

Tetrahedron Letters 40 (1999) 3597-3600

TETRAHEDRON LETTERS

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

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Received 16 February 1999; revised 8 March 1999; accepted 12 March 1999

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

Schemet



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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, 10b¹, and 10c took place by chlorination and cyclization. η^3 -Allylpalladium oxazolidinylpyrazole complexes 6a, 6b² and 6c were synthesized by reaction of appropriate ligands 10 and η^3 -allylpalladium chloride dimer in the presence of AgBF₄.



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) SOCl₂, 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**, AgBF₄, ether, CH₂Cl₂, (**6a** : quant, **6b** : 93%, **6c** : 80%)

¹ **10**b: $[\alpha]_{p}^{28}$: -45.2 (c 0.46, MeOH), m.p. 116-119 °C, Anal. calcd. for $C_{13}H_{21}N_{3}O$; C: 66.35, H: 9.00, N: 17.86, Found; C: 66.08, H: 9.04, N: 17.63; ¹H NMR (CDCl₃, 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 {¹Pr(CH), m}, 1.33 (¹Bu, s, 9H), 1.02 (¹Pr(Me), d, 3H, J = 6.6 Hz), 0.92 {¹Pr(Me), d, 3H, J = 6.6 Hz}; ¹³C NMR (CDCl₃, 150 MHz, 25 °C) δ 157.99 (C6, br), 103.16 (C4), 72.35 (C9), 70.03 (C8), 32.61 {¹Pr(CH)}, 31.38 {¹Bu(C)}, 30.21 {¹Bu(Me)}, 18.93 {¹Pr(Me)}, 17.98 {¹Pr(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; ¹H NMR (DMF-d₇, 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 {¹Pr(CH), m}, 1.41 {¹Bu(Me), s, 9H}, 0.99 {(¹Pr(Me), d, 3H, J = 6.6 Hz}; ¹³C NMR (DMF-d₇, 150 MHz, 25 °C) δ 166.66 (C6), 159.37 (C3), 141.02 (C5), 116.87 {allyl(Ceenter)}, 103.24 (C4), 74.06 (C8), 69.51 (C9), 62.37 {ally(Cterminal)}, 61.65 {allyl(C*terminal)}, 32.30 {¹Bu(C)}, 31.38 {¹Pr(CH)}, 29.92 {¹Bu(Me)}, 18.39 {¹Pr(Me)}, 15.35 {¹Pr(Me)}. ¹⁵N NMR (DMF-d₇, 25 °C, ¹H-¹⁵N PFG-HMBC [5], ext. ref. NH4NO₃ in DMSO-d₆ 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 ¹H NMR (300 MHz). Pure 3a was obtained after dihydroxylation of 4a with OsO_4 and purification by flash chromatography³. 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

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

(a) 51% recovery of 1, (b) $[\alpha]_{D}^{28}$ -21.4 (CHCl₃, 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.



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 $\eta^3 - \eta^1 - \eta^3$ -rearrangement [7]

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].



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 NaHCO3 solution and brine, dried over MgSO4, 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 OsO4 and purification by flash chromatography. Enantiomeric excess was determined by HPLC using Daicel Chiralcel®-OJ (2% of 2-propanol in hexane).

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 ¹H NMR of 16. Interestingly, only two isomers, 16 (A form) and 16 (D form), were observed as a 2.2 : 1 mixture⁵. 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.



Acknowledgment. A.S. gratefully acknowledges financial support from the Special Postdoctoral Researchers Program.

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⁵ 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.