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Discovery of an Ir-ate Catalyst for Ultra-efficient Asymmetric Hydrogenation of Ketones with 3S Character (Stable, Speed and Selectivity)

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Abstract:

Reduction of organocarbonyl compounds occupies a large space in organic synthesis and mass production of fuels, chemicals and materials. [1-9] Instead of using stoichiometric reduction agents, the development of ultra-efficient homogeneous hydrogenation catalysts using green dihydrogen is one of the foremost challenges in the transition from chiral resolution toward selective production of chiral entities, as evidenced from the growing capacity and quantity of production plants. [10,11] However, despite useful enantioselectivities (>98% ee) are

often obtained in asymmetric hydrogenation (AH) of ketones, the celebrated Noyori-type catalysts are currently limited in few million turnover numbers (TONs) and a hundred turnover frequencies (TOFs). [12-24] **Challenges especially remain for nitrogen-containing ketones that are relevant to construction of high-value bioactive compounds where at most 10,000 TONs are reported. Here, by integration of the concepts of multidentate ligation and ate-type complex, we report the first ultra-efficient Ir-ate catalyst for highly selective construction of chiral alcohols via AH of ketones with remarkable, biocatalysis-like 3S capacity of >99% ee (enantiomeric excess) selectivity, 13,425,000 turnover number (TON) and 253 s^{-1} turnover frequency (TOF). With this Ir-ate catalyst a selective industrial route to chiral nicotine at 500 kg batch scale has been established, already providing 40 tons of product. Mechanistic studies reveal a novel ONa/MH bifunctional mechanism of the Ir-ate catalyst. Such concept is yet to be explored and may have a major impact in applied homogeneous catalysis.**

Traditional stoichiometric reduction agents, such as $NaBH_4$ and $LiAlH_4$, are highly reactive ate (short for metalate) compounds compared to their predecessors, *viz.* neutral B_2H_6 and $HAl(iBu)_2$ for reduction of organocarbonyl compounds (Fig. 1A).[11] However, these explosive reagents require tedious storage and usage protocols yet generating significant amounts of waste. Wilkinson and Crabtree introduced transition metal hydrogenation catalysts that are either neutral or cationic compounds for reduction catalysis using safe and green dihydrogen (Fig. 1A).[25-34] Unfortunately, based on either

monodentate or bidentate ligands, these complexes are generally less efficient for mass production due to its coordination unstable nature and facile decomposition upon contacting trace amount of oxygen or other impurities.

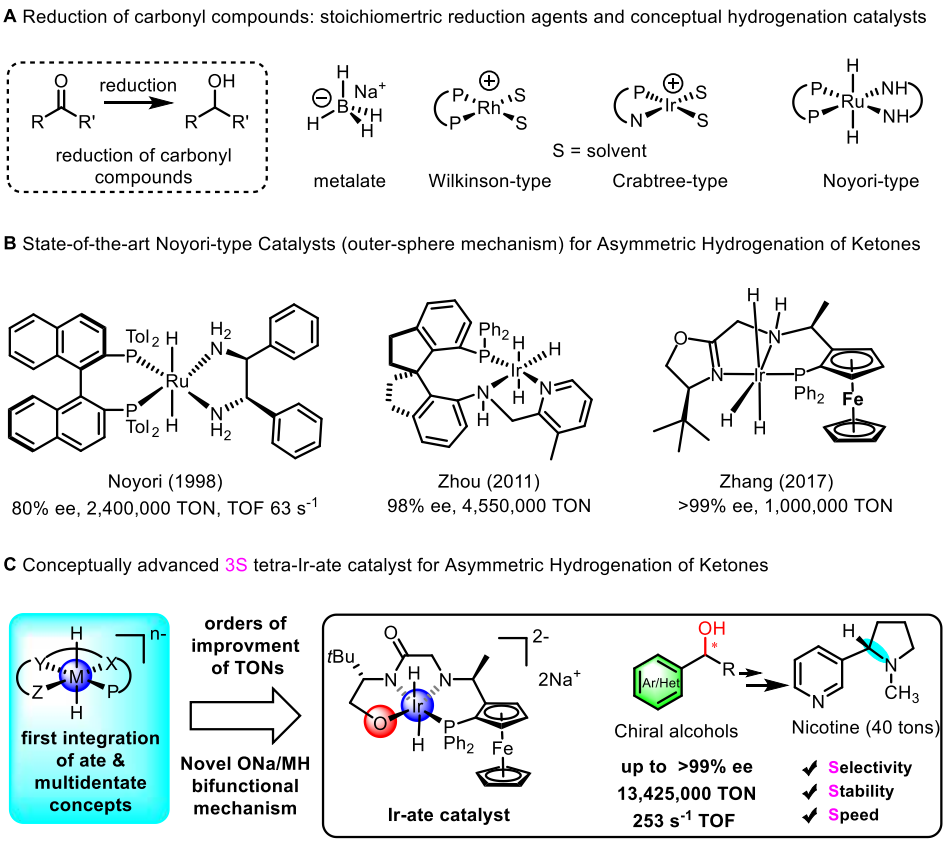

Fig. 1 Reduction of organocarbonyl compounds affording high-value chemicals. A) Stoichiometric ate reduction reagents and conceptual hydrogenation catalysts. B) The state-of-the-art neutral Noyori-type catalysts for Asymmetric Hydrogenation (AH) of ketones. C) Our conceptually advanced 3S tetra-Ir-ate catalyst for ultra-efficient AH of ketones. ee: enantiomeric excess.

Compared to the representative hydrogenation catalysts [28-34] with inner-sphere mechanism, catalysts [35,36] of the outer-sphere mechanism can avoid the contact of substrates to the metal center, thus making it possible to design highly stable,

enantioselective and coordination saturated hydrogenation catalysts (Fig. 1A-B). Indeed, Noyori-type catalysts, i.e. Ru(bisphos)(diamine) system by Noyori [12,37,38], Ir-PNN-complex by Zhou [21-23] and others [15-20,39] operating via NH/MH[38,39] bifunction mechanism are effective ketone asymmetric reducing catalysts (Figs. 1B, S2, ST 3.1 and Table S1 of the Supplementary Information (SI)). Exceptionally, Zhou's tridentate ligand of Ir-PNN-catalyst provides the record-high TONs of 4,550,000 at 98% ee (enantiomeric excess) selectivity. However, despite useful enantioselectivities (>98% ee) are often obtained, the celebrated Noyori-type catalysts are currently limited in few million turnover numbers (TONs) and a hundred turnover frequencies (TOFs) for production of high-value chiral alcohols and their derivatives.[24] Challenges especially remain for nitrogen-containing ketones that are relevant to construction of high-value bioactive compounds where at most 10,000 TONs are reported (Table S2 and Fig. S3).

Given the increasing capital investments, operational costs and sustainability requirements, to obtain ultra-efficient 3S (selectivity, stability and reaction speed) catalysts achieving 10-million TONs and biocatalysis-like reaction turnover frequencies (TOFs), beyond the state-of-the-art NH/MH bifunction catalysts, is highly important and has been the holy grail of the homogeneous transition metal catalysis (Fig. S1). [10,13,14] Inspired by highly reactive ate reduction agents and multidentate Noyori-type hydrogenation catalysts, we envisioned the integration of the concepts of ate compounds and multidentate ligands for developing 3S preeminence asymmetric hydrogenation (AH) catalysts (Fig. 1C). The characteristic ate complexes bearing a formal negative charge can enable high hydricity [40] and accordingly high catalytic

reaction speed. The multidentate ligands can help to stabilize the metal center through coordinative saturated 18 electron complexes and form well-defined chiral environment for converting specific substrates and give rise to highly stable and selective catalysts. We demonstrate a tetradentate PNNO ligand-bearing Ir-ate catalyst that provides unprecedented up to 13 million turnover-numbers (TONs), hundreds of TOFs per second at ultra-high selectivity (>99% ee, 13,425,000 TON and 253 s^{-1} TOF, Fig 1C, and Tables S1-2) comparable to biocatalysts. With this catalyst, even ketones with awkward coordinating basic nitrogen have been hydrogenated at a million TON and >99% ee selectivity. We have thus established a selective industrial route to enantiomeric pure nicotine, already providing 40 tons of product. Compared to traditional NH/MH bifunction catalysts, the Ir-ate catalyst based on a simple and easily fabricated ligand f-phamidol at kilograms-scale demonstrates significantly improved hydricity and a novel ONa/MH bifunctional mechanism.

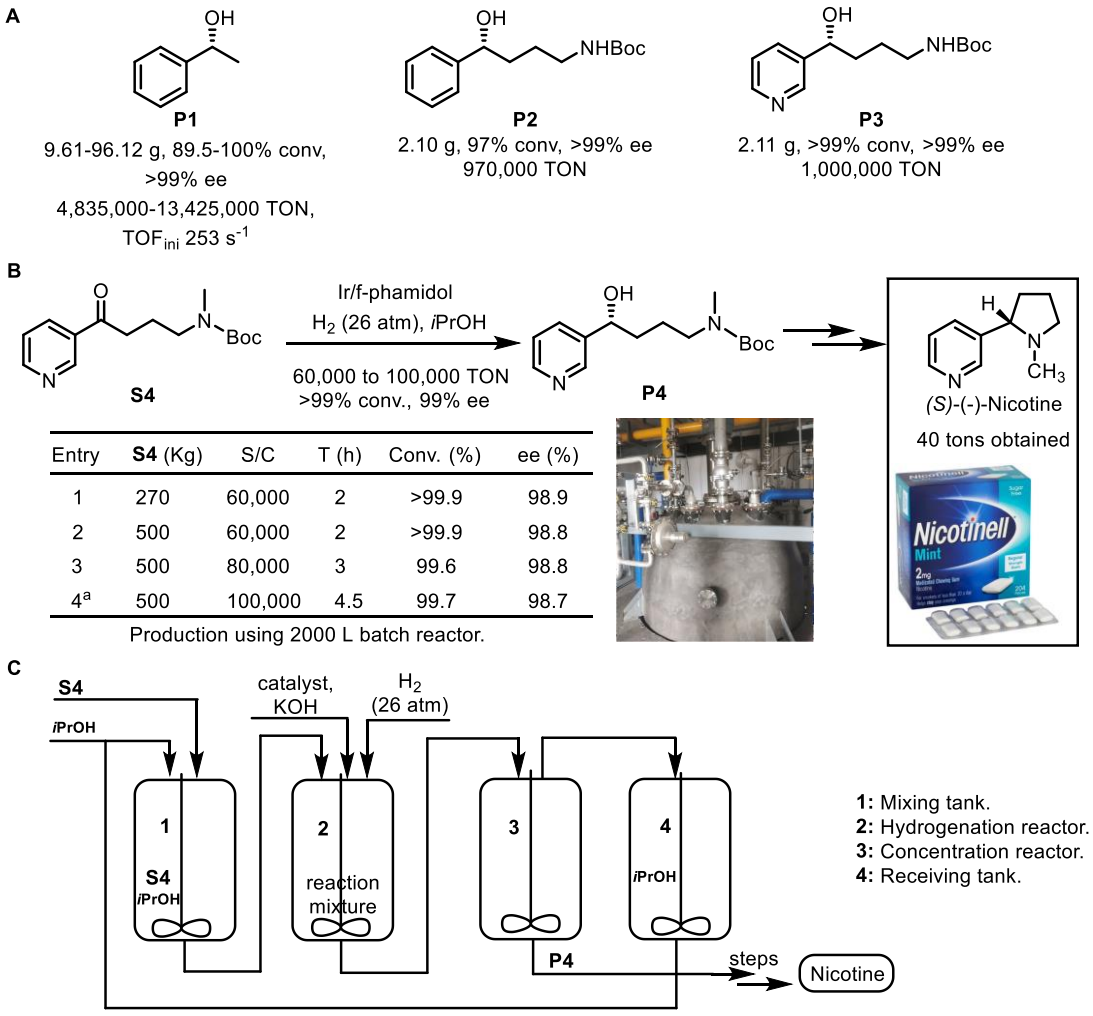

Fig. 2 AH of ketones using Ir/phamidol catalyst. (A) Laboratory scale AH of representative benchmark acetophenone and nitrogen-containing aromatic ketones. (B) Industry scale AH of nitrogen-containing ketone as a selective route to chiral nicotine with schematic of our process displayed in (C).

Initially, on the basis of our previous work [23,41,42], iridium catalysts based on tetradentate PNNO ligand f-phamidol was examined at a substrate/catalyst ratio of 2,000,000 using 80 mmol benchmark acetophenone at ambient temperature (Tables S3-5). All the base gave exceptionally high enantioselectivities >99% ee, whereas the highly basic NaO*t*Bu that leads to 99% conversions in 16 h (corresponding to 1,980,000

TONs) is superior to the others with variation of either the alkali ions or anionic counterions. The addition of suitable amounts of solvent is important for achieving both high enantioselectivity and TON. Under the optimal conditions, high turnover experiments with a variation of the substrate/catalyst ratio from 5,000,000 to 15,380,000 were carried out. Remarkably, a steady increasing TONs from 4,835,000 to 11,535,000 was observed at excellent enantioselectivities of 99% ee and excellent conversions of 75-97%, indicating super-stable, durable and enantioselective Ir/f-phamidol catalyst at the highest loading of substrate (*vide infra*, Fig. 1A, Table S5). Upon increasing the substrate amount to 800 mmol at 100 bar H_2, the highest TON of 13,425,000 together with 89.5% conversion and 99% ee were observed in a 30-days' reaction, implying outstanding averaged production rate of 2,846 $kg_{product}$ $(kg_{precatalyst})^{-1}$ h^{-1}. The initial TOFs were calculated based on a pressure-drop curve (Figs. S4-5). An ultra-high initial TOF of 253 s^{-1} was recorded, which is close to the biocatalytic efficiency of (de)hydrogenase [43-45].

Given the successful application of the Ir/f-phamidol catalyst for AH of benchmark acetophenone, we further examined its efficiency in a more challenging conversion of nitrogen containing ketones as well as in industrial construction of enantiomeric pure nicotine (Fig. 2, S3, Table S2, SM 2.5). Ketone **S2** containing an amide function proceeds smoothly to afford the desired chiral compound at gram-scale in >99% ee, 97% conversion and 970,000 TONs. Remarkably, even though ketone **S3** contains both an amide function and a pyridine function that often results in catalysts deactivation, our

catalyst still gave exceptionally high efficiency (>99% conv., >99% ee and 1,000,000 TONs) at gram scale.

Based on these data, the Ir/f-phamidol catalyst was investigated in a selective industrial route to enantiomeric pure nicotine from easily available ketone **S4**. Nicotine, generally isolated from tobacco, is one of the most important bioactive natural products with estimated consumption of > 1000 tons per year with the tendency of steady increasing. After preliminary testing in laboratory scale (two routes, SM 2.6-7), a 2000 L continuously stirred tank reactor was used for the crucial AH, shown in Fig. 2B-C and SM 2.8. Given economy and safety concerns, 26 bar dihydrogen pressure and much cheaper KOH instead of NaO*t*Bu were applied based on conditions optimization (Table S3). Stepwise scale up the feedstock from 270 to 500 kilograms at substrate/catalyst ratio of 60,000 gave full conversions, 98.9% ee in 2 h (Fig. 2C, entries 1-2). Increasing the substrate/catalyst ratio to 80,000 and 100,000 at 500 kg scale needs 3h and 4.5 h, respectively, and the reaction reached 99.6-99.7% conversion with 98.7-98.8% ee (Fig. 4C, entries 3 and 4). To our surprise, a substrate/catalyst ratio of 100,000 at 500 kg scale using recycled solvents can be operated smoothly, giving rise to a key chiral alcohol intermediate (99.7% conversions, 98.7% ee, 100,000 TON, with catalyst load 0.045 g kg^{-1} product and space-time-yield 55.6 g L^{-1} h^{-1}) for production of nicotine already 40 tons with 99% ee.

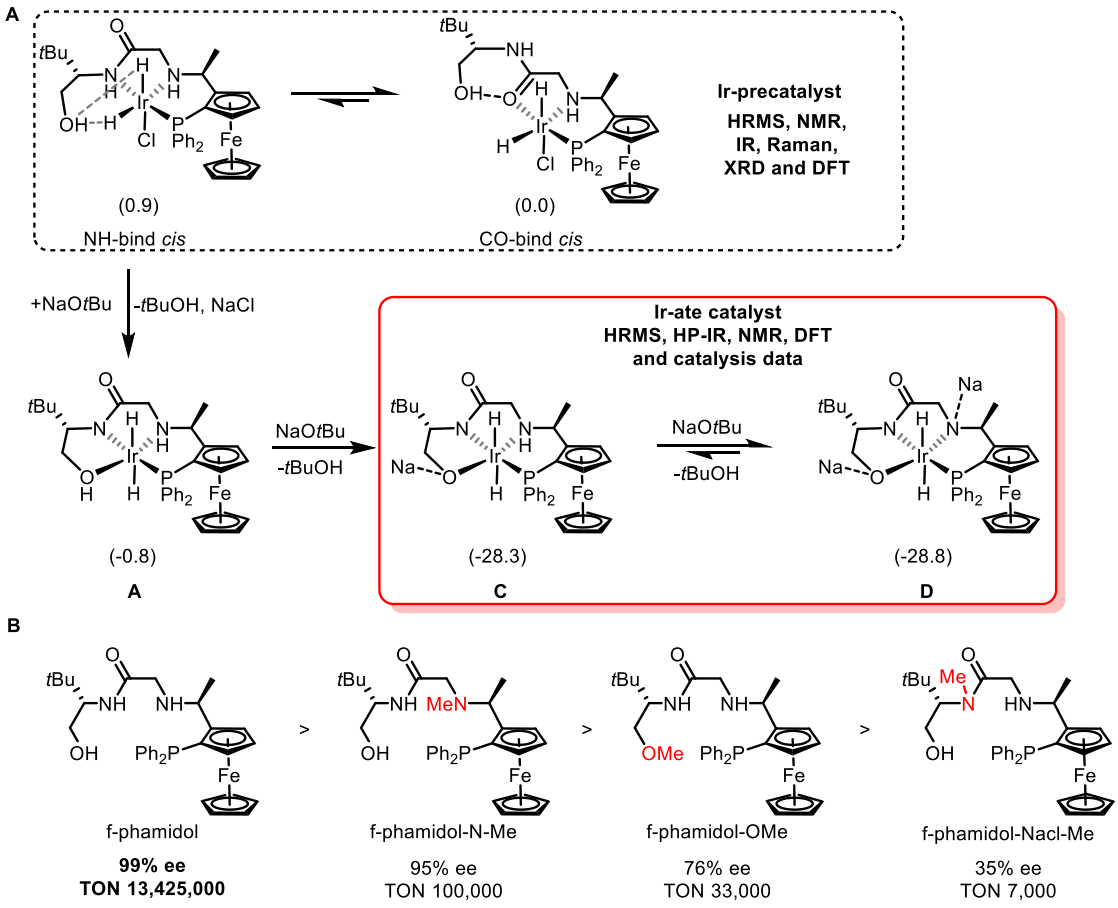

Fig. 3 Characterization of Ir/f-phamidol catalyst. (A) Formation of Ir-ate catalyst from Ir-precatalyst. Calculated relative Gibbs free energies at 298.1 K are given in brackets. (B) Performance of modular modified ligands in comparison with f-phamidol.

To understand the nature of the extremely high efficacy and the reaction mechanism, we performed detailed characterization of the Ir/f-phamidol catalyst via a combination of experimental techniques and quantum-theoretical modelling based on density functional theory (DFT, the theoretical details are given in the SI). Upon mixing f-phamidol with $[Ir(COD)Cl]_2$, monochloride dihydride iridium complexes were identified as the Ir-precatalyst (Fig. 3A, S6-18, Table S12), based on the evidences from HRMS, NMR, ATR-IR, Raman, XRD and DFT calculations. Briefly, DFT calculations, NMR and ATR-IR spectroscopy confirmed that the formation of mixtures of Ir-

precatalysts with *cis*-configuration of hydride and carbonyl binding to Ir-metal (CO-bind *cis*) is slightly favorable. Two *cis*-hydrides instead of *trans*-hydrides are evidenced by ATR-IR analysis of the dry powder at 2229 and 2127 cm^{-1} and DFT modeling (Figs. S9-10). The evidence of amide-carbonyl instead of NH coordination to Ir-metal was supported by the red shifts up to 22 cm^{-1} of the amide-carbonyl group. Upon deprotonation of the alcohol donor of the Ir-precatalyst, favorable tetracoordinated dihydride Ir-ate complexes were formed via likely intermediate neutral complex **A** (Fig. 3A, S19-26 and Table S12). Compared to deprotonation of NH function, OH deprotonation is highly energetically favorable, resulting in Ir-ate catalysts **C** and **D** that are likely under equilibrium at the experimental condition. Such Ir-ate complexes were characterized by HRMS, *in-situ* high-pressure (HP) NMR and ATR-IR spectroscopy and DFT calculations. HRMS of a solution of Ir-precatalyst and NaO*t*Bu in isopropyl alcohol under 30 bar H_2 showed exact mass of 765.1874 $[M-2Na+3H]^+$ and 799.1490 $[M-2Na+2H+Cl]^-$, corresponding to protonated and chlorinated Ir-ate catalysts, respectively, in the positive and negative region. The existence of amide-N instead of amide-carbonyl coordination to Ir-metal was supported by blue shifts observed by *in-situ* high pressure (HP) ATR-IR experiments and DFT calculated infrared spectra (Figs. S24-25).

To confirm the crucial role of tetradentate PNNO ligand for the formation of ultra-efficient Ir-ate catalyst, we prepared slightly modified ligands for AH of acetophenone as references (Fig. 3B, S27). Ligand f-phamidol-N-Me with NH function being methylated gave a maximum 100,000 TON and 95% ee. Ligand f-phamidol-O-Me with

OH function being methylated displayed significantly dropped TON of 33,000 and 76% ee, implying the decisive role of the extra anionic oxygen donor in creating the robust TON, reaction rate and selectivity. Despite the presence of both NH and OH, ligand f-phamidol-Nacyl-Me, which cannot form tetra-coordinated Ir-ate catalysts due to unlikely amide-NH coordination to Ir-metal originated from both steric and electronic reasons, showed a rather small TON of 7,000 and 35% ee. Those control experiments provide unequivocal evidence that the OH functional of tetradentate PNNO ligand plays a critical role in AH of acetophenone, which is different from traditional NH/MH bifunctional catalysts.

To gain further insights into the ultra-efficient Ir-ate catalyst, quantum chemistry studies were performed to address the AH mechanism (see SI 3.3). We have found that upon deprotonation, Ir-complex **B** is significantly higher in energy (ca. > 20 kcal mol^{-1}) than the active Ir-ate complexes (*vide supra*, Fig. 3A, S26 and Table S12). Thus, Ir-ate complexes **C** and **D** were used as starting structures in comparison with **A**. Both the well-known NNa/MH bifunctional mechanism [46] and ONa/MH bifunctional mechanism proposed here were extensively explored computationally. Compared to **A** and Ir-ate catalyst **C** (Figs. S28-39, Tables S12-15), Ir-ate catalyst **D** provides energetically favorable pathways involving NNa/MH and ONa/MH bifunctional mechanisms, as shown in Fig. 4A and S28-30. For both NNa/MH and ONa/MH bifunctional mechanisms, the alkali cation (Na^+) can polarize the carbonyl of the ketone substrate and thus facilitate hydride transfer in the rate and selectivity determining step from the Ir-ate catalyst to form the alkoxide intermediate **III**, which is smoothly

converted to alcohol product and initial active catalyst by taking a dihydrogen molecule. The ONa/MH bifunctional pathway giving the desired enantiomer has a much lower free energy barrier than that of the NNa/MH bifunctional pathway (*viz.* 6.2 vs 10.1 kcal mol^{-1}), consistent with our experimental observations. Additionally, when explicit solvent molecules were considered in the models to simulate the actual solvated cations and hydrogen bonding environment (Fig. S38), the predicted free energy barrier of 12.9 kcal mol^{-1} is comparable to the experimental TOF (Table S15) according to the Arrhenius equation.

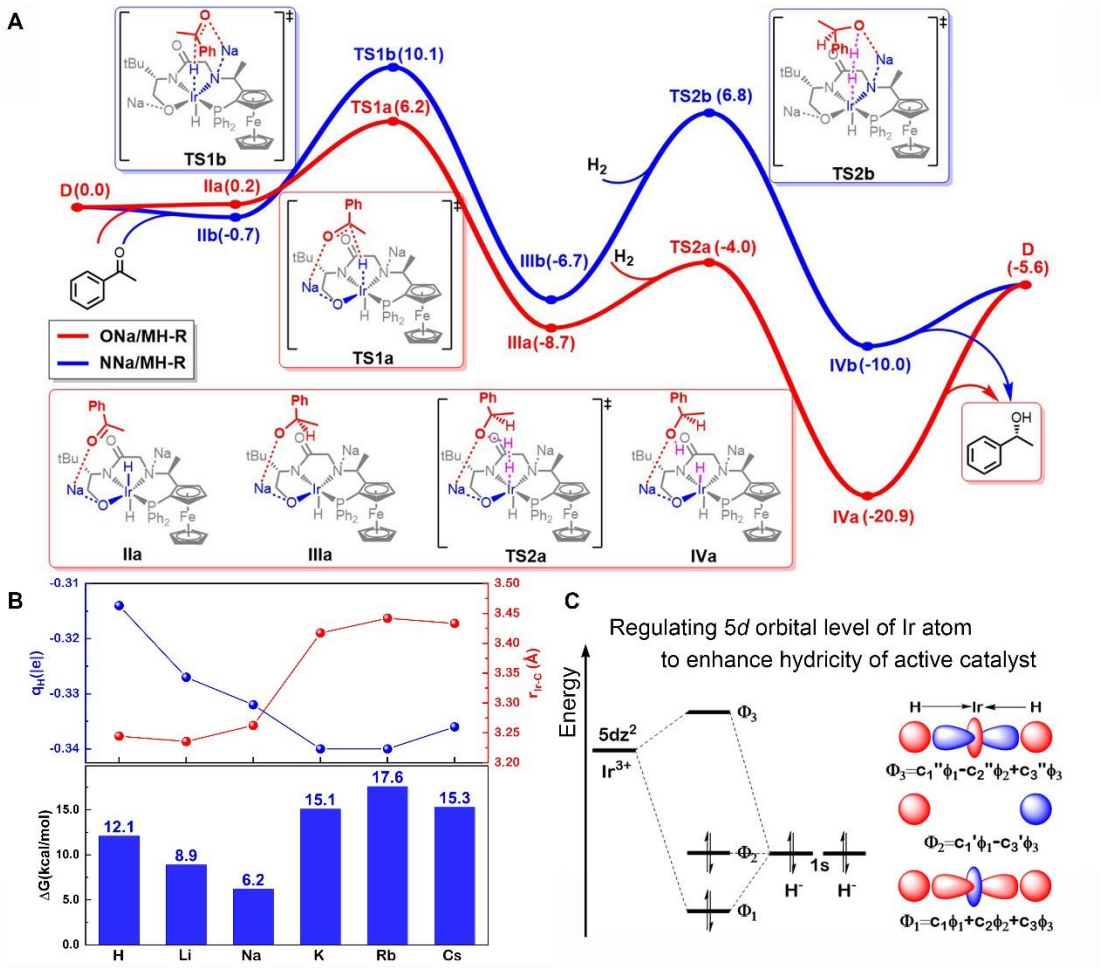

Fig. 4 Proposed mechanisms from DFT calculations. (A) Predicted Gibbs free energy profile for the AH of acetophenone via the active Ir-ate catalyst **D** through ONa/MH

bifunctional (in red) and NNa/MH bifunctional (in blue) paths. (B) Average natural population analysis (NPA) charges of hydrides in active Ir-ate catalyst **D**, distance between C atom of the carbonyl group of the substrate and Ir atom in **TS1a**, and Gibbs free energy barriers of the hydride transfer step for different alkali cations. (C) Schematic three-center-four-electron (3c-4e) orbital interactions between Ir and the hydride atoms.

The origin of the significantly enhanced activity upon introduction of anionic donor can be rationalized by the orbital interactions between the ligation-tunable 5*d* orbitals of Ir atom and 1*s* orbital of hydride (Fig. 4C). The f-phamidol ligand in tetra-dentate manner stabilizes the Ir-ate catalyst (18 electron complex) under basic condition and the anionic donor greatly elevates the 5*d*-orbital energy of Ir atom. Higher 5*d*-orbital energy level of Ir atom leads to weaker orbital mixing with 1*s* orbitals of axial hydride based on Pimentel–Rundle three-center-four-electron (3c-4e) model [47,48], which causes larger composition of H 1*s* orbitals in the bonding/nonbonding orbitals and subsequently larger electron density on hydride atoms as well as stronger hydricity of the catalysts. The Ir atom and two axial hydrides in the Ir-ate catalyst forming 3c-4e bonding is confirmed by DFT and the *ab initio* complete active space self-consistent field (CASSCF) calculations (Figs. S40-43), where the natural orbital occupation numbers (NOONs) of the three orbitals formed by $5d_{z2}$ orbital of Ir atom and 1*s* orbitals of hydrides are 1.99, 1.97, 0.03, respectively.

Based on the new ONa/MH bifunctional mechanism, the Ir-ate catalysts with proton and series of alkali cations (Li^+, Na^+, K^+, Rb^+, Cs^+) were systematically investigated via

DFT modeling (Fig. 4B and Tables S6-10). From H^+ to Na^+, the Ir-hydride becomes more negatively charged, implying increasing hydricity and reactivity of the active Ir-ate catalyst. However, despite the increasing of hydricity from Na^+ to Cs^+, higher free energy barriers for hydride transfer are noticed due to larger distance between the carbonyl group and the hydride atom originated from the increasing radius of cations. Thus, the Ir-ate catalyst with Na^+ of both favorable size and hydricity gives the highest efficiency (*vide supra*).

In summary, we presented an unprecedented Ir-ate catalyst with record-high turnover-numbers of 13-million, 253 s^{-1} TOF and >99% ee for an industrial route to chiral nicotine. HRMS, *in-situ* HP ATR-IR, HP NMR, Raman, XRD characterization and quantum-theoretical modeling demonstrate highly improved metal-hydride hydricity and a novel ONa/MH bifunctional mechanism. This work will likely inspire the development of other ultra-efficient 3S homogeneous catalysts for production of chemicals, fuels and materials.

Methods

Optimal conditions for 10 million turnover number experiments (at S/C = 15,000,000): To a 20.0 mL vial was added the precatalyst (3.2 mg, 4.0×10^{-3} mmol) and anhydrous *i*PrOH (10.0 mL) in an argon-filled glovebox. The mixture was stirred for 0.5 h at 25 °C. And then 800 mmol of acetophenone and NaO*t*Bu (96 mg, 1 mmol) were added into a 300 mL hydrogenation vessel. Then 20 mL anhydrous *i*PrOH was added and a solution of Ir-precatalyst in anhydrous *i*PrOH (133 μL) was added *via* an injection

port. Then the vessel was placed in an autoclave, which was closed and moved out from golvebox. The autoclave was quickly purged with hydrogen gas for three times, and then pressurized to 100 bar H_2 (keeping the hydrogen pressure not lower than 80 bar). The reaction solution was stirred at room temperature until for 30 d, and then the pressure was released carefully. The solution was removed under reduced pressure. Conversion was determined by ^{1}H NMR analysis, and ee was determined by HPLC with a chiral stationary phase. 89.5% conv., 99% ee, TON = 13,425,000.

Applied asymmetric hydrogenation procedure for construction of Nicotine at 40 kilograms-scale: Under nitrogen atmosphere, to a 20.0 mL vial was added Ir-precatalyst (1.92 g, 2.4 mmol) and anhydrous *i*PrOH (10.0 mL). The mixture was stirred for 0.5 h at 25 °C. In a 200 L Hastelloy hydrogenator was charged with 40 kg compound **S4** (144 mol) in 80 L isopropanol at room temperature. 400 g KOH (7.14 mol, 5 mol %) was added to the reactor and the resulting solution was degassed by five cycles of vacuo followed by filling with nitrogen. The previously prepared solution of catalyst (S/C = 60,000) in *i*PrOH was transferred to the hydrogenator under a stream of nitrogen by cannula. Hydrogen was initially introduced into the autoclave at a pressure of 40 bar. The reaction mixture was stirred while maintaining a temperature range of 30-45 °C, monitored by hydrogen consumption and HPLC. The reaction was complete after 5 h. The reaction mixture was cooled to 25 °C, and hydrogen was replaced by nitrogen. The solution was transferred to a glass-lined reactor and concentrated in vacuo. Crude compound **S4-3** was obtained as red oil: 41 kg (99% yield, 99% *ee*). The crude compound **S4-3** was used in the next step without further purification.

A 10-L, 4-neck round-bottom flask was equipped with a mechanical stirrer, a condenser with an N_2 inlet, a thermowell, and an addition funnel. The flask was charged with 400 g of compound **S4-3** (1.43 mol, crude product), 232 g triethylamine (2.3 mol, 1.6 equiv.) and 2.3 L of MTBE at room temperature. The resulting reaction mixture was cooled to -10 ℃, followed by dropwise addition of 229 g methanesulfonyl chloride (2 mol, 1.4 equiv.). The reaction was allowed to stir at -5 ℃ for 2 h. A pale-yellow suspension was observed. After that, the insoluble solids were filtered off and the solids was rinsed with MTBE (2 x 500 mL). The combined organic phase was washed by saturated aqueous $NaHCO_3$ (2 x 1 L). The reaction mixture was cooled to -10 ℃, followed by dropwise addition of 1.86 kg sulfuric acid aqueous solution (30% by weight, 4.0 equiv.). The mixture was then allowed to gradually warm to room temperature and stirred for 2 h. The organic phase was separated to waste and the lower aqueous phase was recharged to the reactor. The reaction mixture was allowed to cool to -10 ℃. Finally, 7 L of sodium hydroxide solution (2 M) was added slowly until the pH reached 10~11. The aqueous phase was extracted with ethyl acetate (3 x 5 L) at room temperature. The combined organic solvent was evaporated under reduced pressure and the resulting residue was further purified by distillation under vacuum at 70 ℃ to afford pure product **(*S*)-Nicotine** as colorless oil (157 g, 0.97 mol, 68% yield in 3 steps, 99% *ee*).

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions

X.Z., J.L., S.T.B, Q.L. conceived the idea and directed the project. C.Y. designed and conducted the experiments with inputs and support from Q.L., F.H. and G.Q.C. Y.F.J. performed all the theoretical computations with guidance of J.L. and C.Q.X. S.T.B. performed the characterizations with support from Y.P. using HRMS, in-situ HP ATR-IR, HP NMR, Raman, XRD spectroscopy. S.T.B. and Y.F.J. analyzed the data and drafted the manuscript. All authors contributed to the manuscript.

Competing interests: X.D., S.G. and Q.L. are inventors on patents (WO 2021/212880 Al, EP 3 925 955 A1, CN 113527187 A, US 2022/0089564 Al, CN 202210771902.X and 202111097411.3), held and submitted by Shenzhen Catalys Technology Co., Ltd.

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