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Organocatalysts: A powerful tool for asymmetric Michael addition

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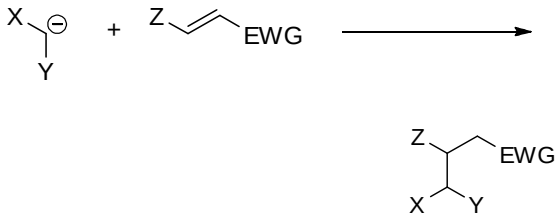
Abstract

In recent years, asymmetric organocatalysis has emerged as powerful tools for the synthesis of a variety of chiral molecules. Ready availability of the catalysts, low toxicity, simple operational procedures and mild reaction conditions associated with organocatalysis makes it an attractive method to synthesise diverse complex structures. Here, a short review on the development and applications of chiral organocatalysts for asymmetric Michael addition reactions has been described.

Key words: Asymmetric reaction; organocatalysis; Michael addition.

Introduction

Michael reaction or Michael addition or conjugate addition is one of the most important methods for the mild formation of C-C bonds.[1] It may be defined as the nucleophilic addition of stabilized anions (e.g. carbanion, enolates, etc.) to an *α, β*-unsaturated carbonyl and related compounds.[2] It was named after an American chemist Arthur Michael (1853-1942) who reported the reaction that bears his name in 1887.[2,3]



X, Y, Z = R or EWG
EWG = COR, CO_2R. CN, NO_2, etc

Scheme 1. Michael addition.

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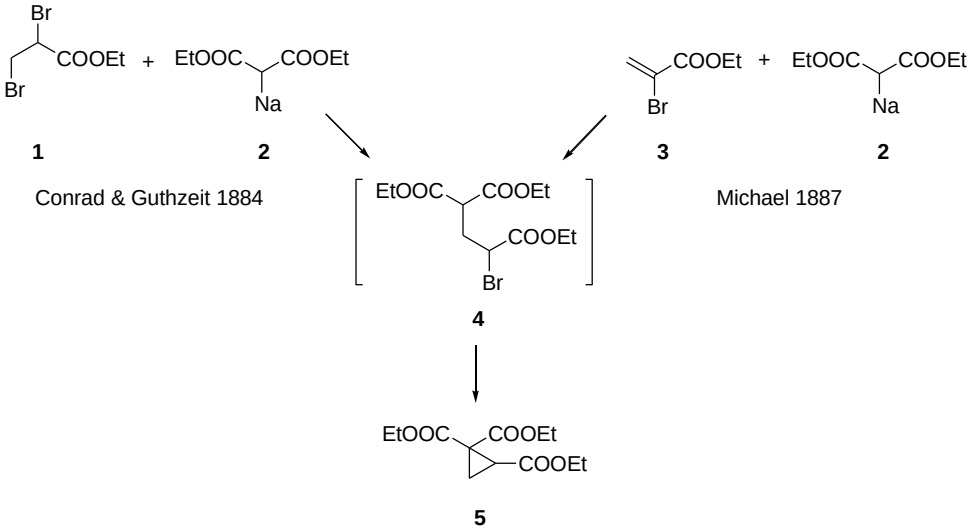
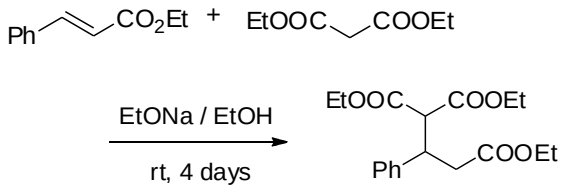
The work done by Arthur Michael in 1887, on the formation of a cyclopropane derivative by the reaction of diethyl 2,3-dibrompropionate with diethyl sodiomalonate (Scheme 2), was motivated by the work of Conrad and Guthzeit.[4]



Scheme 2. Experiments done by Conrad & Guthzeit in 1884 and Michael in 1887.

When Michael treated 2-bromacrylic acid ester with sodiomalonic acid ester, he obtained the same product reported by Conrad & Guthzeit[4] and realized that this reaction could only work by assuming an addition reaction to the double bond of the acrylic acid.[2b,3] He then confirmed this postulation by reacting diethyl malonate and ethyl ester of cinnamic acid obtaining the very first Michael adduct (Scheme 3).[2] Soon after its publication, Claisen[5] claimed priority of the discovery of the reaction. Claisen and Komnenos[6] both observed addition products to double bonds as side-products earlier in 1883 while investigating condensation reactions of malonic acid with aldehydes. However, after the Claisen-Komenos report, condensation-addition products like theirs were also shown to formed in the reaction of formaldehyde with diethyl malonate by Perkin Jr.[7] and in the reaction of benzaldehyde with ethyl acetoacetate by Hantzsch.[8] Hence, according to biographer Tokoroyama,[3] their claim was without merit.

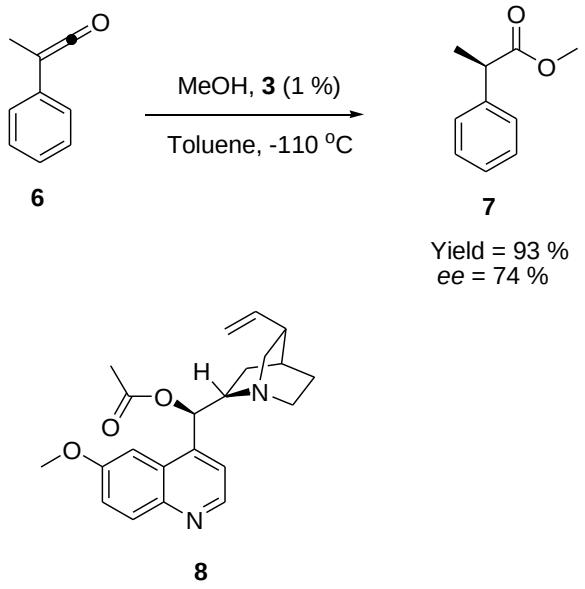


Scheme 3. First example of Michael addition reaction in 1887.

The Michael addition benefits from mild reaction conditions, high functional group tolerance, a large host of polymerizable monomers and functional precursors as well as high conversions and favourable reaction rates.[9a] These features make the Michael addition reaction an important organic transformation and the resultant compounds have been used in the synthesis of several natural products, and drug molecules, numerous emerging technologies including biomedical applications such as gene transfection, cell scaffolds, and tissue replacements.[10a,10b,10c,9b,11,12]

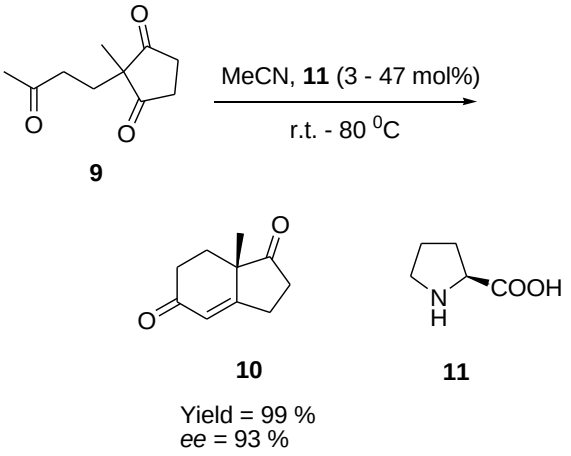
ORGANOCATALYSIS

The term "organocatalysis" was given by Ahrendt *et al.*[13] to sum up a group of organic compounds used as catalysts to promote various asymmetric transformations. It is a branch of catalysis in which a reaction is mediated solely by small organic molecules in sub-stoichiometric quantities.[14] Before 1960, there were few examples of asymmetric organocatalysis but all of them gave low enantiomeric excess (less than 20 %) and hence, have no synthetic values.[15] But in 1960, Pracejus *et. al.*[16a,b] reported that the use of cinchona alkaloid derivative (**8**) catalysed the addition of methanol to phenylmethylketene (**6**), giving (-)-α-phenyl methylpropionate (**7**) with 74 % enantiomeric excess (*ee*).



Scheme 4. Cinchona alkaloid catalysed asymmetric addition of methanol.

Subsequently in 1970s, Hajos *et. al.*[17] also reported for the first time, the use of amino acid L-Proline **11** as a catalyst for highly enantioselective Robinson annulations reaction giving up to 93% *ee*.



Scheme 5. L-Proline catalysed asymmetric Robinson annulations.

Despite these wonderful results, there was not much improvement in the field of organocatalysis for almost thirty years. But, since the year 2000, there was an explosive growth in this field and the use of chiral primary and secondary amines, chiral aziridinium and oxaziridinium salts, cinchona alkaloids, etc. as a catalysts became a powerful tool in asymmetric synthesis.[14d] Recently, asymmetric catalysis has been classified into three fields in which organocatalysis has been placed in between metal catalysis and enzymatic transformation.[18]

ASYMMETRIC MICHAEL ADDITION USING ORGANOCATALYSTS

Asymmetric organocatalytic Michael addition has attracted a great deal of interest in recent years due to its environmental friendliness and the generation of multiple stereogenic centres in a single step. Since the pioneering works of List[19] and Barbas,[20] organocatalytic asymmetric Michael additions have been thoroughly investigated,[21] and in doing so, some well-designed thiourea organocatalysts, such as primary and tertiary amine-thiourea based cata-

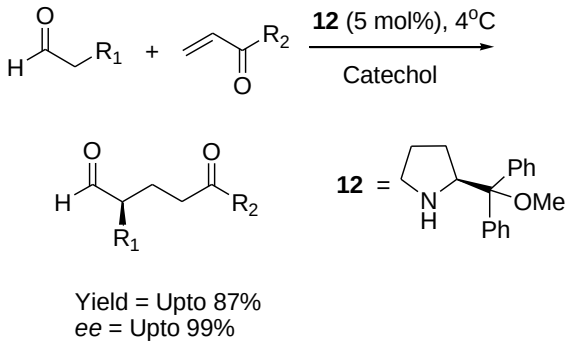
Table 1. Comparison between three classes of asymmetric catalysis.

Metal based catalysts	Organocatalysts	Enzymes
Transition metal as the active centre.	A particular carbon heteroatom skeleton that gives individual characteristics to the active site.	Combination of hundreds of amino acids; however, only some of them are active in the catalytic sites.
Expensive and moisture /oxygen sensitive and give some problem in the purification process, as only small amounts of metals contaminants is tolerated for pharmaceuticals products.	Not harmful in small amounts and often allow mild reaction conditions and simple working procedures.	No toxicity at all.
The catalysts loadings are often very low (up to 1000000/1 in Substrate /Catalyst).	The catalysts loadings are typically under 100/1 in Substrate/Catalyst.	The catalysts loadings are low.
Both the enantiomer can be obtained.	Both the enantiomer can be obtained.	Synthesis of both the enantiomers is difficult.

lysts, proline and its derivatives, and many other amine based organocatalysts have been successfully developed for this reaction.[19-22a] Other classes of catalysts most frequently used in asymmetric Michael additions are cinchona alkaloids and their derivatives.[23] In this review, different types of Michael addition reaction using different organocatalysts will be highlighted.

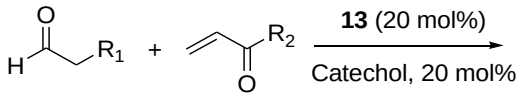
MICHAEL ADDITION OF C-NUCLEOPHILES

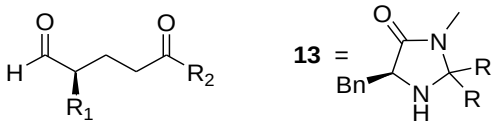
Most of the organocatalysts catalysed Michael addition of *C*-nucleophiles proceeds *via* enamine or iminium ion intermediate. Many successes have been realised by applying organocatalysts such as proline derivatives to highly reactive Michael donors or acceptors, but Michael additions of simple aldehydes to simple enones have received little attention.[24] In 2005, Chi and Gelmann[25] reported that diphenylprolinol methyl ether (**12**) could catalysed intermolecular Michael addition of simple aldehydes to relatively non-activated enones with enantioselectivities up to 99% with catalyst loading of 1-5 mol% (Scheme 6). Although some of the reactions proceeded smoothly with only the chiral pyrrolidine as a catalyst, others required the use of catechol as a co-catalyst, which was believed to electrophilically activate the enone *via* hydrogen-bond donation to the carbonyl oxygen.



Scheme 6. Diphenylprolinol methyl ether-catalysed Michael additions of aldehydes to simple enones.

In the same year, Peelan *et al.*[26] also reported MacMillan imidazolidinone catalyst (**13**) catalysed intermolecular aldehyde-enone Michael addition reaction using catechol as an additive (Scheme 7).





Scheme 7. Imidazolidinone-catalysed Michael additions of aldehydes to simple enones.

Michael additions of highly activated nucleophiles such as malonates[27] or nitroalkanes[28] to simple enones were also reported. Unactivated ketones or aldehydes have also been used with highly activated Michael acceptors such as nitroalkenes.[29] Many other organocatalysts were synthesised and utilized for Michael addition of: nitroalkanes to enones, *α, α*-dicyano olefins to *α, β*-unsaturated aldehydes, sulfonium ylides to *α, β* -unsaturated aldehydes, nitroalkanes to unsaturated ketones and heteroatomic compound to *α, β*-unsaturated aldehydes.[30-34].

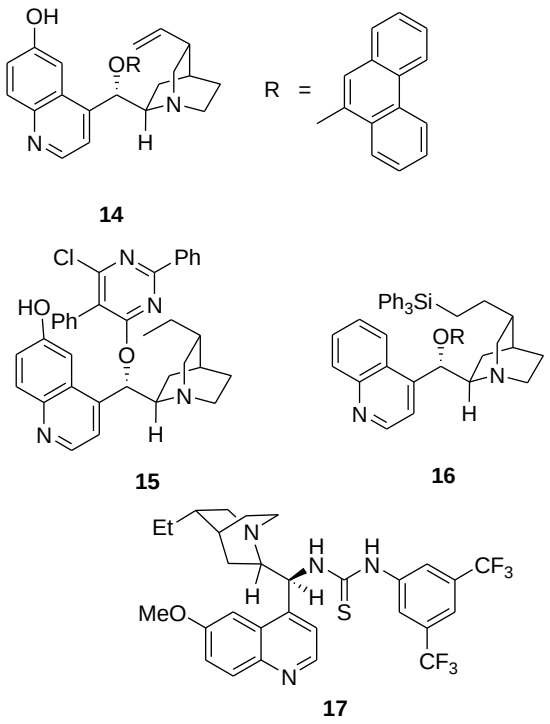


Figure 1. Some cinchona alkaloids derivatives used for Michael addition.

Another important class of organocatalysts for intermolecular Michael addition of *C*-nucleophiles is cinchona alkaloids and its derivatives. Some important reactions includes enantioselective addition of *α*-substituted *β*-keto or *α*-cyano esters to *α, β*-unsaturated aldehydes,[35] *α*-substituted *β*-keto esters to a wide range of vinyl ketones,[36] cyanoacetates to acrolein,[37] *β*-keto esters to acrolein and methyl vinyl ketone,[38] and nitromethane to chalcones[39]. Some of the catalysts used for this transformation are shown in Figure 1.

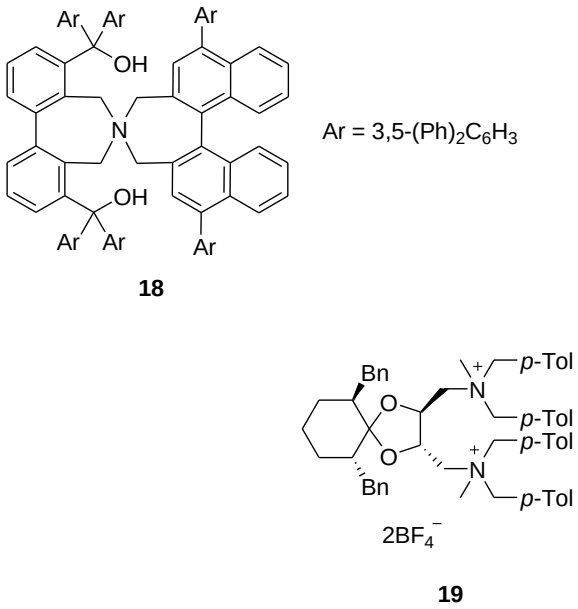
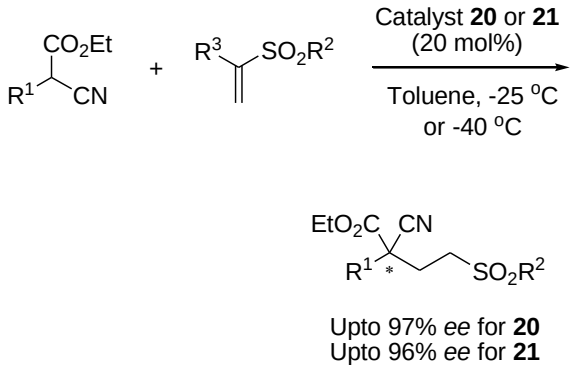


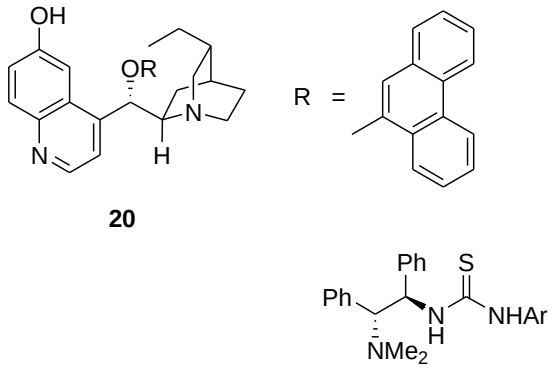
Figure 2. C_2-symmetric phase-transfer catalyst (**18**) and TaDiAS (**19**)

Phase transfer catalysts were also utilized for asymmetric Michael addition and the reactions are usually carried out in two- or three phase system.[24,40a,b,c] *N*-spiro C_2-symmetric chiral quaternary ammonium bromide (**18**) synthesised by Maruoka and co-wokers, and a tartrate-derived diammonium salt (TaDiAS, **19**) have been shown to be efficient in mediating phase-transfer Michael additions.

MICHAEL ADDITIONS OF C-NUCLEOPHILES TO VINYL SULFONES AND α, β-UNSATURATED IMIDES

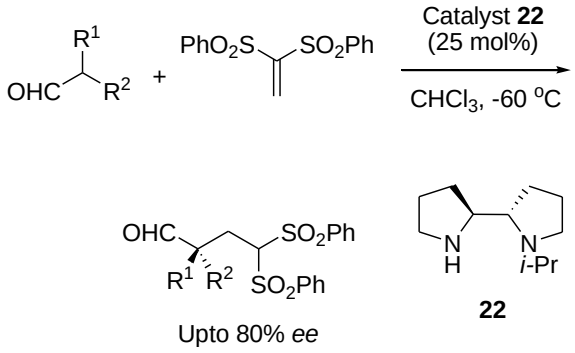
The first highly enantioselective Michael addition of α-alkyl- or α-aryl-α-cyanoacetates to vinyl sulfones was reported by Li *et al.*[41], employing a cinchona alkaloid catalyst **20** (Scheme 8). Liu *et al.*[42] also reported bifunctional thiourea tertiary amine derivatives of simple chiral diamines (**21**) for similar reaction.



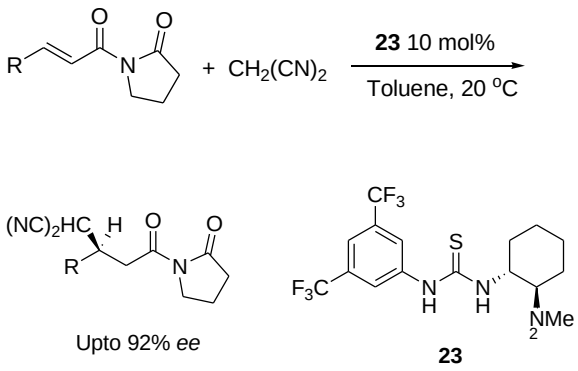


Scheme 8. Cinchona alkaloid- and thiourea-catalysed Michael additions of cyanoacetates to vinyl sulfones.

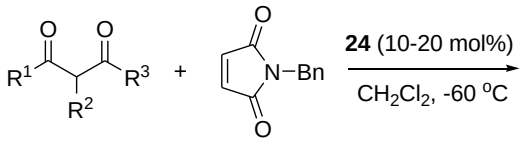
Mosse *et al.*[43a,b] employed *N-i*-Pr-2*S*,2′*S*-bipyrrolidine (*i*PBP) (**22**) for asymmetric condensation of aldehydes onto vinyl sulfones giving up to 80% *ee* (Scheme 9). In 2005, Hoashi *et al.*[44] extended enantioselective organocatalysed Michael addition methodology to *α, β*-unsaturated imides by the use of a bifunctional thiourea as catalyst (Scheme 10). Bartoli *et al.*[45] also showed that cinchona alkaloids were highly efficient catalysts for the Michael addition of 1,3-dicarbonyl compounds to maleimides (Scheme 11).

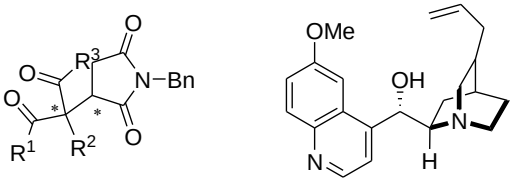


Scheme 9. iPBP-catalysed Michael additions of aldehydes to vinyl sulfones.



Scheme 10. Thiourea catalysed Michael additions of C -nucleophiles to α, β-unsaturated imides.



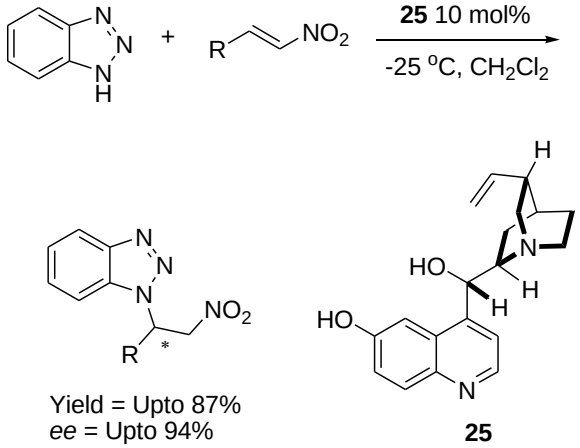


Upto 98% *ee* **24**

Scheme 11. Cinchona alkaloid catalysed Michael additions of C-nucleophiles to α, β-unsaturated imides.

MICHAEL ADDITION OF *N*-, *S*- AND *O*-NUCLEOPHILES

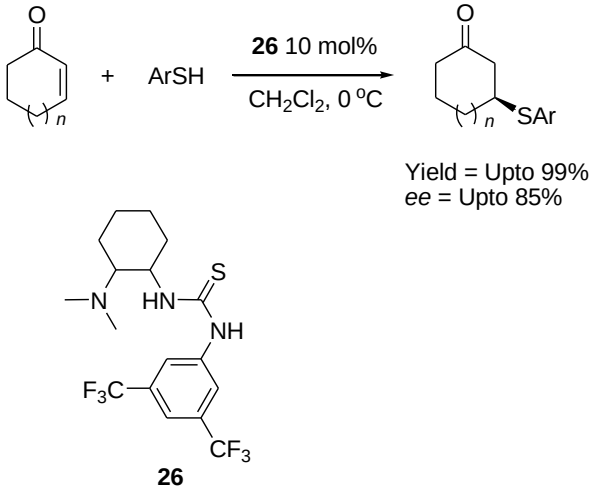
Asymmetric Michael addition of nitrogen-centred heterocyclic nucleophiles to electron deficient olefins is of great importance in the area of heterocyclic chemistry.[24] But, there are only few reports of the use of organocatalysts for this reaction. In 2006, Wang *et al.*[46] employed cinchona alkaloids ***25*** for enantioselective Michael addition of *N*-heterocycles such as 1*H*-benzo[*d*][1,2,3]-triazole to nitro olefins giving the products in moderate to high enantioselectivities (Scheme 12).



Yield = Upto 87%
ee = Upto 94% **25**

Scheme 12. Cinchona alkaloid-Michael additions of N-heterocycle.

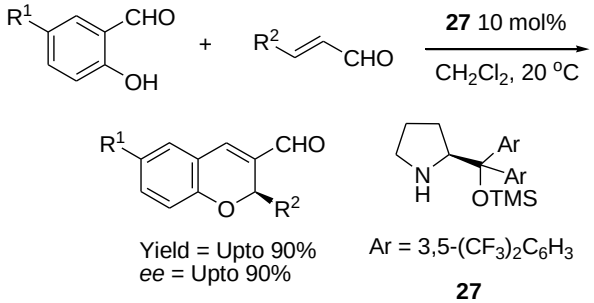
Bifunctional chiral thiourea and tertiary amine organocatalysts were used by Chen and co-workers to promote the enantioselective Michael addition of arylthiols to *α, β*-unsaturated carbonyl compounds (Scheme 13).[47] Three other enantioselective conjugated additions of thiols to *α, β*-unsaturated aldehydes were also reported by Marigo *et al.*,[48] Rios *et al.*[49] and Wang *et al.*[50]



Yield = Upto 99%
ee = Upto 85% **26**

Scheme 11. Thiourea-catalysed Michael additions of arylthiols to enones.

The first organocatalysed asymmetric synthesis of chiral benzopyrans was reported by Govender *et al.*[51] (Scheme 14). The overall reaction chain afforded benzopyrans with aromatic C-2 substituents in up to 60% yield and 60% *ee*, while the C-2 aliphatic analogues could be obtained in up to 90% *ee*, but with only low yields.



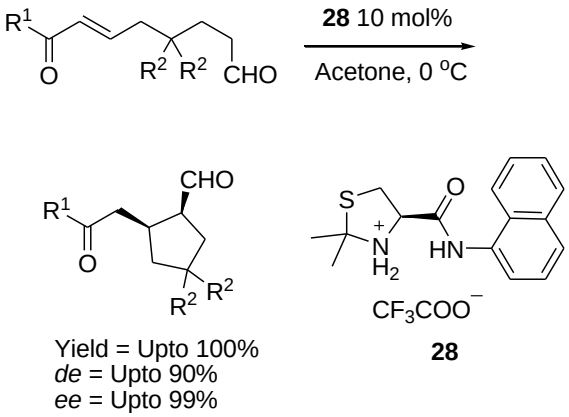
Yield = Upto 90%
ee = Upto 90%

Ar = 3,5-$(CF_3)_2C_6H_3$ **27**

Scheme 14. Oxa-Michael reactions catalysed by L-proline derivative.

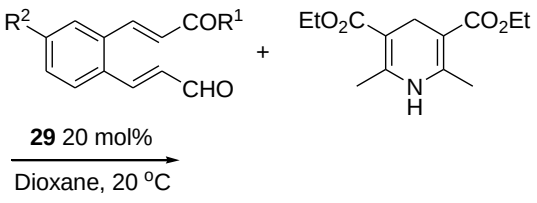
INTRAMOLECULAR MICHAEL ADDITION

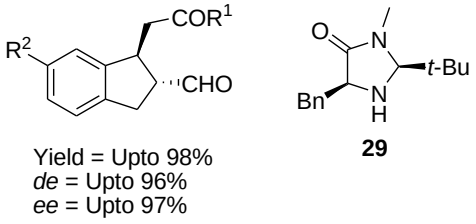
Mangion and MacMillan[52] reported an intramolecular Michael addition of a formyl-enal catalysed by L-proline in DMSO, which they used it for the total syntheses of two biologically active natural products, (-)-brasoside and (-)-littoralisone. In the same year, Hayashi *et al.*[53] have also employed a naphthylamide catalyst derived from cysteine (**28**) for asymmetric intramolecular Michael reactions such as those implicating formyl enones, which led to the stereoselective formation of *cis*-disubstituted cyclopentane skeletons (Scheme 15).



Scheme 15. Intramolecular Michael reactions catalysed by cysteine-derived catalyst.

Yang *et al.*[54] also utilized MacMillan imidazolidinium salt for reductive Michael cyclisation of enal enones in the presence of Hantzsch ester as hydrogen donor, leading to the development of the corresponding keto aldehydes with high enantioselectivity (Scheme 16).

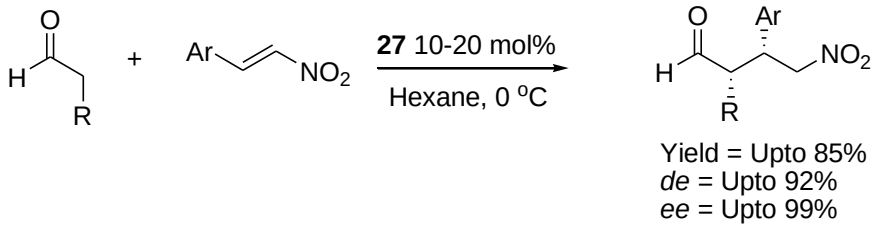




Scheme 16. Intramolecular reductive Michael reactions catalysed by imidazolidinium salt.

NITRO-MICHAEL ADDITIONS OF C-NUCLEOPHILES

Enantioselective Michael addition of carbonyl compounds to nitroalkenes has been of great interest due to its imperturbable approach for the synthesis of synthetically useful γ-nitro carbonyl compounds.[55] L-Proline was first used for intermolecular catalytic conjugate addition of carbon nucleophile to nitroalkenes, but found to be ineffective as it afforded only poor enantioselectivity.[56] Since then, a large number of organocatalysts have been designed and developed for this transformation and among them, pyrrolidine-based catalytic systems was found to be the most successful.[22] A common feature of these catalytic systems is a hydrogen-bond donor substituent at the α-position of the pyrrolidine nitrogen atom, which is believed to play a decisive role in helping the reaction to proceed. One important example is the use of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl) trimethylsilanyloxymethyl]pyrrolidine (**27**) for Michael addition of various aldehydes to nitro olefins, which was reported by Hayashi *et al.* (Scheme 17).[22k] The catalysts was synthesised from a commercially available diphenylprolinol in a single step, and the products were obtained in nearly optically pure form in almost all the cases examined. Some other important organocatalysts used for asymmetric Michael addition of carbonyl compounds to nitro olefins are shown in Figure 3.



Scheme 17. Asymmetric Michael addition using organocatalyst **27**.

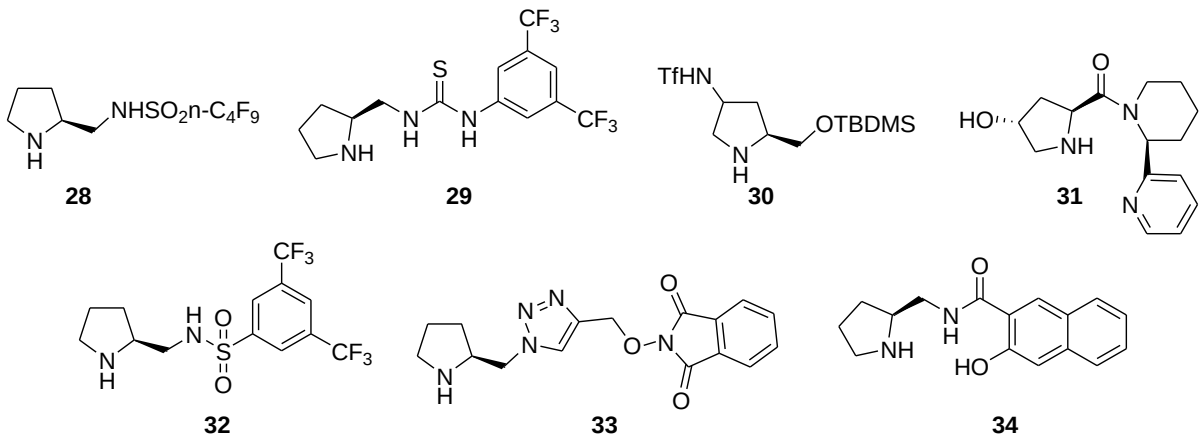


Figure 3. Some organocatalysts used for Michael addition of carbonyl group to nitro olefins.

Conclusion

Organocatalysis have recently emerged as one of the most useful methods for the synthesis of asymmetric compounds. Their reactivity, ease of handling and mild reaction condition makes them a reasonable platform for the development of new powerful transformation. As it is shown in this review, many different types of asymmetric catalysts were developed from organic sources for different asymmetric Michael addition reactions. Although the highlighted methodologies may have several drawbacks such as high catalytic loading and unfavourable reaction conditions, the achievements with these methodologies are immense and many improvements are expected in the future.

Acknowledgement

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