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Cobaloxime-catalyzed hydration of terminal alkynes without acidic promoters†

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Cobaloxime ($Co(dmgBF_2)_2{\cdot}2H_2O$), an inexpensive first-row transition-metal complex, catalyzed hydration of terminal alkynes gave the corresponding methyl ketones in good to excellent yields under neutral conditions (additional protic acids and silver salts are not required). A wide range of functional groups, such as allyl ether, benzyl ethers, carboxylic esters, imides, amides, nitro, and halogens, were tolerated. The mild reaction conditions together with the inexpensive feature and easy availability of the catalyst well address the current challenges in the field of alkyne hydration.

The well-known catalytic hydration of alkynes (Scheme 1) emerges as a very important transformation to produce carbonyl compounds atom-economically with a suitable catalyst. The reaction is classically catalyzed by $HgO–H_2SO_4$ (Kucherov catalyst)[1] or $HgO–BF_3$ (Hennion–Nieuwland catalyst)[2] in acidic media. However, the environmental issue caused by the high toxicity of the mercury salts prevented their larger use. Thus, alternative catalysts for the hydration of alkynes have been extensively searched for over the last few decades; transition-metal-complex catalysts containing Ru,[3] Rh,[4] Pt,[5] Ir,[6] Pd,[7] Cu(II),[8] Fe(III),[9] Ag(I)[10] and Au[11] have been developed as environmentally benign catalysts for such transformation; nevertheless, most of those catalysts are not efficient enough compared to the Hg system. In addition, alkyne hydration in the absence of metals generally requires harsh conditions.[12] Recently, cationic gold(I) species[11f–h,13] $[Au(L)]^+$ (L = phosphine or N-heterocyclic carbene) have emerged as some of the most promising catalysts for alkyne hydration because of their high reactivity and selectivity. However, the high price of both the catalyst and ligand still stimulates people to develop methods based on inexpensive first-row transition metals as catalysts.

More recently, breakthroughs in this field were made by Naka, Lin and Weck, respectively, who employed a Co^{III} porphyrin[14] and its MOF complexes[15] or micelle supported catalysts[16] in the hydration of terminal alkynes, which provided high reactivity and were more importantly compatible with a variety of acid/base- or redox-sensitive functional groups. Nevertheless, the high cost of the porphyrin ligand (*e.g.* NaH_2TPPS: 350$ per mol from Strem) is still a barrier to its application in preparative-scale synthesis. Therefore, a more economical and efficient catalytic system with broad functional group compatibility is still highly desirable.

Cobaloximes (bisdimethylgloximatocobalt complexes) are commonly used as analogs of vitamin B_{12} in research studies. These complexes are bench stable and could be easily prepared in large quantities.[17] Recently, extensive chemical, electrochemical and photochemical studies have focused on characterizing their H_2 evolution reactivity in water splitting.[18] The square planar ligand field in the cobaloximes well mimics the corrin system in vitamin B_{12},[19] which not only well stabilizes the reactive cobalt(III) centre but also provides less steric hindrance at their axial position. In this regard, we envisioned that those complexes might serve as strong Lewis acids that might enable other important transformations. Herein we report the first example of cobaloxime-catalyzed efficient hydration of terminal alkynes under neutral conditions with wide functional group compatibility.

We initiated our investigations into the terminal alkyne hydration by examining cobaloxime complexes (**Cat 1–Cat 5**) using **1a**[20] as the substrate. We were pleased to find that the desired methyl ketone product **2a** was formed in 86% yield at 80 °C either with 2 mol% **Cat 1** or **Cat 2** in methanol (Table 1, entries 1 and 2). However, **Cat 3** and **Cat 4** with additional axial pyridine ligands show a very poor catalytic reactivity (Table 1, entries 3 and 4) in this transformation, which might be due to the relatively rich electronic feature of the cobalt atom leading to a weaker Lewis acidity. It was also found that silver salt additives play an important role when **Cat 2** was used as the

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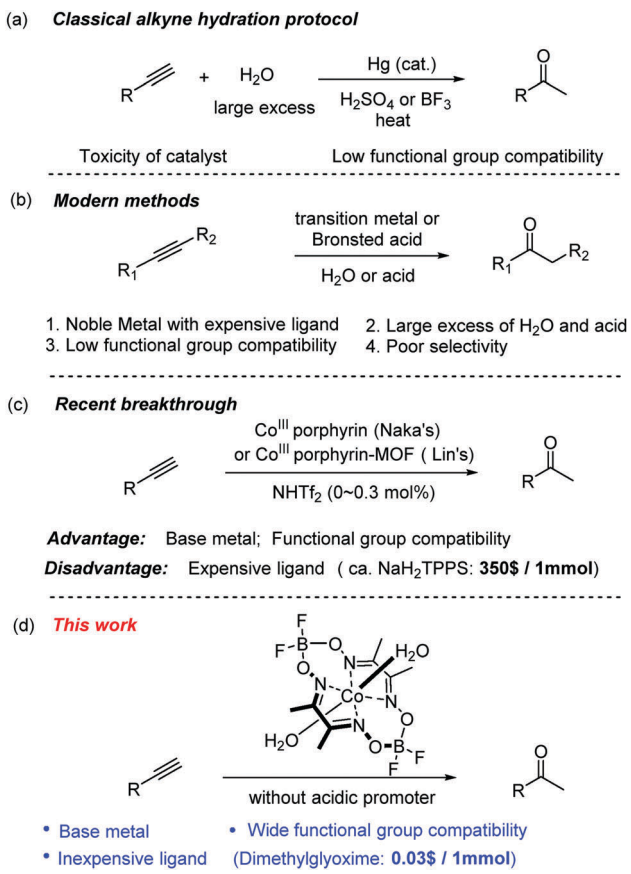
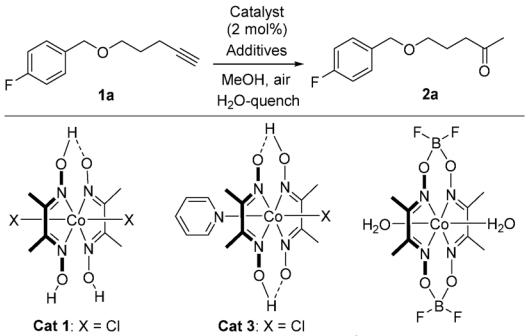


Scheme 1 Hydration of alkynes.

catalyst in this reaction. AgOAc (entry 5) and AgOBz (entry 6) dramatically deactivated the catalyst reactivity (led to low yields or long reaction times) while $AgNO_3$ (entry 7) and AgOTf (entry 8), which might *in situ* form the cationic cobaloxime species, improved the yield to 87% and 97% respectively. A similar effect was also observed with **Cat 3** as the catalyst (entry 9) which led to a 52% yield of **2a** compared to its totally inactive feature previously (entry 3). A tetrafluoronated cobaloxime $Co(dmgBF_2)_2{\cdot}2H_2O$ (**Cat 5**, dmg represents dimethylglyoximate) was later found to be more effective as a single component catalyst. In this case, silver salt additives are no longer required which could greatly reduce the catalyst cost and simplify the experimental operation as well. With this catalyst, the reaction could be finished within a much reduced reaction time (entry 10). A further investigation revealed that the yield could be improved to 99% by increasing the catalyst loading to 5 mol% (entry 11) and by even retaining its reactivity (entry 12) under a lower temperature (65 °C). In comparison, the reactivity of dibromocobaloxime **Cat 2** was inferior to **Cat 5** under the same temperature (entry 13). It is worth noting that replacement of the aerobic atmosphere with argon resulted in a significant decrease in conversion (entry 14), which may indicate that the real catalyst might be the Co(III) species generated *in situ*. The reactions did not proceed when treated with $CoBr_2$ or (salen)$Co^{3+}F$ as the catalyst (entries 15 and 16), which proves that the square planar ligand field in cobaloxime plays a critical role in alkyne hydration.

Table 1 Screening of the catalysts of the hydration of **1a**[a]

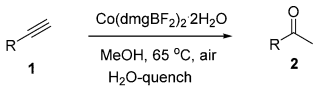


Entry	Catalyst	Additive	Time (h)	Temp. (°C)	Yield[b] (%)
1	Cat 1		3.5	80	86
2	Cat 2		3.5	80	85
3	Cat 3		3.5	80	<10
4	Cat 4		3.5	80	<5
5	Cat 2	AgOAc	3.5	80	11
6	Cat 2	AgOBz	3.5	80	35
7	Cat 2	$AgNO_3$	3.5	80	87
8	Cat 2	AgOTf	3.5	80	97
9	Cat 3	AgOTf	9	80	52
10	Cat 5		3.5	80	87
11[c]	Cat 5		1.5	80	99
12[c]	**Cat 5**		**3.5**	**65**	99 (96[d])
13[c]	Cat 2		3.5	65	85
14[e]	Cat 5		3.5	65	9
15	$CoBr_2$		10	65	<1
16[f]	Salen-$Co^{3+}F$		10	65	<1

[a] Reaction conditions: 0.25 mmol of alkyne **1a**, cobaloxime (2 mol%), and 4 mol% additives in MeOH (1 mL), heated at the indicated temperature under aerobic conditions. [b] Yield based on ^{19}F NMR. [c] 5 mol% cobaloxime was used. [d] Isolated yield. [e] The reaction was carried out under an argon atmosphere. [f] Salen = *N*,*N*′-bis(salicylidene)-1,2-cyclohexanediamine.

Having established the optimized conditions, the hydrations of a variety of alkynes **1** were conducted. As listed in Table 2, phenylacetylene **1b** gave the acetophenone in 90% yield. Phenylacetylenes bearing electron rich groups such as methyl and methoxyl at the *meta*-, *ortho*- or *para*-position were all converted to their corresponding methyl ketones in decent yields (Table 2, entries 2, 3, 8, 10 and 12). Substrates with halogen atoms also gave good yields (entries 4–6). Phenylacetylenes with a strong electron withdrawing nitro group (entries 7, 9 and 11), which were considered difficult to hydrolyze due to their decreased π-basicity, were also converted to methyl ketones albeit in slightly lower yields. Both α- and β-naphthylacetylene provided good yields under the standard conditions (Table 2, entries 13 and 14). In the case of aliphatic alkynes, substrates with a variety of functional groups such as Cl, benzoyl, a silyl group and allyl ether (Table 2, entries 15–18) were tolerated and led to good yields of methyl ketone. Benefiting from the near-neutral conditions of our method, highly acidic sensitive substrates such as **1t** and **1u** (with MOM and Boc groups) were proven to be suitable substrates; the corresponding products **2t** and **2u** were isolated in 91% and 86% respectively (entries 19 and 20). The imide functionality, known as the common protecting group for nitrogen, was also compatible under our conditions and gave excellent yields (entries 21 and 22).

Table 2 Substrate scope of alkyne hydration catalyzed by $Co(dmgBF_2)_2 \cdot 2H_2O$[a]

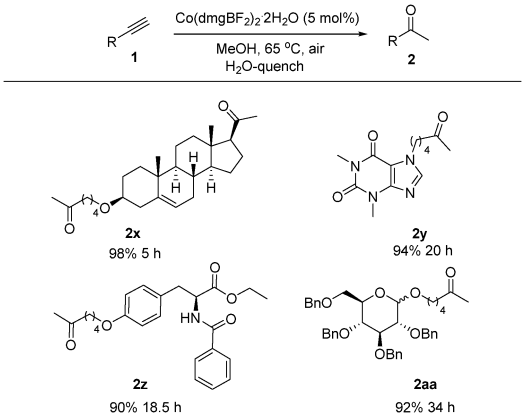


Entry	1	2	Time (h)	Yield[b] (%)
1	**1b**	**2b**	5	90
2	**1c** (R = Me)	**2c** (R = Me)	2.5	95
3	**1d** (R = OMe)	**2d** (R = OMe)	4	90
4	**1e** (R = Cl)	**2e** (R = Cl)	3.5	94
5	**1f** (R = Br)	**2f** (R = Br)	4.5	92
6	**1g** (R = F)	**2g** (R = F)	3.5	94
7	**1h** (R = NO_2)	**2h** (R = NO_2)	60	82
8	**1i** (R = OMe)	**2i** (R = OMe)	2.5	96
9	**1j** (R = NO_2)	**2j** (R = NO_2)	49	91
10	**1k** (R = OMe)	**2k** (R = OMe)	2.5	93
11	**1l** (R = NO_2)	**2l** (R = NO_2)	60	60
12	**1m**	**2m**	2.5	95
13	**1n**	**2n**	3.5	95
14	**1o**	**2o**	2.5	93
15	**1p**	**2p**	2.5	98
16	**1q**	**2q**	12	97
17	**1r**	**2r**	3	60
18	**1s**	**2s**	4.5	96
19	**1t**	**2t**	13	91
20	**1u**	**2u**	20	86
21	**1v**	**2v**	6	80
22	**1w**	**2w**	3.5	99

[a] Reaction conditions: Alkyne **1** (1 equiv.) and cobaloxime (5 mol%) in MeOH (c = 0.25 M), heated at 65 °C under aerobic conditions in sealed tubes unless otherwise noted. [b] Isolated yield. TBDPS = *tert*-butyldiphenylsilyl. Bz = benzoyl. MOM = methoxymethyl. Boc = *tert*-butyloxy carbonyl.

To evaluate the potential use of the current protocol in late-stage manipulation with complex structures and multifunctional groups, terminal alkynes were then incorporated into typical biomolecular scaffolds and tested in the hydration reaction under the standard conditions (Table 3). Alkyne **1x** with a steroid scaffold was smoothly converted to ketone **2x** in 98% yield without any epimerization observed. A selective hydration of alkyne **1y** linked with the caffeine motif gave the corresponding ketone **2y** in 94% yield. Both imidazolyl and amido

Table 3 Substrates with multifunctional groups

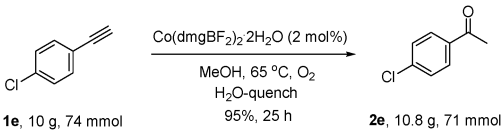


groups could be well tolerated in this transformation. Other substrates conjugated with protected amino acid (**1z**) and benzyl-protected sugar (**1aa**) were also converted to the corresponding ketones in excellent yields. These results render the present method as a useful protocol which could be potentially utilized in the late-stage synthesis.

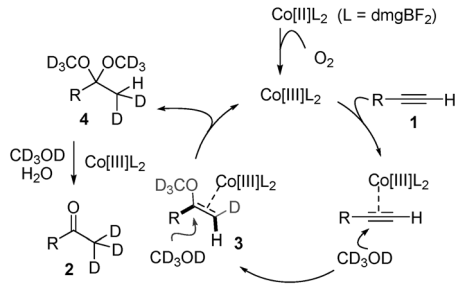
To test the practicality of our protocol, a decagram-scale preparation of **2e** was then investigated (Scheme 2). To our delight, the hydration of **1e** (10 gram scale) was carried out in the presence of **Cat 5** (2 mol%) in MeOH at 65 °C for 25 h to give **2e** in 95% yield. This result illustrated the good scalability of the present method.

To gain mechanistic insight into this reaction, the hydration of **1f** was performed in methanol [D4] at 65 °C. The result revealed that the hydrogen atoms in the methyl ketone were almost deuterated (95%). On the basis of this result together with the GC-MS monitoring of this reaction, a possible pathway for the cobaloxime-catalyzed hydration of terminal alkynes is proposed in Scheme 3. **Cat 5** was first oxidized to a Co(III) species which was later confirmed by the X-ray photoelectron spectroscopy (XPS) of the recovered catalyst.[21] The hydration might involve two-step hydroalkoxylation with methanol (D4) which led to the separable dimethyl acetal (**4**). The subsequent hydrolysis of this intermediate gave completely deuterated methyl ketone **2** as the main product.

In summary, we have developed an efficient cobaloxime-catalyzed terminal alkyne hydration under acid-free conditions. A series of alkynes bearing different functional groups especially with acid-sensitive ones were converted to methyl ketones in high yields with complete regioselectivities. The ready availability of the cobaloxime catalysts together with their bench stability demonstrated the high synthetic potential of this protocol, and



Scheme 2 Decagram-scale hydration of **1e**.



Scheme 3 Proposed mechanism of cobaloxime-catalyzed hydration of alkynes.

we believe that it will find many applications in organic synthesis.

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20 The fluorine atom in **1a** facilitates our yield determination based on ^{19}F NMR.
21 For detailed information, please see S5 and S6 (ESI†).