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Mechanism of the Iron-Mediated Alkene Aziridination Reaction: Experimental and Computational Investigations

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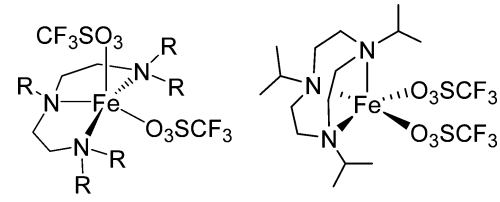
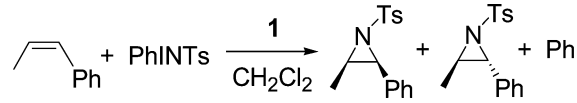
Combined experimental and computational studies suggest that the iron-mediated aziridination of *cis*-1-phenylpropene proceeds along two mechanistic pathways that share a common imidoiron(IV) intermediate. One pathway involves a second species, proposed to be an azametallacyclobutane intermediate, which collapses to provide the *syn*-aziridine product. A second, parallel pathway is responsible for the formation of an *anti*-aziridine.

Metal-mediated transformations of inexpensive hydrocarbon feedstocks into synthetically valuable nitrogenous compounds, such as amines or aziridines, remain under active investigation in organometallic chemistry.[1] Iron is a catalytic metal of emerging significance in such processes.[2] For example, previously reported mono- and dinuclear iron complexes based on polypyridyl ligand frameworks are effective in mediating the intramolecular tosylamidation of aromatic C−H bonds, providing a one-step method for the transformations of arenes into aniline derivatives.[3] A growing family of iron complexes mediate the aziridination of alkenes, including iron porphyrin and corrole complexes,[4] an iron-containing organometallic complex,[5] and a mixed-valent dinuclear nonheme iron complex.[6] Recently, we reported that mononuclear nonheme iron(II) complexes of neutral polyamine ligands serve as effective catalysts for nitrene transfer from the iminoiodinane *N*-(tosylimino)phenyliodinane (PhINTs) to alkenes, generating *N*-tosylaziridines in moderate-to-good yields.[7] A survey of structurally diverse iron(II) complexes revealed that complexes containing at least one pair of cis labile coordination sites were more effective catalysts than those containing trans labile sites or only a single labile site. With knowledge of this structural requirement for efficient alkene aziridination reactivity, we conducted a series of experimental and computational studies designed to provide additional insights concerning the mechanism of this iron-mediated alkene aziridination reaction. Herein, we present evidence that this reaction proceeds through at least two pathways, one of which generates an azametallacyclobutane intermediate. We speculate that an imidoiron(IV) species [formed by oxidation of the iron(II) catalyst by PhINTs] is present in both pathways and that divergent modes of interaction of the alkene substrate with the imidoiron(IV) species provide for the different mechanistic pathways.

Scheme 1. Iron Catalysts for Alkene Aziridination



Scheme 2. Aziridination of *cis*-1-Phenylpropene by **1**



In the present study, we examined the ability of [(Me$_5$dien)Fe(O$_3$SCF$_3$)$_2$] (**1**, where Me$_5$dien = *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine; Scheme 1) to mediate the aziridination of *cis*-1-phenylpropene by PhINTs (Scheme 2). These reactions produce mixtures of *syn*- and *anti*-2-methyl-3-phenyl-1-tosylaziridine, which are easily quantified by ^{1}H

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Table 1. Stereochemical Outcomes of the Aziridination of *cis*-1-Phenylpropene Mediated by **1**−**3**[a]

catalyst	**1**	**2**	**3**
CH_2Cl_2	9:1	1:1	2:1
CH_3CN	2:1	1:1	1:1

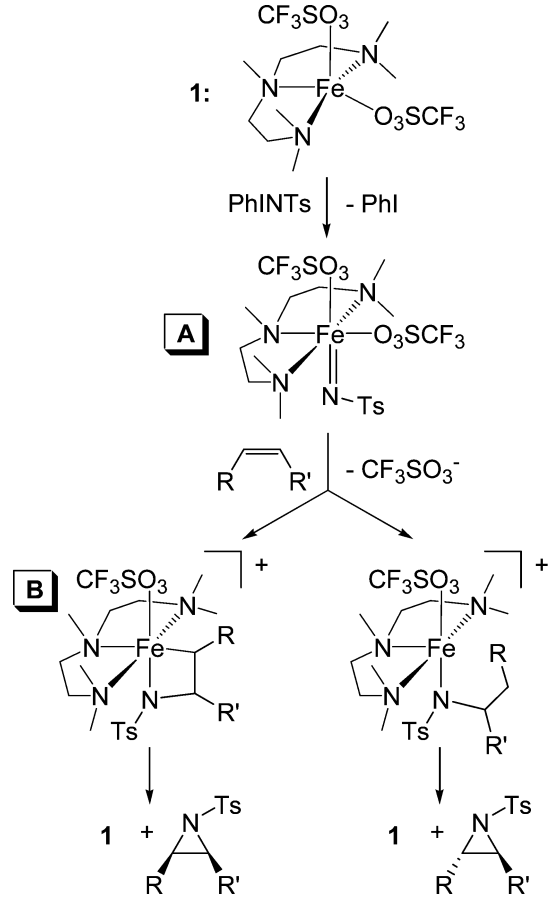
[a] Table entries reflect the ratio of *syn*/*anti*-2-methyl-3-phenyl-*N*-tosylaziridines as determined by ^{1}H NMR analyses of the crude product mixtures. Reactions were conducted at 25 °C in the solvents indicated.

NMR.[8] Thus, using conditions that we described previously for the aziridination of styrene,[7] **1** mediates the aziridination of *cis*-1-phenylpropene to provide a 9:1 syn/anti mixture of 2-methyl-3-phenyl-*N*-tosylaziridines (45% combined yield based on PhINTs; Table 1). However, when **1** mediates the aziridination of *cis*-1-phenylpropene in the coordinating solvent CH_3CN, the syn/anti ratio falls dramatically to 2:1. Thus, the stereochemical outcome of the aziridination of *cis*-1-phenylpropene when mediated by **1** depends on the coordinating ability of the solvent: noncoordinating solvents favor the formation of *syn*-aziridines from *cis*-alkenes, while *anti*-aziridines become more prevalent when reactions are conducted in a coordinating solvent.

The steric properties of the supporting ligands also influence the stereochemical outcome of the aziridination of *cis*-1-phenylpropene. Thus, we examined the ability of $[(Et_5dien)Fe(O_3SCF_3)_2]$ (**2**, where Et_5dien = *N*,*N*′,*N*″,*N*″′-pentaethyldiethylenetriamine; Scheme 1), a hindered derivative of **1**, to mediate the aziridination of alkenes. Complex **2** is isolated as a colorless crystalline solid from the reaction of Et_5dien with $[Fe(CH_3CN)_2(CF_3SO_3)_2]$ in THF and, like **1**, contains a high-spin Fe^{2+} center.[8,9] Just as is observed for **1**, complex **2** is an efficient catalyst for the aziridination of styrene by PhINTs in CH_2Cl_2, providing 2-phenyl-1-tosylaziridine in 80% yield. Unlike **1**, however, complex **2** does not provide high yields of the *syn*-aziridine when mediating the aziridination of *cis*-1-phenylpropene. Rather, a 1:1 mixture of *syn*- and *anti*-aziridines is produced when this aziridination reaction is conducted in either CH_2Cl_2 or CH_3CN (Table 1). Similar results are observed when $[(iPr_3TACN)Fe(O_3SCF_3)_2]$ (**3**, where iPr_3TACN = 1,4,7-triisopropyl-1,4,7-triazacyclononane; Scheme 1),[7,10] which contains sterically demanding isopropyl groups, mediates the aziridination of *cis*-1-phenylpropene. This hindered complex provides a 2:1 mixture of *syn*- and *anti*-aziridines when the aziridination of *cis*-1-phenylpropene is conducted in CH_2Cl_2, while an equimolar mixture of the two aziridines is generated in CH_3CN. Thus, the presence of either a sterically hindered supporting ligand or a coordinating solvent reduces the stereospecificity of the aziridination reaction.

cis-Alkenes have been used previously as mechanistic probes in metal-mediated alkene aziridination studies.[4a,11] The production of *anti*-aziridines from *cis*-alkenes is generally taken as evidence that the new C−N bonds in the product

Scheme 3. Proposed Mechanism for Alkene Aziridination Mediated by **1**



are formed in a stepwise process involving charged or radical intermediates. In contrast, when *syn*-aziridines are produced from *cis*-alkenes, a concerted mechanism for C−N bond formation is often invoked. A [2 + 2] cycloaddition reaction between the alkene and a metal−imido complex, generating an azametallacyclobutane intermediate, is an alternative pathway that can preserve alkene stereochemistry in the aziridine product. We propose a mechanism for iron-mediated alkene aziridination that features at least two parallel pathways and accounts for (i) the experimental factors (solvent coordinating ability and ligand sterics) that influence the stereochemical outcome of the reaction and (ii) the structural requirement of at least one pair of cis labile coordination sites on the iron center. Thus, we suggest that a [2 + 2] cycloaddition pathway produces the *syn*-aziridine in reactions mediated by **1** in noncoordinating solvents, while a stepwise pathway that produces the *anti*-aziridine becomes more favorable when aziridinations are conducted in coordinating solvents or mediated by sterically hindered catalysts such as **2** or **3**. These two pathways diverge after a common intermediate **A**, proposed to be an imidoiron(IV) species, which is generated by oxidation of the iron(II)-containing catalyst by PhINTs (Scheme 3).

A series of density functional theory (DFT) calculations were conducted to assess the structures and energies of two key intermediates in the proposed aziridination mechanism

(8) Procedures for the aziridination reactions and for the synthesis and characterization of **2** are provided as Supporting Information.
(9) Anal. Calcd for $C_{16}H_{33}F_6FeN_3O_6S_2$ (**2**): C, 32.17; H, 5.57; N, 7.03. Found, C, 32.19; H, 5.53; N, 7.01.
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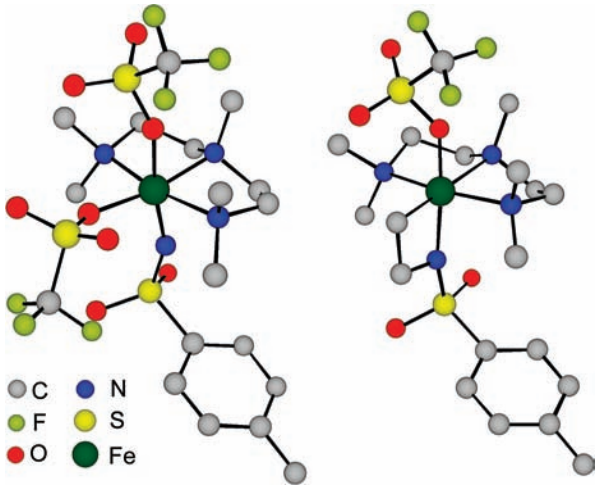

Figure 1. Equilibrium mPWPW91/6-31G(d) geometries of **A** (left) and **B** (right).

(**A** and **B**, Scheme 3).[12] A comprehensive series of possible structures were calculated for **A**, and the lowest-energy structure (considering both gas-phase electronic energies and solvation-free energies) was determined to be an octahedral complex containing a *mer*-Me_5dien ligand, a cis pair of triflate ligands, and an axial =NTs unit (Figure 1, left).[12] The Fe=NTs bond length in **A** was calculated to be 1.74 Å, which is nearly identical with the 1.73 Å Fe=NTs bond length determined by EXAFS for the octahedral imidoiron(IV) complex $[Fe(NTs)(N4Py)]^{2+}$.[13a] Substitution of one of the triflate ligands in **A** with a model alkene, ethylene (Scheme 3; R = R′ = H), resulted in a new energy-minimized structure that converged at the azametallacyclobutane intermediate **B** (Figure 1, right). Intermediate **B** features an elongated Fe−N bond (1.85 Å), consistent with a decrease in the Fe−N bond order in **B** relative to **A**. The C−C bond length within the azametallacyclobutane ring, 1.53 Å, is also lengthened relative to that found in ethylene (calcd, 1.33 Å), which is consistent with conversion of the C=C double bond to a single bond. These structural features compare favorably with those measured for the azametallacyclobutane complex $[(bpy)Ni(NTsCHMeCH_2)]$.[14] In that nickel complex, the C−C bond length within the azametallacyclobutane ring was determined to be 1.500(9) Å (X-ray) and the Ni−N bond length was 1.911(5) Å. The azametallacyclobutane ring in $[(bpy)Ni(NTsCHMeCH_2)]$ is puckered, with a Ni−N−C−C dihedral angle of 12.6(5)°; the comparable dihedral angle in **B** is 3.1°. Thus, DFT calculations demonstrate that **A** and **B** have structural parameters that parallel those of closely related, structurally characterized species.

We speculate that **A** is a common intermediate in the two mechanistic pathways that eventually yield *syn*- and *anti*-aziridines. The generation of such an imidoiron(IV) species from the reaction of an iron(II) complex with PhINTs has direct literature precedent,[13] and similar intermediates have been invoked in other reactions of iron(II) complexes with nitrogen-containing oxidants.[15] In a noncoordinating solvent or when the imidoiron(IV) complex is supported by a ligand with modest steric requirements, an alkene substrate can react with **A** via a formal [2 + 2] cycloaddition to generate **B**. The presence of the azametallacyclobutane ring in **B** provides a rationale for the observation that only iron complexes featuring at least one pair of cis labile sites are effective alkene aziridination catalysts.[7] Reductive elimination of the [TsNCHRCHR′] fragment from **B** with retention of stereochemistry would regenerate the active catalyst and provide the *syn*-aziridine. Such a reductive elimination from a nickel-containing azametallacyclobutane complex with retention of stereochemistry has been reported.[16] However, when the aziridination reaction is conducted in a coordinating solvent such as CH_3CN, we suggest that the donating solvent competes effectively with the alkene carbon for a coordination site on the iron center. Thus, solvent coordination prevents the formation of the azametallacyclobutane ring and forces C−N bond formation to occur in a stepwise manner. Similarly, formation of the azametallacyclobutane ring is also disfavored by sterically hindered ligands that restrict access to the iron center. Thus, the presence of either a coordinating solvent or a sterically hindered ligand favors an alternative mechanistic pathway that involves stepwise C−N bond formation and eventually leads to the formation of the *anti*-aziridine product.

Herein we have described the first experimental and computational studies designed to probe the mechanism of the iron-mediated alkene aziridination reaction. Our results suggest that at least two mechanistic pathways are possible, one of which involves the formation of an azametallacyclobutane intermediate from an imidoiron(IV) precursor. Investigations designed to trap and characterize these intermediates are ongoing in our laboratories.

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Supporting Information Available: General procedure for the aziridination of *cis*-1-phenylpropene and characterization of aziridine products (including a representative ^{1}H NMR spectrum), synthetic details for **2**, and complete computational details (including alternative formulations and structures for **A**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Complete computational details, including alternative formulations and structures for **A**, are provided as Supporting Information.

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