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Asymmetric allylic alkylation of cycloalkenediol diacetates using a chiral phosphine ligand bearing a carboxyl group

Tatsuo Okauchi,* Kouji Fujita, Tsuneyuki Ohtaguro, Satomi Ohshima and Toru Minami*

Department of Applied Chemistry, Kyushu Institute of Technology, Sensuicho, Tobata, Kitakyushu, 804-8550, Japan

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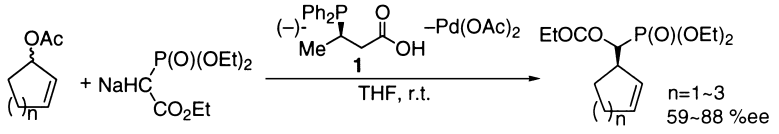
Abstract

Asymmetric induction in the allylic alkylation of cycloalkenediol diacetates was performed using a chiral alkylphosphine ligand bearing a carboxyl group, 3-(diphenylphosphino)butanoic acid. An increase in enantiomeric excess of the monoalkylated products of *cis*-cycloalkenediol diacetates was observed through a sequential asymmetric allylic alkylation–kinetic resolution process.

1. Introduction

Asymmetric allylic alkylations using chiral palladium catalysts have been extensively investigated, and a wide variety of chiral ligands has been developed.[1] While high enantioselectivities (>90% ee) were achieved in certain cases, such high asymmetric induction has mostly been observed for acyclic allyl substrates (i.e., 3-acetoxy-1,3-diphenyl-2-propene). In contrast, the asymmetric induction of cyclic allyl substrates (i.e., 1-acetoxy-2-cyclohexene) has remained difficult so that only a few examples reporting high enantioselectivity (>90% ee) are known.[2–7] Several years ago, we reported the synthesis of novel chiral phosphine ligands bearing a carboxyl group[8,9] and found that the chiral 3-(diphenylphoshino)butanoic acid **1**–palladium catalyst was effective for the asymmetric induction of cyclic allyllic substrates (Eq. (1)).[10] These results prompted us to apply the chiral catalyst to the asymmetric alkylation of other cyclic allyllic substrates. The alkylation of cycloalkenediol derivatives gives useful building blocks in synthetic organic chemistry.[11,12] In this paper, we describe an asymmetric allylic alkylation of cycloalkenediol diacetates using a chiral phosphinocarboxylic acid–palladium complex.



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* Corresponding authors. Fax: +81-(0)93-884-3300; e-mail: minami@che.kyutech.ac.jp

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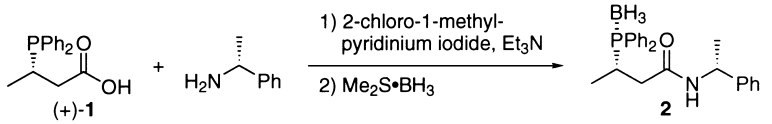
2. Results and discussion

2.1. Absolute configuration of chiral 3-(diphenylphoshino)butanoic acid *1*

The preparation of **1** and its resolution can be easily performed following our previous report;[10] however, its absolute configuration was not known. To establish the configuration, we synthesized a crystalline derivative of **1** for X-ray analysis. The chiral phosphinocarboxylic acid (+)-**1** was condensed with (*R*)-α-methylbenzylamine to afford the corresponding amide. The amide was converted to phosphine–borane complex **2**, which was subjected to X-ray analysis (Eq. (2)). As shown in Fig. 1, the stereochemistry of (+)-**1** was confirmed to have *S*-configuration.



(2)

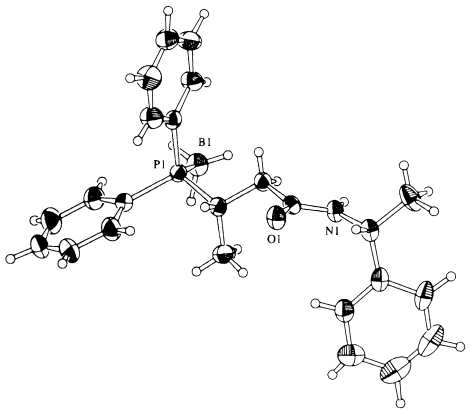
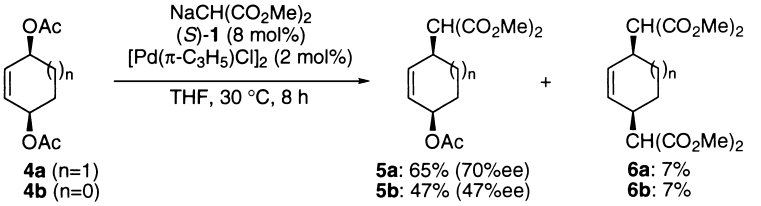


Figure 1. ORTEP diagram of **2**. 30% Probability

2.2. Palladium-catalyzed allylic alkylation of cis-cycloalkenediol diacetates

The reaction of dimethyl sodiomalonate **3** with *cis*-1,4-diacetoxy-2-cyclohexene **4a** or -2-cyclopentene **4b** was carried out in the presence of the chiral phosphine carboxylic acid (*S*)-**1** and π-allylpalladium chloride dimer (Eq. (3)).

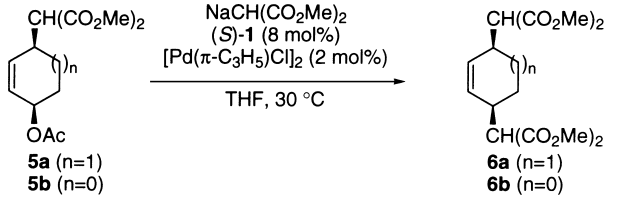


(3)

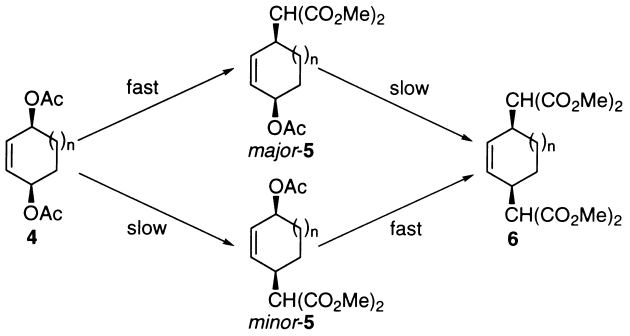
As shown in Eq. (3), monoalkylated products *cis*-(1*R*,4*S*)-1-acetoxy-4-[bis(methoxycarbonyl)-methyl]-2-cyclohexene (+)-**5a** and *cis*-(1*R*,4*S*)-1-acetoxy-4-[bis(methoxycarbonyl)methyl]-2-

cyclopentene (+)-**5b** were obtained in moderate enantiomeric excesses, accompanied by a small amount of dialkylated products **6a**,**b**. Because monoalkylated products **5a**,**b** are potential substrates for allylic alkylation, a kinetic resolution will be coupled to the asymmetric allylic monoalkylation.

Trost et al. reported that a sequential asymmetric allylic alkylation–kinetic resolution process using a chiral diphosphine ligand realized increased enantiomeric excess in the monoalkylated product as the second alkylation proceeded (Scheme 1).[1a,13] This process requires the minor enantiomer of the monoalkylated products to be alkylated faster than the major enantiomer. To investigate whether or not, in analogy with Trost's ligand, our ligand **1** works, asymmetric allylic alkylation of racemic monoalkylated products **5a**,**b** was carried out.



(4)



Scheme 1.

As shown in Table 1, the kinetic resolution was observed. The % ee of recovered (+)-**5** increased with increasing yield of **6** and the sign of the optical rotation of **5** in Eq. (4) was the same as that of **5** in Eq. (3). This indicates that our chiral ligand can also realize the sequential asymmetric alkylation–kinetic resolution process. Thus, we examined the reaction of **4** with the yield of **6** in a range of 7 to 73% (Eq. (1), Table 2). As shown in Table 2, the enantiomeric excesses of **5a**,**b** increased up to 92 and 81% ee, when the yields of **6a**,**b** were 56 and 73%, respectively. The enantiomeric purities of **5a**,**b** were determined by chiral HPLC analysis after conversion of **5a**,**b** to the respective benzoates. This sequential asymmetric allylic alkylation–kinetic resolution process would be a convenient method for the preparation of chiral cycloalkene derivatives.

2.3. *Palladium-catalyzed allylic alkylation of* trans-*cycloalkenediol diacetate*

Next, we examined the reaction of diacetate of *trans*-cyclohexenediol **7** (Scheme 2). The situation differs from that observed with *cis*-substrates. The *trans*-substrate **7** is a racemic mixture. Accordingly, not only the dialkylation step, but also the monoalkylation step is expected to effect

Table 1
Kinetic resolution of racemic mixtures of **5**

entry	substrate	recovered **5**		**6**
		yield(%)[a]	%ee	yield(%)[a]
1	**5a**	79	10	10
2	**5a**	76	11	19
3	**5a**	60	23	26
4	**5a**	59	27	36
5	**5b**	60	9	15
6	**5b**	50	17	26
7	**5b**	37	22	38

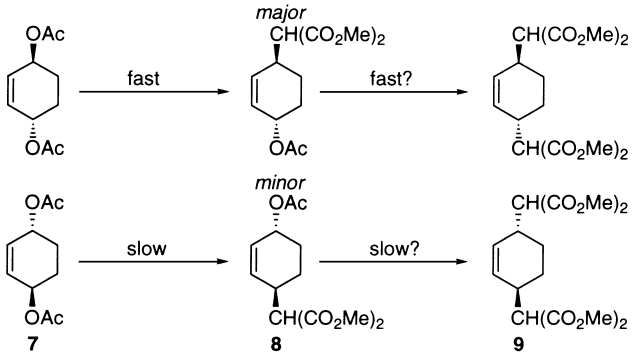
[a] GC yield based on **5**.

Table 2
Sequential asymmetric allylic alkylation–kinetic resolution of **4**

entry	substrate	**5**		**6**
		yield(%)[a]	%ee	yield(%)[a]
1	**4a**	65	70	7
2	**4a**	65	89	46
3	**4a**	41	92[b]	56
4	**4b**	31	47	7
5	**4b**	38	51	20
6	**4b**	35	60	41
7	**4b**	7	81[c]	73

[a]GC yield based on **4**. [b]$[\alpha]_D$ +82.02 (c=0.787) [c]$[\alpha]_D$ +23.61 (c=0.180)

the kinetic resolutions. To obtain monoalkylated product **8** in high enantiomeric excesses, the minor product of the first alkylation must be consumed predominantly in the second alkylation. However, the major products would be alkylated faster than the minor ones, because **7** and **8** have C_2-like symmetry and the allylic carbons of one enantiomer have the same configuration.



Scheme 2.

The asymmetric alkylation of diacetate of *trans*-cyclohexenediol **7** was carried out with different amounts of dimethyl sodiomalonate **3** in the presence of (*S*)-**1** and π-allylpalladium chloride dimer. The kinetic resolution was observed and the monoalkylated product (–)-**8** was obtained in

68% ee when the yield of **8** was 51% (Table 3, entry 1). However, the enantiomeric excess of **8** decreased as the second alkylation proceeded prospectively (Table 3). The enantiomeric purities of **8** were determined by chiral HPLC analysis after conversion to the respective benzoate. The absolute configuration of (–)-**8** has not been determined.

Table 3
Asymmetric allylic alkylation of **7**

entry	**3**	**8**		**9**
	(equiv.)	yield(%)[a]	%ee	yield(%)[a]
1	0.7	51	68[b]	2
2	1.0	65	61	11
3	1.5	52	52	26
4	2.0	44	45	54

[a]GC yield Based on **7**. [b]$[\alpha]_D$ –83.85 (c=0.397)

3. Conclusions

The following pertinent points are noted: (1) asymmetric induction in the allylic alkylation of cycloalkenediol diacetates has been performed using a chiral alkylphosphine ligand bearing a carboxyl group, 3-(diphenylphosphino)butanoic acid; (2) an increase in enantiomeric excess of the monoalkylated products of *cis*-diacetates was observed as the second alkylation proceeded.

4. Experimental

4.1. General procedures

Melting points were determined with a Büchi 530 melting point apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-A500 spectrometer in $CDCl_3$ operating at 500 and 125 MHz, respectively, with Me_4Si as internal standard. IR spectra were recorded with a JEOL JIR-5500 spectrometer. High-resolution mass spectra (HRMS) were recorded on a JEOL DX-300 mass spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out with a Shimadzu HPLC. Optical rotations were measured with a JASCO DIP-1000 polarimeter. All reactions were carried out using degassed solvents under an argon atmosphere.

4.2. Materials

cis-1,4-Diacetoxy-2-cyclohexene **5a**, *cis*-1,4-diacetoxy-2-cyclopentene acetate **5b**, and *trans*-1,4-diacetoxy-2-cyclohexene **7** were prepared according to the reported procedures.[14]

4.3. N-*((*R*)-1-Phenylethyl)-3-diphenylphosphinobutanamide(P–B)borane* **2**

To a CH_2Cl_2 solution (2 mL) of *N*-((*R*)-1-phenylethyl)-3-diphenylphosphinobutanamide (116 mg, 0.31 mmol) prepared from (+)-**1** and (*R*)-1-phenylethylamine was added borane–methyl

sulfide complex (40 mg, 0.53 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed by evaporation in vacuo. The residue was purified over preparative TLC on silica gel using AcOEt:hexane (1:1) as eluent to give the corresponding phosphine–borane complex in quantitative yield. Recrystallization from EtOH/hexane provided a crystal suitable for X-ray analysis.

Compound **2**: IR (KBr): 1640, 1540, 1435, 1100, 1060, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (dd, $J=16.3$, 6.7 Hz, 3H), 1.39 (d, $J=7.0$ Hz, 3H), 2.20 (ddd, $J=15.5$, 9.9, 5.8 Hz, 1H), 2.41 (ddd, $J=14.4$, 10.3, 3.1 Hz, 1H), 3.27–3.38 (m, 1H), 5.04 (dd, $J=7.1$, 7.0 Hz, 1H), 5.75 (d, $J=7.3$ Hz, 1H), 7.22–7.34 (m, 5H), 7.39–7.51 (m, 6H), 7.73–7.86 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.1 (d, $^2J_{C-P}=3.1$ Hz), 21.7, 25.2 (d, $^1J_{C-P}=39.3$ Hz), 38.0 (d, $^2J_{C-P}=5.2$ Hz), 49.2, 126.0, 127.4, 127.9 (d, $^1J_{C-P}=9.3$ Hz), 128.3 (d, $^1J_{C-P}=9.3$ Hz), 128.7, 128.8 (d, $^3J_{C-P}=9.3$ Hz), 129.0 (d, $^3J_{C-P}=9.3$ Hz), 131.3 (d, $^4J_{C-P}=2.1$ Hz), 131.4 (d, $^4J_{C-P}=2.1$ Hz), 132.5 (d, $^2J_{C-P}=3.1$ Hz), 132.6 (d, $^2J_{C-P}=3.1$ Hz), 143.1, 169.6 (d, $^2J_{C-P}=7.3$ Hz). Anal. calcd for $C_{24}H_{29}BNOP$: C, 74.05; H, 7.51; N, 3.59%. Found: C, 74.15; H, 7.51; N, 3.54%.

4.4. Crystal structure determination for **2** (see Fig. 1)

A colorless prismatic crystal of **2** with the dimensions $0.20\times0.20\times0.30$ mm was measured on a Rigaku AFC7R diffractometer using graphite monochromated CuK_α radiation ($\lambda=1.54178$ Å) at $T=20\pm1°C$. Crystal data: $C_{24}H_{29}BNOP$, $M=389.28$, monoclinic, space group $P2_1$(#4), $a=9.209(3)$ Å, $b=9.821(3)$ Å, $c=13.023(2)$ Å, $\beta=104.47(2)°$, $V=1140.5(5)$ Å^3, $Z=3$, $D_{calc}=1.700$ g/cm^3, $F_{000}=624.00$, $\mu(CuK_\alpha)=17.31$ cm^{-1}. Structure solved by direct methods. Final agreement factors are $R=0.034$, $R_w=0.045$. The authors have deposited the atomic coordinates for the structure of **2** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

4.5. Asymmetric allylic alkylation of **4a**,**b**, **5a**,**b** or **7** with **3**

A chiral ligand (*S*)-**1** (0.08 mmol) and $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (7.3 mg, 0.02 mmol) were placed in a two-necked flask equipped with magnetic stirring bar, serum cap and three-way stopcock. The flask was filled with nitrogen after evacuation and to it was added dry THF (3 mL). The mixture was stirred for 0.5 h at room temperature, and a THF solution (2 mL) of **4a**,**b**, **5a**,**b** or **7** (1 mmol) was added. The mixture was stirred for 0.5 h at room temperature, and a solution of **3**, generated from dimethyl malonate (0.7–2.0 mmol) and sodium hydride (60% dispersion in mineral oil, 0.7–2.0 mmol), in dry THF (5 mL) was added. The reaction mixture was kept stirring at given temperatures for 1–8 h. After the reaction mixture was quenched with pH 7 phosphate buffer, the mixture was extracted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified over preparative TLC on silica gel to give **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7**, **8** or **9**. Spectral data are in agreement with those reported for **5a**,[15] **5b**,[16] **6a**,[17] **6b**, **8**[15] and **9**. The enantiomeric purities of **5a**,**b** and **8** were determined by chiral HPLC analysis (**5a**: Daicel Chiralcel OJ, hexane:^{i}PrOH = 95:5, 0.5 mL/min; **5b**: Daicel Chiralcel OJ, hexane:^{i}PrOH = 90:10, 0.5 mL/min; **7**: Daicel Chiralcel AD, hexane:EtOH = 95:5, 0.5 mL/min) after conversion to the respective benzoate by deacetylation with NaOMe/MeOH, followed by benzoylation with benzoyl chloride/pyridine. The absolute configurations of (+)-**5a** and (+)-**5b** were determined by comparison of the optical rotation with that reported in the literature.[16,18]

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