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Sterically Hindered Mono(phosphines) as Supporting Ligands for the Platinum-Catalyzed Hydroamination of Amino Alkenes

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Summary: In an effort to develop more active catalysts for the intramolecular hydroamination of amino alkenes, we have investigated the application of sterically hindered mono(phosphines) as supporting ligands for platinum-catalyzed hydroamination. Here we demonstrate that mixtures of $PtCl_2$ and di(tert-butyl)o-biphenyl phosphines such as $P(t\text{-}Bu)_2[2\text{-}(2\text{-}NMe_2\text{-}C_6H_4)C_6H_4]$ catalyze the hydroamination of 4-pentenyl and 5-hexenyl amines at 60–80 °C. This catalyst system tolerates a number of functional groups and catalyzes the cyclization of unsubstituted amino alkenes.

Introduction

Functionalized nitrogen heterocycles are components of a wide range of naturally occurring[1] and biologically active molecules.[2] This, coupled with the limitations associated with traditional methods for C−N bond formation,[3] has stimulated considerable interest in the development of new and more efficient methods for the synthesis of nitrogen heterocycles. The intramolecular addition of the N−H bond of an amine across an unactivated C=C bond (hydroamination) represents an atom-economical and potentially expedient approach to the synthesis of nitrogen heterocycles.[4] However, despite considerable effort in this area, the intramolecular hydroamination of unactivated C=C bonds with alkylamines remains problematic.[4] For example rare earth,[5] alkali,[6] alkaline earth,[7] and group 4[8] metal complexes catalyze the intramolecular hydroamination of unactivated C=C bonds with alkyl amines, but the synthetic utility of these protocols is compromised by the poor functional group compatibility and extreme moisture-sensitivity of the catalysts. Alkyl 4-pentenyl amines undergo intramolecular hydroamination in the presence of Brønsted acids, but forcing conditions are required.[9] Conversely, late transition metal-catalyzed systems for the intramolecular hydroamination of unactivated C=C bonds with alkylamines have typically been restricted to vinyl arenes and conjugated dienes.[10]

In response to the limitations associated with the hydroamination of unactivated C=C bonds, we have developed an effective Pt-catalyzed protocol for the intramolecular hydroamination of amino alkenes.[11] This system was inspired by the studies of Panuzi and others[12] and, until recently,[13] represented the only late transition metal-catalyzed protocol for the hydroamination of unactivated C=C bonds with alkyl amines. As an example of Pt(II)-catalyzed hydroamination, treatment of

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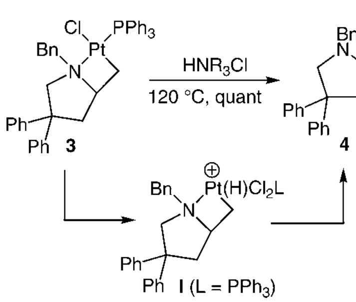
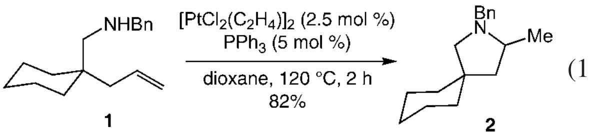
Scheme 1



4-pentenyl amine **1** with a catalytic 1:2 mixture of $[Pt(H_2C{=}CH_2)Cl_2]_2$ (Zeise's dimer) and PPh_3 in dioxane at 120 °C for 2 h led to isolation of pyrrolidine **2** in 82% yield (eq 1). The protocol tolerates substitution at the homoallylic and internal alkene carbon atoms, is compatible with a range of polar functional groups, and displays low sensitivity to moisture.[11] However, platinum-catalyzed hydroamination requires forcing conditions (120 °C), is ineffective for the hydroamination of alkenylamines that lack substitution along the alkenyl chain, and gives poor yields for the 6-*exo* cyclization of 5-hexenylamines.[11]

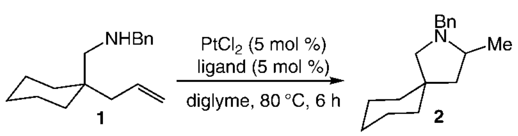


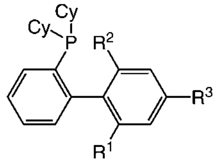
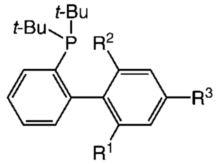
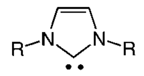
(1)

Mechanistic investigation of the Pt-catalyzed hydroamination of benzyl 2,2-diphenyl-4-pentenylamine established protonolysis of the Pt−C bond of platinum heterobicyclic amine complex **3** with ammonium chloride salt to form pyrrolidine **4** in the turnover-limiting step.[11] One scenario for the conversion of **3** to **4** involves rapid and reversible protonation at platinum followed by rate-limiting C−H reductive elimination from a Pt(IV) complex such as **I** (Scheme 1).[14] Because reductive elimination can be accelerated by sterically hindered ligands,[15] we considered that employment of sterically hindered mono(phosphines) as supporting ligands for the platinum-catalyzed hydroamination of amino alkenes might lead to enhanced activity relative to Pt(II)/PPh_3-based catalysts. Here we report that mixtures of $PtCl_2$ and sterically hindered *o*-biphenyl phosphines catalyze the intramolecular hydroamination of amino alkenes at 60–80 °C and display improved scope and generality relative to the catalyst generated from Zeise's dimer and PPh_3.

Results and Discussion

Table 1. Platinum-Catalyzed Hydroamination of 1 (0.5 M) as a Function of Ligand



entry	ligand	yield (%)[a]
1[b]	P(*o*-tolyl)$_3$	55
2[b]	P(*m*-tolyl)$_3$	22
		
3	$R^1 = R^2 =$ OMe, R^3 = H (**5a**)	72
4	R^1 = *i*-Pr, $R^2 = R^3$ = H (**5b**)	82
5	$R^1 = R^2 = R^3$ = *i*-Pr (**5c**)	79
		
6	$R^1 = R^2 = R^3$ = *i*-Pr, (**6a**)	100
7	$R^1 = R^2 = R^3$ = H (**6b**)	98
8	$R^1 = NMe_2$, $R^2 = R^3$ = H (**6c**)	100
		
9	R = 1-Adamantyl (**7a**)	45[c]
10	R = 2,5-C_6H_3(*i*-Pr)$_2$ (**7b**)	20[c]

[a] GC yield versus *n*-hexadecane internal standard. [b] $[PtCl_2(H_2C{=}CH_2)]_2$ (2.5 mol %) used as Pt source. [c] Sample taken at 3 h.

We initially targeted P(*o*-tolyl)$_3$, which has been applied to good effect in a range of palladium-catalyzed cross-coupling protocols,[16] as a supporting ligand for platinum-catalyzed hydroamination. An initial experiment was encouraging, and reaction of **1** with a catalytic 1:2 mixture of $[Pt(H_2C{=}CH_2)Cl_2]_2$ and P(*o*-tolyl)$_3$ at 80 °C for 6 h led to formation of **2** in 55% yield by GC analysis (Table 1, entry 1). Noteworthy was that mixtures of Zeise's dimer and PPh_3 displayed no activity at 80 °C. The markedly lower activity of $[Pt(H_2C{=}CH_2)Cl_2]_2$/P(*m*-tolyl)$_3$ (Table 1, entry 2) relative to $[Pt(H_2C{=}CH_2)Cl_2]_2$/P(*o*-tolyl)$_3$ for the conversion of **1** to **2** suggested that the steric bulk of P(*o*-tolyl)$_3$ ($\theta = 194°$)[17] was responsible for the enhanced reactivity of P(*o*-tolyl)$_3$ relative to PPh_3.

In an effort to identify even more active hydroamination catalysts, we turned our attention to sterically hindered *o*-

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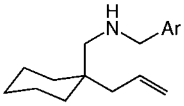
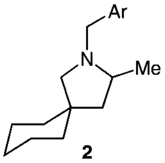
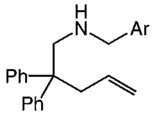
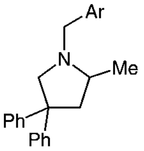
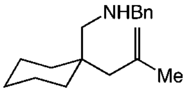
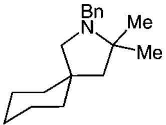
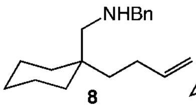
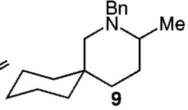
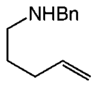
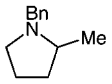
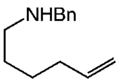
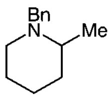
Table 2. Hydroamination of *N*-Alkenyl Amine Derivatives (0.5 M) Catalyzed by a Mixture of $PtCl_2$ (5 mol %) and 6a or 6c (5 mol %) in Diglyme at 60–80 °C

entry	alkenyl amine	heterocycle	cond[a]	time (h)	yield (%)[b]
					
1	Ar = Ph (**1**)	**2**	**A**	10	86
2	Ar = 4-C_6H_4OMe		**A**	10	86
3	Ar = 4-C_6H_4Br		**B**	9	77
4	Ar = 4-$C_6H_4NO_2$		**B**	13	84
5	Ar = 2-naphthyl		**A**	9	81
					
6	Ar = Ph	**4**	**B**	14	86
7	Ar = 2-furanyl		**A**	96	57
8[c]	Ar = 2-thienyl		**C**	96	63
9			**D**	64	85
10	 **8**	 **9**	**A**	9	76
11[c]			**C**	96	48
12[c]			**C**	96	66

[a] Conditions: **A** = **6c**, 60 °C; **B** = **6a**, 60 °C; **C** = **6c**, 80 °C; **D** = **6a**, 80 °C. [b] Isolated material of $\geq$95% purity. [c] Reaction run with 10% catalyst loading.

biphenyl phosphines as supporting ligands for Pt(II)-catalyzed alkene hydroamination. These ligands are readily available and have been used to good effect for a variety of cross-coupling reactions.[18] Although the dicyclohexylphosphines **5a**−**5c** were superior to P(*o*-tolyl)$_3$ (Table 1, entries 3–5), di(*tert*-butyl)phosphines **6a**−**6c** were particularly effective supporting ligands for alkene hydroamination (Table 1, entries 6–8). For example, preparative-scale reaction of **1** with a catalytic 1:1 mixture of $PtCl_2$ and **6c** (5 mol %) for 10 h at 60 °C led to isolation of **2** in 86% yield (Table 2, entry 1). Despite the similar steric and electronic properties of *N*-heterocyclic carbenes **7** relative to **6**, **7a** and **7b** were considerably less effective supporting ligands for the Pt-catalyzed conversion of **1** to **2** (Table 1, entries 9 and 10).

In addition to the higher hydroamination activity of $PtCl_2$/**6** relative to $[Pt(H_2C{=}CH_2)Cl_2]_2/PPh_3$, hydroamination of amino alkenes catalyzed by $PtCl_2$/**6** displayed broader substrate scope under much milder conditions. In addition to **1**, 4-pentenyl amines that possessed an aryl methoxy or nitro group, a heteroaryl group, or a methyl substituent at the internal alkene carbon atom underwent intramolecular hydroamination catalyzed by a mixture of $PtCl_2$ and either **6a** or **6c** at or below 80 °C (Table 2, entries 2–9). Likewise, 5-hexenyl amine **8** underwent 6-*exo* hydroamination to form **9** in 76% isolated yield at 80 °C without the necessity of slow substrate addition that was required to effect the hydroamination of **8** catalyzed by $[Pt(H_2C{=}CH_2)Cl_2]_2/PPh_3$ (Table 2, entry 10). Mixtures of **6c** and $PtCl_2$ also catalyzed the hydroamination of unsubstituted 4-pentenyl and 5-hexenylamines, although long reaction times were required (Table 2, entries 11 and 12). Unfortunately, the **6c**/$PtCl_2$ catalyst system was not effective for the intramolecular hydroamination of internal alkenes.

Summary

A 1:1 mixture of $PtCl_2$ and either **6a** or **6c** catalyzes the intramolecular hydroamination of unactivated C=C bonds with secondary alkyl amines at 60–80 °C. This catalyst system displays considerably higher activity than the previously reported catalyst system comprised of Zeise's dimer and PPh_3. The $PtCl_2$/**6**-catalyzed protocol displays good functional group compatibility and catalyzes the cyclization of 5-hexenyl amines and unsubstituted 4-pentenyl amines.

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Supporting Information Available: Experimental procedures, spectroscopic data, and scans of NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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