Palladium-Catalyzed Intermolecular Hydroamination of Vinylarenes Using Arylamines

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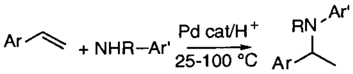
Received June 26, 2000

The catalytic, intermolecular hydroamination of olefins is a highly desired, but difficult process.[1−5] Efficient, intramolecular, lanthanide-catalyzed hydroaminations of alkenes have been developed by Marks,[6,7] but intermolecular reactions are generally slow.[8] Late metal-catalysts would be more desirable for this reaction because they are generally less sensitive to air and more tolerant of polar functionality. However, intermolecular hydroaminations of olefins that are catalyzed by late metals have shown slow rates and limited scope. $RhCl_3$ catalyzes the addition of secondary amines to ethylene at high temperature, but other olefins are unreactive.[9] Phosphine complexes of iridium(I) catalyze the addition of aniline to norbornene,[10,11] but other substrates are unreactive. Phosphine-ligated Rh(I) catalyzes the addition of piperidine to vinylpyridine,[12] and in one case to addition of morpholine to styrene in low yield,[13] but reaction of piperidine or aniline with styrene gives enamine by oxidative amination[14] or product mixtures.[13,15−17] We report an efficient, palladium-catalyzed hydroamination of vinylarenes using aromatic amines to give *sec*-phenethylamine products in the presence of acid cocatalyst (eq 1).



(1)

High-throughput screening studies in our laboratory recently showed that $[Pd(PPh_3)_4]$ was an efficient catalyst for the addition of aniline to dienes in the presence of acetic acid.[18] This result served as a lead for systems that would catalyze the addition of arylamines to vinylarenes. After varying several reaction parameters, we found that the reaction of aniline with styrene occurred to give the Markovnikov addition product in high yields after 12 h at 100 °C when catalyzed by a mixture of $[Pd(PPh_3)_4]$ and TFA or triflic acid cocatalyst.

Table 1. Effect of Catalyst Components and Acid on the Hydroamination of Styrene with Aniline[a]

entry	catalyst	yield, %[b]
1	2% $[Pd(PPh_3)_4]$	0
2	2% $Pd(OC(O)CF_3)_2$/8% PPh_3	28
3	2% $[Pd(PPh_3)_4]$/20% TFA	67
4	2% $[Pd(PPh_3)_4]$/20% TfOH	83
5	2% $Pd(OC(O)CF_3)_2$/8% PPh_3/20% TFA	68
6	2% $[Pd(OC(O)CF_3)_2]$/3% DPPF	78
7	2% $[Pd(OC(O)CF_3)_2]$/3% DPPF/20% TfOH	>99
8	2% $[(DPPF)Pd(OTf)_2]$	96

[a] Reactions were run for 6 h in toluene solvent at 100 °C. Reactions with lower yields did not show complete conversion. [b] Yields are for isolated material and are an average of two runs.

We investigated several acids for this process and found that reactions conducted in the presence of acids weaker than TFA did not occur, but reactions in the presence of triflic acid were faster than those conducted with TFA. Counterion effects, not acid strength, must account for this difference in rates because anilinium is the actual acid when either TFA or HOTf is used as cocatalyst.

The role of the acid is complex and under investigation, but several conclusions may be drawn at this time. One might propose that this reaction occurs by an uncatalyzed addition of acid to the olefin,[19] and a metal-catalyzed conversion of the acid adduct to the final amine. However, the leveling effect of aniline prevents addition reactions by the strong acid, and two experiments suggest that the anilinium acid does not react in an uncatalyzed fashion with free olefin: no reaction occurred between aniline and styrene in the presence of TFA without palladium catalyst, and reactions of the *sec*-phenethyl trifluoroacetate with aniline catalyzed by (*R*)-BINAP/Pd(trifluoroacetate)$_2$ gave racemic product instead of the nonracemic product formed in the overall hydroamination (see below). Moreover, preliminary experiments indicate that the benzylic trifluoroacetate of >92% ee reacts with aniline when catalyzed by $[((R)\text{-BINAP})Pd(OSO_2CF_3)_2]$ to give product that is lower in ee than that formed from the overall catalytic process. Thus, the catalytic cycle is unlikely to involve a product formed from addition of acid to the vinylarene.

The palladium catalyst is more likely to be modified by the acid cocatalyst. Experiments in Table 1 suggest that the acid oxidizes $[Pd(PPh_3)_4]$ to a Pd(II) species and that it plays a second, yet undefined, role in accelerating reaction rates. The yields in Table 1 reflect reaction rates; in general the reactions showed little byproduct other than unreacted starting materials. The oxidative role of the acid is demonstrated by the absence of reaction when using $[Pd(PPh_3)_4]$ alone as catalyst, but the formation of addition product when using 2% $Pd(OC(O)CF_3)_2$/8% PPh_3 (entry 2) or 2% $[Pd(OC(O)CF_3)_2]$/3% DPPF (entry 6). A second cocatalytic role for the acid was demonstrated by the accelerated rates when using 2% $Pd(OC(O)CF_3)_2$ and either PPh_3 or DPPF in the presence of 20% TFA or HOTf (entries 5 and 7 vs 2 and 6) as catalyst. The importance of counterion was shown by the reaction in entry 8, which occurred in the absence of acid. This reaction occurred more rapidly than the reaction in entry 6, which contained trifluoroacetate as counterion and no added acid.

The scope of catalyst is relatively broad, and results using several reaction conditions are provided in Table 1. Reactions employing precatalysts in oxidation state Pd(0) or Pd(II) ligated by either mono- or bisphosphine ligands were effective catalysts. However, catalysts bearing either sterically hindered or unhindered alkylphosphines have not been effective, and nickel and platinum complexes of mono- or bis-arylphosphines have provided no reaction. For studies on reaction scope, we selected the conditions in entries 4 and 7, which involve commercially available catalyst components.

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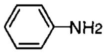
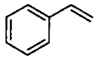
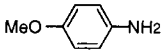
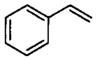
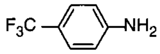
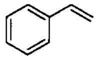
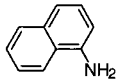
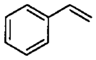
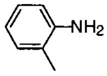
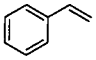
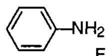
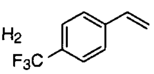
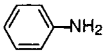
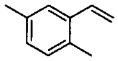
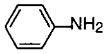
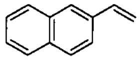
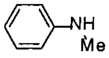
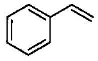
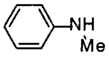
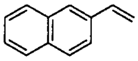
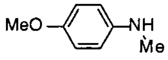
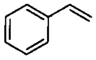
10.1021/ja002284t CCC: $19.00

Table 2. Palladium-Catalyzed Hydroamination of Styrene[a]

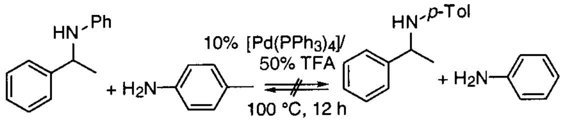
	Amine	Olefin	Cond.	time	Yield[b]
1			A	12 h	83%
2			B	7 h	>99%
3			A	12 h	93%
4			B	7 h	78%
5			A	12 h	64%
6			B	7 h	88%
7			B	7 h	68%
8			B	7 h	99%
9			B	7 h	85%
10			B	7 h	98%
11			C	72 h	98%
12			B	12 h	55%
13			A	12 h	65%
14			B[c]	12 h	54%

[a] Reaction conditions: A, 2% $Pd(PPh_3)_4$/20 triflic acid, 100 °C; B, 2% $Pd(TFA)_2$/3% DPPF, 20% TfOH, 100 °C; C, 5% $(DPPF)Pd(OTf)_2$, generated from $(DPPF)Pd(OTf)_2$ and AgOTf, 25 °C. [b] Yields are for pure, isolated material and are an average of two runs. [c] 5 mol % catalyst used.

The scope of this process for different arylamines and different vinylarenes is shown in Table 2. In general, reaction conditions employing 2 mol % catalyst occurred after 6−12 h at 100 °C. Some reactions occurred at lower temperatures. The scope of vinylarene encompassed electron-poor to electron-neutral styrenes and vinylnaphthalenes. Electron-poor styrenes reacted faster than those that are electron-rich. Styrenes bearing *ortho* substituents reacted in high yields. Reactions of vinylnaphthalenes were particularly rapid and occurred at room temperature in some cases (entry 11). Reactions of α- and β-substituted styrenes were slow, and were not pursued.

A variety of arylamines gave addition products. 1-Aminonaphthalene reacted in high yield and 2-methylaniline gave acceptable yields, demonstrating that *ortho* substituents are tolerated. Electron-rich anisidine and electron-poor trifluoromethylanilines both reacted to form addition products. Reactions of anisidines are particularly valuable because the products can be oxidized with cerric ammonium nitrate or DDQ to provide the parent amine.[20] Reactions of *N*-alkylanilines also occurred. *N*-Methylaniline and *N*-methylanisidine added to styrene or naphthalene, although in lower yields than did primary arylamines. Reactions with purely aliphatic amines gave low turnover numbers.

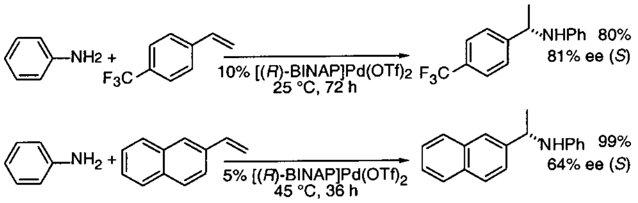
Asymmetric hydroamination of vinylarenes would require an irreversible addition. Because we were unsure of the thermodynamics for this reaction, we tested its reversibility. The product formed from addition of aniline to styrene was subjected to a mixture of toluidine and catalyst (eq 2). After 12 h at 100 °C, only trace amounts of free aniline and product from addition of *p*-anisidine were observed. Thus, we concluded that the reaction was essentially irreversible and that an asymmetric hydroamination was feasible.



(2)

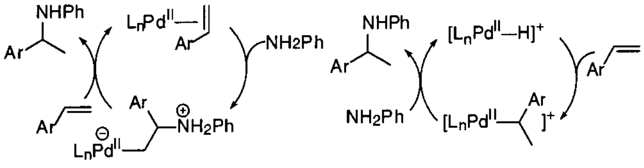
Preliminary studies indicated that enantiopure bisphosphines provide nonracemic amine product (Scheme 1). We focused on the addition reactions that occurred under the mildest conditions so that we could conduct the enantioselective hydroaminations near room temperature. Reaction of aniline with trifluoromethylstyrene catalyzed by $[((R)\text{-BINAP})Pd(OSO_2CF_3)_2]$ at 25 °C gave the addition product in 81% yield and 81% enantioselectivity. Analysis of the enantioselectivity throughout the reaction showed a constant value at both low and high conversion. These results confirmed the irreversibility of the reaction. Reaction of vinylnaphthalene with styrene at 45 °C with the same catalyst gave quantitative yields and 64% ee. These results uncover a new class of asymmetric transformation and constitute the best combination of yield and enantioselectivity for any intermolecular hydroamination.[11]

Scheme 1



Oxidative addition of aniline followed by insertion of olefin is often discussed as a potential pathway for hydroamination.[1,10] The rapid reactions with Pd(II) catalyst precursors and the lack of any observed oxidative addition of amines by Pd(0) or Pd(II) complexes suggests that an alternative mechanism operates here. We envision one of two alternatives in Scheme 2: nucleophilic attack on a coordinated styrene or reaction between free or activated amine and a *sec*-phenethyl palladium species. The latter complex could be formed by reaction of styrene with a Pd(II) hydride. Because reaction occurs in the absence of acid, we favor attack on coordinated olefin. In this mechanism, the aminoalkyl complex must undergo protonolysis[21] faster than β-hydrogen elimination, which occurs in related Wacker oxidation. Moreover, nucleophilic attack must occur at the α-carbon of the styrene. This selectivity contrasts with that of rhodium-catalyzed, anti-Markovnikov oxidative amination, which may occur by attack of piperidine at the β-carbon.[14] Future studies will address these mechanistic issues and will seek to identify catalysts for increased reaction scope and enantioselectivity.

Scheme 2. Two Potential General Mechanisms for the Hydroamination



Acknowledgment. The NIH (R29-GM55382), DOE (DE-FG02-96ER14678), and DuPont are gratefully acknowledged for support. We thank Dr. Sunwoo Lee and Prof. Pat Walsh for helpful comments and assistance in ee measurements.

Supporting Information Available: Reaction procedures, and characterization of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002284T

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