ASYMMETRIC SYNTHESIS BY ORGANOCATALYSIS: A GREENER APPROACH

Abstract

Background: Chirality is an important characteristic of several naturally occurring biological compounds. Thus, asymmetric synthesis i.e., generation of chiral centre in any synthetic compound during a reaction has drawn much attention of organic chemists. Various catalysts are being used by chemists for asymmetric synthesis but organocatalysts have been proved to be most powerful tool due to simple handling, inertness, and easy availability, non-toxicity, being metal-free and economic.

Methods: Organocatalysis has become highly useful technique for asymmetric synthesis. Using this method various chiral heterocyclic compounds can be produced with high yield and optical purity. Here the synthesis of various chiral compounds is discussed using green methods, aldol reaction, Michael addition and various other methods. Synthesis of various chiral scaffolds found in biological active compounds and compounds having agrochemical, medicinal, pharmacological applications has also been discussed. Asymmetric synthesis using aqueous media is also discussed.

Results: The organocatalysts have been used successfully for a wide range of reactions making a large number of building blocks and other useful chiral compounds. Some of these reactions are: aldol reaction, Michael addition, cycloaddition reactions, synthesis of polymers etc. Asymmetric synthesis using organocatalysts leads to the formation of stereoisomers with diverse biological activities.

Conclusion: Organocatalysis has emerged as a versatile and powerful technique for asymmetric synthesis. Being metal free, non-toxic and easy to handle, it does not harm environment and thus fits within the realm of green chemistry.

Keywords: Organocatalysis, green chemistry, cycloaddition, stereoisomers

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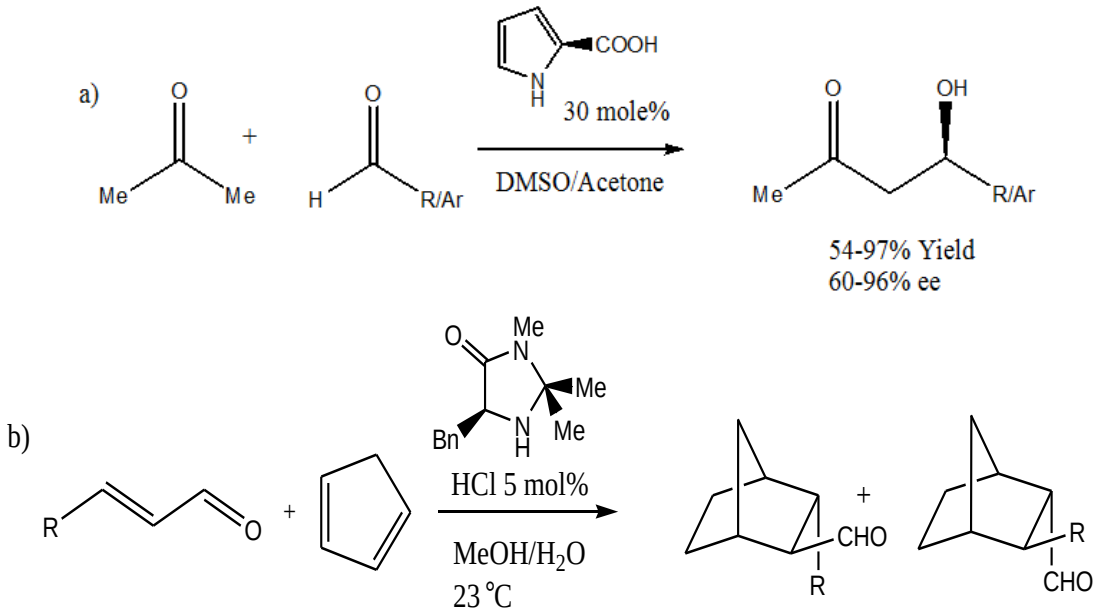
I. INTRODUCTION

Many chemical reactions can be carried out only in the presence of catalysts. Catalysts can control and accelerate the reactions but they do not become part of the final product. Catalysts are highly desired in synthesis of chiral molecule i.e., asymmetric synthesis. Chiral compounds have profound applications in various fields like pharmaceutical industries, agrochemical industries, polymers to name a few. Previously only two types of catalysts were known to chemists: metal catalysts and biocatalysts (enzyme). In 2000 Benjamin List [1] and David Macmillan [2] independently developed a third type of catalyst using small organic molecules, hence called organocatalyst [Scheme 1]. For this work both of them were awarded Nobel Prize in 2021. These are metal free and often contain hetero atom along with carbon atoms. Thus, organocatalysts are environmentally benign and cheap to produce. Organocatalysts can be used to carry out various chemical reactions and asymmetric synthesis is one of them.



Scheme 1: Pioneering work reported by List (a) and Macmillan (b)

Asymmetric synthesis using organocatalysts is also called Asymmetric Organocatalysis. Using this technique many enantiomerically pure compounds and chiral scaffolds can be synthesized which have wide applications as biological active compounds, agrochemical compounds, pharmacological compounds and polymers. Apart this technique is metal free and hence fits well in Green Chemistry.

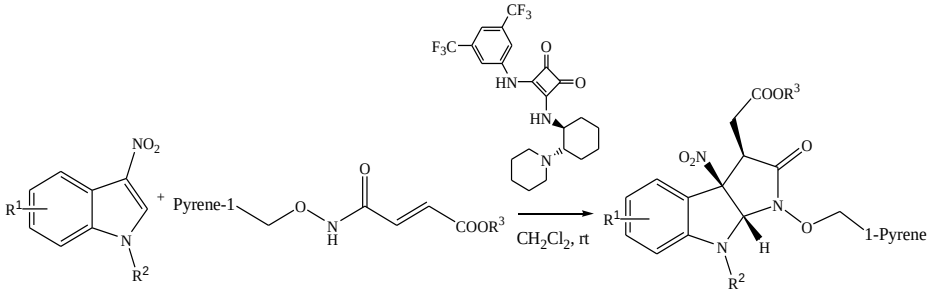
The origin of asymmetric synthesis can be traced back to 1913 where Bredig and Fiske [3, 4] reported asymmetric synthesis using cinchona derivatives as catalysts in their 2 works. The area was later on developed by the work of various chemists but it was still in infancy until 2000. Reason being till that time, the supremacy of metals was so prominent that it was hard to imagine that such simple organic molecules can replace the metals in asymmetric catalysis. But now a days organocatalysts are being used in many processes instead of metal catalysts and in few cases, they have excelled the metal catalysts.

In this chapter we will discuss synthesis of various chiral scaffolds found in biological active compounds and compounds having agrochemical, medicinal, pharmacological and numerous other applications.

II. DISCUSSIONS

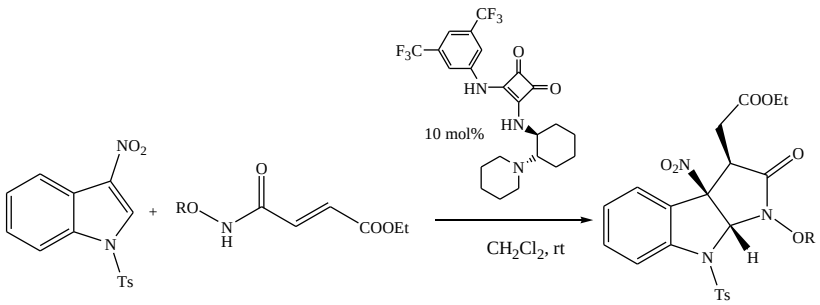
Organocatalysis is the use of specifically designed small organic molecules to accelerate and control organic transformations. Being metal free, it makes chemistry greener. The discovery of asymmetric organocatalysis is very important because the formation of asymmetric molecules has become much simpler as chiral molecules has wide variety of functions as pharmaceuticals, agrochemical compounds etc.

1. **Construction of pyrrolo-indole ring:** Chiral indole derivatives are important structural motifs found in a number of natural products, pharmacological compounds and optoelectronics materials [5]. Specifically, pyrrolo[2,3–b]indoles exhibit antinociceptive activities, antibacterial properties and inhibitor of acetyl cholinesterase [6]. Several studies have been carried out for construction of chiral pyrrolo[2,3–b]indoles skeletons by asymmetric metal-catalytic reactions [7]. In 2022 Tian et al [8] reported the construction of chiral pyrrolo[2,3-b]indole skeletons using organocatalysis. Authors reported the construction of pyrrolo[2,3-b]indole skeletons by an asymmetric dearomative [3+2] annulations between 3-nitroindoles and 1-pyrene methyl fumaric acid amide esters. They used chiral squaramide as catalyst [Scheme 2].



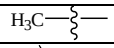
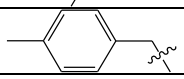
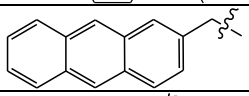
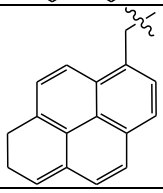
Scheme 2: Construction of chiral pyrrolo[2,3-b]indole skeletons using chiral squaramide as catalyst

Authors also studied the effect of various protective groups on fumaric acid amide esters [Scheme 3]. A range of chiral pyrrolo[2,3-b]indole derivatives were synthesized in good yields and moderate enantioselectivities. Some representative entries are shown in Table 1.



Scheme 3: Construction of chiral pyrrolo[2, 3-b]indole skeleton with fumaric acid amide ester

Table 1: Substrate scope for fumaric acid amide ester

Entry	R	Yield %	ee %
1		88	67
2		36	50
3		90	75
4		88	77
5		91	83

Authors proposed that the catalyst activates the nitro group through multiple hydrogen bonding interactions while its basic tertiary amine site activates the nucleophilic amide. It was found that enantioselectivity of the product was improved on expanding the size of aromatic ring giving rise to conclusion that an ancillary *p-p* interaction between the Ts group and pyrene group was responsible for improved enantioselectivity [Figure 1].

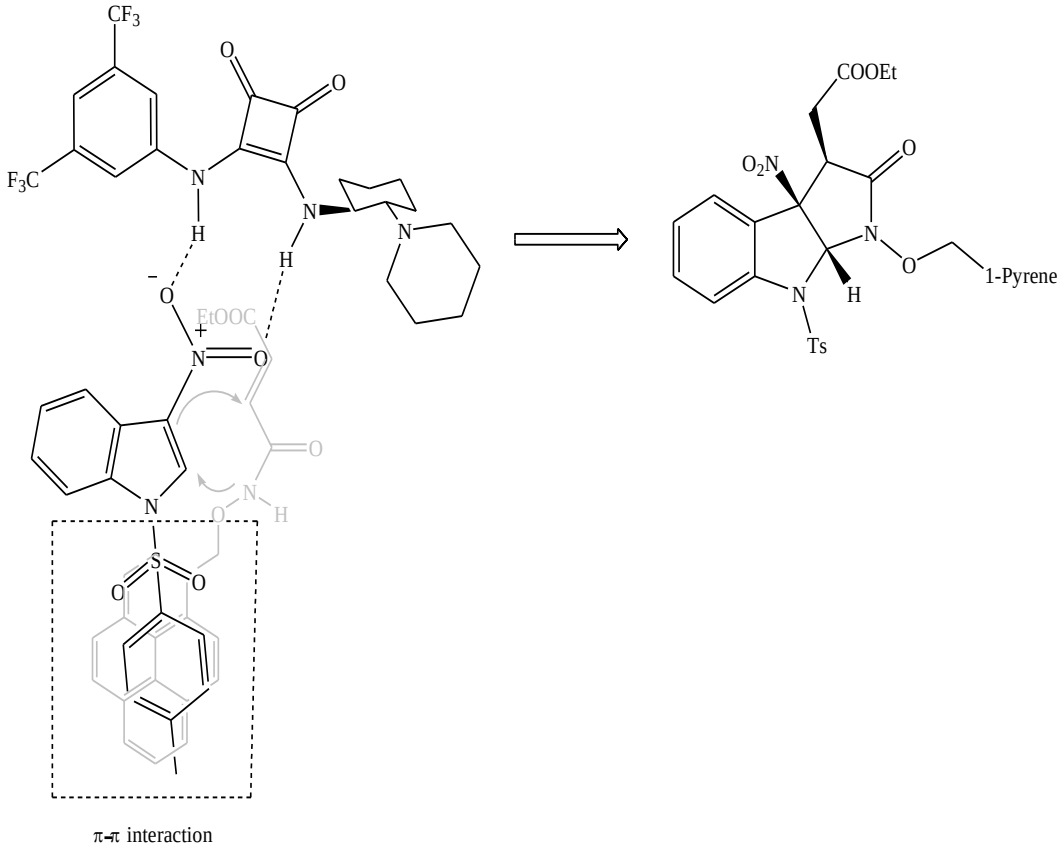
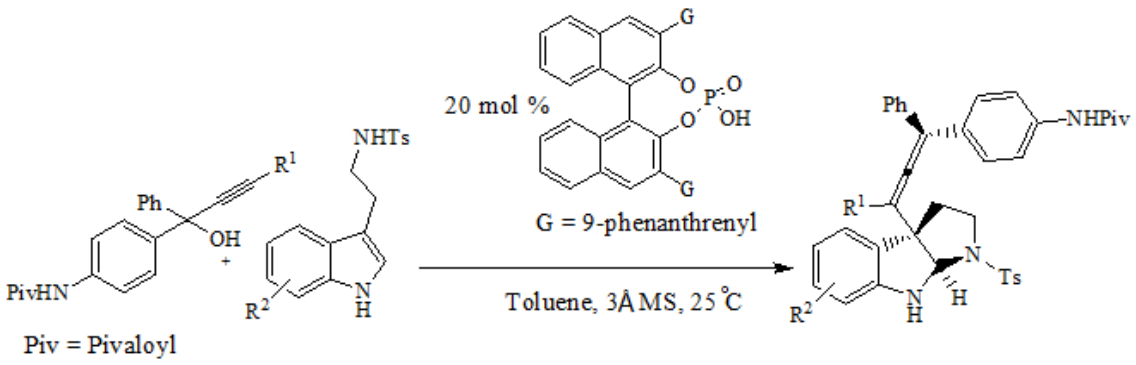


Figure 1: Proposed mechanism for synthesis of chiral pyrrolo[2, 3-b]indole skeletons

Axially chiral allenes are multifaceted building block in organic synthesis because of their diverse reactivity [9-11]. Particularly axially chiral tetra substituted allenes containing hetero-atom are a matter of interest in organic synthesis. Wang et al [12] carried out a cascade 1,8-addition/CADA-cyclization to synthesize hexahydropyrrolo[2,3-b]indole-containing tetra substituted allenes [Scheme 4] with central and axial chirality in good yields with high diastereo- and enantioselectivity. Chiral phosphoric acid was used as organocatalyst and it was found suitable with various substituents for both the reactants. Few representative entries are given in the Table 2.



Scheme 4: Synthesis of hexahydropyrrolo[2,3-b]indole containing tetrasubstituted allenes

Table 2: Substrate scope for synthesis of hexahydropyrrolo[2,3-b]indole-containing tetrasubstituted allenes

Entry	R^1	R^2	Yield %	dr	ee %
1.	Ph	H	87	92:8	86
2.	*p*-$OMeC_6H_4$	H	90	95:5	94
3.	*m*-$OMeC_6H_4$	H	80	91:9	86
4.	*o*-$OMeC_6H_4$	H	79	95:5	94
5.	*o*-ClC_6H_4	H	93	86:14	85
6.	*p*-$OMeC_6H_4$	4-F	83	88:12	92
7.	*p*-$OMeC_6H_4$	5-F	87	87:13	90
8.	*p*-$OMeC_6H_4$	5-Me	74	95:5	94
9.	*p*-$OMeC_6H_4$	5-Ome	52	95:5	93
10.	*p*-$OMeC_6H_4$	6-F	86	91:9	84
11.	*p*-$OMeC_6H_4$	6-Me	50	94:6	93
12.	*p*-$OMeC_6H_4$	7-F	71	93:7	92
13.	*p*-$OMeC_6H_4$	7-Me	80	95:5	95

With this work authors reported first time the use of alkyne derivatives as electrophiles in organo-CADA reactions of tryptamines. They suggested the following mechanism for this reaction [Figure 2].

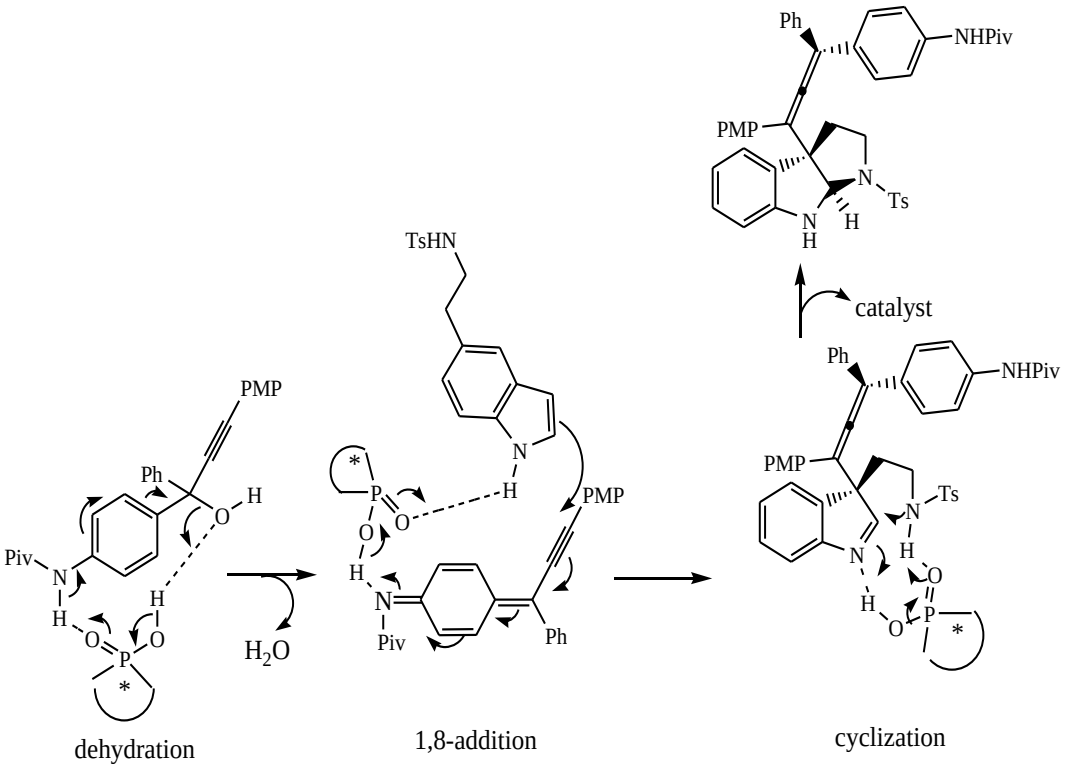
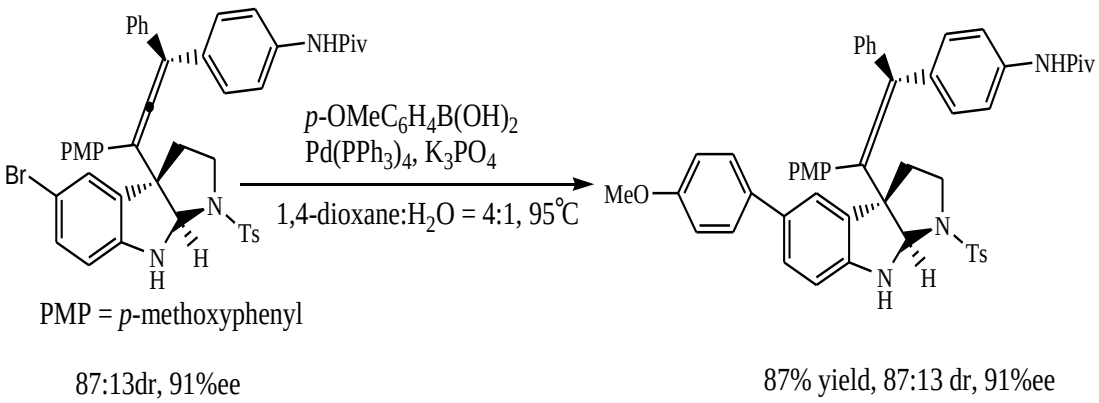


Figure 2: Proposed mechanism for synthesis of hexahydropyrrolo[2,3-b]indole

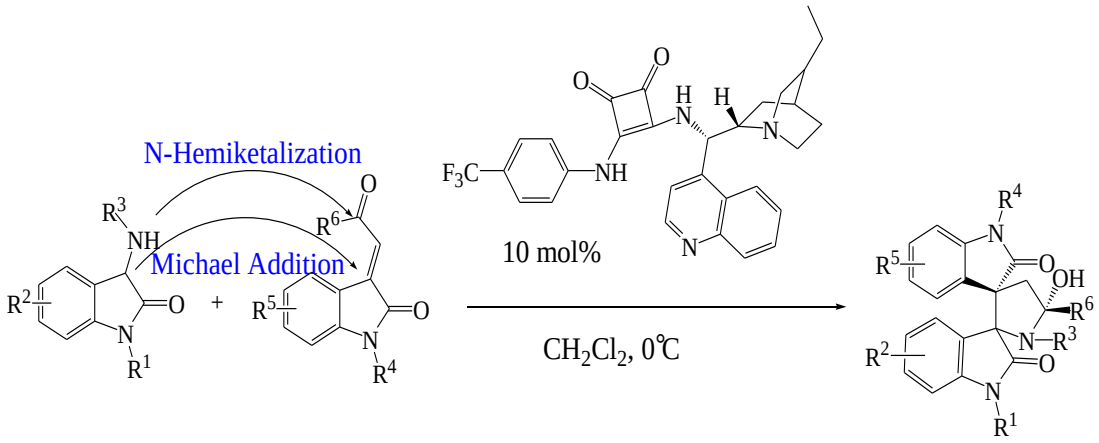
The products were derivatized successfully [Scheme 5] without hampering diastereoselectivity and enantioselectivity. Authors also tested the cytotoxicity of few allenes towards human pancreatic cancer cell line and found that they could inhibit the growth of cancer cells to some extent.



Scheme 5: Derivatization of hexahydropyrrolo[2,3-b]indole containing tetrasubstituted allenes

2. **Construction of spirooxindole ring:** Spirocyclic oxindole core prevail in various alkaloid, natural products and pharmacologically active agents [13-15]. An important class of various spirocyclic oxindole is pyrrolidinyl-spirooxindole due to its rich bioactivities [15] and its subclass 3,3′-pyrrolidinyl-bispirooxindoles has found applications as antimicrobial [15a], antifungal [15b], antibacterial and anticancer

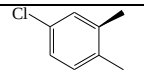
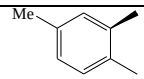
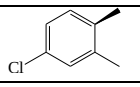
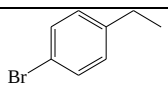
activities [15c]. Lin et al [16] first time reported the use of 3-aminooxindole as nucleophile in the synthesis of 3,3′-pyrrolidinyl-bispirooxindoles [Scheme 6] using bifunctional squaramide as organocatalyst. Another reagent was isatin derived *β,γ*-unsaturated *α*-keto ester. It was a cascade reaction consisting of two steps Michael addition followed by *N*-hemiketalization.

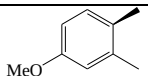
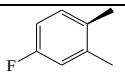
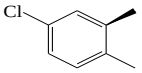


Scheme 6: Synthesis of 3,3′-pyrrolidinyl-bispirooxindoles

The reaction was carried out with various substituents on both the reactants and it was found suitable for variety of substituents. Few representative entries are given in Table 3.

Table 3: Substrate scope for synthesis of 3,3′-pyrrolidinyl-bispirooxindoles with both the reactants

Entry	R^1	R^2	R^3	R^4	R^5	R^6	Yield %	dr	ee %
1.	Bn-	H-	-CHO	Bn-	H-	-CO_2Et	85	16:1	90
2.	Me-	H-	-CHO	Bn-	H-	-CO_2Et	75	6:1	83
3.	H-	H-	-CHO	Bn-	H-	-CO_2Et	86	2:1	85
4.	Bn-		-CHO	Bn-	H-	-CO_2Et	79	4:1	87
5.	Bn-		-CHO	Bn-	H-	-CO_2Et	73	3:1	85
6.	Bn-		-CHO	Bn-	H-	-CO_2Et	68	20:1	90
7.	Bn-	H-	Ac-	Bn-	H-	-CO_2Et	80	12:1	90
8.	Bn-	H-	-CHO	Me-	H-	-CO_2Et	83	9:1	90
9.	Bn-	H-	-CHO		H-	-CO_2Et	75	4:1	91

10.	Bn-	H-	-CHO	Bn-		$-CO_2Et$	73	4:1	86
11.	Bn-	H-	-CHO	Bn-		$-CO_2Et$	68	4:1	71
12.	Bn-	H-	-CHO	Bn-		$-CO_2Et$	63	4:1	79
13.	Bn-	H-	-CHO	Bn-	-H	$-CF_3$			

On the basis of absolute configuration of the major isomer, authors proposed the following transition state. As per this transition state probably the tertiary amine moiety enolized aminooxindole, while the squaramide moiety of the catalyst activated isatin-derived *β,γ*-unsaturated *α*-keto ester by double hydrogen bonding causing *Si*-face attack by 3-aminooxindole on the *Si*-face of keto ester to generate Michael adduct intermediate followed by intramolecular *N*-hemiketalization leading to the formation of desired product [Figure 3].

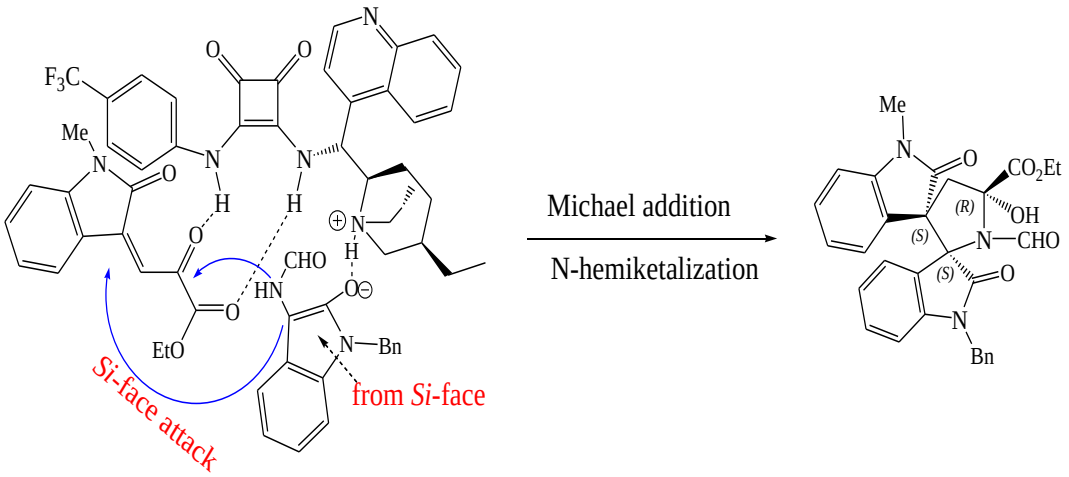


Figure 3: Proposed mechanism for synthesis of 3,3′-pyrrolidinyl-bispirooxindoles

Zhao and Du [17] reported the formation of bispirooxindoles-spirooxindoles in high yield and excellent enantiomeric excess through one-pot three-component Michael/Mannich-Michael/ cyclization cascade reaction. A bifunctional squaramide was used as a catalyst and the product was obtained in good yield and high enantiomeric excess. It contained 7 stereo centres, out of which three were quaternary spiro-stereocentres. For first cascade reaction cinnamoyl-3-ylideneoxindole and trifluoroethylisatinketimine were used as a substrate giving rise to corresponding bispirooxindoles. In second cascade reaction 3-isothiocyanatooxindoles was added to the reaction mixture resulting in the formation of corresponding bispirooxindole-spirooxindole [Figure 4].

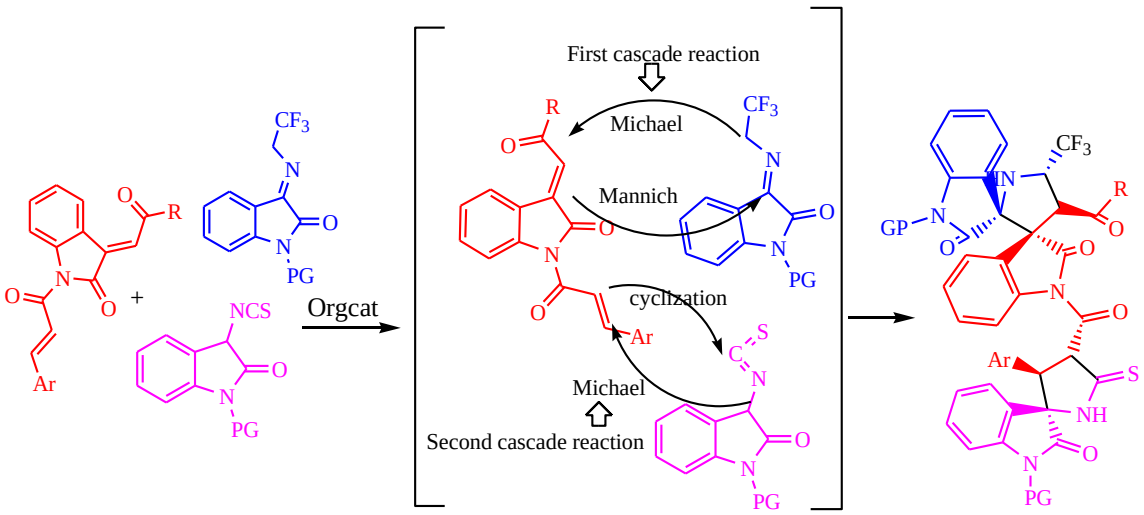
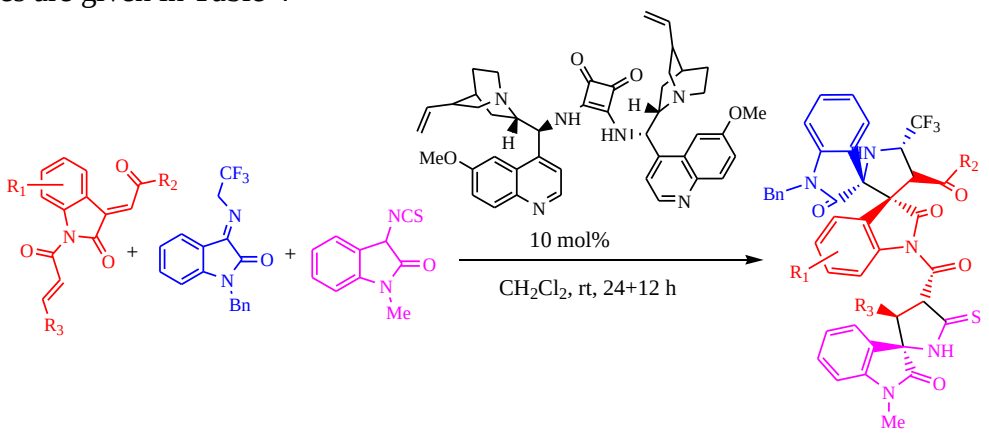


Figure 4: Synthesis of bispirooxindole-spirooxindoles showing both cascade reactions

Authors carried out the reaction by varying the substituents in all the three substrates [Scheme 7] and found the catalyst suitable for all of them. Some representative entries are given in Table 4

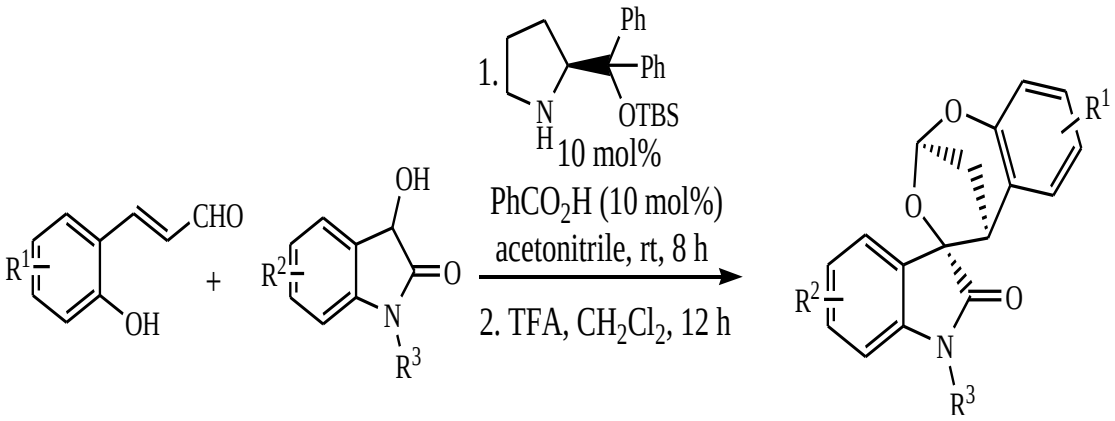


Scheme 7: Synthesis of various bispirooxindole-spirooxindoles

Table 4: Substrate scope for synthesis of bispirooxindole-spirooxindoles with all the reactants

Entry	R_1	R_2	R_3	Yield %	dr	ee %
1	-H	-OEt	-Ph	94	>20:1	99
2	-*p*-Fluoro	-OEt	-Ph	86	20:1	99
3	-*p*-Methyl	-OEt	-Ph	95	>20:1	99
4	-*p*-OMe	-OEt	-Ph	87	>20:1	99
5	-H	-*p*-$C_6H_5CH_3$	-Ph	85	10:1	99
6	-H	-O*t*Bu	-Ph	86	>20:1	99
7	-H	-OEt	-*o*-C_6H_4Cl	92	>20:1	99
8	-H	-OEt	-*p*-$C_6H_4OCH_3$	91	>20:1	99

Chiral *O,O*-acetals exhibit a wide range of bioactivities. They are an important part of numerous natural products and pharmaceuticals [18]. Bahla and Pan [19] reported for the first time asymmetric synthesis of bridged *O,O*-acetal containing spirooxindole skeleton [Scheme 8]. The reaction conditions were simple and the desired product was obtained in good yield with high diastereo- and enantioselctivity.



Scheme 8: Synthesis of bridged *o,o*-acetal containing spirooxindole skeleton

The reaction was carried out successfully with various substituents. Some representative entries are given in table 5.

Table 5: Substrate scope for synthesis of bridged *o,o*-acetal containing spirooxindole skeleton with both the reactants

Entry	R^1	R^2	R^3	Yield %	dr	ee %
1.	H	H	Bn	79	>20:1	98
2.	4-OMe	H	Bn	51	>20:1	98
3.	4-Cl	H	Bn	66	>20:1	97
4.	3-Cl	H	Bn	61	>20:1	99
5.	4,6-diCl	H	Bn	34	>20:1	94
6.	H	Me	H	80	>20:1	98
7.	H	4-CF_3Bn	H	51	>20:1	98
8.	H	Bn	5-Br	37	>20:1	93
9.	H	Bn	6-Br	49	>20:1	98
10.	H	Bn	7-Cl	55	>20:1	93
11.	H	Bn	4-Br	22	>20:1	85

The methodology involves amine catalyzed conjugated addition followed by diastereoselective acetalization with TFA as depicted in Figure given below [Figure 5]

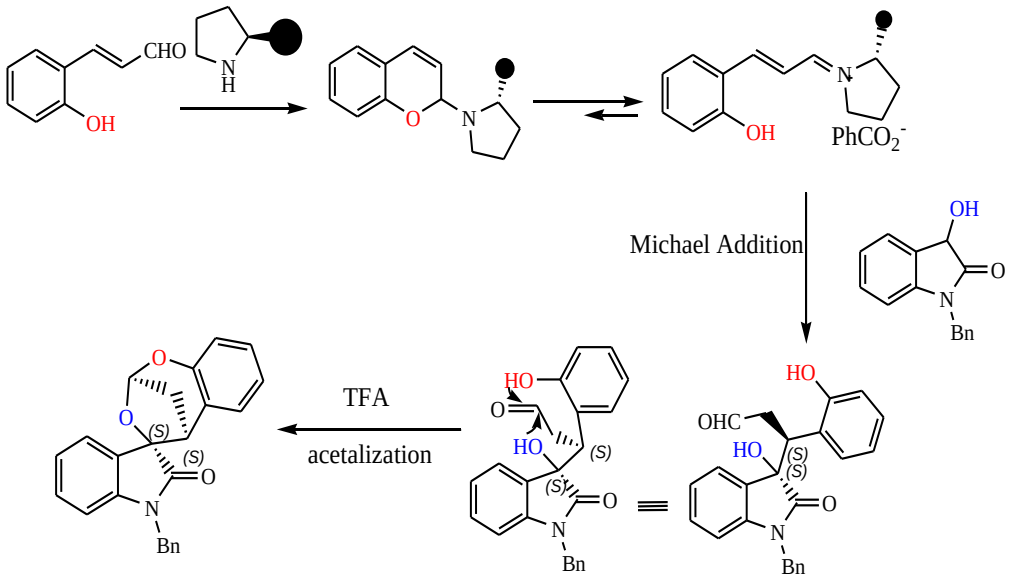
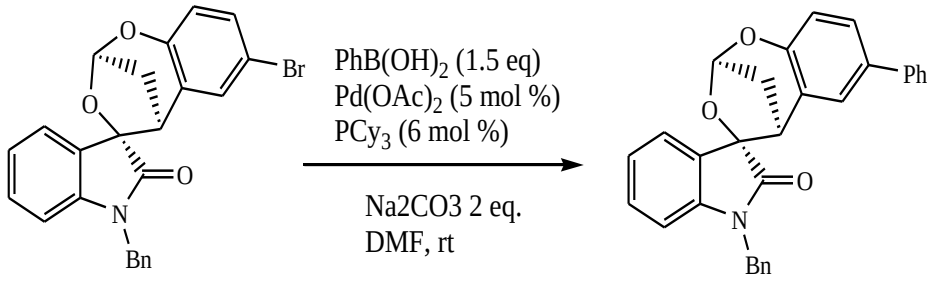


Figure 5: Methodology for synthesis of bridged *o,o*-acetal containing spirooxindole skeleton

Authors successfully functionalized few products via Suzuki Coupling reactions [Scheme 9] giving rise to products with preserved enantiopurity.

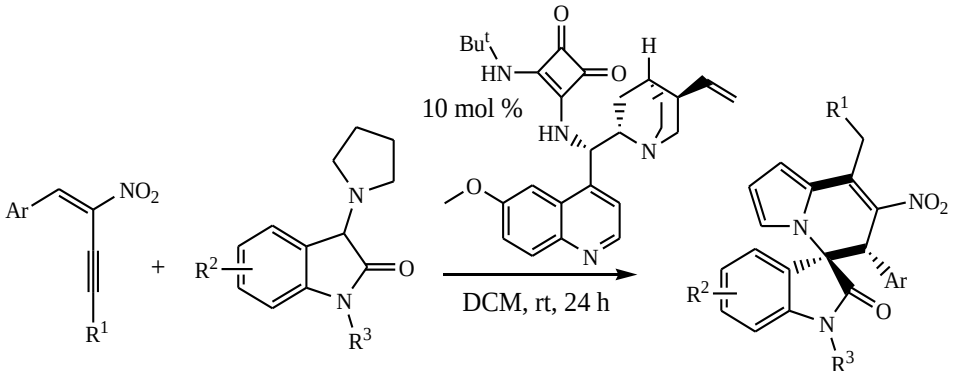


>20:1 dr, 98% ee

43% yield, >20:1 dr, 97% ee

Scheme 9: Functionalization of few bridged *o,o*-acetal containing spirooxindoles via Suzuki coupling reaction

The aza-spirooxindole moiety is prevalently found in natural products and pharmaceuticals [20]. Ni et al [21] reported the synthesis of spiropiperidinyl oxindole [Scheme 10] in good yield and high enantioselectivity. It was an asymmetric cascade Michael/Friedel−Crafts reaction took place between branched nitroenynes and 3-pyrrolyloxindoles using a quinine-derived squaramide as an organocatalyst. The reaction was compatible for various functional groups and successful under mild conditions. Few representative entries are given in table 6.



Scheme 10: Synthesis of spiropiperidinyl oxindoles

Table 6: Substrate scope for synthesis of various spiropiperidinyl oxindoles

Entry	Ar	R^1	R^2	R^3	Yield %	dr	ee %
1.	*p*-$CH_3C_6H_4$	C_6H_5	H	Me	85	3:1	92
2.	C_6H5	C_6H_5	H	Me	79	13:1	88
3.	*p*-FC_6H_4	C_6H_5	H	Me	70	4:1	86
4.	*m*-$CH_3C_6H_4$	C_6H_5	H	Me	72	5:1	90
5.	*m*-FC_6H_4	C_6H_5	H	Me	76	4:1	90
6.	*o*-$CH_3C_6H_4$	C_6H_5	H	Me	48	13:1	65
7.	C_6H_5	*p*-$CH_3C_6H_4$	H	Me	85	4:1	86
8.	C_6H_5	*m*-ClC_6H_4	H	Me	76	6:1	87
9.	C_6H_5	C_6H_5	5-CH_3	Me	84	3:1	92
10.	C_6H_5	C_6H_5	5-Cl	Bn	84	4:1	93
11.	C_6H_5	C_6H_5	6-Cl	Bn	76	10:1	95
12.	C_6H_5	C_6H_5	7-Cl	Bn	92	5:1	95
13.	C_6H_5	C_6H_5	4-Cl	Me	32	2:1	69

Authors proposed that quinuclidine moiety abstracts a proton from 3-pyrrolyloxindole giving rise to formal indol-2-ol. Simultaneously 3-nitroenyne gets activated by double H-bonding between the squaramide moiety and the nitro group. The formal indol-2-ol then undergoes a Michael addition from the *Re*-face. Because of the bulky *N*-tert-butyl group of organocatalyst the nitroenyne approaches with its *Si*-face. The intermediate thus formed gives allenyl by proton transfer. Then the pyrrolyl moiety is added to nitroallene in a 6-endo-trig intramolecular Friedel−Crafts cyclization afterwards isomerization takes place to give aza-spirooxindole as shown in Figure 6.

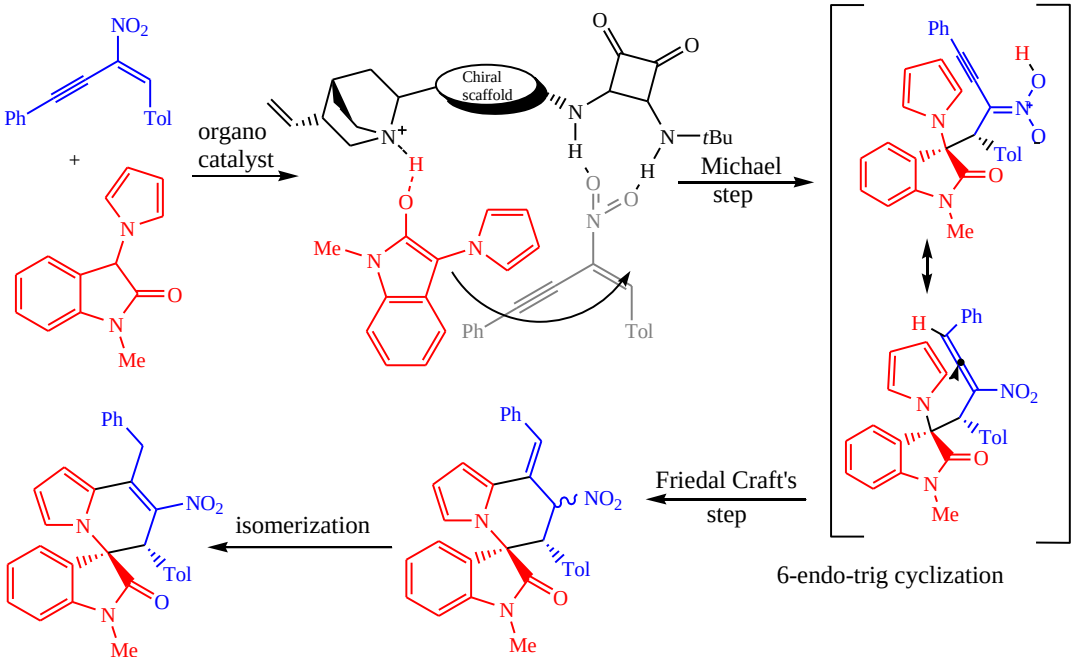
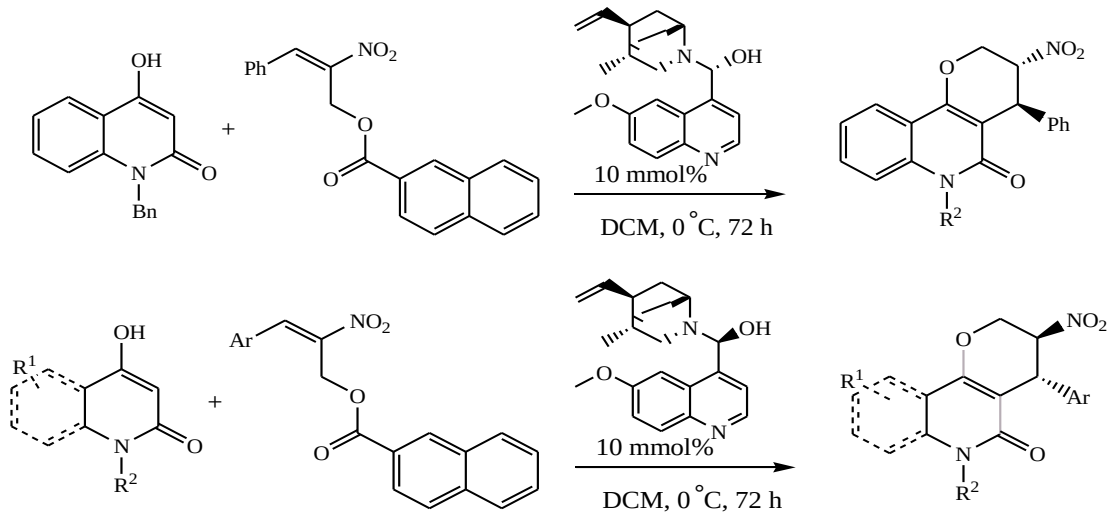


Figure 6: Proposed mechanism for synthesis of spiropiperidinyl oxindoles

Quinolinone fused tetrahydropyran skeletons are important structural unit in drugs and biologically active compounds [22]. Tetrahydropyran[3,2-c]quinolinones of this family also exhibit a wide range of biological activities [23]. Li et al [24] reported the synthesis of tetrahydropyran[3,2-c]quinolinones [Scheme 11] by asymmetric formal [3+3] annulation of 4-hydroxyquinoline-2(1H)-one and Morita-Baylis-Hillman (MBH) 2-naphthoates of nitroolefins. They used natural cinchona alkaloids as organocatalysts. Interestingly by variation of catalyst the products were obtained with opposite configuration as shown below. In both cases the yield and enantioselectivity was high.



Scheme 11: Synthesis of tetrahydropyran[3,2-c]quinolinones

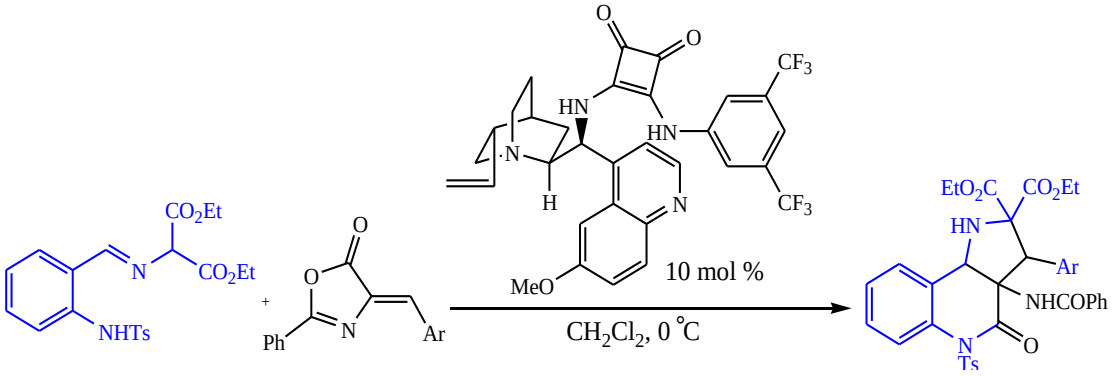
The reaction was successful with various substituents. Some representative entries are given in table 7.

Table 7: **Substrate scope for synthesis of various tetrahydropyran[3,2-c]quinolinones**

Entry	R^1	R^2	Ar	Yield %	dr	ee %
1.	H	Ph	Ph	95	12:1	94
2.	H	Bn	Ph	72	9:1	92
3.	6-F	Bn	Ph	50	8:1	87
4.	6-CF_3	Bn	Ph	71	>20:1	94
5.	8-OMe	Me	Ph	63	71	93
6.	6-Ph	Bn	Ph	95	11:1	94
7.	H	Ph	4-FPh	95	>20:1	93
8.	6-*t*Bu	Bn	2-FPh	69	13:1	92
9.	6-*t*Bu	Bn	3-MePh	86	16:1	95

Nitrogen-containing heterocycle units have biological properties so they are used as pharmaceuticals and agrochemical compounds [25]. Mahto et al [26] first time reported the asymmetric synthesis of pyrrolo[3,2-c]quinoline derivatives via [3+2] cycloaddition followed by lactamization cascade reaction [Scheme 12].

Cinchona alkaloid based bifunctional H-bonding squaramide was used as organocatalyst. The products were obtained in good yields and excellent diastereoselectivities. The products were having 3 consecutive stereocenters tertiary-quaternary-tertiary. The reaction was carried out with variety of substituents on α, β-unsaturated azlactones and found suitable for all. Some representative entries are given in table 8.



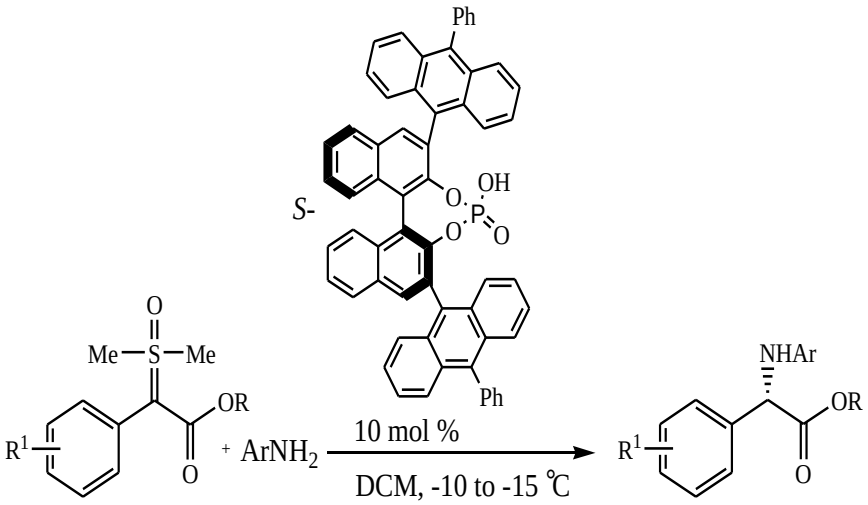
Scheme 12: asymmetric synthesis of pyrrolo[3,2-c]quinoline derivatives

Table 8: Substrate scope for synthesis of various pyrrolo[3,2-c]quinoline derivatives

Entry	Ar	Yield %	ee %
1.	C_6H_5	88	79
2.	4-Br-C_6H_4	50	55
3.	4-NO_2-C_6H_4	65	51
4.	3-Br-C_6H_4	85	62
5.	3-OMe-C_6H_4	70	60
6.	2-Br-C_6H_4	80	80
7.	2-NO_2-C_6H_4	68	73
8.	2,4-Cl-C_6H_3	81	79
9.	2-Br-4-CF_3-C_6H_3	81	81

3. Asymmetric Synthesis of amino acids: α-Aryl glycines are useful building blocks in organic synthesis and an important structural unit of biologically active molecules including pharmaceutical agent [27]. Gou et al [28] reported first time an asymmetric N-H insertion reaction of α-carbonyl sulfoxonium ylides using organocatalyst.

They carried out the reaction of sulfoxonium ylides with various aryl amines in the presence of chiral phosphoric acid catalyst giving rise to *α*-Aryl glycines[Scheme 13] with high enantioselctivity. Highly stable and weakly basic sulfoxonium ylides prevent catalyst decomposition which is crucial to the excellent aminability as aryl amines are weaker nucleophiles. The reaction was carried out successfully with variously substituted reactants. Some representative entries are given in table 9



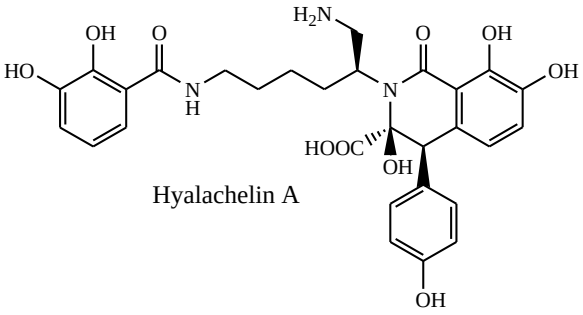
Scheme 13: Asymmetric synthesis of *α*-aryl glycines

Table 9: Substrate scope for synthesis of various *α*-aryl glycines

Entry	R^1	R	Ar	Yield %	ee %
1.	H	Me	*p*-C_6H_4OMe	93	95
2.	H	Ph	*p*-C_6H_4OMe	82	87
3.	*p*-Cl	Bn	*p*-C_6H_4OMe	95	94
4.	*p*-Me	Bn	*p*-C_6H_4OMe	90	97
5.	*p*-CN	Me	*p*-C_6H_4OMe	93	86
6.	*p*-CO_2Me	Bn	*p*-C_6H_4OMe	97	90
7.	H	Bn	C_6H_5	95	94
8.	H	Bn	*p*-$C_6H_4CH_3$	91	95
9.	H	Bn	*p*-C_6H_4Cl	94	92
10.	H	Bn	*p*-C_6H_4CN	85	74
11.	H	Bn	*o*-F-*p*-OCH_3	97	96

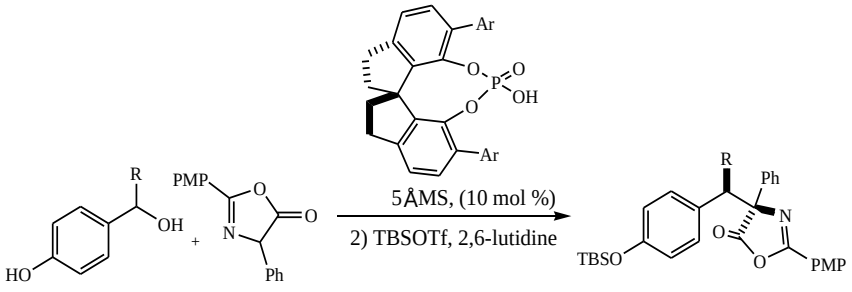
Chiral α-amino acids and their derivatives are found in various natural products and biologically active molecules. Specifically, those containing aryl group at β position show distinguished properties. For example, the natural product hyalachelin-A and its

analogues are known as unusual catecholate siderophores having ion chelating activity [29].



Hyalachelin A

Yan et al [30] reported the synthesis of chiral *β,β*-diaryl-*α*-amino acid derivatives [Scheme 14] by using chiral phosphoric acid catalysts. It was a one pot reaction where *p*-hydroxybenzyl alcohol was dehydrated to generate *p*-quinone methides in situ. The latter was made to react with azalactones by conjugate addition in a stereocontrolled manner. The products were obtained in good yield and high enantio- and diastereoselectivity. With this work authors developed an asymmetric strategy using organocatalyst where both the *α* and *β* chiral centres were directly established in one pot synthesis.



PMP = *p*-methoxyphenyl

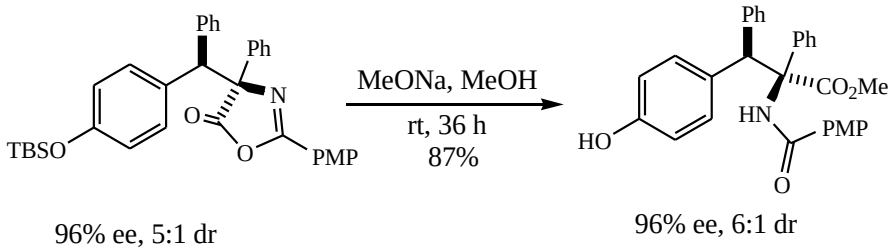
Scheme 14: Synthesis of chiral *β,β*-diaryl-*α*-amino acid derivatives

A variety of substituted *p*-hydroxybenzyl alcohols were used and the reaction was found to be suitable for many of them. Few representative entries are given in the Table 10.

Table 10: Substrate scope for synthesis of chiral *β,β*-diaryl-*α*-amino acid derivatives

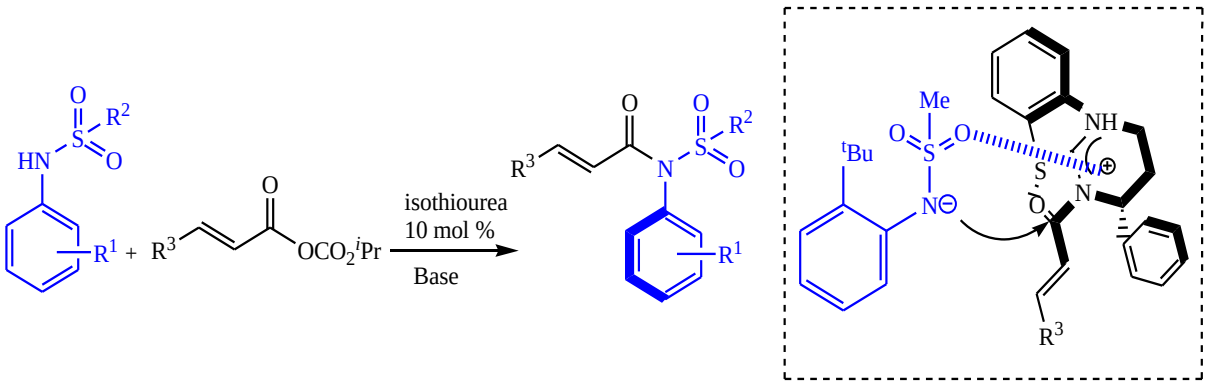
Entry	R	Yield %	ee %	dr
1.	Ph	80	97	6.6:1
2.	*p*-FC_6H_4	44	96	5.6:1
3.	*m*-$OMeC_6H_4$	81	97	7.2:1
4.	Me	69	95	3.6:1
5.	^{n}Bu	80	96	2.5:1
6.	^{t}Bu	<10		

One of the product was converted into *β,β*-diaryl-*α*-amino acid [Scheme 15] with high yield and good enantiomeric excess. The product formed has vicinal tertiary and quaternary stereocentres.



Scheme 15: Conversion of chiral *β,β*-diaryl-*α*-amino acid derivatives into *β,β*-diaryl-*α*-amino acid

4. **Construction of other Heterocyclic Rings:** The nonbiaryl C−N axially chiral compounds are important structural unit of many pharmaceuticals [31] and bioactive natural products [32].Li et al [33] reported the synthesis of numerous atropisomeric sulfonyl substituted anilides in good yields and high enantiomeric excess [Scheme 16]. The reaction was carried out under mild conditions and isothiourea was used as a catalyst. Synthesis involved atroposelective *N*-acylation of sulfonamides with *α,β*-unsaturated carbonic anhydrides.



Scheme 16: Synthesis of atropisomeric sulfonyl substituted anilides

The reaction was studied for substrate scope for both the reactants and found useful for all of them. Some entries are given in Table 11.

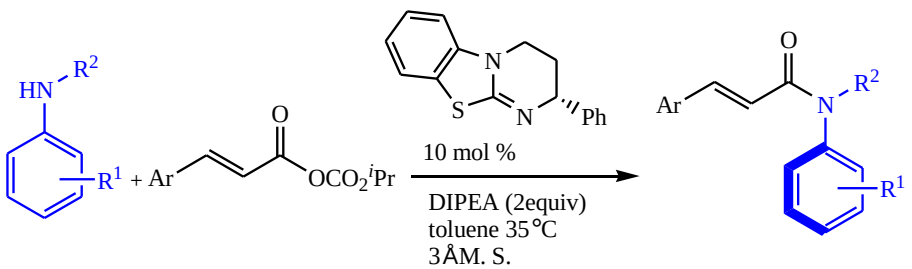
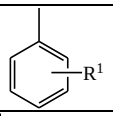
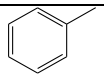
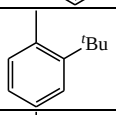
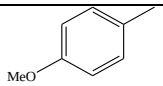
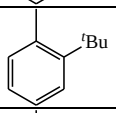
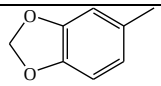
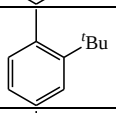
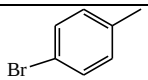
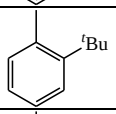
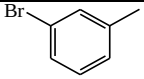
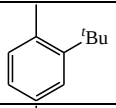
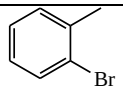
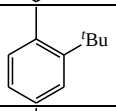
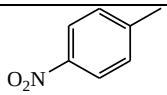
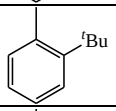
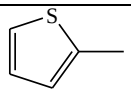
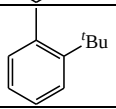
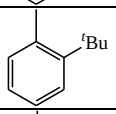
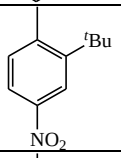
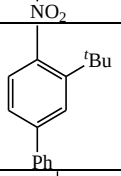
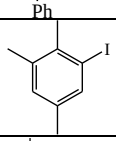
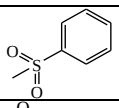
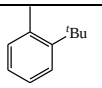
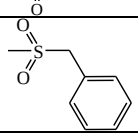
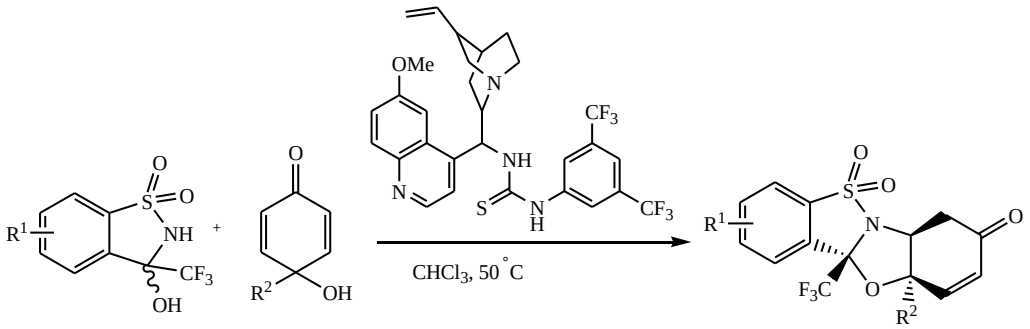


Table 11: Substrate scope for both the reactants for synthesis of atropisomeric sulfonyl substituted anilides

Entry	Ar		R^2	Yield %	ee %
1			Ms	88	95
2			Ms	63	95
3			Ms	90	94
4			Ms	95	94
5			Ms	75	94
6			Ms	73	94
7			Ms	95	93
8			Ms	70	96
9	-CH_3		Ms	95	94
10	-C_6H_5		Ms	80	87
11	-C_6H_5		Ms	80	94
12	-C_6H_5		Ms	82	81
13	-C_6H_5			73	91
14	-C_6H_5			80	94

Chiral *N,O*-ketals and fluoroalkylated compounds are such structure motifs which are used to enhance the pharmacological and agrochemical activities. Gui et al [34] reported the synthesis of various fluoroalkylated *N,O*-ketals [Scheme 17] using quinine based derivative as organocatalyst. Products were obtained in excellent yield with good enantioselectivities.



Scheme 17: Synthesis of various fluoroalkylated *N,O*-ketals

Substrate scope was studies for the reaction and it was found suitable for almost all the substrates. Few representative entries are given in table 12.

Table 12: Substrate scope for synthesis of various fluoroalkylated *N,O*-ketals

Entry	R^1	R^2	Yield %	ee %
1.	6-Me	Me	98	92
2.	H	Me	96	90
3.	6-F	Me	85	88
4.	6-CF_3	Me	93	90
5.	7-Me	Me	88	87
6.	8-F	Me	83	85
7.	6-Me	Et	87	92
8.	6-Me	Ph	93	90
9.	6-Me	*p*-$CH_3C_6H_4$	91	89
10.	6-Me	*p*-BrC_6H_4	86	83
11.	6-Me	*p*-$CF_3C_6H_4$	90	80

Mechanistic studies revealed that bifunctional quinine-thiourea catalyst causes the activation of carbonyl by H-bonding interaction leading the nucleophilic attack of N of tertiary amine catalyst from Si face giving rise to the formation of *S* adduct (Figure 7). The reaction proceeded through asymmetric formal [3+2] annulation and final aza-Michael addition step was responsible for high enantioselectivity.

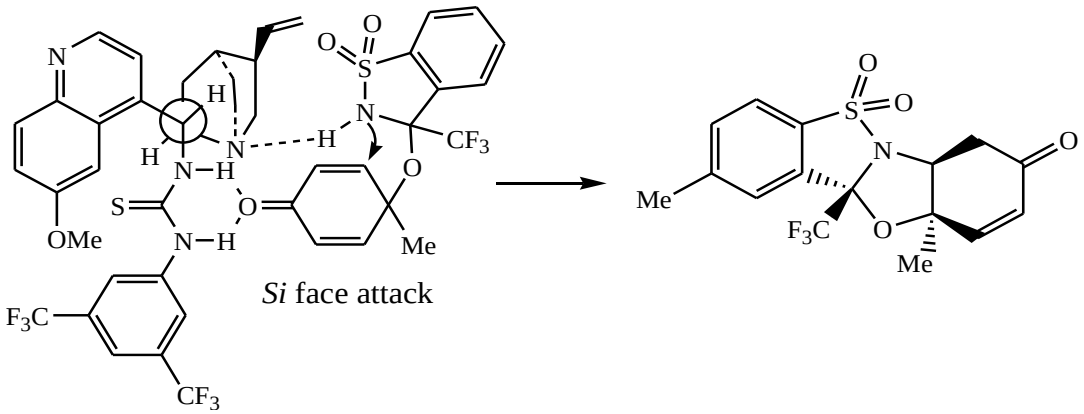


Figure 7: Mechanism for synthesis of various fluoroalkylated *N*,*O*-ketals

Indolin-3-ones with centrally chiral C2 quaternary carbon are privileged structural motifs in natural products and biologically active molecules [35] Yuan et al [36] carried out an interesting study, they synthesized a new kind of arylindolyl indolin-3-one backbones containing both central and axial chirality simultaneously in the same molecule [Figure 8, Scheme 18]. Chiral phosphoric acid was used as a catalyst. Product was obtained in high yield and with excellent enantioselectivity and diastereoselectivity.

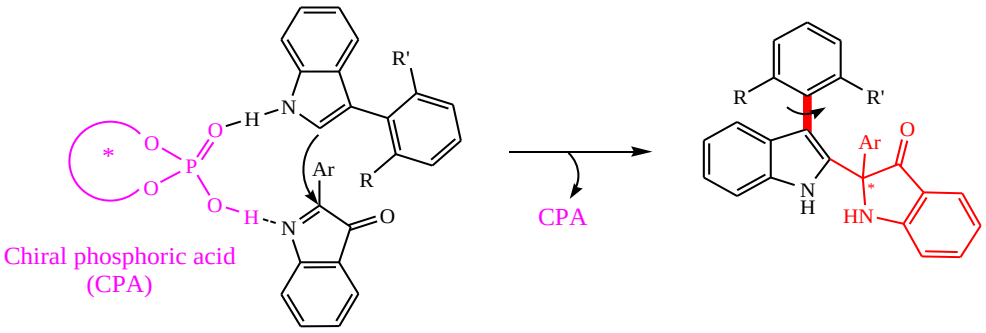
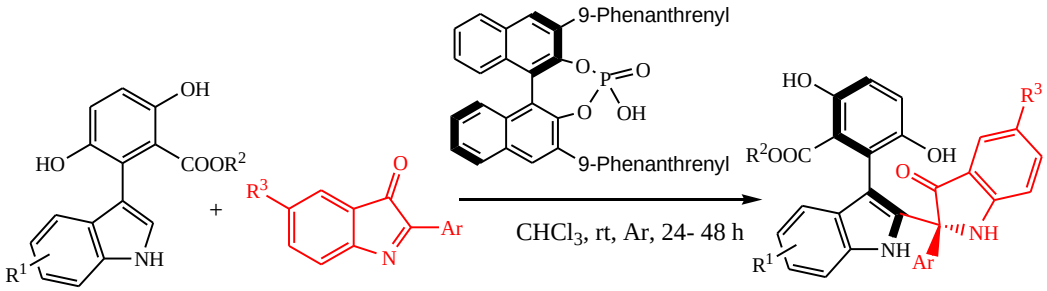


Figure 8: Synthesis of arylindolyl indolin-3-one backbones containing both central and axial chirality

The reaction was studied for substrate scope for both the substrates 3-arylindoles and 2-aryl-*3H*-indole-3-ones and found suitable for various functional groups. Few representative entries are given in the table 13. Authors further reported that chiral products were stable and no racemization took place after treatment with xylene below 120 °C for 12 hours.

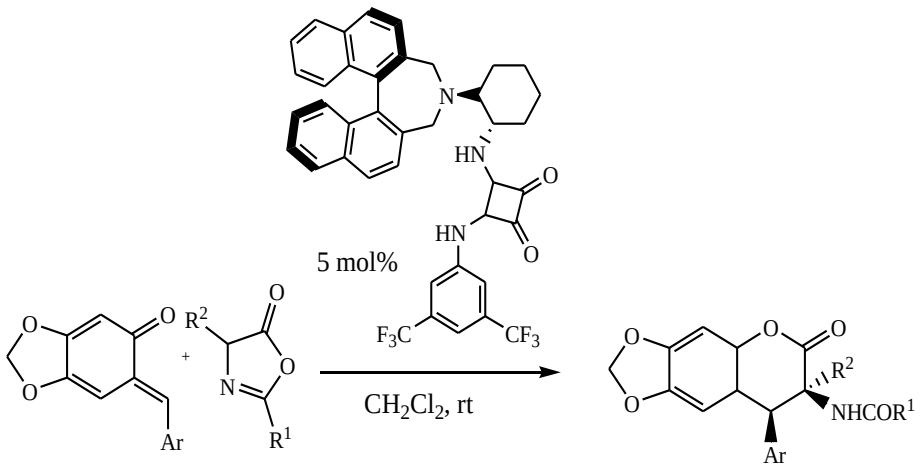


Scheme 18: Synthesis of arylindolyl indolin-3-one backbones containing both central and axial chirality

Table 13: Substrate scope for synthesis of various arylindolyl indolin-3-ones

Entry	R^1	R^2	R^3	Ar	Yield	ee%	dr
1.	H	Me	H	Ph	95	94	>20:1
2.	H	^{t}Bu	H	Ph	78	94	>20:1
3.	H	Bn	H	Ph	98	91	>20:1
4.	H		H	Ph	76	91	>20:1
5.	7-Me-	Me	H	Ph	96	95	>20:1
6.	5-F-	Me	H	Ph	99	94	>20:1
7.	6-Cl-	Me	H	Ph	78	90	>20:1
8.	H	Me	H	*p*-$CH_3C_6H_4$-	99	92	>20:1
9.	H	Me	2-Ph	5-F-	99	90	>20:1

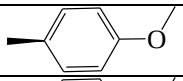
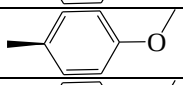
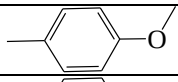
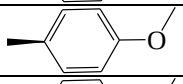
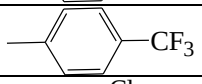
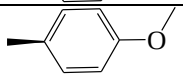
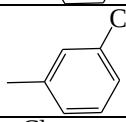
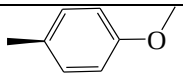
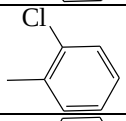
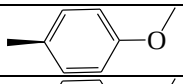
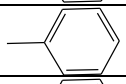
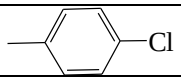
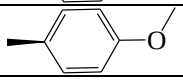
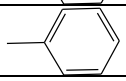
Numerous natural products and biologically active molecules contain dihydrocoumarin core [37]. Enantiopure dihydrocoumarine derivatives have wide applications in pharmacological activities such as antiviral and anti-inflammatory activities [38]. Kim et al [39] reported synthesis of dihydrocoumarin by [4+2] cyclo addition of *o*-quinone methides with oxazolones in presence of chiral bifunctional organocatalyst [Scheme 19]. The product was obtained in high yield and excellent enantioselectivity and diastereoselectivity.



Scheme 19: Synthesis of dihydrocoumarin by [4+2] cycloaddition of *o*-quinone methides with oxazolones

The reaction was carried out with various substituents on reactants and it was found suitable for variety of substituents. Few representative entries are given in Table 14.

Table 14: Substrate scope for synthesis of various dihydrocoumarins

Entry	Ar	R^1	R^2	Time taken	Yield %	ee %
1.		C_6H_5-	Bn-	36 h	79	96
2.			Bn-	44 h	70	97
3.			Bn-	15 h	60	92
4.			Bn-	40 h	75	96
5.			Bn-	52 h	67	90
6.				45 h	47	96
7.			Me-	24 h	53	94

The absolute configuration of chiral dihydrocoumarins was found to be (*3S, 4S*) and to explain the stereochemistry it was proposed that squaramide moiety of bifunctional catalyst activated *o*-quinone methide and simultaneously tertiary amine of the catalyst deprotonated oxazolone causing attack of *Si* face of oxazolone over *Si* face of *o*-quinone methide as shown in the model given below [Figure 9].

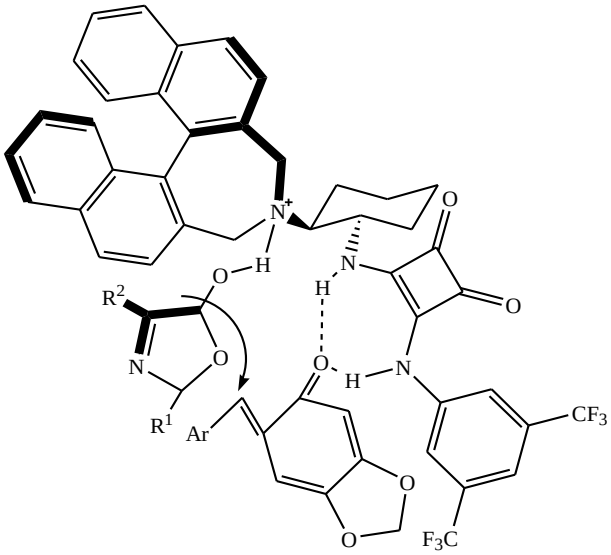


Figure 9: Attack of *Si* face of oxazolone over *Si* face of *o*-quinone methide

Tricyclicchromane framework is found in numerous natural products and pharmaceutical compounds. Due to their biological properties, they have been a matter of interest for synthetic chemists. Kumar et al [40] reported the asymmetric synthesis of

tricyclic chromanes through one-pot quadruple domino reaction [Scheme 20]. Domino reaction involved oxa-Michael/Michael/Michael/Aldol condensation [Figure 10].

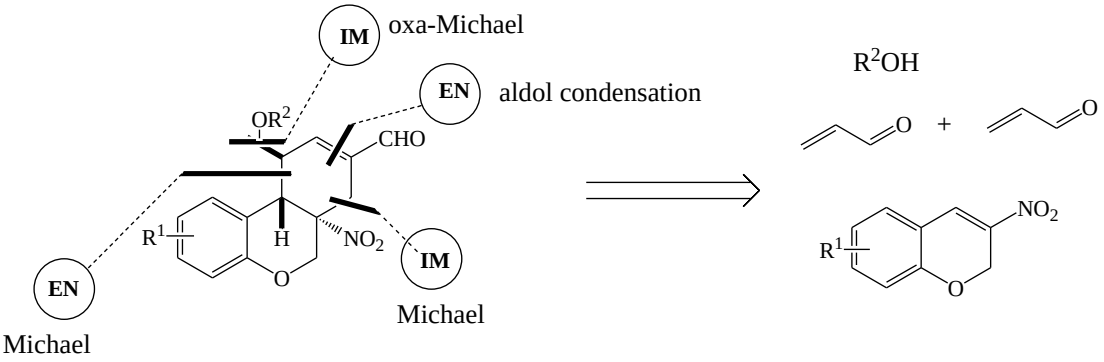
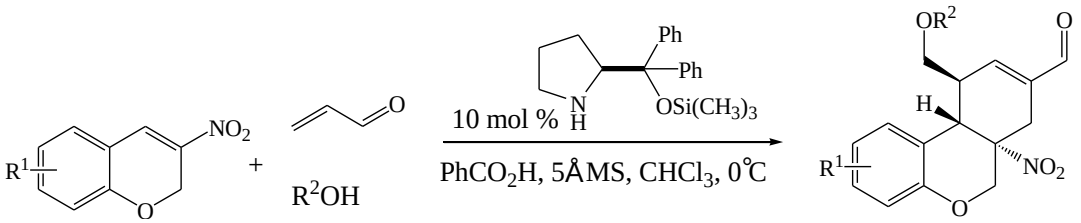


Figure 10: Domino reaction involving oxa-Michael/Michael/Michael/Aldol condensation

The product contained 3 consecutive centres out of which one was tetrasubstituted. The reaction was studies for substrate scope for alcohol and 3-nitro-2*H*-chromene. Few representative entries are given in the table 15.



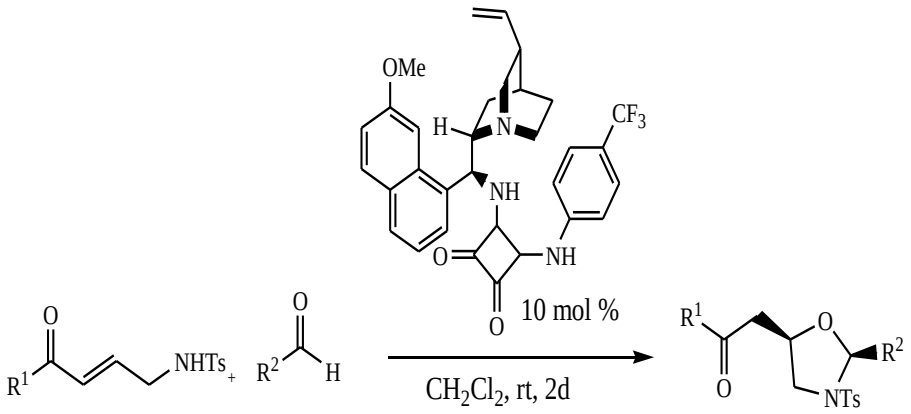
Scheme 20: Asymmetric synthesis of tricyclic chromanes

Table 15: Substrate scope for alcohol and 3-nitro-2*h*-chromene

Entry	R^1	R^2	Yield %	Dr	ee %
1.	H	Me	45	20:1	>99
2.	6-Cl	Me	37	20:1	>99
3.	6-Br	Me	70	20:1	>99
4.	6-NO_2	Me	50	20:1	>99
5.	6-OMe	Me	50	20:1	>99
6.	7-Ome	Me	39	20:1	>99
7.	8-OMe	Me	53	20:1	>99
8.	6,8-dichloro	Me	45	20:1	>99
9.	H	Et	54	20:1	>99
10.	H	Bn	56	20:1	>99
11.	H	Benzal	40	20:1	>99
12.	H	Allyl	46	20:1	>99
13.	H	Propargyl	58	20:1	>99

Chiral oxazolidines find application in various asymmetric transformations as chiral auxiliaries and chiral ligands [41]. Also; they are an important structural motif of

many biologically active natural products [42]. Mukhopadhyay and Pan [43] reported asymmetric synthesis of 2,5-disubstituted oxazolidines first time [Scheme 21]. They were synthesized from alkyl aldehydes and N-tosylaminomethylenones using bifunctional squaramide organocatalyst. The products were obtained in good yields with excellent diastereo- and enantioselectivities with various substituents on both the reactants [Table 16].



Scheme 21: Asymmetric synthesis of 2,5-disubstituted oxazolidines

Table 16: Substrate scope for synthesis of 2,5-disubstituted oxazolidines

Entry	R^1	R^2	Yield %	Dr	ee %
1.	Ph	^{n}Bu	76	>20:1	95
2.	Ph	^{n}Hex	75	>20:1	90
3.	Ph	^{n}Oct	73	>20:1	94
4.	Ph	$PhCH_2CH_2$	76	>20:1	92
5.	Ph	^{n}Undec	70	>20:1	99
6.	4-MeC_6H_5	^{n}Bu	76	>20:1	98
7.	4-FC_6H_5	^{n}Bu	69	>20:1	86
8.	3-MeC_6H_5	^{n}Bu	75	>20:1	98
9.	2-MeC_6H_5	^{n}Bu	70	>20:1	87
10.	2-Naphthyl	^{n}Bu	69	>20:1	96
11.	2-Furyl	^{n}Bu	72	10:1	91

According to proposed mechanism, it was assumed that squaramide moiety of catalyst activated the aldehyde while tosyl amine is protonated by tertiary amino motif of catalyst. Former is then added to aldehyde from *Re* face only as *Si* face is blocked by catalyst giving rise to hemiaminal. Hemiaminal then undergoes an intramolecular oxa-Michael reaction on the *Si* face of activated enone to generate product [Figure 11].

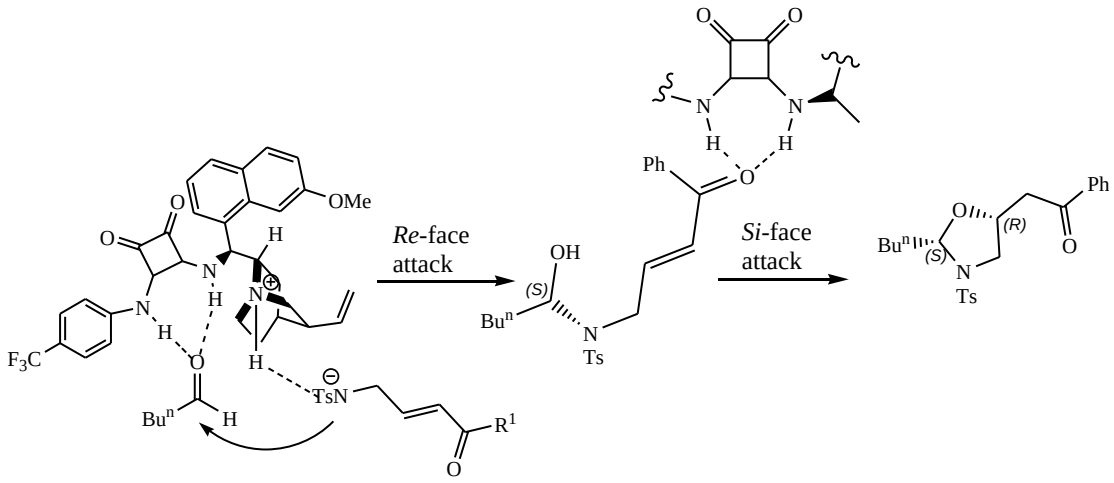
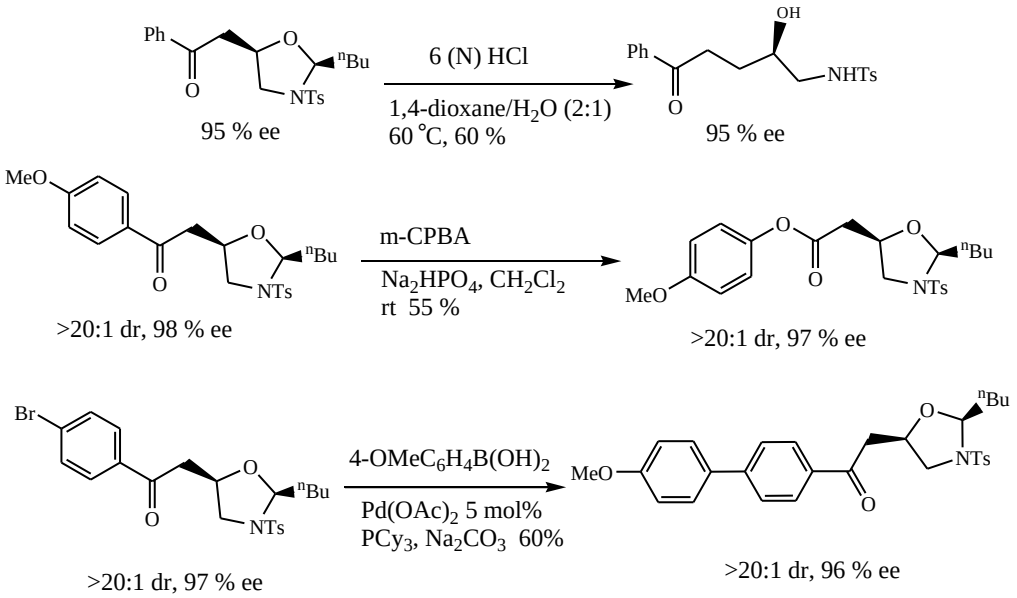


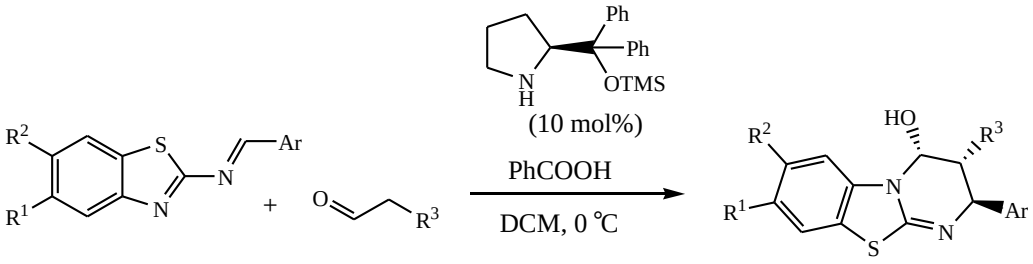
Figure 11: Proposed mechanism for synthesis of 2,5-disubstituted oxazolidines

To find out the synthetic utility of this method authors carried out further reactions of few products and in all the reactions enantioselectivity was almost maintained [Scheme 22].



Scheme 22: Synthetic utility of 2,5-disubstituted oxazolidines

Benzothiazolopyrimidines are important scaffold of various pharmacologically active molecules, such as antitumor agents [44], antitrypanosomal agents [45], phosphodiesterase inhibitors [46] and SHP2 inhibitors [47]. This scaffold is often a part of various organocatalysts [48]. Chen et al [49] synthesized benzothiazolopyrimidines through [4+2] cyclization of 2-benzothiazolimines and aldehydes [Scheme 23]. Chiral secondary amine was used as a catalyst. The products were obtained in high yields with excellent diastereo- and enantioselectivity. The reaction was suitable for a variety of 2-benzothiazolimines and aldehydes [Table 17].

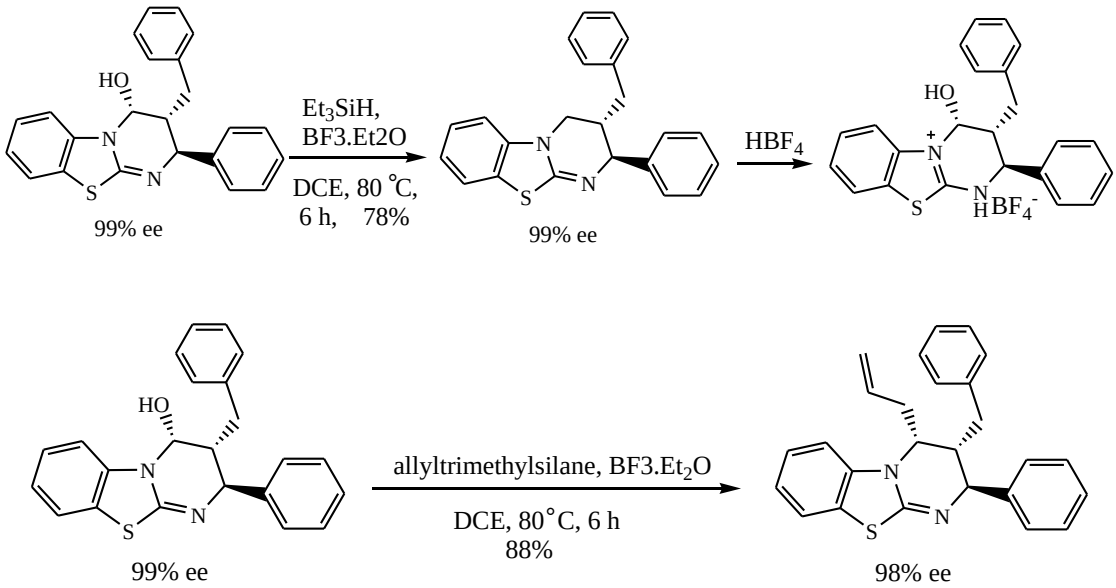


Scheme 23: Synthesis of benzothiazolopyrimidines

Table 17: Substrate scope for synthesis of benzothiazolopyrimidines

Entry	R^1	R^2	R^3	Ar	Yield	dr %	ee %
1.	F	H	Bn-	Ph-	98	14:1	93
2.	CH_3O-	H	Bn-	Ph-	97	19:1	98
3.	H	Cl	Bn	Ph	96	6:1	99
4.	H	H	Bn	Ph	97	20:1	97
5.	H	H	Bn	*p*-$CF_3C_6H_5$-	99	8:1	99
6.	H	H	Bn	*p*-OMeC6H5-	93	6:1	98
7.	H	H	Bn	*o*-FC_6H_5-	98	7:1	97
8.	H	H	^{n}Pr	Ph	90	19:1	98
9.	H	H	3-pyridyl	Ph	90	6:1	94

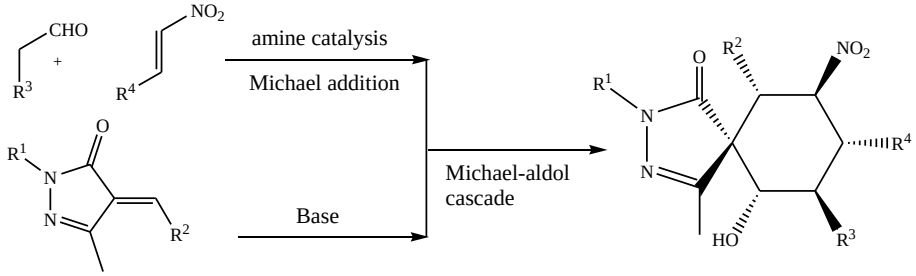
The products of the reaction were found to be easily convertible to other useful chiral building blocks [Scheme 24].



Scheme 24: Conversion of benzothiazolopyrimidines to useful chiral building blocks

5. **Construction of Organometallic Framework:** Organometallic frameworks have special importance in pharmaceuticals. Specifically, ferrocene skeleton which contain central metal ion with two coplanar cyclopentadienyl ligands, is widely used to synthesize

compounds with anti-parasitic, anti-bacterial and anti-tumour properties [50]. With a view to design anti-tumour drug molecule Zhang et al [51] conceived that a spirocyclicpyrazolone-ferrocene hybrid could easily enter into the cavity between helices α2 and α3 in the RaIA allosteric site. RaIA protein is often activated in human cancer cell lines. After entering inside the cavity, the desired therapeutic effects can be exerted by molecule containing ferrocene group. By using rational drug design authors synthesized chiral spirocyclic pyrazolone-ferrocene hybrids [Scheme 25] with multiple stereocentres in good yields and high diastereo- as well as enantioselectivity. These medicinally relevant scaffolds were synthesized via organocatalytic [2+2+2] annulation. Reaction was carried out with various substituents and one of these compounds (entry 8) exhibited the most potent RaIA inhibition. In pancreatic cell they induced mitochondrial injury and apoptosis. Entries for few compounds are given in table 18.



Scheme 25: Synthesis of chiral spirocyclic pyrazolone-ferrocene hybrids

Table 18: Substrate scope for synthesis of chiral spirocyclic pyrazolone-ferrocene hybrids

Entry	R^1	R^2	R^3	R^4	Yield%	dr	ee%
1.	Ph	Ferrocenyl	Me	Ph	65	>20:1	94
2.	2-ClC_6H_4	Ferrocenyl	Me	Ph	58	>20:1	93
3.	Ph	Ferrocenyl	Et	Ph	69	>20:1	95
4.	Ph	Ferrocenyl	Me	3-ClC_6H_4	63	>20:1	93
5.	Ph	Ferrocenyl	Me	4-ClC_6H_4	62	>20:1	97
6.	Ph	Ferrocenyl	Me	4-MeC_6H_4	70	>20:1	98
7.	Ph	Ph	Me	Ferrocenyl	54	86:14	94
8.	4-MeC_6H_4	Ph	Me	Ferrocenyl	64	>20:1	99
9.	Ph	3-ClC_6H_4	Me	Ferrocenyl	60	96:4	99
10.	Ph	4-ClC_6H_4	Me	Ferrocenyl	63	86:14	98
11.	Ph	2-FC_6H_4	Me	Ferrocenyl	55	93:7	96
12.	Ph	Thienyl	Me	Ferrocenyl	52	>20:1	99
13.	Ph	Ph	Et	Ferrocenyl	59	89:11	92

Reactions were successful with ferrocenyl moiety in any of the substrate other than aldehyde.

III. CONCLUSION

The organocatalysts have been used successfully for a wide range of reactions making a large number of building blocks and other useful chiral compounds. Some of these reactions are: aldol reaction, Michael addition, cycloaddition reactions, synthesis of polymers etc. Asymmetric synthesis using organocatalysts leads to the formation of stereoisomers with diverse biological activities, pharmacological activities and agrochemical activities. It can be concluded that organocatalysis has emerged as a versatile and powerful technique for asymmetric synthesis. Being metal free, non-toxic and easy to handle, it does not harm environment and thus fits within the realm of green chemistry.

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