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Diels-Alder trapping of in situ generated Dienes from 3,4-dihydro-2*H*-pyran with *p*-Quinone catalysed by *p*-Toluenesulfonic acid

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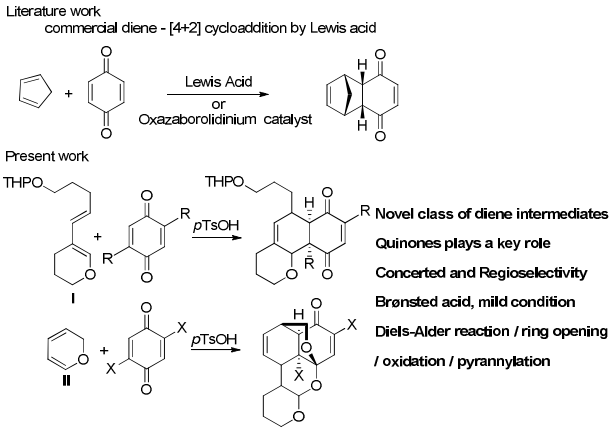
This comprehensive study portrays that *p*-toluenesulfonic acid is the efficient catalyst for the reaction between *p*-quinones and 3,4-dihydro-2*H*-pyran, than the Lewis acids. The products were accomplished by the Diels-Alder cycloaddition and their mechanistic pathway have been formulated. The impact of C_2 and $C_{2,5}$ substituents of the *p*-quinones on the cycloaddition reaction has been explored. Remarkably, it is the first report to explore this kind of in situ generated dienes for Diels-Alder cycloaddition reaction.

Quinones are a large class of compounds endowed with rich and fascinating chemistry.[1] Naturally occurring quinones and hydroquinones are subunits in many biological compounds[2] and possess a variety of biological properties including antitumoral,[3] HIV transcriptase inhibition[4] and immunomodulation.[5] Indeed via Diels-Alder reactions ,the most powerful versions of [4 + 2]-cycloaddition, the 1,4-benzoquinone and various quinone subcategory have been exploited in numerous well known synthesis of natural products (eg. steroids, reserpine, ibogamine, dendrobine, and gibberellic acid).[6] Quinone, a dienophile not only incorporates an extraordinary confluence of functional groups but also displays a high selectivity in reactions with various dienes. This is quite interesting due to the fact that, apart from their electron deficient nature, quinones also contain useful chemical functionality that can form the basis for further transformations after the Diels-Alder reaction.

Numerous reports states that [4+2] cyclic adduct has been obtained as the result of Diels-Alder reaction between various commercial dienes and quinones, catalyzed by either Lewis acid / Brønsted acid, or metal complexes (Scheme 1).[6-9] The asymmetric synthesis of the natural product angiogenesis Inhibitor (+)-epoxyquinol A and related epoxyquinoid dimers has been reported using 2*H*-pyran monomers.[10] This inspired us to explore Diels-Alder reaction between *p*-quinone and more reactive unique species of 2*H*-pyran a non commercially available diene. Hence the focus was on the in situ generation of 2*H*-pyran (II) through the oxidation of 3,4-dihydro-2*H*-pyran. On the other hand another intermolecular diene (I)[11] was obtained from 3,4-dihydro-2*H*-pyran in *p*TsOH, in which case the *p*-quinones has not involved.



Scheme 1. Diels-Alder reaction of *p*-quinones with diene.

Initially, the reaction was performed between 1,4-benzoquinone (**1a**) and 3,4-dihydro-2*H*-pyran (**2**) with the mole ratio of 1:1 in the presence of CF_3COOH (1 mole%) in dichloromethane at 40°C with oxygen atmosphere. The new compound (**3a**) was obtained with an yield of 13% along with unreacted 1,4-benzoquinone (80%). The trial experiment was conducted with different mole ratios (1-4.5) of 3,4-dihydro-2*H*-pyran (**2**). When increasing the mole ratio of **2**, the consumption of quinone was also increased. At the mole ratio of 4.5, the yield of **3a** was 26% along with **4a** (11%). At 15 mol % of the CF_3COOH catalyst, the yield of **3a** was increased to 47% and **4a** (19%) along with the unreacted 1,4-benzoquinone which was recovered in 48 h (Table 1, entry 1). All the compounds obtained were characterized thoroughly by various spectral techniques.

The disappearance of the ^{13}C NMR signals at 185.5, 184.7 ppm

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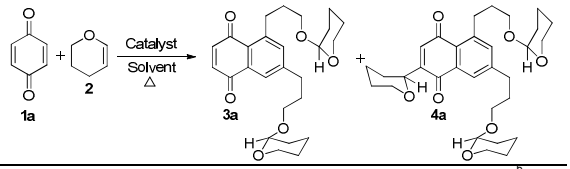
of new compound (**3a**) in DEPT-135° NMR reveals the presence of two carbonyl carbons. The appearance of a new signal corresponding to the aromatic ring at the position of carbon-carbon double bond of 1,4-benzoquinone has been recorded and the same were observed in ^{1}H NMR at δ 7.79, 7.40 ppm. The two protons signal at 6.80 ppm for olefinic (-CH=CH-), two acetal proton signals at 4.55, 4.51 ppm and carbon signals at 98.06, 98.03 ppm were also noticed. In compound (**4a**), the additional ^{1}H NMR signal at 4.47-4.44 ppm and ^{13}C NMR signal at 72.6 ppm disclosed that tetrahydro-2*H*-pyran group was connected in the position of olefinic carbon double bond of *p*-quinone. The newly obtained compounds were further confirmed by ESI-MS spectral data.

To enhance the yield of new compounds, the trial experiments were conducted with 15 mol % of catalyst in different solvents with oxygen atmosphere under reflux condition. The result of which has been depicted in Table 1. When the above reaction was performed using the weak Brønsted acids like CH_3COOH and $LiClO_4$ as catalyst no product was obtained, even when the reaction was carried out for 48 h. The other Brønsted acid catalysts such as methanesulfonic acid and benzenesulfonic acid gave the product (**3a**) with a yield of 69% and 77% along with 10% of **4a** respectively. However, when strong Brønsted acid such as *p*-toluenesulfonic acid (*p*TsOH) was used as a catalyst, the yield of **3a** obtained was reasonably good (83%) along with 10% of **4a**.

Table 1. Optimization studies[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)[b] 3a	4a
1	CF_3COOH	DCM	48	47	19
2	CH_3COOH	DCM	48	-	-
3	$LiClO_4$	DCM	48	-	-
4	CH_3SO_3H	DCM	12	69	10
5	$C_6H_5SO_3H$	DCM	12	77	10
6	*p*TsOH	DCM	8	83	10
7	$InCl_3$	DCM	24	32	<5
8	$Cu(OTf)_2$	DCM	24	45	<5
9	$Bi(OTf)_3$	DCM	24	48	<5
10	$Sn(OTf)_2$	DCM	24	41	<5
11	Et_3N	DCM	48	-	-
12	*p*TsOH	$CHCl_3$	8	87	5
13	*p*TsOH	ACN	24	66	10
14	*p*TsOH	Benzene	24	57	5
15	*p*TsOH	Toluene	24	53	5
16	**pTsOH**	**DCE**	**8**	**93**	**trace**
17[c]	*p*TsOH	DCE	8	74	5
18	-	DCE	48	-	-

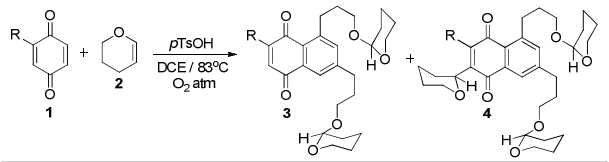
[a] General reaction conditions: **1a** (1.0 mmol), **2** (4.5 mmol) and catalyst (15 mol %) using procedure 1. [b] Isolated yield after column chromatography. [c] Air atmosphere (open condenser)

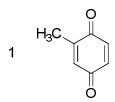
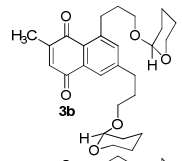
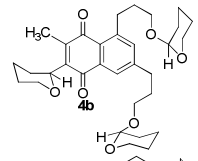
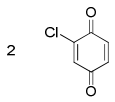
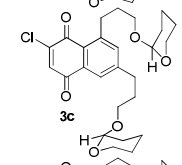
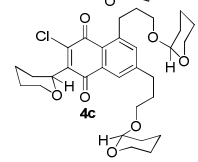
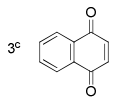
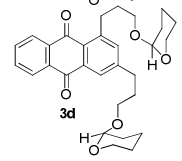
Further, the more strong acids like HCl, H_2SO_4 and HNO_3 made the reactants charred indicating that they are too strong, and hence they are not suitable for this reaction. Lewis acid catalysts such as $InCl_3$, $Cu(OTf)_2$, $Bi(OTf)_3$ and $Sn(OTf)_2$ gave the product **3a** with moderate yield of 32-48% in 24 h along with less than 5% of **4a.** Further, the same reaction with Et_3N, none of the product was obtained, even when the reaction was carried out even upto 48 h.

The solvent effect was also studied by employing various solvents and it was observed that when $CHCl_3$ was used as solvent, the compound **3a** (87%) was obtained along with 5% yield of **4a.**When other solvents such as H_2O, EtOH and DMF were used, the reaction did not proceed at all even after 48 h whereas solvents like acetonitrile, benzene and toluene yielded the compound (**3a**) with 66%, 57% and 53% along with less than 10% of **4a** respectively. When 1,2-dichloroethane (DCE) was used as solvent, it afforded **3a** with significant increased yield of 93% in 8 h with trace amount of **4a** (Entry 16). When the above reaction was carried out under air atmosphere (open condenser) the products were obtained with an yield of **3a (**74%) and **4a** (5%) (Table 1, entry 17) which is lesser yield compared to that in the oxygen atmosphere. Hence all the reactions were carried out only in the oxygen atmosphere. In fact, no product was detected when the reaction was carried out in the absence of the catalyst.

The above observation, indicated that the products were Diels-Alder cycloadduct and also this transformation have been facilitated via the in situ generated diene intermediate from the reaction between *p*-quinones and 3,4-dihydro-2*H*-pyran catalysed by *p*-toluenesulfonic acid which is the novel feature of the present work. Upon analyzing the results the following were set as optimum conditions for this novel transformation that is, *p*-quinones and 3,4-dihydro-2*H*-pyran in the ratio of 1:4.5 equivalent, *p*-toluenesulfonic acid (15 mol %) as catalyst and 1,2-dichloroethane as solvent at 83°C under oxygen atmosphere.

Table 2. Brønsted acid catalysed Diels-Alder reaction of C_2-mono-substituted *p*-quinones with 3,4-dihydro-2*H*-pyran[a]



Entry	Quinone	Product 3	time (h)	Byproduct 4	Yield (%)[b] 3	4
1			12		91	<5
2			10		89	<5
3[c]			16	NA	85	-

[a] General reaction conditions: *p*-quinones (1.0 mmol), **2** (4.5 mmol) and *p*TsOH catalyst (15 mol %) using procedure 1. [b] Isolated yield after column chromatography.

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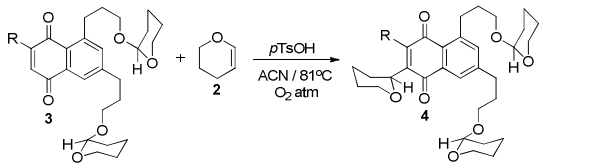
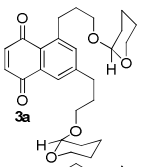
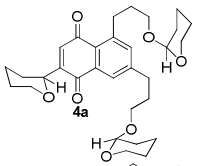
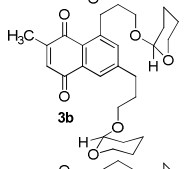
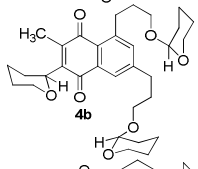
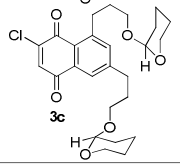
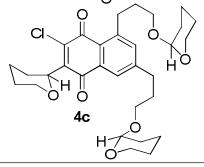
In addition, the generality of this reaction has also been explored by extending it with various substituted quinones. The reactions between 3,4-dihydro-2*H*-pyran (**2**) with several *ortho*-substituted *p*-quinones were carried out under the same optimized condition; the results are summarized in Table 2. The reaction between 2-methyl-1,4-benzoquinone (**1b**) and 3,4-dihydro-2*H*-pyran (**2**) in the presence of *p*TsOH (15 mol%) catalyst, afforded the product (**3b**) with 91% yield in 12 h along with less than 5% of **4b**. Under the same reaction condition, 2-chloro-1,4-benzoquinone (**1c**) furnished the product **3c** (89%), along with less than 5% of **4c** in 10h. And, the unsubstituted 1,4-naphthoquinone (**1d**) afforded only the product (**3d**) with an yield of 85% and compound **4d** which is not possible in this case, due to the fact that the C_2 position of olefinic carbon are sterically substituted. All the compounds were separated by column chromatography and throughly characterized by NMR and ESI-MS spectroscopic techniques as well.

To increase the yield of compound **4**, the reaction was performed individually between the isolated compounds (**3a-c**) and 3,4-dihydro-2*H*-pyran in presence of *p*TsOH catalyst in dry acetonitrile at 81°C under oxygen atmosphere and the results were summarized in Table 3. The compound (**3a**) with 3,4-dihydro-2*H*-pyran (**2**) in presence of *p*TsOH (15 mol%) catalyst, afforded the product (**4a**) with an yield of 94%. Likewise, the compounds **3b** and **3c** gave the products (**4b**) and (**4c**) with the yield of 87% and 89% respectively. All the synthesized compounds were isolated by column chromatography and were confirmed by NMR and ESI-MS as well.

Table 3. Brønsted acid catalysed C-pyrannylation of compound **3**[a]

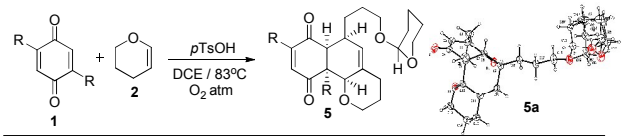


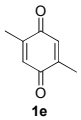
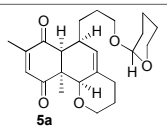
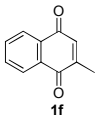
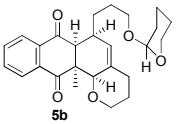
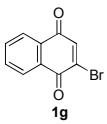
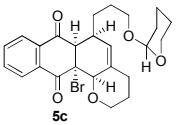
Entry	Reactant 3	Product 4	time (h)	Yield (%)[b] 4
1			8	94
2			12	87
3			10	89

[a] General reaction conditions: **3a-c** (1.0 mmol), **2** (4.5 mmol) and *p*TsOH catalyst (15 mol %) using procedure 2. [b] Isolated yield after column chromatography.

The results of 2,5-disubstituted *p*-quinones under the same optimized condition were tabulated in Table 4. To our surprise, different product (**5a**) was obtained when 2,5-dimethyl-1,4-benzoquinone (**1e**) was used as a substrate with the yield of 95% in 12h. Similarly, the substrates of 2-methyl-1,4-naphthoquinone (**1f**) gave the product (**5b**) with the yield of 91% and 2-bromo-1,4-naphthoquinone (**1g**) gave the product (**5c**) with an yield of 89% respectively. The structural confirmation of these products has also been done by spectral techniques. ^{1}H NMR spectrum of **5a** revealed, the presence of olefinic enone proton signal at 6.43 ppm, one -CH signal of cyclic olefin at 5.50 ppm, one acetal signal at 4.56 ppm and CH signal of -O/CH/C- at 3.38-3.33 ppm. In ^{13}C NMR, two carbonyl carbons at 200.8, 198.5 ppm which is disappeared in DEPT-135° NMR, one acetal (-O/CH/O-) carbon signal at 98.9 ppm, one -CH carbon of (-O/CH/C-) signal at 80.5 ppm. Further, the compound (**5a**) was confirmed by single crystal XRD as shown in Table 4.[12]

Table 4. Brønsted acid catalysed Diels-Alder reaction of $C_{2,5}$-di-substituted *p*-quinones with 3,4-dihydro-2*H*-pyran[a]



Entry	Quinone	Product 8	time (h)	Yield (%)[b] 8
1			12	95
2			16	91
3			12	89

[a] General reaction conditions: *p*-quinones (1.0 mmol), **2** (4.5 mmol) and *p*TsOH catalyst (15 mol %) using procedure 1. [b] Isolated yield after column chromatography.

The suggested stepwise mechanism for the transformation of **3** and **4** has been depicted in Scheme 2, in which as an initiative step, the diene (**I**) has been generated from 3,4-dihydro-2*H*-pyran (**2**) in presence of *p*TsOH catalyst.[13] The diene (**I**) upon reacting with the olefinic carbon-carbon double bond of *p*-quinone forms the regioselective structure **A**. Further this reaction proceeds through ring opening which occurs due to the abstraction of acidic proton by the pyrannyl ether oxygen atom to form an intermediate **B**. Subsequent oxidation, followed by pyrannylation, leads to the formation of the product (**3**) and the products obtained from the unsubstituted and mono-substituted quinones were reported in Table 1 and 2. Further, the electron transfer from 3,4-dihydro-2*H*-pyran to compound (**3**) gave the intermediate **C** which on further reaction with excess 3,4-dihydro-2*H*-pyran forms **D**. The oxidation

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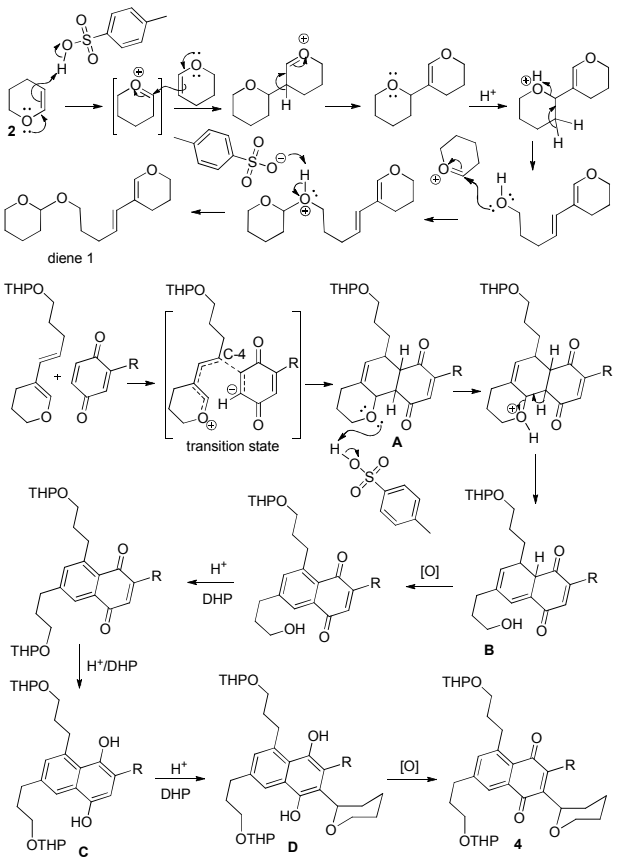
of the same generated the product (**4**) and similar products were reported in Table 3.

On the other hand, when H is replaced by CH_3 at C_2 position in structure **A**, there is no possibility of ring opening and this kind of products (**5**) were reported in Table 4. From this it can be clearly elucidated that the formation of products, depends upon the nature of the substituent in *p*-quinone at C_2 position.

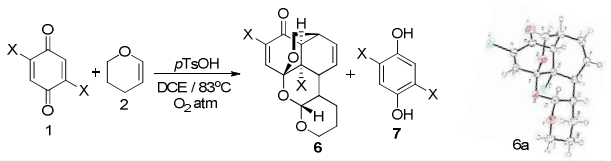


Scheme 2. Plausible mechanism for the transformation of **3, 4** and **5**.

2,5-dichloro-1,4-benzoquinone (**1h**) with 3,4-dihydro-2*H*-pyran (**2**) in *p*TsOH catalyst in 1,2-dichloroethane solvent at 83°C under oxygen atmosphere, afforded the novel tetra cycloadduct (**6a**).Moreover the product was obtained within 90 min of reaction time with 91% yield (Table 5, entry 1). Further, the reaction of 2,5-dibromo-1,4-benzoquinone (**1i**) with 3,4-dihyro-2*H*-pyran (**2**) afforded the product (**6b**) with a yield of 87%. All the compounds were isolated by column chromatography and also throughly characterized by spectral techniques.

^{13}C NMR spectrum of the adduct **(6a)** revealed, that one carbonyl carbon signal at 190.3 ppm which disappeared in DEPT-135° NMR, one quinone olefinic carbon signal at 137.5, two olefinic carbon signals at 132.7, 125.5 ppm, one acetal (-O/C/O-) quaternary carbon signal at 99.7 ppm which disappeared in DEPT-135° NMR, one carbon signal of acetal (-O/CH/O-) group at 92.6 ppm. ^1H NMR spectrum of **6a** displayed, one quinone olefinic proton signal at 6.74, two olefinic proton signals at 5.86, 5.79 ppm and one acetal (-O/CH/O-) proton signal at 5.76 ppm. Further, the structure of the compound (**6a**) has been established by single crystal X-ray analysis as shown in Table 5.[12]

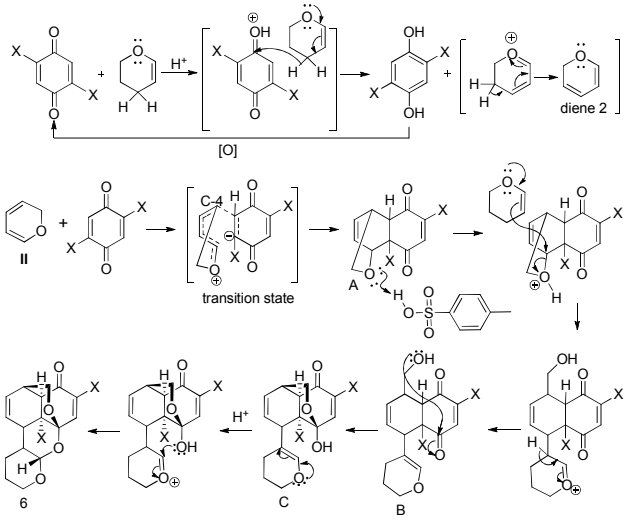
Table 5. Brønsted acid catalysed Diels-Alder reaction of $C_{2,5}$-di-halo substituted *p*-quinones with 3,4-dihydro-2*H*-pyran[a]



Entry	Quinone	Product 6	By product 7	time (min)	Yield (%)[b] 6	7
1	1i	6a	7a	90	91	<5
2	1j	6b	7b	90	87	<5

[a] General reaction conditions: *p*-quinones (1.0 mmol), **2** (4.5 mmol) and *p*TsOH catalyst (15 mol %) using procedure 3. [b] Isolated yield after column chromatography.

In the case of 2,5-dihalo-1,4-benzoquinone, the 2*H*-pyran (**II**) was generated in situ through the redox reaction between 2,5-dihalo substituted *p*-quinone and 3,4-dihydro-2*H*-pyran in the presence of *p*TsOH. The 2*H*-pyran (**II**) was trapped by the olefinic carbon carbon double bond of *p*-quinone, which may be attributed due to the effect of substitution at $C_{2,5}$ position. The formation of cycloadduct (**6**) could be rationalized as outlined in Scheme 3.



Scheme 3. Plausible mechanism for the transformation of **6**.

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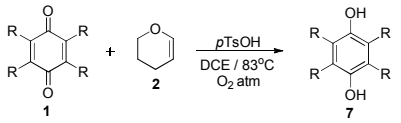
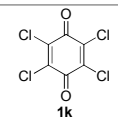
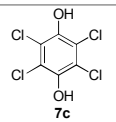
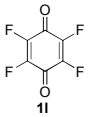
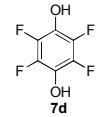
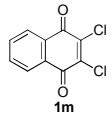
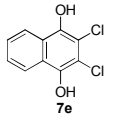
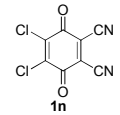
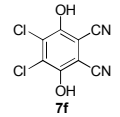
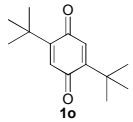
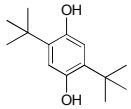
The formation of hydroquinone indicated that 3,4-dihydro-2*H*-pyran should have acted as an electron donor and *p*-quinone as an electron acceptor. Since, the reaction was realized even in dark, the observed redox reaction could not be due to photochemical single electron transfer from 3,4-dihydro-2*H*-pyran to *p*-quinones.

Moreover, the reaction has also been studied with *p*-quinone in which all the four positions (2,3,5,6-) of olefinic carbon carbon double bonds are substituted with group which is depicted in Table 6. In accordance to our expectation, the substrates viz., 2,3,5,6-tetrachloro-1,4-benzoquinone (**1k**), 2,3,5,6-tetrafluoro-1,4-benzoquinone (**1l**), and 2,3-dichloro-1,4-naphthoquinoe (**1m**) gave only the respective reduction products of **7c**, **7d** and **7e** with the yield of 91%, 89% and 51% respectively and no other products were obtained. The reaction was carried out using 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (**1n**) under oxygen atmosphere as well as in air atmosphere (open condenser) but there was no change in the percentage of yield of **7f** because in this reaction, oxygen gas is not needed since DDQ itself is a good oxidant. The compound **7f**, formed under oxygen atmosphere was 97% and in the air atmosphere it was 95%. Furthermore, the reaction of 2,5-di-*tert*-butyl-1,4-benzoquinone (**1o**) gave only the reduction product of 2,5-di-*tert*-butylbenzene-1,4-diol (**7g**) with the yield of 35% only, along with the recovery of the starting material around 60% even when the reaction time was prolonged for about 48 h.

Table 6. Brønsted acid catalysed redox reaction of sterically hindered *p*-quinones with 3,4-dihydro-2*H*-pyran[a]



1 2 7

Entry	Quinone	Product 7	time	Yield (%)[b]
1	 1k	 7c	30 min	91
2	 1l	 7d	30 min	89
3	 1m	 7e	24 h	51
4	 1n	 7f	30 min	97
5	 1o	 7g	48 h	35

[a] General reaction conditions: *p*-quinones (1.0 mmol), **2** (4.5 mmol) and *p*TsOH catalyst (15 mol %) using procedure 3. [b] Isolated yield after column chromatography.

This might be attributed to the fact that $C_{2,5}$ positions are substituted with bulky group and the reaction was inhibited by steric effect. However, with the substrates of 2,3,5,6-tetramethyl-1,4-benzoquinone and 9,10-anthraquinone, the reduction did not proceed even after 48h due to the high reduction potential values.

When the reaction was carried out under stoichiometric condition, only the reduction of *p*-quinones was observed owing to the generation of 2*H*-pyran by the redox reaction. The same reaction was performed with the different mole ratio of the reactants viz. *p*-quinones (2 equivalent), 3,4-dihydro-2*H*-pyran (5 equivalent) with *p*-toluenesulfonic acid catalyst (1 equivalent) in DCE at 83°C under oxygen atmosphere in which case the following were obtained: 2,5-dichloro-1,4-benzoquinone yielded 2,5-dichlorobenzene-1,4-diol (16 %), 2,5-dichloro-1,4-Bis(tetrahydro-2*H*-pyran-2-yloxy)benzene[13] (37%) and the Diels-Alder adduct **6** (46%). In the same way, 1,4-benzoquinone gave an yield of hydroquinone (53%) and the di-O-alkylation product 1,4-Bis(tetrahydro-2*H*-pyran-2-yloxy)benzene[13] (28%). The unsubstituted 1,4-naphthoquinone afforded the reduction product of naphthalene-1,4-diol (41%), additionally, the mono and di-C-alkylated compounds of 2-(tetrahydro-2*H*-pyran-2-yl)naphthalene-1,4-dione and 2,3-bis(tetrahydro-2*H*-pyran-2-yl)naphthalene-1,4-dione products were also isolated with an yield of 25%, 17% respectively. The above results revealed that, the in situ generated diene (2*H*-pyran) did not coordinate with either 1,4-benzoquinone nor 1,4-naphthoquinone for Diels-Alder cycloadduct rather it undergoes oxidation to form pyrylium cation. Since, the unsubstituted pyrylium cation is very unstable; it may be isolated only at low temperature but it decomposes quickly.[14] All the compounds were separated by column chromatography and characterized by spectral techniques.

Conclusions

A novel and efficient protocol for the synthesis of Diels-Alder cycloadduct via the in situ generated diene intermediates from various type of *p*-quinones with 3,4-dihydro-2*H*-pyran in presence of *p*TsOH as a catalyst has been developed. All these reactions proceeded with very good yields and the products with regioselective, which confirm the proposed mechanistic pathways. The regioselective products were obtained due to the coordination of the catalyst to the least sterically shielded C=O lone pair, uniquely syn to the *p*-quinone C_α-H subunit. This indicated that the attack of diene on the less substituted double bond is always favored. The attack of the nucleophilic end (C-4) of the diene at the carbon *β* to the coordinated carbonyl gives further evidence for the orientational regioselectivity.

The products summarized in Table 1, 2 and 4, formed with respect to diene I were obtained from 3,4-dihydro-2*H*-pyran in *p*TsOH, in which case the *p*-quinones has not involved in the formation of diene I. This has been confirmed experimentally by the detection of diene 1, when the reaction was performed in $CDCl_3$ with 3,4-dihydro-2*H*-pyran in *p*TsOH catalyst. Whereas, the products in Table 3, 5 and 6, formed with respect to diene II were obtained from the redox reaction between *p*-quinone and 3,4-dihydro-2*H*-pyran in *p*TsOH catalyst. It is also evident that the reduction occurred only when the olefinic carbon bond of *p*-

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quinone has been sterically hindered by the substituent at $C_{2,3}$ position which has been depicted in Table 6. Further we are intended to confirm the reaction mechanism by DFT calculation, which is under progress.

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