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Hydration of Terminal Alkynes Catalyzed by Water-Soluble Cobalt Porphyrin Complexes

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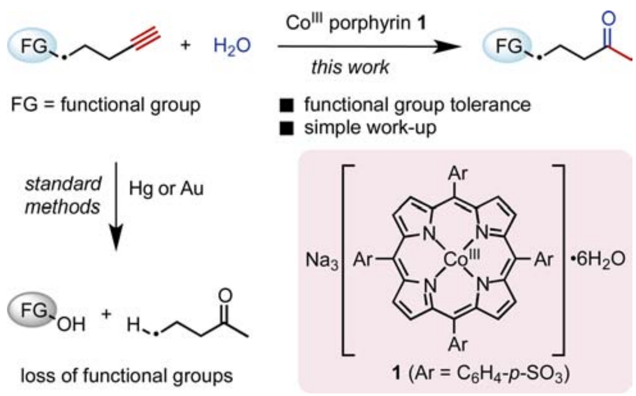
Supporting Information

ABSTRACT: Water-soluble cobalt(III) porphyrin complexes were found to promote the hydration of terminal alkynes to give methyl ketones. The alkyne hydration proceeded in good to excellent yield with 0.1 to 2 mol % cobalt catalyst **1** and was compatible with the presence of acid/base- or redox-sensitive functional groups such as alkyl silyl ethers; allyl ethers; trityl ethers; benzyl ethers; carboxylic esters; boronic esters; carboxamides; nitriles; and nitro, iodo, and acetal groups. Some of the alkyne substrates tested here are otherwise difficult to hydrate. The alkyne hydration can be performed on a gram scale, and the catalyst can be recovered by aqueous workup.

Catalytic hydration of C−C triple bonds is of particular interest in organic synthetic chemistry, as it provides important carbonyl compounds for both the bulk and fine chemical industries. In this respect, Markovnikov hydration of alkynes is an ideal method for the synthesis of ketones; the alkyne hydration should proceed using water as a reagent with 100% atom economy if a suitable catalyst is available.[1] Terminal alkynes are frequently used as substrates because Markovnikov hydration of terminal alkynes generally gives the methyl ketones exclusively.[1a,2−10] Mercury(II) salts combined with acids, such as HgO/H_2SO_4 and HgO/BF_3, are reliable catalysts for the hydration of alkynes and were widely used until the discovery of the potential toxicity of mercury compounds.[2] Alternative metallic catalysts have been sought over the years, mainly among transition metals, such as Pt,[3] Fe,[4] Pd,[5] Ir,[6] Ag,[7] Sn−W,[8] and Au.[9] Whereas most of these metals have lower reactivity and selectivity than mercury, gold complexes can efficiently catalyze the hydration of alkynes. For example, $(Ph_3P)AuCH_3/H_2SO_4$ mediates the hydration of 1-octyne with a high turnover frequency.[9d] Alkyne hydration using the $(IPr)AuCl/AgSbF_6$ [IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] or $(IPr)AuOH/HSbF_6$ system affords a high turnover number.[9g,k] These systems are efficient for the hydration of simple alkynes.[11] A single-component catalyst, $AuSPhosNTf_2$, [SPhos = dicyclohexyl(2′,6′-dimethoxybiphen-2-yl)phosphine] catalyzes the hydration of alkynes bearing various functional groups at room temperature.[9h] Nevertheless, the development of more chemoselective hydration of functionalized terminal alkynes remains a challenge for fine organic synthesis, as certain acid-labile functional groups are not well tolerated under the conditions typically used for mercury- or gold-catalyzed alkyne hydration (Scheme 1). To overcome these deficiencies, we have developed a method for hydration of terminal alkynes in the presence of the water-soluble cobalt(III) porphyrin complex **1**.[12] This complex catalyzes the hydration of various terminal alkynes, including acid-sensitive substrates that are otherwise difficult to hydrate (Scheme 1).

Scheme 1. Hydration of Terminal Alkynes Bearing Functional Groups



We initially found that the combination of cobalt dichloride and a porphyrin ligand promotes the hydration of terminal alkynes (Table 1). When a methanol solution of 1-decyne (**2a**, 0.50 mmol), water (0.4 mL, 22 mmol), cobalt dichloride (2 mol %), and tetrakis(*p*-sulfonatophenyl)porphyrin tetrasodium salt (Na_4H_2TPPS, 2 mol %) was heated at 100 °C for 12 h under an aerobic atmosphere in a closed glass vessel, **2a** was completely consumed, giving 2-decanone (**3a**) in 92% yield (entry 1). Use of other metal chlorides or HCl instead of $CoCl_2$ resulted in decreased conversion of **2a** (entries 2−9). The reaction was not promoted in the absence of $CoCl_2$ or Na_4H_2TPPS (entries 10 and 11). The use of an argon atmosphere instead of and aerobic atmosphere resulted in a decrease in conversion (entry 12).[13] The use of salen ligands instead of Na_4H_2TPPS was less effective, and other ligands such as dipyrromethenes, bipyridines, terpyridines, salans, and salalens gave no desired product. Other substituted porphyrins were also effective (Table S1 in the Supporting Information), but we chose Na_4H_2TPPS because it can easily be separated from the product. At a catalyst loading of 0.1 mol %, $CoCl_2/Na_4H_2TPPS$ promoted the hydration of **2a** but with decreased conversion

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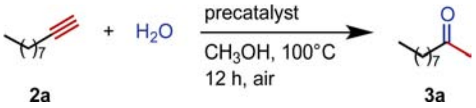
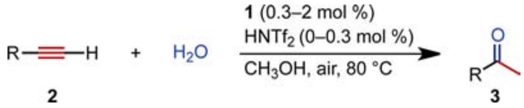
Table 1. Screening of Precatalysts for the Hydration of 1-Decyne (2a) to 2-Decanone (3a)[a]

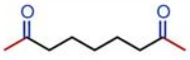
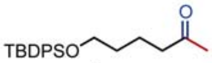
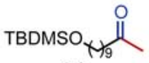
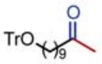
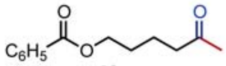
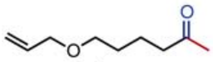
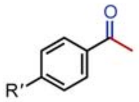
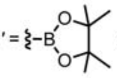


entry	precatalyst (mol %)	conv. (%)[b]
1	$CoCl_2$ (2), Na_4H_2TPPS (2)	>99 (92[c])
2	$CrCl_2$ (2), Na_4H_2TPPS (2)	<5
3	$MnCl_2$ (2), Na_4H_2TPPS (2)	50
4	$FeCl_2$ (2), Na_4H_2TPPS (2)	17
5	$FeCl_3$ (2), Na_4H_2TPPS (2)	21
6	$NiCl_2$ (2), Na_4H_2TPPS (2)	56
7	$CuCl_2$ (2), Na_4H_2TPPS (2)	<1
8	$ZnCl_2$ (2), Na_4H_2TPPS (2)	<1
9	HCl (200), Na_4H_2TPPS (2)	<1
10	Na_4H_2TPPS (2)	<1
11	$CoCl_2$ (2)	<1
12[d]	$CoCl_2$ (2), Na_4H_2TPPS (2)	34
13[e]	$CoCl_2$ (0.1), Na_4H_2TPPS (0.1)	59
14[e]	**1** (0.1)	24
15[e]	**1** (0.1), $HNTf_2$ (0.3)	96
16[d,e]	**1** (0.1), $HNTf_2$ (0.3)	25
17[e,f]	**1** (0.3), $HNTf_2$ (0.3)	>99 (96[c])

[a] Conditions: $[\mathbf{2a}]_0$ = 0.20 M, precatalyst (2 mol %), H_2O (44 equiv). Reactions were carried out at 100 °C for 12 h under aerobic conditions in closed glass vessels, unless otherwise noted. Na_4H_2TPPS denotes tetrakis(*p*-sulfonatophenyl)porphyrin tetrasodium salt. [b] Of alkyne **2a**, determined by GC using tridecane as an internal standard. [c] Isolated yield of **3a**. [d] The reaction was carried out under an argon atmosphere. [e] $[\mathbf{2a}]_0$ = 0.80 M, H_2O (4.4 equiv). [f] 80 °C.

Table 2. Hydration of Terminal Alkynes 2b−n Using 1 To Give Ketones 3b−n[a]



entry	2	product (3)	1 (mol %)	$HNTf_2$ (mol %)	*t* (h)	yield (%)[b]
1[c]	**2b**	 **3b**	0.6	0.3	12	90
2[d]	**2c**	 **3c**	2	0	5	93
3[d]	**2d**	 **3d**	2	0	6	75
4[d]	**2e**	 **3e**	2	0	8	91
5	**2f**	 **3f**	0.3	0.3	14	98
6	**2g**	 **3g**	0.3	0.3	12	92
7	**2h**	 **3h** (R′ = H)	0.3	0.3	12	92
8	**2i**	**3i** (R′ = *t*-C_4H_9)	0.3	0.3	12	96
9	**2j**	**3j** (R′ = $NHCOCH_3$)	0.3	0.3	12	99
10	**2k**	**3k** (R′ = I)	0.3	0.3	12	97
11[d]	**2l**	**3l** (R′ = )	2	0	4	91
12	**2m**	**3m** (R′ = CN)	2	0.3	36	95
13	**2n**	**3n** (R′ = NO_2)	2	0.3	36	89

[a] Reactions were run in methanol with $[\mathbf{2}]_0$ = 0.80 M and H_2O (4.4 equiv) at 80 °C under aerobic conditions in a closed reaction vessel, unless otherwise noted. TBDPS = *tert*-butyldiphenylsilyl [*t*-$C_4H_9(C_6H_5)_2Si$]. TBDMS = *tert*-butyldimethylsilyl [*t*-$C_4H_9(CH_3)_2Si$]. Tr = trityl [$(C_6H_5)_3C$]. [b] Isolated yields. [c] H_2O (8.9 equiv). [d] Without $HNTf_2$, $[\mathbf{2}]_0$ = 0.10 M, H_2O (22 equiv). [e] The rest of the material was deprotected.

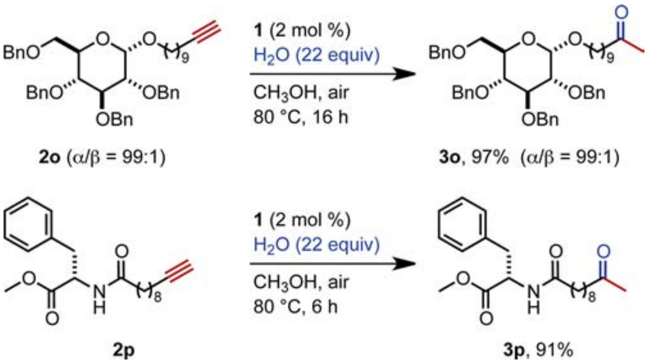
(entry 13). Because the UV−vis spectra of the reaction media indicated the presence of cobalt(III) porphyrin complexes, we prepared tetrakis(*p*-sulfonatophenyl)porphyrin cobalt(III) trisodium salt hexahydrate (**1**).[12,13] Cobalt complex **1** is a bench-stable, purple solid, and its aqueous solution (5 mM) is near-neutral (pH 6.9−7.0). Precatalyst **1** was found to promote the hydration of **2a** to give **3a** under near-neutral pH conditions (entry 14). The alkyne hydration was even faster in the presence of acid [triflimide ($HNTf_2$), 0.3 mol %] (96%; entry 15). Again, the use of an aerobic atmosphere was necessary to maintain high catalytic activity. When the reaction was carried out under argon under otherwise identical conditions, **3a** was obtained in low yield and a reduced cobalt(II) porphyrin complex was detected in the reaction mixture (entry 16). Thus, **2a** (5.0 mmol) was hydrated at 80 °C under aerobic, acidic conditions, giving ketone **3a** in 96% isolated yield (entry 17).

As listed in Table 2, cobalt complex **1** allowed hydration of various terminal alkynes **2**, affording the methyl ketones **3**. Hydration of 1,8-nonadiyne (**2b**) gave diketone **3b** in 90% yield with an increased amount of **1** (entry 1).[11,14] Alkyne **2c** containing an alkyl *tert*-butyldiphenylsilyl (TBDPS) ether group was tested, as the alkyl silyl ether functionality is frequently used in organic synthesis[15] but is often cleaved under the conditions typically used for alkyne hydration using mercury or gold catalysis.[16] To our delight, cobalt porphyrin **1** served as an excellent precatalyst for the hydration of alkyne **2c** to give ketone **3c**. When a methanol solution of **2c**, water, and **1** was heated at 80 °C for 5 h under an aerobic atmosphere with no acidic additive, the corresponding methyl ketone **3c** was obtained in 93% yield (entry 2). The more challenging *tert*-butyldimethylsilyl (TBDMS) and trityl (Tr) ethers showed good stability under the same reaction conditions, providing ketones **3d** and **3e** in 75 and 91% yield, respectively (entries 3 and 4). Hydration of alkyne **2f** bearing a benzoic ester functionality gave the corresponding ketone **3f** satisfactorily (entry 5). The terminal alkene in the allylic ether of **2g** remained intact under the slightly acidic reaction conditions, and **3g** was obtained in 92% yield (entry 6). Thus, this hydration method is complementary to the palladium-catalyzed Wacker reaction of terminal alkenes.[17]

The present catalytic system is also applicable to aromatic alkynes (Table 2, entries 7−13). For instance, phenylacetylene (**2h**) was smoothly hydrated under typical conditions, affording acetophenone (**3h**) in 92% yield (entry 7). Aromatic alkynes **2i−l** were hydrated to give substituted acetophenones **3i−l** in good to excellent yields without loss of the respective *tert*-butyl, amide, iodo, and boronic ester functionalities (entries 8−11). The tolerance of the iodo and boronic ester groups indicates the immediate utility of the product for cross-coupling chemistry. Hydration of electron-deficient aromatic alkynes has been considered difficult to achieve because of the decreased π-basicity of such alkynes toward soft Lewis acid catalysts.[1a] The present cobalt catalysis is effective for these substrates. The use of 2 mol % **1** and 0.30 mol % $HNTf_2$ allowed complete hydration of *p*-cyanophenylacetylene (**2m**) and *p*-nitrophenylacetylene (**2n**) to give the ketones **3m** and **3n**, respectively (entries 12 and 13). Interestingly, the tolerance of the cyano group in **2m** under the cobalt-catalyzed alkyne hydration conditions contrasts with the case of the catalytic activity of cobalt-containing nitrile hydratases[18] and artificial cobalt complexes[19] for hydration of nitriles to amides. No reaction took place with simple internal alkynes such as 3-hexyne or diphenylacetylene.

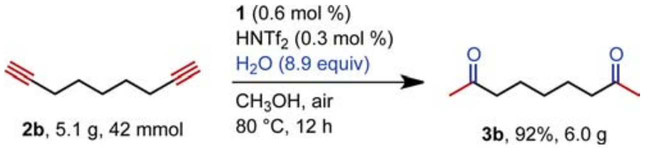
To determine the potential for using the cobalt-catalyzed alkyne hydration in late-stage transformations of complex molecules, the hydration of terminal alkynes attached to biomolecular scaffolds was tested (Scheme 2). Alkyne **2o** conjugated with a benzyl-protected sugar was smoothly hydrated to give ketone **3o** in 97% yield without loss of the glycosyl linkage. The stereochemistry at the anomeric center remained unchanged (α/β = 99:1). Similarly, selective hydration of alkyne **2p** linked with a protected amino acid gave the corresponding ketone **3p** in 91% yield under our standard conditions. Benzyl ether, acetal, alkyl ester, and carboxamide moieties also tolerated the reaction conditions. The results listed in Table 2 and Scheme 2 indicate the potential applicability of the present method to hydration of terminal alkynes in the presence of acid/base- or redox-sensitive functional groups.

Scheme 2. Hydration of Terminal Alkynes on Sugar and Amino Acid Scaffolds



To check the scalability of the present method, a gram-scale hydration of 1,8-nonadiyne (**2b**) was carried out (Scheme 3). Hydration of **2b** (5.1 g, 42 mmol) proceeded smoothly, giving the corresponding diketone **3b** in 92% yield. Because the cobalt porphyrin catalyst **1** is highly water-soluble, the catalyst could be separated by extraction using water and ethyl acetate, and analytically pure product **3b** was obtained by recrystallization. Thus, chromatographic purification was not required in this case.

Scheme 3. Gram-Scale Double Hydration of Terminal Alkyne 2b



In addition, reuse of **1** was tested with **2c** as an alkyne substrate. After the hydration reaction, the water-soluble cobalt complex **1** was recovered by concentration of the water layer after extraction with *n*-hexane and then reused for further reactions to generate ketone **3c** from **2c** (first run, 8 h, 91% yield; second run, 10 h, 90% yield; third run, 14 h, 91% yield; see entry 2 of Table 2 for the reaction conditions).

Preliminary mechanistic studies using alkyne **2h** indicated the following: (1) The hydration essentially involves hydroalkoxylation of the alkyne with methanol followed by hydrolysis of the methyl vinyl ether and/or dimethyl acetal (Table S2). (2) The rate of the hydroalkoxylation reaction is first order in precatalyst, first order in **2h**, and second order in CH_3OH (Figures S1 and S2). (3) The Hammett ρ value of −2.1 for hydroalkoxylation of *p*-substituted phenylacetylenes using methanol indicated the formation of a cationic transition state in the rate-determining step (Figure S3). (4) The primary kinetic isotope effect of 2.6 obtained using methanol-d_1 implied that proton transfer is involved in the rate-determining step (Figure S4). (5) The catalysis is better promoted when electron-deficient porphyrin ligands are used (Table S1). Overall, these results are consistent with a mechanism in which the cobalt porphyrin complex promotes hydroalkoxylation/hydration of the alkyne by activating the alkyne as a monomeric soft Lewis acid.[20] Further experimental and theoretical studies to elucidate the mechanistic details are underway in our laboratory.

In summary, hydration of terminal alkynes to methyl ketones was achieved using water-soluble cobalt porphyrin complex **1**. To our knowledge, this is the first example of cobalt-catalyzed hydration of alkynes. The catalysis is best performed under slightly acidic, aerobic conditions and can be performed under near-neutral conditions that are compatible with the presence of acid-labile functional groups.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data, and supporting figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Hydration of **2c** to **3c** using the $(Ph_3P)AuCH_3/H_2SO_4$ and $AuSPhosNTf_2$ systems resulted in 0 and 80% retention of the silyl ether linkage, respectively.[9h]

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