Low-Valent Ruthenium and Iridium Hydride Complexes as Alternatives to Lewis Acid and Base Catalysts

SHUN-ICHI MURAHASHI* AND
HIKARU TAKAYA

Department of Chemistry, Graduate School of Engineering Science, Osaka University, Machikaneyama 1-3, Toyonaka, Osaka 560-8531, Japan

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ABSTRACT

The discovery of a new chemical reaction often leads to new applications and new chemical principles. Low-valent ruthenium and iridium hydride complexes are highly useful redox Lewis acid and base catalysts. Nitriles are activated by these catalysts and undergo reactions with either nucleophiles or electrophiles under neutral conditions. Hydration of nitriles, esterification of nitriles with alcohols, and amidation of nitriles with amines can be performed catalytically together with formation of ammonia. The catalytic reactions of pronucleophiles such as nitriles and carbonyl compounds with electrophiles such as alkenes, alkynes, carbonyl compounds, imines, and nitriles take place generally.

I. Introduction

Reactions promoted by Lewis acids and bases are fundamental in organic synthesis; however, most such reactions are merely stoichiometric. Therefore, the development of catalytic reactions that use transition-metal complex catalysts under neutral and mild conditions is particularly important; society needs forward-looking technology, which is based on environmental acceptability. The criteria include atom efficiency, formation of little inorganic waste, and selective synthesis of desired products.[1] Salts are the main waste, accounting for 70 wt %. We should use instead environmentally friendly catalytic processes that will not produce such waste. If one could design Lewis acid and base catalysts with low redox potentials, their reactions would occur catalytically under neutral conditions. We have therefore been searching for

transition-metal complex catalysts, which we call redox Lewis acid and base catalysts. We have found that low-valent ruthenium hydride complexes are excellent catalysts.[2] This Account describes how transition-metal hydride complexes can be used as alternatives to conventional Lewis acid and base reagents. Using these complexes, we found the following new catalytic reactions. First, divalent ruthenium dihydride complexes are excellent catalysts for hydration of nitriles, esterification of nitriles with alcohols, and amidation of nitriles with amines together with formation of ammonia. Second, these complexes are useful for the generation of carbon nucleophiles from pronucleophiles by activation of the α-C–H bond adjacent to nitriles and carbonyl groups, and carbon–carbon bonds can be formed catalytically and selectively. Third, iridium hydride complexes are effective catalysts for simultaneous activation of both the α-C–H bonds of pronucleophiles and the CN triple bonds of nitriles, making possible cross-coupling reactions of nitriles. All of these reactions can occur catalytically without salt formation. Important features of these catalysts are that reactions promoted by conventional Lewis acids or bases can be replaced by catalytic reactions under neutral conditions. Ruthenium and iridium catalysts can be used as catalysts to replace both Lewis acids and strong bases, and hence they can be used in combinatorial chemistry.

II. Low-Valent Ruthenium Hydride Complexes as Alternatives to Lewis Acids for Activation of Nitriles

Reactions with transition-metal complexes used as redox Lewis acid catalysts will open up new possibilities, because they proceed catalytically under neutral conditions with high selectivity. To explore the possibilities, we focused on low-valent ruthenium dihydride phosphine complexes, because they have low redox potentials, strong coordination ability to heteroatoms, hydride ligands, which are small and labile, and phosphine ligands, which have flexibility in their basicity and solubility in organic media.[2] As substrates, we selected nitriles because of their strong coordination to metals, and because at present there is no catalytic reaction for nitriles that is synthetically and industrially important. Conventional transformations of nitriles generally require stoichiometric amounts of strong acids or bases; therefore, the catalytic transformation of nitriles under neutral conditions is a subject of interest and may make possible new synthetic processes which have environmental benefits.

By systematic examination of such transition-metal Lewis acid catalysts, we found that low-valent ruthenium hydride complexes had specific catalytic activity and transformed nitriles to amides, esters, lactones, lactams, and polyamides without salt formation.

The concept of transition-metal-based Lewis acid catalysts has been shown by Bosnich et al.[3,4] The underlying principle is widely used in the design of new kinds of catalytic reactions, which include Diels–Alder reactions,

Shun-Ichi Murahashi received his master degree in 1963 at Osaka University and immediately was appointed as Research Associate at the same university. He received his Ph.D. degree (I. Moritani) in 1967. He spent postdoctoral years with Professor R. Breslow at Columbia University in 1968–1970. He was promoted to associate professor in 1972 and full professor in 1979. His earlier work was in carbene chemistry. Recent works are focused on organometallic chemistry directed toward organic synthesis, biomimetic oxidation reactions, palladium chemistry, and ruthenium chemistry. He has been elected as the president of the Chemical Society of Japan for 2000.

Hikaru Takaya, born in Alabama in 1969, completed his undergraduate study and graduate study for his master degree at Osaka University in 1993 and 1995, respectively. His Ph.D. studies on the development of catalytic reactions promoted by transition-metal complexes were carried out under the direction of Prof. Shun-Ichi Murahashi. He joined Osaka University, Faculty of Engineering Science, as a research associate in 1998.

cycloaddition of nitrones, and oxo-ene reactions, with ruthenium catalysts such as $[Ru(salen)(NO)(H_2O)]^+SbF_6^-$,[4a] $[RuCp(C_2H_4)(PPh_3)_2]^+[PF_6]^-$,[4b] and $[RuCp(bipop-F)(acetone)]^+SbF_6^-$.[4c] However, the reactions of nitriles with nucleophiles such as alcohols and amines do not occur with these catalysts. This difficulty may arise if redox processes are important in the reaction.

II-1. Catalytic Hydration of Nitriles. Classical hydration of nitriles requires stoichiometric amounts of strong acids or bases; therefore, catalytic hydrations of nitriles with heterogeneous and homogeneous catalysts have been studied. However, these catalytic reactions require excess amounts of water, and hence isolation of amides from water is tedious. In 1986, we found that ruthenium dihydride complex $RuH_2(PPh_3)_4$ (**1**) is a highly active catalyst, and hydration of nitriles can be performed upon treatment with only 1−2 molar equiv of water in 1,2-dimethoxyethane at 120 °C under neutral conditions, giving amides in excellent yields (eq 1).[5,6] It is noteworthy that when more acidic catalysts such as $RuCl_2(PPh_3)_3$ are used, the hydration of nitriles does not proceed well.

$$R-CN + H_2O \xrightarrow[\text{(cat.)}]{RuH_2(PPh_3)_4\ (\mathbf{1})} R-\overset{O}{\overset{\|}{C}}-NH_2 \quad (1)$$
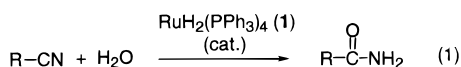
The $RuH_2(PPh_3)_4$ (**1**)-catalyzed hydration is highly useful. The reaction of γ-cyano ketones, which are derived from cyanoethylation of ketones, with 2 equiv of water in the presence of **1** (3 mol %) gives the corresponding ene-lactams, which are highly useful synthetic intermediates. This reaction proceeds via catalytic hydration and subsequent condensation. Various functional groups, such as lactams and esters, tolerate the reaction. The cyclic ene-lactams thus obtained are key intermediates for synthesis of cyclic amides. Typically, the palladium-catalyzed oxidation of the ene-lactam **2** with hydrogen peroxide gives the medium-ring-size amide **3** via intramolecular cyclization (Scheme 1).[7] The usefulness of the present reaction is
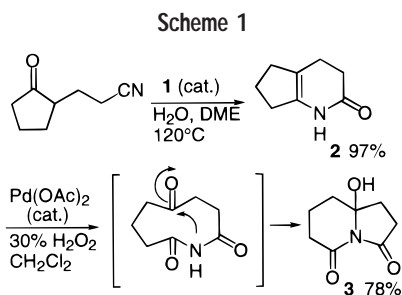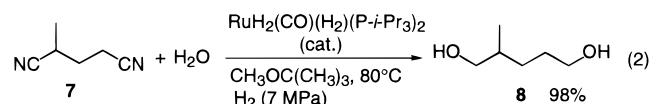
Scheme 1

illustrated by the synthesis of (−)-pumiliotoxin C (**6**),[8] which is an interesting skin alkaloid produced by Central American frog. As shown in Scheme 2, the key step for synthesis of (−)-**6** is the $RuH_2(PPh_3)_4$ (**1**)-catalyzed reaction of **4** with 3 molar equiv of water at 160 °C to give the optically pure ene-lactam **5** via retro-aldol reaction, hydration, and cyclization.

This principle has been applied to reductive hydrolysis of nitriles.[9] For example, the dinitrile **7** can be readily
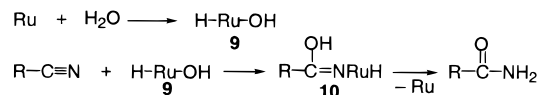
Scheme 2
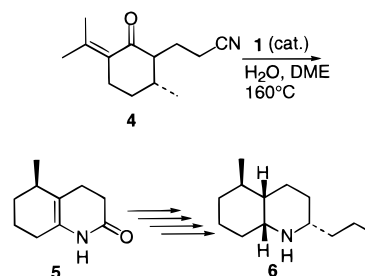
converted to the diol **8** in 98% yield upon treatment with water in the presence of $RuH_2(CO)(H_2)(P\text{-}i\text{-}Pr_3)_2$ catalyst at 80 °C under H_2 pressure (eq 2).

$$\underset{\mathbf{7}}{NC} \cdots CN + H_2O \xrightarrow[\substack{CH_3OC(CH_3)_3,\ 80°C \\ H_2\ (7\ MPa)}]{\substack{RuH_2(CO)(H_2)(P\text{-}i\text{-}Pr_3)_2 \\ \text{(cat.)}}} \underset{\mathbf{8}\quad 98\%}{HO \cdots OH} \quad (2)$$

What is the mechanism of the hydration of nitriles? The hydration can be explained by two pathways. One mechanism involves oxidative addition of low-valent ruthenium to water, subsequent cis addition of the ruthenium hydroxide **9** to nitrile, and reductive elimination of ruthenium from imino intermediate **10** (Scheme 3). The other mechanism involves direct nucleophilic addition of water to the coordinated nitrile to give the intermediate **10** (Scheme 4).
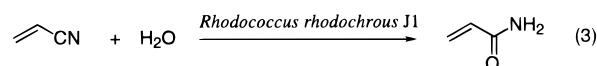
Scheme 3

Scheme 4
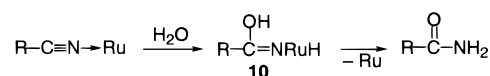
Recently, enzymatic hydrolysis of nitriles to amides has attracted considerable attention from an environmental point of view, and an enzymatic process has been employed for production of acrylamide at 30 000 ton yr^{-1} (eq 3).[10] The X-ray structural investigation of the nitrile hydratase revealed that the iron complex shown in Figure 1 works as catalyst,[11] which is similar to the present hydration of nitriles.

$$\underset{}{\diagup\!\!\!\diagup CN} + H_2O \xrightarrow{\textit{Rhodococcus rhodochrous}\ J1} \underset{O}{\diagup\!\!\!\diagup \overset{}{\underset{\|}{C}}NH_2} \quad (3)$$

II-2. Ruthenium-Catalyzed Esterification of Nitriles with Alcohols under Neutral Conditions. To clarify the mechanism of the ruthenium-catalyzed hydrolysis of nitriles, we carried out the reaction of nitriles in the presence of alcohols. In case of the mechanism shown in Scheme 3, the oxidative addition of low-valent ruthenium species to the oxygen−hydrogen bond of alcohol may occur, and then β-elimination of ruthenium hydride species would produce carbonyl-coordinated ruthenium
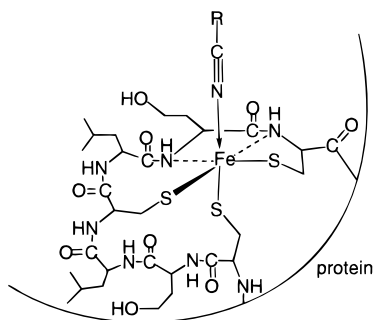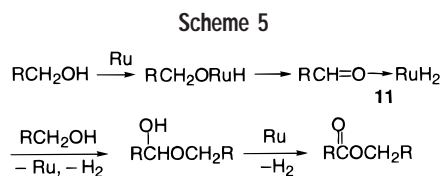
FIGURE 1. Iron center of nitrile hydratase from *Rhodococcus* sp. R312.

hydride intermediate **11** (Scheme 5). Once such a reaction

Scheme 5

takes place, the oxidative condensation of alcohol gives an ester and evolution of molecular hydrogen should take place, because we have already established that the ruthenium-catalyzed oxidative condensation of alcohols takes place under the same reaction conditions.[12] However, we could not detect esters among the products. Accordingly, the mechanism shown in Scheme 6 is likely; nucleophilic attack of alcohol to the coordinated nitrile would give intermediate **12**, which undergoes reductive elimination to give **13**. Subsequent hydrolysis of **13** would give ester and ammonia.
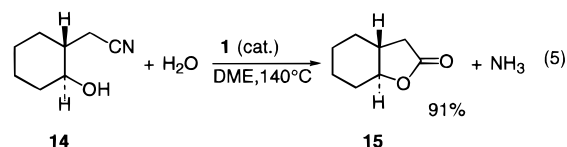
Scheme 6
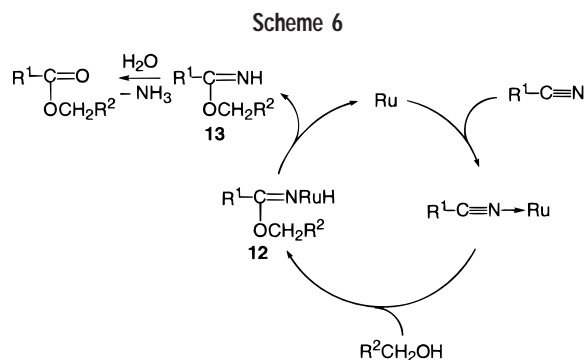
Indeed, the ruthenium-catalyzed reaction of nitriles with alcohols in the presence of 1−2 molar equiv of water under neutral conditions was found to give the corresponding esters along with ammonia (eq 4).[13] Esterifica-

$$R^1\text{-CN} + R^2\text{OH} + H_2O \xrightarrow{\textbf{1} \text{ (cat.)}} R^1CO_2R^2 + NH_3 \quad (4)$$
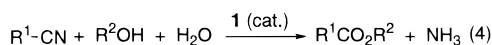
tions of nitriles with alcohols are generally performed by using stoichiometric amounts of strong Lewis acids, and transition-metal-catalyzed esterifications are limited to a few nonselective reactions under extremely severe conditions. The present reaction is advantageous over the previous methods with respect to high efficiency, selectivity, neutral reaction conditions, and facile isolation of products.

This reaction is highly useful for single-step preparation of esters from nitriles under neutral conditions. In particular, the intramolecular version of the reaction provides an efficient method for the preparation of lactones. The ruthenium-catalyzed reaction of γ-hydroxy nitrile **14**, which is readily obtained by ring opening of the corresponding epoxide, proceeds smoothly at 140 °C to give the lactone **15** in 91% yield (eq 5).[13] The efficiency of the reaction is illustrated by the short synthesis of (4*S*,5*R*)-5-hydroxy-4-decanolide, which is an autoregulator of anthracycline biosynthesis isolated from strains of *Streptomyces griseus.*


II-3. Ruthenium-Catalyzed Amidation of Nitriles with Amines under Neutral Conditions. Using the same principle, a new method for synthesis of amides from nitriles and amines under neutral conditions was discovered. Thus, the $RuH_2(PPh_3)_4$ (**1**)-catalyzed reaction of nitriles with amines in the presence of 1−2 molar equiv of water gives amides along with ammonia (eq 6).[5]
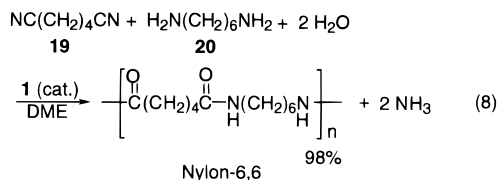
$$R^1\text{-CN} + R^2R^3NH + H_2O \xrightarrow{\textbf{1} \text{ (cat.)}} R^1CONR^2R^3 + NH_3 \quad (6)$$
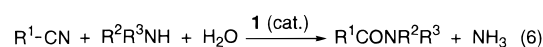
Transition-metal-based Lewis acids such as [Ru(salen)-(NO)(H$_2$O)]$^+$[SbF$_6$]$^-$ [4a] and [RuCp(C$_2$H$_4$)(PPh$_3$)$_2$]$^+$[PF$_6$]$^-$ [4b] showed no catalytic activity, perhaps due to the inability of the cationic ruthenium centers to undergo the same redox process.

The reaction appears to proceed generally, cleanly, and highly efficiently under neutral conditions without formation of salts. Wet acetonitrile is an excellent acetylating reagent when one compares it to the conventional reagents such as acetyl chloride and acetic anhydride, which form salts. Maytenine (**18**) has been prepared selectively by the reaction of cinnamonitrile (**16**) with the triamine **17** in 70% yield without protection of the secondary amino group (eq 7).[5] The important aspect of this reaction is the chemoselective reaction of primary amines in the presence of more basic secondary amines because of a template effect of metals.
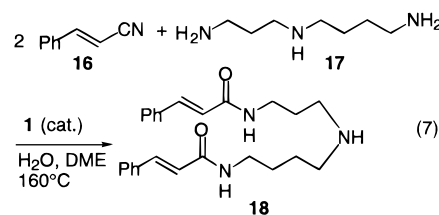

The efficiency of our new catalytic process is highlighted by the synthesis of various industrially important polyamides.[5] Typically, the reaction of adiponitrile (**19**) with 1,6-hexamethylenediamine (**20**) in the presence of 2 molar equiv of water and $RuH_2(PPh_3)_4$ (**1**) catalyst (3 mol %) in dimethoxyethane at 160 °C gave nylon-6,6 in 98%

yield along with ammonia (eq 8). The molecular weight

$$NC(CH_2)_4CN + H_2N(CH_2)_6NH_2 + 2 H_2O$$
$$\textbf{19} \qquad\qquad \textbf{20}$$

$$\xrightarrow[\text{DME}]{\textbf{1 (cat.)}} \left[\begin{matrix} O & O \\ \| & \| \\ C(CH_2)_4C & N(CH_2)_6N \\ & H \quad\quad H \end{matrix} \right]_n + 2 NH_3 \qquad (8)$$

$$98\%$$
Nylon-6,6

was determined to be 8900 (titration) or 7900 (viscosity). The present method illustrated in Scheme 7 is attractive in comparison with the conventional methods, because (i) dinitriles can be readily prepared by nickel-catalyzed hydrocyanation of dienes,[14] (ii) diamines can be easily obtained by catalytic hydrogenation of dinitriles, and (iii) polyamides are obtained without formation of salts. The reported methods for synthesis of polyamides from dinitriles and diamines[15] are limited to a few reactions which require strongly acidic conditions or extremely high temperatures.

Scheme 7
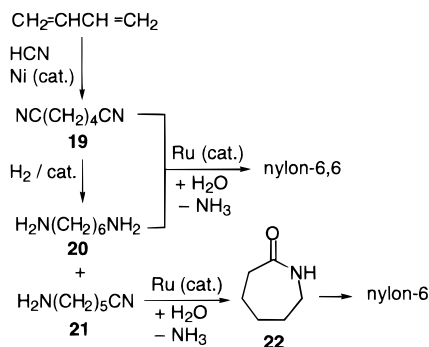
Our catalytic process is useful for synthesis of ε-caprolactam (**22**), which is a precursor of nylon-6. The ruthenium-catalyzed reaction of aminocapronitrile (**21**) derived from catalytic partial hydrogenation of adiponitrile (**19**) with water gives **22** in 78% yield. Recently, an industrial process for synthesis of **21** was established by using a titanium catalyst.[16] The ruthenium-catalyzed reaction of **19** with 1,4-diaminobutane, which is derived from hydrocyanation and subsequent hydrogenation of acrylonitrile, with water gives nylon-4,6, which has unique properties and a higher melting point in comparison with those of nylon-6 and nylon-6,6.[17]

The present amidation of nitriles is highly useful for production of polyamides, because (i) the reaction proceeds under neutral conditions without generation of salts, (ii) a wide variety of combinations of dinitriles and diamines even bearing functional groups can be used, and (iii) the reactions are clean, and ammonia is readily removed from the reaction system.

In summary, low-valent ruthenium hydride complexes work as redox Lewis acid catalysts and can be used for the reaction of nitriles with nucleophiles. The principle leads to a variety of catalytic transformations which occur under neutral conditions and are important in view of industrial and environmental aspects.

III. Activation of C−H Bonds of Pronucleophiles with Transition-Metal Complexes by the Heteroatom Effect

The C−H activation with transition-metal complexes will open a new chemistry of catalytic carbon−carbon bond formation because of its potent ability to generate carbon nucleophiles and to promote reactions under mild conditions. The design of catalytic reactions which involve insertion of metals into C−H bonds and substitution of the metal−carbon bonds thus formed with electrophiles is particularly important in view of environmentally friendly processes,[1] because the conventional reactions of carbon nucleophiles, which are generally formed upon treatment of pronucleophiles with strong bases or transmetalation of organic halides with organometallic reagents, with electrophiles form salts as waste.

The activation of sp[3] C−H bonds with transition-metal complexes is generally difficult in comparison with those of sp and sp[2] C−H bonds, because the reactivity of the C−H bond toward metals depends on the magnitude of the s-character of carbons. For the activation of an sp[3] C−H bond, there may be several approaches, which include (i) oxidative addition of transition metals to the sp[3] C−H bonds,[18] (ii) hydrogen abstraction by metal oxo species and related active species,[19] (iii) the activation of α-C−H bonds adjacent to heteroatoms using the α-heteroatom effect.[20] The last concept is depicted in Scheme 8. Coordination of heteroatom (Y) of substrate **23** to low-
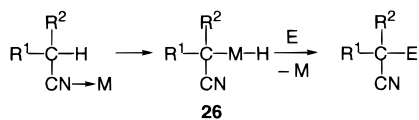
Scheme 8

Y = heteroatom
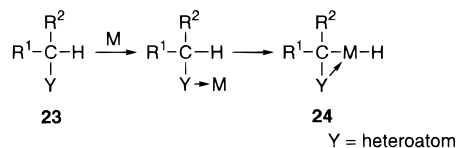
valent-transition metal (M) would increase both the basicity of the metal and the acidity of the C−H bond adjacent to Y, resulting in oxidative addition of the metal into the α-C−H bond to give α-metalated intermediate **24**. In 1978, we discovered the activation of α-C−H bonds adjacent to the nitrogen of amines.[20] Activation of the α-C−H bond of tertiary amines occurs upon treatment with low-valent transition metals such as palladium. Coordination of the metal to the nitrogen of tertiary amines, followed by oxidative addition at the α−C−H bond, may give an iminium ion complex **25**, which is a useful intermediate (Scheme 9). This concept leads to a new methodology for activation of nitriles under neutral conditions.

Scheme 9

25 M = Pd, Ru, Rh.....
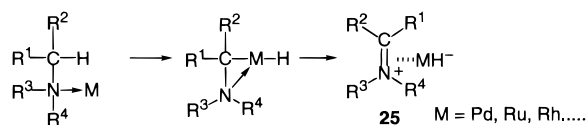
III-1. The C−H Activation of Nitriles: Transition-Metal-Catalyzed Knoevenagel Condensation and Michael Addition. The basic strategy for a new catalytic reaction

Scheme 10

26

of a nitrile which has strong coordination ability to metals is shown in Scheme 10. Coordination of nitrile to low-valent metal complex (M) would increase both the basicity of the metal and the acidity of the C—H bond adjacent to nitrile, and hence oxidative addition of the metal into the α-C—H bond of the nitrile would occur readily to afford α-cyanoalkylmetal hydride complex **26**, which can be trapped with electrophiles to form a carbon—carbon bond at the α-position of nitrile under neutral conditions. In 1989, we discovered that RuH$_2$(PPh$_3$)$_4$ (**1**) is an excellent catalyst for the activation of the α-C—H bond of nitriles.[21] Catalytic Knoevenagel condensation (eq 9), Michael reactions (eq 10), and additions to acetylenic compounds and imines occur highly efficiently under neutral and mild reaction conditions.[21,22]


(9)

(10)
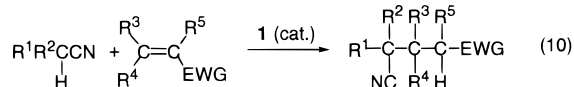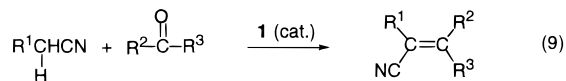
The reaction of nitriles with aldehydes in the presence of RuH$_2$(PPh$_3$)$_4$ (**1**) catalyst proceeds under neutral conditions to give the corresponding α,β-unsaturated nitriles. The reaction of ethyl cyanoacetate with 4-hydroxybenzaldehyde gave ethyl (*E*)-2-cyano-3-(4-hydoroxyphenyl)-2-propenoate (**27**) in 98% yield (eq 11).[21,22] It is noteworthy


(11)

27 98%
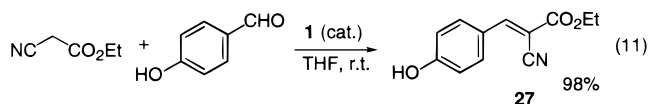
that even acidic substrates tolerate the reaction. After we discovered the catalyst **1**, various similar catalysts have been shown to be useful. RuH(C$_2$H$_4$)(PPh$_3$)$_2$(C$_6$H$_4$PPh$_2$),[23] IrH$_5$(P-*i*-Pr$_3$)$_2$,[24] ReH(N$_2$)(PMe$_2$Ph)$_4$,[25] and Pd$_2$(dba)$_3$·CHCl$_3$/dppe[26] can be used as effective catalysts for Knoevenagel condensation of nitriles.

Using catalyst **1**, Michael reaction of nitriles can be also performed highly efficiently. Importantly, addition to α,β-unsaturated aldehydes proceeds chemoselectively (eq 12).[21,22] RhH(CO)(PPh$_3$)$_3$ is also a good catalyst for Michael


(12)

72%
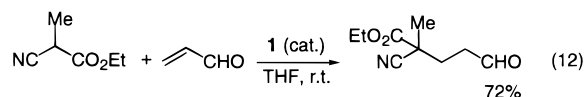
addition of nitriles,[27,28] although no catalytic activity was observed for the condensation with carbonyl compounds.

The principle can be applied to the addition of nitriles to imines. The reaction of 2-methylmalononitrile with 4-methoxycarbonyl-*N*-(4-methylbenzylidene)aniline in the presence of **1**[21,22] or RhH(CO)(PPh$_3$)$_3$[29] gave the cyano amine **28** in 91% yield (eq 13).

(13)

28 91%
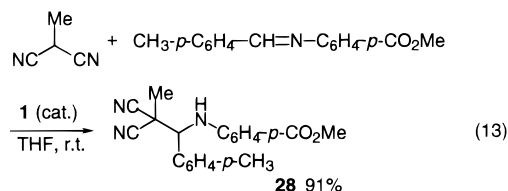
Addition of nitriles to acetylenic compounds proceeds with chemoselectivity in contrast to the corresponding base-promoted reactions, where products derived from acetylides are contaminants. The RuH$_2$(PPh$_3$)$_4$ (**1**)-catalyzed reaction of ethyl 2-cyanopropionate with methyl propiolate at room temperature gave **29** in 90% yield (eq 14).


(14)

29 90%
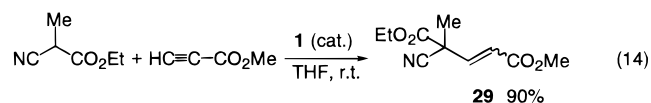
An important feature of the reaction is the chemoselective activation of nitriles in the presence of other active methylene compounds. Typically, the ruthenium-catalyzed reaction of an equimolar mixture of ethyl cyanoacetate and 2,4-pentanedione with benzaldehyde gave (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate exclusively, although both pronucleophiles have similar pK_a values (p$K_a \approx 13$ in DMSO). In contrast, the same reaction in the presence of conventional bases such as AcONH$_4$ or KOH gave a thermodynamic mixture of (*E*)-ethyl 2-cyano-3-phenyl-2-propenoate and 3-benzylidene-2,4-pentanedione (75:25).

The efficiency of the present method is highlighted by highly diastereoselective Michael addition arising from specific chelation control by metals. When a diastereomeric mixture of dimethyl 2-cyano-4-methoxycarbonyl-3-methylpentanedioate (diastereomer ratio = 68:32), which can be readily obtained by the ruthenium-catalyzed addition of dimethyl ethylidenemalonate to methyl cyanoacetate, was allowed to react with methyl vinyl ketone at −78 °C in the presence of catalyst **1**, methyl (3R*,4S*)-2,4-bis(methoxycarbonyl)-4-cyano-3-methyl-7-oxooctanoate was obtained diastereoselectively (96:4) in 74% yield.

Using the concept of these catalytic reactions, asymmetric carbon—carbon bond formation can be performed. The reactions of isopropyl 2-cyanopropanoate with vinyl ketones were carried out highly enantioselectively in the presence of RhH(CO)(PPh$_3$)$_3$ with (*S,S*)-(*R,R*)-TRAP (**30**)[28] (R = C$_6$H$_4$-*p*-OMe; 99%, 89% ee) or Rh(CO)$_2$(acac) with 2,2′-bis(diphenylphosphinomethyl)-7,7′-dimethoxy-1,1′-

binaphthyl (**31**) (R = CH$_3$; 93%, 72% ee) (eq 15).[30]
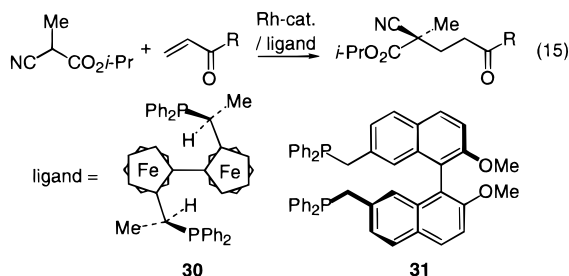
The ruthenium catalysts bearing electron-donating ligands would have higher reactivity for the activation of α-C−H bonds of nitriles. Actually, cyclopentadienylhydridoruthenium complex RuCpH(PPh$_3$)$_2$ (**32**) and pentamethylcyclopentadienylhydridoruthenium complex RuCp*H(PPh$_3$)$_2$ (**33**) are more reactive toward the activation of nitriles than **1**. Thus, in the presence of catalyst **32**, the
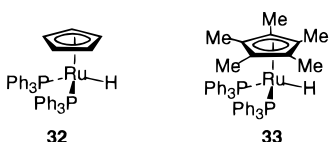

condensation of less reactive phenylacetonitrile with butanal gives (*Z*)-2-phenyl-2-hexenenitrile in 96% yield (eq 16). Furthermore, the Michael addition of 2-methyl-2-phenylacetonitrile to methyl vinyl ketone in the presence of catalyst **33** gives the adduct in 81% yield (reaction time 5 h), whereas the same reaction in the presence of the catalyst **32** gives only 7% yield (reaction time 5 h).
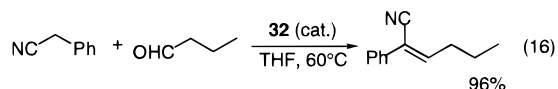
The present Knoevenagel condensation can be rationalized by assuming the mechanism shown in Scheme 11.[22] The catalytically active species seems to be the low-

Scheme 11
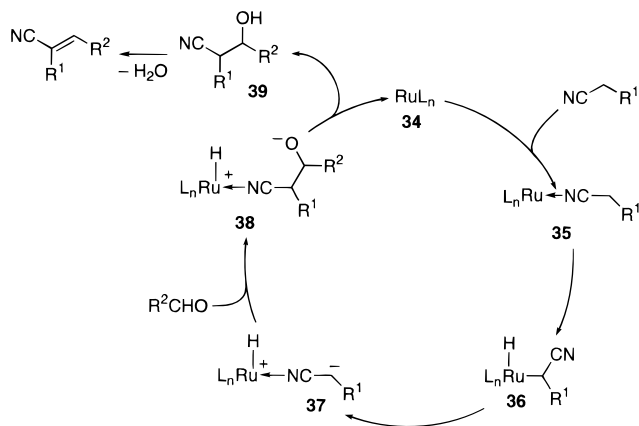
valent ruthenium complex RuL$_n$ (**34**). Coordination of nitrile to **34** gives **35**, and oxidative addition of the ruthenium to the α-C−H bond of nitrile would afford α-cyanoalkylruthenium hydride complex **36**, which is

converted to hydrido(enolato)ruthenium complex **37**. The intermediacy of **37** has been confirmed by isolation of Ru$^+$H(NCC$^-$HCO$_2$Et)(NCCH$_2$CO$_2$Et)(PPh$_3$)$_3$ from the reactions of ethyl cyanoacetate with either RuH(C$_2$H$_4$)(PPh$_3$)$_2$-(PPh$_2$C$_6$H$_4$) or RuH$_2$(PPh$_3$)$_4$ (**1**).[23] The complex Ru$^+$H-(NCC$^-$HCO$_2$Et)(NCCH$_2$CO$_2$Et)(PPh$_3$)$_3$, which is a catalyst for above reactions, was unequivocally characterized by X-ray structural analysis.[22] The reaction of the enolato ligand of **37** with an aldehyde gives hydrido(aldolato)-ruthenium intermediate **38**, which undergoes reductive elimination of **34** to afford the product **39**. Dehydration of **39** proceeds under the reaction conditions.

III-2. The C−H Activation of Carbonyl Compounds. The ruthenium complex RuH$_2$(PPh$_3$)$_4$ (**1**) has been proven to be a highly efficient catalyst for the activation of nitriles; however, this catalyst shows no catalytic activity toward carbonyl compounds. As a result of the systematic study aiming at exploitation of efficient catalysts for activation of carbonyl compounds, we discovered that RuCpH(PPh$_3$)$_2$ (**32**) is an effective catalyst for the activation of 1,3-dicarbonyl compounds. The RuCpH(PPh$_3$)$_2$ (**32**)-catalyzed Michael addition of 3-methyl-2,4-pentanedione to methyl vinyl ketone gave the adduct **40** in 79% yield (eq 17). This is in contrast to the result that the RuH$_2$(PPh$_3$)$_4$ (**1**)-catalyzed reaction gives only 12% yield of **40**.
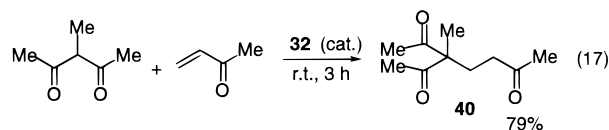
The significant difference in the catalytic activity between **32** and **1** is due to the coordination mode of diketonato ligands to ruthenium complexes. 1,3-Dicarbonyl compounds generally act as bidentate ligands to give stable η^2-*O*-enolate complexes. Actually, the reaction of **1** with 1,3-dicarbonyl compounds gives hydrido(η^2-*O*-enolato)ruthenium complex **41**,[22] which does not show catalytic activity toward Knoevenagel and Michael reactions of 1,3-dicarbonyl compounds. In contrast, when **32** is used
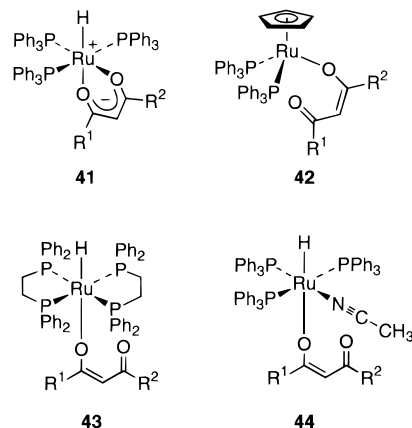
as a catalyst, monohapto *O*-bonded enolate complex **42** is formed and shows catalytic activity toward the Michael reaction of 1,3-dicarbonyl compounds. Ruthenium enolate complexes **43** derived from Ru(COD)(COT), 1,3-dicarbonyl

compounds, and 1,2-bis(diphenylphosphino)ethane showed excellent catalytic activity toward Michael addition of 1,3-dicarbonyl compounds.[31] Interestingly, Echavarren et al. have demonstrated that Michael reaction of 1,3-dicarbonyl compounds can be performed efficiently in the presence of the catalyst **1** when the reaction is carried out in acetonitrile.[32] This may be due to formation of the ruthenium complex **44** from **41** upon coordination to acetonitrile.

The most important aspect is α-C−H activation of simple carbonyl compounds with ruthenium catalysts under neutral conditions. Thus, the reaction of cyclopentanone with methyl vinyl ketone in THF at 60 °C in the presence of the ruthenium catalyst **33** (3 mol %) gave 2-(3-oxobutyl)cyclopentanone (**45**) in 52% yield (eq 18). Michael

$$\text{(18)}$$
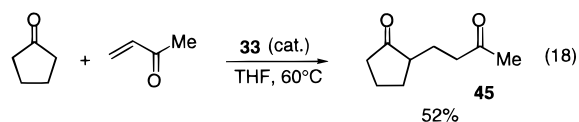
addition of simple ketones is quite difficult because of undesirable side reactions such as polycondensation of ketones and polymerization of olefins. Therefore, synthons of ketones, such as enamines and silyl enol ethers, have been used. In this aspect, the present direct reaction has an advantage over the conventional methods in view of synthetic and environmental aspects.

III-3. Catalytic Addition of Pronucleophiles to Nitriles.
Addition of carbon nucleophiles to the CN triple bonds of nitriles is one of the most attractive transformation reactions of nitriles. However, the reported method is limited to the strong base-promoted intramolecular cyclization reaction of dinitriles (Thorpe−Ziegler reaction). We discovered that low-valent iridium hydride complexes are effective catalysts for activation of both the α-C−H bonds and the CN triple bonds of nitriles. Actually, the iridium hydride complex-catalyzed cross condensation of nitriles can be performed under neutral conditions to give cyanoenamines **46**, which are versatile synthetic intermediates (eq 19).[33]

$$\text{NCCH}_2\text{R}^1 \quad + \quad \text{NC−R}^2 \xrightarrow{\text{Ir-cat.}} \quad \text{(19)}$$
**46**
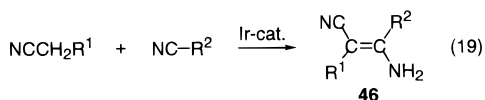
In the presence of iridium hydride complex IrH(CO)-(PPh₃)₃ (**47**) (3 mol %), ethyl cyanoacetate undergoes dimerization to give the corresponding cyanoenamines **48** (>99%) (eq 20). Treatment of **48** thus obtained with sulfuric acid gives 4-amino-3-ethoxycarbonyl-2,6-dioxo-1,2,5,6-tetrahydropyridine (**49**) (96%), which is a building block for antitumor alkaloids.

An important feature of the present reaction is the chemoselective addition of activated nitriles to the CN triple bonds of nitriles in the presence of carbonyl groups, because of the strong coordination ability of nitriles toward metals. The iridium-catalyzed addition of ethyl cyanoacetate to 4-acetylbenzonitrile gives ethyl (Z)-3-(4-acetylphenyl)-3-amino-2-cyano-2-propenoate (**50**, 59%)

$$\text{(20)}$$
48 >99% **49**
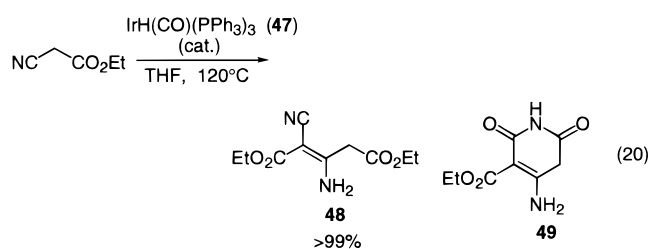
chemoselectively, while the same reaction promoted by a conventional base such as AcONH₄ gives ethyl 2-cyano-3-(4-cyanophenyl)-2-butenoate (**51**) (E:Z = 55:45) (eq 21).

$$\text{(21)}$$
50   **51**

cat. = IrH(CO)(PPh₃)₃ (**47**) 100 : 0
AcONH₄   0 : 100
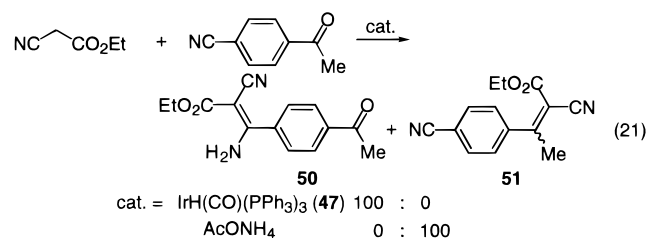
To activate simple alkanenitriles, more active iridium hydride catalysts are required. The iridium polyhydride catalyst IrH₅(P-*i*-Pr₃)₂ (**52**) has proved to be an efficient catalyst for the activation of alkanedinitriles.[33] The IrH₅-(P-*i*-Pr₃)₂ (**52**)-catalyzed cyclization of 1,5-dicyanopentane (**53**) gives cyanoenamine **54** under neutral condition in 72% yield (eq 22).

$$\text{(22)}$$
53   **54** 72%
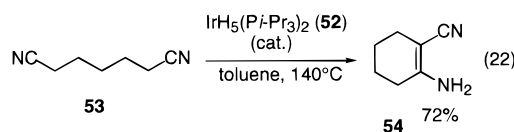
The present reaction can be rationalized by assuming the mechanisms depicted in Scheme 12. Coordination of nitrile to iridium complex IrLₙ (**55**) followed by oxidative

Scheme 12
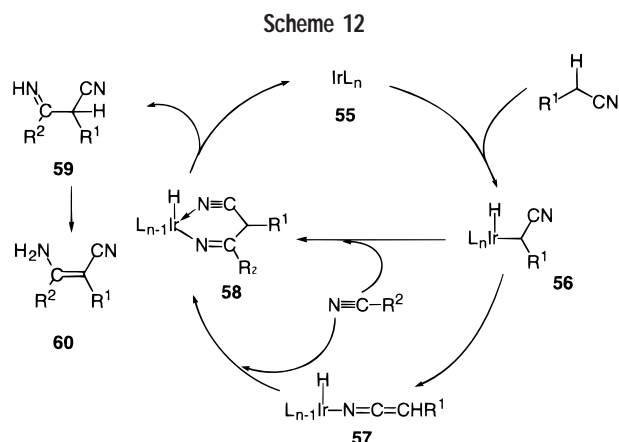

addition of the iridium into the α-C−H bond of nitrile with an α-heteroatom effect would occur to afford α-cyanoalkyliridium hydride complex **56**. Coordination of the second nitrile to **56**, followed by insertion into the nitrile, would give imino intermediate **58**. Bergman and Heathcock have reported that the carbon-bonded rhenium enolate complex undergoes intramolecular addition to the

coordinated nitrile to give the rhenium imino complex.[34] Alternatively, the complex **56** undergoes isomerization to an azaallenyl iridium complex **57**, and subsequent addition of the second nitrile would give **58**. We succeeded in preparation of azaallenyl iridium complex from IrCl(CO)-(PPh$_3$)$_2$ and the potassium salt of ethyl cyanoacetate and confirmed that the azaallenyl iridium complex is an excellent catalyst for the present reaction. Reductive elimination of the iridium complex **55** would afford the imine **59** to complete the catalytic cycle. Isomerization of **59** gives cyanoenamines **60** under the stated reaction conditions.

In summary, the low-valent ruthenium complexes **1**, **32**, and **33**, and iridium complexes **47** and **52,** are efficient catalysts which can be used as alternatives to the conventional bases. Using these catalysts, catalytic Knoevenagel and Michael reactions initiated by activation of α-C−H bond with an α-heteroatom effect can be performed highly efficiently. Catalytic addition of pronucleophiles to nitriles can also be performed. These reactions provide a novel strategy for catalytic carbon−carbon bond formation with pronucleophiles under neutral conditions without formation of salts.

IV. Application to Combinatorial Chemistry

Solid-phase synthesis is of importance in combinatorial chemistry. We discovered that the ruthenium complex RuH$_2$(PPh$_3$)$_4$ (**1**) can be used as an alternative to conventional Lewis acid and base catalysts. When one uses polymer-supported cyanoacetic acid **61**, which can be readily obtained from the commercially available polystyrene Wang resin and cyanoacetic acid, the ruthenium-catalyzed Knoevenagel and Michael reactions can be performed successively. The effectiveness of this reaction is demonstrated by the sequential four-component reaction on solid phase as shown in eq 23. The ruthenium-catalyzed condensation of **61** with propionaldehyde and subsequent addition of diethyl malonate and methyl vinyl ketone in THF at 50 °C gave the adduct **62** diastereoselectively in 40% yield (de = 89:11).
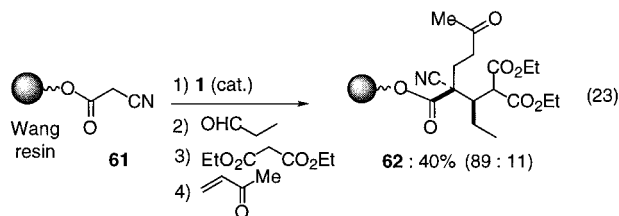
The reaction of iridium hydride catalyst IrH$_5$(P-*i*-Pr$_3$)$_2$ (**52**), which works as both Lewis acid and base catalysts, is shown in eq 24. Addition of ethyl cyanoacetate to
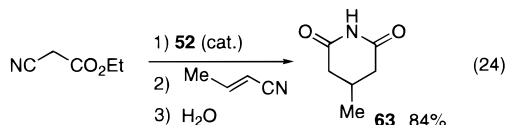
crotononitrile, subsequent multistep hydrations, and cy-

clocondensation gave 4-methyl glutarimide (**63**) in 84% yield. At first, the catalyst **52** likewise acts as a base to generate the carbon nucleophile by α-C−H activation. Thereafter, the catalyst acts as a Lewis acid to perform hydration. In the presence of a polymer-supported iridium hydride catalyst, the reaction also proceeds efficiently; therefore, this reaction can be applicable to combinatorial chemistry for synthesis of heterocyclic compounds. Large chemical libraries of heterocyclic compounds can be obtained based on the combination of various pronucleophiles, alkenes, and nucleophiles.

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