Addition of N−H and O−H Bonds of Amines and Alcohols to Electron-Deficient Olefins Catalyzed by Monomeric Copper(I) Systems: Reaction Scope, Mechanistic Details, and Comparison of Catalyst Efficiency

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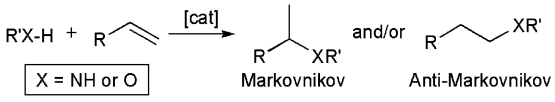
Monomeric copper(I) amido, alkoxide, and aryloxide complexes catalyze the addition of N−H and O−H bonds of amines and alcohols, respectively, to electron-deficient olefins. The ancillary ligands of the active catalysts include the N-heterocyclic carbene (NHC) ligands IPr, IMes, and SIPr {IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene} as well as the chelating bisphosphine ligand dtbpe {dtbpe = 1,2-bis(di-*tert*-butylphosphino)ethane}. For the hydroamination and hydroalkoxylation of olefins, both aromatic and alkyl substituents can be incorporated into the nucleophile, and both primary and secondary amines are reactive. Monosubstituted and disubstituted olefins have been demonstrated to undergo reaction. For the addition of aniline to acrylonitrile, kinetic studies suggest a pathway that is dependent on the concentration of amine, olefin, and catalyst as well as inversely proportional to the concentration of the product 3-anilinopropionitrile. At low concentrations, the addition of *tert*-butylisonitrile increases the rate of catalysis. The proposed mechanism involves N−C or O−C bond formation by an *inter*molecular nucleophilic addition of the amido, alkoxide, or aryloxide ligand to *free* olefin.

Introduction

Carbon−nitrogen and carbon−oxygen bonds are abundant in both fine and commodity chemicals including pharmaceuticals and other biologically active compounds.[1−3] The controlled addition of N−H or O−H bonds across carbon−carbon double bonds provides a convenient and atom economical route to amines and ethers. In the past decade, significant efforts have been directed toward the development of catalysts for olefin hydroamination, hydroalkoxylation, and related reactions.[4−8] For general synthetic application, catalysts should be active under relatively mild conditions and afford control of regio-, chemo-, and stereoselectivity. For example, functionalization of monosubstituted olefins yields two possible regioisomers: (1) branched "Markovnikov" products via heteroatom addition to the substituted carbon and (2) linear "anti-Markovnikov" compounds via heteroatom addition to the unsubstituted carbon (Scheme 1).

The hydroamination, hydroalkoxylation, or hydroaryloxylation of electron-deficient olefins (i.e., Michael acceptors) under acidic or basic conditions is known; however, such reactions generally occur under relatively harsh conditions, including high temperatures, that are often incompatible with functional groups and often do not allow control of selectivity.[4,9−16] In contrast, transition metal-catalyzed reactions offer the possibility of more ambient conditions and enhanced control of product selectivity. Both early and late transition metal complexes as well as lanthanide systems have been developed for olefin hydroamination, including some examples of unactivated olefins, with some of these systems limited to specific substrates or more facile intramolecular reactions.[6,17−22]

Scheme 1. Addition of X−H to a Monosubstituted Olefin Produces Two Regioisomers



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(1) Turcotte, M. G.; Johnson, T. A. In *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, 4th ed.; John Wiley & Sons: New York, 1999; p 95.
(2) Brunet, J. J.; Neibecker, D.; Niedercorn, F. *J. Mol. Catal.* **1989**, *49*, 235−259.
(3) Karas, L.; Piel, W. J. In *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, 4th ed.; John Wiley & Sons: New York, 1999; pp 767−768.
(4) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.
(5) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703.
(6) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673−686.
(7) Roundhill, D. M. *Catal. Today* **1997**, *37*, 155−165.
(8) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507−516.
(9) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, 1st ed.; Pergamon Press: Oxford, 1992; Vol. 9.
(10) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383−387.
(11) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141−2144.
(12) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319−1322.
(13) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615−6616.
(14) Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Chem. Commun.* **2001**, 1240−1241.
(15) Farnworth, M. V.; Cross, M. J.; Louie, J. *Tetrahedron Lett.* **2004**, *45*, 7441−7443.
(16) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542−14543.
(17) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519−2522.
(18) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894−895.
(19) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070−1071.
(20) Douglass, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 1824−1825.

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In general, late transition metal catalysts exhibit greater functional group tolerance than early transition metal systems or lanthanide complexes.[4,6,8,22,23] The majority of late transition metal catalysts for olefin hydroamination are based on group 10 metals.[22,24−30] For example, Tilley et al. have reported a Pt catalyst for the Markovnikov addition of *p*-toluenesulfonamide to olefins.[31] Hartwig and co-workers have observed Pd(II)-catalyzed Markovnikov addition of aniline to styrenes and vinyl naphthalenes including extension to enantioselective variants.[32,33] In addition, examples of ruthenium- and rhodium-catalyzed anti-Markovnikov hydroaminations of vinylarenes have been reported, although these catalytic cycles typically require the addition of acid or result in formation of enamine byproducts.[34,35]

Though methods exist for the formation of ethers via catalytic carbon−oxygen bond formation,[36−39] examples of catalytic hydroalkoxylation or hydroaryloxylation of olefins are relatively scarce. Nonmetal systems include a phosphine-catalyzed hydroalkoxylation of electron-deficient olefins with alcohols and an *N*-bromosuccinimide-catalyzed hydroalkoxylation of styrenes.[40,41] Group 10 metals have proven effective for these transformations as well, with published examples of Pd(0), Pd(II), and Pt(II) catalysts.[42−46] In addition, a Rh(I) catalyst and a Ru(III) catalyst for intramolecular reactions have been reported.[15,47] Au(I)-catalyzed olefin hydroamination and the addition of O−H bonds to olefins, Cu(II)-catalyzed addition of N−H bonds to electron-deficient olefins in ionic liquids, and Cu(II)-catalyzed reactions with unactivated olefins have been reported;[23,48−50] however, recent studies by Hartwig et al. suggest that metal−triflate catalysts may function through the formation of triflic acid.[51]

Our group and others have been interested in the reactivity of late transition metals with nondative heteroatomic ligands (e.g., amido, hydroxide, alkoxide, etc.) and have shown these systems to exhibit nucleophilic and basic reactivity at the nondative functionality.[52−68] We have recently disclosed the synthesis of monomeric Cu(I) complexes of the type (IPr)Cu(X) {IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; X = NHPh, OEt, or OPh} as well as (dtbpe)Cu(NHPh) {dtbpe = 1,2-bis(di-*tert*-butylphosphino)ethane}.[54,58,69] Preliminary studies indicate that these complexes catalyze the addition of amine N−H bonds and alcohol O−H bonds across the carbon−carbon double bonds of electron-deficient olefins.[69] Herein, we report on the scope of these reactions, including the impact of the ancillary ligand "L" of (L)Cu(X) complexes where L = IPr, IMes, SIPr, or dtbpe {IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; X = NHPh, OEt, or OPh} on reactivity. The series of Cu(I) systems studied are displayed in Chart 1.

Results

Catalytic Reactions of Amines Using (IPr)Cu(NHPh) (1). Table 1 depicts results from Cu-catalyzed addition of N−H bonds of amines across carbon−carbon double bonds of electron-deficient olefins using (IPr)Cu(NHPh) (**1**) as catalyst.[70] Control experiments conducted in the absence of Cu catalyst confirm the role of the copper complexes in these reactions (see

(21) Lauterwasser, F.; Hayes, P. G.; Brase, S.; Piers, W. E.; Schafer, L. L. *Organometallics* **2004**, *23*, 2234−2237.
(22) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246−4247.
(23) Zhang, J. L.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798−1799.
(24) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30−31.
(25) Li, K. L.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250−257.
(26) Park, S. *Bull. Korean Chem. Soc.* **2001**, *22*, 15−16.
(27) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047−2067.
(28) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828−1839.
(29) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649−1651.
(30) Jimenez, O.; Müller, T. E.; Sievers, C.; Spirkl, A.; Lercher, J. A. *Chem. Commun.* **2006**, 2974−2976.
(31) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640−12646.
(32) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546−9547.
(33) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166−1167.
(34) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608−5609.
(35) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702−2703.
(36) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882−7883.
(37) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206.
(38) Vorogushin, A. V.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146−8149.
(39) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
(40) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696−8697.
(41) Talluri, S. K.; Sudalai, A. *Org. Lett.* **2005**, *7*, 855−857.
(42) Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S. I. *Chem. Lett.* **1989**, 2001−2004.
(43) Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403−4412.
(44) Matsukawa, Y.; Mizukado, J.; Quan, H. D.; Tamura, M.; Sekiya, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1128−1130.
(45) Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865−5868.
(46) Qian, H.; Han, X. Q.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536−9537.
(47) Oe, Y.; Ohta, T.; Ito, Y. *Chem. Commun.* **2004**, 1620−1621.
(48) Kantam, M. L.; Neeraja, V.; Kavita, B.; Neelima, B.; Chaudhuri, M. K.; Hussain, S. *Adv. Synth. Catal.* **2005**, *347*, 763−766.
(49) Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966−6967.
(50) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561−3564.
(51) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179−4182.
(52) Conner, D.; Jayaprakash, K. N.; Gunnoe, T. B.; Boyle, P. D. *Inorg. Chem.* **2002**, *41*, 3042−3049.
(53) Conner, D.; Jayaprakash, K. N.; Wells, M. B.; Manzer, S.; Gunnoe, T. B.; Boyle, P. D. *Inorg. Chem.* **2003**, *42*, 4759−4772.
(54) Blue, E. D.; Davis, A.; Conner, D.; Gunnoe, T. B.; Boyle, P. D.; White, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 9435−9441.
(55) Conner, D.; Jayaprakash, K. N.; Cundari, T. R.; Gunnoe, T. B. *Organometallics* **2004**, *23*, 2724−2733.
(56) Zhang, J.; Gunnoe, T. B.; Boyle, P. D. *Organometallics* **2004**, *23*, 3094−3097.
(57) Zhang, J. B.; Gunnoe, T. B.; Peterson, J. L. *Inorg. Chem.* **2005**, *44*, 2895−2907.
(58) Goj, L. A.; Blue, E. D.; Munro-Leighton, C.; Gunnoe, T. B.; Petersen, J. L. *Inorg. Chem.* **2005**, *44*, 8647−8649.
(59) Kaplan, A. W.; Ritter, J. C. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 6828−6829.
(60) Fulton, J. R.; Bouwkamp, M. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 8799−8800.
(61) Fulton, J. R.; Holland, A. W.; Fox, D. J.; Bergman, R. G. *Acc. Chem. Res.* **2002**, *35*, 44−56.
(62) Fulton, J. R.; Sklenak, S.; Bouwkamp, M. W.; Bergman, R. G. *J. Am. Chem. Soc.* **2002**, *124*, 4722−4737.
(63) Fox, D. J.; Bergman, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 8984−8985.
(64) Fox, D. J.; Bergman, R. G. *Organometallics* **2004**, *23*, 1656−1670.
(65) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163−1188.
(66) Caulton, K. G. *New J. Chem.* **1994**, *18*, 25−41.
(67) Mayer, J. M. *Comments Inorg. Chem.* **1988**, *8*, 125−135.
(68) Tenn, W. J.; Young, K. J. H.; Bhalla, G.; Oxgaard, J.; Goddard, W. A.; Periana, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 14172−14173.
(69) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpoint, A. W.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2006**, *45*, 9032−9045.
(70) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446.

Chart 1. Cu(I) Catalysts Studied for the Addition of N−H and O−H Bonds to Electron-Deficient Olefins

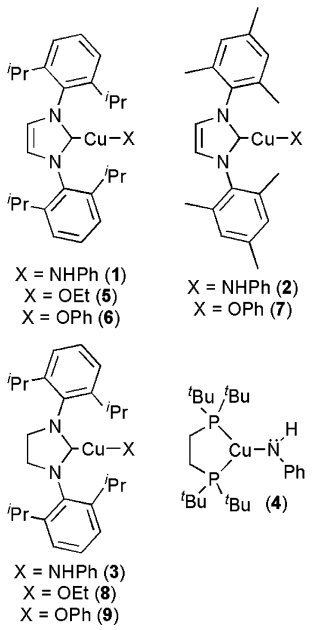
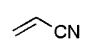
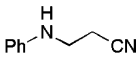
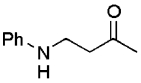
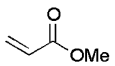
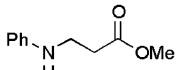
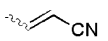
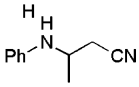
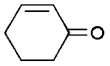
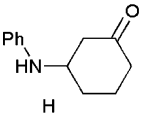
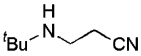
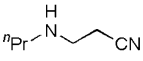
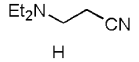
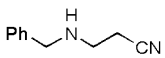
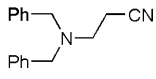
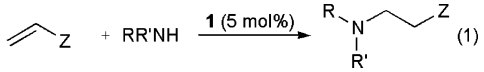


Table 1. Hydroamination of Electron-Deficient Olefins Catalyzed by (IPr)Cu(NHPh) (1) and Uncatalyzed Control Experiments

Olefin	Nucleophile	Time[a]	% conv.[b]	Product	Control expt.[c]
	$PhNH_2$	12 hr	>95		0
	$PhNH_2$	5 min	>95		0
	$PhNH_2$	19 hr	55		0
	$PhNH_2$	40 hr[d]	54		0[d]
	$PhNH_2$	3 hr	85		0
	$^tBuNH_2$	22 hr	57		0
	$^nPrNH_2$	1 hr	>95		0
	Et_2NH	9 hr	>95		14
	$PhCH_2NH_2$	5 min	>95		0
	$(PhCH_2)_2NH$	90 hr	60		0

[a] All reactions performed with 5 mol % of catalyst at room temperature in C_6D_6. [b]% conversions determined by ^1H NMR spectroscopy. [c]Control experiments reported after similar reaction times to the catalyzed reaction and given in % conversion. [d] Reaction conducted at 80 °C.

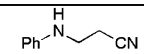
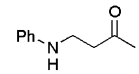
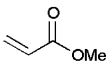
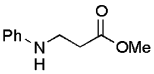
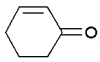
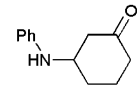
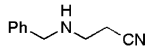
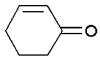
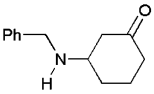
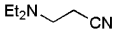
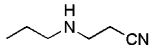
Table 1). For monosubstituted olefins, only "anti-Markovnikov" products are observed by ^1H NMR spectroscopy (eq 1). For example, the reaction of aniline and acrylonitrile is catalyzed by (IPr)Cu(NHPh) (**1**) to give >95% conversion to 3-anilinopropionitrile after 12 h at room temperature. The substrate scope for the catalysis includes a variety of amines including primary alkyl amines, aryl amines, as well as secondary and sterically bulky amines. For example, the reaction of *tert*-butylamine with acrylonitrile in the presence of **1** (5 mol %) produces 3-(*tert*-butylamino)propionitrile in 57% yield after 22 h. In the absence of **1**, no conversion is observed for the reaction of *tert*-butylamine with acrylonitrile after 10 days. Other primary and secondary alkyl amines are reactive under catalytic conditions: *n*-propylamine and diethylamine both react with acrylonitrile in the presence of **1** (5 mol %) to give >95% conversion after 1 and 9 h, respectively. In the absence of copper catalyst no conversion of *n*-propylamine and acrylonitrile is observed after 1 h, and the reaction requires *49 days* to reach >95% conversion. Thus, the uncatalyzed reaction is approximately 1200 times slower than the reaction catalyzed by 5 mol % of complex **1**. Similarly, diethylamine and acrylonitrile react to give >95% conversion after 9 h in the presence of **1**, but a reaction time of 37 days is required to reach ~80% conversion for the uncatalyzed variant. Dibenzylamine is a synthetically useful substrate due to the possibility of manipulation of the benzyl groups. Reaction of dibenzylamine with acrylonitrile in the presence of **1** (5 mol %) yields 60% conversion to 3-[bis(phenylmethyl)-amino]propionitrile after 90 h at room temperature. In control experiments, no product is observed after 6 days. Finally, prochiral cyclohexenone reacts with aniline and **1** to form 3-(phenylamino)cyclohexanone in 85% yield in 3 h, while the uncatalyzed reaction yields no conversion after 6 days (Table 1). The addition of aniline to the disubstituted olefin crotononitrile (~1:1 mixture of cis and trans isomers) is catalyzed by complex **1** with 54% conversion after 40 h at 80 °C. Monitoring the reaction by ^1H NMR spectroscopy reveals that the cis and trans isomers of crotononitrile react at approximately the same rate. In the absence of catalyst, no conversion of crotononitrile and aniline is observed after 40 h. The prochiral substrates cyclohexenone and crotononitrile demonstrate successful catalysis with disubstituted olefins and offer the potential for study of enantioselective bond formation with future catalyst variations.



Variation of Ancillary Ligand. The preparation of a series of monomeric copper−amido complexes of the type (L)Cu-(NHPh) (L = IPr, IMes, or SIPr) has recently been accomplished by our group.[58,69] On the basis of nucleophilic reactions of **1**, (IMes)Cu(NHPh) (**2**), (SIPr)Cu(NHPh) (**3**), and (dtbpe)Cu-(NHPh) (**4**) with ethyl bromide, the nucleophilicity of the amido moieties increases in the order **3** < **1** < **2** < **4**.[69] Given the steric and/or electronic differences between the four systems, we sought to compare the differences in catalytic hydroamination of electron-deficient olefins. Table 2 lists the optimal catalysts for the various transformations.

As reported above, complex **1** (5 mol %) catalyzes the reaction of aniline and acrylonitrile to form 3-anilinopropionitrile in >95% yield after 12 h at room temperature.[70] We have since found that the bisphosphine−copper amido **4** is most efficient for this reaction, with >95% yield after only 3 h. Catalysts **1**, **2**, **3**, and **4** all affect complete conversion of aniline and methyl vinyl ketone to 4-anilino-2-butanone within 5 min. Similar to aniline and acrylonitrile, the most efficient catalyst for the addition of aniline to methyl acrylate is complex **4**, with >95% conversion in 4 h. Complex **1** is the most efficient catalyst for conversion of aniline and the disubstituted olefin cyclohexenone to 3-anilinocyclohexanone, resulting in 85% conversion after 3 h, as well as the reactions of acrylonitrile with both benzyl amine (>95%, 5 min) and diethyl amine (>95%, 9 h) and the conversion of benzyl amine and cyclohexenone to 3-(phenylmethylamino)cyclohexanone (90%, 2.5 h). For reactions with

Table 2. Optimal Catalysts for the Hydroamination of Electron-Deficient Olefins and Corresponding Control Reactions

Olefin	Nucleophile	Cat.	Time[a]	% conv.[b]	Product	Control expt.[c]
	NH_2Ph	**4**	3 hr	>95		0
	NH_2Ph	**1-4**	5 min	>95		0
	NH_2Ph	**4**	4 hr	>95		0
	NH_2Ph	**1**	3 hr	85		0
	NH_2CH_2Ph	**1**	5 min	>95		0
	NH_2CH_2Ph	**1**	2.5 hr	90		24
	Et_2NH	**1**	9 hr	>95		14
	$^nPrNH_2$	**3**	5 min	>95		0

[a] All reactions performed with 5 mol % catalyst at room temperature in C_6D_6. [b]% conversions determined by ^1H NMR spectroscopy. [c]Control experiments reported after similar reaction times and given in % conversion.

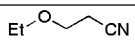
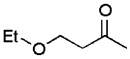
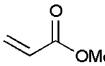
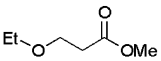
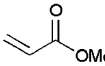
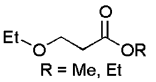
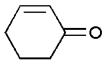
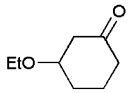
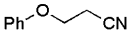
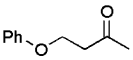
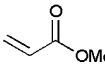
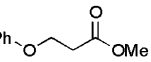
n-propyl amine, **3** offered optimal conversion of acrylonitrile to 3-(*n*-propylamino)propionitrile (>95%, 5 min). Although differences in catalyst activity are measurable, overall they are not particularly striking. Reactions of aniline and methyl acrylate exhibit the widest range of reactivity upon variation of the catalyst with a decrease in activity in the catalyst series complex **4** (>95%, 3 h) > complex **3** (69%, 5.5 h) > complex **2** (65%, 17 h) > complex **1** (55%, 19 h).

Catalytic Reactions of Alcohols and Electron-Deficient Olefins. Hydroalkoxylation and hydroaryloxylation of electron-deficient olefins have been extended from use of (IPr)Cu(OEt) (**5**) and (IPr)Cu(OPh) (**6**) to include (IMes)Cu(OPh) (**7**), (SIPr)-Cu(OEt) (**8**), and (SIPr)Cu(OPh) (**9**) (Table 3). In general, the addition of alcohol O−H bonds to olefins is slower than additions of amines to olefins. For additions of ethanol, complex **5** demonstrates the highest reactivity, catalyzing the conversion of ethanol and acrylonitrile or methyl vinyl ketone to give 3-ethoxypropionitrile or 4-ethoxy-2-butanone in >95% yield in 12 h and 5 min, respectively, at room temperature.[70] In the absence of catalyst, there is no production of either hydroalkoxylation product after 9 days. Complex **8** (5 mol %) catalyzes 25% conversion of ethanol and cyclohexenone to produce 3-ethoxycyclohexanone in 4.5 h. A control experiment conducted in the absence of catalyst did not afford product after 6 days.

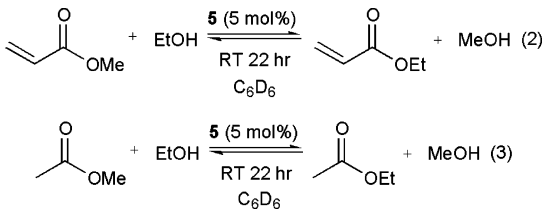
Complex **6** is the most efficient catalyst for addition of phenol to acrylonitrile at 80 °C (64%, 40 h).[70] Complex **6** also catalyzes the reaction of methyl vinyl ketone and phenol to produce 4-phenoxy-2-butanone in 60% yield in 52 h at 80 °C. In the absence of catalyst, no conversion is observed after 8 days. Reaction of phenol and methyl vinyl ketone in the presence of **9** proceeds more rapidly initially, but provides a lower overall yield (48%, 24 h). Complexes **6** and **9** produce methyl 3-phenoxypropionate upon heating to 120 °C in the presence of phenol and methyl acrylate, with complex **6** the most efficient catalyst, yielding 40% conversion after 235 h.

The reaction of ethanol and methyl acrylate with the catalyst (IPr)Cu(OEt) (**5**) does not yield the anticipated hydroalkoxylation product methyl 3-ethoxypropionate. Rather, transesterification to form ethyl acrylate is observed by ^1H NMR spectroscopy (eq 2). Similarly, close examination of the reaction of phenol and methyl acrylate with 5 mol % of **6**, which generates methyl 3-phenoxypropionate in ~60% conversion (see above), reveals minimal conversion to the transesterification product phenyl acrylate. The reaction of ethanol with methyl acrylate with 5 mol % of **5** reaches equilibrium after 22 h at room temperature. Similar reactivity is observed using complex **8**. In addition, the alkyl ester methyl acetate undergoes transesterification in the presence of **5** and ethanol (eq 3). Control experiments performed with ethanol/methyl acrylate and ethanol/methyl acetate in the absence of **5** do not yield products of transesterification under identical reaction conditions and times, which confirms the participation of the copper complexes in these reactions.

Table 3. Hydroalkoxylation and Hydroaryloxylation of Olefins and Uncatalyzed Control Reactions

Olefin	Nucleophile	Cat.	Temp (°C)	Time[a]	% conv.[b]	Products	Control expt.[c]
	EtOH	**5**	RT	20 hr	93		0
	EtOH	**5**	RT	7 hr	>95		0
	EtOH	**5, 8**	RT	–	0[d]		0
	EtOH	**5**	RT	1 hr	>95[e]	 R = Me, Et	0
	EtOH	**8**	RT	4.5 hr	25		0
	PhOH	**6**	80	40 hr	64		0
	PhOH	**6**	80	52 hr	60		0
	PhOH	**6**	120	235 hr	40		0

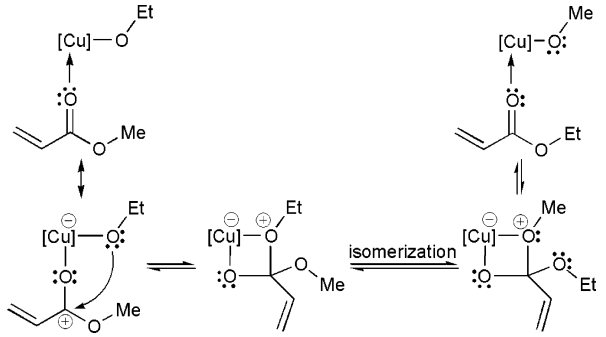
[a] All reactions performed with 5 mol % catalyst in C_6D_6. [b]% conversions determined by ^1H NMR spectroscopy. [c]Control experiments are reported after similar reaction times to catalyzed variants and are given in % conversion. [d]Transesterification observed (see below). [e]Addition of ^{t}BuNC (1 equiv based on EtOH) allows observation of hydroalkoxylation (see below).



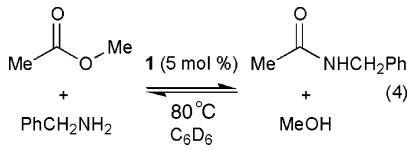
Transesterification reactions are prevalent transformations of organic esters and have been the focus of a substantial amount of study. To our knowledge, these are rare examples of well-defined copper-catalyzed transesterification reactions.[71−73] Rapid transesterification reactions are catalyzed by alkali-metal alkoxide clusters,[74−78] and free N-heterocyclic carbenes have also

(71) Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3622−3626.
(72) Kubota, M.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 146−150.
(73) Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2909−2915.

Scheme 2. Possible Pathway for Cu-Catalyzed Transesterification of Methyl Acrylate {[Cu] = (NHC)Cu}



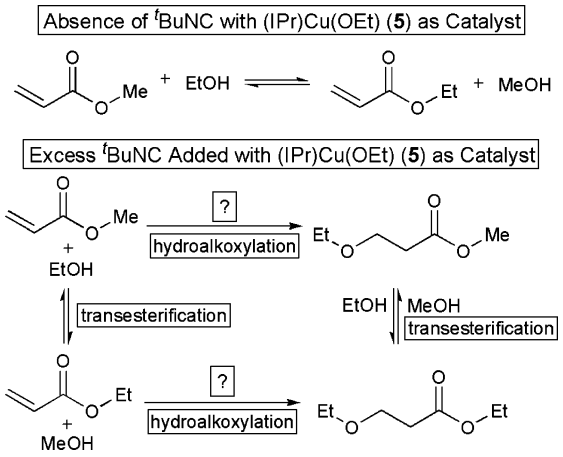
been used as catalysts.[79] Related transamidation reactions have been reported using metal−amido catalysts.[80−82] Analogous reactivity using tunable transition metal complexes is particularly exciting given the potential for application in both fine chemical and polymer synthesis.[83] The reaction of methyl acetate and benzyl amine in the presence of 5 mol % of complex **1** results in formation of methanol and *N*-benzylacetamide in 90% conversion over ∼500 h at 80 °C, at which point catalyst decomposition prevents further reaction (eq 4).

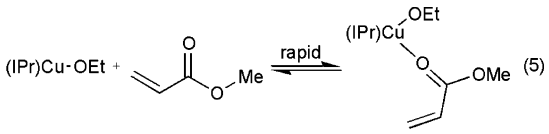


A possible pathway for the transesterification involves initial coordination of the carbonyl group of the ester by the Lewis acidic copper complex, which would increase the electrophilic character of the carbonyl carbon (Scheme 2). Subsequent intramolecular nucleophilic addition by the ethoxide ligand would yield a transient and unobserved metallacycle, which is likely susceptible to isomerization. Formation of the ethyl acrylate then occurs through C−O bond cleavage to yield a Cu−OMe moiety. Consistent with the proposed reaction pathway, a singlet at 4.13 ppm, which corresponds to the anticipated chemical shift of the methoxide ligand of (IPr)Cu(OMe), appears during the reaction of methyl acrylate, ethanol, and 5 mol % (IPr)Cu(OEt) (**5**). Although the pathway in Scheme 2 is feasible, the experimental data do not eliminate carbonyl coordination and addition of free EtOH or intermolecular addition of the ethoxide ligand on free ester as possible pathways.

^{1}H NMR studies were conducted in an attempt to observe the copper complex with methyl acrylate coordinated; however, the addition of methyl acrylate to a C_6D_6 solution of **5** does not afford clean observation of a new copper system. This combination results in broadening of the resonances due to the ethoxide ligand, which is consistent with coordination of methyl acrylate that is rapidly reversible on the NMR time scale (eq 5). The sequential addition of more methyl acrylate shifts the resonances due to the ethoxide ligand upfield of the chemical shift of (IPr)Cu(OEt) (**5**) (4.30 ppm) in the absence of methyl acrylate. Low-temperature ^{1}H NMR studies were also employed in an effort to observe coordination of methyl acrylate to complex **5**; however, at temperatures down to −60 °C, the proposed fluxional process is not sufficiently slow to observe. These results suggest a rapid and reversible coordination of methyl acrylate with $\Delta G^{\ddagger} < 6-7$ kcal/mol.

Scheme 3. Reactivity of Methyl Acrylate in the Absence (top) and Presence (bottom) of a Lewis Base





The proposed pathway for transesterification (Scheme 2) requires coordination of methyl acrylate to the copper catalyst. Thus, we considered the possibility that a competing ligand might promote the olefin hydroxylation reaction, which has previously been suggested to involve *inter*molecular N/O−C bond formation without olefin coordination (see below).[70] Indeed, the reaction of ethanol and methyl acrylate in the presence of **5** and the strong *σ*-donor *tert*-butylisonitrile (1 equiv, based on EtOH) forms methyl 3-ethoxypropionate, ethyl acrylate, and ethyl 3-ethoxypropionate. Although transesterification remains competitive, the addition of *tert*-butylisonitrile appears to slow transesterification relative to hydroalkoxylation and renders hydroalkoxylation kinetically competent. The formation of ethyl 3-ethoxypropionate could result from hydroalkoxylation of ethyl acrylate or transesterification of methyl 3-ethoxypropionate after it is formed via hydroalkoxylation. A control experiment conducted with ethyl 3-ethoxypropionate, methanol (1 equiv), and **5** (5 mol %) produced a 1:1 ratio of methyl 3-ethoxypropionate and ethyl 3-ethoxypropionate. Thus, with available data, we cannot distinguish product formation from (1) transesterification of methyl acrylate to form ethyl acrylate and hydroalkoxylation of both acrylates, (2) hydroalkoxylation of methyl acrylate followed by transesterification, or (3) both reaction pathways occurring. The latter seems most likely (Scheme 3).

Kinetic Studies. In order to probe the mechanism of these reactions, the rate of catalysis with aniline and acrylonitrile at

(74) Kissling, R. M.; Gagné, M. R. *Org. Lett.* **2000**, *2*, 4209−4212.
(75) Kissling, R. M.; Gagné, M. R. *J. Org. Chem.* **2001**, *66*, 9005−9010.
(76) Stanton, M. G.; Gagné, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 5075−5076.
(77) Stanton, M. G.; Allen, C. B.; Kissling, R. M.; Lincoln, A. L.; Gagné, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 5981−5989.
(78) Kantam, M. L.; Neeraja, V.; Bharathi, B.; Reddy, C. V. *Catal. Lett.* **1999**, *62*, 67−69.
(79) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583−3586.
(80) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422−3423.
(81) Kissounko, D. A.; Guzei, I. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208−5210.
(82) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177−5183.
(83) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J. L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652−3711.

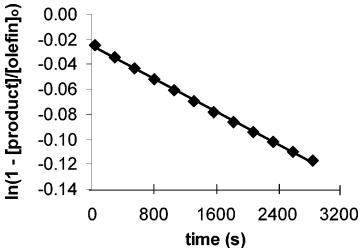


Figure 1. Plot of $\ln(1 - [\text{product}]/[\text{acrylonitrile}]_o)$ versus time for production of 3-anilinopropionitrile with 5 mol % of complex **1** ($R^2 = 0.99$).

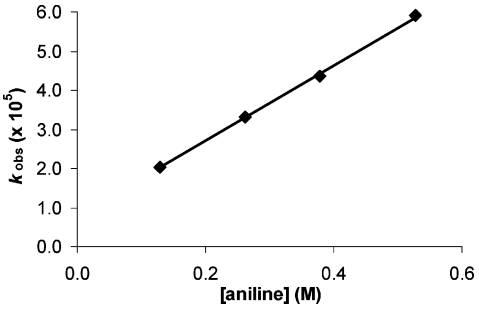


Figure 2. Plot of k_{obs} versus concentration of aniline for production of 3-anilinopropionitrile via hydroamination with 5 mol % **1** ($R^2 = 0.99$).

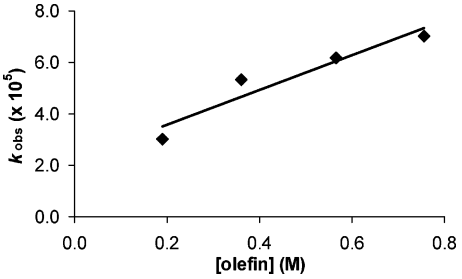


Figure 3. Plot of k_{obs} versus concentration of acrylonitrile for production of 3-anilinopropionitrile via hydroamination with 5 mol % **1** ($R^2 = 0.91$).

room temperature was probed. Reaction progress was monitored by ^{1}H NMR spectroscopy. In the presence of 5 mol % **1**, the concentration of aniline was varied at constant acrylonitrile concentration. Following the reaction through two turnovers (~10% conversion) gives initial rate constants for each concentration. For example, reaction of complex **1** (5 mol %) with a 1:1 ratio of aniline and acrylonitrile gives $k_{obs} = 3.3 \times 10^{-5}$ s^{-1} (Figure 1). A plot of k_{obs} versus concentration of aniline reveals a linear relationship consistent with a first-order dependence (slope $\approx$ 1) on aniline concentration (Figure 2). Similarly, the concentration of acrylonitrile was varied at 5 mol % **1** and constant concentration of aniline, which reveals an increase in rate of catalysis with increasing concentration of acrylonitrile (Figure 3). There appears to be a slight curvature in the plot, suggesting the possibility of "saturation" kinetics. Rate dependence of hydroamination on catalyst concentration was also studied, using solutions with 1, 2.5, 5, and 7.5 mol % **1** and a 1:1 molar ratio of amine to olefin. A plot of k_{obs} versus concentration of copper complex reveals a dependence on catalyst concentration (Figure 4). Kinetic studies with 10 mol % **1**, constant concentration of aniline and acrylonitrile, and varying concentrations of hydroamination product (3-anilinopropionitrile) indicate a nonlinear inverse dependence on concentration of product (Figure 5).

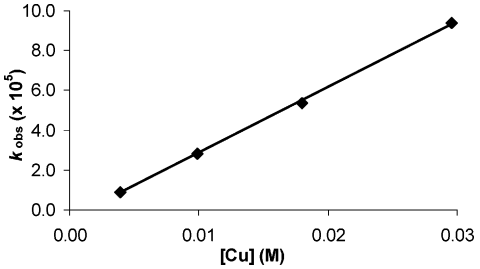


Figure 4. Plot of k_{obs} versus concentration of **1** for production of 3-anilinopropionitrile ($R^2 = 0.99$).

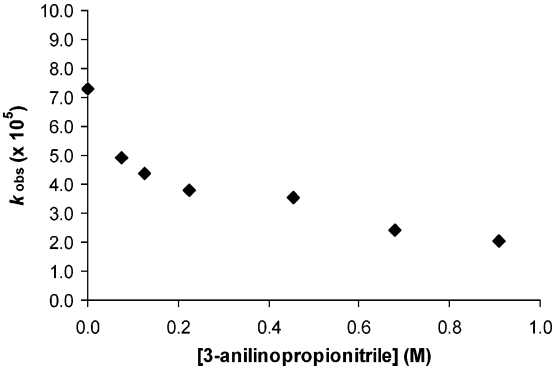
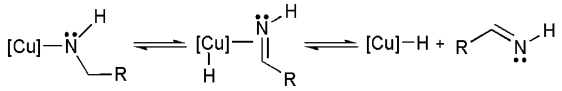


Figure 5. Plot of k_{obs} versus concentration of added 3-anilinopropionitrile.

Scheme 4. Possible β-Hydride Decomposition Route from [Cu]−NHR Complexes Has Not Been Observed



Discussion

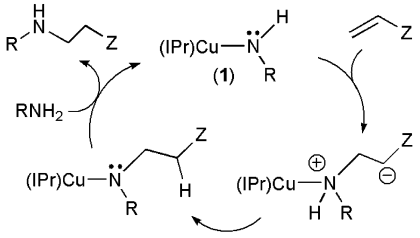
Scope and Mechanism of Catalytic Hydroamination, Hydroalkoxylation, and Hydroaryloxylation of Electron-Deficient Olefins. Exploration of the substrate scope has shown that catalysts **1**−**4** are active for both primary and secondary alkyl amines including *n*-propylamine, diethylamine, *tert*-butylamine, benzylamine, and dibenzylamine. Primary amines react more rapidly than secondary amines. For example, reaction of benzylamine with acrylonitrile in the presence of **1** (5 mol %) results in >95% conversion to 3-(phenylmethylamino)-propionitrile within 5 min, while the analogous reaction with dibenzylamine yields 60% conversion to 3-[bis(phenylmethylamino)]propionitrile after 90 h. The relative rates could be due to steric differences or a manifestation of the catalytic mechanism (see below). Of particular interest is the fact that for substrates that possess β-hydrogens (e.g., *n*-propylamine, benzylamine, ethanol) evidence for β-hydride elimination is not observed. For example, upon formation of the [Cu]−NHR or [Cu]−OR intermediate, a possible decomposition pathway is β-hydride elimination to form a [Cu]−H complex and imine (Scheme 4).[84] Decomposition via β-hydride elimination has been shown in some cases to be more facile for metal−alkyl complexes than for metal−amido complexes.[85]

We have recently proposed a reaction mechanism for the Cu-catalyzed amine addition (and related reactions) to electron-deficient olefins with primary amines that involves intermolecular nucleophilic addition of the amido ligand to the olefin

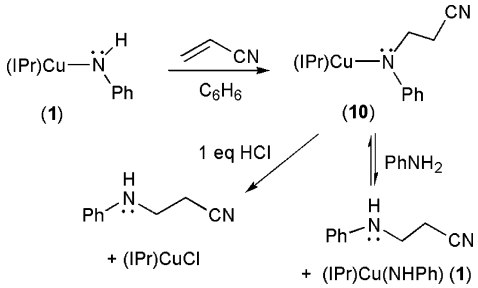
(84) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3633.

(85) Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7010−7011.

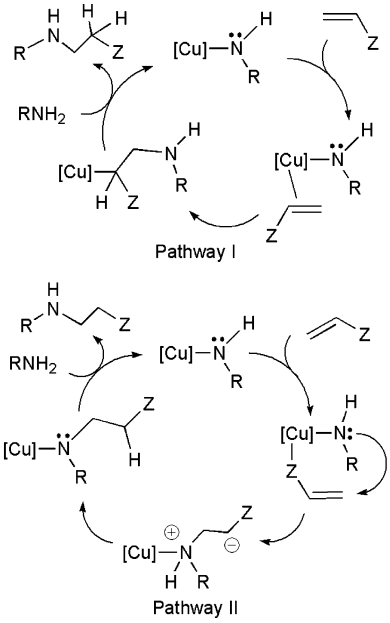
Scheme 5. Proposed Catalytic Cycle for Cu−Anilido Hydroamination Complexes



Scheme 6. Formation and Reactivity of (IPr)Cu(N(Ph)CH$_2$CH$_2$CN) (10)



Scheme 7. Alternate Mechanistic Possibilities for Cu-Catalyzed Hydroamination Include Precoordination of Olefin Followed by Insertion into the Cu−N Bond (Pathway I) and Intramolecular Nucleophilic Addition (Pathway II)



to produce an unobserved zwitterionic intermediate.[70] Subsequent proton transfer yields a new copper amido complex, and reaction with amine (presumably via coordination to Cu) yields free organic product and regenerates the original copper catalyst (Scheme 5). The hydroalkoxylation reactions and hydroamination with secondary amines cannot proceed through an identical pathway, but reaction with these substrates may proceed through a similar mechanism in which the reaction with free alcohol or amine occurs at the zwitterionic intermediate. This may explain why secondary amines react significantly slower than primary amines (e.g., reaction of diethylamine and acrylonitrile in the presence of **1** requires 9 h to reach >95% conversion, while the analogous reaction with *n*-propylamine requires only 1 h; see Table 1).

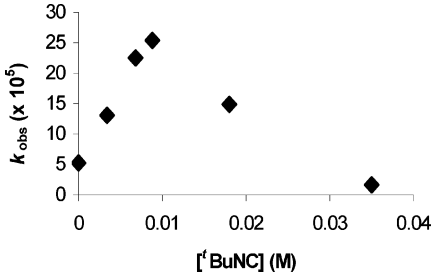


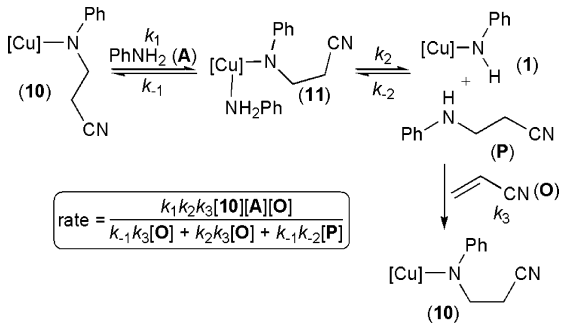
Figure 6. Plot of k_{obs} versus concentration of *tert*-butylisonitrile for production of 3-anilinopropionitrile via hydroamination with 5 mol % **1**.

The relative rates of catalysis are consistent with a nucleophilic addition pathway. For example, reactivity decreases in the order N(H)^{n}Pr > N(H)Ph > OEt > OPh for reactions with acrylonitrile. In addition, the proposed nucleophilic addition explains the highly regioselective transformations with C−N and C−O bond formation occurring exclusively (by ^{1}H NMR) at the most electrophilic carbon of the electron-deficient olefin. Furthermore, complex **1** reacts with acrylonitrile in the absence of aniline to yield a new copper complex with a ^{1}H NMR spectrum consistent with formation of (IPr)Cu(N(Ph)CH$_2$CH$_2$CN) (**10**) (Scheme 6).[70] Two new triplets at 3.20 and 1.74 ppm integrating for two protons each correspond to the methylene positions of **10** and are inconsistent with the product of olefin coordination and insertion into the Cu−NHPh bond. Treatment of **10** with 1 equiv of HCl produces 3-anilinopropionitrile and (IPr)CuCl, while reaction with aniline results in production of **1** and 3-anilinopropionitrile in equilibrium with complex **10** and free aniline {K_{eq} = 0.29(2) at room temperature} (Scheme 6).

It is also possible that olefin coordination precedes N−C or O−C bond formation. Scheme 7 depicts two possible pathways that involve olefin coordination: Pathway I invokes η^2-olefin coordination followed by insertion into the Cu−amido bond, while pathway II involves olefin coordination via the functional group "Z" followed by intramolecular nucleophilic addition. However, olefin coordination and insertion (pathway I) would form an intermediate with a copper−carbon bond, while the reaction of (IPr)Cu(NHPh) (**1**) with acrylonitrile produces copper−amido complex **10**. It is possible that the Cu−alkyl complex formed by olefin coordination and insertion might rapidly rearrange to **10**; however, the addition of strongly coordinating ^{t}BuNC would be expected to slow catalysis proceeding through either pathway I or II by inhibiting coordination of the olefin. Kinetic experiments indicate that the addition of 0.1 to 0.5 equiv of *tert*-butylisonitrile (based on complex **1**) increases the initial rate of reaction relative to reaction in the absence of the isonitrile (Figure 6). These data suggest that the initial step of the reaction does not involve coordination of the olefin to the copper catalyst. Increasing the concentration of *tert*-butylisonitrile beyond 0.5 equiv results in a decrease in the rate of catalysis; however, addition of these quantities of *tert*-butylisonitrile results in observable precipitation, which we presume is a Cu species, and hence, removal of catalyst from solution likely explains the decrease in rate of catalysis (Figure 6).

Scheme 8 depicts a proposed mechanism based on kinetic studies for the catalytic addition of aniline to acrylonitrile using complex **1**. In situ analysis using ^{1}H NMR spectroscopy suggests that complex **10** is the catalyst resting state. Reversible coordination of aniline to **10** would produce (IPr)Cu(N(Ph)-CH$_2$CH$_2$CN)(NH$_2$Ph) (**11**), and intramolecular proton transfer releases organic product and yields (IPr)Cu(NHPh) (**1**). Reaction of **1** with acrylonitrile to produce **10** is proposed as the rate-

Scheme 8. Proposed Mechanism and Derived Rate Law for the Catalytic Addition of Aniline to Acrylonitrile



determining step in the overall catalytic cycle. The rate law for the proposed pathway is given in Scheme 8 and involves Cu catalyst (**10** in the rate law), aniline (A in the rate law), acrylonitrile (O in the rate law), and product 3-anilinopropionitrile (P in the rate law). Linear k_{obs} versus substrate concentration plots indicate that the reaction is first order in aniline and catalyst and approximately 0.7 order in acrylonitrile with inverse dependence on organic product, and the plots are consistent with the proposed mechanism.

Comparative Reactivity of Catalysts. In an attempt to optimize catalyst activity, we sought to adjust the ancillary ligand set with variations on the N-heterocyclic carbene ligand as well as use of a bisphosphine ligand. For the series of Cu−anilido complexes (IPr)Cu(NHPh) (**1**), (IMes)Cu(NHPh) (**2**), (SIPr)Cu(NHPh) (**3**), and (dtbpe)Cu(NHPh) (**4**), recent reactivity studies indicate that the rates of nucleophilic substitution reactions with ethyl bromide increase in the order **3** < **1** < **2** < **4**.[69] Given the proposed dependence of Cu-catalyzed N−H/O−H addition to electron-deficient olefins on amido nucleophilicity, we anticipated that rates of catalysis might correlate with this trend (i.e., complex **4** would affect the most rapid reactions and complex **3** the slowest). In some cases, the anticipated reactivity trend is observed; however, for some substrates the NHC systems proved to be more active catalysts. For example, the reaction of aniline with cyclohexenone is catalyzed more rapidly with **1** than with **4** (85% conversion versus 66% conversion after 3 h, respectively). This result is possibly explained by steric influences. We have previously reported solid-state structures of **1** and **4**,[54,58] and space-filling models based on these structures are shown in Figure 7 with the anilido nitrogen atom in blue. The views indicate that the *tert*-butyl groups of **4** may shield the amido nitrogen to a greater extent than the NHC ligand of **1**. With bulkier substrates such as disubstituted olefins and secondary amines, this steric difference may have a more pronounced influence on relative reaction rates.

Transesterification and Transamidation versus Hydroalkoxylation and Hydroamination. For reactions of acrylates with alcohols or amines, transesterification and ester−amide exchange can compete with hydroalkoxylation and hydroamination transformations (Scheme 9). For example, complexes **5** and **8** do not catalyze the hydroalkoxylation of methyl acrylate with ethanol to give the anticipated methyl 3-ethoxypropanoate. Instead, catalytic transesterification is observed. Given the thermodynamic stability of carboxamides, it is perhaps surprising that complexes **1**−**4** catalyze hydroamination of methyl acrylate with no observation of ester−amide exchange. Ester−amide exchange reactions are known including Zr(IV)-catalyzed reactions as well as free NHCs serving as catalyst.[86,87] Herein, we

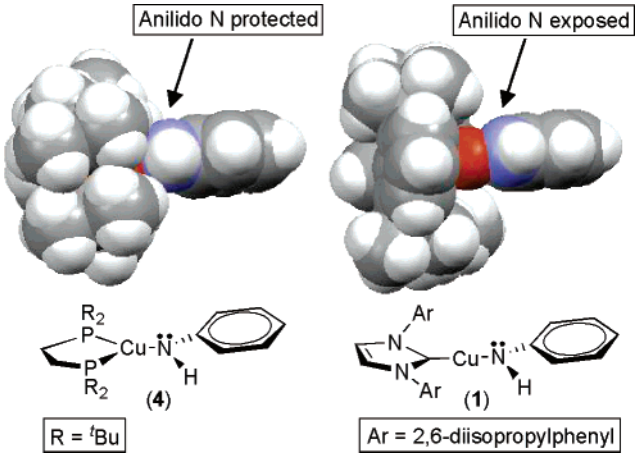
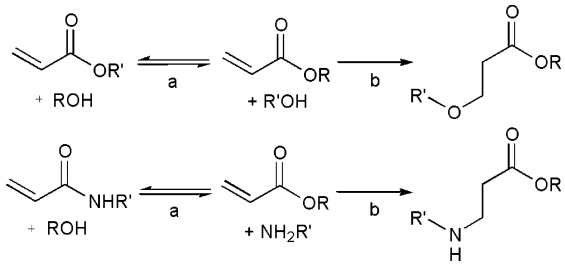


Figure 7. Space-filling diagrams of (dtbpe)Cu(NHPh) (**4**) (left) and (IPr)Cu(NHPh) (**1**) (right) taken from solid-state structures. Shown below each diagram is a skeleton of the structure to illustrate orientation (nitrogen atoms depicted in blue and Cu depicted in red).

Scheme 9. Olefinic Esters Can Undergo Transesterification or Ester/Amide Exchange (a) in Competition with Hydroalkoxylation or Hydroamination (b)



have provided evidence that transesterification proceeds through weak coordination of the ester group to the copper complex. Olefin hydroalkoxylation competes with transesterification, which is proposed to involve *intra*molecular C−O bond formation (see Scheme 2). For Cu−OR systems, the coordination of acrylate and intramolecular C−O bond formation (i.e., transesterification) competes effectively with intermolecular C−O bond formation (i.e., olefin hydroalkoxylation). For (NHC)Cu(NHPh), it is anticipated that the nucleophilicity of the nondative anilido ligand is enhanced relative to (NHC)Cu(OR) systems. Thus, the rate of *inter*molecular hydroamination is enhanced compared with Cu−OR-catalyzed reactions of alcohols, and net N−H addition to the C═C bond of methyl acrylate competes with methyl acrylate coordination and ester−amide exchange. The reaction of methyl acetate and benzyl amine demonstrates that ester−amide exchange is accessible with these Cu systems, but it is a relatively slow reaction (see eq 4 above).

Conclusions. Copper(I) amido, alkoxide, and aryloxide complexes catalyze the hydroamination, hydroalkoxylation, and hydroaryloxylation of electron-deficient olefins. The substrate scope for hydroamination includes primary and secondary alkyl as well as aryl amines including examples of sterically bulky amines. In addition, reactive olefins include monosubstituted Michael acceptors as well as disubstituted prochiral variants such as cyclohexenone and crotononitrile. Comparison of ancillary ligand sets reveals that, in general, the phosphine-ligated (dtbpe)-Cu(NHPh) is most reactive for hydroamination of less sterically imposing monosubstituted olefins, as expected from previously

(86) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 10039−10044.

(87) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453−2456.

reported nucleophilicity studies and the proposed nucleophilic addition pathway for this transformation. For more sterically imposing substrates, the less bulky two-coordinate (NHC)Cu systems are more efficient. Hydroalkoxylation has been observed for ethanol and phenol with electron-deficient olefins including acrylonitrile and methyl vinyl ketone. Copper−phenoxide complexes **6** and **9** exhibit catalytic activity with methyl acrylate.

Complexes **5** and **8** catalyze transesterification with methyl acrylate to yield ethyl acrylate. This is likely due to precoordination of methyl acrylate to the copper complex. The addition of a coordinating Lewis base (e.g., ^{t}BuNC) sufficiently inhibits coordination to allow hydroalkoxylation to become kinetically competitive with transesterification.

Experimental Section

General Methods. All procedures were performed under an inert atmosphere of dinitrogen in a nitrogen-filled glovebox or using standard Schlenk techniques. Glovebox purity was maintained by periodic nitrogen purges and was monitored by an oxygen analyzer {O_2(g) < 15 ppm for all reactions}. Benzene, toluene, and tetrahydrofuran were purified by distillation over sodium/benzophenone. Pentane was distilled over sodium prior to use. Hexanes were purified by passage through a column of activated alumina. Methyl acrylate was washed with aqueous NaOH, dried over $CaCl_2$, and vacuum distilled. Acrylonitrile was washed with dilute H_2SO_4, followed by aqueous Na_2CO_3, shaken over 4 Å molecular sieves, and then distilled. Methyl vinyl ketone was degassed via three freeze−pump−thaw cycles. Aniline was dried over CaH_2 followed by vacuum distillation. Benzylamine was washed with aqueous NaOH prior to distillation from zinc. Diethylamine was dried over potassium hydroxide. Phenol was recrystallized from benzene/hexanes. Benzene-d_6, chloroform-d_1, and methylene chloride-d_2 were degassed via three freeze−pump−thaw cycles and stored under a dinitrogen atmosphere over 4 Å molecular sieves. ^{1}H NMR spectra were acquired using a Varian Mercury spectrometer operating at 300 MHz and referenced to tetramethylsilane using residual proton signals of the deuterated solvent. (IPr)Cu(NHPh) (**1**), (IMes)Cu(NHPh) (**2**), (SIPr)Cu(NHPh) (**3**), (dtbpe)Cu(NHPh) (**4**), (IPr)Cu(OEt) (**5**), (IPr)Cu(OPh) (**6**), (IMes)Cu(OPh) (**7**), (SIPr)-Cu(OEt) (**8**), (SIPr)Cu(OPh) (**9**), and (IPr)Cu(N(Ph)CH_2CH_2CN) (**10**) were prepared according to published procedures.[58,69,70] All other reagents were used as purchased from commercial sources. Production of the following organic products was confirmed by comparison to previously reported ^{1}H NMR data: 3-anilinopropionitrile, 3-anilinocyclohexanone, 4-anilino-2-butanone, methyl 3-anilinopropanoate, 3-benzylaminopropionitrile, 3-benzylaminocyclohexanone, 3-ethoxypropionitrile, 3-ethoxy-2-butanone, 3-ethoxycyclohexanone, 4-phenoxy-2-butanone, methyl 3-phenoxypropanoate, ethyl acrylate, ethyl acetate, and *N*-benzylacetamide.[11,25,40,88−98] All others were compared to authentic samples that were purchased from commercial vendors.

Sample Catalytic Experiment: Reaction of Diethyl Amine and Acrylonitrile with Catalytic (IPr)Cu(NHPh) (1) (5 mol %). An NMR tube was charged with **1** (0.012 g, 0.023 mmol), diethyl amine (40.5 μL, 0.460 mmol), acrylonitrile (32.0 μL, 0.487 mmol), hexamethyldisiloxane as internal standard (2.0 μL, 0.0094 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. The reaction was monitored periodically by ^{1}H NMR spectroscopy at room temperature. After 9 h, amine was consumed (by ^{1}H NMR) and formation of 3-(diethylamino)propionitrile was quantitative. The production of 3-(diethylamino)propionitrile was confirmed by addition of an authentic sample.

Sample Control Experiment: Reaction of Diethyl Amine and Acrylonitrile. An NMR tube was charged with diethyl amine (24.6 μL, 0.278 mmol), acrylonitrile (18.4 μL, 0.280 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. The reaction was monitored by ^{1}H NMR spectroscopy. After 10 h at room temperature, 14% conversion to 3-(diethylamino)propionitrile was observed. After 37 days, 82% conversion was observed.

(IPr)Cu{N(Ph)(CH_2CH_2CN)} (10). Acrylonitrile (14 μL, 0.21 mmol) was added to a solution of **1** (0.114 g, 0.209 mmol) in benzene (5 mL). After stirring overnight, the solvent volume was reduced to 1 mL under reduced pressure. The addition of approximately 30 mL of hexanes resulted in the formation of a cream-colored precipitate, which was collected by vacuum filtration through a fine-porosity frit and washed with 3 × 10 mL of hexanes (0.096 g, 77% yield). ^{1}H NMR (δ, C_6D_6): 7.34 (br m, 2H, *para*-Ph of IPr), 7.08 (d, $^3J_{HH}$ = 8 Hz, 4H, *meta*-Ph of IPr), 7.01 (t, $^3J_{HH}$ = 8 Hz, 2H, *meta*-Ph of anilido ligand), 6.60 (t, $^3J_{HH}$ = 7 Hz, 1H, *para*-Ph of anilido ligand), 6.25 (s, 2H, NC*H*), 6.06 (d, $^3J_{HH}$ = 8 Hz, 2H, *ortho*-Ph of anilido ligand), 3.22 (t, $^3J_{HH}$ = 8 Hz, 2H, CH_2-CN), 2.50 (sept, $^3J_{HH}$ = 7 Hz, 4H, C*H*(CH_3)$_2$), 1.76 (t, $^3J_{HH}$ = 8 Hz, 2H, Cu−NCH_2), 1.28 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$), 1.05 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$). ^{13}C NMR (δ, C_6D_6): 183.3 (N*C*N), 159.2, 146.3, 135.3, 131.3, 129.5, 124.8, 119.4, 112.3 (aryl of IPr and phenyl of anilido), 122.7 (N*C*H of IPr), 47.8 (tt, $^1J_{CH}$ = 134 Hz, $^2J_{CH}$ = 5 Hz, Cu−N*C*H_2), 29.5 {*C*H(CH_3)$_2$}, 25.3 {CH-(*C*H_3)$_2$}, 24.4 {CH(*C*H_3)$_2$}, 20.1 (tt, $^1J_{CH}$ = 134 Hz, $^2J_{CH}$ = 4 Hz, *C*H_2CN). Complex **10** is insufficiently stable to permit elemental analysis.

Reaction of (IPr)Cu{N(Ph)(CH_2CH_2CN)} (10) and HCl. An NMR tube was charged with **10** (0.009 g, 0.01 mmol) and 0.5 mL of C_6D_6 and was sealed with a rubber septum. HCl (1.0 M in diethyl ether; 7 μL, 0.007 mmol) was added via microsyringe. Upon addition of acid, the formation of a white precipitate was noted. A ^{1}H NMR spectrum was acquired and resonances due to 3-anilinopropionitrile were observed as well as a decrease in the intensity of the resonances due to complex **10**. Upon addition of more HCl (8 μL, 0.008 mmol), additional precipitate formed and ^{1}H NMR spectroscopy revealed the complete conversion of **10** to the organic product 3-(phenylamino)propionitrile. Collection of the white solid by filtration, subsequent dissolution in $CDCl_3$, and acquisition of a ^{1}H NMR spectrum indicated formation of (IPr)CuCl, which was confirmed by addition of an authentic sample.[97]

Reaction of (IPr)Cu{N(Ph)(CH_2CH_2CN)} (10) and Aniline. An NMR tube was charged with **10** (0.013 g, 0.019 mmol) and 0.5 mL of C_6D_6 and sealed with a rubber septum. Aniline (1.73 μL, 0.019 mmol) was added via microsyringe. Relative concentrations of **10**, aniline, **1**, and 3-anilinopropionitrile were measured by ^{1}H NMR spectroscopy. Multiple experiments revealed a reproducible K_{eq} at room temperature of 0.29(2).

Reaction of (IPr)Cu(OEt) (5) with Ethanol and Methyl Acrylate. An NMR tube was charged with **5** (0.01 g, 0.02 mmol), ethanol (24 μL, 0.41 mmol), methyl acrylate (37 μL, 0.41 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. The reaction was periodically monitored by ^{1}H NMR spectroscopy. After 22 h

(88) Bartoli, G.; Cimarelli, C.; Palmieri, G. *J. Chem. Soc., Perkins Trans. 1* **1994**, 537−543.
(89) Arora, P. K.; Sayre, L. M. *Tetrahedron Lett.* **1991**, *32*, 1007−1010.
(90) Terasawa, T.; Okada, T. *Tetrahedron* **1977**, *33*, 595−598.
(91) Al-Awadi, S. A.; Abdallah, M. R.; Dib, H. H.; Ibrahim, M. R.; Al-Awadi, N. A.; El-Dusouqui, O. M. E. *Tetrahedron* **2005**, *61*, 5769.
(92) Kowalczuk, M.; Kurcok, P.; Glowkowski, W.; Jedlinski, Z. *J. Org. Chem.* **1992**, *57*, 389−391.
(93) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512−7515.
(94) Chen, C.-T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C.-H.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1188−1197.
(95) Blanco, M.; Perillo, I. A.; Schapira, C. B. *J. Heterocycl. Chem.* **1995**, *32*, 145−154.
(96) Zhang, H.; Zhang, Y.; Liu, L.; Xu, H.; Wang, Y. *Synthesis* **2005**, *13*, 2129−2136.
(97) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191−1193.
(98) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052−9055.

at room temperature, a ^{1}H NMR spectrum revealed an approximate 1:1 ratio of ethanol/methyl acrylate and methanol/ethyl acrylate. Production of ethyl acrylate was confirmed by comparison to published data.[93]

Reaction of (IPr)Cu(OEt) (5) with Ethanol, Methyl Acrylate, and *tert*-Butylisonitrile. An NMR tube was charged with **5** (0.011 g, 0.022 mmol), ethanol (25.8 μL, 0.442 mmol), methyl acrylate (39.8 μL, 0.442 mmol), *tert*-butylisonitrile (50.0 μL, 0.442 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. The reaction was monitored by ^{1}H NMR spectroscopy. After 30 min, a 1:1 mixture of hydroalkoxylation products methyl 3-ethoxypropionate and ethyl 3-ethoxypropionate was observed. Minimal amounts of methyl acrylate and ethyl acrylate (1:1 by ^{1}H NMR spectroscopy) were also present.

Control Reaction: Ethanol and Methyl Acrylate. An NMR tube was charged with ethanol (23.5 μL, 0.402 mmol), methyl acrylate (35 μL, 0.39 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. The reaction was monitored by ^{1}H NMR spectroscopy at room temperature. No reaction was observed after 5 days.

Reaction of (IPr)Cu(OEt) (5) with Methyl Acrylate. A small vial was charged with **5** (0.040 g, 0.080 mmol) and C_6D_6 (2.5 mL). This solution was divided into five NMR tubes, and an NMR spectrum was acquired with no added methyl acrylate. One, two, three, four, or five equivalents of methyl acrylate were added to each tube (1.4 μL, 0.016 mmol; 2.8 μL, 0.031 mmol; 4.2 μL, 0.047 mmol; 5.6 μL, 0.062 mmol; 7.0 μL, 0.078 mmol). Each solution was mixed with shaking, and ^{1}H NMR spectra were collected. To tubes 2, 3, and 5, additional equivalents of methyl acrylate were added, yielding samples with six, nine, and 12 total equivalents of methyl acrylate (5.6 μL, 0.094 mmol total; 8.4 μL, 0.141 mmol; 9.8 μL, 0.188 mmol). The spectra showed resonances due to the [Cu]−OEt and proposed [Cu]−OMe complex shifted upfield in the presence of multiple equivalents of methyl acrylate.

Reaction of (IPr)Cu(OEt) (5) with Ethanol and Methyl Acetate. An NMR tube was charged with **5** (0.011 g, 0.022 mmol), ethanol (25.8 μL, 0.480 mmol), methyl acetate (35.2 μL, 0.423 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. After 1 h, a mixture of approximately 1:1 ethanol/methyl acetate and methanol/ethyl acetate was observed by ^{1}H NMR spectroscopy. Formation of ethyl acetate was confirmed by comparison to published data.[93]

Reaction of (IPr)Cu(OEt) (5) with Ethyl 3-Ethoxypropanoate and Methanol. An NMR tube was charged with **5** (0.010 g, 0.020 mmol), ethyl 3-ethoxypropionitrile (62.5 μL, 0.406 mmol), methanol (16.5 μL, 0.407 mmol), and C_6D_6 (0.5 mL) and sealed with a rubber septum. After 2 h, a mixture of approximately 1:1 ethanol/methyl ester and methanol/ethyl ester was observed by ^{1}H NMR spectroscopy.

Reaction of (IPr)Cu(NHPh) (1) with Benzyl Amine and Methyl Acetate. A J-Young NMR tube was charged with **1** (0.016 g, 0.029 mmol), benzyl amine (15.9 μL, 0.146 mmol), methyl acetate (11.5 μL, 0.145 mmol), and C_6D_6 (0.5 mL) and sealed. After acquiring an initial ^{1}H NMR spectrum, the reaction was heated to 80 °C. Periodic collection of NMR spectra revealed formation of *N*-benzylacetamide in 91% yield after 511 h of heating. After this point, complete catalyst decomposition was observed. Formation of *N*-benzylacetamide was confirmed by comparison to published data.[94]

Kinetic Study of Hydroamination: Dependence on Aniline. A small vial was charged with **1** (0.043 g, 0.078 mmol), hexamethyldisiloxane (10.0 μL, 0.047 mmol) as internal standard, and C_6D_6 (6.0 mL). A 1.5 mL aliquot was delivered to each of four screw-cap NMR tubes. Ten, twenty, thirty, and forty equivalents of aniline were added separately to each tube (17.8 μL, 0.195 mmol; 35.6 μL, 0.391 mmol; 53.4 μL, 0.586 mmol; 72.2 μL, 0.792 mmol). Twenty equivalents of acrylonitrile (25.6 μL, 0.390 mmol) were added to each tube before sealing and immersing in a cold bath (−78 °C) to suppress reaction. Each tube was thawed, and ^{1}H NMR spectra were acquired over the course of an hour. The production of 3-anilinopropionitrile was monitored and plotted {as ln(1 − [product]/[olefin]$_o$)} versus time (s). Values of k_{obs} (× 10^5) and corresponding correlation coefficients (R^2) for 10, 20, 30, and 40 equiv of aniline are as follows: 2.04, 0.99; 3.30, 0.99; 4.35, 0.99; 5.90, 0.99. A plot of k_{obs} versus concentration of aniline gives a linear relationship with $R^2 = 0.99$.

Kinetic Study of Hydroamination: Dependence on Acrylonitrile. A small vial was charged with **1** (0.021 g, 0.038 mmol), hexamethyldisiloxane (8.0 μL, 0.038 mmol) as internal standard, and C_6D_6 (2.1 mL). A 0.5 mL aliquot was delivered to each of four screw-cap NMR tubes. Twenty equivalents of aniline were added to each tube (17 μL, 0.189 mmol). Ten, twenty, thirty, or forty equivalents of acrylonitrile (6.2 μL, 0.094 mmol; 12.4 μL, 0.189 mmol; 18.6 μL, 0.283 mmol; 24.8 μL, 0.377 mmol) were added separately to each tube before sealing and immersing in a cold bath (−78 °C) to suppress reaction. Each tube was thawed, and ^{1}H NMR spectra were acquired over the course of an hour. The production of 3-anilinopropionitrile was monitored and plotted {as ln(1 − [product]/[olefin]$_o$)} versus time (s). Values of k_{obs} (× 10^5) and corresponding correlation coefficients (R^2) for 10, 20, 30, and 40 equiv of acrylonitrile are as follows: 3.01, 0.99; 5.35, 0.99; 6.19, 0.99; 7.03, 0.99. A plot of k_{obs} versus concentration of acrylonitrile gives a linear relationship with a slope of 0.7 and $R^2 = 0.91$.

Kinetic Study of Hydroamination: Dependence on (IPr)Cu(NHPh) (1). A small vial was charged with **1** (0.012 g, 0.022 mmol) and C_6D_6 (0.74 mL). Aliquots of 0.07, 0.17, and 0.5 mL of solution were delivered to three screw-cap NMR tubes. Each tube was diluted to a total volume of 0.5 mL. Hexamethyldisiloxane (2.0 μL, 0.0094 mmol), aniline (18.0 μL, 0.198 mmol), and acrylonitrile (13.0 μL, 0.198 mmol) were added to each tube before sealing and immersing in a cold bath (−78 °C) to suppress reaction. Each tube was thawed, and ^{1}H NMR spectra were acquired over the course of an hour. Production of 3-anilinopropionitrile was monitored and plotted {as ln(1 − [product]/[olefin]$_o$)} versus time (s). Values of k_{obs} (× 10^5) and corresponding correlation coefficients (R^2) for 1, 2.5, and 7.5 mol % complex **1** are as follows: 0.911, 0.99; 2.84, 0.99; 9.40, 0.99. A plot of k_{obs} versus concentration of (IPr)Cu(NHPh) gives a linear relationship with $R^2 = 0.99$.

Kinetic Study of Hydroamination: Dependence on 3-Anilinopropionitrile. A small vial was charged with 3-anilinopropionitrile (0.166 g, 1.13 mmol) and benzene (2.0 mL). Aliquots of 0.2, 0.4, 0.6, and 0.8 mL were delivered to four fresh shell vials, and the solvent was removed. A second vial was charged with **1** (0.025 g, 0.047 mmol), hexamethyldisiloxane (8.0 μL, 0.038 mmol) as internal standard, and C_6D_6 (2.0 mL). Aliquots of 0.5 mL were delivered to each of the shell vials. After transferring each solution to a screw-cap NMR tube, aniline (11.0 μL, 0.121 mmol) and acrylonitrile (8.0 μL, 0.12 mmol) were added to each tube. The NMR tubes were then sealed and immersed in a cold bath (−78 °C) to suppress reaction. Each tube was thawed, and ^{1}H NMR spectra were acquired over the course of an hour. Consumption of acrylonitrile was monitored and plotted {as ln[olefin]} versus time (s). Values of k_{obs} (× 10^5) and corresponding correlation coefficients (R^2) for 10, 20, 30, and 40 equiv of added 3-anilinopropionitrile are as follows: 2.55, 0.99; 3.55, 0.99; 2.43, 0.95; 2.06, 0.99. A similar procedure was followed to obtain k_{obs} (× 10^5) and R^2 values for 0, 3, and 5 equiv of added 3-anilinopropionitrile: 7.29, 0.99; 4.90, 0.99; 4.36, 0.99. A plot of k_{obs} versus concentration of 3-anilinopropionitrile shows a nonlinear inverse dependence.

Kinetic Study of Hydroamination: Addition of ^{t}BuNC. A small vial was charged with **1** (0.023 g, 0.043 mmol), hexamethyldisiloxane (8.0 μL, 0.038 mmol) as internal standard, and C_6D_6 (2.4 mL). Aliquots of 0.6 mL were delivered to each of four NMR

tubes, followed by addition of 0, 0.5, 1, or 2 equiv of *tert*-butylisonitrile (0 μL, 0 mmol; 0.60 μL, 0.0053 mmol; 1.20 μL, 0.0106 mmol; 2.40 μL, 0.0210 mmol). Aniline (11.0 μL, 0.121 mmol) and acrylonitrile (8.0 μL, 0.122 mmol) were added to each tube, which were then sealed with rubber septa and immersed in a cold bath (−78 °C) to suppress reaction. Each tube was thawed, and ^{1}H NMR spectra were acquired over the course of an hour. Production of 3-anilinopropionitrile was monitored and plotted {as $\ln(1 - [\text{product}]/[\text{olefin}]_o)$} versus time (s). For the reaction with 1 and 2 equiv of *tert*-butylisonitrile, a yellow precipitate was observed in the NMR tube following acquisition of the data. Values of k_{obs} ($\times 10^5$) and corresponding correlation coefficients (R^2) for 0, 0.5, 1, and 2 equiv of added *tert*-butylisonitrile are as follows: 5.26, 0.99; 25.4, 0.99; 17.6, 0.95; 1.65, 0.99. A similar procedure was followed to obtain k_{obs} ($\times 10^5$) and R^2 values for 0.18 and 0.36 equiv of added *tert*-butylisonitrile: 13.1, 0.99; 22.5, 0.99. A plot of k_{obs} versus concentration of *tert*-butylisonitrile reveals an increase in reaction rate upon addition of up to 0.5 equiv of *tert*-butylisonitrile, but additional isonitrile results in precipitation of catalyst and thus causes a decrease in reaction rate.

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