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Novel Anti-Markovnikov Regioselectivity in the Wacker Reaction of Styrenes

Joseph A. Wright,[a, b] Matthew J. Gaunt,[a] and Jonathan B. Spencer*[a]

Abstract: The Wacker reaction is one of the longest known palladium-catalysed organic transformations, and in the vast majority of cases proceeds with Markovnikov regioselectivity. Palladium(II)-mediated oxidation of styrenes was examined and *in the absence of reoxidants* was found to proceed in an anti-Markovnikov sense, giving aldehydes. Studies on the mechanism of this unusual transformation were carried out, and indicate the possible involvement of a η^4-palladium–styrene complex. With a heteropolyacid as the terminal oxidant, oxidation of styrene to give the anti-Markovnikov aldehyde as the major product was found to be catalytic.

Keywords: homogeneous catalysis · palladium · reaction mechanisms · styrenes · Wacker reaction

Introduction

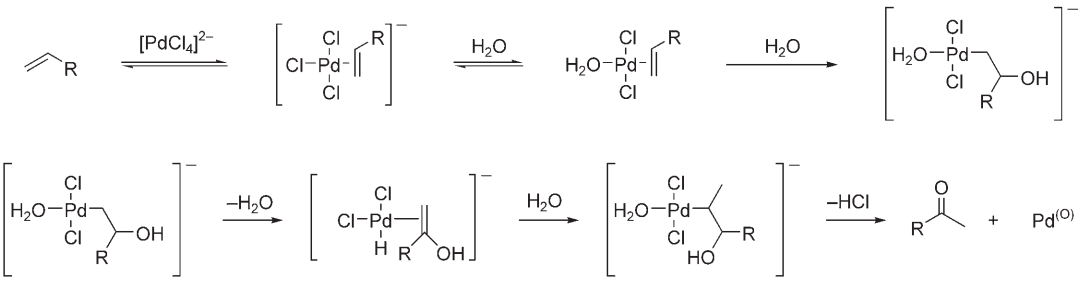
The oxidation of alkenes to carbonyl compounds catalysed by palladium(II) salts, usually referred to as the Wacker reaction, is one of the longest standing palladium-catalysed organic transformations.[1] The mechanism of this oxidation has been the subject of intense study, and a great amount has been learned concerning the pathway of the reaction.[2] The generally accepted mechanism for reaction in aqueous media is summarised in Scheme 1. Co-ordination of the alkene to palladium is followed by nucleophilic attack by water on the double bond. The intermediate formed then re-arranges via an enol to give a second β-hydroxypalladium species, which then breaks down to the carbonyl product and palladium(0).

The σ-bonded (β-hydroxyalkyl)palladium complex has been determined as a key intermediate in this reaction. However, the factors controlling the regiochemistry of the hydroxypalladation step for unsymmetrical alkenes remain obscure. In the majority of cases, the regioselectivity of hydroxypalladation follows Markovnikov's principles. This has been widely used in synthesis[3] to the extent that "terminal alkenes may be viewed as masked methyl ketones".[4] The major source of anti-Markovnikov regioselectivity in the Wacker reaction is the presence of chelating heteroatoms in the substrate.[5] Pellissier and co-workers have shown that this can lead to lowering of the transition state energy for attack by water at the methylene carbon atom of the vinyl group.[6] There are also a very small number of reports of apparent anti-Markovnikov regioselectivity where no heteroatom is present in the substrate. Two related systems have been reported by Feringa[7] and Wenzel,[8] both of which make use of palladium–nitro complexes as catalysts. Feringa suggests a reaction mechanism somewhat different to that of the Wacker reaction (it does not involve the palladium(0)–palladium(II) couple), while the conditions used by Wenzel are selective for aldehyde only with allyl acetate as the substrate.

The importance of aldehydes as useful synthetic intermediates in synthesis has led us to investigate ways in which the regioselectivity in the Wacker oxidation of alkenes can be controlled. Two of us have reported that the apparent anti-Markovnikov ketone is the major product obtained from the oxidation of a number of β-methyl styrenes.[9] In this report, reversal in the regioselectivity of the *stoichiometric* palladium(II)-mediated oxidation of styrenes is reported. Catalysis of this reaction is demonstrated by using a heteropolyacid as the terminal oxidant. Evidence for the mechanism of this unusual transformation is also discussed.[10]

[a] Dr. J. A. Wright, Dr. M. J. Gaunt, Dr. J. B. Spencer
University Chemical Laboratories
University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
Fax. (+44) 1223-336-362
E-mail: jbs20@cam.ac.uk

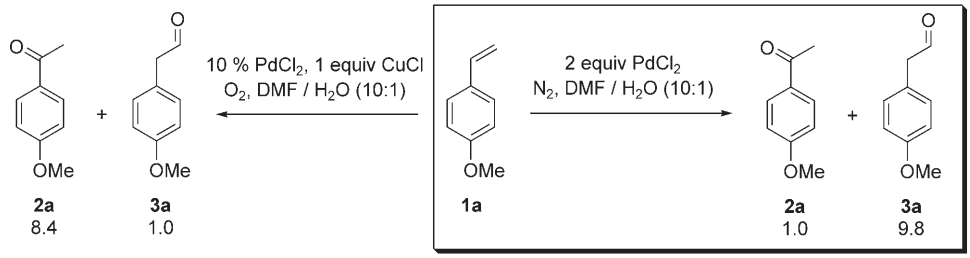
[b] Dr. J. A. Wright
Current address: Department of Chemistry, University of East Anglia, Norwich, NR4 7TJ (UK)



Scheme 1. General mechanism for the Wacker reaction.

Results and Discussion

Anti-Markovnikov reactivity: Under standard catalytic conditions, the Wacker reaction of 4-methoxystyrene proceeds to a mixture of the two possible products. As expected, the Markovnikov product (the methyl ketone **2a**) was found to predominate, and only a small amount of the aldehyde **3a** was observed (Scheme 2).[11] However, when the reaction



Scheme 2. Stoichiometric versus catalytic reaction.

was performed in the absence of the reoxidant a reversal of the usual regioselectivity occurred. Thus, reaction of **1a** with two equivalents of $PdCl_2$ gave the aldehyde **3a** as the major product.[12,13] The reaction did not proceed to completion, and after approximately five hours conversion reached 53% (longer reaction periods did not improve conversion). This surprising reversal in regioselectivity suggested that it might be possible to control the outcome of the reaction by adjusting the reaction stoichiometry and conditions. To fully exploit this potentially useful transformation, we carried out a detailed investigation into the reasons for this unusual regioselectivity.

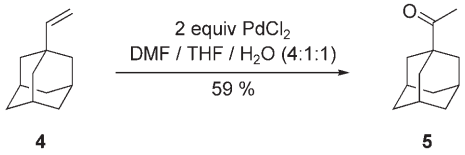
Due to the lack of a reoxidant for palladium(0), the colloidal metal or a zero-valent complex could influence the reaction pathway. If this were the case, the addition of a palladium(0) source would increase aldehyde production in the early stages of the reaction. Three common palladium(0) sources were therefore examined over a reaction time of 30 min (Table 1). None of the sources led to an increase in the production of aldehyde. Indeed, the use of palladium(0) tetrakis(triphenylphosphane) gave a marked reduction in aldehyde formation; this may be attributable to the presence of triphenylphosphane in the reaction mixture, although this was not examined further.

Table 1. Reaction in the presence of palladium(0).[a]

Entry	Pd^0 source	Ratio aldehyde:ketone
1	none (reference)	2.7:1.0
2	Pd black	2.5:1.0
3	$[Pd_2(dba)_3]$	2.3:1.0
4	$[Pd(PPh_3)_4]$	1.7:1.0

[a] Reaction conditions: 1 equiv styrene, 2 equiv $PdCl_2$, 10% Pd^0 source, DMF/H_2O (10:1), 30 min.

An interaction between the aromatic group of the substrate and the palladium(II) centre was a second possible cause of the unusual regioselectivity. To examine this, vinyladamantane **4** was synthesised; it is a non-aromatic system, which like styrene contains no allylic hydrogen atoms. Oxidation under the same conditions as before gave only the methyl ketone **5**, thus confirming that the aromatic group was crucial for the regioselectivity observed (Scheme 3).



Scheme 3. Wacker reaction of adamantyl substrate **4**.

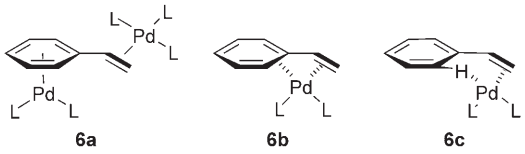
Along with $PdCl_2$, $Pd(OAc)_2$ is a widely used source of palladium(II). Significantly, using $Pd(OAc)_2$ in place of $PdCl_2$ gave exclusively the methyl ketone in good yield (72% isolated). The significant influence of the counter-ion on the pathway of the reaction strongly implicated the presence of an unusual palladium-styrene complex in solution; the stability of this complex would be dependent upon other ligands present in the reaction mixture.[14]

Nature of the palladium–substrate complex: To probe the existence of a palladium–styrene complex, evidence for the formation of such an intermediate was sought. When $PdCl_2$

was stirred overnight in a dry solution of styrene in DMF prior to the addition of water, a product ratio of 6.0:1.0 (aldehyde:ketone) was obtained after a reaction time of 30 min. In comparison, when $PdCl_2$ and water were added concurrently to a solution of the substrate in DMF, the ratio of the products was 2.7:1.0 after the same period (Table 1). This strongly indicated the formation of a type of palladium–styrene complex not previously implicated in the Wacker reaction.

Complexes of palladium(II), alkenes and DMF are known,[15] but have been isolated only as amorphous solids. X-ray quality crystals of the styrene–palladium(II) complex have been obtained from benzene.[16] The marked difference expected in the co-ordination sphere of palladium in DMF and benzene solutions means that the available structure for the palladium–styrene complex has little bearing on the intermediates postulated in the current study.

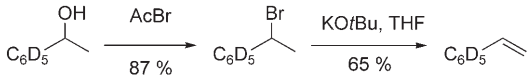
Three possible interactions were envisaged between the palladium and the aromatic ring; a face-on interaction with the aromatic ring **6a** (involving two palladium centres), an η^4 interaction **6b**,[17] or an agostic interaction **6c** (Scheme 4).



6a **6b** **6c**

Scheme 4. Possible palladium–aryl interactions: **6a**: face-on; **6b**: η^4-type; **6c**: agostic (L = DMF, Cl, H_2O).

We[9] and others[18] have shown that agostic interactions can have a strong influence on the regiochemistry of palladium-catalysed reactions. An agostic interaction of type **6c** could show a significant kinetic isotope effect in the reaction of substrates bearing deuterium atoms in the *ortho* positions. The ring-deuterated styrene **9** was readily synthesised from the commercially available alcohol **7** (Scheme 5), and allowed kinetic experiments to be undertaken (Table 2). The results for the deuterated and non-deuterated substrate are



7 **8** **9**

Scheme 5. Synthesis of ring[D_5]styrene **9**.

Table 2. Kinetic isotope studies.[a]

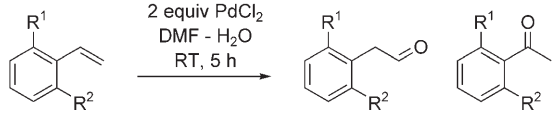
Entry	Reaction time [h]	Conversion [%] ring-H_5	ring-D_5
1	0.5	9.3	9.8
2	1.0	17.0	16.9
3	1.5	20.2	20.6
4	2.0	23.8	24.0

[a] Reaction conditions: 1 equiv substrate, 2 equiv $PdCl_2$, 10% Pd^0 source, DMF/H_2O (10:1), 30 min.

identical within experimental error. No deuterium isotope effect was observed, meaning that an agostic interaction could not be corroborated.

To clarify the nature of the palladium–styrene complex, we tested a series of *ortho*-substituted styrenes under the optimised reaction conditions (Table 3). For styrene (**1b**),

Table 3. Effect of *ortho* substituents.



Entry	Substrate	Ratio aldehyde:ketone
1	R^1, R^2 = H (**1b**)	10.5:1.0
2	R^1 = H, R^2 = Me (**1c**)	1:0
3	R^1, R^2 = Me (**1d**)	1.6:1.0

the anti-Markovnikov aldehyde was produced in a 10.5:1 ratio to the methyl ketone. Increasing the size of one of the *ortho* substituents (H→Me) produced the aldehyde exclusively (**1c**, Table 3, entry 2), whilst if methyl groups occupied both *ortho* positions, the selectivity dropped to 1.6:1.0 in favour of the aldehyde.

The results of these three reactions were markedly different. Unsubstituted styrene **1b** gives good selectivity for the aldehyde, whereas for 2-methylstyrene **1c** only the anti-Markovnikov product was formed. The reaction is thus more selective when only one of the *ortho* positions is occupied by a substituent. However, in the case of the disubstituted styrene **1d** (Table 3, entry 3), the aldehyde and ketone are formed in almost equal amounts. The reaction of 2,4-dimethylstyrene (Table 4, entry 17) demonstrates that this is not due to the presence of two methyl groups.

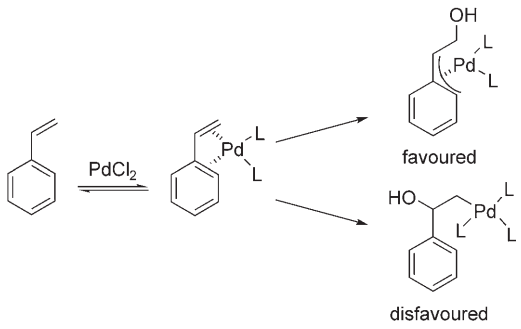
Table 4. Stoichiometric Wacker reaction of a range of styrenes under optimised conditions.[a]

Entry	Compound	R group	Ratio of aldehyde:ketone	Yield [%][b,c]
1	**1a**	4-OMe	9.5:1.0	63
2	**1b**	H	10.8:1.0	71
3	**1c**	2-Me	>25:1	89
4	**1d**	2,6-di-Me	1.6:1.0	60
5	**1e**	n/a	13.1:1.0	38
6	**1f**	4-Me	7.1:1.0	61
7	**1g**	4-Cl	>25:1	76[d]
8	**1h**	4-CF_3	>25:1	69[d]
9	**1i**	4-*t*Bu	8.7:1.0	82
10	**1j**	3-Me	5.0:1.0	50
11	**1k**	3-Cl	>25:1	80
12	**1l**	3-NO_2	16.2:1.0	54[d]
13	**1m**	3,5-di-*t*Bu	6.4:1.0	–
14	**1n**	2-OMe	17.4:1.0	95
15	**1o**	2-F	>25:1	78
16	**1p**	2-Br	>25:1	–
17	**1q**	2,4-di-Me	> 25:1	82

[a] Reaction conditions: 1 equiv substrate, 2 equiv $PdCl_2$, degassed DMF/water (10:1), RT, 5 h. [b] Determined by GC. [c] Measured *versus* an appropriate standard, and based on recovered starting material. [d] Reaction time: 18 h.

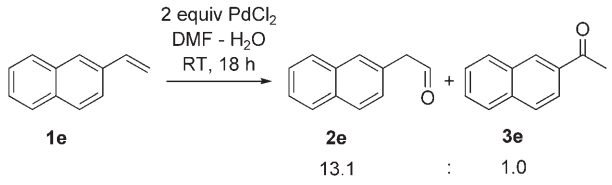
These results strongly implicate a side-on palladium–styrene complex. In the case of a face-on complex (**6a**), altering the size of the *ortho* substituent would be expected to have only a small effect on the reaction outcome. This is clearly not the case, especially for substrate **1d**. Of the two side-on complexes postulated, **6c** should be completely impossible for the disubstituted substrate **1d**. If this were the case, the formation of the aldehyde would be expected to be largely suppressed. However, an approximately 1:1 mixture of products was obtained. This is consistent with the intermediate **6b**, which would be weakened but not completely inhibited for substrate **1d**.

Mechanistic rational preferential formation of the aldehyde could be due to the generation of a more stabilised η^3-intermediate following attack of water on **6b**. In contrast, formation of the ketone requires reaction via a non-delocalised σ-bonded intermediate (Scheme 6). The generation of the η^3-intermediate from the η^4-complex could result from attack of water on the double bond either internally (from palladium) or externally (from the solution); in either case the η^3-intermediate is formed.



Scheme 6. Mechanistic proposal for the reversal of regioselectivity.

The η^4 nature of the proposed reaction mechanism implied that the styrene acts as a *pseudo*-diene under the reaction conditions employed; dienes are known to react to form η^3-palladium intermediates following attack by nucleophiles. Naphthalene shows more alkene-like character than benzene; it was therefore reasoned that 2-vinylnaphthalene **1e** could show enhanced anti-Markovnikov behaviour (Scheme 7). As predicted, the more diene-like nature of the aromatic system led to an increase in the regioselectivity of the reaction providing additional evidence for the involvement of a diene-like η^4-intermediate.



Scheme 7. Reaction of 2-vinylnaphthalene **1e**.

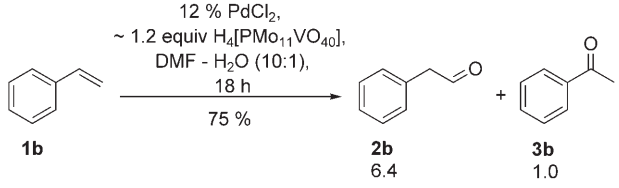
Scope of reaction: To further probe the reaction, a more extended study of the range of styrenes amenable to the reaction conditions was undertaken (Table 4). The anti-Markovnikov product was found to predominate for a large range of commercially available styrenes, from electron-deficient (e.g. **1h**) to electron-rich (**1a**, **1n**). The broad range of styrenes that undergo the reaction implies that it may have potential for application in more complex systems.

Catalysis: To extend the synthetic utility of the transformation, we examined methods for carrying out the anti-Markovnikov transformation catalytically. A number of approaches have been adopted to achieve catalytic cycles with palladium(II) reactions, and so it was hoped that an appropriate reoxidant could be found. It has already been shown that reoxidation using copper(II) (generated in situ from copper(I) and oxygen) was not effective (Scheme 2), giving largely the ketone product. The sensitivity of the reaction products to oxygen (in the presence of palladium(II)) also precluded this method. A number of other reoxidants used in the Wacker reaction were examined (Table 5), making use of 10 mol% $PdCl_2$ as the catalyst, and either **1a** or **1f** as the substrate. The reoxidants gave variable results: some led to catalysis of the Wacker reaction but gave undesired regioselectivity, whilst others gave no detectable catalysis. For example, 1,4-benzoquinone was a good reoxidant but gave almost exclusively the Markovnikov product.

Table 5. Reoxidation attempts.

Entry	Reoxidant	Ratio aldehyde:ketone
1	1,4-benzoquinone	1.0:11.1
2	*t*BuOOH	1.0:3.0
3	H_2O_2	1.3:1.0
4	$FeCl_3$	no reaction
5	MnO_2	ketone only
6	NMO	no reaction

All of the reoxidants above examined are small molecules, and had the potential to alter the co-ordination sphere of palladium. We therefore decided to examine a large, non-co-ordinating reoxidant. Heteropolyacids (HPA) are large, cage molecules; HPAs containing molybdenum and vanadium have been used as catalytic reoxidants in the Wacker reaction, with oxygen as the terminal oxidant.[19] We postulated that as the ions are large and non-co-ordinating, reoxidation using an HPA could be successful. The heteropolyacid $H_4[PMo_{11}VO_{40}]$ was synthesised[20] and used as an approximately stoichiometric reoxidant[21] (Scheme 8). Reaction



Scheme 8. Reoxidation of **1b** using HPA.

overnight successfully led to catalytic turnover: three-quarters of the starting material was converted to products in the presence of only 12 mol% $PdCl_2$, representing approximately 6 turn-over cycles per palladium centre. The major product was the anti-Markovnikov aldehyde; the reason for the degradation of the ratio of products is not entirely clear. We are currently examining the scope of this catalytic method.

Conclusion

In summary, the regioselectivity of the Wacker reaction of styrenes has been shown to be anti-Markovnikov under stoichiometric conditions. A plausible mechanistic explanation for this involves an η^4-interaction between the palladium and the substrate. A full range of styrenes (both electron-rich and electron-poor) undergo anti-Markovnikov addition under the conditions used. A catalytic version of this reaction has been demonstrated, and is the currently the subject of further study.

Experimental Section

General: Dry solvents were obtained from Fluka or were dried by standard methods[22] prior to use, and stored under nitrogen over 4 Å molecular sieves. Solvents were degassed by carrying out three freeze–pump–degas cycles. All air- or moisture-sensitive reactions were carried out under dry nitrogen using standard Schlenk techniques. Solvents were removed by evaporation on a Büchi rotary evaporator, with vacuum provided either by a water-aspirator pump or by a controlled Teflon-membrane pump. All products were dried at oil-pump vacuum for at least one hour before spectroscopic characterization. TLC analysis was performed by using Merck 60 PF_{254} 0.2 mm glass-backed plates; visualization was achieved by UV or using potassium permanganate or phosphomolybdic acid dips as appropriate. Flash chromatography[23] was performed using Merck 9385 Kieselgel 60 silica gel.

NMR spectra were recorded in deuterochloroform ($CDCl_3$) unless otherwise stated. NMR spectra were recorded at 25 °C in 5 mm tubes, at 400.1 MHz (^{1}H) or 100.6 MHz (^{13}C) on a Bruker Avance 400. Chemical shifts are quoted relative to the residual solvent peak ($\delta = 7.24$ ppm for ^{1}H and $\delta = 77.0$ ppm for ^{13}C); coupling constants (J) are given in Hertz (Hz). Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet); br indicates a broad signal. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR with ATR Universal Sampling Accessory as neat solids or liquids. High resolution mass spectra were recorded on Kratos 890 spectrometer. GC analysis was performed on an HP 5890 series II machine, using an HP-1 25 m column.

Synthesis of substrates

2,6-Dimethylstyrene (1d): The method of Suschitzky and co-workers[24] was used with modifications. Methyltriphenylphosphonium bromide (8.93 g, 25.0 mmol) was suspended in dry diethyl ether (100 mL) under nitrogen. Butyllithium in hexane (15% w/w, 16.5 mL, 25.5 mmol) was added dropwise, resulting in a strongly yellow-coloured solution. The reaction mixture was stirred for 1.5 h, after which time the entire solid had dissolved. A solution of 2,6-dimethylbenzaldehdye (3.70 g, 27.6 mmol) in dry diethyl ether (40 mL) was added dropwise to the ylide solution, resulting in rapid formation of a precipitate. The solution was then heated to reflux overnight. The cooled reaction solution was filtered, before being washed with HCl (1 M, 50 mL), aqueous $NaHCO_3$ (50 mL) and aqueous NaCl (50 mL). The organic solution was dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. The residue was distilled in vacuo to give the product as a colourless oil (1.33 g, 40%). B.p. 60–61 °C/5 mbar (Lit. [24] 65–66 °C/10 mm Hg); $R_f = 0.720$ (hexane/diethyl ether (4:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C): $\delta = 2.37$ (s, 6H; Me), 5.32 (dd, $^2J(H,H) = 2.0$ Hz, $^3J(H,H) = 18.0$ Hz, 1H; alkene CH_2 *cis* to ring), 5.59 (dd, $^2J(H,H) = 2.0$ Hz, $^3J(H,H) = 11.6$ Hz, 1H; alkene CH_2 *trans* to ring), 6.75 (dd, $^3J(H,H) = 11.6$, 18.0 Hz, 1H; alkene CH), 7.07–7.11 ppm (m, 3H; aromatic H); ^{13}C{^{1}H} NMR (100.6 MHz $CDCl_3$, 25 °C): $\delta = 20.8$ (Me), 119.3 (CH_2), 126.7 (aromatic CH), 127.7 (aromatic CH), 135.1 (aromatic C), 135.7 (aromatic C), 137.7 ppm (alkene CH); IR (film): $\tilde{\nu} = 3064$, 2952, 2861, 1924, 1850, 1632, 1578, 1466, 1443, 1377, 1163, 1097, 993, 922, 767 cm^{-1}; EI-MS: m/z: 68.9, 117.1, 132.1 [M^+]; HR-MS found (calcd for $C_{10}H_{12}$): m/z: 132.0939 (132.0933); elemental analysis calcd (%) for $C_{10}H_{12}$: C 90.85, H 9.15; found: C 90.98, H 8.89.

3,5-Di-*tert*-butylstyrene (1m): The method of Schlosser and co-workers[26] was used. Potassium *tert*-butoxide (491 mg, 4.38 mmol) was dissolved in a solution of butyllithium in hexane (1.6 M, 2.8 mL, 4.48 mmol). 1,3-Di-*tert*-butylbenzene (0.96 mL, 4.34 mmol) was added, and the dark brown solution stirred overnight. The reaction mixture was cooled to 0 °C, and a solution of DMF (0.34 mL, 4.40 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for 10 min before the addition of methyltriphenylphosphonium bromide (1.57 g, 4.39 mmol). The orange solution was stirred at room temperature for seven hours, before being diluted with water (20 mL) and extracted with hexane (3×10 mL). The organic solution was washed with aqueous NaCl (20 mL), dried over $MgSO_4$ and filtered through a silica pad. The solvent was removed at reduced pressure to give a mixture of the product and 1,3-di-*tert*-butylbenzene, which could not be separated by distillation. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C): $\delta = 1.35$ (s, 18H; *t*Bu), 5.23 (dd, $^2J(H,H) = 0.4$ Hz, $^3J(H,H) = 10.8$ Hz, 1H; alkene CH_2 proton *trans* to ring), 5.75 (dd, $^2J(H,H) = 0.4$ Hz, $^3J(H,H) = 17.6$ Hz, 1H; alkene CH_2 proton *cis* to ring), 6.76 (dd, $^3J(H,H) = 11.2$, 17.6 Hz, 1H; alkene CH), 7.28 (d, $^4J(H,H) = 1.2$ Hz, 2H; aromatic H), 7.36 ppm (t, $^4J(H,H) = 1.2$ Hz, 1H; aromatic H).

2-Methoxystyrene (1n): The method of Suschitzky and co-workers[24] was used. Methyltriphenylphosphonium bromide (8.94 g, 25.0 mmol) was suspended in dry diethyl ether (100 mL) under nitrogen. A solution of butyllithium in hexane (15% w/w, 16.5 mL, 25.5 mmol) was added dropwise, and the solution stirred for 2.5 h. A solution of 2-methoxybenzaldehyde (4.69 g, 34.4 mmol) in dry diethyl ether (40 mL) was added dropwise to the reaction mixture, giving a thick solution. This was heated to reflux and stirred overnight, giving a colourless solution and a precipitate. The solution was cooled and filtered, and the solvent removed at reduced pressure. The residue was distilled at reduced pressure to give the product as a colourless oil (1.35 g, 40%). B.p. 38–39 °C/0.05 mm Hg (Lit. [24] 38–40 °C/0.05 Torr); $R_f = 0.523$ (hexane/diethyl ether (20:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 °C): $\delta = 3.87$ (s, 3H; MeO), 5.30 (dd, $^2J(H,H) = 1.6$ Hz, $^3J(H,H) = 11.2$ Hz, 1H; alkene CH_2 proton *trans* to ring), 5.78 (dd, $^2J(H,H) = 1.6$ Hz, $^3J(H,H) = 17.6$ Hz, 1H; alkene CH_2 proton *cis* to ring), 6.90 (d, $J(H,H) = 8.4$ Hz, 1H; aromatic H), 6.97 (t, $J(H,H) = 7.4$ Hz, 1H; aromatic H), 7.10 (dd, $^3J(H,H) = 11.2$, 17.6 Hz, 1H; alkene CH), 7.27 (dt, $J(H,H) = 2.4$, 7.8 Hz, 1H; aromatic H), 7.51 ppm (dd, $J(H,H) = 2.0$, 8.4 Hz, 1H; aromatic H); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 °C): $\delta = 55.4$ (MeO), 110.8 (aromatic CH), 114.3 (CH_2), 120.5 (aromatic CH), 126.5 (aromatic CH), 126.7 (aromatic C), 128.8 (aromatic CH), 131.6 (alkene CH), 156.7 ppm (aromatic C); IR (film): $\tilde{\nu} = 3073$, 3002, 2957, 2835, 1625, 1598, 1487, 1463, 1437, 1415, 1314, 1291, 1174, 1110, 1036, 997, 909 cm^{-1}; EI-MS: m/z: 68.9, 91.0, 134.1 [M^+]; HR-MS found (calcd for $C_9H_{10}O$): m/z: 134.0734 (134.0732); elemental analysis calcd (%) for $C_9H_{10}O$: C 80.56, H 7.51; found: C 80.53, H 7.45.

Adamantane-1-carbaldehyde (10): The general procedure of Corey and Suggs[27] was used, with reference to the methods of Okamoto and co-workers,[28] Ramsden and Nongkunsarn[29] and Olah and co-workers.[30] Pyridinium chlorochromate(VI) (6.47 g, 20.0 mmol) was suspended in dry dichloromethane (40 mL) under nitrogen. Adamantan-1-ylmethanol (3.32 g, 20.0 mmol) dissolved in dry dichloromethane (40 mL) was added. The reaction mixture was stirred for 70 min, after which time it was diluted with dry diethyl ether (~400 mL) and vigorously stirred. The solution was filtered through a Florisil pad, the residue being flushed with copious diethyl ether. The solvent was removed at reduced pressure, giving the

product as a white, odorous solid (2.93 g, 89%). Attempts to recrystallise the product failed due to its high solubility in most solvents. $R_f = 0.402$ (hexane-ether 4:1); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C): $\delta = 1.70$ (d, J(H,H) = 2.4 Hz 6H; CH_2), 1.66–1.77 (m, 6H), 2.05 (br s, 3H), 9.30 ppm (s, 1H; CHO); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25°C): $\delta = 27.3$ (aliphatic CH), 35.8 (aliphatic CH_2), 36.4 (aliphatic quaternary), 36.5 (aliphatic CH_2), 206.0 ppm (CHO); IR (solid): $\tilde{\nu} = 2901$, 2848, 1722 (C=O), 1451, 1075, 987 cm^{-1}; HR-MS (ESI) found (calcd for $C_{11}H_{16}O$): m/z: 187.1101 (187.1099).

1-Ethenyladamantane (4): Methyltriphenylphosphonium iodide (2.37 g, 5.86 mmol) was dissolved in dry THF (20 mL) under nitrogen. The solution was cooled to 0°C, before dropwise addition of a solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 6.4 mL, 6.4 mmol). The reaction mixture was stirred at room temperature for 1 h, after which time the solution was clear and yellow. The reaction mixture was cooled to −78°C, and a solution of **10** (795 mg, 5.30 mmol) in dry THF (8 mL) was added dropwise. The reaction mixture was allowed to stir overnight, and was then diluted with diethyl ether (50 mL) and hydrochloric acid (1 M, 100 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layers were washed with HCl (1 M, 2×50 mL), aqueous $NaHCO_3$ (2×50 mL), and aqueous NaCl (2×50 mL). The organic solution was dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. Chromatography on silica gel (hexane/diethyl ether (99:1)) gave the product as a clear oil (507 mg, 65%). $R_f = 0.800$ (hexane/diethyl ether (50:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C): $\delta = 1.57$ (d, J(H,H) = 2.4 Hz, 6H; aliphatic CH_2), 1.63–1.75 (m, 6H; aliphatic CH_2), 1.97 (br s, 3H; aliphatic CH), 4.82 (dd, ^2J(H,H) = 1.6 Hz, ^3J(H,H) = 10.4 Hz, 1H; alkene CH_2 proton *trans* to adamantyl), 4.84 (dd, ^2J(H,H) = 2.0 Hz, ^3J(H,H) = 16.8 Hz, 1H; alkene CH_2 proton *cis* to adamantyl), 5.69 ppm (dd, ^3J(H,H) = 10.4, 16.8 Hz, 1H; alkene CH); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25°C): δ = 28.5 (aliphatic CH), 36.9 (aliphatic CH_2), 37.8 (aliphatic quaternary), 41.9 (aliphatic CH_2), 108.9 (alkene CH_2), 150.1 ppm (alkene CH); EI-MS: m/z: 68.9, 131.0, 162.1 [M^+]; HR-MS found (calcd for $C_{12}H_{18}$): m/z: 162.1416 (162.1409); elemental analysis calcd (%) for $C_{12}H_{18}$: C 88.82, H 11.18; found: C 88.97, H 11.33.

(1-Bromoethyl)(D_5)benzene (8): The method of Smith and Amin[31] was used. 1-[(D_5)Phenyl]ethanol (**7**; 5.143 g, 40.4 mmol) was placed in a side-armed flask and flushed with dry nitrogen for 5 min. Acetyl bromide (6.00 mL, 81.1 mmol) was added dropwise to the reaction mixture, which was cooled with an ice bath as soon as the addition was begun.[32] The reaction mixture was stirred for an additional 10 min at 0°C, followed by 10 min at room temperature. The volatile fractions were removed at reduced pressure (100 mbar, water bath 50°C), and the residue distilled, giving a colourless oil (6.679 g, 87%). B.p. 72–74°C/7 mbar; $R_f = 0.582$ (hexane/diethyl ether (20:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C): δ = 2.08 (d, ^3J(H,H) = 7.0 Hz, 3H; CH_3), 5.25 ppm (q, ^3J(H,H) = 7.0 Hz, 1H; CH); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25°C): $\delta = 26.7$ (CH_3), 49.4 (*C*HBr), 126.3 (t, ^1J(C,D) = 24.1 Hz; aromatic CD), 127.7 (t, ^1J(C,D) = 24.8 Hz; aromatic CD), 128.1 (t, ^1J(C,D) = 24.5 Hz; aromatic CD), 143.0 ppm (aromatic quaternary); IR (film): ν bar = 2974, 2921, 1442, 1377, 1186, 1158, 1079, 1039, 967, 954, 841, 825 , 735 cm^{-1}; EI-MS: m/z: 110.1, 68.9, 82.0, 189.0 [M^+]; HR-MS found (calcd for $C_8H_4BrD_5$, ^{79}Br): m/z: 189.0194 (189.0201); elemental analysis calcd (%) for $C_8H_4BrD_5$: C 50.55, "H" 5.07; found: C 50.57, "H" 4.80.

1-Ethenyl(D_5)benzene (9): Potassium *tert*-butoxide (11.25 g, 100.0 mmol) was dissolved in dry THF (100 mL), (1-bromoethyl)(D_5)benzene (**8**; 6.33 g, 33.3 mmol) was added, and the mixture stirred. The solution became yellow and a precipitate formed. After 30 min, no starting material was visible by TLC. The solution was filtered, diluted with diethyl ether (100 mL), and washed with HCl (1 M, 2×50 mL), aqueous $NaHCO_3$ (2×50 mL) and aqueous NaCl (2×50 mL). The organic solution was dried over $MgSO_4$, filtered and the solvent distilled off by using a 200-mm Vigreux column. The residue was then distilled at atmospheric pressure, giving a colourless oil (2.360 g, 65%). B.p. 142–144°C; $R_f = 0.445$ (hexane/diethyl ether (20:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C): δ = 5.26 (dd, ^2J(H,H) = 1.0 Hz, ^3J(H,H) = 10.4 Hz, 1H; alkene CH *trans* to ring), 5.77 (dd, ^2J(H,H) = 1.2 Hz, ^3J(H,H) = 17.6 Hz, 1H; alkene CH *cis* to ring), 6.75 ppm (dd, 3 J(H,H) = 10.4, 17.6 Hz, 1H; alkene CH); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25°C): δ = 113.8 (CH_2) 125.8 (t, ^1J(C,D) = 25.2 Hz; aromatic CD), 127.5 (t, ^1J(C,D) = 25.2 Hz; aromatic CD), 128.0 (t, ^1J(C,D) = 20.0 Hz; aromatic CD), 136.8 (alkene CH), 137.4 ppm (aromatic C); IR (film): $\tilde{\nu} = 3089$, 2982, 1629, 1425, 1325, 1154, 988, 906, 841, 780, 679 cm^{-1}; EI-MS: m/z: 109.1 [M^+], 82.0, 68.9; HR-MS found (calcd for $C_8H_3D_5$): m/z: 109.0941 (109.0940); elemental analysis calcd (%) for $C_8H_3D_5$: C 88.01, "H" 7.74; found: C 88.00, "H" 7.44.

General procedure for stoichiometric Wacker reactions: The following general procedure was adopted for the Wacker reactions, which were carried out at either a 0.25-mmol or 0.50-mmol scale. The substrate and any additives were dissolved in a mixture of degassed DMF (2 mL mmol^{-1} substrate) and degassed water (0.2 mL mmol^{-1} substrate). Once dissolution was complete, the palladium(II) source (2.0 equiv) was added, and the reaction mixture stirred at room temperature. The reaction solution was then poured onto a short pad of silica (approximately 10 g), and eluted with ether (30 mL). The crude mixture was then examined by gas chromatography.

Wacker reaction of 1-ethenyladamantane (4): The reaction was carried out by a modification of the general procedure. $PdCl_2$ (183 mg, 1.03 mmol) was suspended in DMF (0.75 mL) and water (0.25 mL). 1-Ethenyladamantane (**4**; 72.7 mg, 0.490 mmol) was dissolved in DMF (0.25 mL) and THF (0.25 mL),[33] and was added to the $PdCl_2$ suspension. The reaction mixture was stirred overnight, before being poured onto a silica column and eluted with hexane/diethyl ether (4:1). 1-(Adamantan-1-yl)ethanone (**5**) was obtained as a white solid (47.1 mg, 59%). R_f = 0.204 (hexane/diethyl ether (9:1)); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C): δ = 1.66 (d, ^2J(H,H) = 12.0 Hz, 3H; one of C$^4H_2$), 1.73 (d, ^2J(H,H) = 12.0 Hz, 3H; one of C$^4H_2$), 1.78 (d, J(H,H) = 2.4 Hz, 6H; C$^2H_2$), 2.02 (br s, 3H), 2.07 ppm (s, 3H; Me); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25°C): δ = 24.3 (Me), 28.0 (CH of adamantyl), 36.6 (CH_2 of adamantyl), 38.3 ppm (CH_2 of adamantyl), aldehyde carbon not observed: in agreement with literature values.[34]

Reaction using palladium(II) acetate: The general method for the Wacker reactions was modified as follows. Reaction using palladium(II) acetate (229 mg, 1.02 mmol) and 4-methoxystyrene (66.8 mg, 0.498 mmol) under argon was carried out over 90 h. The reaction mixture was added to a silica column and eluted using hexane/ethyl acetate (4:1). The product was obtained as a white solid (53.6 mg, 72%), which was identical by NMR spectroscopy to commercial material. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25°C) δ = 2.53 (s, 3H; H_3CCO), 3.85 (s, 3H; MeO), 6.91 (d, ^3J(H,H) = 9.2 Hz, 2H; aromatic CH), 7.92 ppm (d, ^3J(H,H) = 9.2 Hz, 2H; aromatic CH).

Pre-complexation of styrene and $PdCl_2$: Styrene (52.1 mg, 0.50 mmol) was dissolved in dry DMF (2.0 mL), and the solution freeze-pump degassed three times. $PdCl_2$ (177 mg, 1.00 mmol) was added, and the mixture stirred overnight, giving a dark red-brown solution. Degassed water (0.2 mL) was added, and the reaction stirred for 30 min. It was then poured onto silica and eluted with diethyl ether (50 mL) prior to analysis by gas chromatography.

Formation of 11-molybdo-1-vanadophophoric acid (9): The method of Tsigdinos and Hallada[20] was used. Solutions of disodium hydrogen phosphate (7.15 g, 50.4 mmol) in water (100 mL) and sodium vanadate(v) (6.13 g, 50.3 mmol) in boiling water (100 mL) were prepared, mixed and allowed to cool to room temperature. Concentrated sulfuric acid (5.0 mL) was added, giving a dark red solution. A solution of sodium molybdate decahydrate (133 g, 0.55 mol) in water (200 mL) was added, and the mixture stirred vigorously. Concentrated sulfuric acid (85 mL) was added cautiously, the reaction mixture cooled to room temperature and diluted with diethyl ether (400 mL). Three layers were formed: an ether layer, an aqueous layer, and a bottom layer of deep red liquid. The bottom layer (the product etherate) was isolated, and the diethyl ether evaporated by a stream of nitrogen. The resulting solid was redissolved in water (50 mL), which was then concentrated until crystals were formed. The product was obtained as red crystals (54.0 g).

Catalysis using 11-molybdo-1-vanadophophoric acid: Styrene (98.0 mg, 0.941 mmol) was dissolved in degassed DMF (4.0 mL) and degassed water (0.4 mL). The reoxidant **9** (2.02 g, 1.13 mmol) and $PdCl_2$ (19.4 mg,

0.109 mmol) were added, and the reaction mixture stirred overnight. It was then poured onto silica and eluted using ether (50 mL). Gas chromatographic analysis gave a ratio of aldehyde:ketone of 6.35:1.0, and a ratio of products:starting material of 3.0:1.0.

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[13] The reactions were carried out under a nitrogen atmosphere, in freeze-pump degassed solvents. In the presence of oxygen, the aldehyde products were found to be rapidly degraded to the analogous benzaldehydes. This reaction occurred even in the absence of palladium(II), but was markedly accelerated by the presence of the metal salt.

[14] Of the other palladium(II) salts examined, only $[PdCl_2(MeCN)_2]$ gave predominantly aldehyde; all others either failed to react at all (e.g. PdI_2) or gave predominantly methyl ketone (e.g. $Pd(NO_3)_2$). The addition of external ligand sources, such as LiCl, also led to preferential formation of ketones.

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