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Synergistic Mechanism Between Ir–Phosphinito Catalyst and HFIP Enables Asymmetric Hydrogenation of Ketones Under Acidic Conditions

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ABSTRACT

A novel P*-stereogenic phosphinito pincer iridium complex, in cooperation with hexafluoroisopropanol, enabled an unusually low-energy pathway for hydrogen activation. Following the resolution of the racemic **QuinSPO** ligand (>99% ee) and its coordination to iridium, the resulting catalytic system demonstrated excellent performance and a broad scope in the asymmetric hydrogenation of ketones, achieving up to 96% ee and turnover numbers of 20 000. Remarkably, the reaction proceeded under mild acidic conditions without added base, enabling the reduction of substrates containing phenols and carboxylic acids, functionalities typically incompatible with conventional basic hydrogenation methodologies. Integrated experimental and DFT studies revealed that HFIP facilitates an alternative low-energy hydrogen splitting mechanism responsible for the enhanced activity. Furthermore, noncovalent interaction analysis identified a critical π – π interaction in the transition state that governs enantioselectivity. These findings establish this system as a complementary strategy for the reduction of base-sensitive substrates and introduce P*-stereogenic phosphinito ligands as a powerful platform for asymmetric catalysis.

1 | Introduction

Tertiary phosphine ligands are a cornerstone in organometallic chemistry and homogeneous catalysis. Thanks to their great ability to coordinate and stabilize metal centers, they are often the ligand of choice for the development of new catalysts and transformations [1]. Consequently, the design of these phosphine ligands becomes of particular interest for achieving the desired catalytic activity [2, 3]. Among these ligands, P*-stereogenic bulky electron-rich phosphines have demonstrated high efficiency and selectivity in numerous transformations [4]. However, electron-rich trivalent phosphorus compounds suffer from a major drawback: their tendency to oxidation. The preparation

and manipulation of these molecules often require an inert gas atmosphere and, in many cases, the use of protecting groups such as BH₃, which makes ligand-design chemistry challenging [5].

This problem can be tackled by shifting toward the use of secondary phosphine oxides (SPOs) [6, 7]. These compounds exist in their oxidized P(V) forms, and, consequently, they do not undergo oxidative degradation. Moreover, a tautomeric equilibrium between the P(V) SPO and the P(III) phosphinous acid (PA) allows their coordination to metal centers (Figure 1A) [8]. The chemistry of SPOs has been known for more than 50 years [9], and the applications of these compounds in homogeneous catalysis have been reviewed [10–21].

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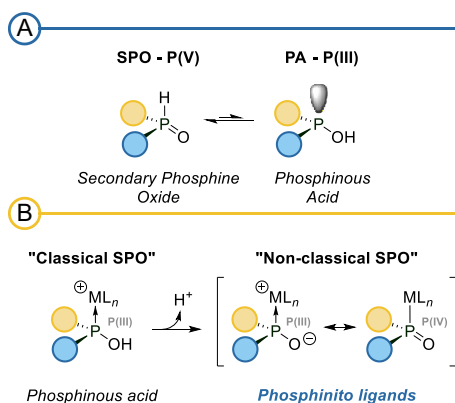


FIGURE 1 | (A) Tautomeric equilibrium between secondary phosphine oxides and phosphinous acids. (B) Representation of "classical SPOs" and "nonclassical SPOs".

Most SPO-derived complexes used in catalysis focus on their coordination as PAs, which we refer to as "classical SPOs" (Figure 1B). PAs are weak acids that can be readily deprotonated to yield what has been called "nonclassical SPOs" [6, 7]. The resulting ligand has a dual character, since it can be considered a negatively charged P(III) neutral ligand or an anionic P(V) ligand, depending on the resonance form we choose to describe. In the literature, these ligands have appeared under different names, including SPOs, phosphoryl ligands, phosphano oxides, O-anionic phosphinitos, and phosphinitos, and have been represented in many ways [22], reflecting a field that is not yet fully established due to a limited understanding of their nature [23].

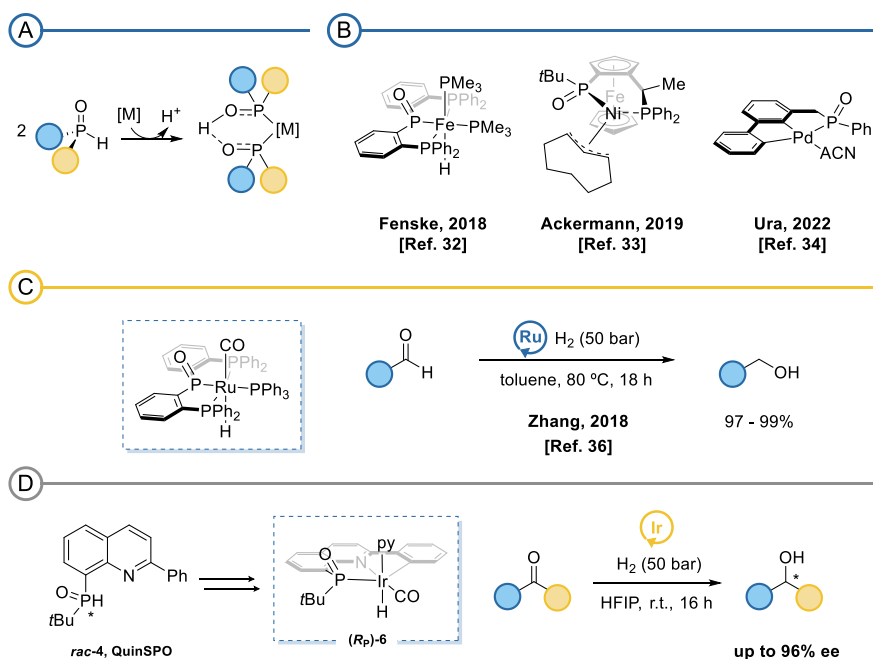
One of the most widely studied complexes containing a phosphinito moiety results from the coordination of two monodentate SPOs to a metal center. Deprotonation of one of the SPO units provides H-bonded bidentate monoanionic PP-chelated ligand

(Scheme 1A) [6]. This behavior is possible because the oxygen atom in the phosphinito moiety is an excellent H-bond acceptor [24]. The corresponding palladium complexes are highly effective in crosscoupling reactions, as phosphinitos are strongly electron-donating ligands, in some cases even surpassing carbenes [24]. In contrast, when the oxygen atom is not locked in a permanent structural backbone interaction, it can act as a base or nucleophile, thereby enabling metal-ligand cooperation [7]. Although bidentate and tridentate ligands containing a phosphinito moiety have been described in the literature (Scheme 1B) [25–34], to our knowledge there is only one report of a free phosphinito used as a hydrogenation catalyst [35]. In 2018, Zhang described an achiral Ru-phosphinito complex that catalyzed the hydrogenation of aldehydes at 80 °C and 50 bar of H_2 pressure (Scheme 1C) [36].

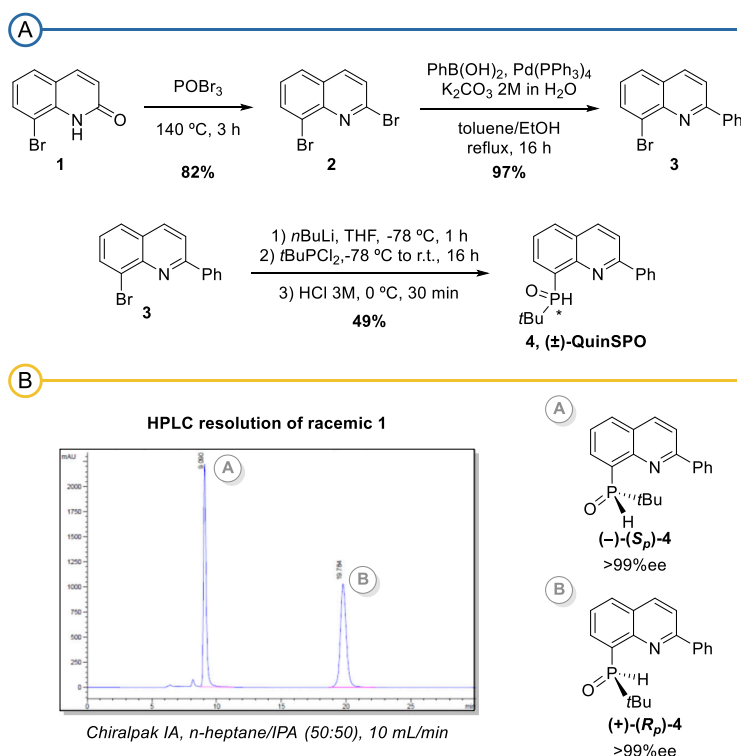
Building on these concepts, here we report a novel P*-stereogenic SPO-quinoline ligand, **QuinSPO**, **4**, and its corresponding iridium complexes. Upon coordination, the SPO is deprotonated into a phosphinito ligand. The resulting optically pure (R_p)-**6** complex proved to be highly active and selective in the asymmetric hydrogenation (AH) of ketones (Scheme 1D). In contrast to most reported hydrogenation catalytic systems, which operate with added base, this system allows the hydrogenation of ketones under acidic conditions. An unprecedented cooperative reaction mechanism for hydrogen splitting that involves a molecule of hexafluoroisopropanol (HFIP) solvent and the oxygen atom of the phosphinito fragment is proposed and corroborated by integrated experimental and Density Functional Theory (DFT) studies.

2 | Results and Discussion

The racemic synthesis of the SPO-ligand is depicted in Scheme 2A. Quinolone **1** was treated with phosphorus oxybromide to synthesize 2,8-dibromoquinoline **2**, which, upon chemoselective



SCHEME 1 | (A) Formation of a bidentate monoanionic PP-chelated ligand with a PA and a phosphinito. (B) Examples of transition-metal complexes bearing a phosphinito ligand. (C) Hydrogenation of aldehydes using a Ru-phosphinito catalyst. (D) AH of ketones using the P*-stereogenic phosphinito iridium catalyst presented in this work.



SCHEME 2 | (A) Synthesis of (±)-QuinSPO, 4. (B) Resolution of the enantiomers of (±)-QuinSPO, 4 by chiral HPLC.

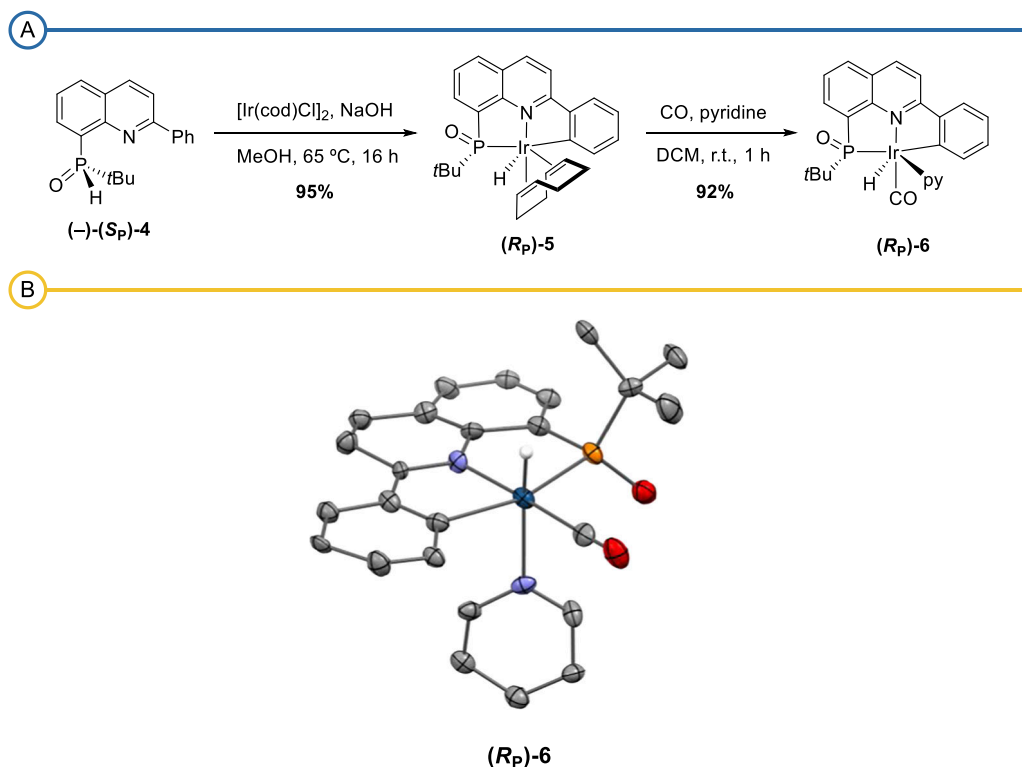
Suzuki coupling with phenylboronic acid, afforded the 8-bromo-2-phenylquinoline **3**. Lithiation of **3** and reaction with *tert*-butyl-dichlorophosphine provided an intermediate chlorophosphine, which was subsequently hydrolyzed to yield the final (±)-QuinSPO, **4** ligand. To obtain the enantiomerically pure ligand, the most cost-effective method was by means of chromatographic resolution (Scheme 2B). The enantiomers of QuinSPO were separated on a semipreparative HPLC equipped with a Chiralpak IA column. Using a mobile phase of *n*-heptane/IPA (50:50) at a flow rate of 10 mL/min, we obtained approximately 100 mg of each enantiomer per hour, with >99% enantiomeric excess (ee).

Next, we addressed the coordination of ligand **4** to iridium (Scheme 3A). After some experimentation, we found that treatment with [Ir(cod)Cl₂] and NaOH in methanol afforded the corresponding cyclometallated Ir–H pincer complex **5** in excellent yield. We believe that NaOH plays a dual role by accelerating cyclometallation and simultaneously deprotonating the phosphinous acid formed to generate the phosphinito ligand. Removal of the cyclooctadiene (COD) ligand by reaction with carbon monoxide and pyridine yielded complex **6**. This new complex contains both a pyridine and a CO ligand. Complexes **5** and **6** are air-stable compounds that can be manipulated in air (see SI for storage conditions used and stability assays).

The single-crystal X-ray structure of complex (*R_p*)-**6** is depicted in Scheme 3B [37]. This analysis allowed us to determine the absolute configuration of the complex and the corresponding QuinSPO ligand. In this structure, the small hydride ligand is positioned *cis* with respect to the phosphinito *tert*-butyl group and *trans* to the pyridine ligand, while the CO ligand occupies an equatorial position. The crystal structure corresponds to a neutral Ir(III) complex with no counterions, thus implying that

the SPO acts as a phosphinito ligand rather than a classical SPO. Also, the tridentate P,N,C-pincer ligand backbone is remarkably planar, with the *tert*-butyl group of the phosphinito being the only element that deviates from this planarity.

After preparing complexes (*S_p*)-**5** and (*R_p*)-**6**, we evaluated them in the asymmetric hydrogenation of ketones [38–45]. We considered the bifunctional character of the phosphinito ligand well suited for metal-ligand cooperative catalysis, which dominates hydrogenation of polar double bonds. Initial tests were conducted using acetophenone as a model substrate (Table 1). While no conversion was observed using complex **5** (1 mol%) under 50 bar of H₂ at room temperature in dichloromethane (DCM), the pyridine complex **6** provided an encouraging 23% conversion (Table 1, entry 1). Low conversions were achieved using **2** in other nonprotic solvents (Table 1, entries 2–6). We then turned our attention to polar protic solvents, which led to a notable improvement in catalytic activity (Table 1, entries 7–10). Methanol, ethanol, and isopropanol resulted in conversions of approximately 80%, with an 88% ee in all three cases, while HFIP further improved the outcome, affording full conversion and 92% ee (Table 1, entry 11). Although comparable results were obtained at 10 bar of H₂, reducing the pressure to 3 bar led to a slight decrease in conversion (92%) while maintaining the same selectivity (92% ee) (Table 1, entries 12–13). Increasing the temperature to 3 bar of H₂ resulted in a modest decrease in selectivity (88% ee), whereas lowering the temperature led to improved selectivity (94% ee) at the expense of a considerable loss of activity, affording only 80% conversion (Table 1, entries 14–15). Finally, the optimal conditions were identified as those that maximized catalytic activity while maintaining good selectivity: 50 bar of H₂ in HFIP at room temperature. Using these conditions, the catalyst loading was decreased to 0.1 mol%, achieving full conversion and 93% ee (Table 1, entry 16).



SCHEME 3 | (A) Synthesis of (*R_P*)-**6**. (B) Solid-state structure of (*R_P*)-**6** showing 20% probability ellipsoids. Hydrogen atoms, except the Ir-coordinated hydrides, have been omitted for clarity.

The optimized conditions were then used to evaluate the scope of the reaction (Scheme 4). Catalyst (*R_P*)-**6** provided complete conversion and up to 96% ee for a wide range of aryl alkyl ketones. Increasing the bulkiness in the alpha carbon did not affect the selectivity (**7b-7d**). *Tert*-Butyl phenyl ketone **7d**, considered a difficult substrate, was hydrogenated with 92% ee. The reaction also proved to be tolerant toward electrophilic substrates; phenacyl bromide **7g** was swiftly hydrogenated in full conversion and 91% ee. Substitution at the aryl moiety was also well tolerated. 4-Nitroacetophenone **7l** was reduced chemoselectively to yield **8l** in 91% ee. The highest selectivity was observed for 2-naphthyl methyl ketone **7t**, providing the corresponding alcohol in 96% ee and suggesting that π - π interactions are crucial in the enantiodetermining reduction step (*vide infra*). Reduction of 2-acetylpyridine **7w** and 2-acetylpyrimidine **7y** proceeded with full conversion but lower selectivity, 68% and 44% ee, respectively. In contrast, 3-acetylpyridine **7x** provided decreased conversion but higher selectivity (78% ee). We hypothesize that the pyridine nitrogen in **7x** is more accessible, which allows substrate coordination to iridium and catalyst inhibition. Reduction of 2,6-diacetylpyridine **7z** afforded full conversion, 83:17 diastereomeric ratio, and 97% ee of the major antiastereoisomer.

Metal-catalyzed hydrogenation of ketones is typically performed under basic conditions, requiring the use of a base additive [38–45]. This implies that the reduction of ketoacids must be conducted with more than one equivalent of base to maintain catalyst activity [46, 47]. In contrast, our catalytic system works efficiently without added base [48–51], as hydrogenation readily proceeds under mild acidic conditions provided by the HFIP solvent. This approach enables the direct reduction of acidic

substrates, including ketone substrates containing acidic functionalities [52–54]. Thus, the phenol-containing substrates **7aa** and **7ab** were readily hydrogenated in 92% and 90% ee, respectively. Likewise, the carboxylic acid-containing substrates **7ac** and **7ad** were hydrogenated in 92% and 91% ee, respectively, leaving the carboxylic acid functionality intact.

To demonstrate the full potential of this new catalytic system, substrates **7ab** and **7ad** were hydrogenated on a gram scale (Scheme 5A). Both reactions proceeded with excellent selectivity, affording 90% ee and 93% ee, respectively. Our system was also useful in the late-stage reduction of biologically active compounds. In this regard, **7ae** was reduced on a gram scale to afford **8ae**, a key intermediate in the synthesis of dTAG13-*m*, with 92% ee (Scheme 5B) [55]. Finally, we were able to reduce catalyst loading to 0.005 mol% (20 000 TON) without any loss of selectivity, thereby demonstrating the robustness and high activity of catalyst (*R_P*)-**6** (Scheme 5C) [56].

2.1 | Mechanistic Investigations

Encouraged by these results, we undertook a more detailed mechanistic study of the new catalytic system. First, we examined whether the free oxygen atom of the phosphinito ligand is essential for the reaction to proceed. To this end, an O-alkylated derivative *rac*-**9** was prepared by treatment of *rac*-**5** with methyl triflate, followed by the introduction of pyridine (Scheme 6A). At 1 mol% catalyst loading, the resulting *rac*-**9** complex afforded only 30% conversion in the hydrogenation of **7a**, thus indicating that the free phosphinito group was key for the high activity of **6**.

TABLE 1 | Optimization of the hydrogenation reaction parameters.

7a $\xrightarrow[\text{H}_2, \text{ solvent, 16 h}]{(R_p)\text{-6 (1 mol\%)}}$ 8a

Entry ^a	Solvent	H ₂ , bar	Temperature, °C	Conversion, % ^b	ee, % ^c
1	DCM	50	r.t.	23	—
2	DCE	50	r.t.	<5	—
3	Toluene	50	r.t.	<5	—
4	TFT	50	r.t.	<5	—
5	EtOAc	50	r.t.	10	—
6	THF	50	r.t.	<5	—
7	H ₂ O	50	r.t.	38	—
8	MeOH	50	r.t.	88	88
9	EtOH	50	r.t.	71	88
10	IPA	50	r.t.	86	88
11	HFIP	50	r.t.	>99	92
12	HFIP	10	r.t.	>99	92
13	HFIP	3	r.t.	92	92
14	HFIP	3	60	94	88
15	HFIP	3	5	80	94
16 ^d	HFIP	50	r.t.	>99	93

^aThe experiments were carried out at 0.1 M. DCE (dichloroethane), THF (tetrahydrofuran).

^bDetermined by ¹H NMR analysis of the crude reaction mixtures.

^cDetermined by HPLC analysis on a chiral stationary phase.

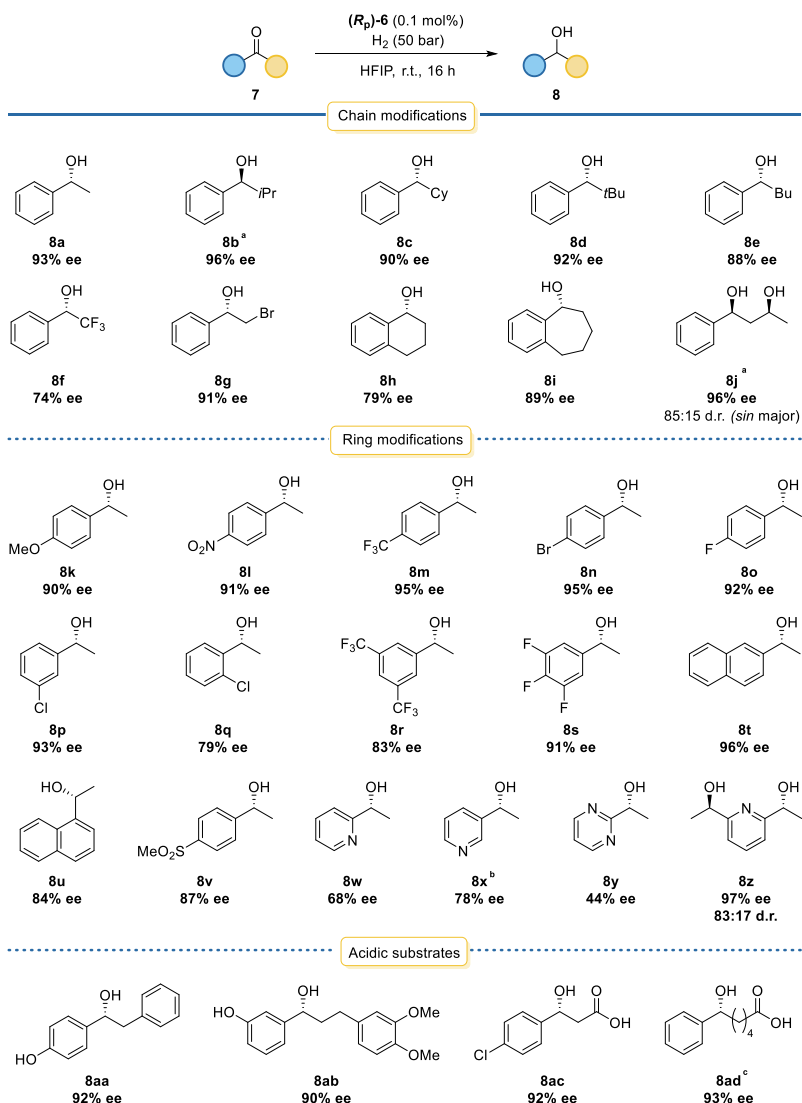
^dThe experiment was carried out at 1.0 M and 0.1 mol% catalyst loading.

Next, we focused on the role of HFIP, which proved to be crucial for the activity of the catalytic system. We examined whether HFIP could be used as an additive instead of solvent. A set of reactions at 0.1 mol% catalyst loading in DCM with different amounts of HFIP was performed (Scheme 6B). As expected, at this catalyst loading, very low conversion was observed without the addition of HFIP. However, when the amount of HFIP was increased, the conversion improved until completion upon the addition of 1 equiv. In these conditions, the alcohol product was obtained with 88% ee, a slightly lower selectivity than when using HFIP as solvent. Notably, as little as 0.1 equiv. of HFIP was enough to obtain high conversion and selectivity, suggesting that HFIP is actively involved in the reaction mechanism. At this point, we examined whether additives with similar properties to HFIP could be used to enable the reaction (see SI). In this regard, the addition of 1 equiv. of phenol showed a similar performance to HFIP and provided full conversion and 90% ee. Following this lead, (*R*)- and (*S*)-Binol were also tested as additives; while providing slightly lower conversions, they afforded similar selectivity. These results suggested that an additive with mild acidity, as both the phenol and the HFIP have a similar pK_a , is needed to facilitate the reaction. However, the additive was likely not involved in the stereodetermining step, as the reaction with opposite enantiomers of Binol provided the same selectivity.

To gain further insight into the reaction mechanism and the key roles of the phosphinito ligand and HFIP, DFT calculations were performed. For this study, we considered the hydrogenation of acetophenone **7a** in DCM with (*R_p*)-**6** and HFIP as additive. Computationally, several routes, with a thorough exploration of the conformational space and location of intermediates and transition states (TSs), were examined using the functional B3LYP-D3, including DCM as solvent in the optimizations through the Solvation Model Density (SMD) method (see SI for extended computational details). To address the role of HFIP in the catalytic process, each step was analyzed with and without the presence of implicit HFIP. Throughout the text, the nomenclature used to describe the catalyst specifies the ligand positioned *trans* to the hydride inside brackets, while the ketone substrate and its corresponding form are listed outside the brackets. When HFIP is employed as an additive, the subscript “hfp” is included.

After discarding a transfer hydrogenation mechanism (see SI), we proposed an outer-sphere hydrogenation pathway where the phosphinito plays an active role in all TSs (Figure 2A). According to our calculations, the most plausible pathway starts with the pyridine dissociation from the complex to generate [**vac**], the active form of the catalyst. We believe that this process is facilitated by the strong *trans* effect exerted by the hydride ligand. Next, a molecule of H₂ coordinates to the complex [**HH**], and H₂ splitting takes place. In the absence of HFIP, this process follows a high-energy five-membered ring transition state **TSI** with a barrier of 21.8 kcal·mol^{−1} (Figure 2B) [58]. When HFIP is included, the corresponding transition state **TSI_{hfp}** involves a seven-membered-ring arrangement in which HFIP acts as a proton shuttle between the phosphinito and the coordinated dihydrogen. Remarkably, this HFIP-assisted pathway lowers the activation barrier to 6.6 kcal·mol^{−1}. This observation suggests that HFIP induces a clear acceleration of the reaction, enabling conversion under conditions in which the system is inert (or nearly so) in its absence. This effect arises from a significant reduction of the energy barrier associated with the H₂ activation step. In the absence of HFIP, the reaction is hindered by a high overall energy barrier of 28.8 kcal·mol^{−1} (21.8 plus 7.0 kcal·mol^{−1} associated with pyridine dissociation). Based on this prediction, experimental studies were carried out, confirming that in DCM without HFIP, reactivity is observed only upon heating to 80 °C or after prolonged reaction times at ambient temperature (see SI) [59].

After H₂ splitting (Figure 2A), the calculations indicate that the reaction pathway is almost identical in the presence or absence of HFIP (see SI). Experimentally, the use of *R*- and *S*-Binol as additives provides the same selectivity, suggesting the additive or HFIP does not actively participate in the stereodetermining step (vide supra). Thus, upon formation of [**H**]_{hfp}, acetophenone is introduced to give the intermediate [**H**]-CO, with concomitant release of an HFIP molecule. The hydrogenation step then occurs via a concerted process in which the metal hydride is transferred to the prochiral carbon of the ketone while the phosphinous acid moiety simultaneously protonates the oxygen atom through a seven-membered-ring arrangement [36]. The corresponding transition state, **TSII** ($\Delta G^\ddagger = 5.9$ kcal·mol^{−1} for the most favorable), is the enantiodetermining step of the reaction. Finally, the alcohol product is formed ([**H**]-COH), and subsequent product dissociation regenerates the catalytically active species [**vac**], closing the catalytic cycle.

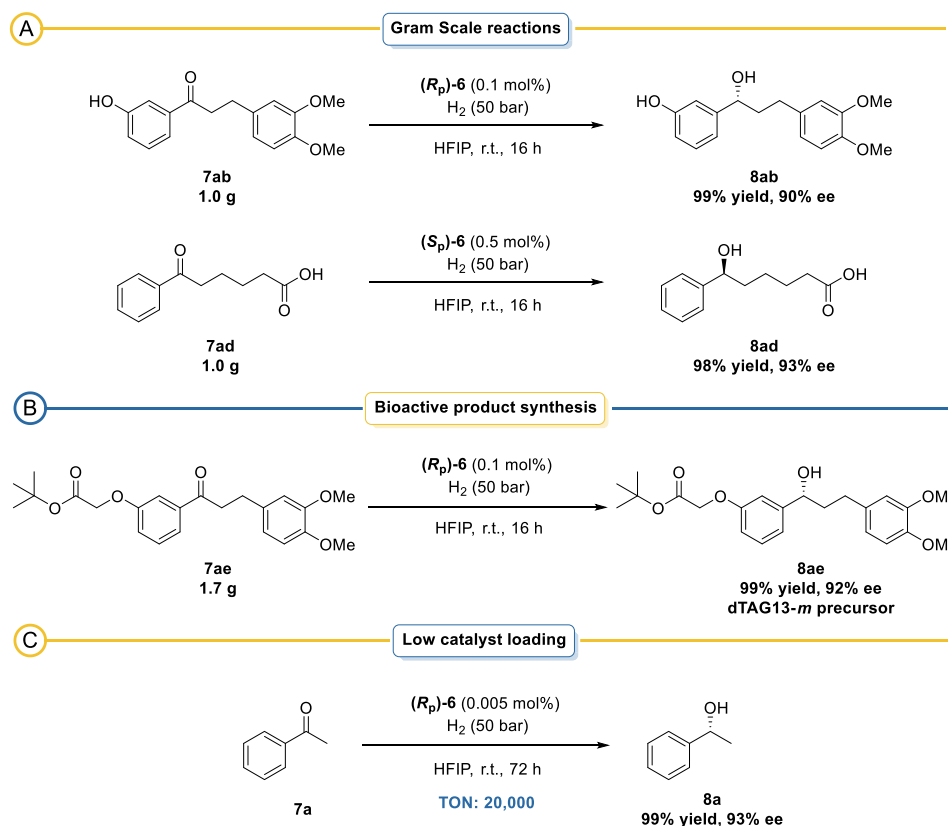


SCHEME 4 | Scope of the AH of ketones **7a-7ad** using $(R_P)\text{-6}$. The reactions were carried out at 1 M concentration. Reactions were very clean, and no byproducts were detected in any hydrogenation reaction. Full conversion was obtained in all cases unless otherwise indicated as determined by ^1H NMR analysis of the crude reaction mixtures. The ee values were determined by chiral HPLC analysis. The absolute configuration was assigned by comparison of the optical rotation of **8a** and was assumed to be the same for all other substrates. ^a $(S_P)\text{-6}$ was used instead of $(R_P)\text{-6}$. ^b1 mol% of catalyst loading was used, and 40% conversion was afforded. ^c0.5 mol% of catalyst loading was used.

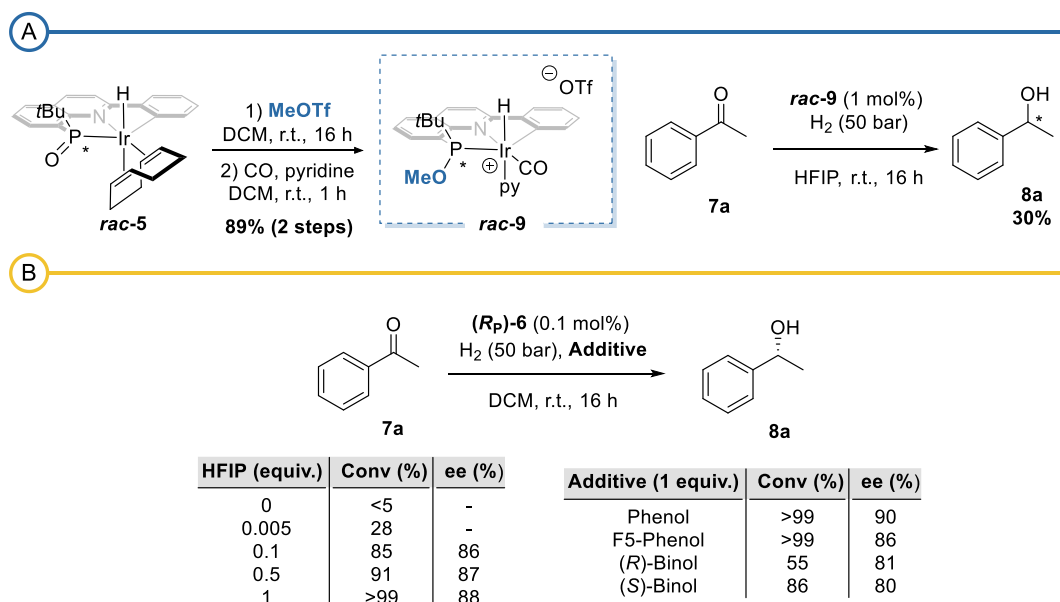
We next studied the origin of the enantioselectivity of the transformation. After extensive exploration of possible substrate orientations and reaction pathways, four distinct transition states were identified for this step (Figure 3A): two leading to the *S* enantiomer and two to the *R* enantiomer. The superscript “IN” or “OUT,” used throughout the text and in the figures, indicates whether the ketone oxygen is pointing toward the ligand or pointing away from it. All four transition states follow the same concerted mechanism, in which hydride transfer to the ketone occurs simultaneously with protonation of the carbonyl oxygen by the phosphinito moiety, which is essential for the reaction to proceed. The lowest-energy transition state, **TSII_{OUT-R}**, involves hydride transfer through the *Re*-face of the ketone and leads to the formation of the *R* alcohol, which corresponds to the experimentally obtained enantiomer. The calculated energy differences between all transition states: **TSII_{IN-R}**, **TSII_{OUT-S}**, and **TSII_{IN-S}**, compared to **TSII_{OUT-R}** are

0.8, 1.2, and 2.3 kcal·mol^{−1}, respectively, corresponding to a predicted 80% ee (*S*), which was subsequently confirmed experimentally in DCM (84% ee) [59]. Single-point energy calculations on the two most favorable transition states leading to opposite enantiomers (**TSII_{OUT-R}** and **TSII_{OUT-S}**) using larger basis sets with the M06-D3 functional further improve the agreement with the experimental value, affording a calculated ee of 85% (*S*) (see SI for full details).

A noncovalent interaction (NCI) analysis of the two most representative transition states, **TSII_{OUT-R}** and **TSII_{OUT-S}**, leading to opposite enantiomers, is shown in Figure 3B. The stabilization of **TSII_{OUT-R}** arises from a large π - π interaction between the phenyl ring of acetophenone and the quinoline moiety of the ligand. In contrast, in **TSII_{OUT-S}**, the substrate phenyl group is slightly displaced from the cyclometallated phenyl ring of the ligand and provides a much smaller stabilizing interaction [62].



SCHEME 5 | (A) Gram-scale hydrogenation of acidic substrates **7ab** with (R_p) -**6** and **7ad** with (S_p) -**6**. (B) Hydrogenation of **7ae**, a dTAG13-*m* precursor. (C) Hydrogenation of **7a** at a 20,000 S/C ratio.



SCHEME 6 | (A) Synthesis of **rac-9** and hydrogenation of **7a** with **rac-9**. (B) Hydrogenation of **7a** using (R_p) -**6** with varying HFIP equivalents and distinct additives.

3 | Experimental Section

3.1 | General Considerations

Unless otherwise indicated, materials were obtained from commercial suppliers and used without further purification.

All reactions that required anhydrous conditions were performed in dried glassware under inert nitrogen atmosphere. Anhydrous THF, Et₂O, and DCM were taken from a solvent purification system (SPS PS-MD-3). Other anhydrous solvents were purchased from commercial suppliers. Hydrogenation reactions were carried out in a Büchi Glas Uster AG miniclave

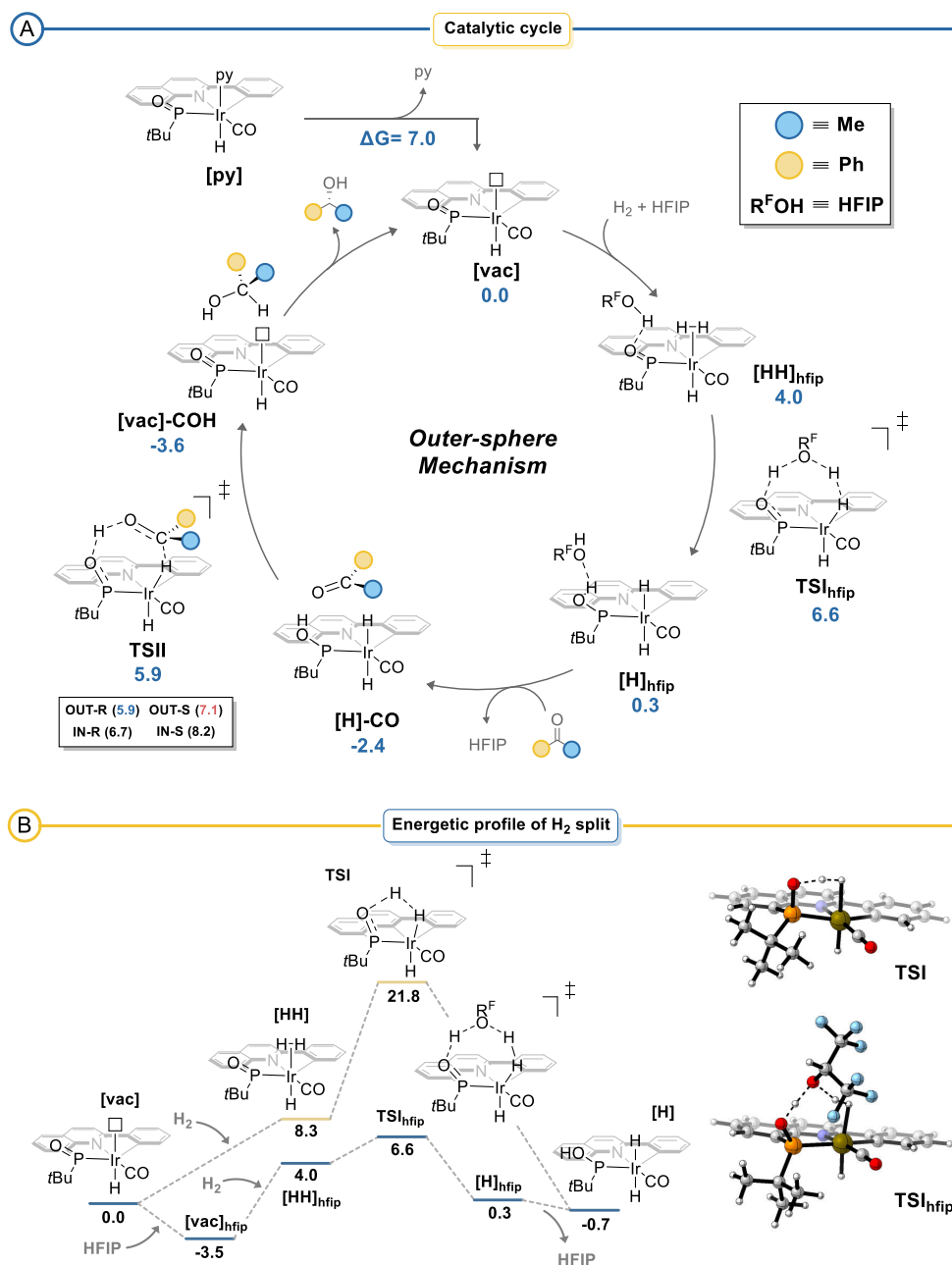


FIGURE 2 | (A) Computed reaction mechanism for the AH of **7a** with (*R_p*)-**6**. (B) Comparison of the energy profile for H₂ splitting with and without the intervention of HFIP alongside representation of key transition states **TSI** and **TSI_{hfp}** in CYLview [57]. Reported Gibbs energies (kcal·mol⁻¹) computed in DCM continuum solvent at B3LYP-D3/def2-TZVP/def2-QZVP(Ir)/SMD//B3LYP-D3/6-31G(d,p)/SDD + f(Ir).

reactor or in a Berghof BR-100 reactor. Alternatively, reactions at low H₂ pressure were performed in Ace glass pressure tubes equipped with a gas inlet manifold and a manometer. ¹H, ¹³C{¹H} and ³¹P{¹H} NMR spectra were recorded using Varian Mercury 400 MHz, Bruker 400 MHz, Bruker 500 MHz, or Bruker 600 MHz spectrometers and were referenced to internal solvent resonances or to tetramethylsilane (TMS). High-resolution ESI-MS spectra were recorded in an LTQ-FT Ultra (Thermo Scientific). IR spectra were recorded in an Agilent Cary 630 FTIR. Melting points were determined using a Büchi M-540 apparatus. Optical rotations were measured using a Jasco P-2000 iRM-800 polarimeter.

3.2 | General Procedure for the Hydrogenation of Arylketones

The ketone (1 equiv.) and (*R_p*)-**6** (0.1 mol%) were placed in a glass tube and dissolved in nonanhydrous HFIP (1 M). The glass tube was introduced into a high-pressure reactor, which was purged three times with nitrogen, three times with hydrogen, and then pressurized at 50 bar. After 16 h, the reactor was depressurized, and the solvent evaporated. The conversion was then determined by ¹H NMR and the enantiomeric excess by chiral HPLC chromatography. Deviations from standard reaction conditions can be found in the Supporting Information.

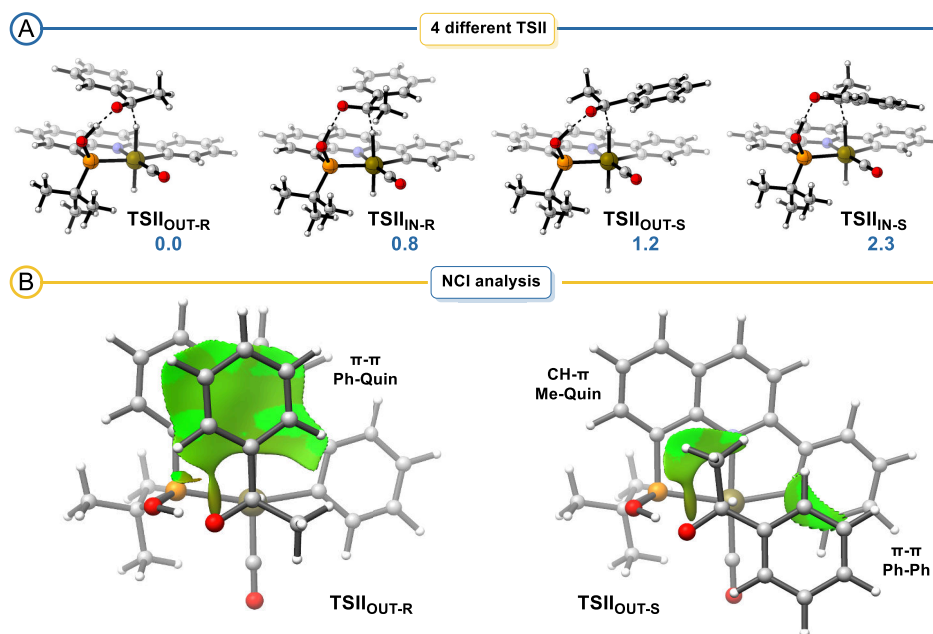


FIGURE 3 | (A) Comparison of the four distinct transition states identified for the hydride transfer **TSII** in the AH of **7a** with (*R_p*)-**6**. (B) Noncovalent interactions analysis of **TSII_{OUT-R}** and **TSII_{OUT-S}** using Multiwfn and Chimera [60, 61]. Reported Gibbs energies (kcal·mol^{−1}) computed in DCM continuum solvent at B3LYP-D3/def2-TZVP/def2-QZVP(Ir)/SMD//B3LYP-D3/6-31G(d,p)/SDD + f(Ir).

3.3 | Computational Details

The hydrogenation of **7a** using (*R_p*)-**6** was studied at DFT level of theory with Gaussian 16 B.01 software [63], using B3LYP functional [64–66] combined with Grimme's D3 correction for dispersion [67]. All TSs were characterized with basis set BS1 in dichloromethane solvent (DCM, ϵ = 8.93) using the SMD continuum model [68]. BS1 includes the 6-31G(d,p) basis set for the main group elements [69,70] and the scalar relativistic Stuttgart-Dresden SDD pseudopotential and its associated double- ζ basis set [71], complemented with a set of f polarization functions [72], for the iridium atom. Frequency calculations, at the same level of theory, were carried out for all the stationary points in order to characterize them as either minima or transition states. Connection of transition states with the corresponding intermediates was confirmed by usual intrinsic reaction coordinate (IRC) calculations and subsequent optimization to minima.

Final Gibbs energies in DCM at 298.15 K were obtained by adding the thermal and entropic corrections obtained with BS1 to the electronic energy in DCM computed with single-point calculations on the BS1-optimized geometries, using an extended basis set (BS2). BS2 consists of the triple- ζ def2-TZVP basis set for the main group elements and the quadruple- ζ def2-QZVP basis set for Ir [73]. A correction of 1.89 kcal mol^{−1} was applied to all Gibbs energy values to change the standard state from gas phase (1 atm) to solution (1 M) at 298.15 K [74].

The NCI analysis reported in this work was first computed using the DFT electron densities of the optimized transition states in Multiwfn [60], and, for clarity, the representation of the isosurfaces was constructed at promolecular level, reporting the DFT density map with Chimera [61].

4 | Conclusion

In summary, we have developed a new P*-stereogenic SPO pincer ligand derived from quinoline (QuinSPO, **4**), in which the phosphorus atom is the only source of chirality. The racemic ligand has been resolved into its corresponding enantiomers by means of chiral chromatography. Coordination of optically pure QuinSPO to iridium provides neutral cyclometallated Ir(III) pincer complexes **5** and **6**, in which the SPO fragment is deprotonated, leading to a phosphinito ligand, as confirmed by X-ray analysis. Complex **6** bearing a labile pyridine ligand showed high activity in the asymmetric reduction of ketones when using HFIP as solvent. Under these conditions, the novel catalytic system showed a large and robust reaction scope, reaching up to 96% ee and 20 000 TON. Most remarkably, the system operates under mild acidic conditions and enables the streamlined reduction of substrates containing phenols and carboxylic acids, without the need for a base as an additive. An integrated experimental–DFT mechanistic analysis showed that cooperative interactions between the phosphinito ligand and HFIP generate a low-energy pathway for H₂ splitting, thereby enabling high catalytic activity under mild conditions. Finally, the reduction step takes place through a concerted 7-membered TS in which the hydride and H⁺ are transferred simultaneously. A strong π - π interaction between the substrate and the quinoline moiety of the ligand accounts for the selectivity. We consider that the new catalytic system described herein is complementary to existing ones and that, upon further development, it should be highly competitive for acidic or base-sensitive substrates. Most importantly, this study establishes the capacity of P*-stereogenic phosphinito ligands to serve as powerful platforms for the development of new catalysts and asymmetric transformations.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article. All computational results are available in the ioChem-BD repository and can be accessed via <https://doi.org/10.19061/iochem-bd-1-433> [75].

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.