Iridium Hydride Complex Catalyzed Addition of Nitriles to Carbon−Nitrogen Triple Bonds of Nitriles

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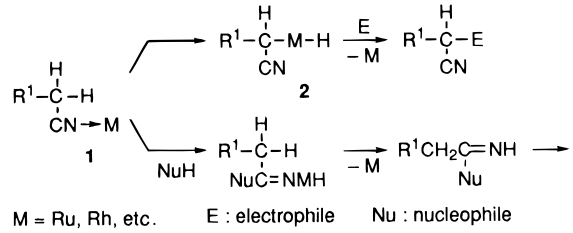
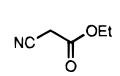
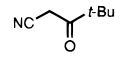
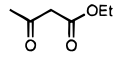
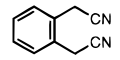
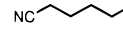
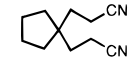
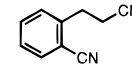
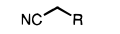
Addition of carbon nucleophiles to CN triple bonds of nitriles is one of the most attractive transformations of nitriles.[1] However, the reported methods are limited to strong base promoted intramolecular cyclization reactions of dinitriles (Thorpe−Ziegler reaction) because of the low reactivity of nitriles.[2] Development of a catalytic method which proceeds under neutral conditions has been waiting to be explored in view of both synthetic and environmental aspects. As a line of our study on the development of redox Lewis acids and bases for exploring environmentally friendly processes,[3] we have found that low-valent ruthenium and rhodium hydride complexes are effective catalysts for the activation of both α-C−H bonds[4] and the CN triple bond[5] of nitriles. Metal-coordinated nitriles **1** undergo either α-C−H activation to give α-metalated nitriles **2**, which react with electrophiles, or direct reaction with nucleophiles as shown in Scheme 1. These

Scheme 1



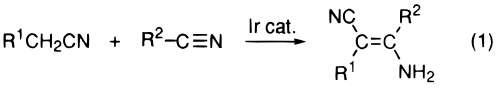
principles have led us to find a novel catalytic carbon−carbon bond formation of nitriles that proceeds by simultaneous activation of both α-C−H bonds and CN triple bonds of nitriles. Addition of nitriles to CN triple bonds of nitriles can be performed under neutral condition by iridium hydride complex catalysts to give cyanoenamines, which are versatile synthetic intermediates, although $RuH_2(PPh_3)_4$, which is the excellent catalyst for the reaction of nitriles with carbonyl compounds, is ineffective.

Table 1. Iridium Hydride Complex-Catalyzed Addition of Nitriles to CN Triple Bonds of Nitriles

entry	nucleophile	nitrile	catalyst	product	yield, %[d]
1			**3**[a]	**4**	>99
2			**3**[a]		R = Me 96 Ac 76
3			**3**[a]		85
4	 **5**		**3**[a]		76[e]
5			**10**[b]		61[f]
6			**10**[b]		82
7			**10**[b]		91
8			**10**[c]		R = H : **11a** 37 = Ph : **11b** 87

[a] A mixture of nucleophile (1.0 mmol), nitrile (2.0 mmol), and $IrH(CO)(PPh_3)_3$ (**3**) (3 mol %) in dry THF (0.25 mL) was stirred at 120 °C for 12 h under argon. [b] A mixture of dinitrile (1.0 mmol) and $IrH_5(P\text{-}i\text{-}Pr_3)_2$ (**10**) (3 mol %) in dry toluene (0.5 mL) was stirred at 140 °C for 12 h under argon. [c] A mixture of nitrile (3.0 mmol) and **10** (3 mol %) in dry toluene (0.5 mL) was stirred at 140 °C for 12 h under argon. [d] Isolated yield based on the starting nitrile. [e] Reaction temperature, 30 °C. [f] Catalyst, 10 mol %.

Herein, we wish to report the novel chemo- and stereoselective iridium-catalyzed addition of nitriles (eq 1).



Iridium hydride complex $IrH(CO)(PPh_3)_3$ (**3**) has proved to be an efficient catalyst for catalytic carbon−carbon bond formation of nitriles. The representative results of the present reaction are shown in Table 1. In the presence of **3** (3 mol %), activated nitriles undergo dimerization to give the corresponding cyanoenamines stereoselectively. Typically, the dimerization of ethyl cyanoacetate proceeds efficiently under neutral conditions to give (*Z*)-cyanoenamine **4** in excellent yield (entry 1). Selective formation of the *Z* enamine is due to the strong hydrogen bonding of the hydrogen of the enamine with the oxygen of the carbonyl moiety. The cyanoenamines thus obtained are useful precursors for synthesis of heterocyclic compounds. Typically, treatment of **4** with sulfuric acid gives 4-amino-3-ethoxycarbonyl-2,6-dioxo-1,2,5,6-tetrahydropyridine (96%), which is an important building block for antitumor alkaloids. Other low-valent iridium complexes such as $Ir(CO)_2(acac)$-PR_3 and $Ir_4(CO)_{12}$-PR_3 and rhodium hydride complexes such as $RhH(CO)(PPh_3)_3$ and $RhH(PPh_3)_4$ are also effective for the present carbon−carbon bond formation. The effectiveness of the present reaction is illustrated by cross-coupling reactions of nitriles. When cyanohydrin derivatives are used as acceptors,[2d] the cross-coupling reaction of activated nitriles proceeds highly efficiently (entry 2). Generally, cross-coupling

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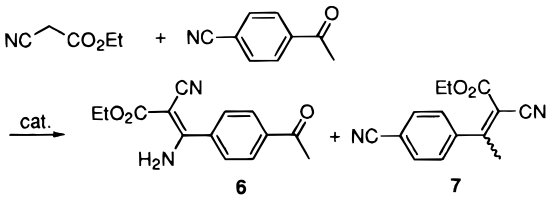
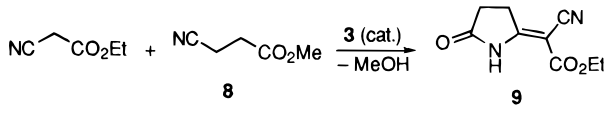
reactions of nitriles are known to be extremely difficult upon treatment with strong bases because of contamination of four possible products. The addition of 1,3-dicarbonyl compounds to nitriles also can be performed under similar conditions (entry 3). Intramolecular cyclization of *o*-xylylene dicyanide (**5**) gave the corresponding cyclic cyanoenamine (entry 4).

An important feature of the present reaction is the chemoselective addition of activated nitriles to CN triple bonds of nitriles in the presence of carbonyl groups. Due to the strong coordination ability of nitriles toward metals, selective addition of ethyl cyanoacetate to the CN triple bond of 4-acetylbenzonitrile occurred to give ethyl (*Z*)-3-(4-acetylphenyl)-3-amino-2-cyano-2-propenoate (**6**, 59%) chemoselectively. In contrast, the same reaction promoted by a conventional base catalyst such as $AcONH_4$ gave ethyl 2-cyano-3-(4-cyanophenyl)-2-butenoate (**7**) (E/Z = 55/45) exclusively.



Chemoselective addition of nitriles to the CN triple bonds of nitriles proceeds exclusively in the presence of other pronucleophiles. Indeed, the treatment of methoxyacetonitrile with an equimolar mixture of ethyl cyanoacetate (pK_a = 13 in DMSO)[6a] and 2,4-pentanedione (pK_a = 13 in DMSO)[6b] in the presence of catalyst **3** gave ethyl 3-amino-2-cyano-4-methoxy-2-butenoate in 96% yield along with 4% of 3-acetoxy-4-amino-5-methoxy-3-penten-2-one.

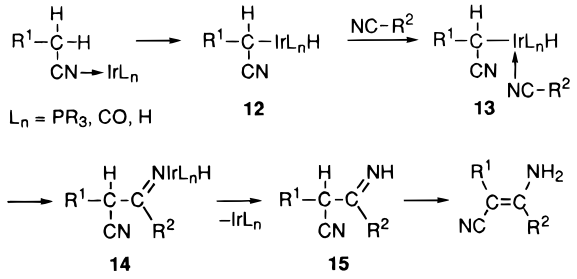
The reactions can be applied to the one-pot synthesis of various multifunctionalized lactams. Typically, when ethyl cyanoacetate was allowed to react with methyl 3-cyanopropionate (**8**) in the presence of catalyst **3**, addition to the CN triple bond of **8** and subsequent cyclocondensation took place to afford ethyl 2-cyano-2-(2-oxo-5-pyrrolidinylidene)acetate (**9**, 87%).



To activate simple alkanenitriles we need more basic iridium hydride catalysts. Indeed, iridium polyhydride catalysts, such as $IrH_5(P\text{-}i\text{-}Pr_3)_2$ (**10**), have proved to be efficient catalyst for the activation of nonactivated alkanedinitriles as shown in Table 1. In the presence of catalyst **10**, alkanedinitriles undergo intramolecular cyclization to give the corresponding cyclic cyanoenamines. Typically, intramolecular cyclization of 1,5-dicyanopentane gave the corresponding six-membered cyclic cyanoenamines under neutral conditions (entries 5 and 6). Bicyclic cyanoenamines were obtained in excellent yields from the corresponding aromatic dinitriles (entry 7). We have also found that the catalyst **10** is an efficient catalyst for activation of nonactivated simple alkanenitriles. Alkanenitriles undergo intermolecular addition−cyclization reaction to give the corresponding pyrimidines. For example, 4-aminopyrimidines **11a** and **11b** (entry 8) were obtained exclusively from the corresponding alkanenitriles.

The present reaction can be rationalized by assuming the mechanisms depicted in Scheme 2. The catalytically active

Scheme 2



species seems to be low-valent unsaturated iridium complexes IrL_n (L = PR_3, CO, H), which would be formed by either dissociation of phosphine ligand[7] from **3** or reductive elimination of molecular hydrogen[8] from **10**. Coordination of nitriles to the IrL_n followed by oxidative addition of the iridium into the α-C−H bonds of nitriles induced by the α-heteroatom effect of nitriles[4a−c] would occur to afford α-cyanoalkyl transition metal complex **12**. It has been reported that α-cyanoalkyl iron complexes $FeH(RCHCN)(dmpe)_2$ are formed upon treatment of nitriles with coordinatively unsaturated iron complex $Fe(dmpe)_2$.[9] Coordination of the second molecule of nitrile to **12** followed by insertion of the coordinated π-complexed nitrile[10] into the metal−carbon bond of **13** would give iridium hydride imino complex **14**. It is noteworthy that Bergman and Heathcock have reported that carbon-bonded rhenium enolate complex undergoes intramolecular addition to the coordinated nitrile to give rhenium imino complexes.[11] Reductive elimination of the imino complex **14** would afford product imine **15** to complete the catalytic cycle. The product imine **15** undergoes 1,3-hydrogen shift under the reaction conditions to give cyanoenamines. The trimerization of alkanenitriles to give pyrimidines **11a**,**b** would occur by subsequent addition of the imino intermediate **14** to the CN triple bond of the third molecule of nitrile under the reaction conditions.

The present iridium hydride complex-catalyzed carbon−carbon bond formation will provide wide scope of selective transformations of nitriles and even other substrates under neutral conditions. The key point of the present reaction is the simultaneous activation of both α-C−H bonds of nitriles as pronucleophiles and CN triple bonds of nitriles as electrophiles.

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Supporting Information Available: Detailed experimental procedures including analytical and spectroscopic data for all new compounds (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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