# Asymmetric Bis(alkoxycarbonylation) Reaction of Cyclic Olefins Catalyzed by Palladium in the Presence of Copper(I) Triflate

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A palladium-catalyzed asymmetric bis(alkoxycarbonylation) reaction of cyclic olefins in the presence of copper(I) triflate was achieved by using a chiral bioxazoline ligand under normal pressure of carbon monoxide and oxygen to give the corresponding optically active *cis*-dicarboxylates with enantioselectivities up to 94% ee. The carbonylated product was well applied to the synthesis of a biologically active hexahydrobenz-[*e*]isoindole derivative.

Transition-metal-catalyzed enantioselective carbonylation reactions are important in organic synthesis to provide efficient entries to a variety of useful oxygen-functionalized compounds in optically active forms,[1] and intensive researches on the asymmetric monocarbonylation of prochiral olefins were reported.[1b,2] To the contrary, reports on the asymmetric dicarbonylation, which can introduce two carbonyl groups stereoselectively in a single operation, were limited.[3] We have studied palladium-catalyzed mono- and bis(alkoxycarbonylation)[4,5] and already reported an asymmetric bis(alkoxycarbonylation) reaction of terminal olefins and homoallylic alcohols in the presence of copper(I) triflate using a chiral bioxazoline ligand, which gave the corresponding optically active succinates and $\gamma$-butyrolactones with moderate enantioselectivities.[6] Herein, we wish to describe an asymmetric bis(alkoxycarbonylation) reaction of cyclic olefins in the presence of copper(I) triflate to give the corresponding optically active *cis*-dicarboxylates with excellent enantioselectivities.

An asymmetric bis(alkoxycarbonylation) reaction of 1,2-dihydronaphthalene (**1a**) in the presence of a 0.02 molar amount of $PdCl_2$ and 0.5 molar amount of $CuOTf(C_6H_6)_{0.5}$ under normal pressure of carbon monoxide and oxygen in MeOH/THF using (4*S*,4′*S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole (**3**) as a chiral ligand, proceeded slowly to give dimethyl *cis*-tetrahydronaphthalene-1,2-dicarboxylate (**2a**) diastereoselectively in 32% yield. To our delight, the optical yield of the obtained diester **2a** was determined to be 93% ee by a HPLC analysis (Entry 1 in Table 1). In order to accelerate the carbonylation, the reaction temperature was increased to 60 °C. Within 2 days, 1,2-dihydronaphthalene (**1a**) almost disappeared and the carbonylated product **2a** was obtained in higher yield without much decrease of enantioselectivity (Entry 2). Methoxycarbonylation products, which were obtained for **1e** as described below, were scarcely identified by analysis of the $^1$H NMR spectrum of the crude products. The asymmetric bis(alkoxycarbonylation) of indene (**1b**) also afforded the corresponding dicarboxylate **2b** with excellent enantioselectivity (Entries 3 and 4). However, the carbonylation of 7-membered cyclic olefin **1c** was so sluggish that yield was poor even at 60 °C (Entry 5). When the benzene ring was substituted by an electron-withdrawing Br group, the reaction was retarded (Entries 6 and 7). In these cases, olefins **1c** and **1d** were not completely consumed. To the contrary, the introduction of electron-donating MeO group at C7 position produced not only desired carbonylated product **2e** with excellent enatioselectivity but also a mixture of optically active *cis*- and *trans*-methoxycarbonylated products **4** and **5** (Entries 8 and 9). MeO-Substituted dihydronaphthalene at C8 position **1f** gave the product **2f** in reasonable yield with excellent enantioselectivity even at 60 °C (Entries 10 and 11).[7,8]

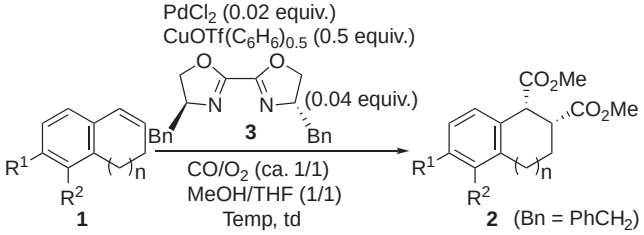
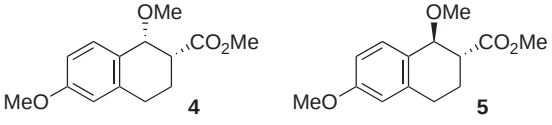


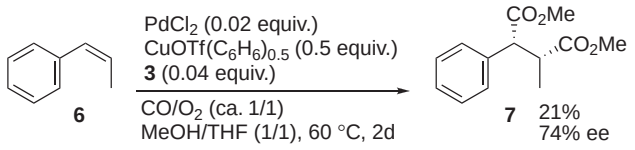

**Table 1.** Asymmetric bis(alkoxycarbonylation) of **1**

| Entry | *n* | $R^1$ | $R^2$ | | Temp | *t*/d | Yield/% | ee/%[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | H | H | **a** | rt | 10 | 32 | 93 |
| 2 | | | | | 60 °C | 2 | 57 | 91 |
| 3 | 0 | H | H | **b** | rt | 9 | 25 | 92 |
| 4 | | | | | 60 °C | 2 | 49 | 89 |
| 5 | 2 | H | H | **c** | 60 °C | 7 | 10 | 78 |
| 6 | 1 | Br | H | **d** | rt | 8 | 14 | 87 |
| 7 | | | | | 60 °C | 13 | 40 | 74 |
| 8 | 1 | MeO | H | **e** | rt | 8 | 24[b] | 92 |
| 9 | | | | | 60 °C | 3 | 25[c] | 92 |
| 10 | 1 | H | MeO | **f** | rt | 11 | 56 | 94 |
| 11 | | | | | 60 °C | 2 | 60 | 92 |

[a]Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel IA). [b]Methoxycarbonylation products **4** (18% yield, 92% ee) and **5** (5% yield, 87% ee) were also produced. [c]Methoxycarbonylation products **4** (24% yield, 87% ee) and **5** (11% yield, 87% ee) were also produced.




Enantioselectivity of the present carbonylation of cyclic olefins is higher than that in the case of terminal olefins.[6b] Asymmetric bis(alkoxycarbonylation) of (*Z*)-1-phenyl-1-propene (**6**) was next carried out. The reaction was sluggish to give the corresponding succinate **7** with 74% ee, which was slightly higher than that in the case of styrene but lower than the cyclic olefins **1** (Scheme 1). This result suggested that excellent enantioselectivity of the present bis(alkoxycarbonylation) was mainly due to the rigid cyclic structure. Although the precise mechanism of the present reaction is still an open question, a possible transition state is shown in Figure 1 based on the assigned absolute stereo-




**Scheme 1.**

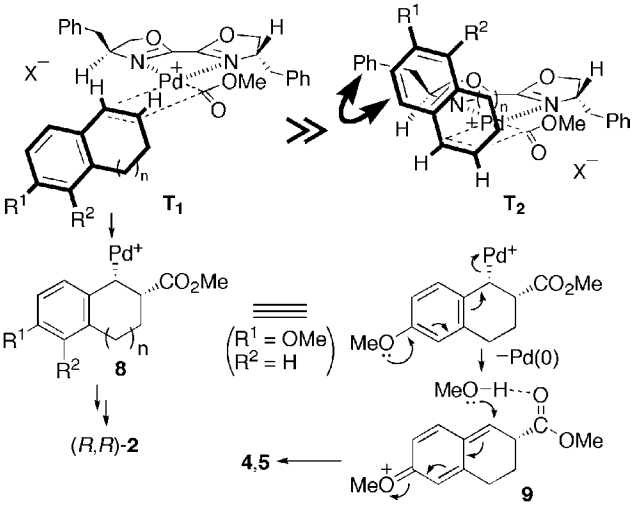
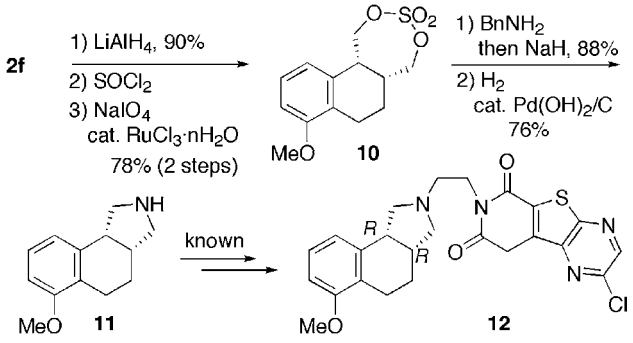



**Figure 1.**

chemistry described below. The enantioselective carbopalladation might proceed via $T_1$ to avoid steric hindrance between benzyl group in **3** and aromatic ring in **1** found in $T_2$. The production of MeO-substituted monocarbonylated compounds **4** and **5** from **1e** with excellent enantioselectivity similar to that of **2e** suggested the regioselective carbopalladation[9] occurred to give **8**, followed by reductive elimination and subsequent addition of MeOH as shown in **9** in the case of **1e**.

Tricyclic hexahydrobenz[*e*]isoindoles are reported to be $\alpha_{1A}$ adrenoceptor antagonists as potential agents for benign prostatic hyperplasia, and a 6-OMe-substituted compound **12** with (R,R) stereochemistry of the ring junction of the benz[*e*]isoindole is most effective.[10] The present bis(alkoxycarbonylation) could provide two vicinal substituents with cis relationship at once in an enantioselective manner, and the products might be good precursors for the hexahydrobenz[*e*]isoindoles. Thus, the construction of a hexahydrobenz[*e*]isoindole skeleton from the carbonylated product **2f** was performed (Scheme 2). Reduction of **2f** (93% ee)[11] by $LiAlH_4$ gave a *cis*-diol, which was converted to the corresponding cyclic sulfonate **10** in good yield. The sulfonate **10** was treated with benzylamine followed by addition of a base to form a hexahydrobenz[*e*]isoindole skeleton. Hydrogenolysis catalyzed by $Pd(OH)_2/C$ furnished a debenzylated amine **11** as a precursor of **12**.[10] The absolute configuration of the amine **11** was determined to be (R,R) by a comparison of its specific rotation with the reported one ($[\alpha]_D^{25}$ −21 (*c* 0.34, MeOH), lit.[10] (R,R) isomer: $[\alpha]_D^{20}$ −22.0 (*c* 1.39, MeOH)).

As described above, we have developed the enantioselective palladium-catalyzed asymmetric bis(alkoxycarbonylation) reaction of 1,2-dihydronaphthalenes and indene to form the optically active *cis*-diesters with excellent enantioselectivities. This carbonylation method provides a useful route to synthesize chiral polycyclic compounds, such as hexahydrobenz[*e*]isoindoles.




**Scheme 2.**

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This paper is dedicated to the memory of the late Professor Yoshihiko Ito.

## References and Notes

1 a) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation*, Plenum Press, New York, **1991**. b) *Catalytic Carbonylation Reactions*, ed. by M. Beller, Springer, Berlin, **2006**.

2 L. F. Tietze, H. Ila, H. P. Bell, *Chem. Rev.* **2004**, *104*, 3453; K. Nozaki, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 215; Y. Kawashima, K. Okano, K. Nozaki, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 347; C. Dong, H. Alper, *J. Org. Chem.* **2004**, *69*, 5011; C. Dong, H. Alper, *Tetrahedron: Asymmetry* **2004**, *15*, 35; Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198, and references cited therein.

3 S. C. A. Nefkens, M. Sperrle, G. Consiglio, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1719; M. Sperrle, G. Consiglio, *J. Mol. Catal. A: Chem.* **1999**, *143*, 263; M. Hayashi, H. Takezaki, Y. Hashimoto, K. Takaoki, K. Saigo, *Tetrahedron Lett.* **1998**, *39*, 7529.

4 K. Inomata, S. Toda, H. Kinoshita, *Chem. Lett.* **1990**, 1567; S. Toda, M. Miyamoto, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600; T. Mizutani, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1251.

5 Related bis(alkoxycarbonylation): Y. Tamaru, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1991**, *56*, 1099; T. Yokota, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2002**, *67*, 5005.

6 a) Y. Ukaji, M. Miyamoto, M. Mikuni, S. Takeuchi, K. Inomata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735. b) S. Takeuchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955.

7 The treatment of **2f** with NaOMe in MeOH at 60 °C for 6 h gave the corresponding isomerized *trans*-diester (60%) and **2f** (33%). The relative stereochemistry of **2f** was confirmed to be cis by NMR spectra in comparison of the coupling constants $J_{1-2}$ 5.12 Hz for **2f** (cis) with 8.54 Hz for trans isomer.

8 The representative procedure for **1f** (Entry 11): Under an Ar atmosphere, $CuOTf(C_6H_6)_{0.5}$ (186 mg, 0.74 mmol) was placed in a flask and a MeOH (6 mL) solution of **1f** (235 mg, 1.47 mmol) and a THF (6 mL) solution of **3** (19 mg, 0.059 mmol) was added. To the mixture, $PdCl_2$ (5.32 mg, 0.030 mmol) was added. The Ar atmosphere was replaced with $CO/O_2$ (ca. 1/1, v/v) and the reaction mixture was stirred for 2 d at 60 °C. A saturated aqueous solution of $NaHCO_3$ was added and the insoluble substance was filtered off. After the filtrate was extracted with ethyl acetate, the extracts were washed with water and brine, dried over $Na_2SO_4$, and condensed in vacuo. The residue was purified by column chromatography and further recycle HPLC to give **2f** (245 mg, 60%, 92% ee).

9 Benzylic Pd intermediate might be dominated over its regioisomer because the contribution of $\eta^3$-character in the resonance between aromatic ring: An example of $\eta^3$-character of benzylic Pd species. A. M. Johns, M. Utsunomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 1828.

10 M. D. Meyer, R. J. Altenbach, F. Z. Basha, W. A. Carroll, S. Condon, S. W. Elmore, J. F. Kerwin, Jr., K. B. Sippy, K. Tietje, M. D. Wendt, A. A. Hancock, M. E. Brune, S. A. Buckner, I. Drizin, *J. Med. Chem.* **2000**, *43*, 1586.

11 The combined substrates obtained from experiments of Entries 10 and 11 in Table 1 were used.

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