Intermolecular Coupling Reaction of Cyclic Amines and Alkenes Catalyzed by a Ruthenium-Hydride Complex $(PCy_3)_2(CO)RuHCl$

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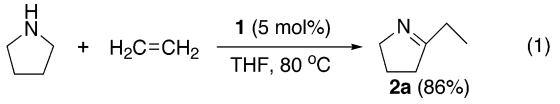
*Summary: The ruthenium-hydride complex $(PCy_3)_2(CO)$-RuHCl (**1**) was found to be an effective catalyst for the dehydrogenative coupling reaction of cyclic amines and alkenes. The reaction of secondary cyclic amines with unactivated alkenes preferentially gave the C−H bond insertion products in which both C−H and N−H bonds of amines have been selectively activated. In contrast, the reaction of amines with vinylsilane gave the N-silylation products. The catalytically active anionic ruthenium-amido complex was isolated from the reaction mixture, and its structure was established by X-ray crystallography. The preliminary mechanistic studies suggested that both C−H and N−H bond activation steps are mediated by a highly unsaturated ruthenium species.*

Transition metal-catalyzed C−H bond activation reactions have been shown to be effective methods for functionalization of unreactive hydrocarbons.[1−5] Since Murai's pioneering report on ruthenium-catalyzed regioselective arene-to-alkene coupling reactions,[2] a number of well-defined late transition metal catalysts have been shown to mediate selective C−H bond activation of hydrocarbons. The notable recent examples include direct C−H bond borylation of alkanes by Cp*Rh(arene) catalysts,[3] dehydrogenation of alkanes by Rh and Ir complexes with P−C−P "pincer" diphosphine ligands,[4] and Ru- and Pd-catalyzed oxidative coupling reactions of arenes and alkenes.[5] Recently, late metal complexes have also been found to catalyze regioselective coupling reactions of nitrogen heterocycles and alkenes[6,7] and sp^3 C−H bond insertion and dehydrogenation of tertiary amines and ethers.[8] Selective C−H bond activation of unprotected amines is especially desired in organic synthesis due to the prevalent occurrence of nitrogen compounds in natural products and pharmaceutical agents. In this article, we wish to report a new catalytic method for forming substituted cyclic imines from regioselective dehydrogenative coupling reaction of cyclic amines and alkenes by using a well-defined ruthenium-hydride complex, $(PCy_3)_2(CO)RuHCl$ (**1**).

We recently reported that complex **1** is an effective catalyst for both hydrovinylation and silylation reactions of alkenes and alkynes.[9] In an effort to extend its synthetic utility, we have begun to explore the catalytic activity of **1** for the coupling reactions of amines and alkenes. For example, the treatment of pyrrolidine (71 mg, 1.0 mmol) with ethylene (6.0 mmol) in the presence of 5 mol % of **1** in THF at 80 °C for 24 h gave the C−H bond insertion product **2a** in 86% yield (eq 1). The



(1)

organic product **2a** was isolated after trap-to-trap vacuum distillation, and its structure was completely established by spectroscopic methods. In particular, the diagnostic imine carbon resonance of **2a** was observed at δ 177.2 by ^{13}C NMR.[10] The initial survey of ruthenium catalysts showed that complex **1** was found to exhibit uniquely high activity among commonly avail-

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(10) See the Supporting Information for spectroscopic data of these complexes.

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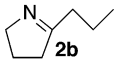
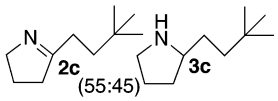
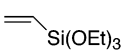
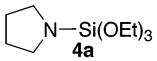
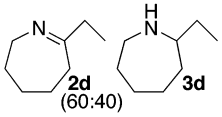
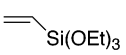
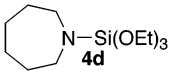
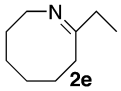
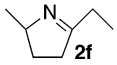
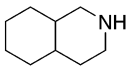
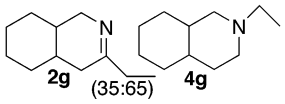
Table 1. Catalytic Coupling Reaction of Cyclic Amines and Alkenes by 1

entry	amine	alkene	product (s)	1 (mol %)	temp (°C)	t (h)	yield (%)[b]
1		$H_2C{=}CH_2$	 **2a**	5	80	24	86 (61)
2			 **2b**	10	120	24	51
3			 **2c** (55:45) **3c**	10	120	24	29
4			 **4a**	5	120	20	88 (82)
5		$H_2C{=}CH_2$	 **2d** (60:40) **3d**	15	80	24	87 (51)
6			 **4d**	5	120	20	88
7		$H_2C{=}CH_2$	 **2e**	3	70	16	76
8		$H_2C{=}CH_2$	 **2f**	10	80	20	84
9		$H_2C{=}CH_2$	 **2g** (35:65) **4g**	10	120	24	55

[a] Reaction conditions: amine (1.0 mmol); **1** (3−15 mol %); alkene (6−10 mmol); THF (2−5 mL); 16−24 h. [b] The product yields were determined by GC. The number in parentheses is the isolated yield from a 1.0 g scale reaction with >95% purity as determined by ^{1}H NMR.

able ruthenium complexes, such as $(PPh_3)_4RuH_2$, $(PPh_3)_3$-RuHCl, (*p*-cymene)$RuCl_2$, [Cp*$RuCl_2$]$_2$, [$(PCy_3)_2(CO)(CH_3$-CN)RuH]BF_4, and $RuCl_3{\cdot}3H_2O$.

The scope of the coupling reaction was explored to demonstrate the synthetic utility of the catalyst **1** (Table 1). In general, secondary cyclic amines with unactivated alkenes produced C−H bond activation products **2** preferentially. A mixture of imine and amine products **2** and **3** was formed for a sterically demanding 3,3-dimethyl-1-butene (entry 3) and with a seven-membered cyclic amine (entry 5). Further treatment of isolated product **3** under the catalytic reaction conditions did not give **2**. In contrast, the reaction with the vinylsilane $CH_2{=}CHSi(OEt)_3$ exclusively formed the *N*-silylation product **4** (entries 4, 6). Acyclic amines gave complex mixtures of dehydrogenation and disproportionation products, while no reaction was observed with piperidines. The organic products were isolated by both trap-to-trap distillation and/or preparatory GC methods and were satisfactorily characterized by standard spectroscopic methods.[10] Catalytic examples of forming cyclic imines are rare; recently, transition and lanthanide metal catalysts have been utilized to form cyclic imines from intramolecular hydroamination reactions of alkenyl- and alkynylamines.[11]

The following experiments were performed to gain mechanistic insights into the catalytic reaction. First, the reaction was found to be strongly inhibited by added phosphines. For example, addition of 10 mol % of PCy_3 (relative to the amine substrate) to the reaction mixture of pyrrolidine, ethylene, and 10 mol % of **1** under the conditions outlined in eq 1 led to <10% of the product **2a** after 24 h at 80 °C. The rate constants, $k_{obs} = 5.4 \times 10^{-2}$ h^{-1} without added PCy_3 and $k_{obs} = 8.8 \times 10^{-3}$ h^{-1} with 10 mol % PCy_3, were measured from the first-order plots of ln[amine] vs time (Supporting Information). Second, normal isotope effect of $k_{NH}/k_{ND} = 1.9 \pm 0.1$ (average of 3 runs at 80 °C) was observed from the reactions of C_4H_8N-H and C_4H_8N-D with ethylene. In contrast, no significant carbon isotope effect was observed on formation of **2d** and **3d** when the α-carbon of hexamethylenimine at 83% conversion was analyzed by ^{13}C NMR following Singleton's carbon isotope measurement technique (^{12}C/^{13}C at $C^{(1)} = 0.997$, $C^{(2)} = 0.997$, and $C^{(3)} = 1.000$ (internal standard); average of 3 runs).[12] Furthermore, the reaction of pyrrolidine with $CD_2{=}CD_2$ gave extensive deuterium incorporation at the α-methylene position of both **2a** and the unreacted pyrrolidine.

In an effort to establish the nature of reactive species, the reaction mixture of **1** (10 mg, 14 μmol), pyrrolidine (6 μL, 5 equiv), and ethylene (1.2 mmol) in THF-d_8 (0.5 mL) was monitored by NMR. After heating at 80 °C for 2 h, the formation of a new ruthenium-hydride peak at

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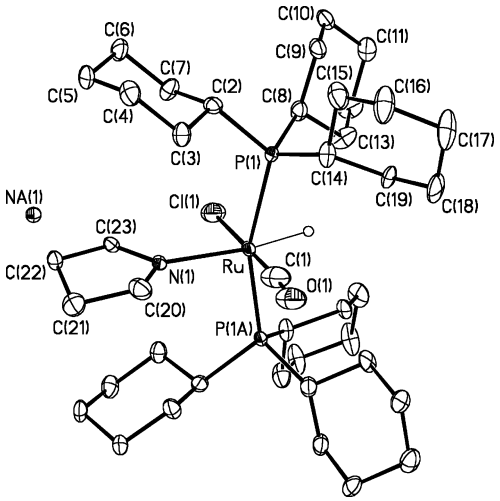
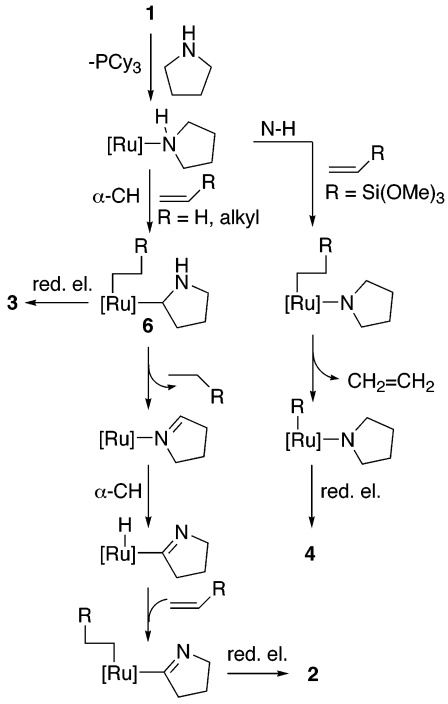


Figure 1. ORTEP diagram of **5** drawn with 50% probability ellipsoids.

δ −15.73 (t, J_{PH} = 20.1 Hz) was detected by ^{1}H NMR. The complex was subsequently isolated as a sodium salt in 75% yield from a preparatory-scale reaction of **1** with pyrrolidine, ethylene, and NaOH, and its structure was established as the anionic ruthenium-amido complex Na[$(PCy_3)_2(CO)(C_4H_8N)RuHCl$] (**5**) by X-ray crystallography (Figure 1). The molecular structure of **5** showed an octahedral ruthenium center with a trans geometry between the amido and the metal-hydride ligands. Even with relatively high uncertainty on bond distances and angles resulting from a disordered X-ray diffraction data, the ruthenium-amido nitrogen bond distance of **5** (Ru−N(1) = 2.26(7) Å) was significantly longer than a neutral Ru(II)-amido complex.[13] The isolated complex **5** was found to be an active catalyst for the coupling reactions of amines and alkenes.[14]

Much of the reaction mechanism is not clear at this point. A possible mechanistic path for the catalytic reaction is outlined in Scheme 1. The previous results on the formation of a ruthenium-ethyl complex from reaction **1** with ethylene along with the current phosphine inhibition study suggest that the reactive species is formed via a reversible dissociation of PCy_3.[15] In light of recent reports on well-defined 14 e$^-$ ruthenium complexes,[16] we suspect that a highly unsaturated ruthenium species is responsible for both N−H and C−H bond activation reactions, though the exact structure of this species is not yet established.[17] The elimination of NaCl and PCy_3 from **5** should form a similar ruthenium-amine/amide complex. The α-CH bond activation of the coordinated amine and subsequent alkene insertion would form the dialkyl species **6**. Similar α-CH

Scheme 1. A Possible Mechanism



bond activation of amines by Ru and Os complexes have been reported.[8b] The formation of imine product **2** can be rationalized by invoking the dehydrogenation of amine and subsequent α-CH imine bond activation/alkene insertion sequence. In support of this argument, the formation of ethane was detected by NMR in the reaction mixture of pyrrolidine and ethylene. To establish the involvement of cyclic imine species, the coupling reaction of independently prepared 1-pyrroline (C_4H_7N) and ethylene was examined. In this case, polymeric $[(CH_2)_3CH{=}N{-}]_n$ was produced predominantly with a trace amount of **2a**.[18] The extensive deuterium incorporation on the α-CH_2 of **2a** suggests that the C−H bond activation and alkene insertion steps are relatively facile and reversible, while the observation of a normal isotope effect of k_{NH}/k_{ND} = 1.9 is consistent with a rate-limiting N−H bond activation step. An alternate mechanism involving the formation of a ruthenium-amide complex from the N−H bond activation would also be consistent with the observed normal isotope effect and cannot be ruled out at this time.

The formation of C−H bond insertion product **3** was observed for the cases with sterically demanding 3,3-dimethyl-1-butene and seven-membered hexamethyleneimine, and this may have resulted from a competitive reductive elimination from **6** due to a slower rate of dehydrogenation of amine. In contrast, the N−H bond activation, alkene insertion, and ethylene elimination pathway is apparently favored for vinylsilanes to form the *N*-silylation product **4**. The formation of ethylene was observed by NMR in the coupling reaction of pyrrolidine with $CH_2{=}CHSi(OEt)_3$ and 5 mol % **1** in a sealed NMR tube.[19] These results indicate that both the steric and electronic nature of alkenes

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(14) Slower rate was observed for **5** ($k_{obs} = 1.9 \times 10^{-2}$ h^{-1}) compared to **1** ($k_{obs} = 3.6 \times 10^{-2}$ h^{-1}) when the reaction described in eq 1 in C_6D_6 was monitored by ^{1}H NMR. Also, the addition NaOH did not increase the rate; in fact, addition of an excess amount (>5 equiv to **1**) actually reduced the product yield substantially.
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(16) (a) Huang, D.; Huffman, J. C.; Bollinger, J. C.; Eisenstein, O.; Caulton, K. G. *J. Am. Chem. Soc.* **1997**, *119*, 7398. (b) Baratta, W.; Herdtweck, E.; Rigo, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1629. (c) Watson, L. A.; Ozerov, O. V.; Pink, M.; Caulton, K. G. *J. Am. Chem. Soc.* **2003**, *125*, 8426.
(17) A referee suggested comparing the activity of **1** with Caulton's $(PCy_3)_2(H_2)RuHCl$ as a way to infer the possible involvement of a 14 e$^-$ complex.[8b] Indeed, this complex was found to be an equally active catalyst under the reaction conditions described in eq 1 (84% **2a**).
(18) Zhang, J.; Gunnoe, T. B. *Organometallics* **2003**, *22*, 2291.
(19) Similar ethylene elimination has been commonly observed in metal-catalyzed silylation reactions. Marciniec, B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 1.

are important for the product selectivity. Clearly, further research is needed to establish the detailed mechanism.

In summary, the ruthenium-hydride complex **1** was found to be an effective catalyst for the intermolecular coupling reaction of cyclic amines and alkenes. The catalytic reaction achieved a regioselective sp^3 C−H bond activation of unprotected amines to give synthetically useful cyclic imines and α-substituted amines. Efforts to establish a detailed mechanism as well as the nature of reactive species for the catalytic reaction are currently underway.

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Supporting Information Available: Experimental procedure and crystallographic data of **5** (PDF). This material is available free of charge via the Internet at http//:pubs.acs.org.

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