RECENT DEVELOPMENTS IN THE MULTICOMPONENT PETASIS REACTION

Reported by Alexander Gomez April 1st, 2021

INTRODUCTION

Petasis and coworkers initially reported the eponymous Petasis Reaction (PR) in 1993 as a type-II multicomponent transformation that yielded allylic amine products from boronic acids, secondary amines, and paraformaldehyde (Figure 1).[1] Many groups have since published modifications expanding the scope of each of the three components. Owing to its utility and versatility, this reaction has been used in the total synthesis of natural products, has been rendered catalytic, enantioselective, and has been modified to include "traceless" reactions that form allene or 1,4-diene products. For the purposes of this seminar, the term PR refers to the addition of an activated boronate nucleophile to an iminium species generated in situ. [2,3]

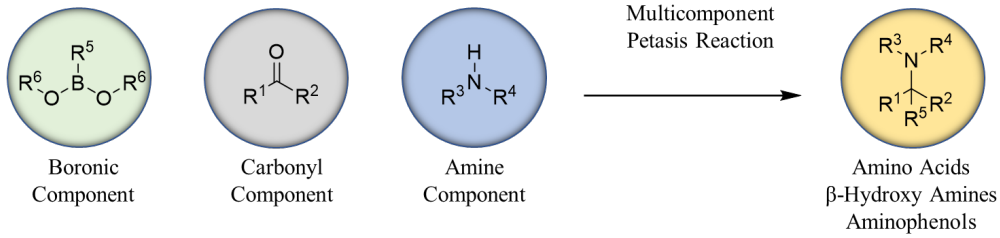


Figure 1. General reaction scheme for Petasis transformations.

APPLICATIONS TO TOTAL SYNTHESIS

PRs involving enantiomerically enriched α-hydroxy carbonyl components form products with a high degree of diastereoselectivity, presumably through a transition state that minimizes allylic strain in the transition state for intramolecular group transfer (Figure 2).[4] For this reason, several groups have used PRs in the synthesis of alkaloid natural products. Pyne and co-workers reported highly diastereoselective PRs in the syntheses of polyhydroxylated alkaloids calystegine B_4 & hyacinthacine C_5,[5,6] while Scheerer and co-workers reported a highly diastereoselective PR of a cyclic α-hydroxy acyl amine in the asymmetric synthesis of the loline alkaloid skeleton.[7]

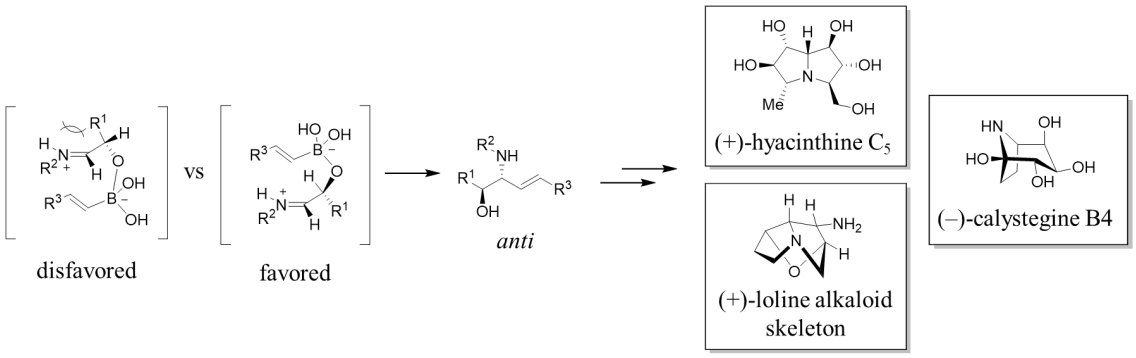
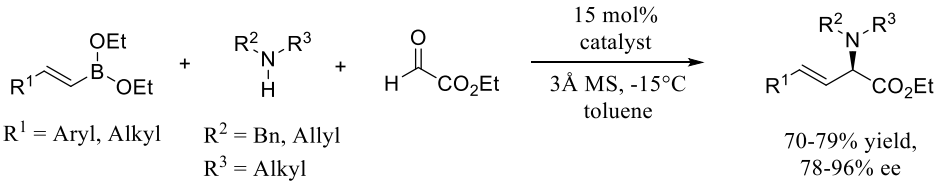


Figure 2. Stereochemical model for diastereoselectivities in PRs toward natural product targets.

CATALYTIC ENANTIOSELECTIVE PETASIS TRANSFORMATIONS

Catalytic PRs that convert racemic or achiral components into enantiomerically enriched products are highly valuable transformations, and many groups have made significant efforts toward the development of such reactions. In recent years, Schaus and coworkers have reported enantioselective, biphenol-catalyzed PRs with a modest range of amine and boronic ester components, as shown in Scheme 1.[8] Mechanistic investigation suggests that the stereochemical course is controlled by the approach of a tetracoordinate boronate intermediate generated by single ligand exchange of the boronic ester component with the chiral biphenol catalyst.

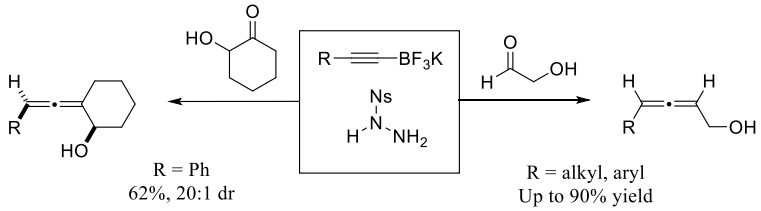
Scheme 1. Chiral Biphenol-Catalyzed Enantioselective Petasis Reaction.



THE TRACELESS PETASIS REACTION

Thomson and coworkers reported the PR of alkynyl boron nucleophiles, α-hydroxy aldehydes, and arylsulfonylhydrazides to generate allylic hydroxyl allenes by a propargylic diazene rearrangement.[9] The authors dubbed this reaction "traceless" because no residual atoms from the hydrazide component exist in the product. Following this initial report, the Thomson and Schaus groups collaborated to develop methods rendering this transformation enantioselective.[10] Enantioenriched propargylic diazenes can be generated by chiral biphenol-catalyzed alkynylation of α-hydroxy aldehydes and by allylation of propargyl aldehydes to access allene products with a high degree of enantioselectivity.

Scheme 2. Traceless Petasis Reaction.



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