Transition Metal-Catalyzed Addition of Amines to Acrylic Acid Derivatives. A High-Throughput Method for Evaluating Hydroamination of Primary and Secondary Alkylamines

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Several new classes of transition metal-catalyzed reactions of amines with the C═C bond of acrylic acid derivatives were discovered using a high-throughput colorimetric assay. This assay is general for the reactions of primary and secondary alkylamines with acrylic acid derivatives, and the screening of potential catalysts using this assay revealed a number of different metal/ligand combinations that promote these hydroaminations. The colorimetric assay revealed catalysts for the addition of piperidine to methacrylonitrile, crotononitrile, ethyl crotonate, and ethyl methacrylate, as well as catalysts for reactions of butylamine and aniline with methacrylonitrile. A catalyst for the addition of aniline to crotononitrile at 100 °C was also discovered. The products of these reactions are basic building blocks for the synthesis of β-amino acids, amino alcohols, and diamines. These reactions may ultimately produce an enantioselective route to optically active difunctional materials from commodity reagents.

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Introduction

The metal-catalyzed addition of amines to carbon−carbon double bonds is an unsolved, synthetically important problem.[1−3] Recent advances have been made using lanthanide[4−6] and precious metal complexes,[7−11] but a catalyst that displays broad functional group tolerance, useful rates, and high turnover numbers for an intermolecular addition has been reported only recently. Specifically, we reported the addition of aromatic amines to both vinylarenes[12] and dienes,[13] and this chemistry included asymmetric additions.

We also have been interested in developing catalysts for the addition of amines to acrylic acid derivatives. Of course, some of these reactions can be conducted in protic solvents under relatively mild conditions without a catalyst, but some cases do occur slowly, and most examples occur slowly in aprotic solvents. Thus, one could develop enantioselective additions of amines to acrylic acid derivatives if transition metal catalysts could be found for these transformations. The products of these additions would be β-amino acid derivatives that can be used in peptide analogues or as precursors to optically active amino alcohols, diamines, and lactams.

Lewis acids and bases catalyze the addition of azide and derivatives of hydroxylamine to substituted acrylates, and some of the catalysts provide nonracemic products in high enantiomeric excess.[14−16] However, these catalysts are likely to be poisoned by alkyl- and arylamine reagents. Trogler reported the addition of anilinium salts to acrylonitrile catalyzed by palladium alkyl complexes ligated by either the PCP ligand (t-Bu)$_2$P(CH$_2$)$_2$CH(CH$_2$)$_2$P(t-Bu)$_2$ or the chelating phosphine Me$_2$PCH$_2$CH$_2$PMe$_2$.[17] Although this work did not extend successfully beyond acrylonitrile as Michael acceptor, we felt that complexes based on these initial findings could be a fruitful starting point for developing catalysts for the hydroamination of acrylic acid derivatives.

Trogler's work prompted us to address several questions connecting catalyst properties and activity: whether a palladium alkyl was necessary; whether alkylphosphines generate the most active catalysts; whether sterically hindered or unhindered ligands would be most effective; whether more synthetically accessible PCP

(1) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703.
(2) Han, L.-B.; Tanaka, M. *Chem Commun.* **1999**, 395−402.
(3) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703−731.
(4) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568−2570.
(5) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633−3639.
(6) Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306.
(7) Coulson, D. R. *Tetrahedron Lett.* **1971**, 429−430.
(8) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306−1319.
(9) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T., E. *Eur. J. Inorg. Chem.* **1999**, 1121−1132.
(10) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738−6744.
(11) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857−10858.
(12) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547.
(13) Loeber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, in press.
(14) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616.
(15) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107.
(16) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.
(17) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744.

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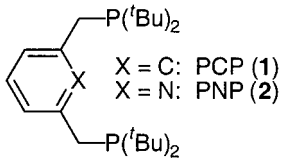
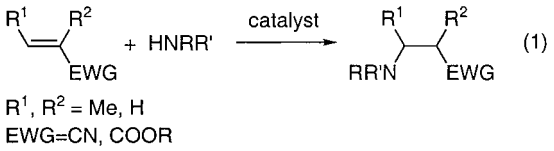


Figure 1. PCP and PNP ligands used in this study.

ligands could be used; whether a catalyst could be generated in situ; and whether a metal complex could catalyze the reaction of substituted acrylates with neutral amines instead of ammonium salts. We report synthetic results that address these questions. We uncovered several late transition metal complexes that catalyze the addition of amines to acrylic acid derivatives (eq 1)[18−20] using a high-throughput colorimetric assay to analyze for the addition of primary and secondary alkylamines to substrates with C=C bonds.



Results and Discussion

1. Background Studies. Our initial studies focused on the addition of aniline to acrylonitrile. We found that palladium acetate complexes formed in situ from $Pd(OAc)_2$ and the readily accessible PCP ligand precursor 1,3-bis[(*tert*-butylphosphino)methyl]benzene (**1**)[21] (Figure 1) catalyzed the addition of anilinium tetraphenylborate to acrylonitrile. The regioselectivity was 100%, and no enamine products from oxidative amination were observed. These oxidative amination products would be analogous to the aldehyde or ketone products formed from Wacker chemistry[22,23] or the enamine products from related styrene oxidative amination.[24] However, control reactions revealed that several individual reaction components catalyzed the addition of anilinium salts to this highly activated substrate. For example, free phosphine catalyzed the addition of anilinium tetraphenylborate to acrylonitrile. MeMgBr or MeLi, which were used to convert the palladium acetate to the corresponding palladium alkyl and could be present as impurities in the palladium complexes, also catalyzed the addition process. Presumably, these alkylating reagents generate alkali or magnesium amides in the control experiments. Reactions of anilinium tetraphenylborate with substituted acrylonitriles such as methacrylonitrile were not as straightforward. In contrast to previous reports,[17] the PCP-ligated catalyst formed from $Pd(OAc)_2$ and 1,5-bis(diphenylphosphino)pentane, as well as those formed from $Pd(OAc)_2$ and **1**, led to the transfer of a phenyl group from anilinium tetraphenylborate to methacrylonitrile. No hydroamination product was observed.

Thus, we focused exclusively on the addition of neutral amines to substituted acrylates. In the absence of catalyst these reactions require either protic solvents or high temperatures.[25] Neither Trogler's PCP-ligated methylpalladium complex nor combinations of $Pd(OAc)_2$ with simple monophosphines catalyzed this reaction. However, the combination of 2 mol % of $Pd(OAc)_2$ and **1** catalyzed the addition of aniline to the substituted acrylic acid derivatives crotononitrile and methacrylonitrile to form simple addition products, albeit at the elevated temperature of 100 °C.

2. High-Throughput Screening Methods. These encouraging results with $Pd(OAc)_2$ and **1** set the stage for a high-throughput evaluation of catalysts for the addition of amines to these activated alkenes and to dienes. Basic solutions of sodium nitroferricyanide(III) dihydrate ($Na_2Fe(CN)_5NO{\cdot}2H_2O$) and acetaldehyde become blue in the presence of secondary alkylamines.[26] This spot test can be used to evaluate the amount of secondary amine present in the reaction, and it allowed us to monitor the consumption of secondary alkylamine reagents or formation of secondary amine products colorimetrically. Because the regioselectivity invariably placed the amino group β to the activating substituent, a simple activity assay was appropriate. Using this assay, we tested the combination of many ligands with several palladium, nickel, rhodium, iridium, and ruthenium catalyst precursors. The reactions were conducted in 96-well glass plates,[27] and aliquots were analyzed colorimetrically.

Figure 2 shows a representative experiment conducted on the addition of piperidine to methacrylonitrile using a subset of the total number of phosphine ligands evaluated. The phosphines studied included analogues of **1** containing Ph and *i*-Pr groups at phosphorus and containing 3-OMe- and 2,3,4-OMe-substituted backbone aryl groups. The ligands also included analogous PNP structures based on a pyridine core, NNN ligands such as pybox, bisphosphines such as BINAP, DMPE, DPPE, and DPPF, and monalkyl- and arylphosphines.[28] We tested $Pd(OAc)_2$, $Pd(TFA)_2$ (TFA = trifluoroacetate), $[Pd(\pi\text{-allyl})Cl]_2$, $[Rh(COD)_2]BF_4$, $[Ir(COD)_2]BF_4$, $NiCl_2$, and $[Ru(p\text{-cymene})Cl_2]_2$ as metal catalyst precursors. The colorimetric assay for addition of piperidine to methacrylonitrile (Figure 2) revealed a variety of catalysts, including $[Rh(COD)_2]BF_4$, $[Ir(COD)_2]BF_4$, $[Ru(p\text{-cymene})Cl_2]_2$, and several phosphine complexes derived from them. Because $(COD)_2Rh$ and $(COD)_2Ir$ cations alone catalyzed the reactions, it was necessary to compare the rates for reactions catalyzed by these complexes both

(18) The addition of diethylamine to ethylacrylate catalyzed by $FeCl_3$ has been reported, but no other acrylate derivatives were included. Cabral, J.; Laszlo, P.; Mahé, L.; Montaufier, M.-T. *Tetrahedron Lett.* **1989**, *30*, 3969−3972.

(19) Nickel-catalyzed diene additions to provide regioisomeric addition products with 1,3-pentadiene in unspecified yields have been reported: Kiji, J.; Sasakawa, E.; Yamamoto, K.; Furukawa, J. *J. Organomet. Chem.* **1974**, *77*, 125−130.

(20) Andell, O. S.; Backvall, J. E.; Moberg, C. *Acta Chem. Scand. B* **1986**, *40*, 184.

(21) Moulton, C. J.; Shaw, B. L. *J. Chem. Soc, Dalton Trans.* **1976**, 1020−1026.

(22) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Ruttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176.

(23) Smidt, J.; Sedlmeier, J.; Hafner, W.; Sieber, R.; Sabel, A.; Jira, R. *Angew. Chem.* **1962**, *74*, 93.

(24) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225−2227.

(25) For example, no reaction between aniline and methacrylonitrile occurred in the absence of catalyst at 100 °C in toluene or dioxane.

(26) Feigl, F. In *Qualitative Analysis by Spot Tests*; Elsevier: New York, 1946; p 371.

(27) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981.

(28) Ligand abreviations: pybox, 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine; BINAP, 2,2′-bis(diphenylphosphino)-1,1-binaphthyl; DMPE, 1,2-bis(dimethylphosphino)ethane; DPPE, 1,2-bis(diphenylphosphino)ethane; DPPF 1,1′-bis(diphenylphosphino)ferrocene; COD, 1,5-cyclooctadiene.

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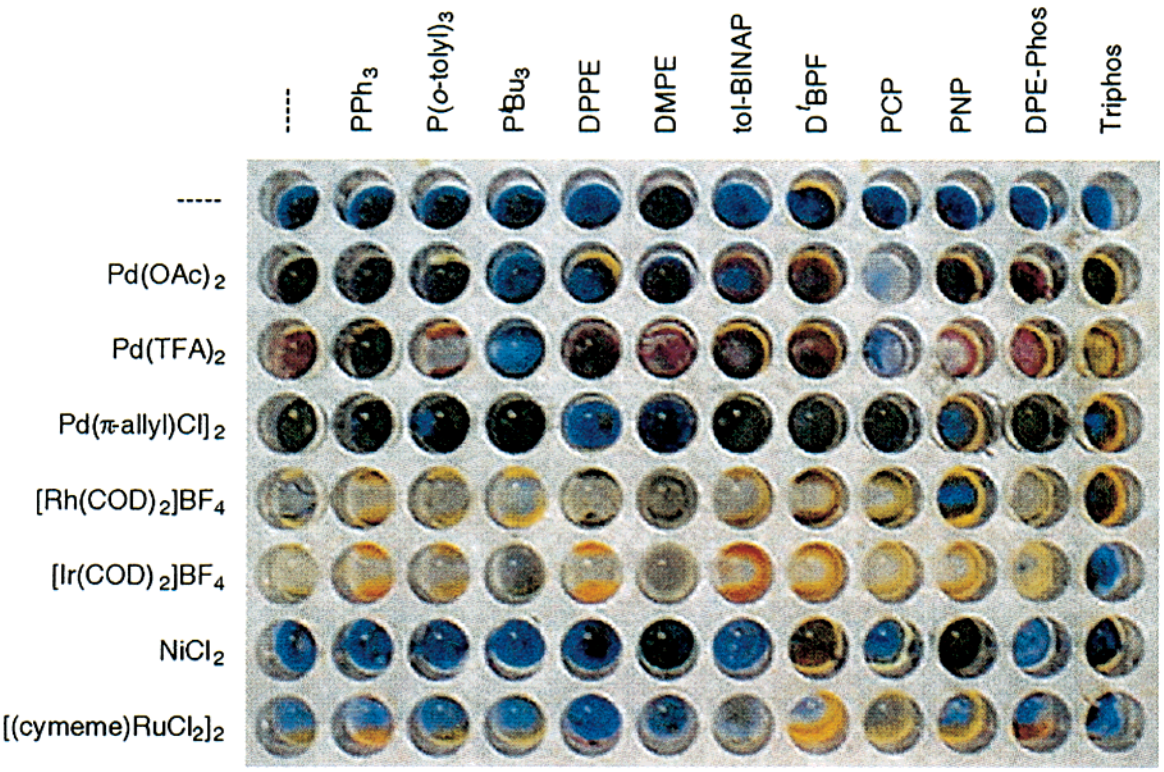

Figure 2. Evaluation of catalysts for the addition of piperidine to methacryonitrile. Reactions are evaluated by adding to the reaction aliquots of acetaldehyde and a solution of sodium nitroferricyanide(III) dihydrate ($Na_2Fe(CN)_5NO{\cdot}2H_2O$) in saturated $NaHCO_3$. DPPE = 1,2-bis(diphenylphosphino)ethane, DMPE = 1,2-bis(dimethylphosphino)ethane, D*t*-BPF = bis(di-*tert*-butylphosphino)ferrocene, PCP = **1**, PNP = **2**, DPE-Phos = 2,2′-bis(diphenylphosphino)diphenyl ether, Triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane.

alone and in the presence of phosphines. The rates were faster for reactions catalyzed by the Rh(I) and Ir(I) complexes in the presence of phosphine (complete reaction in 2 h for L = PPh_3, BINAP, and DPPE, vs 50% conversion with $Ir(COD)_2$). Thus, the rhodium and iridium phosphine complexes are the true catalysts in the reactions of wells E2−E11 and F2−F11 (row A is at the top and column 1 is at the left of Figure 2). In general, palladium complexes were less active than iridium and rhodium complexes for the addition of piperidine to methacrylonitrile. However, the combination of $Pd(OAc)_2$ with PCP **1** and the combination of $Pd(TFA)_2$ with either PCP **1** or the PNP ligand 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine (**2**, Figure 1) gave complete conversion.

Fewer complexes catalyzed the addition of primary alkyl- or arylamines to crotonic acid derivatives. The reaction of octylamine with methacrylonitrile was evaluated after 12 h at room temperature using the same colorimetric assay. In this case, the blue color signified formation of product instead of consumption of starting material. Catalyst activity was easily assessed visually in a qualitative fashion using this method. However, the color faded after a few seconds in these reaction solutions, and a clear photograph of all reactions evaluated simultaneously was not recorded. The reaction between these substrates did not occur at room temperature using the iridium, rhodium, or ruthenium complexes described above, but did occur under these conditions in the presence of catalytic amounts of $Pd(OAc)_2$ and PCP **1**.

A brief comment on the accuracy of the results obtained from these experiments is warranted. Clearly, all wells in these experiments will not contain a single metal−ligand complex. Thus, reactions that contain isolated, purified complexes as catalyst would show, in some cases, higher turnover numbers and faster rates than those containing catalysts generated in situ. However, this reaction format will identify active catalysts for a desired transformation in many cases and can provide a lead for the solution to a synthetic problem. We wish to emphasize that this reaction format, when it contains widely differing catalyst compositions, is unlikely to provide meaningful results on structure−reactivity relationships or on the identity of metal−ligand combinations that do not catalyze the reaction.

3. Scope of the Reaction of Alkylamines with Acrylic Acid Derivatives. Indeed, the metal−ligand combinations identified from the colorimetric assay using the reaction format of Figure 2 were active catalysts for experiments involving product isolation from reactions run on a larger scale. Table 1 summarizes the synthetic results for addition of amines to acrylic acid derivatives using catalysts identified by the high-throughput screening study. In all cases, control experiments without any catalyst that were run in toluene solvent at the temperatures and times required for the catalytic reactions to proceed to completion showed no reaction or less than 10% conversion. Yields for reaction of piperidine with methacrylonitrile using selected catalysts are provided as entries 1−7 in Table 1. Entries 1 and 2 demonstrate that the colorimetric assay is effective in distinguishing an active catalyst from a relatively inactive catalyst. Entries 3−7 confirm the activity of palladium complexes ligated by

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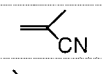
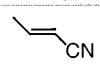
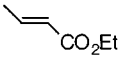
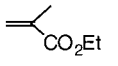
Table 1. Transition Metal-Catalyzed Addition of Amines to Activated Olefins[a]

Entry	Amine	Olefin	Catalyst, mol %	Conditions	Yield[b]
1			$Pd(OAc)_2$, 2%	RT, 12 h	12%
2			$Pd(OAc)_2$, 2% PCP **1**, 2%	RT, 12 h	98%
3			$Pd(TFA)_2$, 2%	RT, 12 h	96%
4			$Pd(TFA)_2$, 2% PNP **2**, 2%	RT, 12 h	99%
5			$[Rh(cod)_2]BF_4$, 2%	RT, 8 h	99%
6			$[Ir(cod)_2]BF_4$, 2%	RT, 8 h	90%
7			$[RuCl_2(p\text{-Cymene})]_2$, 2.5%	RT, 12 h	96%
8	*n*-$BuNH_2$		$Pd(OAc)_2$,10%	RT, 18 h	0%
9			$Pd(OAc)_2$, 2%/PCP **1**, 2%	RT, 12 h	76%
10			$Pd(TFA)_2$, 2%	RT, 12 h	21%
11			$Pd(TFA)_2$, 2%/PNP **2**, 2%	RT, 12 h	99%
12			$Pd(OAc)_2$, 10%	RT, 12 h	5%
13			$Pd(TFA)_2$, 10%	RT, 12 h	71%
14			$Pd(OAc)_2$, 5%/PCP **1**, 5%	RT, 12 h	54%
15			Pd(OAc)2, 5%/BINAP 5%	RT, 12 h	68%
16			$Pd(TFA)_2$, 5%/PNP **2**, 5%/	RT, 12 h	76%
17			$Pd(TFA)_2$, 2%	RT, 18 h	19%
18			$Pd(TFA)_2$, 2%/PNP **2**, 2%	RT, 12 h	45%
19			$Pd(TFA)_2$, 2%/BINAP, 2%	RT, 12 h	80%
20			$Pd(TFA)_2$, 2%/PPh_3, 4%	RT, 12 h	82%
21	$PhNH_2$		$Pd(OAc)_2$, 10%/PCP **1**,10%	100 °C, 48 h	99%
22			$Pd(OAc)_2$, 2%/PCP **1**, 2%	100 °C, 72 h	82%
23			$Pd(TFA)_2$,10%/PNP **2**,10%	RT, 18 h	88%
24	$PhNH_2$		$Pd(OAc)_2$,10%/ PCP **1**,10%	100 °C, 36 h	90%

[a] Reactions were run on a 1 or 2 mmol scale. See the Experimental Section for procedures. [b] Yields are for isolated material and are an average of two runs.

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PCP and PNP ligands for this process, as well as the rhodium, iridium, and ruthenium complexes in the absence of phosphine.

Entries 8 and 9 confirm the ability of the colorimetric assay to evaluate catalysts for the formation of secondary amine products. As shown in entry 9, $Pd(OAc)_2$ and the PCP ligand **1** provide good yields of the addition product, and this reaction required the phosphine ligand. Reactions of piperidine with crotononitrile, ethyl crotonate, and ethyl methacrylate were also catalyzed by a combination of either $Pd(OAc)_2$ or $Pd(TFA)_2$ and phosphine ligand, but not by the rhodium, iridium, or ruthenium complexes described above. The results of experiments with these substrates on a 1 mmol scale are summarized in entries 10−20. The combination of $Pd(TFA)_2$ and PNP **2** was the most effective of the complexes tested as a catalyst for the addition of piperidine to crotononitrile, while $Pd(TFA)_2$ and either PNP **2** or BINAP most effectively catalyzed the addition of piperidine to ethyl crotonate. A combination of $Pd(TFA)_2$ and either BINAP or PPh_3 catalyzed the addition of piperidine to ethyl methacrylate at room temperature.

In some cases, the reactions of aniline could be monitored by the addition of furfural and acetic acid, which creates a red color in the presence of aniline.[26] This assay was used to evaluate catalysts for the addition of amines to dienes.[13] Unfortunately, this assay gave variable results for the reactions of aniline with acrylic acid derivatives. Thus, we evaluated catalysts for the addition of aniline to methacrylonitrile by conventional serial GC methods. Of the systems tested, only a combination of $Pd(OAc)_2$ and PCP **1** or a combination of $Pd(TFA)_2$ and PNP **2** catalyzed the additions of aniline. The latter catalyst combination led to complete addition of this weaker nucleophile after 12 h at room temperature. None of the complexes included in this study catalyzed the addition of aniline to crotononitrile at room temperature. Conventional studies on reactions evaluated by GC techniques showed that a combination of $Pd(OAc)_2$ and PCP ligand **1** was most active for this addition process, and high yields were observed in aprotic solvents at 100 °C after 36 h.

4. Summary and Mechanistic Possibilities. Our screening and synthetic results revealed three dominant trends: complexes of sterically hindered PCP ligands were more effective than those containing smaller alkyl or aryl substituents; Pd(II), Ru(II), Rh(I), and Ir(I) complexes were the effective classes of catalyst; and the most effective catalyst depended on the identity of the amine and substitution pattern at the unsaturated C═C bond. Considering the diverse array of catalysts and substrates that undergo the amine addition processes described here, several distinct mechanisms are likely to be operating. However, one generic mechanism may involve coordination of the C═C bond to the softer of the metal centers and nucleophilic attack on the coordinated olefin. A second mechanism could involve coordination of the oxygen or nitrogen of the acrylic acid derivatives to the harder of the metal centers to provide a mechanism involving Lewis acid catalysis. Detailed studies of these reactions to determine which system operates by which general mechanism, further optimization of catalysts, and the development of asymmetric variants of these reactions will be the subject of future work.

Experimental Section

General Methods. Reactions were conducted using standard Schlenk and drybox techniques. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker AM 500 MHz spectrometer using tetramethylsilane (^1H) or residual protiated solvent (^{13}C) as a reference. $^{31}P\{^1H\}$ NMR spectra were recorded on an Omega 300 MHz spectrometer, with shifts reported relative to an external 85% H_3PO_4 standard; resonances downfield of

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the standard are reported as positive. Low-resolution mass spectra were obtained on a Hewlett-Packard 5890 series II gas chromatograph interfaced with a Hewlett-Packard 5989A mass spectrometer. Toluene and ether were distilled from sodium and benzophenone and were stored in the drybox. 1,3-Bis[(di-*tert*-butylphosphino)methyl]benzene was prepared by literature procedures.[21] All other solvents and compounds were used as received. Yields determined by GC analysis were determined by comparison of the area of product peaks to that of an internal standard (1,3,5-trimethoxybenzene), corrected using response factors determined using authentic materials.

2,6-Bis[(di-*tert*-butylphosphino)methyl]pyridine. To a solution of 2,6-lutidine (5.0 g, 46.7 mmol) in ether (25 mL) was added slowly *n*-BuLi (40 mL of a 2.4 M hexane solution, 95.7 mmol) at 0 °C. The reaction mixture was heated to 40 °C for 15 h and then cooled to −78 °C. Di-*tert*-butylchlorophosphine (18.5 mL, 93.3 mmol) was added slowly, and the reaction mixture was warmed to room temperature. The reaction was quenched with degassed water and extracted with ether. The ether extracts were dried with $MgSO_4$, and the solvent was removed. Recrystallization from ether at −35 °C provided white needles (10.2 g, 55%). ^{1}H NMR: (C_6D_6) δ 7.30 (d, J = 7.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 3.14 (d, J = 2.8 Hz, 4H), 1.18 (d, J = 10.7 Hz, 36H). ^{13}C{^{1}H} NMR: (C_6D_6) δ 161.88 (d, J = 14.3 Hz), 136.21, 121.16 (d, J = 10.0 Hz), 32.74 (d, J = 26.9 Hz), 32.24 (d, J = 23.2 Hz), 30.32 (d, J = 14.1 Hz). ^{31}P-{^{1}H} NMR: (C_6D_6) δ 36.8. Anal. Calcd for $C_{23}H_{43}NP_2$: C, 69.97; H, 10.96; N, 3.54. Found: C, 69.86; H, 10.84; N, 3.41.

General Procedure for the Palladium-Catalyzed Addition of Piperidine to Activated Olefins. The reaction conditions and results are shown in Table 1 (entries 1−7 and 10−20). A typical procedure is given for the reaction in entry 2.

1-Methyl-2-piperidinoethyl Cyanide.[29] $Pd(OAc)_2$ (4.5 mg, 0.020 mmol), 1,3-bis[(di-*tert*-butylphosphino)methyl]benzene (7.9 mg, 0.002 mmol), and 1,3,5-trimethoxybenzene (168 mg, 1.00 mmol; internal standard) were suspended in 0.5 mL of toluene in a screw-capped vial. The vial was sealed with a cap that contained a PTFE septum and was removed from the drybox. Methacrylonitrile (270 mg, 4.00 mmol) and piperidine (85.0 mg, 1.00 mmol) were added to the reaction mixture by syringe. The reaction mixture was stirred at room temperature for 12 h. The yield of 1-methyl-2-piperidinoethyl cyanide was determined by GLC analysis (99%). The product was isolated by silica gel column chromatography (50% ethyl acetate/hexanes) to give 310 mg (100%) of 1-methyl-2-piperidinoethyl cyanide. ^{1}H NMR: (C_6D_6) δ 2.80−2.75 (m, 1H), 2.59 (dd, J = 12.6 Hz, 8.1 Hz, 1H), 2.44−2.41 (m, 4H), 2.38 (dd, J = 12.6, 6.5 Hz, 1H), 1.60−1.56 (m, 4H), 1.45−1.41 (m, 2H), 1.30 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR: (C_6D_6) δ 122.71, 61.74, 54.62, 25.86, 24.21, 24.10, 16.05.

2-Piperidinopropyl cyanide:[30] 97% yield, eluted from silica gel using 50:50 hexanes/ethyl acetate. ^{1}H NMR: ($CDCl_3$) δ 3.04−2.98 (m, 1H), 2.53 (dd, J = 16.6, 5.4 Hz, 1H), 2.52−2.48 (m, 2H), 2.46−2.45 (m, 2H; CH_2), 2.34 (dd, J = 16.6, 7.8 Hz, 1H), 1.61−1.56 (m, 4H), 1.46−1.41 (m, 2H), 1.21 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 118.98, 56.70, 49.34, 26.17, 24.56, 20.52, 15.28.

Ethyl 3-piperidinobutanoate:[31] 90% yield, eluted from silica gel using 30:70 hexanes/ethyl acetate. ^{1}H NMR: ($CDCl_3$) δ 4.13 (q, J = 7.0 Hz, 2H), 3.12 (m, 1H), 2.58 (dd, J = 14.2, 5.5 Hz, 1H), 2.45−2.43 (m, 4H), 2.21 (dd, J = 14.2, 8.5 Hz, 1H), 1.56−1.53 (m, 4H), 1.44−1.41 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 172.64, 59.96, 57.00, 49.32, 38.19, 26.37, 24.79, 14.18, 14.17.

Ethyl 2-methyl-3-piperidinopropanoate:[32] 99% yield, eluted from silica gel using 30:70 hexanes/ethyl acetate. ^{1}H NMR: ($CDCl_3$) δ 4.14 (q, J = 7.3 Hz, 2H), 2.71−2.65 (m, 1H), 2.61 (dd, J = 12.1, 8.7 Hz, 1H), 2.42−2.35 (m, 2H), 2.35−2.30 (m, 2H), 2.27 (dd, J = 12.1, 6.0 Hz, 1H), 1.51−1.56 (m, 4H), 1.41−1.37 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 176.05, 62.34, 59.86, 54.56, 37.91, 25.96, 24.30, 15.48, 14.14.

General Procedure for the Palladium-Catalyzed Addition of Primary Amines to Activated Olefins. The reaction conditions and results are shown in Table 1 (entries 8, 9, and 21−24). A typical procedure is given for the reaction in entry 23.

2-Anilino-1-methylethyl Cyanide. $Pd(TFA)_2$ (33.0 mg, 0.10 mmol) and 2,6-bis[(di-*tert*-butylphosphino)methyl]pyridine (40.0 mg, 0.10 mmol) were suspended in 0.5 mL of toluene in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Methacrylonitrile (270 mg, 4.00 mmol) and aniline (93.1 mg, 1.00 mmol) were added to the reaction mixture by syringe. The reaction mixture was stirred at room temperature for 24 h, after which time it was adsorbed onto silica gel. The product was isolated by eluting with 15% ethyl acetate/hexanes to give 142 mg (89%) of 2-anilino-1-methylethyl cyanide. ^{1}H NMR: ($CDCl_3$) δ 7.22 (t, J = 7.6 Hz, 2H), 6.78 (t, J = 7.6 Hz, 1H), 6.63 (d, J = 7.6 Hz, 2H), 3.71 (brs, 1H) 3.43 (dd, J = 13.8, 8.0 Hz, 1H), 3.37 (dd, J = 13.8, 6.0 Hz, 1H), 2.99 (m, 1H), 1.38 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 146.52, 129.50, 121.81, 118.50, 113.04, 47.04, 25.98, 15.39. Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.75; H, 7.35; N, 17.57.

2-Anilinopropyl cyanide:[33] 90% yield, eluted from silica gel using 80:20 hexanes/ethyl acetate. ^{1}H NMR: ($CDCl_3$) δ 7.22 (t, J = 7.5 Hz, 2H), 6.79 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 7.5 Hz, 2H), 3.90 (m, 1H), 3.70 (brs, 1H), 2.63 (brd, J = 2.3 Hz, 1H), 2.61 (brs, 1H), 1.45 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 145.76, 129.62, 118.53, 117.60, 113.60, 45.45, 24.33, 20.40.

2-(Butylamino)-1-methylethyl cyanide:[34] 81% yield, eluted from silica gel using 90:10 hexanes/ethyl acetate. ^{1}H NMR: ($CDCl_3$) δ 2.88−2.74 (m, 4H), 2.64 (m, 1H), 1.51−1.42 (m, 2H), 1.42 (brs, 1H), 1.39−1.32 (m, 2H), 1.32 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR: ($CDCl_3$) δ 122.28, 52.49, 49.09, 32.09, 26.57, 20.22, 15.58, 13.84.

High-Throughput Analysis of the Addition of Piperidine to Methacrylonitrile. Stock solutions of metal complexes (16.0 or 32.0 μL, 0.0040 mmol), ligands (16.0 mL for bisphosphines or 32.0 μL for monophosphines, 0.0040 mmol), piperidine (20.0 μL, 0.20 mmol), and methacrylonitrile (67.0 μL, 0.80 mmol) were loaded into a 96-well glass plate using a multichannel pipet. The 96-well plate was covered with a Teflon sheet and a glass slide, which was clamped to the plate. The plate was then shaken using a rotary shaker for 24 h at room temperature. Aliquots of the reaction mixture (15 μL) were transferred to another 96-well glass plate using a multichannel pipet. Acetaldehyde (15 μL, 0.270 mmol) and 20% $Na_2Fe(CN)_5NO{\cdot}2H_2O$ in saturated aqueous $NaHCO_3$ (30 μL) were then added to provide the colorimetric signal for the presence or absence of piperidine.

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(29) Pohland, A.; Sallivan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 2817−2818.
(30) Adomeniene, O.; Dienys, G. *Org. React.* **1979**, *16*, 164−173.
(31) Schjelderup, L.; Groth, P.; Aasen, A. J. *Acta Chem. Scand.* **1990**, *44*, 284−287.
(32) Sjoe, P.; Groth, P.; Aasen, A. J. *Acta Chem. Scand.* **1990**, *44*, 957−962.
(33) Kashima, C.; Katoh, A.; Yokota, Y.; Omote, Y. *J. Heterocycl. Chem.* **1981**, *18*, 1469−1470.
(34) Verdizade, N. A.; Akhmedov, R. M.; Amrakhov, T. I. *Azerb. Khim. Zh.* **1982**, 81−83.