Enantioselective Hydrogenation of Imines Using a Diverse Library of Ruthenium Dichloride(diphosphine)(diamine) Precatalysts

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Received: April 11, 2002; Accepted: July 11, 2002

Abstract: A range of aromatic and cyclic imines were subjected to asymmetric hydrogenation with catalysts derived from complexes of the type RuCl2(diphosphine)(diamine). Good to high enantioselectivities were observed. For each imine, a library of chiral complexes based on different diphosphine and diamine combinations was screened. A different combination of diphosphine and diamine was required each time to obtain the optimum enantioselectivity.

Keywords: Asymmetric hydrogenation; DuPHOS; imine hydrogenation; ruthenium

Introduction
Enantiomerically pure amines are highly important building blocks for biologically active molecules and the discovery of new and efficient methods for their preparation is a matter of continued interest. Although numerous methods are available for their preparation, the catalytic asymmetric hydrogenation of imines offers a cheap and industrially viable process as demonstrated by the multi-ton synthesis of (S)-metolachlor.[1] This area, however, is still under development with progress being centred around catalysts based on complexes of Rh, Ir, Ru and Ti.[2] Our own[3] recent experience in the area of non-olefinic hydrogenation has focused on the use of Noyori’s ruthenium(II) dichloride(diphosphine)(diamine) complexes (3).[4] In i-PrOH and in the presence of a strong base, these complexes generate catalysts capable of reducing ketones with very high enantioselectivities even at extremely low catalyst loadings (e.g., molar substrate to catalyst ratio, S/C = 100,000/1).[5] Therefore, we sought to investigate their use in the catalytic asymmetric hydrogenation of imines. We were specifically interested in this class of complex as large libraries of structurally diverse diphosphine and diamine ligands could be used to rapidly generate an array of catalysts with very different stereoelectronic domains.

Results and Discussion
The precatalysts used were readily prepared under inert conditions by reaction of [RuCl2(C6H5)2] with a diphosphine in hot DMF followed by treatment with a diamine at room temperature yielding air stable, easily handled solids.[3] The imines were purchased or prepared by reaction of the requisite ketones and amines in toluene at room temperature in the presence of 4 Å molecular sieves.[2] It should be noted that we observed hydrogenation at lower pressures than reported, but for consistency in screening higher pressures were used. In a preliminary hydrogenation reaction using a molar substrate-to-catalyst-to-base ratio (S/C/B) of 100/1/100 of N-(phenylethylidene)aniline (1), RuCl2[(S)-Tol-BINAP][(S,S)-DPEN] and t-BuOK (1 M solution in t-BuOH) in i-PrOH at 50 °C under 15 bar H2 provided quantitative conversion to amine 2 with 49% ee (Scheme 1). As will be described, we were ultimately able to increase the enantioselectivity to 94% ee (vide infra) by choice of appropriate catalyst and conditions.

Concurrent to this work, Morris et al.[6] reported the hydrogenation of a range of simple ketones and two imines using RuH2(PPh3)2[(R,R)-DACH] or RuHCl(PPh3)2[(R,R)-DACH] but no enantioselectivities were reported. Very recently the same authors reported the use of complexes of the type RuHCl(chiral...
of the related RuCl₂(diphosphine)(diamine) complexes reported. and at best moderate selectivities obtained (up to 71% diamines was tested for the hydrogenation of imines range, however, of chiral diphosphines and chiral that quantitative hydrogenation could be achieved in Figure 1 (see Table 1). In entries 1–10, the DuPHOS family of diphosphines was tested more extensively. Although Me-DuPHOS (entry 1) gave good selectivity it was inferior to Et-DuPHOS (entry 2) and t-Pr-DuPHOS (entry 8) in conjunction with DPEN. A marked stereochemical matching/mismatching effect was observed for diphosphine/diamine combinations (cf. entries 2 and 3). Comparison of different diamines revealed that although DACH (entry 4) provided a slight improvement in selectivity over DPEN (entry 2), DAIPEN (entry 5), ANDEN (entries 6 and 7) and AMP (entry 9) were less selective.

BINAP in combination with a variety of diamines gave low enantioselectivities and conversions (entries 11–14) for this substrate, whilst the more electron-rich Tol-BINAP gave full conversion (entry 15). Conversely, Noyori reported that the parent ketone, acetophenone, was hydrogenated in 91% ee using RuCl₂[(S)-Tol-BINAP][(S)-DAIPEN]. Generally, we observed lower selectivities for imines as compared to those achieved in ketone hydrogenation using Noyori-type precatalysts. Moreover, diphosphine/diamine combinations that were good for ketone hydrogenation (e.g., Tol-BINAP/DPEN and PhanePHOS/DPEN) were poor for imine hydrogenation and vice versa (e.g., Et-DuPHOS/DPEN). Several other biaryl-diphosphines, including the electron-rich HexaPHEMP ligand were tested (entries 16–18) and although conversions were generally high, enantioselectivities were moderate. The PhanePHOS-based family of diphosphines, that we have shown to be as effective as BINAP-based ligands in ketone hydrogenation using Noyori-type precatalysts, provided poor results for imine hydrogenation (entries 19–21). It was evident from this precatalyst screen that even small electronic and steric changes in related ligands were critical to the selectivities and activities obtained. Interestingly RuCl₂[(R,R)-Et-DuPHOS](DMF), which is an intermediate in the synthesis of the RuCl₂[(R,R)-Et-DuPHOS](diamine), and which has been reported to effect styrene hydrogenation in conjunction with t-BuOK in i-PrOH, provided 8% conversion and 16% ee under our standard conditions. In theory, the complex RuCl₂[(R,R)-Et-DuPHOS]₂, could be formed under these reaction conditions by displacement of the diamine ligand with the product 2, however, separate experiments using this prepared separately showed it was only slightly active giving 26% conversion and 8% ee.

We proceeded to optimise the reaction conditions for a more industrially acceptable molar substrate-to-catalyst-to-base ratio of 1000/1/100, with the preferred differences in the conversion or ee was observed. When the base was omitted no reaction occurred.

Having identified optimal conditions for the hydrogenation of 1, we proceeded to test a larger range of precatalysts based on different combinations of the chiral diphosphines and chiral diamines shown in Figure 1. In entries 1–10, the DuPHOS family of diphosphines was tested more extensively. Although Me-DuPHOS (entry 1) gave good selectivity it was inferior to Et-DuPHOS (entry 2) and t-Pr-DuPHOS (entry 8) in conjunction with DPEN. A marked stereochemical matching/mismatching effect was observed for diphosphine/diamine combinations (cf. entries 2 and 3). Comparison of different diamines revealed that although DACH (entry 4) provided a slight improvement in selectivity over DPEN (entry 2), DAIPEN (entry 5), ANDEN (entries 6 and 7) and AMP (entry 9) were less selective.

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Table 1. Precatalyst screening against N-(phenylethylidene)aniline (1).\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>RuCl\textsubscript{2}(diphosphine)(diamine)</th>
<th>Conversion [%]\textsuperscript{[b]}</th>
<th>ee [%]\textsuperscript{[c]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\textit{R},\textit{R})-Me-DuPHOS/(\textit{R},\textit{R})-DPEN</td>
<td>94</td>
<td>85 (\textit{S})</td>
</tr>
<tr>
<td>2</td>
<td>(\textit{R},\textit{R})-Et-DuPHOS/(\textit{R},\textit{R})-DPEN</td>
<td>100</td>
<td>91 (\textit{S})</td>
</tr>
<tr>
<td>3</td>
<td>(\textit{S},\textit{S})-Et-DuPHOS/(\textit{R},\textit{R})-DPEN</td>
<td>60</td>
<td>11 (\textit{R})</td>
</tr>
<tr>
<td>4</td>
<td>(\textit{R},\textit{R})-Et-DuPHOS/(\textit{R},\textit{R})-DACH</td>
<td>92</td>
<td>92 (\textit{S})</td>
</tr>
<tr>
<td>5</td>
<td>(\textit{R},\textit{R})-Et-DuPHOS/(\textit{R},\textit{R})-DAIPEN</td>
<td>43</td>
<td>48 (\textit{S})</td>
</tr>
<tr>
<td>6</td>
<td>(\textit{R},\textit{R})-Et-DuPHOS/(\textit{R},\textit{R})-ANDEN</td>
<td>11</td>
<td>8 (\textit{R})</td>
</tr>
<tr>
<td>7</td>
<td>(\textit{R},\textit{R})-Et-DuPHOS/(\textit{S},\textit{S})-ANDEN</td>
<td>9</td>
<td>9 (\textit{R})</td>
</tr>
<tr>
<td>8</td>
<td>(\textit{S},\textit{S})-i-Pr-DuPHOS/(\textit{R},\textit{R})-DPEN</td>
<td>99</td>
<td>89 (\textit{S})</td>
</tr>
<tr>
<td>9</td>
<td>(\textit{R},\textit{R})-i-Pr-DuPHOS/(\textit{S})-AMP</td>
<td>3</td>
<td>11 (\textit{R})</td>
</tr>
<tr>
<td>10</td>
<td>(\textit{R},\textit{R})-i-Pr-DuPHOS/(\textit{S})-BINAM</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>(\textit{R})-BINAP/EDA</td>
<td>3</td>
<td>24 (\textit{S})</td>
</tr>
<tr>
<td>12</td>
<td>(\textit{R})-BINAP/(\textit{R},\textit{R})-DPEN</td>
<td>22</td>
<td>49 (\textit{S})</td>
</tr>
<tr>
<td>13</td>
<td>(S)-BINAP/(S)-AMP</td>
<td>6</td>
<td>23 (\textit{R})</td>
</tr>
<tr>
<td>14</td>
<td>(R)-BINAP/(S)-AMP</td>
<td>4</td>
<td>19 (\textit{R})</td>
</tr>
<tr>
<td>15</td>
<td>(S)-Tol-BINAP/(\textit{S},\textit{S})-DPEN</td>
<td>99</td>
<td>49 (\textit{R})</td>
</tr>
<tr>
<td>16</td>
<td>(S)-HexaPHEMP/(\textit{S},\textit{S})-DACH</td>
<td>78</td>
<td>56 (\textit{R})</td>
</tr>
<tr>
<td>17</td>
<td>(R)-HexaPHEMP/(\textit{R},\textit{R})-DPEN</td>
<td>98</td>
<td>45 (\textit{S})</td>
</tr>
<tr>
<td>18</td>
<td>(R)-MeO-BIPHEP/(\textit{R},\textit{R})-DPEN</td>
<td>98</td>
<td>50 (\textit{S})</td>
</tr>
<tr>
<td>19</td>
<td>(R)-i-Pr-PhenePHOS/(\textit{S},\textit{S})-DPEN</td>
<td>16</td>
<td>37 (\textit{R})</td>
</tr>
<tr>
<td>20</td>
<td>(R)-Xylyl-PhenePHOS/(\textit{S},\textit{S})-DPEN</td>
<td>26</td>
<td>11 (\textit{R})</td>
</tr>
<tr>
<td>21</td>
<td>(S)-CF\textsubscript{3},Ph-PhenePHOS/(\textit{R},\textit{R})-DPEN</td>
<td>2</td>
<td>35 (\textit{S})</td>
</tr>
<tr>
<td>22</td>
<td>(R,R)-Me-FerroTANE/(\textit{S},\textit{S})-DPEN</td>
<td>20</td>
<td>–</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Conducted in a multi-well hydrogenation apparatus at 15 bar H\textsubscript{2}, 65\textdegree C, for \textit{ca}. 20 h, with 1 mol % RuCl\textsubscript{2}(diphosphine)(diamine) and 100 mol % t-BuOK in t-BuOH.

\textsuperscript{[b]} Determined by \textit{1}H NMR spectroscopy.

\textsuperscript{[c]} Determined by GC analysis using a chiral DEX-CB column. Absolute configuration is in parentheses.

RuCl\textsubscript{2}(\textit{R},\textit{R})-Et-DuPHOS/[(\textit{R},\textit{R})-DACH] precatalyst. At this loading, 20% conversion and 88% ee were obtained at 65\textdegree C, 20 h at 20 bar H\textsubscript{2} at 0.5 M substrate concentration in \textit{i}-PrOH. Although an increase in the hydrogen pressure to 100 bar had little effect, increasing the temperature to 100\textdegree C had a detrimental effect on the selectivity (80% ee) and produced only a modest increase in conversion (48%). The two most important factors leading to an increase in the conversion were time and concentration. Thus, when the reaction was conducted for 69 h at 65\textdegree C in \textit{i}-PrOH (4.1 M) with 5 mol % t-BuOK 97% conversion and 94% ee were obtained. This compares favourably (\textit{ca}. 23% higher ee) to that which Morris\textsuperscript{[7]} reported using a smaller set of Noyori-type precatalysts and to the literature using other catalysts.\textsuperscript{[2a,c,i,12]}

A similar screening approach to that presented in Table 1 was applied to imines 4, 5, 6, and 7 (Figure 2). Hydrogenation of benzylimine 4 with a range of precatalysts proceeded with low selectivities (2–29% ee) when the reaction was conducted in the presence of 100 mol % t-BuOK. A control experiment indicated that under these conditions an equilibrium mixture of 4 and its aldimine tautomer was generated (which would hydrogenate to give a racemic product) accounting for the low selectivities. When the amount of base was reduced to 5 mol % the selectivities were greatly enhanced and 62% ee (97% conversion) was obtained using RuCl\textsubscript{2}(S)-Tol-BINAP/[(\textit{S},\textit{S})-DPEN].

Figure 2. Other imines reduced and the ees of the corresponding amine products.
In our studies we also investigated the enantioselective hydrogenation of cyclic imines. Catalyst screening (15 precatalysts tested in a multi-well vessel) against 2,2,3-trimethylindolenine (5) revealed that RuCl2[(S)-MeO-BIPHEP][(S,S)-ANDEN] provided the highest selectivity (88% ee). Although the dihydroisoquinoline (6) was screened against a smaller set of precatalysts a large difference in selectivities was observed. Whereas RuCl2[(R,R)-Et-DuPHOS][(R,R)-DACH] provided 79% ee and 80% conversion, with RuCl2[(S)-HexaPHEMP][(S,S)-DPEN] 8% ee and 47% conversion were obtained. The conversion with the former precatalyst was improved to near quantitative by raising the reaction temperature to 80 °C.

2-Methylquinoline (7), a challenging aromatic diamine, was hydrogenated using a range of Noyori-type precatalysts under our standard hydrogenation conditions (15 bar H2, 65 °C, i-PrOH, S/C/B = 1000/1/50) with good conversions and a range of ees being obtained. Bianchini et al.[13] have addressed the asymmetric hydrogenation of this aromatic diamine using iridium-based catalysts. Although a high selectivity (90% ee) was observed by these workers for this substrate at 54% conversion, a lower ee (73%) was obtained at higher conversion (97%). In our work, biaryl BINAP-like systems gave the highest selectivity. Given that 2-methylquinoline (7) and its reduced product were not solids under the reaction conditions we saw the opportunity to conduct the hydrogenation in the absence of solvent. Indeed, when the reaction was conducted neat with RuCl2[(R,R)-Et-DuPHOS][(R,R)-DACH] (entry 1, Table 2) at S/C/B = 1000/1/50, at 50 °C and 30 bar H2 40% ee and 98% conversion were obtained. This was very pleasing because we have observed severe retardation of reaction rate in the hydrogenation of ketones using Noyori-type precatalysts when conducted neat, or at very high concentrations.[14] The use of RuCl2[(S)-Tol-BINAP][(S,S)-DPEN] (entry 2) provided quantitative conversion and improved selectivity (68% ee) suggesting that biarylphosphines were better for this particular substrate. A screen against HexaPHEMP and BINAP precatalysts (entries 3–12) revealed an unexpected lack of diphosphine/diamine matching/mismatching effects. Only relatively small differences in selectivity were observed between the two enantiomers of either DPEN or DACH. This was unexpected given previous observations with imine 1, which showed a marked matching/mismatching effect between the stereochemical elements of the chiral diphosphine and diamine ligands. This is also a characteristic of ketone hydrogenation.[10] More surprisingly, there appeared to be a reversal in the usual matching/mismatching for the HexaPHEMP precatalysts bearing the DACH ligand (entries 5 and 6). These results suggested that these diamines had little steric interaction with the imine substrate. When the chiral diamine was substituted for ethylenediamine (EDA), however, markedly lower selectivity (entry 11) was observed suggesting an electronic influence. The ee obtained for the product represented by entry 3 was upgraded to 96% upon single crystallisation from i-PrOH. When precatalysts based on DAIPEN were tested (entries 12 and 13) the expected diphosphine/diamine matching effect was observed.

Finally, some deuterium labelling experiments were performed in order to obtain a better understanding of the reaction (Scheme 2). When imine 1 was treated with deuterium under the standard reaction conditions (5 bar, S/C/B = 1000/1/100, i-BuOK, 65 °C, 51 h) using RuCl2[(R,R)-Et-DuPHOS][(R,R)-DAPEN], 8% deuterium was observed to have been incorporated into the benzylic position and 4% into the methyl group. 89% ee and 99% conversion were obtained as for the standard hydrogenation. These results suggest that solvent is the source of hydrogen. Although we had initially expected almost complete deuterium incorporation into the benzylic position of 2, it appears that hydrogen or deuterium is rapidly transferred between the solvent (e.g., i-PrOH) and ruthenium species as previously suggested in the literature.[15] When the reaction was repeated using i-PrOH-d4 in the presence of hydrogen gas, 56% deuterium was incorporated (determined by 1H NMR spectroscopy) into the benzylic position, with once again an 89% ee and 99% conversion. The reproducible selectivity indicated that no hydrogen/deuterium exchange occurred at the ben-
The methyl group was shown to have undergone a 76% hydrogen/deuterium exchange. When the reaction was conducted under a positive pressure of nitrogen gas under otherwise standard conditions in \(i\)-PrOH-d\(_8\), a 24% conversion of an essentially fully deuterated (benzylic and methyl groups) amine with a 78% ee was produced. The remainder of the product mixture was composed of the starting imine that was shown to have 96% deuterium incorporated into the methyl group. The latter observation was due to base-catalysed hydrogen/deuterium exchange and accounts for the deuterium incorporated in the methyl position in the previous experiment. Upon conducting the same experimental procedure for 66 hours, a 24% conversion and 75% ee were obtained suggesting that both reactions had attained equilibrium. These results together suggest the activated DuPHOS-ruthenium complex catalyses both hydrogenation as well as transfer hydrogenation, the latter being slower and apparently providing lower selectivities. This has not been reported for ketone hydrogenation, most likely due to the greater reaction rates observed for hydrogenation at the milder conditions employed. The competing and lower selectivity of the transfer hydrogenation could account for some erosion in enantioselectivity.

**Conclusion**

In conclusion, we have shown that the readily prepared Noyori-type chiral ruthenium(II) dichloride (diphosphine)(diamine) complexes, once activated in situ with \(t\)-BuOK, reduce a range of aromatic and activated non-aromatic imines to amines in the presence of hydrogen gas. For a given imine substrate a diverse range of diphosphine/diamine combinations needs to be tested to determine the optimum catalyst system. The imines can be hydrogenated neat with good S/C loadings and at reasonable pressures. In contrast to ketone reduction using the same precatalysts, more forcing conditions for reduction are required.

**Experimental Section**

**General Remarks**

Commercially available diamines, DPEN (Fluka), AMP (Aldrich), DAIPEN (Strem), BINAM (Strem), EDA (Aldrich), were used as received. ANDEN[16] and DACH[17] were prepared according to literature procedures. Tol-BINAP (Strem), BINAP (Strem) and MeO-BIPHEP (Roche) were purchased and used as received. Me-DuPHOS, Et-DuPHOS and \(t\)-Pr-DuPHOS were prepared as previously described.[18] Me-FerroTANE was prepared as previously published.[19] HexaPHEMP was prepared as described in a patent application.[9] 2-Methylquinoloxaline (7) (Aldrich), 2,3,3-trimethylindolenine (5) (Aldrich) and 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (6) (Acros) were purchased and distilled before use except for the latter which was used as received. \(N\)-(1-Phenylethylidene)aniline (1) and \(N\)-(1-phenylethylidene)benzylamine (4) were prepared as described in the literature.[21] Racemic amines required for development of analytical methods were prepared as described in the literature.[22] Deuterium gas (99.98%) was purchased from Aldrich. All imines and the corresponding amines are known compounds and reported in the literature.

**Precatalysts**

The precatalysts were prepared as described in the supporting information and as published by Noyori et al.,[5] however, the diphosphines were generally allowed to react with the ruthenium dimer for ca. 30–60 min for BINAP and BIPHEP derivatives, and 2–3.5 h for DuPHOS and PhanePHOS derivatives. Diamines were then reacted with the ruthenium-diphosphine intermediates at room temperature overnight.

**Hydrogenations**

All hydrogenations were carried out in 50 mL Parr hydrogenation vessels or in a Baskerville multi-welled hydrogenation vessel equipped with injection ports with a rubber septum for the addition of the solvent via syringe, a pressure gauge, a tightly fitting removable internal glass liner and a magnetic stirring bar. Commercially available anhydrous \(i\)-PrOH (Fluka) was degassed prior to use by sparging with nitrogen for at least 30 minutes. A commercially available 1.0 M solution of \(t\)-BuOK in \(t\)-BuOH (Aldrich) was used following degassing.
General Procedure

The catalyst (0.01 mmol) and imine substrate (1 mmol) were placed in a glass liner and the vessel assembled. This was purged with nitrogen and then with hydrogen at least three times, by pressurising to 5 bar and releasing the pressure. i-PrOH (4 mL) was added and the reaction was purged a further three times with hydrogen. A solution of t-BuOK in t-BuOH (1.0 M, 1.0 mL, 1.0 mmol) was added and the reaction purged a further three times with hydrogen. Finally, the vessel was pressurised to 15 bar of hydrogen and stirred at 50–65 °C (oil bath) for 18–21 h. The hydrogenations conducted in the multiwell vessel were determined by optical rotation measurement of the product prepared using RuCl₂[(R,R)-Et-DuPHO][[(R,R)-DACH] (c₆)₂] + 18.0° (c 1.0, MeOH) [lit. (23) [c]D₂ – 16° (c 1.0, MeOH) for (R)-2-phenyl-(1-phenylethyl)amine (2)].

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The catalyst (0.008 mmol) was added to the catalyst in the purged vessel as a solution in i-PrOH. The absolute configurations of the hydrogenation products of N-(1-phenethylidene)aniline 1 were determined by optical rotation on a doubly distilled sample of the product prepared using RuCl₂[(R,R)-Et-DuPHO][[(R,R)-DACH] (c₆)₂] + 18.0° (c 1.0, MeOH) [lit. (23) [c]D₂ – 16° (c 1.0, MeOH) for (R)-2-phenyl-(1-phenylethyl)amine (2)].

Deuterium Labelling

The deuterium experiment using D₂ in i-PrOH was conducted as for the general procedure except the reaction was conducted under 5 bar deuterium gas pressure. After 50.5 h the reaction was analysed by GC and shown to have undergone 99% conversion with an enantioselectivity of 89% for (S)-2-phenyl-(1-phenylethyl)amine (2). ¹H NMR (CDCl₃) spectroscopy showed that the methine and methyl proton integrations were 44% and 24% of that expected indicating 56% and 76% incorporation of deuterium, respectively.

The deuterium experiments using i-PrOH-d₅ were conducted as for the general procedure except the reaction was conducted under 0.5 bar nitrogen gas pressure in i-PrOH-d₅ (2 mL) and t-BuOK (112 mg, 1.0 mmol) in i-PrOH-d₅ (2 mL). After 24 h the reaction was analysed by GC and shown to have undergone 99% conversion with an enantioselectivity of 89% for (S)-2-phenyl-(1-phenylethyl)amine (2). ¹H NMR (CDCl₃) spectroscopy showed that the methine and methyl proton positions had essentially full incorporation of deuterium. The methane proton integration was 4% of that expected, indicating 96% incorporation of deuterium.

Acknowledgements

We thank Drs. Guy Casy, Ian Lennon, Raymond McCague, James Ramsden and Antonio Zanotti-Gerosa for their helpful suggestions and David Baldwin, Natasha Cheeseman and Cath Rippe of the ChiroTech analytical team for their skilled technical assistance.

References


