Rhodium-Catalyzed Reaction of *N*-(2-Pyridinyl)piperazines with CO and Ethylene. A Novel Carbonylation at a C−H Bond in the Piperazine Ring

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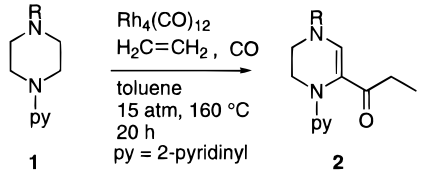
The reaction of *N*-(2-pyridinyl)piperazines with CO (15 atm) and ethylene in the presence of a catalytic amount of $Rh_4(CO)_{12}$ in toluene at 160 °C resulted in a novel carbonylation reaction, which involves dehydrogenation and carbonylation at a C−H bond. The carbonylation takes place regioselectively at a C−H bond α to the nitrogen atom substituted by a pyridine. The presence of an additional nitrogen functionality at the 4-position of the piperazine ring is also essential for the reaction to proceed. The electronic nature of subsituents, both on the 4-nitrogen and in the pyridine ring, affects significantly the reactivity of the substrates. The substitution of an electron-donating group on the 4-nitrogen causes an increase in reactivity, as does the substitution of an electron-withdrawing group in the pyridine ring. It is found that the reaction involves two discrete reactions: (i) dehydrogenation of the piperazine ring and (ii) carbonylation at a C−H bond in the resulting olefin. The reaction proceeds via two cleavages of the C−H bond, first at the sp^3 C−H bond and then at the sp^2 C−H bond. The reaction stops at the dehydrogenation step by replacement of the pyridinyl group with a phenyl group. Rhodium complexes are the only active catalysts for the present reaction.

Introduction

A variety of transition-metal-catalyzed reactions involving cleavage of a C−H bond adjacent to a nitrogen atom have recently been reported. Catalytic alkyl exchange reactions of primary and secondary amines, in the presence of Pd, were reported by Murahashi.[1] Later, Ni,[1c,2] Ru,[1c,3,4] and other transition-metal complexes[1c,4] were also found to be active for the catalytic alkyl exchange reactions. These reactions involve imine intermediates which are formed by dehydrogenation of the amines. The Ru-catalyzed oxidation of secondary and tertiary amines, resulting in the introduction of an oxy functional group at a carbon adjacent to the nitrogen atom, has been extensively studied, and these reactions are proposed to proceed via iminium salts or imines.[5] We wish to report a novel carbonylation at a C−H bond α to the nitrogen atom in a piperazine ring in a $Rh_4(CO)_{12}$-catalyzed reaction of *N*-(2-pyridinyl)piperazines with CO and ethylene (eq 1).



1 2 (1)

a:	R = Me	85%
b:	R = $PhCH_2$	44%
c:	R = Ph	0%
d:	R = 4-$MeOC_6H_4$	37%
e:	R = 2-$MeOC_6H_4$	25%
f:	R = Ac	0%

The overall process involves dehydrogenation and propionylation of piperazines. The pyridine ring has a dramatic effect on both reactivity and regioselectivity.[6] The carbonylation occurs regioselectively at a C−H bond α to the nitrogen atom substituted by a pyridine (N(py)). The presence of an additional nitrogen functionality at the 4-position is also essential for the reaction to proceed.

Results and Discussion

The reaction of 1-methyl-4-(2-pyridinyl)piperazine (**1a**; 1 mmol) with CO (initial pressure 15 atm at 25 °C

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) (a) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1973**, *95*, 3038. (b) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1973**, 307. (c) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.

(2) De Angelis, F.; Grgurina, I.; Nicoletti, R. *Synthesis* **1979**, 70.

(3) (a) Bui-The-Khai; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249. (b) Bui-The-Khai; Concilio, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759.

(4) Catalytic alkyl exchange reaction of tertiary amines was found to be catalyzed by $Ru_3(CO)_{12}$, $Os_3(CO)_{12}$, and $Ir_4(CO)_{12}$ in the presence of water: Shvo, Y.; Laine, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 753.

(5) For recent reviews on metal-catalyzed oxidations of amines and related reactions, see: Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443. Murahashi, S.-I.; Naota, T. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 12, pp 1177−1192.

(6) The utility of a pyridine ring as a directing group for C−H bond cleavage has been described. (a) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc., Chem. Commun.* **1994**, 2267. (b) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201. (c) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Chem. Commun.* **1996**, 585. (d) Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 939. (e) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425. (f) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604.

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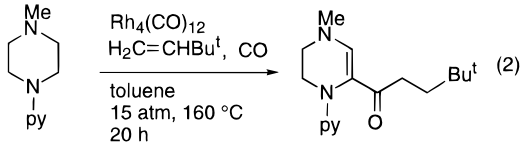
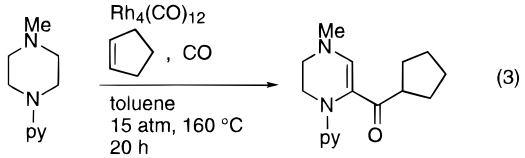
in a 50 mL stainless steel autoclave) and ethylene (initial pressure 10 atm at 25 °C) in toluene (3 mL) in the presence of $Rh_4(CO)_{12}$ (0.04 mmol) at 160 °C for 20 h gave 1-[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (**2a**)[7] in 85% isolated yield after column chromatography (eq 1). This transformation involves two discrete reactions: (i) dehydrogenation[8−11] and (ii) coupling between a C−H bond, CO, and ethylene[12] (vide infra). The catalytic activity of a number of complexes, such as $Co_2(CO)_8$, $Ru_3(CO)_{12}$, and $Ir_4(CO)_{12}$, was examined, and all proved to be totally inactive. While $Rh_6(CO)_{16}$ (72% yield), $[RhCl(CO)_2]_2$ (34%), and $[Rh(OAc)_2]_2$ (57%) showed catalytic activity, some rhodium complexes such as $RhCl(PPh_3)_3$, $[RhClCp^*]_2$, and $Rh(acac)(CO)_2$ were inactive. It was found that the presence of the 4-nitrogen (N−R in eq 1) is also essential for the reaction to proceed. The reaction of 1-(2-pyridinyl)piperidine, 4-(2-pyridinyl)morpholine, and 1-(2-pyridinyl)-4-piperidone failed to give the corresponding carbonylation products, and only starting materials were recovered.

We next examined the effect of substituents on the nitrogen at the 4-position on reactivity. The reaction of benzyl isomer **1b** gave **2b** in somewhat lower yield (44% yield). Although the reaction of the phenyl isomer **1c** did not give **2c**, the reaction of 1-(4-methoxyphenyl)-4-(2-pyridinyl)piperazine (**1d**) and the 1-(2-methoxyphenyl) isomer **1e** improved product yields. The acetyl compound **1f** failed to undergo carbonylation at all.

The scope of the reaction with respect to the olefin is limited. While the reaction of **1a** with CO and *tert*-butylethylene was incomplete within 20 h, the corresponding ketone **3** was formed in 33% yield, along with 60% of unreacted **1a** (eq 2). Use of hexene afforded the



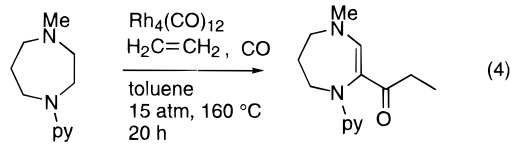
1a **3** 33% (2)



1a **4** 17% (3)

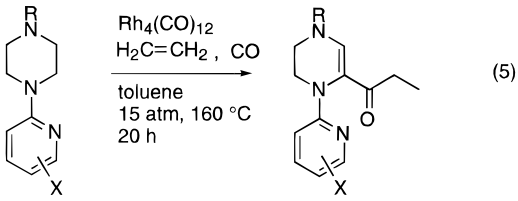
corresponding product in 3% yield, and 90% of **1a** was recovered (equation not shown). The reaction of **1a** with CO and cyclopentene gave the corresponding ketone **4** in 17% yield (eq 3). Olefins such as acrylonitrile, allyl acetate, styrene, trimethylvinylsilane, and allyltrimethylsilane were not effective.[13]

Since the presence of the 4-nitrogen functionality is essential, regioselective carbonylation would be expected for **5**. As expected, the reaction of **5** gave **6** as the sole product, in which carbonylation occurred regioselectively at a C−H bond in the $(CH_2)_2$ chain but not in the $(CH_2)_3$ chain (eq 4).



5 **6** 65% (4)

In order to understand some of the factors influencing reactivity,[14] we examined the reaction of piperazines having a substituted pyridine ring. It is noteworthy that the substitution of an electron-withdrawing group in the pyridine ring causes a significant increase in reactivity (eq 5). The reaction of piperazines bearing



7 **8** (5)

a:	R = Me, X = 5-COOMe	93%
b:	R = Me, X = 4-COOMe	83%
c:	R = Ph, X = 5-COOMe	16%
d:	R = 4-MeOC$_6$H$_4$, X = 5-COOMe	40%
e:	R = Me, X = 5-CF$_3$	95%

an ester group on the pyridine ring, such as **7a**, resulted in complete consumption of the starting material, and the corresponding product **8a** was obtained in 93% yield. On the other hand, 13% of **1a** was recovered, along with 85% of **2a** when the reaction of **1a** was carried out under the same reaction conditions. Although the 1-phenyl isomer **1c** is not reactive, as was shown in eq 1, the reaction of **7c**, having a methoxycarbonyl group on the pyridine ring, gave the corresponding product **8c** in 16% yield. A longer reaction time (40 h) gave **8c** in 23% yield. As stated above, an electron-donating group at

(7) The structure of **2a** was confirmed by X-ray analysis.

(8) For papers on transition-metal-catalyzed dehydrogenation of alkanes to alkenes under thermal conditions, see: Felkin, H.; Fillebeen-Khan, T.; Gault, Y.; Holmes-Smith, R.; Zakrzewski, J. *Tetrahedron Lett.* **1984**, *25*, 1279. Felkin, H.; Fillebeen-Khan, T.; Holmes-Smith, R.; Yingrui, L. *Tetrahedron Lett.* **1985**, *26*, 1999. Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025. Maguire, J. A.; Petrillo, A.; Goldman, A. S. *J. Am. Chem. Soc.* **1992**, *114*, 9492. Gupta, M.; Hagen, C.; Kaska, W. C.; Flesher, R.; Jensen, C. M. *J. Chem. Soc., Chem. Commun.* **1996**, 2083. Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840. Gupta, M.; Kaska, W. C.; Jensen, C. M. *J. Chem. Soc., Chem. Commun.* **1997**, 461. Leitner, W.; Six, C. *Chem. Ber.* **1997**, *130*, 555. For papers on transition-metal-catalyzed dehydrogenation of alkanes by irradiation, see: Nomura, K.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 161. Sakakura, T.; Sodeyama, T.; Tokunaga, M.; Tanaka, M. *Chem. Lett.* **1988**, 263. Maguire, J. A.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1989**, *111*, 7088. Tanaka, M.; Sakakura, T. *Pure Appl. Chem.* **1990**, *62*, 1147 and references cited therein.

(9) Nishiguchi[10] and Masters[11] reported the Rh-catalyzed transfer of hydrogen from 1,4-dioxane to alkene leading to dioxene and alkane.

(10) Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Am. Chem. Soc.* **1972**, *94*, 8916. Nishiguchi, T.; Fukuzumi, K. *J. Am. Chem. Soc.* **1974**, *96*, 1893.

(11) Masters, C.; Kiffen, A. A.; Visser, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 1357. 1,4-Dimethylpiperazine was also used as a hydrogen donor in place of dioxane, albeit with low efficiency.

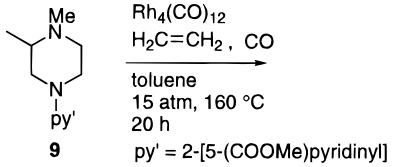
(12) Recently, $Ru_3(CO)_{12}$-catalyzed carbonylation at an sp^2 C−H bond was reported: Moore, E.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493. See also ref 6f.

(13) The inefficiency of these olefins has also been encountered in $Ru_3(CO)_{12}$-catalyzed carbonylation at a C−H bond in pyridinylbenzenes.[6f]

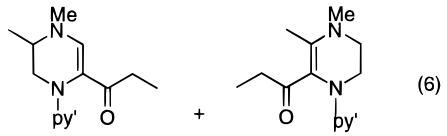
(14) Monitoring by GC shows that most of the reactions described are completed within 20 h. Longer reaction time (40 h) did not increase the product yield. The GC monitoring indicates that the time-course yields and the final yields reflect the rate of the reaction.

the 4-nitrogen has a dramatic effect on the reaction. The combination of an electron-donating group (4-CH_3O) at the 4-nitrogen and an electron-withdrawing group (5-COOMe) in the pyridine ring, as expected, further improved the product yield up to 40% as for the case of 6-[4-(4-methoxyphenyl)-1-piperazinyl]-3-pyridinecarboxylic acid methyl ester (**7d**), while the yield of reaction of **1d** was 37%, as was shown in eq 1.

The monomethyl-substituted piperazine **9** underwent carbonylation, and a 1.5:1 mixture of isomers **10** and **11** was obtained, indicating selective cleavage of the less hindered C−H bond (eq 6). Complete site-selective reaction took place to give **13** when the dimethyl-substituted piperazine **12** was used (eq 7).

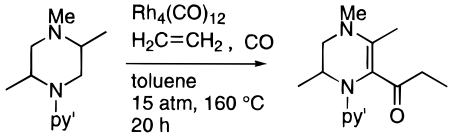


9 py' = 2-[5-(COOMe)pyridinyl]



(6)

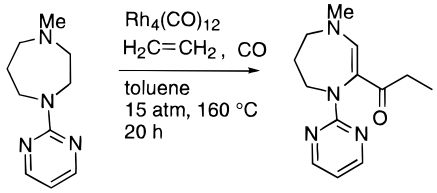
10 45% **11** 29%



(7)

12 **13** 52%

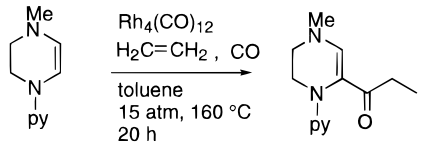
The pyridine ring is not the only directing group for the present reaction. The pyrimidine ring was found to be a more effective directing group than pyridine. The reaction of **14** with CO and ethylene gave **15** in 84% yield (eq 8), while the pyridinyl isomer **5** gave the corresponding ketone in 65% yield, as was shown in eq 4.



(8)

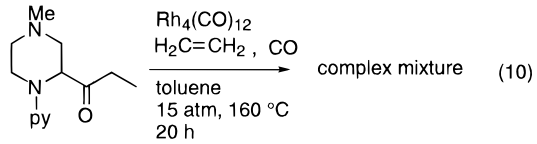
14 **15** 84%

The nature of the initial product in the reaction of **1** with CO and ethylene constitutes the most important issue in this overall reaction. The production of 4-methyl-1-(2-pyridinyl)-1,2,3,4-tetrahydropyrazine (**16**) and 1-[4-methyl-1-(2-pyridinyl)-2-piperazinyl]-1-propanone (**17**) as initial intermediates is most likely. Thus, it would be expected that the reaction proceeds (1) via an initial dehydrogenation[8−11] of **1a** to give **16**,[15] which is then carbonylated[16] to give the final product **2a**, or (2) via carbonylation at an sp^3 C−H bond[17] leading to **17**, followed by further dehydrogenation[18] to give **2a**. Monitoring the progress of the reaction of **1a** with CO and ethylene by GC failed to show the formation of any products, except **2a**. For a better understanding of the reaction mechanism, we prepared the putative primary products **16** and **17**, which were subjected to a carbonylation reaction. The reaction of **16** with CO and ethylene in the presence of $Rh_4(CO)_{12}$ (4 mol %) gave **2a** in 93% isolated yield (eq 9). $Ru_3(CO)_{12}$ was also



(9)

16 **2a** 93%

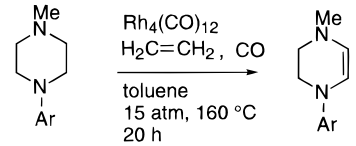


(10)

17

active for eq 9 (95% yield), although it was not active with respect to the saturated substrate **1a**. When **17** was reacted, a complex mixture, including a trace amount of **2a**, was obtained (eq 10). These results clearly show that the latter possibility can be excluded and the former (**1a** → **16** → **2a**) most reasonably explains the reaction pathway.

Further evidence that the reaction involves the initial formation of **16** was obtained by replacing the pyridine ring in **1** by an aryl group. Thus, the reaction of 1-methyl-4-phenylpiperazine (**18a**) with CO (15 atm) and ethylene (10 atm) at 160 °C resulted in dehydrogenation to give **19a** in 28% yield, along with 53% of unreacted **18a**, with no carbonylation product detectable (eq 11). The yield was again affected by an electron-



(11)

18 **19**

a: Ar = Ph 28%
b: Ar = 4-acetylphenyl 46%

withdrawing group on the benzene ring. Use of a 4-acetylphenyl group in place of the phenyl group increased the yield to **19** to 46%. It should be noted that the presence of a pyridine ring is not essential for dehydrogenation; however, it is essential for carbonylation at a C−H bond to take place.

Use of hexene in place of ethylene in the reaction of **18b** did not result in dehydrogenation leading to **19b**.

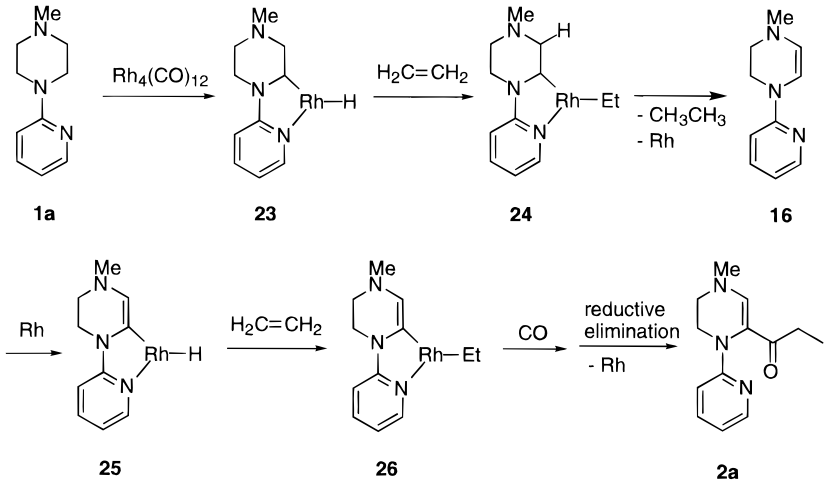
(15) A related ruthenium-catalyzed dehydrogenation was reported. The reaction of *N,N′*-dimethyl-2-imidazolidinone with ethylene (45 kg/cm^2) at 150 °C in the presence of $[C_6H_6RuCl_2]_2$ gave dehydrogenation products. Mitsudo, T.; Furukawa, T.; Ambe, M.; Fujita, K.; Yamamoto, J.; Kondo, T. 70th Annual Meeting of Japanese Chemical Society, Tokyo, 4J207, p 1311 (1996).

(16) We found that carbonylation at an sp^2 C−H bond took place smoothly in a variety of sp^2 C−H systems, such as pyridinyl benzenes,[6f] pyridinyl heteroaromatics,[6f] and pyridinyl olefins: Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. Unpublished data.

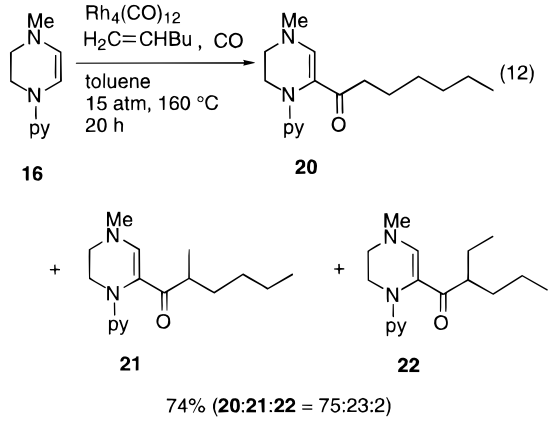
(17) For recent papers on carbonylation of sp^3 C−H bonds, see: Sakakura, T.; Sodeyama, T.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, *112*, 7221.

(18) For a paper on Pd(II)-induced dehydrogenation of β-amino ketones, see: Murahashi, S.-I.; Tsumiyama, T.; Mitsue, Y. *Chem. Lett.* **1984**, 1419. Murahashi, S.-I.; Mitsue, Y.; Tsumiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3285.

Scheme 1



When the reaction of **18b** was carried out in the absence of ethylene, no reaction took place and **18b** was recovered quantitatively. The reaction of a saturated isomer **1a** with CO and hexene resulted in almost no reaction, as has been described above. In contrast, the reaction of the unsaturated substrate **16** with CO and hexene gave the corresponding ketones efficiently (eq 12).



74% (**20**:**21**:**22** = 75:23:2)

These results show that the presence of ethylene is crucial for conversion of **1a** to **16** to take place and **16**, once generated, undergoes carbonylation irrespective of the nature of the olefin.

It was found that $Ru_3(CO)_{12}$ was also active for eq 12. The reaction of **16** with CO and hexene in the presence of $Ru_3(CO)_{12}$ gave the ketones in 69% yield (**20**:**21**:**22** = 58:30:12). However, the reaction of the saturated isomer **1a** in the presence of $Ru_3(CO)_{12}$ did not take place. These results clearly show that $Ru_3(CO)_{12}$ is not able to induce the dehydrogenation of **1a** to **16**, but it is active for carbonylation at a C−H bond.

Key steps for a plausible mechanism are shown in Scheme 1. The pyridine nitrogen coordinates to the metal center so that the metal and a C−H bond adjacent to the piperazine nitrogen are brought into proximity.[19] The C−H bond is cleaved to give the hydride−Rh complex **23**, which reacts with ethylene to afford the ethyl−Rh complex **24**. Following a β-hydride elimination, reductive elimination of the hydride as an ethane occurs to give an olefin, **16**, as the primary product. The olefin **16** again undergoes cleavage of a C−H bond to generate **25**. The successive insertion of ethylene and CO,[20] followed by reductive elimination, gives the final product **2a**.[21]

Although we have no direct evidence that ethane is formed, we propose that ethylene acts as a hydrogen acceptor to give ethane.[9] If H_2 were directly formed from **1a** without assistance of ethylene, along with formation of **16**, the reaction of **1a** with CO and hexene would give a carbonylation product because the reaction of **16** with CO and hexene gave the corresponding ketones, as shown in eq 12. This is not the case. The reaction of **1a** with CO and hexene gave only 3% of the carbonylation product, and 90% of **1a** was recovered. The results show that ethylene is a good hydrogen acceptor, while hexene is a poor acceptor.

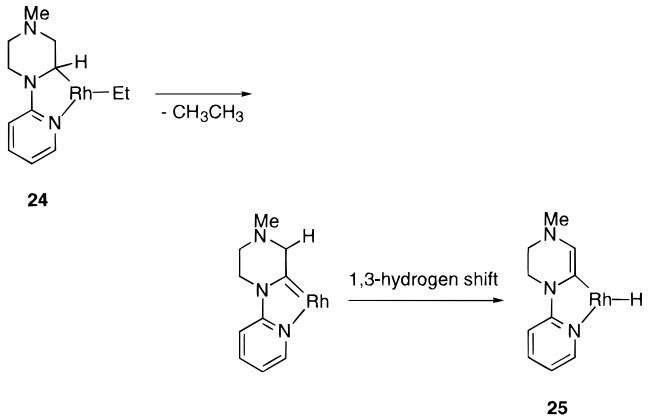
Conclusions

We report a novel carbonylation, which enables the conversion of a saturated fragment into an α,β-unsaturated ketone moiety. In this process, a nitrogen-directed cleavage of C−H bonds is utilized twice, first at the sp^3 C−H bond and then at the sp^2 C−H bond. Both types of cleavages may find further application in synthetic reactions. The electronic nature of the substituents,

(19) Although the presence of a pyridine ring is not essential for the dehydrogenation step (**1a** → **16**), it is clear that the pyridine ring is much more efficient for the dehydrogenation to take place than an aryl group.

(20) Insertion may take place either into the Et−Rh bond or, more likely, into the sp^2 C−Rh bond.

(21) Because **16** could not be detected by GC in the reaction mixture, an alternative path, which does not require the formation of olefin **16**, via α-hydride elimination from **24**, cannot be excluded.



both at the 4-nitrogen and in the pyridine ring, affects significantly the reactivity of the substrate. Although we have no rational explanation for the electronic effects, we propose, on the basis of presently available data, that dehydrogenation steps are much more significantly affected by electronic effects of the substituents than the carbonylation steps. Further detailed investigations of these effects are currently underway in our laboratory.

Experimental Section

Materials. 1-Methyl-4-(2-pyridinyl)piperazine (**1a**), 1-(phenylmethyl)-4-(2-pyridinyl)piperazine (**1b**), 1-phenyl-4-(2-pyridinyl)piperazine (**1c**), 1-(4-methoxyphenyl)-4-(2-pyridinyl)piperazine (**1d**), 1-(2-methoxyphenyl)-4-(2-pyridinyl)piperazine (**1e**), 1-acetyl-4-(2-pyridinyl)piperazine (**1f**), 6-(4-methyl-1-piperazinyl)-3-pyridinecarboxylic acid methyl ester (**7a**), 2-(4-methyl-1-piperazinyl)-4-pyridinecarboxylic acid methyl ester (**7b**), 6-(4-phenyl-1-piperazinyl)-3-pyridinecarboxylic acid methyl ester (**7c**), 6-[4-(4-methoxyphenyl)-1-piperazinyl]-3-pyridinecarboxylic acid methyl ester (**7d**), and 1-methyl-4-(5-(trifluoromethyl)-2-pyridinyl)piperazine (**7e**) were obtained from the corresponding pyridinyl halides and 1-substituted piperazines in the presence of Et_3N.[22] 1-Methyl-4-(2-pyridinyl)hexahydro-1*H*-1,4-diazepine (**5**) and 1-methyl-4-(2-pyrimidinyl)hexahydro-1*H*-1,4-diazepine (**14**) were prepared by the reaction of the corresponding halides and 1-methylhexahydro-1*H*-1,4-diazepine in the presence of Et_3N. 6-(3,4-Dimethyl-1-piperazinyl)-3-pyridinecarboxylic acid methyl ester (**9**), 6-(2,4,5-trimethyl-1-piperazinyl)-3-pyridinecarboxylic acid methyl ester (**12**), 1-methyl-4-phenylpiperazine (**18a**), and 1-[4-(4-methyl-1-piperazinyl)phenyl]-1-ethanone (**18b**) were synthesized from the corresponding 1-substituted piperazines by N-methylation according to the Leuckart−Wallach reaction.[23]

Preparation of 1-Methyl-4-(2-pyridinyl)-1,2,3,4-tetrahydropyrazine (16). A mixture of *N*-methyl-2,2-dimethoxyethanamine (25 g, 210 mmol), 2-(2-bromoethyl)-1*H*-isoindole-1,3(2*H*)-dione (25 g, 98 mmol), and Et_3N (15 mL) in toluene (60 mL) was stirred for 3 h at 90 °C. The reaction mixture was cooled, filtered, and concentrated in vacuo. Hydrazine hydrate (10 mL) and MeOH (200 mL) were added to the resultant mixture, and then the resulting mixture was heated for 10 h at 70 °C. The reaction mixture was cooled and poured into 500 mL of Et_2O. The solid was filtered, and the filtrate was concentrated in vacuo. Distillation of the remaining oil gave 7.9 g (50%) of *N*-(2,2-dimethoxyethyl)-*N*-methyl-1,2-ethanediamine, bp 66−69 °C (2 mmHg). A mixture of *N*-(2,2-dimethoxyethyl)-*N*-methyl-1,2-ethanediamine (7.9 g, 49 mmol), 2-bromopyridine (4.0 g, 25 mmol), copper powder (1.3 g, 20 mmol), and K_2CO_3 (5.6 g, 40 mmol) in toluene (50 mL) was refluxed for 20 h. After it was cooled, the reaction mixture was filtered and concentrated in vacuo. Distillation of the remaining oil afforded a crude product, bp 150−155 °C (2 mmHg). The crude product was further purified by column chromatography on silica gel with MeOH as eluant. Removal of solvent left *N*-(2,2-dimethoxyethyl)-*N*-methyl-*N*′-(2-pyridinyl)-1,2-ethanediamine (2.7 g, 45%) as a colorless oil.

N-(2,2-Dimethoxyethyl)-*N*-methyl-*N*′-(2-pyridinyl)-1,2-ethanediamine (2.7 g, 11 mmol) was heated in 3 N HCl (50 mL) for 2 h at 80 °C. After neutralization with 20% NaOH solution, the mixture was extracted with EtOAc and dried over $MgSO_4$. The solvent was removed in vacuo, and the remaining oil was distilled by bulb-to-bulb distillation (bp 125−130 °C, 2 mmHg) to give 1.26 g (65%) of 1-methyl-4-(2-pyridinyl)-1,2,3,4-tetrahydropyrazine (**16**) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.06 (t, J = 4.8 Hz, 2H), 3.90 (t, J = 4.8 Hz, 2H), 5.34 (d, J = 6.3 Hz, 1H), 6.16 (d, J = 6.3 Hz, 1H), 6.54−6.62 (c, 2H), 7.45 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 8.15 (dd, J = 4.6, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 41.55, 42.70, 49.65, 105.28, 105.97, 112.79, 120.23, 137.29, 147.83, 154.25; IR (neat) 3054, 2938, 2832, 1676, 1651, 1592, 1562, 1483, 1436, 1393, 1320, 1247, 1158, 1083, 1022, 980, 943, 852, 767 cm^{-1}; MS *m*/*z* (relative intensity) 176 (M^+ + 1, 12), 175 (M^+, 100), 160 (32), 133 (33), 119 (90), 118 (22), 105 (11), 94 (13), 92 (12), 88 (12), 82 (20), 81 (12), 80 (14), 79 (53), 78 (73). Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.32; H, 7.52; N, 24.06.

Preparation of 1-[4-Methyl-1-(2-pyridinyl)-2-piperazinyl]-1-propanone (17). A mixture of 1-[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (**2a**; 850 mg, 3.7 mmol) and PtO_2 (100 mg, 0.4 mmol) in EtOH (15 mL) was hydrogenated at 50 atm for 40 h at 50 °C. The catalyst was then filtered off and the solvent removed in vacuo. The product was isolated by preparative thin-layer chromatography on silica gel with MeOH as eluant to give 470 mg (55%) of 1-[4-methyl-1-(2-pyridinyl)-2-piperazinyl]-1-propanone (**17**): colorless oil, bp 160 °C (2 mmHg); R_f = 0.09 (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 2.20 (dt, J = 11.1, 4.0 Hz, 1H), 2.29 (s, 3H), 2.34−2.51 (complex, 3H), 2.74−2.83 (m, 1H), 3.23 (dt, J = 9.2, 2.3 Hz, 1H), 3.43 (dt, J = 11.9, 3.6 Hz, 1H), 3.67 (dt, J = 11.9, 3.3 Hz, 1H), 5.10 (t, J = 3.6 Hz, 1H), 6.61 (dd, J = 7.3, 5.0 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 7.49 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 8.10 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.53, 32.60, 43.07, 46.38, 54.63, 55.71, 61.40, 106.52, 113.46, 137.61, 147.42, 158.80, 210.13; IR (neat) 2938, 2872, 2850, 2798, 1721, 1595, 1563, 1480, 1439, 1377, 1347, 1313, 1292, 1265, 1234, 1212, 1173, 1149, 1113, 1068, 1043, 972, 932, 770 cm^{-1}; MS *m*/*z* (relative intensity) 233 (M^+, 3), 177 (12), 176 ($M^+ - C(O)CH_2CH_3$, 82), 161 (13), 145 (16), 139 (14), 133 (18), 120 (11), 119 (45), 107 (14), 98 (12), 95 (66), 83 (11), 82 (100), 79 (21), 78 (67); exact mass calcd for $C_{13}H_{19}N_3O$ 233.1528, found 233.1520.

General Procedures. In a 50 mL stainless autoclave were placed $Rh_4(CO)_{12}$ (30 mg, 0.04 mmol), 1-methyl-4-(2-pyridinyl)piperazine (**1a**; 1 mmol), and toluene (3 mL). The autoclave was charged with ethylene to 10 atm and carbon monoxide to 15 atm at 25 °C and then heated in an oil bath at 160 °C for 20 h. The autoclave was cooled and depressurized. The solvent was removed in vacuo, and the coupling product was isolated by column chromatography on silica gel with EtOAc/MeOH as eluant. Purification by bulb-to-bulb distillation or recrystallization afforded the analytically pure product.

1-[4-Methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (2a): yellow solid; mp 98−100 °C (hexane/EtOAc = 10/1); R_f = 0.17 (EtOAc/MeOH = 20/1); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 7.6 Hz, 3H), 2.44 (q, J = 7.6 Hz, 2H), 3.04 (s, 3H), 3.12 (t, J = 5.0 Hz, 2H), 3.85−4.15 (br s, 2H), 6.41 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 7.3, 5.0 Hz, 1H), 7.36 (s, 1H), 7.40 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 8.18 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.44, 29.45, 40.74, 42.73, 47.50, 111.54, 114.12, 114.56, 136.91, 138.81, 147.35, 158.04, 194.75; IR (neat) 2936, 2876, 1637, 1589, 1478, 1432, 1399, 1324, 1288, 1237, 1169, 1097, 1063, 1014, 979, 953, 854, 809, 771 cm^{-1}; MS *m*/*z* (relative intensity) 231 (M^+, 47), 203 (14), 202 ($M^+ - CH_2CH_3$, 100), 175 (49), 174 (39), 145 (13), 133 (32), 131 (13), 121 (10), 119 (22), 107 (18), 105 (26), 101 (19), 95 (11), 94 (11), 80 (11), 79 (24), 78 (84). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.57; H, 7.46; N, 18.10.

1-[4-(Phenylmethyl)-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (2b): pale yellow solid; mp 107−109 °C (hexane/EtOAc = 30/1); R_f = 0.34 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.4 Hz, 3H), 2.45 (q, J = 7.4 Hz, 2H), 3.05 (t, J = 5.0 Hz, 2H), 3.80−4.10 (br s, 2H), 4.39 (s, 2H), 6.46 (d, J = 8.6 Hz, 1H), 6.67 (dd, J = 7.3, 5.0 Hz, 1H), 7.22 (dd, J = 8.6, 2.0 Hz, 2H), 7.26−7.39 (c, 3H), 7.45 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 7.54 (s, 1H), 8.18 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.29, 29.80, 41.15, 45.46, 59.68,

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(23) Moore, M. L. *Org. React.* **1949**, *5*, 323.

111.66, 114.41, 115.01, 127.31, 127.92, 128.75, 135.72, 137.09, 137.84, 147.60, 158.17, 195.72; IR (KBr) 3054, 2990, 2934, 2908, 1651, 1585, 1553, 1498, 1469, 1428, 1367, 1351, 1321, 1308, 1285, 1230, 1215, 1195, 1142, 1124, 1092, 1052, 1025, 979, 955, 919, 882, 848, 813, 795, 779 cm^{-1}; MS *m/z* (relative intensity) 307 (M^+, 31), 279 (11), 278 ($M^+ - CH_2CH_3$, 56), 188 (21), 187 (18), 175 (28), 160 (16), 159 (17), 145 (10), 132 (11), 131 (11), 119 (13), 107 (11), 105 (16), 94 (11), 92 (16), 91 ($PhCH_2^+$, 100), 79 (33), 78 (75). Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 73.97; H, 6.88; N, 13.60.

1-[4-(4-Methoxyphenyl)-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (2d): yellow oil; R_f = 0.26 (hexane/EtOAc = 2/3); ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.4 Hz, 3H), 2.51 (q, J = 7.4 Hz, 2H), 3.57 (t, J = 4.8 Hz, 2H), 3.78 (s, 3H), 4.00−4.20 (br s, 2H), 6.49 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 7.3, 5.0 Hz, 1H), 6.88 (d, J = 9.2 Hz, 2H), 7.05 (d, J = 9.2 Hz, 2H), 7.47 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 7.72 (s, 1H), 8.24 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.08, 30.08, 41.80, 46.70, 55.31, 111.86, 114.52, 114.79, 117.75, 119.66, 131.88, 137.16, 138.37, 147.71, 156.10, 157.90, 196.50; IR (neat) 3054, 2936, 2838, 1649, 1586, 1511, 1477, 1432, 1394, 1294, 1245, 1210, 1176, 1150, 1097, 1070, 1025, 964, 821, 772 cm^{-1}; MS *m/z* (relative intensity) 324 ($M^+ + 1$, 21), 323 (M^+, 81), 295 (19), 294 ($M^+ - CH_2CH_3$, 100), 266 (12), 201 (22), 175 (48), 149 (22), 147 (29), 145 (12), 134 (21), 133 (17), 122 (17), 119 (13), 105 (17), 92 (13), 78 (31). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.28; H, 6.62; N, 13.01.

1-[4-(2-Methoxyphenyl)-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (2e): yellow oil; R_f = 0.34 (hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$) δ 1.11 (t, J = 7.4 Hz, 3H), 2.50 (q, J = 7.4 Hz, 2H), 3.53 (t, J = 4.8 Hz, 2H), 3.83 (s, 3H), 4.00−4.30 (br s, 2H), 6.50 (d, J = 8.3 Hz, 1H), 6.70 (dd, J = 6.9, 5.0 Hz, 1H), 6.91−7.00 (c, 2H), 7.11 (dd, J = 7.9, 2.0 Hz, 1H), 7.16−7.26 (m, 1H), 7.47 (ddd, J = 8.3, 6.9, 2.0 Hz, 1H), 7.53 (s, 1H), 8.23 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.40, 30.07, 41.85, 48.48, 55.58, 112.11, 112.20, 114.65, 117.25, 120.99, 125.43, 127.26, 134.72, 135.87, 137.14, 147.73, 153.39, 158.13, 196.17; IR (neat) 2976, 2936, 1646, 1586, 1503, 1472, 1431, 1396, 1344, 1308, 1264, 1201, 1177, 1144, 1118, 1068, 1048, 1019, 993, 978, 961, 911, 841, 801 cm^{-1}; MS *m/z* (relative intensity) 323 (M^+, 51), 294 ($M^+ - CH_2CH_3$, 100), 279 (24), 201 (30), 175 (45), 147 (27), 134 (36), 133 (23), 132 (27), 119 (28), 105 (33), 92 (27), 79 (44), 78 (93). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.48; H, 6.42; N, 13.05.

4,4-Dimethyl-1-[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-pentanone (3): yellow oil; bp 200 °C (2 mmHg); R_f = 0.33 (EtOAc/MeOH = 30/1); ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 9H), 1.49−1.56 (m, 2H), 2.34−2.40 (m, 2H), 3.04 (s, 3H), 3.12 (t, J = 5.0 Hz, 2H), 3.80−4.20 (br s, 2H), 6.42 (d, J = 8.3 Hz, 1H), 6.65 (dd, J = 7.3, 5.0 Hz, 1H), 7.34 (s, 1H), 7.44 (ddd, J = 8.3, 7.3, 2.0 Hz, 1H), 8.18 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.95, 29.98, 32.22, 39.32, 40.77, 42.79, 47.55, 111.59, 114.16, 114.79, 136.89, 138.78, 147.37, 158.08, 194.90; IR (neat) 3056, 2938, 2866, 1638, 1592, 1473, 1431, 1364, 1325, 1295, 1236, 1165, 1123, 1097, 1049, 1014, 980, 955, 915, 872, 809, 770 cm^{-1}; MS *m/z* (relative intensity) 287 (M^+, 23), 231 (23), 203 (12), 202 ($M^+ - CH_2CH_2C(CH_3)_3$, 100), 175 (12), 174 (24), 133 (15), 119 (14), 105 (12), 79 (14), 78 (37). Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 70.82; H, 8.88; N, 14.90.

Cyclopentyl[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]methanone (4): orange oil; R_f = 0.48 (EtOAc/MeOH = 5/1); ^{1}H NMR ($CDCl_3$) δ 1.40−1.60 (c, 2H), 1.50−1.90 (c, 6H), 2.90−3.10 (c, 1H), 3.05 (s, 3H), 3.13 (t, J = 5.0 Hz, 2H), 3.60−4.40 (br s, 2H), 6.41 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 6.9, 5.3 Hz, 1H), 7.35 (s, 1H), 7.42 (ddd, J = 8.4, 6.9, 1.7 Hz, 1H), 8.18 (dd, J = 5.3, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.33, 30.68, 40.88, 42.97, 44.57, 47.84, 111.79, 114.34, 114.97, 137.14, 138.71, 147.57, 158.42, 197.47; IR (neat) 2950, 2870, 1639, 1592, 1475, 1431, 1399, 1359, 1324, 1289, 1237, 1163, 1131, 1097, 1013, 980, 911, 809, 770 cm^{-1}; MS *m/z* (relative intensity) 271 (M^+, 14), 215 (11), 203 (12), 202 (M^+ − cyclopentyl, 100), 174 (19), 133 (15), 105 (12), 79 (14), 78 (41); exact mass calcd for $C_{16}H_{21}N_3O$ 271.1685, found 271.1691.

1-[4-Methyl-1-(2-pyridinyl)-4,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-yl]-1-propanone (6): yellow oil; bp 180 °C (2 mmHg); R_f = 0.26 (EtOAc/MeOH = 30/1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.90−2.25 (c, 3H), 2.25−2.45 (br s, 1H), 2.50−2.70 (br s, 1H), 2.95 (s, 3H), 3.30−3.65 (c, 2H), 4.65−4.85 (br s, 1H), 6.37 (d, J = 8.6 Hz, 1H), 6.49 (dd, J = 6.9, 5.0 Hz, 1H), 7.16 (s, 1H), 7.33 (ddd, J = 8.6, 6.9, 1.7 Hz, 1H), 8.08 (dd, J = 5.0, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.75, 25.50, 29.60, 44.85, 47.12, 48.75, 108.32, 112.53, 116.91, 137.16, 145.44, 147.76, 159.21, 198.31; IR (neat) 2938, 1649, 1597, 1480, 1432, 1401, 1369, 1338, 1288, 1258, 1233, 1214, 1147, 1100, 1085, 1040, 1003, 983, 955, 918, 898, 802, 771 cm^{-1}; MS *m/z* (relative intensity) 245 (M^+, 22), 217 (14), 216 ($M^+ - CH_2CH_3$, 100), 160 (10), 157 (15), 145 (17), 119 (16), 108 (13), 107 (11), 94 (44), 79 (14), 78 (60). Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.46; H, 7.85; N, 17.29.

6-[4-Methyl-2-(1-propionyl)-1,4,5,6-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (8a): orange solid; mp 83−84 °C (hexane/EtOAc = 30/1); R_f = 0.17 (hexane/EtOAc = 1/10); ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.3 Hz, 3H), 2.45 (q, J = 7.3 Hz, 2H), 3.09 (s, 3H), 3.19 (t, J = 4.8 Hz, 2H), 3.87 (s, 3H), 3.90−4.20 (br s, 2H), 6.33 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 7.97 (dd, J = 8.8, 2.3 Hz, 1H), 8.81 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.63, 29.31, 40.00, 42.82, 48.20, 51.39, 110.30, 113.64, 115.78, 137.50, 140.31, 150.10, 159.46, 166.16, 192.83; IR (KBr) 2932, 1713, 1600, 1495, 1434, 1402, 1327, 1272, 1239, 1169, 1099, 1064, 1008, 955, 854, 822, 777 cm^{-1}; MS *m/z* (relative intensity) 289 (M^+, 39), 261 (16), 260 ($M^+ - CH_2CH_3$, 100), 233 (46), 232 (26), 191 (16), 189 (12), 163 (10), 136 (15), 130 (16), 115 (19), 101 (19), 96 (14), 95 (13), 81 (13), 80 (10), 78 (12). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.31; H, 6.62; N, 14.55.

2-[4-Methyl-2-(1-propionyl)-1,4,5,6-tetrahydro-1-pyrazinyl]-4-pyridinecarboxylic acid methyl ester (8b): yellow solid; mp 135−139 °C (hexane/EtOAc = 30/1); R_f = 0.14 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.4 Hz, 3H), 2.46 (q, J = 7.4 Hz, 2H), 3.07 (s, 3H), 3.14 (t, J = 5.0 Hz, 2H), 3.75−4.30 (br s, 2H), 3.87 (s, 3H), 6.95 (s, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.38 (s, 1H), 8.29 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.80, 29.35, 40.77, 42.84, 47.78, 52.20, 111.39, 112.94, 114.18, 138.28, 139.68, 148.09, 158.44, 165.98, 193.80; IR (KBr) 2938, 1723, 1635, 1578, 1480, 1434, 1417, 1367, 1331, 1292, 1263, 1223, 1175, 1149, 1102, 1065, 1025, 1001, 984, 948, 914, 859, 825, 811, 760 cm^{-1}; MS *m/z* (relative intensity) 289 (M^+, 40), 261 (15), 260 ($M^+ - CH_2CH_3$, 100), 241 (10), 233 (45), 232 (28), 191 (15), 166 (10), 163 (11), 136 (20), 131 (12), 130 (18), 108 (14), 104 (13), 100 (22), 96 (12), 95 (16), 81 (14), 80 (13), 78 (15). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.32; H, 6.54; N, 14.47.

6-[4-Phenyl-2-(1-propionyl)-1,4,5,6-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (8c): yellow solid; mp 110−113 °C (hexane/EtOAc = 30/1); R_f = 0.06 (benzene); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.4 Hz, 3H), 2.54 (q, J = 7.4 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 3.88 (s, 3H), 4.08−4.40 (br s, 2H), 6.42 (d, J = 8.9 Hz, 1H), 7.07−7.18 (c, 3H), 7.38 (t, J = 7.9 Hz, 2H), 7.82 (s, 1H), 8.03 (dd, J = 8.9, 2.3 Hz, 1H), 8.86 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.27, 30.37, 41.31, 47.03, 51.75, 110.55, 116.93, 117.81, 117.93, 124.10, 129.65, 132.24, 138.19, 144.33, 150.57, 159.51, 166.18, 195.61; IR (neat) 2954, 2878, 1711, 1651, 1595, 1493, 1467, 1435, 1402, 1351, 1266, 1212, 1151, 1115, 1071, 1011, 961, 919, 821, 778, 753 cm^{-1}; MS *m/z* (relative intensity) 351 (M^+, 38), 323 (19), 322 ($M^+ - CH_2CH_3$, 100), 294 (14), 259 (20), 233 (49), 191 (10), 161 (21), 132 (31), 130 (11), 119 (10), 117 (10), 104 (32), 78 (16), 77 (74). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.23; H, 6.06; N, 11.99.

6-[4-(4-Methoxyphenyl)-2-(1-propionyl)-1,4,5,6-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (8d): colorless solid; mp 122−124 °C (hexane/EtOAc = 30/1);

R_f = 0.03 (benzene/EtOAc = 10/1); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.4 Hz, 3H), 2.53 (q, J = 7.4 Hz, 2H), 3.66 (t, J = 4.8 Hz, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 4.05−4.45 (br s, 2H), 6.41 (d, J = 8.9 Hz, 1H), 6.91 (d, J = 9.1 Hz, 2H), 7.08 (d, J = 9.1 Hz, 2H), 7.73 (s, 1H), 8.02 (dd, J = 8.9, 2.3 Hz, 1H), 8.85 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.38, 30.17, 41.04, 47.78, 51.70, 55.53, 110.60, 114.79, 116.69, 116.86, 120.31, 133.85, 138.06, 138.28, 150.49, 156.71, 159.51, 166.20, 195.06; IR (neat) 2942, 2840, 1711, 1646, 1598, 1512, 1493, 1461, 1434, 1404, 1352, 1320, 1269, 1245, 1213, 1181, 1151, 1118, 1071, 1031, 961, 913, 824, 778 cm^{-1}; MS *m*/*z* (relative intensity) 381 (M^+, 41), 353 (22), 352 ($M^+ - CH_2CH_3$, 100), 324 (11), 259 (22), 233 (51), 191 (13), 177 (17), 176 (30), 169 (13), 163 (12), 155 (12), 149 (44), 147 (15), 136 (12), 134 (39), 122 (29), 107 (15), 92 (22), 78 (11). Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found: C, 65.95; H, 6.08; N, 10.98.

1-[4-Methyl-1-(5-(trifluoromethyl)-2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-propanone (8e): orange oil; R_f = 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.4 Hz, 3H), 2.49 (q, J = 7.4 Hz, 2H), 3.08 (s, 3H), 3.18 (t, J = 5.0 Hz, 2H), 3.85−4.35 (br s, 2H), 6.36 (d, J = 8.9 Hz, 1H), 7.38 (s, 1H), 7.57 (dd, J = 8.9, 2.3 Hz, 1H), 8.39 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.72, 29.29, 40.09, 42.88, 48.12, 110.82, 113.80, 116.15 (q, J = 33 Hz), 124.43 (q, J = 71 Hz), 133.64 (d, J = 3.7 Hz), 140.49, 144.84 (d, J = 4.9 Hz), 159.12, 192.78; IR (neat) 3046, 2938, 2814, 1609, 1498, 1411, 1327, 1242, 1111, 1001, 954, 855, 818, 787, 758 cm^{-1}; MS *m*/*z* (relative intensity) 299 (M^+, 42), 271 (13), 270 ($M^+ - CH_2CH_3$, 87), 243 (31), 242 (33), 201 (25), 173 (10), 147 (10), 146 (29), 135 (19), 126 (18), 96 (13), 95 (15), 81 (20), 80 (14), 70 (86), 69 (20), 68(13), 67 (12), 57 (100). Anal. Calcd for $C_{14}H_{16}F_3N_3O$: C, 56.18; H, 5.39; N, 14.04. Found: C, 55.91; H, 5.42; N, 14.03.

6-[3,4-Dimethyl-6-(1-propionyl)-1,2,3,4-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (10): pale yellow solid; mp 134−136 °C (hexane/EtOAc = 30/1); R_f = 0.14 (EtOAc/MeOH = 40/1); ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 5.6 Hz, 3H), 1.12 (t, J = 6.1 Hz, 3H), 2.40−2.45 (m, 2H), 3.07 (s, 3H), 3.40−3.48 (m, 1H), 3.86 (s, 3H), 4.40−5.40 (br s, 2H), 6.29−6.33 (m, 1H), 7.29 (s, 1H), 7.97 (dd, J = 8.9, 2.3 Hz, 1H), 8.78 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.72, 16.46, 29.47, 40.81, 45.29, 51.45, 54.52, 109.26, 113.08, 115.45, 137.59, 140.13, 150.24, 159.95, 166.25, 191.19; IR (neat) 2974, 2932, 1710, 1597, 1495, 1437, 1404, 1373, 1325, 1270, 1233, 1173, 1153, 1119, 1061, 1029, 1010, 965, 925, 875, 821, 778 cm^{-1}; MS *m*/*z* (relative intensity) 303 (M^+, 41), 275 (15), 274 ($M^+ - CH_2CH_3$, 100), 265 (12), 246 (22), 233 (17), 231 (14), 228 (10), 216 (10), 209 (17), 163 (18), 137 (19), 136 (23), 134 (13), 130 (14), 122 (11), 121 (13), 97 (12), 95 (24), 94 (36), 93 (14), 84 (23), 82 (10), 80 (14), 78 (14). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.21; H, 7.07; N, 13.91.

6-[3,4-Dimethyl-2-(1-propionyl)-1,4,5,6-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (11): yellow solid; mp 116−118 °C (hexane/EtOAc = 30/1); R_f = 0.40 (EtOAc/MeOH = 40/1); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 2.20−2.40 (m, 2H), 2.52 (s, 3H), 3.00 (s, 3H), 3.29 (t, J = 5.0 Hz, 2H), 3.87 (s, 3H), 4.40−5.58 (br s, 2H), 6.45 (d, J = 8.9 Hz, 1H), 7.97 (dd, J = 8.9, 2.3 Hz, 1H), 8.82 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.83, 15.80, 32.11, 38.24, 40.65, 50.78, 51.59, 108.95, 111.63, 115.80, 138.26, 149.20, 150.85, 160.66, 166.22, 197.90; IR (neat) 2944, 1712, 1641, 1600, 1544, 1493, 1435, 1406, 1372, 1347, 1324, 1272, 1236, 1193, 1114, 1047, 1009, 950, 898, 846, 779 cm^{-1}; MS *m*/*z* (relative intensity) 303 (M^+, 7), 274 ($M^+ - CH_2CH_3$, 59), 108 (10), 94 (26), 59 (12), 57 (17), 56 (100). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.35; H, 7.01; N, 13.81.

6-[2-(1-Propionyl)-3,4,6-trimethyl-1,4,5,6-tetrahydro-1-pyrazinyl]-3-pyridinecarboxylic acid methyl ester (13): yellow solid; mp 129−131 °C (hexane/EtOAc = 10/1); R_f = 0.17 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.19 (d, J = 6.9 Hz), 2.10−2.24 (m, 1H), 2.34−2.50 (m, 1H), 2.53 (s, 3H), 2.96 (d, J = 12.5 Hz, 1H), 3.00 (s, 3H), 3.36 (dd, J = 12.5, 5.1 Hz, 1H), 3.87 (s, 3H), 5.42−5.54 (m, 1H, 6H), 6.42 (d, J = 8.9 Hz, 1H), 7.95 (dd, J = 8.9, 2.3 Hz, 1H), 8.82 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.66, 15.37 (=CCH_3), 15.76, 31.32, 38.60, 41.94, 51.47, 55.19, 107.67, 109.13, 115.71, 138.17, 147.66, 150.76, 160.75, 166.06, 198.62; IR (neat) 2938, 1713, 1640, 1603, 1553, 1490, 1404, 1343, 1268, 1242, 1188, 1117, 1064, 1009, 962, 935, 879, 864, 832, 779 cm^{-1}; MS *m*/*z* (relative intensity) 317 (M^+, 7), 289 (10), 288 ($M^+ - CH_2CH_3$, 50), 108 (19), 59 (10), 57 (13), 56 (100). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.47; H, 7.31; N, 13.27.

1-[4-Methyl-1-(2-pyrimidinyl)-4,5,6,7-tetrahydro-1*H*-1,4-diazepin-2-yl]-1-propanone (15): orange oil; bp 160 °C (2 mmHg); R_f = 0.20 (EtOAc/MeOH = 50/1); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.3 Hz, 3H), 1.95−2.30 (br s, 2H), 2.20−2.50 (br s, 2H), 2.55−2.80 (br s, 1H), 3.04 (s, 3H), 3.45−3.75 (c, 2H, 5-H), 4.60−4.90 (br s, 1H), 6.57 (t, J = 4.6 Hz, 1H), 7.16 (s, 1H), 8.36 (d, J = 4.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 8.74, 25.59, 29.53, 44.85, 47.55, 48.61, 110.42, 117.14, 143.29, 157.57, 158.10, 161.98, 198.09; IR (neat) 2940, 1658, 1582, 1551, 1478, 1425, 1362, 1344, 1265, 1234, 1219, 1142, 1097, 1045, 995, 928, 899, 799 cm^{-1}; MS *m*/*z* (relative intensity) 246 (M^+, 26), 218 (12), 217 ($M^+ - CH_2CH_3$, 100), 161 (21), 158 (12), 148 (13), 146 (12), 120 (11), 109 (13), 108 (29), 94 (61), 82 (16), 80 (19), 79 (47). Anal. Calcd for $C_{13}H_{18}N_4O$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.51; H, 7.48; N, 22.81.

1-Methyl-4-phenyl-1,2,3,4-tetrahydropyrazine (19a). Spectral data were obtained from a mixture of **18a** and **19a**: colorless oil; bp 110 °C (2 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 3.02 (t, J = 4.6 Hz, 2H), 3.62 (t, J = 4.6 Hz, 2H), 5.24 (d, J = 6.1 Hz, 1H), 5.79 (d, J = 6.1 Hz, 1H), 6.70−6.85 (c, 1H), 6.85−6.95 (c, 2H), 7.18−7.30 (c, 2H); ^{13}C NMR ($CDCl_3$) δ 42.82, 43.85, 49.67, 108.54, 113.28, 117.93, 118.62, 129.06, 145.71; MS *m*/*z* (relative intensity) 175 ($M^+ + 1$, 11), 174 (M^+, 100), 173 (17), 159 (29), 145 (27), 132 (17), 131 (11), 118 (11), 117 (13), 105 (13), 104 (47), 91 (20), 87 (19), 82 (23), 78 (12), 77 (97); exact mass calcd for $C_{11}H_{14}N_2$ 174.1157, found 174.1156.

1-[4-(4-Methyl-1,2,3,4-tetrahydro-1-pyrazinyl)phenyl]-1-ethanone (19b). Spectral data were obtained from a mixture of **18b** and **19b**: yellow solid; bp 180 °C (2 mmHg); ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.63 (s, 3H), 3.10 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.8 Hz, 2H), 5.39 (d, J = 6.4 Hz, 1H), 5.81 (d, J = 6.4 Hz, 1H), 6.76 (d, J = 9.1 Hz, 2H), 7.86 (d, J = 9.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.97, 42.54, 43.51, 49.29, 105.82, 111.39, 121.31, 126.63, 130.46, 148.25, 196.12; MS *m*/*z* (relative intensity) 217 ($M^+ + 1$, 12), 216 (M^+, 100), 201 (28), 187 (16), 174 (12), 173 (15), 158 (12), 146 (16), 145 (11), 132 (21), 103 (12), 100 (28), 91 (20), 83 (12), 82 (40); exact mass calcd for $C_{13}H_{16}N_2O$ 216.1263, found 216.1252.

1-[4-Methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-heptanone (20): orange oil; R_f = 0.20 (hexane/EtOAc = 1/10); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 6.6 Hz, 3H), 1.18−1.31 (c, 6H), 1.50−1.72 (m, 2H), 2.41 (t, J = 7.3 Hz, 2H), 3.05 (s, 3H), 3.12 (t, J = 4.8 Hz, 2H), 3.75−4.40 (br s, 2H), 6.42 (d, J = 8.6 Hz, 1H), 6.65 (dd, J = 7.3, 5.0 Hz, 1H), 7.35 (s, 1H), 7.42 (ddd, J = 8.6, 7.3, 2.0 Hz, 1H), 8.18 (dd, J = 5.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.84, 22.32, 25.50, 29.02, 31.48, 36.55, 40.81, 42.79, 47.57, 111.64, 114.20, 115.10, 136.95, 138.87, 147.39, 158.10, 194.46; IR (neat) 3052, 2934, 2858, 1720, 1638, 1592, 1475, 1432, 1400, 1325, 1292, 1240, 1220, 1167, 1142, 1099, 1047, 1015, 979, 924, 874, 808, 769 cm^{-1}; MS *m*/*z* (relative intensity) 287 (M^+, 24), 231 (25), 203 (13), 202 ($M^+ - n$-hexyl, 100), 175 (12), 174 (29), 133 (17), 119 (15), 105 (14), 101 (11), 95 (10), 79 (17), 78 (47). Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.05; H, 8.85; N, 14.61.

2-Methyl-1-[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-hexanone (21) and 2-Ethyl-1-[4-methyl-1-(2-pyridinyl)-1,4,5,6-tetrahydro-2-pyrazinyl]-1-pentanone (22). Spectral data were obtained from a mixture of **21** and **22**: yellow oil; R_f = 0.29 (hexane/EtOAc = 1/10). ^{1}H NMR ($CDCl_3$) for **21**: δ 0.86 (t, J = 6.6 Hz, 3H), 1.05 (d, 6.6

Hz, 3H), 1.15−1.40 (c, 5H), 1.55−1.75 (m, 1H), 2.74-2.84 (m, 1H), 3.06 (s, 3H), 3.13 (t, J = 5.0 Hz, 2H), 3.30−4.70 (br s, 2H), 6.42 (d, J = 8.3 Hz, 1H), 6.66 (dd, J = 7.3, 5.0 Hz, 1H), 7.36 (s, 1H), 7.42 (ddd, J = 8.3, 7.3, 2.0 Hz, 1H), 8.18 (dd, J = 5.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) for **21**: δ 14.00, 17.85, 22.82, 29.74, 34.07, 38.69, 40.99, 43.00, 47.80, 111.73, 114.39, 114.75, 137.11, 138.69, 147.55, 158.47, 196.30. IR (neat); 3050, 2958, 2930, 2872, 1637, 1591, 1476, 1431, 1400, 1368, 1324, 1291, 1238, 1219, 1169, 1127, 1098, 1013, 979, 967, 922, 840, 771 cm^{-1}. MS, *m*/*z* (relative intensity): **21**, 287 (M^+, 14), 203 (13), 202 (M^+ − 2-hexyl, 100), 174 (21), 133 (13), 105 (11), 79 (11), 78 (34); **22**, 287 (M^+, 16), 203 (14), 202 (M^+ − 3-hexyl, 100), 174 (22), 133 (16), 105 (12), 79 (12), 78 (37). Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 71.07; H, 8.79; N, 14.70.

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