Organic Syntheses

Synthesis of Optically Active 1,2,3,4-Tetrahydroquinolines *via* Asymmetric Hydrogenation Using Iridium-Diamine Catalyst

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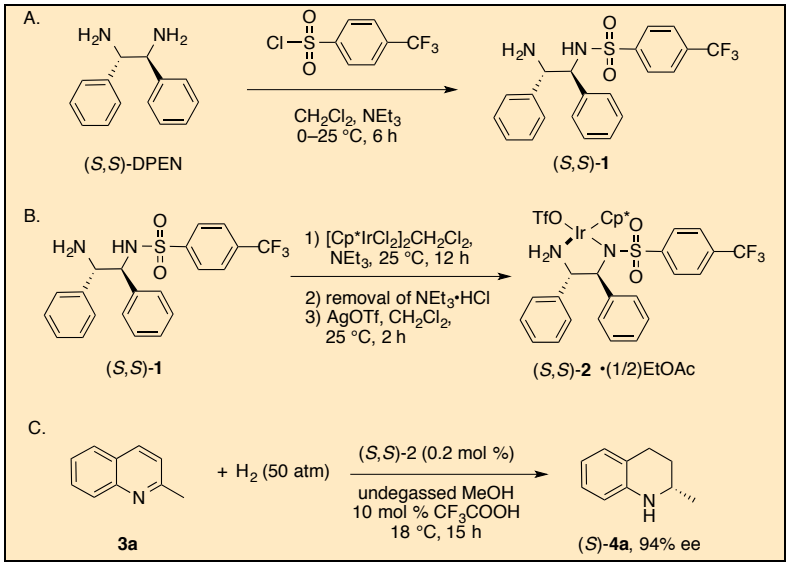
Checked by Douglass C. Duquette and Brian Stoltz



Procedure

A. *(1S,2S)-(–)-N-4-(Trifluoromethyl)benzenesulfonylated-DPEN ((S,S)-**1**).*[2] An oven-dried 100-mL three-necked, round-bottomed flask equipped with an oven-dried 50-mL dropping funnel in the middle neck, an argon line attached to a glass gas adaptor in one of the side necks, a glass stopper in the other side neck, and an octagonal magnetic stir bar (6 mm x 25 mm) is

assembled hot under an atmosphere of argon and cooled to room temperature. The glass stopper is removed under positive pressure of argon, and the flask is charged with (1*S*,2*S*)-(–)-1,2-diphenyl-1,2-ethanediamine (DPEN) (Note 1) (1.06 g, 5.00 mmol, 1.00 equiv), triethylamine (Note 2) (1.30 mL, 10.00 mmol, 2.00 equiv) and dichloromethane (Note 3) (40 mL), after which point the glass stopper is replaced with a rubber septum pierced with a thermometer. The resulting solution is cooled to 1 °C (internal temperature) with an ice bath. A solution of 4-(trifluoromethyl)benzenesulfonyl chloride (Note 4) (1.22 g, 5.00 mmol, 1.00 equiv) in dichloromethane (20 mL) is added dropwise from the dropping funnel over 30 min into the reaction mixture, reaching a maximum internal temperature of 3 °C. After the completion of addition, the resulting mixture is warmed to room temperature (20 °C) and stirred for additional 6 h, at which point the reaction is white and heterogeneous. The reaction mixture is transferred to a 125-mL separatory funnel, washed with water (20 mL) and saturated aqueous sodium chloride (Note 5) solution (20 mL), and then dried over anhydrous sodium sulfate (Note 6) (10 g) for 30 min. After filtration through a medium-porosity fritted funnel, the organic solvent is removed under reduced pressure (40 °C, 30 mmHg) by rotary evaporation to give a white solid (1.90–1.99 g). The resulting crude product is dissolved in ethyl acetate (Note 7) (22 mL) under refluxing conditions, and then petroleum ether (Note 8) (6 mL) is added dropwise until the solution becomes slightly turbid. The mixture is cooled initially to room temperature to provide white crystals, and then left standing at –20 °C in refrigerator for another 4 h. The crystalline product is isolated by filtration through a Büchner funnel (Φ 60 mm), washed with cooled ethyl acetate/petroleum ether solution (1/1, *v*/*v*, 6 mL; –20 °C), and then dried in *vacuo* (50 °C at 6 mmHg for 24 h) to provide 1.71–1.75 g (81–84% yield) of (*S*,*S*)-**1** (Note 9) as white crystals.

B. *[IrOTf(Cp*)((S,S)-N-4-(Trifluoromethyl)benzenesulfonylated-DPEN)] ((S,S)-***2***).* An oven-dried 50-mL round-bottomed flask is equipped with an octagonal magnetic stir bar (6 mm x 25 mm) and a rubber septum fitted with an argon inlet needle. The flask is flushed with argon and charged with (pentamethylcyclopentadienyl)iridium(III) dichloride dimer ($[IrCp^*Cl_2]_2$) (Note 10) (0.796 g, 1.00 mmol, 1.00 equiv) and (*S*,*S*)-**1** (0.840 g, 2.00 mmol, 2.00 equiv). A solution of triethylamine (0.58 mL, 4.00 mmol, 4.00 equiv) in dichloromethane (20 mL) is added to the flask through the septum by syringe. The resulting deep red-orange mixture is stirred at 23 °C for 12 h, and the reaction is monitored by TLC analysis (Note 11).[3] After the

reaction is complete, the organic solvent and the excess triethylamine are removed under reduced pressure (40 °C, 30 mmHg) by rotary evaporation. The resulting residue (1.85 g yellow solid) is dissolved in dichloromethane (6 mL), and subjected to flash column chromatography over silica gel (20 g, dichloromethane/methanol, 100/1, *v*/*v*, 300 mL) (Notes 12 and 13) to remove the triethylamine hydrochloride salt, providing the crude product (1.66–1.71 g) as a light yellow solid.

An oven-dried 50-mL round-bottomed flask is equipped with an octagonal magnetic stir bar (6 mm x 25 mm) and a rubber septum fitted with an argon inlet needle. The flask is flushed with argon and charged with the crude product (1.66–1.71 g) and silver trifluoromethanesulfonate (Note 14) (0.514 g, 2.00 mmol, 1.00 equiv). Dichloromethane (20 mL) is added to the flask through the septum by syringe under argon atmosphere. The resulting mixture is stirred at 25 °C for 2 h. After separation of the silver chloride precipitate by filtration through a Büchner funnel (Φ 60 mm) packed with Celite (Note 15) (3 g), the organic solvent is removed under reduced pressure (40 °C, 30 mmHg) by rotary evaporation to give 1.78 g of dark red solid. The resulting crude product is dissolved in ethyl acetate (6 mL) at 25 °C, and then petroleum ether (3 mL) is added dropwise until the solution becomes slightly turbid. The mixture is left standing at room temperature for 2 h, allowing slow evaporation of the solvent. When little crystal seeds appear, shaking the flask achieves complete crystallization. The crystalline product is isolated by filtration through a Büchner funnel (Φ 60 mm), washed with ethyl acetate/petroleum ether solution (2/1, *v*/*v*, 3 mL), and dried in *vacuo* (50 °C and 5 mmHg for 3 days) (Note 16) to provide 1.55–1.61 g (83–86% total yield) of (*S*,*S*)-**2** (Note 17) as a dark red solid.

C. *2-Methyl-1,2,3,4-tetrahydroquinoline* ((*S*)-**4a**). A 50-mL glass tube equipped with an octagonal magnetic stir bar (6 mm x 25 mm) is charged with 2-methylquinoline (Note 18) (10.00 g, 69.90 mmol, 1.00 equiv) and (*S*,*S*)-**2** (0.125 g, 0.133 mmol, 0.002 equiv). A solution of trifluoroacetic acid (Note 19) (0.797 g, 6.99 mmol, 0.10 equiv) in undegassed methanol (Note 20) (7 mL) is added to the tube under air atmosphere. The glass tube is then placed into a stainless steel autoclave. The autoclave is closed and connected to a hydrogen source from a cylinder (Note 21). After the autoclave is purged with hydrogen three times *via* pressurization and depressurization, the autoclave is pressurized with 50 atm of hydrogen (Note 22). The mixture is stirred at 18 °C (room temperature) for 15 h. During this period of time, the hydrogen pressure is kept at 50 atm by occasional introduction of hydrogen from the cylinder. When the consumption of hydrogen ceases, the gas-inlet tube is disconnected. After the excess hydrogen gas is carefully released by opening the valve, the autoclave is opened. The reddish reaction mixture is transferred into a 125-mL Erlenmeyer flask and diluted with dichloromethane (30 mL) and saturated aqueous sodium carbonate (Note 23) solution (30 mL). The resulting solution is stirred for 20 min and then transferred to a 125-mL separatory funnel. The organic layer is separated, and the aqueous layer is extracted with dichloromethane (30 mL). The combined organic layer is dried over anhydrous sodium sulfate (10.0 g) for 30 min and concentrated under reduced pressure (40 °C, 40 mmHg) by rotary evaporation to afford the crude product. Purification is performed by column chromatography over silica (Note 24) to give 9.84–9.90 g of nearly pure product as a yellow oil. This oil is transferred to a 25 mL round-bottomed flask and distilled using a Kugelrohr apparatus (oven temperature 95 °C, 5–7 mmHg) to afford 9.19–9.28 (91–92% yield) of (*S*)-**4a** (Note 25) as a pale yellow oil. The enantiomeric excess of (*S*)-**4a** is 94% determined by chiral HPLC with a chiral OJ-H column (Notes 26 and 27).

Notes

1. (1*S*,2*S*)-(-)-1,2-Diphenyl-1,2-ethanediamine (98+%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.

2. Triethylamine (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
3. Dichloromethane (99.7+%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
4. 4-(Trifluoromethyl)benzenesulfonyl chloride (98%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
5. Sodium chloride (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
6. Sodium sulfate (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
7. Ethyl acetate (99.5+%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
8. Petroleum ether 40/60 was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
9. (*S*,*S*)-**1**: White crystals; mp 208–211 °C; $[\alpha]_D^{20}$ = +21.4 (*c* 0.5, chloroform), [Lit.[2] $[\alpha]_D^{26}$ = +22.4 (*c* 0.5, chloroform), 100% ee for (1*S*,2*S*) enantiomer]; IR (thin film, NaCl) 3337, 3289, 3085, 2854, 1597, 1454, 1403, 1330, 1162, 1150, 1127, 1108, 1098, 1055 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 3.98 (d, *J* = 7.1 Hz, 1 H), 4.16 (br, s, 3 H), 4.37 (d, *J* = 7.1 Hz, 1 H), 6.94 (d, *J* = 4.1 Hz, 5 H), 7.00–7.21 (m, 5 H), 7.57 (s, 4 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 60.4, 65.0, 122.4, 124.5, 125.6, 125.6, 125.6, 125.7, 126.4, 126.6, 126.7, 127.0, 127.2, 127.3, 127.4, 127.6, 127.8, 130.9, 131.1, 131.4, 131.7, 139.2, 142.4, 144.9; Anal. Calcd. for $C_{21}H_{19}F_3N_2O_2S$ C, 59.99; H, 4.55; N, 6.66; Found C, 60.23; H, 4.73; N, 6.75.
10. (Pentamethylcyclopentadienyl)iridium(III) dichloride dimer (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
11. Checkers performed thin layer chromatography (TLC) using E. Merck silica gel 60 F254 precoated plates (0.25 mm) eluting with dichloromethane/methanol (20/1, *v*/*v*), and visualized by a 254-nm UV lamp. The observed R_f value is 0.48 for (*S*,*S*)-**1**. Submitters report thin layer chromatography (TLC) performed on precoated silica gel plates (SGF254, 0.2 mm±0.03 mm) purchased from Yantai Chemical Industry Research Institute eluting with dichloromethane/methanol (20/1, *v*/*v*), and visualized by a 254-nm UV lamp. The observed R_f value is 0.53 for (*S*,*S*)-**1**.

12. Checkers used Silicycle SiliaFlash® P60 Academic Silica gel (particle size 40–63 nm). Submitters used silica gel 60 (zcx-3 II, 200–300 mesh) purchased from Qingdao Haiyang Chemical Company, Ltd.
13. Flash column chromatography was performed on a silica gel column (3.5 cm width x 10.0 cm length) using 20 g of 40–63 nm particle size silica with 500 mL dichloromethane/methanol (100/1, *v*/*v*) as eluent. The crude product was collected in fractions 3–9 (50 mL each), which were combined and concentrated by rotary evaporation under reduced pressure (40 °C, 30 mmHg) to provide an orange solid.
14. Silver trifluoromethanesulfonate (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
15. Celite was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
16. The organometallic complex was isolated as a 2:1 complex with ethyl acetate, even after drying under the described conditions. In a separate run, the sample was dried on a diffusion pump at 23 °C, 8 x 10^{-3} mmHg for 5 d without any change in the amount of EtOAc present by ^{1}H NMR. A spectrum free of EtOAc could be obtained by dissolving 20 mg of (*S*,*S*)-**2** in 5 mL $CDCl_3$ and removing the solvent under reduced pressure (40 °C, 30 mmHg) by rotary evaporation, repeating this process a total of four times.
17. (*S*,*S*)-**2:** Dark red solid; mp 152–157 °C (dec); $[\alpha]_D^{20}$ = +59.9 (*c* 1.9, chloroform); IR (thin film, NaCl) 3207, 3101, 2922, 1719, 1577, 1496, 1451, 1404, 1323, 1276, 1245, 1157, 1106, 1089, 1062, 1030 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.1 Hz, 1.5 H), 1.87 (s, 15 H), 2.04 (s, 1.5 H), 4.12 (q, *J* = 7.1 Hz, 1 H), 4.25 (s, 1 H), 4.79 (s, 1 H), 5.33 (d, *J* = 13.5 Hz, 1 H), 6.21 (d, *J* = 13.1 Hz, 1 H), 6.86–6.97 (m, 2 H), 7.07–7.23 (m, 8 H), 7.29–7.40 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 10.5, 14.3, 21.2, 60.5, 91.6, 110.1, 119.0, 121.6, 122.2, 124.3, 125.6, 126.6, 126.7, 127.8, 128.5, 128.6, 128.8, 128.9, 133.5, 133.8, 136.3, 137.8, 142.1, 171.3; Anal. Calcd. for $C_{32}H_{33}F_6IrN_2O_5S_2 \bullet 1/2(C_4H_8O_2)$ C, 43.44; H, 3.97; N, 2.98; Found C, 43.22; H, 4.18; N, 2.81.
18. 2-Methyl quinoline (97+%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
19. Trifluoroacetic acid (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
20. Methanol (99.8+%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.

21. The purity of hydrogen gas used by checkers was 99.999%. The purity of hydrogen gas used by submitters was 99.99%.
22. The gas-inlet tube was attached to the autoclave, with a three-way valve. After pressurization of the autoclave, the valve was opened to release extra hydrogen pressure and then turned to repressurize. This procedure was repeated three times.
23. Sodium carbonate (99%) was purchased from Alfa Aesar Chemical Company, Inc., and used without further purification.
24. Column chromatography was performed on a silica gel column (3.5 cm width x 15.0 cm length) using 30 g of 40–63 nm particle size silica gel with 300 mL petroleum ether/triethylamine (95/5, *v*/*v*) as eluent. The product was collected in fractions 2-6 (50 mL each), which were combined and concentrated by rotary evaporation under reduced pressure (40 °C, 30 mmHg) to provide a light yellow oil. The submitters report that the resulting product was dried in a 40 °C oil bath at 5 mmHg.
25. (*S*)-**4a**: Light yellow oil; bp 89 °C (5 mm Hg); IR (thin film, NaCl) 3393, 2961, 2924, 2843, 1727, 1608, 1583, 1491, 1309, 1277 cm^{-1}; 94% ee, $[\alpha]_D^{25}$ = –80.4 (*c* 0.20, chloroform); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 6.3 Hz, 3 H), 1.50–1.70 (m, 1 H), 1.90–1.97 (m, 1 H), 2.70–2.77 (m, 1 H), 2.81–2.90 (m, 1 H), 3.34–3.45 (m, 1 H), 3.80 (br, s, 1 H), 6.49 (d, *J* = 7.8 Hz, 1H), 6.62 (t, *J* = 7.4 Hz, 1 H), 6.97 (t, *J* = 6.5 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 22.7, 26.7, 30.3, 47.4, 114.2, 117.2, 121.3, 126.8, 129.4, 144.8; Anal. Calcd. for $C_{10}H_{13}N$ C, 81.59; H, 8.90; N, 9.51; Found C, 81.19; H, 8.98; N, 9.39.
26. The checkers performed HPLC analysis on an Agilent 1100 series liquid chromatograph with a chiral column (OJ-H, eluent: Hexane/*i*-PrOH = 95/5, *v*/*v*, detector: 254 nm, flow rate: 1.2 mL/min), major isomer (*S*): t_{R1} = 12.8 min, minor isomer (*R*): t_{R2} = 14.5 min. The submitters report HPLC analysis performed on a Varian Prostar 210 liquid chromatograph with a chiral column (OJ-H, eluent: Hexane/*i*-PrOH = 90/10, *v*/*v*, detector: 254 nm, flow rate: 1.0 mL/min), major isomer (*S*): t_{R1} = 10.1 min, minor isomer (*R*): t_{R2} = 11.3 min.
27. The racemic product was prepared according to the published method.[4]

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

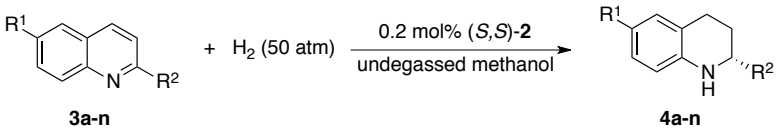
Optically pure tetrahydroquinoline derivatives are important organic synthetic intermediates and building blocks for the stereoselective synthesis of biologically active compounds.[5] The preparation of these chiral tetrahydroquinoline derivatives by the transition metal-catalyzed asymmetric hydrogenation of quinolines is one of the most straightforward and convenient methods. Recently, a number of iridium-phosphine

complexes have been reported to be effective in the asymmetric hydrogenation of quinolines since the first example reported by Zhou and co-workers.[6] However, a frequently encountered problem associated with the use of phosphine-containing catalysts is the air-sensitivity. In addition, most of these reported catalytic systems suffered from low catalyst efficiency.

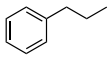
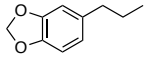
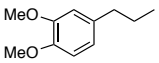
In comparison with chiral phosphorus ligands, chiral diamine ligands are more readily available and air-stable. Their transition metal (Ru, Rh, and Ir) complexes have been extensively studied in the asymmetric transfer hydrogenation of aromatic ketones and imines.[7] However, they are long neglected in the hydrogenation of unsaturated compounds.[8,9] The procedure described herein provides a highly efficient method for the preparation of the desired chiral 2-substituted 1,2,3,4-tetrahydroquinolines in high enantiomeric excess *via* asymmetric hydrogenation using readily available and air stable chiral cationic Cp*Ir(OTf)(*N*-sulfonylated diamine) complexes[10] as catalysts. In addition, the hydrogenation can be carried out in undegassed methanol and with no need for inert gas protection throughout the entire operation.

Hydrogenation of 2-methylquinoline (10.00 g, 69.90 mmol) catalyzed by Ir-catalyst (*S*,*S*)-**2** proceeds smoothly with a substrate-to-catalyst molar ratio as high as 500:1 in undegassed methanol, affording 2-methyl-1,2,3,4-tetrahydroquinoline in 96% isolated yield with 96% ee (Entry 1). In addition, the present method has been successfully applied to the asymmetric hydrogenation of a series of 2-substituted and 2,6-disubstituted quinoline derivatives with catalyst (*S*,*S*)-**2**. Excellent enantioselectivities and reactivities have been obtained in all cases except for 2-phenyl quinoline (see Table 1).

Table 1. Asymmetric Hydrogenation of 2-Substituted Quinoline Derivatives Catalyzed by (*S,S*)-2[a]



3a-n **4a-n**

Entry	Compound	R^1	R^2	Yield (%)[c]	Ee (%)[d]
1[b]	4a	H	Me	96	96 (*S*)[e]
2	4b	H	Et	98	98
3	4c	H	*n*-Pr	98	96
4	4d	H	*n*-Bu	97	97
5	4e	H	*n*-Pentyl	98	96
6	4f	H		97	97
7	4g	H		97	97
8	4h	H		96	96
9	4i	H		97	99
10	4j	H		97	99
11	4k	MeO	Me	97	97
12	4l	Me	Me	95	97
13	4m	F	Me	98	94
14	4n	H	Ph	90	79

[a] Reaction conditions: 0.75 mmol substrate in 1 mL undegassed MeOH, 0.2 mol% (*S,S*)-**2**, 10 mol% TFA, 50 atm H_2, 15 °C, 24-48 h. All manipulations were conducted in air, and the autoclave was purged with H_2 for three times before reaction. [b] Reaction conditions: (10.0 g, 69.9 mmol) 2-methyl quinoline in 7 mL undegassed MeOH, 0.2 mol% (*S,S*)-**2**, 10 mol% TFA, 50 atm H_2, 15 °C, 15 h. [c] Isolated yield (without distillation). [d] Determined by chiral HPLC analysis. [e] Absolute configuration was determined by comparison of optical rotation with literature data.[6]

References

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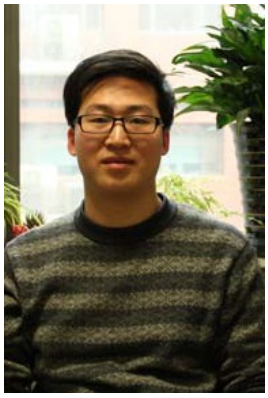
Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-(Trifluoromethyl)benzenesulfonyl chloride; (2991-42-6)
(1*S*,2*S*)-(–)-1,2-Diphenyl-1,2-ethanediamine ; (29841-69-8)
Triethylamine; (121-44-8)
(Pentamethylcyclopentadienyl)iridium(III) Dichloride Dimer; (12354-84-6)
Silver trifluoromethanesulfonate; (2923-28-6)
2-Methyl quinoline: Quinaldine; (91-63-4)
Trifluoroacetic acid; (76-05-1)



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