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Chiral guanidines and their derivatives in asymmetric synthesis

Shunxi Dong, Xiaoming Feng and Xiaohua Liu *

Over the past two decades, chiral guanidines and their derivatives have emerged as one of the most powerful organocatalysts mainly on the basis of their strong basicity and/or hydrogen-bond donor ability. Structurally diverse guanidine catalysts (bicyclic, monocyclic and acyclic types) sprang up and enabled numerous fundamental organic transformations to be realized in high efficiency and stereoselectivity. Moreover, chiral guanidinium salts were successfully employed in H-bond donor catalysis, phase-transfer catalysis and others. Recently, several novel chiral guanidine derivatives [*e.g.*, guanidinium salt, pentanidium, bis(guanidino)iminophosphorane] have been designed and used for the synthesis of valuable molecules. In addition, the combination of chiral guanidines and their derivatives with cationic or anionic metal species dramatically expanded their utility and provided solutions to challenging transformations of importance which cannot be achieved with conventional chiral catalysts. This article reviews current achievements of chiral guanidines and their derivatives in organocatalysis, and updates versatile guanidine–metal salt combinations in asymmetric catalytic reactions. In addition, representative examples of achiral guanidine-related catalysis are also covered.

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Key learning points

(1) The general profile of chiral guanidines as organocatalysts and the activation modes.
(2) Recent advances in guanidines and guanidinium salts catalysis.
(3) The chiral multi-nitrogen containing organobase catalysts and their applications in asymmetric synthesis.
(4) New modes combining guanidines and their derivatives with metal species in asymmetric catalysis.
(5) Perspectives and challenges of chiral guanidine and the related derivatives in catalysis.

1. Introduction

Guanidines, containing the general structure of (R^1R^2N)-$(R^3R^4N)C{=}N{-}R^5$, are known as a type of superbase. Guanidine $[(NH_2)_2C{=}NH]$ was first isolated by Strecker *via* the oxidative degradation of guanine in 1861. However, its definitive structure (including the positions of the hydrogen atoms) was determined by single-crystal neutron diffraction in 2013.[1] In the past several decades, guanidines and their derivatives have covered many research areas of chemistry, including as reagents, auxiliaries and organocatalysts in organic synthesis,[2–11] ligands in coordination chemistry and homogeneous catalysis,[12,13] artificial receptors of oxoanions in molecular recognition,[14] pharmaceutical chemistry,[15] materials science[13,16] and so on. This reveals that guanidine represents a versatile functional group with unique properties. The intrinsic and distinctive property of guanidine is the strong basicity resulting from the formation of an effective conjugated planar guanidinium system after protonation, in which the positive charge could be delocalized over the three nitrogen atoms. Consequently, over a wide pH range (including physiological pH), the guanidine functional group exists in its cationic guanidinium form. Indeed, guanidine and guanidinium salts are frequently found in various drugs and natural products including enzymes.[15] In most cases, the guanidine moiety is essential for their bioactivities. Inspired by the role of the guanidinium residue of arginine in biological systems, the interaction of a guanidinium ion with oxoanions (*e.g.* carboxylate, phosphate, and nitronate) through electrostatic attraction and hydrogen bonding is widely used in molecular recognition.[14] In addition to neutral guanidine and cationic guanidinium, the anionic species (guanidinates) act as useful ligands for metal complexes, in particular for lanthanide metal ions and low oxidation state metallacycles.[13] Herein, we mainly focus on the advances of asymmetric catalysis involving chiral guanidines and

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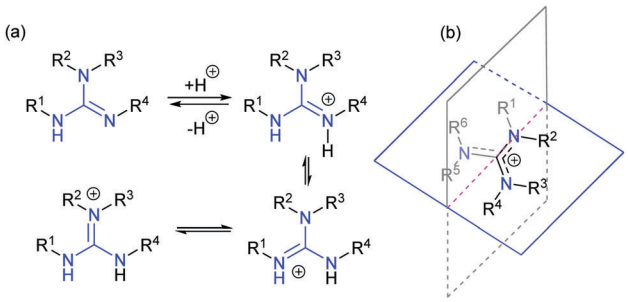
their derivatives. The strong basicity of guanidine coupled with the well-established electrostatic and hydrogen-bonding interactions of its conjugated acid (guanidinium) with oxoanions and other species has led to the development and utilization of chiral guanidines as enantioselective organocatalysts. Over the past two decades, chiral guanidines and their derivatives have emerged as versatile organocatalysts, especially in Brønsted base and hydrogen-bond-donor catalysis. In this context, several excellent reviews and papers have been published to discuss the related achievements between 2002 and 2013.[2–11] The types of organic transformations assisted by chiral guanidines and the related compounds seem to be progressively growing. A number of novel chiral guanidine derivatives including guanidinium salts, pentanidiums and bis(guanidino)iminophosphoranes have been designed and synthesized, providing new and highly effective strategies for the synthesis of valuable chiral molecules. Moreover,



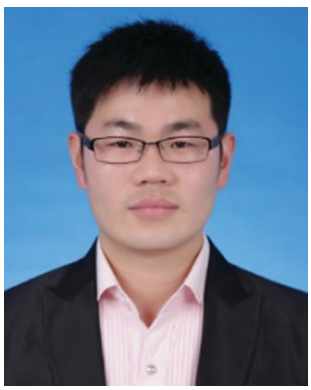
Scheme 1 (a) The resonance structures of protonated guanidine; (b) the symmetrical and planar structure of a guanidinium ion.

the introduction of metal cations or anionic species dramatically expands the utility of chiral guanidines and enables challenging transformations. This brings about an exaltation of guanidines with wider applications as chiral Lewis base catalysts. Herein, we initially present the general profile of chiral guanidines as organocatalysts with several representative activation modes. Recent discoveries involving novel multi-nitrogen-containing chiral organobases and guanidine–metal salt based strategies are discussed. In addition, representative examples of achiral guanidine-related catalysis are briefly covered in the field of catalytic polymerization,[16] Lewis base catalysis[9] and metal–guanidinate induced homogeneous catalysis,[12,13] wherein catalytic asymmetric conversion by the use of chiral guanidines has great potential but is still rarely explored.

2. Chiral guanidine catalysis

2.1 An overview of chiral guanidine catalysts

The basicity of the guanidine moiety (Scheme 1a) along with its interaction with anionic or neutral molecules, makes chiral



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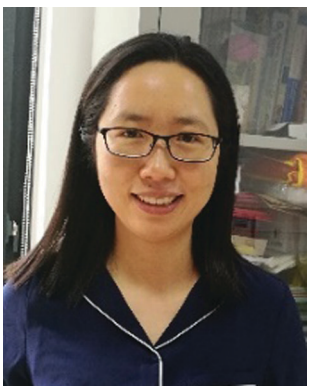
Xiaoming Feng received his BS (1985) and MS (1988) from Lanzhou University. Then, he worked at Southwest Normal University (1988–1993) and became an Associate Professor in 1991. In 1996, he received his PhD from the Institute of Chemistry, CAS under the supervision of Prof. Zhitang Huang and Prof. Yaozhong Jiang. He went to the Chengdu Institute of Organic Chemistry, CAS (1996–2000) and was appointed a Professor in 1997. He did postdoctoral research at Colorado State University (1998–1999) with Prof. Yian Shi. In 2000, he moved to Sichuan University. He was selected as an Academician of the Chinese Academy of Sciences in 2013. He focuses on the design of chiral catalysts, development of new synthetic methods and synthesis of bioactive compounds.



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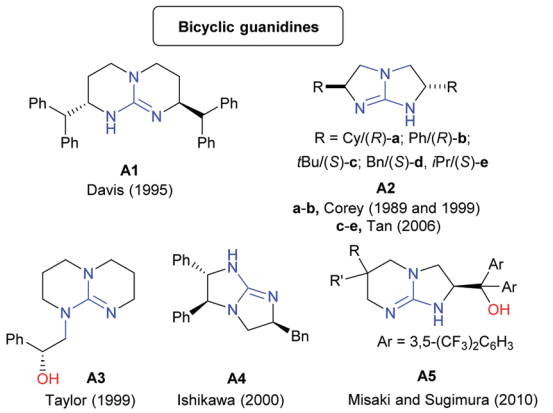


Fig. 1 Literature examples of chiral bicyclic guanidine catalysts.

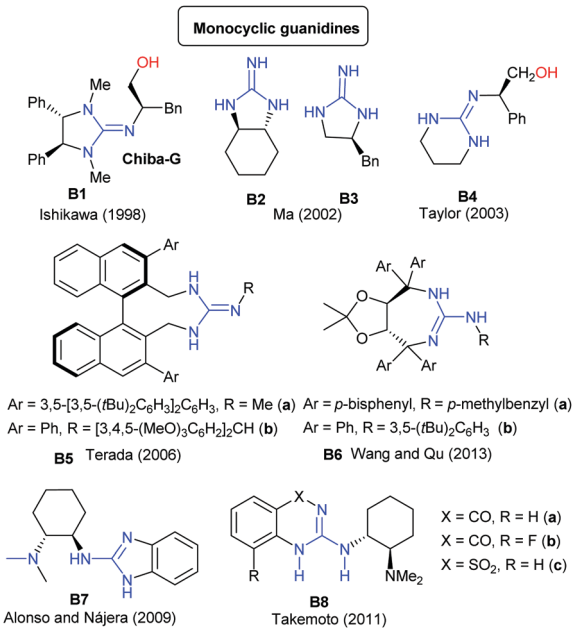


Fig. 2 Literature examples of chiral monocyclic guanidine catalysts.

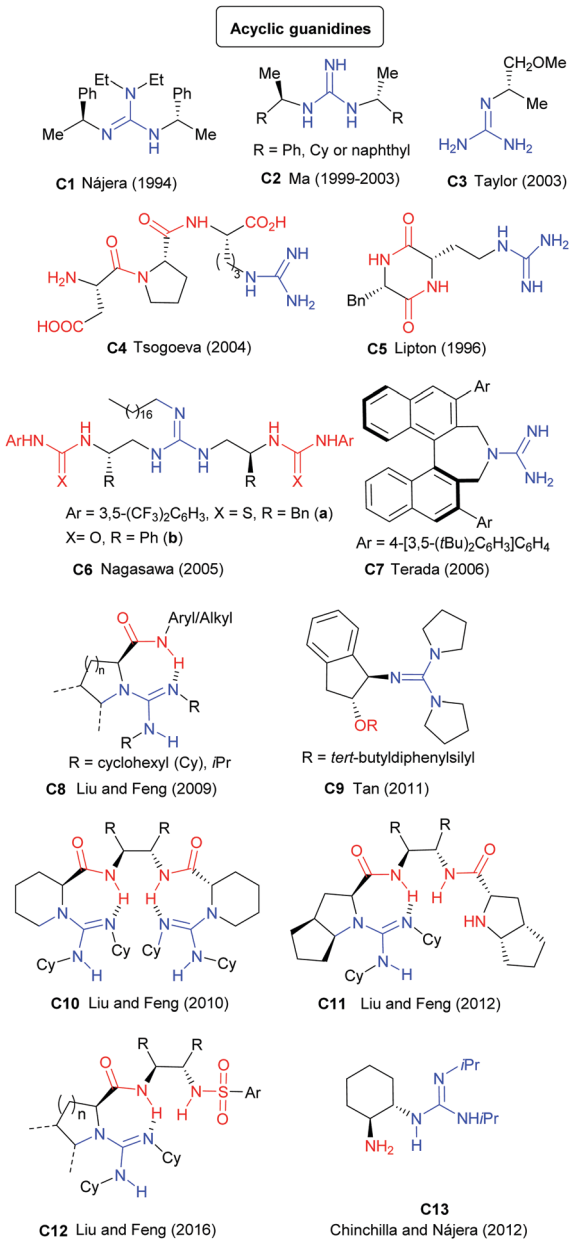


Fig. 3 Literature examples of chiral acyclic guanidine catalysts.

guanidines and their derivatives suitable as enantioselective organocatalysts (Fig. 1–3). However, the development of chiral guanidine catalysts met with several challenges in its infancy: (a) a shortage of general and efficient methods to access the guanidine scaffold; (b) the difficulty in selective incorporation of chiral elements around the guanidine group, and discrimination of the symmetrical structure of the substituted guanidinium moiety (Scheme 1b);[6] and (c) inconvenience of purification resulting from their inherent strong polarity and basicity.

The pioneering studies of chiral guanidine organocatalysts came from Nájera's (**C1**) and Davis' group (**A1**) in the 1990s (Fig. 1–3). However, only moderate enantiocontrol was achieved in asymmetric catalytic reactions, including nitroaldol reaction and conjugate additions. Lipton's group and Corey's group made breakthroughs in asymmetric Strecker reaction with chiral guanidine organocatalysts of **C5** and **A2** in 1996 and 1999, respectively (Fig. 1–3). Inspired by these exciting results, a series of chiral guanidines sprang up in asymmetric catalytic synthesis. Several comprehensive reviews have already summarized the development of these chiral guanidines until 2013, in light of the design concept and the application in asymmetric organocatalysis,[5,6,8] catalytic mechanistic version,[7,10] or classification of asymmetric transformations.[4] As illustrated in Fig. 1 to Fig. 3, representative examples of chiral guanidine-containing catalysts were collected. Structurally, guanidine catalysts can be divided into three types as bicyclic (**A**), monocyclic (**B**) and acyclic ones (**C**) according to whether the guanidine group is incorporated into a ring framework. Selected examples are used to elucidate the general catalytic modes of each structure.

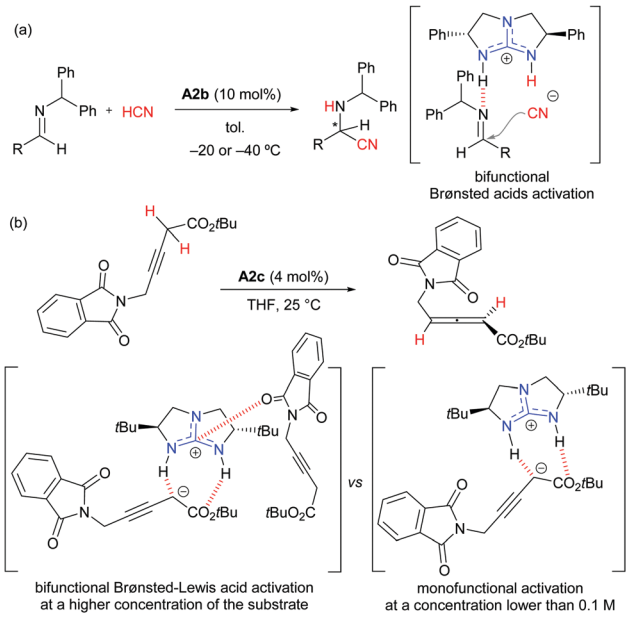
2.2 Guanidines in asymmetric organocatalysis

Bicyclic guanidines. Due to their rigid framework, bicyclic guanidines display dramatically different physical, electronic and chemical properties when compared to their monocyclic and open-chain analogues.[12] Different chiral bicyclic structures including [4.4.0]-, [3.3.0]- and [4.3.0]-guanidines **A1–A5** have been explored (Fig. 1).

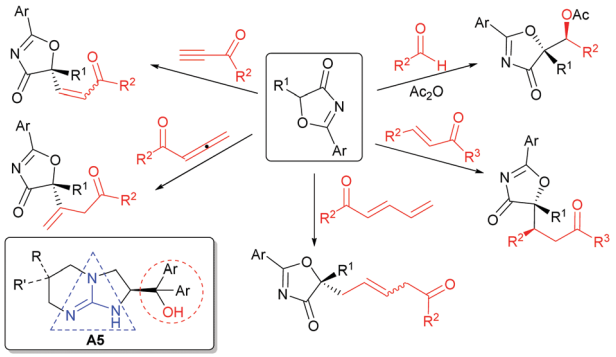
In general, [4.4.0]-bicyclic guanidines exhibit heightened nucleophilicity and basicity over the corresponding [3.3.0]-bicyclic framework. However, the [3.3.0] framework tended to provide better enantiocontrol. The application of chiral [4.4.0]-bicyclic guanidines (**A1** and **A3**) in enantioselective organocatalysis resulted in moderate ee values in most cases.

Chiral [3.3.0]-guanidines **A2** developed by Corey and Tan are particularly useful. In Strecker reaction, a bifunctional Brønsted acid activation mode involves deprotonation, hydrogen bonding of two reactants separately and ion-pairing with CN^- (Scheme 2a). Later on, Tan and co-workers reported an improved synthetic route to TBO-based guanidines **A2c–e**, which was highlighted by scaling up to a 120 gram-scale preparation. Given the excellent performance of these bicyclic guanidines in a variety of reactions, kinetic studies and DFT calculations were performed by Tan, Wong and coworkers; they reveal the potential of bicyclic guanidines as privileged catalysts. As shown in Scheme 2b, the plausible mechanism of action of bicyclic guanidines in enantioselective isomerization of alkynoates is concentration-dependent, and includes monofunctional activation *via* ion-pairing and hydrogen bonding, as well as bifunctional activation *via* Brønsted–Lewis acid interactions.[17]

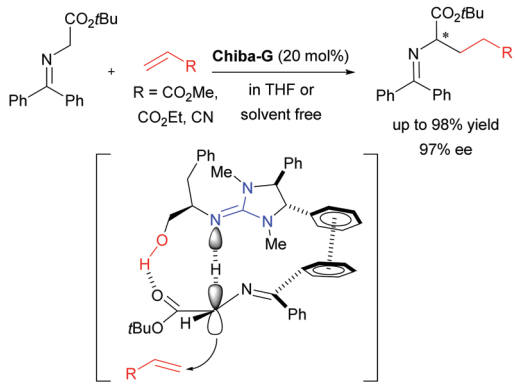
In 2010, Misaki and Sugimura *et al.* described a bifunctional chiral guanidine catalyst **A5** containing a [4,3,0]-bicyclic skeleton and a free hydroxyl group. It is a typical bifunctional organocatalyst that is similar to the privileged L-prolinol catalysts. The **A5**-type catalysts established an excellent template for the enantioselective reactions of oxazolones with a series of electrophiles, including aldehydes, alkynyl carbonyl compounds, allenic carbonyl compounds, vinyl ketones, and dienones (Scheme 3).[18]



Scheme 2 Possible catalytic modes of TBO-based bicyclic guanidine organocatalysis.



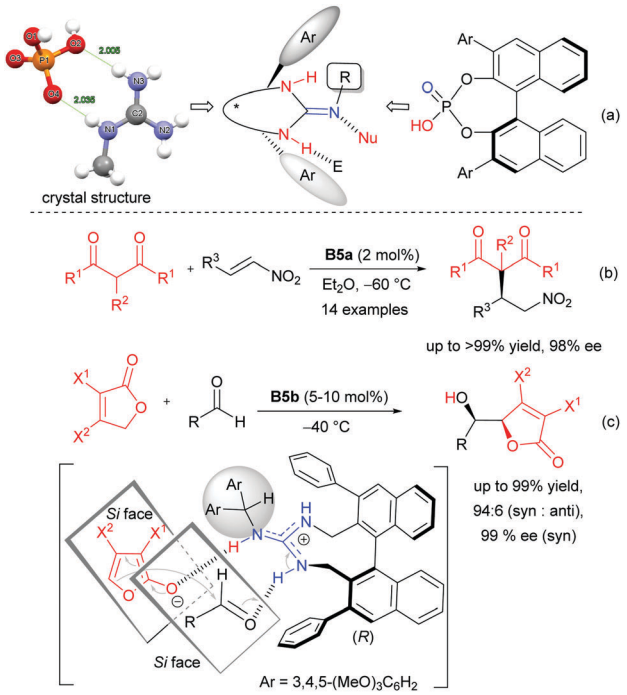
Scheme 3 Asymmetric addition reactions catalyzed by [4,3,0]-bicyclic guanidine **A5**.



Scheme 4 **Chiba-G** mediated Michael addition.

Monocyclic guanidines. Conformationally rigid monocyclic guanidines are usually synthesized from diamines. Accordingly, their structural characteristics are dependent on the amines employed. In terms of the ring size, five-, six-, seven-, and nine-membered ring based guanidines **B1–B6** were explored (Fig. 2). Most of these monoguanidines display pseudo-C_2-symmetry. Moreover, it seems that imine units with the strongest basicity in **B1–B4** are positioned far from the substituents of the diamines; the imines in **B5** and **B6** are situated within the chiral bands of the bulky aryl substituents outside the ring.

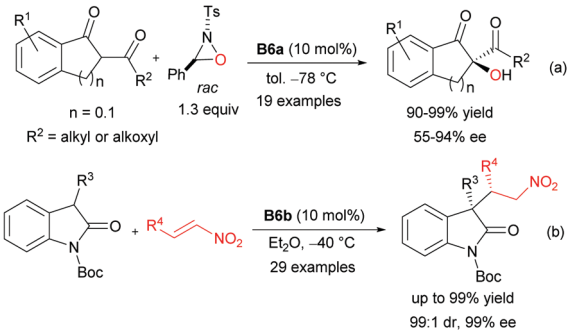
Ishikawa, a pioneer of chiral guanidine catalysis, contributed heavily to imidazoline-2-imine-based guanidine chemistry.[5] One of his key accomplishments was the use of commercially available **Chiba-G** (**B1**) to catalyze asymmetric Michael reaction of glycine imine with acrylate. High yields and excellent ee values (up to 98% yield, and 97% ee) were obtained either in solution or under solvent-free conditions. Both the hydroxyl group and the imine unit of the guanidine are involved in the activation of glycine imine (Scheme 4). Control experiments indicated that the chiral match of the three chiral centers and the existence of the hydroxyl group are essential. In contrast, the structurally simpler



Scheme 5 (a) Design of nine-membered axially chiral guanidine **B5**, and (b and c) its applications in addition reactions.

imidazoline-2-imine based **B2** and **B3** or tetrahydropyrimidin-2-imine-derived **B4** were less efficient in Henry reaction and enone epoxidations. It reflects the synergism of each component of the chiral guanidine catalysts.[5]

In 2006, inspired by the X-ray crystal structure of methylguanidinium dihydrogenorthophosphate (Scheme 5a, left), Terada and co-workers developed a unique family of axially chiral guanidine catalysts, such as **B5**, based on binaphthyl-based chiral phosphoric acids (Scheme 5). The presence of a planar guanidine group as well as an axially chiral binaphthyl backbone with 3,3′-disubstituents rigidified the originally flexible nine-membered ring. Simultaneously, the planar symmetry of the guanidine skeleton was broken, leading to the use of guanidine **B5** as a promising class of chiral organocatalysts for a couple of organic transformations.[6] Chiral guanidine catalyst **B5a** succeeded in enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes (Scheme 5b). The vinylogous aldol reaction of substituted furanones with aldehydes proceeded smoothly in the presence of chiral guanidine **B5b** (Scheme 5c). It was found that the substituent on the imine nitrogen of a guanidine group had a significant influence on both the activity and ee values of the reaction. Based on the absolute configuration of the products, a possible transition state was proposed to elucidate the diastereo- and enantioselectivity of the vinylogous aldol reaction (Scheme 5c). The imine unit of the guanidine would deprotonate the furanone derivative and activate the newly formed enolate; meanwhile the NH group could bind the carbonyl oxygen of the aldehyde *via* a hydrogen bond. The *Si*-face of the enolate approaches from the *Si*-face of the aldehyde to form the *syn*-products with high diastereo- and enantioselectivities.[6]

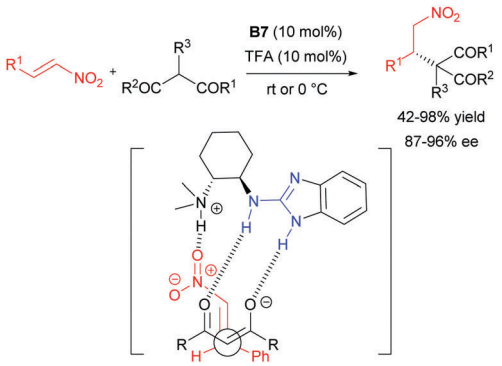


Scheme 6 TADDOL-based guanidine promoted oxidation and addition reactions.

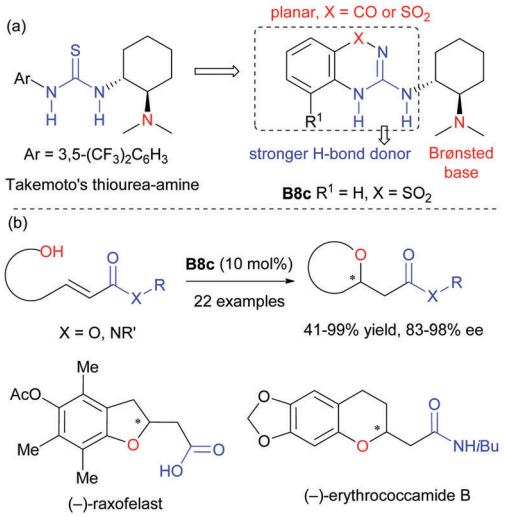
Later on, Wang and Qu designed a type of seven-membered ring-based guanidine catalyst **B6** derived from chiral ethyl L-tartrate (Fig. 2). In asymmetric reactions, such as α-hydroxylation of β-ketoesters and β-diketones with racemic oxaziridine as the oxidant (Scheme 6a), and the Michael reaction of 3-substituted oxindoles with nitroolefins (Scheme 6b),[19] the structure–activity relation of this type of catalyst showed that the substituent on the external amine moiety of guanidine significantly affected the outcomes. This tendency is similar to Terada's axially chiral guanidine **B5**.

2-Aminobenzimidazole as a variation of a monocyclic guanidine structure has also been introduced in organocatalyst development. Cooperating with TFA, the 2-aminobenzimidazole-derived compound **B7** exhibited a high activity for the addition of 1,3-dicarbonyl compounds to nitroolefins, providing the desired products in moderate to high yields with excellent ee values (42–98% yield, 87–96% ee) (Scheme 7).[20] According to DFT calculations, a double activation mode was proposed, where the benzimidazole motif deprotonates and activates the 1,3-dicarbonyl compound, while the nitroolefin is activated by the protonated dimethyl amine unit. It was worth noting that the catalyst could be recovered after the reaction by extractive acid/base workup.

The above cases exhibit that the guanidines work as a type of base for the activation of the nucleophiles at least. Nevertheless, electron-withdrawing substituents attached to the guanidine unit



Scheme 7 Michael addition catalyzed by 2-aminobenzimidazole-derived catalyst **B7**.



Scheme 8 (a) Structural characteristic of guanidine **B8** and (b) the representative applications.

could completely change the catalytic properties. Based on the well-known bifunctional thiourea–amine catalyst, in 2011, Takemoto and co-workers replaced the thiourea unit with acylated or sulfonylated guanidines to obtain a new class of monocyclic guanidines **B8** (Scheme 8a). With regard to the X-ray crystal structure of the catalyst **B8**, the resonance effect is expected to be stronger than the bifunctional thiourea–amine catalyst due to the coplanar feature of the CN_3 unit and the aromatic ring. Indeed, the catalysts **B8** were used as hydrogen-bond-donor catalysts in enantioselective conjugate addition of malonates to nitrostyrenes, α-amination of 1,3-dicarbonyl compounds, and isomerization of *tert*-butyl alkynoates as well. In particular, an enantioselective intramolecular oxa-Michael addition of conjugate amide and ester catalyzed by **B8c** was used for the synthesis of biologically active compound (−)-raxofelast and natural product erythrococcamide B (Scheme 8b).[21]

Acyclic guanidines. The first chiral guanidine catalyst was open-chain type (Fig. 3) denoted as **C1** developed by Nájera and coworkers. Following this study, Ma and Taylor separately designed several chiral open-chain guanidines (**C2** and **C3**) in the early stage of guanidine catalysis. Tsogoeva and Lipton decorated the simplest guanidine unit into the peptide structures (**C4** and **C5**), respectively.[4,10] However, these conformationally flexible open-chain guanidines were easily obtained but less enantioselective compared with the bicyclic and monocyclic analogues. Nowadays, several wonderful strategies have been discovered to enhance the catalytic efficiency of open-chain guanidines, including the introduction of another functional group (**C6** and **C13**), increasing steric hindrance around the guanidine unit (**C7** and **C9**), or the formation of additional intramolecular hydrogen-bonds (**C8, C10–C12**).

If not considering the diverse conformations of a multi-substituted guanidine unit, the basic C=N bond of acyclic guanidines exhibits variable and interesting arrangement (Fig. 4). One is that the imine unit is a pseudo-C_2 symmetry axis, and the other is the corresponding guanidinium salt

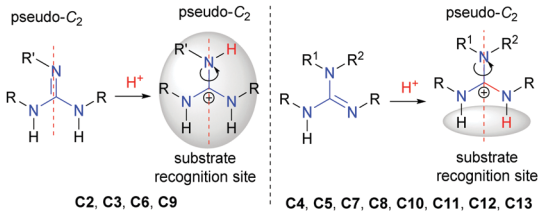
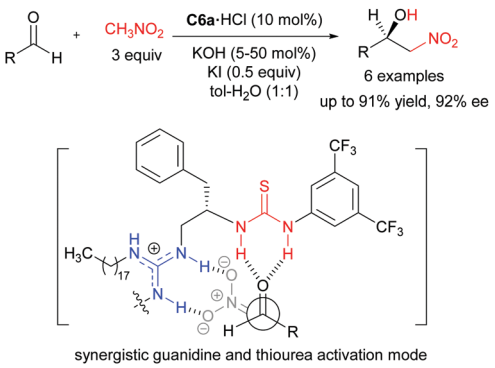


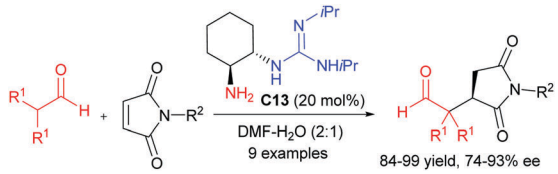
Fig. 4 The structural features of open-chain guanidines and the corresponding guanidinium salts.

(Fig. 4). In the former case, each nitrogen of the guanidinium connects with one hydrogen at least, enabling the recognition of the substrates *via* hydrogen bonds at multiple sites (Fig. 4, left). In the latter case, the guanidines have an amidine unit with the same substituent, thus their related guanidiniums have pseudo-C_2 symmetry (Fig. 4, right), and recognize the substrates at the amidinium unit. There is certainly a third case that each nitrogen of guanidines bears different substituents, leading to much more flexibility and complexity. Therefore, the easy preparation, conformational flexibility,[22] plentiful substituents and convenient modification make open-chain guanidine catalysts powerful in asymmetric catalysis.

In 2005, Nagasawa's group described a useful open-chain guanidine–(thio)urea catalyst **C6** featuring a long alkyl chain on the imine of guanidine. This design was based on the concept that the catalytic functions of enzymes could be easily tuned through conformational changes. In the presence of the catalyst **C6a**·HCl, KOH and KI, enantioselective Henry reaction of nitromethane with diverse aliphatic aldehydes proceeded smoothly under biphasic conditions of toluene–aqueous solvents at 0 °C (Scheme 9), affording the desired products in high yields (70–91%) together with moderate to good ee values (55–92% ee).[8] Based on the absolute configuration of the product and the general activation modes demonstrated in guanidine and thiourea functions, the authors proposed a dual activation mode for the catalysis of **C6a**. The guanidine activates nitromethane, and the aldehyde was bound by a thiourea moiety *via* dual H-bonds. This type of catalyst was successfully used in several other reactions including aza-Henry reaction, Friedel–Crafts reaction, Mannich reaction, and oxidative kinetic resolution reaction of tetralone-derived



Scheme 9 Bifunctional guanidine–thiourea catalyst **C6** in Henry reaction.

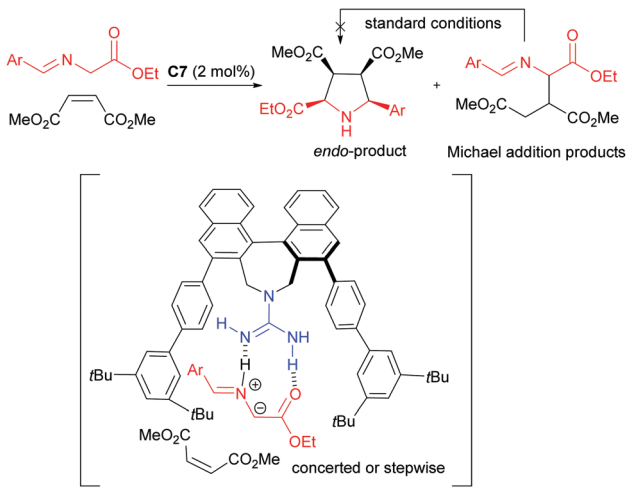


Scheme 10 Conjugated addition promoted by guanidine–amine **C13**.

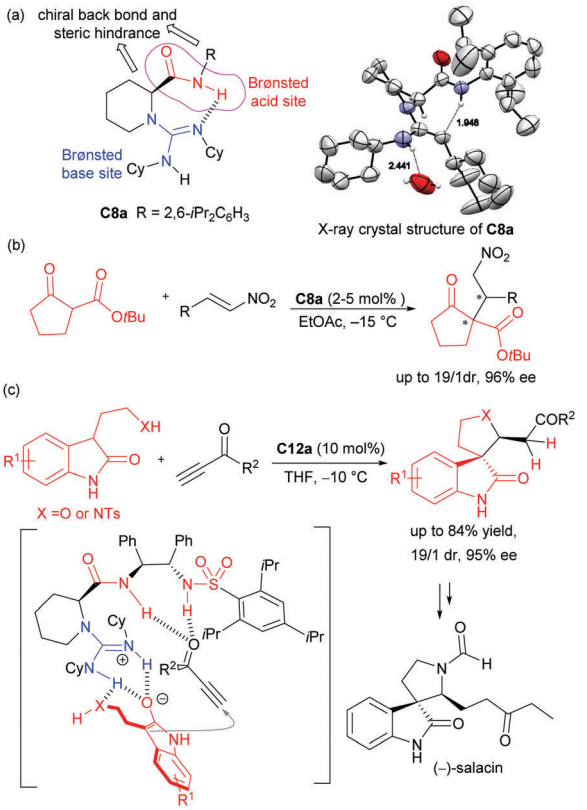
β-ketoesters[23] *etc.* During these investigations, a guanidine–(thio)urea catalyst exhibited a distinctive feature that it was able to regulate self-aggregation and to tune their conformations, in a manner similar to enzymes, with the changes in conditions.[8]

The Nájera group added a primary amino group near the guanidine group to arrive at the catalyst **C13**. The enantioselective conjugate addition of α,α-disubstituted aldehydes to maleimides in DMF/H_2O (2/1) mixture resulted in high yields and good enantioselectivities (Scheme 10).[24] Although the control experiments were insufficient to unveil the mechanism by which **C13** produces asymmetric induction, its activation mode is likely to be different from the amine–thiourea catalysts.

The Terada group also utilized the axially chiral binaphthyl derivatives to construct open-chain guanidine **C7** with a seven-membered ring structure. The catalyst is highly efficient as the catalyst loading could be as low as 0.05 mol% in the amination reaction of unsymmetrical 1,3-dicarbonyl compounds.[6] It should be noted that the substituents at the 3,3′-positions have a significant effect on the reactivity and enantioselectivity of the reaction. The sterically hindered 4-[3,5-(tBu)$_2$C$_6$H$_3$]C$_6$H$_4$ group proved critical, and it could act as a long and big 'arm' to transmit chiral information from the axially chiral backbone to the reaction active center; and the created chiral pocket around the guanidine moiety distinguishes between the two different enantiotopic faces of the enolate form of the substrate. This axially chiral guanidine **C7** is proposed as a monofunctional catalyst, as shown in the asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with dimethyl maleate (Scheme 11).[6]



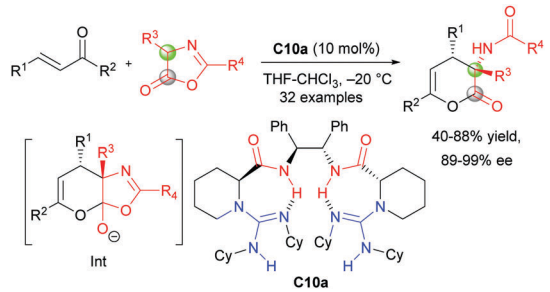
Scheme 11 Axially chiral guanidine **C7** promoted 1,3-dipolar cycloaddition reaction.



Scheme 12 Bifunctional amide–guanidine promoted Michael addition reactions.

Due to the conformational flexibility and rotational freedom of tetra-substituted acyclic guanidines, the activation manner of this kind of catalyst seems elusive. To expand bifunctional organocatalysis, Feng, Liu and coworkers developed a new type of chiral open-chain guanidine **C8**, **C10** and **C12** bearing additional amide substituents as Brønsted acids. An X-ray crystal structure of the guanidine **C8a** indicated that both intramolecular and intermolecular H-bonds exist in this amide–guanidine catalyst (Scheme 12a). Chiral guanidine–amide **C8a** prepared from L-pipecolic acid was found to be a highly efficient organocatalyst for the Michael addition of cyclic β-keto esters to nitroolefins (Scheme 12b). Another type of bifunctional guanidine catalyst **C12** was discovered by introducing a sulfonamide subunit. Catalyst **C12a** shows good performance in double Michael additions of 3-substituted oxindoles to terminal alkynones (Scheme 12c). The utility of this method was demonstrated in the asymmetric synthesis of (–)-salacin.[25] A possible activation mode was proposed to elucidate the origin of the diastereo- and stereocontrol of the reaction. In this mode (Scheme 12c), the guanidine unit functions as a Brønsted base to activate 3-substituted oxindoles through deprotonation and hydrogen-bond interactions; meanwhile the NH groups of the amide and sulfonamide unit act as Brønsted acids to activate terminal alkynones.

Inspired by the essential C_2-symmetric feature possessed by most of the privileged chiral catalysts, Feng and Liu subsequently introduced achiral and chiral diamines as the linkers to



Scheme 13 IEDHDA reaction catalyzed by chiral bisguanidine **C10**.

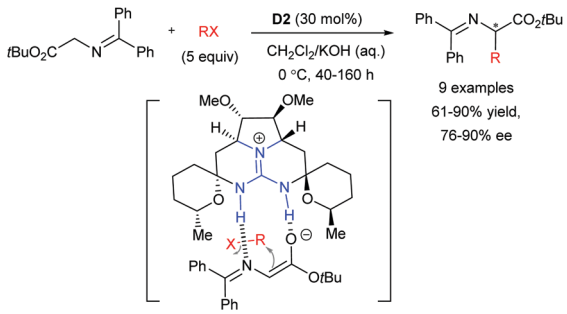
provide a series of C_2-symmetric bisguanidines and the corresponding hemi-bisguanidinium salts.[26] Among them, the catalyst **C10a** was the most outstanding one, which was employed as an efficient organocatalyst for the inverse-electron-demand hetero-Diels–Alder (IEDHDA) reaction of chalcones with azlactones (Scheme 13). Numerous γ,δ-unsaturated δ-lactones were achieved in excellent outcomes. In comparison, monoguanidine **C8a** promoted this IEDHDA reaction with much lower yield along with poor enantioselectivity. Besides, a direct vinylogous Michael reaction of γ-butyrolactams with alkylidene malonates was achieved with high enantioselectivities in the presence of guanidine **C11** which was synthesized from L-ramipril and 1,2-diphenylethane-1,2-diamine but remained an unguanidinated secondary amine moiety.[25]

3. Chiral guanidinium salt catalysis

The guanidines can undergo protonation or quaternization at the imine–nitrogen to form two types of guanidinium cations (Fig. 5). The guanidinium salts of protic acids (**D1–D5**) are charged species capable of binding to polar molecules and oxoanions through directed hydrogen-bonding and electrostatic interactions. An enhanced H-bond donor ability is likely in guanidinium salts, relative to neutral ureas and thioureas.[27] On the one hand, due to the positively charged nature of the guanidinium moiety, chiral quaternized guanidinium salt catalysts (**D6** and **D7**) can serve as phase-transfer catalysts to bring functional anions repeatedly into the organic phase through rapid anion exchange.

3.1 Chiral guanidinium salts as hydrogen-bond donor catalysts

H-bond-donor mediated electrophilic activation has proved to be a successful strategy in catalytic asymmetric reactions. A few examples of chiral guanidinium ions serving as dual H-bond donor catalysts have been reported thus far. Although guanidinium salts can accelerate several organic reactions, including the cleavage of phosphate esters and hetero-Michael additions, the chiral guanidinium catalysts (**D1–D3**) were less enantioselective in these reactions. On the basis of studies about ptilomycalin A, in 2002 Nagasawa's group employed guanidinium salt **D2** for the enantioselective alkylation of *tert*-butyl glycinate Schiff base (Scheme 14). Various alkyl halides were tolerated in this system, delivering the alkylated products in moderate to high yields with good ee values (61–90% yield, 76–90% ee).[28] A monofunctional activation mode was proposed, in which the protonated catalyst forms a complex with the *Z*-enolate of glycinate Schiff base *via* ionic and hydrogen-bonding interactions, then alkylation reagent approaches from the less hindered face to deliver the desired alkylation product. In this case, a strong base of KOH was used, which could promote the formation of an enolate ion. It is also possible that guanidinium salt was used as



Scheme 14 Guanidinium salt participated alkylation reaction.

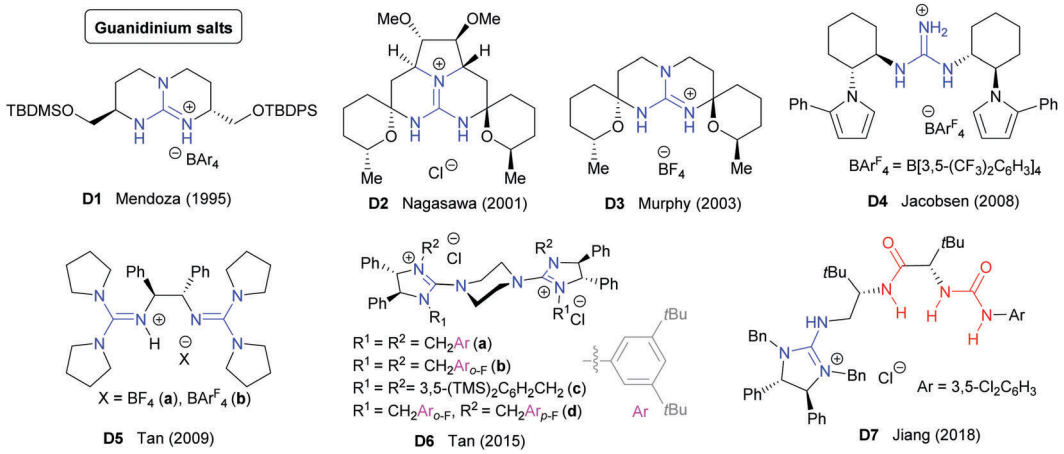
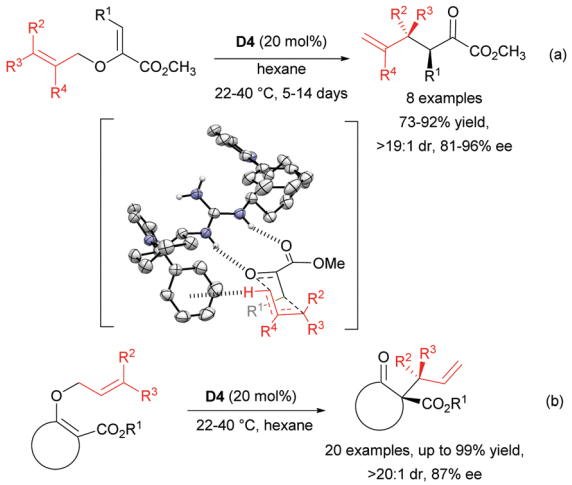


Fig. 5 Literature examples of chiral guanidinium salts.



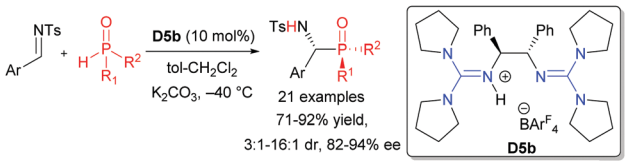
Scheme 15 Enantioselective Claisen rearrangements promoted by guanidinium salt **D4** (for clarity only hydrogen atoms of guanidinium groups are depicted in activation mode).

the precursor of the guanidine catalyst and the active guanidine could be generated *in situ* to activate a glycinate Schiff base. The combination of guanidinium salt and a strong base is a good alternative to using guanidines because of the improved stability and ease of handling of the guanidinium salts.

In 2008, Jacobsen's group reported a landmark achievement in employing guanidinium salts as hydrogen-bond donor catalysts. In the preliminary study, the authors found that diphenylguanidinium salt could promote rate enhancement in the rearrangement of allyl vinyl ethers. In sharp contrast, switching the catalysts to urea or thiourea led to no significant rate acceleration. After a systematic investigation of various substituted chiral guanidinium salts, it was found that the catalyst **D4** was an efficient catalyst for a series of substituted allyl vinyl ethers (Scheme 15a). The corresponding rearrangement products were obtained in high yields with good to excellent enantioselectivities (73–92% yield, 81–96% ee). Detailed experimental investigation and DFT calculations confirmed that the hydrogen-bond interactions between the guanidinium and the negatively charged oxa-allylic fragment were beneficial for the stability of the rearrangement transition state.[29] Moreover, the electrostatic attraction of the π-system in the catalyst with a cationic allyl fragment also contributed to the outstanding performance of the chiral guanidinium catalyst. Furthermore, this catalytic system could extend to asymmetric Claisen rearrangements of *O*-allyl β-ketoesters as well (Scheme 15b).[29]

3.2 Bifunctional bisguanidinium salt catalyst

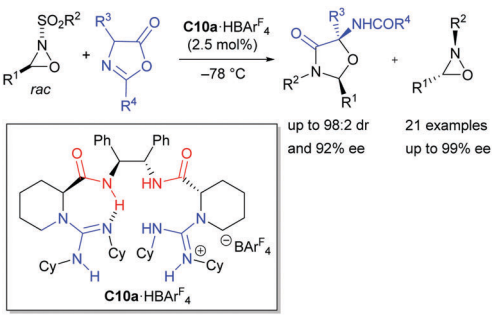
Bisguanidinium hemisalts which contain both a guanidine unit and a guanidinium unit represented a novel strategy of bifunctional catalysis. Tan's group endeavored to develop easily prepared chiral guanidine and guanidinium catalysts. In 2009, they demonstrated a new type of chiral guanidinium hemisalt **D5**, obtained in two steps from a commercially available chiral diamine.[30] In the preliminary studies, both the corresponding bisguanidine and bisguanidinium salts were found to promote



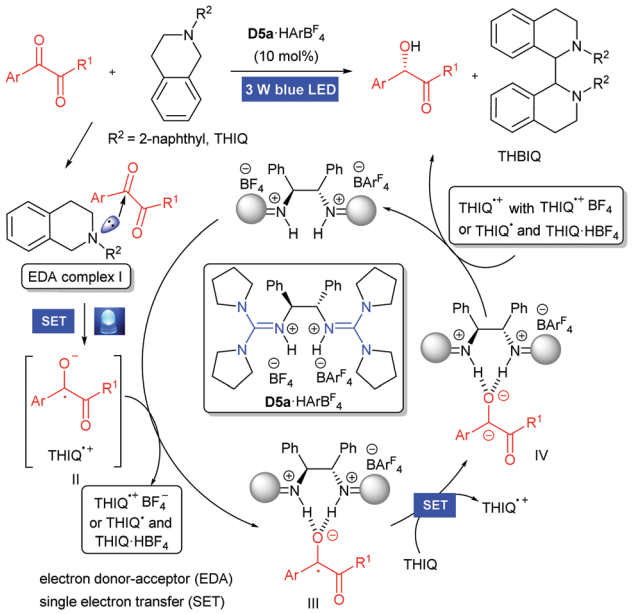
Scheme 16 Bisguanidinium hemisalt **D5** induced phospha-Mannich reaction.

the phospha-Mannich reaction of *N*-Ts substituted imines with phosphine oxide, but the enantioselectivities were much lower than the one obtained by chiral guanidinium hemisalt **D5a** (33% ee and 5% ee *vs.* 82% ee). The screening of different counterions revealed that the non-coordinating counterion ($BAr^F{}_4^-$) was the best choice. Under the optimized conditions by the use of **D5b**, various α-amino phosphine oxides and α-amino phosphinates were afforded in high yield with moderate to good diastereoselectivities and excellent ee values (Scheme 16).

C_2-symmetric chiral bisguanidine **C10** prepared from amino acids and diamines could also be transformed into the related bisguanidinium hemisalt catalyst **C10**·$HBAr^F{}_4$ and showed distinctive stereocontrol ability in the oxyamination of azlactones with racemic oxaziridines.[31] No stereoselectivity was observed by the use of bisguanidine **C10a** but dramatic improvements of the diastero- and enantioselectivities were attained when the bisguanidinium hemisalt bearing one bulky and non-coordinating $BAr^F{}_4^-$ ion was employed (Scheme 17). Remarkably, kinetic resolution of racemic oxaziridines was simultaneously involved in this process. Under the optimized conditions, various enantioenriched oxazolin-4-one derivatives were achieved in high diastereo- and enantioselectivities (up to 98 : 2 dr, 92% ee); meanwhile, diverse chiral oxaziridines with different substituents were recovered with high ee values (up to 99% ee). In comparison, the bisguanidinium salt **C10a**·$2HBAr^F{}_4$ did not promote the reaction at all, indicating that both the guanidine moiety and guanidinium unit are essential for this transformation. As a consequence, a bifunctional catalytic mode of chiral bisguanidinium hemi-salt was proposed where the guanidine moiety might deprotonate and activate azlactones, and the guanidinium unit works as a Brønsted acid to bond and distinguish the enantiomer of oxaziridines. Further applications of this interesting catalyst class were demonstrated in aza-Michael reaction, formal [4+2] and [3+2] cycloaddition reactions as well.[32]



Scheme 17 Formal [3+2] reaction and kinetic resolution catalyzed by bisguanidinium hemisalt **C10**·$HBAr^F{}_4$.

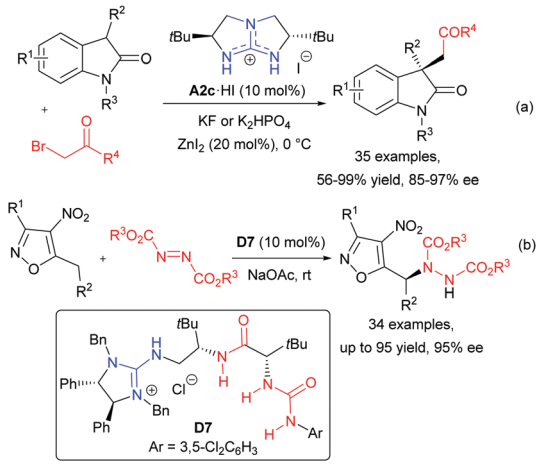


Scheme 18 Photoreduction of 1,2-diketones *via* an electron donor–acceptor complex and plausible catalytic cycle.

The applications of guanidines and related catalysts could be also expanded by complementing it with photocatalysis. In 2017, Jiang and co-workers described a highly enantioselective photoreduction of 1,2-diketones with tetrahydroisoquinoline (THIQ) by synergistic catalysis containing bisguanidinium salt catalysis and the photoredox process (Scheme 18).[33] The reduction of 1,2-diketones proceeded smoothly under irradiation with 3 W blue LEDs, both in the presence and absence of a photoredox catalyst. Assisted by chiral double salt of **D5** (BF_4^- and $BAr^F{}_4^-$ as the counterions of each guanidinium unit) the desired chiral α-hydroxy ketones were provided in high yields with excellent enantioselectivities. Two catalytic cycles were proposed. As depicted in Scheme 18, in the absence of a photocatalyst, the 1,2-diketone interacted with THIQ to form the electron donor–acceptor (EDA) complex **I**, which was reduced to radical species **II** *via* a single-electron transfer (SET) process under irradiation. Then anion exchange of BF_4^- in the catalyst with the newly formed ketyl radical anion afforded the chiral bisguanidinium salt-bound intermediate **III** which was further reduced to carbanion complex **IV** by THIQ. Finally, proton delivery occurs from the *Re*-face of a ketyl anion to afforded the (*S*)-α-hydroxy ketone. In addition, the reaction could also perform well when the dicyanopyrazine-derived chromophore (DPZ) was present. This process might occur *via* similar key guanidinium-bound 1,2-diketone intermediate **III**.

3.3 Chiral guanidinium salt as a phase-transfer catalyst (PTC)

Basic species are frequently involved as counteranions in phase-transfer catalysis. In 2013, Tan, Jiang and coworkers reported that the hydrogen iodide salt of **A2c** enables the highly enantioselective phase-transfer alkylation of 3-substituted-2-oxindoles and activated bromomethanes using K_2HPO_4 as the base (Scheme 19a). The addition of ZnI_2 could dramatically

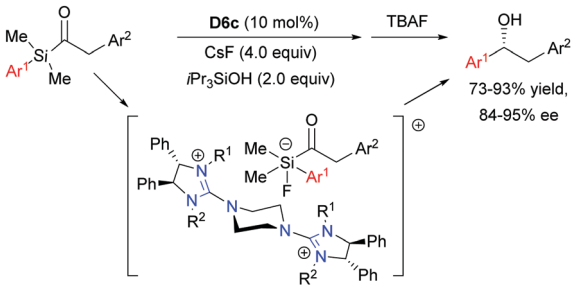


Scheme 19 Guanidinium salt induced alkylation and amination reactions.

increase conversion and enantioselectivity of the reaction.[34] The treatment of **A2c**·HI with different inorganic bases indicated that guanidine **A2c** could be generated in the presence of K_2CO_3 or NaOH, while K_2HPO_4 did not basify **A2c**·HI at all, suggesting that **A2c**·HI probably served as a phase-transfer catalyst.

Jiang and co-workers developed a new type of chiral dipeptide-based urea–amide–guanidinium catalyst. The catalyst **D7** was found to be a highly efficient PTC in the presence of NaOAc for the catalytic asymmetric vinylogous amination of 5-alkyl-4-nitroisoxazoles (Scheme 19b). DFT calculations revealed that both cooperative multiple hydrogen-bonding and ion pair interactions played a significant role in this reaction.[35]

A type of readily accessible quaternized bisguanidinium salt **D6** was designed by Tan's group.[34] The catalyst **D6a** was initially investigated as an efficient PTC for highly enantioselective alkylation of cyclic ketones. Recently, they described a catalytic asymmetric 1,2-anionotropic rearrangement of acylsilanes using chiral bisguanidinium salt **D6c** as the catalyst (Scheme 20). Various chiral secondary alcohols were afforded in high yield with excellent enantioselectivities (73–93% yield, 84–95% ee).[36] Based on the control experiments and theoretical calculations, the bisguanidinium silicate ion pair was proposed as the key intermediate, which subsequently underwent 1,2-anionotropic rearrangement *via* a three-membered ring transition state to form a chiral α-silyl alkoxide. Stereospecific [1,2] Brook rearrangement



Scheme 20 Chiral bisguanidinium salt **D6c** promoted 1,2-anionotropic rearrangement.

followed by treatment with TBAF delivered the desired product. Remarkably, the catalyst was capable of asymmetric induction through electrostatic interactions alone, without the assistance of hydrogen bonding interactions.

Furthermore, switching counter anions of guanidinium into metal anions, the applications of the type of catalysts **D6** were significantly extended, which will be discussed in Section 5. Recently, Nagasawa reported a novel strategy for the phase-transfer oxidative cycloetherfication using *in situ* generated hypoiodite (IO^-) as a counter anion and active oxidation.[37] Therefore, the introduction of other functional anions into guanidinium salts probably open up a new avenue in the utilization of guanidinium salt catalysis.

4. Other chiral multi-nitrogen-containing organocatalysts

To mimic chiral guanidine catalysis and extend the applications of superbases in asymmetric organocatalysis, several groups attempted to design and synthesize new classes of organic superbase catalysts. According to the concept that the basicity of the organobases enhances with increasing resonance forms of the corresponding conjugate acids, other multi-nitrogen-containing organocatalysts, such as pentamidine **E1**, cyclopropenimine **E2** and iminophosphorane derivatives **E3** were developed (Fig. 6).

4.1 Chiral pentanidium salt catalysts

Initially, Tan's group designed a family of biguanides but these chiral diamine derived biguanides exhibited weaker basicity than expected.[34] In a subsequent study, they reported that tetrasubstituted pentanidium salts could function as effective phase-transfer catalysts. To avoid confusion between guanidine and biguanide, the base form is referred to as pentanidine and its conjugate acid as pentanidium.

The first application of this library of catalysts was demonstrated in 2011. The catalyst **E1a** enabled the Michael addition reaction of *tert*-butylglycinate Schiff base to vinyl ketones, acrylates and chalcones (Scheme 21a). Excellent results were obtained and the catalyst loading could be lowered to 0.05 mol% for a gram-scale reaction.[34] As shown in Scheme 21c, the structure of the catalyst **E1a** with four methyl substituents was confirmed by X-ray crystal analysis, indicating that the dihedral angle between the two different N-containing planes is around 51.5°, which provides

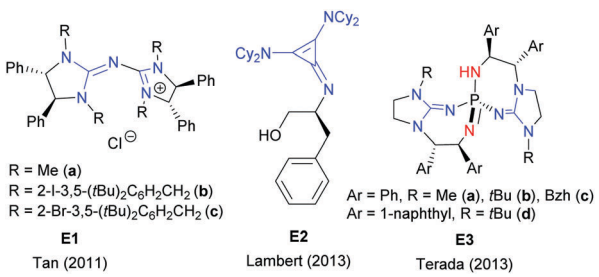
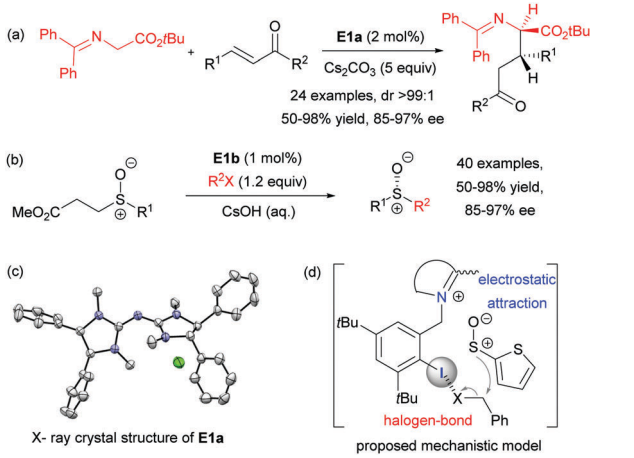


Fig. 6 Representative examples of chiral multi-nitrogen containing organobase catalysts.



Scheme 21 Pentanidium induced additions and the possible working mode.

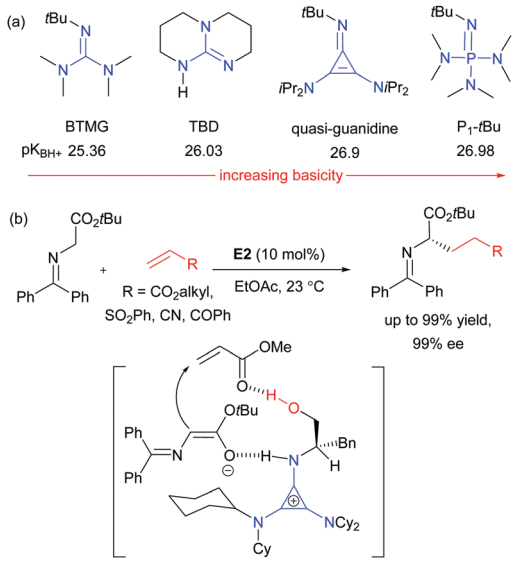
some explanation on the basicity of the obtained pentanidine. On the other side, benefited from this special structure, a tunable chiral cavity was created with the introduction of different substituents on nitrogen atoms of the imidazoline unit, which was found to be able to discriminate two different prochiral faces of the ester enolate intermediate. The performance of these pentanidium salt catalysts was also highlighted in organocatalytic reactions involving other enolates and sulfonate anions (Scheme 21b). It was interesting to note that DFT calculations and experimental studies indicated that not only electrostatic interaction but also halogen-bonds between the catalyst **E1b** and the substrates played significant roles in the stability of the transition state (Scheme 21d).[34]

4.2 Chiral bis(dialkylamino)-cyclopropenimine catalysts

In 2012, Lambert and co-workers reported that 2,3-bis(dialkylamino)cyclopropenimine (Scheme 22) exhibits stronger basicity than guanidine analogues,[38] probably resulting from additional aromatic resonance stabilization provided by a 2π-electron cyclopropenium ion as its conjugate acid. Based on this finding, they designed a new type of chiral bis(dialkylamino)-cyclopropenimine catalyst which is structurally similar to **Chiba-G** developed by Ishikawa. In comparison, they conducted the asymmetric Michael reaction of glycine imine with acrylate (Scheme 4). It was found that the reaction completed within 5 minutes under solvent-free conditions at 10 mol% of the catalyst **E2**, and the product was obtained in quantitative yield with 91% ee. It indicates the superiority of cyclopropenimine over **Chiba-G** in terms of reaction activity. Structural modifications from **E2** revealed that both the hydroxyl group and the bulky substituents on amine units are essential for the high activity and chiral induction. The authors proposed a bifunctional activation mode distinct from that of **Chiba-G**, in which a cyclopropenimine unit could activate glycine imine *via* deprotonation and hydrogen bonding interaction; simultaneously, methyl acrylate was directed by the hydroxyl group for conjugate addition.

4.3 Chiral bis(guanidino)iminophosphorane catalysts

Further progress on chiral superbase catalysts was reported by Terada and co-workers. In 2013, they designed the

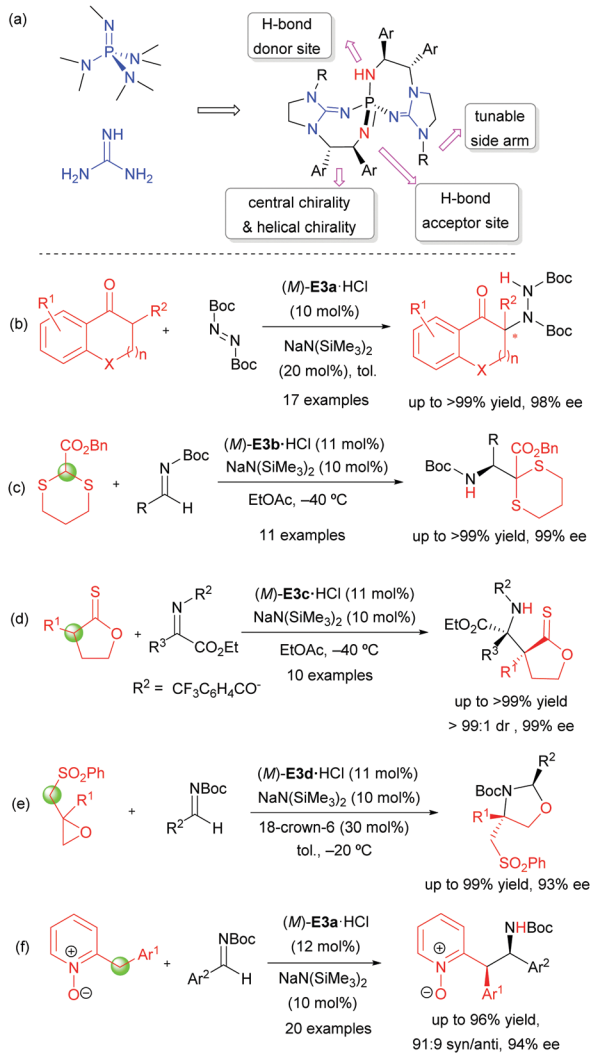


Scheme 22 (a) pK_{BH+} values of several common strong organic bases in CH_3CN; (b) Michael reaction of glycine imine with acrylate catalyzed by compound **E2**.

bis(guanidino)iminophosphoranes by incorporating a pair of guanidine groups into P1-phosphazene bases. Both hydrogen bond donor and acceptor sites were situated around the central phosphorus atom (Scheme 23a). The newly developed chiral iminophosphorane catalysts possess the highest basicity in uncharged catalysts reported to date and their utilization as organosuperbases for the activation of less acidic pro-nucleophiles was described in several organic transformations (Scheme 23b–f).[39,40] Interestingly, in the process of catalyst synthesis, two diastereoisomers were formed due to the innate helical chirality of spiro compounds, which was confirmed by single-crystal X-ray analysis. In the presence of pre-catalyst **E3a**·HCl with (*M*)-configuration and $NaN(SiMe_3)_2$, the electronic amination of a relatively inert cyclic ketone occurred smoothly (Scheme 23b), affording the corresponding α-amination products in high yields (up to >99%) with excellent enantioselectivities (up to >98% ee).[39] In sharp contrast, the corresponding (*P*)-form catalyst supplied nearly racemic mixtures in high yield. Subsequently, the types of pronucleophiles were further extended to 2-alkyoxycarbonyl-1,3-dithiane (Scheme 23c), thionolactones (Scheme 23d), substituted epoxides (Schemes 23e) and 2-benzylpyridine N-oxides (Scheme 23f)[40] with modified or the same catalysts.

5. Combination of chiral guanidines and guanidinium salts with metal species

In addition to their application as organocatalysts, guanidines and their derivatives potentially emerge as a useful class of ligand resulting from their σ-donating character. However, compared with well-established negatively charged guanidinates, the application of the neutral guanidines in coordination



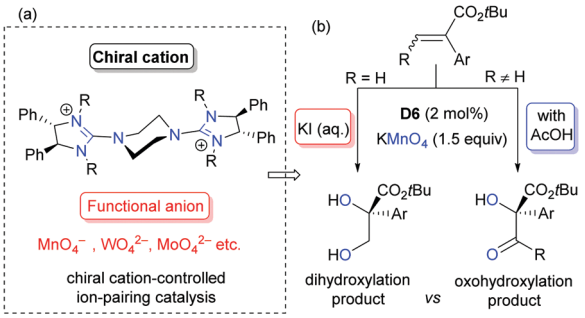
Scheme 23 (a) The design of chiral bis(guanidino)iminophosphorane organosuper bases; (b–f) their utility in asymmetric catalytic transformations.

chemistry is still in its infancy.[41] Bailey, Henkel, and Coles have described the synthesis of diverse metal complexes with either open-chain guanidines[42] or bicyclic guanidines.[12] However, the catalytical behavior of metal–guanidine complexes was seldom investigated. Moreover, guanidinium cations were also found in many complexes. In the past several years, several important achievements of the combination of chiral guanidines and their derivatives with metal species have been acquired.

5.1 Ion-pairing catalysis of metal–guanidinium salt

As mentioned above, guanidinium salts were proved to be a highly efficient class of phase-transfer catalysts. Usually, the basic hydroxide and carbonate were investigated as the functional anion to initiate the reaction. Other kinds of functional anions such as CN^-, ClO^- and IO^- were also described by several groups but with much less successful examples in asymmetric versions.

In this context, the Tan group described chiral guanidinium salt cation catalyzed asymmetric oxidation of multi substituted

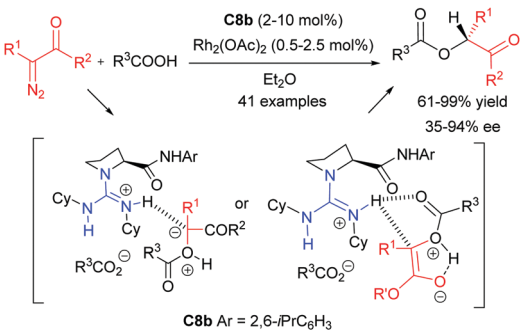


Scheme 24 (a) Chiral guanidinium-controlled ion-paring catalysis; (b) its application in oxidation of alkenes.

α,β-unsaturated esters in the presence of potassium permanganate (Scheme 24).[34,43] Interestingly, under the influence of the catalyst **D6d** and aqueous KI, the dihydroxylation reaction occurred smoothly, delivering the desired diols in moderate to high yields with excellent chiral control (60–72% yield, and 84–96% ee). Alternatively, subjecting trisubstituted alkenes under the conditions of the catalyst **D6b** with acetic acid as the additive afforded enantioenriched 2-hydroxy-3-oxocarbonyl esters in high yields *via* oxohydroxylation. Other anions (*e.g.* WO_4^{2-} and MoO_4^{2-}) were also amenable to ion-paring catalysis.[34] The mechanism and active catalyst were elucidated through Raman spectroscopy, computational studies and X-ray crystal analysis. Tan and co-workers introduced the metallic anions as the counterparts of the chiral guanidinium cations, developing a new strategy of chiral cation induced ion-paring catalysis. This not only provided a complementary approach to chiral anion-controlled ion-pairing catalysis, but also widely extended the applications of chiral guanidinium salts in asymmetric synthesis.

5.2 Cooperative catalysis by chiral guanidine and metal salt

The combination of asymmetric organocatalysis and metal catalysis provided a powerful approach to the creation of unprecedented enantioselective transformations.[44] Liu and coworkers disclosed the first highly enantioselective O–H insertion of carboxylic acid with α-diazo carbonyl compounds catalyzed by chiral guanidine **C8b** and $Rh_2(OAc)_4$ cooperative catalysis (Scheme 25). A broad range of α-diazoesters and



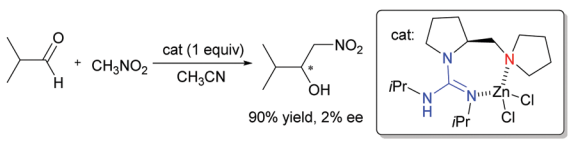
Scheme 25 Synergetic guanidine **C8b** and $Rh_2(OAc)_4$ for O–H insertion with carboxylic acid.

α-diazoketones along different carbonyl acids were studied and afforded optically active α-acyloxy carbonyl compounds in high yields with good to excellent ee values (61–99% yield, 35–94% ee).[45] The reaction of $Rh_2(OAc)_4$ and diazo compounds afforded a metallo-carbene intermediate with the liberation of dinitrogen, which was subsequently attached by the hydroxyl group of carboxylic acid to form the oxonium ylide. The readily formed guanidinium carboxylate served as a chiral proton shutter to transfer the proton to the oxonium ylide or an enolate in an enantioselective manner.

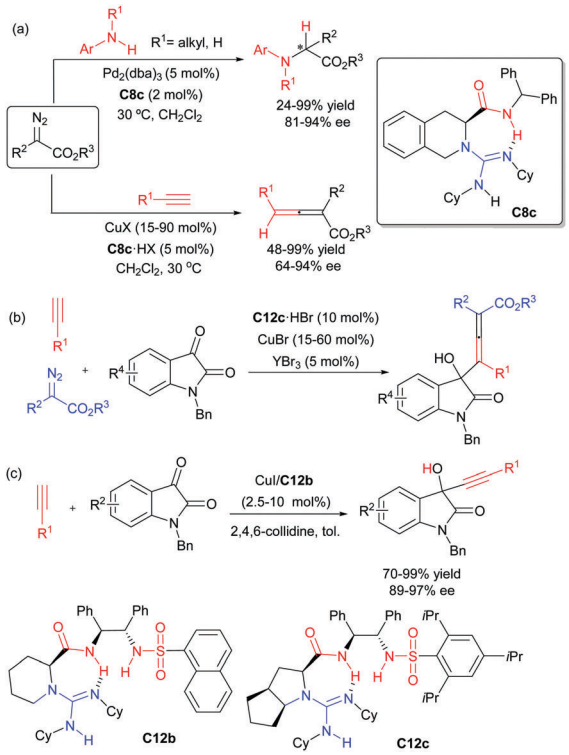
5.3 Chiral metal–guanidine complex catalysis

Typically, in guanidine metal complexes, the imine nitrogen atom in guanidine coordinates to the acceptor orbitals of the metal center through its lone pair. In 2005, the Anders group reported the synthesis of chiral Zn^{II}–guanidine or Mo^0–guanidine complexes and investigated the catalytic behavior of chiral Zn^{II}–guanidine complexes in the Henry reaction, albeit with unsatisfactory outcomes (Scheme 26). The structure of the catalyst was confirmed by X-ray crystal structure analysis,[46] in which both the N^{imine} atom of guanidine and N atom of pyrrolidine coordinated with Zn^{II}.

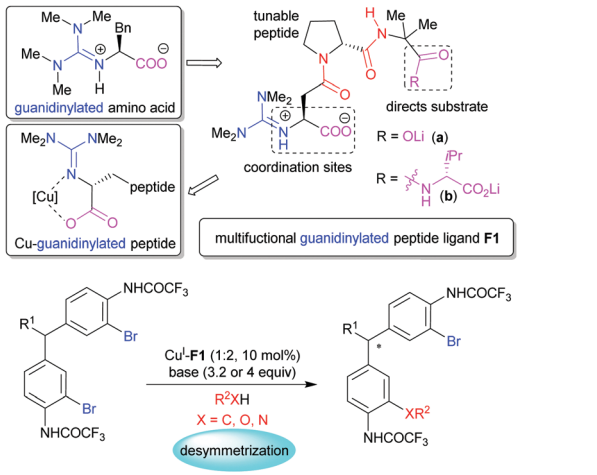
Feng, Liu and co-workers attempted to investigate their chiral guanidines **C8** and **C12** combined with metal salts as new catalysts in asymmetric reaction and made a breakthrough. In 2014, they reported a chiral guanidine **C8c**/palladium(0) mediated N–H insertion of α-diazoesters with secondary and primary anilines (Scheme 27a), and various enantioenriched α-amino acid derivatives were readily achieved in moderate to high yields with excellent ee values (24–99% yield, and 81–94% ee).[47] Although the real active species remains unknown, the interaction between $[Pd_2(dba)_3]$ and guanidine **C8c** was confirmed by fluorescence and UV/vis absorption spectroscopy studies. Subsequently, they employed CuBr·SMe_2 and chiral guandinium **C8c**·HBr as the catalyst in the highly enantioselective C–H insertion of terminal alkynes to α-diazoesters (Scheme 27a).[48] Diverse chiral allenoates were isolated in good yields and high enantioselectivities. An obvious ligand-acceleration effect was observed. On the basis of control experiments, they disclosed that the allenoate products were formed through enantioselective protonation of an organocopper intermediate rather than asymmetric isomerization of alkynoate byproducts. Very recently, asymmetric three-component reaction of terminal alkynes, α-diazoesters and isatins was realized in the presence of chiral guanidinium–CuBr and YBr_3 (Scheme 27b).[49] The combined-acid systems (Lewis acid combined with assisted Lewis acid or Brønsted acid combined with assisted Lewis acid) were proposed to be



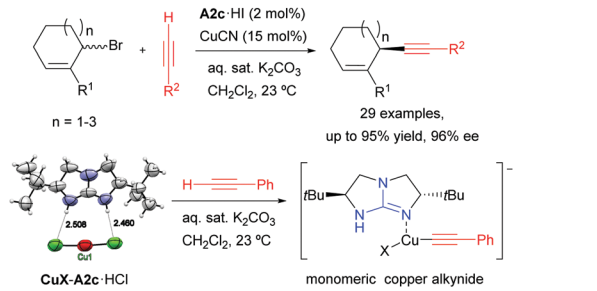
Scheme 26 Chiral Zn^{II}–guanidine complex catalyzed Henry reaction.



Scheme 27 (a) N–H and C–H insertion of α-diazoesters, (b) three-component reaction of alkynes, α-diazoesters and isatins, and (c) alkynylation of isatins.



Scheme 28 Cu^{I}-Guanidinylated peptide catalyzed cross-coupling.



Scheme 29 Guanidine(copper) complex catalyzed-enantioselective allylic alkynylation of racemic cyclic allylic bromides.

responsible for higher reactivity by associative interaction and allow for an equally effective asymmetric environment. Furthermore, in the presence of CuI, chiral guanidine ligand **C12a** and 2,4,6-collidine, the asymmetric alkynylation of isatins with terminal alkynes occurred smoothly, affording a series of optically active propargylic alcohols in high yields (Scheme 27c).[50]

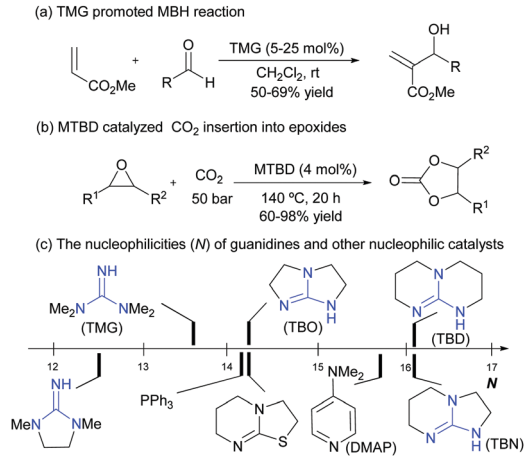
The potential of chiral guanidine–base metal complex catalysis was also discovered by Miller and coworkers in the study of small molecular peptide catalysis. They developed a new family of guanidine-based peptides **F1** which were employed as multifunctional ligands in Cu^{I} catalyzed cross-coupling reactions.[51] It was found that with Cu^{I}–**F1** as the catalyst, malonate derivatives, alcohols, and amines were suitable nucleophiles in the enantioselective desymmetrization of diarylmethanes *via* C–C,[51] C–O,[52] and C–N[53] bond forming cross-coupling (Scheme 28). Both the guanidine unit and vicinal carboxylate moiety were proposed to coordinate with Cu^{I} to form an active species for oxidation addition into the Ar–Br bond. Moreover, the length and stereochemical array of the peptide as well as the ionic-type interaction between the C-terminus and the remote arena in the substrates played important roles in the highly asymmetric induction.

Recently, Tan and co-workers described a highly enantioselective allylic alkynylation of racemic cyclic allylic bromides with terminal alkynes in the presence of CuCN and **A2c**·HI under biphasic conditions.[54] Various six- or seven-membered cyclic 1,4-enynes were obtained in high yields with excellent enantioselectivities (Scheme 29). Although a chiral guanidinium cuprate ion pair containing CuCl and **A2c**·HCl was identified by X-ray diffraction analysis, the control experiments, cold-spray ionization mass spectrometry, and DFT calculations indicate that the chiral guanidinium cuprate ion pair is the catalyst precursor and nucleophilic anionic (guanidine)copper complexes $[\mathbf{A2c}\text{-}Cu(R)X]^{-}$ (R = alkynides; X = Br or CN) might be the active catalytic species.

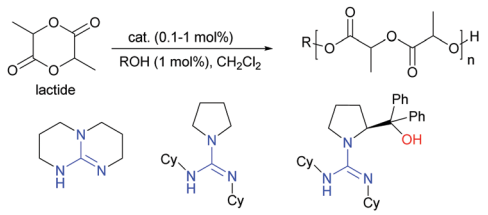
In addition, although various metal–guanidinate complexes were synthesized and well characterized by X-ray crystal diffraction analysis, their applications in homogeneous catalysis are less studied.[13] The unique features of these complexes, coupled with some of the established chiral guanidines, underscores the potential of chiral metal–guanidinate complexes in homogeneous catalysis.

6. Miscellaneous catalysis

The use of guanidine as a Lewis base have been confirmed to be efficient in several classic Lewis bases promoted organic transformations including Morita–Baylis–Hilman (MBH) reaction (Scheme 30a), the activation of CO_2 (Scheme 30b) and so on.[4,9,10] A detailed knowledge of the nucleophilicity of guanidines was demonstrated by Mayr's group with the use of a photometric benzhydrilium ion method, which revealed that the structure of guanidines has a significant effect on the nucleophilicity parameter (*N*). As shown in Schemes 30c, [4,4,0]-bicyclic TBD exhibits



Scheme 30 The nucleophilicities of guanidines and others.



Scheme 31 Guanidine catalyzed ROP of lactide.

the strongest nucleophilicity, while imidazolidine-2-imine-based guanidine is approximately 3.7 orders of magnitude less nucleophilic than TBD.[55]

Employing bicyclic TBD and acyclic guanidine as the catalysts (Scheme 31), Waymouth's group described the ring-opening polymerization (ROP) of lactide with narrow polydispersity, and end-group fidelity as well as predictable molecular weights.[16] They also attempted the stereocontrolled ring-opening polymerization in the presence of a chiral guanidine catalyst, however, only slight stereoselectivity for the ROP of *rac*-lactide was observed. Theoretical calculations combined with NMR studies indicate that a full H-bonding mechanism is favored over the alternative nucleophilic pathway.

Besides, due to the presence of the cationic π_4^6-system, the delocalized guanidinium could serve as a Lewis acid in principle. However, the relative reports in this area are still rare.[10,17]

Conclusions

This tutorial review highlights representative progress in the design and applications of chiral guanidines and their derivatives. Within the past ten years, chiral guanidines and guanidiniums were expanded to be used as Brønsted base catalysts and Brønsted acid catalysts respectively in numerous new reactions. At the same time, several novel chiral guanidine derivatives [*e.g.*, guanidinium salt, pentanidium, bis(guanidino)-iminophosphorane] enabled new and highly effective strategies for the synthesis of complex molecules. Moreover, the combination of chiral guanidines and their derivatives with metal cation or anion species dramatically expanded their utility and provided solutions to challenging transformations of importance that cannot be achieved with conventional chiral Lewis base catalysts. Despite the rapid and fruitful progress described above, this field still leaves space for further development. The activation of less acidic substrates remains a challenge that necessitates the design of improved Brønsted base catalysts with a guanidine moiety or other stronger basic functionalities. Due to the wide variety of possible activation modes and its unique ability to activate inactive chemical bonds as demonstrated by metal catalysis, further combination of chiral guanidines and their derivatives with other metal species could lead to the creation of new step-economical protocols for the synthesis of structurally diverse molecules. The development of chiral guanidines and their derivatives makes them viable for other applications, for example, synthesis of novel precursors for materials science and the synthesis of chiral polymers. On the other hand, mechanistic studies are needed for a better understanding of guanidine catalysis and catalyst design. Finally, the application of chiral guanidine and their derivatives in asymmetric catalysis still demands further exploration.

Conflicts of interest

There are no conflicts to declare.

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