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Pd-catalyzed Aerobic Cross-Dehydrogenative Coupling of Catechols with 2-Oxindoles and Benzofuranones: Reactivity Difference Between Monomer and Dimer

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Abstract: Persistent radicals, which are generated from 2-oxindole or benzofuranone dimers, are useful tools for designing the radical-based cross-coupling reaction to provide molecules containing a quaternary carbon. The persistent radical is accessible from both the dimer and monomer; however, the reactivity difference between these substrates for the oxidative cross-coupling reaction is not fully understood, most likely because of the mechanistic complexity. Here, we present details of an aerobic cross-dehydrogenative coupling (CDC) reaction using various monomers and catechols. UV-Vis analysis and mechanistic control experiments showed that the monomer is less reactive than the dimer under aerobic conditions. Our Pd(II)-BINAP-μ-hydroxo complex significantly improved the reactivity of the monomers for the aerobic CDC reaction with catechols, yielding results comparable to those of the corresponding dimer. The procedure, which enables the generation of the persistent radical in situ, is particularly useful when employing the monomer that is not readily converted to the corresponding dimer.

Introduction

Aerobic oxidative cross-coupling reactions of phenols are one of the ideal synthetic methods for creating substituted phenols.[1,2] However, the order of the oxidation to initiate the reaction, as well as its origin, to explain the rate- and regio-determining steps are still not fully understood in many cases because of the mechanistic complexity. This is one of the reasons why solving the selectivity setting [i.e., coupling-(homo vs. cross), chemo-, and regio-selectivities] in this reaction class still presents a significant challenge.[1a,3] With respect to the coupling selectivity, the HOMO/SOMO interaction between the nucleophilic substrate and phenoxyl radical has been widely recognized as a key mechanistic basis.[4] In this mechanistic scenario, the balance of the redox potential (E_{ox}) and nucleophilicity (N) possessed by the reactants has been considered as a primary factor for achieving oxidative cross-coupling while decreasing the undesired homo-coupling. The anion–radical mechanism helps us to understand the observed cross-coupling selectivity in a generic way, with only minor modification in interpretation, even if the bond-forming event takes place in the inner- or outer-sphere of the metal complex. To date, versatile synthetic methods have been reported for the radical-based cross-dehydrogenative coupling (CDC)[5] reaction of phenols, including transition metal catalysis,[1c,e,6–9] oxidant tuning,[5d,10,11] photoredox catalysis,[12] and electrosynthesis.[13] Recently, Pappo,[14] Kozlowski,[15] and Uchida[16] independently reported catalyst-controlled methods for the CDC reaction with two-distinct phenols having very similar electronic properties for both E_{ox} and N, expanding the substrate-dependent limitation of the anion–radical coupling.

In the course of our research program[17,18] aimed at solving the multiple selectivity issues,[1–3] we formed an alternative strategy by merging persistent radicals[19] and Pd(II)–enolates,[20] leading to the development of the aerobic oxidative cross-coupling reaction of dimer-derived *tert*-carbon radicals **1**$^{\bullet}$[21,22] with catechols **3** (Scheme 1-i).[23] This reaction was designed based on our previous finding that the σ bond in dimer **2** bearing aryl groups at the C3 and C3' positions is elongated so that it is homolytically cleavable by simply heating.[21] The generation of **1**$^{\bullet}$ can be readily traced by temperature-dependent UV/Vis analysis, because the recombination requires slightly higher energy than the homolysis.[21,24] Further, our mechanistic investigations, together with density-functional theory (DFT) calculations, suggest that Pd–catecholate is a key catalytic species; the energy of the Pd–catecholate/**1a**$^{\bullet}$ (**INT-I**, Figure 1-ii) is significantly lower (by 19.4 kcal/mol) than that of the free form of **1a**$^{\bullet}$ (Figure 1-iii).[23] A natural bond orbital (NBO) analysis[25] revealed that **INT-I** is mainly stabilized by hydrogen-bonding interactions as well as π–π interactions between the proximal Pd–catecholate and **1a**$^{\bullet}$ (Tables S1–3). Owing to the

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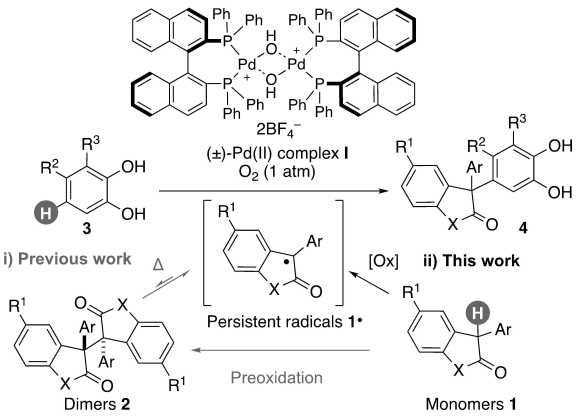


Scheme 1. i) Oxidative cross-coupling of dimers **2** with catechols **3** (previous work). ii) Cross dehydrogenative coupling of monomers **1** with catechols **3** (this work).

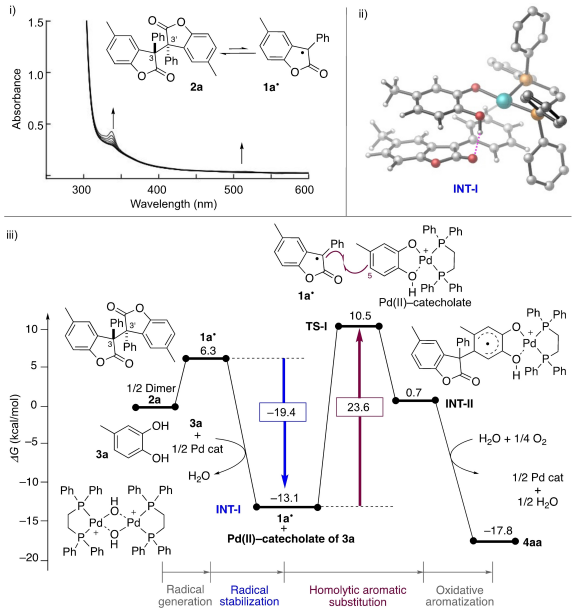


Figure 1. i) Absorption spectrum of dimer **2a** (4 mM in $CHCl_3$) at different temperatures. Reproduced with permission from Ref [21b]. Copyright 2019 Wiley. ii) Lowest-energy structure of **INT-I**. A magenta dashed line represents the hydrogen bond.[23] iii) Reaction-energy diagram for model reaction between **2a** and **3a** with Pd(II)-DPPE-μ-hydroxo complex at the UM06/def2-SVPP level of theory (Pd: LanL2DZ). Each lowest-energy structure is illustrated.[23]

stabilization effect, the net downhill catalytic process resulted, even though the homolytic aromatic substitution (HAS)[26] step (from **INT-I** to **INT-II**) was predicted to be endothermic (energetically uphill).[27]

In the previous study, we also provided an example of the CDC reaction with *N*-Boc oxindole monomer **1b** (R^1 = Me, Ar = Ph, and X = *N*-Boc) with 4-methylcatechol (**3a**: R^2 = Me) (Scheme 1-ii).[23] Based on the pluripotent character of **1**, which is capable of transforming into the carbanion, radical, and carbocation, several distinct C(sp^3)–C(sp^2) bond-forming processes in the CDC reaction of **1** with phenols (or arenes) have been advocated.[19c] Those mechanistic proposals include 1,4-addition,[28,29] umpolung reaction (monomers **1** are converted into carbocations through two-electron oxidation),[30–33] reductive coupling,[34] and HAS.[7,23] With respect to HAS, Pappo recently developed the CDC reaction of 3-alkyl- (not 3-aryl) substituted oxindoles with various phenols.[7] Although the reaction conditions require the use of ^{t}BuOO^{t}Bu as an oxidant at 70 °C in a sealed tube, their work expanded the available substrate scope of the CDC reaction, comprising HAS/oxidative aromatization. For the substituted catechols **3**, catalytic regioselective CDC reactions at the C5 position of **3** have been also reported by Lumb[8b] and Dixon.[28] Mechanistically, both CDC reactions should be initiated by oxidation of **3**. Under relatively strong oxidation conditions, the catechol unit in the product is over-oxidized to convert into the corresponding *ortho*-quinone. Therefore, to obtain the desired product bearing the catechol, a stoichiometric amount of the reductant is required. In contrast, our aerobic protocol with the persistent carbon radicals enables selective access to the CDC adducts having the catechol unit even under reductant-free conditions.

Building on these significant advancements, along with our research goal to pursue the synthesis from a practical standpoint, the following two questions for the aerobic CDC reaction of monomers **1** with catechols **3** are apparent. (1) While it has been reported that monomer **1** and dimer **2** exhibit different reactivities in the CDC reaction with alkylarenes under rather harsh conditions [catalyst: $Pd(OAc)_2$, oxidant: dimethylbenzoquinone or $K_2S_2O_8$, temp.: 95–120 °C],[35] how significant are the differences that can be observed under our conditions? (2) Can we use a range of monomers **1** with different electronic properties? Herein, we begin to probe our questions through the UV-Vis analysis and activity tests to gain insights into the differences between monomers **1** and dimers **2**. These investigations lead to the identification of the crucial role of the Pd catalyst complex **I** in improving the inherent low reactivity of monomer **1** in the CDC reaction with catechols **3**. We show that the high chemo- and regio-selectivities reported for our catalytic protocol with dimers **2** are extrapolated to the CDC reaction with various monomers **1**. The developed protocol using monomers **1** is particularly useful when the yield of dimer **2** obtained via oxidative dimerization is low.

Results and Discussion

The 3,3-disubstituted 2-oxindoles[36] and benzofuranones[37] are present in a wide variety of biologically active molecules. A typical method for accessing these molecules is acid/base catalysis, on the basis of the relatively high nucleophilicity of the corresponding enolate derived from **1**. Although the repertoire of enantioselective acid/base catalysis with **1** bearing an alkyl instead of an aromatic substituent at the C3 position is steadily increasing, most methods are limited to providing less-hindered products. In contrast, our primary interest[19c,21,23] is in exploring the radical-based cross-coupling reaction[38] to synthesize congested molecules possessing a quaternary carbon.[39]

However, our proposed catalytic HAS/oxidative aromatization sequence was mainly based on the characterization of

dimers **2**.[23] Further studies are needed to gain insights into the differences in the inherent reactivities between **1** and **2**. We should also note that the oxidative dimerization of **1** does not always yield the desired dimers **2**. For example, we encountered a low yield (2%) when we prepared benzofuranone dimer **2c** (Ar = 4-MeO-C_6H_4) from **1c** with $K_3[Fe(CN)_6]$,[21b,c] a widely-used oxidant for the oxidative dimerization of **1**.[40] Furthermore, the application of another protocol using a Pd(II) catalyst for the aerobic oxidative dimerization of **1c** resulted in only a slight increase in the yield of **2c** (28%).[21c]

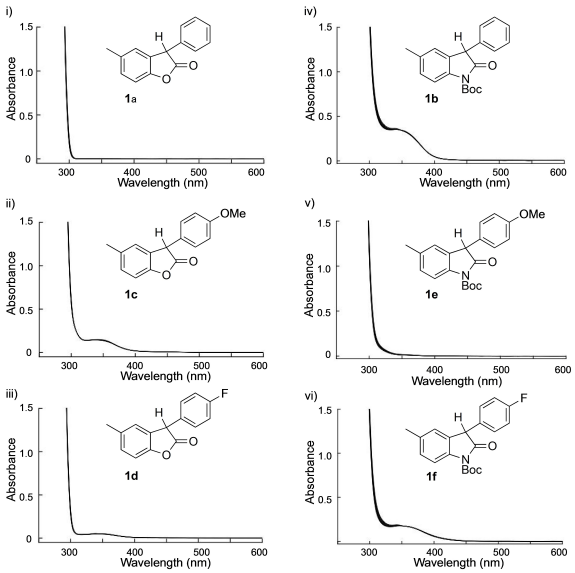
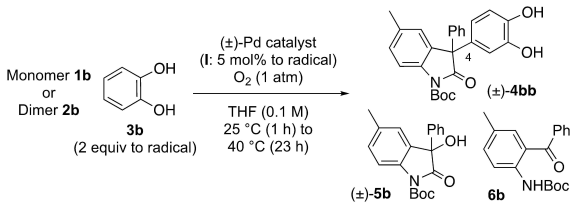


Figure 2. Absorption spectra of monomers **1** (8 mM in $CHCl_3$). Absorption was measured at 5-degree intervals from 25 to 65 °C under air, and each spectrum was overlayed.

Table 1. The reactivity differences between monomer **1b** and **2b** in the oxidative cross coupling with catechol (**3b**).[a]



Entry	Carbonyl compounds	Catalyst	**4bb** [%]	**5b** [%]	**6b** [%]
1[b]	**2b**	none	56	2	13
2[c]	**1b**	none	7	8	n.d.
3[b]	**2b**	**I** (5 mol%)	90	n.d.	n.d.
4	**1b**	**I** (5 mol%)	92	n.d.	n.d.
5[d]	**1b**	**I** (5 mol%)	88	n.d.	n.d.
6[e]	**1b**	**I** (5 mol%)	—	81	8

[a] Reactions were performed on a 0.05 and 0.025 mmol scale for monomer **1a** and dimer **2a**, respectively. The reaction mixture was stirred for 1 h at rt and then for 23 h at 40 °C. Yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [b] Reference [23]. [c] Recovery of monomer **1b** was 42%, and dimer **2b** was obtained in 9% yield. [d] The reaction was run under air instead of O_2. [e] The reaction was examined in the absence of **3b**. Recovery of monomer **1b** was 10%.

We commenced this study by investigating whether radicals are more easily generated from monomers **1** or dimers **2** under air using UV-vis analysis (Figure 2). As shown in Figure 1-i, absorption in the ultraviolet and visible regions of dimer **2a** increased as the temperature increased (also see Figure S3).[21b] In marked contrast, when we simply applied the protocol to a range of monomers **1** having different substituents at the C3 position, no significant changes in both benzofuranones (Figures 2 i, ii, and iii) and *N*-Boc oxindoles (Figures 2 iv, v, and vi) were observed, even though each spectrum was obtained using the sample prepared under air. ^{1}H NMR analysis of each recovered **1** after UV-Vis analysis also revealed that the corresponding dimer was not formed. This empirical evidence showed that the monomer **1** is not easily oxidized by air into the *tert*-carbon radical **1•** in the absence of the Pd(II) complex **I**.

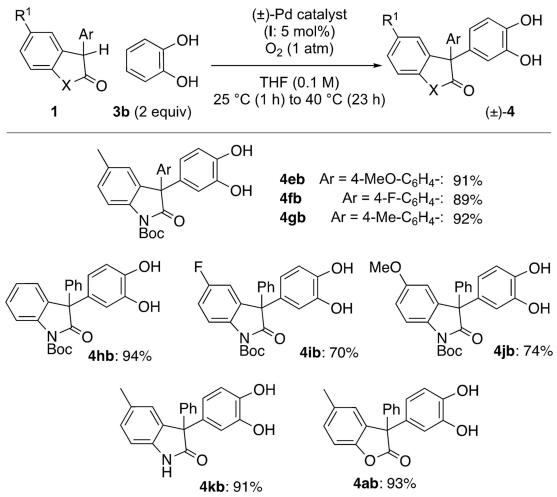
We then examined the reactivity difference between the *N*-Boc oxindole monomer **1b** and dimer **2b** in the reaction with catechol (**3b**), in the absence or presence of the (±)-Pd(II)-BINAP-μ-hydroxo complex **I** (Table 1). The major difficulty in selectively achieving the oxidative cross-coupling reaction with **1b•** using O_2 as an oxidant arises from the oxophilicity of **1b•**. As we described previously,[23] under the catalyst-free conditions with O_2, the reaction of dimer **2b** with **3b** afforded the corresponding cross-coupling adduct **4bb** (56%), as well as the oxygenation adducts **5b** (2%) and **6b** (13%) (Table 1, entry 1).[41] In this investigation, we found that monomer **1b** is indeed far less reactive than dimer **2b** under aerobic conditions (Table 1, entry 2). The yield of **4bb** was reduced to 7%, with the 42% recovery of **1b**. However, from the mechanistic viewpoint, we should note that the dimer **2b** (9%)[21c,42] was formed with concomitant generation of *tert*-alcohol **5b** (8%). These results suggest that the addition of catechol (**3b**) assisted in the generation of **1b•** even in the absence of Pd(II) catalyst **I**. Most importantly, the addition of the Pd(II) complex **I** enhanced the desired CDC reaction using monomer **1b** by eliminating the oxygenation pathway (Table 1, entry 4, **4bb**: 92%). Notably, the yield of **4bb** with monomer **1b** is comparable to that with dimer **2b** (Table 1, entry 3, **4bb**: 90%).[23] Furthermore, the CDC reaction of **1b** with **3b** proceeds smoothly even in air, affording the CDC adduct **4bb** (88%) without loss of chemo- and regio-selectivities (Table 1, entry 5). When Pd(II) catalyst **I** (5 mol%) and the monomer **1b** were exposed under O_2 without adding catechol (**3b**), the dimer **2b** was not detected, but *tert*-alcohol **5b** was formed as the major adduct (Table 1, entry 6, **5b**: 81%, **6b**: 8%). We also note that *tert*-alcohol **5b** was not converted into the CDC adduct under the identical conditions; the exposure of *tert*-alcohol **5b** to a mixture of the Pd(II) catalyst (5 mol%) and catechol (**3b**) under O_2 resulted in the recovery of **5b**.[23] All these results highlight that the Pd(II) catalyst **I** enables the kinetic construction of the C–C bond between the persistent radical **1b•** and catechol (**3b**) even under O_2, while the undesired competitive C–O bond-formation pathway was sufficiently suppressed. Unfortunately, our trial using the (*R*)-Pd(II)-μ-hydroxo BINAP complex under identical conditions resulted in the formation of racemic **4bb**. One plausible reason is that BINAP is far from the bond-forming sites in **TS-I**

(Figure 1-iii). Further screening of the conditions is needed to expand this system to the enantioselective variant.

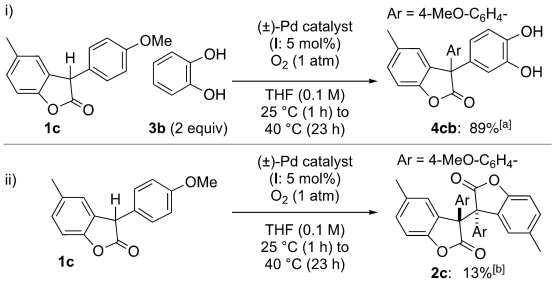
The CDC reaction with catechol (**3b**) using a panel of representative monomers with varying electronic parameters displayed three common features in all cases we examined. (Scheme 2). (1) The reactions took place at the C4 position in **3b** with high regioselectivity. (2) High chemoselectivity (C–C >C–O) was also confirmed; only trace amounts of oxygenation adducts were detected. (3) Furthermore, catechol (**3b**) was recovered even when we used an excessive amount of **3b** (2.0 equiv. to **1**) under O_2. Oxidized adducts of catechol (**3b**), including the *ortho*-quinones, dimers, or polymers were not detected, in contrast to the results of other methods reported by Lumb,[8b] Dixon,[28] and Pietruszka,[29] suggesting that the oxidation of catechol (**3b**) is not the initiating step, even using the less reactive monomer **1**. Rather, the CDC reaction is triggered by the generation of persistent radicals **1**• from the corresponding monomers **1** upon the addition of the Pd catalyst **I**. For example, while the generation of the persistent radicals **1e**• and **1f**• were not detected in the UV/Vis analysis for monomers **1e** and **1f** in the absence of the Pd catalyst **I** (Figure 2-v and vi), the Pd-catalyzed CDC reaction of these monomers worked well to afford **4eb** (91% yield) and **4fb** (89% yield). The monomer **1h** without the substituent at the C5 position in the oxindole core was also available, affording **4hb** in 94% yield. The *N*-Boc oxindole monomers incorporating fluorine or methoxy groups at the oxindole core were also employed to access the corresponding CDC adducts (**4ib**: 70% yield and **4jb**: 74% yield). Thus, while the radicals derived from *N*-Boc oxindoles readily react with O_2, our Pd(II) catalyst **I** suppresses the formation of oxygenation adducts, enabling selective access to the corresponding CDC adducts. Similarly, the Pd-catalyzed CDC reactions of 2-oxindole **1k** without a protecting Boc group and benzofuranone **1a** were applicable under the standard conditions, affording the corresponding CDC adducts (**4kb**: 91% yield and **4ab**: 93% yield).

The observed robustness with various radical precursors **1** further prompted us to apply the developed conditions with the Pd catalyst **I** to benzofuranone **1c** (Ar = 4-MeO-C_6H_4), which has been difficult to control in the radical-based oxidative transformations (Scheme 3).[21b,c] Based on our preliminary DFT calculations for the model reaction of **1a**• and **3a**, we hypothesized that a catalytic amount of the Pd–catecholate/**1c**• should be transiently generated when the benzofuranone **1c** is mixed with catechol (**3b**) under the developed aerobic conditions. If so, **1c**• should be preferentially trapped with the proximal Pd–catecholate, to promote the sequential HAS and oxidative aromatization. As we expected, the catalytic aerobic CDC reaction of **1c** with **3b** proceeded smoothly without modifying the standard conditions with the Pd(II) complex **I**, affording **4cb** in 89% yield with >20/1 regioisomeric ratio (r.r.) (Scheme 3-i). Furthermore, we found that the reaction of **1c** in the absence of catechol (**3b**) under identical conditions resulted in the formation of the corresponding dimer **2c** in only 13% yield, with 47% recovery of **1c** (Scheme 3-ii).[43] These results underscore the synthetic utility of our catalytic CDC protocol starting from monomer **1**, especially when it is difficult to access the corresponding dimer **2**. It is also important to note that the similar control experiment with *N*-Boc oxindole **1b** (Table 1, entry 6) in the absence of **3b** resulted in the predominant formation of the oxygenation adducts (*tert*-alcohol **5b**: 81% yield and ketone **6b**: 8% yield). All these results highlight that our strategy of using Pd–catecholate as a key catalytic species is effective in the aerobic CDC reaction starting from a range of monomers regardless of the oxophilicity of the corresponding persistent radical.

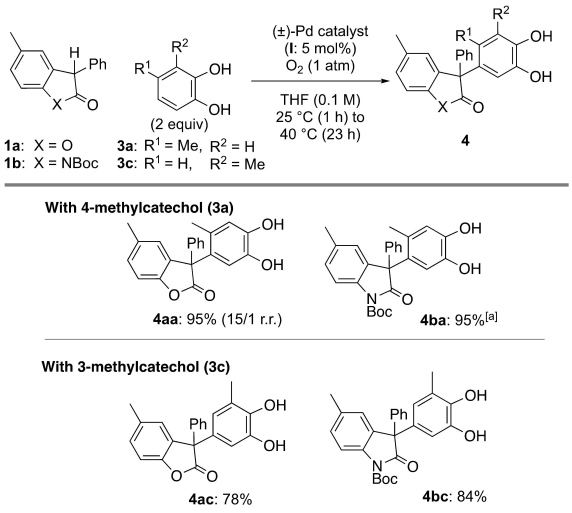
Finally, we examined the CDC reaction with substituted catechols (Scheme 4). The aerobic oxidative cross-coupling reaction using these substituted catechols with dimers **2** under catalyst-free conditions resulted in low chemo-selectivity (C–C/C–O = 4.5/1 ~ 2.1/1).[23] In marked contrast, the addition of Pd(II) catalyst **I** selectively promoted the aerobic CDC reaction with substituted catechols (**3a** and **3c**) at the C5 position of **3**, even when using monomer **1** as the radical precursor. The corre-



Scheme 2. The CDC reaction of various monomers **1** with catechol (**3b**). Reactions were performed on a 0.05 mmol scale. The reaction mixture was stirred for 1 h at 25 °C and then for 23 h at 40 °C. The regioisomeric ratio (r.r.) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Unless otherwise noted, the regioisomer was not detected (>20/1 r.r.). In all entries, isolated yields were given.



Scheme 3. i) Pd-catalyzed aerobic CDC reaction of **1c** with **3b**; ii) Pd-catalyzed aerobic oxidative dimerization of **1c**. Reactions were performed on a 0.1 mmol scale. Each reaction mixture was stirred for 1 h at 25 °C and then for 23 h at 40 °C. [a] Isolated yield; the regioisomeric ratio (>20/1 r.r.) in the reaction of **1c** with **3b** was confirmed by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Yield determined by ^{1}H NMR analysis using CH_2Br_2 as the internal standard.



Scheme 4. Catalytic aerobic CDC reaction of monomers **1** with substituted catechols **3**. The reaction mixture was stirred for 1 h at 25 °C and then for 23 h at 40 °C. The regioisomeric ratio (r.r.) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. Unless otherwise noted, the regioisomer was not detected (> 20/1 r.r.). In all entries, isolated yields were given. [a] Reference [23].

sponding C5 adducts were obtained with high regio- and chemo-selectivities [**4aa**: 89% (C6 adduct was formed in 6% yield), **4ba**: 95%,[23] **4ac**: 78%, and **4bc**: 84%].

An advantage of our protocol is the ease of isolation of CDC adducts **4**. Because our catalytic protocol produces **4** with high chemo-, and regio-selectivities, the CDC adducts **4** and the remaining catechols **3** were separable with typical SiO_2 column chromatography or recrystallization. This is in contrast to the laccase-catalyzed CDC reaction of **1** with **3** reported by Pietruszka and Wang.[29a] In their work, because of the difficulty in isolating CDC adducts **4** possessing an adhesive catechol unit,[44] they were treated with dimethyl sulfate under basic conditions to isolate the corresponding dimethylated adducts.

Conclusion

In summary, we developed an aerobic CDC reaction of a range of monomers **1** with catechols **3**. Although the reaction setting under aerobic conditions involves several undesired reaction pathways, our Pd(II) complex **I** selectively enhanced the CDC reaction with less-reactive monomers, enabling direct access to the CDC adducts with high chemo- and regio-selectivities. Thus, this method improves the synthetic efficiency by eliminating the oxidative dimerization step. We also showed that a mechanistic understanding guided us to achieve the CDC reaction with **1c**, which is difficult to efficiently convert into the dimer. However, our work is still limited to the use of the specific substrate combination of the persistent radicals and Pd–catecholates. The development of the catalytic enantioselective variant using a chiral ligand also remains a major challenge. Further investigations are underway by our group toward solving these issues and exploring other classes of transformations in even more complicated selectivity and energetic settings.

Experimental Section

Typical procedure for Scheme 3-i: A Schlenk flask equipped with a magnetic stirring bar was flame dried under reduced pressure. Upon cooling to rt, the flask was refilled with N_2, and benzofuranone **1c** (25.4 mg, 0.10 mmol), catechol (**3b**: 22.0 mg, 0.2 mmol, 2.0 equiv), and (±)-Pd(II)-BINAP-μ-hydroxo complex **I** (8.5 mg, 0.0050 mmol, 5 mol%) were then added. The reaction tube was again evacuated and refilled with argon three times. THF (1.0 mL, 0.1 M) was added and the mixture was stirred to give a dark brown solution. Then, the argon was replaced with oxygen (1 atm) to initiate the CDC reaction. The reaction mixture was stirred for 1 h at 25 °C and then for 23 h at 40 °C. In order to quench the reaction, the solution was diluted with *n*-hexane at rt, then the Pd catalyst **I** was removed by passing the solution through a pad of SiO_2 with EtOAc as an elutant. The NMR yield and the chemo- (C–C/C–O > 20/1) and regio-selectivities (C5/C6 > 20/1) were determined by ^{1}H NMR analysis of the crude sample in $CDCl_3$ with CH_2Br_2 as the internal standard. The residue was purified by SiO_2 column (*n*-hexane/EtOAc = 10/1, 4/1, and 2/1) to afford CDC adduct **4cb** (32.2 mg, 0.0889 mmol, 89% yield). The spectral data of **4cb** is provided in the Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cross dehydrogenative coupling · catechols · radicals · molecular oxygen · quaternary carbons

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