DOI: 10.1002/adsc.200800675

Palladium-Catalysed Telomerisation of Isoprene with Glycerol and Polyethylene Glycol: A Facile Route to New Terpene Derivatives

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Received: November 1, 2008; Published online: February 2, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800675.

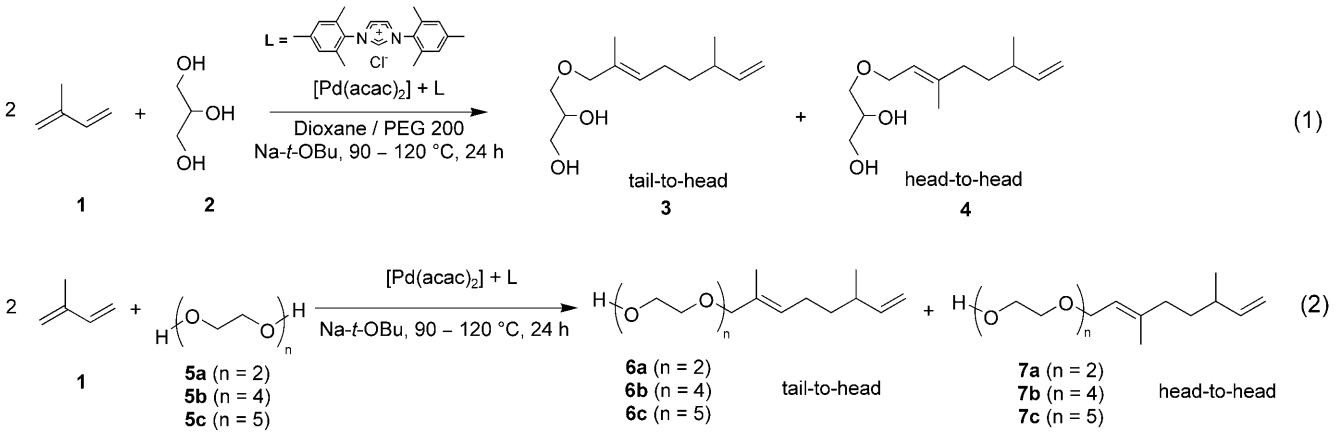
Abstract: We present here the first example of the telomerisation of isoprene with glycerol and polyethylene glycol (PEG-200), opening a facile route to new terpene structures, based on a combination of renewable and petroleum-based feedstocks. The reaction is catalysed by a palladium-carbene complex. Significantly, this system gives >99% of linear monotelomer products. The factors that govern substrate conversion, dimerisation/telomerisation selectivity, and catalyst activity are studied and discussed.

Keywords: carbene; kinetics; palladium; polyethylene glycol (PEG-200); telomerization; terpenes

The chemical industry continually searches for new catalytic conversions of existing bulk chemicals towards high-value products.[1] Much attention is directed towards chemicals from renewable sources and cradle-to-cradle technology.[2] Ideally, such new processes should be wholly sustainable (i.e., use only renewable feedstocks and consume a minimal amount of energy). That being said, catalytic reactions combining petroleum-based feedstocks and renewable ones have an important advantage: They often present viable and pragmatic solutions, since they typically involve lower capital investment and use existing infrastructure. Thus, such reactions are more easily adopted by conservative companies.[3]

In this context, following our recent work on the generation of biodiesel from waste oils using heterogeneous catalysis,[4–6] we investigated catalytic options for adding value to the glycerol by-product. Our attention was drawn by the elegant experiments of Palkovits et al., who showed that crude glycerol can be telomerised with 1,3-butadiene in a biphasic system, in the presence of Pd-phosphine complexes.[7,8] We were interested in adapting this approach to the less active but more lucrative isoprene, the telomerisation of which would yield terpene derivatives with various possible applications in the cosmetics and detergents sectors.[9] Notably, there are only a few examples of isoprene telomerisation. The majority of these employ methanol as the nucleophile,[10,11] with a few examples using water[12,13] or amines.[14,15] To tackle the less reactive isoprene, we turned to Pd-carbene complexes, that were shown to be highly active and selective in several recent studies,[16–19] most notably by Beller and co-workers.[20–22] Since isoprene and glycerol are immiscible at practical concentrations, we achieved a monophasic reaction medium by adding various co-solvents. Surprisingly, we found that mixing glycerol and polyethylene glycol (PEG) gave a highly reactive system, where both the glycerol and the PEG were telomerised in good yields and selectivities. In this paper, we present the first catalytic telomerisation of isoprene with glycerol and PEG, generating a series of new terpene derivatives. We characterise these compounds and explain some of the factors that govern substrate conversion, dimerisation/telomerisation selectivity, and catalyst activity. Significantly, our catalytic system gives >99% of linear monotelomer products.

In a typical reaction [Eq. (1) and Eq. (2)], one equivalent of glycerol was mixed with five equivalents of isoprene in a stainless steel autoclave charged with a 1:1 dioxane:PEG-200 solution (the PEG:glycerol



molar ratio was 2.5:1). The autoclave was heated to 90 °C, and the reaction was started by adding a mixture of 0.05 mol% of $Pd(acac)_2$, 0.075 mol% of the imidazolium salt precusrsor, 1,3-dimesitylimidazolium mesylate (IMesHCl), and a base (NaO-*t*-Bu). Reaction progress was monitored by GC. After 24 h, the reaction was stopped and the products were isolated by column chromatography and analysed by NMR (see Experimental Section for details). Importantly, both the glycerol and the PEG substrates yielded only two products each: the so-called tail-to-head (T2H) and head-to-head (H2H) isomers [respectively (**3**; **6a–c**) and (**4**; **7a–c**)]. To the best of our knowledge, this is the first example of telomerisation of PEG with isoprene. From a practical point of view, the products are interesting because they have both the hydrophobic terpene structure and the hydrophilic PEG chain, with a free hydroxy terminal group.

The Pd-carbene complex catalyses two competing reactions in this system: the above-noted isoprene/alcohol telomerisation, and a side-route isoprene dimerisation. The competition between the two reaction types is highly dependent on the catalyst and reaction conditions, since both reactions stem from the same catalytic cycle (*vide infra*). Importantly, no other reactions, and particularly *no branched products* are observed (this is important because the linear products are the ones sought after by the surfactant industry). Table 1 shows the telomerisation/dimerisation selectivity, the product yield, turnover number (TON) and

Table 1. Telomerisation of isoprene with glycerol and PEG.[a]

Entry	Solvent	Ligand:Pd ratio	Chemoselectivity		**3+4**	**3**:**4**	**6+7**	**6**:**7**	TON	TOF $[h^{-1}]$[d]
			Dimerisation	Telomerisation	Yield[b]	Selectivity[c]	Yield[b]	Selectivity[c]		
1	None	10:1	–	–	–	–	–	–	–	–
2	DMF	10:1	–	–	–	–	–	–	–	–
3	Dioxane/PEG	10:1	13	87	44	5.0:1	18	3.0:1	1780	214
4	Dioxane/PEG	1.5:1	16	84	70	7.0:1	29	3.2:1	2900	241
5[e]	Dioxane/PEG	1.5:1	40	60	21	1.9:1	3	–	5700	237
6[f]	Dioxane/PEG	10:1	25	75	37	2.3:1	12	3.1:1	13400	558
7[g]	Dioxane/PEG	10:1	76	24	–	–	15	3.3:1	300	–

[a] *Reaction conditions:* ratio Gly/PEG 200/isoprene = 1/2.5/5, ratio dioxane/PEG = 1/1, 10 mol% NaO-*t*-Bu, 0.05 mol% $Pd(acac)_2$ based on Gly, 90 °C and 24 h (time not optimised).
[b] Yield of glycerol and PEG 200 were calculated *vs.* an internal standard (tetradecane); some of the reactions yielded traces (< 0.5%) of di-telomers and tritelomers of glycerol and ditelomers of PEG-200, respectively.
[c] Selectivity presented for tail-to-head *vs.* head-to-head.
[d] TOF measured between 4–8 h (entry 3); 2–7 h (entry 4) and 24 h (entry 5–6).
[e] 0.005 mol% $Pd(acac)_2$.
[f] 0.005 mol% $Pd(acac)_2$, 120 °C.
[g] Reaction without glycerol; PEG 200/isoprene = 1/2.5.

turnover frequency (TOF) in various cases. A series of control reactions confirmed that no reaction took place in the absence of Pd precursor, ligand, or base. Performing the reaction in the absence of PEG gave zero conversion, and a biphasic medium was observed (the PEG is needed for dissolving the glycerol). A minimum of 10 mol% of NaO-*t*-Bu was needed for activating the carbene ligand. Furthermore, no products were observed in the absence of a mutually miscible co-solvent, nor in the presence of DMF, the latter probably due to a competition between the DMF and the carbene precursor on the base. The TONs obtained with this system are among the highest reported with isoprene,[10,23] especially considering that glycerol and PEG are much less reactive than methanol.

Comparing entries 3 and 4 in Table 1, we see that the lower ligand:Pd ratio of 1.5:1 considerably increases both substrate conversion and T2H:H2H selectivity, without changing significantly the telomerisation:dimerisation ratio. Figure 1, *top*, shows a typical product formation profile for the glycerol telomerisation products (the PEG telomerisation products gave similar curves, not shown). We can see that both isomers are formed simultaneously, with preferred formation of the T2H isomer. Interestingly, several

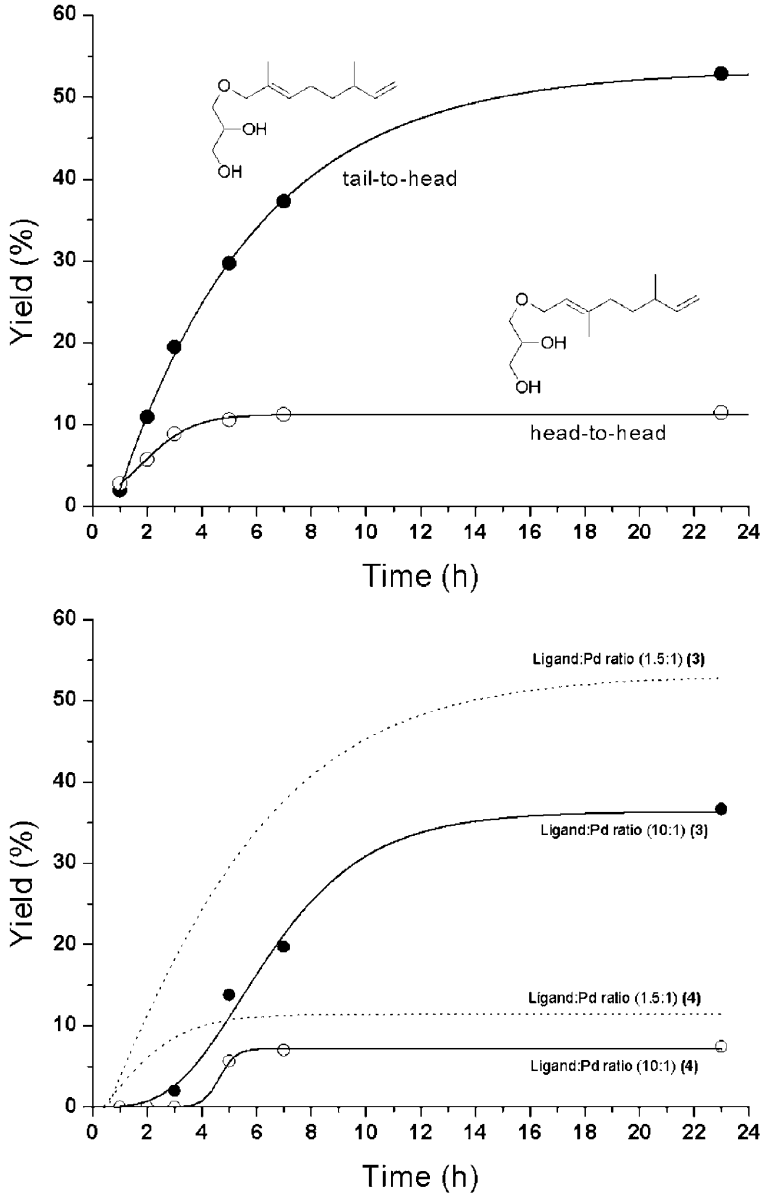
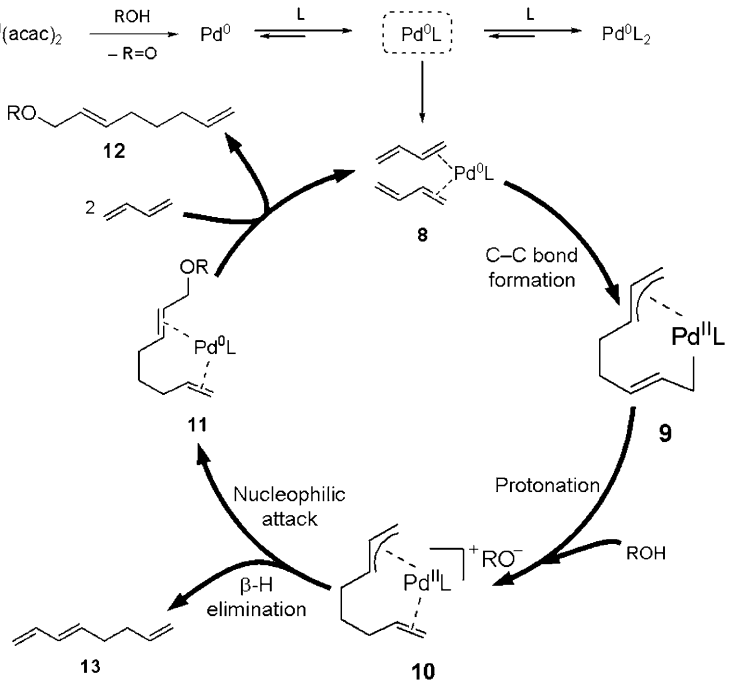


Figure 1. Reaction profile for glycerol telomerisation with isoprene in the presence of 0.05 mol% $Pd(acac)_2$ and 0.075 mol% carbene ligand (*top*), and corresponding reaction profiles using a 10:1 ligand:Pd ratio (0.5 mol% ligand, *bottom*; the dashed grey curves show the 1.5:1 ratio for comparison).



Scheme 1.

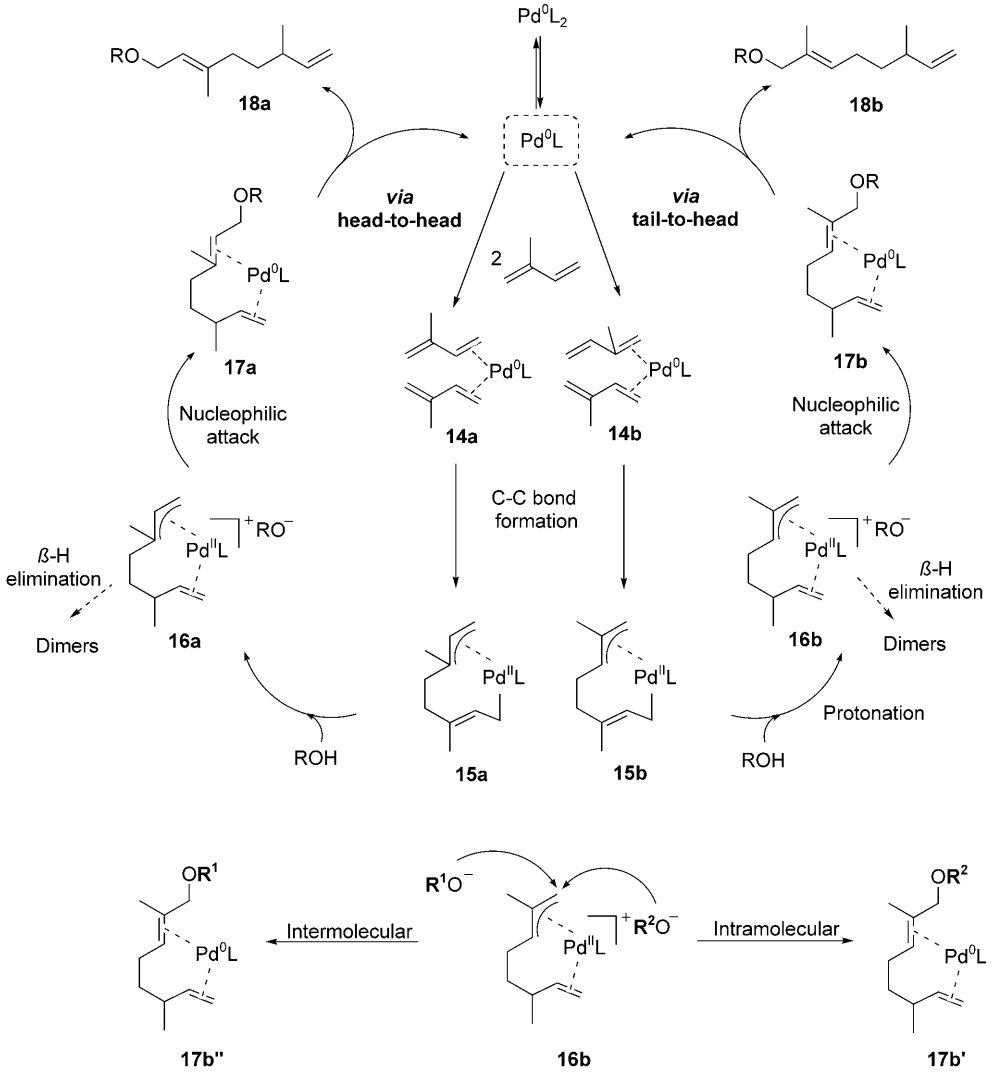
other studies recommend the use of excess ligand (typically a 10:1 ligand:Pd ratio), to avoid catalyst decomposition and improve product yield.[21,24] In our case, however, using a 10:1 ligand:Pd ratio led to a three-hour induction period (Figure 1, *bottom*), and resulted in an overall *lower* yield. The induction period may reflect a pre-equilibrium of the Pd catalyst precursor, $PdL_2 \Leftrightarrow PdL + L$. Thus, we suggest that most of the Pd is present in the inactive PdL_2 form, while a small amount is in the active PdL form.[25]

To study the practical limitations of catalyst concentration, we reduced ten times the Pd precursor and ligand loadings. This gave lower conversions and selectivities (Table 1, entry 5). However, another experiment carried out at 120 °C gave a TON of 13,400, albeit with a decrease in the ratio **3**:**4** from 7.0:1 to 2.3:1 (entry 6). This is significant, because this Pd-carbene complex usually deactivates above 90 °C. Considering the common mechanisms of Pd catalyst deactivation, however, using less catalyst in this case may well lower the chances of deactivation.[26,27]

Interestingly, performing the reaction in the absence of glycerol (entry 7) inverted the telomerisation/dimerisation selectivity. This gives some insight into the reaction mechanism. Because of the system's complexity, let us first consider the analogous and much simpler butadiene/alcohol telomerisation and dimerisation cycle, which was elucidated by Jolly and co-workers[28–30] (Scheme 1, *top*). The Pd catalyst enters the cycle as Pd^0L, forming a dual η^2-complex with two butadiene molecules. It is oxidised to Pd^{II} with the formation of the C–C bond, after which a proton is transferred from the alcohol, giving complex **10**. This complex can then either yield the dimer product *via* β-hydride elimination, or react further with an alkoxy ion, giving the telomerisation product complex.

Scheme 2, *top*, shows the analogous reaction pathways using isoprene, based on the mechanism proposed by Beller and co-workers.[10] Routes **a** (*left*) and **b** (*right*) lead to the H2H and T2H products, respectively. We see that the competition between the dimerisation and the telomerisation reactions depends on the stability of complex **16**, and on the relative rates of the alkoxy attack vs. the β-elimination. The alkoxy attack (Scheme 2, *bottom*) can be either intramolecular (i.e., when the attacking anion is the same one that has transferred the proton and still within the solvent cage), or intermolecular, with another alkoxy anion. This is supported by the reaction kinetics, which fit both 1st order and 2nd order rate laws ($R^2 = 0.993$ for 5 observations and $R^2 = 0.998$ for 6 observations, respectively, see Supporting Information). We suggest that in the absence of glycerol, the PEG-**16** complex is less stable, favouring β-elimination and inverting the telomerisation/dimerisation chemoselectivity. This reflects the importance of the intermolecular attack pathway.

In summary, we present here the first telomerisation reaction of isoprene with glycerol and PEG, giving a facile route to new terpene derivatives. High telomerization/dimerisation chemoselectivity is obtained even though the alcohols employed are much less reactive than methanol. Significantly, this catalyt-



Scheme 2.

ic system gives >99% linear monotelomer products. The possible implementation of this reaction in large-scale production of terpene amphiphiles will be the subject of future research in our laboratory.

Experimental Section

Procedure for Telomerisation Reaction of Isoprene with Glycerol and PEG-200

Glycerol (1.85 g, 0.02 mol) and PEG-200 (10.00 g, 0.5 mol) were added in a home-made autoclave and cooled to ~2 °C with an ice/water bath. Subsequently, isoprene (6.88 g, 0.1 mol), 10.00 g of dioxane, sodium *tert*-butoxide (0.1981 g, 2.00 mmol), carbene ligand (5.1 mg, 15.0 μmol) and Pd-(acac)$_2$ (3.0 mg, 10.0 μmol), were added. The autoclave was flushed three times with 6.0 bar of He and finally pressurised to 20.0 bar with He. The reaction was heated at 90 °C for 24 h, after which the autoclave was cooled back down to ~2 °C with an ice/water bath. Tetradecane (0.200 g, 1.00 mmol) was added as external standard and the conversion was measured by GC. The crude products were washed with water to eliminate dioxane, glycerol and PEG-200. The residue was purified by flash chromatography on silica gel (0.040–0.063 mm) with hexane:EtOAc as follows: 300 mL hexane, 400 mL hexane:EtOAc 3:1, 300 mL hexane:EtOAc 1:1, 400 mL hexane:EtOAc 1:3, and 350 mL hexane:EtOAc 1:6. TLC plates were developed in the corresponding hexane:EtOAc mixtures and then developed with $KMnO_4$ (1 g) and Na_2CO_3 (2 g) dissolved in 100 mL water (rinsing the plates in tap water until the purple colour disappears gives cleaner spots).

Example: Tail-to-head isomer of glycerol (**3**): Purification by flash chromatography with hexane:EtOAc 1:3 (R_f = 0.33); colourless oil; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.94 (d, $^3J_{10,6}$ = 6.5 Hz, 3H, CH_3, H^{10}), 1.31 (m, 2H, H^5), 1.54 (s, 3H, CH_3, H^9), 1.97 (m, 2H, H^4), 2.09 (m, 1H, H^6), 3.18–3.53 (m, 5H, H^a, H^b, H^c), 3.77 (s, 2H, H^1), 4.46 (bs, 1H, OH), 4.60 (bs, 1H, OH), 4.90–4.98 (m, 2H, H^8), 5.34 (t,

$^3J_{3,4}$ = 6.6 Hz, 1H, H^3), 5.69 (m, 1H, H^7); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 14.5 (C^9), 20.7 (C^{10}), 25.6 (C^4), 36.7 (C^5), 37.6 (C^6), 64.0 (C^b), 71.4, 71.9 (C^a, C^c), 77.0 (C^8), 113.9 (C^8), 127.7 (C^3), 133.0 (C^2), 145.1 (C^7); ESI/MS (70 eV): *m/z* (%) = 228 [M$^+$] (1), 213 (1), 199 (1), 171 (5), 158 (7), 145 (5), 137 (16), 136 (23), 121 (34), 107 (41), 95 (55), 81 (100), 67 (48), 55 (48), 41 (40).

Example: Tail-to-head isomer of PEG (**6b**): Purification by flash chromatography with hexane:EtOAc 1:3 (R_f = 0.30); colourless oil; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.94 (d, $^3J_{10,6}$ = 6.5 Hz, 3H, CH$_3$, H^{10}), 1.29 (m, 2H, H^5), 1.54 (s, 3H, CH$_3$, H^9), 1.98 (m, 2H, H^4), 2.08 (m, 1H, H^6), 3.32–3.49 (m, 16H, PEG), 3.78 (s, 2H, H^1), 4.57 (bs, 1H, OH), 4.90–4.98 (m, 2H, H^8), 5.35 (t, $^3J_{3,4}$ = 6.6 Hz, 1H, H^3), 5.69 (m, 1H, H^7); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 14.5 (C^9), 20.7 (C^{10}), 25.6 (C^4), 36.7 (C^5), 37.5 (C^6), 61.0 (CH$_2$OH), 69.1 (C-PEG), 70.6 (C-PEG), 73.1 (C-PEG), 76.8 (C^1), 113.9 (C^8), 127.9 (C^3), 132.9 (C^2), 145.1 (C^7); ESI/MS (70 eV): *m/z* (%) = 281 (1), 216 (2), 167 (1), 136 (27), 121 (21), 107 (32), 89 (46), 81 (49), 67 (22), 55 (22), 45 (100).

Supporting Information

Detailed information on the materials and instrumentation used, as well as product characterisation specifications (^{1}H, ^{13}C NMR, and, where appropriate, 2D ^{1}H-^{13}C HSQC experimental data), data of kinetic experiments, and original spectra are available in the Supporting Information.

Acknowledgements

We thank Dr. R. Palkovits for discussions and J. M. Ernstig for expert technical assistance with the 2D-NMR spectra. A.G. thanks the Spanish Ministry of Science and Innovation for an FPU short stay grant.

References

[1] G. Rothenberg, *Catalysis: Concepts and Green Applications*, Wiley-VCH, Weinheim, **2008**, ISBN 978-3-527-31824-7.
[2] P. T. Anastas, J. B. Zimmerman, *Environ. Sci. Technol.* **2003**, *37*, 95A.
[3] For a good critical review on the upgrading of biomass to bulk chemicals, see: J. van Haveren, E. L. Scott, J. Sanders, *Biofuels, Bioprod. Biorefin.* **2008**, *2*, 41.
[4] A. A. Kiss, A. C. Dimian, G. Rothenberg, *Adv. Synth. Catal.* **2006**, *348*, 75.
[5] A. A. Kiss, F. Omota, A. C. Dimian, G. Rothenberg, *Top. Catal.* **2006**, *40*, 141.
[6] A. A. Kiss, A. C. Dimian, G. Rothenberg, *Energy Fuels* **2008**, *22*, 598.
[7] R. Palkovits, I. Nieddu, R. J. M. Klein Gebbink, B. M. Weckhuysen, *ChemSusChem* **2008**, *1*, 193.
[8] R. Palkovits, I. Nieddu, C. A. Kruithof, R. J. M. Klein Gebbink, B. M. Weckhuysen, *Chem. Eur. J.* **2008**, *14*, 8995.
[9] M. Hidai, H. Mizuta, H. Yagi, Y. Nagai, K. Hata, Y. Uchida, *J. Organomet. Chem.* **1982**, *232*, 89.
[10] R. Jackstell, A. Grotevendt, D. Michalik, L. El Firdoussi, M. Beller, *J. Organomet. Chem.* **2007**, *692*, 4737.
[11] R. C. Nunes, M. H. Araujo, E. N. dos Santos, *Catal. Commun.* **2007**, *8*, 1798.
[12] J. P. Bianchini, B. Waegell, E. M. Gaydou, H. Rzehak, W. Keim, *J. Mol. Catal.* **1981**, *10*, 247.
[13] J. P. Bianchini, E. M. Gaydou, B. Waegell, A. Eisenbeis, W. Keim, *J. Mol. Catal.* **1985**, *30*, 197.
[14] S. M. Maddock, M. G. Finn, *Organometallics* **2000**, *19*, 2684.
[15] F. Leca, R. Reau, *J. Catal.* **2006**, *238*, 425.
[16] K. J. Cavell, D. S. McGuinness, *Coord. Chem. Rev.* **2004**, *248*, 671.
[17] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768.
[18] H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem. Int. Ed.* **2007**, *46*, 834.
[19] P. Hauwert, G. Maestri, J. W. Sprengers, M. Catellani, C. J. Elsevier, *Angew. Chem.* **2008**, *120*, 3267; *Angew. Chem. Int. Ed.* **2008**, *47*, 3223.
[20] N. D. Clement, L. Routaboul, A. Grotevendt, R. Jackstell, M. Beller, *Chem. Eur. J.* **2008**, *14*, 7408.
[21] F. Vollmuller, W. Magerlein, S. Klein, J. Krause, M. Beller, *Adv. Synth. Catal.* **2001**, *343*, 29.
[22] F. Vollmuller, J. Krause, S. Klein, W. Magerlein, M. Beller, *Eur. J. Inorg. Chem.* **2000**, 1825.
[23] Jackstell et al.[10] obtained at a Pd loading of 0.002 mol% a TON of 33,000 for isoprene + MeOH, using a ligand:Pd ratio of at least 4:1. The best results were achieved at 50–70 °C. Higher temperatures gave slightly less conversion (independent of the ligand:Pd ratio), probably due to a faster decomposition of the active species.
[24] A. Behr, M. Urschey, *Adv. Synth. Catal.* **2003**, *345*, 1242.
[25] G. Rothenberg, S. C. Cruz, G. P. F. Van Strijdonck, H. C. J. Hoefsloot, *Adv. Synth. Catal.* **2004**, *346*, 467.
[26] P. W. N. M. van Leeuwen, *Appl. Catal. A: Gen.* **2001**, *212*, 61.
[27] A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, H. J. W. Henderickx, M. A. M. Walet, J. G. de Vries, *Adv. Synth. Catal.* **2002**, *344*, 996.
[28] P. W. Jolly, R. Mynott, B. Raspel, K. P. Schick, *Organometallics* **1986**, *5*, 473.
[29] R. Benn, P. W. Jolly, R. Mynott, G. Schenker, *Organometallics* **1985**, *4*, 1136.
[30] R. Benn, P. W. Jolly, R. Mynott, B. Raspel, G. Schenker, K. P. Schick, G. Schroth, *Organometallics* **1985**, *4*, 1945.

