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COMMUNICATIONS

Published on Web 01/12/2006

Anti-Markovnikov N−H and O−H Additions to Electron-Deficient Olefins Catalyzed by Well-Defined Cu(I) Anilido, Ethoxide, and Phenoxide Systems

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Conjugate addition reactions represent a class of versatile reactions for the construction of small organic molecules.[1] Diastereoselective and enantioselective variants are particularly attractive for the formation of natural products and compounds of biological interest, and the use of enantiopure transition metal catalysts can obviate the need for stoichiometric incorporation of chiral auxiliaries.[1−3] Copper reagents have been widely incorporated for conjugate addition reactions but have been primarily limited to reactions that involve C−C bond formation.[3−7] The addition of N−H or O−H bonds to electron-deficient olefins provides a pathway for N−C and O−C bond formation,[8,9] respectively, and can be catalyzed under acidic or basic conditions or using simple Lewis acidic metal catalysts that likely coordinate and activate the olefin toward nucleophilic addition;[1,8,10−16] however, such conditions are often incompatible with functionality and do not generally afford opportunities to control selectivity (e.g., diastereo- or enantioselectivity).

Recently, Kawatsura and Hartwig have reported screening of Pd catalysts for the addition of amines to acrylic acid derivatives based on the lead from Trogler on Pd-catalyzed addition of aniline to acrylonitrile.[17,18] Alkylphosphines have been demonstrated as catalysts for the hydration and hydroalkoxylation of electron-deficient olefins as well as addition of oxygen nucleophiles to 2-alkynoates.[19,20] Ni(II) catalysts for the hydroamination of activated olefins that likely coordinate the olefin and activate toward amine nucleophilic addition have been reported.[21] Herein, we report catalytic addition of N−H and O−H bonds across C=C bonds of electron-poor olefins using monomeric Cu(I) anilido, phenoxide, or ethoxide complexes through a proposed mechanism that involves initial nucleophilic addition of the nondative ligand to the electron-deficient olefin.

The preparation of the catalyst precursors (IPr)Cu(NHPh) (**1**), (IPr)Cu(OEt) (**2**), and (IPr)Cu(OPh) (**3**) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) has recently been reported (Scheme 1).[22] Complexes **1**−**3** catalyze the addition of amine N−H bonds or alcohol O−H bonds across the C=C bond of electron-deficient olefins (Table 1). For all reactions that we have studied, the transformations are selective for the anti-Markovnikov product. For example, in the presence of 5 mol % of complex **1** in C_6D_6, aniline and methyl vinyl ketone (MVK) are converted within 5 min at room temperature to the anti-Markovnikov product 4-(phenylamino)-2-butanone (entry 2). In the absence of catalyst, aniline and MVK react only to 50% completion over the course of *10 days*, strongly implicating copper as an active catalyst. Similarly, in the presence of 5 mol % of complex **1**, the N−H bond of aniline is added across the carbon−carbon double bonds of acrylonitrile (>95% conversion, entry 1) and methyl acrylate (55% conversion, entry 3), and benzylamine is added to acrylonitrile with 100% conversion after 5 min at room temperature (entry 5). Reaction of benzylamine with acrylonitrile in the absence of **1** proceeds at a much slower rate and is not complete after 37 days at room temperature (slower by a factor of ~27,000 compared to the reaction with 5 mol % of **1**). In the absence of **1**, neither acrylonitrile nor methyl acrylate shows evidence of reaction with aniline at room temperature after 3 and 14 days, respectively. Using only 1 mol % of **1**, the combination of acrylonitrile and aniline yields 95% conversion to 3-(phenylamino)propionitrile after 145 h at room temperature. Catalysis with disubstituted olefins to generate chiral products is also possible. For example, a mixture of cis and trans crotononitrile with 5 mol % of **1** proceeds to 54% conversion at 40 h at 80 °C (entry 4).

Scheme 1. Catalyst Precursors (IPr)Cu(NHPh) (**1**), (IPr)Cu(OEt) (**2**), and (IPr)Cu(OPh) (**3**)

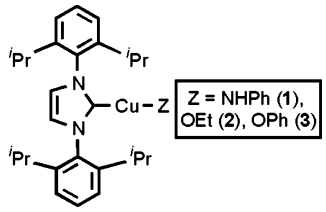
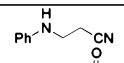
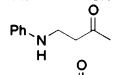
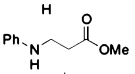
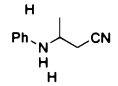
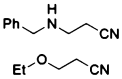
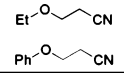


Table 1. Cu-Catalyzed Addition of Amine N−H Bonds and Alcohol O−H Bonds Across Electron-Deficient C=C Bonds (C_6D_6, % conversions determined by ^{1}H NMR spectroscopy)

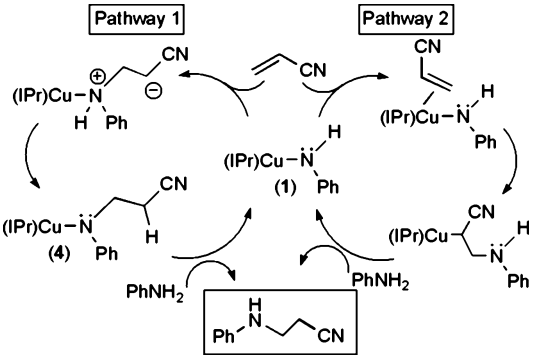
entry	olefin	nucleophile	cat. (5mol%)	temp (°C)	time	product	% conversion
1		NH_2Ph	1	RT	12 hr		>95
2		NH_2Ph	1	RT	5 min		100
3		NH_2Ph	1	RT	19 hr		55
4		NH_2Ph	1	80	40 hr		54
5		NH_2CH_2Ph	1	RT	5 min		100
6		EtOH	2	RT	20 hr		93
7		PhOH	3	80	40 hr		64

Control reactions were performed with (IPr)CuCl (precursor to **1**), $[Cu(OTf)]_2{\cdot}C_6H_6$ (OTf = trifluoromethanesulfonate), and free IPr ligand. None of these substrates catalyzes the addition of aniline to acrylonitrile at room temperature (no reaction observed after 140 h for copper systems and no reaction after 113 h for the IPr ligand). (IPr)Cu(OTf), however, affects approximately 52% conversion after 20 h. It is likely the (IPr)Cu(OTf) complex coordinates aniline, and in the presence of base (i.e., excess aniline), a small amount of (IPr)Cu(NHPh) can be produced and is responsible for the observed catalytic reaction (see below). Indeed, the amine complex [(IPr)Cu(NH_2Ph)][OTf] has been independently synthesized, and under catalytic conditions affects 46% conversion to 3-(phenylamino)propionitrile after 19 h.

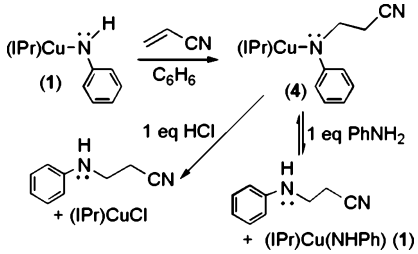
The catalytic reactions can be extended to alcohols. For example, in the presence of **2** (5 mol %), ethanol and acrylonitrile are

10.1021/ja057622a CCC: $33.50 © 2006 American Chemical Society

Scheme 2. Two Possible Pathways for Net Addition of N−H to Acrylonitrile



Scheme 3. Reactivity of **4** to Yield 3-(Phenylamino)propionitrile



converted to 3-ethoxypropionitrile with 90% conversion after 20 h (Table 1, entry 6). Similarly, **3** (5 mol %) catalyzes the conversion of acrylonitrile and phenol to 3-phenoxypropionitrile at 80 °C with 64% conversion (Table 1, entry 7). In the absence of catalyst, no reaction is observed between EtOH or PhOH and acrylonitrile.

We have considered two likely pathways for the catalytic transformations (Scheme 2). In Pathway 1, initial nucleophilic addition of the amido ligand to the olefin produces a zwitterionic intermediate, which undergoes a proton transfer to yield the new copper amido complex **4**. Subsequent proton transfer from aniline (presumably via coordination to Cu) to the amido ligand would yield organic product and regenerate **1**. The anti-Markovnikov selectivity would be dictated by the nucleophilic N−C bond-forming step. Alternatively, olefin coordination to **1** (Pathway 2) could precede olefin insertion into the $Cu-N_{amido}$ bond and form a new Cu−C bond. Direct observation of olefin insertions into metal−amido bonds is rare.[23] Subsequent proton transfer from aniline would yield organic product and **1**. We have previously demonstrated that (IPr)Cu(R) (R = Me or Et) systems react cleanly with OH or NH bonds to yield RH and (IPr)Cu(X) (X = amido, alkoxide, or aryloxide).[22] Thus, the product-forming step in Pathway 2 is feasible.

The stoichiometric reaction of **1** and acrylonitrile (in the absence of aniline) produces (IPr)Cu(N(Ph)CH_2CH_2CN) (**4**) (Scheme 3). Two new triplets at 3.20 and 1.74 ppm, integrating for two protons each, correspond to the methylene positions of **4** and are inconsistent with the product from olefin insertion depicted in Pathway 2. Importantly, treatment of **4** with 1 equiv of aniline results in production of **1** and 3-(*N*-phenyl)propionitrile in equilibrium with complex **4** and free aniline [K_{eq} = 0.29(2) at room temperature], while reaction with 1 equiv of HCl with **4** produces 3-(phenylamino)propionitrile and (IPr)CuCl (Scheme 3). During catalysis, complex **4** is not present in sufficient concentration to be observed by ^{1}H NMR spectroscopy, and the amido complex **1** is the only copper system observed.

Thus, we propose that the preliminary data support Pathway 1 (Scheme 2) as the most likely route for the catalytic transformations. However, we cannot, at this point, definitively rule out the possibility of olefin coordination, insertion followed by rapid isomerization to complex **4**, nor olefin coordination and intramolecular nucleophilic addition by the nondative ligand. These results also indicate that a mechanism in which copper serves as a simple Lewis acid to activate olefin toward nucleophilic attack from *free aniline* without direct involvement of the amido ligand is an unlikely pathway. Important from a synthetic perspective is the lack of observation of products due to β-hydride elimination pathways. We are presently working to delineate the full scope of these transformations, extend our mechanistic understanding, and access more active as well as enantioselective catalyst variants.

Acknowledgment. We acknowledge the NSF (CAREER Award, CHE 0238167) and Alfred P. Sloan Foundation for financial support. E.D.B. acknowledges the NSF (Graduate Fellowship) and the American Association of University Women Educational Foundation for an American Fellowship.

Supporting Information Available: Details of synthesis and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA057622A