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Communication

Construction of diaminobenzoquinone imines *via* ferrocene-initiated radical reaction of benzoquinone with amines

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ABSTRACT

A ferrocene-initiated radical reaction of benzoquinone with amines has been successfully developed for the direct access to diaminobenzoquinone imines in high yields, in which the commercially available and cheap ferrocene was employed as a radical initiator and TBHP was used as an oxidant. Moreover, this reaction could be achieved with low loading of ferrocene (0.5 mol%). This protocol is highly efficient with good substrate tolerance and provides a new approach for the construction of benzoquinone imines with potential pharmaceutical interest.

Substituted benzoquinones are key structural motifs, existing in a broad spectrum of biologically active natural products and important pharmaceuticals [1]. Among them, benzoquinone imines are important synthons in organic synthesis, which are also widely used in the dye industry and inhibitors against the photo-oxidation of polymers [2]. For example, early in 1983, Rajappa group reported a novel synthesis of 5-acylaminobenzimidazole-2-carbamates through intramolecular regioselective addition of benzoquinone imines [3]. In 2001, Nair group reported a dipolar cycloaddition of carbonyl ylides to *para*-benzoquinone imines, which could be used as a facile route to bicyclo[3.2.1] and [2.2.1] systems [4]. After that, Nair group reported a three component reaction involving isocyanides, dimethyl acetylenedicarboxylate and benzoquinone imines as a facile synthesis of spiro-fused γ-iminolactams [5]. In addition, Parker group reported an annulation of enolizable vinyl benzoquinone imines for the synthesis of dihydroquinolines, quinolines and indoles [6]. Recently, catalytic transformation of C–H bonds into valuable C–N bonds offers an efficient synthetic approach to constructN-functionalized molecules [7]. Over the last few decades, transition-metal catalysis proves as a powerful tool for the direct C–H bonds amination reactions. For example, in 2008, Gaunt group reported an oxidative Pd(II)-catalyzed C–H bond amination to synthesize carbazoles at room temperature [8]. In 2012, White group reported an Iron-catalyzed intramolecular allylic C–H amination to synthesize sulfonamides [9]. Recently, our group has developed a series of Ir-catalyzed direct C–H bond amination of arylquinazolinones [10]. On the other hand, radical C–H bond functionalization has emerged as a promising approach because of their high reactivity with high atom- and step-economy [11]. For example, Studer and co-workers have disclosed effective methods of iron-initiated radical C–H functionalization for the direct synthesis of phenanthridines, fluorenones and xanthones starting from commercially available aromatic aldehydes [12]. For this direction, our group has developed a ferrocene-initiated oxidative cyclization of benzaldehyde with alkyne as a new strategy to substituted indenones [13]. In our continuing effort to demonstrate the clean C–H functionalization [14], herein, we present a new ferrocene-initiated radical reaction of benzoquinone with amines to synthesize diaminobenzoquinone imines (Scheme 1). This protocol features easy operation, low loading of ferrocene (0.5 mol%), cheap and easily available starting materials, high efficiency and tolerance of a broad range of substrates.

Initially, the reaction of benzoquinone (BQ) (**1a**) with aniline (**2a**) was chosen as a model reaction to optimize various reaction conditions (Table 1). The results revealed that (*E*)-2,5-bis(phenylamino)-4-(phenylimino)cyclohexa-2,5-dienone (**3a**) was obtained as a main product in 78% yield in toluene at 80 °C when $FeBr_3$ (0.5 mol%) was used as an initiator and *t*-BuOOH (TBHP) (3.0 equiv.) was used as the oxidant (Table 1, entry 1). Only

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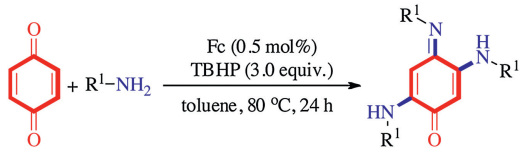
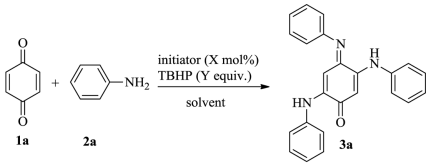


Scheme 1. Ferrocene-initiated radical reaction of benzoquinone with amine.

Table 1
Optimization of the reaction conditions.[a]



(*E*)-2,5-bis(phenylamino)-4-(phenylimino)cyclohexa-2,5-dienone

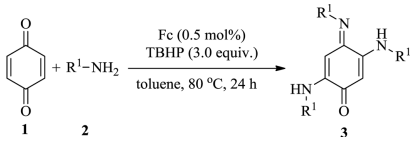
Entry	Initiator (mol%)	TBHP (equiv.)	Solvent	Temp (°C)	Yield (%)[b]
1	$FeBr_3$ (0.5)	3.0	Toluene	80	78
2	–	3.0	Toluene	80	33
3	$FeCl_3$ (0.5)	3.0	Toluene	80	87
4	$Fe_2(SO_4)_3$ (0.5)	3.0	Toluene	80	65
5	Fc (0.5)	3.0	Toluene	80	95
6	$FeCl_2$ (0.5)	3.0	Toluene	80	74
7	Fc (1.0)	3.0	Toluene	80	93
8	Fc (0.2)	3.0	Toluene	80	54
9	Fc (0.5)	–	Toluene	80	nd
10	Fc (0.5)	2.5	Toluene	80	90
11	Fc (0.5)	0.5	Toluene	80	21
12	Fc (0.5)	3.5	Toluene	80	92
13	Fc (0.5)	3.0	DMF	80	trace
14	Fc (0.5)	3.0	DMSO	80	40
15	Fc (0.5)	3.0	NMP	80	75
16	Fc (0.5)	3.0	Dioxane	80	69
17	Fc (0.5)	3.0	Toluene	90	80
18	Fc (0.5)	3.0	Toluene	70	56
19[c]	Fc (0.5)	3.0	Toluene	80	95
20[d]	Fc (0.5)	3.0	Toluene	80	77

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (1.0 mmol), TBHP (70% solution in ethyl acetate), solvent (2.0 mL), 24 h.
[b] Isolated yields. nd = not detected.
[c] 26 h.
[d] 22 h.

33% yield of the target **3a** was achieved when the reaction was carried out in the absence of an initiator (Table 1, entry 1 *vs.* 2). Iron salts, such as $FeCl_3$, $Fe_2(SO_4)_3$, $FeCl_2$ and ferrocene (Fc), were screened. Ferrocene gave the highest yield (95%) (Table 1, entry 1 *vs.* entries 3–6). Better result was achieved with 0.5 mol% of ferrocene (Table 1, entry 5 *vs.* entries 7–8). Moreover, 3.0 equiv. of TBHP favor this reaction (Table 1, entry 5 *vs.* entries 9–12). Toluene was demonstrated to be better than other solvents, such as DMF, DMSO, NMP (*N*-methyl pyrrolidone) and dioxane (Table 1, entry 5 *vs.* entries 13–16). The yield of **3a** decreased when the reaction temperature and reaction time were changed (Table 1, entries 17–20). Based on the results, the optimal reaction conditions were identified as follows: toluene as solvent, at 80 °C, ferrocene (0.5 mol%) as an initiator and *t*-BuOOH (TBHP) (3.0 equiv.) as an oxidant (Table 1, entry 5).

With the optimized reaction conditions in hand, the scope of the substrates was examined (Table 2). Benzoquinone (**1a**) reacted smoothly with aniline (**2a**) and its derivatives (**2b**-**1o**) to give the desired products (**3a**-**3o**) in moderate to good yields (61%–95%). Methyl group at the *ortho*-, *meta*-, and *para*-position of aniline provided the corresponding products **3b**-**3d** in 69%, 72% and 93%

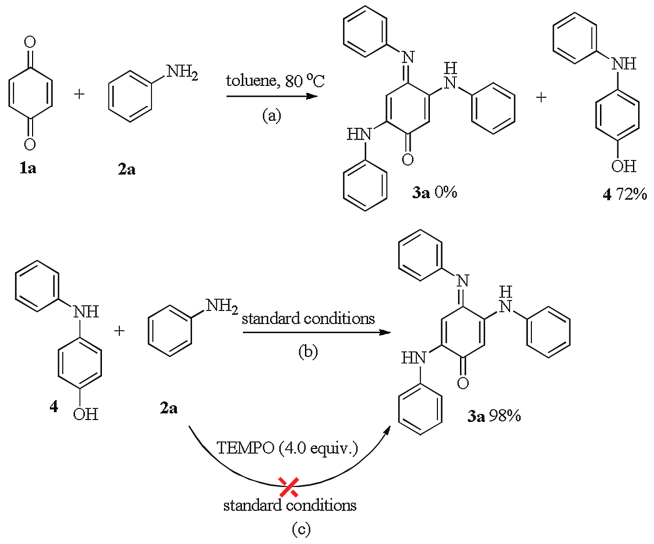
Table 2
Scope of substrates.[a]



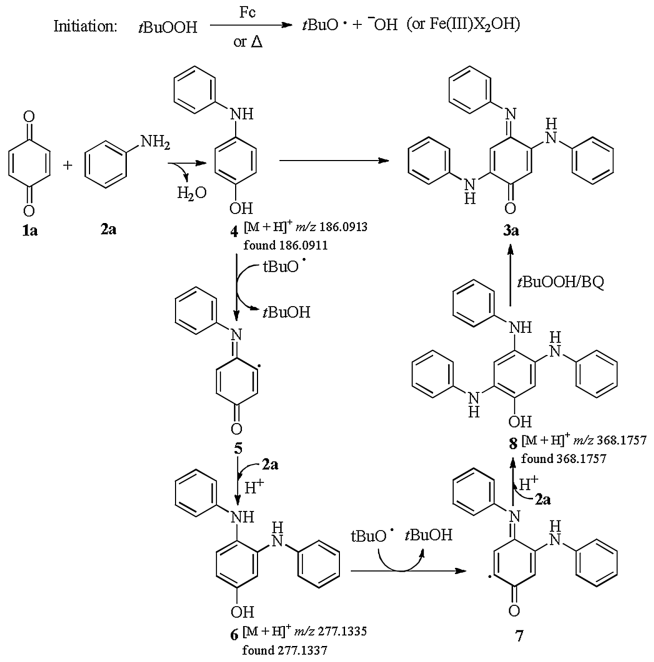
Entry	R^1	2	3	Yield of 3 (%)[b]
1	Ph	**2a**	**3a**	95
2	2-$CH_3C_6H_4$	**2b**	**3b**	69
3	3-$CH_3C_6H_4$	**2c**	**3c**	72
4	4-$CH_3C_6H_4$	**2d**	**3d**	93
5	4-FC_6H_4	**2e**	**3e**	67
6	4-ClC_6H_4	**2f**	**3f**	90
7	4-BrC_6H_4	**2g**	**3g**	85
8	4-IC_6H_4	**2h**	**3h**	77
9	4-$OCH_3C_6H_4$	**2i**	**3i**	75
10	4-$CF_3C_6H_4$	**2j**	**3j**	67
11	2-$OCH_3C_6H_4$	**2k**	**3k**	65
12	3-$OCH_3C_6H_4$	**2l**	**3l**	61
13	2-ClC_6H_4	**2m**	**3m**	76
14	3-ClC_6H_4	**2n**	**3n**	65
15	2-BrC_6H_4	**2o**	**3o**	68

[a] Reaction conditions: **1** (0.20 mmol), **2** (1.0 mmol), Fc (0.5 mol%), TBHP (3.0 equiv.), solvent (2.0 mL).
[b] Isolated yields.

yields, which indicated that steric effect of substituted groups slightly affected this transformation. Halogen groups, such as F, Cl, Br and I at the 4-position of aniline provided the corresponding products **3e**-**3h** in 67%, 90%, 85% and 77% yields, respectively. Other groups, such as methoxyl and trifluoromethyl, were well tolerated and gave the corresponding products in satisfactory yields (**3i** and **3j**) (75% and 67%). Compared to the yield of **3d**, these results indicated that the electron-withdrawing groups have certain influence on the efficiency of this coupling reaction. Moreover, methoxyl and halogen groups, such as Cl, and Br at the 2- or 3-position of aniline could also provide the corresponding products **3k**-**3o** in 65%, 61%, 76%, 65% and 68% yields, respectively. However, other quinones, aliphatic amines, or amides, such as 2-methylcyclohexa-2,5-diene-1,4-dione, 2-(*tert*-butyl)cyclohexa-2,5-diene-1,4-dione, benzylamine, propylamine or benzamide, failed to give the desired products.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction mechanism.

To clarify the reaction mechanism, control experiments were carried out (Scheme 2). First, no **3a** was achieved and 72% yield of 4-(phenylamino)phenol (**4**) was generated in the absence of an initiator and an oxidant (Scheme 2a). Additionally, 4-(phenylamino) phenol (**4**) could react with **2a** to give the expected product **3a** in 98% yield under the optimized conditions (Scheme 2b). These results suggested that compound **4** could be a key intermediate in this reaction. When a radical scavenger, TEMPO, was introduced into the reaction, no target product (**3a**) was achieved, which suggested that a radical pathway might be involved in this reaction (Scheme 2c).

Based on the results obtained, a plausible reaction mechanism is proposed as shown in Scheme 3. First, initiation occurs by reducing *t*-BuOOH with ferrocene to give the *tert*-butoxyl radical as well as an Fe(III)-complex. The *tert*-butoxyl radical then abstracts the H-atom from the 4-(phenylamino)phenol (**4**) generated from **1a** and **2a** to give a radical intermediate **5**, which could reacted with **2a** to generate 3,4-bis(phenylamino)phenol (**6**). Subsequently, another radical intermediate **7** was generated from the reaction of *tert*-butoxyl radical with compound **6**, which could reacted with **2a** to generate 2,4,5-tris(phenylamino)phenol (**8**). Then, the intermediate **8** could be oxidized by TBHP or benzoquinone to the target product **3a**. In this reaction, intermediates **4**, **6**, and **8** were detected by HRMS (Figs. S1-S3 in Supporting information)

In summary, we have demonstrated a ferrocene-initiated radical reaction of benzoquinone with amines for direct access to diaminobenzoquinone imines, which was initiated by low loading of ferrocene (0.5 mol%) with high yields and a broad substrate scope was tolerated. Reaction mechanism studies have demonstrated the formation of two radical species as key intermediates, which might be responsible for the sequential formation of C–N bonds. Further study on the application of this radical reaction system is ongoing in our laboratory.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.026.

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