Synthesis of a Benzodiazepine-derived Rhodium NHC Complex by C-H Bond Activation

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The synthesis and characterization of a Rh(I)-NHC complex generated by C-H activation of 1,4-benzodiazepine heterocycle are reported. This complex constitutes a rare example of a carbene tautomer of a 1,4-benzodiazepine aldimine stabilized by transition metal coordination and demonstrates the ability of the catalytically relevant $RhCl(PCy_3)_2$ fragment to induce NHC-forming tautomerization of heterocycles possessing a single carbene-stabilizing heteroatom. Implications for the synthesis of benzodiazepines and related pharmacophores via C-H functionalization are discussed.

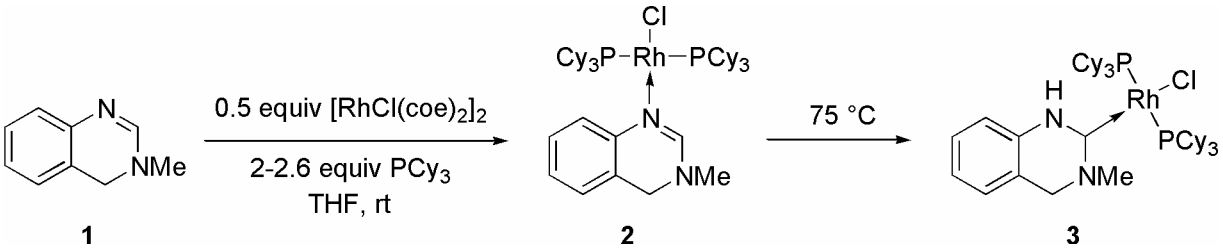
KEYWORDS Benzodiazepines, C-H Activation, Tautomerization, Rhodium, N-Heterocyclic Carbenes, Pre-agostic Interactions, DFT Calculations.

BRIEFS (WORD Style "BH_Briefs"). A rare example of a C5 metallated NHC tautomer of a 1,4-benzodiazepine heterocycle has been prepared under mild conditions via tautomerization of the corresponding aldimine induced by the catalytically-relevant $RhCl(PCy_3)_2$ metal fragment.

MANUSCRIPT TEXT:

The formation of N-heterocyclic carbene (NHC) complexes by direct reaction of common nitrogen-containing heterocycles with transition metal reagents, first discovered by Taube and co-workers with ruthenium imidazole complexes,[1] has become an important reaction in organometallic chemistry. This process is significant due to the ubiquity of NHCs as spectator ligands in homogeneous catalysis,[2] the possible existence of NHC ligands in the chemistry of some metalloenzymes,[1,3] the ability to stabilize uncommon and otherwise unfavorable organic structures via transition metal coordination, and the promise of developing atom-economical catalytic reactions that take advantage of the modified reactivity of the heterocycle NHC tautomer.[4,5] Accordingly, tautomerization reactions involving interconversion of NHC complexes with either N-coordinated or free heterocycles have received intense scrutiny in the last several years.[6] Computational studies by Crabtree and Eisenstein have contributed substantially to elucidating the factors that control the thermodynamics of metal-induced imidazole tautomerization.[3] In addition, more recent work by Ruiz and coworkers[6e] has shown that basic additives are capable of generating kinetically stable NHC complexes from N-bound imidazoles even when the characteristics of the metal fragment are predicted to favor N-coordination.[3] Mechanistic work in our laboratories on the Rh(I)-induced tautomerization of N-bound complex **2** of N-methyl-3,4-dihydroquinazoline **1** to its corresponding C2-metallated carbene tautomer **3** (Scheme 1) revealed a major NHC-forming pathway involving direct participation of only the N1 nitrogen atom, leading us to conjecture that unsaturated heterocycles containing only a single nitrogen atom might engage in similar reactivity.[6a]

Scheme 1.



This hypothesis has received subsequent support by the reports of NHC-forming tautomerization reactions of pyridines and quinolines induced by complexes of iridium, ruthenium, and osmium,

developed independently by the groups of Carmona[6c,i] and Esteruelas.[6b,g,h] Subsequent to their initial reports,[6b,c] our own group found that quinolines and 2-substituted pyridines undergo alkylation[7] by alkenes in the presence of a Rh(I)/PCy_3/HCl-based catalyst system[5c,8] which has been found to generate NHC tautomers of benzimidazole substrates under catalytically-relevant conditions.[9] Consequently, we have become interested in elucidating the scope of heterocycles capable of NHC-forming tautomerization reactions induced by the rhodium catalysts employed in our earlier development of C-H functionalization chemistry.

Here we wish to report the synthesis and characterization of the Rh(I)-(amino)(aryl)carbene complex **7** (Scheme 2, Figures 2 and 5), which is a rare example of an NHC tautomer of a 1,4-benzodiazepine ring system (Figure 1) stabilized via transition metal coordination. The formation of this material also demonstrates the ability of the strongly π-basic $RhCl(PCy_3)_2$ fragment to induce NHC-forming tautomerization of heterocycles possessing only a single carbene-stabilizing heteroatom, a reaction we believe may have significance to the recently disclosed Rh catalyzed alkylation of quinolines and 2-substituted pyridines.[7] The stability of **7** with respect to its N-bound tautomer **8** (Figure 3) and the mild conditions of its formation suggest that transition metal NHC complexes may be

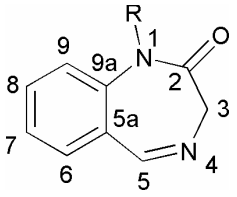


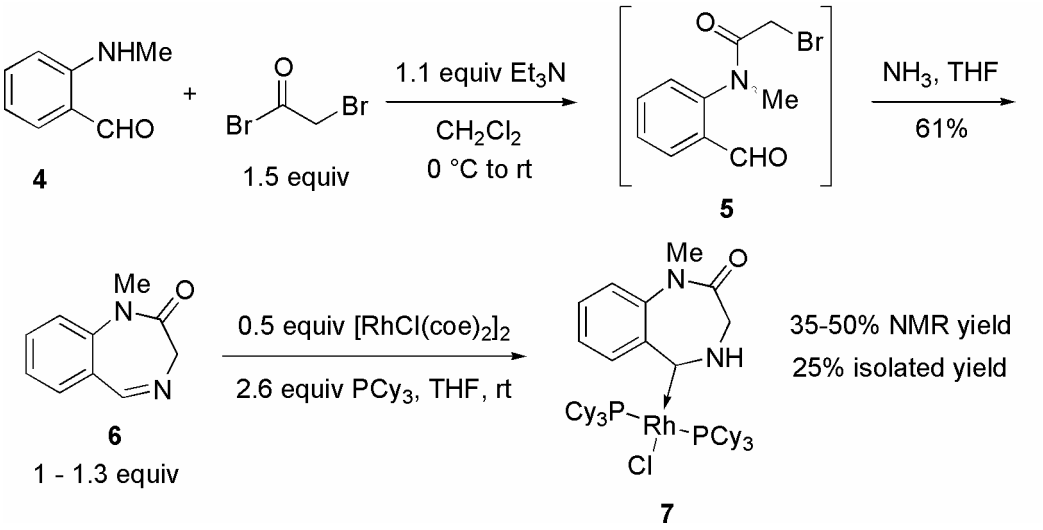
Figure 1. Numbering Scheme Employed in Reference to 1,4-Benzodiazepine Heterocycles.

synthesized by direct reactions with a wider array of heterocycles than previously thought, including stabilized[10] cyclic aldimines of varying ring sizes as well as 6-membered aromatic heterocycles such as pyridines and quinolines.

Benzodiazepine **6**, prepared from 2-methylamino-benzaldehyde **4** as illustrated in Scheme 2, was identified as a promising substrate for investigating NHC-formation on the basis of DFT calculations

using PMe_3 as a computational model for the PCy_3. These predicted the model NHC complex **7'** (Figure 2) to be close in energy to its N-bound tautomer **8'** (Figure 3, also see supporting information).[11]

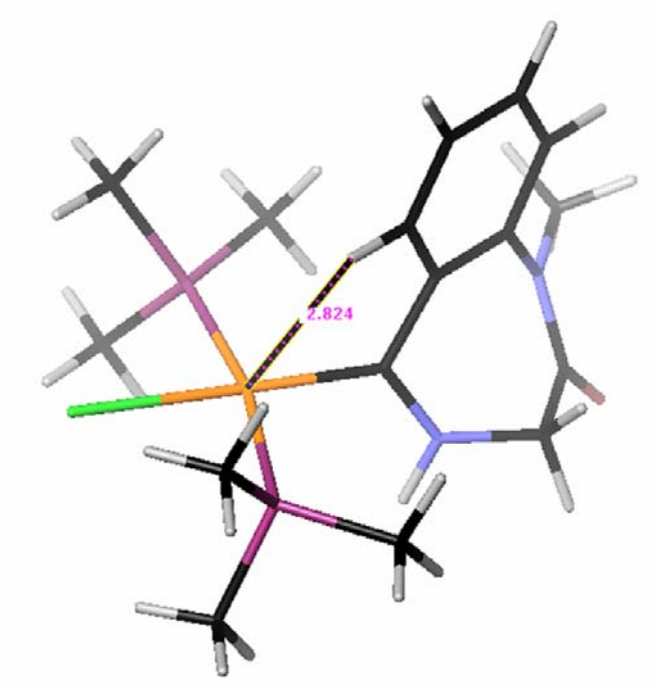
Scheme 2.

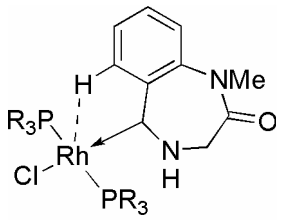


Further, we anticipated that transformations involving the 'activated' NHC ligand could provide new strategies for modular syntheses of 5-aryl and alkyl 1,4-benzodiazepines, which have been categorized as privileged structures due to their wide-ranging biological activity.[12] Most notably, the 1,4-benzodiazepine sedative/hypnotics are among the most widely prescribed of all psychoactive drugs due to their efficacy and relative safety in the treatment of anxiety disorders, insomnia, and epilepsy.[13]

Addition of **6** to a THF solution containing $RhCl(PCy_3)_2$ generated *in situ* from the reaction of $[RhCl(coe)_2]_2$ with 2.6 equivalents of PCy_3[14] under an inert atmosphere[15] resulted in the formation of a brown solution that within hours developed an intense yellow-green hue. Monitoring the progress of the reaction by NMR spectroscopy[16] (Figure 4) led to the observation of clean formation of a new complex exhibiting two singlets in the ^1H NMR spectrum at δ_H = 3.35 (3 H) and δ_H = 9.35 (1 H), accompanied by a broad doublet in ^{31}P NMR spectrum at δ_P = 20.75 with J_{RhP} = 146 Hz. After one day, these signals began to decay with concomitant formation of **7**, as determined by the appearance of its diagnostic resonances at δ_H = 9.6, 8.55, 7.1, 4.1, and 3.7. Although we have been unable to isolate the transient species, its spectroscopic features are consistent with its assignment as **8**, because N-binding is

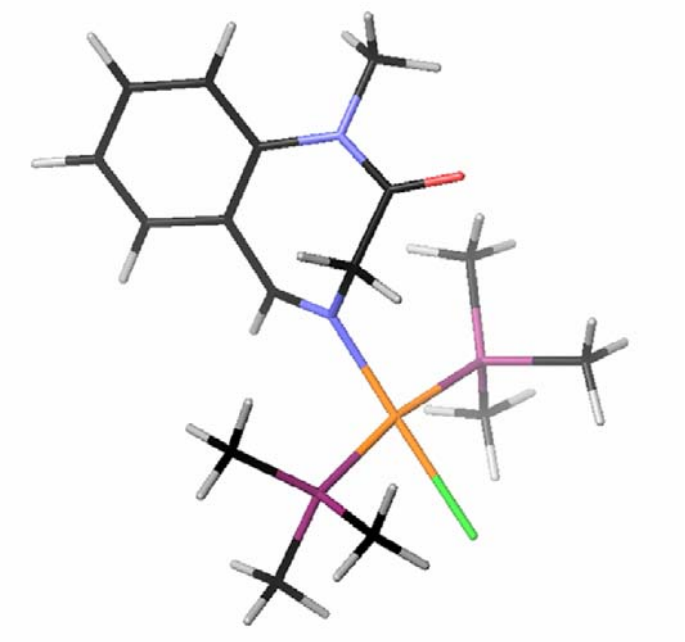
expected to induce a downfield shift the resonance corresponding to the C5-H proton of **6**, as is observed for the C2-H resonance of **2**. Additional support for this assignment arises from the established intermediacy of **2** in the analogous tautomerization of N-methyl-3,4-dyhyroquinazoline,[6a] the comparable energies predicted for the model structures **7'** and **8'**,[11] and the

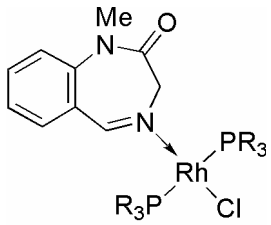




7: R = Cy
7': R = Me

Figure 2. DFT geometry-optimized Structure of **7'** Illustrating the Pre-agostic Interaction between the C6-H Bond and the Rhodium Center.





8: R = Cy
8': R = Me

Figure 3. DFT Geometry-optimized Structure for **8'**.

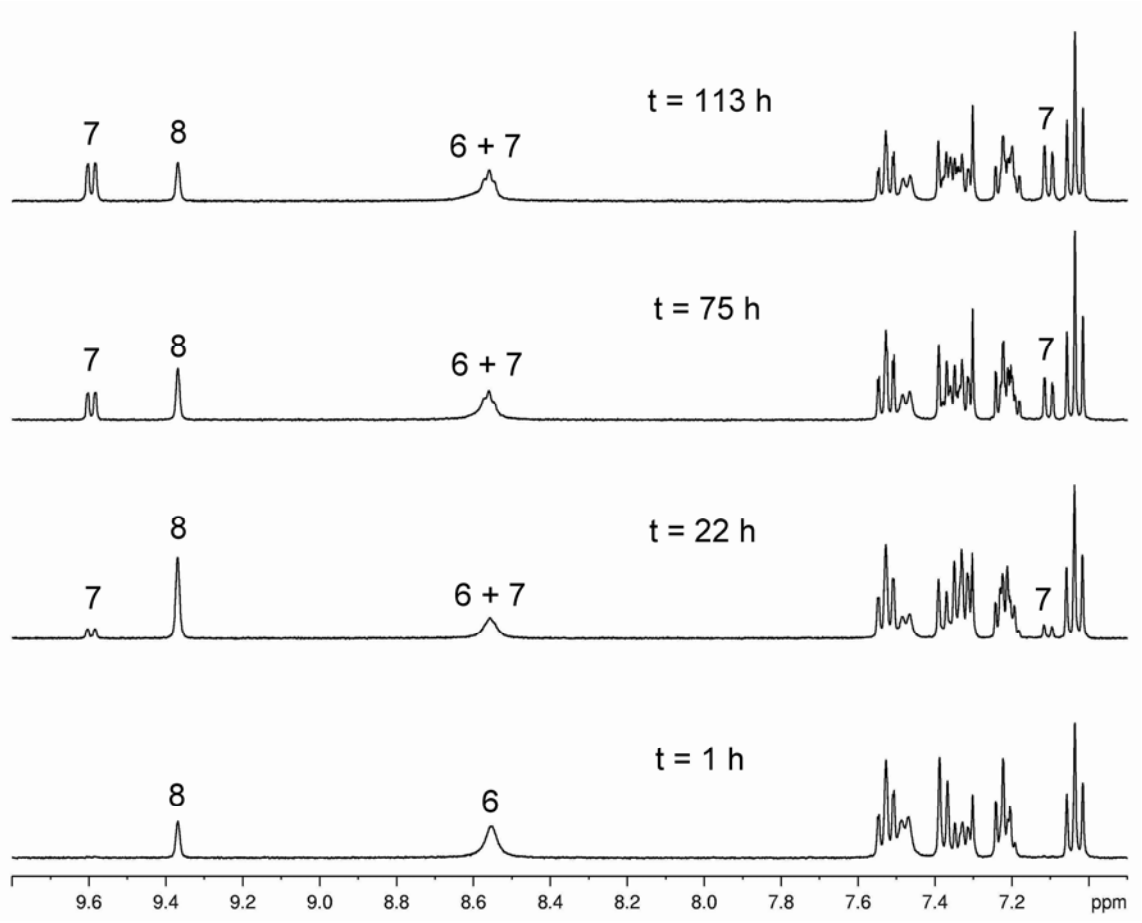


Figure 4. NMR Spectra of a Representative Tautomerization Reaction, Showing Selected Diagnostic Resonances of compounds **6**, **7**, and **8**.

well-known propensity of the 14-electron $RhCl(PCy_3)_2$ fragment to accept a fourth ligand to achieve a stable square planar d^8 coordination geometry.

The X-ray crystal structure of **7** (Figure 5) reveals a distorted square-planar coordination geometry about Rh and a Rh1-C1 bond distance of 1.914(3) Å, comparable to the Rh-C_{NHC} bond distance reported by Bertrand and coworkers for a somewhat related Rh(I) (alkyl)(amino)carbene complex,[17] although substantially shorter than those found for square planar Rh(I) (amino)(aryl) and (alkyl)(amino)carbene complexes reported by the same authors.[18] The C5-N4 and C5-C5a bond distances of 1.330(4) and 1.506(4) Å are typical of sp^2-sp^2 C-N double bonds and C-C single bonds, respectively, indicating

relatively little delocalization of electron density from the π system of the aryl ring over the vacant carbene p orbital.

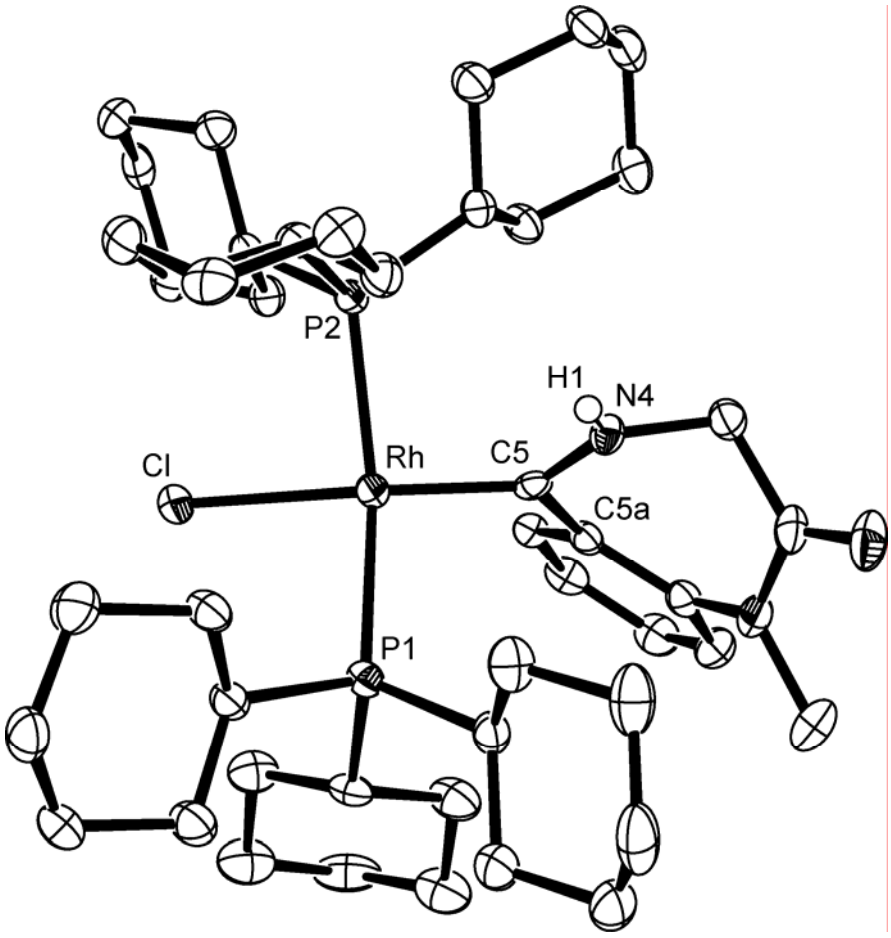


Figure 5. Ortep drawing of **7**.[19] Thermal ellipsoids are drawn at the 50 % probability level. Two molecules of THF have been deleted for clarity. Hydrogens other than H(1) have been omitted for clarity. Selected bond distances (Å) and angles (deg): Rh-C(5), 1.914(3); C(5)-N(4), 1.330(4); C(5)-C(5a), 1.506(4); N(1)-H(1), 0.79(3); Rh-P(1), 2.345(1); Rh-P(2), 2.3333(8); Rh-Cl, 2.4456(8); N(4)-C(5)-C(5a), 113.1(3); Rh-C(5)-N(4), 129.4(2); Rh-C(5)-C(5a), 117.4(2); P(1)-Rh-P(2), 159.05(3); Cl-Rh-C(5), 166.15(9); Cl-Rh-P(1), 88.67(3); Cl-Rh-P(2), 87.66(3); P(1)-Rh-C(5), 94.10(9); P(2)-Rh-C(5), 94.37(9)

The ^{1}H and ^{31}P NMR spectra of **7** in THF-d_8 exhibit several noteworthy features. First, the resonance of the C6-H proton of the benzodiazepine ligand is shifted dramatically downfield from ca. 7.4 ppm (in **6**) to 9.59 ppm due to a pre-agostic interaction with the rhodium center similar to that observed in the analogous N-bound complex of N-methyl-3,4-dihydroquinazoline. The geometry-optimized model structure **7'** (figure 2) closely reproduces the structure of **7** and places the hydrogen atom at the 6 position of the benzodiazepine ligand at a distance of 2.824 Å away from the rhodium center, which is

within the upper range of separations observed for pre-agostic interactions.[20] Second, the resonances of the methylene protons appear as distinct doublets of doublets, revealing coupling to the N4-H proton as required by the NHC structural assignment and indicating that the protons have become diastereotopic. Replacement of the C5 H atom of **6** with the bulky $RhCl(PCy_3)_2$ fragment at C5 renders interconversion of the enantiomeric conformers of the benzodiazepine ring slow on the NMR time scale, as is well-documented for 1,4-benzodiazepines with organic substituents at the N1 and C5 positions.[21] Consequently, the phosphine ligands also become diastereotopic and give rise to an ABX double quartet in the ^{31}P NMR spectrum of **7**.

In conclusion, a rare example of stabilization of the 5-carbene tautomer of a 1,4-benzodiazepine substrate has been demonstrated via direct reaction with $RhCl(PCy_3)_2$ fragment, suggesting that C-metallation of nitrogen heterocycles via metal-induced tautomerization may be feasible with a substantially broader range of substrates than has previously been envisioned. Investigation of the stoichiometric reactivity of this novel NHC complex is ongoing in our group. Further, as the Rh(I) complex employed in this study and closely related complexes have shown good activity toward catalytic C-H functionalization of a wide range of substrates, we are currently also pursuing the development of catalytic transformations of **6** and related heterocycles (e.g. benzotriazepines), in the interest of providing new methods for modular, atom-economical syntheses of drugs and drug analogues based on these pharmacologically very important structures.

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SUPPORTING INFORMATION PARAGRAPH Experimental procedures for the synthesis of compounds **4**, **5**, and **6**, details regarding computational methodology, energies for DFT geometry optimized structures **7'** and **8',** and the X-ray structural solution and crystal data for **7** are provided. This material is available free of charge via the internet at http://pubs.acs.org.

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10) In an effort to determine whether aryl substitution at the C atom of the imine function is important to promoting the tautomerization reaction, an analogous transformation of 3,4,5,6-tetrahydropyridine generated in situ from the stable trimer β-tripiperidein was attempted. This reaction failed to provide significant conversion to either an N-bound or NHC complex by ^{1}H NMR spectroscopy, yielding instead a lilac-colored precipitate attributed to $[RhCl_2(PCy_3)_2]_2$ within several minutes. Substantial equilibrium concentrations of the monomeric imine were not detected under the experimental conditions. The NHC-forming tautomerization is evidently applicable only to heterocycles capable of efficiently ligating the active $RhCl(PCy_3)_2$ fragment, and consequently only to imines that exist in solution primarily in the monomeric form. As crystallographic data for **7** imply minimal interaction between C5 and the aryl π-system, it is plausible that the importance of the aryl substituent consists in stabilizing the reactive form of the heterocycle. Crude tripiperidein was prepared in a modification of De Kimpe's procedure using Rapoport's method to generate N-chloropiperidine, and was purified to give β-tripiperidein according to the recyrstallization protocol described by Claxton et al. (a) Bender, D. R.; Bjeldanes, L. F.; Knapp, D. R.; Rapoport, H. J. *J. Org. Chem.* **1975**, *40*, 1264. (b) Claxton, G. P.; Allen, L.; Grissar, J. M. *Org. Syn.* **1977**, *56*, 118, and references therein. (c) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904. See also (d) Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745.

11) Gas-phase calculations at the B3LYP/LACVP** level of theory place the model N-bound adduct **8'** 4.17 kcal/mol lower in free energy than the NHC model complex **7'**, at variance with experimental observation of the greater stability of **7** with respect to **8** in THF solution at ambient temperature.

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14) Preparation of *trans*-Chloro(1-methyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]diazepin-2-one-5-ylidene)bis(tricyclohexylphosphine)rhodium(I) (**7**)**.** An oven-dried 40 mL glass-walled vessel fitted with a Kontes HI-VAC valve employing a PTFE Kontes plug (8 mm bore diameter, no O-ring) opening to a glass sidearm terminating in a 14-20 female ground-glass joint was taken inside a nitrogen glovebox. This vessel was charged with a solution of **6** (90.0 mg, 517 μmol), $[RhCl(coe)_2]_2$ (185 mg, 258 μmol), and tricyclohexylphosphine (374 mg, 1.33 mmol) in THF (18 mL). The valve was stoppered with the Teflon plug and the reaction mixture was subjected to four freeze-pump-thaw cycles on a dual manifold. The reaction mixture was blanketed with an atmosphere of argon and the reaction vessel was resealed. The resulting reaction mixture was stored at room temperature in the dark for 45 days, at which time crystallization of the NHC complex was apparently complete. The crystals were collected on a glass frit inside a nitrogen glove-box, washed with pentane, and dried under high vacuum for ca. 10 min to provide **7** as red, blade-like crystals confirmed by X-ray crystallographic analysis and elemental analysis to incorporate two molecules of THF per molecule of the NHC complex into the crystal lattice (132 mg, 25% yield). The low solubility of this complex in common organic solvents precluded acquisition of satisfactory ^{13}C NMR data. ^{1}H NMR data were acquired using crystals grown from THF-d_8 solutions, as the downfield non-deuterated THF resonance partially obscured one of the NHC methylene resonances; NMR spectra obtained from crystals grown from non-dueterated THF are otherwise identical. Crystals incorporating THF-d_8 were obtained from NMR-scale experiments of the type described below (footnote 16). All other analytical data pertain to material obtained from preparative-scale reactions. ^{1}H NMR (400 MHz, THF-d_8): δ 9.60 (apparent d, 1H, J = 6.8 Hz, C_6-H),

8.55 (br m, 1H, N-*H*), 7.36 (m, 1H, Ar-*H*), 7.20 (m, 1H, *J* = Ar-*H*), 7.11 (apparent d, 1 H, *J* = 8.4 Hz, C_9-*H*), 4.06 (dd, 1 H, J = 13.6, 6.4 Hz, methylene C-*H*), 3.68 (dd, 1 H, *J* = 13.6, 4.8 Hz, methylene C-*H*), 3.32 (s, 3H, N-*Me*). ^{31}P NMR (162 MHz, THF-d_8): δ 24.18 (ABX dq, *J* = 290, 160 Hz). IR (solid): 3371, 2922, 2846, 1669, 1593, 1564, 1469, 1445, 1371, 1344, 1295, 1264, 1230, 1173, 1129, 1066, 1005, 910, 899, 846, 773, 731, 655 cm^{-1}. HR-MS (FAB+): Calcd. for $[M\text{-}Cl]^+$, $C_{46}H_{76}N_2OP_2Rh$: 837.448795. Found: 837.450660. Anal. calcd. for **4**•2THF, $C_{54}H_{92}ClN_2O_3P_2Rh$: C, 63.73; H, 9.11; N, 2.75. Found: C, 63.64; H, 9.50; N, 2.80.

15) NMR scale experiments may be conducted simply by sealing the tube under high vacuum while the reaction mixture is frozen. However, preparative scale experiments must be performed under an atmosphere of argon using de-nitrogenated solvent in order to prevent competitive formation of the dinitrogen adduct $RhCl(PCy_3)_2(N_2)$, a reaction first reported in Van Gaal, H. L. M.; Moers, F. G.; Steggerda, J. J. *J. Organomet. Chem.* **1974**, *65*, C43. The dinitrogen complex otherwise crystallizes simultaneously with **7**

16) Representative procedure for monitoring the formation of *trans*-Chloro(1-methyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]diazepin-2-one-5-ylidene)bis(tricyclohexylphosphine)rhodium(I) (**7**) by NMR: inside an nitrogen glove-box, a solution of $[RhCl(coe)_2]_2$ (6.2 mg, 8.5 μmol) and tricyclohexylphosphine (12.5 mg, 45 μmol) in THF-d_8 (600 μL) was used to transfer **6** (3.0 mg, 17 μmol), and 2,6-dimethoxytoluene (2.6 mg, 17 μmol) to an oven-dried medium-walled Wilmad NMR tube. The NMR tube was inserted into a Cajon adapter and flame-sealed under vacuum while the reaction mixture was frozen in liquid nitrogen. Upon thawing, the reaction mixture was monitored by ^{1}H NMR (400 MHz) and ^{31}P NMR (162 MHz) spectroscopy, allowing the reaction mixture to stand at ambient temperature for the duration of the experiment. The reaction mixture took on a dark greenish-brown color shortly after preparation, and gradually became reddish-brown. After 7-10 d, the NHC complex began to crystallize as thin, dark red blades suitable for X-ray crystallographic analysis. ^{1}H NMR yields of **7** were determined prior to the onset of crystallization by comparison of the integral corresponding to the C_6-H proton resonance of **7** to the integral of the resonance arising from the two protons *meta* to the

methyl group of the internal standard (2,6-dimethoxytoluene). Yields of 35% are typical for the above procedure; higher NMR yields can be observed (up to 50%) by increasing the volume of solvent to 900 μL and by increasing the number of equivalents of **6** with respect to rhodium to 1.3.

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SYNOPSIS TOC

Synthesis of a Benzodiazepine-derived Rhodium NHC Complex by C-H Bond Activation

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