Transition-Metal Catalysis

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Silver-Catalyzed Intermolecular Amination of C–H Groups**

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Despite advances made in the past, the direct transformation of saturated C–H bonds into different functional groups remains a challenging task.[1] Nitrogen-containing functional groups are prevalent in various natural products and pharmaceutical reagents. As a result, new methods to introduce C–N functionality by direct C–H activation are both important and highly desirable. In recent years, iminoiodanes ($PhI{=}NSO_2R$) have been broadly utilized as nitrene precursors to access nitrogen-containing molecules. However, success has been mostly restricted to aziridination of olefins, sulfoxide imination, and intramolecular C–H amidation.[2]

C–H amination chemistry has long been an active research area. In the past two decades, various catalysts utilizing iron, manganese, rhodium, ruthenium, and copper have been developed to mediate nitrene insertion reactions.[3–7] Advances have also been made in the amination of unactivated hydrocarbons, including a copper trispyrazolylborate system[7b] as well as rhodium-based systems.[5] We have reported a disilver(I) compound $[Ag_2(t\mathrm{Bu_3tpy})_2(NO_3)](NO_3)$ (**1**; $t\mathrm{Bu_3tpy}$ = 4,4′,4″-tri-*tert*-butylterpyridine) that efficiently catalyzes olefin aziridination[8] and intramolecular C–H amidation reactions.[9] However, the intramolecular C–H amidation reactions with **1** must be carried out at 82 °C. Also, **1** fails to induce intermolecular C–H amination even at high temperatures. These shortcomings prompted us to seek ways to improve the efficiency of the silver-based system.

We hypothesized that with a less electron-donating ligand system, we might enhance the electrophilicity of the putative silver intermediate responsible for oxidation of C–H groups. We tested a range of different synthetic and commercially available bidentate ligands. To our delight, a complex of silver(I) trifluoromethanesulfonate (AgOTf) with 4,7-diphenyl-1,10-phenanthroline (bathophenanthroline, bp) worked as an excellent catalyst for intramolecular C–H amidations. This new catalyst **2** efficiently converts a secondary C–H bond (**3a**) into the cyclized product at 50 °C in dichloromethane with $PhI(OAc)_2$ as the oxidant [Eq. (1)]. The 75% yield of isolated product for this reaction is significantly higher than that obtained with catalyst **1** at 82 °C (58%).[9] Other substrates could be readily oxidized to give the expected products in good yields, as well [Eqs. (2)–(4)]. Furthermore, **2** is easily prepared from cost-efficient and commercially available chemicals.[10a]

We then tested the more challenging intermolecular C–H amination reaction. As shown in Table 1, silver complex **2** was able to catalyze intermolecular C–H aminations using the oxidant PhI=NNs (Ns = *p*-nitrosulfonyl) as the nitrene source; the resulting NsNH group is easily deprotected to afford amines. Good yields were achieved with exclusive regioselectivity for benzylic C–H bonds (entries 1–5, Table 1). While exploring related reactions, Pelletier and Powell reported a copper phenanthroline system that is capable of catalyzing amination of benzylic C–H bonds.[7c] Previously, Pérez and co-workers reported intermolecular aminations of inert C–H bonds catalyzed by a copper-based system; however, a special electron-deficient ligand had to be employed in that case.[7a] Our catalyst seems to be more reactive than the copper phenanthroline system in its ability to functionalize inert C–H bonds of alkanes. We observed amination of cyclohexane and cyclopentane, albeit with lower yields than for benzylic C–H groups (entries 6–9, Table 1).[10] With mesitylene as the hydrocarbon substrate, primary benzylic C–H activation could also be observed (entry 10,

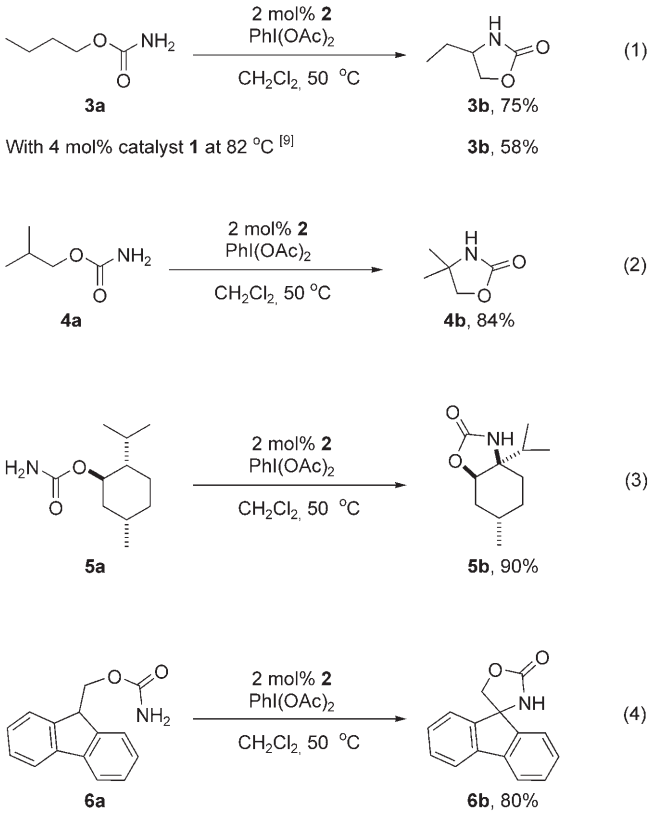

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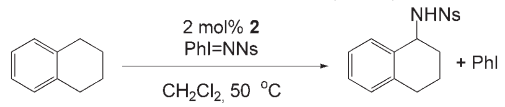
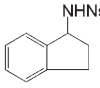
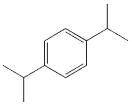
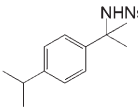
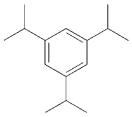
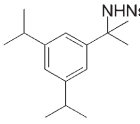
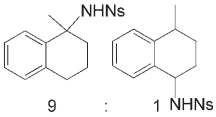
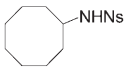
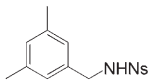
Table 1: Intermolecular C–H amination catalyzed by **2**.



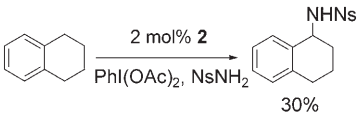
Entry	Substrate	Product	Yield[a]
1			70[b]
2			68[b]
3			57[b]
4			65[b]
5			71[b,c]
		9 : 1	
6			40[d]
7			35[d]
8			33[d]
9			39[b,e]
10			25

[a] Yield of isolated product. [b] Carried out on a 0.25-mmol scale with 5:1 hydrocarbon/PhI=NNs in 4 mL CH_2Cl_2. [c] The product ratio was determined by ^{1}H NMR spectroscopy. [d] Carried out on 0.5-mmol scale with 10:1 hydrocarbon/PhI=NNs in 4 mL CH_2Cl_2. [e] Other two isomers were also detected by ^{1}H NMR spectroscopy as minor products. Major product/minor products = 88:12.

Table 1). Although modest yields were obtained for inert C–H substrates with the current catalytic system, this discovery of intermolecular C–H amination is the first for silver-based catalysis and opens opportunities for further developments.

Instead of PhI=NNs, we also attempted to use $NsNH_2$ as the nitrene source in combination with commercially available oxidants. The use of $PhI(OAc)_2$ gave the expected amination product with a lower yield [ca. 30%, Eq. (5)] than with PhI = NNs, while persulfate and peroxides showed no reactivity.

Why is **2** an active catalyst? The crystal structure of this compound shows a disilver(I) core with two bp ligands



(5)

stacked over each other (Figure 1). The stacking pattern of this complex is similar to that of dipalladium(II) phenanthroline complexes.[12] Ag2 is coordinated in a distorted square-

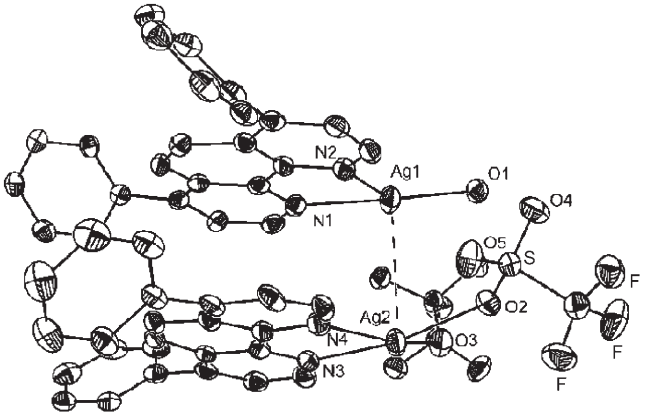
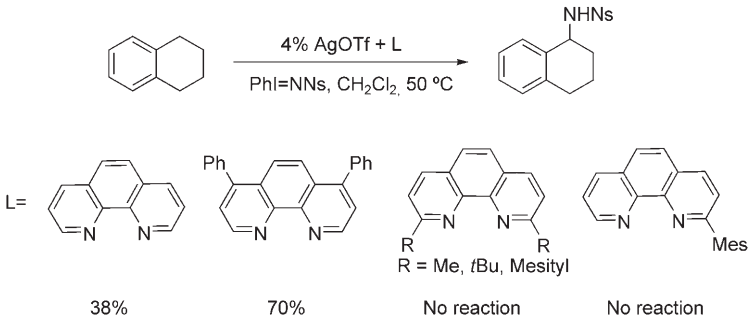


Figure 1. Crystal structure of complex **2**. Thermal ellipsoids are set at 50% probability. H atoms are not shown. Selected bond lengths [Å] and angles [°]: Ag1-Ag2 3.386(1), N1-Ag1 2.248(3), N2-Ag1 2.319(3), O1-Ag1 2.194(2), N3-Ag2 2.318(3), N4-Ag2 2.352(3), O2-Ag2 2.349(2), O3-Ag2 2.547(3); N1-Ag1-N2 72.78(10), N1-Ag1-O1 152.24(10), N2-Ag1-O1 131.93(10), O2-Ag2-N3 164.41(9), O3-Ag2-N4 154.41(9), N3-Ag2-N4 70.95(11), O2-Ag2-O3 81.79(9).

planar geometry by two nitrogen atoms from bp and two OTf^- ions. Ag1 is bound in a distorted three-coordinate geometry with a terminal water ligand, which is within hydrogen-bonding distance (O1···O4 and O1···O5 ca. 2.8 Å) of the OTf^- ions bound to Ag2. The silver–silver separation of 3.386 Å observed in the structure indicates a weak interaction.[11]

A common feature shared by precatalysts **1** and **2** is a disilver core in their crystal structures. It is hard to believe that this similarity is just a coincidence. Many other silver compounds have been tested and failed to mediate C–H amination. To probe whether the dinuclear feature is important for the catalytic oxidation activity, we investigated the reactivity of various substituted phenanthroline derivatives. Studies of substitution effects on palladium phenanthroline complexes have shown that 2,9-substituted phenanthrolines prevent formation of dinuclear palladium species in the crystalline form, while dinuclear structures are favored with complexes of palladium with unsubstituted phenanthroline.[12,13] Using the intermolecular amination reaction shown in Scheme 1, we probed the activity of silver complexes with different phenanthroline derivatives. None of the complexes with derivatives substituted in the 2- and 9-positions catalyze the C–H amination reaction.[10] The silver(I) complex with unsubstituted phenanthroline showed some conversion, but its low solubility in organic solvents limited its activity and thus its utility. We then tested a phenanthroline ligand with monosubstitution in the 2-position. Again, no activity was observed when its silver complex was employed in the test reaction. Substitution in the 2- or 9-position (or both) of phenanthroline prevents formation of dinuclear metal complexes.[12,13] These results, together with our pre-



Scheme 1. The effect of ligand substitution on silver amination chemistry. All reactions were carried out with 0.25 mmol PhI=NNs and five equivalents hydrocarbon; yields of isolated product are given.

vious observation of C–H functionalization with disilver(I) catalyst **1**, strongly indicate the requirement of a dinuclear core for catalyzing nitrene transfer oxidation chemistry in silver complexes. Considering the high oxidation potentials of silver ions, a two-electron oxidation of the disilver(I) catalyst to form a disilver(II) nitrene intermediate with the nitrene species bridging two silver ions is an attractive hypothesis. Moreover, with two silver(I) ions involved in catalysis, potential radical pathways with mononuclear silver compounds may be avoided.

We report herein a silver-catalyzed intermolecular amination of saturated C–H bonds to install C–N groups. This catalytic system is not only efficient at activating benzylic C–H bonds but also capable of functionalizing inert cycloalkanes.[14] Structural characterization of the catalyst revealed a disilver core, a feature resembling the only other known silver-based nitrene transfer catalyst **1**, discovered by us previously. Based on this common feature and on studies of substitution effects of phenanthroline ligands, we believe a dinuclear core is key to silver-based nitrene transfer. Future mechanistic studies to understand the system, together with catalyst design for achieving better reactivity, will focus on exploiting this unique property. These investigations are currently underway.

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[1] a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808 – 1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698 – 1712; b) S. Doye, *Angew. Chem.* **2001**, *113*, 3455 – 3457; *Angew. Chem. Int. Ed.* **2001**, *40*, 3351 – 3353; c) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861 – 2903; d) K. Godula, D. Sames, *Science* **2006**, *312*, 67 – 72; e) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483 – 11498; f) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928 – 8933; g) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911 – 935.

[2] a) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571 – 1586; b) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905 – 2919; c) H. M. L. Davies, M. S. Long, *Angew. Chem.* **2005**, *117*, 3584 – 3586; *Angew. Chem. Int. Ed.* **2005**, *44*, 3518 – 3520; d) H. Okamura, C. Bolm, *Chem. Lett.* **2004**, *33*, 482 – 487; e) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217 – 6254; f) Z. Li, C. He, *Eur. J. Org. Chem.* **2006**, 4313 – 4322; g) S. S. Stahl, *Science* **2005**, *309*, 1824 – 1826.

[3] a) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728 – 6729; b) X.-Q. Yu, J.-S. Huang, X.-G. Zhou, C.-M. Che, *Org. Lett.* **2000**, *2*, 2233 – 2236; c) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *Acc. Chem. Res.* **1997**, *30*, 364 – 372.

[4] a) I. B. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087 – 1105; b) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378 – 15379.

[5] a) R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013 – 5016; b) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd, P. Dauban, *Angew. Chem.* **2006**, *118*, 4757 – 4760; *Angew. Chem. Int. Ed.* **2006**, *45*, 4641 – 4644; c) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562 – 568; d) H. Lebel, K. Huard, *Org. Lett.* **2007**, *9*, 639 – 642; e) C. G. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618 – 620; *Angew. Chem. Int. Ed.* **2001**, *40*, 598 – 600.

[6] S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung, C.-M. Che, *J. Am. Chem. Soc.* **1999**, *121*, 9120 – 9132.

[7] a) A. Caballero, M. M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *J. Am. Chem. Soc.* **2003**, *125*, 1446 – 1447; b) M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc.* **2006**, *128*, 11784 – 11791; c) G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031 – 6034.

[8] a) Y. Cui, C. He, *J. Am. Chem. Soc.* **2003**, *125*, 16202 – 16203; b) Z. Li, X. Ding, C. He, *J. Org. Chem.* **2006**, *71*, 5876 – 5880.

[9] Y. Cui, C. He, *Angew. Chem.* **2004**, *116*, 4306 – 4308; *Angew. Chem. Int. Ed.* **2004**, *43*, 4210 – 4212.

[10] For experimental details, please see the Supporting Information.

[11] S.-L. Zheng, J.-P. Zhang, W.-T. Wong, X.-M. Chen, *J. Am. Chem. Soc.* **2003**, *125*, 6882 – 6883.

[12] C. Borriello, R. Centore, G. Roviello, *Inorg. Chem. Commun.* **2005**, *8*, 755 – 758.

[13] R. Santi, A. M. Romano, R. Garrone, R. Millini, *J. Organomet. Chem.* **1998**, *566*, 37 – 43.

[14] For preliminary results with aliphatic linear hydrocarbons, please see the Supporting Information.

