Mechanism of the (Diimine)copper-Catalyzed Asymmetric Aziridination of Alkenes. Nitrene Transfer via Ligand-Accelerated Catalysis

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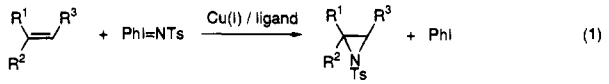
The recently discovered asymmetric alkene aziridination reaction (eq 1) is a mechanistically intriguing transformation that holds considerable potential as a synthetic method.[1] The



(1)

identification of Cu(I) complexes as the most effective catalysts for this process[2,3] has raised the possibility that aziridination might share fundamental mechanistic features with olefin cyclopropanation, a reaction long known to be catalyzed by the same class of complexes.[4] By analogy to cyclopropanation, for which the generally accepted mechanism involves a discrete Cu–carbenoid intermediate,[5] copper-catalyzed aziridination might thus proceed via a discrete Cu–nitrenoid intermediate (Scheme 1a). However, a very legitimate mechanistic alternative involves the copper complex functioning as a Lewis acid catalyst. Support for the latter includes the fact that epoxidations with iodosylbenzene (PhIO) and aziridinations with PhI=NTs have been effected with simple Lewis acids incapable of redox chemistry,[2b,6] and that PhI=NTs is the only nitrene source that has been used successfully thus far in asymmetric catalytic aziridinations. We report here an investigation into the mechanism of aziridination with (diimine)copper(I) catalysts that provides strong evidence for a discrete Cu(III)–nitrene as the reactive intermediate and that suggests a remarkable similarity in the transition structure geometries in asymmetric cyclopropanation and aziridination reactions.

The role of the aryl iodide moiety in PhI=NTs is fundamentally different in the two mechanisms outlined in Scheme 1. In the redox mechanism (Scheme 1a), PhI is fully dissociated from the aziridinating species, whereas it is covalently attached to the active intermediate in the Lewis acid catalysis mechanism (Scheme 1b). Thus, structural modifications on the aryl iodide would be expected to exert an influence on enantioselectivity only in the latter case. As demonstrated in Table 1, aziridinations of several alkenes catalyzed by $CuPF_6$ in the presence of ligand **15** occurred with indistinguishable enantioselectivities with either PhI=NTs or the tosyliminoiodoarene **17**.

Scheme 1

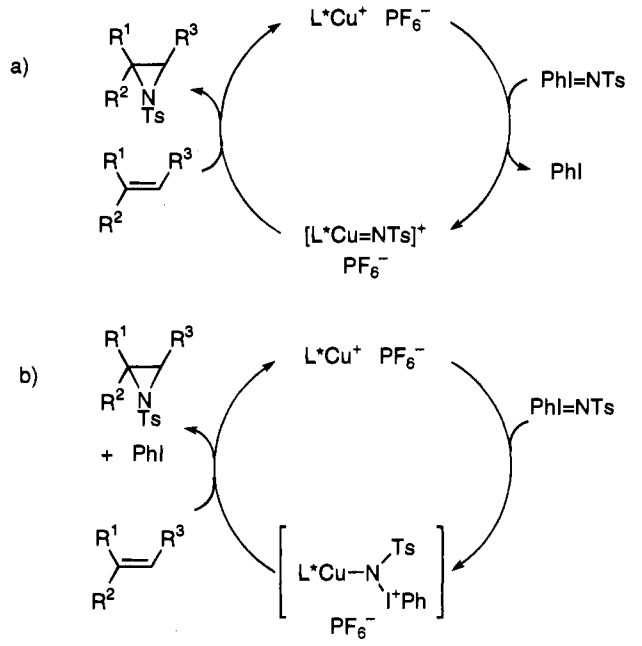
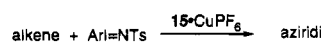
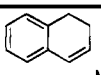
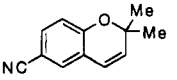
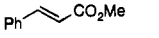
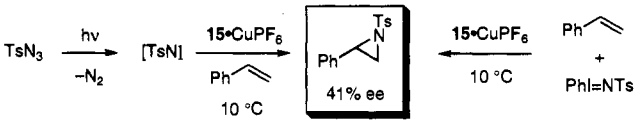


Table 1



Entry	Substrate	aziridine ee (%) Ar = Ph	aziridine ee (%) Ar = t-Bu, Me, Me (Me (17))
1		62	63
2		82-85	84
3		71	70
4		42	39-43

Scheme 2



The most compelling evidence for the intermediacy of a discrete (diimine)Cu=NTs intermediate was obtained from studies using tosyl azide (TsN_3) as a stoichiometric nitrene source. Under photochemical conditions, TsN_3 is known to extrude dinitrogen to generate a reactive free nitrene intermediate.[7,8] In the presence of catalytic amounts of the (diimine)-copper(I) complex **15**•$CuPF_6$, the photochemical reaction of TsN_3 with styrene afforded aziridine with the same enantioselectivity obtained in the catalytic aziridination reaction (Scheme 2). This parity is clearly indicative of a common Cu–nitrene intermediate.

(1) (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326–7. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–9. (c) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631–4.

(2) The utility of Cu-based catalysts in olefin aziridination was first identified by Evans. (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744–6. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. See also: (c) Pérez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1993**, *12*, 261–2.

(3) Aziridination with non-copper-based catalysts: (a) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161–3. (b) O'Connor, K. J.; Wey, S.-J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001–4. (c) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469–71.

(4) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–8.

(5) Doyle, M. P. in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 3.

(6) Yang, Y.; Diederich, F.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7195–205.

(7) Smolinsky, G.; Wasserman, E.; Yager, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3220–1.

(8) Thermal, metal-catalyzed aziridinations with tosyl azide: (a) Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951–3. (b) Migita, T.; Chiba, M.; Takahashi, K.; Saiton, N.; Nakaido, S.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3943–4. (c) Reference 2b. The thermal reaction between styrene and TsN_3 catalyzed by Cu(diimine) complexes was found to be slow relative to the photochemical reaction.

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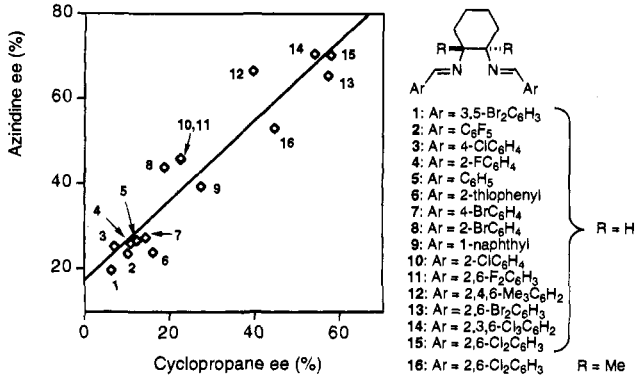

Figure 1. Plot of enantioselectivities obtained in the $CuPF_6$-catalyzed cyclopropanation and aziridination of 1,2-dihydronaphthalene using various chiral diimine ligands. Cyclopropane ee's correspond to those of the major, *trans*-cyclopropane product (trans/cis = 3−10:1). Reaction parameters for cyclopropanation and aziridination are provided in the supplementary material.

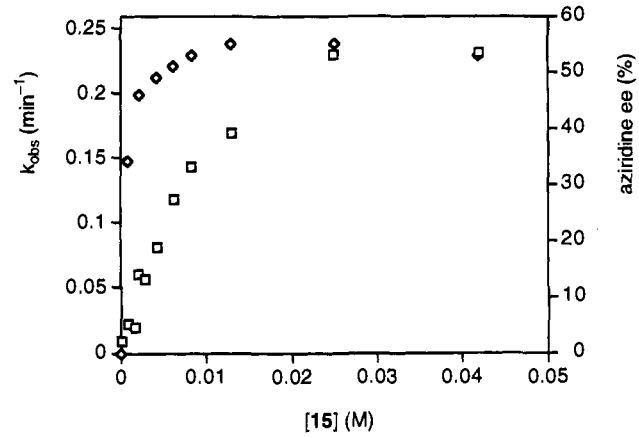

Figure 2. Plot of diimine ligand concentration vs observed rate constant k_{obs} (■) and % ee (◇) for the catalytic aziridination of 1,2-dihydronaphthalene. Conditions: CH_2Cl_2, 23 °C, [olefin] = 0.14 M, $[CuPF_6]$ = 8.3×10^{-3} M, PhI=NTs 1.1 equiv relative to olefin. Olefin disappearance was monitored by GC analysis relative to an internal standard.

The apparent involvement of a discrete, monomeric[9] copper−nitrene intermediate reinforces the mechanistic analogy between aziridination and cyclopropanation. A further comparison was drawn by relating the effect of ligand structure and electronics on enantioselectivity in the two reactions. The $CuPF_6$-catalyzed cyclopropanation of 1,2-dihydronaphthalene with ethyl diazoacetate was compared with aziridination of the same substrate with PhI=NTs as a function of different diimine ligands. As illustrated graphically in Figure 1, a reasonably good linear correlation exists between enantioselectivites in the two reactions.[10] This suggests that they not only proceed by similar mechanisms but the transition structure geometries in their selectivity-determining steps may be very similar.[11]

Despite the insolubility of PhI=NTs, well-behaved, reproducible kinetic measurements were readily obtainable in the (diimine)copper-catalyzed aziridination reaction. Thus, olefin disappearance was monitored over >3 half-lives and found to follow strict pseudo-first-order kinetics.[12] Reaction rates were not significantly affected by changes in the rate of stirring or by the amount of added PhINTs, but they were found to be strongly dependent on the concentration of added diimine ligand. For example, under the conditions outlined in Figure 2, aziridination of 1,2-dihydronaphthalene occurred with a pseudo-first-order rate constant $k_{obs} = 9.4 \times 10^{-3}$ min^{-1} in the absence of ligand; k_{obs} was found to increase asymptotically as a function of ligand to a maximum level of ≈0.24 min^{-1}. Thus, this catalytic reaction exhibits significant ligand acceleration, an important phenomenon which has been identified in several other asymmetric catalytic reactions.[13] As previously observed with ligand-accelerated reactions, enantioselectivities reached a maximum value at ligand concentrations lower than those required to obtain maximum rate.[14]

On the basis of the precedent for oxygen-atom transfer with PhIO,[6] it is reasonable to assume that catalytic aziridinations with PhINTs can occur by more than one mechanism. However, the evidence obtained thus far in the (diimine)copper-catalyzed reaction strongly implicates a redox mechanism in this particular system. Experiments aimed toward direct characterization of the Cu−nitrene intermediate are in progress.

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Supplementary Material Available: Full characterization of ligands **1**−**16** and experimental procedures for the aziridination and cyclopropanation reactions and for the kinetic experiments (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Evidence that Cu(diimine) intermediates involved in the aziridination reaction are monomeric was provided by examining the reaction of alkenes with PhI=NTs using ligands of varying enantiomeric composition.[1a] Essentially perfectly linear correlations between ligand ee and product ee were observed for several alkenes. Although the absence of nonlinear effects does not fully preclude participation of aggregated intermediates, it is clearly most consistent with a monomeric active species. See: (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. J. Am. Chem. Soc. **1986**, *108*, 2353−7. (b) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9 and references therein.

(10) For a study in which the diastereoselectivities in two different auxiliary-controlled reactions were correlated, see: Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184−6.

(11) For discussions of the mechanism of stereochemical induction in copper-catalyzed cyclopropanation reactions, see: Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553−65.

(12) Experimental details are provided as supplementary material.

(13) (a) Jacobsen, E. N.; Markó, I. E.; Mungall, W. S.; Schröder, G. W.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.*, in press.

(14) Jacobsen, E. N.; Markó, I. E.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.