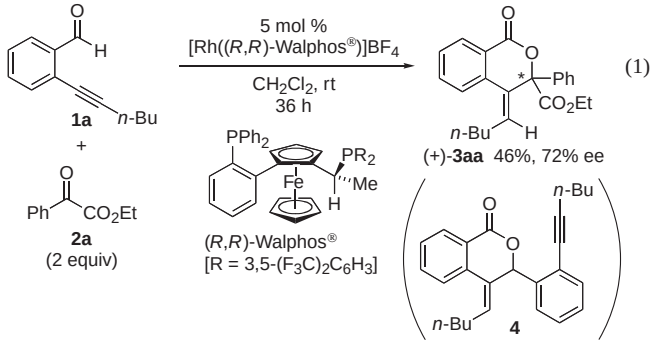
Rhodium-catalyzed Highly Enantioselective [4 + 2] Annulation of 2-Alkynylbenzaldehydes with Acyl Phosphonates

Ken Tanaka,*[1] Rie Tanaka,[1] Goushi Nishida,[1] Keiichi Noguchi,[2] and Masao Hirano[1]
[1]*Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588*
[2]*Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588*

(Received June 12, 2008; CL-080589; E-mail: tanaka-k@cc.tuat.ac.jp)

A cationic rhodium(I)/(*R*)-Segphos® [(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine)] complex catalyzes the highly enantioselective [4 + 2] annulation of 2-alkynylbenzaldehydes with acyl phosphonates, leading to benzopyranones with a phosphonate-substituted quaternary carbon center in moderate to high yields with excellent ee's.

The [4 + 2] cycloaddition of five-membered acylmetal intermediates with unsaturated compounds is a useful method for the synthesis of six-membered carbonyl compounds.[1–3] The convenient generation of five-membered acylrhodium intermediates was realized by intramolecular cis addition of a rhodium acyl hydride to a metal-bound triple bond of 4-alkynals.[3] We have recently reported that the reactions of 2-alkynylbenzaldehydes with slight excess (1.1 equiv) of electron-deficient cyclic dicarbonyl compounds in the presence of a catalytic amount of a cationic Rh^I/(*R*,*R*)-Walphos® complex furnished spirocyclic benzopyranones in high yields with high ee's presumably through the cross-[4 + 2] cycloaddition between five-membered acylrhodium intermediates and the carbonyl groups of the cyclic dicarbonyl compounds.[4] The use of chelating cyclic dicarbonyl compounds efficiently suppressed the homo-[4 + 2] annulation. However, the reaction of 2-alkynylbenzaldehyde **1a** with excess electron-deficient acyclic ketoester **2a** (2 equiv) in the presence of the same rhodium catalyst furnished the corresponding benzopyranone **3aa** in moderate yield and ee, together with the homo-[4 + 2] annulation product **4** as a major by-product (eq 1).[4,5]

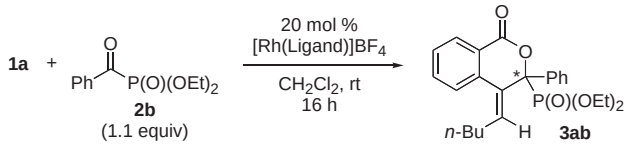


(1)

On the other hand, transition-metal-catalyzed [2 + 2 + 2] cycloadditions of diynes or enynes with carbonyl compounds have been developed for the preparation of six-membered oxygen heterocycles by using Ni,[6] Ru,[7] and Rh[8] complexes. Our recent investigation revealed that not only ketoesters but also acyl phosphonates could be employed as a coupling partner for the cationic Rh^I/H_8–BINAP-catalyzed [2 + 2 + 2] cycloaddition [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl].[9] We anticipated that the reaction of **1a** with benzoyl phosphonate **2b**, that may be more coordinative to the cationic rhodium than ketoester **2a**, would show high chemoselectivity toward the cross-annulation over the homo-annulation. Thus, the reaction of 2-alkynylbenzaldehyde **1a** with benzoyl phosphonate **2b** was investigated in the presence of the cationic Rh^I/(*R*,*R*)-Walphos® catalyst, but no reaction was observed (Table 1, Entry 1). Fortunately, the use of (*R*)-H_8–BINAP as a ligand, which is effective for the [2 + 2 + 2] cycloaddition of α,ω-diynes with acyl phosphonates,[9] furnished **3ab** in moderate yield without employing excess **2b**, although the enantioselectivity was low (Entry 2). To improve the yield and ee of **3ab**, various axially chiral biarylbisphosphine ligands were screened (Entries 2–5). The study revealed that the ee value of **3ab** is dependent on the dihedral angle of the biarylbisphosphine ligands [dihedral angle: (*R*)-H_8–BINAP (Entry 2) > (*R*)-BINAP (Entry 3) > (*R*)-Segphos® (Entry 4),[10] ee value of **3ab**: Entry 2 < Entry 3 < Entry 4].[11] The use of (*R*)-Segphos® that possesses the narrowest dihedral angle furnished **3ab** with the highest ee and, furthermore, significantly improved yield was also realized (Entry 4).[12] The effect of the steric bulk of the aryl group on the phosphorus was also examined, which revealed that increasing the steric bulk decreases both the yield and ee of **3ab** (Entry 5).[11]

Thus, we explored the scope of this process with respect to both 2-alkynylbenzaldehydes and acyl phosphonates as shown in Table 2.[13] With respect to the substituents at the alkyne terminus of 2-alkynylbenzaldehydes, not only *n*-butyl- (**1a**, Entry 1) but also phenyl- (**1b**, Entry 2), 1-cyclohexenyl- (**1c**, Entry 3), and cyclohexyl (**1d**, Entry 4)-substituted 2-alkynylbenzaldehydes could react with **2b**, while the yield was moderate in the reaction of 1-cyclohexenyl-substituted 2-alkynylbenzaldehyde **1c** with

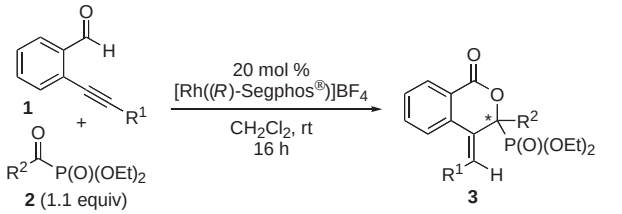
Table 1. Screening of ligands for Rh-catalyzed enantioselective [4 + 2] annulation of 2-alkynylbenzaldehyde **1a** with benzoylphosphonate **2b**



Entry	Ligand	Yield/%[a]	ee/%
1	(*R*,*R*)-Walphos®	0	—
2	(*R*)-H_8–BINAP	43	7 (+)
3	(*R*)-BINAP	40	78 (+)
4	(*R*)-Segphos®	85	99 (+)
5	(*R*)-tol-BINAP	37	55 (+)

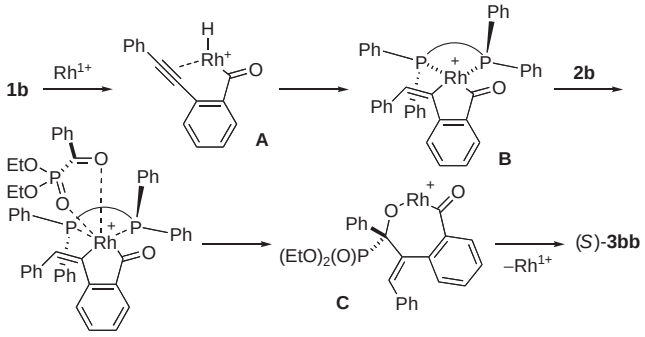
[a]Isolated yield.

Table 2. Cationic $Rh^I/(R)$-Segphos®-catalyzed enantioselective [4 + 2] annulation of 2-alkynylbenzaldehydes **1** with acyl phosphonates **2**[a]



Entry	**1** (R^1)	**2** (R^2)	**3**	Yield/%[b]	ee/%
1	**1a** (*n*-Bu)	**2b** (Ph)	(+)-**3ab**	85	99
2	**1b** (Ph)	**2b** (Ph)	(*S*)-(−)-**3bb**	85	>99
3	**1c** (1-cylohexenyl)	**2b** (Ph)	(+)-**3cb**	40	99
4	**1d** (Cy)	**2b** (Ph)	(+)-**3db**	84	96
5	**1e** [($Cl(CH_2)_3$]	**2b** (Ph)		0	—
6[c]	**1e** [($Cl(CH_2)_3$]	**2b** (Ph)	(+)-**3eb**	49	>99
7	**1a** (*n*-Bu)	**2c** (Me)	(−)-**3ac**	43	99
8	**1b** (Ph)	**2c** (Me)	(−)-**3bc**	38	92

[a][Rh((*R*)-Segphos®)]BF_4 (0.030 mmol), **1** (0.150 mmol), **2** (0.165 mmol), and CH_2Cl_2 (1.5 mL) were used. See Supporting Information in detail.[16] [b]Isolated yield. [c]In the presence of ethyl phenylglyoxylate (0.165 mmol).



Scheme 1. Possible mechanism for the selective formation of (*S*)-**3bb**.

2b (Entry 3). Interestingly, although no reaction was observed in the reaction of 3-chloropropyl-substituted 2-alkynylbenzaldehyde **1e** with **2b** (Entry 5), the reaction proceeded in moderate yield in the presence of ethyl phenylglyoxylate (Entry 6).[14] With respect to acyl phosphonates, the use of benzoyl phosphonate **2b** furnished the corresponding benzopyranones in higher yields than that of acetyl phosphonate **2c** (Entries 1, 2 vs. 7, 8). The absolute configuration of (−)-**3bb** was determined to be S by X-ray crystallographic analysis.[15,16]

Scheme 1 shows a possible mechanism for the selective formation of (*S*)-**3bb**. Oxidative addition of the aldehyde C–H bond to rhodium(I) affords the rhodium acyl hydride **A**. Cis addition of the rhodium hydride to the metal-bound alkyne then provides the five-membered acylrhodium intermediate **B**. Complexation of benzoyl phophonate **2b**, followed by regio- and stereoselective insertion to form oxarhodacycle **C** so as to avoid the steric interaction between the diethoxyphosphinoyl group of **2b** and the axial phenyl group of (*R*)-Segphos®. Reductive elimination furnishes benzopyranone (*S*)-**3bb** and regenerates the rhodium catalyst.

As acyl phosphonates are commercially available and 2-alkynylbenzaldehydes can be prepared in one step through the Sonogashira coupling, this method serves as an attractive two step route to enantioenriched benzopyranones with the phosphonate-substituted quaternary carbon center.

This work was partly supported by a Grant-in-Aid for Scientific Research [No. 19028015 (Chemistry of Concerto Catalysis), 19·8995, 19350046, and 20675002] from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Takasago International Corporation for the gift of Segphos® and H_8–BINAP.

References and Notes

1 For pioneering work, see: L. S. Liebeskind, S. L. Baysdon, M. S. South, *J. Am. Chem. Soc.* **1980**, *102*, 7397.
2 M. Murakami, T. Itahashi, Y. Ito, *J. Am. Chem. Soc.* **2002**, *124*, 13976.
3 a) K. Tanaka, G. C. Fu, *Org. Lett.* **2002**, *4*, 933. b) K. Tanaka, Y. Hagiwara, K. Noguchi, *Angew. Chem., Int. Ed.* **2005**, *44*, 7260. c) K. Kundu, J. V. McCullagh, A. T. Morehead, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 16042. d) K. Tanaka, Y. Hagiwara, M. Hirano, *Angew. Chem., Int. Ed.* **2006**, *45*, 2734. e) K. Tanaka, Y. Hagiwara, M. Hirano, *Eur. J. Org. Chem.* **2006**, 3582. f) K. Tanaka, D. Hojo, T. Shoji, Y. Hagiwara, M. Hirano, *Org. Lett.* **2007**, *9*, 2059.
4 D. Hojo, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem., Int. Ed.* **2008**, *47*, 5820.
5 Dimer **4** was generated in ca. >15% yield, and an unidentified complex mixture was also generated other than **3aa** and **4**.
6 a) T. Tsuda, T. Kiyoi, T. Miyane, T. Saegusa, *J. Am. Chem. Soc.* **1988**, *110*, 8570. b) T. N. Tekavec, J. Louie, *J. Org. Chem.* **2008**, *73*, 2641. c) M. Murakami, S. Ashida, T. Matsuda, *J. Am. Chem. Soc.* **2006**, *128*, 2166.
7 a) Y. Yamamoto, H. Takagishi, K. Itoh, *J. Am. Chem. Soc.* **2002**, *124*, 6844. b) B. M. Trost, R. E. Brown, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 5877.
8 a) B. Bennacer, M. Fujiwara, S.-Y. Lee, I. Ojima, *J. Am. Chem. Soc.* **2005**, *127*, 17756. b) J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16040. c) K. Tanaka, Y. Otake, A. Wada, K. Noguchi, M. Hirano, *Org. Lett.* **2007**, *9*, 2203. d) K. Tsuchikama, Y. Yoshinami, T. Shibata, *Synlett* **2007**, 1395. e) K. Tanaka, Y. Otake, H. Sagae, K. Noguchi, M. Hirano, *Angew. Chem., Int. Ed.* **2008**, *47*, 1312.
9 K. Tanaka, R. Tanaka, G. Nishida, M. Hirano, *Synlett* **2008**, doi: 10.1055/S-2008-1077968.
10 H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron* **2005**, *61*, 5405.
11 Although conversions of **1a** were >80% and formation of dimer **4** was suppressed in <5% yield in Entries 2 and 5, unidentified complex mixtures were generated other than **3aa** and **4**. In Entry 3, the conversion of **1a** is low (ca. 50%).
12 Decreasing the catalyst loading to 10 mol % significantly lowered the yield of **3ab**.
13 In Entries 3, 7, and 8, yields of the desired cycloaddition products were low owing to the formation of unidentified complex mixtures.
14 No cycloaddition product between **1e** and ethyl phenylglyoxylate was generated, while dimer of **1e** and an unidentified complex mixture were generated other than **3eb**. The role of ethyl phenylglyoxylate in this reaction is not clear at the present stage.
15 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-683326. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) August 2, 2008; doi:10.1246/cl.2008.934