Articles

Selective Rhodium-Catalyzed Insertion of Carbon Monoxide into the Nitrogen–Oxygen Bond of Isoxazolidines. New Reduction, Migration, and Rearrangement Reactions Catalyzed by Iridium Complexes

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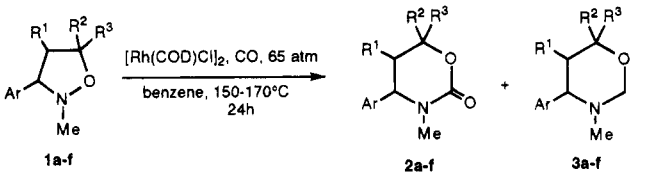
Reaction of isoxazolidines with carbon monoxide in benzene, catalyzed by the dimer of chloro(1,5-cyclooctadiene)rhodium, results in the formation of tetrahydro-1,3-oxazin-2-ones as the major or only product, often in fine yields. A novel conversion of 3-arylisoxazolidines to tetrahydro-1,3-oxazines occurs using an iridium catalyst (i.e. $IrCl_3 \cdot 3H_2O$, $Ir(CO)_3Cl$) and carbon monoxide. This remarkable reaction was shown to proceed by an intermolecular hydrogen transfer process. In some cases, an isomeric tetrahydro-1,3-oxazine, resulting from methyl migration from nitrogen to the carbon atom arising from carbon monoxide insertion, was isolated as a byproduct in the reaction. Isoxazolidines containing an alkyl group at the 3-position undergo a novel iridium-catalyzed rearrangement and ring expansion reaction. This transformation also occurred, albeit in lower yield, by treatment of 3-alkylisoxazolidines with hydrochloric acid in *p*-xylene.

The transition-metal-catalyzed direct carbonylation of heterocycles is an attractive method in organic synthesis. A number of valuable carbonyl-containing compounds can be prepared in this way from the corresponding simple heterocyclic substrates.[1] There have been several reports describing the insertion of CO into one of the ring C–N bonds in three-, four-, and five-membered-ring heterocycles.[2–15] It has also been reported that a novel rearrangement reaction can occur with certain five- to eight-membered-ring N-heterocycles.[14] Quite drastic reaction conditions are required for this transformation as well as for the simple carbonylation of five-membered rings, presumably because the ring lacks strain energy. Both the expected carbonyl insertion and a novel ketene elimination reaction occurred in the rhodium(I)-catalyzed carbonylation of thiazolidines, where the heteroatoms are in a 1,3-relationship.[15] We were interested in determining the site selectivity for carbonylation in a five-membered-ring heterocycle having heteroatoms at adjacent positions. We now describe the fascinating results obtained when isoxazolidines, which contain an N–O bond, were exposed to CO in the presence of catalytic amounts of rhodium and iridium complexes. In addition to the anticipated carbonyl insertion process, unusual reduction, methyl migration, and rearrangement reactions were observed in certain cases.

Results and Discussion

The carbonylation of isoxazolidines[16] **1a–f** was carried out in dry benzene under 65 atm of CO and at 150–170 °C for 24 h, using $[Rh(COD)Cl]_2$ or hydrated $IrCl_3$ as the catalyst precursor.[17,18] The concentration of the catalyst in all cases was 1 mol %. The results are shown in Table 1. The structure of the products was assigned using a combination of NMR techniques (^1H, ^{13}C, DEPT, COSY, and HMQC), as well as mass and infrared spectroscopy.

Using (1,5-cyclooctadiene)rhodium(I) dimer as the catalyst, insertion of carbon monoxide occurs into the N–O bond of **1a–d**, affording tetrahydro-1,3-oxazin-2-ones **2a–d** in 64–82% yield. No products of insertion into the C–N or C–O bond were detected in these reactions. The tetrahydro-1,3-oxazine **3d**, apparently



1-3a R^1 = $MeCOOCH_2$, R^2 = Ph, R^3 = H, Ar = Ph
b R^1 = $MeCOOCH_2$, R^2 = Ph, R^3 = H, Ar = p-Me-C_6H_4
c R^1 = EtO_2C, R^2 = R^3 = Me, Ar = Ph
d R^1 = EtO_2C, R^2 = R^3 = Me, Ar = p-MeO-C_6H_4
e R^1 = $MeCOOCH_2$, R^2 = Ph, R^3 = H, Ar = p-MeO-C_6H_4
f R^1 = MeO_2C, R^2 = Me, R^3 = H, Ar = Ph

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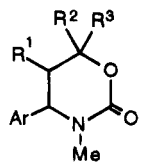
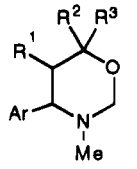
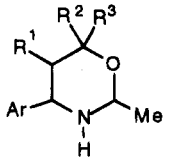
Table 1. Carbonylation of Isoxazolidines (1a–f)

Substrate		2a-f (% yield)	3a-f (% yield)	4d, 4f (% yield)
1a	[Rh]	2a (80)	-	-
	[Ir]	-	3a (45)	-
1b	[Rh]	2b (82)	-	-
	[Ir]	-	3b (37)	-
1c	[Rh]	2c (72)	-	-
	[Ir]	-	3c (39)	-
1d	[Rh]	2d (64)	3d (10)	-
	[Ir]	-	3d (37)	4d (8)
1e	[Rh]	2e (20)	3e (20)	-
	[Ir]	-	3e(42)	-
1f[20]	[Rh]	-	3f (24)	-
	[Ir]	-	3f (35)	4f (7)

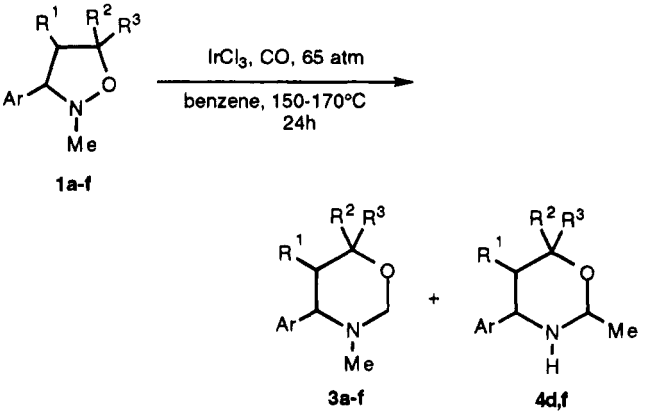
resulting from reduction of the carbonyl unit of **2d**, was formed as a byproduct in low yield from **1d**. Both **2e** and **3e** were obtained from **1e**, while only a modest yield of the reduced heterocycle **3f** was isolated from **1f**.

In the ^{1}H NMR spectra of **2a–e**, the signals for the protons attached to the carbons next to the N and/or O atom are shifted downfield by approximately 0.5 ppm upon introduction of the CO unit. The ^{13}C NMR spectra display the carbamate carbonyl signal in the expected chemical shift region of δ 153–155 ppm.[19]

Unlike the Rh-catalyzed carbonylation processes, the reactions run in the presence of Ir complexes did *not* lead to the expected tetrahydro-1,3-oxazin-2-ones **2**. Rather, tetrahydro-1,3-oxazines **3a–f** were formed as the principal **(3d,f)** or only products **(3a–c,e)**, with a small amount of a rearranged product **(4d,f)** isolated in two cases. The yields of tetrahydro-1,3-oxazines are good, especially when one considers that 1 equiv of starting material is consumed in the reduction of **2** → **3** (*vide infra*).

In the ^{1}H NMR spectra of **3**, the methylene group displays an AB spin pattern (two doublets), showing no coupling with any other protons in the COSY spectra. However, coupling to the aminal carbon was observed in the HMQC spectra. Molecular ions were observed in the mass spectra of **3**.

Exposure of $IrCl_3 \cdot 3H_2O$ to carbon monoxide results in the generation of chlorotricarbonyliridium under the reaction conditions.[18] For comparison, the reactions of isoxazolidines were carried out using $[Ir(CO)_3Cl]$, anhydrous $IrCl_3$, or $[Ir(COD)Cl]_2$ as catalyst and it was found



that, in all cases, the product distribution was almost identical with that obtained in the reactions using $IrCl_3 \cdot 3H_2O$.

It was assumed that the tetrahydro-1,3-oxazines **3a–f** are secondary products resulting from *in situ* reduction of the corresponding tetrahydro-1,3-oxazin-2-ones **2a–f**. Since the maximum yield did not exceed 50%, it is possible that the hydrogen source was the starting heterocycle **1a–f**. To test this possibility we exposed oxazinone **2a** (from the Rh-catalyzed carbonylation of **1a**)

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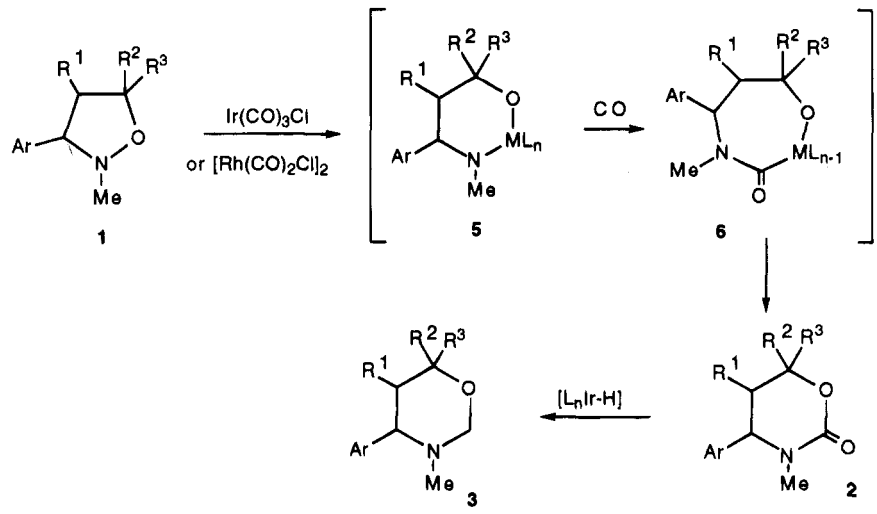
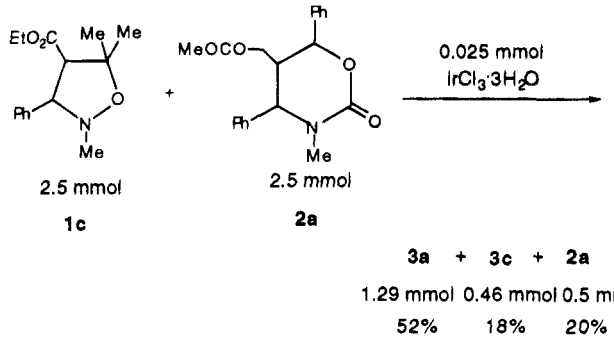
(20) Tufariello, J. J.; Pinto, D. J. P.; Milowsky, A. S.; Reinhardt, D. V. *Tetrahedron Lett.* **1987**, *28*, 5481.

Scheme 1



to the standard carbonylation conditions in the presence of $IrCl_3 \cdot 3H_2O$. Under these conditions, **3a** was *not* produced and **2a** was recovered unchanged. However, when the reaction was performed under the same conditions using equimolar amounts of *both* isoxazolidine **1c** and oxazolidinone **2a**, the reduction product **3a** was obtained in 52% yield. The results of this experiment are as follows:



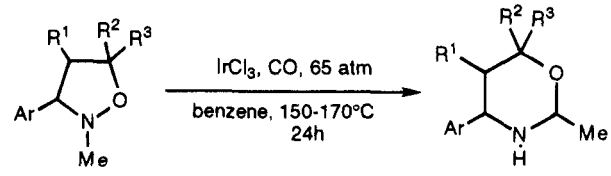
3a	+	3c	+	2a
1.29 mmol		0.46 mmol		0.5 mmol
52%		18%		20%

Using 1% $IrCl_3 \cdot 3H_2O$ (0.025 mmol), we found that oxazolidinone **2a** was reduced to **3a** in 52% yield and 20% of the starting oxazolidine **2a** was recovered. Compound **3c**, resulting from the carbonylation and reduction of **1c**, was obtained in 18% yield. These results confirm that the carbonylation product (i.e. 1,3-oxazin-2-one **2a**) is reduced in the presence of isoxazolidines (i.e. **1c**).

It was demonstrated by Braude[21] and Entwistle[22] that cyclohexene can act as a hydrogen source in the Pd-catalyzed transfer-hydrogenation of many compounds, including alkenes, alkynes, and even nitroaromatics. We therefore attempted the iridium-catalyzed carbonylation reaction of isoxazolidine **1d** in the presence of 1 equiv of cyclohexene. Under these conditions, the yield of **3d** increased from 37% to 61%.

In two cases (**1d** and **1f**), a second product (**4d** and **4f**, respectively), in which the methyl group had migrated from the nitrogen to the adjacent methylene carbon in the ring expansion reaction, was isolated in less than 10% yield.

The ^{1}H NMR spectra of **4d,f** show a signal for the C*H*–CH_3 unit as a multiplet at δ 4.68 which is integrated as one proton. (Note that the signal of the CH_2 group in tetrahydro-1,3-oxazine (**3d,f**) consists of two AB doublets centered at δ 3.93, 4.55.) The signal at δ 4.68 is also coupled with the aminal carbon in the HMQC spectrum.



1d, 4d $R^1 = EtO_2C$, $R^2 = R^3 = Me$, Ar = p-OMe-C_6H_4

1f, 4f $R^1 = MeO_2C$, $R^2 = Me$, $R^3 = H$, Ar = Ph

Furthermore, the *N*-methyl resonances at δ 2.50 observed in the spectra of **1d,f** disappeared and new methyl signals (doublets at 1.10–1.20 ppm) were observed in the spectra of **4d,f**. This metal-catalyzed methyl migration process affording **4**, albeit a low-yield reaction, is novel and is, to our knowledge, unprecedented.

A proposed mechanism for the reactions described above is outlined in Scheme 1. The first step is the insertion of the metal into the N–O bond to give **5**. Subsequent insertion of carbon monoxide followed by reductive elimination would afford the oxazolidin-2-one **2** as the product in the case of the rhodium(I)-catalyzed reaction. When Ir complexes were employed, the initially formed oxazolidin-2-one (**2**) was reduced, yielding the corresponding tetrahydro-1,3-oxazine (**3**) as the major product. We have demonstrated that the starting isoxazolidine **1** is required for this reduction.[23] However, the mechanism of this process remains unknown and could be rather complex. It is likely that the Ir complex is reduced by **1** to give a hydrido species, $[L_nIrH]$, which is responsible for the conversion of **2** to **3**. As for the formation of **4**, it might arise from the corresponding *N*-ethyl derivative via the HCl-catalyzed rearrangement (see below). The conversion of the N–Me moiety to the N–Et fragment would involve C–H bond activation, followed by carbonylation and subsequent reduction.[24]

A different rearrangement was observed in the $IrCl_3 \cdot 3H_2O$-catalyzed reaction of isoxazolidines bearing

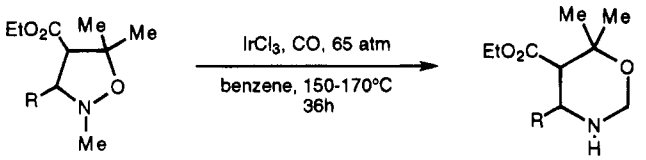
(21) Braude, E. A.; Linstead, R. P.; Mitchell, P. W. D. *J. Chem. Soc.* **1954**, 3578.

(22) Entwistle, I. D.; Johnstone, R. W. A.; Povall, T. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1300.

(23) We cannot rule out the possibility that the water-gas shift reaction participates in the reduction. However, since no reduction was observed in the absence of starting isoxazolidine 1, we can state that the water-gas shift reaction itself is not responsible for the conversion of **2** to **3**. Laine, R. M.; Thomas, D. W.; Cary, L. W.; Buttrill, S. E. *J. Am. Chem. Soc.* **1978**, *100*, 6527.

(24) We thank a reviewer for suggesting this possibility to us.

an *alkyl* substituent at the 3-position. In substrates **1g,h**, the *N*-methyl substituent was observed to migrate *into* the ring, forming a tetrahydro-1,3-oxazine (**7g,h**). Unlike

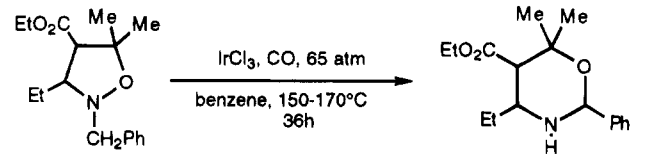


1g R = i-Propyl **7g** 53%

1h R = CH_2CH_2Ph **7h** 65%

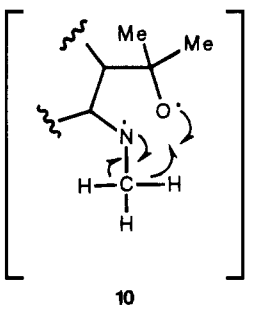
the carbonylation/reduction observed in the aryl-substituted systems, this rearrangement occurred in >50% yield (53% and 65%, respectively). The substrates **1g,h** are not as reactive as those having an aryl substituent at the 3-position (the reaction time for these substrates is somewhat longer (36 h)). Also, these reactants (**1g,h**) were unreactive when a rhodium complex was used as the catalyst. It should be noted that the iridium-catalyzed reaction occurs only under a CO atmosphere and does not proceed under nitrogen.

To prove that products of type **7g,h** result from the migration of the substituent at the nitrogen to the ring, we synthesized *N*-benzylisoxazolidine **8** and subjected it to the conditions which were used for **1g,h**. We were gratified to find that the benzyl group on nitrogen did migrate to form **9** in 32% yield, with some starting material recovered in this case.



8 **9**

A related rearrangement was reported by Lebel et al. for *N*-methylisoxazolidines.[25] They showed that isoxazolidines isomerized to tetrahydro-1,3-oxazines when exposed to light or strong base and proposed **10** as the key reaction intermediate.



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Since there was no carbon monoxide incorporated in the product, we were not sure whether the rearrangement process was iridium-catalyzed or promoted by a trace amount of HCl which is produced by the *in situ* reduction of $IrCl_3 \cdot 3H_2O$. To test this hypothesis, two reactions were carried out using **1h** as the starting material. In the absence of $IrCl_3 \cdot 3H_2O$, the reaction was attempted using 2% concentrated HCl and also using 1% $Ir(CO)_3Cl$ as the catalyst (which should not produce HCl) under the same conditions as described above (CO 65 atm, 150–170 °C, 36 h). When 2% concentrated HCl was employed, the rearrangement product (**7h**) was obtained in 23% isolated yield. Furthermore, the rearrangement product was isolated in 47% yield when **1h** was refluxed in *p*-xylene with 2% concentrated HCl for 36 h at 138 °C under 1 atm of nitrogen. When $Ir(CO)_3Cl$ was employed, **7h** was isolated in only 9% yield.

Since the reaction performed with HCl gave a higher yield than that using $Ir(CO)_3Cl$, we cannot rule out the possibility that the rearrangement is catalyzed by heat and/or acid and does not require iridium. However, it must be emphasized that the yield of the rearrangement product was appreciably higher (65% yield) using 1% $IrCl_3 \cdot 3H_2O$ than using hydrochloric acid (47% yield).

In conclusion, rhodium- and iridium-complex-catalyzed carbonylation reactions of saturated heterocycles containing heteroatoms at the 1,2-positions proceed in both anticipated and unexpected ways. Rhodium(I) catalyzes the expected insertion of carbon monoxide into the isoxazolidine ring, affording tetrahydro-1,3-oxazin-2-ones as the major or only product, often in fine yields. Some 1,3-oxazin-2-ones are antibiotics, and some tetrahydro-1,3-oxazines are known to be antifungal and antibacterial agents.[26] Iridium complexes were active catalysts for the novel conversion of 3-arylisoxazolidines to 1,3-oxazines, by an intermolecular hydrogen transfer reaction. An isomeric 1,3-oxazine byproduct, obtained in modest yield in several cases, is formed by migration of the methyl group from nitrogen to the carbon atom arising from carbon monoxide insertion. Finally, another unique rearrangement pathway occurs in the Ir(I)-catalyzed reaction of isoxazolidines containing an alkyl group at the 3-position. This rearrangement was also observed in lower yield in refluxing *p*-xylene in the presence of HCl.

Experimental Section

General Procedure for the Preparation of Isoxazolidines 1a–h and 8.[16] To a suspension of *N*-methylhydroxylamine hydrochloride (16.6 g, 20 mmol) in benzene (100 mL) was added potassium hydroxide (2.24 g, 40 mmol) and the requisite aldehyde (20 mmol). The reaction mixture was refluxed, and the water was removed using a Dean–Stark apparatus. After the calculated amount of water was removed, the reaction mixture was worked up by removing the solvent and then extracting with CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to yield the nitrone, which was used in the next step without further purification. In the cases of **1g** and **8** the reactions were stirred overnight at room temperature in the presence of 4 Å molecular sieves.

A mixture of the nitrone (10 mmol) and the requisite dipolarophile (10 mmol) in dry toluene was refluxed under a slow stream of nitrogen for 24 h. The reaction mixture was concentrated by rotary evaporation, affording a crude oily material. This oily material was then chromatographed using silica gel and 10–25% ethyl acetate in hexane as the eluant to form the isoxazolidine derivative **1a–h**.

4-(Acetoxymethyl)-3,5-diphenyl-2-methylisoxazolidine (1a): 78% yield; IR (neat) ν(CO) 1738 cm^{-1}; ^1H NMR δ 1.95 (s, 3H), 2.68 (s, 3H), 2.96 (m, 1H), 3.47 (d, J = 10 Hz, 1H), 4.25 (dd, J = 1.2, 8 Hz, 2H), 4.98 (d, J = 8 Hz, 1H), 7.25–7.65 (m, 10H); ^{13}C NMR δ 21.28, 44.08, 61.16, 63.77, 76.80, 81.67, 126.56, 128.09, 128.59, 128.83, 128.94, 129.16, 129.36, 138.18, 171.41; calcd mass for $C_{19}H_{21}NO_3$ 311.152 13, HRMS (m/e) 311.152 88 [M^+].

(25) Lebel, N. A.; Lajiness, T. A.; Ledlie, D. B. *J. Am. Chem. Soc.* **1967**, *89*, 3067.

(26) Eckstein, Z.; Urbanski, T. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1978; Vol. 23, and references cited therein.

4-(Acetoxymethyl)-3-(*p*-methylphenyl)-2-methyl-5-phenylisoxazolidine (1b): 71% yield; IR (neat) ν(CO) 1734 cm^{-1}; ^{1}H NMR δ 1.85 (s, 3H), 2.25 (s, 3H), 2.55 (s, 3H), 2.84 (m, 1H), 3.33 (d, J = 11.2 Hz, 1H), 4.15 (dd, J = 2, 11.2 Hz, 2H), 4.90 (d, J = 8 Hz, 1H), 7.00–7.50 (m, 9H); ^{13}C NMR δ 20.39, 20.84, 43.12, 60.15, 62.88, 76.34, 80.80, 125.70, 127.15, 127.60, 128.24, 129.15, 134.10, 137.67, 142.55, 170.49; calcd mass for $C_{20}H_{23}NO_3$ 325.167 78, HRMS (m/e) 325.168 65 [M$^+$].

4-(Ethoxycarbonyl)-3-phenyl-2,5,5-trimethylisoxazolidine (1c): 80% yield; IR (neat) ν(CO) 1736 cm^{-1}; ^{1}H NMR δ 1.22 (t, J = 8 Hz, 3H), 1.29 (s, 3H), 1.60 (s, 3H), 2.55 (s, 3H), 3.17 (d, J = 11 Hz, 1H), 3.95 (d, J = 11 Hz, 1H), 4.12 (q, J = 8 Hz, 2H), 7.35 (m, 5H); ^{13}C NMR δ 14.77, 24.50, 30.51, 43.61, 61.32, 67.26, 76.72, 80.57, 128.52, 128.71, 129.28, 138.16, 171.18; calcd mass for $C_{15}H_{21}NO_3$ 263.152 13, HRMS (m/e) 263.152 52 [M$^+$].

4-(Ethoxycarbonyl)-3-(*p*-methoxyphenyl)-2,5,5-trimethylisoxazolidine (1d): 82% yield; IR (neat) ν(CO) 1732 cm^{-1}; ^{1}H NMR δ 1.12 (t, J = 8 Hz, 6H), 1.29 (s, 3H), 2.49 (s, 3H), 3.02 (d, J = 12 Hz, 1H), 3.29 (s, 3H), 3.78 (d, J = 12 Hz, 1H), 4.00 (q, J = 8 Hz, 2H), 6.75, 7.20 (q, 4H); ^{13}C NMR δ 14.77, 24.56, 30.51, 43.49, 55.81, 61.26, 67.07, 76.23, 80.37, 114.64, 129.64, 129.90, 132.57, 160.05, 171.20; MS (m/e) 293 [M$^+$]. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.53; H, 7.85; N, 4.78. Found: C, 65.22; H, 7.72; N, 4.62.

4-(Acetoxymethyl)-3-(*p*-methoxyphenyl)-2-methyl-5-phenylisoxazolidine (1e): 67% yield; IR (neat) ν(CO) 1738 cm^{-1}; ^{1}H NMR δ 1.89 (s, 3H), 2.55 (s, 3H), 2.82 (tt, 1H), 3.31 (d, J = 10 Hz, 1H), 3.68 (s, 3H), 4.15 (dd, J = 10 Hz, 2H), 4.88 (d, J = 8 Hz, 1H), 6.75–7.50 (m, 9H); ^{13}C NMR δ 20.42, 43.01, 54.97, 60.01, 62.91, 76.21, 80.72, 114.67, 125.63, 128.24, 128.83, 128.92, 142.57, 159.23, 170.52; MS (m/e) 341 [M$^+$].

2,5-Dimethyl-4-(methoxycarbonyl)-3-phenylisoxazolidine (1f):[20] 83% yield; IR (neat) ν(CO) 1738 cm^{-1}; ^{1}H NMR δ 1.40 (d, J = 8 Hz, 3H), 2.55 (s, 3H), 2.98 (t, J = 8 Hz, 1H), 3.68 (s, 3H), 3.88 (d, J = 8 Hz, 1H), 4.40 (quintet, J = 8 Hz, 1H), 7.25 (m, 5H); ^{13}C NMR δ 21.65, 43.86, 51.78, 52.65, 61.76, 76.77, 128.12, 128.73, 129.24, 139.03, 172.46; MS (m/e) 235 [M$^+$]. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.26; H, 7.23; N, 6.15.

4-(Ethoxycarbonyl)-3-isopropyl-2,5,5-trimethylisoxazolidine (1g): 64% yield; IR (neat) ν(CO) 1739 cm^{-1}; ^{1}H NMR δ 0.72 (d, J = 9.7 Hz, 3H), 0.79 (d, J = 9.7 Hz, 3H), 1.08 (s, 3H), 1.12 (t, J = 10 Hz, 3H), 1.29 (s, 3H), 1.70 (m, 1H), 2.53 (s, 3H), 2.79 (m, 2H), 4.02 (q, J = 10 Hz, 2H); ^{13}C NMR δ 14.80, 17.13, 20.76, 24.02, 28.86, 29.79, 44.84, 59.35, 61.19, 77.49, 80.10, 172.72; calcd mass for $C_{12}H_{23}NO_3$ 229.167 78, HRMS (m/e) 229.166 60 [M$^+$].

4-(Ethoxycarbonyl)-3-phenethyl-2,5,5-trimethylisoxazolidine (1h): 61% yield; IR (neat) ν(CO) 1737 cm^{-1}; ^{1}H NMR δ 1.12 (s, 3H), 1.18 (t, J = 10 Hz, 3H), 1.40 (s, 3H), 1.75 (m, 2H), 2.50 (m, 2H), 2.61 (s, 3H), 2.82 (d, J = 12 Hz, 1H), 3.00 (m, 1H), 4.10 (q, J = 10 Hz, 2H), 7.15 (m, 5H); ^{13}C NMR δ 14.86, 24.34, 30.19, 32.74, 34.00, 44.42, 61.40, 63.94, 71.99, 80.28, 126.62, 128.77, 129.04, 142.14, 172.07; MS (m/e) 291 [M$^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.10; H, 8.59; N, 4.81. Found: C, 69.93; H, 8.21; N, 4.90.

2-Benzyl-4-(ethoxycarbonyl)-3-ethyl-5,5-dimethylisoxazolidine (8): 68% yield; IR (neat) ν(CO) 1740 cm^{-1}; ^{1}H NMR δ 0.82 (t, J = 7 Hz, 3H), 1.13 (s, 3H), 1.18 (t, J = 7 Hz, 3H), 1.38 (s, 3H), 1.50 (m, 2H), 2.80 (d, J = 10 Hz, 1H), 3.18 (m, 1H), 3.90 (AB dd, J = 16, 45 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 7.25 (m, 5H); ^{13}C NMR δ 10.03, 14.25, 23.73, 24.77, 29.29, 60.34, 60.66, 62.56, 70.52, 78.82, 126.82, 128.10, 128.27, 138.31, 171.75; calcd mass for $C_{17}H_{25}NO_3$ 291.183 43, HRMS (m/e) 291.183 05 [M$^+$].

Carbonylation of Isoxazolidines 1a–h. Carbonylation of Isoxazolidines 1a–f using [Rh(COD)Cl]$_2$ as the Catalyst (General Procedure). A mixture of the isoxazolidine (5 mmol), [Rh(COD)Cl]$_2$ (0.025 g, 0.05 mmol), and dry benzene (10 mL) was placed in an autoclave containing a glass liner and stirring bar. The autoclave was purged several times with carbon monoxide and pressurized to 65 atm, and the reaction mixture was stirred at 150–170 °C for 24 h. The reaction mixture was then cooled to room temperature and filtered through acidic alumina using CH_2Cl_2 and then ethyl acetate as eluants. The ethyl acetate fraction which contains the product was purified by preparative thin-layer chromatography using 35% ethyl acetate in hexane as the developer. It should be noted that the 1,3-oxazin-2-one product is quite polar. The product is usually found close to the base line on the chromatogram.

5-(Acetoxymethyl)-4,6-diphenyl-3-methyltetrahydro-1,3-oxazin-2-one (2a): 80% yield; IR (neat) ν(CO) 1704, 1738 cm^{-1}; ^{1}H NMR δ 2.02 (s, 3H), 2.33 (m, 1H), 2.70 (s, 3H), 3.75 (ddd, J = 2, 15, 90 Hz, 2H), 4.42 (d, J = 11 Hz, 1H), 5.23 (d, J = 12 Hz, 1H), 7.30 (m, 10H); ^{13}C NMR δ 21.22, 35.31, 48.52, 61.08, 64.07, 79.58, 127.63, 127.89, 129.34, 129.56, 129.82, 129.88, 136.64, 139.19, 155.55, 170.84; MS (m/e) 339 [M$^+$]. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 71.22; H, 6.04; N, 4.06.

5-(Acetoxymethyl)-4-(*p*-methylphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazin-2-one (2b): 82% yield; IR (neat) ν(CO) 1700, 1736 cm^{-1}; ^{1}H NMR δ 1.90 (s, 3H), 2.22, 2.25 (m, 4H), 2.62 (s, 3H), 3.38, 3.75 (ddd, J = 4, 13, 76 Hz, 2H), 3.70 (s, 3H), 4.30 (d, J = 10 Hz, 1H), 5.11 (d, J = 12 Hz, 1H), 6.95–7.30 (m, 9H); ^{13}C NMR δ 20.31, 20.81, 34.33, 47.68, 60.24, 62.91, 78.71, 114.32, 126.74, 126.91, 128.43, 128.85, 129.63, 135.22, 135.83, 138.38, 154.63, 169.93; calcd mass for $C_{21}H_{23}NO_4$ 353.162 69, HRMS (m/e) 353.160 69 [M$^+$].

5-(Ethoxycarbonyl)-4-phenyl-3,6,6-trimethyltetrahydro-1,3-oxazin-2-one (2c): 72% yield; IR (neat) ν(CO) 1705, 1733 cm^{-1}; ^{1}H NMR δ 0.95 (t, J = 8 Hz, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 2.62 (s, 3H), 2.87 (d, J = 15 Hz, 1H), 3.90 (q, J = 8 Hz, 2H), 4.58 (d, J = 15 Hz, 1H), 7.20 (m, 5H); ^{13}C NMR δ 13.98, 21.66, 27.95, 34.11, 57.82, 61.23, 61.74, 77.75, 127.20, 128.46, 129.04, 137.89, 160.09, 153.48, 171.46; MS (m/e) 291 [M$^+$]. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.98; H, 7.22; N, 4.81. Found: C, 65.83; H, 7.65; N, 4.75.

5-(Ethoxycarbonyl)-4-(*p*-methoxyphenyl)-3,6,6-trimethyltetrahydro-1,3-oxazin-2-one (2d): 64% yield; IR (neat) ν(CO) 1706, 1735 cm^{-1}; ^{1}H NMR δ 1.05 (t, J = 8 Hz, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 2.70 (s, 3H), 2.87 (d, J = 10 Hz, 1H), 3.80 (s, 3H), 4.05 (q, J = 8 Hz, 2H), 4.77 (d, J = 10 Hz, 1H), 6.85, 7.22 (m, 4H); ^{13}C NMR δ 13.98, 19.73, 27.95, 34.94, 55.23, 58.97, 60.88, 61.74, 77.98, 114.00, 128.28, 128.70, 129.96, 132.84, 159.12, 171.41; MS (m/e) 321 [M$^+$]. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.55; H, 7.16; N, 4.36. Found: C, 63.61; H, 6.98; N, 4.43.

5-(Acetoxymethyl)-4-(*p*-methoxyphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazin-2-one (2e): 20% yield; IR (neat) ν(CO) 1702, 1738 cm^{-1}; ^{1}H NMR δ 1.95 (s, 3H), 2.22 (m, 1H), 2.65 (s, 3H), 3.60 (m, 2H), 3.70 (s, 3H), 4.28 (d, J = 10 Hz, 1H), 5.12 (d, J = 12 Hz, 1H), 7.20 (m, 9H); ^{13}C NMR δ 20.31, 34.25, 47.74, 55.05, 60.26, 62.62, 78.69, 114.32, 126.72, 128.21, 128.43, 128.85, 130.08, 135.85, 159.54, 154.57, 169.94; MS (m/e) 369 [M$^+$]. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.49; H, 5.82; N, 4.11.

Carbonylation of Isoxazolidines 1a–h using IrCl$_3$ as a Catalyst (General Procedure). The procedure described for the rhodium-catalyzed reaction was used, except for substitution of the rhodium complex by $IrCl_3$ (0.015 g, 0.05 mmol). The use of other iridium catalysts such as [Ir(CO)$_3$Cl] and [Ir(COD)Cl]$_2$ in the case of **1a–f** (1 mol % each) gave the same product ratios as those for $IrCl_3 \cdot 3H_2O$. The purification of the products was effected using preparative thin-layer chromatography with 25% ethyl acetate in hexane as the eluant.

5-(Acetoxymethyl)-4,6-diphenyl-3-methyltetrahydro-1,3-oxazine (3a): 45% yield; IR (neat) ν(CO) 1736 cm^{-1}; ^{1}H NMR δ 1.82 (s, 3H), 1.92 (s, 3H), 2.15 (m, 1H), 3.29 (d, J = 11 Hz, 1H), 3.40 (m, 2H), 3.93 (d, J = 10 Hz), 4.55 (dd, J = 10, 48 Hz, 2H), 7.25 (m, 10H); ^{13}C NMR δ 21.20, 38.16, 47.29, 62.45, 70.07, 82.89, 88.27, 127.86, 128.65, 128.91, 129.05, 129.21, 129.33, 140.04, 170.98; MS (m/e) 325 [M$^+$]. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.85; H, 7.08; N, 4.31. Found: C, 74.25; H, 7.12; N, 4.16.

5-(Acetoxymethyl)-4-(*p*-methylphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazine (3b): 37% yield; IR (neat) ν(CO) 1740 cm^{-1}; ^{1}H NMR δ 1.81 (s, 3H), 1.90 (s, 3H), 2.10 (m, 1H), 2.25 (s, 3H), 3.11 (d, J = 12.8 Hz, 1H), 3.38 (m, 2H), 3.90 (d, J = 11.4 Hz), 4.52 (dd, J = 11, 48 Hz, 2H), 7.00–7.30 (m, 9H); ^{13}C NMR δ 20.28, 20.82, 37.19, 46.35, 61.62, 69.43, 82.06, 87.42, 126.94, 127.86, 128.29, 129.09, 129.89, 135.98, 137.40,

139.19, 170.11; calcd mass for $C_{21}H_{23}NO_3$ 339.183 43, HRMS (*m/e*) 339.184 83 [M$^+$].

5-(Ethoxycarbonyl)-4-phenyl-3,6,6-trimethyltetrahydro-1,3-oxazine (3c): 39% yield; IR (neat) ν(CO) 1734 cm^{-1}; ^{1}H NMR δ 0.85 (t, J = 7 Hz, 3H), 1.32 (s, 6H), 1.88 (s, 3H), 2.90 (d, J = 15 Hz, 1H), 3.55 (d, J = 15 Hz, 1H), 3.76 (q, J = 7 Hz, 2H), 4.18 (dd, J = 11, 45 Hz, 2H), 7.30 (m, 5H); ^{13}C NMR δ 14.45, 20.15, 30.79, 37.20, 57.61, 60.74, 65.82, 73.97, 81.22, 128.39, 128.89, 129.14, 140.15, 171.42; MS (*m/e*) 277 [M$^+$]. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 68.95; H, 8.58; N, 4.70.

5-(Ethoxycarbonyl)-4-(*p*-methoxyphenyl)-3,6,6-trimethyltetrahydro-1,3-oxazine (3d): 37% yield; IR (neat) ν(CO) 1740 cm^{-1}; ^{1}H NMR δ 0.95 (t, J = 8 Hz, 3H), 1.33 (s, 6H), 1.90 (s, 3H), 2.92 (d, J = 10 Hz, 1H), 3.55 (d, J = 10 Hz, 1H), 3.75 (s, 3H), 3.85 (q, J = 8 Hz, 2H), 4.22 (dd, J = 9, 32 Hz, 2H), 6.82, 7.22 (m, 4H); ^{13}C NMR δ 13.61, 19.24, 29.90, 36.14, 54.89, 56.74, 59.82, 64.16, 73.11, 80.35, 113.33, 129.28, 131.33, 158.79, 170.60; MS (*m/e*) 307 [M$^+$]. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14; N, 4.56. Found: C, 66.20; H, 8.02; N, 4.28.

5-(Acetoxymethyl)-4-(*p*-methoxyphenyl)-3-methyl-6-phenyltetrahydro-1,3-oxazine (3e): 42% yield; IR (neat) ν(CO) 1736 cm^{-1}; ^{1}H NMR δ 1.82 (s, 3H), 1.90 (s, 3H), 2.10 (m, 1H), 3.11 (d, J = 12.8 Hz, 1H), 3.40 (m, 2H), 3.80 (s, 3H), 3.91 (d, J = 11.4 Hz), 4.54 (dd, J = 10, 50 Hz, 2H), 6.68, 7.25 (m, 9H); ^{13}C NMR δ 21.23, 38.04, 47.35, 55.84, 62.52, 69.92, 82.98, 88.30, 113.82, 127.74, 127.84, 129.01, 129.20, 129.89, 131.95, 140.07, 159.87, 171.02; calcd mass for $C_{21}H_{25}NO_3$ 355.178 34, HRMS (*m/e*) 355.179 65 [M$^+$].

5-(Methoxycarbonyl)-3,6-dimethyl-4-phenyltetrahydro-1,3-oxazine (3f): 24% yield (Rh), 35% yield (Ir); IR (neat) ν(CO) 1742 cm^{-1}; ^{1}H NMR δ 1.15 (d, J = 8 Hz, 3H), 1.90 (s, 3H), 2.61 (t, J = 12 Hz, 1H), 3.32 (s, 3H), 3.40 (d, J = 12 Hz, 1H), 3.72 (m, 1H), 3.92, 4.50 (dd, J = 10, 140 Hz), 7.21 (m, 5H); ^{13}C NMR δ 20.45, 37.04, 52.10, 55.51, 69.84, 75.81, 87.61, 128.56, 129.14, 139.74, 172.44; MS (*m/e*) 249 [M$^+$]. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62. Found: C, 67.73; H, 7.85; N, 5.44.

5-(Ethoxycarbonyl)-4-(*p*-methoxyphenyl)-2,6,6-trimethyltetrahydro-1,3-oxazine (4d): 8% yield; IR (neat) ν(CO) 1737 cm^{-1}; ^{1}H NMR δ 0.97 (t, J = 7 Hz, 3H), 1.20 (d, J = 8 Hz, 3H), 1.27 (s, 3H), 1.30 (s, 3H), 1.55 (br s, 1H), 2.75 (d, J = 10 Hz, 1H), 3.87 (s, 3H), 4.00 (q, J = 7 Hz, 2H), 4.32 (d, J = 10 Hz, 1H), 4.75 (q, J = 8 Hz, 2H), 6.75, 7.14 (m, 4H); ^{13}C NMR δ 13.96, 20.47, 22.09, 30.94, 55.24, 56.73, 57.14, 66.10, 73.24, 77.85, 114.01, 128.33, 132.97, 159.12, 171.81; MS (*m/e*) 307 [M$^+$]. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.14; N, 4.56. Found: C, 66.24; H, 8.35; N, 4.26.

5-(Methoxycarbonyl)-2,6-dimethyl-4-phenyltetrahydro-1,3-oxazine (4f): 7% yield; IR (neat) ν(CO) 1749 cm^{-1}; ^{1}H NMR δ 1.13 (d, J = 10 Hz, 3H), 1.28 (d, J = 7 Hz, 1H), 1.57 (br s, 1H), 2.35 (t, J = 12 Hz, 1H), 3.37 (s, 3H), 3.82 (dt, J = 2, 10 Hz, 1H), 4.05 (d, J = 12 Hz, 1H), 4.40 (q, J = 7 Hz), 7.20 (m, 5H); ^{13}C NMR δ 20.01, 22.25, 52.10, 55.87, 62.27,74.84, 85.27, 127.45, 128.64, 129.04, 140.64, 173.20; MS (*m/e*) 249 [M$^+$]. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62. Found: C, 67.41; H, 7.82; N, 5.20.

Carbonylation of a Mixture of Isoxazolidine 1c and Tetrahydro-1,3-oxazin-2-one 2a using $IrCl_3$ as the Catalyst. A mixture of **1c** (0.66 g, 2.5 mmol), **2a** (0.85 g, 2.5 mmol), and $IrCl_3{\cdot}3H_2O$ (7.5 mg, 0.025 mmol) in dry benzene (10 mL) was reacted under the standard conditions described for the carbonylation of isoxazolidines **1a–h**. After 24 h, the crude reaction mixture was evaporated and purified by preparative thin-layer chromatography using 35% ethyl acetate in hexane as the developer, affording **3a** (0.42 g, 52%), **3c** (0.13 g, 18%), and recovered **2a** (0.17 g, 20%).

Carbonylation/Reduction of Isoxazolidine 1d using $IrCl_3$ as a Catalyst in the Presence of Cyclohexene. A mixture of **1d** (1.5 g, 5 mmol), dry cyclohexene (0.5 mL, 5 mmol), and $IrCl_3{\cdot}3H_2O$ (15 mg, 0.05 mmol) in dry benzene (10 mL) was reacted under the standard conditions. After 24 h the crude reaction mixture was worked up and purified using the method described above, affording **3d** (0.94 g, 61%).

5-(Ethoxycarbonyl)-6,6-dimethyl-4-isopropyltetrahydro-1,3-oxazine (7g): 53% yield; IR (neat) ν(CO) 1733 cm^{-1}; ^{1}H NMR δ 0.75 (d, J = 9.7 Hz, 3H), 0.92 (d, J = 9.7 Hz, 3H), 1.13 (t, J = 10 Hz, 3H), 1.18 (s, 3H), 1.23 (s, 3H), 1.41 (br s, 1H), 1.55 (m, 1H), 2.30 (d, J = 14.4 Hz, 2H), 4.02 (q, J = 10 Hz, 2H), 4.33 (dd, J = 3.2, 10.3 Hz, 2H); ^{13}C NMR δ 13.91, 14.54, 19.59, 20.18, 29.36, 30.51, 55.54, 56.31, 59.89, 72.21, 73.00, 172.07; MS (*m/e*) 291 [M$^+$]. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.88; H, 10.04; N, 6.11. Found: C, 62.27; H, 9.68; N, 5.83.

5-(Ethoxycarbonyl)-6,6-dimethyl-4-phenethyltetrahydro-1,3-oxazine (7h): 65% yield; IR (neat) ν(CO) 1722 cm^{-1}; ^{1}H NMR δ 1.12 (t, J = 10 Hz, 3H), 1.19 (s, 6H), 1.33 (m, 1H), 1.68 (m, 1H), 2.12 (d, J = 11.4 Hz, 1H), 2.58 (m, 1H), 2.82 (m, 1H), 3.10 (m, 1H), 4.05 (m, 2H), 4.35 (dd, J = 4.3, 10 Hz, 2H), 7.12 (m, 5H); ^{13}C NMR δ 14.81, 20.53, 31.34, 32.34, 37.56, 52.61, 59.33, 60.94, 73.06, 73.78, 126.44, 128.97, 142.60, 172.80; MS (*m/e*) 291 [M$^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.10; H, 8.59; N, 4.81. Found: C, 70.24; H, 8.33; N, 4.71.

5-(Ethoxycarbonyl)-6,6-dimethyl-4-phenethyltetrahydro-1,3-oxazine (9): 32% yield; IR (neat) ν(CO) 1724 cm^{-1}; ^{1}H NMR δ 0.90 (t, J = 8 Hz, 3H), 1.17 (t, J = 10 Hz, 3H), 1.28 (s, 3H), 1.32 (s, 3H), 1.50 (m, 2H), 2.14 (d, J = 12 Hz, 1H), 3.19 (m, 1H), 4.09 (m, 2H), 5.30 (s, 1H), 7.25 (m, 5H); ^{13}C NMR δ 9.80, 14.25, 20.58, 27.80, 30.92, 53.91, 57.57, 60.27, 73.36, 81.66, 125.97, 128.06, 128.27, 140.79, 172.87; MS (*m/e*) 291 [M$^+$]. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.10; H, 8.59; N, 4.81. Found: C, 70.14; H, 8.67; N, 4.66.

Reaction of Isoxazolidine 1h in The Absence of $IrCl_3{\cdot}3H_2O$. In the Presence of 2% Concentrated HCl. A mixture of **1h** (2.91 g, 10 mmol) and 37% HCl (0.006 mL, 0.2 mmol) in dry benzene (10 mL) was run under standard conditions as described for the iridium-catalyzed carbonylation reaction for 36 h. The crude reaction mixture was worked up and purified by the usual method to form **7h** (0.67 g, 23%). When the reaction mixture was refluxed in benzene under an atmospheric pressure of nitrogen, there was no **7h** formed. However, when the solvent was changed to *p*-xylene, **7h** was formed in 47% isolated yield using 2% concentrated HCl and a nitrogen atmosphere.

In the Presence of 1% $Ir(CO)_3Cl$. The reaction was performed as described for the carbonylation using $IrCl_3$ as the catalyst, but with $Ir(CO)_3Cl$ (1 mol %, 15.6 mg, 0.05 mmol) instead. After the usual workup and purification, **7h** was obtained in 9% yield.

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Supporting Information Available: Figures giving ^{1}H and/or ^{13}C and/or 2D NMR spectra of **1a–e,g,h**, **2a–e**, **3a–f**, **4d,f**, **7g,h**, **8**, and **9** (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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