Acylation of Five-Membered *N*-Heteroaromatic Compounds by Ruthenium Carbonyl-Catalyzed Direct Carbonylation at a C−H Bond

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The ruthenium-catalyzed carbonylation at the C−H bond of five-membered *N*-heteroaromatic compounds is described. The reaction of imidazoles with CO and olefins in toluene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ results in carbonylation of the C−H bond at the 4-position (adjacent to the sp^2-nitrogen) of the imidazole ring to give acylated imidazoles in good to high yields. A wide range of olefins can be utilized in the carbonylation reaction, and a variety of functional groups are compatible under the reaction conditions. Other five-membered *N*-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, can also be used for the carbonylation reaction, and in all cases, carbonylation takes place exclusively at a C−H bond α to the sp^2 nitrogen. The reactivity of the five-membered heterocycles corresponds to the pK_a of the conjugate acid of these heterocycles. The higher the pK_a of the substrate, the higher is the reactivity. This indicates that the pK_a values are related to the ability of the nitrogen atom in the substrates to coordinate to a ruthenium center. The coordination of the substrates to the ruthenium center in the catalyst complex is a necessary prerequisite for the carbonylation to proceed.

Introduction

A number of natural products and related biologically active compounds contain heteroaromatic moieties.[1] Thus, the development of strategies for the construction of, or the functionalization of, heteroaromatic compounds is an important subject in organic synthesis and medical chemistry. Because of the importance of this, a variety of methods for the functionalization of heteroaromatics have been reported to date, and continue to be a subject of study. Acyl-substituted heterocycles are among the most important of these substructures because the acyl group can be transformed into a variety of other functional groups. Although the Lewis acid-promoted Friedel−Crafts acylation is the most commonly used method for the acylation of an aromatic ring, it cannot be used for imidazoles, due to deactivation of the Lewis acids.[2,3] Other azoles, such as oxazoles and thiazoles, are also not amenable, because of their electron-deficient aromatic character.[2,3] This type of acylation, however, proceeds only via a strong activation from electron-donating groups, such as alkoxy, amino, or arylthio groups, in the substrates.[4]

In previous papers, we reported on a series of the direct carbonylation reactions at sp^2 C−H bonds, as catalyzed by $Ru_3(CO)_{12}$.[5−9] The direct carbonylation at a C−H bond provides a new and useful method for the introduction of an acyl substituent into a simple starting material, with no prior need for prefunctionalization.[5−10] In a preliminary study, we reported that imidazoles can be acylated in a site-selective manner during the $Ru_3(CO)_{12}$-catalyzed reaction of imidazoles with CO and olefins.[6] In this reaction, the acylation took place exclusively at the 4-position, which is adjacent to an sp^2 nitrogen in the imidazole ring, to give imidazolyl ketones in good to excellent yields, in favor of a linear-isomer (eq 1). We have investigated details of this acylation of imidazoles

(1) *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, 6. *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Elsevier: Oxford, 1996; Vol. 3.

(2) For reviews on azoles, see: Grimmett, M. R. *Adv. Heterocycl. Chem*. **1980**, *27*, 241. Grimmett, M. R.; Iddon, B. *Heterocycles* **1994**, *37*, 2087. Iddon, B.; Ngochindo, R. I. *Heterocycles* **1994**, *38*, 2487.

(3) It is known that acylation at the 2-position of imidazoles can be achieved in the presence of amines. Grimmett, M. R. *Adv. Heterocycl. Chem*. **1980**, *27*, 241 and references therein. The acylation of imidazo-[1,5-*a*]pyridine and imidazo[1,2-*a*]pyridine in the presence of $AlCl_3$ are known. Bower, J. D.; Ramage, G. R. *J. Chem. Soc*. **1955**, 2834. Hlasta, D. J. *Tetrahedron Lett*. **1990**, *31*, 5833. Hlasta, D. J.; Silbernagel, M. J. *Heterocycles*, **1998**, *48*, 1015.

(4) (a) For acylation of oxazole having electron-donating groups at the 2-position under Friedel−Crafts conditions, see: Bossio, R.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Org. Prep. Proceed. Int*. **1991**, *23*, 670. Mekonnen, B.; Crank, G. *J. Heterocycl. Chem*. **1997**, *34*, 567. (b) For the acylation of 2-aminothiazole, see: Dondoni, A.; Medici, A.; Venturoli, C.; Forlani, L.; Bertolasi, V. *J. Org. Chem*. **1980**, *45*, 621. Medici, A.; Pedrini, P.; Venturoli, C.; Dondoni, A. *J. Org. Chem*. **1981**, *46*, 2790.

(5) For a review of the direct carbonylation at a C−H bond, see: Chatani, N.; Murai, S. *Yuki Gosei Kagaku Kyokaishi* (*J. Synth. Org. Chem. Jpn*.) **1998**, *56*, 443; Chem. Abstr. **1998**, *129*, 4250m.

(6) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1996**, *118*, 493.

(7) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1998**, *120*, 11522.

(8) (a) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1997**, *62*, 2604. (b) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1997**, *62*, 5647. (c) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1998**, *63*, 5129. (d) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **2000**, *65*, 1475.

(9) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Tetrahedron Lett*. **1997**, *38*, 7565.

(10) Moore reported that pyridine derivatives were carbonylated site selectively at the 2-position via the $Ru_3(CO)_{12}$-catalyzed reaction of pyridines with CO and olefins. Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc*. **1992**, *114*, 5888. Moore, E. J.; Pretzer, W. R. U.S. Patent 5,081,-250, 1992; *Chem Abstr*. **1992**, *116*, 174011.

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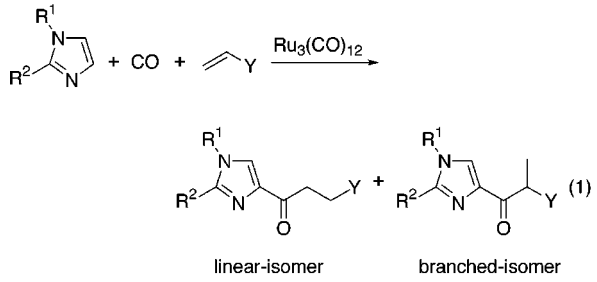
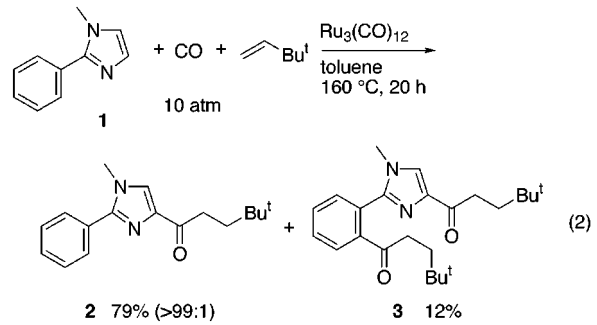
and expanded these earlier studies to the acylation of other five membered *N*-heterocycles. In this paper, we report on the direct carbonylation at a C−H bond in various five-membered *N*-heterocycles with CO and olefins in the presence of catalytic amounts of $Ru_3(CO)_{12}$. The reaction provides a new and useful method for the preparation of acyl-substituted *N*-heteroaromatics.



Results and Discussion

Our initial investigation focused on the direct carbonylation at a C−H bond in a benzene ring.[8a,b,d] This effort eventually resulted in the successful carbonylation of imidazoles, as is described below. At the time this project was initiated, there were nearly no examples of the direct carbonylation at a C−H bond[11] in a benzene ring, except for the Rh-catalyzed carbonylation of benzene to benzaldehyde under photoirradiation.[12] We prepared a variety of benzene derivatives which contain a functional group which is capable of coordinating a metal into close proximity to the *ortho* C−H bond. In most cases, no reaction took place and the starting materials remained in intact. After numerous attempts, we were finally able to obtain carbonylation products when an imidazole ring was used as the directing group, as in the case of 1-methyl-2-phenylimidazole (**1**). The reaction of **1** with CO and *tert*-butylethylene in the presence of $Ru_3(CO)_{12}$ as the catalyst gave two carbonylation products **2** and **3** in 91% total yield (eq 2), along with the minor product **3**, produced via carbonylation of the benzene ring.[8a,b,d] To our surprise, C−H bond carbonylation took place on the imidazole ring in both products. As a result, we directed our objective to explore the carbonylation at a C−H bond in an imidazole ring and initiated a study of the reaction of imidazoles without a phenyl group at the 2-position.



The reaction of 1,2-dimethylimidazole (**4**) (1 mmol) with 1-hexene under CO (initial pressure 20 atm at 25 °C in a 50-mL stainless autoclave) in the presence of $Ru_3(CO)_{12}$ (0.04 mmol) at 160 °C for 20 h gave 1-(1,2-dimethyl-1*H*-imidazol-4-yl)-1-heptanone (**5**) and its branched-isomer in a combined yield of 68% in a ratio of 94:6 (entry 1 in Table 1). The linear isomer was obtained as the major product. No other products were detected by GC and ^1H NMR of the crude reaction mixtures. The reaction of **4** with CO and a variety of olefins are summarized in Table 1. Identical products were obtained from the reaction of **4** with 2-hexene (cis/trans mixture) with exactly the same ratio of linear to branched components (entry 2). The reaction of 3-hexene (trans isomer) also gave a similar linear-to-branched ratio, albeit in low yield (entry 3). The linear-to-branched ratio was affected by steric factors. Thus, the reaction of *tert*-butylethylene gave the linear product **6** as the sole product in 88% yield (entry 4). The reaction of **4** with trimethylvinylsilane also afforded only the linear isomer in 66% yield (entry 5), while the ratio was 94:6 in the case of allyltrimethylsilane (entry 6). The use of styrene as a reactant resulted in a low ratio (75:25), and substitution of an electron-donating group (OMe) and -withdrawing group (CF_3) at the *para*-position on the phenyl ring failed to improve this ratio (entry 7). However, *o*-methylstyrene resulted in a favorable linear-to-branched ratio (93:7, entry 8). Olefins which contain cyano or ester groups could be used in the present reaction and gave the corresponding ketones **13** or **14** (entries 9 and 10), while the reaction of electron-deficient olefins, such as acrylonitrile and methylacrylate, gave no coupling product. Allyl alcohol and allyl acetate was not applicable, but the silyl-protected allyl alcohol gave corresponding ketone **15** (entry 11). The reaction of **4** with 6-siloxy-1-hexene gave the coupling product **17** in 41% yield, while the reaction with 5-hexenyl acetate resulted in a poor yield (entry 12). When the reaction of 6-siloxy-1-hexene was carried out for 70 h, the yields increased to 55%. Cyclic olefins, such as cyclohexene and norbornene, were applicable to the present reaction (entries 13 and 14), but cyclooctene and cyclododecene failed to yield a product (vide infra). The reaction of α-methylstyrene led to a single isomer (entry 14). When butyl vinyl ether was used as an olefin, the branched isomer **21** and ethyl ketone **22** were obtained (entry 15). No linear isomer could be detected by GC. The mechanism for the formation of ethyl ketone **22** is presently unclear. Protected amino group-substituted olefin reacted with imidazole and CO to give the protected δ-amino ketone **23** (entry 17). In this reaction, it was observed that some isomerized olefins, such as *N*-(2-butenyl)phthalimide, and unreacted imidazole remained. The yield of **23** was not improved, even after 70 h. The reaction of **4** with the olefin, prepared from β-D-glucose pentaacetate and allyltrimathylsilane,[13] gave the corresponding ketone **23** in 34% yield (entry 18).

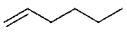
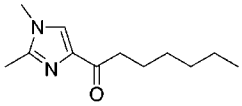
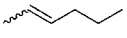
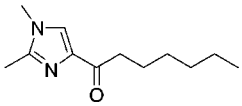
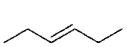
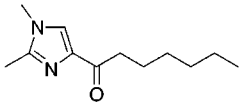
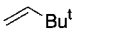
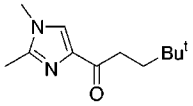
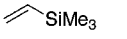
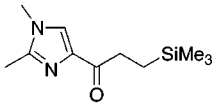
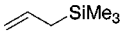
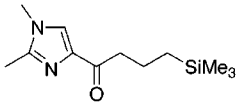
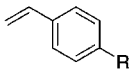
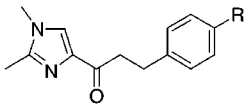
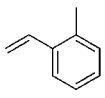
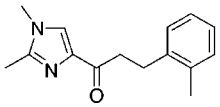
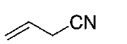
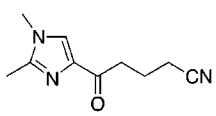
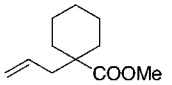
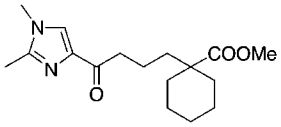
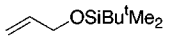
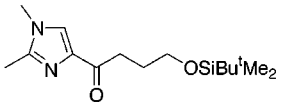
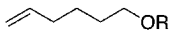
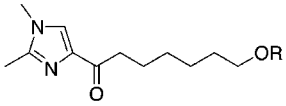
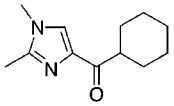
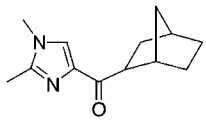
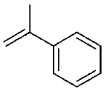
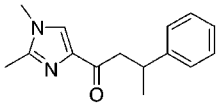
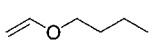
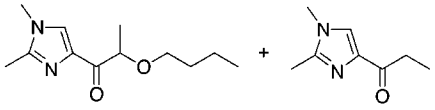
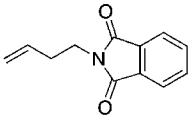
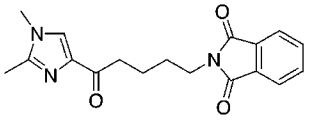
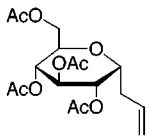
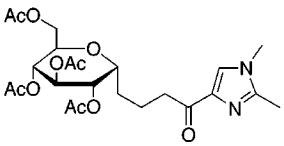
As described above, a variety of olefins were applicable to the reaction of **4**. We next examined some other imidazoles (Table 2). In the reaction of 1-methylimidazole (**25**), which has no substituent at the 2-position, carbonylation preferentially took place at the 2-position to give 2-imidazolyl ketone **26** as a major product, along with 4-imidazolyl ketone **27** (entry 1). Some protected groups,

(11) Hong, P.; Yamazaki, H. *Chem. Lett.* **1979**, 1335.

(12) Fisher, B. J.; Eisenberg, R. *Organometallics* **1983**, *2*, 764. Kunin, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **1986**, *108*, 535. Kunin, A. J.; Eisenberg, R. *Organometallics* **1988**, *7*, 2124. Gordon, E. M.; Eisenberg, R. *J. Mol. Catal.* **1988**, *45*, 57. Sakakura, T.; Tanaka, M. *Chem. Lett.* **1987**, 249. Sakakura, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1987**, 758. Sakakura, T.; Sodeyama, T.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, *112*, 7221.

(13) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.

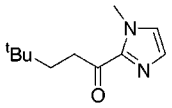
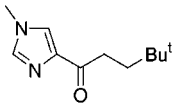
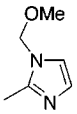
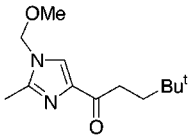
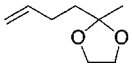
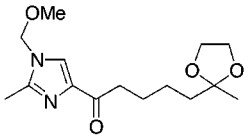
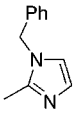
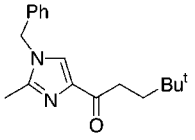
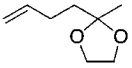
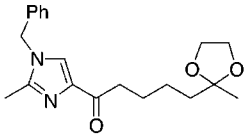
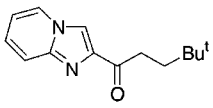
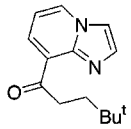
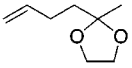
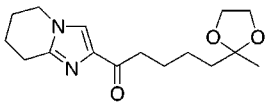
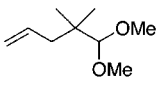
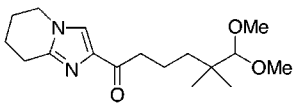
Table 1. $Ru_3(CO)_{12}$-Catalyzed Reaction of 1,2-Dimethylimidazole (4) with CO and Olefins[a]

entry	olefin	product(s) [b]
1		 **5** 68% (94:6)
2		 **5** 41% (94:6)
3		 **5** 15% (93:7)
4		 **6** 88% (>99:1)
5		 **7** 66% (>99:1)
6		 **8** 61% (94:6)
7		 R = H **9** 74% (75:25) R = OMe **10** 57% (58:42) R = CF_3 **11** 64% (48:52)
8		 **12** 77% (93:7)
9		 **13** 42% (87:13)
10		 **14** 77% (>99:1)
11		 **15** 19%
12		 R = Ac **16** 9% R = $SiBu^tMe_2$ **17** 41% (96:4)
13		 **18** 50%
14		 **19** 56% (72:28) [c]
15		 **20** 42% (>99:1)
16		 **21** 23% **22** 31%
17		 **23** 13%
18		 **24** 34%

[a] Reaction conditions: imidazole (1 mmol), olefin (4 mmol), CO (20 atm), $Ru_3(CO)_{12}$ (0.04 mmol), toluene (3 mL), 160 °C, 20 h. [b] Isolated yields. The ratio of linear to branched isomers is in parentheses. [c] The diastereoisomeric ratio.

such as methoxymethyl and benzyl, on the nitrogen of the imidazole ring can be utilized in this reaction (entries 2−5). 1,2-Fused bicyclic imidazole also reacted with CO and olefin to give an α-carbonylated product **35** in 45% yield, along with the *β*-carbonylated product[7] **36** in 45% yield (entry 6). The reaction of 5,6,7,8-tetrahydroimidazo-[1,2-*a*]pyridine (**37**) gave the corresponding ketones in high yields (entries 7 and 8). The use of unsaturated ketal and acetal gave the corresponding monoprotected diketones and keto-acetals (entries 3, 5, 7, and 8).

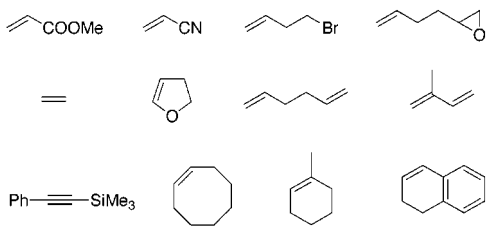
Table 2. $Ru_3(CO)_{12}$-Catalyzed Reaction of Imidazoles with CO and Olefin[a]

entry	imidazole	olefin	product(s) [b]
1	 **25**		 **26** 25% (>99:1)  **27** 6% (>99:1)
2	 **28**		 **29** 95% (>99:1)
3	**28** 		 **30** 51% (>99:1)
4	 **31**		 **32** 96% (>99:1)
5	**31** 		 **33** 72% (97:3)
6	 **34**		 **35** 45% (>99:1)  **36** 45% (>99:1)
7	 **37**		 **38** 78% (92:8)
8	**37** 		 **39** 90% (>99:1)

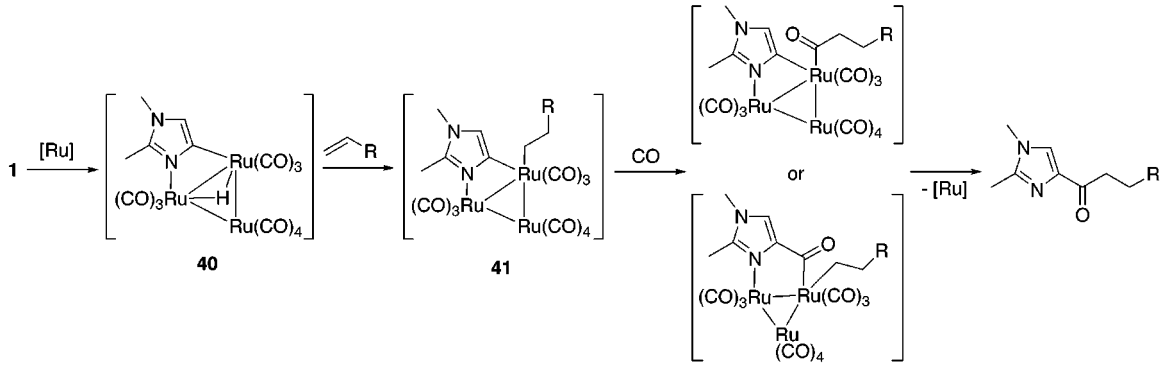
[a] Reaction conditions: imidazole (1 mmol), olfin (4 mmol), CO (20 atm), $Ru_3(CO)_{12}$ (0.04 mmol), toluene (3 mL), 160 °C, 20 h. [b] Isolated yields. The ratio of linear to branched isomers is in parentheses.

Although the present reaction can be applied to a wide range of olefins, those which are listed in Chart 1 were not applicable. No reaction occurred in the case of olefins such as methyl acrylate, acrylonitrile, and 4-bromo-1-butene. It is interesting that, in the reaction with ethylene, various acylated products, such as the corresponding ethyl ketone, isopropyl ketone, butyl ketone, and diketone, each were obtained in low yields, suggesting that the dimerization of ethylene and/or metathesis of the resulting olefins took place under the reaction conditions leading to propene, butenes, and higher olefins. Olefins such as 1,2-dihydrofuran and 1,5-hexadiene monoepoxide led to complex mixtures. Dienes, such as

Chart 1



Scheme 1. Plausible Mechanism of Carbonylation of Imidazoles



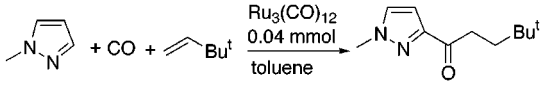
isoprene and 1,5-hexadiene, and acetylene also resulted in complex mixtures. Although cyclohexene gave the corresponding ketone in good yield (entry 13 in Table 1), no reaction took place when cyclooctene and cyclododecene were used.

A plausible mechanism for this reaction is shown in Scheme 1. The coordination of the sp^2 nitrogen to ruthenium leads to the oxidative addition of a C−H bond at the 4-position to give the hydride−ruthenium complex **40**.[14] It has been reported that the triosmium carbonyl complex, which is analogous to complex **40**, is obtained via the stoichiometric reaction of $Os_3(CO)_{10}(CH_3CN)_2$ with 2-methylimidazole.[15a,b] The hydride complex **40** reacts with an olefin to give the alkyl−ruthenium complex **41**. The alkyl−ruthenium complex **41** undergoes CO insertion, followed by reductive elimination to give the final product. The issue of whether the insertion of CO occurs into the alkyl−ruthenium bond or imidazolyl−ruthenium bond is not known.

In the stoichiometric reaction of 1-substituted imidazole with $Ru_3(CO)_{12}$, C−H bond cleavage occurred at the 2, and not at the 4-position.[15c] This is the same trend as was observed for the reaction of 1-methylimidazole (**25**) which has no subsituent at the 2-position, and which gave the 2-acylated product as the major product (entry 1 in Table 2).

We next examined the issue of whether *N*-heterocycles, other than imidazoles, can be carbonylated. The reaction of *N*-methylpyrazole (**42**) with CO and *tert*-butylethylene under the same reaction conditions that were used for the reaction of imidazoles gave only small amount of the expected carbonylation product **43** (entry 1 in Table 3). A higher temperature (180 °C) and longer reaction time (40 h) gave the coupling product in moderate yields (entries 2 and 3). Numerous attempts have been made to determine the reaction conditions required to obtain the carbonylation product **43** in high yield, and it was eventually found that the product **43** could be obtained in good yield when the reaction was carried out under low CO pressure. Interestingly, a decrease of CO pressure resulted in an increase in product yields (entries 1, 4, and 5). When the reaction was carried out under 3 atm of CO for 40 h, the yield of the coupling product was increased to 57% (entry 6).

Table 3. $Ru_3(CO)_{12}$-Catalyzed Reaction of 1-Methylpyrazole (37) with CO and *tert*-Butylethylene



42 1 mmol 4 mmol **43**

entry	CO (atm)	temp. (°C)	time (h)	yield [a]
1	20	160	20	trace
2	20	180	40	16%
3 [b]	20	180	40	37%
4	5	160	20	16%
5	3	160	20	46%
6	3	160	40	57%

[a] Isolated yield. [b] $Ru_3(CO)_{12}$ (0.1 mmol) was used.

Table 4. $Ru_3(CO)_{12}$-Catalyzed Reaction of 42 with CO and Olefins[a]

entry	olefin	product(s) [b]
1 [c]	=	**44** 66%
2		**45** 59% (94:6)
3	SiMe3	**46** 56% (>99:1) + **44** 2%
4		**47** 7%

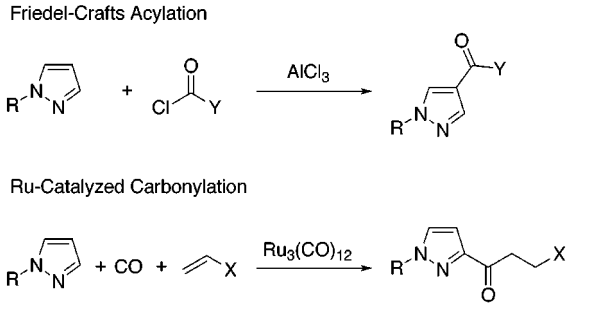
[a] Reaction conditions: **42** (1 mmol), olefin (4 mmol), CO (3 atm), $Ru_3(CO)_{12}$ (0.04 mmol), toluene (3 mL), 160 °C, 40 h. [b] Isolated yields. The ratio of linear to branched isomers is in parentheses. [c] Ethylene (4 atm).

Table 4 shows the results of the reaction of **42** with some olefins at conditions of 3 atm of CO at 160 °C for 40 h. The reaction of **42** with ethylene (4 atm) gave the carbonylation product **44** in 66% yield (entry 1), while the reaction of 1,2-dimethylimidazole (**4**) with ethylene gave complex mixtures. In the case of the reaction of *o*-methylstyrene, **45** and its isomer were obtained in 59%

(14) We have no evidence that triruthenium cluster, such as **40**, or the monoruthenium complex function as the actual active catalyst.

(15) (a) Shapley, J. R.; Samkoff, D. E.; Bueno, C.; Churchill, M. R. *Inorg. Chem.* **1982**, *21*, 634. (b) Churchill, M. R.; Missert, J. R. *J. Organomet. Chem.* **1983**, *256*, 349. (c) Agarwala, R.; Azam, K. A.; Dilshad, R.; Kabir, S. E.; Miah, R.; Shahiduzzaman, M.; Hardcastle, K.; Rosenberg, E.; Hursthouse, M. B.; Malik, K. M. A. *J. Organomet. Chem.* **1995**, *492*, 135.

Scheme 2



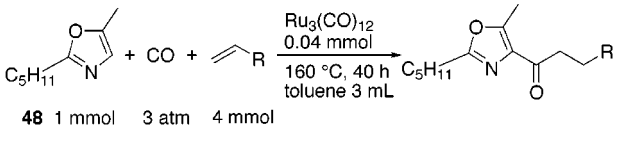
total yield, in favor of the linear isomer (entry 2). The reaction of **42** with trimethylvinylsilane afforded the corresponding ketone **46** in 56% yield, along with **44** in a yield of 2% (entry 3). It is likely that ethyl ketone **44** arises from ethylene, which is generated in situ from the trimethylvinylsilane.[16,17] The use of 1-hexene gave the corresponding ketone **47** in 7% yield under same reaction conditions, probably the results of the isomerization to internal hexenes, which do not serve as the olefin for the present carbonylation very well.

It has been reported that the Friedel−Crafts acylation of a pyrazole ring takes place at the 4-position of the pyrazole ring to give the 4-pyrazolyl ketone.[18] On the other hand, the $Ru_3(CO)_{12}$-catalyzed carbonylation of pyrazoles, which is described herein, occurs at the 3-position to give the 3-pyrazolyl ketone (Scheme 2). The difference in the site selectivity between the present reaction and the conventional Friedel−Crafts acylation strongly indicates that the present carbonylation does not proceed via electrophilic substitution. It has been reported that the stoichiometric reaction of N−H pyrazole with $Os_3(CO)_{11}(CH_3CN)$ gives the triosumium carbonyl complex, in which C−H bond cleavage occurs at the 3-position of the pyrazole ring.[15a,c] These acylation reactions are complementary to one another in the preparation of acyl-substituted pyrazoles.

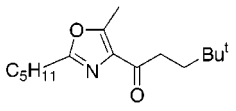
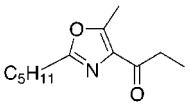
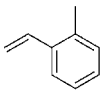
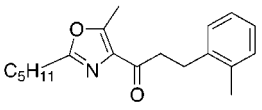
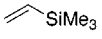
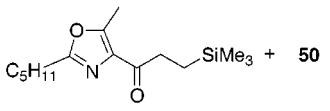
The reaction of oxazole derivative **48** with CO and olefin results in the cleavage of a C−H bond at the 4-position in the oxazole ring to give the corresponding oxazolyl ketones (Table 5). A few methods for the acylation of an oxazole ring have been reported, and they have a drawback in term of substrate limitation. For example, the 4-position of an oxazole can be acylated under Friedel−Crafts conditions only when the oxazole ring is activated by a 2-arylthio, 5-alkoxy group, or 2-amino group.[4a]

In the reaction of thiazole (**53**), the ketone **54**, in which carbonylation occurred at the 2-position, was obtained as a major product (50% yield), along with 4-thiazolyl ketone **55** in 14% yield (eq 3), similar to the reaction of 1-methylimidazole (**25**) shown in Table 2. It has been reported that the acylation of thiazole at the 2-position

Table 5. $Ru_3(CO)_{12}$-Catalyzed Reaction of Oxazole 48 with CO and Olefins

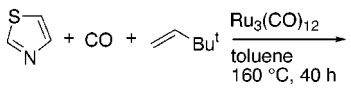


48 1 mmol 3 atm 4 mmol

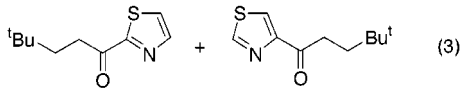
entry	olefin	product(s) [a]
1		 **49** 62% (>99:1)
2 [b]		 **50** 78%
3		 **51** 72% (91:9)
4		 **52** 81% (>99:1) 4%

[a] Isolated yields. The ratio of linear to branched isomers is in parentheses. [b] Ethylene (4 atm).

occurs during the reaction of thiazoles with ketene, or an acid halide.[4b]

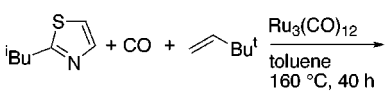


53 10 atm

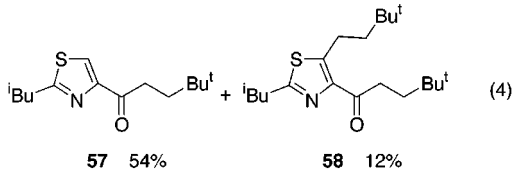


54 50% **55** 14% (3)

The substitution of an alkyl group at the 2-position of a thiazole would be expected to lead to the selective carbonylation at a C−H bond at the 4-position, as was the case for 2-substituted imidazoles and oxazoles, and this is true. The reaction of 2-isobutylthiazole (**56**) with CO (6 atm) and *tert*-butylethylene gave the expected product **57** in 54% yield, along with **58** in 12% yield (eq 4). It is noteworthy that product **58** arises via both



56 6 atm



57 54% **58** 12% (4)

carbonylation at a C−H bond and the addition of a C−H

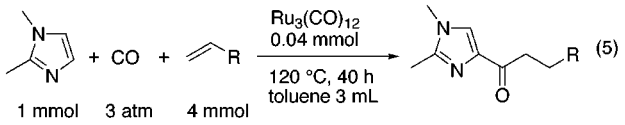
(16) Ethyl ketone was also obtained in the related direct carbonylation at a C−H bond in a benzene ring when trimethylvinylsilane was used as the olefin. See ref 8a,b,d.

(17) Marciniec, B.; Pietraszuk, C. *J. Organomet. Chem.* **1991**, *412*, C1. Seki, Y.; Takeshita, K.; Kawamoto, K. *J. Organotmet. Chem.* **1989**, *369*, 117. Wakatsuki, Y.; Yamazaki, H.; Nakano, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 703.

(18) Fusco, R. *The Chemistry of Heterocyclic Compounds*; Wiley, R. H., Ed.; Wiley: New York, 1967; Vol. 22, Chapter 5, p 121. Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347.

bond to olefins. Thus, the product **58** would be produced via the C−H/olefin coupling[19] of **57**. In fact, the reaction of **57** with *tert*-butylethylene under same reaction conditions gave **58** in 14% yield.

As mentioned above, carbonylation of pyrazole, oxazole, and thiazole proceeds smoothly, provided the reaction is carried out under lower CO pressure than that of imidazole. As a result, we reinvestigated the reaction conditions for the carbonylation of imidazole **4**, and the finding showed that the carbonylation of **4** takes place, even under mild conditions. The reaction of **4** with CO (3 atm) and *tert*-butylethylene at 120 °C for 40 h gave **3** in 80% yield (eq 5). Trimethylvinylsilane also underwent

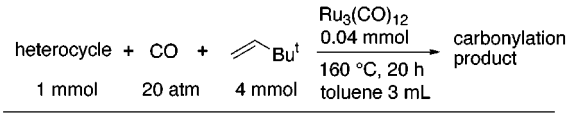


(5)

R = Bu^t	**6**	80% (>99:1)
R = $SiMe_3$	**7**	90% (>99:1)
R = Ph	**9**	75% (55:45)
R = 2-$CH_3C_6H_4$	**12**	76% (94:6)
R = Bu	**5**	15% (95:5)
R = CH_2SiMe_3	**8**	27% (95:5)

a coupling reaction to produce the corresponding ketone in high yield. The reaction with styrene gave a low linear-to-branched ratio, but in good yield. Again, the ratio was improved by use of *o*-methystyrene. The mild reaction conditions found here can be applied to only olefins which contain no hydrogen at the allylic position, such as *tert*-butylethylene, styrene, and vinylsilane. In fact, the reaction of 1-hexene and allylsilane gave the coupling products in only 15% and 27% yield, respectively.

Table 6. pK_a Values of Conjugate Acid of Heterocycles and Obtained Yields



yield [a]	88 %	8 %	5 %	trace	0 %
pK_a	7.85	3.37 [b]	2.91 [c]	2.09	- 2.97

[a] Isolated yield. [b] The p*K*a value of 2-ethylthiazole. [c] The p*K*a value of 2,4-dimethyloxazole.

It is noteworthy that carbonylation is sensitive to CO pressure. When the reactions of these heterocycles with *tert*-butylethylene were carried out under a pressure of 20 atm of CO at 160 °C for 20 h, only small amounts of carbonylation products were obtained (**42**; trace, **48**; 5%, **56**; 8%). In contrast, when the reaction was carried out under lower CO pressure (3−6 atm), good yields of the carbonylation product were obtained, as described above (**42**: 57%; **48**: 62%; **56**: total 66%). It is noteworthy that the reactivity of the five-membered heterocycles corresponds to the pK_a values of the conjugate acid of these heterocycles (**4**: (7.85) ≫ **56**: (3.37)[20] > **48**: (2.91)[21] > **42**: (2.09)), as shown in Table 6. This suggests that the pK_a values are related to the ability of the nitrogen to coordinate to a ruthenium center. Weakly basic heterocyclic compounds would coordinate with difficulty to the ruthenium center in a preequilibrium step under high CO pressure and, as a result, they show low reactivities relative to imidazole, which has a higher basicity. A similar trend between reactivity and pK_a was observed in the case of the $Ru_3(CO)_{12}$-catalyzed carbonylation at a C−H bond β to the sp^2 nitrogen.[7]

Conclusion

In summary, we report the development of a new method for the acylation of *N*-heteroaromatic compounds by the direct carbonylation at a C−H bond. Heteroaromatic compounds, such as imidazole, pyrazole, oxazole, and thiazole, could be carbonylated in good yields in the presence of catalytic amounts of $Ru_3(CO)_{12}$. These reactions involve the cleavage of a C−H bond, which is adjacent to sp^2 nitrogen atom in the heteroaromatic ring. Present direct carbonylation of heteroaromatic compounds constitutes a useful method for the preparation of acyl-substituted heterocycles from simple starting materials without the need for prefunctionalization.

Experimental Section

General Procedure. In a 50-mL stainless autoclave were placed $Ru_3(CO)_{12}$ (25.6 mg, 0.04 mmol), 1,2-dimethylimidazole (**4**) (1 mmol), olefin (4 mmol), and toluene (3 mL). The autoclave was charged with carbon monoxide to 20 atm at 25 °C and then heated in an oil bath at 160 °C for 20 h, followed by cooling and depressurization. The solvent was removed in vacuo, and the coupling product isolated by column chromatography on silica gel (Wako gel) with EtOAc or EtOAc/MeOH or hexane/EtOAc as eluent. An analytical sample was obtained by bulb-to-bulb distillation or recrystallization.

Products **2**, **5**, **6**, **7**, **8**, **9**, **12**, **13**, **18**, **20**, **29**, **33**, and **39** have already been reported in the preliminary report.[6]

4,4-Dimethyl-[2-(2-(4,4-dimethylpentanoylphenyl))]-1-methyl-1*H*-imidazol-4-yl]-1-pentanone (3). White solid; R_f = 0.10 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 9H), 0.92 (s, 9H), 1.45−1.53 (c, 2H), 1.58−1.66 (c), 2.60−2.68 (c, 2H), 2.88−2.97 (c, 2H), 3.50 (s, 3H), 7.44−7.50 (m, 1H), 7.54−7.62 (m, 2H), 7.65 (s, 1H), 7.74−77.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.06, 29.29, 29.87, 30.08, 34.00, 34.22, 36.89, 37.47, 37.59, 125.12, 128.23, 128.59, 129.92, 131.16, 131.52, 140.73, 141.15, 147.28, 197.07, 203.92; IR (KBr) 1675 cm^{-1}; MS, *m*/*z* (rel intensity) 382 (M^+, 1), 297 (100); HRMS calcd for $C_{24}H_{34}N_2O_2$ (M^+): 382.2620, found 382.2629.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-3-(4-methoxyphenyl)-1-propanone (*n*-10). Yellow oil; bp 220 °C (1 mmHg); R_f = 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.97 (t, J = 7.4 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H), 3.60 (s, 3H), 3.77 (s, 3H), 6.80 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.87, 29.08, 33.26, 40.45, 55.20, 113.68, 125.10, 129.34, 133.66, 139.87, 145.80, 157.74, 195.17; IR (neat) 1669 cm^{-1}; MS, *m*/*z* (rel intensity) 258 (M^+, 10), 96 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.51; H, 7.03; N, 10.81.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-2-(4-methoxyphenyl)-1-propanone (*i*-10). Yellow oil; bp 220 °C (1 mmHg); R_f = 0.14 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 7.3 Hz, 3H, CH_3-CH), 2.38 (s, 3H, 2-CH_3), 3.55 (s, 3H), 3.75 (s, 3H), 4.77 (q, J = 7.0 Hz, 1H), 6.81 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.92, 18.31, 33.23, 45.97,

(19) For a recent paper on the catalytic reaction involving addition of a C−H bond to olefins, see: Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083 and references therein.

(20) This pK_a value is that of 2-ethylthiazole.

(21) This pK_a value is that of 2,4-dimethyloxazole.

55.15), 113.86, 126.04, 129.09, 133.73, 139.21, 145.71, 158.27, 196.26; IR (neat) 1670 cm^{-1}; MS, *m/z* (rel intensity) 258 (M^+, 15), 123 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.61; H, 7.08; N, 10.85.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-3-(4-(trifluoromethyl)phenyl)-1-propanone (*n*-11). White solid; mp 107 °C (1 mmHg); R_f = 0.11 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.09 (t, J = 7.4 Hz, 2H), 3.28 (t, J = 7.4 Hz, 2H), 3.61 (s, 3H), 7.36 (d, J = 7.9 Hz, 2H), 7.48 (s, 1H), 7.51 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.87, 29.60, 33.30, 39.57, 124.33 (q, J = 271.8 Hz), 125.13 (q, J = 4.9 Hz), 128.13 (q, J = 32.4 Hz), 128.82, 139.73, 145.80, 145.84, 194.5; IR (KBr) 1670 cm^{-1}; MS, *m/z* (rel intensity) 296 (M^+, 5), 96 (100). Anal. Calcd for $C_{15}H_{15}N_2OF_3$: C, 60.81; H, 5.10; N, 9.45. Found: C, 60.81; H, 5.09; N, 9.32.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-2-(4-(trifluoromethyl)phenyl)-1-propanone (*i*-11). Yellow oil; bp 200 °C (1 mmHg); R_f = 0.23 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 6.9 Hz, 3H), 2.39 (s, 3H), 3.57 (s, 3H), 4.97 (q, J = 7.1 Hz, 1H), 7.47 (s, 1H), 7.52 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 12.85, 18.06, 33.26, 46.42, 124.22 (q, J = 273.8 Hz), 125.22 (q, J = 3.7 Hz), 128.52, 128.69 (q, J = 31.3 Hz), 138.94, 145.57, 145.86, 195.42; IR (neat) 1668 cm^{-1}; MS, *m/z* (rel intensity) 296 (M^+, 2), 123 (100). Anal. Calcd for $C_{15}H_{15}N_2OF_3$: C, 60.81; H, 5.10; N, 9.45. Found: C, 60.80; H, 5.21; N, 9.27.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-4-(1-(methoxycarbonyl)cyclohexyl)-1-butanone (14). Colorless oil; bp 200 °C/0.1 mmHg; R_f = 0.08 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.1−1.8 (m, 12 H), 2.0−2.2 (m), 2.39 (s, 3H), 2.85 (t, J = 6.6 Hz, 2H), 3.60 (s, 3H), 3.66 (s, 3H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.67, 18.74, 22.99, 25.70, 33.10, 33.78, 38.56, 39.76, 46.79, 51.14, 125.87, 139.75, 145.61, 176.98, 195. 43; IR (neat) 1725, 1666 cm^{-1}; MS, *m/z* (rel intensity) 306 (M^+, 2), 128 (100); Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N,9.14. Found C, 66.78; H, 8.66; N, 9.41.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-4-(dimethyl-1,1-dimethylethylsiloxy)-1-butanone (15). Colorless oil; bp 220 °C/0.5 mmHg; R_f = 0.1 (hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.92 (tt, J = 6.6, 7.1 Hz), 2.40 (s, 3H), 2.95 (t, J = 7.1 Hz, 2H), 3.61 (s, 3H), 3.68 (t, J = 6.6 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.44, 12.78, 18.17, 25.82, 27.33, 33.19, 34.86, 62.45, 125.05, 139.82, 145.75, 195.61; IR (neat) 1669 cm^{-1}; MS, *m/z* (rel intensity) 296 (M^+, 1), 239 (100); Anal. Calcd for $C_{15}H_{28}N_2O_2Si$: C, 60.77; H, 9.52; N, 9.45. Found C, 61.03; H, 9.90; N, 9.50.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-7-(dimethyl-1,1-dimethylethylsiloxy)-1-heptanone (17). Colorless oil; bp 175 °C/0.7 mmHg; R_f = 0.2 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.28−1.80 (m, 8H), 2.40 (s, 3H), 2.89 (t, J = 7.6 Hz, 2H), 3.58 (t, J = 6.5 Hz, 2H), 3.60 (s, 3H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.35, 12.87, 18.27, 24.21, 25.63, 25.90, 29.09, 32.67, 33.25, 38.58, 63.18, 124.92, 140.02, 145.70, 196.30; IR (neat) 1672 cm^{-1}; MS, *m/z* (rel intensity) 323 (M^+-15, 1), 281 (100). Anal. Calcd for $C_{18}H_{34}N_2O_2Si$: C, 63.86; H, 10.13; N, 8.28. Found C, 63.78; H, 9.99; N, 8.25.

2-Butoxy-1-(1,2-dimethyl-1*H*-imidazol-4-yl)-1-propanone (21). White solid; mp 51−54 °C; R_f = 0.14 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.29−1.42 (m, 2H), 1.45 (d, J = 6.8 Hz, 3H), 1.54−1.64 (m, 2H), 2.42 (s, 3H), 3.40 (dt, J = 9.2, 6.5 Hz, 1H), 3.53 (dt, J = 9.2, 6.5 Hz, 1H), 3.64 (s, 3H), 4.62 (q, J = 6.8 Hz, 1H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.80, 13.75, 19.10, 19.23, 31.83, 33.25, 69.69, 78.92, 127.15, 136.86, 146.11, 196.10; IR (KBr) 1673 cm^{-1}; MS, *m/z* (rel intensity) 224 (M^+, 3), 123 (100). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found C, 63.94; H, 8.94; N, 12.49.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-1-propanone (22). White solid; mp 71−74 °C; R_f = 0.08 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 2.89 (q, J = 7.2 Hz, 2H), 3.58 (s, 3H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 8.14, 12.85, 31.79, 33.23, 124.80, 139.82, 145.66, 196.76; IR (KBr) 1669 cm^{-1}; MS, *m/z* (rel intensity) 152 (M^+, 18), 123 (100); HRMS calcd for $C_8H_{12}N_2O$ (M^+): 152.0950, found 152.0956.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-5-phthalimido-1-pentanone (23). Colorless oil; R_f = 0.10 (EtOAc/MeOH = 40/1); ^{1}H NMR ($CDCl_3$) δ 1.62−1.82 (m, 4H), 2.38 (s, 3H), 2.85−3.00 (m, 2H), 3.60 (s, 3H), 3.63−3.75 (m), 7.47 (s, 1H), 7.60−7.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.21, 21.40, 28.05, 33.25, 37.65, 37.89, 123.02, 125.14, 132.02, 133.73, 139.73, 145.77, 168.27, 195.43; IR (neat) 1671 cm^{-1}; MS, *m/z* (rel intensity) 325 (M^+, 18), 123 (100); HRMS calcd for $C_{18}H_{19}N_3O_3$ (M^+): 325.1427, found 325.1429.

(24). Colorless oil; R_f = 0.11 (EtOAc/MeOH = 30/1); ^{1}H NMR ($CDCl_3$) δ 1.45−1.73 (m, 2H), 1.75−2.10 (m, 14H), 2.40 (s, 3H), 2.88−3.08 (m), 3.62 (s, 3H), 3.85−3.97 (m, 1H), 4.00−4.29 (m, 3H), 4.98 (t, J = 9.2 Hz, 1H,), 5.07 (dd, J = 9.5, 6.0 Hz, 1H), 5.27 (t, J = 9.2 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.92, 19.23, 20.54, 20.61, 24.57, 33.28, 37.49, 62.16, 68.34, 68.72, 70.32, 70.46, 72.45, 124.96, 139.75, 145.80, 169.49, 169.58, 70.04, 170.66, 195.29; IR (neat) 1748, 1668 cm^{-1}; MS, *m/z* (rel intensity) 496 (M^+, 6), 138 (100), 123 (87); HRMS calcd for $C_{23}H_{32}N_{10}O_2$ (M^+): 496.2057, found 496.2050.

1-(1,2-Dimethyl-1*H*-imidazol-4-yl)-2-(bicyclo[2.2.1]hept-2-yl)methanone (19). Spectral data were obtained from a mixture of exo and endo ketone (major isomer not determined). White solid; mp 75 °C (1 mmHg); R_f = 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.09−1.13 (c, 1H), 1.26−1.34 (c, 1H), 1.34−1.59 (c, 5H), 1.88−1.95 (c, 1H), 2.30 (c, 1H), 2.41 (s, 3H, 2-CH_3), 2.47 (c, 1H), 2.76 (c, 1H), [3.25 (dd, J = 5.6, 3.3 Hz, 1H, major), 3.71 (m, 1H, minor)], 3.61 (s, 3H), [7.46 (s, 1H, 5-H, major), 7.48 (s, 1H, 5-H, minor)]; ^{13}C NMR ($CDCl_3$) δ 12.78, 24.17, [28.77 (major), 28.99 (minor)], [29.62 (major), 29.90 (minor)], [33.14 (minor), 33.26 (major)], [36.07 (major), 37.23 (minor)], [40.94 (major), 41.78 (minor)], [49.15 (major), 49.44 (minor)], [124.96 (minor), 125.36 (major)], [139.44 (major), 140.34 (minor)], 145.70, [196.76 (minor), 197.21 (major)]; IR (KBr) 1664 cm^{-1}; MS, *m/z* (rel intensity) 218 (M^+, 14), 123 (100). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.29; H, 8.29; N, 12.65.

1-(1-Methyl-1*H*-imidazol-2-yl)-4,4-dimethyl-1-pentanone (26). Colorless oil; R_f = 0.26 (hexane/EtOAc = 3/1); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9H), 1.56 (c, 2H), 3.10 (c, 2H), 3.99 (s, 3H), 7.10 (s, 1H), 7.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.17, 30.07, 34.67, 36.16, 37.54, 126.71, 128.79, 143.05, 193.75; IR (neat) 1677 cm^{-1}; MS, *m/z* (rel intensity) 194 (M^+, 1), 82 (100); HRMS calcd for $C_{11}H_{18}N_2O$ (M^+): 194.1419, found 194.1420.

6-Ethylenedioxolane-1-(1-(methoxymethyl)-2-methyl-1*H*-imidazol-4-yl)-1-heptanone (30). White solid; R_f = 0.20 (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.47−1.81 (m, 6H), 2.47 (s, 3H), 2.94 (t, J = 7.3 Hz, 2H), 3.30 (s, 3H), 3.91 (s, 4H), 5.19 (s, 2H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.72, 23.51, 23.58, 24.06, 38.51, 38.74, 55.99, 64.31, 77.14, 109.76, 124.08, 139.91, 145.89, 195.94; IR (neat) 1672 cm^{-1}; MS, *m/z* (rel intensity) 296 (M^+, 22), 87 (100); HRMS calcd for $C_{15}H_{24}N_2O_4$ (M^+): 296.1736, found 296.1735.

4,4-Dimethyl-1-(2-methyl-1-phenylmethyl-1*H*-imidazol-4-yl)-1-pentanone (32). Colorless oil; bp 230 °C/1 mmHg; R_f = 0.31 (hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9H), 1.58−1.65 (c, 2H), 2.38 (s, 3H), 2.88−2.95 (c, 2H), 7.07−7.11 (m, 2H), 7.34−7.37 (m, 3H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.25, 29.22, 30.08, 34.25, 37.56, 50.33, 124.38, 126.84, 128.36, 129.11, 135.02, 140.38, 145.64, 196.87; IR (neat) 1667 cm^{-1}; MS, *m/z* (rel intensity) 284 (M^+, 2), 91 (100). Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found C, 76.04; H, 8.57; N, 9.99.

4,4-Dimethyl-1-(imidazo[1,2-*a*]pyridin-2-yl)-1-pentanone (35). White solid; mp 85−87 °C; R_f = 0.26 (hexane/EtOAc = 2/1); ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H), 1.64−1.73 (c, 2H), 3.10−3.19 (c, 2H), 6.86 (t, J = 8.2 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.67 (t, J = 9.2 Hz, 1H), 8.14 (s, 1H), 8.17 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.15, 30.03, 34.79, 37.29, 113.77, 114.57, 118.89, 125.82, 126.33, 144.08, 144.82, 198.51; IR (KBr) 1679, 1639 cm^{-1}; MS, *m/z* (rel intensity) 230 (M^+, 7), 173 (100). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 73.04; H, 7.76; N, 12.16.

4,4-Dimethyl-1-(imidazo[1,2-*a*]pyridin-8-yl)-1-pentanone (36). White solid; mp 52−54 °C; R_f = 0.26 (hexane/EtOAc = 2/1); ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H), 1.62−1.73 (c, 2H), 3.46−3.60 (c, 2H), 6.88 (t, J = 7.0 Hz, 1H), 7.68 (s, 1H), 7.72 (s, 1H), 7.79 (dd, J = 7.0, 1.2 Hz, 1H), 8.30 (dd, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.24, 30.14, 37.63, 38.91, 113.77, 111.48,

112.83, 126.54, 127.39, 129.15, 133.75, 143.18; IR (KBr) 1668, 1622 cm^{-1}; MS, *m/z* (rel intensity) 230 (M^+, 4), 173 (100); Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 73.27; H, 7.95; N, 11.85.

6-Ethylenedioxolane-1-(5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-2-yl)-1-heptanone (38). Colorless oil; R_f = 0.10 (EtOAc); ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.38−2.10 (m, 10H), 2.82−2.99 (m, 4H), 3.83−3.95 (m, 4H), 4.00 (t, J = 5.4 Hz, 2H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.54, 22.46, 23.40, 23.52, 24.12, 24.26, 38.32, 38.62, 45.03, 64.22, 109.65, 122.41, 140.25, 145.27, 195.88; IR (neat) 1665 cm^{-1}; MS, *m/z* (rel intensity) 292 (M^+, 9), 87 (100). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found C, 65.73; H, 8.26; N, 9.63.

4,4-Dimethyl-1-(1-methyl-1*H*-pyrazol-3-yl)-1-pentanone (43). Colorless oil; bp 130 °C/1.0 mmHg; R_f = 0.20 (hexane/EtOAc = 4/1); ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.57−1.68 (c, 2H), 2.92−3.00 (c, 2H), 3.97 (s, 3H), 6.77 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.22, 30.17, 34.45, 37.74, 39.48, 106.90, 131.54, 151.24, 196.78; IR (KBr) 1680 cm^{-1}; MS, *m/z* (rel intensity) 194 (M^+, 1), 109 (100); Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found C, 68.02; H, 9.48; N, 14.61.

1-(1-Methyl-1*H*-pyrazol-3-yl)-1-propanone (44). Colorless oil; bp 90 °C/1.0 mmHg; R_f = 0.13 (hexane/EtOAc = 3/1); ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.3 Hz, 3H), 21.95 (t, q, J = 7.3 Hz, 2H), 3.91 (s, 3H), 6.71 (d, J = 2.3 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.98, 31.84, 39.36, 106.67, 131.50, 150.85, 196.57; IR (neat) 1680 cm^{-1}; MS, *m/z* (rel intensity) 138 (M^+, 14), 109 (100). Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found C, 60.55; H, 7.18; N, 20.19.

1-(1-Methyl-1*H*-pyrazol-3-yl)-3-(2-methylphenyl)-1-propanone (*n*-45). Colorless oil; bp 180 °C/0.9 mmHg; R_f = 0.18 (hexane/EtOAc = 3/1); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.97−3.08 (c, 2H), 3.22−3.32 (c, 2H), 3.92 (s, 3H), 6.77 (d, J = 2.0 Hz, 1H), 7.05−7.25 (m, 5H, 5-C,); ^{13}C NMR ($CDCl_3$) δ 19.21, 27.33, 39.09, 106.78, 125.88, 126.00, 128.61, 130.03, 131.55, 135 92, 139.46, 150.82, 195.06; IR (neat) 1681 cm^{-1}; MS, *m/z* (rel intensity) 228 (M^+, 6), 210 (100). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found C, 73.64; H, 7.09; N, 12.32.

1-(1-Methyl-1*H*-pyrazol-3-yl)-2-(2-methylphenyl)-1-propanone (*i*-45). Colorless oil; bp 130 °C/1.0 mmHg; R_f = 0.20 (hexane/EtOAc = 3/1); ^1H NMR ($CDCl_3$) δ 1.46 (d, J = 6.9 Hz, 3H, C*H*$_3$CH), 2.52 (s, 3H, C*H*$_3$C$_6$H$_4$), 3.89 (s, 3H, CH$_3$N), 5.08 (q, J = 6.9 Hz, 1H, C*H*CH$_3$), 6.60 (d, J = 2.3 Hz, 1H, 4-H), 7.03−7.31 (m, 5H, 5-H, C$_6$H$_4$); MS, *m/z* (rel intensity) 228 (M^+, 4), 210 (23), 200 (20), 119 (19), 109 (100); HRMS calcd for $C_{14}H_{16}N_2O$ (M^+): 228.1263, found 228.1251.

1-(1-Methyl-1*H*-pyrazol-3-yl)-3-trimethylsilyl-1-propanone (46). Colorless oil; bp 120 °C/0.7 mmHg; R_f = 0.19 (hexane/EtOAc = 4/1); ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.84−0.94, 2.90−3.01, 3.97 (s, 3H), 6.77 (d, J = 2.3 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.83, 10.41, 33.08, 39.39, 106.85, 131.48, 150.84, 196.98; IR (neat) 1686 cm^{-1}; MS, *m/z* (rel intensity) 195 (M^+ − 15, 48), 73 (100). Anal. Calcd for $C_{10}H_{18}N_2OSi$: C, 57.10; H, 8.63; N, 13.32. Found C, 57.15; H, 8.38; N, 13.37.

4,4-Dimethyl-1-(5-methyl-2-pentyloxazol-4-yl)-1-pentanone (49). Colorless oil; bp 120 °C/0.9 mmHg; R_f = 0.06 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.86−0.94 (m, 3H), 0.93 (s, 9H), 1.28−1.42 (m, 4H), 1.52−1.62 (c, 2H), 1.68−1.82 (m, 2H), 2.57 (s, 3H), 2.72 (t, J = 8.1 Hz, 2H), 2.84−2.93 (c, 2H); ^{13}C NMR ($CDCl_3$) δ 12.06, 13.80, 22.16, 26.60, 27.85, 29.15, 29.99, 31.16, 35.55, 37.14, 134.16, 153.80, 161.83, 197.90; IR (neat) 1687 cm^{-1}; MS, *m/z* (rel intensity) 265 (M^+, 14), 205 (100). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found C, 72.45; H, 10.26; N, 5.46.

1-(5-Methyl-2-pentyloxazol-4-yl)-1-propanone (50). Colorless oil; bp 80 °C/0.8 mmHg; R_f = 0.14 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.87−0.97 (m, 3H), 1.15 (t, J = 7.3 Hz, 3H), 1.30−1.43 (m, 4H), 1.67−1.84 (m, 2H), 2.59 (s, 3H), 2.72 (t, J = 7.8 Hz, 2H), 2.94 (q, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 7.50, 12.02, 13.79, 22.14, 16.63, 27.85, 31.16, 33.17, 133.94, 153.75, 161.92, 197.79; IR (neat) 1688 cm^{-1}; MS, *m/z* (rel intensity) 209 (M^+, 31), 153 (100). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found C, 68.74; H, 9.11; N,6.79.

1-(5-Methyl-2-pentyloxazol-4-yl)-3-(2-methylphenyl)-1-propanone (51). Colorless oil; bp 150 °C/0.9 mmHg; R_f = 0.14 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.88−0.94 (m, 3H), 1.32−1.39 (m, 4H), 1.65−1.80 (m, 2H), 2.36 (s, 3H), 2.66 (s, 3H), 2.71 (t, J = 7.8 Hz, 2H), 2.93−3.02 (c, 3H), 3.16−3.25 (c, 2H), 7.10−7.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 12.11, 13.84, 119.27, 22.18, 26.58, 26.97, 27.85, 31.18, 40.38, 125.91, 126.02, 128.68, 130.08, 133.98, 136.01, 139.41, 154.11, 161.99, 196.39; IR (neat) 1685 cm^{-1}; MS, *m/z* (rel intensity) 299 (M^+, 6), 105 (100). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8. 42; N, 4.68. Found C, 76.24; H, 8.36; N,4.70.

1-(5-Methyl-2-pentyloxazol-4-yl)-3-trimethylsilyl-1-propanone (52). Colorless oil; bp 90 °C/0.9 mmHg; R_f = 0.17 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.02 (s, 9H), 0.79−0.97 (m, 5H), 1.28−1.43 (m, 4H), 1.66−1.82 (m, 2H), 2.57 (s, 3H), 2.71 (t, J = 8.0 Hz), 2.83−2.92 (c, 2H); ^{13}C NMR ($CDCl_3$) δ −1.85, 9.83, 12.01, 13.79, 22.14, 26.60, 27.84, 31.16, 34.31, 133.87, 153.73, 161.83, 198.09; IR (neat) 1688 cm^{-1}; MS, *m/z* (rel intensity) 281 (M^+, 3), 73 (100). Anal. Calcd for $C_{15}H_{27}NO_2Si$: C, 64.01; H, 9.67; N,4.98. Found C, 64.09; H, 9.86; N, 5.03.

4,4-Dimethyl-1-(thiazol-2-yl)-1-pentanone (54). Colorless oil; bp 42−43 °C; R_f = 0.14 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.96 (s, 9H), 1.60−1.72 (c, 2H), 3.08−3.20 (c, 2H), 7.66 (d, J = 3.1 Hz, 1H), 8.00 (d, J = 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.13, 30.17, 34.27, 37.47, 126.00, 144.58, 167.33, 194.50; IR (neat) 1692 cm^{-1}; MS, *m/z* (rel intensity) 197 (M^+, 3), 112 (100). Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found C, 60.69; H, 7.52; N, 7.22.

4,4-Dimethyl-1-(thiazol-4-yl)-1-pentanone (55). R_f = 0.03 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.96 (s, 9H), 1.60−1.70 (c, 2H), 3.06−3.16 (c, 2H), 8.20 (d, J = 2.1 Hz, 1H), 8.83 (d, J = 2.1 Hz, 1H); MS, *m/z* (rel intensity) 197 (M^+, 23), 140 (100); HRMS calcd for $C_{10}H_{15}NOS$ (M^+): 197.0874, found 197.0865.

1-[2-(2-Methylpropyl)thiazol-4-yl]-4,4-dimethyl-1-pentanone (57). White solid; mp 42−43 °C; R_f = 0.26 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.02 (d, J = 6.5 Hz, 6H), 1.59−1.67 (c, 2H), 2.05−2.25 (m, 1H), 2.91 (d, J = 7.3 Hz, 2H), 2.99−3.07 (c, 2H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.16, 29.17, 29.54, 30.14, 35.96, 37.72, 42.21, 124.42, 154.63, 170.15, 196.15; IR (KBr) 1679 cm^{-1}; MS, *m/z* (rel intensity) 253 (M^+, 3), 57 (100). Anal. Calcd for $C_{14}H_{23}NOS$: C, 66.36; H, 9.15; N, 5.53. Found C, 66.28; H, 9.17; N, 5.37.

1-[5-(3,3-Dimethylbutyl-2-(2-methylpropyl)thiazol-4-yl]-4,4-dimethyl-1-pentanone (58). Colorless oil; bp 170 °C/1.0 mmHg; R_f = 0.14 (hexane/EtOAc = 20/1); ^1H NMR ($CDCl_3$) δ 0.93 (s, 9H), 0.96 (s, 9H), 1.00 (d, J = 6.8 Hz, 6H), 1.49−1.56 (c, 2H), 1.54−1.63 (c, 2H), 2.00−2.18 (m, 1H), 2.79 (d, J = 7.3 Hz, 2H), 2.99−3.07 (c, 2H), 3.11−3.19 (c, 2H); ^{13}C NMR ($CDCl_3$) δ 22.27, 23.31, 29.15, 29.26, 29.45, 30.19, 30.73, 37.32, 37.94, 42.16, 45.81, 147.17, 149.99, 164.69, 198.67; IR (neat) 1679 cm^{-1}; MS, *m/z* (rel intensity) 337 (M^+, 5), 280 (100). Anal. Calcd for $C_{20}H_{35}NOS$: C, 71.16; H, 10.45; N, 4.15. Found C, 71.17; H, 10.58; N, 4.25.

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Supporting Information Available: Full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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