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Quinonediimine-Induced Oxidative Coupling of Organomagnesium Reagents

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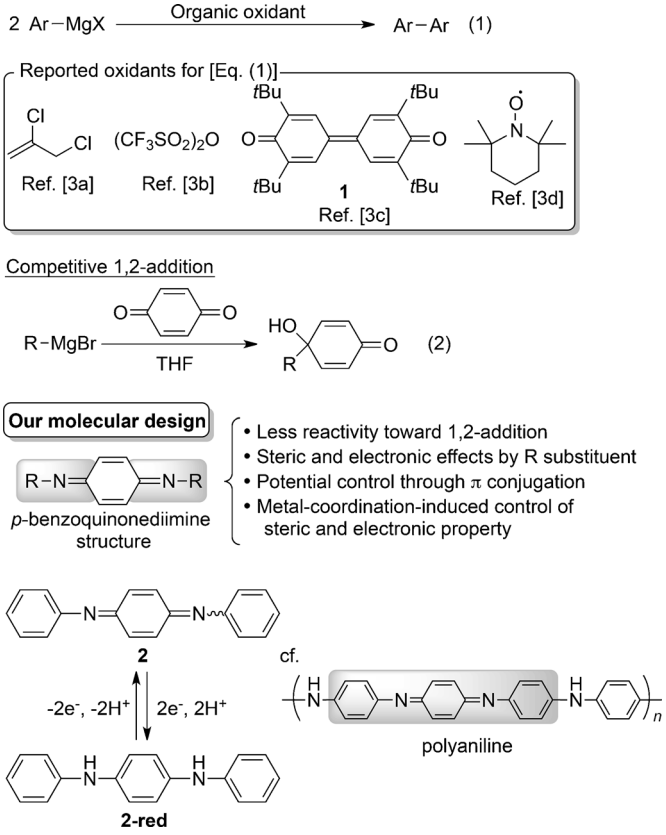
Abstract: *N,N′*-Diphenyl-*p*-benzoquinonediimine, a redox-active unit of polyaniline, efficiently induced the oxidative homocoupling of various aryl- and vinylmagnesium reagents in suppressing the side reactions, such as 1,2- or 1,4-addition reaction.

Grignard reagents are generally recognized as a nucleophile or a base in organic synthesis. In some cases, they can act as a reductant to donate an electron, resulting in a reduced product.[1] It should be interesting and challenging to make the electron-transfer-type reaction take place in preference to the nucleophilic addition in the competitive situation.

The reaction described herein is oxidative homocoupling of arylmagnesium reagents ([Eq. (1)] in Scheme 1), in which two-electron oxidation from the two arylmagnesium reagents is formally required. This reaction is one of the efficient methods for the synthesis of symmetrical biaryls. Such reaction generally relies on high-valent transition-metal oxidants.[2] On the other hand, the methodology employing organic oxidants is not frequently used. The representative organic oxidants are shown in Scheme 1.[3] In 2006, Mayr, Knochel, and co-workers proved the utility of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**1**) for the coupling reaction of a broad range of organomagnesium reagents, such as aryl and alkenyl ones through an electron-transfer reaction.[3c] This finding should be a milestone in this area from the viewpoint of metal-free coupling. Later, the benefit of 2,2,6,6-tertramethylpiperidine-*N*-oxyl radical (TEMPO) has been demonstrated by Studer's group.[3d] Phenylmagnesium bromide in ionic liquid was also discovered to undergo the oxidative homocoupling by *p*-benzoquinone, which in contrast attacks the carbonyl group in THF to give the corresponding 1,2-adduct (R = Ph, [Eq. (2)] in Scheme 1).[3e] In this way, *p*-benzoquinone compounds have a higher risk of the undesired addition reactions, such as 1,2- or 1,4-addition, although they generally work as a two-electron acceptor in other oxidation reactions. From a standpoint of molecular design, the carbonyl groups in diphenoquinone **1** appear to be protected by bulky *tert*-butyl groups in both sides.



Scheme 1. Oxidative coupling of arylmagnesium reagent induced by an organic oxidant and the reported ones. The competitive 1,2-addition in the above-described reaction by using *p*-benzoquinone. Molecular design of the oxidant and the redox scheme for *N,N′*-diphenyl-*p*-benzoquinonediimine (**2**) and its reduced form **2-red**.

In this context, we present herein an advanced molecular design employing *p*-benzoquinonediimines as an organic oxidant (Scheme 1). In principle, imine moiety is much less reactive toward the 1,2-addition of Grignard reagents than the corresponding aldehyde or ketone due to the weaker electrophilic nature.[4] The substituent on imino nitrogen can control the steric and electronic properties. The aryl substitution can induce the expansion of π conjugation of quinonediimine, by which the redox potential will be tuned. Furthermore, the coordination property of imino nitrogen can change the steric effect and redox potential through the complexation. In this reaction, magnesium cation can contribute to the increasing

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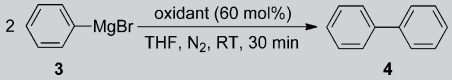
the oxidizing ability of the quinonediimine. *N*,*N*′-Diphenyl-*p*-benzoquinonediimine (**2**) is a redox-active unit of polyaniline, which is one of the most famous conductive and redox-active π-conjugated polymers.[5] The quinonediimine moiety can accept two electrons and two protons to give the reduced form, *N*,*N*′-diphenyl-*p*-phenylenediamine (**2-red**; Scheme 1). To date, we have demonstrated the catalytic aerobic oxidative coupling reaction of 2,6-di-*tert*-butylphenol by using quinonediimine compounds as an organic catalyst.[6] Similarly, polyaniline exhibits the efficiency for the catalytic aerobic dehydrogenation of amines.[7] We have also developed the hybrid redox catalyst with transition metals and metal nanoparticles based on the redox function of polyanilines and *p*-benzoquinonediimine derivatives.[8] Herein, we report the *p*-benzoquinonediimine-induced oxidative homocoupling of aryl- and vinylmagnesium reagents. Notably, this *p*-benzoquinonediimine oxidant **2** exhibited superior activity for typical Grignard reagents than diphenoquinone **1**.

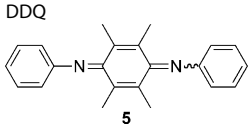
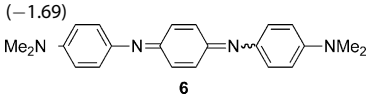
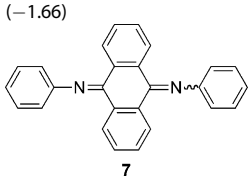
p-Benzoquinonediimine **2** was prepared from the commercially available **2-red** by Cu^{II}-catalyzed aerobic oxidation in a high yield (see the Supporting Information).[9] This reaction is easy to operate and scalable. Pure **2** can be easily obtained by recrystallization as orange crystals. Thus-prepared **2** was used for the following investigation. Table 1 shows the dependence on the oxidant in the homocoupling of phenylmagnesium bromide (**3**). To the THF solution of **2** (60 mol% to **3**), compound **3** was added dropwise at room temperature, and the orange color was immediately changed to dark greenish black. After work-up, the mixture was purified by silica-gel column chromatography. In the chromatographic analysis, the desired biphenyl (**4**) was eluted with dichloromethane/hexane (quantitative, Table 1, entry 1), and then the reduced form **2-red** was eluted with ethyl acetate/hexane. In this way, the purification of **4** and recovery of **2-red** is quite easy. Because **2-red** can be catalytically oxidized to give **2** in a good yield as described above, *p*-benzoquinonediimine **2** is formally recyclable. On the other hand, use of diphenoquinone **1** as an oxidant resulted in some products, in which the yield for **4** is only 14% (Table 1, entry 2). Stronger oxidant, such as 2,3,5,6-tetrachloro-*p*-benzoquinone (chloranil) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), also gave the complex mixture (Table 1, entries 3 and 4). *N*,*N*′-Diphenyl-(2,3,5,6-tetramethylbenzoquinone) 1,4-diimine (**5**)[10] induced the homocoupling in a moderate yield (58% yield, Table 1, entry 5) without any by-products (except benzene). Neither the desired reaction nor any side reactions proceeded well in the case of bis-dimethylamino derivative **6**[11] and anthraquinonediimine **7**[12] (Table 1, entries 6 and 7). First reduction potential of some oxidants, which was obtained based on differential pulse voltammetry measurement, is also shown in Table 1. The trend of the reactivity might reflect the reduction potential of quinonediimine-type oxidants. Therefore, these results suggest that the reaction might be controlled depending on the redox potential tuned by the substituent.

Some phenylmagnesium derivatives and phenyl-lithium were investigated in Table 2. Phenylmagnesium chloride homocoupled in 98% yield (Table 2, entry 1). Diphenylmagnesium was also quantitatively transformed to **4** (Table 2, entry 2). However, the reaction of the ate complex [$Ph_3Mg^-Li^+$·LiBr]

Table 1. Oxidative homocoupling of phenylmagnesium bromide (**3**) by using various oxidants.

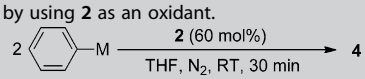


3 **4**

Entry	Oxidant (first reduction potential [V] vs. Fc/Fc^+)[a]	Yield [%][b,c]
1	**2** (−1.50)	100 (100)[d]
2	**1** (−1.09)	14
3	chloranil	9
4	DDQ	trace
5	 **5** (−1.69)	58
6	 **6** (−1.66)	2
7	 **7** (−1.87)	6[d]

[a] Reduction potential was obtained based on differential-pulse voltammetry measurement (0.5 mM in THF, $[Bu_4NClO_4] = 0.1$ M, Pt electrode). [b] Yield determined by ^1H NMR analysis by using 1,3,5-trimethoxybenzene as an internal standard. [c] Calculated as follows: (mole of **4**)×2/(mole of **3**)×100. [d] Isolated yield.

Table 2. Oxidative homocoupling of phenylmagnesium derivatives and phenyl-lithium by using **2** as an oxidant.



Entry		Yield [%][a,b]
1		98
2		100[d]
3		3[f]
4		6

[a] Yield determined by ^1H NMR analysis by using 1,3,5-trimethoxybenzene as an internal standard. [b] Calculated as follows: (mole of **4**)×2/(mole of PhMg)×100. [c] Prepared by addition of dry dioxane to the THF solution of **3**. [d] The molar ratio of Ph_2Mg/**2** is 1:1.2 in this entry. The yield was calculated as follows: (mole of **4**)/(mole of Ph_2Mg)×100. [e] Prepared by addition of two equivalents of phenyl-lithium to the THF solution of **3**. [f] The molar ratio of $Ph_3Mg^-Li^+$·LiBr/**2** is 1:1.8 in this entry. The yield was calculated as follows: (mole of **4**)/[(mole of $Ph_3Mg^-Li^+$·LiBr)×1.5]×100.

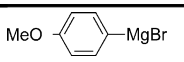
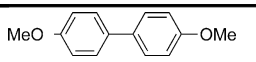
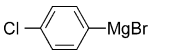
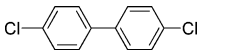
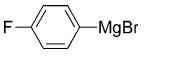
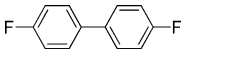
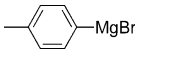
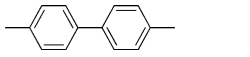
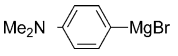
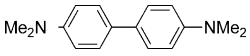
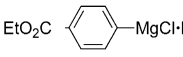
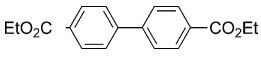
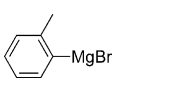
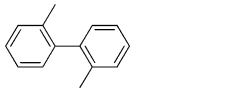
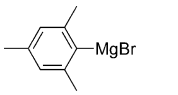
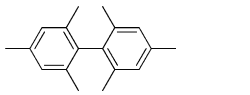
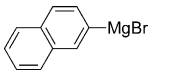
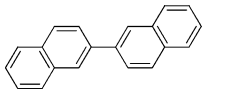
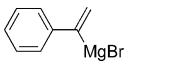
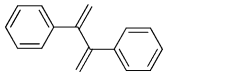
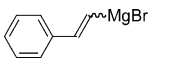
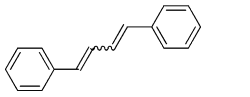
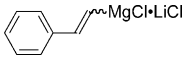
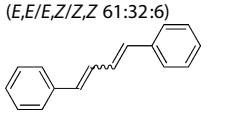
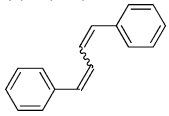
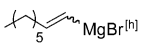
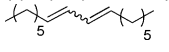
gave **4** in only 3% yield (Table 2, entry 3). The reaction of phenyl-lithium gave a complex mixture under the similar conditions (mono-adduct was suggested as a main by-product from GC-MS analysis), in which the desired **4** was obtained in a low yield (Table 2, entry 4). It is likely due to the stronger nucleophilicity of organolithium than the corresponding organomagnesium.

Table 3 shows a scope of organomagnesium reagents in the oxidative coupling by using **2** as an oxidant. Various *p*-substituted phenylmagnesium reagents were investigated (Table 3, entries 1–6). Following groups MeO-, Cl-, F-, Me-, and Me_2N were tolerated to give the corresponding homocoupling product in high yields (Table 3, entries 1–5). In the case of [(4-EtO_2C)PhMgCl·LiCl] generated from the corresponding iodide with [*i*PrMgCl·LiCl] through I/Mg exchange, **2** also induced the homocoupling in a good yield (Table 3, entry 6). The o*rtho*-methylated substrates were tried as sterically hindered examples (Table 3, entries 7 and 8). As a result, the corresponding biaryls were obtained in high yields (entries 7 and 8). 2-Naphtylmagnesium bromide resulted in the quantitative homocoupling (Table 3, entry 9). Some examples of the oxidative homocoupling for vinylmagnesium compounds were investigated. 1-Phenylvinylmagnesium bromide homocoupled in a high yield (Table 3, entry 10). In the case of styrylmagnesium bromides and octenylmagnesium bromide, the coupling products were the mixture of isomers based on the olefin geometry (Table 3, entries 11, 13, 14). This may be because the employed magnesium bromides were the *E*/*Z* mixtures. *E*-Styrylmagnesium compound generated from the corresponding iodide with [*i*PrMgCl·LiCl] through I/Mg exchange selectively afforded the *E*,*E*-form of the diene product in a high yield (Table 3, entry 12). (2-Phenylethynyl)magnesium bromide, as a representative example for alkynylmagnesium compounds, did not undergo the oxidative homocoupling efficiently under the conditions employed here (2% yield). The reactivity of diphenoquinone **1** was also investigated for comparison with **2** in the reaction of some arylmagnesium reagents. Coupling of 4-MeO-, 4-Cl-, and 4-F-phenylmagnesium bromide gave the biaryls in lower yields (43, 42, and 47%, respectively). Mesitylmagnesium bromide led in the biaryl even in a lower yield (7% yield). On the other hand, diphenoquinone **1** efficiently induced the coupling reaction of [(4-EtO_2C)PhMgCl·LiCl] (83% yield).[13]

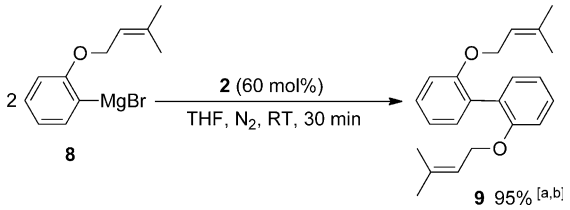
To gain insight into the mechanism, 2-prenyloxyphenylmagnesium bromide (**8**) was treated with **2** (Scheme 2). If a free-radical-like species is generated, the 5-*exo*-radical cyclization would proceed. For example, it was revealed that aryl radical generated from the one-electron reduction of *o*-allyloxybenzenediazonium ion rapidly cyclizes intramolecularly.[14] The result obtained herein showed the selective formation of the homocoupling product **9**, in which the ring-closed products were not observed. Therefore, a free-radical-like species is not likely for the one-electron oxidized intermediate in this reaction. These results are consistent with the related experiments reported in refs. [3c] and [3d].

The reaction was also followed by ^{1}H NMR spectroscopy (Figure S1 in the Supporting Information). An equimolar amount of phenylmagnesium bromide (**3**) was added to the [D_8]THF solution of **2** (●) at room temperature. Biphenyl (**4**; *) was observed with decreasing of **2** (Figure S1a in the Supporting Information). In the meantime, broadened peaks (■) also appeared at $\delta = 6$–7 ppm. The comparison with the spectrum

Table 3. Oxidative homocoupling of aryl- and vinylmagnesium derivatives by using *p*-benzoquinonediimine **2** as an oxidant.

Entry	Ar–MgX	Product	Yield [%][a,b]
1			93
2			100
3			100
4			96
5			97
6			74
7			90
8			100
9			100
10			91[d]
11	 (*E*/*Z* 4:1)[e]	 (*E*,*E*/*E*,*Z*/*Z*,*Z* 61:32:6)	99
12	 (*E*/*Z* 24:1)[f]	 (*E*,*E*/*E*,*Z*/*Z*,*Z* 93:3:trace)	96
13	 (*E*/*Z* 1:4.5)[g]	 (*E*,*E*/*E*,*Z*/*Z*,*Z* 3:16:51)	70
14		 (*E*,*E*/*E*,*Z*/*Z*,*Z* 29:54:24)	97

[a] Yield determined by ^{1}H NMR analysis by using 1,3,5-trimethoxybenzene as an internal standard. [b] Calculated as follows: (mole of product) × 2/(mole of arylmagnesium reagent) × 100. [c] Generated from the corresponding iodide with *i*PrMgCl·LiCl by I/Mg exchange.[3c] [d] Isolated yield. [e] Prepared from pure *trans*-2-bromostyrene with Mg turnings in THF at reflux. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy after quenching the styrylmagnesium bromide with D_2O. [f] Generated from the corresponding iodide with *i*PrMgCl·LiCl by I/Mg exchange. The *E*/*Z* ratio was determined by ^{1}H NMR after quenching with TMSCl.[3c] [g] Prepared from pure *cis*-2-bromostyrene with Mg turnings in THF at reflux. The *E*/*Z* ratio was determined by ^{1}H NMR after quenching the styrylmagnesium bromide with TMSCl. [h] Prepared from pure (*E*)-1-bromooct-1-ene with Mg turnings in THF at reflux. The resulting magnesium bromide compounds are the *E*/*Z* mixtures.



Scheme 2. Oxidative coupling of **8**. [a] Yield determined by ^{1}H NMR analysis by using 1,3,5-trimethoxybenzene as an internal standard. [b] The yield was calculated as follows: (mole of **9**)×2/(mole of **8**)×100.

for the complex separately prepared from the reaction of **2-red** with **3** suggests the formation of the MgBr complex of *p*-phenylenediamide **10** (■; Figure S1 c in the Supporting Information). The complicated spectrum can be possibly explained by the aggregation through bridging. Further addition of an equimolar amount of **3** led to the quantitative formation of **4** and the complete consumption of **2** and **3** (Figure S1 a in the Supporting Information). As shown in Figure S1 b in the Supporting Information, the solution of **2** was added to **3** (○), which also resulted in the quantitative formation of **4** (*) and the complete consumption of **2** and **3**. However, the intermediate, such as radical–anion species of **2**, were not captured in these experiments. Although the mechanism is ambiguous, the stepwise electron transfer has been reported.[3c]

In conclusion, *p*-benzoquinonediimine **2**, a redox-active unit of polyaniline, efficiently induced the selective oxidative homocoupling of various Grignard reagents in suppressing the side reactions, such as 1,2- or 1,4-addition reaction. It should be noted that *p*-benzoquinonediimine **2** surpassed diphenoquinone **1** in the reaction of usual arylmagnesium reagents. This molecular design utilizing *p*-benzoquinonediimine is expected to be promising with regard to the selective oxidative transformation by electron transfer.

Experimental Section

A representative procedure

To an orange suspension of *N*,*N*′-diphenyl-*p*-benzoquinonediimine (**2**; 155 mg, 0.60 mmol) in dry THF (6.0 mL) a THF solution (1.03 M) of phenylmagnesium bromide (**3**; 0.97 mL, 1.0 mmol, titrated with iodine before use) was dropwise added at RT under nitrogen, and the color was changed to dark greenish black. After stirring for 30 min at RT, the reaction mixture was quenched with water. Aqueous layer was extracted with diethyl ether twice. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration, the mixture was concentrated in vacuo. The residue was purified by silica-gel chromatography (0 to 20% dichloromethane/*n*-hexane) to give biphenyl (**4**) as a white solid (77 mg, 0.50 mmol, quant.). After elution of **4**, treatment with 30% ethyl acetate in *n*-hexane recovered the mixture of **2** and **2-red** (153 mg, quant.). The reactions shown in Tables 1–3 were conducted in a half scale of the above-described conditions.

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