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Asymmetric cyclization–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols

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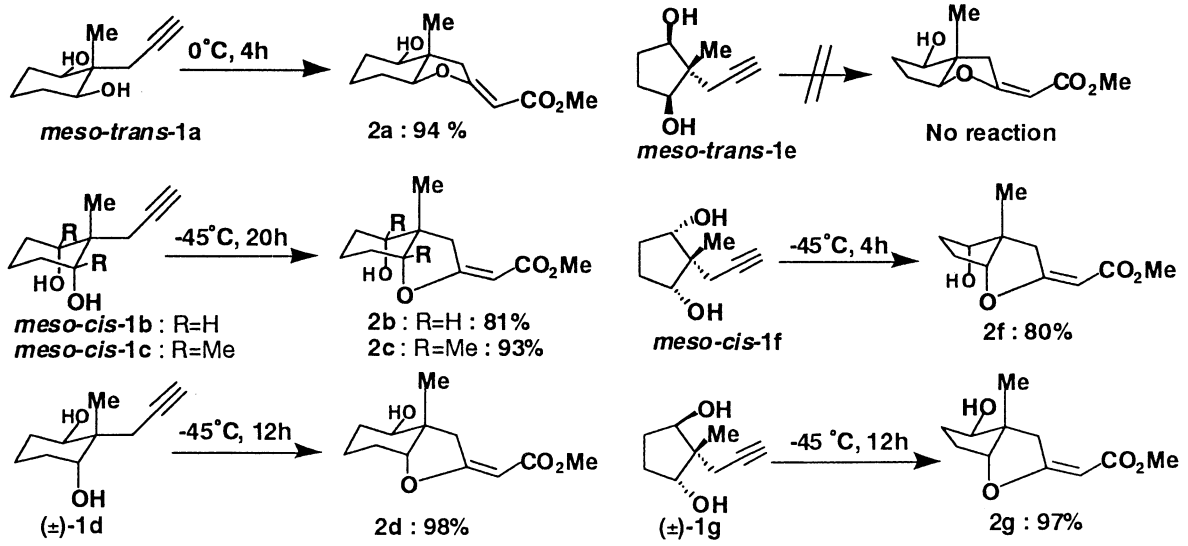
Abstract—The first example of asymmetric cyclization–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols **1** catalyzed by palladium(II) with chiral bisoxazolines was investigated. The reaction of **1** in the presence of palladium(II)-chiral ligands/*p*-benzoquinone in methanol at 0 to −45°C under carbon monoxide atmosphere (balloon) afforded (*E*)-bicyclic-β-alkoxyacrylates **2** in excellent yields with moderate enantioselectivities. © 2002 Elsevier Science Ltd. All rights reserved.

Palladium(II)-catalyzed reactions are fundamentally important in organic transformations.[1] Compared with the impressive evolution of asymmetric reactions with palladium(0) catalyst, [2] palladium(II)-catalyzed asymmetric oxidative reactions have received only scant attention. To our best knowledge, previous work on palladium-catalyzed asymmetric carbonylation[3] and Wacker-type reactions[4] has been limited to the reactions of alkenes. Recently, we have reported oxidative cyclization–methoxycarbonylation of cyclic- and acyclic-4-yn-1-ols using a Pd(II)/*p*-benzoquinone catalytic system under mild conditions.[5] An asymmetric version of this type reaction has not been reported yet. Now we wish to report here the first example of asymmetric cyclization–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols **1** catalyzed by palladium(II) with chiral bisoxazoline ligands.



Scheme 1. All reactions were carried out by using $Pd(CH_3CN)_2Cl_2$ (5mol%)/*p*-benzoquinone (1.1 equiv.) under CO (balloon) atmosphere in MeOH.

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As a preliminary experiment, seven kinds of substrates **1a**–**g** were examined for the cyclization–methoxycarbonylation reaction without a chiral ligand (Scheme 1). The cyclization–methoxycarbonylation of *meso*-*trans*-**1a** in the presence of bis(acetonitrile)-dichloro-palladium(II)/*p*-benzoquinone in methanol at 0°C under carbon monoxide atmosphere (balloon) afforded (*E*)-bicyclic-β-alkoxyacrylates **2a** in 94% yield. In the case of cyclopentane derivative *meso*-*trans*-**1e**, the reaction did not proceed and substrate **1e** was recovered. The reaction of *meso*-*cis*-**1b**,**c** and **1f** proceeded at low temperature to afford the products **2b**, **2c** and **2f** in 81, 93 and 80% yields, respectively. In the case of 1,3-diols (±)-**1d** and (±)-**1g** possessing 1,3-*trans* relationship, a specific hydroxyl group bearing *cis*-relationship against the propargyl group was reacted selectively to provide the products **2d** and **2g** in 98 and 97% yields, respectively.

As shown in Table 1 (entry 1), asymmetric cyclization–methoxycarbonylation of *meso*-*trans*-**1a** in the presence of $Pd(CF_3CO_2)_2$/ligand **A**[6]/*p*-benzoquinone in methanol at −30°C under carbon monoxide atmosphere (balloon) afforded 65% ee of (*E*)-cyclic-β-alkoxyacrylates **2a** in 98% yield.[7] When the same reaction of **1a** as the previous case was performed at 0°C, ee of **2a** was slightly decreased (entry 2). In the absence of a ligand, the reaction proceeded at room temperature to afford racemic-**2a** in 85% yield (entry 3). Although $Pd(CH_3CN)_4(BF_4)_2$ was also effective for this reaction, the ee of the product was slightly lower than that (entry 1) obtained on using $Pd(CF_3CO_2)_2$ (entry 4). Next we examined the use of seven other kinds of chiral ligands (entries 5–11). Among them, ligand **E**[4] reported by Uoszumi et al. gave a moderate result (entry 8). In the case of ligands **B**,[8] **C**,[6] **F**[6] and **G**,[6] the reaction smoothly proceeded to afford **2a** in good yield with low enantioselectivity (entries 5, 6, 9 and 10). The use of ligands **D**[6] and **H**[6] showed that the reaction scarcely proceeded (entries 7 and 11). When we examined the use of $CH_2Cl_2/MeOH = 10/1$ or *i*-PrOH as solvents, the product **2a** was obtained in good yield with moderate enantioselectivity (entries 12 and 13). The reaction in THF/MeOH = 10/1 was very slow to give low yield of **2a** with low enantioselectivity (entry 14). The result using *meso*-*cis*-**1b** and **1f** was in great contrast to that of *meso*-*trans*-**1a**. The reaction of *meso*-*cis*-**1b** and **1f** afforded the products **2b** and **2f** as a racemic form, respectively (entries 15 and 16). Although the absolute configuration of **2c** has not been determined yet, in the case of *meso*-*cis*-**1c** possessing two hydroxyl groups in axial position and two methyl groups in equatorial position, the enantioselectivity of the product **2c** was almost the same as that of **2a** (entry 17). These results suggested that the presence of the equatorial substituents in the substrate **1a**, **1b** and **1c** play an important role in the enantioselectivity of the reaction. We

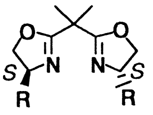
Table 1. Asymmetric cyclization–methoxycarbonylation of cyclic-2-propargyl-1,3-diols[a]

Entry	Substrates	Pd cat. (5 mol%)	Ligand (10 mol%)	Condition	Yield (%)	Solvent	% ee (Config.)[b]
1	**1a**	$Pd(CF_3CO_2)_2$	A	−30°C, 20 h	98	MeOH	65 (*S*)
2	**1a**	$Pd(CF_3CO_2)_2$	A	0°C, 2.5 h	90	MeOH	57 (*S*)
3	**1a**	$Pd(CF_3CO_2)_2$	None	rt, 24 h	85	MeOH	–
4	**1a**	$(CH_3CN)_4$-$Pd(BF_4)_2$	A	−30°C to −10°C, 48 h	94	MeOH	63 (*S*)
5	**1a**	$Pd(CF_3CO_2)_2$	B	−15°C, 20 h	99	MeOH	0
6	**1a**	$Pd(CF_3CO_2)_2$	C	−30°C to −10°C, 60 h	81	MeOH	0
7	**1a**	$Pd(CF_3CO_2)_2$	D	rt, 72 h	15	MeOH	0
8	**1a**	$Pd(CF_3CO_2)_2$	E	−10°C, 40 h	67	MeOH	56 (*S*)
9	**1a**	$Pd(CF_3CO_2)_2$	F	rt, 24 h	88	MeOH	5 (*S*)
10	**1a**	$Pd(CF_3CO_2)_2$	G	rt, 48 h	88	MeOH	33 (*R*)
11	**1a**	$Pd(CF_3CO_2)_2$	H	−10°C, 40 h	35	MeOH	0
12	**1a**	$Pd(CF_3CO_2)_2$	A	−10°C, 48 h	86	$CH_2Cl_2/MeOH = 10/1$	52 (*S*)
13	**1a**	$Pd(CF_3CO_2)_2$	A	−15°C, 20 h	90[c]	*i*-PrOH	60 (*S*)
14	**1a**	$Pd(CF_3CO_2)_2$	A	rt, 48 h	26	THF/MeOH = 10/1	35 (*S*)
15	**1b**	$Pd(CF_3CO_2)_2$	A	−45°C, 24 h	81	MeOH	0
16	**1f**	$Pd(CF_3CO_2)_2$	A	−45°C, 24 h	80	MeOH	0
17	**1c**	$Pd(CF_3CO_2)_2$	A	−45°C, 24 h	99	MeOH	63 (N.D.)

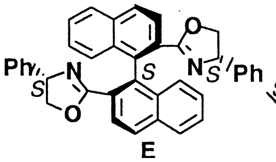
[a] 1.1 equiv. of *p*-benzoquinone was used for all reactions.

[b] Absolute configuration of quaternary carbon bearing a methyl group is only presented.

[c] *i*-Pr ester was obtained.



R=Ph: **A**
R=*i*-Pr: **B**
R=Bn: **C**
R=*t*-Bu: **D**



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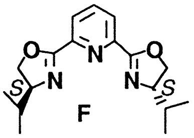

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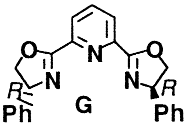

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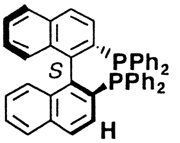

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confirmed that racemization of the products **2a–c** was not observed during the reaction.[9] The products **2b** and **2c** were resolved by chiral HPLC, and single enantiomers **2b** and **2c** or enriched **2a** were again exposed to the reaction condition and recovered with no racemization.

In summary, we have presented an asymmetric cyclization–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols **1** catalyzed by palladium(II) with chiral bisoxazolines. This is the first example of an asymmetric version of the present reaction.

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7. Absolute configuration of the quaternary carbon in **2a** was determined by consideration of relative stereochemical correlation between the quaternary carbon and the secondary alcohol, because absolute configuration of the secondary alcohol was confirmed by applying modified Mosher's method. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. 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 (4 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 at −50°C. 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 (6/1–4/1) afforded **2** as a colorless oil or colorless needles. Satisfactory analytical data were obtained for all new compounds. **2a** (65% ee): colorless needles, mp 95°C; $[\alpha]^{28}_{D}$ −126 ($c=0.55$, $CHCl_3$); ^1H NMR (400 MHz, CD_3COCD_3): δ 0.82 (3H, s), 1.28–1.62 (3H, m), 1.67–1.73 (1H, m), 1.79–1.86 (2H, m), 2.51 (1H, dd, $J=16.8$, 1.2 Hz), 3.37 (1H, d, $J=16.8$ Hz), 3.59 (3H, s), 3.62–3.68 (2H, m), 5.25 (1H, dd, $J=2.4$, 1.2 Hz); ^{13}C NMR (400 MHz, CD_3COCD_3): δ 11.7, 21.5, 23.5, 30.2, 45.1, 47.0, 50.7, 74.6, 87.0, 91.7, 168.9, 177.0; FAB-MS *m*/*z*: 227 ($M^{+}+1$). Anal. calcd. for $C_{17}H_{20}O_5$: C, 63.70; H, 8.02. Found: C, 63.55; H, 8.02%.
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9. Compounds **2a** (65% ee), **2b** (99% ee) and **2c** (99% ee) were used for racemization experiments.