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ARTICLE

Bis(imino)pyridine Iron Complexes for Catalytic Carbene Transfer Reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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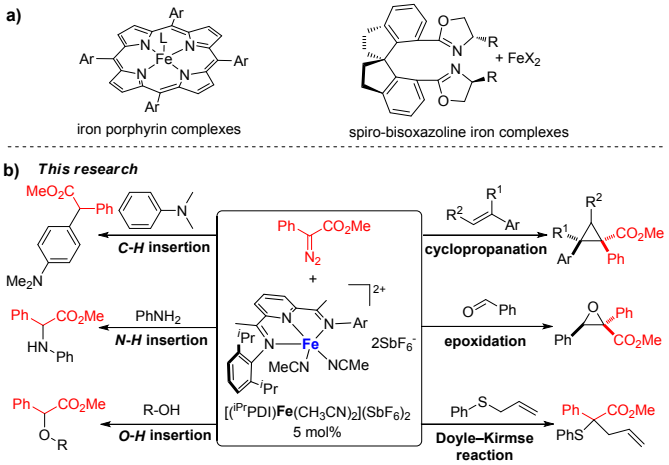
Bis(imino)pyridine iron complex, for the first time, is developed as an effective metal carbene catalyst for carbene transfer reactions of donor-acceptor diazo compound. Its board catalytic capability is demonstrated by a range of metal carbene reactions from cyclopropanation, cyclopropenation, epoxidation, Doyle–Kirmse reaction to O–H insertion, N–H insertion, and C–H insertion reactions. The asymmetric cyclopropanation of styrene and methyl phenyldiazoacetate was successfully achieved by a new chiral bis(imino)pyridine iron catalyst, which delivers a new gateway for the development of chiral iron catalysis for metal carbene reactions.

Introduction

Transition-metal catalyzed carbene transfer reactions occurring through the metal carbene intermediates encompass a vast array of reactants and catalysts to achieve novel and selective strategies for organic synthesis.[1] The reactive carbenoid intermediates can be catalytically generated from diazo compounds by metal catalyzed dinitrogen extrusion,[2] and their reactions extend from addition and insertion to cycloaddition and ylide formation.[3] Dirhodium complexes have been established as the most successful catalysts for carbene transfer reactions of diazo compounds,[4] great achievements have also been accomplished recently by copper and other precious metal catalysts (e.g. ruthenium, palladium, gold)[5]. Iron, the second most abundant metal alone with its biological relevance, is emerging as an important metal for catalytic metal carbene reactions.[6] However, iron catalysis is comparatively underdeveloped than the enduring dominance of precious metal catalysis in metal carbene chemistry.

Since the launching of iron porphyrin catalyzed cyclopropanation by Woo,[7] various carbene transfer processes of diazo compounds, including cyclopropanation, heteroatom-hydrogen bond insertions, and intramolecular C–H inversion, have been achieved by porphyrin and related macrocyclic iron complexes, however, generally occurred with active α-hydrogen-diazocarbonyl compounds, diazoalkanes, or the corresponding precursors.[8] The spiro-bisoxazoline iron complexes developed by Zhou group have exhibited high catalytic activities and selectivities for heteroatom-hydrogen bond insertions and intramolecular cyclopropanation reactions of α-diazoesters.[9] Despite these achievements, iron has not been developed as a catalyst to the same extent as other late transition metals regarding usage in metal carbene reactions. The advance of iron catalysis for general carbene transfer reactions with broad substrate schemes, especially asymmetric processes, and under mild reaction conditions remains a wide-open field for discovery and innovation. We report here, for the first time, the bis(imino)pyridine iron complexes serve as effective catalysts for a range of metal carbene reactions under mild reaction conditions (at room temperature or 40 °C), including cyclopropanation/cycopropenation, epoxidation, Doyle–Kirmse reaction, O–H insertion, N–H insertion, and C–H insertion (Scheme 1). To the best of our knowledge, this bis(imino)pyridine iron catalyst represents the most broad-ranging catalytic activities towards metal carbene reactions of diazo compounds than the previous reported iron catalysis system.[6] The bis(imino)pyridine iron catalyzed cyclopropanation proceeds on a wide range of aryldiazoacetates, vinyldiazoacetate, with styrenes and



Scheme 1 a) Selected iron catalysis for metal carbene reactions. b) This research: bis(imino)pyridine iron catalyzed metal carbene reactions.

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phenylacetylene. Notably, a new chiral bis(imino)pyridine ligand derivatized from *L*-valine methyl ester has been synthesized, and the corresponding enantiopure, C_1-symmetric iron catalyst enabled the asymmetric cyclopropanation of styrene and phenyl diazoacetate.

In the past decade, bis(imino)pyridine chelated iron complexes have emerged as an effective class of catalysis for ethylene polymerization, olefin hydrogenation, hydrosilation, and [2π+2π]-cycloaddition reactions.[10] Owing to its ease of preparation, the bis(imino)pyridine ligand is easily modifiable allowing versatility in ligand design, synthesis, and screening.[10a,b] However, the catalytic metal carbene reactions by bis(imino)pyridine iron complexes have not been achieved. Recently, Chirik reported the formation of a bis(imino)pyridine iron carbene complexes **B** from a stoichiometric amount of bis(imino)pyridine iron dinitrogen complex **A** and diphenyldiazomethane by dinitrogen extrusion (Figure 1).[11] While the attempts to metal carbene reactions, such as cyclopropanation, and C–H insertion, were unsuccessful by this bis(imino)pyridine iron carbene complex.[11,12]

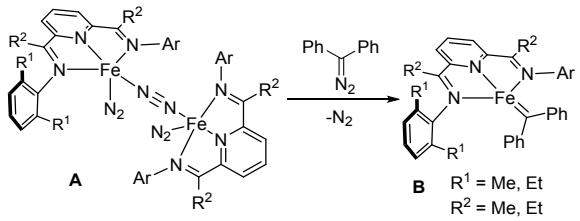


Figure 1 Formation of a bis(imino)pyridine iron carbene from bis(arylimino)pyridine iron dinitrogen complexes and diphenyldiazomethane.[11]

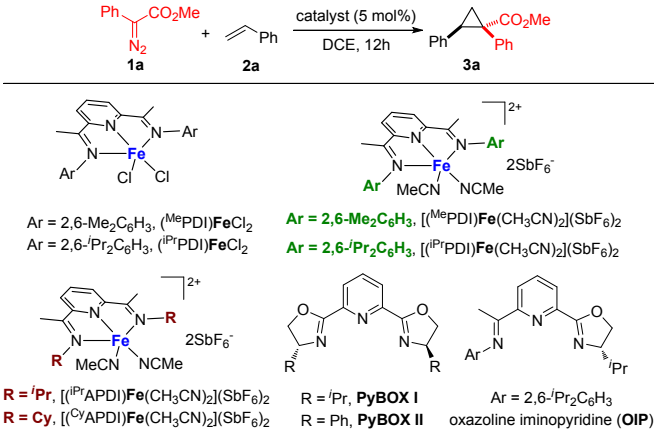
We hypothesized that one reason for the lack of reactivity for bis(imino)pyridine iron carbene complexes **B** in carbene transfer process is due to the charge delocalization induced by the diphenyl group. To address this issue, we predicted that augmenting the electrophilicity of the disubstituted diazo compound would increase the reactivity of the corresponding iron carbene, thus it could more readily engage in carbene transfer reactions.[2b,c] It has been documented that the donor-acceptor metal carbene, which can be produced from donor-acceptor diazo compound by metal catalyzed dinitrogen extrusion, exhibited higher reactivity than the one from diphenyldiazomethane due to its stronger electrophilicity.[1c,3c,4a] Herein, donor-acceptor diazo compound, aryldiazoacetate, was selected as the carbene precursor in this study to investigate the bis(imino)pyridine iron catalyzed metal carbene reactions. Additionally, recent computational studies of bis(imino)pyridine iron complexes for C–H functionalization of donor-acceptor diazo compound also suggests feasibility.[13]

The catalytic cycle for the conversion of a diazo compound to a metal-stabilized carbene intermediate is initiated from the metal catalyzed dinitrogen extrusion of nucleophilic diazo compound. We predicted that, compared to the formally iron(0) complex **A,** the more electrophilic bis(imino)pyridine iron (II) complexes would exhibit higher reactivity towards the nucleophilic diazo compound and facilitate the subsequent metal carbene transfer. Therefore, we aimed to electronically and sterically tune the bis(imino)pyridine iron (II) complexes to achieve the carbene transfer reactions of donor-acceptor diazo compound under mild reaction conditions.

Results and discussion

As a starting point, we focused on the evaluation of a series of bis(imino)pyridine iron(II) catalysts for the cyclopropanation reaction of styrene **2a** with methyl phenyldiazoacetate **1a** (Table 1). As proposed, in the presence of 5 mol% of bis(arylimino)pyridine iron(II) dichloride complexes (entries 1 and 2), the reaction of **2a** and phenyldiazoacetate **1a** afforded the cyclopropanation product **3a**, however, in low yields with predominately recovered starting material. To improve the catalytic activity of iron complexes, the examination of noncoordinating counterions was performed. The employment of more electrophilic iron complexes with hexafluoroantimonate (SbF_6^-) as counterions (entries 3 and 4) led to a marked increase in yield. The combination of

Table 1. Screening of Iron Catalysts for Cyclopropanation.[a]



Entry	Catalyst	T (°C)	Yield[b]
1	$(^{Me}PDI)FeCl_2$	50	14
2	$(^{iPr}PDI)FeCl_2$	50	18
3	$[(^{Me}PDI)Fe(CH_3CN)_2](SbF_6)_2$	rt	65
4	**$[(^{iPr}PDI)Fe(CH_3CN)_2](SbF_6)_2$**	**rt**	**86**
5[c]	$[(^{iPr}PDI)Fe(CH_3CN)_2](SbF_6)_2$	rt	68
6	$[(^{iPr}APDI)Fe(CH_3CN)_2](SbF_6)_2$	50	8
7	$[(^{Cy}APDI)Fe(CH_3CN)_2](SbF_6)_2$	50	< 5
8	$FeCl_2$/PyBOX(I)/$AgSbF_6$	50	< 5
9	$FeCl_2$/PyBOX(II)/$AgSbF_6$	50	< 5
10	$FeCl_2$/OIP/ $AgSbF_6$	50	9

[a] Reaction condition unless otherwise noted: **1a** (0.20 mmol, 1.0 equiv.) in dry DCE (1.0 ml) was added to a 1.0 mL DCE solution of **2a** (1.0 mmol, 5.0 equiv.), and catalyst (0.01 mmol) under N_2 within 1 hour. [b] Yield of isolated product **3a** based on the limiting reagent **1a**. [c]The reaction was performed with **1a**:**2a** = 1:1. (1,2-dichloroethane = DCE).

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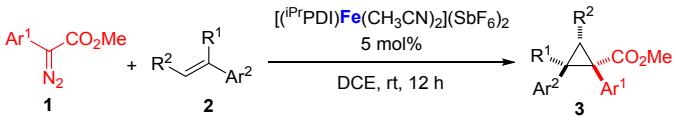
(^{iPr}PDI)FeCl$_2$ and NaBAr$^F_4$ also delivered **3a** with enhanced yield (48%, Table S1). [(^{iPr}PDI)Fe(CH$_3$CN)$_2$](SbF$_6$)$_2$ bearing bulky 2,6-diisopropylphenyl substituents was identified as the best catalyst,[14] which catalyzed the cyclopropanation under room temperature generating **3a** in 86% yield with excellent diastereoselectivity (dr > 20:1). The lower yield of **3a** (entry 5, 68%) was obtained when the reaction was performed with **1a**:**2a** = 1:1 in the presence of [(^{iPr}PDI)Fe(CH$_3$CN)$_2$](SbF$_6$)$_2$. To reveal the imino-substituents effect on the catalyst, iron complexes containing *N*-alkyl substituents were examined. However, they resulted in low catalytic activity with recovery of starting material (entries 6 and 7), which could be due to electronic and/or steric constraints from the imino-alkyl groups. Additionally, neither iron complexes of pyridine bis(oxazoline) ligands, nor oxazoline iminopyridine iron complexes were effective catalysts for this transformation (entries 8 to 10). These results demonstrate the indispensability of the imino-aryl substituent in the ligand frame to conduct active iron catalyst for metal carbene reaction of donor-acceptor diazo compound.

Table 2. Scope of Bis(imino)pyridine iron Catalyzed Cyclopropanation.[a]

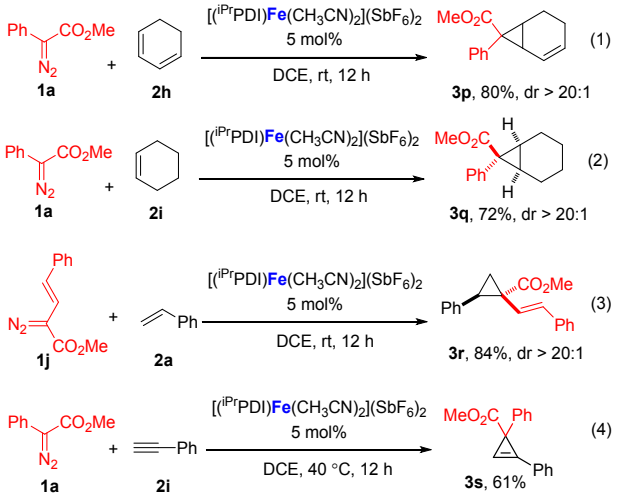


Entry	1	2	yield[b]
1	**1b**, 4-MeC$_6$H$_4$	**2a**, Ph, H, H	**3b**, 81
2	**1c**, 4-MeOC$_6$H$_4$	**2a**, Ph, H, H	**3c**, 83
3	**1d**, 4-ClC$_6$H$_4$	**2a**, Ph, H, H	**3d**, 88
4	**1e**, 4-BrC$_6$H$_4$	**2a**, Ph, H, H	**3e**, 83
5	**1f**, 2-naphthyl	**2a**, Ph, H, H	**3f**, 81
6[c]	**1g**, 4-NO$_2$C$_6$H$_4$	**2a**, Ph, H, H	**3g**, <5
7	**1h**, 2-MeOC$_6$H$_4$	**2a**, Ph, H, H	**3h**, 52
8	**1i**, 2-ClCH$_6$H$_4$	**2a**, Ph, H, H	**3i**, 58
9	**1a**, Ph	**2b**, 4-MeC$_6$H$_4$, H, H	**3j**, 91
10	**1a**, Ph	**2c**, 4-MeOC$_6$H$_4$, H, H	**3k**, 88
11	**1a**, Ph	**2d**, 4-ClC$_6$H$_4$, H, H	**3l**, 90
12	**1a**, Ph	**2e**, 4-CF$_3$C$_6$H$_4$, H, H	**3m**, 67
13[c]	**1a**, Ph	**2f**, Ph, Ph, H	**3n**, 73
14[c]	**1a**, Ph	**2g**, Ph, H, CH$_3$	**3o**, 70

[a] For experimental details, see supporting information. [b] Isolated yield. [c] Reactions were performed at 40°C.

With the optimized condition, we investigated the scope of this bis(arylimino)pyridine iron catalyzed cyclopropanation across a range of aryldiazoacetates and styrene derivatives (Table 2). As indicated by entries 1 to 5, aryldiazoacetates with electron-rich, halogen *para*-substituents and 2-naphthyl group all reacted smoothly with styrene, generating the corresponding cyclopropanes in good yields (81–88%, **3b**-**3f**) with excellent diastereoselectivities (dr > 20:1). However, no reaction occurred with the electron-deficient system even at 40 °C (**1g**, entry 6). Reactions of aryldiazoacetates **1h** and **1j** bearing *ortho*-substituents on the aromatic ring resulted in lower yields (entries 7 and 8). We rationalize that such lower reactivity can be attributed to a higher kinetic barrier for the generation of corresponding iron carbene intermediate, which is caused by the increased steric hindrance between *ortho*-substituent and the bulky bis(imino)pyridine ligand frame. The cyclopropanes **3j**-**3l** derived from styrene derivatives **2b**-**2d** were obtained in yields ranging from 88 to 91%, whereas moderate yield (67%, entry 12) were obtained with 4-(trifluoromethyl)styrene **2e**. Disubstituted styrenes, including *α*-phenylstyrene **2f** and *trans*-*β*-methylstyrene **2g**, were also ideal reagents for this iron catalyzed cyclopropanation, producing products **3n** and **3o** in good yields.

In addition to the styrene derivatives, the reaction of 1,3-cyclohexadiene and **1a** also effectively catalyzed by [(^{iPr}PDI)Fe(CH$_3$CN)$_2$](SbF$_6$)$_2$ affording the cyclopropane product **3p** in 80% yield with dr > 20:1 (eq. 1). Furthermore, as shown in eq. 2, the [(^{iPr}PDI)Fe(CH$_3$CN)$_2$](SbF$_6$)$_2$ catalyzed cyclopropanation of cyclohexene and 1a was also successfully achieved affording the desired product **3q** in 72% yield. To further probe the diazo substrate generality, vinyl-diazoacetate **1j** was subjected to bis(imino)pyridine iron catalyzed cyclopropanation with styrene (eq. 3). Gratifyingly, the cyclopropane product **3r** was obtained in 84% yield, which demonstrates the catalytic capability of bis(imino)pyridine iron for a broader scope of donor-acceptor diazo compounds. Remarkably, [(^{iPr}PDI)Fe(CH$_3$CN)$_2$](SbF$_6$)$_2$ was also capable to catalyze the cylcopropenation of **1a** and phenylacetylene furnishing the product **3s** in 61% yield at 40 °C (eq. 4), which has not been achieved by other reported iron catalysis.



With the accomplishment of achiral bis(arylimino)pyridine iron catalyzed cyclopropanation, we have sought to modify the ligand architecture to generate chiral iron catalyst for asymmetric cyclopropanation. Our catalysts screening (Table 1) indicated that the *N*-aryl substituent in bis(imino)pyridine ligand is indispensable for the effective catalytic activity of iron complexes. Guided by these experimental results and Bianchini's original design of chiral bis(imino)pyridine ligand,[15] we synthesized an enantiopure, C_1-symmetric chiral bis(imino)pyridine ligand [(*S*)-^{VME}PDI] (Scheme 2), in which one

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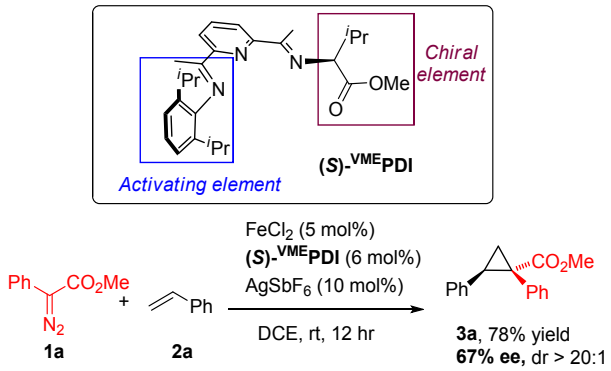
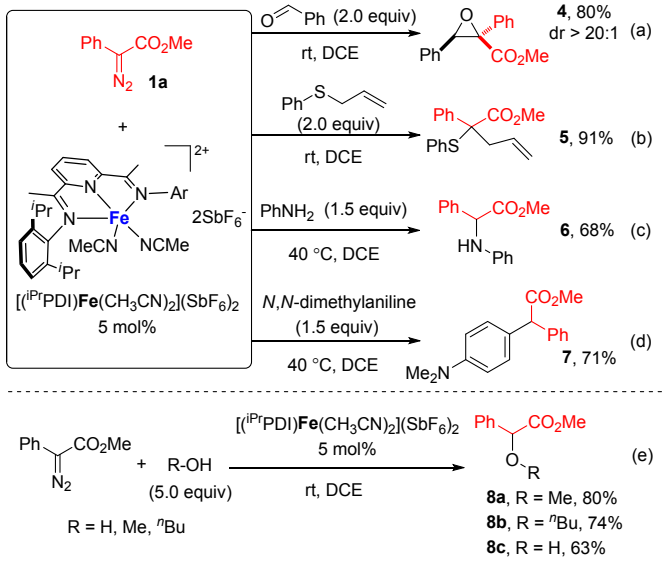


Scheme 2. Chiral bis(imino)pyridine iron catalyzed cyclopropanation.

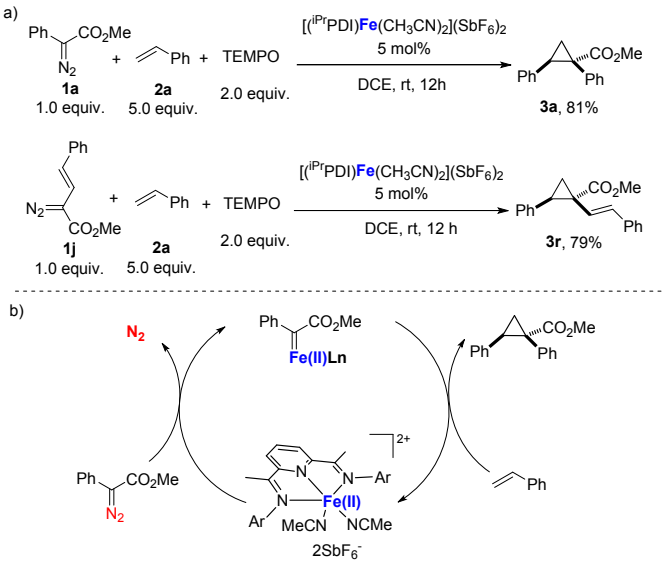
imine is "anchored" by 2,6-diisopropylphenyl group (Activating element) and the other is prepared from *L*-valine methyl ester (Chiral element). To our delight, the asymmetric cyclopropanation reaction of **1a** and styrene was successfully achieved by *in situ* prepared chiral iron catalyst from (*S*)-^{VME}PDI, $FeCl_2$, and $AgSbF_6$ at room temperature. The cyclopropane product **1a** was isolated in 78% yield with 67% enantiomeric excess.[16] Although with moderate enantioselectivity, the success of this asymmetric cyclopropanation reaction provides a strong basis for the development of new chiral bis(imino)pyridine iron catalysis for metal carbene reactions.

Encouraged by the success of bis(arylimino)pyridine iron(II) catalyzed cyclopropanation, we then sought to examine the generality of this iron catalyst for metal carbene reactions. As depicted in Scheme 3, a range of metal carbene reactions of phenyldiazoacetate **1a,** including epoxidation, Doyle–Kirmse reaction, N–H insertion, C–H insertion, and O–H insertion, were all successfully catalyzed by [(^{iPr}PDI)Fe(CH_3CN)$_2$](SbF_6)$_2$. The bis(arylimino)pyridine iron catalyzed reaction of **1a** and benzaldehyde yielded epoxide product **4** in 80% yield with excellent diastereoselectivity at room temperature (Scheme 3a). Under the same condition (Scheme 3b), allyl phenyl sulfide reacted with **1a** smoothly to form the Doyle–Kirmse product **5** in 91% yield. [(^{iPr}PDI)Fe(CH_3CN)$_2$](SbF_6)$_2$ was also capable to catalyze the N–H insertion of aniline and C–H insertion of *N*,*N*-dimethylaniline, although higher reaction temperatures were required (Scheme 3c and 3d). Furthermore, in the presence of 5 mol% [(^{iPr}PDI)Fe(CH_3CN)$_2$](SbF_6)$_2$, O–H insertion reactions of **1a** with methanol, *n*-butanol, and water were achieved furnishing the corresponding products **8a**-**8c** in good to moderate yields (Scheme 3e).

As documented, bis(imino)pyridines have been recognized as radical-based, redox non-innocent ligands, that can directly participate in the electronic structure of metal complexes.[10d,f,17] Chirik's study demonstrated that a carbene radical is engaged in bis(imino)pyridine iron carbene complexes **A,** which is obtained from a formally iron(0) complex (Scheme 2).[11] Therefore, considering the redox activity of bis(imino)pyridine ligand, radical tapping experiments were conducted to address whether a radical carbene involved in this bis(arylimino)pyridine iron(II) catalyzed carbene transfer reactions.[19] As shown in Scheme 4a, addition of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide) did not harm the [(^{iPr}PDI)Fe(CH_3CN)$_2$](SbF_6)$_2$ catalyzed cyclopropanation reactions of **1a** or vinyl-diazoacetate **1j**, and the corresponding products were isolated with similar yields to that from the reactions in the absence of TEMPO. These results reveal the unlikely involvement of the carbene radical intermediate in [(^{iPr}PDI)Fe(CH_3CN)$_2$](SbF_6)$_2$ catalyzed cyclopropanation reactions. Moreover, the achievement of C–H insertion reaction of **1a** with *N*,*N*-dimethylaniline (Scheme 3d) imply the likely generation of donor-acceptor iron(II) carbene intermediate.[1c,6] Based on the obtained experimental results and mechanism study, we propose that the donor-acceptor diazo compound was decomposed by bis(arylimino)pyridine iron(II) catalyst to generate an iron(II) carbene intermediate, which readily undergo cyclopropanation of olefins to afford the cyclopropane product (Scheme 4b).



Scheme 3. Bis(arylimino)pyridine iron catalyzed a) Epoxidation; b) Doyle–Kirmse reaction; c) N–H insertion; d) C–H insertion; and e) O–H insertion.



Scheme 4. a) Mechanism study. b) Proposed mechanism of bis(arylimino)pyridine iron(II) catalyzed cyclopropanation.

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Conclusions

In summary, the effective catalytic activity of bis(arylimino)pyridine iron(II) complexes for carbene transfer reactions of donor-acceptor diazo compounds has been demonstrated by a range of metal carbene transformations from cyclopropanation, insertions, to ylide formation. Notably, asymmetric cyclopropanation of methyl phenyldiazoacetate and styrene has been achieved by a new chiral iron catalyst based on the bis(imino)pyridine ligand derivatized from *L*-valine methyl ester. Future studies will be aimed at developing new asymmetric bis(imino)pyridine iron catalysis for highly enantioselective metal carbene reactions, as well as elucidating the mechanism of such process and nature of the iron carbene intermediate.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Support for this research from Western Kentucky University and the National Science Foundation under Cooperative Agreement No. 1355438 (OIA-1355438, 3200000271-19-136) is gratefully acknowledged.

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