

Ruthenium clay catalyzed reduction of α -iminoesters and α -iminoketones, and the reductive amination of α -ketoesters

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Dedicated to Professor Fausto Calderazzo, a wonderful person who has made outstanding contributions to science.

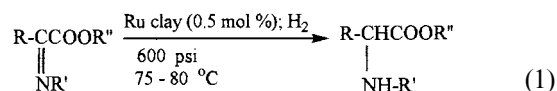
Abstract

The reduction of α -iminoesters and α -iminoketones to the corresponding amino compounds was accomplished using ruthenium clay as the catalyst, at 75–100°C and 600–900 psi H₂. The same catalyst proved efficient for the reductive amination of α -ketoesters (100°C, 600 psi H₂). Diastereomeric excesses of up to 78% were obtained in the reductive amination reaction. © 2000 Elsevier Science S.A. All rights reserved.

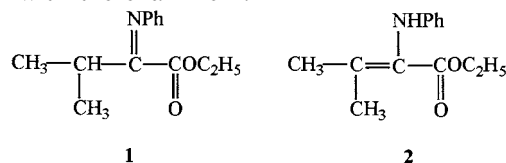
Keywords: Ruthenium; Iminoesters; Iminoketones; Ketoesters; Reductive amination

The catalytic hydrogenation of imines to amines has attracted much interest in recent years, especially in terms of diastereoselective and enantioselective reduction [1–6]. Complexes of transition metals (Ti, Ir, Rh, Ru) have been used as catalyst precursors under homogeneous conditions [7–10]. Ruthenium complexes were developed for the reduction of imines by hydrogen transfer. Bäckvall et al. demonstrated that imines are reduced by hydrogen transfer in propan-2-ol, in the presence of catalytic amounts of [RuCl₂(PPh₃)₃] and a base (K₂CO₃) [11]. [Ru₃(CO)₁₂] also proved active for this process [8]. Significant progress was made by Noyori's group [12] in demonstrating that a ruthenium based complex, in the presence of suitable chiral 1,2-diamines, efficiently catalyzes the asymmetric reduction of imines with a formic acid–triethylamine mixture. The number of heterogeneous systems reported for the reduction of the imine group is less than those for the corresponding homogeneous catalytic systems. Usually palladium on carbon or Raney nickel is used under heterogeneous conditions [13]. Recently, ruthenium clay [14] (ruthenium anchored on Fluka K10 montmorillonite through reaction of RuCl₃·H₂O with phosphinated montmorillonite) was found to be of value for the hydrogenation of unsaturated esters, epoxides, sulfones and phosphonates [14]. We reasoned that Ru clay

should be capable of reducing the α -imine unit of α -iminoesters and α -iminoketones. We now report the results of this investigations and, as well, the reductive amination of α -ketoesters. Several α -iminoesters were prepared by the condensation reaction of an α -ketoester with different amines [15,16]. The hydrogenation reactions were carried out at 600 psi H₂ and 75–80°C using a 200/1 ratio of substrate/Ru (Eq. (1)).



The reactions are clean, and the only product formed is the α -aminoester. For the α -iminoesters which are derivatives of aniline, the conversion is almost complete after 41 h (Table 1, entries 1, 2). In the case of the *N*-butyl derivative, after the same reaction time, the conversion to aminoester is 59% (Table 1, entry 3). The *N*-phenyl iminoderivative of ethyl 3-methyl-2-oxo-butyrate was also considered as a possible starting material. Hydrogenation of the α -iminoester **1** resulted in incomplete conversion of the substrate after 64 h and the reaction mixture contained the aminoalcohol together with the enamine **2**.



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The tautomerization of the imine **1** to enamine **2** probably takes place under the reaction conditions and reduction of the tetrasubstituted double bond is more difficult to accomplish with the present catalytic system. This fact is in agreement with our previous observations that a fully substituted alkene was not hydrogenated using the Ru clay [14].

The α -ketoimines used in the hydrogenation reactions were synthesized by direct condensation between benzil and aniline or an aniline derivative using the conditions described by Knoevenagel [17]. The main difference in reactivity of α -ketoimines in comparison with α -iminoesters is that more severe conditions are necessary: increase of pressure to 900 psi H₂ and an increase of temperature to 100°C. The reaction of the aniline derivative (Table 1, entry 4) afforded the corresponding α -aminoketone as the only product in 95% yield. The reaction of the *p*-tolyl derivative gave complete conversion of the starting material (42 h) but diastereomeric α -aminoalcohols (40%) are formed in addition to the aminoketone. The yield of the α -aminoketone was only 60%.

Table 1
Hydrogenation of α -iminoesters and α -iminoketones catalyzed by Ru clay^{a,b}

No.	Substrate	Pressure (psi H ₂)	Temperature (°C)	Time (h)	Conversion [isolated yield (%)]
1.		600	75	41	97 (86)
2.		600	75	41	94 (82)
3.		600	75	40	59 (51)
4.		900	100	44	100 (95)
5.		900	100	42	100 (60) ^b

^a Reaction conditions: 1 mmol substrate; 0.005 mmol Ru; 8 ml dry benzene.

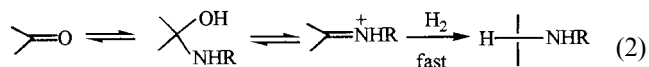
^b Diastereomeric α -aminoalcohols were also formed.

Table 2
Reductive amination of α -ketoesters in the presence of Ru clay^a

No	α -Ketoester	Amine	Product	Isolated yield (%)
1.				65
2.				28
				72
3.				51
4.				76 (75% de)
5.				81 (78% de)

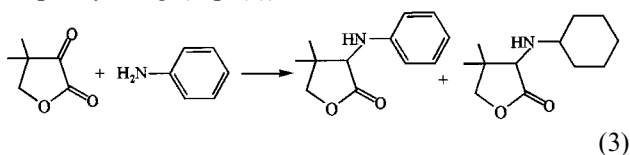
^a Reaction conditions: 1 mmol substrate; 1.1 mmol amine; 0.005 mmol Ru; 0.6 g molecular sieves; 600 psi H₂; 100°C; 24 h.

The good activity of Ru clay for the reduction of the imine bond of α -iminoesters suggested that direct formation of the α -aminoesters without isolation of the imine derivative may be possible. Reductive amination has previously been studied using heterogeneous catalytic systems based on palladium and nickel. The process is envisioned to proceed via the formation of an iminium ion which is then rapidly reduced to the amine [2] (Eq. (2)).



The possibility that ruthenium clay catalyzes this process was first investigated using achiral amines. The reaction of ethyl 2-oxo-4-phenylbutyrate with *n*-butylamine at 600 psi H₂ and 100°C, in the presence of ruthenium clay, gives the α -aminoester in 65% yield (Table 2, entry 1). The reaction was carried out in the presence of molecular sieves as drying agents. No hydrogenation product is formed if the reaction proceeds only in the presence of molecular sieves, without Ru clay. The conversion of the α -ketoester is complete. The reaction mixture also contains the excess of the amine

(0.1 M excess), small amounts of α -hydroxyester and traces of another product which was not identified. For substrates in which the α -carbonyl moiety is bound directly to the phenyl ring a competitive process-reduction of the keto unit-occurs more quickly. Methyl mandelate is formed in 72% yield, while the aminoester is the minor product (Table 2, entry 2). In the reaction of ketopantolactone with *n*-butylamine, the amino derivative of pantolactone was obtained in 51% isolated yield as the major product of the reaction (Table 2, entry 3). No ketopantolactone was recovered from the reaction mixture. If ketopantolactone is reacting with an aromatic amine (e.g. aniline), the products obtained include that resulting from a simultaneous reduction of the phenyl ring (Eq. (3)).



The presence of *N*-cyclohexylamine in the mixture suggests that the hydrogenation of the aromatic ring may occur before the reaction with ketopantolactone. No hydrogenation occurs in the aromatic moiety once the imine bond is formed, as shown by the reduction of the *N*-phenyl-imino-derivative of ketopantolactone.

Reductive aminations are often utilized in organic synthesis in conjunction with the use of chiral amines. In reactions carried out using Pd/C, the diastereomeric excess was postulated to arise from interaction of the Schiff base with the catalyst-adsorption onto the catalyst from the less bulky face of the molecule [18]. In order to examine if any diastereoselectivity would be obtained using Ru clay, methyl pyruvate was reacted with (*R*)-(+)- α -methyl benzylamine and (*R*)-(+)-1-(1-naphthyl) ethylamine. We were concerned that the use of chiral aromatic amines could be problematic as reduction of the aromatic ring may occur giving a complex mixture of products. Contrary to the result obtained with ketopantolactone and aniline, the reaction between methyl pyruvate and the chiral amines proceeded with very good selectivity affording *N*-aryl-aminoesters as the major product of the reactions.

The reaction of methyl pyruvate with either a phenyl or a naphthyl amino derivative produced two diastereoisomers. In the case of (*R*)-(+)- α -methyl benzylamine the diastereomeric mixture was isolated in 76% yield and in 75% diastereomeric excess (determined by ¹H-NMR, Table 2, entry 4). Using (*R*)-(+)-1-(1-naphthyl) ethylamine the yield of aminoester was 81% and the diastereomeric excess was 78% (Table 2, entry 5). It was reported that the hydrogenation of Schiff bases of *i*-butyl pyruvate with (*R*) or (*S*) alanine, over palladium on charcoal, gave products in 71–81% d.e., and the same catalyst afforded 40–70% de in the

hydrogenation of Schiff bases prepared from benzyl esters of pyruvic acid and amino acid esters [18,19].

It can be concluded that the ruthenium based catalytic system represents a new alternative for the reduction of iminoesters and iminoketones, even if it requires more severe reaction conditions than the Pd based system. The new catalytic system is, to our knowledge, the first which uses ruthenium on clays for the reductive amination process. The results obtained have similar, and in several cases, higher values in terms of yield and diastereomeric excess compared to previously reported systems (palladium or nickel) for reductive amination.

1. Experimental

1.1. General procedure for the Ru clay catalyzed hydrogenation of α -iminoesters and α -iminoketones

A mixture of the substrate (1 mmol) and ruthenium clay (0.005 mmol Ru) in dry benzene (8 ml) was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized to the desired level (600–900 psi H₂). The reactor was placed in an oil bath and maintained at constant temperature (75 or 100°C) for 40–44 h. The autoclave was cooled to room temperature (r.t.), the excess hydrogen gas was released, and the reaction mixture was filtered through Celite. The filtrate was concentrated by rotary evaporation. Purification of the products was effected by silica gel column chromatography using different ratios of hexane and ethyl acetate as eluant.

1.2. General procedure for the reductive amination of α -ketoesters in the presence of Ru clay

A mixture of the α -ketoester (1 mmol), amine (1.1 mmol), ruthenium clay (0.005 mmol Ru) and molecular sieves (4 Å, 0.6 g), in dry benzene (8 ml), was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized to 600 psi H₂. The reactor was placed in an oil bath and maintained at 100°C. The decrease of the hydrogen pressure was observed on the gauge. The autoclave was cooled to r.t., excess hydrogen gas was released and the reaction mixture was filtered through Celite. The filtered material was washed with benzene, and the filtrate was concentrated by rotary evaporation. Purification of the products was effected by silica gel column chromatography using different ratios of hexane/ethyl acetate as eluant, or by preparative HPLC.

The physical and spectroscopic data for the compounds obtained were compared to the data reported in the literature [18–22]. Diastereomeric excesses were determined by ¹H-NMR.

Acknowledgements

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References

- [1] Q.-C. Zhu, R.O. Hutchins, M. Hutchins, *Org. Prep. Proc. Int.* 26 (1994) 193.
- [2] K. Harada, T. Munguni, in: B.M. Trost, M. Fleming (Eds.), *Comprehensive Organic Synthesis*, Pergamon Press, New York, 1991, p. 152.
- [3] C.A. Willoughby, S.L. Buchwald, *J. Am. Chem. Soc.* 116 (1994) 8952.
- [4] M.J. Burk, J.E. Feaster, *J. Am. Chem. Soc.* 114 (1992) 6266.
- [5] G.E. Ball, W.R. Cullen, M.D. Fryzuk, W.J. Henderson, B.R. James, K.S. MacFarlane, *Inorg. Chem.* 33 (1994) 1464.
- [6] C. Lesink, J.G. deVries, *Tetrahedron Asymm.* 4 (1993) 215.
- [7] Z. Zhou, B.R. James, H. Alper, *Organometallics* 14 (1995) 4209.
- [8] P.A. Chaloner, M.A. Esteruelas, F. Joo, L.A. Oro, in: R. Ugo, B.R. James (Eds.), *Homogeneous Hydrogenation*, Kluwer Academic Publishers, Dordrecht, 1994, p. 131.
- [9] D.E. Fogg, B.R. James, M. Kilner, *Inorg. Chim. Acta* 222 (1994) 85.
- [10] B.R. James, *Chem. Ind.* 62 (1995) 167.
- [11] J.-E. Bäckvall, G.-Z. Wang, *J. Chem. Soc. Chem. Commun.* (1992) 980.
- [12] N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 118 (1996) 4916.
- [13] R.L. Augustine, *Heterogeneous Catalysis for the Synthetic Chemist*, Marcel Dekker, New York, 1996.
- [14] R. Aldea, H. Alper, *J. Organomet. Chem.* 551 (1998) 349.
- [15] K. Taguchi, F.H. Westheimer, *J. Org. Chem.* 36 (1971) 1570.
- [16] M. Boeykens, N. DeKimpe, K.A. Tehrani, *J. Org. Chem.* 59 (1994) 6973.
- [17] E. Knoevenagel, *J. Praktische Chem.* 89 (1914) 1.
- [18] K. Harada, S. Shiono, *Bull. Chem. Soc. Jpn* 57 (1984) 1367.
- [19] K. Harada, K. Matsumoto, *Bull. Chem. Soc. Jpn* 44 (1971) 1068.
- [20] F.P. Cossío, C. López, M. Oiarbide, C. Palomo, D. Aparicio, G. Rubiales, *Tetrahedron Lett.* 29 (1988) 3133.
- [21] (a) W.J. Greenlee, *J. Org. Chem.* 49 (1984) 2632. (b) E. Ammermann, H. Theobald, B. Zeeh, E.H. Pommer, A.-G. Basf, Ger. Offen. DE 3 013 908, October 22, 1981.
- [22] B. Alcaide, R. Escobar, R. Perez-Ossurio, J. Plumet, *Ann. Quim. Ser. C.* 82 (1986) 111.