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Highly Enantioselective Construction of Axial Chirality by Palladium-Catalyzed Cycloisomerization of *N*-Alkenyl Arylethynylamides

Hidetomo Imase,[†] Takeshi Suda,[†] Yu Shibata,[†] Keiichi Noguchi,[‡] Masao Hirano,[†] and Ken Tanaka*,[†]

Department of Applied Chemistry, Graduate School of Engineering, and Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

tanaka-k@cc.tuat.ac.jp

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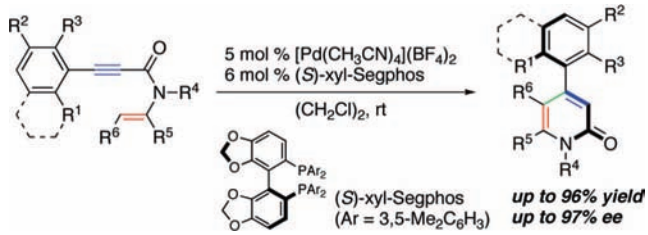
ABSTRACT



A cationic palladium(II)/(*S*)-xyl-Segphos complex catalyzes enantioselective cycloisomerizations of *N*-alkenyl arylethynylamides leading to axially chiral 4-aryl-2-pyridones in high yields with high ee values. The present catalysis represents the first enantioselective construction of axial chirality by the transition-metal-catalyzed cycloisomerization.

Axially chiral biaryls are valuable structures for a large number of chiral ligands and biologically active compounds. Therefore, various atroposelective syntheses of these compounds have been reported to date.[1] As a conceptually new approach, asymmetric aromatization through transition-metal-catalyzed [2 + 2 + 2] cycloadditions has proven to be a powerful method for this purpose.[2] Following the pioneering work by Gutnov and Heller using chiral cobalt catalysts,[2a] a number of axially chiral biaryl syntheses have been achieved through enantioselective [2 + 2 + 2] cycloadditions catalyzed by Co(I),[2a] Ir(I),[2b] and Rh(I) complexes.[2c] For the synthesis of axially chiral 6-aryl-2-pyridones, we developed the rhodium-catalyzed enantioselective [2 + 2 + 2] cycloaddition of 1,6-diynes with isocyanates.[2d]

On the other hand, we have recently reported that a cationic Au(I)/PPh_3 complex catalyzes the cycloisomerization of *N*-alkenyl alkynylamides, that can be readily prepared by *N*-acylation of imines with alkynoyl chlorides, leading to substituted 2-pyridones at room temperature.[3] We anticipated that *N*-alkenyl arylethynyl-amide **1** bearing a 2,6-disubstituted phenyl group at an alkyne terminus would cyclize to give axially chiral 4-aryl-2-pyridone **2** by using a chiral π-electrophilic transition-metal complex as a catalyst (Scheme 1).[4−6] In this reaction, π-complexation of the chiral transi-

[†] Department of Applied Chemistry.
[‡] Instrumentation Analysis Center.

(1) For recent reviews, see: (a) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

(2) (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795. (b) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. (c) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510. (d) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737.

(3) Imase, H.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 3563.

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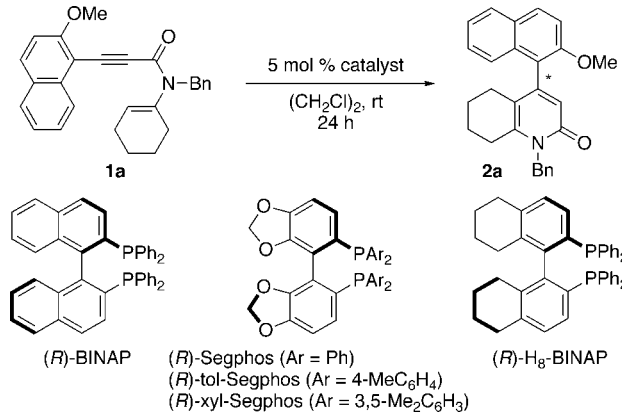
Table 1. Screening of Chiral Catalysts[a]



entry	catalyst	convn (%)	yield (%)[b]	ee (%)
1[c]	AuSMe/(*R*)−BINAP/$AgBF_4$	100	50	<5
2[c]	$[Ag(CH_3CN)_4]BF_4$/(*R*)−BINAP	8	<2	−
3[c]	[Rh((*R*)−BINAP)]BF_4	100	59	64 (+)
4	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*R*)−BINAP	100	62	81 (+)
5	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*R*)−H_8−BINAP	87	64	89 (+)
6	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*R*)−Segphos	100	79	90 (+)
7[d]	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*R*)−Segphos	100	93	88 (+)
8[d]	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*R*)−tol−Segphos	100	86	87 (+)
9[d]	$[Pd(CH_3CN)_4](BF_4)_2$/1.2(*S*)−xyl−Segphos	100	96	94 (−)

[a] Catalyst (0.0050 mmol), **1a** (0.10 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. [b] Isolated yield. [c] Catalyst: 10 mol %. [d] Catalyst (0.010 mmol), **1a** (0.20 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used.

tion-metal complex with the triple bond would facilitate the cyclization and induce enantioselective construction of axial chirality through close interaction between the chiral catalyst and the aryl group adjacent to the triple bond.

Importantly, a number of 4-aryl-2-pyridone derivatives, especially 4-arylquinolin-2(^{1}H)-one derivatives such as **3**[7] and **4a**[8] (Figure 1), showed potent pharmaceutical activities. The method shown in Scheme 1 can provide new analogues of this important class of compounds in enantiomerically enriched forms.

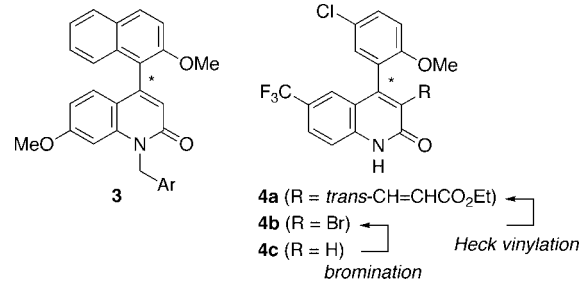


Figure 1. Biologically active 4-aryl-2-pyridone derivatives.

We first investigated the reaction of *N*-cyclohexenyl alkynylamide **1a** bearing a 2-methoxynaphthyl group at an alkyne terminus as a model substrate (Table 1). In our

(4) Recently, a Au(I)-catalyzed cycloisomerization of (arene)chromium complexes with 1,5-enynes directed towards axially chiral biaryls was reported; see: Michon, C.; Liu, S.; Hiragushi, S.; Uenishi, J.; Uemura, M. *Synlett* **2008**, 1321.

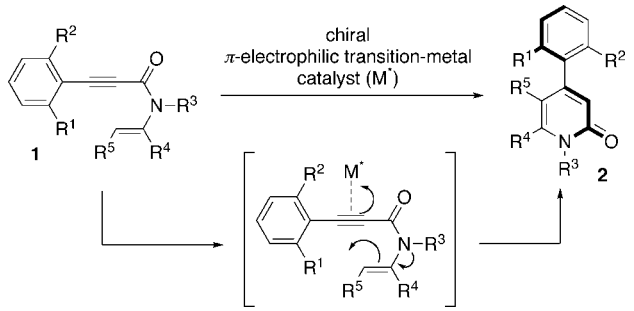
(5) For recent reviews of cycloisomerizations of 1,n-enynes, see: (a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (d) Añorbe, L.; Domı´nguez, G.; Pérez-Castells, J. *Chem.−Eur. J.* **2004**, *10*, 4938.

(6) For selected recent examples of π-electrophilic transition-metal complex-catalyzed cycloisomerizations of 1,5-enynes leading to six-membered heterocycles and carbocycles, see: (a) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287. (b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. (c) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705. (d) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411. (e) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 4592. (f) Nieto-Oberhuber, C.; MuNunez, M. P.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.−Eur. J.* **2006**, *12*, 1677. (g) Grise, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905. (h) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. (i) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451. (j) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (k) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.−Eur. J.* **2004**, *10*, 4556. (l) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (m) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762, and references therein.

(7) Compounds **3** are patented by Teikoku Hormone Mfg. Co., Ltd. as oxytocin antagonists; see: Shiraiwa, M.; Ota, S.; Takefuchi, K.; Uchida, H.; Saegusa, M.; Mitsubori, T.; Yoshizawa, M. JP 2003146972, 2003.

(8) Compound **4a** and its derivatives have been identified by Bristol-Myers Squibb as potent maxi-K channel openers useful for the treatment of male erectile dysfunction; see: (a) Hewawasam, P.; Fan, W.; Ding, M.; Flint, K.; Cook, D.; Goggings, G. D.; Myers, R. A.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Starret, J. E.; Lodge, N. J. *J. Med. Chem.* **2003**, *46*, 2819. (b) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864, and references therein.

Scheme 1. Our Concept for Enantioselective Cycloisomerization



previous report, cationic Au(I) and Ag(I) complexes showed higher catalytic activity than that of cationic Rh(I) and Pd(II) complexes for the cycloisomerization of *N*-alkenyl alkynylamide leading to 2-pyridones.[3] On the contrary, screening of cationic transition-metal complexes with (*R*)-BINAP ligand (entries 1−4) revealed that the Rh(I) and Pd(II) complexes (entries 3 and 4)[9] showed significantly higher catalytic activity and/or enantioselectivity than that of the Au(I) and Ag(I) complexes (entries 1 and 2),[10,11] and the use of the cationic Pd(II)/(*R*)-BINAP complex furnished the desired axially chiral 4-aryl-2-pyridone **2a** with the highest yield and ee (entry 4). Among axially chiral biaryl bisphosphine ligands examined (entries 4−6), the use of (*R*)-Segphos furnished **2a** with both high yield and ee (entry 6). Further improved yield and ee were achieved by using (*S*)-xyl-Segphos as a ligand at high concentration (entry 9).

Thus, we next explore the scope of this enantioselective cycloisomerization (Table 2). The reaction of *N*-neopentylamide **1b** (entry 2) slightly lowered both yield and ee of the corresponding 2-pyridone than those of *N*-benzylamide **1a** (entry 1). Not only *N*-cyclohexenyl (**1a**) but also *N*-cyclopentenyl (**1c**, entry 3) and acyclic *N*-alkenyl (**1d** and **1e**, entries 4 and 5) alkynylamides furnished the desired pyridones in high yields with high ee's. The present cycloisomerization is not restricted to the naphthalene derivatives. Both 2-methoxytetrahydronaphthalene (**1g**, entry 7) and 2-methoxy-6-methylbenzene (**1h**, entry 8) derivatives furnished the corresponding pyridones in high yields with high ee's. Furthermore, methyl- (**1i**, entry 9) and chloro-substituted benzodioxole derivatives (**1j**, entry 10) could also participate in this reaction. The presence of the 2-alkoxy-substituted aryl group at the alkyne terminus is important to realize both high reactivity and enantioselectivity. Although 2-methylnaphthalene derivative **1f** could participate in this reaction, the reaction was sluggish and the ee was moderate (entry 6).

Table 2. Enantioselective Cycloisomerization of **1a**−**j**[a]

entry	substrate **1**	time (h)	product **2** / % yield[b] (% ee)
1	**1a** (R = Bn)	24	(−)-**2a** 96 (94)
2	**1b** [R = $CH_2C(CH_3)_3$]	40	(*R*)-(−)-**2b** 88 (85)
3	**1c**	24	(−)-**2c** 93 (91)
4	**1d** (R = Et)	24	(−)-**2d** 87 (94)
5	**1e** (R = Ph)	62	(−)-**2e** 75 (90)
6	**1f**	72	(−)-**2f** 77[c] (51)
7	**1g**	72	(−)-**2g** 89 (94)
8	**1h**	28	(+)-**2h** 91 (97)
9	**1i** (R = Me)	48	(+)-**2i** 64 (94)
10	**1j** (R = Cl)	48	(+)-**2j** 64 (87)

[a] Reactions were conducted using $[Pd(CH_3CN)_4](BF_4)_2$ (0.010 mmol), (*S*)-xyl-Segphos (0.012 mmol), **1a**−**j** (0.20 mmol), and $(CH_2Cl)_2$ (1.0 mL) at rt. [b] Isolated yield. [c] Nine percent recovery of **1f**.

(9) For examples of cationic Pd(II)/chiral biaryl bisphosphine complex-catalyzed enantioselective cycloisomerizations of 1,6- and 1,7-enynes, see: (a) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764. (b) Mikami, K.; Hatano, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5767. (c) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (d) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249.

(10) For an example of a cationic Au(I)/chiral biaryl bisphosphine complex-catalyzed enantioselective cycloisomerization of 1,6-enynes, see: Munoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293.

(11) For an example of a cationic Ag(I)/chiral biaryl bisphosphine complex-catalyzed enantioselective cycloisomerization of 1,6-enynes, see: Bardaj, M.; Crespo, O.; Laguna, A.; Fischer, A. K. *Inorg. Chim. Acta* **2000**, *304*, 7.

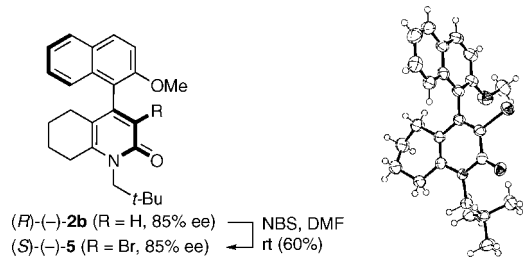


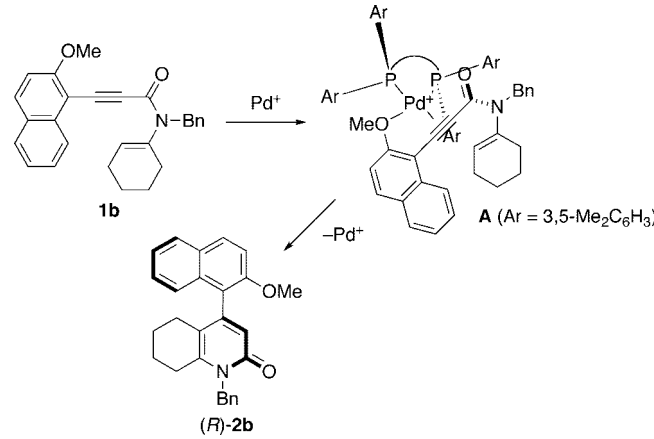
Figure 2. Synthesis (left) and ORTEP drawing (right) of (*S*)-(−)-**5**.

To introduce various substituents at the 3-position of the pyridone ring by coupling reactions, the synthesis of a 3-bromo derivative was then examined by the same method for the preparation of pharmaceutical intermediate **4b**.[8b] Pleasingly, bromination of pyridone (−)-**2b** proceeded by treatment with NBS to give 4-aryl-3-bromo-2-pyridone (−)-**5** in 60% isolated yield without racemization. The absolute configuration of (−)-**5** was determined to be *S* by X-ray crystallographic analysis (Figure 2).

Possible mechanism for the selective formation of axially chiral 4-aryl-2-pyridone (*R*)-**2b** through the cationic Pd(II)/(*S*)-xyl-Segphos complex-catalyzed enantioselective cycloisomerization of *N*-cyclohexenyl alkynylamide **1b** is shown in Scheme 2. Avoidance of the steric interaction between the alkene moiety of **1b** and equatorial aryl group on the phosphorus atom of (*S*)-xyl-Segphos in chelating intermediate **A** might control the axial chirality of 4-aryl-2-pyridone (*R*)-**2b**.

In conclusion, we have achieved the first enantioselective construction of axial chirality by the chiral π-electrophilic transition-metal complex-catalyzed cycloisomerization. Future studies will focus on the application of this strategy to the enantioselective synthesis of various chiral aromatic compounds.

Scheme 2. Possible Mechanism for Enantioselection



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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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