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Palladium-Catalyzed Asymmetric α-Allylations of Carbonyl Compounds via Chiral Imines Derived from Optically Active α-Amino Acid Allyl Esters

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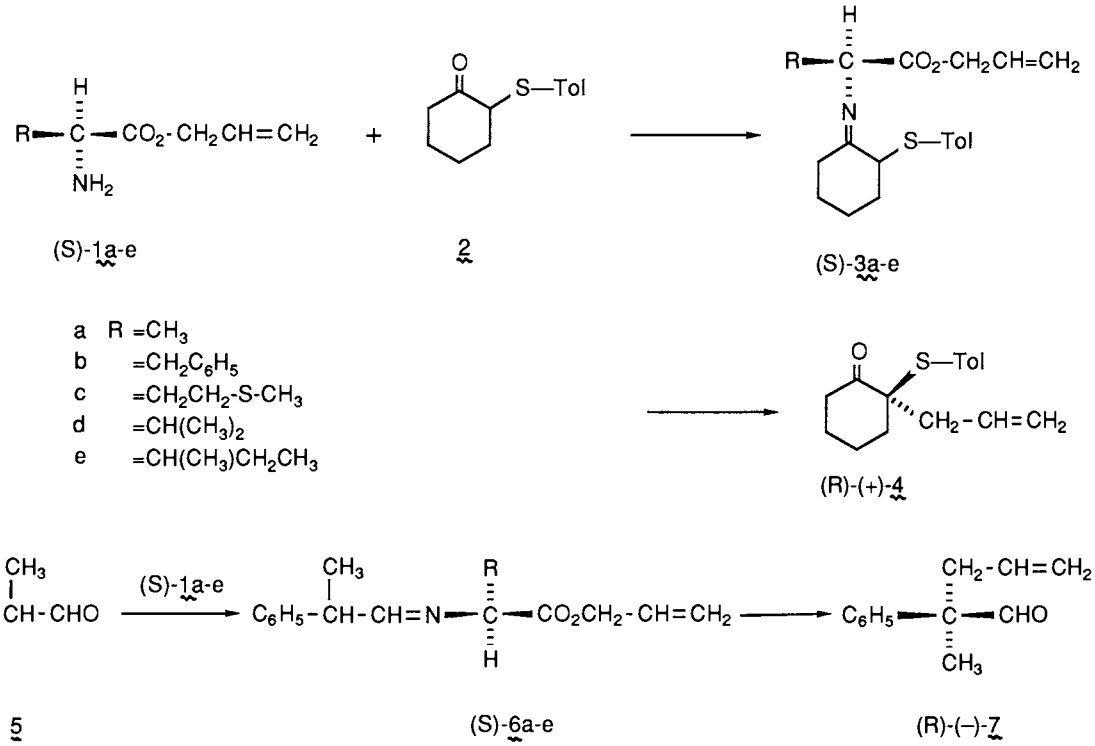
Palladium-catalyzed asymmetric allylations of ketones and aldehydes were successfully executed via chiral imines derived from optically active α-amino acid allyl esters. The mechanistic pathway for this asymmetric induction is proposed on the basis of stereochemical results obtained.

Recently much attention has been devoted to palladium-catalyzed allylations, especially using chiral π-allylic palladium compounds,[1] since metal-catalyzed reactions have made a great contribution to development of new methodologies for asymmetric synthesis and the stereochemical results have provided more detailed mechanisms for the palladium-catalyzed reactions. From these points of view, we have studied on palladium-catalyzed reactions in allylic systems and successfully developed new methodologies for asymmetric allylations with chiral allylic sulfinates or sulfones[2] and (S)-proline allyl ester enamines[3] or amides.[4] Along these lines, we have further made an effort to develop more useful and advantageous methods for asymmetric allylations, using many kinds of chiral allyl esters.

We wish to communicate herein a novel method for efficient asymmetric α-allylations of carbonyl compounds by palladium-catalyzed reactions of chiral imines derived from optically active α-amino acid allyl esters.

Optically active α-amino acid allyl esters (S)-1a-e were readily prepared by acid-catalyzed esterification of the corresponding (S)-α-amino acids with allyl alcohol upon heating for 18 h in the presence of a catalytic amount of conc. sulfuric acid. Chiral imines 3a-e were obtained quantitatively by azeotropic dehydration of α-sulfenyl ketone 2 with 1a-e in refluxing benzene for 6 h with a Dean-Stark apparatus.

Treatment of chiral imines 3a-e with tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] (0.16 equiv.) and triphenylphosphine (PPh_3) (0.66 equiv.) in tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), or benzene, followed by hydrolysis with 10% aqueous hydrochloric acid (refluxed for 1.5 h), afforded optically active α-allyl ketone (R)-(+)-4 with high enantiomeric excess in good yields. The reaction conditions and the results are summarized in Table 1. Among many kinds of optically active primary amines examined, (S)-valine allyl ester represented



the highest optical yield (87%) of (R)-(+)-4, as shown in Table 1.

The optical yields were calculated by NMR spectral analysis of the product 4 with a shift reagent, (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)[Eu(hfc)$_3$]). The absolute configuration of the product 4 was determined by applying the Octant Rule in the circular dichroism spectrum.

This method was applicable to an aldehyde-imine. The palladium-catalyzed reactions of chiral imines (S)-6a-e, prepared from (S)-1a-e and 2-phenylpropionaldehyde (5) in the same manner as mentioned above, were carried out in refluxing THF for 18 h in the presence of $Pd(PPh_3)_4$ (0.16 equiv.) and PPh_3 (0.66 equiv.), followed by hydrolysis with 10% aqueous hydrochloric acid (refluxed for 1 h), giving (R)-(-)-7 in good yields. The results are summarized in Table 1. It should be noted that the excellent optical yield (99%) was observed in the case of (S)-valine allyl ester imine (S)-6d.

The optical yields were calculated on the basis of the optical rotation of the optically pure (R)-7: $[\alpha]_D$-38.0°(MeOH).[3b] The absolute configuration of 7 has been determined previously by us.[3b]

On the basis of the stereochemical results obtained above, the mechanistic pathway for this asymmetric induction is presented as follows. Intramolecular allylation via π-allylic palladium carboxylate 8c,d, chelated with nitrogen atom of the imine 3, would not be accessible, since the allyl group in the intermediate 8c,d is conformed with the anti configuration to the sulfenyl group and therefore located too far for attack to α-carbon of the imine. In the other intermediate, the π-allylic palladium is chelated with sulfur atom of the tolylsulfenyl group and nitrogen atom of the imino part to form a five-five membered transition state 8a,b, in which the allyl group is conformed with the

Table 1. Palladium-catalyzed Allylations of Carbonyl Compounds via Chiral Imines[a)]

Carbonyl comounds	Reaction conditions for allylations[b)] Amines	Solvent	Reaction temp /°C	Reaction time /h	Product yield/%[c)]		Product $[\alpha]_D$/°[d)]	e.e./%[e)]
2	1a	THF	66	18	4	31	+104.1	41
2	1a	DME	82	18	4	52	+92.7	36
2	1b	THF	r.t.	48	4	25	+187.0	73
2	1b	THF	66	18	4	85	+165.7	65
2	1b	Benzene	80	20	4	31	+182.0	71
2	1b	DME	82	20	4	58	+149.7	59
2	1c	THF	66	16	4	48	+96.4	38
2	1c	DME	82	20	4	56	+114.1	45
2	1d	THF	66	18	4	58	+223.2	87
2	1d	DME	82	18	4	42	+204.5	80
2	1e	THF	66	18	4	80	+195.6	77
5	1a	THF	66	18	7	80	-5.4	14
5	1b	THF	66	18	7	77	-23.4	62
5	1c	THF	66	18	7	85	-19.4	51
5	1d	THF	66	18	7	67	-37.5	99
5	1e	THF	66	18	7	89	-30.9	81

a) The imines 3a-e and 6a-e were prepared by reaction of 2 or 5 with 1a-e in refluxing benzene for 4-6 h using a Dean Stark apparatus.

b) The imines 3a-e and 6a-e were treated with $Pd(PPh_3)_4$ (0.15 equiv.)-PPh_3 (0.66 equiv.) under the conditions listed above, followed by refluxing in 10% aqueous HCl for 1-1.5 h, affording (R)-(+)-4 and (R)-(-)-7.

c) Yields based on the recovered starting materials.

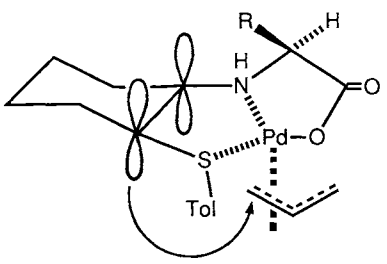
d) Measured in ethanol(4) and methanol(7).

e) The enantiomeric excess (e.e.%) was determined by the NMR spectral analysis with a shift reagent [Eu(hfc)$_3$].

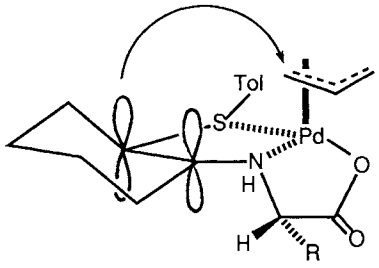
anti configuration to the largest substituent (R). The axial allylation through 8a would be preferred to the reaction of the allyl group from equatorial direction (8b), resulting in formation of (R)-(+)-4.

Stereochemistry in the allylation of the aldehyde-imine 6 is rationalized in the similar way. In the stable (E)-enamine form (the large amino group is located anti to the phenyl group), formation of π-allylic palladium complexes 9a,b chelated with the imino nitrogen atom would be possible. The intermediate 9a would be more preferable to 9b, because of existence of severe steric hindrance between the substituent R and the methyl group in 9b. Therefore allylation would occur preferentially via 9a to furnish (R)-(-)-7 in high optical yield.

Thus, use of (S)-valine allyl ester provides the highest enantioselectivity in this palladium-catalyzed allylation. Therefore this novel method by intramolecular allylation via chiral imines represents a potentially great advantage to control enantioselectivity with extremely high efficiency.



8a



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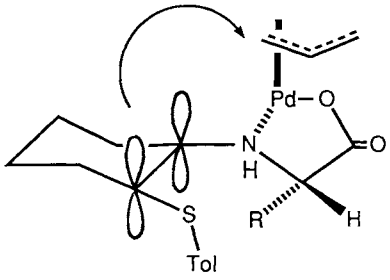

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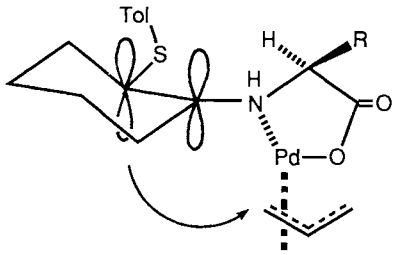

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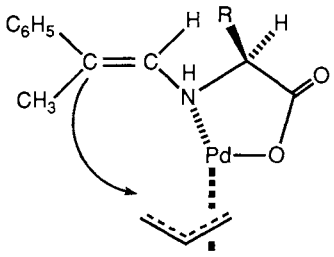

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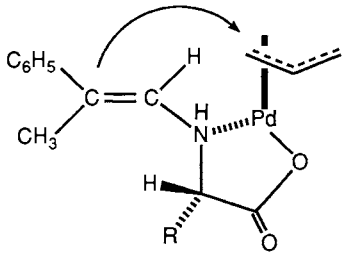

9b

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