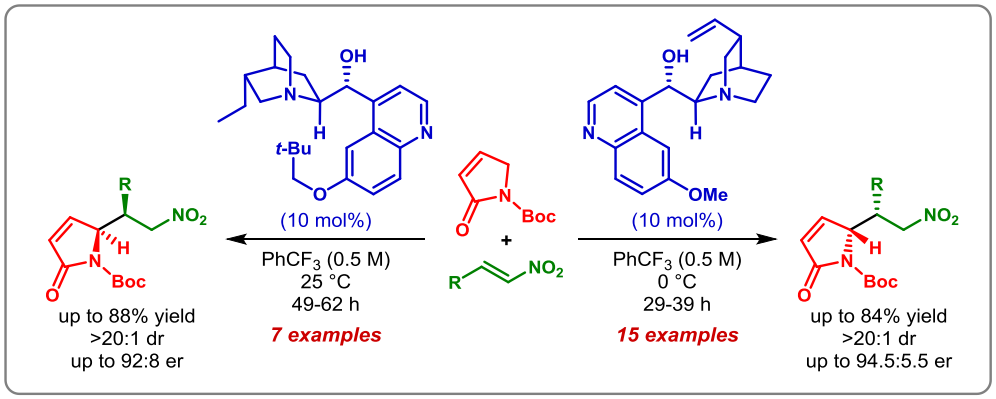
Synopsis

The thesis entitled "**Enantioselective Carbon-Carbon and Carbon-Heteroatom Bond Formation: from Bifunctional to Anion-Binding Catalysis**" is divided into four chapters.

Chapter 1: Organocatalytic Asymmetric Direct Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam to Nitroolefins

Chiral γ-butyrolactams are privileged structural motifs present in a plethora of natural products as well as pharmaceutically important compounds, such as haplophytine and (+)-lactacystin. They are also been used as a key intermediate for the stereoselective synthesis of anti-influenza drug A-315675. Though the initial works were concentrated over 2-silyloxy pyrroles as nucleophile, the direct use of γ-butyrolactam as nucleophile in enantioselective transformation gained pace during the past decade. Direct use of α,β-unsaturated γ-butyrolactam in vinylogous Michael reaction is not only desirable but also a challenging task due to the need of controlling regio-, diastereo- and enantioselectivity simultaneously. The presence of rather poorly acidic protons at the γ-position of butyrolactam makes the activation via an organocatalyst even more difficult.

In this chapter, the first organocatalytic direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam to nitroolefins has been demonstrated. Using quinidine and a simply modified dihydroquinine derivative as the bifunctional catalysts, both the product enantiomers are accessible as single regioisomer (only γ-addition product) and diastereomer with moderate to good enantioselectivity. A range of nitroolefins, bearing aryl, alkyl and heteroaryl substituents were found to be suitable electrophilic partner for this direct vinylogous Michael reaction. We have also successfully utilized α,β-unsaturated moiety of the butyrolactam as a Michael acceptor in a vinylogous Michael/oxa-Michael cascade reaction for the diastereo- and enantioselective synthesis of a tricyclic compound. A plausible mechanistic model is also presented to rationalize the observed stereochemical outcome.

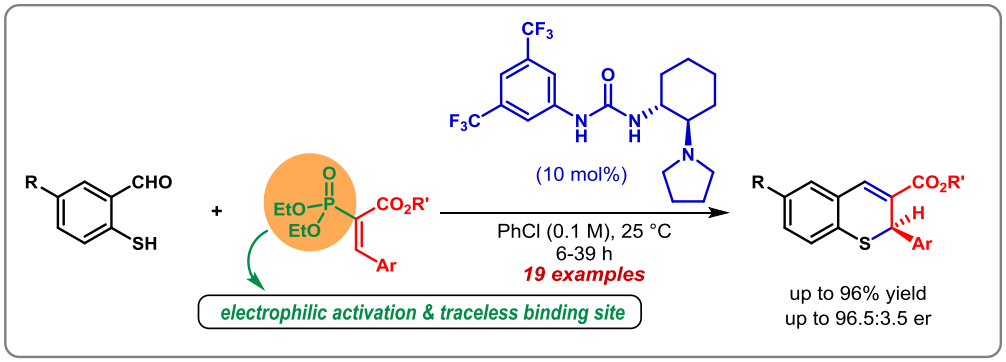


Reference: Ray Choudhury, A.; Mukherjee, S. *Org. Biomol. Chem.* **2012**, *10*, 7313-7320.

Chapter 2: A Catalytic Sulfa-Michael Addition/Horner-Wadsworth-Emmons Cascade Reaction for Enantioselective Synthesis of Thiochromenes

Thiochromene derivatives are venerable bioactive molecules having found application as analgesics, anti-cancer, anti-inflammatory and anti-bacterial agents. Although hetero-Michael-initiated cascade reactions involving α,β-unsaturated aldehydes and ketones has been profoundly used for their enantioselective synthesis, similar reactions of the corresponding ester equivalents remained relatively underexplored and almost always require an additional binding site.

In this chapter, a catalytic enantioselective sulfa-Michael addition/Horner-Wadsworth-Emmons olefination cascade is presented. This cascade sequence is initiated by a sulfa-Michael addition to a vinylphosphonate catalyzed by a chiral bifunctional urea derivative and provides an easy access to enantioenriched 2,3-disubstituted thiochromene derivatives. Several aryl and heteroaryl substituted thiochromenes were obtained in excellent yield with high level of enantioselectivity. Our report represents the first example of the use of phosphonate as a traceless binding site in a catalytic asymmetric transformation. The use of a simple catalyst, mild reaction conditions (ambient temperature) and one-pot strategy highlights the benefits of our protocol. Synthetic utility of the products is demonstrated and a model is proposed to rationalize the stereochemical outcome of the reaction.

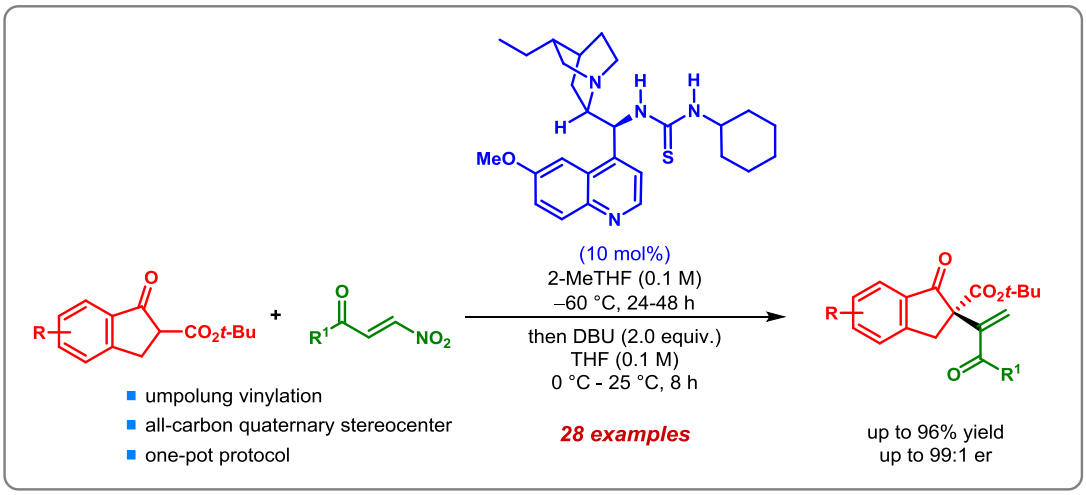


References: Ray Choudhury, A.; Mukherjee, S. *Adv. Synth. Catal.* **2013**, *355*, 1989-1995.

Chapter 3: Organocatalytic Enantioselective Umpolung Vinylation of Cyclic β-Ketoesters

Considering the wide abundance of natural products having vinyl containing quaternary stereocenter, we became interested in an efficient protocol for enantioselective vinylation. We became aware of the fact that all C-H vinylation reported till date couples nucleophile with β-carbon of an electron withdrawing group. However, there is no example of C-H vinylation which couples nucleophile with α-carbon of an electron withdrawing group. Considering the fact that α-carbon of an electron withdrawing group is nucleophilic in nature, such a combination would lead to "*mismatched polarity*" and render the reaction electronically impossible. Therefore, a reversal of polarity or umpolung reactivity would be necessary for this coupling.

In this chapter, an efficient formal enantioselective umpolung α-vinylation of cyclic β-ketoester by an one-pot two-step sequence is described. This two-step protocol consists of a catalytic enantioselective Michael reaction followed by base mediated nitrous acid elimination. The products, bearing an all-carbon quaternary stereocenter including a vinyl moiety, was synthesized in high yield with excellent er. β-Nitroenones containing substituted aryl or heteroaryl group produced the vinylated product with excellent enantioselectivity. Our protocol demonstrates the first use of β-nitroenones as an electrophilic component in an enantioselective reaction. This is also the first example of a catalytic umpolung vinylation reaction of β-ketoester. The reaction could be scaled up at least to 1.0 mmol scale without hampering the yield or enantioselectivity. A model based on the bifunctional nature of the catalyst was proposed to rationalize the observed stereochemical outcome of the reaction.



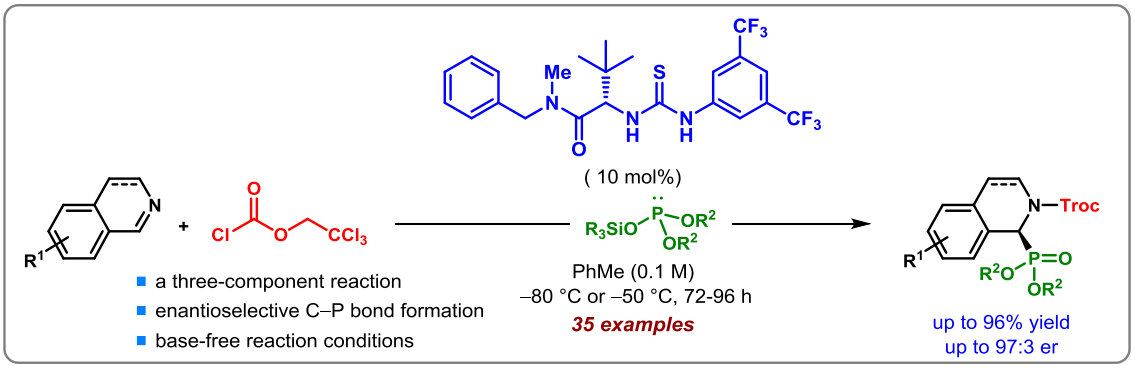
References: Ray Choudhury, A.; Manna, M. S.; Mukherjee, S. *manuscript under preparation*.

Chapter 4: Enantioselective Dearomatization of Isoquinolines by Anion-Binding Catalysis en Route to Cyclic α-Aminophosphonates

α-Aminophosphonates and related α-aminophosphonic acid derivatives are used extensively in medicinal and pharmaceutical sciences as surrogates of α-amino acids. The strong correlation between the biological activities of compounds containing α-aminophosphonic acids and their absolute configuration renders the enantioselective synthesis of α-aminophosphonates imperative to such studies. Considerable advancement has taken place in the catalytic enantioselective synthesis of acyclic α-aminophosphonates using various strategies. In contrast, enantioselective synthesis of cyclic α-aminophosphonates remains elusive, despite their prominent abundance in biologically active molecules.

In this chapter, the development of an enantioselective dearomatization of diversely substituted isoquinolines through acyl activation and nucleophilic addition of silyl phosphites is presented.

Using a simple and easy to prepare *tert*-leucine derived thiourea as the anion-binding catalyst, this base-free protocol delivers cyclic α-aminophosphonates in excellent yields with moderate to high enantioselectivities. The reaction was found to be general with respect to different isoquinolines when applied to monosubstituted isoquinolines bearing substituent at nearly every position and even to disubstituted isoquinolines. Our protocol was also found to be suitable for dihydroisoquinolines. This is the first example of the use of silyl phosphites as the nucleophile in asymmetric dearomatization reactions driven by anion-binding catalysis. In fact, this is also the first time asymmetric anion-binding catalysis has been applied to the synthesis of α-aminophosphonates. A preliminary experiment with quinoline points toward potential applicability of this strategy to other nitrogenous heteroaromatics.



References: Ray Choudhury, A.; Mukherjee, S. *under revision*.