Enantio-Convergent Nucleophilic Substitution Reaction of Racemic Electrophiles Catalyzed by Chiral Brønsted Acid

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Among the methods for asymmetric synthesis, enantioselective catalysis is one of the representatives to produce enantio-enriched molecules in an efficient and practical manner. Catalytic enantioselective nucleophilic addition to pro-chiral electrophiles such as aldehydes, ketones, imines, and electron deficient double bonds is one of the most extensively investigated reactions, and substantial achievements have been established through reactions at the pro-chiral sp²-hybridized carbon atom of double bonds using chiral metal catalysts, enzymes, and organocatalysts. In contrast, despite being one of the most fundamental methods for the formation of covalent bonds, enantioselective nucleophilic substitution at the sp³-hybridized carbon atom has received much less attention than the enantioselective nucleophilic addition reactions. In particular, substitution reaction at the chiral sp³-hybridized carbon atom of racemic electrophiles has rarely been exploited as a catalytic enantioselective transformation, presumably because the chiral information of racemic electrophiles is transferred to the corresponding substitution product through inversion at the stereogenic center via the S_N₂ pathway. Therefore, in the conventional approach, kinetic resolution of racemic electrophiles has been used to afford the substitution product in an enantio-enriched form. In an alternative approach to the S_N₂ pathway (i.e., the S_N₁ protocol), the cationic intermediate generated as an electrophile forms a contact ion pair with a leaving group that makes enantio-control of the substitution product difficult. To circumvent this intrinsic feature of S_N₁ reactions, several specific methods for enantioselective nucleophilic substitution at the racemic stereogenic center have been reported, such as S_N₁-type reactions by virtue of contriving the reaction system and allylic substitution as well as cross coupling reactions using transition metal catalysts. The challenge of governing the stereochemical outcome in enantioselective substitution reactions of racemic electrophiles provides a new frontier of enantioselective catalysis for nucleophilic substitution, in which enantio-convergence can be achieved from the racemic electrophile to the enantio-enriched substitution product without recovering unreacted enantiomer of the electrophile. Herein I present that enantioselective substitution reaction of racemic propargyl alcohols complexed with a cobalt carbonyl species with benzenethiol in the presence of a chiral phosphoric acid catalyst achieves enantio-convergent synthesis of various propargyl sulfides in a highly enantioselective manner.¹

References