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Iridium(III)-Catalyzed Dehydrogenative Coupling of Salicylic Acids with Alkynes: Synthesis of Highly Substituted 1-Naphthol Derivatives

Keishi Hirosawa,[a] Yoshinosuke Usuki,[a] and Tetsuya Satoh[a,*]

[a] Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan
Fax: +81-6-6605-2522
E-mail: satoh@sci.osaka-cu.ac.jp

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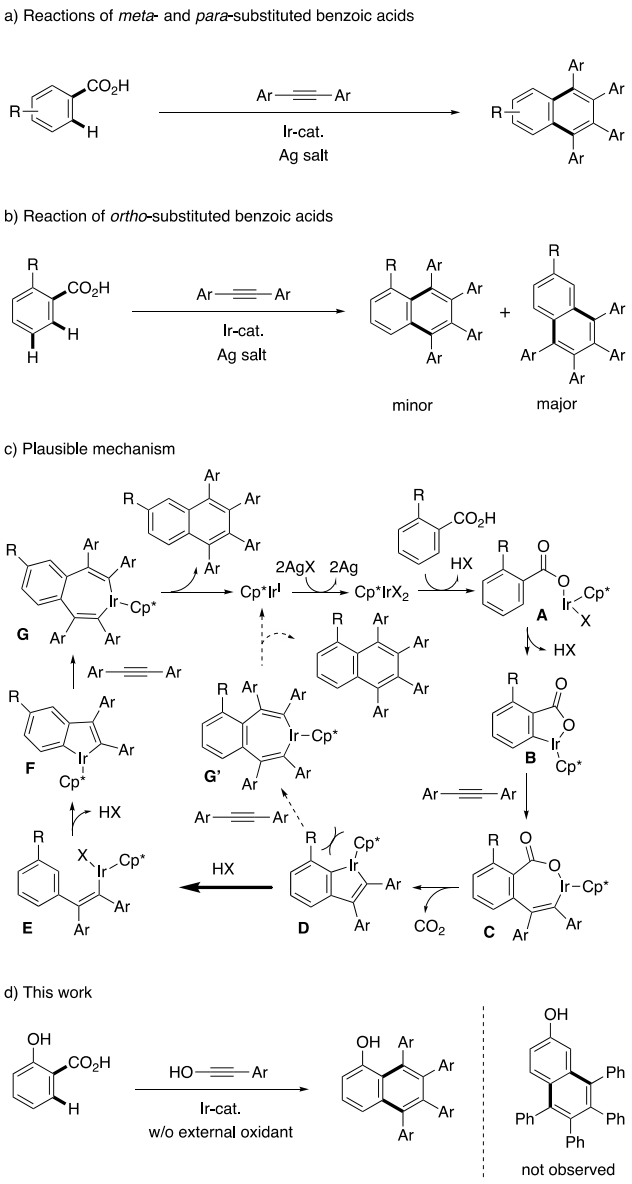
Abstract. The iridium(III)-catalyzed dehydrogenative coupling of salicylic acids with diarylacetylenes proceeds smoothly accompanied by decarboxylation to produce 5,6,7,8-tetraarylnaphthalen-1-ols selectively. This reaction can be conducted even without addition of external oxidant. The same kind of naphthalen-1-ol derivative can also be synthesized predominantly by the reaction of 4-hydroxybenzoic acid with diphenylacetylene. Some of naphthalen-1-ols prepared exhibits unique optical properties.

Keywords: Carboxylic acids; C-C coupling; C-H activation; Homogeneous catalysis; Iridium



The transition-metal-catalyzed C–H functionalization reactions have been recognized as useful tools in modern organic synthesis because of their atom- and step-economy.[1] Various kinds of directing groups have been developed and utilized for regioselective C–H bond cleavage at their neighboring position.[2] A carboxylic group loaded on aromatic substrates is a unique directing group because of its ready removability, which allows regioselective functionalization at its *ortho*- as well as *ipso*-position.[3] For example, we have reported that benzoic acid undergoes iridium(III)-catalyzed decarboxylative, dehydrogenative coupling with diarylacetylenes accompanied by carboxyl group-directed *ortho* C–H bond cleavage and subsequent decarboxylation to produce highly substituted naphthalenes (Scheme 1a, R = H).[4,5] This enables aromatic homologation providing a simple synthetic route to fused aromatic compounds from readily available arenecarboxylic acids. Actually, the reactions of *meta*- and *para*-substituted benzoic acids with diarylacetylene selectively give 2-substituted 5,6,7,8-tetraarylnaphthalenes. However, this procedure is not applicable to the synthesis of 1-substituted 5,6,7,8-tetraarylnaphthalenes from *ortho*-

Scheme 1. Decarboxylative Coupling of Benzoic Acids with Diarylacetylenes.

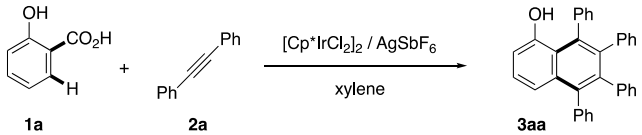
substituted benzoic acids. This reaction seems to involve isomerization of metallacycle intermediate **D**, generated through cyclometallation, alkyne insertion, and decarboxylation steps, to **F** due to steric hindrance to give 2-substituted 5,6,7,8-tetraarylnaphthalenes predominantly (Schemes 1b and 1c).[4,5]

During our further studies on the annulation of (hetero)arenecarboxylic acids,[6] we have found that *ortho*-hydroxybenzoic acids, salicylic acids, couple with diarylacetylenes at the sterically crowded positions to exclusively produce 5,6,7,8-tetraarylnaphthalen-1-ols (Scheme 1d).[7] This dehydrogenative coupling proceeds smoothly even under external oxidant-free conditions. It should be noted that *peri*-arylated 1-naphthol derivatives have gained much attention due to their optical properties induced by the interaction between their *peri*-hydroxy and aryl groups.[8] Unexpectedly, the sterically hindered 5,6,7,8-tetraphenylnaphthalen-1-ol can also be prepared predominantly in the reaction of *para*-hydroxybenzoic acid with diphenylacetylene. These results are described herein.

In an initial attempt, salicylic acid (**1a**) (0.3 mmol) was treated with diphenylacetylene (**2a**) (0.9 mmol) in the presence of $[Cp^*IrCl_2]_2$ (0.01 mmol, 3.3 mol %), $AgSbF_6$ (0.04 mmol), and $Cu(OAc)_2•H_2O$ (0.05 mmol) in xylene under O_2 (1 atm) at 170 °C for 23 h. As a result, 5,6,7,8-tetraphenylnaphthalen-1-ol (**3aa**) was selectively formed in 53% GC yield (Table 1, entry 1). In the reaction mixture, almost the same amount (0.16 mmol) of stilbene was also detected by GC and GC-MS. The fact suggests that alkyne **2a** can act as hydrogen accepter in the present dehydrogenative coupling system.[9] Therefore, we next eliminated $Cu(OAc)_2•H_2O$ (0.05 mmol) and O_2 (entry 2). As expected, even under such conditions without external oxidant, **3aa** was obtained in 69% yield (entry 2). At 150 °C, the reaction was sluggish (entry 3). The addition of $AgSbF_6$ as a cocatalyst was found to be essential for the reaction. Thus, the yield of **3aa** considerably decreased in the absence of $AgSbF_6$ (entry 4). Other silver salts such as AgOAc and $AgNTf_2$ were less effective than $AgSbF_6$ (entries 5 and 6 versus entry 2). Finally, slight increase of reaction temperature to 180 °C enhanced the yield up to 75% (entry 7). In addition, the reaction could be readily scaled up to a 1 mmol scale. Thus, the reaction of **1a** (1 mmol) with **2a** (3 mmol) gave **3aa** in a reasonable yield (314 mg, 70%) (entry 8).

Under the conditions in entry 7 of Table 1, the reactions of **1a** with various alkynes **2b**-**g** were next examined (Table 2). Diphenylacetylenes possessing methyl-, *tert*-butyl-, methoxy-, and chloro-substituents at the *para* positions **2b-e** underwent the coupling to produce the corresponding 5,6,7,8-tetraarylnaphthalen-1-ols **3ab**-**ae**. The reactions with electron-deficient bis[4-(trifluoromethyl)phenyl]acetylene (**2f**) and 4-octyne (**2g**) did not proceed at all.[10] Meanwhile, variously substituted salicylic acids are now commercially available. Some of them were employed for the coupling with **2a**. The reactions of 4-chloro- (**1b**), 3-methoxy- (**1c**), and 3,4-dimethoxy-salicylic acid (**1d**) gave 3-chloro- (**3ba**), 2-methoxy- (**3ca**), and 2,3-dimethoxy- (**3da**) 5,6,7,8-tetraphenylnaphthalen-1-ols in 45-68% yields. 2,5,6,7,8-Pentaphenylnaphthalen-1-ol (**3ea**) could also be synthesized in 62% yield from 3-phenylsalicylic acid (**1e**) and **1a**. In contrast, 3-nitrosalicylic acid (**1f**) and 1-hydroxy-2-naphthoic acid (**1g**) did not react with **2a** at all.

Table 1. Reaction of Salicylic Acid (**1a**) with Diphenylacetylene (**2a**)[a].

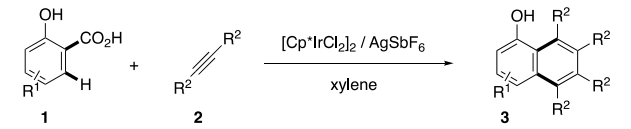


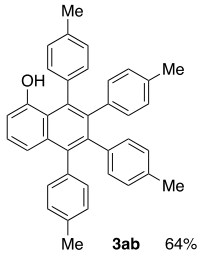
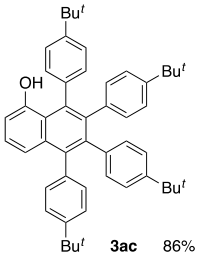
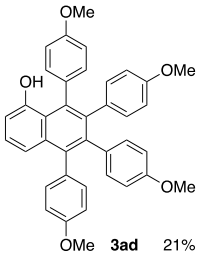
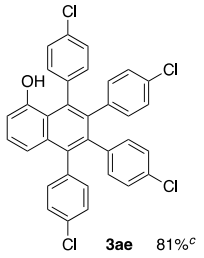
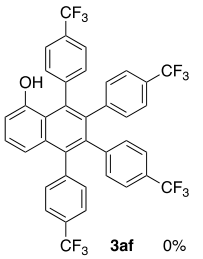
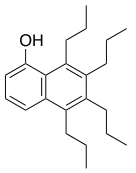
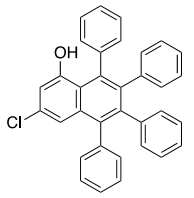
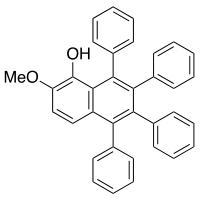
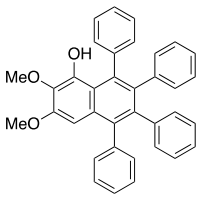
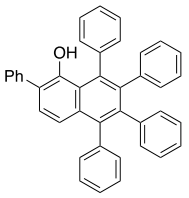
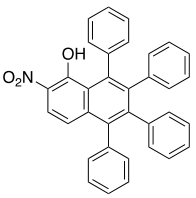
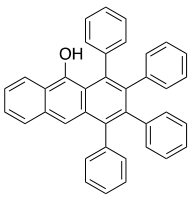
1a 2a 3aa

Entry	Temp. [°C]	Time [h]	Yield [%][b]
1[c]	170	23	53
2	170	19	69
3	150	72	38
4[d]	170	24	20
5[e]	170	21	8
6[f]	170	20	Tr.
7	180	25	75 (72)
8[g]	180	20	(70)

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol) in xylene (2.5 mL) under Ar, unless otherwise noted. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] With $Cu(OAc)_2•H_2O$ (0.05 mmol) under O_2 (1 atm). [d] Without $AgSbF_6$. [e] AgOAc was employed in place of $AgSbF_6$. [f] $AgNTf_2$ was employed in place of $AgSbF_6$. [g] **1a** (1 mmol), **2a** (3 mmol), $[Cp^*IrCl_2]_2$ (0.03 mmol), $AgSbF_6$ (0.13 mmol), and xylene (7 mL) were employed.

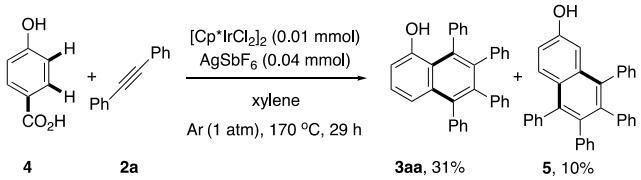
Table 2. Reaction of Salicylic Acids **1** with Alkenes **2**[a].



product	% yield[b]
 **3ab**	64%
 **3ac**	86%
 **3ad**	21%
 **3ae**	81%[c]
 **3af**	0%
 **3ag**	0%
 **3ba**	67%
 **3ca**	45%
 **3da**	68%
 **3ea**	62%
 **3fa**	0%
 **3ga**	0%

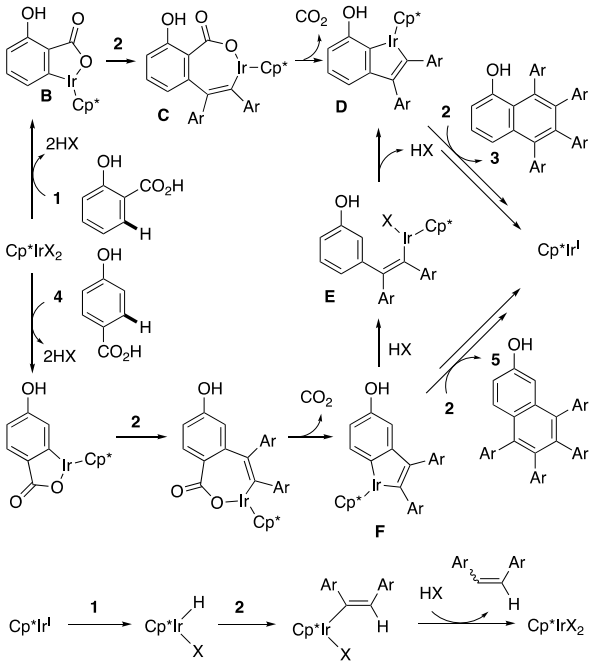
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol) in xylene (2.5 mL) at 180 ºC under Ar for 24 h, unless otherwise noted. [b] Isolated yield based on the amount of **1** used. [c] **1** (0.1 mmol), **2** (0.3 mmol), $[Cp^*IrCl_2]_2$ (0.003 mmol), $AgSbF_6$ (0.013 mmol) were used.

As described above, the reaction of *para*-hydroxybenzoic acid (**4**) with **2a** also gave 5,6,7,8-tetraphenylnaphthalen-1-ol (**3aa**) predominantly, along with a minor amount of 5,6,7,8-tetraphenylnaphthalen-2-ol (**5**) (Scheme 2). This preference is rather unexpected because **3aa** seems to be sterically crowded compared to **5**.



Scheme 2. Reaction of **4** with **2a**.

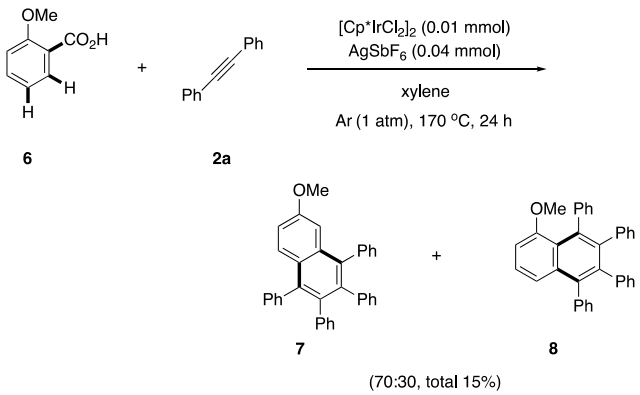
Plausible pathways for the reactions of **1** and **4** with **2** are depicted in Scheme 3. The reaction of salicylic acid **1** with alkyne **2** appears to proceed in a similar way to that shown in Scheme 1c, through carboxyl group-directed C–H bond cleavage to form **B**, alkyne insertion to form **C**, decarboxylation to form **D**, the second alkyne insertion, and reductive elimination steps. The Cp^*Ir^I species formed at the last step seems to be reoxidized in the presence of **2** and HX to generate an active $Cp^*Ir^{III}X_2$ species.[9,11] Exclusive formation of 1-naphthol **3** indicates that the path from intermediate **D** toward the second alkyne insertion leading to the formation of **3** is preferred rather than that involving isomerization to form **5**. In the reaction of *para*-hydroxybenzoic acid **4**, on the other hand, a similar five-membered metallacycle intermediate **F** may be formed in a similar manner to that of **D**. The fact, predominant formation of **3aa** in Scheme 2, suggests that **F** may undergo isomerization to **D** via **E**. It is possible that coordination of the hydroxy group[12] of **D** toward its Ir center is a key to stabilize the intermediate **D** and promote the isomerization to lead to preferential formation of **3aa**.



Scheme 3. Reaction Pathways to Produce **3** and **5**.

As expected, substituting methoxy group for the hydroxy altered the predominant pathway. Thus, as shown in Scheme 4, treatment of *ortho*-

methoxybenzoic acid (**6**) with **2a** under the standard conditions gave 2-methoxy-5,6,7,8-tetraphenylnaphthalene (**7**) predominantly, along with a minor amount of 1-methoxy isomer (**8**).



Scheme 4. Reaction of **6** with **2a**.

It has been reported that 8-arylnaphthalen-1-ol derivatives show interesting photophysical properties of a bathochromic shift of emission and a large Stokes shift.[8] These appear to be due to the through-space interaction between the *peri*-hydroxy and aryl groups stabilizing the excited state. Therefore, the products 5,6,7,8-tetraarylnaphthalen-1-ols possessing an aryl group at the peri-position are expected to show similar properties. In a preliminary investigation on the optical properties of **3aa**, a large Stokes shift was also observed in the measured emission and excitation spectra in DMSO solution (Figure 1).

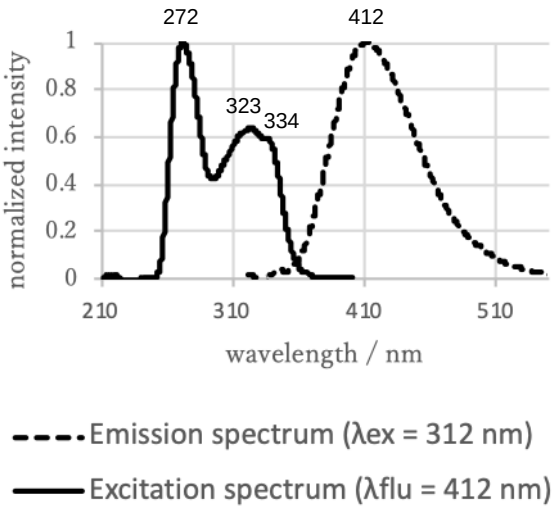


Figure 1. Emission and Excitation Spectra of **3aa** in DMSO Solution (0.01 mM).

In conclusion, we have demonstrated that salicylic acids undergo dehydrogenative, decarboxylative coupling upon treatment with diarylacetylenes in the presence of a iridium(III) catalyst to give 5,6,7,8-tetraarylnaphthalen-1-ols. The reaction of 4-hydroxybenzoic acid has also been found to give the same naphthalen-1-ol derivative predominantly. Plausible reaction pathways have been proposed. Work is underway for further understanding the mechanism.

Experimental Section

Experimental Details: To a 20 mL two-necked flask with a reflux condenser, a balloon, and a rubber cup were added salicylic acid **1** (0.3 mmol), $[Cp^*IrCl_2]_2$ (0.01 mmol, 8 mg), $AgSbF_6$ (0.04 mmol, 14 mg), and xylene (2.5 mL). The mixture was stirred under air at room temperature for 10 min. Then, alkyne **2** (0.9 mmol) and 1-methylnaphthalene (ca. 50 mg) as internal standard were added and the resulting mixture was stirred under argon (1 atm) at 180 °C (bath temperature) for 24 h. The reaction mixture was diluted by ethyl acetate (50 mL). The organic layer was washed by water (50 mL, two times) and brine (50 mL) and dried over Na_2SO_4. After evaporation of the solvents under vacuum, product **3** was isolated by column chromatography on silica gel using hexane−ethyl acetate as eluent. Further purification by GPC (gel permeation chromatography) was performed, if needed.

Acknowledgements

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