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Rapid Formation of Fluoren-9-ones via Palladium-Catalyzed External Carbon Monoxide-Free Carbonylation

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Abstract. A Pd-catalyzed carbonylation reaction for the synthesis of fluoren-9-ones from 2-halogenated biphenyls using phenyl formate as a carbon monoxide surrogate was achieved. The combined use of cesium carbonate and *o*-anisic acid resulted in a remarkable rate enhancement, where the reaction was complete within 3 min in some cases. Mechanistic studies indicated that the turnover-limiting step of the reaction was the C–H bond-cleaving step or the oxidative addition step, depending on the substrate used.

Keywords: carbon monoxide surrogate; carbonylation; cyclization; fluoren-9-one; Pd catalysis

Fluoren-9-ones are an important class of compounds used in material sciences and biological research.[1] Due to the broad utility of fluoren-9-ones, a variety of synthetic methods have been developed, including the classical oxidation of fluorenes and Friedel Crafts-type acylation of 2-phenylbenzoic acid derivatives.[2] Recently, cyclization of acyl radicals,[3] metal-catalyzed C(sp^2)–C(sp^2) bond-forming reactions of 2-arylbenzoic acids,[4] and double C–H coupling via 2-arylbenzaldimines[5] have appeared as elegant methods, despite several issues such as harsh reaction conditions or relatively low product yields. On the other hand, the metal-catalyzed carbonylation of 2-halogenated biphenyls under carbon monoxide (CO) is generally a high-yielding method to produce structurally diverse fluoren-9-ones.[6] While a number of easily accessible substrates can be applied in the carbonylation, the reaction relies on the use of CO as a carbonyl source. Generally, the use of CO, which is a highly toxic gas, should be avoided due to safety concerns.

The use of CO surrogates, which can generate CO by chemical reactions or physical stimuli, instead of gaseous CO, is attractive for the realization of practical synthetic methods.[7] Our laboratory has been interested in the potential utility of CO surrogates, and has contributed to the development of novel CO surrogates such as phenyl formate,[8] 2,4,6-trichlorophenyl formate,[9] and *N*-formylsaccharin.[10] These formic acid derivatives can be handled with ease and can form CO under weakly basic conditions. We envisaged that if the CO used in the catalytic synthesis of fluoren-9-ones from 2-halobiphenyls was replaced with a CO surrogate, this synthetic method would offer simple and practical access to fluoren-9-ones. Actually, a similar concept was reported by Morimoto, Kakiuchi, and co-workers, who utilized formaldehyde[11] and furfural[12] as CO surrogates. Although the use of CO gas was replaced with that of surrogates in these methods, they remain to be improved in terms of by-product formation, reaction time, and amount of catalyst required. Herein, we describe a Pd-catalyzed external CO-free carbonylation for the synthesis of fluoren-9-ones using a CO surrogate, phenyl formate. The appropriate choice of carboxylate base facilitated the extremely rapid reaction. Furthermore, mechanistic studies of the reaction are discussed.

The Pd-catalyzed carbonylation to give fluoren-9-one **3a** was optimized using 2-iodobiphenyl (**1**) as a model substrate and phenyl formate (**2**) as a CO surrogate. Initial experiments showed that the base was important for selectively obtaining **3a**, with sodium acetate and *in situ*-formed cesium adamantane-1-carboxylate resulting in a high yield of the product (entries 3 and 4). Carboxylate screening revealed that the *in situ*-formed aromatic carboxylates were effective for affording **3a** in a high yield (entries 5–10). Surprisingly, the reaction proceeded very rapidly, completing within 3 min, even when reduced amounts of cesium carbonate and *o*-anisic acid were used (entry 14).[13] This carboxylate base was better than CsOPiv (entry 15), which was used for the reaction under CO gas.[6] The carboxylate of *o*-anisic acid gave better yield of **3a** within a short reaction time than other aromatic carboxylates. These results might be ascribed to the subtle balance between steric and electronic effects (entries 11–14). Therefore, *o*-anisic acid was used to examine the substrate scope. On the other hand, the use of *N*-formylsaccharin[10] as a CO surrogate instead of **2** hardly promoted the reaction (entry 16).

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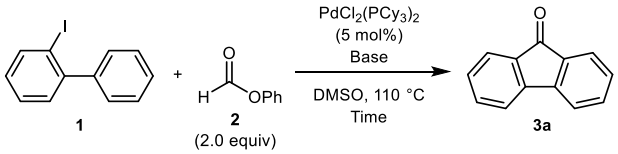
Table 1. Optimization of reaction conditions.

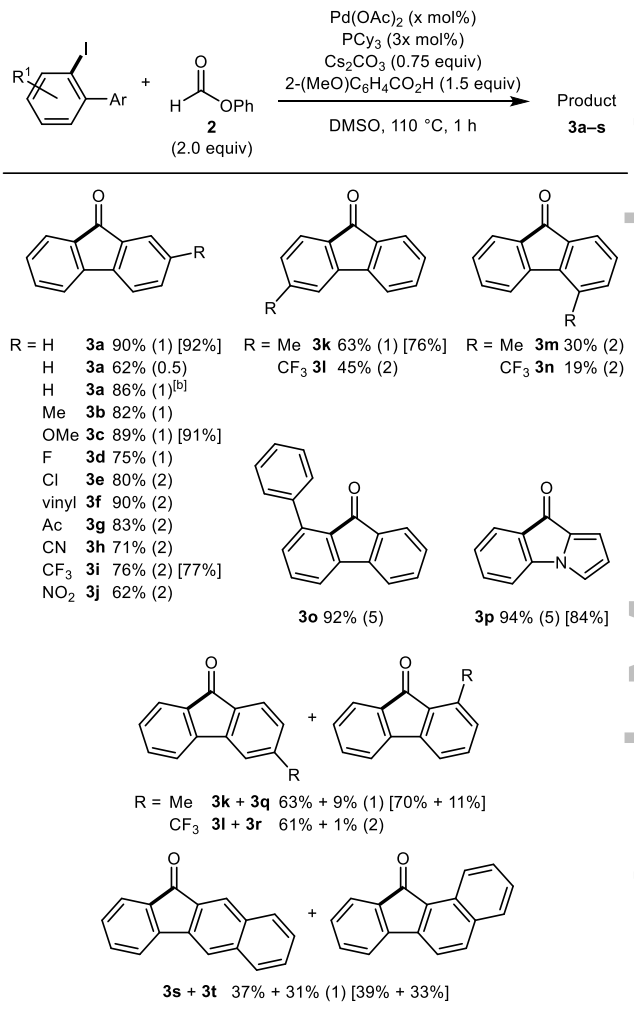


Entry	Base (equiv)	Time	Yield (%)[a]
1	NBu_3 (3.0)	14 h	11
2	Na_2CO_3 (3.0)	14 h	0[b]
3	NaOAc (3.0)	14 h	78
4	Cs_2CO_3 (1.5) + 1-$AdCO_2H$ (3.0)	14 h	89
5	Cs_2CO_3 (1.5) + $PhCO_2H$ (3.0)	14 h	82
6	Cs_2CO_3 (1.5) + 4-$FC_6H_4CO_2H$ (3.0)	14 h	84
7	Cs_2CO_3 (1.5) + 4-$(MeO)C_6H_4CO_2H$ (3.0)	14 h	94
8	Cs_2CO_3 (1.5) + 4-$(Me_2N)C_6H_4CO_2H$ (3.0)	14 h	95
9	Cs_2CO_3 (1.5) + 2-$(MeO)C_6H_4CO_2H$ (3.0)	14 h	94
10	Cs_2CO_3 (1.5) + 2,4-$(MeO)_2C_6H_3CO_2H$ (3.0)	14 h	92
11[c]	Cs_2CO_3 (0.75) + 4-$(MeO)C_6H_4CO_2H$ (1.5)	3 min	70
12[c]	Cs_2CO_3 (0.75) + 4-$(Me_2N)C_6H_4CO_2H$ (1.5)	3 min	53
13[c]	Cs_2CO_3 (0.75) + 2-$MeC_6H_4CO_2H$ (1.5)	3 min	89
14[c]	Cs_2CO_3 (0.75) + 2-$(MeO)C_6H_4CO_2H$ (1.5)	3 min	92
15[c]	CsOPiv (1.5)	3 min	58
16[c,d]	Cs_2CO_3 (0.75) + 2-$(MeO)C_6H_4CO_2H$ (1.5)	1 h	3

[a] Isolated yield. [b] Phenoxycarbonylated by-product was obtained in 99% yield. [c] $Pd(OAc)_2$ (5 mol%) and PCy_3 (15 mol%) were used instead of $PdCl_2(PCy_3)_2$. [d] *N*-Formylsaccharin was used instead of **2**.

Various 2-iodobiphenyls were tested to illustrate the substrate scope in the presence of 1–5 mol% Pd catalyst (Table 2). In most cases, a reaction time of 1 h was sufficient for the conversion of the 2-iodobiphenyls. Although 2′-substituted 2-iodobiphenyls resulted in low yields of **3m** and **3n** probably due to the steric bulk of the 2-iodobiphenyls, 4- or 4′-substituted iodobiphenyls afforded the desired fluoren-9-ones **3b–l** in moderate to high yields in the presence of 1 or 2 mol% Pd catalyst. Sterically hindered 2,6-diphenyliodobenzene and a pyrrole-containing substrate smoothly reacted to afford **3o** and **3p**, respectively, although in both cases, 5 mol% of the catalyst was required. 3′-Substituted and naphthyl-type substrates afforded two regioisomeric products, with the yields reflecting the steric effects of the substrates. Notably, extremely rapid formation of fluoren-9-ones from several 2-iodobiphenyls, which required only 3 min for reaction time under 5 mol% of Pd catalyst, was achieved (Table 2, yields of the products are shown in brackets). Moreover, the catalyst loading could be lowered to 0.5 mol%, albeit resulting in a lower yield of **3a** (62%). Gram-scale (12.0 mmol scale) synthesis of **3a** was also feasible, showing the scalability of the present synthetic method.

Table 2. Substrate scope of 2-iodobiphenyls[a]



[a] Isolated yield of each product is shown followed by catalyst loading (x) in parenthesis. Isolated yield of the product obtained from the reaction using 5 mol% Pd catalyst for 3 min is shown in square bracket. [b] The reaction was performed in 12.0 mmol scale, with 1.86 g of **3a** being obtained.

Furthermore, the same reaction was applicable to 2-bromobiphenyls (Table 3). While the reaction required 5 mol% Pd catalyst and a prolonged reaction time (14 h), fluoren-9-ones **3a**, **3c**, **3i**, and **3u–w** were successfully obtained from 4′-substituted 2-bromobiphenyls and 2-thien-3-ylbromobenzene. Notably, a bromoalkene was found to be a good substrate for the synthesis of indenone **3x**. In these reactions, a considerable amount (~10% yield) of the

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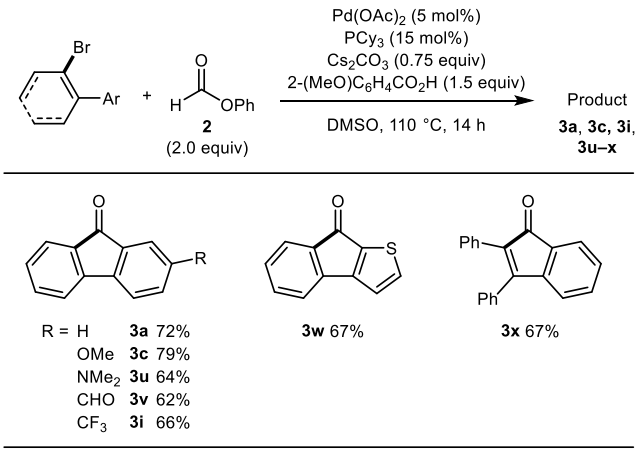
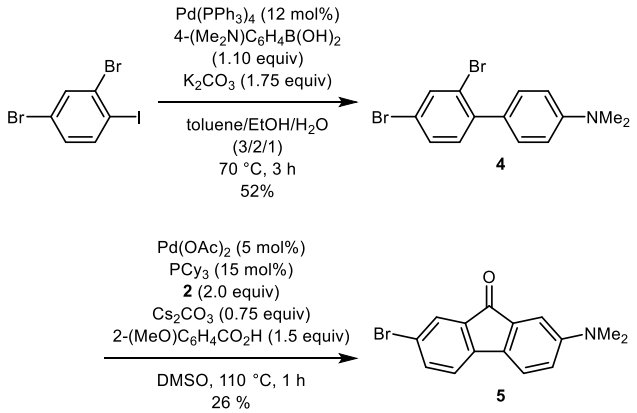
phenoxycarbonylated by-product was observed, which caused a slight decrease in the product yield.

Table 3. Substrate scope of 2-bromobiphenyls and a bromoalkene[a]



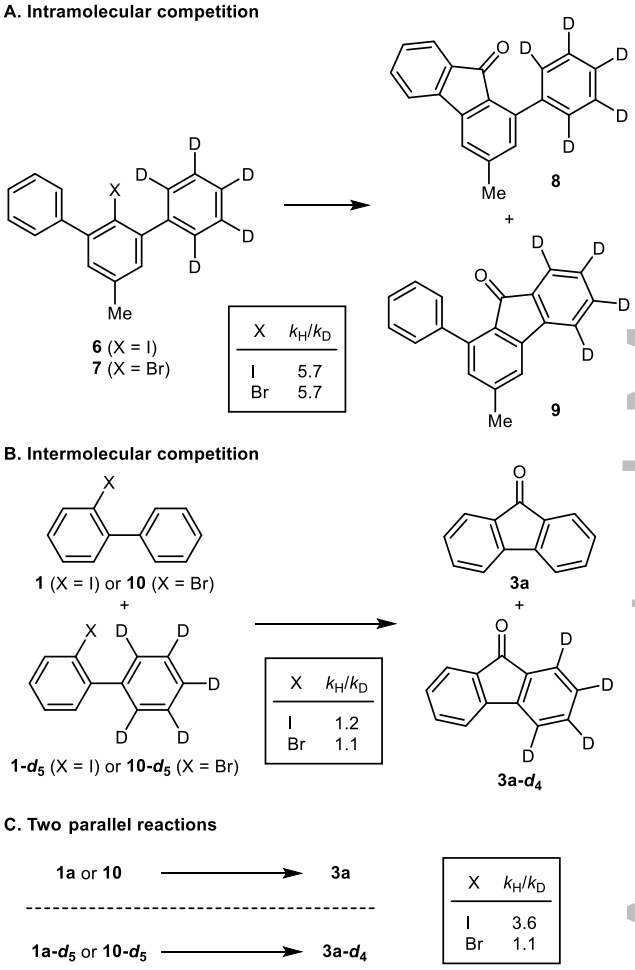
[a] Isolated yield of each product is shown.

To demonstrate the utility of the reaction, we applied it to the synthesis of a potentially diagnostic compound for Alzheimer's disease, which selectively binds to β-amyloid plaques in the brain.[14] The Suzuki-Miyaura coupling of 2,4-dibromo-1-iodobenzene and 4-(*N*,*N*-dimethylamino)phenylboronic acid afforded bromobiphenyl **4**, which was converted into **5** via the cyclocarbonylation using **2**. Although the yield was low due to the presence of two bromo groups in **4**, the target compound was concisely accessed *via* a two-step procedure from commercially available materials.



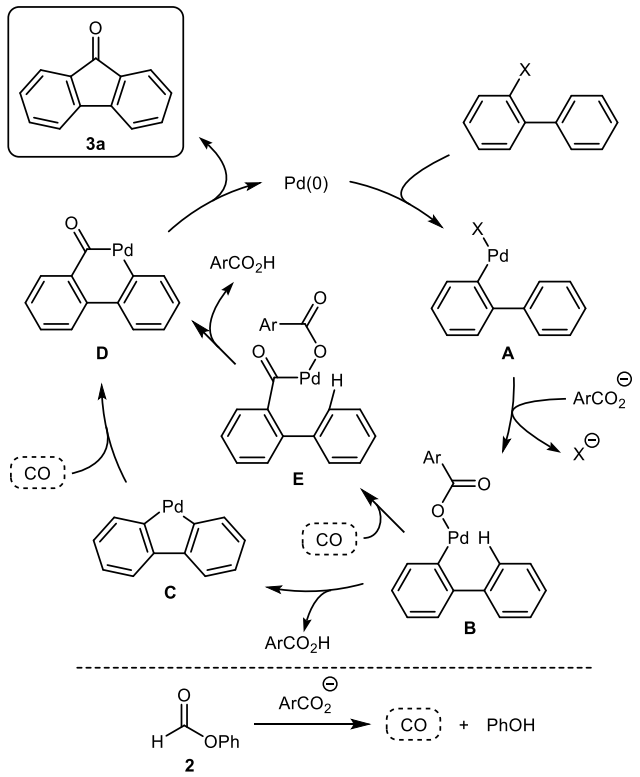
Scheme 1. Two-step synthesis of bioactive compound **5**.

To obtain insight into the reaction mechanism, kinetic isotope effects (KIEs) were measured using the appropriately deuterated 2-iodo- and 2-bromobiphenyls.[15] A large KIE value was obtained from the reaction of partially deuterated iodobiphenyl **6** and bromobiphenyl **7**, which possessed both C–H and C–D bonds at the relevant reactive sites (k_H/k_D = 5.7 for both **6** and **7**, Scheme 2A). This large KIE value was consistent with a concerted metalation–deprotonation (CMD) mechanism,[16,17] which has been proposed in many Pd-catalyzed, carboxylate-assisted C–H functionalization reactions.[18] On the other hand, intermolecular competitive experiments using iodobiphenyls (**1** and **1-*d*$_5$**) or bromobiphenyls (**10** and **10-*d*$_5$**) exhibited almost no KIE (1.2 and 1.1, Scheme 2B). The same situation was also observed when two parallel reactions using bromobiphenyls (**10** and **10-*d*$_5$**) were performed (1.1, Scheme 2C). However, two parallel reactions using iodobiphenyls (**1** and **1-*d*$_5$**) afforded relatively large KIE (3.6, Scheme 2C). These results clearly indicated that the turnover-limiting step (TLS) of the reaction depended on the substrate used; the TLS of the reaction of 2-iodobiphenyl was the C–H bond-cleaving step, while that of 2-bromobiphenyl was not the C–H bond-cleaving step.



Scheme 2. KIE experiments. Conditions: $Pd(OAc)_2$ (5 mol%), PCy_3 (15 mol%), Cs_2CO_3 (0.75 equiv), *o*-anisic acid (1.5 equiv), **2** (2 equiv) in DMSO at 110 °C, unless otherwise noted below. In the reactions of **1** and **1-*d*$_5$**, $Pd(OAc)_2$ (0.5 mol%) and PCy_3 (1.5 mol%) were used. For the intermolecular competition (B), **2** (4 equiv) was used.

The proposed reaction mechanism is shown in Scheme 3. Pd(II) intermediate **A**, which is formed via the oxidative addition of the substrate to Pd(0), exchanges an anionic ligand from a halide to a carboxylate to generate intermediate **B**. It reacts intramolecularly to dissociate the C–H bond at the 2′-position, and to generate palladacycle **C** via CMD. Then, CO generated from the reaction of phenyl formate (**2**) and a carboxylate undergoes coordination and migratory insertion. Finally, the reductive elimination of acylpalladium(II) intermediate **D** affords the desired fluoren-9-one **3a** and regenerates Pd(0). Another pathway from **B** to **D** in which CO insertion occurs to form intermediate **E** prior to CMD is also feasible. The KIE studies indicated that the TLS was the C–H bond-cleaving step for the iodides but not for the bromides. Considering the reactivity difference between the iodides and bromides, the oxidative addition step was assumed to be the TLS for bromides.



Scheme 3. Proposed reaction mechanism (Ar = 2-$MeOC_6H_4$).

In conclusion, a Pd-catalyzed simple, practical, and external CO-free carbonylation reaction for the synthesis of fluoren-9-ones was achieved using phenyl formate as a CO surrogate. The reaction time was effectively shortened by the combined use of cesium carbonate and *o*-anisic acid. Mechanistic studies using isotopically labelled compounds suggested that concerted metalation–deprotonation was involved and that the turnover-limiting step was the C–H bond-cleaving step for iodides and the oxidative addition step for bromides. Studies on the expanded substrate scope, effect of *o*-anisic acid, and origin of acceleration of the reaction are currently underway.

Experimental Section

All Pd catalysts, PCy_3, Cs_2CO_3, **1**, **10**, 2-(2-bromoethene-1,1,2-triyl)tribenzene (substrate used for synthesis of compound **3x**), all carboxylic acids and bases were purchased from TCI, Wako, Kanto, and Aldrich, and used as received. Tributylamine was purchased from Wako, and was purified by distillation prior to use. All solvents except DMSO were purified by distillation prior to use. Anhydrous DMSO ("Super Dehydrated" grade) was purchased from Wako and used as received. 2-Iodo-4'-vinyl-1,1'-biphenyl (substrate used for the synthesis of **3f**) and 2-iodo-2'-(trifluoromethyl)-1,1'-biphenyl (substrate used for the synthesis of **3n**), and **7** were synthesized by halogenation of corresponding 2-aminobiphenyls (for details, see Supporting Information). Other substrates[6b,19] including **2**,[8a] **6**,[15a] **1-*d*$_5$**,[20] and **10-*d*$_5$**[19a] were synthesized according to known methods.

Representative experimental procedure of the synthesis of fluoren-9-one (3a) (Table 2)

$Pd(OAc)_2$ (2.23 mg, 10.0 μmol, 5 mol%), PCy_3 (8.40 mg, 30.0 μmol, 15 mol%), **1** (56.0 mg, 0.200 mmol), *o*-anisic acid (45.6 mg, 0.300 mmol, 1.50 equiv), Cs_2CO_3 (48.8 mg, 0.150 mmol, 0.750 equiv) and DMSO (4.0 mL) were added in a 30-mL two-necked flask containing a magnetic stirring bar equipped with an Ar balloon. The flask was evacuated and backfilled with Ar three times. The flask was warmed to 110 °C in an oil bath and stirred for 10 min. Then, **2** (43.6 μL, 0.400 mmol, 2.00 equiv) was added to the flask by using a syringe through a septum cap. The reaction mixture was stirred at 110 °C for 3 min. The reaction mixture was immediately cooled to rt and was diluted with EtOAc and 2 M aq. NaOH, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was purified by preparative TLC twice (1st: CH_2Cl_2/hexane 1/1, 2nd: hexane/EtOAc 5/1) to afford **3a** (33.1 mg, 0.184 mmol, 92%) as a yellow solid.

Gram-scale synthesis of compound 3a (Table 2)

$Pd(OAc)_2$ (26.9 mg, 0.120 mmol, 1 mol%), PCy_3 (101 mg, 0.360 mmol, 3 mol%), **1** (3.36 g, 2.08 mL, 12.0 mmol), *o*-anisic acid (2.74 g, 18.0 mmol, 1.50 equiv), Cs_2CO_3 (2.93 g, 9.00 mmol, 0.750 equiv) and DMSO (240 mL) were added in a 1000-mL three-necked flask with an Ar balloon, a magnetic stirring bar, and a thermocouple temperature probe. The flask was evacuated and backfilled with Ar three times. The flask was warmed to 110 °C (internal temperature) in an oil bath and stirred for 30 min. Then, **2** (2.61 mL, 24.0 mmol, 2.00 equiv) was added to the flask by using a syringe through a septum cap. The flask was warmed to 110 °C in an oil bath and stirred for 1 h. The reaction mixture was cooled to rt and was diluted with EtOAc, washed with H_2O three times, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was purified by column chromatography (1st: CH_2Cl_2/hexane 1/1, 2nd: hexane/EtOAc 5/1) to afford **3a** (1.86 g, 10.3 mmol, 86%) as a yellow solid.

Acknowledgements

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