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Intramolecular Hydroamination of Unbiased and Functionalized Primary Aminoalkenes Catalyzed by a Rhodium Aminophosphine Complex

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Abstract: We report a rhodium catalyst that exhibits high reactivity for the hydroamination of primary aminoalkenes that are unbiased toward cyclization and that possess functional groups incompatible with more electrophilic hydroamination catalysts. The rhodium catalyst contains an unusual diaminophosphine ligand (**L1**) that binds to rhodium in a κ^3-P,O,P mode. The reactions catalyzed by this complex typically proceed at mild temperatures (room temperature to 70 °C) and occur with primary aminoalkenes lacking substituents on the alkyl chain that bias the system toward cyclization, with primary aminoalkenes containing chloride, ester, ether, enolizable ketone, nitrile, and unprotected alcohol functionality, and with primary aminoalkenes containing internal olefins. Mechanistic data imply that these reactions occur with a turnover-limiting step that is different from that of reactions catalyzed by late-transition-metal complexes of Pd, Pt, and Ir. This change in the turnover-limiting step and resulting high activity of the catalyst stem from favorable relative rates for protonolysis of the M−C bond to release the hydroamination product versus reversion of the aminoalkyl intermediate to regenerate the acyclic precursor. Probes of the origin of the reactivity of the rhodium complex of **L1** imply that the aminophosphine groups lead to these favorable rates by effects beyond steric demands and simple electron donation to the metal center.

Introduction

The hydroamination of unactivated alkenes is a conceptually simple method for the preparation of alkylamines.[1−5] The intramolecular version of this process is an attractive route to nitrogen-containing heterocycles, a common structural motif in biologically active molecules,[6] from readily available aminoalkenes. Because of the utility of this reaction in academic, pharmaceutical, and industrial settings, much effort has been spent on developing catalysts to effect this transformation.

Specifically, complexes based on rare-earth,[7−10] alkaline-earth,[11,12] and group IV[13−19] metals are known to catalyze the intramolecular hydroamination of primary and secondary aminoalkenes; however, these catalysts are often highly air- and moisture-sensitive and incompatible with many functional groups. For example, aminoalkenes containing acidic protons (such as unprotected alcohols) and carbonyl functionality (such as ketones and esters) have not been reported to undergo hydroamination catalyzed by complexes of rare-earth- and alkaline-earth-metal catalysts.[7,13,20] In a similar vein, complexes of group IV metals have not catalyzed hydroaminations of aminoalkenes containing carbonyl or ether functionalities. The group IV catalyst that reacts with the broadest scope was reported recently by Schafer and co-workers[19] and is based on a tethered ureate ligand. However, even this catalyst has been shown to tolerate a limited range of functionality (an aromatic dioxolane, an *N*-alkylpyrrole, and a tertiary aromatic amine), and substrates containing functional groups are all secondary amines with a bias toward cyclization. All primary aminoalkenes that react with this catalyst have lacked additional functionality, and all reported reactions of primary aminoalkenes lacking *gem*-diphenyl substituents with this catalyst were conducted at 145 °C.

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Catalysts derived from zinc complexes[21,22] and Bronsted acids[23−26] have also been shown to catalyze intramolecular hydroamination with a limited range of reactivities. For example, the reaction of a secondary aminoalkene lacking geminal substitution in the presence of a catalyst derived from diethylzinc and a protic additive required 21 days at 180 °C. Primary aminoalkenes containing geminal disubstitution of the alkyl linker required 120 °C, and a single example of a substrate lacking geminal disubstitution on the alkyl chain (2-aminohex-5-ene) gave the product with only 19% conversion after 36 h.[21] Hydroaminations catalyzed by Brønsted acids required high temperatures or protection of the nitrogen with an electron-withdrawing group.[24−26]

Complexes of late transition metals are more stable toward air and moisture and more tolerant of polar functional groups than complexes containing early transition metals and lanthanides.[27] However, intramolecular hydroaminations catalyzed by late-transition-metal complexes often require a N−H donor in which the nitrogen is electron-deficient and contained in an amide, carbamate, or sulfonamide functionality.[26,28−31] In the last five years, complexes of platinum,[32,33] copper,[34] rhodium,[35−37] and iridium[38−40] have been shown to catalyze the intramolecular hydroamination of aminoalkenes containing more basic secondary alkylamines. In 2008, the author's group reported a cationic rhodium complex that catalyzed the cyclization of both secondary and primary aminoalkenes.[35]

Although data for this rhodium catalyst[35,37] and for catalysts based on copper[34] and iridium[40,46] reported since that time have demonstrated that primary aminoalkenes can undergo cyclization, reactions of such amines catalyzed by these systems have significant limitations. First, the cyclization of primary aminoalkenes catalyzed by late-metal systems has been limited to cases that are biased toward cyclization by a Thorpe−Ingold effect. Second, these reactions have been limited to aminoalkenes containing terminal olefins. Third, these reactions require high temperatures (>100 °C). Finally, reactions of primary aminoalkenes containing a second functional group have not been reported with any catalyst. Thus, the identification of a complex containing a late transition metal that catalyzes the cyclization of unactivated, unbiased aminoalkenes, as well as an understanding of the factors controlling the reactions of primary amines catalyzed by late-transition-metal complexes, is needed.[26,41,42]

We previously investigated the cyclization of a secondary aminoalkene catalyzed by a series of rhodium complexes containing bisphosphine ligands.[35] One example of the cyclization of a secondary aminoalkene catalyzed by the combination of bis(diethylamino)xantphos ligand **L1′** (see Table 1)[43] and a cationic rhodium precursor was included in that study. Complexes of aminophosphines have rarely been investigated as components of catalysts, let alone for hydroamination.[44] Thus, we have investigated the structure of this catalyst and its reactivity toward a broader range of aminoalkenes.

Here we report a full account of our findings, which reveal the high reactivity of this unusual metal−ligand system for the hydroamination of primary amines, along with detailed mechanistic studies that reveal the origins of the high reactivity of this system. These new studies show that the active catalyst possesses a rhodium−POP-pincer structure and is highly active for the hydroamination of primary amines. The reactions catalyzed by this complex typically proceed at mild temperatures (room temperature to 70 °C), occur with primary aminoalkenes lacking any substituents on the alkyl chain that would bias the system toward cyclization, and exhibit a high degree of tolerance for polar functional groups, including aryl chlorides, esters, ethers, enolizable ketones, nitriles, and unprotected alcohols. Initial results imply that the aminophosphine groups on the ligand are involved in creating the high rates and selectivity, and mechanistic data show that the reactions of primary amines catalyzed by these complexes occur with a turnover-limiting step that is different from that of secondary aminoalkenes catalyzed by complexes of Pd,[45] Pt,[32] and Ir.[46]

Results and Discussion

Our prior observation that bis(diethylamino)xantphos **L1′** and $Rh(COD)_2BF_4$ catalyze the cyclization of a secondary aminoalkene, in combination with the novelty of a diaminophosphine as a component for catalysis, the potential flexibility and ease of synthesis of this class of ligand, and the possibility that this catalyst combination could lead to more hydroaminations than just the cyclization of secondary amines with geminal disubstitution, led us to explore the reactivity of this catalyst toward aminoalkenes that have resisted cyclization with previous late-transition-metal catalysts. To do so, we explored the activity of the catalyst generated from **L1** and cationic rhodium(I) precursors for reactions of primary aminoalkenes possessing and lacking geminal disubstitution on the alkyl linker. We found that just a 1 mol % loading of the complex generated from $[Rh(CH_3CN)_2COD]BF_4$ and **L1** catalyzed the hydroamination of primary aminoalkene **1a**, containing 3,3-diphenyl substituents, in THF at 70 °C to form the pyrrolidine product **2a** with high selectivity (14:1:1:0.4) over the combination of imine product **3a** and

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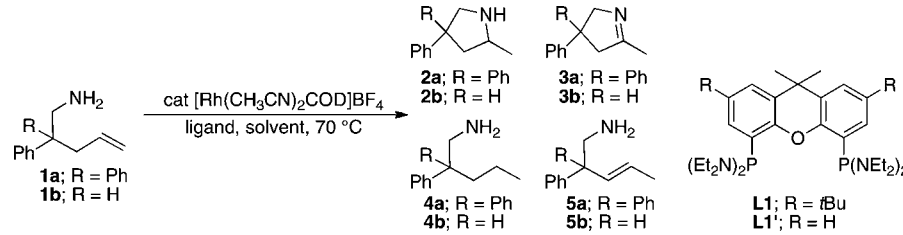
Table 1. Rh-Catalyzed Hydroamination of Primary Aminoalkenes: Initial Results



entry	R	mol % [Rh]	ligand	solvent	time (h)	conversion (%)[a]	**2**:**3**:**4**:**5** ratio[a]	isolated yield (%)
1	Ph	1	**L1**	*t*BuOH	2	100	18:1:1:0.7	80
2	Ph	1	**L1′**	*t*BuOH	2	100	11:1:1:0.2	
3	Ph	1	**L1**	THF	2	100	14:1:1:0.4	71
4	H	3	**L1**	*t*BuOH	15	100	9:1:1:0.5	66[b]
5	H	3	**L1′**	*t*BuOH	15	100	12:1:1:0.5	
6	H	3	**L1**	THF	15	77	6:1:0.6:1.6	

[a] Determined by ^{1}H NMR spectroscopy. [b] A 1.3:1 ratio of diastereomers was obtained.

hydrogenation product **4a** (Table 1, entry 3). The pure amine was isolated in 71% yield. The pairwise formation of the imine and hydrogenation products occurs by oxidative amination and transfer of the hydrogen to the olefin unit of the starting aminoalkene. The internal alkene **5a**, which results from isomerization of the terminal olefin in the starting material, was observed in only trace amounts. On the basis of the possibility that proton transfer is the turnover-limiting step of the catalytic cycle (see below), we also studied reactions in alcohol solvents. The same reaction of **1a** occurred with higher selectivity and higher isolated yield in *tert*-butyl alcohol (Table 1, entry 1).

Encouraged by these initial results, we investigated reactions of primary aminoalkenes that have not undergone cyclization with previous late-transition-metal catalysts. Initial studies conducted on the hydroamination of aminoalkene **1b** lacking geminal disubstitution on the alkyl linker in the presence of catalytic amounts of $[Rh(CH_3CN)_2COD]BF_4$ and **L1** showed that the rate and selectivity of the reaction were significantly lower than those of the gem-disubstituted substrate **1a** (Table 1, compare entries 3 and 6). However, the reaction of **1b** in *t*BuOH, rather than THF, led to the first cyclization of an unbiased primary amine with a late-metal catalyst at an acceptable rate with high selectivity (9:1 amine:imine) for the desired amine product (entry 4). The pyrrolidine product **2b** was isolated from this reaction in 66% yield as a 1.3:1 mixture of diastereomers (see also Table 2, entry 1).

Control experiments showed that the *t*Bu groups on the xanthene backbone had little effect on the reactivity or selectivity of the catalyst (Table 1, compare entries 1 and 2 and entries 4 and 5). Thus, **L1** (R = *t*Bu) or **L1′** (R = H) can be used interchangeably in catalytic hydroaminations. During the latter course of this work, **L1′** became available commercially, but the two ligands can be prepared by similar one-pot metalations of 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene and 9,9-dimethylxanthene, respectively, followed by quenching with bis(diethylamino)chlorophosphine.[47]

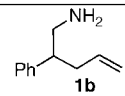
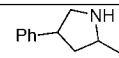
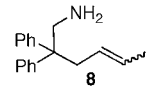
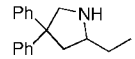
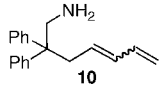
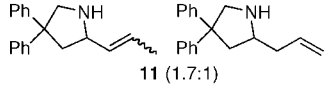
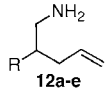
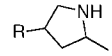
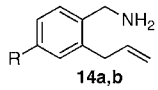
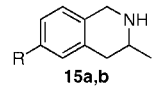
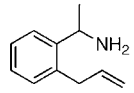
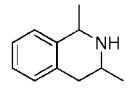
1. Scope of the Intramolecular Hydroamination. 1.1. Cyclization of Unbiased Aminoalkenes and Internal Alkenes. The scope of the hydroamination of primary aminoalkenes that lack geminal disubstitution on the alkyl chain or contain internal olefins or dienes catalyzed by the combination of $[Rh(CH_3CN)_2COD]BF_4$ and **L1** is illustrated in Table 2. As noted in the previous section, the reaction of substrate **1b** containing just one substituent on the carbon β to the amino group and alkene unit (Table 2, entry 1) gave a 9:1 ratio of amine to imine and led to isolation of the amine in 66% yield. The high activity of this catalyst system for reactions of primary aminoalkenes in *t*BuOH solvent was particularly exemplified by reactions of aminoalkenes lacking any substituents on the linker between the amino group and the alkene. Reactions of these aminoalkenes occurred to generate both five- and six-membered-ring products. For example, 1-aminopentene and 1-aminohexene underwent cyclization in the presence of 4 mol % $[Rh(CH_3CN)_2COD]BF_4$ and **L1** to afford 2-methylpyrrolidine (**7a**) and 2-methylpiperidine (**7b**) (Table 2, entries 2 and 3). Internal olefins also underwent cyclization. In these cases, the solvent had little effect on the conversion or selectivity of hydroamination, and intramolecular additions to monoene **8** and diene **10** (entries 4 and 5) were accomplished in dioxane at 100 °C; a higher catalyst loading (18 mol %) was required in order to achieve high conversion of the unactivated internal alkene **8** as a result of competitive catalyst decomposition. These reactions constitute the first examples of cyclization of a primary amine with an internal alkene catalyzed by a complex of a late transition metal.

Free diethylamine was detected in the crude reaction mixtures by GC and ^{1}H NMR spectroscopy, and this observation suggests that one pathway for catalyst decomposition occurs by displacement of the diethylamino groups on the phosphorus by the primary amine substrate. For substrates with lower rates of hydroamination (i.e., unactivated internal olefins), the rate of catalyst decomposition becomes competitive with the rate of cyclization.

1.2. Tolerance for Auxiliary Functional Groups. The objective of developing a late-transition-metal catalyst for hydroamination stems from the expectation that hydroamination with this type of catalyst should occur with a high tolerance for auxiliary functional groups. To determine the validity of this assertion, we studied cyclizations of substrates that are unbiased for cyclization and also possess potentially reactive functional groups. Indeed, such cyclizations catalyzed by the combination of $[Rh(CH_3CN)_2COD]BF_4$ and **L1** occurred with aminoalkenes containing a siloxy group (entry 6), a methoxycarbonyl group (entry 7), a cyano group (entry 8), an acetyl group (entry 9), and even an unprotected hydroxyl group (entry 10). Cyclization of the aminoalkene containing the unprotected alcohol (**12e**)

(47) See the Supporting Information for experimental details.

Table 2. Scope of Rh-Catalyzed Hydroamination of Primary Amines[a]

entry	mol % [Rh]	aminoalkene	product	time (h)	yield[b] (dr)[c]	ratio (amine:imine)[c]
1	3	 **1b**	 **2b**	15	66% (dr = 1.3:1)	9:1
2[d]	4	 **6a,b**	 **7a,b**	7	**a;** n=1; 76%[e]	>95:5
3[d]	4			8	**b**; n=2; 77%	>95:5
4[f, g]	18	 **8**	 **9**	15	40%	>95:5
5[f, h]	3	 **10**	 **11** (1.7:1)	14	64%[i]	7:1
		 **12a-e**	 **13a-e**			
6[j]	3	**a**; R=OTBDPS		18	71% (dr = 1.6:1)	>95:5
7	3	**b**; R=4-$(CO_2Me)C_6H_4$		21	64% (dr = 1.6:1)	10:1
8	5	**c**; R=4-$(CH_2CN)C_6H_4$		12	79% (dr = 1.5:1)	>95:5
9	5	**d**; R=4-$(CH_3(O)C)C_6H_4$		16	61% (dr = 1.5:1)	10:1
10	5	**e**; R=4-$(CH_2OH)C_6H_4$		8	56%[k] (dr = 1.1:1)	7:1
		 **14a,b**	 **15a,b**			
11	1	**a**; R = H		5	87%	>95:5
12	2	**b**; R = Cl		6	84%	>95:5
13	1	 **16**	 **17**	7	74% dr = (1.1:1)	>95:5

[a] Reaction conditions: aminoalkene (0.5 mmol), $[Rh(CH_3CN)_2COD]BF_4$ (1−18 mol %), and **L1** (1.2−19 mol %) in *t*BuOH (1 mL) at 70 °C, unless otherwise specified. [b] Isolated yield. [c] Ratio determined by ^1H NMR spectroscopy. [d] Product isolated as the Boc carbamate. [e] NMR yield; the product was isolated in 67% yield as a 10:1:1 **7a**−Boc:BocNEt$_2$:*N*-Boc-1-amino-3-pentene mixture. [f] Reaction run at 100 °C in dioxane. [g] Reactant **8** was a 3.3:1 mixture of *E* and *Z* isomers. [h] Reactant **10** was a 10:1 mixture of *E* and *Z* isomers. [i] Isolated as a 1.7:1 mixture of olefin isomers (internal:terminal). [j] Reaction run on a 0.25 mmol scale. [k] Isolated as a 97:3 mixture of alcohol and aldehyde products.

occurred with a small amount of competitive formation of an aldehyde byproduct at high conversions, but the hydroxyl-substituted product **13e** was isolated in 56% yield. Cyclizations of substrates containing esters, ketones, and alcohols using catalysts based on lanthanides or group IV metals have not been reported to date.

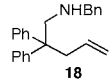
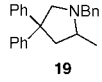
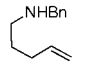
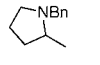
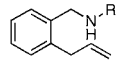
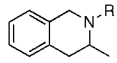
Tetrahydroisoquinolines are a common structural motif in numerous biologically active molecules.[48,49] 3-Methyltetrahydroisoquinolines were readily synthesized by hydroamination of 2-allylbenzylamines in excellent yield and selectivity (entries 11−13) with low catalyst loadings (1−2 mol %). The hydroamination of the parent 2-allylbenzylamine **14a** occurred even at *room temperature* (10 mol % Rh, THF, 24 h), affording the product in 77% isolated yield. Although reactions of a broad range of functionalized 2-allylbenzylamines were not explored, the aryl chloride function was tolerated, as demonstrated by the high-yielding cyclization of substrate **14b** (entry 12). In addition, while reactions of aminoalkenes branched at the α position have not occurred previously with catalysts of the late transition metals,[50] the α-branched aminoalkene **16** (entry 13) readily formed the tetrahydroisoquinoline product in the presence of catalytic amounts of $[Rh(CH_3CN)_2COD]BF_4$ and **L1**.

1.3. Reactions of Secondary Aminoalkenes. The reactivity of this catalyst was not limited to primary amines. Secondary amines also underwent hydroamination in good to excellent yields with low catalyst loadings (1−3 mol %), furnishing *N*-alkylpyrrolidines and *N*-alkyltetrahydroisoquinolines (Table 3). The commonly studied aminoalkene **18** containing *gem*-diphenyl substituents cyclized in high yield with a high ratio of amine to imine. However, secondary aminoalkene **20** containing no substituents in the linking unit also underwent cyclization with a high ratio of amine to imine to give a 65% yield of pyrrolidine product. Even the sterically encumbered *N*-*i*Pr-substituted aminoalkene **22a** readily underwent cyclization (entry 3). Finally, hydroamination with the secondary aminoalk-

(48) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1169.
(49) Chrzanowaska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(50) One example of an α-branched aminoalkene (2-aminohex-5-ene) was reported to undergo cyclization in the presence of a zinc catalyst to give the product with low conversion (19%). See ref 21.

Table 3. Rh-Catalyzed Hydroamination of Secondary Amines[a]

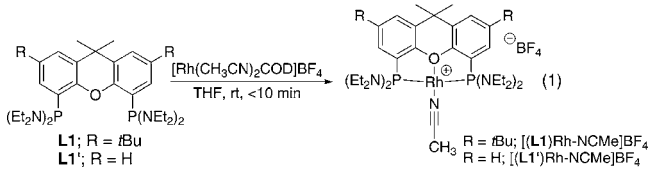
entry	mol% [Rh]	aminoalkene	product	time (h)	yield[b, c]
1	1	 **18**	 **19**	5	83%
2	3	 **20**	 **21**	5	65%[d]
		 **22a,b**	 **23a,b**		
3	1	**a**; R = *i*Pr		8	78%
4	1	**b**; R = Bn		5	86%
5[e]	10	**b**; R = Bn		24	74%

[a] Reaction conditions: aminoalkene (0.5 mmol), $[Rh(CH_3CN)_2COD]BF$ (1−3 mol %), and **L1** (1.2−3.5 mol %) in *t*BuOH (1 mL) at 70 °C, unless otherwise specified. [b] Isolated yield. [c] Ratio of amine:imine was >95:5 in every case. [d] NMR yield. [e] Reaction run at room temperature.

ene **22b** occurred at room temperature (entry 5) to give the corresponding product **23b** in good yield (74%).

1.4. Current Limitations on the Scope of the Cyclizations of Aminoalkenes. The results in the previous three sections demonstrate that the complex derived from $[Rh(CH_3CN)_2COD]BF_4$ and **L1** is currently the most active late-transition-metal catalyst for intramolecular hydroaminations of unactivated primary aminoalkenes. However, we also identified limitations of this catalyst system. For example, substrates containing internal olefins, such as substituted styrenes and cyclohexenes, which would generate bicyclic ring systems, did not undergo cyclization. Moreover, a basic amine is so far required; aminoalkenes lacking a basic amine, such as *N*-aryl- and *N*-Cbz-protected aminoalkenes, did not react with this catalyst under these conditions. Finally, the reaction of 2,2-diphenylhept-6-en-1-amine with catalytic amounts of $[Rh(CH_3CN)_2COD]BF_4$ and **L1** afforded only small amounts of the seven-membered-ring product. Isomerization of the starting aminoalkene was the major reaction of the heptenylamine substrate.

2. Identification of the Structure of the Active Catalyst. To understand the origins of the high reactivity of this catalyst system for cyclization of primary aminoalkenes, we identified the structure of the active catalyst and the factors that control the reaction rates and selectivity for formation of hydroamination versus oxidative amination products. The reactions of $[Rh(CH_3CN)_2COD]BF_4$ with **L1** and **L1′** in THF at room temperature formed [(**L1**)Rh(NCMe)]BF_4 and [(**L1′**)Rh(NCMe)]BF_4 in yields of 89 and 67%, respectively (eq 1).



These complexes of **L1** and **L1′** were characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy and elemental analysis, and the structure of [(**L1′**)Rh(NCMe)]BF_4 was determined by X-ray diffraction. An ORTEP diagram of this complex is shown in Figure 1. This structure shows that **L1** is bound in a κ^3 fashion to the rhodium atom to generate a square-planar POP-pincer

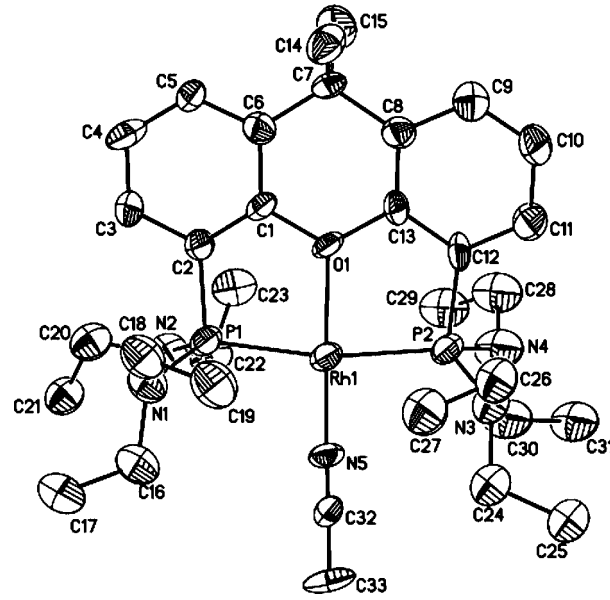
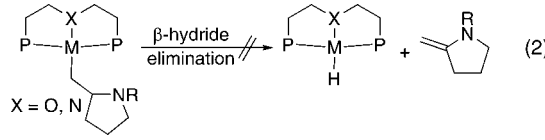


Figure 1. ORTEP drawing of catalyst [(**L1′**)Rh(NCMe)]BF_4 (35% ellipsoids, hydrogens and BF_4 counterion omitted). Selected bond distances (Å) and angles (deg): Rh1−O1, 2.129; Rh1−P1, 2.250; Rh1−P2, 2.242; Rh1−N5, 1.943; P1−Rh1−P2, 168.0; N5−Rh1−O1, 178.8; O1−Rh1−P1, 84.1; O1−Rh1−P2, 83.9; N5−Rh1−P1, 96.9; N5−Rh1−P2, 95.0.

structure. The Rh−O bond distance (Rh−O = 2.129 Å) is similar to that in known cationic Rh−POP complexes reported previously.[51,52]

These complexes catalyzed the hydroamination of aminoalkenes with reactivities and selectivities similar to those for the reactions catalyzed by the combination of the rhodium precursor $[Rh(CH_3CN)_2COD]BF_4$ and ligand **L1** or **L1′**. For example, cyclization of substrate **1b** with 5 mol % [(**L1**)Rh(NCMe)]BF_4 in *t*BuOH at 70 °C resulted in full conversion of starting material after 7 h to afford a 10:1 ratio of amine **2b** and imine **3b**, as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. Under otherwise identical reaction conditions, the combination of 5 mol % $[Rh(CH_3CN)_2COD]BF_4$ and 6 mol % ligand **L1** gave complete conversion of aminoalkene to a 9:1 ratio of **2b:3b**. The tridentate "pincer" coordination mode of the xantphos derivative is likely integral to the selectivity for hydroamination over oxidative amination by inhibiting the β-hydride elimination step that leads to the formation of the imine byproduct (eq 2).[53] Additional discussion of the influence of the pincer structure on the selectivity is presented in Mechanistic Conclusions.

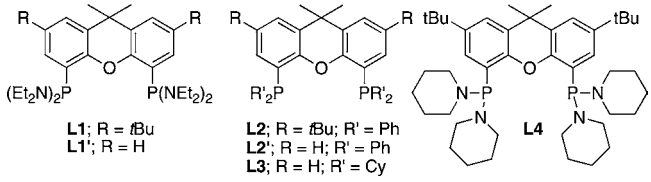


3. Effect of the Phosphine Ligand on Reactivity. To probe the influence of the phosphine substituents on the reactivity and

(51) Alcock, N. W.; Brown, J. M.; Jeffery, J. C. *J. Chem. Soc., Dalton Trans.* **1976**, 583.
(52) Sandee, A. J.; van der Veen, L. A.; Reek, J. N. H.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3231.
(53) Hartwig, J. F. In *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010; pp 398−400.

Table 4. Evaluation of Xantphos Ligands in the Hydroamination of **1a**[a]

entry	% Rh	ligand	time (h)	conv (%)[b]	**2a**:**3a**:**4a**:**5a** ratio
1	1	**L1**	2	100	18:1:1:0.7
2	1	**L1′**	2	100	11:1:1:0.2
3	3	**L2**	2	83	1:0.1:0:4.4
4	3	**L2′**	2	62	1:0.2:0:9.1
5	3	**L3**	2	47	2:1:1:0[c]
6	3	**L4**	2	100	5.7:1:1:0.4

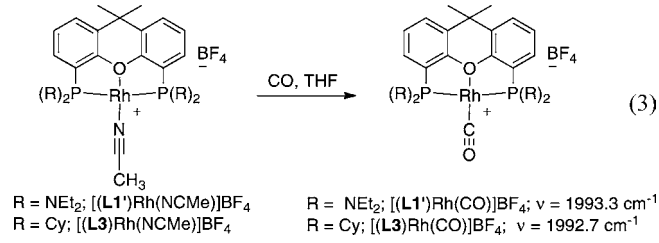


[a] Reaction conditions: **1a** (0.2−0.3 mmol), $[Rh(CH_3CN)_2COD]BF_4$ (1−3 mol %), and ligand (1.2−3.5 mol % in *t*BuOH (0.4−0.6 mL) at 70 °C. [b] Determined by ^1H NMR spectroscopy. [c] Trace amount of isomerization was observed.

selectivity in the hydroamination reaction, we investigated the reactions of aminoalkene **1a** catalyzed by complexes of xantphos ligands containing diaryl- and dialkylphosphino groups. Specifically, we evaluated the parent xantphos ligands **L2** and **L2′** containing diphenylphosphino groups[54] (Table 4, entries 3 and 4) and Cy-xantphos ligand **L3** containing dicyclohexylphosphino groups[55] (entry 5). Reactions catalyzed by complexes of these ligands occurred with lower conversions and selectivities than those catalyzed by the complex of bis(diethylamino)xantphos ligands **L1** and **L1′** (entries 1 and 2). Specifically, the reaction catalyzed by the combination of ligand **L2** or **L2′** and $[Rh(CH_3CN)_2COD]BF_4$ afforded mainly the isomerized product **5a**, and the reaction catalyzed by the combination of ligand **L3** and the same rhodium species occurred with low conversions and poor selectivity for hydroamination versus oxidative amination (2:1 ratio of **2a** and **3a**).

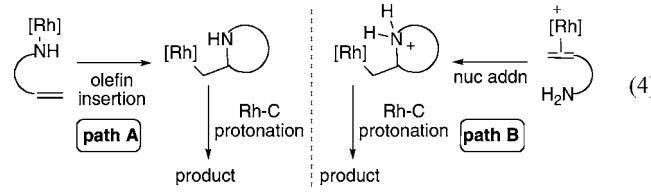
We hypothesized that the amino groups on the phosphorus ligand could be responsible for the enhanced rate and selectivity observed in the catalytic hydroamination reaction. To distinguish between steric and electronic effects of the amino groups on this reactivity and selectivity, we prepared **L4**,[56] an aminophosphine analogue of Cy-xantphos ligand **L3**. Ligand **L4** contains piperidinyl groups that are nearly isosteric with cyclohexyl groups. The cyclization of **1a** catalyzed by the combination of **L4** and $[Rh(CH_3CN)_2COD]BF_4$ generated the amine product with higher conversion and selectivity for hydroamination (100% conversion, 5.7:1 **2a**:**3a** ratio; entry 6) than the reaction catalyzed by the complex of **L3** (47% conversion, 2:1 **2a**:**3a** ratio; entry 5) and with selectivity close to that of the reactions catalyzed by rhodium and **L1** or **L1′**. These results suggest that the amino groups on the phosphorus ligand are integral to the enhanced rate and selectivity.

The electron-donating property of the aminophosphine was assessed by preparing the carbonyl adducts of LRh^+ fragments (eq 3). The ν_{CO} values in the IR spectra of the aminophosphine complex $[(\mathbf{L1'})Rh(CO)]^+$ and the Cy-xantphos complex $[(\mathbf{L3})Rh(CO)]^+$ were nearly identical (1993.3 and 1992.7 cm^{-1}, respectively). Thus, the aminoxantphos and Cy-xantphos ligands have similar electron-donating properties. These results, in combination with the above results comparing the reactivities of the sterically similar Cy-xantphos and piperidinylxantphos complexes, demonstrate that the effect of the substituents on phosphorus likely stems from properties beyond steric demands and degree of electron donation to the metal center.



(3)

4. Mechanistic Studies. Two mechanistic pathways are typically proposed for the hydroamination of aminoalkenes catalyzed by late transition metals (eq 4): one involves insertion of the alkene into the metal−amide bond (path A), and the other involves nucleophilic addition of the amine to a coordinated olefin (path B).[3,57] With few exceptions, electron-deficient late-transition-metal catalysts, such as those based on platinum,[32,33] palladium,[45] and iridium,[46] have been shown to react by nucleophilic attack of an amine on a coordinated olefin. To distinguish between these two mechanisms and determine which step of the deduced catalytic cycle is influenced by the aminophosphine ligand, we determined the rhodium species present in the catalytic reaction and measured the kinetic isotope effects (KIEs).



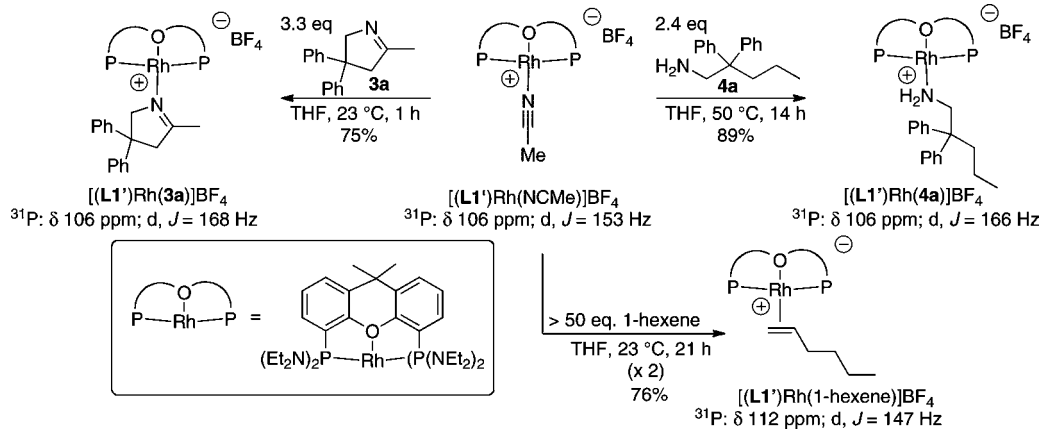
(4)

4.1. Identification of Catalyst Resting States in Hydroamination Reactions of Primary Aminoalkenes. The rhodium species present in the catalytic reaction were identified by monitoring reactions of aminoalkene **1b** with catalytic and stoichiometric quantities of $[(\mathbf{L1})Rh(NCMe)]BF_4$ by ^1H and ^{31}P NMR spectroscopy and comparing the spectra to those of rhodium complexes prepared independently. Likely intermediates were readily prepared (see below) and were distinguishable by the corresponding magnitudes of the Rh−^{31}P coupling constant. Reactions were conducted in both THF and *t*BuOH to gain insight into the origin of the accelerating effect of the *t*BuOH solvent.

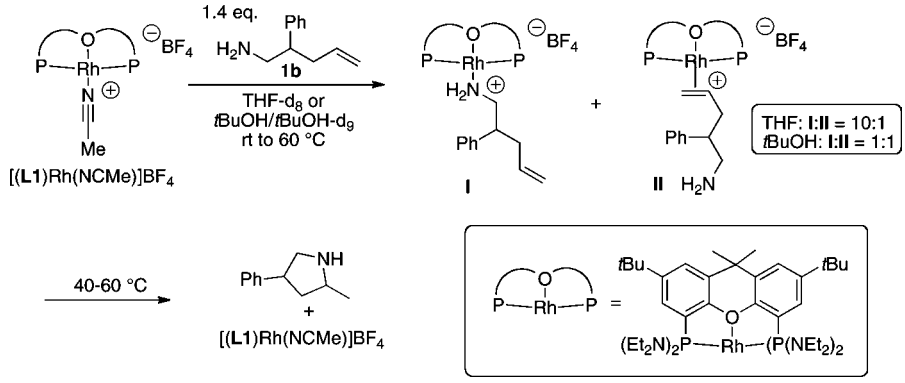
Model rhodium complexes containing alkene $\{[(\mathbf{L1'})Rh(1\text{-hexene})]BF_4\}$, primary amine $\{[(\mathbf{L1'})Rh(\mathbf{4a})]BF_4\}$, and imine $\{[(\mathbf{L1'})Rh(\mathbf{3a})]BF_4\}$ ligands were synthesized from the acetonitrile complex $[(\mathbf{L1'})Rh(NCMe)]BF_4$ (Scheme 1). The imine ligand **3a** was found to displace the acetonitrile ligand at room temperature in THF after 1 h to afford the corresponding imine complex $[(\mathbf{L1'})Rh(\mathbf{3a})]BF_4$ in 75% isolated yield. The primary amine complex $[(\mathbf{L1'})Rh(\mathbf{4a})]BF_4$ was prepared in 89% yield by heating a solution of the acetonitrile complex $[(\mathbf{L1'})Rh(NCMe)]BF_4$ and 2.3 equiv of primary amine **4a** at 50 °C in THF for 14 h. Displacement of the coordinated acetonitrile with 1-hexene required a large excess of olefin (>50 equiv) to drive the equilibrium. Even after the mixture was fully equilibrated, ∼10% of the acetonitrile complex remained, on the basis of

(54) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.
(55) Kuwano, R.; Kusano, H. *Chem. Lett.* **2007**, *36*, 528.

Scheme 1. Synthesis of Model Rhodium Complexes for the Determination of Catalyst Resting States



Scheme 2. Reaction of Aminoalkene **1b** with Stoichiometric [(**L1**)Rh(NCMe)]BF_4



analysis by ^{31}P NMR spectroscopy after 21 h in THF at room temperature. After removal of the free acetonitrile under vacuum and resubjection of the crude mixture containing this ~10:1 ratio of rhodium complexes to the reaction conditions, complete conversion of [(**L1′**)Rh(NCMe)]BF_4 to the olefin complex [(**L1′**)Rh(1-hexene)]BF_4 was achieved. [(**L1′**)Rh(1-hexene)]BF_4 was obtained in 76% isolated yield. All three model rhodium complexes were characterized by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.

The phosphorus−rhodium coupling constants for the acetonitrile, olefin, and amine/imine complexes are significantly different, thus enabling the identification of intermediates containing coordinated alkenes, primary amines/imines, or acetonitrile by ^{31}P NMR spectroscopy (Scheme 1). The ^{31}P chemical shifts and phosphorus−rhodium coupling constants for the amine and imine complexes [(**L1′**)Rh(**4a**)]BF_4 and [(**L1′**)Rh(**3a**)]BF_4 were found to be similar ($\delta = 106$ ppm, $J_{Rh-P} = 166$ and 168 Hz, respectively, in *t*BuOH); however, a diagnostic downfield signal near ~4.5 ppm in the ^{1}H NMR spectrum of the imine complex, assigned to the methylene protons α to the imine nitrogen, allowed us to distinguish between these two species.

Spectral data for these model complexes matched closely with the spectral data for compounds observed in the reaction of **1b** catalyzed or mediated by [(**L1**)Rh(NCMe)]BF_4. Specifically, the reaction of **1b** in THF or *t*BuOH in the presence of stoichiometric amounts of [(**L1**)Rh(NCMe)]BF_4 was monitored by ^{1}H and ^{31}P NMR spectroscopy. In THF, substrate **1b** displaced the acetonitrile ligand, and a 10:1 ratio of amine complex to olefin complex (**I**:**II**) was observed at room temperature (Scheme 2). Further heating to 40 °C resulted in formation of the cyclized product. After the reaction mixture was heated at 60 °C for 25 min, aminoalkene **1b** was consumed, and the catalyst reverted to the acetonitrile complex [(**L1**)Rh(NCMe)]BF_4. Similar results were obtained for the reaction of **1b** and [(**L1**)Rh(NCMe)]BF_4 in *t*BuOH. However, only ~60% conversion of [(**L1**)Rh(NCMe)]BF_4 to a 1:1 ratio of **I** and **II** was observed upon addition of aminoalkene **1b** to the rhodium complex. These results demonstrate that the ability of the primary amine to coordinate to the rhodium center is attenuated in *t*BuOH and that the equilibrium ratio of amine complex to olefin complex lies closer to the olefin complex in *t*BuOH than it does in THF.[58]

The reaction of aminoalkene **1b** catalyzed by 5 mol % [(**L1**)Rh(NCMe)]BF_4 in *t*BuOH at 62 °C was also monitored by ^{1}H and ^{31}P NMR spectroscopy. In this experiment, amine complex **I** and olefin complex **II** were identified as the catalyst resting states throughout the course of the reaction (~3:1 to 6:1 **I**:**II** ratio) (Figure 2a−d). However, the imine complex was observed (Figure 2b−e) as the reaction progressed, and the concentration of the imine byproduct **3b** increased. The imine complex was identified as the final resting state of the catalyst upon consumption of **1b** (Figure 2e). Although the imine product **3b** was formed in minor amounts, it was tightly bound to the

(56) **L4** was synthesized from 4,5-dibromo-2,7-di-*tert*-butyl-9,9-dimethylxanthene and known bis(piperidinyl)chlorophosphine. See: Amigues, E. J.; Hardacre, C.; Keane, G.; Miguad, M. E. *Green Chem.* **2008**, *10*, 660. See the Supporting Information for experimental details.

(57) Hartwig, J. F. In *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010; pp 713−716.

(58) Fu, X.; Wayland, B. B. *J. Am. Chem. Soc.* **2005**, *127*, 16460.

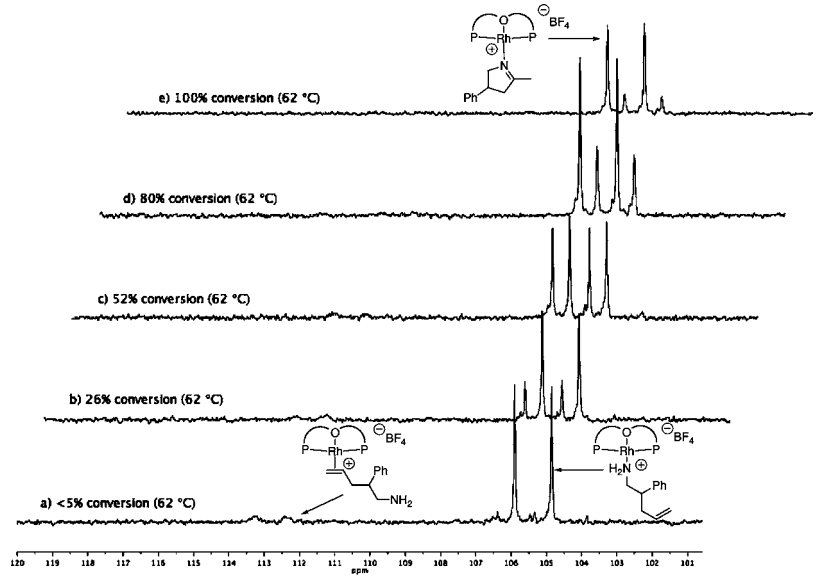


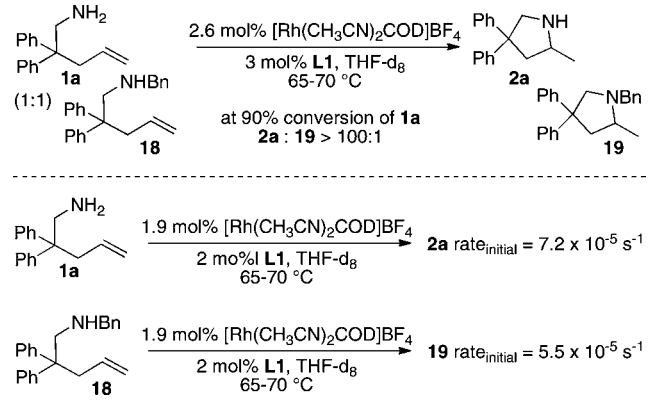
Figure 2. Stacked plots of ^{31}P NMR spectra obtained at various conversions of aminoalkene **1b** catalyzed by 5 mol % [(**L1**)Rh(NCMe)]BF_4 in *t*BuOH at 62 °C.

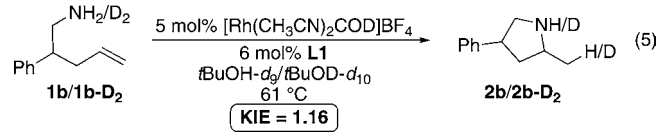
cationic rhodium center, outcompeting the binding of the primary amine reactant, the pyrrolidine product, and acetonitrile.

The presence of the coordinated olefin intermediate **II** and the absence of neutral rhodium−amido and rhodium−hydride species in reactions mediated or catalyzed by [(**L1**)Rh(NCMe)]BF_4 are consistent with a mechanism involving nucleophilic attack of the primary amine on a coordinated olefin (eq 4, path B). The observation of the amine and olefin complexes **I** and **II** as the resting states suggests two possible reaction sequences. Nucleophilic attack of the primary amine on the coordinated olefin could be irreversible and turnover-limiting. Alternatively, nucleophilic attack of the primary amine on the coordinated olefin could be reversible and followed by irreversible protonolysis of the Rh−C bond. In the latter case, the combination of reversible nucleophilic attack and irreversible protonolysis together would control the rates of the catalytic reactions (see Scheme 4, steps ii and iii).

4.2. Measurement of Kinetic Isotope Effects. The magnitude of the KIE should distinguish between the pathway in which nucleophilic attack is the first irreversible ("turnover-limiting") step and the one in which proton transfer is the first irreversible step. Thus, we measured the KIE for reaction of aminoalkene **1b** and the N-deuterated substrate **1b-D$_2$** (eq 5). A small KIE would be expected for the pathway involving turnover-limiting nucleophilic attack because N−H(D) bond cleavage is not involved in this step; however, a large primary KIE would be expected for the pathway involving turnover-limiting Rh−C bond cleavage by proton transfer from an amine or ammonium nitrogen. At 61 °C with 5 mol % [Rh(CH_3CN)$_2$COD]BF_4 and 6 mol % **L1** in *tert*-butyl alcohol-d_9 or -d_{10}, the value of k_H/k_D for reactions of aminoalkenes **1b** and **1b-D$_2$** deduced from the initial rates was small (1.16 ± 0.10).[47] This small value is consistent with turnover-limiting nucleophilic attack of the amine onto the alkene. This result differs from the large primary isotope effect of 3.4 measured for cyclization of an aminoalkene catalyzed by [Ir(COD)Cl]$_2$ and the observation of aminoalkyl−metal complexes as the resting states in reactions catalyzed by complexes of palladium and platinum. The small KIE implies that the relative rates of protonolysis of the metal−carbon bond and reversion to the acyclic reactant (the reverse of step ii in Scheme 4) favor protonolysis more for the rhodium aminophosphine complex than for other systems containing late metals.

Scheme 3. Competition Experiment between Primary and Secondary Aminoalkenes





4.3. Investigation of Relative Rates. The relative rates of reaction of the primary and secondary amines were different when the reactions were conducted in separate systems versus in the same system (Scheme 3). When the rates were measured independently, the rate of hydroamination of secondary amine **18** to form **19** was similar to the rate of hydroamination of primary amine **1a** to form **2a** (the value of k_{1a}/k_{18} deduced from initial rates was 1.3) However, the primary amine reacted exclusively before the secondary amine when the two were present in the same system. This difference reflects a difference in the resting state of the catalyst in separate systems versus the system containing both substrates.

The resting state in the reactions of secondary amines consists of a combination of the olefin-bound secondary aminoalkene **18** complex and the acetonitrile complex [(**L1**)Rh(NCMe)]BF_4.

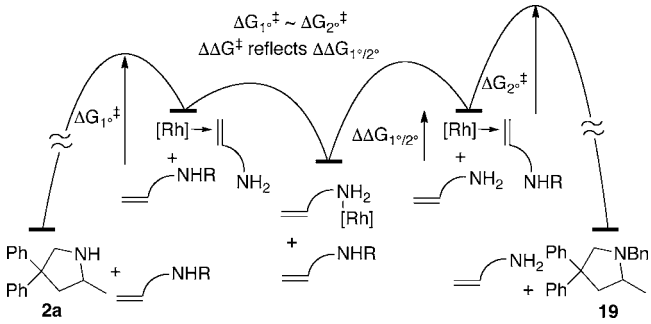
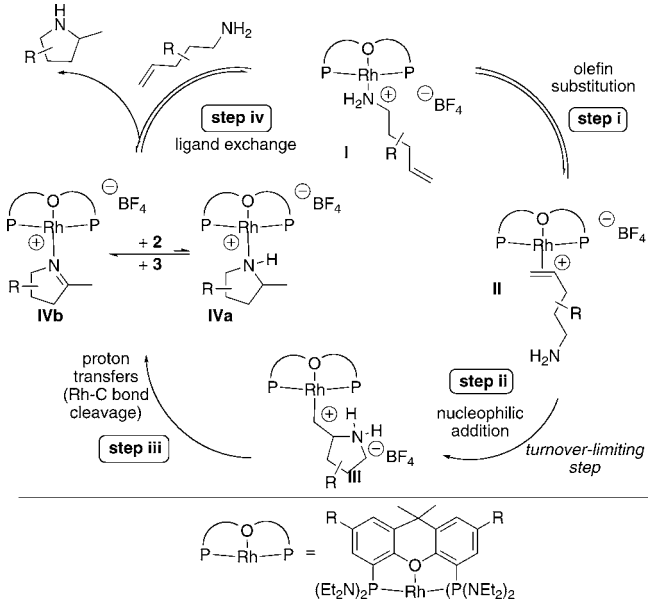


Figure 3. Relative ground- and transition-state energies for reactions of primary and secondary aminoalkenes deduced from competition binding and catalytic reactions.

Scheme 4. Proposed Catalytic Cycle



The resting state of the catalyst in reactions of primary aminoalkenes in THF is the primary amine complex. The order of affinities of a primary amine, secondary amine, and alkene follow the trend 1° amine > alkene > 2° amine. Treatment of alkene complex [(**L1′**)Rh(1-hexene)]BF_4 with 1.5 equiv of benzylamine in THF led to a 26:1 ratio of the primary amine complex to the alkene complex after 16 h, whereas treatment of this alkene complex with the secondary amine *N*-methylbenzylamine formed a 2.5:1 ratio of the olefin complex to the secondary amine complex. Thus, the relative energies for the resting states and transition states can be represented as shown in Figure 3, and reaction of the substrates together yields the product from the primary amine over the secondary amine.

5. Mechanistic Conclusions. On the basis of these experiments, we propose the mechanism shown in Scheme 4 involving nucleophilic attack of the amine on a coordinated olefin. In this mechanism, substitution of the tethered olefin for the primary amine in complex **I** occurs, delivering olefin complex **II**. The equilibrium ratio of the amine and olefin complexes was significantly influenced by the solvent (i.e., THF vs *t*BuOH). In the protic solvent *t*BuOH, the ratio of olefin to amine complex was larger than it was in the aprotic THF solvent. Increased concentrations of the olefin complex should increase the rate of nucleophilic addition, and this increased concentration is one factor that explains the higher rates of catalytic reactions performed in *t*BuOH relative to those of reactions conducted in THF. The coordinated olefin subsequently undergoes rate-limiting nucleophilic attack (step ii) to generate an ammonium alkylrhodium adduct, **III**, that could undergo either protonolysis to generate the hydroamination product or β-hydride elimination to afford the oxidative amination product. As the reaction progresses and the concentration of the imine increases, the imine complex **IVb** becomes the resting state.

The pincer coordination mode of the xantphos derivative likely affects the selectivity for hydroamination over oxidative amination. Previously, a dicationic PNP−palladium complex was shown to catalyze the hydroamination of amide- and carbamate-protected aminoalkenes.[28] It was proposed that the tridentate PNP ligand inhibits β-hydride elimination of an alkylmetal intermediate because it occupies the remaining three coordination sites in the square plane of the metal. β-Hydride elimination is typically faster when a coordination site is available in the square plane (eq 2).[53] The POP-pincer structure of the rhodium complex likely favors hydroamination over oxidative amination for related reasons. The POP-pincer structure, although less tightly bound to monocationic rhodium in a κ^3 structure than the PNP ligand is bound to dicationic palladium, could still discourage β-hydrogen elimination and favor formation of hydroamination over oxidative amination products. The use of pincer-type ligands in hydroamination reactions catalyzed by late metals therefore appears to be a general strategy for inhibiting an oxidative amination pathway and favoring a hydroamination pathway.

The complementarity of hydroaminations with basic amines catalyzed by rhodium and hydroamination with less basic amides and carbamates catalyzed by palladium[28] likely results from differences in the charges of the two complexes. The monocationic rhodium complex competitively binds the alkene and the amine, but the coordinated alkene is less electrophilic than that in the dicationic palladium complex. Thus, a more nucleophilic amine is needed for cyclization to occur by nucleophilic attack on the rhodium-bound alkene. On the other hand, the dicationic palladium complex bears a more electrophilic coordinated alkene, and less nucleophilic amides will attack this coordinated alkene. Hydroamination with more basic nitrogen nucleophiles, such as alkylamines, do not occur with this palladium system, perhaps because these nucleophiles bind tightly to the highly electrophilic Pd center and prevent the alkene binding that precedes C−N bond formation.

Our measured KIE and the observed catalyst resting states imply that the series of proton transfer steps (step iii), including cleavage of the rhodium−carbon bond to generate the cyclized product, occurs faster than reversion to the reactant by C−N bond cleavage. Cleavage of the rhodium−carbon bond could occur by either direct protonation of the σ bond or a mechanism involving initial formation of a Rh^{III}−H intermediate followed by reductive elimination to release the product.[59] We propose that the aminophosphine ligand affects these relative rates by promoting proton transfer, perhaps with assistance by the electron pair on nitrogen. We are currently investigating this hypothesis further. In contrast to platinum-, palladium-, and iridium-catalyzed hydroaminations of secondary amines, protonation of the metal−carbon bond is not the turnover-limiting

(59) DFT calculations showed that reductive elimination from a neutral Ir(III)−hydride intermediate is a lower-energy pathway than direct protonolysis of the Ir−C bond in the hydroamination of a secondary aminoalkene catalyzed by $[Ir(COD)Cl]_2$. See ref 46.

step for the hydroamination of primary amines catalyzed by [(**L1**)Rh(NCMe)]BF_4.

Summary

We have developed a highly active catalyst for the intramolecular hydroamination of unprotected primary aminoalkenes that is based on an unusual diaminophosphine ligand. For the first time with a late-metal catalyst, primary aminoalkenes that do not contain geminal disubstitution on the alkyl chain have been shown to undergo cyclization in high yields at mild temperatures. The substrate scope includes aminoalkenes containing various reactive functional groups that would not be tolerated by previously reported catalysts for the hydroamination of primary amines. We also have presented initial results demonstrating that this catalyst cyclizes aminoalkenes containing internal olefins.

The diaminophosphine ligand appears to be important for achieving high rates and selectivities in the intramolecular hydroamination of primary amines. A detailed mechanistic study of this catalytic reaction has been conducted. Our data support a mechanism involving turnover-limiting nucleophilic attack of the amine on a coordinated olefin, followed by rapid proton transfer to cleave the metal−carbon bond. We suggest that the aminophosphine groups on the ligand create favorable relative rates for the proton transfer steps.

We have also identified the primary pathway for catalyst decomposition, which will allow us to design future catalysts with improved stability. We are currently seeking to use these conclusions to develop catalysts that are even more active for intermolecular hydroaminations of unactivated olefins and to develop asymmetric hydroaminations with catalysts bound by ligands containing chiral diamino groups.

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Supporting Information Available: Experimental procedures, compound characterization data, kinetic data, and details of the crystal structure of [(**L1′**)Rh(NCMe)]BF_4, including a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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