From PTA to novel CAP: application of water soluble phosphines in catalysis and medicinal chemistry

Antonella Guerriero

Consiglio Nazionale delle Ricerche (CNR)
Istituto di Chimica dei Composti Organometallici (ICCOM)
Sesto Fiorentino (Florence), Italy
Water: green solvent for homogeneous and biphasic catalytic processes

- environmentally benign (not volatile and not toxic)
- replacement of organic solvents and their disposal
- reduction of risks (not flammable)
- separation of organic products from catalysts (recovery and recycling)
- low cost, abundant

WATER SOLUBLE P-LIGANDS

PTA: the long story of a versatile water soluble phosphine

1. “Soft metal” coordination: catalysis and biological activities

2. Upper rim functionalisation with C-alkylation: bidentate ligands and introduction of a stereocentre

3. Lower rim functionalisation with N-alkylation: catalysis (hydroformylation)

4. “Hard metal” coordination: grafting, heterogenisation, polymerization

5. Cage opening: P,N chelates for catalysis

PTA: 1,3,5-triaza-7-phosphadamantane
- Neutral phosphine synthesized in 80-90% yield
- Thermally stable (dec. Temp. >260°C)
- Solid stable to air and moisture
- Soluble in water (S = ca. 235 g/L)
- Small cone angle (103°)

PTA upper rim functionalisation

**GENERAL SYNTHETIC ROUTE**

**Synthesis of Ir(I) and Ru(II) Complexes**

<table>
<thead>
<tr>
<th>Solubility in water @ 20 °C (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PZA= 1050</td>
</tr>
<tr>
<td>PZA-NMe₂= 1.8</td>
</tr>
<tr>
<td>PTA-CH(1Melm)OH= 320</td>
</tr>
<tr>
<td>PTA-C(1Melm)₂OH= 78</td>
</tr>
</tbody>
</table>

Ir(I) and Ru(II) Complexes for *Transfer Hydrogenation* Reactions

**CATALYSTS**

- Ir(I) and Ru(II) Complexes for *Transfer Hydrogenation* Reactions

**SUBSTRATES**

- CNA: R = H
- BZA: R = CH₃

**TH PROTOCOLS**

- **CNA** → conv. 96.6% (6h) @40 °C [cat/sub 1:100]
  - C=O selectivity

- **BZA** → conv. 55.1% (24h) @60 °C [cat/sub 1:100]
  - C=C selectivity

- **KOH/iPrOH**
  - conv. 83.3% (5h) @80 °C [cat/sub 1:500]
  - C=O and C=C hydrogenation

- **¹BuOK/iPrOH**
  - conv. 84.1% (4h) @25 °C [cat/sub 1:250]
  - conv. 97.9% (4h) @40 °C [cat/sub 1:500]
  - conv. 89.7% (4h) @40 °C [cat/sub 1:1000]

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**Lower rim functionalisation**

**GENERAL SYNTHETIC ROUTE**

- Easily synthesised
- Design of steric and electronic properties
- Tunable water solubility

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**Long-chain alkene biphasic HF with cyclodextrins (CDs) as mass transfer promoters**

- Formation of ADDUCTS (CD/Substrate and CD/catalyst)
  - van der Waals interactions
  - hydrophobic interactions
  - electrostatic forces
  - steric effects

- Native β-CD: $R = H$
- RAME-β-CD: $R = H \circ CH_3$
  (substitution degree = 1.7 per glucopyranose unit)
- RAME = randomly methylated

**Native β-CD**

**RAME-β-CD**

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**LEGEND**

- [LEGEND IMAGE]

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Rh-catalysed hydroformylation of long chain olefins in biphasic media

- Basicity > [N-Bz-PTA]Cl ($J_{\beta,se} = 815$ Hz)
- $S([H_2O])_{298} ^c = 10$ g/L
- Interaction between tert-butyl group and RAME-$\beta$-CD

Experimental conditions:
- $T = (20.35$ mmol), 1500 rpm, CO/$H_2$ in (1/1): 50 bar, 6 h.

**CD-based thermocontrolled catalytic process**

<table>
<thead>
<tr>
<th>Olefin</th>
<th>CD</th>
<th>$T$ (°C)</th>
<th>Conv. (%)$^b$</th>
<th>Sel. (%)$^c$</th>
<th>l/b$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-decene</td>
<td>–</td>
<td>80</td>
<td>26</td>
<td>99</td>
<td>2.1</td>
</tr>
<tr>
<td>1-decene</td>
<td>RAME-$\beta$-CD</td>
<td>80</td>
<td>10</td>
<td>97</td>
<td>1.8</td>
</tr>
<tr>
<td>1-decene</td>
<td>–</td>
<td>100</td>
<td>56</td>
<td>99</td>
<td>1.7</td>
</tr>
<tr>
<td>1-decene</td>
<td>RAME-$\beta$-CD</td>
<td>100</td>
<td>72</td>
<td>99</td>
<td>2.0</td>
</tr>
<tr>
<td>1-dodecene</td>
<td>RAME-$\beta$-CD</td>
<td>120</td>
<td>98</td>
<td>99</td>
<td>1.8</td>
</tr>
<tr>
<td>1-dodecene</td>
<td>RAME-$\beta$-CD</td>
<td>80</td>
<td>11</td>
<td>99</td>
<td>1.7</td>
</tr>
<tr>
<td>1-dodecene</td>
<td>RAME-$\beta$-CD</td>
<td>100</td>
<td>75</td>
<td>99</td>
<td>1.7</td>
</tr>
<tr>
<td>1-tetradecene</td>
<td>RAME-$\beta$-CD</td>
<td>80</td>
<td>14</td>
<td>95</td>
<td>1.6</td>
</tr>
<tr>
<td>1-tetradecene</td>
<td>RAME-$\beta$-CD</td>
<td>100</td>
<td>88</td>
<td>97</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Experimental conditions: Rh(acac)($CO_2$) (4.07 × 10$^{-2}$ mmol), water-soluble ligand (0.21 mmol), CD (0.48 mmol), $H_2O$ (11.5 mL), 1-alkene (20.35 mmol), 1500 rpm, CO$/H_2$ (1/1): 50 bar, 6 h. $^a$ Calculated with respect to the starting olefin. $^b$(mol of aldehydes)/(mol of converted olefins) × 100. The side products were mainly isomeric olefins. $^c$Ratio of linear to branched aldehyde products.

Immobilization of Ir-PTA complex on DOWEX resins

ION –EXCHANGE RESINS AS CATALYST CARRIERS:
- Water tolerant
- Swell in water giving a porous structure
- Commercially available and low cost
- Resistance to thermal, mechanical and chemical stress
- Easy separation

DOWEX resin sulfonated gel-type

Tethered catalysts  | Ir loading (w/w)  | Ir immobilised (%)
-----------------|-----------------|------------------
H+ - D50WX2      | 1.73 (1)        | 64.3%
Li+ - D50WX2     | 1.68 (1)        | 62.4%

* Experimental conditions: resin 700 mg (3.36 meq, ion exchange capacity), metal complex 0.102 mmol, H2O:MeOH=3:1, 24h, r.t. * ICP-OES value

Larger downfield shift due:
- Ionic interactions
- Acid-base interactions

MORE ROBUST CATALYST

### RESULTS

- 100% selectivity to desired products in all cases
- Heterogenized catalyst more active than the homogeneous ones
- No catalytic activity shown by the solution recovered after catalysis (minor metal leaching)
- Easy and quantitative recovery of the resin by decantation

**Pharmaceutically relevant molecules:** antidepressants, antitumoral, antibiotics etc.

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**Substrate** | **Product** | **Phase** | **Yield (%) [time h]** | **TOF (h⁻¹)** | **Leaching (ppm)\(^i\)**
--- | --- | --- | --- | --- | ---
2-methylquinoxaline | 2-methyl-1,2,3,4-tetrahydroquinoline | Hetero\(^b\) | 92.2 [22] | 6 | 0.2
 | | Homo\(^b\) | 91.1 [16] | 9 |
5-methylquinoxaline | 5-methyl-1,2,3,4-tetrahydroquinoline | Hetero\(^c\) | 89.2 [22] | 6 | 0.32
 | | Homo\(^c\) | 32.0 [17] | 3 |
2,6-dimethylquinoline | 2,6-dimethyl-1,2,3,4-tetrahydroquinoline | Hetero\(^d\) | 26.0 [29] | 1 | 0.08
 | | Homo\(^d\) | 3.5 [29] | 1 |
3,4-dihydroisoquinoline | 1,2,3,4-tetrahydroisoquinoline | Hetero\(^e\) | 99.9 [1] | 300 | 7.6
 | | Homo\(^e\) | 11.0 [1] | 34 |
 | | Hetero\(^g\) | 89.7 [2] | 374 | 4.0 |
Harmaline | Leptaflorine | Hetero\(^f\) | 99.1 [24] | 4 | 8.5
 | | Homo\(^f\) | 9.3 [22] | 5 |
4,4'-dimethylfuran-2,3-dione | Pantolactone | Hetero\(^g\) | 89.0 [4] | 22 | 0.37
 | | Homo\(^g\) | 99.9 [4] | 25 |

\(^a\) Experimental batch conditions: \(P = 20\) bar \(H_2\), \(T = 80^\circ\)C; \(^b\) \(H_2O, S/C = 150\); \(^c\) \(H_2O, S/C = 150\); \(^d\) \(50\) bar \(H_2\); \(^e\) \(H_2O: MeOH = 4:1, S/C = 50\); \(^g\) \(H_2O, S/C = 305\); \(^i\) \(H_2O: MeOH = 1.5:1, S/C = 100\); \(^j\) \(H_2O, S/C = 830\); \(^k\) \(H_2O, S/C = 100\); \(^l\) determined by ICP-OES.
New ligand CAP: the higher homologue of PTA

Nine-membered macrocycle

CAP: 1,4,7-triaza-9-phosphatricyclo[5.3.2.1]tridecane

• Stable to air and moisture as solid and in solution
• Soluble in water (S = ca. 2 g/100 mL)
• Thermal stability comparable with that of PTA
• Small cone angle (109°)
• Soluble in MeOH, EtOH, 'PrOH, CH$_3$CN
• Highly soluble in CHCl$_3$, CH$_2$Cl$_2$ (S = ca. 10 g/100 mL)

THP = tris-(hydroxymethyl)phosphine
TACN = 1,4,7-triazacyclononane

MeOH best solvent choice
No reaction in THF or acetone
Formation of amorphous byproducts

Figure 1. Dodecahedral crystals of free ligand CAP (adapted from original ref.)
CAP cage architecture: a stereochemically intermediate between PTA and Verkade’s ligand

PTA

CAP

P=O Verkade’s aminophosphine

Same environment at P (bridging P-C-N)

TACN macrocycle embedded in the cage

 Samaritan: SAME CONFORMATION OF TACN
 Samaritan: HIGH CONFORMATIONAL FLEXIBILITY


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Different reactivity between CAP and PTA


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Improvement of CAP synthesis

\[
\text{THPC= tetrakis-(hydroxymethyl)phosphonium chloride}
\]
\[
\text{THP = tris-(hydroxymethyl)phosphine}
\]
\[
\text{TACN = 1,4,7-triazacyclononane}
\]

- air-stable
- commercially available

- air-sensitive
- not isolated

- easy workup
- high purity

ca. 25% yield after recrystallization in hot EtOH

THPC = \text{tetrakis-(hydroxymethyl)phosphonium chloride}
THP = \text{tris-(hydroxymethyl)phosphine}
TACN = \text{1,4,7-triazacyclononane}

Synthesis of Ru(II) CAP complexes

Comparison of $^{31}$P($^1$H) NMR chemical shifts and water solubility values.

<table>
<thead>
<tr>
<th></th>
<th>$^{31}$P($^1$H) NMR (ppm)</th>
<th>$S(H_2O)_{20^\circ C}$ (g L$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>47.80 (s), CDCl$_3$</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>46.72 (s), D$_2$O</td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>$-102.34$ (s), CDCl$_3$</td>
<td>230.0</td>
</tr>
<tr>
<td></td>
<td>$-98.61$ (s), D$_2$O</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>52.83 (s), CDCl$_3$</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>57.48 (s), D$_2$O</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>51.60 (s) -144.26 (sept, $J_{PF} = 707.5$ Hz), acetone-$d_6$</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>56.80 (s) -145.10 (sept, $J_{PF} = 707.5$ Hz), D$_2$O</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>48.17 (s) -144.27 (sept, $J_{PF} = 707.8$ Hz), acetone-$d_6$</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>56.80 (s) -145.10 (sept, $J_{PF} = 707.5$ Hz), D$_2$O</td>
<td></td>
</tr>
<tr>
<td>RAPTA-C</td>
<td>$-36.63$ (s) in CDCl$_3$</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Solid-state characterisation of Ru(II) compounds

RACAP-C. Selected bond distances (Å) and angles (deg): Ru-Cl1=2.4184(5), Ru-Cl2=2.4205(5); Ru-P=2.3180(5); Ru-centroid(C1-C6)=1.709; Cl1-Ru-Cl2=87.601(19); Cl1-Ru-P=86.937 (19); Cl2-Ru-P=83.775(18)

CRYSRALS GROWN FROM EtOH/CH₂Cl₂

- CAP with same [333] conformation of free ligand
- Same PN and NN distances as in free ligand
- Ru-P bond length longer than RAPTA-C
- Ru-C bond lengths longer than RAPTA-C

- Same CAP conformation of 2
- Ru-P and Ru-C bond lengths longer than in 2
  (less strong Ru-p-cymene interaction)
- Ru-Cl bond lengths shorter than in 2

Compound 3 2MeOH/H₂O. Selected bond distances (Å) and angles (deg): Ru-Cl=2.4026(7); Ru-P1=2.3254(7); Ru-P2=2.3353(7); Ru-centroid(C1-C6)=1.768; Cl-Ru-P1=83.59(2); Cl-Ru-P2=87.90(3); P1-Ru-P2=93.37(3)

Stability tests of new Ru(II) complexes

Pseudo-pharmacological conditions:

- NaCl/D$_2$O (100 mM)
- Complexes (4 mM) in NaCl/D$_2$O
- T= 37 °C

Details of $^{31}$P{$^1$H} NMR spectra of complexes in NaCl/D$_2$O @ 37 °C
Ru(II)-CAP complexes: in vitro antitumor tests

<table>
<thead>
<tr>
<th></th>
<th>A2780</th>
<th>A2780cisR</th>
<th>HEK293</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>2</td>
<td>55.3 ± 18.6</td>
<td>108 ± 10</td>
<td>102 ± 26</td>
</tr>
<tr>
<td>3</td>
<td>48.1 ± 2.2</td>
<td>99.2 ± 15.9</td>
<td>80.7 ± 12.4</td>
</tr>
<tr>
<td>4</td>
<td>65.2 ± 18.0</td>
<td>70.6 ± 3.1</td>
<td>163 ± 46</td>
</tr>
<tr>
<td>RAPTA-C</td>
<td>230</td>
<td>270</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Cytotoxicity tests (IC$_{50}$, μM, 72 h) of CAP and its complexes.

- Only minor cytotoxicity effects of CAP
- Similar IC$_{50}$ values of 2-4 due to the same species in solution
- Equal cytotoxicity of 4 toward A2780 and A2780cisR
- High cell selectivity of 2-4 against A2780 compared to HEK293
- Higher cytotoxicity of 2-4 compared to RAPTA-C


A2780 = human ovarian carcinoma cells
A2780cisR = cells resistant to cisplatin
HEK293 = noncancerous human embryonic kidney cells
**Ru(II)-CAP complexes: catalytic transfer hydrogenation of BZA**

- **Active @ 80°C**
- **Highly stable**
- **More active than RAPTA-C**
- **Selective for C=C bond reduction**

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**Catalytic transfer hydrogenation of BZA with compounds 2 – 4**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>% conv.</th>
<th>time (h)</th>
<th>yield A (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield B (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield C (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>60</td>
<td>60.0</td>
<td>24</td>
<td>45.3</td>
<td>13.0</td>
<td>1.7</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>60</td>
<td>18.7</td>
<td>24</td>
<td>14.2</td>
<td>4.4</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>80</td>
<td>99.4</td>
<td>4</td>
<td>82.0</td>
<td>5.2</td>
<td>12.2</td>
</tr>
<tr>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>80</td>
<td>76.3</td>
<td>4</td>
<td>61.7</td>
<td>12.8</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>80</td>
<td>82.6</td>
<td>4</td>
<td>68.9</td>
<td>11.5</td>
<td>2.2</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4</td>
<td>80</td>
<td>51.9</td>
<td>4</td>
<td>40.4</td>
<td>10.8</td>
<td>0.7</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>80</td>
<td>71.8</td>
<td>24</td>
<td>52.3</td>
<td>15.8</td>
<td>3.7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>96.0</td>
<td>68.7</td>
<td>13.5</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>80</td>
<td>66.5</td>
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<td>46.6</td>
<td>17.8</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.5</td>
<td>73.5</td>
<td>13.0</td>
</tr>
<tr>
<td>9</td>
<td>RAPTA-C</td>
<td>80</td>
<td>99.5</td>
<td>24</td>
<td>93.2</td>
<td>3.2</td>
<td>3.1</td>
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<tr>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>RAPTA-C</td>
<td>80</td>
<td>30.0</td>
<td>24</td>
<td>23.8</td>
<td>6.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>General conditions: catalyst, 9.8 x 10<sup>-3</sup> mmol; BZA, 0.98 mmol; HCOONa, 9.8 mmol; MeOH:H<sub>2</sub>O (1:1), 6 mL; catalyst/substrate/HCOONa = 1:100:1000. <sup>b</sup> GC values based on pure samples: A = 4-phenyl-2-butanone; B = 4-phenyl-3-buten-2-ol; C = 4-phenyl-2-butanol. <sup>c</sup>Hg(0) added (one drop).
### Catalytic transfer hydrogenation of cyclic imines with complex 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>solvent</th>
<th>Substrate</th>
<th>Productb</th>
<th>yieldc</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>H₂O</td>
<td>3,4-dihydroisoquinoline</td>
<td>1,2,3,4-tetrahydroisoquinoline</td>
<td>39.9</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>MeOH/H₂O 1:1</td>
<td>2-methylquinoxaline</td>
<td>2-methyl-1,2,3,4-tetrahydroquinoxaline</td>
<td>10.9</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>MeOH/H₂O 1:1</td>
<td>5-methylquinoxaline</td>
<td>5-methyl-1,2,3,4-tetrahydroquinoxaline</td>
<td>74.1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.5</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>MeOH/H₂O 1:1</td>
<td>quinoline</td>
<td>1,2,3,4-tetrahydroquinoline</td>
<td>0.4</td>
<td>24</td>
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<tr>
<td>5</td>
<td>80</td>
<td>MeOH/H₂O 1:1</td>
<td>2-methylquinoxaline</td>
<td>2-methyl-1,2,3,4-tetrahydroquinoxaline</td>
<td>–</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>MeOH/H₂O 1:1</td>
<td>5-methylquinoxaline</td>
<td>5-methyl-1,2,3,4-tetrahydroquinoxaline</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup>General conditions: catalyst, 1.0 x 10^{-2} mmol; substrate, 1.0 mmol; HCOONa, 10.0 mmol; MeOH:H₂O (1:1), 6 mL; catalyst/substrate/HCOONa= 1:100:1000. <sup>b</sup>Products confirmed by GC and GC-MS analyses. <sup>c</sup>GC values based on pure samples.

- active @80°C
- good conversion
- mild reduction protocol

Investigation of catalytically active species

I. NMR scale experiment under pseudo-catalytic conditions:

\[ \text{3} + \text{HCOONa} (50 \text{ eq}) \xrightarrow{\text{MeOH/H}_2\text{O (1:1)}} \text{4} \]

- T = 60 °C \rightarrow 100\% conv. after 24 h
- T = 80 °C \rightarrow 100\% conv. after 17 h

II. Independent synthesis:

\[ \text{3} + \text{HCOONa} (50 \text{ eq}) \xrightarrow{\text{MeOH/H}_2\text{O (1:1)}} \text{4} \]

100\% conv. after 28 h

Figure 4. \(^1\text{H}\) (left) and \(^1\text{H}^{(31}\text{P})\) NMR (right) spectra (negative region only, \(\text{CD}_2\text{Cl}_2\)) showing the change from triplet to singlet for the Ru-H signal in 4.

Summary of results

- Synthesis of a library of PTA upper-rim and lower-rim modified ligands
- Homogeneous Ru and Ir catalyzed C=O and C=C bond hydrogenations
- Biphasic Rh-catalyzed olefin hydroformylation with CDs
- Heterogeneous Ir-catalyzed C=N and C=O bond hydrogenations
- Improved synthesis of CAP
- Anticancer activity in vitro of Ru-CAP complexes
- Ru-CAP complexes active in catalytic TH reactions using HCOONa

Future perspectives of CAP project

- To explore the coordination properties of CAP to other TMss
- To study the capability of CAP to bind by both P and N donors to different metals and assess the structural properties of the materials obtained
- To test the obtained complexes in other catalytic reactions
- Use of CAP to bind Ag(I) and test the compounds as antimicrobial agents
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Prof. P. J. Dyson
Dr. T. Riedel
Prof. G. Laurenczy
Prof. Donald A. Krogstad
Prof. Frédéric Hapiot
Prof. Eric Monflier

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