Remarkably Efficient Olefin Aziridination Mediated by a New Copper(II) Complex

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Summary: *The structurally characterized copper complex [(i-Pr$_3$TACN)Cu(O$_2$CCF$_3$)$_2$] (**1**) mediates nitrene transfer from PhINTs to olefins to form N-tosylaziridines in good to excellent yields, in catalytic amounts (0.5 mol %) 1 order of magnitude less than is required for other copper catalysts, such as [Cu(acac)$_2$]. Nitrene transfer reactivity has also been observed with substituted styrenes, internal and terminal aliphatic olefins, and sulfides, suggesting that **1** may be a general nitrene transfer catalyst for use on organic synthesis.*

The efficient catalytic preparation of aziridines remains an enticing goal, due both to the importance of the aziridine ring in organic synthesis[1] and also to the presence of functionally significant aziridine groups in several naturally occurring antitumor antibiotics.[2] Two complementary catalytic routes to aziridines involve either transition metal mediated nitrene transfer to alkenes[3a−c] or Lewis acid (or transition metal) promoted carbene addition to imines;[3d−g] both of these routes have been exploited in asymmetric applications.[4] Copper-catalyzed alkene aziridinations, such as those developed by Evans and co-workers,[3a,c] are typically conducted using *N*-tosyliminophenyliodinane (PhINTs) as the nitrene source,[5] with 5−10 mol % copper catalyst. This methodology has been shown to yield a variety of aziridines in good to excellent yields. Indeed, this aziridination, catalyzed by [Cu(acac)$_2$], was incorporated into the total synthesis of pancratistatin, an antitumor alkaloid.[6] Our interest in metal-mediated group transfer reactions led us to examine catalytic aziridinations with the intent of preparing well-defined precatalysts possessing both high reactivity and broad substrate tolerance. Herein we report the synthesis and structural characterization of a new copper(II) complex that exhibits remarkable reactivity in the aziridination of styrene, such that as little as 0.5 mol % of the complex (*an order of magnitude less* than for other copper catalysts) provides high yields of *N*-tosyl-2-phenylaziridine. Furthermore, the demonstrated reactivity of this complex in nitrene transfer to other substrates suggests potential broad applicability in organic synthesis.

Consideration of the proposed active intermediate in copper-catalyzed olefin aziridinations, a highly oxidized (yet poorly characterized) copper−nitrene species,[7] led us to speculate that such an intermediate could be stabilized by the presence of an electron-rich, sterically hindered ancillary ligand. Furthermore, formation of this intermediate from its precursors (a copper complex and PhINTs) might be expedited by the presence of other labile ligands or counterions bound to the precatalyst. Such a species, [(*i*-Pr$_3$TACN)Cu(O$_2$CCF$_3$)$_2$] (**1**; *i*-Pr$_3$TACN = 1,4,7-triisopropyl-1,4,7-triazacyclononane),[8] was prepared by the reaction of *i*-Pr$_3$TACN with anhydrous CuCl$_2$ in CH$_3$CN, followed by addition of AgO$_2$CCF$_3$ (2 equiv). Filtration of AgCl followed by recrystallization from Me$_2$CO/Et$_2$O provided large blue crystals of **1** in 75−85% yield on a multigram scale.[9] The X-ray crystal structure of **1** (Figure 1) reveals a typical distorted-square-pyramidal geometry ($\tau = 0.22$) for the central copper(II) ion as well as two monodentate trifluoroacetate ligands.[10] Significant differences exist between the solid-state structures of **1** and the related compound [(*i*-Pr$_3$TACN)Cu(O$_2$CCH$_3$)$_2$],[11] in which one

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(9) Full synthetic details and characterization data are provided as Supporting Information.

(10) Blue crystals of **1** ($C_{19}H_{33}N_3F_6O_4Cu$) are monoclinic, space group $P2_1/n$, with $a = 11.016(2)$ Å, $b = 16.460(3)$ Å, $c = 13.460(3)$ Å, $\beta = 94.01(3)°$, $V = 2434(2)$ Å^3, and $Z = 4$ at 25 °C. Full-matrix least-squares refinement on F^2 provided the current residuals R1 = 0.0833, wR2 = 0.2513, and GOF = 1.045 for 2274 reflections with $I > 2\sigma(I)$, 298 variables, and 30 geometric restraints on the $-CF_3$ groups.

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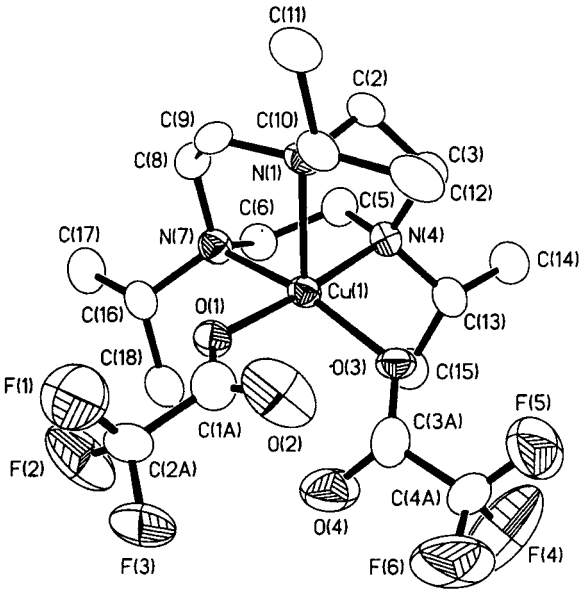

Figure 1. Thermal ellipsoid representation of the X-ray crystal structure of **1** (35% probability boundaries) with hydrogen atoms omitted for clarity. Selected interatomic distances (Å) and angles (deg): Cu1−O1, 1.962(5); Cu1−O3, 1.936(6); Cu1−N1, 2.242(7); Cu1−N4, 2.066(7); Cu1−N7, 2.084(7); O1−Cu1−O3, 94.5(2); N4−Cu1−N7, 84.9(3); O1−Cu1−N4, 174.8(3); O1−Cu1−N7, 90.3(2); O3−Cu1−N4, 90.7(2); O3−Cu1−N7, 161.7(3); N1−Cu1−N4, 85.1(3); N1−Cu1−N7, 85.9(3); N1−Cu1−O1, 92.7(2); N1−Cu1−O3, 111.4(3).

of the acetate ions binds to the central copper ion in an asymmetric bidentate fashion. The lack of such behavior in the trifluoroacetate ligands of **1** may be rationalized by invoking unfavorable steric interactions between the trifluoromethyl groups and the *N*-isopropyl groups on the triaza macrocycle. In CH_3CN solution **1** exhibits an electronic transition at 684 nm ($\epsilon = 110\ M^{-1}\ cm^{-1}$), the energy and intensity of which remains constant over a concentration range of 12−0.5 mM. Thus, **1** is stable toward decomposition (i.e., dissociation of *i*-Pr_3TACN) in dilute solutions, such as those in which catalytic nitrene transfer reactions were examined.

The efficacy of **1** to catalyze the aziridination of olefins using PhINTs as the nitrene source was probed using styrene as a model substrate (Scheme 1). As shown in Table 1, the reaction of styrene with PhINTs in the presence of **1** (5 mol % vs PhINTs, entry 1) proceeded smoothly to provide high yields of pure *N*-tosyl-2-phenylaziridine.[9] Most remarkable were the results obtained when smaller amounts of **1** were added to the reaction mixture. Yields of pure aziridine remained excellent and reaction times reasonable even when as little as 0.5 mol % of **1** was added (entries 2−4). Parallel aziridination experiments conducted in the presence of catalytic amounts of $[Cu(acac)_2]$ (0.5 mol %) provided lower yields of *N*-tosyl-2-phenylaziridine (45−55% yield vs PhINTs), and extended reaction times (36−48 h) were required for completion of the reaction. Below 0.5 mol % of **1** (entry 5, 0.34 mol % of **1**), pure aziridine product could still be isolated, albeit in slightly lower (67%) yield. Thus, the active catalyst generated from **1** retains its high reactivity and selectivity (aziridination vs decomposition of the iodinane to *p*-toluenesulfonamide) even when used in the presence of a large molar excess of PhINTs. The choice of solvent was important for the reactivity of **1**, as aziridinations conducted either in CH_2Cl_2 or in neat styrene yielded negligible amounts of aziridine product, an observation which suggests that a solvento complex, such as $[(i\text{-}Pr_3TACN)Cu(CH_3CN)_n]^{2+}$ ($n \geq 1$), may be important for catalysis.

Scheme 1

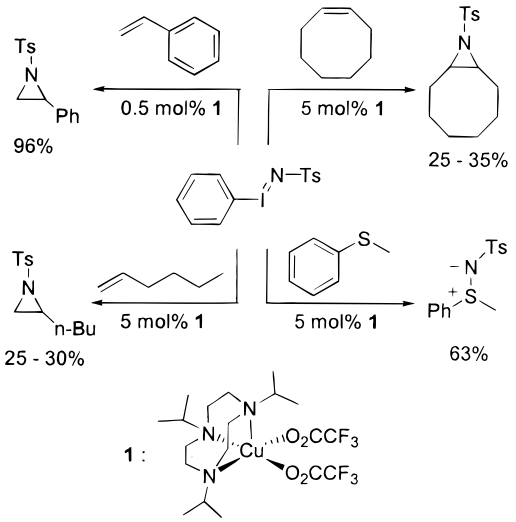

Table 1. Aziridination of Styrene Mediated by 1[a]

entry	amt of **1**, mol %[b]	yield, %[c]	time, h[d]
1	5.0	95	3
2	1.0	99	16
3	0.75	99	16
4	0.50	96	16
5	0.34	67	20
6	0	0	24

[a] All reactions were conducted with 0.3−1.0 mmol of PhINTs and 10−20 equiv of styrene vs PhINTs, in 1−2 mL of CH_3CN at 25 °C. [b] Calculated vs PhINTs. [c] Yield of isolated, recrystallized product vs PhINTs as the limiting reagent, which represents the average yield of at least three independent trials. [d] Reaction time elapsed before workup. Reactions were complete (as judged by the dissolution of PhINTs) prior to this time.

Preliminary experiments indicate that **1** is a general catalyst for nitrene transfer to organic substrates (Scheme 1). Electronically diverse *para*-substituted styrenes undergo aziridination by PhINTs in the presence of **1**. For example, *N*-tosyl-2-(4-methoxyphenyl)-aziridine and *N*-tosyl-2-(4-chlorophenyl)aziridine were produced in 73% and 84% yields, respectively, from their appropriately *para*-substituted precursors (1 mol % of **1**, 6 h).[9] Nitrene transfer reactivity is not limited to aromatic alkenes; aziridination of 1-hexene and *cis*-cyclooctene afforded the corresponding pure *N*-tosyl-aziridines (5 mol % of **1**, 50 equiv of substrate, 24 h), although yields were modest (25−35%) and large excesses of the aliphatic alkenes were required.[9,12,13] Furthermore, the catalytic sulfimidation of thioanisole was examined (PhINTs, 1 equiv of PhSMe, 5 mol % of **1**), which resulted in the production of *S*-methyl-*S*-phenyl-*N*-tosylsulfilimine in 63% yield (24 h).[9,13,14] While

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(12) The *cis* stereochemistry of the aziridine derived from cyclooctene, *N*-tosyl-9-azabicyclo[6.1.0]nonane, was confirmed by X-ray crystallography: Emerson, J. P.; Halfen, J. A. Unpublished results.

(13) A catalyst loading of 5 mol % **1** vs PhINTs was used in order to expedite completion of these rather sluggish reactions.

the scope of the reactivity of **1** in nitrene transfer reactions has yet to be completely delineated, it is evident that the complex possesses significant substrate tolerance and potential broad applicability in catalyzing organic transformations.

Herein we have demonstrated that catalytic amounts of **1** effect the aziridination of styrene using PhINTs as the nitrene source. Most significant is the discovery that only very small amounts of **1** (0.5 mol % vs PhINTs) are required to cleanly catalyze nitrene transfer to styrene. This represents an improvement by 1 order of magnitude over the efficiency of other reported copper catalysts, such as $[Cu(acac)_2]$, which afforded substantially reduced yields of aziridine products under parallel reaction conditions. Demonstration of reactivity with other alkene and sulfide substrates indicates that **1** may find use in a variety of metal-catalyzed nitrene transfer reactions. The scope of the reactivity and the mechanism(s) of nitrene transfer to alkenes and sulfides catalyzed by **1** are topics of continued study in this laboratory.

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Supporting Information Available: Text giving synthetic details and characterization data for **1** and all aziridine products and methodology for the catalytic nitrene transfer reactions and tables giving X-ray structural information for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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