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Asymmetric Cyclopropanation of Ketene Silyl Acetal with Allylic Acetate Catalyzed by a Palladium Complex

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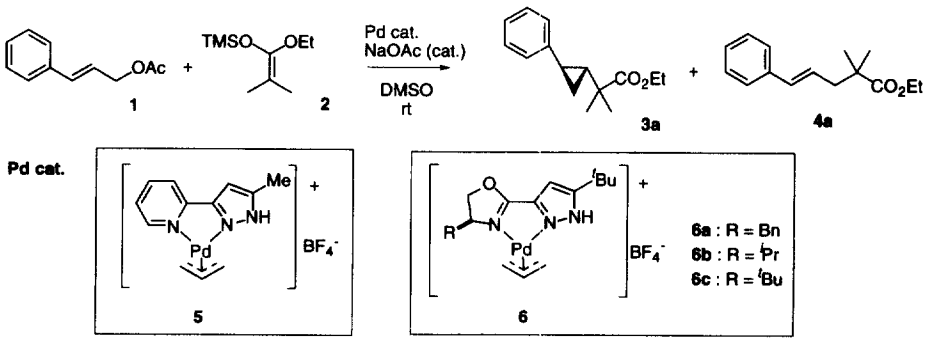
Abstract

The first asymmetric cyclopropanation of ketene silyl acetal with allylic acetate was achieved. New chiral oxazolidinylpyrazole ligands and their η^3-allylpalladium complexes were synthesized. Reaction of cinnamyl acetate with ketene silyl acetal of ethyl isobutylate in the presence of a palladium complex gave a phenyl cyclopropane derivative in 20~ 54%ee. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; cyclopropanation; palladium and compounds; catalyst

The cyclopropane structure exists in a wide range of naturally occurring compounds, and the effective synthesis of which has been a significant objective in organic synthesis [1,2]. Catalytic asymmetric cyclopropanation has been one of the most efficient methods because a small amount of a chiral source produced a large amount of optically active products. Actually, [2+1] addition of substituted olefin and diazo compounds in the presence of a chiral copper or rhodium catalyst was achieved with high enantioselectivity [3]. We recently reported that reaction of ketene silyl acetals with cinnamyl acetate (**1**) gave cyclopropane **3a** and unsaturated ester **4a** in the presence of palladium pyridinylpyrazole complexes **5** (Scheme 1) [4] and pyridinylimidazole complexes

Scheme1



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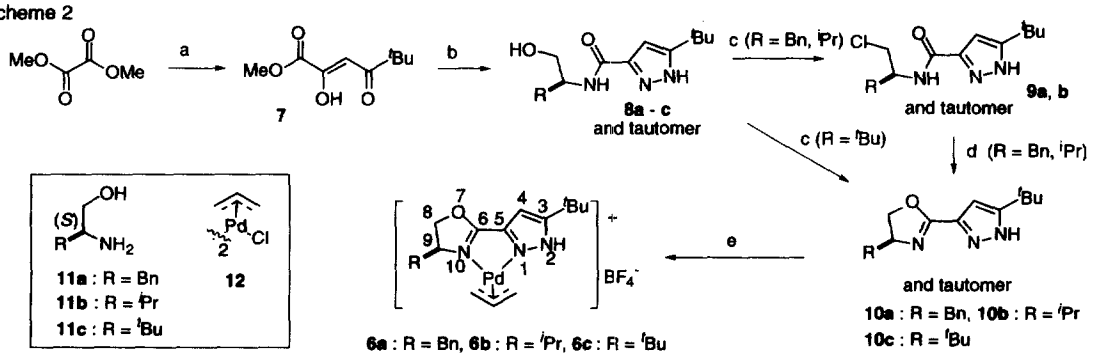
[5]. The rare cyclopropanation proceeds by nucleophilic attack of the ketene silyl acetal to the central carbon of the η^3-allyl moiety in the η^3-allylpalladium complex **5**, and subsequent reductive elimination of the palladacyclobutane. After the reductive elimination the palladium (0) species react with cinnamyl acetate (**1**) to produce the η^3-1-phenylpropenylpalladium complex. The cyclopropanation is considered to be applicable to chiral synthesis by use of chiral pyrazole derivatives as a ligand. In this paper we report the first asymmetric cyclopropanation of ketene silyl acetal with allylic acetate catalyzed by η^3-allylpalladium oxazolidinylpyrazole complexes **6a**, **6b** and **6c**.

Oxazolidinylpyrazole ligands **10** were synthesized from dimethyl oxalate in short steps (Scheme 2). Hydroxyamides **8a** - **c** were obtained by reaction of ester **7** with chiral hydroxyamines **11a** - **c**, respectively, and subsequent treatment of hydrazine. Conversion of **8a** - **c** into oxazolidinylpyrazoles **10a**, **10b**[1], and **10c** took place by chlorination and cyclization. η^3-Allylpalladium oxazolidinylpyrazole complexes **6a**, **6b**[2] and **6c** were synthesized by reaction of appropriate ligands **10** and η^3-allylpalladium chloride dimer in the presence of $AgBF_4$.

Scheme 2



Reagents and conditions: (a) NaH, 3,3-dimethyl-2-butanone, THF, reflux (69%); (b) aminoalcohol **11**, EtOH, 80 °C; hydrazine monohydrate, EtOH, 80 °C (**8a**: R = Bn; 49%, **8b**: R = iPr; 82%, **8c**: R = tBu; 23%) ; (c) $SOCl_2$, 1,2-dichloroethane, 40 °C (**9a**: R = Bn; 99%, **9b**: R = iPr; 56%, **10c**: 86%) ; (d) NaOMe, MeOH, reflux (**10a**: 94%, **10b**: 99%); (e) **12**, $AgBF_4$, ether, CH_2Cl_2, (**6a** : quant, **6b** : 93%, **6c** : 80%)

[1] **10b**: $[\alpha]_D^{28}$: -45.2 (c 0.46, MeOH), m.p. 116-119 °C, Anal. calcd. for $C_{13}H_{21}N_3O$; C: 66.35, H: 9.00, N: 17.86, Found; C: 66.08, H: 9.04, N: 17.63; ^{1}H NMR ($CDCl_3$, 600MHz, 25 °C) δ 11.29 (NH, br), 6.60 (H4, s), 4.40 (H8, m), 4.13 (H8, m), 4.13 (H9, m), 1.87 {^{i}Pr(CH), m}, 1.33 (^{t}Bu, s, 9H), 1.02 {^{i}Pr(Me), d, 3H, J =6.6 Hz}, 0.92 {^{i}Pr(Me), d, 3H, J = 6.6 Hz}; ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C) δ 157.99 (C6, br), 103.16 (C4), 72.35 (C9), 70.03 (C8), 32.61 {^{i}Pr(CH)}, 31.38 {^{t}Bu(C)}, 30.21 {^{t}Bu(Me)}, 18.93 {^{i}Pr(Me)}, 17.98 {^{i}Pr(Me)}. (Signals of C3 and C5 are missing because of the tautomerism on the pyrazole.)

[2] **6b**: m.p. 90 °C (dec), Anal. calcd. for $C_{16}H_{26}ON_3PdBF_4$; C: 40.92, H: 5.58, N: 8.95, Found; C: 40.49, H: 5.59, N: 8.71; ^{1}H NMR (DMF-d_7, 600 MHz, 25 °C) δ 14.80 (NH, br), 6.94 (H4, s), 5.85 {allyl(Hcenter), tt, J = 13.0, 7.0 Hz}, 4.96 (H8, dd, J = 9.5, 9.5 Hz), 4.90 (H8, dd, J =9.5, 7.3 Hz), 4.58 {allyl(Hsyn), d, J = 7.0 Hz}, 4.57 {allyl(H*syn), d, J = 7.0 Hz}, 4.40 (H9, ddd, J =9.5, 7.3, 4.4 Hz), 3.37 {allyl(H*anti), d, J = 13.0 Hz}, 3.40 {allyl(Hanti), d, J =13.0 Hz}, 2.14 {^{i}Pr(CH), m}, 1.41 {^{t}Bu(Me), s, 9H}, 0.99 {(^{i}Pr(Me), d, 3H, J = 6.6 Hz}, 0.88 {(^{i}Pr(Me), d, 3H, J =6.6 Hz}; ^{13}C NMR (DMF-d_7, 150 MHz, 25 °C) δ 166.66 (C6) , 159.37 (C3), 141.02 (C5), 116.87 {allyl(Ccenter)}, 103.24 (C4), 74.06 (C8), 69.51 (C9), 62.37 {ally(Cterminal)}, 61.65 {allyl(C*terminal)}, 32.30 {^{t}Bu(C)}, 31.38{^{i}Pr(CH)}, 29.92 {^{t}Bu(Me)}, 18.39{^{i}Pr(Me)}, 15.35{^{i}Pr(Me)}. ^{15}N NMR (DMF-d_7, 25 °C, ^{1}H-^{15}N PFG-HMBC [5], ext. ref. $\underline{N}H_4NO_3$ in DMSO-d_6 at 0 ppm) δ 223.4 (N1), 189.3 (N2), 165.9 (N10).

Catalytic cyclopropanation of **1** with **2** was carried out in the presence of palladium complexes **6**, and the results are listed in Table 1. After the reaction was completed, a mixture of **3a** and **4a** was isolated, and the ratio was determined by ^{1}H NMR (300 MHz). Pure **3a** was obtained after dihydroxylation of **4a** with OsO_4 and purification by flash chromatography[3]. The ratio of cyclopropane **3a** to unsaturated ester **4a** varied with the kind of **R** group on the ligands. When the complex **6b** was used, the selectivity of **3a** to **4a** was 9.5 : 1. Use of **6c** which had a bulky *t*-butyl group heightened the enantiomeric excess of **3a** up to 54%ee but lowered the selectivity of cyclopropane **3a**.

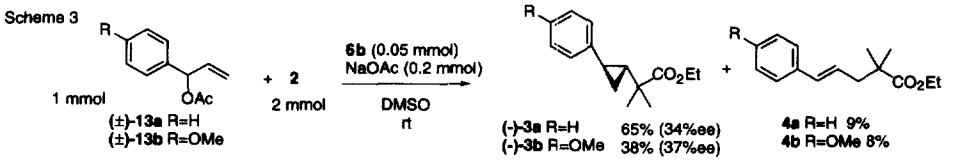
Table 1
Reaction of **1** and **2** in the presence of palladium catalysts **6a-c**

Pd complex	Yield (**3a** + **4a**)	Ratio (**3a** : **4a**)	%ee of **3a**[4]
6a	56%	2.8 : 1	20%ee (-)-(*R*,*R*)
6b	49%[a]	9.5 : 1	35%ee (-)-(*R*,*R*)[b]
6c	34%[c]	1.9 : 1	54%ee (-)-(*R*,*R*)

(a) 51% recovery of **1**, (b) $[\alpha]_D^{28}$ -21.4 ($CHCl_3$, c 0.65), (c) 14% recovery of **1**

When racemic secondary allylic acetate **13a** was used instead of cinnamyl acetate (**1**), (-)-**3a** was obtained in 34%ee. (4-Methoxyphenyl)propenyl acetate **13b** also reacted with **2** to give (-)-**3b** (37%ee) and **4b**.

Scheme 3



In the present reaction, four kinds of η^3-(1-phenylpropenyl)palladium complexes (**A**, **B**, **C**, and **D**) are considered as intermediates as shown in Figure 1. If η^3-η^1-η^3-rearrangement [7]

[3] **Experimental procedure**

Cinnamyl acetate (1 mmol) and ketene silyl acetal **2** (2 mmol) were added to a solution containing palladium catalyst **6** (0.05 mmol) and NaOAc (0.2 mmol) in DMSO (4 mL). The reaction mixture was stirred at rt for 24 h. Diethyl ether and diluted HCl solution were added to the reaction mixture, and the mixture was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated *in vacuo*. A mixture of cyclopropane derivatives and allylated compounds was obtained by flash chromatography. Yields and ratio were determined by 300 MHz NMR with n-decane as an internal standard. Pure cyclopropane derivatives were obtained after dihydroxylation with OsO_4 and purification by flash chromatography. Enantiomeric excess was determined by HPLC using Daicel Chiralcel®-OJ (2% of 2-propanol in hexane).

[4] The absolute configuration of synthetic (-)-**3a** was determined after transformation into hydroxycyclopropane (-)-**14** by referring to the authentic hydroxycyclopropane (-)-**15** which was prepared from (*R*, *R*)-phenylcyclopropanecarboxylic acid [6].

Scheme 4

Scheme 5

and/or apparent rotation of an allyl group [8] occurs in the complexes (**A**, **B**, **C**, and **D**), these complexes can be interconverted. From the complexes **A** and **B**, (*R,R*)-**3a** is considered to be given as a chiral cyclopropane whereas (*S,S*)-**3a** will be furnished from **C** and **D**. Therefore, the selection of **A** and **B**, or, **C** and **D** is an important factor for attaining high enantioselectivity. In order to examine the reaction course we synthesized η^3-1-phenylpropenylpalladium complex **16** from ligand **10b** and η^3-1-phenylpropenylpalladium chloride dimer, and measured ^{1}H NMR of **16**. Interestingly, only two isomers, **16** (**A** form) and **16** (**D** form), were observed as a 2.2 : 1 mixture[5]. The phenyl group in the allyl moiety was located at only the oxazolidine side in both isomers. Thus, the protons shielded by the phenyl group were observed on the oxazolidine ring in **16** (**A** form) and **16** (**D** form)[6]. On the contrary, the proton on the pyrazole ring was not shielded (Figure 2). This result suggests that the asymmetric cyclopropanation proceeds via only **16** (**A** form) and **16** (**D** form), and ligands **10** having only one asymmetric carbon center have possibility to perform highly enantioselective cyclopropanation. Now, we are investigating new chiral ligands and examining the reaction mechanism.

Figure 1

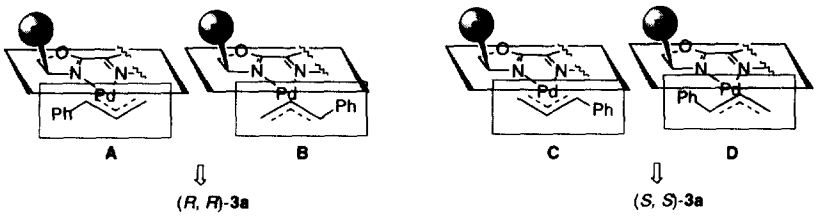
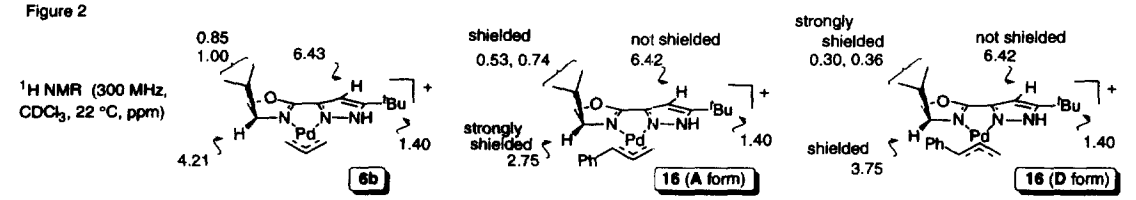


Figure 2



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[5] ^{1}H NMR of **6b** and **16** was measured at various temperatures because chemical exchange of the allyl moiety occurred and the width of the signals varied.

[6] We assigned the species whose methine proton on oxazoline was shielded more strongly as **A** form. On the contrary, **D** form was assigned as its 2-propyl group on oxazoline was shielded more strongly.