Ambiphilic Lewis Acid and Base Catalyst

Transition-Metal-Based Lewis Acid and Base Ambiphilic Catalysts of Iridium Hydride Complexes: Multicomponent Synthesis of Glutarimides**

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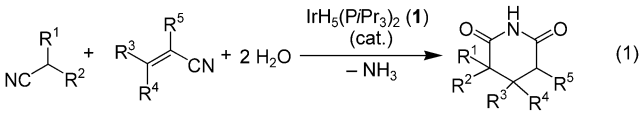
The majority of reactions promoted by Lewis acids or bases are stoichiometric. Catalysts based on transition metals instead of conventional Lewis acids and bases might be useful, because the neutralization of reagents would not be necessary, and salts would not form. We found that such transition-metal-based Lewis acid[1–4] and base[1,5] catalysts that have low redox potentials are environmentally benign and useful for organic synthesis. This concept can be extended to ambiphilic catalysts based on transition metals.[6] These catalysts make possible both acid- and base-promoted reactions in a single container without the mutual destruction of reagents by neutralization, and multicomponent catalytic reactions that may be useful for combinatorial chemistry can be constructed.

We report herein that the iridium polyhydride complex $[IrH_5(PiPr_3)_2]$ **1** is an excellent Lewis acid and base ambiphilic catalyst based on a transition metal, and that a novel three-component reaction of nitriles, olefins, and water occurs in the presence of catalyst **1** to gave glutarimides, which are highly versatile intermediates for synthesis of biologically active compounds [Eq. 1].[7] Iridium complex **1** is important as both



(1)

a redox base and Lewis acid catalyst.[8] The α-C–H activation of nitriles occurs to give a carbanion equivalent species for Michael addition,[5,9] and activation of the C≡N triple bond promotes hydration and amidation of nitriles.[4] In this way, the ambiphilic iridium complex **1** catalyzes the one-pot reaction of a mixture of nitriles, olefins, and water to give glutarimides efficiently.

Glutarimides have recently attracted attention as useful pharmaceuticals with pharmacological effects such as immunomodulatory, neuroplegic, and antitumor activity,[10] and hence methods for the ready synthesis of these compounds are needed. A variety of glutarimides can be prepared by the three-component reaction reported herein. Representative reactions are listed in Table 1. A range of substituents needed for pharmacological activity can be easily introduced into the 2- or 3-position of the glutarimide ring. The reaction of a mixture of α-aryl alkanenitrile, acrylonitrile **2**, and water (1:1:5) gave the corresponding 2-arylglutarimides in a yield of 92% or more (Table 1, entries 1 and 2). The conventional methods for the synthesis of these glutarimides, with Triton B and sulfuric acid used in that order, gave less than a 37% yield.[11] The glutarimide **3** thus obtained is an useful sedative Glutethimide and a precursor of Aminoglutethimide, an anticancer drug. The reaction of methyl 2-cyanopropanoate proceeds efficiently to give the corresponding 2-substituted glutarimide accompanied by removal of the ester group (Table 1, entry 3). The reaction of methyl 3-(4-chlorophenyl)-2-cyanopropanoate gave the corresponding glutarimide **4,** which may be a useful anticonvulsant (Table 1, entry 4).[12] The esterolytic reaction is useful for the synthesis of 3-substituted glutarimides. The treatment of methyl cyanoacetate **5** with β-substituted cyanoolefin in the presence of water gave the corresponding 3-substituted glutarimide **6** (Table 1, entry 5). α,β-Unsaturated esters also can be used as starting substrates. In fact, glutarimide **6** was also obtained from methyl crotonate. Similar three-component reactions of 1,3-dicarbonyl compounds can be carried out by α-C–H activation of the carbonyl group. In this way, 4-methyl-4,6,7,8-tetrahydro-1*H*,3*H*-quinoline-2,5-dione was obtained from 1,3-cyclohexanedione, crotononitrile, and water (Table 1, entry 7).[13]

The efficiency of such reactions is highlighted by the stereoselective synthesis of glutarimides. The reaction of a mixture of (benzenesulfonyl)acetonitrile **7**, cyanoolefin **8a**, and water gave **9a** ($R^1 = Me$) selectively in a 64% yield (**9a**:**10a** = 96:4) [Eq. 2].[14] It is noteworthy that a diastereomer **9b** ($R^1 = Ph$)[14] was obtained exclusively in 52% yield from the reaction of a mixture of **7**, **8b**, and water. The reaction of a mixture of **7** (*Z*)-2-phenyl-2-hexenenitrile, and

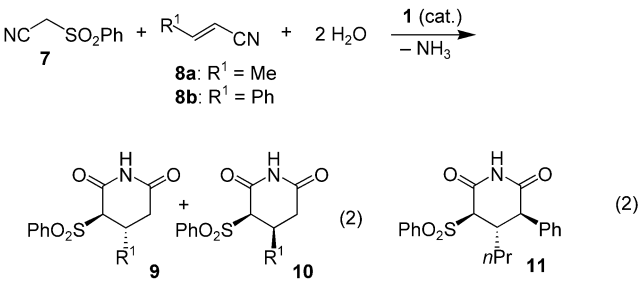


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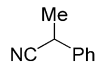
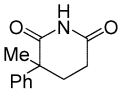
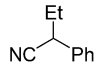
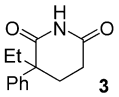
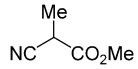
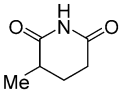
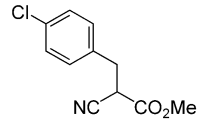
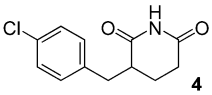
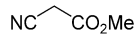
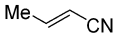
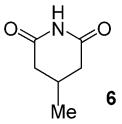
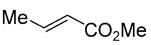
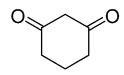
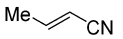
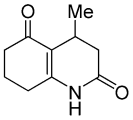
Table 1: Iridium-catalyzed three-component reaction.[a]

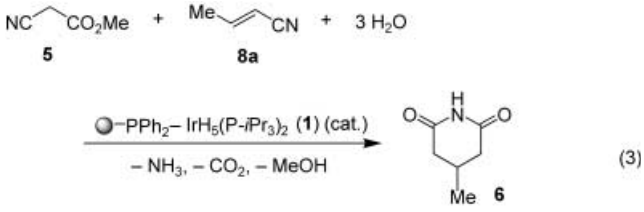
Entry	Pronucleophile	Olefin	Product	Yield[b] (%)
1		 **2**		94
2		**2**	 **3**	92[c]
3		**2**		98
4		**2**	 **4**	90
5	 **5**		 **6**	91
6	**5**		**6**	69
7				68

[a] A mixture of nitriles (1.0 mmol), olefins (1.1 mmol), H_2O (5.0 mmol), and $IrH_5(PiPr_3)_2$ (**1**) (0.10 mmol) in THF (0.25 mL) was stirred in a sealed glass tube at 150 °C for 20 h under an argon atmosphere. [b] Yield of isolated product based on starting pronucleophiles. [c] 2.0 mmol of **2** was added and the reaction was carried out at 180 °C for 30 h.

water gave only one diastereomer **11**[15] (yield 30%) among the four possible diastereomers.

This reaction might be explained in terms of the mechanism shown in Scheme 1. The catalytically active species seems to be the coordinatively unsaturated iridium species (L_nIr), formed by the dissociation of molecular hydrogen. The coordination of nitrile to L_nIr and α-C–H activation of nitriles would give the C-bound α-cyanocarbanion complex of iridium **12**. Isomerization of **12** to the corresponding N-bound cyanocarbanion complex **13**[5b,16] would occur, and the addition of **13** to olefin followed by isomerization would give cyanocarbanion intermediate **14**.[17,18] Isomerization of **14** to a ketenimino iridium intermediate[19] followed by the nucleophilic addition of water and proton transfer would give amide complex **15**.[13] The amide intermediate was detected at the earlier stage of the reaction; however, the Michael adduct could not be detected during the reaction. Iridium-promoted intramolecular addition of the amide moiety of **15** to the coordinated nitrile and subsequent hydrolysis[4,20] would afford glutarimide, ammonia, and (L_nIr) to complete the catalytic cycle. The stereoselective formation of glutarimides can be ascribed to the isomerization of **15** by α-C–H activations of the amide and nitrile.[21] In the three-component reaction, the iridium catalyst acts as a base to generate the carbon nucleophile by α-C–H activation and also acts as a Lewis acid to activate and hydrolyze the C≡N triple bonds of nitriles.

We have found that $RuH_2(PPh_3)_4$ is an efficient transition-metal-based-base catalyst and can be used for selective four-component condensation reactions in combinatorial chemistry.[22] Such reactions can lead to the combinatorial synthesis of glutarimides. A polymer-supported iridium catalyst would be an excellent catalyst for the one-pot, three-component synthesis of glutarimides. In the presence of polystyrene-supported **1** (10 mol%), the three-component reaction of **5**, **8a**, and water gave 3-methylglutarimide (**6**) in 69% yield [Eq. 3].



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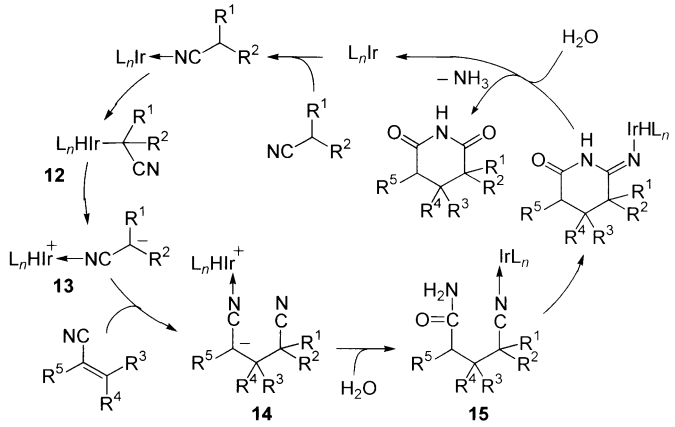

Scheme 1.

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Keywords: ambiphilic catalyst · C-H activation · glutarimide · iridium · multicomponent reactions

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[14] The stereochemistries of **9a** and **9b** were unequivocally determined by X-ray crystal structure analysis.

[15] The stereochemistry of **11** was determined by NOE and NOESY experiments.

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[19] Stable ketenimino iridium complexes have been isolated. The IR spectra of the complexes show $\tilde{\nu}$(CN) at 2140 cm^{-1} and their ^{13}C NMR chemical shifts shifted to extremely lower magnetic field (about 149 ppm), indicating high reactivity of the C≡N group of iridium complexes towards water.

[20] The iridium-catalyzed reaction of 4-cyano-4-phenylpentanamide and water gave 2-methyl-2-phenylglutarimide in 99% yield.

[21] The iridium-catalyzed Michael addition proceeds nonstereoselectively, but the iridium-catalyzed cyclocondensation of 3-methyl-2-(phenylsulfonyl)-pentanedinitrile proceeds with high diastereoselevtivity (**9a**:**10a** = 96:4).

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