Nature inspired catalytic systems using sulfonamido-phosphorus based complexes: Increasing complexity in transition metal catalysis

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Chapter 3

« Effector » Enhanced Enantioselective Catalysis
3.1 Introduction

The increase in the global population, the fast depletion of resources and the degradation of the environment incites us to constantly improve the way we produce chemicals. Living organisms are formidable chemical factories which are able to transform matter in a clean way at ambient temperature and pressure. This is why Nature-inspired chemistry is believed to be one of the keys to meet tomorrow’s needs. Catalysts found in Nature, enzymes, operate within Complex Systems, very different from the reaction mixtures designed by chemists, who usually aim for systems as pure and simple as possible. In a natural reaction mixture, among the large number of various chemical species, biochemists identified additives-like molecules which contribute to the activity of enzymes. They can be divided in two categories: cofactors and effectors. Cofactors bind close to the active site and assist the catalytic transformation. They can be chemically transformed during the reaction before being regenerated. Effectors typically bind far away from the active site of the enzyme, changing their shape and thus their activity, in a reversible manner. They are called allosteric activators when they increase the reaction rate or allosteric inhibitors when they decrease it. A few successful examples of allosteric control and cofactor assisted transformation in homogeneous catalysis have been reported.

Bimetallic rhodium complexes with four sulfonamidophosphoramidite METAMORPhos ligands (Scheme 1, top) have recently emerged as powerful catalysts for asymmetric hydrogenation. Noticeably, the challenging tetrasubstituted enamide S3 (Scheme 1, bottom) could be hydrogenated with 99% enantioselectivity, but the activity of the complex was modest (56% conversion). Initial in-situ characterization of the resting state of the catalytic cycle suggested the formation of a neutral bimetallic complex consisting of two rhodium (I) centers bridged by two deprotonated P-N ligands and two chelating protonated P-O ligands (scheme 1, structure 2(H)2). In a more recent study, crystal structures of the “resting state” complex were obtained. They confirm the coordination modes of the ligand, but the bond lengths unambiguously correspond to a dianionic complex with chelating ligands deprotonated by triethylamine (scheme 1, structure 1A2). The anionic character of the complex was further established by ESI mass spectrometry.

Scheme 1. Top: METAMORPhos ligand 1A, proposed neutral dinuclear structure of the catalytically active species 2(H)2, and crystallized structure 2A2 (binaphthol on the phosphorus have been omitted for clarity); bottom: catalytic hydrogenation of cyclic enamide substrates.
In homogeneous catalysis, especially in asymmetric hydrogenation, counterions are usually designed to be non-interacting with the transition metal, in order to leave additional vacant sites for the substrates and the desired ligands.\textsuperscript{11} However, counterions can also be employed to steer activity and selectivity: interesting anion effects are observed in gold catalysis,\textsuperscript{12} and chiral ions can be designed to induce enantioselectivity.\textsuperscript{13,5} The ionic character of $2^2$ gives us additional handles to control its catalytic properties and integrate it into a synthetic Complex System. As a prerequisite, it is crucial to determine if these counterions are orthogonal,\textsuperscript{14} promotors or inhibitors for the transformations catalyzed by this bimetallic complex. To elucidate the role of these ions, three strategies were implemented: a) modification of the ligand by replacing the original triethylammonium counterion by various cations, b) use of various salts as additives for catalysis and c) computational modeling.

### 3.2 Results and discussions

Ligand 1 is conveniently synthesized as a triethylammonium salt 1A (Scheme 2). The triethylammonium A$^+$ can be replaced by various cations such as quaternary ammonium B$^+$ and C$^+$, phosphonium D$^+$ and bis(triphenylphosphine)iminium E$^+$ by ion metathesis. Adding two equivalents of 1A or 1D to [Rh(nbd)$_2$]BF$_4$ under hydrogen atmosphere results in the formation of the same dianionic complex: the phosphorus NMR spectrum of this new complex 2D$_2$ is identical to the characteristic spectrum of 2A$_2$ (see figure 17 in the experimental section).

![Scheme 2](image)

Unfragmented 2D$_2^+$ could be detected by mass spectrometry, which confirms the dinuclear nature of the complex and shows that the cationic counterions D$^+$ are strongly associated to 1$^{2-}$ (see Figures 15 and 16).

We were curious to know the impact of the change of counterion on the catalytic properties of the complex. When complexes based on ligands 1B-E are used for the asymmetric hydrogenation of selected cyclic enamides substrates, the conversion is lower than when the complex based on the initial ligand 1A is used. 1B-D based complexes give similar results while 1E based complex (bulky PNP counterion) give intermediate conversions (Table 1). In all cases, the enantiomeric excess (ee) of the products hydrogenated by those modified complexes slightly decreases compared to the ee obtained with the reference complex 2A$_2$. On the opposite, when an excess of the initial counterion A$^+$ (protonated triethylamine) is
added to the reaction mixture as its BF$_4^-$ salt, the conversion increases significantly for all substrates, and also the ee increases substantially (Table 1, entries 6 and 7). Notably, the difficult substrate S3 could be quantitatively hydrogenated for the first time, without affecting the enantioselectivity (ee >99%).

### Table 1. Asymmetric hydrogenation of cyclic enamides using modified ligands or HNEt$_3$BF$_4$ as an additive.

<table>
<thead>
<tr>
<th>no.</th>
<th>p (bars)</th>
<th>ligand</th>
<th>S1$^c$ conv. (%) ee (%)</th>
<th>S2$^e$ conv. (%) ee (%)</th>
<th>S3$^d$ conv. (%) ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>20</td>
<td>1A</td>
<td>53</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>2$^a$</td>
<td>20</td>
<td>1B</td>
<td>21</td>
<td>79</td>
<td>43</td>
</tr>
<tr>
<td>3$^a$</td>
<td>20</td>
<td>1C</td>
<td>23</td>
<td>78</td>
<td>42</td>
</tr>
<tr>
<td>4$^a$</td>
<td>20</td>
<td>1D</td>
<td>27</td>
<td>74</td>
<td>47</td>
</tr>
<tr>
<td>5$^a$</td>
<td>20</td>
<td>1E</td>
<td>43</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td>6$^b$</td>
<td>20</td>
<td>1A</td>
<td>85</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>7$^b$</td>
<td>50</td>
<td>1A</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

$^a$ Conditions: [Rh(nbd)$_2$]BF$_4$/ ligand / substrate = 1:2.2:100; [Rh] = 0.001 M; 14 h. $^b$ Same conditions as entry 1 except that HNEt$_3$BF$_4$ is added, HNEt$_3$BF$_4$ / ligand = 100:1. $^c$ Conversions and ee were determined by chiral GC. $^d$ Conversions were determined by GC, ee by HPLC.

The hydrogenation of S1 with various amounts of HNEt$_3$BF$_4$ revealed that the activity increases with the additive to ligand ratio (Figure 1). The use of small quantities of the additive increases the ee from 80 to 90%, and from 50 equivalents of HNEt$_3$BF$_4$, the ee reaches a plateau.$^{15}$ No change in the characteristic phosphorus NMR spectrum of the bimetallic complex is observed when an excess of HNEt$_3$BF$_4$ (up to 100 equivalents per ligand) is added to 2A$_2$, indicating that the coordination mode of the ligand is retained in the presence of this additive (see Figure 18 in the experimental section).

![Figure 1](image.png)

**Figure 1.** Dependency of the conversion and the enantiomeric excess on the additive to ligand ratio for the hydrogenation of S1; Conditions: [Rh(nbd)$_2$]BF$_4$/ 1A / substrate = 1:2.2:100; [Rh] = 0.001 M; 20 bar H$_2$; 1.5 h.

A series of control experiments was carried out to elucidate the role of the ammonium ion in the catalytic hydrogenation. If HNEt$_3$BF$_4$ is replaced by the non-protic NBu$_4$BF$_4$ salt as additive in the hydrogenation of S1 with 2A$_2$ as ligand, the conversion decreases significantly. This shows that the tetrafluoroborate anion is not responsible for the conversion enhancement,
but that the protic cation A\(^+\) is (Table 2, entries 1 vs. 2). Next we checked if the triethylammonium ion activates the substrate rather than the catalyst: we hydrogenated S1 with a rhodium complex made of the BINAP ligand. The results in presence and in absence of salt are similar (Table 2, entries 3 vs. 4). This result clearly establishes that A\(^+\) has a cofactor or effector role, specifically on the Rh-METAMORPhos complex. When deuterium gas is used instead of hydrogen for the reduction of S1 in the presence of 100 equivalent of HNEt\(_2\)BF\(_4\) (with respect to the substrate), only the deuterated product is observed. This result rules out all mechanisms involving proton shuttling or a proton responsive ligand and reveals that A\(^+\) plays the role of an effector rather than a cofactor.

Table 2. Control experiments (hydrogenation of S1)

<table>
<thead>
<tr>
<th>no.</th>
<th>ligand</th>
<th>additive</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>1A</td>
<td>NBu(_4)BF(_4)</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td>2(^a)</td>
<td>1A</td>
<td>none</td>
<td>13</td>
<td>75</td>
</tr>
<tr>
<td>3(^b)</td>
<td>BINAP</td>
<td>HNEt(_2)BF(_4)</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>4(^b)</td>
<td>BINAP</td>
<td>none</td>
<td>22</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: [Rh(nbd)\(_2\)]BF\(_4\) / ligand / substrate / additive = 1:2.2:100:100; [Rh] = 0.002 M; 20 bar H\(_2\); 1.5h. \(^b\) Conditions: [Rh(nbd)\(_2\)]BF\(_4\) / ligand / substrate / additive = 1:1.05:100:100; [Rh] = 0.001 M; 10 bar H\(_2\); 1h.

Next, we investigated the effect of other protic ammonium salts as additives for the hydrogenation of substrate S1 (Table 3.). All tertiary and primary alkyamines show similar effects as the triethylamine salt: under the same conditions, an average increase of the conversion of 10% and an increase of the ee of 5% compared to the system without additive is observed. The pKa of the cations does not seem to be an important parameter except for lutidinium (HLut\(^+\)) and anilinium: those acidic additives (pKa < 5) are detrimental to the hydrogenation as no conversion is observed in their presence. Secondary amines give better results both for conversions and enantioselectivities: 79 % conversion and 96% ee are obtained when H\(_2\)NEt\(_2\)BF\(_4\) is used.

Table 3. Effect of various additives for the hydrogenation of S1\(^a\)

<table>
<thead>
<tr>
<th>Additive</th>
<th>pKa (DMSO)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>/</td>
<td>22</td>
<td>87</td>
</tr>
<tr>
<td>HNEt(_2)BF(_4) (ABF(_4))</td>
<td>9.0(^17)</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>HNBnMe(_2)BF(_4)</td>
<td>7.6(^18)</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>HNEt'Pr(_2)BF(_4)</td>
<td>/</td>
<td>33</td>
<td>93</td>
</tr>
<tr>
<td>HNMe(_2)BF(_4)</td>
<td>8.4(^19)</td>
<td>35</td>
<td>92</td>
</tr>
<tr>
<td>H(_2)NEt(_2)BF(_4) (FBF(_4))</td>
<td>10.5(^19)</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td>H(_2)NOct(_2)BF(_4)</td>
<td>/</td>
<td>66</td>
<td>96</td>
</tr>
<tr>
<td>H(_3)NBuBF(_4)</td>
<td>11.1(^17)</td>
<td>37</td>
<td>93</td>
</tr>
<tr>
<td>H(_3)NOctBF(_4)</td>
<td>/</td>
<td>38</td>
<td>93</td>
</tr>
<tr>
<td>H(_3)NPhBF(_4)</td>
<td>3.8(^17)</td>
<td>&lt;1</td>
<td>/</td>
</tr>
<tr>
<td>HLutBF(_4)</td>
<td>4.46(^20)</td>
<td>&lt;1</td>
<td>/</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: [Rh(nbd)\(_2\)]BF\(_4\) / 1A / substrate / additive = 1:2.2:100:10; [Rh] = 0.001 M; 20 bar H\(_2\); 5h.
The effect of the best additive of Table 3 (\( \text{H}_2\text{NEt}_2\text{BF}_4 \)) on the complex \( 2\text{A}_2 \) was studied by spectroscopic techniques. Adding \( \text{H}_2\text{NEt}_2\text{BF}_4 \) to \( 2\text{A}_2 \) does not change the coordination mode of the ligand as indicated by the \( ^{31}\text{P} \) NMR spectra. \( 2\text{F}_2^+ \), together with its \( \text{F}^+ \) and \( \text{A}^+ \) adducts could be detected by mass spectrometry (see Figure 19 in the experimental section). The detection of larger aggregates \( (2\text{F}_2\text{BF}_4^+ + 2\text{F}_2\text{ABF}_4^+ + 2\text{F}_2\text{BF}_4^+ + 2\text{F}_3\text{A} \text{(BF}_4\text{)}_2^+) \) can be attributed to the ability of \( \text{F}^+ \) to make two ionic hydrogen bonds and the tendency of \( \text{BF}_4^- \) to make (strong) penetrated ion pairs with alkylamines.\(^{11}\)

The effect of one of the worst additives (\( \text{HLutBF}_4 \)) on the complex \( 2\text{A}_2 \) was studied by NMR spectroscopy as well. \( 2\text{A}_2 \) reacts with lutidinium tetrafluoroborate to selectively form a new species \( 3 \). The same complex \( 3 \) is produced when \( 1\text{A} \), [\( \text{Rh(nbd)}_2 \text{BF}_4 \)] and \( \text{HLutBF}_4 \) are mixed under hydrogen atmosphere. \( ^1\text{H} \) and \( ^1\text{H}\{^{31}\text{P}\} \) (selective and full decoupling) NMR experiments revealed the formation of a bimetallic species with one bridging hydride (Scheme 3). Control experiments with \( \text{D}_2 \) instead of \( \text{H}_2 \) yielded the same complex \( 3 \), revealing that the bridging monohydride stems from the lutidinium salt, and is not formed by oxidative addition of dihydrogen. As this monohydridic complex is inactive in hydrogenation, it explains the deactivation of \( 2\text{A}_2 \) by moderately strong acids.

![Diagram](image)

**Figure 2.** Top: protonation of \( 2\text{A}_2 \) to form \( 3 \); bottom left: phosphorus NMR of \( 2\text{A}_2 \) (a) and \( 3 \) (b); bottom right: proton NMR of 3: not decoupled (c), decoupled from the \( ^{31}\text{P} \) signal at 125 ppm and fully \( ^{31}\text{P} \) decoupled (e).

To quantify the dependence of the reaction rate on the ionic environment, we performed gas-uptake experiments at a constant pressure of 20 bars with (a) catalyst \( 2\text{A}_2 \), (b) catalyst \( 2\text{D}_2 \), (c) catalyst \( 2\text{A}_2 \) and additive \( \text{HNEt}_2\text{BF}_4 \) and (d) catalyst \( 2\text{A}_2 \) and additive \( \text{H}_2\text{NEt}_2\text{BF}_4 \). Detailed analysis of the curves (displayed in figure 3) shows that reactions (a), (c) and (d) have an order of 1.1 in substrate (see Figures 6, 10 and 12 in the experimental section). The order in substrate for reaction (b) is not constant in time (average 1.5; see Figure 8), which suggests that the catalyst does not keep its integrity during the whole conversion. The
turnover frequency (TOF) was determined for each system at 5% conversion with the derivatives of the fitted curves (see Figure 3 and the experimental section). In line with the low conversions observed when 1D is used as a ligand, the aprotic system is the slowest (TOF of 16 mol$_{\text{substrate}}$/mol$_{\text{Rh}}$/h). The fastest reaction occurs when H$_2$NEt$_2^+$ is used as an additive (TOF of 117 mol$_{\text{substrate}}$/mol$_{\text{Rh}}$/h). Importantly, these data show that a more than fivefold increase of the activity of the catalyst is possible just by adding an effector to the solution.

![Figure 3](image)

Figure 3. Conversion of S1 as a function of time determined by gas-uptake (at constant pressure and temperature) with (a) 1A as ligand, (b) 1D as ligand, (c) 1A as ligand with HNEt$_2$BF$_4$ as additive, (d) 1A as ligand with H$_2$NEt$_2$BF$_4$ as additive. Respective TOFs and relative TOFs. (a) Conditions: [Rh(nbd)$_2$]BF$_4$ / 1A / substrate = 1:2.2:100; [Rh] = 0.004 M; 20 bar H$_2$; 5h; 30˚C. (b) additive / [Rh(nbd)$_2$]BF$_4$ = 50. at 5% conversion, in mol$_{\text{substrate}}$/mol$_{\text{Rh}}$/h. (c) TOF / TOF of (a).

With these experimental data in hand, we decided to investigate the influence of the protonation state of the chelating ligands on the energy profile of the proposed catalytic cycle (Figure 4). Dianionic (path I) and neutral (path II) complexes were optimized with DFT at the BP86 level of theory. We used a simplified model of $\text{2}^-$ in which the binaphthol units of the ligands were replaced by smaller -OCH$_2$CH$_2$O- fragments and we used ethylene as a model substrate. We also modeled dianionic complexes hydrogen-bonded to dimethylamine (structures i and iv to ix): they converge to dianionic, monoanionic or neutral complexes, depending on the intermediate (see Figure 23 in the experimental section). This variability suggests that the proton can easily hop from the protonated complex to the hydrogen-bonded amine and vice versa.

It should be noted that in our model, for path II, the highest energy barrier corresponds to TS2 (oxidative addition of H$_2$). This contradicts a pseudo 1$^{\text{st}}$ order in substrate. However, since the substrate used in the kinetic experiments is more bulky and hence should bind more weakly to rhodium than the model substrate (ethene) the energies corresponding to the structures vii to TS4 are underestimated (in both pathways).

The protonation state has an impact on the geometry of the boat shaped complexes: during the whole catalytic cycle, the Rh-Rh distances are shorter for path II than for path I (see Figure 24 in the experimental section). The rhodium-oxygen distance is elongated when the chelating ligand is protonated. The differences between I and II do not significantly affect the
energy level of the transition states TS1 and TS2 ($\Delta\Delta G_{TS} < 2$ kcal/mol), but the migratory insertion is easier for path II ($\Delta\Delta G_{TS3} = 2.7$ kcal/mol). As the alkyl-Rh intermediate x is significantly lower in energy than i in path I ($\Delta G_{x} = -5.8$ kcal/mol), the actual energy barrier corresponding to TS4 (14.3 kcal/mol) is significantly higher than in path II ($\Delta\Delta G_{x,TS4} = 3.8$ kcal/mol). This can be rationalized by the difference in electronic properties of the ligands. The structures viii and ix correspond to 18 electron complexes. As such, they are destabilized by the more electron-donating anionic ligands of path I and stabilized by less electron-donating protonated ligands of path II. On the opposite, the 16 electron complex x is destabilized in path II (less electron-donating ligands) and stabilized in path I (more electron-donating ligands).

These DFT calculations suggest that delocalization of the proton from the counterions to the chelating ligands of the dinuclear complex stabilizes the migratory insertion (TS3) and destabilizes the alkyl-Rh intermediate (x) by modulating the electronic properties of the ligand.

**Figure 4.** DFT calculated mechanistic pathway (top) and corresponding energy profile (bottom).
3.3 Conclusion

We demonstrated that the dinuclear anionic complex consisting of 4 METAMORPhos ligands and 2 rhodium centers has an allosteric relation with protic cations in solution when it is used as catalyst for the asymmetric hydrogenation reactions. In reaction mixtures lacking proton donors, the catalyst is less active. If strong acids are used, irreversible deactivation of the catalyst is observed, a result of the formation of an inactive bridging hydride complex. Secondary ammonium salts were found to be the best additives since they can make two hydrogen bonds with the negatively charged complex, which increases the proximity of the effector and favors the delocalization of protons from the counterion to the catalyst. Computational modelling show that energy barriers are affected to some extent by the presence of an effector and suggest that the effectors destabilize the last catalytic intermediate and thus lower the highest energy barrier of the catalytic cycle. In that sense, our system is different from reported examples of synthetic allosteric catalyst where the effector typically lowers transition states or triggers a switch of the catalyst from a dormant state to an active state.\(^5\) The use of mild acids as allosteric effector additives results in a more than fivefold increase of the turnover frequency and improved the enantioselectivity. By using the proper effector, challenging tetrasubstituted enamides could be hydrogenated quantitatively for the first time in 99% enantioselectivity.

3.4 Experimental section

3.4.1 General

[Rh(nbd)\(_2\)]BF\(_4\) were purchased from Alfa. Ligands and substrates were synthesized according to literature procedures.\(^{1,23}\) All reactions were carried out in dry glassware under argon or nitrogen atmosphere. Every solution addition or transfer was performed via syringes or in a glovebox. All solvents were dried and distilled with standard procedures. The water content of dichloromethane was tested with a Karl-Fisher titrator (the value was always below 4 ppm). Nuclear Magnetic Resonance experiments were performed on a Varian Inova spectrometer (\(^1\)H: 500 MHz, \(^{31}\)P: 202.3 MHz, \(^{13}\)C: 125.7 MHz). Chemical shifts are referenced to the solvent signal (7.27 ppm in \(^1\)H and 77.0 ppm in \(^{13}\)C NMR for CDCl\(_3\)). High resolution ESI (electrospray ionization) mass spectra were obtained on a time-of-flight JEOL AccuTOF LC-plus mass spectrometer (JMS-T100LP) equipped with an ESI source. Unless otherwise stated, all reactions were done at room temperature (21-22°C).

3.4.2 Ion metathesis

Typical procedure: 0.2 mmol (1 eq.) 1\(A\) and 0.4 mmol (2 eq.) of the chloride salt of the desired counterion is stirred overnight in THF. The solution is filtered on a small plug of basic alumina. The plug is subsequently washed with 5 mL of THF. THF phases are combined and evaporated to dryness. The modified ligand was obtained in close to quantitative yield in all case. The absence of Cl\(^-\) is tested with silver nitrate. The absence of triethylammonium is assessed by proton NMR.

\(1\)B
\(^{31}\)P{\(^1\)H} NMR (162 MHz, CD\(_2\)Cl\(_2\), r.t.) \(\delta\) (ppm): 168.40 (q, \(\quad J_{P,F} = 11.0\) Hz).
\(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\), r.t.) \(\delta\) (ppm): 7.94-7.08 (aromatic region, 17H), 3.74 (s, 2H, CH\(_2\) of benzyl-N), 2.70 (m, 6H, CH\(_2\) of Et-N), 0.94 (t, \(\quad J_{H,H} = 7.3\) Hz, 9H, CH\(_3\) of Et-N).

\(1\)C
\(^{31}\)P{\(^1\)H} NMR (162 MHz, CD\(_2\)Cl\(_2\), r.t.) \(\delta\) (ppm): 168.52 (q, \(\quad J_{P,F} = 11.1\) Hz).
\(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\), r.t.) \(\delta\) (ppm): 7.97-7.14 (aromatic region, 12H), 2.68 (m, 8H, CH\(_2\) of Et-N), 0.84 (m, 12H, CH\(_3\) of Et-N).
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$^{31}$P($^1$H) NMR (162 MHz, CD$_2$Cl$_2$, r.t.) $\delta$(ppm): 168.10 (q, $^4J_{P-F} = 10.3$ Hz), 23.12 (s, phosphonium cation).

$^1$H NMR (400 MHz, CD$_2$Cl$_2$, r.t.) $\delta$(ppm): 7.95-7.17 (aromatic region)

**IE**

$^{31}$P($^1$H) NMR (162 MHz, CD$_2$Cl$_2$, r.t.) $\delta$(ppm): 170.03 (q, $^4J_{P-F} = 10.4$ Hz, anionic ligand), 22.96 (s, bis(triphenylphosphine)iminium cation)

$^1$H NMR (400 MHz, CD$_2$Cl$_2$, r.t.) $\delta$(ppm): 7.92-7.12 (aromatic region)

### 3.4.3 Ammonium tetrafluoroborate salts

**General procedure:** 10 mmol of amine (or lutidine) was dissolved in 5 mL of Me-THF (under air). 10 mmol of HBF$_4$ (48% in water) was added dropwise under magnetic stirring. The stirring is continued for 5 min and the solvents are subsequently evaporated. To remove all water, the residue is azeotroped 3 times (or more) with anhydrous Me-THF. The residue is washed with anhydrous THF (if not soluble) and then diethylether (if not soluble) or pentane. The salts were obtained in quasi-quantitative yield.

The absence of free base or excess of acid was checked by dissolving a small amount of salt in water and checking the neutrality of the solution with pH paper.

### 3.4.4 Asymmetric hydrogenation

**General**

All data belonging to the same figure or table were done simultaneously with the same stock solutions to minimize sources of uncertainties (small change in temperature, concentration of stock solutions, stirring rates or pressure)

**Typical procedure**

Stock solutions of ligands, rhodium precursor, substrates and additives were prepared in DCM, in a glovebox. A 2 mL vial equipped with a stirring bar was subsequently charged, under inert conditions, with 0.25 mL of ligand stock solution, 0.25 mL [Rh(nbd)$_2$]BF$_4$ stock solution, 0.25 mL of substrate stock solution and 0.25 mL of additive stock solution (if applicable) at the required concentrations (see footnotes of respective tables in the main text). If the solubility of the additive in DCM is not sufficient (it is the case for H$_3$NEt$_2$BF$_4$, H$_3$NBuBF$_4$ and H$_2$NPh.HBF$_4$), the additive is loaded as a solid prior to aliquot addition. If required, 0.25 mL of DCM is added to the vial to have a 1 mL reaction mixture. The resulting solution was then stirred at room temperature for 5 minutes. The solution was then exposed to H$_2$ atmosphere, and left to stir at room temperature (magnetic stirring: 500 rpm) for the appropriate amount of time.

NB: For the Figure 1 (dependency towards the amount of additive), HNEt$_3$BF$_4$ was added as a solid for a better accuracy.

**Analysis**

Conversions were determined by chiral GC for all substrates (Interscience Focus GC Ultra with FID detector and with a Chiralsil DEX-CB column (25m x 0.32mm)). Enantioselectivities were determined by the same chiral GC for substrates S1 and S2. Enantioselectivities were determined by chiral HPLC for substrated S3 (AD column, detection 254 nm).

GC method and retention times for S1: 160˚C, 1˚C/min until 190˚C, 5˚C until 220˚C. Substrate 26.4 min, first enantiomer 19.3 min, second enantiomer 19.6 min.

GC method and retention times for S2: 160˚C, 1˚C/min until 190˚C, 40˚C until 220˚C. Substrate 26.9 min, first enantiomer 17.0 min, second enantiomer 19.4 min.

GC method and retention times for S3: 190˚C, 1˚C/min until 212˚C, 40˚C until 220˚C. Substrate 20.9 min, first enantiomer 19.4 min, second enantiomer 19.5 min ($ee$ determination impossible).

HPLC method and retention time for S3: Heptane/iPrOH (90:10), 0.6mL/min. Substrate 14.9 min, first enantiomer 19.8 min, second enantiomer 21.3 min.

### 3.4.5 Turnover frequency determination

The experiments were carried out in the AMTEC SPR16 equipment consisting of 16 parallel reactors equipped with internal temperature and pressure sensors, and a mass flow controller. The apparatus is suited for monitoring gas uptake profiles during the catalytic reactions. Prior to catalytic experiments,
the autoclaves were heated to 110°C and flushed with argon (22 bar) five times. Next, the reactors were cooled to room temperature and flushed again with argon (22 bar) five times. Then, the autoclaves were charged with solutions of the rhodium precursor $[\text{Rh(nbd)}_2]\text{BF}_4$, ligand, substrate, additive (if desired) in CH$_2$Cl$_2$ (8ml) with concentrations and ratios as follow: $[\text{Rh}] = 0.004$ M, $[\text{Rh(nbd)}_2]\text{BF}_4$ / [ligand] / [substrate] = 1:2.2:100, and $[\text{Rh(nbd)}_2]\text{BF}_4$ / additive = 50 (if applicable). The reactors were pressurized with H$_2$ (20 bars) and heated up to 30°C. The pressure was kept constant during the whole reaction, and the gas uptake was monitored and recorded for every reactor. After catalysis (typically 20h) the pressure was reduced to 2.0 bar, the reactor was flushed with argon, and samples were taken for further analysis. Final conversions were determined by GC analysis.

The gas consumption vs. time (raw data) were converted to conversion vs. time (conversion at t = gas uptake at t / final gas uptake * measured final conversion). These curves are presented in Figure 2 (main text).

To determine the TurnOver Frequency (TOF), the conversions vs. time were smoothed, to minimize the noise inherent in the integral measurements (to capture important patterns in the data, while leaving out noise) with the Origin 8.0 software, applying the exponential mode ($A_1e^{t/t_1}+A_2e^{t/t_2}+A_3e^{t/t_3}+y_0$) (see table 4 and figure 5). The correctness of the model used was evaluated and confirmed by the analysis of the residuals of the fitting (calculated as: (experimental conversion – model conversion) / experimental correction * 100 (see figure 6).

Table 4. Data and constants for the model corresponding to the gaz-uptake experiments.

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Conversion in the end of the run</th>
<th>Measured gas uptake in the end of the run</th>
<th>models</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>96.35%</td>
<td>76.88 mL</td>
<td>y0</td>
</tr>
<tr>
<td>(b)</td>
<td>81.57%</td>
<td>63.64 mL</td>
<td>A1, t1</td>
</tr>
<tr>
<td>(c)</td>
<td>99.82%</td>
<td>81.82 mL</td>
<td>A2, t2</td>
</tr>
<tr>
<td>(d)</td>
<td>100%</td>
<td>69.89 mL</td>
<td>A3, t3</td>
</tr>
</tbody>
</table>

Figure 5. Experimental and modeled conversion as a function of time for each reactor.
Figure 6. Residuals of the fitting for each reactor (% residual as a function of % conversion).

Figure 7. ln(rate) as a function of ln[S1] between 10 and 90% conversion for reactor (a).
Figure 8. $\ln(\text{rate})$ as a function of $\ln[\text{S1}]$ between 10 and 80% conversion for reactor (b).

Figure 10. $\ln(\text{rate})$ as a function of $\ln[\text{S1}]$ between 10 and 80% conversion for reactor (c).

Figure 11. $\ln(\text{rate})$ as a function of $\ln[\text{S1}]$ between 10 and 90% conversion for reactor (d).
Figure 13. TOF at any conversion (calculated from the derivative of the fitting function (d(conversion)/d(time)).

Table 5. Absolute and relative TOF\(^a\) at 5, 10, 15, 20 and 25% conversion.

<table>
<thead>
<tr>
<th></th>
<th>(a)</th>
<th>(b)</th>
<th>(c)</th>
<th>(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial TOF (mol/mol/h)</td>
<td>32</td>
<td>21</td>
<td>52</td>
<td>144</td>
</tr>
<tr>
<td>relative initial TOF</td>
<td>1</td>
<td>0.7</td>
<td>1.6</td>
<td>4.5</td>
</tr>
<tr>
<td>TOF at 5% conv. (mol/mol/h)</td>
<td>22</td>
<td>16</td>
<td>48</td>
<td>117</td>
</tr>
<tr>
<td>relative TOF at 5% conv.</td>
<td>1</td>
<td>0.7</td>
<td>2.2</td>
<td>5.3</td>
</tr>
<tr>
<td>TOF at 10% conv. (mol/mol/h)</td>
<td>18</td>
<td>13</td>
<td>43</td>
<td>94</td>
</tr>
<tr>
<td>relative TOF at 10% conv.</td>
<td>1</td>
<td>0.7</td>
<td>2.4</td>
<td>5.2</td>
</tr>
<tr>
<td>TOF at 15% conv. (mol/mol/h)</td>
<td>16</td>
<td>11</td>
<td>39</td>
<td>83</td>
</tr>
<tr>
<td>relative TOF at 15% conv.</td>
<td>1</td>
<td>0.7</td>
<td>2.4</td>
<td>5.2</td>
</tr>
<tr>
<td>TOF at 20% conv. (mol/mol/h)</td>
<td>15</td>
<td>10</td>
<td>36</td>
<td>76</td>
</tr>
<tr>
<td>relative TOF at 20% conv.</td>
<td>1</td>
<td>0.7</td>
<td>2.4</td>
<td>5.1</td>
</tr>
<tr>
<td>TOF at 25% conv. (mol/mol/h)</td>
<td>14</td>
<td>10</td>
<td>32</td>
<td>69</td>
</tr>
<tr>
<td>relative TOF at 25% conv.</td>
<td>1</td>
<td>0.7</td>
<td>2.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

\(^a\) Relative TOF = TOF / TOF of (a) at a given conversion.

3.4.6 In-situ spectroscopic studies

Complex 2A\(_2\) was prepared according to a reported procedure\(^9\). All spectroscopic measurements were in agreement with previous data. ESI (negative mode) was measured to confirm its negative charge. MS (ESI-): \(m/z\) calcd. for C\(_{84}\)H\(_{80}\)F\(_{12}\)N\(_{4}\)O\(_{16}\)P\(_{4}\)Rh\(_{2}\)S\(_{4}\) (2\(^2-\) plus H\(^+\): [MH\(^-\)]: 2054.9; obsd.: 2054.3

Figure 14. Top: experimental MS spectrum of 2A\(_2\); bottom: simulated MS spectrum.
Complex 2D₂ was prepared like 2A₂: Ligand 1D (0.025 mmol, 2 eq.) was dissolved in 0.5 mL of CD₂Cl₂ and mixed with [Rh(nbd)₂]BF₄ (0.0125 mmol, 1 eq.). The solution becomes purple and then orange-yellow within a few minutes. The solution was then submitted to 5 bars of H₂ gas, leading immediately to (the) bimetallic species 2D₂ as the only complex present in solution.

³¹P{¹H} NMR (162 MHz, CD₂Cl₂, r.t.) δ(ppm): 141.8 (dd, ¹Jₚ–Rh = 281.2, ²Jₚ–P 37.0 Hz, chelating ligand), 116.3 (dm, ¹Jₚ–Rh = 348.1 Hz, bridging ligand), 23.08 (s, PPh₃ counter ion).

MS (ESI+): m/z calcd. for C₁₃₂H₸₈F₁₂N₆O₁₆P₆Rh₂S₄ (2D₂: [M]⁺) : 2733.2; obsd.: 2733.1

Figure 15. Top: simulated MS spectrum of 2D₂; bottom: experimental MS spectrum. Top: simulated MS spectrum, bottom: experimental MS spectrum.

Figure 16. Top: simulated MS spectrum of 2D₂; bottom: experimental MS spectrum.
Figure 17. Top: $^{31}\text{P}${'H} NMR of 2A$_2$; bottom: $^{31}\text{P}${'H} NMR of 2D$_2$.

Effect of additive ABF$_4$ on 2A$_2$
Ligand 1A (0.025 mmol, 2 eq.) and [Rh(nbd)$_2$]BF$_4$ (0.0125 mmol, 1 eq.) were dissolved in 0.25 mL CD$_2$Cl$_2$ and added to H$_2$NEt$_2$BF$_4$ (2.5 mmol, 100 eq.). The resulting thick solution ($\approx$ 0.7 mL) was then submitted to 5 bars of H$_2$ gas, leading immediately to a bimetallic species as attested by the characteristic pattern on the phosphorus NMR spectrum (the signals were slightly shifted compared to the signals of the bimetallic 2A$_2$ complex which was previously fully characterized, but the coupling constants were unchanged).

Despite the extremely high concentration of HNEt$_2$BF$_4$ (> 3.5 M), all the solids dissolved.

Figure 18. Top: $^{31}\text{P}${'H} NMR of 2A$_2$; bottom: $^{31}\text{P}${'H} NMR of 2A$_2$ with 100 eq. of HNEt$_2$BF$_4$.

Effect of additive FBF$_4$ on 2A$_2$
Ligand 1A (0.025 mmol, 2 eq.) and [Rh(nbd)$_2$]BF$_4$ (0.0125 mmol, 1 eq.) were dissolved in 0.5 mL CD$_2$Cl$_2$ and added to H$_2$NEt$_2$BF$_4$ (0.25 mmol, 10 eq.). The resulting solution was then submitted to 5 bars of H$_2$ gas, leading immediately to a bimetallic species as attested by the characteristic pattern on the phosphorus NMR spectrum (the signals were slightly shifted compared to the signals of the bimetallic 2A$_2$ complex which was previously fully characterized, but the coupling constants were unchanged).

H$_2$NEt$_2$BF$_4$ did not completely dissolve (presence of a colorless solid), however, its presence in solution is attested by the change in proton NMR (additional signals corresponding to the ethyl fragment of H$_2$NEt$_2$) and by mass.

Figure 19. Experimental profile of the MS analysis of 2A$_2$ + FBF$_4$. 
\textbf{Chapter 3}

Table 6. Assignment of the signals in the mass spectrum (ESI+) of $2\text{A}_2 + \text{FBF}_4$.

<table>
<thead>
<tr>
<th>species</th>
<th>formula</th>
<th>calculated $m/z$</th>
<th>observed $m/z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$2\text{F}_2^+$</td>
<td>$\text{C}<em>{10}\text{H}</em>{27}\text{F}_{12}\text{N}<em>4\text{O}</em>{16}\text{P}_2\text{Rh}_2\text{S}_4$</td>
<td>2203.1</td>
<td>2203.3</td>
</tr>
<tr>
<td>$2\text{AF}^+$</td>
<td>$\text{C}<em>{19}\text{H}</em>{27}\text{F}_{12}\text{N}<em>4\text{O}</em>{16}\text{P}_2\text{Rh}_2\text{S}_4$</td>
<td>2231.1</td>
<td>2231.2</td>
</tr>
<tr>
<td>$2\text{A}_2^+$</td>
<td>$\text{C}<em>{19}\text{H}</em>{27}\text{F}_{12}\text{N}<em>4\text{O}</em>{16}\text{P}_2\text{Rh}_2\text{S}_4$</td>
<td>2259.1</td>
<td>2259.4</td>
</tr>
<tr>
<td>$2\text{F}_2\text{BF}_4^+$</td>
<td>$\text{C}<em>{9}\text{H}</em>{28}\text{BF}_{16}\text{N}<em>4\text{O}</em>{16}\text{P}_4\text{Rh}_2\text{S}_4$</td>
<td>2364.2</td>
<td>2364.4</td>
</tr>
<tr>
<td>$2\text{F}_2\text{ABF}_4^+$</td>
<td>$\text{C}<em>{9}\text{H}</em>{28}\text{BF}_{16}\text{N}<em>4\text{O}</em>{16}\text{P}_4\text{Rh}_2\text{S}_4$</td>
<td>2392.2</td>
<td>2392.4</td>
</tr>
<tr>
<td>$2\text{FA}_3\text{BF}_4^+$</td>
<td>$\text{C}<em>{10}\text{H}</em>{28}\text{BF}_{16}\text{N}<em>4\text{O}</em>{16}\text{P}_4\text{Rh}_2\text{S}_4$</td>
<td>2420.2</td>
<td>2420.4</td>
</tr>
<tr>
<td>$2\text{F}_2(\text{BF}_3)_2^+$</td>
<td>$\text{C}<em>{10}\text{H}</em>{28}\text{BF}_{26}\text{N}<em>4\text{O}</em>{16}\text{P}_2\text{Rh}_2\text{S}_4$</td>
<td>2524.3</td>
<td>2524.5</td>
</tr>
<tr>
<td>$2\text{FA}_2(\text{BF}_3)_2^+$</td>
<td>$\text{C}<em>{10}\text{H}</em>{28}\text{BF}_{26}\text{N}<em>4\text{O}</em>{16}\text{P}_2\text{Rh}_2\text{S}_4$</td>
<td>2552.3</td>
<td>2552.5</td>
</tr>
</tbody>
</table>

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure20.png}
\caption{Top left: $^{31}\text{P}^{1}\text{H}$ NMR of $2\text{A}_2$; bottom left: $^{31}\text{P}^{1}\text{H}$ NMR of $2\text{A}_2$ with 100 eq. of $\text{H}_2\text{NEt}_3\text{BF}_4$; top right: $^1\text{H}$ NMR of $2\text{A}_2$; bottom right: $^1\text{H}$ NMR of $2\text{A}_2$ with 100 eq. of $\text{H}_2\text{NEt}_3\text{BF}_4$.}
\end{figure}

\section*{Complex 3}

Method A: Ligand 1A (0.025 mmol, 2eq.) was dissolved in 0.5 mL of CD$_2$Cl$_2$ and mixed with [Rh(nbd)]$_2$BF$_4$ (0.0125 mmol, 1 eq.) and lutidinium tetrafluoroborate (0.0625 mmol, 5eq.). The resulting solution was then submitted to 5 bars of H$_2$ gas. Complex 3 quantitatively formed overnight (increasing the amount of lutidinium tetrafluoroborate reduces the formation time).

Method B: Ligand 1H (protonated version of 1 reported in ref 8) (0.025 mmol, 2eq.) was dissolved in 0.5 mL of CD$_2$Cl$_2$ and mixed with [Rh(nbd)(acac)]] (0.0125 mmol, 1 eq.). The resulting solution was then submitted to 5 bars of H$_2$ gas. Complex 3 quantitatively formed overnight.

$^{31}\text{P}^{1}\text{H}$ NMR (162 MHz, CD$_2$Cl$_2$, r.t.) $\delta$(ppm): 125.11 (broad d, $^1J_{\text{P,Rh}} = 240.1$ Hz), 108.05 (dm, $^1J_{\text{P,Rh}} = 267.9$ Hz).

$^1\text{H}$ NMR (400 MHz, CD$_2$Cl$_2$, r.t.) (method B) $\delta$(ppm): 8.28-6.13 (aromatic area), 5.50 (s, acetylacetone, enol form), 4.61 (s, dissolved H$_2$), 3.62 (s, acetylacetone diketone form), 2.63- 0.75 (alkyl region), -11.92 (ddt, $^2J_{\text{H,Rh}^0}=2J_{\text{H,P}} \approx 22$ Hz).

\subsection*{3.4.7 Computational studies}

\textbf{General}

All geometry optimizations were carried out with the Turbomole program\textsuperscript{25} coupled to the PQS Baker optimizer.\textsuperscript{26} Geometries were fully optimized as minima or transition states at the (ri-)BP86\textsuperscript{27,28} level using the SV(P) basis set\textsuperscript{29} on all atoms. All stationary points (minima and transition states) were characterized by vibrational analysis (analytical frequencies); ZPE and gas phase thermal corrections (entropy and enthalpy, 298 K, 1 bar from these analyses were calculated according to standard formulas of statistical thermodynamics. Roughly estimated condensed phase (1 L mol$^{-1}$) free energies, entropies and enthalpies were obtained from these data by subsequent correction for the condensed phase reference volume ($S_{\text{CP}}= S_{\text{GP}}+ R^* \ln(1/24.53)$. All energy values presented in the text and in the graphs are corrected values.

\section*{Figure 20.} Top left: $^{31}\text{P}^{1}\text{H}$ NMR of $2\text{A}_2$; bottom left: $^{31}\text{P}^{1}\text{H}$ NMR of $2\text{A}_2$ with 100 eq. of $\text{H}_2\text{NEt}_3\text{BF}_4$; top right: $^1\text{H}$ NMR of $2\text{A}_2$; bottom right: $^1\text{H}$ NMR of $2\text{A}_2$ with 100 eq. of $\text{H}_2\text{NEt}_3\text{BF}_4$.
An approximation of the transition states $\text{TS1}$ was found by exploring the reaction coordinate energy profiles through constrained geometry optimizations from the respective intermediates with fixed bond distances towards the transition states. Transition states corresponding to $\text{TS2}$, $\text{TS3}$ and $\text{TS4}$ in ref 8 were taken as approximations. Accurate transition states were found from those approximations by unconstrained full transition state searches. The identity of the transition states was confirmed by following the single negative eigenvalue vibration in both directions (IRC), followed by unconstrained geometry optimizations, which confirmed the connection between the transition states and the respective intermediates.

**Influence of the substituent at the sulfur atom (path II)**

In accordance to what is experimentally observed,\(^8\) energy barriers are significantly lowered when trifluoromethyl substituted ligands are used instead of the methylated one:\(^{30}\) the energies corresponding to transition states $\text{TS2}$, $\text{TS3}$ and $\text{TS4}$ respectively decrease from 16 to 14, 23 to 11 and 15 to 10 kcal/mol.

The structures with a methyl substituent at the sulfur were taken from ref 8 and reoptimized.\(^{31}\)

**Energy profile of path III**

For this model, dimethylammonium ions were added to the structures of path I, in close proximity to the chelating ligands. The relevance of the energy profile that we obtained can be questioned, as solvation effects (which are not explicitly included in our gas phase model) are expected to play a major role for ionic species. Nonetheless, the results obtained show that the pK\(_a\) of the protonated complex is very close to the pK\(_a\) of dimethylammonium and that the protons of the counterions can easily hop between the ammonium ion and $\text{2\textsuperscript{2}}$.\(^{32}\)

Figure 21. Top left: structure used in our study (path II); top right: structure used in ref 8; bottom: energy profile obtained for path II with both structures.

Figure 22. Energy profile of path III.
### Table

<table>
<thead>
<tr>
<th>Structure</th>
<th>Protonation State of the Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>Bis protonated</td>
</tr>
<tr>
<td>iv</td>
<td>Mono protonated</td>
</tr>
<tr>
<td>v (TS2)</td>
<td>Mono protonated</td>
</tr>
<tr>
<td>vi</td>
<td>Deprotonated</td>
</tr>
<tr>
<td>vii</td>
<td>Mono protonated</td>
</tr>
<tr>
<td>viii (TS3)</td>
<td>Deprotonated</td>
</tr>
<tr>
<td>ix</td>
<td>Mono protonated</td>
</tr>
<tr>
<td>x</td>
<td>Deprotonated</td>
</tr>
<tr>
<td>xi (TS4)</td>
<td>Mono protonated</td>
</tr>
</tbody>
</table>

**Figure 23.** Left: Protonation state of the complex in each step of the catalytic cycle (path III); right: dimethylamine/dimethylammonium hydrogen bonded to a chelate of the complex.

**Structural differences between path I, II and III**

**Figure 24.** Rh-Rh distance for each complex, for each path.

### 3.5 References

1. This notion is defined in Chapter 1.
10. See experimental section 3.4.6


We can tentatively explain the dependence of the ee towards HNEt$_3$BF$_4$ concentration by a background reaction which is significant only at low A$^+$ concentration. The increase in A$^+$ concentration accelerates the mechanism leading to the product in a higher ee and does not modify (or inhibit) the background reaction which gives the product in a smaller ee.


The unsaturated complex iii and the associated transition state TS1 have not been considered in ref 8.

On the BP86 level using the SV(P) basis set


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Ligands with a methyl substituent on the sulfur were used as a simplified model in ref 7; only path I had been considered in that study.

In ref 8, an energy value of 8.1 kcal mol$^{-1}$ was obtained for the energy of structure x. The structure of that study may have converged to a local minimum. It does not affect the conclusions of that article. For the other structures, we obtained very similar energies as those reported previously. Any energy differences are negligible and can be attributed to different methods used to calculate the hessians/vibrations: we used analytical hessians, the authors of ref 8 calculated the hessians in a numerical way.