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# $Cu^{II}$–Hydrotalcite as an Efficient Heterogeneous Catalyst for Huisgen [3+2] Cycloaddition

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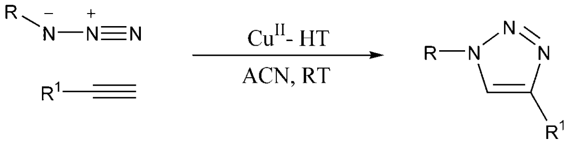
Click chemistry[1]—"a modular synthetic approach towards the assembly of new molecular entities"—finds extensive applications, ranging from functionalizing biological molecules,[2] solubilizing carbon nanotubes,[3] to forming supramolecules.[4] The Huisgen 1,3-dipolar cycloaddition[5] of azides to alkynes to yield 1,2,3-triazoles[6] has emerged as a highly useful and premier example of click chemistry (Scheme 1).



Scheme 1.

In 2002, Sharpless and co-workers[7] and Meldal and co-workers[8] independently discovered the copper-catalyzed version of the regiospecific azide–alkyne cycloaddition which displayed a dramatic rate acceleration of up to $10^7$ times.[9] This reaction seems to be catalyzed by $Cu^I$ species, which are either added directly as cuprous salts (CuI, CuBr) with triphenylphosphine,[10] iminopyridine,[11] or mono- (or) polydentate nitrogen ligands,[12,2b] as N-heterocyclic copper carbene complexes,[13] or generated by the reduction of $Cu^{II}$ salts[14,7] or by comproportionation of a $Cu^0/Cu^{II}$ couple,[9,15] and by copper nanoclusters.[16] Recent research in this area has concentrated on heterogeneous catalytic systems,[17] which can have several advantages such as faster and simpler isolation of the reaction products by filtration, as well as recovery and recycling of the catalyst systems. $Cu^I$ species immobilized onto various supports such as silica,[18] zeolites,[19] activated charcoal,[20] and amine-functionalized polymers[21] were reported recently. However, heterogeneous catalysts immobilized with $Cu^I$ species frequently suffer from the general thermodynamic instability of $Cu^I$, which results in its easy oxidation to $Cu^{II}$ and/or disproportionation to $Cu^0$ and $Cu^{II}$. Consequently most of the reports require an inert atmosphere and anhydrous solvents. Fokin et al.[12d] introduced polytriazolylamines as powerful stabilizing ligands for copper(I), without the need for any reducing agent and inert atmosphere. In contrast to the copper-catalyzed version, ruthenium complexes ([Cp*RuCl($PPh_3$)$_2$], [Cp*RuCl]) are found to be efficient catalysts for producing 1,5-disubstituted triazoles regioselectively.[22] Herein we report copper–aluminum hydrotalcite (3:1) (Cu/Al–HT (3:1) abbreviated hereafter as $Cu^{II}$–HT), as a novel, environmentally benign, recyclable, efficient, and heterogeneous $Cu^{II}$ catalyst system for the Huisgen [3+2] cycloaddition of azides and alkynes, without any sacrificial reducing agents and ligands.

Hydrotalcite-like compounds constitute a class of two-dimensional materials, which are represented by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2][A_{x/n}^{n-}]\cdot mH_2O$, where $M^{II}$ is a bivalent metal cation ($Mg^{II}$, $Cu^{II}$, $Zn^{II}$),[23] $M^{III}$ is a trivalent metal cation ($Al^{III}$, $Cr^{III}$), and $x$ can have values between 0.2 to 0.4. A is the interlayer anion (with a charge $n$), mainly $CO_3^{2-}$ or $NO_3^{-}$. Recently, Angel and Burgess, in their studies on the copper-mediated Huisgen addition of azides to alkynes in the presence of carbonate bases, have observed oxidative dimerization to give 5,5′-bistriazole.[24]

Preliminary investigations in the reaction of benzyl azide with phenylacetylene in the presence of $Cu^{II}$–HT with carbonate ions as interlayer stabilizing anions, revealed they give the expected adduct as a single regioisomer. The $Cu^{II}$ species present in the clay framework has shown excellent reactivity at room temperature without the need for an inert atmosphere. Cu/Al–HT (3:1) was prepared[25] and characterized by powder XRD.[26] To the best of our knowledge, in only one instance, $Cu^{II}$ (as $Cu^{II}$ acetate) was reported to promote the regioselective synthesis of 1,4-disubstituted 1,2,3-

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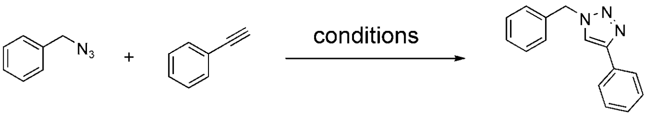
triazoles in water,[27] a result consistent with experimental findings of the rate acceleration in water, since formation of copper acetylide is exothermic by 11.7 kcal mol$^{-1}$ in aqueous medium. However, the chemistry of the click reaction in the present study is largely different as it is carried out in a non-aqueous medium, in which (in the absence of a decreased HOMO–LUMO gap and a consequent rate acceleration in water) this Huisgen [3+2] cycloaddition requires external nitrogen ligands or reducing agents to activate the acetylide or to stabilize the Cu$^{I}$ species to obtain regioselectivity.

In sharp contrast to the use of Cu(NO$_3$)$_2$ alone as a catalyst, Cu$^{II}$–HT affords the corresponding 1,4-disubstituted-1,2,3-triazoles at room temperature as a single regioisomer in good to excellent yields (the remainder (10–15 %) corresponds to recovered starting materials as evident from GC). Control experiments (Table 1) with Mg/Al–HT (Table 1, entry 5) and Zn/Al–HT (Table 1, entry 6), clearly highlight the specific role of Cu$^{II}$ in hydrotalcite layers.[28] We have also investigated the effect of the solvent on the "click" reaction (Table 1), and a marginal decrease in yield is observed when the reaction is performed in toluene, dichloromethane, and methanol (Table 1, entries 7–9). Only in case of THF does the reaction lead to lower conversion. Thus, when the reactions are conducted in acetonitrile, pure products are isolated in good to excellent yields, and a simple workup procedure is sufficient without the need for chromatographic separations. The reusability of the Cu$^{II}$–HT catalyst was also investigated. It was recovered and reused five times without any significant loss in yield (Table 2, entry 1).

Table 1. Synthesis of 1,4-disubstituted-1,2,3-triazoles with different catalysts and solvents.[a]

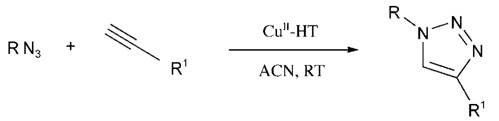


| Entry | Catalyst | Solvent | Time [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | none | ACN | 48 | 0 |
| 2 | Cu/Al–HT | ACN | 6 | 86 |
| 3 | Cu(NO$_3$)$_2$·3 H$_2$O | ACN | 48 | 0 |
| 4 | Al(NO$_3$)$_2$·9 H$_2$O | ACN | 48 | 0 |
| 5 | Mg/Al–HT | ACN | 48 | 0 |
| 6 | Zn/Al–HT | ACN | 48 | 0 |
| 7 | Cu/Al–HT | PhCH$_3$ | 6 | 74 |
| 8 | Cu/Al–HT | CH$_2$Cl$_2$ | 6 | 72 |
| 9 | Cu/Al–HT | MeOH | 6 | 77 |
| 10 | Cu/Al–HT | THF | 6 | 53+ others[c] |

[a] Reaction conditions: benzyl azide (0.37 mmol), phenylacetylene (0.44 mmol), catalyst (10 mg), solvent (1.5 mL), room temperature. [b] Yield of isolated product. [c] Unidentified by-products.

To evaluate the scope of this new Cu$^{II}$-catalyzed process further, reactions of benzyl azide with several aliphatic and aromatic terminal alkynes substituted by electron-donating as well as electron-withdrawing groups were carried out. Likewise, the reactivity of alkynes with various alkyl and aryl azides was also studied. In all the cases, very good yields of a single regioisomer, namely 1,4-disubstituted 1,2,3-triazoles, are obtained. Only in the case of an azide with an electron-withdrawing nitro group (Table 2, entry 5) was the yield lower.

Table 2. Synthesis of 1,4-disubstituted-1,2,3-triazoles with different azides and alkynes.[a]

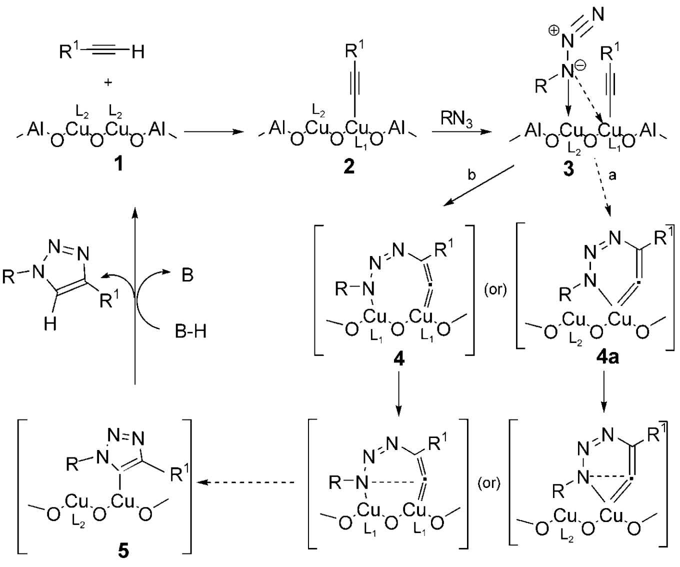


| Entry | Azide R | Alkyne R$^1$ | Time [h] | Yield[b] [%] |
|---|---|---|---|---|
| 1 | C$_6$H$_4$CH$_2$ | C$_6$H$_5$ | 6 | 86, 84[c], 85[d],83[e] |
| 2 | p-ClC$_6$H$_4$CH$_2$ | C$_6$H$_5$ | 8 | 88 |
| 3 | p-CH$_3$C$_6$H$_4$CH$_2$ | C$_6$H$_5$ | 12 | 84 |
| 4 | p-OCH$_3$C$_6$H$_4$CH$_2$ | C$_6$H$_5$ | 10 | 80 |
| 5 | p-NO$_2$C$_6$H$_4$CH$_2$ | C$_6$H$_5$ | 12 | 75 + others[f] |
| 6 | C$_6$H$_5$ | p-CH$_3$C$_6$H$_4$ | 11 | 86 |
| 7 | 3-NH$_2$C$_6$H$_4$ | p-CH$_3$C$_6$H$_4$ | 12 | 82 |
| 8 | C$_6$H$_5$CH$_2$ | p-CH$_3$C$_6$H$_4$ | 10 | 83 |
| 9 | C$_6$H$_5$CH$_2$ | p-OCH$_3$C$_6$H$_4$ | 10 | 78 |
| 10 | C$_6$H$_5$CH$_2$ | p-FC$_6$H$_4$ | 10 | 82 |
| 11 | C$_6$H$_5$CH$_2$ | 3-NH$_2$C$_6$H$_4$ | 9 | 86 |
| 12 | C$_6$H$_5$CH$_2$ | CH$_3$OOC | 7 | 89 |
| 13 | C$_6$H$_5$CH$_2$ | C$_2$H$_5$OOC | 8 | 88 |
| 14 | C$_6$H$_5$CH$_2$ | HOCH$_2$ | 7 | 89 |
| 15 | C$_6$H$_5$CH$_2$ | cyclopropyl | 8 | 86 |

[a] Reaction conditions: azide (0.37 mmol), alkyne (0.44 mmol), catalyst (10 mg), ACN (1.5 mL), room temperature. [b] Yield of isolated pure product. [c, d, e] Yield of successive reused runs. [f] Unidentified by-products.

We have also developed an experimentally convenient one-pot, regioselective synthesis of 1,2,3-triazole from benzyl bromide, sodium azide, and phenylacetylene. Here too, the corresponding 1,2,3-triazole is obtained (in 78 % yield) as a single regioisomer. Since the formation of copper acetylide is exothermic by 11.7 kcal mol$^{-1}$ in aqueous solution,[1f] Cu$^{II}$ species can catalyze this click reaction in aqueous medium. However, in acetonitrile, the same reaction is endothermic by 0.6 kcal mol$^{-1}$. Recently, Fokin et al.,[29] demonstrated that dinuclear alkynyl copper complexes exhibit superior reactivity toward organic azides compared to their monomeric analogues. The barrier to the addition is calculated to be 10.5 kcal mol$^{-1}$, compared to the value of 17 kcal mol$^{-1}$ calulated for the mononuclear copper acetylides.

By analogy with previous reports,[1f,15] a stepwise mechanism involving an initial Cu$^{II}$–acetylide complex **2** is proposed. The role of the second copper atom seems to be the activation of the azide functionality as in **3** and **4/4a** (Scheme 2) towards nucleophilic attack by reducing the electron density of the alkyne. A six-membered-ring intermediate **4a**, as previously proposed,[15] is also likely, in which the neighboring Cu can accelerate the rate by coordination of the Cu to the alkynyl moiety of the reaction center. Since, the chance of having adjacent Cu$^{II}$ ions in the HT framework is very high, the energy barrier for the addition decreases considerably and this thereby accelerates the



Scheme 2. Proposed mechanism for Cu$^{II}$-HT catalyzed [3+2] cycloaddition.

click reaction without any additives. Ring contraction from **4** or **4a** to give **5** is expected to be very fast and this is supported by DFT calculations,[15] which show that the energy barrier for **4a** to **5** is only 0.2 kcal mol$^{-1}$ with acetonitrile as ligand. Protonation of the triazole–copper derivative **5** followed by dissociation of the product completes the reaction and regenerates the catalyst (Scheme 2). The presence of interlayer carbonate ions and surface hydroxyls assists the formation of acetylide.

In conclusion, we have reported for the first time, Cu$^{II}$ as an active species in the Huisgen [3+2] cycloaddition of azides with terminal alkynes in a nonaqueous medium. Furthermore, Cu$^{II}$–HT serves as a novel environmentally benign, highly reactive, recyclable and efficient heterogeneous catalyst without any additives under aerobic conditions.

## Experimental Section

In a 10 mL flask fitted with a magnetic stirrer, the catalyst (10 mg), the azide (0.37 mmol), and the alkyne (0.44 mmol) were stirred in the desired solvent (1.5 mL) at room temperature for 6–12 h. The reaction was monitored by TLC, and after the starting azide had almost disappeared, the reaction was quenched, and the mixture was extracted with dichloromethane (6 mL). The mixture was stirred at room temperature for an additional 2 h. The combined extracts were centrifuged and the solid catalyst was separated, and washed successively with dichloromethane. After being dried, the catalyst can be reused directly without further purification. The organic layer was washed with brine, dried over $Na_2SO_4$, and the solvent was removed by using a rotary evaporator that left a pure triazole.

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**Keywords:** copper · click chemistry · cycloaddition · heterogeneous catalysis · regioselectivity · triazoles

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