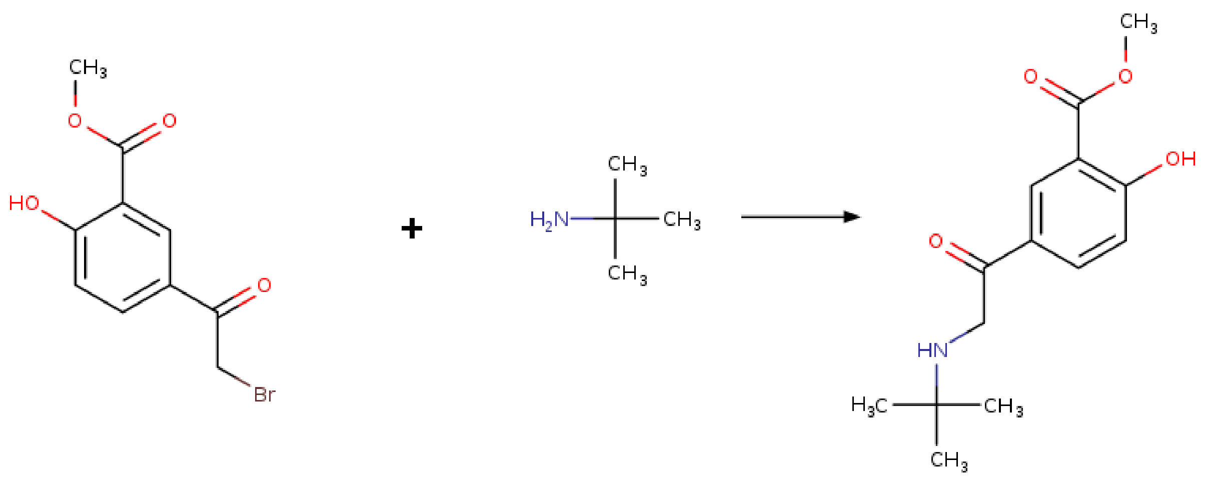
AI-driven synthesis Pre-Assignment

1 Retrosynthesis of (R)-salbutamol

Here is a route to a synthesis the target compound:
In step 1, **Methyl 5-(2-bromoacetyl)-2-hydroxybenzoate (CAS#: 36256-45-8)** and **tert-Butylamine (CAS#: 75-64-9)** are cheap and easy to obtain.

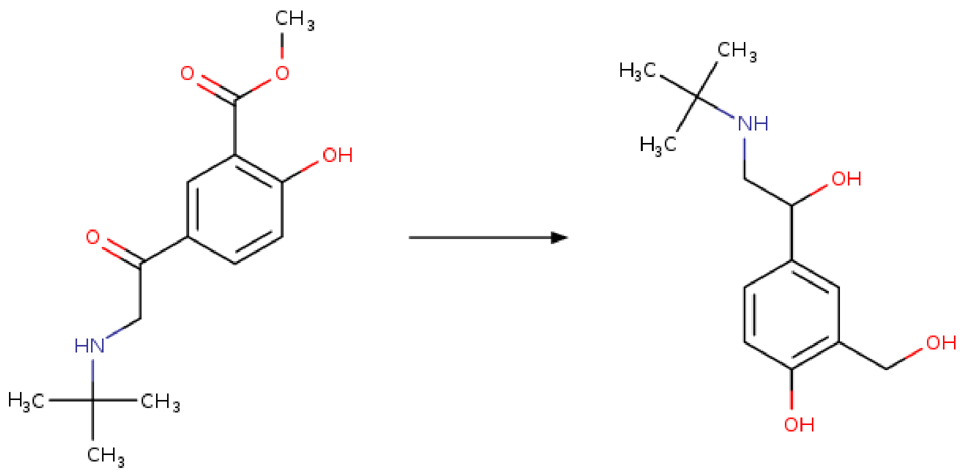
Step 1:



In isopropyl alcohol at 10 - 50°C; for 3h; Temperature; Solvent; Inert atmosphere;

Add Methyl 5-(2-bromoacetyl)-2-hydroxybenzoate to isopropanol, protect with nitrogen, cool and add tert-butylamine dropwise. After the addition is complete, heat in an oil bath, stir and heat to 45-50, keep stirring for 3h, monitor by TLC until the reaction is complete, cool to 20-25 and stir for 5h. Filter by suction and dry to constant weight to obtain Intermediate 2 with a yield of 83.2%

Step 2:



Stage #1: C14H19NO4 With lithium aluminium tetrahydride In tetrahydrofuran at -10 - 5°C; for 2h;

Stage #2: With sodium hydroxide In water at 0 - 30°C; for 1h;

Add 40.00g of intermediate 2 to 240ml of tetrahydrofuran, cool to -10-0, slowly add 11.44g of lithium aluminum hydride, control the temperature at -10-0 during the addition, and control the temperature at -10-5 for 2h after the addition. Add 34.32g of purified water and 11.44g of 15% sodium hydroxide solution to the reaction solution, respectively, control the internal temperature at 0-10 during the addition, and heat the reaction solution to 20-30 and stir for 1h after the addition. Then add anhydrous sodium sulfate, filter, wash the filter cake with tetrahydrofuran twice, and concentrate the filtrate to dryness to obtain crude salbutamol. Add 120ml of isopropanol and 120ml of ethyl acetate to the crude product, heat the reaction solution to reflux under stirring, stir for 0.5h, cool to 0-5, and keep warm for 3h to crystallize. Filter and dry to obtain salbutamol.

2 Python programming and reaction modeling

2.1 Data Processing and Plot Scatter

```python
import pandas as pd
from matplotlib import pyplot as plt

from rxn_logger import logger


class RxnDataProcessing:
    def __init__(self, file_path):
        self.file_path = file_path
        self.results = []
        self.yields_dict = {}
        self.temp_dict = {}

    def csv_data_loader(self, chunk_size=10000):
        """
        Read and process large CSV files in chunks, avoid memory overflow
        """
        for chunk in pd.read_csv(self.file_path, chunksize=chunk_size):
            processed_chunk = self.chunk_standardization(chunk)
            self.create_dicts(processed_chunk)
            self.results.append(processed_chunk)
            logger.info(
                f'f"Finished processing chunk {len(self.results)}, containing
{len(processed_chunk)} rows"')

        final_df = pd.concat(self.results, ignore_index=True)
        return final_df

    @staticmethod
    def chunk_standardization(chunk):
        chunk = chunk[chunk['reaction_SMILES'].notna() & (chunk['reaction_SMILES'] != '')]
        # remove unexpected yield rows
        numeric_fields = ['eqv1', 'eqv2', 'eqv3', 'eqv4', 'eqv5', 'reaction_temperature', 'time',
                          'product1_yield', 'product2_yield']

        # change fields to numeric, none as NaN
        for field in numeric_fields:
            chunk[field] = pd.to_numeric(chunk[field], downcast='float', errors='coerce')

        chunk['reaction_ID'] = pd.to_numeric(chunk['reaction_ID'], downcast='signed',
                                             errors='coerce')

        chunk = chunk[
            (chunk['product1_yield'] >= 0) & (chunk['product1_yield'] <= 100) &
            (chunk['product2_yield'] >= 0) & (chunk['product2_yield'] <= 100)
            ]

        chunk = chunk.dropna(subset=['reaction_ID'])
        # when 'eqv1', 'eqv2', 'eqv3', 'eqv4', 'eqv5', 'reaction_temperature'
        # is none, delete row from chunk
        chunk = chunk.dropna(
            subset=['eqv1', 'eqv2', 'eqv3', 'eqv4', 'eqv5', 'reaction_temperature'])

        return chunk

    def create_dicts(self, chunk):
        # create yields and temperature dicts
        for _, reaction in chunk.iterrows():
            reaction_id = reaction['reaction_ID']
            self.yields_dict[reaction_id] = [reaction['product1_yield'],
reaction['product2_yield']]
            self.temp_dict[reaction_id] = reaction['reaction_temperature']

    def plot_scatter(self):
        # Prepare data: each reaction has two yields, so temperature and yield lists need to be
expanded accordingly
        temperatures = []
        yields = []
        for rid, temperature in self.temp_dict.items():
            reaction_yields = self.yields_dict[rid]
            temperatures.extend([temperature] * len(reaction_yields))
            yields.extend(reaction_yields)

        plt.figure(figsize=(10, 6))
        plt.scatter(temperatures, yields, alpha=0.6, s=50)
        plt.xlabel('Reaction Temperature', fontsize=12)
        plt.ylabel('Product Yield (%)', fontsize=12)
        plt.title('Correlation between Reaction Temperature and Product Yield', fontsize=14)
        plt.grid(True, alpha=0.3)
        plt.tight_layout()
        plt.show()


if __name__ == '__main__':
    rxn_process = RxnDataProcessing('test_organic_reactions.csv')
    df = rxn_process.csv_data_loader()
    print(df.head(10))
    rxn_process.plot_scatter()
```

2.2 Build model and prediction a reaction yield

2.2.1 Merge vectors

This method extracts features and labels from the DataFrame, then concats fingerprint vector with extra features (eqv1-5, temperature and time), finally divides them into training and testing sets, and converts them into tensor format.

```
def gen_train_test_data(self):
    X_list = []
    y_list = []

    for _, row in self.df.iterrows():
        _x = [row['eqv1'], row['eqv2'], row['eqv3'], row['eqv4'], row['eqv5'],
              row['reaction_temperature'], row['time']]
        X = np.concatenate((row['fps'], _x))
        y = np.array([row['product1_yield'], row['product2_yield']])
        X_list.append(np.array(X))
        y_list.append(y)

    X_train, X_test, y_train, y_test = train_test_split(
        X_list, y_list, test_size=0.3, random_state=42
    )

    X_train = torch.tensor(X_train, dtype=torch.float32)
    X_test = torch.tensor(X_test, dtype=torch.float32)
    y_train = torch.tensor(y_train, dtype=torch.float32)
    y_test = torch.tensor(y_test, dtype=torch.float32)

    return X_train, X_test, y_train, y_test
```

2.2.2 build a simple model

There are to ways for building models:

1. For a single model, the output layer directly outputs two values (multiple outputs).
2. Use two independent models (or two independent output heads) to output each value separately.

Each of these approaches has advantages and disadvantages, which are discussed in more detail below:

Method 1: Single model, the output layer directly outputs two values

- Structure: On the last layer of the model, set two nodes. If the two values have different types (such as one classification and one regression), two different output layers may be required (such as one softmax for classification and one linear for regression).
- Advantages: The model shares most feature extraction layers, which can reduce the amount of computation, and the two tasks may promote each other. By sharing the feature extraction layer, the model can learn features that are useful for both tasks.
- Disadvantages: Two tasks may interfere with each other, especially when the correlation between the two tasks is not high. In addition, the balance of the loss function may require careful adjustment.

```
class YieldPredict(nn.Module):
    def __init__(self, input_size=263, hidden_size=128, output_size=2):
        super(YieldPredict, self).__init__()
        self.fc1 = nn.Linear(input_size, hidden_size)
        self.fc2 = nn.Linear(hidden_size, hidden_size)
        self.fc3 = nn.Linear(hidden_size, output_size)
        self.dropout = nn.Dropout(0.3)
        self.relu = nn.ReLU()

    def forward(self, x):
        x = self.fc1(x)
        x = self.relu(x)
        x = self.dropout(x)
        x = self.fc2(x)
        x = self.relu(x)
        x = self.dropout(x)
        out = self.fc3(x)
        return out
```

Method 2: Use two different models (or two independent weight outputs)

- Structure: Build an independent model for each output value, or set an independent output header for each output value based on a model (that is, fork from a certain intermediate layer, pass through different fully connected layers, etc., and finally output two values).
- Advantages: The two tasks will not interfere with each other and can be optimized independently. This approach may be more effective if the two tasks differ greatly.
- Disadvantages: More parameters are required, the computational volume may be greater, and if the two tasks share features, feature extraction cannot be shared, which may cause the features learned by each model to be less comprehensive than the method.

```
class MultiHeadYieldPredict(nn.Module):
    def __init__(self, input_dim, hidden_dim):
        super().__init__()
        self.shared_backbone = nn.Sequential(
            nn.Linear(input_dim, hidden_dim),
            nn.ReLU()
        )
        self.head1 = nn.Sequential(
            nn.Linear(hidden_dim, hidden_dim // 2),
            nn.ReLU(),
            nn.Linear(hidden_dim // 2, 1)
        )
        self.head2 = nn.Sequential(
            nn.Linear(hidden_dim, hidden_dim // 2),
            nn.ReLU(),
            nn.Linear(hidden_dim // 2, 1)
        )

    def forward(self, x):
        shared_features = self.shared_backbone(x)
        output1 = self.head1(shared_features)
        output2 = self.head2(shared_features)
        return output1, output2
```

2.2.3 Train model and Evaluate

These two methods are designed for model training and evaluation.

Training: save model every 10 epochs.

```
def train(self, X_train, y_train, num_epochs):
    criterion = nn.MSELoss()
    optimizer = optim.Adam(self.model.parameters(), lr=0.001)

    for epoch in range(num_epochs):
        outputs = model(X_train)
        loss = criterion(outputs, y_train)

        optimizer.zero_grad()
        loss.backward()
        optimizer.step()

        if (epoch + 1) % 10 == 0:
            torch.save(model.state_dict(), "yield_predictor.pth")
```

```
                logger.info(f'Epoch [{epoch + 1}/{num_epochs}], Loss: {loss.item():.4f}')

        return self.model

    @torch.no_grad()
    def evaluate(self, X_test, y_test):
        criterion = nn.MSELoss()
        outputs = model(X_test)
        _loss = criterion(outputs, y_test)
        logger.info(f'Test Loss: {_loss.item():.4f}')

        predicted_yields = outputs.numpy()
        logger.info(f'Predicted yields: {predicted_yields}')
```

The complete code has been uploaded to GitHub