Articles

Synthesis of Cyclopropylpyrrolidines via Reaction of *N*-Allyl-*N*-propargylamides with a Molybdenum Carbene Complex. Effect of Substituents and Reaction Conditions

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Previous studies have demonstrated that group 6 carbene complexes react with α,ω-enynes to form vinylcyclopropane derivatives in good to excellent yield, and that the length and composition of the tether between the alkyne and the alkene often has a dramatic impact on the viability of this reaction pathway. The reactivity of allylpropargyl amine derivatives with pentacarbonyl(1-methoxypentylidene)molybdenum(0) (**14a**) was investigated in order to provide further insight into the steric and electronic factors controlling this reaction. Treatment of allylpropargyl amines with **14a** failed to produce the desired cyclization products while treatment of allylpropargyl amides with **14a** led to the expected cyclopropylpyrrolidine systems in good to excellent yields. Higher yields are obtained when the reaction is conducted in a sealed vial in the presence of atmospheric oxygen.

Studies of the reactivity of molybdenum and chromium carbene complexes with 1,6- and 1,7-enynes (**1**) have demonstrated that the length and composition of the tether between the alkyne and the alkene and the nature of the substituents on the alkene play critical roles in determining the outcome of this cyclization reaction.[1,2] Generally, molybdenum carbene complexes (**2**, M = Mo) react with these substrates to produce vinylcyclopropanes **3** in good to excellent yield (see Scheme 1). Though the enol ethers can generally be isolated, they are frequently sensitive to hydrolysis and are often directly converted to the corresponding ketone, **4**. Substrates having an unsubstituted alkane tether give vinylcyclopropanes provided that an appropriate electron-withdrawing substituent is situated on the olefin.[1a,c] Alternatively, substituents appropriately situated on the tether can increase the propensity for intramolecular cyclopropanation, again leading to the formation of vinylcyclopropanes.[1a,i] Allyl propargyl ethers have also been found to participate in this reaction (Scheme 1, X = O).[1a,i] Successful cyclization of **1** (X = O) was demonstrated to result from the σ-electron-withdrawing ability of the ether oxygen.

In order to expand the scope of this reaction, we sought to investigate the reactivity of allyl propargyl amine derivatives (**1**, X = RN) with group 6 Fischer carbene complexes. Our motives for doing so were two-fold. Mechanistically, since nitrogen can be bound to a third substituent it was envisioned that there might be significant potential for the study of more subtle details of the steric and electronic factors governing this process with these substrates. Synthetically, the cyclopropylpyrrolidine system (**4**, X = RN) produced in this reaction is found in several biologically active natural product frameworks, such as CC-1065 and the duocarmycins[3] and is also potentially convertible to a variety of other nitrogen-containing polycyclic assemblies.

Shortly after the studies described herein were initiated, two examples of related reactions of allylpropargyl amine derivatives with chromium carbene complexes were reported. In their studies of reactions of enynes with chromium carbene complexes bound to a solid support, Katz and Yang demonstrated that, following adsorption on silica gel, amine **5** reacts with complex **6** to give, after enol ether hydrolysis, cyclopropane derivative **7** in 51% yield.[2] Additionally, Mori and Watanuki reported that allyl propargyl sulfonamides, such as **8**, readily react with chromium carbene complex **9** to give cyclopropane derivative **10** in 91% overall yield after conversion to the corresponding ketone.[4]

Results and Discussion

Substrate Preparation. Amine **5** was prepared in two steps from allylamine. Initial treatment of an excess (6 equiv) of allylamine with benzyl bromide gave *N*-allyl-*N*-benzylamine in 92% yield.[5] Subsequent exposure to propargyl bromide in the presence of sodium hydride in THF produced **5** in 60% yield (eq 3).[6] Amine **11** was prepared via reductive amination of 4-nitrobenzaldehyde

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

(1) (a) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424−8434. (b) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737−738. (c) Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461−1463. (d) McCallum, J. S.; Kunng, F. A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346−2360. (e) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676−2678. (f) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070−2071. (g) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 2014−3015. (h) Hoye, T. R.; Rehberg, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 2841−2842. (i) Harvey. D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311−6314.

(2) Katz, T. J.; Yang, G. X. Q. *Tetrahedron Lett.* **1991**, *32*, 5895−5898.

(3) For recent reviews, see: (a) Boger, D. L. *Advances in Heterocyclic Natural Products Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; vol. 2, pp 1−177. (b) Boger, D. L. *Pure Appl. Chem.* **1993**, *65*, 1123−1132. (c) Boger, D. L.; Johnson, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3642−3649.

(4) Mori, M. Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082−1084.

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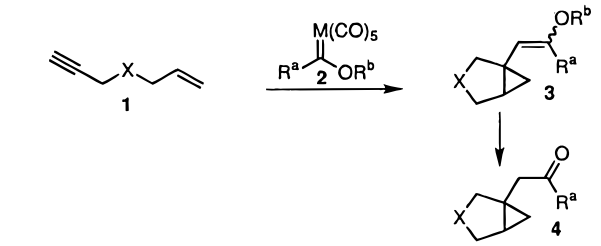
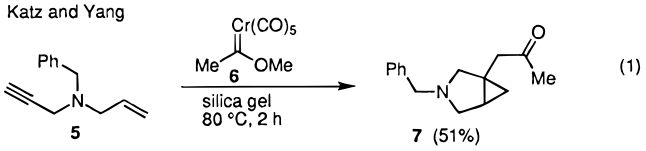
Scheme 1

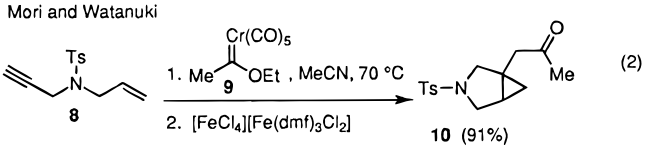


Katz and Yang



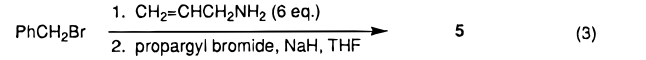
(1)

Mori and Watanuki

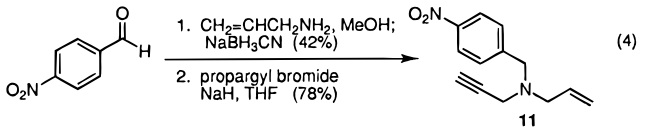


(2)

with allylamine followed by alkylation with propargyl bromide in the presence of sodium hydride in 33% overall yield (eq 4).

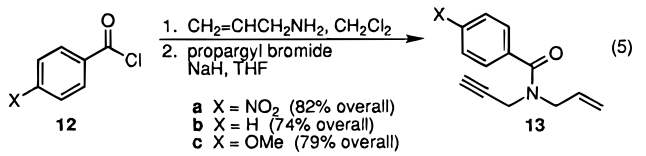


(3)



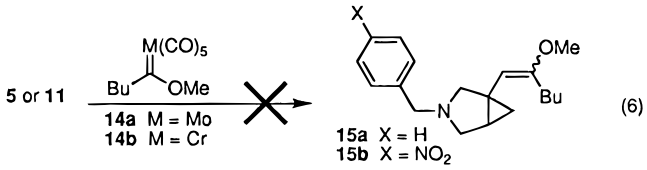
(4)

Amides **13a**−**c** were prepared by treatment of allyl amine with the appropriate aroyl chloride **12a**−**c** in CH_2Cl_2 to give the corresponding *N*-allylamides.[7] Subsequent alkylation of the *N*-allylamides with propargyl bromide in the presence of sodium hydride[8] produced *N*-allyl-*N*-propargylamides **13a-c** in overall yields ranging from 74 to 82%.



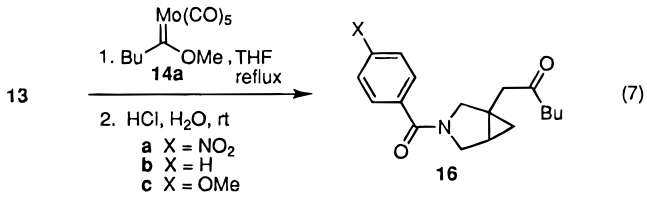
(5)

Carbene Complex Cyclization Studies. Although **5** reacted smoothly with **6** when bound to silica gel,[2] treatment of either **5** or **11** with molybdenum complex **14a** or chromium complex **14b** under a variety of solution-based reaction conditions did not lead to facile formation of the desired cyclopropane derivative **15** or the corresponding enol ether hydrolysis product. Though amines **5** and **11** were consumed in this reaction, only a complex mixture of nonisolable products was produced. It appears that the carbene complex reacts with the alkyne, presumably forming the desired vinylcarbene complex intermediate. However, subsequent intramolecular cyclopropanation of the in situ-generated vinylcarbene complex does not occur, with oligomerization/polymerization of the alkyne occurring instead.



(6)

The reactivity of amides **13a**−**c** with complex **14a** was next investigated. Previous studies had demonstrated that related cyclization reactions proceed well at reflux in both THF and benzene.[9] Treatment of 4-nitrobenzamide derivative **13a** with **14a** in THF at reflux under nitrogen, followed by treatment with dilute hydrochloric acid, produced cyclopropane **16** in 38% yield. Though the starting material had been consumed, no other isolable products were obtained. Under the same reaction conditions, benzamide **13b** produced **16b** in 35% yield while 4-methoxybenzamide derivative **13c** gave **16c** in 34% yield.



(7)

In previous studies of the reactivity of allyl propargyl ethers with molybdenum and chromium carbene complexes, sealed vial conditions, wherein the solvent and reaction components are heated in a closed container, were found to give optimum results.[1a,i] The improved yield under these conditions was thought to be primarily due to reduction of the amount of volatile enyne substrate lost during the reaction. Though evaporative loss of substrate is not a problem with the higher molecular weight amides **13a**−**c**, improved product yields were obtained with all three substrates under sealed vial conditions. Thermolysis of **13a** with complex **14a** in THF in a sealed vial at 100 °C gave, after acid-catalyzed enol ether hydrolysis, cyclopropanation product **16a** in 74% yield. Likewise, complexes **13b** and **13c** produced cyclopropanation products **16b** and **16c** in 56% and 58% yield, respectively.

This dramatic improvement in isolated yield led us to explore in more detail the effect of variations in the reaction conditions. The reaction of **13a** with complex **14a** to produce **16a** was used as the standard reaction in this study. The results are summarized in Table 1. The reaction was performed with air and nitrogen atmospheres under both sealed vial and atmospheric pressure conditions. Sealed vial conditions allowed for temperatures higher than reflux to be employed. While attempting to ensure that temperature alone was not responsible for the improved yield, 1,4-dioxane, which was anticipated to function as a higher boiling surrogate

(5) For a related procedure for the preparation of secondary amines, see: Ben-Efraim, D. A. *Tetrahedron* **1973**, *29*, 4111−4125.

(6) Amine **5** has been previously prepared by a different route. See ref 2.

(7) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman Scientific & Technical: Essex, England, 1989; p 709.

(8) Related procedures for the preparation of dialkylamides have previously been reported. See: Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802−4809.

(9) (a) Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 7806−7807. (c) Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559−5561.

Table 1. Reaction Conditions Investigated for the Conversion of 13a and 14a to 16a

entry	atmosphere	pressure	temp °C	solvent	yield, %
1	air	sealed vial	100	THF	74
2	air	sealed vial	67	THF	72
3	air	sealed vial	100	benzene	57
4	air	sealed vial	100	1,4-dioxane	21
5	N_2	sealed vial	100	THF	50
6	N_2	sealed vial	100	1,4-dioxane	<10
7	N_2	sealed vial	67	THF	54
8	air	atmospheric	67	THF	52
9	air	atmospheric	100	1,4-dioxane	16
10	N_2	atmospheric	67	THF	38
11	N_2	atmospheric	100	1,4-dioxane	0

of tetrahydrofuran, was employed in reactions 4, 6, 9, and 11. Under sealed vial conditions, carbon monoxide produced during the reaction cannot escape from the reaction flask. Reactions performed at atmospheric pressure were carried out under a flow of the indicated atmosphere so that carbon monoxide produced during the reaction might be flushed from the reaction medium after diffusion into the gas phase. All reactions were heated for 1 h, at which time starting material appeared to be completely consumed, based on analysis of the reaction mixture by thin layer chromatography.

Better yields were consistently obtained when air was present than when a nitrogen atmosphere was employed (1 vs 5; 4 vs 6; 8 vs 10; 9 vs 11). Under sealed vial conditions, it was found that the thermolysis temperature did not dramatically alter the outcome of the reaction (1 vs 2; 5 vs 7). Though anticipated to be of similar coordination ability to THF, reactions carried out in 1,4-dioxane were found to produce lower yields of **16a** than reactions performed in THF. Replacement of THF with benzene also gave poorer results (1 vs 3). Open flask conditions, in which carbon monoxide can dissipate from the reaction, gave consistently lower yields than those performed under sealed vial conditions in which carbon monoxide would be contained in the reaction environment (2 vs 8; 4 vs 9).

The containment of carbon monoxide in the reaction medium may enhance the outcome of the reaction in several ways. The initial step in this and many other group 6 carbene complex reaction pathways is thought to be dissociation or displacement of carbon monoxide from the carbene complex. As summarized in Scheme 2, alkyne coordination and insertion leads to vinylcarbene intermediate, **18**. Subsequent olefin coordination (**19**) followed by addition and reductive elimination leads to **20** and "$Mo(CO)_4$". The "$Mo(CO)_4$" produced in this reaction is envisioned to be transiently coordinated to either the product, the solvent, or both. Some of the "$Mo(CO)_4$" is converted to $Mo(CO)_6$, which can be recovered from the reaction mixture. The additional equivalents of CO necessary to convert "$Mo(CO)_4$" to $Mo(CO)_6$ are obtained either by recoordination of the metal to the carbon monoxide initially dissociated from the carbene complex or by abstraction of carbon monoxide from carbene complex **14a**.

The presence of a reactive "$Mo(CO)_4$" unit during the reaction could adversely effect the desired reaction pathway in a number of different ways. It could coordinate to substrate **13**, through the arene, alkyne, alkene, or amide moiety, or react with the product **20**, via the strained cyclopropane ring.[10] Carbon monoxide may convert the reactive "$Mo(CO)_4$" to the air stable, relatively nonreactive $Mo(CO)_6$.

Tetrahydrofuran may also be responsible for modifying the reactivity of the "$Mo(CO)_4$". Ligand exchange is quite rapid with molybdenum(0) complexes[11] and the formation of mixed carbon monoxide/THF complexes, such as $Mo(CO)_5(THF)$, $Mo(CO)_4(THF)_2$, and $Mo(CO)_3(THF)_3$, will certainly occur when the reaction is performed in THF.[12] Though the THF ligands in these complexes are relatively labile, they are probably less reactive than analogous coordination complexes of 1,4-dioxane and η^2- and η^4-benzene complexes. The η^6-benzene complex, $(C_6H_6)Mo(CO)_3$, which is anticipated to eventually be produced in benzene via loss of an additional 1 equiv of carbon monoxide, is entropically more stable than the η^2- and η^4-benzene complexes but undergoes relatively rapid ligand substitution.[11]

Oxygen may enhance the viability of the desired reaction pathway by partially oxidizing the "$Mo(CO)_4$", thus generating less reactive metal material.[13] Material of this type, though not characterized in these studies, appears to precipitate from the reaction mixture during the reaction.[14] Partial oxidation of the metal center is expected to reduce the ability of "$Mo(CO)_4$" to react in a deleterious fashion with either the substrate or the desired product. Reactions involving chromium carbene complexes are often treated with air after the reaction has been completed in order to destroy remaining Cr(0) material and facilitate isolation of the organic product.[14]

In summary, cyclopropylpyrrolidines are readily prepared via reaction of *N*-allyl-*N*-propargylbenzamide derivatives with molybdenum carbene complexes while the corresponding *N*-allyl-*N*-propargyl-*N*-benzylamine derivatives fail to smoothly cyclize. Though we initially anticipated that the electron-donating/electron-withdrawing ability of substituents on the aromatic ring might dramatically influence the outcome of this reaction, their effect in the case of the benzamide derivatives was relatively slight, with the 4-nitro derivative giving higher yields of the desired product than the corresponding unsubstituted or 4-methoxy-substituted derivatives. The reaction proceeds best when carried out in a sealed vial in the presence of air with THF as the solvent.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were recorded at either 300 MHz or 500 MHz. IR spectra were recorded on a FT-IR spectrophotometer. Low resolution mass spectra were recorded on a mass-selective detector (20 eV) interfaced with a gas chromatograph. High resolution mass spectra were performed at the University of California at Riverside Mass Spectrometry Facility. Elemental analysis were performed by Galbraith Laboratories, Inc. Column chromatography was performed with florisil (100−200 mesh) or silica gel (200−425 mesh). All reagents were obtained from commercial suppliers and used as received unless otherwise

(10) Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204−211.

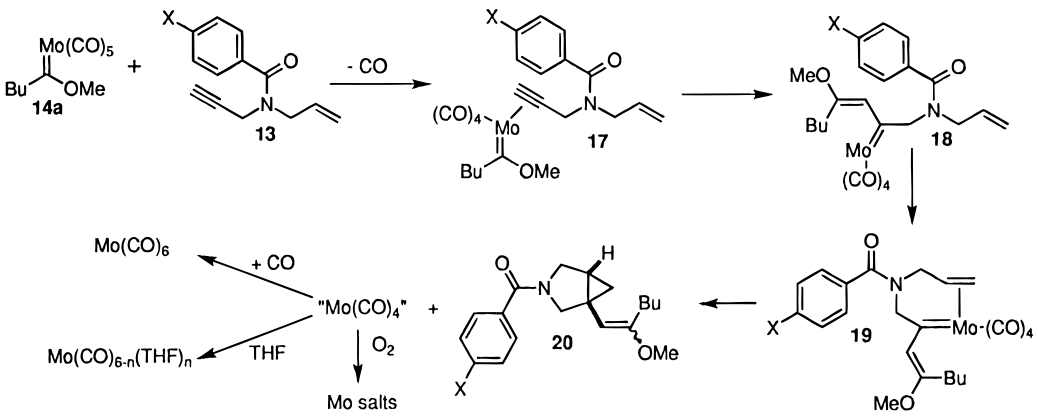
(11) For a recent discussion, see: Li, J.; Schreckenbach, G. Ziegler, T. *J. Am. Chem. Soc.* **1995**, *117*, 486−494.

(12) (a) Werner, R. P. M.; Coffield, T. H. *Chem. Ind.* **1960**, 936−937. (b) Muetterties, E. L.; Bleeke, J. R.; Sievert, A. C. *J. Organomet. Chem.*, **1979**, *178*, 197−216. (c) Hoff, C. D. *J. Organomet. Chem.* **1985**, *282*, 201−214. (d) Nolan, S. P.; Lopez de la Vega, R.; Hoff, C. D. *Organometallics* **1986**, *5*, 2529−2537.

(13) Less than stoichiometric quantities of oxygen are present in the reaction flask when "sealed vial" conditions are employed. Approximately 0.31 mmol of substrate and approximately 20 mL of solvent are sealed in a reaction flask with a 25 mL capacity. Approximately 0.14 equiv of O_2 are present.

(14) McGuire, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538−5540.

Scheme 2



indicated. Benzene and tetrahydrofuran were distilled from potassium/benzophenone ketyl under a nitrogen atmosphere. Diethyl ether was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. 1,4-Dioxane was purified according to a literature procedure.[15] Disappearance of starting material was monitored by thin layer chromatography.

***N*-Allyl-*N*-benzylamine.** Benzyl bromide (2.00 g, 11.7 mmol) was added dropwise to neat allylamine (5.26 mL, 70.2 mmol) at 0 °C. After 16 h at room temperature, the reaction was quenched with aqueous $NaHCO_3$ solution (10 mL), extracted with Et_2O (3 × 10 mL), and dried over K_2CO_3. Purification by silica gel chromatography gave *N*-allyl-*N*-benzylamine (1.58 g, 92%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 1 H), 3.23 (d, J = 5.9 Hz, 2 H), 3.73 (s, 2 H), 5.06 (dd, J = 10.3, 0.8 Hz, 1 H), 5.14 (dd, J = 17.4, 1.2 Hz, 1 H), 5.88 (ddt, J = 17.4, 10.3, 5.9 Hz, 1 H), 7.17−7.27 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 53.2, 115.9, 126.9, 128.1, 128.3, 136.8, 140.2; IR (neat) 1643 cm^{-1}; LRMS (EI) *m*/*z* (%) 147 (M^+, 16), 146 (36), 91 (100), 70 (17), 56 (39), 41 (16); HRMS (EI) calcd for $C_{10}H_{13}N$ (M^+) 147.1048, found 147.1043.

***N*-Allyl-*N*-benzyl-*N*-propargylamine (5).** To a solution of *N*-allyl-*N*-benzylamine (250 mg, 1.70 mmol) in THF (10 mL) was added NaH (80% dispersion in mineral oil, 60.0 mg, 2.04 mmol). Propargyl bromide (80% in toluene) was then added in 3 portions (182 μL per addition, 546 μL total, 5.95 mmol) over an 8 h period. After 16 h, the reaction mixture was quenched with H_2O, extracted with Et_2O (3 × 15 mL), dried over K_2CO_3, concentrated in vacuo, and chromatographed on silica gel to give **5** (175 mg, 60%). Spectral data for **5** were in agreeement with that previously reported.[2]

***N*-Allyl-*N*-(4-nitrobenzyl)amine.** To a solution of 4-nitrobenzaldehyde (1.00 g, 6.62 mmol) in MeOH (20 mL) was added allylamine (1.00 mL, 13.2 mmol). After 4 h, the reaction mixture was cooled to 0 °C and $NaBH_3CN$ (276 mg, 4.39 mmol) was added. The reaction mixture was slowly warmed to room temperature and, after 24 h, sequentially quenched with 10% aqueous HCl (10 mL) and brought to basic pH with 10% aqueous NaOH (approximately 20 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organics were dried over K_2CO_3, concentrated in vacuo and chromatographed on silica gel to give *N*-Allyl-*N*-(4-nitrobenzyl)amine (532 mg, 42%) which was >98% pure by NMR and taken on without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (br s, 1 H), 3.27 (d, J = 6.0 Hz, 2 H), 3.90 (s, 2 H), 5.14 (dd, J = 10.3, 1.0 Hz, 1 H), 5.20 (dd, J = 17.4, 1.3 Hz, 1 H), 5.91 (ddt, J = 16.9, 10.3, 6.0 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 2 H), 8.18 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 52.3, 116.5, 123.6, 128.6, 136.2, 148.1, 158.1; IR (neat) 3337, 1604 cm^{-1}; LRMS (EI) *m*/*z* (%) 193 (6), 192 (M^+, 54), 136 (100), 56 (45), 41 (64).

***N*-Allyl-*N*-(4-nitrobenzyl)-*N*-propargylamine (11).** To a solution of *N*-allyl-*N*-(4-nitrobenzyl)amine (224 mg, 1.17 mmol) in THF (10 mL) was added NaH (80% dispersion in mineral oil, 38.5 mg, 1.28 mmol) followed by propargyl bromide (80% in toluene, 779 μL, 6.99 mmol). After 36 h, the reaction mixture was quenched with H_2O, extracted with Et_2O (3 × 15 mL), dried over K_2CO_3, concentrated in vacuo, and chromatographed on silica gel to give **11** (216 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (br s, 1 H), 3.18 (d, J = 6.4 Hz, 2 H), 3.32 (s, 2 H), 3.74 (s, 2 H), 5.20 (d, J = 10.1 Hz, 1 H), 5.29 (dd, J = 17.1, 1.5 Hz, 1 H), 5.84 (ddt, J = 17.0, 6.5, 10.3 Hz, 1 H), 7.54 (d, J = 8.3 Hz, 2 H), 8.54 (d, J = 7.81 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.5, 56.4, 56.6, 73.7, 77.7, 118.6, 123.5, 129.5, 134.8, 146.5, 147.2; IR (neat) 3297, 3079, 1604, 1521, 1346, cm^{-1}; LRMS EI *m*/*z* 231 (7), 230 (M^+, 37), 229 (35), 203 (100), 191 (46), 136 (74), 94 (77), 78 (75), 41 (37). HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$ (M^+) 230.1055, found 230.1055.

General Procedure for the Preparation of *N*-Allylamides. The benzoyl chloride was added dropwise to a solution of allylamine in CH_2Cl_2. After the specified time, 10% aqueous NaOH was added and the reaction mixture was extracted with CH_2Cl_2. The combined organics were dried over K_2CO_3 and concentrated in vacuo.

***N*-Allyl-4-nitrobenzamide.**[16] Following the general procedure, a solution of allylamine (404 μL, 5.39 mmol) in CH_2Cl_2 (5.0 mL) was treated with 4-nitrobenzoyl chloride (1.00 g, 5.39 mmol). After 1.5 h, *N*-Allyl-4-nitrobenzamide (1.05 g, 95%) was obtained as a white solid: mp = 119−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (t, J = 5.8 Hz, 2 H), 5.22 (d, J = 10.6, 1 H), 5.27 (dd, J = 17.2, 1.1 Hz, 1 H), 5.91 (ddt, J = 16.7, 11.0, 5.6 Hz, 1 H), 6.40 (s, 1 H), 7.94 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.7, 117.4, 123.8, 128.2, 133.4, 140.0, 149.6, 165.3; IR (KBr) 3291, 3238, 1640 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{10}N_2O_3$ (M^+) 206.0691, found 206.0697.

***N*-Allylbenzamide.** Following the general procedure, at 0 °C allylamine (1.31 mL, 17.5 mmol) in CH_2Cl_2 (5.0 mL) was treated with benzoyl chloride (2.03 mL, 17.5 mmol). After 1 h, *N*-allylbenzamide was purified by chromatography on silica gel (2.45 g, 87%); ^{1}H NMR (300 MHz, C_6D_6) δ 3.84 (t, J = 5.7 Hz, 2 H), 4.90 (dd, J = 10.3, 1.1 Hz, 1 H), 4.97 (dd, J = 17.3, 1.3 Hz, 1 H), 5.60−5.72 (m, 2 H containing 5.66 (ddt, J = 16.3, 10.9, 5.5 Hz, 1 H)), 7.00−7.12 (m, 3 H), 7.62 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 42.5, 115.7, 127.6, 128.5, 131.2, 135.08, 135.14, 167.1; IR (KBr) 3309, 1642 cm^{-1}.

***N*-Allyl-4-methoxybenzamide.** Following the general procedure, 4-methoxybenzoyl chloride (400 μL, 2.96 mmol) was added to a solution of allylamine (244 μL, 3.25 mmol) in CH_2Cl_2 (5.0 mL). After 20 h, *N*-allyl-4-methoxybenzamide was purified by chromatography on silica gel (513 mg, 91%): mp = 44−47 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 3.20 (s, 3 H), 3.95 (br t, J = 5.6 Hz, 2 H), 4.93 (d, J = 9.9 Hz, 1 H), 5.05 (dd, J = 17.0, 1.2 Hz, 1 H), 5.76 (ddt, J = 16.6, 10.9, 5.5 Hz, 1 H), 6.44 (br s, 1 H), 6.67 (d, J = 8.7 Hz, 2 H), 7.80 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 42.6, 54.8, 113.8, 115.6, 127.5, 129.6, 135.4, 162.4, 167.1; IR (KBr) 3320, 3079, 1637 cm^{-1};

(15) Perrin D. D., Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press Ltd: Oxford, England, 1988, pp 164−165.

(16) This compound has been reported previously. See: (a) Agwada, V. C. *J. Chem. Eng. Data* **1984**, *29*, 231−235. (b) Agwada, V. C. *Biomed. Mass Spec.* **1984**, *11*, 497−501.

LRMS EI *m/z* (%) 191 (M^+, 10), 135 (100), 107 (14), 92 (21), 77 (24); HRMS (EI) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0935.

General Procedure for the Preparation of *N*-Allyl-*N*-propargylamides (13a−c). To a solution of the *N*-allylbenzamide in THF was added NaH (80% dispersion in mineral oil) followed by propargyl bromide (80% in toluene). After 36 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The combined organics were dried over K_2CO_3, concentrated in vacuo, and chromatographed on silica gel to give the *N*-allyl-*N*-propargylamide.

***N*-Allyl-*N*-propargyl-4-nitrobenzamide (13a).** Following the general procedure, N-allyl-4-nitrobenzamide (2.90 g, 14.1 mmol) in THF (50 mL) was treated with NaH (80% dispersion in mineral oil, 507 mg, 16.9 mmol) and propargyl bromide (80% in toluene, 9.41 mL, 84.5 mmol) to give **13a** (2.96 g, 86%): mp = 41−42 °C; ^{1}H NMR (300 MHz, C_6D_6, 80 °C) δ 1.91 (t, J = 2.3 Hz, 1 H), 3.79 (br s, 4 H), 4.91−4.97 (m, 2 H), 5.42−5.55 (m, 1 H), 7.08 (d, J = 8.5 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 49.2, 72.8, 78.8, 118.2, 123.6, 127.9, 132.5, 141.8, 148.8, 168.6; IR (neat) 3291, 3081, 2120, 1643 cm^{-1}; LRMS EI *m/z* (%) 243 (M^+ − 1, 4), 205 (13), 203 (6), 150 (100). HRMS (EI) calcd for $C_{13}H_{12}N_2O_3$ (M^+) 244.0848, found 244.0848. Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

***N*-Allyl-*N*-propargylbenzamide (13b).**[17] Following the general procedure, a solution of *N*-allylbenzamide (2.46 g, 15.3 mmol) in THF (50 mL) was treated with NaH (550 mg, 80% dispersion in mineral oil, 18.3 mmol) and propargyl bromide (80% in toluene, 5.11 mL, 45.8 mmol) to give **13b** (2.59 g, 85%). Spectral data for **13b** was in agreement with that previously reported.[17] ^{1}H NMR (300 MHz, C_6D_6, 70 °C) δ 1.92 (t, J = 2.3 Hz, 1 H), 3.96 (br s, 4 H), 4.94 (d, J = 9.3 Hz, 1 H), 4.98 (d, J = 15.4 Hz, 1 H), 5.57 (ddt, J = 16.6, 10.9, 5.5 Hz, 1 H), 7.04−7.06 (m, 3 H), 7.38−7.41 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 35.9, 49.2, 72.3, 79.6, 117.7, 127.4, 128.4, 129.7, 133.3, 136.7, 170.7; IR (neat) 3291, 3082, 1641 cm^{-1}; LRMS (EI) *m/z* (%) 198 (M^+, 16), 158 (18), 105 (100), 77 (86); HRMS (EI) calcd for $C_{13}H_{12}NO_2$ (M^+ − H) 198.0919; found 198.0922.

***N*-Allyl-*N*-propargyl-4-methoxybenzamide (13c).** Following the general procedure, *N*-allyl-4-methoxybenzamide (560 mg, 2.93 mmol) in THF (20 mL) was treated with NaH (80% dispersion in mineral oil, 104 mg, 3.52 mmol) and propargyl bromide (80% in toluene, 0.98 mL, 8.80 mmol) to give **13c** (580 mg, 87%): ^{1}H NMR (300 MHz, C_6D_6, 70 °C) δ 1.89 (t, J = 2.0 Hz, 1 H), 3.23 (s, 3 H), 4.01 (br s, 4 H), 4.97 (d, J = 11.0 Hz, 1 H), 5.02 (d, J = 18.3 Hz, 1 H), 5.62 (ddt, J = 16.7, 11.0, 5.6 Hz, 1 H), 6.64 (d, J = 8.6 Hz, 2 H), 7.45 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6, 70 °C) δ 36.2, 49.4, 54.9, 72.1, 79.9, 114.0, 117.6, 128.8, 129.5, 133.6, 161.5, 170.6; IR (neat) 3290, 3078, 1633 cm^{-1}; LRMS EI *m/z* 228 (M^+ − 1, 1), 190 (2), 188 (3), 135 (100), 107 (8). HRMS (EI) calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1105.

General Procedure for "Sealed Vial" Conditions (16a−c). The N-allyl-N-propargylamide derivative and the carbene complex were dissolved in THF (20.0 mL) in a 25 mL sealable glass vial. The vial was then sealed with a rubber-lined screw cap and Teflon tape. After heating at 100 °C behind a blast shield, the reaction was cooled to room temperature and treated with 10% aqueous HCl (2 mL) for 1 h. The reaction mixture was then concentrated in vacuo and chromatographed on silica gel to give the indicated product.

(5*β*)-*N*-(4-Nitrobenzoyl)-1*β*-(2-oxohexanyl)-3-azabicyclo-[3.1.0]hexane (16a). Following the general procedure, **13a** (50.0 mg, 0.205 mmol) and **14a** (103 mg, 0.307 mmol) in THF gave **16a** (49.0 mg, 74%): mp = 73−75 °C; ^{1}H NMR (500 MHz, C_6D_6, rt, approximately a 1:1 mixture of amide rotamers) δ 0.14 (t, J = 4.4 Hz, 1 H), 0.20−0.27 (m, 3 H), 0.76 (t, J = 7.3 Hz, 3H), 0.80−0.88 (m, 5 H containing 0.83 (t, J = 7.3 Hz, 3 H), 1.10 (sextet, J = 7.3 Hz, 2 H), 1.17 (sextet, J = 7.3 Hz, 2 H), 1.37 (pentet, J = 7.3 Hz, 2 H), 1.45 (pentet, J = 7.3 Hz, 2 H), 1.80 (d, J = 17.6 Hz, 1 H), 1.84−1.93 (m, 6 H), 2.10 (d, J = 17.6 Hz, 1 H), 2.82 (d, J = 10.3 Hz, 1 H), 3.06 (d, J = 10.3 Hz, 1 H) 3.18 (dd, J = 10.3, 3.9 Hz, 1 H), 3.27 (d, J = 11.7 Hz, 1 H), 3.31 (d, J = 10.3 Hz, 1 H), 3.40 (dd, J = 11.7, 3.9 Hz, 1 H), 4.23 (d, J = 11.7 Hz, 1 H), 4.32 (d, J = 11.7 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 2 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H); IR (neat) 1713, 1634, 1523 cm^{-1}; LRMS EI *m/z* (%) 330 (M^+, 6), 245 (35), 150 (100), 104 (45); HRMS (CI, CH_4) calcd for $C_{18}H_{23}N_2O_4$ (MH^+) 331.1658, found 331.1662. Anal. ($C_{18}H_{22}N_2O_4$) C, H, N.

(5*β*)-*N*-Benzoyl-1*β*-(2-oxohexanyl)-3-azabicyclo[3.1.0]-hexane (16b). Following the general procedure, **13b** (50.0 mg, 0.251 mmol) and **14a** (127 mg, 0.380 mmol) were heated in THF for 1 h to give **16b** (40.1 mg, 56%): ^{1}H NMR (300 MHz, C_6D_6, 80 °C) δ 0.25−0.34 (m, 2 H), 0.78 (t, J = 7.3 Hz, 3 H), 0.96 (dt, J = 7.8, 3.9 Hz, 1 H), 1.15 (sextet, J = 7.3 Hz, 2 H), 1.41 (pentet, J = 7.3 Hz, 2 H), 1.98 (t, J = 7.2 Hz, 2 H), 2.08 (s, 2 H), 3.25 (d, J = 11.0 Hz, 1 H), 3.39 (dd, J = 10.9, 3.6 Hz, 1 H) 3.5−4.2 (very br s, 2 H), 7.06−7.08 (m, 3 H), 7.38−7.42 (m, 2 H); IR (neat) 1713, 1630 cm^{-1}; LRMS EI *m/z* (%) 285 (M^+, 2), 105 (100); HRMS (CI, CH_4) calcd for $C_{18}H_{24}NO_2$ (MH^+) 286.1807, found 286.1816.

(5*β*)-*N*-(4-Methoxybenzoyl)-1*β*-(2-oxohexanyl)-3-azabicyclo[3.1.0]hexane (16c). Following the general procedure, **13c** (50.0 mg, 0.218 mmol) and **14a** (110 mg, 0.327 mmol) were heated in THF for 1 h to give **16c** (36.5 mg, 58%): ^{1}H NMR (300 MHz, C_6D_6, 80 °C) δ 0.28−0.36 (m, 2 H), 0.79 (t, J = 7.3 Hz, 3 H), 0.94−1.01 (m, 1 H), 1.16 (sextet, J = 7.4 Hz, 2 H), 1.42 (pentet, J = 7.4 Hz, 2 H), 2.00 (t, J = 7.3 Hz, 2 H), 2.11 (s, 2 H), 3.29 (d, J = 11.0 Hz, 1 H), 3.33 (s, 3 H), 3.44 (dd, J = 11.0, 3.9 Hz, 1 H), 3.85 (very br s, 1 H), 4.05 (very br s, 1 H), 6.68 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.6 Hz, 2 H); IR (neat) 1713, 1623, 1610 cm^{-1}; LRMS EI *m/z* 315 (M^+, 1), 230 (7), 135 (100). HRMS (CI, CH_4) for $C_{19}H_{26}NO_3$ (MH^+) calcd 316.1913, found 316.1909.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for *N*-allyl-*N*-benzylamine, **5**, *N*-allyl-*N*-(4-nitrobenzyl)-amine, **11**, *N*-allylbenzamide, *N*-allyl-*4*-methoxybenzamide, *N*-allyl-*4*-nitrobenzamide, **13a**, **13b**, **13c**, and ^{1}H NMR for **16a**, **16b**, and **16c** (23 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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(17) This compound has been reported previously. See: Brown, S. W.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1205−1209.