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Rhenium-Catalyzed Addition of Carbonyl Compounds to the Carbon−Nitrogen Triple Bonds of Nitriles: α-C−H Activation of Carbonyl Compounds

Hikaru Takaya,† Masatsugu Ito,† and Shun-Ichi Murahashi*,†,‡

Department of Chemistry, Graduate School of Engineering Science, Osaka University, Machikaneyama, 1-3, Toyonaka, Osaka, 560-8531, Japan, and Department of Chemistry, Okayama University of Science, Ridai-cho 1-1, Okayama 700-0005, Japan

Received May 12, 2009; E-mail: murahashi@high.ous.ac.jp

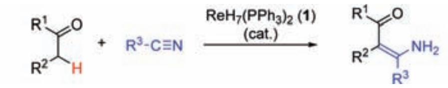
Addition of carbon nucleophiles to the carbon−nitrogen triple bond of nitriles is one of the important transformations of nitriles.[1] Such a transformation requires stoichiometric strong bases because of the low reactivity of nitriles, and the selectivity is low because of self-condensation of the starting substances. The reported methods are still limited to a few reactions, which include addition of organozinc compounds (Blaise reaction)[2] and addition of the magnesium enolate of *tert*-butyl acetate.[3] Therefore, catalytic and atom-economical methods for the selective reaction of carbonyl compounds with nitriles under neutral conditions are awaiting development.

It is known that sp^3 C−H activation induced by the α-heteroatom effect takes place.[4] Low-valent transition metal complexes of ruthenium and iridium are excellent catalysts for α-C−H activation of various substrates such as nitriles and isonitriles. The α-transition metalated intermediates undergo reaction with electrophiles to give the corresponding condensation or addition products catalytically and selectively under neutral conditions.[5,6] This principle led to finding the unique Ir-catalyzed addition of nitriles to the carbon−nitrogen triple bonds of nitriles,[7] which corresponds to a catalytic Thorpe−Ziegler reaction under neutral conditions.

Nitriles have a stronger coordination ability to metals in comparison with other substrates such as carbonyl compounds. Generally, α-C−H activation of carbonyl compounds with transition metal complexes does not take place in the presence of nitriles. For the purpose of organic synthesis, we must have a catalyst that can activate the α-C−H bond of carbonyl compounds in the presence of nitriles.

We found that rhenium hydride complexes have a unique property and are excellent catalysts for the α C−H activation of carbonyl compounds in the presence of nitriles. Herein we wish to report chemo- and stereoselective addition of carbonyl compounds to nitriles to give ketoenamines, which are useful intermediates for organic synthesis.[8] Using this principle, a highly useful greener Blaise reaction under neutral conditions can be constructed. There has been, to our knowledge, no example of the chemoselective C−H activation of carbonyl compounds in the presence of nitriles, although recent progress in Re-catalyzed reactions is striking.[9]

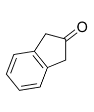
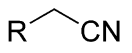
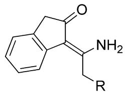
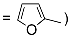
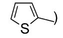
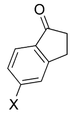
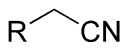
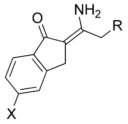
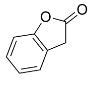
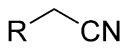
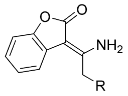
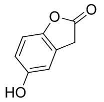
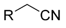
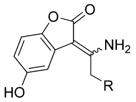
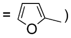
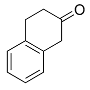
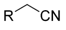
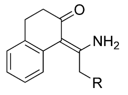
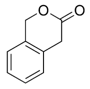
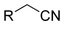
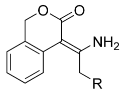
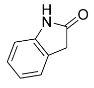
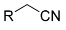
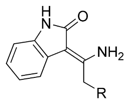
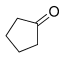
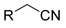
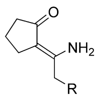
The rhenium heptahydride complex $ReH_7(PPh_3)_2$ (**1**) has proved to an excellent catalyst among those examined. In the presence of catalyst **1** (5 mol %), the reaction of carbonyl compounds with nitriles gave the corresponding (*Z*)-ketoenamines selectively without formation of the self-condensation products derived from carbonyl compounds or nitriles (eq 1).



(1)

Representative results of the present reaction are shown in Table 1. The reactions of 2-indanone with various nitriles gave the corresponding (*Z*)-ketoenamines **2a**−**2f** (Entry 1). The reaction of simple acetonitrile required a longer reaction time.

Table 1. Re-Catalyzed Reaction of Carbonyl Compounds with Nitriles

entry	carbonyl compound	nitrile	product	yield / %^{b}
1				2a : (R = H) 45 (91^c) 2b : (R = OMe) 97 2c : (R = OCOPh) 88 2d : (R = CO_2Et) 59 2e : (R = ) 96 2f : (R = ) 83
2				3a : (R = OMe X = H) 84 3b : (R = OMe X = F) 81 3c : (R = OMe X = Cl) 73
3				4a : (R = OMe) 92 4b : (R = SO_2Ph) 73
4				5a : (R = OMe) 94^d 5b : (R = ) 96
5				6 : (R = OMe) 76
6				7 : (R = OMe) 88
7				8 : (R = OMe) 76
8				9 : (R = OMe) 37

[a] A mixture of carbonyl compound (1.0 mmol), nitrile (2.0 mmol), and $ReH_7(PPh_3)_2$ (**1**) (0.05 mmol) in THF (0.5 mL) was reacted at 150 °C for 5 h under an argon atmosphere. [b] Isolated yield. [c] Reaction time 24 h. [d] *E*/*Z* = 13/87.

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† Osaka University.
‡ Okayama University of Science.

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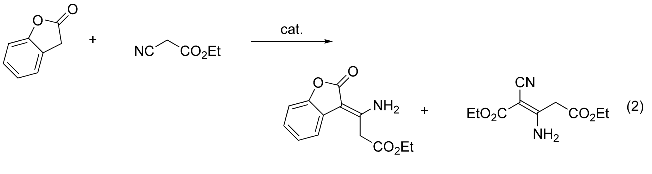
Selective formation of the *Z* isomer is due to the strong H-bonding between the amino proton and the oxygen atom of the carbonyl group. The reactions of substituted 1-indanones with methoxyacetonitrile gave the corresponding ketoenamines **3** (entry 2). Importantly, the C−H activation of ketones can be extended to esters. Thus, the reaction of 2-benzofuranone with methoxyacetonitrile or phenylsulfonylnitrile gave **4a** and **4b**, respectively (entry 3). Note that the reaction tolerates functional groups. Typically, the reaction of 4-hydroxybenzofran-2-one with methoxyacetonitrile and 2-franacarbonitrile gave the aminonitrile **5a** and **5b**, respectively, in excellent yields (entry 4). Under similar conditions, the direct addition of six-membered cyclic ketones and esters to nitriles also proceeded efficiently to give the corresponding enamines **6** and **7**, respectively (entries 5 and 6). The effectiveness of the reaction was demonstrated by the direct addition of less-reactive amides to nitriles. Thus, the reaction of indol-2-one with methoxyacetonitrile gave (*Z*)-3-(1′-amino-2′-methoxy)ethylindene indol-2-one (**8**) (entry 7). Moreover, the direct addition of cyclopentanone gave (*Z*)-2-(1′-amino-2′-methoxy)ethylindenecyclopentanone (**9**) (entry 8). The Re-catalyzed reaction of aliphatic ketones gave the corresponding enaminones, which are useful for synthesis of heterocyclic compounds. Typically, the Ru-catalyzed reaction of *N*-(2-cyanophenyl)-3-oxobutanamide gave 3-acetyl-4-amino-2-(1*H*)quinolinone.

The direct catalytic reaction of ketones with nitriles under neutral conditions has an advantage in view of atom economy over the conventional Blaise reaction. In the latter reaction carbonyl compounds have to be halogenated α to carbonyl, followed by a Zn-promoted Reformatsky reaction with the nitrile. This two-step process is not atom economical, and the products were obtained in low overall yields.

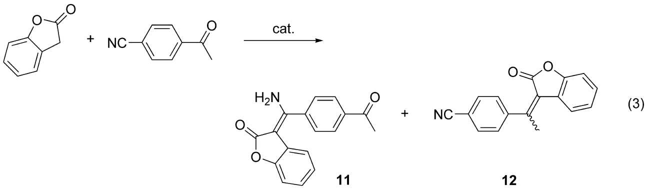
The unique property of the Re catalyst **1** for the C−H activation of carbonyl compounds in the presence of nitrile was proved by the reaction of 2-indanone with ethyl cyanoacetate (eq 2). In the presence of catalyst **1** the C−H activation of the ketone took place to give ethyl (*Z*)-2-amino-2-(2′-indanoylidene)propanoate (**2d**) (59%) exclusively, while in the presence of $IrH(CO)(PPh_3)_3$ catalyst the C−H activation of the nitrile took place to give diethyl (*Z*)-3-amino-2-cyano-2-pentanedione (**10**) (79%) exclusively.



2d **10**

cat. = $ReH_7(PPh_3)_2$ (**1**)	100 (59%) :	0
$IrH(CO)PPh_3)_3$	0	: 100

An important feature of the present reaction is chemoselective addition of esters to the carbon−nitrogen triple bonds of nitriles in the presence of a ketone group (eq 3). Thus, the Re-catalyzed addition of 2-benzofuranone to the carbon−nitrogen triple bonds of 4-acetylbenzonitrile occurred to give the corresponding (*Z*)-enaminoester **11** in 82% yield chemoselectively (**11**/**12** = 100/0). In contrast, the similar reactions of 2-benzofranone in the presence of a conventional base of $AcONH_4$ and Ru catalyst of $RuH_2(PPh_3)_4$ gave the normal Knoevenagel reaction product **12** in 66% and 61% yield, respectively (**11**/**12** = 0/100) (*E*/*Z* = 40/60). A similar reaction in the presence of the Ir catalyst $IrH_5(PPh_3)_2$ gave a mixture of **11** (35%) and **12** (38%).



11 **12**

cat. = $ReH_7(PPH_3)_2$ (**1**)	100	:	0
$RuH_2(PPh_3)_4$	0	:	100
NH_4OAc(1 equiv.)	0	:	100

An active Re catalyst may be a low-valent Re species $ReH_m(PPh_3)_2$ ($m < 7$) derived from losing hydrogen from $ReH_7(PPh_3)_2$.[10] It is known that $ReH_7(PPh_3)_2$ is converted to $Re_2H_8(PPh_3)_4$ under heating conditions.[10] However, we confirmed that $Re_2H_8(PPh_3)_4$ is not effective to the present catalytic reactions; i.e., **2a** was obtained in only 7% yield. It may be reasonable to assume that oxidative addition of the α-C−H bonds of carbonyl compounds to a low-valent Re species affords an α-keto alkylrhenium intermediate. Insertion of a nitrile to a Re−C bond of the intermediate followed by reductive elimination and 1,3-H shift may give the ketonenamine product. It is noted that addition of carbon-bound rhenium enolate to a carbon−nitrogen triple bond of a coordinated nitrile has been reported to form a rhenium imino complex in a stoichiometric reaction.[11]

In conclusion, we have found a novel and efficient Re-catalyzed reaction of carbonyl compounds with nitriles by chemoselective α-C−H activation of carbonyl compounds and subsequent insertion of nitriles. The reaction is highly useful and will provide scope for finding new types of catalytic reactions for the synthesis of fine chemicals.

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Supporting Information Available: Experimental details of the preparation and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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