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Synthesis of perinaphthenones through rhodium-catalyzed dehydrative annulation of 1-naphthoic acids with alkynes†

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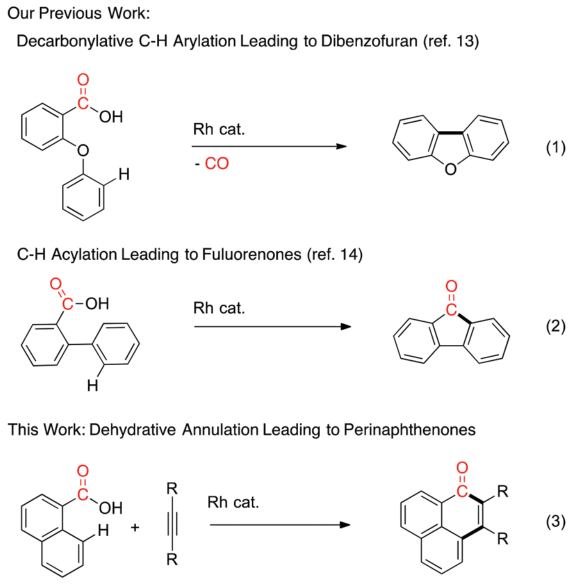
An efficient approach to the synthesis of perinaphthenones *via* the rhodium-catalyzed dehydrative annulation of 1-naphthoic acids with internal alkynes was developed. Norbornadiene can act as an acetylene equivalent to give unsubstituted perinaphthenones at the 2- and 3-positions *via* dehydrative annulation followed by a retro Diels–Alder reaction.

Perinaphthenones (also called phenalenones) and their derivatives have attracted intense attention because of their unique physical and biological properties.[1] Their structures can be found in widely used $^1O_2$ photosensitizers.[2] Perinaphthenone derivatives also exhibit diverse biological qualities that make them antifungal,[3] anticancer,[4] antioxidant,[5] anti-HIV,[6] and anti-malarial.[7] Therefore, the development of a straightforward method using readily available substrates to construct perinaphthenone skeletons[8] is highly desired.

The use of carboxylic acids as a carbon resource for transition-metal-catalyzed reactions has been a steadily growing area of research for the past few decades.[9–12] We recently reported the rhodium-catalyzed synthesis of dibenzofurans[13] and fluorenones[14] *via* decarbonylative C–H arylation of 2-aryloxybenzoic acids and C–H acylation of 2-arylbenzoic acids, respectively (Scheme 1, eqn (1) and (2)). As suggested, we used acylrhodium species to form the key intermediates for these two reactions. We envisaged that intermolecular trapping of the acylrhodium species derived from 1-naphtohoic acids by alkynes followed by C–H activation[15] at a *peri*-position[16] would lead to the formation of perinaphthenones (Scheme 1, eqn (3)). Herein we report the Rh-catalyzed dehydrative annulation[17] of 1-naphthoic acids with alkynes, which led to a novel synthesis of perinaphthenones.

The reaction of 1-naphthoic acid (**1a**) with 4-octyne (**2a**) was investigated as a model reaction. When the reaction of **1a** with **2a** (3 equiv.) was carried out in the presence of $[RhCl(cod)]_2$ (5 mol%), PPh_3 (10 mol%), KI (50 mol%), and Piv_2O (3 equiv.) at 160 °C for 20 h, perinaphthenone **3a** was obtained in a 52% yield. The reaction also gave naphthalene in 6% yield together with unreacted **1a** (18%) and a mixed anhydride of **1a** with pivalic acid (25%) (Table 1, entry 1). Similar results were obtained when bis(diphenylphosphino)-methane (DPPM) and bis(diphenylphosphino)ethane (DPPE) were used as a ligand (entries 2 and 4). In the absence of KI, the reaction became quite sluggish (entry 3), which would suggest that the *in situ* ligand exchange on rhodium between Cl and I was effective.[13] The use of bis(diphenylphosphino)propane (DPPP) and bis(diphenylphosphino)butane (DPPB) gave lower yields of **3a**



Scheme 1 Rh-Catalyzed cyclization reactions of aromatic carboxylic acids.

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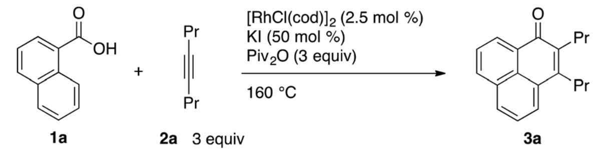
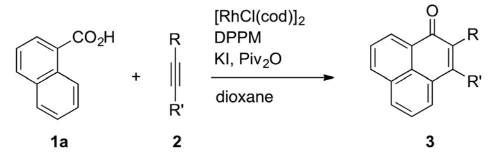
Table 1 Reaction of 1-naphthoic acid **1a** with 4-octyne **2a**[a]

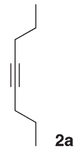
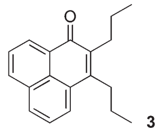
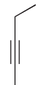
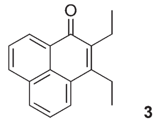
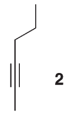
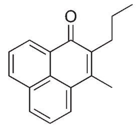
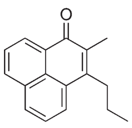
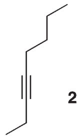
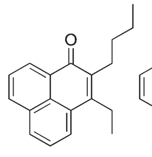
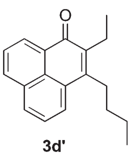
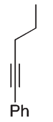
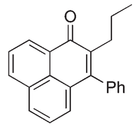
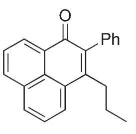
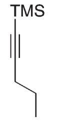
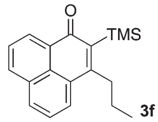
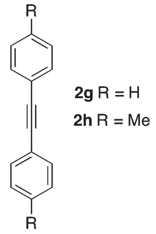
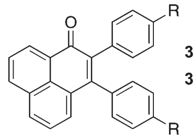


Entry	Ligand (mol%)	Solvent	Time (h)	Yield[b] (%)
1	PPh_3 (10)	Toluene	20	52
2	DPPM (5)	Toluene	20	54
3	DPPM (5)	Toluene	20	15[c]
4	DPPE (5)	Toluene	20	50
5	DPPP (5)	Toluene	20	38
6	DPPB (5)	Toluene	20	18
7	DPPM (5)	Dioxane	20	79
8	DPPM (5)	Dioxane	30	94(88)

[a] Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $[RhCl(cod)]_2$ (2.5 mol%), cod = 1,4-cyclooctadiene, ligand (5 or 10 mol%), KI (0.25 mmol), Piv_2O (1.5 mmol), solvent (0.5 mL), 160 °C. [b] Yield was determined by ^{1}H-NMR analysis using $Cl_2CHCHCl_2$ as an internal standard. The isolated yield appears in parenthesis. [c] The reaction was carried out without KI.

Table 2 Rh-Catalyzed dehydrative annulation of **1a** with alkynes **2** leading to perinaphtenones[a]



Entry	2	3	Yield[b] (%)
1	 **2a**	 **3a**	88
2	 **2b**	 **3b**	77
3	 **2c**	 **3c**  **3c'**	94(45 : 55)[c]
4	 **2d**	 **3d**  **3d'**	85(47 : 53)[c]
5	 **2e**	 **3e**  **3e'**	75(44 : 56)[c]
6	 **2f**	 **3f**	44%
7 8		 **3g** **3h**	49[d](63)[e] 21[d](49)[e]

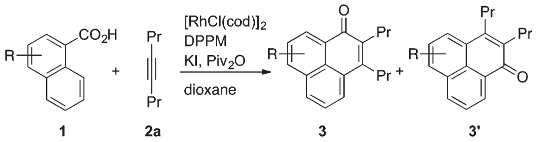
[a] **1** (0.5 mmol), **2** (1.5 mmol), $[RhCl(cod)]_2$ (2.5 mol%), cod = 1,4-cyclooctadiene, DPPM (5 mol%), KI (0.25 mmol), Piv_2O (1.5 mmol), dioxane (1 mL), 160 °C, 30 h. [b] Isolated yield after chromatography on SiO_2. [c] The product ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] 40 h. [e] 96 h.

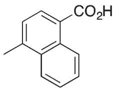
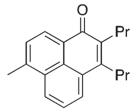
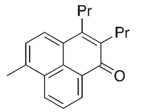
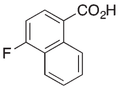
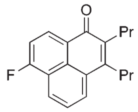
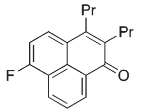
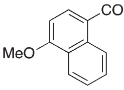
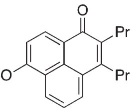
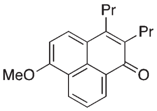
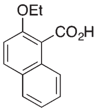
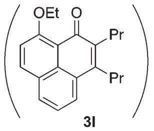
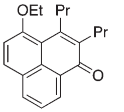
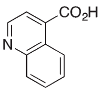
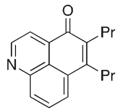
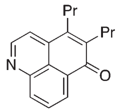
(entries 5 and 6). Consequently, we were pleased when the use of 1,4-dioxane as a solvent in place of toluene dramatically increased the yield of **3a** (79%, entry 7). Then, an extended reaction time of 30 h improved the isolated yield of **3a** to 88% (entry 8).

Having the optimized conditions (DPPM, dioxane, 30 h) in hand, we then examined the scope of the present perinaphthenone synthesis (Table 2). The reaction of **1a** with 3-hexyne (**2b**) gave diethyl-substituted perinaphthenone **3b** in 77% yield (Table 2, entry 2). Unsymmetrical dialkylalkynes, such as 2-hexyne (**2c**) and 3-octyne (**2d**), gave the corresponding perinaphthenones as a mixture of regioisomers in 94 and 85% yields, respectively (Table 2, entries 3 and 4). The reaction of **1a** with 1-phenylpentyne **2g** gave a 44 : 56 mixture of **3e** and **3e′** in 75% yield (Table 2, entry 5). In contrast to these three examples, the reaction of **1a** with 1-trimethylsilylpentyne (**2f**) gave **3f** selectively, albeit in a modest yield (Table 2, entry 6). The reaction of **1a** with diarylacetylenes, such as diphenylacetylene (**2g**) and di-*para*-tolylacetylene (**2h**), was sluggish in giving the corresponding perinaphthenones **3g** and **3h** in yields of 49 and 21%, respectively. A prolonged reaction time of 96 h improved the yields of **3g** and **3h** to 63 and 49%, respectively (Table 2, entries 7 and 8).

We next investigated the reaction of substituted naphthoic acids **1b–e** and quinoline carboxylic acid **1f** with 4-octyne (**2a**), and the results are summarized in Table 3. When the reaction of 4-methyl-1-naphthoic acid (**1b**) with **2a** was carried out under standard conditions (160 °C, 30 h), a 64/36 mixture of **3i** and **3i′** with carbonyl migration was obtained (Table 3, entry 1). In a similar manner, the reaction of 4-furuoro- and 4-methoxy-1-naphthoic acid (**1c** and **1d**) gave a mixture of products in similar ratios (Table 3, entries 3 and 5). In these cases, the formation of the migrated products was effectively suppressed at <8% by simply employing an elevated temperature (180 °C) (entries 2, 4 and 6). Interestingly, the reaction of *ortho*-ethoxynaphthoic acid **1e** gave carbonyl-migrated product **3l′** selectively (entry 7). In this case, steric repulsion between the *ortho*-substituent and a carbonyl group would accelerate the formation of an arylrhodium complex from an acylrho-

Table 3 Rh-Catalyzed dehydrative annulation of substituted naphthoic acids **1** with alkynes **2**[a]



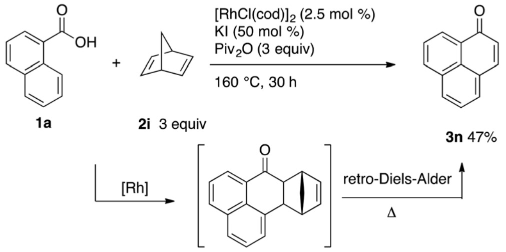
Entry	2	3		Yield[b] (%)
1 2[c]	 **1b**	 **3i**	 **3i'**	86(64 : 36) 82(93 : 7)
3 4[c]	 **1c**	 **3j**	 **3j'**	79(66 : 34) 77(92 : 8)
5 6[c]	 **1d**	 **3k**	 **3k'**	85(67 : 33) 87(92 : 8)
7	 **1e**	 **3l**	 **3l'**	54(0 : 100)
8[d]	 **1f**	 **3m**	 **3m'**	54(94 : 6)

[a] **1** (0.5 mmol), **2** (1.5 mmol), [RhCl(cod)]$_2$ (2.5 mol%), cod = 1,4-cyclooctadiene, DPPM (5 mol%), KI (0.25 mmol), Piv$_2$O (1.5 mmol), dioxane (1 mL), 160 °C, 30 h. [b] Isolated yield after chromatography on SiO$_2$. The product ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. [c] 180 °C. [d] Dioxane (3 mL).

dium complex (*vide infra*). Quinoline carboxylic acid reacted with **2a** to give **3k** in good selectivity even at 160 °C (entry 8).

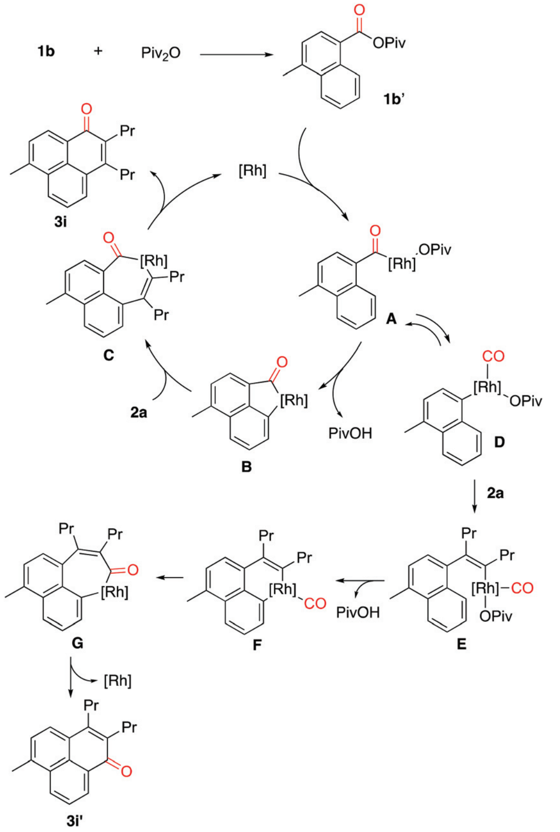
Since the use of acetylene gas is somewhat tedious, we then tested a theory for a synthetically equivalent reaction of **1a** with norbornadiene (**2i**), wherein the annulation product would undergo a subsequent retro-Diels–Alder reaction (Scheme 2). As expected, non-substituted perinaphthenone **3n** was obtained in a 47% yield.[18]

A possible reaction mechanism for the formation of perinaphthenones uses the reaction of **1b** with **2a** as a model and is outlined in Scheme 3. The oxidative addition of the acyl–O bond of the *in situ*-formed mixed anhydride **1b′** into the rhodium(I) catalyst would give acylrhodium species **A**, which would then undergo C–H cleavage *via* a concerted metalation/deprotonation (CMD) process[19] to give the rhodacycle **B.** Insertion of **2a** into the rhodium–aryl bond followed by reductive elimination would give the perinaphthenone **3i** and regenerate the key rhodium(I) species. This catalytic reaction system includes the decarbonylation of acylrodium species **A** to give arylrhodium species **D.**[20] Insertion of **2a** into the rhodium–aryl bond of **D** would give vinylrhodium species **E.** The CMD process would then give six-membered rhodacycle **F.** Reinsertion of CO followed by reductive elimination gives **3i′**.[21] We speculate that higher temperature would promote the cyclization of **A** to **B** and lead to the selective formation of **3i.**



Scheme 2 The use of norbornadiene (**2i**) as an acetylene equivalent.

A comparison with work from the Miura group is insightful. They previously reported that the dehydrogenative annulation of 1-naphthoic acid with diphenyl acetylene in the presence of a catalytic amount of [Cp*RhCl$_2$]$_2$ and a stoichiometric amount of Cu(OAc)$_2$ gave naphthopyranones. In that process, cyclization took place at an *ortho* C–H bond.[22] With the present reaction system, however, naphthopyranones were not



Scheme 3 Possible mechanism for rhodium-catalyzed dehydrative annulation.

detected, since the formation of mixed anhydrides and the oxidative addition of a C–O bond preceded C–H activation at the *ortho* position.

In summary, we have developed a convenient method for the synthesis of perinaphthenones *via* rhodium-catalyzed dehydrative annulation of naphthoic acids with alkynes, which gave good to high yields of perinaphthenones. Norbornadiene served as an acetylene equivalent in the present dehydrative annulation. With substituted naphthoic acids, carbonyl migrated products were formed, but this was effectively suppressed by elevated reaction temperatures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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