Palladium-Catalyzed Reactions for the Synthesis of Fine Chemicals, 16**

Highly Efficient Palladium-Catalyzed Telomerization of Butadiene with Methanol

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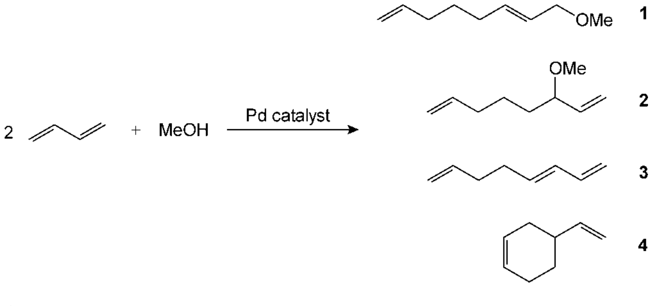
The palladium-catalyzed telomerization of 1,3-dienes with nucleophiles assembles simple starting materials in a 100% atom efficient manner to give functionalized octa-2,7-dienes.[2] Due to their ready availability and their low price,[3] 1,3-butadiene and methanol are especially attractive starting materials for this reaction (Scheme 1). The resulting major product 1-methoxyocta-2,7-diene (**1**) (*n*-product) is useful as a precursor for plasticizer alcohols (octanols), solvents, corrosion inhibitors, and monomers (octenes).[4] In addition, the by-products of this reaction, mainly the 3-substituted methoxyocta-1,7-diene (**2**) (*iso*-product) and 1,3,7-octatriene (**3**) (formed by the linear dimerization of butadiene) and 4-vinylcyclohexene (**4**) (formed by the Diels-Alder reaction of two molecules of butadiene) are also of some commercial interest. Hence, this telomerization process has been the subject of much attention in both academic and industrial laboratories.[5]

In spite of the economic attractiveness of the starting materials, a prerequisite for an industrial application of the telomerization reaction is catalyst efficiency. So far no detailed study with regard to turnover numbers of the catalyst (TON) has been reported. In the past, most reports about this reaction use 0.01–0.1 mol% of palladium derivatives as catalysts (TON < 10000). However, from simple economic calculations it is clear that TON > 10^5 have to be realized in order to make this reaction commercially viable. In this paper we describe the important factors determining the catalyst activity and stability with regard to the telomerization of butadiene and methanol. Based on our study we developed a practical solution to this problem which leads to extremely productive palladium catalysts (TON up to 100000).



Scheme 1.

Although the mechanism[6] of the palladium-catalyzed telomerization reaction has been carefully examined and numerous synthetic applications have been published, little attention has been given towards catalyst efficiency. As a starting point of our investigation, we tested several phosphine ligands (triphenylphosphine, tri-*o*-tolylphosphine, tricyclohexylphosphine, trisulfonated triphenylphosphine, 1,4-bis(diphenylphosphi-

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no)butane, and 2-(2-diphenylphosphinophenyl)-4,4-dimethyl-4,5-dihydrooxazole) in the presence of a small amount of palladium catalyst (0.0018–0.002 mol% $Pd(OAc)_2$) at 90 °C. In general, 3 eq. of ligand relative to Pd and a butadiene to methanol ratio of 1 : 2 were used. The patent literature describes a positive influence of added amines on the catalyst efficiency.[5g–i] Hence, 0.2–0.23 mol% of triethylamine were added to the reaction mixture. As shown in Table 1, among the various ligands tested, only triphenylphosphine (entry 2; Table 1) and tricyclohexylphosphine (entry 3; Table 1) gave significant yields of 1-methoxy-2,7-octadiene (**1**) (47% and 16%, respectively) at this low catalyst loading.

Next we were interested in the influence of the ligand concentration on catalyst stability and activity. Therefore, catalytic runs with 3, 10, and 50 eq. of the most productive ligand (triphenylphosphine) relative to palladium were performed (Table 2).

In order to examine catalyst activities (TOF), the experiments were stopped after 0.5, 2, and 16 h. There is a clear trend that the catalyst productivity is increased with increasing P/Pd ratio. Total turnover numbers of 75000 were realized after 16 h with P/Pd ratio of 10 and at 90 °C (entry 16; Table 2). Entry 20 (Table 2) demonstrates that the catalyst in the presence of a large excess of phosphine is still active after 16 h, thus achieving a total turnover number of TON = 97000. To our best knowledge this is the highest catalyst productivity ever reported in the open literature for a palladium-catalyzed telomerization reaction. In contrast to the catalyst productivity, the catalyst activity is higher at low P/Pd ratios. Thus, the high catalyst productivity at high P/Pd ratios is at the expense of the catalyst activity (turnover frequency (TOF) = 1600 h^{-1}; entry 20; Table 2). As shown in Table 2, the product selectivity is also largely influenced by the concentration of the phosphine ligand.

The observed regioselectivities are in agreement with our recent findings that the decrease in regio-

Table 1 Influence of phosphine ligands on the catalyst productivity.

Entry[a]	Catalyst	Catalyst concentration (mol%)	Conversion	Yield of **1**	Yield of **2**	Yield of **3**	TON (**1** + **2** + **3**)
1	$Pd(OAc)_2$	2×10^{-3}	4%	0.6%	0%	0.5%	550
2	$Pd(OAc)_2/3\ PPh_3$	1.8×10^{-3}	58%	47%	2.5%	5.4%	30500
3	$Pd(OAc)_2/3\ PCy_3$	2×10^{-3}	22%	16%	1.5%	4.5%	11000
4	$Pd(OAc)_2/3\ P(o\text{-}Tol)_3$	2×10^{-3}	9%	7%	0.3%	1.7%	4500
5	$Pd(OAc)_2/3$ H-TPPTS	2×10^{-3}	5%	2.5%	0%	0.4%	1450
6	$Pd(OAc)_2/3$ dppb	2×10^{-3}	7%	0.5%	0%	6%	3250
7	$Pd(OAc)_2/3$ dppdmo[b]	2×10^{-3}	0.5%	< 0.1%	0%	< 0.1%	< 100

[a] Conditions: 1.0 mol butadiene, 2.2 mol methanol, 2 mmol NEt_3, 90 °C, 2.5 h.

[b] dppdmo = 2-(2-diphenylphosphinophenyl)-4,4-dimethyl-4,5-dihydrooxazole).

Table 2 Catalyst productivities (TON) and activities (TOF).[a]

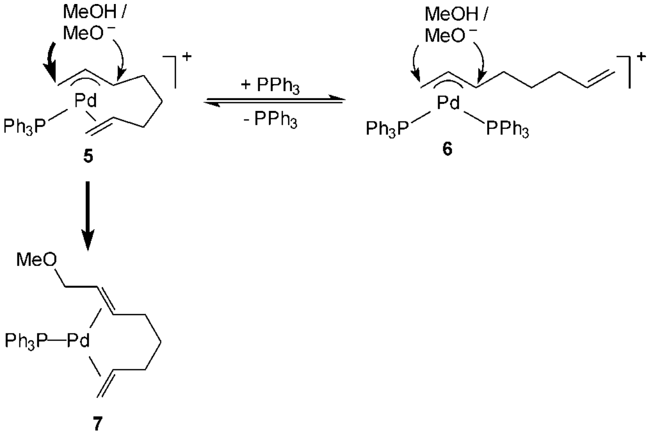
Entry	Ratio Pd/P	Reaction conditions	TON (**1** + **2** + **3**)	TOF (TON h^{-1})	Chemoselectivity (**1** + **2**)	Regioselectivity (*n/iso*)
1	1 : 3	50 °C/16 h	21500	1350[b]	96%	9 : 1
2	1 : 3	50 °C/16 h; 100 eq. NEt_3	19000	1200[b]	95.5%	9 : 1
3	1 : 3	50 °C/2 h	4500	2250	97%	8 : 1
4	1 : 3	50 °C/2 h 100 eq. NEt_3	6200	3100	98%	8 : 1
5	1 : 10	50 °C/16 h	17000	1050[b]	96%	7 : 1
6	1 : 10	50 °C/16 h 100 eq. NEt_3	15200	950[b]	97%	7 : 1
7	1 : 10	50 °C/2 h	2900	1450	98%	7 : 1
8	1 : 10	50 °C/2 h 100 eq. NEt_3	3700	1850	98.5%	8 : 1
9	1 : 50	50 °C/16 h	28000	1750[b]	99%	7 : 1
10	1 : 50	50 °C/60 h	87000	1450[b]	98%	7 : 1
11	1 : 3	90 °C/16 h	55000	3500[b]	66%	15 : 1
12	1 : 3	90 °C/16 h 100 eq. NEt_3	59000	3700[b]	61%	14 : 1
13	1 : 3	90 °C/0.5 h	8900	17800	79%	13 : 1
14	1 : 3	90 °C/0.5 h 100 eq. NEt_3	12500	**25000**	86%	15 : 1
15	1 : 10	90 °C/16 h	71000	4400[b]	66%	13 : 1
16	1 : 10	90 °C/16 h 100 eq. NEt_3	75000	4700[b]	67%	13 : 1
17	1 : 10	90 °C/0.5 h	5500	11000	85%	8 : 1
18	1 : 10	90 °C/0.5 h 100 eq. NEt_3	6000	12000	88.5%	7 : 1
19	1 : 50	90 °C/16 h	70000	4400[b]	75%	7 : 1
20	1 : 50	90 °C/60 h	**97000**	1600[b]	67%[c]	7 : 1

[a] All experiments were carried out with a substrate ratio butadiene/methanol = 2 : 1

[b] Average number over 16 h/60 h reaction time.

[c] 11% 4-vinylcyclohexene (**4**).

selectivity with increasing phosphine concentration is due to the loss of the coordination of the double bond to the palladium center (Scheme 2).[7]



Scheme 2.

In the presence of an excess of phosphine, the intermediate η^2,η^3-octadienyl-palladium mono(phosphine) complex **5** is in equilibrium with the η^3-octadienyl-palladium bis(phosphine) complex **6**. The regioselectivity of the nucleophilic attack of methanol or methoxide on **6** is no longer determined by the formation of the favorable complex **7** with a chelating 1,6-diene ligand. Hence, the regioselectivity is only determined by steric and electronic effects.

As mentioned above, it is often stated in the patent literature[5g–i] that the addition of reducing agents such as sodium formate, sodium borohydride, or bases such as alkoxides and trialkylamines has a positive effect on the reaction rate and/or the product selectivity of the telomerization of butadiene with methanol. This prompted us to investigate the influence of added base on the efficiency of Pd(II)-catalyst systems. Initial studies were performed using triethylamine as a co-catalyst. As shown in Table 2, the addition of triethylamine has no positive influence on the product selectivity or on the catalyst productivity, using an *in situ* catalyst mixture [Pd(OAc)$_2$/n PPh$_3$]. For example, at 50 °C and with a metal to ligand ratio of 1 : 3, the catalyst productivity is TON = 21500 (entry 1; Table 2) compared to TON = 19000 under the same conditions in the presence of triethylamine (entry 2; Table 2). At a metal to ligand ratio of 1 : 10, similar results were obtained (entries 5, 6; Table 2). At 90 °C and Pd/P ratios of 1 : 3 or 1 : 10, the catalyst productivity and selectivity are not significantly influenced by the addition of NEt$_3$ (compare entry 11 with 12 and entry 15 with 16; Table 2). However, instead of affecting selectivity and productivity, the addition of triethylamine accelerates the rate of the reaction in the beginning. At a ligand to metal ratio of 3 : 1, the turnover frequency is increased from TOF = 2250 h^{-1} to TOF = 3100 h^{-1} at 50 °C (entries 3, 4; Table 2). The same trend holds true at 90 °C, with the catalyst activity rising from 17800 TON h^{-1} to 25000 TON h^{-1} upon addition of NEt$_3$ (entries 13, 14; Table 2). By comparing these results with reactions with an increased phosphine to palladium ratio of 10 : 1 (entries 7, 8, 17, and 18; Table 2), it is shown that this acceleration of the reaction is less pronounced.

These observations were confirmed by calorimetry experiments (Figure 1).

As shown in Figure 1, the induction period of the reaction is significantly reduced in the presence of triethylamine. Also the time to reach the maximum catalyst activity is shortened. In the presence of amine, the maximum catalyst activity is observed after 3 h, whereas without amine, 8.5 h are required to reach the maximum activity. These results demonstrate that the role of added amines is to facilitate the reduction of Pd(II) species to Pd(0) complexes. McCrindle et al.[8] described a possible mechanism for this reduction.

In order to study the influence of amine on the telomerization more closely, reactions were carried out at various temperatures and with different bases (Table 3).

At −10 °C and atmospheric pressure, the palladium(II) acetate/1 eq. PPh$_3$ system is not active at all (entry 1; Table 3). However, when triethylamine was added as co-catalyst, consumption of butadiene was observed with concomitant formation of products (entry 2; Table 3). On the other hand, at 90 °C there is no significant difference between the catalytic runs without triethylamine and in the presence of 100 eq. (relative to Pd) triethylamine (TON = 49000 or 53000; entries 3, 4; Table 3). These results are in agreement with our proposal, since reduction of Pd(II) to Pd(0) is easy at that temperature. The addition of other amines such as pyridine and DABCO (entries 5, 6; Table 3) or the use of a large excess of

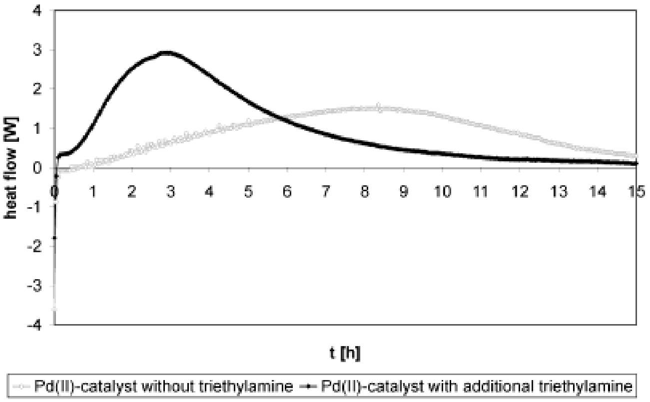


Figure 1 Influence of triethylamine on the palladium-catalyzed telomerization reaction.

Table 3 Telomerization experiments in the presence of different bases.

Entry	Ratio butadiene/ methanol	Catalyst	Catalyst concentration (mol%)	Temp.	Reaction time	Additives [eq. per Pd]	Conversion	TON **1+2+3**	Yield **1 + 2**	Yield **3**	Chemo-selectivity (**1 + 2**)	Regio-selectivity (*n/iso*)
1	2 : 1	$Pd(OAc)_2$/ 1 PPh_3	7×10^{-2}	–10 °C	7 h	–	0%	0	–	–	–	–
2	2 : 1	$Pd(OAc)_2$/ 1 PPh_3	7×10^{-2}	–10 °C	7 h	100 eq. NEt_3	44%	628	43%	1%	98%	34 : 1
3	1 : 2	$Pd(OAc)_2$/ 3 PPh_3	1×10^{-3}	90 °C	2.5 h	–	49%	49000	44%	5%	90%	18 : 1
4	1 : 2	$Pd(OAc)_2$/ 3 PPh_3	2×10^{-3}	90 °C	2.5 h	100 eq. NEt_3	57%	53000	48%	5%	84%	19 : 1
5	1 : 2	$Pd(OAc)_2$/ 3 PPh_3	2×10^{-3}	90 °C	2.5 h	100 eq. pyridine	34%	17500	32%	3%	94%	19 : 1
6	1 : 2	$Pd(OAc)_2$/ 3 PPh_3	4×10^{-3}	90 °C	2.5 h	100 eq. DABCO	80%	20250	72%	8%	90%	15 : 1
7	1 : 2	$Pd(OAc)_2$/ 3 PPh_3	2×10^{-3}	90 °C	2.5 h	40 ml NEt_3	4%	2000	2%	2%	50%	6 : 1

triethylamine (entry 7; Table 3) results in lower turnover frequencies (TOF = 7000, 8100, 800 h^{-1}, respectively). Here, the blocking of free coordination sites on the central metal atom seems to be responsible for this effect.

In conclusion, we describe here a study of the palladium-catalyzed telomerization of 1,3-butadiene with methanol concerning catalyst efficiency. Both catalyst activity and productivity are influenced by the nature of the ligand and the ligand to palladium ratio. By optimization of these control elements, extremely high turnover numbers of about 100 000 and turnover frequencies of about 1600 h^{-1} were realized at a PPh_3/Pd ratio of 50 : 1. This catalyst productivity and activity seems to be useful for industrial applications. With regard to activity, the best results were obtained at lower PPh_3/Pd ratios (TOF up to 25 000). Our results demonstrate that the addition of bases as co-catalysts facilitates the reduction of Pd(II) pre-catalysts to the active Pd(0) complex. However, the content of NEt_3 in the reaction influences neither the chemo- nor the regioselectivity of the telomerization, and has no influence on the catalyst productivity.

Experimental Section

General Procedure

37 mg (0.14 mmol) of triphenylphosphine and 11 mg (0.05 mmol) of palladium(II) acetate are dissolved in 56 g (2.21 mol) of methanol under argon. The mixture is transferred into a cooled (dry ice) autoclave (Parr model 4561). Subsequently, 54 g (1.00 mol) of butadiene are condensed into the autoclave and the vessel is heated to the reaction temperature. After the reaction is finished the autoclave is cooled down and the remaining butadiene is recondensed. The conversion is determined by the mass difference of butadiene. The yield of telomerization products is determined by GC (with dodecane as the internal standard) using an HP 6869A gas chromatograph. In order to isolate the octadienyl ethers the reaction mixture is distilled in vacuo.

cis/trans-1-Methoxyocta-2,7-diene (1)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.49 (q, J = 8.0 Hz, 2 H), 2.68–2.76 (m, 4 H), 3.31 (s, 3 H), 3.86 (dd, J = 6 Hz, J = 2 Hz, 2 H), 4.95–4.99 (m, 2 H), 5.49–5.61 (m, 1 H), 5.64–5.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.97, 28.30, 28.73, 31.69, 33.21, 57.67, 57.90, 68.13, 73.25, 114.58, 126.30, 126.47, 133.29, 134.44, 138.54, 138.62.

3-Methoxyocta-2,7-diene (2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34–1.68 (m, 4 H), 2.01–2.10 (m, 2 H), 3.26 (s, 3 H), 3.46–3.54 (m, 1 H), 4.90–5.20 (m, 2 H), 5.14–5.22 (m, 1 H), 5.58–5.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.62, 33.70, 34.81, 56.14, 82.92, 114.53, 117.03, 138.72, 138.85.

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