

## Mechanistic Studies of Copper-Catalyzed Alkene Aziridination

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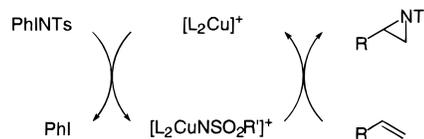
**Abstract:** The mechanism of the copper-catalyzed aziridination of alkenes using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhINTs) as the nitrene source has been elucidated by a combination of hybrid density functional theory calculations (B3LYP) and kinetic experiments. The calculations could assign a Cu(I)/Cu(III)-cycle to the reaction and demonstrate why a higher oxidation state of copper cannot catalyze the reaction. A mechanism whereby Cu(II)–catalyst precursors can enter the Cu(I)/Cu(III)-cycle is suggested. Three low-energy pathways were found for the formation of aziridines, where the two new N–C bonds are formed either in a nonradical concerted or consecutive fashion, by involvement of singlet or triplet biradicals. A close correspondence was found between the title reaction and the Jacobsen epoxidation reaction in terms of spin-crossings and the mechanism for formation of *cis/trans* isomerized products. The kinetic part of the study showed that the reaction is zero order in alkene and that the rate-determining step is the formation of a metallanitrene species.

## Introduction

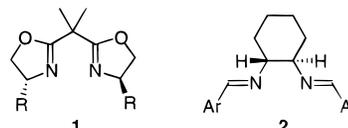
Enantioselective functionalization of simple alkenes by oxidative methods has experienced an explosive growth in the past decade. Reactions such as the Sharpless dihydroxylation<sup>1</sup> and aminohydroxylation,<sup>2</sup> and Jacobsen epoxidation<sup>3</sup> of unfunctionalized alkenes have had a tremendous impact in the field of asymmetric synthesis. Transition-metal catalyzed aziridination<sup>4</sup> has been less exploited despite the significant utility of aziridines in organic synthesis.<sup>5</sup> A recent development of this reaction makes use of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhINTs) as the nitrene source and a metal catalyst which mediates the cycloaddition to the alkene, yielding *N*-tosylaziridines (Scheme 1). The synthetic utility of the sulfonlated products has recently been enhanced by development of methods for selective cleavage of the protecting group<sup>6</sup> and introduction of alternative nitrogen sources.<sup>7</sup>

The literature on the metal-catalyzed<sup>8</sup> aziridination of alkenes is dominated by the work of Evans<sup>9,10</sup> and Jacobsen,<sup>11,12</sup> who also designed chiral ligands for the asymmetric reaction. The bisoxazoline ligands **1** of Evans are most successful for *trans*-

## Scheme 1. Copper-Catalyzed Aziridination of Alkenes



alkenes, whereas the Jacobsen system using dibenzylidene diimines **2** is better suited for aziridination of *cis*-alkenes.



In the title reaction, both Cu(I) and Cu(II) metal sources form competent catalysts and several observations strongly indicate that a common oxidation state is reached in both cases. Evans and co-workers showed that degree of *cis/trans* isomerization in the aziridination of (*Z*)-alkenes as well as the relative reactivity of various alkenes are independent of the initial catalyst oxidation state.<sup>10</sup> In the asymmetric version of the reaction, bisoxazolines **1** result in the same levels of asymmetric induction with CuOTf and Cu(OTf)<sub>2</sub>.<sup>9</sup>

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The authors suggest that the active catalyst is in the +II oxidation state and that PhINTs may act as an oxidant for Cu(I). This was supported by experiments where treatment of the CuOTf precatalyst with PhINTs in the absence of alkene gave a species indistinguishable (UV-vis) from that produced with Cu(OTf)<sub>2</sub> under identical conditions.<sup>8b,9</sup>

On the basis of kinetic studies using Cu(I)-bis(imine) catalysts, Jacobsen has concluded that the reaction is strictly first order in alkene and suggests a Cu(III)-nitrene species to be the reactive intermediate in a Cu(I)/Cu(III) catalytic cycle.<sup>12</sup> On the other hand, Pérez and co-workers suggest the catalytically active species to be Cu(II) in systems with monoanionic hydridotrispyrazolylborate ligands, thus involving a Cu(II)/Cu(≥II) cycle.<sup>13</sup>

The carbon-nitrogen bond formation step(s) may be either concerted or consecutive. Pérez investigated the Cu(II)-hydridotrispyrazolylborate-catalyzed aziridination by means of Hammett studies, which suggested a reaction between the alkene and an electrophilic radical species. The experimental data could be nicely fitted to a linear combination of Jackson's  $\sigma^*$  substituent constants and Hammett  $\sigma^+$  constants.<sup>13</sup>

Counterions markedly influence the stereochemical outcome of aziridination of (*Z*)-alkenes. Strongly coordinating counterions such as acetylacetonate and chloride favor isomerization of *cis*-stilbene and *cis*- $\beta$ -methylstyrene to the *trans*-aziridine products, possibly indicating an involvement of radical intermediates in the system.<sup>10</sup> In an attempt to find evidence for such species, aziridinations were carried out using a so-called hypersensitive radical probe as substrate. These experiments suggest a concerted reaction pathway for alkyl-substituted alkenes using CuClO<sub>4</sub> as catalyst in acetonitrile. However, *cis*-4-octene did not isomerize in the same system.<sup>10</sup> Thus, in parallel with results for the Jacobsen epoxidation reaction,<sup>14</sup> radicals might only be intermediates for substrates where significant stabilization occurs.

Further development of this reaction requires an increased understanding of the reaction mechanism. We have therefore performed a theoretical study using quantum chemical calculations in combination with kinetic experiments.

## Methods

**Computational Details.** All calculations reported in this work were conducted using the Gaussian 98 program.<sup>15</sup> Geometry optimizations were performed using the B3LYP hybrid functional,<sup>16</sup> together with the LANL2DZ ECP and basis set<sup>17</sup> (BSI). Intermediate energies were determined using B3LYP together with the 6-311+G(d) for Cu, N, O, S and alkene carbons; 6-31G was used for other atoms, whereas the SDD<sup>18</sup> ECP and basis set augmented with one set of f-polarization

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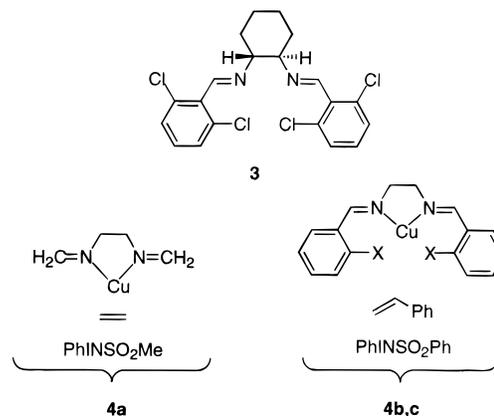
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**Figure 1.** Diimine **3**, used in the kinetic study and systems **4a-c** used in the calculations (**4b**:X = H, **4c**:X = Cl).

functions were used for iodine (BSII). An optimized f-polarization function was obtained by minimizing the B3LYP energy of the free atom in the ground state, resulting in an exponent of 0.2.<sup>19</sup> Final energies were determined using B3LYP together with the 6-311+G(2d) for Cu, N, O, S and C(alkene); 6-31G(d,p) was used for other atoms and BSII for iodine (BSIII). Normal modes and zero point corrections (ZPC) were calculated for some selected points using B3LYP/BSI.

**Model System.** A neutral ligand was chosen due to the high enantioselectivities obtained using such ligands. The diimine ligand **3** of Jacobsen was selected due to the published kinetic study<sup>12</sup> and the simple synthesis of this ligand.<sup>11,20</sup> The calculations were performed both on a minimal model system **4a** with methyl or hydrogen as models for the aryl moieties, and on larger systems where all aromatic moieties were retained, **4b** and **c** (Figure 1).

The calculations were mainly performed using Cu(I) as the initial oxidation state as postulated by Jacobsen.<sup>12</sup> A catalytic cycle starting with Cu(II) reacting with PhINTs would formally yield a Cu(IV)-nitrene species, which in our opinion seems unlikely to be a catalytically active species. Some calculations were performed on the dicationic Cu(II) system in order to compare its relevance with that of the Cu(I)/Cu(III) catalytic cycle.

**Kinetic Experiments.** Kinetic data were obtained from the aziridination of 1,2-dihydronaphthalene by (*N*-(*p*-toluenesulfonyl)imino)-phenyliodinane (PhINTs) with a catalyst generated in situ from Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> and diimine **3**, and the reaction was performed at 0-2 °C. Alkene consumption was monitored by gas chromatography, using *n*-dodecane as internal standard.

## Experimental Section

**General Methods.** All reactions were run under an argon atmosphere, using oven-dried glassware and magnetic stirring. Molecular sieves were activated at 250 °C and 0.5  $\mu$ bar for 24 h and then stored in a drybox. Methanol was heated at reflux over magnesium turnings for several hours and then distilled and stored over activated 3 Å molecular sieves under argon. Dichloromethane was distilled from powdered CaH<sub>2</sub> under nitrogen just prior to use. 1,2-Dihydronaphthalene was filtered through neutral alumina and freshly distilled. Diimine **3** was prepared according to a literature procedure.<sup>11</sup> Analytical GC was carried out using a Varian OV-5 column (30 m, 0.32 mm i.d., 0.25  $\mu$ m film) and N<sub>2</sub> as carrier gas. Neutral alumina (Merck, activity I) was used for the filtration of GC samples.

**Typical Procedure for the Kinetic Analyses.** In a 5 mL pear-shaped flask Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> (16 mg, 43  $\mu$ mol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) and stirred for 10 min under argon. The solution was filtered through a plug of glass wool to a three-necked flask containing a suspension of 1,2-dihydronaphthalene (130-260 mg, 1.0-2.0 mmol),

(19) For a similar determination, see Ehlers, E. W.; Böhme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 111.

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diimine ligand **3** (26 mg, 50  $\mu$ mol), internal standard (*n*-dodecane,  $\sim$ 110 mg) and activated MS 4 Å powdered molecular sieves ( $\sim$ 1 g) in  $\text{CH}_2\text{Cl}_2$  (10.0 mL). Complete transfer of  $\text{CuPF}_6$  was ensured by washing the glass wool with one portion of  $\text{CH}_2\text{Cl}_2$ , (1.0 mL). The mixture was stirred at room temperature for 45 min. The three-necked flask was immersed in an ice–water bath and its internal temperature allowed to stabilize at  $+0.4$  °C. An aliquot was taken at this point to establish the initial alkene/dodecane ratio, and then PhINTs<sup>21</sup> (500 mg, 1.3 mmol) was added in 4–6 portions during  $\sim$ 90 s.<sup>22</sup> Aliquots of 25  $\mu$ L were taken at intervals of ca. 40 s, diluted with EtOAc ( $\sim$ 1 mL), and filtered through a plug of neutral alumina.

**[*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane (PhINTs), Modified Procedure.**<sup>23</sup> A suspension of *p*-toluenesulfonamide (6.8 g, 40 mmol) and 85% KOH (6.5 g, 99 mmol) in methanol (60 mL), was cooled in an ice–water bath, and iodosobenzene diacetate (15 g, 47 mmol) was added portionwise over a period of 10–20 min, so that the internal temperature was maintained below  $+10$  °C. The reaction mixture was refrigerated at  $+5$  °C overnight and then filtrated. The filter-cake was washed with ice-cold MeOH (20 mL), and the solids were then dried at 0.5  $\mu$ bar for 10 h in a Kugelrohr oven at 25 °C, affording PhINTs as an off-white to yellowish solid (12 g, 80%), with properties as previously reported in the literature.<sup>23</sup>

## Results and Discussion

**The Dicationic System.** Calculations on dicationic systems are inherently less reliable than neutral or monocationic systems, as solvent and counterions (neglected in the calculations) can be expected to have a larger influence for the more charged systems. Nevertheless, some important clues to the mechanistic puzzle can be obtained from the calculations. The Cu–PhINTs complex **7** (Scheme 2) is easily formed, and will dissociate PhI in an exothermic reaction ( $\Delta E = -71$  kcal/mol). However, the dicationic form of **8** is unstable, with a very high electron affinity, more than sufficient to oxidize PhI or the alkene. Thus, a more facile reaction of **7** is to dissociate  $\text{PhI}^+$ , yielding monocationic **8** ( $\Delta E = -148$  kcal/mol). Further calculations on the dicationic PES also indicate that complex **11** would act as a thermodynamic sink for the reaction, requiring more than 30 kcal/mol to liberate the product and re-form **8**. To conclude, the calculations do not support Cu(II) as the active oxidation state but instead show a favorable path for conversion of Cu(II) to Cu(I) under the reaction conditions. Thus, the results rationalize why Cu(I) and Cu(II) salts yield the same active species and indicate that the catalytic cycle involves Cu(I)/Cu(III), as suggested by Jacobsen.<sup>12</sup> For details on the dicationic system, see Supporting Information.

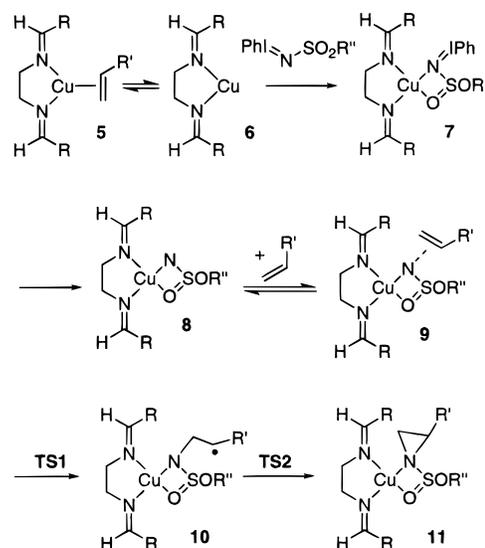
**The PES of the Monocationic Systems 4a–c.** The calculations were performed for the species depicted in Scheme 2 and the respective energies are shown in Tables 1 and 2. Energies cited in the text have been calculated at B3LYP/BSIII with ZPE at B3LYP/BSI unless otherwise stated (see Figure 2).

(21) The quality of PhINTs proved to have a significant influence on the reaction. Reproducible rates and full alkene conversions were more securely obtained using PhINTs prepared by the modified version of the Yamada protocol (see Experimental Section and ref 23).

(22) Due to the exothermic nature of the aziridination reaction, the addition PhINTs was added in portions. A simple setup that we found useful for the portionwise, yet quick addition of solids under inert atmosphere is described as follows: Onto the reaction vessel is mounted a Schlenck-type assembly having a female joint with the inlet in parallel with the surface of the reaction medium. In this joint is fixed a rubber septum with a hole of appropriate size to provide a gastight fit around the body of an open-front, 1 mL plastic syringe (i.e., cut off near the position of the 0 mL mark) containing PhINTs. The apparatus is flushed with argon and the PhINTs addition may in this way be efficiently controlled. The internal temperature is monitored via a thermocouple probe, and by vigorous stirring, the temperature could easily be kept between  $+0.5$  and  $1.5$  °C, variations, which were found not to interfere with the results at this level of precision.

(23) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

## Scheme 2. Species Evaluated in the Quantum Chemical Study<sup>a</sup>



<sup>a</sup> Small system: R = R' = H, R'' = Me, large systems: R = Ph or 2-Cl-Ph, R' = R'' = Ph.

**Table 1.** Potential Energy Surface of System **4a** (kcal/mol) Including ZPC

species	<i>m</i> <sup>a</sup>	BSI	BSII	BSIII
<b>5</b>	1	-30.5	-32.0	-31.8
<b>6</b>	1	0.0	0.0	0.0
<b>7</b>	1	-53.4	-44.4	-44.0
<b>8</b>	1	-43.3	-38.6	-39.0
<b>8</b>	3	-50.4	-38.7	-38.9
<b>9</b>	3	-54.4	-41.1	-40.0
<b>TS1</b>	3	-52.0	-38.7	-37.3
<b>10</b>	3	-68.6	-59.5	-56.7
<b>10</b>	1 <sup>b</sup>	-71.2 <sup>c</sup>	-59.1	-57.2
<b>TS2</b>	1 <sup>b</sup>	-70.0 <sup>c,d</sup>	<sup>e</sup>	<sup>e</sup>
<b>11</b>	1	-87.9	-85.1	-79.5
<b>6+product</b>	1	-63.4	-60.6	-55.0

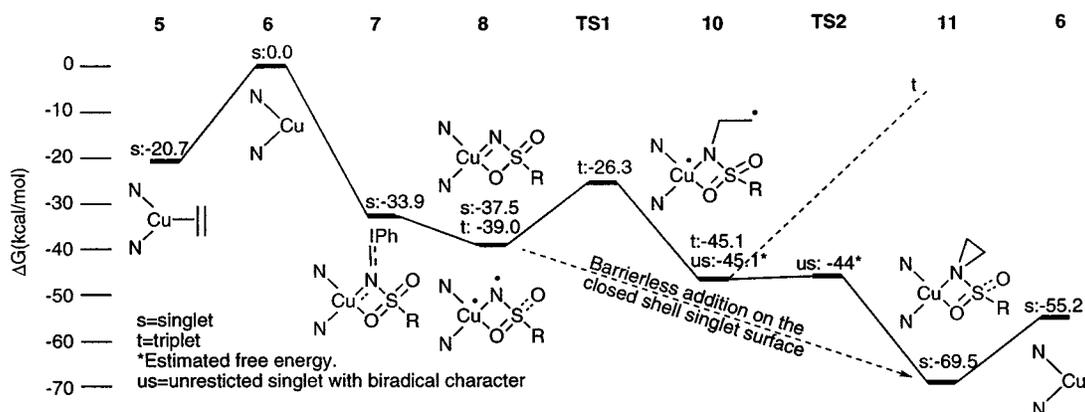
<sup>a</sup> *m* = multiplicity. <sup>b</sup> Open-shell singlet with biradical character converged in Gaussian 94. <sup>c</sup> ZPC transferred from the triplet of **10**. <sup>d</sup>  $\Delta E^{\ddagger} = 1.2$  kcal/mol calculated from the open-shell singlet **10**. <sup>e</sup> Did not converge.

**Table 2.** Potential Energy Surface of System **4b** and **c**<sup>a</sup>

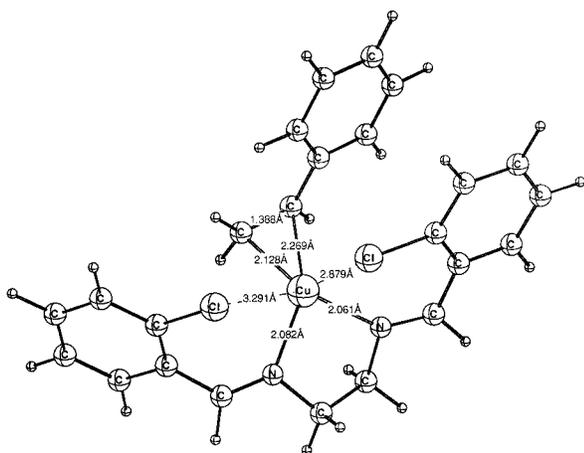
species	<i>m</i> <sup>b</sup>	system			
		4b	4c	BSII	BSIII
<b>5</b>	1	-21.5	-12.5	-14.6	-13.7
<b>6</b>	1	0.0	0.0	0.0	0.0
<b>8</b>	1	-34.1	-23.4	<sup>c</sup>	
<b>8</b>	3	-45.5	-33.3	-22.3	-23.5
<b>10</b>	3	-70.4	-55.0	-49.3	-47.8
<b>11</b>	1	-89.6	-73.0	-73.0	-69.4
<b>6</b>	1	-51.9	-51.9	-55.8	-54.3

<sup>a</sup> Zero point corrections from system **4a**. <sup>b</sup> *m* = multiplicity <sup>c</sup> Not calculated.

**Copper–Alkene Complex 5.** Before the catalytic cycle is initiated, the catalyst is mixed with the alkene, resulting in a reversible formation of a Cu(I)–alkene complex. Such complexes are well-known and the structure of a complex between styrene and a Cu(I)–complex of an analogue of **3** has recently been determined<sup>20</sup> (see also Figure 3). The calculations on the small system **4a** show a strong binding of ethylene to copper by 30.5 kcal/mol (BSI). This complexation energy is dramatically reduced (to 21.5 kcal/mol) by introducing steric bulk at



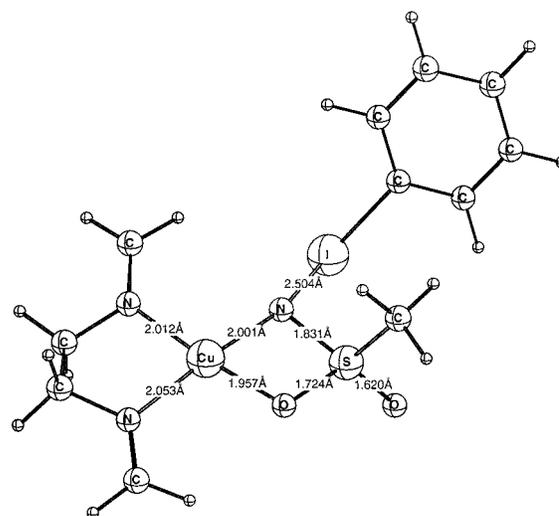
**Figure 2.** Potential free energy surface of the small model system **4a** (BSIII/298 K).



**Figure 3.** Styrene complex **5c** highlighting the Cu(I)–chlorine attraction.

the imine and increasing the size of the alkene as in system **4b**. Further, in system **4c**, the complexation energy drops to only 12.5 kcal/mol because of a favorable copper–chlorine interaction. The entropic and solvation gain upon dissociation is expected to negate this small energy difference.<sup>24</sup>

**Copper–PhINTs Complex 7.** Addition of PhINTs to the catalyst/alkene mixture results in a fast aziridination reaction, starting with decomplexation of the alkene and coordination of PhINTs to the catalyst. Binding of the iminoiodinane is considerably stronger than ethylene coordination, 44.0 vs 31.8 kcal/mol for the small system **4a**. According to the B3LYP calculations, the NSO<sub>2</sub>-moiety shows a strong preference for an *N,O*-bidentate coordination to the Cu–diimine complex and this *N,O*-binding mode was used throughout the investigation (Figure 4).<sup>25</sup> It should be noted at this point that this coordination creates a chiral center at sulfur, which might be of importance in asymmetric versions of the reaction. In this complex, the N–I bond of the iodine is elongated from 2.11 to 2.50 Å, indicating a very weak bond. The barrier for breaking this bond equals the bond dissociation energy (5.0 kcal/mol at B3LYP/BSIII), thus a real transition state is missing. Considering the favorable free energy of the N–I bond-breaking process (see Figure 2), –3.6 kcal/mol, the Cu–PhINTs complex could not be the resting state for the catalytic cycle. Excitation of this species to



**Figure 4.** Cu–[*N*-(methylsulfonyl)imino]phenyliodinane complex **7a**.

the triplet state results in immediate dissociation of iodobenzene forming triplet Cu–nitrene **8**.

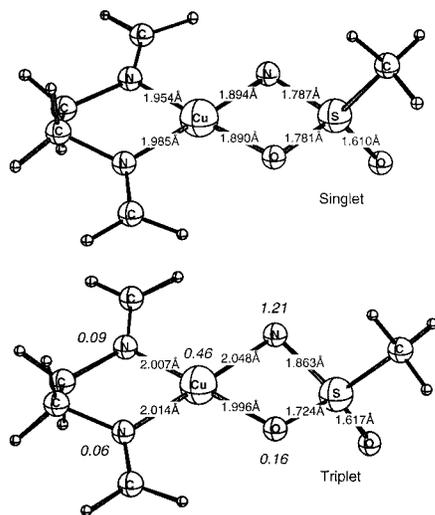
**Cu–Nitrene 8.** It is generally accepted that metal-bound nitrenes are involved in the Cu/PhINTs aziridination reaction of alkenes as evidenced by the equal selectivity in reactions using PhINTs or photogenerated TsN–nitrene from TsN<sub>3</sub>.<sup>12</sup> Jacobsen and co-workers have also convincingly demonstrated that the PhI moiety of PhINTs does not affect the outcome of the reaction. Hence, a Lewis-acid mechanism involving PhI in the selectivity-determining TS could be ruled out.<sup>12</sup> It may thus be concluded that even though the Cu–[*N*-(methylsulfonyl)imino]phenyliodinane complex **7** is very nitrene-like, this species is not reactive enough to attack the alkene before dissociation of PhI.

Aziridination of *cis*-substituted styrenes often gives significant amounts of *trans*-aziridines, which indicates that a radical pathway could be involved. This is supported by the Hammett study of Pérez.<sup>13</sup> In contrast to these observations, experiments performed by Evans using an *aliphatic* radical trap as substrate did not show any indications of radical intermediates.<sup>10</sup> These facts indicate that a concerted pathway exists but do not rule out a radical pathway for certain stabilized substrates.

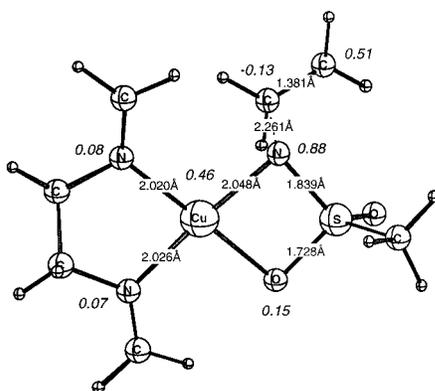
The singlet and triplet states of the nitrene differ very slightly in energy, for system **4a** only by 0.1 kcal/mol; hence, a branching radical pathway could be envisioned. According to the B3LYP/BSI energies, the triplet states seem to be more stable for the larger systems **4b** and **c** (Tables 1 and 2). The singlet state of nitrene **8a** shows a short Cu–N distance and a square planar coordination of the ligands as would be expected

(24) The entropic contribution to the free energy of dissociation is around 6–8 kcal/mol. The solvation cannot be reliably estimated for a metal-containing species by any methods available to us, but the increase in surface area and coordination of a solvent molecule to Cu will definitely provide several kcal/mol of stabilization.

(25) No monodentate nitrenes were ever located in this study.



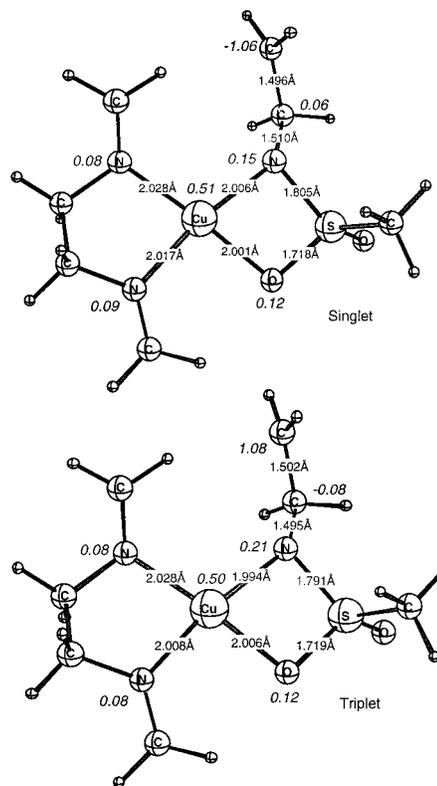
**Figure 5.** Cu–nitrene **8a**; singlet (top) and triplet (bottom). Selected Mulliken spin densities (from B3LYP/BSIII) are shown in italics for the triplet.



**Figure 6.** The triplet TS for the reaction between **8a** and ethene. Mulliken spin densities from B3LYP/BSIII in italics.

of a formal  $d^8$  Cu(III) species. The restricted closed-shell singlet wave function showed no instability toward unrestricted solutions. The triplet state of nitrene **8a** has an elongated Cu–N bond and a slightly distorted square planar coordination geometry, thus resembling a formal  $d^9$  Cu(II) complex. Structures are shown in Figure 5 together with Mulliken spin densities for the triplet. In systems **4b** and **c**, these species are destabilized in a way similar to that for the alkene complex **5**, but still, no minimum with monodentate coordination (i.e., lacking the Cu–O bond) could be located.

**Transition State for the Formation of Nitrogen–Carbon Bond(s) TS1.** For the addition of ethylene to the Cu–nitrenes **8a**, barriers can only be found on the unrestricted PES's. This is not surprising, considering the very large driving force for the reaction at the closed-shell PES (47 kcal/mol using BSI). On the triplet surface, the presence of an intermediate ethyl radical **10** reduces the driving force, and an early TS could be located at an N–C distance of 2.26 Å (Figure 6). This TS is slightly lower in energy than the free reactants, indicating the presence of a molecular complex (Table 1). Calculating the activation energy from this van der Waals complex, the barrier was found to be 2.5 kcal/mol using BSI, and insignificantly higher (2.7 kcal/mol) using BSIII. The free energy of activation calculated from the triplet nitrene is 12.7 kcal/mol. TS optimizations of systems **2b** and **c** could not be performed due to the large size of these systems. Considering the increased driving



**Figure 7.** Two spin states of intermediate **10a**. Mulliken spin densities from B3LYP/BSIII in italics.

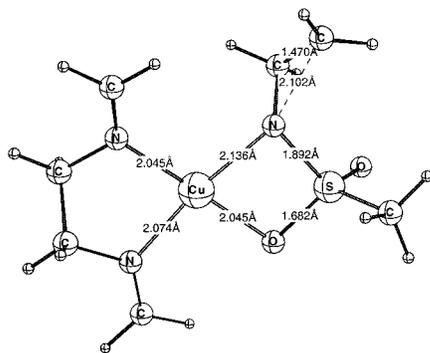
force for these systems (Table 2), it is reasonable to assume even lower activation energies.

**Intermediate Carbon-Centered Radical 10.** The intermediacy of an ethyl radical is probably a prerequisite for *cis*/*trans* isomerization in the aziridination of *cis*-alkenes. The triplet state of this species has one unpaired electron at Cu and one at the terminal carbon of the former alkene. This biradical was found to be stable with respect to ring-closure as expected from the very high singlet-to-triplet excitation energy for product **11** (vide infra). Thus, an efficient isomerization of *cis*-alkenes could be expected for this state. The structure together with Mulliken spin densities of system **10a** is shown in Figure 7.

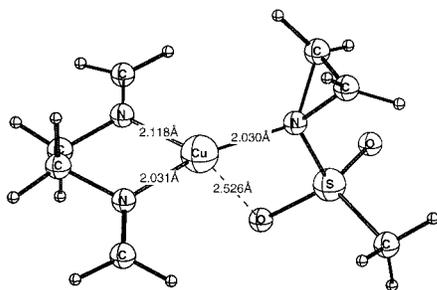
An alternative electronic state for this intermediate would be a biradical singlet. Most interestingly, this wave function could be converged, and the energy was found equal to that of the triplet state. The reaction may thus take place in a biradical fashion without the involvement of spin crossing. The TS for the formation of this singlet biradical could not be located due to convergence problems, but considering the equal energy of the singlet and triplet nitrenes as well as of the two ethyl radicals it is reasonable to assume a similar activation energy for the open-shell singlet pathway.

**The Transition State for Ring Closure, TS2.** Due to the presence of the singlet biradical intermediate **10**, we could locate a transition state for the subsequent ring closure to form the final aziridine product. The TS was found by means of a scan where we started from structure **10** and the corresponding UB3LYP singlet wave function and decreased the N–C–C angle. This resulted in an activation energy of only 1.2 kcal/mol at BSI, a barrier that most likely will be shifted by radical stabilizing substituents (e.g., phenyl) on the alkene. Ring closure at the triplet surface is efficiently hindered by the high endothermicity of this process (Figure 8).

**The Catalyst Bound Aziridine Product 11.** The formation of the aziridine is accomplished without loss of coordination to



**Figure 8.** The transition state for ring-closure, TS2.

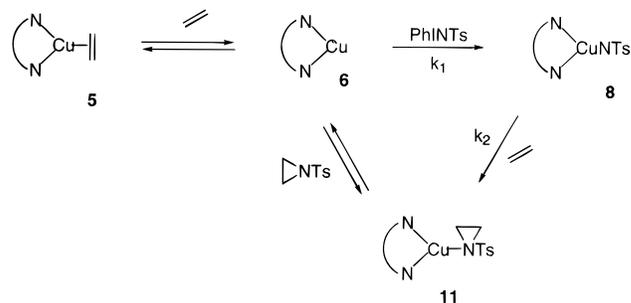


**Figure 9.** Cu-aziridine complex **11a**.

copper, leading to complex **11**. This species has a singlet ground state, with a vertical excitation energy of 67 kcal/mol to the triplet state (B3LYP/BSI, **11a**) (Figure 9)). The bond energy for the Cu-aziridine complex is 25 kcal/mol, reduced to 15 kcal/mol for the larger system **11c** due to attractive interactions between copper and the chlorine substituents. As for the alkene complex **5**, the free energy of binding cannot be reliably predicted, mainly due to the difficulties in determining the solvation contribution. From the computational results, either **5**, **6** (with coordinated solvent molecules), or **11** could be plausible resting states of the catalytic system. The actual resting state has important implications for the kinetics. A strong coordination of aziridine to copper would result in product inhibition, providing an alternative rationalization for the apparent first-order alkene dependence reported previously<sup>12</sup> (vide infra). In the case of the analogous copper-catalyzed cyclopropanation reaction, it has been shown that the reaction is inhibited by addition of bipyridine.<sup>26</sup> This was interpreted in terms of a ligand dissociation preequilibrium before the copper-ethylidiazacetate interaction.

**Cis/Trans Isomerization.** Cis/trans isomerization in the copper-catalyzed aziridination of *cis*- $\beta$ -methylstyrene is well-known experimentally,<sup>4</sup> and the close resemblance between this reaction and Jacobsen epoxidation of *cis*-alkenes<sup>27</sup> calls for a comparison of the two reactions. In the epoxidation reaction, isomerization has been suggested to be a consequence of an ethyl radical intermediate which rotates before collapsing to the epoxide, and the *cis*/*trans* ratio of the products simply reflecting the partition between the possible pathways, direct collapse (to give *cis*-epoxide) and rotation/collapse (leading to *trans*-epoxide).<sup>9</sup> However, both epoxidation<sup>1d</sup> and aziridination<sup>10</sup> experiments using phenyl-substituted radical traps give reason to believe that non-isomerized products are formed by a concerted mechanism. In a recent study by Svensson and co-

**Scheme 3.** Catalytic Cycle Used in the Derivation of Kinetic Rate Laws



workers,<sup>28</sup> exploring the Jacobsen epoxidation reaction by means of hybrid density functional theory (B3LYP), the isomerization process has been rationalized in terms of the location of an obligatory spin crossing. Thus, the formation of *cis*-products is accompanied by an early triplet-quintet spin crossing taking place before the isomerization of an ethyl radical intermediate. These arguments are not readily applicable to the copper-catalyzed aziridination, as the reactant Cu-nitrene **8** exhibits isoenergetic singlet and triplet states. This implies that the aziridination reaction does not actually require the involvement of a spin crossing; the singlet surface shows overall low activation energies and favorable thermodynamics. The fact that *cis*/*trans* isomerization is still observed for some substrates might reflect the fact that, for larger systems, the triplet Cu-nitrene is instead the spin state lowest in energy. This is indicated by the fact that the triplet-singlet splitting at the B3LYP/BSI level is increased for the larger systems **4b** and **c** (vide supra). In this case, the same arguments will apply to both the copper-catalyzed aziridination and the Jacobsen epoxidation of *cis*-alkenes.<sup>26</sup> However, in contrast to the Jacobsen epoxidation, *cis*/*trans* isomerization might also occur in the singlet biradical of **10** for the aziridination reaction.

**Kinetics.** A postulated catalytic cycle used in the discussion of the kinetics is depicted in Scheme 3. The computational results indicate that the rate-determining step (rds) in the reaction is formation of the copper-nitrene **8**. This result is seemingly in conflict with the reported first-order dependence on the alkene concentration.<sup>12</sup> A true first-order reaction would result from a rate-limiting addition of alkene to **8**, forming **11** (equation 1;  $x$  is used for the alkene concentration). Postulating steady-state concentration of the metal nitrene **8** and integrating gives the standard expression for a first-order linear plot (equation 2;  $x_0$  is the initial alkene concentration).

$$r = \frac{\partial[\text{aziridine}]}{\partial t} = -\frac{\partial x}{\partial t} = k_2[\mathbf{8}]x; \quad x = [\text{alkene}] \quad (1)$$

$$\ln \frac{x_0}{x} = k_2[\mathbf{8}]t \quad (2)$$

Our calculations do not support the suggestion that the reaction of **8** with alkene is rate-limiting (Table 1). Furthermore, a reaction truly first-order in alkene would require either a reversible formation of **8** or a buildup of **8** in the reaction mixture. In the case of a catalytic cycle starting with a Cu(I)-diimine complex, the reaction between Cu-aziridine complex **11** and PhINTs is calculated to be exothermic by  $\sim 8$  kcal/mol for systems **4b** and **c** and is further favored by entropic contributions due to the increased molecularity. Thus, in

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(27) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.

(28) Linde, C.; Åkermark, B.; Norrby, P.-O.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121*, 5083-5084.

**Table 3.** Kinetic Data for the Aziridination of 1,2-dihydronaphthalene Using Ligand **3** and Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> to Generate the Catalyst

[alkene] <sub>i=0</sub> (mM)	[aziridine] <sub>i=0</sub> (mM)	[Cu] <sub>Tot</sub> (mM)	initial rate/[Cu] <sub>Tot</sub> s <sup>-1</sup>
65	0	3.1	0.22 ± 0.02 <sup>a</sup>
128	0	3.1	0.20
125	0	6.2	0.21
64	10	3.1	0.17
67	79	3.1	0.26

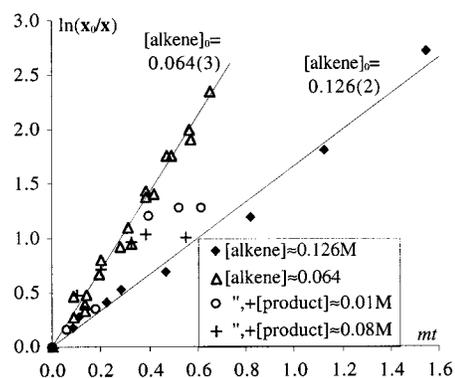
<sup>a</sup> Standard deviation, experiment performed four times.

combination with the low calculated barrier for the further reaction between nitrene and alkene, formation of **8** is expected to be effectively irreversible.

An irreversible formation of **8** in combination with a rate-limiting reaction between **8** and alkene would imply that **8** is the resting state of the catalyst. It is our experience that complex **6** will consume PhINTs rapidly even in the absence of alkene, presumably by a reaction of **8** with other species present in the reaction mixture (solvent, PhINTs, or more **8**). Furthermore, the barrier for the reaction between the alkene and the copper–nitrene is extremely low for both the singlet and the triplet state. The mechanism suggested by the calculations is instead that the rds is formation of the copper–nitrene **8**, with either free copper–ligand complex **6**, product complex **11**, or alkene complex **5** as the resting state (the latter can be excluded based on the observed kinetics). It should be noted, however, that the *selectivity*-determining step, affecting the ratio of aziridine isomers, must by necessity involve the alkene.

In a simplified view, a rds that does not involve the alkene should result in a zero-order rate law, in conflict with observations. However, the observations only show that *some* essential reactant is depleted, not necessarily the alkene. Strong complexation of copper by a product or byproduct in the reaction or catalyst decomposition could lead to the same apparent behavior. To test whether the rate-determining step of the reaction does involve the alkene, we studied the kinetics of the reaction while varying the initial conditions. Due to insolubility, the effective concentration of PhINTs (and of course the molecular sieves) could not be controlled. Every effort was made to keep the reaction conditions as constant as possible, to minimize the variation in effective concentration of these reactants. Alkene and metal–ligand complex were tested at two different concentrations each. To test the hypothesis of inhibition, aziridine product was also added in two different concentrations. In all cases, the reaction displayed apparent first order in alkene, at least in the initial stages of the reaction. Apparent first-order rate constants were determined by fitting to eq 2. Points at the end of the run (where the catalyst had presumably decomposed) were discarded, on the basis of maximizing the information content according to an *F*-test. From the apparent rate constants initial rates were calculated by multiplication with the initial alkene concentration. The initial rates divided by the total metal concentration are listed for all reactions in Table 3.

The data in Table 3 conclusively shows that the initial reaction rate is independent of alkene concentration and directly proportional to the metal concentration, in accordance with the calculated reaction path. The effect of aziridine product addition is not entirely clear, but from the last result, it is obvious that the apparent first order is *not* a result of product inhibition. If product inhibition was effective, the last entry should correspond approximately to entry 2 at 50% conversion, with about half the initial rate, but instead a slight rate increase (probably within

**Figure 10.** Plots of  $\ln(x_0/x)$  vs  $mt$  for two different initial alkene concentrations  $x_0$  and metal concentrations  $m$  and also with added aziridine product.

experimental uncertainty) is observed. To illustrate the observed behavior, all data points are plotted according to eq 2 in Figure 10.

It is clear from Figure 10 that in the absence of added aziridine, the fit to apparent first order is very good within each run but varies proportionally to the initial concentration of alkene (the slope is halved by doubling the alkene concentration). However, the reactions with added aziridine fit less well. It can be seen that the catalyst is deactivated more rapidly at a higher aziridine concentration. It has been verified that the aziridine is stable to the reaction end conditions. Together with the observed catalyst deactivation upon aziridine addition (Figure 10) this indicates that the active catalyst is somehow decomposed by the aziridine into a form that will neither give aziridination nor aziridine breakdown. Such a decomposition upon increasing aziridine concentration might also rationalize the apparent first order in alkene observed for each separate run.

## Conclusions

The mechanism of the copper-catalyzed aziridination of alkenes has been elucidated by high-level quantum chemical calculations. The calculations strongly indicate that the active catalyst is a Cu(I) species, as suggested by Jacobsen.<sup>12</sup> It has also been shown how Cu(II) can enter the Cu(I)/Cu(III) cycle through reaction with PhINTs.

In the calculations, three different spin states have been characterized along the reaction path; a closed-shell singlet surface that leads directly to aziridine in a concerted manner from the singlet nitrene **8**, an open-shell singlet pathway that could lead to an extremely short-lived *N*-ethyl singlet biradical intermediate, and finally, a triplet surface leading to an *N*-ethyl radical intermediate that has to change spin to singlet before ring-closure. The resting state of the catalyst is a copper(I) complex, possibly with coordinating solvent molecules, but not involving either the product aziridine or the alkene. The calculated reaction profile suggests that the rate-determining step in the reaction is the formation of metallanitrene **8**, in conflict with a previous report.<sup>12</sup>

Kinetic measurements confirmed that the reaction is indeed zero order in alkene, despite the fact that single experiments appear to obey a first-order kinetics. This behavior could be rationalized in terms of decomposition of the catalytically active metal complex.

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**Supporting Information Available:** Results and discussion for dicationic complexes (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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