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Novel Amido-Complexes for the Efficient Asymmetric Hydrogenation of Imines

Kathrin Kutlescha,[a] Torsten Irrgang,[a,b] and Rhett Kempe[a,*]

[a] Lehrstuhl für Anorganische Chemie II, Universität Bayreuth, Universitätsstraße 30, 95440 Bayreuth, Germany
Fax: (+49)-921-55-2157; phone: (+49)-921-55-2541; e-mail: kempe@uni-bayreuth.de
[b] AIKAA-Chemicals GmbH, Kämmereigasse 11, 95444 Bayreuth, Germany

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Abstract: Novel N,N,P ligand stabilized rhodium complexes exhibiting high activities and enantioselectivities in the asymmetric hydrogenation of *N*-aryl imines are introduced. The ligands were synthesized from inexpensive starting materials and their modular design allows for the introduction of a broad variety of substitution patterns. Additionally, a rather low catalyst loading could be employed.

Keywords: amido-ligands; asymmetric catalysis; hydrogenation; imines; rhodium

Given that 80% of the pharmaceuticals in the product-pipeline are chiral and that the launch of enantiopure drugs will be facilitated, there is an increasing demand for chiral intermediates such as amines, alcohols or acids.[1] Asymmetric hydrogenation technologies, which are (atom) economic and easily up-scalable, provide an excellent access to those substances.[2] During the last decade various enantioselective imine hydrogenation catalysts were introduced,[3–7] most of them being cationic iridium complexes based on neutral P,N ligands, for instance, phosphine oxazolines or P,N ferrocenyls.[3] Neutral ligands might be easier replaced by strongly coordinating substrates like imines and consequently we became interested in developing anionic ligands for the enantioselective hydrogenation of imines.

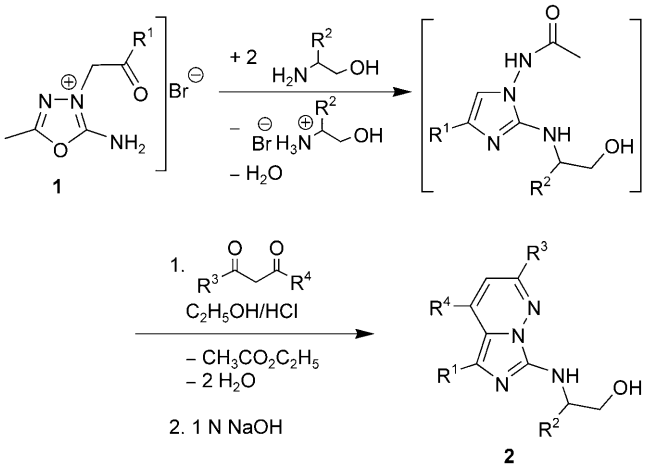
Recently, we introduced imidazo[1,5-*b*]pyridazine-substituted amido-ligands, which stabilize late and early transition metal complexes.[8] Chiral imidazo-[1,5-*b*]pyridazine-substituted amino alcohols **2** are of special interest thereby. They can be synthesized in a one-pot approach *via* the nucleophilic ring transformation of oxadiazolium halides **1** with amino alcohols followed by a cyclocondensation reaction with 1,3-diketones (Scheme 1).

The resulting iridium amido-complexes exhibit good activities and excellent enantioselectivities in the asymmetric ketone hydrogenation.[9]

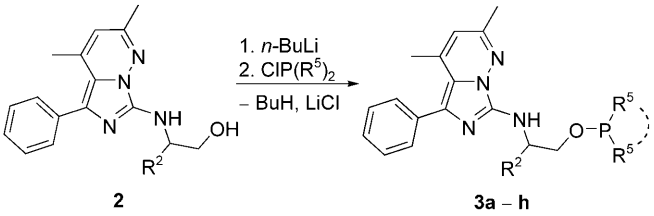
Herein, the synthesis of novel imidazo[1,5-*b*]pyridazine-substituted amines **3** is reported. Upon deprotonation they act as monoanionic tridentate amido-ligands and are suitable for the stabilization of group 9 metal complexes. The chiral amido-complexes **4** show high efficiency and very good enantioselectivity in the asymmetric hydrogenation of imines.[10]

The novel amines **3** can be synthesized *via* P-functionalization of **2** in good to excellent yields and high purities (Scheme 2). Lithiation with *n*-BuLi selectively occurs at the O-atom of the hydroxy group. Subsequently one equivalent of dialkylchlorophosphine, diarylchlorophosphine or ethylene chlorophosphite is added, giving rise to **3a–h** as orange viscous products.

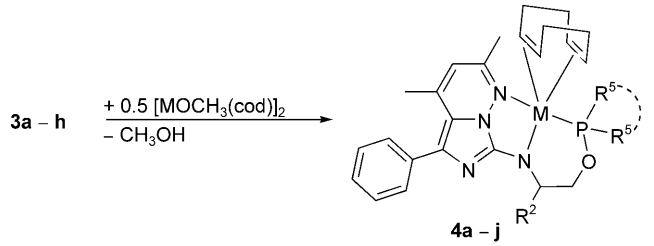
The amido-complexes **4a–j** can be obtained *via* an alcohol elimination route with $[MOCH_3(cod)]_2$[11]



Scheme 1. One-pot synthesis of **2**.



Scheme 2. Synthesis of **3a–h** (**3a**: $R^2 = i$-Bu, $R^5 = Ph$; **3b**: $R^2 = i$-Bu, $R^5 = i$-Pr; **3c**: $R^2 = i$-Bu, $R^5\widehat{R^5} = OCH_2CH_2O$; **3d**: $R^2 = Me$, $R^5 = i$-Pr; **3e**: $R^2 = Bn$, $R^5 = i$-Pr; **3f**: $R^2 = i$-Bu, $R^5 = Et$; **3g**: $R^2 = i$-Bu, $R^5 = t$-Bu; **3h**: $R^2 = i$-Bu, $R^5 = Cy$).



Scheme 3. Synthesis of amido-complexes **4a–j** (M = Rh: **4a:** $R^2 = i$-Bu, $R^5 = Ph$; **4b:** $R^2 = i$-Bu, $R^5 = i$-Pr; **4c:** $R^2 = i$-Bu, $R^5\widehat{R^5} = OCH_2CH_2O$; **4d:** $R^2 = Me$, $R^5 = i$-Pr; **4e:** $R^2 = Bn$, $R^5 = i$-Pr; **4f:** $R^2 = i$-Bu, $R^5 = Et$; **4g:** $R^2 = i$-Bu, $R^5 = t$-Bu; **4h:** $R^2 = i$-Bu, $R^5 = Cy$; M = Ir: **4i:** $R^2 = i$-Bu, $R^5 = i$-Pr; **4j:** $R^2 = i$-Bu, $R^5\widehat{R^5} = OCH_2CH_2O$).

(M = Ir, Rh) (Scheme 3). Addition of 0.5 equivalents of the metal precursor to a solution of **3a–h** in THF gives rise to **4a–j**, which is accompanied by a color change to blue/green. The NMR spectra show a single signal set for the deprotonated ligand and coordinated 1,5-cyclooctadiene. The Rh(I)-P coupling constant of 158.40 Hz (**4a**) is in accordance with the literature value.[12]

An X-ray crystal structure analysis of **4a** was performed to determine the molecular structure (Figure 1).

The monoanionic ligand coordinates the Rh atom *via* a five-membered chelate (Rh1, N4, C9, N2, N1). The complex is further stabilized by coordination of the P atom (P1–Rh1). Since the N4–Rh1 bond length of 2.233 Å is significantly shorter than the N1–Rh1 bond length (2.350 Å), the anionic charge of the ligand is localized at the amido N atom. The phenyl substituents of the P atom are orientated 93.16° to each other and point away from the imidazopyridazine plane.

Complexes **4b** and **c** (Rh) and **4i** and **j** (Ir) (Scheme 3) were utilized for the asymmetric hydrogenation of *N*-(1-phenylethylidene)aniline **5a** at 40 °C and 60 bar H_2 pressure (Table 1). Hereby, the dialkylphosphine-substituted rhodium amido-complex **4b** was the most promising catalyst system. Upon addition of KO-*t*-Bu complete conversion and 82% *ee*

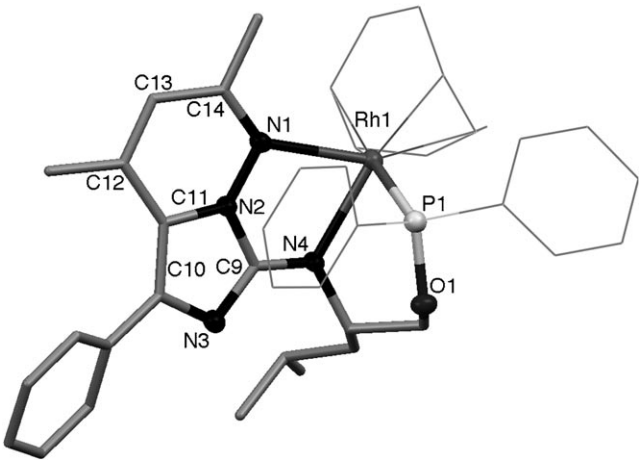


Figure 1. Molecular structure of **4a**; selected bond length [Å] and -angles [°]: N4–Rh1 2.233(2), N1–Rh1 2.349(2), P1–Rh1 2.2423(8), O1–P1 1.608(2); N1–Rh1–N4 74.02(8), N4–Rh1–P1 79.67(7), N2–N1–Rh1 107.84(16), C9–N4–Rh1 113.83(18), O1–P1–Rh1 112.30(8).

Table 1. Results of the asymmetric hydrogenation of **5a**.[a]

Entry	Pre-Catalyst	Base	Conversion[b] [%]	*ee*[c] [%]
1	**4b**	–	0	–
2	**4b**	KO-*t*-Bu	>99	82
3	**4c**	–	46	*rac*
4	**4c**	KO-*t*-Bu	41	21
5	**4i**	–	0	–
6	**4i**	KO-*t*-Bu	37	17
7	**4j**	–	0	–
8	**4j**	KO-*t*-Bu	98	30

[a] *Reaction conditions:* 0.1 mol% **4**, 24 h, 40 °C, 60 bar H_2.
[b] Determined *via* GC.
[c] Determined *via* HPLC.

could be achieved in 24 h with a catalyst loading of only 0.1 mol%.

The selectivity in the asymmetric hydrogenation of **5a** with **4b** could be increased from 82% (40 °C, 60 bar) to 90% (room temperature, 20 bar) by optimization of the reaction conditions. A pressure dependence of the selectivity was not observed (5–60 bar). The addition of an excess of KO-*t*-Bu (see Supporting Information) generates the best activity and enantioselectivity.

Due to the modular design of **4**, the steric and electronic properties of the ligand can easily be fine-tuned towards the substrate. Hereby the influence of amino alcohol and P substituents on the activity and enantioselectivity was investigated (Table 2).

The combination of electron-donating phosphine substituents (*i*-Pr, Cy) and amino alcohols (*i*-Bu) gave the best results in the hydrogenation of **5a** (Table 2, entries 2 and 7).

Table 2. Catalyst screening for the hydrogenation of **5a**.[a]

Entry	Pre-Catalyst	Conversion[b] [%]	*ee*[c] [%]
1	**4a**	62	70
2	**4b**	>99	90
3	**4d**	79	81
4	**4e**	63	84
5	**4f**	85	85
6	**4g**	88	86
7	**4h**	96	90

[a] *Reaction conditions:* 0.1 mol% **4**, KO-*t*-Bu, 24 h, 20 °C, 20 bar H_2.
[b] Determined *via* GC.
[b] Determined *via* HPLC.

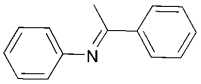
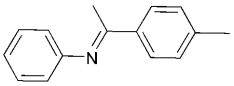
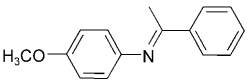
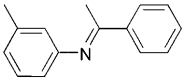
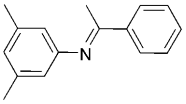
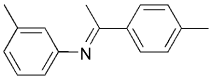
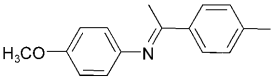
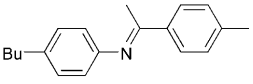
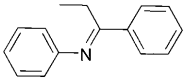
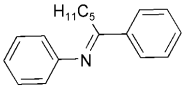
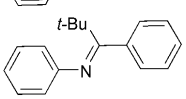
High enantioselectivities, which are similar to the best known literature systems[4d,e;3e,f], could be obtained in the asymmetric hydrogenation of various *N*-aryl imines **5** with **4b** (Table 3).

Due to the anionic nature of the supporting ligand, a higher hydrogenation efficiency in comparison to most of these literature systems was observed. The catalyst loading could be reduced to 0.1–0.2 mol% (typically 1 mol% in the literature).

The high efficiency and enantioselectivity could furthermore be verified in a preparative experiment. Therein 2.5 g of *N*-(1-phenylethyl)aniline were isolated (83% yield and 89% *ee*).

In conclusion, the reported amido-complexes represent a novel class of efficient and easily accessible catalysts for the asymmetric hydrogenation of imines.

Table 3. Hydrogenation of *N*-aryl imines with **4b**.[a]

Entry		Imine	Conversion[b] [%]	*ee*[c] [%]	Best literature[d] *ee* [%]
1[#]	**5a**		>99	90	95[4e]
2	**5b**		97	86	94[3f]
3	**5c**		>99	82	97[4e]
4	**5d**		>99	89	91[3f]
5*[#]	**5e**		98	91	99[4d]
6	**5f**		>99	87	–
7[#]	**5g**		>99	75	97[4e]
8[#]	**5h**		>99	83	–
9	**5i**		>99	76	78[3e]
10*[#]	**5j**		>99	74	–
11*	**5k**		>99	57	–

[a] *Reaction conditions:* 0.1 mol% (* 0.2 mol%) **4b**, KO-*t*-Bu, 48 h ([#] 24 h), 20 °C, 20 bar H_2.
[b] Determined *via* GC.
[c] Determined *via* HPLC.
[d] *Literature conditions*:[3e] 0.5 mol% Ir complex, 25 °C, 20 bar H_2; [3f] 1 mol% Ir complex, 10 °C, 1 bar H_2. [4d] 1 mol% $[Ir(cod)_2]BArF$, 2 mol% (*S*)-PipPhos, room temperature, 1 bar H_2. [4e] 1 mol% Ir-complex, 20 °C, 20 bar H_2.

Due to the modular ligand design, broad substitution patterns can be realized. The high efficiency and good selectivity combined with the novel structural motif opens up new prospects for the enantioselective hydrogenation of imines.

Experimental Section

General Procedure for the Asymmetric Hydrogenation

Stock solutions of the pre-catalysts (3.01 μmol/mL) were prepared in THF *via* alcohol elimination reaction of the ligand (stock solution in THF) and 0.5 equiv. of $[MOCH_3(cod)]_2$ (M = Rh, Ir). Stock solutions of the imines (1.51 mmol mL^{-1}) were prepared in THF. The solutions were prepared and stored in a glove box. A high-pressure steel autoclave (Parr Instruments; 300 mL, 200 bar, 350 °C) with an aluminum insert for multiple reaction tubes (5 or 20) was taken into a glove box. Then the reaction tube (placed in a 20- or 5-well insert for the autoclave, equipped with a magnetic stir bar) was loaded with additive (base if required), the pre-catalyst-solution (e.g., 200 μL = 0.1 mol%) and 400 μL (0.60 mmol) of the substrate solution. Then the autoclave was sealed and taken out of the glove box. The autoclave was attached to a high-pressure hydrogen line and purged with H_2. The autoclave was sealed under the appropriate H_2 pressure and the mixture was stirred for, for example, 24 h at the appropriate pressure at room temperature or at the appropriate temperature (external heating mantle). In order to stop the hydrogenation reaction, the pressure was released and water and dodecane (standard for GC) were added to the reaction solution. The samples were extracted with diethyl ether (3 mL) and the organic phase was centrifugalized at 12,000 rpm and filtered through 0.2 μm PTFE-syringe filters. This solution was directly used for determination of the conversion (GC, Lipodex E or Chirasil-DEX column). For HPLC (Chiralpak IB column) purposes the samples were diluted (40×) with diethyl ether (determination of *ee*).

Acknowledgements

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References

[1] M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, Th. Zelinski, *Angew. Chem.* **2004**, *116*, 806–843; *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[2] I. C. Lennon, P. H. Moran, *Curr. Opin. Drug Disc. Dev.* **2003**, *6*, 855–875.

[3] For Ir catalysts with P,N ligands, see: a) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 4003–4009; b) W.-J. Lu, Y.-W. Chen, X.-L. Hou, *Adv. Synth. Catal.* **2010**, *352*, 103–107; c) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449–5453; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349; d) M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089–3092; e) A. Trifonova, J. S. Diesen, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 2318–2328; f) S. F. Zhu, J. B. Xie, Y. Z. Zhang, S. Li, Q. L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886–12891; g) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736–7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567; h) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827; i) C. Blanc, F. Agbossou-Niedercorn, G. Nowogrocki, *Tetrahedron: Asymmetry* **2004**, *15*, 2159–2163; j) P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, 833–836; k) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40–44; l) S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, *J. Am. Chem. Soc.* **1999**, *121*, 6421–6429; m) P. Schnider, G. Koch, R. Pretot, G. Z. Wang, F. M. Bohnen, C. Kruger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887–892.

[4] For miscellaneous Ir catalysts, see: a) G. Hou, R. Tao, Y. Sun, X. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2010**, *132*, 2124–2125; b) W. Li, G. Hou, M. Chang, X. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 3123–3127; c) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C.-Y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883; d) N. Mrsić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358–8359; e) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451; f) A. Dervisi, C. Carcedo, L. Ooi, *Adv. Synth. Catal.* **2006**, *348*, 175–183; g) T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289–2292; h) S. Vargas, M. Rubio, A. Suarez, D. del Rio, E. Alvarez, A. Pizzano, *Organometallics* **2006**, *25*, 961–973; i) B. Pugin, H. Landert, F. Spindler, H. U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 974–979; j) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533–3536; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; k) R. Sablong, J. A. Osborn, *Tetrahedron: Asymmetry* **1996**, *7*, 3059–3062.

[5] For titanocene catalysts, see: a) M. Ringwald, R. Sturmer, H. H. Brintzinger, *J. Am. Chem. Soc.* **1999**, *121*, 1524–1527; b) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952–8965; c) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714; d) C. A. Willoughby, S. L. Buchwald, *J. Org. Chem.* **1993**, *58*, 7627–7629; e) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564.

[6] For Ru catalysts, see: a) P. Cheruku, T. L. Church, P. G. Andersson, *Chem. Asian J.* **2008**, *3*, 1390–1394; b) M. Jackson, I. C. Lennon, *Tetrahedron Lett.* **2007**, *48*, 1831–1834; c) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; d) C. J. Cobley, E. Foucher, J.-P. Lecouve, I. C. Lennon, J. A. Ramsden, G. Thominot, *Tetrahedron: Asymmetry* **2003**, *14*, 3431–3433; e) A. B. Charette, A. Giroux, *Tetrahedron Lett.* **1996**, *37*, 6669–6672; f) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117–4120.

[7] For Rh catalysts, see: a) D. S. Matharu, J. E. D. Martins, M. Wills, *Chem. Asian J.* **2008**, *3*, 1374–1383; b) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736–

7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567; c) F. Spindler, H. U. Blaser, *Adv. Synth. Catal.* **2001**, *343*, 68–70; d) V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron: Asymmetry* **1999**, *10*, 4009–4015; e) R. Sablong, J. A. Osborn, *Tetrahedron Lett.* **1996**, *37*, 4937–4940; f) G. J. Kang, W. R. Cullen, M. D. Fryzuk, M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266–6267; g) J. Bakos, A. Orosz, B. Heil, M. Laghmari, P. Lhoste, D. Sinou, *J. Chem. Soc. Chem. Commun.* **1991**, 1684–1685; h) A. G. Becalski, W. R. Cullen, M. D. Fryzuk, B. R. James, G. J. Kang, S. J. Rettig, *Inorg. Chem.* **1991**, *30*, 5002–5008; i) B. R. James, J. P. Kutney, *J. Chem. Soc. Chem. Commun.* **1988**, 1466–1467.

[8] a) T. Irrgang, R. Kempe, *Eur. J. Inorg. Chem.* **2005**, 4382–4392; b) K. Kutlescha, T. Irrgang, R. Kempe, *New J. Chem.* **2010**, *34*, 1954–1960.

[9] a) R. Kempe, T. Irrgang, D. Friedrich, *PCT Int. Appl.* WO/061663 A1, **2008**; b) T. Irrgang, D. Friedrich, R. Kempe, *Angew. Chem.* DOI: 10.1002/anie.201004665.

[10] R. Kempe, T. Irrgang, K. Kutlescha, *Patent Application* 210ak01.DE.

[11] R. Uson, L. A. Oro, J. A. Cabeza, *Inorg. Synth.* **1985**, 23, 126–130.

[12] Selected examples for Rh(I)-P coupling constants: a) C. Borriello, M. E. Cucciolito, A. Panunzi, F. Ruffo, *Inorg. Chim. Acta* **2003**, 283–244; b) I. D. Kostas, *J. Organomet. Chem.* **2001**, 90–98; c) C. J. Elsevier, B. Kowall, H. Kragten, *Inorg. Chem.* **1995**, *34*, 4836–4839; d) M. Bressan, F. Morandini, P. Rigo, *Inorg. Chim. Acta* **1983**, L139–L142.

