Electronic Supplemental Information (ESI)

**P-Trifluoromethyl ligands derived from Josiphos in the Ir-catalysed hydrogenation of 3,4-dihydroisoquinoline hydrochlorides**

Rino Schwenk and Antonio Togni*
Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zurich, Vladimir-Prelog-Weg 2, CH-8093 Zurich, Switzerland.

Content

General procedures

NMR spectra of the:
- Applied ligands
- Applied complexes
- Amides
- DHIQ species
- Racemic THIQ chlorides

HPLC traces of the racemic and enantioenriched samples
General procedures

Amides

All amides were synthesized following a general procedure, adding the corresponding acid chloride to a solution of the corresponding 2-phenylethanamine and triethylamine in DCM at 0 °C. The amides could all be precipitated as pure compounds by dropwise addition of an alkane (hexane, pentane) or ether (diethyl ether, tert. butylmethyl ether) to a solution of the crude amide in DCM or chloroform under stirring.

DHIQ*HCl / HI / HPF₆

All DHIQs investigated in this work were isolated starting from the amides, applying either a mixture of POCl₃ and P₂O₅ or following Movassaghis procedure applying Tf₂O in presence of 2-chloropyridine.¹ The crude reaction products were immediately protonated by hydrogen chloride in diethyl ether, hydrogen iodide or hexafluorophosphoric acid in water and purified by crystallization, precipitation or chromatography.

Racemic THIQ*HCl

To establish analytics for the screening samples, all racemic THIQ chlorides were prepared. The direct reduction of the DHIQ chlorides was achieved in a few cases by palladium on charcoal under hydrogen atmosphere. The pure product was conveniently obtained by filtration and evaporation of the solvent. Unfortunately, in several cases a sluggish conversion was observed even at 100 bar hydrogen pressure overnight. Hence, most samples were reduced by sodium borohydride, requiring subsequent reprotonation.

Standard screening experiment

A standard screening experiment for the enantioselective hydrogenation of 1-substituted 3,4-dihydroisoquinolinium chlorides was conducted as follows:

A 3 mL flat bottomed glas tube with a magnetic stirring bar was charged with 500 µmol of the substrate and 2.5 µmol (0.5 mol-%) of the precatalyst as [Ir(L)(cod)X]. The tube was purged with argon by means of three vacuum/argon cycles. 1 mL crown-capped solvent was added and the suspension (calculated to result a ~0.5 M solution) stirred for ten minutes under an argon atmosphere.
For the hydrogenation, the tube was closed by a screw cap with a hole for gas exchange. After tightly closing the autoclaves, the atmosphere was first inertized by three cycles of five bar nitrogen and subsequent pressure release. To change the atmosphere to hydrogen, ten bar hydrogen were applied and pressure released before the autoclaves were set to target reaction pressure. Then, stirring was switched on and the autoclaves heated to target temperature by external jacket heater.

After the reaction, heating was switched off and the autoclaves were kept under pressure for at least 30 minutes to cool below 30 °C. Thereafter, pressure was released and the autoclaves set under nitrogen again.

Analysis of the screening samples

To the samples was added 1,3,5-trimethoxybenzene (150 µmol) as internal standard and methanol until a clear homogeneous solution was obtained. Around 0.2 mL of this solution was directly evaporated to dryness in NMR tubes for determination of conversion and yield by integration of well separated signals (one scan, zero dummy scans).

Around 0.1 mL of the same solution was partitioned between NaOH (2 M in water, 1 mL) and hexane (1 mL). The hexane phase was separated, dried over Na₂SO₄ and filtered over a syringe filter. The clear colorless solutions were directly injected in HPLC for determination of ee.

Acetamidation of reaction products

If the enantiomers of the free tetrahydroisoquinoline were not separable or potentially overlapping with side products, internal standard or starting material, the reaction products were derivatized to their acetamide.

After determining conversion and yield by NMR spectroscopy, the remaining sample solution was evaporated to dryness. Acetic anhydride (0.5 mL) and triethylamine (1 mL) were added and the dark samples stirred overnight. After removing all volatiles under HV, the residue was filtered over silica before a sample was prepared for HPLC analysis.
Derivatization of 1-methyl-THIQ 13b for GC analysis

Derivatization for GC analysis: 1-Methyl-1,2,3,4-tetrahydroisoquinolin-2-ium chloride 13b•HCl (3.0 mg, 16.33 µmol, 1.0 eq.) was dissolved in acetonitrile (1 mL), triethylamine (30 µL, 21.78 mg, 215.24 µmol, 13.2 eq.) and (-)-(R)-menthyl chloroformate (20 µL, 20.4 mg, 93.27 µmol, 5.7 eq.) were added and the solution shaken for some minutes. This solution was directly injected into GC.²

Determination of optical rotation sign

To assign the HPLC peaks to the corresponding enantiomers, the hydrogenation sample with the highest observed ee was purified and dissolved as hydrochloride in chloroform with a concentration of around 0.5 g/100 mL. The derivatized sample (acetamide) was used for determination of optical rotation where applicable. The optical rotations of these samples were recorded at 589 nm, in a 10 cm measuring cell at 20 °C. The assignment of the major peak in HPLC with the observed sign was possible in all the cases, although some of the observed optical rotation angles were rather small.
Ligands

$(S_P)$-(CF$_3$)Ph-Xylihos $(S_P)$-5

500 MHz $^1$H NMR in CD$_2$Cl$_2$

126 MHz $^{31}$C NMR in CD$_2$Cl$_2$

$^{31}$P and $^1$H decoupled
471 MHz $^{19}$F NMR in CD$_2$Cl$_2$

203 MHz $^{31}$P NMR in CD$_2$Cl$_2$

H decoupled
$(R_P)$-$\text{(CF}_3\text{)}$Ph-Xylihos $(R_P)$-5

$500$ MHz $^1$H NMR in CD$_2$Cl$_2$

$126$ MHz $^3$C NMR in CD$_2$Cl$_2$

$^3$P and $^1$H decoupled
282 MHz $^{19}$F NMR in CD$_2$Cl$_2$

203 MHz $^{19}$F NMR in CD$_2$Cl$_2$

$^1$H decoupled
Complexes

$[\text{Pt}((S)_{p}-\text{(CF}_{3}\text{)}\text{Ph-Xyliphos})\text{Cl}_{2}] (S)_{p}-11$
[Pt((R)−(CF₃)Ph−Xylihos)Cl₂] (R)−11

700 MHz ¹H NMR in CDCl₃

126 MHz ¹³C NMR in CDCl₃

¹¹³P and ¹H decoupled
658 MHz $^1$F NMR in CDCl$_3$,
$\text{Ir}((S)_P)-(\text{CF}_3\text{Ph-Xyphos})(\text{cod})\text{Cl}] (S)_P-9\text{Cl}$

500 MHz $^1\text{H}$ NMR in CD$_2$Cl$_2$
residual diethyl ether

126 MHz $^{31}\text{C}$ NMR in CD$_2$Cl$_2$
$^{31}\text{P}$ and $^1\text{H}$ decoupled
282 MHz $^1$H NMR in CD$_2$Cl$_2$

121 MHz $^1$H NMR in CD$_2$Cl$_2$

$^1$H decoupled
[Ir((R)\text{-}(CF}_3\text{)Ph-Xylirophos})(\text{cod})Cl] (\text{R})-9\text{Cl}

300 MHz $^1\text{H}$ NMR in CDCl$_3$
contains residual pentane

126 MHz $^3\text{C}$ NMR in CDCl$_3$
$^{31}\text{P}$ and $^1\text{H}$ decoupled
292 MHz $^{19}$F NMR in CDCl$_3$

122 MHz $^{19}$F NMR in CDCl$_3$

$^1$H decoupled
[Ir(S\text{P})-(CF\text{3})\text{Ph-Xyliophos})(\text{cod})\text{I}] (S\text{P})-9I

500 MHz $^1$H NMR in CD$_2$Cl$_2$
- all signals obviously broadened due to dynamic behavior

126 MHz $^1$C NMR in CD$_2$Cl$_2$
$^{31}$P and $^1$H decoupled
[Ir((S)p)-(CF₃)Ph-Xylihos)(cod)]PF₆ (S)p-9PF₆

300 MHz ¹H NMR in CDCl₃

126 MHz ¹³C NMR in CDCl₃

¹³P and ¹H decoupled
282 MHz $^{31}P$ NMR in CD$_2$Cl$_2$

121 MHz $^{31}P$ NMR in CD$_2$Cl$_2$

$^1$H decoupled
[Ir((R,S)-Xyliophos)(cod)]PF_6 10PF_6
292 MHz $^1$H NMR in CD$_2$Cl$_2$

122 MHz $^3$P NMR in CD$_2$Cl$_2$

$^1$H decoupled
Ph-Amide

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
Me-Amide

300 MHz $^1$H NMR CD$_2$Cl$_2$

75 MHz $^{13}$C NMR CD$_2$Cl$_2$
Bn-Amide

300 MHz ¹H NMR in CDCl₃

75 MHz ¹³C NMR in CDCl₃
$i\text{Pr-Amide}$

360 MHz $^1\text{H}$ NMR in $\text{CDCl}_3$

75 MHz $^{13}\text{C}$ NMR in $\text{CDCl}_3$
pOMePh-Amide

300 MHz $^1$H NMR in CD$_2$Cl$_2$

75 MHz $^{13}$C NMR in CD$_2$Cl$_2$
$o$-Tol-Amide

$300$ MHz $^1$H NMR in CD$_2$Cl$_2$

$75$ MHz $^{13}$C NMR in CDCl$_3$
$p$BrPh-Amide

300 MHz $^1H$ NMR in CDCl$_3$

75 MHz $^1C$ NMR in CDCl$_3$
$p$CF$_3$Ph-Amide

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^1$C NMR in CDCl$_3$
282 MHz ¹H NMR in CDCl₃
pCOOMePh-Amide

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
6,7-OMe-Amide

300 MHz $^1$H NMR in CD$_2$Cl$_2$

75 MHz $^1$C NMR in CD$_2$Cl$_2$
Penta-OMe-Amide

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
1-Ph-DHQ*HCl 12a*HCl

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
1-Me-DHIQ*HCl 12b*HCl

300 MHz 1H NMR in CDCl$_3$

75 MHz 13C NMR in CDCl$_3$
1-Bn-DHQ·HCl 12c·HCl
1-iPr-DHIQ*HCl 12d*HCl

300 MHz/¹H NMR in CDCl₃

highly hygroscopic

75 MHz/¹³C NMR in CDCl₃
1-pOMePh-DHQ·HCl 12e·HCl

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
1-\textit{o}Tol-DHIQ\textsuperscript{+}HCl 12f\textsuperscript{+}HCl

300 MHz $^1$H NMR in CD$_2$Cl$_2$

75 MHz $^1$C NMR in CD$_2$Cl$_2$
1-pBrPh-DHIQ*HCl 12g*HCl

300 MHz $^1$H NMR in CD$_2$Cl$_2$

75 MHz $^{13}$C NMR in CD$_2$Cl$_2$
1-pCF<sub>3</sub>Ph-DHIQ·HCl 12h·HCl
292 MHz $^1$H NMR in CD$_2$Cl$_2$
1-pCOOMePh-DHIQ*HCl 12i*HCl

300 MHz $^1$H NMR in CD$_2$Cl$_2$

75 MHz $^1$C NMR in CD$_2$Cl$_2$
Penta-OMe-DHIQ\*HCl 12k\*HCl

300 MHz \(^1\)H NMR in CD\(_2\)Cl\(_2\)

Light sensitive!

75 MHz \(^13\)C NMR in CD\(_2\)Cl\(_2\)
1-Ph-7-OMePh-DHQ·HCl 121·HCl

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
1-Ph-DHQ*HI 12a*HI

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
1-Ph-DHIQ*HPF₆ 12a*HPF₆
1-Ph-THIQ·HCl 13a·HCl
1-Me-THIQ*HCl 13b*HCl

300 MHz ¹H NMR in CDCl₃

75 MHz ¹³C NMR in CDCl₃
1-Bn-THIQ*HCl 13c*HCl

300 MHz 1H NMR in CDCl₃

75 MHz 13C NMR in CDCl₃
1-\textit{tPr}-THIQ*HCl 13d*HCl

300 MHz 1H NMR in CD$_2$Cl$_2$

75 MHz $^1$C NMR in CD$_2$Cl$_2$
1-pOMePh-THIQ\textsuperscript{+}HCl 13e\textsuperscript{+}HCl

300 MHz \textsuperscript{1}H NMR in d\textsubscript{6}-DMSO

126 MHz \textsuperscript{13}C NMR in d\textsubscript{4}-MeOH
1-oTol-THIQ*HCl 13f*HCl

300 MHz 1H NMR in CDCl$_3$

75 MHz 13C NMR in CDCl$_3$
1-oTol-THIQ acetamide 13f acetamide
1-pBrPh-THIQ·HCl 13g·HCl

300 MHz 1H NMR in d6-DMSO

75 MHz 13C NMR in d6-DMSO
1-pCF\textsubscript{3}Ph-THIQ\textsuperscript{*}HCl 13h\textsuperscript{*}HCl

300 MHz \textsuperscript{1}H NMR in d\textsubscript{2}-DMSO

75 MHz \textsuperscript{13}C NMR in d\textsubscript{2}-DMSO
282 MHz 19F NMR in d$_2$-DMSO
1-pCOOMePh-THIQ*HCl 13i*HCl

300 MHz $^1$H NMR in $d_2$-DMSO

75 MHz $^{13}$C NMR in $d_2$-DMSO
1-Ph-6,7-OMe-THIQ*HCl 13j*HCl

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^3$C NMR in CDCl$_3$
Penta-OMe-THIQ*HCl 13k*HCl

500 MHz 1H NMR in D2O at 80 °C

126 MHz 13C NMR in D2O at 80 °C
1-Ph-7-OMe-THIQ*HCl 131*HCl

300 MHz $^1H$ NMR in $d_2$-DMSO

75 MHz $^{13}C$ NMR in $d_2$-DMSO
HPLC traces

1-Ph-THIQ 13a

HPLC (OD-H, hexane:2-propanol 95:5, 0.7 mL/min, 30 °C): $t_R(+) = 10.4$ min and $t_R(-) = 15.8$ min, $t_DHIQ = 11.4$ min.
1-Me-THIQ 13b (R)-menthyl carbamate

\[
\begin{align*}
13b & \text{ (R) - menthyl carbamate} \\
& \text{GC (OPTIMA-5, 30 m x 0.25 mm, 0.5 } \mu \text{m coating, 80 } ^\circ \text{C, 5 min, 10 } ^\circ \text{C/min, 200 } ^\circ \text{C, 43 min): } t_R(+) = 48.6 \text{ min and } t_R(-) = 50.4 \text{ min, } t_{DHIQ} = 13 \text{ min, the stated sign for optical rotation corresponds to the underivatized 1-methyl-1,2,3,4-tetrahydroisoquinolin-2-ium chloride.}
\end{align*}
\]
1-Bn-THIQ 13c

HPLC (AD-H, hexane:2-propanol 90:10, 0.5 mL/min, 25 °C): $t_{R}(+) = 11.3$ min and $t_{R}(-) = 16.9$ min, $t_{DHIQ} = 13.8$ min.
HPLC (OD-H, hexane:2-propanol 99.5:0.5, 0.7 mL/min, 30 °C): $t_R(-) = 8.2$ min and $t_R(+) = 8.9$ min, $t_{DHIQ} = 7.5$ min.
1-pOMePh-THIQ 13e

HPLC (OD-H, hexane:2-propanol 95:5, 0.7 mL/min, 25 °C): $t_R(+) = 15.9$ min and $t_R(-) = 21.6$ min, $t_{DHIQ} = 14.8$ min.
1-oTol-THIQ 13f acetamide

HPLC (OD-H, hexane:2-propanol 98:2, 0.5 mL/min, 25 °C): $t_R(-) = 39.7$ min and $t_R(+) = 43.2$ min, $t_{DHIQ} = 18.4$ min, signs were determined for the acetamide.
1-pBrPh-THIQ 13g

HPLC (AD-H, hexane:2-propanol 98:2, 0.7 mL/min, 25 °C): t<sub>R</sub>(-) = 11.8 min and t<sub>R</sub>(+) = 13.4 min, t<sub>DHIQ</sub> = 9.8 min.
1-\textit{pCF}_{3}\textit{Ph-THIQ} 13h

**HPLC** (OD-H, hexane:2-propanol 95:5, 0.7 mL/min, 30 °C): $t_R(+) = 11.5$ min and $t_R(-) = 17.6$ min, $t_{DHIQ} = 6.9$ min.
HPLC (OD-H, hexane:2-propanol 95:5, 0.7 mL/min, 30 °C): $t_{R}(-) = 28.3$ min and $t_{R}(+) = 37.8$ min, $t_{DHIQ} = 11.3$ min.
HPLC (OD-H, hexane:2-propanol 80:20, 0.6 mL/min, 30 °C): \( t_R(+) = 14.4 \text{ min} \) and \( t_R(-) = 18.7 \text{ min} \), \( t_{DHIQ} = 11.0 \text{ min} \).
Pent-OMe-THIQ 13k

**HPLC** (AD-H, hexane:2-propanol 60:40, 0.5 mL/min, 25 °C): \( t_R(-) = 14.3 \text{ min} \) and \( t_R(+) = 19.5 \text{ min} \), \( t_{DHIQ} = 9.8 \text{ min} \).
**1-Ph-7-OMe-THIQ 13I**

HPLC (OD-H, hexane:2-propanol 95:5, 0.7 mL/min, 30 °C): $t_R(-) = 14.2$ min and $t_R(+) = 18.2$ min, $t_{DHIQ} = 12.9$ min.

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>[mA[U*s]]</td>
<td>[mA[U]]</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>4.779 VV</td>
<td>0.1771</td>
<td>6380.02490</td>
<td>527.69714</td>
</tr>
<tr>
<td>2</td>
<td>14.191 BB</td>
<td>0.3526</td>
<td>1622.54517</td>
<td>69.44540</td>
</tr>
<tr>
<td>3</td>
<td>18.163 BB</td>
<td>0.4587</td>
<td>1617.16296</td>
<td>53.80482</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>[mA[U*s]]</td>
<td>[mA[U]]</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>8.527 VB</td>
<td>0.1763</td>
<td>4861.37549</td>
<td>416.11179</td>
</tr>
<tr>
<td>2</td>
<td>12.966 BV</td>
<td>0.3014</td>
<td>841.97705</td>
<td>42.82686</td>
</tr>
<tr>
<td>3</td>
<td>13.966 VV</td>
<td>0.3429</td>
<td>1444.98083</td>
<td>64.13174</td>
</tr>
<tr>
<td>4</td>
<td>17.470 BB</td>
<td>0.4444</td>
<td>1.02063e4</td>
<td>349.82849</td>
</tr>
</tbody>
</table>
Literature
