

# Asymmetric Induction in Catalyzed Synthesis of Organic Compounds as an Important Stage in the Evolution of Life on Earth

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**Abstract**—It is shown that natural chiral catalysts, which could be formed e.g., from optically active amino acids on basic natural minerals, could lead, at early stages of evolution, to the formation of rather complex optically active products from starting achiral compounds. Using biomimetic combinations of vanadium ion complexes and chiral ligands synthesized from widely occurring natural compounds, we created novel catalytic systems, permitting the transfer of optical activity in the course of catalytic chemical transformations of achiral compounds. We found that in the presence of natural clay, optically active terpenoids from the pinane series undergo multistage transformations, forming unexpected new products with preservation of optical purity.

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## INTRODUCTION

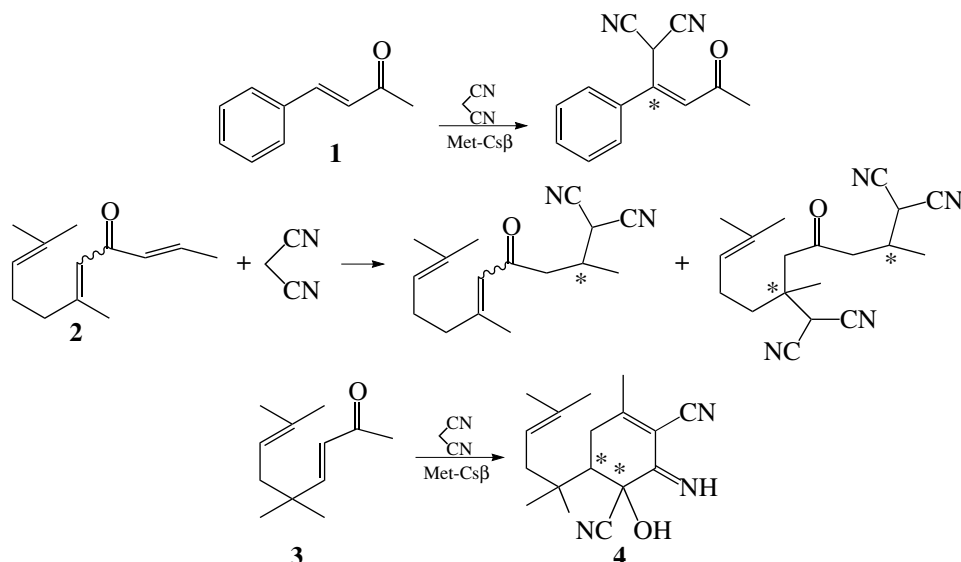
The problem of how chirality arises in nature and how it is preserved in complex compounds formed from simple ones is a key issue in the understanding of the origin and evolution of life on earth. Even if we assume that the first chiral molecules (primarily, chiral amino acids) were brought from space (Macdermott, 2002), the transfer of optical activity (asymmetric induction) from small molecules of abiogenic origin to more complex molecules essential to the emergence of life is an open question.

One of the possible mechanisms of asymmetric induction is participation of simple asymmetric molecules in creation of heterogeneous or homogeneous cat-

alysts capable of promoting the formation of optically active products apart from accelerating acid- or base-catalyzed transformations or redox reactions. Possible catalysts for these processes include, for example, natural clays and zeolites bearing natural chiral compounds.

To verify this assumption, we undertook efforts to modify basic zeolite Csβ, which is a more active model of natural basic zeolites, using the natural optically active amino acid L-methionine. The resulting chiral catalyst Met-Csβ proved to be an effective catalyst for reactions of malononitrile with various achiral compounds (benzalacetone (**1**) and several α,β-unsaturated carbonyl compounds from the terpenoid series (**2**, **3**)) (Scheme 1). All the products with asymmetrical centers possess optical activity.

Scheme 1:

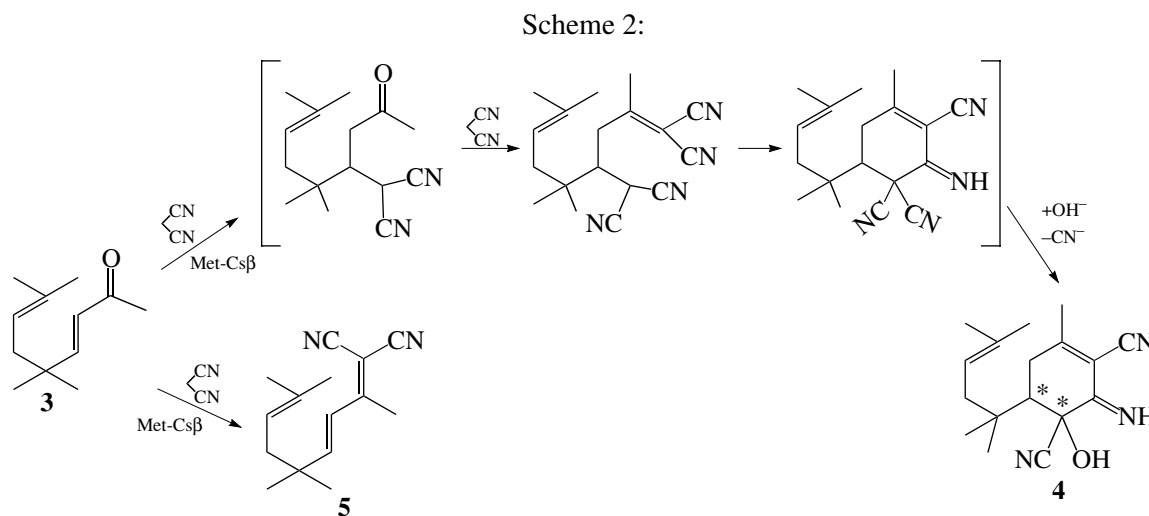


**Table 1.** Interaction of ketone (**3**) with malononitrile

No.	Catalyst	Conversion, %	Reaction time, day	Yield <sup>a</sup> , %		[ $\alpha$ ] <sub>D</sub> <sup>20</sup> ( <b>4</b> )	ee, %
				( <b>4</b> )	( <b>5</b> )		
1	Cs $\beta$	73	2	7	40	0	0
2	Cs <sub>x</sub> O <sub>y</sub>	100	2	0	30	–	–
3	Met-Cs $\beta$ (8 wt % L-methionine)	98	14	10	28	+11°	3.3
4	Met-Cs $\beta$ (11 wt % L-methionine)	67	28	11	44	+20°	6
5	Met-Cs $\beta$ (14 wt % L-methionine)	100	18	25	5	0	0
6	Cesium L-methionate	100	18	15	10	0	0

Note: <sup>a</sup> Yield given based on the changed terpenoid (**3**).

It is noteworthy that an optically active product (**4**) was synthesized even in multistage tandem transformations (Scheme 2).



For several products, optical purity was determined by <sup>1</sup>H NMR using a chiral shift reagent. The enantiomeric excess (ee) of one of the isomers varied from 3 to 10% depending on the reaction conditions and the reagents used.

To establish the role of the structure of zeolite in the modified catalyst, reactions of benzalacetone (**1**) and ketone (**3**) with malononitrile were conducted on calcined cesium formate modified with L-methionine; alternatively, the reactions were carried out in the presence of cesium L-methionate. In both cases, the products isolated from the reaction mixture were optically inactive. Thus, the presence of a crystal structure in zeolite proved to be essential to enantioselective catalysis.

Let us see how the quantity of the amino acid applied to zeolite affected the course of the reaction with ketone (**3**).

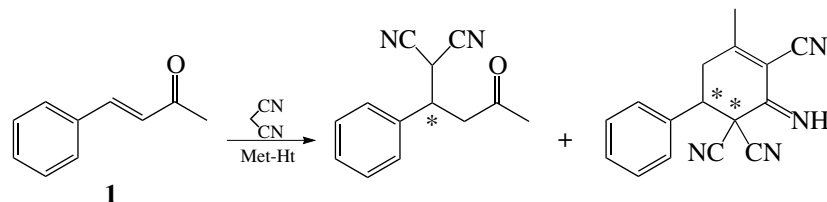
In the reaction of ketone (**3**) (Scheme 2) with malononitrile on modified Cs $\beta$  containing 8 wt % L-methionine, the product yields of (**4**) and (**5**) were 10 and 28%, respectively, while the starting compounds were fully converted (Table 1). Compound (**4**) isolated from the reaction mixture was optically active, its optical purity being 3.3%.

At a higher L-methionine content in the catalyst (11%), the total yield of reaction products increased to 55% (conversion 67%); the optical purity of the product of the tandem transformations polyfunctional compound (**4**) was 6%.

However, racemic compound (**4**) was the major product of this reaction when the L-methionine content increased to 14%. The absence of optically active products in this case may be explained by the fact that the crystal structure of zeolite did not affect the catalytic action of cesium methionate on the surface of zeolite because of the excessive amount of L-methionine applied to the latter (Table 1, nos. 5, 6).

Another basic chiral catalyst was prepared by applying cesium methionate to hydrotalcite (natural basic clay). The first results indicated that the products formed from benzalacetone (**1**) (Scheme 3) were optically active.

Scheme 3:



Note that all of the above transformations were conducted at room temperature, without a solvent; zeolites and clays were used in catalytic amounts.

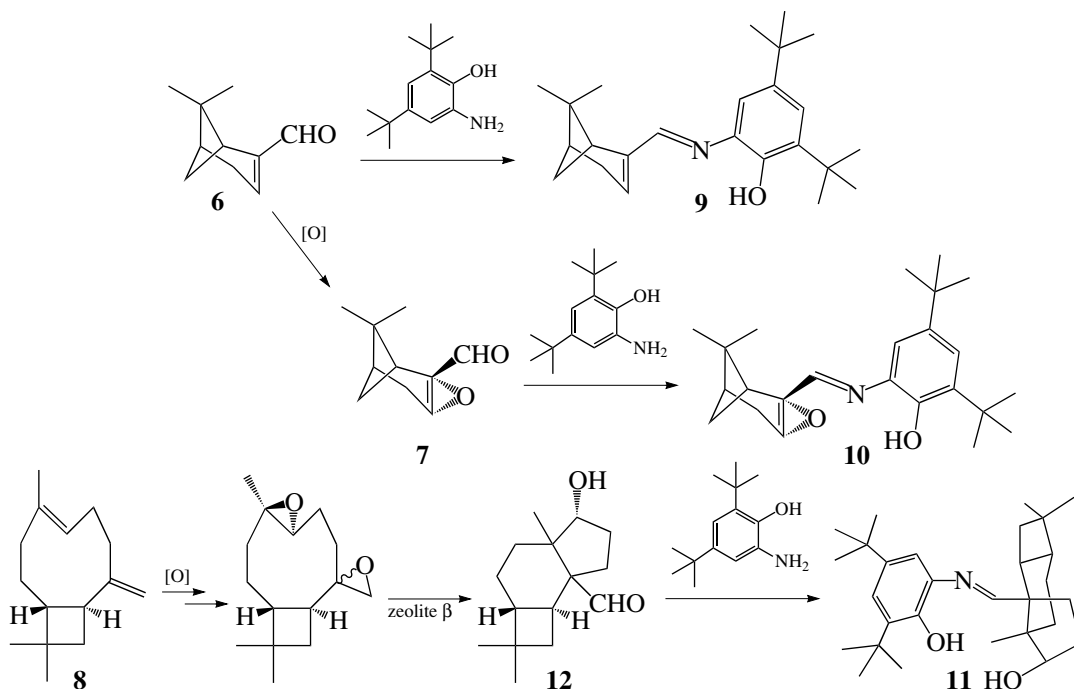
These results confirmed that natural chiral catalysts, which could be formed, e.g., from optically active amino acids on basic natural minerals, could lead, at early stages of evolution, to the formation of rather complex optically active products from starting achiral compounds.

In the homogeneous case, possible catalysts could be complexes of transition metal salts with natural compounds. Powell et al. (2003) assumed that, at early stages of evolution, transition metals such as tungsten and vanadium were widespread and accessible elements. Therefore, to study the applicability of homogeneous biomimetic asymmetric catalysis to synthesis of polyfunctional optically active sulfoxides (analogs of

complex natural compounds), we chose a metal complex catalytic system based on vanadium ions, which is often treated as a functional model of vanadium-dependent haloperoxidase. It is important that effective application of this system does not need special conditions hardly accessible in nature such as dry inert atmosphere or use of organic oxidants, as was the case with the widespread modified Sharpless systems (Volcho et al., 2003).

Three new chiral ligands—Schiff bases (compounds **9–11**)—were synthesized by the reactions of di-tert-butylaminophenol (scheme 4) with accessible and widely occurring natural compounds: monoterpene myrtenal (**6**), its epoxide (**7**), and sesquiterpene caryophyllene (**8**). Aldehyde (**12**), a key intermediate in the synthesis of compound (**11**), was prepared by the acid zeolite-catalyzed rearrangement of caryophyllene diepoxide.

Scheme 4:



The catalytic metal complex systems obtained *in situ* by the reaction between the above ligands and vanadium acetylacetonate showed high activity with simple model sulfides and complex polyfunctional compounds, oxidized with hydrogen peroxide into corresponding sulfoxides.

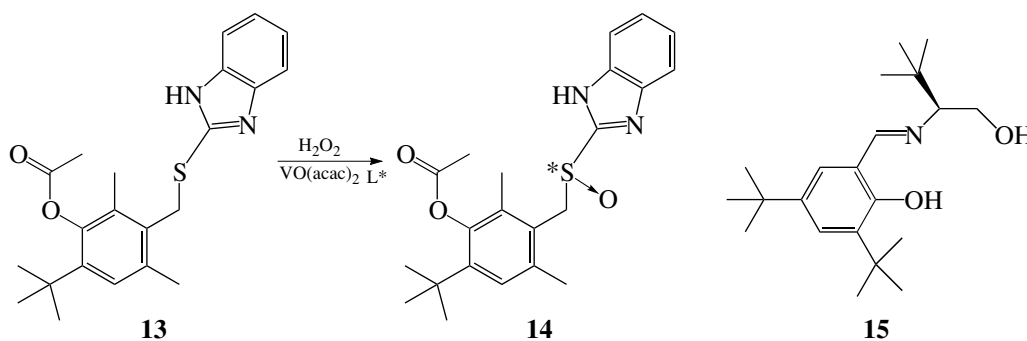
For example, when sulfide (**13**) was oxidized into sulfoxide (**14**) (Scheme 5), which is an analog of the antiulcer drug esomeprazol, using ligand (**11**) proved most effective with respect to the chemical yield, and ligand (**10**) with respect to the optical yield (Table 2). Importantly, using commercially available ligand (**15**), generally employed in asymmetric sulfoxidation sys-

**Table 2.** Asymmetric sulfoxidation of compound (**13**)

Ligand	Yield, %	$[\alpha]_D^{20}$	<i>ee</i> , %
<b>9</b>	68	1.5	1
<b>10</b>	60	-33	21
<b>11</b>	94	7.1	5
<b>15</b>	74	3.6	3

tems based on vanadium ion catalysis, proved less effective; the chemical yield of the product was moderate, and the optical yield was very low.

Scheme 5:



It is interesting that on passing from the catalytic system with compound (**9**) to the system with epoxide (**10**) the optical purity of the sulfoxide product drastically increased, and the sign of optical rotation of the sulfoxide product reversed.

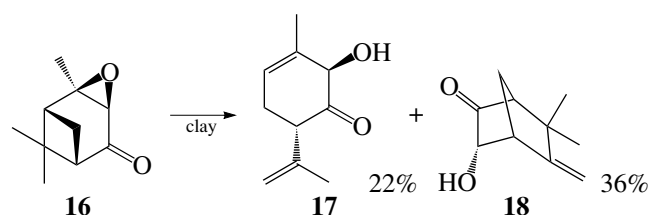
Thus, using biomimetic combinations of vanadium ion and chiral ligands synthesized from widely occurring natural compounds, we created novel catalytic systems permitting the asymmetric induction in the course of catalytic chemical transformations of achiral compounds.

Another mechanism that presumably formed complex optically active compounds at the dawn of life on Earth could involve intra- and intermolecular transformations of simple compounds in the presence of natural catalysts, of which clays were certainly most accessible. To model these processes we chose askanite-bentonite natural clay as an acid catalyst and pinane terpenoids as substrates. The choice of pinane compounds as objects of research was dictated by their extremely high lability in acid media, as well as the ability to undergo racemization in the presence of acid catalysts.

We found that in the presence of natural clay, oxygen-containing terpenoids from the pinane series often undergo multistage rearrangements, forming unex-

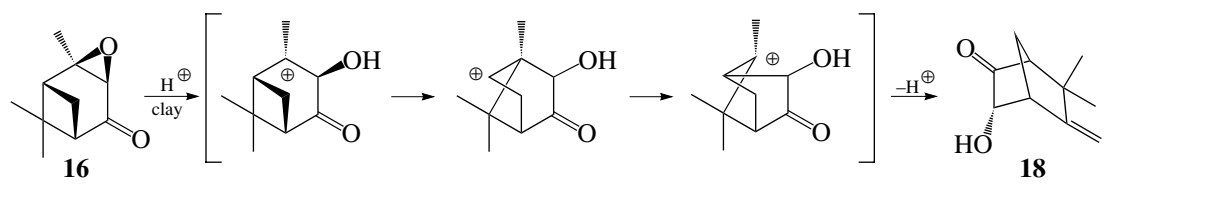
pected optically active products. For example, storage of verbenone epoxide (**16**) on clay gave compound (**17**) with a p-menthane framework, as well as an unusual ketoalcohol with a camphene framework—compound (**18**) (Scheme 6).

Scheme 6:



To explain how compound (**18**) formed in this process we suggested a sequence of complex rearrangements affecting the asymmetric centers and not observed previously for oxygen-containing pinenes (Scheme 7). A similar rearrangement takes place only for  $\alpha$ - and  $\beta$ -pinenes themselves, and the resulting camphene is a racemate. In this case, we selectively obtain one enantiomer.

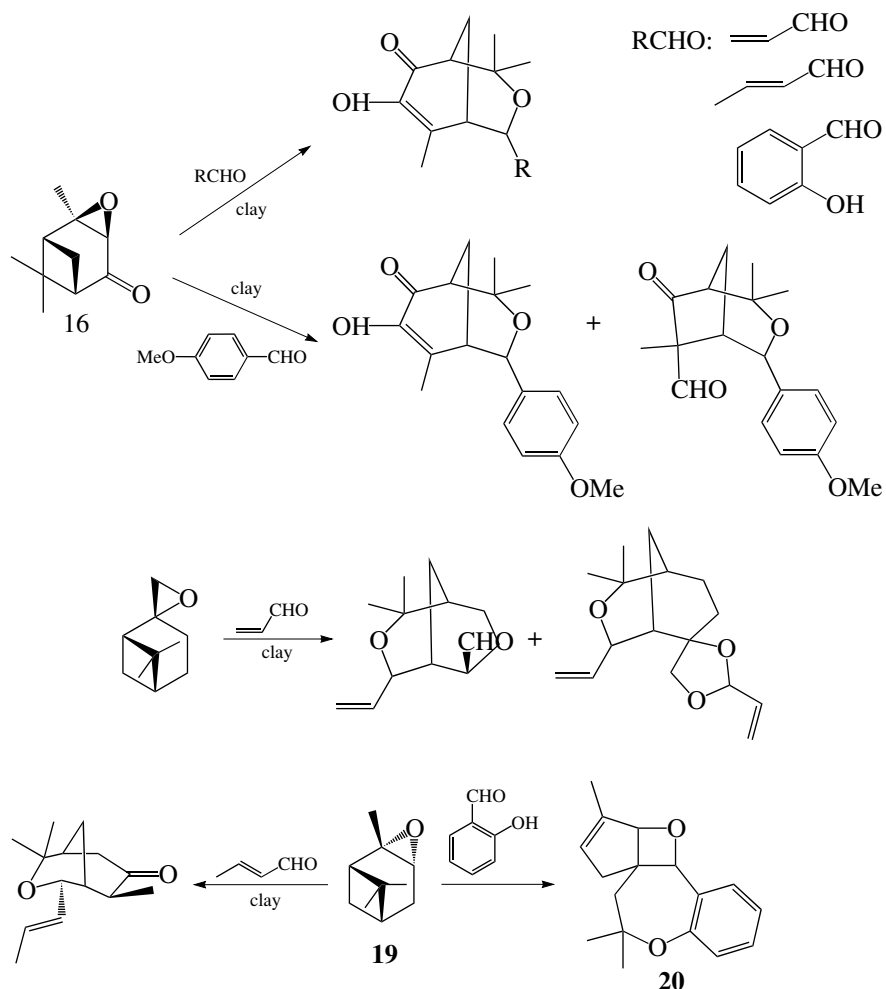
Scheme 7:



We succeeded in synthesizing a number of new optically active polycyclic ethers. Syntheses were performed by reactions of accessible oxygen-containing

terpenoids from the pinane series with aldehydes in the presence of askanite-bentonite natural clay (Scheme 8).

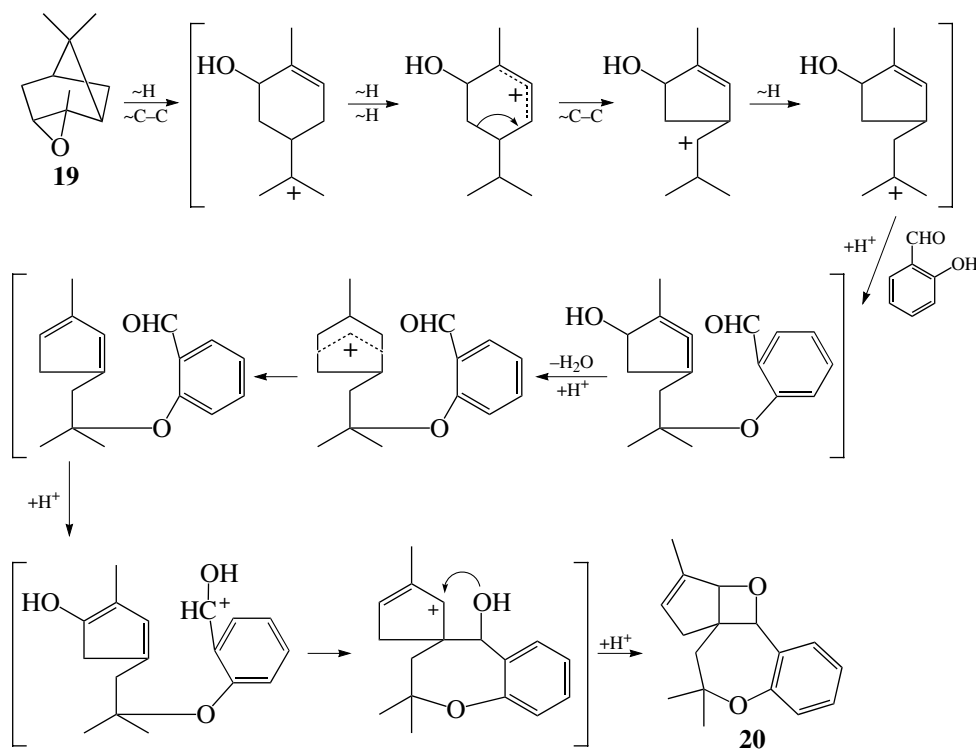
Scheme 8:



To explain the transformation of  $\alpha$ -pinene epoxide (**19**) and salicylic aldehyde to polyheterocyclic compound (**20**) with seven-, six-, five-, and four-membered

rings in its structure we suggest a number of multistage rearrangements (Scheme 9), selectively forming a complex optically active product.

Scheme 9:



Thus, in the presence of natural clay optically active pinane derivatives undergo multistage transformations, forming new unexpected products with preservation of optical purity.

### CONCLUSIONS

Thus, our study has demonstrated that complex transformations of natural compounds can take place in the presence of heterogeneous natural acid catalysts, with products retaining the optical activity of the substrate. Based on a combination of natural basic heterogeneous catalysts or their analogs and natural chiral compounds, as well as vanadium ion complexes and chiral ligands synthesized from widely occurring natural compounds, we created new asymmetric catalytic systems to model natural systems that possibly formed complex optically active products from achiral starting compounds at the earliest stages of evolution.

### ACKNOWLEDGMENTS

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### REFERENCES

1. A. J. Macdermott, "The Origin of Biomolecular Chirality," in *Chirality in Natural and Applied Science*, Ed. by W. J. Lough and I. W. Wainer (Blackwell Science, Oxford, 2002).
2. W. G. Powell, P. A. Johnston, and C. J. Collom, *Palaeogeogr., Palaeoclimatol., Palaeoecol.* **201**, 249–268 (2003).
3. K. P. Volcho, N. F. Salakhutdinov, and A. G. Tolstikov, "Metal Complexes in Asymmetric Oxidation of Sulfides," *Zh. Org. Khim.* **39** (11), 1607–1622 (2003) [*Russian J. Org. Chem.* **39** (11), 1537–1552 (2003)].