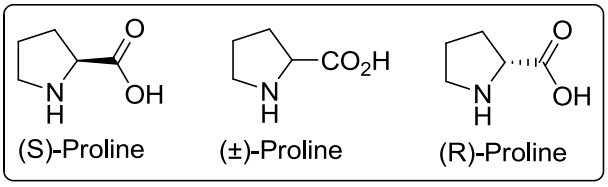
Lecture 34

10.1 Chiral Proline Based Reactions

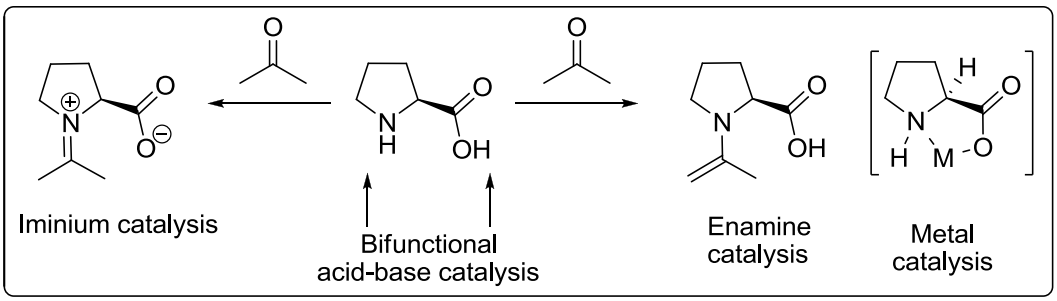
Enantioselective organocatalysis has emerged as a powerful synthetic method complementary to the metal- and enzyme-catalyzed reactions. The low toxicity associated with organocatalysis and operational simplicity makes it an attractive method to synthesize complex structures. Among the organocatalysts, small molecules like chiral proline, chiral thiourea, chiral TADDOL and chiral alkaloids have special reactivity in the asymmetric synthesis.

Chiral proline is termed as the simplest bifunctional organocatalysts (Scheme 1). This amino acid is called as "simplest enzyme" due to its ability to catalyze reactions with high stereoselectivity.



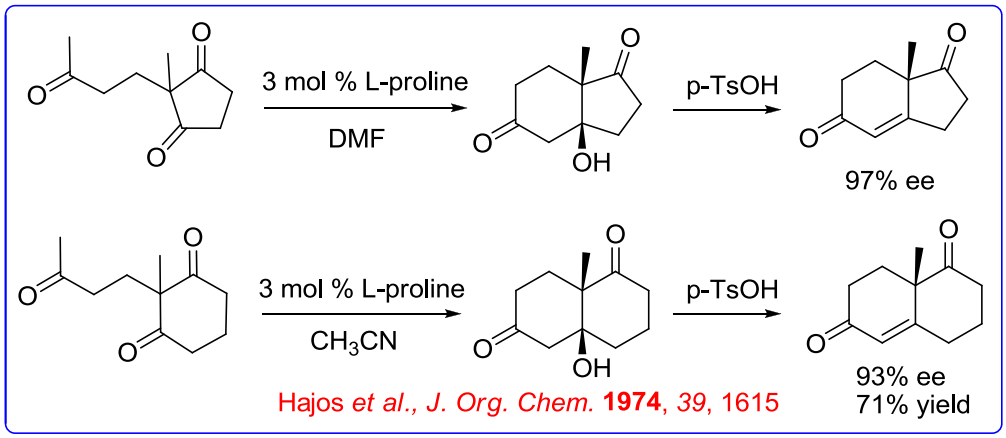
Scheme 1. Forms of Proline Available

L-Proline is a small molecule, non-toxic, inexpensive, readily available in both enantiomeric forms having bifunctional acid-base sites (Scheme 2). The reaction may proceed through either iminium catalysis, or enamine catalysis or bifunctional acid–base catalysis.

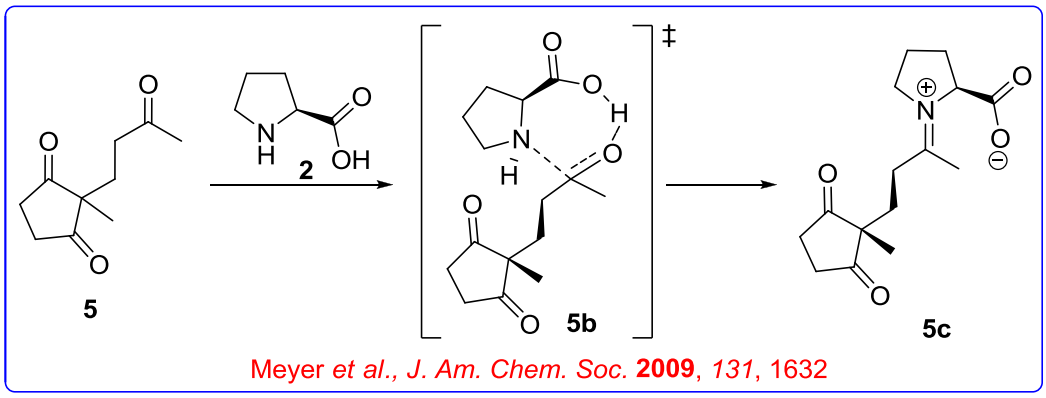


Scheme 2. Reactivity Modes of L-Proline

In the early 1970, the first L-proline-catalyzed aldol cyclization was appeared (Scheme 3). After nearly 25 years, the expected transition state for the reaction has been illustrated (Scheme 4).



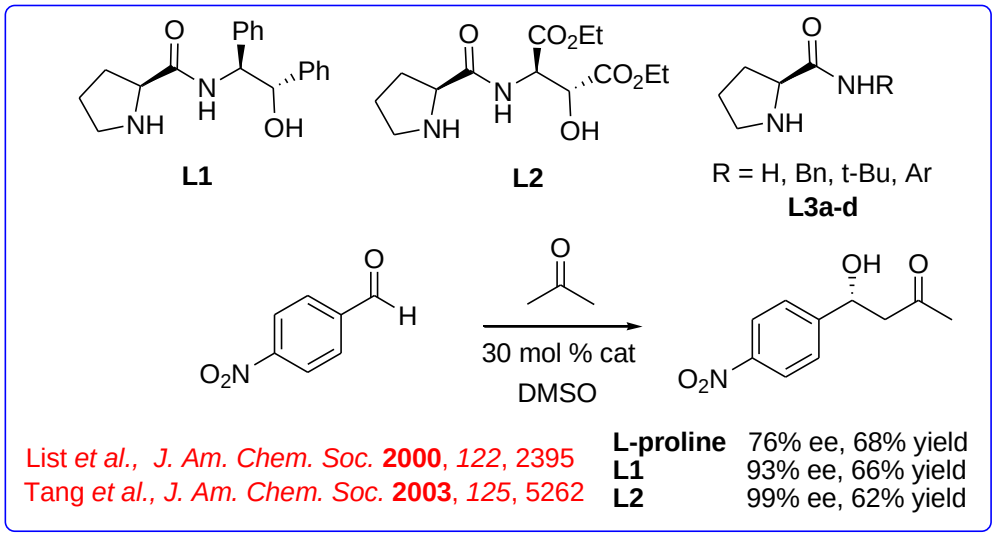
Scheme 3. L-Proline-Catalyzed Robinson Annulation Through Aldol Reaction



Scheme 4. Expected Transition State

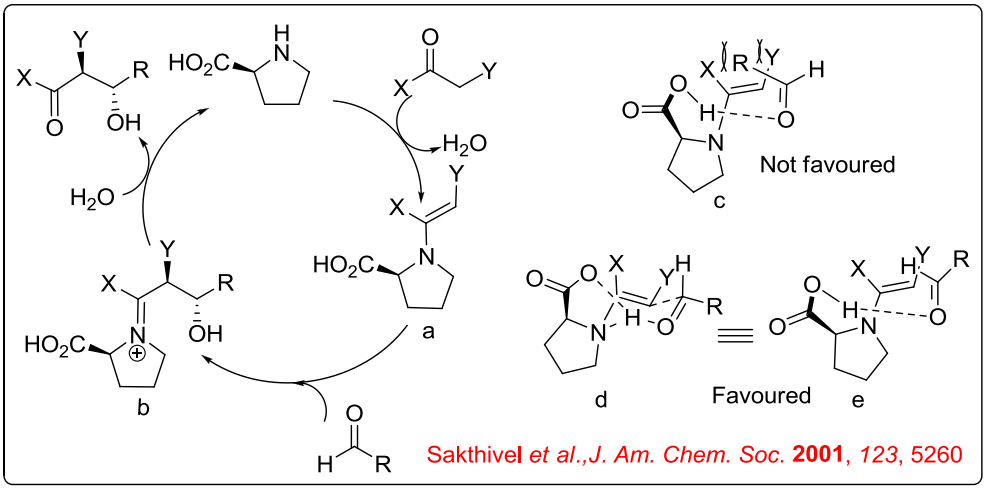
10.1.1 Intermolecular Aldol Reaction

The enantioselective aldol reaction is one of the most powerful methods for the construction of chiral polyol. The first intermolecular direct enantioselective aldol reaction catalyzed by L-proline appeared employing acetone and 4-nitrobenzaldehyde as the substrates (Scheme 5). This result sparked high interest from several groups in further investigating proline-catalyzed direct asymmetric aldol reactions. Subsequently, modified chiral proline derived catalysts **L1-3** has been developed to enhance the selectivity of the reaction.



Scheme 5. First L-Proline Catalyzed Direct Aldol Reaction

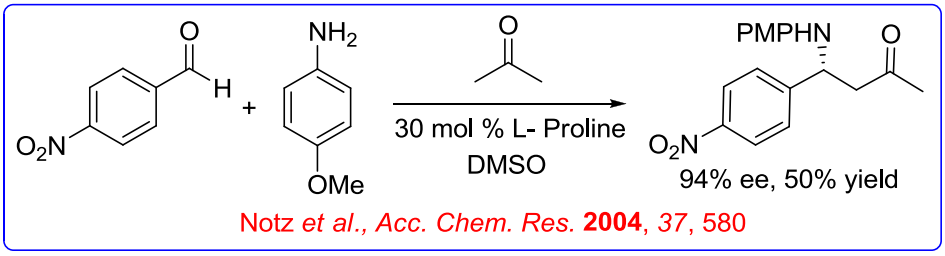
For the mechanism, reaction of pyrrolidine with the carbonyl donor can give enamine **a** that could proceed reaction with the *re*-face of the aldehydes to give the iminium ion **b** (Scheme 6). The latter can undergo hydrolysis to afford chiral β-hydroxyketone. The proposed transition state illustrates that enamine attack occurs on the *re*-face of the aldehyde **d** and **e**. This facial selectivity of attack by the enamine is dictated by minimizing steric interactions between the aldehyde substituent and the enamine substituent. The attack of the enamine on the *si*-face of the aldehyde leads to the unfavorable transition state **c**.



Scheme 6. Mechanism for Proline Catalyzed Aldol Reaction

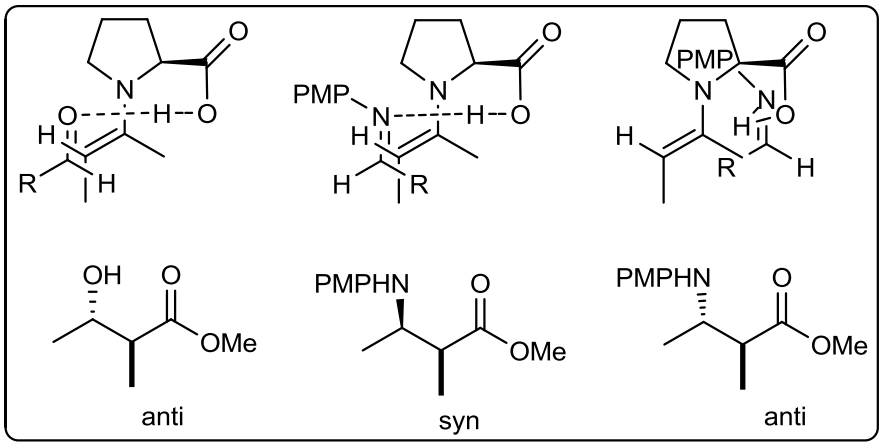
10.1.2 Mannich Reaction

Parallel to the aldol reaction, enantioselective *Mannich* reaction of aldehyde, acetone and *p*-anisidine as the substrates has been explored with 50% yield and 94% ee (Scheme 7).



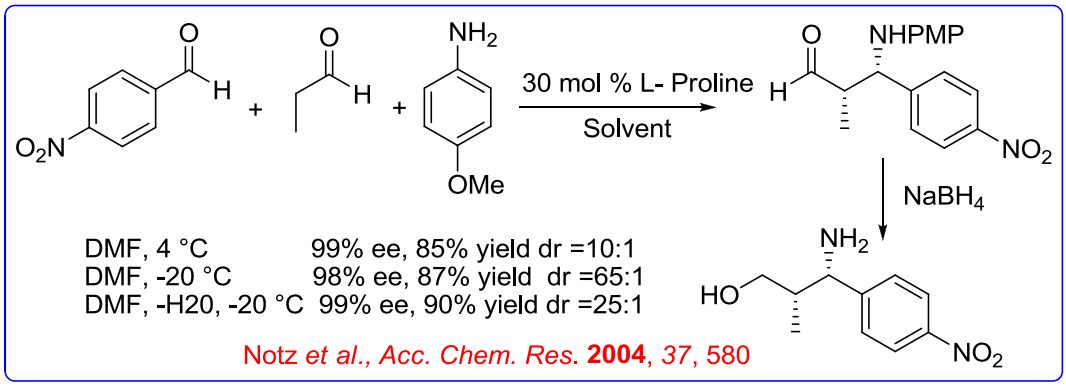
Scheme 7. L-Proline-Promoted One-Pot Three-Component Mannich-Type Reaction

The mechanism is analogous to that of the aldol reactions (Scheme 8). The reaction of proline with aldehyde or ketone can give *enamine* that could undergo reaction with the imine to form new stereocenters as iminium product. The latter on hydrolysis can give the target *Mannich* product. The reaction of (*E*)-aldimine with the enamine on its *si*-face can give the *syn* product. Because of the *re*-face is blocked by steric interactions between the aromatic ring of the *p*-methoxyphenyl group and the ring of proline.



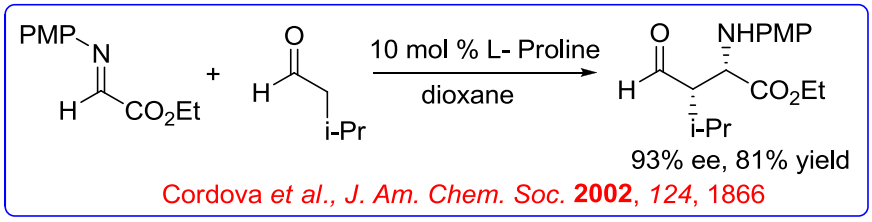
Scheme 8. Proposed Transition States and Products for the *Mannich* Reactions

The proline-catalyzed *Mannich* reactions of *N*-PMP-protected α-imino ethyl glyoxylate with a variety of ketones afford functionalized α-amino acids (Scheme 9). These reactions can generate two adjacent stereogenic centers simultaneously upon C-C bond formation with complete *syn*-stereocontrol and can be performed in a gram scale with operational simplicity.



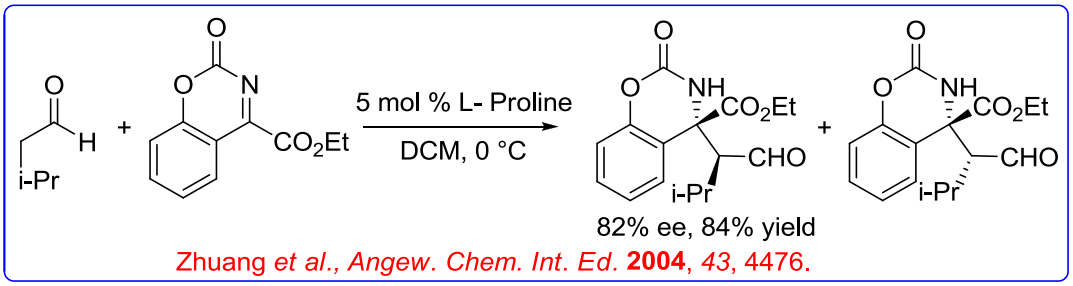
Scheme 9. One-Pot Three-Component Mannich-Type Reaction

The proline-catalyzed reaction of *N*-PMP-protected α-imino ethyl glyoxylate with aliphatic aldehydes provides a general method for synthesis of β-amino and α-amino acid derivatives (Scheme 10). The diastereoselectivity depends on the bulkiness of the substituents of the aldehyde donor. In most of cases high *syn* stereoselectivity can be achieved.



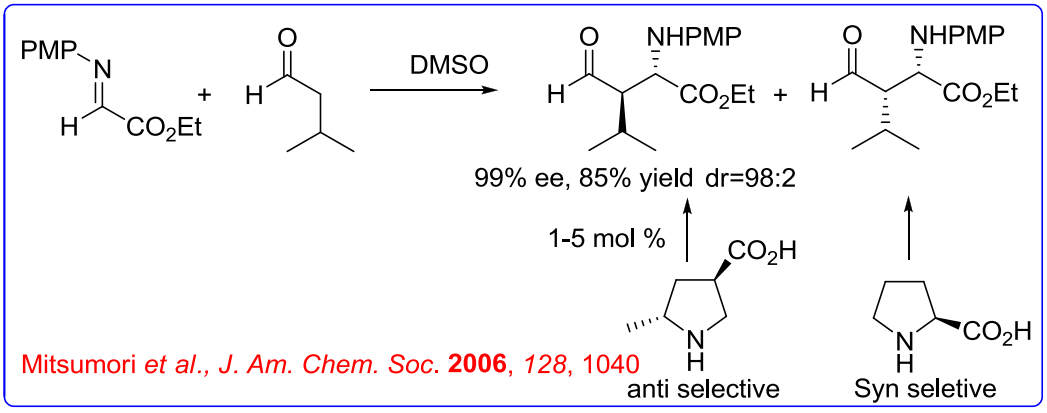
Scheme 10. Mannich Reactions of Unmodified Aldehydes with Preformed Aldimines

The synthesis of chiral quaternary amino acid derivatives can be accomplished using proline based catalysis (Scheme 11). The nitrogen is tethered to the □-aryl amine in order to increase the reactivity through ring strain and the products are obtained with high enantioselectivity.



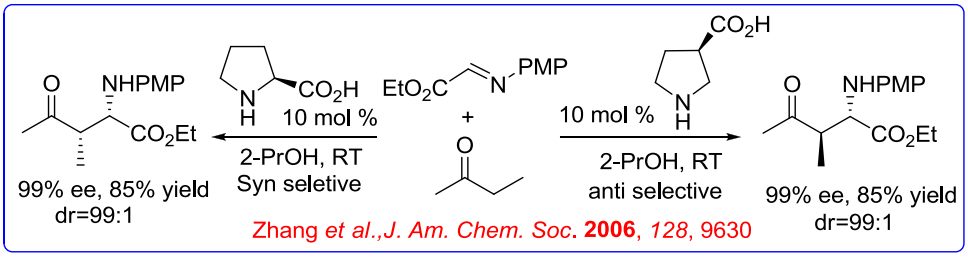
Scheme 11. Mannich Reaction of Unmodified Aldehyde with Ketimines

(*S*)-Proline-catalyzed Mannich-type reaction of aldehydes with α-imino ethyl glyoxylate affords *syn*-products, while the reaction utilizing (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid gives *anti*-selective product (Scheme 15).



Scheme 15. *Anti* and *Syn* Selectivity in Mannich reaction

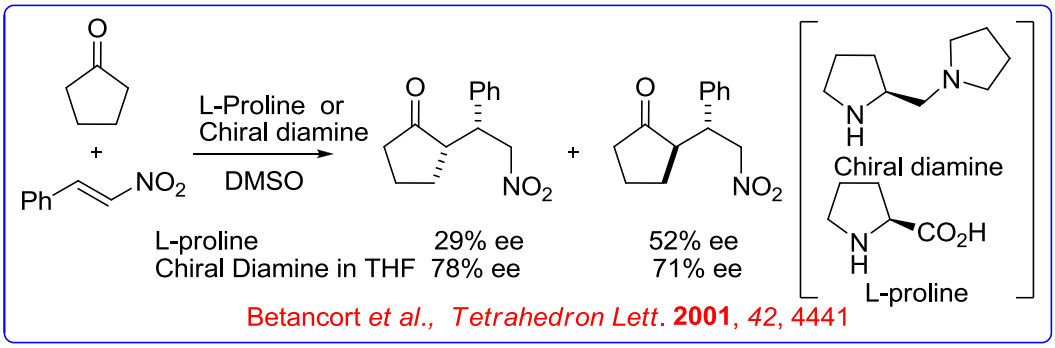
In addition, *(R)*-3-pyrrolidinecarboxylic acid catalyzes the Mannich-type reactions of ketones with α-imino ethyl glyoxylate to give *anti*-products, while *(S)*-proline based reactions give *syn*-products (Scheme 17). Thus, the position of the carboxylic acid group on the pyrrolidine ring directs the stereoselection of the catalyzed reaction providing either *syn*- or *anti*-Mannich products.



Scheme 16. *Anti* and *syn* Mannich-type Reactions of Ketones

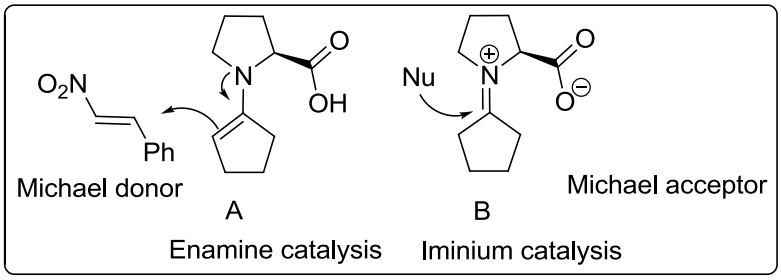
10.1.3 Michael Reaction

In 2001, the first example for a direct asymmetric Michael reaction employing an enamine-activated donor appeared. The proline-catalyzed reaction of acetone and cyclopentanone with benzalmalonate and nitrostyrene affords the Michael product with low enantiomeric excess. However, the use of chiral diamine improves the *ee* significantly with both nitrostyrene and alkylidene malonates as acceptors and ketone donors (Scheme 17).



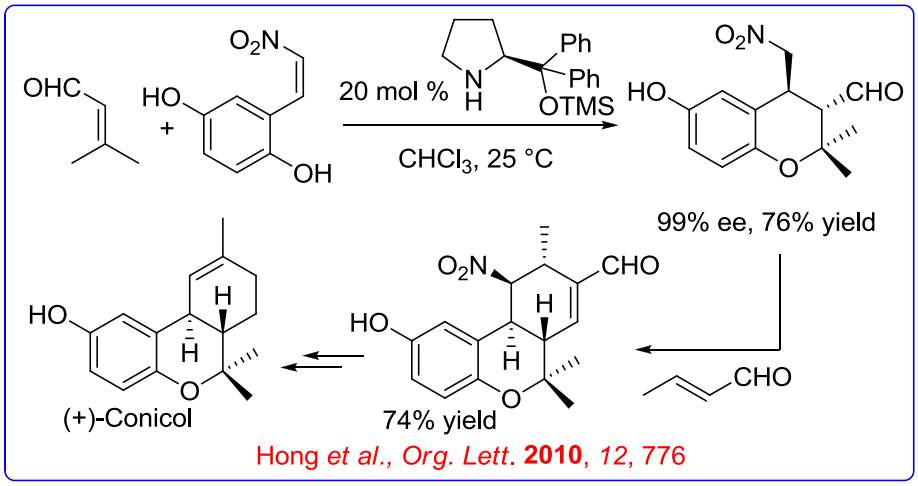
Scheme 17

Possible stereochemical result has been accounted by assuming acyclic transition states **A** and **B**. These Michael reactions constituted the first direct catalytic asymmetric reactions of any types involving aldehyde donors and encouraged the development of aldehyde-based reactions with a range of electrophiles (Scheme 18).



Scheme 18. Mode of Action in Chiral Michael Reaction

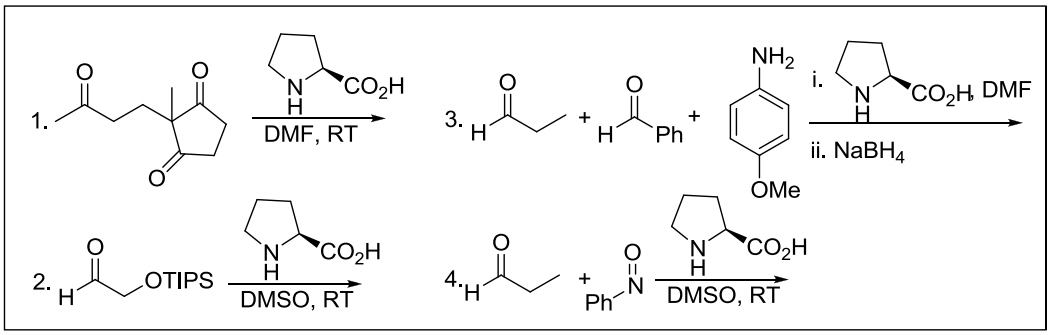
The iminium-enamine activation mode can be envisaged to explain the domino oxa-Michael–Michael reaction occurring between 3-methylbut-2-enal and (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol upon catalysis with chiral diphenyl prolinol silyl ether, which afford the corresponding enantiopure oxa-Michael–Michael cycloadduct in 76% yield and 99% ee (Scheme 19). The latter can be further implicated in a Michael–aldol sequence through the reaction with crotonaldehyde to afford corresponding hexahydro-6H-benzo-chromene in 74% yield. These two domino reactions have constituted the key steps of the first asymmetric total synthesis of the natural biologically active product (+)-conicol.



Scheme 19. Domino oxa-Michael–Michael Reaction in the Synthesis of (+)-Conicol

Problems

Complete the following reactions.



Reference/Text Book

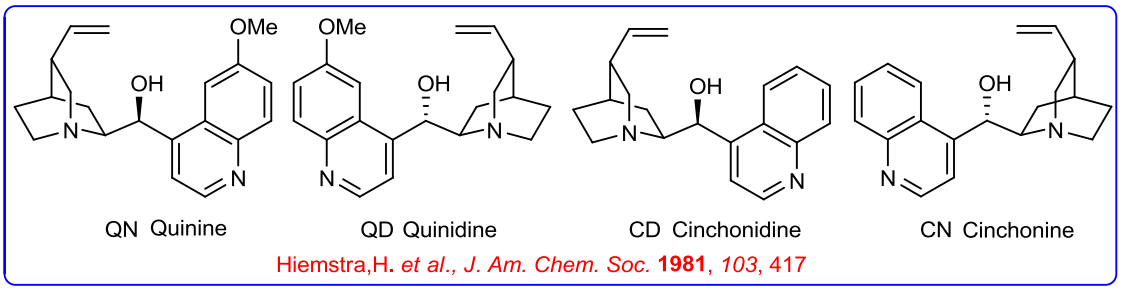
1. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.
2. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

Lecture 35

10.2 Alkaloid Based Reactions

10.2.1 Conjugate Addition Reactions

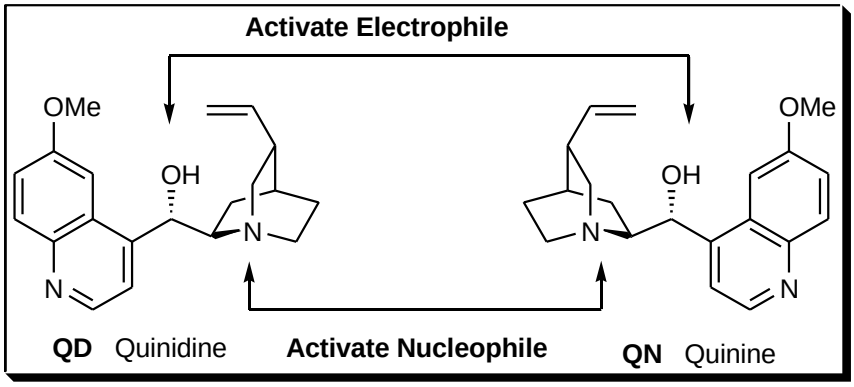
Cinchona alkaloids are a large class of compounds extracted from the bark of homonym trees cultivated in equatorial climatic zones, between Bolivian and Venezuelan Andes, and Indonesia. In the extract of the bark are present more than 30 alkaloids (5-15% w/w). Four of them represent 50% of all the alkaloids such as quinine (QN), quinidine (QD), cinchonidine (CD) and cinchonine (CN) (Scheme 1).



Scheme 1. Bifunctional Alkaloid Based Organocatalysts

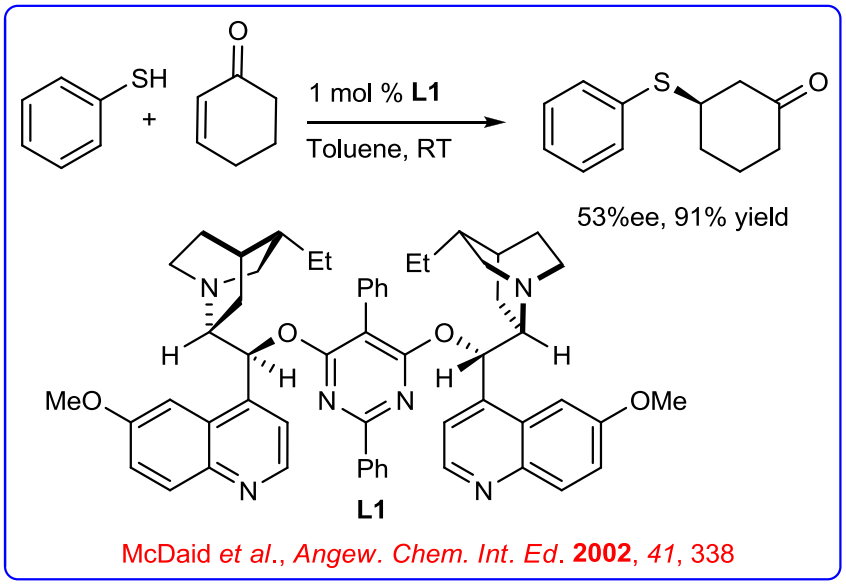
QN is the most well known alkaloid and used as the anti-malarial drug of choice for over 400 years until chloroquine discovered, while QD is used as an anti-arrhythmic agent. In chemistry, all these compounds (QN, QD, CD and CN) are used as cheap chiral source. These molecules activate the nucleophile by enamine and carbanion formation, and electrophile via hydrogen bond.

These compounds are diastereomers having five stereogenic centers and the chiral quinuclidinyl nitrogen is the most important as it is responsible of the direct transfer of chirality during catalysis. Quinine *vs* quinidine and cinchonidine *vs* cinchonine have opposite absolute configuration this means that very often these pairs of diastereomers act as enantiomers at C-9 position. Furthermore, the C-9 OH group acts as Brønsted acid. So acid and base coexist in these molecules, and thus, it is possible to activate both the nucleophile and the electrophile simultaneously to use as *bifunctional organocatalysts* (Scheme 2).



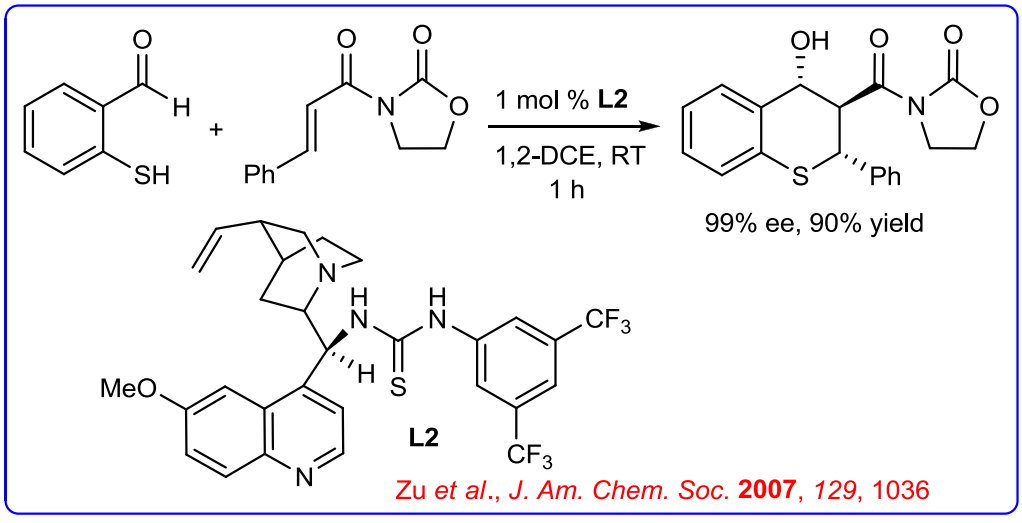
Scheme 2. Dual Activation Modes by Bifunctional Basic QD and QN Organocatalysts

The catalytic asymmetric 1,4-addition of thiols to cyclic enones with modified cinchona alkaloid has been demonstrated (Scheme 3). The Michael products can be isolated with high yield and enantioselectivity for a range of substances.



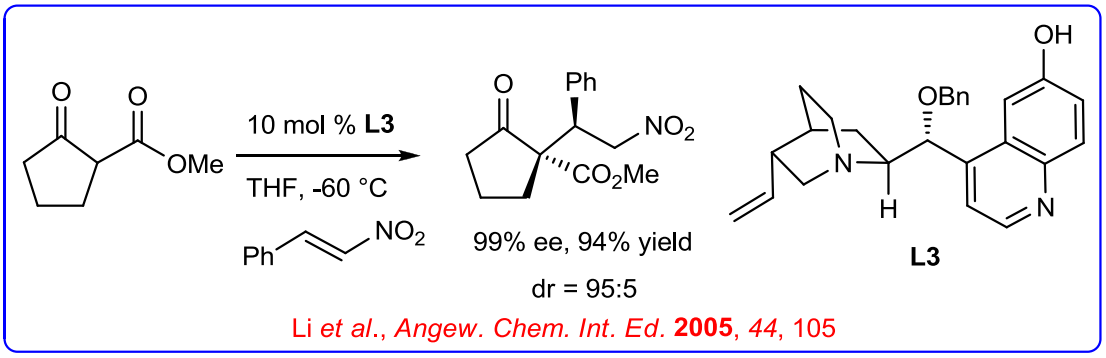
Scheme 3. Enantioselective Michael Addition of Thiophenols to Enones

Later, tandem Michael-aldol reactions have been developed for the preparation of medicinally important chiral thiochromanes (Scheme 4). This new one-pot process proceeds with 1 mol % of the cinchona alkaloid derived thiourea catalyst **L2**, which synergistically activates both the Michael donor and acceptor.



Scheme 4. Reaction of 2-Mercaptobenzaldehyde with α,β-Unsaturated oxazolidinone

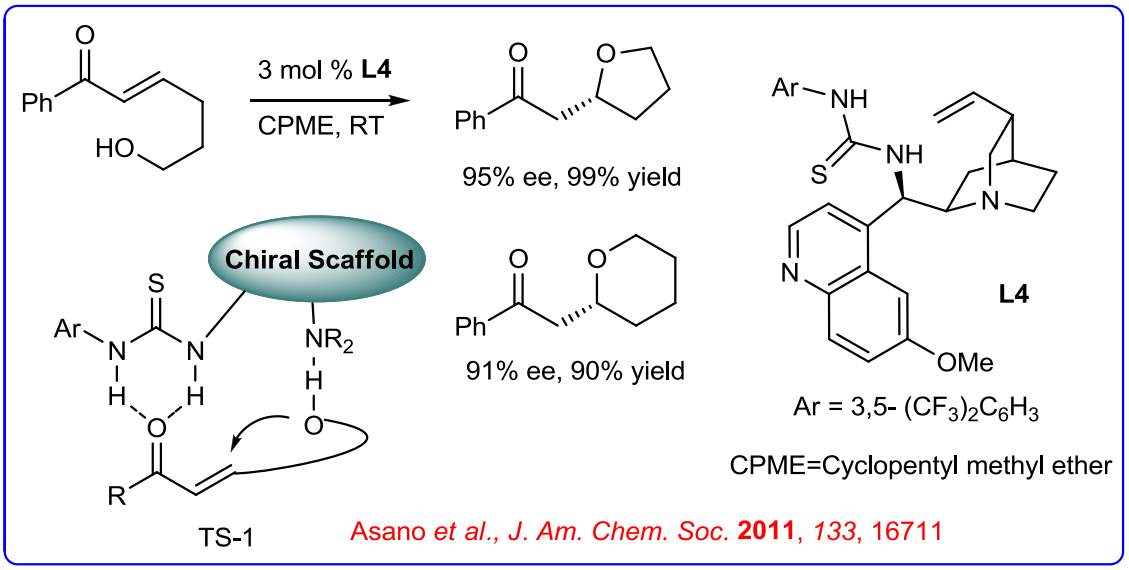
Similarly, the conjugate addition has been reported with catalyst **L3** for a direct, stereocontrolled construction of adjacent carbon- or heteroatom-substituted quaternary and tertiary stereocenters from readily available starting β-ketoester (Scheme 5).



Scheme 5. Asymmetric Michael Addition Reaction

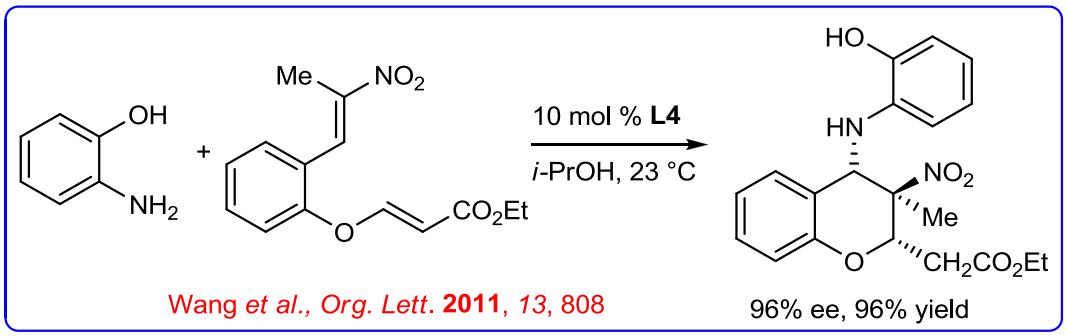
Chiral oxacyclic structures such as tetrahydrofuran rings are commonly found in many bioactive

compounds. Cinchona-alkaloid-thiourea **L4** catalyzes the cycloetherification of ε-hydroxy-α,β-unsaturated ketones with excellent enantioselectivity, even with low catalyst loadings at room temperature. The probable activation intermediate might go through TS-1.



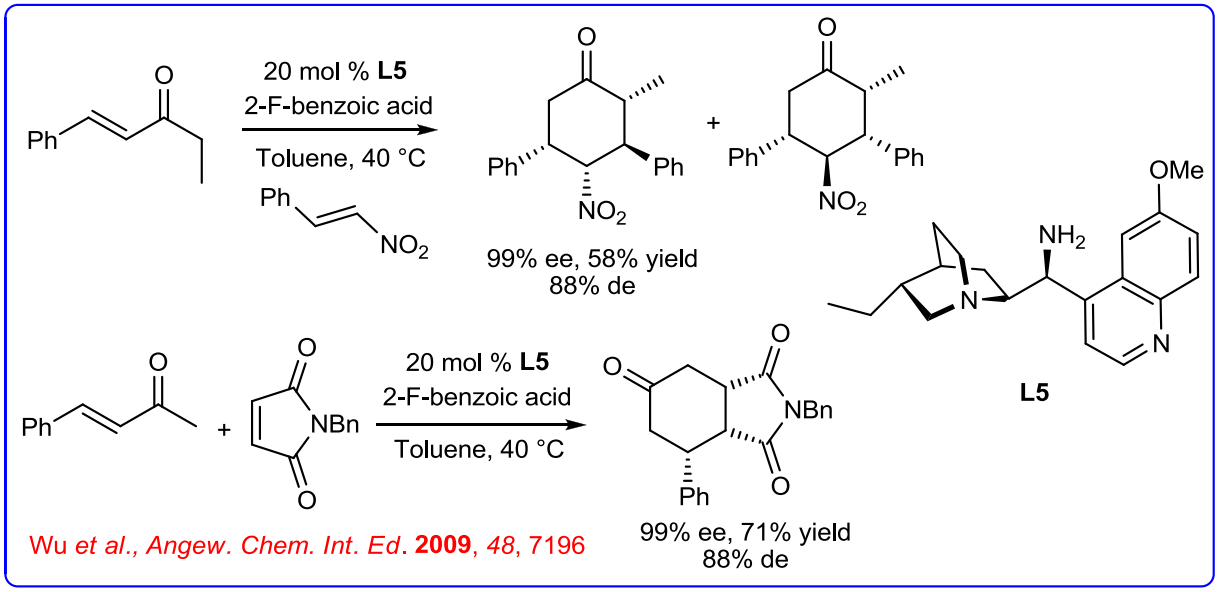
Scheme 6. Cycloetherification via intramolecular oxy-Michael addition reaction

The catalyst **L4** can also catalyze the domino aza-Michael–Michael reactions of anilines with nitroolefin enoates to afford chiral 4-aminobenzopyrans bearing two consecutive stereogenic centers and one quaternary stereocenter (Scheme 7). The products can be isolated with high yield and enantioselectivity.



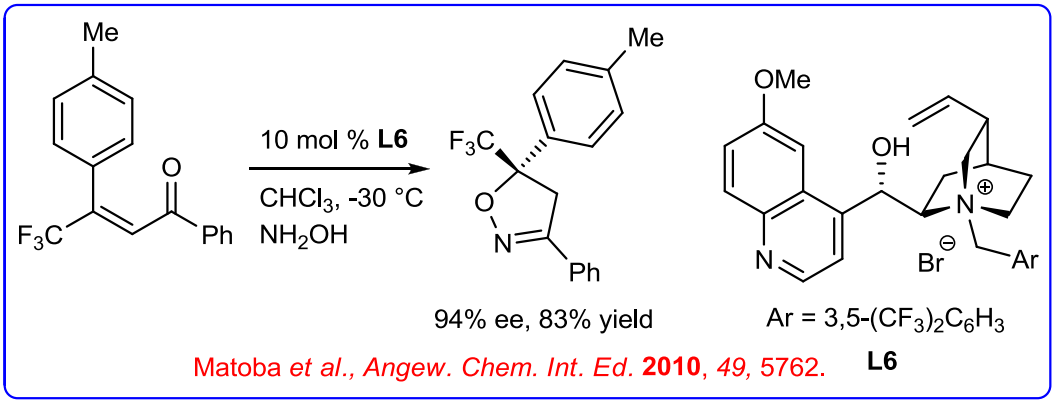
Scheme 7. Domino aza-Michael–Michael Reactions

Chiral amine **L5** has been used to activate α,β-unsaturated enones with nitro alkenes toward a well-defined enamine-iminium activation mode in presence of 2-fluorobenzoic acid as an additive. The reaction affords the Diels–Alder adduct bearing three or four stereogenic centers with high enantioselectivity (Scheme 8). The extension of this process to other Michael acceptors such as *N*-benzyl maleimide leads to the formation of cyclohexanones with up to >99% ee.



Scheme 8. Asymmetric Domino Michael–Michael Reactions

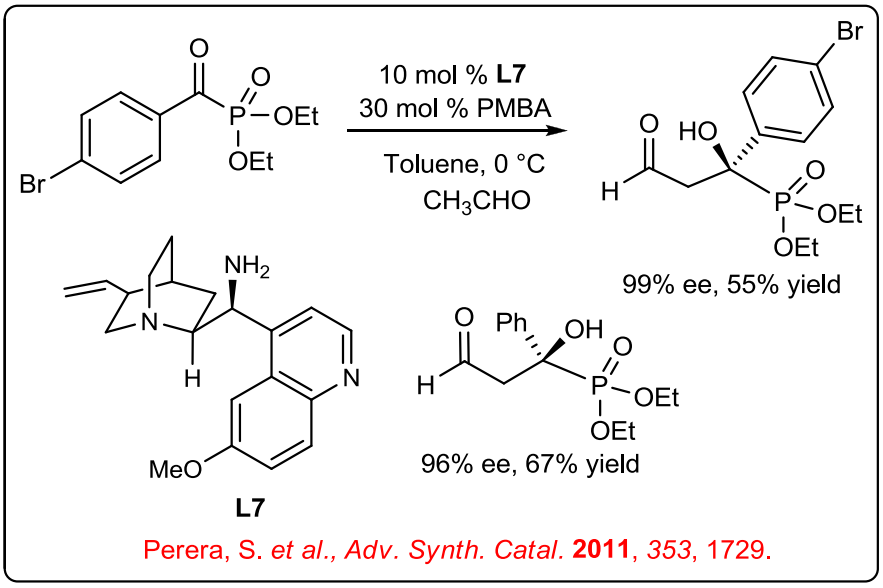
The synthesis of trifluoromethyl-substituted 2-isoxazolines can be accomplished by a domino Michael–cyclization–dehydration reaction of hydroxylamine (NH_2OH) with a range of *(E)*-trifluoromethylated enone derivatives in the presence of *N*-3,5-bis(trifluoromethyl benzyl) quinidinium bromide **L6** as a chiral phase transfer catalyst (Scheme 9).



Scheme 9. Synthesis of Trifluoromethyl Substituted 2-Isoxazolines

10.2.2 Aldol Reaction

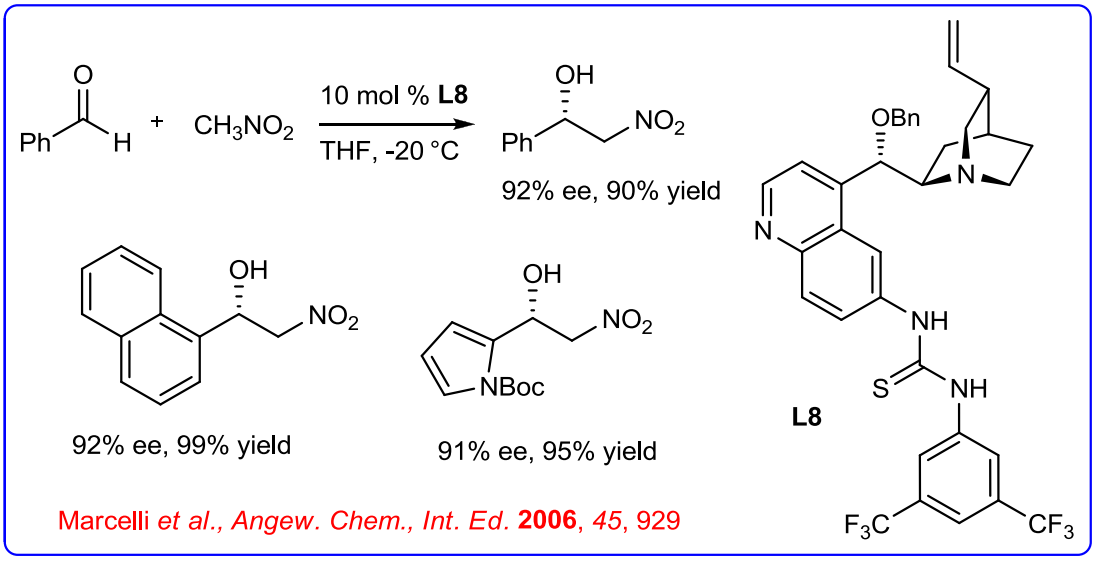
The cross-aldol reaction between enolizable aldehydes and α-ketophosphonates can be achieved using 9-amino-9-deoxy-*epi*-quinine **L7** (Scheme 10). The reaction works especially well with acetaldehyde, which is a tough substrate for organocatalyzed cross-aldol reaction.



Scheme 10

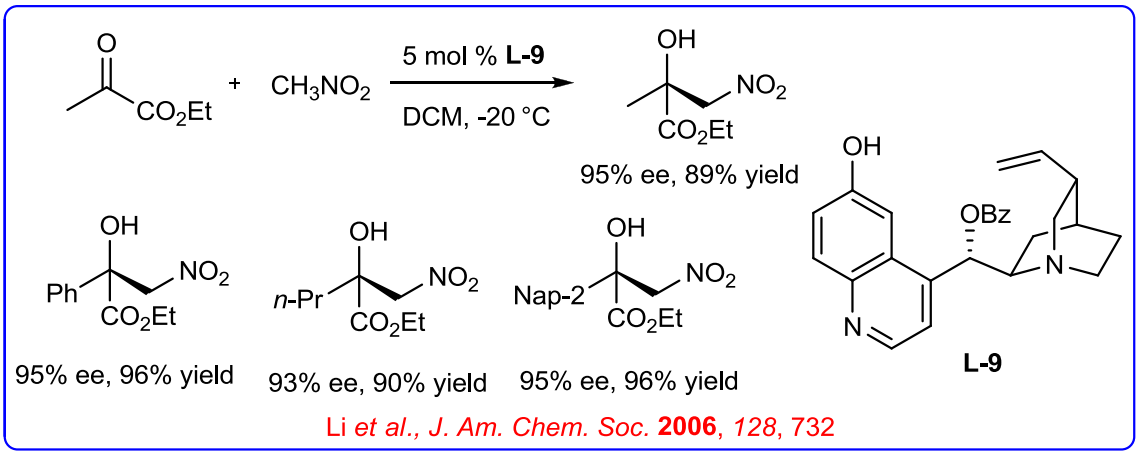
10.2.3 Henry Reaction

Henry reaction is a classical carbon-carbon bond forming reaction in organic synthesis. Aryl aldehydes react with nitromethane in the presence of 6'-thioureasubstituted cinchona alkaloid **L8** with high enantioselectivity (Scheme 11). Hydrogen-bond donor at the C6′ of **L8** has been found to induce preferential formation of one enantiomer.



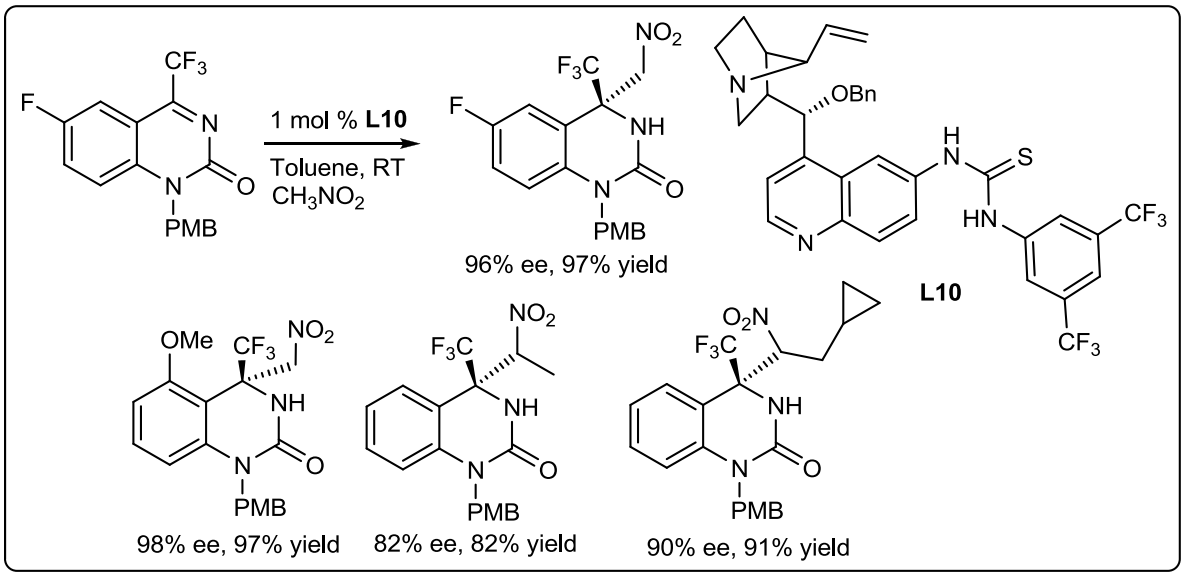
Scheme 11

The 6'-OH cinchona alkaloid **L-9** is an excellent catalyst for the reaction of α–ketoesters with nitromethane (Scheme 12). The highly enantioenriched products from the Henry reaction could be elaborated to aziridines, *β*–lactams and α-alkylcysteines. This reaction is operationally simple and affords high enantioselectivity as well as good to excellent yield for a broad range of α-ketoesters.



Scheme 12. Cinchona-Catalyzed in Henry Reaction

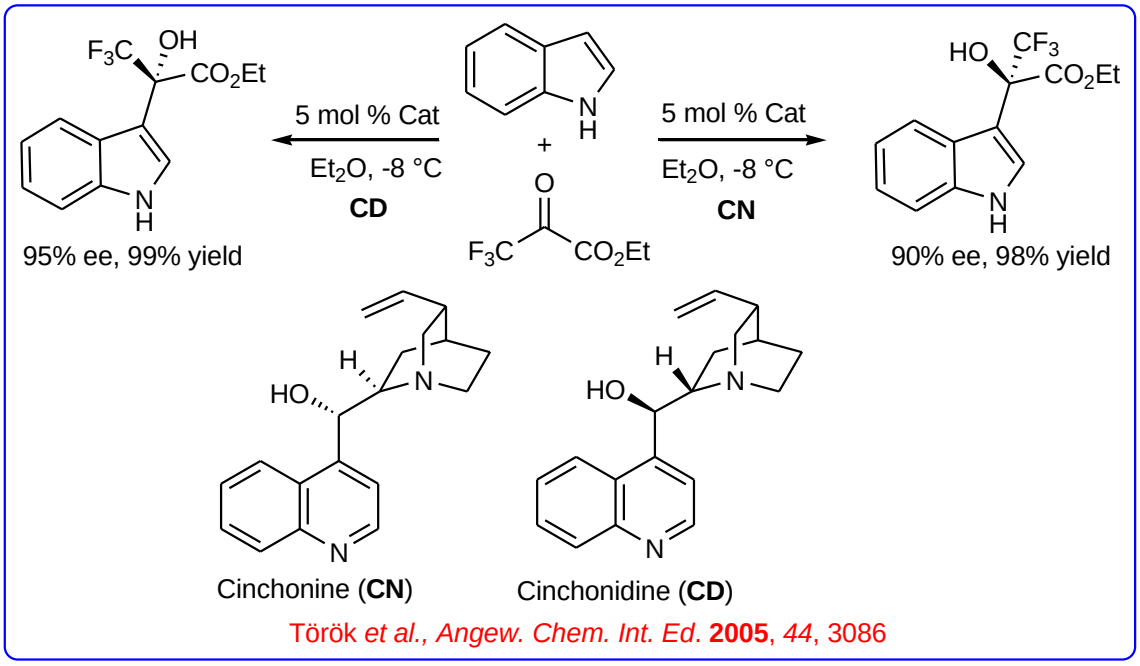
Bifunctional cinchona alkaloid-thiourea **L10** can catalyze efficiently the aza-Henry reaction of cyclic trifluoromethyl ketimines with nitromethanes (Scheme 13). The title reaction can provide biologically interesting chiral trifluoromethyl dihydroquinazolinone frameworks with high yield and enantioselectivity.



Scheme 13. Cinchona-Catalyzed in Henry Reaction

10.2.4 Hydroxyalkylation Reaction

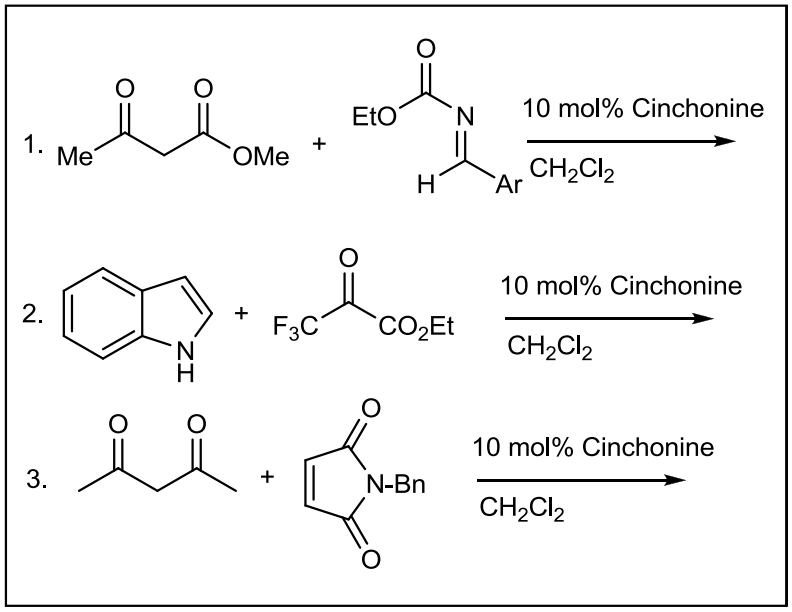
The readily available cinchonidine (CD) and cinchonine (CN) can be used for the catalysis of the hydroxyalkylation of heteroaromatics. For example, the hydroxyalkylation of indoles with ethyl-3,3,3-trifluropyruvate occurs to afford corresponding 3-substituted products in high yields and *ee* values (Scheme 14).



Scheme 14. Hydroxyalkylation of Indoles with Ethyl-3,3,3-trifluropyruvate

Problems

A. Complete the following reactions.



Reference/Text Book

3. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

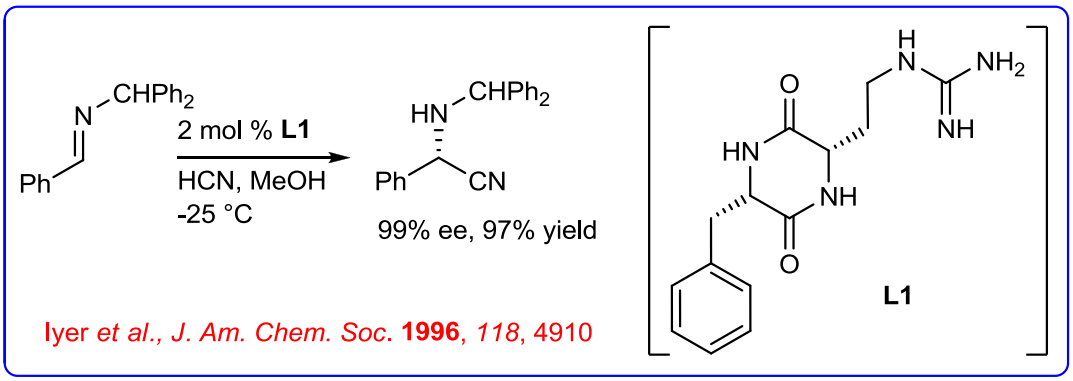
4. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.

Lecture 36

10.3 Thiourea Based Catalysis

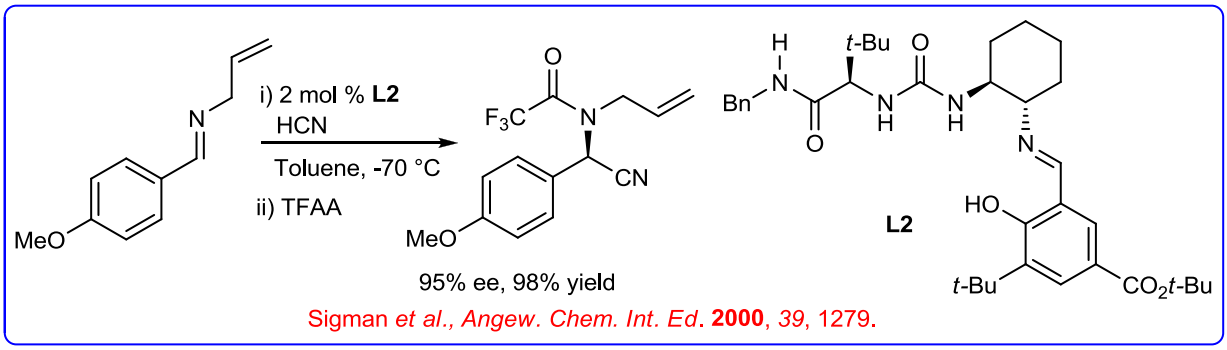
10.3.1 Strecker Synthesis

In 1996 the first asymmetric organocatalytic *Strecker* synthesis appeared employing **L1** as a catalyst (Scheme 1). The reaction involves the addition of *HCN* to imines in the presence of diketopiperazine derivative with up to >99% ee.



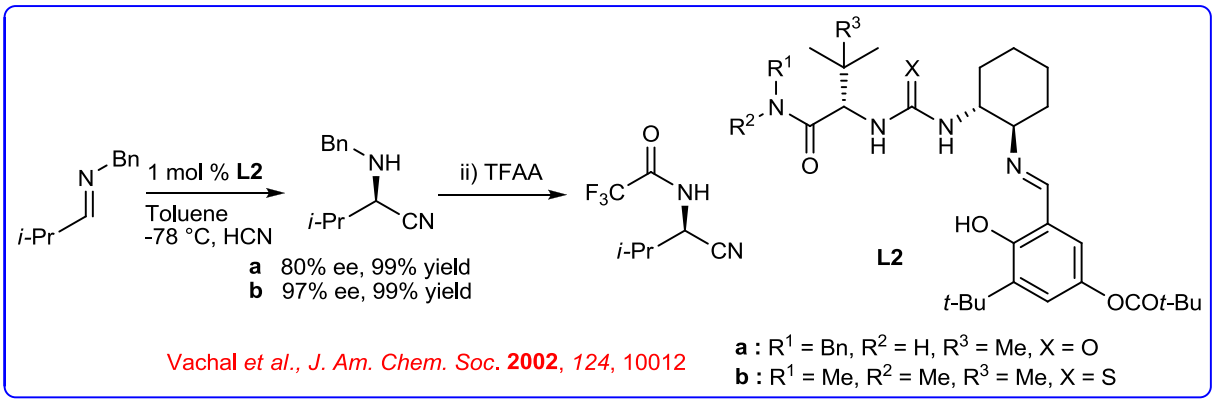
Scheme 1

Subsequently, chiral thiourea derivative **L2** has been used for this reaction to afford the cyanohydrins with 98% ee (Scheme 2).



Scheme 2

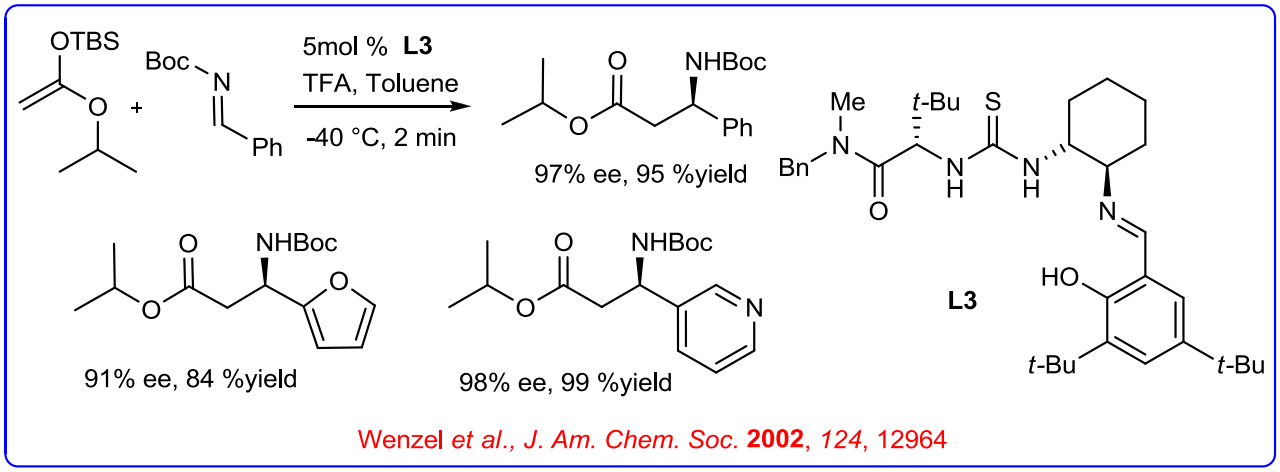
Further improvement in this reaction has been made employing thiourea derivative **L3** (Scheme 3). The active site of the catalyst, the relevant stereoisomer of the imine substrate and the solution structure of the imine–catalyst complex are elucidated using kinetics, structural activity and NMR experiments. An unusual bridging interaction between the imine and the urea hydrogens of the catalyst is identified.



Scheme 3. Improved Asymmetric Addition of HCN to Imines

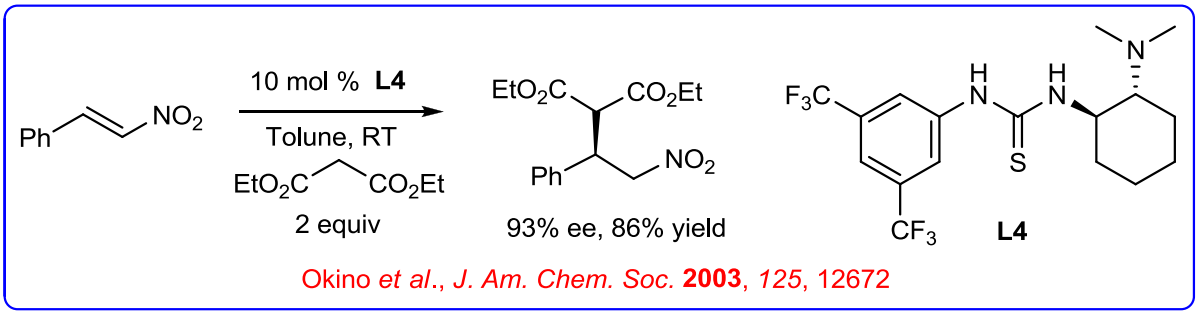
10.3.2 Mannich Reaction

In parallel to Strecker reaction, Mannich reaction of a wide variety of *N*-Boc aryl imines is studied in the presence of thiourea derivative **L3** with high enantioselectivity (Scheme 4). The catalyst **L3** is as highly effective for the asymmetric addition of silyl ketene acetal derivatives to aldimines. From a steric and electronic standpoint, the *N*-Boc imine substrates utilized in this reaction are fundamentally different from the *N*-alkyl derivatives employed in the Strecker reaction.



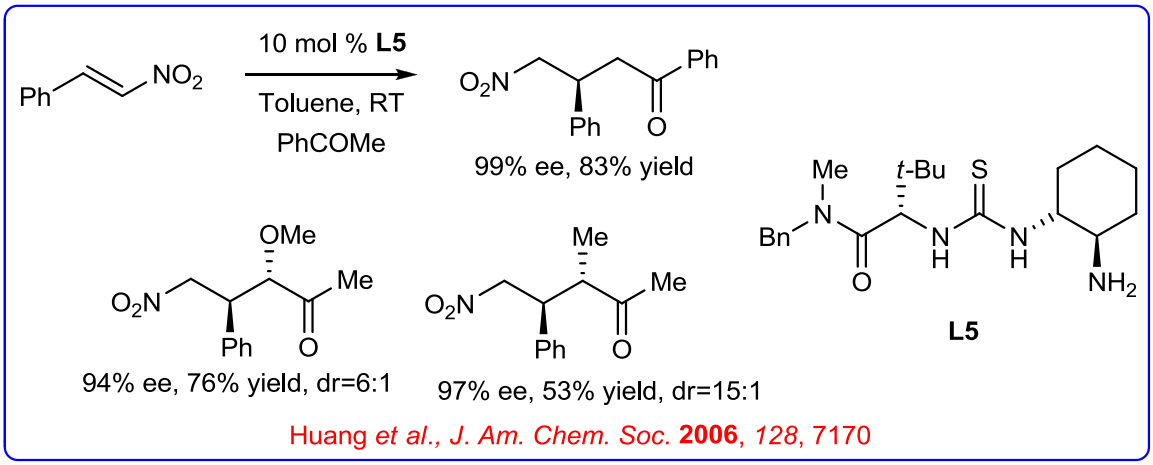
Scheme 4

Bifunctional thiourea derivative **L4** can catalyze the Michael reaction of malonates with various nitro olefins in high enantioselectivity (Scheme 5). The catalyst activates nucleophile by general base catalysis and electrophile by H-bonding to the nitro group. This methodology has been applied for enantioselective additions of substituted keto ester and double Michael additions of α,β-unsaturated ketoesters.



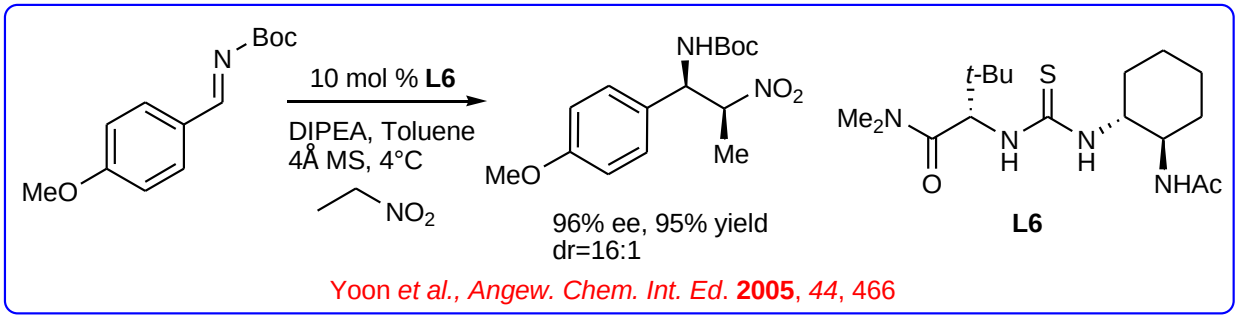
Scheme 5

Chiral primary amine-thiourea **L5** is effective for the direct conjugate addition of ketones to nitroalkenes (Scheme 6). The observed *anti* diastereoselectivity suggests the participation of a (*Z*)-enamine intermediate which is complementary to the diastereoselectivity obtained in analogous reactions involving (*E*)-enamines generated from secondary amine catalysts.



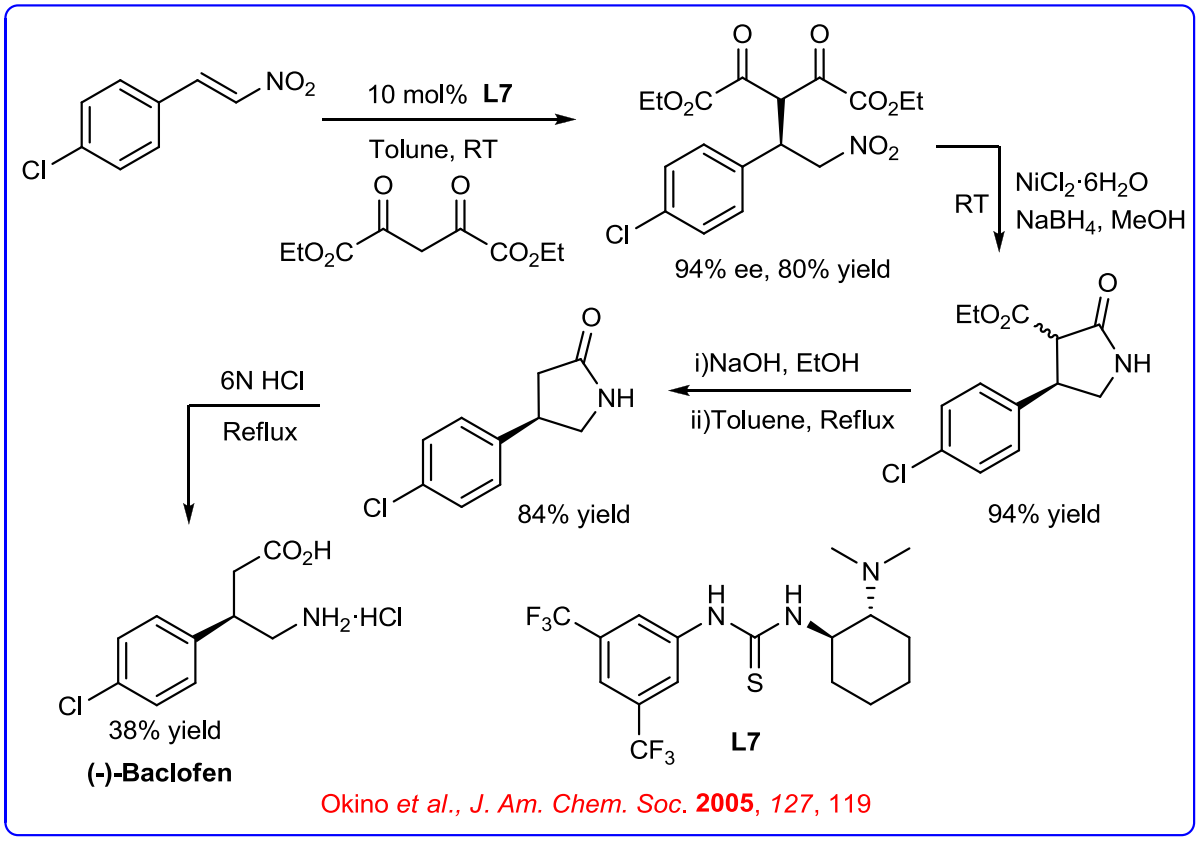
Scheme 6

Likewise, the addition of a range of nitroalkanes to aromatic *N*-Boc imines has been shown using the thiourea derivative **L6** with mostly *anti* diastereoselectivity (Scheme 7).



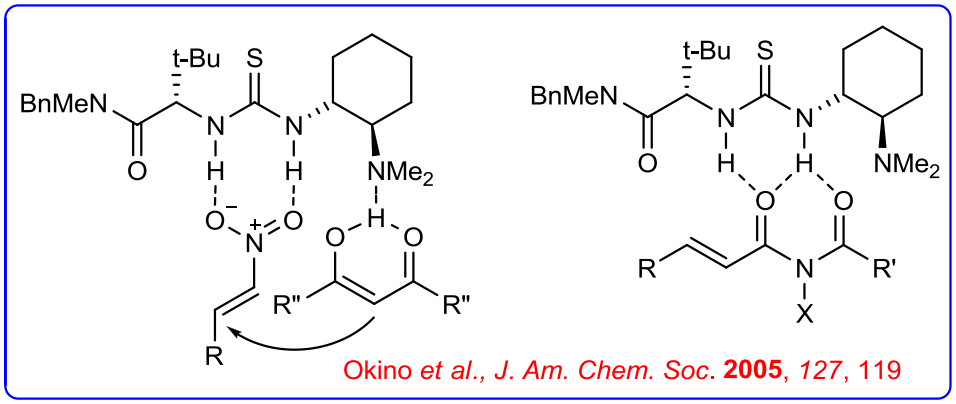
Scheme 7

The thiourea catalyst **L7** bearing 3,5-bis(trifluoromethyl) benzene and dimethylamino groups has been revealed to be efficient for the asymmetric Michael reaction of 1,3-dicarbonyl compounds to nitroolefins (Scheme 8). This methodology has been applied for the total synthesis of (*R*)-(−)-baclofen. Reaction of 4-chloronitrostyrene and 1,3-dicarbonyl compound generates quaternary carbon center with 94% ee. Reduction of the nitro group to amine and subsequent cyclization, esterification and ring opening provides (*R*)-(−)-baclofen in 38% yield.



Scheme 8.Total Synthesis of (*R*)-(−)-Baclofen

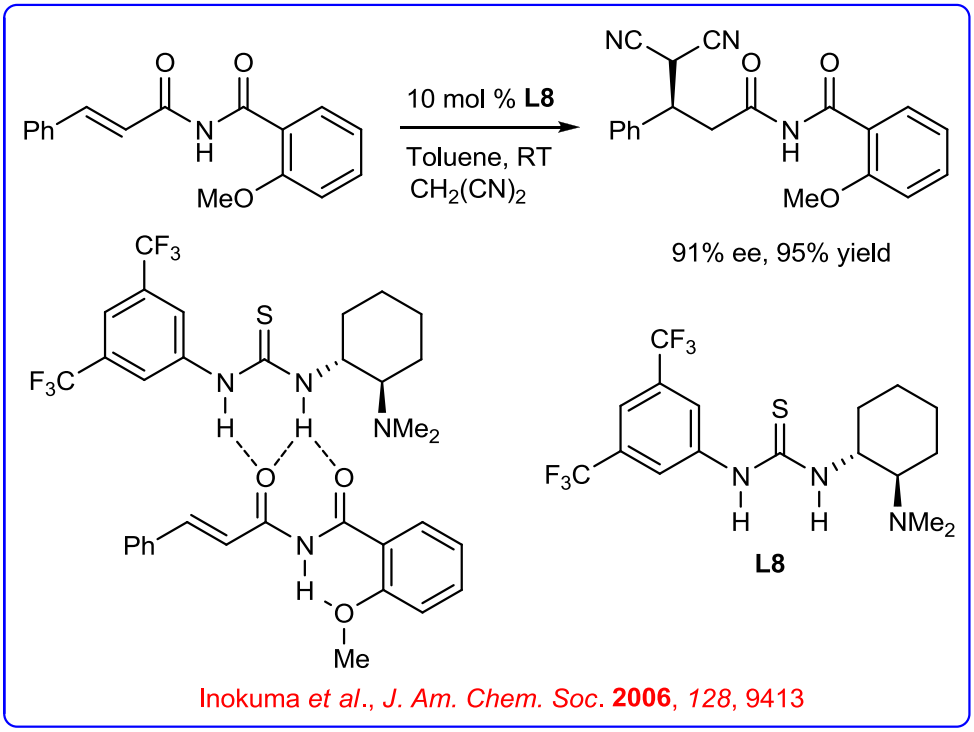
The mechanism of above enantioselective Michael addition of acetyl acetone to a nitroolefin catalyzed by a thiourea-based chiral bifunctional organocatalyst has been investigated using density functional theory calculations and the results suggests that both substrates coordinate preferentially via bidentate hydrogen bonds (H-bond) (Scheme 9). The deprotonation of the enol form of acetylacetone by the amine of the catalyst is found to occur easily, leading to an ion pair characterized by multiple H-bonds involving the thiourea unit as well. Two distinct reaction pathways have been explored toward the formation of the Michael product that differs in the mode of electrophile activation. Both reaction channels are shown to be consistent with the notion of non-covalent organocatalysis in that the transition states leading to the Michael adduct are stabilized by extensive H-bonded networks.



Scheme 9

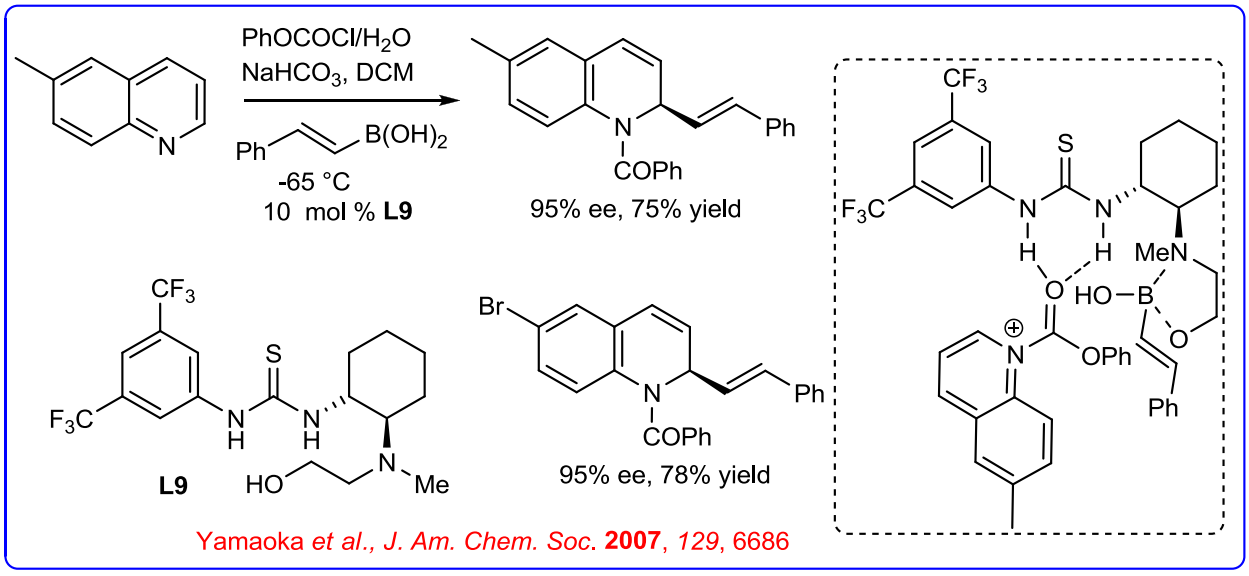
A thiourea-catalyzed asymmetric Michael addition of activated methylene compounds to α,β–

unsaturated imides have been developed (Scheme 10). *N*-Alkenoyl-2-methoxybenzamide is the best substrate among the corresponding benzamide derivatives bearing different substituents on the aromatic ring and react with several activated methylene compounds such as malononitrile, methyl □-cyanoacetate, and nitromethane with up to 93% ee. The reactivity can be attributed to the intramolecular H-bonding interaction between the N-H of the imide and the methoxy group of the benzamide moiety.



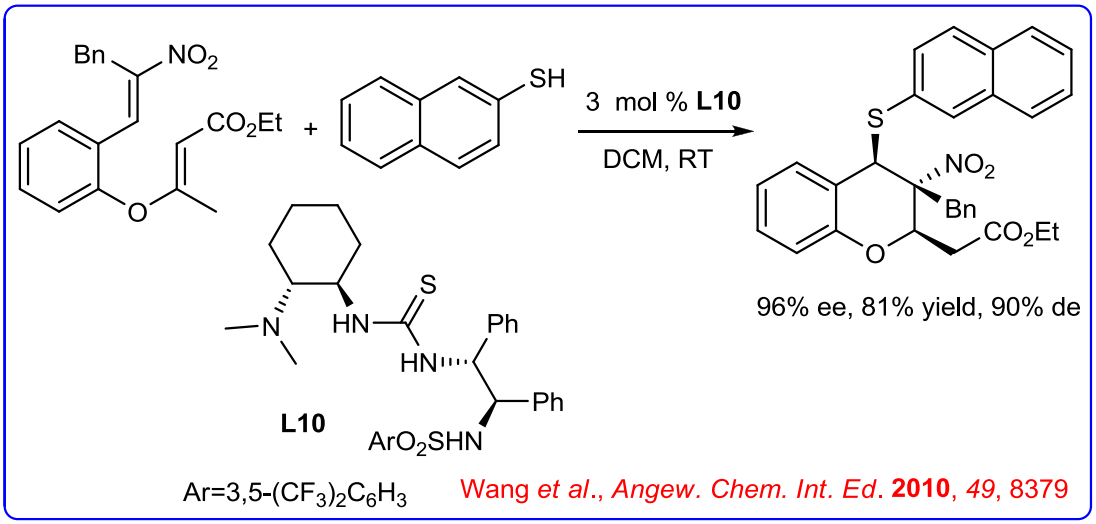
Scheme 10. Dual-activation of *N*-Alkenoyl-2-methoxybenzamide

Thiourea catalyst **L9** has been explored for the activation of quinoline with organoboronic acids to facilitate stereocontrol in the Petasis transformation even at low temperatures (Scheme 11). The quinoline gets activated by formation of N-COBz with PhCOCl and a high degree of stereo control can be achieved using a combination of H_2O and $NaHCO_3$ as additives.



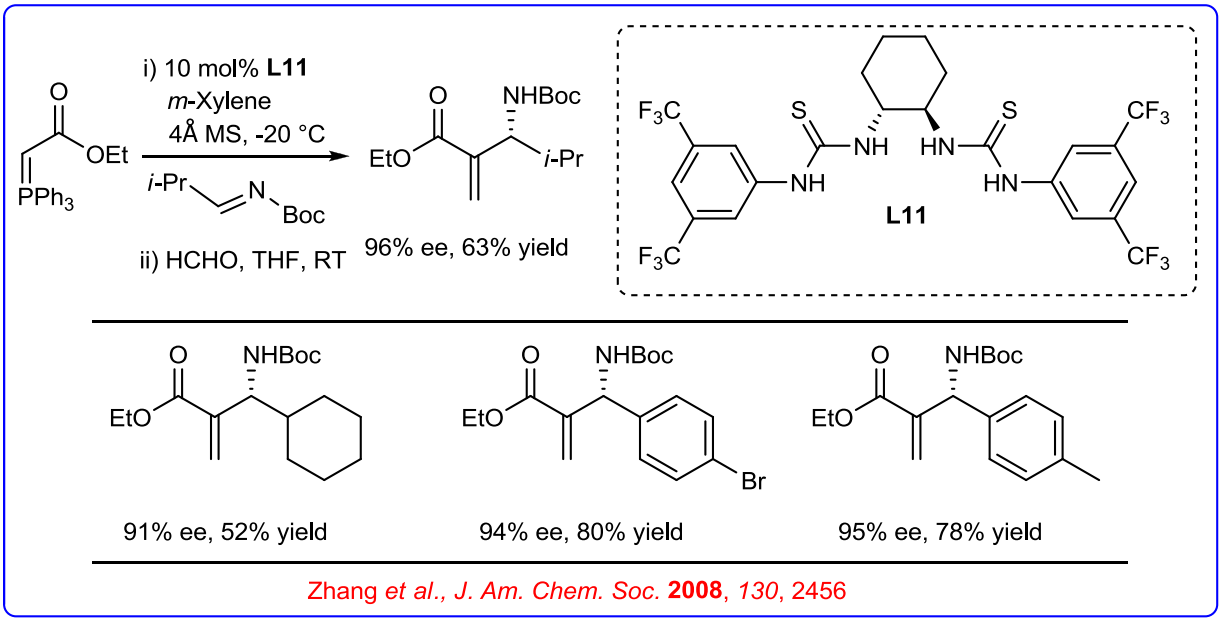
Scheme 11

The domino thia-Michael–Michael reaction of thiols with nitro olefin enoates provides polyfunctionalized chroman derivatives in a highly stereoselective manner in the presence of thiourea **L10**. Three consecutive stereogenic centers including one quaternary stereocenter can be generated with high enantioselectivity (Scheme 12). The catalyst **L10** activates nitroolefin enoates through H-bonding activation, and its tertiary amino moiety activates the nucleophilic thiols, forming an intermediate which undergo the intermolecular thia-Michael addition.



Scheme 12

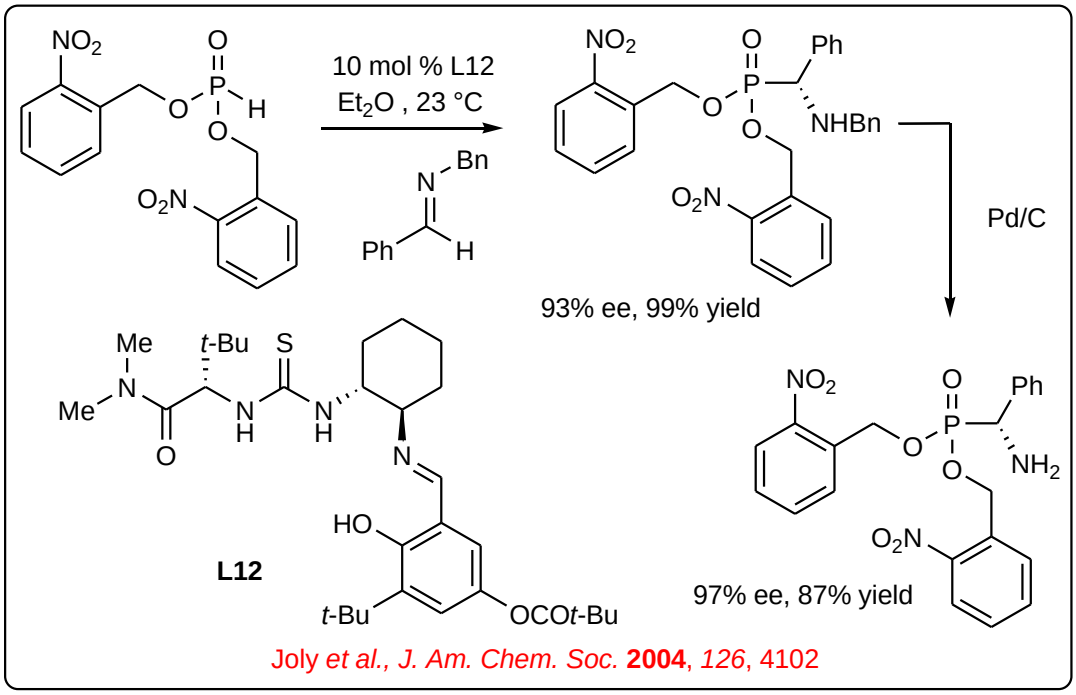
The synthesis of chiral N-Boc-β-Amino-α-methylene carboxylic esters can be performed by reaction of stabilized phosphorus ylides and Boc-protected aldimines in presence of readily available bisthiourea **L11** (Scheme 13). Subsequent reaction with formaldehyde provides a facile access to chiral *N*-Boc–β–amino–α–methylene carboxylic esters. The catalyst has been found to be recyclable.



Scheme 13. Mannich-type Reaction of Phosphorus Ylides

10.3.3 Hydrophosphonylation Reactions

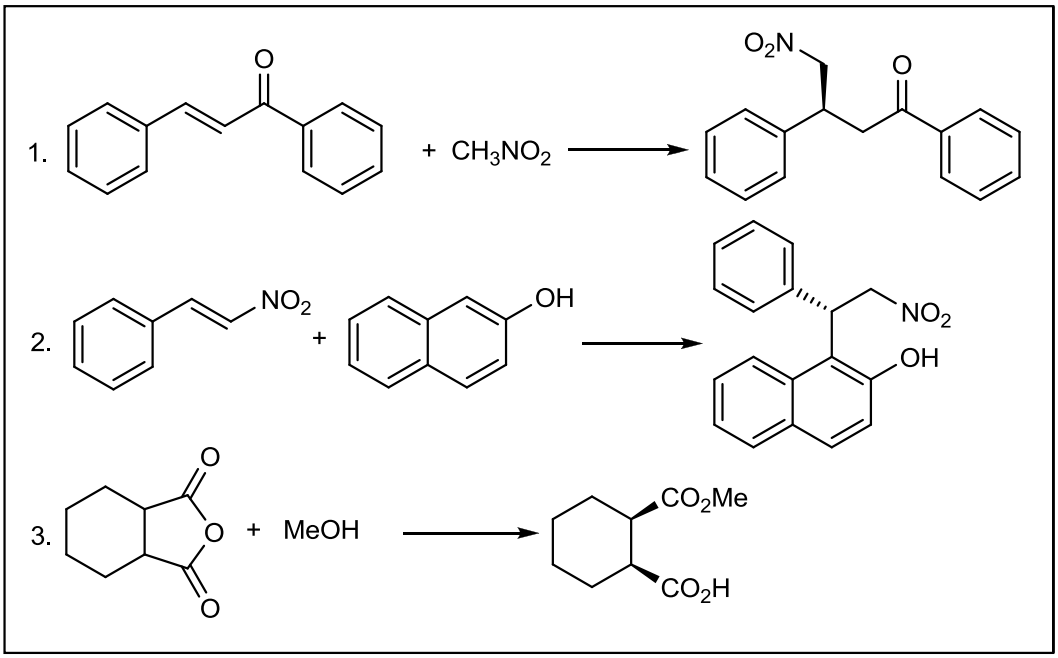
Chiral thiourea catalyst **L12** has been used for highly enantioselective hydrophosphonylation of a wide range of *N*-benzyl imines (Scheme 14). The hydrophosphonylated products can be readily deprotected by hydrogenolysis using Pd/C to provide chiral α-amino phosphonic acids with high enantioselectivity. This methodology provides general and convenient access for the synthesis of optically active α-amino phosphonates.



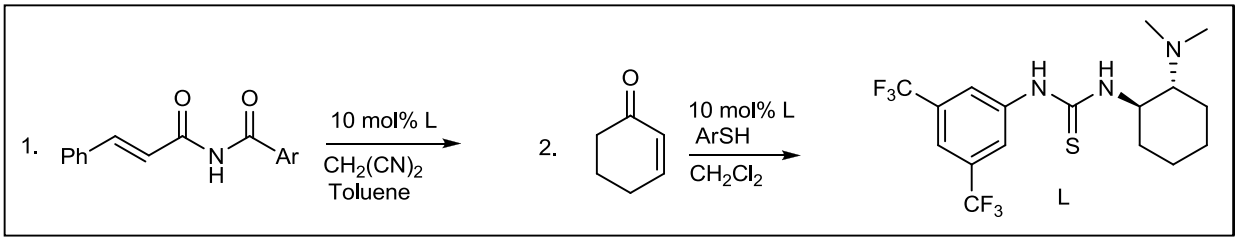
Scheme 14. Thiourea-Catalyzed Enantioselective Hydrophosphonylation of Imines: Practical Access to Enantiomerically Enriched α-Amino Phosphonic Acids

Problems

B. How will you carry out the following using thiourea based organocatalysis?



C. Complete the following reactions.



Reference/Text Book

5. I. Ojima, *Catalytic Asymmetric Synthesis*, 3rd ed., Wiley, New Jersey, 2010.

6. M. B. Smith, *Organic Synthesis*, 2nd edition, McGraw Hill, New Delhi, 2004.