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A General Bifunctional Catalyst for the Anti-Markovnikov Hydration of Terminal Alkynes to Aldehydes Gives Enzyme-Like Rate and Selectivity Enhancements

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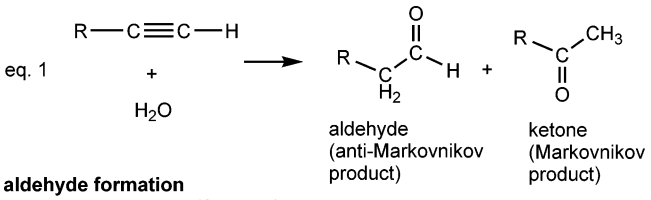
There is great interest in designing reactions for atom economy, where preferably all reactant atoms are found in the desired products.[1] Hydration of alkynes (eq 1) is one promising reaction for introducing oxygen-containing moieties with complete atom economy. Generally, these additions follow Markovnikov's rule, where it applies. For example, a terminal alkyne may be hydrated to the corresponding methyl ketone, using a number of acidic and/or metal-containing catalysts (e.g., Hg(II), often under strongly acidic conditions).[2] Thus, even though the overall reaction is atom economical, standard conditions are anything but environmentally friendly. Moreover, catalytic anti-Markovnikov additions of water and amines to unsaturated moieties remain a general challenge.[3]



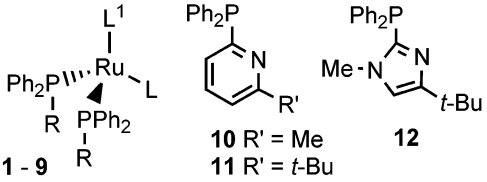
aldehyde formation
uncatalyzed: < 1 x 10^{-10} mol h^{-1} = half-life > 600,000 years
catalyzed by **6**: up to 23.8 mol (mol **6**)$^{-1}$ h^{-1} and 10,000 : 1
changes in rate and selectivity: > 2.4 x 10^{11} and 300,000

Natural enzymes are archetypal, efficient catalysts for green chemistry. For example, uncatalyzed hydrolysis of an amide at pH 7 and 25 °C has a half-life of hundreds of years,[4,5] whereas the enzyme carboxypeptidase completes such reactions in seconds, giving a rate enhancement of 4×10^{11}.[5] The cooperativity of a metal ion and organic acids and bases in the active site is thought to be responsible for catalytic activity.

Here we report two significant findings: first, a general organometallic bifunctional catalyst (**6**) for hydration of alkynes to *aldehydes* at neutral pH, and second, determination that the catalyst shows rate enhancement and selectivity comparable to those given by enzymes, turning a reaction with a half-life of at least 600 000 years to one with a half-life of a matter of minutes, with aldehyde-to-ketone ratios of up to 10 000 to 1.

As part of our program to use the cooperativity of suitably placed functional groups and a transition metal center to accelerate organic reactions, in 2001 we reported the anti-Markovnikov hydration of terminal alkynes using a bifunctional catalyst with a CpRu fragment and imidazole-containing phosphines (**4**).[2b] At 70 °C, this resulted in the near-quantitative production of aldehydes from a variety of terminal *alkyl*-substituted alkynes. Concurrently, Wakatsuki et al.[6] found that using chelating or electron-rich phosphines on a CpRu unit (e.g., **2**) also results in good yields of aldehydes, albeit at higher temperatures (100 °C), and Gimeno et al. reported that combined use of an indenyl ligand and surfactants allowed >90% alkyne hydration after 24 h at 60 °C,[7a] though the aldehyde-to-ketone ratios ranged from about 8:1 to 84:1. Prior to these significant advances, alkyne-to-aldehyde conversion required stoichiometric hydroboration or hydrosilylation and subsequent oxidation.

Table 1. Discovery of a General Catalyst for Anti-Markovnikov Alkyne Hydration[a]



entry	cat.	L^1	2 Ph_2PR	L	nonanal yield % (time, h)	TOF (h^{-1})
1[b]	**1**	Cp	PPh_3	Cl	1.0 (21)	nd
2	**2**	Cp	dppm[c]	Cl	5.2 (96)	0.0206
3	**3**	Cp	**10**	*d*,*e*	39.7 (72)	0.28
4	**4**	Cp	**12**	H_2O[e]	99.8 (36)	1.88
5	**5**	Cp	**11**	Cl	98.3 (48)	2.45
6	**6**	Cp	**11**	CH_3CN[e]	**99.9** (3)	23.8
7[f]	**6**	Cp	**11**	CH_3CN[e]	99.6 (8)	24.7
8	**7**	Tp	**11**	Cl	3.2 (4)	0.760
9	**8**	indenyl	**11**	Cl	0	0
10	**9**	Cp*	**11**	Cl	0	0

[a] Conditions: 2 mol % catalyst, water (5 equiv) in acetone, 70 °C, initial concentration of 1-nonyne = 0.50 M. [b] 1-Hexyne used. [c] $PPh_2CH_2PPh_2$.[d] L = one nitrogen of a phosphine ligand in η^2-P,N coordination. [e] Counterions: **3** and **6**, PF_6^-; **4**, triflate. Counterion affects solubility but not rate. [f] Using 1% **6**.

However, in using prior catalyst systems, *aryl*alkynes presented several challenges, giving reduced yields, lower selectivity, or requiring higher catalyst loading (e.g., 10%). Another drawback was the elevated temperatures required. Here, we report an improved and general catalyst (**6**), which for alkyl-substituted alkynes can even be used at room temperature, because it is more than 1000 times faster than the Wakatsuki catalyst **2**.[6] In addition, both alkyl- and arylalkynes are hydrated to give aldehydes in similarly high yields with excellent selectivity.

We examined both a variety of phosphines on a CpRu fragment, as well as several fragments related to CpRu. As can be seen clearly from entries 1−6 of Table 1,[8] ligands containing pendant heterocyclic bases, bifunctional ligands, generally create a better local environment than chelating or small ligands. By far, the best ligand overall on CpRu (entry 6) was determined to be the hindered pyridine derivative **11**.[9]

In optimizing the metal center for alkyne hydration, several ligands thought to resemble the Cp ligand electronically and sterically were screened (entries 6−10). Unfortunately, Gimeno's proposed indenyl effect[7] did not help the anti-Markovnikov process here. The Cp* and Tp[10] ligands were also of little utility. A more careful NMR examination of these reactions suggested that the catalyst degradation pathway first observed by Bruce and studied

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Table 2. Scope of Alkyne Hydration[a]

entry	alkyne	aldehyde yields 1 h	3 h	later (time)
1	$CH_3(CH_2)_6C{\equiv}CH$	55.0	**99.9**	nd
2[b]	$CH_3(CH_2)_6C{\equiv}CH$	nd	30.2[b]	**98.6** (48 h)
3	$C_6H_5C{\equiv}CH$	11.8	33.1	**99.8** (20 h)
4	$4\text{-}MeOC_6H_4C{\equiv}CH$	14.0	42.7	**99.8** (24 h)
5	$4\text{-}O_2NC_6H_4C{\equiv}CH$	0.31[d]	nd	nd
6	$N{\equiv}C(CH_2)_3C{\equiv}CH$	3.6	12.0	**97.8** (96 h)
7	$HC{\equiv}C(CH_2)_4C{\equiv}CH$	47.7[c]	nd	**71.2**[c] (8 h)
8	$THPOCH_2C{\equiv}CH$	26.1	76.2	**98.0** (9 h)
9	$TsNHCH_2CH_2C{\equiv}CH$	nd	97.0[e]	**98.1**[e] (6 h)
10	$CH_3C{\equiv}CSi(CH_3)_3$	6.7[f]	24.3[f]	**100**[f] (66 h)
11	$(CH_3)_2C(OH)C{\equiv}CH$	nd	nd	**80.7**[g] (168 h)
12	1-ethynylcyclohexene	nd	nd	**41.0**[g,h](168 h)

[a] Unless otherwise specified, using **6** (2 mol %), H_2O (5 equiv), acetone, 70 °C, initial alkyne concentration 0.50 M. [b] Room-temperature reaction with 5 mol % catalyst; 30.2% after 5.5 h. [c] Yields of dialdehyde and ynal (double and single hydration products) at 1 and 8 h = 27.9 + 19.8 and 51.6 + 19.6%, respectively. [d] In addition, 2.1% of corresponding alkane and deactivated catalyst. No further reaction seen. [e] Product formed as 1:8 mixture of aldehyde and its cyclized form (*N*-tosyl-2-hydroxypyrrolidine). [f] Product is propanal. [g] Room-temperature reaction. [h] 34.2 and 6.9% β,γ- and isomerized α,β-unsaturated aldehydes, respectively.

extensively by Bianchini et al.[11] is operative, giving a Ru−CO complex and the alkane RCH_3 from RC≡CH. Our conclusion for now is that the $CpRu^+$ metal center is ideally suited for the anti-Markovnikov hydration of terminal alkynes. A more electron-rich or more sterically crowded metal center may favor phosphine loss and alkyl migration, ultimately resulting in alkane and carbonyl complex. In contrast, a more electron-deficient and less sterically demanding metal center may not favor the isomerization of the alkyne to a vinylidene ligand,[12] thought to be a necessary step in the anti-Markovnikov mechanism.[11,13]

With an optimized catalyst composition in hand, we determined that either acetone or *i*-PrOH were the best cosolvents. Table S1[8] illustrates the use of catalyst **6** in a variety of solvents, both polar and nonpolar, protic and aprotic. We note that the catalyst can operate on water-immiscible liquid alkynes *without any cosolvent or surfactant*, although the rate of hydration is slower.

Focusing on a variety of alkyne substrates, Table 2 shows the scope of successful hydration. Several important classes of functional groups are tolerated and unaffected: a cyanide (entry 6), the acid-sensitive protecting group THP (entry 8), a tertiary hydroxyl group (entry 11), and a sulfonamido group (entry 9). The conversion shown in entry 8 suggests an alternative route to aldol products (acetylide addition to a ketone, followed by hydration). Although the yield of aldehyde in entry 12 is relatively low, it is remarkable that most of the product remains as the unconjugated isomer. The conversion of $CH_3C{\equiv}CSi(CH_3)_3$ to propanal (entry 10) illustrates a high-yielding in situ deprotection and hydration. Significantly, both electron-rich and normal arylalkynes are effectively hydrated at the same 2 mol % loading (entries 3 and 4), unlike results seen before.[2b,6] The hydration of cyanonitrile in entry 6 is slow for an alkyl-substituted alkyne, an effect seen using **2**[6] but not seen using **4**,[2b] in which the resting state of the catalyst includes a coordinated water molecule and excludes a nitrile. Finally, entry 2 of Table 2 shows for the first time that *practical hydration may be carried out at 25 °C.*

Because these promising results prompted comparison of the rate acceleration of our best bifunctional catalyst with those accomplished by enzymes in other reactions, we conducted the first determination of the uncatalyzed rate of alkyne hydration.[14] As detailed in Supporting Information,[8] a GC protocol was developed such that the estimated lower limit of product detection was 2 ppm. Under our standard reaction conditions (acetone, 70 °C, 5 equiv of H_2O), neither ketone nor aldehyde product was seen for 1-nonyne after 28 days.[15] Given that we could detect 2 ppm product if it were present, we can infer that the rate of the uncatalyzed product formation is $<3 \times 10^{-9}$ mol h^{-1}, meaning a half-life of at least 20 000 years. Even more striking is our observation that when the Brønsted−Lowry acid $HNTf_2$[16] is used to catalyze hydration of 1-nonyne, the ratio of ketone to aldehyde formed at low conversion is 33 to 1.[8] Thus, since under protic catalysis appearance of aldehyde is 33 times slower than appearance of ketone, in the experiment under neutral conditions, an upper bound for the rate of aldehyde formation is 1×10^{-10} mol h^{-1}, or a half-life of at least 600 000 years! Finally, since **6** gives initial TOF of 23.8 mol aldehyde mol catalyst^{-1} h^{-1}, we calculate a rate acceleration of $>2.4 \times 10^{11}$. As for selectivity, there is no detectable ketone from the hydration of 1-nonyne by **6** under conditions where we could detect one part ketone in the presence of 10,000 parts aldehyde. Thus, compared with protic catalysis, **6** changes the selectivity of alkyne hydration by a factor of over 300 000, all within the realm of enzymatic performance.

In conclusion, bifunctional catalyst **6** is the most general to date for anti-Markovnikov hydration of terminal alkynes and should be practical for fine chemical synthesis applications. The catalyst also exhibits enzyme-like rate acceleration and selectivity. We are actively exploring the mechanism of this reaction, the synergy of this and related metal−ligand systems, and applying enzyme-inspired design principles to other reactions.

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Supporting Information Available: Procedures for preparation of catalysts and their evaluation, determination of uncatalyzed hydration rates, and exemplary GC traces of hydration reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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