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$Ru_3(CO)_{12}$-Catalyzed C−H/CO/Olefin Coupling of *N*-Pyridylindolines. Direct Carbonylation at a C−H Bond δ to the Pyridine Nitrogen

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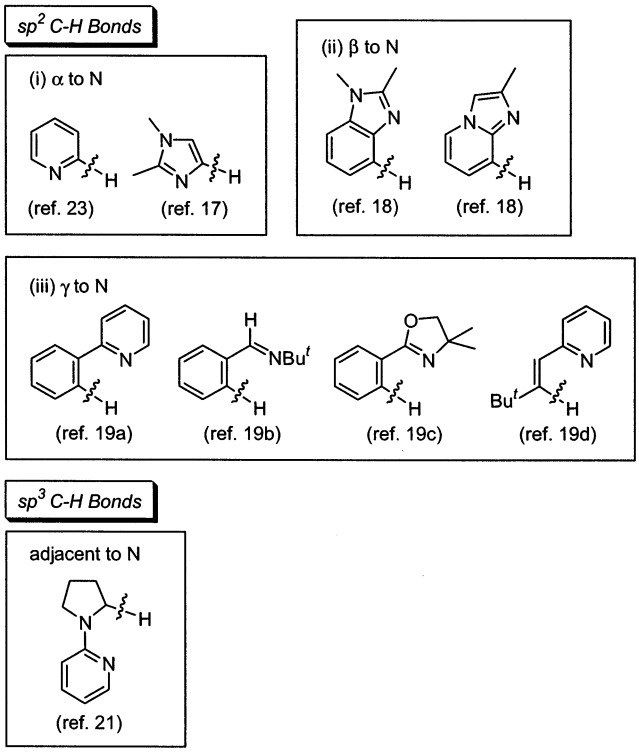
Abstract: The reaction of *N*-pyridylindolines with CO and ethylene in the presence of $Ru_3(CO)_{12}$ results in direct carbonylation at a C−H bond δ to the pyridine sp^2 nitrogen, which represents a new type of C−H/CO/olefin coupling. The presence of a pyridine ring as a directing group on the substrates is essential for the reaction to proceed. The choice of *N*,*N*-dimethylacetamide (DMA) as the solvent is crucial for the reaction to proceed efficiently.

Catalytic reactions, in which C−H bonds are directly converted to C−C bonds, represent a useful methodology in organic synthesis, because transforming C−H bonds into C−X bonds (X = Br, OTf, etc.) prior to the formation of C−C bonds is not necessary.[1,2] Since our report on the Ru-catalyzed addition of the ortho C−H bond in acetophenones across alkenes in 1993,[3] related transformations involving the cleavage of C−H bonds have also been reported by our group[4] as well as by a number of other research groups.[5−16] We previously reported on three types of catalytic reactions which involve C−H bond cleavage; (i) C−H/olefin coupling,[3,4] (ii) C−H/CO/olefin coupling,[17−21] and (iii) C−H/SiR_3 coupling.[22] C−H/CO/olefin coupling can be classified into four types, depending on the position where the cleavage of C−H bonds takes place: (i) sp^2 C−H bonds α to an sp^2 nitrogen,[17,23,24] (ii) sp^2 C−H bonds β to an sp^2 nitrogen,[18] (iii) sp^2 C−H bonds γ to an sp^2 nitrogen,[19,20,24] and (iv) sp^3 C−H bonds adjacent to an amine nitrogen[21] (Chart 1). All substrates applicable to direct carbonylation involve the presence of an sp^2-hybridized nitrogen. The coordination of the sp^2 nitrogen to the catalyst is responsible for both the high efficiency and regioselectivity of these reactions.

CHART 1. Site-Selective Direct Carbonylation at C−H Bonds



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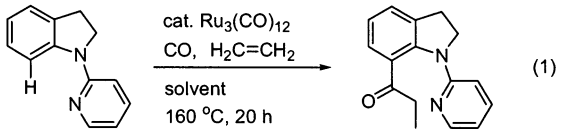
In an attempt to extend the scope of C−H/CO/olefin coupling reactions, various types of substrates were examined. In the course of these investigations, we discovered a new type of direct carbonylation, in which the C−H bond δ to the sp^2 nitrogen is cleaved.

The reaction of 1-(2-pyridinyl)-2,3-dihydro-1*H*-indole (**1a**) (1 mmol) with CO (initial pressure 10 atm at 25 °C) and ethylene (initial pressure 5 atm at 25 °C) in toluene (3 mL) in the presence of $Ru_3(CO)_{12}$ (0.05 mmol) at 160 °C for 20 h gave 1-[1-(2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (**2a**) in 6% isolated yield (eq 1), along with 75% of **1a** being recovered.[25] As a result of screening of the solvents used in the reaction, it was found that the efficiency of the reaction is sensitive to the nature of solvents. The use of *N*,*N*-dimethylacetamide (DMA), which is the best of all the solvents examined, improved the product yield to 41%, with 39% of **1a** being recovered (eq 1). Though additional and extensive surveys on the reaction conditions; e.g., the pressures of CO and ethylene, reaction temperatures and additives, were undertaken, the yields were not dramatically improved. A prolonged reaction time (40 h) slightly improved the product yield to a 50% yield, even under these conditions, **1a** was not completely consumed (42% recovery).



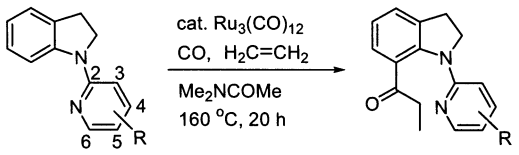
(1)

toluene	6%
THF	4%
dioxane	trace
^{i}PrOH	6%
CH_3CN	25%
N,*N*-dimethylacetamide	41%

We have already observed the dramatic electronic effects of a directing group on the efficiency of direct carbonylation at C−H bonds, suggesting that the coordination of the sp^2 nitrogen to the catalyst is extremely important in order for the reaction to proceed.[17b,21,26] The nature of these substituents on the pyridine ring have a significant effect on the product yield, as shown in Table 1.

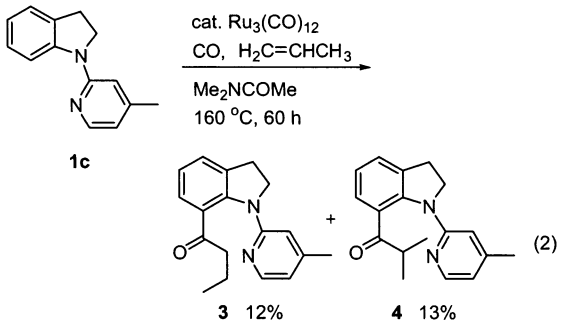
The presence of a methyl group at the 4-position on the pyridine ring, as in **1b**, resulted in an increase in the yields of product. The use of the 5-methyl isomer, as in **1c**, resulted in lower yields, although the reasons for this are presently not clear. Substitution at the 6-position, as in **1d**, led to no reaction, due to steric hindrance around the pyridine nitrogen. The replacement of a pyridine ring with a phenyl group failed to give a coupling product, and the starting material was recovered. These results indicate that the coordination of the pyridine nitrogen to the ruthenium is important for the carbonylation to proceed.

TABLE 1. Substituent Effects



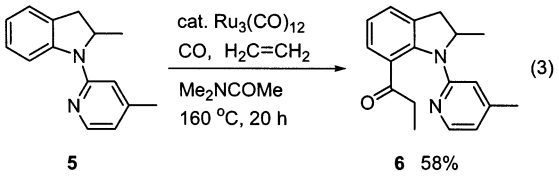
entry	R	**2**,[b] %	recovery of **1**,[c] %
1	H(**1a**)	41	39
2[d]		50	42
3	4-Me (**1b**)	65	32
4	5-Me (**1c**)	27	70
5	6-Me (**1d**)	trace	nd[e]

[a] Reaction conditions: **1** (1 mmol), $Ru_3(CO)_{12}$ (0.05 mmol), CO (initial pressure 10 atm at 25 °C in 50-mL stainless autoclave), ethylene (5 atm), *N*,*N*-dimethylacetamide (3 mL) at 160 °C for 20 h. [b] Isolated yields based on **1**. [c] Isolated yields of the unreacted **1**. [d] For a reaction time of 40 h. [e] **1d** was recovered, but the amount was not determined.



(2)

Several other olefins were examined as coupling partners. The reaction of **1c** with propylene gave a mixture of linear and branched propyl ketones, albeit in low yields (eq 2). The reaction with hexene gave no carbonylation product. The similar narrow scope with respect to olefins was also encountered in carbonylation at C−H bonds γ to the sp^2 nitrogen.[19,21]



(3)

We next examined the nature of the substrates. The reaction of **5** with CO and ethylene gave the expected product **6** in moderate yield (eq 3). It was found that the present reaction is unique to *N*-pyridylindolines. Thus, even a slight change of the structure of the substrates has a serious effect on their reactivity (Chart 2). Changing a five-member to a six-member, as in **7**, led to no reaction. Acyclic amines **8** and **9** also failed to react. Aromatization of the indoline ring to an indole ring, as in **10**, prevented this reaction from proceeding, although **5** functioned as a substrate. *N*-Acetylindoline **11** and pyridylanthracene **12** were also not applicable to this carbonylation reaction. The reason for the narrow scope of this reaction is not clear at present.

(25) All new compounds were characterized by NMR, IR, mass spectral data, and by elemental analyses or high-resolution mass spectra. See Supporting Information.

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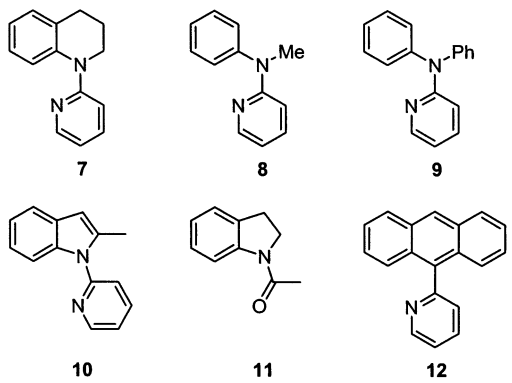
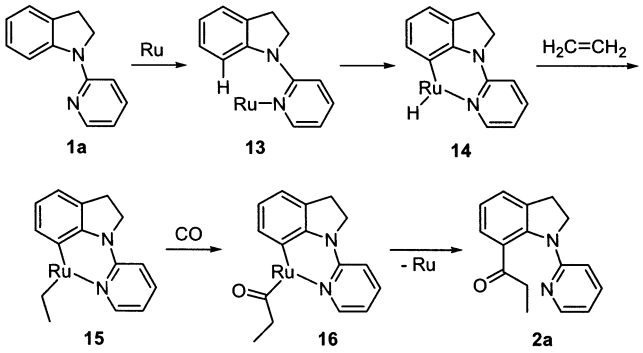
CHART 2. Substrates Not Applicable for the Present Carbonylation



SCHEME 1. A Proposed Reaction Mechanism



A proposed reaction mechanism is shown in Scheme 1. The mechanism of the present carbonylation is proposed to be similar to that previously reported.[19,21] The coordination of the pyridine nitrogen of **1a** to the Ru catalyst provides complex **13**, in which the C−H bond δ to the pyridine nitrogen is selectively cleaved to form the six-membered metallacycle **14**. The insertion of ethylene into the H−Ru bond in **14** gives the ethyl Ru complex **15**. The insertion of CO into the ethyl−Ru bond provides an acyl Ru intermediate **16**, from which reductive elimination gives the final product **2a**, regenerating the active Ru species.

In summary, we demonstrated that direct carbonylation at a C−H bond δ to the pyridine nitrogen can be achieved, which represents a new type of C−H/CO/olefin coupling. The presence of a pyridine ring on the substrates is essential for this reaction to proceed. The choice of *N*,*N*-dimethylacetamide (DMA) as the solvent is crucial for the reaction to proceed efficiently. While the available substrates are extremely limited, this reaction demonstrates that the methodology, in which directing groups promotes the site-selective cleavage of C−H bonds, is effective in exploring new types of carbonylation at C−H bonds. Further studies on other related carbonylation reactions are currently under investigation.

Experimental Section

Materials. $Ru_3(CO)_{12}$ was prepared according to the literature procedure[27] and used, after recrystallization from hexane. Pyridylindolines **1a**,[26] **1b**, **1c**, **1d**, and **5** were obtained by Pd-catalyzed amination procedure reported by Buchwald.[28]

Typical Procedure for Carbonylation. A 50-mL stainless autoclave was charged with 1-(2-pyridinyl)-2,3-dihydro-1*H*-indole (**1a**) (1 mmol, 196 mg), *N*,*N*-dimethylacetamide (3 mL), and $Ru_3(CO)_{12}$ (0.05 mmol, 32 mg). After the system was flushed with 10 atm of ethylene three times, it was pressurized with ethylene to 5 atm and then with carbon monoxide to an additional 10 atm. The autoclave was then immersed in an oil bath at 160 °C. After 20 h had elapsed, it was removed from the oil bath and allowed to cool for ca. 1 h. The gases were then released. The contents were transferred to a round-bottomed flask with toluene, and the volatiles were removed in vacuo. The residue was subjected to column chromatography on silica gel (eluent; hexane/Et_2O = 5/1) to give 1-[1-(2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (**2a**) (103 mg, 41% yield) as a pale yellow solid. Purification by HPLC afforded the analytically pure product.

1-[1-(2-Pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (2a). Pale yellow solid; mp 133−135 °C; R_f 0.029 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 2.66 (q, J = 7.3 Hz, 2H), 3.23 (t, J = 8.6 Hz, 2H), 4.17 (t, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 1H), 6.79 (dd, J = 7.3 Hz, 6.9 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 6.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.57 (td, J = 7.8 Hz, 1.8 Hz, 1H), 8.12 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.09, 28.08, 34.27, 51.25, 109.77, 115.73, 121.22, 125.47, 126.20, 127.73, 132.50, 137.60, 140.42, 145.55, 154.79, 198.79; IR (KBr) 1691; MS, *m*/*z* (relative intensity, %) 252 (M^+, 5.4), 223 (100). HRMS Calcd for $C_{16}H_{16}N_2O$: 252.1263. Found: 252.1262.

1-[1-(4-Methyl-2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (2b). Pale yellow solid; mp 138−139 °C; R_f 0.029 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 2.30 (s, 3H), 2.67 (q, J = 7.3 Hz, 2H), 3.21 (t, J = 8.2 Hz, 2H), 4.17 (t, J = 8.2 Hz, 2H), 6.50 (s, 1H), 6.61 (d, J = 4.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 7.23−7.30 (c, 2H), 7.93 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.33, 21.41, 28.42, 34.31, 51.81, 110.63, 117.56, 121.14, 125.86, 126.51, 128.20, 132.94, 141.23, 146.04, 148.75, 155.90, 202.91; IR (KBr) 1690; MS, *m*/*z* (relative intensity, %) 266 (M^+, 3.2), 237 (100). HRMS Calcd for $C_{17}H_{18}N_2O$: 266.1419. Found: 266.1426.

1-[1-(5-Methyl-2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (2c). Yellow oil; bp 220 °C (0.7 mmHg); R_f 0.029 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 2.21 (s, 3H), 2.67 (q, J = 7.3 Hz, 2H), 3.20 (t, J = 8.6 Hz, 2H), 4.14 (t, J = 8.6 Hz, 2H), 6.61 (d, J = 8.3 Hz, 1H), 6.90 (dd, J = 7.9 Hz, 7.3 Hz, 1H), 7.23 (dd, J = 7.3 Hz, 1.3 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.37 (dd, J = 8.2 Hz, 2.1 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.42, 17.64, 28.34, 34.28, 51.96, 109.88, 120.85, 125.21, 125.89, 126.51, 127.76, 132.86, 138.43, 141.48, 146.05, 153.88, 202.93; IR (neat) 1693; MS, *m*/*z* (relative intensity, %) 266 (M^+, 4.8), 237 (100). HRMS Calcd for $C_{17}H_{18}N_2O$: 266.1419. Found: 266.1413.

1-[1-(4-Methyl-2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-butanone (3) and 2-Methyl-1-[1-(4-methyl-2-pyridinyl)-2,3-dihydro-7(1*H*)-indolyl]-1-propanone (4). Spectral data were obtained from a mixture of linear and branched ketones. Yellow oil; bp 230 °C (0.7 mmHg); R_f 0.029 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ [0.82 (t, J = 7.6 Hz, 1.20H), 1.50 (sextet, J = 7.6 Hz, 0.80H), 2.28 (s, 1.20H), 2.61 (t, J = 7.6 Hz, 0.80H), 3.19 (t, J = 8.6 Hz, 0.80H), 4.17 (t, J = 8.6 Hz, 0.80H), 6.51 (s, 0.40H), 6.62 (d, J = 4.6 Hz, 0.40H), 6.92 (t, J = 7.6 Hz, 0.40H), 7.24 (d, J = 7.3 Hz, 0.40H), 7.30 (d, J = 7.6 Hz, 0.40H), 7.94−7.98 (c, 0.40H), linear], [0.87 (d, J = 6.9 Hz, 3.60H), 2.28 (s, 1.80H), 3.01 (septet, J = 6.9 Hz, 0.60H), 3.19 (t, J = 8.6 Hz, 1.20H), 4.17 (t, J = 8.6 Hz, 1.20H), 6.51 (s, 0.60H), 6.62 (d, J = 4.6 Hz, 0.60H), 6.91 (t, J = 7.6 Hz, 0.60H), 7.24 (d, J = 7.3 Hz, 0.60H), 7.30 (d, J = 7.6 Hz, 0.60H), 7.94−7.98 (c, 0.60H), branched]; ^{13}C NMR ($CDCl_3$) δ [17.75, 18.51, 21.29, 28.33, 43.09, 51.94, 110.68, 117.60, 121.08, 125.92, 126.55, 128.11, 132.96, 141.36, 146.01, 148.68, 156.08, 202.05, linear], [13.96, 21.29, 28.33, 38.13, 51.82, 110.37, 117.52, 121.22, 126.51, 127.00, 127.20, 132.82, 141.51, 146.42, 148.79, 156.21, 205.65, branched]; IR (neat) 1686; MS, *m*/*z* (relative intensity, %) [280 (M^+, 1.3), 237 (100), linear], [280 (M^+,

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2.7), 237 (100), branched]. HRMS Calcd for $C_{18}H_{20}N_2O$: 280.1576. Found: [280.1573 (linear), 280.1577 (branched)].

1-[1-(4-Methyl-2-pyridinyl)-2,3-dihydro-2-methyl-7(1*H*)-indolyl]-1-propanone (6). Yellow solid; mp 106−107 °C; R_f 0.029 (hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.48 (d, J = 6.6 Hz, 3H), 2.29 (s, 3H), 2.45 (dt, J = 17.2 Hz, 7.3 Hz, 1H), 2.61−2.78 (c, 2H), 3.48 (dd, J = 15.8 Hz, 9.2 Hz, 1H), 4.48 (m, 1H), 6.55 (s, 1H), 6.60 (d, J = 5.4 Hz, 1H), 6.96 (dd, J = 7.9 Hz, 7.3 Hz, 1H), 7.26 (d, J = 7.3 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.28, 21.42, 21.98, 34.02, 36.62, 59.11, 108.99, 117.42, 121.74, 126.05, 127.07, 128.76, 131.97, 140.21, 146.38, 148.84, 155.38, 201.34; IR (KBr) 1684; MS, m/z (relative intensity, %) 280 (M^+, 3.1), 251 (100). HRMS Calcd for $C_{18}H_{20}N_2O$: 280.1576. Found: 280.1573.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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