ORGANIC LETTERS

2012
Vol. 14, No. 6
1492–1495

Rhodium-Catalyzed C–H Bond Activation/[4 + 2] Annulation/Aromatization Cascade To Produce Phenol, Naphthol, Phenanthrenol, and Triphenylenol Derivatives

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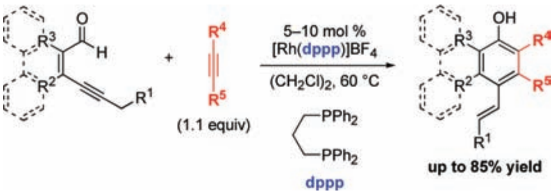
Received January 30, 2012

ABSTRACT



It has been established that a cationic rhodium(I)/dppp complex catalyzes the aldehyde C–H bond activation/[4 + 2] annulation/aromatization cascade to produce phenol, naphthol, phenanthrenol, and triphenylenol derivatives from readily available conjugated alkynyl aldehydes and alkynes.

The [4 + 2] annulation of five-membered acylmetal intermediates with alkenes or alkynes is a valuable method for the synthesis of six-membered carbonyl compounds.[1] Five-membered acylmetal intermediates can be generated through the reactions of transition-metal carbonyl complexes with alkynes[2,3] and the C–C bond cleavage of cyclobutenediones[4,5] or cyclobutanones[6,7] with transition-metal complexes. However, these strategies suffer from the toxicity of transition-metal carbonyl complexes or the difficult preparation of cyclobutenediones and cyclobutanones. Recently, convenient generation of five-membered acylmetal intermediates has been reported in the reactions of benzo-fused six-membered carbonyl compounds with nickel complexes through elimination of small organic fragments[8a,b] or acyl migration,[8c] while the atom replacement strategy conceptually lacks atom economy.[8a,b]

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(1) For reviews of transition-metal-catalyzed [4 + 2] carbocyclization reactions, see:(a) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 241. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (c) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (f) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.

(2) For a review, see:Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Iyer, S.; Leeds, J. P. *Tetrahedron* **1985**, *41*, 5839.

(3) (a) Reppe, W.; Vetter, H. *Justus Liebigs Ann. Chem.* **1953**, *582*, 133. (b) Maruyama, K.; Shio, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1877. (c) Foust, D. F.; Rausch, M. D. *J. Organomet. Chem.* **1982**, *239*, 321. (d) Cabrera, A.; Mondragón, J.; Torres, F.; Gómez, L. J. *Rev. Soc. Quim. Mex.* **1983**, *27*, 311.

(4) (a) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397. (b) Baysdon, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771. (c) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815. (d) Liebeskind, L. S.; Baysdon, S. L. *Tetrahedron Lett.* **1984**, *25*, 1747. (e) South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 4181. (f) Liebeskind, L. S.; Leeds, J. P.; Baysdon, S. L.; Iyer, S. *J. Am. Chem. Soc.* **1984**, *106*, 6451. (g) Liebeskind, L. S.; Baysdon, S. L.; Goedken, V.; Chidambaram, R. *Organometallics* **1986**, *5*, 1086. (h) Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759.

(5) For the rhodium-catalyzed [3 + 2] cycloaddition of cyclopropenones with alkynes, see:Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814.

(6) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.

(7) For construction of eight-membered rings from cyclobutanones, see: (a) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (b) Matsuda, T.; Fujimoto, A.; Ishibashi, M.; Murakami, M. *Chem. Lett.* **2004**, *33*, 876.

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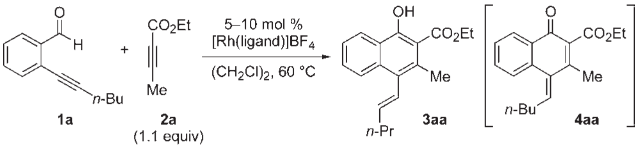
On the other hand, aldehyde C−H bond activation with rhodium followed by intramolecular *cis* addition of a rhodium acyl hydride to a C≡C triple bond affords a five-membered acylrhodium intermediate from a substituted 4-pentynal in a convenient and atom economical manner.[9] The five-membered acylrhodium intermediates thus generated have been utilized in [4 + 2] annulation reactions with alkynes,[9,10] alkenes,[10,11] and isocyanates.[12] Not only substituted 4-pentynal but also 2-alkynylbenzaldehydes are able to participate in the [4 + 2] annulation with carbonyl compounds[13] as well as alkenes[11] and isocyanates.[12] However, the aldehyde C−H bond activation/[4 + 2] annulation cascade of 2-alkynylbenzaldehydes with alkynes has not been reported.

We have previously reported the aldehyde C−H bond activation/[4 + 2] annulation/aromatization cascade of 2-vinylbenzaldehyde with alkynes, while accessible products and usable alkyne substrates were limited to 4-methyl-1-naphthol derivatives and terminal alkynes, respectively.[14,15] Herein, we disclose the synthesis of phenol, naphthol, phenanthrenol, and triphenylenol derivatives via the aldehyde C−H bond activation/[4 + 2] annulation/aromatization cascade of readily available conjugated alkynyl aldehydes including 2-alkynylbenzaldehydes and both internal and terminal alkynes by using a cationic rhodium(I)/dppp complex as a catalyst.

As electron-deficient internal alkynes exhibited high reactivity in the cationic rhodium(I)/dppe complex-catalyzed [4 + 2] annulation with substituted 4-pentynals,[9] we first examined the [4 + 2] annulation of 2-alkynylbenzaldehyde **1a** with electron-deficient internal alkyne **2a** (Table 1). In this annulation, not the expected tetralone **4aa** but the aromatized product **3aa** was isolated. The ligand screening (Figure 1 and Table 1, entries 1−4) revealed that the use of dppp furnished **3aa** in the highest yield with perfect regioselectivity (entry 2).[16] The catalyst loading could be reduced to 5 mol % under the prolonged reaction time without erosion of the product yield (entry 5).

Table 1. Optimization of Reaction Conditions for Rh-Catalyzed Reaction of 2-Alkynylbenzaldehyde **1a** and Alkyne **2a**[a]



entry	ligand	catalyst (mol %)	time (h)	conv (%)[b]	yield (%)[c]
1	dppe	10	18	50	<5
2	dppp	10	18	100	55
3	dppb	10	18	91	21
4	dppf	10	18	29	5
5[d]	dppp	5	36	100	56

[a] [Rh(ligand)]BF$_4$ (0.010 mmol), **1a** (0.10 mmol), **2a** (0.11 mmol), and (CH$_2$Cl)$_2$ (1.0 mL) were used. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] [Rh(dppp)]BF$_4$ (0.010 mmol), **1a** (0.20 mmol), **2a** (0.22 mmol), and (CH$_2$Cl)$_2$ (1.0 mL) were used.

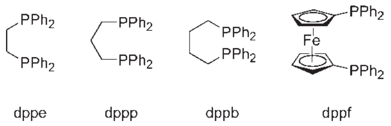


Figure 1. Structures of bisphosphine ligands.

We then explored the scope of this process with respect to both alkynes and alkynylarylaldehydes by employing the above optimal reaction conditions (Table 2). With respect to alkynes, not only ethyl 2-butynoate (**2a**, entry 1) but also ethyl 3-phenylpropiolate (**2b**, entry 2) could participate in this reaction to give the corresponding 1-naphthol in moderate yield.[17] Interestingly, electron-rich internal alkyne **2c** was found to be more reactive than electron-deficient ones by using dppf as a ligand (entry 3 vs entries 1 and 2);[18] however, not 1-naphthol but tetralone **4ac** was isolated.[19] Terminal alkyne **2d** could also

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(9) Tanaka, K.; Fu, G. C. *Org. Lett.* **2002**, *4*, 933.

(10) Recently, the novel rhodium-catalyzed aldehyde C−H bond activation/intramolecular [6 + 2] annulation of 4-allenals with alkynes or alkenes was reported. See: Oonishi, Y.; Hosotani, A.; Sato, Y. *J. Am. Chem. Soc.* **2011**, *133*, 10386.

(11) (a) Tanaka, K.; Hagiwara, Y.; Noguchi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7260. (b) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Eur. J. Org. Chem.* **2006**, 3582.

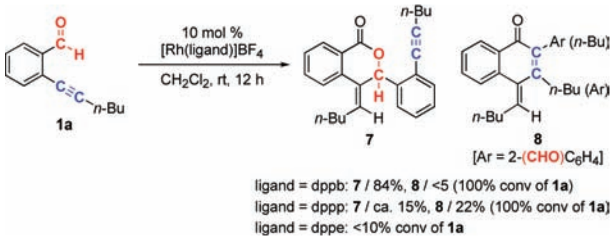
(12) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734.

(13) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820.

(14) (a) Tanaka, K.; Hojo, D.; Shoji, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 2059. For the homo-[4 + 2] annulation of 2-vinylbenzaldehyde, see: (b) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

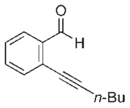
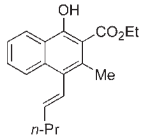
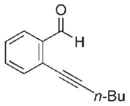
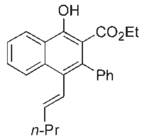
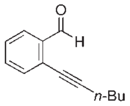
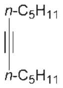
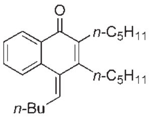
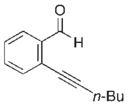
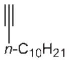
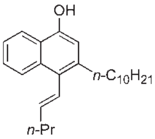
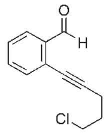
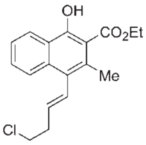
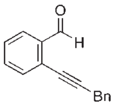
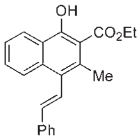
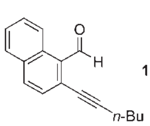
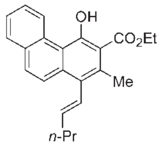
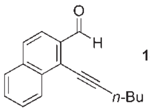
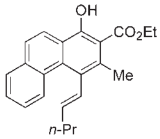
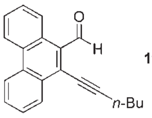
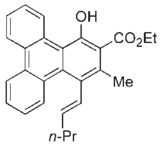
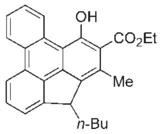
(15) For recent reviews of cascade reactions, see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (c) Arns, S.; Barriault, L. *Chem. Commun.* **2007**, 2211. (d) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (e) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (g) Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129. (h) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, Germany, 2006. (i) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (j) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

(16) The observed ligand effect is consistent with the chemoselectivity in the homo-[4 + 2] annulation of **1a**. In our previous report, the reaction of **1a** in the presence of a cationic rhodium(I)/dppb complex furnished dimer **7** in high yield through the homo-[4 + 2] annulation with the carbonyl moiety of **1a** (ref 12). On the other hand, the use of dppp as a ligand furnished dimer **8** as well as dimer **7**, through the homo-[4 + 2] annulation with the alkyne moiety of **1a**. The use of dppe, possessing a smaller dihedral angle, as a ligand led to poor conversion of **1a**.



ligand = dppb: **7** / 84%, **8** / <5 (100% conv of **1a**)
ligand = dppp: **7** / ca. 15%, **8** / 22% (100% conv of **1a**)
ligand = dppe: <10% conv of **1a**

Table 2. Rh-Catalyzed Synthesis of Substituted Naphthol, Phenanthrenol, and Triphenylenol Derivatives[a]

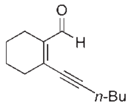
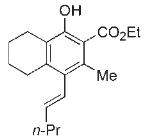
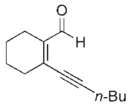
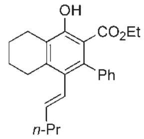
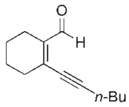
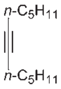
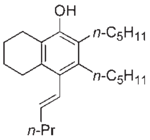
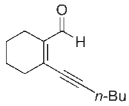
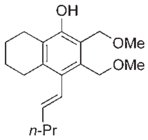
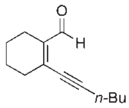
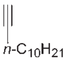
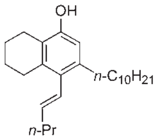
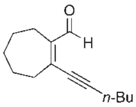
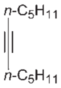
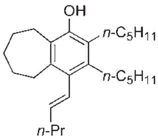
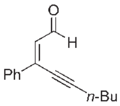
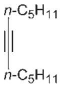
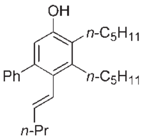
entry	1		2		catalyst / time	3 / yield[b]	
1		1a		2a	5 mol % 36 h		3aa 56%
2		1a		2b	10 mol % 12 h		3ab 43%
3		1a		2c	10 mol % 18 h		4ac 81%[c]
4		1a		2d	10 mol % 12 h		3ad 38%
5		1b		2a	10 mol % 18 h		3ba 44%
6		1c		2a	5 mol % 72 h		3ca 46%
7		1d		2a	10 mol % 36 h		3da 71%
8		1e		2a	10 mol % 36 h		3ea 37%
9		1f		2a	10 mol % 18 h		3fa 31%
							5fa 21%

[a] Reactions were conducted using [Rh(dppp)]BF_4 (0.010−0.020 mmol), **1a**−**f** (0.20 mmol), and **2a**−**d** (0.22 mmol) in $(CH_2Cl)_2$ (1.0 mL) at 60 °C. [b] Isolated yield. [c] Ligand: dppf.

participate in this reaction, although the product yield was low (entry 4). With respect to 2-alkynylbenzaldehydes, not only **1a** but also chloropropyl- and benzyl-substituted 2-alkynylbenzaldehydes **1b**,**c** could participate in this reaction (entries 5 and 6).[20] Furthermore, phenanthrenol derivatives (**3da** and **3ea**, entries 7 and 8) could be synthesized from alkynylnaphthaldehydes **1d**,**e**. Alkynyl phenanthrene aldehyde **1f** was also able to react with **2a** to produce triphenylenol **3fa** along with pentacyclic compound **5fa**, which would be generated through the intramolecular Friedel−Crafts alkylation of **3fa** (entry 9).

In our previous aldehyde C−H bond activation/[4 + 2] annulation/aromatization cascade of 2-vinylbenzaldehyde with alkynes,[14] 2-vinyl-1-cyclohexene-1-carboxaldehyde could not be employed in place of 2-vinylbenzaldehyde. However, pleasingly, 2-alkynyl-1-cyclohexene-1-carboxaldehyde **1g** could be employed in place of 2-alkynylbenzaldehydes. Alkynyl aldehyde **1g** reacted with various internal

Table 3. Rh-Catalyzed Synthesis of Substituted Phenol Derivatives[a]

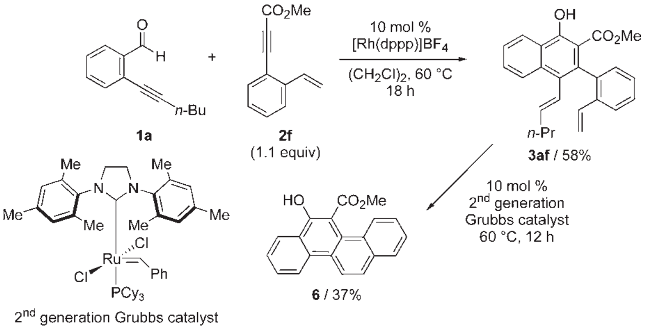
entry	1		2		catalyst / time	3 / yield[b]	
1		1g		2a	5 mol % 36 h		3ga 68%
2		1g		2b	5 mol % 36 h		3gb 75%
3		1g		2c	5 mol % 36 h		3gc 85%
4		1g		2e	5 mol % 36 h		3ge 65%
5		1g		2d	5 mol % 72 h		3gd 61%
6		1h		2c	10 mol % 72 h		3hc 51%
7		1i		2c	10 mol % 72 h		3ic 77%

[a] Reactions were conducted using [Rh(dppp)]BF_4 (0.010−0.020 mmol), **1g**−**i** (0.20 mmol), and **2a**−**e** (0.22 mmol) in $(CH_2Cl)_2$ (1.0 mL) at 60 °C. [b] Isolated yield.

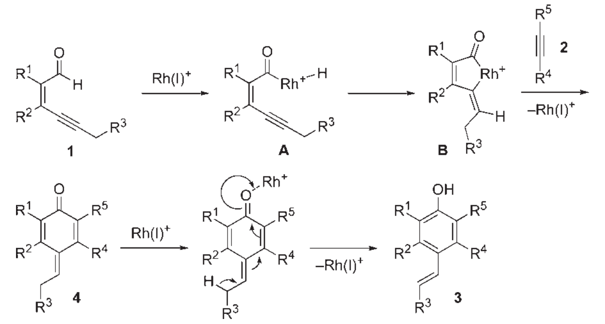
and terminal alkynes **2a**−**e** to give bicyclic phenol derivatives in higher yields (Table 3, entries 1−5) than the use of 2-alkynylbenzaldehyde **1a** (Table 1, entries 1−4).[17] In this annulation, the use of electron-rich internal alkynes **2c**,**e** furnished not the corresponding tetralones but aromatized products **3gc** and **3ge** in good yields (entries 3 and 4).[19] Although the product yield was moderate, 2-alkynyl-1-cycloheptene-1-carboxaldehyde **1h** could participate in this reaction (entry 6). Finally, acyclic alkynyl aldehyde **1i** reacted with **2c** to give monocyclic phenol **3ic** in good yield (entry 7).

A combination of the present cascade reaction and intramolecular olefin metathesis was able to provide a chrysenol derivative. The reaction of 2-alkynylbenzaldehyde **1a** with enyne **2f** furnished diene **3af**. Treatment of **3af** with the second generation Grubbs catalyst [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium] furnished chrysenol **6** (Scheme 1).

Scheme 1



Scheme 2



A possible mechanism for the present [4 + 2] annlation is shown in Scheme 2. The rhodium catalyst oxidatively inserts into the aldehyde C−H bond of alkynyl aldehyde **1**, affording rhodium acyl hydride **A**. Then *cis* addition of the rhodium hydride to the metal-bound $C\equiv C$ triple bond provides five-membered acylrhodium intermediate **B**. Insertion of alkyne **2** followed by reductive elimination furnishes 4-alkylidene-1-tetralone **4** and regenerates the rhodium catalyst. This 4-alkylidene-1-tetralone **4** is aromatized to phenol **3** presumably through the coordination of the cationic rhodium to the carbonyl oxygen.[21]

In conclusion, we have developed the aldehyde C−H bond activation/[4 + 2] annulation/aromatization cascade to produce phenol, naphthol, phenanthrenol, and triphenylenol derivatives from readily available conjugated alkynyl aldehydes and alkynes by using a cationic rhodium(I)/dppp complex as a catalyst. Future work will focus on further utilization of cyclic acylrhodium intermediates in organic synthesis.

Acknowledgment. This work was supported partly by a Grant-in-Aid for Scientific Research (No. 20675002) from MEXT, Japan. We thank Umicore for generous support in supplying a rhodium complex.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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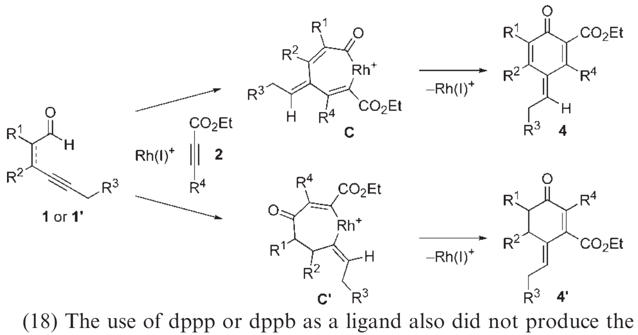
(17) In the previous rhodium-catalyzed [4 + 2] annulations of nonconjugated 4-alkynals **1′** with alkynes **2** or acrylamides, the electron-deficient groups were located at the meta position with respect to the ketone moiety (refs 9 and 11). On the contrary, the electron-deficient ethoxycarbonyl group was located at the ortho position with respect to the ketone moiety in the present [4 + 2] annulation of conjugated 4-alkynals **1** with alkynes **2**. A possible explanation of these opposite regioselectivities is the site-selective alkyne insertion to generate intermediate **C** or **C′**, which furnishes product **4** or **4′**, although the precise reason is not clear at the present stage.



(18) The use of dppp or dppb as a ligand also did not produce the corresponding 1-naphthol and lowered the yield of tetralone **4ac**.

(19) The bulky rhodium(I) complex might coordinate weakly to the sterically crowded carbonyl oxygen of 4-alkylidene-1-tetralone **4ac**, which deters the aromatization to the 1-naphthol. On the other hand, the aromatization to 1-naphthol **3ad** proceeds smoothly presumably due to the low steric hindrance, and that to hydroxycarboxylic acid esters also proceeds smoothly presumably due to the facile bidentate chelation of rhodium to two carbonyl oxygen atoms of 2-ethoxylcarbonyl-1-tetralones. On the other hand, the aromatization of 4-alkylidene-1-cyclohexadienones to phenols proceeds smoothly presumably due to the thermodynamic stability of products.

(20) The reactions of 2-phenylethynylbenzaldehyde and 2-cyclohex-1-enylethynylbenzaldehyde with alkynes were also investigated, while complex mixtures of products were generated.

(21) For an example of the acid-mediated aromatization of 4-alkylidene-1-tetralone derivatives to 4-alkenylphenol derivatives through protonation of the carbonyl oxygen, see: Jansen, R.; Gerth, K.; Steinmetz, H.; Reinecke, S.; Kessler, W.; Kirschning, A.; Müller, R. *Chem.—Eur. J.* **2011**, *17*, 7739.