CHEMCOMM Communication
www.rsc.org/chemcomm

Evidence that the availability of an allylic hydrogen governs the regioselectivity of the Wacker oxidation

Matthew J. Gaunt, Jinquan Yu and Jonathan B. Spencer*

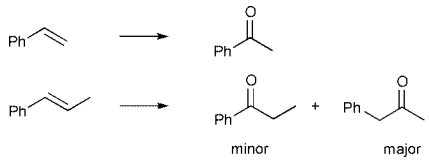
University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: jbs20@cam.ac.uk; Fax: +44 1223 336913; Tel: +44 1223 331696

Received (in Cambridge, UK) 4th April 2001, Accepted 24th July 2001
First published as an Advance Article on the web 4th September 2001

The allylic hydrogen is found to have a dramatic effect on the regioselectivity of the Wacker oxidation, leading to the postulation that an agostic hydrogen or enyl (σ + π) complex helps to stabilise the key intermediate.

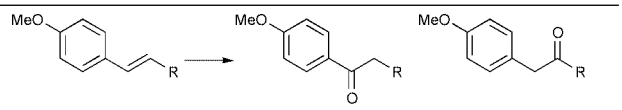
The Wacker oxidation is a versatile reaction that has found broad application in synthetic chemistry for the functionalisation of alkenes.[1] The σ-bonded (β-hydroxyalkyl)palladium complex has been determined as the key intermediate in this reaction.[2] However, the factors controlling the regiochemistry of the hydroxypalladation step to form this intermediate remain obscure. Although terminal alkenes nearly always give methyl ketones, suggesting that hydroxypalladation takes place according to Markovnikov's principles, disubstituted alkenes give products that do not always obey these rules.[3] A striking example of this paradox is the dramatically different regioselectivity observed with styrene (Markovnikov) and that of β-methylstyrene (apparent anti-Markovnikov).[4] In this study we have identified that there are two key factors that control the regioselectivity: electronic effects (Markovnikov) and the availability of a hydrogen atom allylic to the double bond.

It is intriguing that the substitution of a methyl group on the terminal carbon atom of styrene (Scheme 1) or 4-methoxystyrene (Table 1) switches the regioselectivity from Markovnikov to anti-Markovnikov. To test whether the availability of an allylic hydrogen is responsible for the change in regioselectivity the oxidation of the β-methyl (4-methoxy)styrene **1b** was directly compared with that of the β-*tert*-butylstyrene **1c**. The result clearly demonstrates that the removal of the allylic hydrogen switches the regioselectivity back to the Markovnikov product (Table 1).



Scheme 1 *Reagents and conditions*: $PdCl_{2(0.1)}$, DMF, H_2O, CuCl, O_2, 50 °C.

Table 1 Oxidation of β-substituted styrenes

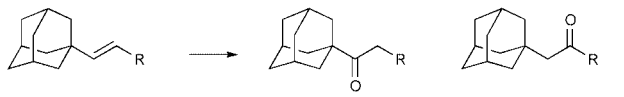


	1[a]	2	3
a	R = H	1	—
b	R = CH_3	1	10
c	R = $C(CH_3)_3$	2.2	1

[a] *Representative procedure for the Wacker oxidations of **1a–c** and **4a–b**.* A solution of palladium(II) chloride (44 mg, 0.25 mmol) and alkene (0.25 mmol) in *N*,*N*-dimethylformamide (1 ml) and water (1 ml) was stirred at 100 °C until completion shown by TLC. The cooled reaction mixture was filtered, concentrated and purified by flash silica gel chromatography and the product analysed by ^{1}H NMR. Stoichiometric conditions were adopted due to the low reactivity of the sterically hindered alkenes. The oxidation of **1a** and **1b** under catalytic Wacker oxidation conditions [palladium(II) chloride (35.4 mg, 0.2 mmol) and copper(I) chloride (198 mg, 2 mmol) in *N*,*N*-dimethylformamide (1 ml) and water (1 ml)] gave the same regioselectivity as observed when the reactions were carried out under the stoichiometric conditions shown in Table 1.

Both the substitution of the methyl group and the *tert*-butyl group onto styrene increases the steric effects on the terminal carbon of the double bond; however, they have the opposite effect on the regioselectivity. To further probe the steric effect on the reaction, the phenyl group in styrene and β-methylstyrene was substituted by an adamantyl group (Table 2). The results show that despite the bulk of the adamantyl group, the availability of the hydrogens on the methyl group still governs the outcome of the reaction (Table 2).[5] This suggests that the steric environment does not have an overriding influence on the regioselectivity of the Wacker oxidation.

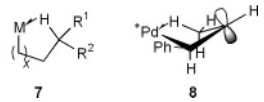
Table 2 Probing steric effects in the Wacker oxidation[a]



	4	5	6
a	R = H	1	—
b	R = CH_3	1	2.2

[a] Reaction conditions are the same as those in Table 1.

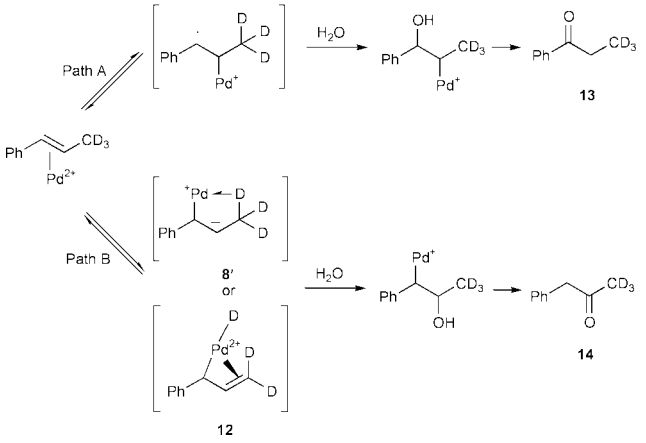
These results implicate the involvement of the allylic hydrogens in the reaction mechanism. It has been demonstrated that C–H can coordinate to a transition metal centre and form a sigma agostic structure **7** (Scheme 2).[6] σ-Electrons can serve as electron donors to an empty metal orbital, and the high lying C–H σ* orbital serves as a π-acceptor from a filled metal orbital. When the palladium adds remote to the methyl group the electronic effect from the carbocation next to the allylic hydrogen could weaken the C–H bond and should therefore make the C–H σ* more accessible and hence a better π acceptor for the palladium (Scheme 2).[7] The agostic intermediate **8** could account for the formation of the anti-Markovnikov product.



Scheme 2

It has also been shown that interaction between palladium(II) and an alkene with allylic hydrogens can result in the formation of a π-allylic complex.[8] In fact, these complexes have been isolated in the Wacker reaction and found to be stable species that do not react further.[9] In order to establish whether a π-allylic species could be involved in the reaction mechanism β-methylstyrene labelled at the methyl group with deuterium was oxidised (Scheme 3). The deuterium is completely retained in the products **13** and **14** which is not consistent with a π-allylic

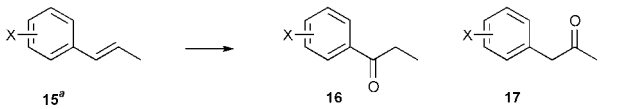
 DOI: 10.1039/b103066n



Scheme 3

intermediate since deuterium should either be lost from the methyl position or partially transferred to the benzylic position.[10] This also confirms that isomerisation to the terminal alkene followed by oxidation, which would require the loss of a deuterium atom from the methyl group, is not the mechanism that can account for the preferential formation of the anti-Markovnikov product. It has been shown previously that enyl (σ+π) intermediates are precursors for π-allylic complexes,[11] and therefore may be formed in the Wacker reaction. While the π-allylic complex **11** is probably too stable to react with water, it is possible that an enyl (σ+π) complex **12** with the proton still attached to the palladium could be intramolecularly reprotonated allowing this intermediate to react with water (Scheme 3). The labelling studies are therefore consistent with either a mechanism involving the stabilisation of the anti-Markovnikov intermediate occurring through an agostic C–H **8** or a mechanism where the intermediate is stabilised by an enyl (σ+π) complex **12** that can be intramolecularly reprotonated.

Table 3 Probing electronic factors in the oxidation of β-methylstyrenes



	15[a]	16	17
a	X = 4-CF_3	1	> 19
b	X = 4-H	1	7.5
c	X = 4-CH_3	1	3.8
d	X = 2-OCH_3	1	2.7
[b]	X = 4-OCH_3	1	2.0
e	X = 2,4-OCH_3	1.2	1
f	X = 2,4,6-OCH_3	2.3	1

[a] *Representative procedure for the Wacker Oxidations of methylstyrenes* **15a–f**. A flask containing a suspension of palladium(II) chloride (35.4 mg, 0.2 mmol) and copper(I) chloride (198 mg, 2 mmol) in *N*,*N*-dimethylformamide (1 ml) and water (1 ml) was stirred under an oxygen atmosphere for 1 h. Alkene, 1b, (296 mg, 2 mmol) in *N*,*N*-dimethylformamide (0.5 ml) and water (0.5 ml) was added and the reaction mixture was stirred at 50 °C for 24 h. The crude reaction mixture was applied directly to a pad of silica (ethyl acetate–hexane; 1:4) and the concentrated filtrate was analysed by ^{1}H NMR. Purification by flash silica gel chromatography afforded ketones **2b** and **3b** (in the ratio 1:2.0) as a pale yellow oil (195 mg, 59%). [b] It is interesting to note that the temperature of the reaction (compare to the result at 100 °C, Table 1) can affect the regioselectivity of the reaction. At higher temperatures the 'anti-Markovnikov' product is further favoured.

To investigate if the balance between path A (Markovnikov) and B (anti-Markovnikov) can be influenced by altering the electronic properties of the aromatic ring, a series of analogues of β-methylstyrene, **15a–f**, were oxidised under standard Wacker conditions.

The results clearly show that as the electron density of the aromatic system is increased, path A (Scheme 3) is enhanced, which is consistent with the greater stabilisation of the carbocation at the benzylic position (Table 3). The dramatic influence on the regioselectivity of the oxidation by involvement of the allylic hydrogens is clearly illustrated since path A only becomes dominant when the aromatic ring is substituted with three methoxy groups, **15f**.

This study provides evidence that the regioselectivity of the Wacker oxidation can be greatly influenced by the availability of an allylic hydrogen. The allylic hydrogen might participate in the Wacker oxidation by being involved in either an agostic C–H or enyl (σ+π) complex. The involvement of these complexes could account for preferential formation of the anti-Markovnikov product when the substrate bears an allylic hydrogen.

We thank The Wellcome Trust (M. J. G.), St. John's College, Cambridge (J.-Q. Y) and the Royal Society (J. B. S.) for funding.

Notes and references

1 J. Tsuji, in *Comprehensive Organic Synthesis*, Eds. B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, **Vol. 7**, pp. 449–467.

2 O. Hamed, C. Thompson and P. M. Henry, *J. Org. Chem.*, 1997, **62**, 7082; O. Hamed and P. M. Henry, *Organometallics*, 1997, **16**, 4903; K. Zaw and P. M. Henry, *Organometallics*, 1992, **11**, 2008; B. Akermark, B. C. Soderberg and S. S. Hall, *Organometallics*, 1987, **6**, 2608; J. E. Bäckvall, B. Akermark and S. O. Ljunggren, *J. Am. Chem. Soc.*, 1979, **101**, 2411.

3 B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1986, 909; H. Ogawa, S. Miyamoto, T. Mandai, S. Wakabayashi and J. Tsuji, *Tetrahedron Lett.*, 1988, **29**, 5181; H. Pellissier, P. Y. Michellys and M. Santelli, *Tetrahedron*, 1997, **53**, 7577.

4 E. Keinan, K. K. Seth and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 3474; J. Tsuji, in *Comprehensive Organic Synthesis*, Eds. B. M. Trost and I. Fleming, Pergamon Press, New York, 1991, Vol. 7, pp 465–466.

5 The reaction was monitored by GC which determined that approximately 1% of the terminal double bond was formed by double bond shift during the reaction course. This eliminates the possibility that the major pathway for the formation of the anti-Markovnikov product is from oxidation of the terminal alkene (also see the deuterium labeling studies with β-methylstyrene later in the text).

6 M. Brookhart and M. L. H. Green, *J. Organometal. Chem.*, 1983, **250**, 395.

7 R. H. Crabtree, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 799.

8 B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.*, 1980, **102**, 3572; H. Grennberg, V. Simon and J. E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1994, 265; R. G. Brown, R. V. Chaudhari and J. M. Davidson, *J. Chem. Soc., Dalton Trans.*, 1977, 176.

9 A. D. Ketley and J. Braatz, *J. Chem. Soc., Chem. Commun.*, 1968, 169; F. Conti, M. Donati, G. F. Pregaglia and R. Ugo, *J. Organomet. Chem.*, 1971, **30**, 421.

10 When compound **4b**, labelled with deuterium at position 2, was oxidised, 90% of the deuterium was found to be located at position 1 and 10% at 3. Although the presence of 10% deuterium at the position 3 suggests the involvement of a π-allylic complex as a minor pathway, GC analysis of the reaction mixture showed the formation of small amount (1%) of terminal alkene that if oxidised could give this result.

11 D. N. Lawson, J. A. Osborn and G. Wilkinson, *J. Chem. Soc. A*, 1966, 1733; P. A. Evans and J. D. Nelson, *J. Am. Chem. Soc.*, 1998, **120**, 5581.