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Asymmetric Allylic Substitution Reaction with Nitrogen and Oxygen Nucleophiles using Monodentate Chiral Phosphine, 9-PBN

Yasumasa Hamada*[a], Noriko Seto[b], Yoshie Takayanagi[b], Takeshi Nakano[a], and Osamu Hara[a]

[a]Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan
[b]Faculty of Pharmaceutical Sciences, Nagoya City University, Tanbe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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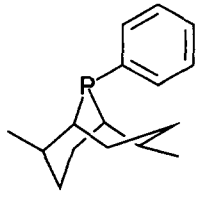
Abstract: Asymmetric allylic substitution reactions between 1,3-diphenyl-2-propenyl acetate and various hetero nucleophiles were efficiently carried out using the catalysts derived from the monodentate phosphine ligands, (1*R*, 2*S*, 5*R*, 6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1] nonane and its enantiomer ((-)- and (+)-9-PBNs), and palladium (0).

Keywords: Allylation: Phosphines; Palladium and compounds: Asymmetric Synthesis

The transition-metal catalyzed asymmetric synthesis[1] is one of the most expedient and environmentally benign processes and attracts attention for practical use. In addition the design and development of chiral ligands for the transition-metal catalyzed reactions are most fascinating and a challenging task.[2] Recently, we have succeeded in the development of new monodentate chiral phosphines, (1*R*, 2*S*, 5*R*, 6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane and its enantiomer ((+)- and (-)-9-PBNs),[3] and demonstrated that these phosphines in combination with palladium are efficient catalysts for carbon-carbon bond forming reactions through asymmetric allylic alkylation. The palladium-catalyzed allylic substitution reaction[4,5,6] is a valuable synthetic transformation which is employed for the synthesis of various chiral compounds and natural products. Especially, using nitrogen and oxygen nucleophiles[7,8] provides valuable methods for the preparation of amino acid derivatives and building blocks for the construction of heterocyclic compounds. We describe here an extension using (+)-9-PBN in combination with bis(benzylidene)palladium to the asymmetric allylic substitution reaction between 1,3-diphenyl-2-propenyl acetate and various hetero nucleophiles.

Using the efficient asymmetric synthesis on carbon nucleophiles, we have investigated asymmetric allylic aminations using various nitrogen nucleophiles as shown in Table I. The reaction of 1,3-diphenyl-2-propenyl acetate with benzylamine in dichloromethane was sluggish and incomplete. However, 1,2-dichloroethane was the solvent of choice and provided a complete reaction with high enantioselection. Finally, a slight excess of nucleophile was effective and afforded the product with up to 98%ee.[9] The absolute stereochemistry was unequivocally determined by comparisons with the authentic sample.[8a] The reaction of the glycine ethyl ester took place to produce the N-



(-)-9-PBN

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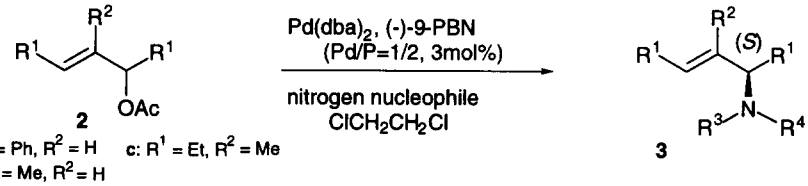
alkyl glycine derivative with high enantiomeric excess but the yield was moderate due to the easy polymerization of the glycine ester itself. Secondary amines also were excellent nucleophiles for the asymmetric allylic amination (runs 5,6). The sodium salts derived from the sulfonamides and imide were found to serve as good nucleophiles to afford the N-allylated products with excellent enantioselection. Analogous 1,3-dialkyl allylic substrates **2b**, **2c** underwent allylic amination in the range of 51 – 91%ee.

Table I. Asymmetric Allylic Amination using (-)-9-PBN Coordinated with Palladium[a]



a: R^1 = Ph, R^2 = H **c**: R^1 = Et, R^2 = Me
b: R^1 = Me, R^2 = H

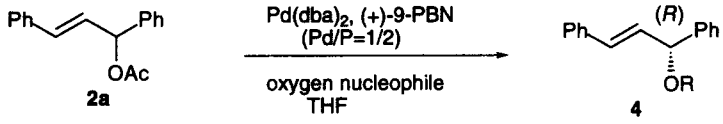
run	substrate	nitrogen nucleophile	base	conditions	yield and ee
1[b]	**2a**	**$PhCH_2NH_2$** (1.1 eq)	-	rt, 5 h	40 %, 96 %ee[c]
2[d]	**2a**	**$PhCH_2NH_2$** (1.1 eq)	-	rt, 5 h	95 %, 91 %ee[c]
3	**2a**	**$PhCH_2NH_2$** (1.8 eq)	-	rt, 5 h	94 %, 98 %ee[c]
4	**2a**	**$NH_2CH_2CO_2Et$** (1.4 eq)	-	rt, 27 h; 50°C, 4 d	57 %, 96 %ee[c]
5	**2a**	**$PhCH_2NHCH_3$** (1.4 eq)	-	rt, 5 h	88 %, 92 %ee[c]
6	**2a**	**morpholine** (1.4 eq)	-	rt, 5 h	100 %, 94 %ee[e]
7	**2a**	***p*-$TsNH_2$** (1.8 eq)	NaH (1.4eq)	rt, 4 d; 50°C, 44 h	42 %, 94 %ee[e]
8	**2a**	**$HN(Boc)_2$** (1.4 eq)	NaH (1.4 eq)	rt, 23 h	100 %, 96 %ee[c]
9	**2a**	***p*-$TsNHCH_2Ph$** (1.42 eq)	NaH (1.86 eq)	rt, 4 h	92 %, 89 %ee[c]
10[f]	**2b**	**$PhCH_2NH_2$** (2.5eq)	-	rt, 3.5 h ; 50°C, 1.5 h	100%, 51 %ee[g]
11	**2b**	***p*-$TsNHCH_2CH{=}CH_2$** (3 eq)	NaH (3 eq)	rt, 37 h	47 %, 56 %ee[e]
12[h]	**2c**	***p*-$TsNHCH_2CH{=}CH_2$** (3 eq)	Cs_2CO_3 (1.5eq)	rt, 46 h	38 %[i], 91 %ee[e]

a) All reactions unless stated otherwise were carried out using **2** (1 eq), $Pd(dba)_2$ (0.03 eq), (-)-9-PBN (0.06 eq), and nitrogen nucleophile in 1,2-dichloroethane under an argon atmosphere. b) Dichloromethane instead of 1,2-dichloroethane was used. c) Determined by Chiralcel OD. d) 1mol % of $Pd(dba)_2$ was used. e) Determined by Chiralcel OJ. f) AcOH (2.5eq) was added. g) Determined by Chiralcel OD-H after derivatization with 3,5-dinitrobenzoyl chloride. h) The corresponding methyl carbonate in place of the acetate **2c** was used as a substrate. i) The yield bases on the consumed starting materials.

Encouraged by these results, we turned our attention to the allylic substitution reaction using oxygen nucleophiles.[10] An initial attempt using methanol was disappointing and gave the ether **4** in good yield but poor enantiomeric excess (run 1). Our efforts to find a substitute for methanol showed that trialkyl borates serve as efficient substitutes and undergo the asymmetric allylic substitution reaction to give the ether **4** with moderate to high enantioselection. The reaction of the allylic substrate **2a** with trimethyl borate alone in the presence of the

catalyst derived from $Pd(dba)_2$ (3 mol %) and (-)-9-PBN (6 mol %) took place sluggishly but afforded the product with 96 % ee. Furthermore, the addition of potassium carbonate to this reaction enabled completion of the reaction giving both a satisfactory yield and enantioselection.[11] The absolute stereochemistry of **4** (R = Me) was unambiguously determined as the (*R*)-configuration by comparison of the authentic sample derived from the resolution product using Sharpless asymmetric epoxidation.[12] We subsequently expected this asymmetric etherification to be extended to the various trialkyl borates derived from the higher alcohols. However, the reactions using triethyl borate and tributyl borate were unexpectedly found to proceed with low yields and moderate enantioselection.

Table II. Asymmetric Etherification using Trialkyl Borate[a]



run	palladium (mol %)	oxygen nucleophile and additive	conditions	yield and ee[c]	recovery of SM
1[b]	3	MeOH	60°C, 15 h	88 %, 10 %ee	2 %
2	3	$B(OMe)_3$ (10 eq)	60°C, 13 h	23 %, 96 %ee[d]	76 %
3	10	$B(OMe)_3$, K_2CO_3	60°C, 15 h	92 %, 94 %ee	-[e]
4	10	$B(OMe)_3$, KF	60°C, 14 h	67 %, 93 %ee[d]	6 %
5	10	$B(OEt)_3$, K_2CO_3	60°C, 14 h	45 %, 42 %ee	31%
6	10	$B(On\text{-}Bu)_3$, K_2CO_3	60°C, 14 h	20 %, 79 %ee	48%

a) All reactions unless stated otherwise were carried out using **2a** (1 eq), $Pd(dba)_2$ (0.03-0.1 eq), (+)-9-PBN (0.06-0.2 eq), and trialkyl borate (3 eq) in THF under a nitrogen atmosphere. b) Methanol was used as the solvent. c) Determined by Chiralcel OD-H. d) (-)-9-PBN in place of (+)-isomer was used. e) Not determined.

In summary we have described that the asymmetric allylic amination using 1,3-diphenyl-2-propenyl acetate and various nitrogen nucleophiles with new monodentate chiral phosphines, 9-PBNs, coordinated with palladium (0) produces an excellent yield and enantioselection. Furthermore, we have demonstrated the asymmetric etherification using trialkyl borates as the oxygen nucleophiles for the first time. We are now intensively working to explore the asymmetric synthesis using 9-PBNs and to apply it to the synthesis of medicinally important natural products.

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9) Typical procedures for the asymmetric allylic amination: To a stirred suspension of $Pd(dba)_2$ (17.3 mg, 0.03 mmol) in dichloroethane (6 ml) under an argon atmosphere at 23°C was added one portion a 0.1M solution of (-)-9-PBN in hexane (0.6 ml, 0.06 mmol) and the mixture was stirred at 23°C for 20 min. After cooling to 0°C, a solution of 1,3-diphenyl-2-propenyl acetate (254 mg, 1 mmol) in dichloroethane (3 ml) followed by benzylamine (0.2 ml, 1.08 mmol) were added via double ended needles. The reaction mixture was allowed to warm to 23°C and stirred for 5 h. Removal of the volatiles under reduced pressure and column chromatography on silica gel using hexane/ethyl acetate (10:1) furnished the product (281 mg, 94 %) as a pale yellow oil: $[\alpha]_D^{25}$ +25.3 (*c* 1.2, $CHCl_3$) (98 % ee (*S*) judged by HPLC analysis using CHRALCEL OD); IR ν_{max}^{neat} 3324, 3027, 1601, 1495, 1453, 1119, 1073, 1028, 967, 912 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.64 (1H,br s), 3.76-3.81 (2H, ABq, *J* = 13.2 Hz), 4.4 (1H, d, *J* = 7.26 Hz), 6.31 (1H, dd, *J* = 15.8 Hz, *J* = 7.26 Hz), 6.58 (1H, d, *J* = 15.8 Hz), 7.11-7.45 (15H, m).

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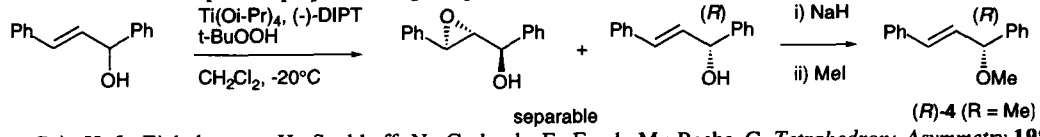
11) Typical procedures for the asymmetric etherification: To a stirred suspension of $Pd(dba)_2$ (22 mg, 0.03 8mmol) and anhydrous K_2CO_3 (161mg, 1.1mmol) in THF(2 ml) under an argon atmosphere at rt was added in one portion a solution of 1,3-diphenyl-2-propenyl acetate (98 mg, 0.38mmol) in THF (3 ml) via a double ended needle and the mixture was stirred at 23°C for 5 min. A 0.1M solution of (+)-9-PBN in hexane (0.7 ml, 0.07mmol), followed by $B(OCH_3)_3$ (0.2 ml, 1.08mmol) were added at rt. The reaction mixture was heated at 60°C and stirred for 15 h. After filtration using a celite pad, removal of the solvent under reduced pressure and column chromatography on silica gel using hexane/ethyl acetate (20:1) furnished the product (80 mg, 92 %) as a pale yellow oil: $[\alpha]_D^{22}$ +29.2 (*c* 1.1, $CHCl_3$) (94 % ee (*R*) judged by HPLC analysis using CHRALCEL OD-H); IR ν_{max}^{neat} 1085cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 3.38 (3H, s), 4.80 (1H, d, *J* = 7.0Hz), 6.28 (1H, dd, *J* =7.0, 15.8Hz), 6.63 (1H, d, *J* = 15.8Hz) 7.22-7.37(10H, m)

12) The authentic sample was prepared using the procedure of H.-J. Gais *et al.* [13] as shown below.



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