Hydroamination of Alkynes Catalyzed by a Cationic Rhodium(I) Complex

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The cationic Rh(I) dicarbonyl complex [{Rh((mim)$_2$CH$_2$)(CO)$_2$}$^+$BPh$_4^-$] (**1**), containing a bidentate bisimidazolylmethane ligand [mim = *N*-methylimidazol-2-yl], acts as an efficient catalyst for the intramolecular hydroamination of both terminal and nonterminal alkynes. The complex catalyzes the regioselective formation of nitrogen-containing heterocycles from aliphatic aminoalkynes and the cyclization of *o*-alkynylanilines to 2-substituted indoles in high yield.

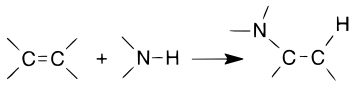
Introduction

The formation of C−N bonds via the addition of N−H to carbon−carbon double and triple bonds is a process of fundamental importance in the synthesis of organic compounds (Schemes 1 and 2).[1] Compounds containing C−N bonds are common in biologically active natural and synthetic products,[2] and the industrial production of amino compounds would be significantly improved if an efficient catalytic system for the hydroamination of unsaturated organic compounds were available.[3,4]

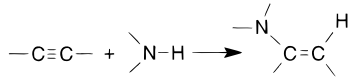
Transition metal and alkali earth metal catalyzed hydroaminations of alkenes and alkynes have been described previously.[3c,5] The use of alkali metals as catalysts typically requires relatively harsh reaction conditions and affords modest yields. Transition metal mediated systems are often stoichiometric or have poor efficiency and limited reaction scope.

Transition metal catalyzed intramolecular hydroamination of aminoalkenes and aminoalkynes has been more successful than intermolecular hydroamination. It is recognized that metal activation of either the olefinic/acetylenic bond or the amine is generally required as a preliminary step in catalyzed hydroamination reactions.[3a,c] Pd(II) complexes have been employed for the production of cyclic amines and enamines, particularly in the synthesis of substituted indoles, by cyclization and coupling reactions of substituted *o*-alkynylanilines.[3b,6] Amines have a strong affinity for

Scheme 1



Scheme 2



coordination to the Pd(II) site. Therefore, olefins that are activated for nucleophilic attack by coordination with the metal center are often competitively displaced by the amine, and this has resulted in the use of stoichiometric (or near stoichiometric) amounts of Pd(II) for the reaction. The problem has been overcome to some extent by initial protection of the amine with various electron-withdrawing groups.[7]

Muller and Pleier[8] have reported the intramolecular cyclization of aminoalkynes by a range of transition metal complexes, with the Cu(I) complex [Cu(CH$_3$CN)$_4$]-PF$_6$ being the most effective catalyst for the cyclization of 6-hexyn-1-amine. More recently, several examples of intermolecular hydroamination reactions have been reported using Rh and Ir phosphine complexes[9] and organoactinide complexes[10] as catalysts.

Organolanthanides act as efficient catalysts for the intramolecular hydroamination/cyclization of both aminoalkenes[11] and aminoalkynes[12] to form five- and six-membered nitrogen heterocycles regioselectively. Organolanthanides have also been used for the successful tandem formation of C−N and C−C bonds, both in-

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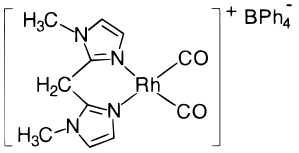
tramolecularly and intermolecularly.[13] Zirconium bisamides, acting as heterocarbenes, mediate the hydroamination of alkynes in a regioselective fashion, both stoichiometrically and catalytically.[14] Titanium-based heterocarbene reactions are also known to be relatively efficient systems for the hydroamination of alkynes[15] and have been used in the total synthesis of the indolizidine alkaloid (±)-monomorine[15b] and the antifungal agent (+)-preussin.[15c]

In this paper, we report the intramolecular hydroamination of alkynes catalyzed by a cationic rhodium(I) complex with a nitrogen-donor ligand set.

Results and Discussion

Recently we reported the synthesis of a new reactive cationic Rh(I) dicarbonyl complex [{Rh((mim)$_2$CH$_2$)(CO)$_2$}$^+$BPh$_4^-$] (**1**), with a bidentate bisimidazolylmethane ligand [mim = *N*-methylimidazol-2-yl].[16] Complex **1** acts as a catalyst for a range of organic reactions including the hydrosilation of double and triple bonds, the alcoholysis of silanes, and the cyclization of alkynols and alkynoic acids to oxygen-containing heterocycles.[17] We have also established that complex **1** acts as a catalyst for hydroamination reactions, specifically for the facile intramolecular cyclization of aminoalkyne substrates.

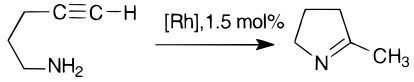


1

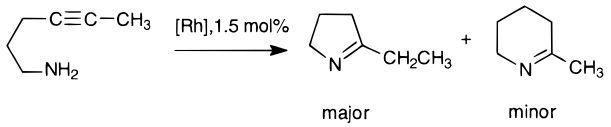
The catalytic formation of carbon−nitrogen bonds was investigated through the reaction of a series of *o*-alkynylaniline and aminoalkyne substrates in the presence of complex **1**. Complex **1** was prepared by reaction of the bidentate imidazole ligand (mim)$_2$CH$_2$ (**3**) with [Rh$_2$(CO)$_4$Cl$_2$]. The ligand **3** was prepared by a Wolff−Kishner reduction of the analagous ketone-bridged ligand (mim)$_2$C=O (**2**).

Complex **1** is an efficient catalyst for the intramolecular hydroamination of aliphatic and aromatic alkynes (Table 1). The terminal aliphatic substrate 4-pentyn-1-amine was catalytically cyclized, regioselectively, to produce a single imine product, 2-methyl-1-pyrroline.[18] In refluxing THF solvent with 1.5 mol % catalyst, conversion of 50% of substrate to product was achieved in less than 10 min, and the reaction is complete within 1.5 h (Scheme 3). The initial reaction rate is rapid, but the reaction slows with time. At lower temperatures, the conversion rates were still significant, with 50% conversion in 2 h and >98% in 12 h at 60 °C.

Scheme 3

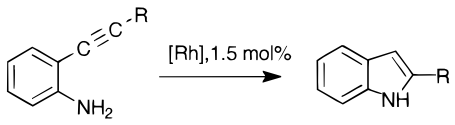


Scheme 4



major minor

Scheme 5



R = H, C_6H_5

Complex **1** also successfully catalyzed the cyclization of the nonterminal alkyne 4-hexyn-1-amine, although at a rate that was significantly slower than for terminal alkyne substrates. At 60 °C, 50% of the substrate was converted to 2-ethyl-1-pyrroline[18] in 5 h, and the reaction was complete after 48 h with 96% conversion. While the reaction is essentially regioselective, a second minor isomeric product (ca. 4%) was detected by GC/MS and NMR. This compound was identified as the six-membered heterocycle 2-methyl-3,4,5,6-tetrahydropyridine,[19] resulting from cyclization of 4-hexyn-1-amine with amine attack at C5 rather than at C4 (Scheme 4).

Increasing the temperature to reflux in THF (67 °C) increased the rate of cyclization of 4-hexyn-1-amine, with 50% conversion of 4-hexyn-1-amine in 1 h and 95% conversion within 6 h. Increasing the concentration of the catalyst also increased the rate of reaction. With 3 mol % of complex **1**, 50% conversion of 4-hexyn-1-amine was achieved in 65 min at 60 °C.

Complex **1** also catalyzes the formation of indoles from alkynylanilines. Specifically, 2-ethynylaniline is converted to indole[20] (Scheme 5) with 50% conversion after 2.5 h at 55 °C in acetone. The reaction was complete after approximately 9 h with 1.5 mol % catalyst. Similarly, 2-(phenylethynyl)aniline was catalytically cyclized to 2-phenylindole[20] at 55 °C, with 50% conversion after only 3 h, and the reaction was complete within 40 h.

The mechanism of addition of N−H bonds to carbon−carbon double and triple bonds has been investigated for a number of the metal-mediated systems. Classical oxidative addition/reductive elimination reaction pathways have been proposed using catalysts containing metal centers such as lanthanides,[12] actinides,[10] and Rh(I).[3a] This mechanism involves initial oxidative addition of the N−H bond of the amine to the metal center followed by a migratory insertion to produce a metal-coordinated heterocyclic enamine. Li and Marks[12] have previously identified enamine intermediates in the cyclization of primary and secondary aminoalkynes by an organolanthanide complex.

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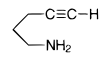
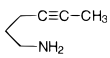
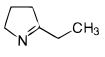
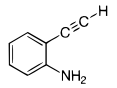
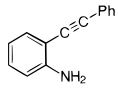
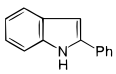
(18) The product was identified by comparison of spectral data with that reported in the literature (ref 12).
(19) 2-Methyl-3,4,5,6-tetrahydropyridine was identified by comparison of ^{1}H and ^{13}C NMR data with literature data for this compound: Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.
(20) The identity of the product was confirmed by comparison with an authentic sample.

Table 1. Rates of Intramolecular Hydroamination with $[\{Rh((mim)_2CH_2)(CO)_2\}^+BPh_4^-]$ (1)

Substrate	Product	Turnover Number[a] /N_t h^{-1}	Time /h, at 50% conversion	Solvent, T /°C
		>222	<0.15	thf-d_8, reflux
		17	2	thf-d_8, 60
		33	1	thf-d_8, reflux
		15[b]	4	thf-d_8, 60
		13	2.5	acetone-d_6, 55
		17[b]	3	acetone-d_6, 55

[a] At 50% conversion of substrate, 1.5 mol % of catalyst. [b] At 50% conversion of substrate for 1 mol % of catalyst.

An alternative mechanism, proposed to rationalize the catalytic ability of late transition metals and metals where oxidative addition is not possible (or not favorable), involves the initial coordination of the alkyne to the metal center.[3b,7a] This activates the C≡C to nucleophilic attack by the amine group to form a metal-coordinated heterocyclic enamine.[8]

In the cyclization of aminoalkynes by **1**, we have not observed the formation of metal hydrides, metal-coordinated enamines, or free CO by NMR. The pyrrolines, which are formed as the final products in the cyclization of aliphatic aminoalkynes, undoubtedly form by isomerization of the corresponding enamines (either as the free enamine or while still coordinated to the metal). We are currently further investigating the mechanism of the intramolecular hydroamination.

Finally, it should be noted that, in the course of this work, we have established that aminoalkynes are cyclized by a range of other similar cationic Rh(I) complexes. The efficiency of the catalyst changes remarkably even with small changes to the ligand donor set as well as with the nature of the counterion. It is not yet possible to identify the key factors that determine the catalytic efficiency, and work is ongoing in this area.

Experimental Section

All manipulations of metal complexes and air-sensitive reagents were carried out using standard Schlenk or vacuum techniques or in a Vacuum Atmospheres argon-filled drybox.

All organic starting materials were obtained from Aldrich Chemical Co. Inc. and were distilled prior to use. Rhodium(III) trichloride hydrate was obtained from Aldrich or Johnson Matthey and was used without further purification.

The amine substrates 4-pentyn-1-amine,[12] 4-hexyn-1-amine,[12] 2-ethynylaniline,[6a] and 2-(phenylethynyl)aniline[6a] were prepared according to literature methods. Tetracarbonyldichlorodirhodium $[Rh_2(CO)_4Cl_2]$ was synthesized by the procedure described by Cleverty and Wilkinson.[21] The ligands $(mim)_2C{=}O$ (**2**) and $(mim)_2CH_2$ (**3**) were prepared by modifications of literature methods.[22]

Tetrahydrofuran was stored over sodium wire and distilled under nitrogen immediately prior to use from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide under nitrogen. Deuterated solvents for NMR purposes were obtained from Merck and Cambridge Isotopes. Chloroform-*d* was used as supplied. Acetone-d_6 was dried over P_2O_5, and tetrahydrofuran-d_8 was dried over Na. Solvents were degassed using three consecutive freeze−pump−thaw cycles and vacuum distilled immediately prior to use.

Bulk compressed gases were obtained from British Oxygen Company (BOC Gases). Argon (>99.99%) and nitrogen (>99.5%) were used as supplied without further purification.

Mass spectra of organic compounds were recorded on a Finnigan Mat TSQ 4600 mass spectrometer by chemical ionization. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrometer. Gas chromatograph analyses were performed using a Hewlett-Packard 5890A gas chromatograph with a flame ionization detector and an SGE 25QC2/BPX5-0.25 column. Melting points were determined using a Gallenkamp apparatus and are uncorrected.

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX400 spectrometer at 400.13 and 100.62 MHz, respectively. ^1H and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonances. All spectra were recorded at 300 K for characterization purposes and at 328 or 333 K for NMR-monitored catalytic reactions.

Synthesis of Bis(*N*-methylimidazol-2-yl)ketone (2). *n*-Butyllithium (70 mL, 110 mmol) was added dropwise to a solution of *N*-methylimidazole (10 mL, 125 mmol) in THF (150 mL) at −70 °C under nitrogen. The mixture was stirred for 1.5 h at −70 °C, after which time diethyl carbonate (6 mL, 50 mmol) in THF (10 mL) was added. The mixture was maintained at −70 °C for 1.5 h, warmed to −40 °C, and quenched by the addition of solid carbon dioxide. After allowing the reaction mixture to warm to room temperature, water (20 mL) was added followed by hydrochloric acid (3 M) to acidify the aqueous layer. The mixture was filtered, and the organic layer was separated and extracted with hydrochloric acid (3 M, 4 × 10 mL). The combined aqueous phases were neutralized with sodium carbonate, filtered, and extracted continuously with chloroform for 16 h in a liquid−liquid extractor. The solvent was removed under reduced pressure, and the resulting brown oil was redissolved in chloroform and dried with magnesium sulfate. After filtration through Celite, the solvent was removed under reduced pressure and the product recrystallized from hexane/dichloromethane, producing bis(*N*-methylimidazol-2-yl)ketone (**2**) as fine white crystals (5.38 g, 56%), mp 147−148 °C (lit.[22b] 145−148 °C).^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 2H, *H4*), 7.09 (s, 2H, *H5*), 4.02 (s, 6H, N−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.8 (*C*=O), 143.7 (*C2*), 131.1 (C4), 127.3 (*C5*), 36.6 (N−*C*H_3) ppm. MS *m*/*z* (%): 190 (M^+, 57), 175 (6), 161 (60), 120 (7), 109 (87), 95 (50), 82 (88), 68 (17), 54 (100).

Synthesis of Bis(*N*-methylimidazol-2-yl)methane (3). Bis(*N*-methylimidazol-2-yl)ketone (**2**) (3.5 g, 18 mmol), hydrazine monohydrate (10 mL, 180 mmol), and sodium hydroxide (1.5 g, 36 mmol) were loaded in a glass sleeve and placed into a stainless steel high-pressure reaction vessel (bomb). The bomb was sealed and heated for 4 h at 150 °C. After cooling, the residue was dissolved in dichloromethane and then filtered. The solvent was removed in vacuo to produce the crude product as a cream-colored solid. Bis(*N*-methylimidazol-2-yl)methane (**3**) was obtained as a cream-colored crystalline solid after recrystallization from acetone (1.92 g, 60%), mp 151−153 °C (lit.[22b] 143−148 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (d, 2H, $^3J_{H5-H4}$ = 1.2 Hz, *H5*), 6.77 (d, 2H, $^3J_{H4-H5}$ = 1.2 Hz, *H4*), 4.23 (s, 2H, CH_2), 3.65 (s, 6H, N−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.0 (*C2*), 127.6 (*C4*), 122.3 (*C5*), 33.9 (N−*C*H_3), 27.2 (*C*H_2) ppm. MS *m*/*z* (%): 176 (M^+, 70), 161 (17), 134 (9), 121 (9), 107 (14), 95 (100), 81 (28), 66 (7), 54 (85).

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Synthesis of (Bis(*N*-methylimidazol-2-yl)methane)dicarbonylrhodium(I) Tetraphenylborate (1). The complex $[\{Rh((mim)_2CH_2)(CO)_2\}^+BPh_4^-]$ (**1**) was synthesized using a modification of the method reported by Elgafi et al.[16] A solution of bis(*N*-methylimidazol-2-yl)methane (**3**) (200 mg, 1.13 mmol) in methanol (5 mL) was added to a solution of $[Rh_2(CO)_4Cl_2]$ (190 mg, 0.49 mmol) in methanol (20 mL) at room temperature. The yellow precipitate that formed initially disappeared as the reaction stirred for 30 min. An excess of sodium tetraphenylborate (350 mg) in methanol (5 mL) was added. The resulting precipitate was isolated by filtration and washed with methanol, producing fine yellow crystals of (bis(*N*-methylimidazol-2-yl)methane)dicarbonylrhodium(I) tetraphenylborate (**1**) (570 mg, 84%), mp 176 °C (dec) (lit.[16] 175 °C (dec)). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.48 (d, 2H, $^3J_{H5-H4}$ = 1.7 Hz, *H5*), 7.41 (d, 2H, $^3J_{H4-H5}$ = 1.7 Hz, $^3J_{H4-Rh}$ = 0.8 Hz, *H4*), 7.33−7.30 (m, 8H, B*Ph*$_4$), 6.93 (t, 8H, B*Ph*$_4$), 6.78 (t, 4H, B*Ph*$_4$), 4.56 (s, 2H, CH_2), 3.83 (s, 6H, N−CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ 185.7 (d, $^1J_{Rh-CO}$ = 68.2 Hz, Rh-**C**O), 166.0−164.6 (m, B−*C*), 144.1 (*C2*), 137.4 (B*Ph*$_4$), 131.3 (*C5* or *C4*), 126.4 (B*Ph*$_4$), 124.9 (*C4* or *C5*), 122.6 (B*Ph*$_4$), 35.1 (N−*C*H$_3$), 24.7 (*C*H$_2$) ppm. ν (Nujol): 2083 (Rh−CO), 2021 (Rh−CO) cm^{-1}. Anal. $C_{35}H_{32}BN_4O_2Rh$ found: C, 64.5; H, 5.2; N, 8.4. Requires: C, 64.2; H, 4.9; N, 8.6.

General Procedures for Monitoring Catalytic Reactions. Catalytic reactions were performed on a small scale in an NMR tube fitted with a concentric Teflon valve. Reactions were performed in the NMR spectrometer with 0.5 mmol of substrate and 1.5 mol % of complex **1** in approximately 0.5 mL of solvent under argon. The progress of the reaction was monitored by ^{1}H NMR at 10 min intervals; the reactions were clean, and there were no additional products visible in the NMR spectra. Reactions with 2-ethynylaniline and 2-(phenylethynyl)aniline were carried out in acetone-d_6 at 55 °C. Reactions with 4-pentyn-1-amine and 4-hexyn-1-amine were carried out in tetrahydrofuran-d_8[23] at 60 °C. Reactions performed at reflux were heated outside the spectrometer and monitored periodically by ^{1}H NMR.

The conversion of starting material to product was determined by integration of the product resonances relative to the substrate peaks in the ^{1}H NMR spectrum; 100% conversion was taken to be the time where no remaining substrate peaks (<1%) were evident in the NMR. The turnover rate (N_t/h) was calculated as the number of moles of product/mole of catalyst/hour and was calculated at the point of 50% conversion of substrate to product.

Acknowledgment. We gratefully acknowledge financial support from the Australian Research Council (ARC), the Australian Government for an Australian Postgraduate Award (S.B.), and the generous loan of rhodium salts from Johnson Matthey Pty Ltd.

OM9902737

(23) The aliphatic aminoalkynes reacted preferentially with the solvent when catalysis was performed in acetone-d_6.