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Development and Application of a Multielectron-Accepting Organic Oxidant for the Catalytic Transition-Metal-Free Oxidative Homocoupling of Grignard Reagents in Air

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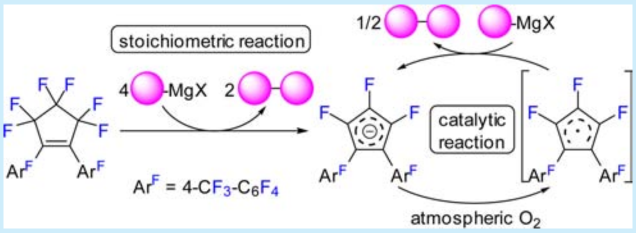
Supporting Information

ABSTRACT: Heptafluorotolyl-substituted perfluorocyclopentene acts as a four-electron oxidant for the homocoupling of Grignard reagents. It can also be used for catalytic homocoupling with a low catalyst loading (up to 2 mol %) in the presence of atmospheric oxygen. The organocatalytic cycle involves the generation of an organic radical and a perfluorocyclopentadienyl anion.



Transition-metal-free oxidizing reactions using organic oxidants are now widely used in organic syntheses because of their environmental sustainability.[1] Although these organic oxidants are typically used to oxidize alcohols, they may also be applied toward oxidative C−C coupling reactions in certain cases.[2] For instance, the transition-metal-free homocoupling reactions of Grignard reagents can be effectively mediated by organic oxidants.[3] The homocoupling of Grignard reagents[4] has potential value for the industrial synthesis of symmetrical biaryls or polyaromatic conjugated compounds, as Grignard reagents are widely used.[5] However, current transition-metal-free homocouplings require large amounts of the organic oxidant upward of 50 mol %.[3] Therefore, large-scale applications require the development of a new reaction methodology that utilizes a relatively smaller amount of an organic oxidant. In terms of the electron-accepting mechanism, a trailblazing transition-metal-free homocoupling of Grignard reagents was reported by Knochel and Mayr.[3c] They used 55 mol % of a quinone derivative as an oxidant, which was aromatized by accepting two electrons from Grignard reagents (Figure 1a). Studer also later reported on a homocoupling reaction that used 108 mol % of TEMPO,[3e] which was reduced with one electron from a Grignard reagent (Figure 1b).[6] In this case, the catalytic reaction was performed with 14 mol % of TEMPO through successive cycles, where each cycle consists of a stoichiometric reaction and an in situ regeneration of the oxidant.[3e] Organic halides have also been used as oxidants: 300 mol % 1,2-dibromoethane by O'Shea[3f] and 50 mol % 2,3-dichloropropene by Luo.[3a] In the latter case, 2,3-dichloropropene accepted two electrons and both the allylic and vinylic chlorides were eliminated (Figure 1c). To apply the halide elimination mechanism, we hypothesized that the perhalo-2-butene unit would act as a multielectron acceptor, accepting three or more electrons (Figure 1c, below).

Accordingly, we focused on the readily available octafluorocyclopentene (**1a**) as a potential multielectron acceptor.

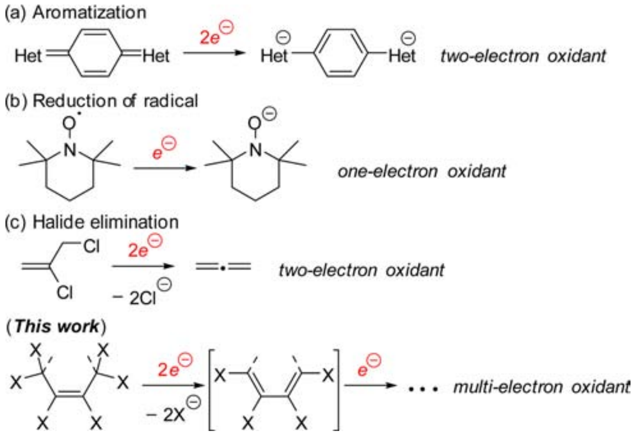


Figure 1. Electron-accepting mechanism of organic oxidant.

Previously, **1a** had been used as a precursor for photochromic diarylethenes,[7] which were prepared by substituting the vinylic fluorides of **1a** with ArLi or ArMgX, indicating that **1a** was attacked by Grignard reagents. We were thus able to design novel perfluorocyclopentene derivatives with fluoroaromatic groups (Ar^F) (Figure 2). By introducing strong electron-withdrawing Ar^F at the vinylic position of **1a**, we expected to

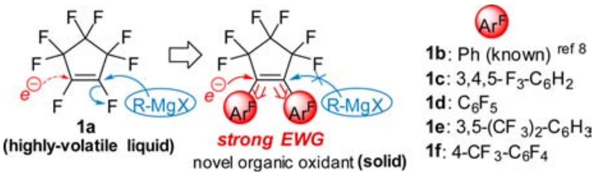


Figure 2. Perfluorocyclopentene derivatives as a novel organic oxidant.

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increase its oxidizability as an oxidant, decrease its reactivity in substitution reactions with nucleophiles,[8] and eliminate its high volatility. Here, we report on the development of a novel organic oxidant that can act as both a four-electron oxidant and a catalyst in the presence of atmospheric oxygen.

The novel perfluorocyclopentene derivatives, Ar^F = 3,4,5-F_3-C_6H_2 (**1c**), C_6F_5 (**1d**), 3,5-$(CF_3)_2$-C_6H_3 (**1e**), and 4-CF_3-C_6F_4 (**1f**) (Figure 2), were prepared in moderate to high yields from **1a** with treatment of Ar^F-Li. All of the compounds **1** were stable in air. The homocouplings of phenylmagnesium bromide (**2a**) in the presence of 50 mol % of **1** were performed in THF at 20 °C for 0.5 h under an argon atmosphere (Table 1). The **1a**-mediated reaction of **2a** produced a homocoupled biphenyl (**3a**) product (33%) and a substitution product from **1a**, 1-phenyl-perfluorocyclopentene (10%) (entry 1).[8] The reaction using the phenyl-substituted **1b** did not proceed (entry 2). In contrast, the reactions in the presence of novel organic oxidants bearing Ar^F (**1c**−**1f**) afforded **3a** (entries 3−6) without any substitution products. In particular, the heptafluorotolyl-substituted **1f** exhibited a good oxidizing capacity (entry 6).

Table 1. Homocoupling Reaction of PhMgBr (2a) Using Perfluorocyclopentene Derivatives[a]

$$\underset{\mathbf{2a}}{\text{Ph-MgBr}} \xrightarrow[\substack{\text{THF} \\ \text{25 °C} \\ \text{under argon}}]{\text{oxidant } \mathbf{1}} \text{1/2 } \underset{\mathbf{3a}}{\text{Ph-Ph}}$$

entry	Ar^F of oxidant	oxidant (mol %)	yield (%)[b]	LUMO (eV)[c]
1	F (**1a**)	50	33	−2.07
2	Ph (**1b**)	50	0	−2.31
3	3,4,5-F_3-C_6H_2 (**1c**)	50	32	−3.07
4	C_6F_5 (**1d**)	50	23	−3.09
5	3,5-$(CF_3)_2$-C_6H_3 (**1e**)	50	58	−3.31
6	4-CF_3-C_6F_4 (**1f**)	50	82	−3.46
7[d]	**1f**	50	99	
8[d,e]	**1f**	25	99	
9[d,f]	**1f**	10	37	

[a] All reactions were carried out using 0.50 mmol of **2a** (1.0 M THF solution, which was titrated with 1,10-phenanthroline and *i*-PrOH) purchased from Aldrich, and 0.25 mmol of **1** for 30 min. [b] Isolated yields. [c] LUMO energy levels were calculated at the B3LYP/6-31+g(d) level. [d] For 1 h. [e] 0.125 mmol of **1f**. [f] 0.05 mmol of **1f**.

The performances of these organic oxidants **1** were roughly proportional to their LUMO levels, which indicated that the strong electron-withdrawing effect of Ar^F at the vinylic position increased their oxidizing capabilities. The reaction of **2a** with 50 mol % of **1f** for 1 h proceeded almost to completion (entry 7). After the reaction, roughly half of **1f** remained in the reaction solution.[9] When the reaction was performed with 25 mol % of **1f** for 1 h, the product **3a** was obtained almost quantitatively (entry 8) and **1f** was not observed in the reaction solution.[9] A reaction that used 10 mol % of **1f** for 1 h gave the product **3a** (entry 9) with a ca. 40% yield (37%). Based on these results, we have concluded that **1f** behaves as a novel four-electron oxidant. To the best of our knowledge, this is the first example of an organic four-electron oxidant. However, the experimental results indicate that the stoichiometric amount of **1f** cannot be reduced to less than 25 mol %.

The reactions of other Grignard reagents with 25 mol % of **1f** also proceeded smoothly under the same conditions (see the Supporting Information).

In order to reduce the amount of **1f** in the reaction from 25 mol %, we decided to further evaluate the catalytic oxidative homocoupling reaction from another perspective. Studer et al. previously attempted a TEMPO-catalyzed homocoupling of a Grignard reagent, where **2a** was reacted in the presence of 20 mol % of TEMPO with a continual bubbling of pure O_2 throughout the reaction mixture to give **3a** and a phenol with 61% and 24% yields, respectively.[3e] They then attempted several sequential reaction cycles with 14 mol % of TEMPO. This consisted of a stoichiometric TEMPO-mediated coupling of **1a**, an in situ regeneration of TEMPO with pure O_2, and the readdition of **1a** to give **3a** with an 81% yield.[3e] This catalytic system relied on the oxidation of the TEMPO−MgBr complex with pure O_2 to regenerate the TEMPO catalyst. When we originally viewed our devised system, we noticed that a coupling reaction with 25 mol % of **1f** under argon produced a dark greenish-brown solution at the end of the reaction (Table 1, entry 8). However, this solution immediately changed into a dark purple color upon exposure to the atmosphere. This inspired us to consider that the residue from **1f** after homocoupling was readily oxidized with atmospheric oxygen to give radical species. Therefore, we attempted **1f**-catalyzed homocoupling of the Grignard reagent by completely exposing the reaction to the atmosphere (Table 2). The reaction of **2a** in the presence of 10 mol % of **1f** at 25 °C in dry air gave **3a** with an 84% yield after 6 h (entry 1). The yield of **3a** increased to 93% when the reaction temperature was increased to 50 °C (entry 2). Increasing the reaction time also slightly improved the yield of **3a** to 96% (entry 3). When the catalyst loading was reduced to 5 mol % for 24 h or 2 mol % for 3 days, **3a** was obtained with an 87% or a 76% yield, respectively (entries 4, 5). To the best of our knowledge, this is the first successful example of an organocatalyzed homocoupling of a Grignard reagent with atmospheric oxygen.

Table 2. 1f-Catalyzed Homocoupling of 2a[a]

$$\mathbf{2a} \xrightarrow[\substack{\text{THF} \\ \textbf{in dry air}}]{\text{catalyst } \mathbf{1f}} \text{1/2 } \mathbf{3a}$$

entry	catalyst (mol %)	temp (°C)	time (h)	yield (%)[b]
1	10	25	6	84
2	10	50	6	93
3	10	50	12	96
4[c]	5	50	24	87
5[d]	2	60	3 days	76

[a] All reactions were carried out using 1.0 mmol of **2a** (1.0 M THF solution, which was titrated with 1,10-phenanthroline and *i*-PrOH) purchased from Aldrich, and 0.1 mmol of **1f**. [b] Isolated yields. [c] 0.05 mmol of **1f**. [d] 0.02 mmol of **1f**.

The mechanism of the redox process of **1f** was considered. After the stoichiometric homocoupling of 100 mol % **2a** using 25 mol % **1f** under argon, the trifluorocyclopentadienyl anion **4**[10] was observed as the principal fluorine component in a dark greenish brown solution by ^{19}F NMR under argon (Figure 3, NMR1, ○). Due to the loss of three fluorine atoms from **1f**, it is presumed that the anion **4** was produced from **1f** through a halide elimination process where the oxidant could readily accept four electrons. A previous report[11] has stated that the metal salts of the perfluorocyclopentadienyl anion ($C_5F_5^-$) in THF were unstable at temperatures that were greater than −30 °C. In contrast, the anion **4** with a Mg salt in THF at room

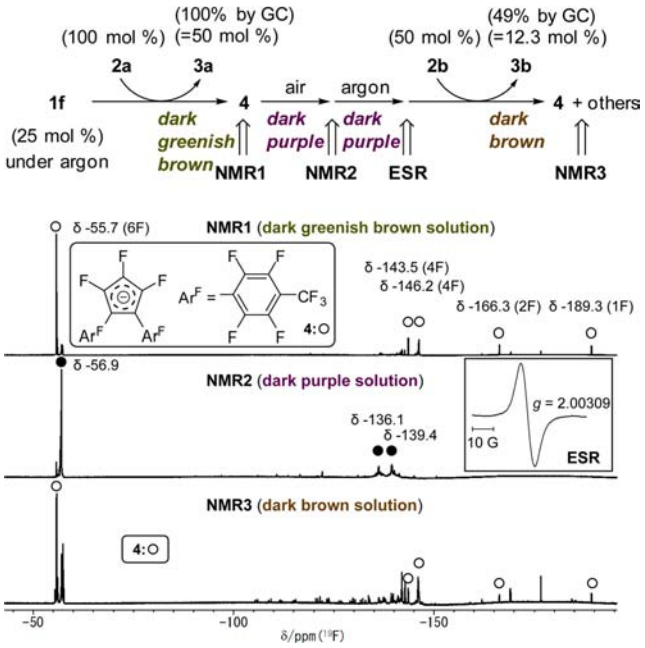


Figure 3. NMR study of redox process of **1f**.

temperature showed stability under argon; however, it was very unstable in air. As above-mentioned, the dark greenish brown solution containing anion **4** immediately changed to a dark purple color when it was exposed to the atmosphere. A ^{19}F NMR spectrum of the dark purple solution verified that **4** was not present, based on the presence of broad signals, which suggested that a radical species must be present within the solution (NMR2). The presence of the organic radical species was further confirmed by an ESR spectrum of the dark purple solution under an argon atmosphere.[12] When 50 mol % of 4-tolyl-MgBr (**2b**) was added to the dark purple solution under an argon atmosphere, the color turned dark brown and produced a biaryl compound **3b** with a 49% yield (12.3 mol %).[9] This indicated that the radical species oxidized **2b** by acting as a one-electron oxidant. In the dark brown solution, a ^{19}F NMR spectrum showed that the anion **4** was present along with an unknown species (NMR3). Based on these results, we propose that the most viable candidate for the active catalytic species is an organic radical species **5** (see Figure 4).[13] The unknown structure in NMR3 can be narrowed down to two possible species: (1) an inactive species formed through the breakdown of the active catalytic species or (2) another active catalytic species such as an oligomeric derivative.

Based on our results, a plausible mechanism for the redox process of **1f** through catalytic homocoupling is shown in Figure 4. Initially, the stoichiometric homocoupling of the Grignard reagent proceeds by four-electron oxidation with **1f**, followed by catalytic homocoupling with radical species **5** derived from **4** in the presence of atmospheric oxygen.

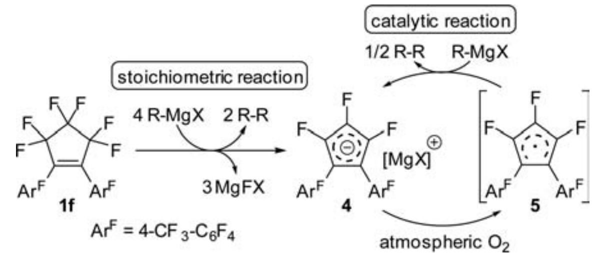
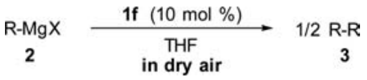
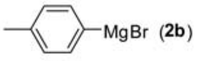
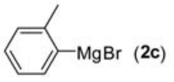
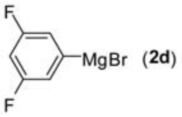
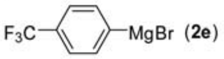
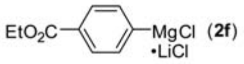
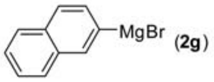
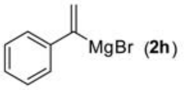
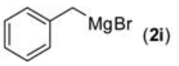


Figure 4. Plausible reaction pathway of the catalytic homocoupling using **1f**.

The catalytic homocoupling reactions of other Grignard reagents were also performed (Table 3). The reactions of ArMgX (**2b**–**2g**) or phenylvinylmagnesium bromide (**2h**) in the presence of 10 mol % of **1f** gave C(sp^2)–C(sp^2) coupled products (**3b**–**3h**) in high yields (89%–92%, entries 1–7). The reaction of BnMgBr (**2i**) also gave a C(sp^3)–C(sp^3) coupled product (**3i**) with a high yield (91%, entry 8).

Table 3. 1f-Catalyzed Homocoupling of 2[a]



entry	Grignard reagents	products	temp (°C)	yield (%)[b]
1[c]	 MgBr (**2b**)	**3b**	50	91
2[d]	 MgBr (**2c**)	**3c**	50	92
3[d]	 F, F, MgBr (**2d**)	**3d**	50	90
4	 F$_3$C, MgBr (**2e**)	**3e**	50	91
5	 EtO$_2$C, MgCl•LiCl (**2f**)	**3f**	50	90
6	 MgBr (**2g**)	**3g**	50	90
7[c]	 MgBr (**2h**)	**3h**	25	89
8[e]	 MgBr (**2i**)	**3i**	25	91

[a] All reactions were carried out using 1.0 mmol of RMgX (**2**) THF solution, which was titrated with 1,10-phenanthroline and *i*-PrOH, and 0.1 mmol of **1f** for 6 h. [b] Isolated yields. [c] For 9 h. [d] For 12 h. [e] Et$_2$O solution of Grignard reagent was used.

In the **1f**-catalyzed homocoupling reactions, atmospheric oxygen was used as an inexpensive and environmentally friendly source to renew the catalytic species. Therefore, the additional co-oxidant, which was typically used in TEMPO-mediated oxidation reactions,[1a] was not required. Even for transition-metal-catalyzed homocoupling of Grignard reagents, there have not been many examples using atmospheric oxygen,[4l–q] and many reactions required a stoichiometric amount of a terminal organic oxidant.[4a–k] Furthermore, there is still a great demand for other catalytic systems that employ atmospheric oxygen, since catalytic aerobic-oxidation systems can provide environmentally sustainable benefits.[14] Therefore, the design of a viable system that allows for organocatalyzed C–C coupling reactions under atmospheric oxygen is highly valuable for the scientific community.

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In summary, we have developed a novel organic oxidant **1f** that acts as a four-electron oxidant for the homocoupling of Grignard reagents. A low catalyst loading of up to 2 mol % of **1f** can also be used for catalytic homocoupling reactions in air to give the desired coupled products in high yields. We envision that **1f** will be highly utilized in the future toward a variety of oxidative C−C coupling reactions or the oxidation of organic substrates with atmospheric oxygen.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02887.

Representative experimental procedure, spectroscopic data for novel oxidants **1c**, **1d**, **1e**, **1f** and coupling products **3**; Tables for stoichiometric homocoupling reactions using **1f**; Cartesian coordinates of **1**, **4**, and **5**; Consideration of the structures of **4** and **5** using ^{19}F NMR and GIAO calculations (PDF)

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Notes

The authors declare no competing financial interest.

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(9) GC analysis.

(10) The structure of **4** was identified by comparison of calculated ^{19}F chemical shifts at the GIAO/B3LYP/6-31+G(2d,p) level and observed chemical shift. See the Supporting Information.

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(12) In the ESR spectrum, a broad singlet peak at the position of g = 2.00309 was observed at room temperature, which is evidence of the presence of a radical in the THF solution. The radical can be expected to be the cyclopentadienyl radical **5** generated by one-electron oxidation of the cyclopentadienyl anion **4**, considering the g-value is in good agreement with those of the cyclopentadienyl radical species reported previously. See references: (a) Sitzmann, H.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 971. (b) Tian, Y.; Uchida, K.; Kurata, H.; Hirao, Y.; Nishiuchi, T.; Kubo, T. *J. Am. Chem. Soc.* **2014**, *136*, 12784.

(13) The present structure **5** was also predicted by comparison of calculated ^{19}F chemical shifts (NMR2, ●) at the GIAO/uB3LYP/6-31+G(2d,p) level and observed chemical shift. See the Supporting Information.

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