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PALLADIUM-CATALYZED ASYMMETRIC ALLYLATIONS OF ALDEHYDES VIA (S)-PROLINE ALLYL ESTER ENAMINES

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Abstract: Treatment of chiral enamine 3, derived from (S)-proline allyl ester (1) and 2-phenylpropionaldehyde (2), with tetrakis(triphenylphosphine)-palladium provided (R)-(-)-2-methyl-2-phenyl-4-pentenylaldehyde (5) with high enantiomeric excess. The mechanism for this asymmetric induction is discussed.

Much attention has been devoted to development of new methodologies for asymmetric induction with high enantioselectivity.[1] Quite recently much efforts have been made to reveal reaction mechanisms of palladium-catalyzed reactions in especially allylic systems[2] by stereochemical studies with chiral models involving chiral sulfinates,[3] esters from chiral allylic alcohols,[4] and chiral ligands.[5]

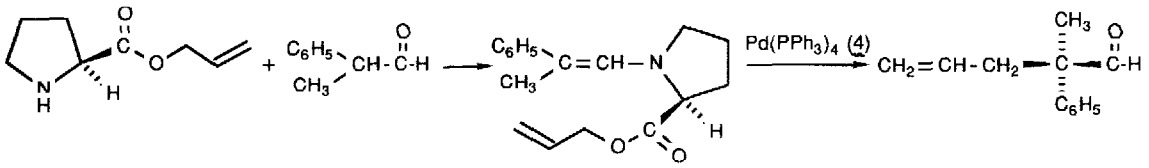
We wish to communicate herein stereochemistry of palladium-catalyzed asymmetric allylations of aldehydes via (S)-proline allyl ester enamines[6] and rationalization of the mechanistic pathway for the asymmetric induction.

Chiral enamine 3, obtained by azeotropic dehydration of (S)-proline allyl ester (1) and 2-phenylpropionaldehyde (2) in refluxing benzene, was treated with 0.15 equiv of tetrakis(triphenylphosphine)palladium (4) in the presence of 0.66 equiv of triphenylphosphine in refluxing tetrahydrofuran (THF) for 19 h, followed by acidic hydrolysis (heated in aqueous 10% HCl for 4 h), to provide (R)-(-)-2-methyl-2-phenyl-4-pentenylaldehyde (5) in 74% yield with 76% enantiomeric excess. The reaction at room temperature led to the formation of (R)-(-)-5[7] with higher optical yield (90%). The results of the reactions under other reaction conditions are summarized in Table I. The absolute configuration of the newly created asymmetric carbon was determined by chemical correlation of the produced (R)-(-)-5 with (R)-(-)-2-methyl-2-phenylpentanoic acid of known configuration[8] (reduction of (R)-(-)-5 with diimide followed by oxidation with chromic acid). The enantiomeric excess of the product (R)-5 was confirmed by NMR spectral analysis with a shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III)). The chiral aldehyde (R)-(-)-5 having an optical rotation of $[\alpha]_D$ -18.3°(MeOH) was determined to exhibit 48% enantiomeric excess by the NMR spectral analysis with the shift reagent. Therefore the optically pure (R)-(-)-5 was calculated to have an optical rotation of $[\alpha]_D$ -38.0°(MeOH) and the enantiomeric excess of the aldehyde 5 produced under other reaction conditions was given on the basis of this value, as listed in Table I. The chiral aldehyde

Table I. Palladium-Catalyzed Reactions of Enamine 3[a)]

Solvent	Reaction temp.(°C)	Reaction time (h)	Product Yield (%)	(R)-(-)-5 $[\alpha]_D$ (MeOH)	e.e.(%)
THF	r.t.	45	41	-34.2°(c 1.0, 21°C)	90
THF	66	19	74	-28.8°(c 2.8, 23°C)	76
DME	83	19	60	-19.7°(c 1.3, 22°C)	52
DME	66	19	30	-30.0°(c 1.0, 24°C)	79
C_6H_6	80	19	63	-25.9°(c 1.0, 22°C)	68

a) Enamine 3 was treated with 4 (0.1 equiv)-PPh_3 (0.4 equiv) followed by hydrolysis with heating 10% aqueous HCl.

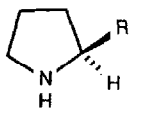


(S)-1 2 3 (R)-(-)-5

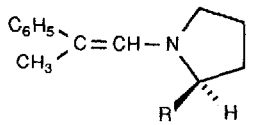
(R)-(-)-5 ($[\alpha]_D$-18.3°(MeOH)) showed an optical rotation of $[\alpha]_D$ -33.8° in a chloroform solution, which is consistent with the value reported previously.[7b)]

Reaction of (S)-proline ethyl ester enamine 7a with allyl acetate (2.0 equiv) was carried out in THF at room temperature for 24 h in the presence of 4 (0.2 equiv) and triphenylphosphine (0.66 equiv), followed by acidic hydrolysis, to give (S)-(+)-5 with 14% enantiomeric excess. Allylations of other chiral enamines 7b,c, derived from (R)-2-methylpyrrolidine (6b) or (S)-2-methoxymethylpyrrolidine (6c), were excecuted under the same conditions to afford (S)-(+)-5 and the results are listed in Table II.

Based on the stereochemical outcome obtained above, the plausible mechanistic pathway is presented as follows. Allylation to the β-carbons of the enamines 7a-c by the allylating agent activated with the palladium catalyst would occur from the back side of the chiral centers in enamine 8c, which is the most preferred conformer in the conformational equilibrium of 8a-c (8b,c are more preferable than 8a by severe steric hindrance between the amino moieties and the phenyl group in 8a) because of the more severe steric interference of the chiral part (R) with the methyl group in 8b than with the hydrogen atom in 8c. In the (S)-proline allyl ester enamine 3, however,



6a R = $CO_2C_2H_5$
b = CH_3
c = CH_2OCH_3



7a R = $CO_2C_2H_5$
b = CH_3
c = CH_2OCH_3

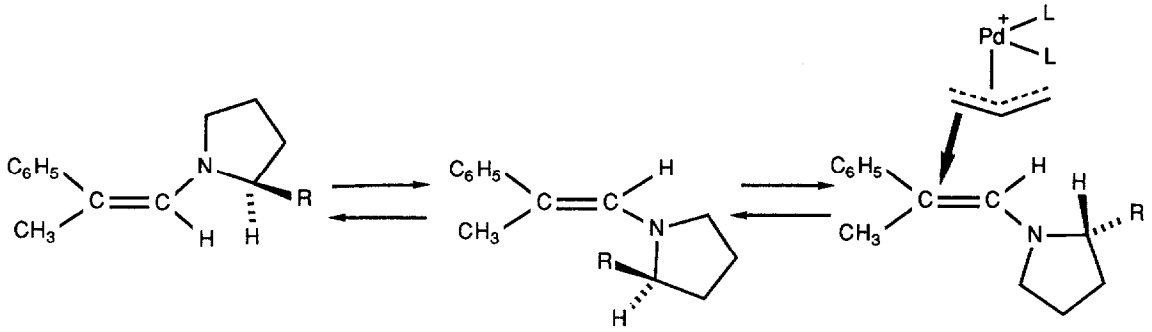
6a-c 7a-c

Table II. Palladium-Catalyzed Reactions of Enamines 7a-c[a)]

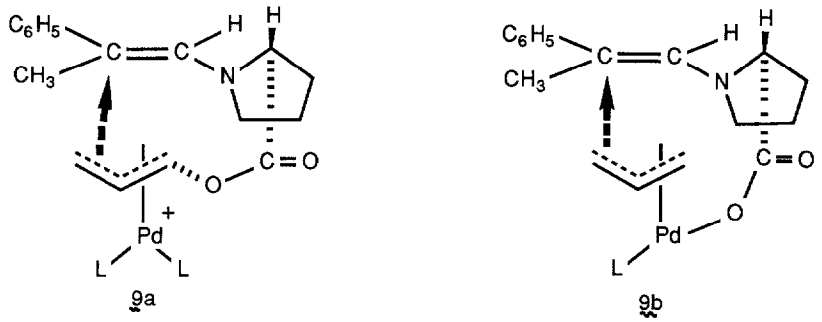
Enamines 7	Reaction temp.(°C)	Reaction time (h)	Product (S)-(+)-5 Yield(%)[b)]	$[\alpha]_D$ (MeOH)	e.e.(%)
7a	40	19	60 (89)	+3.3°(c 2.8, 24°C)	9
7a	r.t.	24	53 (84)	+5.3°(c 2.4, 25°C)	14
7b	40	19	51 (86)	+2.0°(c 1.0, 21°C)	5
7b	r.t.	24	38 (71)	+2.6°(c 2.3, 21°C)	7
7c	40	19	50 (76)	+2.5°(c 2.4, 24°C)	7
7c	r.t.	24	47 (80)	+6.0°(c 1.3, 24°C)	16

a) The reactions of 7a-c with allyl acetate (2.0 equiv) were carried out in the presence of 4 (0.2 equiv) and PPh_3 (0.66 equiv) in THF followed by hydrolysis with heating 10% aqueous HCl.

b) The corrected yields based on the recovered starting material are listed in parentheses.

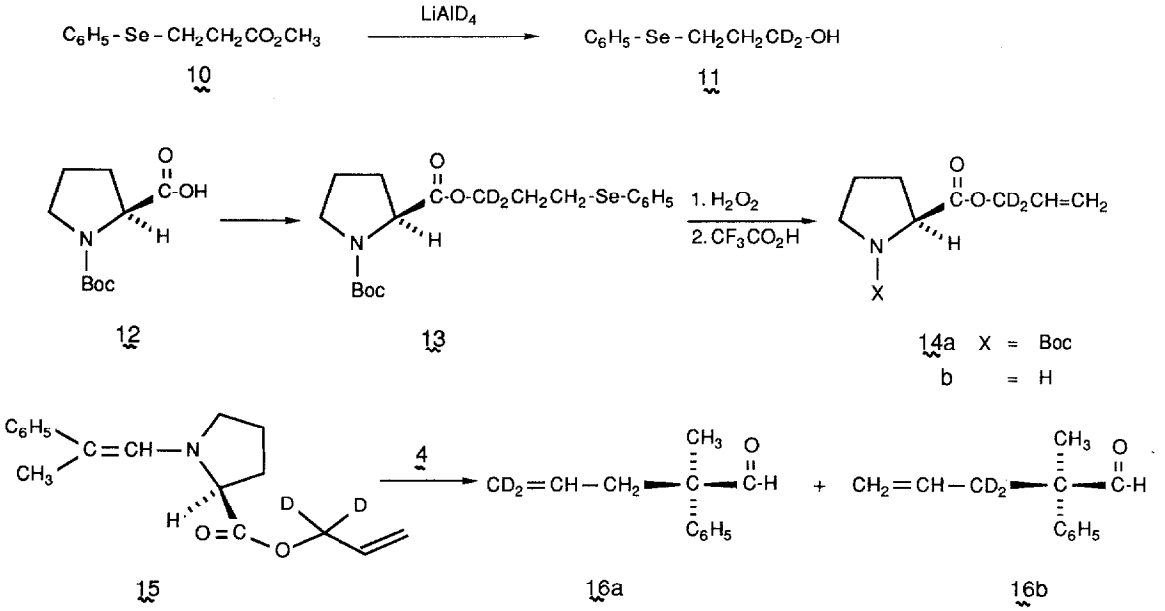


8a 8b 8c



9a 9b

intramolecular allylation via a transition state 9 would occur to furnish (R)-5. It should be noted that the palladium-catalyzed reaction (in refluxing THF for 19 h) of chiral enamine 15, obtained from 2 and (S)-proline 1,1-dideuterated-allyl ester 14b (prepared by esterification of 12 with 11 followed by oxidative elimination of the selenenyl group in 13 and debutoxycarbonylation with trifluoroacetic acid) produced a 1 : 1 mixture of 16a and 16b in 57% yield. Therefore the palladium-catalyzed reaction of 3 would proceed through a transition state 9b coordinated with the palladium catalyst.



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