

Bifunctional Thiourea–Amine based Organocatalyst excelling in Multi Component Reactions

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Abstract:

Recently, exclusive feature of small organic molecules i.e., organocatalysts like low cost, environment benign, nonmetallic, solubility, stability in normal conditions, easy availability has made it, a very attractive catalyst to unified diverse fields in synthetic organic chemistry. Organocatalysts specifically based on thiourea-amine based attained a great attention among research propagators. These catalysts are capable of activating an electrophile through hydrogen bond formation and at the same time, activate nucleophile by involving amine group. In spite of great advantage of this catalyst, a very little work has been done with it in multicomponent reactions (MCRs). To explore the applications of these catalysts in MCRs we focused on the utilization of these dual functionality containing moieties in MCRs.

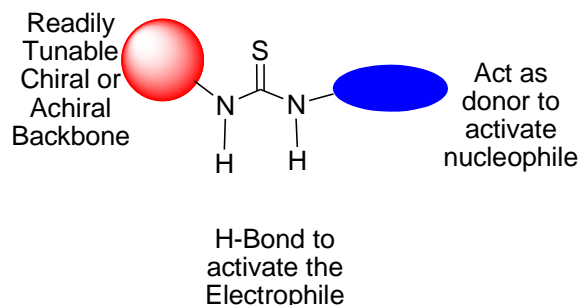
Keywords: *Hydrogen bond, catalyst, nonmetallic, green chemistry, environment*

INTRODUCTION

Organocatalysis,¹ is a promising field of research in chemistry today. Many forms of catalysis have been introduced by organocatalysis in the organic chemistry which showed a remarkable increase in the rate of reaction by using sub-stoichiometric concentration of a substance made up of hydrogen, carbon, oxygen, sulfur, nitrogen and phosphorous without involving any metal in its framework. Reactions catalyzed by organic moieties pay enormous advantages over conventional metal mediated methodologies. Usually these catalysts are not costly and also do not impose toxicity on the environment. This confers a great advantage in the generation of pharmaceutical moieties as compare to metal catalyst². The organocatalysts are less harmful, easy to handle and easily available it labels them an attractive and unconventional one³. Until late 1990s, this vibrant domain was overlooked by researchers. And now it attained a great deal of attention in recent times.

Amongst these, bi-functional organocatalyst attained great focus of researchers and scientists as they have the ability to activate an electrophile by double hydrogen bonding and nucleophilic moiety by amino group.⁴ Organocatalysts having dual functionality have found great role in asymmetric synthesis.⁵ Amine functional groups and thiourea play a vibrant character in triggering nucleophilic moieties and electrophile all together in a spatial configuration.⁶ These catalysts produces an asymmetric center in some cyclization processes through intramolecular Michael addition.⁷ Here, the catalyst supports in the greatest distinct conformation and in the transition state of reactant.⁸ Current investigations show that an enantioselective reaction generally takes place as dynamic kinetic resolution,

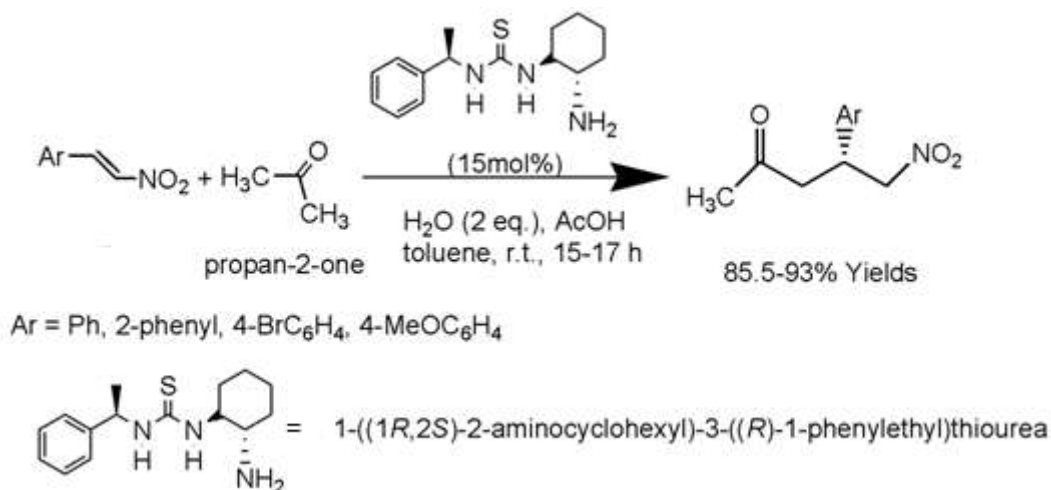
desymmetrization and chirality which encourage us to expand the benefits of this catalyst.⁹ The dual nature and versatility of the organocatalysts are also used for construction of enantioselective axial chiral molecules.¹⁰ So looking at these tremendous applications of organocatalysis¹¹ we summed up a write up from of past ten years approach of bifunctional organocatalyst.¹²



As it can be seen in the image given above, the role of thiourea moiety is to activate the electrophile by forming the H- bond, where as basic functionality present in this molecule activate the nucleophile.¹³ By using thiourea amine based organocatalysts, both the types of stereoselective i.e., diastereoselectives as well as enantioselective compounds can be obtained with good yield.¹⁴ Along with these, many aromatic ketones were also exposed to bifunctional organocatalysts produces stereogenic centers in good yields.¹⁵ This catalyst is also useful in the stereocontrolled creation.¹⁶ When co-catalysts is used as additive along with these organocatalysts, improved the reactivity and enntioselectivity.¹⁷ However, when trans- compounds like isobutylaldehyde, trans-nitro styrene or acetone are involved, hydrogen bonding interaction takes place in between the substrate and bifunctional organocatalysts. Further, various types of urea, thiourea, amides have been tested as donor for hydrogen bonding. Although only with Amine thiourea catalyst, good yields and enantioselectivity achieved.¹⁸ N-H bonds is acidic in thiourea but that is not related to the catalytic activity rather substrate of reaction and condition determine the catalytic behavior.

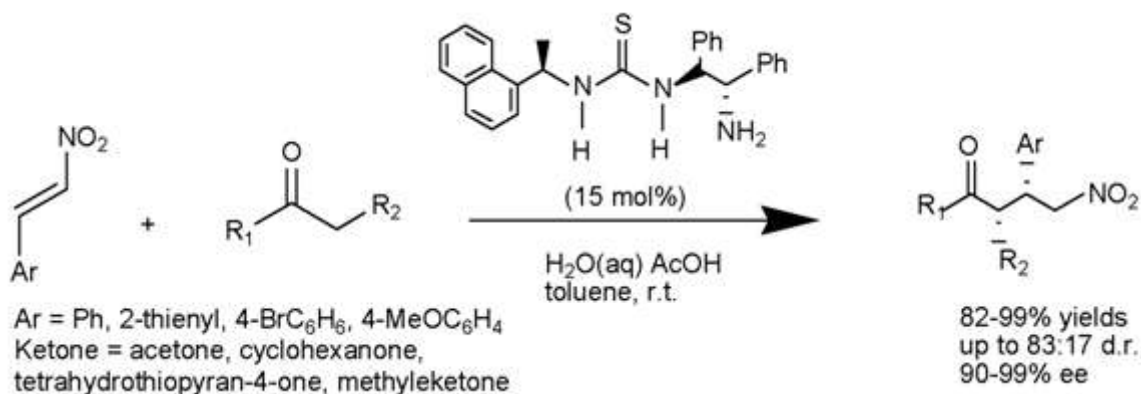
Literature Review:

In 2006 Tsogoeva *et al* briefed the dual functionality of organocatalyst containing thiourea and amine group as a competent catalyst to the various diverse aromatic nitro olefins with propane-2-one for the generation of chiral scaffolds as γ -nitro ketones in good yield along with high enantioselectivities (Scheme 1).¹⁹



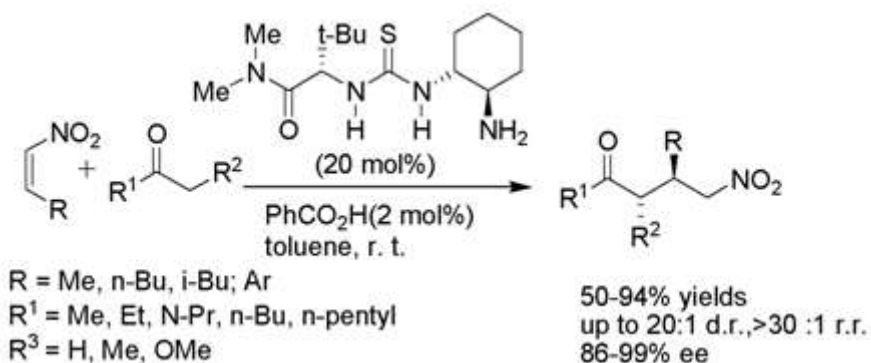
(Scheme 1)

In 2006 Wei, S et al. reacted different aromatic nitroolefins with the bifunctional thiourea amine organocatalyst to catalyze the ketones through addition reaction (Michael addition). The product was attained in high yield along with high selectivity (Scheme 2).²⁰

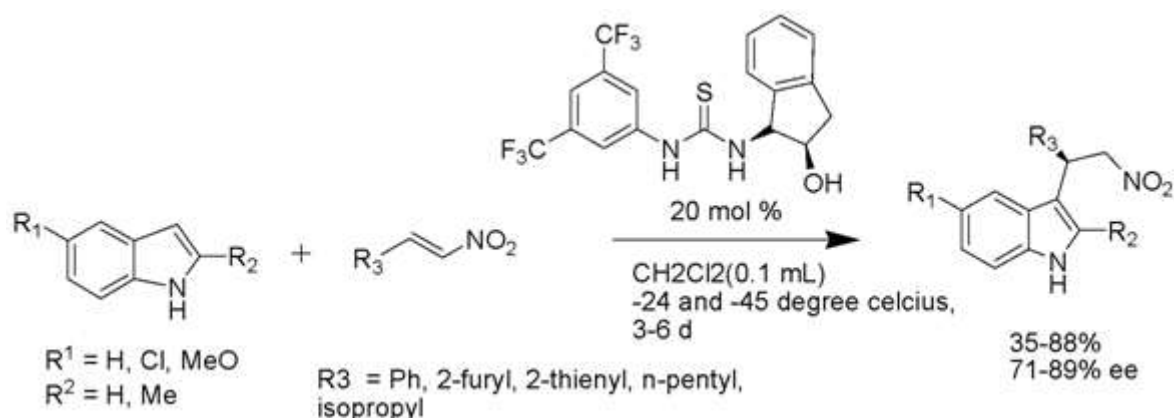


(Scheme 2)

Jacobsen and co worker in 2006 described an addition of olefins and ketones using thiourea amine organocatalyst. In this reaction, addition of R¹ = Ethyl, n-Butyl, n-pentyl; and R² = Methyl, n-alkyl ethyl ketones to nitrostyrene got 30:1 regioselectivity, have enantiomeric excess up to 99% as well as supporting the anti isomer also (20:1). While the reaction of nitrostyrene occurred in less normal with n-alkyl ethyl ketone, provides product along with regioselectivity (Scheme 3).²¹



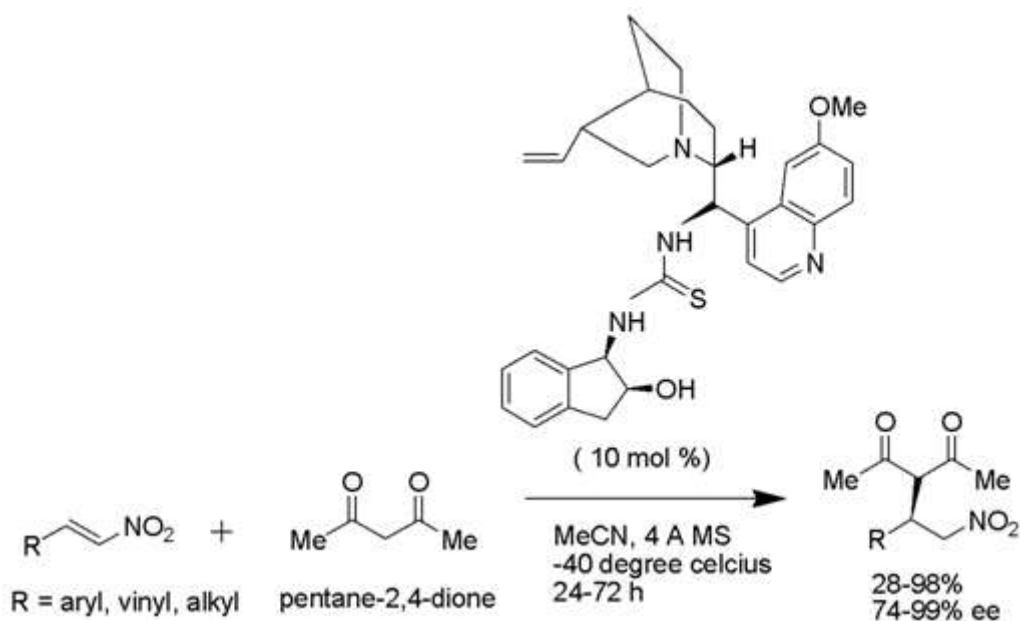
(Scheme 3)



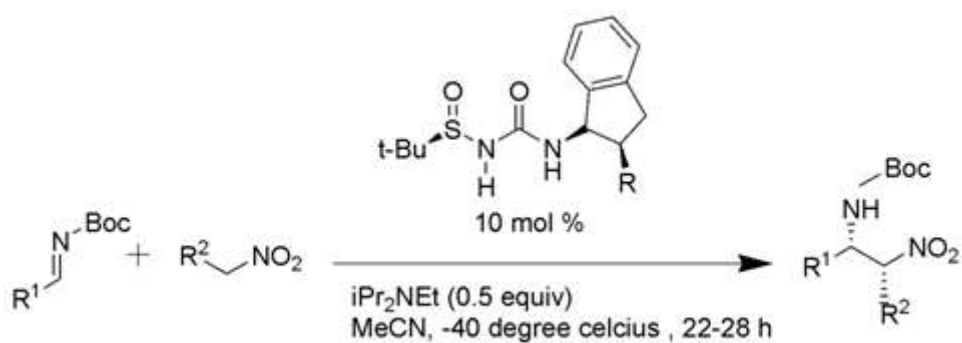
(Scheme 4)

In 2014, Herrera and co-workers (Scheme 4) worked on the non symmetric Friedel craft alkylation of nitroalkene and indole is described by using aminoindanole derived thiourea organocatalyst. It is hydroxyl group which preferentially attacked on indole rather than nitro alkene determining the selectivity in reaction²².

Later in 2011, He's group described about the application of some multiple hydrogen bond which provide amine in the non symmetric additive form of acetylacetone grounded on an organocatalysts to the β -nitroalkenes. Thiourea worked as catalyst very effectively and also brought chirality in the reaction. Under optimized conditions this technique gave the γ -nitrocarbonyl compound with highly yield and highly enantioslctivity (Scheme 5).²³

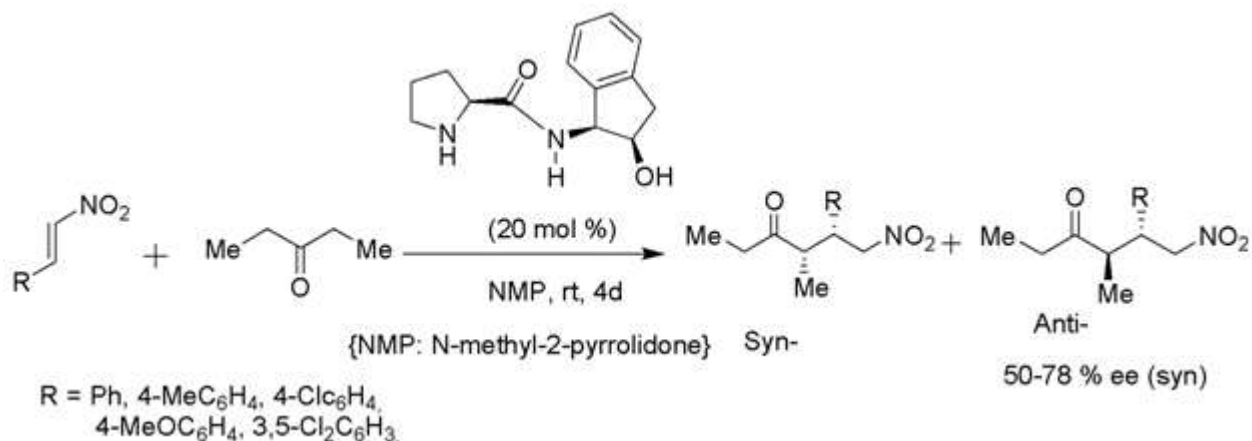


(Scheme 5)



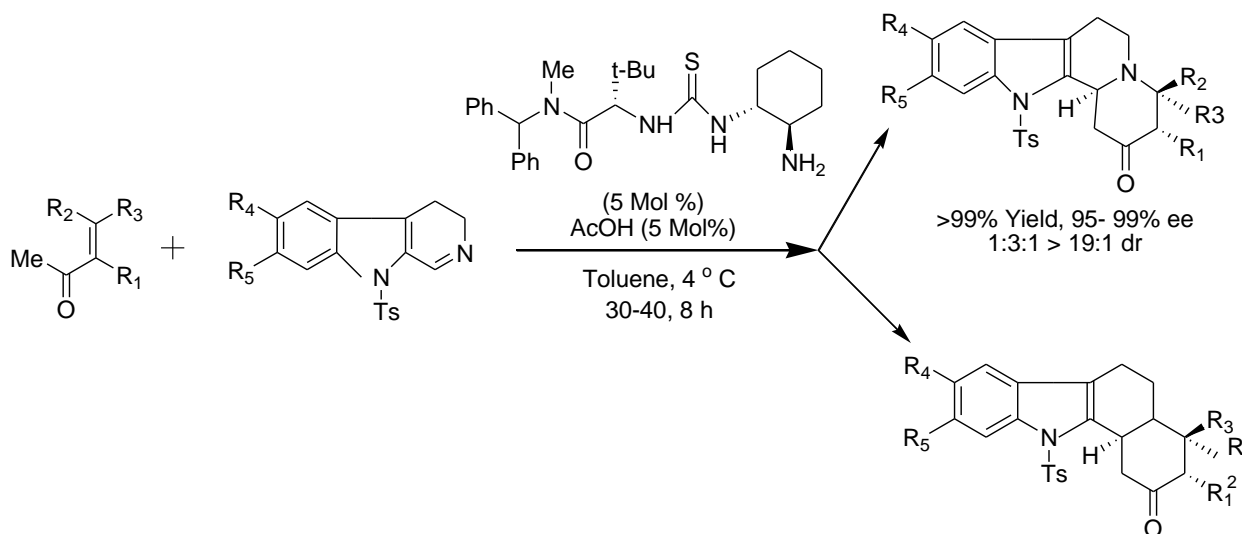
(Scheme 6)

The above process (Scheme 6)²⁴ given is Aza-Henry reaction. Here, Ellman *et al* presented a group of advanced organocatalyst having thiourea framework containing *N*-sulfinyl moiety with hydrogen bonding. Here catalyst is acidic and also function as chiral organizer. So due to the catalyst, excess of nitroalkanes react with the *N*-Boc-protected imines and produced a product with good yield and enantioselectivity.



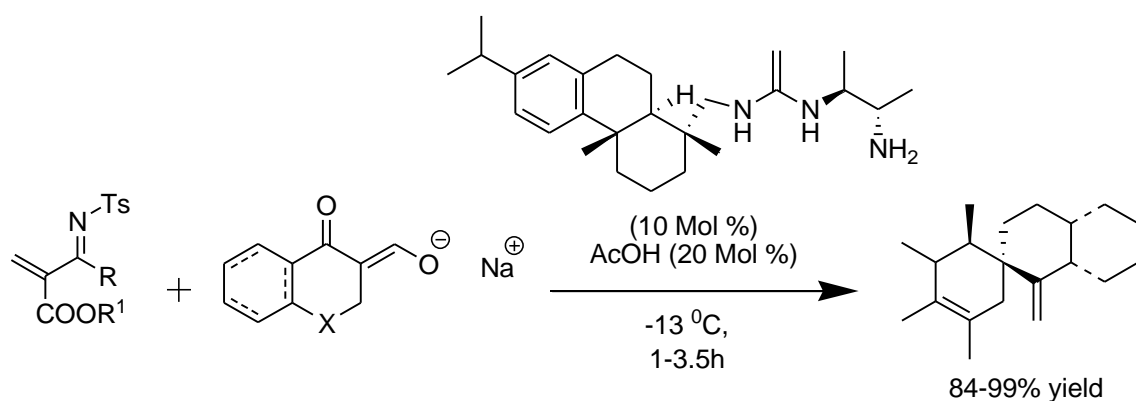
(Scheme 7)

Asymmetric Michael addition reaction (Scheme 7)²⁵ of 3-pentanone and nitroalkenes during the amino catalysis is shown above. The catalyst used here is Aminoindanol derived thiourea amine based organocatalyst. Some examples of this catalyst are available in the literature, here, nitroalkene compounds gave enantioselective ketones which are supplemented to this moiety. Najera, in 2006, presented organocatalysts which involve different alcoholic amino prolin-amide and introduced a non symmetric reaction of Michael addition via organocatalysis involving the reaction of nitrostyrenes and 3-pentanone. It gave syn-adduct along with anti-products in good quantity along with higher selectivity.



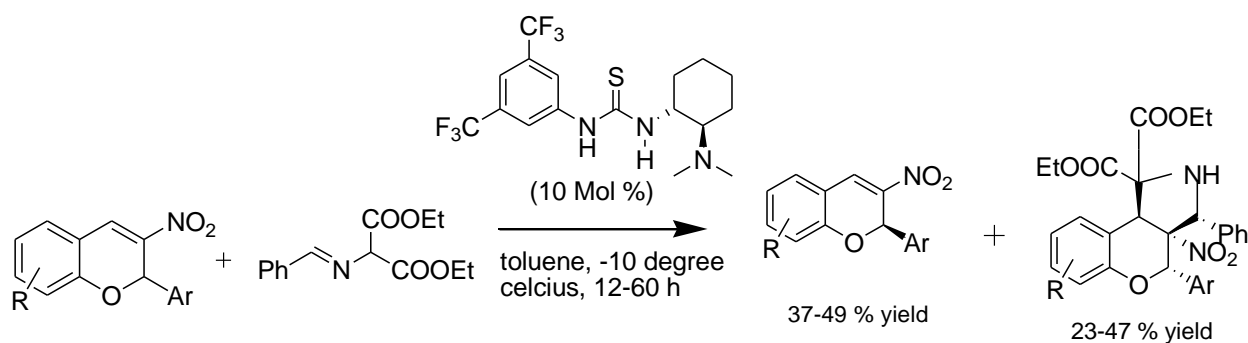
(Scheme 8)

Above reaction (Scheme 8)²⁶ involved the combination of toluene and AcOH (5mol %) along with thiourea amine based organocatalyst at 4 °C and provided the products as diastereoselective and enantioselective products in good yield (50- 99%). Jacobson *et al* in 2013 presented this diastereoselective and enantioselective route for the creation of chiral benzoquinolizidine and indole by the reaction amid the cyclic imines and enones promoted by thiourea–amine catalyst.



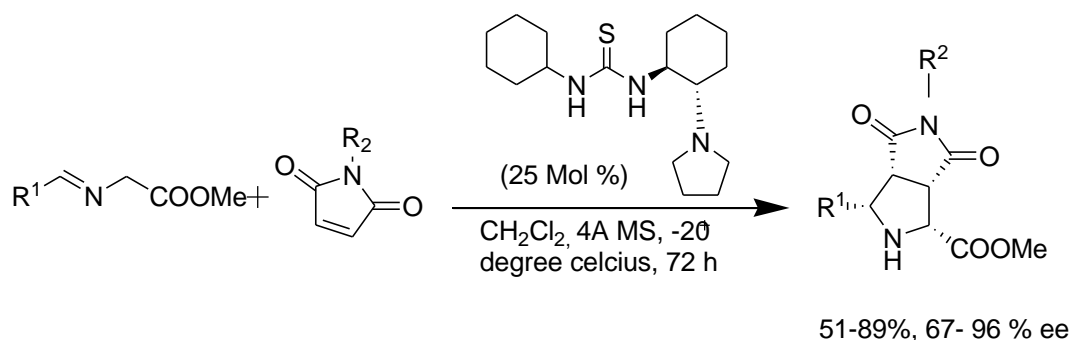
(Scheme 9)

In 2012, Wang's groups announced an important organocatalysed (thiourea-amine along with Bronsted acid additive as acetic acid) Diels-Alder reaction generates aza-spirocyclic compounds by cycloaddition of [4+2] reaction at -13°C gave a higher yield of 84% to 99% which was highly enantioselective (Scheme 9).²⁷



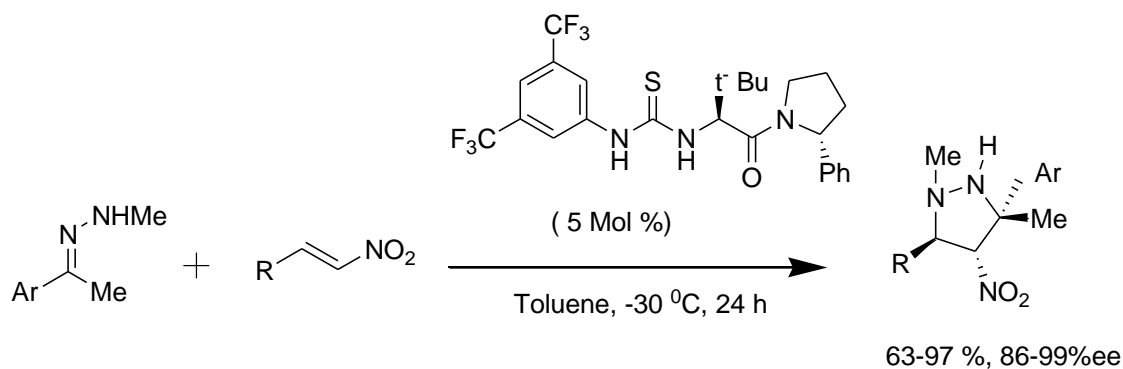
(Scheme 10)

A [3+2] cycloaddition reaction is described by Xie's *et al* where he identified a resolution of derivatives of racemic 3-nitro-2H-chromene using cyclization along with α -amino malonate imine via Takemoto's chiral bifunctional organocatalyst. The process goes with four vicinal carbons with multi functional derivatives (Scheme 10).²⁸



(Scheme 11)

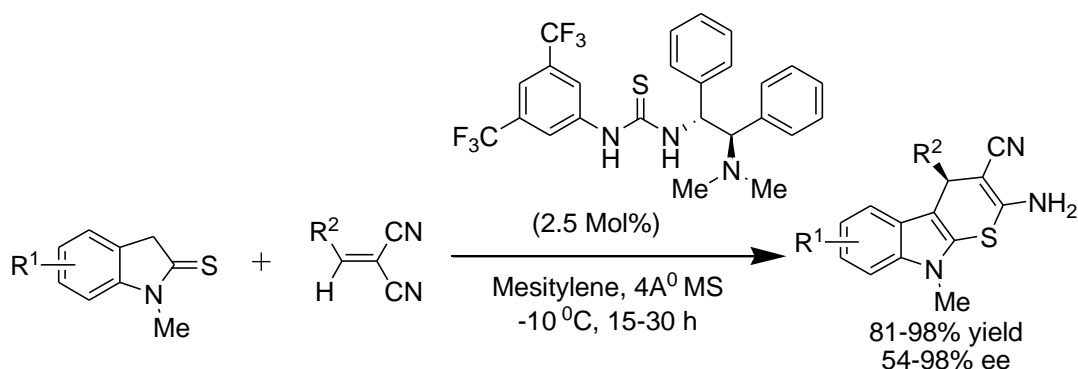
Wang *et al* illustrated a 1,3-dipolar reaction and produced optically active functionalized pyrrolidines in very good yield along with enantioselectivities. Enantioselective products having aromatic substituents are obtained via this cycloaddition reaction in very good yields (Scheme 11).²⁹



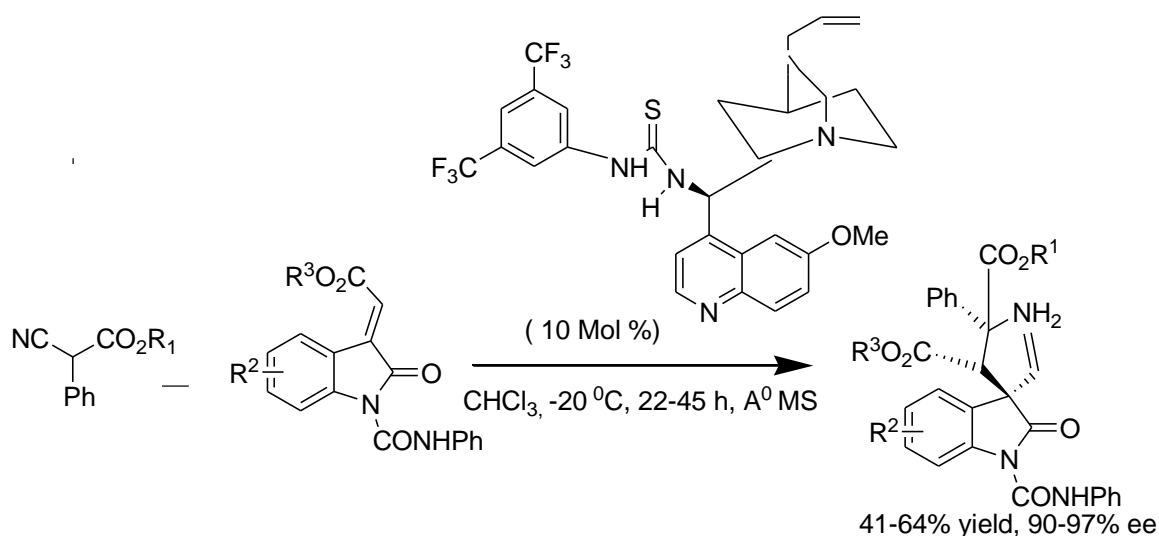
(Scheme 12)

In 2014, Jorgensen *et al* discussed (Scheme 12)³⁰ the diastereoselective and enantioselective production of 4-nitropyrrolidines. Thiourea-amine organocatalyzed cycloaddition reaction in the presence of toluene at -30 °C yielded the expected products in good to moderate yield (63-97%) with high enantioselectivities (86-99%).

In 2014, Wang *et al* announced an organocatalytic asymmetric route towards thiopyranoindole annulated heterocycles as enantioselective product in high yield (81-98%) via [3+3] cycloaddition reaction in the presence of thiourea-amine organocatalyst, at -10 °C (Scheme 13).³¹

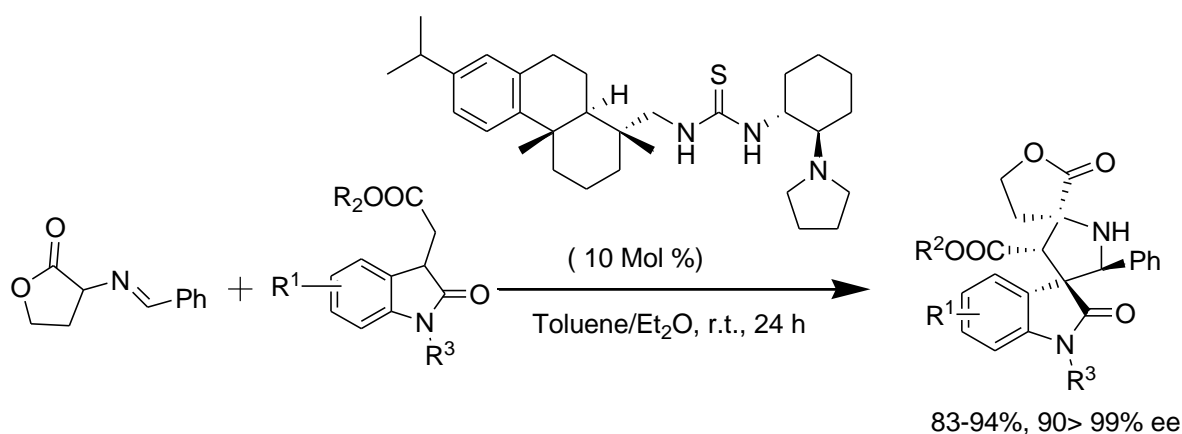


(Scheme 13)



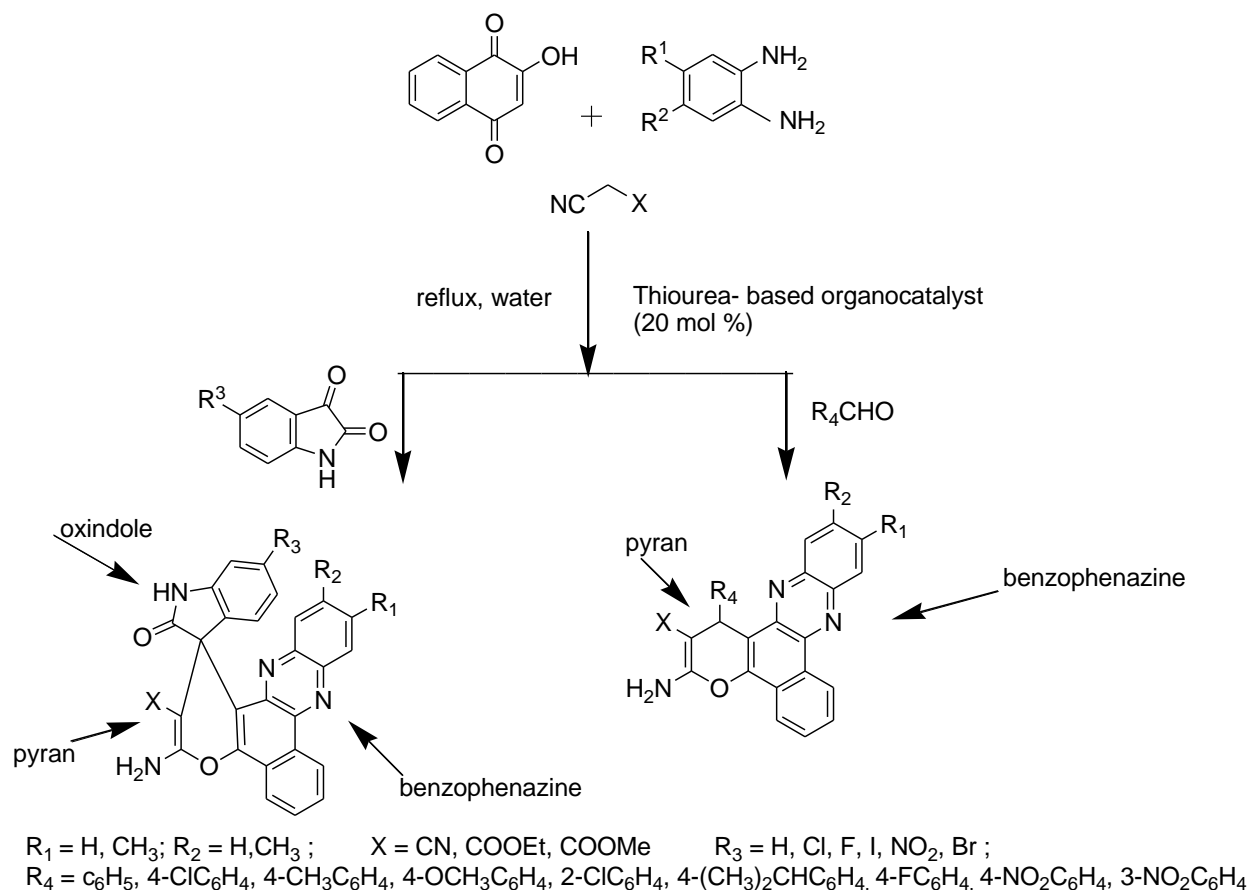
(Scheme 14)

Another stereoselective [3+2] cycloaddition reaction was explained by Wang, xu *et al* in 2012. They did the reaction of isocyanooesters and methylene indolinones with thiourea amine catalyst in chloroform under -20 °C to give 3,3- pyrrolidinyl spirooxindoles in good yield and high enantioselectivities (Scheme 14).³²



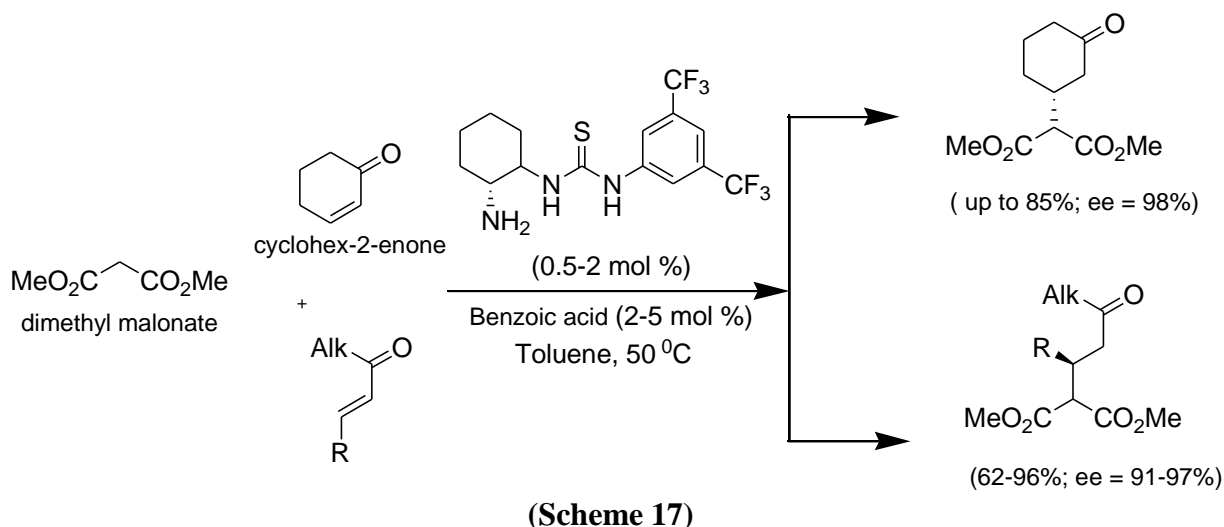
(Scheme 15)

In 2013, Wang *et al* developed an enantioselective pathway via 1,3-Dipolar addition reaction. The reaction took place by addition of imino esters to Methylene indolinones having four stereocenters. Two centres among these four were spiro quaternary stereocenters. The reaction gave better results in addition of thiourea amine based organocatalyst and C₆H₅CH₃ (Scheme 15).³³



(Scheme 16)

Further, a Thiourea-amine organocatalyzed MCRs were reported by Bharti *et al* which involved the production of pyrano-fused phenazine. Initially they synthesized a series of new organocatalysts and further implemented them in the production of biologically important heterocycles as pyrano-fused benzophenazines by the combination of *o*-phenylenediamines, malononitriles, 2-hydroxy-1,4-naphthoquinone and diverse aldehydes or isatins under reflux condition (Scheme 16).³⁴



Later, A highly enantioselective Michael cycloaddition reaction was described where malonates were converted to enones with 1,2-diaminocyclohexanane promoted by thiourea-amine organocatalysts. This protocol was performed in the presence of weak acid as solvent at 50 °C in good yields (Scheme 17)³⁵.

Conclusion:

Organocatalysts have a huge opportunity in the synthetic organic chemistry. The way it activates the substrate makes it a very indistinct one providing great yield and high enantioselectivity. At many places the activity and behavior of this remarkable catalyst is supported by computational calculations and experiments. By involving this bifunctional organocatalysts variety of products have been successfully synthesized.

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