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Mechanistic Insights into the Palladium^{II}-Catalyzed Hydroxyalkoxylation of 2-Allylphenols

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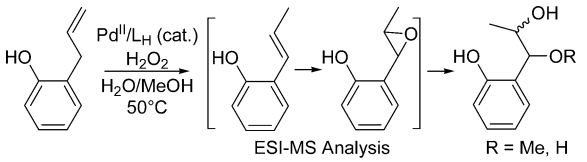
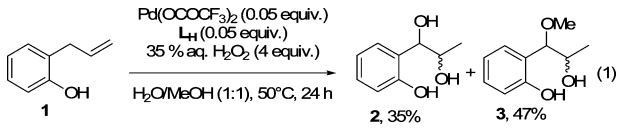
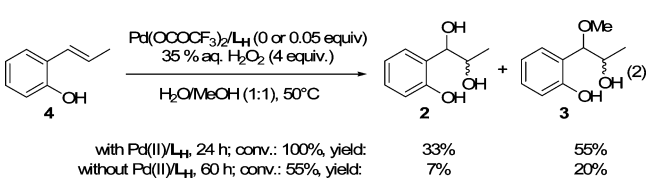


The Pd(OCOCF$_3$)$_2$/[(HOCH$_2$CH$_2$NHCOCH$_2$)$_2$NCH$_2$]$_2$-catalyzed oxidation of *o*-allylphenol with H$_2$O$_2$ in water/methanol affords a *syn* and *anti* mixture of 2-(1,2-dihydroxypropyl)-phenol and 2-(2-hydroxy-1-methoxypropyl)phenol. Mechanistic experiments and ESI-MS studies support a pathway wherein isomerization of the C=C bond followed by its epoxidation and oxirane opening led to the products. Recycling of the catalytic system led to gradual lost of activity.

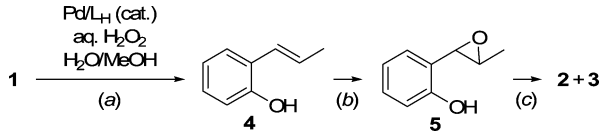
Recently, we disclosed the one-pot transformation of 2-allylphenols into 2-(1,2-dihydroxypropyl)phenol derivatives under the conditions depicted in eq 1 (**L$_H$** = [(HOCH$_2$CH$_2$NHCOCH$_2$)$_2$-NCH$_2$]$_2$) for the reaction of *o*-allylphenol (**1**) in aqueous methanol.[1] This transformation has been explained by the cascade reaction shown in Scheme 1, and we have demonstrated the large palladium increase of the oxidation efficiency of 2-((*E*)-prop-1-enyl)phenol (**4**) into **2** and **3** by an aqueous methanolic solution of H$_2$O$_2$ (eq 2).[1] Nevertheless, the different steps of Scheme 1 were only suggested.



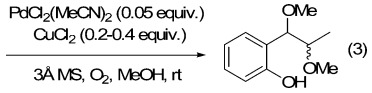


(1) Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J. *Synthesis* **2005**, 2615−2618.

SCHEME 1. Proposed Steps and Intermediates for Formation of 2-(1,2-Dihydroxypropyl)phenol and 2-(2-Hydroxy-1-methoxypropyl)phenol from *o*-Allylphenol

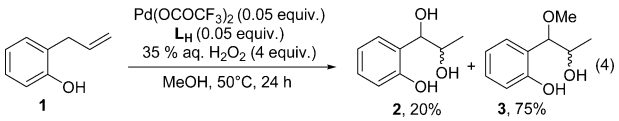


Shortly after our report, Schultz and Sigman disclosed the Pd-catalyzed aerobic dialkoxylation of **1** and **4** in methanol (eq 3).[2] Although both the reaction conditions and the proposed



mechanisms are strongly different, the results are rather similar. Sigman's paper[2,3] urges us to report our studies devoted to the mechanism of the Pd(OCOCF$_3$)$_2$/**L$_H$**-catalyzed formation of **2** and **3** from **1**.

Heating a 1:1 H$_2$O/MeOH solution of **1** at 50 °C for 24 h in the presence of catalytic amounts of Pd(OCOCF$_3$)$_2$ and **L$_H$** (0.05 equiv each) led to 2-((*E*)-prop-1-enyl)phenol (**4**).[4] Furthermore, carrying out the oxidation of **1** for 4.5 h instead of 24 h led to a mixture of **1**, **2**, **3**, and **4** (**1** + **4**, 22%; **2**, 14%; **3**, 17%).[5] Since **4** has been oxidized into **2** and **3** (eq 2), step *a* of Scheme 1 can be considered as demonstrated. Such a step was also involved in the reaction mechanism proposed by Sigman et al. for their dialkoxylation of **1**.[2] The second step of the Sigman mechanism is a Wacker-type addition of MeOH to the *β*-carbon of the propenyl moiety.[2] Such a possibility was discarded under our conditions because the Pd(OCOCF$_3$)$_2$/**L$_H$**-catalyzed oxidation of **1** with 35% aqueous H$_2$O$_2$ in MeOH (eq 4) instead of 1:1 H$_2$O/MeOH (eq 1) solution did not produced the dimethoxylation adduct.



At this level, we have to point out that the careful analysis of ^{1}H NMR spectra of **2** and **3** (obtained from **1** and **4** as

(2) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460−1461.

(3) Sigman et al. have subsequently reported the Pd-catalyzed aerobic hydroalkoxylation of **4** using PdCl$_2$[(−)-sparteine] as the catalyst: (a) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794−2795. (b) Zhang, Y.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 5557−5560.

(4) For Pd^{II}-catalyzed isomerization of allylphenol, see: (a) Golborn, P.; Scheimann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870−2875. (b) Davies, N. R.; DiMichiel, A. D. *Aust. J. Chem.* **1973**, *26*, 1529−1543. (c) Gross, J. L. *Tetrahedron Lett.* **2003**, *44*, 8563−8565. (d) ref. 2.

(5) The oxidation of 2-allyl-6-methylphenol with the same catalytic system, at room temperature for 72 h in a 1:2 H$_2$O/MeOH solution, led to 2-((*E*)-prop-1-enyl)-6-methylphenol (17%), 2-(1,2-dihydroxypropyl)-6-methylphenol (15%), and 2-(2-hydroxy-1-methoxypropyl)-6-methylphenol (30%).

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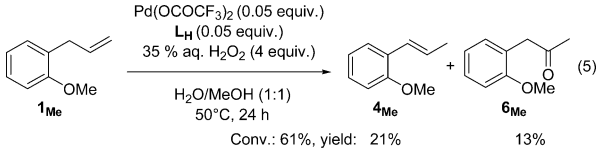
depicted in eqs 1 and 2) has shown that these two products were in fact a 75:25 mixture of *syn* and *anti* diastereoisomers.[6]

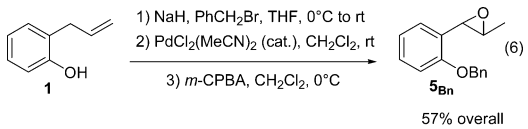
Under the experimental conditions of eq 1, 1-allyl-2-methoxybenzene (**1$_{Me}$**) afforded 1-methoxy-2-((*E*)-prop-1-enyl)-benzene (**4$_{Me}$**) and 1-(2-methoxyphenyl)propan-2-one (**6$_{Me}$**) (eq 5). The formation of methyl ketone **6$_{Me}$** could occur via a

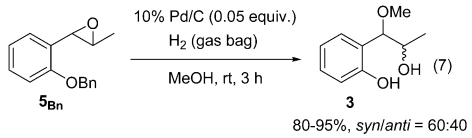


Wacker-type reaction[2,7] or from the rearrangement of 2-(2-methoxyphenyl)-3-methyloxirane (**5$_{Me}$**),[8,9] this latter compound being produced by epoxidation of **4$_{Me}$**. The exchange of **1$_{Me}$** for allylbenzene as the substrate led to a 54:46 mixture of propenylbenzene and 1-phenylpropan-2-one (conversion 100%). These results demonstrate the requirement of the *o*-hydroxy substitutent to obtain the 1,2-dihydroxypropyl derivatives.

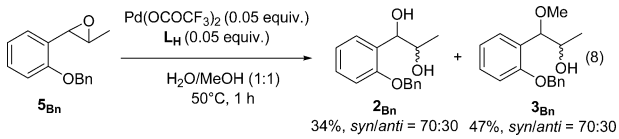
Before examining the hypothesis of epoxide **5** as intermediate, we verified that **3** was not obtained from **2** under our Pd-catalyzed oxidation conditions. This implies that **2** is not an intermediate leading to **3** in the oxidations depicted in eqs 1 and 2.

We tested the epoxidation of **4** using the $VO(acac)_2$/*t*-BuOOH catalytic system, but only 1-(2-hydroxyphenyl)propan-2-one (**6**) instead of **5** was isolated. Such a reaction pathway was already reported from **4** using either peracetic acid[8] or metal-catalyzed oxidation with *t*-BuOOH,[9] and it was proposed that **6** was produced from the rearrangement of the intermediate epoxide **5** via benzylic C−O bond cleavage followed by 1,2 hydride migration.[9] This led us to investigate the preparation of **5** via 2-(2-(benzyloxy)phenyl)-3-methyloxirane (**5$_{Bn}$**), which was obtained from **1** as depicted in eq 6.[10] However, the Pd-catalyzed hydrogenolysis of **5$_{Bn}$** (eq 7) induced also the cleavage of the epoxide ring to afford a mixture of **3-*syn*** and **3-*anti***.[11]





Subjecting a 1:1 H_2O/MeOH solution of **5$_{Bn}$** to catalytic amounts of $Pd(OCOCF_3)_2$ and **L$_H$** at 50 °C led to a fast reaction affording **2$_{Bn}$** and **3$_{Bn}$** (eq 8); their Pd-catalyzed hydrogenolysis



produced **2** and **3** quantitatively. The formation of both a diol and an hydroxyether from **5$_{Bn}$** is in agreement with step *c* of Scheme 1, and the absence of 1-(2-benzyloxyphenyl)propan-2-one (**6$_{Bn}$**) demonstrates that in eq 5, the appearance of **6$_{Me}$** occurs via a Wacker-type reaction of **1$_{Me}$** rather than from the rearrangement of **5$_{Me}$**. The diastereoselectivity of the oxirane opening was also examined using CF_3CO_2H, i.e., a Brönstedt acid, instead of $Pd(OCOCF_3)_2$. In water at 50 °C for 3 h, the conversion of **5$_{Bn}$** induced by 0.05 equiv of CF_3CO_2H was low and a 80:20 mixture of **2$_{Bn}$-*syn*** and **2$_{Bn}$-*anti*** was isolated (10% yield). The reaction was much more efficient in MeOH, a 60:40 mixture of **3$_{Bn}$-*syn*** and **3$_{Bn}$-*anti*** being obtained in 95% yield for a reaction time of 1.5 h. Therefore, it appears that the diastereoselectivity of the epoxide opening of **5$_{Bn}$** is not greatly dependent on the nature of the reagent and catalyst. Furthermore, it seems interesting to note the similarity of the diol/hydroxyether ratios obtained from the Pd-catalyzed reactions of **1**, **4**, and **5$_{Bn}$** carried out in 1:1 H_2O/MeOH solutions (eqs 1, 2, and 8).

According to the literature,[8,9,12] epoxide **5** cannot be isolated under our conditions that use a catalyst having Lewis acid properties. Nevertheless, epoxidation of alkenes using Pd catalysts and peroxides[13] or palladium superoxo complexes obtained from reaction of Pd^{II} with H_2O_2[14] has been reported. Furthermore, the phenol-mediated epoxidation of alkenes by H_2O_2 disclosed by Jacobs et al.[15] can rationalize the results of eq 2 obtained in the absence of palladium and the absence of the formation of **2$_{Me}$** and **3$_{Me}$** from **1$_{Me}$** under conditions depicted in eq 5. In eq 2, **2** and **3** would be obtained via epoxidation of **4** by H_2O_2 promoted intramolecularly by the phenolic moiety, whereas in eq 5, the protection of the hydroxy group precludes such an assistance and, consequently, the appearance of **2$_{Me}$** and **3$_{Me}$**.

We have recently disclosed the interest of ESI-MS analysis to determine the mechanism of Pd/**L$_H$**-catalyzed allylic substitu-

(6) See Supporting Information for the determination of the *syn* and *anti* structures via the synthesis of 2-(2,2,5-trimethyl-1,3-dioxolan-4-yl)phenol and ^{1}H NMR analysis.

(7) (a) Roussel, M.; Mimoun, H. *J. Org. Chem.* **1980**, *45*, 5387−5390. (b) Barak, G.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1266−1267. (c) Alandis, N.; Rico-Lattes, I.; Lattes, A. *New J. Chem.* **1984**, *18*, 1147−1149. (d) Namboodiri, V. V.; Varma, R. S.; Sahle-Demessie, E.; Pillai, U. R. *Green Chem.* **2002**, *4*, 170−173.

(8) Tinsley, S. W. *J. Org. Chem.* **1959**, *24*, 1197−1199.

(9) Lattanzi, A.; Senatore, A.; Massa, A.; Scettri, A. *J. Org. Chem.* **2003**, *68*, 3691−3694.

(10) **5$_{Bn}$** has also been prepared from **4** in two steps (benzylation followed by epoxidation), but this procedure was less convenient.

(11) The Pd-catalyzed hydrogenolysis of epoxides leads usually to the corresponding alcohols even in alcoholic solvents (Schultze, L. M.; Chapman, H. H.; Dubree, N. J. P.; Jones, R. J.; Kent, K. M.; Lee, T. T.; Louie, M. S.; Postich, M. J.; Prisbe, E. J.; Rohloff, J. C.; Yu, R. H. *Tetrahedron Lett.* **1998**, *39*, 1853−1856), but the formation of 2-methoxy-2-phenylethanol from styrene oxide under such conditions is documented (Sajiki, H.; Hattori, K.; Hirota, H. *Chem. Commun.* **1999**, 1041−1042).

(12) For Lewis acid catalyzed alcoholysis of epoxides, see: (a) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett* **1992**, 673−676. (b) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett* **1992**, 673−676. (c) Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152−1154. (d) Likhar, P. R.; Kumar, M. P.; Bandyopadhyay, A. K. *Synlett* **2001**, 836−838.

(13) (a) Nagata, R.; Matsumura, T.; Saito, I. *Tetrahedron Lett.* **1984**, *25*, 2691−2694. (b) Zhou, X.-G.; Huang, J.-S.; Yu, X.-Q.; Zhou, Z.-Y.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **2000**, 1075−1080. (c) Nishida, M.; Torii, A. Jpn. Kokai, Tokkyo, Koho, JP 187,792; *Chem. Abstr.* **2001**, *135*, 92546. (d) Corey, E. J.; Yu, J.-Q. *Org. Lett.* **2002**, *4*, 2727−2730.

(14) (a) Talsi, E. P.; Babenko, V. P.; Likholobov, V. A.; Nekipelov, V. M.; Chinakov, V. D. *J. Chem. Soc., Chem. Commun.* **1985**, 1768−1769. (b) Talsi, E. P.; Babenko, V. P.; Shubin, A. A.; Chinakov, V. D.; Nekipelov, V. M.; Zamarev, K. I. *Inorg. Chem.* **1987**, *26*, 3871−3878.

(15) Wahlen, J.; De Vos, D. E.; Jacobs, P. A. *Org. Lett.* **2003**, *5*, 1777−1780.

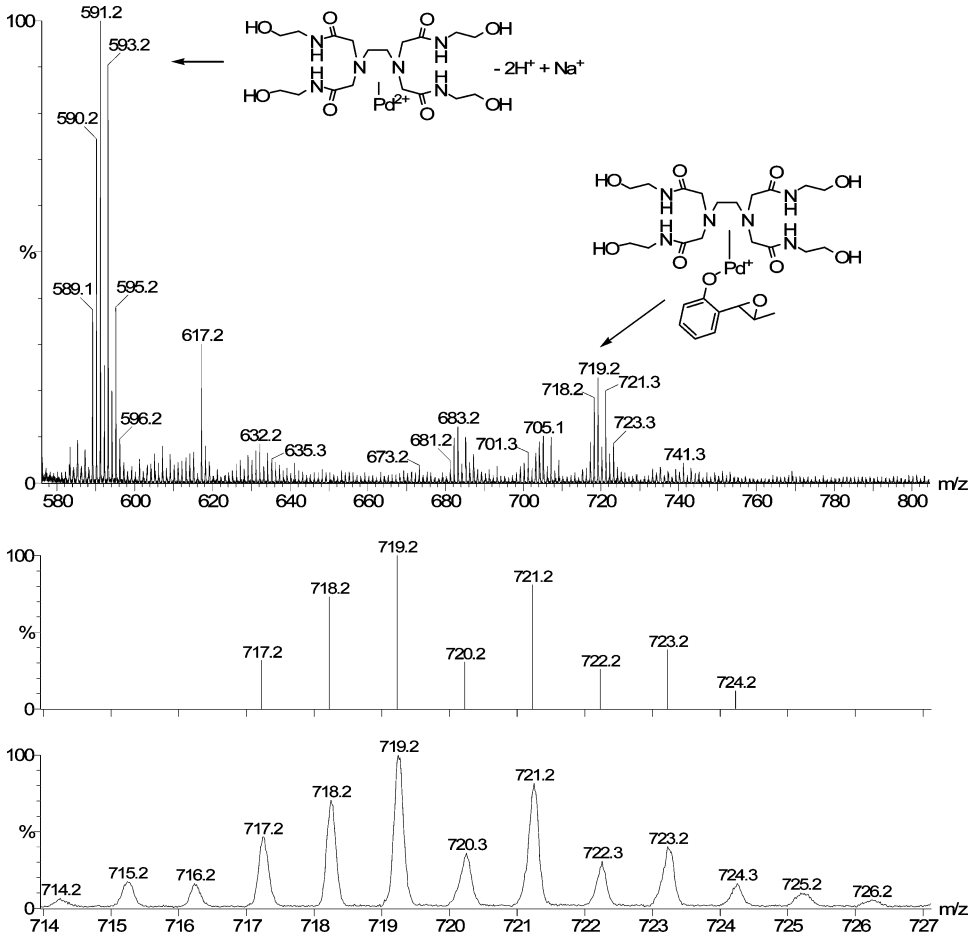
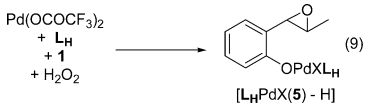


FIGURE 1. ESI(+)-MS spectrum of the reaction medium after 4 h and expanded ESI(+)-MS spectrum of the species detected at $m/z = 719$ with its corresponding theoretical spectrum.

tions in water.[16] The tandem version, ESI-MS/MS, is also a valuable tool for identification and structural assignments of charged palladium complexes.[17] We have used these analytical techniques to study the reaction depicted in eq 1, the identification of the detected species being aided by comparison between the observed and calculated isotope distribution patterns. Because palladium displays six isotopes, the ions containing this atom should be mass-detected as clusters of isotopomeric ions centered on the most abundant isotope, i.e., 106.

The ESI(+)-MS spectrum of an equimolecular amount of $Pd(OCOCF_3)_2$ and $\mathbf{L_H}$ dissolved in a 1:1 H_2O/MeOH mixture showed three clusters at $m/z = 569$, 683, and 705 (Figure S1, Supporting Information) attributable to the cationic species $[\mathbf{L_H}Pd - H]^+$, $[\mathbf{L_H}PdOCOCF_3]^+$, and $[\mathbf{L_H}PdOCOCF_3 - H + Na]^+$, respectively. The analysis of the ESI(−)-MS spectrum of the same mixture revealed three clusters at $m/z = 567$, 681, and 795 (Figure S2, Supporting Information) corresponding to $[\mathbf{L_H}Pd - 3H]^-$, $[\mathbf{L_H}PdOCOCF_3 - 2H]^-$, and $[\mathbf{L_H}Pd(OCOCF_3)_2 - H]^-$, respectively. All of these clusters are consistent with the formation of the $\mathbf{L_H}Pd(OCOCF_3)_2$ complex. After addition of **1** (5 equiv/Pd) and H_2O_2 (20 equiv/Pd) to the solution and heating at 50 °C for 4 h, the ESI(+)-MS spectrum contained a cluster at $m/z = 719$ (Figure 1), confirmed by high resolution ($C_{27}H_{45}N_6O_{10}{}^{104}Pd$ calcd 717.2237, obsd 717.2231), attributable to $[\mathbf{L_H}Pd(\mathbf{5}) - H)]^+$. The ESI(+)-MS/MS spectrum of this cluster with the proposed fragmentations is shown in Figure 2. According to these analysis, the solution contains $[\mathbf{L_H}PdX(\mathbf{5}) - H]$ species, X being probably $OCOCF_3$ (eq 9).



From the above experiments and analytical studies, we can now conclude that the formation of 2-(1,2-dihydroxypropyl)-phenols and 2-(1-alkoxy-2-hydroxypropyl)phenols from 2-allylphenols occurs via the cascade reaction depicted in Scheme 1, i.e., isomerization of the C=C bond, followed by its epoxidation and the opening of the resulting oxirane.

In the framework of this study, we have also examined the recycling of the catalytic system. After extraction of the products with diethyl ether, a new batch of substrate and H_2O_2 was added to the aqueous phase, and the reaction proceeded as previously, leading to **2** (24%) and **3** (49%). The recycling was repeated

(16) (a) Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J.; Pla-Quintana, A.; Roglans, A.; Pleixats, R. *Organometallics* **2004**, *23*, 4796−4799. (b) Chevrin, C.; Le Bras, J.; Roglans, A.; Harakat, D.; Muzart, J. *New J. Chem.* **2007**, *31*, 121−126.

(17) (a) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514−2518. (b) Guo, H.; Qian, R.; Liao, Y.; Ma, S.; Guo, Y. *J. Am. Chem. Soc.* **2005**, *127*, 13060−13064. (c) Enquist, P.-A.; Nilsson, P.; Sjöberg, P.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 8779−8786.

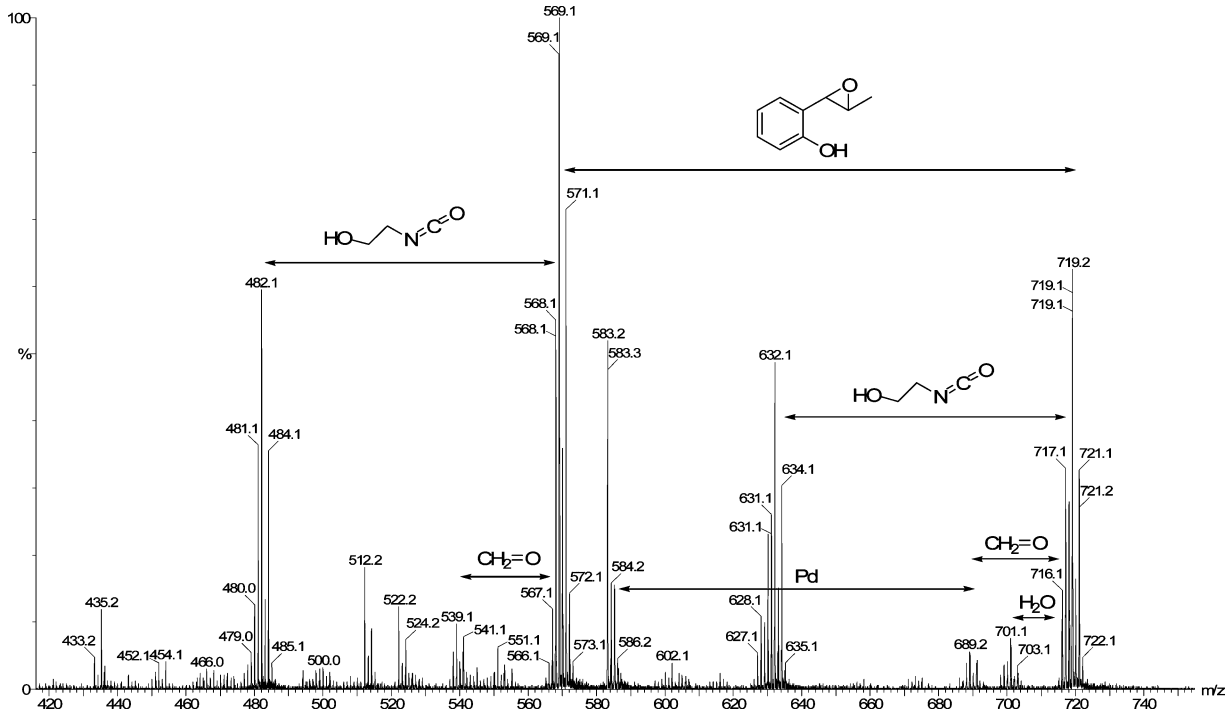


FIGURE 2. ESI(+)-MS/MS spectrum for the cluster at $m/z = 719$.

four times (Graph S1, Supporting Information) affording in the last run **2** and **3** in 35% and 24% yields, respectively.

Experimental Section

Oxidation of *o*-Allylphenol and Recycling Experiments. To a stirred solution of $Pd(OCOCF_3)_2$ (25 mg, 0.075 mmol) and $\mathbf{L_H}$ (35 mg, 0.075 mmol) in water (1 mL) were added *o*-allylphenol (206 mg, 1.5 mmol), 35% aqueous H_2O_2 (0.51 mL, 6 mmol) and methanol (1 mL). After stirring at 50 °C for 24 h, extraction with Et_2O, following by drying of the organic phases over $MgSO_4$, evaporation of the solvent, and column chromatography (silica gel, petroleum ether/EtOAc, 70:30) led to **2** (88 mg, 0.52 mmol, 35%) and **3** (128 mg, 0.70 mmol, 47%). To the recovered aqueous phase was added a new batch of *o*-allylphenol and 35% aqueous H_2O_2, and the reaction proceeded as above.

2-(1,2-Dihydroxypropyl)phenol 2-*syn* and 2-*anti*. Yellow oil. IR (film): ν 3326, 1590, 1490, 1456, 1242, 1021. ^{1}H NMR-($CDCl_3$): δ 1.09 (d, $J = 6.3$ Hz, 2.25H, *syn*), 1.14 (d, $J = 6.7$ Hz, 0.75H, *anti*), 3.92−4.20 (m, 1H), 4.48 (d, $J = 8.0$ Hz, 0.75H, *syn*), 4.75 (d, $J = 4.1$, 0.25H, *anti*), 6.74−6.89 (m, 2H), 7.02 (d, $J = 7.5$, 1H), 7.20 (t, $J = 8.0$, 1H). **2-*syn*** (measured in a mixture with **2-*anti***) ^{13}C NMR ($CDCl_3$): δ 19.2 (CH_3), 70.6 (CH), 80.1 (CH), 117.3 (CH), 120.1 (CH), 124.5 (C), 129.1 (CH), 129.6 (CH), 155.5 (C).

2-(2-Hydroxy-1-methoxypropyl)phenol 3-*syn* and 3-*anti*. Yellow gum. IR (film): ν 3336, 1606, 1458, 1240, 1100. ^{1}H NMR-($CDCl_3$): δ 1.05 (d, $J = 6.3$, 2.25H, *syn*), 1.20 (d, $J = 6.2$ Hz, 0.75H, *anti*), 3.40 (s, 0.75H, *anti*), 3.45 (s, 2.25H, *syn*), 4.03−4.15 (m, 2H), 6.84−6.90 (m, 2H), 6.99−7.03 (m, 1H), 7.20−7.27 (m, 1H). **3-*syn*** (measured in a mixture with **3-*anti***) ^{13}C NMR ($CDCl_3$): δ 18.7 (CH_3), 57.9 (CH_3), 69.5 (CH), 90.6 (CH), 117.2 (CH), 120.1 (CH), 121.5 (C), 129.9(CH), 130.0 (CH), 155.6 (C).

Acknowledgment. We are indebted to "Région Champagne-Ardenne" and "Ville de Reims" for Ph.D. studentships to C.C. and E.T., respectively.

Supporting Information Available: Experimental procedures; determination of the *syn* and *anti* structures; characterization data and ^{1}H and ^{13}C NMR spectra of products; ESI(+)-MS spectra This material is available free of charge via the Internet at http://pubs.acs.org.

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