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Accounts

A New Way for Efficient Catalysis by Using Low Valent Ruthenium Complexes as Redox Lewis Acid and Base Catalysts

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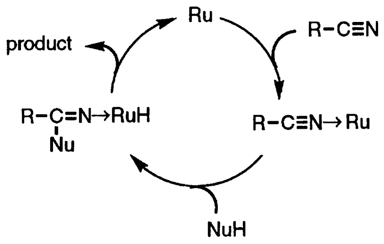
Low valent ruthenium hydride complexes are excellent catalysts which act as either redox Lewis acid or base catalysts. Nitriles are substrates which have strong coordination ability towards transition metals, so new types of catalytic transformations of nitriles have been explored using these catalysts. As redox Lewis acid catalysts, hydration of nitriles, amidation of amines, and esterification of alcohols with nitriles can be achieved. The same catalyst can be used for direct formation of carbon nucleophiles by C–H activation of pronucleophiles, such as nitriles and carbonyl compounds, hence catalytic aldol-type reactions and Michael-type additions can be performed under neutral and mild conditions.

Lewis acid and base promoted reactions are two of the most fundamental reactions in organic chemistry. Owing to the current need to develop forward-looking technology that is environmentally acceptable with respect to, for example, negligible formation of inorganic wastes, efficiency, high selective formation of products, many aspects must be considered in the search for new catalytic reactions. The majority of reactions using Lewis acids and bases are still stoichiometric reactions with those reagents; therefore if one could carry out these reactions by designing and using Lewis acids and bases bearing low redox potentials, these reactions, which occur catalytically under neutral and mild conditions, will provide useful processes. Bearing these factors in mind, we have been searching for such transition metal complex catalysts, which we call redox Lewis acid and base catalysts. We found divalent ruthenium hydride complexes are excellent such catalysts which can be used as both Lewis acids and bases. We selected nitriles as substrates because we focused on strong coordination ability of nitriles to transition metals and their α-heteroatom effects. This account describes the importance of low valent transition metal complexes as redox Lewis acid and base catalysts. i) Divalent ruthenium dihydride complexes are excellent Lewis acid catalysts for hydration of nitriles, amidation of amines, and esterification of alcohols with nitriles. ii) The same complexes can be also used for direct formation of carbon nucleophiles by C–H activation of pronucleophiles such as nitriles and carbonyl compounds. Hence, catalytic aldol-type reactions and Michael-type additions can be performed highly efficiently under neutral and mild conditions.

1. Low Valent Ruthenium Complexes as Redox Lewis Acid Catalysts for Activation of Nitriles

The use of transition metal complexes as redox Lewis acid catalysts will open up new chemistry because these reactions have the potential ability to proceed under neutral conditions and with high selectivity owing to chelation control. To validate this proposal, we selected low valent ruthenium dihydride complexes, because we have noticed that low valent ruthenium complexes have strong coordination ability towards heteroatoms.[1] We selected nitriles as substrates because nitriles have strong coordination ability to metals and hence perturbation would occur on the carbon–nitrogen bond. Transformations of nitriles to carbonyl compounds such as carboxylic acids, esters, and amides are highly useful;[2] in general, however, the reactions must be carried out under acidic or basic conditions, and as a result many side reactions, such as hydrolysis of other functional groups, occur faster than the desired transformations of cyano group. Therefore, development of the transformations of nitriles under neutral and mild conditions is a subject of continued interest that promises a variety of new synthetic processes complying well with recent environmental requirements. However there has been no systematic study on the activation of CN triple bond of nitriles with transition metal complex catalysts. We found that low valent ruthenium hydride complexes show remarkable and specific Lewis acidity and are highly efficient catalysts for the activation of CN triple bond of nitriles. The basic concept is shown in Scheme 1. Nitriles are activated upon coordination to low valent ruthenium complexes; capture of the activated



Scheme 1. Activation of nitriles with a low valent ruthenium catalyst.

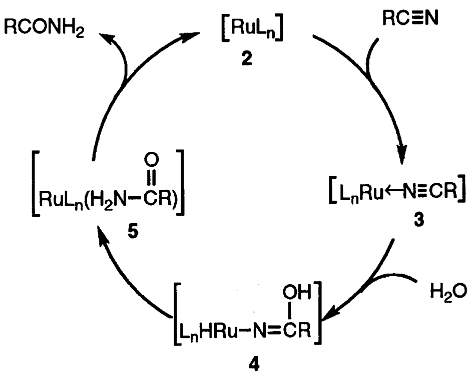
intermediate with various nucleophiles would provide a new type of catalytic transformations of nitriles which proceed under mild and neutral conditions. Thus, we have explored convenient methods for transformations of nitriles to amides, esters, lactones, lactams, and polyamides.

1.1 Hydration of Nitriles. On the basis of the concept shown in Scheme 1, we first examined the catalytic hydration of nitriles using water as a nucleophile. Although many methods for hydration of nitriles to amides have been performed under strong acidic and basic conditions,[3] appreciable hydrolysis of the product amides to the carboxylic acids frequently occurs faster than nitrile hydration. Therefore, hydration of nitriles under neutral conditions has been studied extensively using heterogeneous[4] and homogeneous[5] catalysts. The problems of these methods are that the reactions require a large excess of water and an extremely high reaction temperature. Hence, an effective method for hydration of nitriles using an equimolar amount of water under mild and neutral conditions is waiting to be explored.

Using $[RuH_2(PPh_3)_4]$ catalyst (**1**), the hydration of nitriles proceeds smoothly upon treatment with only 1—2 molar amounts of water under neutral conditions to give the corresponding amides (Eq. 1).[6] In a typical case, the reaction of acetonitrile with 2 molar amounts of water in 1,2-dimethoxyethane, in the presence of 0.03 molar amount of $[RuH_2(PPh_3)_4]$ (**1**) at 120 °C, gave acetamide (conversion of acetonitrile, 100%: yield, 92%). Various aliphatic and aromatic nitriles can be converted into the corresponding amides efficiently. Since the reaction proceeds with an equimolar amount of water under neutral conditions, other functional groups are tolerated in the hydrolysis. The present hydration is advantageous over the previous methods[3—5] because of its simple operation, neutral reaction conditions, and high efficiency.

$$\text{R-CN} + H_2O \xrightarrow{\substack{[RuH_2(PPh_3)_4] \\ \text{(1) (cat.)}}} RCONH_2 \qquad (1)$$

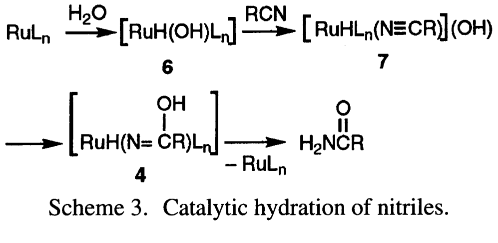
The present hydration reaction of nitriles can be rationalized simply by assuming the mechanism shown in Scheme 2. The catalytically active species seems to be coordinatively unsaturated Ru(II) complex **2**, which undergoes coordination to nitriles to give nitrile complex **3**. Nucleophilic attack of water on **3** would provide 1-hydroxyalkylideneamido complex **4**, which undergoes isomerization to give amide complex **5**. Dissociation of amide gives **2** to complete the catalytic cycle.



Scheme 2. Catalytic cycle of hydration of nitriles.

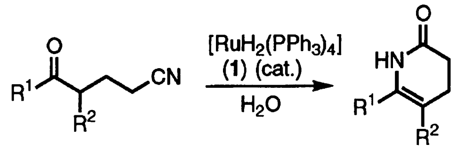
An alternative pathway for amide formation is the oxidative addition of water and the insertion of RuOH into the CN bond of the coordinated nitrile. Thus, oxidative addition of zerovalent ruthenium complex to water gives hydridohydroxyruthenium complex **6**, which undergoes coordination of nitrile to give cationic complex hydroxide **7** (Scheme 3). Nucleophilic attack of hydroxide ion on the coordinated nitrile gives 1-hydroxyalkylideneamido complex **4**. Kinetic studies on the hydration of nitriles with $[PtH(H_2O)(PR_3)_2]$-(OH) catalyst revealed that the hydration reaction proceeds via the cationic intermediate complex $[PtH(RCN)(PR'_3)_2]$-(OH), which undergoes nucleophilic attack of hydroxide ion on the coordinated nitrile as a key step.[5k] The possibility of oxidative addition of water has been eliminated by deuterium-labeling experiments in the $[PtH(H_2O)(PR_3)_2](OH)$-catalyzed hydration of nitriles, although such a pathway has been postulated in the platinum-catalyzed hydration of nitriles.[5i,5j] In the present $[RuH_2(PPh_3)_4]$ (**1**)-catalyzed hydration reaction, the addition of electron donating phosphine ligands such as PBu_3, dppe, and dppp does not accelerate the reaction, which suggests that the oxidative addition of water is not involved.

The principle of the present hydration reaction can be extended to the catalytic transformation of γ-cyano ketones to ene-lactams,[6,7] which are versatile intermediates for synthesis of piperidine and hydroquinoline ring systems. The ruthenium-catalyzed reaction of γ-cyano ketones, which are obtained readily by cyanoethylation of ketones, proceeds highly efficiently upon treatment with 2 molar amounts of water under similar reaction conditions (Eq. 2). γ-Cyano ketones can be converted into the corresponding ene-lactams with high efficiency. Cyano ketones bearing ester groups were converted into the corresponding ene-lactams without hydrolysis of the ester groups (Scheme 4). The reaction of cyano ketones derived from 1,3-diketones gave the corre-



Scheme 3. Catalytic hydration of nitriles.

sponding keto ene-lactams, which are highly useful intermediates for synthesis of lycopodium alkaloids. The formation of ene-lactams can be rationalized by assuming nucleophilic attack of water upon the coordinated nitriles to give amides, which undergo further ruthenium-induced cyclization to give ene-lactams.

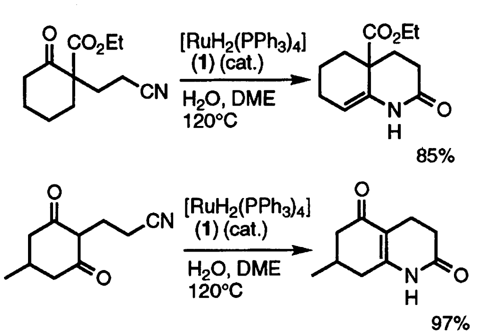


(2)

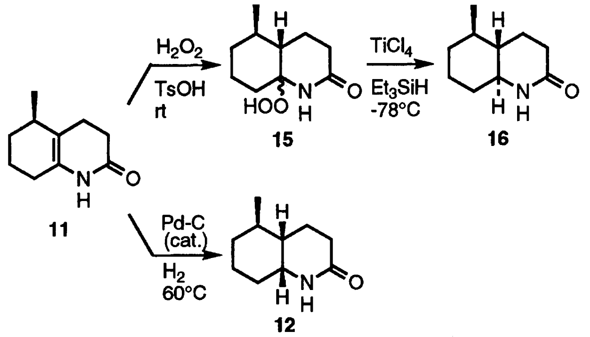
The effectiveness of the present reaction is illustrated by the synthesis of (−)-pumiliotoxin C (**8**),[8] which is an interesting toxic skin alkaloid produced by Central American frogs *Dendrobates pumilio* and *D. auratus*.[9] The strategy for a concise synthesis of (−)-**8** is shown in Scheme 5, in which the ruthenium-catalyzed cyclization and diastereoselective hydrogenations are key steps.[7] As a starting material we chose the cyanoethylated compounds (**10**) derived from (*R*)-(+)-pulegone (**9**). When the $[RuH_2(PPh_3)_4]$-catalyzed reaction of **10** was carried out with excess amount of water at 160 °C, deisopropylidenation of **10** and cyclization occurred sequentially to give optically pure ene-lactam **11**. We found that hydrogenation of **11** in EtOH–acetic acid (5/1, containing concd HCl), in the presence of 5% Pd–C under hydrogen pressure at 60 °C, gave the lactam **12** in 90% yield with high selectivity (*cis*/*trans*=98/2). The lactam **12** can be selectively converted into **8**, as shown in Scheme 5.

As a consequence of the synthetic utility of ene-lactams, we developed a novel method for selective transformation of ene-lactams to the corresponding *trans*-fused lactams.[7] Acid-catalyzed reaction of ene-lactams with hydrogen peroxide gives 5-hydroperoxy-5-pentanolactams, which can be converted into *trans*-fused lactams upon treatment with Et_3SiH in the presence of $TiCl_4$. Typically, treatment of **11** with 30% aqueous H_2O_2 solution in the presence of TsOH catalyst in CH_2Cl_2 at room temperature gave a diastereomeric mixture of 8a-hydroperoxydecahydro-2-quinolinone **15** in 77% yield (Scheme 6). Then treatment of the mixture of **15** with Et_3SiH (3.0 molar amounts), in the presence of $TiCl_4$(2.0 molar amounts) in CH_2Cl_2 at −78 °C, followed by recrystallization, gave pure *trans*-fused lactam **16**. Therefore, we are in a position to be able to prepare either *cis*- or *trans*-fused decahydroquinolines selectively by use of either the acid-promoted catalytic hydrogenation of ene-lactams or the present method.

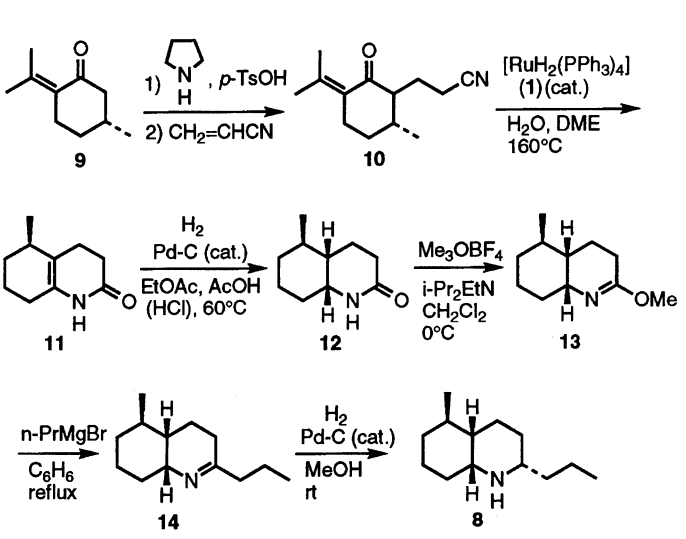
1.2 Condensation of Nitriles with Alcohols. The hydration of nitriles can be rationalized simply by assuming the mechanism which involves nucleophilic attack of water to the coordinated nitriles, as shown in Scheme 2. With the possibility of nucleophilic attack by alcohols instead of water, the condensation of nitriles with alcohols would proceed directly



Scheme 4. Ruthenium-catalyzed synthesis of ene-lactams.



Scheme 6. Synthesis of *trans*- and *cis*-fused lactams.



Scheme 5. Synthesis of (−)-pumiliotoxin C (**8**).

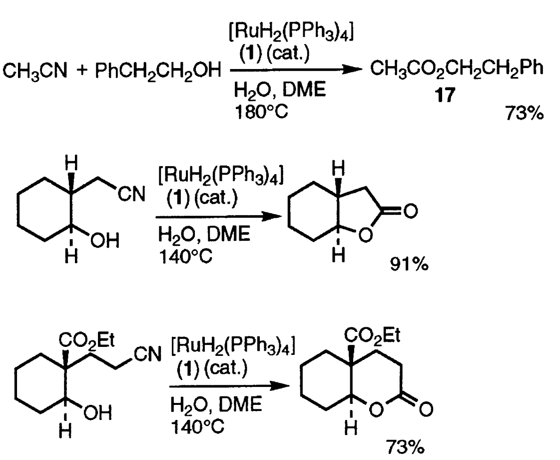
to afford esters. Indeed, the ruthenium-catalyzed reaction of nitriles with alcohols in the presence of 1—2 molar amounts of water proceeds under neutral conditions to give the corresponding esters along with evolution of ammonia (Eq. 3).[10] Although there are many reports on the nucleophilic reactions of nitriles with alcohols giving esters[11] and imidates,[12] most reactions have been performed under strongly acidic conditions. The reported methods for transition metal-catalyzed reactions of nitriles with alcohols to form the esters are limited to a few non-selective reactions,[13] which require severe conditions, and the competitive hydration reaction of nitriles cannot be avoided. The present reaction is advantageous over the previous methods[11,13] with respect to its high efficiency and selectivity, neutral reaction conditions, and facile isolation of the desired products.

$$\mathrm{RCN + R^1OH + H_2O \xrightarrow{[RuH_2(PPh_3)_4]\ (\mathbf{1})\ (cat.)} RCO_2R^1 + NH_3} \qquad (3)$$

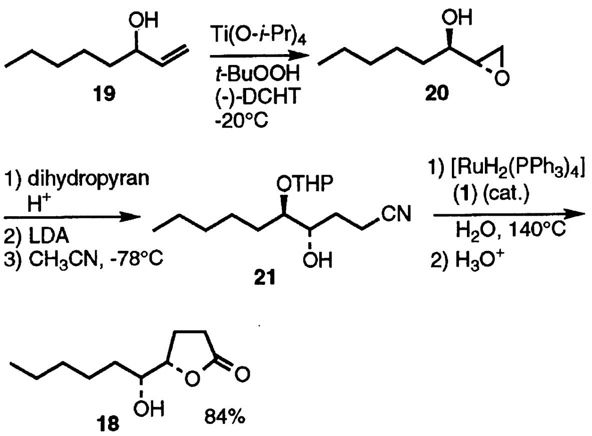
The present reaction provides a highly useful method for single-step preparation of esters from nitriles under neutral conditions. Acetylation of alcohols can be performed conveniently upon treatment of acetonitrile, eliminating aqueous work-up, as shown in Scheme 7. A variety of perfume esters such as **17** (peach fragrance) can be readily prepared from commercially available nitriles and alcohols. The intramolecular version of the present reaction provides an efficient method for synthesis of lactones. The reactions of 1,4- and 1,5-hydroxy nitriles proceed smoothly at 140 °C to give five- and six-membered lactones in excellent yields. ω-Hydroxy nitriles other than 1,4- and 1,5-derivatives undergo intermolecular condensation to give the corresponding polyesters.

The efficiency of the reaction is illustrated by the short-step synthesis[10] of (4*S*,5*R*)-5-hydroxy-4-decanolide (**18**), which is the autoregulator of anthracycline biosynthesis isolated from strains of *Streptomyces griceus*.[14] The synthesis of **18** has been performed as shown in Scheme 8. The key step is the ruthenium(II)-catalyzed lactonization of **21**.

The present reaction can be rationalized by assuming the mechanism shown in Scheme 9. Catalytically active Ru(II) species **2** undergoes coordination to nitrile to give the complex **3**. Nucleophilic attack of alcohol to the activated nitrile occurs faster than the attack of water to afford imidate complex **22**. Transition metal imidate complexes have been isolated from the reaction of nitrile complexes with alcohols.[15] Hydrolysis of the intermediate **22** gives esters, ammonia, and Ru(II) complex to complete the catalytic cycle.

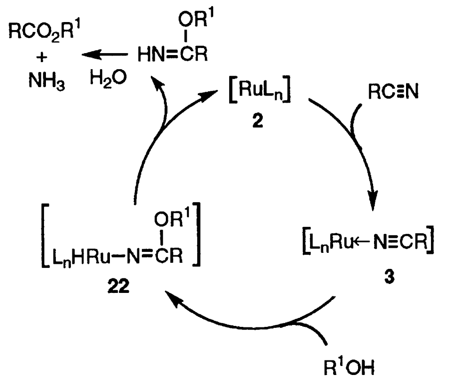


Scheme 7. Ruthenium-catalyzed reaction of nitriles with alcohols.



Scheme 8. Synthesis of (4*S*,5*R*)-(+)-5-hydroxy-4-decanolide (**18**).

An alternative pathway for the present condensation is internal nucleophilic attack of alkoxide ion on the coordinated nitrile of the complex [RuH(N≡CR)L$_n$](OR^1) (**23**). Thus, the reaction of dihydridoruthenium complex with alcohols gives an alkoxohydrido complex [RuH(OR^1)L$_n$] (**24**) which undergoes coordination of nitrile to give **23**. We have found that primary alcohols undergo oxidative condensation upon treatment with [RuH$_2$(PPh$_3$)$_4$] catalyst (**1**) to give esters and molecular hydrogen.[16] The key step of the reaction is the oxidative addition of ruthenium [RuL$_n$] into the OH bonds of alcohols to give **24** and subsequent β-elimination of RuH species to give the corresponding carbonyl compounds. In the present reaction of nitriles with alcohols, the coordination of nitrile would strongly prevent the β-elimination of **23**. Nucleophilic attack of alkoxide ion in **23** gives imidate complex **22**. Reductive elimination of **22** gives the corresponding imidate, which undergoes hydrolysis to give an



Scheme 9. Catalytic cycle of the ruthenium-catalyzed reaction of nitriles with alcohols.

ester along with ammonia.

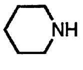
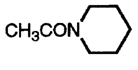
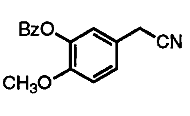
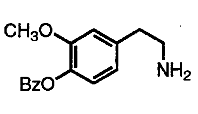
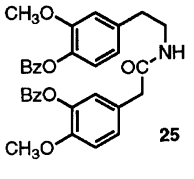
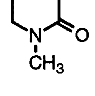
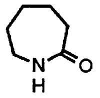
1.3 Catalytic Amidation of Nitriles with Amines. Considering the mechanism of the condensation of nitriles with alcohols shown in Scheme 9, we see that a ruthenium amidine intermediate could be formed when an amine is employed as a nucleophile in the above condensation reaction. Similar hydrolysis of amidine complex would give the corresponding amides. Indeed, a novel catalytic synthesis of amides from nitriles and amines under neutral conditions has been performed. Thus, the $[RuH_2(PPh_3)_4]$ (**1**)-catalyzed reaction of nitriles with amines in the presence of 1—2 molar amounts of water gives the corresponding amides along with evolution of ammonia (Eq. 4).[17] The addition reactions of nitriles with amines have been performed under strongly acidic conditions to give the corresponding amidines.[18] Metal-induced reactions of nitriles with amines[19] and amino alcohols[20] have been reported to give amidines and oxazolines, respectively. *N*-Substituted amides have been prepared from nitriles and amines at extremely high temperature[21] or by using catalysts such as strong acids,[22] or strong bases;[23] however, these methods require severe reaction conditions and lack the generality of substrates. The present reaction appears to proceed generally, cleanly, and highly efficiently under neutral conditions in a single step.

$$\mathrm{RCN} + \mathrm{R^1R^2NH} + \mathrm{H_2O} \xrightarrow[\textbf{(1)}\ \text{(cat.)}]{[\mathrm{RuH_2(PPh_3)_4}]} \mathrm{RCONR^1R^2} + \mathrm{NH_3} \tag{4}$$

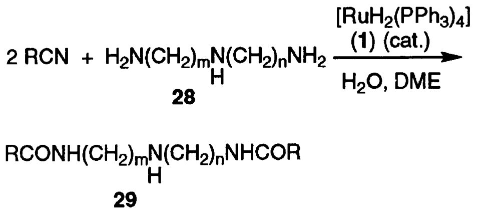
Acetylation of amines with acetonitrile is practical, because of simple isolation of the acetamides without a washing process (Table 1). Amide **25**, which is an important precursor of isoquinoline alkaloids such as reticuline or *N*-norreticuline, has been prepared readily upon treatment of 3-(benzyloxy)-4-methoxybenzyl cyanide with 2-(4-benzyloxy-3-methoxyphenyl)ethylamine. The intramolecular version of the present reaction provides an efficient method for synthesis of lactams such as compounds **26** and **27**.

Chemoselective acylation of polyamines is of importance in view of the synthesis of naturally occurring polyamines such as spermidine and spermine alkaloids,[24] which show potent antibiotic and antineoplastic properties. Several direct[25] and multistep[24a,24b,26] methods for selective acylation of polyamines have been reported; however, the general methods available are limited, because of the high nucleophilicity of secondary amines. Using the present reaction, we can acylate the primary amino groups of polyamines chemoselectively with nitriles in the presence of secondary amino groups (Eq. 5). The present reaction provides a convenient method for selective *N*-acylation of the primary amino groups of polyamines, because of the simple operation of the reaction and facility of preparing various nitriles. Actually, acetonitrile undergoes the condensations with *N*-(3-aminopropyl)-1,3-propanediamine (**28a**, *m*=3, *n*=3) and spermidine (**28b**, *m*=3, *n*=4) to give the corresponding amides **29a** (R=CH_3) and **29b** (R=CH_3) in 84 and 93% yields, respectively. The reaction of $C_6H_5CH_2CN$ with **28a** gave *N*-[3-(phenylacetylamino)propyl]-*N*′-(phenylacetyl)-1,3-propanediamine (**29c**, R=$PhCH_2$) in 86% yield along with only 3% of the triacyl compounds. Maytenine[27] (**30**) has been prepared by the reaction of cinnamonitrile with **28b** in 70% yield (Scheme 10). Although maytenine has been synthesized by several routes,[25e,25f,25g,27] this is one of the best methods because of its simple operation and high selectivity.

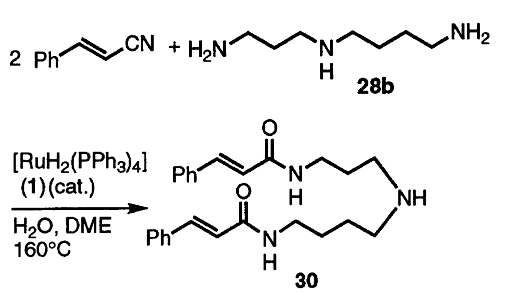
Table 1. Ruthenium-Catalyzed Reaction of Nitriles with Amines[a)]

Nitrile	Amine	Amide	Isolated yield[b)]/%
CH_3CN			97
CH_3CN	$PhCH_2NHCH_3$	$CH_3CON(CH_3)CH_2Ph$	95
		 **25**	80
$NC(CH_2)_4NHCH_3$		 **26**	99
$NC(CH_2)_5NH_2$		 **27**	74

a) A mixture of nitrile, amine (1.1 molar amount), H_2O (2 molar amounts), and $[RuH_2(PPh_3)_4]$ (**1**) (0.03 molar amount) in DME was heated at 160 °C for 24 h in a sealed tube under argon. b) Based on the starting nitrile.



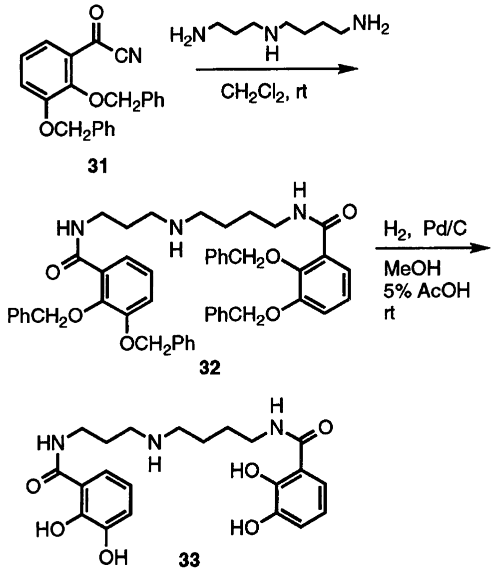
$$2\ RCN + \underset{\mathbf{28}}{H_2N(CH_2)_m\underset{H}{N}(CH_2)_nNH_2} \xrightarrow[H_2O,\ DME]{[RuH_2(PPh_3)_4]\ (1)\ (cat.)} \underset{\mathbf{29}}{RCONH(CH_2)_m\underset{H}{N}(CH_2)_nNHCOR} \qquad (5)$$



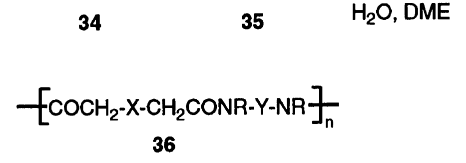
Scheme 10. Synthesis of maytenine (**30**).

It is noteworthy that an alternative chemoselective benzoylation of primary amines in the presence of secondary amines can be performed upon treatment with acyl cyanides.[28] Typically, the acylation of spermidine with two molar amounts of 2,3-bis(benzyloxy)benzoyl cyanide (**31**) proceeds selectively to afford the corresponding dibenzoylspermidine **32** in 87% yield (Scheme 11). Removal of benzyl groups by catalytic hydrogenation gave **33** (95%) which is a microbially produced iron transport compound isolated from *Micrococcus denitrificans.*

The efficiency of our new catalytic process is highlighted by the synthesis of various industrially important polyamides. Thus, the catalytic condensation of dinitriles **34** with diamines **35** in the presence of water gives the corresponding polyamides **36** efficiently, as depicted in Eq. 6. Industrially polyamides have been prepared by the condensation of dicarboxylic acids with diamines.[29] Direct preparation of polyamides from dinitriles and diamines is of importance from a commercial viewpoint.[30] The new strategy for polyamide synthesis is illustrated for the preparation of nylon-6,6, as shown in Scheme 12. The method is advantageous over the conventional method by the condensation of adipic acid with hexamethylenediamine,[29] because i) dinitriles can be readily prepared by industrial processes[31] such as hydrocyanation of dienes[32] or reductive dimerization of acrylonitrile,[33] ii) diamines can be easily obtained by catalytic hydrogenation of dinitriles,[31] and iii) the ruthenium-catalyzed condensation gives polyamides and ammonia, which can be efficiently reutilized as a nitrogen source. In spite of the wide recognition of the importance of the direct preparation of polyamides from dinitriles and diamines, the reported methods from dinitriles and diamines[23,34] or amino nitriles[35] are limited to those reactions which require strongly basic conditions or extremely high temperatures. As a consequence of examining the scope and limitation of the present catalytic reaction, we have found that the reaction is quite efficient for the polycondensation reaction of various dinitriles and amino nitriles. The reaction provides a useful and convenient method for polyamide synthesis because i) the reaction proceeds under neutral conditions, ii) a wide variety of dinitriles, diamines and amino nitriles can be used, and iii) the reaction is clean and ammonia is readily removed.

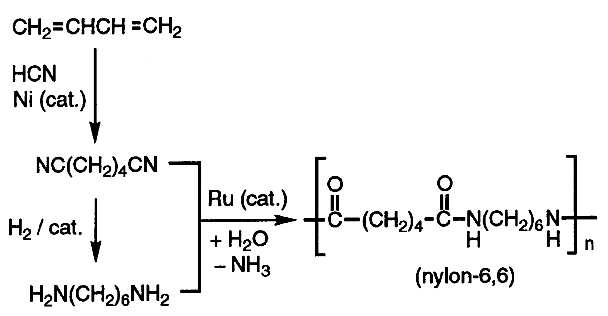


Scheme 11. Synthesis of iron transport compounds (**33**).



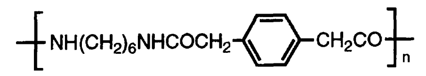
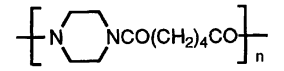
$$\underset{\mathbf{34}}{NCCH_2\text{-}X\text{-}CH_2CN} + \underset{\mathbf{35}}{RNH\text{-}Y\text{-}NHR} \xrightarrow[H_2O,\ DME]{[RuH_2(PPh_3)_4]\ (1)\ (cat.)} \underset{\mathbf{36}}{-\!\!\left[COCH_2\text{-}X\text{-}CH_2CONR\text{-}Y\text{-}NR\right]_n\!\!-} \qquad (6)$$

As a model reaction, the polycondensation of hexanedinitrile with 1,6-hexanediamine was investigated in the presence of water (2 molar amounts) and $[RuH_2(PPh_3)_4]$ catalyst (0.03 molar amount) in DME at 160 °C for 24 h. The polyamide **37** was obtained in 98% yield. The molecular weight (M_n) was determined to be 8900 by titration of the terminal amino group. The viscosity η in *m*-cresol was 0.7 dL g^{-1}, which corresponds to M_n 7900 and is consistent with the M_n value obtained above. Other representative examples of the polyamide synthesis are shown in Table 2. Nylon-*m*,*n* can be readily prepared by the reaction of linear dinitriles with linear



Scheme 12. Ruthenium-catalyzed synthesis of nylon-6,6.

Table 2. Polyamide Synthesis from Dinitriles and Diamines[a)]

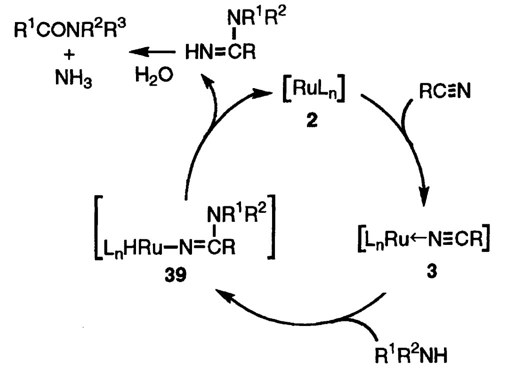
Polyamide	Mp/°C	$M_n^{b)}$	Yield/%
$-\!\!\left[NH(CH_2)_6NHCO(CH_2)_4CO\right]_n\!\!-$ **37**	255	8900	98
$-\!\!\left[NH(CH_2)_{12}NHCO(CH_2)_{10}CO\right]_n\!\!-$	>300	3800	99
	>300	14000	93
	230	7200	73

a) Polymerization was carried out with each monomer in the presence of H_2O (2 molar amounts) and $[RuH_2(PPh_3)_4]$ (**1**) (0.03 molar amount) in DME at 160 °C for 24 h in a sealed tube under argon. b) Molecular weight was determined by titration of the terminal amino group with *p*-toluenesulfonic acid using Thymol-Blue.

diamines. The reaction of aromatic dinitriles with diamines gives the polyamides which have been used as heat resistant resins. Since various dinitriles have been prepared as the precursor of diamines,[33,34)] the present reaction provides a wide-scope method for synthesis of polyamides without using diacids and diesters. Aminonitriles undergo similar polycondensation efficiently; the ruthenium-catalyzed reaction of 3-aminopropionitrile gave nylon-3, $-(NH(CH_2)_2CO)_n-$ (**38**, M_n 1600), in 98% yield, as shown in Eq. 7.

$$H_2N(CH_2)_2CN + H_2O \xrightarrow[\text{DME}]{[RuH_2(PPh_3)_4]\ \textbf{(1)}\ \text{(cat.)}} -\!\!\left[NH(CH_2)_2CO\right]_n\!\!- \quad \textbf{38} \qquad (7)$$

The present reaction can be rationalized by the following mechanism (Scheme 13) which is similar to that of the ester synthesis. Nucleophilic attack of amine on the activated nitrile **3** affords amidine complex **39**. Transition-metal amidine complexes have been isolated from the reaction of the nitrile complexes of Re and Pt with amines.[36)] It has also been reported that the metal-catalyzed reaction of nitriles with amines gives the corresponding amidines.[19)] Complex **39** undergoes hydrolysis to give *N*-substituted amide, ammonia, and complex **2** to complete the catalytic cycle. An alternative mechanism is internal nucleophilic attack of an amino group on the coordinated nitrile of cationic intermediate $[RuHL_n(R^1CN)](NR^2R^3)$, which would be formed according to a mechanism similar to the ester synthesis.



Scheme 13. Catalytic cycle of the reaction of nitriles with amines.

In conclusion, we have found low valent ruthenium complexes act as efficient Lewis acid catalysts for the reaction of nitriles with nucleophiles.[37)] The principle leads to a variety of catalytic transformations of nitriles under neutral conditions, which are of particular importance from industrial and environmental points of view. These reactions provide facile and versatile methods for the synthesis of various useful compounds such as nitrogen containing biologically active compounds and industrially important functional materials.

2. Transition Metal Catalyzed Activation of C–H Bonds of Pronucleophiles by Heteroatom Effects. Transition Metal Complexes as Redox Bases

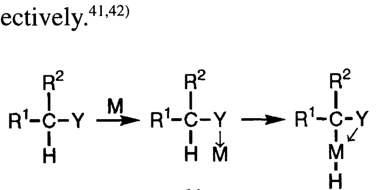
The C–H activation with transition metal complexes will open a new chemistry of catalytic carbon–carbon bond formation because of its potent ability to generate carbon nucleophiles and to promote reactions under neutral and mild conditions. The design of catalytic reactions which involve the process of insertion of metals into C–H bonds and substitution of the metal–carbon bonds thus formed, with electrophiles, will provide fundamental reactions for organic synthesis. These reactions will be more practical than the general methods which use halogenated substrates in both ecological and economical aspects. The reactivity of the C–H bond towards metals depends upon the magnitude of the s-character of carbons. That is, the order is as follows: sp carbon–hydrogen > sp^2 carbon–hydrogen (vinyl, aryl) > sp^3 carbon–hydrogen. The most difficult process is the direct C–H activation of sp^3 carbons (Scheme 14). For the activation of a sp^3 C–H bond, there are three types of approaches. i) The first is the oxidative additions of metals to the sp^3 carbon–hydrogen

$$R\text{-}H \xrightarrow{M} R\text{-}M\text{-}H$$

$$R\text{-}H \xrightarrow{M=O} R\bullet MOH \longrightarrow ROH$$

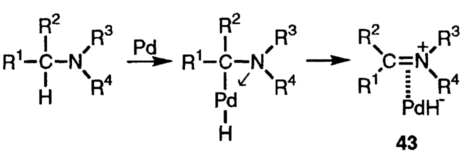
Scheme 14. The C–H activation of sp^3 carbon.

bond, which has been reported with the complexes of late transition metals such as Ir, Pt, Os, and Re.[38,39] Typically, the alkyl(hydrido)iridium complexes thus formed undergo *β*-elimination to give alkenes.[39a] The insertion of CO into the alkyl-metals thus formed also results in carbonylation of hydrocarbons.[39b] ii) The second approach is hydrogen abstraction by metal oxo species resembling cytochrome P-450.[40] As an example, the reaction of cyclohexane with molecular oxygen (1 atm) in the presence of acetaldehyde, iron powder catalyst and acetic acid at room temperature gives cyclohexanol and cyclohexanone selectively.[40i] In this reaction an oxo-iron species, which may correspond to the cytochrome P-450 Fe=O species, is formed and abstracts hydrogen, and the recombination of the intermediate gives alcohols. iii) The third process is the activation of *α*-C–H bonds adjacent to heteroatoms using the *α*-heteroatom effect.[1] The last concept is depicted in Scheme 15. Coordination of a heteroatom (Y) of substrate **40** to low valent metal M increases both the basicity of metal complexes and the acidity of the C–H bonds adjacent to Y, resulting in oxidative addition of metal into the *α*-C–H bond to give **42**. Our first approach was an investigation of the activation of an *α*-C–H bond adjacent to nitrogen. The activation of an *α*-C–H bond of tertiary amines proceeds upon treatment with palladium(0) catalyst. As we expected, coordination of palladium to the nitrogen of amines, followed by oxidative addition at the *α*-C–H bond, gives an iminium ion palladium complex **43** (Scheme 16).[1] This concept leads to a new methodology for the activation of nitriles under neutral conditions. The basic strategy for constructing a new catalytic reaction is shown in Eq. 8. Coordination of nitriles to low valent metal complexes (M) would increase both the basicity of the metal and the acidity of the *α*-C–H bond, and hence oxidative addition of the metal into the *α*-C–H bond of nitriles would occur readily to afford (*α*-cyanoalkyl)hydrido complex **44**, which can be trapped with electrophiles to form a carbon–carbon bond at the *α*-position of nitriles under neutral conditions. Actually, we have found that the low valent hydrido(phosphine)ruthenium complexes are effective catalysts for the activation of the *α*-C–H bond of nitriles. Upon treatment with carbon electrophiles, catalytic aldol and Michael reactions of nitriles can be performed under neutral and mild reaction conditions, as depicted in Eqs. 9 and 10, respectively.[41,42]



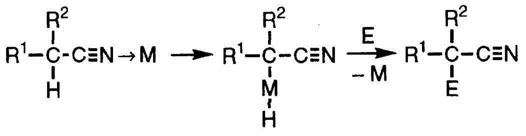
40 **41** **42**

Scheme 15. Concept of the C–H activation by heteroatom effect.

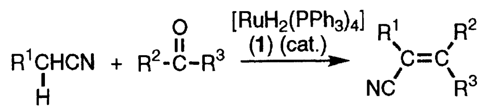


43

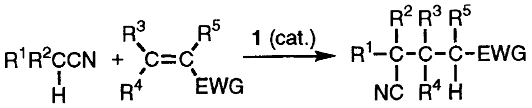
Scheme 16. The C–H activation of tertiary amines.



44 (8)



(9)



(10)

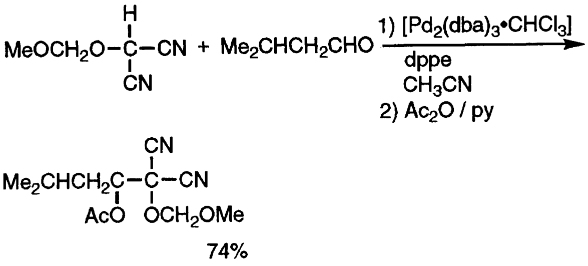
Transition metal-catalyzed aldol and Michael reactions are attractive methods for carbon–carbon bond formation, since these provide a novel strategy which can be used catalytically under neutral reaction conditions and can also be used for controlling stereoselectivity through chelation effects. Catalytic aldol and Michael reactions promoted by transition metal complexes have been reported; however, these are limited to the Lewis acid catalyzed reactions of silyl enolates,[43,44] and the reactions of active methylene compounds with basic metal salt catalysts.[45,46] Development of catalytic methods that proceed under neutral conditions is still waiting to be explored. In this respect, the present ruthenium-catalyzed reaction, which proceeds under neutral and mild reaction conditions, is highly efficient. Further, the present reactions show chemo- and stereoselectivities for carbon–carbon bond formation of nitriles which have never been observed with the conventional base catalyzed reactions. The key step of the catalytic reaction is the oxidative addition of low valent ruthenium into the *α*-C–H bond of nitriles.

2.1 Catalytic Reactions of Nitriles with Carbonyl Compounds. The reaction of nitriles with aldehydes in the presence of hydridoruthenium complex catalysts proceeds under neutral conditions to give the corresponding *α*,*β*-unsaturated nitriles, as shown in Eq. 9. The catalytic activity of low valent metal complexes has been examined with respect to the reaction of the less reactive benzyl cyanide with butanal. In the presence of 0.03 molar amount of catalyst in dry THF at room temperature under argon atmosphere, the conversions of the reaction of benzyl cyanide with butanal to give (*E*)-2-phenyl-2-hexenenitrile (**45**) were determined. $[RuH_2(PPh_3)_4]$ (**1**) is the best catalyst among the catalysts examined. Ethyleneruthenium complex, $[Ru(C_6H_4PPh_2)H(C_2H_4)(PPh_3)_2]$ (**46**), also gave satisfactory results. $[IrH_5(PPr^i{}_3)_2]$,[47] $[ReH_7(PPr^i{}_3)_2]$,[47] and $[ReH(N_2)(PMe_2Ph)_4]$,[48] and a combination of $[Pd_2(dba)_3{\cdot}CHCl_3]$[49] and dppe have been reported as effective catalysts for aldol reactions of nitriles; however, these complexes require a higher reaction temperature or activated substrates. $[RhH(CO)(PPh_3)_3]$ has proven to be a good catalyst for Michael addition of nitriles,[50,51] although no catalytic activity was observed for the present condensation reaction.

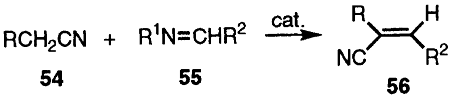
Representative results of the $[RuH_2(PPh_3)_4]$-catalyzed reaction of nitriles with carbonyl compounds are shown in Table 3. Various activated nitriles, such as alkyl cyanoacetates, malononitrile, and benzyl cyanides, undergo condensation with aldehydes and ketones under mild conditions to afford the corresponding (*E*)-α,β-unsaturated nitriles selectively. Selective formation of *E*-olefins is ascribed to the thermodynamic control of the dehydration reaction. Protic substituents such as hydroxy groups tolerate the reaction (Entry 3). Addition of a diphosphinoalkane ligand enhances the condensation remarkably. The conversion of the reaction of less reactive benzyl cyanide with butanal for 1 h was 51% at 60 °C; however, under the same reaction conditions, addition of a catalytic amount of a diphosphinoalkane such as bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,3-bis(diphenylphosphino)propane (dppp), raised the conversion to 96—98%, although addition of PPh_3 (68%), or triethyl phosphite (62%) promoted the reaction only moderately.

When it is required to isolate the alcohols derived from carbonyl compounds and nitriles before dehydration, $[Pd_2(dba)_3 \cdot CHCl_3]$ should be used as a catalyst and the alcohols formed are trapped upon treatment with acetic anhydride and pyridine (Scheme 17).[52)]

2.2 Catalytic Reactions of Nitriles to Imines. The present condensation can be applied to the reaction of nitriles with imines. The $[RuH_2(PPh_3)_4]$-[42)] and $[RhH(CO)(PPh_3)_3]$-[53)] catalyzed reaction of nitriles with imines gives the corresponding alkenes by addition and subsequent elimination of amines, as shown in Eq. 11. Typically, the $RuH_2(PPh_3)_4$-catalyzed reaction of ethyl cyanoacetate (**54**, R=CO_2Et) with *N*-benzylideneaniline (**55**, $R^1=R^2=Ph$) gave the corresponding alkene in 82% along with aniline. When electron-deficient imines were employed as a substrate, the elimination reaction is retarded and the addition products of the cyanides are obtained (Eq. 12). Typically, the $RhH(CO)(PPh_3)_3$-catalyzed reaction of nitrile (**57**, R=CO_2Me, Y=Me) with imine (**58**, $R^1=C_6H_4CO_2Me$, R^2=*p*-tolyl) gave the corresponding adduct (**59**) in 72% yield.[53)] Furthermore, aldol reaction of activated imines with carbonyl compounds such as malonate takes place in the presence of nickel catalyst $[NiCl_2(PPh_3)_2]$.[54)]

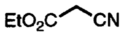
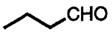
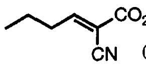
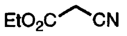
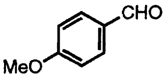
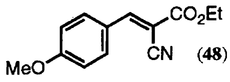
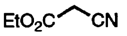
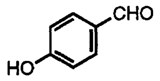
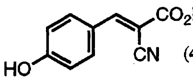
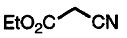
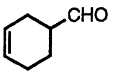
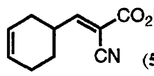
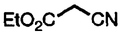
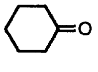
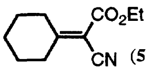
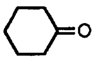
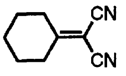
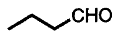
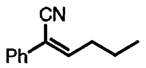


Scheme 17. Palladium-catalyzed addition of cyanide to aldehyde.

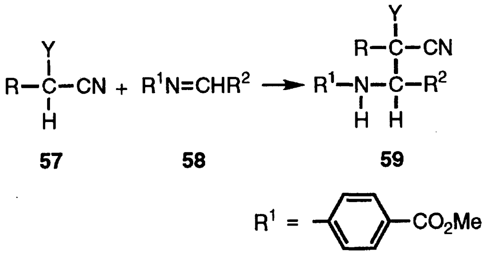


(11)

Table 3. Ruthenium-Catalyzed Aldol Condensation of Nitriles with Carbonyl Compounds[a)]

Entry	Nitrile	Carbonyl compound	Product	Yield[b)]/%
1			 (47)	83
2			 (48)	95
3			 (49)	98
4			 (50)	69
5			 (51)	69
6			 (52)	79
7	PhCH$_2$CN		 (53)	51[c)](98)[d)]

a) A mixture of nitrile, carbonyl compound (1.1 molar amount), and $[RuH_2(PPh_3)_4]$ (**1**) (0.03 molar amount) in dry THF was stirred at room temperature for 24 h under argon. b) Isolated yield based on the starting nitrile. c) 60 °C. d) Addition of 1,3-bis(diphenylphosphino)propane (dppp).

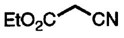
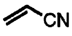
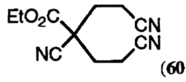
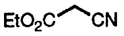
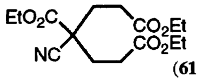
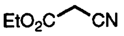
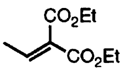
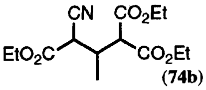
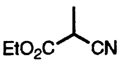
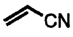
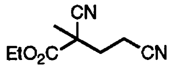
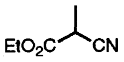
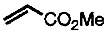
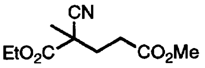
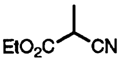
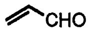
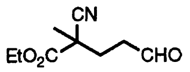
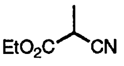
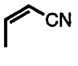
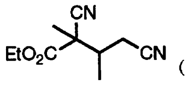
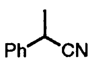
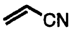
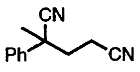
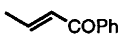
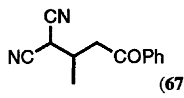


(12)

2.3 Catalytic Michael Addition of Nitriles to Olefins. The reaction of nitriles with olefins bearing electron-withdrawing groups proceeds highly efficiently to give the corresponding Michael adducts. The catalytic activity of various transition metal complexes has also been examined for the reaction of benzyl cyanide with crotononitriles (*E*/*Z*=61/39, 1.1 molar amount), in dry THF at room temperature under argon atmosphere. Low valent ruthenium hydride complexes, $[RuH_2(PPh_3)_4]$ (**1**), $[Ru(C_6H_4PPh_2)H(C_2H_4)(PPh_3)_2]$ (**46**), and rhodium hydride complex $[RhH(CO)(PPh_3)_3]$, have proven to be effective catalysts for the reaction;[42,50] however, other transition metal complexes such as $[RuH_2(CO)(PPh_3)_3]$ and $[IrH(CO)(PPh_3)_3]$ require a higher reaction temperature (60 °C) to complete the reaction. The remarkable effect of bidentate phosphine ligands was also observed. Addition of a catalytic amount of dppp gave the best results, while other bidentate phosphine ligands such as dppm, dppe, 1,4-bis(diphenylphosphino)butane (dppb) and 1,5-bis(diphenylphosphino)pentane also accelerate the reaction considerably.

Table 4 summarizes the representative results of the $[RuH_2(PPh_3)_4]$-catalyzed addition of nitriles to olefins. Various olefins bearing electron-withdrawing groups undergo addition of activated nitriles under neutral and mild conditions. Dialkylation of cyanoacetates proceeds efficiently upon treatment with 2—3 molar amounts of olefins (Entries 1 and 2). Importantly, the addition to α,β-unsaturated aldehydes proceeds chemoselectively without contamination by

Table 4. Ruthenium-Catalyzed Michael Addition of Nitriles with Olefins[a)]

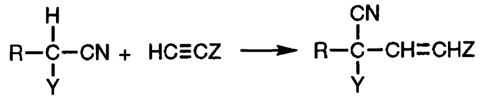
Entry	Nitrile	Olefin	Product	Yield[b)]/%
1			 (**60**)	85
2			 (**61**)	95
3			 (**74b**) diastereomer ratio=69/31	90
4			 (**62**)	71 (77)[c)]
5			 (**63**)	99 (85)[c)]
6			 (**64**)	72
7			 (**65**) diastereomer ratio=65:35	90
8[d)]			 (**66**)	50[c)]
9			 (**67**)	68

a) A mixture of nitrile, olefin (1.1 molar amount), and $[RuH_2(PPh_3)_4]$ (**1**) (0.03 molar amount) in dry THF was stirred at room temperature for 24 h under argon. b) Isolated yield based on the starting nitrile. c) $[Ru(C_6H_4PPh_2)H(C_2H_4)(PPh_3)_2]$ (**46**). d) 1,4-Bis(diphenylphosphino)butane (0.06 molar amount) was added.

the condensation product of the aldehyde (Entry 6), although such a contamination is often observed using conventional bases. The reaction is also catalyzed efficiently by ethylene-ruthenium complex **46** (Entries 4 and 5). The reaction of less reactive benzyl cyanides is enhanced by addition of a catalytic amount of dppb (Entry 8).

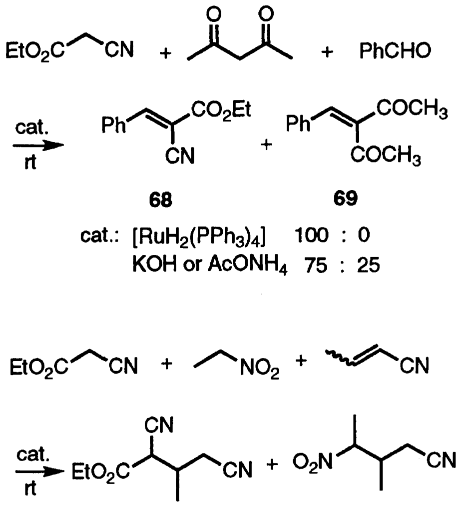
An important feature of the reaction is the chemoselective reaction of nitriles with either carbonyl compounds or Michael acceptors in the presence of other active methylene compounds, as shown in Scheme 18. Typically, the $RuH_2(PPh_3)_4$-catalyzed reaction of benzaldehyde with an equimolar mixture of ethyl cyanoacetate and 2,4-pentanedione, which has a similar pK_a value (pK_a=9.0), gave ethyl (*E*)-2-cyano-3-phenyl-2-propenoate (**68**) (80%) exclusively. In contrast, the same reaction in the presence of a catalytic amount of a conventional base such as $AcONH_4$ gave a mixture (75 : 25) of **68** and 3-benzylidene-2,4-pentanedione (**69**). Similar selectivity has been observed in other catalytic additions. Thus, the $[RuH_2(PPh_3)_4]$-catalyzed reaction of crotononitrile (*E*/*Z*=1/8) with an equimolar mixture of ethyl cyanoacetate and nitroethane (pK_a=8.6) gave ethyl 2,4-dicyano-3-methylbutanoate (**70**) chemoselectively, while similar treatment with Triton B (benzyltrimethylammonium hydroxide aqueous solution) catalyst afforded an 83 : 17 mixture of **70** and 3-methyl-4-nitropentanenitrile (**71**).

Importantly, addition of nitriles to acetylenic compounds proceeds with high chemoselectivity (Eq. 13). Generally, such an addition to acetylenic compounds is very difficult, because competitive 1,2-addition,[55] polycondensation,[56] and nucleophilic reactions of the acetylide anion[57] give complex products. Successful addition reactions reported are limited to a few cases which include additions of organocuprates[58] and $TiCl_4$-promoted addition of silyl enolates.[59] The $[RuH_2(PPh_3)_4]$-catalyzed reaction of ethyl cyanoacetate with ethyl propiolate at room temperature gives diethyl 4-cyano-4-methyl-2-pentenedioate (**72**) in 90% (*E*/*Z*=1/1) isolated yield. Similar treatment with 3-butyn-2-one gives ethyl 2-cyano-2-methyl-5-oxo-3-hexenoate (**73**) in 81% (*E*/*Z*=65/35) isolated yield. These reactions proceed cleanly without contamination by the coupling products, although it is well known that terminal acetylenic compounds undergo dimerization reaction[60] or codimerization with olefins[61] in the presence of ruthenium catalysts. This indicates that the activation of the α-C–H bond of nitriles proceeds much faster than that of acetylenic C–H bonds.



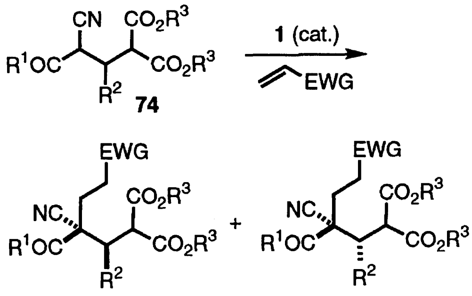
$$R-\underset{Y}{\overset{H}{C}}-CN + HC\equiv CZ \longrightarrow R-\underset{Y}{\overset{CN}{C}}-CH{=}CHZ$$

72: R = Me, Y = Z = CO_2Et
73: R = Me, Y = CO_2Et, Z = COMe (13)



Scheme 18. Competitive catalytic reactions of active methylene compounds.

2.4 Stereoselective Addition of Pronucleophiles to Alkenes. The efficiency of the present method is highlighted by high diastereoselectivity of addition arising from specific chelation control. Thus, the ruthenium-catalyzed addition of cyano ester **74** bearing malonate moiety proceeds with high diastereoselectivity, as depicted in Eq. 14. Many methods for diastereoselective Michael reactions have been reported using stoichiometric amounts of lithium enolates,[62] silyl enolates,[63] tin enolates,[64] and enamines.[65] However, catalytic Michael reactions reported are limited to a few reactions, which include $SbCl_2$–$Sn(OTf)_2$[66] and trityl salts catalyzed reactions.[67] In most of the reported methods, stereocontrol is observed only at the two reacting carbon centers. This method presents a rare example of diastereoselection control of the stereochemistry of α- and β-positions of the starting mixture of nitriles.



(3*R**, 4*S**)-**75** (3*S**, 4*S**)-**76**

74a : R^1 = OMe, R^2 = R^3 = Me
74b : R^1 = OEt, R^2 = Me, R^3 = Et
74c : R^1 = OEt, R^2 = Et, R^3 = Et
74d : R^1 = O-*t*-Bu, R^2 = Me, R^3 = Et
74e : R^1 = NH_2, R^2 = Me, R^3 = Et

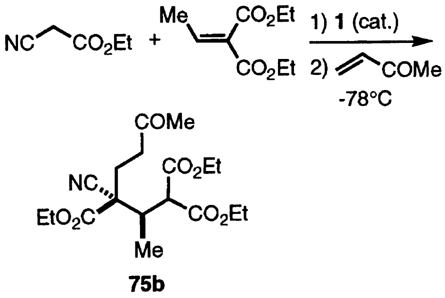
EWG = electron withdrawing group (14)

When a diastereomeric mixture of cyano ester **74a** (R^1= OMe, R^2, R^3=Me, diastereomer ratio=68/32), which can be readily obtained by the catalytic addition of dimethyl ethylidenemalonate to methyl cyanoacetate, was allowed to react with methyl vinyl ketone at −78 °C in the presence of catalyst **1**, a mixture of (3*R**,4*S**)-**75a** and (3*S**,4*S**)-**76a** was obtained in 77% yield in the diastereomer ratio of **75a**/**76a** of 96/4. The stereochemistry of **75a** was unequivocally established by X-ray crystal structure analysis. Similar treatment of cyano ester **74b** (R^1=OEt, R^2=Me, R^3=Et, diastereomer ratio=60/40) with either methyl vinyl ketone or acrylonitrile gave **75b** or **75c** selectively (**75b**/**76b**=97/3, 73%; **75c**/**76c**=90/10, 41%). In contrast, the reactions of **74b** in the presence of a base catalyst such as Triton B gave **75** nonselectively (**75b**/**76b**=75/25, 89%; **75c**/**76c**=44/56, 37%). Representative results of diastereoselective reactions of **74** are summarized in Table 5. The cyano esters derived from alkylidenemalonate diesters and activated nitriles undergo addition reactions to various electron deficient olefins with high diastereoselectivity. When the ethyleneruthenium complex **46** is used as a catalyst, similar high diastereoselectivity was obtained (Entry 5). The observed high diastereoselectivity is due to the malonate moiety of the nitrile substrates. Indeed, the $[RuH_2(PPh_3)_4]$-catalyzed reaction of diethyl 2-cyano-3-methylpentanedioate (diastereomer ratio=50/50) with methyl vinyl ketone at −78 °C gave a diastereomeric mixture (66/34) of the corresponding adducts in 60% yield, indicating that the chelation of malonate moiety of **74** plays an important role for the present diastereoselection, which we discuss later.

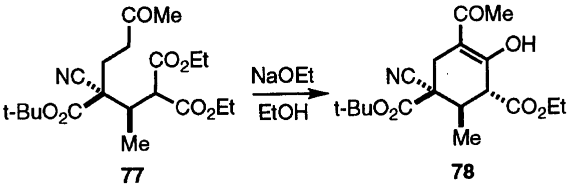
Tandem addition reactions of α-cyanocarboxylic acid derivatives can be performed conveniently (Scheme 19). Typically, the $[RuH_2(PPh_3)_4]$-catalyzed reaction of ethyl cyanoacetate with diethyl ethylidenemalonate and subsequent addition of methyl vinyl ketone at −78 °C gave **75b** in 75% isolated yield (**75b**/**76b**=97/3).

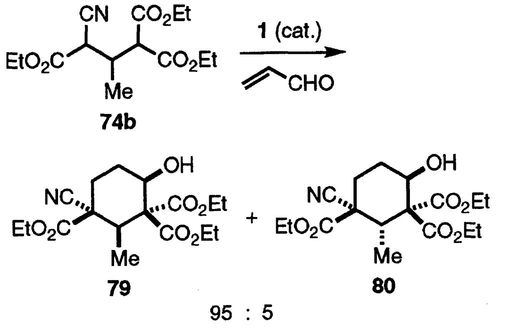
The adducts thus obtained undergo Claisen-type condensation, giving functionalized cyclohexene derivatives. Typically, the reaction of **77** with sodium ethoxide in ethanol at 0 °C gave cyclohexenol derivative **78** in 62% yield as the sole product.

When cyano ester **74** was allowed to react with acrylaldehyde, sequential Michael-aldol ring closure occurred to afford the corresponding cyclohexanol with high diastereoselectivity (Scheme 20). The ruthenium-catalyzed reaction of **74b** with acrylaldehyde gave triethyl (2*S**,3*S**,6*R**)-3-cyano-6-hydroxy-2-methylcyclohexane-1,1,3-tricarboxylate (**79**) selectively in 54% yield (**79**/**80**=95/5). The structures



Scheme 19. Diastereoselective ruthenium- catalyzed addition reaction.



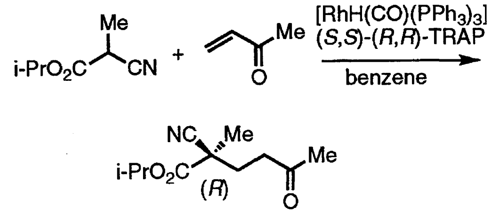


Scheme 20. Selective catalytic tandem addition-condensation.

Table 5. Diastereoselective Michael Reaction of Cyano Ester **74**[a]

Entry	Cyanoester **74**[b]				EWG	Product	Diastereomer
	R^1	R^2	R^3			(Yield[b]/%)	ratio of **75**/**76**
1	OMe	Me	Me	(**74a**)[c]	COMe	**75a**/**76a** (77)	96/4
2	OEt	Me	Et	(**74b**)[d]	COMe	**75b**/**76b** (73)	97/3
3	OEt	Me	Et	(**74b**)	CN	**75c**/**76c** (41)[g]	90/10
4	OEt	Me	Et	(**74b**)	COPh	**75d**/**76d** (77)	97/3
5	OEt	Me	Et	(**74b**)	COPh	**75d**/**76d** (62)[h]	96/4
6	OEt	Et	Et	(**74c**)[e]	COPh	**75e**/**76e** (87)	90/10
7	O-*t*-Bu	Me	Et	(**74d**)[f]	COMe	**75f**/**76f** (77)	98/2
8	NH_2	Me	Et	(**74e**)[d]	COPh	**75g**/**76g** (63)[g]	96/4

a) A mixture of cyanoester **74**, olefin (equimolar amount), and $[RuH_2(PPh_3)_4]$ (**1**) (0.03 molar amount) in dry THF was stirred at −78 °C for 6 h under argon. b) Isolated yield based on **74**. c) Diastereomer ratio=68/32. d) Diastereomer ratio=69/31. e) Diastereomer ratio=60/40. f) Diastereomer ratio=77/23. g) The reaction was carried out at room temperature. h) $[Ru(C_6H_4PPh_2)H(C_2H_4)(PPh_3)_2]$ (**46**) was used instead of **1**.

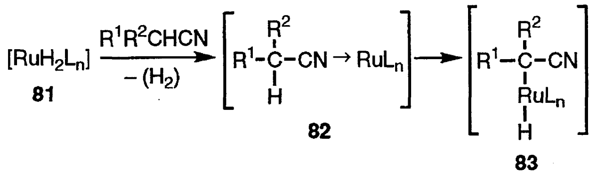


Scheme 21. Asymmetric catalytic addition reaction of pronucleophile.

of **79** and **80** were determined by difference NOE experiments. This result is in contrast to a similar reaction with Triton B catalyst, which gives **79** and **80** non-selectively (**79**/**80**=72/28, 49% yield).

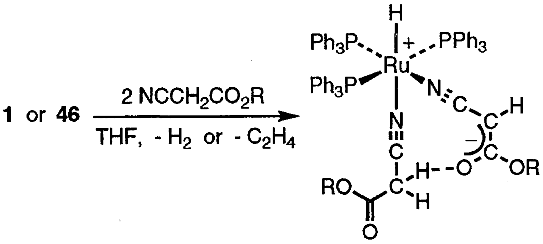
Using a similar concept, Ito and Sawamura recently developed a fascinating asymmetric Michael addition reaction of α-cyano carboxylates (86% ee) catalyzed by rhodium complexes having a large trans chelating ligand (*R*,*R*)-2,2″-bis[(*S*)-1-(diphenylphosphino)ethyl]-1,1′-biferrocene ((*S*,*S*)-(*R*,*R*)-TRAP) (Scheme 21).[51]

2.5 Oxidative Addition of Active Methylene Compounds to Ruthenium(0) Complexes. The present aldol and Michael reactions can be explained by assuming oxidative addition of α-sp^3 C–H bonds of nitriles to a low valent ruthenium complex (Eq. 15). Dihydridoruthenium complex [RuH$_2$L$_n$] **81** is converted into zerovalent ruthenium complex **82** by reductive elimination of molecular hydrogen and coordination of nitrile. The basicity of ruthenium and the acidity of the α-C–H bond of nitrile would increase, resulting in oxidative addition of the ruthenium(0) to the α-C–H bond of the coordinated nitrile to give complex **83**. In the case of the ethylene ruthenium complex **46**, dissociation of ethylene would occur to afford the same intermediate **83**. Ittel et al. observed the formation of [FeH(RCHCN)(dmpe)$_2$] from the reaction of nitriles with coordinatively unsaturated Fe(dmpe)$_2$ which is generated in situ from FeHNp(dmpe)$_2$ (dmpe=1,2-bis(dimethylphosphino)ethane, Np=2-naphthyl).[68]



(15)

Komiya et al. succeeded in the isolation of a formal oxidative addition product of alkyl cyanoacetate for the first time.[69] When [Ru(C$_6$H$_4$PPh$_2$)H(C$_2$H$_4$)(PPh$_3$)$_2$] (**46**) was allowed to react with alkyl cyanoacetates in THF at room temperature, yellow (enolato)hydridoruthenium(II) complexes of *mer*-[RuH(NCCHCO$_2$R)(NCCH$_2$CO$_2$R)(PPh$_3$)$_3$] (R=Me (**84a**), Et (**84b**)) were obtained with liberation of a quantitative amount of ethylene (Eq. 16). The ruthenium complex **46** is known to be in an equilibrium with Ru(0) species in spite of its orthometallated structure,[70] and various substrates undergo oxidative addition to the Ru(0) species.[71] Similarly, the reaction of [RuH$_2$(PPh$_3$)$_4$] (**1**) with alkyl cyanoacetates gave **84a** and **84b** with evolution of molecular hydrogen. The (enolato)hydridoruthenium(II) complexes **84**, which are relatively stable but undergo decomposition slowly in air, are characterized by IR and NMR spectroscopies, elemental analysis, and X-ray structure analysis.[42,69]



84a: R = Me
84b: R = Et (16)

The molecular structure of **84b** has been reported by Komiya as shown in Fig. 1. Essentially the same molecular geometry is observed for **84a**, which has been reported in a preliminary form.[69] In both cases, three phosphine ligands coordinate to ruthenium in meridional positions around the octahedron and the hydrido ligand is considered to occupy the site *cis* to the three P ligands. The ethyl cyanoacetate coordinates *trans* to the hydrido and the enolato ligand *cis* to the hydrido. An interesting feature in the structures of **84a** and **84b** is the coordination mode of the enolato ligand. The cyano group directly bonds to ruthenium; π electrons are considered to be delocalized along the C(2)–C(3)–O(1) linkage to increase the nucleophilicity of the enolato ligand (vide infra).

The catalytic activities of the isolated hydrido(enolato)ruthenium(II) complexes **84** were examined for aldol and

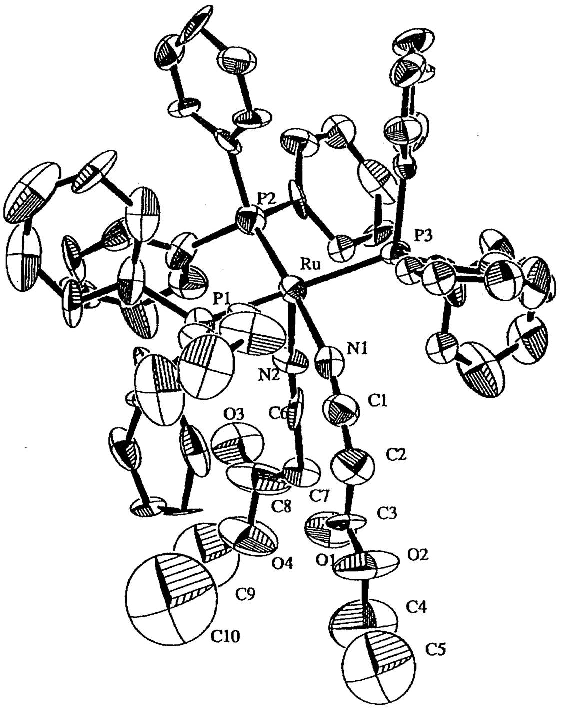
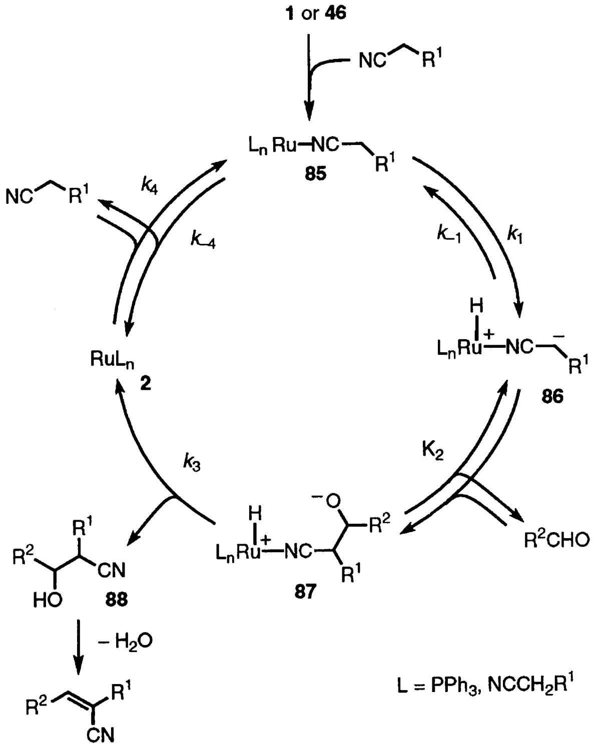


Fig. 1. Molecular structure of [RuH(NCCHCO$_2$Et)-(NCCH$_2$COOEt)(PPh$_3$)$_3$] (**84b**).[42]

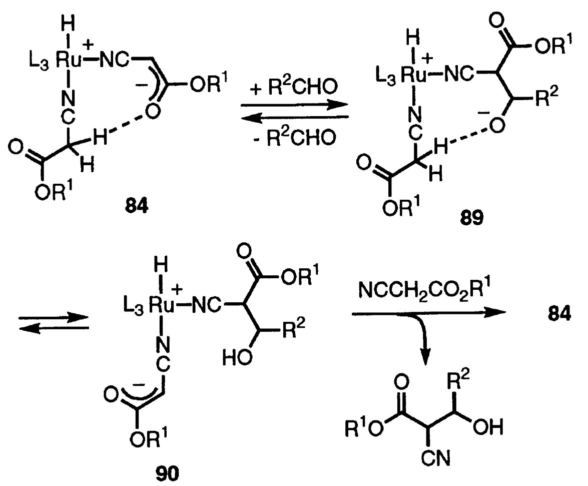
Michael reactions in comparison with **1** or **46**. In the case of aldol reactions of ethyl cyanoacetate with benzaldehyde, complexes **1**, **46**, and **84b** showed similar catalytic activity, and **68** was obtained in 50—70% yields. A similar trend was also observed in the catalytic Michael addition reaction to acrylonitrile. In the presence of **1**, **46**, and **84b** catalysts, a double Michael addition product **60** was obtained in excellent yield.

2.6 The Mechanistic Aspect of Aldol Type Reaction. The aldol reaction can be explained by assuming the mechanism shown in Scheme 22.[42] The catalytically active species seems to be the zerovalent ruthenium complex **85**, which is formed by coordination of nitrile to dihydridoruthenium complex **1** and subsequent reductive elimination of molecular hydrogen. When ethyleneruthenium complex **46** was used as a catalyst, dissociation of ethylene would occur upon coordination of nitrile to **46** to give **85**. Oxidative addition of ruthenium into the α-C–H bond of nitrile[68] affords hydrido (α-cyanoalkyl)ruthenium complex, which is converted into stable (enolato)hydridoruthenium complex **86**. Direct interaction of the enolato ligand with an aldehyde takes place to give (aldolato)hydridoruthenium(II) intermediate **87**, which undergoes elimination of aldol product **88** to give coordinatively unsaturated ruthenium complex **2**. Coordination of nitrile to **2** regenerates **85** to complete the catalytic cycle. Alternatively, complex **85** can be formed directly upon coordination of nitrile to **87** with dissociation of **88**. Dehydration of **88** may proceed under the reaction conditions.

The formation of **84** from the reaction of **1** or **46** suggests the alternative non-redox mechanism shown in Scheme 23.



Scheme 22. Catalytic cycle for the ruthenium-catalyzed aldol-type reaction.

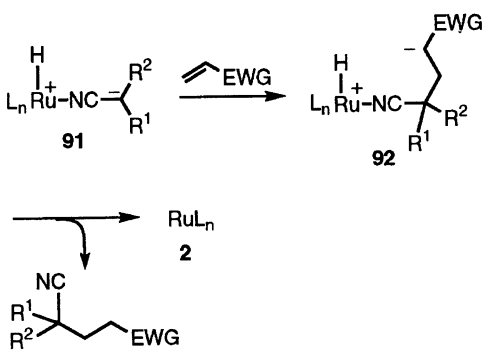


Scheme 23. Alternative mechanism for the addition to aldehydes.

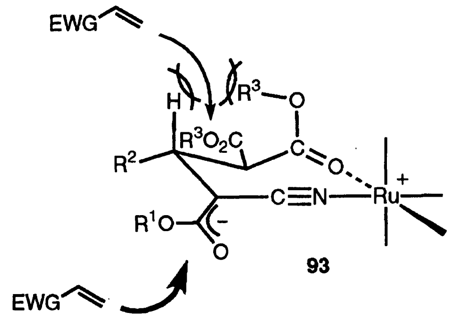
That is, the reaction of **84** with aldehyde gives (aldolato)-hydridoruthenium(II) **89**. Intramolecular hydrogen abstraction from the coordinated alkyl cyanoacetate gives enolato complex **90**. Dissociation of product followed by coordination of alkyl cyanoacetate regenerates **84** to complete the catalytic cycle.

Michael reaction of nitriles with olefins bearing electron withdrawing groups can be rationalized by the pathway shown in Scheme 24, which is similar to the mechanism of aldol reactions (Scheme 22). The addition of (enolato)-hydridoruthenium **91** to the olefin bearing an electron withdrawing group gives complex **92** which undergoes reductive elimination of Michael adducts and **2** to complete the catalytic cycle.

The highly diastereoselective Michael reaction of cyano ester **74** can be rationalized by assuming Scheme 25, where chelation of the malonate moiety to the ruthenium plays an important role. The reaction of **1** or **46** with a diastereomeric mixture of cyano ester **74** would give enolato complex **93**, in which the cyano group and one carbonyl group of the malonate moiety coordinate to the ruthenium and the other alkoxycarbonyl groups are located at pseudo-equatorial positions. Complex **93** is attacked by the olefin to afford **75** with high diastereoselectivity by avoiding congestion of the pseudo-axial R^3O group. It is natural that the Michael reaction of diethyl 2-cyano-3-methylpentanedioate proceeds



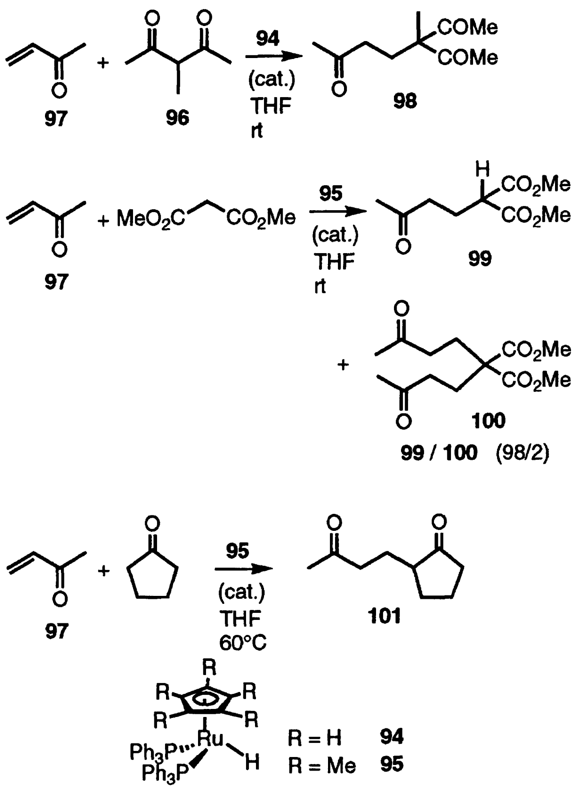
Scheme 24. Catalytic cycle for the ruthenium-catalyzed addition of nitriles.



Scheme 25. The reaction of alkenes with high diastereoselectivity.

non-selectively, since the absence of alkoxycarbonyl group results in relaxation of R^3O group from the strict pseudo-axial allowing the olefin to be easily attacked from either side.

2.7 Exploitation of the C–H Activation Induced by Heteroatom Effect. In order to activate the substrates which have weaker coordination ability towards transition metals in comparison with nitriles, we designed more basic ruthenium complexes and utilized them in the catalytic reactions. The (cp)hydridoruthenium complex **94** and the (cp*)hydridoruthenium complex **95** seem to be such more basic hydridoruthenium complexes (Scheme 26). The aldol-type reaction and addition of nitriles takes place readily using the (cp)ruthenium complex catalyst **94**, and the intermediate complex $[Ru(NCCHCO_2Me)(cp)(PPh_3)_2]$ has been isolated.[72] The (cp)hydridoruthenium complex **94** catalyzed addition reaction of 3-methyl-2,4-pentanedione (**96**) to methyl vinyl ketone (**97**) at room temperature in THF gave the adduct **98** in 79% yield, although the yield is only 12% when $[RuH_2(PPh_3)_4]$ (**1**) was used as a catalyst. Another synthetically interesting and important feature of the addition reaction is the selective formation of mono adducts of alkenes.[73] Thus, the (cp*)ruthenium-catalyzed addition of dimethyl malonate to **97** gave the mono adduct **99** highly selectively in the ratio of **99**/**100** : 98/2. Most importantly, the activation of simple carbonyl compounds can be performed readily, and addition products are obtained under neutral conditions. Thus, the reaction of cyclopentanone with methyl vinyl ketone in THF at 60 °C in the presence of 0.03 molar amount of (cp*)hydridoruthenium complex **95** gave 2-(3-oxobutyl)cyclopentanone (**101**) in 52% yield.[73]



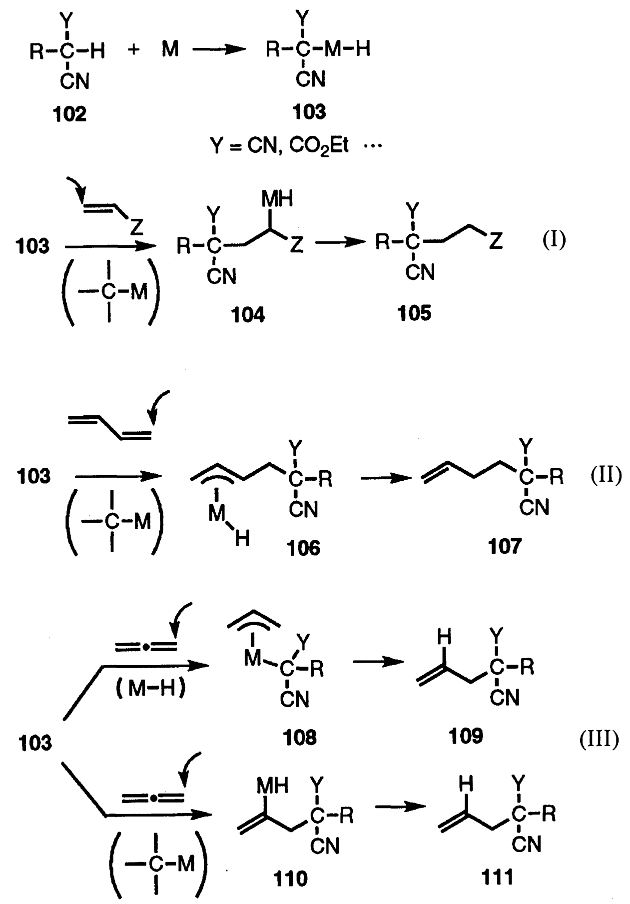
Scheme 26. Addition reaction of carbonyl compounds to methyl vinyl ketone (**97**) catalyzed by (cp)- and (cp*)-hydridoruthenium complexes **94**, **95**.

The addition of (α-cyanomethyl)hydridometal (**103**), derived from the oxidative addition of the cyanides (**102**) to metal (M), to the carbon–carbon double bond is dependent on the substrates, because the reaction occurs in an energetically downhill direction. One can consider three pathways for the reaction of **103**: One is the addition of **103**, which may correspond to metal–carbon species, to alkenes bearing an electron-withdrawing group in a similar manner to the Michael reaction to give **104**, and subsequent reductive elimination to give **105**, as shown in (I) of Scheme 27.[41,42] The second pathway is the addition to dienes. *Cis* addition of **103** would give stable π-allyl metal complex intermediate **106**, which undergoes reductive elimination to give **107** as shown in Eq. II. The driving force of the reaction is apparently the formation of stable π-allyl complex **106**, and the regioselectivity is simply due to steric effects.[74]

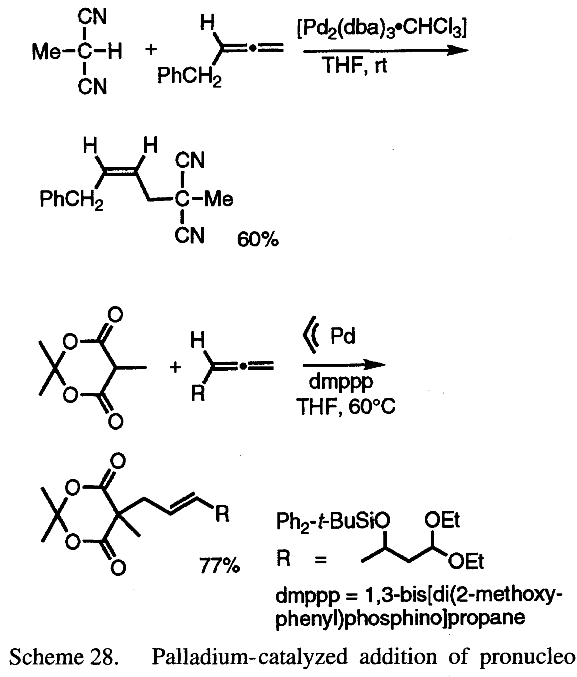
The case of the addition of **103** to allene is extremely interesting (Eq. III).[75—77] The formation of stable π-allylmetal complexes may be again the driving force of this reaction. The addition of **103** as a metal hydride[78] would give the rather stable π-allyl complex **108**, which undergoes reductive elimination to give **109**. In contrast, the addition of **103** as a carbon–metal species to allene would give the rather unstable vinylmetal species **110**, which undergoes reductive elimination to give the same product **111**.

The present reaction follows case (I). The addition of pronucleophiles to butadienes has been reported with palladium catalyst.[74] Recently Yamamoto,[75] Trost,[76] and Goré[77] reported that the addition to allenes gives the corresponding adducts according to the pathway (III) of Scheme 28.

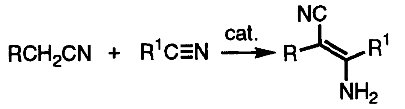
Finally, if our mechanisms are correct, the addition of α-metalated nitriles derived from the C–H activation to the activated nitriles by coordination with metal, followed by hydride transfer, would give the corresponding enamino nitriles, which are versatile intermediates for synthesis of various heterocyclic compounds as shown in Eq. 17. Typical examples of the iridium-catalyzed cross condensation of nitriles are shown in Scheme 29.[79]



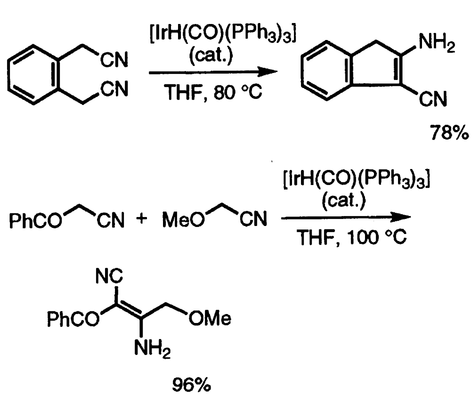
Scheme 27. The addition of the (α-cyanomethyl)-hydridometal **103** to alkenes with electron withdrawing group, dienes and allenes.



Scheme 28. Palladium-catalyzed addition of pronucleophiles to allenes.



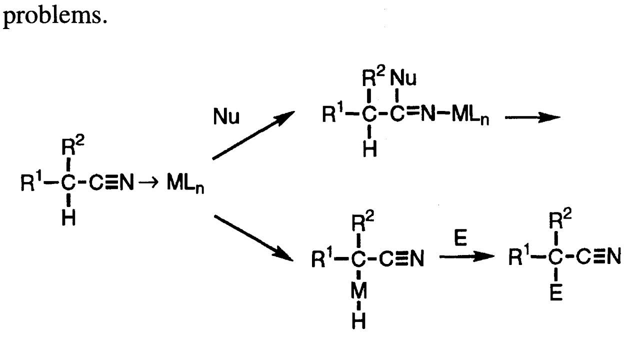
(17)



Scheme 29. Catalytic cross condensation of nitriles.

In conclusion, we have found the first catalytic aldol and Michael reactions initiated by C–H activation of the α-position of nitriles using low valent ruthenium complex catalysts such as **1** and **46**. These reactions provide a novel strategy for catalytic carbon–carbon bond formation of nitriles under mild and neutral conditions. The efficiency of the reaction has been demonstrated by the chemoselective aldol and Michael reactions of nitriles in the presence of other active methylene compounds, and novel diastereoselection in Michael, sequential Michael–Michael and sequential Michael-aldol reactions of cyano esters, all of which could never have been realized using conventional base catalysts.

In summary, hydridoruthenium complexes are effective redox Lewis acid and base catalysts for the activation of nitriles and other substrates bearing heteroatoms. Nitriles coordinated to metals can be trapped by either nucleophiles or electrophiles. Catalytic addition reactions of nucleophiles to the carbon–nitrogen triple bonds of nitriles take place generally,37) while in the presence of electrophiles, coordination to metals induces the C–H activation to form metal carbanions, which undergo subsequent reaction with electrophiles. These concepts will introduce a new chemistry for a variety of acid- and base-catalyzed reactions, which will be one approach in the future towards solving pollution problems.



Scheme 30. Catalytic reactions of nitriles with either nucleophiles or electrophiles.

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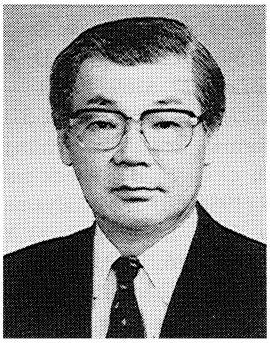

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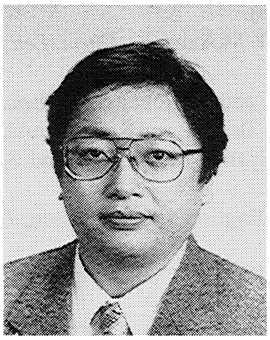

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