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The Palladium-catalyzed Asymmetric Allylations of Chiral Hydrazones Bearing Phosphine Groups. Stereoelectronic Effects of Allylating Reagents on Asymmetric Induction

Kunio HIROI,* Mitsuhiro HARAGUCHI, Yoko MASUDA, and Jun ABE
Department of Synthetic Organic Chemistry, Tohoku College of Pharmacy,
4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981

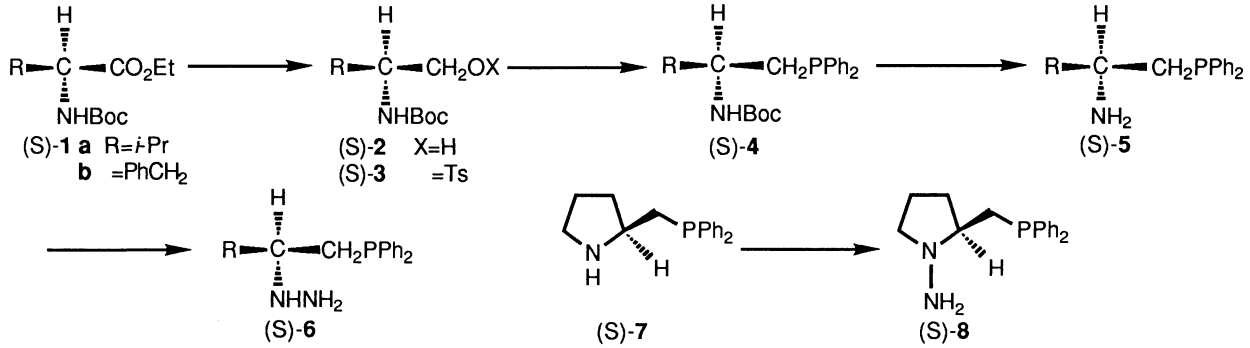
The palladium-catalyzed allylations of chiral hydrazones bearing phosphine groups were executed successfully under neutral reaction conditions with various allylating reagents, affording optically active α–allyl carbonyl compounds. The systematic and stereochemical investigation of these reactions shows that the intramolecularly-substituted phosphine groups served as chiral ligands and the anionic counterparts in the allylating reagents were markedly stereoelectronically effective on asymmetric induction.

In the past decade, the palladium-catalyzed asymmetric reactions[1] have received much attention in transition metal-catalyzed enantioselective organic synthesis.[2]

We have previously developed a new method for asymmetric α-allylations of carbonyl compounds via π-allylpalladium complexes of chiral enamines[3] or imines[4] derived from (S)-proline and other (S)-amino acid allyl esters. In the course of our continuous investigation of the palladium-catalyzed asymmetric allylations with various kinds of chiral auxiliaries, we have found an alternative method for asymmetric allylations using intramolecularly-substituted phosphine groups in chiral enamines as chiral ligands in the palladium-catalyzed reactions.[5] We wish to demonstrate herein the great stereoelectronic effects of anionic counterparts of allylating reagents in the palladium-catalyzed asymmetric reactions of chiral hydrazones[6] bearing phosphine substituents in the molecules under neutral reaction conditions.

The chiral hydrazines (S)-**6a,b** and (S)-**8** were prepared starting from readily available (S)-valine, (S)-phenylalanine, and (S)-proline as follows. The $LiAlH_4$ reduction (at 0 °C in THF) of the esters (S)-**1a,b** followed by tosylation (with tosyl chloride in pyridine at 0 °C) of the alcohols (S)-**2a,b** gave the tosylates (S)-**3a,b**. The phosphinylation (with diphenylphosphine-n-BuLi in THF at -20 °C) of (S)-**3a,b** followed by removal (with CF_3CO_2H) of the protecting group in (S)-**4a,b** afforded (S)-**5a,b**. The nitrosation of the amino compounds (S)-**5a,b** followed by the $LiAlH_4$ reduction of the intermediary N-nitroso groups gave chiral hydrazines (S)-**6a,b**. The same reaction sequences of (S)-**7**[7] prepared starting from (S)-proline provided a chiral hydrazine (S)-**8**. Azeotropic dehydration of 2-phenylpropanal with the chiral hydrazines (S)-**6a,b** and (S)-**8** was achieved by refluxing in benzene for 4 h with a Dean-Stark apparatus to furnish chiral hydrazones (S)-**9a,b** and (S)-**10** in quantitative yields.

The palladium-catalyzed allylation of the chiral hydrazone (S)-**9a** with allyl acetate (**11a**) (2.0 equiv.) was carried out in THF at 40 °C in the presence of tetrakis(triphenylphosphine)palladium $[Pd(PPh_3)_4]$(0.2 equiv.), followed by acidic hydrolysis with 10% aqueous HCl, resulting in the facile formation of (S)-(+)-**12** with 18%



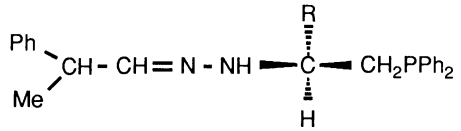
enantiomeric excess. The enantiomeric excess was determined on the basis of the optical rotation of optically pure (R)-(-)-**12** ($[\alpha]_D$-38.0°(MeOH)).[3b] Chemical changes of the anionic counterparts in the allylating reagents **11a-g** were greatly stereoelectronically effective on the asymmetric induction. Use of allyl benzoate derivatives **11b-e**, instead of allyl acetate, in the above reaction provided the much higher optical yields of (S)-(+)-**12**. The grade of asymmetric induction was increasing with the increasing electronegativity of the anionic counterparts in the allylating reagents such as **11d**(16%), **11b**(25%), **11e**(26%), **11c**(43%), as shown in Table 1. The much higher optical yields were observed on the use of allyl *p*-toluene-(**11f**) (48%) and methanesulfonate(**11g**) (47%).

The palladium-catalyzed reactions of the chiral hydrazone (S)-**9b** with **11a-g** produced (S)-(+)-**12** in somewhat lower optical yields, showing a similar tendency of the grade of the asymmetric induction by the effect of the allylating reagents **11a-g** to that in the chiral hydrazone (S)-**9a** mentioned above, as shown in Table 1.

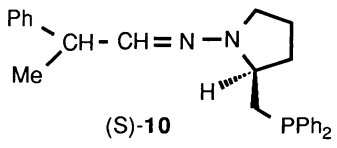
However, the palladium-catalyzed reactions of the chiral hydrazone (S)-**10** provided much higher optical yields of (R)-(-)-**12**. Similarly, among the allyl benzoates **11b-e**, the reaction of (S)-**10** with **11c** gave (R)-(-)-**12** with the highest enantiomeric excess(74%). The much higher optical yields were observed on the use of allyl sulfonates, **11f**(80%) and **11g**(75%).

Thus, the above results clearly show that the anionic counterparts in the allylating reagents were greatly effective not only sterically, but also electronically on the asymmetric induction in the palladium-catalyzed allylations of chiral hydrazones bearing phosphine groups in the molecules. The grades of the asymmetric induction by the effect of the allylating reagents **11a-g** in these reactions of the chiral hydrazones were increasing approximately in the following order, **11d≤11a<11e≤11b<11c<11g<11f**.

The mechanistic pathways for the asymmetric allylations of the chiral hydrazones (S)-**9a,b** and (S)-**10** are rationalized on the basis of the stereochemical results obtained as follows. In the most stable planar zigzag conformation of the CH-NH-NH-CH structure of the stable (E)-enamine forms **13** (the large hydrazino



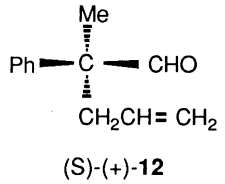
(S)-**9a** R=*i*-Pr
b =PhCH$_2$



(S)-**10**

$CH_2=CH-CH_2-X$

11a X=AcO
b =PhCO$_2$
c =*p*-NO$_2$C$_6$H$_4$CO$_2$
d =*p*-CH$_3$OC$_6$H$_4$CO$_2$
e =*p*-BrC$_6$H$_4$CO$_2$
f =*p*-CH$_3$C$_6$H$_4$SO$_3$
g =CH$_3$SO$_3$



(S)-(+)-**12**

Table 1. The Palladium-catalyzed Asymmetric Allylations of Chiral Hydrazones (S)-**9a,b** and (S)-**10**[a)]

Hydrazones	Allylating reagents	Yields of **12**[b)] %	$[\alpha]_D$/°(MeOH) of **12** (c, t/°C)	e.e. of **12** /%[c)] (Abs. confign.)
(S)-**9a**	**11a**	42 (80)	+7.0 (1.0, 25)	18 (S)
(S)-**9a**	**11b**	51 (78)	+9.5 (2.0, 25)	25 (S)
(S)-**9a**	**11c**	40 (70)	+16.3 (1.8, 23)	43 (S)
(S)-**9a**	**11d**	47 (72)	+6.2 (1.0, 23)	16 (S)
(S)-**9a**	**11e**	58 (86)	+10.0 (1.2, 27)	26 (S)
(S)-**9a**	**11f**	43 (88)	+18.2 (0.7, 24)	48 (S)
(S)-**9a**	**11g**	45 (79)	+17.8 (0.8, 26)	47 (S)
(S)-**9b**	**11a**	55 (86)	+5.0 (1.5, 22)	13 (S)
(S)-**9b**	**11b**	50 (76)	+6.8 (1.2, 24)	18 (S)
(S)-**9b**	**11c**	57 (73)	+8.5 (1.5, 22)	22 (S)
(S)-**9b**	**11d**	62 (79)	+4.8 (0.6, 25)	13 (S)
(S)-**9b**	**11e**	52 (78)	+7.2 (0.7, 25)	19 (S)
(S)-**9b**	**11f**	49 (81)	+10.5 (1.0, 26)	28 (S)
(S)-**9b**	**11g**	60 (74)	+10.2 (0.7, 27)	27 (S)
(S)-**10**	**11a**	36 (88)	-23.6 (1.2, 25)	62 (R)
(S)-**10**	**11b**	44 (76)	-25.2 (1.0, 27)	66 (R)
(S)-**10**	**11c**	49 (83)	-28.1 (1.5, 27)	74 (R)
(S)-**10**	**11d**	41 (88)	-18.3 (0.8, 24)	48 (R)
(S)-**10**	**11e**	41 (85)	-19.8 (1.4, 25)	52 (R)
(S)-**10**	**11f**	31 (73)	-30.3 (0.8, 26)	80 (R)
(S)-**10**	**11g**	30 (82)	-28.5 (1.0, 25)	75 (R)

a) The reactions of chiral hydrazones (S)-**9a,b** and (S)-**10** with **11a-g** (2.0 equiv.) were carried out in the presence of $Pd(PPh_3)_4$ (0.2 equiv.) in THF at 40 °C for 19 h.
b) The corrected yields based on the recovered starting material are listed in parentheses.
c) The enantiomeric excess (e.e.) was calculated on the basis of the optical rotation of optically pure (R)-(-)-**12**.

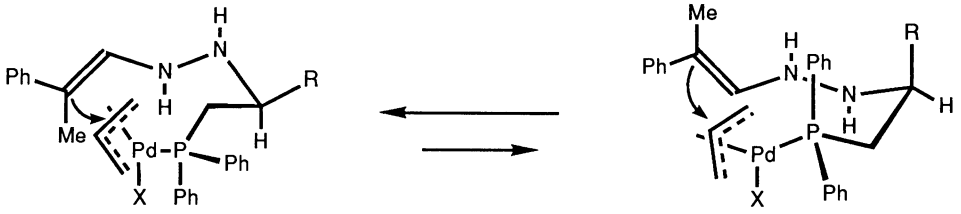
groups have *anti*-configuration to the phenyl rings), the rather severe steric hindrace is observed between the substituents R, and the *syn* N-H bond and the phenyl group on the phosphine in **13b**, upon the allylation as depicted by a solid arrow in **13b**. Therefore the allylation would occur preferentially via the intermediate **13a**, as shown by a solid arrow in **13a**, to furnish (S)-(+)-**12**.

It should be noted that the palladium-catalyzed intramolecular asymmetric allylation of chiral imines derived from (S)-valine and (S)-phenylalanine allyl esters[4)] provided the different stereochemical results from those via the corresponding chiral hydrazones (S)-**9a,b** and chiral imines derived from (S)-**5a,b**.

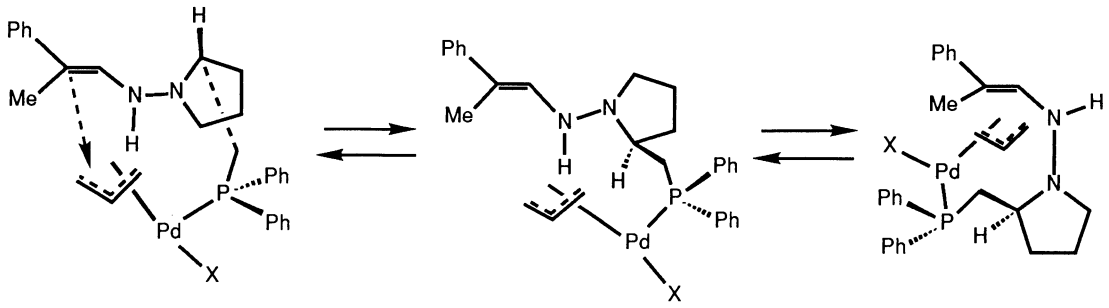
The stereochemical results via the chiral hydrazone (S)-**10** are rationalized in the similar way. In the stable (E)-enamine system **14** in which the large hydrazino group has *anti*-configuration to the phenyl ring, the conformers **14a,b** would be more preferable to the other **14c**, because of the steric interference of the methyl group with the hydrazino substituent in **14c**. The π–allylpalladium part is not accessible to the reactive site in **14b**. Therefore, the allylation would occur via **14a** from the downward direction as depicted by a dotted arrow in **14a**, like an intramolecular fashion, to furnish (R)-(-)-**12** in high optical yields.

The anionic counterparts of the allylating reagents would coordinate to the palladium catalyst in the aforementioned intermediary π-allylpalladium complexes, and affect sterically the allylation to provide various degrees of the enantioselectivity as described earlier, since the contribution of the coordination would change depending on the stereoelectronic characteristics of the anionic counterparts.

Thus, this method provides the different stereochemical results from those by the previous methods via the



13a 13b



14a 14b 14c

palladium-catalyzed reactions of chiral imines[4] and non-catalyzed reactions of chiral enamines.[8] Therefore we can control the stereochemistry of the products by selecting the amino parts in the chiral models. Accordingly, this method is useful for asymmetric α-allylations of carbonyl compounds and is also advantageous for organic synthesis, since the chiral auxiliaries were recyclable as the starting chiral sources by the efficient recovery.

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