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Enantioselective telomerization

I. Telomerization of butadiene with formaldehyde, β-dicarbonyl compounds, nitroalkanes, and enamines *

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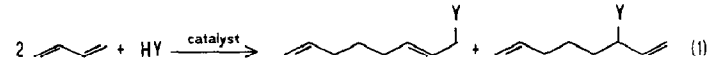
Abstract

Enantioselective telomerization reactions catalyzed by homogeneous palladium catalysts are described. Applying the concept of chiral bidentate phosphorus ligands and low temperatures proved useful in telomerizing butadiene with formaldehyde, with a β-dicarbonyl compound and with a nitroalkane. Excess of enantiomers up to 41% could be obtained. With a chiral enamine as nucleophile ee values of 72% have been observed.

Introduction

In homogeneous catalysis telomerization is defined as the oligomerization of dienes under the concomitant addition of a nucleophilic reagent as exemplified in eq. 1 for butadiene [1].



A variety of nucleophiles has been employed in this general reaction which can be quite useful for the synthesis of various natural products such as terpenols, jasmonates and pheromones [2]. For these chemicals the stereocontrolled introduction of stereogenic centers is of substantial interest [3].

* Dedicated to Prof. G. Wilke on the occasion of his 65th birthday.

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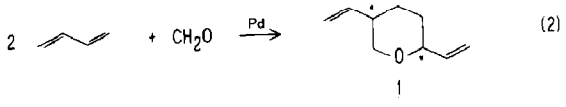
To our knowledge there are only two examples of an enantioselective telomerization described. Hidai reported the enantioselective conversion of isoprene and methanol yielding 1-methoxy-2,6-dimethyl-2,7-octadiene, a potential precursor for citronellol [4]. By using various chiral monodentate menthylphosphorus derivatives in combination with allylic complexes of palladium he reported a maximum ee value of 35% for menthyldiisopropylphosphine. Dzhemilev described the nickel catalyzed enantioselective telomerization of butadiene with amines. Maximum ee values for the synthesis of the morpholine telomer of 37% are claimed [5]. In this paper we report the enantioselective telomerization of butadiene with formaldehyde, a β-dicarbonyl compound, a nitroalkane and an enamine.

The general concept upon which our investigations are based make use of the general principles that chelate ligands and low reaction temperatures favour enantioselective syntheses [6]. It is assumed that the chelates will narrow the multiplicity of conformers of the catalytically active species. The second criterion concerning the temperature can be rationalized by the fact that the interconversion of diastereomers is slowed down at lower temperatures. In extreme cases the more stable diastereomer may even become kinetically "frozen out".

Enantioselective telomerization of butadiene with formaldehyde

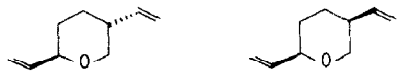
The telomerization of butadiene with formaldehyde yielding 2,5-divinyltetrahydropyran according to eq. 2 has been reported in the literature [7].



(2)

1

It is stated that in the presence of diphosphines as ligands the telomerization according to eq. 2 is prevented. We could show that the chelate containing catalyst $Pd(OAc)_2/Ph_2PCH_2CH_2PPh_2$ at 20 °C gave **1** in a yield of 50%. These results prompted us to introduce chiral diphosphine ligands listed in Table 1. Indeed, the enantiomers **1a** and **1b** are formed in ee values of up to 36% with (2*R*,3*R*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene (NORPHOS).



1a (trans) 1b (cis)

For the assignment of the diastereomers to structures **1a** and **1b**, we separated the isomers by column liquid chromatography. The NMR data, which are in agreement with those in the literature [7], show that in the excess diastereomer both vinylic groups are equatorial, because of the trans isomer.

Due to the unknown optical rotation of **1a** and **1b** we determined the enantiomeric excess by capillary gas chromatography. For the first time we could coat a fused-silica capillary with a cyclodextrin phase which allowed an elegant product separation of all four stereoisomers. This separation is shown in Fig. 1.

As is also obvious from Table 1, the *trans* isomer **1a** is always formed in an excess explainable by the thermodynamically favourably equatorial position of the

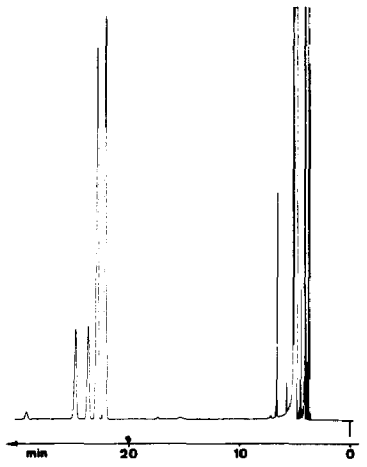


Fig. 1. Separation of a racemic sample of 2,5-divinyltetrahydropyran by capillary gaschromatography (90 °C/1.0 bar N_2).

Table 1

Enantioselective telomerization of formaldehyde with butadiene
(Reaction conditions: 0.075 mmol $Pd(OAc)_2$; metal/ligand ratio: 1/1.5; solvent: 5 ml isopropanol; cat./substrate: 1/500; *t*: 44 h; *T*: 20 °C)

Run	Chiral ligand	Chemical yield (%)	Diasteromeric ratio **1a**/**1b** [g]	% ee of **1b**	% ee of **1a**
1	(+)-DIOP [a]	65	5.0	26	18
2	(−)-DIOP	64	5.5	25	17
3	BPPM [b]	45	2.6	5	2
4	CIRA [c]	30	3.6	20	15
5	NORPHOS [d]	55	5.6	36	3
6	NMDPP [e]	25	3.9	30	13
7	PHEN [f]	45	3.9	24	5

[a] DIOP = 2,2-dimethyl-1,3-dioxolan-4,5-bis(methylene)bis(diphenylphosphine). [b] BPPM = (2*S*,4*S*)-*N*-t-butoxycarbonyl-2,4-bis(diphenylphosphino)-methylpyrrolidine. [c] CIRA = (2*R*,3*R*)-2,3-bis(diphenylphosphino)butane. [d] NORPHOS = (2*R*,3*R*)-2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene. [e] NMDPP = (1*R*,2*R*,5*S*)-neomenthyldiphenylphosphan. [f] PHEN = (*R*)-1,2-bis(diphenylphosphino)-3-phenylpropane. [g] **1a** has the (2*R*,5*R*)/(2*S*,5*S*) configuration, **1b** has the (2*S*,5*R*)/(2*R*,5*S*) configuration. The absolute configuration of the excess isomer was not determined.

vinylic substituents. However the greatest influence of the ratio of the enantiomers is found in the cis derivative.

Enantioselective telomerization of butadiene with a β-dicarbonyl compound

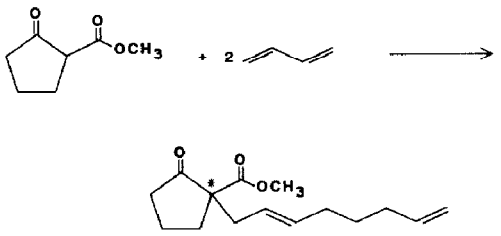
The telomerization of β-dicarbonyl compounds with butadiene was first described by Takahashi and coworkers [8]. In an attempt to obtain optically active telomers with 2-methoxycarbonylcyclopentanone and butadiene we conducted experiments according to eq. 3 with chiral phosphine/$Pd(OAc)_2$ complexes.

Table 2

Enantioselective telomerization of butadiene and 2-methoxycarbonylcyclopentanone (eq. 3) (Reaction conditions: 0.023 mmol $Pd(OAc)_2$; metal/ligand/NaOH ratio: 1/1.5/50; solvent: 7 ml isopropanol; cat./substrate: 1/650; *t*: 20 h)

Run	Chiral [a] ligand	*T* (°C)	Chemical Yield (%)	% ee
1	(+)-DIOP	20	79	2
2	(+)-DIOP	0	67	3
3	CIRA	20	80	4
4	CIRA	0	85	6
5	BPPM	20	80	7
6	BPPM	0	85	20
7	BPPM	−10	86	30
8	BPPM	−10	86	41 [b]
9	NORPHOS	20	60	7
10	NORPHOS	0	85	10

[a] See Table 1 for exact nomenclature. [b] Cat./substrate 1/350.

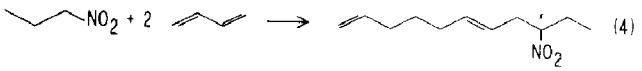


(3)

As is evident from our results listed in Table 2 ee values of 41% could be obtained at −10 °C using the ligand (2*S*,4*S*)-*N*-t-butoxycarbonyl-2,4-bis(diphenylphosphino)methylpyrrolidine (BPPM). The enantiomeric excess is determined by ^1H NMR analysis of the telomerization product in the presence of the chiral shift reagent $Eu(hfc)_3$ [9]. The resonance of the methoxy group then splits into its corresponding enantiomeric signals. This reaction shows potential for the synthesis of chiral cyclopentanone derivatives, important for many fine chemicals.

Enantioselective telomerization of butadiene with 1-nitropropane

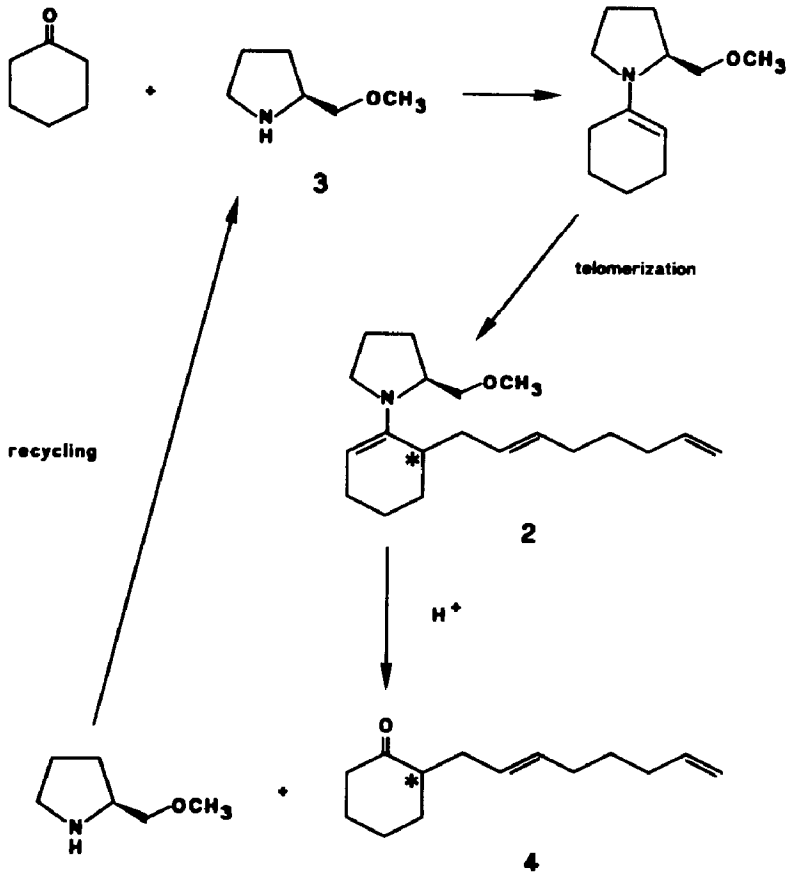
The smooth telomerization of nitroalkanes has been reported [10]. Again, applying the concept of chelate ligands and low temperature, 1-nitropropane could be telomerized with butadiene according to eq. 4.



(4)

Here, 2,2-dimethyl-1,3-dioxolan-4,5-bis(methylene)bis(diphenylphosphine) [(+)-DIOP] turned out to be the best ligand tested. At 4 °C ee values of 16% could be obtained. The other chiral phosphines **2**–**6** exhibited in Table 1 gave chiral derivatives, but the ee values ranged only between 4 and 10%. It may be postulated that the diphosphines possessing larger P–P distances perform best.

For the determination of the enantiomeric excess of the 9-nitro-1,6-undecadiene of eq. 4, the nitro derivative was reduced to the corresponding amine followed by



Scheme 1. Telomerization of enamines with butadiene

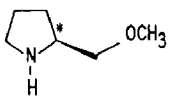
reaction with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [11]. As expected, two ^{19}F NMR-signals in different ratio are obtained (δ −69.30 and −69.43 ppm in $CDCl_3$ using $CFCl_3$ as external standard).

Diastereoselective telomerization of butadiene with an enamine

It is possible to conduct the telomerization with monoketones or aldehydes via enamines as intermediates as shown in Scheme 1 [12].

For instance, cyclohexanone can be converted into the chiral pyrrolidine enamine followed by telomerization with butadiene. Hydrolysis of the telomer **2** yields an alkyl chain substituted cyclohexanone derivative which, as is elucidated in Scheme 1, may possess a chiral center. By this route chiral α-alkyl substituted ketones are accessible. So far we could not introduce optical activity by applying chiral chelates such as exhibited in Table 1 compounds **1**–**6**.

It is of interest to conduct this telomerization with (*S*)-(−)-2-(methoxymethyl)pyrrolidine **3** as a chiral auxiliary.



3

This chiral auxiliary has been used very successfully by Enders [13] and is commercially available [14].

According to Scheme 1 the chiral auxiliary **3** can be recycled.

At 10 °C (*S*)-1-(2′-methoxymethyl)pyrrolidinocyclohexene can be telomerized with butadiene using PPh_3 as ligand giving ee values of **2** up to 72%. The ^1H NMR spectrum of **4** is identical with that reported in the literature [12].

Again the enantiomeric excess was determined by capillary gas chromatography applying a fused-silica capillary, coated with 10% heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin.

Conclusion

The conducted experiments support that telomerization reactions can be carried out enantioselectively. The here obtained ee values of up to 72% make this route interesting for the synthesis of a variety of fine chemicals.

Experimental

All reactions were carried out under argon. For all syntheses dry solvents were used.

For the gas chromatographic separation a Siemens Sichromat with split injection and a flame-ionization detector was used. The 2,5-divinyltetrahydropyran samples were injected as air-diluted vapors drawn from "head-space" vials and the *α*-chiral ketones were solved in cyclohexane. As carrier gas H_2 was used for the cyclodextrin phase.

General procedure for the telomerization with formaldehyde

In a typical experiment for the tetrahydropyran synthesis, in a glass autoclave 22.5 mg of palladium acetate (0.1 mmol) and 0.15 mmol of the diphosphine were dissolved in 5 ml of isopropanol; 1.5 g of paraformaldehyde was added to this yellow solution. After cooling to −30 °C, 5.24 g of butadiene (97 mmol) was added. The reaction mixture was then stirred for 40 h at room temperature. The 2,5-divinyltetrahydropyran yield was determined by distillation (b.p. 60 °C/14 mmHg) (see Table 1).

General procedure for the telomerization with 2-methoxycarbonylcyclopentanone

For the telomerization of butadiene and the *β*-ketoester, a solution of 5.2 mg of palladium acetate (0.023 mmol), 0.035 mmol of the diphosphine and 38 mg of sodium hydroxide (0.95 mmol) in 7 ml of isopropanol was prepared. To this homogeneous solution 15 mmol of the *β*-diketone was added. The mixture was cooled to −30 °C and 2.7 g of butadiene (50 mmol) was added. Upon stirring for 20 h at the temperatures listed in Table 2 the products could be obtained by vacuum distillation.

General procedure for the telomerization with nitroalkanes

Typically 30 mmol of the nitroalkane was added to a solution of 18.3 mg (0.06 mmol) of palladium acetylacetonate, 0.06 mmol of a diphosphine, 0.12 mmol of a monophosphine and 168 mg of potassium hydroxide (3 mmol) in 15 ml of isopro-

panol. The solution was cooled with dry ice/ethanol to $-60\,^{\circ}C$ and 3.25 g of butadiene (60 mmol) was added. After completion of the reaction the excess of butadiene was removed followed by vacuum distillation.

General procedure for telomerization with enamines

First 10.1 mg of palladium acetate (0.045 mmol) and 0.045 mmol of the diphosphine or 0.09 mmol of a monophosphine were dissolved in 4 ml acetonitrile. Then 10 mmol of the enamine and after cooling to $-30\,^{\circ}C$ 1.2 g of butadiene (22 mmol) was added. At the end of the reaction the reaction mixture was hydrolyzed with HCl.

Synthesis of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin

A solution of waterfree β-cyclodextrin in dimethylsulfoxide was allowed to react with a twofold molar excess of sodium hydride and 1.5 equiv. of methyl iodide [15]. The crude permethyl-β-cyclodextrin was purified by repeated crystallization from chloroform/n-hexane and cyclohexane.

Chiral fused-silica-capillary

A 50 m × 0.32 mm ID fused-silica capillary was coated with a 10% solution of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin in OV-1701 [16].

Acknowledgement

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