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FeCl₃ as an Ion-Pairing Lewis Acid Catalyst. Formation of Highly Lewis Acidic FeCl₂⁺ and Thermodynamically Stable FeCl₄⁻ To Catalyze the Aza-Diels-Alder Reaction with High Turnover Frequency

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Supporting Information

ABSTRACT: The aza-Diels-Alder reaction of nonactivated dienes and imines was realized through the action of the ionpaired Lewis acid catalyst [FeCl₂]⁺[FeCl₄]⁻ generated by the in situ disproportionation of FeCl₃. The uniquely high reactivity of [FeCl₂]⁺[FeCl₄]⁻ was attributed to both the highly Lewis acidic FeCl₂⁺ and thermodynamically stable FeCl₄⁻ acting as an ion-paired catalyst. Synchrotron-based X-



ray absorption fine structure measurements provided fundamental insights into the disproportionation and structure of the resulting ion-paired iron complex. A theoretical study was performed to analyze the catalytic reaction and better understand the "ion-pairing effect" which transforms simple FeCl₃ into a high turnover frequency Lewis acid catalyst in the aza-Diels-Alder reaction of nonactivated dienes and imines.

nderstanding the unique character of first-row transition metals as abundant, nontoxic metal catalysts has become an important topic of research since such fundamental findings can help develop new transformations that can realize the practical chemical production of valuable organic materials.¹ Herein, we report that readily available FeCl₃ shows high Lewis acidity as a catalyst for the aza-Diels-Alder reactions of nonactivated dienes and imines to provide tetrahydropyridines. Although recognized as a simple reaction, it is, in fact, difficult to accomplish due to the low energy level of the HOMO of the diene (compared to those of activated dienes such as the Danishefsky and Rawal types) as well as the high energy level of the imine LUMO. Thus, the development of a practical Lewis acid catalyst with a high turnover frequency (TOF) for convenient transformation is still in demand.² Furthermore, considering that a late-stage aza-Diels-Alder reaction with a nonactivated diene and imine could be a powerful tool that would offer an alternative strategy for the total synthesis of natural compounds and manufacture of medicinal drugs, the development of a new catalyst that promotes the highly chemoselective reaction based on an abundant, nontoxic metal would be quite desirable.

Swanson and Laurie originally described the disproportionation of FeCl₃ upon the coordination of polar solvents such as DMF and pyridine (Scheme 1).³ On the basis of their findings, FeCl₃ disproportionation has been applied to generate reactive oxidation catalysts in organic synthesis, as exemplified by the independent seminal works of Tobinaga, Frazier, Jr., Overmann, and MacMillan.⁴ We envisioned that the disproportionation of FeCl₃ would also be triggered upon coordination with an imine, e.g., as the dienophile in the aza-Diels-Alder





reaction, instead of a polar solvent molecule, forming the highly Lewis acidic FeCl₂⁺ species along with the thermodynamically stable FeCl₄-. Consequently, the LUMO of the imine would be lowered and the dienophile's reactivity with a nonactivated diene would be enhanced to accomplish a simple, convenient metal-catalyzed aza-Diels-Alder reaction. To prove our hypothesis, we initially examined the Lewis acidity of FeCl₃ via IR spectroscopy, measuring the carbonyl stretching vibration of its 2,6-dimethyl-y-pyrone complex in nonpolar solution (Figure 1),⁵ where a larger shift $(\Delta \nu_{C=0})$ in the carbonyl absorption peak indicates higher Lewis acidity. In the event, FeCl₃, which disproportionates to [FeCl₂]⁺[FeCl₄]⁻, shows high Lewis acidity relative to various common Lewis acids. Encouraged by these results, we next investigated the disproportionation of FeCl₃ upon coordination with Nsulfonylated imine 1a, which contains a Lewis basic oxygen atom to coordinate with the Lewis acid (Scheme 2). The disproportionation and formation of ion-paired complex $[FeCl_2(1a)_2]^+[FeCl_4]^-$ (CP1) was confirmed spectroscopically. Formula determination by MALDI-MS was consistent

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Figure 1. IR C=O stretching vibration analysis. (a) 2,6-Dimethyl- γ -pyrone with 1 equiv of Lewis acid. (b) MAD: methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). (c) With addition of an equivalent amount of the 1-butyl-3-methylimidazolium salt [Bmim]⁺[X]⁻.

Scheme 2. Disproportionation of FeCl₃ upon Coordination with Imine 1aTo Form Ion-Paired Complex [FeCl₂(1a)₂]⁺[FeCl₄]⁻ (CP1)



with that theoretically calculated for a cationic iron complex with two imine and two chloride ligands, which is identical to that of $[M(CP1)-FeCl_4^-]^+$, i.e., $[FeCl_2(1a)_2]^+$. Furthermore, the UV-vis spectrum revealed the formation of FeCl₄⁻ by comparison with the spectrum for [Bmim][FeCl₄] as a reference compound. To gain further insight into CP1, Fe K-edge X-ray absorption spectroscopy (XAS) was performed using a synchrotron radiation beamline, where the ultrahigh brightness made solution-phase XAS accessible for in situ structural investigation. Analysis of the extended X-ray absorption fine structure (EXAFS) spectrum of the solution of FeCl₃ with imine 1a in toluene clearly indicated good agreement with the theoretically calculated CP1 model (Figure 2). A significant pre-edge peak in the X-ray absorption near edge structure (XANES) also indicated the formation of an iron species with tetrahedral geometry (Supporting Information).⁶ Furthermore, a calculated absorption spectrum using the finite difference method for postulated complex CP1 resulted in good agreement with the experimentally obtained XANES spectrum. Based on these results, we confirmed that the disproportionation of FeCl₃ generates the highly Lewis acidic $FeCl_2^+$ via the coordination of two imine molecules along with the formation of the thermodynamically stable FeCl₄⁻, which leads to the in situ generation of ion-paired iron complex CP1.



Figure 2. Solution-phase Fe K-edge EXAFS analysis (Fourier transform of k^3 -weighted spectrum: experimentally determined (solid line) and FEFF-calculated fitting of DFT model **CP1** (dashed line).

To assess the catalytic reactivity of in situ generated **CP1**, we next examined the aza-Diels–Alder reaction of imine **1a** and diene **2a** in the presence of FeCl₃ in toluene at 25 °C for 2 h (Figure 3). The reaction afforded cycloadduct **3aa** in almost

Ph	H H	2a	Lewis acid catalyst (1 mol %) toluene, 25 °C, 2 h	Ts N Ph 3aa
Lewis acid yield $(\%)^{b}$			Lewis acid	yield $(\%)^b$
none	<1		$B(C_{6}F_{5})_{3}$	<1
FeCl ₃	>99	$(92)^{c}$	RuCl ₃	<1
FeCl ₃ ^d	78		$FeCl_3 + Cl^{-e}$	<1
FeCl ₂	<1		$FeCl_3 + SbF_6^{-e}$	>99
AlCl ₃	22		$FeCl_3 + FeCl_4^{-e}$	>99
MAD	<1		$\operatorname{FeCl}_3 + \operatorname{FeCl}_4^{-d,e}$	75

Figure 3. Effect of Lewis acid catalysts on the aza-Diels–Alder reaction of imine 1a with diene 2a. (a) Lewis acid (1 mol %), imine 1a (0.2 mmol), diene 2a (0.4 mmol), solvent (2 mL), 25 °C, 2 h. (b) NMR yields. (c) Isolated yields. (d) Reaction for 1 h in dichloromethane. (e) Reactions were carried out with the addition of imidazolium salt $[Bmim]^+[X]^-$ (1 mol %) in dichloromethane.

quantitative yield, even with 1 mol % catalytic loading. The reaction with other Lewis acids such as AlCl₃, MAD, $B(C_6F_5)_3$, and RuCl₃ resulted in lower yields. To gain insight into the disproportionation of FeCl₃ to form cationic FeCl₂⁺ and anionic $FeCl_4^-$ in terms of catalytic reactivity, the reaction was examined with FeCl₃ in the presence of imidazolium salts which possessed the counteranions Cl⁻, SbF₆⁻, and FeCl₄⁻. The addition of Cl⁻ dramatically retarded the reaction because the excess Cl⁻ coordinated with FeCl₃ to form the stable but inactive anion FeCl_4^- . In contrast, in the presence of SbF_6^- , the reaction proceeded without any inhibition of reactivity. Notably, with the addition of FeCl₄⁻, the reaction was not impeded, since FeCl₄⁻ behaves as a noncoordinating anion. These results are consistent with the aforementioned IR-based Lewis acidity estimates for the 2,6-dimethyl- γ -pyrone-coordinated iron complexes with or without imidazolium salts (the last three rows in Figure 1). Therefore, the disproportionation of FeCl₃ concomitantly generates the strongly Lewis acidic $FeCl_2^+$ with coordination of imine 1a, which indeed facilitates the aza-Diels-Alder reaction with nonactivated diene 2a. To demonstrate the scope of the in situ generated CP1-catalyzed aza-Diels-Alder reaction, we examined the reactions of various imines 1 with conjugated dienes 2 (Figure 4). Under the optimized reaction conditions, functional groups such as nitro, ester, ether, and halogen groups were tolerated, giving the



Figure 4. Aza-Diels–Alder reactions. (a) $FeCl_3$ (1 mol %), imine 1 (0.2 mmol), diene 2 (0.4 mmol), toluene (2 mL), 2 h. (b) Isolated yields. (c) 6 h. (d) $FeCl_3$ (3 mol %), 25 °C, 6 h. (d) $FeCl_3$ (5 mol %), 50 °C, 6 h.

corresponding substituted cycloadducts in high yields (3baia). These results highlight the excellent functional group compatibility of the CP1-catalyzed reaction, which is ascribed to the selective and substantial Lewis acid/base affinity of CP1 toward the oxygen atom on the *N*-sulfonylated imine. The reaction using *N*-substituted imines with simple alkyl or aryl substitutes resulted in low yields.

To understand the electronic character of the ion-paired Lewis acid catalyst **CP1** in the aza-Diels–Alder reaction, we performed a series of DFT calculations. Based on spectroscopic observations, the $[FeCl_2(1a)_2]^+[FeCl_4]^-$ (**CP1**) species formed via the coordination of two molecules of imine **1a** to FeCl₃ was reasonably employed as the active species of this catalytic reaction. The DFT calculations supported the catalytic cycle involving the $[FeCl_2]^+[FeCl_4]^-$ complex, as shown in Figure 5a. First, the coordination of imine **1a** to

FeCl₃ forms CP1; then C–C bond formation with the addition of diene 2a occurs with a Gibbs activation energy of 21.1 kcal/ mol via TS1, which is the TOF-determining transition state (TDTS, vide infra). This is followed by cyclization to form the C-N bond in an "energy-concerted bonding stepwise manner" to afford CP2.⁷ The dissociation of 3aa from an iron atom proceeds via coordination of another imine laa to form thermodynamically stable five-coordination trigonal bipyramidal complex CP3, which is the TOF-determining intermediate (TDI, vide infra). Finally, cycloadduct 3aa is dissociated from iron with small endergonic energy (2 kcal/mol) to regenerate initial active species CP1'. To better understand how the $[FeCl_2]^+[FeCl_4]^-$ catalyst accelerates the addition of diene to imine with TS1, we investigated the step electronically through fragment molecular orbital (FMO) analysis (Figure 5b).8 During formation of the C–C bond at TS1, the dienyl HOMO overlaps well with the imino LUMO (π^*_{C-N} antibonding orbital). The population of the imino LUMO considerably increases to 0.587 e in TS1, while the population of the dienvl HOMO considerably decreases to 1.398 e. These results clearly indicate that charge transfer (CT) substantially occurs from the diene π orbital to the antibonding LUMO of the imine. That is, this CT stabilizes the TS1 and increases the electron population of the imine moiety, which contributes to C-C bond formation. Next, the proposed catalytic cycle for the aza-Diels-Alder reaction was analyzed by the energetic span model.⁹ In this model, the TOF of the catalytic cycle can be measured with the energetic span δG , which is the difference in the Gibbs energy between the TOF-determining transition state (TDTS) and the TOF-determining intermediate (TDI), with the addition of the global Gibbs energy of the reaction when the TDTS appears before the TDI. TDTS and TDI are the most unstable and most stable species in the catalytic cycle, respectively. Therefore, δG is a genuinely effective barrier of the global reaction in the catalytic cycle, which can be subsequently used to estimate the TOF. Calculated δG values for this reaction and other catalytic systems are summarized in Figure 6, to compare the unique catalytic reactivity of FeCl₃ with analogous ion-paired catalysts $[AlCl_2]^+[AlCl_4]^-$ (via disproportionation of $AlCl_3)^{10}$ and $[RuCl_2]^+[RuCl_4]^-$ (via disproportionation of RuCl_3), and nonion-paired cationic iron catalyst [FeCl₂]⁺ without [FeCl₄]⁻. The reaction with $[AlCl_2]^+[AlCl_4]^-$ has slightly larger δG (27.5 kcal/mol) and slightly lower relative TOF (relTOF) values compared to [FeCl₂]⁺[FeCl₄]⁻, which is mainly attributed to the high energy TDTS involving the coordination of four



Figure 5. (a) Calculated free energy profile for the transformation. (b) Important Kohn–Sham MOs (electron population and orbital energy) of imine and diene moieties in TS1. (c) Natural bond orbital analysis in TS1.

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catalyst	TDTS ^a	TDI^{a}	δG^b	<i>rel</i> TOF ^c
$[FeCl_2]^+[FeCl_4]^-$	21.1 (TS1)	-16.2 (CP3)	23.1	1
$[AlCl_2]^+[AlCl_4]^-$	24.5 (TS1)	-17.2 (CP3)	27.5	1.2×10^{-2}
$[RuCl_2]^+[RuCl_4]^-$	23.3 (TS1)	-28.2 (CP3)	34.7	1.0×10^{-7}
$[FeCl_2]^+$	40.6 (TS1)	-14.2 (CP1')	40.6	2.6×10^{-8}

Figure 6. Energetic spans in several catalytic systems. (a) Gibbs free energy (kcal/mol). (b) Energetic span (kcal/mol). (c) Relative turnover frequency normalized to the value for $[FeCl_2]^+[FeCl_4]^-$.

imine molecules to form $[AlCl_2(1a)_4]^+[AlCl_4]^-$ as the initial active species with decreased Lewis acidity. The reaction with $[RuCl_2]^+[RuCl_4]^-$ has a very low-lying TDI (CP3) that results in a large δG (34.7 kcal/mol) and low relTOF. This is essentially because the ruthenium(III) complex has a longer metal-ligand bond than iron(III), and thus, a thermodynamically stable five-coordination trigonal bipyramidal geometry with less steric repulsion is preferred. We also found that the reaction of the [FeCl₂]⁺ catalyst without a counteranion has an energetically high-lying **TDTS** leading to a high δG (40.6 kcal/ mol). Therefore, in the ion-paired complex $[FeCl_2]^+[FeCl_4]^-$, both [FeCl₂]⁺ and [FeCl₄]⁻ promote the reaction efficiently by lowering the TDTS and also raising the TDI, respectively, narrowing the δG in the catalytic cycle. Of note, second-order perturbation theory analysis in NBO basis for donor-acceptor orbital interactions corresponding to the TS1 of [FeCl₂]⁺[FeCl₄]⁻ catalysis shows only faint orbital interactions between $[FeCl_4]^-$ and the remainder of the reacting fragment (Figure 5c), suggesting that a long-range electrostatic interaction dominates over the short-range orbital interaction for thermodynamic stabilization to realize the low-lying activation energy of TS1 as TDTS.

In conclusion, we succeeded in developing a practical catalyst for the aza-Diels-Alder reactions of nonactivated dienes and imines using FeCl₃, which forms the highly Lewis acidic $FeCl_{4}^{+}$ and thermodynamically stable $FeCl_{4}^{-}$ that act as the ion-paired catalyst $[FeCl_2]^+[FeCl_4]^-$ after in situ disproportionation upon imine coordination. The disproportionation was confirmed spectroscopically, and the catalytic cycle was analyzed theoretically. The high TOF reactivity of the catalyst was rationalized with the energetic span model; $[FeCl_2]^+[FeCl_4]^-$ realizes both a low-energy TOF-determining transition state (TDTS) and a high-energy TOF-determining intermediate (TDI). The obtained fundamental understanding of this first-row transition metal Lewis acid catalyst will provide new ideas for promoting catalytic reactions with high TOFs in other reactions. Asymmetric Lewis acid catalyzed reactions with high TOFs as a practical organic synthetic method should also be realizable; these studies are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

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Experimental procedures; spectroscopic and analytical data for new compounds (PDF)

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Notes

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