# ‘COMBINED ACID’ STRATEGY FOR ASYMMETRIC CATALYSIS

Reported by Rulin Ma April 07, 2014

## INTRODUCTION

Combined acid catalysts are bifunctional catalysts consisting of at least two acid components. The coordination between two acids achieves a new complex with unprecedented reactivity and selectivity compared with their single functional counterparts.[1] Combined acid catalysts can be classified into four general categories based on the activation mode: Lewis acid-assisted Lewis acids (LLA), Brønsted acid-assisted Lewis acids (BLA), Lewis acid-assisted Brønsted acids (LBA), and Brønsted acid-assisted Brønsted acids (BBA).[1] This seminar will present the discovery and development of combined acid catalysis into a powerful method for asymmetric induction, as demonstrated in enantioselective Diels Alder reactions, enantioselective protonation reactions and enantioselective organoboronate addition reactions.

## ENANTIOSELECTIVE CYCLOADDITION REACTION

Pioneering work with the enantioselective Diels-Alder reaction has shown that boron-based Lewis acid catalysts can be activated by acidic ligands.[2] Similarly, chiral oxazaborolidines (Figure 1) can be activated by protonation (at N) using very strong Brønsted acids[3,5] (e.g. $CF_3SO_3H$) or coordination (at N) using very strong lewis acids (e.g. $AlBr_{3)}$[4,5] to form stronger, chiral Lewis acids.

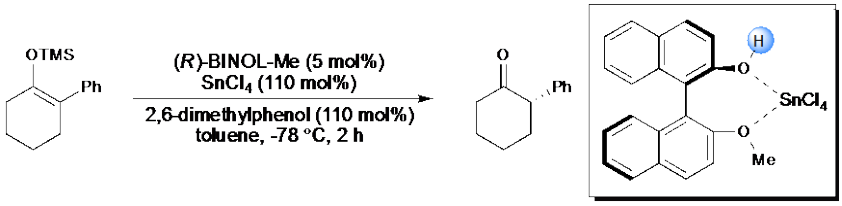
**Figure 1**. Chiral BLA and LLA oxazaborolidine catalysts

The resulting chiral Lewis acids can effectively catalyze many Diels Alder reactions with high enantioselectivity.[5] Their usefulness has been well demonstrated by applications in enantioselective complex molecule synthesis.[5]

## ENANTIOSELECTIVE PROTONATION

A fundamental method for generating a tertiary carbon stereocenter is to deliver a proton to a carbanion intermediate. However, enantioselective proton transfer presents the challenge of manipulating very small hydrogen atom and avoiding product racemization.[6] A variety of Lewis

acid-assisted Brønsted acids[1,7](e.g. BINOL•$SnCl_4$) have shown high yields and enantioselectivities in protonation of silyl enol ethers (Figure 2). Their usefulness has been well demonstrated by applications in proton-induced polyene cyclization reaction.[1,8,9]




**Scheme 1**. Enantioseletive protonation of silyl enol ethers

## ENANTIOSELECTIVE ALLYLBORONATE ADDITION

Nitrogen or oxygen-substituted carbon stereocenters are ubiquitous in biologically active molecules. Thus, readily available catalysts for efficient, enantioselective addition reactions to aldehydes, ketones and imines are highly sought after. Pioneering work with chirally modified allylic boranes has shown high yield and high selectivity due to the organized transition structures[10] and the rate of the reaction can be enhanced by external Lewis acids[10]. Recently, chiral Brønsted acidic ligands such as BINOLs[11] and amino alcohols[12] have been introduced to form Brønsted acid-assisted Lewis acids with organoborane substrates by hydrogen bonding (Figure 2). Such interactions increase Lewis acidity of the boron centers and thus enhance reaction rate, Moreover, the rigid catalyst-substrate complex engenders high enantioselectivity,[12] making allylboration a diastereoselective and enantioselective process.


**Figure 2**. Proposed transition state for enantioselective allylboration

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