JOC The Journal of Organic Chemistry

J. Org. Chem., 1998, 63(18), 6084-6085, DOI:10.1021/jo9809332

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General Procedure for the preparation of Oximes from Ketones

Following a standard protocol,[1] sodium acetate (330 mmol) was added to a suspension of hydroxylamine hydrochloride (330 mmol) in methanol (150 ml). After allowing to stir for 0.5 h, ketone (300 mmol) was added dropwise (either as a neat liquid or as a solution in methanol) over 1.5 h. The mixture then was allowed to stir for 2-8 h until the reaction was complete (monitored disappearance of ketone and appearance of oxime by GC). Water (150 ml) was added dropwise over 1 h and then the resultant suspension was stirred for a further 1 h, filtered and the solid precipitate was washed with water and dried under vacuum to afford the ketoxime, typically in >90% yield. This same procedure was employed for all entries in this manuscript.

Procedures for the preparation of Novel Enamides from Oximes

N-(1-*tert*-Butyl-vinyl)-acetamide

Acetic anhydride (398 g, 3.9 mol) was added, in portions, to a solution of pinacolone oxime (150 g, 1.3 mol) in toluene (1 L) under a nitrogen atmosphere. Acetic acid (234 g, 3.9 mol) was then added, followed by Fe powder (Aldrich; 325 mesh) (145.2 g, 2.6 mol). The mixture was then heated to 70 °C for 4 h. The reaction was then cooled to room temperature and filtered through celite to remove solid residues, which were then washed with toluene (2 x 100 ml). The combined filtrates were cooled in an ice-bath and washed with 2M NaOH (2 x 1 L). The organic phase was separated, dried ($MgSO_4$) and evaporated to afford the desired enamide (104 g, 57% yield) as a colorless solid of suitable purity for the subsequent asymmetric hydrogenation process.

^{1}H-NMR ($CDCl_3$): δ 6.48 (s, 1H), 5.63 (s, 1H), 4.80 (s, 1H), 2.10 (s, 3H), 1.13 (s, 9H).
^{13}C-NMR ($CDCl_3$): δ 168.85 (CO), 147.97 (CCH_2), 98.94 (CCH_2), 35.26 ($(CH_3)_3C$), 28.31 ($(CH_3)_3C$), 24.72 (CH_3CO).

N-(1-Adamantan-1-yl-vinyl)-acetamide

Acetic anhydride (7.8 g, 76.4 mmol), followed by acetic acid (4.3 g, 76.4 mmol), was added to a solution of the 1-adamantylmethylketone oxime (5.0 g, 25.9 mmol) in toluene (50 ml), under a nitrogen atmosphere. Fe powder (Aldrich; 325 mesh) (2.9 g, 51.6 mmol) was then added and the mixture heated to 70 °C for 8 h. The reaction was then cooled to room temperature and filtered through celite to remove solid residues which subsequently were washed with toluene (2 x 10 ml). The combined filtrates were cooled in an ice-bath and washed with 2M NaOH (2 x 50 ml). The organic phase was separated, dried ($MgSO_4$) and evaporated to give an oily residue. This was purified by column chromatography (SiO_2 60-mesh, 30g)

(25 % EtOAc in pentane as eluent) to afford the desired enamide as a colorless solid (2.42 g, 43% yield).

^{1}H-NMR ($CDCl_3$): δ 6.50 (s, 1H), 5.64 (s, 1H) 4.76 (s, 1H) 1.5 - 2.2 (m, 18H).
^{13}C-NMR ($CDCl_3$): 168.79 (CO), 148.27 (*C*CH_2), 99.21 (C*C*H_2), 46.50 (C), 40.24 (CH_2), 36.58 (CH_2), 28.23 (CH), 24.33 (*C*H_3CO).

_N_-(3,4-Dihydro-naphthalen-1-yl)-acetamide

Acetic anhydride (85.0 g, 837 mmol), followed by acetic acid (50.3 g, 837 mmol), was added to a solution of the 1-tetralone oxime (45.0 g, 279 mmol) in toluene (400 ml), under a nitrogen atmosphere. Fe powder (Aldrich; 325 mesh) (31.2 g, 558 mmol) was then added and the mixture heated to 70 °C for 4 h. The reaction was cooled to 40 °C and filtered through celite to remove solid residues which were then washed with toluene (2 x 50 ml). The combined filtrates were diluted with dichloromethane (500 ml) and the mixture cooled in an ice-bath and washed with 2M NaOH (2 x 300 ml). The organic phase was then separated, dried ($MgSO_4$) and evaporated to volume of 300 ml from which a solid crystallised. The the precipitate was filtered to afford directly the desired enamide as an off-white solid (28.0 g, 54% yield).

^{1}H-NMR ($CDCl_3$) (3 : 1 mixture of rotamers): δ 7.05 - 7.30 (m, 4H), 6.84 (brs, 0.75H), 6.70 (brs, 0.25H), 6.44 (brt, 0.75H), 5.98 (brt, 0.25H), 2.68 - 2.88 (m, 2H), 2.24 - 2.48 (m, 2H), 2.18 (s, 2.25H), 1.96 (s, 0.75H).
^{13}C-NMR (CD_3OD): 172.81 (CO), 137.69 (CN), 133.62 (C-bridge head), 132.95 (C-bridge head), 128.53 (CH), 128.49 (CH), 127.30 (CH), 123.00 (CH), 122.87 (CH), 28.46 (CH_2), 23.37 (CH_2), 23.05 (CH_3).

_N_-(3*H*-Inden-1-yl)-acetamide

Acetic anhydride (10.4 g, 102 mmol), followed by acetic acid (6.1 g, 102 mmol), was added to a solution of the 1-indanone oxime (5.0 g, 34 mmol) in toluene (50 ml), under a nitrogen atmosphere. Fe powder (Aldrich; 325 mesh) (3.8 g, 68 mmol) was then added and the mixture heated to 70 °C for 0.25 h. The reaction was then cooled to room temperature and filtered through celite to remove solid residues which subsequently were washed with toluene (2 x 10 ml). The combined filtrates were cooled in an ice-bath and washed with 2M NaOH (2 x 50 ml). The organic phase was then separated, dried ($MgSO_4$) and evaporated to afford a residue. This was purified by column chromatography (SiO_2 60-mesh, 100g) (40% EtOAc in pentane as eluent) to afford the desired enamide as a tan solid (1.80 g, 30% yield).

^{1}H-NMR ($CDCl_3$): δ 7.40 - 7.56 (m, 2H), 7.16 - 7.34 (m, 3H), 6.88 (brt, 1H), 3.44 (m, 2H), 2.25 (s, 3H).

^{13}C-NMR ($CDCl_3$): 168.60 (CO), 142.84 (CN), 139.64 (C-bridge head), 135.32 (C-bridge head), 125.99 (CH), 125.44 (CH), 124.31 (CH), 115.99 (CH), 115.73 (CH), 36.57 (CH_2), 24.22 (CH_3).

_N_-(2-Methyl-1-phenyl-propenyl)-acetamide

Acetic anhydride (9.4 g, 91.8 mmol), followed by acetic acid (5.5 g, 91.8 mmol), was added to a solution of the isobutyrophenone oxime (5.0 g, 30.6 mmol) in toluene (50 ml), under a nitrogen atmosphere. Fe powder (Aldrich; 325 mesh) (3.42 g, 558 mmol) was then added and the mixture heated to 70 °C for 4 h. The reaction was then cooled to room temperature and filtered through celite to remove solid residues which subsequently were washed with toluene (2 x 10 ml). The combined filtrates were cooled in an ice-bath and washed with 2M NaOH (2 x 50 ml). The organic phase was then separated, dried ($MgSO_4$) and evaporated to volume of 15 ml, heptane (15 ml) was added to induce crystallisation. The resultant solid was filtered to afford the enamide as a white solid (3.43 g, 60%).

^{1}H -NMR ($CDCl_3$) (3 : 1 mixture of rotamers): δ 7.20 - 7.45 (m, 5H) 6.76 (brs, 0.25H), 6.66 (brs, 0.75H), 2.05 (s, 2.25H), 1.70 - 1.94 (m, 6.25H).
^{13}C-NMR (CD_3OD): 171.83 (CO), 140.20 (CN), 131.09 (Ar), 130.27 (Ar), 129.74 ($C(CH_3)_2$), 129.02 (Ar), 128.25 (Ar), 22.70 (CH_3CO), 21.27 and 20.85 ($C(CH_3)_2$).

Procedure for the Asymmetric Catalytic Hydrogenation of Enamides

Preparation of _N_-(3,3-Dimethyl-2-butyl)-acetamide

_N_-(1-*tert*-Butyl-vinyl)-acetamide (0.5 g, 3.56 mmol) and [((*S,S*)-Me-DuPHOS)-Rh-(COD)]BF_4 (4.2 mg, 0.2 mol%) were placed in a glass lined 50 ml pressure vessel, which was then purged with hydrogen (200 psi x 3). Degassed methanol (10 ml, sparged with nitrogen for 2 h) was then added and the vessel further purged with hydrogen (200 psi x 2) and charged to 200 psi hydrogen. After stirring for 20 h the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*R*)-*N*-(3,3-dimethyl-2-butyl)-acetamide (0.47 g, 95% yield) as a colorless solid. Absolute stereochemical assignment was achieved by comparsion of the sign of optical rotation and chiral gc elution order with a standard sample prepared by acetylation of authentic (*R*)-3,3-dimethyl-2-aminobutane (commercially available; Lancaster Chemicals) using Ac_2O/pyridine.

$[\alpha]^{20}_D$ = -2.9 (*c* 1.0, MeOH).
Enantiomeric excess: >99% by chiral GC (see gc trace below).

^{1}H-NMR ($CDCl_3$): δ 5.51 (d, ^{3}J = 9.8 Hz, 1H), 3.88 (dq, ^{33}J = 9.8 / 6.8 Hz, 1H), 2.00 (s, 3H), 1.07 (d, ^{3}J = 6.8 Hz, 3H), 0.90 (s, 9H).
^{13}C-NMR ($CDCl_3$): δ 169.3 (CO), 52.69 (HCN), 34.06 ($(CH_3)_3C$), 26.15 ($(CH_3)_3C$), 23.63 (CH_3CO), 16.14 (CH_3CH).
m.p. (determined by DSC) 81 °C [lit. 70-71 °C (racemate)][2]
HRMS mass calculated: 144.13884, found 144.13858.

Preparation of *N*-(1-Adamantan-1-yl-ethyl)-acetamide

N-(1-Adamantan-1-yl-vinyl)-acetamide (0.5 g, 2.28 mmol) and [((*R,R*)-Me-DuPHOS)-Rh-(COD)]BF_4 (2.8 mg, 0.2 mol%) are placed in a glass lined 50 ml pressure vessel, which was then purged with hydrogen (200 psi x 3). Degassed methanol (10 ml; sparged with nitrogen for 2 h) was then added and the vessel further purged with hydrogen (200 psi x 2) and charged to 200 psi hydrogen. After stirring for 20 h the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-(1-adamantan-1-yl-ethyl)-acetamide (0.49 g, 97% yield) as a white solid.

Enantiomeric excess: >99% by chiral HPLC (see trace for racemate below)
^{1}H-NMR ($CDCl_3$): δ. 5.42 (d, ^{3}J = 10 Hz, 1H), 3.7 (dt, ^{33}J = 10 / 7 Hz, 1H), 2.15 - 1.40 (m, 18H), 1.02 (d, ^{3}J = 7 Hz, 3H).
^{13}C-NMR ($CDCl_3$): δ 169.45 (CO), 52.98 (HCN), 38.36 (CH_2), 37.05 (CH_2), 35.69 (C), 28.44 (CH), 23.65 (CH_3CO), 14.57 (CH_3CH).
m.p. (determined by DSC) 135 °C [lit. 135 °C (racemate)][3]
HRMS mass calculated: 221.17796, found 221.17790.

Preparation of *N*-Indan-1-yl-acetamide

N-(3*H*-Inden-1-yl)-acetamide (0.5 g, 2.84 mmol) and [((*S,S*)-Me-BPE)-Rh-(COD)]OTf (3.5 mg, 0.2 mol%) are placed in a glass lined 50 ml pressure vessel, which was then purged with hydrogen (200 psi x 3). Degassed methanol (10 ml; sparged with nitrogen for 2 h) was then added and the vessel further purged with hydrogen (200 psi x 2) and charged to 200 psi hydrogen. After stirring for 20 h the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-Indan-1-yl-acetamide (0.49 g, 99% yield) as a tan solid. Absolute stereochemical assignment was achieved by comparsion of the sign of optical rotation and chiral gc elution order with a standard sample prepared by acetylation of authentic (*S*)-1-aminoindane (commercially available; Lancaster Chemicals) using Ac_2O/pyridine.

$[\alpha]^{20}_D$ = -122.4 (*c* 1.0, MeOH).
Enantiomeric excess: > 99% by chiral GC (see chromatograms below)

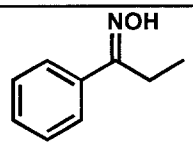
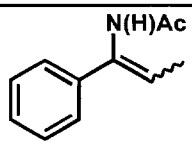
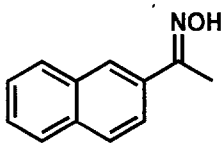
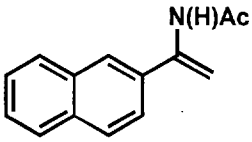
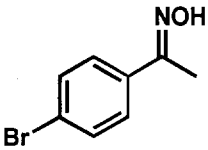
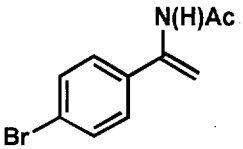
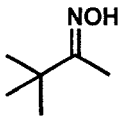
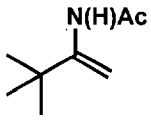
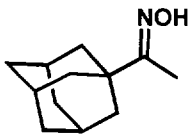
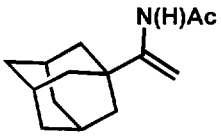
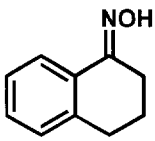
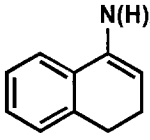
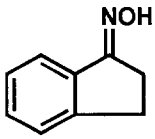
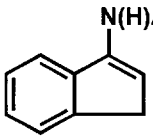
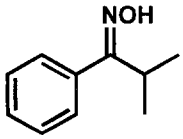
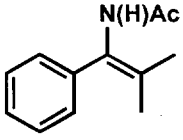
^{1}H-NMR ($CDCl_3$): δ 7.16 - 7.32 (m, 4H), 5.74 (d, ^3J = 9 Hz, 1H), 5.48 (q, ^3J = 7.4 Hz, 1H), 2.98 (m, 1H), 2.87 (m, 1H), 2.62 (apparent ddt, ^2J = 12.9 Hz, ^{333}J = 4.4 / 7.4 / 7.5 Hz, 1H), 2.04 (s, 3H), 1.81 (apparent ddt, ^2J = 12.9, ^{333}J = 7.4 / 7.7 / 8.8 Hz, 1H).
^{13}C-NMR ($CDCl_3$): δ 169.81 (CO), 143.45 (C-bridge head), 143.11 (C-bridge head), 128.00 (Ar), 126.76 (Ar), 124.82 (Ar), 124.01 (Ar), 54.73 (HCN), 34.07 (CH_2), 30.21 (CH_2), 23.47 (CH_3CO).
m.p. (determined by DSC) 154 °C [lit. 125-126 °C (racemate)][4]
HRMS mass calculated: 175.09972, found 175.09946.

Preparation of *N*-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-acetamide

N-(3,4-Dihydro-naphthalen-1-yl)-acetamide (0.5 g, 2.67 mmol) was placed in a glass lined 50 ml pressure vessel, which was then purged with hydrogen (200 psi x 3). Degassed methanol (10 ml) was then added and the vessel further purged with hydrogen (200 psi x 2) and charged to 200 psi hydrogen and then cooled such that the internal temperature was 0 °C. The vessel was then vented and [((*S,S*)-Me-BPE)-Rh-(COD)]OTf (3.2 mg, 0.2 mol%) in degassed methanol (0.5 ml) added, the vessel was then repressurised to 200 psi. After stirring for 20 h the reaction mixture was evaporated to afford a residue. This residue was dissolved in EtOAc (5 ml) and the solution filtered through a short silica plug to remove catalyst residues. The solvent was then evaporated to afford (*S*)-*N*-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-acetamide (0.49 g, 99%) as a tan solid.

Enantiomeric excess: 92% by chiral GC (see trace for racemate below)
^{1}H-NMR ($CDCl_3$): δ 7.04 - 7.30 (m, 4H), 5.87 (brd, 1H), 5.10 - 5.20 (m, 1H), 2.68 - 2.86 (m, 2H), 1.90 - 2.08 (m, 2H), 2.00 (s, 3H), 1.72 - 1.88 (m, 2H).
^{13}C-NMR ($CDCl_3$): δ 169.27 (CO), 137.57 (C-bridge head), 136.65 (C-bridge head), 129.15 (Ar), 128.73 (Ar), 127.26 (Ar), 126.21 (Ar), 47.42 (HCN), 30.07 (CH_2), 29.20 (CH_2), 23.50 (CH_3), 19.88 (CH_2).
m.p. (determined by DSC) 144 °C [lit. 145-146 °C (racemate)][5]
HRMS mass calculated: 189.11536, found 189.11558.

Table 1. Oximes and enamides produced; yields are unoptimized.

Entry	Oxime	Enamide
1	 91%	 74% (*E*/*Z* mixture)
2	 70%	 80%
3	 95%	 63%
4	 95%	 57%
5	 77%	 43%[b]
6	 81%	 54%
7	 84%	 30%[b]
8	 87%	 60%

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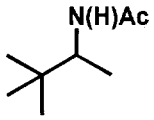
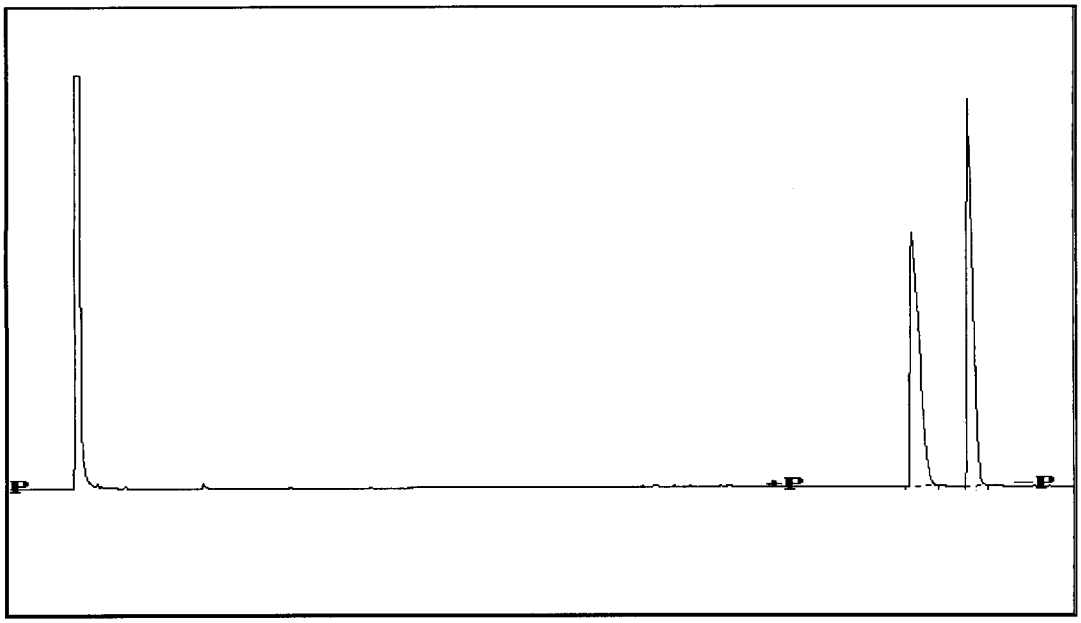
Analytical Methods for Enantiomeric Excess Determination

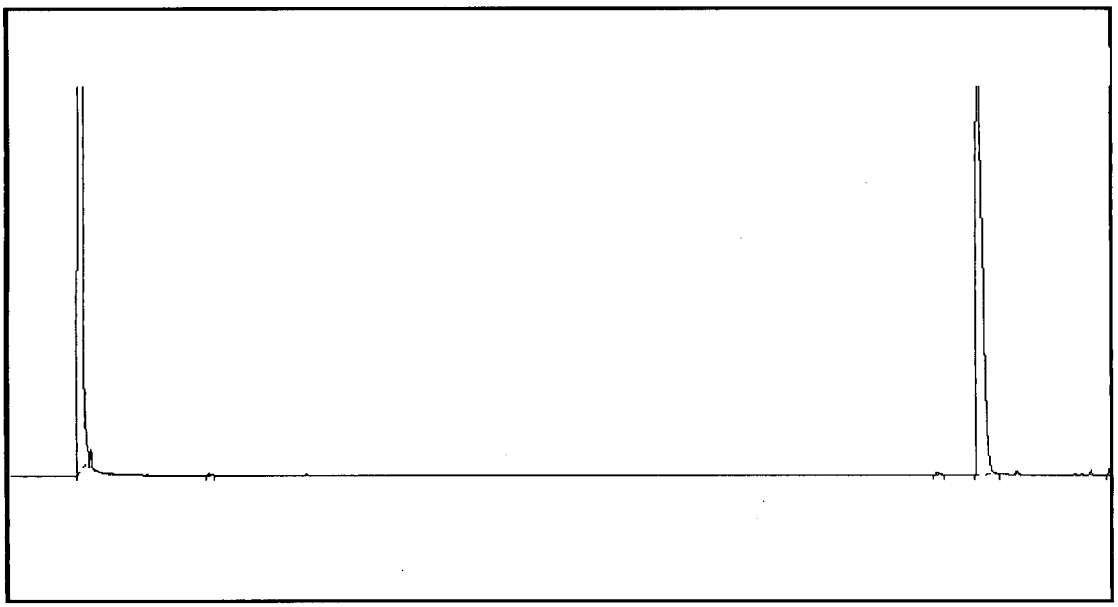


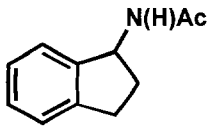
GC Conditions:
Chirasil DEX CB column - 25m x 0.25mm - 0.25μm film thickness
Temp program - 90°C for 15 minutes
Detection - FID at 200°C
Sample solvent - acetone
Retention times: t_1 (*S*) - 12.79 minutes, t_2 (*R*) - 14.18 minutes

Racemic *N*-acetyl-3,3-dimethyl-2-aminobutane



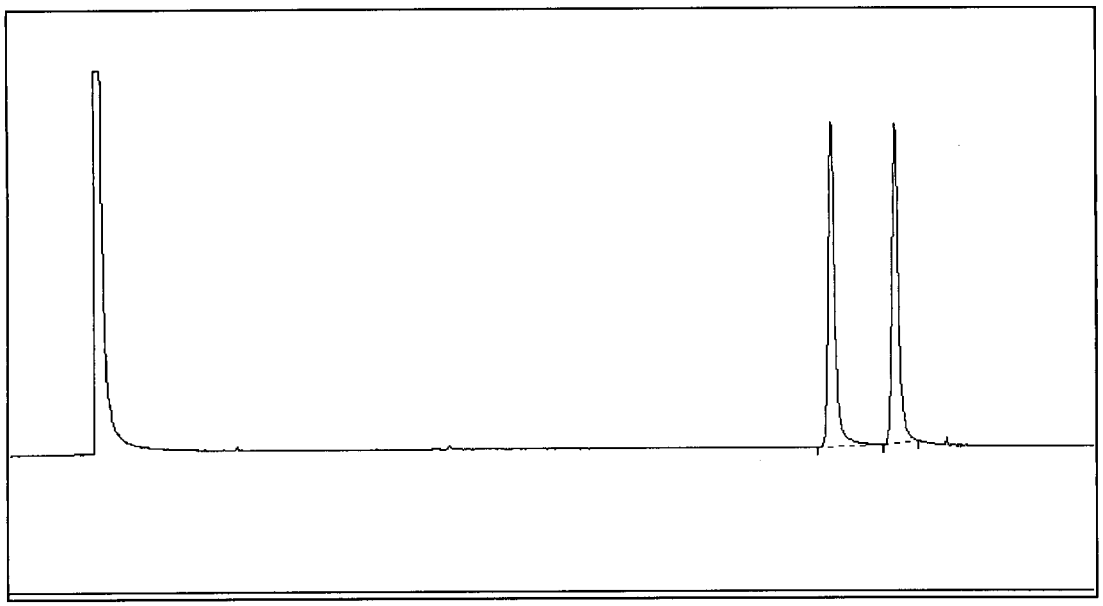
Crude product 9 (*R*)-*N*-acetyl-3,3-dimethyl-2-aminobutane obtained from (*S,S*)-Me-DuPHOS-Rh catalysed hydrogenation of the enamide 8



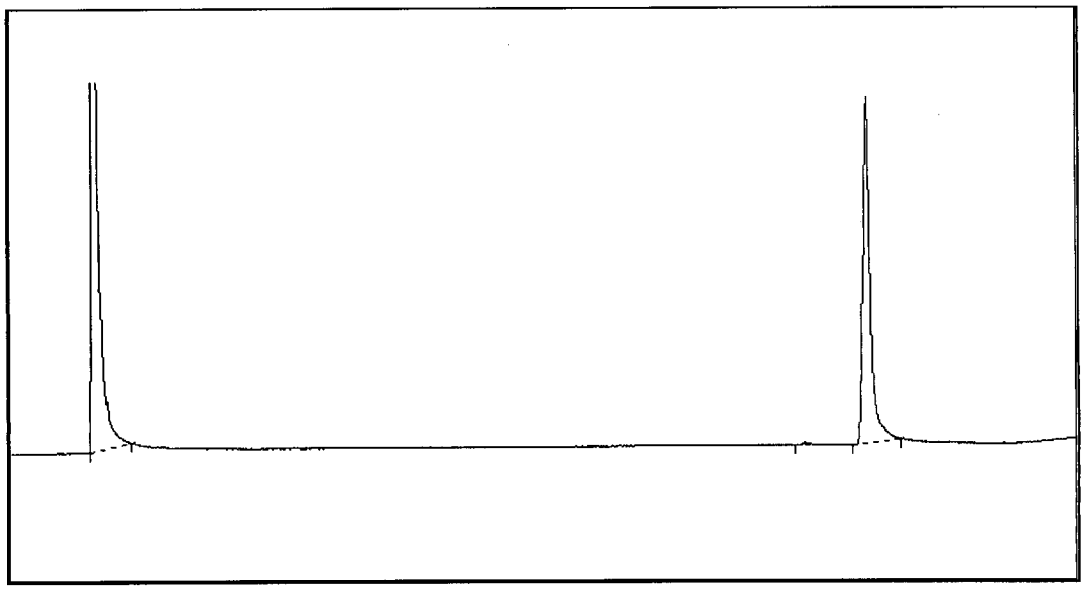


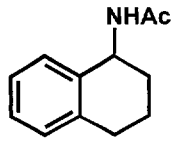
GC Conditions:
Chirasil DEX CB column - 25m x 0.25mm - 0.25μm film thickness
Temp program - 160°C for 15 minutes
Detection - FID at 200°C
Sample solvent - acetone
Retention times: t_1 (*S*) - 12.21 minutes, t_2 (*R*) - 13.15 minutes

Racemic *N*-acetyl-1-aminoindane

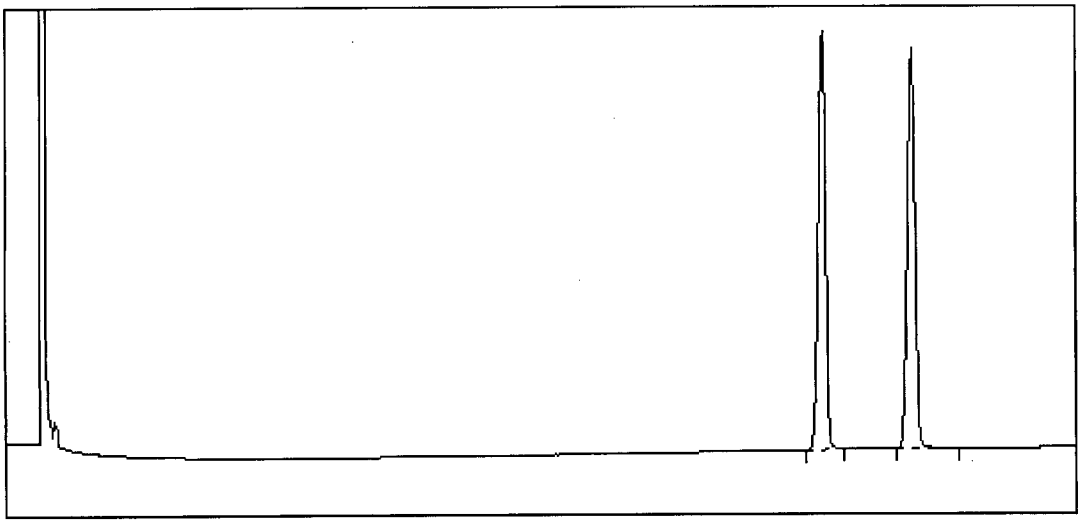


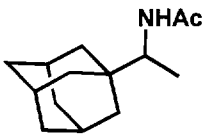
Crude product, (*R*)-*N*-acetyl-1-aminoindane obtained from (*R*,*R*)-Me-BPE-Rh catalysed hydrogenation of the enamide 4



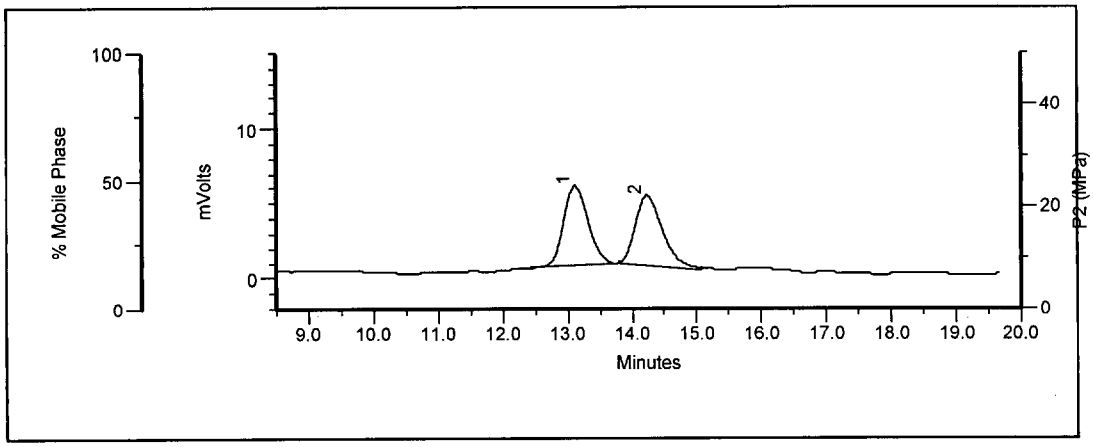


GC Conditions:
Chirasil DEX CB column - 25m x 0.25mm - 0.25μm film thickness
Temp program - 170°C for 15 minutes
Detection - FID at 200°C
Carrier gas - helium at 20 psi
Sample solvent - acetone
Retention times: t_1 - 12.85 minutes, t_2 - 14.43 minutes





SFC Conditions:
Chiralcel OD column - 250 x 4.6mm - 10μm particle size
Mobile phase - 98% CO_2 2% methanol
Flow rate - 3.0ml/min, Pressure - 3000psi
Column temperature - 35°C, Detection - UV at 210nm
Retention times: t_1 - 13.12 minutes, t_2 -14.23 minutes



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References for Supporting Information

1. For standard protocol, see Bousquet, E.W.; Carothers, W.H.; McEwen, W.L. *Organic Synthesis*, Coll. Vol. II, Wiley and Sons: New York, 1943, pp. 313-315. For a specific procedure, see, Holmes, A.B.; Smith, A.L.; Williams, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.
2. Fu, S.-C. J; and Birnbaum, S.M. *J. Am. Chem Soc.* **1953**, *75*, 918.
3. Manchand, P.S.; Cerruti, R.L.; Martin, J.A.; Hill, C.H.; Merrett, J.H.; Keech, E.; Belshe, R.B.; Connell, E.V.; Sim, I.A. *J. Med. Chem.* **1990**, *33*, 1992.
4. Huebner,C.F.; Donoghue, E.M.; Strachan, P.L.; Beak, P.; Wenkert, E. *J. Org. Chem.* **1962**, *27*, 4465
5. Drefahl, G.; Ponsold, K. *Chem. Ber.* **1960**, *93*, 519.