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Ru–BINAP-catalyzed asymmetric hydrogenation of keto esters in high pressure carbon dioxide

Olga V. Turova,[a] Ilya V. Kuchurov,[a] Eugenia V. Starodubtseva,[a] Vladimir A. Ferapontov,[a] Nikolai S. Ikonnikov,[b] Sergei G. Zlotin[a] and Maxim G. Vinogradov*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: ving@ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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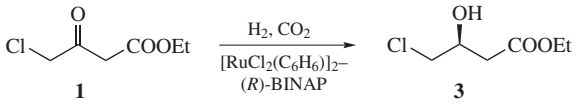
Asymmetric hydrogenation of ethyl 4-chloro-3-oxobutyrate and dimethyl acetylsuccinate in high pressure CO_2 using $[RuCl_2(C_6H_6)]_2$–(*R*)-BINAP as the catalyst provides high *ee* values for the products.

In the past decade, neoteric solvents have found a wide application in chemical reactions as green-chemistry substitutes for toxic organic solvents.[1] Among them, liquid or supercritical carbon dioxide ($scCO_2$) is considered as one of the most promising,[2–5] in particular, in asymmetric hydrogenation of compounds containing C=C,[6–24] C=N[25–27] or C=O[28–30] bonds catalysed by chiral metal complexes. However, a poor solubility of some polar substrates in $scCO_2$ may create problems, making the mass transfer during the reactions less efficient.[5] Promising approaches to solve these problems are based on using the carbon dioxide in combination with appropriate co-solvents[2–5] or carrying out the reactions in a two or three-phase (in the case of using a heterogeneous catalyst) systems CO_2/reagents[31–33] or CO_2/ionic liquid.[34] In these systems a polar, saturated with CO_2 and H_2 liquid phase, a so called 'expanded liquid', facilitates the mass transfer because of a low viscosity, high solute diffusivity and negligible interfacial tension.[35] However, to the best of our knowledge, such heterogeneous high pressure carbon dioxide systems have not previously been used as media for asymmetric hydrogenation of compounds bearing the prochiral C=O bonds.

Herein, we report on asymmetric hydrogenation of keto esters, namely, ethyl 4-chloro-3-oxobutyrate **1** and dimethyl acetylsuccinate **2**, in CO_2-expanded substrate or CO_2-expanded ionic liquid systems (Schemes 1 and 2).† The hydrogenation product of compound **1**, scalemic ethyl 4-chloro-3-hydroxybutyrate **3**, finds use in the synthesis of pharmaceutical carnitine (vitamin B_T).[36] Asymmetric hydrogenation of acetylsuccinate **2** affords scalemic paraconic acid derivatives[37] possessing the pharmacological activity of various types. The catalyst obtained *in situ* from the ruthenium source $[RuCl_2(C_6H_6)]_2$ and (*R*)-BINAP, the chiral atropoisomeric ligand, was used in both reactions, with the amounts of these components was taken to provide the [Ru]/[BINAP] ratio of 1:1.5.



Scheme 1

Before testing CO_2 as a component of the reaction medium, we examined this reaction under neat conditions. After 1 h at 75 °C, the hydrogenation product **3** was obtained in moderate enantioselectivity (66% *ee*, see Table 1, entry 1). However, no reaction occurred in the CO_2-containing medium under the same conditions (entry 2). Presumably, the catalytically active ruthenium complex was not generated *in situ* from $[RuCl_2(C_6H_6)]_2$ and (*R*)-BINAP[38] in the presence of the apolar carbon dioxide.

To solve the problem, we attempted to prepare *in situ* the active catalyst by keeping a mixture of $[RuCl_2(C_6H_6)]_2$, (*R*)-BINAP and the substrate **1** under argon for 1 h at 75 °C before CO_2 to be introduced in the reaction vessel. Then, the autoclave was successively filled with H_2 and CO_2 up to the required pressure, and the hydrogenation reaction was further performed at the same temperature. The complete conversion of substrate **1** and high enantioselectivity (93% *ee*) were achieved using this procedure (Table 1, entry 3). A control experiment in a sapphire window equipped reactor showed that the CO_2-expanded liquid (CXL)[35] was formed under the reaction conditions (80–120 atm CO_2, 75 °C), in which the catalyst was completely soluble.

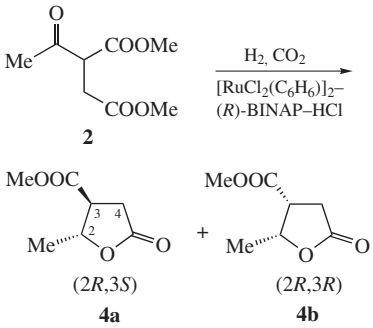
We were pleased to find out that preparation of the catalyst during the separate step could be eliminated if the hydrogena-

Table 1 Asymmetric hydrogenation of ethyl 4-chloro-3-oxobutyrate **1** in different media using the catalytic system $[RuCl_2(C_6H_6)]_2$–(*R*)-BINAP.[a]

Entry	Medium	P_{total}/atm	*t*/h	Conversion (mol%)	(*S*)-**3** (% *ee*)
1	Neat	27	1	100	66
2	CO_2–**1**	150	2	0	—
3[b]	CO_2–**1**	150	1	100	92.5
4	CO_2–**1**–[bmim]BF_4	110	2	72	96.5
5[c]	CO_2–**1**–[bmim]BF_4	110	2	100	97
6	CO_2–**1**–[bmim]BF_4	150	2	69	95

[a] 0.0032 mmol $[RuCl_2(C_6H_6)]_2$, 0.0096 mmol (*R*)-BINAP, 3.86 mmol **1** ([S]/[Ru] = 600), 0.5 ml ionic liquid (entries 4–6); 27 atm H_2, 75 °C. [b] The preliminary formation of the catalyst (stirring of the mixture of the ruthenium precursor, the ligand and ketoester **1** for 1 h at 75 °C before introducing H_2 and CO_2). [c] [S]/[Ru] = 200.

† Commercial $RuCl_3$, (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene [(*R*)-BINAP], dimethyl acetylsuccinate, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) (Aldrich) and ethyl 4-chloro-3-oxobutyrate (Fluka) were used as purchased. $[RuCl_2(C_6H_6)]_2$ was prepared according to the known procedure.[43] Argon was purified by passing through columns containing nickel-chromium catalyst, copper supported on Kieselguhr (80 °C) and molecular sieves (4 Å). Hydrogen was purified by passing through columns with a nickel-chromium catalyst and molecular sieves (4 Å). The conversion was determined by ^{1}H NMR (Bruker AM-300). An enantiomeric composition of the products was monitored by GLC using a GC-1000 gas chromatograph and quartz capillary column (25 m×0.23 mm×0.12 μm) with 2,6-dipentyl-3-(trifluoroacetyl)-γ-cyclodextrin stationary phase.



Scheme 2

tion was performed using $[bmim]BF_4$ as a co-solvent (Table 1, entries 4–6).‡ In this case, hydrogenation in CXL (substrate + IL + + CO_2) at 80 atm CO_2, and 75 °C provided high conversions (70–100%) and enantioselectivities (96–97% *ee*). It is of note that such a procedure did not require use of organic solvents commonly applied in similar cases (EtOH or CH_2Cl_2), that makes our method efficient and environment-friendly.[36,38,39]

Our attempts to carry out asymmetric hydrogenation of dimethyl acetylsuccinate **2** under the high pressure CO_2 (80 atm) in the presence of the $RuCl_3$–(*R*)-BINAP[37] or $[RuCl_2(C_6H_6)]_2$–(*R*)-BINAP catalytic systems§ failed probably because of active catalyst was not generated in the apolar CO_2-containing medium as it was also observed for hydrogenation of ketoester **1** (see above). Yet, the desired *trans*-lactone **4a** was obtained with enantiomeric excess of 86% *ee* at the 96% conversion of diester **2** when HCl was added as a co-catalyst[40–42] to the CO_2-expanded substrate mixture, though enantiomeric excess of diastereomeric *cis*-lactone **4b** was low (Table 2, entry 1). At a higher CO_2 pressure, a single supercritical liquid phase formed, in which the catalyst was poorly soluble, and moderate conversion and enantioselectivity values were attained (*cf.* entries 1, 2 and 5).

Luckily, we succeeded to improve the enantiomeric excess of both isomeric lactones **4a**,**b** up to 90 and 83% *ee*, respectively, by carrying out the reaction in the presence of ionic liquid ($[bmim]BF_4$) additive (entry 6). The presence of the acidic co-catalyst (HCl) was also compulsory: elimination of the acid from the catalytic system caused a decrease in both the reaction rate and the enantiomeric excess values for the reaction products (entry 7).

In summary, an efficient environment-friendly methodology for asymmetric hydrogenation of keto esters has been developed using ethyl 4-chloro-3-oxobutyrate **1** and dimethyl acetylsuccinate **2** as model substrates. The hydrogenation is carried out in CO_2-expanded liquids containing the starting reagent or the starting reagent and ionic liquid in the presence of the $[RuCl_2(C_6H_6)]_2$–(*R*)-BINAP pre-catalyst, at that the active catalyst obtained *in situ* is soluble in the CXL-phase (homogeneous catalysis). The presence of CO_2 in CXL-phase decreases its viscosity and at the same time increases the H_2 solubility resulting in a growth of the reaction rate. Addition of ionic liquid as a polar co-solvent allows substantial increasing the hydrogenation enantioselectivity to give the target hydroxy ester **3** and lactones **4a**,**b**.

Table 2 Asymmetric hydrogenation of dimethyl acetylsuccinate **2** catalysed by the $[RuCl_2(C_6H_6)]_2$–(*R*)-BINAP–HCl system in the CXL media.[a]

Entry	Medium	P_{total}/ atm	*T*/°C	Conversion (mol%)	(2*R*,3*S*)-**4a** (% *ee*)	(2*R*,3*R*)-**4b** (% *ee*)
1	CO_2–**2**	110	75	96	85.5	28
2	CO_2–**2**	150	75	92	77	22.5
3	CO_2–**2**	150	60	88	70.5	8.5
4	CO_2–**2**	150	40	59	71	10
5	CO_2–**2**	230	75	14	59	22
6	CO_2–**2**–$[bmim]BF_4$	110	75	95	90.5	83
7[b]	CO_2–**2**–$[bmim]BF_4$	110	75	59	67	35

[a] 0.0026 mmol $[RuCl_2(C_6H_6)]_2$, 0.0078 mmol (*R*)-BINAP, 0.052 mmol HCl in dioxane ([HCl]/[Ru] = 10), 3.08 mmol **2** ([S]/[Ru] = 600); 0.5 ml ionic liquid (entries 6, 7); the preliminary formation of the catalyst (stirring of the mixture of the ruthenium precursor, the ligand and **2** for 1 h at 75 °C before introducing H_2 and CO_2); 27 atm H_2, 13 h. [b] In the absence of HCl as a co-catalyst.

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‡ *Asymmetric hydrogenation of ethyl 4-chloro-3-oxobutyrate* **1**. $[RuCl_2(C_6H_6)]_2$ (1.6 mg, 0.0032 mmol), (*R*)-BINAP (6.0 mg, 0.0096 mmol), keto ester **1** (0.525 ml, 3.86 mmol) and the ionic liquid $[bmim]BF_4$ (0.5 ml) were placed into an argon-filled stainless-steel autoclave (10 ml). The vessel was pressurized with hydrogen (27 atm) and then filled with CO_2 (80 atm) by means of a high-pressure liquid pump. After that the mixture was stirred at 75 °C for 2 h, and the vessel was slowly depressurized. The reaction mixture was extracted with Et_2O (3×10 ml), the extract was concentrated *in vacuo* to leave the target hydroxy ester **3**. To determine the enantiomeric excess for product **3**, it was preliminarily O-acetylated with acetic anhydride according to the standard procedure. GLC (He, 145 °C; enantiomer, t_R/min): *O*-acetyl-(*R*)-**3** (minor), 8.490; *O*-acetyl-(*S*)-**3** (major), 9.067.

§ *Asymmetric hydrogenation of dimethyl acetylsuccinate* **2**. $[RuCl_2(C_6H_6)]_2$ (1.3 mg, 0.0026 mmol), (*R*)-BINAP (4.9 mg, 0.0079 mmol), keto ester **2** (0.5 ml, 3.08 mmol), $[bmim]BF_4$ (0.5 ml) and 1.38 N solution of HCl in dioxane (38 μl, 0.052 mmol) were placed into an argon-filled stainless-steel autoclave (10 ml). The mixture was stirred at 75 °C for 1 h. After that the vessel was pressurized with hydrogen (27 atm) and then filled with CO_2 by means of a high-pressure liquid pump to reach total pressure of 110 atm. After stirring at 75 °C for 13 h, the vessel was slowly depressurized. Distillation of the residue *in vacuo* gave a mixture of diastereomeric lactones **4a**,**b** (2:1 based on ^1H NMR data[37]). GLC (He, 145 °C; enantiomer, t_R/min): (2*S*,3*R*)-**4a** (minor), 5.037; (2*R*,3*S*)-**4a** (major), 5.198; (2*R*,3*R*)-**4b** (major), 6.628; (2*S*,3*S*)-**4b** (minor), 7.120.

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