Palladium-Catalyzed Hydroamination of 1,3-Dienes: A Colorimetric Assay and Enantioselective Additions

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Mild, selective 1:1 reactions of amines with dienes to form allylic amines are rare[1] and limited to the reaction of cyclic dialkylamines catalyzed by nickel.[2] Late transition metal-catalyzed, amine-induced telomerizations of butadiene[1] and oxidative 1,4 addition of nucleophiles to dienes[3] are now well known, and the palladium-catalyzed additions of amines to more reactive eneynes[4] and allenes[5] have been reported. However, reactions of dienes with amines generally occur at high temperatures and produce isomeric mixtures.[1c,f,g] We report the use of a high-throughput colorimetric assay to identify catalysts for the regioselective 1:1 hydroamination of dienes at room temperature.[6,7] The scope of the diene hydroamination is broad and includes enantioselective examples.

To evaluate simultaneously a large number of potential catalysts for the hydroamination, we developed a colorimetric method to monitor the presence or absence of anilines. Furfural undergoes a condensation and ring opening with 2 equiv of aniline, but not with the allylic amine product, in the presence of acid to create a red product.[8] Thus, addition of furfural and acid to catalytic reactions of aromatic amines will reveal which catalysts are most active; reactions that consume the largest amount of aniline will show an absence of the red color. Typically, the reactions were diluted to distinguish the colors.

Figure 1 displays the results of this colorimetric assay for the reaction of aniline with cyclohexadiene. A set of potential catalysts generated from commercially available coordination complexes and common phosphines was assembled from stock solutions in a 96-well glass plate prior to the addition of reactants. Acids have been shown to inhibit telomerization of butadiene, eneynes, and allenes. Thus, we conducted reactions in the presence and absence of 10 mol % of TFA. After 4 h, some reactions conducted in the presence of acid showed, by the colorimetric assay, complete conversion of aniline, while reactions in the absence of acid required longer times to observe reaction. GC/MS analysis of solutions showing conversion of aniline indicated formation of

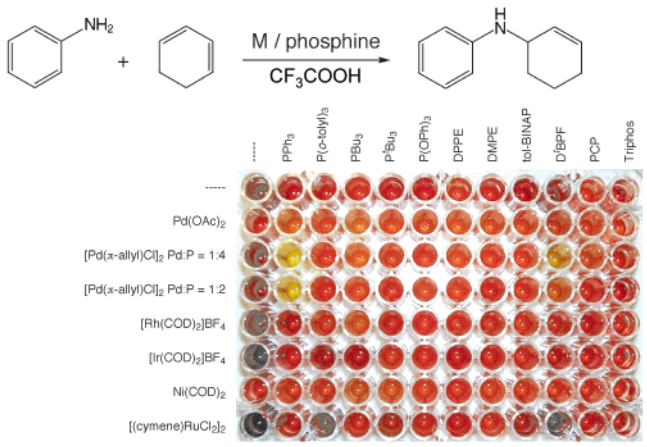
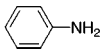
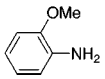
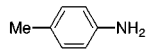
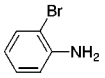
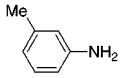
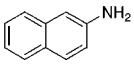
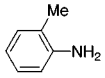
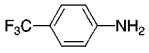
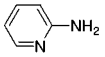
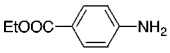
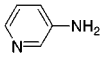
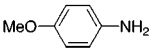
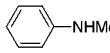
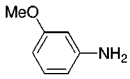
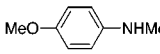


Figure 1. Use of a simple spot test to screen catalysts for the hydroamination of cyclohexadiene with aniline. A red color indicates remaining aniline reactant.

Table 1. Pd-Catalyzed Addition of Arylamines to Cyclohexadiene[a]

Entry	Amine	Yield[b] (%)	Entry	Amine	Yield[b] (%)
1		99	9		80
2		85	10		95
3		89	11		96
4		88	12		97
5[c]		91	13[d]		79
6[c]		96	14[d]		88
7		78	15		97
8		95	16		98

[a] Reaction conditions: 0.5 mmol amine, 2 mmol cyclohexadiene, 2 mol % $Pd(PPh_3)_4$, 10 mol % TFA, toluene, 25 °C, 24 h. [b]Yields are for pure, isolated compounds and are an average of two runs. [c]Reaction time: 48 h. [d]Reaction conditions: 2.5 mol % $[Pd(\pi\text{-allyl})Cl]_2$, 10 mol % PPh_3, toluene, 100 °C, 24 h.

1:1 adducts without telomerization. These experiments showed that complexes formed from $[Pd(\pi\text{-allyl})Cl]_2$ and PPh_3 were the most active (Figure 1). These two materials are known to form PPh_3-ligated Pd(0),[9] and NMR experiments in THF showed formation of $Pd(PPh_3)_4$ immediately upon mixing. Thus, we used the readily available $Pd(PPh_3)_4$ for preparative-scale reactions.

Table 1 shows results from preparative reactions containing 2 mol % $Pd(PPh_3)_4$ and 10 mol % TFA as catalyst and cocatalyst. Reactions were typically run at room temperature in toluene for 24 h, but shorter times could be used. All reactions occurred in high yield regardless of the presence of an electron-withdrawing, electron-donating, or ortho substituent on the aniline. Both the electron-rich (entries 7, 9) and electron-poor anilines (entries 5, 6) gave the addition products in high yields, although reactions

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Table 2. Reactions of Arylamines with Various Dienes

Entry	Diene	Amine	Yield[a] (%)	Entry	Diene	Amine	Yield[a] (%)
1[b]		$PhNH_2$	71	4[e]		$PhNH_2$	73
2[c]		$PhNH_2$	89[d]	5[b]		PhNHMe	84
3[c]		PhNHMe	84				

[a] Yields are for pure, isolated compounds and are an average of two runs. [b]Reaction conditions: 0.5 mmol amine, 2 mmol diene, 1 mol % $Pd(PPh_3)_4$, 50 mol % acetic acid. [c]Same reaction conditions except 2 mol % $Pd(PPh_3)_4$, 10 mol % TFA. [d]6% of diallylamine obtained for this reaction with excess diene. [e]Four-fold excess of aniline used.

of the electron-poor anilines required longer times. Reaction of *o*-toluidine, *o*-anisidine, *o*-bromoaniline, and 1-aminonaphthalene showed that ortho substituents are tolerated. Addition of *N*-alkylanilines also occurred under standard conditions (entries 15, 16). However, pyridylamines reacted only in the absence of acid cocatalyst. Reactions at 100 °C containing $[Pd(\pi\text{-allyl})Cl]_2/PPh_3$ as catalyst gave high yields of the pyridylamine products (entries 13, 14). Anisyl groups can be removed by oxidation;[10] thus, the reactions of anisidine and *N*-alkyl anisidine are the synthetic equivalent of adding ammonia or primary alkylamines.

The scope of the process for different 1,3-dienes is provided in Table 2. Cycloheptadiene reacted slower than cyclohexadiene but gave good yields. Cyclooctadiene did not react under the standard conditions. Reactions of acyclic dienes occurred in good yields in many cases, but the scope was less straightforward than that for cyclic dienes. The reaction of aniline with 2,3-dimethyl-1,3-butadiene formed the 1:1-adduct as the major product, and formation of the competing *N*,*N*-diallylamine product was suppressed by adding a four-fold excess of aniline. Isoprene reacted with aniline and *N*-methylaniline to give almost exclusively a single product from reaction at the less hindered end of the diene, whereas butadiene gave complex reaction mixtures.

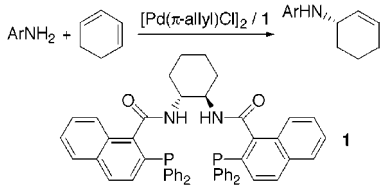
Studies at low catalyst loadings showed complete conversion after 24 h at room temperature when using only 0.5 mol % Pd and 1 mol % TFA. Complete conversion was even observed when we used 0.01 mol % Pd and 0.02 mol % TFA at room temperature, although after the long reaction time of 7 d.

With a catalyst system for reaction of a broad range of arylamines in hand, we sought an enantioselective version of this process. Preliminary experiments with added TFA, various optically active phosphines instead of PPh_3, and $[Pd(\pi\text{-allyl})Cl]_2$ as catalyst precursors showed good conversions but little or no stereoselection. Although slower, the reaction without added acid containing a catalyst comprised of $[Pd(\pi\text{-allyl})Cl]_2$ and Trost's ligand **1**,[11a] a naphthyl version of the parent ligand in entry 2,[11b] showed a promising combination of stereoselection and conversion. Optimization of reaction conditions showed that 5 mol % $[Pd(\pi\text{-allyl})Cl]_2$ and 11 mol % ligand **1** at 1.25 mM in THF solvent at room temperature provided the highest combination of yield and enantioselectivity for a broad range of arylamines (entries 7, 9−12). Higher temperatures provided lower final conversions, presumably because of catalyst deactivation. Monitoring of the reaction by HPLC showed that the enantioselectivity was constant throughout the reaction, demonstrating that the process is favorable enough thermodynamically, even without telomerization, to be irreversible. Applying the same conditions to the reaction of cycloheptadiene gave the 1,4 addition product in 22% yield with 66% ee (Table 3).

Initial mechanistic studies have evaluated the role of the acid cocatalyst. We considered that the reaction in the presence of acid could be initiated by formation of an allylic acetate or benzoate, which would undergo a well-known allylic amination.[12] However, benzoic, acetic, and trifluoroacetic acids do not react with cyclohexadiene at room temperature in the presence of amine. Moreover, hydroamination occurred without acid cocatalyst when the catalyst contained PPh_3 or **1** as ligand, although the reactions were slower. Thus, the reactions do not involve allylic carboxylate intermediates. We present two plausible pathways in Scheme 1; some different steps have been proposed for telomerizations. The first path involves attack on an η^2-diene complex by amine to form an allylpalladium product that can undergo proton transfer to produce free allylic amine. This mechanism is related to one presented and supported by unpublished data in a review by Jolly.[13] The second mechanism involves insertion of diene into a palladium hydride and nucleophilic attack on the resulting allyl. Perhaps the first mechanism occurs in the absence of acid cocatalyst, while the second occurs with acid cocatalyst.

Experiments to distinguish these mechanisms, to develop catalysts for additions of aliphatic amines, and to use organic spot tests for reaction discovery will be performed in the future.

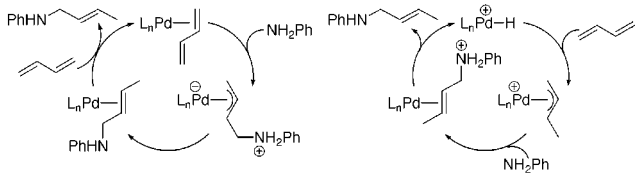
Table 3. Enantioselective Addition of Arylamines to Cyclohexadiene



entry	amine	ligand	M	time (h)	yield[a](%)	ee[b](%)
1[c]	$PhNH_2$	(*R*,*R*)-**1**	1.2	72	61	91 (*S*)
2[c]	$PhNH_2$	(*R*,*R*)-Trost	1.2	72	65	11 (*S*)
3[c]	$PhNH_2$	(*R*)-BINAP	1.2	72	99	7 (*R*)
4[c]	$PhNH_2$	(*S*,*S*)-DIOP	1.2	72	84	4 (*R*)
5[c]	$PhNH_2$	(*S*,*S*)-BDPP[e]	1.2	72	31	34 (*R*)
6[c]	$PhNH_2$	(*R*,*R*)-**1**	neat	72	94	50 (*S*)
7[d]	$PhNH_2$	(*R*,*R*)-**1**	1.2	120	87	89 (*S*)
8[d]	$PhNH_2$	(*R*,*R*)-**1**	0.6	120	63	92 (*S*)
9[d]	*p*-$MeC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	78	86 (*S*)
10[d]	*o*-$MeC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	59	90 (*S*)
11[d]	*p*-$EtO_2CC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	83	95 (*S*)
12[d]	*p*-$F_3CC_6H_4NH_2$	(*R*,*R*)-**1**	1.2	120	73	95 (*S*)

[a] Yields are for pure, isolated compounds. [b]Values for ee were determined by chiral HPLC; assignment of absolute configuration by comparison with retention time of product synthesized by arylation of commercially available (*S*)-2-cyclohexen-1-amine with phenyl bromide applying a previously reported method (arylation of chiral amines: Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458; of allylic amines: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157). [c]Reaction conditions: 0.25 mmol aniline, 1 mmol cyclohexadiene, 2.5 mol % $[Pd(\pi\text{-allyl})Cl]_2$, 5 mol % ligand, RT. [d]Reaction conditions: 0.125 mmol aniline, 0.5 mmol cyclohexadiene, 5 mol % $[Pd(\pi\text{-allyl})Cl]_2$, 11 mol % ligand, RT. [e](2*S*,4*S*)-(−)-2,4-Bis(diphenylphosphino)pentane.

Scheme 1. Possible Mechanisms for the Hydroamination in the Absence and Presence of Acid



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Supporting Information Available: Spectroscopic and analytical data of new compounds and information on procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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