PROCEDURE OF ASYMMETRIC TRANSFER HYDROGENATION USING RUTHENIUM COMPLEX

[Procedure]

(1) A dry, four-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser bearing an inert gas (argon or nitrogen) inlet tube, a thermometer and a dropping funnel is evacuated and filled with an inert gas (argon or nitrogen) three times. (Figure 1)

(2) The catalyst is placed into the flask under an inert gas atmosphere and the evacuation/inert gas refill cycle is repeated three times. (Note 1)

(3) The substrate and dry solvent (Note 2) are charged into the flask by syringes. (Note 3)

(4) Triethylamine in a separate flask is cooled below 4°C in an ice bath and formic acid is added slowly under an inert gas atmosphere. (Note 4) (When the suitable ratio of formic acid and triethylamine is 5:2, please refer to "Preparation of Formic Acid-Triethylamine (5:2) Azeotrope" below.)

(5) The mixture of formic acid and triethylamine is transferred into the dropping funnel of the flask by a syringe and then is added to the solution of substrate and catalyst dropwise (Note 5) at ambient temperature.

(6) The reaction mixture is stirred at a specific temperature for a specific length of time.

(7) The conversion and enantiomeric excess of the obtained product are determined by gas chromatography (GC) analysis or high-performance liquid chromatography (HPLC) analysis.

FOR MORE DETAILED INFORMATION, PLEASE CHECK THE REFERENCE.

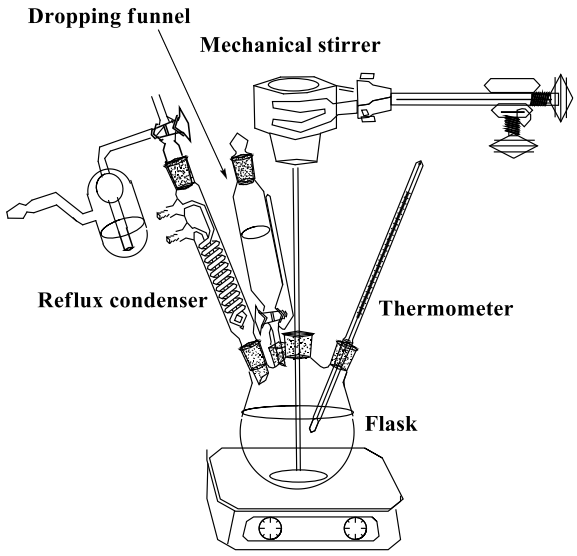

Figure 1. A transfer hydrogenation apparatus.

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[Notes]

1. After the system turned into inert conditions, it is strongly recommended that the system is kept at slightly positive pressure to secure the inert condition. This can be attained by gentle flow of inert gas vented through the bubbler.

2. Guaranteed grade solvent is distilled under an inert gas (argon or nitrogen atmosphere).

3. The substrate can be charged as a solution.

4. Apparatus of choice is at operators' discretion as long as the resulting reagent meets requirements for inert condition.

5. Addition speed would not be so much critical. Dropwise addition is recommended to avoid unexpected event happen.

Caution! All procedures should be carried out under anaerobic conditions using degassed solvents.
These procedures do not constitute a guarantee, warranty, or prediction regarding the outcome of your legal matter.
Please check and follow the regulations on the use of chemicals in each nation and region.

[Waste Disposal Information]

All toxic materials should be disposed of in accordance with "Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards, Updated Version"; National Academy Press; Washington, DC, 2011. doi. 10.17226/12654

[Reference]

(1) Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R. *Org. Synth.* **2005**, *82*, 10. doi. 10.15227/orgsyn.082.0010

[Preparation of Formic Acid-Triethylamine (5:2) Azeotrope]

(1) 346.5 mL (422.7 g) of 98% formic acid (9.0 mol) is charged into a 1 L, four-necked, round-bottomed flask.

(2) The flask is equipped with a mechanical stirrer, a reflux condenser bearing an inert gas (argon or nitrogen) inlet tube, a thermometer and a dropping funnel.

(3) The flask is evacuated, filled with an inert gas (argon or nitrogen) and cooled to 4 °C in an ice bath.

(4) 500.0 mL (363.6 g, 3.6 mol) of triethylamine is then placed into the dropping funnel of the flask and added portionwise into the flask over a 1.5 h period with cooling in an ice bath.

(5) Reflux condenser is replaced with distillation head under inert gas stream (CAUTION!! excessively applying the inert gas may cause suffocation, operations should be executed in hood) to keep the system away from atmospheric oxygen/moisture, then the mixture is distilled at 89 °C under 2.1 kPa.

(6) The distillate* is stored under inert gas (argon or nitrogen).
*The ratio of formic acid and triethylamine (2.5~2.3:1) is determined by ^{1}H-NMR analysis ($CDCl_3$).

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