Formal Aerobic Oxidative Cross-Coupling of Benzofuranones with Azo Compounds Using Pd-μ-hydroxo Complex

Rikako Ohnishi, Masumi Sugawara, Tetsuya Ezawa, Yoshihiro Sohtome, and Mikiko Sodeoka

Abstract
We have developed a catalytic aerobic oxidative dimerization reaction of benzofuranones using a Pd(II)-μ-hydroxo complex. Radical-radical cross-coupling of the resulting dimers with azo compounds enabled the one-pot synthesis of structurally congested benzofuranones having two distinct vicinal all-carbon quaternary centers.

Key words palladium; molecular oxygen; radical; oxidative cross-coupling

Introduction
Oxidation is a key methodology to increase the molecular complexity of simple starting materials, but there is still a need for an efficient, selective, economical and environmentally friendly approach. In this context, the development of catalytic aerobic oxidation with the use of molecular oxygen (O₂) as an oxidant has been attracting attention. A key to achieving selective aerobic oxidation is to suppress undesired pathways involving reactive oxygen species (ROS). Furthermore, in order to ensure safe operation, we require mild reaction conditions that avoid the use of high temperatures and pressures.

We recently reported the development of a radical-radical cross-coupling between the persistent (long-lived) radical 1• and the transient (short-lived) radical 4•, affording 5 with two contiguous all-carbon centers. The persistent radical 1• is readily generated from 2, which contains an elongated C(sp³)–C(sp³) bond, simply by heating without the assistance of redox-active transition metals. However, the requisite dimers 2 were synthesized from the corresponding monomers 1 using a stoichiometric amount of K₃[Fe(CN)₆] as an oxidant under basic conditions at 80°C according to the literature procedure. In this Note, we describe a mild protocol for aerobic oxidative dimerization of 1 to provide the dimers 2 by using Pd-μ-hydroxo complex 1, previously employed as an acid-base catalyst (Chart 1, i). We also successfully applied this catalytic aerobic dimerization to a formal oxidative cross-coupling (cross-dehydrogenative coupling) reaction, comprising dimerization of 1/cross-coupling of 2 with azo compounds 3 (Chart 1, ii). This reaction sequence enables the one-pot synthesis of 5 starting from 1.

Results and Discussion
To establish milder conditions for preparing 2, we planned to apply our Pd-μ-hydroxo catalyst 1 to catalytic aerobic oxidative dimerization of 1, focusing on the functional inertness of 1 to O₂, ROS and water. We postulated that the highest occupied molecular orbital (HOMO)-raising activation of 1 with catalyst 1 would enhance the generation of 1• via single-electron transfer to O₂, allowing the homo-coupling to proceed smoothly to give the corresponding dimer 2 under aerobic conditions (Chart 1, step i). We also anticipated that cross-coupling of the resulting dimers 2 with azo compounds 3, corresponding to a formal aerobic oxidative cross-coupling reaction, would afford 5 with single-flask operation (Chart 1, step ii).

We began by focusing on aerobic dimerization of benzofuranones 1 (Table 1). Although 1 has been widely used in

Chart 1. Formal Oxidative Cross-Coupling with Single-Flask Operation
*To whom correspondence should be addressed. e-mail: sohtome@riken.jp; sodeoka@riken.jp

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acid-base catalysis, its use in radical reactions is relatively rare. We initiated this study with use of racemic Pd complex I as a catalyst for the proposed aerobic dimerization of 1 because the C(sp)^3–C(sp)^3 bond in 2 is readily cleavable even at room temperature, providing thermodynamically stable meso-2, rather than dl-2, as the major product. We found that the use of CH_3CN as the solvent is critical to obtain a high yield of meso-2a (Table 1, entry 1 vs. entry 2). When we examined the reaction of 1a in the presence of Pd complex I (5 mol%) under an oxygen atmosphere in tetrahydrofuran.

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### Table 1. Catalytic Aerobic Oxidative Dimerization of 1

| Entry | Catalyst | Solvent | Ar      | Yield of 2 (%) | Recovery of 1 (%) |
|-------|----------|---------|---------|----------------|------------------|
| 1     | I        | THF     | Ph      | 2a: n.d.       | 1a: 94           |
| 2     | I        | CH_3CN  | Ph      | 2a: 77         | 1a: n.d.         |
| 3     | II       | CH_3CN  | Ph      | 2a: n.d.       | 1a: 99           |
| 4     | III      | CH_3CN  | Ph      | 2a: 1          | 1a: 98           |
| 5     | None     | CH_3CN  | Ph      | 2a: n.d.       | 1a: 99           |
| 6     | I        | CH_3CN  | 4-F-C_6H_4 | 2b: 85       | 1b: n.d.         |
| 7     | I        | CH_3CN  | 4-Me-C_6H_4 | 2c: 57       | 1c: 1            |
| 8     | I        | CH_3CN  | 4-MeO-C_6H_4 | 2d: 28      | 1d: 9            |

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*a) Reactions were run on a 0.1 mmol scale. b) Isolated yield. c) NMR yield determined by using CH_2Br_2 as an internal standard.

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**Chart 2. Sequential Catalytic Oxidative Dimerization and Cross-Coupling of Various Compounds 1 and Azo Compounds 3 in the Presence of (±)-Pd Catalyst I**
corresponding dimer was recovered in 94% yield (Table 1, entry 1). In contrast, the reaction in CH₂CN under the same conditions gave meso-2a in 77% yield (Table 1, entry 2). Pd complexes II and III are not effective under the conditions (Table 1, entries 3 and 4), suggesting that the rather basic character of I is an important factor to promote the aerobic oxidative dimerization of 1a. In a control experiment without I, we recovered 1a in 99% yield (Table 1, entry 5), and this result also indicates a key role of I in the aerobic oxidative dimerization of 1a. Benzo[def]naphthoquinones having different substituents on the aromatic group at the C(3) position in I also reacted under these aerobic conditions, giving the corresponding dimers (Table 1, entries 6–8). The electronic properties of the substituent on the aromatic ring in I influence the yield of dimers 2. For example, 1b (R = F) gave the best yield of the corresponding dimer 2b (85%). Meanwhile, 1d (R = MeO) was less reactive under our conditions, and the dimer 2d was obtained in only 28% yield, with recovery of 1d in 9% yield. Generally the yields of 2 in the developed reactions are higher than those in the previous method using stoichiometric amounts of K₂[Fe(CN)₆] and KOH (see Table S1).

With suitable conditions in hand for the Pd-catalyzed aerobic oxidative dimerization of 1, we examined the feasibility of sequential reactions to achieve a formal one-pot oxidative cross-coupling synthesis of benzo[def]naphthoquinone 5 having two contiguous all-carbon quaternary centers (Chart 2). In the developed procedure, CH₂CN is evacuated after the reaction mixture has been stirred for 24 h under aerobic conditions. The second reaction was then performed by adding 3 (2 equiv. to 1) in toluene after replacing O₂ with Ar, according to a previously developed procedure. As we expected, upon heating the reaction mixture to 100°C, we obtained the cross-coupling adducts 5 in reasonable yields. Benzo[def]naphthoquinones 1a, 1b and 1c are efficiently transformed to the corresponding cross-coupling adducts (5aa: 69%, 5ba: 64%, 5ca: 52%) with the use of AIBN (3a: azobis(isobutyronitrile) as a precursor of the transient radical. Azo compounds V-70 [3b: 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)] and V-40 [3e: 1,1′-azobis(cyclohexane-1-carbonitrile)] are also available for this one-pot procedure starting from 1a, affording 5ab (72%, 1/1 diastereomeric ratio) and 5ac (63%), respectively. Importantly, the differences in yields of 5 between the developed one-pot protocol and the previous protocol using isolated 2±,3,4,5) were small, suggesting that the presence of (±)-Pd catalyst 1 does not interfere with the cross-coupling of 2 with 3.

Conclusion

In conclusion, we have developed a formal aerobic oxidative cross-coupling reaction of benzo[def]naphthoquinones 1 with azo compounds 3. The key to success in this sequential single-flask transformation is the chemoselectivity of Pd catalyst 1. This catalyst selectively activates benzo[def]naphthoquinones 1 to form the corresponding dimer 2 under aerobic conditions, whereas it is functionally inert to radical species, including O₂. Further studies on catalyst-controlled aerobic oxidations are underway.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials.

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31) Insoluble by-products were formed, although we could not determine their structures.
32) Half-life time ($t_{1/2}$) in toluene; AIBN (3a: 10 h at 65°C), V-70 (3b: 10 h at 30°C) and V-40 (3c: 10 h at 88°C).
33) Even when we examined the reaction with (R)-Pd catalyst 1, we obtained diastereo mixtures of 5ab with 1/1 diastereomeric ratio.
34) The isolated yields of 5 in the reaction with the use of isolated dimer 2 were reported in ref. 9 [5aa: 86%, 5ba: 89%, 5ca: 85%, 5ab: 71% (1/1 dr), 5ac: 57%].
35) The reaction of isolated dimer 2 with AIBN (3a: 4.0 equiv. to 2) in the presence of 1 (10 mol% to 2), under the conditions described in Chart 2, gave 5aa in 84% isolated yield.