Application of UV-Vis spectroscopy to high throughput screening of hydroamination catalysts

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Potential catalysts for the hydroamination of 2-(2-phenylethynyl)aniline **2** which have been identified through high throughput screening methods were investigated. Two complexes were shown to be highly active hydroamination catalysts in acetone: the *in situ* combinations of $[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$ (mesBIAN = bis(2,4,6-trimethylphenylimino)acenapthene) and $[Ir(COD)Cl]_2$–$NaBF_4$ (COD = 1,5-cyclooctadiene). The isolated complexes $[M(N–N)XCl]BF_4$ (M = Rh, Ir; N–N = bidentate nitrogen donor ligand; X = CO or Cp*) were found to be inactive as catalysts for the conversion of **2** to **3**. However, chloride abstraction from these complexes through the addition of $AgBF_4$ was found to generate extremely active catalysts. Particularly active was the complex [Rh(CO)ClmesBIAN]–$AgBF_4$ (5 mol%) which achieved complete conversion of **2** to **3** in 12 minutes at 50 °C. Also identified was the formation of the unusual product, *N*-(2-methylvinyl)-2-phenylindole **5**, catalysed by $[IrCp^*Cl_2]_2$–$NaBF_4$ from starting material **2** *via* the incorporation of one molecule of acetone.

Introduction

The indole nucleus is commonly found in biologically active molecules and is an important target for pharmaceutical applications. The synthesis of indoles has been widely investigated using homogeneous organometallic catalysts.[1,2] Organometallic catalysts are effective in promoting the synthesis of indoles under much milder conditions than would be employed using traditional synthetic routes, and often achieve better selectivity providing access to a wider range of substituted indoles.

The intramolecular hydroamination of aromatic *o*-alkynylanilines has been extensively studied previously as a route to indoles.[3] Palladium catalysts such as $Pd(PPh_3)_4$ are known to promote the intramolecular reaction at relatively high temperatures. Rhodium(I) and iridium(I) catalysts have also been studied previously, and the rhodium complex [Rh(bis(*N*-methylimidazolyl)methane)$(CO)_2$]BPh_4, **1**, is effective under much milder conditions and lower catalyst loading than is employed in palladium catalysed reactions.[4] Recently, Crabtree and coworkers have identified an extremely active Ir(III) hydride complex which can promote intramolecular hydroamination at room temperature (rt).[5]

The identification of the most effective transition metal catalysts for any given transformation can be a time-consuming and expensive process when individual catalysts are synthesised and tested. One approach to reducing the time required to identify the most appropriate active catalysts is to utilise the parallel synthesis of libraries of metal complexes and subsequent *in situ* high throughput screening for catalytic activity.[6–8]

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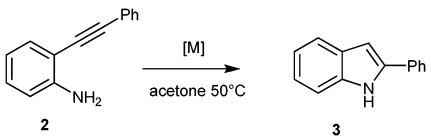
We are particularly interested in finding highly efficient catalysts for indole synthesis *via* hydroamination. Recently, we reported the application of parallel factor (PARAFAC) analysis to UV-Vis data obtained from high throughput catalyst screening for the intramolecular cyclisation of alkynylanilines.[9] A library of rhodium and iridium complexes were generated *in situ* and were screened as catalysts for the hydroamination of 2-(2-phenylethynyl)aniline **2**, Scheme 1. The progress of the hydroamination reactions was monitored using UV-visible spectroscopy and PARAFAC analysis was used to deconvolute the spectral components due to the solvent, starting material and product in an automated fashion. The catalysts were ranked using the ratio of relative amounts of product to starting material and product at a fixed time point. The use of PARAFAC leads to a qualitative ranking of catalysts to identify any 'hits'. By focussing only on the product formation, the method did not allow for the identification of novel products.

Here we report the application of an alternative method of data analysis to the screening of hydroamination catalysts using UV spectroscopy. Data from the same high throughput screening as described previously[9] were analysed independently and the method of data analysis was validated using a thorough study of a portion of the library *via* ^1H NMR spectroscopy. 'Hits' identified by both methods of data analysis (PARAFAC[9] and UV) were investigated further and highly active catalysts were identified, synthesised and tested as catalysts for the hydroamination of **2**. As a result of



2 **3**

Scheme 1

the application of this alternative method of data analysis, a novel product, *N*-(2-methylvinyl)-2-phenylindole **5**, was identified.

Experimental

General procedures

The handling of all air sensitive reagents was performed in a glove bag purged with argon. Reagents were purchased from Aldrich and used as received unless otherwise stated. All solvents were pre-dried and distilled under an atmosphere of argon. Acetone and acetone-d_6 were dried with $CaSO_4$ and distilled under argon prior to use. Methanol was dried over molecular sieves (4 Å) and distilled from CaH_2. 1,1,2,2-Tetrachloroethane (TCE) was dried with $CaCl_2$ and distilled under argon. Thf-d_8 was distilled from Na–benzophenone immediately prior to use. 1,2,3,4,5-Pentamethylcyclopentadiene was purchased from Lancaster and used without further purification. Ir(III) chloride hydrate and rhodium(III) chloride hydrate were obtained from Precious Metals Online (PMO) and were used without further purification. Sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBArF_{24}$),[10] $[Ir(COD)Cl]_2$,[11] $[Ir(CO)_2Cl]_n$,[12] $[Ir(COE)_2Cl]_2$,[11] $[Rh(COD)Cl]_2$,[13] $[Rh(CO)_2Cl]_2$,[14] $[Rh(COE)_2Cl]_2$,[11] $[RhCpCl_2]_2$,[15] $[RhCp^*Cl_2]_2$ and $[IrCp^*Cl_2]_2$,[15] bis(1-pyrazolyl)methane (bpm),[16] bis(*N*-methylimidazolyl)methane (bim),[17] *N*,*N*-bis(*p*-tolyl)diazabutadiene (ptolDAD),[18] *N*,*N*-bis(*p*-tolyl)1,2-dimethyldiazabutadiene (dmptolDAD),[19,20] *N*,*N*-(bismesityl)1,2-dimethyldiazabutadiene (dmmesDAD),[21] *N*,*N*-(bismesityl)diazabutadiene (mesDAD), bis(2,4,6-trimethylphenylimino)acenapthene (mesBIAN),[22,23] 2-(2-phenylethynyl)aniline **2**,[24] $[Rh(bim)(CO)_2]BPh_4$ **1**,[4,25] $[Ir(bpm)(CO)_2]BPh_4$[26] and $[Cp^*IrCl(bpm)]BF_4$, $[Cp^*IrCl(dmbpm)]BF_4$, $[Cp^*IrCl(bim)]BF_4$, $[Cp^*IrCl(bik)]BF_4$, $[Cp^*IrCl(mesim\text{-}mim)]BF_4$ and $[Cp^*IrCl(mesBIAN)]BF_4$[15] were prepared by literature methods.

^{1}H NMR spectra were recorded on a Bruker DPX300, DMX500 and 600 spectrometers. All spectra were recorded at 323 K unless otherwise specified. ^{1}H NMR chemical shifts were referenced internally to residual solvent resonances. UV spectra were recorded in Helma quartz 96-well plates using Bio-Tek PowerWave XS plate reader and analysed using KC4 Microplate Data Analysis Software.

Screening of hydroamination in acetone–MeOH with $NaBF_4$ as counterion

Full experimental details describing the generation of the library of rhodium and iridium complexes screened as catalysts can be found in our previous report.[9] The library of complexes was generated *in situ* by reacting standard solutions of 2 molar equivalents of ligand and 1 molar equivalent of bimetallic metal precursor in acetone at rt, along with 2 molar equivalents of $NaBF_4$ which was added as a MeOH standard solution. Fig. 1 illustrates the components in each well of the 96-well plate. An acetone solution of substrate **2** was then immediately added to each of the wells and an aliquot was taken from each well for analysis. The reaction block was sealed and heated at 50 °C for 18 hours, after which time an aliquot was again taken from each well,

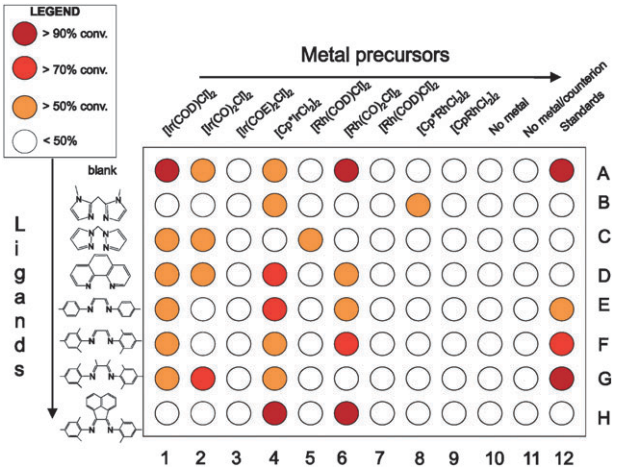


Fig. 1 Graphical representation of well components and catalytic conversions of **2** using direct UV analysis. Each well contains 10 mol% $[M]_2$, 20 mol% ligand and 20 mol% $NaBF_4$, and the reaction was performed at 50 °C for 18 h in acetone–MeOH (2.5 : 1) and was analysed using a direct UV analysis.

diluted and analysed *via* UV spectroscopy. The UV absorbance data for each time point were normalised using an isosbestic point in the data set and the internal standard series included in column 12, Fig. 1, was utilised for calibration of the UV absorbances.

Synthesis of [RhClCO(MesBIAN)] (6)

$[Rh(CO)_2Cl]_2$ (27 mg, 0.07 mmol) and bis(2,4,6-trimethylphenylimino)acenapthene (mesBIAN) (53 mg, 0.13 mmol) were dissolved in dichloromethane (15 mL) to give a dark green solution. The reaction mixture was stirred at rt, under an atmosphere of nitrogen, for 10 min. The solvent volume was reduced to approximately a third of the volume and hexane (5 mL) was added. A dark green solid began to precipitate out. The mixture was cooled in an ice-bath to give a dark green solid and a light green filtrate. The solid was collected by filtration, washed with hexane (2 × 1 mL) and dried *in vacuo*. [RhCl(CO)(mesBIAN)] was obtained as a dark green powder (50 mg, 70%), mp 246–252 °C (dec.); Anal (%) found: C, 63.06; H, 5.32; N, 4.28. $C_{31}H_{28}N_2OClRh \times 0.5\ H_2O$, requires C, 62.68; H, 4.74; N, 4.79; ν_{max}/cm^{-1} (nujol): 1980s (Rh–CO); ^{1}H NMR (δ, 600 MHz, tetrahydrofuran-d_8): 8.21 (1H, d, $^3J_{H5\text{-}H4}$ = 8.2 Hz, 5-H), 8.17 (1H, d, $^3J_{H5'\text{-}H4'}$ = 8.2 Hz, 5′-H), 7.53 (1H, dd, $^3J_{H4'\text{-}H5'}$ = 8.2 Hz, $^3J_{H4'\text{-}H3'}$ = 7.2 Hz, 4′-H), 7.40 (1H, dd, $^3J_{H4\text{-}H5}$ = 8.2 Hz, $^3J_{H4\text{-}H3}$ = 7.2 Hz, 4-H), 7.14 (2H, s, 10-H), 7.04 (2H, s, 10′-H), 6.80 (1H, d, $^3J_{H3'\text{-}H4'}$ = 7.2 Hz, 3′-H), 6.65 (1H, d, $^3J_{H3\text{-}H4}$ = 7.2 Hz, 3-H), 2.43 (3H, s, *p*-CH_3), 2.404 (3H, s, *p*′-CH_3), 2.399 (6H, s, *o*-CH_3), 2.32 (6H, s, *o*′-CH_3) ppm; ^{13}C NMR (δ, 125 MHz, tetrahydrofuran-d_8): 188.3 (d, $^1J_{Rh\text{-}CO}$ = 79.8 Hz, Rh-CO), 175.0 (C1′), 166.9 (C1), 148.7 (C8), 145.0 (C7), 144.4 (C8′), 138.5 (C11), 137.6 (C11′), 133.7 (C6), 132.7 (C5′), 131.3 (C4), 130.9 (C10), 130.6 (C4′), 130.5 (C9′), 130.4 (C10′), 130.3 (C2), 130.0 (C5), 129.6 (C9), 128.1 (C2′), 125.5 (C3′), 122.8 (C3), 21.9 (*p*′-CH_3), 21.7 (*p*-CH_3), 19.2 (*o*′-CH_3), 18.3 (*o*-CH_3) ppm; *m*/*z*: (ES^+) 605 (M + Na, 32%), 519 (100).

Synthesis of *N*-(2-methylvinyl)-2-phenylindole (5)

Under argon, **2** (100.8 mg, 0.521 mmol) and $[IrCp^*Cl_2]_2$ (19.5 mg, 24.5 μmol) were dissolved in 10 mL acetone. The mixture was refluxed at 55 °C for 18 h. The solution was cooled and the majority of the Ir was removed *via* filtration. The filtrate was run through a small silica column to remove the remaining Ir and the acetone was removed *in vacuo*. The compound **5** was isolated as a beige solid (77.8 mg, 0.33 mmol, 64%). The compound was found to be unstable in acidic solutions losing the vinyl group generating **3**. Anal (%) found: C, 87.45; H, 6.67; N, 6.31. $C_{17}H_{15}N$ requires C, 87.51; H, 6.48; N, 6.01; ^{1}H NMR (δ, 300 Hz, 298 K, acetone-d_6): 7.68 (2H, m, *o*-Ph), 7.59 (1H, m, 5-H) 7.49–7.32 (4H, m, 8-H and m/p-Ph), 7.17 (1H, m, 7-H), 7.09 (1H, m, 6-H) 6.71 (1H, s, 3-H), 5.53 (1H, d, J = 1.51 Hz, CH_2), 5.30 (1H, s, CH_2), 1.79 (3H, s, Me) ppm; ^{13}C {^{1}H} NMR (75 MHz, acetone-d_6): δ 141.4 (C10), 139.5 (C2), 138.0 (C4), 133.3 (C9), 128.4 (Ph), 127.8 (Ph), 127.6 (Ph), 122.0 (C7), 120.239 (C6 or C5), 120.220 (C6 or C5), 114.0 (CH_2), 110.5 (C8), 103.2 (C3), 21.4 (CH_3) ppm; GC-MS 19.43 min (ES^+) m/z: 233 (M^+, 95%), 217 (100).

Typical experimental procedure for the catalysed hydroamination of 2 monitored by ^{1}H NMR spectroscopy

An example of a typical procedure: **2** (47.5 mg, 0.25 mmol), $[IrCp^*Cl_2]_2$ (4.8 mg, 6.0 μmol), mesBIAN (6.3 mg, 15.1 μmol) and $NaBF_4$ (1.5 mg, 13.7 μmol) were weighed into a NMR tube fitted with a concentric Teflon valve. The tube was then evacuated and acetone-d_6 was vacuum-transferred into the tube. The NMR tube was taken into an argon filled glove box where the concentric valve was exchanged for a septum. TCE was injected into the tube (20.9 mg, 0.124 mmol), the concentric valve was replaced under a cone of argon and the sealed tube was placed into the NMR probe heated at 50 °C. The reaction progress was monitored by ^{1}H NMR spectroscopy. % Conversions given are determined directly from the ^{1}H NMR spectra using TCE as an internal standard.

Results and discussion

Previously we have reported an efficient approach to the identification of hydroamination catalysts utilising UV-Vis spectroscopy as a screening method.[9] A library of *in situ* generated complexes were prepared and screened as catalysts for the hydroamination of 2-(2-phenylethynyl)aniline **2**, Scheme 1. PARAFAC data analysis was used to identify active catalysts. The catalysts were ranked according to the ratio of product to starting material and product at a given time. The PARAFAC analysis worked very well as a qualitative screening technique in thf and several novel catalysts were identified, Table 1.

Investigation of 'hits' and direct analysis of UV data

A detailed further investigation of the catalysts ranked in the top 10 by PARAFAC analysis was performed. Each of the reactions were repeated, generating the catalysts *in situ* on a larger scale using ^{1}H NMR spectroscopy to monitor the conversion of **2**. All but 3 of the top ten PARAFAC ranked catalysts in thf were confirmed as active catalysts using ^{1}H NMR, with 6 achieving >95% conversion within 18 h at 50 °C, Table 1. However, in the screening where acetone was solvent, the top PARAFAC ranked catalysts did not reach complete conversion after 18 h using ^{1}H NMR to monitor the course of the reactions and several of the other catalysts ranked in the top 10 by PARAFAC were found not to be highly effective catalysts, Table 2. Due to the limited number of highly active catalysts in acetone the application of PARAFAC rankings to identify 'hits' in the screening results in false positive identification of several complexes.

In order to identify the most active catalysts from the screening in acetone and to obtain quantitative conversions, the UV-Vis spectra from the catalyst screening obtained in acetone solvent were reanalysed. The spectra were normalised using the isosbestic point of the data set. The conversion of 2-(2-phenylethynyl)aniline **2** was determined using a calibration curve generated from the internal standard series included in the same plate. The conversion obtained in each well using this direct UV analysis method is depicted schematically in Fig. 1, with increasing colour intensity indicating increasing conversion of 2-(2-phenylethynyl)aniline **2**.

Verification of direct UV analysis using ^{1}H NMR spectroscopy

The results obtained from the direct UV analysis of the screening results were confirmed using ^{1}H NMR spectroscopy. Each of the reactions from one column of the 96-well plate (column 2 in Fig. 1 with $[Ir(CO)_2Cl]_2$ metal precursor) were repeated individually and monitored using ^{1}H NMR spectroscopy. These reactions were performed with 5 mol% $[M]_2$, 10 mol% $NaBF_4$ and 10 mol% ligand (where applicable) and **2** in acetone-d_6. The catalyst loading was decreased in these experiments relative to the loading used in the screening, and the ratio of catalyst was decreased to minimize the interference which the catalysts cause in the NMR spectra. The trend of the catalytic results obtained from the ^{1}H NMR study is consistent with the results obtained in the UV screening, Fig. 2. The most efficient catalyst from the screening in column 2 contained $[Ir(CO)_2Cl]_2$–dmmesDAD–$NaBF_4$. This *in situ* generated complex also proved to be the most active catalyst when individually repeated and monitored *via* ^{1}H NMR.

To further confirm the direct UV analysis method each of the *in situ* generated complexes which achieved >90% conversions were also repeated and monitored using ^{1}H NMR spectroscopy. These reactions were performed with 2.5 mol% $[M]_2$, 5 mol% $NaBF_4$ and 5 mol% ligand (where applicable) in acetone-d_6 and the reactions were again monitored *via* ^{1}H NMR spectroscopy. When individually repeated and monitored, each of the four complexes achieved >95% conversion within 18 h. These results confirm that the direct analysis of UV-Vis spectra can be used to screen for active catalysts using internal calibration standards to determine the conversion of starting material.

Synthesis of [RhCl(CO)(mesBIAN)] 6

One of the most efficient *in situ* generated catalysts was $[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$ achieving >95% conversion in 5 hours. The complex assumed to be the active catalyst

Table 1 PARAFAC ranking for *in situ* generated catalysts from screening after 18 h along with efficiency of conversion of **2** by *in situ* generated catalysts in isolated reactions monitored by ^{1}H NMR spectroscopy in thf-d_8

In situ generated complex	Ranking using PARAFAC[a]	% Conv. *via* ^{1}H NMR
$[Ir(COD)Cl]_2$–$NaBF_4$	9	>95
$[IrCp^*Cl_2]_2$–$NaBF_4$	1	95
$[IrCp^*Cl_2]_2$–mesBIAN–$NaBF_4$	2	>95
$[IrCp^*Cl_2]_2$–bpm–$NaBF_4$	3	15
$[Rh(CO)_2Cl]_2$–$NaBF_4$	5	86
$[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$	6	>95
$[Rh(CO)_2Cl]_2$–bpm–$NaBF_4$	7	>95
$[RhCpCl_2]_2$–$NaBF_4$	10	>95
$[RhCpCl_2]_2$–bpm–$NaBF_4$	4	48
$[RhCp^*Cl_2]_2$–bpm–$NaBF_4$	8	0

[a] PARAFAC ranking gave relative efficiency of the catalysts in order 1–96.

Table 2 Comparison of PARAFAC ranking and conversion by direct UV analysis for *in situ* generated catalysts from screening after 18 h with conversion of **2** by *in situ* generated catalysts in isolated reactions monitored by ^{1}H NMR spectroscopy in acetone-d_6

In situ generated complex	PARAFAC ranking	% Conv. direct UV analysis	% Conv. *via* ^{1}H NMR
$[Ir(COD)Cl]_2$–$NaBF_4$	3	>90	>95
$[Ir(COD)Cl]_2$–bpm–$NaBF_4$	9	50–70	—
$[Ir(CO)_2Cl]_2$–dmesDAD–$NaBF_4$	4	70–90	50
$[Ir(CO)_2Cl]_2$–bpm–$NaBF_4$	8	70–90	75
$[Rh(CO)_2Cl]_2$–$NaBF_4$	7	70–90	>95
$[IrCp^*Cl_2]_2$–mesBIAN–$NaBF_4$	2	>90	90
$[IrCp^*Cl_2]_2$–dmesDAD–$NaBF_4$	6	50–70	—
$[Rh(CO)_2Cl]_2$–$NaBF_4$	1	>90	80
$[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$	10	>90	>95
$[Rh(CO)_2Cl]_2$–bpm–$NaBF_4$	5	<50	—

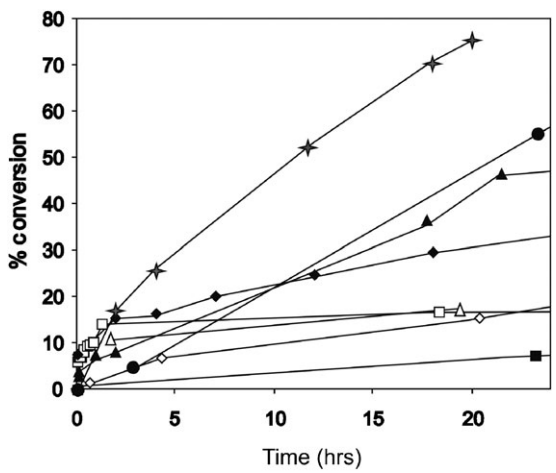


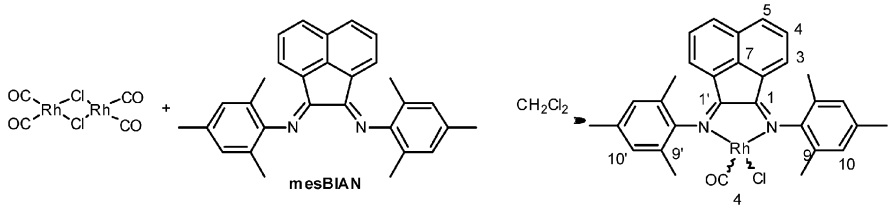
Fig. 2 Comparison of *in situ* generated catalysts for the hydroamination of **2**, 5 mol% $[Ir(CO)_2Cl]_2$, 10 mol% L and $NaBF_4$ in acetone-d_6 50 °C monitored *via* ^{1}H NMR. L = ▲ none, ◇ bim, □ bpm, ● phen, ■ ptolDAD, △ mesDAD, ✦ dmmesDAD, ◆ mesBIAN.

[RhCl(CO)(mesBIAN)] **6** was synthesised, Scheme 2. Complex **6** was synthesised using an adaptation of the method of Gonsalvi *et al.*, for the preparation of the complex [RhI(CO)(dmmesDAD)], Scheme 2.[27] Complex **6** was isolated as a dark green air-stable powder, prepared in 70% yield.

Coordination of the mesBIAN ligand to the rhodium centre was confirmed using NMR spectroscopy. In the ^{1}H NMR spectrum a loss of symmetry of the ligand and the downfield shift of the ligand resonances were observed. The ^{13}C NMR spectrum revealed a resonance for a carbonyl bound to the rhodium centre at 188.3 ppm, with a rhodium–carbon coupling of 79.8 Hz. This coupling is typical of couplings seen for rhodium–carbonyl complexes with rhodium in the +1 oxidation state.[28] The IR spectrum revealed a single strong peak for the carbonyl stretch at 1980 cm^{-1}, confirming a mono-carbonyl complex had been formed.

Investigation of $[Ir(COD)Cl]_2$ and $[Rh(CO)_2Cl]_2$ derived complexes as hydroamination catalysts

One of the most active catalysts identified in the screening was the metal precursor $[Ir(COD)Cl]_2$. The influence of catalyst



Scheme 2

Table 3 Conversion of **2** to **3** by *in situ* generated complexes 5 mol% in acetone-d_6, 50 °C monitored *via* ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard

Catalyst	$TOF_{50\%}/h^{-1}$	Time >95% conv.	% Conv. 18 h
$[Ir(COD)Cl]_2$–$NaBF_4$[a]	5.2	2.5 h	>95
$[Ir(COD)Cl]_2$–$NaBF_4$	1.67	11 h	>95
$[Ir(COD)Cl]_2$–mesDAD–$NaBF_4$	0	N/A	0
$[Rh(CO)_2Cl]_2$–$NaBF_4$[a]	0.4	N/A	80
$[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$	1.7	5 h	>95
[Rh(mesBIAN)(CO)Cl]–$NaBF_4$	0	N/A	0
[Rh(mesBIAN)(CO)Cl]–$AgBF_4$	87	12 min	>95
[Cp*IrCl(mesBIAN)]BF_4–$AgBF_4$	27	24 min	>95

[a] 10 mol% [M].

loading, the presence of counterion, $NaBF_4$, and the effect of ligand on the catalytic activity were investigated, Table 3. In the first instance, 2-(2-phenylethynyl)aniline **2** was treated with 5 mol% $[Ir(COD)Cl]_2$ and 10 mol% $NaBF_4$ in acetone-d_6 at 50 °C and the reaction was monitored by ^{1}H NMR spectroscopy. Full conversion to 2-phenylindole **3** was achieved after 2.5 hours with a $TOF_{50\%}$ of 5.2 h^{-1}.† Decreasing the catalyst loading to 2.5 mol% $[Ir(COD)Cl]_2$ significantly decreases the catalytic activity per mole of catalyst decreasing the $TOF_{50\%}$ to 1.67 with complete conversion not achieved until 11 h.

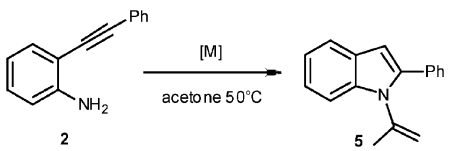
Another series of complexes which were identified as active hydroamination catalysts were those generated from the $[Rh(CO)_2Cl]_2$ metal precursor. The precursor 2-(2-phenylethynyl)-aniline **2** in the presence of 5 mol% $[Rh(CO)_2Cl]_2$ and 10 mol% $NaBF_4$ led to 80% conversion to 2-phenylindole **3** after 18 hours at 50 °C in acetone. Incorporation of ligand into the catalyst significantly increased the catalytic activity, with the *in situ* catalyst generated from 2.5 mol% $[Rh(CO)_2Cl]_2$, 5 mol%, mesBIAN and 5 mol% $NaBF_4$ achieving >95% conversion after 5 hours. The equivalent isolated complex [Rh(CO)Cl(mesBIAN)] (either with or without additional counterion ($NaBF_4$)), however, did not catalyse the conversion of **2**, even after 18 hours. This indicates that the active catalyst formed *in situ* is not the expected complex [Rh(CO)Cl(mesBIAN)]. Chloride abstraction from metal complexes using silver salts has been shown previously to generate an active catalyst *in situ*.[29–31] Chloride abstraction results in a coordinatively unsaturated metal complex and significantly increases the catalytic activity of an otherwise stable complex. Abstraction of the chloride anion from the isolated complex [Rh(CO)Cl(mesBIAN)] with $AgBF_4$ led to a significant increase in catalytic activity for the hydroamination of **2** generating the most active catalyst identified in this study. A $TOF_{50\%}$ of 87 h^{-1} was obtained with complete conversion of **2** to **3** obtained after 12 min. This reaction rate is also amongst the best reported in the literature for the hydroamination of **2**, especially with the mild conditions which are employed, in acetone at 50 °C.

Investigation of $[IrCp^*Cl_2]_2$ complexes as hydroamination catalysts—the catalysed formation of an *N*-alkyl substituted indole

An interesting result identified in the high throughput catalysis study was the complete conversion of 2-(2-phenylethynyl)-aniline **2** by the metal precursor $[IrCp^*Cl_2]_2$ as well as the *in situ* generated complexes of the type [Cp*Ir(N–N)Cl]BF_4 (N–N = bidentate sp^2-hybridised nitrogen donor ligand). The indole product identified here by ^{1}H NMR was, however, not the expected 2-phenylindole **3**, Scheme 1, but *N*-(1-methyl-vinyl)-2-phenylindole **5**, Scheme 3. This *N*-alkyl substituted compound has not been reported previously. The vinylindole, **5**, was isolated from the catalytic mixture and fully characterised. The mechanism for the formation of this compound is of interest; it is currently being investigated and will be the subject of a future paper.

All of the complexes generated *in situ* from a combination of $[IrCp^*Cl_2]_2$, bidentate N-donor ligands and $NaBF_4$ promoted the conversion of **2** to the unusual substituted indole **5** by incorporating one molecule of acetone, Table 4. The most efficient catalyst combination found was 5 mol% $[IrCp^*Cl_2]_2$–$NaBF_4$ giving a $TOF_{50\%}$ of 4.8 h^{-1} and complete conversion after 4 hours.

A series of complexes of the type [Cp*IrCl(N–N)]BF_4, presumed to be the complexes generated *in situ*, were synthesised. The isolated complexes were tested as catalysts for the cyclisation of 2-(2-phenylethynyl)aniline **2**, Table 5. All of the isolated complexes of this type which were tested were inactive as catalysts for the cyclisation of **2** to form either **3** or **5**. Chloride abstraction from these complexes *via* the addition of one equivalent of $AgBF_4$ to the complexes **7–9** generated active catalysts which catalysed the hydroamination of **2** to generate **3** with 100% conversion. Complex **10** promoted complete conversion of the starting material **2** with **3** as the major product and **5** as the minor product. Complexes **11** and **12** did not promote complete conversion of **2** but promoted the generation of **3** and **5** in approximately a 1 : 1 ratio. The abstraction of the chloride from these complexes provides a readily available site on the metal for the binding of either **2** or acetone, generating an active catalyst. The bidentate nitrogen ligand was thought to be effective in stabilising the activated catalyst as the activity of the $[IrCp^*Cl_2]_2$ metal precursor after chloride abstraction is initially high but drops off quickly as the catalyst decomposes and deposits as an iridium film on the reaction vessel.



Scheme 3

† $TOF_{50\%}$ was calculated as the mole of product/mole of catalyst/time (h) at 50% conversion.

Table 4 Conversion of **2** to **5** by *in situ* generated complexes 5 mol% in acetone, 50 °C monitored *via* ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard

Catalyst	$TOF_{50\%}/h^{-1}$	Time/h >95% conv.
$[IrCp^*Cl_2]_2$	5.7	21
$[IrCp^*Cl_2]_2$–$NaBF_4$	4.8	4
$[IrCp^*Cl_2]_2$–$NaBArF_{24}$	3.9	4 (90% conv.)[a]
$[IrCp^*Cl_2]_2$–$AgBF_4$	7.3	12
$[IrCp^*Cl_2]_2$–mesBIAN–$NaBF_4$	2.1	18 (90% conv.)[a]
[Cp*IrCl(mesBIAN)]BF_4	0	N/A

[a] No further conversion observed.

Table 5 Conversion (%) of **2** to **3** and/or **5** by *in situ* generated complexes 5 mol% [Cp*Ir(N–N)Cl]BF_4 and 5 mol% $AgBF_4$ in acetone, 50 °C for 3 h monitoring by ^{1}H NMR

Catalyst	Conv.	Conv. to **3**	Conv. to **5**
[Cp*IrCl(bpm)]BF_4 **7**	99	99	0
[Cp*IrCl(dmbpm)]BF_4 **8**	99	99	0
[Cp*IrCl(mesBIAN)]BF_4 **9**	99	99	0
[Cp*IrCl(bik)]BF_4 **10**	99	80	20
[Cp*IrCl(bim)]BF_4 **11**	63	27	36
[Cp*IrCl(mesim-mim)]BF_4 **12**	65	37	27

Using ^{1}H NMR to monitor the course of the reaction the isolated complexes **7–9** were shown to be active catalysts for the conversion of **2** to **3**. The most active catalyst is the combination of 5 mol% [Cp*IrCl(mesBIAN)]BF_4 **9** and 5 mol% $AgBF_4$ in acetone-d_6, Table 3 and Fig. 3. The catalyst achieved complete conversion of **2** to **3** in 25 min in acetone-d_6 at 50 °C. The efficiency of the silver salt $AgBF_4$ as a catalyst for the hydroamination of **2** was also tested, Fig. 3. It was found to be an active catalyst for this reaction; with 5 mol% catalyst 50% conversion was reached after 40 minutes, but $AgBF_4$ alone was much less efficient than the combination of [Cp*IrCl(mesBIAN)]BF_4 **9** and $AgBF_4$. However, the activity of $AgBF_4$ alone as a catalyst is interesting to note as it is frequently used to generate active catalysts *in situ* without consideration of its own potential role as a catalyst. Further studies into the catalytic activity of $AgBF_4$ and other Ag(I) complexes are currently being pursued by the authors of this paper.

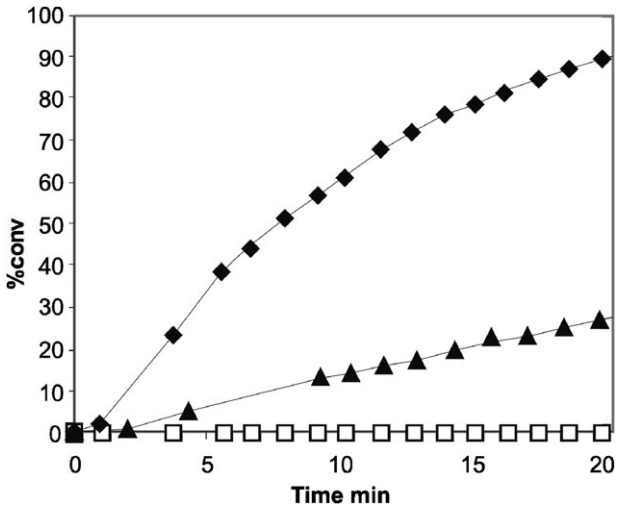


Fig. 3 Conversion of **2** to **3** by □ 5 mol% **9**, ◆ 5 mol% **9**–$AgBF_4$ and ▲ 5 mol% $AgBF_4$.

Conclusions

Catalysts identified through high throughput screening of a library of Rh and Ir complexes were investigated further for application to the hydroamination of 2-(2-phenylethynyl)-aniline **2**. Three complexes were identified to be highly active hydroamination catalysts in acetone: the *in situ* combinations of $[Rh(CO)_2Cl]_2$–mesBIAN–$NaBF_4$ and $[Ir(COD)Cl]_2$–$NaBF_4$ and also Rh(CO)Cl(mesBIAN)–$AgBF_4$ combination. The most efficient catalyst, Rh(CO)Cl(mesBIAN) **6**–$AgBF_4$, promoted the complete conversion of **2** to **3** within 12 minutes at 50 °C.

The isolated complexes of the type [Cp*IrCl(N–N)]BF_4 were found to be inactive as hydroamination catalysts, however, abstraction of the chloride by $AgBF_4$ created active catalysts *in situ* with the best catalyst in the series the combination of [Cp*IrCl(mesBIAN)]BF_4 **9** and $AgBF_4$.

Also identified from this work was the formation of the unusual *N*-vinylindole, **5**, from **2** *via* the incorporation of one molecule of acetone, catalysed by $[IrCp^*Cl_2]_2$–$NaBF_4$. The mechanism of this transformation will be the subject of a future paper.

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References

1 I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127–2198.
2 S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.
3 F. Pohlki and S. Doye, *Chem. Soc. Rev.*, 2003, **32**, 104–114.
4 S. Burling, L. D. Field and B. A. Messerle, *Organometallics*, 2000, **19**, 87–90.
5 X. Li, A. R. Chianese, T. Vogel and R. H. Crabtree, *Org. Lett.*, 2005, **7**, 5437–5440.
6 O. Lavastre and J. P. Morken, *Angew. Chem., Int. Ed.*, 1999, **38**, 3163–3165.
7 O. Löber, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 4366–4367.
8 J. Stambuli and J. F. Hartwig, *Curr. Opin. Chem. Biol.*, 2003, **7**, 420–426.
9 D. Ebrahimi, D. F. Kennedy, B. A. Messerle and D. B. Hibbert, *Analyst*, 2008, **133**, 817–822.
10 N. A. Yakelis and R. G. Bergman, *Organometallics*, 2005, **24**, 3579–3581.
11 J. L. Herde, J. C. Lambert and C. V. Senoff, *Inorg. Synth.*, 1974, **15**, 18–19.
12 D. Roberto, E. Cariati, R. Psaro and R. Ugo, *Organometallics*, 1994, **13**, 4227–4231.
13 C. Köcher and W. A. Herrmann, *J. Organomet. Chem.*, 1997, **532**, 261–265.
14 J. A. McCleverty and G. Wilkinson, *Inorg. Synth.*, 1990, **28**, 84–86.
15 C. White, A. Yates and P. M. Maitlas, *Inorg. Synth.*, 1992, **29**, 228–234.
16 S. Juliá, J. M. Mazo and L. Avila, *Org. Prep. Proced. Int.*, 1984, **16**, 299–307.
17 S. Elgafi, L. D. Field, B. A. Messerle, T. W. Hambley and P. Turner, *J. Chem. Soc., Dalton Trans.*, 1997, 2341–2345.

18 I. E. Buys, S. Elgafi, L. D. Field, T. W. Hambley and B. A. Messerle, *Inorg. Chem.*, 1994, **33**, 1539–1542.
19 L. Stamp and H. Tom Dieck, *Inorg. Chim. Acta*, 1987, **129**, 107–114.
20 J. M. Kleigman and R. K. Barnes, *Tetrahedron*, 1970, **26**, 2555–2560.
21 H. Tom Dieck and I. W. Renk, *Chem. Ber.*, 1971, **104**, 92–102.
22 R. van Asselt, C. J. Elsevier, W. J. Smeets, A. L. Spek and R. Benedix, *Recl. Trav. Chim. Pays-Bas*, 1994, **113**, 88–98.
23 M. Gasperini, F. Ragaini and S. Cenini, *Organometallics*, 2002, **21**, 2950–2957.
24 A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, 1989, **30**, 2581–2584.
25 S. Elgafi, L. D. Field, B. A. Messerle, P. Turner and T. W. Hambley, *J. Organomet. Chem.*, 1999, **588**, 69–77.
26 L. D. Field, B. A. Messerle, L. P. Soler, M. Rehr and T. W. Hambley, *Organometallics*, 2003, **22**, 2387–2395.
27 L. Gonsalvi, J. A. Gaunt, H. Adams, A. Castro, G. J. Sunley and A. Haynes, *Organometallics*, 2003, **22**, 1047–1054.
28 B. E. Mann and B. F. Taylor, in *^{13}C NMR Data for Organometallic Compounds*, Academic Press, London, 1981.
29 F. E. Michael and B. M. Cochran, *J. Am. Chem. Soc.*, 2006, 4246–4247.
30 C. Brouwer and C. He, *Angew. Chem., Int. Ed.*, 2006, **45**, 1744–1747.
31 S. R. Beeren, S. L. Dabb and B. A. Messerle, *J. Organomet. Chem.*, 2009, DOI: 10.1016/j.jorganchem.2008.10.038.

