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Platinum-Catalyzed, Terminal-Selective C(sp^3)–H Oxidation of Aliphatic Amines

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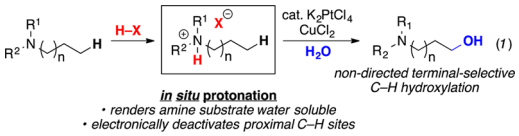
Supporting Information

ABSTRACT: This Communication describes the terminal-selective, Pt-catalyzed C(sp^3)–H oxidation of aliphatic amines without the requirement for directing groups. $CuCl_2$ is employed as a stoichiometric oxidant, and the reactions proceed in high yield at Pt loadings as low as 1 mol%. These transformations are conducted in the presence of sulfuric acid, which reacts with the amine substrates *in situ* to form ammonium salts. We propose that protonation of the amine serves at least three important roles: (i) it renders the substrates soluble in the aqueous reaction medium; (ii) it limits binding of the amine nitrogen to Pt or Cu; and (iii) it electronically deactivates the C–H bonds proximal to the nitrogen center. We demonstrate that this strategy is effective for the terminal-selective C(sp^3)–H oxidation of a variety of primary, secondary, and tertiary amines.

The development of methods for the selective functionalization of strong primary (1°) C(sp^3)–H bonds in the presence of weaker tertiary (3°) and secondary (2°) C(sp^3)–H bonds remains a major challenge in the burgeoning field of transition-metal-catalyzed C–H functionalization.[1−3] The Pt-catalyzed oxidation of alkanes offers a promising approach to tackle this challenge.[4] In the 1970s, Shilov demonstrated that aqueous solutions of Pt^{II} and Pt^{IV} salts effect the C–H hydroxylation of alkanes.[5] These transformations generally afford selective functionalization of 1° C–H bonds over 2° C–H bonds.[4,6] However, despite the great promise of Shilov-type Pt catalysis, these transformations have found minimal applications in organic synthesis over the past 40 years.[7] This is due, in large part, to three key limitations: (1) the scope of substrates remains extremely narrow (predominantly due to the low water solubility of most organic molecules); (2) the selectivity remains modest (1° vs 2° C(sp^3)–H bond selectivity generally ranges from 1.5:1 to 3:1); and (3) costly Pt^{IV} salts are typically used as the terminal oxidant (rendering the reactions impractical even on small scales).

We reasoned that all of these challenges could potentially be addressed in the context of the Pt-catalyzed C(sp^3)–H oxidation of aliphatic amines. Aliphatic amines are a very important class of compounds that serve as the core structures of diverse organic materials, natural products, and bioactive molecules.[8] Most existing methods for the C(sp^3)–H functionalization of aliphatic amines involve either (1) functionalization at the highly activated C–H site α-to nitrogen[9] or (2) the use of the amine nitrogen as part of a directing group.[7c,10,11] We sought to utilize Pt catalysis to achieve complementary reactivity, namely, terminal-selective C–H functionalization at sites remote to nitrogen.[12]

We hypothesized that terminal-selective, Pt-catalyzed C–H oxidation would be enabled by protonation of the amine substrates (eq 1). The formation of ammonium salts would



address two of the existing challenges of Shilov catalysis. First, quaternization should render the substrates water-soluble. Second, the inductive electron-withdrawing effect of the ammonium cation[13] is expected to electronically deactivate C–H sites proximal to nitrogen, thereby enhancing selectivity for remote 1° C(sp^3)–H bonds.[14] In addition, we sought to leverage prior work by Sames[7c] and Sen[7d] demonstrating that Cu^{II} salts can be used as oxidants for Shilov-type reactions in place of costly K_2PtCl_6.[15] Our protonation strategy is also crucial in this context, since unprotonated amines could potentially undergo undesired side reactions with the Cu^{II} oxidant.[16]

Our initial studies focused on the K_2PtCl_4-catalyzed C–H hydroxylation of dipropylamine, which was protonated *in situ* with H_2SO_4. We started with traditional Shilov conditions, using 10 mol% of K_2PtCl_4, 1 equiv of K_2PtCl_6 as the terminal oxidant (and limiting reagent), and 2 equiv of the amine H_2SO_4 salt at 120 °C. As shown in Table 1, entry 1, these conditions afforded the C(sp^3)–H hydroxylation product with high terminal selectivity (>10:1 ratio of **1** to **1a**) but only modest yield (36%) over 48 h. Changing the terminal oxidant to $CuCl_2$ under otherwise analogous conditions provided an enhanced yield (66%), while maintaining high selectivity (>10:1; entry 2). Increasing the temperature to 150 °C afforded a similar yield (63%) over 30 h (entry 3). At this temperature, the catalyst loading could be dropped to 1 mol%, with minimal impact on the yield or selectivity (although this reaction now required 48 h; entry 5). Upon moving to 5 equiv of amine H_2SO_4 salt relative to Cu, the hydroxylated product was obtained in 97% yield (97 turnovers of Pt) and 8:1 selectivity for **1** over **1a** (entry 6). To our knowledge, this result represents the highest combination of terminal selectivity and TON reported to date for Shilov-type Pt catalysis.[4] Importantly, control reactions

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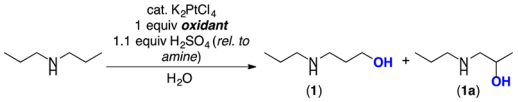
Table 1. Optimization of Pt-Catalyzed C−H Hydroxylation of Protonated Dipropylamine



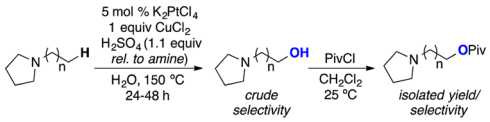
entry	equiv of amine	oxidant	temp (°C)	K_2PtCl_4 loading (mol%)	yield of **1** + **1a**[a] (%)	**1**:**1a**[a]
1[b]	2	K_2PtCl_6	120	10	36	>10:1
2[b]	2	$CuCl_2$	120	10	66	>10:1
3[c]	2	$CuCl_2$	150	10	63	>10:1
4[c]	2	$CuCl_2$	150	1	40	>10:1
5[b]	2	$CuCl_2$	150	1	70	8:1
6[c]	5	$CuCl_2$	150	1	97	8:1
7[c]	5	–	150	1	nd[e]	–
8[c]	5	$CuCl_2$	150	–	nd[e]	–
9[c,d]	5	$CuCl_2$	150	1	<1	–

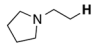
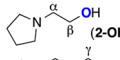
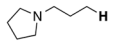
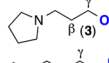
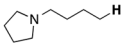
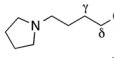
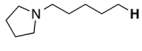
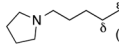
[a]Yield and ratio of products determined by ^{1}H NMR. Reactions were conducted in sealed vials under an atmosphere of ambient air. Yields are calculated based on the oxidant (K_2PtCl_6 or $CuCl_2$) as the limiting reagent. [b]48 h. [c]30 h. [d]No H_2SO_4 added. [e]Products **1** and **1a** were not detected.

show that no product is formed in the absence of Cu or Pt (entries 7 and 8). Furthermore, <1% of the C−H hydroxylation product was observed under the standard conditions but in the absence of added acid (entry 9). This is consistent with our hypothesis that protonation of the amine is essential for this transformation.

We next examined the Pt-catalyzed C−H hydroxylation of a series of *N*-alkylpyrrolidine substrates to probe the impact of chain length on selectivity (Table 2). In all cases, the major

Table 2. Pt-Catalyzed C−H Functionalization of *N*-Alkylpyrrolidines



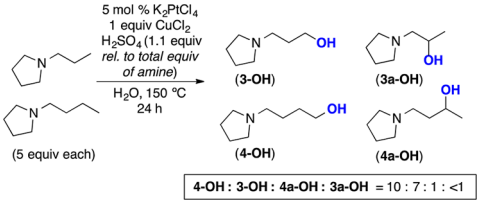
substrate	major product	isolated yield	isolated selectivity (crude selectivity)[a]
	 (**2-OH**)	25%[b]	(β : α = >20 : 1)
	 (**3**)	85%	γ : β = >20 : 1 (γ : β = 10 : 1)
	 (**4**)	126%	δ : γ = 4 : 1 (δ : γ = 4 : 1)
	 (**5**)	73%	ε : δ = 3 : 1 (ε : δ = 2 : 1)

[a]Crude selectivity determined by ^{1}H NMR spectroscopic analysis prior to treatment with PivCl. [b]Yield determined by ^{1}H NMR spectroscopic analysis prior to treatment with PivCl.

product derived from C−H hydroxylation at the terminal position. As the terminal methyl group is moved closer to the amine nitrogen, the terminal selectivity increases sequentially from 2:1 in **5** to >20:1 in **2**.[17] In all cases, the site selectivity was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (see Supporting Information for spectra). The amino alcohol products were then derivatized with pivaloyl chloride (PivCl) to facilitate product isolation and characterization. Using these conditions, the oxygenated amino ester products **3**−**5** were isolated in high yields.[18]

The observed increase in selectivity with shorter chain length correlates with a decreased rate of C−H functionalization at sites that are proximal to the ammonium cation. For example, the C−H hydroxylation of *N*-ethylpyrrolidine to form **2** proceeded in modest 25% yield under conditions analogous to those used to obtain products **3**−**5**. This is consistent with *β*-C(sp^3)−H bonds being significantly less reactive than more remote C−H sites. In addition, competition between *N*-propyl- and *N*-butylpyrrolidine afforded a 10:7:1:<1 ratio of products **4-OH**:**3-OH**:**4a-OH**:**3a-OH** (Scheme 1). Again, the selectivity

Scheme 1. Competition between *N*-Propyl- and *N*-Butylpyrrolidine



for **4-OH** over **3-OH** as well as for **4a-OH** over **3a-OH** is consistent with higher reactivity of C−H sites that are more remote from nitrogen. Overall, these results support our hypothesis that quaternization of the amine deactivates the C(sp^3)−H sites proximal to nitrogen via an inductive electron-withdrawing effect.

Our standard conditions proved effective for the C−H hydroxylation of a variety of other 2° and 3° aliphatic amine substrates (Table 3). In all cases, the site selectivity was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures (see Supporting Information for spectra).[17] The amino alcohol products were then derivatized with PivCl to facilitate isolation and characterization. Notably, the oxidant is used as the limiting reagent in these transformations. As such, yields greater than 100% reflect regeneration of the Cu oxidant (presumably by ambient air).[19]

All of the examples in Table 3 display modest to excellent terminal selectivity.[17] Notably, the derivatization and purification sequence generally results in an upgrade of selectivity for the terminal product. The terminal selectivity partially reflects the inherent steric preference of Pt for the activation of 1° over 2° or 3° C−H bonds.[4,6] However, selectivity is highest in the formation of the products in entries 1, 4, 5, and 7−10, where the competing 2° C(sp^3)−H sites are *β* or *α* to the quaternized nitrogen. Again, these results implicate significant inductive deactivation by the ammonium cation. Nitrogen heterocycles including pyrrolidine, piperidine, and morpholine are compatible with the reaction conditions, and minimal C−H oxidation of the ring (<5%) is observed in these systems. Although terminal *β*-C(sp^3)−H sites are electronically deactivated, triethylamine does undergo high-yielding *β*-C−H oxygenation under slightly modified reaction conditions (15 equiv of amine relative to $CuCl_2$ over 48 h; entry 7). Minimal oxidation of *tert*-butyl groups is observed, even in the absence of competing terminal sites for C−H oxidation (e.g., entries 11 and 12). Similar observations have been made by Hartwig in Ir-catalyzed alkane borylation[2] and can be attributed to steric deactivation of the *tert*-butyl C−H bonds.

We next compared this C−H hydroxylation reaction to Ir-catalyzed C−H borylation, the current state-of-the-art method for terminal-selective alkane C−H functionalization.[2] Hartwig

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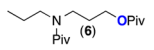
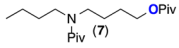
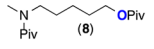
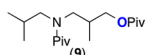
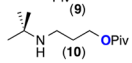
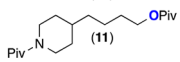
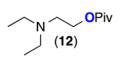
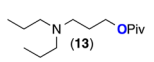
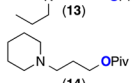
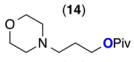
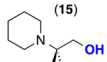
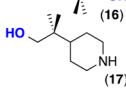
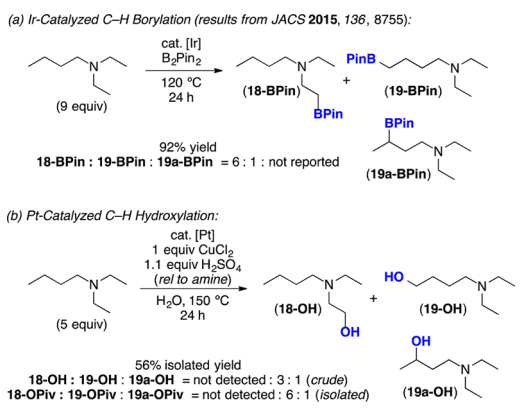
Table 3. Substrate Scope of Pt-Catalyzed C−H Hydroxylation of Secondary and Tertiary Amines[a]

entry	major product	isolated yield	isolated selectivity (crude selectivity)
1	 (6)	87%	>20 : 1 (8 : 1)
2	 (7)	76%	7 : 1 (5 : 1)
3	 (8)	47%	>10 : 1 (3 : 1)
4	 (9)	54%	>20 : 1 (8 : 1)
5	 (10)	46%	>20 : 1 (>20 : 1)
6[b]	 (11)	65%	>10 : 1 (5 : 1)
7[c]	 (12)	88%	>20 : 1 (>20 : 1)
8[d]	 (13)	102%	>20 : 1 (7 : 1)
9[e]	 (14)	90%	>20 : 1 (14 : 1)
10[e]	 (15)	122%	>20 : 1 (10 : 1)
11[f]	 (16)	<5%[g]	----
12[f]	 (17)	<5%[g]	----

[a]General conditions: 1 mol% K_2PtCl_4, 1 equiv of $CuCl_2$, 5 equiv of amine, 5.5 equiv of H_2SO_4 (1.1 equiv relative to amine), 150 °C, 24−48 h. [b]Entry 6: amine used as HCl salt, 10 mol% K_2PtCl_4. [c]Entry 7: 15 equiv of amine, 16.5 equiv of H_2SO_4. [d]Entry 8: 0.5 mol% K_2PtCl_4, 15 equiv of amine, 16.5 equiv of H_2SO_4. [e]Entries 9−11: 5 mol % K_2PtCl_4. [f]Entries 11 and 12: amine used as HCl salt, 10 mol% K_2PtCl_4; [g]Yields estimated by ^{1}H NMR analysis of crude reaction mixtures; <5% of C(sp^3)−H hydroxylation or C(sp^3)−H chlorination products was observed.

has recently reported that the 3° amine substrate diethylbutylamine undergoes Ir-catalyzed C−H borylation to afford the terminal β-C(sp^3)−H borylation product **18-BPin** with 6:1 selectivity over the analogous terminal δ-C(sp^3)−H borylation product **19-BPin** (Scheme 2a).[12] In this system, none of the 2° C(sp^3)−H borylation product **19a-BPin** was reported. In contrast, the Pt-catalyzed hydroxylation of this same substrate provides completely different site selectivity, affording a >20:1

Scheme 2. Comparison of Selectivity of (a) Ir-Catalyzed C−H Borylation versus (b) Pt-Catalyzed C−H Oxygenation of Diethylbutylamine



preference for **19-OH** over **18-OH**, and a 3:1 ratio of **19-OH** to **19a-OH** (Scheme 2b). These results highlight the complementarity of the two methods. Notably, Pt catalysis has the additional advantages of compatibility with ambient air and moisture as well as applicability to 1°, 2°, and 3° amine substrates.

A final set of investigations focused on probing the mechanism of this transformation. In particular, we noted that C−H hydroxylation products are formed exclusively under our reaction conditions, despite the presence of a high concentration of chloride. In other studies of Shilov-type alkane C−H oxidation, mixtures of C−H chlorination and C−H hydroxylation products have been reported under related conditions.[5,6,20] When the Pt-catalyzed C−H oxidation of dipropylamine was monitored by ^{1}H NMR spectroscopy, we observed rapid initial formation of an intermediate (**A**), which then fully converted to the C−H hydroxylation product over 24 h (Figure 1). Intermediate **A** was identified as the terminal C−

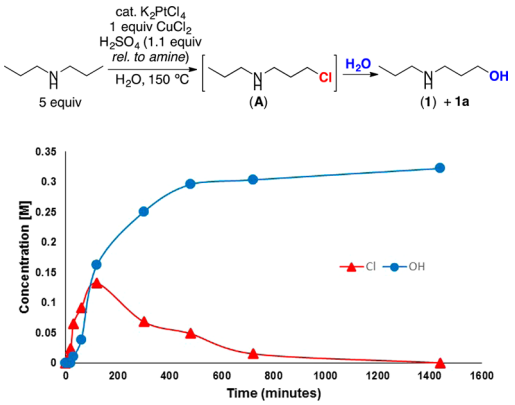


Figure 1. Formation and decay of intermediate **A** in the Pt-catalyzed C−H oxidation of dibutylamine.

H chlorination product, based on *in situ* characterization by ^{1}H NMR spectroscopy, as well as independent synthesis of this compound. We also confirmed that an authentic sample of **A** undergoes quantitative conversion to **1** over 24 h at 150 °C in H_2O, both in the presence and in the absence of the Pt catalyst. This suggests that a significant quantity of the hydroxylated product **1** is formed from **A** via a nucleophilic substitution reaction.

The data in Figure 1 suggest the feasibility of selectively accessing C(sp^3)−H chlorination products, particularly with substrates in which nucleophilic substitution with H_2O is slow. As proof-of-principle, we subjected substrates **20** and **24** to our Pt-catalyzed C−H oxidation conditions for short reaction times (2 h). Analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy showed exclusive formation of the C−H chlorination products **21** and **25**. While **21** and **25** proved challenging to isolate due to their high volatility, work-up of these reactions with $KHCO_3$ resulted in the formation of the corresponding oxazinones **23** and **26**, which were isolated in 65% and 55% isolated yield, respectively (Scheme 3). In addition, the treatment of **21** with phenyl isothiocyanate afforded **22** in 73% yield.

In conclusion, this Communication describes a Pt-catalyzed method for the terminal-selective C(sp^3)−H oxidation of protonated aliphatic amines using Cu^{II} as the terminal oxidant. These reactions proceed with some of the highest TONs and selectivities reported to date for Pt-catalyzed alkane oxidation.

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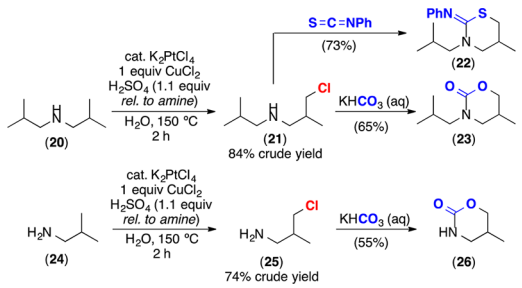
Scheme 3. Pt-Catalyzed C(sp^3)−H Chlorination and Subsequent Functionalization of 20 and 24



We propose that protonation of the amine is critical to the success of these transformations for several reasons. First, protonation renders the substrates water-soluble. Second, protonation prevents deactivation of the catalyst/oxidant by amine binding. Finally, the inductive electron-withdrawing ammonium cation electronically deactivates proximal C−H bonds, resulting in high selectivity for terminal C(sp^3)−H sites that are remote to nitrogen. Efforts to design second-generation Pt catalysts that exhibit enhanced efficiencies and terminal selectivities in this transformation are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09099.

Experimental and spectral details for all new compounds and all reactions reported as well full details on selectivity determination from crude reactions (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (c) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437. (d) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (e) Pérez, P. J. *Alkane C-H Activation by Single-Site Metal Catalysis*; Pérez, P. J., Ed.; Catalysis by Metal Complexes, Vol. *38*; Springer: Dordrecht, The Netherlands, 2012.

(2) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992.

(3) (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (c) Nam, W. *Acc. Chem. Res.* **2007**, *40*, 522. (d) White, M. C. *Science* **2012**, *335*, 807.

(4) (a) Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. (c) Shilov, A. E.; Shteinman, A. A. *Coord. Chem. Rev.* **1977**, *24*, 97.

(5) (a) Gol'dshlger, N. F.; Tyabin, M. B.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1969**, *43*, 2174. (b) Gol'dshlger, N. F.; Eskova, V. V.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim.* **1972**, *46*, 1353.

(6) (a) Labinger, J. A.; Herring, A. M.; Lyon, D. K.; Luinstra, G. A.; Bercaw, J. E.; et al. *Organometallics* **1993**, *12*, 895. (b) Labinger, J. A.; Herring, A. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 5628.

(7) For synthetic applications, see: (a) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1242. (b) Basickes, N.; Sen, A. *Polyhedron* **1995**, *14*, 197−202. (c) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (d) Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. *J. Am. Chem. Soc.* **2001**, *123*, 1000. (e) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375. (f) Weinberg, D. R.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2007**, *26*, 167. (g) Chen, G. S.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2009**, *28*, 4899.

(8) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(9) For examples of the α-C−H oxygenation of amines, see: (a) Kim, S.; Ginsbach, J. W.; Lee, J. Y.; Peterson, R. L.; Liu, J. J.; Siegler, M. A.; Sarjeant, A. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2015**, *137*, 2867. (b) Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. *J. Am. Chem. Soc.* **2013**, *135*, 12346. (c) Ling, Z.; Yun, L.; Liu, L.; Fu, X.; Wu, B. *Chem. Commun.* **2013**, *49*, 4214. (d) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M. *Chem. Sci.* **2011**, *2*, 2187. (e) Park, J.; Morimoto, Y.; Lee, Y.-M.; You, Y.; Nam, W.; Fukuzumi, S. *Inorg. Chem.* **2011**, *50*, 11612. (f) Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

(10) (a) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129. (b) Smalley, A. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 10632.

(11) For examples of protected amines as directing groups for C(sp^3)−H oxidation, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Zhang, S.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (c) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J. Q. *Nat. Chem.* **2014**, *6*, 146.

(12) For a complementary strategy involving terminal-selective, Ir-catalyzed C−H borylation of aliphatic amines, see: Li, Q.; Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 8755.

(13) Isaacs, N. S. *Physical Organic Chemistry*. 2nd ed.; Longman Group Limited: London, 1995; p 146−192.

(14) Inductive electron-withdrawing groups are known to deactivate adjacent C−H bonds toward Pt-catalyzed C(sp^3)−H activation. For example, see ref 7d and the following: Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560.

(15) For a later example of $CuCl_2$ as an oxidant in Shilov chemistry, see ref 7e and the following: Wang, Z.; Sugiarti, S.; Morales, C. M.; Jensen, C. M.; Morales-Morales, D. M. *Inorg. Chim. Acta* **2006**, *359*, 1923.

(16) (a) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.

(17) The only internal chain oxidation products detected in more than trace quantities were at the site that is one carbon away from the terminal position. Additionally, only small amounts of products derived from C−H functionalization on the pyrrolidine ring were observed, except with *N*-ethylpyrrolidine. In the latter case, we estimate that ∼15% of ring oxidation products are formed.

(18) The yields are based on $CuCl_2{\cdot}2H_2O$ as the limiting reagent. Since Cu is a $1e^-$ oxidant, 100% yield = 0.5 × mmol $CuCl_2{\cdot}2H_2O$ added to the reaction. Yields above 100% reflect regeneration of Cu by ambient air.

(19) The NMR yield of the C−H hydroxylation to form **4** under our standard conditions was 142%. When this same reaction was conducted under an atmosphere of N_2 (rather than air), a significantly lower yield of 41% was obtained. Furthermore, when the reaction under air was conducted in a small vessel (4 mL vs 10 mL sealed vial), the yield decreased to 47%. All of these pieces of data are consistent with the proposal that the O_2 (in air) is turning over the Cu.

(20) (a) Luinstra, G. A.; Wang, L.; Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Organomet. Chem.* **1995**, *504*, 75. (b) DeVries, N.; Roe, D. C.; Thorn, D. L. *J. Mol. Catal. A: Chem.* **2002**, *189*, 17.

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