Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 15 (2004) 1121–1126
Tetrahedron: *Asymmetry*

New perfluoroalkylated BINAP usable as a ligand in homogeneous and supercritical carbon dioxide asymmetric hydrogenation

Mikaël Berthod,[a] Gerard Mignani[b] and Marc Lemaire[a,*]

[a]*Laboratoire de Catalyse et de Synthèse Organique, UMR 5181, UCBL, CPE Bat. 308, 43, Boulevard du 11 Novembre 1918 69622 Villeurbanne Cedex, France*

[b]*Rhodia, Centre de recherches de Lyon, 85, avenue des Frères-Perret, BP 62, 69192 Saint-Fons Cedex, France*

Received 14 January 2004; accepted 4 February 2004

Abstract—New (*R*)- or (*S*)-4,4′- and 5,5′-perfluoroalkylated BINAP have been synthesized in four steps from enantiomerically pure BINAP. These new ligands were used in the homogeneous asymmetric hydrogenation of ethyl acetoacetate in ethanol and in the asymmetric hydrogenation of methyl-2-acetamidoacrylate in supercritical carbon dioxide. In the supercritical media, the addition and nature of a co-solvent have been discussed. Very good conversion and selectivity were obtained in each case.

1. Introduction

Over the last decade, the use of supercritical carbon dioxide ($scCO_2$) has found increasing interest as a non-toxic and environmentally benign solvent for metal-catalyzed processes.[1–3] Supercritical CO_2 has been used as an alternative medium for a number of asymmetric hydrogenations,[4] although catalyst solubility, especially with metal-complexes, has been a problem.[5] Chiral BINOL and BINAP are among the most useful and popular ligands for catalytic asymmetric reactions[6] and although asymmetric hydrogenation with metal BINAP complexes is one of the most extensively used reactions in these types of syntheses, only a few examples of fluoroalkylated BINAP ligands have been reported in the literature. Moreover, the strategy to synthesize these fluorinated BINAP[7] was to phosphinate the corresponding fluorinated BINOL. Even though chiral fluorous BINOL can easily be synthesized by Heck reactions,[8] Ulmann cross-coupling reactions[9] or lithiation reactions,[10] these approaches are time consuming and lengthy with low yields often being observed during the phosphination step.

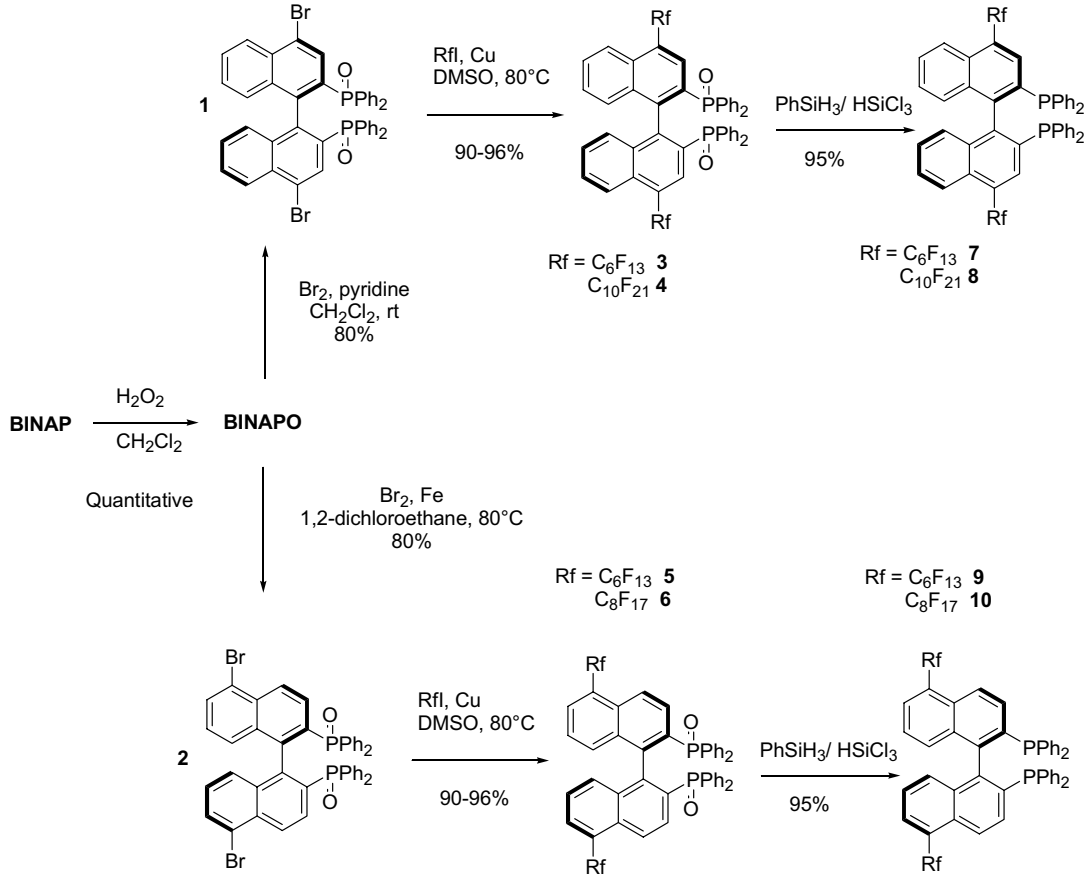
Recently we have reported the synthesis of 4,4′- and 5,5′-dibromoBINAP.[11] These ligands were obtained by direct functionalization of BINAP protected by its oxide form. Herein we report the synthesis of perfluoro-BINAP, using the same strategy, from the BINAP itself in only four steps with excellent overall yields along with examples of use of these perfluoroalkylated BINAP in homogeneous and $scCO_2$ catalytic hydrogenation of various substrates.

2. Results and discussions

(*R*)- or (*S*)-4,4′- and 5,5′-perfluoroBINAP were prepared from commercially available (*R*)- or (*S*)-BINAP. BINAP was first transformed quantitatively into the corresponding dioxide via the reaction with aqueous H_2O_2 (35%) in dichloromethane. This protection step was followed by a regioselective bromination to reach 4,4′- and 5,5′-dibromoBINAPO **1** and **2**.[11] The perfluoroalkyl chains were then directly attached. This simple and easy to use method is an analogue of the century-old Ulmann reaction. The attachment of the fluoroalkyl chain to the BINAP oxide was directly available via copper-mediated cross coupling reactions between perfluoroalkyliodide and the (*R*)- or (*S*)-4,4′ or 5,5′-dibromoBINAPO. This was performed at 80 °C for 3 days in C_6H_5F–DMSO (1:1) to give (*R*)- or (*S*)-4,4′- or 5,5′-bis(perfluoroalkyl)BINAPO in 90–95% yield after recrystallization in toluene (Scheme 1). Little to no symmetric cross-coupling products were observed. Reduction of the phosphine oxide was performed with a mixture of

* Corresponding author. Tel.: +33-4-72-43-14-07; fax: +33-4-72-43-14-08; e-mail: marc.lemaire@univ-lyon1.fr

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.02.004



Scheme 1. Synthesis of perfluoroalkylated BINAP.

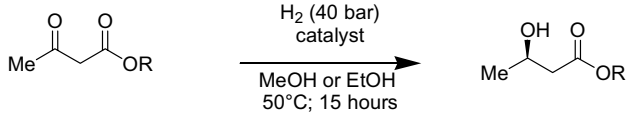
$PhSiH_3/HSiCl_3$[11] to give perfluoroalkylBINAP in 85–90% yield overall.

In order to evaluate the activities of these new ligands and the influence of the perfluoroalkyl groups, the corresponding ruthenium complexes were prepared by the reaction of $[RuCl_2(benzene)]_2$ according to the general procedures described by Noyori et al.[12] The complexes were tested for the catalytic hydrogenation of various keto esters (Table 1).

The perfluoroalkylBINAP showed the same activities and enantioselectivities as 4,4′- and 5,5′-diamBINAP and BINAP itself. Perfluoroalkyl groups seemed to have no influence when compared to BINAP while the length of the perfluoroalkyl chains did not affect either the activity or selectivity.

PerfluoroalkylBINAP was tested in the hydrogenation of the methyl-2-acetamidoacrylate in $scCO_2$. [(COD)Ru(2-methallyl)$_2$] was used as the metal complex. The use of supercritical fluids as reaction media offers us the opportunity to replace conventional organic solvents and also optimize and potentially control the effect that solvent properties can have on selectivities.[13] The relatively mild critical point of carbon dioxide (CO_2:

Table 1. Ruthenium catalyzed reduction of keto-esters with 4,4′- and 5,5′-perfluoroalkylated BINAP ligands



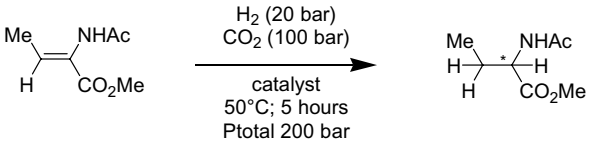
Entry	Ligand	Complex	R	Substrate/catalyst	Conversion (%)[a]	Ee (%)[a]
1	(*R*)-**7**	$[RuCl_2(benzene)]_2$	Me	1000	100	99
2	(*R*)-**8**	$[RuCl_2(benzene)]_2$	Me	1000	100	98
3	(*R*)-**9**	$[RuCl_2(benzene)]_2$	Me	1000	100	99
4	(*R*)-**7**	$[RuCl_2(benzene)]_2$	Et	1000	100	96
5	(*R*)-**9**	$[RuCl_2(benzene)]_2$	Et	2000	100	98
6	(*R*)-**10**	$[RuCl_2(benzene)]_2$	Et	2000	100	99

[a] Conversion and enantioselectivity were determined by GC with a Macherey–Nagel Lipodex-A (25 m, 0.25 mm) capillary column.

$T_c = 31\,°C$, $P_c = 72.9\,atm$) and its benign nature are particularly attractive for asymmetric catalytic applications. Several recent reports have shown that $scCO_2$ can replace organic solvents in various transformations.[14] Herein, we demonstrate that asymmetric catalytic hydrogenation reactions with perfluoroalkylBINAP can be conducted in $scCO_2$ and that, for specific substrates, higher enantioselectivities can be achieved in this solvent relative to conventional solvents.

First, we examined the hydrogenation of methyl-2-acetamidoacrylate in $scCO_2$, without co-solvent. BINAP and perfluoroalkylBINAP were tested under these conditions with no conversion being observed at all (Table 2).

Table 2. Hydrogenation in $scCO_2$ without co-solvent



Entry	Substrate/ catalyst	Catalyst	Conversion (%)[a]	Ee (%)[a]
1	500	(*R*)-BINAP	0	0
2	500	(*R*)-**7**	0	0
3	500	(*R*)-**8**	0	0
4	500	(*R*)-**9**	0	0

[a] Conversion and selectivity were determined by GC on a Supelco beta-DEX (60 m, 0.25 mm) capillary column.

It seems that the perfluoroalkyl group were not enough to solubilize perfluoroBINAP in $scCO_2$.[15] Thus, we added a co-solvent, soluble in $scCO_2$ to increase the polarity of our media. At first we used 1,1,1,3,3,3-hexafluoro-2-propanol (Table 3).

Table 3. Hydrogenation in $scCO_2$ with 1,1,1,3,3,3-hexafluoro-2-propanol as co-solvent (reactor 30 mL)

Entry	Substrate/ catalyst	Catalyst	Co-solvent (mL)	Conversion (%)[a]	Ee (%)[a]
1	500	(*R*)-BINAP	0.5	100	54
2	500	(*R*)-**7**	0.5	100	63
3	500	(*R*)-**9**	0.5	100	64

[a] Conversion and selectivity were determined by GC on a Supelco beta-DEX (60 m, 0.25 mm) capillary column.

Complete conversions were obtained with good selectivity. This time, both BINAP and perfluoroBINAP were soluble in the media. The perfluoroBINAP gave 10% better selectivity than BINAP. The presence of the perfluoroalkyl groups increased the solubility and thus making it a more effective catalyst.

Another parameter had to be studied: the acidity of the co-solvent seemed to have some importance in the selectivity. Therefore, we tried another co-solvent, trifluorotoluene (Table 4).

Table 4. Hydrogenation in $scCO_2$ with trifluorotoluene as co-solvent

Entry	Substrate/ catalyst	Catalyst	Co-solvent (mL)	Conversion (%)[a]	Ee (%)[a]
1	500	(*R*)-BINAP	0.5	100	60
2	500	(*R*)-**7**	0.5	100	74
3	500	(*R*)-**9**	0.5	100	74

[a] Conversion and selectivity were determined by GC on a Supelco beta-DEX (60 m, 0.25 mm) capillary column.

While the hexafluoropropanol and trifluorotoluene increased the solubility of our catalyst in the reaction media, we observed that when the acidity decreased, the selectivity increased.

3. Conclusion

In conclusion, we have synthesized new perfluoroalkylBINAP's, which were tested in $scCO_2$ asymmetric hydrogenation of methyl-2-acetamidoacrylate giving good results. However, many optimizations still remain to be done and other substrates tested in order to validate the efficiency of this environmentally safe method.

4. Experimental

4.1. General

Solvents were dried with molecular sieves (4 Å) and distilled under an argon stream on $LiAlH_4$ or purchased anhydrous (Aldrich or Acros). For catalytic uses, solvents were deoxygenated by repeated evacuation and argon purging. NMR spectra were recorded on a Bruker AC 200 and DRX 300. Chemical shifts are given in ppm from the internal standard, tetramethylsilane, for ^1H and ^{13}C NMR spectra, and ^{31}P NMR from H_3PO_4. Coupling constants are reported in Hz. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. For the air-sensitive compounds, elemental analyses were not performed. Mass spectra were recorded on LCQ Advantage Thermofinnigan. Conversions and enantioselectivities were determined by GC on a Lipodex A (25 m × 0.25 mm) column. All the yields are isolated yields.

4.2. (*R*)- or (*S*)-BINAPO[11]

The compound was synthesized as described in the Ref. 11. ^1H NMR (300 MHz, $CDCl_3$): 6.80 (d, 4H, $J = 3.7$), 7.2–7.3 (m, 8H), 7.3–7.5 (m, 12H), 7.6–7.7 (m, 4H), 7.8–7.9 (m, 4H). ^{31}P NMR (81 MHz, $CDCl_3$): 28.67. Mp: 256–258 °C. $[\alpha]_D^{25} = +198.1$ for (*R*) (*c* 1, benzene).

4.3. (*S*)-4,4′-DibromoBINAPO 1[11]

The compound was synthesized as described in the Ref. 11. ^1H NMR (300 MHz, $CDCl_3$): 6.80 (d, 2H, $J = 8.3$), 6.85 (ddd, 2H, $J = 0.9$, 6.7, 15.1), 7.2–7.5 (m, 18H),

7.6–7.7 (m, 4H), 7.75 (s, 2H), 8.23 (d, 2H, $J = 8.4$). ^{13}C NMR (75 MHz, $CDCl_3$): 123.3, 123.5, 127.1, 127.5, 127.8, 128.3, 128.5, 128.7, 129.0, 130.3, 131.6, 131.7, 131.8, 131.8, 131.9, 131.9, 132.3, 132.4, 132.7, 132.8, 132.9, 133.0, 133.1, 133.3, 134.4, 134.7, 134.9, 142.2, 142.3, 142.4. ^{31}P NMR (81 MHz, $CDCl_3$): 27,60. $[\alpha]_D^{25} = -96.4$ for (*S*) (*c* 1, DMF). ESI^+: $MH^+ = 813.33$. Mp: >300 °C. Calcd C 65.05, H 3.72, O 3.94, P 7.62, Br 19.67; found C 65.13, H 3.82, O 3.73, P 7.81, Br 19.42.

4.4. (*R*)-5,5′-DibromoBINAPO 2[11]

The compound was synthesized as described in the Ref. 11. ^1H NMR (200 MHz, $CDCl_3$): 6.62 (t, 2H, $J = 15.0$), 6.72 (d, 2H, $J = 9.0$), 7.2–7.5 (m, 20H), 7.55 (dd, 2H, $J = 3.0, 1.0$), 7.6–7.8 (m, 2H), 8.3 (dd, 2H, $J = 1.7, 9.0$). ^{13}C NMR (75 MHz, $CDCl_3$): 123.2, 126.5, 127.1, 127.3, 128.5, 128.7, 129.9, 131.6, 131.8, 132.1, 132.3, 132.5, 132.8, 132.9, 133.4, 135.0. ^{31}P NMR (81 MHz, $CDCl_3$): 29.20. $[\alpha]_D^{25} = +97.7$ for (*R*) (*c* 1, DMF). ESI^+: $MH^+ = 813.32$. Mp: >300 °C. Calcd C 65.05, H 3.72, O 3.94, P 7.62, Br 19.67; found C 65.34, H 4.05, O 3.41, P 7.46, Br 19.44.

4.5. Typical procedure for the (*R*)- or (*S*)-perfluoroalkylBINAPO

A mixture of (*R*)- or (*S*)-4,4′- or 5,5′-dibromoBINAPO (2.46 mmol, 1 equiv), perfluoroalkyliodide (7.38 mmol, 3 equiv), copper powder (14.76 mmol, 6 equiv), 2,2′-bipyridine (0.5 mmol, 0.2 equiv), C_6H_5F (20 mL) and DMSO (20 mL) was stirred for 3 days at 80 °C. After cooling to room temperature, the reaction mixture was diluted with water (40 mL) and DCM (50 mL) and then filtered. The organic layer was separated and washed with water (20 mL), a solution of hydrochloric acid (0.1 M, 30 mL), a solution of sodium bicarbonate (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The resulting solid was crystallized in toluene to give a white solid (2.34 mmol, 95%).

4.6. (*R*)-4,4′-PerfluorohexylBINAPO 3

The compound was synthesized as described in the typical procedure. ^1H NMR (200 MHz, $CDCl_3$): 6.76–6.86 (m, 4H), 7.22–7.50 (m, 20H), 7.67–7.77 (m, 4H), 8.24 (d, 2H, $J = 8.6$). ^{13}C NMR (75 MHz, $CDCl_3$): 115.8, 119.4, 125.1, 126.8, 127.1, 127.4, 127.7, 128.1, 128.4, 128.4, 128.6, 128.7, 128.8, 128.9, 129.2, 129.3, 130.5, 131.0, 131.8, 132.1, 132.3, 132.8, 132.9, 150.4. ^{31}P NMR (81 MHz, $CDCl_3$): 28.93. ^{19}F NMR (282 MHz, $CDCl_3$): −126.38 (s, 4F), −122.98 (s, 4F), −121.78 (s, 4F), −120.62 (s, 4F), −105.21 (m, 4F), −81.14 (s, 6H). $[\alpha]_D^{25} = +33.2$ (*c* 2.3, DMF). ESI^+: $MH^+ = 1291.43$. Mp: >300 °C. Calcd C 52.11, H 2.34, F 38.27; found C 51.57, H 2.56, F 38.13.

4.7. (*R*)-4,4′-perfluorodecylBINAPO 4

The compound was synthesized as described in the typical procedure. ^1H NMR (300 MHz, $CDCl_3$): 6.77–6.87 (m, 4H), 7.22–7.55 (m, 20H), 7.68–7.79 (m, 4H), 8.25 (d, 2H, $J = 9$). ^{13}C NMR (75 MHz, $CDCl_3$): 113.8, 115.8, 119.5, 125.0, 126.7, 126.9, 127.7, 128.1, 128.4, 128.6, 128.7, 128.9, 129.3, 130.2, 130.3, 130.9, 131.2, 131.7, 131.8, 132.1, 132.3, 132.6, 132.7, 132.8, 132.9, 134.1, 147.7, 150.4. ^{31}P NMR (81 MHz, $CDCl_3$): 29.07. ^{19}F NMR (282 MHz, $CDCl_3$): −126.60 (s, 4F), −123.16 (s, 4F), −122.17 (d, 16F, $J = 53.8$), −121.64 (s, 4F), −120.57 (s, 4F), −105.2 (s, 4F), −81.14 (s, 6H). $[\alpha]_D^{25} = +31.3$ (*c* 2.3, DMF). ESI^+: $MH^+ = 1691.36$. Mp: >300 °C. Calcd C 45.46, H 1.79, F 47.19; found C 44.93, H 1.83, F 47.13.

4.8. (*R*)-5,5′-PerfluorohexylBINAPO 5

The compound was synthesized as described in the typical procedure. ^1H NMR (300 MHz, $CDCl_3$): 6.73–6.91 (m, 4H), 7.17–7.41 (m, 18H), 7.51 (dd, 2H, $J = 9.4, 11.7$), 7.63–7.72 (m, 4H), 8.27 (d, 2H, $J = 8.3$). ^{13}C NMR (75 MHz, $CDCl_3$): 116.3, 120.2, 124.5, 124.8, 125.3, 126.5, 128.4, 128.5, 128.6, 128.7, 128.9, 129.4, 129.7, 130.1, 130.3, 130.4, 131.1, 131.4, 131.6, 132.1, 132.2, 132.3, 132.7, 132.8, 133.1. ^{31}P NMR (81 MHz, $CDCl_3$): 28.33. ^{19}F NMR (282 MHz, $CDCl_3$): −126.37 (s, 4F), −123.01 (s, 4F), −121.79 (s, 4F), −120.64 (s, 4F), −105.21 (s, 4F), −81.15 (s, 6H). $[\alpha]_D^{25} = +72.1$ (*c* 1, DMF). ESI^+: $MH^+ = 1291.24$. Mp: >300 °C. Calcd C 52.11, H 2.34, F 38.27; found C 52.02, H 2.47, F 38.45.

4.9. (*R*)-5,5′-PerfluorooctylBINAPO 6

The compound was synthesized as described in the typical procedure. ^1H NMR (300 MHz, $CDCl_3$): 6.75–6.96 (m, 4H), 7.19–7.40 (m, 18H), 7.56 (dd, 2H, $J = 9.4, 11.7$), 7.65–7.73 (m, 4H), 8.28 (d, 2H, $J = 8.6$). ^{13}C NMR (75 MHz, $CDCl_3$): 124.5, 124.9, 125.2, 126.7, 128.4, 128.5, 128.6, 128.7, 128.8, 129.3, 129.7, 130.1, 130.2, 130.4, 130.9, 131.5, 131.6, 132.0, 132.2, 132.3, 132.7, 132.8, 132.9. ^{31}P NMR (81 MHz, $CDCl_3$): 28.58. ^{19}F NMR (282 MHz, $CDCl_3$): −126.54 (s, 4F), −123.09 (s, 4F), −122.26 (s, 8F), −121.64 (s, 4F), −120.19 (s, 4F), −104.35 (s, 4F), −81.18 (s, 6F). $[\alpha]_D^{25} = +73.4$ (*c* 1, DMF). ESI^+: $MH^+ = 1491.54$. Mp: >300 °C. Calcd C 48.34, H 2.03, F 43.33; found C 48.91, H 1.88, F 43.67.

4.10. Typical procedure for the (*R*)- or (*S*)-perfluoroalkylBINAP (reduction procedure)

In a 25 mL round-bottomed flask under an inert atmosphere in a reflux condenser was placed (*R*)- or (*S*)-4,4′- or 5,5′-perfluoroalkylBINAPO (0.6 mmol, 1 equiv). Degassed phenylsilane (8 mL) added. The mixture was heated to 130 °C and trichlorosilane was added in three portions (3 × 1 mL) after 1, 3 and 15 h. After the last addition the solution was stirred for 2 h, cooled and evaporated till a white solid was obtained. This was washed with cyclohexane, filtered on Millipore and evaporated. The resulting solid was dissolved in DCM, filtered on a thin pad of silica gel and evaporated to give a white crystalline solid in 95% yield.

4.11. (*R*)-4,4′-PerfluorohexylBINAP 7

The compound was synthesized as described in the typical procedure. ^{1}H NMR (300 MHz, $CDCl_3$): 6.78–6.94 (m, 4H), 7.15–7.53 (m, 20H), 7.61–7.82 (m, 4H), 8.22 (d, 2H, $J = 7.5$). ^{13}C NMR (75 MHz, $CDCl_3$): 119.1, 124.3, 124.4, 125.2, 125.5, 126.0, 126.3, 126.4, 127.1, 127.4, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 128.8, 128.9, 129.1, 129.3, 130.1, 130.4, 131.1, 131.3, 132.1, 132.1, 132.8, 132.9, 135.2, 135.4, 142.0, 142.7. ^{31}P NMR (81 MHz, $CDCl_3$): −14.25. ^{19}F NMR (282 MHz, $CDCl_3$): −126.41 (s, 4F), −122.98 (s, 4F), −121.68 (s, 4F), −120.61 (s, 4F), −105.17 (s, 4F), −81.12 (s, 6H). $[\alpha]_D^{25} = +37.5$ (*c* 1, DCM). HRLSIMS: MH^+. Calcd 1259.1408, found 1259.1411.

4.12. (*R*)-4,4′-PerfluorodecylBINAP 8

The compound was synthesized as described in the typical procedure. ^{1}H NMR (200 MHz, $CDCl_3$): 6.76–6.97 (m, 4H), 7.13–7.54 (m, 20H), 7.63–7.81 (m, 4H), 8.22 (d, 2H, $J = 7.3$). ^{13}C NMR (75 MHz, $CDCl_3$): 120.3, 124.3, 124.5, 125.2, 125.4, 125.9, 126.2, 126.6, 126.9, 127.2, 127.6, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.9, 129.1, 129.2, 129.9, 130.1, 131.0, 131.3, 132.2, 132.3, 132.5, 132.6, 135.1, 135.4, 143.2, 143.5, 144.6. ^{31}P NMR (81 MHz, $CDCl_3$): −14.3. ^{19}F NMR (282 MHz, $CDCl_3$): −126.57 (s, 4F), −123.21 (s, 4F), −122.19 (d, 16F, $J = 54.0$), −121.69 (s, 4F), −120.65 (s, 4F), −105.22 (s, 4F), −81.17 (s, 6F). $[\alpha]_D^{25} = +37.3$ (*c* 1, DCM). Mp: >300 °C. HRLSIMS: MH^+. Calcd 1659.1152, found 1659.1164.

4.13. (*R*)-5,5′-PerfluorohexylBINAP 9

The compound was synthesized as described in the typical procedure. ^{1}H NMR (200 MHz, $CDCl_3$): 6.78–6.98 (m, 4H), 7.13–7.47 (m, 18H), 7.50–7.61 (m, 2H), 7.65–7.78 (m, 4H), 8.29 (d, 2H, $J = 7.3$). ^{13}C NMR (75 MHz, $CDCl_3$): 123.1, 123.3, 124.5, 124.6, 124.8, 125.6, 126.5, 127.1, 127.3, 128.1, 128.2, 128.4, 128.5, 128.7, 130.0, 131.4, 131.8, 132.1, 132.2, 132.4, 132.8, 132.9, 133.2, 133.4, 133.6, 134.4, 134.5, 135.0, 135.4, 135.7, 138.1, 138.4, 143.9, 144.2, 144.7, 145.1. ^{31}P NMR (81 MHz, $CDCl_3$): −13.27. ^{19}F NMR (282 MHz, $CDCl_3$): −126.37 (s, 4F), −123.01 (s, 4F), −121.79 (s, 4F), −120.64 (s, 4F), −105.21 (s, 4F), −81.15 (s, 6H). $[\alpha]_D^{25} = +35.7$ (*c* 1, DCM). Mp: >300 °C. HRLSIMS: MH^+. Calcd 1259.1408, found 1259.1398.

4.14. (*R*)-5,5′-PerfluorooctylBINAP 10

The compound was synthesized as described in the typical procedure. ^{1}H NMR (300 MHz, $CDCl_3$): 6.77–6.96 (m, 4H), 7.02–7.10 (m, 4H), 7.26–7.42 (m, 14H), 7.55–7.61 (m, 6H), 8,29 (d, 2H, $J = 8.9$). ^{13}C NMR (75 MHz, $CDCl_3$): 124.4, 125.4, 126.6, 128.3, 128.4, 128.4, 128.5, 128.6, 128.6, 128.7, 128.8, 128.8, 128.9, 129.3, 129.5, 130.8, 132.0, 132.2, 133.0, 133.2, 133.3, 133.4, 133.6, 133.7, 134.4, 134.5, 134.9, 135.2, 135.4, 135.8, 137.0, 137.4, 137.5, 138.2, 144.0, 144.3, 144.6. ^{31}P NMR (81 MHz, $CDCl_3$): −13.18. ^{19}F NMR (282 MHz, $CDCl_3$): −126.59 (s, 4F), −123.17 (s, 4F), −122.29 (s, 8F), −121.72 (s, 4F), −120.35 (s, 4F), −104.46 (s, 4F), −81.27 (s, 6H). $[\alpha]_D^{25} = +35.5$ (*c* 1, DCM). Mp: >300 °C. HRLSIMS: MH^+. Calcd 1459.1280, found 1459.1277.

4.15. Typical procedure for the homogeneous ruthenium catalyzed reduction of β-ketoesters

Catalysts were prepared from 4,4′- and 5,5′-perfluoroalkylated BINAP and $[RuCl_2(benzene)]_2$ according to the Noyori and co-workers procedure.[16] Under Ar, to the preceding catalysts dissolved in EtOH (1 mL), the β-ketoesters were added (substrate/catalyst: 1000 or 2000). This mixture was allowed to stir and stand overnight in a stainless steel hydrogenation vessel at 50 °C under 40 bars H_2. The resulting reduced mixture was extracted three times with pentane, which was evaporated to give the reduced product.

4.16. Typical procedure for the hydrogenation in $ScCO_2$

The catalysts were prepared in a 30 mL reactor as described in 4.14. Under Ar, to the preceding catalysts were added the co-solvent or not (0.5 mL), methyl-2-acetamidoacrylate (substrate/catalyst: 500). The reactor was placed in a stainless steel hydrogenation vessel at 50 °C under 20 bars H_2 and 100 bars CO_2 ($P_{total} = 200$ bars). After 5 h, the autoclave was cooled down and slowly degassed. The resulting reduced mixture was diluted with CH_2Cl_2 filtered on a pad of silica gel and evaporated to reach the reduced product.

References and notes

1. *Chemical synthesis using supercritical fluids*; Jessop, P. G., Leitner, W., Ed.; Wiley-VCH: Weinheim, 1999.
2. Jessop, P. G.; Ikariya, T.; Noyori, R. *Sciences* **1995**, *269*, 1065–1069.
3. Leitner, W. *Top. Curr. Chem.* **1999**, *206*, 107–133.
4. Jessop, P. G.; Ikaria, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–493.
5. Xiao, J.; Nefkens, S. C. A.; Jessop, P. G.; Ikariya, T.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 2813–2816.
6. *Catalytic Asymmetric Synthesis*; Ojima, I., 2nd, ed., New York: Wiley-VCH, 2000.
7. (a) Birdsall, D. J.; Hope, E. G.; Stuart, A. M.; Chen, W.; Hu, Y.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8551–8553; (b) Nakamura, Y.; Takeuchi, S.; Zhang, S.; Okumura, K.; Ohgo, Y. *Tetrahedron Lett.* **2002**, *43*, 3053–3056.
8. Weiping, C.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 4275–4278.
9. Tian, Y.; Chan, S. *Tetrahedron Lett.* **2000**, *41*, 8813–8816.
10. Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351–356.
11. Berthod, M.; Saluzzo, C.; Mignani, G.; Lemaire, M. *Tetrahedron: Asymmetry*. **2004**, *15*, 639–645.

12. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163.
13. Kaupp, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1452; Boock, L.; Wu, B.; Lamarca, C.; Klein, M.; Paspek, S. *Chem. Tech.* **1992**, 719.
14. Jessop, P.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231; Jessop, P.; Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1995**, 707; Desimone, J. M.; Guan, Z.; Elsbernd, C. S. *Science* **1992**, *257*, 945.
15. *Chemical synthesis using supercritical fluids*; Jessop, P. G., Leitner, W., Eds.; Wiley-VCH: Weinheim, 1999; p 357.
16. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163–4166.