*Russian Chemical Reviews* **84** (11) 1077 – 1099 (2015) © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4562

# $C_2$-Symmetric diamines and their derivatives as promising organocatalysts for asymmetric synthesis

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The review is devoted to the application of $C_2$-symmetric diamines and their derivatives as organocatalysts for asymmetric reactions (aldol, Michael, Mannich, Diels – Alder reactions, desymmetrization, allylation, *etc.*). Amino acid derivatives, di- and polyamides (sulfamides), bisureas, bisthioureas, bisamidines and bisguanidines are considered. Significant attention is given to the effect of the catalyst structure on the mechanism of catalytic action. Successful applications of such catalysts in enantioselective synthesis of chiral biologically active compounds are summarized.
The bibliography includes 181 references.

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## I. Introduction

Asymmetric organocatalysis is one of the main trends in modern organic chemistry.[1,2] Chiral organocatalysts (COC) are enantiomerically pure metal-free organic compounds able to enantioselectively catalyze the conversion of achiral or racemic substrates into chiral products. Unlike organometallic catalysts, COC do not contaminate the products with toxic heavy metals, which is particularly important for the synthesis of drugs.[3,4]

To date a wide range of different types of COC for various organic reactions have been developed and studied. Of particular interest are bi- and multifunctional COC the properties of which can be simply tuned *via* modification of the incorporated structural moieties.[5] Among them, axially symmetric (first of all, $C_2$-symmetric, *i.e.*, those having a two-fold symmetry axis) structures based on available, in particular, chiral diols and diamines attract special attention. Usually, these compounds are used as chelating ligands in enantioselective catalysis by metal complexes.[6–8] However, recently they started to be used as catalysts in the absence of metals. In this case, the incorporated heteroatoms and functional groups are not coordinated to the metal ion and can activate organic reagents by a reversible formation of covalent, coordination or hydrogen bonds with them. The presence of two or more such bonds provides optimal location of reactants in a transition state, which ensures high stereo- and enantioselectivity of the reactions. Depending on the type of catalytic reaction and its conditions, chemically identical active centres of $C_2$-symmetric COC can perform either the same or different functions. Their electronic and steric properties can be adjusted to specific processes *via* application of cocatalysts (as a rule, achiral organic acids or bases). Of course, optimal choice of the auxiliary compound, which is commonly made empirically, requires testing of a huge array of potential cocatalysts. However, the effect achieved is worth the efforts, since the development of original unsymmetric bifunctional catalysts is even more complicated. An additional advantage of $C_2$-symmetric catalysts which enhances the efficiency of their application in asymmetric synthesis is the possibility to reach the maximal yield of products and enantioselectivity of the catalytic process by varying spacer groups (achiral and chiral).

Organocatalytic reactions catalyzed by axially symmetric diol derivatives are considered in several reviews.[9–11] However, the data on catalytic performance of axially symmetric chiral 1,2-diamines and their derivatives have not yet been summarized. To fill in the gap, we classified the catalysts of this type in terms of structure and demonstrated with specific examples how the nature of their structural moieties and functional groups affects the mechanism of

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Received 23 March 2015
*Uspekhi Khimii* **84** (11) 1077 – 1099 (2015);
translated by N M Vinogradova

catalytic action and application scope of the catalysts. The review covers the most important catalytic asymmetric reactions accompanied by the formation of a carbon–carbon bond (aldol condensations, Michael, Mannich and Diels–Alder reactions, allylation, desymmetrization) and widely used in asymmetric synthesis, in particular, in the key stages of preparation of biologically active compounds. Some other practically valuable reactions catalyzed by different types of $C_2$-symmetric derivatives of chiral di- and polyamines are also considered.

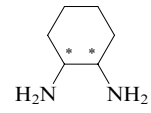
## II. Classification of organocatalysts based on $C_2$-symmetric diamines

$C_2$-Symmetric COC contain two similar structural moieties, which provide for activation and proper spatial location of reactants in the transition states of catalytic reactions, and a spacer, which links these fragments with each other. Depending on the structure of active sites, chiral organocatalysts under consideration can be divided into the following groups: di- and polyamines (**1**–**6**),† amino acid derivatives (**7**–**15**), polyamides and sulfamides (**16**–**21**), bisureas and bisthioureas (**22**–**25**), and bisamidines and bisguanidines (**26**–**32**).

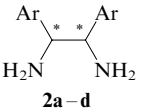
Most of these catalysts can be prepared from relatively available $C_2$-symmetric diamines **1**–**4** and their analogues *via* known carboxylation, sulfonylation or cross-coupling reactions or by treatment with reagents bearing isocyanate, isothiocyanate, carbodiimide and some other groups. Ethylene, cyclohexane, benzene, binaphthyl, 9,10-dihydro-9,10-ethanoanthracene and some other bidentate groups are used as spacers. The number of stereocentres in catalyst molecules can range from two to six depending on the symmetry of active sites and spacer groups. This makes it possible to achieve the maximal catalyst activity and enantioselectivity of the catalytic reactions by varying the diastereomeric composition of catalytic systems. The comprehensive information on the synthesis and properties of $C_2$-symmetric organocatalysts **1**–**32** can be found in the references cited in Section III of the current review.

† The salt of polyamine **5** and phosphotungstic acid is considered as an organocatalyst, since the metal incorporated in the inorganic polymer acts as a solid support which heterogenizes the catalyst and does not participate in the catalytic process (see Section III.1.c, Scheme 13).

**Structures 1 – 14**

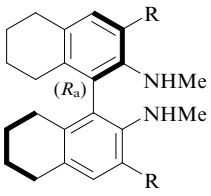


(*S*,*S*)- or (*R*,*R*)-**1**



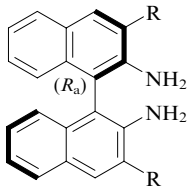
**2a**–**d**

Ar = Ph (**a**), 2-MeC$_6$H$_4$ (**b**), 1-Naph (**c**), 4-FC$_6$H$_4$ (**d**); Naph is naphthyl



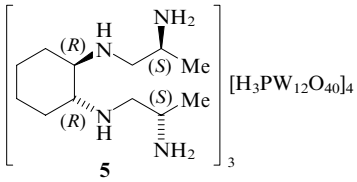
**3a**,**b**

R = Ph (**a**), 4-Bu$^t$C$_6$H$_4$ (**b**)

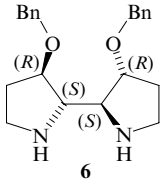


**4a**–**c**

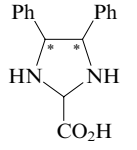
R = Ph (**a**), 4-Bu$^t$C$_6$H$_4$ (**b**), 3,5-Bu$^t_2$C$_6$H$_3$ (**c**)



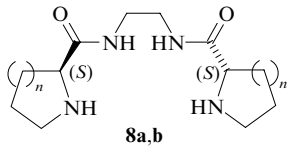
**5**



**6**

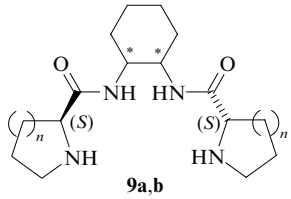


(*S*,*S*)- or (*R*,*R*)-**7**



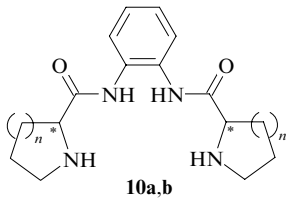
**8a**,**b**

*n* = 1 (**a**), 2 (**b**)



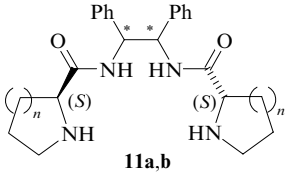
**9a**,**b**

*n* = 1 (**a**), 2 (**b**)



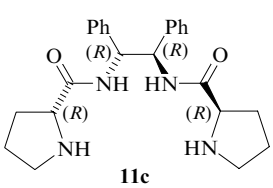
**10a**,**b**

*n* = 1 (**a**), 2 (**b**)

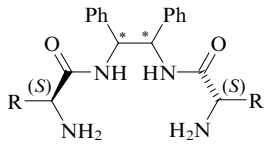


**11a**,**b**

*n* = 1 (**a**), 2 (**b**)

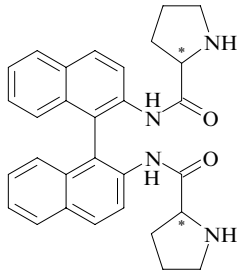


**11c**

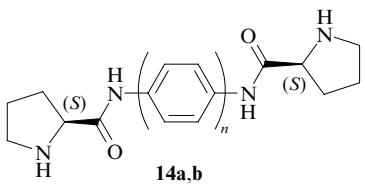


**12a**–**c**

R = Ph (**a**), Pr$^i$ (**b**), $CH_2OSiPh_2Bu^t$ (**c**)



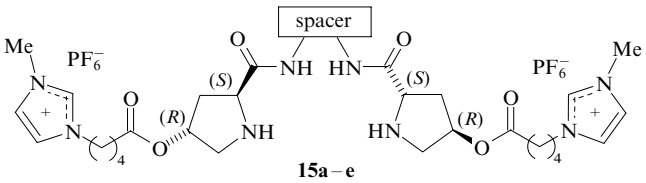
($R_a$,*S*,*S*)-, ($S_a$,*S*,*S*)- or ($R_a$,*R*,*R*)-**13**



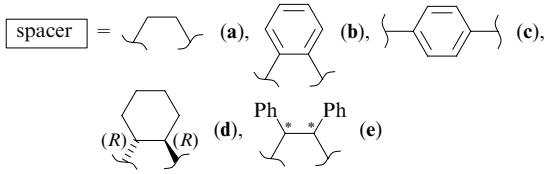
**14a**,**b**

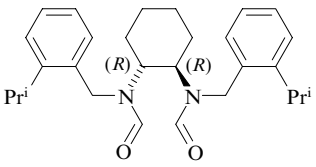
*n* = 1 (**a**), 2 (**b**)

**Structures 15 – 32**

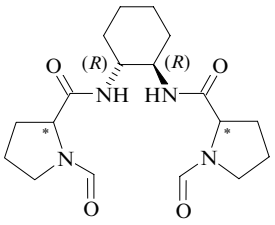



**15a – e**

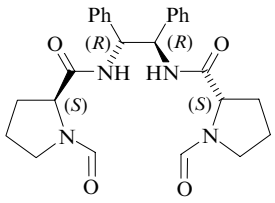


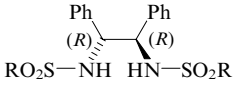

**16**




(*S*,*S*)- or (*R*,*R*)-**17**

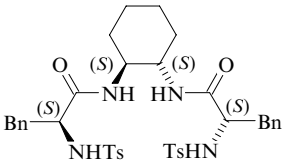



**18**



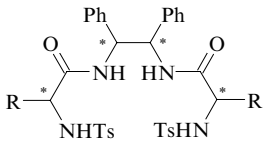

**19a**,**b**

R = $CF_3$ (**a**), n-$C_4F_9$ (**b**)



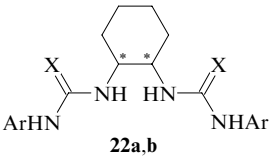

**20**

Ts = $SO_2C_6H_6Me$-4



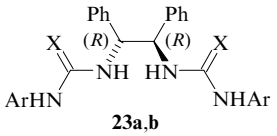

**21a**,**b**

R = Me [(*S*,*S*,*S*′,*S*′)-**21a**],
Bn [(*S*,*S*,*S*′,*S*′)-, (*S*,*S*,*R*′,*R*′)-
(*R*,*R*,*S*′,*S*′)- or (*R*,*R*,*R*′,*R*′)-**21b**]



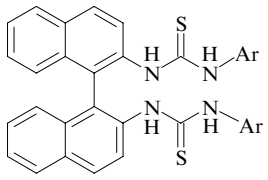

**22a**,**b**

X = O (**a**), S (**b**);
Ar = 3,5-$(CF_3)_2C_6H_3$



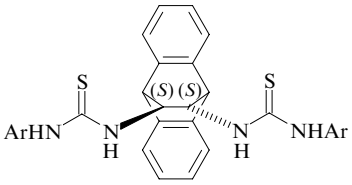

**23a**,**b**

X = O (**a**), S (**b**);
Ar = 3,5-$(CF_3)_2C_6H_3$



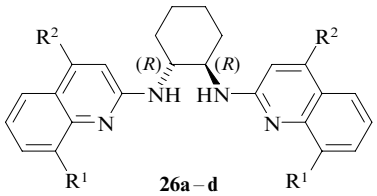

($S_a$)- or ($R_a$)-**24**

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



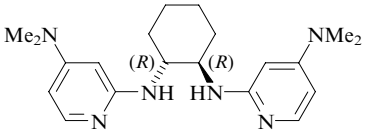

**25**

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

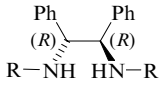



**26a – d**

$R^1$ = H: $R^2$ = H (**a**), OMe (**b**),
pyrrolidin-1-yl (**c**);
$R^1$ = OMe, $R^2$ = pyrrolidin-1-yl (**d**)

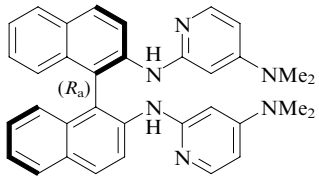



**27**

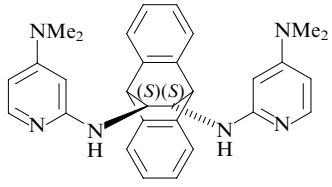



**28a**,**b**

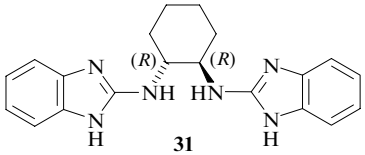
R = 4-pyrrolidin-1-yl-quinolin-2-yl (**a**),
4-$NMe_2$-pyrrolidin-1-yl (**b**)



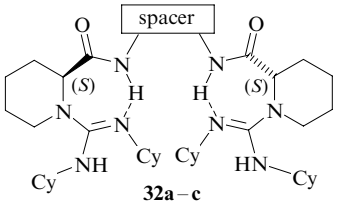

**29**




**30**

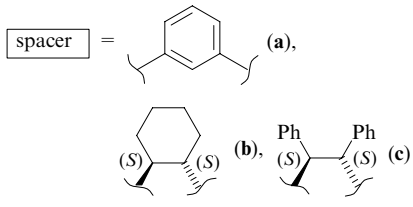



**31**




**32a – c**

Cy = cyclo-$C_6H_{11}$




## III. Application of $C_2$-symmetric diamines and their derivatives as catalysts of asymmetric reactions

The types of reactions catalyzed by $C_2$-symmetric di- and polyamines and their derivatives and the mechanisms of catalysis are determined by the structures of catalyst active sites. The latter can activate the reactants and perform the stereoinduction in the following ways:

— by forming enamines or iminium ions with the reactants containing carbonyl groups;

— by forming active coordination intermediates with the reactants;

— by acid-base interactions with the reactants possessing acid or base properties;

— by forming stereodifferentiating hydrogen bonds with the proton donors or acceptors.

As will be shown below, in many cases, the active sites of $C_2$-symmetric catalysts act in enantioselective reactions concertedly, thus increasing the reaction rates and selectivities.

### III.1. Reactions catalyzed by $C_2$-symmetric di- and polyamines (enamine and iminium catalysis)

A characteristic feature of COC containing amino groups is the ability to form, with carbonyl compounds, enamines (**En**) or iminium cations (**Im**), which enantioselectively react with the electrophiles (E) or nucleophiles (NuH) present in the system, giving rise to the corresponding addition products (Fig. 1). After completion of the addition step, the catalyst returns to the reaction mixture *via* hydrolytic cleavage of C–N and C=N bonds. Below we consider the most important catalytic asymmetric reactions of these types.

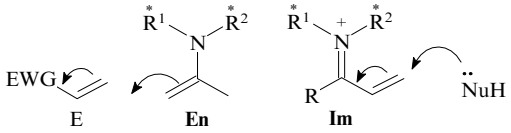



**Figure 1.** Active species of asymmetric reactions catalyzed by chiral amines.
R* is a chiral group; EWG is an electron-withdrawing group.

#### III.1.a. Michael reactions

Organocatalytic conjugate addition of nucleophiles to α,β-unsaturated aldehydes (the Michael reaction) is extensively used in the key stereodifferentiating stages in the synthesis of natural compounds and the most active enantiomers of clinically used medicines and their analogues.[3, 12–14] These reactions can be divided into two groups. The first one includes the processes in which the iminium ion is generated from the catalyst and α,β-unsaturated carbonyl compound. This ion reacts with the nucleophile affording intermediate **A**, which gives rise to adduct **B** with elimination of the catalyst (iminium catalysis). In the reactions of the second group, the catalyst activates the nucleophile (usually a carbonyl compound) *via* formation of enamine, which further adds an electrophile (as a rule, electron-deficient alkene), and the resulting intermediate **A′** converts to the corresponding Michael adduct **B′**, eliminating the catalyst (enamine catalysis) (Scheme 1). In some cases, these two types of catalysis can proceed simultaneously in asymmetric reactions catalyzed by $C_2$-symmetric diamines.

Li, Wang and co-workers[15] found that in the presence of (*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclohexane (**1**)–adipinic acid (**33**) catalytic system, cyclopentanone (**34a**) adds to chalcones **35** to afford the Michael adducts **36** with excellent enantioselectivity: enantiomeric excess (*ee*) reaches 99% (Scheme 2).‡

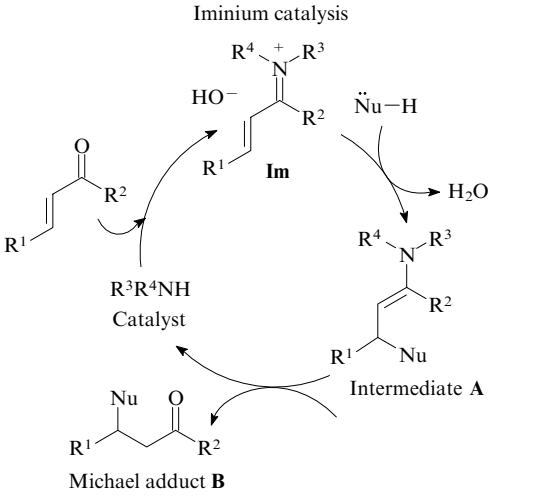
The diastereoselectivity, *i.e.*, the ratio of *anti*- and *syn*-diastereomers [*dr* (*anti* : *syn*)] ⩽ 3 : 1, and the reaction rate is not high. The addition of acid **33** plays a key role in this case; without **33**, the catalyst activity and reaction selectivity decrease. The authors suppose that in transition state **TS1**, one of the amino groups of catalyst **1** forms the enamine intermediate with cyclopentanone (**34a**), while the second one activates chalcone **35** by forming an iminium ion with it.

The suggested catalytic system appeared rather efficient in the vinylogous reaction of chalcones **35** with butenolides **37**, in which, owing to the keto–enol tautomerism, position 5 of the butenolide ring has nucleophilic properties.[16] The Michael adducts **38** formed as the major *syn*-diastereomers (*syn* : *anti* ratio up to 99 : 1 ) with *ee* ⩽ 96%.

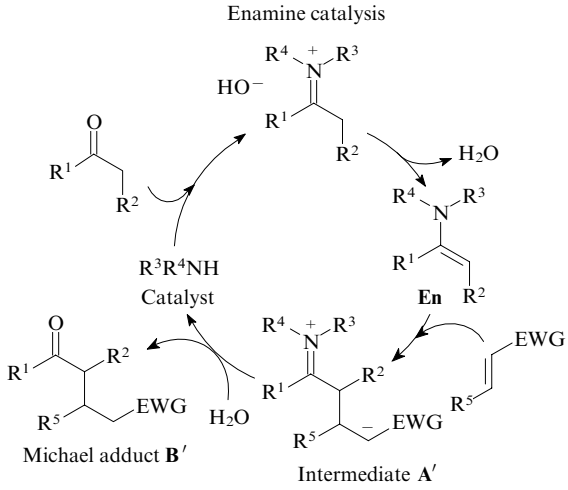
Chin and co-workers[17] found that 4-hydroxycoumarin (**39a**) reacts with benzylideneacetone (**40a**) in the presence of chiral diamines (*R*,*R*)-**2a**–**c**, affording the *R*-enantiomer of Michael adduct **41a** (Scheme 3).

This product represents the active substance of warfarin anticoagulant widely used in clinical practice for thrombosis treatment.[18] The highest yields of product (*R*)-**41a** (99%) and reaction enantioselectivity (92% *ee*) were attained in the presence of (*R*,*R*)-**2b**–AcOH catalytic system in THF.

**Scheme 1**



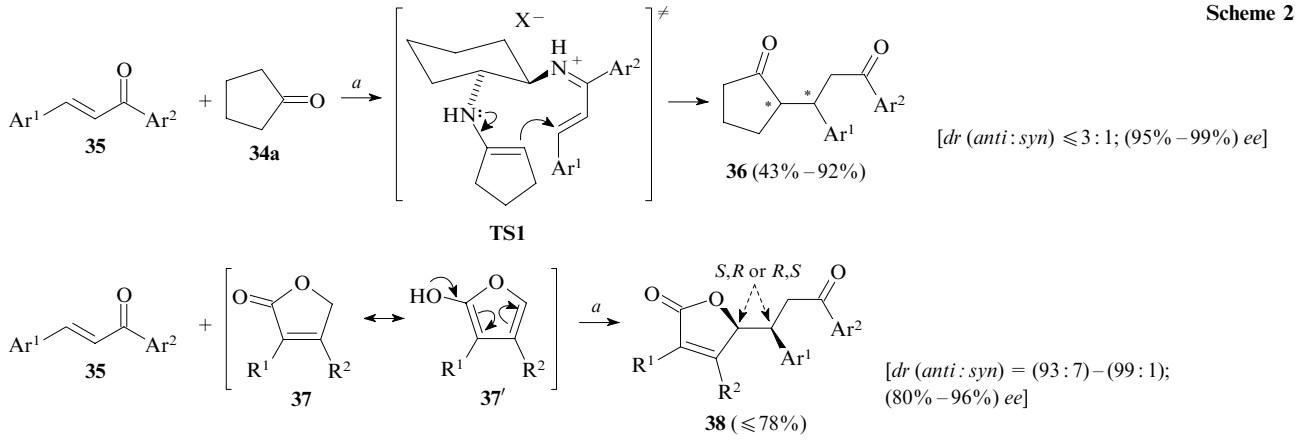

NuH = CH-acid, ROH, RR′NH, *etc.*




EWG = $NO_2$, CN, $SO_2R'$, *etc.*

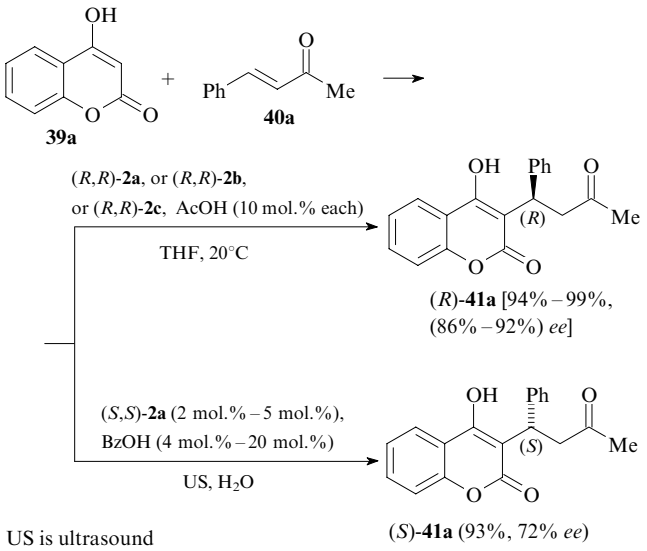
‡ Hereinafter, unless otherwise stated, Ar indicates unsubstituted or substituted phenyl group.

**Scheme 2**




$Ar^1$ = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-$MeC_6H_4$; $Ar^2$ = Ar, 2-Th, 2-Fu; $R^1$, $R^2$ = Ar;
(*a*) (*S*,*S*)- or (*R*,*R*)-**1** – $HO_2C(CH_2)_4CO_2H$ (**33**) (20 mol.% each), MeOH – $CHCl_3$, 20 °C, 72 h; Th is thienyl, Fu is furyl

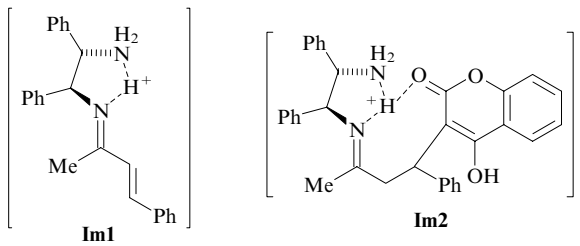
**Scheme 3**




US is ultrasound

The acid additive is likely to assist the formation of key iminium cations **Im1** and **Im2** with the molecular masses of 341.20 and 503.23, respectively, which were subsequently detected by Chinese researchers[19] by electrospray ionization mass spectrometry (ESI-MS).

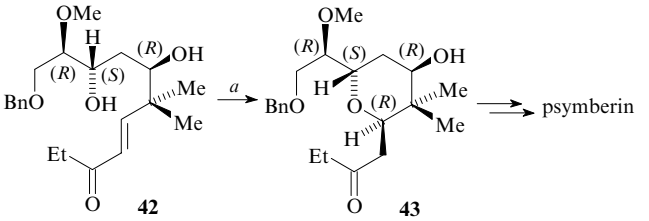
**Structure Im1 and Im2**




The reaction between compounds **39a** and **40a** catalyzed by diamine (*S*,*S*)-**2a** was found to proceed with moderate enantioselectivity (up to 72% *ee*) also in aqueous media in the presence of benzoic acid as the cocatalyst.[20] The reaction gives the *S*-enantiomer of warfarin (see Scheme 3), which appreciably (2 – 5 times) surpasses the *R*-enantiomer in the anticoagulant activity.[21] The enantiomeric excess of the product increases to 99.9% after one recrystallization from an acetone – water mixture, which testifies to the practical importance of the method. For more efficient emulsification of the poorly water-soluble reaction mixture, the process should be carried out in an ultrasonic bath, which increases the yield of (*S*)-warfarin up to 93%.

The asymmetric Michael reactions catalyzed by chiral diamines can also involve heteronucleophiles. Thus, diamines (*R*,*R*)-**2a**,**b** efficiently promote diastereoselective cyclization of compound **42** *via* the nucleophilic addition of one of the hydroxyl groups to the α,β-unsaturated ketone moiety.[22] The authors succeeded in selecting the conditions (anthracene-9-carboxylic acid as a cocatalyst, EtOAc as a solvent) that allowed them to stereoselectively obtain the target cyclization product **43** with *R*-configuration of the new stereocentre (Scheme 4).

**Scheme 4**



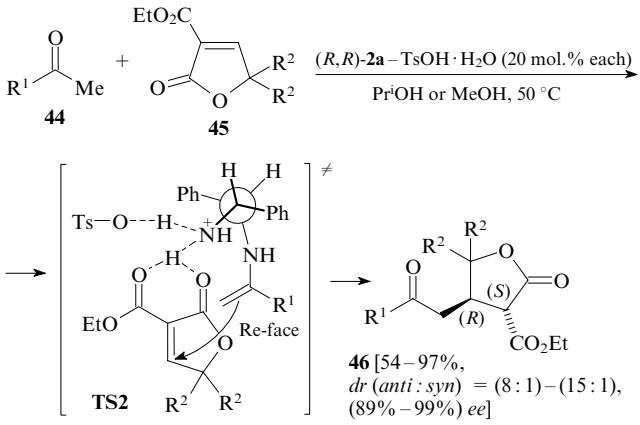

(*a*) (*R*,*R*)-**2a** or (*R*,*R*)-**2b** (40 mol.%), anthracene-9-carboxylic acid (1 equiv.), EtOAc, 0 °C, 48 h

Tetrahydropyran **43** was further used in the synthesis of psymberin, a drug that inhibits proliferation of cancer cells.[23, 24]

Recently Wang, Li and co-workers[25] successfully used the *R*,*R*-enantiomer of 1,2-diphenylethylenediamine (**2a**) for asymmetric catalysis of reactions between the low reactive aryl methyl ketones **44** and 5,5-disubstituted furan-2-ones **45**. As a result, chiral γ-lactones **46** were obtained, the structural moiety of which is present in many natural compounds, including those possessing antibacterial and antitumour activities (Scheme 5).[26]

This is the enamine version of asymmetric catalysis (see Scheme 1). The highest values of diastereo- and enantioselectivity of the reactions were achieved in the presence of *p*-toluenesulfonic acid monohydrate.

**Scheme 5**

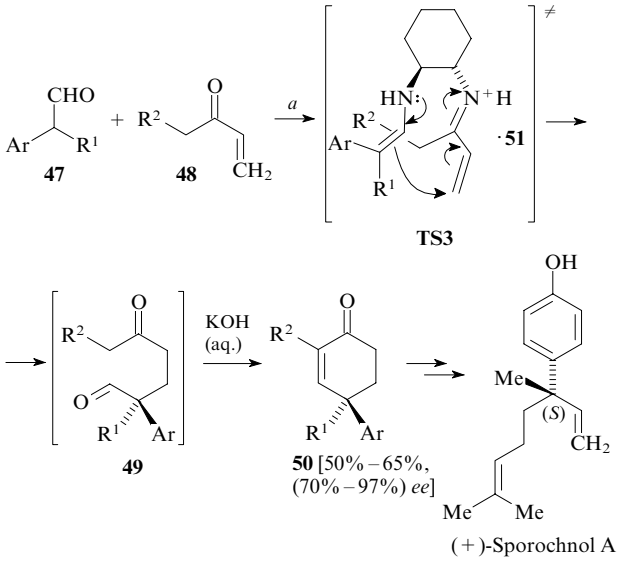



$R^1$ = Ar, 3-Py, 3-Fu, 2-Th; $R^2$ = Me, Et; Py is pyridyl

The authors suggested the bifunctional mechanism of catalysis according to which one of the amino groups of catalyst (*R*,*R*)-**2a** forms enamine with aryl methyl ketone **44** and the second one activates (fixes in space) the electrophilic component **45** by means of the acid cocatalyst (transition state **TS2** ).

As noted above (see Scheme 2), catalysis of the asymmetric Michael reactions by $C_2$-symmetric chiral diamines can proceed with simultaneous participation of both enamines and iminium salts. An interesting example of such bifunctional catalysis is the enantioselective catalytic annulation of aldehydes **47** with α,β-unsaturated ketones **48**, developed by Kotsuki and co-workers.[27] The process includes a sequence of nucleophilic addition of the aldehyde across the electron-deficient multiple bond and intramolecular crotonic condensation of adduct **49** promoted by KOH, resulting in the formation of cyclohexenone derivatives **50** (Scheme 6).

**Scheme 6**



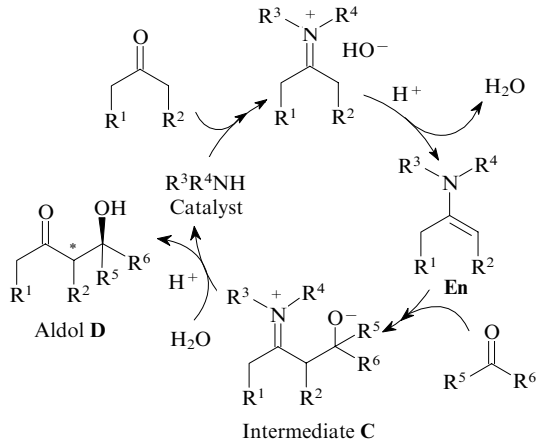

Ar = Ph, 4-MeOC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-Naph; $R^1$ = Me, Et; $R^2$ = H, Me; (*a*) (*S*,*S*)-**1**–**51** (30 mol.% each)

The high enantioselectivity of this reaction was attained in the presence of (*S*,*S*)-**1**–(*S*,*S*)-cyclohexane-1,2-dicarboxylic acid catalytic system (**51**). The use of other chiral amines and(or) dicarboxylic acids reduced the level of asymmetric induction. The authors proposed that in the presence of acid (*S*,*S*)-**51**, one of the amino groups of bifunctional catalyst (*S*,*S*)-**1** is condensed with aldehyde **47** and the second one reacts with α,β-unsaturated ketone **48**, resulting in enamine-iminium intermediate (transition state **TS3**), which furnishes adduct **49** *via* the intramolecular asymmetric Michael reaction. The developed method was used by the authors in the synthesis of (+)-sporochnol A, a natural compound extracted from *Sporochnus bolleanus* alga and used as a deterrent (means to deter fishes).[28, 29]

### III.1.b. Aldol reactions

Asymmetric catalytic aldol reactions are widely spread in nature (for example, aldolase-catalyzed enzymatic synthesis of hydrocarbons)[30] and extensively used in organic synthesis for enantioselective formation of carbon–carbon bonds in organic compounds.[31–34] In the presence of chiral amines, the catalytic cycle of these reactions includes, as a rule, the formation of enamine from a catalyst and a donor compound capable of enolization, the addition of the carbonyl acceptor to the enamine and hydrolytic cleavage of the amino catalyst from adduct **C**, giving rise to aldol **D** (Scheme 7).[35]

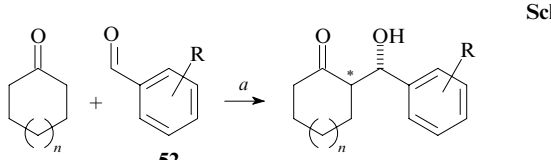
**Scheme 7**




Considering the ability of natural aldolases to catalyze the enzymatic reactions in living systems,[36] attempts were made to develop organocatalysts suitable for aldol reactions in water.[37–41] Some axially symmetric amines and their derivatives appeared to be appropriate for this role.

Li, Lai and co-workers[42] found that diamine (*R*,*R*)-**2a**, in combination with trifluoromethanesulfonic acid, catalyzes the reactions of cycloalkanones **34a**,**b** with aromatic aldehydes **52** in the presence of water to give the corre-

**Scheme 8**

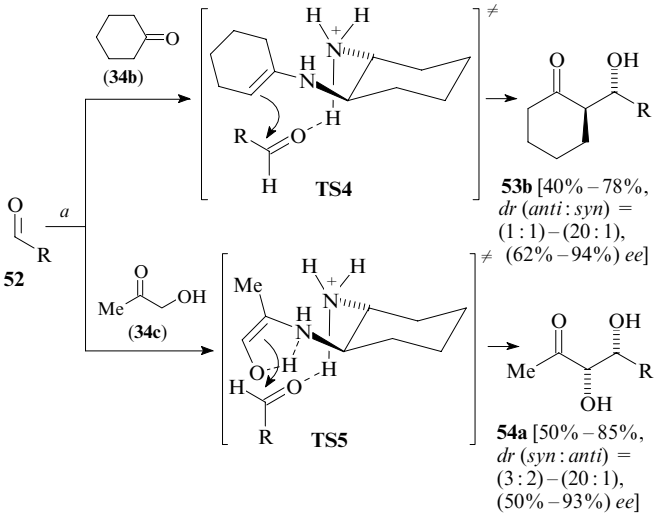



*n* = 0 (**a**), 1 (**b**); R = 4-NO$_2$, 4-Cl, 4-Br, 4-Me, 4-OMe, 2-NO$_2$; (*a*) (*R*,*R*)-**2a** (10 mol.%), TfOH (20 mol.%), H$_2$O, 20 °C; Tf is trifluoromethanesulfonyl (triflyl)

sponding aldols **53** with enantioselectivity of 45% – 93% *ee* (Scheme 8). However, the diastereoselectivity of the reactions and the yields of products were, as a rule, moderate. Acetone does not react with 4-nitrobenzaldehyde under the mentioned conditions.

Subsequently, (*R*,*R*)-**1** – adipinic acid (**33**) catalytic system was used in asymmetric aldol reactions of cyclohexanone (**34b**) and hydroxyacetone (**34c**) with aromatic aldehydes **52** in aqueous methanol (Scheme 9).[43]

**Scheme 9**

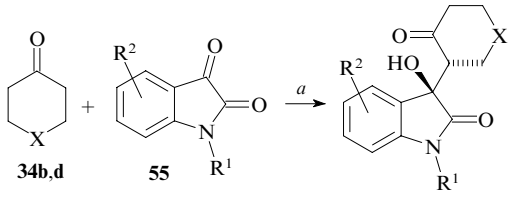



R = Ar, 3-Py, 4-Py;
(*a*) (*R*,*R*)-**1** – **33** (20 mol.% each), MeOH – $H_2O$ (1 : 1), 20 °C

The pathway of these reactions depends on the ketone type: cyclohexanone (**34b**) predominantly forms aldols with *anti*-aldols **53b**, while hydroxyacetone (**34c**) leads to *syn*-aldols **54a** with high diastereo- and enantioselectivity. As in some cases of Michael reaction considered above (see, for example, Schemes 3 and 5), the amino groups of catalyst (*R*,*R*)-**1** play different roles: one of them forms enamine with ketone **34** and the other one, protonated by acid **33**, determines the site of attack of aldehyde **52** by forming a hydrogen bond with it. The observed difference in the stereochemistry of the reactions was attributed to different arrangements of the aldehyde component in enamine–ammonium transition states **TS4** and **TS5**. It is assumed that in complex **TS5**, the aryl group of aldehyde **52** is remote from the hydroxyl group of ketone **34c** as a result of steric repulsion.

Catalyst (*R*,*R*)-**1** in combination with adipinic acid (**33**) efficiently promotes asymmetric aldol condensations between two ketones, in particular, the reactions of cyclohexanone (**34b**) or tetrahydropyran-4-one (**34d**) with isatin derivatives **55**.[44] Products **56** are formed in an aqueous alcohol medium in high yields and with good diastereo- and enantioselectivity (Scheme 10). The resulting compounds contain the structural moiety of 3-hydroxyindolin-2-one, which is present in many biologically active compounds, and are of particular interest for medicinal chemistry and pharmacology.[45 – 47]

**Scheme 10**



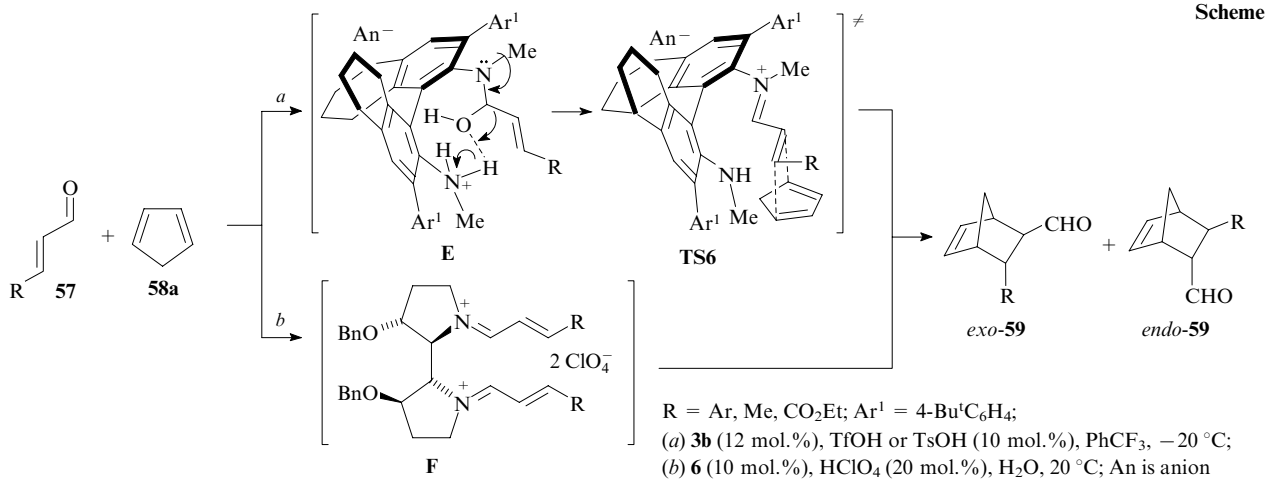

X = $CH_2$ (**b**), O (**d**); $R^1$ = H, Me, Bn; $R^2$ = H, 5-$NO_2$, 5-OMe, 5-Cl, 5-Br, 6-Br; (*a*) (*R*,*R*)-**1** – **33** (20 mol.% each), MeOH – $H_2O$ (1 : 1), 20 °C

### III.1.c. Diels – Alder reactions

The catalytic asymmetric Diels – Alder reaction is one the most powerful tools in modern organic synthesis and is widely used in the key stages of synthesis of natural compounds and biologically active substances.[48] Maruoka and co-workers[49] were among the first to successfully use $C_2$-symmetric diamines as catalysts for this reaction. They found that β-substituted α,β-unsaturated aldehydes **57** react with cyclopentadiene (**58a**) in the presence of ($R_a$)-(1,1′-octahydrobinaphthyl)-2,2′-diamine **3b** and acid additive (trifluoromethanesulfonic or *p*-toluenesulfonic acid), giving rise to cycloadducts **59** in 80% – 99% yields with high stereo- (*exo* : *endo* ratio from 5 : 1 to 20 : 1) and enantioselectivity [(87% – 98%) *ee*] (Scheme 11).

Bulky 4-(*tert*-butyl)phenyl substituents in positions 3 and 3′ of octahydrobinaphthyl moiety of molecule **3b**

**Scheme 11**



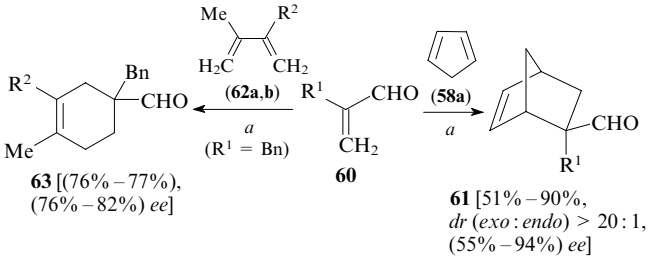

R = Ar, Me, $CO_2Et$; $Ar^1$ = 4-$Bu^tC_6H_4$;
(*a*) **3b** (12 mol.%), TfOH or TsOH (10 mol.%), $PhCF_3$, −20 °C;
(*b*) **6** (10 mol.%), $HClO_4$ (20 mol.%), $H_2O$, 20 °C; An is anion

facilitate the high level of stereoinduction: upon catalysis with diamine **3a** bearing the phenyl groups at these positions, the enantiomeric excess of products **59** was essentially lower (27%–53%). It is the authors' opinion that during the reaction one of the amino groups of catalyst **3b** adds to the aldehyde group of compound **57**, while the second one promotes the dehydration of semiaminal **E** into the iminium cation, which stereoselectively interacts with diene **58a** in transition state **TS6**.[50]

Later, Zhang and co-workers[51] used $C_2$-symmetric 3,3′-dialkoxy-2,2′-bipyrrolidines as catalysts for the Diels–Alder reaction between unsaturated compounds **57** and **58a**. Dibenzyl derivative **6** in combination with acid cocatalyst $HClO_4$ manifested the best catalytic properties (see Scheme 11). An advantage of this catalytic system is its tolerance to water, which not only does not hamper the reaction, but also essentially accelerates the process. In an aqueous medium, cycloadducts **59** were generated in 62%–95% yields with *ee* ⩽91%; however, the reaction stereoselectivity was lower than that in the presence of catalyst **3b**: the ratio of *exo*:*endo* stereoisomers ranged from 0.8:1 to 2.7:1. Catalyst **6**·2 $HClO_4$ was readily regenerated and recycled in the reaction with the same efficiency three times; however, in the fourth and, especially, in the fifth cycle, the reaction rate and yield of product **59** essentially reduced. $^1$H NMR and X-ray diffraction studies confirmed the formation of diiminium intermediates **F** involving catalyst **6**·2 $HClO_4$ and α,β-enals **57** during the reaction.

α-Substituted α,β-unsaturated aldehydes **60** can also be involved into the organocatalytic asymmetric Diels–Alder reactions with cyclopentadiene (**58a**) (Scheme 12).[52] In this case, binaphthyl primary diamines **4a**–**c** in combination with an acid cocatalyst, namely, trifluoromethanesulfonic acid, proved to be the most efficient catalysts.

**Scheme 12**

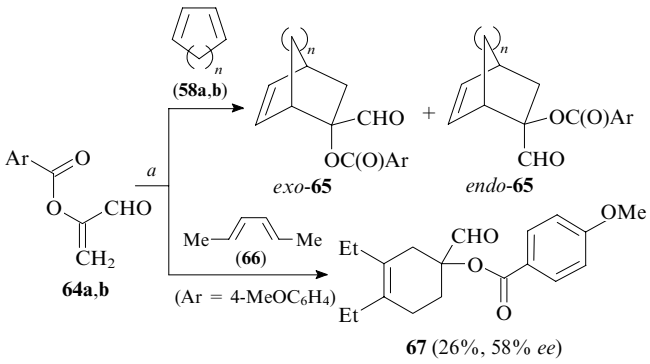



$R^1$ = Me, Et, $Pr^n$, All, Bn, $(CH_2)_2OBn$, $CH_2OAc$; **62**: $R^2$ = H (**a**), Me (**b**); (*a*) **4c** (20 mol.%), TfOH (10 mol.%), mesitylene, −20 °C; All is allyl

The highest *ee* values for cycloadducts **61** (up to 90%) were achieved in mesitylene at −20 °C in the presence of diamine **4c** bearing bulky 3,5-di(*tert*-butyl)phenyl groups in positions 3 and 3′ of the binaphthyl moiety. The level of stereoinduction depended on the bulk of α-substituent in compound **60**: the *ee* of product **61a** ($R^1$ = Me) was 55% and that of **61b** ($R^1$ = Et) was 92%. Under the proposed conditions, acyclic dienes also participate in this reaction, in particular, 2-methylbutadiene **62a** and 2,3-dimethylbutadiene **62b** are converted to the corresponding Diels–Alder adducts **63** with good enantioselectivity.

Luo, Cheng and co-workers[53] suggested using $C_2$-symmetric chiral tetramines protonated with phosphotungstic acid ($H_3PW_{12}O_{40}$) as recyclable chiral catalysts for asymmetric Diels–Alder reactions. The acid, which is not directly involved in the catalytic process, in this case, plays a role of a solid support and modifier of the activity and stereodiscriminating ability of the heterogeneous catalyst. In the presence of hybrid catalyst **5**, the derivatives of α-(aryloxy)acrolein **64** react with cyclopentadiene (**58a**) and cyclohexa-1,3-diene (**58b**) to afford the corresponding cycloadducts **65** in 84%–97% yield and with 78%–83% *ee* (Scheme 13).

**Scheme 13**




**58**: *n* = 1 (**a**), 2 (**b**); **64**: Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**); (*a*) **5** (1.67 mol.%), THF, $H_2O$, 4 → 20 °C (6 cycles)

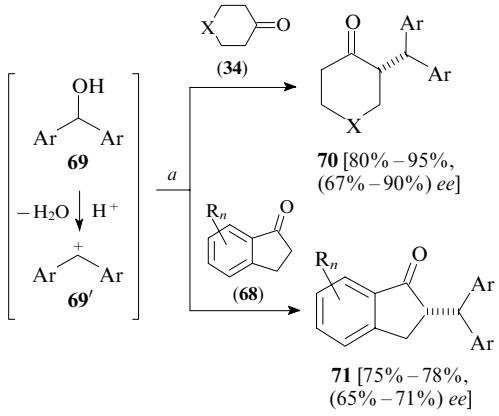
The stereochemistry of reactions depends on the size of the ring in the diene component: in the case of cyclopentadiene (**58a**), the *exo*-isomer of product **65** predominates (*dr* = 80:20), while in the case of cyclohexadiene (**58b**), the *endo*-isomer prevails (*dr* = 95:5). Linear hexa-2,4-diene (**66**) also reacted with α-(aryloxy)acrolein **64b** under the proposed conditions; however, in this case, the yield and *ee* of adduct **67** were substantially lower. After reaction completion, catalyst **5** was precipitated from the reaction mixture with diethyl ether and reused 5 times, although the yield and, to a lesser extent, enantiomeric excess of products **65** decreased.

### III.1.d. Miscellaneous reactions

Among other asymmetric reactions catalyzed by di- and polyamines devoid of other functional groups, special mention should be made of α-alkylation of carbonyl compounds. This reaction is a widespread method for constructing C–C bonds in synthetic organic chemistry.[54] However, there are only a few examples of catalytic enantioselective α-alkylation of ketones that involve the formation of enamine intermediates.[55, 56] Kim and co-workers[57] accomplished α-alkylation of cyclic ketones **34** and indanone derivatives **68** with bis(4-dimethylaminophenyl)methanol (**69**) in the presence of $C_2$-symmetric chiral diamines (*S*,*S*)-**2a**, (*S*,*S*)-**2c** and (*S*,*S*)-**2d** (Scheme 14).

The best results were achieved in the case of (*S*,*S*)-**2a**–TFA–$PPh_3$ catalytic system in which the corresponding α-diarylmethyl ketones **70**, **71** were formed in 75%–95% yields with *ee* of 65%–90%. The reaction is likely to proceed by the $S_N1$ mechanism, which includes a Brønsted acid (TFA) promoted formation of stabilized cation **69′** from diarylmethanol **69** containing donor aryl groups, and reaction of **69′** with the key enamine intermediate formed from ketone **34** or **68** and catalyst (*S*,*S*)-**2a** during the catalytic process.

**Scheme 14**



Ar = 4-$Me_2NC_6H_4$; X = $CH_2$, O, S, NEt, 1,3-dioxolan-2,2-diyl; $R_n$ = H, 5,6-$(OMe)_2$; (*a*) (*S*,*S*)-**2a** (20 mol.%), TFA – $PPh_3$ (30 mol.% each), $Et_2O$, 20 °C; TFA is trifluoroacetic acid

## III.2. Reactions catalyzed by $C_2$-symmetric diamino compounds containing structural moieties of amino acids and their derivatives (bifunctional catalysis)

Among COC of this type, amides of α-amino acids (mainly, proline) based on axially symmetric diamines are most widely used in asymmetric reactions. $C_2$-Symmetric derivatives of α-amino acids containing free carboxyl group are applied as catalysts much more rarely.

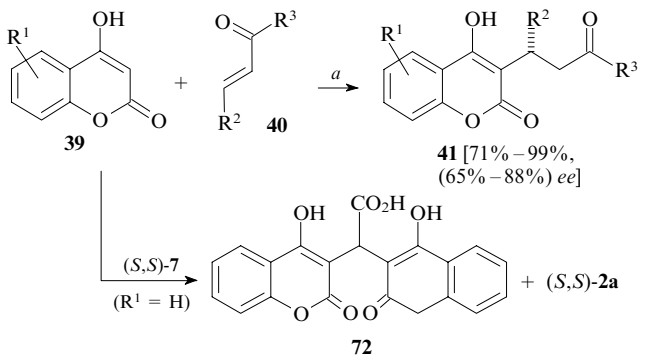
### III.2.a. Michael reactions

The organocatalysts based on α-amino acid derivatives similar to nonfunctionalized polyamines can act as activators of both acceptor (α,β-unsaturated carbonyl compound) and(or) donor components (aldehyde or ketone) in asymmetric Michael reactions. These reactions also include the formation of enamines or iminium ions. However, stereodiscriminating hydrogen bonds formed by the amide and amine groups of the catalyst with reactants play an important role in these transformations (bifunctional catalysis [58–61]). A rare example of organocatalytic application of $C_2$-symmetric diamines containing a carboxyl group is the reaction between 4-hydroxycoumarin derivatives **39** and α,β-enones **40** in the presence of 4,5-diphenylimidazolidine-2-carboxylic acid (**7**) developed by Jørgensen and co-workers.[62] It allows catalytic synthesis of Michael adducts **41**, including the above-mentioned (see Section III.1.a) anticoagulant warfarin **41a** (*S*-enantiomer) with fairly good enantiomeric purity (Scheme 15). Importantly, this method is applicable to asymmetric synthesis of products **41** on a kilogram scale.

Later, the data were obtained that showed that the true catalyst of this reaction is not amino acid **7** but 1,2-diphenylethylenediamine (*S*,*S*)-**2a** formed from **7** and 4-hydroxycoumarin (**39a**, $R^1$ = H) during the catalytic process [17] (see Section III.1.a). 4-Hydroxycoumarin derivative **72** was detected as by-product of this transformation.

Feng and co-workers [63] found that $C_2$-symmetric bisprolinamides bearing both chiral and achiral spacers also catalyze the addition of 4-hydroxycoumarin (**39a**) to α,β-enones **40**.

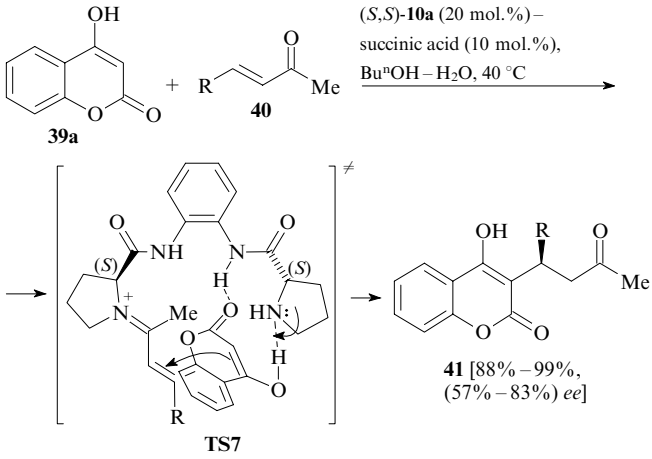
**Scheme 15**



$R^1$ = H, Hal, Me, OMe; $R^2$ = Ar, Alk, 2-Th, 2-Fu; $R^3$ = Me, Et, $Pr^i$; (*a*) (*S*,*S*)-**7** (10 mol.%), $CH_2Cl_2$, 20 °C

Among the catalysts explored, most active were bisamides **8a**, (*S*,*S*)-**9a** and (*S*,*S*)-**10a**; and the highest level of stereoinduction was attained in the case of *o*-phenylenediamine (*S*,*S*)-**10a**. In the presence of the (*S*,*S*)-**10a** – succinic acid catalytic system, hydroxycoumarin **39a** reacts with arylidene- and alkylideneacetone **40** in aqueous butanol to afford adducts **41** (including *R*-enantiomer of warfarin) in high yields with up to 83% *ee* (Scheme 16). The authors assumed that one of the prolinamide moieties of catalyst (*S*,*S*)-**10a** forms the electrophilic iminium ion with α,β-enone **40**, while the second one favourably locates the 4-hydroxycoumarin molecule *via* hydrogen bonding involving the amine and amide groups in transition state **TS7**.

**Scheme 16**

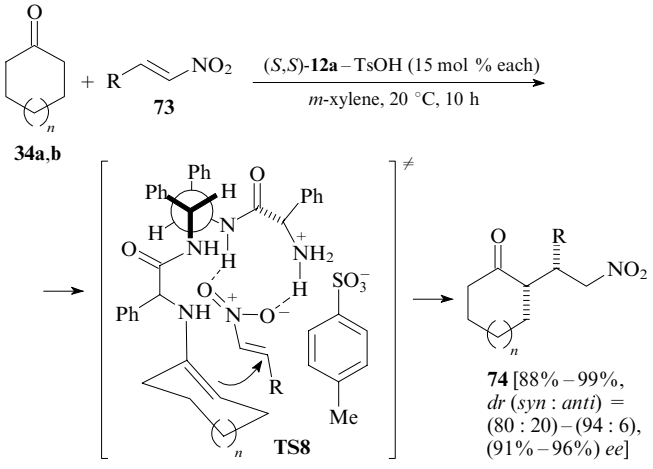


R = Ar, 2-Naph, $Pr^n$, $Pr^i$

The enamine type of catalysis takes place in asymmetric reactions developed by Feng and co-workers [64] between cycloalkanones **34** and α-nitroalkenes **73** catalyzed by bisamides (*S*,*S*)-**11a**, (*R*,*R*)-**11a** and (*R*,*R*)-**12a** containing 1,2-diphenylethylenediamine and α-amino acid, in particular, (*S*)-proline or (*S*)-phenylglycine, structural units (Scheme 17).

In this case, ketone **34** forms enamine with one of the catalyst amino groups, while the second aminoamide moiety activates nitroalkene **73** by forming hydrogen bonds with the oxygen atoms of the nitro group (see Scheme 17, transition state **TS8**).

**Scheme 17**




R = Ar, 2-Fu, 1-Naph; **34**: $n$ = 0 (**a**), 1 (**b**)

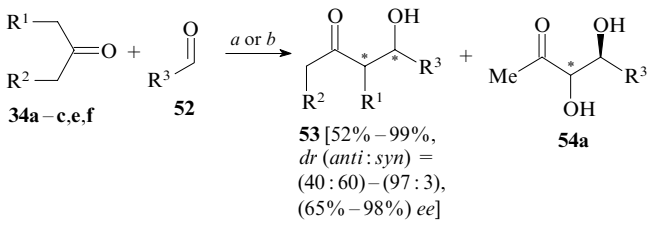
The highest yields of *syn*-adducts **74** and promising diastereo- and enantioselectivity of the reactions are observed in the presence of (*R*,*R*)-**12a** – TsOH (1 : 1) catalytic system in which TsOH protonats one of the catalyst amino groups and endows it with the ability to form hydrogen bonds with an acceptor component. The addition of 2 equiv. of TsOH leads to protonation of both amino groups and completely deactivates the catalyst, depriving it of the ability to form the enamine intermediates with ketone **34**, required for the catalytic process to take place. (*R*,*R*)-Diphenylethylenediamine **2a**, which lacks amide groups, does not catalyze the Michael reaction between compounds **34** and **73** under these conditions, which indicates the important role of these groups in nitroalkene activation. Along with cycloalkanones, acetone also adds to β-nitrostyrene under suggested conditions; however, the enantioselectivity of the reaction in this case is considerably lower (73% *ee*).

### III.2.b. Aldol reactions

$C_2$-symmetric α-amino amides are extensively used as organocatalysts for asymmetric aldol reactions. Zhao and coworkers [65] found that bis(prolinamides) **8**, (*S*,*S*)-**11a** and (*R*,*R*)-**11a** efficiently catalyze asymmetric cross-aldol reactions of aldehydes **52** with an excess of acetone (**34e**) (Scheme 18).

The best performance was found for catalyst (*S*,*S*)-**11a** in the presence of which the corresponding aldols **53e** ($R^1 = R^2 = H$) are formed at −35 °C with enantioselectivity of 82% – 98% *ee*. Catalyst (*S*,*S*)-**11a** is appreciably more

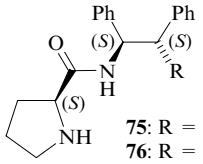
**Scheme 18**




**34**: $R^1 - R^2 = (CH_2)_2$ (**a**), $(CH_2)_3$ (**b**); $R^1$ = H: $R^2$ = OH (**c**), H (**e**), Me (**f**); $R^3$ = Ar, $Pr^i$, $Bu^t$, cyclo-$C_6H_{11}$; (*a*) (*S*,*S*)-**11a** (10 mol.%), $Me_2CO$, $CH_2Cl_2$ or THF, −35 °C; (*b*) ($S_a$,*S*,*S*)- or ($R_a$,*R*,*R*)-**13** (10 mol.%), BzOH (20 mol.%), DMF – $H_2O$ (1 : 1), 0 °C or DMF, 20 °C

active than analogues **75** and **76** lacking axial symmetry, which indicates the participation of both prolinamide units in the catalytic process.

**Structures 75, 76**



**75**: R = NHAc;
**76**: R = OH

Apart from acetone, cycloalkanones **34a**,**b** and hydroxyacetone (**34c**) also react with 4-nitrobenzaldehyde (**52a**) in the presence of bisamide (*S*,*S*)-**11a**; these reactions are carried out in inert organic solvents ($CH_2Cl_2$ or THF). The diastereomeric composition of cyclic aldols **53a**,**b** [$R^1 - R^2 = (CH_2)_n$; $n$ = 2 (**a**), 3 (**b**)] depends on the ketone: in the case of cyclopentanone (**34a**), *syn*-isomer predominates (*dr* = 60 : 40), while cyclohexanone (**34b**) gives *anti*-aldol **53b** with very high diastereoselectivity (*dr* = 97 : 3). Hydroxyacetone (**34c**) forms a mixture of aldols **53d** and **54a** of different structure with *dr* = 50 : 38 (97% and 66% *ee*, respectively).

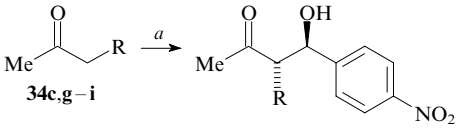
Najera and co-wokers [66] synthesized $C_2$-symmetric proline amides ($R_a$,*S*,*S*)-, ($S_a$,*S*,*S*)- and ($R_a$,*R*,*R*)-**13** bearing binaphthyl structural units and tested them in asymmetric aldol reactions between compounds **34e** and **52a**. The highest activity was found for enantiomers ($S_a$,*S*,*S*)- and ($R_a$,*R*,*R*)-**13** (see Scheme 18). Upon catalysis with diastereomeric (*S*)-prolinamides [($R_a$,*S*,*S*)- and ($S_a$,*S*,*S*)-**13**] with different absolute configurations of the binaphthyl moiety, the same *S*-enantiomer of aldol **53e** was generated, while (*R*)-prolinamide derivative ($R_a$,*R*,*R*)-**13** afforded its antipode, *ent*-**53e**, having *R*-configuration of the stereocentre. These data, which were confirmed latery by other research groups,[67, 68] imply that the stereochemical outcome of the reaction is determined by the configuration of the proline moiety, and the binaphthyl group plays an auxiliary, though important, role in the transition state. Thus, aldol reactions catalyzed by $C_2$-symmetric compounds **13** and **11** [65] proceed as a rule at a higher rate and, in some cases (although not always),[67] also with higher enantioselectivity than the corresponding reactions catalyzed by proline or bis(prolinamides) with achiral spacer groups.[68]

Good results were achieved for catalytic aldol reactions in aqueous DMF (1 : 1) where water was found to enhance the aldolization rate. Under proposed conditions, various aldehydes react with ketones **34b**,**e**,**f** to give the corresponding aldols **53** in good yields and up to 95% *ee*. Catalyst ($S_a$,*S*,*S*)-**13** can be regenerated and recycled in the reaction without an essential drop in the yield or enantiomeric purity of the product. Unfortunately, the regeneration procedure of the catalyst (acidification of the reaction mixture, product extraction, neutralization of the aqueous phase followed by catalyst crystallization) is rather complicated and is likely to be accompanied by its considerable loss.

The asymmetric aldol reaction of compounds **34e** and **52a** catalyzed by diamine ($S_a$,*S*,*S*)-**13** is significantly accelerated upon addition of a Brønsted acid (BzOH), w hereas enantioselectivity remains at the same level.[69] The observed effect is likely to be due to the favourable impact of the acid on the key stages of the catalytic cycle, in particular, on enamine formation and hydrolysis of zwitter-ion **C**, which leads to the release of the catalyst (see Scheme 7).

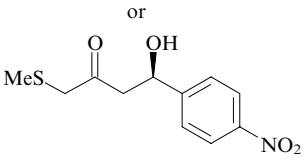
The regiochemistry of the asymmetric aldol condensations catalyzed by $C_2$-symmetric bis(prolinamides) is affected by the structure of reactants and reaction conditions. Hydroxyacetone (**34c**) and its ethers **34g**,**h** react with aldehyde **52a** in the presence of the ($S_a$,*S*,*S*)-**13** (5 mol.%) – BzOH (10 mol.%) catalytic system without a solvent to give 1,2-diol derivatives **54a** – **c** (Scheme 19, *rr* is the regioisomer ratio).[70]

**Scheme 19**




**54a** – **c** [90% – 96%, *rr* = (88 : 12) – (98 : 2), *dr* (*anti* : *syn*) = (64 : 36) – (86 : 14), (20% – 86%) *ee*]

or



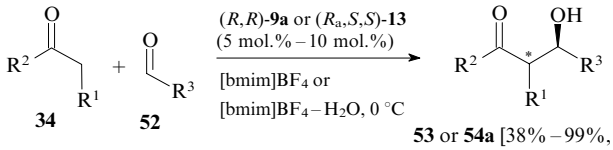

**53g** (83%, *rr* = 84 : 16, 90% *ee*)

R = OH (**34c**, **54a**), OMe (**34g**, **54b**), OBn (**34h**, **54c**), SMe (**34i**); (*a*) 4-$O_2NC_6H_4CHO$ (**52a**), ($S_a$,*S*,*S*)-**13** (5 mol.%), BzOH (10 mol.%), 0 °C

However, similar reaction of methylthioacetone **34i** with aldehyde **52a** under the same conditions proceeds along a different pathway yielding aldol **53g** with 1,4-positions of the hydroxyl and methylsulfanyl groups. Products **54b**,**c** had high enantiomeric purity but in the case of diol **54a**, it did not exceed 20%. An increase in the *ee* of aldol **54a** to 85% was achieved in reaction in a polar solvent (DMSO).[71] The authors regenerated catalyst ($S_a$,*S*,*S*)-**13** from the reaction mixture and reused it in the aldol condensation.

With participation of an author of the current review, it was ascertained [72] that in polar ionic liquids (IL) [in particular, 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmim]$BF_4$)], asymmetric aldol reactions of ketones **34** with aldehydes **52** catalyzed by bis(prolinamides) (*R*,*R*)-**9a** proceed at a higher rate than the corresponding reactions in the presence of (*S*)-proline, the enantioselectivity being retained (Scheme 20). Furthermore, the catalyst recycling is essentially simplified, since it remains in the IL solution after product extraction with diethyl ether and can be used repeatedly.

**Scheme 20**



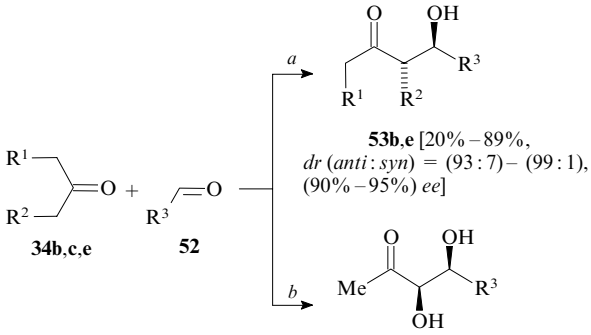

**53** or **54a** [38% – 99%, *dr* (*anti* : *syn*) = (3 : 7) – (9 : 1), (40% – 82%) *ee*]

$R^1 - R^2 = (CH_2)_4$; $R^1$ = H: $R^2$ = Me, Et, cyclo-$C_3H_5$, $(CH_2)_2CH{=}CMe_2$; $R^1$ = OH, $R^2$ = Me; $R^3$ = Ar, 5-nitrothiophen-2-yl, 2-Py, $CpMn(CO)_3$; Cp is cyclopentadienyl

The aldol reactions catalyzed by bis(prolinamides) (*R*,*R*)-**9a** and ($R_a$,*S*,*S*)-**13** in the binary IL – water systems appeared to be quite promising.[73] In this case, the reaction rate increased even to a greater extent (similar effect was observed upon application of aqueous organic solvents) [66] and the consumption of IL diminished. The IL : water ratio was found to affect the enantioselectivity of reaction between cyclohexanone (**34b**) and aldehyde **52a**, the minimal enantioselectivity [(25% – 35%) *ee*] being observed for the water content of 20 vol. % – 25 vol. % and the local maximum [(80% – 82%) *ee*] being at 50 vol.% of water. At the maximum point, the product *ee* is not inferior to those corresponding to the reactions in anhydrous IL. Moreover, in the IL – water systems, the operation period of the catalyst increases (3 cycles in water-free IL *vs.* 5 cycles in aqueous IL).

Bis(prolinamide) (*S*,*S*)-**11a** and bis(valinamide) (*S*,*S*)-**12b** catalyze the asymmetric aldol reactions in water even in the absence of a cosolvent. Under these conditions, cyclohexanone (**34b**) and acetone (**34e**) react with aldehydes **52** to give the *anti*-isomers of aldols **53** with fairly high diastereo- (*dr* < 99 : 1) and enantioselectivity (up to 95% *ee*). The Lewis [$Zn(OTf)_2$] or Brønsted (TFA) acids enhance the catalyst activity, especially, that of compound (*S*,*S*)-**11a** (Scheme 21).[74]

**Scheme 21**

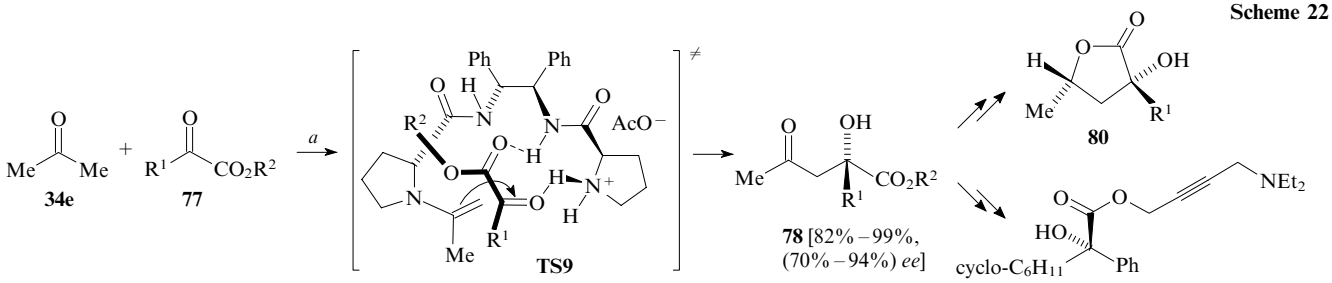



$R^1 - R^2 = (CH_2)_3$ (**34b**, **53b**); $R^1$ = H: $R^2$ = OH (**34c**), H (**34e**, **53e**); $R^3$ = Ar, $Pr^i$, $CHPh_2$, cyclo-$C_6H_{11}$; (*a*) for **34b**,**e**: (*S*,*S*)-**11a** or (*S*,*S*)-**12b** (5 mol.%), TFA (10 mol.%), $H_2O$, 0 – 20 °C; (*b*) for **34c**: (*S*,*S*)-**12c** (5 mol.%), THF – $H_2O$ (1 : 1), 20 °C

In the presence of serine bisamide (*S*,*S*)-**12c** modified with silyloxy groups, hydroxyacetone (**34c**) reacts with aldehydes **52** to yield *syn*-diols **54a**. The solvent of choice for this reaction is aqueous THF in which the diastereo- and enantiomeric purity of products **54a** reach the high values: *dr* = 99 : 1 and *ee* of 99%. Unfortunately, to reach the acceptable yields of products **54a** (35% – 95%), a considerable excess of the the donor ketone is required, which restricts the synthetic value of the method. In an aqueous medium as well as in organic solvents, the asymmetric aldol reactions proceed through the formation of enamine intermediates (see Scheme 7), which were detected by mass spectrometry (ESI MS).

The $C_2$-symmetric amides of α-amino acids catalyze asymmetric cross-aldol reactions between two ketones. Feng and co-workers [75] found that in the presence of bis(prolinamide) **11c**, acetone (**34e**) reacts with α-ketoesters **77** to give α-hydroxy-γ-ketoesters **78** having a quaternary carbon atom as a stereocentre. Under the optimal conditions (AcOH as the cocatalyst, −20 °C), aldols **78** are formed in 82% – 99% yields with up to 94% *ee* (Scheme 22).

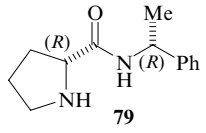
**Scheme 22**




$R^1$ = Ar, 2-Th, 1-Naph, 2-Naph, cyclo-$C_6H_{11}$; $R^2$ = Me, Et, cyclo-$C_5H_9$; (*a*) **11c** (15 mol.%), AcOH (150 mol.%), $Me_2CO$, −20 °C

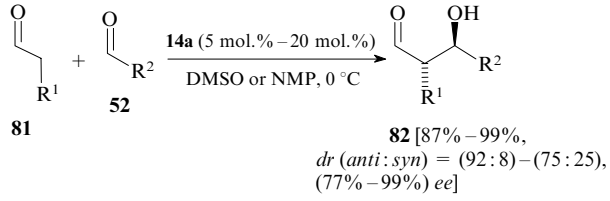
Analogous bisamides **9a**, **11a**,**b** and **12a** appeared less active and(or) less selective catalysts for this reaction. It should be noted that upon catalysis by *N*-(1-phenylethyl)-prolinamide **79** bearing just one of the two $C_2$-symmetric structural units of catalyst **11c**, the yield and *ee* of aldol **78** ($R^1$ = Ph, $R^2$ = Me) decreased to 32% and 11%, respectively, which indicates the concerted action of prolinamide groups.

**Structure 79**




In the proposed transition state **TS9**, one of the pyrrolidine rings of catalyst **11c** forms enamine with the molecule of acetone **34e**, while the second (acid-protonated) prolinamide moiety coordinates to α-ketoester **77** *via* hydrogen bonding. The developed method can be used to prepare multifunctional chiral biologically active compounds containing a quaternary stereocentre, in particular, derivatives of α-hydroxy-γ-butyrolactone (a fragment present in a range of natural compounds)[76–80] and the most active *S*-enantiomer of muscarinic receptor antagonist oxybutynin.[81,82]

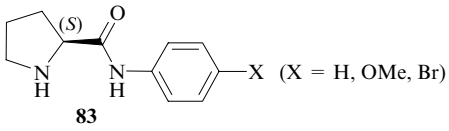
**Scheme 23**




$R^1$ = Me, $Pr^n$, $Pr^i$, $Bu^n$; $R^2$ = Ph, 4-$O_2NC_6H_4$, 2-Naph, Bz, C(O)CH=CHPh; NMP is *N*-methylpyrrolidin-2-one

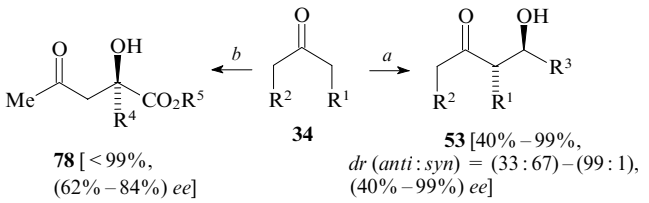
$C_2$-Symmetric bis(prolinamides) **10a** and **14a**,**b** catalyze the asymmetric cross-aldol reactions between two aldehydes (Scheme 23).[83] The best results in cross-aldolizations of aldehydes **52** and **81** are achieved in the presence of *p*-phenylenediamine derivative **14a**. It this case, *anti*-aldols **82** are formed in high yields and with enantioselectivity of up to 99% (see Scheme 23).[83] The reactions proceed also when catalyzed by proline anilides **83** lacking the axial symmetry; however, the diastereoselectivity becomes somewhat lower.

**Structures 83**




In order to facilitate the isolation of enantiomerically enriched products and recycle the valuable chiral catalysts, the authors of the current review synthesized hybrid $C_2$-symmetric catalytic systems **15a**–**e** modified with hydrophilic imidazolium cations and $PF_6^-$ hydrophobic anions (fragments of ionic liquids[84]). Among them, *p*-phenylenediamine derivative **15c**,[85] 1,2-diaminocyclohexane derivative **15d**[86] and 1,2-diamino-1,2-diphenylethane derivative **15e**,[87] appeared the best catalysts for asymmetric cross-aldol reactions. In the presence of these catalysts ketones **34** and aldehydes **52** generated in an aqueous medium corresponding aldols **53** with high *trans*-diastereo- and enantioselectivity (Scheme 24).

**Scheme 24**




$R^1$–$R^2$ = $(CH_2)_2$, $(CH_2)_3$, $CH_2CHMeCH_2$, $CH_2OCH_2$, $CH_2SCH_2$, $CH_2N(CO_2Et)CH_2$; $R^1$ = H: $R^2$ = H, n-Alk, Bn, $(CH_2)_2Ph$, $(CH_2)_2C_6H_3OMe$-3-OH-4; $R^3$ = Ar, 2-Naph, 2-Th, 5-nitrothiophen-2-yl, 2-Fu, 2-Py; $R^4$ = Me, Et, Ar; $R^5$ = Me, Et, Bn; (*a*) $R^3CHO$ (**52**), **15c**, or **15d**, or **15e** (10 mol.%), $H_2O$ (100 equiv.), 20 °C (up to 15 cycles); (*b*) for **34e**: $R^4C(O)CO_2R^5$ (**77**), **15e** (20 mol.%), $H_2O$ (2 equiv.), AcOH (0.5 equiv.), neat, −30 °C (5 cycles)

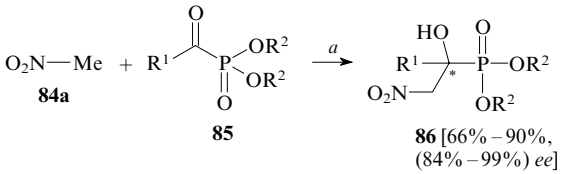
Furthermore, amide **15e** catalyzes the reactions of acetone (**34e**) with α-ketoesters **77** under mild conditions (−30 °C), leading to α-hydroxy-γ-keto esters **78**. The intermolecular aldol reactions involving two ketones previously have not been carried out in the presence of immobilized catalysts. In this case, the best results were attained under neat conditions in the presence of water and acid cocatalyst (AcOH) (see also Scheme 22). Catalysts **15c**–**e** are readily recycled: for this purpose, it is enough to add fresh portions of the starting compounds to the catalyst after extraction of the reaction product with ether and repeat the reaction.

Even after 15 cycles, the $^1$H NMR spectrum of the recovered catalyst is identical to that of freshly prepared sample, which proves the diamine stability.

#### III.2.c. Miscellaneous reactions

Feng, Hu and co-workers[88] found that $C_2$-symmetric (*S*)-pipecolic acid derivatives **8b**, (*R*,*R*)-**9b**, (*S*,*S*)-**11b** and (*R*,*R*)-**11b** containing different spacer groups, unlike proline analogue (*R*,*R*)-**11a**, efficiently catalyze the nitroaldol reaction (Henry reaction) of nitromethane (**84a**) with α-ketophosphonates **85** to afford α-hydroxy-β-nitrophosphonates **86** (Scheme 25). The maximal yields (66% – 90%) and (84 – 99%) *ee* of products **86**, which have *R*-configuration of the stereocentre (X-ray diffraction data), were achieved in the presence of (*R*,*R*)-**11b** – 2,4-dinitrophenol catalytic system in the binary Bu$^t$OMe – PhOMe solvent mixture at −20 °C. The formation of an iminium ion from amino catalyst (*R*,*R*)-**11b** and ketone **85** containing a strong electron-withdrawing substituent in the α-position relative to the keto group seems to be unlikely in this reaction. The quantum chemical calculations suggest that in this case, a different scenario takes place in the transition state. Apparently piperidine moiety of the $C_2$-symmetric molecule (*R*,*R*)-**11b** protonated by the acid additive activates α-ketophosphonate **85** by hydrogen bond, whereas the second piperidine unit deprotonates nitromethane and stabilizes the resulting nitronate-anion.

**Scheme 25**




$R^1$ = Ar, 2-Th, Me, Bn; $R^2$ = Me, Et, Pr$^i$;
(*a*) (*R*,*R*)-**11b** (5 mol.%), 2,4-dinitrophenol (6 mol.%), Bu$^t$OMe – PhOMe (2 : 1), −20°C

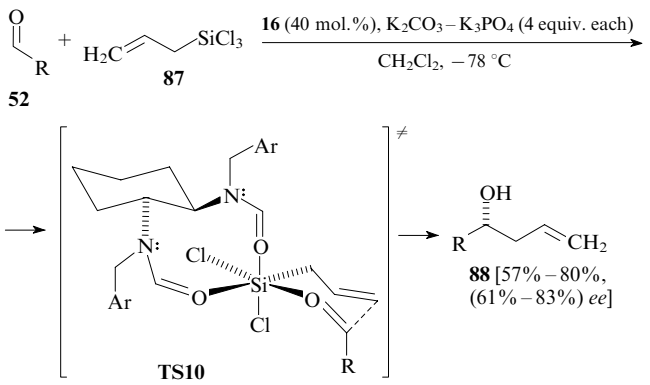
### III.3. Reactions catalyzed by $C_2$-symmetric polyamides and sulfamides (catalysis based on coordination interactions or hydrogen bonding)

Chiral organocatalysts that do not contain amino groups, unlike most of amino catalysts considered in Sections III.1 and III.2, cannot form enamine or iminium ions in organocatalytic reactions. However, they perform other, no less effective activation modes that are based on donor – acceptor or coordination interactions[89,90] and on the formation of stereodifferentiating hydrogen bonds in the transition state.[91,92] Noncovalent interactions of the catalyst with one of the reactants (as a rule, with the acceptor component) are also involved in reactions catalyzed by amides (sulfamides) of amino acids; however, there they play an auxiliary role which supplements the enamine or iminium catalysis (see, for example, Schemes 16, 17, 22).[58,59,61] At the same time, in asymmetric reactions catalyzed by compounds lacking amino groups (amides, sulfamides, urea and thiourea derivatives, amidines, guanidines, *etc.*), these processes most often predominate.[89,93]

#### III.3.a. Allylation reactions

The reaction of catalytic asymmetric allylation of aldehydes is a facile method for synthesis of chiral alcohols.[94] Recently, Tanimura and co-workers[95,96] used for the first time (*R*,*R*)-1,2-diaminocyclohexane-derived Lewis basic $C_2$-symmetric bisformamide **16** as a catalyst for allylation of aldehydes **52** with allylchlorosilane **87** (Scheme 26).

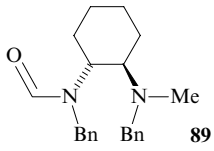
**Scheme 26**




R = Ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-Naph;
Ar = 2-Pr$^i$C$_6$H$_4$

The best results were obtained in the presence of mild inorganic bases ($K_2CO_3$ and $K_3PO_4$) which is likely to decrease the solution acidity and facilitate the bisformamide **16** return to the catalytic cycle. Under optimal conditions, allylation products **88** with *R*-configuration of the stereocentre are formed in 57% – 80% yields with the enantiomeric purity of up to 83%. According to the authors' opinion, bisformamide **16** is coordinated in the bidentate fashion to the silicon atom of the allylating agent in transition state **TS10**. This assumption is in agreement with a pronounced decrease in the reaction enantioselectivity in the case where catalyst **16** is replaced by by analogue **89** containing just one formamide group.

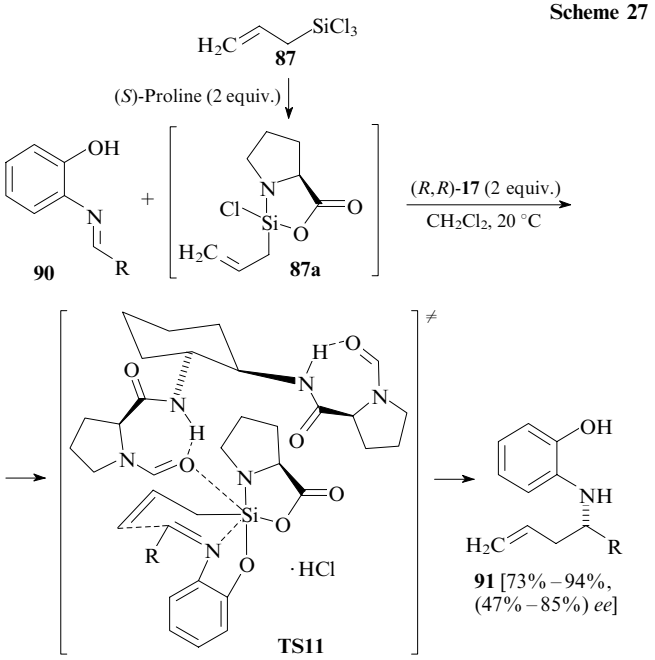
**Structure 89**




Fairly attractive 'building blocks' for the synthesis of valuable organic compounds, in particular, natural products are chiral homoallylamines.[97,98] However, attempts to prepare them *via* relatively simple route of enantioselective allylation of aldimines with allyltrichlorosilane **87** did not meet with success for a long time. Jagtap and Tsogoeva[99] solved this challenge using aldimines **90**, obtained from aldehydes and 2-aminophenol, as substrates and bis(*N*-formyl)prolinamide **17** or **18** – (*S*)-proline systems as organocatalysts. Among the prolinamides explored, the highest activity in allylation was manifested by bisformamide (*R*,*R*)-**17** in the presence of which homoallylamines **91** were synthesized in high yields with up to 85% *ee* (Scheme 27).

The role of (*S*)-proline in this reaction appeared to consist in *in situ* conversion of allyltrichlorosilane **87** to the more active allylating reagent **87a** the structure of which was confirmed by ESI MS and EI MS (EI is electron impact ionization) as well as by $^1$H NMR spectroscopy. The authors assume that in transition state **TS11**, the silicon atom of intermediate **87a** is coordinated to the oxygen atom of bisformamide (*R*,*R*)-**17** and aldimine **90**, which increases

**Scheme 27**



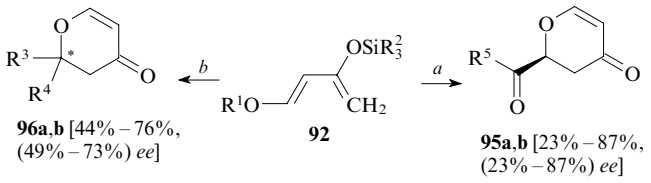

R = Ar, 2-Naph, 2-Fu, CH=CHPh

the nucleophilicity of the allylating agent. Indeed, aldimines based on hydroxyl-free aniline derivatives do not react with silane **87** under proposed conditions. A drawback of the developed method is the necessity to use a substantial (2 equiv.) excess of valuable chiral catalyst (*R*,*R*)-**17**.

### III.3.b. Miscellaneous reactions

Tonoi and Mikami[100] and Jørgensen and coworkers[101] established independently that $C_2$-symmetric sulfamides **19a**,**b** containing (*R*,*R*)-1,2-diphenylethylenediamine structural unit and perfluoroalkyl groups are able to catalyze the hetero-Diels–Alder reaction. Under the proposed conditions (from −20 to −78 °C), Danishefsky's dienes **92** react with glyoxylic acid esters (**93a**), ketoaldehydes (**93b**), pyruvic acid esters (**94a**) and benzaldehyde derivatives (**94b**) to give the corresponding cycloadducts **95a**,**b** and **96a**,**b** in fairly good yields and with moderate enantioselectivity (*ee* ⩽ 87%) (Scheme 28). The authors assume that the reactants are activated in this case owing to hydrogen bonding between the sulfamide groups of catalyst **19** and the oxygen atoms of the carbonyl compound. This assumption is confirmed by a strong downfield shift of the signals of sulfamide protons in the $^1$H NMR spectrum of catalyst **19b** ($\Delta\delta$ = 3.00 ppm) after its addition to a solution of model 2,6-dimethylpyran-4-one in $CDCl_3$ (the corresponding proton shift for BnNHTf analogue bearing one sulfamide group is 0.83 ppm).[100]

**Scheme 28**




$R^1$ = Alk; $R^2$ = Me, Pr$^i$, Bu$^t$; $R^3$ = Me, $R^4$ = $CO_2$Alk (**94a**, **96a**); $R^3$ = H, $R^4$ = Ar (**94b**, **95b**); $R^5$ = OAlk (**93a**, **95a**), Ar (**93b**, **95b**); (*a*) $R^5C(O)CHO$ (**93a**,**b**), **19a** (10 mol.%), PhMe, −20 to −78 °C; (*b*) $R^3C(O)R^4$ (**94a**,**b**), **19b** (10 mol.%), PhMe or $CHCl_3$, −24 to −40 °C

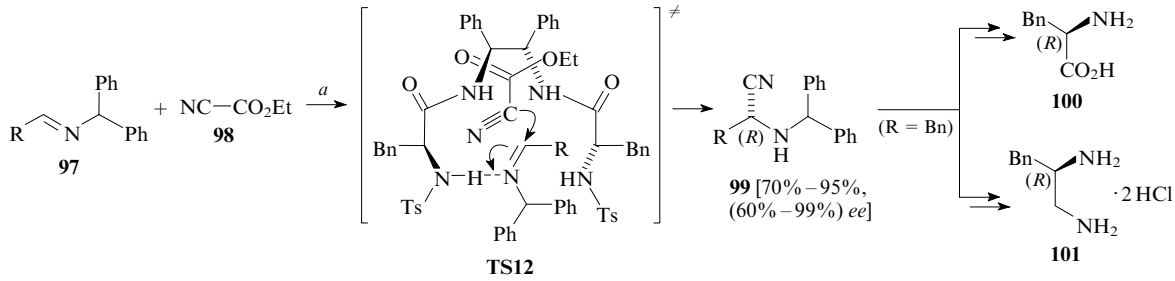
The sulfamide type catalysts are also efficient in the Strecker reaction (hydrocyanation of imines), which is one of the simplest and atom-economical reactions widely used in synthesis of α-amino nitriles serving as precursors for natural and unnatural α-amino acids.[102,103] Saravanan *et al.*[104] used $C_2$-symmetric 1,2-diamines to synthesize multifunctional organocatalysts **20** and **21**, which contain sulfamide and amide groups in highly organized spatial structure comprising up to four stereocentres with different absolute configurations. The authors studied their catalytic performance towards asymmetric cyanation of imines **97** with ethyl cyanoacetate **98** (cyanide anion source) (Scheme 29).

It was found that the activity and selectivity of catalysts **20** and **21** in the Strecker reaction are affected by the structures of both 1,2-diamine spacer and amino acid moieties. The highest values of yield (up to 95%) and *ee* (up to 99%) of amino nitriles **99** were achieved in the presence of 1,2-diphenylethylenediamine-derived tosylated bisamides **21b** having the same (*S* or *R*) configuration of all four stereocentres.

An important role in the reaction is played by isopropyl alcohol additive (2 equiv.), which serves as a proton source necessary for the hydrocyantaion process to occur. A plausible reaction scheme includes the activation of the C=N bond in imine **97** *via* formation of the hydrogen bond with the sulfamide hydrogen atom of catalyst **21b** followed by enantioselective attack of this bond by ethyl cyanoformate **98** in transition state **TS12** (see Scheme 29).

After completion of the reaction, organocatalyst **21b** was recovered *via* precipitation from the reaction mixture with n-hexane and recycled three times without a drop in its activity or reaction enantioselectivity. The synthetic utility

**Scheme 29**




R = Ar, Bu$^i$, Bu$^t$, 3-Py, 2-Naph; (*a*) (*S*,*S*,*S*′,*S*′)-**21b** (10 mol.%), Pr$^i$OH (2 equiv.), PhMe, −10 °C

of this method was demonstrated by the conversion of amino nitrile **99** (R = Bn) to (*R*)-phenylalanine (**100**) and (*R*)-diamine **101**, which serves as a precursor to aminopeptidase N inhibitor.[105]

## III.4. Reactions catalyzed by $C_2$-symmetric bisureas and bisthioureas (catalysis based on hydrogen bonding)

In the past decade, Brønsted acids containing urea and thiourea groups have attracted growing interest of researchers owing to their ability to form strong hydrogen bonds with the nitrogen, oxygen and sulfur atoms present in molecules of many organic compounds.[106, 107] Owing to this ability, the introduction of (thio)urea moieties into carefully chosen parts of functionally substituted COC molecules often endows them with properties of bifunctional catalysts, which activate and locate in the optimal manner two or more reacting compounds in the transition state, providing high enantioselectivity of the catalytic reaction.[91, 108 – 113] However, chiral urea or thiourea derivatives containing no other active sites in the molecule are much more rarely used in asymmetric catalysis.[114] Herein recent applications of $C_2$-symmetric bisureas and bisthioureas as organocatalysts for enantioselective reactions of organic compounds are reviewed.

### III.4.a. Michael reactions

Among organocatalytic reactions, the Michael addition of different nucleophiles to α-nitroalkenes is one of the most important, since it allows a sinlge-step synthesis of enantiomerically enriched functionalized nitroalkanes, valuable intermediates for organic synthesis.[115 – 117] Singh and co-workers[118] developed the catalytic asymmetric addition of stabilized phosphorane **102** to nitroalkenes **73**, resulting in the formation of phosphorylated adducts **103**, which were converted without isolation to α-(nitroalkyl)acrylates **104** by the Wittig-type reaction *via* treatment with formaldehyde (Scheme 30).

The Michael reaction, which is the key stage in this synthetic sequence, proceeds in the presence of different $C_2$-symmetric bisthioureas (*S*,*S*)-**22b**, **23b** or ($S_a$)-**24**. Higher (although still moderate) yields of products **104** and reaction enantioselectivity were achieved with 1,2-diaminocyclohexane-derived catalyst (*S*,*S*)-**22b**.

Xiao and co-workers[119] used $C_2$-symmetric derivatives of urea (*R*,*R*)-**22a** and thiourea **23a**, **23b** and ($S_a$)-**24** as organocatalysts for reactions of sulfur ylides **105** with β,γ-unsaturated α-ketoesters **106**, to afford functionalized cyclopropanes **107** (Scheme 31).

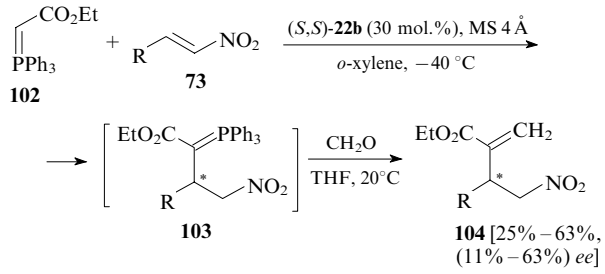
This transformation belongs to widely explored organocatalytic domino reactions[120, 121] and its key stages are stereoselective addition of ylides **105** across the electron-deficient C=C bond of compounds **106** followed by diastereoselective cyclization of the Michael adducts accompanied by elimination of dimethyl sulfide. In this case, higher level of strereoinduction was provided by bisureas (*R*,*R*)-**22a** and **23a** among which (*R*,*R*)-diphenylethylenediamine derivative **23a** was most active. In its presence (10 mol.%), products **107** were generated in 35% – 86% yields with diastereomeric (*anti* : *syn* ratio up to 16 : 1) and enantiomeric purity (*ee* up to 80%) quite good for this type of reactions. The absolute (1*S*,2*R*,3*R*)-configuration of product **107a** ($R^1$ = 4-$BrC_6H_4$, $R^2$ = Ph, $R^3$ = Me) was established by X-ray diffraction. The authors assume that compounds **105** and **106** form strong hydrogen bonds with catalyst **23a** in transition state **TS13**; an associate of **23a** with ylide **105** is detected by a considerable shift of proton signals of urea and methine groups in $^1$H NMR spectra upon mixing of the catalyst and reactant solutions in $CDCl_3$.

### III.4.b. Miscellaneous reactions

Barbas III and co-workers[122] developed an elegant synthetic route to carbazolespirooxindole derivatives serving as analogues of biologically active compounds.[123 – 125] The method is based on the asymmetric Diels – Alder reaction of Boc-protected derivatives of 3-methylideneindole **108** (dienophiles) with substituted 3-vinylindoles **109** (dienes) catalyzed by bisthiourea (*R*,*R*)-**22b** to give products **110** (Scheme 32; the positions of substituents $R^2$ and $R^3$ in the starting indoles are indicated).

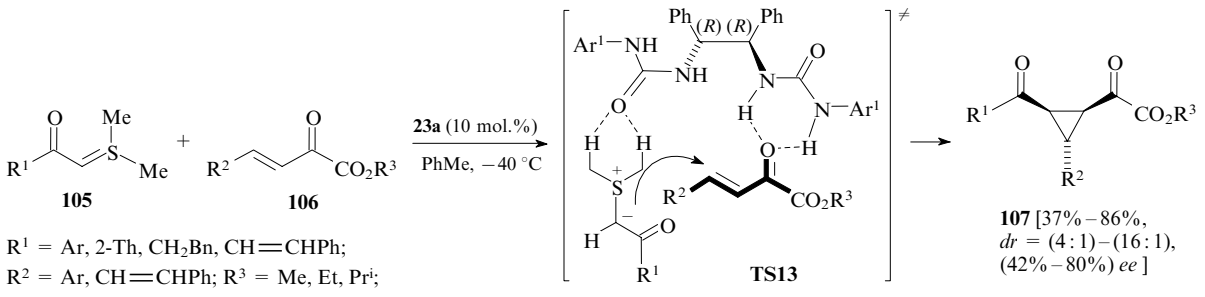
This reaction has a wide scope of applications and, unlike most of the known organocatalytic Diels – Alder reactions lasting from several hours to several days, proceeds to completion at room temperature in only 5 – 10 minutes with exceptionally high diastereo- (*dr* > 99:1) and enantioselectivity (*ee* up to 99%). The efficiency of this process is retained upon increase in the reactant amounts to several grams. The catalyst can be readily separated from the products (by centrifugation or filtration) and can be

**Scheme 30**



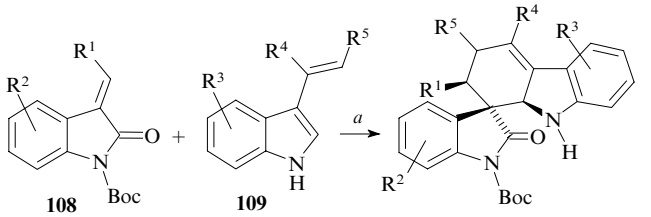

R = Ar, 2-Th, $CH_2$Bn, cyclo-$C_6H_{11}$; MS is molecular sieves

**Scheme 31**




$R^1$ = Ar, 2-Th, $CH_2$Bn, CH=CHPh;
$R^2$ = Ar, CH=CHPh; $R^3$ = Me, Et, Pr$^i$;
$Ar^1$ = 3,5-$(CF_3)_2C_6H_3$

**Scheme 32**




$R^1$ = $CO_2Alk$ (Alk = Me, Et, Bu$^t$, Bn), Ph, Ac, Bz, CN, Ts;
$R^2$ = H, 5-Br, 5-F, 6-Cl, 5-Me, 5-OMe; $R^3$ = H, 5-Br, 5-Cl;
$R^4$, $R^5$ = H, Me; (*a*) (*R*,*R*)-**22b** (15 mol.%), hexane, 20 °C, < 10 min; Boc is *tert*-butyloxycarbonyl

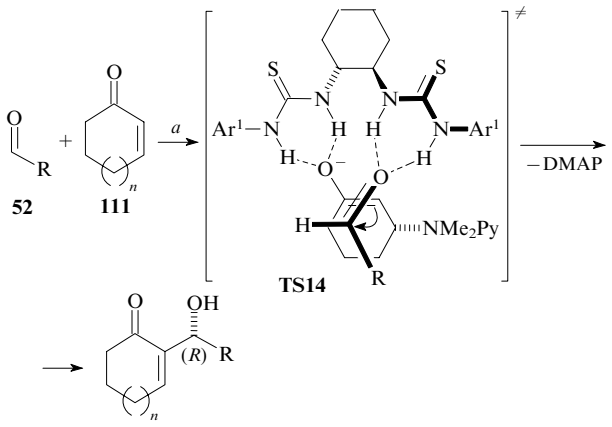
recycled 5 times although with a slight decrease in the reaction rate and selectivity. Upon replacement of $C_2$-symmetric catalyst (*R*,*R*)-**22b** by other thiourea derivatives (with two different substituents), the level of asymmetric induction markedly decreases, which attests to synchronous activation of dienophile **108** and diene **109** by two thiourea groups of catalyst (*R*,*R*)-**22b** by means of stereodifferentiating hydrogen bonds. Furthermore, the reactants are likely to coordinate to each other in the transition state *via* weak π–π-interactions and hydrogen bonding between the Boc group of dienophile **108** and the NH group of diene **109**. The removal of the Boc-protection, which is of key impotance for catalysis, from compounds **108** or introduction of an N-substituent into 3-vinylindoles **109** results in the formation of almost racemic products **110**.

The catalytic asymmetric addition of aldehydes to α,β-unsaturated carbonyl compounds — vinyl ketones, acrylic acid derivatives, *etc*. (Morita – Baylis – Hillman reaction) — is widely used for enantioselective synthesis of allyl alcohols.[126, 127] Usually this reaction is catalyzed by Lewis bases, in particular, alkaloid derivatives.[128 – 130] However, there are several examples of a different approach when α,β-unsaturated carbonyl compound is activated by achiral Lewis base, for example, 1,4-diazabicyclo[2.2.2]octane (DABCO) ot 4-dimethylaminopyridine (DMAP), and the asymmetric inductor is the chiral Brønsted acid able to form stereodiscriminating H-bonds with the reactants.[131, 132]

Nagasawa and co-workers[133, 134] applied $C_2$-symmetric chiral bisthiourea (*R*,*R*)-**22b** as an acid cocatalyst for this reaction. They found that in the presence of (*R*,*R*)-**22b** – DMAP catalytic system, aromatic, aliphatic and alicyclic aldehydes **52** react with cyclic α,β-unsaturated ketones **111** to give β-hydroxyketones **112** in the yields from moderate to high (33% – 99%) and fairly good enantioselectivity [(33% – 90%) *ee*] (Scheme 33). Relying on the $^1$H NMR spectral data indicating the formation of hydrogen bonds between (*R*,*R*)-**22b** and *R*-enantiomers of products **112**, the authors assume that in transition state **TS14**, two thiourea groups of the catalyst are hydrogen-bonded to the carbonyl groups of aldehyde **52** and cyclic enone **111**. As a result, the effective stereocontrol of the reaction is accomplished and the elimination of the auxiliary tertiary amine (DMAP) is facilitated.

The Morita – Baylis – Hillman reaction and its aza-modification[135 – 137] are often used to obtain β-aminocarbonyl compounds bearing α-alkylidene groups — a valuable class of organic compounds used in medicine.[127, 138, 139] However,

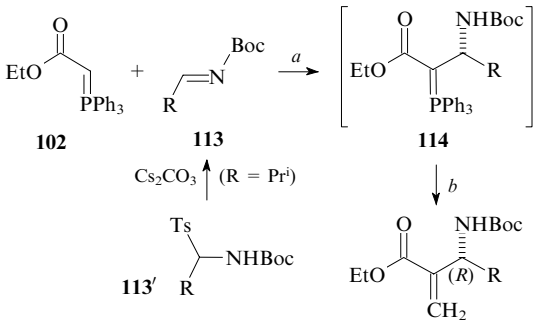
**Scheme 33**




R = Ar, Pr$^i$, $CHEt_2$, n-$C_6H_{13}$, cyclo-$C_5H_9$, cyclo-$C_6H_{11}$, $(CH_2)_2Ph$; *n* = 0, 1; $Ar^1$ = 3,5-$(CF_3)_2C_6H_3$; $NMe_2Py$ = DMAP; (*a*) (*R*,*R*)-**22b** – DMAP (40 mol.% each), MS 4 Å

Chen and co-workers[140] suggested another quite efficient approach to enantioselective synthesis of this type of compounds based on organocatalytic reaction of stabilized phosphorus ylides with actiavated imines, which represents a modification of the classical Mannich reaction. It was found that in the presence of $C_2$-symmetric bisthioureas (*R*,*R*)-**22b** or **23b**, phosphoranes **102** add to N-Boc-protected imines **113** (in particular generated *in situ* from α-aminotosylates **113′** under the action of a base) giving relatively stable functionalized P-ylides **114**. The latter can be readily converted to α-(aminoalkyl)acrylates **115** *via* reaction with formalin (Scheme 34).

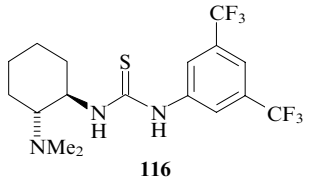
**Scheme 34**




R = Pr$^n$, Pr$^i$, cyclo-$C_6H_{11}$, Ar, 2-Th;
(*a*) (*R*,*R*)-**22b** or **23b** (10 mol.%), MS 4 Å, *m*-xylene, –20 °C;
(*b*) $CH_2O$, THF, 20 °C

The developed tandem sequence of the Mannich and Wittig reactions provides high-yield synthesis of compounds **115** with various aromatic, heteroaromatic and aliphatic substituents at the α-position relative to the amino group with *ee* values in most cases exceeding 90%. In the presence of bifunctional catalyst **116** with one thiourea group, the enantioselectivity of the reaction essentially decreases (down to 15%), which is indicative of the concerted catalytic action of the two thiourea groups in compounds (*R*,*R*)-**22b** and **23b**.

**Structure 116**

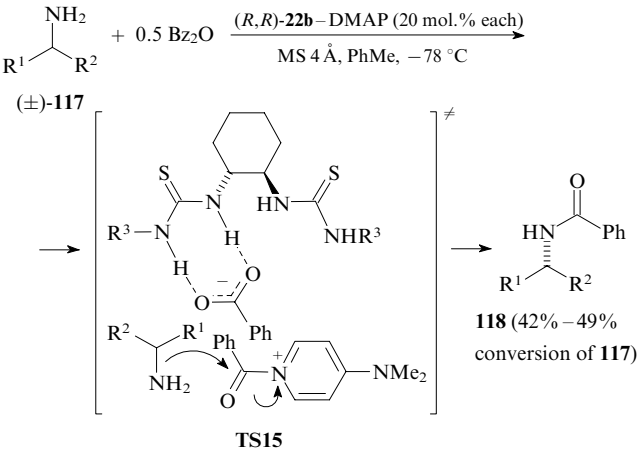


**116**

One more advantage of catalyst (*R*,*R*)-**22b** is the possibility of regeneration (by flash-chromatography) and recycling for three times in the same reaction without a reduction in the yield and enantiomeric purity of the product.

$C_2$-Symmetric bisthioureas proved to be efficient cocatalysts of practically important processes of kinetic resolution of racemic amines to the enantiomers *via* asymmetric acylation. The transfering agents for acylium cations often used in these processes are chiral derivatives of DMAP,[141 – 143] the synthesis of which is rather laborious. Seidel and co-workers [144] suggested an alternative approach to desymmetrization of amines that includes the application of available achiral acylium salts of DMAP as acylating agents in combination with thiourea derivatives capable of coordinating the anion of acylpyridinium salt (benzoate anion), thus forming the chiral complex providing for process enantioselectivity (Scheme 35, transition state **TS15**). Among the explored thiourea derivatives **22** – **25**, compound **22b** containing a (*R*,*R*)-diaminocyclohexane structural unit was found to be the most efficient stereoinductor. In the presence of 20 mol.% of this compound, benzoylation of racemic α-substituted benzylamines **117** proceeded with a conversion of up to 49%, giving *S*-enantiomers of the corresponding benzamides **118** (*s*-factor = 7 – 24).

**Scheme 35**



$R^1$ = Ar, 1-Naph, 2-Naph; $R^2$ = Me, Et, $Bu^n$, Bn; $R^3$ = 3,5-$(F_3C)_2C_6H_3$

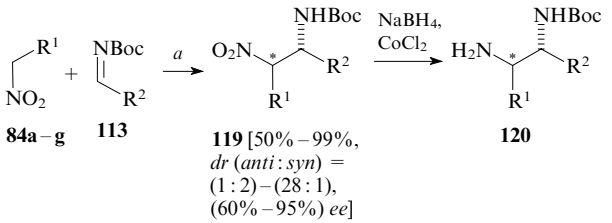
## III.5. Reactions catalyzed by $C_2$-symmetric bisamidines and bisguanidines (acid-base catalysis and catalysis *via* hydrogen bonding)

The chiral compounds containing amidine and guanidine structural moieties belong to the promising class of Brønsted bases, which have been widely used in recent years as organocatalysts for enantioselective reactions of organic compounds (see structures **26** – **32**).[145 – 152] These bifunctional catalysts, like the above-mentioned $C_2$-symmetric bis(thio)ureas, contain hydrogen atoms capable of hydrogen bonding with heteroatoms of reactants. Moreover, unlike compounds with a thiourea group, they can efficiently activate some types of nucleophilic precursors *via* deprotonation. Owing to the high value of p$K_a$ and pronounced ability to form hydrogen bonds, the guanidine group plays an important role in the molecular recognition processes and enzymatic reactions in biological systems.[153 – 156]

### III.5.a. Mannich reactions (aza-Henry reactions)

$C_2$-Symmetric 2-aminoquinoline derivatives **26**, which can formally be considered as amidine derivatives, were found to be efficient catalysts for asymmetric additions of various carbon acids to aldimines, including the Mannich reaction and its modification also known as the aza-Henry reaction. These reactions allow a convenient synthesis of chiral multifunctional amines of variable structure, in particular, precursors of important biologically active compounds.[157] Johnston and co-workers found that asymmetric addition of nitroalkanes **84a** – **f** (Ref. 158) and nitroacetic esters **84g** (Ref. 159) to N-Boc-imines **113** efficiently proceeds in the presence of the bisamidine **26a** – TfOH catalytic system. Commonly these reactions afford *anti*-isomers of β-nitroamines **119** as the major products with the diastereoselectivity from relatively low (in the case of nitroacetates **84g**) to high and with good enantioselectivity (Scheme 36).

**Scheme 36**



**84a** – **g** **113** **119** [50% – 99%, *dr* (*anti* : *syn*) = (1 : 2) – (28 : 1), (60% – 95%) *ee*] **120**

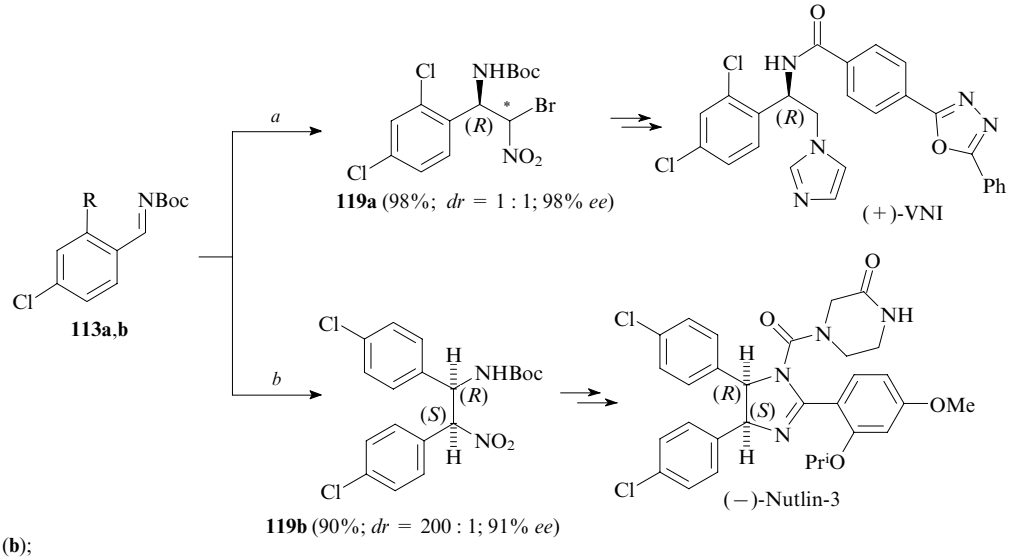
**84**: $R^1$ = H (**a**), Me (**b**), Et (**c**), $Pr^n$ (**d**), $Pr^i$ (**e**), $CH_2C_6H_{11}$-cyclo (**f**), $CO_2$Alk (**g**); $R^2$ = Ar, Naph, Fu, Th; (*a*) **26a**, or **26b**, or **26c** – TfOH (by 5 mol.% – 15 mol.%), PhMe or neat, – 20 °C

Comparable or better catalytic performance in the aza-Henry reactions is shown by bisamidines **26b**,**c** containing the methoxy group or pyrrolidine ring in position 4 of the quinoline moiety.[160] The yield of products **119** as well as stereo- and enantioselectivity of the reactions are affected by amidine **26** : TfOH ratio; in the absence of the acid additive, the selectivity was lower. Adducts **119** can be readily reduced with $NaBH_4$ – $CoCl_2$ to give valuable chiral 1,2-diamines **120**, in particular, biologically active α,β-diamino acid derivatives.[161 – 165]

This method is also applicable to synthesis of more complex biologically active compounds. Thus, the reaction of imine **113a** with bromonitromethane (**84h**) in the presence of catalyst **26c** (1 mol.%) afforded, with high enantioselectivity, β-nitroamine **119a**, which is a key precursor to (+)-VNI, an experimental drug against Chagas' disease (Scheme 37).[166]

Bisamidine **26d** containing the methoxy group in position 8 of the quinoline moiety appeared to be even more active catalyst of the aza-Henry reaction. Only 0.5 mol.% of this catalyst provided for stereoselective addition of 4-chlorophenylnitromethane **84i** to carbamate **113b** to

**Scheme 37**



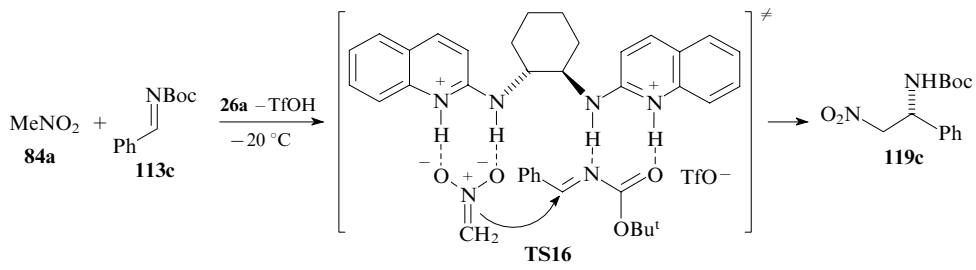
R = Cl (**a**), H (**b**);
(*a*) for **113a**: $BrCH_2NO_2$ (**84h**), **26c** (1 mol.%), PhMe, −20 °C; (*b*) for **113b**: 4-$ClC_6H_4CH_2NO_2$ (**84i**), **26d** (0.5 mol.%), PhMe, −20 °C

afford adduct **119b**, which is a close precursor of the most active laevorotatory enantiomer of nutlin-3 — a promising anticancer drug developed by Hoffmann-La Roche (Switzerland).[167] These enantioselective reactions are readily scalable and can be used to obtain intermediates **119a**,**b** in amounts necessary for the synthesis and biological tests of the target medications (17 – 20 g in one experimental step).

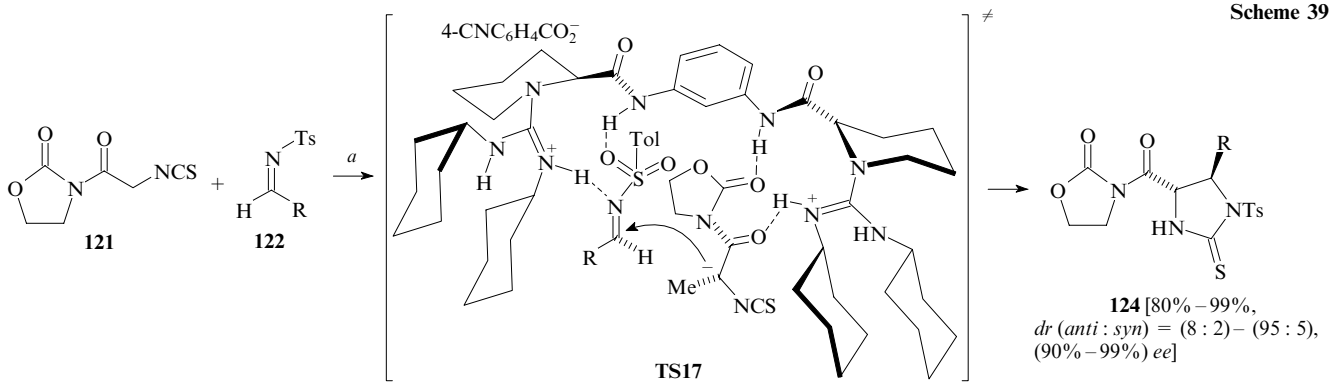
The density functional theory (DFT) investigation showed that the rate-limiting step of asymmetric aza-Henry reaction between nitromethane **84a** and *N*-Boc-phenylaldimine **113c** catalyzed by **26a** – TfOH is the deprotonation of compound **84a** under the action of the catalyst.[168] However, this is not the only role of the catalyst in the reaction. It also activates the electrophile by forming stereo-differentiating hydrogen bonds with **113c** in transition state **TS16**; and these bonds contribute to high rate and selectivity of the carbon – carbon bond formation (Scheme 38).

Interesting results were obtained upon application of $C_2$-symmetric guanidine derivatives as catalysts for the asymmetric Mannich reaction. Feng and co-workers[169] synthesized guanidine derivatives of bis-(*S*)-pipecolinamides bearing various spacer groups and examined them in asymmetric reactions of 3-(isothiocyanateacetyl)oxazolidin-2-one (**121**) with *N*-tosylimines **122**. Under comparable conditions, bisguanidine **32a** with the *m*-phenylene spacer appeared to be more active and selective than its analogues **32b**,**c** containing (*S*,*S*)-cyclohexane or (*S*,*S*)-1,2-diphenylethane structural units, respectively. Interestingly, the reac-

**Scheme 38**



**Scheme 39**



R = Ar, 1-Naph, 2-Naph, 3-Fu, 2-Th, CH=CHPh, n-$C_5H_{11}$, cyclo-$C_6H_{11}$; (*a*) **32a** (5 mol.% – 10 mol.%), **123** (7.5 mol.%), THF – $CHCl_3$, −20 °C; Tol is *p*-tolyl

tion selectivity increased upon addition of 4-cyanobenzoic acid (**123**). In the presence of **32a** – **123** catalytic system, the cascade process (Mannich addition – heterocyclization) takes place, leading to (4*S*,5*R*)-imidazolidine-2-thiones **124** in high yields and with excellent diastereo- and enantioselectivity (Scheme 39).

The reaction is experimentally simple and scalable. Both base and acid components of the catalytic system play important roles: with the tetrafluoroborate salt **32a** · 2 $HBF_4$ instead of parent **32a**, the process does not take place. Relying on the experimental results, the authors hypothesize that in transition state **TS17**, acid **123** protonates one of the guanidine moieties of catalyst **32a**, and the resulting guanidinium salt activates the molecule of imine **122** (already associated by hydrogen bond with the amide group of the catalyst) *via* hydrogen bonding to the iminium nitrogen atom. Simultaneously, another amidoguanidine group deprotonates the active methylene unit of isothiocyanate **121** and, in turn, stabilizes the resulting anion and arranges it in the position favourable for nucleophile attack by means of two hydrogen bonds, which accounts for the observed *si*-stereochemistry of the process.

### III.5.b. Miscellaneous reactions

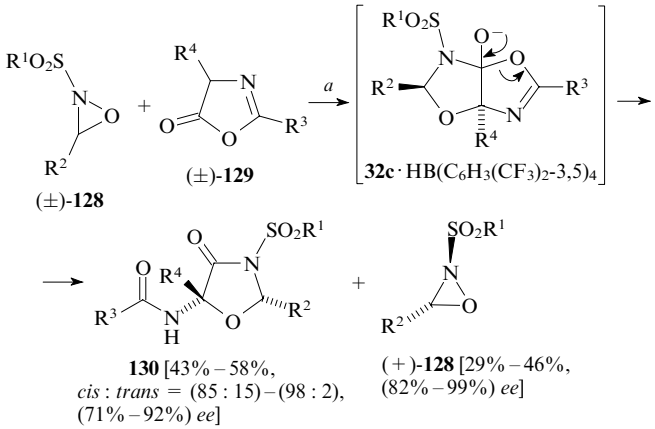
Nájera and co-workers [170, 171] successfully used the bis(2-aminobenzimidazole) **31** – TFA catalytic system in asymmetric reactions of 1,3-dicarbonyl compounds **125** with N-substituted maleimides **126** (Scheme 40). The Michael adducts **127** were obtained in high yields with high enantiomeric purity (*ee* up to 99%), while the heterogeneous catalyst can be regenerated from the reaction mixture by washing with isopropyl alcohol and reused with just a slight decrease in the process enantioselectivity (from 96% to 93%).

The authors assume that two guanidine moieties in $C_2$-symmetric catalyst **31** act concertedly. One of them deprotonates CH-acid **125** and determines the approach of the resulting enolate to maleimide **126**. The other moiety protonated by the acid (TFA) activates acceptor **126** *via* hydrogen bonding in transition state **TS18**. When analogues of compound **31** with only one benzimidazole group were used as catalysts, a considerable decrease in the rate and enantioselectivity of the process was observed [down to (11% – 41%) *ee*].

Recently Liu, Feng and co-wokers [172] applied $C_2$-symmetric bisguanidines **32** as catalysts for asymmetric synthesis of intermediates for biologically active compounds.[173] Racemic oxaziridines **128** and oxazolinones (azalactones) **129** served as starting compounds and the formation of oxazolin-4-ones **130** was accompanied by kinetic resolution of oxaziridines **128** (Scheme 41).

Kinetic resolution of racemic mixtures to enantiomers is widely used for preparation of enantiomerically pure compounds.[142, 174] However, the reaction between **128** and **129** is a special case, as unlike most organocatalytic reactions, both of the reactants and the catalyst are chiral compounds.

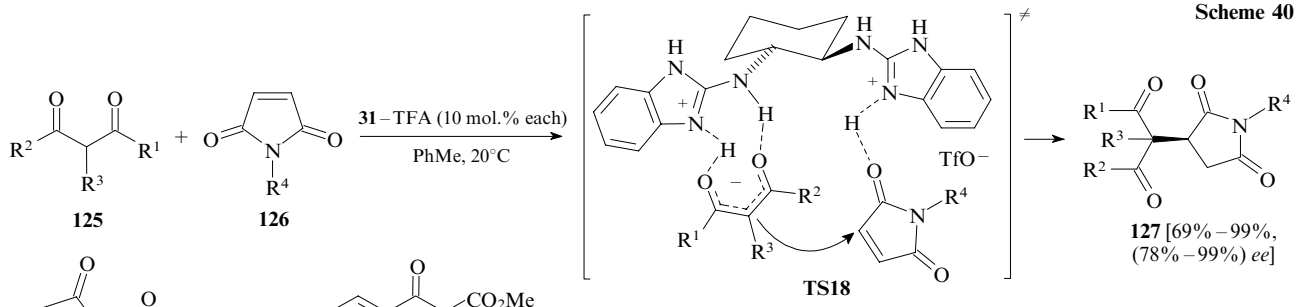
**Scheme 41**

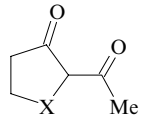
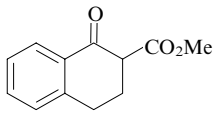



$R^1$, $R^3$ = Ar; $R^2$ = Et, Bn, Ar, 3-Fu, 3-Th, 1-Naph; $R^4$ = Bn, $CH_2C_6H_4OH$-4, $CH_2$Ind-3; (*a*) **32c** · $HB(C_6H_3(CF_3)_2$-3,5$)_4$ (2.5 mol.%), THF – $Bu^tOMe$ (1 : 2 v/v), MS 4 Å, −78 °C; Ind is indolyl

Furthermore, one more stereocentre in product **130** is formed during the reaction, which appreciably complicates the prediction of its stereochemical outcome. Nevertheless, it was found that in the presence of a 'half-salt' of bisguanidine **32c** containing (*S*,*S*)-1,2-diphenylethane spacer, with arylboronic acid $HBAr_4$ [Ar = 3,5-$(CF_3)_2C_6H_3$] the reactions afforded substituted oxazolin-4-ones **130** with high diastereo- and enantioselectivities (*cis* : *trans* ratio up to 98 : 2, *ee* up to 92%). The (−)-enantiomer of oxaziridine **128** reacted predominantly, while the unreacted residue consisted of the (+)-enantiomer of the starting compound (*ee* ⩽ 99%). The complexity of the processes of triple stereodiscrimination in the **32c** · $HBAr_4$ – **128** – **129** system is emphasized by the fact that similar reactions catalyzed by salts of **32c** with HCl or $HBF_4$ yield racemic products. Free base **32c** and salt **32c** · 2 $HBAr_4$ containing two protonated guanidine moieties do not catalyze azalactone oxyamination. In this respect, the authors assume that salt **32c** · $HBAr_4$ acts as a bifunctional catalyst in which the

**Scheme 40**

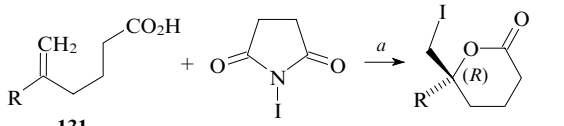



**125** =  (X = $CH_2$, O),  ; $R^1$ = $R^2$ = Me, OMe; $R^1$ = Ph: $R^2$ = Me, OEt; $R^3$ = H, Me; $R^4$ = H, Me, Bn, Ph, 4-$BrC_6H_4$, 4-$AcC_6H_4$

basic guanidine group is likely to activate azalactone **129** and the guanidinium salt moiety coordinates and activates (*S*,*S*)-oxaziridine **128**.

Catalytic halocarboxylation is one of promising methods for the synthesis of valuable derivatives of halogenated carboxylic acids,[175] in particular, lactones. However, most known versions of asymmetric iodolactonization rections are characterized by the low diastereo- and enantioselectivities[176,177] or require iodinating agents that are difficult to prepare.[178] Recently, Dobish and Johnston[179] described the enantioselective reaction of δ-unsaturated carboxylic acids **131** with *N*-iodosuccinimide (NIS) catalyzed by salts of $C_2$-symmetric chiral bisamidines **26c** and **28a** with fluorinated Brønsted acids, resulting in lactones **132** (Scheme 42).

**Scheme 42**

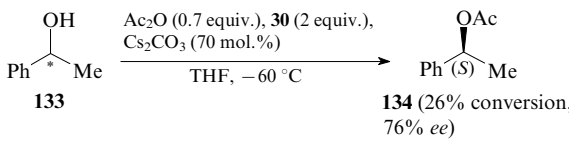



R = Ar, 1-Naph, $Pr^i$, $Bu^n$;
(*a*) **28a** · $HNTf_2$ (5 mol.%), PhMe, −20 °C

The highest yields (up to 99%) and *ee* (up to 98%) of the products were achieved in the presence of bisamidine **28a** – bis(trifluoromethane)sulfonimide ($HNTf_2$) catalytic system. The replacement of $HNTf_2$ by perfluorosulfonic acids TfOH or NfOH (Nf is n-$C_4F_9SO_2$) resulted in *ee* of products **132** decreasing to 49% – 53%. Such a strong effect of the achiral counter-ion on the stereochemical outcome of the reaction implies that the counter-ion not only stabilizes the ionic catalyst, but also directly interacts with the substrate in a transition state. The acid part of the catalyst is likely to activate NIS, while the basic part activates carboxilic acid **131**. The bifunctional nature of the catalyst plays an important role: catalyst **28a** · $2NTf_2$, in which both amidine moieties are salt-like, affords racemic lactone **132**.

$C_2$-Symmetric amidines can be used for catalysis of alcohol desymmetrization — the reaction widely used in organic synthesis.[180] Thus, Yazicioglu and Tanyeli[181] applied compounds **27**, **28b**, **29** and **30** as mediators to enantioselectively transfer acyl groups from acetic anhydride to racemic 1-phenylethanol **133** (Scheme 43).[142] As a result, *S*-enantiomer of acetate **134** was produced in the (11*S*,12*S*)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine (**30**) – $Cs_2CO_3$ catalytic system with 76% *ee*.

**Scheme 43**




## IV. Conclusion

The present review demonstrates that $C_2$-symmetric chiral diamines and their derivatives possessing acidic or basic properties catalyze various asymmetric reactions which lead to enantioselective formation of valuable chiral compounds. The advantages of these catalysts are relative simplicity of their synthesis (compared to unsymmetric bifunctional catalysts) and chemical stability and the possibility to scale up the catalytic reactions. In the presence of these catalysts, some asymmetric reactions (aldol, Michael, *etc.*) can be smootly carried out in aqueous medium in which enzymes — prototypes of organocatalysts — catalyze enzymatic reactions in nature. This creates opportunities for the development of novel environmentally benign industrial processes for enantioselective protection of practically important compounds and materials. The utility of $C_2$-symmetric COC in asymmetric synthesis can be substantially extended by varying the active sites and spacers groups. The roles of chemically identical functional groups in $C_2$-symmetric COC can be differentiated to tune the catalysts for particular catalytic procesess by using different cocatalysts, in particular, acids and bases.

The synthesis of $C_2$-symmetric catalysts containing up to six stereocentres requires the application of several enantiomerically pure compounds, which are still fairly expensive (especially unnatural enantiomers). Therefore, regeneration of valuable catalysts, which is often impossible without labour-intensive chromatographic methods is of particular interest. This problem can be solved by development of stable and recyclable immobilized forms of COC like tetramine **5** immobilized on an inorganic polymer[53] and prolinamides **15** modified with ionic groups.[85–87] Undoubtedly, the range of catalysts of this type will be contsantly extending. Promising approaches to solving this challenge can be, in particular, application of polymeric or ionic spacers in the design of catalysts and development of virtually unexplored recyclable forms of (thio)ureas, amidines, guanidines and some other types of catalysts capable of forming stable hydrogen bonds with the reactants.

We hope that the analytical information presented in this review will be useful for researchers who work in the field of asymmetric synthesis and catalysis as well as medicinal and green chemistry and will stimulate them to develope novel areas of research and extensively apply organocatalytic methods in chemistry and fine chemical engineering.

This review was written with the supprot of the Russian Science Foundation (Project No. 14-50-00126).

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