Transfer Hydrogenation of Acetophenone Catalyzed by Half-Sandwich Ruthenium(II) Complexes Containing Amino Amide Ligands. Detection of the Catalytic Intermediates by Electrospray Ionization Mass Spectrometry

Paolo Pelagatti,* Mauro Carcelli, Francesca Calbiani, Claudio Cassi, Lisa Elviri, Corrado Pelizzi, Umberto Rizzotti, and Dominga Rogolino

Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, Università degli Studi di Parma, Parco Area delle Scienze 17/A, 43100 Parma, Italy

Received June 23, 2005

A series of natural amino acid (alanine, valine, phenylalanine, and isoleucine) amides have been synthesized and fully characterized. They have been used as supporting ligands in the Ru(II)-catalyzed asymmetric transfer hydrogenation (*ath*) of acetophenone in the presence of *i*-PrOH/KOH. Secondary amides impart high reactivity to the corresponding Ru(II) complexes, with TOFs up to 1680 h^{-1} and ee's up to 47%. The amino acid and the substituents of the amide nitrogen govern the activity and the enantioselectivity of the catalytic processes. The precatalysts obtained by reacting (L)-phenylalanine *p*-anisidineamide and (L)-valine *o*-anisidineamide with $[Ru(p\text{-cymene})Cl_2]_2$ have been isolated and characterized as the *half-sandwich* complexes [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-aminoamidato)Cl] (**10** and **11**, respectively). An ESI-MS study conducted on the acetophenone reduction catalyzed by **11** has led to the detection of the organometallic intermediates involved in the catalytic cycle: the precatalyst **11**, the 16e⁻ complex [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-diamide)] **12**, and the hydride [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-aminoamidato)H] **13**.

Introduction

The asymmetric reduction of prochiral ketones using catalytic hydrogen-transfer conditions represents a mild and highly attractive route for the formation of enantiomerically enriched secondary alcohols, an important class of fine chemicals.[1] Recently, (η^6-arene)Ru^{II}(LL′) complexes (LL′ = chiral amino alcohols[2] or chiral 1,2-diamines[3]) have been successfully used in asymmetric transfer hydrogenation (*ath*), reaching excellent productivities and enantiomeric excesses.[4] α-Amino acids, one of the cheapest and most readily available classes of natural chiral compounds, have been deeply used as reagents in the synthesis of optically active molecules,[5] but they have found limited applications as ligands in homogeneous catalysis.[6] As regards the *ath* reaction, amino acid-based Ru(II) catalysts count a limited number of reports,[7] and the same is true for amino acid amides, for which the literature is limited to some proline derivatives[8] and peptide-analogue ligands.[9]

Amino amides seem to appear promising as ligands for the *ath* reaction for several reasons: (i) they can be

* To whom correspondence should be addressed. E-mail: paolo.pelagatti@unipr.it.

(1) *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; John Wiley & Sons: Chichester, 1997.

(2) (a) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (b) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226. (c) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749. (d) Alonso, D. A.; Nordin, S. J. M.; Roth, P.; Tarnai, T.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 3116. (e) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818.

(3) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841.

(4) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem Rev*. **1992**, *92*, 1051. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res*. **1997**, *30*, 97. (d) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(5) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(6) (a) Joó, F.; Trócsányi, E. *J. Organomet. Chem.* **1982**, *231*, 63. (b) Laidler, D. A.; Milner, D. J. *J. Organomet. Chem.* **1984**, *270*, 121. (c) Griffin, J. H.; Kellogg, R. M. *J. Org. Chem.* **1985**, *50*, 3261. (d) Nakagawa, M.; Nakao, H.; Watanabe, K. *Chem. Lett.* **1985**, 391. (e) Colonna, S.; Manfredi, A.; Spadoni, M.; Casella, L.; Gullotti, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 71. (f) Mori, A.; Ohno, H.; Nitta, H.; Tanaka, K.; Inoue, S. *Synlett* **1991**, 563. (g) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227. (h) Mori, A.; Abe, H.; Inoue, S. *Appl. Organomet. Chem*. **1995**, *9*, 189.

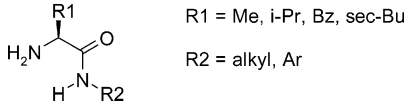
(7) (a) Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Chem. Lett*. **1998**, 491. (b) Carmona, D.; Lahoz, F. J.; Atencio, R.; Oro, L. A.; Lamata, M. P.; Viguri, F.; José, E. S.; Vega, C.; Reyes, J.; Joó, F.; Kathó, Á. *Chem. Eur. J.* **1999**, *5*, 1544. (c) Kathó, A.; Carmona, D.; Viguri, F.; Remacha, C. D.; Kovács, J.; Joó, F.; Oro, L. A. *J. Organomet. Chem.* **2000**, *593*−*594*, 299. (d) Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Appl. Organomet. Chem*. **2001**, *15*, 699. (e) Carmona, D.; Lamata, M. P.; Viguri, F.; Dobrinovich, I.; Lahoz, F. J.; Oro, L. A. *Appl. Synth. Catal.* **2002**, *344*, 499.

(8) (a) Rhyoo, H. Y.; Yoon, Y.; Park, H.; Chung, Y. K. *Tetrahedron Lett*. **2001**, *42*, 5045. (b) Faller, J. W.; Lavoie, A. R. *Organometallics* **2001**, *20*, 5245. (c) Rhyoo, H. Y.; Park, H.; Chung, Y. K. *Chem. Commun*. **2001**, 2064. (d) Rhyoo, H. Y.; Park, H.-J.; Suh, W. H.; Chung, Y. K. *Tetrahedron Lett.* **2002**, *43*, 269. (e) Burguete, M. I.; Collado, M.; Escorihuela, J.; Galindo, F.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Tetrahedron Lett*. **2003**, *44*, 6891.

(9) (a) Pastor, I. M.; Västilä, P.; Adolfsson, H. *Chem. Commun*. **2002**, 2046. (b) Bøgevig, A.; Pastor, I. M.; Adolfsson, H. *Chem. Eur. J.* **2004**, *10*, 294.

10.1021/om050519+ CCC: $30.25
Publication on Web 10/18/2005

Scheme 1. General Scheme of the Amino Amides



easily made by standard synthetic protocols; (ii) they contain two coordinating nitrogens connected through a chiral backbone; (iii) their steric properties can be tuned by the selection of the appropriate α-carbon substituents (R1, Scheme 1); (iv) with the exception of the tertiary amides, they are protic ligands able to form robust metal complexes under basic conditions. Recently, we have reported that the novel half-sandwich complex [Ru(η^6-*p*-cymene)(κ^2-*N*,*N*′-(L)-phenylalanineamido)Cl][10] is an active catalyst in the reduction of ketones in the presence of *i*-PrOH/*t*-BuOK. Unfortunately, a very low ee has been obtained with acetophenone. The observed activity has however encouraged us to investigate other amino amides as supporting ligands in *ath*. Our attention has immediately been directed to the secondary amides, since they present an additional attractive possibility of functionalization through the R2 substituent (Scheme 1). This allows a further tuning of their steric and electronic properties or the introduction of an additional chiral center. Then, a series of secondary amides of natural amino acids (alanine, valine, phenylalanine, and isoleucine) has been synthesized and characterized; for the sake of comparison, the tertiary amide (L)-valine diethylamide has also been prepared.

In the design of the ligands, amino acid precursors with additional coordinating moieties on R1 have been avoided in order to obtain pure bidentate ligands. Phenylglycine derivatives have also been avoided on the basis of their tendency to racemize under basic conditions.[10]

The general structure of the secondary amides is depicted in Scheme 1, and they are collected in Table 1.

All the amino amides have been used as chiral supporting ligands in the Ru(II)-catalyzed *ath* from *i*-PrOH to acetophenone, in the presence of KOH as cocatalyst (Scheme 2).

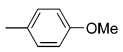
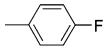
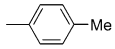
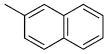
In all the cases [Ru(η^6-*p*-cymene)Cl_2]$_2$ has been used as ruthenium source and the active catalysts have been generated in situ. The experimental conditions have been optimized in terms of Ru:base and Ru:ligand molar ratio, Ru−ligand precontact time, and temperature.

To get information about the nature of the precatalytic species, the complexes deriving from the reactions between (L)-phenylalanine *p*-anisidineamide (**4b**) and (L)-valine *o*-ansidineamide (**3c**) with [Ru(*p*-cymene)Cl_2]$_2$ have been isolated and characterized. Moreover, an ESI-MS study conducted on the acetophenone reduction catalyzed by **11** has allowed the identification of all the Ru-containing intermediates involved in the catalytic cycle.

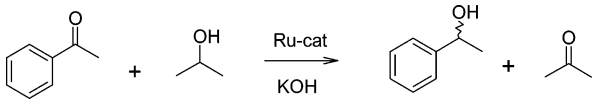
Results and Discussion

Synthesis of the Ligands. The synthesis of the ligands has been accomplished as illustrated in Scheme 3. Treatment of the previously activated Boc-protected α-amino acids with the appropriate amines has allowed the isolation of the corresponding Boc-protected amino amides **1a**−**k**, **2a**,**b**,**f**−**j**, **5**, and **6** (Table 1). Initially, two different coupling agents have been tested, DCC (dicyclohexylcarbodiimide) and triethylamine/ethylchloroformiate (methods A and B in Scheme 3).[11] The products obtained with the different procedures are equivalent in terms of optical as well as analytical purity, but since higher yields have been obtained with method A, this has been more widely used. To remove any doubt about a possible racemization during the synthesis of the Boc-protected ligands, the commercially available (L)-phenylalanine 2-naphthylamide has been prepared. A comparison of the specific alphas indicates that the coupling occurs with retention of configuration ($[\alpha]_D^{25}$ = +87° vs +83° of the commercial product, *c* = 1, MeOH). Removal of the protecting group with trifluoroacetic acid has led to the final amino amides **3a**−**k**, **4a**,**b**,**f**−**j**, **7**, and **8** in good yields. In some cases (**3a**, **3c**, **3f**, **3h**, **4g**, and **4h**), the ligands have been isolated as salts (trifluoroacetate or chloride, see Experimental Section).

Table 1. Amino Amide Ligands and BOC-Protected Precursors

BOC-protected	Ligand	R1	R2
1a/2a	**3a/4a**	i-Pr/Bz	
1b/2b	**3b/4b**	i-Pr/Bz	
1c	**3c**	i-Pr	
1d	**3d**	i-Pr	
1e	**3e**	i-Pr	
1f/2f	**3f/4f**	i-Pr/Bz	
1g/2g	**3g/4g**	i-Pr/Bz	$C(CH_3)_3$
1h/2h	**3h/4h**	i-Pr/Bz	
1i/2i	**3i/4i**	i-Pr/Bz	
2j	**4j**	Bz	
5	**7**	Me	
6	**8**	sec-Bu	

Scheme 2. Hydrogen Transfer from *i*-PrOH to Acetophenone



(10) Pelagatti, P.; Bacchi, A.; Calbiani, F.; Carcelli, M.; Elviri, L.; Pelizzi, C.; Rogolino, D. *J. Organomet. Chem.*, in press.

(11) (a) Christoffers, J.; Mann, A. *Chem. Eur. J.* **2001**, *7*, 1014. (b) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447.

Scheme 3. Synthesis of the Amino Amide Ligands

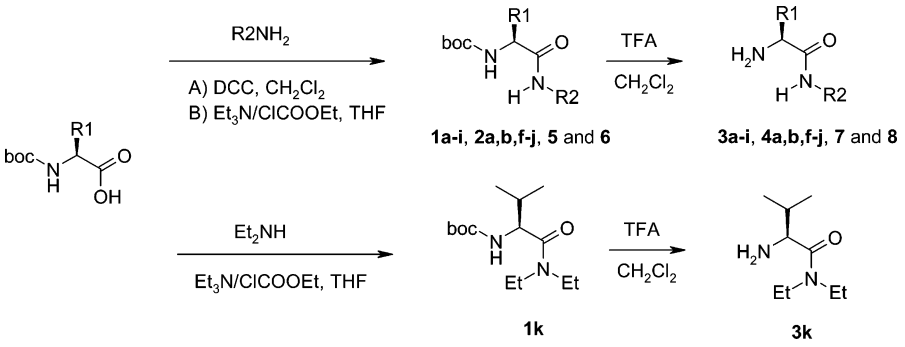
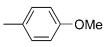


Table 2. Catalytic *ath* of Acetophenone at 25 °C[a]

Ligand	R1	R2	Conversion(%)[b]	*ee*(*R*, %)	TOF(h^{-1})[c]
3b	i-Pr		66	26	132
4j	Bz		83	5	166

[a] Conditions: solvent = *i*-PrOH; Ru:ketone:KOH 1:100:2. [b]30 min of reaction; determined by GC monitoring. [c]TOF = (mol product/mol Ru) × h^{-1}.

Reduction of Acetophenone. Since Boc-protected dipeptide analogues have been successfully employed as supporting ligands in the *ath* of ketones,[9] we have first tested the Boc-protected amino amides **1a** and **2a**. These have been dissolved in 2-propanol, and [Ru(*p*-cymene)Cl_2]$_2$ has been added (Ru:Boc-amide = 1:1 molar ratio). The solution has then been stirred at room temperature for 40 min, after which time acetophenone and KOH have been added (Ru:ketone:KOH = 1:100:2 molar ratio). With both ligands, the addition of the base has not provoked any color change of the starting orange-yellow solution, and no conversion has been observed after 24 h. The same has been observed by using a Ru:KOH = 1:4 molar ratio. Raising of the temperature to 90 °C (referred to the oil bath) has led to decomposition.

Our attention has then been directed to the amino amides **3a**−**k** and **4a**,**b**,**f**−**j**. Acetophenone and KOH have been added after having reacted [Ru(*p*-cymene)-Cl_2]$_2$ with the ligand for 40 min at room temperature (Ru:ketone:KOH = 1:100:2 molar ratio; when the saline forms of the amino amides have been used, an extra equivalent of KOH has been added). In general, a Ru:KOH = 1:1 molar ratio is not sufficient to trigger the reaction. The first test has been conducted with the tertiary amide (L)-valine diethylamide **3k** at room temperature. After the addition of KOH the starting orange-yellow solution has not changed color, and no consumption of acetophenone has been observed within the next 24 h. In contrast, with the ligands **3b** and **4j**, both secondary amides, the initial orange-yellow solutions have turned red immediately after the addition of KOH; after 30 min of reaction 66% and 83% conversions to 1-phenylethanol have been obtained (Table 2). In both the cases the *R*-isomer of 1-phenylethanol has been preferentially formed, with ee's = 26% and 5%, respectively. Although these values are far from satisfactory, the TOFs are rather good (132 and 166 h^{-1} for **3b** and **4j**, respectively). In fact they are certainly higher than those obtained with similar ligands, like amino acids,[7] proline amide derivatives,[8] and tosylated 1,2-diamines[3] under comparable conditions. The unreactivity of **3k** is indicative of the importance of the protic character of the ligands: the amidic function deprotonation is essential for the formation of a stable Ru−N−C−C(O)−N chelation ring, a necessary prerequisite for catalysis (the catalytic activity of [Ru(*p*-cymene)Cl_2]$_2$ under the applied experimental conditions is negligible). The catalytic activity is greatly enhanced if the reactions are conducted at 90 °C (referred to the oil bath), without detriment of the ee's (entries 3 and 10, Table 3). In both cases in fact, conversions higher than 90% have been obtained after 15 min of reaction, with TOFs of 392 and 368 h^{-1} with **3b** and **4j**, respectively (TOF values up to 1680 h^{-1} have been obtained with a Ru:acetophenone = 1:1000 molar ratio with **3b** under the same experimental conditions). For this reason, all the other amino secondary amides have been used at 90 °C, and the conversions have been checked after 15 min of reaction. The catalytic results are collected in Table 3.

Table 3. Catalytic *ath* of Acetophenone at 90 °C[a]

entry	ligand	conversion (%)[b]	ee (%)	TON[c]	TOF (h^{-1})[d]
1	**3a**	70	30(*R*)	70	280
2	**4a**	86	17(*R*)	86	344
3	**3b**	98	33(*R*)	100	392
4	**4b**	98	10(*R*)	100	392
5	**3c**	98	30(*R*)	100	392
6	**3d**	98	23(*R*)	100	392
7	**3e**	96	33(*R*)	96	384
8	**3f**	77	22(*R*)	77	308
9	**4f**	87	13(*R*)	87	348
10	**4j**	92	5(*R*)	92	368
11	**3g**	30			120
12	**4g**	34			136
13	**3h**	61	12(*S*)	61	244
14	**4h**	73	19(*S*)	73	292
15	**3i**	44	45(*R*)	44	176
16	**4i**	76	27(*R*)	76	304
17	**7**	95	30(*R*)	95	380
18	**8**	46	47(*R*)	46	184
19	**9**	42[e]	3(*R*)	42	8.4

[a] Conditions: solvent = *i*-PrOH; Ru:ketone:KOH molar ratio = 1:100:2. [b]15 min. of reaction; determined by GC monitoring. [c]TON = mol product/mol Ru. [d]TOF = TON/h. [e]5 h of reaction.

The ligands **3a**−**g** and **4a**,**b**,**f**,**g**,**j**, containing only one chiral center, generate active catalysts that in some cases cause the nearly complete conversion of the substrate, with TOFs up to 392 h^{-1} (entries 3−6, Table 3). Disappointingly, the ee's remain unsatisfactory (up to 33% with ligands **3b** and **3e**, entries 3 and 7 in Table 3). The aliphatic secondary amides **3g** and **4g** lead to

Table 4. Catalytic Reduction of Acetophenone after 5 min of Reaction[a]

entry	ligand	conversion (%)[b]	ee (*R*,%)	TOF (h^{-1})[c]
1	**3a**	77	34	924
2	**3b**	70	30	840
3	**3d**	64	29	768
4	**3e**	75	33	900

[a] Conditions: solvent = *i*-PrOH; *T* = 90 °C; Ru:ketone:KOH molar ratio = 1:100:2. [b]Determined by GC monitoring. [c]TOF = TON/h.

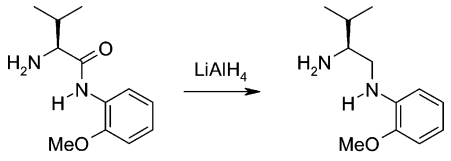
the lowest conversions with formation of racemates of 1-phenylethanol (ee ≤ 1%, entries 11 and 12, Table 3). This can be attributed to two factors: the excessive steric hindrance of the *t*-Bu group or, more likely, the low acidity of the amide proton that disfavors the formation of a stable chelation ring. As regards electronic effects, both electron-donating (MeO or Me, entries 3 and 7, Table 3) and electron-withdrawing (F, entry 6 in Table 3) groups increase the reaction speed in comparison with **3a** and **4a** (entries 1 and 2, Table 3). The *para* or *ortho* position of the MeO group in the phenyl ring does not affect the reaction course, either in terms of conversion or in terms of ee (ligands **3b** and **3c**, entries 3 and 5, Table 3). A moderate increase of the ee, the conversion being practically equal, is instead observed on passing from (L)-phenylalanine 2-naphthylamide to (L)-phenylalanine 1-naphthylamide (entries 10 and 9, Table 3), probably because of steric effects. In general, the ligands deriving from (L)-phenylalanine are less capable of transferring chirality than the (L)-valine derivatives, and this is in accord with the general observation that more branched substituents are more efficient in asymmetric catalysis. In all cases, (*R*)-1-phenylethanol is preferentially produced, as commonly observed with the natural amino acid-based Ru(II) catalysts.[7,8] The ee's do not vary with time, as indicated by the catalytic results collected with **3a**, **3b**, **3d**, and **3e** after 5 min of reaction (Table 4); in these cases conversions higher than 60% have always been obtained (TOFs up to 924 h^{-1}), indicating that the reactions start immediately after the addition of KOH without any induction time.

After two consecutive catalytic runs with **3a**, **3d**, **4a**, **4b**, and **4j**, the activities and the ee's have not significantly diminished (Table S1 of the Supporting Information). However, a third catalytic run is possible only with the phenylalanine derivatives, since decomposition has been observed with **3a** and **3d**.

To verify if the low ee's were due to a temperature-induced ligand racemization, the temperature has been varied in different stages of the catalysis. Hence, the ligand **3e** has been reacted with $[Ru(p\text{-cymene})Cl_2]_2$ at 90 °C, and the resulting solution has been cooled at 0 °C prior to the addition of the ketone and KOH; 36% conversion with ee = 44% has been obtained after 18 h of reaction. When also the precatalyst has been formed at 0 °C, 43% conversion and ee = 44% have been obtained after 24 h. The modest increments of the ee's observed in both cases with respect to the standard procedure (entry 7, Table 3) rule out any significant racemization during the precatalyst formation or during the reduction process.

With the ligand **3e** other catalytic parameters have been varied, like Ru concentration, Ru−ligand contact time, and Ru−ligand molar ratio. Lowering of the Ru concentration, from 1.6 mM (the standard concentration in this work) to 1 mM, has not significantly varied either the ee (from 33% to 31%) or the conversion (from 96% to 93%, Table S2 of the Supporting Information). The use of a Ru:ligand = 1:2 molar ratio has led to the same catalytic results obtained with a Ru:ligand = 1:1 molar ratio, in terms of both conversion and ee. In contrast, a Ru:ligand = 1:4 molar ratio has completely inhibited the catalysis (Table S3 of the Supporting Information). This indicates that the catalytically active molecular species contains a Ru bound to one ligand molecule.

Scheme 4. Synthesis of the Ligand 9



3c **9**

The amide functionality imparts a unique reactivity to the in situ-generated Ru catalysts, as evidenced by the low activity found for the catalyst containing the diamine **9** (**9** has been obtained by reduction of **3c** with $LiAlH_4$, Scheme 4).

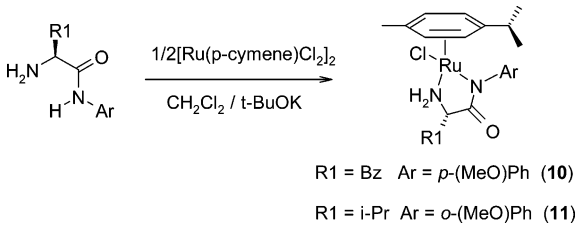
After 5 h of reaction in fact, 42% conversion and ee = 3% in favor of (*R*)-1-phenylethanol (entry 19, Table 3) have been obtained. An increase of the amount of KOH (Ru:KOH = 1:4 molar ratio) has slowed the reaction further (10% conversion after 30 min, racemate).

To have a comparison between the activities of the Ru-amino amide and the Ru-amino acid catalysts, the reduction of acetophenone has been carried out using (L)-phenylalanine as supporting ligand. Under standard conditions, 50% conversion (TOF = 200 h^{-1}) and ee = 15% in favor of (*R*)-1-phenylethanol have been obtained after 15 min of reaction. Thus, though the ee's are similar, the conversions are always inferior to those obtained with the (L)-phenylalanine amides **4a**, **4b**, **4f**, and **4j** (entries 2, 4, 9, and 10 in Table 3).

In an attempt to improve the enantioselectivity of the catalytic process, a second chiral center has been introduced close to the amide nitrogen. The four diastereoisomers **3h**, **3i**, **4h**, and **4i**, behave differently in the reduction of acetophenone under standard conditions (entries 13−16, Table 3). As for the ee's, the most effective ligands are those having the *R*-configured amide substituent (entries 15 and 16, Table 3); in particular, ligand **3i** has led to ee = 45%. The methylbenzyl group attached to the amide nitrogen seems to play an important role in the stereochemical course of the reaction. In fact, the configuration of the favored 1-phenylethanol isomer is now governed by the configuration of the amide substituent. Thus, (*R*)-1-phenylethanol is preferentially produced with the ligands **3i** and **4i** (*R*-configured amide substituent), whereas (*S*)-1-phenylethanol is preferentially produced with the ligands **3h** and **4h** (*S*-configured amide substituent). These amino-amides behave similarly to the β-amino alcohols,[2e] where the most effective substituent is the most distant from the amine function.

The influence of R1 on the speed and the enantioselectivity of the catalytic processes can be inferred from the results obtained with the ligands **3i**, **4i**, **7**, and **8**.

Scheme 5. Synthesis of the Complexes 10 and 11



R1 = Bz Ar = *p*-(MeO)Ph (**10**)

R1 = i-Pr Ar = *o*-(MeO)Ph (**11**)

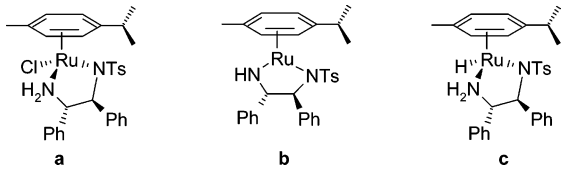
Thus, branched R1 groups (*i*-Pr and *sec*-Bu) lead to the highest ee's (45% and 47% with **3i** and **8**, respectively) but low conversions (44% and 46% with **3i** and **8**, respectively), while R1 = Me leads to the highest conversion (95% conversion with **7**) but to a lower ee (30%, entry 17 in Table 3). Intermediate values have been reached with the phenylalanine derivative **4i** (entry 16, Table 3).

Reduction of Other Substrates. The catalytic study has been extended to other carbonyl compounds. The ligand **4a** has been used in the reduction of 2′- and 4′-bromoacetophenone, α-tetralone, 2-acetonaphthone, and 2-salicylaldehyde, under the same experimental conditions applied with acetophenone (Table S4 of the Supporting Information). The complete reduction of the bromoacetophenones occurs within 15 min (TOFs = 400 h^{-1}) with low ee's (19% *R* and 11% *R* for 2′-bromoacetophenone and 4′-bromoacetophenone, respectively). More difficult is the reduction of bulky ketones: 80% conversion after 72 h has been observed in the reduction of α-tetralone to α-tetralol, while 54% conversion has been observed in the reduction of 2-acetonaphthone to 1-(1-naphthyl)ethanol after 18 h. In both cases negligible ee's have been obtained. The hydrogenation of 2-salicylaldehyde proceeds sluggishly too: 39% conversion to 2-hydroxybenzyl alcohol has been obtained after 30 min (TOF = 78 h^{-1}), but after 3 h the reaction is practically blocked (43% conversion, TOF = 14 h^{-1}). The deactivation is likely imputable to the KOH-assisted deprotonation of salicylaldehyde: the phenoxy group can enter into the Ru coordination sphere, thus hampering the formation of the hydride intermediate or the ketone coordination. Much more easier is the reduction of 2-nitrobenzaldehyde with the ligand **4j**: its complete conversion has been achieved after 1 h of reaction (TOF = 100 h^{-1}).

Synthesis of the Precatalysts. To evidence the interaction that occurs between the secondary amides and ruthenium, the ligands **3c** and **4b** have been reacted with [Ru(*p*-cymene)Cl_2]$_2$ in dichloromethane in the presence of a stoichiometric amount of *t*-BuOK. In both cases the chloride complexes [(η^6-*p*-cymene)Ru(κ^2-N,N′-(L)-amino amidato)Cl] (**10** and **11** in Scheme 5) have been isolated in satisfactory yields. The complexes have been characterized by ^{1}H NMR, elemental analysis, and, in the case of **11**, ESI-MS spectrometry (vide infra). The spectroscopic data indicate the formation of half-sandwich Ru(II) complexes equivalent to those obtained with amino acid primary amides.[10] The ligand coordinates the metal in an anionic NN′ bidentate fashion and the pseudotetrahedral coordination is completed by a chloride ligand and a η^6-*p*-cymene molecule.

The ^{1}H NMR spectrum of **10** recorded in CD_2Cl_2 at room temperature shows the presence of two different sets of signals, indicative of the presence of both the diastereoisomers, $R_{Ru}S_C$ and $S_{Ru}S_C$,[12] in an approximate 60:40 ratio. They can be distinguished by the presence of two singlets at 3.83 and 3.82 ppm belonging to the OCH_3 group of the *p*-anisidine moiety, as well as by the presence of two singlets at 2.06 and 1.87 ppm due to the CH_3 group of the *p*-cymene ring. The ^{1}H NMR spectrum of **11** recorded in $CDCl_3$ at room temperature shows somewhat broad signals, probably indicative of a slow exchange regime, which is maintained even at −30 °C, between the two diastereoisomers $R_{Ru}S_C$ and $S_{Ru}S_C$. Again, the methoxy signal of the anisidine moiety gives rise to two singlets centered at 3.93 and 3.81 ppm, in an approximate 60:40 ratio.

Scheme 6. Catalytic Intermediates Isolated with Noyori's Catalyst



ESI-MS Experiments. The definition of the mechanism that governs a catalytic transformation is crucial for the development of efficient catalysts. Noyori has definitively demonstrated that half-sandwich Ru(II) complexes containing chiral monotosylated-1,2-diamines promote the asymmetric reduction of ketones through a mechanism that does not take into account a direct interaction between the metal and the reagents (ketone and *i*-PrOH), but rather it is an amine function of the ligand that plays a key role in the activation of both *i*-PrOH and the ketone; for this new type of catalysis the term "metal−ligand bifunctional catalysis" has been coined.[13] With (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine all three intermediates **a**, **b**, and **c** in Scheme 6 have been isolated and structurally characterized;[14] the coordinatively unsaturated 16e$^-$ intermediate **b** is the real catalyst.

ESI-MS technique allows the detection in solution of species at low concentration, and this makes it attractive to define the metal-containing molecules involved in a catalytic cycle.[15] We have then undertaken an ESI-MS study aimed at detecting the key intermediates involved in the *ath* of acetophenone catalyzed by the Ru-amino amidato complexes. Complex **11** has been chosen as a model.

Initially, we have monitored the formation of the complex from reacting **3c** (previously neutralized with an equimolar amount of KOH) with [Ru(*p*-cymene)Cl_2]$_2$ in *i*-PrOH at 90 °C. The ESI(+) spectra have been acquired every 5 min, following the disappearance of the signal belonging to [Ru(*p*-cymene)Cl_2]$_2$. The Ru

(12) Brunner, H.; Weber, M.; Zabel, M. *Coord. Chem. Rev*. **2003**, *242*, 3.

(13) Yamakawa, M.; Ito, M.; Noyori, R. *J. Am. Chem. Soc*. **2000**, *122*, 1466.

(14) Haack, K.-J.; Haschiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed*. **1997**, *36*, 285.

(15) (a) Feichtinger, D.; Plattner, D. A.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 7125. (b) Ogo, S.; Makihara, N.; Watanabe, Y. *Organometallics* **1999**, *18*, 5470. (c) Kenny, J. A.; Versluis, K.; Heck, A. J. R.; Walsgrove, T.; Wills, M. *Chem. Commun.* **2000**, 99. (d) Plattner, D. A.; Feichtinger, D. *Chem. Eur. J.* **2001**, *7*, 591. (e) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490. (f) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832. (g) Fürmeier, S.; Metzger, J. O. *J. Am. Chem. Soc.* **2004**, *126*, 14485.

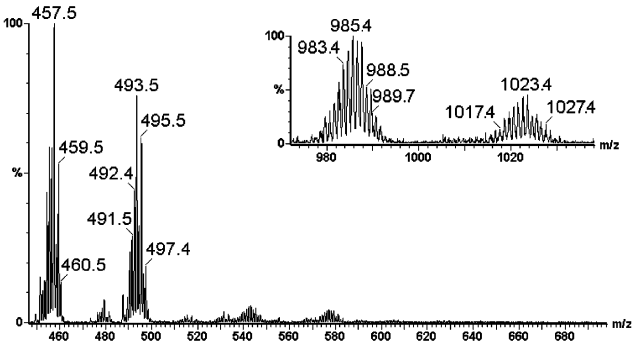
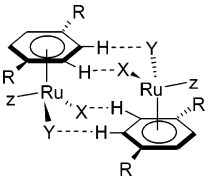


Figure 1. ESI(+) mass spectrum of an *i*-PrOH solution of **3c** and $[Ru(p\text{-cymene})Cl_2]_2$ after 40 min of reaction. The isotope patterns centered around m/z = 457 ($[\mathbf{11}-Cl^-]^+$) and 493 ($[\mathbf{11}+H^+]^+$) account for the formation of the complex **11**. The isotope clusters showed in the inset at m/z = 985 and 1023 are attributable to the dimeric species $[\mathbf{11}_2+H^+]^+$ and $[\mathbf{11}_2+K^+]^+$, respectively.

Scheme 7. Inverted Piano-Stool Dimers for Half-Sandwich Ru(II) Complexes of Formula [(η^6-Ar)RuXYZ]



source is completely consumed within 40 min of reaction, and the formation of **11** is indicated by two isotope clusters centered at m/z = 493 ($[\mathbf{11}+H^+]^+$) and m/z = 457 ($[\mathbf{11}-Cl^-]^+$, base peak), respectively (Figure 1). In addition, isotope clusters centered at m/z = 985 and m/z = 1023 account for the presence of the dimeric species $[\mathbf{11}_2+H^+]^+$ and $[\mathbf{11}_2+K^+]^+$, respectively (Figure 1, inset).

These signals appear in the early stages of the reaction and are attributable to inverted piano-stool dimers of the type depicted in Scheme 7. This is a common feature for half-sandwich Ru(II) complexes of the type [(η^6-Ar)RuXYZ], where X and Y are electronegative substituents,[12] and it has been recently observed by us with (L)-phenylalanineamide.[10]

The addition of acetophenone (Ru:ketone = 1:100 molar ratio) has not led to any change in the ESI spectrum, while after the addition of KOH (Ru:KOH = 1:2 molar ratio), the solution has turned red and the ESI(+) spectrum exhibits a base peak at m/z = 495 (Figure 2) belonging to the potassium adduct of the coordinatively unsaturated 16e$^-$ intermediate **12** (Scheme 8); a signal at m/z = 951 accounts for the presence of the dimer $[\mathbf{12}_2+K^+]^+$ (Figure 2, inset). Residual signals of $[\mathbf{11}-Cl^-]^+$, $[\mathbf{11}_2+H^+]^+$, and $[\mathbf{11}_2+K^+]^+$ are still present.

Under catalytic conditions the hydride intermediate **13** (Scheme 8) is not detectable, and this can be attributed to the fast hydride transfer to acetophenone. Therefore, with the aim of detecting **13**, we have analyzed an *i*-PrOH solution of **11**. The ESI(+) spectrum shows the base peak at m/z = 515 ($[\mathbf{11}+Na^+]^+$) and a small signal at m/z = 493 ($[\mathbf{11}+H^+]^+$). The peaks of the dimers $[\mathbf{11}_2+H^+]^+$ (m/z = 985) and $[\mathbf{11}_2+Na^+]^+$ (m/z = 1007) are also present. After the addition of 2 equiv of KOH the solution has turned from yellow to red and the ESI(−) spectrum shows the base peak at m/z = 457

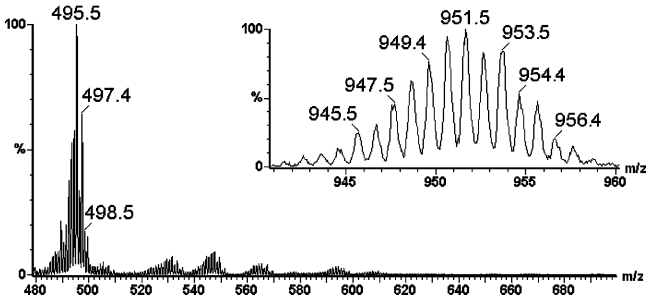


Figure 2. ESI(+) mass spectrum of an *i*-PrOH solution of **3c** and $[Ru(p\text{-cymene})Cl_2]_2$ after 60 min of reaction and the addition of acetophenone (Ru:ketone = 1:100 molar ratio) and of 2 equiv of KOH. The presence of the 16e$^-$ intermediate **12** is confirmed by the potassium adduct ion centered around m/z = 495 and by the isotope pattern centered around m/z = 951 ($[\mathbf{12}_2+K^+]^+$).

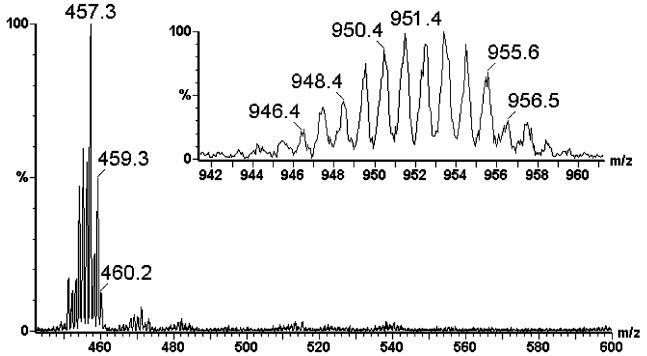
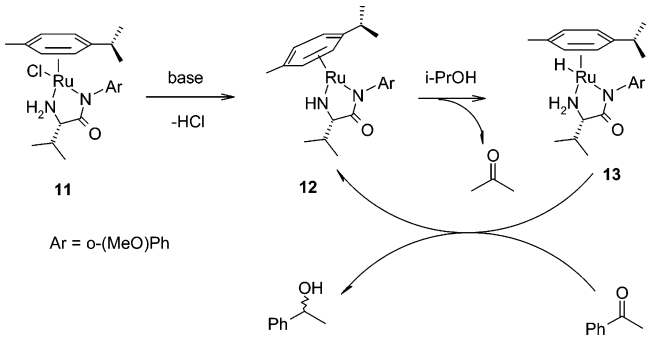


Figure 3. ESI(−) mass spectrum of an *i*-PrOH solution of the precatalyst **11** after the addition of 2 equiv of KOH. The ion signal at m/z = 457 ($[\mathbf{13}-H^+]^-$) and the isotope cluster at m/z = 951 ($[\mathbf{13}_2+Cl^-]^-$) (inset) indicate the presence of the hydride **13** and of the corresponding dimer.

Scheme 8. Catalytic Mechanism for the *ath* of Acetophenone Catalyzed by Ru(II) Amino-Amide Complexes



and a cluster at m/z = 951, indicating the presence of the hydride **13** ($[\mathbf{13}-H^+]^-$) and of the corresponding dimer ($[\mathbf{13}_2+Cl^-]^-$) (Figure 3). The ESI(+) spectrum exhibits the same signals as potassium adducts (m/z = 497, base peak, $[\mathbf{13}+K^+]^+$; m/z = 955, $[\mathbf{13}_2+K^+]^+$).

In this case the undetected species is the 16e$^-$ intermediate **12**, probably because of its fast conversion into **13** in the presence of *i*-PrOH. We have then decided to perform ESI-MS experiments with **11** in a non-hydrogen-donor solvent such as acetonitrile. In this solvent the ESI(+) spectrum of **11** shows the base peak at m/z = 457 ($[\mathbf{11}-Cl^-]^+$) and signals at m/z = 515 and m/z = 949 belonging to $[\mathbf{11}+Na^+]^+$ and $[\mathbf{11}_2-Cl^-]^+$,

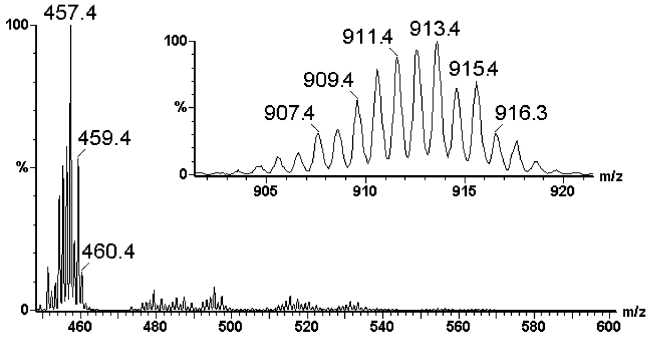


Figure 4. ESI(+) mass spectrum of an acetonitrile solution of the precatalyst **11** after the addition of 2 equiv of NaOH. While the isotope pattern at $m/z = 457$ could arise from both the $[\mathbf{12}+H^+]^+$ and $[\mathbf{11}\text{-}Cl^-]^+$ ions, the signal in the inset centered around $m/z = 913$ is attributable exclusively to the $[\mathbf{12}_2+H^+]^+$ ion of the dimeric form of the $16e^-$ intermediate **12**.

respectively. After the addition of 2 equiv of solid NaOH the solution has become red, but no significant changes are observable in the ESI spectrum (Figure 4). In fact, the base peak is again centered at $m/z = 457$ and the signal at $m/z = 515$ is only decreased slightly. However, it must be taken into account that also the signal generated by $[\mathbf{12}+H^+]^+$ would be centered at $m/z = 457$, and then an overlapping with the signal arising from $[\mathbf{11}-Cl]^+$ cannot be ruled out. The confirmation of the presence of **12** comes from the cluster at $m/z = 913$, accounting for the presence of $[\mathbf{12}_2+H^+]^+$ (Figure 4, inset). In addition, the dimer of the starting chloride complex **11** is still visible at $m/z = 949$ ($[\mathbf{11}_2-Cl^-]^+$).

On the basis of these results, it is possible to conclude that the *ath* of acetophenone catalyzed by the title compounds is governed by the "bifunctional catalysis" mechanism depicted in Scheme 8.

The first step is the KOH-promoted deprotonation of **11** to generate the real catalyst **12**. This quickly reacts with *i*-PrOH to form the hydride **13** and acetone. **13** then reacts with acetophenone to give 1-phenylethanol and the $16e^-$ intermediate **12,** which reenters the catalytic cycle.

Conclusions

A series of amino-amides have been tested as supporting ligands for the Ru(II)-catalyzed asymmetric transfer hydrogenation of acetophenone and other carbonyl substrates in an *i*-PrOH/KOH mixture. The catalytic reductions proceed with high TOFs, up to 1680 h^{-1}. A study on the effects of the α-carbon and of the N-amide substituents has allowed us to define the following important points: (a) the protic character of the ligands is a necessary prerequisite in order to have catalytic activity; the following reactivity order can be written: aromatic secondary amides > aliphatic secondary amides ≫ tertiary amides; (b) the amino-amide ligands generate more active catalysts than the corresponding diamines and amino acids; (c) contrary to that reported for proline-based catalysts, the isolation and full characterization of the precatalysts have been possible (complexes **10** and **11**); (d) as for the ee's, branched R1 groups (*i*-Pr and *sec*-Bu) are more effective in the transfer of chirality than linear substituents (Me and Bz); (e) with the ligands containing only one chiral center (**3a**−**f** and **4a**, **4b**, and **4f**) (*R*)-1-phenylethanol is always formed, with an ee up to 33%; (e) the introduction of a second *R*-configured chiral center close to the amide nitrogen (**8**) improves the ee, up to 47%; (f) with the diastereomeric ligands **3h**−**i**, **4h**−**i**, **7**, and **8** the configuration of the produced 1-phenylethanol is that of the amide substituent.

The metal-configuration lability inferred by ^1H NMR analysis of the complexes **10** and **11** could be one of the reasons for the modest ee values obtained in this work. In fact, both diastereoisomers, $R_{Ru}S_C$ and $S_{Ru}S_C$, are probably present in the catalytic solutions, leading to the opposite 1-phenylethanol isomers. Another explanation could reside in the presence of only one chiral center in the chelation ring: the importance of 1,2-*anti*-disubstitution in monotosylated diamines has been recently elucidated both experimentally[16] and theoretically.[13,17]

An ESI-MS study has allowed the identification of all the intermediate organometallic species involved in the catalytic cycle. These are the precatalyst chloride complex [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-aminoamidato)Cl] **11**, the coordinatively unsaturated $16e^-$ species [(η^6-*p*-cymene)-Ru(κ^2-N,N′-bis-amidato)] **12**, and the hydride [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-aminoamidato)H] **13**.

Finally, an intriguing aspect arising from this work is the constant presence, even under catalytic conditions, of ESI-MS signals attributable to dimers of **11**, **12**, and **13**. Although the formation of dimers, in both the solid state and solution, has already been reported by us for the complex [(η^6-*p*-cymene)Ru(κ^2-*N*,*N*′-phenylalanieamidato)Cl],[10] and by others for [(η^6-*p*-cymene)-Ru(Tsdpen)Cl] (Tsdpen = (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine)) and [(η^6-*p*-cymene)-Ru(aminoacidato)Cl] complexes,[18] here we first report the detection of dimers not only of the precatalyst but also of the key intermediate species implicated in the hydrogen transfer of ketones. It would then be desirable to investigate their possible involvement and/or effect in catalysis.

Experimental Section

General Methods. All reactions were carried out under nitrogen, by using standard Schlenk techniques; the solvents were dried according to literature methods and stored over activated molecular sieves. All reagents of commercial quality were used without further purification. Optical pure Boc-protected amino acids and optically pure (L)-phenylalanine 2-naphthylamide were purchased from Aldrich. [Ru(η^6-*p*-cymene)Cl_2]$_2$ was prepared by a standard procedure.[19] Proton NMR spectra were recorded at 27 °C on a Bruker 300 FT spectrophotometer by using $SiMe_4$ as internal standard. Elemental analyses were performed by using a Carlo Erba Model EA 1108 apparatus. Optical activity of the ligands was measured by means of a Perkin-Elmer polarimeter, by using a 1 mL cell with a 1 cm optical length. The GC analyses were performed by means of a Dani HP 3800 flame-ionization gas chromatograph, equipped with a CP Chirasil Dex CB capillary

(16) Hayes, A.; Clarkson, G.; Wills, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2079.
(17) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818.
(18) Zuccaccia, D.; Clot, E.; Macchioni, A. *New J. Chem.* **2005**, *29*, 430.
(19) Bennet, M. A.; Huang, T. N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, 74.

column. A Quattro LC triple quadrupole instrument (Micromass, Manchester, UK) equipped with an electrospray interface and a Masslynx v. 3.4 software (Micromass) was used for ESI-MS data acquisition and processing. The nebulizing gas (nitrogen, 99.999% purity) and the desolvation gas (nitrogen, 99.998% purity) were delivered at a flow rate of 80 and 500 L/h, respectively. ESI-MS analyses were performed by operating the mass spectrometer in both positive (PI) and negative (NI) ion mode, acquiring mass spectra over the scan range *m/z* 100−1300, using a step size of 0.1 Da and a scan time of 1.2 s. The operating parameters of the interface were as follows: source temperature 70 °C, desolvation temperature 70 °C, ES(+) voltage 3.0 kV, ES(−) voltage 2.5 kV, cone voltage 30 and 50 V, rf lens 0.3 V.

General Procedure for the Preparation of the Boc-Protected Amino Amides. Method A. The Boc-protected amino acids were dissolved in dry dichloromethane at 0 °C. DCC (1,3-dicyclohexylcarbodiimide, 1.1 equiv) was added in small portions to the solution, followed by the addition of the amine (1.4 equiv). The solution was stirred at room temperature one night, filtered on Celite, and then concentrated under vacuum. The crude product was eluted on silica gel (ethyl acetate/*n*-hexane, 4:1), affording the pure Boc-protected amino amide in good yields. **Method B.** The Boc-protected amino acids were dissolved in dry THF at 0 °C in the presence of an equimolar amount of triethylamine. Ethylchloroformiate (1 equiv) was added to the solution, and after stirring for 10 min, a white precipitate was filtered off. A stoichiometric amount of the appropriate amine was added, and the solution was stirred at room temperature for 24 h. The solvent was then removed under vacuum and the residue dissolved in dicholoromethane and treated with solutions of citric acid (5% aqueous solution), sodium carbonate (5% aqueous solution), and brine. The organic layer was finally dried over anhydrous sodium sulfate. After the partial removal of the solvent, the protected amino amide precipitated. They are stable in plain air for months.

***N*-(*tert*-Butoxycarbonyl)-L-valine *p*-anisidineamide, 1b:** white powder. Yield: 65%. Mp = 159−161 °C. $[\alpha]_D^{25}$ = −15° (*c* = 0.020 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 3H); 1.02 (d, 3H); 1.45 (s, 9H); 2.21 (m, 1H); 3.78 (s, 3H); 4.00 (m, 1H); 5.14 (sbr, 1H); 6.83 (d, 2H); 7.38 (d, 2H); 7.91 (sbr, 1H). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.12; N, 8.68. Found: C, 63.75; H, 8.46; N, 8.66.

***N*-(*tert*-Butoxycarbonyl)-L-valine *o*-anisidineamide, 1c:** white powder. Yield: 70%. Mp = 131−132 °C. $[\alpha]_D^{25}$ = −31° (*c* = 0.016 g/mL, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3H); 1.02 (d, 3H); 1.46 (s, 9H); 2.24 (m, 1H); 3.87 (s, 3H); 4.09 (m, 1H); 5.14 (sbr, 1H); 6.85 (d, 1H); 6.95 (t, 1H); 7.05 (t, 1H); 8.18 (sbr, 1H); 8.35 (d, 1H). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.12; N, 8.68. Found: C, 63.75; H, 8.17; N, 8.78.

***N*-(*tert*-Butoxycarbonyl)-L-valine *p*-fluoroanilineamide, 1d:** white powder. Yield: 28%. Mp = 141−142 °C. $[\alpha]_D^{25}$ = −18° (*c* = 0.010 g/mL, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.00 (d, 3H); 1.02 (d, 3H); 1.44 (s, 9H); 3.46 (m, 1H); 4.04 (m, 1H); 5.23 (sbr, 1H); 6.93 (t, 2H); 7.43 (dd, 2H); 8.41 (sbr, 1H). Anal. Calcd for $C_{16}H_{23}N_2O_3F$: C, 61.92; H, 7.46; N, 9.02. Found: C, 62.38; H, 7.72; N, 9.18.

***N*-(*tert*-Butoxycarbonyl)-L-valine (*S*)-methylbenzylamide, 1h:** white powder. Yield: 70%. Mp = 129−130 °C. $[\alpha]_D^{25}$ = −33° (*c* = 0.015 g/mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.86−0.97 (m, 6H); 1.42 (s, 9H); 1.48 (d, 3H); 2.22 (m, 1H); 3.85 (m, 1H); 5.11 (m, 2H); 6.35 (dbr, 1H); 7.22−7.35 (m, 5H). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.80; N, 8.73. Found: C, 66.84; H, 9.10; N, 8.85.

***N*-(*tert*-Butoxycarbonyl)-L-valine (*R*)-methylbenzylamide, 1i**: white powder. Yield: 85%. Mp = 124−127 °C. $[\alpha]_D^{25}$ = +34° (*c* = 0.013 g/mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H); 0.96 (d, 3H); 1.42 (s, 9H); 1.48 (d, 3H); 2.15 (m, 1H); 3.82 (t, 1H); 4.99 (sbr, 1H); 5.11 (m, 1H); 6.19 (d, 1H); 7.24−7.31 (m, 5H). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.80; N, 8.73. Found: C, 67.43; H, 8.55; N, 8.58.

***N*-(*tert*-Butoxycarbonyl)-L-alanine (*R*)-methylbenzylamide, 5:** white powder. Yield: 87%. Mp = 86 °C. $[\alpha]_D^{25}$ = −5.4° (*c* = 0.02 g/mL, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 1.42 (s, 12H); 4.13 (m, 1H); 4.88 (sbr, 1H), 5.12 (m, 1H); 6.54 (sbr, 1H); 7.21−7.34 (m, 5H). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.57. Found: C, 65.72; H, 8.62; N, 9.74.

***N*-(*tert*-Butoxycarbonyl)-L-isoleucine (*R*)-methylbenzylamide, 6:** white powder. Yield: 85%. Mp = 147 °C. $[\alpha]_D^{25}$ = +17.4° (*c* = 0.02 g/mL, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.89 (d, 3H); 0.92 (d, 3H); 1.42 (s, 9H); 1.47 (s, 3H); 1.49 (d, 4H); 3.84 (sbr, 1H); 5.1 (sbr, 1H); 6.22 (sbr, 1H); 7.24−7.34 (m, 5H). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.37. Found: C, 68.54; H, 9.33; N, 8.32.

General Procedure for the Preparation of the Amino Amides. The protecting group was removed by adding trifluoroacetic acid (10 equiv) to a dichloromethane solution of the Boc-protected amino amide at room temperature. The reaction was monitored by TLC (CH_2Cl_2/MeOH, 12:1). The volatile was removed under vacuum. The trifluoroacetate salt of the amino amide can be isolated at this step; otherwise the crude product was dissolved in water and the pH adjusted to 8 with KOH 10%. The solution was extracted with dichloromethane and dried over anhydrous Na_2SO_4. Purification on silica gel (CH_2Cl_2/MeOH, 5%) afforded the desired amino amide in good yields. In the case of oils, the corresponding hydrochloride forms can be obtained by slow evaporation of a 0.1 M HCl methanol solution. All the amino amides were stored under nitrogen at −18 °C.

L-Valine *p*-anisidineamide, 3b: white powder. Yield: 65%. Mp = 65−66 °C. $[\alpha]_D^{25}$ = −69° (*c* = 0.010 g/mL, CH_2Cl_2). ^{1}H NMR $CDCl_3$: δ 0.90 (d, 3H); 1.01 (d, 3H); 2.39 (m, 1H); 3.19 (sbr, 2H); 3.69 (d, 1H); 3.76 (s, 3H); 6.81 (d, 2H); 7.50 (d, 2H); 9.56 (s, 1H). FAB-MS: *m/z* = 223 $[M]^+$. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.59. Found: C, 64.75; H, 8.18; N, 12.08.

L-Valine *o*-anisidineamide·HCl, 3c: white powder. Yield: 62%. Mp > 250 °C. $[\alpha]_D^{25}$ = +36° (*c* = 0.010 g/mL, CH_3OH). ^{1}H NMR CD_3OD: δ 1.04 (dd, 3H); 1.02 (dd, 3H) 2.17 (m, 1H); 3.79 (s, 3H); 3.92 (m, 1H); 6.84 (td, 1H); 6.95 (dd, 1H); 7.07 (td, 1H); 7.51 (dd, 1H). FAB-MS: *m/z* = 223 $[M-Cl]^+$. Anal. Calcd for $C_{12}H_{18}N_2O_2$·HCl: C, 55.70; H, 7.40; N, 10.82. Found: C, 55.84; H, 7.51; N, 10.67.

L-Valine *p*-fluoroanilineamide, 3d: white powder. Yield: 96%. Mp = 113 °C. $[\alpha]_D^{25}$ = +32° (*c* = 0.010 g/mL, CH_3OH). ^{1}H NMR (CD_3OD): δ 0.98 (d, 3H); 1.01 (d, 3H); 2.16 (m, 1H); 3.68 (d, 1H); 6.96 (m, 2H); 7.49 (m, 2H). FAB-MS: *m/z* = 211 $[MH]^+$. Anal. Calcd for $C_{11}H_{15}FN_2O$: C, 62.84; H, 7.19; N, 13.31. Found: C, 62.39; H, 7.42; N, 12.90.

L-Valine (*S*)-methylbenzylamide·HCl, 3h: white powder. Yield: 89%. Mp = 69 °C. ^{1}H NMR (CD_3OD): δ 1.05 (dd, 6H); 1.62 (d, 3H); 2.24 (m, 1H); 3.79 (d, 1H); 5.17 (m, 1H); 7.36 (sbr, 1H), 7.46 (m, 5H). FAB-MS: *m/z* = 221 [100, $(M-Cl)^+$]. Anal. Calcd for $C_{13}H_{20}N_2O$·HCl: C, 60.81; H, 8.24; N, 10.91. Found: C, 60.71; H, 8.18; N, 11.05.

L-Valine (*R*)-methylbenzylamide·HCl, 3i: white powder. Yield: 48%. Mp = 172 °C. $[\alpha]_D^{25}$ = +115° (*c* = 0.016 g/mL, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H); 0.99 (d, 3H); 1.47 (d, 3H); 2.12 (m, 1H); 3.98 (m, 1H); 4.96 (m, 1H); 6.23 (d, 1H); 7.30 (m, 5H); 7.72 (sbr, 3H); 8.36 (sbr, 1H). FAB-MS: *m/z* = 221 [100, $(M-Cl)^+$]. Anal. Calcd for $C_{13}H_{20}N_2O$·HCl: C, 60.81; H, 8.24; N, 10.91. Found: C, 60.71; H, 8.18; N, 11.05.

L-Alanine (*R*)-methylbenzylamide·HCl, 7: white powder. Yield: 82%. Mp = 90 °C. $[\alpha]_D^{25}$ = +89° (*c* = 0.02 g/mL, CH_3OH). ^{1}H NMR ($CDCl_3$): δ (m, 6H); 2.32 (d, 1H), 3.44 (d, 1H); 5.77 (sbr, 1H), 7.13 (m, 5H), 7.18 (sbr, 3H). Anal. Calcd for $C_{11}H_{17}N_2OCl$: C, 57.89; H, 7.46; N, 12.35. Found: C, 57.81; H, 7.42; N, 12.60.

(L)-Isoleucine (*R*)-methylbenzylamide·HCl, 8: white powder. Yield: 71%. Mp = 181 °C. $[\alpha]_D^{25} = +79.4°$ (c = 0.020 g/mL, CH_3OH). ^1H NMR (CD_3OD): δ 0.97 (d, 3H); 1.02 (d, 3H); 1.21 (m, 1H); 1.45 (d, 3H); 1.57 (m, 1H); 1.90 (m, 1H); 3.67 (d, 1H); 5.00 (m, 1H); 7.20−7.35 (m, 5H). Anal. Calcd for $C_{14}H_{23}N_2OCl·1/2H_2O$: C, 60.09; H, 8.65; N, 10.01. Found: C, 60.62; H, 8.59; N, 9.97.

Synthesis of the Diamine Ligand *N*-(*o*-Anisidine)-1-isopropylethylenediamine, 9. 3c was dissolved in 20 mL of distilled THF. A 6 equiv portion of $LiAlH_4$ was added slowly at 0 °C. After the evolution of hydrogen had ceased, the solution was heated at reflux for 2 days; then, it was carefully quenched with water and the white precipitated was filtered off and washed with dichloromethane. The organic layer was washed with 1 M NaOH and brine and then dried over anhydrous sodium sulfate. The solvent was removed under vacuum, affording the pure product as a yellowish oil. Yield: 65%. $[\alpha]_D^{25} = +34°$ (c = 0.001 g/mL, i-PrOH). ^1H NMR ($CDCl_3$): δ 0.94 (d, 3H); 0.99 (d, 3H); 1.73 (m, 1H); 2.34 (sbr, 2H); 2.79−2.85 (m, 1H); 2.89−2.96 (m, 1H); 3.26 (dd, 1H); 3.84 (s, 3H); 6.60−6.69 (m, 2H); 6.76 (d, 1H); 6.86 (t, 1H); 7.16 (t, 1H).

Synthesis of the Ru(II) Complexes. The ligand was dissolved in 20 mL of dichloromethane and a stoichiometric amount of potassium t-BuOK was added. The solution was stirred at room temperature for 1 h, then cooled to −80 °C, and the appropriate amount of $[Ru(p\text{-cymene})Cl_2]_2$ and an additional 22 mg of t-BuOK were added. The solution was allowed to warm to room temperature and stirred for at least 4 h. After filtration on Celite, the solution was concentrated, n-hexane was added, and the mixture was cooled to −18 °C, affording an ochre powder.

(η^6-*p*-Cymene)Ru(κ^2-*N*,*N*′-(L)-phenylalanine-*p*-anisidineamidato)Cl, 10. Yield: 80%. ^1H NMR (CD_2Cl_2): isomer I: δ 1.20−1.07 (m, i-Pr-p-cymene, overlapping of the two isomers' signals); 1.87 (s, 3H, CH_3-p-cymene); 2.14 (m, 1H, i-Pr-p-cymene); 3.11 (m, CH_2, overlapping of the two isomers' signals); 3.42 (m, CH_2, overlapping of the two isomers' signals); 3.65 (mbr, C*H, overlapping of the two isomers' signals); 3.83 (s, 3H, OCH_3); 4.47 (mbr, NH); 4.69 (d, 1H, p-cym); 4.76 (d, 1H, p-cym); 4.90−4.83 (m, p-cymene, overlapping of the two isomers' signals); 4.95 (d, p-cym, overlapping of the two isomers' signals); 5.05 (d, 1H, p-cym), 6.86 (m, An + NH, overlapping of the isomers' signals); 7.52−7.27 (m, Ph + An, overlappong of the isomers' signals); isomer II: δ 2.06 (s, 3H, CH_3-p-cymene); 3.82 (s, 3H, OCH_3). Anal. Calcd for $C_{25}H_{31}ClN_2O_2Ru$: C, 57.85; H, 5.74; N, 5.18. Found: C, 58.03; H, 5.90; N, 5.32.

(η^6-*p*-Cymene)Ru(κ^2-*N*,*N*′-(L)-valine-*o*-anisidineamidato)Cl, 11. Yield: 53%. ^1H NMR (CD_2Cl_2): δ 0.74−1.29 (m, i-Pr); 2.00 (s, 3H); 2.71 (m, 1H); 3.81 (s); 3.92 (s, 3H, OCH3); 4.64−4.92 (m, 4H, p-cym); 6.84−7.10 (m, 3H); 7.56 (dd, 1H). Anal. Calcd for $C_{22}H_{31}ClN_2O_2Ru$: C, 53.70; H, 6.35; N, 5.69. Found: C, 53.30; H, 6.50; N, 5.66.

Reduction of Acetophenone. A 0.016 mmol (10 mg) amount of $[Ru(p\text{-cymene})Cl_2]_2$ was dissolved in 10 mL of i-PrOH and the solution thermostated at the desired temperature, under a gentle flux of nitrogen. A solution of the amino amide (0.032 mol) in i-PrOH (8 mL) was added, and the solution stirred for 40 min. A 3.2 mmol portion of substrate was added, followed by the addition of the base (2 mL of KOH in i-PrOH, 0.032 M). Small portions of the reactant solution were withdrawn, quenched with water, and extracted with diethyl ether. The organic solution was dried with anhydrous Na_2SO_4 and eluted through a short silica column with diethyl ether, and finally analyzed by GC.

ESI-MS Experiments. The solutions were prepared as described for the catalytic experiments. When complex **10** was employed, the final Ru concentration was 1.6×10^{-3} M. Aliquots of the reactant solution were withdrawn and immediately analyzed by ESI-MS. All the experimental isotope clusters were in agreement with the theoretical masses and with the reconstructed singly charged ESI isotope patterns.

Acknowledgment. Carmen Maria Rodriguez Argüelles (University of Vigo, Spain) is thanked for FAB-MS spectra registration. The CIM (Centro Interfacoltà di Misure "Giuseppe Casnati", University of Parma) is thanked for technical support.

Supporting Information Available: Included are catalytic data concerning the recycling of the catalysts (Table S1), the influence of the Ru concentration (Table S2), the influence of the Ru/ligand molar ratio (Table S3), and the hydrogenation of substrates other than acetophenone (Table S4). Moreover, the analytical and spectroscopic data of the Boc-protected amino amides (**1a**, **1e**−**g**, **1k**, **2a**,**b**, **2f**−**i**) and of the Boc-free amino amides (**3a**, **3e**−**g**, **3k**, **4a**,**b**, **4f**−**j**) already reported in the literature are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

OM050519+