# Conjugate Addition of Alcohols to Acrylic Compounds Catalyzed by a Bifunctional Ruthenium−Acetamido Complex

Chae S. Yi,* Sang Young Yun, and Zhengjie He

*Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53201-1881*

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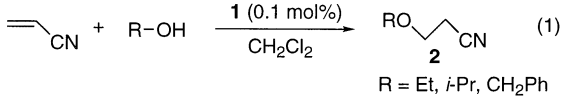
*Summary: The ruthenium−acetamido complex [(PCy$_3$)$_2$(CO)(CH$_3$CONH)(i-PrOH)RuH] (**1**) was found to be an effective catalyst for the conjugate addition of alcohols to acrylic compounds under mild reaction conditions to form β-alkoxynitrile compounds. The bifunctional activity of **1** from the Lewis acid ruthenium center for facilitating N-coordination of acrylonitrile and the basic amido ligand for mediating heterolytic alcohol O−H bond cleavage have been proposed for the catalytic reaction.*



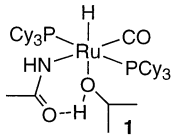
The conjugate addition reactions of heteroatom nucleophiles with α,β-unsaturated carbonyl compounds have been shown to be effective methods for forming biologically important β-amino acid derivatives and β-alkoxy ketones.[1] In comparison to the traditional methods based on stoichiometric reagents, transition-metal-catalyzed conjugate addition reactions are highly desirable for large-scale synthesis, for these can lead to selective product formation under environmentally benign conditions without formation of a copious amount of byproducts.[2−5] Since the pioneering examples of Murahashi's $(PPh_3)_4RuH_2$ and Ito's chiral Rh-TRAP catalysts,[2] a number of late-transition-metal catalysts have been found to be effective for the Michael addition and other conjugate addition reactions.[3] Recently, chiral Lewis acid−metal catalysts have been successfully developed for asymmetric conjugate addition of nitrogen nucleophiles to form β-amino acid derivatives.[4] By employing a high-throughput combinatorial screening method, Hartwig found that Pd catalysts with "pincer" ligands are effective for conjugate addition of amines to acrylic compounds.[5]

Late-metal−amido complexes have been implicated as key intermediates for a number of synthetically useful catalytic amination, hydrogenation, and hydration reactions.[6] We recently found that the well-defined ruthenium−acetamido complex [(PCy$_3$)$_2$(CO)(CH$_3$CONH)(*i*-PrOH)RuH] (**1**) is an effective catalyst for transfer hydrogenation of carbonyl compounds.[7] In an effort to extend the catalytic activity of ruthenium−amido complexes, we have begun to explore the activity of **1** toward polar bond activation reactions. Herein we wish to report that the amido complex **1** is a highly effective catalyst for the conjugate addition of alcohols to acrylic compounds under mild reaction conditions.

The treatment of acrylonitrile with an excess amount of EtOH in the presence of 0.1 mol % of **1** in $CH_2Cl_2$ led to clean formation of the addition product **2a** at room temperature (eq 1). Analytically pure product **2a** was




(1)




**1**

readily isolated in 96% yield after simple filtration through a silica plug and subsequent solvent evaporation. The analogous treatment with *i*-PrOH and $PhCH_2OH$ gave the products **2b**,**c**, respectively, under similar conditions. The initial activity survey showed that the amido complex **1** exhibited uniquely high catalytic activity among selected ruthenium complexes, even higher than for the strong base KO-*t*-Bu, under mild conditions without any other additives. The apparent low activity for both the acetate complex (PCy$_3$)$_2$(CO)(CH$_3$CO$_2$)RuH and the 18-electron dicarbonyl amido complex (PCy$_3$)$_2$(CO)$_2$(CH$_3$CONH)RuH suggests that the presence of both a basic amido group and an empty coordination site is important for promoting the catalyst activity.[8]

The scope of conjugate addition reaction was explored by using **1** as the catalyst (Table 1). In general, acryl-

(1) Recent reviews: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, U.K., 1992. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991. (c) Stowell, J. C. *Carbanions in Organic Synthesis*; Wiley: New York, 1987.

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(3) (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436−12451. (b) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553−8565. (c) Takaya, H.; Naota, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 4244−4245. (d) Hou, Z.; Koizumi, T.; Fujita, A.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 5812−5813.

(4) (a) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem. Int. Ed.* **1995**, *34*, 455−457. (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (c) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240−1241. (d) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616. (e) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030−9031.

(5) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960−1964.

(6) (a) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 2002; Vol. 1. (b) Kempe, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 468−493. (c) Holland, A. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 14684−14695.

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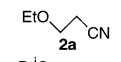
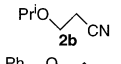
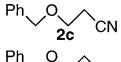
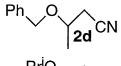
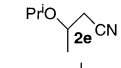
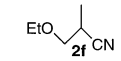
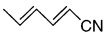
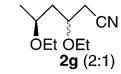
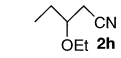
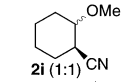
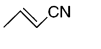
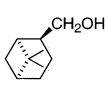
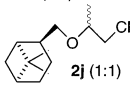
**Table 1. Conjugate Addition of Alcohols to Acrylic Compounds Catalyzed by 1**[a]

| entry | substrate | alcohol | product (s) | **1** (mol%) | t (h) | yd (%) |
|---|---|---|---|---|---|---|
| 1 |  | EtOH |  **2a** | 0.1 | 6 | 96 |
| 2 | | i-PrOH |  **2b** | 0.1 | 6 | 92 |
| 3 | | $PhCH_2OH$ |  **2c** | 0.1 | 6 | 94 |
| 4 |  | $PhCH_2OH$ |  **2d** | 1.0 | 20 | 93 |
| 5 |  | i-PrOH |  **2e** | 1.0 | 20 | 94 |
| 6 |  | EtOH |  **2f** | 1.0 | 20 | 87 |
| 7 |  | EtOH |  **2g** (2:1) | 5.0 | 24 | 63 |
| 8 |  | EtOH |  **2h** | 1.0 | 20 | 85 |
| 9 |  | MeOH |  **2i** (1:1) | 5.0 | 24 | 66[b] |
| 10 |  |  |  **2j** (1:1) | 5.0 | 24 | 60 |

[a] Reaction conditions: 2 mmol of acrylic compound; 2 mmol of alcohol; 2−5 mL of solvent; room temperature. [b] Reaction at 40 °C. Combined yield of cis and trans isomers.

onitrile compounds were found to be the most suitable substrates among acrylic acid derivatives. The fact that both crotonitrile and allyl nitrile gave the same product, **2d**, indicated that the olefin isomerization might have proceeded before the addition reaction for the allyl nitrile case (entries 4 and 5). Due to the sluggish reaction rate at room temperature, the reaction temperature was elevated to 40 °C for cyclohexenenitrile, in which case led to a ∼1:1 mixture of cis and trans products **2i** (entry 9). The reaction of crotonitrile with (−)-myrtanol also gave the addition product **2j** in a ∼1:1 mixture of diastereoisomers (entry 10).

The conjugate addition reaction of benzyl alcohol and acrylonitrile was used for probing the reaction mechanism. First, the reaction rate was found to be virtually independent of $[PCy_3]$ at room temperature. For example, the rate of reaction in the presence of 0.5 mol % of **1** was found to decrease only <5% upon adding 10 equiv of $PCy_3$. The observation of a lower rate in coordinating solvents such as $Et_2O$ and THF ($k_{obs} = 1.6 \times 10^{-4}$ and $9.6 \times 10^{-5}$ $s^{-1}$, respectively) compared to noncoordinating ones such as $CH_2Cl_2$ and benzene ($k_{obs} = 2.3 \times 10^{-4}$ and $6.5 \times 10^{-4}$ $s^{-1}$, respectively) suggested that ether solvents inhibit the reaction by competitively coordinating to the ruthenium center. Second, the reaction rate was found to be moderately accelerated by alcohols with an electron-withdrawing group. The correlation of the Hammett $\sigma_p$ value with the rates for a series of para-substituted benzyl alcohols *p*-X-$C_6H_4$-$CH_2OH$ (X = OMe, $CH_3$, H, Cl) led to the $\rho$ value of +0.18. Third, the significant carbon isotope effect was observed at the terminal carbon of acrylonitrile. For example, the most pronounced carbon isotope effect was observed at the $\beta$-carbon when the addition product $CH_3C^{(4)}H_2-O-C^{(3)}H_2C^{(2)}H(CH_3)C^{(1)}N$ (**2f**) at 10% conversion was analyzed by NMR following Singleton's carbon isotope measurement technique at natural abundance ($C^{(2)} = 1.007$, $C^{(3)} = 0.979$, and $C^{(4)} = 1.002$; average of three runs using $\alpha$-$CH_3$ as the internal standard).[9] Previously, we also observed a facile H/D exchange at the amido NH of **1** upon treatment with $(CD_3)_2CDOD$ at room temperature.[7]

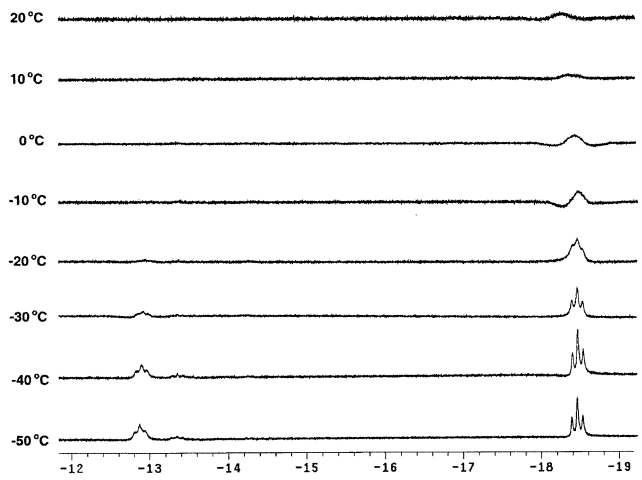



**Figure 1.** Metal−hydride region of $^1H$ VT NMR spectra of the reaction mixture of **1**, acrylonitrile, and benzyl alcohol in $CD_2Cl_2$.

In an effort to further gain insights on the nature of reactive species, we monitored the reaction mixture of **1**, benzyl alcohol, and acrylonitrile in 1:4:4 ratio at low temperature by NMR. Two Ru−H peaks at $\delta$ −18.4 (t, $J_{PH} = 14$ Hz) and −12.8 (pseudo t, $J_{PH} = 18$ Hz) in a 1.6:1 ratio were observed by $^1H$ NMR in $CD_2Cl_2$ at −50 °C, and both peaks exhibited characteristic fluxional behavior of the amido species (Figure 1). The hydride peak at $\delta$ −18.4 was due to the parent amido complex,[10] while the hydride peak at $\delta$ −12.8 was assigned to the nitrile-coordinated amido complex **3** by comparing the spectroscopic data with the similar acetonitrile complex.[11]

These results are consistent with the mechanism shown in Scheme 1. The apparent lack of rate inhibition

(8) The complex **1** gave the product in 94% yield after 1 h under the following reaction conditions: 2 mmol of acrylonitrile; 2 mmol of benzyl alcohol; 1.0 mol % of catalyst; 2 mL of $CH_2Cl_2$; 20 °C. Under the same reaction conditions, $(PCy_3)_2(CO)(CH_3CO_2)RuH$ (15%), $(PCy_3)_2$-$(CO)RuHCl$ (12%), $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ (13%), $PCy_3$ (13%), and $KOC(CH_3)_3$ (35%) showed considerable catalytic activity, while $(PCy_3)_2(CO)_2(CH_3CONH)RuH$, $(PPh_3)_3RuCl_2$, $(PPh_3)_3(CO)RuHCl$, and $RuCl_3 \cdot 3H_2O$ produced only a trace amount of products.

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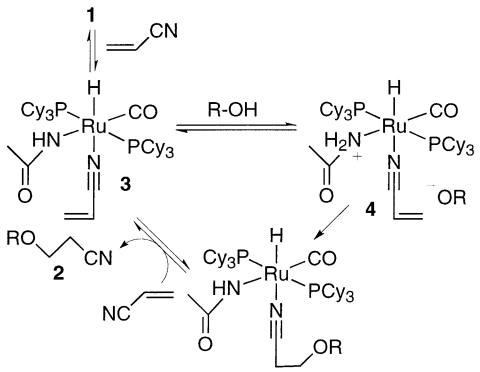
(10) The Ru−H peak of **1** appeared at $\delta$ −18.38 on $^1H$ NMR in $CD_2Cl_2$. See ref 7 for the complete spectroscopic data for **1**.

(11) Experimental procedure for the VT NMR study: the complex **1** (20 mg, 25 $\mu$mol) was dissolved in 0.3 mL of $CD_2Cl_2$ in a Wilmad J-Young NMR tube with screw cap. Excess benzyl alcohol (2.5 $\mu$L, 0.1 mmol) and acrylonitrile (6.5 $\mu$L, 0.1 mmol) were added via syringe, and the tube was occasionally shaken for 10 min. The sample tube was inserted into the NMR probe, and the probe was cooled to −50 °C by a cold stream of $N_2$. The sample was allowed to equilibrate for 10 min before each data acquisition (−50 to +20 °C, 10 °C intervals). Selected spectroscopic data for **3**: $^1H$ NMR (300 MHz, $CD_2Cl_2$, −50 °C) $\delta$ 4.75 (br s, NH), −12.8 (t, $J_{PH} = 13$ Hz, Ru−H); $^{31}P\{^1H\}$ NMR (121 MHz, $CD_2Cl_2$) $\delta$ 45.4 (s, $PCy_3$). The acetonitrile-coordinated amido complex was independently generated from the reaction of **1** with $CH_3CN$ by using an analogous procedure. Selected spectroscopic data for $(PCy_3)_2(CO)(CH_3CONH)(CH_3CN)RuH$: $^1H$ NMR (300 MHz, $CD_2Cl_2$, −60 °C) $\delta$ 4.64 (br s, NH), −13.26 (br s, Ru−H); $^{31}P\{^1H\}$ NMR (121 MHz, $CD_2Cl_2$, −60 °C) $\delta$ 44.37 (s, $PCy_3$).

**Scheme 1**




by added phosphine ligand and in situ observation of nitrile-coordinated complex **3** suggest that acrylonitrile is associatively coordinated to the amido complex **1**. Both the observation of a $\beta$-carbon isotope effect and the positive Hammett $\rho$ value are consistent with the rate-limiting nucleophilic addition of alkoxide via the zwitterionic species **4**. We propose that the Lewis acidic ruthenium center facilitates N-coordination of acrylonitrile, while the basic amido ligand mediates heterolytic O−H bond cleavage of the alcohol substrate. Both the observation of a lower rate in coordinating solvents and the diminished activity for the 18-electron dicarbonyl complex $(PCy_3)_2(CO)_2(CH_3CONH)RuH$ also suggest that the N-coordination of acrylonitrile promoted the nucleophilic addition of the alcohol substrate. Such N-coordination of nitriles has been commonly proposed for a number of different ruthenium-mediated reactions.[12] Noyori recently proposed that the similar bifunctional activity of a chiral ruthenium−amido complex was responsible for asymmetric transfer of proton and hydride to carbonyl compounds.[13] In summary, we found that the well-defined ruthenium amido complex **1** is an effective catalyst for the conjugate addition reaction of alcohols to acrylic nitriles. Efforts to develop an asymmetric version of the reaction by using chiral ruthenium catalysts are currently underway.

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(13) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (b) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285−288. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. (d) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478.