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Hydroxyapatite-supported copper(II)-catalyzed azide–alkyne [3+2] cycloaddition with neither reducing agents nor bases in water

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ABSTRACT

Copper(II)-exchanged hydroxyapatite, prepared by ion-exchanging of Ca(II) in calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] with $Cu(NO_3)_2$ at 70 °C in water, functions as a reusable heterogeneous catalyst with neither reducing agents nor bases for azide–alkyne [3+2] cycloaddition at 50 °C in water under air.

Cu(I)-catalyzed azide–alkyne [3+2] cycloaddition is one of the most versatile reactions in click chemistry,[1–3] and has been applied to drug discovery[4] and material sciences[5] as a synthetic tool. It has been proposed that Cu(I) catalysis is essential to the azide–alkyne cycloaddition.[6–8] Cu(II) species such as $CuSO_4$ can also be reduced in situ with reducing agents such as sodium ascorbate to be applied to the azide–alkyne cycloaddition.[3] Heterogeneous Cu(I)-supported catalysts have been applied to the azide–alkyne cycloaddition in repetitive uses. The Cu(I) species have been directly immobilized onto inorganic supports[9,10] or organic polymers,[11] or have been generated in situ from Cu(0)[12,13] or Cu(II)[14] species. γ-Keggin silicotungstate containing dicopper(II) core can be applied to the azide–alkyne cycloaddition without any additives such as reducing agents or nitrogen bases.[15] It was postulated that its actual catalysts were Cu(I) species to which copper(II) species in the γ-Keggin silicotungstate were reduced with terminal alkynes. At that time the alkynes caused oxidative homocoupling to produce 1,4-disubstituted 1,3-butadiynes. Using azides bearing Cu(II)-co-ordinate N-containing groups such as 2-pyridyl or amino groups or multidentate nitrogen ligands chelating to Cu(II), a homogeneous catalytic process with $Cu(OAc)_2$ was also realized without reducing agents.[16] In the $Cu(OAc)_2$-catalyzed cycloaddition, it was speculated that the partial reduction of Cu(II) species to Cu(I) species would take place under either alcohol oxidation or alkyne oxidative homocoupling to prepare a catalytically active Cu(II)/Cu(I) mixed valency dinuclear species.[16c] Cu(I) species seem to be active catalysts in most of the cycloadditions described above. No direct role of Cu(II) species in the azide–alkyne cycloaddition has been recognized, whereas a few Cu(II)-immobilized catalysts have been found to serve as the cycloaddition reducing agents such as sodium ascorbate, in the development of heterogeneous catalytic systems.[17,18]

The availability of hydroxyapatites (HAP) for supporting transition metals has been demonstrated; this must be attributed to their cation-exchange ability and adsorption capability. Some HAP-supported transition metals, such as ruthenium, palladium, copper, and silver, have been applied as heterogeneous catalysts to environmentally benign organic syntheses. These have been prepared by four kinds of methods: adsorption, incorporation, ion-exchange, and nanoparticle formation.[19] We have recently reported that an ion-exchanged HAP-supported palladium(II) (PdHAP), easily prepared from calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and $Pd(NO_3)_2$ in water, functions as a reusable catalyst for the allylic alkylation of allyl methyl carbonate with carbon nucleophiles in water.[20] An ion-exchanged HAP-supported copper(II) (CuHAP), prepared from calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] and $Cu(OAc)_2$ in water, has been applied only as a heterogeneous catalyst to the three-component coupling of aldehydes, amines, and alkynes in refluxing acetonitrile.[21] Thus, we planned to demonstrate the direct role of Cu(II) species in the azide–alkyne [3+2] cycloaddition without any additives such as reducing agents or bases. We would use CuHAP, easily prepared from [$Ca_{10}(PO_4)_6(OH)_2$] and $Cu(NO_3)_2$ in water similarly to PdHAP. Thus we would establish a reusable process of CuHAP in water under air with the aim of advancing ion-exchanged CuHAP for environmentally benign catalysis.

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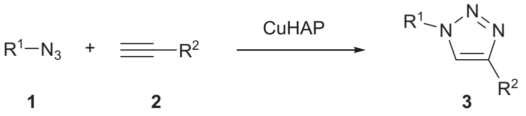


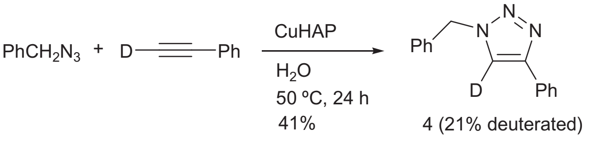
(1)

A calcium hydroxyapatite of Ca/P = 1.67 [$Ca_{10}(PO_4)_6(OH)_2$] (HAP)[22] (2 mmol) was added to a solution of $Cu(NO_3)_2$ (0.20 mmol) in water (150 mL). The solution was stirred at 70 °C for 24 h. The obtained slurry was filtered, washed with deionized water, and dried overnight at 110 °C to afford a Cu(II)-exchanged hydroxyapatite (CuHAP, Cu content: 0.10 mmol g^{-1}) as a blue powder. Inductively coupled plasma (ICP) analysis revealed that Cu^{2+} was absent in the filtrate and that in the filtrate there was a 1.4 molar quantity of Ca^{2+} to that of Cu^{2+} employed. XRD showed that the isomorphic substitution of Ca for Cu had occurred.[23]

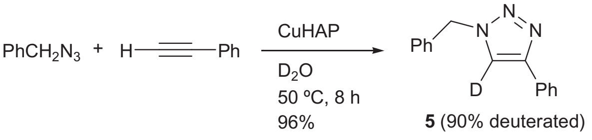
The catalytic activity of the CuHAP was investigated for the [3+2] cycloaddition of benzyl azide (**1**; $R^1 = PhCH_2$) and phenylacetylene (**2**; R^2 = Ph) (Eq. 1). The results are summarized in Table 1. The cycloaddition with CuHAP occurred at 50 °C for 8 h in water under air to afford 1-benzyl-4-phenyl-1,2,3-triazole (**3**; $R^1 = PhCH_2$, R^2 = Ph) regioselectively in 97% yield (entry 1).[24] The cycloaddition with CuHAP needed neither reducing agents such as sodium ascorbate nor bases such as triethylamine,[1,2] and smoothly proceeded under air, in contrast to that with dicopper(II) substituted γ-Keggin silicotungstate.[15] Water (97%) as a solvent was superior to ethanol (37%), dioxane (4%), or toluene (13%) (entries 1–4). Since the cycloaddition with either $Cu(NO_3)_2$ (0.02 mmol) or HAP (0.20 g) afforded almost the same yield (13–14%) as that without CuHAP at 50 °C for 24 h in water (entries 5–7), neither $Cu(NO_3)_2$ nor HAP would serve as a catalyst for the cycloaddition. Benzyl azide (**1**; $R^1 = PhCH_2$) and octyl azide [**1**; $R^1 = CH_3(CH_2)_7$] can be applied to the [3+2] cycloaddition with various alkynes in H_2O, as shown in Figure 1. Internal alkynes such as 1-phenylpropyne and 5-decyne did not react with **1** ($R^1 = PhCH_2$) at all under the same reaction conditions as those of the typical procedure.

The reusability of CuHAP for the [3+2] cycloaddition of **1** ($R^1 = PhCH_2$) and **2** (R^2 = Ph) was demonstrated by maintaining its catalytic activity in eight repetitive uses under almost the same conditions as those of the typical procedure in H_2O (Table 1, entry 1), as shown in Table 2. Although the ionic radius of Cu^{2+} is smaller than that of Ca^{2+}, the powder X-ray diffraction (XRD) peaks for ion-exchanged CuHAP were the same as those of calcined HAP, and then did not change even after eight repetitive uses. X-ray photoelectron spectroscopy (XPS) confirmed no variation of binding energy and intensity of Cu $2p_{3/2}$ peaks between fresh CuHAP and eight repetitively used CuHAP; a small peak of 934.3 eV that would be assigned to Cu(II) was observed even after eight repetitive uses. X-ray fluorescence (XRF) analyses revealed that most of the copper had remained in the HAP matrix even after eight repetitive uses.

The [3+2] cycloaddition of **1** ($R^1 = PhCH_2$, 1.0 mmol) and 1-deutero-2-phenylethyne (1.5 mmol) slowly proceeded at 50 °C in H_2O (1 mL) to produce only 41% yield of 21%-deuterated **4** at 5-position even after 24 h (Eq. 2), while the [3+2] cycloaddition of **1** ($R^1 = PhCH_2$, 1.0 mmol) and **2** (R^2 = Ph, 1.5 mmol) at 50 °C for 8 h in D_2O (1 mL) afforded 90%-deuterated **5** at 5-position in 96% yield (Eq. 3).



(2)



(3)

Table 1
[3+2] Cycloaddition of **1** ($R^1 = PhCH_2$) and **2** (R^2 = Ph)[a]

Entry	Catalyst	Cu (mmol)	Solvent	Time (h)	**3**, Yield (%)
1	CuHAP	0.02	H_2O	8	97
2	CuHAP	0.02	Ethanol	8	37
3	CuHAP	0.02	Dioxane	8	4
4	CuHAP	0.02	Toluene	8	13
5	$Cu(NO_3)_2$	0.02	H_2O	24	13
6	HAP	0	H_2O	24	14
7	—	0	H_2O	24	14

[a] The [3+2] cycloaddition of benzyl azide (1.0 mmol) and phenylacetylene (1.5 mmol) was carried out with CuHAP (Cu 0.02 mmol) at 50 °C in a solvent (1 mL).

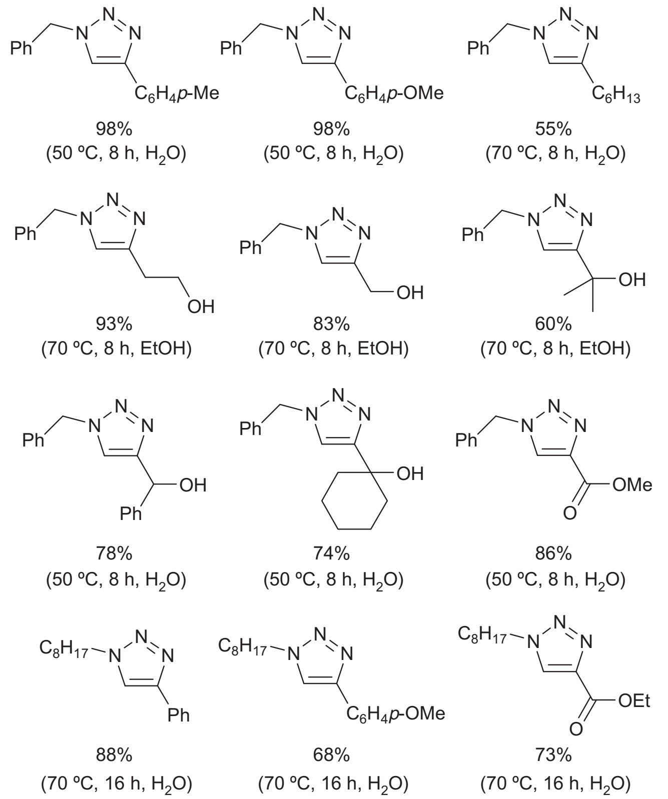


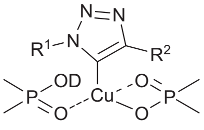
Figure 1. CuHAP-catalyzed azide–alkyne [3+2] cycloaddition.

Table 2
Reusability of CuHAP for the azide–alkyne [3+2] cycloaddition[a]

Repetitive use	1st	2nd	3rd	4th	5th	6th	7th	8th
Yield (%)	95	96	94	95	86	78	80	80

[a] The [3+2] cycloaddition of benzyl azide (1.0 mmol) and phenylacetylene (1.5 mmol) was carried out with CuHAP (Cu 0.05 mmol) at 50 °C for 16 h in H_2O (1 mL).

On the basis of (1) the performance without either any reducing agent or any base, (2) no detection of alkyne oxidative homocoupling products, namely 1,4-disubstituted 1,3-butadiynes, in the reaction with excess alkynes under air, (3) the XPS assignment of Cu(II) species in repeatedly used CuHAP, (4) the extremely slow reaction of 1-deutero-2-phenylethyne in H_2O, in contrast to the reaction of **2** (R^2 = Ph) in D_2O (Eqs. 2 and 3), and (5) no availability of internal alkynes, the direct participation of Cu(II) species and the formation of Cu(II)-acetylide complex as a key and rate-determin-



A

Figure 2. A final intermediate **A** for preparing **4** (21%-deuterated) in H_2O.

ing step was suggested.[18] Part of deuterated phosphoric acids in HAP, generated from 1-deutero-2-phenylethyne together with the initial Cu(II)-acetylide intermediate, were probably maintained until forming a final intermediate **A**[6–8] as shown in Figure 2, similar to the general 5-cuprated 1,2,3-triazole intermediates in Cu(I)-catalyzed azide–alkyne cycloadditions. Thus, 21%-deuterated **4** would be produced in dependence on the D–H exchange of deuterated phosphoric acids with H_2O.

In conclusion, at this point in time from the results of no detection of alkyne oxidative homocoupling products and XPS assignment of Cu(II) species, we speculated that Cu(II) species on CuHAP served as a reusable catalyst for the azide–alkyne [3+2] cycloaddition without either any reducing agent or any base in H_2O under air. The phosphate group of HAP would serve efficiently for the retention of Cu(II) species to HAP support. The smooth progress of the [3+2] cycloaddition in H_2O seems to be attributable to the locally high concentration of liquid substrates, namely both azides and alkynes on the CuHAP surface, which probably bases on the substrate-dispersing effect of H_2O and the substrate-adsorbing effect of CuHAP. Therefore the CuHAP-catalyzed azide–alkyne [3+2] cycloaddition will be considered as one of the most environmentally-benign processes.

Acknowledgment

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Supplementary data

Supplementary data (XRD of HAP, fresh CuHAP and repetitively reused CuHAP, XPS and XRF of fresh CuHAP and repetitively reused CuHAP, and IR and NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.060.

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24. *Typical procedure for CuHAP-catalyzed azide–alkyne* [3+2] *cycloaddition*: To a suspension of CuHAP (0.2 g, Cu 0.02 mmol) in water (1 mL) were added benzyl azide (**1**; $R^1 = PhCH_2$, 0.13 g, 1 mmol) and phenylacetylene (**2**; $R^2 = Ph$, 0.15 g, 1.5 mmol). After the suspension was shaken at 50 °C for 8 h under air in a shaking aluminum block (Nissinrika Co., Block Shaker NX-70B, stroke: 10 mm, speed: 220–230 rpm), ethyl acetate (8 mL) was added to the suspension. The solution was separated from CuHAP by centrifugation followed by decantation. The same operation with ethyl acetate (8 mL) was repeated five times. The separated CuHAP was reused after being evacuated to dryness. Dichloromethane (100 mL) was added to the residue after removing ethyl acetate and water in the combined solution. The solution was dried over anhydrous $MgSO_4$. After evaporation of dichloromethane and purification by column chromatography (silica gel, hexane/ethyl acetate = 3:1), 0.23 g (97%) of 1-benzyl-4-phenyl-1,2,3-triazole (**3**; $R^1 = PhCH_2$, $R^2 = Ph$) was obtained as a colorless solid. The structures of all products were confirmed by the comparison of spectroscopic values (IR and NMR) with those of authentic samples in the literature: see Supplementary data.