Highly Enantioselective Transfer Hydrogenation of α,βunsaturated Ketones

Nolwenn J. A. Martin and Benjamin List*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim an der Ruhr, Germany list@mpi-muelheim.mpg.de

Supporting Information

General Information: All reactions were carried out under argon atmosphere in oven dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agent prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (0.25 mm thickness, 60F-254, E. Merck). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using anisaldehyde stain. Flash column chromatography was performed using silica gel 60 (particle size 0.040–0.063 mm) from Merck.

¹H and ¹³C NMH spectra were recorded in CDCl₃ (unless otherwise noted) on Bruker DPX-300 and AV-400 spectrometers. Chemical shifts (δ ppm) are relative to tetramethylsilane (TMS) with the resonance of the deuterated solvent or TMS as internal standard. ¹H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants (Hz) and assignment. Mass spectra were measured on a Finnigan MAT 8200 (70 eV) by electron ionization, chemical ionization, of fast atom/ion bombardment techniques. Accurate mass determinations were obtained on a Bruker APEX III FT-MS (7 T magnet). Gas chromatography (GC) was performed on Hewlett-Packard 6890 and 5890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using chiral stationary columns¹ specified in the individual experiments. High performance liquid chromatography (HPLC) was performed on a

¹ Lipodex-A (25 m x 0.25 mm) stationary phase: hexakis-2,3,6-tri-o-pentyl-α-cyclodextrin. BGB 176 /SE 52 (30 m x 0.25 mm) and BGB 178/OV 1701 (30 m x 0.25 mm): 2,3-dimethyl-6-*tert*-butyl-dimethylsilyl-β-cyclodextrin. Ivadex-7 (25 m x 0.25 mm) stationary phase: diethyl-*tert*-butyl-dimethyl-β-cyclodextrin. Lipodex G (25 m x 0.25 mm,) stationary phase: octakis-2,3-O-dipentyl-6-O-methyl-γ-cyclodextrin.

Shimadzu LC-10A HPLC-system equipped with a spectrophotometric detector (monitoring at 220 nm) using a Daicel Co. Chiralcel OD-H or Chiralpak AS-H column.²

Racemic ketones (**2a-I**) were prepared by reduction of the olefin substrates under hydrogen atmosphere catalyzed by Pd/C.³ Enantiomeric ratios (*er*) were determined by GC or HPLC analysis. The absolute configuration of phenethylcyclohexanone (**2e**) was determined by measuring its optical rotation.⁴ The absolute configuration of 3-methylcyclopentanone (**2g**) was determined by chiral GC analysis and comparison with commercially available (*R*)-3-methylcyclopentanone. All other absolute configurations were assigned by analogy. Because most products are volatile, yields have been determined by GC or HPLC. However, if the product was isolated (product **2e**), chromatographically determined and isolated yields were essentially identical.

Preparation of the Catalysts: Most of the α-amino acid esters were purchased from commercial suppliers as α-amino acid ester hydrochloride salts. To obtain the free α-amino acid esters, the commercially available salts were dissolved in a 10% KOH solution and the aqueous phase was extracted with Et₂O (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. Trifluoroacetate and chiral binaphthol derived phosphate salts were prepared by reacting the free α-amino acid esters with a stoichiometric amount of trifluoroacetic acid or chiral binaphthol derived phosphoric acid, respectively. L-*tert*-Leucine *tert*-butyl ester and L-valine *tert*-butyl ester were obtained according to the procedure of Roeske.⁵ Chiral binaphthol derived phosphoric acids where prepared according or in analogy to the reported procedures.^{6,7}

² Chiralcel OD-H (25 cm x 0.46 cm) stationary phase: 3,5-dimethylphenylcarbamate of cellulose. Chiralpak AS-H (25 cm x 0.46 cm) stationary phase: 1-phenylethylcarbamate of amylase.

³ Chordia, M. D.; Harman, W. D. J. Am. Chem. Soc. 2000, 122, 2725-2736.

⁴ Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. Proc. Natl. Acad. Sci. USA 2004, 101, 5834-5838.

⁵ Roeske, R. W. Chem. Ind. (London, U. K.) **1959**, 1121-1122.

⁶ (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Angew. Chem., Int. Ed. 2004, 43, 1566-1568. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. Org. Lett. 2005, 7, 2583-2585; also see: (c) T. Akiyama, PCT Int. Appl. WO 200409675, 2004. (d) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. Adv. Swith. Catal. 2005, 347, 1523-1526.

Morita, H.; Fuchibe, K. Adv. Synth. Catal. 2005, 347, 1523-1526.
⁷ (a) Uraguchi, D.; Terada, M. J. Am. Chem. Soc. 2004, 126, 5356-5357. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. J. Am. Chem. Soc. 2004, 126, 11804-11805. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. J. Am. Chem. Soc. 2005, 127, 9360-9361; also see: (d) Terada, M.; Uraguchi, D.; Sorimachi, K.; Shimizu, H. PCT Int. Appl. WO 2005070875, 2005.

General Procedure for the Synthesis of β -Substituted- α , β -Unsaturated Ketones: 3-Methylcyclohexenone 1a and 3-methylcyclopentenone 1g were purchased from Aldrich. The cyclic substrates were prepared according to the following procedure.⁸



3-Ethylcyclohexenone (1b): A flame-dried flask was charged with ethylmagnesium bromide (14.3 mL, 42.8 mmol, 3.0 M in Et₂O) and cooled to 0 °C. 3-Ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) was added to the Grignard reagent dropwise. Once the addition was complete the reaction mixture was left at room temperature until complete disappearance of the starting material. After 25 h the reaction was slowly quenched with a solution of HCl (1 N, 100 mL). The aqueous phase was separated and extracted further with 25 mL Et₂O (3x). The combined organic phase was washed successively with a saturated aqueous solution of NaHCO₃, brine, and water, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (15% EtOAc/hexanes) to provide the title compound as a yellow oil (1.4 g, 53% yield, reduced yield due to high volatility). The physical data were identical in all respect to those previously reported.⁹

3-Isobutylcyclohexenone (1c): The general procedure for the preparation of substrates using 3-ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) and isobutylmagnesium bromide (21.4 mL, 42.8 mmol, 2.0 M in Et₂O) gave, after

28 h and flash chromatography (15% EtOAc/hexanes), the title compound as a yellow oil (2.5 g, 77% yield). The physical data were identical in all respect to those previously reported.¹⁰



3-Isopropylcyclohexenone (1d): The general procedure for the preparation of substrates using 3-ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) and isopropylmagnesium chloride (21.4 mL, 42.8 mmol, 2.0 M in Et₂O) gave, after

⁸ Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. J. Am. Chem. Soc. 2000, 122, 6797-6798.

⁹ Chong, B.-D.; Ji, Y.-I.; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. J. Org. Chem. 1997, 62, 9323-9325.

¹⁰ D'Augustin, M.; Palais, L.; Alexakis, A. Angew. Chem., Int. Ed. 2005, 44, 1376-1378.

30 h and flash chromatography (10-20% Et_2O /pentane), the title compound as a yellow oil (2.0 g, 68% yield, reduced yield due to high volatility). The physical data were identical in all respect to those previously reported.¹¹

3-Phenethylcyclohexenone (**1e**): Mg turnings (1.25 g, 51.0 mmol) and THF (25 mL) were placed into a dry flask. 2-Phenylethylbromide (7.0 mL, 51.0 mmol) was placed into a separated dry flask, dissolved in THF (25 mL) and then added via syringe to the magnesium solution. The resulting mixture

was then heated at 60 °C and after 15 h cooled to 40 °C (at room temperature the magnesium solution solidifies). The solution of Grignard reagent was then separated from remaining Mg solid by transferring the solution via syringe to another dry flask. The general procedure for the preparation of substrates using 3-ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) and the Grignard reagent described above gave, after 34 h and flash chromatography (20-30% EtOAc/hexanes), the title compound as a yellow oil (3.9 g, 91% yield). The physical data were identical in all respect to those previously reported.¹²

3-Phenylcyclohexenone (1f): The general procedure for the preparation of substrates using 3-ethoxycyclohexenone (3.0 g, 21.4 mmol) in THF (15 mL) and phenylmagnesium chloride (12.3 mL, 42.8 mmol, 3.0 M in Et₂O) gave, after 20 h and flash chromatography (10-20% Et₂O/pentane), the title compound as a

yellow oil (2.8 g, 76% yield). The physical data were identical in all respect to those previously reported.¹³

3-Ethylcyclopentenone (1h): The general procedure for the preparation of substrates using 3-ethoxycyclopentenone (2.0 g, 15.9 mmol) in THF (15 mL) and ethylmagnesium bromide (8.0 mL, 24.0 mmol, 3.0 M in Et₂O) gave after 34 h a dark mixture, which was distilled (0.1 mbar, oil bath temperature: 100-150°C). Further purification by flash chromatography (50% Et₂O/pentane) provided the title compound as a pale yellow oil (0.6 g, 34% yield, reduced yield due to high volatility). The physical data were identical in all respect to those previously reported.¹⁴

¹¹ Jun, J.-G.; Hee Ha, T.; Mundy, B. P.; Bartelt, K. E.; Bain, R. S.; Cardellina, J. H. J. Chem. Soc. Perkin Trans. 1 1994, 2643-2645.

¹² Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett* **2003**, *5*, 2417-2420.

¹³ Denmark, S. E.; Amishiro, N. J. Org. Chem. **2003**, 68, 6997-7003.

¹⁴ Bestmann, H. J.; Schade, G.; Lütke, H.; Mönius, T. Chem. Ber. 1985, 118, 2640-2658.

THF (20 mL) were placed into a dry flask. 2-Phenylethylbromide (5.5 mL, 40.0 mmol) was placed into a separated dry flask, dissolved in THF (20 mL) and then added via syringe to the magnesium solution. The resulting mixture was then heated at 60 °C and after 15 h cooled to 40 °C. The solution of Grignard reagent was then separated from remaining Mg solid by transferring the solution via syringe to another dry flask. The general procedure for the preparation of substrates using 3-ethoxycyclopentenone (2.0 g, 15.9 mmol) in THF (10 mL) and the Grignard reagent described above gave, after 34 h and flash chromatography (20-30% EtOAc/hexanes), the title compound as an orange oil (2.6 g, 88% yield). The physical data were identical in all respect to those previously reported.¹⁵

3-Phenethylcyclopentenone (1i): Mg turnings (972 mg, 40.0 mmol) and

3-Methylcycloheptenone (1j): 3-Ethoxycycloheptenone was prepared according to the procedure of de Meijere et al.¹⁶ In a flame-dried flask equipped with a condenser and a Dean-stark apparatus a mixture of cycloheptane-1,3-dione (1.5 g, 12.2 mmol), ethanol (3 mL), and a catalytic amount of p-TsOH (35 mg, 0.2 mmol) in benzene (80 mL) was heated under reflux. After 36 h the reaction was stopped and the solvent was evaporated in vacuo. The resulting mixture of cycloheptane-1,3-dione/3ethoxycycloheptenone (about 2:1 according to NMR, 1.5g,) was used without further purification for the synthesis of 3-methylcycloheptenone. The general procedure for the preparation of substrates using this mixture cycloheptane-1,3-dione/3-ethoxycycloheptenone in THF (8 mL) and methylmagnesium bromide (5.2 mL, 15.6 mmol, 3.0 M in Et₂O) gave after 14 h and flash chromatography (20-25% Et₂O/pentane) the title compound as a pale yellow oil (0.7 g, 46% overall yield). ¹H NMR: (400 MHz, CDCl₃) δ 1.74-1.85 (m, 4H, 2x -CH₂CH₂CH₂-), 1.96 (s, 3H, -CH₃), 2.42 (t, J=3.5 Hz, 2H, =C(CH₃)CH₂-), 2.58 (t, J=3.9 Hz, 2H, =COCH₂-), 5.93 (s, 1H, -COCH=). ¹³C (100 MHz, CDCl₃): 203.7, 158.4, 129.9, 42.5, 34.6, 27.6, 25.2, 21.5. MS (EI): m/z (%) = 124 (66), 109 (24), 95 (100), 82 (82), 67 (50), 53 (20), 39 (36), 27 (18). HRMS: exact mass calculated for $[M]^+$ (C₈H₁₂O₁) requires m/z124.0887, found *m*/*z* 124.0888.

(*E*)-Ethyl 2-methyl-4-oxopent-2-enoate (1k): This substrate was prepared according to the literature.¹⁷ Ethyl piruvate (2.0 g; 17.2 mmol) was added all at once to a suspension of 1-(triphenylphosphoranylidene)-2-propanone (5.3 g, 16.6 mmol) in

¹⁵ Matsuyama, H.; Miyazawa, Y.; Takei, Y.; Kobayashi, M. J. Org. Chem. 1987, 52, 1703-1710.

¹⁶ Hadjiarapoglou, L.; Klein, I.; Spitzner, D.; de Meijere, A. Synthesis 1996, 525-528.

¹⁷ Schoda, P.; Ebner, C. B.; Potlock, S. T. Synthesis 1987, 1055-1057.

benzene (40 mL). The reaction was stirred at room temperature for 5 h, during which time it became homogeneous. The benzene was then evaporated *in vacuo* and extracted with Et₂O (6x 20 mL). The combined extract was concentrated *in vacuo* and purified by flash column chromatography (20% Et₂O/pentane) to give the title compound as a yellow oil: (*E*)-isomer (1.6 g, 62% yield) and (*Z*)-isomer (0.3 g, 12% yield). (*E*)-isomer (1k) ¹H NMR: (300 MHz, CDCl₃) δ 1.27 (t, *J*=7.9 Hz, 3H, -CH₂CH₃), 2.15 (d, *J*=1.7 Hz, 3H, =C(CH₃)CO₂Et), 2.41 (s, 3H, CH₃CO-), 4.19 (q, *J*=7.9 Hz, 2H, -CH₂-CH₃), 7.01 (q, *J*=1.7 Hz, 1H, -COCH=). ¹³C (75 MHz, CDCl₃): 199.55, 167.74, 140.97, 132.45, 61.71, 32.19, 14.41, 14.09.

(*E*)-4-Phenylpent-3-en-2-one (11): A solution of acetoacetone (5.2 g, 51.48 mmol) in THF (50 mL) was added dropwise over 30 min to a solution of phenylmagnesium bromide (25.7 mL, 77.23 mmol, 3.0 M in Et₂O) in THF (50 mL) at room temperature. The resulting mixture was stirred at room temperature during 24 h and then poured into ice-cold, saturated aqueous NH₄Cl (200 mL) with stirring. The phases were separated, the aqueous phase was extracted with 100 mL Et₂O (3x) and the combined organic phase was dried (MgSO₄) and filtered. The solvents were evaporated to leave an orange oil containing crude 4-hydroxy-4-phenylpentan-2-one.¹⁸ The crude keto-alcohol was then combined with oxalic acid (6.0 g, 66.67mmol) and 100 mL of water. The mixture was heated under reflux condition for 30 min. Et₂O (100 mL) was then added.¹⁹ The phases were separated, the aqueous phase was extracted with Et₂O (3x) and the combined organic phases were dried (MgSO₄), filtered and concentrated *in vacuo*. After flash chromatography (3 % Et₂O/pentane) the title compound was obtained as an orange oil (2.8 g, 73% yield). The physical data were identical in all respect to those previously reported.²⁰

¹⁸ Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. Org. Lett. 2003, 5, 2111-2114.

¹⁹ Bunnelle, W. H; Rafferty, M. A.; Hodges, S. L. J. Org. Chem. **1987**, 52, 1603-1605.

General Procedure for the Asymmetric Transfer Hydrogenation of β-Substituted-α,β-Unsaturated Ketones:



To β -substituted- α , β -unsaturated ketone **1** (0.10 mmol) in Bu₂O (0.3 mL, 0.33M), catalyst **3f** (4.6 mg, 0.005 mmol) and Hantzsch ester **4** (30.4 mg, 0.12 mmol) were added. The reaction mixture was stirred at 60 °C under argon atmosphere for 48 h and then treated with 2N NaOH aqueous solution. The two layers were separated and the organic phase combined, dried (MgSO₄), and filtered. For volatile products, the resulting solution was analyzed by GC for yield and *er* determination. Pure products were isolated by flash chromatography in reduced yields and characterized spectroscopically.

3-Methylcyclohexanone (2a): Spectroscopic data were identical with the commercially available compound (Aldrich). The enantiomers were analyzed by GC using a chiral GBG-178 column (2 min at 50 °C, 5 °C/min until 100 °C, 1 min at 100 °C, 20 °C/min until 150 °C, 2 min at 150 °C). Major enantiomer: $t_R = 12.38$ min, minor enantiomer: $t_R = 12.19$ min.

3-Ethylcyclohexanone (2b): The physical data were identical in all respect to those previously reported. ²⁰ The enantiomers were analyzed by GC using a chiral Lipodex-A column (5 min at 50 °C, 0.5 °C/min until 70 °C, 18 °C/min until 180 °C, 15 min at 180 °C). Major enantiomer: $t_R = 30.53$ min, minor enantiomer: $t_R = 30.03$ min.

²⁰ Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. J. Am. Chem. Soc. 1998, 120, 7649-7650.

3-Isobutylcyclohexanone (2c): ¹H NMR: (300 MHz, CDCl₃) δ 0.87 (d, *J*=7.3 Hz, 6H, CH(CH₃)₂), 1.46-1.23 (m, 4H, CH), 1.63-1.67 (m, 2H, CH), 1.85-2.01 (m, 3H, CH), 2.38-2.42 (m, 3H, CH). ¹³C (75 MHz, CDCl₃): 212.2, 48.4, 46.1, 41.6, 36.7, 31.6, 25.4, 24.8, 22.7, 22.6. MS (EI): *m/z* (%) = 154 (16), 139 (7), 111 (27), 97 (100), 83 (9), 69 (15), 55 (40), 41 (27), 27 (6). HRMS: exact mass calculated for [M]⁺ (C₈H₁₂O₁) requires *m/z* 154.135802, found *m/z* 154.135765. The enantiomers were analyzed by GC using a chiral Lipodex-A column (50 °C, 1 °C/min until 120 °C, 18 °C/min until 180 °C, 15 min at 180 °C). Major enantiomer: t_R = 32.58 min, minor enantiomer: t_R = 31.97 min.

3-Isopropylcyclohexanone (2d): The physical data were identical in all respect to those previously reported. ²¹ The enantiomers were analyzed by GC using a chiral Lipodex-A column (10 min at 50 °C, 1.2 °C/min until 120 °C, 18 °C/min until 180

°C, 5 min at 180 °C). Major enantiomer: $t_R = 24.69$ min, minor enantiomer: $t_R = 24.29$ min.

3-Phenethylcyclohexanone (2e): Purification by flash chromatography (5-10% Et₂O/pentane). The physical data were identical in all respect to those previously reported. ²² The enantiomers were analyzed by HPLC using a chiral Chiralpak AS-H column (n-heptane/2-propanole = 90:10, flow rate = 0.5 mL/min, wavelength = 220 nm). Major enantiomer: $t_R = 16.55$ min, minor enantiomer: $t_R = 14.98$ min.

3-Phenylcyclohexanone (2f): The physical data were identical in all respect to those previously reported.²² The enantiomers were analyzed by GC using a chiral BGB 176 column (100 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: $t_R = 41.20$ min, minor enantiomer: $t_R = 41.76$ min.

3-Methylcyclopentanone (2g): Spectroscopic data were identical with the commercially available compound (Aldrich). The enantiomers were analyzed by GC using a chiral GBG-178 column (2 min at 50 °C, 5 °C/min until 100 °C, 1 min at 100 °C, 20 °C/min until 150 °C, 2 min at 150 °C). Major enantiomer: $t_R = 10.25$ min, minor enantiomer: $t_R = 10.08$ min.



3-Ethylcyclopentanone (2h): The physical data were identical in all respect to those previously reported.²² The enantiomers were analyzed by GC using a chiral

²¹ Liu, J.-Y; Jang, Y.-J., Lin, W.-W, Liu, J.-T.; Yao, C.-F. J. Org. Chem. 2003, 68, 4030-4038.

BGB 178 / OV-1701 column (10 min at 50 °C, 2 °C/min until 130 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: $t_R = 35.95$ min, minor enantiomer: $t_R = 35.55$ min.



3-Phenethylcyclopentanone (2i): The physical data were identical in all respect to those previously reported.²² The enantiomers were analyzed by HPLC using a chiral Chiralcel OD-H column (n-heptane/2-propanole = 90:10, flow rate = 0.5 mL/min, wavelength = 220 nm). Major enantiomer: $t_R = 19.40$ min, minor enantiomer: $t_R = 16.74$ min.

3-Methylcycloheptanone (2j): ¹H NMR: (400 MHz, CDCl₃) δ 1.00 (d, *J*= 4.2 Hz, 3H, -CH₃, 1.19-1.34 (m, 1H, CH), 1.36-1.47 (m, 1H, CH), 1.56-1.67 (m, 1H, CH), 1.80-1.94 (m, 4H, CH), 2.40-2.44 (m, 2H, CH), 2.45-2.50 (m, 2H, CH). ¹³C (100 MHz, CDCl₃): 214.4, 51.8, 44.1, 39.2, 31.3, 28.6, 24.2, 23.6. The enantiomers were analyzed by GC using a chiral Ivadex-7 column (80 °C, 1.2 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: $t_R = 11.09$ min, minor enantiomer: $t_R = 12.86$ min.

(E)-Ethyl 2-methyl-4-oxopentanoate (2k): The physical data were identical in all respect to those previously reported.²³ The enantiomers were analyzed by GC using a chiral BGB 176 / SE 52 column (10 min at 60 °C, 0.8 °C/min until 90 °C, 18 °C/min until 220 °C, 5 min at 220 °C). Major enantiomer: t_R = 31.11 min, minor enantiomer: $t_R = 29.50$ min.

(E)-4-Phenylpentan-2-one (21): The physical data were identical in all respect to those previously reported.²⁴ The enantiomers were analyzed by GC using a chiral BGB 176 / SE 52 column (10 min at 60 °C, 0.8 °C/min until 90

°C, 18 °C/min until 220 °C, 5 min at 220 °C). Major enantiomer: $t_R = 43.52$ min, minor enantiomer: $t_R = 43.07$ min.

²² Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. J. Org. Chem. 1987, 52, 774-782.

 ²³ Xue, S.; Liu, Y.-K.; Li, L.-Z.; Guo, Q.-X. J. Org. Chem. 2005, 70, 8245-8247.
²⁴ Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. J. Org. Chem. 1982, 47, 119-126.

Screening of Catalysts



Catalyst- cation	Counter- anion	Conversion (%)	er	Counter- anion	Conversion (%)	er
	TFA ⁻	< 1	51:49	Cl	8	81:19
	TFA ⁻	27	68:32	Cl	10	78:22
	TFA ⁻	42	62:38	Cl	11	78:22
Bn O	TFA ⁻	78	60:40	Cl	16	69:31
Ph O	TFA ⁻	74	51:49	Cl	21	52:48
	TFA ⁻	23	75:25	Cl	5	87:13
	TFA ⁻	66	77:23	Cl	5	72:28
	TFA ⁻	72	76:24	Cl ⁻	6	71:29
	TFA ⁻	20	58:42			
	TFA ⁻	29	44:56			
O W H ₂	TFA ⁻	3	43:57			
	TFA ⁻	40	25:75			

TFA: trifluoroacetate



Catalyst (20 mol%)

1,4-dioxane, 60°C, 48 h

2a

CO₂Et

N H

4

EtO₂C

1a

TRIP: 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ^a Results in Bu₂O.



R- substituent of the chiral	Conversion (%)	er
counteranion		
$\stackrel{i \mapsto Pr}{\longrightarrow} i \mapsto Pr$	75	98:2
^{<i>i</i>·Pr} <i>i</i> ·Pr <i>i</i> ·Pr <i>(S</i>)-TRIP	45	58:42
	9	87:13
	8	94:6
	18	92:8
	7	89:11
124	5	89:11
	10	72:28

GC and HPLC traces of the Products











2431.972.422532.5897.6













No.	min.	area-%
10	43.03	49.8
11	43.47	50.2



25	41.20	92.2
26	41.76	7.77







1535.551.471635.9598.5



P	'eak #	Ret. Lime	Area %	0
	1	16.40	48.21	(+)
	2	19.01	48.96	(-)
	3	23.37	1.65	
	4	25.13	1.17	
	Total		100.00	







No.	min.	area-%
21	11.21	49.9
22	12.86	50.1





No.	min.	area-%
16	28.78	50.2
17	30.45	49.8



No.	min.	area-%
13	29.50	8.40
14	31.11	91.6





NMR Traces of the Substrates:

































NMR Traces of the Products:





S-37

















.....

50

100

ppm 200 150

.....



















