INTRA- AND INTERMOLECULAR PALLADIUM-CATALYZED ASYMMETRIC ALLYLATIONS OF CHIRAL ENAMINES

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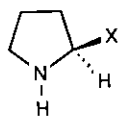
Abstract — Stereochemistry of intramolecular palladium-catalyzed asymmetric allylations of chiral enamines involving allylating species in the molecules is discussed, compared with that of intermolecular reactions. The mechanistic pathway for this asymmetric induction is proposed on the basis of the stereochemical results.

Recently much attention has been paid for π-allylic palladium chemistry in organic synthesis,[1] especially focussed on the stereochemistry of reactions of π-allylic palladium compounds involving chirality in the systems. We have already published successful palladium-catalyzed asymmetric allylations of chiral allylic sulfinates or sulfones,[2] and (S)-proline allyl ester enamines[3] or amides.[4] We wish to communicate herein intramolecular palladium-catalyzed asymmetric allylations of aldehydes, including allylating functionality in the molecules, via chiral enamines prepared from (S)-proline derivatives.

Chiral enamine 3b was prepared from (S)-proline ethyl ester (1a) and an aldehyde 2b quantitatively by azeotropically reacting in refluxing benzene for 4 h with a Dean-Stark apparatus. Upon treatment with tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] or bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] (0.20 equiv.) and tiphenylphosphine (PPh_3)(0.40 equiv.) in tetrahydrofuran (THF) at 40 or 66°C for 19h, the chiral enamine 3b underwent an intramolecular allylation to afford an α-allyl hemiacetal 4, of which oxidation with chromic acid produced an optically active lactone (S)-(-)-5 with 14-32 % enantiomeric excess in good yield. The reaction of 3b in refluxing 1,2-dimethoxyethane, benzene, or toluene afforded (+)-5. However, the more reactive allyl carbonate 3c showed higher chemical and optical yields. Treatment of chiral enamine 3c, prepared from 1a and 2c in the same way as descrived above, with $Pd(PPh_3)_4$ (0.20 equiv.) and PPh_3 (0.40 equiv.) at room temperature, 40, and 66 °C in THF, followed by oxidation with chromic acid afforded (S)-(-)-5 with 48, 36, and 27 % enantio-



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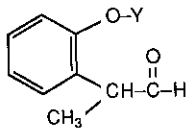
b =$CO_2CH_2CH{=}CH_2$
c =CH_2PPh_2



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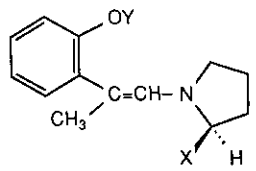
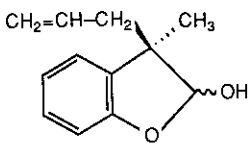
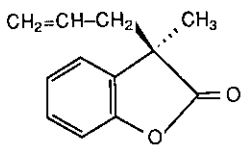
b =$CH_2CH{=}CH_2$
c =$CO_2CH_2CH{=}CH_2$



3 a Y=H X=$CO_2C_2H_5$
b =$CH_2CH{=}CH_2$ =$CO_2C_2H_5$
c =$CO_2CH_2CH{=}CH_2$ =$CO_2C_2H_5$
d =H =$CO_2CH_2CH{=}CH_2$
e =H =CH_2PPh_2
f =$CH_2CH{=}CH_2$ =CH_2PPh_2



(R)-4



(R)-(+)-5

meric excess, respectively, in good yield. On the other hands, the intermolecular asymmetric allylation provided a little lower enantioselectivity. The reaction of chiral enamine 3a, derived from 1a and 2a, with allyl acetate (2.0 equiv.) in the presence of $Pd(PPh_3)_4$ (0.20 equiv.) and PPh_3 (0.40 equiv.) in THF at 40 or 66 °C for 19 h, followed by oxidation gave (S)-(-)-5 with 28 or 10 % enantiomeric excess, respectively.

However, intramolecular allylations of chiral enamine 3d, derived from (S)-proline allyl ester (1b) and 2a, demonstrated higher enantioselectivity. The palladium-catalyzed reaction of 3d was carried out at room temperatrure, 40, or 66 °C under the same conditions as mentioned above, followed by oxidation to give (R)-(+)-5 in good yield with 84, 43, or 23 % enantiomeric excess, respectively. Similarly, chiral enamine 3e, prepared from optically active secodary amine 1c possessing a phosphine ligand in the chiral site and 2a, provided (R)-(+)-5 with 29, 18, or 6 % enantiomeric excess, upon treatment with allyl acetate (2.0 equiv.) in THF in the presence of a catalytic amount of $Pd(PPh_3)_4$ at room temperature, 40, or 66 °C followed by oxidation, respectively. The same sequence of 3f gave (R)-(+)-5 with a little higher enantiomeric excess. The whole results are summarized in Table 1. The enantiomeric excess (%) of the product 5 was calculated by the nmr spectral analysis with a shift reagent, (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)). The absolute configuration of the product 5 was deduced on the basis of the same

Table 1. Palladium-catalyzed Asymmetric Allylation of Chiral Enamines

Enamines	Reaction conditions for allylation[a] Reaction temp /°C	Reaction time/h	Yields of 4/%[b]	$[\alpha]_D$ (CH_3OH) of 5 (Abs. Confign.)	e.e.[f] of 5/%
3a	40	19	97[c]	- 4.0°(c 1.1, 27°C) (S)	28
3a	66	19	97[c]	- 1.4°(c 1.0, 18°C) (S)	10
3b	40	19	87	- 4.5°(c 2.0, 28°C) (S)	32
3b	66	19	97[d]	- 2.6°(c 3.5, 28°C) (S)	18
3b	66	19	90	- 2.0°(c 1.0, 26°C) (S)	14
3c	room temp	45	85	- 6.8°(c 1.2, 27°C) (S)	48
3c	40	19	81	- 5.0°(c 1.2, 28°C) (S)	36
3c	66	19	85	- 3.8°(c 0.8, 28°C) (S)	27
3d	room temp	45	88	+11.8°(c 1.0, 28°C) (R)	84
3d	40	19	83	+ 6.0°(c 1.5, 27°C) (R)	43
3d	66	19	91	+ 3.3°(c 1.6, 28°C) (R)	23
3e	room temp	45	79[c,e]	+ 4.1°(c 1.7, 17°C) (R)	29
3e	40	19	84[c,e]	+ 2.5°(c 1.3, 23°C) (R)	18
3e	66	19	81[c,e]	+ 0.8°(c 1.0, 20°C) (R)	6
3f	40	19	80[e]	+ 4.0°(c 0.8, 27°C) (R)	28
3f	66	19	88[e]	+ 1.4°(c 2.1, 29°C) (R)	10

a) The reactions were carried out in THF in the presence of $Pd(PPh_3)_4$ (0.20 equiv.) and PPh_3 (0.40 equiv.).

b) The corrected yields based on the recovered starting material.

c) Allyl acetate (2.0 equiv.) was used as an allylating agent.

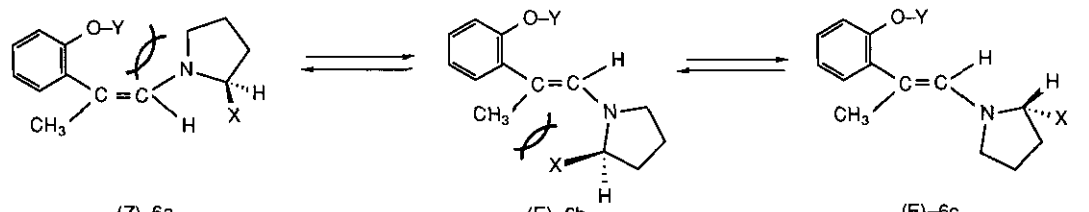
d) The palladium catalyst $Pd(dba)_2$ was used.

e) The reactions were carried out without PPh_3.

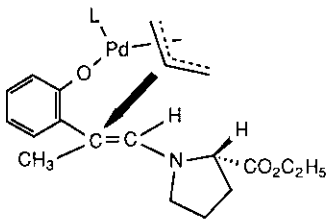
f) The enantiomeric excess (e.e.) was determined by the nmr analysis with a shift reagent.

mechanistic path as that of (S)-proline allyl ester-2-phenylpropionaldehyde enamine.[3b]

Based on the stereochemical outcome obtained, the mechanistic pathway for this asymmetric induction is presented as follows. The chiral enamine (E)-6 is more stable than the other geometrical isomer (Z)-6 by the reason of steric interference between the amino part and the phenyl ring in (Z)-6. The most preferable conformation of the enamine (E)-6 would be 6c, due to steric hindrance between the methyl group and the chiral center of the amino part in 6b. The π-allyl palladium complex formed from allyl acetate was reacted intermolecularly via 8 from the reversed side of the ester group in 3a to furnish (S)-(-)-5. On the palladium catalysis of 3b,c, an allyl species attacked intramolecularly from the back side of the ester group via the π-allylic



(Z)-6a (E)-6b (E)-6c



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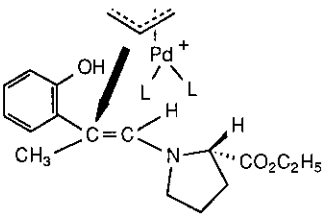

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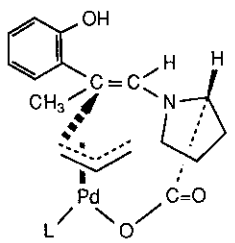

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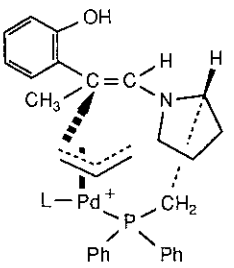

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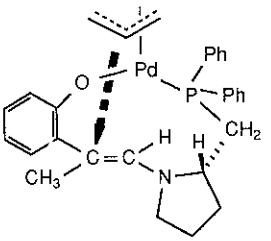

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palladium complex 7 chelated by the oxygen atom of the phenol part, resulting in a little increase of degree of asymmetric induction, compared with the intermolecular reaction of 3a. On the other hand, intramolecular allylation of 3d occurred via 9 from the same direction as the ester group, giving (R)-(+)-5 in high optical yield. In the similar way, the reactions of enamines 3e and 3f proceeded through intermediary π-allyl palladium complexes 10 and 11, chelated intramolecularly with the phosphine ligand involved in the chiral amino part, to afford (R)-(+)-5.

Thus, it should be concluded that intramolecular palladium-catalyzed allylations of 3b, 3c, 3d, and 3f resulted in a little increase of the optical yields, compared with the intermolecular reactions of 3a and 3e.

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