JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Synthesis of Aziridines from Alkenes and Aryl Azides with a Reusable Macrocyclic Tetracarbene Iron Catalyst

S. Alan Cramer and David M. Jenkins*

Department of Chemistry, The University of Tennessee, Knoxville, Tennessee 37996-1600, United States

Supporting Information

ABSTRACT: A new iron aziridination catalyst supported by a macrocyclic tetracarbene ligand has been synthesized. The catalyst, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$, was synthesized from the tetraimidazolium precursor $(^{Me,Et}TC^{Ph})(I)_4$ and characterized by NMR spectroscopy, electrospray ionization mass spectrometry, and single-crystal X-ray diffraction. This iron complex catalyzes the aziridination of electron-donating aryl azides and a wide variety of substituted aliphatic alkenes, including tetrasubstituted ones, in a "$C_2 + N_1$" addition reaction. Finally, the catalyst can be recovered and reused up to three additional times without significant reduction in yield.

Despite the successful development of catalytic epoxidation from alkenes over the last 30 years, the nitrogen analogue, catalytic aziridination, has languished behind.[1] Part of the reason is the lack of nitrogenous variants of peroxides or dioxygen, which are used to form epoxides in conjunction with alkenes.[2] Since the aziridine functional group is found in natural products[3] and also used in pharmaceuticals, broadening the scope of the aziridination reaction is significant.[4] Today, "$C_2 + N_1$" aziridination reactions that combine an alkene and a nitrene fragment typically use iodoimine reagents such as PhI=NTs (Ts = tosylate),[1,2,5] chloramine-T,[6] or tosyl azide[7] as the nitrene reagent. The disadvantage of these reactions is that the tosyl group must be removed before the desired final substituent can be placed on the ring, which reduces the atom economy and can lead to ring degradation.[1]

Organic azides are an alternative to these current nitrene reagents. Aryl azides can be easily synthesized in one step from amines[8] and are tolerant of a wide variety of functional groups.[9] Finally, since the correct functionality can be installed on the organic azide prior to catalysis, the use of organic azides instead of PhI=NTs should improve the atom economy of these reactions, thereby eliminating the step of removing the tosylate group before installing the desired moiety on the nitrogen atom.[10] A catalytic "$C_2 + N_1$" aziridination that is successful with a wide variety of substrates, both for alkenes and organic azides, would be a significant advance in chemical synthesis.

A very limited number of catalytic ruthenium and iron porphyrin systems have been developed that perform "$C_2 + N_1$" aziridination with organic azides, but they are limited to strongly electron-withdrawing aryl azides (such as *p*-nitrophenyl azide)[11] and/or styrene derivatives for the alkene.[12] This communication presents a new tetracarbene iron(II) complex that acts as a catalyst for aziridination with electron-donating and -withdrawing aryl azides and a variety of substituted aliphatic alkenes. In addition, the catalyst is robust and can be recovered and reused for multiple aziridination runs.

We previously reported the synthesis of the macrocyclic tetraimidazolium $(^{Me,Et}TC^{Ph})(I)_4$ (**1**), which can be deprotonated in the presence of divalent transition metals such as Pt to prepare tetracarbene complexes.[13] Unlike our previously reported platinum complex $[(^{Me,Et}TC^{Ph})Pt](PF_6)_2$,[13] an iron complex could not be prepared via deprotonation with a weak base. However, an in situ carbene strategy proved successful in ligating the macrocyclic carbene to the iron center (Scheme 1).[14] Lithium diisopropylamide deprotonates **1** at room temperature in tetrahydrofuran (THF) in 5 min. Addition of a THF solution of iron(II) iodide to this mixture followed by the addition of thallium hexafluorophosphate in acetonitrile gives the octahedral complex $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ (**2**). Complex **2** constitutes a tetracarbene iron complex with easily accessible coordination sites for catalytic reactions.[15]

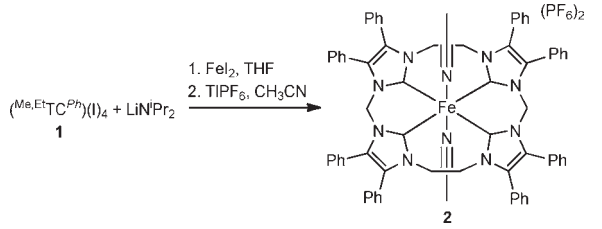
Spectroscopic characterization of **2** was consistent with a tetracarbene complex. Electrospray ionization mass spectrometry (ESI-MS) analysis of **2** showed a peak at m/z 506.2 associated with $[(^{Me,Et}TC^{Ph})Fe]^{2+}$ and another at m/z 1157.3 associated with $\{[(^{Me,Et}TC^{Ph})Fe](PF_6)\}^+$, both with the correct isotopic ratios. ^{1}H NMR analysis demonstrated that the acetonitrile ligands on **2** exchange in CD_3CN solution, since **2** crystallized from CH_3CN solution (see below) showed peaks only for unbound acetonitrile. ^{13}C NMR analysis showed a resonance for the carbene carbon at 196.65 ppm, consistent with other Fe^{II} N-heterocyclic carbene (NHC) complexes.[16] In addition, complex **2** was found to be air-stable in the solid state.

The X-ray crystal structure of **2** shows that the acetonitrile ligands are bound in the solid state (Figure 1), giving an octahedral complex. The average Fe−C bond distance is 2.01 Å, which is slightly longer than that in the only other previously reported Fe^{II} tetracarbene complex (1.96 Å).[15] The trans C−Fe−C angles are 169.7 and 172.2°, demonstrating that there is only a minimal distortion about the equatorial plane formed by the macrocycle. Unlike four-coordinate Co and Ni complexes bearing a 24-atom ringed macrocyclic tetracarbene ligand,[17] **2** has space for apical ligands to bind to the metal center.

To determine the best catalytic reaction conditions for aziridination with an electron-donating aryl azide, a series of test reactions were run with *p*-tolyl azide, 1-decene, and **2**. The best

Received: September 27, 2011
Published: November 14, 2011

Scheme 1. Synthesis of $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ (2)



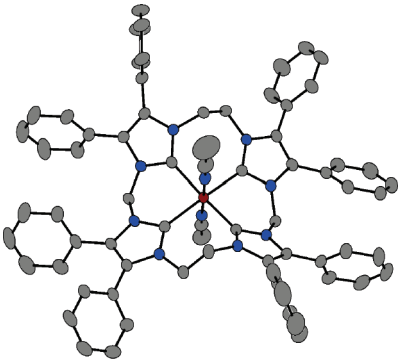
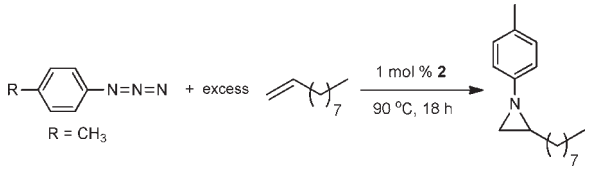


Figure 1. X-ray crystal structure of $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$ (**2**). Red, blue, and gray ellipsoids (50% probability) represent Fe, N, and C, respectively. Counteranions, solvent molecules, and H atoms have been omitted for clarity.

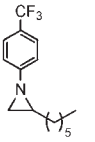
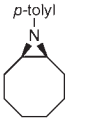
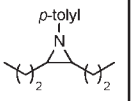
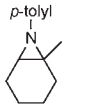
Scheme 2. Sample Aziridination Reaction Catalyzed by 2



results were obtained by using a 0.1 mol % catalyst loading of **2** with a 29-fold excess of alkene and no additional solvent (Scheme 2). After 18 h at 90 °C, the reaction was complete (all of the organic azide had reacted), and the reaction mixture was cooled to room temperature and the catalyst removed by filtration over Celite. Removal of the remaining organics under reduced pressure followed by column chromatography yielded pure 2-octyl-(*p*-tolyl)aziridine in 70% isolated yield (Table 1, entry 1). The identity of the product was determined by ^1H and ^{13}C NMR spectroscopy, GC−MS, and high-resolution MS [see the Supporting Information (SI)]. Increasing the catalyst loading to 1% (entry 2) improved the isolated yield to 82%. One advantage of this methodology is the ease of catalyst separation from the product, since **2** is insoluble in the reaction mixture at room temperature.

To test the effectiveness of the catalytic system, additional azides and alkenes were evaluated (Table 1). The catalyst successfully performed aziridination with 1-decene and electron-withdrawing azides such as 1-azido-4-(trifluoromethyl)benzene (entry 3) with a slightly higher yield than for previously reported Ru−porphyrin systems.[11a] Disubstituted alkenes, including cis- and trans-substituted examples, were both successful (entries 4 and 5,

Table 1. Aziridination Reactions with 2 as the Catalyst

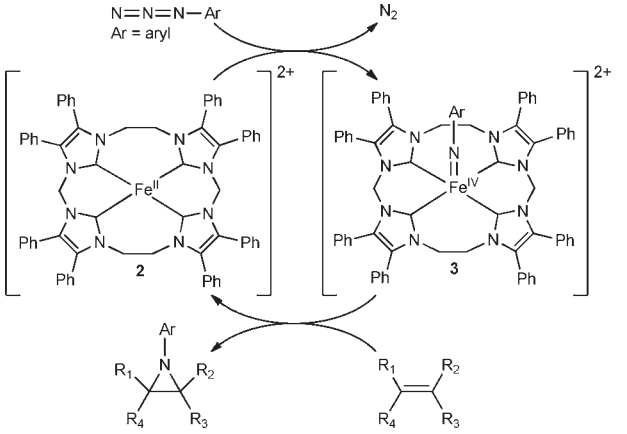
Entry	Alkene	Azide R-group	Catalyst Loading	Temp. (°C)	Time (h)	Aziridine	Yield[a]
1	1-decene	CH_3	0.1%	90	18		70%[b]
2	1-decene	CH_3	1%	90	18		82%[b]
3	1-octene	CF_3	0.1%	90	18		37%[b]
4	*cis*-cyclooctene	CH_3	0.1%	90	12		97%
5	*trans*-4-octene	CH_3	1%	90	144		30%[b]
6	1-methyl-cyclohexene	CH_3	1%	90	144		39%[b]
7	2,3-dimethyl-2-butene	CH_3	0.1%	70	160		20%[b]

[a] Isolated yields. [b] Required chromatography.

respectively). The yield for 9-(*p*-tolyl)-9-azabicyclo[6.1.0]nonane (entry 4) was almost quantitative (97% yield) with just 0.1% catalyst loading. The reaction with *trans*-4-octene (entry 5) was much slower and lower-yielding, probably because of the steric bulk of the propyl groups. Furthermore, tri- and tetrasubstituted alkenes such as 1-methylcyclohexane and 2,3-dimethyl-2-butene (entries 6 and 7, respectively) were successful. The reaction with 2,3-dimethyl-2-butene was run at 70° because of its lower boiling point, which may have contributed to the lower yield. In contrast, Gallo's group reported that trisubstituted alkenes did not react with aryl azides and a Ru−porphyrin catalyst.[12] Likewise, previous examples of similar tetrasubstituted aziridines have been prepared only by photolysis of electron-withdrawing organic azides to make the free nitrene prior to reaction with the alkene.[18] In these two cases (entries 6 and 7), we have catalyzed the first examples of "$C_2 + N_1$" aziridinations involving those classes of alkenes and an aryl azide.

Since the catalyst **2** is insoluble in the reaction mixture at room temperature, we believed that it could be recovered and reused once the catalysis was complete. Since the reaction with *cis*-cyclooctene (Table 1, entry 4) gave the best yield with low catalyst loading, we repeated the reaction three times with the same batch of catalyst. The results demonstrated that the catalyst is reusable for this reaction with only a negligible decrease in yield by the fourth run (see Table 2 in the SI). In addition to improving the atom economy of the reaction by using aryl azides, the ability to reuse the catalyst without significant loss of yield is quite beneficial.

Scheme 3. Proposed Reaction Mechanism for the Aziridination



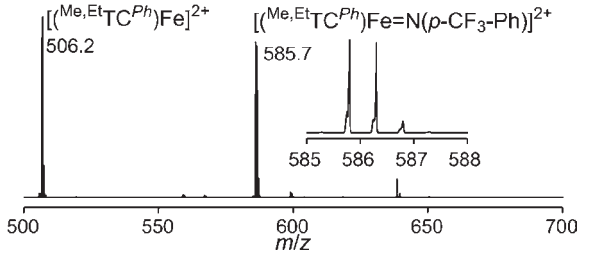


Figure 2. Example ESI-MS spectrum measured for an acetonitrile solution of $[(^{Me,Et}TC^{Ph})Fe{=}N(p\text{-}CF_3{-}Ph)](PF_6)_2$ (a variant of **3**). The inset shows the highlight for the $[(^{Me,Et}TC^{Ph})Fe{=}N(p\text{-}CF_3{-}Ph)]^{2+}$ ion.

On the basis of previously studied aziridination reactions with aryl azides, a potential intermediate in this reaction mechanism is an iron(IV) imide, **3** (Scheme 3).[5] Threefold-symmetric strong σ-donor ligands have been demonstrated to stabilize iron imides in the 2+,[19] 3+,[20] and 4+[21] oxidation states, but these complexes do not react with alkenes to give aziridines. While we have not been able to isolate $[(^{Me,Et}TC^{Ph})Fe{=}NAr](PF_6)_2$ (**3**), the ESI-MS data are consistent with its formation. Addition of 1-azido-4-(trifluoromethyl)benzene to a solution of **2** at room temperature in acetonitrile gave an ESI-MS spectrum with a peak at m/z 585.7 associated with $[(^{Me,Et}TC^{Ph})Fe{=}N(p\text{-}CF_3Ph)]^{2+}$ (Figure 2).

In conclusion, we have synthesized a new iron aziridination catalyst supported by a macrocyclic tetracarbene ligand. This tetracarbene iron complex, $[(^{Me,Et}TC^{Ph})Fe(NCCH_3)_2](PF_6)_2$, was synthesized from the tetraimidazolium precursor $(^{Me,Et}TC^{Ph})(I)_4$ and characterized by NMR spectroscopy, mass spectrometry, and single-crystal X-ray diffraction. This catalyst reacts with aryl azides and a wide variety of substituted aliphatic alkenes to give aziridines in a "$C_2 + N_1$" addition reaction. We were able to form 9-(*p*-tolyl)-9-azabicyclo[6.1.0]nonane in nearly quantitative yield from *cis*-cyclooctene and *p*-tolyl azide. In addition, we were able synthesize aziridines with 2,3-dimethyl-2-butene, a tetrasubstituted alkene. These aliphatic alkenes are generally considered to be more challenging reagents than the styrene variants studied previously. Furthermore, the catalyst can be recovered and reused up to three additional times with only a nominal reduction in yield. To investigate the potential intermediate in the reaction, mass spectrometry data were collected and are consistent with an Fe(IV) imide. These results showcase a more direct approach to the formation of aziridines from readily available substrates with improved atom economy.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
Jenkins@ion.chem.utk.edu

■ ACKNOWLEDGMENT

This research was funded in part by a Joint Research and Development Grant from the State of Tennessee.

■ REFERENCES

(1) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.
(2) Abu-Omar, M. M. *Dalton Trans.* **2011**, *40*, 3435.
(3) (a) Kasai, M.; Kono, M. *Synlett* **1992**, 778. (b) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785. (c) Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587.
(4) (a) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675. (b) Sharma, P.; Kumar, A.; Upadhyay, S.; Sahu, V.; Singh, J. *Eur. J. Med. Chem.* **2009**, *44*, 251. (c) Nemeikaite-Ceniene, A.; Sarlauskas, J.; Anusevicius, Z.; Nivinskas, H.; Cenas, N. *Arch. Biochem. Biophys.* **2003**, *416*, 110.
(5) Fantauzzi, S.; Caselli, A.; Gallo, E. *Dalton Trans.* **2009**, 5434.
(6) Aviv, I.; Gross, Z. *Chem. Commun.* **2007**, 1987.
(7) (a) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 354. (b) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629. (c) Liu, Y.; Che, C.-M. *Chem.—Eur. J.* **2010**, *16*, 10494.
(8) Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2438.
(9) Li, Y.; Gao, L.-X.; Han, F.-S. *Chem.—Eur. J.* **2010**, *16*, 7969.
(10) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
(11) (a) Cenini, S.; Tollari, S.; Penoni, A.; Cereda, C. *J. Mol. Catal. A: Chem.* **1999**, *137*, 135. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Macchi, P.; Casati, N.; Cenini, S. *Organometallics* **2005**, *24*, 4710. (c) Piangiolino, C.; Gallo, E.; Caselli, A.; Fantauzzi, S.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 743.
(12) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 6053.
(13) Bass, H. M.; Cramer, S. A.; Price, J. L.; Jenkins, D. M. *Organometallics* **2010**, *29*, 3235.
(14) (a) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109* 3677. (b) Peris, E. *Top. Organomet. Chem.* **2007**, *21*, 83.
(15) McGuinness, D. S.; Gibson, V. C.; Steed, J. W. *Organometallics* **2004**, *23*, 6288.
(16) Kaufhold, O.; Hahn, F. E.; Pape, T.; Hepp, A. *J. Organomet. Chem.* **2008**, *693*, 3435.
(17) (a) McKie, R.; Murphy, J. A.; Park, S. R.; Spicer, M. D.; Zhou, S.-z. *Angew. Chem., Int. Ed.* **2007**, *46*, 6525. (b) Park, S. R.; Findlay, N. J.; Garnier, J.; Zhou, S.; Spicer, M. D.; Murphy, J. A. *Tetrahedron* **2009**, *65*, 10756. (c) Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S.-z.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 15462.
(18) (a) Soundararajan, N.; Platz, M. S. *J. Org. Chem.* **1990**, *55*, 2034. (b) Poe, R.; Schnapp, K.; Young, M. J. T.; Grayzar, J.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 5054.

(19) Brown, S. D.; Peters, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 1913.
(20) (a) Brown, S. D.; Betley, T. A.; Peters, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 322. (b) Betley, T. A.; Peters, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 10782. (c) Mehn, M. P.; Brown, S. D.; Jenkins, D. M.; Peters, J. C.; Que, L., Jr. *Inorg. Chem.* **2006**, *45*, 7417. (d) Lu, C. C.; Saouma, C. T.; Day, M. W.; Peters, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 4. (e) Scepaniak, J. J.; Young, J. A.; Bontchev, R. P.; Smith, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3158.
(21) (a) Thomas, C. M.; Mankad, N. P.; Peters, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 4956. (b) Nieto, I.; Ding, F.; Bontchev, R. P.; Wang, H.; Smith, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 2716.