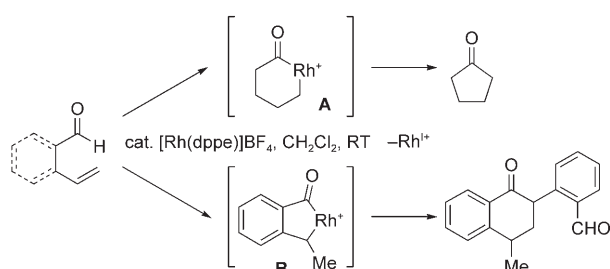


Enantioselective Synthesis of Spirocyclic Benzopyranones by Rhodium-Catalyzed Intermolecular [4+2] Annulation**

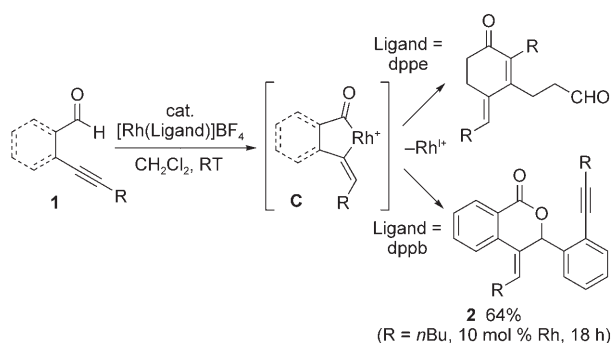
Daiki Hojo, Keiichi Noguchi, Masao Hirano, and Ken Tanaka*

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-hexynyl-



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

benzaldehyde (**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.

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.

[*] D. Hojo, Dr. M. Hirano, Prof. Dr. K. Tanaka
Department of Applied Chemistry
Graduate School of Engineering
Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)
Fax: (+81) 42-388-7037
E-mail: tanaka-k@cc.tuat.ac.jp

Prof. Dr. K. Noguchi
Instrumentation Analysis Center
Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)

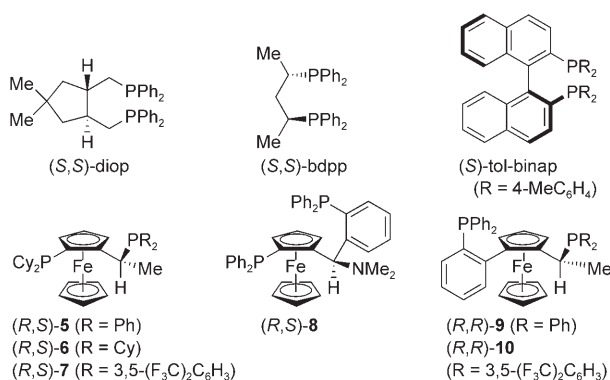
[**] This work was partly supported by a Grant-in-Aid for Scientific Research (No. 19028015) from MEXT Japan and the Kato Memorial Foundation. We thank Solvias AG for the gift of chiral ferrocenyl bisphosphine ligands under their University Ligand Kit program. We also thank Y. Hagiwara for his preliminary experiments.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801642>.

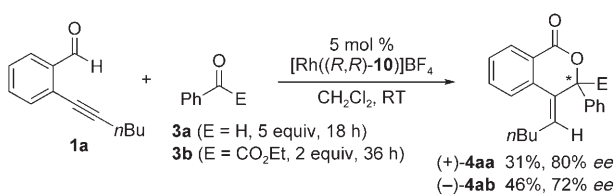
Table 1: Screening of ligands for the Rh-catalyzed [4+2] annulation of 2-alkynylbenzaldehyde **1a** with benzaldehyde (**3a**).^[a]

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)]BF₄ (0.010 mmol, 10 mol %), **1a** (0.10 mmol), and **3a** (0.50 mmol, 5 equiv) in CH₂Cl₂ (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**.

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)

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 (<i>n</i> 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 ₆ H ₄)	3c	(–)- 4ec , 90, 98
6	1a	3d	(–)- 4ad , 96, 92
7	1a	3e	(–)- 4ae , 78, 89
8	1a (<i>n</i> Bu)	3f	(–)- 4af , 77, 93
9 ^[e]	1a (<i>n</i> 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**)]BF₄ (0.010 mmol, 5 mol %), **1a–e** (0.20 mmol), and **3c–f** (0.22 mmol, 1.1 equiv) in CH₂Cl₂ (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 %.

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 CH₂Cl₂ (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-

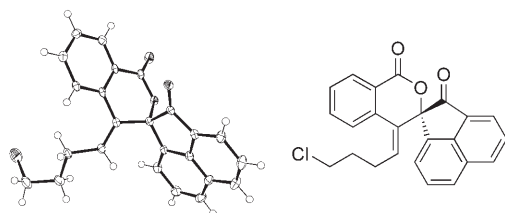


Figure 1. ORTEP drawing (S)-(-)-**4cf** drawn at the 50% probability level.

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 $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (4.1 mg, 0.010 mmol; cod = cycloocta-1,5-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; $[\alpha]_D^{25} = -52.9^\circ$ ($c = 3.23 \text{ g cm}^{-3}$ in CHCl_3 , 93% ee); $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 8.23\text{--}8.14$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{Na}$: 370.1419, found: 370.1408 [$M+\text{Na}$] $^+$; 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).

Received: April 8, 2008

Published online: June 23, 2008

Keywords: aldehydes · alkynes · annulation · asymmetric catalysis · rhodium

- [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 $\text{Rh}^{\text{I}}/\text{H}_8\text{-binap}$ -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 $\text{Rh}^{\text{I}}/\text{H}_8\text{-binap}$ -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.