Organic Syntheses

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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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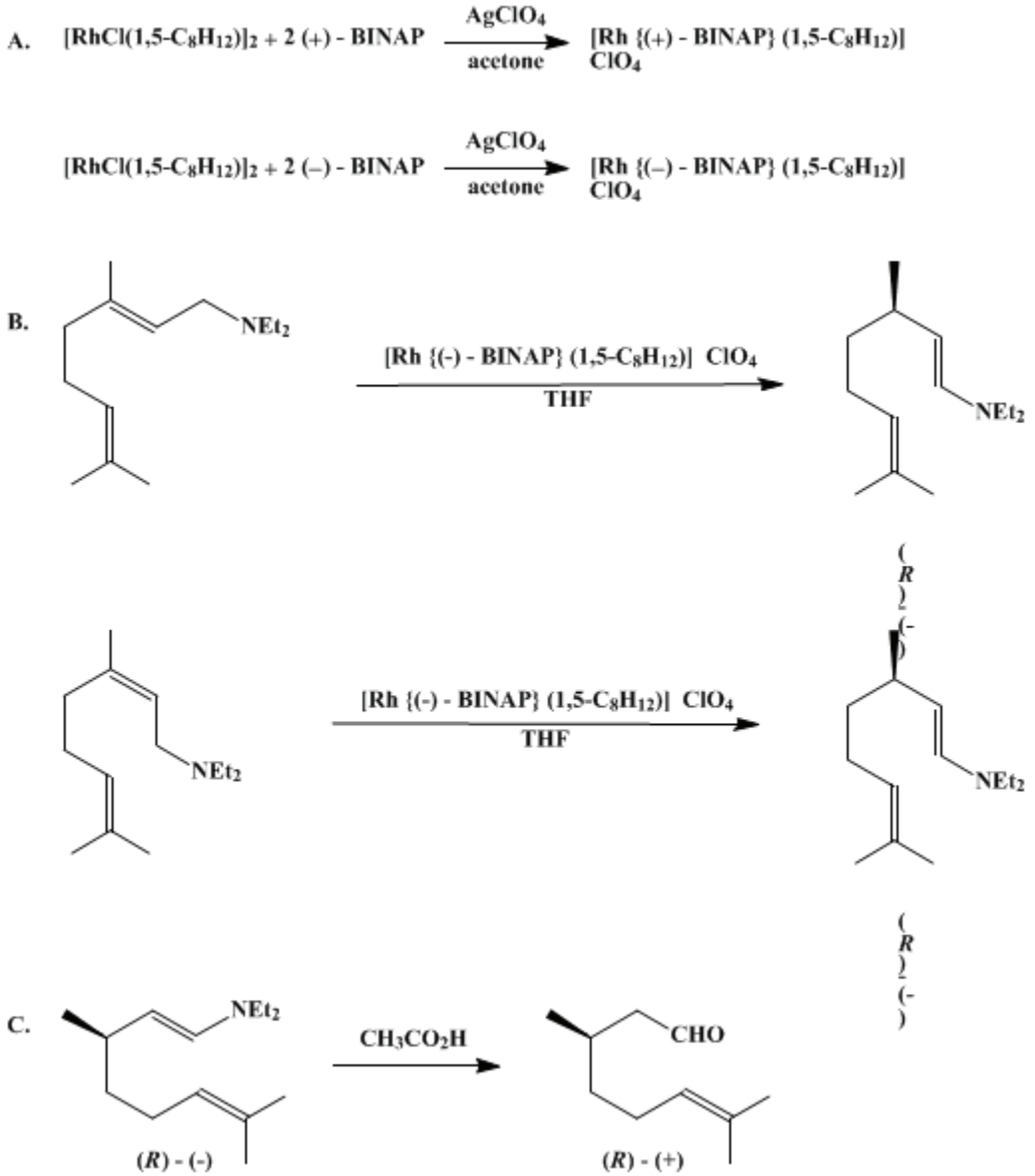
(*R*)-(−)-*N*,*N*-DIETHYL-(*E*)-CITRONELLALENAMINE AND (*R*)-(+)-CITRONELLAL VIA ISOMERIZATION OF *N*,*N*-DIETHYLGERANYLAMINE OR *N*,*N*-DIETHYLNERYLAMINE

[1-(*E*), 6-Octadienamine, (*R*)-(−)-*N*,*N*-diethyl-3,7-dimethyl- and 6-octenal, 3,7-dimethyl-, (*R*)-(+)-]



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1. Procedure

Caution! All manipulations for the preparation of the transition-metal complexes and the catalytic isomerization should be carried out under dry nitrogen or argon. All solvents used are distilled under dry nitrogen over metallic sodium, or after drying over calcium sulfate (in the case of acetone)

immediately before use.

A. [*(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl*]-*(η⁴-1,5-cyclooctadiene) rhodium(I) perchlorate*. [*Rh{(+)-BINAP} (1,5-C_8H_{12})*] *ClO_4*. A dry, 250-mL Schlenk flask, filled with dry nitrogen or argon and equipped with a magnetic stirring bar, is charged with 0.53 g (1.08 mmol) of chloro-(1,5-cyclooctadiene)rhodium(I) dimer (Note 1). Then 40 mL of dry acetone is added using an airtight syringe. The flask is protected from light by wrapping it with aluminum foil and 0.45 g (2.17 mmol) of silver perchlorate is added to the stirred suspension. The mixture is stirred for 1 hr at ambient temperature. The colorless precipitate of silver chloride is removed by suction filtration under argon through a stainless-steel cannula fitted with a filter tip (Note 2). The precipitates are washed with 5 mL of acetone. To the pale-orange filtrate and the washings is added 1.34 g (2.16 mmol) of (+)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl [(+)-BINAP] (Note 3) and the resulting dark-red solution is stirred under argon for 18 hr at ambient temperature. The reaction mixture is concentrated under reduced pressure (60 mm) to ca. 3 mL. Then 30 mL of ether is slowly added with a syringe. The resulting mixture is stirred at ambient temperature for 18 hr. The orange solid is filtered off under argon and washed with 5 mL of ether. The crude product is dissolved in 50 mL of dry acetone and the solution is concentrated to ca. 3 mL under 60 mm pressure. Dry ether (30 mL) is slowly added and the mixture is stirred for 18 hr. The deep-orange crystals are collected by filtration, washed with 5 mL of dry ether, and dried under vacuum to afford 2.07 g of recrystallized product, 230–235°C (dec) (Note 4).

[*(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl*] *(η⁴-1,5-cyclooctadiene) rhodium(I) perchlorate*: [*Rh{(−)-BINAP}(1,5-C_8H_{12})*] ClO_4 is similarly prepared from 0.53 g (1.08 mmol) of chloro-(1,5-cyclooctadiene)rhodium(I) dimer, 0.45 g (2.17 mmol) of silver perchlorate, and 1.34 g (2.16 mol) of (−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(−)-BINAP] (Note 5) in acetone. The crude product is recrystallized from acetone–ether as above to give 2.02 g of orange powder, mp 230°C (dec) (Note 6).

B. *(R)-(−)-N,N-Diethyl-(E)-citronellalenamine* [*(R)-(−)-N,N-Diethyl-3,7-dimethyl-1(E),6-octadienylamine*]. *From N,N-diethylgeranylamine*. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer, a reflux condenser and an argon inlet is charged with 373 mg (0.40 mmol) of [(−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η⁴-1,5-cyclooctadiene)rhodium(I) perchlorate. The flask is evacuated and refilled with argon 4 times. Another 500-mL, three-necked, round-bottomed flask is charged with 83.8 g (0.40 mol) of *N,N*-diethylgeranylamine (Note 7) and 250 mL of distilled tetrahydrofuran (Note 8) under an argon blanket. This solution is transferred under argon by cannula to the flask containing the catalyst, which is then evacuated and refilled with argon twice. The reaction mixture is stirred and heated at reflux for 21 hr (Note 9). The solution is cooled to room temperature and the solvent is removed under vacuum (60 mm) at 45°C. The residue is vacuum-distilled through a 10-cm Vigreux column to give 78.7 g (93.9%) of *(R)-(−)-N,N*-diethyl-(*E*)-citronellalenamine as a colorless liquid, bp 84–85°C (1.1 mm), $[\alpha]_D^{25}$ −66.5° (hexane, *c* 10.2). The product is 97.2% chemically pure by GLC analysis (Note 10),(Note 11),(Note 12).

From N,N-diethylnerylamine. Similarly, 83.8 g (0.40 mol) of *N,N*-diethylnerylamine (Note 13) is isomerized with 373 mg (0.40 mmol) of [(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](η⁴-1,5-cyclooctadiene)rhodium(I) perchlorate catalyst in 250 mL of THF (Note 8) at reflux for 70 hr (Note 9) to give 77.2 g (92.1%) of (*R*)-(−)-*N,N-diethyl*-(*E*)-citronellalenamine, $[\alpha]_D^{25}$ −66.9° (hexane, *c* 10.7). The chemical purity of the product is 91.7% by GLC (Note 10), (Note 12), and (Note 14).

C. *(R)-(+)-Citronellal*. [*(R)-(+)-3,7-Dimethyl-6-octanal*]. A 500-mL, round-bottomed flask equipped with a magnetic stirrer and an ice bath is charged with 33.4 g (0.16 mol) of (*R*)-(−)-*N,N*-diethyl-(*E*)-citronellalenamine in 80 mL of ether at 0°C. To this stirred solution is added 80 mL of a 1 : 4 glacial acetic acid–deionized water solution in one portion (Note 15). The reaction mixture is stirred for 5 min at 0°C and then at room temperature for 25 min. The ether layer is separated and washed successively with 50 mL of water, two 50-mL portions of saturated aqueous sodium bicarbonate solution, 50 mL of water, and 50 mL of saturated brine. The ether layer is dried over anhydrous sodium sulfate and filtered (Note 16). The ether solution is concentrated at 40°C under reduced pressure (60 mm) to a pale-yellow liquid. The liquid is distilled through a 10-cm Vigreux column to give 22.5 g (91.4%) of (+)-citronellal as a colorless liquid, bp 79–80°C (7 mm), $[\alpha]_D^{25}$ +15.7° (neat, d 0.851). The product is 99.4% chemically pure by GLC and has an optical purity of 95.2% (Note 17).

2. Notes

1. Chloro(η⁴-1,5-cyclooctadiene)rhodium(I) dimer [RhCl(1,5-C_8H_{12})] can be prepared according to the method described in *Inorganic Syntheses*.[3] The checkers used material purchased from the Aldrich Chemical Company, Inc.

2. This can also be done as previously described in *Inorganic Syntheses*.[4]

3. (*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl was prepared according to Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth., Coll. Vol. VIII*, **1993**, 57.

4. The submitters obtained 1.5–1.7 g of analytically pure material with mp 164°C (dec). The ^{1}H NMR (CD_2Cl_2) of this product showed signals at δ: 2.00–2.62 (m, 8 H, -CH_2-), 4.58 (br signal, 2 H, -CH=), 4.84 (br signal, 2 H, -CH=), 6.42–8.22ppm (m, 32 H, aromatic). Anal. calcd. for ($C_{52}H_{44}ClO_4Rh$): C, 66.93; H, 4.75; Cl, 3.80. Found: C, 66.66; H, 4.89; Cl, 3.92.

5. (*S*)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl was prepared according to the *Organic Syntheses* procedure; see (Note 3).

6. The submitters used THF–ether for recrystallization, in which case the product was obtained as a THF-solvated complex, [Rh{(−)-BINAP} (1,5-C_8H_{12})]ClO_4 THF, in the form of deep-orange crystals, mp 153°C (dec). Its ^{1}H NMR (CD_2Cl_2) spectrum clearly showed the presence of the solvating tetrahydrofuran; δ: 1.60–2.00 (m. 4 H, -CH_2- of THF), 2.00–2.62 (m, 8 H, -CH_2-), 3.40–3.80 (m, 4 H, -CH_2O- of THF), 4.58 (br signal, 2 H, -CH=), 4.82 (br, signal, 2 H, -CH=), 6.40–7.97 (m, 32 H, aromatic). Anal. calcd. for ($C_{52}H_{44}ClO_4RhC_4H_8O$): C, 66.90; H, 5.21; Cl, 3.53. Found: C, 66.55; H, 5.62; Cl, 3.68.

7. *N,N*-Diethylgeranylamine was prepared according to the method described in *Org. Synth., Coll. Vol. VIII*, **1993**, 188. The submitters used material of 99.7% purity (determined by GLC; Hitachi 063 with OV-101 in fused silica, 0.2-mm × 25-m column) that was obtained by careful distillation through a column with one hundred theoretical plates, bp 70°C (2 mm), and redistilled over calcium hydride before use. The checkers used a 32-cm Goodloe column and collected the amine at 105°C (2.4 mm), which had a purity of 100% (GLC).

8. Acetone or methanol also may be used. However, tetrahydrofuran gives the best results. The solvents should be strictly dry because water deactivates the catalyst.

9. The submitters ran the reaction at 60°C for 24 hr.

10. Purity of the product and progress of the isomerization can be determined by GLC (Triton X 305 packed in a 0.2 mm × 30 m glass column from Gasukuro Kogyo Co. Ltd., or a column-crosslinked 5% phenylmethyl silicone, 25-m high-performance capillary column supplied by Hewlett Packard. Starting temperature, 125°C; rate 3°/min; final temperature, 180°C). The product enamine is 100% (*E*)-isomer. The spectral properties of the product are as follows: IR (neat) cm^{-1}: 3045, 2960, 2915, 2860, 2720, 1660, 1655, 1450, 1377, 1298, 1245, 1196, 1100, 985, 937, 886, 830, 784, 740; ^{1}H NMR (acetone d_6) δ: 0.96 (d, 3 H, J = 7.2), 1.01 (t, 6 H, J = 7.1), 1.1–1.4 (m, 2 H), 1.58 (br s, 3 H), 1.66 (br s, 3 H), 1.8–2.1 (m, 3 H), 2.92 (q, 4 H, J = 7.1), 3.93 (d of d, 1 H, J = 14.6, 8.4), 5.11 (br t, 1 H, J = 7.3), 5.79 (d of d, 1 H, J = 14.6, 0.8).

11. The submitters report 92–96% yields of 98% chemically pure product, bp 80–82°C (1 mm), $[\alpha]_D^{25}$ −74.3° (hexane, *c* 10.0). The specific rotation was corrected for this purity (Note 12). A specific rotation of $[\alpha]_D^{25}$ −77.6° (hexane) is estimated for the pure enamine.

12. The product is very moisture sensitive and should be handled under dry nitrogen or argon. Despite this precaution, the product is always contaminated by small amounts of (+)-citronellal, which has an optical rotation opposite to that of the enamine. To determine the optical purity of the product enamine, the specific rotation measured therefore must be corrected for the (+)-citronellal impurity. It is more reliable to base optical purity on the specific rotation of the citronellal obtained by hydrolysis of the enamine (Part C). The absolute method using HPLC of the diastereomeric amide derivative[5] also may be useful as a check of the optical purity.

13. *N,N*-Diethylnerylamine was prepared according to the method described in *Org. Synth., Coll. Vol. VIII*, **1993**, 190, and distilled over calcium hydride and stored under nitrogen below −20°C. GLC–MS analysis (Hitachi 063 and Hitachi RMU-6MG with OV-101 in fused silica, 0.2-mm × 25-m column) of *N,N*-diethyl-nerylamine used by the submitters showed a purity of 94.9%, and contained *N,N*-diethyl-2-ethylede-6-methyl-5-heptenylamine (0.2%), *N,N*-diethyl-2,7-dimethyl-2,6-octadienylamine (1.5%), *N,N*-diethyl-3-methylene-7-methyl-6-octenylamine (2.1%), and unidentifiable products (1.3%) as impurities, but not the (*E*)-isomer, *N,N*-diethylgeranylamine. The checkers distilled the nerylamine

through a 32-cm Goodloe column, bp 102°C (3 mm), and achieved a purity of 98.6%.
14. The submitters obtained 90–95% yields of 94% chemically pure product, $[\alpha]_D^{24}$ −73.1° (hexane, *c* 10.0; corrected for the citronellal impurity).
15. The submitters conducted the hydrolysis step in a mixture of 2 *N* sulfuric acid and toluene. The acid is added dropwise at 0°C at a rate that keeps the pH of the mixture at 4–5. Control of pH is critical.
16. Rapid workup after the acid hydrolysis is desirable.
17. A specific rotation of $[\alpha]_D^{25}$ +16.5° (neat) is reported for optically pure citronellal.[6]

3. Discussion

(*R*)-(+)-Citronellal is a useful, key intermediate for the preparation of several important, optically active compounds such as citronellol, 1-menthol,[6] muscone,[7] and α-tocopherol.[8] The optical purity of citronellal from natural sources is at most 77% ee, however. This new procedure gives (*R*)-(+)-citronellal of high optical purity (> 95% ee).

The intermediate enamine, (*R*)-(−)-*N,N*-diethyl-(*E*)-citronellalenamine, is also a key intermediate for preparation of useful, optically active compounds, such as (+)-7-hydroxydihydrocitronellal.[9]

Isomerization of *N,N*-diethylnerylamine with [Rh{(−)-BINAP} (1,5-C_8H_{12})] ClO_4 and *N,N*-diethylgeranylamine with [Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4 under conditions similar to those described in the text ([substrate]/[Rh] = 100, in THF, 40°C, 23 hr) proceed equally efficiently to give (+)-*N,N*-diethyl-(*E*)-citronellalenamine in good chemical (97 and 95%, respectively) and optical yields (92 and 96%, respectively). Thus, unnatural (*S*)-(−)-citronellal with high optical purity (> 95% ee) can also be prepared by the new procedure. The substrates must be geometrically pure and the chiral ligands enantiomerically pure in order to achieve optimal results.

If extreme care is taken to purify the substrate and the solvent, the [substrate]/[Rh] ratio can be raised much higher. For example, *N,N*-diethylgeranylamine can be isomerized in tetrahydrofuran in the presence of 0.00125 mol% of [Rh{(−)-BINAP} (1,5-C_8H_{12})] ClO_4 at 100°C in a glass autoclave during 3–7 hr to give (−)-*N,N*-diethyl-(*E*)-citronellalenamine with 97% ee in almost quantitative yield.

With the same catalyst systems, other prochiral *N*-alkyl- or *N,N*-dialkylallylamines can also be isomerized efficiently to the corresponding optically active imines or (*E*)-enamines, respectively. For example, with [Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4, ([substrate]/[Rh] = 100, in THF, 40°C, 23 hr) a secondary allylamine, *N*-cyclohexylgeranylamine, and an allylamine with styrene-type conjugation, *N,N*-dimethyl-3-phenyl-2(*E*)-butenylamine, are isomerized to give (*S*)-(−)-*N*-cyclohexylcitronellalimine (chemical yield, 100%; optical yield, 96%) and (*R*)-(−)-*N,N*-dimethyl-3-phenyl-1(*E*)-butenylamine (chemical yield, 84%; optical yield, 90%), respectively.

Under similar conditions, various kinds of *N,N*-dialkylamines with substituents at δ-or γ-positions; for example, *N,N*-dimethyl-2-propenylamine, *N,N*-dimethyl-2(*E*)-butenylamine, *N,N*-dimethyl-2-methyl-2-propenylamine, and *N,N*-dimethyl-3-methyl-2-butenylamine can also be isomerized to the corresponding (*E*)-enamine in medium to good yields (60, 52, 97, and 100%). However, *N,N*-dimethyl-2(*E*)-butenylamine and *N*-phenyl- or *N,N*-diphenylgeranylamine were found to be poor substrates.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 57

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

(R)-(−)-N,N-DIETHYL-(E)-CITRONELLALENAMINE

1-(E), 6-Octadienamine, (R)-(−)-N,N-diethyl-3,7-dimethyl- and 6-octenal, 3,7-dimethyl-, (R)-(+)-

[Rh{(+)-BINAP} (1,5-C_8H_{12})] ClO_4

chloro-(1,5-cyclooctadiene)rhodium(I) dimer

(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(+)-BINAP]

[Rh{(−)-BINAP}(1,5-C_8H_{12})] ClO_4

(−)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(−)-BINAP]

(R)-(−)-N,N-Diethyl-(E)-citronellalenamine [(R)-(−)-N,N-Diethyl-3,7-dimethyl-1(E),6-octadienylamine]

[Rh{(−)-BINAP} (1,5-C_8H_{12})]ClO_4 THF

N,N-diethyl-2-ethylede-6-methyl-5-heptenylamine

muscone

(+)-7-hydroxydihydrocitronellal

[Rh{(−)-BINAP} (1,5-C_8H_{12})] ClO_4

(S)-(−)-citronellal

(−)-N,N-diethyl-(E)-citronellalenamine

N-phenyl- or N,N-diphenylgeranylamine

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium bicarbonate (144-55-8)

silver chloride (7783-90-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

calcium sulfate (7778-18-9)

acetone (67-64-1)

toluene (108-88-3)

sodium (13966-32-0)

Allylamine (107-11-9)

Tetrahydrofuran,
THF (109-99-9)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

1,5-cyclooctadiene

citronellal,
(+)-citronellal (106-23-0)

silver perchlorate (7783-93-9)

N,N-Diethylnerylamine,
N,N-diethyl-nerylamine (40137-00-6)

N,N-Diethylgeranylamine (40267-53-6)

rhodium(I) perchlorate

citronellol (106-22-9)

1-menthol

α-tocopherol (59-02-9)

cyclohexylcitronellalimine

(S)-(-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl,
(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl (76189-56-5)

(R)-(+)-Citronellal (2385-77-5)

N,N-diethyl-2,7-dimethyl-2,6-octadienylamine

N,N-diethyl-3-methylene-7-methyl-6-octenylamine

(+)-N,N-diethyl-(E)-citronellalenamine

N-cyclohexylgeranylamine

N,N-dimethyl-3-phenyl-2(E)-butenylamine

dimethyl-3-phenyl-1(E)-butenylamine

N,N-dimethyl-2-propenylamine (2155-94-4)

N,N-dimethyl-2(E)-butenylamine

N,N-dimethyl-2-methyl-2-propenylamine

N,N-dimethyl-3-methyl-2-butenylamine