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Mild, Rhodium-Catalyzed Intramolecular Hydroamination of Unactivated Terminal and Internal Alkenes with Primary and Secondary Amines

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The hydroamination of olefins[1] is one of the simplest and most atom-economical methods to prepare alkylamines, and much effort has now been spent to develop catalysts for this process. Some of most reactive catalysts contain lanthanides[2] and group IV transition metals.[3] However, the high sensitivity of these catalysts toward air and moisture and their low tolerance of polar functional groups have limited their use and motivated efforts to develop late-metal hydroamination catalysts. Although several catalysts based on late metals have been published for additions of amines to vinylarenes[4–6] and for the addition of amides and sulfonamides to alkenes, allenes, and dienes,[7] few catalysts for additions of amines to alkenes, arguably the most important donors and acceptors, have been reported.

The existing late-metal catalyst for the intramolecular additions of amines to olefins[8] is generated from $[PtCl_2(H_2CdCH_2)]_2$ and PPh^3. This system operates at 120 °C, catalyzes only reactions of secondary amines, not primary amines, and catalyzes additions to only terminal olefins, not internal olefins.[9] Moreover, this catalyst requires substituents that bias the substrate toward cyclization. Alterative palladium catalysts for additions of amides and carbamates at lower temperature have been reported,[10] but these N−H bond donors require installation and removal of the activating group in most synthetic sequences and do not provide products that would result from addition of a secondary amine. Thus, a catalyst that tolerates polar functional groups and that induces additions of both primary and secondary amines without activating groups to both terminal and internal alkenes is needed.

We report the identification of such a system. We report a rhodium catalyst for the hydroamination of terminal and internal alkenes with primary and secondary amines, with or without substituents that favor cyclization to form five- or six-membered ring products. In addition to spanning a broader scope of amine and alkene than other late metal catalysts, this system operates in the presence of functional groups, including esters and free hydroxyl groups, which do not tolerate early metal and lanthanide catalysts. These results demonstrate that complexes of group 9 metals, which are classic catalysts for alkene hydrogenation and hydrosilylation, can also be made useful for alkene hydroamination.

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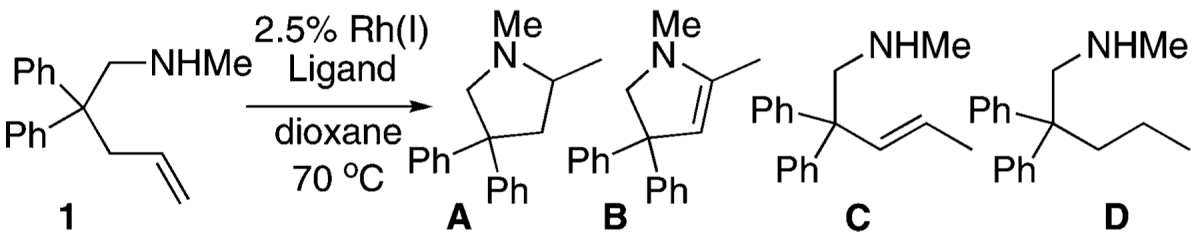
Supporting Information Available: All experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.



(1)

Stimulated by our previous studies on rhodium-catalyzed additions of amines to vinylarenes,[5,6] we investigated combinations of rhodium precursors and dative ligands as catalysts for cyclization of the *N*-methyl aminopentene in eq 1. Experiments to develop conditions for the cyclization of aminoalkene **1** are summarized in Table 1. These reactions were conducted at 70 °C over 7 h, unless otherwise stated.

Reaction of aminoalkene **1** in the presence of 2.5 mol % [Rh-$(COD)_2$]BF_4 and 2.5 mol % DPEphos, which catalyzed the anti-Markovnikov hydroamination of vinylarenes,6 formed none of the cyclized pyrrolidine product. The major product of this reaction resulted from isomerization of the olefin from the terminal to the internal position.[11] Reactions catalyzed by 2.5% [$Rh(COD)_2$]BF_4 and 2.5% DPPB (1,4-*bis*(diphenylphosphino)butane), which catalyzed the intramolecular hydroamination of vinylarenes,[5] led to a mixture of cyclic amine, isomerized olefin, cyclic enamine, and alkylamine, with the cyclic amine comprising only 10% of the material. Reactions catalyzed by complexes of other ligands (entries 3–6) also formed mixtures, but two systems formed exclusively cyclic amine. The catalyst generated from [$Rh(COD)_2$]BF_4 and an amino analogue of Xantphos **L1** or the biarylphosphine ligand **L2** developed in the Buchwald laboratory for cross-coupling[12] formed the cyclic amine as the sole detectable product in 86 and 93% yield by GC (entries 7 and 8). Studies with various rhodium precursors (entries 8–11) showed that [$Rh(COD)_2$]BF_4 formed the most active catalyst. Reactions with protic acid as catalyst, which could be generated from the rhodium precursor,[13a] formed no product (entry 12).[13b]

The scope of the hydroamination of 5- and 6-*N*-alkyl aminoalkenes to form pyrrolidines and piperidines under these reaction conditions are summarized in Table 2. Cyclizations to form five-membered rings with aminoalkenes containing not only *N*-methyl (Table 1), but more bulky *N*-cyclohexylmethyl and *N*-benzyl amines (Table 2, entries 1–2) generated high yields of cyclized products. These cyclizations occurred for substrates with (entries 1–4) or without (entries 5–7) *gem*-disubstitution on the linker chain. Likewise, cyclizations to form six-membered rings occurred with substrates possessing (entry 8) or fully lacking substituents in the linking chain (entry 9).

In addition, these reactions occurred in the presence of a variety of functional groups, such as halides, nitriles, and esters (entries 5–7). Perhaps most remarkable, reaction of the substrate in entry 10 containing an allylic alcohol function occurred in good yield with high diastereoselectivity without significant decomposition of the alcohol or deactivation of the catalyst. The reaction of *N*-benzyl-2,2-diphenylpent-4-en-1-amine even occurred in an 82% yield in the presence of 5.0 equiv of added water.

Most additions of amines to alkenes have been conducted with terminal, monosubstituted olefins. However, reactions with disubstituted olefins catalyzed by this rhodium system also formed cyclized products. Additions of amines occurred across geminally substituted olefins

(entries 11 and 12), including those in relatively unbiased substrates, and across an unstrained internal olefin (entry 13).[14]

The rhodium catalyst also increased the scope of amines that would add to alkenes. For example, the species generated from 5% $Rh(COD)_2BF_4$ and 6% of **L2** catalyzed the cyclization of aminoalkenes containing primary amine units (Table 3). Reactions of primary aminoalkenes to form five- and six-membered rings occurred in good yields.

In summary, we report a rhodium complex that catalyzes cyclizations of aminoalkenes under mild conditions with substrates containing primary or secondary amines, terminal or internal alkenes, and linkers that possess or lack substituents that bias the substrate toward cyclization. This reaction tolerates a variety of common functional groups. Studies on the mechanism of this process and development of enantioselective versions of this process are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. The side products were identified by signals in the crude ^{1}H NMR spectrum and by GC–MS.

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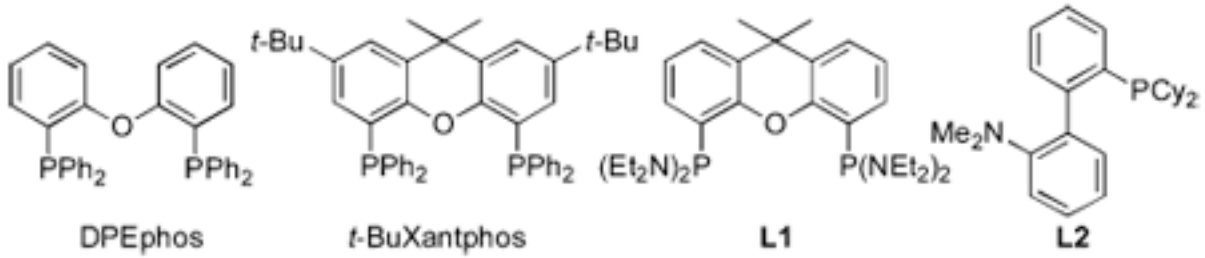
Table 1

Effect of Ligand on the Selectivity for Rhodium-Catalyzed Intramolecular Hydroamination of the Aminoalkene in Equation 1[a]



entry	catalyst	ligand [b]	%A[c]	%B[c]	%C[c]	%D[c]
1	$[Rh(COD)_2]BF_4$	DPEphos	0	0	93	0
2	$[Rh(COD)_2]BF_4$	DPPB	10	40	10	30
3	$[Rh(COD)_2]BF_4$	PPh_3	0	0	92	0
4	$[Rh(COD)_2]BF_4$	PCy_3	0	30	30	30
5	$[Rh(COD)_2]BF_4$	DPPF	20	30	10	30
6	$[Rh(COD)_2]BF_4$	*t*-BuXantphos	60	10	10	10
7	$[Rh(COD)_2]BF_4$	L1	86	0	0	0
8	$[Rh(COD)_2]BF_4$	L2	93	0	0	0
9	$[Rh(MeCN)_2(COD)]BF_4$	L2	92	0	0	0
10[d]	$[Rh(COE)_2Cl]2$	L2	28	0	0	0
11[d]	$[Rh(COD)Cl]_2$	L2	9	0	0	0
12	5% $HBF_4{\cdot}OEt_2$	L2	0	0	0	0

[a] Reaction conditions: 0.5 mmol of amine **1**, 2.5 mol % of Rh, and 2.5 mol % of biphosphine or 5 mol % monophosphine in 0.5 mL of dioxane at 70 °C for 7 h unless otherwise specified.

[b] Ligand structures are shown above the table.

[c] GC yields.

[d] Reaction run using 1.25 mol % catalyst.

Table 2

Rhodium Catalyzed Intramolecular Hydroamination of Secondary Aminoalkene [a]

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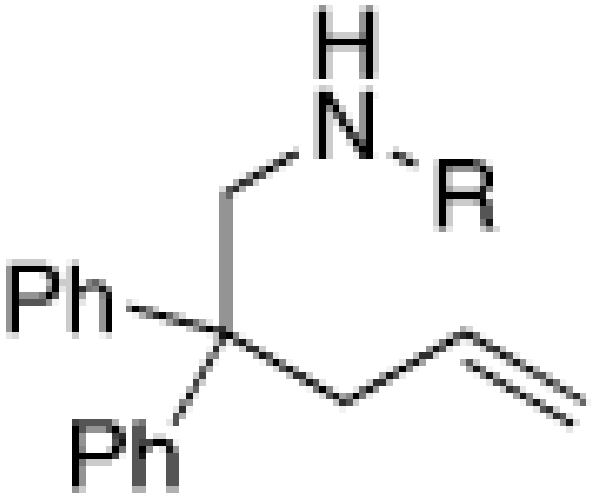
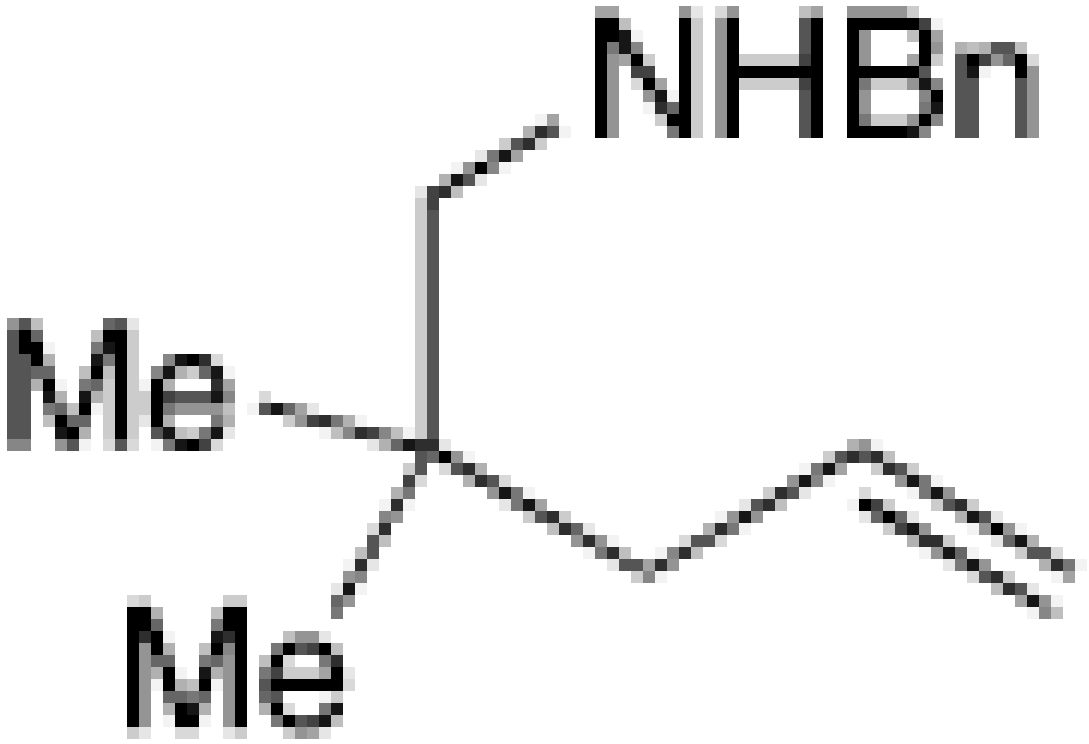
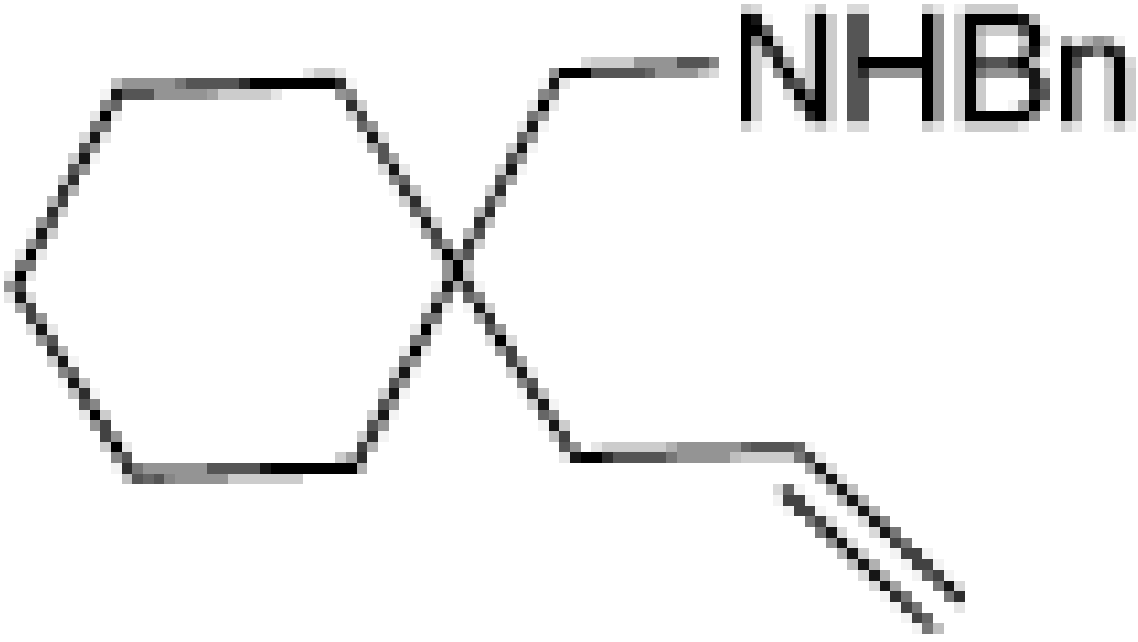
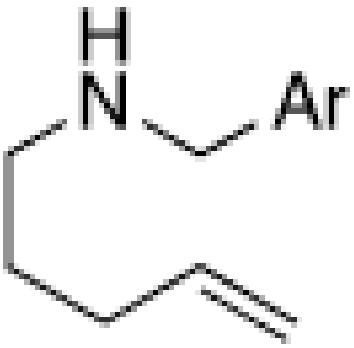
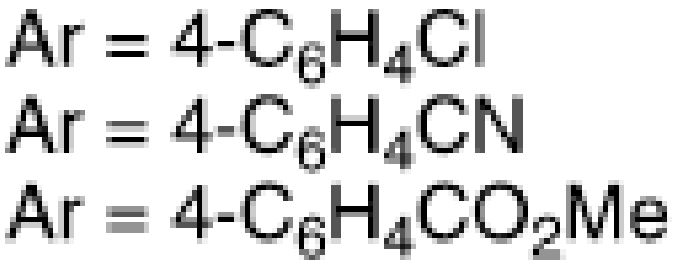
1	 
2	

entry	alkenyl amine
3	
4	

entry	alkenyl amine
5	
6	 
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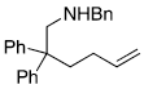
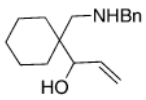
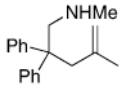
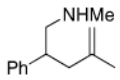
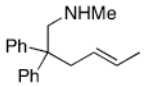
8	

entry	alkenyl amine
9	

entry	alkenyl amine
10	
11	

entry	alkenyl amine
12	
13	

[a] Reaction conditions: 0.5 mmol aminoalkene, 2.5 mol % of $[Rh(COD)_2]$-BF_4, and 3 mol % of **L2** in 0.5 mL of dioxane at 70 °C for 7 h unless otherwise specified.

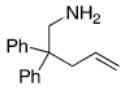
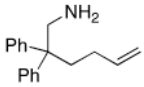
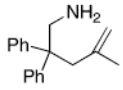
[b] Isolated yield (average of two runs).

[c] Reaction run using 7.5 mol % of catalyst and 9 mol % of ligand at 120 °C.

[d] Reaction run using 5 mol % of catalyst and 6 mol % of ligand at 100 °C.

Table 3

Rhodium Catalyzed Intramolecular Hydroamination of Primary Aminoalkene [a]

entry	aminoalkene
1	
2	
3	

entry	aminoalkene
4	

[a] Reaction conditions: 0.5 mmol aminoalkene, 5 mol % of rhodium, and 6 mol % of **L2** in 0.5 mL of dioxane at 100 °C for 10 h unless otherwise specified.

[b] Isolated yield.

[c] Reaction was run for 1 d.

[d] NMR yield.