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Telomerization of Isoprene and Methanol Assisted by Palladium-Chiral Phosphine and/or -Chiral Amine Complexes

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A reação do isopreno em presença de metóxido de sódio e de quantidades catalíticas de compostos de paládio(II) associados a uma série de fosfinas e aminas mono e bidentadas quirais produz essencialmente o telômero 1-metóxi-2,6-dimetil-2,7-octadieno **2** e o dímero 2,7-dimetil-1,3,7-octatrieno **4**. A formação do dímero e do telômero pode ser controlada pela escolha do ligante quiral. Desta maneira, o telômero **2** é obtido seletivamente na presença de um ligante bidentado quiral contendo fósforo e nitrogênio mas com baixos excessos enantioméricos (e.e. até 12%). Por outro lado, o dímero do isopreno **4** é formado preferencialmente usando-se um ligante contendo somente nitrogênio.

In the presence of sodium methoxide and catalytic amounts of palladium(II) compounds in conjunction with a series of mono and bidentate chiral phosphines and amines isoprene produces mainly the telomer 1-methoxy-2,6-dimethyl-2,7-octadiene **2** and the isoprene dimer 2,7-dimethyl-1,3,7-octatriene **4.** The formation of the dimer and telomer can be modulated by the appropriate choice of the chiral ligand. Thus, the telomer **2** is obtained almost exclusively in the presence of bidentate phosphine-amine, but with very modest e.e.'s (up to 12%). On the other hand, the isoprene dimer **4** is preferentially formed when only a nitrogen-containing ligand is employed.

Keywords: *telomerization, oligomerization, isoprene, palladium*

Introduction

Among the various routes to chiral non-racemic compounds, homogeneous transition metal catalysis has been shown to provide very useful enantioselective C-C and C-Y (Y = H, O, Si, ...) bond-forming reactions[1-3]. A particular advantage of using transition metal compounds in catalysis is that the selectivity can, in principle, be "tuned" by ligand variations (ligand tailoring)[3]. The telomerization of dienes and nucleophilic reagents by transition metal compounds is a well-studied reaction in homogeneous catalysis[4-6]. Although the telomerization of isoprene can lead to very useful precursors of natural products, especially chiral terpenes[7], in only one case has its enantioselectivity been investigated[8,9]: the telomerization of isoprene and methanol using palladium allyl complexes and chiral monophosphines and phosphites yielding 1-methoxy-2,6-dimethyl-2,7-octadiene **2**, with a maximum e.e. value of 35%[8,9]. In this paper we present our results from the telomerization of isoprene and methanol in the presence of palladium (II) compounds and a series of mono and bidentate chiral phosphorus and nitrogen-containing ligands.

Experimental

General

All manipulations were performed under dry, oxygen-free argon using standard techniques. All solvents were dried and distilled under argon prior to use. Infrared (nujol mulls) spectra were recorded in the region of 4000-400 cm^{-1} using a Mattson 3020 FTIR spectrophotometer. The ^{1}H and $^{13}C-\{^{1}H\}$ NMR spectra were recorded at 200.13 and 50.32 MHz, respectively, using a Varian VXR-200 instrument. Proton and carbon shifts (δ/p.p.m., *J*/Hz), are positive down field relative to external $SiMe_4$. Elemental analyses were carried out by the Central IQ/UFRGS (Porto Alegre, Brazil). Mass spectra were obtained with GC-MS HP5988A (EI, 70 eV). The reaction products were analyzed

by gas chromatography on a Varian 3400 chromatograph equipped with an OV1 column (30 m x 0.25 mm x 0.2 μm) and FID detector, N_2 was the carrier, and the temperature program was from 80 °C to 180 °C (10 min) at a heating rate of 10 °C/min.

The compounds Pd(dba)$_2$10 (dba = *trans, trans*-dibenzylideneacetone), $PdCl_2(PhCN)_2$, $[Pd(MeCN)_4][BF_4]_2$12 and PPh_2(OMen) (Men = (-) menthyl)[13] were prepared according to procedures described in the literature. All other reagents were obtained from commercial sources and were used as received without further purification.

Synthesis of cyclopalladated compound **1**

N-benzylidene-(S)-(-)-α-methylbenzylamine (0.46 g, 4.4 mmol) was slowly added to a solution of palladium acetate (0.5 g, 2.2 mmol) in acetic acid (50 mL). The reaction mixture was heated under reflux for 1 h and then evaporated to dryness under reduced pressure. The remaining solid was washed with hexane (3 x 50 mL) and dissolved in acetone (50 mL). A large excess of LiBr (7 mmol) was then added, and after 1 h of stirring the reaction mixture was concentrated to *ca.* 10 mL. The addition of water (250 mL) afforded a yellow-green solid that was recovered by filtration. This solid was dissolved in dichloromethane and filtered through a plug of alumina (grade III) affording a yellow solution. The concentration of this solution (*ca.* 10 mL) and addition of hexane (70 mL) yielded **1** as a yellow solid that was recovered by filtration and dried under vacuum (0.39 g, 45%). Calculated for $C_{15}H_{14}BrNPd$: C 45.66, H 3.58, N 3.55; found: C 45.26, H 3.92, N 3.53.IR (nujol mulls): 1 607 cm^{-1} ν(C=N). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.74 (d, 3H, CH_3, ^3J = 6.8 Hz), 5.43 (q, 1H, **CH**Me, ^3J = 6.7 Hz), 6.83-7.09 (m, 3H, arom), 7.29-7.38 (m, 5H, arom), 7.51-7.56 (m, 1H, arom), 7.59 (s, 1H, **CH**=N).

Catalytic experiments

Isoprene (3.0 mL, 30 mmol), methanol (0.6 mL), sodium methoxide (10.8 mg, 0.2 mmol), palladium compound (0.015 mmol) and the ligand (0.015 or 0.03 mmol) were introduced into a Schlenk flask with dichloromethane (1.0 mL) under argon and the reaction mixture was stirred for 3 days at room temperature. The isoprene conversion and selectivity were determined by capillary gas chromatography using undecane as the internal standard. The e.e.'s were determined by enantioselective gas chromatography, which was performed at 70 °C using a chiral capillary column OV 1701 20% heptakis(2,6-di-O-methyl-3-O-pentyl) β-cyclodextrin 25 m x 0.25 mm[14]. The characterization of compounds **2-5** was done by CG-MS, and by comparing their ^{1}H- and ^{13}C-NMR spectra with those described in the literature[15].

Results and Discussion

Catalyst precursors

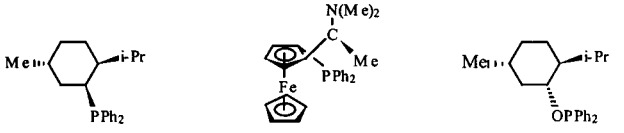
The ligands used in this study are shown in Chart 1.

The new chiral cyclopalladated complex **1**, was prepared in a 45% yield by the classic orthopalladation reaction (see Experimental and Scheme 1).

Telomerization of isoprene with methanol

In a typical experiment, freshly distilled isoprene, methanol, sodium methoxide, Pd(II) compound and the ligand were introduced into a Schlenk flask under argon, and the reaction mixture was stirred for 3 days at room temperature. In all of the cases studied only two major products were observed: the expected head-to-tail isoprene-methanol telomer 1-methoxy-2,6-dimethyl-2,7-octadiene **2** and the tail-to-tail isoprene dimer 2,7-dimethyl-1,3,7-octatriene **4**. The minor products were 1-methoxy-1,7-dimethyl-1,7-octadiene **3** and 2,6-dimethyl-1,3,7-octatriene **5** (Scheme 2). It is important to note that the fraction containing the isoprene dimers **4** and **5** can be easily separated from their telomers **2** and **3** by simple fractional distillation. The results obtained from the different catalytic systems studied are summarized in Table 1.

It is immediately apparent that the selectivities are independent of the palladium (II) catalytic precursor used (compare entries 1, 11 and 13, Table 1). In all cases studied, the best selectivities in compound **2** were accomplished when bidentate phosphine-amine and triphenylphosphine



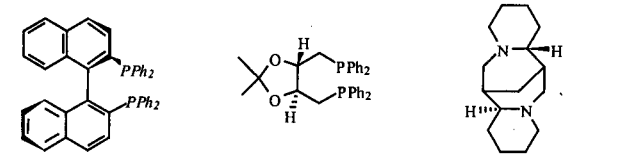
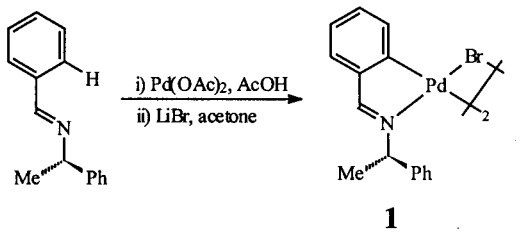
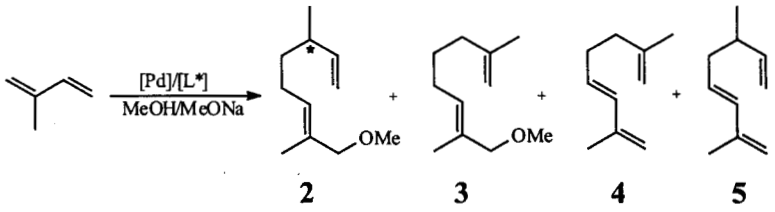


Chart 1.



Scheme 1.



Scheme 2.

Table 1. Conversion, turn over (TO), e.e. and selectivity of isoprene telomerization and dimerization. [Pd]:Isoprene:Methanol:MeONa:Dichloromethane = 1:2000:1000:13:1000 at 25 °C during 72 h.

Entry	Complex	Ligand	Pd:L	Conv.(%)[a]	TO(h^{-1})	e.e. (%)[b]	Selectivity[a] (%)			
						2	2	3	4	5
1	*[Pd(MeCN)4][BF4]2*	*(+)-nmdpp*	1:1	59	16.4	10	45	4	30	21
2	*[Pd(MeCN)4][BF4]2*	*(+)-nmdpp*	1:2	26	7.2	10	49	4	28	19
3	*[Pd(MeCN)4][BF4]2*	*(S,P)-ppfa*	1:1	3	0.8	5	67	16	5	12
4	*[Pd(MeCN)4][BF4]2*	*(S,P)-ppfa*	1:2	4	1.1	5	72	19	3	6
5	*[Pd(MeCN)4][BF4]2*	*PPh2(OMen)*	1:1	51	14.2	1	39	20	36	4
6	*[Pd(MeCN)4][BF4]2*	*(R)-binap*[c]	1:1	22	6.1	2	54	11	4	3
7	*[Pd(MeCN)4][BF4]2*	*(S,S)-diop*[d]	1:1	32	8.9	3	61	15	10	2
8	*[Pd(MeCN)4][BF4]2*	*sparteine*	1:1	2	0.6	6	6	9	85	--
9	/	*PPh2(OMen)*	1:1	20	5.6	2	51	14	31	4
10	/	*PPh3*	1:1	21	5.8	1	67	22	9	2
11	*Pd(dba)2*	*(+)-nmdpp*	1:1	65	18.1	11	42	4	35	19
12	*Pd(dba)2*	*(+)-nmdpp*	1:2	17	4.7	10	59	6	20	15
13	*PdCl2(PhCN)2*	*(+)-nmdpp*	1:1	39	10.8	12	44	4	35	17
14	*PdCl2(PhCN)2*	*(+)-nmdpp*	1:2	46	12.8	7	54	7	25	14

a) The isoprene conversion and selectivity were determined by capillary gas chromatography using undecane as internal standard.
b) The e.e.'s were determined by enantioselective gas chromatography which was performed at 70 °C using a 25 m capillary column with heptakis(2,6-di-O-methyl-3-O-pentyl)-b-cyclodextrin.
c) Formation of isoprene:methanol (1:1) adducts in 28% selectivity.
d) Formation of isoprene:methanol (1:1) adducts in 12% selectivity.

ligands were employed (entries 3, 4 and 10), although with low isoprene conversions. On the other hand, the highest selectivity on **4** was observed when the nitrogen-containing ligand sparteine was employed (entry 8). It is interesting to note that isoprene:methanol (1:1) adducts were formed in the case of bidentate phosphines (entries 6 and 7).

It is worth noting that the dimerization and telomerization reactions only occur in the case of complex **1** when phosphines are used in conjunction (entries 9 and 10). This suggests that phosphines are necessary to generate and/or stabilize the catalytic active species. The best isoprene conversions were obtained when *(+)-nmdpp* (entries 1 and 11) was used; however, the telomers (**2** and **3**) and the dimers (**4** and **5**) were obtained in almost equal amounts. The same behavior was observed in the case of *PPh2(OMen)* (entries 5 and 9). The addition of more than one equivalent of the phosphine ligands per Pd atom decreased the isoprene conversion without any significant changes in the selectivity (compare entries 1 and 2, 11 and 12, and 13 and 14).

Surprisingly, no telomerization products were detected in the absence of sodium methoxide even when Pd(0) ($Pd(dba)_2$ in the presence of 2 equivalents of PPh_3) was used as the catalyst precursor. This suggests that the role of sodium methoxide is not only to reduce Pd(II) to Pd(0), as previously proposed[17] but also to increase the concentration of the nucleophile (^-OMe) in the reaction mixture.

Only modest e.e.'s were observed for compound **2** (up to 12%) in the case of *(+)-nmdpp* (entry 13). However, it is worth noting that *sparteine* is also able to induce some enantioselectivity (entry 8), although with very low isoprene conversion. It is also interesting to note that the (-)

enantiomer was obtained in excess when *(+)-mndpp* was employed, whereas an excess of the (+) enantiomer was observed for the *sparteine* and *(S,P)-ppfa* catalytic systems.

In summary, we have shown that, depending upon the ligand used, either the isoprene dimer **4** or the telomer **2** can be obtained with good selectivities.

The use of phosphines containing a phosphorus stereogenic center and chiral N-containing ligands in isoprene dimerization and telomerization reactions is currently being investigated.

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