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One-pot reductive amination of carbonyl compounds with ammonia via 'hydrogen borrowing' using hydrido- and bis-ammine P,O(Me)-ruthenacycles

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The novel cationic  $[RuH{PPh_2(2-OMeC_6H_4)}_2]BPh_4$  and neutral *trans*- $[Ru(NH_3)_2{PPh_2(2-OMeC_6H_4)}_2]BPh_4$ 11  $OC_6H_4$ ]<sub>2</sub>] complexes were isolated from phosphine substitution reactions with [RuH(1,5-12 cod)(NH<sub>2</sub>NMe<sub>2</sub>)<sub>3</sub>]BPh<sub>4</sub> and [RuCl(1,5-cod)(NH<sub>3</sub>)<sub>2</sub>(NH<sub>2</sub>NMe<sub>2</sub>)]BPh<sub>4</sub> respectively. Ligand 13 14 induced bisdemethylation of the pendent ether moieties of the phosphines occurred to give rise to the bis-phosphanylphenoxy moieties. Both complexes catalyzed the one-pot reductive 15 16 amination of carbonyl compounds where excellent selectivity of aryl aldehydes over aryl ketones as precursors to the alcoholic species existed. Through substrate screening and <sup>1</sup>H-17 18 NMR studies, both steric and electronic effects of the substrates were found to influence the hydrogenation/amination mechanistic pathway, as well as direct the alcohol:amine 19 20 selectivity.

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22 Keywords: ruthenium(II); hemilability; reductive amination; transfer hydrogenation

#### 24 1. Introduction

The availability of a vacant coordination site(s) on a metal complex through ligand mobility is an important property usually exhibited by atom efficient, highly catalytically active transition metal complexes [1-12]. Transition-metal complexes containing ether and thioether phosphine ligands, and their dealkylated oxo- and thio-donor ligands, especially phosphanylphenoxides, have received much attention due to their wide-range of utility in homogeneous asymmetric and transfer hydrogenation catalysis [7, 11, 13-16], small molecule activation [17], biological applications [18], and chemosensors [17, 19, 20].

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Ruthenium(II) complexes bearing phosphines with pendant ether and thio-ether moieties in particular have been investigated as highly active regio-, stereo-, and chemo-selective catalysts by various groups [6, 9, 13] over the last 15 years because of the advantageous selfmodifying properties of the ligands. This is because phosphorous(III) and their ether O- or Satoms may coordinate to and stabilize a low valent metal centre, where after the ancillary ligand-assisted demethylation of the ether moiety may readily occur to form a hemilabile thio- or oxo-functionality when it is required in a catalytic or biological process [4, 6, 21].

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The reductive amination of carbonyls is a popular class of C-N asymmetric catalysis that 41 continues to be investigated because of the sought after primary, secondary, and tertiary 42 43 amines that are obtainable [22-28]. Numerous Ru(II) systems bearing rigid and hemilabile ligand systems have been reported to exhibit catalytic activity in asymmetric transfer 44 45 hydrogenation reactions, although much less in reductive amination as a class of carbonyl/alcohol transformation reactions [14, 19, 26, 27, 29-31]. The ability to atom-46 47 economically convert alcohols into primary amines using ammonia remains a challenge, where in some respects considerable progress has been made [28, 32-36]. Apart from the 48 49 known [Cp\*IrCl(Tsdpen-H)] [16],  $[Rh(Cp*)Cl_2]_2$  [14], and  $Ti(O^iPr)_4$  [15] catalysts known to be able to help produce primary amines from ketones and aldehydes, the catalysts [((R)-tol-50 binap)RuCl<sub>2</sub>(DMF)<sub>x</sub>] [14], [Ru(OAc)<sub>2</sub>((*R*)-dm-segphos)] [29], [RuHCl(CO)(PNP)] [28, 33, 51 36], [RuHCl(CO)(triphos)] [34, 35], and the combination of [Ru<sub>3</sub>(CO)<sub>12</sub>] with phosphine 52 ligands are to date the only known Ru(II) catalysts with the ability to use NH<sub>3</sub> as feedstock 53 for transformation into primary amines (Figure 1). To the best of our knowledge, there are no 54 existing isolated mono- and bis-ammine Ru(II) catalysts that may actively provide an 55 additional source of NH<sub>3</sub> as part of the catalytic intermediates involved in these reactions 56 [37]. 57



Figure 1: Reductive amination: (1) (NH<sub>4</sub>)(OOCH), NH<sub>3</sub>/MeOH, 85 °C, 17-48h. (2)
(NH<sub>4</sub>)(OOCCH<sub>3</sub>), (NH<sub>4</sub>)(OOCC<sub>6</sub>H<sub>4</sub>OH), 30 bar H<sub>2</sub>(g), 80 °C, 15h. (3) 6 bar NH<sub>3</sub>, 140-170
°C, 20h, molecular sieves; excess NH<sub>3</sub>(aq), 140 °C, 21h (4) 76 bar NH<sub>3</sub>, 135 °C, 18-36h; 3540 bar NH<sub>3</sub>, 135 °C, 12h (5) 35-40 bar NH<sub>3</sub>, NH<sub>4</sub>Cl, 155-165 °C, 12-15h. For
[Ru(CO)ClH(PPh<sub>3</sub>)<sub>3</sub>]: 4-9 bar NH<sub>3</sub>, dppe (1.1 mol%), 10 mol% Al(OTf)<sub>3</sub>, 120 °C, 16h. (6)
(NH<sub>4</sub>)(OOCCH<sub>3</sub>), NH<sub>4</sub>OH, NaBH<sub>4</sub>/EtOH, 90 °C, 24h.

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We recently published the syntheses of cationic ruthenium(II) mono- and bis-ammine 66 complexes of  $[RuH(1,5-cod)(NH_2NMe_2)_3]A$ ,  $[RuH(1,5-cod)(NH_3)(NH_2NMe_2)_2]A$ , and 67  $[RuCl(1,5-cod)(NH_3)_2(NH_2NMe_2)]A$  (A = PF<sub>6</sub>, BPh<sub>4</sub>) [38]. Of particular interest to us, was 68 the novel hydrido- and chlorido-ammine phosphine-bearing complexes obtained from the 69 70 reactions of these precursors with chelating phosphines. This study focuses on (i) the syntheses of two new Ru(II) complexes bearing  $PPh_2(2-OMeC_6H_4)$  and  $PPh_2(2-OC_6H_4)$ 71 moieties; (ii) full characterisation of both complexes including the X-ray structure 72 determination of 4; (iii) and the results of the one-pot reductive amination catalytic study 73 performed using both complexes. 74

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#### 76 2. Experimental

77 2.1 General

All experiments were carried out under an argon atmosphere using standard Schlenk 78 techniques [39], using solvents that were dried using standard techniques [40]. The 79 complexes [RuH(1,5-cod)(NH<sub>2</sub>NMe<sub>2</sub>)<sub>3</sub>]BPh<sub>4</sub> (1) and [RuCl(1,5-cod)(NH<sub>2</sub>)<sub>2</sub>(NH<sub>2</sub>NMe<sub>2</sub>)]BPh<sub>4</sub> 80 (2) were prepared according to the reported procedure [38]. All other chemicals were 81 purchased from Sigma-Aldrich and used without further purification.  ${}^{1}H$  (400 MHz),  ${}^{13}C{H}$ 82 (101 MHz), and <sup>31</sup>P{H} (162 MHz) and <sup>15</sup>N-<sup>1</sup>H HMBC NMR spectra were recorded on a 83 Bruker Avance III Ultrashield 400 MHz spectrometer fitted with a B-ACS 60 auto-sampler 84 using CDCl<sub>3</sub> solutions. Chemical shifts were referenced to the internal residual protio 85 impurities in the solvent ( $\delta_{\rm H}$  7.24 ppm) or carbon signals ( $\delta_{\rm H}$  77.0 ppm in CDCl<sub>3</sub>). Solid state 86 FT-IR experiments were carried out on a Bruker Tensor 27 FT-IR as pressed KBr pellets in 87 air. Melting points were performed in air on a Stuart SMP10 and are uncorrected. 88 Microanalytical analyses (%CHNS) were performed at Rhodes University (RSA) using an 89 Elementar Vario Micro cube instrument with a TCD detector. Gas chromatography (FID) 90 analyses were performed on a Shimadzu GC-2010 Plus equipped with a 30 m Restek Rtx-5 91 capillary column, and GC/MS analyses using a Shimadzu GCMS-QP2010. 92

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### 94 2.2 Synthesis of $[RuH{PPh_2(2-MeOC_6H_4)]_2]BPh_4(3)$

A brown solution of  $[RuH(1,5-cod)(NH_2NMe_2)_3]BPh_4$  (1, 0.496 g, 0.7 mmol) in MeOH (12 mL) containing PPh<sub>2</sub>(2-MeOC<sub>6</sub>H<sub>4</sub>) (0.497 g, 1.7 mmol) was heated under reflux for 2 hours. EtOH (10 mL) was added to the dark brown solution and concentrated to 5 mL. The reaction mixture was vacuum-filtered, washed with EtOH/Et<sub>2</sub>O (8 mL), which gave a dark blue powder (0.231 g, 33%). Full characterization details are included in the Supplementary Information.

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### 102 2.3 Synthesis of trans- $[Ru(NH_3)_2\{PPh_2(2-OC_6H_4)\}_2]$ (4)

103 A brown solution of  $[RuCl(1,5-cod)(NH_3)_2(NH_2NMe_2)]BPh_4$  (2, 0.518 g, 1.1 mmol) in N<sub>2</sub>-104 purged acetone (12 mL) containing PPh<sub>2</sub>(2-MeOC<sub>6</sub>H<sub>4</sub>) (0.794 g, 2.7 mmol) was stirred at 105 room temperature overnight. EtOH (10 mL) was added to the yellow-orange solution, 106 concentrated (~5 mL), vacuum filtered, and washed with EtOH/Et<sub>2</sub>O (10 mL) from which 107 yellow-orange cuboid crystals were isolated. These were recrystallized using CHCl<sub>3</sub>/EtOH 108 (0.431 g, 58%). Full characterization details are included in the Supplementary Information.

In a typical experiment the carbonyl substrate (0.6 mmol), catalyst (1 mol%, 6 mg for 3, 5 mg 111 for 4), (NH<sub>4</sub>)(OOCCH<sub>3</sub>) (6 mmol, 460 mg), NH<sub>4</sub>OH (0.3 mmol, 42 µL of a 28% w/w 112 aqueous solution, or NH<sub>4</sub>Cl, 0.3 mmol, 16 mg; either of the two added as an additive), n-113 decane (0.6 mmol, 117 µL, internal standard), and EtOH (5 mL) were added together in a 114 Schlenk flask fitted with a dropping funnel and a bubbler. A solution of NaBH<sub>4</sub> (0.6 mmol, 115 23 mg; or 1.2 mmol in the case of glyoxal, 46 mg) in EtOH (5 mL) was added dropwise over 116 117 30 minutes after which the reaction mixture was heated at the desired temperature (60 °C, 90 °C) for several hours (12 h, 24 h, 48 h) under Ar(g), depending on the specific experiment. 118 After cooling, the mixture was quenched with water, extracted with EtOAc, and purified 119 using flash column chromatography (silica, EtOAc). The collected fractions were 120 concentrated to near-dryness and made up as a solution with either CH<sub>2</sub>Cl<sub>2</sub> or EtOH 121 (depending on the product solubility), and analysed using GC(FID) and GC/MS. 122

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### 124 2.5 <sup>1</sup>H-NMR reductive amination experiments

In a typical experiment a <sup>1</sup>H-NMR spectrum of a heated (90 °C) EtOD solution (4 mL) of the 125 carbonyl substrate (0.1 mmol), catalyst (1 mol%, 0.9 mg for 4), (NH<sub>4</sub>)(OOCCH<sub>3</sub>) (1 mmol, 126 77 mg), and NH<sub>4</sub>OH (50 µmol, 7 µL of a 28% w/w aqueous solution) was taken as a 127 reference time = 0 min spectrum. Thereafter a EtOD solution (1 mL) of NaBH<sub>4</sub> (0.1 mmol, 4 mmol, 4 mmol)128 mg) was added and heated in a Schlenk flask fitted with a dropping funnel and a bubbler 129 under Ar(g) at 90°C for 24 hours. <sup>1</sup>H-NMR spectra of a sample of the resulting reaction 130 mixture was taken at intervals of 25, 60, 80, 120, 200, 400, 600, 900, 1100, and 1400 min 131 respectively, after which the NMR sample was returned to the reaction mixture after 132 measurement. All <sup>1</sup>H-NMR yields and conversions are based on the integration ratios 133 obtained between the aldehyde, alcohol, amine, and imine products observed. 134

135

### 136 **3. Results and Discussion**

#### 137 3.1 Synthesis and Characterisation of 3 and 4

Reaction of a methanolic solution of  $[RuH(1,5-cod)(NH_2NMe_2)_3]BPh_4$  (1) with 2.4 equivalents of PPh<sub>2</sub>(2-MeOC<sub>6</sub>H<sub>4</sub>) gave the novel five-coordinate complex *trans*-[RuH{PPh<sub>2</sub>(2-MeOC<sub>6</sub>H<sub>4</sub>)}<sub>2</sub>]BPh<sub>4</sub> (3) (Scheme 1). This complex was found to be airsensitive, with an associated molecule of H<sub>2</sub>O stabilising the vacant coordination site which is suggested through FTIR, <sup>1</sup>H-NMR, and CHN analyses of 3. The source of the H<sub>2</sub>O is reasoned to originate from the hygroscopic complex 1, which is usually crystallised from a wet DCM/EtOH solvent mixture.





In contrast, reaction of  $[RuCl(1,5-cod)(NH_3)_2(NH_2NMe_2)]BPh_4$  (2) with 2.4 molar 147 equivalents of the phosphine in boiling acetone gives the novel ruthenacycle trans-148  $[Ru(NH_3)_2{PPh_2(2-OC_6H_4)}_2]$  (4). Bisdemethylation of the phosphine ligands to form  $\sigma$ -149 donating oxo-functionalities, along with the subsequent *cis*-coordination of both oxo-moieties 150 151 with respect to the ruthenium atom is rare, since mono-demethylation usually occurs in neutral Ru and Pd systems [7, 11, 13, 41]. Only one account reports the loss of both methyl 152 groups of the 2-MeOC<sub>6</sub>H<sub>4</sub> moieties through ligand-assisted C-O bond cleavage in the 153 chelating phosphine to form the Ru(II) complex  $[Ru(CH_3CN)_2 \{PPh_2(2-OC_6H_4)\}_2]$  [41]. Two 154 mechanisms for the transformation of the latter product were proposed by Hsu et al. [41], one 155 involving successive reductive elimination reactions of OMe moieties and coordinated 156 chloride ligands to expel CH<sub>3</sub>Cl in the reaction mixture with subsequent coordination of oxo-157 moieties to the ruthenium atom. This mechanism was adapted for the formation of 4, and is 158 included in the Supplementary Information. 159

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The UV/vis spectra of both the (formal) coordinatively unsaturated dark blue complex 3, and 161 162 orange colored octahedral complex 4 revealed peak absorptions at  $\lambda$  453 nm (3) and 616 nm (4) (Supplementary Information). The presence of the hydride ligand in [RuH{PPh<sub>2</sub>(2-163 MeOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>]BPh<sub>4</sub> (**3**) was confirmed by FTIR (v(Ru-H) = 2038 cm<sup>-1</sup>), and <sup>1</sup>H-NMR with  $\delta_{\rm H}$ 164 -8.57 (t,  ${}^{3}J_{HP} = 36$  Hz), with none observed for 4.  ${}^{1}H$ -NMR resonances for the symmetrical 165 OMe-groups in 3 were observed at  $\delta_H$  3.30 (s, OCH<sub>3</sub>), with none observed in 4. No 166 fluxionality in the hemilabile phenoxy moieties were observed in the <sup>1</sup>H-NMR spectra of 167 both **3** and **4**, which would indicate that hemilability is ligand-induced [7]. The <sup>31</sup>P-NMR 168 spectrum of **3** revealed a singlet at  $\delta_P$  49.9 for the two equivalent phosphines, which appears 169

- upfield from the singlet at  $\delta_P$  66.3 observed for **4**. The two phenyl substituents of each *cis*-
- 171 coordinated phosphorous atom contribute to an asymmetric steric environment which renders
- the two  $NH_3$  ligands non-equivalent [7]. The non-equivalence of the *trans*- $NH_3$  ligands in 4
- 173 were confirmed by FTIR (v(NH) = 3264 and 3155 cm<sup>-1</sup>;  $\delta$ (NH, asym) = 1580 and 1544 cm<sup>-1</sup>;
- 174  $\delta$ (NH, sym) = 1056 and 1026 cm<sup>-1</sup>), and <sup>1</sup>H-NMR ( $\delta_{\rm H}$  0.91 and 1.89).





(b)

Figure 2: (a) Molecular diagram of the X-ray crystal structure of trans-[Ru(NH<sub>3</sub>)<sub>2</sub>{PPh<sub>2</sub>(2-OC<sub>6</sub>H<sub>4</sub>)}<sub>2</sub>] (4), with thermal ellipsoids drawn at 50% probability level. Hydrogen atoms are omitted for clarity. (b) Molecular packing of 4 along the *b*-axis.

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The neutral complex **4** exhibits a distorted octahedral geometry, bearing two Ru-P,O metallacycles (mean P-Ru-O =  $82.87^{\circ}$ ) with two NH<sub>3</sub> ligands *trans* to each other in the axial positions (Figure 2) [32]. In each ruthenacycle, the average Ru-P bond distance (2.2438 Å) was slightly longer than the average Ru-O bond distance (2.1263 Å). Interestingly, the Ru1-N2 bond is observed to be slightly elongated as compared to the Ru1-N1 bond, with Ru1-N2 = 2.120(2) Å and Ru1-N1 = 2.104(2) Å (Table A, Supplementary Information).

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### 186 3.2 Reductive amination catalysis

The catalytic activity of complexes 3 and 4 were evaluated in the reductive amination 187 reaction of different aryl ketones and aldehydes with NH<sub>3</sub>. Our initial attempts were aimed at 188 the one-pot conversion of ketones into primary amines through reduction, transfer 189 190 hydrogenation, followed by subsequent amination using excess (NH<sub>4</sub>)(OOCCH<sub>3</sub>) as a major NH<sub>3</sub> stock feed. However, neither **3** nor **4** showed any appreciable amination activity with 191 acetophenone, and gave almost exclusively the corresponding alcohols (Table 1). This was 192 surprising since a moderate transfer hydrogenation activity under the experimental conditions 193 employed, at the very least, was expected. In the absence of catalyst and reductant almost no 194

conversion took place (entry 1). Using complex 4, a higher conversion of ketone was 195 observed as compared to 3 (entries 2, 3), despite a more sterically congested environment in 196 4. This is ascribed to the simpler substrate coordination to the vacant coordination site in 3, 197 and leads to higher transfer hydrogenation activity of the alcoholic species. The blank 198 experiment with absence of 4, and presence of NaBH<sub>4</sub> was also performed and showed a 199 slight increase in conversion, still with exclusive alcohol formation (entry 2). Despite the 200 201 possibility of 4 that could additionally act as an NH<sub>3</sub> reservoir directly in the inner coordination sphere with the bound substrate, 4 failed to exhibit any amination activity with 202 ketones, even in the presence of NH<sub>4</sub>OH as additive (entry 4). It was initially reasoned that a 203 strong solvent effect might be evident in these reactions, similar to what Schaub et al. [34] 204 found where less polar solvents (toluene) proved more efficient over polar solvents (THF). If 205 toluene was used as solvent, solubility and work-up issues hampered the full exploitation of 206 the catalytic transformation, leading to lower conversions of the ketone species observed. 207 Separate increases in temperature and reaction times lead to expected increased yields of 208 alcohol products (entry 7-9). Steric and electronic variations in the ketone moieties also 209 affected the conversions, a slightly lower conversion was observed for the electron-poor p-210 Cl-acetophenone (79%, entry 10), with less conversion for the bulky benzophenone (50%, 211 212 entry 11) and 2-isonitrosoacetophenone (43%, entry 12) substrates.

213

#### **Table 1**: Screening of hydrogenation/amination conditions.

$(NH_4)(OOCCH_3) \xrightarrow{4 (1 \text{ mol}\%)}_{\text{EtOH, NaBH}_4} + (NH_4)(OOCCH_3)$									
Entry	Ketone	Additive	Time	Temp ( ° C)	Cat (mol%)	Conv. (%)	Selectivity (A:B)		
1	acetophenone	-	24	60	<b>4</b> (0)	4 <sup>a</sup>	100:0		
2	acetophenone	-	24	60	<b>4</b> (1)	67 (77 <sup>b</sup> )	100:0 (100:0 <sup>b</sup> )		
3	acetophenone	-	24	60	<b>3</b> (1)	50	100:0		
4	acetophenone	NH <sub>4</sub> OH	24	60	<b>3</b> (1)	36	100:0		
5	acetophenone	NH <sub>4</sub> OH	24	60	<b>4</b> (1)	69	100:0		
6	acetophenone	NH <sub>4</sub> Cl	24	60	<b>4</b> (1)	33	100:0		

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7	acetophenone	NH <sub>4</sub> OH	24	90	<b>4</b> (1)	91	91:0:9 <sup>c</sup>	
8	acetophenone	NH <sub>4</sub> OH	12	90	<b>4</b> (1)	51	100:0	
9	acetophenone	NH <sub>4</sub> OH	48	90	<b>4</b> (1)	100	94:0:6 <sup>c</sup>	
10	4-chloro-acetophenone	NH <sub>4</sub> OH	18	90	<b>4</b> (1)	79	89:0:11 <sup>c</sup>	
11	benzophenone	NH <sub>4</sub> OH	18	90	<b>4</b> (1)	50	100:0	
12	2-isonitrosoacetophenone	NH <sub>4</sub> OH	18	90	<b>4</b> (1)	43	100:0	

<sup>a</sup> Absence of NaBH<sub>4</sub> and 4. <sup>b</sup> Absence of 4, but with added NaBH<sub>4</sub>. <sup>c</sup> Additional ester-adduct
 products were observed.

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A notable increase in selectivity towards the amine-adducts was observed when aldehydes 218 were employed under the same optimized conditions (Table 2, Figure in Supplementary 219 Information). Near quantitative conversions of benzaldehyde to its reduced species were 220 obtained with alcohol: amine ratios of 1:0 with no catalyst present (entry 1), for which the 221 selectivity increases to 2:3 with 4 (1 mol%) present (entry 2). A final yield of 57% for 222 benzylamine was achieved, which is comparable to the 68% achieved by Hofmann et al. [33], 223 considering that they employed 20 mol% of catalyst (20 times more), 20 equivalents of NH<sub>3</sub> 224 (two times more), and 145 °C (55 °C higher) for similar reaction times. It is important to note 225 226 that they added 1-octanol (0.8 equiv) in the reaction mixture, for which they proved that the alcohol facilitates the reductive amination of the aldehyde. 227

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229 The latter is in contrast to the recent work of Schaub et al. [28] where they were able to reductively aminate ketones in high yields using a [Ru(CO)HCl(PPh<sub>3</sub>)] (1 mol%)/dppe (1.1 230 231 mol%) catalyst system together with Al(OTf)<sub>3</sub> (10 mol%) as an additive that they found to be crucial for amine selectivity. They also found that benzaldehyde could be reductively 232 aminated using the same catalyst system, employing  $H_2(g)$  (40 bar) as reductant and  $NH_3(g)$ 233 (4 bar) as an amine source, giving rise to excellent alcohol: amine selectivity (1:95). They 234 235 found that the more electron donating ancillary phosphines decreases the activity of the resultant Ru(II) complexes, leading to lower substrate conversions. Additionally, they also 236 observed lowering of alcohol:amine selectivities as the bite angle of the ancillary 237 diphosphines employed increased. For example, when 1,2-bis(diphenyl)phosphinobenzene (a 238 ligand closest to our P,O-chelating phosphine) were employed, the selectivity in the 239 conversion of acetophenone decreased to 1:11 (as compared to their usual 1:99). This drastic 240 lowering of selectivity could be indicative of induced ligand strain and/or a degree of steric 241

bulk which in turn limits substrate coordination, and lowers amination activity. Interestingly, amendment of our protocol to employ  $H_2(g)$  (30 bar) and a methanolic ammonia solution (excess) lead to a slightly lower conversion (92%, entry 1), albeit with a higher alcohol:amine ratio (1:2) (Supporting Information). The presence of  $H_2(g)$  as opposed to NaBH<sub>4</sub> appears to aid in the transfer hydrogenation step to form benzaldehyde, which in turns facilitates the hydrogenation of the *in situ* formed imines.

Entw	Aldohydo	Conv.	Selectivity (%)				
Entry	Aldenyde	(%)	Alcohol	Amine	Other		
<b>1</b> <sup>a</sup>		99	OH 98 <sup>a</sup>	NH <sub>2</sub> 1 <sup>a</sup>	0		
2		99 (92 <sup>b</sup> )	он 37 (24 <sup>b</sup> )	NH <sub>2</sub> 57 (48 <sup>b</sup> )	6 (20 <sup>b</sup> )		
3	O <sub>2</sub> N	98	Он 0 <sub>2</sub> N 47	NH <sub>2</sub> O <sub>2</sub> N 53	0		
4		100	ОН  49	NH <sub>2</sub>	0		
5		100	он но 27°	$H_2N$	NH <sub>2</sub> HO 38 <sup>e</sup>		

249 **Table 2**: Reductive amination of aldehydes with **4** 

General reaction conditions: aldehyde (0.6 mmol), 4 (1 mol%), NaBH<sub>4</sub> (0.6 mmol),
NH<sub>4</sub>OOCCH<sub>3</sub> (6 mmol), NH<sub>4</sub>OH (0.3 mmol), EtOH (10 mL), 90°C, 24 hours. <sup>a</sup> Absence of 4,
but with added NaBH<sub>4</sub>. <sup>b</sup> H<sub>2</sub>(g) (30 bar), NH<sub>3</sub> (2M in MeOH). <sup>c</sup> Bis-alcohol product, ethylene
glycol. <sup>d</sup> Bis-aminated product, ethylene diamine. <sup>e</sup> Partially aminated product, ethanolamine.

Changes in the electronic and steric substrate environment only slightly affected the 255 conversions, however, slightly lower alcohol:amine chemoselectivities were observed. The 256 electron withdrawing 4-NO<sub>2</sub>-benzaldehyde and the less bulky propionaldehyde were gave 257 poor amine to alcohol selectivity (~1:1, entries 3,4). Complex 4 exhibited better stability in 258 solution, allowing for easier substrate coordination through its hemilabile P,O-metallacycle 259 ammine ligand system. However, it appears with the more electron-withdrawing substrates, 260 261 electron density is perturbed with less stability within the resulting substrate-adduct Ru(II)species, leading to catalytically non-active Ru(II)-species. The dialdehyde, glyoxal, were 262 similarly reductively aminated to give an additional product, the partially aminated 263 ethanolamine (entry 5). Complex 4 also appears to aid in the reduction of the bis-aldehyde 264 functionality to give ethylene glycol as an intermediate, followed by the less effective 265 amination reaction, to give a mono-aminated adduct as main product. 266

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### 268 3.3 <sup>1</sup>*H-NMR study*

The course of the reductive amination of benzaldehyde was evaluated using <sup>1</sup>H-NMR taken 269 over a 24 hour period, in order to gain more insight on the intermediate species formed 270 during the reaction. At time = 0 min (1 in Figure (a)), two signals are observed at  $\delta$  = 9.1 ppm 271 272 (aldehyde) and 7.1 (imine) (Figure 3(a)). Immediate imine formation is expected with high concentrations of the carbonyl moiety in an ammonia-saturated solution prior to reduction. 273 Upon addition of NaBH<sub>4</sub>, an (expected) immediate decrease in concentration of the aldehyde 274 is observed, along with an associated increase in corresponding alcohol concentration, and a 275 276 decrease in imine concentration (Figure 3(b)). At time = 80 min (4 in Figure (a)), Ru(II)catalyzed transfer hydrogenation of the formed alcohol is evident through a decreasing 277 278 concentration of the alcohol, and increasing concentrations of the ketone, imine, and amine. The continued formation of the amine, and low, but noticeable concentrations of the ketone 279 and imine throughout the course of the reaction is evident of the latter two species acting as 280 the intermediate species. The absence of acetaldehyde (from the transfer hydrogenation of 281 ethanol) and ethanamine, follows from the energetically unfavorable transformation of 282 ethanol (as opposed to the also present benzyl alcohol), into the ketone, followed by the 283 imine, and finally the amine. This is in accordance with the classical Ru(II)-mediated 284 reductive amination mechanism proposed [32-34], whereby relatively slowly formed ketone, 285 is followed by fast imine formation, and even faster reduction to the amine species. In 286 addition, similar to what Pingen et al. [32] found, under these reaction conditions the 287 reversible formation of the secondary imine is limited due to the higher nucleophilicity of the 288

formed primary amine, and as a result no secondary amine products were observed. The catalytic transformation of the benzyl alcohol species continues over the period of 24 hours to yield an eventual <sup>1</sup>H-NMR yield of 54% benzylamine.

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Figure 3: (a) Time-resolved <sup>1</sup>H-NMR of the reductive amination of benzaldehyde; (b)
Corresponding conversion of the reactant and intermediate species involved.

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From time = 600 min (8 in Figure (a)) onwards, a gradual decrease in catalyst efficiency is 297 observed through gradual downturn of amine formation and alcohol consumption. Hofmann 298 et al. [33] observed a moderate inhibitory effect of the amine product on the reaction rate, 299 which helps explain the slow, but gradual alcohol transformation. Furthermore, eventual 300 catalyst decomposition and/or poisoning due to the harsh reducing environment during 301 reaction are also not excluded. If, however, NaBH<sub>4</sub> is excluded from the reaction, and benzyl 302 alcohol is employed as the reduced form of the substrate, an interesting distribution of 303 products is observed (Figure 4). The transfer hydrogenation activity of 4 is better 304 demonstrated with 14% of the alcohol oxidized to benzaldehyde, along with concomitant 305 imine formation (19%). These two species are hardly observed during the <sup>1</sup>H-NMR time-306 resolved study, and is reasoned to be less efficiently hydrogenated due to the absence of 307 NaBH<sub>4</sub> and lower benzyl alcohol concentration. Overall, the absence of NaBH<sub>4</sub> had a minor 308 inhibitory effect on amine formation leading to a lower yield of benzyl amine (starting from 309 benzyl alcohol), but with a higher alcohol:amine selectivity (1:2.2). 310

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Figure 4: Amination of alcohols with NH<sub>3</sub>. General reaction conditions: benzyl alcohol (0.6 mmol), 4 (1 mol%), NH<sub>4</sub>OOCCH<sub>3</sub> (6 mmol), NH<sub>4</sub>OH (0.3 mmol), EtOH (10 mL), 90°C, 24 hours.

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320 *3.3 Mechanistic considerations* 

We are in agreement with the thorough experimental and computational findings of Schaub et 321 al. [34, 35] with respect to the need to include cationic Ru(II) species as the catalytically 322 active species in the reductive amination transformation. However, for our catalytic system, 323 we have adapted their mechanism to include neutral Ru(II)-P,O(H) metallacycles bearing a 324 hydride ligand as the catalytically active species (Figure 5). This mechanism is based on 325 experimental (<sup>1</sup>H- and <sup>31</sup>P-NMR, see Supplementary Information) evidence for partial 326 conversion of the Ru-P,O bound metallacycle to Ru-P-OH species, along with concomitant 327 hydride formation. This is inherent of the presence of both cationic and neutral Ru(II)-328 hydride species in the reaction mixture. 329



**Figure 5**: Neutral Ru(II)-hydride alcohol amination mechanism.

In agreement with both our experimental observations and those of Schaub et al. [34], the 332 active hydride species are formed via protonolysis with  $NH_4^+$  species. This leads to a 333 coordinatively unsaturated Ru(II) species bearing a hydride, one chelating P,O- phoshine, and 334 another monodentate (protonated) P-OH ligand. Similar to the common reductive amination 335 336 mechanism, a molecule of aldehyde reacts with ammonia to for the corresponding imine, which coordinates side-on to the 5-coordinate Ru species. Imine reduction via hydride 337 338 transfer, followed by coordination of a molecule of alcohol leads to the neutral octahedral Ru complex bearing a coordinated amine moiety. Cleavage of the  $\alpha$ -agostic hydride interaction 339 of the newly formed Ru-amide species has been proven to be the rate-determining step [34]. 340 Subsequent dissociation of the formed amine, oxidation of the coordinated alcohol to the 341 corresponding aldehyde via hydride transfer, leads to a neutral octahedral Ru-H complex with 342 the aldehyde side-bound. Dissociation of the aldehyde and subsequent association of a new 343 imine molecule completes the cycle. A similar mechanism also exists for cationic Ru species 344 present, which essentially leads to the same organic products, albeit with possible differences 345 in the rate-determining step, stability of all the cationic species involved, as well as the 346 overall efficiency of the transformation. 347

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#### 349 **4.** Conclusion

 $[RuH{PPh_2(2-OMeC_6H_4)}_2]BPh_4$ The novel complexes (3) and 350 two trans-351  $[Ru(NH_3)_2{PPh_2(2-OC_6H_4)}_2]$  (4) were synthesised from the previously reported complexes [RuH(1,5-cod)(NH<sub>2</sub>NMe<sub>2</sub>)<sub>3</sub>]BPh<sub>4</sub> and [RuCl(1,5-cod)(NH<sub>3</sub>)<sub>2</sub>(NH<sub>2</sub>NMe<sub>2</sub>)]BPh<sub>4</sub> respectively. 352 353 Ligand-assisted bis-demethylation occurs in the reaction mixture of 4 to yield the bisammine, bis-oxo containing ruthenacycles. Complexes 3 and 4 exhibits poor transfer 354 hydrogenation (and subsequent amination) activity with aryl ketones, while in contrast 355 performs better (in both transfer hydrogenation and reductive amination) when using aryl 356 aldehydes. A decent chemoselectivity was observed between ketones and aldehydes, and is 357 mainly ascribed to associated steric effects, and overall reactivity of aldehydes versus 358 ketones. The higher overall catalytic activity of 4 (as compared to 3) was attributed to the 359 higher solution stability of 4, the efficient hemi-labile P,O ligand system, as well as the 360 presence of the bis-ammine moieties that aided in additional provision of free NH<sub>3</sub> to the 361 catalytic cycle involved. 362

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- 369

### 370 Appendix A. Supplementary Information

- 371 CCDC numbers 1425248 (4) and 1485450 (benzylaminium cyclohexanoate, Supplementary
- 372 Information) contains the supplementary crystallographic data, which can be accessed from
- 373 The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.
- 374 Supplementary data to this article can be found in the online version,
- 375

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- 445 446

## Highlights

- Two novel cationic and neutral chelating phosphine Ru(II) complexes are reported.
- X-ray structure of the novel bis-ammine Ru(II) complex reported.
- High reductive amination activity for aldehydes.
- <sup>1</sup>H-NMR study and mechanistic considerations discussed.