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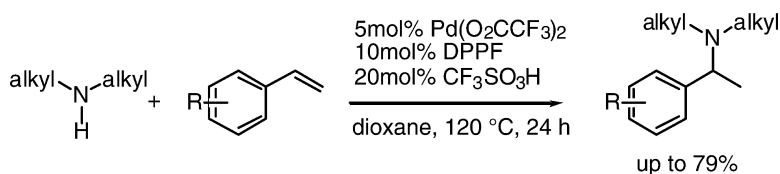
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Intermolecular, Markovnikov Hydroamination of Vinylarenes with Alkylamines

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Catalysts for the hydroamination of olefins have been actively pursued because this process could create an efficient synthesis of amines with regio- and enantiocontrol.[1,2] However, few intermolecular additions of amines to olefins have been reported.[3–11] Only one high-yield Markovnikov addition of an alkylamine to an alkene or vinylarene catalyzed by a d- or f-block metal is known,[11] and this reaction was conducted with 20 mol % of a lanthanide catalyst and a 70:1 ratio of olefin to amine.

Late transition-metal catalysts are likely to be more convenient to handle and tolerant of functional groups than lanthanide or early metal catalysts. However, late metal-catalyzed pathways for hydroaminations with alkylamines initiated by activation of amine or activation of olefin have been challenging to develop. Activation of alkylamines by oxidative addition remains unknown, and although addition of amines to coordinated olefins is common, the aminoalkyl group resulting from this addition is difficult to cleave from the metal under catalytic conditions. Acid could cleave this group in a catalytic cycle,[12] but the high basicity of alkylamine reagents level the strength of strong acids.

We recently showed that palladium-catalyzed additions of arylamines to vinylarenes occurred by addition of the amine to an η^3-phenethylpalladium intermediate instead of N–H activation or attack of amine on a coordinated olefin.[13] We now report the first transition metal-catalyzed olefin hydroamination with alkylamines to form products with Markovnikov regiochemistry (eq 1). Mechanistic studies show that the palladium catalysts confront a new hurdle in this process: reaction of the more basic alkylamine with the η^3-phenethylpalladium intermediate leads to an elimination of olefin that is competitive with the addition of amine to form the hydroamination product.

$$\text{(1)}$$

75% isolated yield
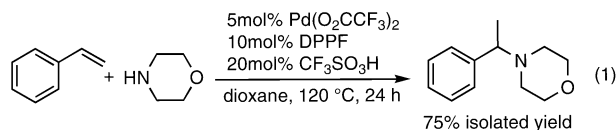
The previously reported, palladium-catalyzed additions of aromatic amines to vinylarenes occurred in toluene solvent with catalysts bearing either mono- or bidentate ligands.[8] In contrast, the addition of aliphatic amines to vinylarenes required an alternative reaction medium, higher temperatures, and a change in catalyst composition. After testing a variety of reaction conditions, the addition of morpholine to styrene was found to occur in 79% yield at 120 °C in dioxane solvent with a catalyst generated from 2 equiv of the bidentate ligand DPPF (DPPF = 1,1′-bis(diphenylphosphino)-ferrocene) and palladium trifluoroacetate (Table 1, entry 1).

The reactions of morpholine with styrene in toluene at 120 °C separated into two phases and occurred in only 25% yield (Table 1, entry 2). These two phases consisted of vinylarene in toluene and, presumably, the ammonium salt from amine and acid. Reactions in ether solvents consisted of a single phase, and the reaction of morpholine with styrene in dioxane occurred faster than it occurred in toluene and in high yield.

Table 1. Effects of Catalyst, Acid, and Solvent on the Hydroamination of Styrene with Morpholine at 120 °C[a]

entry	catalyst	solvent	yield[b]
1	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF/20% TfOH	dioxane	79
2	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF/20% TfOH	toluene	25
3	5% Pd(O$_2$CF$_3$)$_2$/5% DPPF/20% TfOH	dioxane	2
4	5% Pd(DPPF)(OTf)$_2$	dioxane	1
5	5% Pd(DPPF)(OTf)$_2$/5% DPPF/10% TfOH	dioxane	74
6	5% Pd(PPh$_3$)$_4$/20% TfOH	dioxane	6
7	20% TfOH	dioxane	1
8	5% Pd(O$_2$CF$_3$)$_2$/20% TfOH	dioxane	1
9	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF	dioxane	2
10	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF/20% TFA	dioxane	19
11	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF/20% NFA[c]	toluene	72
12	5% Pd(O$_2$CF$_3$)$_2$/10% DPPF/20% NFA[c]	dioxane	67

[a] Reaction conditions: 0.4 mmol morpholine, 0.8 mmol styrene, 0.2 mL dioxane, 24 h. [b] GC yields, in percent. [c] NFA = nonafluorobutane sulfonic acid.

Results from reactions with different catalyst compositions are summarized in Table 1. Reactions of vinylarenes with aliphatic amines conducted with a 1:1 ratio of metal to bisphosphine and reactions catalyzed by isolated (DPPF)Pd(OTf)$_2$ occurred in low yield (entries 3 and 4). However, reactions catalyzed by 5% (DPPF)-Pd(OTf)$_2$ with 5% added DPPF and TfOH cocatalyst (entry 5) occurred in good yield. Reactions catalyzed by Pd(PPh$_3$)$_4$ and TfOH as cocatalyst were slow (entry 6), despite the high activity of this catalyst for addition of aromatic amines to vinylarenes.[8]

Palladium, ligand, and acid cocatalysts were each required to form substantial amounts of product. As shown in Table 1, entries 7–9, reactions lacking one or more of these components occurred in low yield. Reaction with trifluoroacetic acid instead of TfOH as cocatalyst (entry 10) also occurred in low yield.

Reaction of morpholine with styrene in the presence of catalyst and the longer chain fluoroalkylsulfonic acid, nonafluorobutane-sulfonic acid (NFA), consisted of a single phase in toluene and occurred in good yield (Table 1, entry 11). However, the longer chain sulfonic acid did not improve reaction yields in dioxane (entry 12), and reaction of other amines with styrene in the presence of NFA in toluene solvent occurred in lower yields than they did with TfOH in dioxane.

The scope of the reaction of alkylamines with vinylarenes is summarized in Table 2. The reaction of morpholine with electron-rich or electron-poor vinylarenes occurred in moderate to good yields (Table 2, entries 1–6). Reactions of 2-vinylnaphthalene occurred fastest and in the highest yields, as was observed for reactions of aromatic amines.

Modestly basic cyclic aliphatic or benzylic amines such as N-phenylpiperazine, N-Boc piperazine, isoindoline, and 1,2,3,4-tetrahydroisoquinoline also reacted with styrene in good yields (Table 2, entries 7–10). The more basic[14] piperidine reacted with lower conversions and formed the products from addition to 2-vinylnaphthalene (entry 11) and styrene in lower 52% and 20% yields. Pyrrolidine also reacted with styrene in low yields.

Table 2. Pd-Catalyzed Hydroamination of Alkylamines with Vinylarenes

$$\text{HNRR' + R-[-]-CH=CH}_2 \xrightarrow[\text{dioxane, 120 °C, 24 h}]{\begin{array}{c}\text{5mol\% Pd(O}_2\text{CCF}_3)_2 \\ \text{10mol\% DPPF} \\ \text{20mol\% CF}_3\text{SO}_3\text{H}\end{array}} \text{R-[-]-CH(NRR')CH}_3$$

entry	product	yield[b]	entry	product	yield[b]
1		75%	8[g]		63%
2[c]		51%	9[e]		71%
3		76%	10		58%
4[d]		79%	11[g]		52%
5[e,f]		51%	12[h]		63%
6[e,f]		48%	13[e,f,g]		43%[i]
7		72%	14[g,j]		53%

[a] Amine/vinylarene/Pd(TFA)$_2$/DPPF/TfOH = 1:2:0.05:0.10:0.20 (1 mmol of amine) in 0.50 mL of dioxane. [b] Isolated yield. [c] 48 h. [d] 100 °C. [e] 4.0 mmol of vinylarene was used. [f] 0.20 mL of dioxane. [g] 110 °C. [h] 80 °C. [i] 10% of dibenzylmethylamine was obtained as side product. [j] 18 h.

Acyclic aliphatic and benzylic amines also underwent hydroamination with vinylarenes. *N*-Benzylmethylamine added to 2-vinylnaphthalene in 63% yield (Table 2, entry 12) and to 4-methyl styrene in 43% yield (entry 13). The purely aliphatic acyclic *n*-hexyl methylamine added to 2-vinyl naphthalene in moderate yield (entry 14).

The known exchange of alkyl groups between amines[15] competed with hydroamination. For example, dibenzylmethylamine was formed from reaction of *N*-methylbenzylamine with 4-methylstyrene. The formation of this exchange product decreased the yield of product formed by hydroamination.

To understand the differences in reactions of alkyl and arylamines, we evaluated if the C−N bond in the alkylamine products was formed by addition of alkylamine to an η^3-phenethylpalladium complex as it was during palladium-catalyzed additions of arylamines to vinylarenes.[13] Thus, DPPF-ligated η^3-4-methylphenylethylpalladium complex **1** in eq 2 was allowed to react with 2 equiv of morpholine in the presence of added DPPF to trap a Pd(0) product. Reaction at 110 °C for 5 min formed (DPPF)$_2$Pd in 93% yield, *N*-1-(4-methylphenethyl)morpholine in 13% yield, and morpholinium triflate together with free 4-methylstyrene in 84% yield.

To determine if the 13% of hydroamination product was generated directly from the reaction of amine with **1** or from a catalytic reaction of the amine with the released vinylarene, the reaction of **1** with morpholine was conducted in the presence of 2 equiv of added styrene. The initial *N*-arylethylamine product contained the tolyl group of **1**. This result demonstrates that morpholine reacted directly with **1** to form the arylethylamine product.

These data reveal a new challenge in conducting hydroaminations of vinylarenes with basic amines. Reaction of basic amines with the η^3-arylethyl complex leads to an elimination of free vinylarene that can be faster than the addition of amine to the benzylic carbon.

Most likely, this elimination is reversible and retards, but does not prohibit, hydroamination. Regeneration of a palladium hydride by protonation of Pd(0) by the ammonium salt and reinsertion of

vinylarene would regenerate the η^3-arylethyl intermediate. Because the formation of this intermediate from alkylammonium salts is thermodynamically less favorable than that from arylammonium salts, the concentration of the η^3-arylethyl intermediate should be lower and the concentration of Pd(0) species higher in reactions of alkylamines. Indeed, the major palladium phosphine complex in solution during the catalysis with alkylamines is (DPPF)$_2$Pd(0).

$$\text{(eq 2)}$$
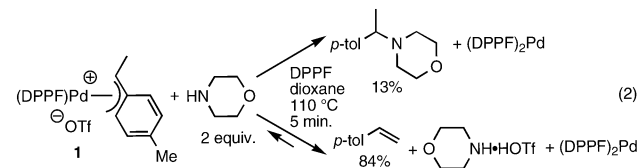
To test for the potential to develop an enantioselective hydroamination[16] of alkylamines, several nonracemic chiral ligands were examined. Reaction of *N*-methylbenzylamine with 2-vinylnaphthalene catalyzed by Pd(O$_2$CCF$_3$)$_2$ and (*R,R*)-Et-FerroTANE[17] occurred in 36% yield and 63% ee (eq 3) Though modest in yield and selectivity, these data demonstrate the feasibility of enantioselective additions of alkylamines.

$$\text{(eq 3)}$$
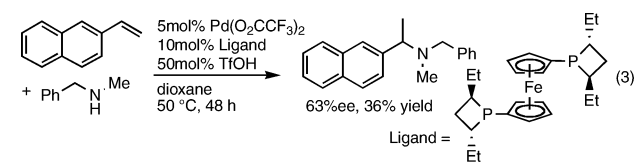
Thus, the scope of the palladium-catalyzed hydroamination of vinylarenes has been significantly expanded, and mechanistic data show a challenge confronted when conducting palladium-catalyzed reactions of vinylarenes with aliphatic amines. Further investigations to increase catalyst activity, reaction scope, and selectivities are in progress.

Supporting Information Available: Procedures for synthetic and mechanistic studies and characterization of reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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