Hydration and hydroamination of 1-alkynes with ruthenium catalysts

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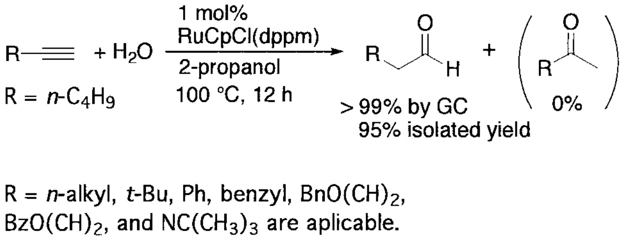
Ruthenium complexes that efficiently catalyze hydration and hydroamination of 1-alkynes have been found. The hydration described here is the first example of *anti*-Markovnikov regioselectivity to produce aldehydes. A mechanism involving Ru(IV)-hydride-vinylidene intermediate is proposed. A highly practical catalytic hydroamination method has also been developed which was applied to synthesis of nitrogen containing heterocycles.

Introduction

The addition of water and amines to C–C triple bond is desirable in terms of atom economy in forming C–O and C–N double-bond compounds. These reactions should produce no stoichiometric by-products and meet the increasing demand for environment benign organic synthesis processes. However, there have been very few practically useful catalytic systems known to date. In the present paper, we report the successful transformations of 1-alkynes performed by ruthenium catalysts.



Scheme 1.

Hydration of 1-alkynes to aldehydes

The addition of water to alkynes with Hg(II) salts to form carbonyl compounds was first reported in 1860, and since then, the reaction is known as a textbook example that follows Markovnikov's rule. Likewise, all the known addition of water to terminal alkynes reported thus so far using Hg(II), Au(III), Ru(III), Rh(I), Pt(II), Pt(IV), and other metal catalysts exclusively gave methyl ketones.

In 1998, we reported the first *anti*-Markovnikov hydration of terminal alkynes to give aldehydes.[1, 2] The hydration was catalyzed by $RuCl_2$/phosphine mixture (system-1), where phosphine had to be rather special ones though they are commercially available, i.e., $PPh_2(C_6F_5)$ or $P(C_6H_4\text{-}3\text{-}SO_3Na)_3$ (TPPTS). Activity of system-1 was not very high, since *ca.* 10 mol% of the catalyst was required and a small amount of the conventional Markovnikov product, i.e. ketone, was always present in the reaction products.

We found out later that complexes of type $RuCpCl(PR_3)_2$ (system-2) are excellent catalysts both in terms of high activity and selectivity for the *anti*-Markovnikov hydration of 1-alkynes (Scheme 1).[3] System-2 includes a family of discrete complexes, $RuCpCl(PR_3)_2$ or its cationic form $[RuCp(MeCN)(PR_3)_2]PF_6$, where $(PR_3)_2$ is either bidentate phosphine typically dppm, or two monodentate ones such as $(PMe_3)_2$, and operates in 2-propanol/H_2O at 100°C in most cases. Addition of water to 1-hexyne catalyzed by 1 mol% of RuCpCl(dppm) gives hexanal with 95% isolated yield. The turnover number of 167 was achieved using 0.5 mol% of the catalyst. Phenylacetylene and *t*-butyl acetylene, which were not reactive in system-1, were also converted to corresponding aldehydes with good yields.

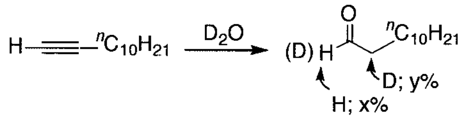
Regarding the mechanism, closely related stoichiometric reactions of 1-alkynes and water assisted by iron-group metals have been reported to result in C–C triple-bond cleavage, which proved the participation of Ru(II)-vinylidene intermediate and successive generation of a metal-acyl intermediate. Therefore, it appears very likely that our catalytic reaction also involves isomerization of η^2-coordinated 1-alkyne to a vinylidene form prior to the attack by water.

However, deuterium-labeled experiments using our systems has clearly indicated that the reaction mechanism operating in water solvent is not very straightforward.[2] The hydration reactions of 1-dodecyne and D-labeled 1-dodecene were carried out in $(CH_3)_2COD/D_2O$ and $(CH_3)_2COH/H_2O$, respectively. Formyl hydrogen exclusively originates from acetylenic hydrogen while the two hydrogen atoms of the methylene group next to the carbonyl carbon are from water (Scheme 2). The assumed interconversion of η^2-alkyne to vinylidene should bring acetylenic hydrogen to carbon substituted with group R and eventually should give RCH(D)-CHO in the case of H_2O addition to RC≡CD and RCH(D)-CDO in the case of D_2O addition to RC≡CH.

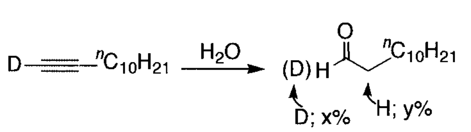
In addition, under the optimized reaction conditions for system-2 (100°C, 12 h)[3], [RuCp(=C=CHPh)(dppm)]PF_6 was found to be unreactive for hydration of PhC≡CH. Thus, these observations provide evidence that Ru(II)-vinylidene is not an intermediate of the present *anti*-Markovnikov hydration.

Alternatively, the result of DFT theoretical calculation suggests that (*vide infra*) Ru(IV)-vinylidene is likely to be the true intermediate. As a model for the calculation, we chose $[RuCp(\eta^2\text{-MeC}{\equiv}CH)(PH_3)_2]^+$ ([**1**]) and thoroughly examined tautomerization of the alkyne fragment in this complex (Fig. 1).

Complex [**2**] was found to be slightly unstable, 9 kcal/mol higher in energy than [**1**]. The transition state [$\mathbf{TS_{12}}$] that connects [**1**] with [**2**], *via* "vertical alkyne rotatomer" [**1′**], has transition energy as high as 40 kcal/mol. An alternative tautomer, the vinylidene complex [**3**], is more stable than the η^2-alkyne complex [**1**] by 10 kcal/mol. The transition state to [**3**], [$\mathbf{TS_{13}}$], has transition energy of 24.5 kcal/mol. However, it is obvious from experimental results that the Ru(II)-vinylidene complex [**3**] is not involved in the catalytic *anti*-Markovnikov hydration. The calculated transition energies suggest that [**2**] is not involved either.



cat.	aldehyde yield (%)	Incorporation of H; x (%)	D; y(%)
$RuCl_2(C_6H_6)(PPh_2C_6F_5)$ + 3 $PPh_2C_6F_5$)	15	> 95	92
$[RuCl(C_6H_6)(TPPTS)_2]Cl$ + 2 TPPTS	15	> 95	88
$RuCpCl(PPh_3)_2$ (**1**)	30	90	92



cat.	aldehyde yield (%)	Incorporation of D; x (%)	H; y(%)
$RuCl_2(C_6H_6)(PPh_2C_6F_5)$ + 3 $PPh_2C_6F_5$)	27	94	> 95
$[RuCl(C_6H_6)(TPPTS)_2]Cl$ + 2 TPPTS	30	90	> 95
$RuCpCl(PPh_3)_2$ (**1**)	30	93	> 95

Scheme 2.

To determine a plausible reaction process, we next examined the possibility that a proton from water may attack the η^2-MeC≡CH moiety of complex [**1**]. The geometries of the proton-addition products [**4**] and a complex ([**5**]) derived from one of the vinyl intermediates, together with a transition state to it ([$\mathbf{TS_{45}}$]) are shown in Fig. 2. When protonation occurs on the terminal carbon of η^2-alkyne, [$\mathbf{4_{gem}}$] is the most stable vinyl complex. In actual reactions, however, the phosphine ligand used, *e.g.*, dppm, is much bulkier than $(PH_3)_2$ and steric repulsion would not allow such close loca-

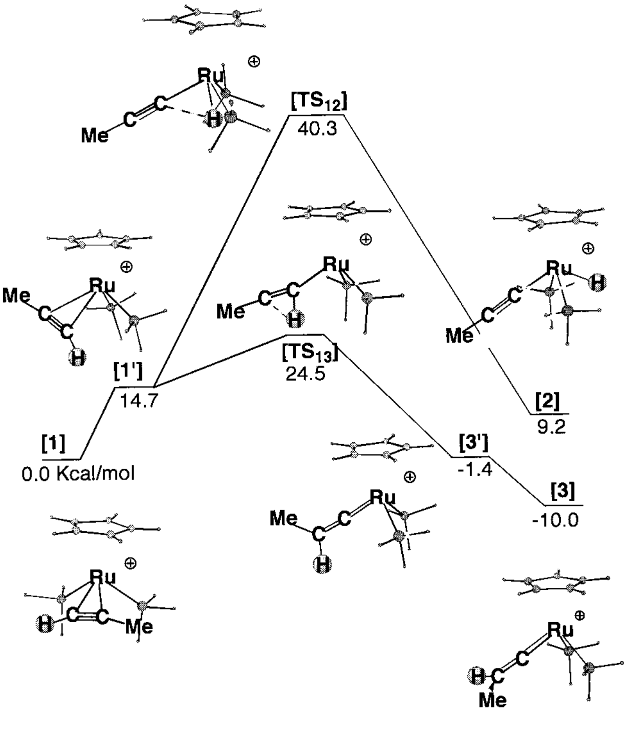


Fig. 1. Energy diagram for the tautomerization of complex [1].

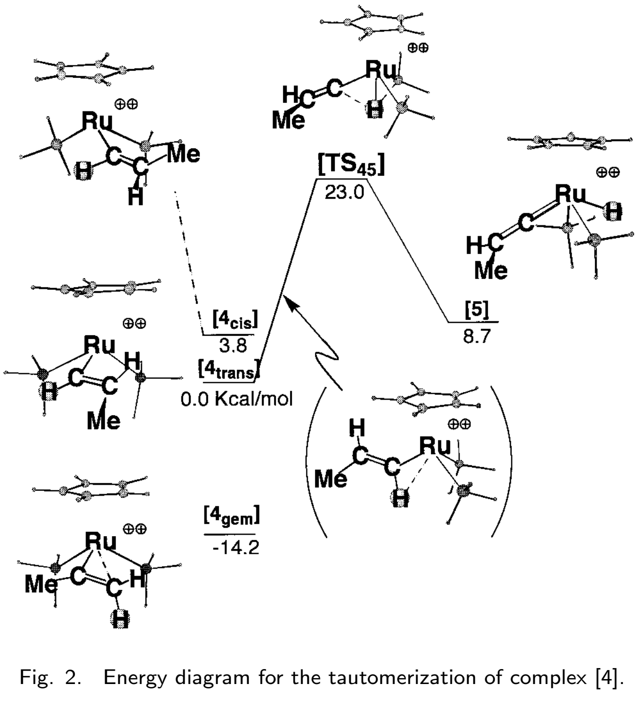


Fig. 2. Energy diagram for the tautomerization of complex [4].

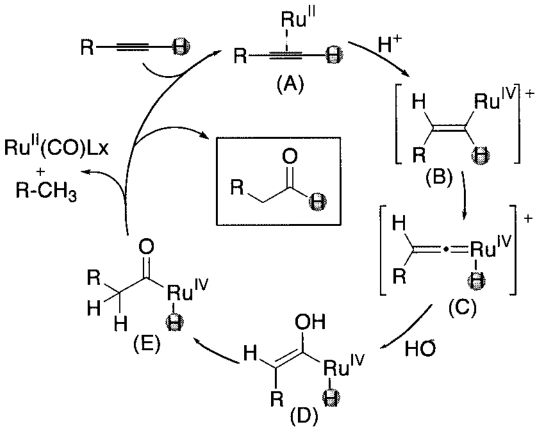
tion of Ru and C(H$_2$). Starting from [$\mathbf{4}_{\mathbf{trans}}$], we found the path to a new Ru(IV)-hydride-vinylidene complex [**5**] with activation barrier of 23 kcal. The migrating hydrogen is best regarded as a hydride through this transition state.

Based on all the experimental results and calculations discussed above, the most reasonable catalytic cycle may be described as shown in Scheme 3. The *anti*-Markovnikov regioselection must be originating from the proton addition step (A) → (B). Formation of $\mathbf{4}_{\mathbf{gem}}$ is electronically favored but should be sterically disfavored because it bears bulky substituent R on C(α) (Scheme 4).

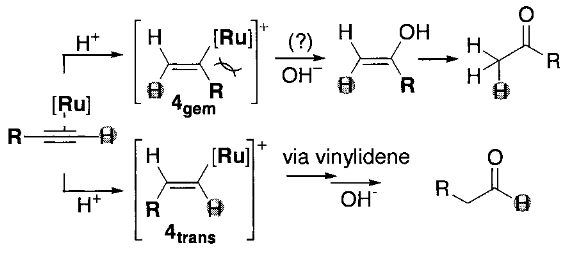
Hydroamination of 1-alkynes to ketimines

The addition of amines to alkynes to give imines is a fundamental reaction but only few successful examples of intramolecular reaction are known. Compared to intramolecular cyclizations, intermolecular hydroamination of alkynes is much more difficult. Stoichiometric reaction with toxic mercury is still the only practical method for synthetic organic chemists.

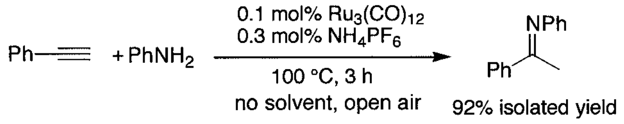
We have developed a practical method of ruthenium-catalyzed hydroamination of 1-alkynes.[4] Anilines react with 1-alkynes, yielding ketimins in the presence of 0.1–1.0 mol% [Ru$_3$(CO)$_{12}$] at 100°C for 3–12 h (Scheme 5). Exclusion of air and moisture from the reaction system is not necessary. The reaction can be carried out basically without a solvent, so that simple distillation from the reaction mixture gives products in pure form. This system is quite useful when ordinary dehydrative synthesis of ketimines from ketones and amines gives unsatisfactory results. Indeed, a ketimine compound of acetophenone was successfully synthesized by our hydroamination system after all the attempts using conventional method have failed.[5]



Scheme 3.



Scheme 4.



Scheme 5.

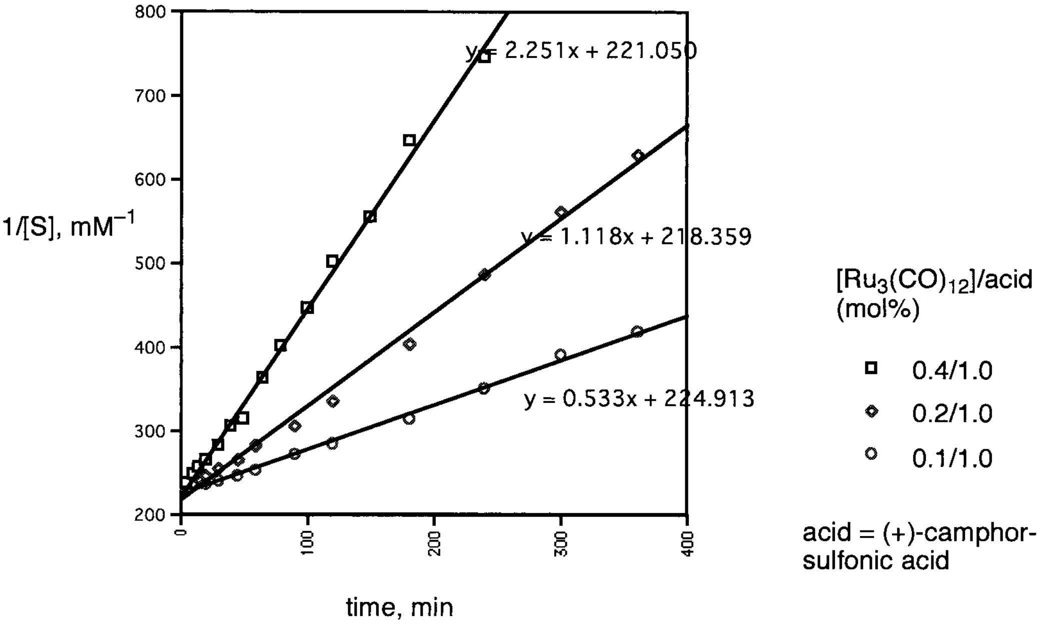
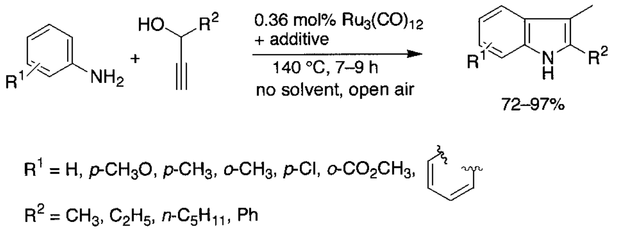


Fig. 3. Second-order plot for the ruthenium catalyzed aniline addition to phenylacetylene.

In this catalytic hydroamination, rate enhancement by addition of a small amount of acid or its ammonium salt is crucial. For example, addition of 3 equiv. of NH_4PF_6 to $[Ru_3(CO)_{12}]$ (1 equiv. for Ru atom) accelerates the reaction by about 500 times faster than without addition. Almost all strong acids are found to have similar effects but hydrohalogenic acids (HI, HBr, HCl) show only a weak effect on rate enhancement. Kinetics study on the aniline addition to phenylacetylene catalyzed by $[Ru_3(CO)_{12}]$ exhibited 1st order kinetics in both Ru (Fig. 3) and alkyne, ~0.5th order in aniline. The effect of acid concentration (NH_4PF_6 and camphor sulfonic acid) showed saturation at about 1 or slightly less than 1 equiv. per Ru atom added, while further addition did not improve the rate. Thermodynamic parameters were calculated as $\Delta G^{\neq} = 124\,\mathrm{kJ/mol}$, $\Delta H^{\neq} = 92$ kJ/mol, and $\Delta S^{\neq} = 87$ J/kmol based on temperature dependence of the reaction rate.

We have applied the present catalytic hydroamination to the synthesis of nitrogen heterocycles, such as quinolines[4] and indoles.[6] In particular the indole synthesis is highly valuable because the reaction can employ inexpensive unsubstituted anilines. Almost all other known methods require derivatization of anilines. Even Fischer method, which is regarded as the most practical method, requires conversion of anilines to unstable and toxic hydrazines.

Applying our catalytic hydroamination system to the reaction of anilines and 1-subsituted-2-propyne-1-ols (Scheme 6) at slightly higher temperature (140°C), 3-methyl-2-substituted indoles were formed regioselectively. Regioselective synthesis of this kind of indoles is difficult by Fischer method. From the viewpoint of green chemistry, the process is also favorable because it yields only H_2O as the stoichiometric by-product.



Scheme 6.

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