Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3089–3092

TETRAHEDRON LETTERS

Asymmetric cyclization–carbonylation of 2-propargyl-1,3-dione

Keisuke Kato,[a,*] Maki Tanaka,[a] Shigeo Yamamura,[a] Yasuhiro Yamamoto[b] and Hiroyuki Akita[a,*]

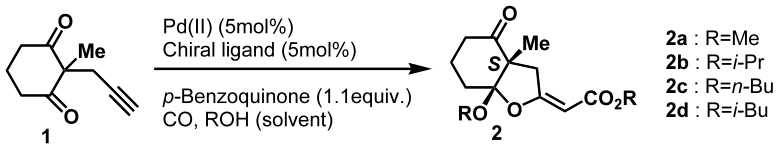
[a]*School of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*
[b]*Department of Chemistry, Faculty of Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*

Received 29 January 2003; revised 21 February 2003; accepted 21 February 2003

Abstract—The first example of asymmetric cyclization–carbonylation of 2-propargyl-1,3-dione **1** catalyzed by palladium(II) with chiral bisoxazolines (C.H.-BOX) was investigated. The use of bulky alcohols increased the ee of the products **2**. The product **2d** was converted into bicyclic enones **7** and **8**, a useful intermediate for the synthesis of natural products.

Palladium(II)-catalyzed intramolecular oxycarbonylation of alkynols is an important transformation of alkynes into β-ketoesters or β-alkoxyacrylates.[1] Recently, we have reported that the oxidative cyclization–methoxycarbonylation of 4-yn-1-ones[2] and propargylic acetates[3] is also a useful reaction for the above transformation. An asymmetric version of this type reaction has not been reported so far.[4] Now we wish to report here the first example of asymmetric cyclization–carbonylation of 2-propargyl-1,3-dione **1** catalyzed by palladium(II) with chiral bisoxazoline ligands (Scheme 1).

As shown in Table 1 (entry 1), asymmetric cyclization–methoxycarbonylation of 2-propargyl-1,3-diketone **1** in the presence of $Pd(CF_3CO_2)_2$/ligand **A**/*p*-benzoquinone in methanol at −30°C under carbon monoxide atmosphere (balloon) afforded 8% ee of *cis*-**2a** as a single diastereomer in 90% yield.[5] As a preliminary experiment, many kinds of ligands (**A** to **I**) were examined in MeOH; however the ee of the product **2a** was not improved. The bulkiness of alcohol affected the enantioselectivity and yield of the products **2** as shown in entries 2–4. When the reaction was performed in bulky alcohols, ee of **2b**–**d** was increased (*n*-BuOH 27% ee<*i*-PrOH 33% ee<*i*-BuOH 43% ee). The use of $Pd(CH_3CN)_4(BF_4)_2$, the chiral palladium complex did not dissolve in *i*-BuOH; the reaction proceeded by addition of CH_2Cl_2 to afford 25% ee of **2d** in 48% yield (entry 5). On addition of $Cu(OTf)_2$ and $LiClO_4$, the yields improved but the ee values were lowered (entries 6 and 7). Next, we examined the use of seven types of mixed solvents (DMF, DMSO, benzene, THF, 1,2-dichloroetane, CCl_4, CH_2Cl_2) containing 10 equiv. of *i*-BuOH. Among them, only CH_2Cl_2 is effective for the present reaction; the ee of **2d** was slightly increased, though the yield was reduced (entry 8). The use of *i*-BuOH/CH_2Cl_2 = 1/1 gave a similar result (entry 9) to that obtained by using only *i*-BuOH (entry 4). The use of 1:1 ratio of the ligand and $Pd(CF_3CO_2)_2$ gave 43% ee of **2d** in 49% yield (entry 10), which was comparable to the result using 2:1 ratio of the ligand and palladium catalyst (entry 4). Thus, the following reactions were performed in *i*-BuOH using 1:1 ratio of the ligand and $Pd(CF_3CO_2)_2$. The palladium catalyst with ligands **D** and **E** did not show any catalytic activity. When the reaction was performed in the presence of ligands **B**, **C**, **F**[4b], **G**, **H** and **I**[6], the product **2** was obtained in low yields with low enantioselectivities, although these chiral oxazolines have been successfully used for some other asymmetric reactions (entries 11–16). These mis-

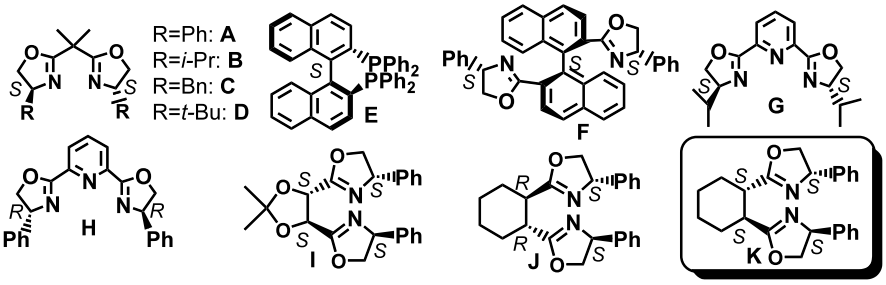


Scheme 1.

* Corresponding authors. Fax: +047-472-1825; e-mail: kkk@phar.toho-u.ac.jp

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00547-1

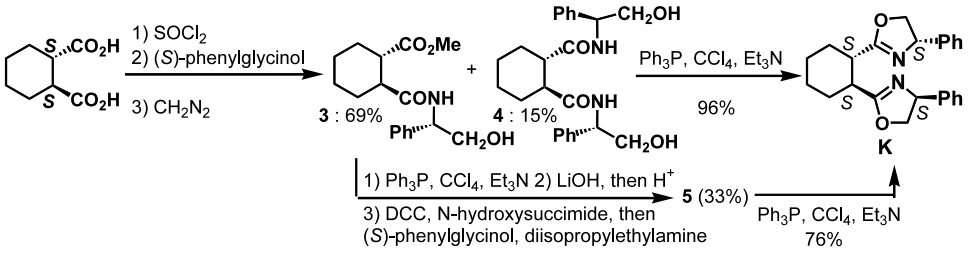
Table 1. Asymmetric cyclization–carbonylation of 2-propargyl-1,3-dione **1**



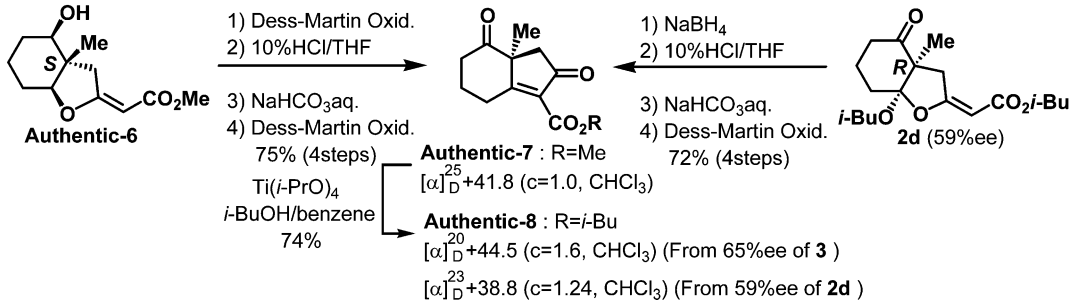
Entry	Pd cat.	Ligand (mol%)	Conditions	Yield (%)	Solvent	% ee (config.)[a]
1	$Pd(CF_3CO_2)_2$	**A** (10)	−30°C, 24 h	90	MeOH	8 (*R*)
2	$Pd(CF_3CO_2)_2$	**A** (10)	0–10°C, 20 h	54	*i*-PrOH	33 (*S*)
3	$Pd(CF_3CO_2)_2$	**A** (10)	0°C, 23 h	62	*n*-BuOH	27 (*S*)
4	$Pd(CF_3CO_2)_2$	**A** (10)	0°C, 20 h	48	*i*-BuOH	43 (*S*)
5	$(CH_3CN)_4Pd(BF_4)_2$	**A** (10)	r.t., 72 h	48	*i*-BuOH/CH_2Cl_2 = 2/1	25 (*S*)
6	$Pd(CF_3CO_2)_2$	**A** (10)[b]	0°C, 12 h	71	*i*-BuOH	25 (*S*)
7	$Pd(CF_3CO_2)_2$	**A** (10)[c]	0°C, 15 h	54	*i*-BuOH	9 (*R*)
8	$Pd(CF_3CO_2)_2$	**A** (10)	r.t., 16 h	29	*i*-BuOH in CH_2Cl_2	48 (*S*)
9	$Pd(CF_3CO_2)_2$	**A** (10)	0°C, 24 h	49	*i*-BuOH/CH_2Cl_2 = 1/1	43 (*S*)
10	$Pd(CF_3CO_2)_2$	**A** (5)	0°C, 20 h	49	*i*-BuOH	43 (*S*)
11	$Pd(CF_3CO_2)_2$	**B** (5)	0°C, 23 h	25	*i*-BuOH	31 (*S*)
12	$Pd(CF_3CO_2)_2$	**C** (5)	0°C–r.t., 26 h	47	*i*-BuOH	0
13	$Pd(CF_3CO_2)_2$	**F** (5)	0°C, 23 h	36	*i*-BuOH	6 (*R*)
14	$Pd(CF_3CO_2)_2$	**G** (5)	0°C–r.t., 24 h	40	*i*-BuOH	24 (*S*)
15	$Pd(CF_3CO_2)_2$	**H** (5)	0°C–r.t., 24 h	42	*i*-BuOH	19 (*R*)
16	$Pd(CF_3CO_2)_2$	**I** (5)	0°C–r.t., 23 h	21	*i*-BuOH	3 (*R*)
17	$Pd(CF_3CO_2)_2$	**J** (5)	r.t., 72 h	27	*i*-BuOH	11 (*R*)
18	$Pd(CF_3CO_2)_2$	**K** (5)	0°C, 22 h	54	*i*-BuOH	59 (*R*)

[a] Absolute configuration of quaternary carbon bearing a methyl group is only presented.
[b] $Cu(OTf)_2$ (5 mol%) and ligand A (10 mol%) were used.
[c] $LiClO_4$ (50 mol%) was used.

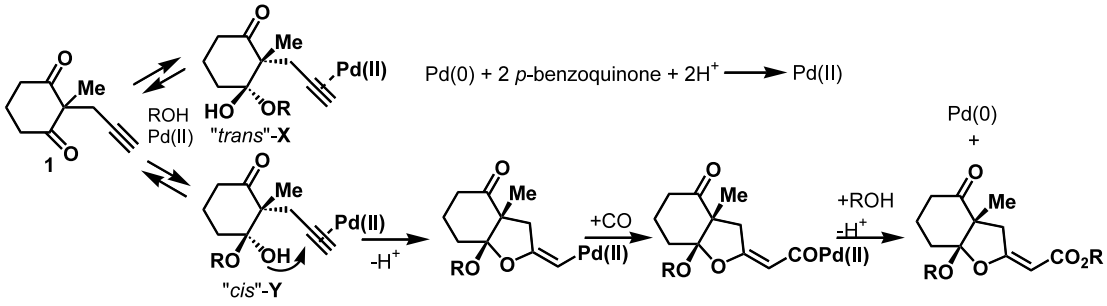
erable results prompt us to the synthesis of another kind of chiral ligand. In recent years, a number of conformationally constrained box ligands were prepared.[4b,c,f,7] For example, Takacs et al. reported box ligands built around bicyclo[2.2.1] and bicyclo[2.2.2]-backbones.[7a] We were puzzled by the absence of box ligands based on simple *trans*-1,2-cyclohexane fragment. The cyclohexane template is present in a number of useful chiral ligands[8] and chiral auxiliary[9] as a result of its ability to rigidify the *trans* configuration of substituents. We therefore prepared chiral box ligand based on *trans*-1,2-cyclohexane skeleton (C.H.-BOX) as shown in Scheme 2. Condensation of (*S*)-phenylglycinol with (*S*,*S*)-cyclohexanedicarboxylic acid[10] followed by esterification afforded diamide **4** (15%) along with monoamide **3** (69%). The ligand **K** was obtained by treatment of **4** with $Ph_3P/CCl_4/Et_3N$ in 96% yield. The monoamide **3** was also converted into ligand **K**. Formation of an oxazoline ring followed by hydrolysis of the ester group and subsequent condensation with (*S*)-phenylglycinol afforded monoamide **5** having the oxazoline ring in 33% overall yield. The ligand **K** was obtained by treatment of **5** with $Ph_3P/CCl_4/Et_3N$ in 76% yield. The ligand **J** was also prepared in a similar manner to that described above. Next, we examined the present reaction in the presence of ligand **J**/$Pd(OCOCF_3)_2$ and ligand **K**/$Pd(OCOCF_3)_2$ catalysts. Although the use of ligand **J** did not give good result (27%, 11% ee), that of ligand **K** bearing the (*S*,*S*)-1,2-cyclohexane skeleton ((*S*,*S*)-ph-C.H.-BOX) gave the



Scheme 2.



Scheme 3.



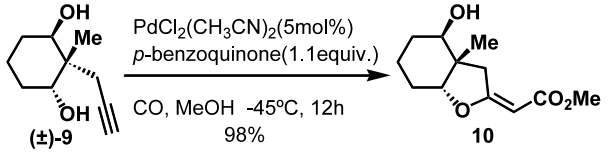
Scheme 4.

best result (54%, 59% ee) in Table 1 (entries 17 and 18).[11]

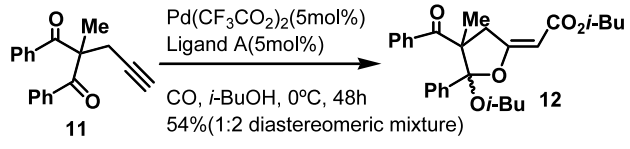
As shown in Scheme 3, the absolute stereochemistry of **2d** was determined by conversion into authentic bicyclic-diketone **8**. The authentic **8** was synthesized from authentic **6** (65% ee) which has (*S*)-configuration of the quaternary carbon bearing a methyl group.[4g] Oxidation of the secondary alcohol group in **6** gave the ketone which was treated with 10%HCl/THF to give a β-keto ester. Knoevenagel condensation of the β-keto ester followed by oxidation afforded authentic (+)-**7** in 75% overall yield. Treatment of (+)-**7** with Ti(*i*-PrO)$_4$/*i*-BuOH in benzene gave authentic (+)-**8** in 74% yield. On the other hand, the product **2d** was also converted to (+)-**8** by the following four-step sequence. Reduction of ketone in **2d** followed by acid hydrolysis and subsequent Knoevenagel condensation afforded bicyclic alcohol which was treated with Dess-Martin reagent to give (+)-**8**. Thus, the absolute configuration of the quaternary carbon bearing a methyl group in **2d** was determined to be *R*.

A conceivable mechanism of the present reaction would be proposed as shown in Scheme 4 based on the following experimental results. (I) The bulkiness of alcohols affected enantioselectivity and yield of **2** as shown in Table 1 (entries 1–4), which suggested that the alcohol incorporated into the substrate as a hemiacetal before cyclization.[12] (II) The addition of Lewis acid might accelerate the hemiacetal formation, and the yields were increased (entries 6 and 7). (III) We have recently reported that the cyclization carbonylation of 2-propargyl-1,3-diol **9** afforded the product **10** in 98% yield as a single diastereomer (Scheme 5).[4g] This result suggested that a specific hydroxyl group bearing *cis*-relationship against the propargyl group was more reactive than that of a '*trans*'-hydroxyl group. At first, two kinds of hemiacetal intermediates **X** and **Y** which have a '*trans*' and a '*cis*' hydroxyl group against the propargyl group should be produced, respectively. The coordination of the alkyne to Pd(II) could be induced by attack of the '*cis*' hydroxyl group in intermediate **Y** to produce the vinyl palladium intermediate followed by CO insertion and subsequent reaction with ROH to provide *cis*-**2** as a single diastereomer (Scheme 4). Actually, the cyclization–carbonylation of non-cyclic substrate **11** using the same reaction conditions as that of entry 10 in Table 1 afforded **12** as an inseparable 1:2 mixture of diastereomers in 54% yield (Scheme 6).[13]

In summary, we have presented the first example of an asymmetric cyclization-carbonylation of 2-propargyl-



Scheme 5.



Scheme 6.

1,3-dione **1** catalyzed by palladium(II) with chiral bisoxazolines. Chiral bisoxazoline ligand **K** based on the 1,2-cyclohexane skeleton ((*S*,*S*)-ph-C.H.-BOX) was more effective than ligands **A**–**J**. Optically active bicyclic enones **7** and **8**, being a useful intermediate of natural products, was synthesized.

Acknowledgements

We are grateful to Dr. M. Seki and Dr. T. Furutani, Tanabe Seiyaku Co., Ltd. for providing binaphthyl dicarboxylic acid for the preparation of (*S*,*S*)-ph-boxax.

References

1. (a) Gabriele, B.; Salerno, G.; Pascali, F. D.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2000**, *593-594*, 409; (b) Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717; (c) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203; (d) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 643.
2. Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915.
3. Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 6587.
4. Pd(II) mediated oxidative asymmetric Wacker-type reaction of alkene. (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318; (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063; (c) Arai, A. M.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907; (d) El-qisairi, A.; Hamed, O.; Henry, M.-P. *J. Org. Chem.*, **1998**, *63*, 2790; (e) El-qisairi, A.; Qaseer, A.-H.; Henry, M.-P. *Tetrahedron Lett.* **2002**, *43*, 4231. Pd(II) mediated oxidative asymmetric aminocarbonylation of alkene. (f) Shinohara, H.; Arai, A. M.; Wakita, K.; Atai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711. Pd(II) catalysed oxidative asymmetric reaction of alkynols. (g) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 1511.
5. The structure of racemic-**2a** was unequivocally determined by X-ray analysis. X-ray data for **2a** has been deposited at the Cambridge Crystallographic Data Centre as supplementary material. General procedure: A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $Pd(CF_3CO_2)_2$ (0.015 mmol), Chiral ligand (0.03 mmol), *p*-benzoquinone (0.33 mmol) and MeOH (6 mL) was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping-filling via the three-way stopcock. A solution of the substrate **1** (0.3 mmol) in MeOH (2 mL) was added dropwise to the stirred mixture via a syringe. After being stirred for the period of time and at a temperature, CH_2Cl_2 (30 mL) was added dropwise to the stirred mixture, washed with 5% NaOH aq (40 mL), and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (50/1) containing Et_3N (1%) afforded **2** as a colorless oil or colorless needles. The ee was determined by HPLC analysis using a chiral column.
6. (a) Imai, Y.; Zhang, W.; Kida, Y.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453; (b) Bedekar, V.-A.; Andersson, G.-P. *Tetrahedron Lett.* **1996**, *37*, 4073.
7. (a) Takacs, M. J.; Quincy, A. D.; Shay, W.; Jones, E. B.; Ross, R. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3079; (b) Clariana, J.; Comelles, J.; Moreno-Manas, M.; Vallribera, A. *Tetrahedron: Asymmetry* **2002**, *13*, 1551.
8. Caiazzo, A.; Dalili, S.; Yudin, K. A. *Org. Lett.* **2002**, *4*, 2597 and references cited therein.
9. For example Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron* **1994**, *50*, 3315.
10. Longeau, A.; Durand, S.; Spiegel, A.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 987.
11. The use of 2:1 ratio of ligand **K** and $Pd(CF_3CO_2)_2$ gave 59% ee of **2d** in 57% yield, which was comparable to the result using 1:1 ratio of the ligand **K** and $Pd(CF_3CO_2)_2$.
12. Pd(II)-catalyzed cyclization of alkynyl aldehydes via the hemiacetal intermediate has been recently reported. In this case, the palladium catalyst acts as a Lewis acid to promote the hemiacetal formation. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.
13. The ee of **12** could not be determined.