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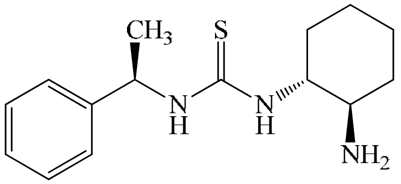
CHIRAL ORGANIC CATALYSTS IN THE DIELS-ALDER REACTION

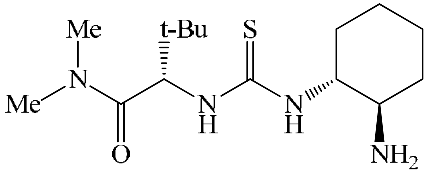
Abstract. The analysis of scientific investigations in the field of application of chiral organic catalysts in the reaction of diene synthesis has been carried out. The directions of using of synthesized adducts in the different part of industry have been described. The effect of used catalysts to stereo- and enantioselectivity of reactions have been studied.

Key words: diene synthesis, chiral organocatalysts, optically active compounds.

It is known that chiral organic catalysts find wide application in the reaction of diene synthesis and a huge amount of work has been done in this direction. However, research in this field continues to develop intensively and the search for new chiral organocatalytic systems remains relevant to this day [1-18].

Thus, in [19] new highly enantioselective bifunctional organocatalysts for enantioselective addition reactions, including [4+2] -cycloaddition reactions, were developed. These catalysts contain fragments of thiourea and a primary amino group or amine-sqvaramid groups:





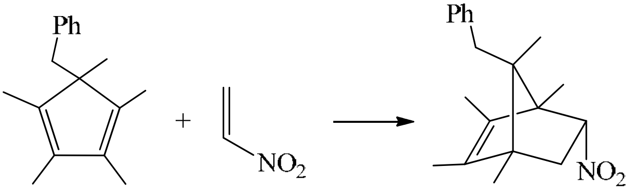
Synthesized catalysts are widely used in the Diels-Alder reaction (DA) for the synthesis of structured complex spirocyclic skeletons and indolo- and benzoquinolizidine derivatives, which belong to pharmaceutical compounds.

An unusual reaction of cycloaddition of 2-pyrones with aliphatic nitroalkenes, catalyzed by new bifunctional catalysts based on cinchon alkaloid derivatives, is associated with a cumbersome ethereal group at position 9 [20]. Bicyclic [2.2.2] -adducts with good yield and high diastereo- and enantioselectivity were obtained. The isotope effects of the C atom were studied by the C13-NMR spectroscopy method and the reaction mechanism was proposed. At the end, the areas of application of synthesized adducts are shown.

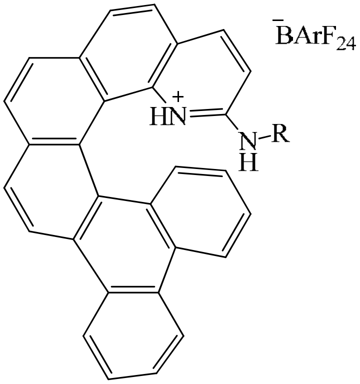
In [21], the Sc (OTf) 3 / bis (oxazoline) complex was proposed as a catalyst for the asymmetric reaction of DA 2-arylidene-1,3-indanediones with 2-vinyl-indoles. It was shown that the reaction is a convenient and important practical approach to biologically valuable and synthetically advantageous spiro-tetrahydrocarbazoles in good yield (92%) and high enantioselectivity (ee 94%).

A bimetallic heme-DNA cofactor containing Fe and Cu centers was synthesized as new hybrid catalysts for stereoselective synthesis, in particular for DA reactions [22].

Enantiomeric and periselective D-A reactions were performed with the participation of nitroalkenes in the presence of catalysts that are donors of a helico- chiral double hydrogen bond [23]. As a diene, 5-substituted pentamethylcyclopentadiene was used:



The reaction was carried out in a CH_2Cl_2 medium at a temperature of (-78^0) C for 20 hours and in the presence of 10 mol% % of catalyst



where -BArF24 is tetrakis [3,5-bis(trifluoromethyl) phenyl] borate.

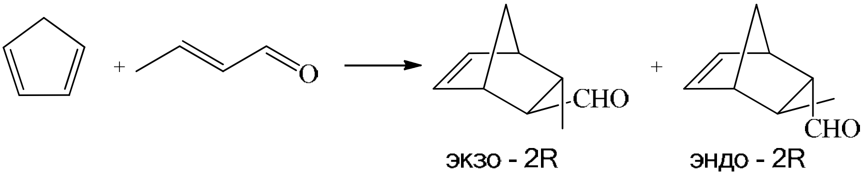
The authors note that the yield of the adduct in this reaction was 70-84%, and e.e. 67-70%.

In [24], chiral supramolecular B-containing Lewis acids were obtained from chiral 3-phosphoryl-1, 11-bis-2-naphthol, (2-cyanophenyl) boronic acid and tri (pentafluorophenyl) borane containing CN … B coordination bonds and PO ... B. It is shown that these catalysts increase the acidity of the active site in the Lewis acid. They were tested in the DA reaction between acrolein and cyclic (acyclic) dienes, proceeding in good yield and high enantioselectivity.

It was noted in [25] that the asymmetric D-A reaction is one of the convenient and effective methods for obtaining optically active compounds, for the production of which various kinds of catalysts are widely used. Most often, complexes based on Schiff bases and transition metal ions, in particular the Salen complex, are used. Chiral salen ligands can easily be synthesized from enantiomerically pure diamines and two moles of salicylic aldehyde or its derivatives. Mn, Cr, Co, V, Cu, Ti, Ru, Pd, Au, Zn and Al are used as the transition metals.

Chiral sulphinamide urea together with the cochlear-an a chiral strong Bronsted acid (o-nitrobenzenesulfonic acid) was used as a catalyst system in the (4 + 2) -cycloaddition of N-arylimines with electron-enriched olefins, such as vinyllactams and dihydropyrroles [26]. These catalysts have been successfully applied for the synthesis of tetrahydroisoquinolines, which form the basis of a number of natural and synthetic biologically active compounds, such as martinellin, skueryrin and tubocurarine.

Chiral polyoxometallate-imidazolidinones were used as catalysts for the D-A reaction between cyclopentadiene and crotonaldehyde in [27]. The reaction was carried out in the presence of 5 mol. % catalyst in a medium of 0.5 M CH2Cl2 for 3 days according to the scheme:



The yield of adducts ranged from 45-95%, e.e. 46-54%, the ratio of exo-endo isomers was 2: 1 to 1: 3.

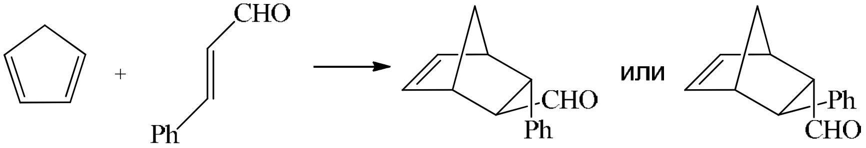
In [28], phosphorylated imidazolidinones were used in the asymmetric D-A reaction involving 1,2-unsaturated aldehydes with good yield and high enantioselectivity.

(S) - (-) - 2- (α-hydroxyethyl) benzimidazole and (S) - (-) - 2- (α-hydroxybenzyl) benzimidazole were used as chiral Bronsted bases in the DA reaction between anthrone t maleimide in moderate conditions [29].

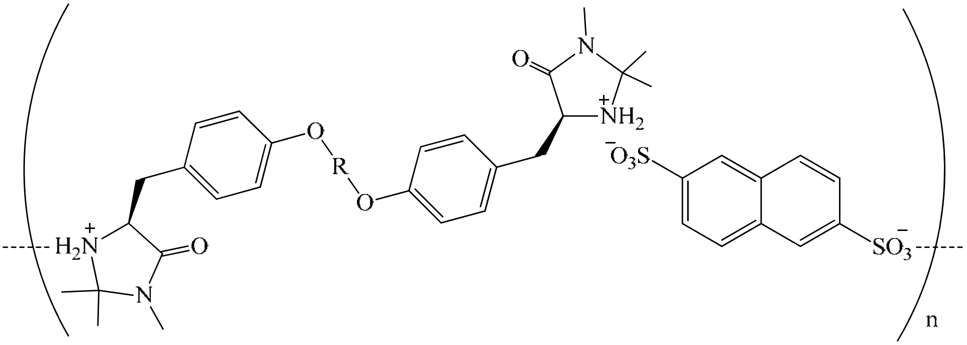
It is shown that chiral C-H acids during the silylation reaction generate silicon carbanion, which is an extremely active acidic Lewis catalyst for the enantioselective D-A reaction between cinnamate and cyclopentadiene. The ratio of enantiomers in the reaction was 97: 3, and the ratio of the diastereomers is 20: 1, respectively [30].

In [31], new main chain polyesters, functionalized with chiral imidazolidine salts, were synthesized. These polyesters were used as heterogeneous organocatalysts in the asymmetric D-A reaction between cyclopentadiene and trans-cinnamaldehyde. The authors note that the enantioselectivity of the reaction reaches up to 97%.

In another paper by the same authors [32], the main chain polymers of chiral imidazolidinones were successfully synthesized by the reaction of dimers of chiral imidazolidinone with disulfonic acid. The fatty imidazolidinones were introduced into the main polymer chain through ionic bonding. These compounds can be used as polymer chiral organocatalysts for asymmetric D-A reaction according to the scheme:



The yield of the adduct was 99%, e.e. up to 99%, the endo: exo ratio is 45: 55. The catalyst has the following structure:



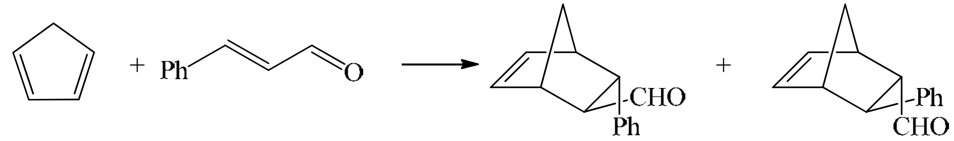
Ionic liquids were used to regenerate the McMillan catalyst in the D-A reaction [33]. The catalyst is an imidazolidinone derivative.

In work [34], benzopyrans were used as starting compounds for the organocatalytic reaction DA, leading to the formation of tricyclic systems. As catalysts, imidazolidinones were used. At the same time, the asymmetric induction was 96%. Synthesized tricyclic scaffold-tetrahydrocannabinol systems form the basis of many natural compounds.

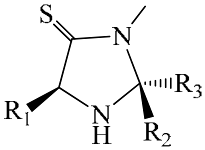
It was noted that in the first successfully implemented catalytic asymmetric reaction of D-A in 1979, Koga and co-workers. The chiral aluminum complex was used as the Lewis acid, and after that the researchers developed a huge number of catalytic systems for these reactions [35]. In particular, chiral organic compounds, such as imidazolidinone or TADDOL salts, have been used as catalysts in the asymmetric reaction of DA. In this paper, chiral amines were proposed as catalysts for these reactions on the basis of the theory of frontal molecular orbitals. It is shown that they exhibit high chemo-, regio- and stereoselectivity.

In [36, 37], derivatives of chiral phosphoric acids derived from linear chiral biaryls, as well as analogous chiral Bronsted acids, were used as effective and widely used compounds - enantioselective organocatalysts for various organic transformations, including DA reactions.

Endo- and S-selective retro-D-A reactions catalyzed by chiral imidazolethioles were studied [38]. The process between cyclopentadiene and cinnamaldehyde was carried out in a methanol-water or methyl cyanide-water solvent system with a high yield of adduct and good enantioselectivity according to the scheme:

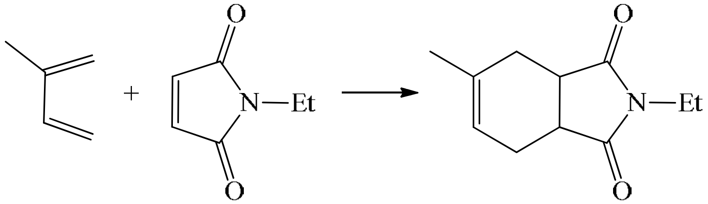


The yield of the adduct is 85-96%, e.e. 56-95%.
The ratio of exo: endo = 1.1: 1 - 1.3: 1. The catalyst used was

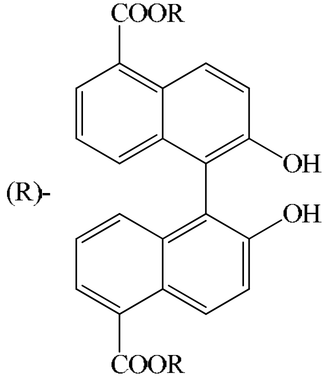


R_1 = Benz, indolyl
R_2 = H, CH_3, Cyclohexyl
R_3 = CH_3, t-Butyl, Cyclohexyl

A new homochiral porous metal-organic complex (MOF) was synthesized on the basis of (R) -2,21-dihydroxy-1,11-binaphthyl-4,41-dibenzoic acid as a chiral ligand [39]. It was shown that this complex is an effective heterogeneous catalyst for the enantioselective D-A reaction between isoprene and N-ethylmaleimide according to the scheme:



The catalyst used was a complex of the type:



The reaction was carried out at a temperature of 200°C for 24 hours in the presence of various solvents. The authors give the results of the studies in the form of table 1.

The authors also studied the effect of the catalyst in this reaction in the presence of the solvent AcOEt at 0^0C for 48 hours. The results of these studies are given in table 2.

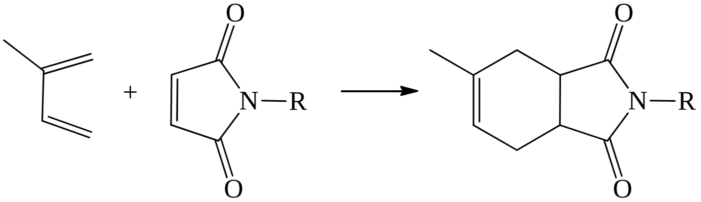
Table 1 – Effect of solvents on the yield and enantiomeric composition of the adduct in the reaction of isoprene with N-ethylmaleimide

Solvents	Yield of adduct, %	E.e., %
Methanol	48	0
Ethanol	66	21
Isopropanol	87	33
AcOEt	49	71
$CHCl_3$	85	13
Toluene	77	21
Cyclohexane	59	63
n-Hexane	80	31

Table 2 – Effect of catalyst on the yield and enantiomeric composition of the adduct in the reaction of isoprene with N-ethylmaleimide

Catalyst	Yield of adduct, %	E.e., %
–	10	0
$Cu(OAc)_2$	25	0
(R)- BINOL	21	0
$Cu(OAc)_2$ + (R)- BINOL	10	0
(R)-MOF	81	75

In conclusion, the authors also studied the effect of the substituent R in N-alkylmaleimide in the same reaction in the presence of an AcOEt solvent at 0^0C for 48 hours.



The results of these studies are presented in table 3.

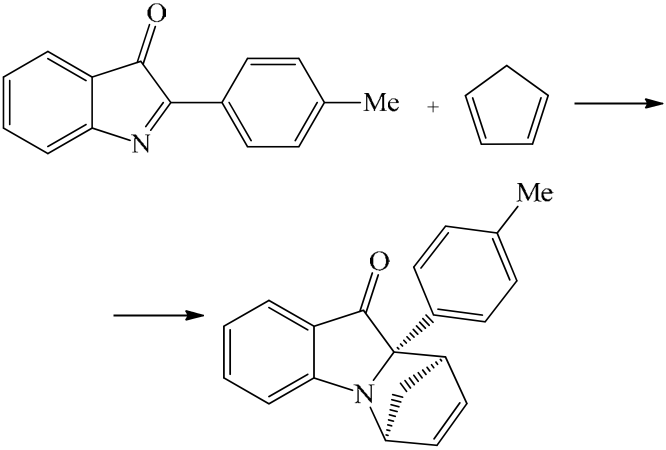
Table 3 – Effect of substituent R on the yield and enantiomeric composition of the adduct in the reaction of isoprene with N-alkylmaleimide

Substituent R	Yield of adduct, %	E.e., %
Me	37	87
Et	31	75
n-Pr	11	5
Ph	17	7
Cyclohexyl	18	0

It was shown in [40] that imino reactions of DA are an effective method for the synthesis of aza-heterocycles Zn / BINOL complex was used as catalysts.

The hetero-D-A reaction between o-quinone methides and azlactones has been studied, leading to the formation of important pharmacophore dihydrocoumarins catalyzed by the Sc (III) N, N1-Sci-III chiral complex [41]. It was shown that the reaction proceeds with a high diastereoisomer and enantioselectivity (94% ee, adduct yield 96%, diastereomer ratio 19: 1).

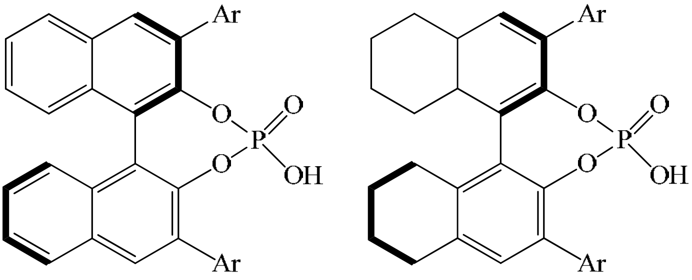
The catalyzed aza-reaction of D-A cyclic C-acylimines with cyclopentadiene catalyzed by new chiral acids of Brönsted [42]. As a result of the reaction, optically active aza-tetracycles with good yields and high diastereo- and enantiostereoselectivity are formed under moderate reaction conditions according to the scheme:



The reaction was carried out at a temperature of (-78^0) C and a duration of 2-16 hours in the presence of a solvent (toluene, a mixture of toluene and hexane, CH_2 Cl_2, $CHCl_3$). and 1-5 mol. % of catalyst.

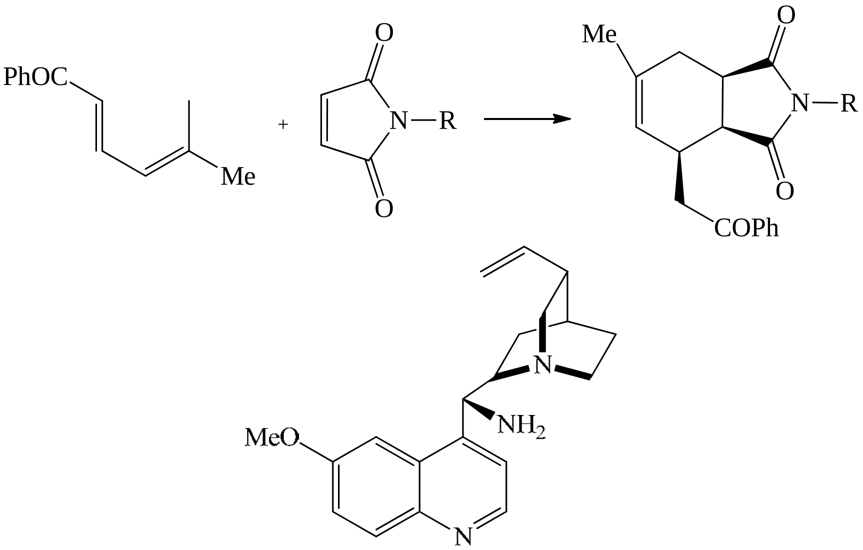
The yield of the adduct was 73-91%, e.e. 8-94%.

Trieneamine intermediates were used as chiral catalysts in the asymmetric reaction DA according to the scheme:



where R = H, CH_3, Ph.

The reaction was carried out at a temperature of 60^{0}C in toluene medium in the presence of the following catalyst:



Thus, the presented literature review shows that the use of chiral organic catalysts in the DA reaction continues to develop intensively and the number of works devoted to these studies is continuously growing.

In our studies, N-methylpyrrolizidone derivatives, which can be considered as one of the new versions of catalytic systems in the diene synthesis reaction, will be used as catalysts in the DA reaction.

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Резюме

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ДИЛЬС-АЛЬДЕР РЕАКЦИЯСЫНДАҒЫ ХИРАЛЬДЫ ОРГАНИКАЛЫҚ КАТАЛИЗАТОРЛАР

Диенді синтездеу реакциясында хиральды органикалық катализаторларды қолдану саласындағы ғылыми зерттеулерге талдау жүргізілді. Өндірістің әртүрлі салаларында синтезделген аддуктерді қолдану бағыттары көрсетілді. Қолданылған катализаторлардың стерео- және энантиоселективті реакцияларға әсері зерттелді.

Түйін сөздер: диенді синтез, хиральды органокатализаторлар, оптикалық белсенді қосылыстар.

Резюме

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ХИРАЛЬНЫЕ ОРГАНИЧЕСКИЕ КАТАЛИЗАТОРЫ В РЕАКЦИИ ДИЛЬСА-АЛЬДЕРА

Осуществлен анализ научных исследований в области применения хиральных органических катализаторов в реакции диенового синтеза. Показаны направления применения синтезированных аддуктов в различных отраслях промышленности. Изучено влияние использованных катализаторов на стерео- и энантиоселективность реакций

Ключевые слова: диеновый синтез, хиральные органокатализаторы, оптически активные соединения.