Synthetic Methods

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Enantioselective Synthesis of Spirocyclic Benzopyranones by Rhodium-Catalyzed Intermolecular [4+2] Annulation**

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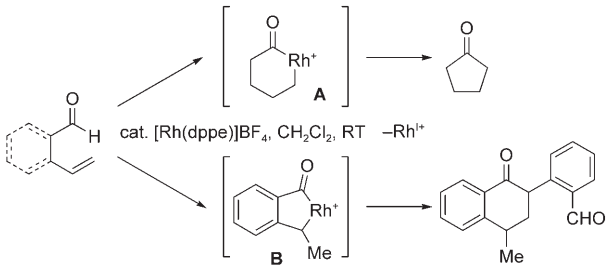
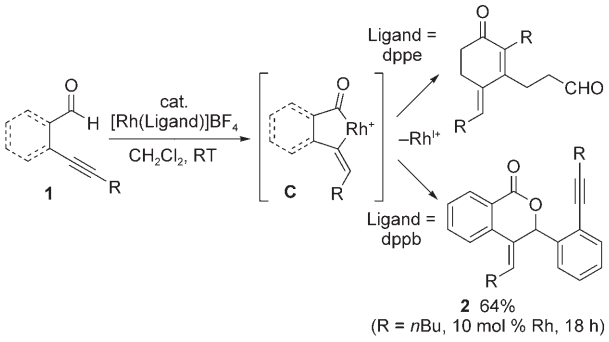
The hydroacylation of 4-alkenals[1,2] and 4-alkynals[3,4] catalyzed by a cationic rhodium(I)/bisphosphine complex is a well-established method for the synthesis of cyclopentanones and cyclopentenones, respectively, in an atom-economical manner. The hydroacylation of 4-pentenal to give cyclopentanone in high yield via the six-membered rhodacycle **A** is catalyzed by a cationic rhodium(I)/1,2-bis(diphenylphosphino)ethane (dppe) complex (Scheme 1).[5] In contrast, the



Scheme 1. Rh-catalyzed cyclization and dimerization of 4-alkenals.

reaction of a benzene-linked 4-alkenal, namely 2-vinylbenzaldehyde, with the same rhodium catalyst furnishes an unexpected dimerization product in high yield by an intermolecular homo-[4+2] annulation between five-membered rhodacycle **B** and the double bond of 2-vinylbenzaldehyde (Scheme 1).[6–8] The reaction of a 4-alkynal with the cationic rhodium(I)/dppe complex furnishes a similar dimerization product in high yield by an intermolecular homo-[4+2] annulation between five-membered rhodacycle **C** and the triple bond of the 4-alkynal (Scheme 2).[9] Thus, we examined the reactions of a benzene-linked 4-alkynal, namely, 2-hexynylbenzaldehyde (**1a**), with various cationic rhodium(I)/bisphosphine complexes. Surprisingly, the unexpected dimerization product **2** was obtained in good yield at room temperature by using the cationic rhodium(I)/1,4-bis(diphenylphosphino)-butane (dppb) complex, presumably by an intermolecular homo-[4+2] annulation between five-membered rhodacycle **C** and the carbonyl group of **1a** (Scheme 2),[10–12] although no reaction was observed in the presence of the cationic rhodium(I)/dppe complex.



Scheme 2. Rh-catalyzed dimerizations of 4-alkynals.

A cross-[4+2] annulation of **1a** with excess benzaldehyde (**3a**, 5 equiv) was investigated in the presence of 10 mol% of the cationic rhodium(I)/dppb or rhodium(I)/1,1′-bis(diphenylphosphino)ferrocene (dppf) complexes, but the desired cross-annulation product **4aa** was only obtained in low yields (Table 1, entries 1 and 2).[13] A number of cationic rhodium(I)/chiral bisphosphine complexes were screened for their ability to effect a chemo- and enantioselective cross-[4+2] annulation (Scheme 3; Table 1, entries 3–11). We were pleased to find that the use of (*R*,*R*)-walphos ((*R*,*R*)-**10**) as a chiral ligand furnished **4aa** in an improved yield with good enantioselectivity (Table 1, entry 11).

The reaction of **1a** with **3a** could be carried out using 5 mol% of the Rh catalyst to furnish **4aa** with an identical *ee* value, while the yield decreased to 31% (Scheme 4). The amount of carbonyl compound could be reduced to two equivalents by using electron-deficient ketoester **3b**, although slight erosion of the *ee* value was observed (Scheme 4).[14] Fortunately, the reaction of 2-alkynylbenzaldehyde **1a** with only a slight excess of the cyclic electron-deficient carbonyl compound *N*-methylisatin (**3c**) in the presence of 5 mol% of the cationic rhodium(I)/(*R*,*R*)-**10** complex proceeded at room temperature to give the corresponding spirocyclic benzopyranone **4ac** in high yield and high enantioselectivity (Table 2, entry 1).[15,16]

We then explored the scope of this process with respect to both 2-alkynylbenzaldehydes and cyclic carbonyl compounds.

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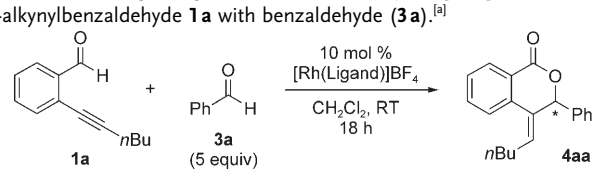
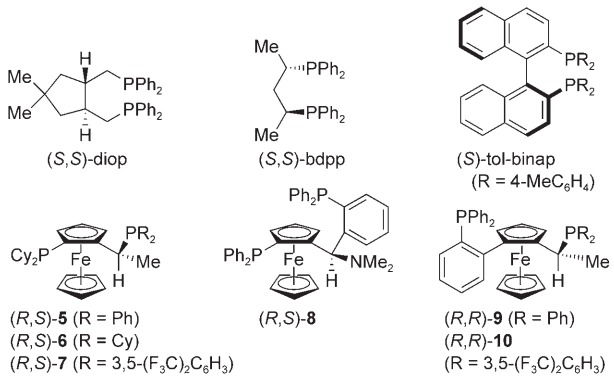
Table 1: Screening of ligands for the Rh-catalyzed [4+2] annulation of 2-alkynylbenzaldehyde **1a** with benzaldehyde (**3a**).[a]

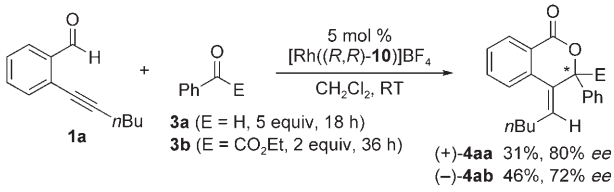


Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	dppb	28	–
2	dppf	13	–
3	(*S*,*S*)-diop	< 5	< 5 (−)
4	(*S*,*S*)-bdpp	12	9 (−)
5	(*S*)-tol-binap	23	19 (+)
6	(*R*,*S*)-**5**	31	14 (+)
7	(*R*,*S*)-**6**	11	26 (+)
8	(*R*,*S*)-**7**	23	< 5 (+)
9	(*R*,*S*)-**8**	0	–
10	(*R*,*R*)-**9**	26	6 (+)
11	(*R*,*R*)-**10**	47	80 (+)

[a] [Rh(ligand)]BF_4 (0.010 mmol, 10 mol%), **1a** (0.10 mmol), and **3a** (0.50 mmol, 5 equiv) in CH_2Cl_2 (1.0 mL) were used. [b] Yield of isolated product. [c] All the *ee* values were measured by HPLC on chiral stationary phases.



Scheme 3. Structures of chiral bisphosphine ligands. Cy = cyclohexyl.



Scheme 4. Rh-catalyzed enantioselective [4+2] annulation of **1a** with benzaldehyde (**3a**) and linear dicarbonyl compound **3b**.

Table 2: Rh-catalyzed enantioselective [4+2] annulation of **1a–e** with cyclic dicarbonyl compounds **3c–f**.[a]

Entry	**1** (R)	**3**	**4**, yield [%][b], *ee* [%][c]
1	**1a** (*n*Bu)	**3c**	(−)-**4ac**, 95, 93
2	**1b** (Cy)	**3c**	(−)-**4bc**, 84, 93
3[d]	**1c** ($Cl(CH_2)_3$)	**3c**	(−)-**4cc**, 97, 93
4	**1d** (Ph)	**3c**	(−)-**4dc**, 96, > 99
5[e]	**1e** (2-ClC_6H_4)	**3c**	(−)-**4ec**, 90, 98
6	**1a**	**3d**	(−)-**4ad**, 96, 92
7	**1a**	**3e**	(−)-**4ae**, 78, 89
8	**1a** (*n*Bu)	**3f**	(−)-**4af**, 77, 93
9[e]	**1a** (*n*Bu)	**3f**	(−)-**4af**, 86, 93
10[e]	**1b** (Cy)	**3f**	(−)-**4bf**, 87, 92
11[e]	**1c** ($Cl(CH_2)_3$)	**3f**	(*S*)-(−)-**4cf**, 77, 94
12[e]	**1d** (Ph)	**3f**	(−)-**4df**, 73, 98

[a] Reactions were conducted using [Rh((*R*,*R*)-**10**)]BF_4 (0.010 mmol, 5 mol%), **1a–e** (0.20 mmol), and **3c–f** (0.22 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) at RT for 18–72 h. [b] Yield of isolated product. [c] All the *ee* values were measured by HPLC on chiral stationary phases. [d] Catalyst: 7.5 mol%. [e] Catalyst: 10 mol%.

Both alkyl- (**1a** and **1b**; Table 2, entries 1 and 2) and chloroalkyl-substituted (**1c**; Table 2, entry 3) 2-alkynylbenzaldehydes reacted with **3c** to give the corresponding spirocyclic benzopyranones in high yields and high *ee* values. Not only alkyl but also phenyl- (**1d**; Table 2, entry 4) and 2-chlorophenyl-substituted (**1e**; Table 2, entry 5) 2-alkynylbenzaldehydes could participate in this reaction to give products with higher *ee* values. With respect to the cyclic carbonyl compounds, *N*-phenylisatin (**3d**; Table 2, entry 6) and NH-isatin (**3e**; Table 2, entry 7) could also participate in this reaction. Furthermore, acenaphthenequinone (**3f**) reacted with 2-alkynylbenzaldehydes **1a–d** in high yields and high enantioselectivity in the presence of the cationic rhodium(I)/(*R*,*R*)-**10** complex, despite its poor solubility in CH_2Cl_2 (Table 2, entries 8–12).[17] The absolute configuration of (−)-**4cf** was determined to be *S* by X-ray crystallographic analysis (Figure 1).[18]

In conclusion, we have developed a cationic rhodium(I)/(*R*,*R*)-walphos-catalyzed highly enantioselective [4+2] annulation of 2-alkynylbenzaldehydes with cyclic electron-deficient carbonyl compounds that leads to enantioenriched spirocyclic benzopyranones and isatin derivatives.[19] As cyclic electron-deficient carbonyl compounds (both isatin derivatives and acenaphthenequinone) are commercially available, and 2-alkynylbenzaldehydes can be prepared in one step by the Sonogashira coupling of commercially available terminal alkynes with 2-bromobenzaldehyde, this method serves as an attractive two-step route to enantioenriched spirocyclic benzopyranones and isatin derivatives starting from commer-

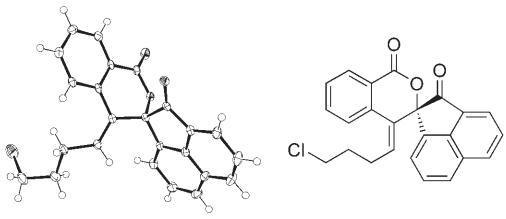


Figure 1. ORTEP drawing (*S*)-(−)-**4cf** drawn at the 50% probability level.

cially available reagents. Further expansion of the reaction scope is currently underway.

Experimental Section

Representative procedure (Table 2, entry 1): In an argon atmosphere, a solution of (*R*,*R*)-**10** (9.3 mg, 0.010 mmol) in CH_2Cl_2 (0.3 mL) was added to a solution of $[Rh(cod)_2]BF_4$ (4.1 mg, 0.010 mmol; cod = cycloocta-l,5-diene) in CH_2Cl_2 (0.3 mL), and the mixture was stirred at room temperature for 5 min. H_2 was then introduced to the resulting solution in a Schlenk tube. After stirring the mixture at room temperature for 1 h, the resulting solution was concentrated to dryness and dissolved in CH_2Cl_2 (0.5 mL). A solution of **1a** (37.3 mg, 0.200 mmol) and **3c** (35.5 mg, 0.220 mmol) in CH_2Cl_2 (1.5 mL) was added to this solution, and the mixture stirred at room temperature for 18 h. The resulting solution was concentrated and purified by preparative TLC (hexane/EtOAc 4:1), which furnished (−)-**4ac** (66.5 mg, 0.191 mmol, 95% yield, 93% *ee*) as a brown solid. M.p. 96–97 °C; $[\alpha]_D^{25} = -52.9°$ ($c = 3.23\ g\,cm^{-3}$ in $CHCl_3$, 93% *ee*); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.23$–8.14 (m, 1H), 7.65 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.55–7.45 (m, 2H), 7.40 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.21 (dd, $J = 7.5$, 1.2 Hz, 1H), 7.10 (dt, $J = 7.5$, 0.6 Hz, 1H), 6.88 (d, $J = 7.5$ Hz, 1H), 5.72 (dd, $J = 8.1$, 6.3 Hz, 1H), 3.12 (s, 3H), 2.54–2.29 (m, 2H), 1.48–1.18 (m, 4H), 0.86 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.2$, 163.9, 143.8, 136.4, 134.9, 133.1, 131.0, 129.7, 128.5, 127.8, 126.8, 126.0, 125.7, 125.4, 123.1, 108.8, 84.8, 31.6, 28.8, 26.3, 22.2, 13.7 ppm; IR (KBr): $\tilde{\nu} = 3437$, 3073, 2928, 1727, 765 cm^{-1}; HRMS (ESI): calcd for $C_{22}H_{21}NO_3Na$: 370.1419, found: 370.1408 $[M+Na]^+$; CHIRALCEL OD-H, hexane/2-PrOH 90:10, 1.0 mL min^{-1}, t_r: 18.5 min (minor isomer) and 30.1 min (major isomer).

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[1] For pioneering work on the Rh-catalyzed hydroacylation of 4-alkenals, see: K. Sakai, J. Ide, O. Oda, N. Nakamura, *Tetrahedron Lett.* **1972**, *13*, 1287.
[2] For reviews, see: a) K. Sakai, *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 733; b) B. Bosnich, *Acc. Chem. Res.* **1998**, *31*, 667; c) M. Tanaka, K. Sakai, H. Suemune, *Curr. Org. Chem.* **2003**, *7*, 353.
[3] For pioneering work on the Rh-catalyzed hydroacylation of 4-alkynals, see: K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 11492.
[4] For reviews, see: a) G. C. Fu in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, p. 79; b) K. Tanaka, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 351.
[5] a) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 936; b) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 946.
[6] a) K. Kundu, J. V. McCullagh, A. T. Morehead, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 16042; b) K. Tanaka, D. Hojo, T. Shoji, Y. Hagiwara, M. Hirano, *Org. Lett.* **2007**, *9*, 2059.
[7] For pioneering work on the [4+2] annulation via acylmetal intermediates generated by cleavage of a C−C bond of cyclobutenediones, see: L. S. Liebeskind, S. L. Baysdon, M. S. South, *J. Am. Chem. Soc.* **1980**, *102*, 7397.
[8] For the [4+2] annulation via acylrhodacylces generated by cleavage of a C−C bond of cyclobutanones, see: M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976.
[9] K. Tanaka, G. C. Fu, *Org. Lett.* **2002**, *4*, 933.
[10] For examples of carbonyl insertion into a Rh−C bond, see: a) C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1674; b) T. Fujii, T. Koike, A. Mori, K. Osakada, *Synlett* **2002**, 298; c) B. Bennacer, M. Fujiwara, S.-Y. Lee, I. Ojima, *J. Am. Chem. Soc.* **2005**, *127*, 17756; d) J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16040; e) K. Tanaka, Y. Otake, A. Wada, K. Noguchi, M. Hirano, *Org. Lett.* **2007**, *9*, 2203; f) K. Tsuchikama, Y. Yoshinami, T. Shibata, *Synlett* **2007**, 1395.
[11] Very recently, we reported the Rh^I/H_8-binap-catalyzed regio-, diastereo-, and enantioselective [2+2+2] cycloaddition of 1,6-enynes with electron-deficient ketones, see: K. Tanaka, Y. Otake, H. Sagae, K. Noguchi, M. Hirano, *Angew. Chem.* **2008**, *120*, 1332; *Angew. Chem. Int. Ed.* **2008**, *47*, 1312.
[12] For a Rh-catalyzed [4+2] annulation of 4-alkynals with electron-deficient alkenes, see: a) K. Tanaka, Y. Hagiwara, K. Noguchi, *Angew. Chem.* **2005**, *117*, 7426; *Angew. Chem. Int. Ed.* **2005**, *44*, 7260; b) K. Tanaka, Y. Hagiwara, M. Hirano, *Eur. J. Org. Chem.* **2006**, 3582; with isocyanates, see: c) K. Tanaka, Y. Hagiwara, M. Hirano, *Angew. Chem.* **2006**, *118*, 2800; *Angew. Chem. Int. Ed.* **2006**, *45*, 2734.
[13] Possible chelation of 2-alkynylbenzaldehyde **1a** to the cationic rhodium center may account for the higher reactivity observed for **1a** compared to benzaldehyde (**3a**).
[14] The higher reactivity of ketoester **3b** than **1a** and **3a** is presumably due to its electron-deficient nature and the strong bidentate coordination of its two carbonyl groups to the cationic rhodium center.
[15] Synthesis of a chiral spirocyclic compound by the Rh^{I+}/H_8-binap-catalyzed enantioselective [2+2+2] cycloaddition of an 1,6-enyne with *N*-methylisatin has been reported; see: Ref. [11].
[16] Although the precise mechanism for the high enantioselectivity and reactivity observed with cyclic dicarbonyl compounds **3c**–**f** is not clear at the present stage, the rigid bidentate coordination of their two carbonyl groups to the cationic rhodium center may construct the rigid chiral environment and enhance the reactivity.
[17] Although acenaphthenequinone (**3f**) was initially suspended in CH_2Cl_2, a clear solution was generated after completion of the reaction.
[18] CCDC 683327 [(*S*)-(−)-**4cf**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[19] Spirocyclic isatin derivatives are found in pharmaceutically important compounds, see: S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron* **2007**, *63*, 5579, and references therein.

