free (Mw)	0.05	98
10	**C**	Solvent free (Mw)	0.05	75
11	**D**	Solvent free (Mw)	0.05	58[d]

[a] Catalytic loading used is 10 mg g^{-1} of a. [b] 5 ml g^{-1} of the reactant. [c] Isolated but not optimised yield. [d] Mixture of products obtained.

Copper-manganese spinels have attracted significant attention for their potential applications in electrochemical systems.[16] Recently Cu–Mn spinel oxide catalysts were used[17] in the combined steam reforming of methanol. Tang[18] and his team studied the load of Cu–Mn/zeolite–Y for the synthesis of dimethyl ether from CO–H_2. Despite their low surface areas, these catalysts displayed activity comparable to a commercial Cu–Zn–Al catalyst. We conceptualized that the incorporation of low concentrations of p-type semiconductors like CuO in the matrix of an n-type manganese oxide may result in an increase in acceptor centres, allowing absorption of a considerable amount of substrates. Consequently in a Cu–Mn bimetallic catalyst the reaction between CuO and Mn_2O_3 through electron transfer from Mn^{3+} to Cu^{2+} may result in the formation of an Mn^{4+} ion having a bias for d^2sp^3 bonds preferring the octahedral site, and a Cu^+ ion by virtue of its preference to form sp^3 bonds will be stabilized at the tetrahedral site thus obviating the need for an external reagent. In order to substantiate the above concept, we prepared four different bimetallic catalysts by varying the Cu : Mn ratio. The catalytic activities of all four copper containing catalysts were examined in a model reaction between benzylazide and methylpropiolate in a 1 : 1 molar ratio (Scheme 1) in different solvent systems at room temperature as well as under solvent free conditions using microwaves (MW) (Table 1). The specific surface area of the catalysts was also determined in order to examine its effect on catalytic activity (Table 2).



Scheme 1

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† Electronic supplementary information (ESI) available: General information, experimental procedures and ^1H NMR and ^{13}C NMR spectra of some selected compounds. See DOI: 10.1039/c005088a

Table 2 Relation between catalytic activity and specific surface area[a] of the catalyst

Catalyst	Composition Cu : Mn (mol ratio)	Calcination temp./°C	Specific surface area of the catalyst/m^2 g^{-1}
E	Only CuCl	450	21.0
D	Only CuCl$_2$	450	4.62
C	3 : 0.25	450	8.30
B	1 : 0.25	450	16.4
A	2 : 0.25	450	18.30
	2 : 0.25	350	11.31
	2 : 0.25	300	9.21

[a] Determined from Chembet-3000TPR/TPD.

Table 3 Comparisons of reaction conditions and yields in the synthesis of **c** by catalyst A

S.No.	Method[a]	Time	Yield (%)
1	a	8 h.	99
2	b	5 h.	90
3	c	3 h.	Mixture of products
4	d	30 min.	95
5	e	3 min.	99

[a] a. Reaction with CH_3CN at room temperature. b. Reaction with CH_3CN under reflux c. Solvent free conventional heating. d. MW-acetonitrile. e. MW-solvent free. In all cases catalyst-A was used.

The results revealed that catalyst A was the most effective among all other catalysts, thus yielding the corresponding 1,4-substituted 1,2,3-triazole as a sole reaction product. During the standardisation of the reaction conditions with catalyst A (Table 3), it was observed that the reaction without solvent under MW was the most favourable condition for complete conversion.

In order to explore the versatility and functional group tolerance of the bimetallic catalyst **A**, we performed a series of click reactions to produce 1,4-disubstituted 1,2,3-triazoles in good to excellent yields under both solution and MW conditions (Table 4). Carbohydrate based alkynes reacted smoothly without affecting acetonide and acetate protection, affording the corresponding triazoles (entries 12, 13, 14) in good to excellent yields. After getting positive results from initial experiments we turned our attention to the β-hydroxy-1,2,3-triazole unit due to its importance as a replacement for peptide groups in HIV-1 protease inhibitors.[19] The new catalyst system also facilitated the formation of furan derived β-hydroxy triazole derivatives (entries 6, 11, 12, 13, 14). Triazole glycoconjugates have also been synthesised possessing a β-hydroxy furan group. The most striking feature of the reaction was the synthesis of a silylated triazole by the reaction of TMS-acetylene with the iodoazide derivative of DHF (entry 15), whereas the formation of TMS triazoles has reportedly been a failure under other catalytic systems.[11]

In order to understand the efficiency of catalytic activity as a function of overall composition, it is imperative to locate the kind of phase/s making the largest contribution to the metal surface area and thus performing the main burden of catalytic action. Thus, the powder X-ray diffraction (XRD) of the samples were recorded (Fig. 1) and results for the four catalysts are summarized in Table 5. The data reveal that copper manganese oxide (M-C) phases are essential for the catalytic activity. While Cat-C, having a very small amount of M-C phases [lin (count) 600], showed moderate activity, Cat-D, which is completely devoid of M-C phases, showed poor catalytic activity. On the other hand, enhanced activity was observed with Cat-B having distinct M-C phases. Optimum activity was observed with Cat-A having maximum M-C phases [lin (count) 800]. Greater activity of spinel oxide may be due to the formation of phases with less ordered arrangements.

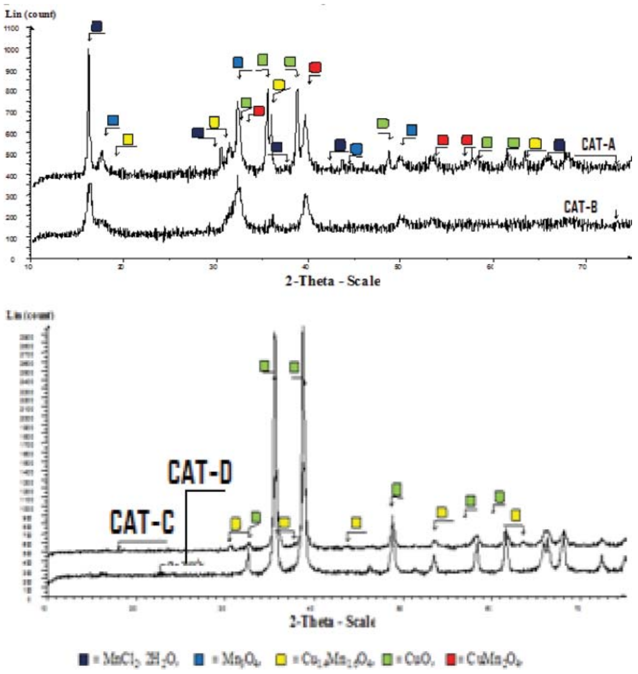


Fig. 1 Powder X-ray diffraction (XRD) of the samples.

However, a small increase in the amount of Cu or Mn results in lower activity, which may be due to blocking of the active sites of the spinel.

The new bimetallic catalyst was easily recovered by filtration after each experiment and could be reused for 1,2,3-triazole synthesis in more than nine successive reactions without significant loss of the catalytic activity (Fig. 2).

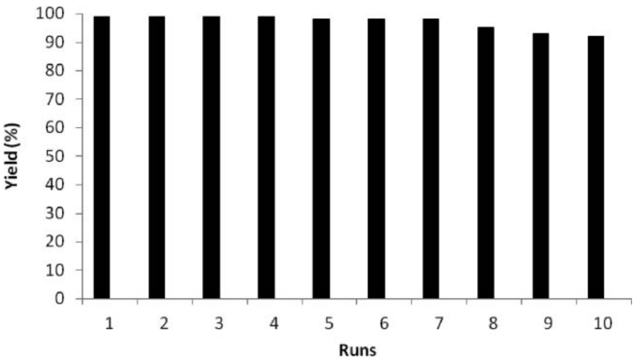
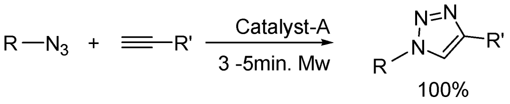
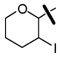
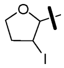
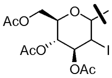
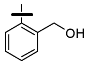
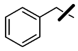
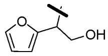
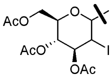
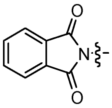
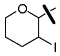
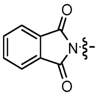
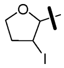
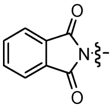
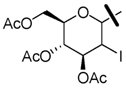
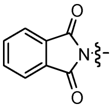
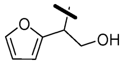
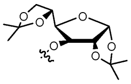
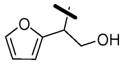
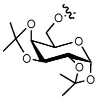
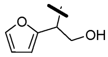
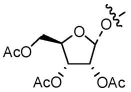
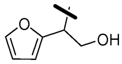
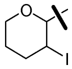


Fig. 2 Recyclability of Cat-A for 1,2,3-triazole synthesis.

It can be clearly seen from the SEM images (Fig. 3) that the morphology and the structural integrity of the Cu–Mn spinel remain almost uniform at the end of run 10, also supported by the XRD spectra of the used catalyst (Supporting information†).

Table 4 Azide–alkyne cycloaddition by bimetallic catalyst-A



Entry	R	R′	Time for solution phase a (hr)/MW conditions/min	Yield for solution phase/Mw conditions%[a]
1	-ξ-CO_2Me		4/3	95/99
2	-ξ-CO_2Me		4/3	96/99
3	-ξ-CO_2Me		4/3	95/99
4	-ξ-CO_2Me		4/3	95/99
5	-ξ-CO_2Me		4/3	95/99
6	-ξ-CO_2Me		4/3	96/99
7	-|-CO_2Et		4/3	95/99
8			5/3	96/99
9			5/3	94/99
10			5/3	95/98
11			5/3	96/99
12			5/5	95/99
13			5/5	95/99
14			5.5/3	96/99
15	ξ-TMS		5/5	90/97

[a] All refer to isolated yield

Table 5 Results of XRD for the catalyst

Sample no	Phases present[a]
CAT-A	Tenorite (CuO); Copper Manganese Oxide (Cu1.4Mn1.6O$_4$); Hausmannite, (Mn_3O_4); Manganese Chloride Hydrate, ($MnCl_2{\cdot}2H_2O$); Crednerite ($CuMn_2O_4$)
CAT-B	Tenorite (CuO); Copper Manganese Oxide (Cu1.4Mn1.6O$_4$); Hausmannite, (Mn_3O_4); Manganese Chloride Hydrate, ($MnCl_2{\cdot}2H_2O$); Crednerite ($CuMn_2O_4$)
CAT-C	Tenorite (CuO); Copper Manganese Oxide (Cu1.4Mn1.6O$_4$)
CAT-D	Tenorite (CuO)

[a] The phases are identified by a search match procedure with the help of DIFFRACPLUS software using JCPDS databank.

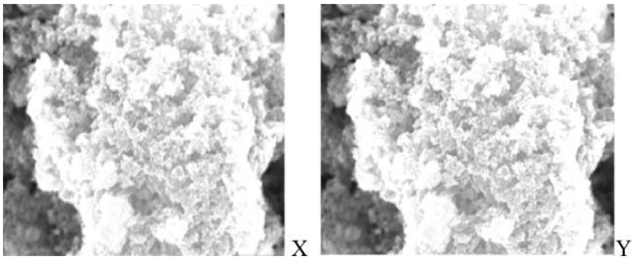


Fig. 3 SEM images of catalyst-A before use (X) and after run 10 (Y).

Finally, the amount of Cu–Mn contamination in the product (crude triazole) after filtration was tested by atomic absorption spectrometer (Supporting information†). It was observed that the amount of Cu-contamination was below detection level in the products, while the levels of Mn were registered in the range of ~110 ppb after 10 cycles.

In summary we have demonstrated the applicability of the first example of a Cu–Mn bimetallic catalyst for an azide–alkyne cycloaddition reaction (CuAAC). The catalyst is robust and can be reused with negligible loss in catalytic activity, both in solution phase and under MW conditions, without the need of a stabilizing agent. Recyclability of the catalyst, the solvent free MW conditions and the atom economy make the process green. It is remarkable that despite its low intrinsic catalytic activity, Mn can significantly influence the activity and selectivity of a Cu–Mn spinel oxide.

Experimental section

Catalyst preparation

Aqueous solutions of $CuCl_2{\cdot}2H_2O$ and $MnCl_2{\cdot}4H_2O$ in a molecular weight ratio of 2 : 0.25 were co-added at a rate of 1 mL min^{-1} under vigorous mechanical stirring at room temperature to form a uniform solution. To the solution, ammonium solution was added drop by drop until pH 8.5 to 8.7 and allowed to stand overnight to form a gel, filtered and washed with double distilled water till free from chloride ions. After keeping overnight at room temperature the cake was allowed to dry in an air oven at 110 °C for 24 h and finally calcined (10 °C min^{-1}) in a muffle furnace at 425 °C for three hours.

General experimental procedure for microwave assisted reactions

Equimolecular amounts of azide (1.0 mmol) and alkyne (1.ommol) were dissolved in 0.5 mL of CH_3CN and the solution was adsorbed on a bimetallic catalyst (10 mg g^{-1} of reactant) in a beaker, placed into the microwave cavity. Microwave irradiation of 100 W was used, the temperature being ramped from room temperature to 120 °C. Once 120 °C was reached, the reaction mixture was held at this temperature for 3 min. After completion of the reaction by TLC, ethyl acetate–acetone (5 : 1 v/v, 10 mL) was added to the reaction mixture, stirred for 15 min, centrifuged and filtered. The bimetallic catalyst was washed twice with ethyl acetate–acetone (5 mL × 2) and dried for further use. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed by evaporation under reduced pressure to afford the corresponding triazole. The product was recrystallized from 95% ethanol or purified by column chromatography on silica gel using petroleum ether–ethyl acetate as the eluent to obtain the pure product.

Acknowledgements

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