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Chapter 4

Recent Advances in Guanidine-Based Organocatalysts in Stereoselective Organic Transformation Reactions

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Additional information is available at the end of the chapter

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Abstract

Tremendous efforts have been put toward the design and synthesis of newer enantioselective organocatalysts for the enanatioselective synthesis. Recently, guanidine-containing chiral organocatalysts have attracted considerable attention due to their ease of synthesis and high enantioselective catalytic activities. This chapter highlights the successive development of chiral guanidine organocatalysts in asymmetric organic transformation reactions in the past few decades.

Keywords: asymmetric organocatalysis, biologically active molecule, stereoselective organic transformation, guanidine group, asymmetric reactions

1. Introduction

Synthesis of enantiomerically pure molecules having multiple chiral centers is one of the ultimate goals in organic chemistry due to their importance in pharmaceutical science. It led to the development of stereospecific reactions, the most challenging fields in organic chemistry. As a result, asymmetric organocatalysts have become an interesting research field for chiral molecule synthesis. Small organic molecules have versatile functions such as efficient and selective catalytic properties that attribute toward their important roles in the construction of complex and enantiopure molecular skeletons [1].

Indeed, catalytic asymmetric inductions were successfully achieved in the second half of the twentieth century by employing transition metal catalysts [2]. Enantioselective C–C bonds and C–heteroatom bond formations have since been demonstrated by numerous research groups

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worldwide using the power of transition metals. Chiral ligands (organic molecule) form complexes with transition metals such as palladium, ruthenium, and rhodium that provide necessary chiral environment for an asymmetric induction. The versatility of transition metal complex was continually explored for the development of interesting methodologies in the chiral transformation reactions [3]. The quote "*Organic Synthesis—Where now?*" given by Professor Dieter Seebach, often cited from his famous review article, is so promising in the field of transition metal catalysis [4].

The experimental conditions for transition metal catalysts have been proved challenging despite the promising catalysts. One of the greatest challenges of transition metal catalysis is that such reactions required very stringent conditions such as rigorous Schlenk and degassing techniques or preparation and reaction in glove boxes. Moreover, these catalysts are often air and moisture sensitive which pose problems especially in their long-term storage and handling.

In the turn of twentieth century, the historical landmark in the field of asymmetric catalysis was witnessed with the onset of asymmetric organocatalysis. Chiral motifs bearing organic molecules derived from nature's chiral pool such as amino acids have been designed and used in catalytic amounts for enantioselective bond formation.

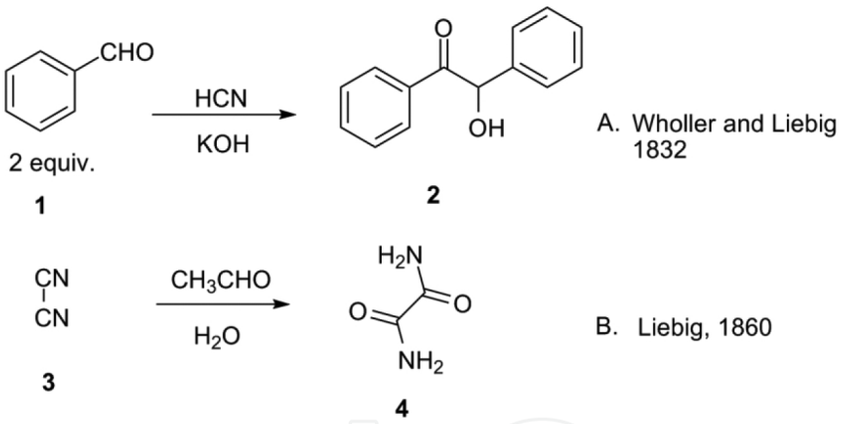


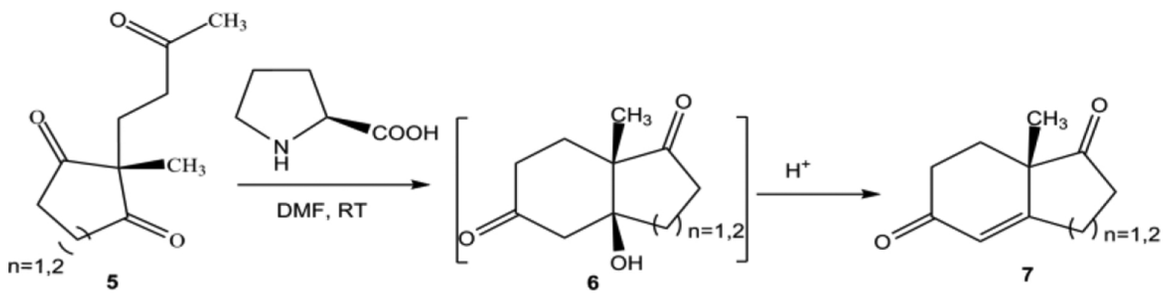
Figure 1. Organocatalyzed reactions.

Wohler and Liebig first time reported organocatalyzed Benzoin reaction [5] for the formation of the α-hydroxyl ketone in the presence of cyanide organocatalyst using two equivalents of benzaldehyde (**Figure 1A**). Liebig [6] in 1860 synthesized oxamide in the presence of acetaldehyde as organocatalyst from dicyn and water (**Figure 1B**). Another organocatalyzed reaction was the Knoevenagel condensation achieved by Emil Knoevenagel [7] in 1896 by reacting dimethyl malonate with benzaldehyde using piperidine as organocatalyst to generate the condensation product.

Subsequently, later in the turn of the twentieth century, some sporadic reports of organocatalytic reactions came up. Bredig and Fiske [8] used cinchona alkaloid as organocatalyst for asymmetric addition of HCN to benzaldehyde with low enantioselectivity (10%). Later, in 1960 Pracejus [9] reported chiral cinchona alkaloid-catalyzed methanolysis of a ketene with

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moderate enantioselectivity (74%). Pracejus used the German terminology "Organische Katalysatoren" which nowa days is used by scientists as the term "organocatalysis." Sheehan et al. [10] in 1966 first time used *N*-heterocyclic carbene as organocatalyst. The major breakthrough in the field of organocatalyst research field was seen in 1971 and 1974, when L-proline was used in the aldol condensation reaction with excellent enantioselectivity and this reaction is better known as Hajos-Parrish-Eder-Sauer-Wiechert reaction (**Scheme 1**) [11]. Subsequently, there was no activity in the organocatalysis research field in the next two decades despite the pioneering efforts by industrial chemists in organocatalysis. At the turn of the twenty-first century, List et al. [12] reinvestigated the asymmetric organocatalyzed intermolecular aldol reaction of the Hajos-Parrish-Eder-Sauer-Wiechert reaction.



Scheme 1. L-Proline organocatalyzed intramolecular aldol condensation reaction.

A variety of small organic molecules have since been employed as asymmetric organocatalysts such as proline [13], proline derivatives [14], cinchona derivatives [15], binapthol derivatives [16] (Marouka's catalyst), and guanidinium-based catalysts [17] in various chemical reactions. Moreover, lately sincere efforts have been made to design and synthesize newer organocatalysts having superior and effective properties in asymmetric organic transformation reactions. Here, we provide an overview on the recent developments in the field of guanidine-based catalysts and their ability to act as chiral catalysts in various chemical reactions.

Generally, organocatalysts can be subdivided into various categories based on their binding ability with the substrate through covalent bond, noncovalent interactions such as hydrogen bonding or electrostatic/ion pair interactions as shown in **Figure 2**.

In the first category, chiral organocatalyst forms covalent bond with an achiral substrate leading to a chiral transition complex including enamine and iminium activation. For such type of catalytic activation, proline and proline-derived secondary amines or cinchona alkaloid-derived primary amines have been widely used as asymmetric organocatalyst in many organic reactions. *N*-Heterocyclic carbene and phosphine-derived organocatalysts for stereoselective Morita-Baylis-Hillman or aza-Morita-Baylis-Hillman type reactions using covalent bond forming activation are well documented [18]. The second category includes asymmetric organocatalyst that forms H-bond with an achiral substrate resulting in a chiral transition state. The example includes Brønsted acid catalysts such as derived phosphoric acids, phosphoryl triflylamides, thiourea, and squaramide which form H-bond with the

substrate through activation [19]. The last category includes electrostatic interactions between chiral organocatalyst and achiral substrate for an active chiral transition state. List et al. developed newer concept involving asymmetric counteranion-directed catalysis (ACDC) for the activation mode where a chiral counteranion formed an enantioselective product through an activated transition state [20]. Here, chiral ammonium salts or other protonated bifunctional catalysts such as thioamide or guanidinium catalysts were used as chiral countercations and these are also called phase-transfer catalysts.

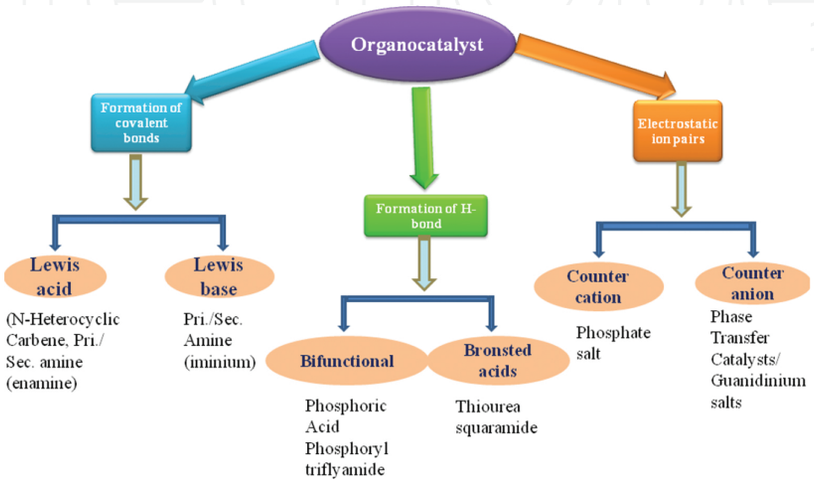


Figure 2. General classification of organocatalysts based on their activation mode.

2. Guanidine-based asymmetric organocatalysis

Guanidine, discovered over 150 years ago, is well recognized as a very strong base (superbase). Useful chemical functionalities are shown by guanidine and their corresponding salts. Free guanidine displays dual behavior, Brønsted basicity, as well as hydrogen bond donating and accepting abilities [21]. While guanidinium salts show weak Brønsted acidity, cationic hydrogen bond donating capability and the possibility of delocalizing guanidinium cationic π-Lewis acids are shown in **Figure 3**.

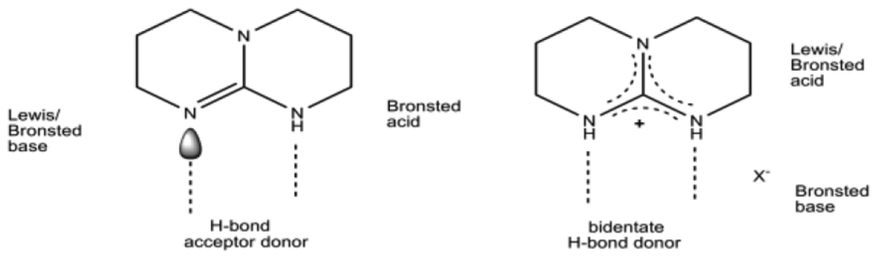


Figure 3. Guanidine as a Brønsted base as well as a hydrogen bond donor/acceptor.

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Despite the diverse functionalities present in the guanidine group, its synthesis for newer organocatalytic applications of guanidine is a relatively new research area in chiral compound synthesis. Structurally, guanidine organocatalysts can be classified into several categories such as open chain **8**, monocyclic **9**, and bicyclic **10** structures as shown in **Figure 4**.

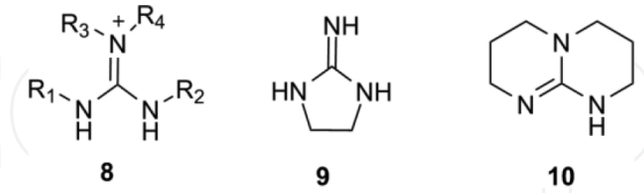
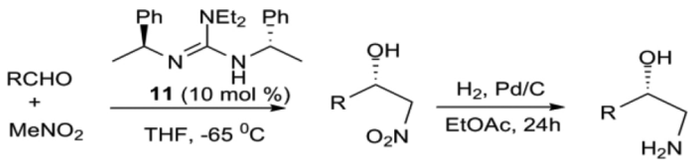


Figure 4. Structures of bicyclic, monocyclic, and open-chain guanidine scaffolds.

The guanidine and guanidinium salts possess similar features as urea and thiourea, such as dual hydrogen bonding, which is a key interaction in the electrophilic activation as well as transition state organization. Najera et al. for the first time used open chain guanidine **11** in the early 1990s for enantioselective organocatalyzed Henry reaction [22], affording amino alcohols up to 54% ee (**Scheme 2**).



Scheme 2. Open chain guanidinium **11** organocatalyzed Henry reaction.

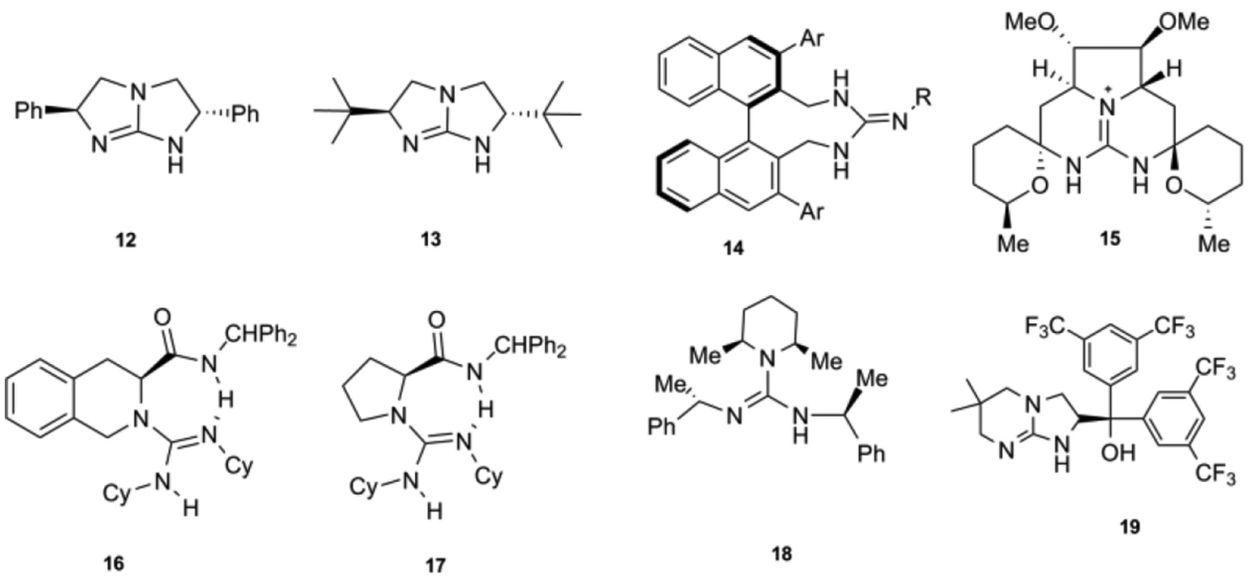


Figure 5. Guanidine-containing asymmetric organocatalysts.

Later in 1999, Lipton et al. reported cyclic dipeptide organocatalyzed highly enantioselective Strecker reaction using 10 mol% of organocatalyst [23]. Further, Corey and Grogan repeated the Strecker reaction using bicyclic guanidinium chiral organocatalyst [24]. Nagasawa et al. used pentacyclic guanidine organocatalyst **15** for the enantioselective alkylation reactions [25]. Tan et al. reported bicyclic guanidine to catalyze stereoselective alkylation and Michael reactions [26]. Subsequently, several chiral guanidinium organocatalyst were used for stereoselective organic transformation reactions.

Some of the well-documented guanidine-based asymmetric organocatalysts are shown in **Figure 5**.

3. Applications of asymmetric organocatalysts

Asymmetric organocatalysis is recognized as an independent synthetic toolbox in addition to asymmetric metallic and enzymatic catalysis for the synthesis of chiral molecules (**Figure 6**).

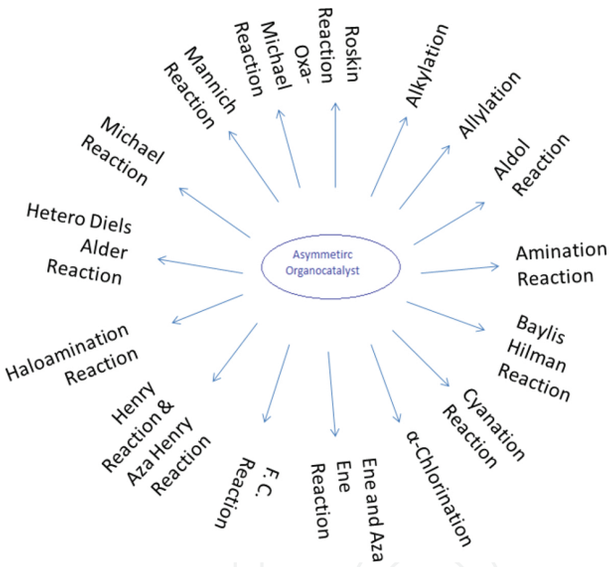


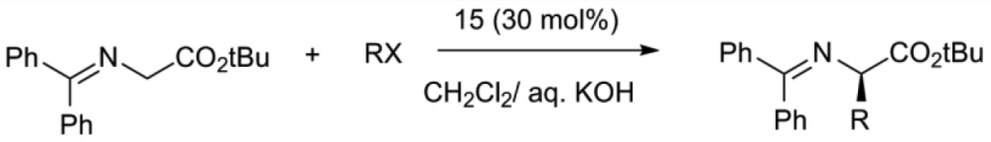
Figure 6. Application of asymmetric organocatalysis in various stereoselective organic transformation reactions.

In the present chapter, we have focused on the enantioselective reactions catalyzed by chiral guanidinium and their salts.

3.1. Asymmetric alkylation

Asymmetric alkylation by phase-transfer catalyst is a well-established approach. Nagasawa et al. designed pentacyclic guanidinium salts for the enantioselective alkylation of glycinate Schiff base [25]. Glycinate Schiff base underwent alkylation reaction with various alkyl halides under phase-transfer conditions in the presence of guanidinium salt **15** (**Table 1**). It was proposed that the spiro ether rings determined the configuration of the newly formed chiral center. The methyl group of the spiro ether ring played a crucial role in the enantioselectivity.

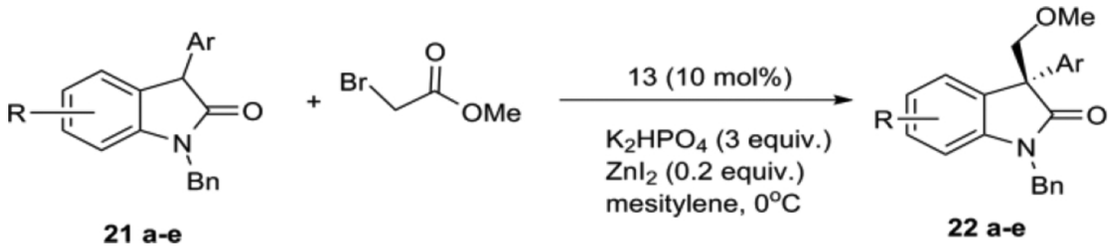
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Entry	RX	Product	*t* (h)	Yield (%)	ee (%)
1	BnBr	20a	160	55	90
2	MeI	20b	145	80	76
3	OctI	20c	145	83	80
4	CH_2=$CHCH_2Br$	20d	140	61	81
5	CH_2=$C(Me)CH_2Br$	20e	145	85	81

ee = enantiomeric excess.

Table 1. Pentacyclic guanidinium **15** catalyzed asymmetric alkylation reaction with various alkyl halides.



Entry	*t* (h)	21 (*R*, Ar)	Yield (%)	ee (%)
1	44	21a (5-F, Ph)	98	94
2	37	21b (5-Cl, Ph)	99	94
3	51	21c (5-Br, Ph)	99	93
4	59	21d (5-Me, Ph)	96	93
5	63	21e (MeO, Ph)	90	93

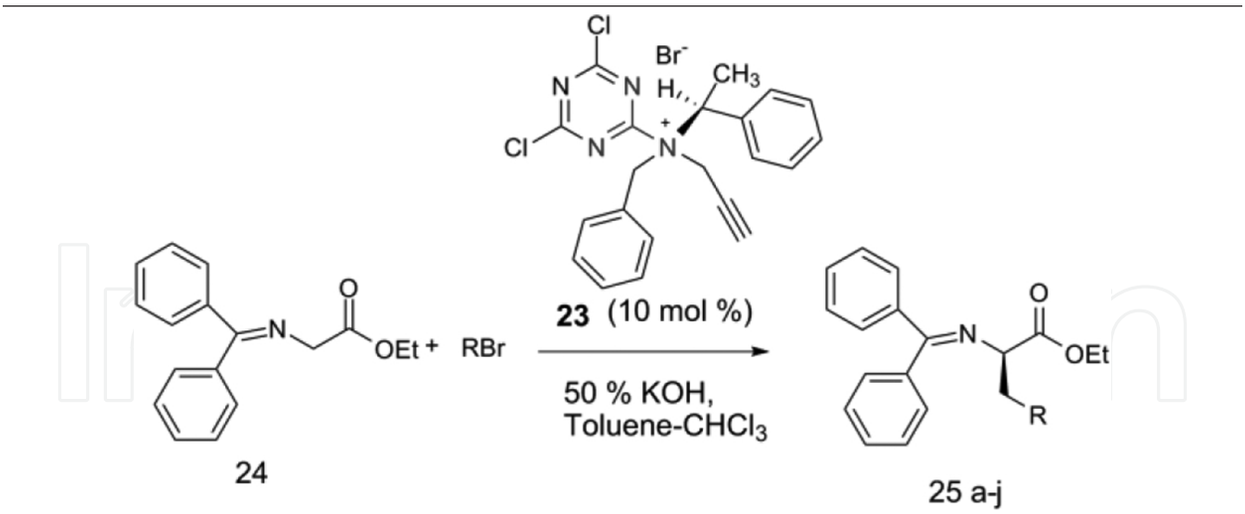
ee = enantiomeric excess.

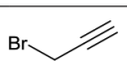
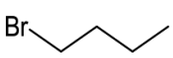
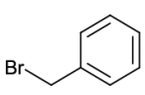
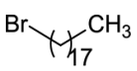
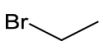
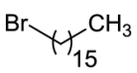
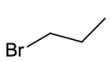
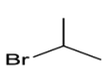
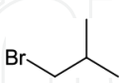
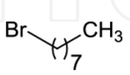
Table 2. Alkylation of 3-substituted 2-oxiindoles using activated bromomethanes.

Tan et al. used bicyclic guanidinium **13** as chiral phase-transfer catalyst [27] for enantioselective alkylation of 3-substituted 2-oxiindoles shown in **Table 2**.

The position and electronic properties of the substituents on the para- and meta-positions of aromatic ring at the C-3 position of 3-aryl-2-oxindoles did not affect the enantioselectivity.

Guanidine containing *s*-triazene asymmetric organocatalyst has been synthesized and used for asymmetric alkylations [28] as shown in **Table 3**.



Entry	Electrophile (RBr)	Product	*t* (h)	Yield (%)	ee (%)
1		25a	3.5	75	95
2		25b	3.5	85	89
3		25c	4.5	90	82
4		25d	6.0	67	81
5		25e	4.5	55	75
6		25f	5.5	85	85
7		25g	5.5	80	77
8		25h	4.5	76	68
9		25i	4.5	90	83
10		25j	4.5	85	90

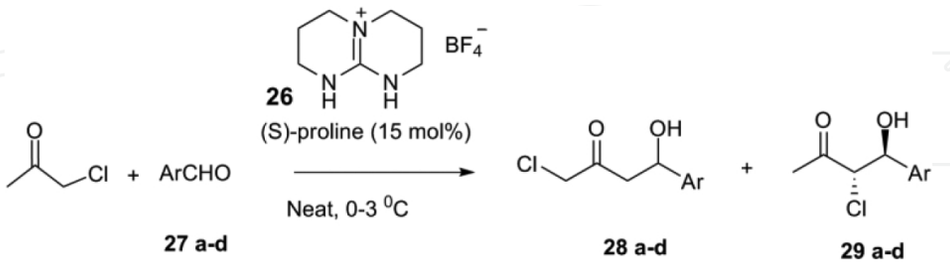
ee = enantiomeric excess.

Table 3. Alkylation of glycinate Schiff base using s-triazene based asymmetric organocatalyst.

3.2. Asymmetric aldol reaction

List et al. reported enantioselective intermolecular aldol reaction using proline organocatalyst [17]. In these years, hundreds of research articles were published on the stereoselective

aldol reactions using various asymmetric organocatalysts. Moreover, *l*-proline and guanidine salts as cocatalysts were also used for enantioselective aldol reaction [29] using various aldehydes 42 a-k, which reacted with chloroacetone (**Table 4**, Entries 1–5) smoothly, with good yield and high regio-, diastereo-, and enantioselectivity.



Entry	ArCHO		Conversion	Regioselectivity	d.r. (%)	ee (%)
1	27a	4-NO_2–C_6H_4	99	96:4	91:9	98
2	27a	4-NO_2–C_6H_4	99	99:1	83:17	95
3	27b	3-NO_2–C_6H_4	97	96:4	92:8	97
4	27c	2-NO_2–C_6H_4	98	>99:1	93:7	97
5	27d	4-CO_2Me–C_6H_4	96	99:1	91:9	97

[a]d.r. = distereomeric ratio; ee = enantiomeric excess.

Table 4. Synthesis of chlorohydrins using (S)-proline/guanidine salt as cocatalyst.

3.3. Asymmetric epoxidation

Taylor et al. investigated the asymmetric epoxidation [30] reaction using chiral guanidines 30 a–c (**Figure 7**).

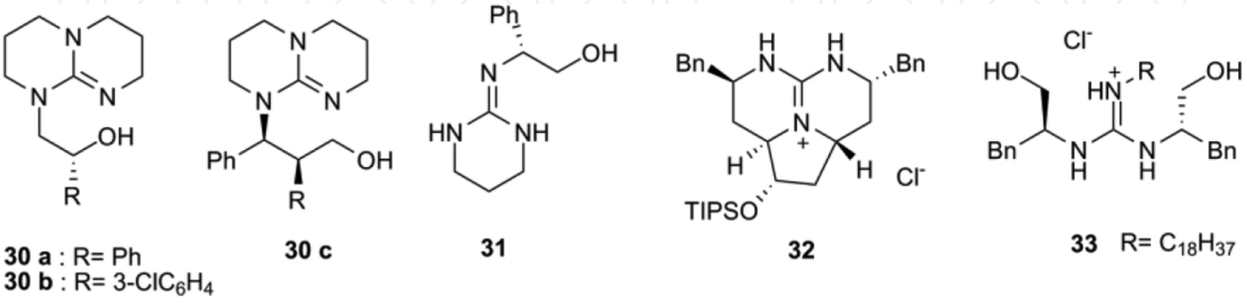
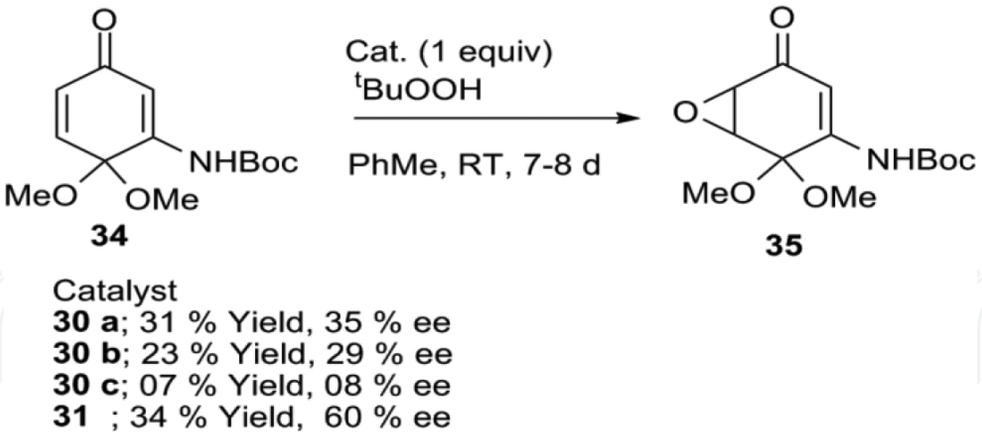


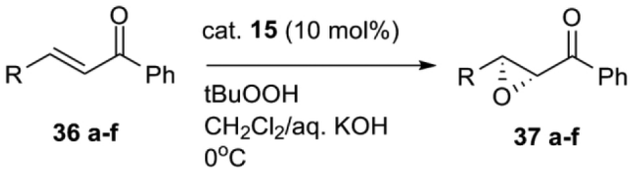
Figure 7. Structure of guanidine catalyst for asymmetric epoxidation.

Epoxide of amidoquinone analogs were obtained in poor-to-moderate ee using the stoichiometric amounts of these guanidine-based chiral organocatalysts (**Scheme 3**).



Scheme 3. Asymmetric epoxidation of amidoquinone using various chiral guanidine organocatalysts.

Acyclic guanidine **31** when used in stoichiometric amount shows better ee (60%) in comparison to cyclic guanidines (30a–c). Epoxidation of trans-chalcone and 2-methyl-napthoquinone with chiral guanidine was also carried out. Good yields were obtained but the ee were very poor [31].



Entry	*R*	*t* (h)	Yield (%)	ee (%)
1	Ph	110	35	39
2	2-naphthyl	140	51	50
3	1-naphthyl	140	77	60
4	9-anthracenyl	140	>99	35
5	4-NO_2 C_6H_4	130	82	38
6	4-$MeOC_6H_4$	160	22	36

ee = enantiomeric excess.

Table 5. Asymmetric epoxidation reactions of various chalcones with pentacyclic guanidinium salt 15.

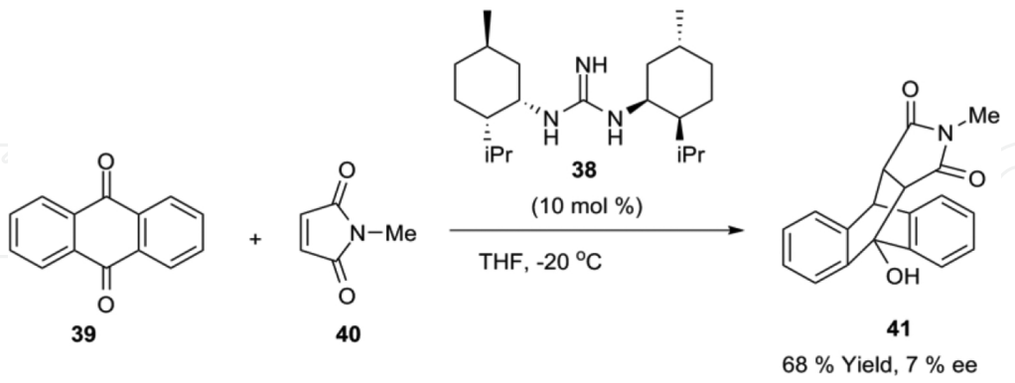
Nagasawa et al. used pentacyclic guanidine salt **15** as phase-transfer catalyst for the epoxidation of chalcones [32] up to 60% ee ratio (**Table 5**).

3.4. Asymmetric Diels-Alder reaction

Enantioselective cycloaddition is a large area of research catalyzed by Lewis acids [33]. However, the base catalyzed stereoselective Diels-Alder reaction has remained largely

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unexplored. Ma et al. used chiral guanidines **38** as asymmetric organocatalyst for the cycloaddition reaction of anthrone and methyl maleimide (**Scheme 4**) [34].

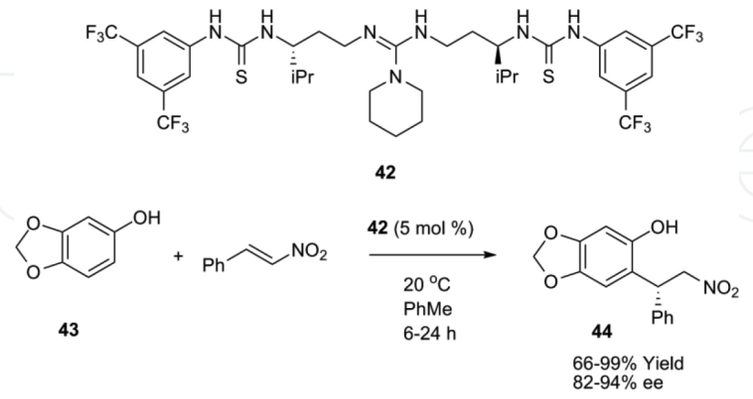


Scheme 4. Diels-Alder reaction between anthrone and methyl maleimide.

Tan et al. describe a highly enantioselective guanidine catalyzed Diels-Alder reaction between anthrones and activated olefins [35].

3.5. Asymmetric Friedel-Craft reaction

Friedel-Craft alkylation has been widely used for the synthesis of relevant and promising biological entities [36]. Despite the aromatic substitution reactions, catalytic and asymmetric versions of Friedel-Craft reactions have been described in the mid 1980s. Recently, chiral organocatalysts such as imidazolidinone, cinchona alkaloids, diaryl prolinol derivatives, phosphoric acids, thiourea-mediated and guanidine-based catalysts have become more popular for these transformations.



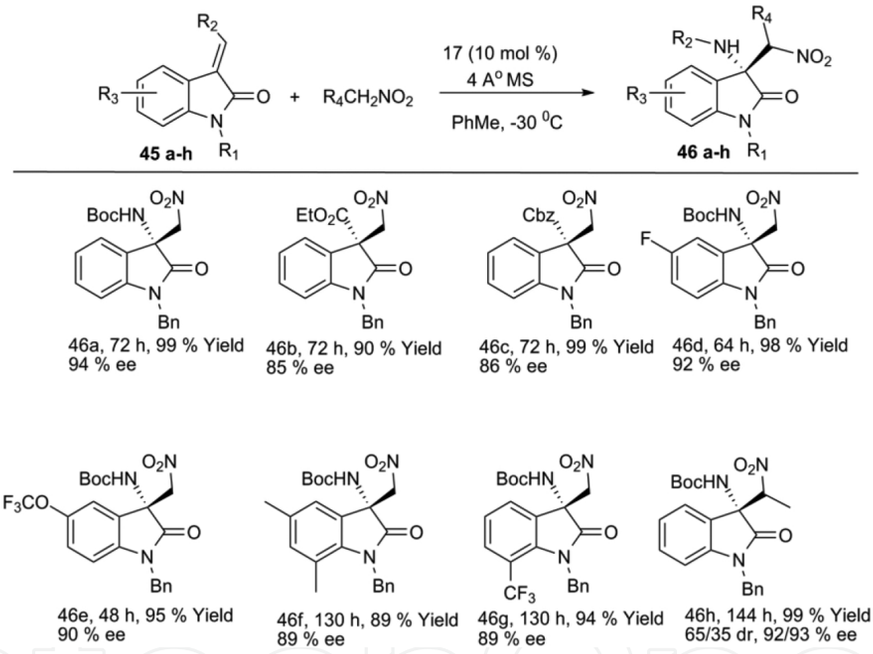
Scheme 5. Chiral organocatalyzed 1,4-type Friedel-Craft reaction of phenols.

Nagasawa et al. present conformationally flexible stereoselective guanidine/bisthiourea organocatalysts for chemo-, regio-, and enantioselective 1,4-type Friedel-Craft reaction of phenols as shown in **Scheme 5** [37].

3.6. Asymmetric Henry reaction

The Henry reaction (nitro-aldol) is one of the oldest C–C bond formation reactions in organic synthesis. Shibasaki et al. in 1992 for the first time reported the asymmetric version of the Henry reaction [38]. Later, Najera et al. in 1994 used guanidine organocatalyst for the enantioselective Henry reaction [22]. Since then, various newer guanidine-based chiral organocatalysts for the asymmetric Henry reaction have been developed. Some bifunctional acyclic/cyclic and bisguanidine catalysts were also designed for stereoselective Henry reaction (**Figure 5**).

Nagasawa et al. used effective linear guanidine-thiourea-based bifunctional catalyst 14 for an enantio- as well as diastereoselective Henry reaction [39]. Chiral guanidine-amide organocatalyst **17** has been used for an efficient asymmetric aza-Henry reaction [40] of isatin-derived ketimines (**Scheme 6**).



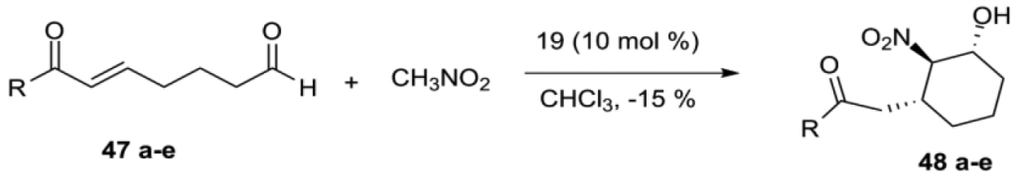
Scheme 6. Organocatalyst **17** catalyze aza-Henry reaction.

Ma et al. studied the diastereoselective Henry reactions [41] of α-aminoaldehyde with nitromethane using open-chain chiral guanidine organocatalyst.

Murphy and coworkers used tetracyclic guanidinium salt for the Henry reaction of nitromethane and isovaleraldehyde with 20% enantioselectivity [42].

Recently, Zhao and coworkers developed a new protocol for the highly stereoselective tandem Henry-Michael reaction using Misaki-Sugimura guanidine catalyst **19** to synthesize trisubstituted cyclohexanols [43]. Using the optimized reaction conditions, the desired trisubstituted cyclohexanols obtained in both high enantioselectivities and diastereoselectivities are shown in **Table 6**.

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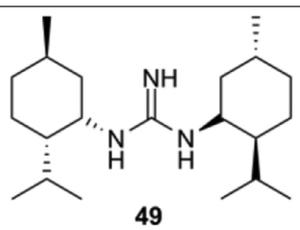
47 a-e

48 a-e

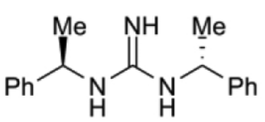
Entry	R	Product	Yield (%)	d.r. (%)	ee (%)
1	Ph	48a	99	>99:1	98
2	4-FC_6H_4	48b	98	>99:1	96
3	4-ClC_6H_4	48c	95	>99:1	96
4	4-BrC_6H_4	48d	99	>99:1	97
5	4-CNC_6H_4	48e	98	>99:1	98

d.r.= diastereomeric ratio; ee = enantiomeric excess.

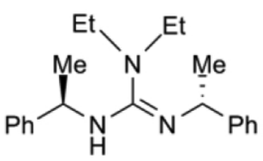
Table 6. Misaki-Sugimura guanidine 19 catalyzed tandem Henry-Michael reaction.



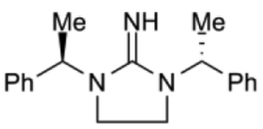
49



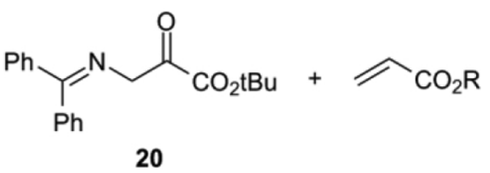
50



51



52



20

53 a-f

Entry	Catalyst	R	Product	Yield (%)	ee (%)
1	49	Et	53a	99	30
2	50	Et	53b	95	6
3	52	Et	53c	97	17
4	51	Et	53d	85	26
5	49	Me	53e	95	16
6	49	tBu	53f	98	30

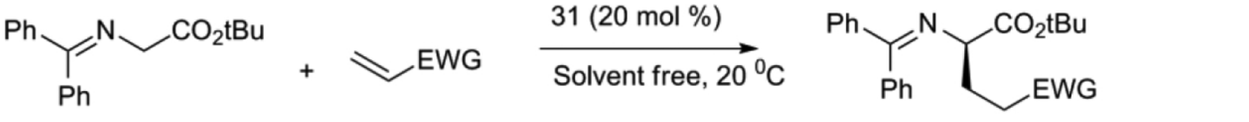
ee = enantiomeric excess.

Table 7. Asymmetric conjugate additions of glycinate to various acrylates using various organocatalysts.

3.7. Asymmetric Michael reaction

Michael reaction is the most common approach toward C–C or C–X bond formation via conjugate addition of nucleophiles to electron-deficient alkenes [44]. Michael reaction between glycinate and ethyl acrylate was described by Ma et al. using chiral guanidine organocatalysts (**Table 7**) [34a].

Chiral guanidine catalyst **49** was also used for the enantioselective synthesis of the core structure of (−)-huperzine **A** by the Michael-aldol annulations reaction [34b]. Ishikawa et al. catalyzed the enantioselective Michael reaction of glycinate with various Michael acceptors using the chiral guanidine organocatalyst **31** under solvent-free condition affording excellent enantiomeric excess (**Scheme 7**) [45].



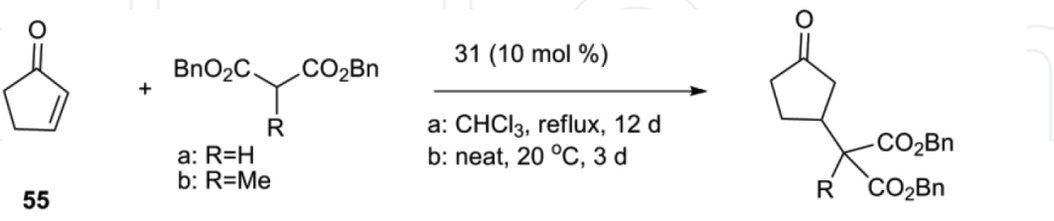
54a, EWG= CO_2Et, 85 % Yield, 97 % ee

54b, EWG= CO_2Me, 98 % Yield, 93 % ee

54c, EWG= CO_2CN, 79% Yield, 55 % ee

Scheme 7. Enantioselective conjugate addition reaction of glycinate with various Michael acceptors.

Ishikawa et al. also attempted the Michael reaction [46] of 2-cyclo-penten-1-one with dibenzyl malonate using the same guanidine organocatalyst **31** (**Scheme 8**).



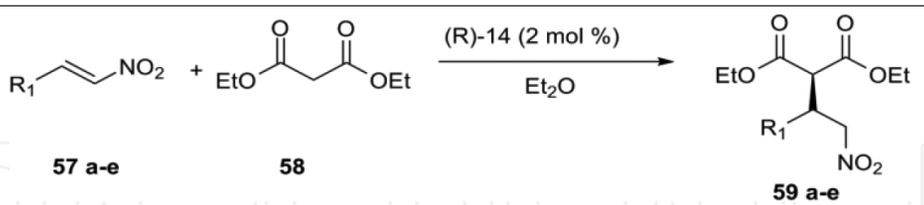
56a: 65 % yield, 43 % ee
56b: 82 % yield, 40 % ee

Scheme 8. Michael reactions between cyclo-penten-1-one and dibenzyl malonate using the guanidine organocatalyst **31**.

Terada et al. developed axially chiral guanidine organocatalyst **14** that facilitates the highly enantioselective 1,4-Michael reaction with 1,3-dicarbonyl compounds [47] as shown in

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Table 8. Michael conjugated products provide various types of optically active nitroalkane derivatives of synthetic and biological importance.



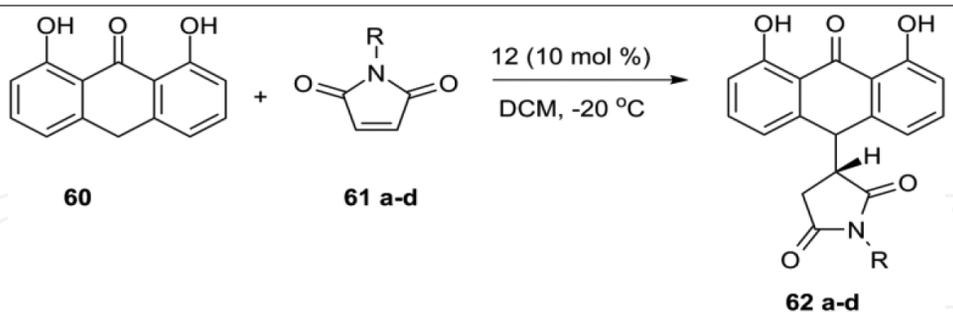
57 a-e 58 59 a-e

Entry	R_1	Product	*t* (h)	Yield (%)	ee (%)
1	2-$MeOC_6H_4$–	59a	2	98	97
2	2-BrC_6H_4–	59b	2	>99	98
3	2-$NO_2C_6H_4$–	59c	4	86	91
4	3-$MeOC_6H_4$–	59d	2	94	94
5	3-BrC_6H_4–	59e	2	90	95

ee = enantiomeric excess.

Table 8. 1,4-Michael reaction of various conjugate reactions with diethyl malonate using organocatalyst **14**.

Linton et al. designed pentapeptide organocatalyst incorporated with arginine for the Michael reaction of nitrocarbonyl compounds [48]. Tan et al. used guanidine organocatalyst **12** for the Michael reaction between anthrone **60** and maleimides **61 (a–d**) to obtained cycloadducts **62 (a–d)** in excellent yields and enantioselectivities (**Table 9**) [35a, 49].



60 61 a-d 62 a-d

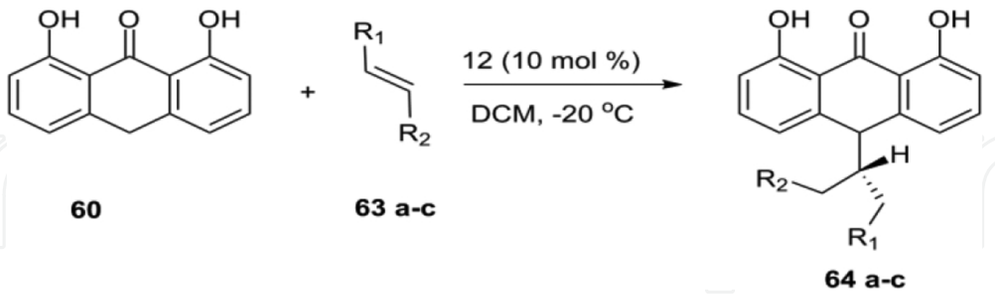
–

Entry	R	Product	*t* (h)	Yield (%)	ee (%)
1	Ph	62 a	7	80	99
2	2-$NO_2C_6H_4$	62 b	8	87	97
3	3,4-$Cl_2C_6H_3$	62 c	8	89	98
4	Bn	62 d	8	86	93

ee = enantiomeric excess.

Table 9. Bicyclic guanidine organocatalyst 12 catalyzed enantioselective Michael reaction.

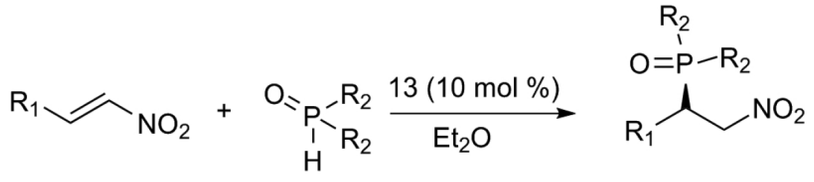
Bicyclic guanidine organocatalyst **12** worked well with maleimide (**Table 9**) and other activated olefins (**Table 10**) with excellent enantioselectivities and regioselectivities.



Entry	R_1	R_2	Product	*t* (h)	Yield (%)	ee (%)
1	CO_2Me	PhCO	64 a	6	92	98
2	CO_2Et	MeCO	64 b	7	92	95
3	CN	CN	64 c	7	90	94

ee = enantiomeric excess.

Table 10. Asymmetric Michael reaction of anthrone and activated olefins using chiral organocatalyst **12**.



Entry	R_1	R_2	*T* (°C)	*t* (h)	Yield (%)	ee (%)[a]
1	Ph	Ph	0	13	64	60 (96)
2	Ph	4-FC_6H_4	0	14	92	60 (>99)
3	Ph	4-PhC_6H_4	0	40	85	50 (91)
4	Ph	2-EtC_6H_4	−40	40	77	75
5	Ph	2-naphthyl	0	6	92	65 (99)

ee = enantiomeric excess.
[a]ee values obtained after single recrystallization.

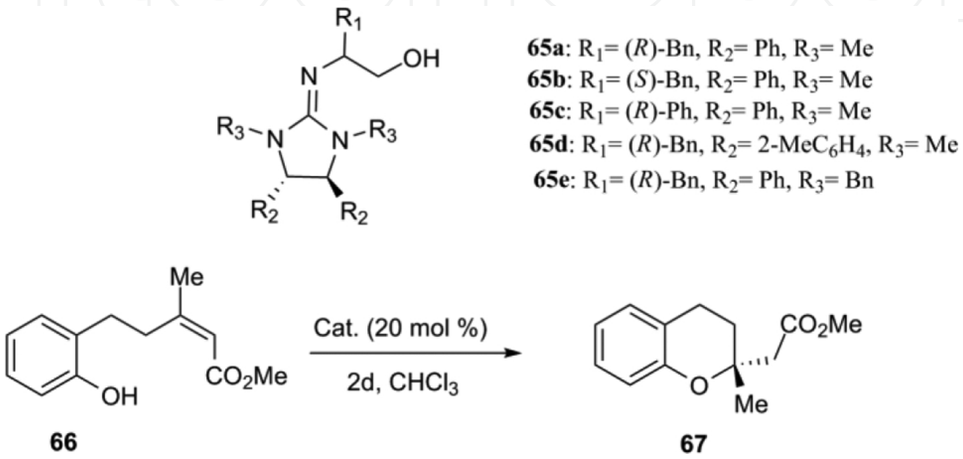
Table 11. Phospha Michael reaction of various diaryl phosphine oxide and nitroalkenes using bicyclic guanidine organocatalyst 13.

Tan et al. used chiral bicyclic guanidine organocatalyst for the phospha-Michael reaction of nitroalkenes (**Table 11**) [50]. Various nitroalkenes with di-(1-naphthyl) phosphine oxide at −40°C gave excellent enantioselectivities.

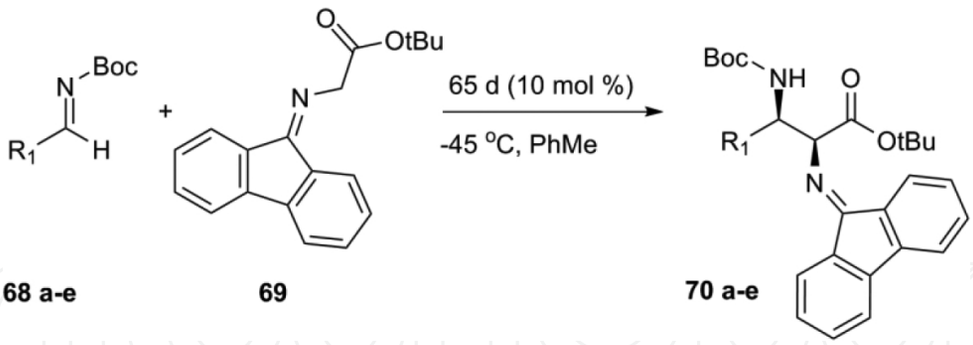
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Terada et al. demonstrated that axially chiral binaphthyl organocatalyst **14** (Ar = 3,5-di-$tBuC_6H_4$; R = Bn) can used for the phospha-Michael reaction of diphenyl phosphite to nitroalkenes with high enantioselectivities [51].

Ishikawa et al. investigated the 6-exo-trig intramolecular oxa-Michael cyclization reaction for the chiral chromane **67** synthesis using guanidine organocatalyst [52] **65** as per **Scheme 9**. The E/Z geometry of the α, β unsaturated ester played a crucial role in the enantiomeric excess determination of chromane moiety.



Scheme 9. Intramolecular oxa-Michael cyclization reaction of the chiral chromane synthesis.



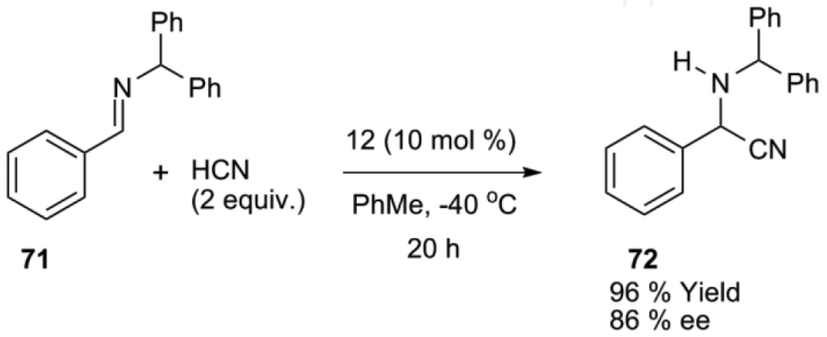
Entry	R_1	Product	*t* (h)	Yield (%)	Syn:Anti	ee (%)
1	Ph	70 a	12	>99	>99:1	96
2	4-$MeOC_6H_4$	70 b	48	76	36:1	90
3	2-furyl	70 c	36	88	9:1	98
4	$Ph(CH_2)_2$	70 d	24	87	29:1	92
5	*c*-C_6H_{11}	70 e	48	84	11:1	96

ee = enantiomeric excess.

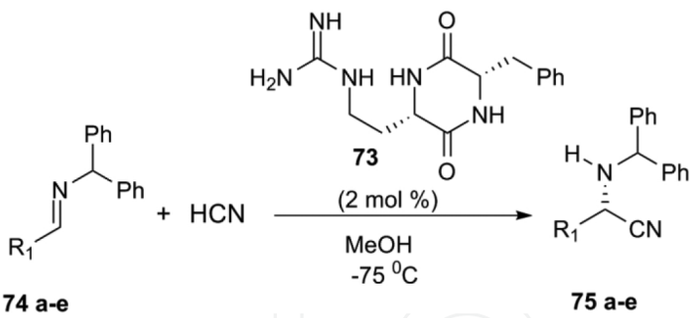
Table 12. Enantioselective Mannich reactions of various *N*-Boc protected imines using guanidine organocatalyst 65 d.

3.8. Asymmetric Mannich reaction

The asymmetric Mannich reaction ranks among the most potent enantioselective and diastereoselective C–C bond forming reactions to obtain chiral β-aminocarbonyl compounds from imines. Asymmetric organocatalytic reactions had been successfully developed for the well-known Mannich reaction in particular. In the Mannich reaction, a key species, an iminium intermediate is formed which is susceptible to nucleophilic attack. Recently, Kobayashi et al. [53] reported the Mannich reaction of fluorenone imine of glycine ester and its phosphonic acid analogs using the guanidine organocatalyst **65d** (**Table 12**).



Scheme 10. Strecker reaction using bicyclic guanidine organocatalyst **12**.



Entry	R_1	Product	Yield (%)	ee (%)
1	Ph	75 a	97	>99
2	4-ClC_6H_4	75 b	94	>99
3	4-$MeOC_6H_4$	75 c	90	96
4	3-ClC_6H_4	75 d	80	>99
5	3-$MeOC_6H_4$	75 e	82	80

ee = enantiomeric excess.

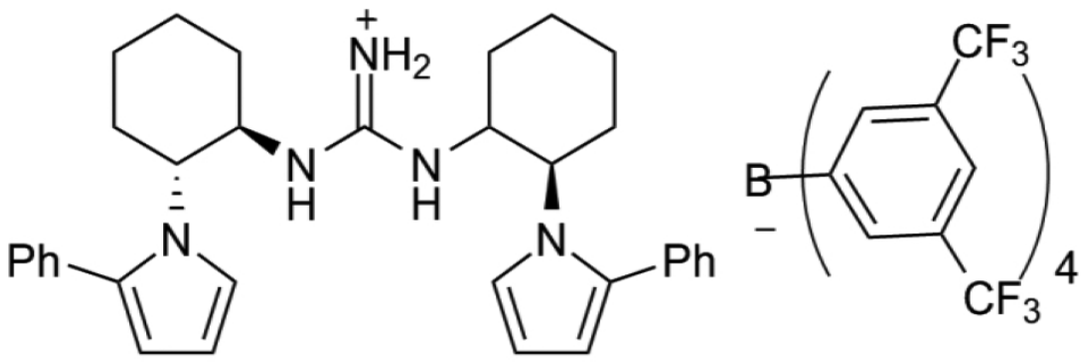
Table 13. Asymmetric Strecker of *N*-benzhydryl imines catalyzed by dipeptide organocatalyst **73**.

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3.9. Asymmetric Strecker reaction

Strecker reaction is an excellent way for the synthesis of α-amino acids [54]. Lipton group in 1996 for the first time reported the asymmetric version of the Strecker reaction [23]. In addition, the metal-catalyzed asymmetric cynation and chiral organocatalytic process had been used for the enantioselective Strecker reaction. Interestingly, chiral organocatalyst possess high catalytic properties for the hydrocynation reaction. Corey group used chiral bicyclic guanidine as an efficient catalyst in the asymmetric addition of hydrogen cyanide to imine [24]. The hydrocynation of the benzaldehyde-derived imine gave the corresponding (*R*)-amino nitrile in 96% yield and high enantiomeric excess (86%) using 10 mol% of bicyclic guanidine organocatalyst **12** shown in **Scheme 10**.

Lipton et al. used guanidine-based dipeptide organocatalyst **73** for the stereoselective Strecker reaction (**Table 13**) [23]. Further, the replacement of the guanidine functional group of the organocatalyst **73** with an imidazole ring failed to achieve any enantioselectivity. It confirms that the guanidine group plays a crucial role in enantioselectivity determination.



76

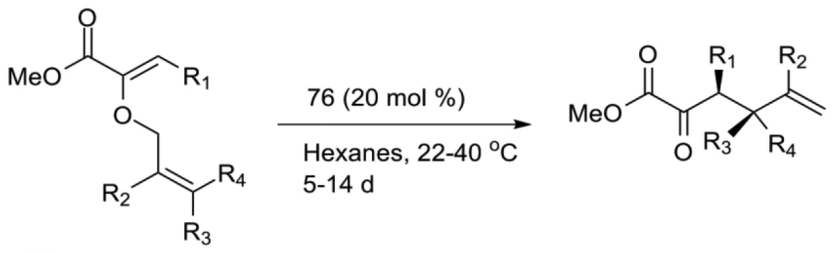
Figure 8. C_2-Symmetric guanidinium salt **76** for Claisen rearrangement.

3.10. Asymmetric Claisen rearrangement

Rainer Ludwig Claisen discovered [3, 3]-sigmatropic rearrangement of allyl vinyl ethers which led to one of the most powerful C–C bond forming reactions [55]. Jacobsen and coworkers used catalytic amount of the C_2-symmetric guanidinium salt **76** for the asymmetric Claisen rearrangement (**Figure 8**) [56] and obtained greater enantioselectivity with high yield (**Table 14**).

3.11. Asymmetric reduction reaction

Basavaih et al. reported the borane-mediated asymmetric reduction of phenacyl bromide using the chiral guanidine organocatalyst **79** [57]. When the reaction was carried out at room temperature, it gave *R*-configured alcohol with 37% ee, while under reflux condition, the *S* alcohol was obtained with improvement in ee value to 83% (**Scheme 11**).

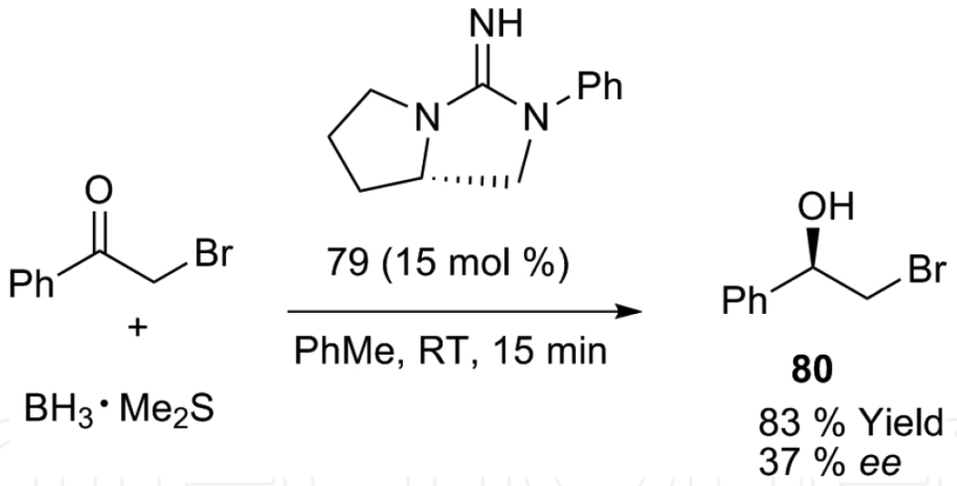


77 a-e 78 a-e

Entry	R_1	R_2	R_3	R_4	Product	Yield (%)	ee (%)
1	Me	H	H	H	78 a	80	92
2	Et	H	H	H	78 b	86	92
3	Et	H	H	*n*Pr	78 c	92	85
4	Et	H	H	Ph	78 d	91	81
5	Me	Me	H	H	78 e	73	96

ee = enantiomeric excess.

Table 14. Guanidine salt **76** catalyzed enantioselective Claisen rearrangement.

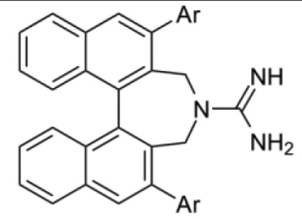


Scheme 11. Asymmetric reduction of phenylacyl bromide using chiral guanidine organocatalyst **79**.

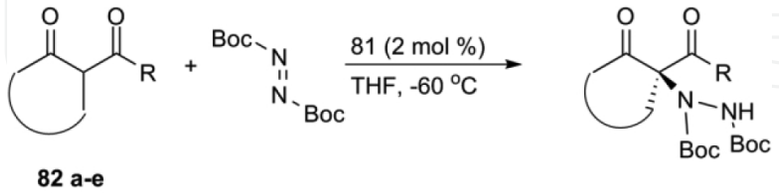
3.12. Asymmetric amination reaction

Asymmetric electrophilic amination reaction of 1,3-dicarbonyl compounds was achieved by Terada et al. with a C_2-symmetrical axially chiral guanidine organocatalyst **81** which has a seven-membered ring structure [58]. The reaction was conducted using 2 mol% catalyst loading with di-*tert*-butyl azidocarboxylate at –60°C temperature. Bulkiness of the azidocarboxylate played a crucial role in the enantioselectivity. The scope of the reaction is shown in **Table 15** with the optimal reaction conditions.

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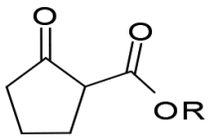
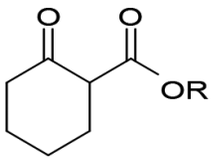
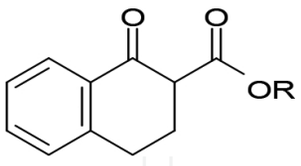
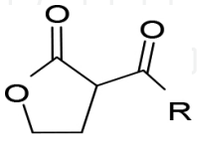
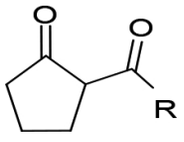


81, Ar= 4-(3,5-di-*t*BuC$_6$H$_3$)C$_6$H$_4$



82 a-e

83 a-e

Entry	Reactant	R	Product	*t* (h)	Yield (%)	ee (%)
1		–CH_2CH_3	83 a	4	>99	97
2		–CH_2CH_3	83 b	24	>99	98
3		–CH_2CH_3	83 c	1	>99	97
4		–CH_3	83 d	24	>99	15
5		–CH_3	83 e	5	99	91

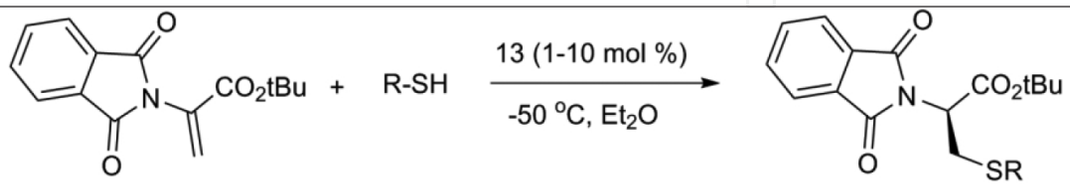
ee = enantiomeric excess.

Table 15. Asymmetric electrophilic amination reactions of various 1,3-dicarbonyl ketones.

4. Other important reactions using chiral guanidine organocatalyst

4.1. Asymmetric protonation reaction

Protonation reaction is a direct approach for the preparation of carbonyl compounds with a stereogenic center of enolates. A transient enolate is first generated through a conjugate addition reaction, followed by an in situ enantioselective protonation reaction. Tan et al. investigated the protonation of 2-phthalimidoacrylate **84** with thiophenols and obtained a series of arylthiols **85** with excellent yields and enantioselectivities (**Table 16**) [59].

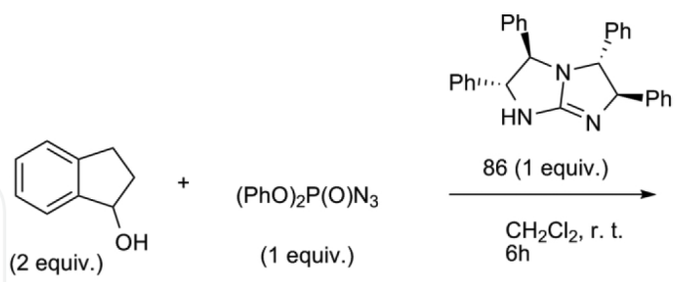


84 **85 a-e**

Entry	R	20 (mol %)	Product	*t* (h)	Yield	ee (%)
1	Ph	10	85 a	0.5	99	90
2	2-$CF_3C_6H_4$	10	85 b	3	99	93
3	2-$MeO_2CC_6H_4$	10	85 c	2.5	98	90
4	4-BrC_6H_4	10	85 d	4	99	90
5	4-*t*BuC_6H_4	10	85 e	3	92	93

ee = enantiomeric excess.

Table 16. Enantioselective protonations of 2-phthalimidoacrylate using the bicyclic guanidine organocatalyst **13**.



87 **88** **89**

Scheme 12. Guanidine catalyst **86** mediated asymmetric azidation reaction of 1-indanol.

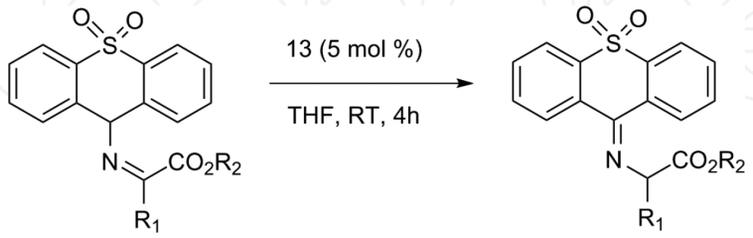
4.2. Asymmetric azidation reaction

Ishikawa et al. used bicyclic guanidine catalyst for the asymmetric azidation reaction of 1-indanol in the 30% ee with diphenylphosphoryl azide (**Scheme 12**) [60]. Excess *R* isomer was produced with the use of C_2-symmetric bicyclic guanidine catalyst 86 in the 58% yield and 30% ee.

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4.3. Asymmetric transamination reaction

Transamination process is a (1,3) proton-transfer reaction using imines which plays an important role in the biological systems for the production of amino acids. Berg and coworkers catalyzes transamination reaction [61] using the bicyclic guanidine organocatalyst **13** (**Table 17**).



90 a-d **91 a-d**

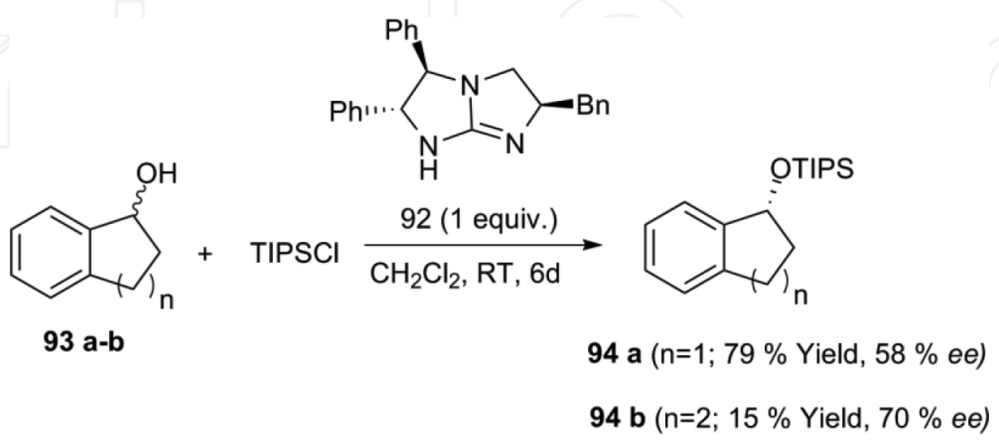
Entry	R_1	R_2	Product	Yield (%)	ee (%)
1	Ph	Me	91 a	63	43
2	*i*Pr	Et	91 b	95	45
3	Me	Et	91 c	98	24
4	$MeO_2C(CH_2)_2$	Me	91 d	98	0

ee = enantiomeric excess.

Table 17. Stereoselective transamination reactions of an imine catalyzed by bicyclic guanidine organocatalyst **13**.

4.4. Asymmetric silylation reaction

The kinetic resolution of secondary alcohols has been done through asymmetric silylation [62] using the bicyclic guanidine organocatalyst **92** in the stoichiometric amount (**Scheme 13**).



93 a-b

94 a (n=1; 79 % Yield, 58 % *ee*)

94 b (n=2; 15 % Yield, 70 % *ee*)

Scheme 13. Kinetic resolution of secondary alcohols through asymmetric silylation using chiral bicyclic guanidine organocatalyst **92**.

5. Conclusion

Guanidines containing chiral molecules have been successfully employed as chiral organocatalysts for the important asymmetric reactions. Guanidine-containing organocatalysts will continue to play an important role in asymmetric synthesis and catalysis in chemistry in coming years.

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Appendix 1

	Reaction	**Page nos**.
1.	Aldol reaction	11
2.	Diels-Alder reaction	13
3.	Friedel-Craft reaction	14
4.	Henry reaction	14, 15, 16
5.	Michael reaction	16,17,18,19,20
6.	Mannich reaction	21
7.	Strecker reaction	21, 22
8.	Claisen rearrangement	23

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