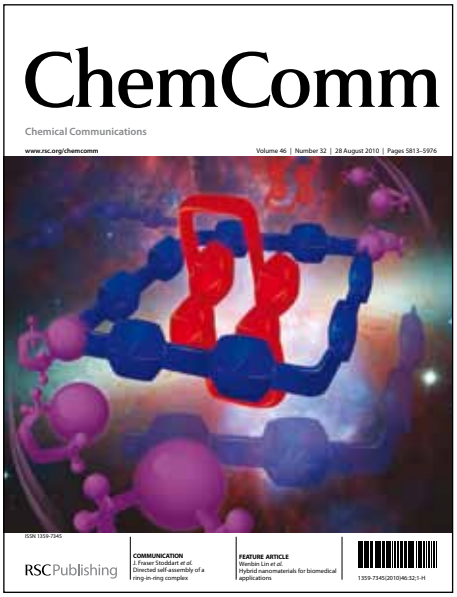
ChemComm

Accepted Manuscript



View Article Online
ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Synergistic Dual Activation Catalysis by Palladium Nanoparticles for Epoxide Ring Opening with Phenols

Kapileswar Seth, Sudipta Raha Roy, Bhavin V. Pipaliya, and Asit K. Chakraborti*

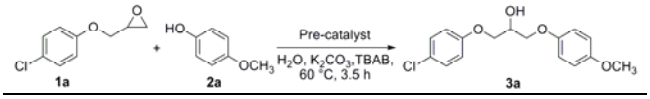
Received (in XXX, XXX)
First published on
DOI:

Synergistic dual activation catalysis has been devised for epoxide phenolysis wherein palladium nanoparticles induce electrophilic activation via coordination with the epoxide oxygen followed by nucleophilic activation through anion-*π* interaction with the aromatic ring of the phenol and water (reaction medium) also renders assistance through 'epoxide-phenol' dual activation.

Epoxide ring opening by phenols is a challenging task due to the poor nucleophilicity of phenols and necessitates suitable activation protocol. The nucleophilic activation strategy requires basic conditions and use a large amount of the phenolate or the base and stoichiometric or excess quantities of a phase transfer catalyst.[1] A more effective strategy has been reported for activation of the electrophile (epoxide) and the nucleophile (phenol) through metal Lewis acid-based catalyst system in which the central metal ion activates the epoxide and the nucleophilic activation is achieved through a basic moiety present either as an integral structural feature (covalently attached to the metal ion) of the catalyst system[2] or an associated counter anion but requires excess of the epoxide.[3] Herein we report a new model for electrophile-nucleophile synergistic dual activation catalysis by palladium nanoparticles (PdNP).

In a model study, the 4-chlorophenyl glycidyl ether **1a** was treated with 4-methoxyphenol **2a** under various conditions (Table 1). The best result was obtained in the presence of $PdCl_2$ (1 mol%), K_2CO_3 (25 mol%), and TBAB (25 mol%) at 60 °C in water after 3.5 h (entry 1). The $PdCl_2$ alone was not effective (entry 3) and needs to be present alongwith K_2CO_3 and TBAB as the reaction did not occur using either K_2CO_3 (entry 4) or TBAB (entry 5). The reaction mixture becomes dark black when both K_2CO_3 and TBAB are present along with $PdCl_2$. This indicated the formation of PdNP and was supported by the absorption at 283 nm in the UV.[4,5] The TEM analysis of the reaction mixture identified PdNPs (≈ 30 nm) and was characterised by EDX spectra.[5] The TBAB is required as the stabilizer to prevent agglomeration of the PdNPs through electrosteric stabilisation[6] as otherwise poor result was obtained even using one equiv of K_2CO_3 (entries 4 and 14). The lack of formation of any significant amount of **3a** in using stoichiometric amount of K_2CO_3 in the presence (entry 4) and absence (entry 6) of $PdCl_2$ suggests that it is not a base-promoted (p*K*a driven) event[1] to generate the phenolate anion and that a distinct catalytic effect is rendered by the PdNP. The role of K_2CO_3 can be envisaged as a reducing agent[7] to form the PdNP. In the absence of K_2CO_3 (entry 5) or replacement of K_2CO_3 by a Brönsted acid (entry 1, footnote d) no epoxide phenolysis takes place. The use of sodium 4-methoxyphenolate (25 mol%) instead of K_2CO_3 gave 10% yield (entry 1, footnote e) and 11% yield was obtained when all components (K_2CO_3, TBAB, $PdCl_2$, **1a** and **2a**) were added at a time (entry 1, footnote f). In these cases the PdNP formation was not observed (absence of blackening of the reaction mixture).

Table 1. The phenolysis of the epoxide ring of **1a** with **2a** to form **3a**.[a]



Entry	Pre-catalyst (mol %)[b]	K_2CO_3 (equiv)[b]	TBAB (equiv)[b]	Yield (%)[c]
1	$PdCl_2$ (1)	0.25	0.25	74[d,e,f]
2	None	0.25	0.25	10
3	$PdCl_2$ (1)	None	None	0
4	$PdCl_2$ (1)	1.0	None	10
5	$PdCl_2$ (1)	None	1.0	0
6	None	1.0	None	0
7	$PdCl_2$ (1)	0.25	0.25	18[g]
8	$PdCl_2$ (1)	0.25	0.25	59[h]
9	$PdCl_2$ (1)	0.25	0.25	78[i]
10	$PdCl_2$ (0.5)	0.25	0.25	53
11	$PdCl_2$ (2)	0.25	0.25	75
12	$PdCl_2$ (1)	0.1	0.1	54
13	$Pd(OAc)_2$ (1)	0.25	0.25	70
14	$Pd(OAc)_2$ (1)	1.0	None	16
15	Na_2PdCl_4 (1)	0.25	0.25	20
16	$Pd(PPh_3)_2Cl_2$ (1)	0.25	0.25	18
17	$Pd(PPh_3)_4$ (1)	0.25	0.25	53
18	Pd/C (1)	0.25	0.25	20

[a]The mixture of K_2CO_3 (except for entries 3 and 5), the pre-catalyst (except for entries 2 and 6) and TBAB (except for entries 3, 4, 6, and 14) in water (8 mL) was stirred magnetically for 15 min followed by addition of **1a** (2 mmol) and **2a** (2 mmol) at 60 °C (except for entry 7) and stirring for further 3.5 h (except for entries 8 and 9). [b]The amount of the pre-catalyst used with respect to **3a**. [c]Isolated yield of **3a**. [d]No epoxide phenolysis took place in using pivalic acid (25 mol%) instead of K_2CO_3. [e]**3a** was formed in 10% yield in using pre-formed sodium 4-methoxyphenolate (25 mol%) instead of K_2CO_3. [f]**3a** was formed in 11% yield when the reaction was performed in mixing K_2CO_3, $PdCl_2$, TBAB, **1a** and **2a** at a time. [g]The reaction was performed at 40 °C. [h]The reaction was carried out for 1.5 h. [i]The reaction carried out for overnight.

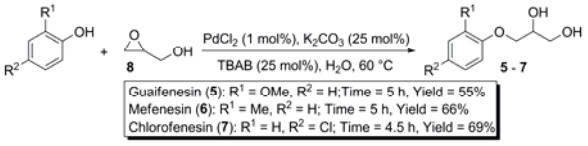
Other Pd compounds were used (entries 13-17) and only $Pd(OAc)_2$ gave comparable yield (entry 13). The necessity to use TBAB was further indicated by the fact that when the reaction was performed using $Pd(OAc)_2$ (1 mol%) in the absence of TBAB poor result was obtained even using one equiv of K_2CO_3 (entry 14) and further demonstrated that the reaction is not p*K*a driven (formation of phenolate anion). The use of Pd(0) species such as $Pd(PPh_3)_4$ (entry 17) and

palladium adsorbed on carbon (entry 18) indicate the specific activation rendered by the PdNP. Various anionic (SDS, SDOSS), cationic (tetrabutylammonium salts, CTAB, and Triton X 100), and neutral (Tween 40, Span 80 and PEGs[8]) surfactants were used as stabiliser.[5] In general the tetraalkylammonium halides exhibited prominent effect and TBAB afforded the best result. Replacement of K_2CO_3 by other alkali metal carbonates (Li, Na, and Cs) led to lesser yields (63-70%). The other bases such as KOH, LiOH, $KHCO_3$ and other potassium salts such as KBr and KI were also less effective (38-59% yield).[5] The solvent played a crucial role and the best results were obtained in water. Other solvents such as hexane, PhMe, THF, dioxane, MeCN, DCE, $MeNO_2$ were either ineffective or afforded inferior yields. The use of PEG 400 gave poor yields (22-25%)[5] in the presence or absence of TBAB.[8] The amount of water also has some implication on the yield and 4 mL/mmol of the substrate was found to be the optimal.[5]

The general applicability is demonstrated by Table 2. The reactions with phenols bearing electron withdrawing substituents (entries 4-8, 11, 12, 16, 18, 20, and 21) took lesser time indicating that the reaction is not dictated by the relative nucleophilicity of the phenol (or phenolate anion). The presence of *ortho* substituent exhibited steric hindrance as the reactions required longer time (entries 15, 17, and 19). The steric effect is also reflected by the longer time required with 1-naphthol than that of 2-naphthol (entries 22 and 23). No competitive epoxide[9]/ester hydrolysis was observed (entries 6 and 20) demonstrating chemoselectivity. The PdNPs can be recycled up to five consecutive uses to afford 72, 71, 69, 66, and 60% yields of **3a**, respectively.[5]

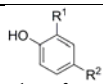
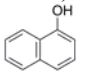
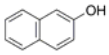
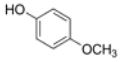
For evaluating regioselectivity, styrene oxide **4** was treated with a few representative electron rich and electron deficient phenols (Table 3). In each case regioselective formation of the Aα product was observed in contrary to the Aβ product obtained during the base promoted reactions.[1c] The regioselective formation of the Aα product is in conformity with the regioselectivity observed during the Lewis acid-catalysed reaction with aromatic amines/thiols.[10] These suggest electrophilic activation of the epoxide ring and is implied by the shorter reaction time and better regioselectivity with poor nucleophilic phenols (entries 3 and 4).

The applicability of the PdNP-catalyzed epoxide phenolysis is demonstrated by synthesis of a few representative drugs guaifenesin (**5**) used for the treatment of cough and cold, mefenesin (**6**) and chlorofenesin (**7**) used as muscle relaxants by phenolysis of glycidol (**8**) with appropriate phenol (Scheme 1).



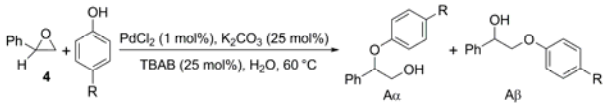
Scheme 1. Synthesis of a few representative drug molecules.

Table 2. The PdNP-catalysed phenolysis of epoxides with phenols.[a]

Entry	Epoxide	Phenol	Time (h)	Yield (%)[b]
				
1	Ar = 4-Cl-C_6H_4	$R^1 = R^2 = H$	3.5	83
2		$R^1 = H$, $R^2 = OCH_3$	3.5	74
3		$R^1 = H$, $R^2 = Br$	3	82
4		$R^1 = H$, $R^2 = CHO$	2	86
5		$R^1 = H$, $R^2 = COCH_3$	2	86
6		$R^1 = H$, $R^2 = CO_2CH_3$	2.5	89
7		$R^1 = H$, $R^2 = CN$	2.5	86
8		$R^1 = H$, $R^2 = NO_2$	2	88
9	Ar = 4-$COCH_3$-C_6H_4	$R^1 = R^2 = H$	3	86
10		$R^1 = H$, $R^2 = OCH_3$	3	84[c]
11		$R^1 = H$, $R^2 = NO_2$	2	91[d]
12		$R^1 = H$, $R^2 = COCH_3$	2	90
13	Ar = Ph	$R^1 = R^2 = H$	3.5	87
14		$R^1 = H$, $R^2 = OCH_3$	3.5	82
15		$R^1 = OCH_3$, $R^2 = H$	4	87
16		$R^1 = H$, $R^2 = CHO$	2	89
17		$R^1 = CHO$, $R^2 = H$	4.5	82
18		$R^1 = H$, $R^2 = COCH_3$	2	87
19		$R^1 = COCH_3$, $R^2 = H$	4.5	84
20		$R^1 = H$, $R^2 = CO_2CH_3$	2	88
21		$R^1 = H$, $R^2 = NO_2$	2	87
22			4	90
23			2	89
24	R = ^{t}Bu	$R^1 = H$, $R^2 = OCH_3$	4	69
25	Ar = 2-Furfuryl	$R^1 = H$, $R^2 = OCH_3$	3.5	89
26	Ar = 1-Naphthyl		4.5	83
27			4.5	88

[a]The mixture of $PdCl_2$ (1 mol%), K_2CO_3 (25 mol%), and TBAB (25 mol%) in water (8 mL) was stirred magnetically at 60 °C for 15 min followed by addition of the epoxide (2 mmol) and the phenol (2 mmol). [b]The isolated yield of the desired product. [c]The reaction of the (*S*)-4-acetyl phenyl glycidyl ether (optical purity 80.06%) gave the corresponding product in 85% yield with 76.85% ee. [d]The reaction of the (*S*)-4-acetyl phenyl glycidyl ether (optical purity 80.06%) gave the corresponding product in 91% yield with 82.79% ee.

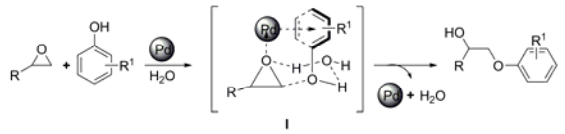
Table 3. PdNP-Catalysed regioselective ring opening of **4** with phenols.[a]



Entry	Phenol	Time (h)	Ratio (Aα : Aβ)[b]	Yield (%)[c]
1	R = OCH_3	4.5	65 : 35	86 (54)
2	R = Br	3	69 : 31	71 (48)
3	R = CN	2.5	74 : 26	70 (51)
4	R = NO_2	2.5	75 : 25	81 (60)

[a]The mixture of $PdCl_2$ (1 mol%), K_2CO_3 (25 mol%), and TBAB (25 mol%) in water (8 mL) was stirred magnetically at 60 °C for 15 min followed by addition of **4** (2 mmol) and the phenol (2 mmol). [b]The α/β ratio was determined by GCMS. [c]Isolated yield of the mixture of α- and β- regioisomers with the yield of the purified α-isomer in the parenthesis.

The necessity of the PdNP as the catalyst and water as the reaction medium suggest specific role played by the PdNP and water in epoxide phenolysis. The PdNP activates the epoxide ring through coordination with one of the lone pair of electrons of the epoxide ring oxygen.[11] The rate enhancement of organic reaction in water has been popularly attributed to the hydrogen bonding (HB) effect.[12] The water molecule further activates the epoxide through HB formation[13] with the second lone pair of electrons of the epoxide ring oxygen. The oxygen atom of the water molecule in turn forms HB with the OH of the phenol and induces nucleophilic activation[14] and brings the phenolic oxygen in close proximity to the activated epoxide ring for nucleophilic attack. A charge transfer interaction between the electron rich PdNP and the aromatic ring of the phenol[15] provides rigidity to the transition state **I** (Scheme 2). Thus, the PdNP and water constitute a synergistic dual activation model for simultaneous activation of the epoxide and the phenol to promote the epoxide phenolysis.



I

Scheme 2. Synergistic epoxide-phenol dual activation by PdNP and water.

The poor nucleophilicity of the phenolic hydroxyl group requires assistance by Lewis/Brönsted acids to activate the electrophile (leaving group) that results in C-C bond formation through the *para*-position of the phenolic moiety.[16] No C-C bond formation between the phenol and the epoxide moiety takes place and signifies the involvement of the hydrogen-bonded structure **I** as it would direct C-O bond formation involving the phenolic OH group and the epoxide ring and would not facilitate any C-C bond formation with the phenolic moiety. The lesser reaction time required for phenols with electron withdrawing group is due to their better HB donor ability as well as better electronic charge acceptor ability (through the anionic-π interaction with the electron rich PdNP) in forming a more rigid transition state **I**. The implication of HB involving the phenolic OH group is realised by the fact that no epoxide alcoholysis took place in replacing the phenol separately by MeOH, EtOH, and benzyl alcohol. The 83:17 selectivity towards the epoxide phenolysis product of **1a** with 4-nitrophenol during the treatment of **1a** with equimolar mixture of 4-methoxyphenol and 4-nitrophenol provided further evidence for the involvement of hydrogen bond of the phenolic OH group in the transition state (Scheme 2).[5]

In conclusions, a new model for epoxide-phenol dual activation through the synergistic action of PdNP and water has been devised to provide an efficient protocol for epoxide phenolysis that finds application for the synthesis of drug molecules. This work represents the first example of metal NP-catalysed epoxide ring activation.

The authors K. S. and S. R. R. thank CSIR (New Delhi) for senior research fellowships and B. V. P. thanks UGC (New Delhi) for junior research fellowship.

Notes and references

[a]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar 160 062, Punjab, India. E-mail: akchakraborti@niper.ac.in; akchakraborti@rediffmail.com*

† Electronic Supplementary Information (ESI) available: Spectroscopic data of all compounds, scanned spectra of new compounds. See DOI: 10.1039/b000000x/

1 (*a*) B. Das, M. Krishnaiah, P. Thirupathi and K. Laxminarayana, *Tetrahedron Lett.*, 2007, **48**, 4263; (*b*) M. A. Brimble, Y.-C. (William) Liu and M. Trzoss, *Synthesis*, 2007, 1392; (*c*) K. Surendra, N. S. Krishnaveni, Y. V. D. Nageswar and K. Rama Rao, *J. Org. Chem.*, 2003, **68**, 4994; (*d*) Epoxide phenolysis catalysed by polystyrene-supported strong base requires prolonged reaction time (A. Zvagulis, S. Bonollo, D. Lanari, F. Pizzo and L. Vaccaro, *Adv. Synth. Catal.*, 2010, **352**, 2489).

2 S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 2252.

3 (*a*) D. N. Annis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 4147; (*b*) Extension of the similar strategy using porphyrin-based ligand reports GC-based conversion (K. Venkatasubbaiah, X. Zhu, E. Kays, K. I. Hardcastle and C. W. Jones, *ACS Catal.*, 2011, **1**, 489).

4 J. Xu, A. R. Wilson, A. R. Rathmell, J. Howe, M. Chi and B. J. Wiley, *ACS Nano*, 2011, **5**, 6119.

5 See supporting information.

6 (*a*) D. Astruc, F. Lu and J. R. Aranzaes, *Angew. Chem. Int. Ed.*, 2005, **44**, 7852; (*b*) A. Roucoux, J. Schultz and H. Patin, *Chem. Rev.*, 2002, **102**, 3757.

7 (*a*) R. E. Huie, C. L. Clifton and P. Neta, *Radiat. Phys. Chem.*, 1991, **38**, 477; (*b*) B. G. Ershov, E. Janata, M. Michaelis and A. Henglein, *J. Phys. Chem.*, 1991, **95**, 8996.

8 W. Han, C. Liu and Z. Jin, *Adv. Synth. Catal.*, 2008, **350**, 501.

9 M. Tokunga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

10 (*a*) B. Pujala, S. Rana and A. K. Chakraborti, *J. Org. Chem.*, 2011, **76**, 8768; (*b*) Shivani, B. Pujala and A. K. Chakraborti, *J. Org. Chem.*, 2007, **72**, 3713; (*c*) Shivani and A. K. Chakraborti, *J. Mol. Catal. A: Chem.*, 2007, **263**, 137; (*d*) A. K. Chakraborti, A. Kondaskar and S. Rudrawar, *Tetrahedron*, 2004, **60**, 9085; (*e*) A. K. Chakraborti, S. Rudrawar and A. Kondaskar, *Eur. J. Org. Chem.*, 2004, 3597; (*f*) A. K. Chakraborti, S. Rudrawar and A. Kondaskar, *Org. Biomol. Chem.*, 2004, **2**, 1277; (*g*) A. K. Chakraborti and A. Kondaskar, *Tetrahedron Lett.*, 2003, **44**, 8315.

11 The AgNPs activate sulfur in organosulfur compounds [W. Gan, B. Xu and H.-L. Dai, *Angew. Chem. Int. Ed.*, 2011, **50**, 6622].

12 (*a*) Y. Zheng and J. Zhang, *ChemPhysChem*, 2010, **11**, 65; (*b*) Jung, Y. and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492.

13 (*a*) D. N. Kommi, D. Kumar, K. Seth and A. K. Chakraborti, *Org. Lett.*, 2013, **15**, 1158; (*b*) D. N. Kommi, D. Kumar and A. K. Chakraborti, *Green Chem.*, 2013, **15**, 756; (*c*) I. Viotijevic and T. F. Jamison, *Science*, 2007, **317**, 1189.

14 HB-assisted dual activation by water for other organic reactions [(*a*) D. N. Kommi, P. S. Jadhavar, D. Kumar and A. K. Chakraborti, *Green Chem.*, 2013, **15**, 798; (*b*) D. N. Kommi, D. Kumar, R. Bansal, R. Chebolu and A. K. Chakraborti, *Green Chem.*, 2012, **14**, 3329; (*c*) E. Vohringer-Martinez, B. Hansmann, H. Hernandez, J. S. Francisco, J. Troe and B. Abel, *Science*, 2007, **315**, 497; (*d*) S. V. Chankeshwara and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 3259; (*e*) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2433; (*f*) A. K. Chakraborti, S. Rudrawar, K. B. Jadhav, G. Kaur and S. V. Chankeshwara, *Green Chem.*, 2007, **9**, 1335].

15 Cation-π interactions between aromatic molecules and NP surface-bound Au^+ [A. Kumar, S. Mandal, S. P. Mathew, P. R. Selvakannan, A. B. Mandale, R. V. Chaudhari and M. Sastry, *Langmuir*, 2002, **18**, 6478].

16 (*a*) C. Piemontesi, Q. Wang and J. Zhu, *Org. Biomol. Chem.*, 2013, **11**, 1533; (*b*) B. Alcaide, P. Almendros, M. T. Quirós; R. López, M. I. Menéndez and A. Sochacka-Ćwikła, *J. Am. Chem. Soc.*, 2013, **135**, 898; (*c*) F. Zhou, Z.-Y. Cao, J. Zhang, H.-B. Yang and J. Zhou,*Chem. Asian J.*, 2012, **7**, 233.