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Synthesis of Fluorenones through Rhodium-Catalyzed Intramolecular Acylation of Biarylcarboxylic Acids

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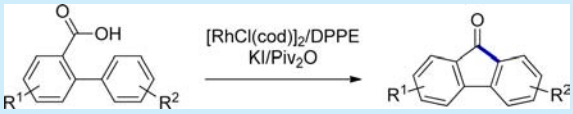
Supporting Information

ABSTRACT: An efficient approach to the synthesis of fluorenones via the rhodium-catalyzed intramolecular acylation of biarylcarboxylic acids was developed. Using this procedure, fluorenones with various substituents can be synthesized in good to high yields. This work marks the first recorded use of catalytic intramolecular acylation to synthesize fluorenones.



Fluorenones have attracted much attention due to their presence in many optoelectronically and biologically active compounds.[1] Thus, several synthetic strategies have been reported for the construction of the structural motifs: the oxidation of fluorenes;[2] radical cyclization;[3] transition-metal-catalyzed cyclization of benzophenone skeletons,[4] biphenyl-2-carbonitriles,[5] and benzoic anhydrides;[6] and the cyclocarbonylation of 2-halobiaryls.[7] One of the most venerable, and practical, of the methods used to prepare fluorenones is the Friedel−Crafts acylation of biarylcarboxylic acids and their derivatives.[8] However, known protocols using carboxylic acids require treatment with a large excess amount of Brønsted acids such as sulfuric acid,[8d] methanesulfonic acid,[8e] and polyphosphoric acid (PPA).[8a,d] Protocols that begin with acid chlorides require the use of a stoichiometric amount of Lewis acids, such as aluminum trichloride[8a] or tin tetrachloride,[8b] which produces large volumes of waste products through a work-up procedure. Because of the aforementioned importance of fluorenones, the development of an efficient and general synthetic route from biarylcarboxylic acids with reduced waste is strongly desired.

The use of carboxylic acids as a carbon resource for transition-metal-catalyzed reactions is a rapidly growing area of research.[9] We recently developed an efficient method for the synthesis of olefins from aliphatic carboxylic acid via iridium- and iron-catalyzed dehydrative decarbonylation.[10] We also reported that decarbonylative C−H arylation[11] of 2-aryloxybenzoic acids to give dibenzofurans was effectively catalyzed by rhodium complexes (Scheme 1, eq 1).[12] When 2-phenyl benzoic acid was used as the substrate, we found that no such decarbonylative arylation leading to biphenylene took place, but the acylation product fluorenone was formed.[13] This result prompted a detailed study on the synthesis of fluorenones from biaryl carboxylic acids, and herein we report that the Rh-catalyzed reaction was effective in synthesizing a variety of fluorenone derivatives (Scheme 1, eq 2).

When 2-phenylbenzoic acid (**1a**) was treated with a catalytic amount of $[RhCl(cod)]_2$ ([Rh] = 5 mol %, cod = 1,5-cyclooctadiene) and Ac_2O (Ac = acetyl, 300 mol %) at 160 °C for 20 h under argon, the intramolecular acylation proceeded sluggishly to give fluorenone (**2a**) in a 20% yield (Table 1, entry 1). The use of KI (50 mol %) as an additive increased the yield of **2a** to 61% (entry 2), suggesting that the in situ ligand exchange on rhodium between Cl and I was effective.[14] In this case, a small amount of methyl 2-phenylbenzoate was detected, which was assumed to have derived from **1a** and Ac_2O. This led us to use Piv_2O (Piv = pivaloyl) instead of Ac_2O, which prevented the formation of the corresponding *tert*-butyl ester and pushed the yield of **2a** to 73% (entry 3). We then tested a series of phosphine ligands. The additions of PPh_3, PCy_3 (Cy = cyclohexyl), and DPPM (1,2-bis(diphenylphosphino)methane) did not affect the reaction at all (entries 4−6). DPPE (1,2-bis(diphenylphosphino)ethane) was the most effective phosphine ligand and gave **2a** in a 95% isolated yield (entry 7). The reaction did not occur in the absence of a rhodium catalyst (entry 8). A shorter reaction time of 3 h resulted in a low yield of **2a** (entry 9), but microwave irradiation dramatically shortened the reaction time to 30 min (entry 10).

With the optimized conditions of entries 7 and 10 in hand, we explored the scope of biarylcarboxylic acids for fluorenone

Scheme 1. Two Types of Cyclization Using ortho-Substituted Benzoic Acids

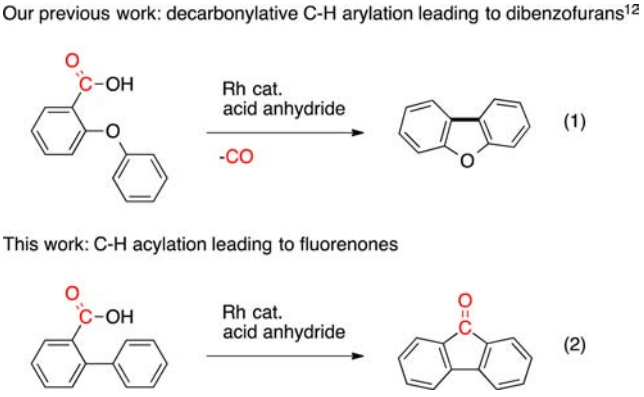


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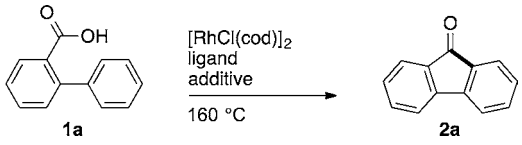
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	ligand (mol %)	additive[b]	time (h)	yield (%)[c]
1	none	Ac_2O	20	20
2	none	KI, Ac_2O	20	61[d]
3	none	KI, Piv_2O	20	73
4	PPh_3 (10)	KI, Piv_2O	20	74
5	PCy_3 (10)	KI, Piv_2O	20	35
6	DPPM (5)	KI, PivaO	20	59
7	DPPE (5)	KI, Piv_2O	20	95[e]
8[f]	DPPE (5)	KI, Piv_2O	20	0
9	DPPE (5)	KI, Piv_2O	3	34
10[g]	DPPE (5)	KI, Piv_2O	0.5	98[e]

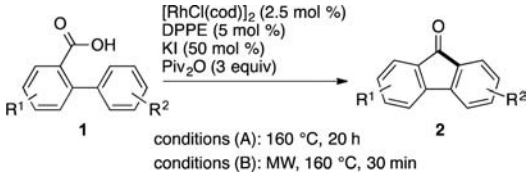
[a]Conditions: 2-phenylbenzoic acid (**1a**, 0.5 mmol), $[RhCl(cod)]_2$ (2.5 mol %), 160 °C, under an argon atmosphere. [b]KI (50 mol %), Ac_2O, or Piv_2O (300 mol %). [c]GC yield using hexadecane as an internal standard. [d]Methyl 2-phenylbenzoate was formed in a 12% yield. [e]Isolated yield. [f]Without $[RhCl(cod)]_2$. [g]Under microwave irradiation at 160 °C.

synthesis using conditions A (conventional heating, 160 °C, 20 h) and B (MW heating, 160 or 200 °C, 30 min) (Table 2). Use of 2-phenylbenzoic acids bearing electron-donating groups such as Me and OMe at the 4′-position of the phenyl ring afforded the corresponding fluorenones **2b** and **2c** in high yields, respectively (entries 3−6). Substrates with electron-withdrawing groups such as Ac and CF_3 in the 4′-position also worked well to give **2d** and **2e**, respectively (entries 7−10). F- and Cl-substituted fluorenones **2f** and **2g** were also obtained in good yields (entries 11−14), whereas the reaction of the Br-substituted carboxylic acid was sluggish (entries 15 and 16). Substrates with *ortho*-substituents **1i** and **1j** also reacted smoothly to afford **2i** and **2j**, respectively (entries 17−20). The reaction of **1k**, having two unequivalent *ortho* C−H substituents, proceeded regioselectively at the sterically less hindered position to give **2k** as the sole product (entries 21 and 22). Biarylcarboxylic acid **1l** had two methyl groups at the *meta* positions and the reaction was rather sluggish, but it afforded the corresponding fluorenone **2l** in a high yield at an elevated temperature of 180 °C (entry 23). Substrates **1m** and **1n** had a methyl group at the position *ortho* to the carboxylic acid moiety and gave the corresponding products **2m** and **2n** in good yields (entries 24 and 25).

To gain insight into the mechanism, the reaction was carried out in the presence of ^{13}CO generated from ^{13}C-labeled formic acid and sulfuric acid.[15] We found that ^{13}C-labeled fluorenone **2a*** was formed with incorporation of ^{13}CO (Scheme 2). This suggested that a CO ligand exchange via the rhodium−carbonyl complex had taken place during the reaction.

A possible mechanism for the present rhodium-catalyzed intramolecular acylation of biarylcarboxylic acids is shown in Scheme 3. The oxidative addition of the acyl-O bond of the *in situ* formed mixed anhydride **1a′** into the rhodium(I) catalyst would take place to give acylrhodium species **A**, which would then undergo an intramolecular C−H acylation to afford the rhodacycle **B**. The reductive elimination would give **2a** and regenerate the key rhodium(I) species (path a). On the basis of the ^{13}C-labeling experiment, Rh-carbonyl complexes, such as **C** and **D**, would be formed in an equilibrium with **A** and **B**, which supports path b.

Table 2. Rhodium-Catalyzed Intramolecular C−H Acylation of Biarylcarboxylic Acids[a]



1 2

entry	1	conditons	2	yield (%)[b]
1	R = H **1a**	A	**2a**	95
2	R = H **1a**	B	**2a**	98
3	R = Me **1b**	A	**2b**	90
4	R = Me **1b**	B	**2b**	92
5	R = OMe **1c**	A	**2c**	86
6	R = OMe **1c**	B	**2c**	90
7	R = Ac **1d**	A	**2d**	76
8	R = Ac **1d**	B	**2d**	93
9	R = CF_3 **1e**	A	**2e**	95
10	R = CF_3 **1e**	B	**2e**	97
11	R = F **1f**	A	**2f**	96
12	R = F **1f**	B	**2f**	98
13	R = Cl **1g**	A	**2g**	74[c]
14	R = Cl **1g**	B	**2g**	54[d]
15	R = Br **1h**	A	**2h**	22[e,f]
16	R = Br **1h**	B	**2h**	3[d,f]
17	**1i**	A	**2i**	82
18	**1i**	B	**2i**	96[d]
19	**1j**	A	**2j**	68
20	**1j**	B	**2j**	93
21	**1k**	A	**2k**	80
22	**1k**	B	**2k**	95
23	**1l**	A	**2l**	81[e]
24	**1m**	A	**2m**	76[e]
25	**1n**	A	**2n**	90[e]

[a]**1** (0.5 mmol), $[RhCl(cod)]_2$ (2.5 mol %), DPPE (5 mol %), KI (50 mol %), Piv_2O (3 equiv). Conditions A: Conventional heating (160 °C, 20 h). Conditions B: Microwave irradiation (160 °C, 30 min). [b]Isolated yield. [c]40 h. [d]MW, 200 °C. [e]180 °C. [f]NMR yield using 1,1,2,2-tetrachloroethane.

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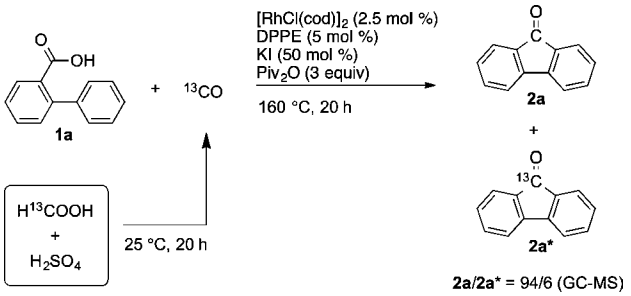
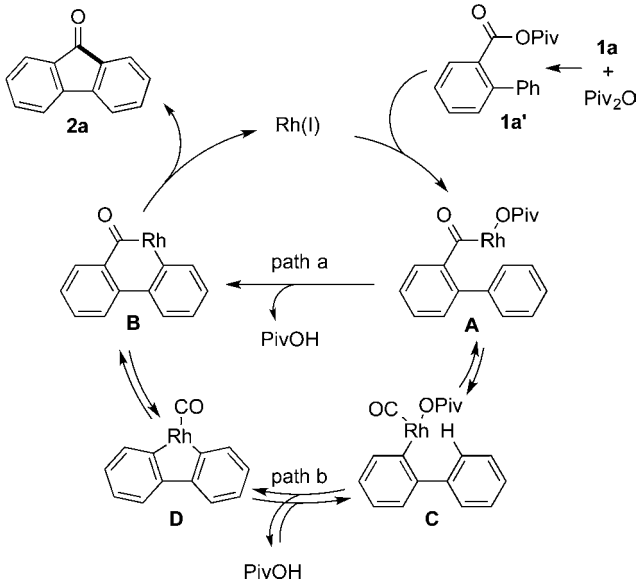
Scheme 2. Reaction under a ^{13}CO Atmosphere

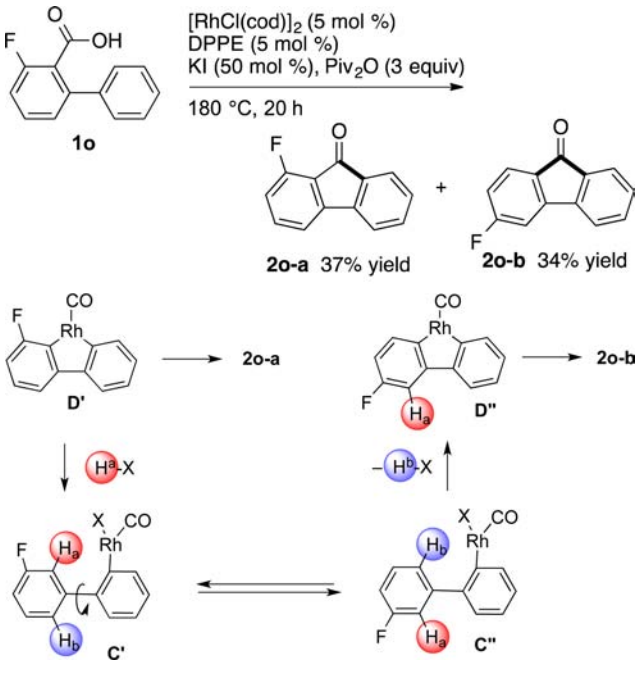


Scheme 3. Proposed Reaction Mechanism



With two positional isomers, **2o−a** and **2o−b**, from 2-fluoro substituted substrate **1o** (Scheme 4), we believe there was an equilibrium between **C** and **D**. Thus, the reaction of **1o** gave a nearly 1:1 mixture of 2-fluoroflorenone (**2o−a**) and 3-fluoroflorenone (**2o−b**). The formation of the unusual product **2o−b** suggested that rhodafluorene **D′** would be formed, which would undergo C−Rh bond cleavage by protonolysis to give **C′**.[16] The free rotation and recyclization at C−H would form rhodafluorene **D″**, which is a key species leading to **20-b**.

Scheme 4. Reaction of 2-Fluoro-6-Phenyl Benzoic Acid (1o)



In summary, we developed the first transition-metal-catalyzed approach to the synthesis of fluorenones by intramolecular acylation of biarylcarboxylic acids. $[RhCl(cod)]_2$/DPPE gave the most effective transformation. Microwave irradiation shortened the reaction time significantly. Mechanistic studies suggested an equilibrium for rhodaphenanthrenone and rhodafluorenes. Further applications of these catalytic acylation methods are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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