Asymmetric organocatalysis: from a breakthrough methodology to sustainable catalysts and processes

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The evolution of modern catalytic methodologies for asymmetric organic synthesis, including transition metal and organocatalysis, is briefly considered. The results of the authors′ research group comprise the development of convenient, efficient, and reusable metal-free amine-containing catalysts (aminocatalysts) for manufacturing enantiomerically enriched organic compounds. The efficiency of the obtained catalysts is demonstrated for asymmetric aldol reactions, Michael reactions, and domino reactions, including green chemistry processes. The applicability of the developed catalysts and processes for the synthesis of natural product analogs and the most active enantiomers of clinically used drugs is demonstrated.

Key words: organocatalysis, asymmetric synthesis, green chemistry, pharmaceuticals.

1. Development of the methodology of asymmetric organocatalysis

The need to prepare chiral organic compounds in enantiomerically pure state is caused by the chirality of living nature. The antipodes of chiral drugs that constitute a significant part of the pharmaceutical market[1] act differently on the chiral receptors of the body, and the presence of one of the enantiomers may cause severe side effects.[2] A classic example is thalidomide, which was used in a number of European countries in 1956—1962 as an efficient tranquilizer and sleeping pills. After the use of this drug, which was manufactured as a racemate, by pregnant women, the babies were born with with shortened, flipper-like, or absent limbs.[3] According to different estimates, 8000 to 12000 such cases were recorded. It turned out that the tragedy was caused by the *R*-enantiomer of thalidomide, which is a teratogen.

Enantiomerically pure compounds valuable for pharmacology (amino acids, carbohydrates, steroids, *etc*.) are present in plants. However, the industrial isolation of a desired component from biomass is often a nontrivial task requiring the use of chromatography, which is not industrially feasible. A more rational approach is the chemical synthesis of enantiomerically pure drugs from substantially more readily available achiral or racemic precursors in the presence of a catalytic amount of a chiral source.

The natural chiral sources are enzymes.[4] Enzymatic catalysis is responsible for the formation of a considerable part of Earth′s biomass. In organic chemistry, asymmetric catalysis was long associated with metal (Rh, Ru, Ti) complexes with enantiopure phosphite type ligands or natural α-hydroxy acid derivatives, discovered in the 1970s and 1980s, which efficiently catalyzed asymmetric hydrogenation[5,6] and oxidation[7,8] reactions. This discovery brought asymmetric catalysis to the forefront of chemical science. Complexes of numerous transition metals[9] (*e.g.*, Pd,[10] Fe,[11] Co,[12] Ni,[13] Cu,[14] Ag,[15] Au[16]) with chiral oxazoline derivatives,[17—19] *N*-heterocyclic carbenes,[20—22] *N*,*N*′-dioxides,[23—25] and a number of other ligands[26—29] have been synthesized to date (usually *in situ*). This substantially expanded the range of catalytic asymmetric reactions and the assortment

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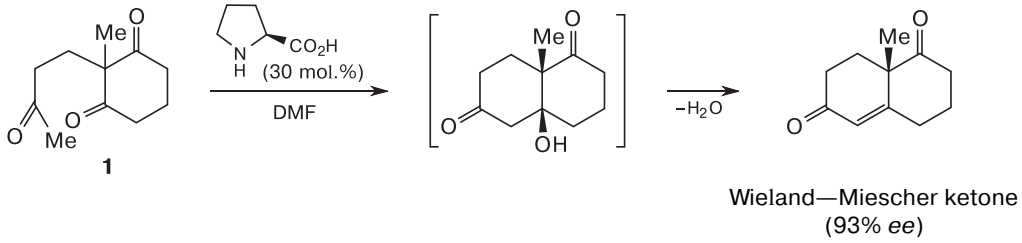
Scheme 1



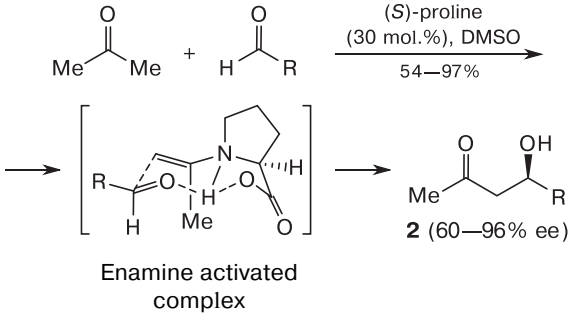
of enantiomerically enriched organic compounds that can be prepared in this way. The outstanding role of the transition metal catalysis in organic chemistry was recognized by awarding W. S. Knowles, R. Noyori, and K. B. Sharpless, who created this method, the Nobel Prize 2001 in chemistry.

However, the most efficient catalysts based on transition metal complexes are rather expensive. Some of them are toxic and/or unstable in air or in the presence of moisture.[30] Therefore, as soon as in the 1970s, scientists started to think how necessary the metal is in the catalyst and whether enantiomerically pure organic molecules designed in a certain way would be able not only to transfer the stereochemical information to the reactants, like ligands do, but also to catalyze chemical reactions by taking on the function of the metal. The positive answer to this question was provided by German chemists Z. G. Hajos and D. R. Parrish[31] and U. Eder, G. R. Sauer, and R. Wiechert,[32] who independently patented in 1971 the enantioselective synthesis of the Wieland—Miescher ketone, the key intermediate in steroid synthesis. The desired intermediate was obtained with 93% *ee* by asymmetric cyclization of triketone **1** *via* intramolecular aldol reaction catalyzed by a simple amino acid, (*S*)-proline (Scheme 1). This reaction was also useful for the enantioselective synthesis of other chiral biologically active compounds, including naturally occurring compounds, containing carbocyclic structural moieties.[33]

Two decades later, research groups of E. P. Serebryakov,[34,35] Y. Shi,[36] S. E. Denmark,[37] D. Yang,[38] E. N. Jacobsen,[39] and E. J. Corey[40] described metal-free enantioselective catalytic olefin cycloaddition, epoxidation, and cyanation reactions, in which chiral derivatives of pyrrolidine, carbohydrates, thiourea, and guanidine were used as catalysts. These studies confirmed that small organic molecules of various types could act as catalysts in asymmetric synthesis. Unfortunately, the authors were unable to turn their results into a new promising research area, and these studies did not attract much attention of the scientific community.

The situation drastically changed in 2000, when B. List, R. A. Lerner, and C. F. Barbas discovered that proline enantioselectively catalyzed not only intramolecular, but also intermolecular asymmetric cross-aldol reactions of acetone with various aldehydes[41] (Scheme 2). It became clear that simple amino acids, in particular proline (115 g mol^{-1}), could catalyze the same reactions (formation of linear aldols **2**) as native enzymes, type I aldolases, which are macromolecular peptides (~$1.6 \cdot 10^5$ g mol^{-1}) with a markedly more complex structure.[42] Furthermore, the mechanisms of catalysis (enamine mechanism, in this particular case) are also similar.

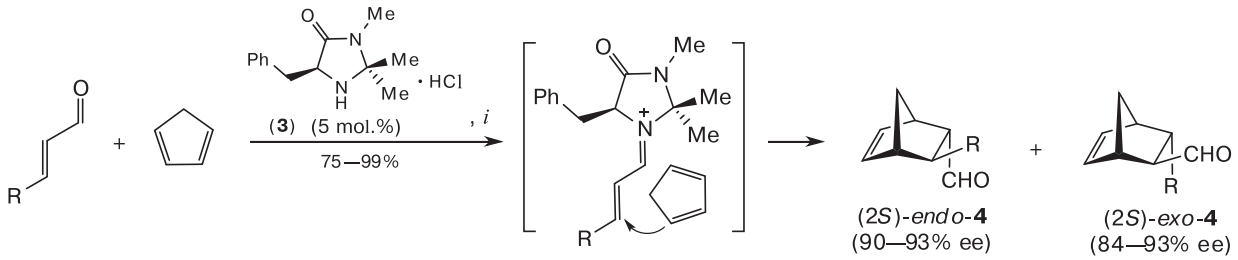
Scheme 2



R = Ar, 2-naphthyl, Pr^i

Shortly, D. W. C. MacMillan and co-workers[43] found that the chiral imidazolidinone salts **3** obtained from α-amino acids were highly selective catalysts for asymmetric [4+2]-cycloaddition reactions of α,β-unsaturated aldehydes to dienes, which resulted in cycloadducts **4** (Scheme 3). The chemists proposed a conceptually new and, as the practice showed,

Scheme 3



R = Alk, Ph, furyl

Conditions: *i*. MeOH, H_2O.

highly fruitful strategy for reactant activation in organocatalytic reactions *via* the formation of iminium ions with the catalyst. In addition, the term "asymmetric organocatalysis" was introduced, thus positioning this subject as a new research area comparable in its scope with the enzymatic and transition metal catalysis.[44]

These pioneering studies initiated large-scale research, which is still in progress, in the field of asymmetric organocatalysis.[45,46] These works provided the synthesis and successful application in asymmetric reactions of new effective organocatalysts, particularly of chiral amines containing primary,[47] secondary,[48,49] and tertiary amino groups,[50—53] axially chiral Brønsted acids,[54—57], *N*-heterocyclic carbenes,[58,59] chiral ammonium salts, [60—62] and other types of catalysts[63—65] (Table 1). Metal-free catalysts are more environmentally benign and convenient for handling than moisture- and atmospheric oxygen-sensitive metal complexes, and they have simpler structures than natural macromolecular enzymes. For the outstanding contribution to the development of organocatalysis, a promising area of modern organic chemistry, B. List and D. W. C. MacMillan were awarded the Nobel Prize 2021 in chemistry.

2. From a promising methodology to practical aminocatalysts and processes

Despite the diversity of novel organocatalysts and successful application of the catalysts for enantioselective syntheses of biologically active compounds,[66—72] organocatalysis (including aminocatalysts) has not yet found extensive use in pharmaceutical industry. The available chiral amines, in

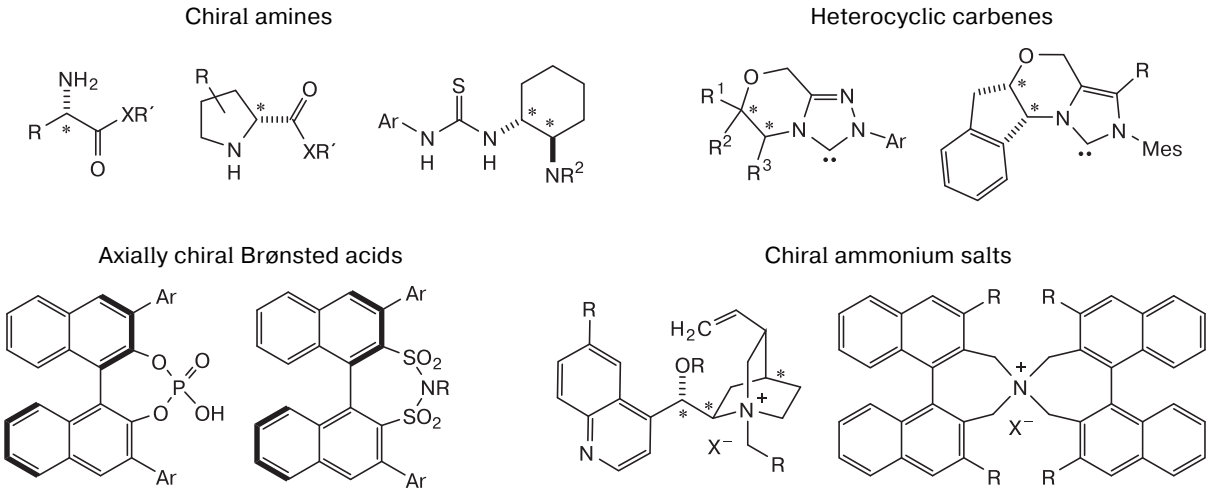


Fig. 1. Some types of chiral organocatalysts.

particular proline, are usually less active than metal complexes (they must be added in amounts up to 30 mol.%), while more efficient bi- and polyfunctional catalysts are much more expensive. Organocatalysts containing primary and secondary amino groups are deactivated during catalytic reactions because of the side transformations of enamine and iminium intermediates;[73–77] thus requires development of more stable catalysts of this type. The stereoinduction for reactions involving tertiary amines, which activate reactants *via* hydrogen bonding, is usually higher in aprotic solvents, including toxic chlorinated solvents, than in environmentally benign protic media such as ethanol and water.[78,79] Furthermore, separation of organocatalysts from the products usually requires chromatography, which is inconvenient for industry.

The studies aimed at solving these problems were started by our research group in 2006.[80] We assumed that the stability of organocatalysts and the environmental friendliness of the asymmetric reactions they catalyze could be increased by introducing auxiliary ionic groups as quaternized or protonated nitrogen heterocycles (imidazole, pyridine, quinoline, and piperidine). We expected that these structural blocks would decrease the catalyst solubility in the reaction mixture (and would thus "heterogenize" the catalyst) and facilitate the catalyst separation from the products. In addition, it was assumed that they would structurize the activated complex *via* ion—dipole interactions and formation of additional hydrogen bonds with the reactants, which may result in increasing reaction rate and improved stereoinduction. Finally, by changing the cation and anion structure, we planned to regulate the ratio of the hydrophilic and hydrophobic properties of the catalyst and the phase composition of the catalytic system and thus to attain the highest enantioselectivity of reactions and easy regeneration of the catalyst[81] (Fig. 2). As research objects, we chose asymmetric aldol reactions,[82] conjugate addition to activated double bonds,[83] and asymmetric domino reactions,[84,85] which are widely used in medicinal chemistry for the enantioselective preparation of chiral biologically active compounds.

2.1. Asymmetric aldol reactions

As the starting point of research, we took the proline hybrid catalyst tagged to imidazolium cation developed by Chinese chemists in 2006.[86] This compound could be recycled three times in the asymmetric cross-aldol reaction between aldehydes and ketones in DMSO; however, the product yields and reaction enantioselectivities were moderate (68 and 85%, respectively). We decided to find out how changes in the structures of ionic and spacer groups and also an auxiliary functional group in the pyrro-

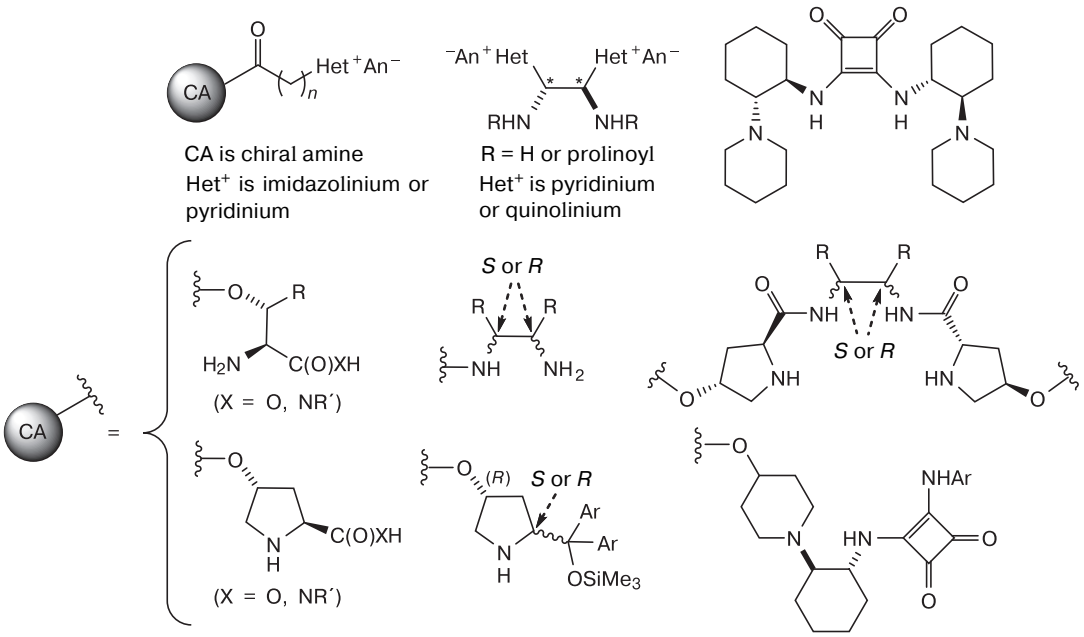


Fig. 2. Strategy of the design of stable aminocatalysts.

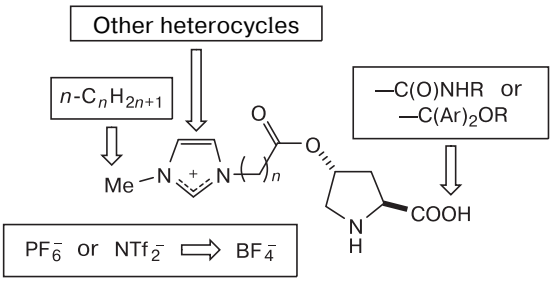


Fig. 3. Modification pathways of proline catalysts.

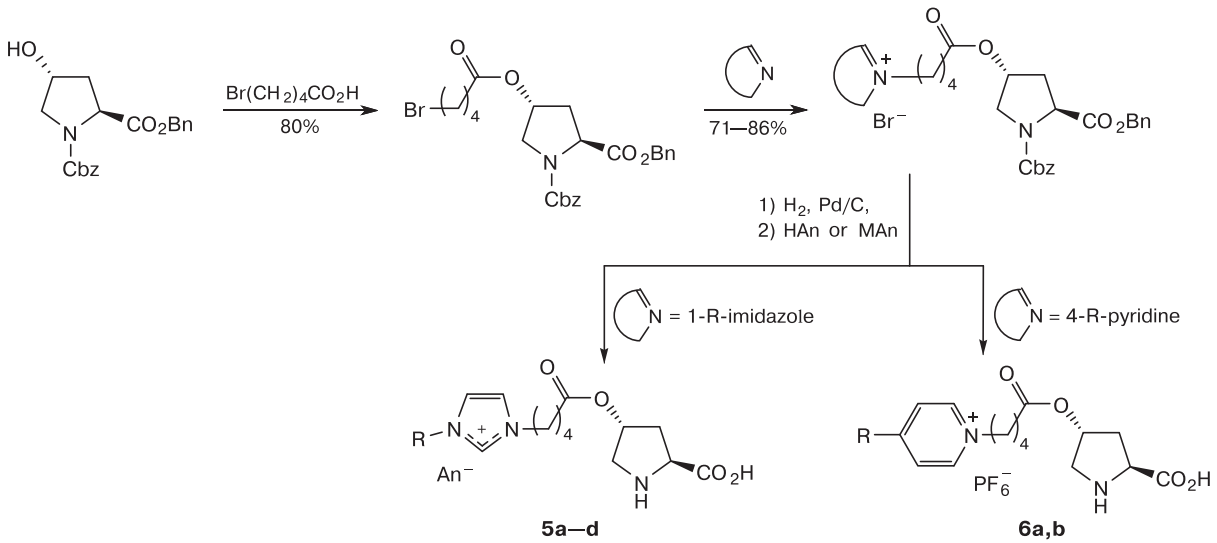
lidine ring would affect the catalytic properties of the molecule (Fig. 3). In particular, we assumed that long-chain alkyl groups and fluorine-containing anions would endow the catalyst with hydrophobic properties and thus enable asymmetric aldol reactions in water under heterogeneous conditions (as is the case of natural aldolases), which Nobel Prize 2022 winner K. B. Sharpless defined as "on water reactions". [87]

To verify this assumption, we synthesized new proline-containing amphiphilic imidazolium[88] and pyridinium[89] salts with hydrophilic (BF_4^-) and hydrophobic (PF_6^-, NTf_2^-) anions. The synthetic route included esterification of Cbz,Bn-protected (4*R*)-hydroxy-(*S*)-proline with 5-bromopentanoic acid and the reaction of brominated ester thus formed with the heterocycle (Scheme 4). The products were converted to target compounds **5** and **6** *via* hydrogenation and replacement of the anion (An). The prepared amino acids had different water solubility: they were readily water soluble if at least one part of the ionic group (cation or anion) was hydrophilic (compounds **5a**,**b** and **6a**), but the compounds that contained long-chain alkyl groups and hydrophobic anions formed suspensions in water (compounds **5c**,**d** and **6b**).

It turned out that the water solubility of the compounds determined their catalytic performance. Hydrophilic salts **5a**,**b** and **6a** did not catalyze the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in an aqueous medium, whereas in the presence of hydrophobic compounds **5c**,**d** and **6b**, this reaction proceeded with a high yield and excellent *anti*-diastereo- (*dr*) and enantioselectivity (*ee*) (Scheme 5, Table 1). The best catalysts were selected considering their recyclability. After the reaction was over, product **7a** was extracted with diethyl ether, and then the reactants were added to the remaining suspension of the catalyst in water, and the reaction was carried out once again. Hexafluorophosphates **5c** and **6b** retained the catalytic properties in eight such cycles, while more lipophilic bis(triflyl imide) **5d** was already deactivated in the third cycle, apparently, due to the catalyst loss during extraction of the product.

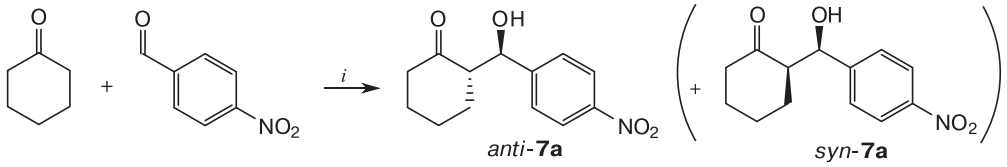
In the presence of catalysts **5c** and **6b**, various cyclic ketones react with aromatic and heteroaro-

Scheme 4



5: R = Me, An = PF_6 (**a**); R = *n*-$C_{12}H_{25}$, An = BF_4 (**b**), PF_6 (**c**), NTf_2 (**d**);
6: R = H (**a**), *n*-C_9H_{19} (**b**)

Scheme 5



Reagents and conditions: *i*. **5** or **6** (15 mol.%), H_2O, ~20 °C, 15 h.

Table 1. Model reaction of cyclohexanone with 4-nitrobenzaldehyde in reactants—water suspension

Catalyst	Conversion (%) (cycle)	*dr* **7a**, *anti/syn*	*ee anti*-**7a** (%)
5a	< 5	—	—
5b	< 5	—	—
5c	99 (1), 99 (2), 99 (3), 99 (4), 98 (5)	97 : 3*	99*
5d	99 (1), 98 (2), 58 (3)	98 : 2*	99*
6a	< 5	—	—
6b	97 (1), 98 (2), 95 (3), 98 (4), 98 (5), 96 (6), 94 (7), 96 (8)	97 : 3*	99*

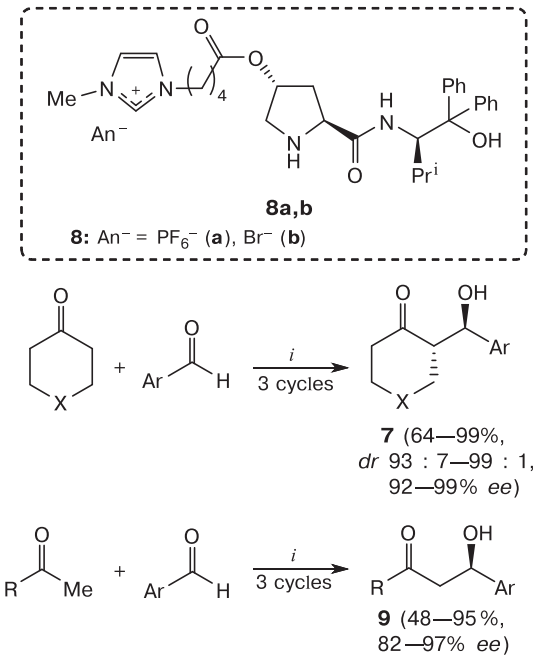
* In all cycles.

matic (furan, thiophene) aldehydes to give *anti*-aldols **7** with diastereoselectivity of up to 98 : 2 (*anti/syn*) and enantiomeric purity of up to 99%[90].

Prolinamide derivatives proved to be even more efficient catalysts. This is especially true for compounds containing an additional H-donor group (hydroxy or one more amide group) needed for the formation of a stereodifferentiating hydrogen bond network in the transition state of asymmetric reactions. We synthesized amphiphilic derivatives of prolinamide **8** modified with a diphenylvalinol moiety and an ionic group.[91] In this case, hydrophobic hexafluorophosphate **8a** was more active and more selective than bromide **8b**, so that reactions could be conducted in water at reduced temperature (3 °C) in the presence of a minimum amount of the catalyst (1 mol.%). Under these conditions, both cyclic and linear ketones reacted with aldehydes to give chiral aldols **7** and **9** with excellent diastereo- and enantioselectivity (Scheme 6), although the conversion decreased after the third catalytic cycle due to gradual leaching of the catalyst into the organic solution during extraction of the product.

The hydrophilicity of catalyst **8a** was increased by introducing a peripheral carboxy group into its

Scheme 6

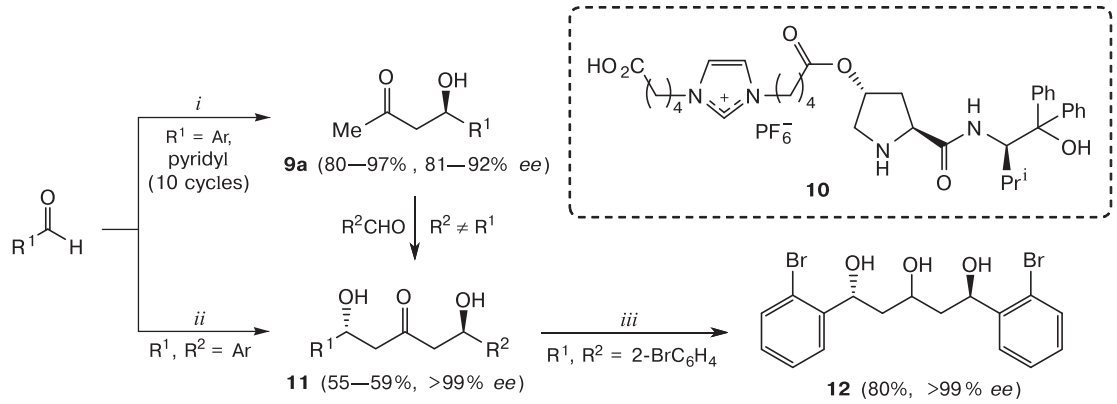


X = CH_2, O, S; R = *n*-C_3H_7, *n*-C_6H_{13}, *cyclo*-C_3H_5, Bn;
R = *cyclo*-C_3H_5, *n*-C_6H_{13}, Bn, prenyl;
Ar = 2-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-NCC_6H_4, 4-$MeO_2CC_6H_4$, 4-FC_6H_4, 3-$PhOC_6H_4$, C_6F_5, 2-naphthyl

Reagents and conditions: *i*. **8a** (1—5 mol.%), H_2O (100 equiv.), 3 °C.

molecule as an anchor to keep the heterogeneous catalyst on the surface of the aqueous phase during the product extraction.[92] Indeed, amide **10** modified in this way was much more efficient even in reactions with problematic water-soluble substrates such as acetone, and could be recycled at least 10 times (Scheme 7). Moreover, it was found that reactions of acetone with excess aldehyde stereospecifically gave bis-aldols **11**, which were previously obtained only in an anhydrous medium.[93] Product **11** was reduced to an enantiomerically pure triol **12**, valuable for pharmacology.

Scheme 7



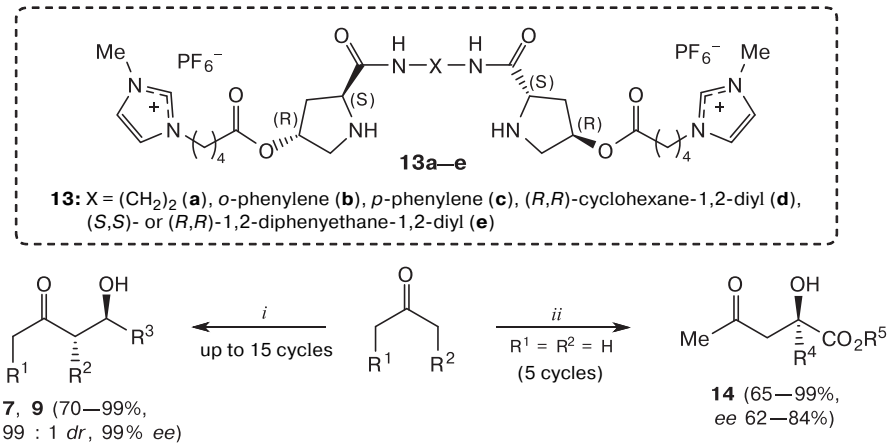
Reagents and conditions: *i*. acetone (3 equiv.), **10** (5 mol.%), H_2O, ~20 °C; *ii*. acetone (0.3 equiv.), **10** (5 mol.%), H_2O, ~20 °C; *iii*. $NaBH_4$, EtOH, ~20 °C, 3 h.

An even higher stability was found for C_2-symmetric catalysts **13** containing two prolinamide moieties modified with ionic groups.[94,95] In this case, the efficiency and selectivity of the catalysis of cross-aldol reactions in water were retained during 15 reaction—regeneration cycles (Scheme 8). In addition, in the presence of catalyst **13e** based on 1,2-diphenylethane-1,2-diamine, acetone reacted not only with aldehydes, but also with α-keto esters to give α-hydroxy-γ-keto esters **14**.[96] These compounds are precursors of chiral γ-lactones[97] present in many natural compounds.

Enantiomerically pure diamines **15a—c** containing pyridine and quinoline moieties necessary for the preparation of pyridine- and quinoline-derived organocatalysts were obtained from (*S,S*)-1,2-bis-(*o*-hydroxyphenyl)ethane-1,2-diamine and the appropriate hetarenecarbaldehydes *via* the diaza-Cope rearrangement.[98] These heterocycles capable of protonation and *N*-alkylation make it possible to locate the positive charge near the stereocenter where its effect is most significant. Diamines **15a,b** containing 2- and 4-pyridyl substituents were converted to bis-heteryl prolinamides **16a,b** *via* a sequence of amidation, *N*-methylation, and deprotection reactions (Scheme 9).

It turned out that compounds **16a,b** stereoselectively catalyzed a broad range of asymmetric cross-

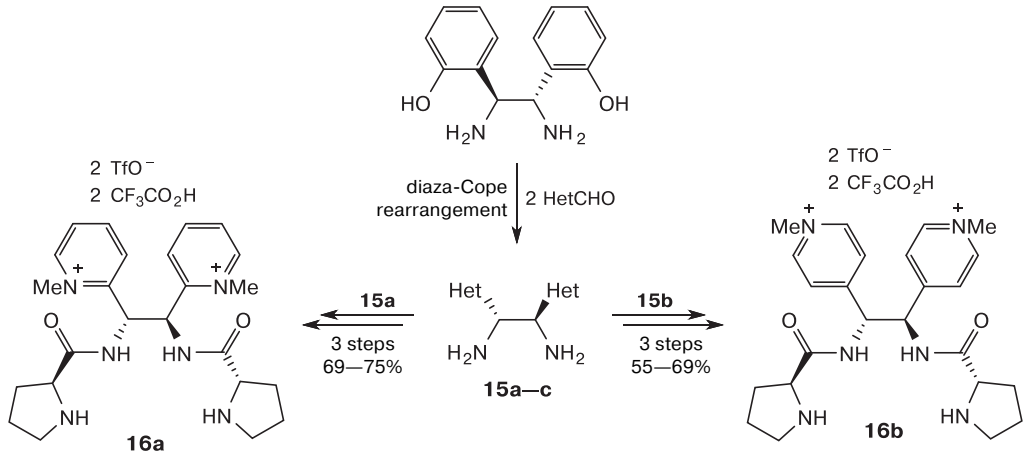
Scheme 8



7: $R^1 + R^2 = CH_2YCH_2$ (Y = CH_2, CHMe, O, S, NCO_2Et)
9: R^1 = H, *n*-Alk, Bn, CH_2Bn, Ar; R^2 = H
14: R^4 = Ar, Alk; R^5 = Alk, Bn

Reagents and conditions: *i*. R^3CHO, **13a—e** (10 mol.%), H_2O, 20 °C; *ii*. $R^4C(O)CO_2R^5$, **13e** (20 mol.%), neat, −30 °C.

Scheme 9



Het = 2-pyridyl (**a**), 4-pyridyl (**b**), and quinolin-8-yl (**c**)

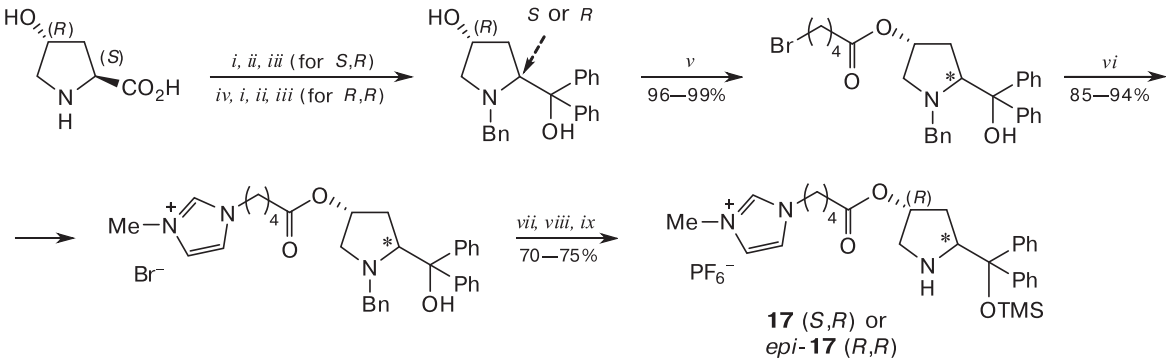
aldol reactions (between two aldehydes, a ketone and an aldehyde, and two ketones) without any solvent.[99] Owing to the ionic group located in the pyridine ring, these catalysts are readily separated from the products and can be reused up to 25 times, without decrease in the rate and selectivity of the reaction. The long operation period (more than 800 h) makes these catalysts promising candidates for the use in industrial production processes of pharmaceutical drugs.

2.2. Asymmetric conjugate addition reactions

The proposed methods for immobilization of aminocatalysts of asymmetric aldol reactions by attaching them to *N*-alkylated achiral heterocycles (imidazole or pyridine) proved to be also useful for the design of reusable catalysts for asymmetric conjugate addition of nucleophiles to activated C=C double bonds. Thus we converted natural (2*S*,4*R*)-4-hydroxyproline to new hybrid forms of diarylprolinol silyl esters **17** and *epi*-**17** (Scheme 10). The synthetic sequence resembled the preparation process of amino acid type catalysts: the epimerization and Grignard reactions were followed by esterification, alkylation, deprotection, silylation, and anion replacement.[100] The catalysts of this type are more nucleophilic than proline catalysts: they form iminium ions with α,β-unsaturated carbonyl compounds, thus activating them towards the reactions with nucleophiles.[101]

Hybrid **17** catalyzed the reaction of dialkyl malonates with α,β-unsaturated aldehydes in water;

Scheme 10



Reagents and conditions: *i*. MeOH, $SOCl_2$; *ii*. BnBr, Et_3N, CH_2Cl_2; *iii*. PhMgBr, THF; *iv*. 1) Ac_2O, AcOH, Δ, 5.5 h, 2) HCl, Et_3N; *v*. $Br(CH_2)_4CO_2H$, DCC, DMAP; *vi*. 1-methylimidazole, 100 °C, 10 min; *vii*. H_2, Pd/C, MeOH; *viii*. Me_3SiCl, Et_3N, CH_2Cl_2; *ix*. KPF_6, H_2O.

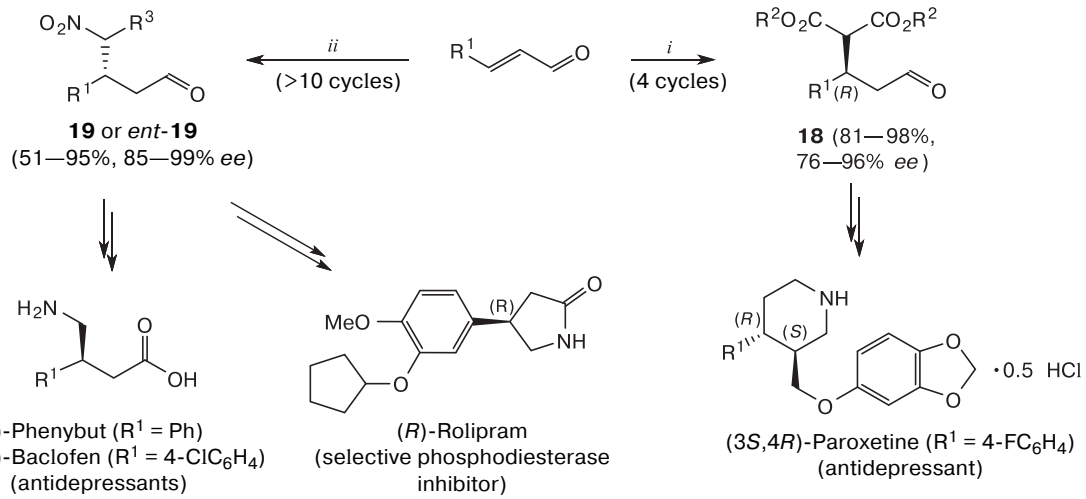
however, in this case, the best results were attained in 96% ethanol,[100] in which adducts **18** were formed in up to 98% yields and with up to 96% *ee* (Scheme 11). It substantially surpassed in activity the non-immobilized catalyst; no activating acid additives were required, as this role was played by the ionic group. This provided a considerable increase in the yield and enantiomeric excess for the adduct of dibenzyl malonate with 4-fluorocinnamaldehyde, the key intermediate in the synthesis of chiral antidepressant paroxetine, in comparison with the known method.[102] Paroxetine is widely used in psychiatric medicine as an efficient drug for the treatment of depression and anxiety. Importantly, the (3*S*,4*R*)-isomer of this compound is a more active drug than the other enantiomer.

The asymmetric reactions of α,β-enals with nitroalkanes proceed under the same conditions, giving rise to γ-nitroaldehydes **19**[103] (see Scheme 11). The use of isomeric catalysts **17** and *epi*-**17** with the opposite configurations of the key stereocenter enabled the stereodivergent synthesis of both enantiomers of the product in up to 95% yield and up to 99% *ee*. In the absence of an oxidant (air oxygen), the rate and selectivity of the reaction were preserved in ten catalytic cycles.[104] This method was used to prepare the key precursors of the most active (*R*)-enantiomers of phenybut, baclofen, and rolipram, used for the treatment of nervous disorders, which are derivatives of γ-aminobutyric acid (GABA), the most important natural neurotransmitter. The proposed method is one of the most convenient approaches for enantioselective synthesis of these compounds.

Unlike the conjugate addition of nucleophiles to α,β-enals, the corresponding reactions involving sterically more hindered α,β-unsaturated ketones proceed more efficiently in the presence of organocatalysts containing a primary amino group.[105] We synthesized immobilized forms of these catalysts, in particular catalysts **20**, from enantiomerically pure 1,2-diphenylethane-1,2-diamine *via* a simple sequence of transformations comprising the selective protection of one amino group, attachment of the imidazolium cation to the other amino group, replacement of the anion, and deprotection[106] (Scheme 12). In addition, we expected that primary diamines **15**, obtained by the aza-Cope rearrangement and containing basic pyridine and quinoline moieties (see Scheme 9), in combination with an acid additive, could serve as the structural bases for environmentally benign recyclable organocatalysts for asymmetric reactions of α,β-enones.

In the presence of catalysts **20**, 4-hydroxycoumarin and its sulfur analog react with α,β-unsaturated ketones to give Michael adducts **21** in good yields

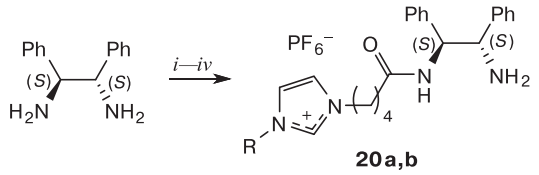
Scheme 11



18: R^1 = Ar, R^2 = Alk, Bn
19: R^1 = Ar, ferrocenyl, Me; R^3 = H, Et

Reagents and conditions: *i*. $CH_2(CO_2R^2)_2$ (**17**) (10 mol.%), 96% EtOH, 4 °C; *ii*. $R^3CH_2NO_2$ (**17** or *epi*-**17**) (10 mol.%), 96% EtOH, ~20 °C, argon.

Scheme 12

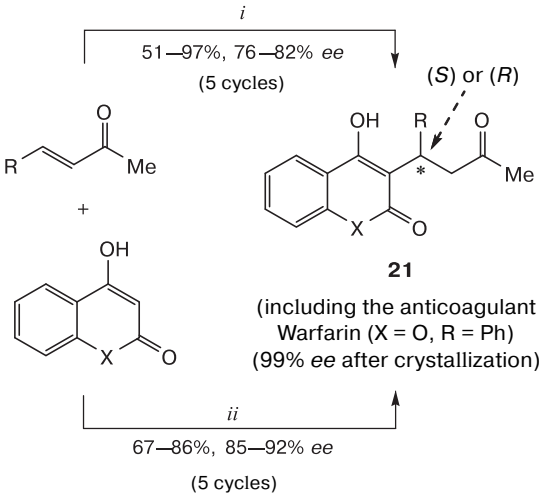


20: R = Me (**a**), $(CH_2)_4CO_2H$ (**b**)

Reagents and conditions: *i*. PhOC(O)OBn; *ii*. $Br(CH_2)_4CO_2H$; *iii*. 1-R-imidazole; *iv*. anion exchange resin (deprotection).

and a rather high enantioselectivity, which were retained in five cycles of catalyst use (Scheme 13, conditions *i*).[107] In particular, this method was employed to prepare the (*S*)-enantiomer of warfarin, a clinically used anticoagulant. The (*S*)-enantiomer is two to five times more active than the (*R*)-enantiomer.[108] The previously unknown warfarin analogs containing ferrocene and cymantrene moieties, present in compounds with anticancer activity, were also prepared in this way.[109]

Scheme 13



X = O, S
R = Ar, 3-pyridyl, 2-thienyl, *cyclo*-C_6H_{11}, ferrocenyl (Fc), cymantrenyl ($(OC)_3MnC_5H_4$)

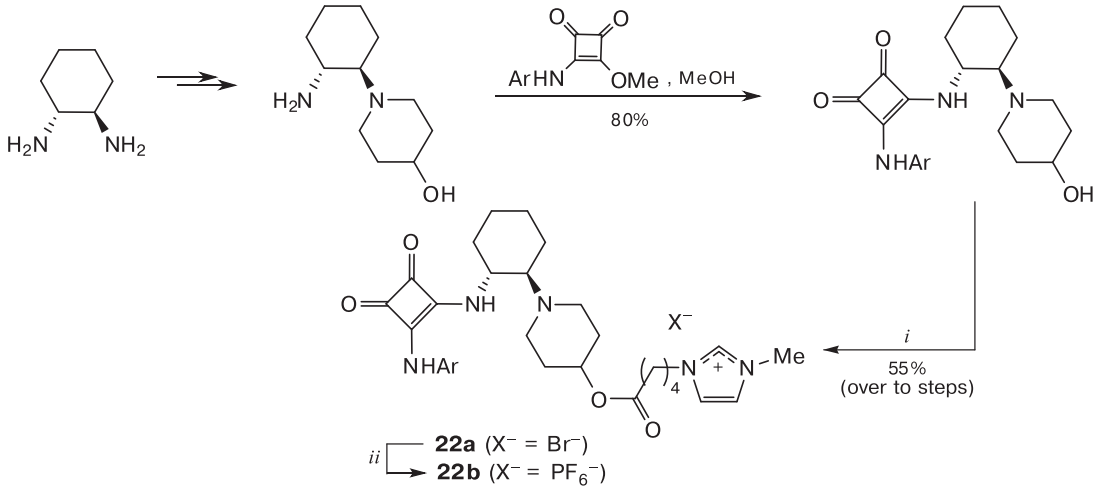
Reagents and conditions: *i*. **20a** or **20b** (20 mol.%), AcOH, THF, ~20 °C; *ii*. **15c** (10 mol.%), mandelic acid (20 mol.%), H_2O, ~20 °C.

Bis(quinolinyl)ethanediamine **15c** in combination with mandelic acid (see Scheme 13, conditions *ii*) proved to be even a more active catalyst for warfarin synthesis. Unlike primary amines **20a,b**, this catalytic system perfectly operated in aqueous medium.[110] Crude warfarin had an enantiomeric purity of 92%, which is an unprecedented result for aqueous systems. The product isolation did not require the use of chromatography: the chemically pure drug precipitated from the aqueous solution, and after a single recrystallization, it did not contain the minor enantiomer. Elimination of the chromatographic purification stage makes the developed process attractive for the pharmaceutical industry.

Unlike primary and secondary amines, tertiary amines cannot generate enamines or iminium ions with carbonyl compounds; they activate reactants only by hydrogen bonding. Most efficient are bi- and polyfunctional compounds of this type, which contain, apart from the tertiary amino group, H-donor structural moieties such as the thiourea group,[111,112] squaramide moiety,[113—115] and other.[116,117] Using enantiomerically pure *trans*-1,2-diaminocyclohexane as a chiral matrix, we synthesized new stable bifunctional tertiary amines **22a,b** containing an imidazolium cation and a squaramide moiety (Scheme 14).[118] The catalytic properties of obtained hybrids **22a,b** were studied in the model reaction between acetylacetone and nitrostyrene (Scheme 15). It was found that in this case, like in aldol reactions, the solvent nature and the counter-ion in the catalyst molecule played an important role. For both catalysts, the reactions proceeded more rapidly in water than in organic solvents. However, the hydrophilic bromide **22a** catalyzed the reaction non-selectively, giving racemic product **23a**, while the reaction with hydrophobic hexafluorophosphate **22b** resulted in only (*R*)-enantiomer.

In the presence of enantiomeric catalysts **22b** and *ent*-**22b**, CH acids add to nitroolefins to give the corresponding adducts **23** and/or *ent*-**23** in nearly quantitative yields and with up to 99% *ee* (Scheme 16). In the plausible transition state, catalyst **22b** is probably located at the interface between the organic and aqueous phases where the reactants are protected from the racemizing action of water by structural groups of the catalyst *via* Coulombic and hydrophobic interactions ("on water catalysis"). Due to poor solubility in water and organic solvents, the catalyst can be easily separated from the products and can be reused 30 times without reactivation. Enantiomerically enriched adducts **23** are valuable synthons for the synthesis of useful biologically active compounds. They were used to prepare chiral β-amino acids, precursors of antibiotics

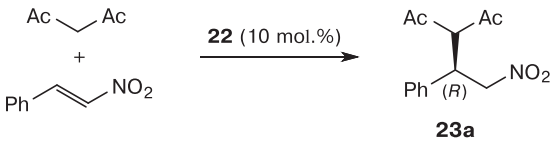
Scheme 14



Ar = 3,5-$(F_3C)_2C_6H_4$

Reagents and conditions: *i*. 1) $Br(CH_2)_4CO_2H$, 2) 1-methylimidazole; *ii*. KPF_6.

Scheme 15



23a

Catalyst	Solvent	*t*/h	Yield of **23a**	*ee* (%)
22a	H_2O	0.3	98	4
22b	H_2O	0.2	99	98
22b	Toluene	3.0	99	90
22b	THF	3.0	99	88

Conditions: solvent, ~20 °C.

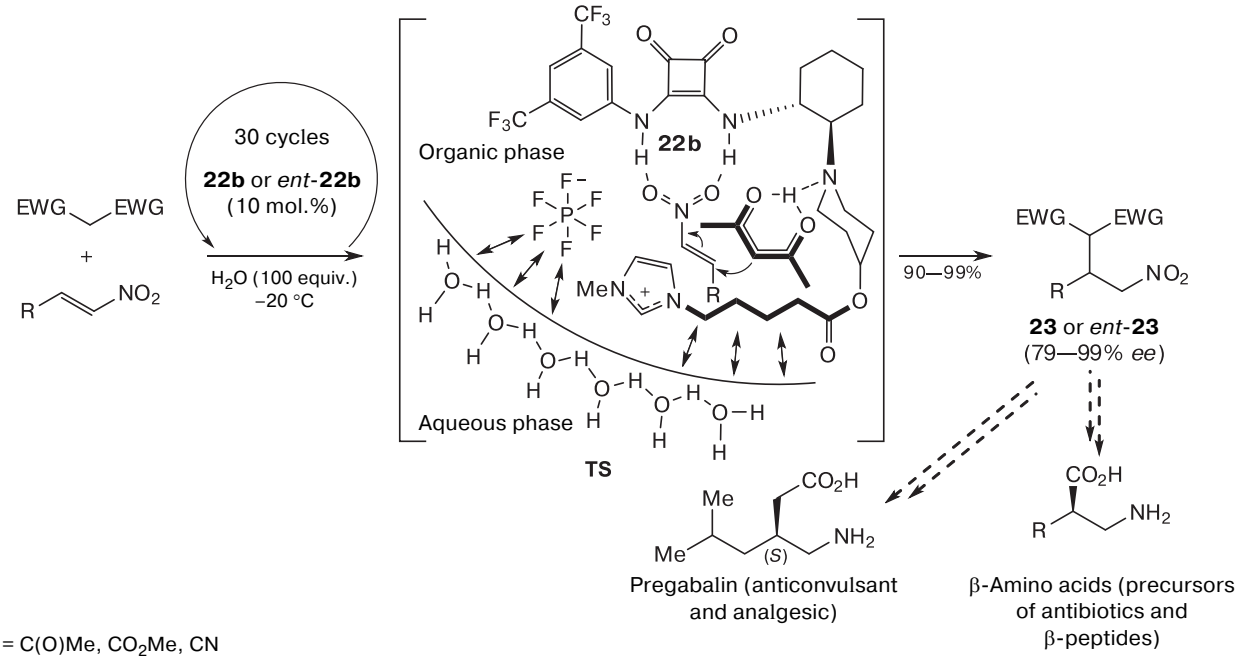
and β-peptides, and the most active (*S*)-enantiomer of pregabalin, an anticonvulsant and analgesic drug.

Heterocyclic catalysts containing no ionic groups can also be recyclable. We synthesized C_2-symmetric tertiary diamine **24**, containing a diamide linker, from accessible reactants in two steps.[119] In the presence of only 1 mol.% of this catalyst, nitroolefins enantioselectively add kojic acid, a natural compound that exhibits useful biological properties, and its derivatives (Scheme 17). In this case, the best results were attained in green protic solvents (water or ethanol), in which addition products **25** were formed in enantiomeric purity of up to 99%. The process is heterogeneous: catalyst **24** poorly soluble in most organic solvents is easily separated from the products and can be reused many times. Compounds **25** were converted to esters of pharmacologically valuable acids **26**, including dimethyldecadienoic acid, which reduces cholesterol level, and lipoic acid, a cofactor of enzymes.

One more environmentally benign method for conducting asymmetric reactions of carbo- and heteronucleophiles with nitroolefins in the presence of bifunctional tertiary amines is based on the use of liquid or supercritical carbon dioxide, which is a non-toxic and non-combustible green solvent promising for industry and requiring no disposal.[120] Despite the possibility of competitive nonselective binding of amide (thiourea) protons of the catalyst to oxygen atoms of CO_2, the enantioselectivity of reactions of nitroolefins with malonates catalyzed by thiourea **27**, which give γ-nitro esters (nitriles) **23** in liquid CO_2, (up to 89% *ee*) proved to be comparable with the selectivity of reactions in organic solvents, and the required amount of the catalyst did not exceed 5 mol.%[121] (Scheme 18). The reactions are easily scaled-up; after decompression, products **23** can be isolated by usual methods, and volatile carbon dioxide can be recycled if necessary.

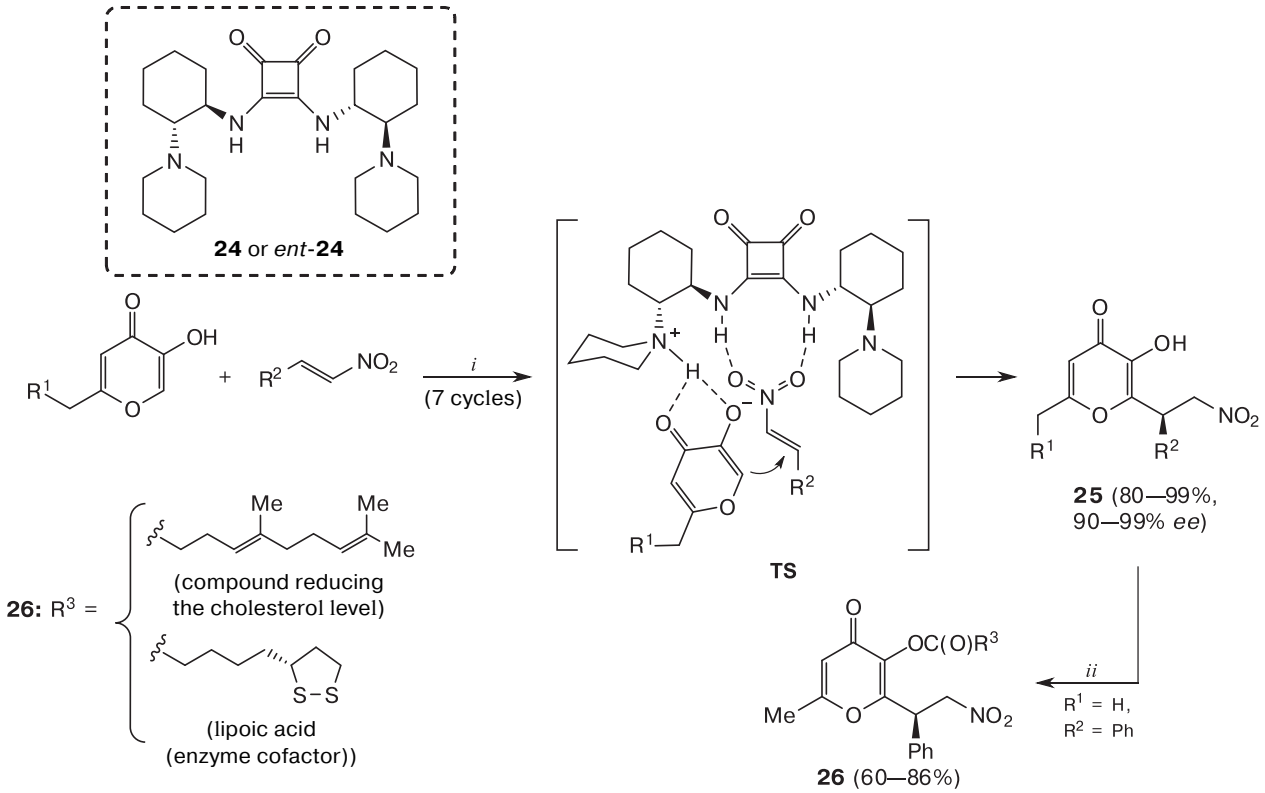
Diphenyl phosphite also adds to nitroolefins in CO_2 to give β-nitro phosphonates **28** in moderate to high yields and with up to 94% *ee*.[122] In this case, the best results were obtained under supercritical conditions in the presence of pseudo-enantiomeric

Scheme 16



EWG = C(O)Me, CO_2Me, CN
R = Ar, 2-thienyl, Alk, Fc, $(OC)_3MnC_5H_4$, MeCH=CH, PhCH=CH

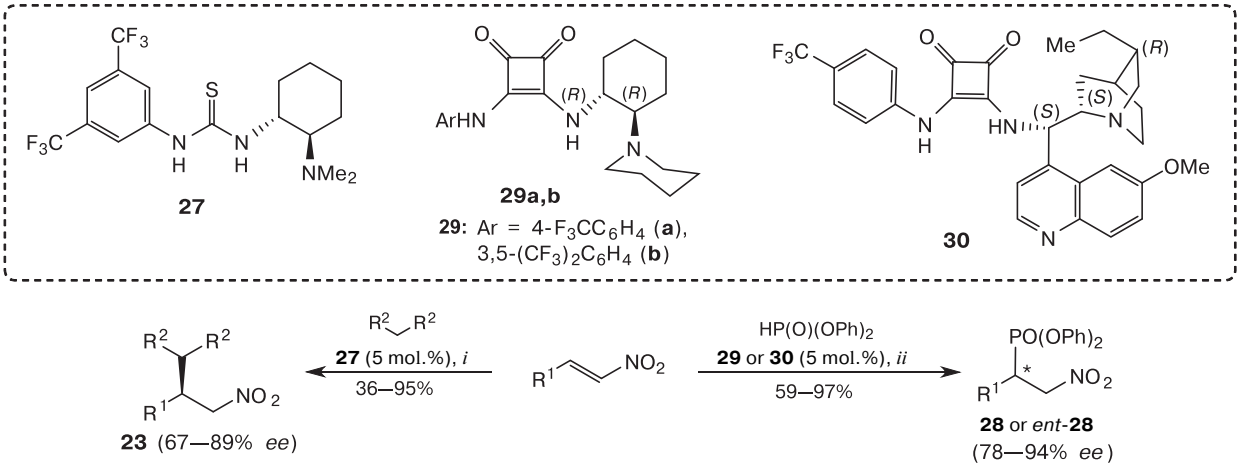
Scheme 17



R^1 = H, Cl, OMe, SAr, piperidin-1-yl, morpholin-4-yl; R^2 = Ar, thienyl

Reagents and conditions: *i*. **24** (1 mol.%), H_2O or EtOH; *ii*. R^3CO_2H, DCC, DMAP.

Scheme 18



23: R^1 = Ar, Bu^t; R^2 = CO_2Me, CO_2Et, CO_2Pr^i, CN
28: R^1 = Ar, 2-furyl, 2-thienyl, Bu^i

Conditions: *i*. liquid CO_2 (100 bar), ~20 °C; *ii*. supercritical CO_2 (100 bar), ~35 °C.

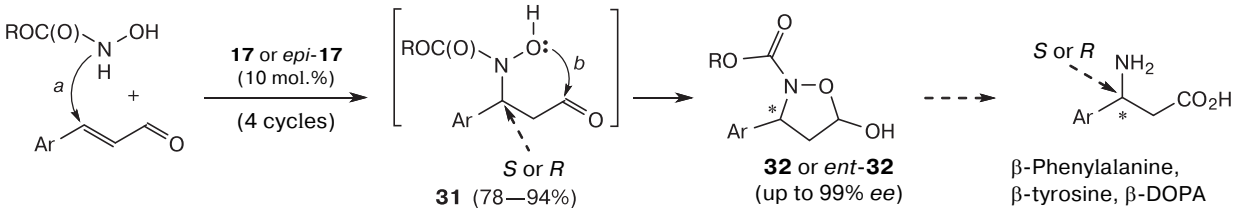
catalysts **29a** and **30** containing a squaramide moiety (see Scheme 18). Both enantiomers of compounds **28**, precursors of pharmacologically valuable β-amino phosphonic acids, were prepared in this way.[123] It is noteworthy that supercritical CO_2 served in these reactions not only as an environmentally benign reaction medium, but also as an extractant of products from the reaction mixture.

2.3. Asymmetric domino reactions

Domino reactions, which produce several chemical bonds over single experimental operation in the presence of the same catalyst, are promising in terms of green chemistry principles. This approach considerably decreases the energy and resource expenditures and reduces the amount of waste.[124,125] Before our studies, no data on the application of immobilized organocatalysts in asymmetric domino reactions were available.

We showed that imidazolium salt **17** and its epimer *epi*-**17** (see Scheme 10), which proved to be efficient in Michael conjugate addition reactions, enantioselectively catalyzed the reactions of electron-deficient olefins with binucleophiles, *N*-protected hydroxylamines.[126] In this case, the best result was obtained in toluene in which primary adducts **31** spontaneously cyclized to give 5-hydroxyisoxazolidines **32** or *ent*-**32** of high enantiomeric purity (Scheme 19). The catalyst retained activity in four reaction cycles, and heterocycles **32** could be easily converted to important β-amino acids: β-phenylalanine, β-tyrosine, and β-(3,4-dihydroxyphenyl)-α-alanine (β-DOPA).

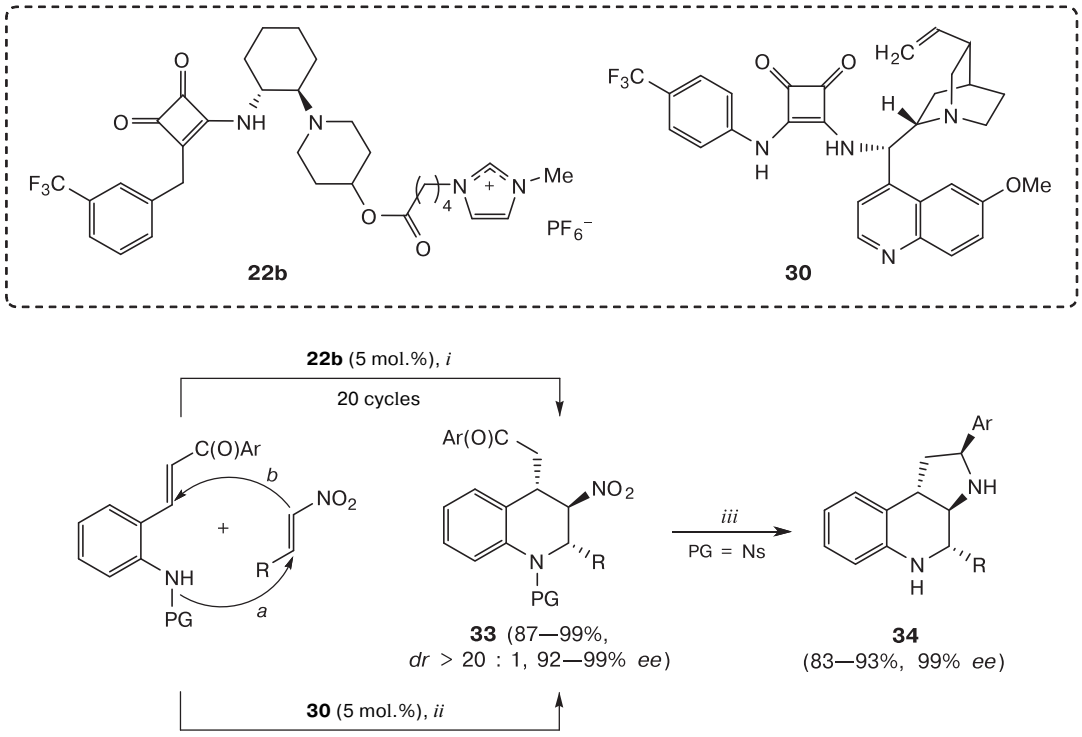
Scheme 19



R = Bn (**a**), Bu^t (**b**)
Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 3-(*cyclo*-C_5H_9O)-4-$MeOC_6H_3$

Conditions: *i*. toluene, 20 °C.

Scheme 20

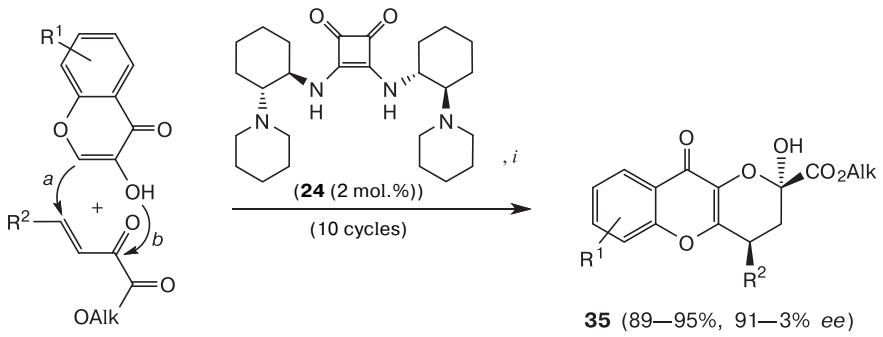


PG (protective group) = Ts, 2-$O_2NC_6H_4S(O)_2$ (Ns); R = Alk, Ar, thienyl, Fc, $(OC)_3MnC_5H_4$

Reagents and conditions: *i*. CH_2Cl_2, 20 °C; *ii*. supercritical CO_2 (200 bar), 75 °C; *iii*. 1) PhSH, 2) Zn, AcOH.

Bifunctional tertiary amine **22b** modified with the ionic group proved to be useful for asymmetric domino reactions. In the presence of this catalyst, *N*-protected aminochalcones underwent [4+2]-annulation reactions with nitroolefins, which included two successive Michael reactions (Scheme 20, steps *a* and *b*) to give tetrahydroquinoline derivatives **33** with exceptionally high *trans*-diastereo- and enantioselectivity in one experimental operation.[127] After completion of the cascade reaction, the catalyst was separated from the products by decantation or centrifugation. The regenerated catalyst was reusable for 20 times without the loss of catalytic properties. A drawback of this method is the use of toxic dichloromethane as the solvent. Conducting the reaction in supercritical CO_2 in the presence of quinine

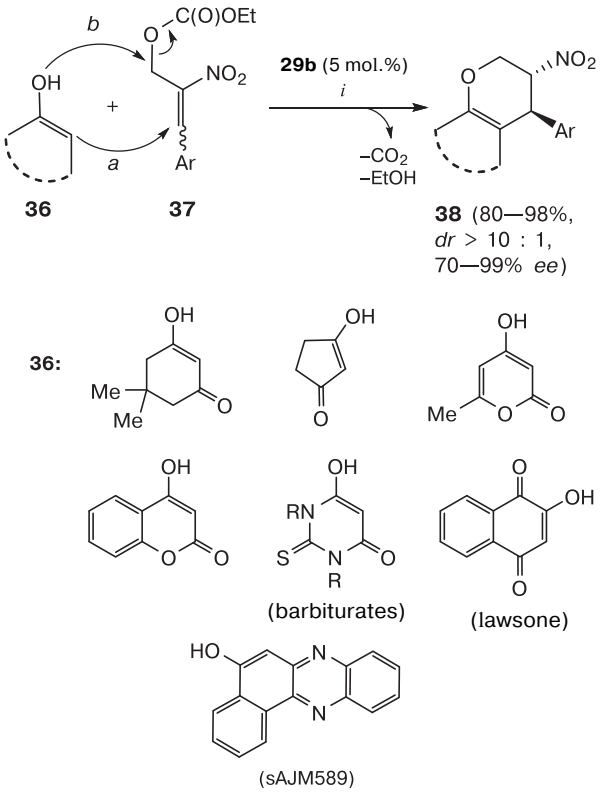
Scheme 21



R^1 = H, Br, OMe; R^2 = H, Me

Reagents and conditions: *i*. 95% EtOH, 20 °C.

Scheme 22



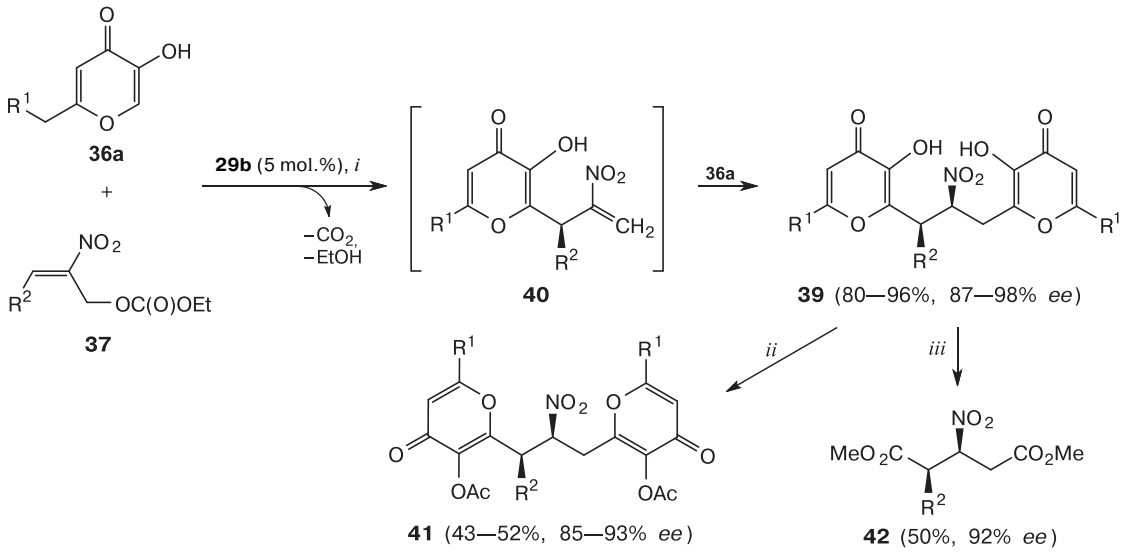
Conditions: *i*. solvent, 20 °C.

derivative **30** made it possible to improve the environmental characteristics of the process, without deteriorating its efficiency.[128] Heterocycles **33** were converted to pyrrolidino-tetrahydroquinolines **34**, a structural motif for some natural alkaloids.

In some cases, bifunctional tertiary amines containing no ionic groups can also be recycled after asymmetric domino reactions. In the presence of C_2-symmetric chiral tertiary amine **24**, chromenes, benzannulated analogs of kojic acid, enantioselectively react with β,γ-unsaturated α-keto esters in 95% ethanol to give hemiketals **35** (Scheme 21).[129] First, chromene adds to the double bond of enone (step *a*), which is followed by intramolecular ketalization (step *b*). Owing to low solubility of the catalyst in organic solvents, no problem arises with its regeneration. Exceptional simplicity and excellent performance of catalyst **24** make it promising for practical use.

In the presence of structurally similar tertiary amine **29b** (see Scheme 18), cyclic enols **36** react with 2-nitroallyl carbonates **37**, a new type of bis-electrophilic reagents.[130] The domino reaction includes nucleophilic addition of enol to nitroolefin and the subsequent cyclization with elimination of the carbonate group, giving rise to annulated tetrahydropyrans **38** in high yield with high stereoselectivity (Scheme 22). The reaction gives no acidic by-products, which would poison the catalyst. The enantiomerically enriched barbiturates, hennatannic acid (lawsone) and benzo[*a*]phenazine (anticancer drug sAJM589) derivatives, obtained in this way are of interest for the subsequent pharmacological studies.

Scheme 23



Reagents and conditions: *i*. solvent, 20 °C; *ii*. Ac_2O, 5% Pd/C, ~20 °C, 1 h; *iii*. 1) $RuCl_3$, $NaIO_4$; 2) $SOCl_2$, MeOH.

The reactions of 2-nitroallyl carbonates **37** with kojic acid **36a** derivatives unexpectedly give bis-adducts **39**, instead of annulation products **38**, irrespective of the component ratio.[131] The abnormal reaction route may be attributed to deactivation of the hydroxy group by the pyranone ring, which blocks the annulation process. Instead, primary Michael adducts eliminate the carbonate group, and nitroolefin **40** thus formed adds the second nucleophile molecule (Scheme 23). Bis-adducts **39** were converted to acetates **41** and nitrodicarboxylates **42** *via* catalytic acylation and oxidative fragmentation. The latter reaction can be used for asymmetric synthesis of aminoglutaric acid derivatives difficult to obtain by other methods.

In conclusion, in recent years, studies directed towards the development of simple and convenient methods for the asymmetric synthesis of enantiomerically pure organic compounds for medicinal purposes have been carried out at prominent research centers of various countries. The environmentally benign, metal-free catalysts (organocatalysts) developed, in particular, by our research group are of considerable interest for pharmaceutical industry, as they do not contaminate the product by a metal and are easily separated, while preserving the activity and high stereoinduction level over several catalytic cycles. The efficiency of the catalysts was demonstrated in practically important asymmetric aldol reactions, conjugate addition of nucleophiles to activated olefins, and domino reactions carried out using green reactants and solvents (water, ethanol, liquid and supercritical carbon dioxide). Intermediates for the synthesis of natural compound analogs and the most active enantiomers of clinically used drugs were prepared under proposed conditions. This research may give rise to new efficient processes for selective preparation of active drugs without adverse side effects.

No human or animal subjects were used in this research.

The authors declare no competing interests.

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