The First Iron-Mediated Catalytic Carbon−Nitrogen Bond Formation: [4 + 1] Cycloaddition of Allenyl Imines and Carbon Monoxide

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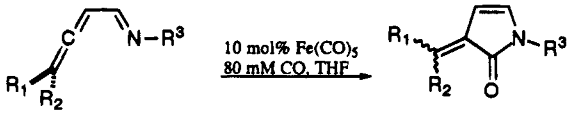
Catalytic carbon−nitrogen bond formation was achieved by iron carbonyls in the [4 + 1] cycloaddition of allenyl imines with CO. The $Fe(CO)_5$ photochemically catalyzed reaction of allenyl imines and CO gives preparatively useful yields of 3-alkylidene-4-pyrrolin-2-ones. These reactions take place under mild conditions and only require fluorescent light! Good control of alkylidene bond stereochemistry is achieved when the terminal allene groups are *tert*-butyl and methyl. Experiments in the dark show that stoichiometric $Fe_2(CO)_9$ can mediate [4 + 1] assembly by a purely thermal reaction to give good yields of the pyrrolinone products. These new methods for the construction of 3-alkylidene-4-pyrrolin-2-ones are complimentary to existing procedures and allow for a greater variety of alkylidene substituents.

Recently transition-metal-mediated assembly of five-membered heterocycle rings has been shown to provide new options for synthetic strategies. Transition metal-mediated photochemical cycloaddition of imines has been reported previously to prepare β-lactams.[1] Pyrrolidines have been constructed by palladium catalyzed [3 + 2] cycloaddition of trimethylene methane precursors and imines[2] and [4 + 1] intramolecular cycloaddition of conjugated dienes with an amide group.[3] We now report iron-mediated catalytic [4 + 1] cycloaddition involving both carbon−carbon and carbon−nitrogen bond formation. Allenyl imines[4] can be cyclized by $Fe(CO)_5$ in the presence of CO to prepare 3-alkylidene-4-pyrrolin-2-ones, which have been shown to possess potent antibiotic and antifungal properties.[5] In analogy to our work on [4 + 1] cycloaddition of allenyl aldehydes[6] it seemed reasonable to propose that allenyl imines could undergo catalytic iron-mediated cycloaddition. However, imines are strong ligands[7] and it was unclear whether catalytic chemistry would be achieved. In addition, reactions involving $Fe(CO)_5$ require elevated temperatures or high energy photochemical irradiation, which could cause decomposition of the allenyl imines.

Results and Discussion

Table 1. Assembly of 2-Alkylidene-4-pyrrolin-2-ones from Allenyl Imines and Carbon Monoxide

	R^1	R^2	R^3	yield, %	*E*/*Z*
1, **6**	$C(CH_3)_3$	CH_3	$C(CH_3)_3$	62	92/8
2, **7**	$C(CH_3)_3$	CH_3	$CH_2(CH_2)_2CH_3$	72	90/10
3, **8**	$C(CH_3)_3$	CH_3	C_6H_5	69	93/7
4, **9**	CH_3	CH_3	$CH_2(CH_2)_2CH_3$	66	
5, **10**	CH_3	CH_3	$C(CH_3)_3$	70	



1 - 5 **6 - 10** (1)

Under surprisingly mild conditions (22 °C, 80 mM CO, fluorescent light) allenyl imines undergo $Fe(CO)_5$ catalyzed [4 + 1] cycloaddition with carbon monoxide to form 3-alkylidene-4-pyrrolin-2-ones (eq 1).[8] Good stereoselectivity can be achieved in alkylidene bond formation when the terminal allene substituents are methyl and *tert*-butyl (Table 1). Previous syntheses of 3-alkylidene-4-pyrrolin-2-ones entail condensation of an aldehyde with a pyrrolinone, limiting the groups that may be attached to the alkylidene since aldehydes that contain α-hydrogen could undergo mixed aldol reactions.[5] In addition, the preparation of **6**−**8** would not be accessible via condensation of *tert*-butyl methyl ketone with pyrrolinone. In contrast to these previous synthetic strategies for the synthesis of 3-alkylidene-4-pyrrolin-2-ones, the method described here allows for a wider variety of pyrrolinone substituents.

The reactions depicted by eq 1 may be catalyzed at preparatively useful rates by fluorescent light! Because these reactions occur under atypical conditions for $Fe(CO)_5$, the relative quantum yield of **5** forming **10** was determined in C_6D_6.[9] Adjusting for the differences in absorbance for the actinometer and $Fe(CO)_5$ gave a relative quantum yield of 0.2 (Figure 1).

Consistent with the difference in σ-donor ability, the imines cyclize with CO at a slower rate than their aldehyde counterparts perhaps due to stabilization of an intermediate. Another explanation for the slower reaction of imines may be because of differences in steric bulk since in all examples the imine bears a non-hydrogen

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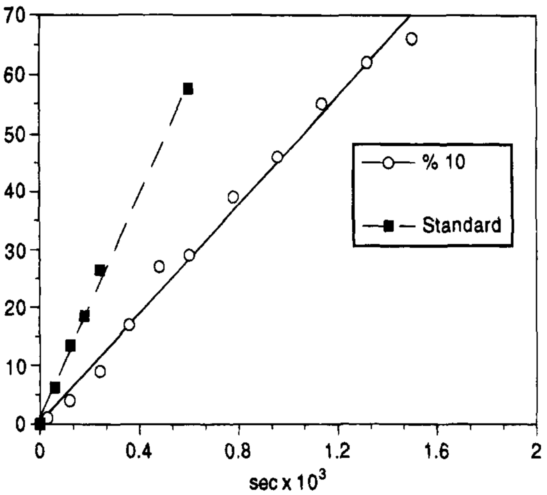


Figure 1. Actinometry plot of $Fe(CO)_5$ catalyzed [4 + 1] cycloaddition irradiated at 350 nm.

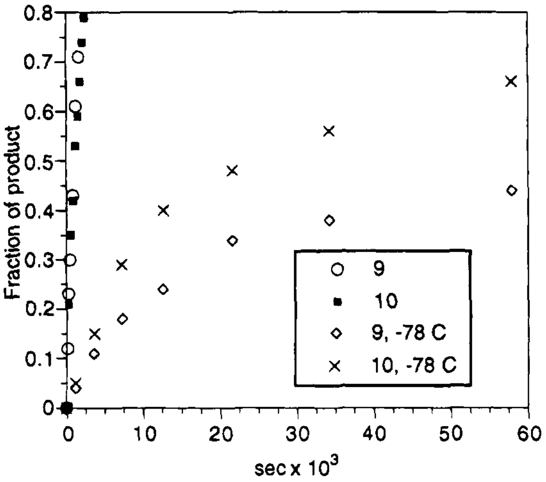


Figure 2. The effect of two imine substituents on the rate of [4 + 1] cycloaddition at 22 and −78 °C at 16 mM CO.

substituent. It was anticipated that if coordination of the iron to the C–N π-bond was occurring in the rate determining step that it would either be unaffected or decreased with an increase in size of the nitrogen substituent. To test the effect of the group attached to the imine nitrogen, the relative rates were studied of **4** and **5** treated with $Fe(CO)_5$ (10 mol %), and CO (16 mM) and irradiated at 350 nm (Figure 2). Within experimental error there is no difference in the rate of formation of **9** and **10** at 22 °C. Under identical conditions except lower temperature (−78 °C) a significant difference in relative rates was observed (Figure 2). In addition, the rate of formation of **9** and **10** was slowed dramatically, indicating that a thermal step could be made rate limiting.

The steric interactions that could account for this difference in reactivity would vary greatly depending on whether the catalyst iron complex contained a single iron or was a cluster. It was important to determine if metal clusters can facilitate [4 + 1] cycloaddition of allenyl imines with CO. Comparison of cycloaddition rates of **5** forming **10** when using $Fe(CO)_5$, $Fe_2(CO)_9$, and $Fe_3(CO)_{12}$ showed that $Fe(CO)_5$ gave significantly faster rates suggesting that mononuclear species are the active cycloaddition mediators. Consistent with these results the rate of formation of **10** from **5** showed a first-order dependence in $Fe(CO)_5$ (Figure 3).

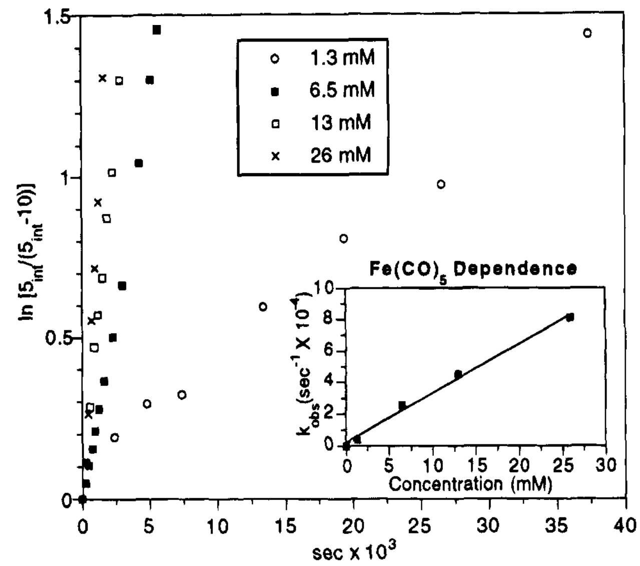


Figure 3. The dependence of $Fe(CO)_5$ concentration on the rate of [4 + 1] cycloaddition at 22 °C under continuous irradiation at 350 nm.

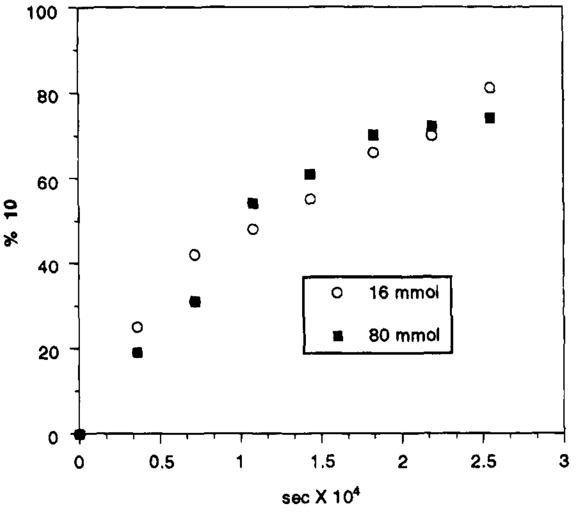


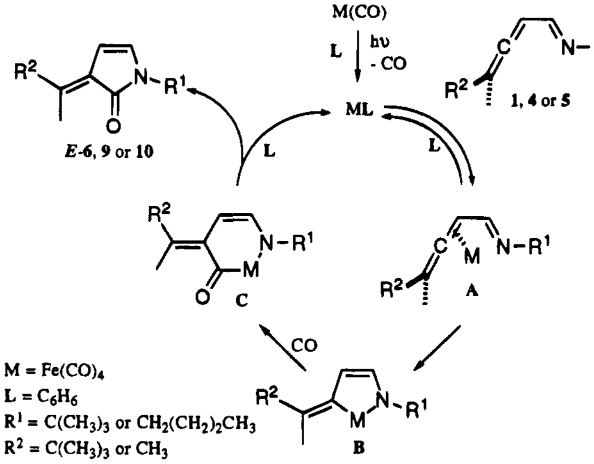
Figure 4. The dependence of CO concentration on the rate of [4 + 1] cycloaddition irradiated by fluorescent room lights.

The CO dependance of **5** reacting to form **10** was also investigated. Essentially no CO dependance was observed ruling out rate-determining formation of coordinatively unsaturated intermediates and consistent with photochemical activation of $Fe(CO)_5$ and rapid coordination of the allenyl substrate (Figure 4).

In an attempt to isolate intermediates along the cycloaddition reaction path and gain insight into which step was photochemical, **5** was treated in the dark with $Fe_2(CO)_9$. In contrast to $Fe(CO)_5$, **5** reacted completely with $Fe_2(CO)_9$ in the dark to form **10** (73%). This result suggests rate determining photochemical activation of $Fe(CO)_5$ in the metal catalyzed chemistry with subsequent coordination of the allenyl imine and thermal [4 + 1] cycloaddition.

The following proposed mechanism is used to summarize these results. Irradiation of $Fe(CO)_5$ would give the metal solvate **ML**. Coordination of **1** forms the η^2-allenyl imine complex **A**. Precedent for facial selectivity in iron coordination to conjugated allenes has been observed recently for related vinyl allenes.[10] Isomerization of **A** would form the metallacyle **B**. These proposed

Scheme 1



intermediates have precedent in the closely related vinyl ketone,[11] vinyl amide,[12] and allenyl ester[13] iron carbonyl complexes. At 22 °C no CO dependence on the rate was observed, ruling out rate-determining CO insertion as in going from **B** to **C**. To account for the effect of lower temperature (−78 °C) on the rate of reaction of **4** compared to **5** either the rate-determining step would be reductive elimination of **C** to form the product or the CO insertion from **B** to **C**.[14] Considering that the *more* sterically demanding allenyl imine **5** gave the *faster rate* at reduced temperature would be consistent with relief of steric strain, which could occur in either process and would appear inconsistent with rate-determining isomerization from **A** to **B**.

In conclusion the Fe(CO)$_5$ catalyzed [4 + 1] cycloaddition of allenyl imines and CO gives preparatively useful yields of 3-alkylidene-4-pyrrolin-2-ones. Good control of alkylidene bond stereochemistry is achieved when the terminal allene groups are *tert*-butyl and methyl. Photochemical activation of Fe(CO)$_5$ is required to bring the allenyl imine substrate into the coordination sphere of the metal. Experiments in the dark show that stoichiometric Fe$_2$(CO)$_9$ can mediate [4 + 1] assembly by a purely thermal reaction to give good yields of the pyrrolinone products.

Experimental Section

All reactions and manipulations were conducted under a dry argon atmosphere either using an inert atmosphere glove-box or standard Schlenk techniques. All allenyl imines were prepared as previously reported.[4] Irradiation was performed with either Phillips Econ-o-watt F40CW/RS/EW-II cool white bulbs (four) or a Rayonet photochemical reactor (350 nm bulbs (ten)). All NMR data were recorded on either a Nicolet (200 MHz ^{1}H) or a Bruker AMX (300 MHz ^{1}H). IR were recorded on a Perkin-Elmer 1600 FTIR. Mass spectral data were obtained from the departmental facility at Washington State University. Elemental analysis was obtained from Desert Analytics, Tucson, AZ. Melting points were recorded on a Mel-Temp apparatus and are uncorrected.

General Synthetic Procedure. In a typical experiment 96 mg (634 μmol) of **5** was added to 7 mL of freshly distilled (from Na/K benzophenone) THF, in a thick walled glass bomb equipped with a Teflon vacuum valve, followed by 12.4 mg (10 mol %, 63.4 μmol) of Fe(CO)$_5$. The bomb was pressurized to give 80 mM CO in solution.[15] The bomb was irradiated 48 h with fluorescent light. After demetalation (1 g flash silica gel, 1% triethylamine in CH$_2$Cl$_2$) and filtration, column chromatography of the residue on flash silica gel (CH$_2$Cl$_2$) yielded 80 mg of a pale yellow oil **10** (70%). All cycloadditions were run under identical conditions. Alkylidene bond isomers were separated by the same chromatography conditions described above.

(*E*)-*N*-*tert*-Butyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (6): 57% yield of a pale yellow solid; mp 73.5−75 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.24 (s, 9H), 1.45 (s, 9H), 2.42 (d, J = 0.9 Hz, 3H), 5.92 (d, J = 5.2 Hz, 1H), 6.59 (dq, J= 0.9, 5.2 Hz, 1H); ^{13}C{^{1}H} (75 MHz, CDCl$_3$) δ 16.48, 28.29, 30.46, 39.11, 54.18, 101.84, 127.42, 127.93, 163.06, 169.01; IR (CH$_2$Cl$_2$) 1686 cm^{-1}; MS m/z (M$^+$) 221. Anal. Calcd for C$_{14}$H$_{23}$NO: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.62; H, 10.37; N, 6.33.

(*Z*)-*N*-*tert*-Butyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (6): 5% yield of a pale yellow solid; Mp 73.5−75 °C; ^{1}H NMR (300 MHz, C$_6$D$_6$) δ 1.28 (s, 9H), 1.43 (s, 9H), 1.78 (s, 3H), 5.56 (d, J = 5.2, 1H), 6.30 (d, J = 5.2, 1H); ^{13}C{^{1}H} (75 MHz: CDCl$_3$) δ 21.19, 27.98, 28.29, 37.28, 54.22, 102.49,-128.06, 130.27, 163.27, 165.49; IR (CH$_2$Cl$_2$) 1697 cm^{-1}; MS m/z (M$^+$) 221; HRMS m/z for C$_{14}$H$_{23}$NO calcd 221.1780, found 221.1790.

(*E*)-*N*-Butyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (7): 65% yield of a pale yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.23 (s, 9H), 1.30 (hex, J = 7.3 Hz, 2H), 1.52 (pent, J = 7.3 Hz, 2H), 2.45 (s, 3H), 3.43 (t, J = 7.3 Hz, 2H), 5.96 (d, J = 5.1 Hz, 1H), 6.37 (d, 5.1 Hz, 1H); ^{13}C{^{1}H} (75 MHz, CDCl$_3$) δ 11.19, 14.13, 17.49, 27.96, 28.70, 36.61, 39.26, 100.11, 124.20, 126.37, 161.93, 165.86; IR (CDCl$_3$) 1702 cm^{-1}; MS m/z (M$^+$) 221; HRMS m/z for C$_{14}$H$_{23}$NO calcd 221.1780, found 221.1774.

(*Z*)-*N*-Butyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (7): 7% yield of a pale yellow oil; ^{1}H NMR (300 MHz: C$_6$D$_6$) δ 0.71 (t, J = 7.3 Hz, 3H), 1.06 (hex, J = 7.3 Hz, 2H), 1.25 (pent, J = 7.3 Hz, 2H), 1.45 (s, 9H), 1.77 (s, 3H), 3.22 (t, J = 7.3 Hz, 2H), 5.57 (d, J = 5.0 Hz, 1H), 5.95 (d, J = 5.0 Hz, 1H); ^{13}C{^{1}H} (75 MHz, CDCl$_3$) δ 13.72, 20.04, 21.32, 28.02, 31.21, 37.42, 42.02, 103.40, 129.01, 129.32, 164.86, 166.22; IR (CDCl$_3$) 1672 cm^{-1}; MS m/z (M$^+$) 221. HRMS m/z for C$_{14}$H$_{23}$NO calcd 221.1780, found 221.1787.

(*E*)-*N*-Phenyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (8): 64% yield of a pale yellow solid; mp 32−33 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.31 (s, 9H), 2.51 (d, J = 0.8 Hz, 3H), 6.23 (d, J = 5.2 Hz, 1H), 6.80 (dq, J = 0.8, 5.2 Hz, 1H), 7.18 (m, 1H), 7.45 (m, 4H); ^{13}C{^{1}H} (50 MHz, CDCl$_3$) δ 17.02, 30.49, 39.42, 104.68, 122.11, 125.41, 126.50, 128.40, 128.98, 137.45, 165.94, 167.10; IR (CDCl$_3$) 1683 cm^{-1}; MS m/z (M$^+$) 241. Anal. Calcd for C$_{16}$H$_{19}$NO: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.44; H, 7.83; N, 5.73.

(*Z*)-*N*-Phenyl-3-(1,2,2-trimethylpropylidene)-4-pyrrolin-2-one (8): 5% yield of a pale yellow solid; mp 48−50 °C; ^{1}H NMR (300 MHz, C$_6$D$_6$) δ 1.41 (s, 9H), 1.73 (s, 3H), 5.63 (d, J = 5.1Hz, 1H), 6.38 (d, J = 5.1Hz, 1H), 6.89 (m, 1H), 7.08 (m, 2H), 7.42 (m, 2H); ^{13}C{^{1}H} (75 MHz, CDCl$_3$) δ 21.57, 27.97, 37.59, 105.58, 122.08, 125.36, 128.36, 128.84, 128.93, 137.55, 163.73, 166.52; IR (CDCl$_3$) 1688 cm^{-1}; MS m/z (M$^+$) 241; HRMS m/z for C$_{16}$H$_{19}$NO calcd 241.1462, found 241.1459.

***N*-Butyl-3-(1-methylethylidene)-4-pyrrolin-2-one (9)**: 66% yield of a pale yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.27 (hex, J = 7.3 Hz, 2H), 1.47 (pent, J = 7.3 Hz, 2H), 1.96 (s, 3H), 2.34 (s, 3H), 3.40 (t, J = 7.3 Hz, 2H), 5.66 (d, J = 4.9 Hz, 1H), 6.34 (d, J = 4.9 Hz, 1H); ^{13}C{^{1}H} (75 MHz, CDCl$_3$) δ 13.57, 19.87, 20.20, 23.83, 31.11, 41.46, 100.79, 127.64, 129.38, 151.09, 166.95; IR (CDCl$_3$) 1672 cm^{-1};

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MS m/z (M^+) 179; HRMS m/z for $C_{11}H_{17}NO$ calcd 179.1306, found 179.1305.

***N-tert*-Butyl-3-(1-methylethylidene)-4-pyrrolin-2-one** (**10**): 70% yield of a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.97 (s, 3H), 2.33 (s, 3H), 5.63 (d, $J = 5.1$ Hz, 1H), 6.56 (d, $J = 5.1$ Hz, 1H); $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 20.13, 23.98, 28.29, 54.17, 100.09, 127.99, 128.85, 150.00, 167.73; IR ($CDCl_3$) 1678 cm^{-1}; MS m/z (M^+) 179; HRMS m/z for $C_{11}H_{17}NO$ calcd 179.1306, found 179.1292.

Relative Quantum Yield Measurement. Two 5 mm Wilmad 5-28 NMR tubes were silanized prior to use. One tube contained the actinometer solution of 13.8 mg (75 μmol) of benzhydrol and 13.7 mg (75 μmol) of benzophenone in 750 μL of C_6D_6 vacuum-transferred from Na/K benzophenone. Benzhydrol was recrystallized three times from petroleum ether prior to use. The second tube was equipped with a J. Young valve and contained 13 mg (86 μmol) of **5** in 669 μL of C_6D_6. Both tubes were freeze-pump-thawed in vacuo in the dark. The NMR tube containing the actinometer was sealed under vacuum (1 μmHg) and stored in the dark frozen until needed. The tube containing **5** was charged with $Fe(CO)_5$ (10 mol %) followed by 10 psi CO to make the solution 16 mM in CO and pressurized again after collecting each data point. Irradiation was carried out in a Rayonet photochemical reactor using 350 nm bulbs. Reaction progress was monitored by ^{1}H NMR (200 MHz). This procedure was repeated four times and gave reproducible reaction rates.

Kinetics. Experiments were performed in silanized Wilmad 522-PP 5 mm high pressure or J. Young valve NMR tubes (consistent for each set of experiments). In a typical experiment 12.2 mg (86 μmol) of **5** and 600 μL of a 0.13 mM $Fe(CO)_5$ C_6D_6 solution are added to a tube. The solution was freeze-pumped-thawed three cycles and pressurized to the desired CO pressure. The tube was irradiated with four 34 W Phillips Econ-o-watt F40CW/RS/EW-II cool white bulbs at 22 °C or in a Rayonet photochemical reactor using 350 nm bulbs (10 × 10 W) at 22 °C and monitored by ^{1}H NMR. The tube was pressurized again after collecting each data point. The residual benzene ^{1}H resonance was used as an internal standard.

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Supplementary Material Available: Copies of ^{1}H NMR spectra for (*Z*)-**6**, (*E*)-**7**, (*Z*)-**7**, (*E*)-**8**, **9**, and **10** (6 pages). This information 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.