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RESEARCH ARTICLE

Iridium-catalyzed enantioselective hydrogenation of oxocarbenium ions: a case of ionic hydrogenation

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Dedication ((optional))

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Abstract: Compared to the classic "inner-sphere" transition metal catalyzed homogeneous hydrogenation reactions, ionic hydrogenation has been a far less explored area. This type of hydrogenation reaction, however, has its advantages for some challenging substrates such as unsaturated intermediates. We herein report an iridium-catalyzed hydrogenation of oxocarbenium ions to afford chiral isochromans smoothly with high enantioselectivities. A variety of functionalities are compatible with this catalytic system. In the presence of catalytic amount of Brønsted acid HCl, α-chloroether was *in situ* generated and subsequentially reduced. Kinetic studies suggested 1st-order kinetics in the substrate and half-order kinetics in the catalyst. A positive nonlinear effect, together with the half kinetic order, revealed a dimerization off the catalytic cycle. Several possible reaction pathways based on the monomeric iridium catalyst were proposed and DFT computational studies revealed an ionic hydrogenation pathway. Chloride abstraction and the cleavage of dihydrogen occur at the same step.

Introduction

Platinum group metal catalyzed hydrogenation of C=C, C=O and C=N bonds plays a crucial role in the realm of homogeneous catalysis[1]. The addition of dihydrogen to unsaturated compounds has undoubtedly found its merit in both pharmaceutical and chemical industries[2]. The mechanisms of the above-mentioned hydrogenation catalyzed by various transition metals (namely rhodium, ruthenium and iridium) have been well studied and documented, which could be summarized as the classic "inner-sphere" hydrogenation reactions having a coordinating-insertion pattern (Figure 1a). On the other hand, ionic hydrogenation[2-3], which delivers proton and hydride separately, shows a different reaction pattern that does not involve the coordination of substrate and the insertion of the unsaturated bond (Figure 1b, 1c). This different reaction pattern typically requires a metal hydride complex and a Brønsted acid: an *in situ* formed carbenium intermediate is prone to be reduced by a hydride species. Compared to "inner-sphere[4]" hydrogenation reactions which dominate the asymmetric hydrogenation processes, ionic hydrogenation is far less developed. Advantages of ionic hydrogenation include: (1) noninvolvement of change in the valence of the transition metal having the potential to enable a high turnover number (TON); (2) chemoselectivity for polar C=O and C=X bonds over nonpolar C=C bonds. The formation of a carbenium species generally requires an acid, under which condition a majority of metal hydride complexes are not compatible.

Oxocarbenium ions are a special class of carbocations. With a resonance structure of the $C=O^+$ unit, the carbon cation could be stabilized with the conjugation from the adjacent oxygen atom. This feature makes them much more stable and therefore in a higher concentration. Asymmetric transformations based on oxocarbenium ions have drawn chemical practitioners' attention in the recent decade. Since Jacobsen and co-workers' studies on thiourea-catalyzed addition reaction[5], many catalytic methodologies based on oxocarbenium ions have been developed, such as nucleophilic addition of enolate[6], alkynylation[7], acetalization[8], oxa-Pictet-Springler reaction[9] and reduction[10]. A practical and commonly applied method to access oxocarbenium ions is the elimination of a leaving group. In this equilibrium, if the leaving anion could be trapped by another molecule via molecular recognition, the formation of oxocarbenium ions will be favored. We recently developed a bifunctional ligand, ZhaoPhos[11], aiming to incorporate a thiourea moiety on a bisphosphine ligand to render a secondary interaction with a substrate. Anion binding of thiourea with substrates assists to achieve high efficiencies and high enantioselectivities in homogeneous hydrogenation of cationic C=N bonds present in iminium[12], (iso)quinolinium[13] and indolinium ions[14]. We

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envisioned that this type of highly reactive intermediates could be captured by thiourea[15] and be reduced by metal hydride complexes in an ionic hydrogenation manner[16]. Herein, we report an iridium catalyzed hydrogenation of oxocarbenium ions to afford chiral isochromans smoothly with high enantioselectivities.

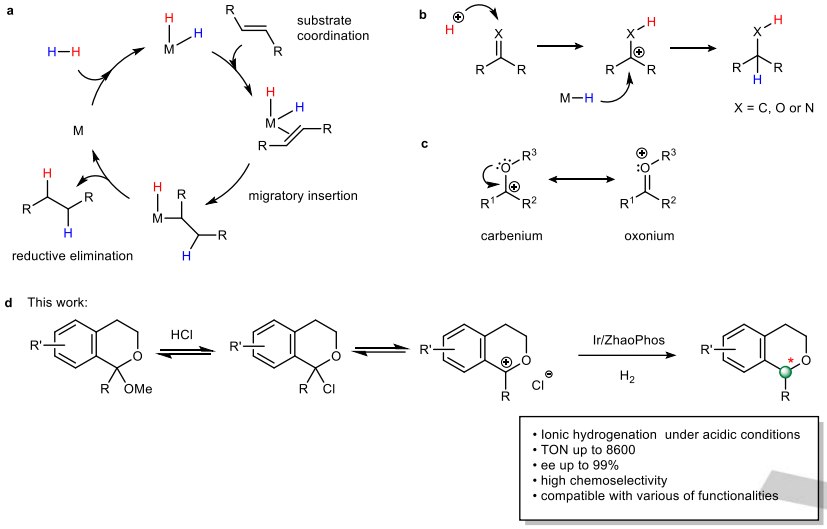

Figure 1. Ionic hydrogenation of carbocation intermediate. **a**, General mechanism of the classic "inner-sphere" hydrogenation of olefins. **b**, A stepwise ionic hydrogenation reaction. **c**, Resonance structures of oxocarbenium ions. **d**, A practical strategy to generate oxocarbenium ions and ionic hydrogenation.

Results and Discussion

Condition optimization. 1-Methyl-1-methoxy isochroman (ketal **1a)** was selected as the oxocarbenium precursor. Initially, trimethylsilyl triflate[7c] (TMSOTf) was applied as Lewis acid and $[Rh(COD)Cl]_2$ as the transition metal precursor. Commonly used chiral ligands in asymmetric hydrogenation reactions, such as DuanPhos, BINAP, QuinoxP* and the Josiphos family, failed to catalyze this reaction. In contrast, catalyzed by a Rh/ZhaoPhos complex, the hydrogenation reaction proceeded with full conversion, although the enantioselectivity was poor (only 12% ee, Table 1, entry 1). Lewis acid boron trichloride and Brønsted acid HCl also worked in this reaction with a minor improvement of ee. Alternation of transition metal to palladium and iridium resulted in two different enantioselectivities: $Pd(TFA)_2$ gave almost racemic product while $[Ir(COD)Cl]_2$ boosted the ee up to 97%. After further screening, the optimal condition was obtained: 1-methylisochromane was cleanly formed with remarkably high enantioselectivity and full conversion (99% ee in toluene). Isochroman ketal was also fully consumed in DCM, DCE, and THF but by-products, which we were unable to identify, were observed in these solvents. We hypothesize that a cation-π interaction could stabilize the highly reactive oxocarbenium ion, making the hydrogenation reaction proceeding smoothly[17]. Other commercial HCl solutions, such as HCl in dioxane, do not show noticeable differences (entry 9). However, there was no hydrogenation product in the reaction without acid (entry 10).

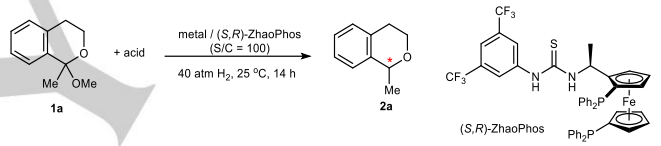

Table 1. Condition optimization for hydrogenation: from isochroman ketal to isochroman.

entry	metal precursor	acid	solvent	conv. [a]	ee [b]
1	$[Rh(COD)Cl]_2$	TMSOTf (1.0 eq)	DCM	>95%[e]	12%
2	$[Rh(COD)Cl]_2$	BCl3 (0.35 eq)	DCM	>95%[e]	36%
3	$[Rh(COD)Cl]_2$	HCl (1.0 eq) [c]	DCM	>95%[e]	39%
4	$Pd(TFA)_2$	HCl (1.0 eq) [c]	DCM	>95%[e]	<2%
5	$[Ir(COD)Cl]_2$	HCl (1.0 eq) [c]	DCM	>95%[e]	97%
6	$[Ir(COD)Cl]_2$	HCl (1.0 eq) [c]	DCE	>95%[e]	97%
7	$[Ir(COD)Cl]_2$	HCl (1.0 eq) [c]	THF	>95%[e]	92%
8	$[Ir(COD)Cl]_2$	HCl (1.0 eq) [c]	toluene	>95%	99%
9	$[Ir(COD)Cl]_2$	HCl (1.0 eq) [d]	toluene	>95%	99%
10	$[Ir(COD)Cl]_2$	No acid	toluene	0	N.A.

[a] Reaction condition: **1a** (0.1 mmol) in 1.0 mL solvent, **1a**/metal/ligand ratio=100/0.50/1.0. Conversion was determined by ^1H NMR analysis. [b] The ee value was determined by HPLC on a chiral stationary phase. [c] 0.10 mL of HCl (1.0 M in AcOH) was added. [d] 0.025 mL of HCl (4.0 M in dioxane) was added; [e] Detectable impurities were observed in the reaction mixture.

The reactive nature of oxocarbenium ion favors a high TON in this chemical transformation and the experimental results approved the hypothesis mentioned above: under a minor-modified condition, the TON could approximately reach 8600 at a large scale. In addition, at a lower hydrogen pressure (e.g. 10 atm) or even at ambient condition, 1-methylisochroman was formed with high enantioselectivity (99% ee). In addition, lowering

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the loading of the Brønsted acid HCl to 10% did not diminish the conversion or enantiomeric excess dramatically. [For reaction details, see supporting information.]

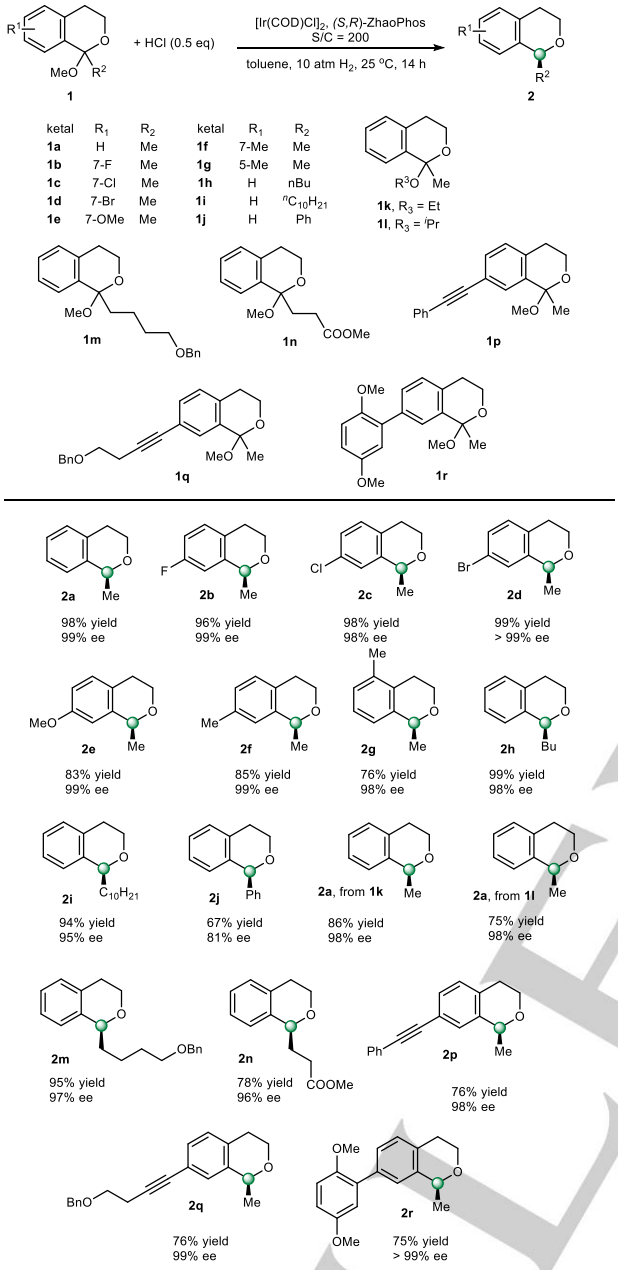

Figure 2. Asymmetric hydrogenation of oxocarbenium ions: from isochroman ketals to chiral isochromans. Reaction condition: 1 (0.2 mmol), 1/[Ir(COD)Cl]2/ZhaoPhos = 400:1.0:2.05/2.0, 0.1 mL HCl (1 M in acetic acid) in 1.0 mL toluene, Isolated yields. Enantiomeric excesses were determined by HPLC on a chiral stationary phase.

Scope of asymmetric hydrogenation of oxocarbenium ions. Various isochroman ketals were prepared and tested under the optimal condition (Figure 2). Different substituents did not bring significant change in reactivities or enantioselectivities. Isochroman ketals with either electron-donating group (-OMe) or electron-withdrawing group (-F) on the benzene ring could be transformed to chiral isochroman with high enantioselectivities. Other halogen atoms (Cl, Br) on the benzene ring did not bring significant changes. Altering the substituents on 1-position afforded various chiral isochromans with this method. However, isochroman acetal with a phenyl group led to an eroded enantioselectivity (**2j**). Ethyl or isopropyl acetal was prepared when the acetal cyclization was conducted in different alcoholic media (**1k** and **1l**). No obvious difference in enantioselectivity was observed when performing this hydrogenation reaction using methyl, ethyl or isopropyl isochroman ketal (**2a, 2k** or **2l**). Functional groups like ether and ester could tolerate the reaction condition (**2m** and **2n**). Interestingly, a C≡C bond, which is often sensitive in many transition metal catalyzed hydrogenation systems[2], is finely compatible in this system (**2p** and **2q**). This chemoselectivity suggests an ionic hydrgeonation mechanism.

In order to exploit the potential application of this method in synthetic communities, robustness of the catalyst and compatibility with different functionalities should be evaluated. We applied Glorius' method[18] to carry out a fast screening (see supporting information). This chemical transformation showed compatibility with many functionalities, such as carboxylic acid, amide, nitro, nitrile, phenol and ketone. In accordance with the reaction of alkynyl substrates, various alkynes survived in this reaction. Moreover, the introduction of thiophene did not influence this reaction, while pyridine made it sluggish and less enantioselective. The excellent chemoselectivity demonstrated the potential application of this method in synthetic chemistry.

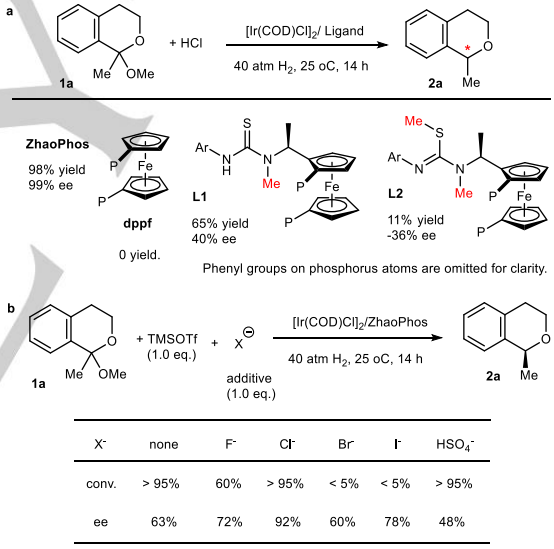

Figure 3. Examination of the role of the thiourea-chloride anion binding. a, control experiments with ferrocene-based bisphosphine ligands analogical to ZhaoPhos demonstrated the importance of the double hydrogen donor. b. introduction of various counterions indicates the superiority of chloride.

Control experiments. To evaluate the role of anion binding between thiourea and chloride in this catalysis, we conducted a series of control experiments: iridium with dppf fails to catalyze this hydrogenation, resulting in a recovery of most of the substrate; methylation of thiourea leads to a sharp decrease in both yield and enantioselectivity (Figure 3a, **L1** and **L2**). The hydrogen bond donor, thiourea, undoubtedly plays a crucial role in this reaction. In addition, counter-ion effect was also evaluated: triflate ion gives poor enantioselectivity when using TMSOTf as the Lewis acid; the introduction of various anions in this reaction alters both the conversion and the ee (Figure 3b). Chloride gives the highest enantioselectivity (92% ee, close to the result from the

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optimized condition), showing its superiority over other counterions.

Reaction pathway. A question emerged after the success of this enantioselective chemical transformation: what is the reaction pathway? Hydrogen chloride was applied in the formation of *α*-chloroamide via a proposed S_N1 pathway[19]. In this case, we hypothesized that the formation of chloroisochroman occurs before the oxocarbenium ion[5]. To verify our assumption, many attempts were made to isolate 1-chloro-1-methylisochroman. To our disappointment, we failed to obtain a pure form of it, probably because it is less stable than 1-chloroisochroman in Jacobsen's case[5]. However, evidences were still collected to support this reaction pathway. The mixing of HCl (4.0 M in dioxane, 1.0 eq.) and **1a** yielded a product with a methyl signal at δ 2.0 ppm (Figure 4a, marked purple) in ^{1}H NMR spectrum. The signal belongs to neither the isochroman acetal (δ ~1.6 ppm) nor a carbenium ion intermediate[20] (δ > 3 ppm), suggesting that this compound is likely to be chloroisochroman (**1a'**)[21]. In addition, each set of diastereotopic protons on the ring merged to one triplet peak (Figure 4a, marked red and blue), indicating an equilibrium between the two enantiomers of 1-chloro-1-methylisochroman via an oxocarbenium intermediate. The broadened methyl peak at δ 2.0 also indicated the existence of this equilibrium. The mixture of **1a** and HCl in benzene-d6 gave a similar spectrum (see supporting information). Variating the ratio of HCl to **1a** makes the methyl peak shift from 1.6 to 2.0 (Figure 4b), suggesting a fast equilibrium between **1a** + HCl and **1a'** + MeOH. DFT calculation results (*vide infra*) showed that the formation of **1a'** and MeOH is thermodynamically favored by 2.1 kcal/mol in toluene.

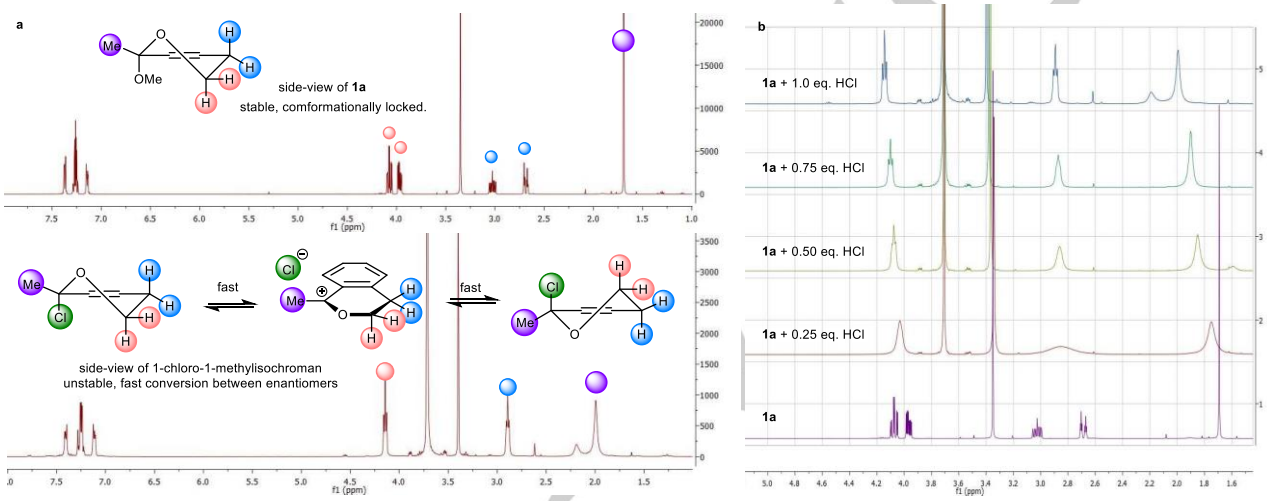
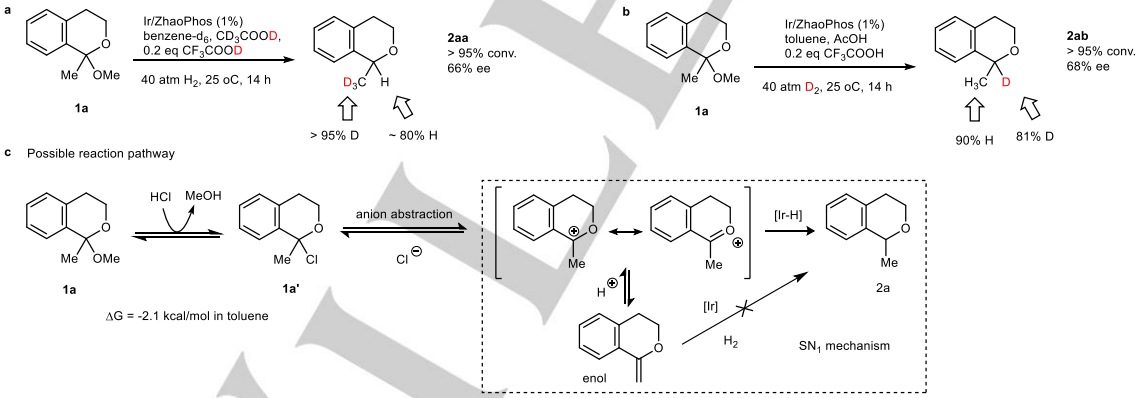


Figure 4. The transformation of acetal **1a** to α-chloroether.



Scheme 1. Deuterium labelling experiments and proposed reaction pathway.

Isotope labeling experiments (Scheme 1a and 1b) were also conducted to reveal the reaction pathway of this reaction. The combination of hydrogen gas with deuterated solvents and acid gave a methyl deuterated isochroman. High abundance of D atoms on the methyl group suggested a fast equilibrium between an oxocarbenium ion and a terminal enol ether. On the other hand, the combination of deuterium gas with normal solvent and acid gave expected C-1 deuterated compound. Noteworthy, the abundance of H or D atoms at C-1 position in each case was not 100%, suggesting a possible H-D exchange under the reaction condition[22]. Based on these studies, we proposed a plausible reaction pathway (Scheme 1c): in the presence of hydrogen chloride, isochroman acetal is converted to chloroisochroman, which forms a reactive oxocarbenium ion after anion abstraction with thiourea catalyst[23]. An iridium hydride complex reduces this oxocarbenium ion to afford the chiral isochroman product.

Kinetic and nonlinear effect experiments. Kinetic profiles were obtained with *in situ* attenuated total reflectance Fourier-

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transform infrared (ATR FTIR) spectroscopy. In a minor-modified condition (0.5 eq. HCl, 20 atm H_2 pressure, see supporting information), graphical rate equation[24] displayed a 1st order dependence on the substrate. This reaction, however, has an induction period with higher catalyst loading (e.g. S/C = 125). Kinetic studies with different catalyst concentration revealed that this reaction exhibits half-order kinetics in catalyst (see supporting information). This behavior suggested a dimerization of the catalyst and that Kagan's reservoir effect[25] might apply in this case. In other words, the monomeric species, rather than the dimeric ones, catalyze this transformation[26]. Rate equation was derived and the constant was obtained ($k'_{cat} = (9.85 \pm 0.18) \times 10^{-3}\ \mathrm{M}^{-\frac{1}{2}} \cdot \mathrm{s}^{-1}$). Catalytic monomeric species seemed in a very low proportion in the reaction mixture. The potential aggregation of the catalyst encouraged us to examine the relationship of enantio-purity of the catalyst and the enantioselectivity. A pronounced positive nonlinear effect was observed, which suggested that the heterochiral dimer is much favored over the homochiral ones in this equilibrium ($K \gg 1$).

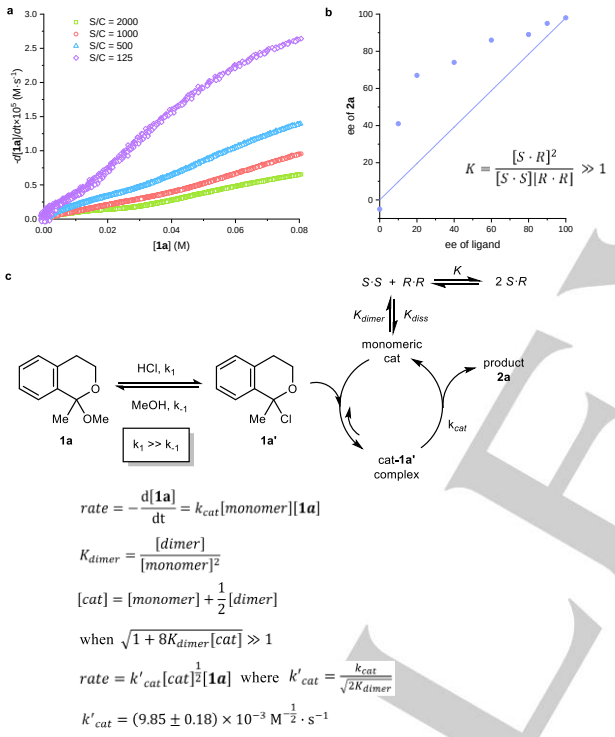

Figure 5 Kinetic profiles of asymmetric hydrogenation of oxocarbenium ions. **a**. Graphical rate equation with different catalyst concentration at 20 atm H_2 pressure. **b**. Nonlinear relationship between ligand ee and product ee. c. Proposed catalytic model involving dimerization of the catalyst.

DFT calculation to reveal an ionic hydrogenation mechanism. Due to the non-coordinating feature of oxocarbenium ions, classic "inner-sphere" model could not explain this reaction. The ionic hydrogenation pattern is therefore highly favored in this case[16, 27]. The H_2 activation and hydride transfer are two key steps involved in the mechanism of hydrogenation reactions. Here, we report the results of our DFT calculations of the reaction mechanism. For simplicity, the results for some unfavorable pathways are given in the supporting information.

After mixing with $[Ir(COD)Cl]_2$, the bisphosphine ligand Zhaophos is expected to replace COD to form a square planar Ir(I) complex **I** (Figure 6). The Brønsted acid HCl oxidizes this d^8 complex, giving an octahedral d^6 Ir(III) hydride complex **II'**. Isomerization of **II'** occurs to give a thermodynamically more stable trigonal bipyramidal Ir(III) complex **II**, which enters the catalytic cycle (Figure 6a), with the Cl^- anion binding to the thiourea moiety. This isomerization offers a vacant coordinating site, which facilitates the coordination of dihydrogen to form a dihydrogen $Ir^{III}(\eta^2\text{-}H_2)$ complex **III**. From this dihydrogen complex **III**, there are serval possible pathways for the H_2 activation. The most favorable pathway is the heterolytic cleavage of H_2 with the help of **1a'**, having an energy barrier of 11.4 kcal/mol, to give the intermediate **IV** (Figure 6b). Assembling **III** with **1a'** is thermodynamically favorable to gives a van der Waals complex **III+1a'**, suggesting that the van der Waals interaction can counteract the entropy cost in this two-to-one process. Formation of the intermediate **IV** accompanies the release of HCl that functions as the reagent to convert the substrate **1a** to **1a'**. The intermediate **IV**, which is a van der Waals complex of dihydride $Ir^{III}(H)_2$ with the resulting carbenium ion, then undergoes a hydride transfer reaction. This is the enantio-determining step: the hydride reducing the carbenium ion gives the product (*S*)-**2a** via an overall barrier of 11.9 kcal/mol (Figure 6b) while the formation of (*R*)-**2a** incurs a higher overall barrier of 14.0 kcal/mol, giving a DFT-calculated ee value of 94.5% (Figure 7).

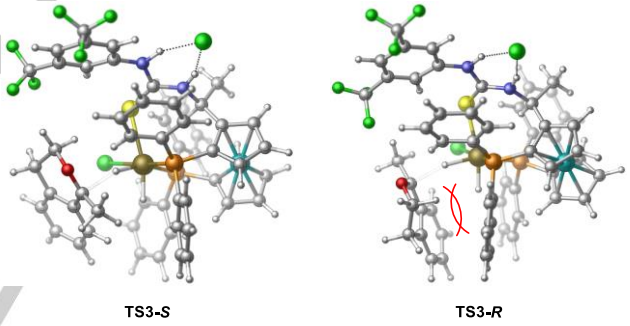

Figure 7. Transition states calculated for the hydride transfer step to generate both enantiomers of 2a.

Thiourea-assisted anion abstraction has been demonstrated effective in the *in-situ* formation of oxocarbenium ions[5, 23a]. In the current system, thiourea-assisted chloride abstraction would first require to generate a thiourea-coordinated complex, such as the dihydride Ir(III) complex **V** shown in Figure 6a. However, the thiourea-Cl^- complexation with a six-member-ring structure, is very stable, indicating that the regeneration of free thiourea is challenging. To generate the Ir(III) complex **V**, H_2 activation may go through other pathways, which were calculated to have noticeably higher energy barriers compared to the most favorable pathway shown in Figure 6b. Other H_2 activation pathways, including homolytic (oxidative addition of H_2 to Ir(III) in **III**) and heterolytic (the coordinated S acting as a base for deprotonation), were also calculated and found to have noticeably higher energy barriers (15.3 and 15.2 kcal/mol for **TS2-1** and **TS2-2** shown in Figure S6). A HCl-assisted heterolytic split of dihydrogen, which involves an external HCl as a proton shuttle to protonate the thiourea needs a much higher barrier of 24.8 kcal/mol (Figure S6, **TS2-3**). After HCl elimination from the protonated thiourea, the

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reactive thiourea-coordinated complex **V** would be generated. Clearly, the formation of **V** is both thermodynamically and dynamically unfavorable, suggesting that thiourea-assisted chloride abstraction is not possible in the current catalytic system.

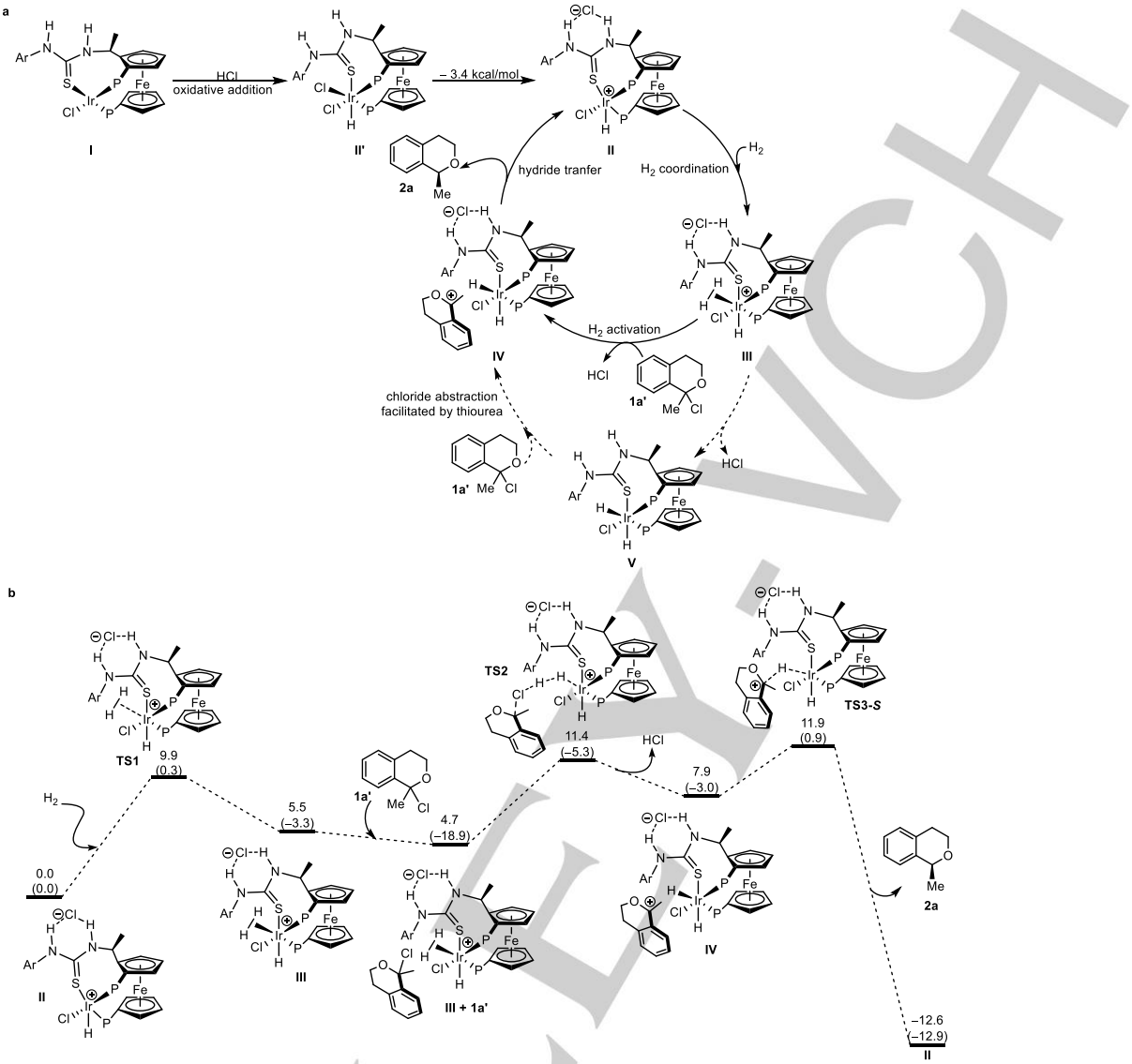

Figure 6. DFT calculated reaction mechanism. a. Proposed catalytic cycle in this reaction. b. Energy profile for the most favorable reaction pathway. Ar = 3,5-di-CF3Ph, the phenyl groups on the phosphorus atoms are omitted for clarity, and the relative Gibbs free energies and electronic energies (in parentheses) are given in kcal/mol.

Conclusion

Oxocarbenium ions have been brought into transition metal catalyzed ionic hydrogenation in this work. In the presence of Brønsted acid HCl, the isochroman acetal substrate and *α*-chloroisochroman are in fast equilibrium. Highly reactive oxocarbenium ions, which are *in situ* formed from chloride abstraction, is then reduced by an iridium hydride complex. High enantioselectivities were achieved in this chemical transformation. A remarkable efficiency and excellent chemoselectivities indicate its potential application in synthetic chemistry. Mechanistic studies, both experimental and computational, were carried out. Kinetic profile of this reaction suggests a 1st order dependence on the substrate and a half-order dependence on the catalyst. Dimerization of the catalyst was proposed for this reaction. DFT computational studies revealed that the cleavage of C-Cl bond and the split of dihydrogen occurred in one single step, which is different from previous studies that the thiourea plays a crucial role in the *in situ* formation of oxocarbenium ions via chloride abstraction. Moreover, this acid-tolerant catalytic system provides us a tool to hydrogenate reactive intermediates in an acidic condition.

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Keywords: asymmetric catalysis • ionic hydrogenation • oxocarbenium • iridium • mechanistic study

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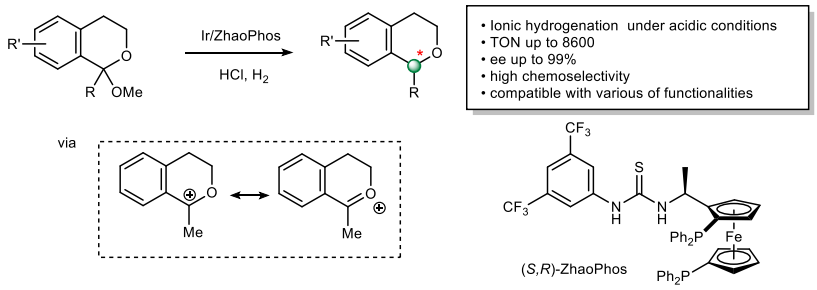

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