Chemistry for Sustainable Development **16** (2008) 433–439

Effect of Csβ Zeolite Modification by Chiral Substances on the Course of 5,5,8-Trimethylnona-3,7-diene-2-one Reaction with Malonitrile

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(Received March 6, 2008; revised April 1, 2008)

Abstract

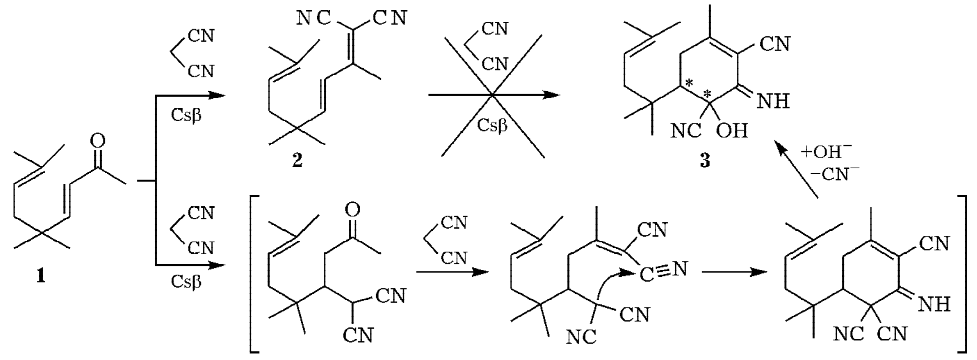
Influence of the nature and amount of a chiral modifier applied onto zeolite Csβ upon the product ratio and enantioselectivity has been investigated for the reaction between 5,5,8-trimethylnona-3,7-diene-2one and malonitrile. The catalysts synthesized have allowed us to obtain for the first time optically active 1-hydroxy-2-imino-4-methyl-6-(1,1,4-trimethylpent-3-enyl)-cyclohex-3-ene-1,3-dinitryle.

Key words: basic zeolite, chiral heterogeneous catalysis, malonitrile, terpenoids, Michael reaction

INTRODUCTION

Earlier we have shown that basic zeolite Csβ is efficient enough heterogeneous catalyst for the reactions of α,β-unsaturated carbonyl compounds of the terpenoid series with malonitrile [1, 2]. The reactions were carried out without solvent; the catalyst could be used repeatedly with no loss of catalytic activity. For example, during the interaction of ketone **1** with malonitrile in the presence of zeolite Csв (Scheme 1) the Knoevenagel and Michael competing reactions occur resulting in the formation of products **2** and **3**, in this connection the Michael reaction initiates the tandem transformations those give rise to the formation of a complex polyfunctional compound **3**. The mechanism suggested for the formation of compound **3** is supported by the fact that keeping compound **2** under the conditions of the reaction with malonitrile does not result in the formation of any products, the initial dinitrile **2** returning in the unchanged form.

It should be noted that compound **3** being complex enough in structure contains a number of various functional groups which compound is of a considerable interest for studying its biological activity. It is known that the



Scheme 1.

TABLE 1

Reaction between ketone **1** and malonitrile

No.	Catalyst	Conversion level, %	Reaction time, days	Yield,[a] %		Ratio	$[\alpha]_D^{20}$	*ee*[b], %
				2	**3**	**2/3**	**3**	
1	Csβ	73	2	40	7	5.7	–	–
2	8 % *l*-Met-Csβ	98	14	28	10	2.8	+11	3.3
3	11 % *l*-Met-Csβ	67	28	44	11	4	+20	6
4	14 % *l*-Met-Csβ	100	18	5	25	0.2	0	0
5	*l*-Met-Cs	100	18	10	15	0.67	0	0
6	Cs_xO_y	100	2	30	0	–	–	–
7	8 % *l*-Met-Csβ[c]	88[c]	18	–[c]	9	–	0	0
8	11 % *l*-Met-Csβ[d]	95	14		10		+	6

Note. Here and in Table 2: the number in the names of modified zeolites stands for the amount of modifier applied onto zeolite (mass %); an abbreviation or a figure after a symbol of percentage designates the type of a modifier applied.

[a] The yield calculated with respect to ketone **1** reacted or for dinitrile **2**.

[b] The value determined according to ^{1}H NMR spectra with the addition of Eu(hfc)$_3$ as a chiral shifting reagent.

[c] Compound **2** was used as the initial substance.

[d] Compound **3** was used as the initial substance.

compounds containing the CN group in в position with respect to the nitrogen atom exhibit antitubercular [3] and anticancer [4] activity. Unfortunately, the main product of ketone **1** and malonitrile interaction in the presence of zeolite Csβ is compound **2**, whereas polyfunctional compound **3** is formed in small amounts (7 %) (Table 1).

The occurrence of the asymmetric centres in the products of the Michael reaction and tandem transformations those take place during the interaction of α,β-unsaturated carbonyl compounds of terpenoid series with malonitrile in the presence of zeolite Csβ, has motivated us to the creation heterogeneous asymmetric catalysts based on Csβ.

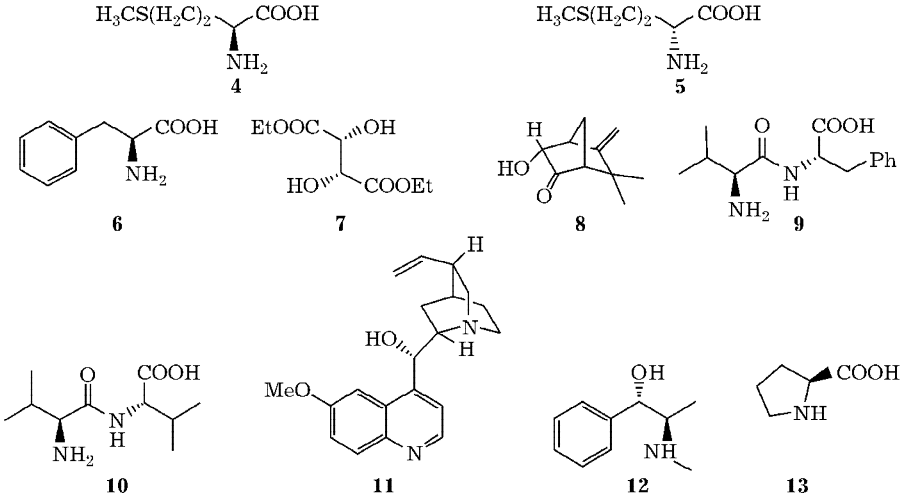
As a rule, various metal complex homogeneous catalysts are used for asymmetric catalysis of the Michael reaction [5]. However, the application of homogeneous chiral catalysts in the Michael reaction quite often results in low selectivity, complications in the isolation of products. Moreover, these catalysts are difficult to regenerate. At the same time the use heterogeneous catalysts allows one to avoid these disadvantages inherent in homogeneous systems. It should be noted that there are no heterogeneous chiral catalysts nowadays those could be used for the asymmetric catalysis of the reactions of non-chiral α,β-unsaturated carbonyl compounds with malonitrile.

There is a description of several heterogeneous chiral catalysts available in the literature those are based on the modification of zeolites by optically active compounds. The authors of [6] carried out the Norrish–Young photoreaction on NaX and NaY zeolites modified with (–)- and (+)-ephedrine. G. J. Hutchings [7] modified HY zeolite with chiral 1,3-dithiane-1-oxide and studied obtained the dehydration reaction on the zeolite for the mixture of *S*- and *R*-isomers of butane-2-ol. We revealed no examples in the literature concerning the application of chiral compounds onto zeolites with the purpose of obtaining asymmetric basic catalysts.

The purpose of the present work consisted in studying the influence of the nature of chiral modifier applied onto zeolite Csβ upon the ratio between products and upon optical purity of polyfunctional compound **3** formed due to the interaction of non-chiral 5,5,8-trimethylnona-3,7-diene-2-one with malonitrile.

EXPERIMENTAL

Zeolite Csβ has been prepared according the technique described in [1]. The product obtained has been characterized using the methods of powder X-ray diffractometry (HZG-4 diffractometer, CuK_α radiation), elemental analysis (BLIRD ICP spectrometer) and argon adsorp-



Scheme 2.

tion at 77 K. The Csβ zeolite obtained exhibited the chemical composition such as $Cs_{4.47}[Al_{4.47}Si_{59.53}O_{128}] \cdot 8.84Cs_2O$. The free surface area of Csβ after calcination at 500 °C amounted to 51 m^2/g.

We used the following chiral modifiers in the experiments (Scheme 2): *l*-methionine **4** (*l*-Met) (Fluka, *ee* ≥ 99 %), *d*-methionine **5** (*d*-Met) (Aldrich, *ee* 99 + %), *l*-phenylalanine **6** (*l*-Phe) (Acros, *ee* 98.5 + %), *l*-diethyltartrate **7** (*l*-DET) (Aldrich, *ee* 99 + %), compound **8** [8] (*ee* 64 %), *l*-valine-*l*-phenylalanine **9** (*l*-Val-*l*-Phe), *l*-valine-*l*-valine **10** (*l*-Val-*l*-Val), (−)-quinine **11** (Fluka, *ee* ≥ 98 %), (−)-ephedrine **12** (Fluka, *ee* ≥ 98 %), *l*-proline **13** (Z-Pro) (Alfa Aesar, *ee* 99 %), as well as malonitrile (Acros, 99 + %) and 5,5,8-trimethylnona-3,7-diene-2-one synthesized using the technique described in [9].

Dipeptides **9** and **10** were synthesized using the standard method of mixed anhydrides [10]. Methyl ester of *l*-valine was condensed with corresponding N-*tert*-butoxycalbonyl-(N-Boc)-*l*-aminoacids under the action of isobutyl chloroformate. Then, after saponifying the ester groups (NaOH/THF/H_2O) and removing the Boc group (2 M HCl/CH_3COOH), we obtained dipeptide hydrochlorides.

General preparation technique for heterogeneous chiral catalysts

To 0.1 g of zeolite Csβ was added a calculated amount of a modifier in 10 mL of a solvent. In the cases of *l*-diethyltartrate **7** (*l*-DET) and ketoalcohol **8** we used diethyl ether as the solvent, whereas for *l*-methionine **4** (*l*-Met), *d*-methionine **5** (*d*-Met), *l*-phenylalanine **6** (*l*-Phe), (−)-quinine **11**, (−)-ephedrine **12** and *l*-proline **13** (*l*-Pro) we used methanol. In order to apply the peptides such as *l*-valine-*l*-phenylalanine **9** (*l*-Val-*l*-Phe) and *l*-valine-*l*-valine **10** (*l*-Val-*l*-Val) onto zeolite Csβ we used 3 % methanol solution in chloroform. The suspension obtained was stirred during 30 min, and then the solvent was distilled off. The catalysts were held before using under vacuum (0.07 Torr) at 50 °C during 2 h.

General technique for carrying out the reaction of 5,5,8-trimethylnona-3,7-diene-2-one 1 with malonitrile

To 0.05 g of a basic chiral catalyst was added a solution of 0.144 g (2.2 mmol) of malonitrile in 2 mL of diethyl ether. The solvent was removed using a rotary evaporator, and then have added 0.106 g (0.6 mmol) of ketone **1** was added. The reaction mixture was held at room temperature during necessary time (see Tables 1 and 2), and then the extraction with ethyl acetate from the catalyst was performed. The catalyst was filtered. The solvent was removed using a rotary evaporator. The separation of reaction products was carried out with the help of column chromatography on siica gel (Merck, 60−200 μm); diethyl ether in hexane (from 0 to 100 %) was used as an eluent. The ratio of crude product to the adsorbent ranged within

TABLE 2

Reaction between ketone **1** and malonitrile in the presence of various chiral catalysts

No.	Catalyst	Conversion level, %	Reaction time, days	Yield[a], %			Ratio	$[\alpha]_D^{20}$	ee[b], %
				2	**3**	Total	**2/3**		**3**
1	11 % *d*-Met-Csβ	92	7	46	22	68	2.1	–	5
2	12 % *l*-Phe-Csβ	95	14	32	29	61	1.1		0
3	*l*-Val-*l*-Phe[c]	100	24	22					–
4	11 % *l*-Val-*l*-Phe-Csβ	100	7	41	9	50	4.6	+	2
5	11 % *l*-Val-*l*-Val-Csβ	97	7	28	19	47	1.5	+	3
6	12 % *l*-DET-Csβ	98	14	34	23	57	1.5	+	2
7	17 % *l*-DET-Csβ	98	14	46	7	53	6.5	+	1
8	11 % 8-Csβ	96	14	14	10	24	1.5	+	1.5
9	15 % 8-Csβ	98	57	20	6	26	3.3	+	1
10	11 % (–)-Quinine-Csβ	99	14	20	10	30	2.1	+	2
11	11 % (–)-Ephedrine-Csβ	95	14	46	10	56	4.6		0
12	11 % *l*-Pro-Csβ	97	14	46	17	63	2.7	+	10
13	Caesium *l*-prolinate	100	12	37	3	40	12.3	0	

[a] The yield calculated with respect to ketone **1** reacted or for dinitrile **2**.

[b] The value determined according to ^{1}H NMR spectra with the addition of Eu(hfc)$_3$ as a chiral shifting reagent.

[c] The reaction was carried out in the mixture of DMSO : H_2O ~ 1 : 1.

1/20–1/50. The joining of individual fractions was carried out basing on TLC data (Sorbfil plates, STH-1VE silica gel 8–12 μm size used as the stationary phase, hexane : ethyl acetate mixture 3 : 1 being used as an eluent). ^{1}H NMR spectra of compounds **2** and **3** those we have isolated from the reaction mixtures coincided with the spectra presented in [1].

The optical purity of compound **3** formed was determined according to ^{1}H NMR spectra with a chiral shift reagent such as europium (III) [tris-(3-(heptafluoropropylhydroxo-methylene))]-*d*-camphorate. We took about 2 mg of the europium complex (~0.22 equivalents) for 1 mg of compound **3**. NMR spectra were registered using an AM-400 spectrometer (Bruker) with working frequency of 400.13 MHz (^{1}H) for the solutions of substances in the mixture of $CDCl_3$ and CCl_4 (~1 : 1 in volume). The signal of chloroform (δ_H = 7.24 ppm) was used as an internal standard. The results obtained are presented in Tables 1 and 2.

RESULTS AND DISCUSSION

Zeolite Csβ under our use has caesium oxide clusters included in the structure (the content of caesium amounting to about 34 mass %) [1]. At the first stage we have chosen *l*-methionine **4** as a chiral modifier. Due to the interaction with caesium oxides, this substance converted into caesium methionate that is insoluble in low-polarity solvents and being reliably retained on the surface of zeolite.

The use of zeolite Csβ modified with *l*-methionine **4** (*l*-Met-Csβ) has allowed us to obtain for the first time optically active products in the interaction of initially non-chiral α,β-unsaturated carbonyl compounds with malonitrile under the conditions of heterogeneous catalysis [11, 12] (see Table 1). By the example of *l*-Met-Csβ zeolite use as the catalyst of the reaction between ketone **1** and malonitrile we have demonstrated that has basic zeolite Csβ containing less than 15 % of *l*-methionine **4** exhibits quite satisfactory catalytic activity.

The increase in the content of *l*-methionine **4** in zeolite Csβ from 8 to 11 mass % results in an increase in the optical purity of compound **3** formed from 3 up to 6 % (see Tables 1, Nos. 2 and 3). The further increase in the content of *l*-methionine **4** in zeolite Csβ up to 14 % results in the formation of racemic compounds **3** (see Table 1, No. 4). This fact could be explained by that that owing to excessively much *l*-methionine **4** applied onto zeolite the reaction is catalyzed by caesium methionate located on the surface of zeolite with no influence of zeolite crystal structure.

This assumption can be supported by the fact that running the reaction between ketone **1** and malonitrile in the presence of caesium oxides modified with *l*-methionine **4** also results in the formation of optically inactive compound **3** (see Table 1, No. 5). Thus, the presence of zeolite crystal structure is an important condition for enantioselective catalysis to occur.

It is interesting that carrying out the reaction between ketone **1** and malonitrile in the presence of caesium oxides non-modified by methionine results in the formation of the only dinitrile **2** [1] (see Table 1, No. 6).

It should be noted that when *l*-Met-Csβ containing 8 mass % of *l*-methionine **4** is used as a catalyst, dinitrile **2** reacts with malonitrile (see Table 1, No. 7) to form compound **3**, whereas in the presence of non-modified Csβ zeolite the reaction does not occur [1] (see Table 1, No. 1). The compound **3** formed appeared racemic substance therefore from the standpoint of achieving high enantioselectivity this process is undesirable.

In order to verify the assumption of possible change in optical purity of the product formed in the reaction, for example, due to its racemization or kinetic separation we have held compound **3** over 11 % *l*-Met-Csβ catalyst under the reaction conditions of during 14 days. This has resulted in significant resinification of compound **3** (only 10 % of compound **3** was returned) with no change in its optical purity (see Table 1, No. 8).

The amount of *l*-methionine **4** applied onto zeolite exerts a significant effect not only on the optical purity of compound **3**, but also on the ratio between products formed. So, the increase in the amount of applied *l*-methionine **4** from 8 up to 14 % results in a 2.5-fold increase in the yield of compound **3** (see Table 1, Nos. 2 and 4).

The use of *d*-methionine **5** as a chiral modifier has resulted in changing optical rotation to opposite with almost same *ee* value for multifunctional compound **3** formed (see Table 2, No. 1).

Searching for a more efficient optically active modifier we used another optically active α-amino acid instead of methionine such as *l*-phenylalanine **6**, however, the compound **3** obtained appeared racemic one. It should be noted that the use of *l*-phenylalanine **6** as the modifier of zeolite results (at the total yield of compounds **2** and **3** comparable to that for 11 % *l*-Met-Csβ) in a considerable increase in the yield of compound **3**, from 11 up to 29 % (see Table 2, No. 2).

For the last years there have been the works appeared those are devoted to using peptides as homogeneous catalysts for basic-catalyzed reactions [13, 14]. Earlier dipeptide *l*-Val-*l*-Phe **9** was successfully used as the catalyst for aldol condensation of cyclohexanone with *p*-nitrobenzaldehyde [14], the reaction was carried out in the mixture such as DMSO : H_2O ~ 1 : 1. The case of our performing the reaction between ketone **1** and malonitrile under the same conditions results in the formation of the only Knoevenagel reaction product from compound **2** with a low yield as low as 22 % (see Table 2, No. 3).

The use of the mentioned peptide as a modifier of zeolite Csβ results in an increase in the yield of dinitrile 2 up to 41 % as well as in the formation of compound **3** with the yield of 9 % (see Table 2, No. 4). Modifying Csβ zeolite with another dipeptide such as *l*-Val-*l*-Val **10** gives rise to a decrease in the yield of compound **2** down to 28 %, however, in this case an increase in the yield of compound **3** up to 19 % is observed (see Table 2, No. 5). The optical purity of compound **3** in both cases amounted to 2–3 %. It should be noted that the values of enantiomer surplus equal to 1–2 % are near the validity margin of determination.

In connection with the fact that the use of compounds containing the basic groups as chiral modifiers, can result in the formation of racemic compound **3** due to the interaction between dinitrile **2** and malonitrile, say, in the case of *l*-methionine, we have decided to use optically active modifiers those contain no nitrogen atoms such as compounds **7** and **8**.

Such compound as *l*-diethyltartrate **7** is already applied successfully for a long time as a ligand for asymmetric catalysis [15]. The use of zeolite Csβ containing 12 mass % of *l*-DET results in the formation of dinitrile **2** (34 %), as well as of multifunctional compound **3** with the yield of 23 %, however with a low optical purity (see Table 2, No. 6). The increase in the amount of *l*-DET applied onto zeolite up to 17 % results in a significant decrease in the yield of compound **3** down to 7 %, with an increase in the yield of dinitrile **2** up to 46 % (see Table 2, No. 7). The compound **3** obtained has appeared almost racemic one.

A similar situation is also observed in the case of using bicyclic ketoalcohol **8** (see Scheme 2) as a chiral modifier that contains two vicinal oxygen atoms in the structure as in the case with *l*-diethyltartrate. The increase in the amount of compound **8** applied onto zeolite from 11 up to 15 % (see Table 2, Nos. 8 and 9) results in a certain increase in the yield of dinitrile **2** as well as in a more than 1.5-fold decrease in the yield of compound **3**. The total yield of compounds **2** and **3** appeared approximately 2 times lower than in the case of using *l*-DET-Csβ zeolite as a catalyst. In both the cases of using 8-Csβ the compound **3** formed is characterized by very low optical purity.

The paper [16] describes the use of (−)-quinine **11** and its derivatives as homogeneous asymmetric catalyst of the Michael reaction between benzalacetophenone and various CH acids. Our application of (−)-quinine **11** as a chiral modifier of zeolite Csβ results in the formation of both dinitrile **2** (20 %), and compound **3** (10 %) with the low enantiomer surplus amounting to 2 % only (see Table 2, No. 10).

Such compound as (−)-ephedrine **12** was used earlier as a chiral catalyst for the Michael reaction between benzalacetophenone and thiophenol [17]. Our use of zeolite Csβ modified with (−)-ephedrine **12** as a catalyst resulted in the formation of dinitrile **2** with a good enough yield (46 %), as well as of racemic product **3** whose yield amounted to 10 % (see Table 2, No. 11).

Recently many works have appeared those are devoted to the use of proline **13** and its derivatives as catalysts for the Michael reaction [18–20]. Our use of *l*-proline **13** as an optically active modifier of zeolite Csβ to the extent of 11 % has resulted in an increase in the *ee* of compound **3** up to 10 %. It is the best result we achieved for the present time (see Table 2, No. 12). The yield of compound **3** amounted to 17 %.

Verifying the assumption that the presence of zeolite crystal structure is required for occurring enantioselective catalysis we have run the reaction between ketone **1** and malonitrile in the presence of caesium *l*-prolinate. Compounds **2** and **3** (see by Table 2, No. 13) have been isolated from the reaction mixture. As in the case of use of caesium *l*-methionate as a catalyst (see Table 1, No. 5), the obtained compound **3** appeared racemic one. Obviously, the presence of zeolite crystal structure represents an important factor for enantioselective catalysis to occur.

CONCLUSION

Using the modification of basic zeolite Csβ with various optically active compounds we have prepared a set of novel basic chiral catalysts suitable for carrying out the reactions of α,β-unsaturated carbonyl compounds with CH acids. It is demonstrated by the example of the reaction between 5,5,8-trimethylnona-3,7-diene-2-one and malonitrile that the presence of zeolite crystal structure represents an important condition for the asymmetric catalysis. It has been revealed that the nature of modifier exerts a profound effect both on the ratio between the products of ketone **1** and malonitrile reaction, and on the optical purity of compound **3**.

The highest yield of compound **3** (29 %) was observed with the use of zeolite Csβ modified with *l*-phenylalanine **6**, whereas the best value of enantiomer excess (10 %) was observed for *l*-Pro-Csβ catalyst. The optical purity of compound **3** formed with the use *l*-proline modified Csβ zeolite as the catalyst, is comparable with optical purity of the products obtained using neutral and acidic zeolites modified by chiral compounds in photochemical and acid catalyzed reactions.

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