The Development and Application of the Asymmetric Pictet-Spengler Reaction

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Introduction

In 1911, Amé Pictet and Theodor Spengler discovered that β-phenylethylamine in presence of strong acid could condense with formaldehyde dimethyl acetal and cyclize to give tetrahydroisoquinoline(THIQ).[1] This reaction was expanded by Tatsui to include tryptamine derivatives to give tetrahydro-β-carbolines(THβCs) (Figure 1).[2] The THβC ring system is a privileged ring scaffold found in the indole alkaloid natural products which have important pharmaceutical properties.[3] The Pictet-Spengler reaction is the premiere way to synthesize these structures, so asymmetric variants are highly desirable.

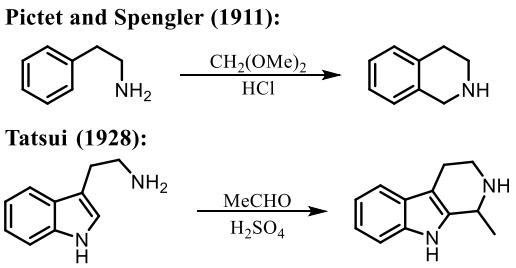

Figure 1. Discovery of Pictet-Spengler Reaction

Diastereoselective Pictet-Spengler Reaction:

In 1979, Cook et. al. reported a diastereoselective Pictet-Spengler reaction between *N*-benzyl tryptophan methyl esters and bulky aldehydes. Cook also found that that mixtures of diastereomers underwent acid-catalyzed epimerization to give the *trans* product without eroding enantioenrichment.[4] In 2004, Bailey published the first synthetically useful *cis* selective Pictet-Spengler reaction between tryptophan allyl ester and aryl aldehydes.[5] A general *cis*-selective reaction with diverse aldehydes remains challenging. Similarly, stereogenic centers on the aldehyde partner can also direct the selectivity of the Pictet-Spengler reaction. Following condensation of an enantioenriched aldehyde with an amine substrate, the existing stereogenic center can control the addition of the indole group up into the imine.[6a,6b]

Chiral Auxiliary Strategies:

To synthesize THβC's with a single stereogenic center on the ring, attaching chiral auxiliaries to the tryptamine substrates was done. Using *N*-phthaloyl amino acids to form the *N*-acyl iminium ion on a preformed imine, the resulting THβCs can be formed in good yield and diastereoselectivity.[7] This method has been applied to the total synthesis of quinolactacin A2 and B.[8]

Catalytic Enantioselective Pictet-Spengler Reactions

In 2006, List et. al. reported a chiral Brønsted acid catalyzed Pictet- Spengler reaction. The method gave good yields and enantiomeric ratios but was hampered by a limited substrate scope (Figure 2).[9]In 2012, Wang showed that using SPINOL phosphoric acid catalysts could improve the yields and

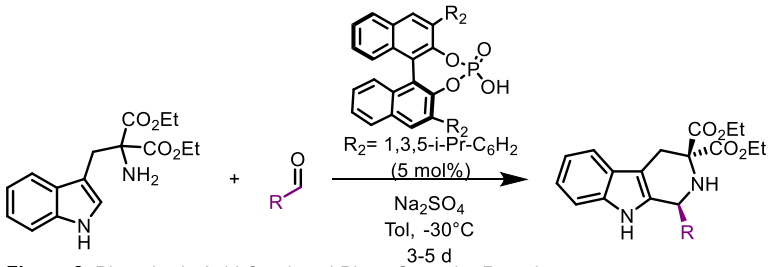

Figure 2. Phosphoric Acid Catalyzed Pictet-Spengler Reaction

enantioselectivities for a variety of substrates. The system was still limited by the need for a bulky amine protecting group.[10]

In 2004, Jacobsen reported an *N*-acyl-Pictet-Spengler reaction catalyzed by chiral thioureas using anion abstraction catalysis to make enantioenriched THβC. Forming the acyliminium ion increased the electrophilicity of the intermediate and allowed for the synthesis of THβCs in 65-81% yield with up to 97.5:2.5 er.[11] Later Jacobsen et. al. demonstrated a non-acyl enantioselective Pictet-Spengler reaction using Brønsted Acid co-catalysis (Figure 3). Both aryl and aliphatic aldehydes are competent, and the THβCs are accessed in good yields and enantiomeric ratios.[12] This method has been applied to natural product synthesis for the total synthesis of Peganumine A.[13] In 2017, Jacobsen reported an mechanistic study. [14]

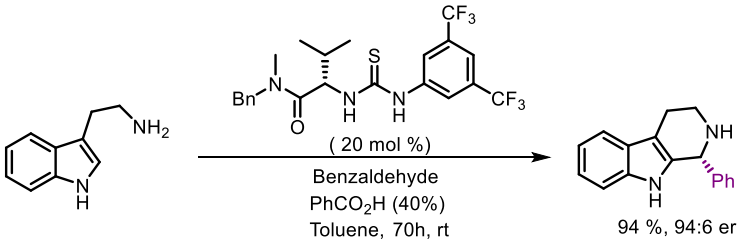

Figure 3. Jacobsen Enantioselective Catalytic Pictet- Spengler

Conclusion:

While there is still room for improvement, the asymmetric Pictet-Spengler reaction is a synthetically useful transformation for the synthesis of THβCs. It has been used for total syntheses of indole alkaloids, and is used in industrial syntheses of pharmaceuticals.

References:

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