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PTSA–catalyzed functionalization of hydroquinones with benzhydryl alcohols in water

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ABSTRACT

An intriguing and operationally simple direct benzylation of hydroquinones with benzhydryl alcohols has been developed using PTSA in water, affording functionalized hydroquinones in good to excellent yields. The advantages of being environmentally benign, metal-free, base-free, easy workup and having a wide substrate scope make it a promising process for the synthesis of symmetrically and unsymmetrically benzylated hydroquinones as well as for industrial applications.

Introduction

The quinone skeletons are ubiquitous in nature, source of secondary metabolites in many organisms and endowed with rich and attractive chemistry.[1] Especially, hydroquinones are essential to life and play a vital role in biological functions being intimately related to the oxidative processes in cells.[2] In addition, hydroquinones are versatile chemicals with significant applications in cosmetics, photography and dyes.[3] A variety of pharmacologically important agents contain hydroquinone moiety and shown to have potential bioactivities such as anti-oxidant, anti-microbial, anti-HIV, anti-inflammatory[4a] and anti-cancerous activity[4b] (Fig. 1). Moreover, 2,5-di-*tert*-butyl-1,4-benzohydroquinone and its derivatives are of particular interest which act as potent inhibitors for the enzyme sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA).[5]

Benzhydryl alcohols are readily accessible substrates for the functionalization of many nucleophiles.[6] These alcohols have attracted attention to chemical community as benzylating agents due to commercial availability, low cost and releasing environmentally benign H_2O as by-product from their reactions.[7] In contrast to benzhydryl alcohols, benzylic halides are toxic and produce huge amounts of halogenated waste in benzylation reactions, which is unpleasing from the perspective of sustainable and green chemistry.

In recent years there has been an upsurge in developing low cost and reliable methods by using water as a medium for synthetic transformations.[8] Water is a non-flammable, nontoxic, highly polar and green solvent flourished with exclusive chemical and physical properties such as strong tendency for hydrogen bonding, amphoteric nature, high dielectric constant, large heat capacity and optimum oxygen solubility to sustain the aquatic life forms.[9] Water is not only the choice of solvent for nature to carry out her reactions and also useful for electron transport which has been exemplified by many synthetic and biological reactions.[10] Water offers many attractive advantages as a solvent over traditional organic solvents such as environmental benignity, inherent safety, relative abundance and availability.[11] Therefore, the unique properties of water aroused the interest of the scientific community to the development of water mediated organic transformations over the past few decades.

p-Toluenesulfonic acid monohydrate (PTSA) catalyzed direct nucleophilic substitution of alcohols has evolved as one of the efficient, cost-effective and eco-friendly strategies for alkylation or benzylation.[12] These reactions occur in a high atom economical fashion through an attractive salt-free process in organic solvents which afford the desired products with generation of water as the only side product. To date, there are no reports on benzylation of hydroquinones in water. In continuation of our interest in quinone chemistry and in carbon–carbon and carbon–heteroatom bond formation,[13] herein we report the first examples of direct functionalization of hydroquinones catalyzed by PTSA *via* S_N1 dehydrative reaction with benzhydryl alcohols in water

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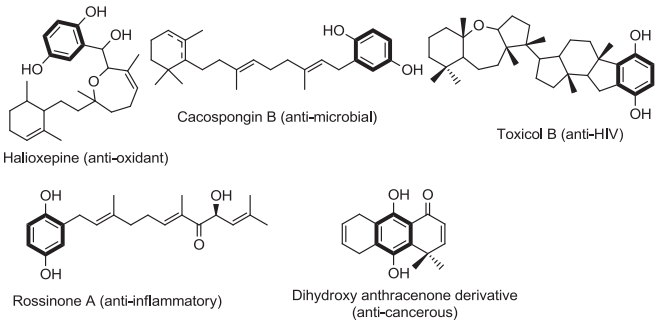
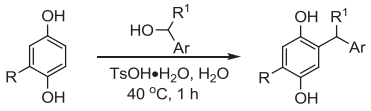


Fig. 1. Pharmaceutically relevant hydroquinones.



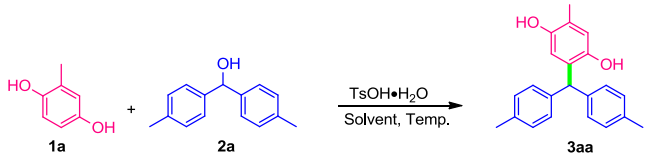
Scheme 1.

(Scheme 1). This protocol offers a simple, economical and green approach for the synthesis of symmetrically and unsymmetrically benzylated hydroquinones with high atom economy.

We embarked our study by selecting, methylhydroquinone (**1a**) and di-*p*-tolylmethanol (**2a**) as model substrates to identify the best reaction conditions. The results are shown in Table 1. At the outset, we performed the reaction in MeOH at 80 °C and the desired product **3aa** was obtained in 10% yield in 52 h. (Table 1, entry 1). However, the substitution of **1a** to **2a** did not proceed in polar aprotic solvent; whereas the only traces of **3aa** were observed in CH_3CN (entries 2 and 3). When the present reaction was carried out in water at 80 °C, benzylated product **3aa** was formed in poor yield (entry 4). Further, yield of **3aa** was increased as the temperature of the reaction was elevated to 100 °C (entry 5). Surprisingly, the rate of reaction and yield of **3aa** were increased when the reaction was heated in the presence of PTSA (10 mol%) in water (entry 6). No product was detected when the reaction was performed under neat conditions (entry 7) which demonstrated that solvent is necessary to facilitate the functionalization of hydroquinone. The current transformation indicating the solvent dependency of the reaction and proceeded slowly in CH_3CN but only gave 20% of **3aa** in DCE (entries 8 and 9). After achieving the optimum yield in PTSA and water system, we studied the effect of temperature variation; the rate of reaction as well as the yield of **3aa** was conserved while reducing the temperature to 40 °C (entries 10 and 11). The rate of reaction and product yield were decreased when the above reaction was conducted at 25 °C (entry 12). Further optimization study revealed that lowering the loading of catalyst did not affect the rate of reaction and the yield of **3aa** (entry 13). An essential requirement of water to promote the benzylation of **1a** by **2a** shown in entry 6 and therefore, this forced us to further study the influence of water on the reaction outcome. The quantity of water governs the efficiency of the reaction. Addition of excess amount of water diminished the yield of **3aa** (entry 14). Among these optimization conditions, tuning of PTSA (2 mol%) in water (2 mL) with model substrates at 40 °C was found to be optimum in terms of the reaction efficiency and yield. Benzylated hydroquinone could be extracted easily from reaction mixture with ethyl acetate.

With the optimized reaction conditions in hand we moved toward the synthesis of symmetrically benzylated hydroquinones (Table 2). Benzhydrol (**2b**) and other symmetrical derivatives bearing electron-withdrawing halo groups **2c** and **2d** worked well with 2-methylhydroquinone (**1a**) and afforded the corresponding products **3ab**, **3ac** and **3ad** in good to excellent yields. Remarkably, replacement of methyl group with methoxy group on hydroquinone enhanced the yield of the products (**3aa**–**3ad** *vs* **3ba**–**3bd**) up to 95% as a result of the increased electron–density on aromatic ring. Further, the current protocol was extended to 2-phenylhydroquinone (**1c**) in combination with **2a**–**2d** and all were

Table 1
Optimization of reaction conditions.[a]



Entry	Solvent (mL)	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	MeOH (5)	–	80	52	10
2	Dioxane (5)	–	80	52	nr
3	CH_3CN (5)	–	80	72	Trace
4	H_2O (2)	–	80	48	14
5	H_2O (2)	–	100	48	30
6	H_2O (2)	PTSA (5)	80	1	92
7	–	PTSA (5)	80	24	nr
8	CH_3CN (5)	PTSA (5)	80	24	54
9	DCE (10)	PTSA (5)	80	24	20
10	H_2O (2)	PTSA (5)	60	1	92
11	H_2O (2)	PTSA (5)	40	1	92
12	H_2O (2)	PTSA (5)	25	8	73
13	**H_2O (2)**	**PTSA (2)**	**40**	**1**	**92**
14	H_2O (5)	PTSA (2)	40	3	85

The optimized condition is indicated in bold font.
[a] Reactions of **1a** (0.5 mmol) with **2a** (0.6 mmol) were performed.
[b] Yield of pure and isolated product.

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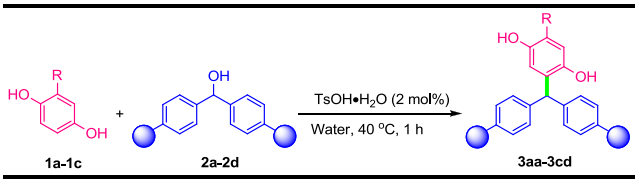
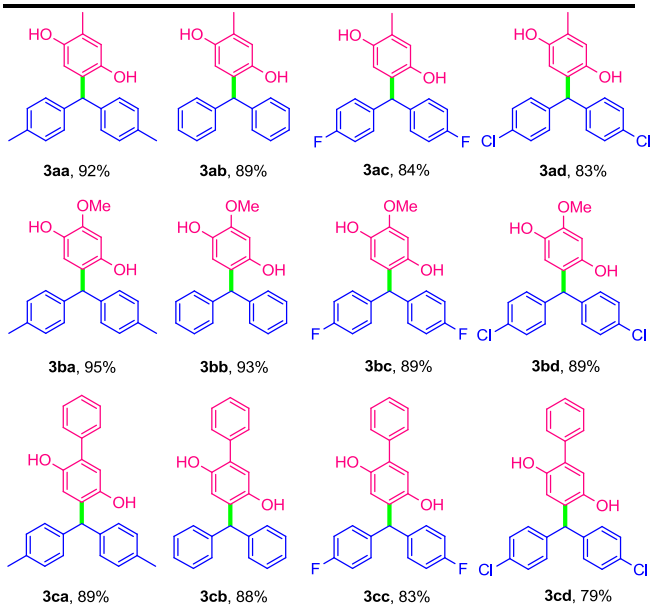
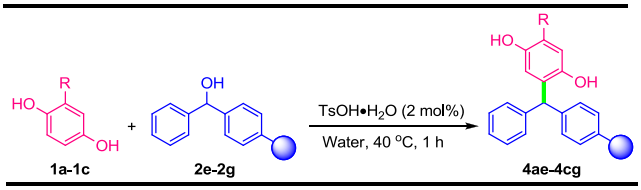
Table 2
Synthesis of symmetrical benzylated hydroquinones.[a]

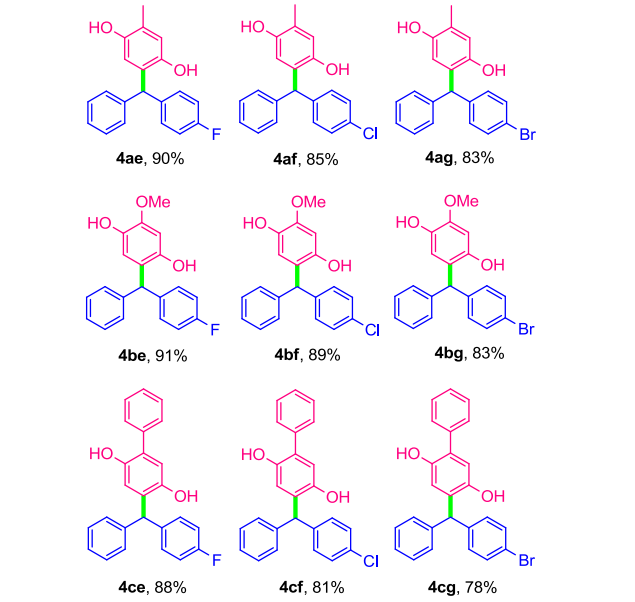




[a] Reaction conditions: hydroquinone **1** (0.5 mmol), benzhydryl alcohol **2** (0.6 mmol), PTSA (2 mol%), H_2O (2 mL).

Table 3
Synthesis of unsymmetrical benzylated hydroquinones.[a]





[a] Reaction conditions: hydroquinone **1** (0.5 mmol), benzhydryl alcohol **2** (0.6 mmol), PTSA (2 mol%), H_2O (2 mL).

converted in there corresponding products **3ca**–**3cd** in good to very good yields.

With the promising results in hand, we explored this protocol to synthesize unsymmetrically benzylated hydroquinones. Further experiments showed the generality for secondary alcohols **2e**–**2g** having phenyl and monosubstituted phenyl groups with hydroquinones **1a**–**1c** (Table 3). It was observed that these unsymmetrical benzhydrols were tolerable to hydroquinone **1a** and provided the corresponding products **4ae**–**4ag** in good to very good yields. The reaction of **1b** with **2e**–**2g** furnished the target products **4be**–**4bg** in the yields ranging from 83 to 91%. Moreover, 2-phenylhydroquinone (**1c**) was also found to be an ideal reaction partner with **2e**–**2g**, yielding the target products **4ce**, **4cf** and **4cg** in very good amounts.

In case of benzhydryl alcohols, phenyl ring bearing electron–withdrawing halo groups generally gave the benzylated product in lower yield compared to electron–donating substituents. These results could be interpreted as high stabilization of cationic intermediates by increased electron density on aromatic ring of benzhydryl alcohols.

Furthermore, direct benzylation of **1b** with 1-phenylethyl alcohol (**2h**) also afforded the desired **4bh** in 88% yield (Fig. 2). In contrast, the reaction of **1b** with unsubstituted benzyl alcohol (**2i**) did not proceed.

It is noteworthy to mention here that Shirakawa and Kobayashi during their studies of organic reaction in water have described that dodecylbenzenesulfonic acid (DBSA) catalyzes the nucleophilic substitution of benzylic alcohols with various nucleophiles in water.[14] Soon after, Liu et al. reported a substantially similar work, where they acknowledged the previous work and claimed a few advantages in terms of catalyst recycling.[15] Cozzi et al. indicated that water enabled direct use of ferrocenyl alcohols for alkylation with indoles.[16] In contrast to these reports, the developed protocol facilitated the functionalization of hydroquinones under mild conditions in short reaction time, which is a novel entry in dehydrative nucleophilic substitution of benzylic alcohols. The possible reason for this efficient process might be that these quinones are much better nucleophiles than indoles, and/or are more water-soluble.

Thus, present metal-free and base-free protocol could functionalize substituted hydroquinones with a variety of secondary alcohols, affording symmetrically and unsymmetrically benzylated hydroquinones *via* clean process. Despite the fact that functionalized hydroquinones do the valuable structural motifs possess important therapeutic applications and bioactive profiles there were no approaches for the synthesis of functionalized hydroquinones in water. Therefore, to the best of our knowledge, this is the first ever report for merging the hydroquinones with unactivated benzylic alcohols in water to accomplish the highly functionalized quinones which holds an immense potential for finding novel pharmaceutically important agents.

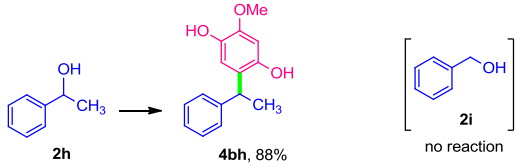
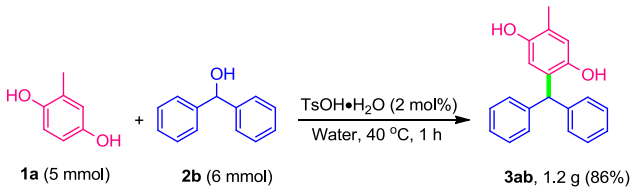
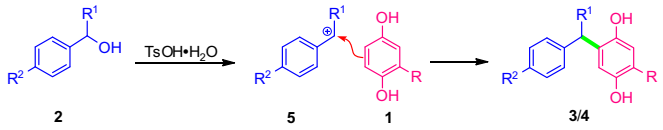


Fig. 2. Scope of alcohols **2**. Reaction conditions: **1b** (0.5 mmol), benzyl alcohol **2h**, **i** (0.6 mmol), PTSA (2 mol%), H_2O (2 mL), 40 °C, 1 h.



Scheme 2. Gram-scale synthesis of benzylated hydroquinone **3ab**.



Scheme 3. Plausible reaction mechanism.

Additionally, the dehydrative substitution of 2-methyl hydroquinone (**1a**) and benzhydryl alcohol (**2b**) could be performed at 5 mmol scale under the optimized conditions to produce the corresponding 2-benzyl-5-methylbenzene-1,4-diol (**3ab**) in a very good yield (Scheme 2).

On the basis of our results and literature reports,[17] a plausible mechanism is outlined in Scheme 3 to account for the benzylation of hydroquinones. These reactions presumably proceed *via* dehydrative S_N1 mechanism. A benzyl carbocation **5** generated from diaryl carbinol **2** in the presence of PTSA and **5** could be attacked by hydroquinone **1** to afford the products **3** and **4**.

In conclusion, we have developed a simple and straightforward sustainable method for the direct nucleophilic substitution of hydroquinones to benzhydryl alcohols using PTSA as a catalyst in water. The established metal-free and eco-friendly process is one of the most efficient synthetic routes for the functionalization of hydroquinones. The demonstrated protocol shows compatibility of benzhydrols bearing substituents of different electronic nature with a variety of hydroquinones. Large-scale preparation of functionalized hydroquinones with high atom economy under aerobic conditions marked the clear and practical utility of this economic synthetic process.

*General procedure for the synthesis of benzylated hydroquinones **3** and **4***

A mixture of hydroquinones **1** (0.5 mmol), TsOH·H_2O (2 mol%) and benzhydryl alcohols **2** (0.6 mmol) in H_2O (2 mL) was heated at 40 °C for 1 h. Then it was cooled, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was dried over anhyd. Na_2SO_4, and concentrated in a rotatory evaporator. The residue was purified by silica gel column chromatography (step gradient with 10–20% ethyl acetate in hexanes as the eluent) to afford the desired products **3** and **4**.

*2-(Di-p-tolylmethyl)-5-methylbenzene-1,4-diol (**3aa**)*

Yield: 146 mg (92%) as white solid; mp: 147–148 °C; IR (KBr): ν_{max} 3412, 3026, 2922, 2860, 1597, 1415, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.6 Hz, 4H), 7.02 (d, J = 8.0 Hz, 4H), 6.61 (s, 1H), 6.19 (s, 1H), 5.54 (s, 1H), 4.27 (s, 1H, OH), 4.25 (s, 1H, OH), 2.33 (s, 6H), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 147.0, 139.5, 136.4, 129.4, 129.3, 129.2, 123.2, 118.8, 116.8, 50.1, 21.1, 15.6 ppm; HRMS (ESI+): m/z calcd for $C_{22}H_{22}O_2$ $[M+H]^+$: 319.1692, found: 319.1697.

*2-((4-Chlorophenyl)(phenyl)methyl)-5-methylbenzene-1,4-diol (**4af**)*

Yield: 138 mg (85%) as brown viscous liquid; IR (KBr): ν_{max} 3429, 3027, 2923, 2849, 1603, 1452, 1189 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 8.0 Hz, 3H), 7.13 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.60 (s, 1H), 6.24 (s, 1H), 5.74 (s, 1H), 4.97 (s, 1H, OH), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 146.8, 142.5, 141.5, 132.4, 130.8, 129.4, 128.7, 128.6, 126.9, 123.6, 118.7, 117.0, 49.7, 15.7 ppm; HRMS (ESI+): m/z calcd for $C_{20}H_{17}ClO_2$ $[M+Na]^+$: 347.0809, found 347.0805.

*2-Methoxy-5-(1-phenylethyl)benzene-1,4-diol (**4bh**)*

Yield: 107 mg (88%) as brown viscous liquid; IR (KBr): ν_{max} 3435, 3062, 2929, 2854, 1640, 1450, 1368, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.18 (m, 5H), 6.84 (s, 1H), 6.36 (s, 1H), 4.24 (q, J = 7.2 Hz, 1H), 3.76 (s, 3H), 1.57 (d, J = 7.2 Hz, 3H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 145.7, 145.5, 139.5, 129.0, 127.6, 126.7, 124.4, 113.8, 100.9, 56.2, 38.6, 21.5 ppm; HRMS (ESI+): m/z calcd for $C_{15}H_{16}O_3$ $[M+H]^+$: 245.1172, found 245.1153.

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