Published in final edited form as:

ACS Catal. 2019 July 5; 9(7): 6223–6233. doi:10.1021/acscatal.9b01306.

Elucidation of the Reaction Mechanism of $C_2 + N_1$ Aziridination from Tetracarbene Iron Catalysts

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Abstract

A combined computational and experimental study was undertaken to elucidate the mechanism of catalytic $C_2 + N_1$ aziridination supported by tetracarbene iron complexes. Three specific aspects of the catalytic cycle were addressed. First, how do organic azides react with different iron catalysts and why are alkyl azides ineffective for some catalysts? Computation of the catalytic pathway using density functional theory (DFT) revealed that an alkyl azide needs to overcome a higher activation barrier than an aryl azide to form an iron imide, and the activation barrier with the first-generation catalyst is higher than the activation barrier with the second-generation variant. Second, does the aziridination from the imide complex proceed through an open-chain radical intermediate that can change stereochemistry or, instead, via an azametallacyclobutane intermediate that retains stereochemistry? DFT calculations show that the formation of aziridine proceeds via the open-chain radical intermediate, which qualitatively explains the formation of both aziridine diastereomers as seen in experiments. Third, how can the formation of the side product, a metallotetrazene, be prevented, which would improve the yield of aziridine at lower alkene loading? DFT and experimental results demonstrate that sterically bulky organic azides prohibit formation of the metallotetrazene and, thus, allow lower alkene loading for effective catalysis. These multiple insights of different aspects of the catalytic cycle are critical for developing improved catalysts for $C_2 + N_1$ aziridination.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b01306.

Complete computational details, experimental details, annotated NMRs, and X-ray figure (PDF)

X-ray CIF (CIF)

Atomic coordinates of calculated reactants, products, catalysts, intermediates, and transition states (XYZ)

The authors declare no competing financial interest.

Keywords

aziridine; tetrazene; catalysis; organic azides; reaction pathway; density functional theory; density fitting

INTRODUCTION

Catalytic aziridination has made noteworthy strides in the past decade due to the development of many new catalysts.^{1–8} These advances are significant since aziridines not only are found in natural products^{9–11} but also are critical intermediates that can be ring-opened stereospecifically or transformed into a plethora of more complex heterocyclic ring systems via ring expansion.^{12–18} For example, Kang¹⁹ and Ghorai²⁰ have showcased chiral ring-opening reactions with *meso* aziridines, while Zhao, Chai, and Wang developed the first pyrroloindoline synthesis from aziridines and indoles.^{21–23} Although synthesis of primary aziridines has advanced recently with improved stereochemical control, a cost-effective method for the synthesis of biologically significant aziridines that is compatible with a variety of R-groups off the nitrogen is still a critical synthetic challenge. A C₂ + N₁ route is an effective method of catalytic aziridination, which can be improved further with a greater understanding of its mechanism.

A C₂ + N₁ approach to aziridination features an alkene (C₂) and a nitrene fragment (N₁) combining to make the aziridine.²⁴ Nitrene fragments most commonly come from protected azides (e.g., TsN₃,^{25–27} TcepN₃,²⁸ and (SES)-N₃),^{27,29} aryl azides,^{30–32} and, more recently, alkyl azides,³³ all of which are easy to synthesize.^{32,34–36} While porphyrin and salen complexes are successful catalysts for *N*-substituted aziridination,^{5,27,30,37,38} very few mechanistic studies have been performed for these systems.^{39,40} This lack of mechanistic studies for group transfer for the nitrene is in direct contrast to the numerous studies that have investigated the mechanisms for epoxidation and the associated group transfer from metal oxos to alkenes.^{41–43}

We have reported two iron *N*-heterocyclic carbene (NHC) based catalysts for aziridine synthesis using aliphatic alkenes with aryl as well as alkyl azides.^{31,33} This pair of catalysts yields the first set that is effective with aliphatic alkenes and these two classes of nitrene reagents, making them an ideal showcase for a comprehensive mechanistic study. While the basic components of a catalytic cycle for our tetracarbene iron catalysts have been proposed previously (Scheme 1),⁴⁴ the individual elementary steps within each component of the cycle (shown as A, B, and C) have not been examined.

These individual steps have considerable implications for the effectiveness of the aziridination reaction and understanding them can answer several key questions about the catalysis. For example, why do alkyl azides react catalytically with the second-generation system (1) but not with the first-generation system (2)? Many other aziridination catalysts are limited to reactions with aryl azides as well.^{30,32} More critically, how does the alkene react with the purported iron imide intermediate? Does it proceed through an azametallacyclobutane intermediate or a series of one-electron radical reductions? This question is particularly critical because of the implications for stereochemical control.

Finally, what is the role of the metallotetrazene during catalysis? Does prevention of metallotetrazene allow for catalysis to occur using lower alkene loadings, thus making it much more economical? Elucidating these aspects of the mechanism for our catalytic systems will allow for the development of more effective aziridination catalysts supported by strong σ -donors.

In this manuscript, we report the first mechanistic study of aziridination catalysis on the tetracarbene iron system by modeling the reaction pathways of the first- and second-generation tetracarbene-iron catalysts using density functional theory (DFT) and corroborating the DFT results with new and previously reported experimental evidence. These results show that incorporation of boron atoms into the ligand backbone significantly accelerates iron-imide formation with the second-generation catalyst, $\left[\left(\text{BMe}_2, \text{EtTC}^H\right)\text{Fe}\right]$ (**1**) compared to the first-generation catalyst, $[(\text{Me}, \text{EtTC}^{Ph})\text{Fe}(\text{NCCH}_3)_2](\text{PF}_6)_2$ (**2**). In both catalysts, the predicted iron(IV) imide intermediate has an effective Fe–N double bond. Calculations also strongly suggest that the iron imide directly reacts with alkene through an open-chain radical mechanism. The calculated results are consistent with associated experimental studies with stereoisomers of the aziridines. However, disparate activation energies between the two catalysts leads to different levels of stereo retention. Finally, the steric properties of the organic azide can lead to the preclusion of metallotetrazene formation, which in turn, allows for lower alkene loadings during catalysis.

RESULTS AND DISCUSSION

When aziridines are formed catalytically from organic azides and alkenes, metal imides are widely believed to be the key intermediates.^{31,44–46} Gallo³⁹ and Ghosh⁴⁰ employed DFT to investigate the mechanisms of imide formation and subsequent aziridination by Ru- and Co-based porphyrin catalysts, respectively. Notably, the imide intermediates in these porphyrin systems were not isolated. In both catalytic systems that we have studied (**1** and **2**), no imide intermediates have been isolated despite extensive investigations.^{31,33} Conversely, there are numerous examples of stable imides on Fe, Ru, and Co formed via organic azides, but these imides generally do not perform catalytic aziridination.^{47–54} In a similar manner, we found that moving to a smaller 16-atom ringed tetra-NHC macrocycle does allow stabilization of Fe(IV) imide complexes in both $S = 0$ and $S = 1$ spin states, but these species are not effective catalysts.⁵⁵ The notable exceptions to this observation are a Ru^{VI} diimide isolated by the Che group and an Fe^{III} radical imide isolated by the Betley group, both of which perform aziridination.^{56,57}

Virtually all aziridination catalysts for organic azides (N_3R) are only effective with aryl azides and not alkyl azides. For example, Ceneni's and Zhang's Ru and Co porphyrin systems only react with aryl azides.^{32,58} In the present study, catalyst **1** reacts with both aryl and alkyl azides, but **2** reacts catalytically only with aryl azides.^{31,33} Since no imides have been isolated, DFT can assist in understanding the difference in reactivity between the two NHC systems and elucidating how the key intermediate is formed. We have computed three important steps of the catalytic pathways using DFT to understand how the aziridination mechanism operates for catalysts **1** and **2** and analyze some of the critical differences

between them. These steps are (A) formation of the iron imide, (B) formation of aziridine from the iron imide, and (C) formation of a metallotetrazene. All calculations were performed using *p*-tolyl azide as the aryl azide, *n*-octyl azide as the alkyl azide, and 1-decene as the alkene.

Formation of Iron Imides. Step A.

The first test case was studied between *p*-tolyl azide and **1** (Figure 1A). In this system, the lowest-energy spin state of all intermediates and transition states was $S = 1$, i.e., a spin triplet. An iron imide could be formed through initial binding of the α -nitrogen or γ -nitrogen of the azide to the catalyst, so both intermediates were investigated.^{59–63} Similar to Co and Ru systems, the energy of the α -bound intermediate was lower than that of the γ -bound case.^{39,40,64} The free energy of activation for formation of the imide from the α -bound intermediate was calculated to be $G^\ddagger = 9.9$ kcal/mol, suggesting that the formation of imide via this route is highly facile at room temperature (rt) (no route to an imide was found for the γ -bound case). This low free-energy barrier is consistent with experimental results that show reactivity of organic azides with **1** at room temperature. The formation of the imide from **1** and *p*-tolyl azide is highly exergonic ($G = -38.4$ kcal/mol).

The reaction of *n*-octyl azide with **1** yielded similar results for imide formation as that of *p*-tolyl azide with **1** (Figure 1B). The ground spin state of all species in the pathway was a triplet. The α -bound azide intermediate was energetically more stable than the γ -bound azide intermediate. The free energy of activation to form the imide ($G^\ddagger = 13.7$ kcal/mol) was greater than that for the *p*-tolyl azide case ($G^\ddagger = 9.9$ kcal/mol), but lower than corresponding energies for imide formation from other reactive organic azides reported by Ghosh and Gallo.^{39,40} Experimental results show that *n*-octyl azide also reacts with **1** at room temperature, albeit quite slowly. In this case, the formation of the imide intermediate from azide and catalyst is also very exergonic ($G = -28.1$ kcal/mol), but it is less so than imide formation from **1** and *p*-tolyl azide.

An analysis of the calculated imide intermediates with $S = 1$ ground states demonstrates why these species are effective for aziridination. The imide intermediate for **1** with *p*-tolyl azide ($S = 1$) has a bond order of two between the iron and nitrogen. The calculated Fe–N bond distance is 1.72 Å and the Fe–N–C bond angle is 144.5° (see Supporting Information, .xyz files of calculated structures). While the bond distance is within the range of stable iron imides, the bond angle would be one of the tightest angles recorded for an iron imide.^{49,56,65} A bond order of two is consistent with an analysis of the populated orbitals, which show a fully populated d_{xy} (nonbonding) and two singly populated π -antibonding orbitals that align with the Fe–N bond (see Supporting Information, Figure S14). Therefore, this iron imide would be more reactive than the more typical iron imides that have a bond order of three.^{66,67} Other calculated imide intermediates from this set of iron complexes with $S = 1$ ground states had similar bond metrics and molecular orbital diagrams.

The differences between **1** and **2** become apparent when comparing the free-energy diagrams for the reactions of the two catalysts with *p*-tolyl azide (Figures 1A and 2A). The free energy of activation to form the imide from the α -bound *p*-tolyl azide of **2** was calculated to be $G^\ddagger = 14.9$ kcal/mol, and this value is similar to activation energies for

systems that have been studied by Gallo and Ghosh.^{39,40} The greater free energy of activation for imide formation from *p*-tolyl azide using **2** compared to **1** ($G^\ddagger = 14.9$ kcal/mol versus $G^\ddagger = 9.9$ kcal/mol) is corroborated by their experimental reactivity. While **1** reacts with *p*-tolyl azide rapidly at room temperature, **2** only reacts with *p*-tolyl azide at 40 °C.⁴⁴ Similar to the case with **1**, in reactions with **2**, the free energy of activation to form the imide is greater for the alkyl azide ($G^\ddagger = 18.7$ kcal/mol) than for the aryl azide ($G^\ddagger = 14.9$ kcal/mol) (Figure 2). The α -bound azide was calculated to be lower in energy than the corresponding γ -bound azide in reactions of aryl and alkyl azides with **1** and **2**. In the case of *n*-octyl azide reacting with **2**, the iron imide was calculated to have an $S = 0$ ground state, although the free-energy gap between the $S = 0$ and $S = 1$ spin states of the imide was calculated to be only $G = 0.5$ kcal/mol suggesting that both spin states would be populated.

The computational results in Figures 1 and 2 show that the free energy of activation for imide formation increases by $G^\ddagger = 5.0$ kcal/mol when the catalyst is changed from **1** to **2** using the same azide, and by $G^\ddagger = 3.8$ kcal/mol when the azide is changed from *p*-tolyl azide to octyl azide using the same the catalyst. Calculation of the Boltzmann factor ($\exp(-G^\ddagger/RT)$) shows that changing the catalyst from **1** to **2** reduces the rate constant of imide formation by a factor of 4624 at room temperature (a factor of 1242 at 80 °C), whereas changing the azide from *p*-tolyl azide to octyl azide reduces the rate constant of imide formation by a factor of 610 at room temperature (a factor of 224 at 80 °C). A comparison of Figures 1A versus 2A and Figures 1B versus 2B shows that the increase in free energy of activation upon change of catalyst from **1** to **2** occurs primarily due to the decrease in free energy of the α -bound intermediate. The Fe center in doubly positively charged **2** is more electron deficient than the Fe center in charge-neutral **1** and is more strongly attracted to the α -nitrogen lone pair of the azide, thereby forming a significantly more stable α -bound intermediate that requires a greater activation energy to dissociate into an imide and N₂. In contrast, a comparison of Figures 1A versus 1B and 2A versus 2B shows that the increase in free energy of activation upon change from *p*-tolyl azide to octyl azide occurs because the transition state to form the imide, which oxidizes Fe(II) to Fe(IV), is stabilized by the less electron-donating *p*-tolyl group compared to *n*-octyl group.

The greater free energy of activation for imide formation from alkyl azide versus aryl azide using **2** is consistent with experimental results. Compound **2** is not an active catalyst with alkyl azides in the presence of excess alkenes (the conditions that are necessary for aryl azides).³¹ Furthermore, reactions with *n*-octyl azide and **2** show limited direct reactivity. A reaction with *n*-octyl azide and **2** in toluene showed no reactivity even up to 80 °C. A similar reaction in acetonitrile showed no reaction at room temperature and only a partial reaction, to the expected metallotetrazene, at 80 °C. The combination of a less effective catalyst for imide formation and a greater activation energy for alkyl azides versus aryl azides demonstrates why this combination is ineffective for aziridination.

Formation of Aziridines. Step B.

While a metal imide is thought to be a key intermediate in C₂ + N₁ aziridination with organic azides, the steps upon addition of alkene to form the aziridine are less well understood. The two leading candidates are a concerted reaction that goes through an

azametallacyclobutane intermediate, and a radical pathway that goes through a pair of single electron transfers. The Ghosh and Gallo groups have supported radical pathways for the Co porphyrin and Ru porphyrin systems, respectively, for aziridination, while, to date, no one has provided definitive evidence that an azametallacyclobutane intermediate is favorable.^{39,40} Since our macrocyclic systems are more flexible than porphyrins and we previously synthesized metallotetrazenes, we have evaluated both pathways for an azide and alkene that form aziridines with our catalysts.⁴⁴

The first test reaction was computed between the *p*-tolyl imide of **1** and 1-decene (Figure 3). This combination was chosen because we have previously reported that this permutation of azide and alkene yielded the expected aziridine, 2-octyl-1-(*p*-tolyl)aziridine, in 95% yield.³³ Calculations showed that the spin triplet pathway was the minimum-energy pathway for the reaction. The formation of aziridine can conceivably proceed through two intermediates, an azametallacyclobutane intermediate and an open-chain radical intermediate. The azametallacyclobutane intermediate strictly preserves the stereochemistry of the alkene in the resulting aziridine, whereas the chain intermediate can change the stereochemistry via intramolecular rotation prior to ring closing. Therefore, an important goal of our computational study was to compare the chain-mediated and azametallacyclobutane-mediated pathways to examine the stereochemical retention by the catalyst. The free energy of activation (TS1) to form the open-chain radical intermediate from the imide was calculated to be $G^\ddagger = 25.5$ kcal/mol, whereas the activation energy to form the azametallacyclobutane intermediate from the imide was calculated to be more than 25 kcal/mol greater than that to form the open-chain radical intermediate (comparison of activation energies performed using relaxed potential-energy scans; see Supporting Information, Figure S26). Such a large difference in activation energies for azametallacyclobutane formation versus open-chain radical formation from the imide suggests that the azametallacyclobutane intermediate is inaccessible through this reaction. The free-energy gap between the azametallacyclobutane intermediate and the open-chain radical intermediate is relatively small ($G = 6.6$ kcal/mol) due to the flexible nature of the macrocyclic tetracarbene ligand. Since the azametallacyclobutane intermediate can be accessed via the chain intermediate, we calculated transition states to form the aziridine from either intermediate. We found that while the free energy of activation to form the aziridine from the open-chain intermediate (TS2) is $G^\ddagger = 10.8$ kcal/mol, the activation energy to form the aziridine from the azametallacyclobutane intermediate is more than 25 kcal/mol greater than that from the open-chain radical intermediate (comparison of activation energies performed using relaxed potential-energy scans; see Supporting Information, Figure S27). Notably, Ghosh and Gallo both reported no energy barriers for the formation of aziridine in their porphyrin systems.^{39,40}

These calculations of the transition states and intermediates yield two primary conclusions about the mechanism. First, the reaction proceeds solely through a radical mechanism of one electron reductions without employing an azametallacyclobutane intermediate. Second, the rate-determining step for the reaction is addition of alkene to the iron imide. This conclusion is distinct from the previously studied porphyrin systems where the rate-determining step is the addition of organic azide to the porphyrin.^{39,40} It is supported by the experimental

finding that azides react with **1** at room temperature, but aziridination only occurs if the reaction is heated. Finally, the presence of an energy barrier to form aziridine from the open-chain radical intermediate suggests that there could be stereochemical scrambling if the activation energy for intramolecular rotation of the intermediate about the pro-chiral center is similar to the activation energy for transformation to aziridine. The free energy of activation for intramolecular rotation was calculated to be $G^\ddagger = 10.4$ kcal/mol (Figure 3, pink line), which is very similar to the free energy of activation for formation of aziridine ($G^\ddagger = 10.8$ kcal/mol), strongly suggesting that there will be considerable stereochemical scrambling of the product aziridine. Importantly, the calculated free energy of the rotated intermediate was almost the same as that of the initial intermediate, and it is assumed that the activation energies to form aziridine from the two intermediates are either the same or very similar. Of course, the competition between free energies of activation for aziridine formation versus intramolecular rotation is sensitive to the nature of the alkene. For example, we expect greater stereo retention with sterically bulkier alkenes, such as 2-octene, due to a greater activation energy for intramolecular rotation.

A second test reaction was computed between the *p*-tolyl imide of **2** and 1-decene (Figure 4), following the same open-chain radical pathway as that for catalyst **1**. The free energy of activation to form the open-chain radical intermediate from the imide was calculated to be $G^\ddagger = 25.3$ kcal/mol, which is very similar to the corresponding imide-to-open-chain-radical free energy of activation of $G^\ddagger = 25.5$ kcal/mol for **1**. The free-energy gap between the azametallacyclobutane intermediate and the open-chain radical intermediate is even smaller for **2** ($G = 1.3$ kcal/mol) than for **1** ($G = 6.6$ kcal/mol) due to the even more flexible nature of the macrocyclic ligand. Critically, the free energy of activation to form the aziridine from the open-chain radical intermediate is just $G^\ddagger = 4.1$ kcal/mol, compared to the corresponding free energy of activation of $G^\ddagger = 10.8$ kcal/mol for **1**. The intramolecular rotational barrier was calculated to be $G^\ddagger = 10.5$ kcal/mol (Figure 4, pink line), which is very similar to the corresponding barrier of $G^\ddagger = 10.4$ kcal/mol for **1**. These results predict that **2** should show greater stereochemical control on aziridine formation than **1**. Similar to **1**, the rate-determining step in **2** is the addition of alkene to the iron imide. Also similar to **1**, the activation energy to form aziridine from the azametallacyclobutane intermediate was calculated to be more than 25 kcal/mol greater than that from the open-chain radical intermediate, eliminating the azametallacyclobutane-mediated pathway for **2** (comparison of activation energies performed using relaxed potential-energy scans; see Supporting Information, Figure S28). These results are consistent with the formation of an aziridino complex by Smith formed from an iron nitride complex and styrene.^{68,69}

To experimentally test the results of the DFT calculations, we ran a series of reactions that yields distinct stereoisomers. A general reaction is shown in Scheme 2. Depending on the mechanism of aziridination, we would expect the stereochemistry to be fully retained, partially retained, or fully lost. Test reactions included *cis*-2-octene and *trans*-2-octene with both catalysts **1** and **2**. Except for a single study by the Betley group using *cis*- β -deuterostyrene, no one has experimentally probed these mechanisms through product distribution with organic azides and *cis* and *trans* alkenes.⁷⁰

Initial tests focused on reactions of **1** with *cis*-2-octene and *trans*-2-octene. The reaction of neat *cis*-2-octene, *p*-tolyl azide, and 1% **1** as catalyst yielded two recoverable products that were separated by careful gradient elution of ethyl acetate and hexanes over silica gel. ¹H and ¹³C NMR showed only modest differences between the two species with the primary distinctions between 1.5 and 2.2 ppm in the ¹H NMR (Figures S1 and S7). COSY and HSQC confirmed that the two peaks for the major product at 2.03 and 2.16 ppm in the ¹H NMR were the expected single protons off the aziridine ring (Figure S3 and S4). In a similar manner, the minor product's peaks at 1.91 and 2.15 ppm correspond to the protons on an aziridine ring, which would be the alternate stereoisomer. To distinguish between *syn* aziridine and *anti* aziridine, we employed homonuclear decoupling NMR to compare the coupling between the two protons on the aziridine ring.^{70–73} The major product showed coupling constants of *J* = 6.6 and 6.5 Hz, while the minor product showed coupling constants of *J* = 2.3 and 2.0 Hz (Figures S5, S6, S11, and S12). The larger coupling constants are consistent with a *syn* aziridine, while the smaller values are consistent with an *anti* stereochemistry.^{70,74–77} We thus assigned the major product as *syn*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine (**3**) and the minor product as *anti*-2-methyl-3-pentyl-1-(*p*-tolyl)aziridine (**4**). The isolated yields for **3** and **4** were 67% and 28%, respectively, which gives a total yield of 95% (Table 1, entry 1). The d.r. for this reaction is 2.4:1.

The reaction of neat *trans*-2-octene, *p*-tolyl azide and 1% **1** yielded the same two products, albeit in lower yield. In this case, **3** was formed in 12% yield, while **4** was formed in 58% yield, giving a total yield of 70% (Table 1, entry 2). The d.r. for this reaction is 4.8:1.

In both *cis* and *trans* alkene with catalyst **1**, the expected diastereomer was the major product, but a considerable amount of the opposite diastereomer was produced. Since the stereochemistry would be retained if the azametallacyclobutane was the sole intermediate formed by reaction with alkene, these results confirm that aziridination occurs via the radical open-chain mechanism, in qualitative agreement with results from DFT. Intramolecular rotation of the radical intermediate prior to aziridine formation will result in formation of the opposite diastereomer. As expected for this type of mechanism, the *trans* case leads to greater retention of stereochemistry since there is less steric repulsion in the radical intermediate.

We repeated the same two reactions with the *cis*- and *trans*-2-octene with **2**. After 18 h, which was the complete reaction time for catalyst **1**, the reaction was not complete with *cis*-1-octene (as determined by following consumption of organic azide), but only one aziridine product was detected. Aziridine **3** was isolated in 24% yield showing complete retention of stereochemistry (Table 1, entry 3). A second reaction was run for 6 days to ensure that all organic azide reacted. In this case, both **4** and **5** were produced in 44% and 7% yield, respectively (d.r. ratio of 6.3:1). This is much improved stereocontrol, and at low reaction times there is very high d.r. Regrettably, test reactions with *trans*-2-octene did not yield sufficient aziridine for analysis of products, which is not surprising, since **2** is a less reactive catalyst than **1** as observed experimentally.³¹ These results support the DFT calculations, which show that going through an open-chain radical intermediate is acceptable for stereochemical control provided the activation energy for radical recombination to form

aziridine is much lower than the activation energy for rotation-induced stereochemical scrambling.

Our combined theoretical and experimental studies of steps A and B reveal that while the rate of imide formation is faster with the second-generation catalyst (**1**) than with the first-generation catalyst (**2**), the rate of aziridine formation is faster with the first-generation catalyst than with the second-generation catalyst. A faster rate of imide formation makes a catalyst reactive with both aryl and alkyl azides, whereas a faster rate of aziridine formation from the open-chain radical intermediate enhances stereochemical control on the product. Both differences between the two catalysts arise because the Fe(II) center in doubly positively charged **2** is more electron deficient than in charge-neutral **1**. In step A, **2** forms more stable α -bound azides than **1** that require more energy to dissociate into iron imides and nitrogen molecules. In step B, the imide of **2** undergoes alkene addition (reduction of Fe(IV) to Fe(III)) and subsequent radical recombination faster than the imide of **1**. The significantly more facile radical recombination in **2** compared to **1** is evident in the calculated distance between the ring-closing carbon and nitrogen atoms (C–N) in the TS2 transition states of Figures 3 and 4. The C–N distances are 2.50 and 2.51 Å in the open-chain radical intermediates of **1** and **2**, respectively, and 1.46 Å in the product aziridine. Notably, the C–N distance is 2.00 Å in TS2 of **1** and 2.21 Å in TS2 of **2**, demonstrating that TS2 of **2** is a significantly earlier transition state than TS2 of **1** and consequently has a much lower activation energy. One approach to developing the next-generation tetracarbene–iron catalyst that accelerates imide and aziridine formations more equally might be to modify **1** using electron-withdrawing substituents such that the electron density at the Fe center is less than that in **1** but more than that in **2**.

Formation of Metallotetrazenes. Step C.

The reaction to form aziridine from the metal-imide intermediate is complicated by a competing reaction, the formation of metallotetrazene via addition of a second equivalent of organic azide (Scheme 1). The metallotetrazene forms through a formal [2 + 3] cycloaddition reaction between the metal imide and organic azide.^{78,79} While previous iron tetrazenes prepared by Riordan,⁸⁰ Holland,⁷⁹ and Chirik⁸¹ were not reactive, some iron tetrazenes react to give the corresponding azoarenes (RNNR).⁸² This reaction was studied by Cundari through DFT calculations on a nickel complex.⁸³ Our first-generation catalyst forms a metallotetrazene that can reform the catalyst and yield diazene.⁴⁴ Preventing this competing reaction is critical for effective catalysis, particularly for expensive alkenes. Therefore, we investigated the mechanism of metallotetrazene formation through DFT calculations. These DFT calculations motivated a series of experiments that suggest possible ways to prevent the formation of metallotetrazene.

Calculations for the second-generation catalyst (**1**) with *p*-tolyl azide show why excess alkene is necessary for this pairing. Similar to our study of aziridination formation from the iron imide (step B), we explored both stepwise and concerted mechanisms to form metallotetrazene from the iron imide, as shown in Figure 5. The competition between conversion of the iron imide to aziridine via reaction with 1-decene versus conversion of iron imide to metallotetrazene via reaction with *p*-tolyl azide will determine the extent of

reaction inhibition by metallotetrazene formation. While a stable radical of energy very similar to that of the open-chain radical intermediate was computed in the stepwise reaction between the iron imide and *p*-tolyl azide, the free energy of activation to form this radical ($G^\ddagger = 40.2$ kcal/mol) is much greater than the free energy of activation to form the open-chain radical intermediate ($G^\ddagger = 25.5$ kcal/mol) (Figure 3). However, the free energy of activation to undergo a direct, concerted [2 + 3] cycloaddition from the iron imide was calculated to be $G^\ddagger = 20.8$ kcal/mol, showing that in contrast to the stepwise mechanism of aziridine formation, the concerted pathway is the dominant mechanism to form metallotetrazene. Importantly, the free energy of activation to form metallotetrazene via [2 + 3] cycloaddition is lower than the free energy of activation of the rate-determining aziridination step by 4.7 kcal/mol. Consequently, the reaction can be driven to form aziridine over tetrazene by employing a considerable excess of alkene during catalysis.^{31,33}

The relative energies of aziridination and metallotetrazene formation will, of course, depend on the nature of the azide and alkene. Very little research on the mechanism of formation of metallotetrazenes has been conducted,^{78,84–86} and while a concerted pathway has been previously postulated, to our knowledge, the azide-based radical intermediate (stepwise pathway) has not been considered as an intermediate to a metallotetrazene.⁸² To test the DFT results, we reacted *p*-tolyl azide with **1**. This reaction formed the tetrazene, $\left[\left(\text{BMe}_2, \text{Et}^H\right)\text{TC}^H\right]\text{Fe}((p\text{-tolyl})\text{N}_4)(p\text{-tolyl})$ (**5**) (Figure S13). Complex **5** is a distorted trigonal prismatic complex and spectroscopically similar to our previously reported Fe(IV) tetrazene with the first-generation catalyst.⁴⁴

These results suggested that destabilizing the tetrazene relative to formation of aziridine may allow for lower loading of alkene by shutting off the path to metallotetrazene formation. We postulated that a bulkier organic azide would be one manner of achieving this outcome. DFT calculations were performed for a reaction pathway with **1**, mesityl azide, and 1-decene. The same intermediates were calculated for the formation of aziridine and metallotetrazene. In sharp contrast to the results for **1**, *p*-tolyl azide, and 1-decene, the formation of the tetrazene complex with mesityl azide is highly endergonic ($G = 31.3$ kcal/mol relative to the corresponding iron imide), suggesting that the free energy of activation to form the tetrazene would be very high. The analogous formation of the tetrazene complex with *p*-tolyl azide is exergonic ($G = -1.7$ kcal/mol). The free energy of aziridine formation from the iron imide is similar for both cases with **1** ($G = -0.8$ kcal/mol for *p*-tolyl azide and $G = 0.4$ kcal/mol for mesityl azide). Therefore, while the formation of tetrazene competes with formation of aziridine in the case of *p*-tolyl azide, it does not compete with formation of aziridine in the case of mesityl azide.

This computational prediction was verified by experiments, which show that no tetrazene complex is formed from addition of mesityl azide to **1**. If there is no competition reaction during aziridination catalysis, then the formation of aziridine should be feasible using a lower loading of alkene. To test this hypothesis, we ran catalytic reactions with **1**, 1-octene, and either *p*-tolyl azide or mesityl azide. A catalytic reaction of neat 1-octene, *p*-tolyl azide, and 1% loading of **1** (versus azide) yielded the expected aziridine, 2-hexyl-1-(*p*-tolyl)aziridine (**6**), in 91% isolated yields after purification with column chromatography

(Table 2, entry 1). This high yield for a primary alkene is consistent with yields from our previous research with **1**.³³ However, reducing the alkene loading to five equivalents of alkene and running the reaction in toluene led to an isolated yield of only 32%. In contrast, when mesityl azide was employed with excess alkene, 2-hexyl-1-mesitylaziridine (**7**) was formed in 45% isolated yield (Table 2, entry 2). But in this case, lowering the loading to five equivalents of 1-octene produced **7** in 44% yield, which is effectively no lower than that using excess alkene. Thus, experiments confirm that a bulkier organic azide prohibits the competition reaction and makes the reaction more effective with lower alkene loading due to destabilization of the metallotetrazene relative to aziridine formation.

CONCLUSIONS

We have investigated three steps of the catalytic aziridination cycle with macrocyclic tetracarbene iron catalysts, organic azides, and alkenes. By performing a detailed computational study of the reaction pathways of two tetracarbene iron catalysts using DFT and experimentally testing the results, we can deduce some of the key elementary steps of the cycle. The first key step is the formation of an iron-imide intermediate. The calculations show that the pathway goes through an α -bound azide and direct loss of N₂. The calculated energy barriers for imide formation using **1** are lower than those for **2**, much lower than other aziridination catalysts, and are consistent with the experimental results that organic azides react at room temperature.

The second key step is the formation of the aziridine from the iron imide. The addition of alkene to imide is the rate determining step for our system, which is contrary to porphyrin systems where the addition of azide is the rate determining step. One additional question was whether this step proceeded through a radical pathway, which could lose stereochemical information, or through an azametallacyclobutane pathway, which would retain the stereochemistry. DFT calculations and experimental results show that the radical pathway is favored for both catalysts. The key experimental result is that *cis* and *trans* isomers of 2-octene form both the *syn* and *anti* aziridines. DFT calculations show that the rotational free-energy barrier for the open-chain radical intermediate has roughly the same height as reductive elimination for **1**. However, catalyst **2** does not show loss of stereochemistry for the same reactions, and this experimental result is supported by calculations that show a lower free-energy barrier for reductive elimination to give aziridine. Keeping this barrier low for the ring closing step is critical for effective stereocontrol in this catalytic reaction and a key insight for producing value-added aziridines.

Finally, the aziridination reaction is in competition with the formation of a metallotetrazene. It is critical to prevent the formation of this species for effective use of high-value alkenes. DFT results for **1** and *p*-tolyl azide show that the free energy of activation to form metallotetrazene is lower than the free energy of activation to form aziridine, putting tetrazene formation in direct competition with aziridine formation. However, increasing the steric bulk of the organic azide flips the relative stability of product aziridine and metallotetrazene, vastly favoring the formation of aziridine. This calculation is corroborated by experimental results that show no tetrazene is formed when mesityl azide is used, and lower alkene loading is as effective as excess alkene during catalysis with mesityl azide.

These combined computational and experimental results will allow us to develop the next generation of aziridination catalysts supported by macrocyclic tetracarbene ligands as well as provide important chemical insight into the performance of first-row transition metals for catalytic aziridination.

METHODS

The computational study was performed using DFT within the Gaussian09 quantum-chemistry software package.⁸⁷ Catalyst **1** has 59 atoms and 240 electrons, while catalyst **2** has 127 atoms and 528 electrons after removing the counterions and axial acetonitrile ligands. All electrons of the catalysts, reactants, and products were treated explicitly in the calculations. The TPSS exchange-correlation functional⁸⁸ was used in conjunction with the Ahlrichs def2-SVP basis set^{89,90} and density fitting^{89,90} to optimize geometries of all structures and calculate their vibrational frequencies. The electronic energies of the optimized geometries were calculated using the TPSSh exchange-correlation functional^{88,91,92} in conjunction with the Ahlrichs def2-TZVPP basis set.^{89,90} This combination of TPSS/def2-SVP and TPSSh/def2-TZVPP was chosen due to its accurate description of geometric properties,^{93–96} as well as computational efficiency, especially in the case of the larger catalyst **2**. All calculations were corrected for dispersion using Grimme's D3 empirical dispersion scheme⁹⁷ with Becke-Johnson damping parameters.⁹⁸ Free energies of all species were calculated at 298 K. All calculated structures of reactants, products, catalysts, and intermediates have no imaginary vibrational frequencies, and each calculated transition state has one imaginary vibrational frequency along the reaction coordinate, except the concerted transition state for tetrazene formation, which has an additional 9 cm⁻¹ imaginary frequency corresponding to a single methyl rotation on one of the two *p*-tolyl groups away from the reaction site. The evaluation and validation of the functionals and density fitting are presented in the Supporting Information.

Experimental methods and annotated spectra are included in the Supporting Information.

Supplementary Material

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ACKNOWLEDGMENTS

We thank Dr. Carlos Steren for assistance with NMR experiments. The computational work was performed on the Advanced Computing Facility (ACF) high-performance computing cluster located at the University of Tennessee, Knoxville. P.P.C. and D.M.J. gratefully acknowledge the National Science Foundation (NSF-CAREER/CHE-1254536); S.B.I., S.R., and D.M.J. gratefully acknowledge the National Institute of Health (NIH-R15-GM117494-01A1); and J.L.K. and S.R. gratefully acknowledge the University of Tennessee for financial support of this work.

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Figure 1.

DFT-computed free-energy pathway for formation of iron imide from reaction between an organic azide and **1**. All species are in $S = 1$ (triplet) spin state unless designated with an * in which case they are in $S = 0$ (singlet) spin state. TS designates a transition state. (A) Depicts reaction between *p*-tolyl azide and **1**. (B) Depicts reaction between *n*-octyl azide and **1**. Free energies (G) are given in kcal/mol.

Figure 2.

DFT-computed free-energy pathway for formation of iron imide from reaction between an organic azide and **2**. All species are in $S = 1$ (triplet) spin unless designated with an * in which case they are in $S = 0$ (singlet) spin state. TS designates a transition state. (A) Depicts reaction between *p*-tolyl azide and **2** (B) Depicts reaction between *n*-octyl azide and **2**. Free energies (ΔG) are given in kcal/mol.

Figure 3. DFT-computed free-energy pathway for formation of aziridine from *p*-tolyl imide and 1-decene using catalyst **1**. All species are in S = 1 (triplet) spin state. TS designates a transition state. Free energies (*G*) are given in kcal/mol. The pink line represents barrier for internal rotation of the open-chain radical intermediate (*G*[‡] = 10.4 kcal/mol), which would lead to the opposite stereoisomer upon formation of aziridine.

Figure 4.

DFT-computed free-energy pathway for formation of aziridine from *p*-tolyl imide and 1-decene using catalyst **2**. All species are in $S = 1$ (triplet) spin state. TS designates a transition state. Free energies (G) are given in kcal/mol. The pink line represents the barrier for internal rotation of the open-chain radical intermediate ($G^\ddagger = 10.5$ kcal/mol), which would lead to the opposite stereoisomer upon formation of aziridine.

Figure 5.

DFT-computed free-energy pathway for formation of tetrazene from *p*-tolyl azide and **1**. All species are in $S = 1$ (triplet) state unless designated with an * in which case they are $S = 0$ (singlet) spin state. Free energies (G) are given in kcal/mol. Black lines depicts reaction between *p*-tolyl azide and **1** to form tetrazene in concerted reaction. Blue line compares reaction to form aziridine with **1** as the catalyst (full reaction coordinate shown in Figure 3).

Scheme 1.

Catalytic Cycle for the Formation of Aziridine from Tetracarbene Iron Catalysts 1 and 2

Scheme 2.
General Catalytic Reaction

Table 1.

Aziridination Reactions with 1 and 2^a

Entry	Alkene	Azide	Catalyst	Aziridine	Yield
1			1	3	3: 67% 4: 28%
2			1	4	3: 12% 4: 58%
3			2	3	3: 24% 4: 0% 3: 44% ^a 4: 7% ^a

^aReaction run over 6 days.

Table 2.

Aziridination Reactions with 1^a

Entry	Alkene	Azide	Catalyst	Aziridine	Yield
1			1	6	91 % ^a 32% ^b
2			1	7	45% ^a 44% ^b

^aKey: a = reaction run with excess alkene; b = reaction run with 5 equiv of alkene with toluene as solvent.