Chiral Amine Catalyzing Enantioselective Fluorination of α-Branched Aldehydes

Application

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\begin{align*}
\text{E1267} & \quad \text{(10 mol\%)} \\
3,5-\text{(NO}_2\text{)}_2\text{C}_6\text{H}_4\text{CO}_2\text{H} & \quad \text{(10 mol\%)} \\
\text{(PhSO}_2\text{)}_2\text{NF} & \quad \text{(5.2 eq.)}
\end{align*}
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\[
\begin{align*}
\text{NaBH}_4 & \quad \text{(6 eq.)} \\
\text{MeOH/CH}_2\text{Cl}_2, \text{rt, 1 h} & \quad \text{Reduction} \\
\text{(EIO)P(O)CH}_2\text{CO}_2\text{Et} & \quad \text{(5.2 eq.)} \\
\text{NaH} & \quad \text{(5.2 eq.)} \\
\text{THF, 0 °C, 1 h} & \quad \text{HWE Reaction} \\
\text{NaOR}_2 & \quad \text{(5 eq.)} \\
\text{R}_2\text{OH, 60 °C, 8-12 h} & \quad \text{C-F Bond Cleavage} \\
\text{Hydroxyacetals} & \quad \text{up to 87\% yield} \\
& \quad \text{up to 94\% ee}
\end{align*}
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Advantages

- Catalyze the asymmetric fluorination of α-branched aldehydes using N-fluorobenzenesulfonimide (NFSI) as a fluorine source.
- The generated chiral tertiary fluorides can be converted into various optically-active compounds.

Ethyl (11bR)-4-Amino-2,6-bis(3,5-di-tert-butylphenyl)-4,5-dihydro-3H-cyclohepta-[1,2-α:7,6-α']dinaphthalene-4-carboxylate

This product was produced by collaboration with Assoc. Prof. Kazutaka Shibatomi, Toyohashi University of Technology.

Related Products

- 3,5-Dinitrobenzoic Acid 25g / 500g [D0824]
- N-Fluorobenzenesulfonimide (= NFSI) 5g / 25g [F0335]
- Sodium Borohydride 25g / 100g / 500g [S0480]
- Triethyl Phosphonoacetate 25g / 100g / 500g [D1523]

For further information please refer to our website at www.TCIchemicals.com.
The Shibatomi group aims to develop the new synthetic methods of organic molecules, especially focusing on design and synthesis of novel chiral catalysts and their application to the asymmetric reactions. The Shibatomi group is also developing the efficient synthetic method for chiral pharmaceutical and agricultural compounds with the above-mentioned chiral catalysis. Recently, the Shibatomi group found highly enantioselective halogenation of carbonyl compounds and applied this method for the synthesis of a GPR119 agonist which is a potential drug for type 2 diabetes.

**Research Description**

To a solution of E1267 (20 mg, 0.026 mmol, 10 mol%) in toluene (0.54 mL) is added 3,5-dinitrobenzoic acid (5.5 mg, 0.026 mmol, 10 mol%), 2-phenylpropionaldehyde (52 mg, 0.39 mmol, 1.5 eq.), and N-fluorobenzenesulfonyl fluoride (NFSI) (0.26 mmol, 82 mg, 1 eq.) at 0 ºC. The reaction mixture is stirred at 0 °C for 48 h, then poured into CH₃OH/CH₂Cl₂ (1:4, 1.3 mL) at 0 °C. To this solution, NaBH₄ (1.6 mmol, 6 eq.) is added, and the mixture is stirred at room temperature for 1 h. The reaction is quenched with saturated aq. NH₄Cl, and the mixture is extracted with Et₂O. The organic layer is dried over Na₂SO₄, and concentrated. The residue is purified by silica gel chromatography (eluent: hexane/ethyl acetate = 3/1) to give (S)-2-fluoro-2-phenylpropan-1-ol (34.5 mg, 86% yield based on NFSI, 95% ee) as a white solid.