Tetrahedron Letters, Vol. 31, No. 12, pp 1743-1746, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

Asymmetric Allylic Amination Catalyzed by Chiral Ferrocenylphosphine-Palladium Complexes

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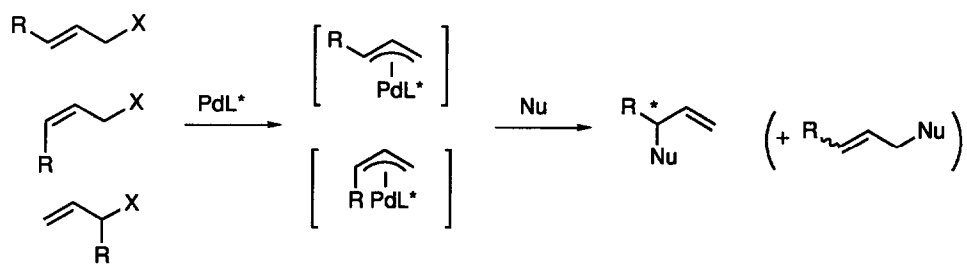
Abstract: A palladium complex bearing chiral (hydroxyalkyl)ferrocenylphosphine ligand was found to be a highly regio-and stereoselective catalyst for the asymmetric allylic amination of 2-butenyl acetates with benzylamine, the nucleophilic attack of the amine taking place selectively on the more substituted end of the π-allylpalladium intermediate to give optically active 3-benzylamino-1-butene of up to 84% ee.

Our continuing studies utilizing chiral ferrocenylphosphine-palladium complexes for catalytic asymmetric allylic substitution reactions have led to several approaches to the synthesis of optically active compounds.[1-5] One of the major problems in developing the palladium-catalyzed asymmetric reactions is the limitation of the substitution patterns of allylic substrates.[6] Most of the substrates so far reported are those giving π-allylpalladium intermediates containing the same two aryl or alkyl groups at 1 and 1,[7] or 1 and 3 positions.[1,8] Here we wish to report a new type of asymmetric allylic substitution where π-allyl intermediates undergo regioselective nucleophilic attack on the substituted end of π-allyl group containing an alkyl group at one of the terminal positions (Scheme 1).

Scheme 1



We have examined several nitrogen nucleophiles and chiral phosphine-palladium catalysts for regioselectivity and stereoselectivity in allylic amination of (*E*)-2-butenyl acetate ((*E*)-**2a**). It was found that the combination of benzylamine (**3a**) and chiral ferrocenylphosphine ligand, (*R*)-*N*-methyl-*N*-bis(hydroxymethyl)methyl-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine ((*R*)-(*S*)-**1a**)[1,9] gave rise to regioselective carbon-nitrogen bond formation at the methyl substituted position yielding branched allylamine, 3-benzylamino-1-butene (**4a**) preferentially (Scheme 2). The results are summarized in Table 1. The ratio of **4a** to linear allylamine, 1-benzylamino-2-butene (**5a**) was 97 to 3 in the amination at 0 °C (entry 1).[10] The enantiomeric purity of **4a**

([α]$^{20}_D$ +7.2° (c 2.1, chloroform)), determined by HPLC analysis with a chiral stationary phase column, was 84% ee. The configuration of (+)-**4a** was determined to be (*S*) by converting[11] it into known alanine derivative, (–)-(*S*)-methyl *N*-benzyl-*N*-trifluoroacetylalaninate (**6**).[1b] Similar regioselectivity was observed with ferrocenylphosphine ligand **1b** though **4a** of opposite configuration was formed with lower stereoselectivity (entry 4). Other phosphine ligands, DIOP,[12] BINAP,[13] and chiraphos,[14] all gave the amination products with much lower regio- or stereoselectivity (entries 5-7).

Scheme 2

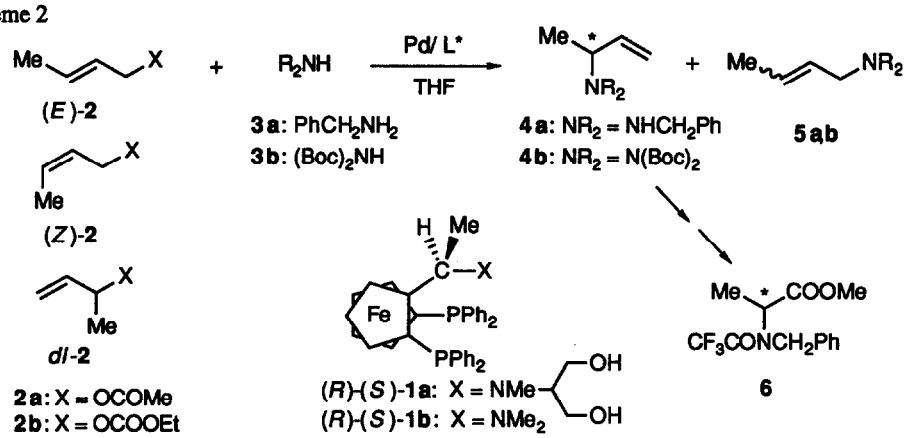


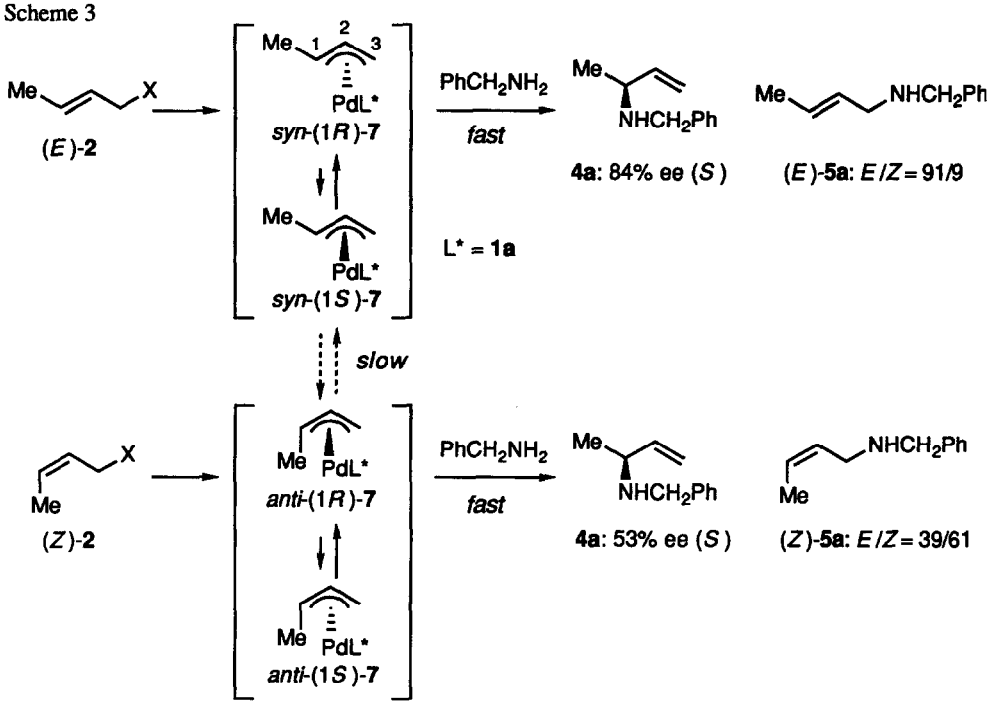
Table 1. Asymmetric Allylic Amination of (*E*)-2-Butenyl Acetate ((*E*)-**2a**) and Related Compounds in the presence of Chiral Phosphine-Palladium Catalysts.[a]

entry	allylic substrate	amine	chiral ligand	temp (°C)	time (h)	yield[b](%) of 4 + 5	ratio[c] 4/5	% ee 4[d] (config)	5[d] E/Z
1	(*E*)-**2a**	**3a**	(*R*)-(*S*)-**1a**	0	90	87	97/3	84 (*S*)	91/9
2	(*E*)-**2a**	**3a**	(*R*)-(*S*)-**1a**	25	21	75	93/7	69 (*S*)	89/11
3	(*E*)-**2b**	**3a**	(*R*)-(*S*)-**1a**	0	91	70	98/2	80 (*S*)	88/12
4	(*E*)-**2a**	**3a**	(*R*)-(*S*)-**1b**	0	86	73	95/5	49 (*R*)	80/20
5	(*E*)-**2a**	**3a**	(+)-DIOP	0	87	83	78/22	7 (*S*)	88/12
6	(*E*)-**2a**	**3a**	(+)-BINAP	25	44	58	62/38	41 (*S*)	94/6
7	(*E*)-**2a**	**3a**	(–)-chiraphos	25	44	68	81/19	9 (*R*)	86/14
8	(*Z*)-**2a**	**3a**	(*R*)-(*S*)-**1a**	0	112	76	95/5	53 (*S*)	39/61
9	(*Z*)-**2a**	**3a**	(*R*)-(*S*)-**1b**	0	43	67	94/6	51 (*R*)	72/28
10	*dl*-**2a**	**3a**	(*R*)-(*S*)-**1a**	0	66	87	96/4	64 (*S*)	64/36
11	*dl*-**2a**	**3a**	(*R*)-(*S*)-**1b**	0	20	62	93/7	53 (*R*)	77/23
12	(*E*)-**2b**	**3b**	(*R*)-(*S*)-**1a**	0	260	37	85/15	61 (*S*)	81/19
13	(*Z*)-**2b**	**3b**	(*R*)-(*S*)-**1a**	0	260	30	88/12	63 (*S*)	81/19

[a] A mixture of $Pd_2(dba)_3 \cdot CHCl_3$ (0.0075 mmol), a chiral phosphine ligand (0.03 mmol), butenyl acetate or carbonate **2** (0.50 mmol), and amine **3** (1.25 mmol) in 2.5 mL of dry THF was stirred at a given temperature. For a typical procedure, see text. [b] Isolated yield by preparative TLC. [c] Determined by GLC analysis. [d] Determined by HPLC analysis.

The amination of (*Z*)-2-butenyl acetate ((*Z*)-**2a**) with the (*R*)-(*S*)-**1a**/Pd catalyst gave **4a** of lower enantiomeric purity (53% ee) though the regioselectivity was still high (**4a**/**5a**) = 95/5) (entry 8). It should be noted that *E* or *Z* geometry of the double bond in the starting acetate was retained in the linear product **5a**. Thus, the *E*/*Z* ratios of **5a** formed in the amination of (*E*)-**2a** and (*Z*)-**2a** were 91/9 and 39/61, respectively (entries 1 and 8). The allylic amination of **2a** must proceed via π-(1-methylallyl)palladium(II) intermediates **7** which can undergo *syn*-*anti* isomerization (*syn*-**7** and *anti*-**7**) and epimerization ((1*R*)-**7** and (1*S*)-**7**) by the σ-π-σ mechanism.[6] The stereochemical results obtained for the amination of (*E*)- and (*Z*)-**2a** indicate that the nucleophilic attack of benzylamine takes place before an equilibration of the *syn*-*anti* isomerization is reached (Scheme 3).

Scheme 3



The epimerization of the π-allylpalladium complexes is fast compared with the nucleophilic attack, which may be suggested by the result that the reaction of *dl*-**2a** gave optically active **4a** (entry 10). The % ee value (64% ee) and *E*/*Z* ratio (64/36) are between those observed with (*E*)-**2a** and (*Z*)-**2a**. The reaction of a series of the isomeric butenyl acetates (*E*)-, (*Z*)-, and *dl*-**2a** with benzylamine in the presence of **1b** as a ligand resulted in the formation of the amination products **4a** and **5a** with essentially the same regio- and stereochemistry (entries 4, 9, and 11), demonstrating that the benzylamine attacked the π-allylpalladium intermediates after its *syn*-*anti* isomerization was completed. Hydroxy groups on the side chain of ferrocenylphosphine ligand **1a** are supposed to accelerate the nucleophilic attack of benzylamine or to retard the *syn*-*anti* isomerization of the π-allylpalladium intermediates.

Use of di-*tert*-butyl iminodicarbonate (**3b**)[15] as a nucleophile for the reaction of (*E*)- and (*Z*)-2-butenyl carbonates **2b** in the presence of **1a**/Pd catalyst gave amination products **4b**[16] and **5b** with lower regio- and

stereoselectivity (entries 12 and 13). The same stereochemical results obtained with (*E*)- and (*Z*)-**2b** indicate that the nucleophilc attack of **3b** is slow compared with the isomerizations of **7**.

A typical procedure is given for entry 1 in Table 1. To an orange solution of palladium catalyst prepared by mixing 7.8 mg (0.0075 mmol) of $Pd_2(dba)_3{\cdot}CHCl_3$ and 20.6 mg (0.03 mmol) of ferrocenylphosphine **1a** in 2.5 mL of dry THF was added 57.1 mg (0.50 mmol) of butenyl acetate (*E*)-**2a**, and the mixture was stirred at room temperature for 20 min. Benzylamine (**3a**) (134 mg, 1.25 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 90 h. Hydrolysis with 15% NaOH followed by GLC analysis showed the amination products, 3-benzylamino-1-butene (**4a**) and 1-benzylamino-2-butene (**5a**) were formed in a ratio of 97/3. Extraction with ether followed by preparative TLC on silica gel (hexane/ethyl acetate =1/1) gave 68.3 mg (85%) of **4a** and 2.1 mg (3%) of **5a**. The enantiomeric purity of **4a** and *E*/*Z* ratio of **5a** were determined to be 84% ee and 91/9, respectively, by HPLC analysis of 3,5-dinitrophenylureas, prepared by treatment of amines **4a** and **5a** with ArNCO in chloroform, with a chiral stationary phase column (Sumitomo Chemical Co., Sumipax OA-4500, hexane/dichloroethane/ethanol = 50/15/1).

We thank the Akiyama Foundation for partial financial support of this work.

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10 The regioselectivity (97/3) is one of the highest in the allylic substitution reactions of butenyl esters. For a discussion concerning the regioselectivity, see ref 6 and references cited therein.

11 Trifluoroacetylation ($(CF_3CO)_2O/Et_3N/DMAP/CH_2Cl_2$) of (+)-**4** ($[\alpha]^{20}_D$ +4.0° (*c* 1.3, chloroform)) gave 87% yield of 3-(*N*-trifluoroacetylbenzylamino)-1-butene ($[\alpha]^{20}_D$ –43.9° (*c* 1.4, chloroform)), which was subjected to oxidation ($KMnO_4/NaIO_4$) and esterification (CH_2N_2) to give 40% yield of (–)-(*S*)-**6** ($[\alpha]^{20}_D$ –23.1° (*c* 1.6, chloroform)) (ref 1b).

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16 The enantiomeric purity and configuration was determined by converting **4b** into **4a** by acidic removal of Boc group ($CF_3COOH/HCl/THF$) followed by *N*-benzylation ($PhCH_2Cl/Et_3N/CH_2Cl_2$).

(Received in Japan 17 January 1990)