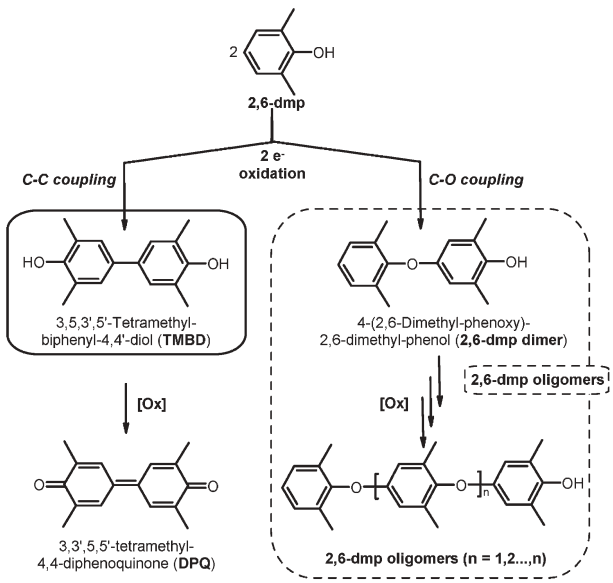
Selective oxidative *para* C–C dimerization of 2,6-dimethylphenol

Christophe Boldron,[a] Guillem Aromí,[b] Ger Challa,[a] Patrick Gamez[a] and Jan Reedijk*[a]

Received (in Cambridge, UK) 21st July 2005, Accepted 13th October 2005
First published as an Advance Article on the web 28th October 2005
DOI: 10.1039/b510378a

Mechanistic investigations on the oxidative coupling of 2,6-dimethylphenol have led to the development of a selective and efficient procedure to prepare 3,5,3′,5′-tetramethyl-biphenyl-4,4′-diol, *via* a C–C coupling, mediated by a hypervalent form of iodine, *i.e.* (diacetoxyiodo)benzene and for which a mechanism is proposed.

The copper(II)-catalyzed oxidative coupling of 2,6-dimethylphenol (2,6-dmp) is a very important process from the industrial point of view.[1,2] It has been generally accepted that the reaction may proceed through two distinct pathways (Scheme 1). One possibility is the coupling of the oxygen atom of one molecule with the *para*-carbon atom of another one, giving rise to a dimeric phenol which can react further to form longer oligomers. This pathway is highly favored in the case where the oxidative system is composed of catalytic amounts of a copper(II) salt, a nitrogen donor ligand and a base as co-catalyst.[3–5] A second alternative is the C–C coupling of two phenol molecules leading to the formation of 3,5,3′,5′-tetramethyl-biphenyl-4,4′-diol (TMBD) which is subsequently oxidized to 3,5,3′,5′-tetramethyl-4,4′-diphenoquinone (DPQ)



Scheme 1 Two pathways for the oxidative coupling of 2,6-dmp molecules.

[a]*Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, 2300 RA, Leiden, The Netherlands. E-mail: reedijk@chem.leidenuniv.nl; Fax: +31 71527 4671; Tel: +31 71527 4459*
[b]*Departament de Química Inorgànica, Universitat de Barcelona, Diagonal 647, 08028, Barcelona, Spain*

under the reaction conditions. TMBD is a key phenol derivative and finds a large number of industrial applications. For example, TMBD is used as reducing agent of the silver ion (developer) in the composition of photothermographic elements,[6] or as the main component of phenolepoxy resins, which are essential to the microelectronic industry (CD, DVD, and so on).[7]

In contrast to the C–O pathway, no highly selective oxidative system for the formation of C–C coupling derivatives from 2,6-dmp has been reported in the literature. The selective formation of C–C coupling products from 2,6-dialkylphenols has only been described for phenols with bulky groups at the *ortho* positions, which prevent the formation of C–O adducts.[8] Moreover it is difficult to control the 2,6-dmp oxidative C–C coupling reaction and stop the process at the stage of TMBD formation. Consequently, only a few methods have been reported for the synthesis of TMBD through the oxidation of 2,6-dmp.[9–12]

We now describe an oxidative system based on a hypervalent form of iodine, *i.e.* (diacetoxyiodo)benzene (PIDA). Hypervalent iodine compounds have become widely used as safe and ecologically friendly alternatives to heavy-metal reagents.[13–16] The use of PIDA for the oxidation of 2,6-dmp completely suppresses the formation of C–O coupling products, generating only the C–C coupling derivatives, namely DPQ and TMBD through a straightforward procedure. A mechanism for this unusual coupling is proposed based on ^{1}H NMR studies, which also show that the intermediate oxidation product TMBD can be obtained from comproportionation between DPQ and 2,6-dmp if an excess of the latter reagent is used. The comproportionation between these two molecules was first reported more than forty years ago,[17,18] but has obviously been overlooked as a potential synthetic route to TMBD using 2,6-dmp as the starting material.

We have analysed by ^{1}H NMR the products formed during the oxidative coupling reaction of 2,6-dmp using various oxidants in chloroform (Table 1).† Three oxidants have been employed, *i.e.* dichlorodicyano-*p*-quinone (DDQ), Cu(II)/Neocuproine and PIDA.‡ Interestingly, among the three oxidants used, PIDA both at room temperature (RT) and 50 °C leads to the sole formation of C–C coupled products (entries 3, 4, 5 and 3′), while large amounts of 2,6-dmp oligomers are also produced with DDQ (entries 1 and 1′) or Cu(II)/Neocuproine (entries 2 and 2′). In order to investigate the mechanism of the selective C–C coupling achieved with PIDA, the reaction of 5 equivalents 2,6-dmp with 1 equivalent of the oxidant (Table 1, entry 3) has been followed by ^{1}H NMR (Fig. 1, Table 2). This study has led to a clear mechanistic proposal for the oxidation with PIDA as the oxidant (Scheme 2). Immediately after the addition of PIDA, 2 equivalents of 2,6-dmp are consumed leading to the formation of a (diphenoxyiodo)benzene intermediate (step ***a***).[14,15] Surprisingly, this consumption of 2,6-dmp (after *ca.* 2 minutes, [**1**] in Fig. 1) does not result in the formation of

Table 1 Oxidation of 2,6-dmp using various oxidants

Entry		2,6-dmp	Oxidant	*Products*[a] *DPQ*	*TMBD*	*2,6-dmp Oligomers*
1		*5 eq*	*DDQ (1 eq)*	0.44	0.41	0.32[b]
2	*50 °C*	*5 eq*	*Cu(II)/Neo$_2$ (2 eq)*	/	0.59	0.31[b]
3		*5 eq*	*PIDA (1 eq)*	/	0.85	/
4	*50 °C*	*2 eq*	*PIDA (1 eq)*	0.26	0.51	/
5		*1 eq*	*PIDA (1 eq)*	0.42	0.14	/
1′		*5 eq*	*DDQ (1 eq)*	0.33	0.15	0.68
2′	*RT*	*5 eq*	*Cu(II)/Neo$_2$ (2 eq)*	0.18	0.26	0.23[b]
3′		*5 eq*	*PIDA (1 eq)*	0.37	0.34	/

[a] Values in mmol of phenol units. Those values must be divided by 2 in order to get the number of mmol of DPQ, TMBD or 2,6-dmp dimer. [b] Only the C–O coupled dimer was observed.

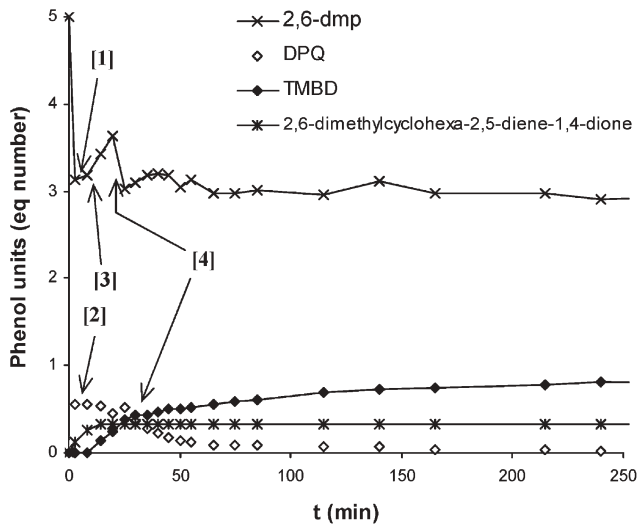


Fig. 1 ^{1}H NMR study of the 2,6-dmp oxidation in the presence of PIDA.

TMBD, as would be expected from Scheme 1, but in the direct formation of DPQ ([**2**]). This one-step 4-electron oxidation of two 2,6-dmp molecules to DPQ obviously implies the participation of two molecules of PIDA. In the proposed mechanism, the monoelectronic transfer from one activated 2,6-dmp unit to the iodine(III) center (step ***b***) leads to a radical cation **I**, with the simultaneous release of one 2,6-dimethylphenoxide (PhO^-) molecule [**3**]. The formation of **I** is followed by the C–C coupling of two such units (step ***c***) to form the dication **II**. This species can rearrange to produce **III** while liberating two protons (step ***d***). A second one-electron (per aromatic ring) oxidation (step ***e***) yields DPQ and iodobenzene. It is crucial to note that such a mechanism indeed completely prevents the formation of C–O coupling products, as evidenced by the experimental results. After 10 minutes of reaction time, TMBD starts appearing with the concomitant disappearance of DPQ and 2,6-dmp ([**4**], step ***f***). The formation of TMBD through the comproportionation of DPQ and 2,6-dmp (step ***f***) has been already assumed from the experiments reported in Table 1. Indeed, when PIDA is reacted at 50 °C with decreasing amounts of 2,6-dmp (2 or 1 equivalents, entries 4 and 5 respectively), TMBD could not be obtained selectively and increasing amounts of DPQ are observed. In addition, no DPQ is detected when the 2,6-dmp oxidation reaction is performed at 50 °C with Cu(II)/Neocuproine (entry 2), or with PIDA (entry 3), while the presence of DPQ is observed when both experiments are performed at RT (entries 2′ and 3′).§ This series of experiments evidences the requirement of an excess 2,6-dmp at 50 °C for the total conversion of DPQ into TMBD through comproportionation. The reaction of 1 equivalent of DPQ with an excess of 2,6-dmp at 50 °C in chloroform produces 2 equivalents of TMBD,¶ whereas no reaction is observed at room temperature.

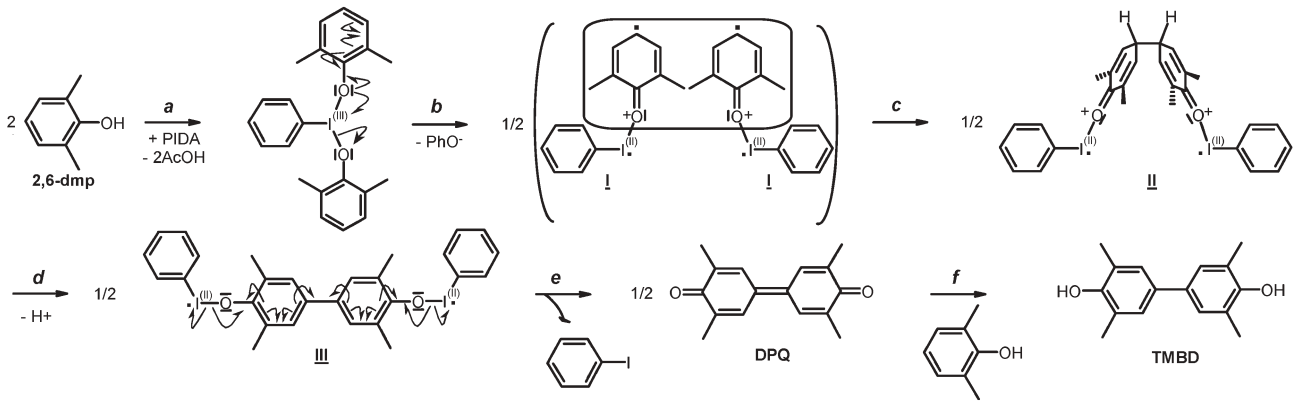
This comproportionation was mentioned about four decades ago,[17,18] but has never been cited in the abundant scientific papers reporting coupling and/or oxidation reactions involving 2,6-dmp. However, it appears to be an excellent synthetic procedure to prepare selectively the two-electron oxidation product TMBD from 2,6-dmp.

The oxidation reaction with PIDA as the oxidant has also been performed with the sodium salt of 2,6-dmp using the experimental conditions reported in Table 1, entry 3. This procedure leads to large amounts of 2,6-dmp oligomers resulting from C–O couplings (in a C–C/C–O ratio of approximately 1 : 3). The predominance of the C–O pathway is presumably due to the presence of an excess of phenoxide, an anion which can undergo the nucleophilic attack at the *para*-position of the (diphenoxyiodo)benzene intermediate. The oxygen atom of the non-deprotonated 2,6-dmp is probably not nucleophilic enough to achieve this nucleophilic addition. As a result, the formation of a radical cation (step ***b***) and its self-condensation (step ***c***) leading to the exclusive formation of C–C coupling products are most likely due to the absence of a good nucleophile in the reaction mixture.

All experiments described above have been performed in chloroform or in deuterated chloroform even without requiring further purification. The best yielding reaction to generate TMBD (Table 1, entry 3) has also been carried out in molten 2,6-dmp at 50 °C, under argon in the presence of activated molecular sieves.‖ The conversion to bisphenol is as high as 70% based on the 1,2,4,5-tetrabromobenzene internal standard (compared to 52% when the reaction is performed in chloroform, entry 3 of Table 1). At the end of the reaction, the mixture consists of only two phenol derivatives, namely 2,6-dmp and TMBD. The oxidized by-product 2,6-dimethylcyclohexadiene-1,4-dione, which can be detected by ^{1}H NMR (Fig. 1), is clearly not formed using these dry conditions. The fact that molecular oxygen is not involved in this process is indicated by the yield of the reaction which is comparable when the coupling is performed under pure dioxygen. A straightforward work-up gives 62% of pure TMBD. The synthetic procedure

Table 2 ^{1}H NMR ($CDCl_3$) chemical shifts (ppm) of the 2,6-dmp derivatives observed during this study

	Ph–OH	Ph–O–**H**	Ph–C**H$_3$**
2,6-dmp	6.96 (2H,d) 6.75 (1,t)	4.60 (1,s)	2.23 (6,s)
TMBD	7.14 (4,s)	4.62 (2,s)	2.29 (12,s)
DPQ	7.72 (4,s)	/	2.16 (12,s)
2,6-dmp dimer	7.07 (3,m) 6.37 (2,s)	4.23 (1,s)	2.17 (6,s) 2.12 (6,s)
2,6-dmp polymers	7.05 (3, tail) 6.47 (internal) 6.37 (2, head)	4.23 (1,s)	2.17 (6, tail) 2.09 (internal) 2.12 (6, head)
2,6-dimethylcyclohexa-2, 5-diene-1,4-dione	6.56 (2, s)	/	2.06 (6, s)



Scheme 2 Proposed mechanism for the PIDA-mediated oxidation of 2,6-dmp.

herein reported thus represents a simple and novel method to selectively produce at will, either DPQ by oxidation and coupling of 2,6-dmp, or TMBD by means of comproportionation of the quinone DPQ formed with additional 2,6-dmp added in the same reaction mixture at 50 °C.

In summary, the use of PIDA as an oxidant for the oxidative coupling of 2,6-dmp allows the selective synthesis of TMBD. Methodical investigations of this unprecedented PIDA-mediated selective C–C coupling have allowed the proposition of a reaction mechanism which significantly differs from the expected one for a classical 2,6-dmp coupling reaction. Thus, the coupling of two radical intermediates at their *para*-phenyl position directly leads to the formation of DPQ which spontaneously comproportionates at 50 °C in the presence of an excess of 2,6-dmp to produce TMBD. This PIDA-induced oxidative C–C coupling is therefore a convenient, simple and selective procedure for the preparation of TMBD.

Support by NRSC Catalysis (a Research School Combination of HRSMC and NIOK) and the Spanish Ministry of Science and Technology (GA) is kindly acknowledged.

Notes and references

† 0.82 mmol (DDQ or PIDA) or 1.64 mmol ([$CuCl_2(neo)_2$]) of oxidant was added to a solution of 2,6-dmp (0.5 g, 4.09 mmol, for **1–3** and **1′–3′**; 0.2 g, 1.64 mmol, for **4** or 0.1 g, 0.82 mmol for **5**) in $CHCl_3$ (33 mL) under argon at RT or 50 °C. After stirring overnight, 0.332 g (0.82 mmol) of 1,2,4,5-tetrabromobenzene (internal standard) was added and the solvent was evaporated under reduced pressure. The crude residue was analyzed by ^{1}H NMR and the yields were determined with respect to the internal standard.
‡ DDQ, Cu(II) complexes and PIDA are known to mediate the oxidation of phenol derivatives. DDQ is a quinone based stoichiometric 2-electron oxidant.[19] Cu(II)/Neocuproine is a 1-electron stoichiometric oxidant due to the extreme stability of the bis-neocuproine–Cu(I) complex formed during the reaction preventing the reoxidation to Cu(II).[20] PIDA is a stoichiometric 2-electron oxidant.[14,15]
§ In the specific case of the quinone derivative DDQ, the comproportionation reaction was not observed. This phenomenon is under investigation.
¶ A mixture of 2,6-dmp (1 g, 8.18 mmol) and DPQ (0.655 g, 2.73 mmol) in 4 mL of chloroform was stirred 6 h at 50 °C. After cooling down to RT, 1,2,4,5-tetrabromobenzene (0.322 g, 0.818 mmol, internal standard) was added and the solvent evaporated under reduced pressure. The crude residue was analyzed by ^{1}H NMR and the yield of the reaction was determined with respect to the internal standard. All DPQ had been consumed and 1.17 g of TMBD was formed (yield = 89%).
‖ 4 Å molecular sieves were activated at 180 °C under vacuum. 2,6-dmp (1.86 g, 15.21 mmol) and activated 4 Å molecular sieves (1 g) were stirred for 1 h at 50 °C under argon. The reaction was started upon addition of PIDA (1 g, 3.04 mmol) in powder. After 6 h of stirring, 1,2,4,5-tetrabromobenzene (0.120 g, 0.304 mmol) and 50 mL of hexane were added and the reaction mixture was refluxed for 1 h. Cooling down to RT, and filtration of the solution afforded 0.46 g of TMBD as a light yellow precipitate (yield = 62%).

1 A. S. Hay, *Prog. Polym. Sci.*, 1999, **24**, 45.
2 A. S. Hay, *J. Polym. Sci., Part A: Polym. Chem.*, 1998, **36**, 505.
3 Mitsubishi Gas Chemical Co, *US4211857*, 1979.
4 General Electric, *US4471068*, 1984.
5 P. Gamez, J. A. P. P. v. Dijk, W. L. Driessen, G. Challa and J. Reedijk, *Adv. Synth. Catal.*, 2002, **344**, 890.
6 Konica Minolta Holdings Inc, *JP2004085774*, 2004.
7 General Electric, *US2003198892*, 2003.
8 Honshu Chemical Ind, *EP856504*, 1998.
9 Mitsubishi Petrochemical Co, *US4564713*, 1986.
10 M. J. S. Dewar and T. Nakaya, *J. Am. Chem. Soc.*, 1968, **90**, 7134.
11 G. Pandey, C. Muralikrishna and U. T. Bhalerao, *Tetrahedron Lett.*, 1990, **31**, 3771.
12 H. Nishino, N. Itoh, M. Nagashima and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 620.
13 T. Wirth, *Angew. Chem., Int. Ed.*, 2005, **44**, 3656.
14 L. Kürti, P. Herczegh, J. Visy, M. Simonyi, S. Antus and A. Pelter, *J. Chem. Soc., Perkin Trans. 1*, 1999, 379 and references therein.
15 A. Pelter and R. S. Ward, *Tetrahedron*, 2001, **57**, 273.
16 T. Dohi, K. Morimoto, Y. Kiyono, A. Maruyama, H. Tohma and Y. Kita, *Chem. Commun.*, 2005, 2930.
17 General Electric, *US3631208*, 1971.
18 A. S. Hay, *Tetrahedron Lett.*, 1965, **47**, 4241.
19 H. D. Becker, *J. Org. Chem.*, 1965, **30**, 982.
20 C. Boldron, P. Gamez, D. M. Tooke, A. L. Spek and J. Reedijk, *Angew. Chem., Int. Ed.*, 2005, **44**, 3585.

