Rational Design of Efficient Rhodium Catalysts for the Anti-Markovnikov Oxidative Amination of Styrene

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Cationic rhodium(I) complexes containing the flexible hemilabile phosphine ligand (3-ethoxypropyl)diphenylphosphine efficiently catalyzed the anti-Markovnikov oxidative amination of styrene in tetrahydrofuran at 80 °C to produce (*E*)-1-styrylpiperidine with turnover frequencies up to 75 h⁻¹ with excellent enamine selectivity (96%).

The direct addition of ammonia, primary or secondary amines to alkenes or alkynes is potentially the most efficient approach towards the synthesis of nitrogen-containing products.¹ The homogeneous transition-metal catalyzed hydroamination is emerging like an alternative route to the organic classic synthesis since this method represents the most atom economic process for the preparation of amines and enamines, important bulk and fine chemicals or building blocks in organic synthesis.² The most versatile catalysts for the intermolecular alkene hydroamination are based on late transition-metal that give rise either to amines, as a consequence of a formal N-H bond addition to the unsaturated carbon-carbon bond, or enamines, as a result of an oxidative amination. In both cases, the control of the regioselectivity is an important issue as the anti-Markovnikov products are of significant industrial interest.³

Palladium complexes catalyze the Markovnikov addition of amines to vinylarenes.⁴ In contrast, the regioselective anti-Markovnikov hydroamination of vinylarenes was observed with the systems [Ru(cod)(2-methylallyl)₂]/DPPPent/HOTf (DPPPent = 1,5-bis(diphenylphosphino)pentane⁵ and [Rh(cod)(DPEPhos)][BF₄] (DPEPhos = bis-(2-diphenylphosphinophenyl)ether), although with the later the oxidative amination to form enamines compete with hydroamination.⁶ Noteworthy, Beller *et al* have described the chemo- and regioselective oxidative anti-Markovnikov amination of vinylarenes under mild conditions using the catalytic system [Rh(cod)₂][BF₄]/2PPh₃.⁷ However, the efficiency was generally low and a maximum TOF of 1.5 turnovers per hour was attained using styrene and piperidine as secondary amine.⁸

We have recently reported the great activity of cationic rhodium(I) complexes containing flexible hemilabile functionalized phosphine ligands of the type Ph₂P(CH₂)_nZ (Z = OR, NR₂, SR) for the stereoregular phenylacetylene polymerization giving remarkably high number-average molecular weights.⁹ In the light of the active role of the hemilabile fragment in some of these systems we have also explored their potential for the design of efficient hydroamination catalysts. Preliminary catalyst screening showed a general positive effect on the catalytic activity and,

interestingly, a remarkable catalyst efficiency was observed with those systems based on the functionalized P,O-phosphine ligand (3-ethoxypropyl)diphenylphosphine, Ph₂P(CH₂)₃OEt.¹⁰ We report herein the design and optimization of an efficient rhodium catalyst for the regioselective anti-Markovnikov oxidative amination of styrene with piperidine, a benchmark reaction for the intermolecular alkene hydroamination.

We have prepared a series of mononuclear cationic rhodium complexes containing the ligand Ph₂P(CH₂)₃OEt (Chart 1). Complexes **1** and **3** were prepared by reaction of Ph₂P(CH₂)₃OEt with the solvato species [Rh(cod)(Me₂CO)_x]⁺ or [Rh(coe)₂(Me₂CO)_x]⁺, generated in situ, in the suitable molar ratio. Compound **2** was prepared by reaction of **1** with one molar equiv of PPh₃. The compounds were crystallized from slow diffusion of diethyl ether into concentrated solutions of the complexes in acetone and obtained as yellow-orange crystalline solids.

Chart 1

Complexes **1–4** have been fully characterized by elemental analysis, mass spectra and multinuclear NMR spectroscopy. The spectroscopic data are in agreement with the expected square planar geometry of the complexes. The number and multiplicity of the =CH resonances in the ¹³C{¹H} NMR spectra were particularly informative as both are sensitive to the molecular symmetry and the presence of a P-donor atom in *trans* position, respectively. The coordination of the –OEt fragment of the ligand (**1** and **4**) produces a downfield shift by 5–6 ppm of the resonance of the >CH₂ compared to complexes **2** and **3** which is diagnostic of the coordination mode of the hemilabile ligand. On the other hand, the ³¹P{¹H} NMR spectra of the complexes feature the expected doublet with a *J*_{P-Rh} in the range 140–150 Hz but two doublets of doublets for **2** in agreement with the presence of two different P-donor ligands. Also, the large *J*_{P-Rh} of 205 Hz for **4** evidences a *trans* ligand different from cod.

The structural analysis of **4**⁺ reveals the expected square-planar coordination around the rhodium atom with a *cis* disposition of the two chelate etherphosphine ligands. Interestingly, the existence of an intramolecular π - π interaction between two phenyl groups (G-G 3.939(3) Å, Ph-Ph dihedral angle 7.4(2)°) of different phosphines could be partially responsible of this arrangement.

Figure 1. Thermal ellipsoid (50% probability) plot of the cationic complex **4**. Selected geometrical data (bond lengths [Å] and angles [°]): Rh-P(1) 2.1735(10), Rh-P(2) 2.1880(11), Rh-O(1) 2.171(3), Rh-O(2) 2.166(3); P(1)-Rh-P(2) 98.49(4), P(1)-Rh-O(1) 90.58(8), P(1)-Rh-O(2) 169.09(8), P(2)-Rh-O(1) 170.60(8), P(2)-Rh-O(2) 90.36(8), O(1)-Rh-O(2) 80.90(11).

The hydroamination of styrene with piperidine using the catalysts precursors containing the $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}$ ligand was carried out under the optimized conditions set up by Beller *et al* for the catalytic system $[\text{Rh}(\text{cod})_2][\text{BF}_4]/2\text{PPh}_3$ (Table 1).^{7, 8} Thus, the reaction of piperidine with styrene (1:4 molar ratio) using a 2.5% of **1** in THF at 80 °C gave (*E*)-1-styrylpiperidine (73%) and 1-phenylethylpiperidine (2%), the anti-Markovnikov oxidative amination and hydroamination products, respectively (entry 3). A roughly equimolar amount of ethylbenzene (74%) coming from the hydrogenation of the styrene added in excess was also obtained as main product which is in agreement with its hydrogen acceptor role in the generally accepted mechanism for the oxidative amination¹¹ and related boration and silation of alkenes.¹² The attained piperidine conversion with catalyst **1** (75% in 20 h) improves the catalytic activity exhibited by the system $[\text{Rh}(\text{cod})_2]^+ / 2\text{PPh}_3$ (entry 1) with excellent enamine selectivity (97%), and also the performance of $[\text{Rh}(\text{cod})(\text{DPEPhos})]^+$ both in terms of activity and selectivity (entry 2), in spite of having only a P-donor ligand κ -P,O coordinated.

As expected a slight improvement of conversion (82%) was attained with catalyst **2** that contains mixed P,O-hemilabile and PPh_3 ligands (entry 4). However, further evidence of the positive effect of the hemilabile ligand comes from the great catalytic activity exhibited by catalyst **3a**, featuring two κ -P coordinated ligands, that produce similar conversion values in only 4 hours with similar enamine selectivity (entry 5). We have observed a marked counteranion effect on the catalytic activity of complexes $[\text{Rh}(\text{cod})\{\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}\}_2]\text{X}$ and in fact, conversions up to 92% (enamine selectivity 95%) have been attained using **3b** ($\text{X} = \text{PF}_6$) under the same conditions (entries 5–7). The GC/MS analysis of the catalytic solutions

resulting from the hydroamination experiments invariably showed the presence of a tiny peak at *m/z* mass of 191 that corresponds to 1-(cyclooctadien-1-yl)piperidine. This observation strongly supports that the hydroamination of the cod ligand in complexes **1-3** could be a requirement for the generation of the active catalytic species. Bearing this in mind, we anticipated the potential for higher catalytic activity of a cod free catalyst precursor and prompted us to the synthesis of complex $[\text{Rh}\{\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}\}_2][\text{PF}_6]$ (**4**) that holds two hemilabile ligands κ -P,O coordinated. In fact, complex **4** showed an unprecedented catalytic activity reaching a 96% conversion in only 2 hours with a 96% of enamine selectivity (entry 8).

Table 1. Rh-catalyzed hydroamination of styrene with piperidine^a

Entry	Catalyst	Time (h)	Yield (%) ^b			
			5	6	7	
1	$[\text{Rh}(\text{cod})_2]/2\text{PPh}_3^c$	20	55	57	0	
2	$[\text{Rh}(\text{DPEPhos})]^d$	72	63	63	37	
3	1	20	73	74	2	
4	2	20	80	83	2	
5	3a	4	79	81	3	
6	3b	4	88	88	4	
7	3c	4	66	64	4	
8	4	2	92	98	4	

^a Reaction conditions: styrene (4 mmol), piperidine (1 mmol), Rh catalyst 2.5 mol % relative to piperidine, THF (2.5 mL) at 80 °C. ^b Yields (referred to piperidine) were determined by GC analysis using tetradecane as internal standard. ^c ref 8 ^d ref 6

The influence of the catalyst loading, solvent and temperature on the catalytic performance by compound **4** has been studied in detail and is shown in Table 2. The course of the reaction of piperidine with styrene in the presence of 2.5 mol % of **4** in THF at 80 °C (entries 1-3) shows the gradual increase of conversion with time, while maintaining the enamine selectivity, which suggests that the amine byproduct is formed along with the main enamine product. Interestingly, the turnover frequency for enamine reached 75 h⁻¹ at 50% piperidine conversion (entry 1). By reducing the amount of catalyst from 2.5 to 1.25 mol % the expected activity decrease was accompanied by a slightly decrease of selectivity (92%, entry 4). Complete piperidine conversion in 1 hour can be achieved by using a catalyst loading of 5 mol % also with high enamine selectivity (entries 5 and 6). On the other hand, catalyst **4** is also active in toluene or dioxane although the activity with the later is lower (entries 7 and 8). The effect of the temperature has been studied in the range 60-100 °C (entries 2, 9 and 10). The temperature strongly influences the catalytic activity but not the enamine selectivity. Catalyst **4** showed a reasonable catalytic activity at 60 °C and a 47% of piperine conversion was attained in 2 hours. However, an upsurge in the catalytic activity was observed at higher temperatures and in fact, the piperidine conversion increase

from 66% to 83% (0.5 hours) when the temperature was raised from 80 to 100 °C.

Table 2. Oxidative amination of styrene with piperidine catalyzed by complex $[\text{Rh}\{\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}\}_2][\text{PF}_6]$ (**4**)^a

Entry	T ^a	Solvent	4 (%)	Time (h)	Conversion (%) ^b	Enamine:Amine ratio ^b
1	80	THF	2.5	0.25	49	96 : 4
2	80	THF	2.5	0.5	66	95 : 5
3	80	THF	2.5	1	93	96 : 4
4	80	THF	1.25	1	56	94 : 6
5	80	THF	5	0.5	86	94 : 6
6	80	THF	5	1	100	94 : 6
7	80	Toluene	2.5	1	86	95 : 5
8	80	Dioxane	2.5	1	70	97 : 3
9	60	THF	2.5	2	47	94 : 6
10	100	THF	2.5	0.5	83	94 : 6

^a Reaction conditions: styrene (4 mmol), piperidine (1 mmol), solvent (2.5 mL), catalyst loading relative to piperidine. ^b Determined by GC analysis using tetradecane as internal standard.

The outstanding hydroamination activity exhibited by complex **4** raises the question about the role of the hemilabile ligand along the reaction pathway. There is no doubt about the potential of the flexible $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}$ ligand for the reversible protection of a coordination site but also the stabilization of polar catalytic intermediates. Interestingly, the decoordination of the ether arms in **4** furnishes two accessible coordination sites in *cis* position as a result of the geometrical disposition of the hemilabile ligands. On the other hand, the notable difference in the catalytic activity exhibited by complexes **3** and **4** could be related to the highest concentration of catalytic active species as a consequence of the difficulty associated to their generation from **3** due to the presence of the cod ligand. Preliminary mechanistic studies by ^{31}P { ^1H } NMR ($\text{THF}-d_8$) have shown that in the presence of a moderate excess of piperidine compound **4** is easily converted at RT into $[\text{Rh}\{\text{Ph}_2\text{P}(\text{CH}_2)_3\text{OEt}\}_2(\text{piperidine})_2]$ (**8**). After heating of this solution at 70 °C for 2 hours the formation of a new predominant unsymmetrical species **9** became evident. Interestingly, compound **9** was competent for hydroamination and under catalytic conditions the addition of styrene resulted in the steady formation of (*E*)-1-styrylpiperidine along with ethylbenzene (^1H NMR evidence). In addition, the only P-containing species detectable under these conditions was **9**.

This result suggests that the mechanism of oxidative amination of styrene proceeds through the activation of the amine. However, the spectroscopic data strongly suggests that compound **9** could be a reactive neutral amido rhodium(I) complex (Scheme 1) formed by deprotonation by piperidine of either an amino ligand in **8** or an intermediate hydrido complex resulting from the oxidative addition of amine.¹³ In fact, the intermolecular transfer of amido ligands to unactivated olefins has been recently demonstrated.¹⁴ Further work concerning both the application scope of catalyst **4** and mechanistic studies are currently in progress.

Scheme 1

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Notes and references

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† Electronic supplementary information (ESI) available: Full experimental details for the synthesis and characterization of complexes **1–4**, spectroscopic data for **8** and **9**, the general procedure for the hydroamination catalytic experiments, and the crystallographic data in CIF format for complex **4**, CCDC XXXXXX. See: DOI: 10.1039/b000000x/

‡ Crystal data for complex **4**: $\text{C}_{34}\text{H}_{42}\text{F}_6\text{O}_2\text{P}_3\text{Rh}$, $M = 792.50$, crystal size $0.23 \times 0.08 \times 0.07 \text{ mm}^3$, orthorhombic, $Pbca$, $a = 18.813(2)$, $b = 17.919(2)$, $c = 20.796(2) \text{ Å}$, $V = 7010.14(14) \text{ Å}^3$, $Z = 8$, $D_c = 1.502 \text{ g cm}^{-3}$, $T = 100.0(2) \text{ K}$, Smart APEX diffractometer, $\mu(\text{Mo-K}\alpha) = 0.686 \text{ mm}^{-1}$, 7662 independent reflections (6198 observed), 562 parameters, $R_{\text{int}} = 0.069$, $R_1 = 0.055$, $wR(F^2) = 0.130$. CCDC XXXXXX.

- (a) M. Beller, A. Tillack J. Seayad, in *Transition Metals for Organic Synthesis*, ed. M. Beller, C. Bolm, Wiley-VCH, Weinheim, 2004, 2nd edn., vol. 2, 403; (b) J. P. Collman, B. M. Trost, T. R. Veerooven, in *Comprehensive Organometallic Chemistry*, vol. 8; eds. G. Wilkinson, F. G. A. Stone, Pergamon Press, Oxford, 1982, 892.
- (a) T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* 2008, **108**, 3795; (b) S. Hong, T. J. Marks, *Acc. Chem. Res.* 2004, **37**, 673; (c) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* 2002, **344**, 795. (a) T. E. Müller in *Encyclopedia of Catalysis*, vol 3; ed. I. Horváth, J. Wiley 2002; 492.
- J. Haggins, *Chem. Eng. News* 1993, **71**, 23.
- (a) M. Utsunomiya, J. F. Hartwig, *J. Am. Chem. Soc.* 2003, **125**, 14286; (b) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* 2000, **122**, 9546.
- (a) M. Utsunomiya, J. F. Hartwig, *J. Am. Chem. Soc.* 2005, **127**, 5756; (b) J. Takaya, J. F. Hartwig, *J. Am. Chem. Soc.* 2004, **126**, 2702.
- M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* 2003, **125**, 5608.
- M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller, O. R. Thiel, *Chem. Eur. J.* 1999, **5**, 1306.
- M. Beller, M. Eichberger, H. Trauthwein, *Angew. Chem., Int. Ed. Engl.* 1997, **36**, 2225.
- M. V. Jiménez, J. J. Pérez-Torrente, M. I. Bartolomé, E. Vispe, F. J. Lahoz, L. A. Oro, *Macromolecules* 2009, **42**, 8146.
- M. V. Jiménez, J. J. Pérez-Torrente, M. I. Bartolomé, L. A. Oro, *Synthesis* 2009, **11**, 1916.
- T. E. Müller, M. Beller, *Chem. Rev.* 1998, **98**, 675.
- (a) *ibid.*, *J. Am. Chem. Soc.* 1994, **116**, 866; (b) J. M. Brown, G. C. Lloyd-Jones, *J. Chem. Soc., Chem. Commun.* 1992, 710.
- J. Zhao, A. S. Goldman, J. F. Hartwig, *Science*, 2005, **307**, 1080.
- (a) J. W. Tye, J. F. Hartwig, *J. Am. Chem. Soc.* 2009, **131**, 14703; (b) P. Zhao, C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* 2005, **127**, 12066.