

Review

The Enantiopure 1,2-Diphenylethylenediamine (DPEDA) Motif in the Development of Organocatalysts for Asymmetric Reactions: Advances in the Last 20 Years

Shilashi Badasa Oljira ¹, Martina De Angelis ², Andrea Sorato ³, Giulia Mazzocanti ¹, Simone Manetto ¹, Iliara D'Acquarica ^{1,*} and Alessia Ciogli ^{1,*}

- ¹ Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P.le Aldo Moro 5, 00185 Rome, Italy; shilashibadasa.oljira@uniroma1.it (S.B.O.); giulia.mazzocanti@uniroma1.it (G.M.); simone.manetto@uniroma1.it (S.M.)
- ² Dipartimento di Chimica, Sapienza Università di Roma, P.le Aldo Moro 5, 00185 Rome, Italy; m.deangelis@uniroma1.it
- ³ PAT Way Solutions S.r.l., via Appia Antica 75, 00178 Rome, Italy; andrea.sorato@patway.it
- * Correspondence: ilaria.dacquarica@uniroma1.it (I.D.); alessia.ciogli@uniroma1.it (A.C.)

Abstract: 1,2-Diphenylethylenediamine (DPEDA) is a privileged chiral scaffold being used in the construction of a broad variety of organocatalysts and ligands for enantioselective organic reactions. This molecule gave a significant contribution in the synthesis of structurally different bi-/multifunctional organocatalysts. DPEDA played an essential role in the development of organocatalysts capable of yielding important information on the different reaction mechanisms, like enamine, iminium, hydrogen-bonding and anion-binding catalysis. The aim of the present review is to highlight and summarize the achievements reached in the last 20 years (2004–2024) in the chemistry of DPEDA-based organocatalysts for asymmetric synthesis.

Keywords: 1,2-Diphenylethylenediamine; asymmetric reactions; organocatalyst



Citation: Oljira, S.B.; De Angelis, M.; Sorato, A.; Mazzocanti, G.; Manetto, S.; D'Acquarica, I.; Ciogli, A. The Enantiopure 1,2-Diphenylethylenediamine (DPEDA) Motif in the Development of Organocatalysts for Asymmetric Reactions: Advances in the Last 20 Years. *Catalysts* **2024**, *14*, 915. <https://doi.org/10.3390/catal14120915>

Academic Editor: Shaofeng Liu

Received: 7 November 2024

Revised: 3 December 2024

Accepted: 6 December 2024

Published: 12 December 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The use of small chiral organic molecules as catalysts in organic reactions (i.e., the asymmetric organocatalysis) is a well-established tool for the synthesis of enantiomerically enriched molecules [1,2]. Benjamin List and David MacMillan were awarded the Nobel Prize in Chemistry 2021 with the motivation, “for the development of asymmetric organocatalysis” [3]. 1,2-Diphenylethylenediamine (DPEDA, aka, 1,2-diamino-1,2-diphenylethane) is a chiral diamine with C_2 symmetry containing two stereogenic centers and available in the two enantiomeric (+)-(1*R*,2*R*)-DPEDA [CAS Number 35132-20-8] and (−)-(1*S*,2*S*)-DPEDA [CAS Number 29841-69-8] versions (Figure 1). A convenient gram-scale of both enantiopure diamines was reported in 2006 [4]. DPEDA has become an excellent chiral building block in the construction of hydrogen-bond donor (HBD) organocatalysts for asymmetric synthesis [5], as well as in the preparation of chiral silica-based materials for chromatography [6–8] and for the design of pharmaceutical compounds [9]. DPEDA-derived scaffolds, which range from small molecules to macromolecules, have found large applicability in enantioselective organic reactions. Since the DPEDA scaffold provides a well-defined conformationally restrained environment, it proved advantageous in the preparation of synthetic anion transporters [10]. As an organocatalyst, DPEDA is widely employed in the enantioselective functionalization of carbonyl compounds by means of aldol, Michael, Mannich and Diels–Alder reactions [11–13]. The most dominant substrates in these reactions are ketones, aldehydes, 3-substituted oxindoles and 1,3-dicarbonyl compounds.

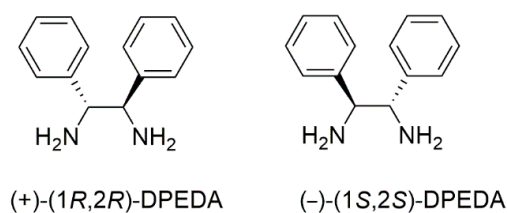
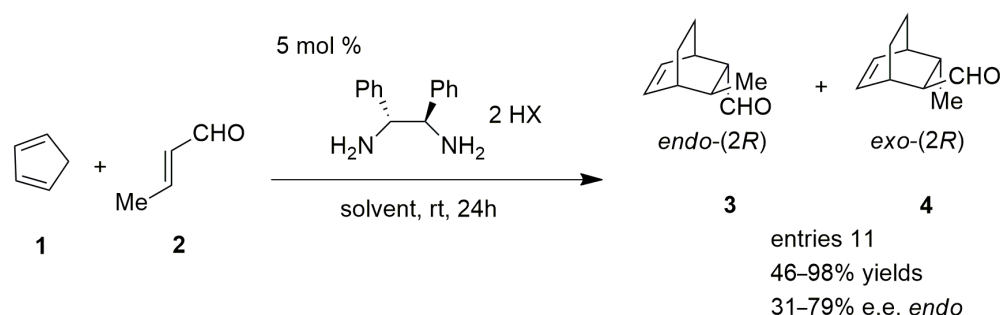


Figure 1. Chemical structure of the chiral organocatalyst 1,2-diphenylethylenediamine (DPEDA). $C_{14}H_{16}N_2$ (MW 212.29). Alternate names: 1,2-diphenyl-1,2-ethanediamine; 1,2-diamino-1,2-diphenylethane; stilbenediamine; α,β -diaminodihydrostilbene [11].

We recently became interested in the remarkable results achieved by resorting to DPEDA-based organocatalysts in the outcome of stereoselective organic reactions. We selected from the literature (2004–2024) the relevant articles dealing with the application of organocatalysts containing the DPEDA scaffold in asymmetric syntheses. Different model reactions in each asymmetric synthesis were illustrated and discussed.

2. Underivatized 1,2-Diphenylethylenediamine (DPEDA)

In this section, we have considered the role of the DPEDA molecule as vicinal diamine in asymmetric reactions. In 2005, the ammonium salts of (1*R*,2*R*)-DPEDA proved capable of directly catalyzing the enantioselective Diels–Alder reaction between cyclopentadiene **1** and (*E*)-crotonaldehyde **2** (Scheme 1) [14]. The reactions were performed using different solvent systems (MeOH/ H_2O , THF/ H_2O , DME/ H_2O , dioxane/ H_2O and H_2O) in the presence of several HX acids (HCl, HBr, $HClO_4$, *p*-TsOH, CF_3CO_2H and $CH_3(CH_2)_{11}C_6H_4SO_3H$). In all the cases, yields up to 98% and *endo* enantiomeric excesses (e.e.) ranging between 31% and 79% were obtained.



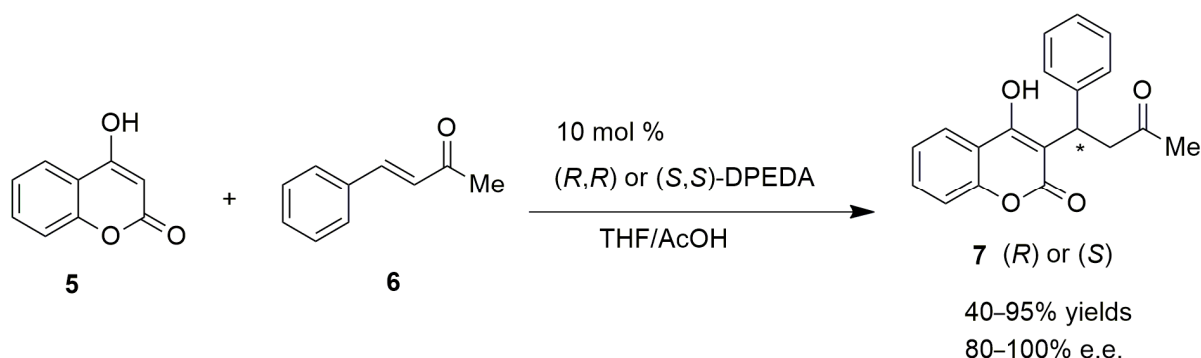
Scheme 1. Enantioselective Diels–Alder cycloaddition between cyclopentadiene and (*E*)-crotonaldehyde catalyzed by bisammonium salts of (1*R*,2*R*)-DPEDA.

In 2010, a green enantioselective approach to the synthesis of (*R*) or (*S*)-warfarin **7** for an undergraduate organic laboratory was developed, based on the Michael addition of 4-hydroxycoumarin **5** to (*E*)-4-phenyl-3-buten-2-one **6** and using 10 mol % (1*R*,2*R*)- or (1*S*,2*S*)-DPEDA, respectively, as the catalysts. Good yields (40–95%) and enantiopurities (80–100% e.e.) were typically obtained for the anticoagulant drug, after recrystallization by ethanol (Scheme 2) [15]. In line with this approach, a green protocol for the Michael addition in water was proposed in 2016 [16].

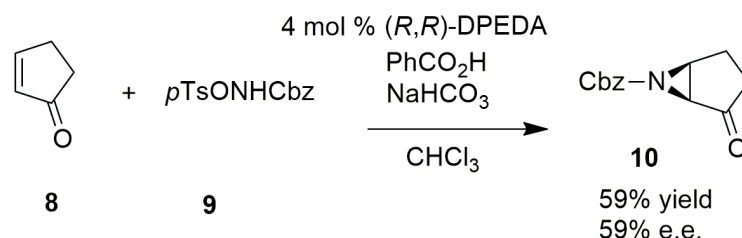
The asymmetric aziridination of cyclic enones (e.g., **8**) with *N*-tosyloxy benzylcarbamate **9** as the nitrogen source and using (1*R*,2*R*)-DPEDA as the catalyst (Scheme 3) was reported in 2011 [17], with the aim of yielding chiral aziridines (e.g., **10**), which are key building blocks in the synthesis of amino acids, natural products and pharmaceuticals [18].

The stereoselective synthesis of functionalized cyclopropanes plays a key role in the synthesis of pharmaceutical and natural products. In 2013, the asymmetric cyclopropanation of cinnamone derivatives **11** with stabilized sulfur ylide **12** (Scheme 4) was achieved using (1*S*,2*S*)-DPEDA as the catalyst [19]. The desired cyclopropanation adduct **13** was obtained under mild conditions with a good enantioselectivity (e.e., 73%) and an excellent

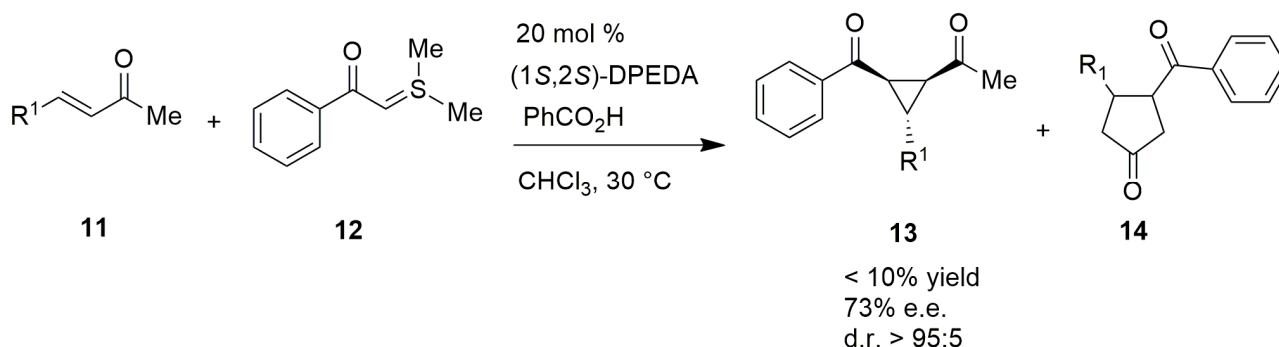
diastereoselectivity (d.r. > 95:5), but in very low yield (<10%). This strategy provides a potential method for the formation of 1,2,3-trisubstituted cyclopropane compounds.



Scheme 2. Synthesis of (*R*)- or (*S*)-warfarin **7** in the presence of DPEDA as the catalyst.



Scheme 3. Aziridination of cyclic enones in the presence of (*R,R*)-DPEDA as the catalyst.



Scheme 4. Asymmetric cyclopropanation of cinnamone ($R^1 = \text{Ph}$) with a stabilized sulfur ylide catalyzed by (1*S*,2*S*)-DPEDA.

3. Monofunctionalized 1,2-Diphenylethylenediamine (DPEDA)

The introduction of functional groups (G) on one of the two primary amino groups of DPEDA leads to primary-secondary and primary-tertiary diamine scaffolds (Figure 2). The concept that (bi)multifunctional catalysts enhance the importance of catalytic asymmetric synthesis as a method for preparing optically active compounds was born a long time ago [20,21]. In contrast, an increasing production of multifunctional catalysts has been well documented starting from the last 15–20 years [22].

3.1. Primary-Secondary Diamine Organocatalysts

The primary-secondary diamine system has shown to lead to better results in terms of yield and stereoselectivity of the catalyzed reaction, with respect to the underivatized catalyst. For instance, by the introduction of one cyclohexyl substituent in the (1*S*,2*S*)-DPEDA catalyst structure, compound **13** (Scheme 4) was obtained in a 61% yield and 85% e.e.

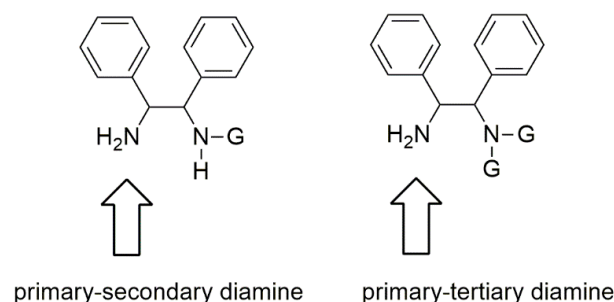
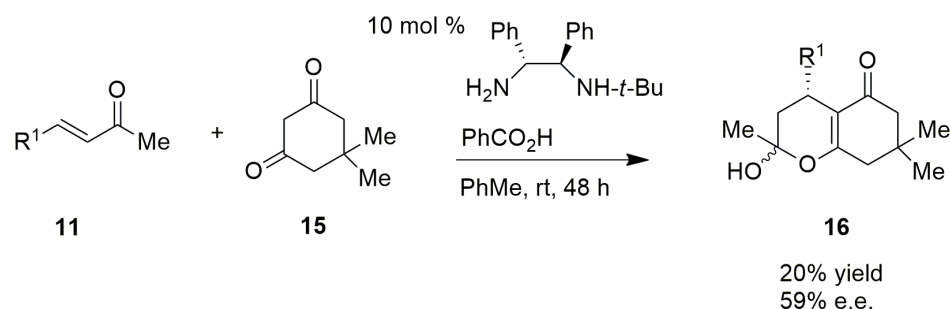


Figure 2. Monofunctionalization of the DPEDA catalyst.

The asymmetric Michael cyclization of aliphatic cyclic 1,3-dicarbonyl compounds with unactivated α,β -unsaturated ketones is a powerful method to synthesize biologically active chiral compounds. In 2012, the addition of cinnamone derivative **11** and dimedone **15** was used as a model reaction to screen the optimal conditions to obtain enantiopure 3,4-dihydropyran derivatives (e.g., **16**) in the presence of DPEDA-based catalysts (Scheme 5) [23]. Compound **16** was confirmed to exist as a mixture of rapidly interconverting anomers [23].



Scheme 5. Enantioselective synthesis of 3,4-dihydropyran derivatives ($R^1 = \text{Ph}$).

In this study, however, the simple unmodified (1*R*,2*R*)-DPEDA molecule yielded superior results in terms of reaction yield and stereoselectivity with respect to the monofunctionalized ($G = t\text{-Bu}$) diamine (30% and 92% e.e. vs. 20% and 59% e.e., respectively).

Various monofunctional thiourea derivatives of DPEDA (Figure 3) have been developed in the literature and applied as organocatalysts for different enantioselective reactions [24–27]. The basic idea under the design of such catalysts is the double activation [28] of the two reacting partners, i.e., the electrophile substrate and the nucleophile donor through hydrogen bonds formation [24,25]. A comprehensive review (with 121 references cited) on the progress in thiourea-, urea-, and squaramide-based Brønsted base/H-bonding (BB/HB) bifunctional catalysts was published in 2023 [29], highlighting the pioneering ideas and the most recent contributions to the area.

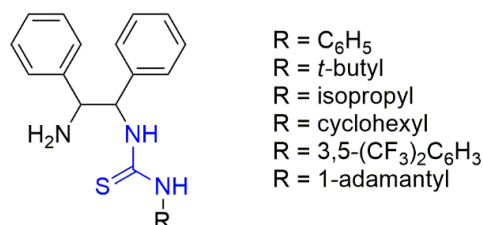
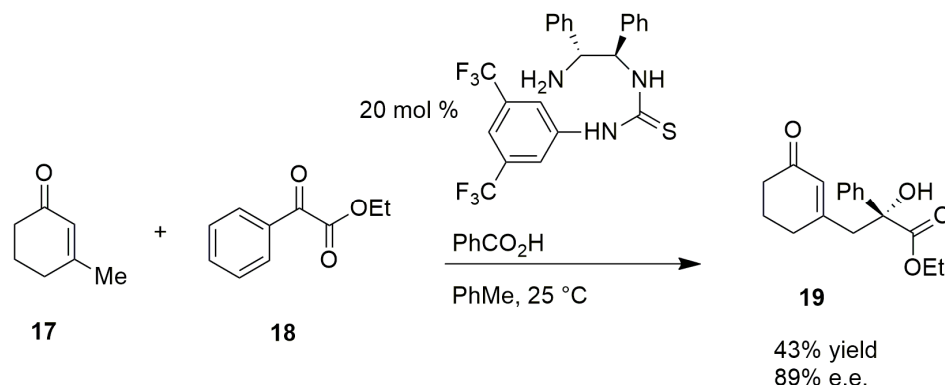


Figure 3. Monofunctional thiourea derivatives of the DPEDA catalyst.

The catalyst bearing the 3,5-bis(trifluoromethyl)phenyl moiety (Figure 3, $R = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$) has been employed in the enantioselective direct vinylogous aldol reaction of 3-methylcyclohex-2-enone **17** with α -ketoesters (e.g., **18**), affording the aldolic adduct **19** with a satisfactory level of stereoinduction (89% e.e.) (Scheme 6) [25].



Scheme 6. Enantioselective vinylogous aldol reaction with (*R,R*)-DPEDA-thiourea catalysts.

A plausible bifunctional mode of action of the catalyst, which accounts for the observed stereochemical outcome, is depicted in Figure 4 [25].

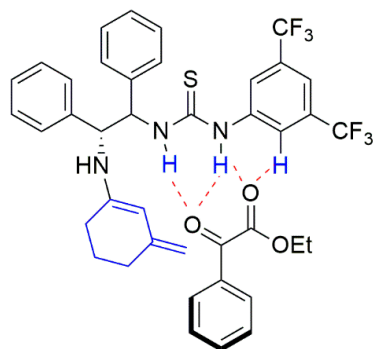


Figure 4. Plausible bifunctional mode of action of the primary DPEDA thiourea catalyst with $R = 3,5\text{-(CF}_3)_2\text{-C}_6\text{H}_3$.

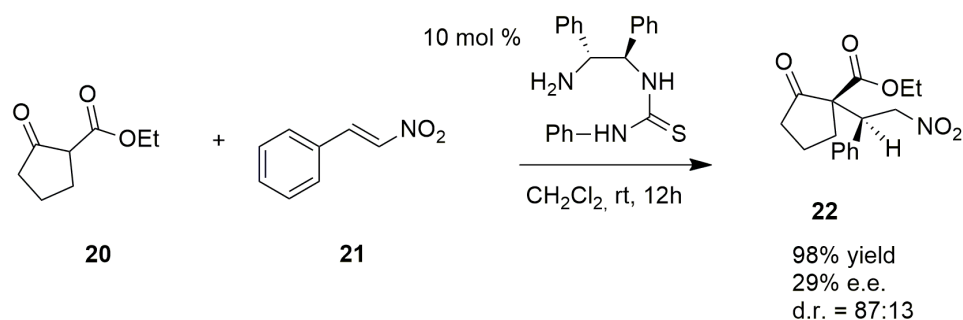
Another interesting synthetic approach was developed for the asymmetric Michael addition of nitroalkenes under neutral conditions [26]. Due to the highly electron-deficient properties of the nitro group, which is, furthermore, easily converted into other functional groups, including ketones, esters, amine and carboxylic acids, nitro-group-containing Michael acceptors are considered an attractive tool for the construction of highly functionalized building blocks.

Different (*1R,2R*)-DPEDA-derived thioureas were investigated in the asymmetric Michael addition reactions of β -ketoesters (e.g., ethyl 2-oxocyclopentanecarboxylate **20**) to *trans*- β -nitrostyrene **21** (Scheme 7) [26]. The desired product **22** was obtained in high yield (98%), but with minor enantioselective performance (87:13 d.r. and 29% e.e.) compared to the results yielded by introducing a further substituent group (e.g., 3-pentyl) on the free DPEDA amino group (see Section 4.5).

The same research group explored the performances of the (*1R,2R*)-DPEDA-derived thiourea catalysts in the enantioselective ring-opening of cyclic anhydrides by thiolysis and aminolysis at low temperatures [27]. The presence of an alkyl group on the free DPEDA amino group was confirmed as a crucial requirement for the stereochemical outcome of these reactions (see Section 4.5).

In 2022, novel C_2 -symmetric primary amine-1,3-bis-thiourea organocatalysts (**23–26**) were described (Figure 5) [30] and applied in the enantioselective Michael addition of carbonyl compounds to α,β -unsaturated systems, obtaining products with excellent yields (73–97%) and enantioselectivities (95–99%). Nitroalkenes and *N*-phenylmaleimide were investigated as model electrophiles in the reactions. Based on B3LYP density functional theory (DFT) calculations, the authors of the study demonstrated that the reactions take place within the cleft of the catalysts where noncovalent supramolecular interactions are

established with the substrate via hydrogen bonding. Notably, also, the immobilized organocatalyst **26** gave good yields and enantioselectivities in the above-mentioned reactions, under heterogeneous conditions.



Scheme 7. Asymmetric Michael addition of β -ketoesters to *trans*- β -nitrostyrene.

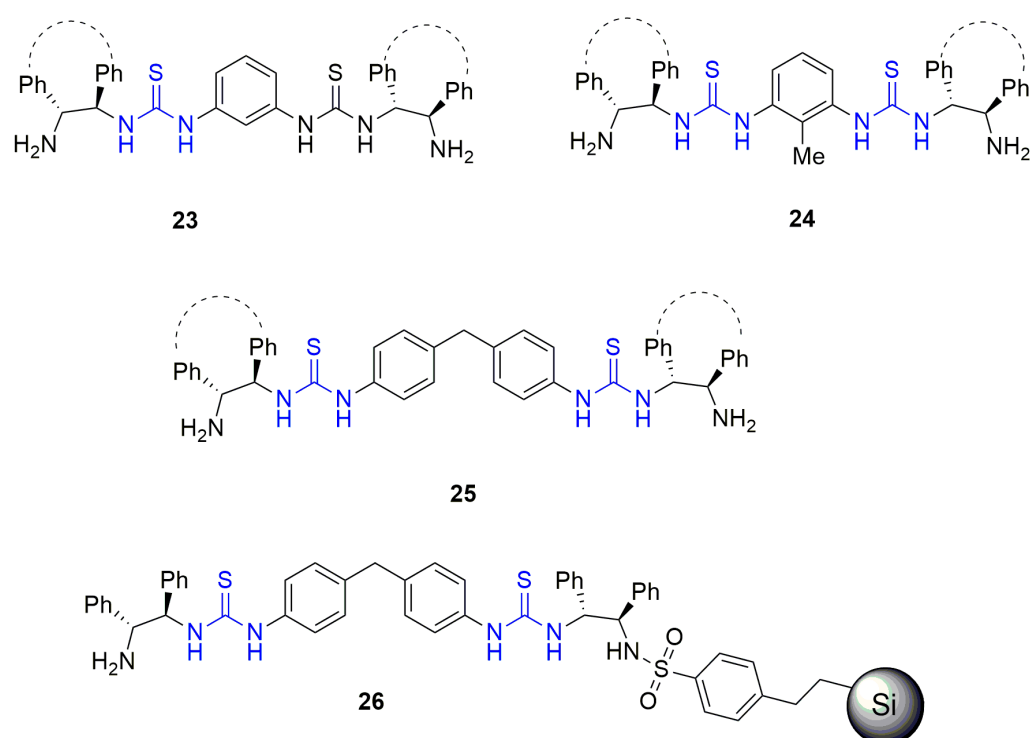


Figure 5. Structures of C_2 -symmetric (1*R*,2*R*)-DPEDA-1,3-bis-thiourea organocatalysts.

3.2. Primary-Tertiary Diamine Organocatalysts

The introduction of two substituents on the same nitrogen atom of the DPEDA molecule led to primary-tertiary diamine scaffolds (Figure 2). In 2014, the (1*R*,2*R*)-DPEDA-based organocatalysts **27–33** (Figure 6) were synthesized, featuring aliphatic groups with different sizes on the nitrogen atom. Such catalysts were fine-tuned for the enantioselective cross-aldol reaction between trifluoromethyl aromatic ketones (e.g., **35**) and linear aliphatic ketones (e.g., acetone **36**) (Scheme 8) [31]. Under optimized reaction conditions (5% mol catalyst **33**, 10% mol *p*-toluenesulfonic acid, toluene, 0° C, 24 h) excellent yields (up to 99%) and enantioselectivities (up to 94% e.e.) for the desired (*S*)-trifluoromethyl tertiary alcohols (e.g., **37**) were obtained.

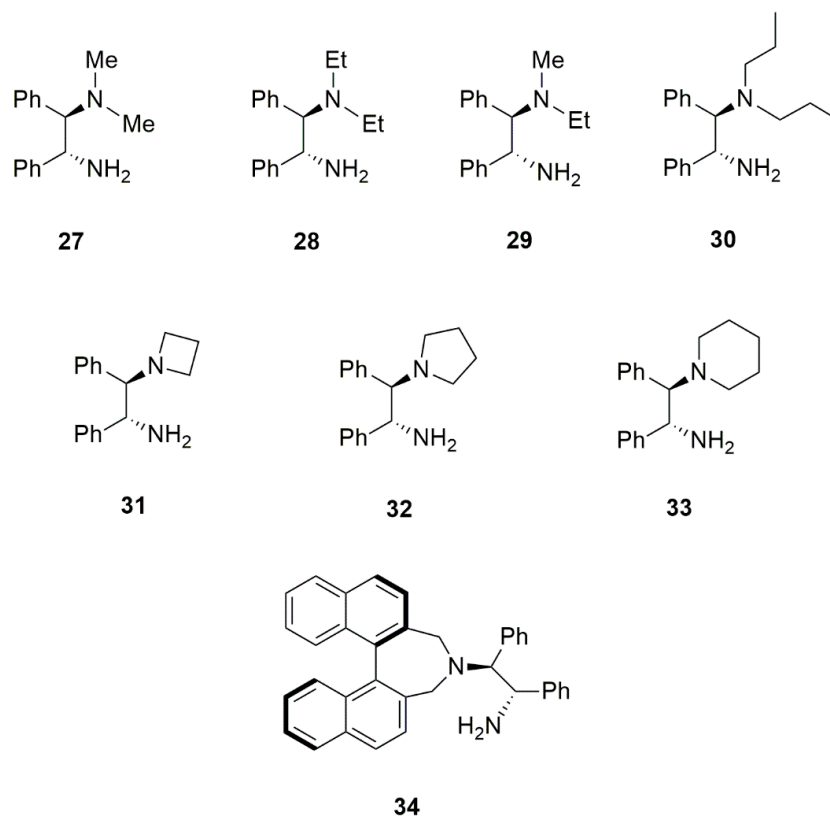
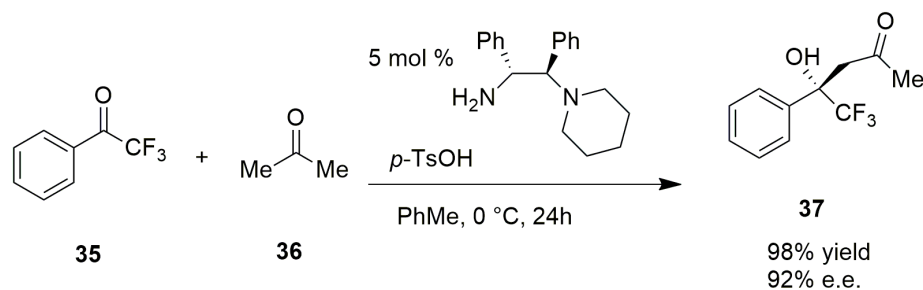


Figure 6. Structures of primary-tertiary (1*R*,2*R*)-DPEDA-based (27–33) and (1*S*,2*S*)-DPEDA-based (34) organocatalysts.

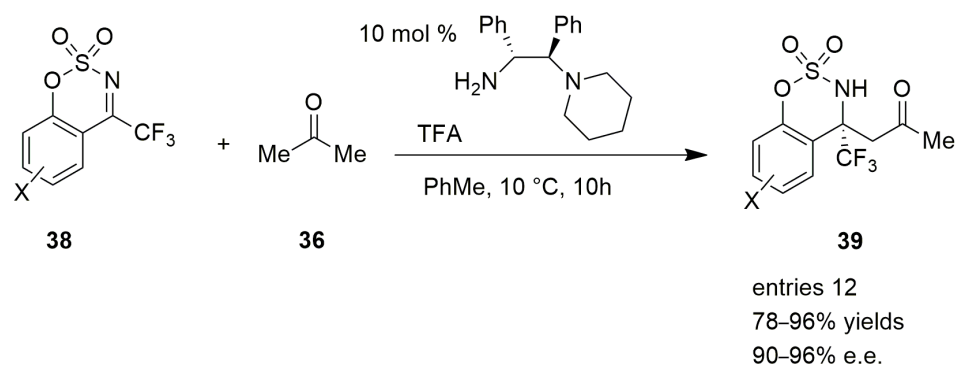


Scheme 8. Asymmetric cross-aldol reactions of trifluoromethyl aromatic ketones with linear aliphatic ketones using primary-tertiary (1*R*,2*R*)-DPEDA-based organocatalysts.

The authors of the study also investigated the (1*R*,2*R*)-1,2-diaminocyclohexane (DACH) backbone by synthesizing the corresponding *N,N*-disubstituted primary-tertiary diamine catalysts [31]. The DPEDA-based scaffold proved better than the DACH-based one in catalyzing the considered aldol reactions.

Two years before, another research group had synthesized binaphthyl-modified (1*S*,2*S*)-DPEDA catalyst **34** (Figure 6) [32], which was tested in the Michael addition reaction between 4-hydroxycoumarin **5** and (*E*)-4-phenyl-3-buten-2-one **6** (see Scheme 2 for structures). The reaction afforded biologically valuable derivatives of (*R*)-warfarin **7** (Scheme 2) with up to 90% enantiomeric excesses and up to 80% yields obtained. Notably, the (*S,S*)-stereochemistry of catalyst **34** influenced the stereochemical outcome of the reaction in an opposite way with respect to the case of the underivatized DPEDA catalyst [15], as a result of the difference in the steric hindrance of the iminium-ion intermediate.

More recently, catalyst **33** (Figure 6) was used in the Mannich reaction of cyclic *N*-sulfonyl trifluoromethylated ketimines **38** with methyl ketones (e.g., acetone **36**) (Scheme 9) [33], affording the desired products (e.g., **39**) with high enantioselectivity (90–96% e.e.).



Scheme 9. Asymmetric Mannich reaction of trifluoromethyl ketimines (X = F, Cl, Br, CF₃, Me, Ph, *t*-Bu, OMe) with acetone.

This study provided a new synthetic access to diverse enantioenriched benzo-fused cyclic sulfamidate *N*-heterocycles bearing a trifluoromethylated α -tetrasubstituted carbon stereocenter.

3.3. Squaramide-Type Organocatalysts

The squaramide motif (Figure 7) has recently entered organocatalysis for a wide range of asymmetric reactions, which provide convenient methods for the construction of complex molecular structures and chiral biologically active compounds [34]. Since the first report in 2008 demonstrating the capability of the squaramide unit to act as dual H-bond donor in bifunctional BB catalysis [35], many examples of amino-squaramides as bifunctional organocatalysts have appeared in the literature [36]. The squaramide functionality differs significantly from thiourea for several reasons, mostly for the distance between the two N–H groups, which was calculated to be approximately 2.72 Å for *N,N'*-dimethylsquaramide [35].

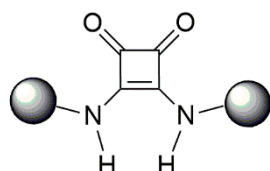


Figure 7. General structure of bifunctional squaramides catalysts.

In 2018, an environmentally friendly Michael addition reaction affording warfarin and related Michael adducts was developed by using 10 mol % catalysts (1*R*,2*R*)-**40** and (1*S*,2*S*)-**40** (Figure 8) and 2-methyltetrahydrofuran as green solvent [37]. Starting from 4-hydroxycoumarin **5** and (*E*)-4-phenyl-3-buten-2-one **6** (see Scheme 2 for structures), warfarin was directly produced in high yields (81–84%) and enantioselectivities (up to 99% e.e.). The (1*R*,2*R*)-**40** catalyst gave access to (*R*)-warfarin in > 99% e.e., whereas the (1*S*,2*S*)-**40** yielded (*S*)-warfarin in 92% e.e.

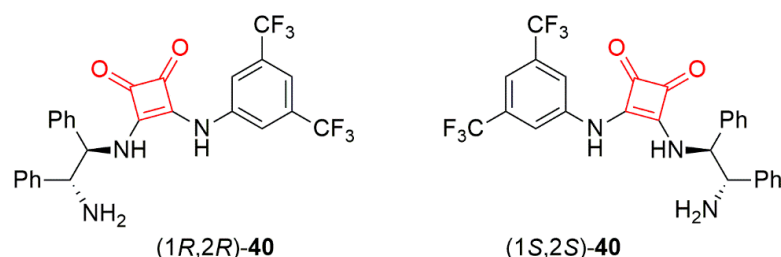


Figure 8. Structures of primary-amine squaramide (1*R*,2*R*)-DPEDA- and (1*S*,2*S*)-DPEDA-based organocatalysts.

DFT calculations at the ω B97XD/6-31G* level supported a stereochemical model where the catalyst promotes the reaction via an iminium activation of the enone and concomitant hydrogen-bond activation of the coumarin moiety (Figure 9).

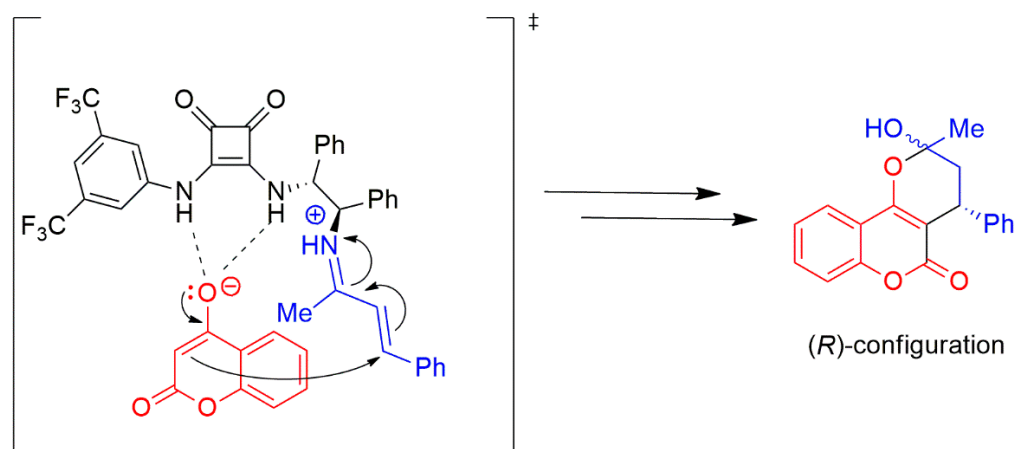


Figure 9. Stereochemical model for the Michael reaction of 4-hydroxycoumarin (red) with (*E*)-4-phenyl-3-buten-2-one (blue) catalyzed by catalyst (1*R*,2*R*)-40.

4. Bifunctionalized 1,2-Diphenylethylendiamine (DPEDA)

4.1. Bis(amino)-Functionalized Organocatalysts

The introduction of a functional group (G) on both the primary amino groups of DPEDA leads to bis-secondary and secondary-tertiary diamine scaffolds (Figure 10). The presence of one methyl group (G = Me) on each nitrogen atom of DPEDA yielded to a poorer organocatalyst in the Michael reaction between cinnamone **11** and dimedone **15** (Scheme 5), compared to the unmodified (1*R*,2*R*)-DPEDA and the monofunctionalized (with G = *t*-Bu) organocatalyst [23]. An interesting application of a secondary-tertiary DPEDA-based catalyst was reported in 2019 for the enantioselective synthesis of useful β -amino acid analogues [38].

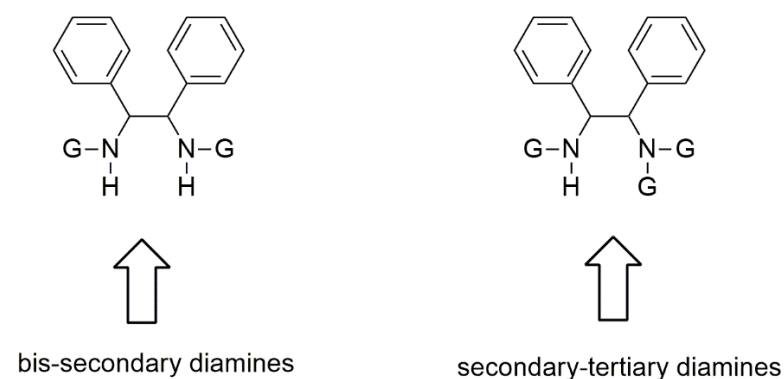
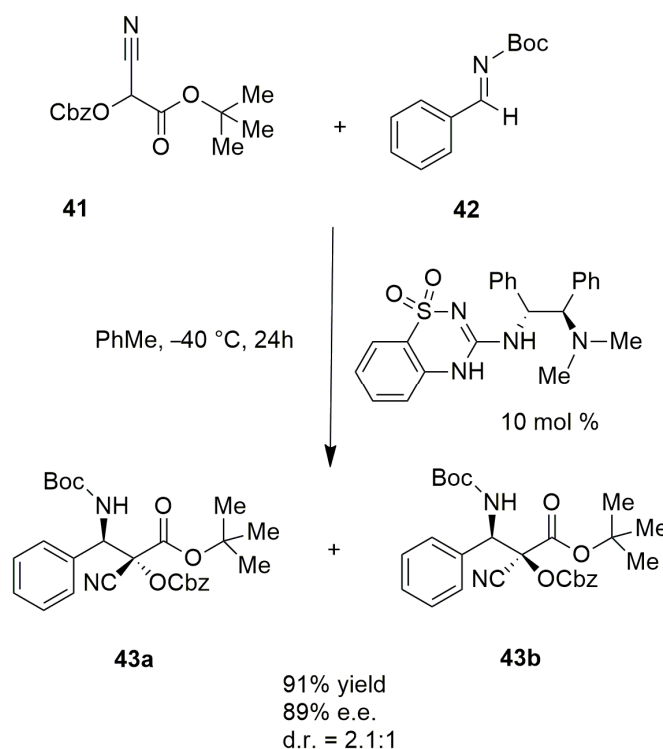


Figure 10. Bifunctionalization of the DPEDA catalyst.

The authors of the study focused on the cyanohydrin motif, which is regarded as a carbonyl equivalent in Mannich-type reactions. In particular, they envisaged to use a glyoxylate cyanohydrin (e.g., **41**) as the nucleophile, which was reacted at low temperature with a variety of both aliphatic and aromatic *N*-Boc-imines (e.g., **42**) (Scheme 10) [38]. The desired diastereomeric adducts **43a** and **43b** were obtained in 91% yields by using a benzothiadiazine derivative of the (1*R*,2*R*)-DPEDA molecule, but with a 2.1:1 diastereoselectivity ratio, and 89% e.e. for both the diastereomers.



Scheme 10. Enantioselective addition of glyoxylate cyanohydrins to *N*-Boc-imines catalyzed by a benzothiadiazine DPEDA bifunctional derivative.

The glyoxylate scaffold had been used in the functionalization of the DPEDA molecule to yield imidazoline (*S,S*)-**44** and (*R,R*)-**44** organocatalysts as a 1:1 mixture of diastereomers (Figure 11) [39]. Such catalysts have been tested in the Michael addition of cyclic 1,3-dicarbonyl compounds to α,β -unsaturated carbonyl compounds, including 4-hydroxycoumarin **5** and (*E*)-4-phenyl-3-buten-2-one **6** (Scheme 2), to give access to a number of important optically, biologically and pharmaceutically active compounds, besides warfarin. The latter was obtained in 90–96% yields and 80–82% e.e., whereas the similar (*S*)-proline catalyst yielded racemic warfarin in an 85% yield. As a possible explanation of the observed reaction stereochemistry, i.e., (*S*)-warfarin from (*S,S*)-**44** and (*R*)-warfarin from (*R,R*)-**44**, both an iminium-ion and a protonated-aminal intermediate species have been envisaged [39].

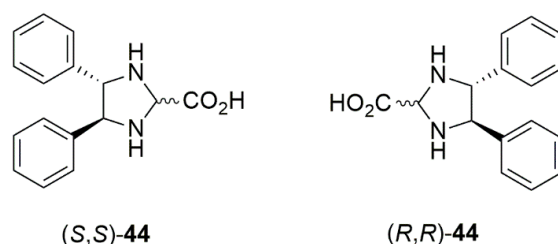


Figure 11. Structures of imidazoline DPEDA-based organocatalysts. Each catalyst was obtained as a 1:1 mixture of diastereomers.

4.2. Mixed-Amino-Amido-Functionalized Organocatalysts

With the aim of developing more efficient organocatalysts for asymmetric synthesis, including DPEDA-based catalysts, the multifunctional approach was investigated. In 2022, the mixed-amino-amido-functionalized (1*R*,2*R*)-DPEDA-based catalyst **45** (Figure 12) was developed, among others [40]. Besides the two *N,N*-dimethylamino- and *N*-amido-functionalities concurrently introduced into the diamine backbone, the bottom line was to enrich the catalyst with noncovalent interaction sites, i.e., halogen bonding (XB), hydrogen bonding (HB), Lewis basic sites and π -interactions (Figure 12).

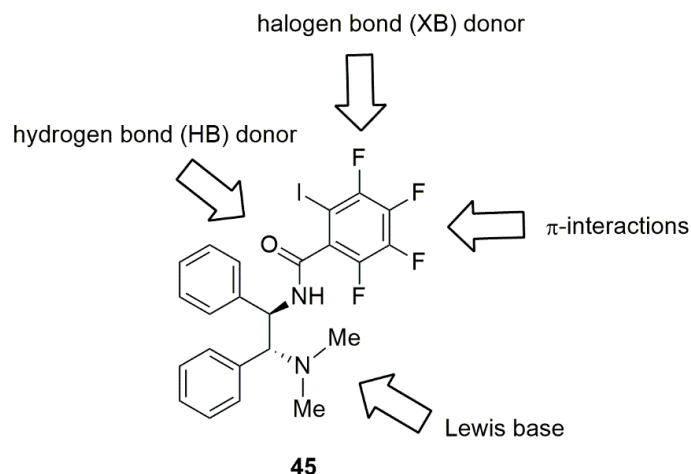
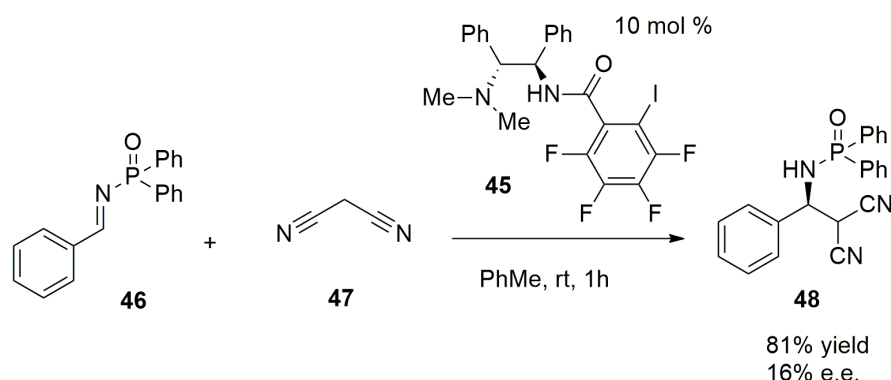


Figure 12. Multifunctional (1*R*,2*R*)-DPEDA-based organocatalyst.

The multifunctional catalyst **45** was applied in a model enantioselective Mannich reaction between diphenylphosphinoyl-protected aldimine **46** and malononitrile **47** (Scheme 11) [40], affording the expected (*S*)-product **48** in an 81% yield, but with low enantiomeric purity (16% e.e.). By replacing the (1*R*,2*R*)-DPEDA chiral fragment of catalyst **45** with the more rigid (1*R*,2*R*)-DACH one, the reaction yield became quantitative and the enantiomeric purity of compound **48** raised to 46% e.e.



Scheme 11. Asymmetric Mannich reaction of *N*-phosphinoylimines with malononitrile catalyzed by the mixed-amino-amido-functionalized (1*R*,2*R*)-DPEDA-based organocatalyst.

4.3. Bis(Amido)-Functionalized Organocatalysts

Amido- and sulfonamido-derived chiral ligands have been extensively studied in asymmetric catalysis [41,42] for their role as tunable hydrogen-bond donors and acceptors. In 2012, a series of C_1 - and C_2 -symmetric organocatalysts having sulfonamide and amide groups of variable steric features with one to four chirality centers were synthesized [43]. Among these, catalysts **49–52** (Figure 13) were constructed by the condensation of *N*-protected-amino acids (namely, phenylalanine and alanine) with DPEDA, by changing the absolute stereochemistry either of the diamine or of the amino acid (only for phenylalanine). In this way, the authors of the study developed homochiral and heterochiral DPEDA-based organocatalysts, which were compared in the asymmetric Strecker reaction of various aliphatic and aromatic *N*-benzhydrylimines (e.g., **53**) with ethyl cyanofornate **54** as cyanide source, at moderate temperatures (-10 °C to room temperature) (Scheme 12). Notably, homochiral organocatalysts **49a** (*all-S* chirality centers) and **50b** (*all-R* chirality centers), which are a couple of enantiomers, were found to be most effective to give 73% e.e. (with *R* in excess) and 71% e.e. (with *S* in excess), respectively, for nitrile **55**. On the contrary, the heterochiral catalysts **49b** and **50a** (Figure 13) gave the enantiomeric products with lower 42% and 33% e.e., respectively. After the screening of the additive, solvent and temperature,

catalyst **49a** was employed under optimized conditions (i.e., 2-propanol, toluene, $-10\text{ }^{\circ}\text{C}$) for the preparation of fifteen analogue compounds obtaining a high yield (up to 70%) and moderate to high enantiomeric excesses (60–99%; only one failed).

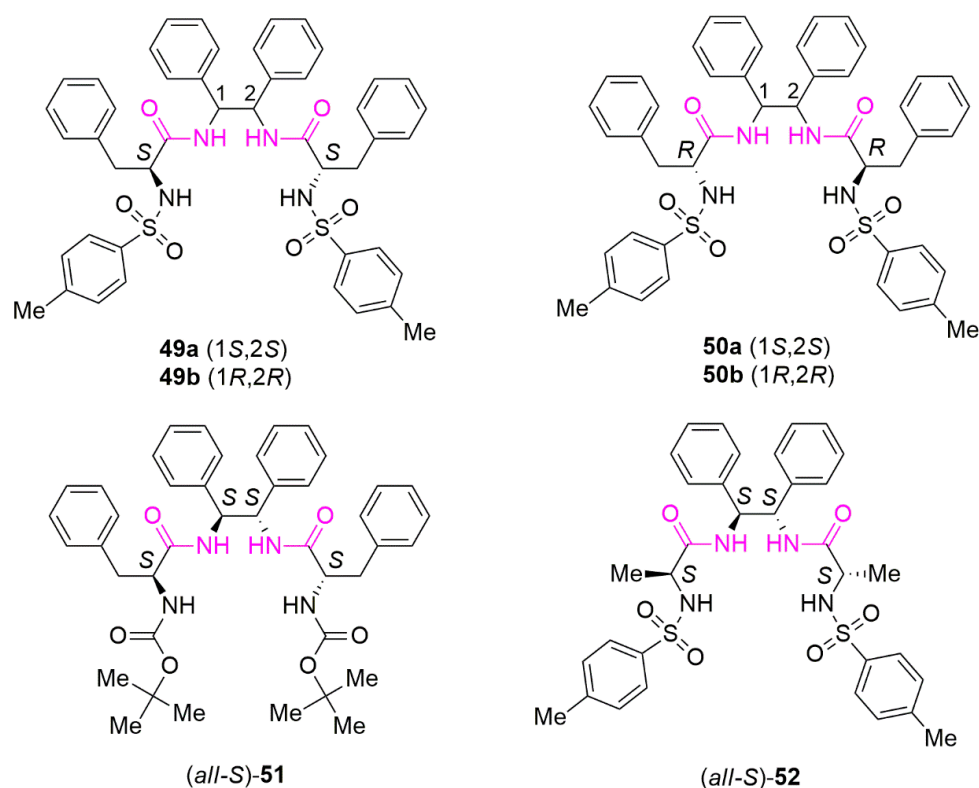
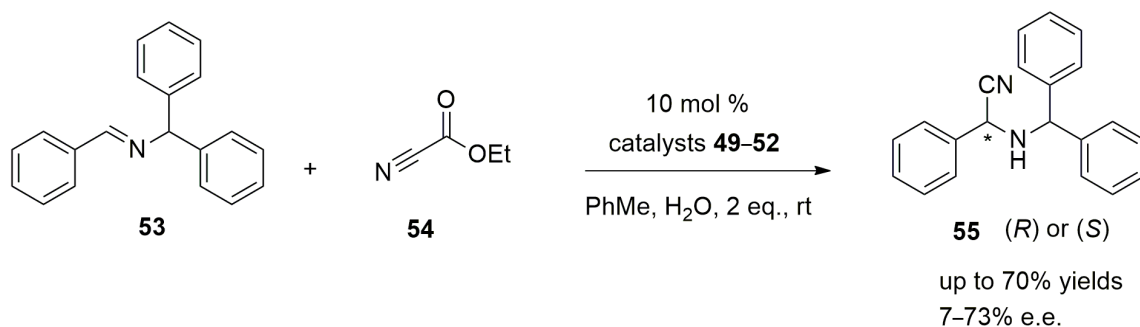


Figure 13. Structures of bis(amido)-DPEDA-based organocatalysts.



Scheme 12. Asymmetric Strecker reaction of *N*-benzhydrylimines with ethyl cyanoformate catalyzed by homochiral and heterochiral bis(amido)-DPEDA-based organocatalysts.

4.4. Bis-Prolinamides and Bis-Siloxyserinamides

The construction of carbohydrate ligands and substrates typically needs several synthetic steps and time-consuming protecting-group manipulation [44]. The enzyme-catalyzed synthesis of carbohydrates has found tremendous application in organic synthesis, due to the compatibility of enzymes (typically aldolases) with aqueous media and their stereospecificity. However, the more recent resort to organocatalyzed aldol reactions has made it easy for stereochemical information to be correctly installed in the expected carbohydrate [45]. In 2014, the synthesis of various 5,6-*O*-isopropylidene-1-deoxy-ketoses and ketoses was accomplished starting from unprotected hydroxyacetone (HA) and dihydroxyacetone (DHA), respectively [44], by using bis-prolinamido **56,57** and bis-siloxyserinamido **58,59** organocatalysts (Figure 14). In particular, the direct aldol reaction of HA (**60**) with

(*R*)-glyceraldehyde acetonide (**61**) was investigated, using organocatalysts **56–59** (Figure 14), at room temperature (Scheme 13) [44].

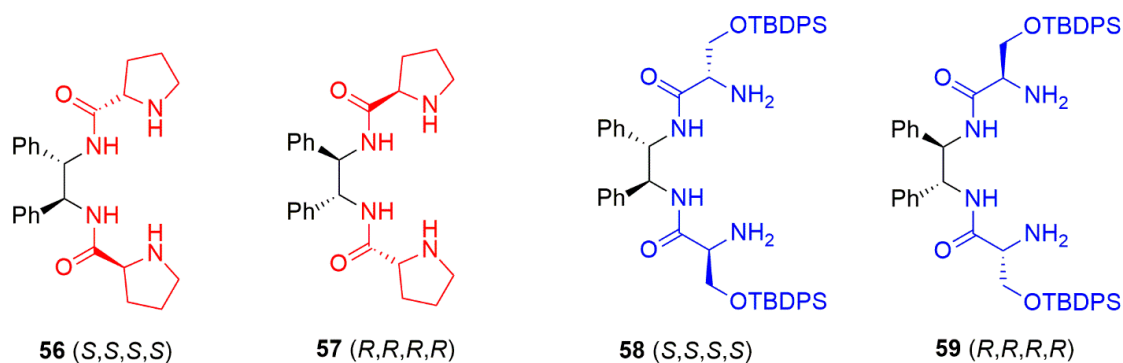
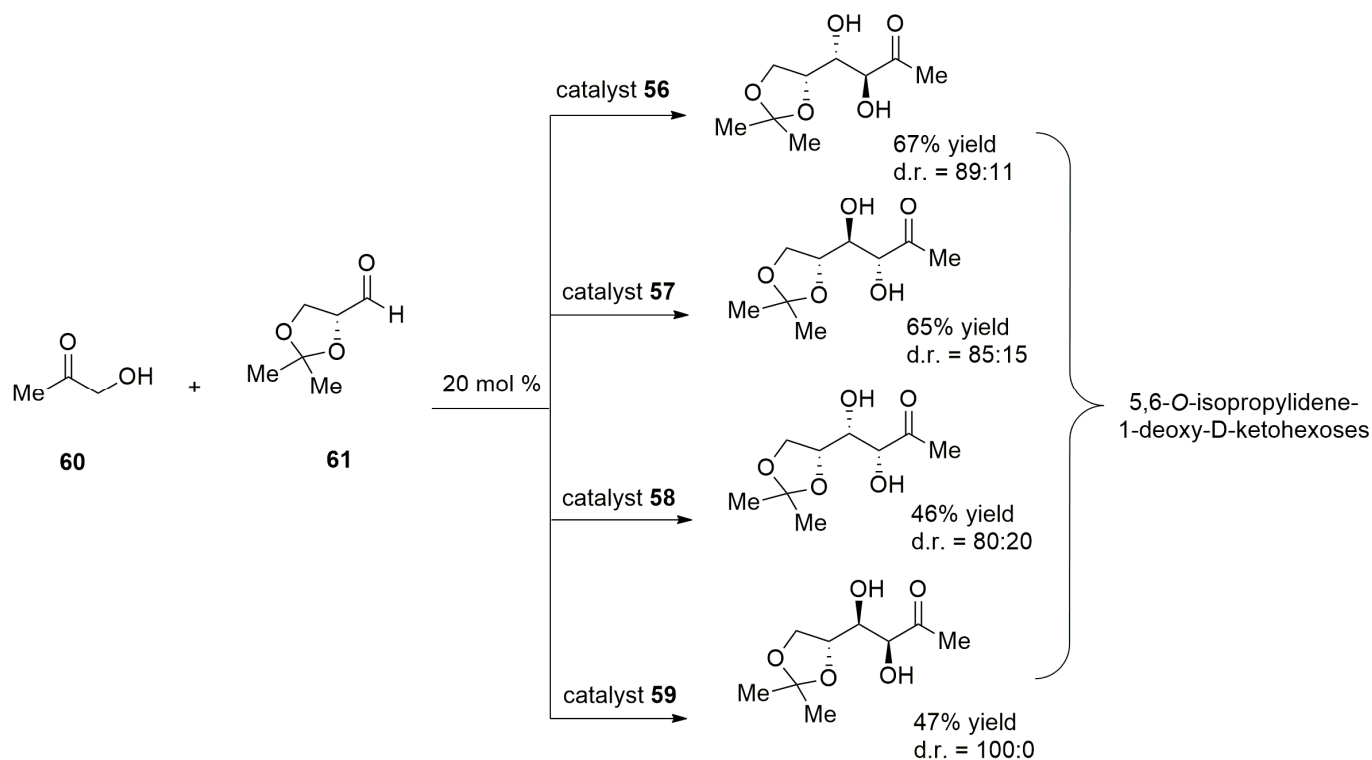


Figure 14. Structures of bis-prolinamido- (**56,57**) and bis-siloxyserinamido- (**58,59**) DPEDA-based organocatalysts.



Scheme 13. Stereoselective synthesis of 1-deoxy-D-ketohexoses catalyzed by bis-prolinamido- and bis-siloxyserinamido-DPEDA-based organocatalysts.

The four organocatalysts **56–59** perfectly controlled the stereoselective formation of diastereomeric 5,6-*O*-isopropylidene-1-deoxy-D-ketohexoses with yields ranging from 49% to 65%. Notably, catalyst **59** gave free access solely to 5,6-*O*-isopropylidene-1-deoxy-D-fructose (d.r. = 100:0).

4.5. Bifunctional Amino-Thiourea Organocatalysts

As reported in Section 3.1, the introduction of an *N*-substituted thiourea on one of the two amino groups of DPEDA led to monofunctional thiourea organocatalysts (Figure 3); the introduction of a further substitution on the other free amino group was identified as a strategy to prepare highly enantioselective bifunctional amino-thiourea organocatalysts (Figure 15) [46]. Catalyst **62** was applied in 2006 in the Michael addition of α -aryl cyanoacetates (e.g., **64**) to phenyl vinyl sulfone (**65**), producing the desired products (e.g.,

66) in good (73%) to excellent (96%) yields and in very good enantioselectivities (91–96%) (Scheme 14) [47].

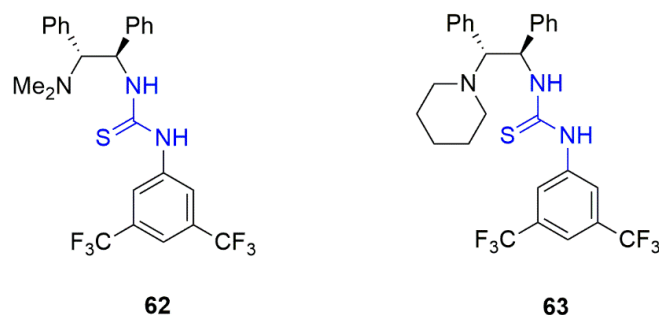
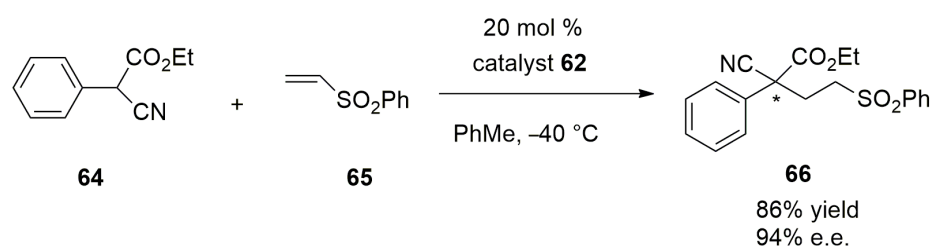


Figure 15. Bifunctional amino-thiourea derivatives of the (1*R*,2*R*)-DPEDA catalyst.



Scheme 14. Asymmetric Michael addition of aromatic cyanoacetates to phenyl vinyl sulfone.

The obtained Michael adducts were afterwards converted into synthetically important protected β -amino acid precursors.

The introduction of a 3-pentyl substituent on the free amino group of DPEDA (Figure 16) was investigated in the enantioselective Michael addition of nitroalkenes under neutral conditions [26].

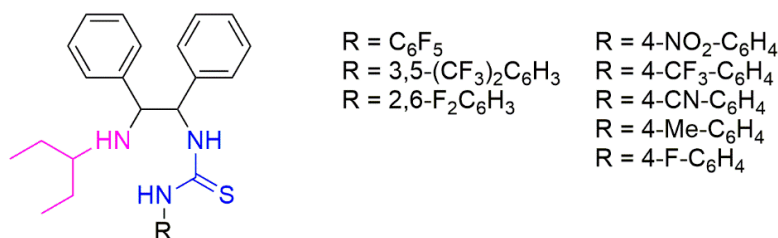
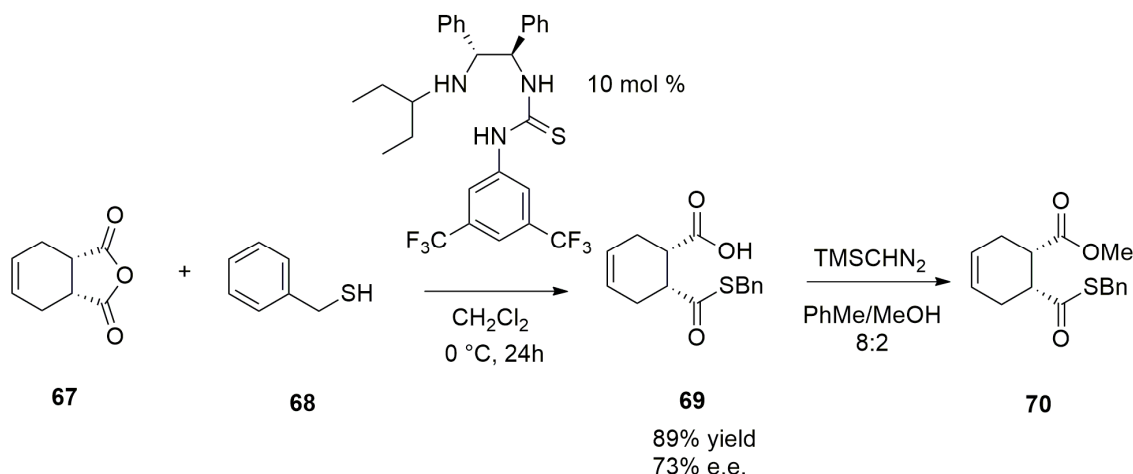


Figure 16. Bifunctional 3-pentylamino-thiourea derivatives of the DPEDA catalyst.

In the addition reaction of ethyl 2-oxocyclopentanecarboxylate **20** to *trans*- β -nitrostyrene **21** (Scheme 7), the highest enantioselectivity (93% e.e.) for the product **22** was obtained with the pentafluorophenyl-substituted catalyst (Figure 16, R = C₆F₅). Overall, the catalysts bearing electron-withdrawing groups (EWG) on the thiourea nitrogen provided higher enantioselectivities than those with electron-donating groups (EDG). The 3-pentyl-substitution provided, in any instances, the highest enantioselectivity, compared to the primary amino thiourea catalysts [23] (see Section 3.1).

In the asymmetric organocatalyzed ring-opening reaction of *cis*-1,2,3,6-tetrahydrophthalic anhydride **67** by benzyl mercaptan **68** (Scheme 15) [27], the most effective thiourea catalyst proved to be the one bearing the 3,5-bis(trifluoromethyl)phenyl moiety (Figure 16, R = 3,5-(CF₃)₂C₆H₃), which furnished *S*-benzyl thioester monocarboxylic acid **69** in an 89% yield and e.e. of 73%. Moreover, the scope of the reaction was extended to many prochiral cyclic anhydrides with thiols and aniline by using only 5 mol % of catalyst loading.



Scheme 15. Asymmetric ring-opening reaction of cyclic anhydrides using a bifunctional amino-thiourea (1*R*,2*R*)-DPEDA-based catalyst.

4.6. Bifunctional Amido-Thiourea Organocatalysts

The synthesis of chiral tertiary alcohols from achiral starting materials has been receiving much attention in the last 10 years [48]. Despite the significant progress in the insertion of centers of chirality by aldol reactions, a challenge still remains in synthesizing chiral tertiary alcohols using ketones as electrophilic partners, due to their poor reactivity and the difficulty in differentiating the two faces of the carbonyl moiety. In 2011–2012, prolinamide-thiourea **71**–**74** catalysts (Figure 17) were developed, among others, by the same research group [48–50]. Catalysts **71**,**72** were synthesized by using (*S*)-proline and (1*S*,2*S*)-DPEDA as building blocks, whereas (*S*)-di-*tert*-butyl aspartate was added as a third component of the tripeptide-like backbone in catalysts **73**,**74**.

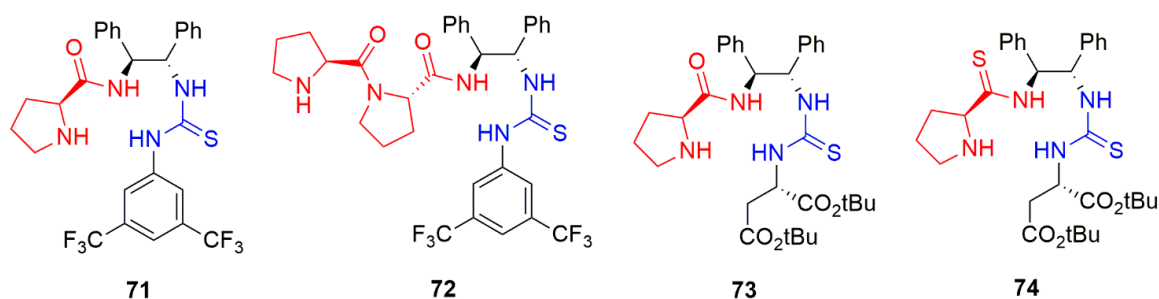


Figure 17. Prolinamide-thiourea derivatives of the (1*S*,2*S*)-DPEDA catalyst.

Catalyst **73** (all-*S* chiral configuration) was tested in the reaction between trifluoromethyl ketones (e.g., **35**) and linear aliphatic ketones (e.g., acetone **36**) (see Scheme 8 for structures) [48]. Under optimized reaction conditions (2% mol catalyst **73**, toluene, 0 °C), tertiary alcohol **37** (Scheme 8) was obtained in high-to-quantitative yields and high enantioselectivities (up to 80% e.e.). The research group contributed to highlighting that both the chiral centers of the DPEDA unit are essential for catalytic activity, whereas the two thiourea hydrogen atoms play a predominant role in the HB formation [50].

4.7. Bifunctional Sulfonamido-Thiourea Organocatalysts

Focusing on BB/HB bifunctional architectures, a catalytic system comprising a tertiary amine (BB) and a sulfonamido-thiourea DPEDA derivative (HB) proved to be particularly effective [51–59]. The asymmetric conjugate Michael addition of acetylacetone to nitroolefins, using sulfonamido-thiourea diastereomeric organocatalysts **75** (Figure 18), bearing an additional tertiary amine, has been effectively catalyzed (95% e.e.), with low catalyst loadings (0.1% mol) [51]. Following studies attested the potential of such catalysts in Michael addi-

tions of cyclopentanones and nitroalkanes to nitroolefins [52,53], the aza-Henry reaction between nitroalkanes and *N*-Boc aldimines [54], the reaction between cyclic beta-keto esters and azodicarboxylates [55] and the reaction between alkynyl methyl ketones and nitroolefins [56]. Catalyst **75a** performed also in sulfa-Michael reactions affording high enantiocontrol both for the addition of aryl thiols to *Z*-trifluorocrotonates (e.e. > 90%) [57] and for the reaction between thiols and structurally unconventional dienone systems lacking a trifluoromethyl group (Scheme 16A) [58,59].

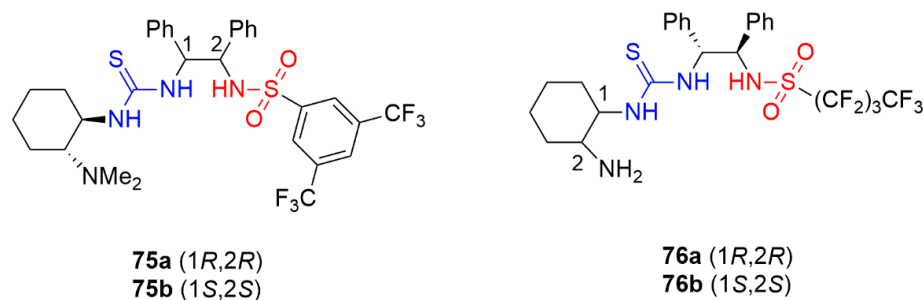
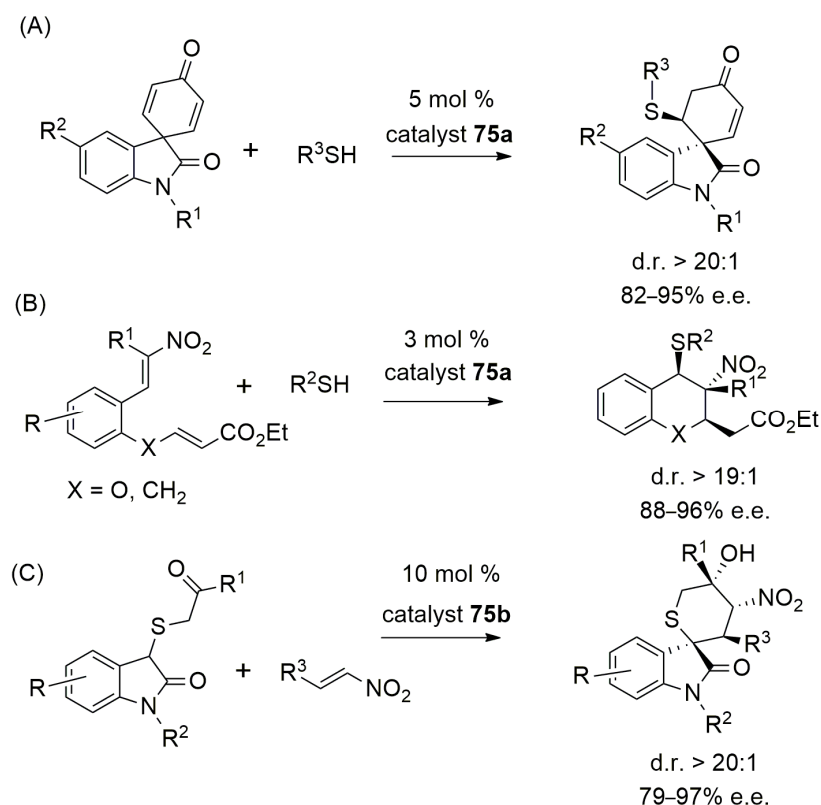


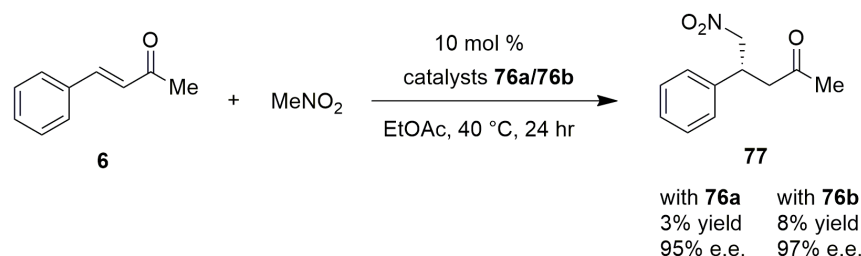
Figure 18. Sulfonamido-thiourea derivatives of the DPEDA catalyst.



Scheme 16. Applications of sulfonamido-thiourea-DPEDA-based catalysts. Sulfa-Michael reactions of dienone systems (A) and nitroolefin enoates (B) to thiols; (C) Michael/Henry cascade reaction of spirocyclic tricyclic compounds and nitroolefins.

Expanding on the catalytic potential in more complex reactions, the activity of catalyst **75a** (3 mol % loading) was examined in a domino sulfa-Michael/Michael reaction involving thiols and nitroolefin enoates (Scheme 16B) [60,61]. The reaction afforded chromane derivatives (*X* = O) with both high diastereo- and enantioselective controls. Notably, the diastereomeric sulfonamido-thiourea catalyst **75b** performed in a Michael/Henry cascade reaction affording enantioenriched spirocyclic tricyclic compounds in mild conditions and highly diastereo/enantioselective manner (Scheme 16C) [62].

The replacement of the tertiary amine with the corresponding primary one (either the 1*R*,2*R*- or the 1*S*,2*S*-DACH) and the introduction of the perfluorobutanesulfonamide motif afforded the diastereomeric catalysts **76** (Figure 18). The catalysts were tested in the asymmetric conjugate addition of nitromethane to (*E*)-4-phenyl-3-buten-2-one **6** (Scheme 17) [63], which gave the corresponding γ -nitro carbonyl product **77** in the (*R*)-configuration with excellent enantioselectivities (95–97% e.e.). Unfortunately, the yields were very low ($\leq 8\%$).



Scheme 17. Conjugate additions of nitroalkanes to α,β -unsaturated ketones catalyzed by sulfonamido-thiourea-DPEDA-based catalysts.

The substitution of the DACH moiety with the 9-amino(9-deoxy)epiquinine scaffold provided the novel *Cinchona*-sulfonamido-thiourea-DPEDA catalyst **78** (Figure 19), which proved to be highly efficient in conjugate additions of diketones to nitroolefins (Scheme 18A) [64] and vinyl sulfones [65].

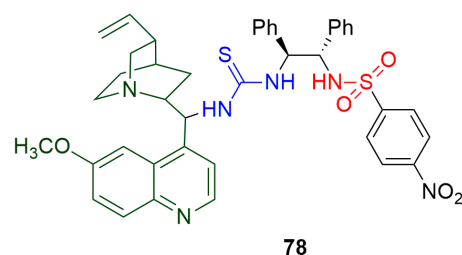
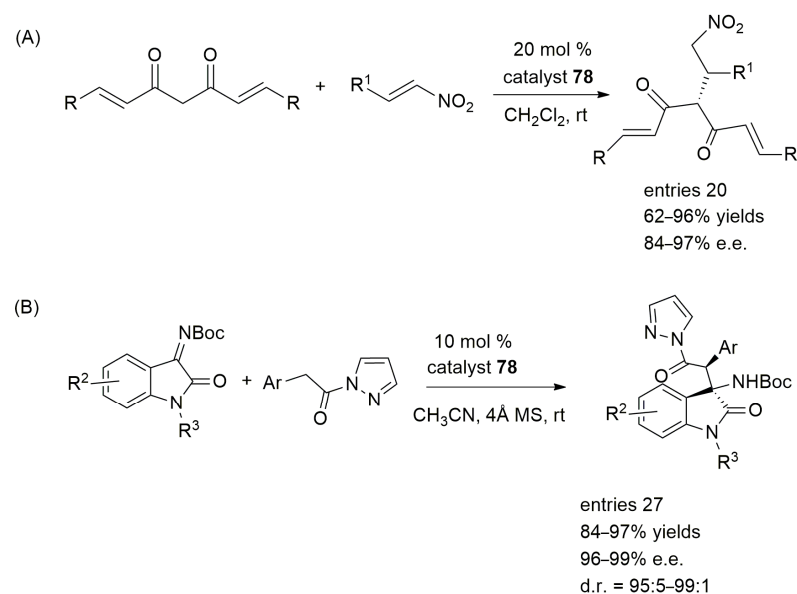


Figure 19. *Cinchona* alkaloid-derived bifunctional sulfonamide-thiourea derivative of the (1*S*,2*S*)-DPEDA catalyst.



Scheme 18. Applications of *Cinchona* alkaloid-derived sulfonamido-thiourea-DPEDA-based catalysts. (A) Conjugate additions of diketones to nitroolefins; (B) Mannich-type reaction of pyrazole amides and protected ketimines.

Cinchona alkaloid-derived catalyst **78** has been employed as well in a Mannich-type reaction between pyrazole amides and protected ketimines (Scheme 18B) [66].

4.8. Tetraamino-Bis-Thiourea Cyclic Organocatalysts

Macrocyclic compounds have gained attention in catalysis due to their enzyme-like cavities and preorganized binding sites, which enhance substrate binding and reaction specificity [67,68]. An innovative approach to synthesize chiral macrocycle catalysts was introduced in 2020 [69]. The macrocycles contain two thiourea and two (1*S*,2*S*)-DPEDA moieties (Figure 20) and dimerize with sulfate to form a sandwich-like assembly. They were applied in the decarboxylative Mannich reaction between cyclic sulfamate-aldimines and β -ketoacids (e.g., benzoyl acetic acid) (Scheme 19A) [69]. Under optimized conditions (5% mol catalyst loading, THF, $-10\text{ }^{\circ}\text{C}$, 24 h), the reaction proceeded well and gave highly efficient yields ($\geq 95\%$) and enantioselectivities (88% e.e.).

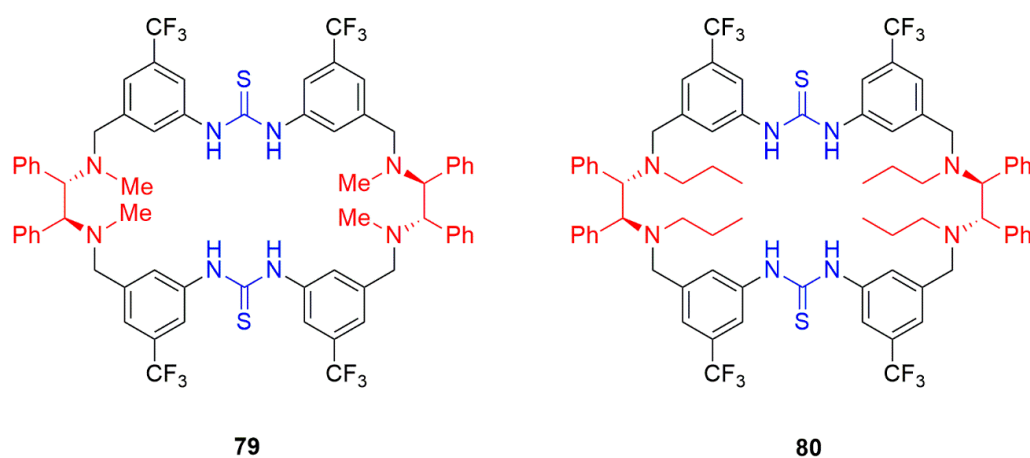
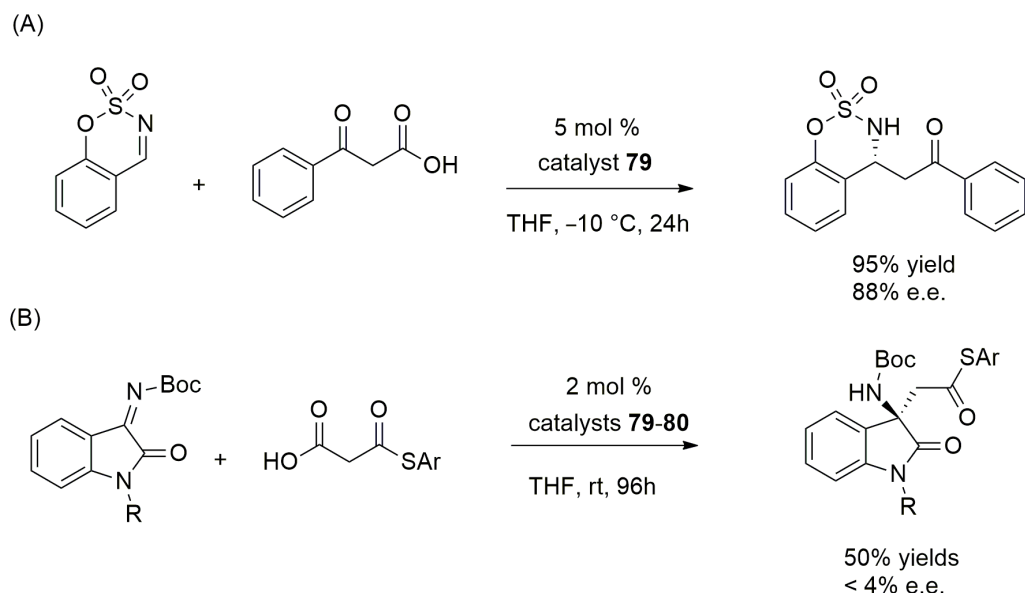


Figure 20. Structures of tetraamino-bis-thiourea-DPEDA-based cyclic organocatalysts.



Scheme 19. Applications of tetraamino-bis-thiourea-DPEDA-based cyclic organocatalysts. Decarboxylative Mannich addition of cyclic sulfamate-aldehydes and benzoyl acetic acid (A) and malonic acid half thioesters to isatin-derived ketimines (B).

Through in situ ESI-MS experiments, the authors of the study explored the reaction mechanism, showing that sulfamate-induced dimerization of the chiral macrocycles forms

a cooperative hydrogen-bonding network that activates the imine substrate for nucleophilic attack by the β -ketoacid.

To expand the application field of tetraamino-bis-thiourea chiral macrocycles, the same research group investigated the decarboxylative Mannich addition of malonic acid half thioesters to isatin-derived ketimines (Scheme 19B) [70]. Both catalysts **79** and **80**, however, showed very low enantioselectivities and moderate yields, the optimal catalysts being those bearing a DACH unit in the place of DPEDA. On another hand, the authors considered the electrophilic/nucleophilic cooperative catalysis of tertiary amine groups. Furthermore, size and steric effects of the substituents were evaluated by incorporating different alkyl groups like methyl, *n*-propyl, isopropyl and 3-pentyl on the diamine unit.

4.9. Acen-H Type Organocatalysts

Cyclic organic carbonates have played a privileged role as chemical intermediates, effectively serving as scaffolds for carbon dioxide (CO_2) capture [71–74]. A significant progress has been achieved in synthesizing cyclic carbonates using metal-free catalysts, with notable advancements over the past decade [75]. Within this context, metal-free salophen-type catalysts, containing synergistically active HBD and imino groups, have emerged as a promising strategy for the chemical fixation of CO_2 into cyclic carbonates [76–78]. In contrast to the typically employed 1,2-diaminobenzene or 1,2-diaminocyclohexane (DACH) core of the salophen scaffold, salophen-like catalysts **81–83** based on (1*R*,2*R*)-DPEDA were reported in 2020 (Figure 21) [79].

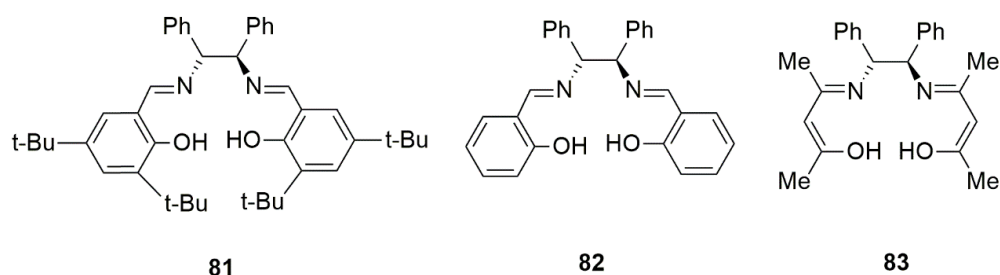
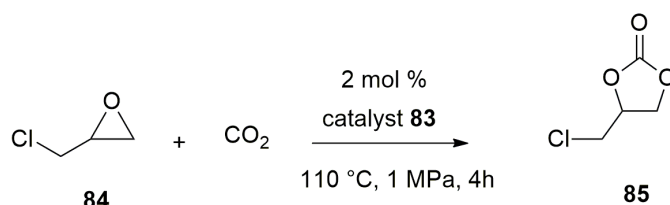


Figure 21. Structures of salophen-H ligands (**81**, **82**) and Acen-H catalyst **83** based on (1*R*,2*R*)-DPEDA.

Catalysts **81–83** were tested in the cycloaddition of CO_2 to different epoxides (e.g., epichlorohydrin **84**) to synthesize cyclic carbonates (e.g., **85**) (Scheme 20) [79]. Salophen-H ligands **81,82** were found to have no effect on the cycloaddition reaction. However, under the same reaction conditions (catalyst loading 2 mol %, 110 °C, 1.0 MPa, 4 h), the Acen-H catalyst **83** exhibited an epichlorohydrin conversion of 98.5% and an excellent selectivity (99%). Surprisingly, despite the presence of the chiral DPEDA synthon, data concerning chiral induction are not reported in the article.



Scheme 20. Ring-opening addition of CO_2 to epoxides catalyzed by Acen-H catalysts based on (1*R*,2*R*)-DPEDA.

4.10. Bis-Squaramide-Type Organocatalysts

As introduced in Section 3.3, the hydrogen-bonding ability of the squaramide moiety in the design of multifunctional chiral organocatalysis is well documented. The majority of the reported squaramide-based organocatalysts have a C_1 symmetry [29,36,80–83]. An interesting approach was developed in 2018 providing a series of C_2 -symmetric amine-squaramide organocatalysts [84,85]. The research group introduced, in the structure of the

catalysts, two squaramide units spaced out by a 1,2-diphenylethane bridge and bearing either a (1*S*,2*S*)-DPEDA molecule or an *N*-piperidine-substituted (1*R*,2*R*)-DACH pendant, to yield diastereomeric bis-squaramide-type DPEDA-based **86a**/**86b** and **87a**/**87b** organocatalysts, respectively (Figure 22). Furthermore, the pyridine analogues of catalysts **86** were prepared by replacing the phenyl rings of the 1,2-diamino bridge by two pyridine groups, yielding the ensemble of diastereomeric catalysts **88** (Figure 22). The catalytic performance of catalysts **87a**/**87b** was investigated in the model reaction of pentane-2,4-dione **89** with *trans*- β -nitrostyrene **21** (Scheme 21) [84] under comparable reaction conditions (toluene, room temperature, 72h). The corresponding Michael adduct **90** in the (*R*)-configuration was produced in a high yield (87–92%) and with moderate (61% e.e.) to high (83% e.e.) stereinduction, for **87a** and its (*all-R*)-**87b** diastereomer, respectively.

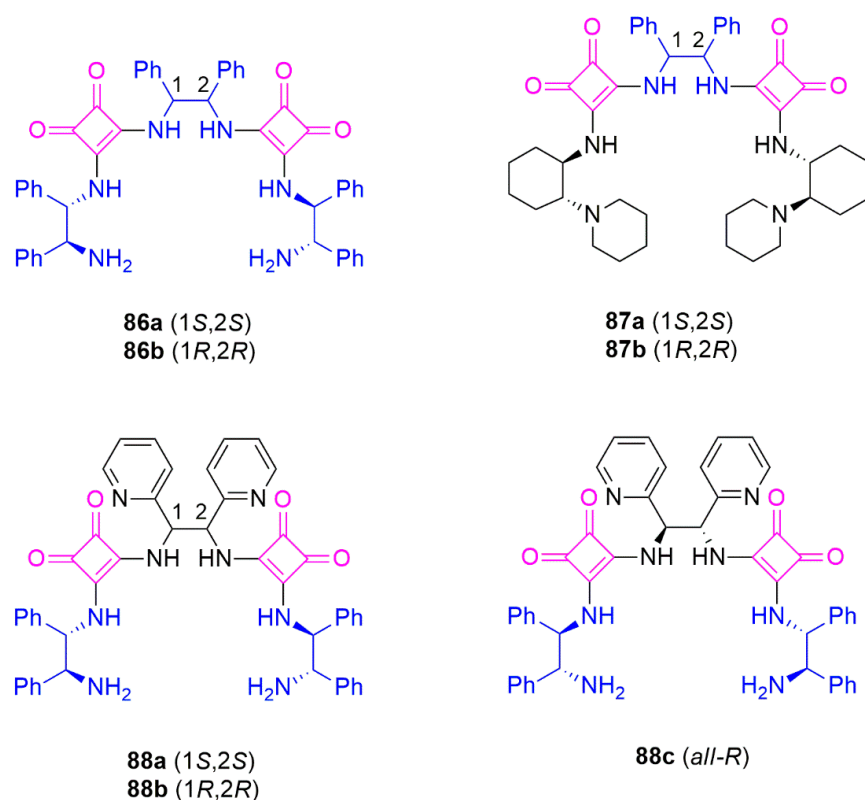
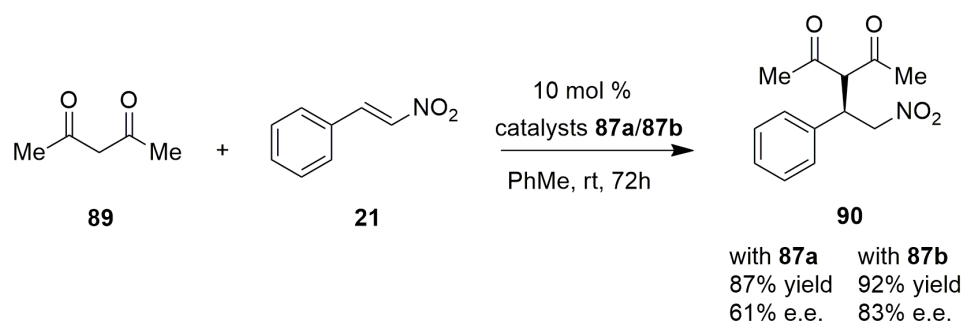


Figure 22. Structures of bis-squaramide-type DPEDA-based organocatalysts.



Scheme 21. Asymmetric Michael addition of β -diketones to *trans*- β -nitrostyrene catalyzed by bis-squaramide-type DPEDA-based organocatalysts.

Bis-squaramide organocatalysts **86** and **88**, bearing two free primary amino groups, were applied in the synthesis of warfarin by the asymmetric addition of 4-hydroxycoumarin **5** to (*E*)-4-phenyl-3-buten-2-one **6** (see Scheme 2 for structures) [85]. Both enantiomers of the anticoagulant were produced in up to a 97% yield and up to 96% e.e. enantiopurities,

using different solvent systems and additives. Notably, the pyridine-containing **88** catalysts performed better than the pyridine-free **86** counterparts, which proved unable to form extra H-bonds with the nucleophilic reagent [85].

4.11. Imidazoline Derivatives of 1,2-Diphenylethylenediamine (DPEDA)

Imidazoline (IUPAC name 4,5-dihydro-1H-imidazole), as a structural analogue of oxazolines, is a widely used privileged chiral ligand in metal-catalyzed asymmetric reactions due to its basicity and nucleophilicity and the Brønsted acidity of its salts [86,87]. For the same reasons, imidazoline derivatives were investigated in organocatalysis as well. However, the early applications of imidazoline-based catalysts did not afford high enantioselectivity values [88–90]. In 2010, C_3 -symmetric chiral trisimidazoline **91** (Figure 23) was designed and synthesized as a new entry of organocatalyst with the concept of constructing C_3 -symmetric molecules with three C_2 -symmetric chiral components [91]. The authors of the study also prepared the corresponding bisimidazoline derivative **92** (C_2 symmetry) for comparison (Figure 23).

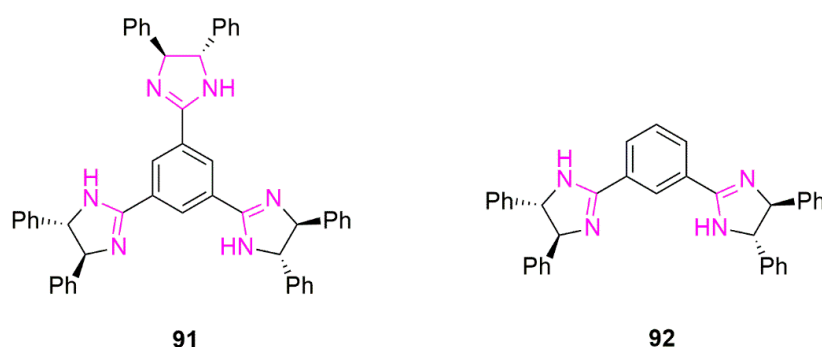
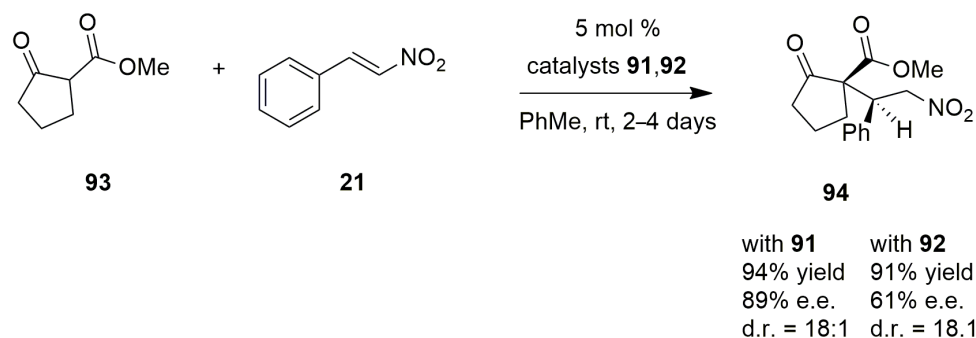


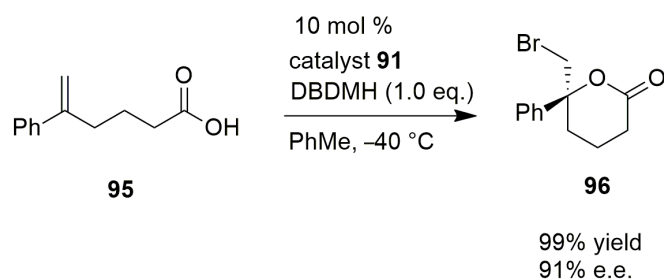
Figure 23. Structures of C_3 -symmetric trisimidazoline (left) and C_2 -symmetric bisimidazoline (right) derivatives of (1*S*,2*S*)-DPEDA.

Imidazoline catalysts **91** and **92** were evaluated in the enantioselective conjugate Michael addition of α -substituted β -ketoesters (e.g., methyl 2-oxocyclopentanecarboxylate **93**) to nitroolefins (Scheme 22) [91], as a model reaction. Trisimidazoline organocatalyst **91** showed a better enantioselectivity towards Michael adduct **94** (89% e.e.) with respect to bisimidazoline **92** (61% e.e.), under the same reaction conditions (catalyst loading 5 mol, toluene, room temperature, 2–4 days). The reduction in catalyst **91** loading and the increase in **92** loading did not have significant influence on the selectivity. Lowering the reaction temperature to $-10\text{ }^{\circ}\text{C}$ led to an improvement in the enantioselectivity of up to 95% e.e. for organocatalyst **91**. The reaction scope was investigated using several nitroolefins and β -ketoesters in optimized conditions, affording the corresponding adducts in good yields (up to 99%) with high diastereo- (>20:1) and enantioselectivities (up to 96% e.e.) [91].



Scheme 22. Asymmetric Michael addition of β -ketoesters to *trans*- β -nitrostyrene catalyzed by imidazoline derivatives of (1*S*,2*S*)-DPEDA.

The same research group envisioned that trisimidazoline organocatalyst **91** (Figure 23) could be suitable for a strong interaction with carboxylic acids providing the formation of 1:3 complexes in the field of material sciences. Therefore, they investigated the enantioselective bromolactonization of 5-substituted 5-hexenoic acids (e.g., **95**) in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source (Scheme 23) [92]. The desired (*S*)-lactone **96** was obtained in a 99% yield and 91% e.e. in toluene at $-40\text{ }^{\circ}\text{C}$. The catalytic performance of trisimidazoline organocatalyst **91** was also maintained at a gram-scale.



Scheme 23. Asymmetric bromolactonization of 5-substituted 5-hexenoic acids catalyzed by a C_3 -symmetric chiral trisimidazoline derivative of (1*S*,2*S*)-DPEDA.

More recently, a constitutional isomer of C_2 -symmetric bisimidazoline catalyst **92** was developed [93]. Despite that the catalyst allowed a medium level of enantioselectivity in Diels–Alder reactions, its preparation results in a simple and effective procedure consisting in the single-step reaction of (1*R*,2*R*)-DPEDA with 1,2-dicyanobenzene in the presence of N-acetyl cysteine (94% yield).

4.12. Guanidine-Based Organocatalysts

Guanidines are emerging as a new class of organo-superbases [94] due to their capability of directly deprotonating pronucleophiles bearing slightly acidic protons. Notably, chiral guanidines proved to be effective in introducing enantioselectivity in catalytic reactions, where their high basicity as organo-superbases is exploited [95–99]. Among chiral organo-superbases—including amidines, cyclopropenimines and iminophosphoranes (*vide infra*)—DPEDA-derived guanidines are notable for their reactivity and selectivity [94,100,101]. Their strong basicity lies in the high resonance stability of their conjugated protonated forms and, based on the structure where the guanidinyll group is incorporated, they can be classified into acyclic, monocyclic and bicyclic guanidines. At the beginning of 2000, monocyclic and bicyclic guanidines incorporating the enantiopure (1*S*,2*S*)-DPEDA in the ring of the final catalyst were developed (Figure 24) [102–104]. Monocyclic guanidine catalyst **97** efficiently provided a Mannich reaction between diphenyliminoglycinate **99** and ethyl acrylate **100** under solvent-free conditions (Scheme 24A) [104], quantitatively yielding (*R*)-adduct **101** with 97% e.e.

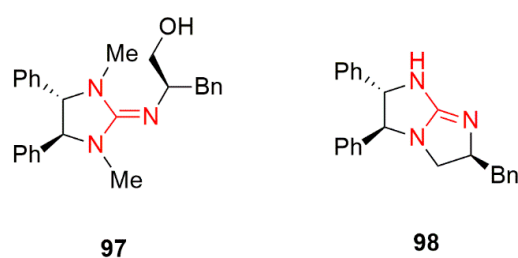
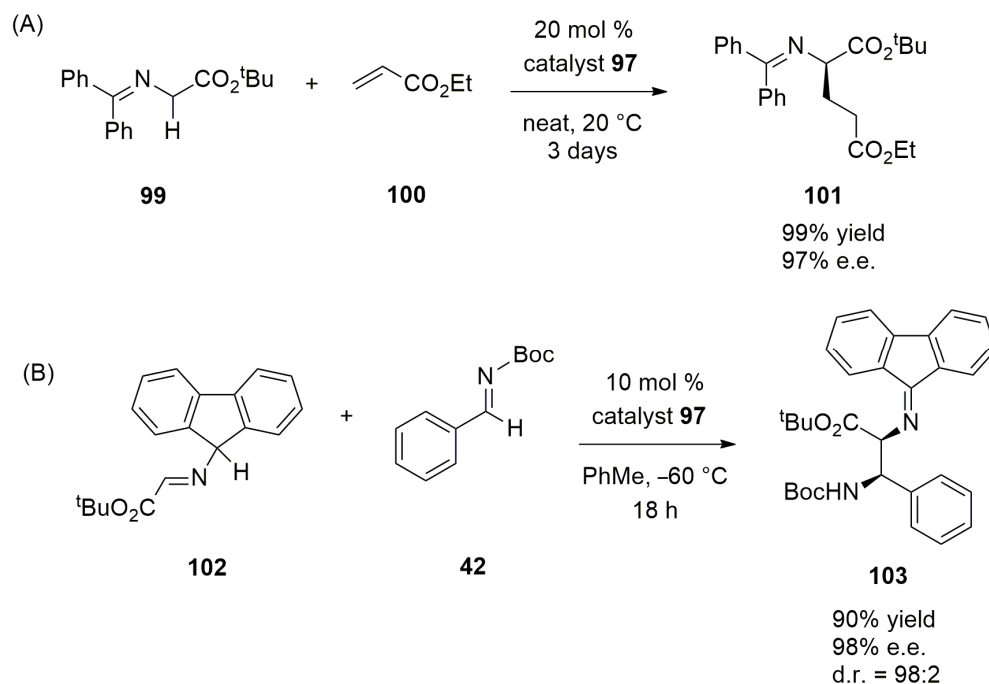


Figure 24. Structures of monocyclic (left) and bicyclic (right) guanidine catalysts incorporating (1*S*,2*S*)-DPEDA.



Scheme 24. Applications of a monocyclic guanidine catalyst incorporating (1*S*,2*S*)-DPEDA. (A) Mannich reaction between diphenyliminoglycinate and ethyl acrylate; (B) Imine-imine cross-coupling reaction between glyoxylate imine and *N*-Boc imines.

In 2014, catalyst **97** was applied by another research group in the first example of the catalytic asymmetric imine-imine cross-coupling reaction between glyoxylate imine **102** and *N*-Boc imine **42** (Scheme 24B) [105]. Product **103** was obtained with 98:2 d.r. and 98% e.e.

Acyclic guanidine organocatalysts based on the DPEDA scaffold were also designed (Figure 25) by a different research group in the years 2009–2018 and applied for enantioselective phospho-Mannich reactions [106,107].

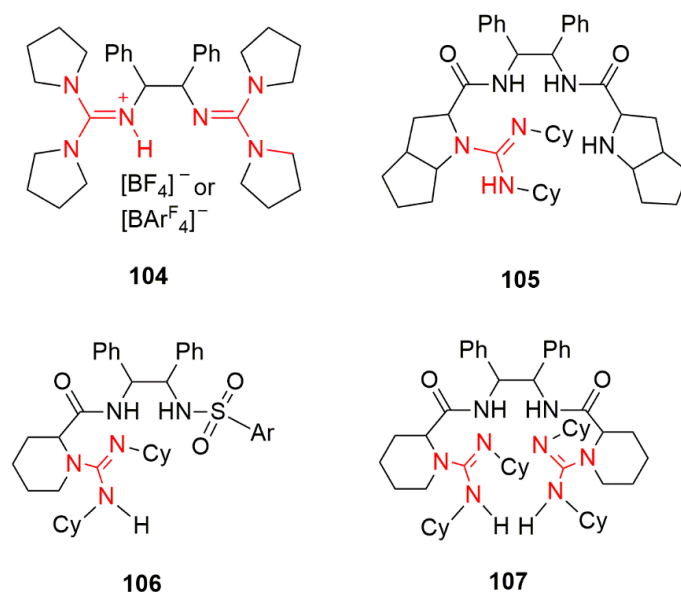


Figure 25. Structures of acyclic guanidine DPEDA-based organocatalysts. Cy = cyclohexyl. Ar = 4-MeC₆H₄; 2,6-F₂C₆H₃.

2013–2018 by the same research group [114–116], with the idea of combining the central chirality of DPEDA with the helical chirality of the 7,7-membered spirocyclic system.

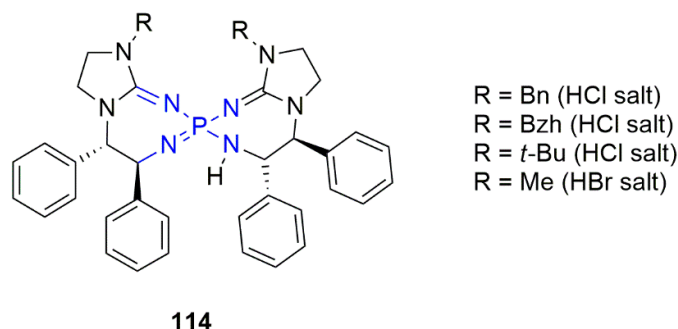
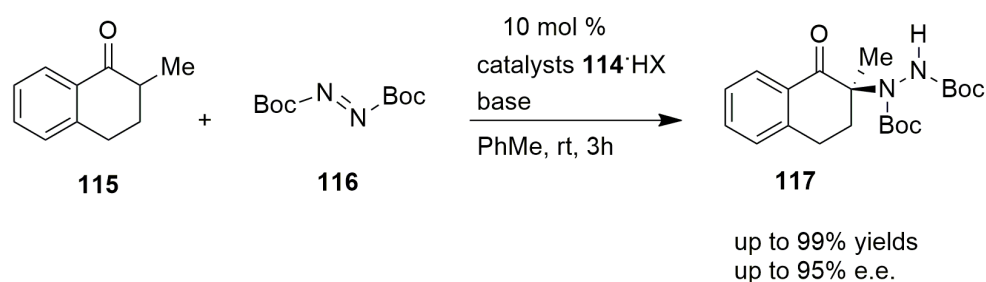


Figure 26. Structure of Type 1-iminophosphorane derivatives of (1*S*,2*S*)-DPEDA.

Type 1-iminophosphorane organocatalysts **114** demonstrated a wide applicability, being employed in the electrophilic amination of 2-alkyltetralones (e.g., **115**) and analogues with azodicarboxylates (e.g., **116**) (Scheme 27) [114], in enantioselective direct Mannich-type reactions with *N*-Boc imines and 2-benzylpyridine *N*-oxides (e.e. up to 94%) [115] and in the synthesis of 1,3-oxazolidines with quaternary stereogenic centers through a [3+2] cycloaddition of epoxides with imines (72–93% e.e.) [116].



Scheme 27. Electrophilic amination of 2-alkyltetralones with azodicarboxylates catalyzed by Type 1-DPEDA-based iminophosphoraness (13 salts of catalysts were tested).

Type 2-DPEDA-based iminophosphorane **118** was developed in 2013 by introducing a thiourea as HBD group (Figure 27) [117].

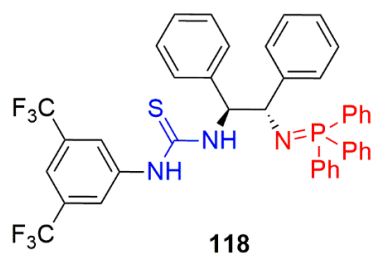
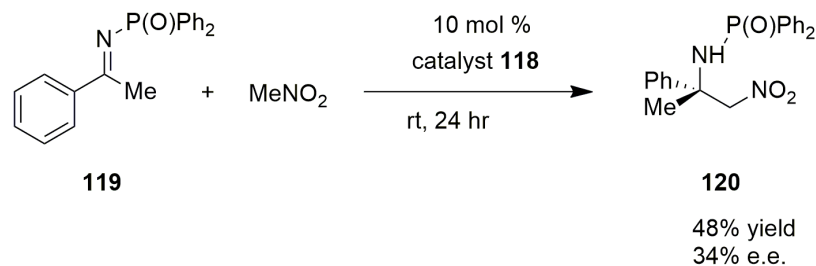


Figure 27. Structure of Type 2-iminophosphorane derivatives of (1*S*,2*S*)-DPEDA.

Catalyst **118** was tested in the enantioselective organocatalytic nitro-Mannich (or aza-Henry) reaction of nitromethane with *N*-diphenylphosphinoyl ketimine **119** (Scheme 28) [117]. The desired (*S*)-product was obtained in a moderate yield (48%) and with a poor e.e. (34%). A catalyst bearing the *L*-tert-Leucine scaffold instead of the DPEDA outperformed in terms of enantioselectivity (85% e.e.) and was selected for the optimization studies.



Scheme 28. Nitro-Mannich reaction of nitromethane with *N*-diphenylphosphinoyl ketimines catalyzed by Type 2-DPEDA-based iminophosphoranes.

5. Conclusions

In the family of chiral vicinal diamines, enantiopure 1,2-diphenylethylenediamine (DPEDA) attracted a great deal of attention as scaffold in the construction of efficient organocatalysts for asymmetric synthesis. Starting from the underivatized diamine and following the structural modifications that produce derivatives bearing at least one active amino group, DPEDA-based organocatalysts enable a number of base-initiated asymmetric reactions, mostly, aldol, Michael, Mannich and Diels–Alder reactions. Moreover, when the design of modified DPEDA focuses on the introduction of additional functionalities (hydrogen-bonding or other weak interactions), which assists the catalytic reaction, the derived bifunctional catalysts allow the high stereoselectivity of the reaction products. In particular, the introduction of thiourea, sulfonamide and squaramide, alone or in combination, resulted as a favorite choice in the development of multifunctional DPEDA-based organocatalysts: outstanding examples were provided by the C_2 -symmetric or C_3 -symmetric imidazoline structural arrangements. Furthermore, it is worth mentioning the recent incorporation of the DPEDA molecule in the preparation of organo-superbases for asymmetric reactions of weakly acidic pronucleophiles. The literature data inspection reveals that the DPEDA scaffold serves to carry out potential catalytic activity both in single amino-mediated organocatalysis and in structural combination with other well-known amino-type catalysts (i.e., 1,2-diaminocyclohexane and 9-amino-9-deoxy-epiquinine). Compared to the last ones, the DPEDA motif is less represented in the literature, and a review focused on DPEDA-based organocatalysts is missing, to our knowledge. The different organocatalysts that we selected from the literature of the last 20 years demonstrated a wide applicability and, at the same time, a notable reaction selectivity: in some cases, the DPEDA-based organocatalysts outperformed the control catalysts (i.e., DACH-based), whereas in other cases, they showed lower enantioselectivities and moderate yields with respect to the more rigid cyclohexane diamine-catalysts. This is the case, for example, of tetraamino-bis-thiourea DPEDA-based macrocycles used in decarboxylative Mannich reactions. Since the differently functionalized DPEDA-based organocatalysts presented here were evaluated towards different asymmetric reactions, a comparison between them can be performed only in the case of the model asymmetric synthesis of warfarin: the squaramide-monofunctionalized DPEDA gave the best results in terms of both yield (81–84%) and enantioselectivity (92–99%), with respect to the underivatized DPEDA (40–95% and 80–100%), the binaphthyl-modified-DPEDA (78% and 90%), the imidazoline-DPEDA (90–96% and 80–82%) and the bis-squaramide-DPEDA (60–97% and 55–96%), respectively.

This work aims to summarize the results obtained by using the enantiopure DPEDA molecule in organocatalysis over the past two decades in order to stimulate further exploration in this field and the discovery of new asymmetric organocatalyzed transformations.

Author Contributions: Conceptualization, A.C. and I.D.; investigation, S.B.O., S.M. and A.S.; writing—original draft preparation, S.B.O. and M.D.A.; writing—review and editing, I.D. and G.M.; supervision, A.C. and I.D.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: Author A.S. was employed by the company PAT Way Solutions S.r.l. but he declares that the research was conducted in the absence of any commercial or financial relationships. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Xu, L.-W.; Luo, J.; Lu, Y. Asymmetric catalysis with chiral primary amine-based organocatalysts. *Chem. Commun.* **2009**, 1807–1821. [CrossRef] [PubMed]
2. Alemán, J.; Cabrera, S. Application of asymmetric organocatalysis in medicinal chemistry. *Chem. Soc. Rev.* **2013**, *42*, 774–793. [CrossRef] [PubMed]
3. Fernholm, A. The Nobel Prize in Chemistry 2021: Popular Science Background. Brzezinski, P.; Somfai, P.; Aqvist, J. Science Eds., the Nobel Committee for Chemistry, The Royal Swedish Academy of Sciences, 6 October 2021. Available online: <https://www.nobelprize.org/uploads/2021/10/popular-chemistryprize2021.pdf> (accessed on 6 November 2024).
4. Braddock, D.C.; Redmond, J.M.; Hermitage, S.A.; White, A.J.P. A convenient preparation of enantiomerically pure (+)-(1R,2R) and (−)-(1S,2S)-1,2-diamino-1,2-diphenylethanes. *Adv. Synth. Catal.* **2006**, *348*, 911–916. [CrossRef]
5. Lewis, K.G.; Ghosh, S.K.; Bhuvanesh, N.; Gladysz, J.A. Cobalt (III) Werner complexes with 1,2-diphenylethylenediamine ligands: Readily available, inexpensive, and modular chiral hydrogen bond donor catalysts for enantioselective organic synthesis. *ACS Central Sci.* **2015**, *1*, 50–56. [CrossRef] [PubMed]
6. Zhang, J.-Y.; Chen, J.; Yin, C.-Q.; Li, S.-R.; Bai, Z.-W. Preparation and enantioseparation of copolymer chiral stationary phases with (1R,2R)-(+)-1,2-diphenylethylenediamine as the chiral building block. *J. Liq. Chromatogr. Relat. Technol.* **2010**, *33*, 46–60. [CrossRef]
7. Payagala, T.; Wanigasekara, E.; Armstrong, D.W. Synthesis and chromatographic evaluation of new polymeric chiral stationary phases based on three (1S,2S)-(−)-1,2-diphenylethylenediamine derivatives in HPLC and SFC. *Anal. Bioanal. Chem.* **2011**, *399*, 2445–2461. [CrossRef]
8. Yu, J.J.; Ryoo, J.J. Synthesis and application of N-3,5-dinitrobenzoyl and C3-symmetric diastereomeric chiral stationary phases. *Chirality* **2022**, *34*, 587–596. [CrossRef]
9. Marino, S.T.; Stachurska-Buczek, D.; Huggins, D.A.; Krywult, B.M.; Sheehan, C.S.; Nguyen, T.; Choi, N.; Parsons, J.G.; Griffiths, P.G.; James, I.W.; et al. Synthesis of chiral building blocks for use in drug discovery. *Molecules* **2004**, *9*, 405–426. [CrossRef]
10. Akhtar, N.; Saha, A.; Kumar, V.; Pradhan, N.; Panda, S.; Morla, S.; Kumar, S.; Manna, D. Diphenylethylenediamine-based potent anionophores: Transmembrane chloride ion transport and apoptosis inducing activities. *ACS Appl. Mater. Interfaces* **2018**, *10*, 33803–33813. [CrossRef]
11. Ohkuma, T.; Noyori, R.; Silverberg, L.J. (*R,R*)- and (*S,S*)-Diphenylethylenediamine. In *The Encyclopedia of Reagents for Organic Synthesis*; Wiley & Sons: Hoboken, NJ, USA, 2001.
12. Sibi, M.P.; Manyem, S. Enantioselective conjugate additions. *Tetrahedron* **2000**, *56*, 8033–8061. [CrossRef]
13. Hamilton, R.J.; Bergens, S.H. An unexpected possible role of base in asymmetric catalytic hydrogenations of ketones. Synthesis and characterization of several key catalytic intermediates. *J. Am. Chem. Soc.* **2006**, *128*, 13700–13701. [CrossRef] [PubMed]
14. Kim, K.H.; Lee, S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. Organocatalysis using protonated 1,2-diamino-1,2-diphenylethane for asymmetric Diels–Alder reaction. *Tetrahedron Lett.* **2005**, *46*, 5991–5994. [CrossRef]
15. Wong, T.C.; Sultana, C.M.; Vosburg, D.A. A green, enantioselective synthesis of warfarin for the undergraduate organic laboratory. *J. Chem. Educ.* **2010**, *87*, 194–195. [CrossRef]
16. Rogozińska-Szymczak, M.; Mlynarski, J. Unmodified primary amine organocatalysts for asymmetric Michael reactions in aqueous media. *Eur. J. Org. Chem.* **2015**, 6047–6051. [CrossRef]
17. Menjo, Y.; Hamajima, A.; Sasaki, N.; Hamada, Y. Asymmetric aziridination of cyclic enones using chiral diamine catalysts and its application to the total synthesis of (−)-agelastatin A. *Org. Lett.* **2011**, *13*, 5744–5747. [CrossRef]
18. Ha, H.-J.; Jung, J.-H.; Lee, W.K. Application of regio- and stereoselective functional group transformations of chiral aziridine-2-carboxylates. *Asian J. Org. Chem.* **2014**, *3*, 1020–1035. [CrossRef]
19. Wang, J.; Liu, X.; Dong, S.; Lin, L.; Feng, X. Asymmetric organocatalytic cyclopropanation of cinnamone derivatives with stabilized sulfonium ylides. *J. Org. Chem.* **2013**, *78*, 6322–6327. [CrossRef]
20. Hiemstra, H.; Wynberg, H. Addition of aromatic thiols to conjugated cycloalkenones, catalyzed by chiral β -hydroxy amines. A mechanistic study of homogeneous catalytic asymmetric synthesis. *J. Am. Chem. Soc.* **1981**, *103*, 417–430. [CrossRef]
21. Yu, J.-S.; Zhou, J. Asymmetric multifunctional catalysis. In *Multicatalyst System in Asymmetric Catalysis*; Zhou, J., Ed.; Wiley: Hoboken, NJ, USA, 2015; pp. 159–289.
22. García Mancheño, O.; Waser, M. Recent developments and trends in asymmetric organocatalysis. *Eur. J. Org. Chem.* **2023**, *26*, e202200950. [CrossRef]
23. Liu, Y.; Liu, X.; Wang, M.; He, P.; Lin, L.; Feng, X. Enantioselective synthesis of 3,4-dihydropyran derivatives via organocatalytic Michael reaction of α,β -unsaturated enones. *J. Org. Chem.* **2012**, *77*, 4136–4142. [CrossRef]
24. Mei, R.-Q.; Xu, X.-Y.; Li, Y.-C.; Fu, J.-Y.; Huang, Q.-C.; Wang, L.-X. Highly effective and enantioselective Michael addition of 4-hydroxycoumarin to α,β -unsaturated ketones promoted by simple chiral primary amine thiourea bifunctional catalysts. *Tetrahedron Lett.* **2011**, *52*, 1566–1568. [CrossRef]

25. Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. Asymmetric vinylogous aldol reaction via H-bond-directing dienamine catalysis. *Org. Lett.* **2013**, *15*, 220–223. [[CrossRef](#)] [[PubMed](#)]
26. Shim, J.H.; Lee, M.J.; Lee, M.H.; Kim, B.-S.; Ha, D.-C. Enantioselective organocatalytic Michael reactions using chiral (R,R)-1,2-diphenylethylenediamine-derived thioureas. *RSC Adv.* **2020**, *10*, 31808–31814. [[CrossRef](#)] [[PubMed](#)]
27. Shim, J.H.; Park, S.J.; Ahn, B.K.; Lee, J.Y.; Kim, H.S.; Ha, D.-C. Enantioselective thiolysis and aminolysis of cyclic anhydrides using a chiral diamine-derived thiourea catalyst. *ACS Omega* **2021**, *6*, 34501–34511. [[CrossRef](#)] [[PubMed](#)]
28. Chen, Z.; Yang, Q.-Q.; Du, W.; Chen, Y.-C. Asymmetric organocatalysis involving double activation. *Tetrahedron Chem.* **2022**, *2*, 100017. [[CrossRef](#)]
29. Vera, S.; García-Urricelqui, A.; Mielgo, A.; Oiarbide, M. Progress in (thio)urea- and squaramide-based Brønsted base catalysts with multiple H-bond donors. *Eur. J. Org. Chem.* **2023**, *26*, e202201254. [[CrossRef](#)]
30. Cruz, H.; Servín, F.A.; Aguirre, G.; Pérez, S.; Madrigal, D.; Chávez, D.; Cooksy, A.L.; Somanathan, R. Chiral C₂-symmetric bis-thioureas as enzyme mimics in enantioselective Michael addition. *Chirality* **2022**, *34*, 877–886. [[CrossRef](#)]
31. Zong, H.; Huang, H.; Bian, G.; Song, L. Fine-tuning the structures of chiral diamine ligands in the catalytic asymmetric aldol reactions of trifluoromethyl aromatic ketones with linear aliphatic ketones. *J. Org. Chem.* **2014**, *79*, 11768–11773. [[CrossRef](#)]
32. Lim, Y.J.; Kim, D.Y. Enantioselective conjugate addition of 4-hydroxycoumarin to enones catalyzed by binaphthyl-modified primary amine organocatalyst. *Bull. Korean Chem. Soc.* **2012**, *33*, 1825–1826. [[CrossRef](#)]
33. Duan, H.-X.; Zhang, Y.; Zhang, Z.-Z.; Wang, Y.-Q. C₂-symmetric 1,2-diphenylethane-1,2-diamine-derived primary–tertiary diamine-catalyzed asymmetric Mannich addition of cyclic N-sulfonyl trifluoromethylated ketimines. *J. Org. Chem.* **2020**, *85*, 11331–11339. [[CrossRef](#)]
34. Zhao, B.-L.; Li, J.-H.; Du, D.-M. Squaramide-catalyzed asymmetric reactions. *Chem. Rec.* **2017**, *17*, 994–1018. [[CrossRef](#)] [[PubMed](#)]
35. Malerich, J.P.; Hagihara, K.; Rawal, V.H. Chiral squaramide derivatives are excellent hydrogen bond donor catalysts. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. [[CrossRef](#)] [[PubMed](#)]
36. Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K.A. Squaramides: Bridging from molecular recognition to bifunctional organocatalysis. *Chem. Eur. J.* **2011**, *17*, 6890–6899. [[CrossRef](#)] [[PubMed](#)]
37. Modrocká, V.; Veverková, E.; Mečiarová, M.; Šebesta, R. Bifunctional amine-squaramides as organocatalysts in Michael/hemiketalization reactions of β,γ -unsaturated α -ketoesters and α,β -unsaturated ketones with 4-hydroxycoumarins. *J. Org. Chem.* **2018**, *83*, 13111–13120. [[CrossRef](#)] [[PubMed](#)]
38. Nanjo, T.; Zhang, X.; Tokuhira, Y.; Takemoto, Y. Divergent and scalable synthesis of α -hydroxy/keto- β -amino acid analogues by the catalytic enantioselective addition of glyoxylate cyanohydrin to imines. *ACS Catal.* **2019**, *9*, 10087–10092. [[CrossRef](#)]
39. Halland, N.; Hansen, T.; Jørgensen, K.A. Organocatalytic asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds and α,β -unsaturated ketones—A highly atom-economic catalytic one-step formation of optically active warfarin anticoagulant. *Angew. Chem. Int. Ed.* **2003**, *42*, 4955–4957. [[CrossRef](#)]
40. Kriis, K.; Martõnov, H.; Miller, A.; Erkman, K.; Järving, I.; Kaasik, M.; Kanger, T. Multifunctional catalysts in the asymmetric Mannich reaction of malononitrile with N-phosphinoylimines: Coactivation by halogen bonding versus hydrogen bonding. *J. Org. Chem.* **2022**, *87*, 7422–7435. [[CrossRef](#)]
41. Pellissier, H. Chiral sulfur-containing ligands for asymmetric catalysis. *Tetrahedron* **2007**, *63*, 1297–1330. [[CrossRef](#)]
42. Antenucci, A.; Dughera, S.; Renzi, P. Green chemistry meets asymmetric organocatalysis: A critical overview on catalysts synthesis. *ChemSusChem* **2021**, *14*, 2785–2853. [[CrossRef](#)]
43. Saravanan, S.; Sadhukhan, A.; Khan, N.H.; Kureshy, R.I.; Abdi, S.H.R.; Bajaj, H.C. C₂-symmetric recyclable organocatalyst for enantioselective Strecker reaction for the synthesis of α -amino acid and chiral diamine—An intermediate for APN inhibitor. *J. Org. Chem.* **2012**, *77*, 4375–4384. [[CrossRef](#)]
44. Popik, O.; Pasternak-Suder, M.; Lesniak, K.; Jawiczuk, M.; Górecki, M.; Frelek, J.; Mlynarski, J. Amine-catalyzed direct aldol reactions of hydroxy- and dihydroxyacetone: Biomimetic synthesis of carbohydrates. *J. Org. Chem.* **2014**, *79*, 5728–5739. [[CrossRef](#)] [[PubMed](#)]
45. Markert, M.; Mahrwald, R. Total syntheses of carbohydrates: Organocatalyzed aldol additions of dihydroxyacetone. *Chem. Eur. J.* **2008**, *14*, 40–48. [[CrossRef](#)] [[PubMed](#)]
46. Liu, Y.; Wang, Y.; Song, H.; Zhou, Z.; Tang, C. Asymmetric organocatalytic cascade Michael/hemiketalization/retro-aldol reaction of 2-[(E)-2-nitrovinyl]phenols with 2,4-dioxo-4-arylbutanoates: A convenient access to chiral α -keto esters. *Adv. Synth. Catal.* **2013**, *355*, 2544–2549. [[CrossRef](#)]
47. Liu, T.-Y.; Long, J.; Li, B.-J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. Enantioselective construction of quaternary carbon centre catalysed by bifunctional organocatalyst. *Org. Biomol. Chem.* **2006**, *4*, 2097–2099. [[CrossRef](#)] [[PubMed](#)]
48. Kokotos, C.G. Construction of tertiary alcohols bearing perfluoroalkyl chains catalyzed by prolinamide-thioureas. *J. Org. Chem.* **2012**, *77*, 1131–1135. [[CrossRef](#)]
49. Fotaras, S.; Kokotos, C.G.; Tsandi, E.; Kokotos, G. Prolinamides bearing thiourea groups as catalysts for asymmetric aldol reactions. *Eur. J. Org. Chem.* **2011**, 1310–1317. [[CrossRef](#)]
50. Fotaras, S.; Kokotos, C.G.; Kokotos, G. A tripeptide-like prolinamide-thiourea as an aldol reaction catalyst. *Org. Biomol. Chem.* **2012**, *10*, 5613–5619. [[CrossRef](#)]

51. Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. Chiral amine-thioureas bearing multiple hydrogen bonding donors: Highly efficient organocatalysts for asymmetric Michael addition of acetylacetone to nitroolefins. *Chem. Commun.* **2008**, 1431–1433. [\[CrossRef\]](#)
52. Dong, X.-Q.; Teng, H.-L.; Wang, C.-J. Highly enantioselective direct Michael addition of nitroalkanes to nitroalkenes catalyzed by amine–thiourea bearing multiple hydrogen-bonding donors. *Org. Lett.* **2009**, *11*, 1265–1268. [\[CrossRef\]](#)
53. Dong, X.-Q.; Teng, H.-L.; Tong, M.-C.; Huang, H.; Tao, H.-Y.; Wang, C.-J. Organocatalytic asymmetric Michael addition of α -aryl cyclopentanones to nitroolefins for construction of adjacent quaternary and tertiary stereocenters. *Chem. Commun.* **2010**, 46, 6840–6842. [\[CrossRef\]](#)
54. Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.-L. Highly anti-selective asymmetric nitro-Mannich reactions catalyzed by bifunctional amine-thiourea-bearing multiple hydrogen-bonding donors. *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Zhang, Z.-H.; Dong, X.-Q.; Tao, H.-Y.; Wang, C.-J. Asymmetric amination of cyclic β -keto esters catalyzed by aminethiourea bearing multiple hydrogen bonding donors. *Arkivoc* **2011**, 137–150.
56. Dong, X.-Q.; Fang, X.; Wang, C.-J. Organocatalytic asymmetric sulfa-Michael addition of thiols to 4,4,4-trifluorocrotonates. *Org. Lett.* **2011**, *13*, 4426–4429. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. Highly efficient catalytic asymmetric sulfa-Michael addition of thiols to trans-4,4,4-trifluorocrotonoylpyrazole. *Adv. Synth. Catal.* **2012**, *354*, 1141–1147. [\[CrossRef\]](#)
58. Fang, X.; Li, J.; Wang, C.-J. Organocatalytic asymmetric sulfa-Michael addition of thiols to α,β -unsaturated hexafluoroisopropyl esters: Expeditious access to (R)-thiazesim. *Org. Lett.* **2013**, *15*, 3448–3451. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Yao, L.; Liu, K.; Tao, H.-Y.; Qiu, G.-F.; Zhou, X.; Wang, C.-J. Organocatalytic asymmetric desymmetrization: Efficient construction of spirocyclic oxindoles bearing a unique all-carbon quaternary stereogenic center via sulfa-Michael addition. *Chem. Commun.* **2013**, 49, 6078–6080. [\[CrossRef\]](#)
60. Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. Organocatalytic asymmetric sulfa-Michael/Michael addition reactions: A strategy for the synthesis of highly substituted chromans with a quaternary stereocenter. *Angew. Chem.* **2010**, *122*, 8557–8561. [\[CrossRef\]](#)
61. Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J.; Lu, L.-Q.; Li, F.; An, J.; et al. Construction of Fused Heterocyclic Architectures by Formal [4+1]/[3+2] Cycloaddition Cascade of Sulfur Ylides and Nitroolefins. *Angew. Chem.* **2009**, *121*, 9706–9709.
62. Wang, S.; Guo, Z.; Chen, S.; Jiang, Y.; Zhang, F.; Liu, X.; Chen, W.; Sheng, C. Organocatalytic asymmetric synthesis of spiro-tetrahydrothiophene oxindoles bearing four contiguous stereocenters by one-pot Michael–Henry-cascade–rearrangement reactions. *Chem. Eur. J.* **2018**, *24*, 62–66. [\[CrossRef\]](#)
63. Kawada, M.; Nakashima, K.; Hirashima, S.; Yoshida, A.; Koseki, Y.; Miura, T. Asymmetric conjugate addition of nitroalkanes to enones using a sulfonamide–thiourea organocatalyst. *J. Org. Chem.* **2017**, *82*, 6986–6991. [\[CrossRef\]](#)
64. Li, W.; Wu, W.; Yu, F.; Huang, H.; Liang, X.; Ye, J. Catalytic asymmetric Michael addition with curcumin derivative. *Org. Biomol. Chem.* **2011**, *9*, 2505–2511. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Zhao, M.-X.; Zhou, H.; Tang, W.-H.; Qu, W.-S.; Shi, M. Cinchona alkaloid-derived thiourea-catalyzed diastereo- and enantioselective [3+2] cycloaddition reaction of isocyanoacetates to isatins: A facile access to optically active spirooxindole oxazolines. *Adv. Synth. Catal.* **2013**, *355*, 1277–1283. [\[CrossRef\]](#)
66. Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. Organocatalyzed enantioselective Mannich reaction of pyrazoleamides with isatin-derived ketimines. *J. Org. Chem.* **2014**, *79*, 4332–4339. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Gröger, H.; Berkessel, A. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.
68. Kauerhof, D.; Niemeyer, J. Functionalized macrocycles in supramolecular organocatalysis. *ChemPlusChem* **2020**, *85*, 889–899. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Guo, H.; Zhang, L.-W.; Zhou, H.; Meng, W.; Ao, Y.-F.; Wang, D.-X.; Wang, Q.-Q. Substrate-induced dimerization assembly of chiral macrocycle catalysts toward cooperative asymmetric catalysis. *Angew. Chem.* **2020**, *132*, 2645–2649. [\[CrossRef\]](#)
70. Guo, H.; Ao, Y.-F.; Wang, D.-X.; Wang, Q.-Q. Bioinspired tetraamino-bisthiourea chiral macrocycles in catalyzing decarboxylative Mannich reactions. *Beilstein J. Org. Chem.* **2022**, *18*, 486–496. [\[CrossRef\]](#)
71. Guo, L.; Lamb, K.J.; North, M. Recent developments in organocatalysed transformations of epoxides and carbon dioxide into cyclic carbonates. *Green Chem.* **2021**, *23*, 77–118. [\[CrossRef\]](#)
72. D’Elia, V.; Kleij, A.W. Surface science approach to the heterogeneous cycloaddition of CO₂ to epoxides catalyzed by site-isolated metal complexes and single atoms: A review. *Green Chem. Eng.* **2022**, *3*, 210–227. [\[CrossRef\]](#)
73. Shaikh, R.R.; Pornpraprom, S.; D’Elia, V. Catalytic strategies for the cycloaddition of pure, diluted, and waste CO₂ to epoxides under ambient conditions. *ACS Catal.* **2018**, *8*, 419–450. [\[CrossRef\]](#)
74. Martín, C.; Fiorani, G.; Kleij, A.W. Recent advances in the catalytic preparation of cyclic organic carbonates. *ACS Catal.* **2015**, *5*, 1353–1370. [\[CrossRef\]](#)
75. Mori, T.; Nishiyori, R.; Sumida, S.; Furuya, Y.; Shirakawa, S. Chiral organocatalysts in enantioselective CO₂ utilization reactions. *Eur. J. Org. Chem.* **2023**, *26*, e202300551. [\[CrossRef\]](#)

76. Fonseca-López, D.; Ezenarro-Salcedo, D.; Zapata-Rivera, J.; Rojas, R.S.; Hurtado, J.J. Salophen-type organocatalysts for the cycloaddition of CO₂ and epoxides under solvent, halide, and metal-free conditions. *ACS Omega* **2024**, *9*, 19385–19394. [[CrossRef](#)] [[PubMed](#)]
77. Kawka, A.; Bester, K.; Bukowska, A.; Bukowski, W. Salophen-type Schiff bases functionalized with pyridinium halide units as metal-free catalysts for synthesis of cyclic carbonates from carbon dioxide and terminal epoxides. *Catalysts* **2024**, *14*, 658. [[CrossRef](#)]
78. Guo, C.-H.; Lianga, M.; Jiao, H. Cycloaddition mechanisms of CO₂ and epoxide catalyzed by salophen—An organocatalyst free from metals and halides. *Catal. Sci. Technol.* **2021**, *11*, 2529–2539. [[CrossRef](#)]
79. Yue, Z.; Pudukudy, M.; Chen, S.; Liu, Y.; Zhao, W.; Wang, J.; Shan, S.; Jia, Q. A non-metal Acen-H catalyst for the chemical fixation of CO₂ into cyclic carbonates under solvent and halide-free mild reaction conditions. *Appl. Catal. A* **2020**, *601*, 117646. [[CrossRef](#)]
80. Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional amine-squaramides: Powerful hydrogen-bonding organocatalysts for asymmetric domino/cascade reactions. *Adv. Synth. Catal.* **2015**, *357*, 253–281. [[CrossRef](#)]
81. Han, X.; Zhou, H.B.; Dong, C. Applications of chiral squaramides: From asymmetric organocatalysis to biologically active compounds. *Chem. Rec.* **2016**, *16*, 897. [[CrossRef](#)]
82. Di Iorio, N.; Soprani, L.; Crotti, S.; Marotta, E.; Mazzanti, A.; Righi, P.; Bencivenni, G. Michael addition of oxindoles to *N*-(2-*tert*-butylphenyl) maleimides: Efficient desymmetrization for the synthesis of atropisomeric succinimides with quaternary and tertiary stereocenters. *Synthesis* **2017**, *49*, 1519–1530.
83. Dajek, M.; Pruszczyńska, A.; Konieczny, K.A.; Kowalczyk, R. Cinchona squaramide-catalyzed intermolecular desymmetrization of 1,3-diketones leading to chiral 1,4-dihydropyridines. *Adv. Synth. Catal.* **2020**, *362*, 3613–3620. [[CrossRef](#)]
84. Kochetkov, S.V.; Kucherenko, A.S.; Zlotin, S.G. Recyclable C₂-symmetric tertiary amine-squaramide organocatalysts: Design and application to asymmetric synthesis of γ -nitrocarbonyl compounds. *Tetrahedron* **2018**, *74*, 4769–4776.
85. Kochetkov, S.V.; Kucherenko, A.S.; Zlotin, S.G. Asymmetric synthesis of warfarin and its analogs catalyzed by C₂-symmetric squaramide-based primary diamines. *Org. Biomol. Chem.* **2018**, *16*, 6423–6429. [[CrossRef](#)] [[PubMed](#)]
86. Li, J.; Yu, B.; Lu, Z. Chiral imidazole ligands and their applications in metal-catalyzed asymmetric synthesis. *Chin. J. Chem.* **2021**, *39*, 488–514. [[CrossRef](#)]
87. Liu, H.; Du, D.-M. Recent advances in the synthesis of 2-imidazolines and their applications in homogeneous catalysis. *Adv. Synth. Catal.* **2009**, *351*, 489–519. [[CrossRef](#)]
88. Tsogoeva, S.B.; Dürner, G.; Bolte, M.; Göbel, M.W. A C₂-chiral bis(amidinium) catalyst for a Diels–Alder reaction constituting the key step of the Quinkert–Dane estrone synthesis. *Eur. J. Org. Chem.* **2003**, *9*, 1661–1664. [[CrossRef](#)]
89. Akalay, D.; Dürner, G.; Bats, J.W.; Bolte, M.; Göbel, M.W. Synthesis of C₂-symmetric bisamidines: a new type of chiral metal-free Lewis acid analogue interacting with carbonyl groups. *J. Org. Chem.* **2007**, *72*, 5618–5624. [[CrossRef](#)]
90. Ahmad, S.M.; Braddock, D.C.; Cansell, G.; Hermitage, S.A.; Redmond, J.M.; White, A.J.P. Amidines as potent nucleophilic organocatalysts for the transfer of electrophilic bromine from *N*-bromosuccinimide to alkenes. *Tetrahedron Lett.* **2007**, *48*, 5948–5952. [[CrossRef](#)]
91. Murai, K.; Fukushima, S.; Hayashi, S.; Takahara, Y.; Fujioka, H. C₃-symmetric chiral trisimidazole: Design and application to organocatalyst. *Org. Lett.* **2010**, *12*, 964–966. [[CrossRef](#)]
92. Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. Asymmetric bromolactonization catalyzed by a C₃-symmetric chiral trisimidazole. *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177. [[CrossRef](#)]
93. Goldberg, M.; Nakajima, M.; Bolte, M.; Göbel, M.W. Facile conversion of 1,2-dicyanobenzene into chiral bisamidines. *Arkivoc* **2022**, 225–238. [[CrossRef](#)]
94. Wang, Y.-H.; Cao, Z.-Y.; Li, Q.-H.; Lin, G.-Q.; Zhou, J.; Ping Tian, P. Activating pronucleophiles with high pK_a values: Chiral organo-superbases. *Angew. Chem. Int. Ed.* **2020**, *59*, 8004–8014. [[CrossRef](#)]
95. Taylor, J.E.; Bull, S.D.; Williams, J.M.J. Amidines, isothioureas, and guanidines as nucleophilic catalysts. *Chem. Soc. Rev.* **2012**, *41*, 2109–2121. [[CrossRef](#)] [[PubMed](#)]
96. Hosoya, K.; Odagi, M.; Nagasaw, M. Guanidine organocatalysis for enantioselective carbon-heteroatom bond-forming reactions. *Tetrahedron Lett.* **2018**, *59*, 687–696. [[CrossRef](#)]
97. Zhang, Y.; Ning, L.; Zhu, T.; Xie, Z.; Dong, S.; Feng, X.; Liu, X. Chiral guanidine catalyzed cyclization reactions of 1,3-enynes for lactone synthesis: Switchable H-bond catalysis. *Org. Chem. Front.* **2024**, *11*, 2897–2904. [[CrossRef](#)]
98. Bartolo, G.; Della Ca', N.; Mancuso, R.; Veltri, L.; Ziccarelli, I. Amidine- and guanidine-based synthetic methods for CO₂ capture and utilization. *Curr. Opin. Green Sustain. Chem.* **2023**, *41*, 100793.
99. Krawczyk, H.; Dziegielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. Chiral iminophosphoranes—an emerging class of superbase organocatalysts. *Chem. Eur. J.* **2015**, *21*, 10268–10277. [[CrossRef](#)]
100. Vazdar, K.; Margetić, D.; Kovačević, B.; Sundermeyer, J.; Leito, I.; Jahn, U. Design of novel uncharged organic superbases: Merging basicity and functionality. *Acc. Chem. Res.* **2021**, *54*, 3108–3123. [[CrossRef](#)]
101. Li, X.; Song, Q. Recent advances in asymmetric reactions catalyzed by chiral phosphoric acids. *Chin. Chem. Lett.* **2018**, *29*, 1201–1208. [[CrossRef](#)]

102. Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. Modified guanidines as potential chiral superbases. 3. Preparation of 1,4,6-triazabicyclooctene systems and 1,4-disubstituted 2-iminoimidazolidines by the 2-chloro-1,3-dimethylimidazolinium chloride-induced cyclization of guanidines with a hydroxyethyl substituent. *J. Org. Chem.* **2000**, *65*, 7779–7785.
103. Isobe, T.; Fukuda, K.; Ishikawa, T. Simple preparation of chiral 1,3-dimethyl-2-iminoimidazolidines (monocyclic guanidines) and applications to asymmetric alkylative esterification. *Tetrahedron Asymmetry* **1998**, *9*, 1729–1735. [[CrossRef](#)]
104. Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. Modified guanidines as chiral superbases: Application to asymmetric Michael reaction of glycine imine with acrylate or its related compounds. *Chem. Commun.* **2001**, 245–246. [[CrossRef](#)]
105. Matsumoto, M.; Harada, M.; Yamashita, Y.; Kobayashi, S. Catalytic imine–imine cross-coupling reactions. *Chem. Commun.* **2014**, *50*, 13041–13044. [[CrossRef](#)] [[PubMed](#)]
106. Fu, X.; Loh, W.T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H.; Wang, J.; Tan, C.-H. Chiral guanidinium salt catalyzed enantioselective phospho-Mannich reactions. *Angew. Chem. Int. Ed.* **2009**, *48*, 7387–7390. [[CrossRef](#)] [[PubMed](#)]
107. Ruan, S.; Lin, X.; Xie, L.; Lin, L.; Feng, X.; Liu, X. Asymmetric synthesis of 3-aminodihydrocoumarins via the chiral guanidine catalyzed cascade reaction of azlactones. *Org. Chem. Front.* **2018**, *5*, 32–35. [[CrossRef](#)]
108. Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. Bifunctional guanidine via an amino amide skeleton for asymmetric Michael reactions of β -ketoesters with nitroolefins: A concise synthesis of bicyclic β -amino acids. *Angew. Chem. Int. Ed.* **2009**, *48*, 5195–5198. [[CrossRef](#)] [[PubMed](#)]
109. Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. Chiral bisguanidine-catalyzed inverse-electron-demand hetero-Diels–Alder reaction of chalcones with azlactones. *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651. [[CrossRef](#)]
110. Dong, S.; Liu, X.; Zhang, Y.; Lin, L.; Feng, X. Asymmetric synthesis of 3,4-diaminochroman-2-ones promoted by guanidine and bisguanidium salt. *Org. Lett.* **2011**, *13*, 5060–5063. [[CrossRef](#)]
111. Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. Chiral guanidine-catalyzed asymmetric direct vinylogous Michael reaction of α,β -unsaturated γ -butyrolactams with alkylidene malonates. *Chem. Commun.* **2012**, *48*, 5040–5042. [[CrossRef](#)]
112. Chen, X.; Dong, S.; Qiao, Z.; Zhu, Y.; Xie, M.; Lin, L.; Liu, X.; Feng, X. Guanidine organocatalyst for the asymmetric Mannich-type reaction between α -isothiocyanato imide and sulfonyl imines. *Chem. Eur. J.* **2011**, *17*, 2583–2586. [[CrossRef](#)]
113. Dong, S.; Liu, X.; Zhu, Y.; He, P.; Lin, L.; Feng, X. Organocatalytic oxyamination of azlactones: Kinetic resolution of oxaziridines and asymmetric synthesis of oxazolin-4-ones. *J. Am. Chem. Soc.* **2013**, *135*, 10026–10029. [[CrossRef](#)]
114. Takeda, T.; Terada, M. Development of a chiral bis(guanidino)iminophosphorane as an uncharged organosuperbase for the enantioselective amination of ketones. *J. Am. Chem. Soc.* **2013**, *135*, 15306–15309. [[CrossRef](#)]
115. Hu, Q.; Kondoh, A.; Terada, M. Enantioselective direct Mannich-type reactions of 2-benzylpyridine N-oxides catalyzed by chiral bis(guanidino)iminophosphorane organosuperbase. *Chem. Sci.* **2018**, *9*, 4348–4351. [[CrossRef](#)] [[PubMed](#)]
116. Kondoh, A.; Akahira, S.; Oishi, M.; Terada, M. Enantioselective formal [3+2] cycloaddition of epoxides with imines under Brønsted base catalysis: Synthesis of 1,3-oxazolidines with quaternary stereogenic center. *Angew. Chem. Int. Ed.* **2018**, *57*, 6299–6303. [[CrossRef](#)] [[PubMed](#)]
117. Núñez, M.G.; Farley, A.J.M.; Dixon, D.J. Bifunctional iminophosphorane organocatalysts for enantioselective synthesis: Application to the ketimine nitro-Mannich reaction. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.