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Copper-Catalyzed Olefin Aminoacetoxylation

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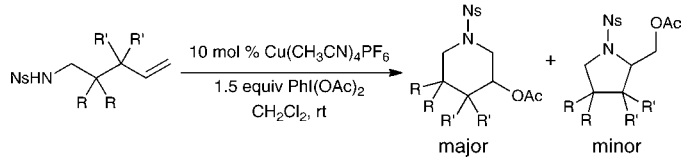
ABSTRACT



A new catalyst system for intramolecular olefin aminoacetoxylation is described. In contrast to previously reported palladium- and copper-catalyzed systems, the conditions outlined in this communication favor piperdine formation with terminal olefin substrates and induce cyclization with traditionally less reactive disubstituted olefins.

Vicinal amino alcohols are present in a wide variety of medicinally important compounds, perhaps most famously exemplified by the Taxol side chain. Although there are many conceivable approaches to this important chemical motif, including the Mannich reaction and epoxide or aziridine opening reactions, one of the most attractive strategies for 1,2-amino alcohol synthesis remains the direct aminohydroxylation of an olefin. Following its discovery in 1996, Sharpless' osmium-catalyzed asymmetric aminohydroxylation rapidly rose in prominence to become the premier reaction for 1,2-amino alcohol synthesis.[1] Despite more than a decade of development, issues with regioselectivity as well as catalyst toxicity, combined with the prominence of the 1,2-amino alcohol motif, have ensured that olefin aminohydroxylation remains a high-profile problem for the synthetic community. Recent advances in this area include the Lewis acid promoted addition of oxaziridines to olefins developed by Yoon and co-workers[2] and the hypervalent iodine-induced palladium-catalyzed amino-oxygenation reactions reported by Sorensen,[3] Stahl,[4] and Sanford.[5] Additionally, the Chemler group recently reported a copper-catalyzed enantioselective amino-oxygenation reaction.[6] While these recent methodologies represent important advances in the field, the palladium- and copper-catalyzed reactions outlined above are generally limited to monosubstituted terminal olefins[7] and, in intramolecular cases, show a preference for 5-*exo*-cyclization, leading to pyrrolidine formation.

Recently, both Michael and Wardrop reported metal-free intramolecular oxy-amination reactions that provide access to the complementary 6-*endo* cyclization products.[8] In both cases, acidic media are required to accelerate the reaction and provide useful levels of conversion (typically TFA is utilized as both an additive and an oxygen source in the amino-oxygenation reaction).

(1) (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169. (c) Muniz, K. *Chem. Soc. Rev.* **2004**, *33*, 166.

(2) (a) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866. (b) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610. (c) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, *65*, 5118. (d) Benkovics, T.; Du, J.; Guzei, I. A.; Yoon, T. P. *J. Org. Chem.* **2009**, *74*, 5545.

(3) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690.

(4) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

(5) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737.

(6) (a) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (b) Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915.

(7) Although one example of a *cis*-1,2-disubstituted olefin is provided by Liu and Stahl (ref 4), they state that "in general, internal olefins appear to be ineffective substrates".

(8) (a) Lovick, H. M.; Michael, F. M. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (b) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188. (c) For a copper-promoted 6-*endo* cylization, see: Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009**, *351*, 467. (d) For metal-free 5-*exo*-selective olefin oxyamination, see: Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316.

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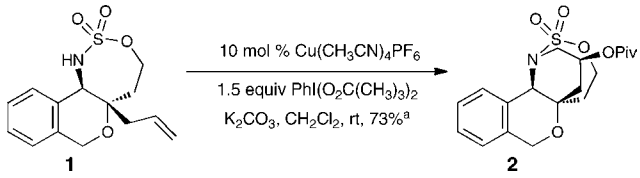
As part of our research program investigating alternative catalysts for metallonitrene/alkyne cascade processes,[9] we discovered that the cationic copper(I) complex $Cu(CH_3CN)_4PF_6$ could catalyze the regio- and diastereoselective olefin aminooxygenation of sulfamate ester **1**, providing 3-pivaloylpiperidine **2** (Scheme 1).

Scheme 1. Copper-Catalyzed Olefin Aminooxygenation Favors Piperidine Ring Formation

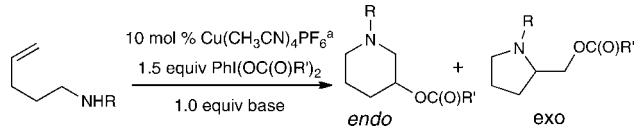


Relative stereochemistry assigned by X-ray crystallography; see the Supporting Information for details.

The exclusive formation of the piperidine ring system stood in stark contrast to the previously reported metal-catalyzed olefin aminooxygenation reactions, and the moderately basic reaction conditions offered a useful complement to the metal-free olefin oxamidation protocols.

However, it was not apparent whether this unusual outcome arose from the rigid nature of the starting material or was a more general feature associated with the reaction conditions. Thus, a small number of simple 5-aminopentene derivatives were prepared to assess these reaction conditions in an unbiased system (Table 1).

Table 1. Optimization of a Simple Copper-Catalyzed Olefin Amino-Oxygenation Protocol



entry	R	R′	base	solvent	% yield[b]	*endo*/*exo*
1	Ns	Me	K_2CO_3	CH_2Cl_2	88	9:1
2	Ts	Me	K_2CO_3	CH_2Cl_2	47	8:2
3	Ac	Me	K_2CO_3	CH_2Cl_2	0	–
4	Boc	Me	K_2CO_3	CH_2Cl_2	0	–
5	Ns	*t*-Bu	K_2CO_3	CH_2Cl_2	73	9:1
6	Ns	$C(Me)_2Ph$	K_2CO_3	CH_2Cl_2	70	9:1
7	Ns	Me	K_2CO_3	THF	0	–
8	Ns	Me	K_2CO_3	C_6H_6	29	95:5
9	Ns	Me	K_2CO_3	$CF_3C_6H_5$	72	92:8
10	Ns	Me	K_2CO_3	$CH_3C_6H_5$	18	70:30
11	Ns	Me	K_2CO_3	MeCN	6	–
12	Ns	Me	Bu_4NOAc	CH_2Cl_2	34	9:1
13	Ns	Me	$CsCO_3$	CH_2Cl_2	72	9:1
14	Ns	Me	KO^{t}Bu	CH_2Cl_2	43	9:1

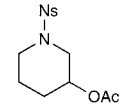
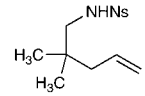
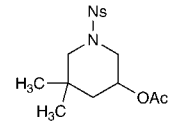
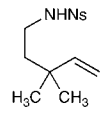
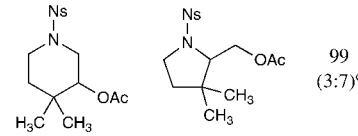
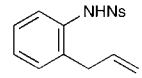
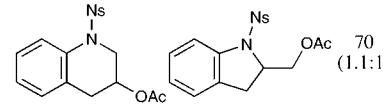
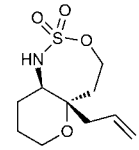
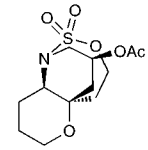
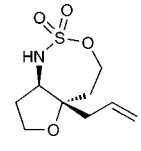
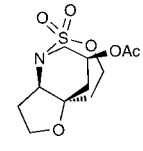
[a] CuI, CuOTf, and $Cu(OTf)_2$ were also investigated but were found to be significantly less effective catalysts. [b] Yield and ratio determined by ^{1}H NMR assay using 1,3,5-trimethoxybenzene as an internal standard.

During this study, we quickly established that the $Cu(CH_3CN)_4PF_6$-catalyzed olefin amino-oxygenation reaction was indeed selective for piperidine formation. Activation of the nitrogen atom with a nosyl substituent was important for reaction efficiency, with tosyl, acyl, and carbamoyl alternatives all observed to be less effective (entries 1−4). The nature of the carboxylate in the hypervalent iodine oxidant did not significantly effect the reaction outcome, with acetate, pivaloate, and dimethylphenyl acetate all effectively incorporated into the product (entries 1, 5, and 6). The nature of the solvent had a profound effect both on reaction yield and regioselectivity, with dichloromethane and trifluorotoluene observed to be the most effective media for efficient 3-acetoxypiperidine fomation (entries 1, 7−11).

Carbonate bases (entries 1 and 13) were found to be more effective than soluble tetrabutylammonium acetate (entry 12) or stronger alkoxide alternatives (entry 14).

Under the optimized conditions (Table 1, entry 1) a variety of monosubstituted γ-aminoolefins could be cyclized, and a preference for 3-acetoxypiperidine formation was observed (Table 2). How-

Table 2. Intramolecular Aminoacetoxylation of Terminal Olefins[a]

entry	substrate	product(s)	% yield[b]
1			85
2			77
3			99 (3:7)[c]
4			70 (1.1:1)
5			80
6			66

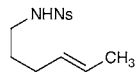
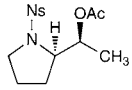
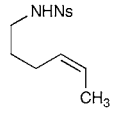
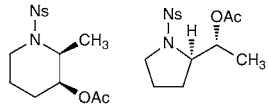
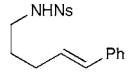
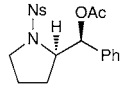
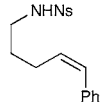
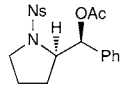
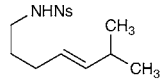
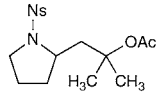
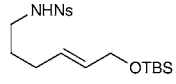
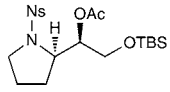
[a] Reaction conditions: 10 mol % of $Cu(CH_3CN)_4PF_6$, 1.5 equiv of $PhI(OAc)_2$, 1.0 equiv K_2CO_3, rt, CH_2Cl_2. [b] Isolated yield. In cases where two regioisomers were obtained, the combined yield is reported with product ratio in parentheses (determined by ^{1}H NMR analysis of the crude reaction mixture). [c] Reaction conducted in trifluorotoluene at 70 °C.

ever, significant steric congestion adjacent to the olefin reduced the reaction rate (it was necessary to conduct this reaction at 70 °C for efficient cyclization) and led to a reversal in the regioselectivity (entry 3).

We also observed a loss of regioselectivity in the cyclization of the aromatic substrate *N*-nosyl-2-allylaniline (entry 4). For the bicyclic sulfamate ester substrates outlined in entries 5 and 6, cylization proceeded both regio- and diastereoselectivly to provide the piperidine products in good yields as single diastereomers.

Additionally we have investigated the aminoacetoxylation of 1,2-disubstituted olefins (Table 3). Importantly, the

Table 3. Intramolecular Aminoacetoxylation of 1,2-Disubstituted Olefins[a]

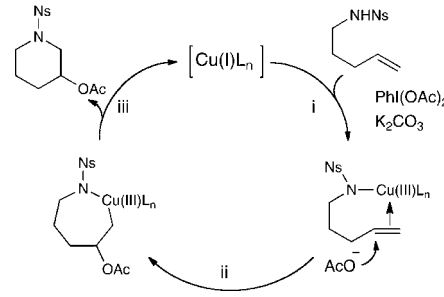
entry	substrate	product(s)	% yield[b]
1			77[c]
2			95 (1.6[d]:1[c])
3			50[c]
4			56
5			66
6			52[c]

[a] Reaction conditions: 10 mol % of $Cu(CH_3CN)_4PF_6$, 1.5 equiv of $PhI(OAc)_2$, 1.0 equiv of K_2CO_3, rt, CH_2Cl_2. [b] Isolated yield. In cases where two regioisomers were obtained, the combined yield is reported with the product ratio in parentheses. [c] The stereochemistry was determined by X-ray crystallography; see the Supporting Information for details. [d] The stereochemistry was determined by NOE experiments; see the Supporting Information for details.

standard reaction conditions provide cyclic aminoacetoxylation products in good to excellent yields. In most cases, we observe a significant preference for 5-*exo* cyclization to provide the pyrrolidine products, with only *cis*-*N*-nosyl-1-amino-4-hexene providing significant quantites of the piperidine product (entry 2). For 1,2-dialkylolefins, we observe an *anti* addition of the nitrogen and acetate across the double bond, regardless of the regiochemical outcome of the reaction (entries 1, 2, and 6). This outcome is in contrast to the previously reported metal free system, in which 5-*exo* cyclizations gave *syn* addition products and 6-*endo* cyclizations exhibited *anti* selectivity.[8a] For the phenyl-substituted olefins (entries 3 and 4), both olefin isomers converge on a single product diastereomer, corresponding to *anti*aminoacetoxylation across the *trans*-olefin. In the case of the isopropyl-substituted olefin (entry 5), an unusual 1,3-aminoacetoxylated product was obtained.

These reaction outcomes are consistent with a mechanism in which the copper catalyst and the *N*-nosylamine combine under the oxidative conditions to form an electrophilic copper(III) amido species (Scheme 2).[10,11]

Scheme 2. Proposed Catalytic Cycle Accounting for Observed Regio- and Diastereoselectivity: (i) Initial Oxidation to Cu(III) Amide; (ii) Nucleophile Attacks Carbon Most Able To Stabilize a Positive Charge Resulting in *Anti* Addition of the Nucleophile and Copper Across the Olefin; (iii) Reductive Elimination



Coordination of the tethered olefin to the Cu(III) center activates the double bond for *anti* attack by an external acetate, with the nucelophile attacking at the position most able to stabilize a positive charge. Thus, in the case of monosubstituted olefins, acetate attack occurs at the internal position, leading to the observed *endo* cyclization.[12] If the

(9) (a) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020. (b) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.

(10) For exaples of well-defined oganometallic Cu(III) complexes, see: (a) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1633. (b) Naumann, D.; Roy, T.; Tebbe, K.-F.; Crump, W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1482. (c) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2000**, *122*, 803. (d) Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2991. (e) Santo, R.; Miyamoto, R.; Tanaka, R.; Nishioka, T.; Sato, K.; Toyota, K.; Obata, M.; Yano, S.; Kinoshita, I.; Ichimura, A.; Takui, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7611.

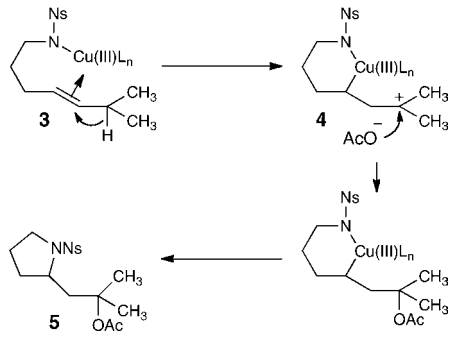
(11) For C−N bond formation from Cu(III) coumpounds, see: (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, DOI: 10.1039/c0sc00245c.

(12) For related *anti* nucleometalations, see: (a) Åkermark, B.; Bäckvall, J. E.; Siirala-Hansén, K.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett.* **1974**, *15*, 1363. (b) Åkermark, B.; Bäckvall, J. E.; Hegedus, L. S.; Zetterberg, K.; Siirala-Hansén, K.; Sjöberg, K. J. *Organomet. Chem.* **1974**, *72*, 127. (c) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674. (d) Bäckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335.

internal position is significantly hindered (e.g., Table 2, entry 3), then these steric factors may overide the electronic bias leading the nucleophile to preferentially attack the primary carbon. The preference for acetate attack on the carbon most able to stablilize positive charge is also observed in the reaction of the styrenal substrates (Table 3, entries 3 and 4). The convergence of both olefin isomers to a single product diastereomer suggests that in these cases the olefins themselves may isomerize under the reaction conditions. In the case of 1,2-dialkyl-substituted olefins, there is no significant electronic bias, so the regiochemical outcome of the reaction is most likely dictated by subtle geometric factors, leading in some cases to selective reactions (e.g., Table 3, entry 1) and in other cases to mixtures of regioisomeric products (Table 3, entry 2). Such a mechanism would also explain the formation of the 1,3-aminoacetoxylated product observed in the reaction of the isopropyl-substituted olefin (Table 3, entry 5).

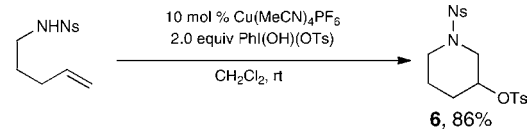
In this case, a 1,2-hydride shift in the activated olefin complex **3** would provide stable tertiary cation **4** prior to external acetate attack, accounting for the observed product **5** (Scheme 3). In all cases, a reductive elimination step would complete the reaction and regenerate the Cu(I) catalyst.

Scheme 3. A 1,2-Hydride Shift Leads to the Formation of 1,3-Aminoacetoxylation Product **5**



Based on our proposed mechanism, we predicted that alternative nucleophiles included in the reaction mixture could be used to trap the activated olefin complex. Accordingly, the use of Koser's salt in place of the bisacetoxyiodobenzene oxidant led to the incorporation of the tosylate into the product **6** (Scheme 4).[13]

Scheme 4. Alternative Oxidant for Olefin Aminotosylation



In conclusion, we have developed a new aminoacetoxylation protocol that provides complementary regioselectivity to previously reported palladium- and copper-catalyzed reactions. The new reaction proceeds under complementary pH conditions to recently reported metal free reactions, allowing for the selective formation of 3-acetoxy piperidine products from γ-aminoolefins. Experiments based on our mechanistic hypothesis demonstrated that alternative nucleophiles can also be incorporated into the product under similar reaction conditions.

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Supporting Information Available: Experimental procedures, structural proofs, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A related metal-free olefin amino-oxytosylation was reported in a review article, but no experimental details were provided. See: Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365.