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Article

Cyclometalation of allylbenzene by $EtAlCl_2$ and Mg in the presence of Zr *ansa*-complexes as synthetic route to dibenzyl-butane and 9,8′-neo- lignans

Pavel V. Kovyazin[1]*, Pavel V. Ivchenko[2,3], Ilya E. Nifant'ev[2,3], Lyudmila V. Parfenova[1]

[1] Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, Prospekt Oktyabrya, 141, 450075 Ufa, Russia; kpv38@mail.ru (P.V.K.); luda_parfenova@ipc-ras.ru (L.V.P)
[2] A. V. Topchiev Institute of Petrochemical Synthesis RAS, Lenuinsky Avenue 29, Moscow 119991, Russian Federation
[3] Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory 1–3, Moscow 119991, Russian Federation
* Correspondence: kpv38@mail.ru

Abstract: The aim of the research is the development of a one-pot method for the synthesis of lignans, the natural compounds, which show a wide spectrum of biological activity. For this purpose, the *ansa*-zirconocenes of various structures were tested as the catalysts of the allylbenzene cyclometalation with ethylaluminum dichloride ($EtAlCl_2$) and Mg. The effect of organophosphorus compounds hexamethylphosphoramide (HMPA) and triphenylphosphine (PPh_3) on the chemo- and regioselectivity of the reaction was studied. The use of η^5-indenyl or fluorenyl *ansa*-complexes with ethanediyl or dimethylsilylene bridges as well as a biscyclopentadienyl complex with Si-bound ligands as catalysts in the presence of HMPA provides the formation of cyclometalation products in total yield of 70%. Cyclometalation product composition is represented by two regioisomers 3,4-dibenzyl- and 2,4-dibenzyl-substituted alumolanes with a ratio (1-2):1, which hydrolysis provides corresponding dibenzylbutane lignan and 9,8'-neo- lignan.

Keywords: cyclometalation; alkenes; zirconocenes; lignane

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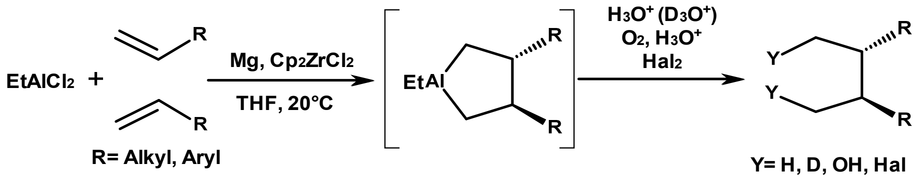
1. Introduction

Since 1989 the catalytic cycloalumination of alkenes and acetylenes (Dzhemilev reaction) have been developing as one of the directions of organoaluminum compound (OAC) chemistry. The reaction provides an effective and stereoselective route for the synthesis of various classes of organic compounds [1,2].

Among the developed methods, the reaction of terminal alkenes or alkynes with OAC and Mg, catalyzed by Cp_2ZrCl_2, which goes through the formation of disubstituted alumolanes, affords 2,3-disubstituted butanes or 1,4-butanediols with high diastereoselectivity (Scheme 1) [1-5]. The use of allylbenzenes in the reaction [6, 7] allowed to develop the one-pot diastereoselective method for the synthesis of dibenzylbutane lignans, a group of natural compounds with a wide range of biological activity [8-14]. In continuation of these studies, the *ansa*-zirconocenes of various structures were tested as the catalysts of the allylbenzene cyclometalation with ethylaluminum dichloride ($EtAlCl_2$) and Mg. The effect of organophosphorus compounds hexamethylphosphoramide (HMPA) and triphenylphosphine (PPh_3) on the chemo- and regioselectivity of the reaction was studied as well.

Scheme 1

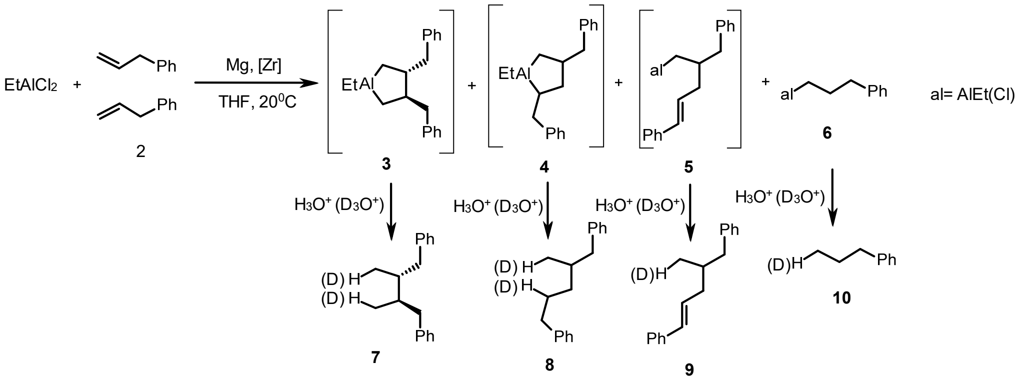


2. Results and Discussion

The catalytic action of zirconocenes of various structures (**1a-o**) in the reaction of allylbenzene with ethyl aluminum dichloride ($EtAlCl_2$) and metallic Mg in tetrahydrofuran (THF) was studied (Scheme 2, Table 1). Hexamethylphosphoramide (HMPA) or triphenylphosphine (PPh_3) were used as nucleophilic solvating agents. Due to the high solvating ability of HMPA or PPh_3 towards the inorganic ions, they are used in organic reactions, in particular, with the participation of organometallic reagents [15-18]. The idea of introducing HMPA or PPh_3 into the reaction medium was determined by the need to stabilize the intermediates responsible for the cyclometalation pathway to increase the yield of target products.

It was found that the reaction of allylbenzene with $EtAlCl_2$ and Mg, catalyzed with zirconocenes in the presence of HMPA or PPh_3 affords alumolane regioisomers **3** and **4** (Scheme 2). The acyclic OAC with double bond **5** and hydroalumination product **6** were identified in the product mixture as well. The hydrolysis or deuterolysis of cyclometalation products **3** and **4** provide dibenzylbutane lignan **7** and 9,8'-neo- lignan **8**.

Scheme 2



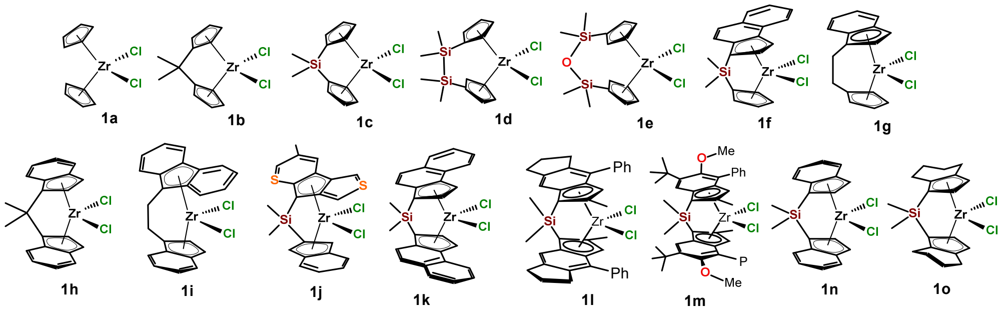


Table 1. Reaction of allylbenzene with $EtAlCl_2$ and Mg, catalyzed by Zr complexes 1a-o (22°C, 72 h, HMPA or PPh_3, THF, mole ratio [Zr]:[Mg]:[$EtAlCl_2$]:[allylbenzene]:[HMPA or PPh_3]=1:20:25:20:20).

Entry	[Zr]	HMPA/ PPh3	Alkene conversion, %	Product yield, %			
				3 (**7**)	**4** (**8**)	**5** (**9**)	**6** (**10**)
1	**1a**	-	98	58	8	23	6
2	**1a**	HMPA (0.6 eq)[a]	97	46	24	14	13
3	**1a**	HMPA [a]	99	44	23	20	12

4	**1a**	HMPA (2 eq) [a]	99	49	23	17	10
5	**1a**	PPh_3	63	29	9	15	10
6	**1a**	PPh_3 (3 eq.)	61	23	9	26	5
7	**1b**	HMPA	<1	-	-	-	-
8	**1c**	HMPA	82	24	15	16	25
9	**1d**	HMPA	63	25	15	7	15
10	**1e**	HMPA	48	22	4	7	12
11	**1f**	HMPA	58	22	10	3	6
12	**1g**	HMPA	76	27	25	12	8
13	**1h**	HMPA	<1	-	-	-	-
14	**1i**	HMPA	83	35	23	14	9
15	**1i**	HMPA	70	29	21	2	15
16	**1j**	HMPA	82	36	26	11	7
17	**1k**	HMPA	96	38	41	4	13
18	**1l**	HMPA	98	41	40	5	12
19	**1m**	HMPA	87	46	31	6	4
20	**1n**	-	70	47	13	5	2
21	**1o**	HMPA	6	2	<1	<1	<1

[a] reaction time – 48 h.

The addition of HMPA to the reaction mixture with catalyst **1a** significantly shortens the reaction time (Table 1, entries 2-4). As a result, the reaction proceeds in 48 hours with an allylbenzene conversion of 97-99%. The addition of PPh_3 led to a decrease in the substrate conversion to 61-63% (entries 5,6). In catalytic systems based on *ansa*-metallocenes, the degree of alkene conversion reached 70-98%. Biscyclopentadienyl and bisindenyl complexes with isopropylidene bridge **1b** and **1h** (entries 7, 13) were an exception; in their presence, the conversion of allylbenzene in 72 hours was less than 1%. The presence of HMPA also increased the chemoselectivity of the reaction towards the formation of cyclic OACs (up to 81%), however, the regioselectivity of the process decreased.

The most active catalysts in the reaction of allylbenzene with Et_2AlCl and Mg was found to be *ansa*-complexes with an ethanediyl (**1g**, **i**) (entries 12,14) or dimethylsilylene (**1i-m**) bridges (entries 15-20), containing η^5-indenyl or fluorenyl fragments, as well as a biscyclopentadienyl complex with Si-bound ligands (**1c**) (entry 8). In the presence of these complexes, the conversion of allylbenzene was 70-98% and the reaction proceeded with the predominant formation of cyclometallation products **3**,**4** with a total yield of up to 70% and a regioisomer ratio 3:4=(1-3.6):1. However, despite the increase in the activity and chemoselectivity of catalytic systems based on Zr *ansa*-complexes due to the introduction of HMPA, the regioselectivity of the reaction decreased (see, for example, complex **1m**,**n**, entries 19,20). The use of a Si-bound bistetrahydroindenyl (**1o**) instead of a bisindenyl ligand (**1m**) in the catalyst structure leads to an almost complete loss of activity.

3. Materials and Methods

3.1. General Procedures

All operations for organometallic compounds were performed under argon according to Schlenk technique. THF and diethyl ether were dried and distilled from sdium/ benzophenone before use. Commercially available allylbenzene (98%, Acros) and $EtAlCl_2$ (97%, Merck). CAUTION: pyrophoric nature of aluminum alkyl compounds require special safety precautions in their handling. Zirconocenes 1a-1o were synthesized according to known procedures: 1a [19], 1b [20], 1c [21], 1d [22], 1e [23], 1f, 1g, 1i [24, 25], 1h [26], 1j [27, 28], 1k [29, 30], 1l [31], 1m [32], 1n [33], 1o [34] from $ZrCl_4$ (98%, Acros).

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-400 spectrometer (400.13 MHz (1H), 100.62 MHz (^{13}C)) (Bruker, Rheinstetten, Germany). As the solvents and the internal standards, CD_2Cl_2 and $CDCl_3$ were employed. 1D and 2D NMR spectra (COSY HH, HSQC, HMBC, NOESY) were recorded using standard Bruker pulse sequences. The yields of OAC products were determined by analyzing the mixture of deuterolysis or hydrolysis products 7-10 using a gas chromatograph-mass spectrometer GCMS-QP2010 Ultra (Shimadzu, Tokyo, Japan) equipped with the GC-2010 Plus chromatograph (Shimadzu, Tokyo, Japan), TD-20 thermal desorber (Shimadzu, Tokyo, Japan), and an ultrafast quadrupole mass-selective detector (Shimadzu, Tokyo, Japan).

The obtained NMR and the mass spectral characteristics of compounds 7-10 correspond to the literature data [6,7].

4. Conclusions

It was shown that the structure of the η^5-ligand at the Zr atom significantly affects the activity of the system, and the presence of HMPA increases the yield of cyclometalation products up to 77%. The reaction proceeds with the formation of regioisomers of 3,4-dibenzyl- and 2,4-dibenzyl-substituted alumolanes with a ratio (1-2):1, which hydrolysis provides corresponding dibenzylbutane and 9,8'-neo- lignans.

Supplementary Materials: Not applicable.

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