Pergamon

Tetrahedron Letters 43 (2002) 7761–7764

TETRAHEDRON LETTERS

Novel chiral xylofuranose-based phosphinooxathiane and phosphinooxazinane ligands for palladium-catalyzed asymmetric tandem allylic allylation

Hiroto Nakano,* Jun-ichi Yokoyama, Reiko Fujita and Hiroshi Hongo

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

Received 31 July 2002; revised 22 August 2002; accepted 23 August 2002

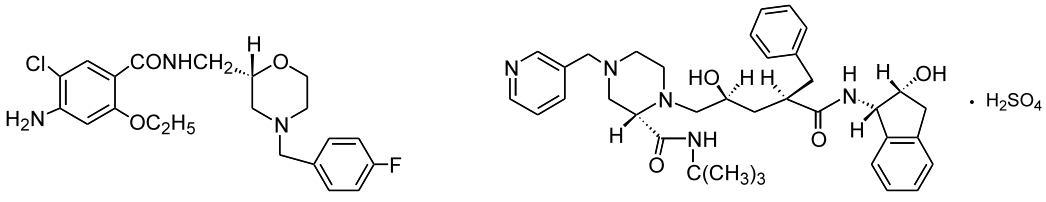
Abstract—Novel chiral xylofuranose-based phosphinooxathiane and phosphinooxazinane ligands have been synthesized and found to be effective ligands for palladium-catalyzed asymmetric tandem allylic allylations of 1,4-diacetoxy-*cis*-2-butene with 2-(benzylamino)ethanol or 1,2-bis[benzylamino]ethane to give chiral 4-benzyl-2-vinylmorpholine (94% ee) or 1,4-dibenzyl-2-vinylpiperazine (70% ee).

Palladium-catalyzed allylation[1] is an important method for carbon–carbon bond formation and the asymmetric version has been extensively studied during the past decade.[2] The tandem allylic allylation[3] is versatile reaction for the construction of chiral morpholine or piperazine skeletons that are present in many biologically active compounds such as mosapride and indinavir sulfate (Scheme 1).[4]

Catalytic syntheses of these compounds have been difficult, but a few examples using this tandem allylation have been reported by the Hayashi and Achiwa groups.[5] The best enantioselectivities realized up to 83% ee for morpholines and up to 60% ee for piperazines (Scheme 2).

Herein, we wish to report the synthesis of new chiral xylofuranose-based phosphinooxathiane and phosphinooxazinane ligands (**1** and **2a–d**) and their application in the Pd-catalyzed tandem allylic allylation to produce chiral morpholines and piperazines.

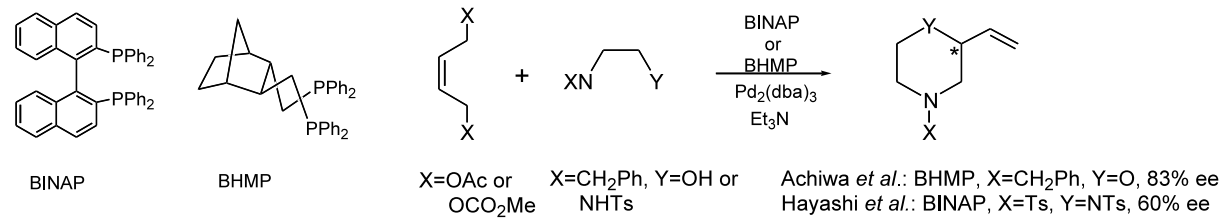
Phosphinooxathiane **1** and phosphinooxazinanes **2a–d** were synthesized easily from commercially available xylofuranose **3** (Scheme 3). Diol **3** was converted to **5** by monotosylation followed by acetylation. The displacement of the tosylate group with potassium thioacetate and the treatment of **6** with potassium carbonate afforded the mercapto-alcohol **7**. The condensation of **7** with 2-(diphenylphosphino)benzaldehyde **8** gave the desired chiral phosphinooxathiane ligand **1** in 43% yield. Similarly, chiral ligands **2a–d** were also easily prepared by the reaction of tosylate **4** with the corresponding amines followed by the condensations of **9a–d** with **8** in good yields (63–76%). In all five cases (**1** and **2a–d**), the assigned stereochemistry at the α-position of the 1,3-oxathiane ring was determined by the NOE difference spectrum (NOEDS). Enhancement was



Scheme 1.

Keywords: asymmetric tandem allylic allylation; phosphinooxathiane; phosphinooxazinane; palladium.
* Corresponding author. Tel:+81 22 234 4181; fax:+81 22 275 2013; e-mail: hnakano@tohoku-pharm.ac.jp

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01830-0

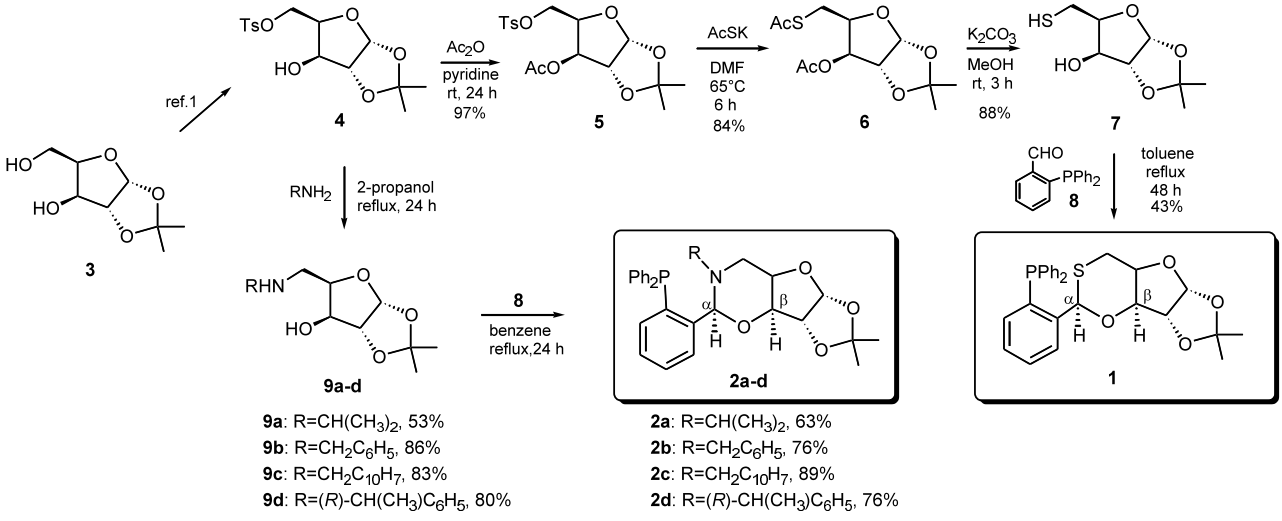


Scheme 2.

observed between the hydrogen at the α-position and the hydrogen at the β-position when the α- and β-protons were irradiated, respectively (Scheme 3).[6]

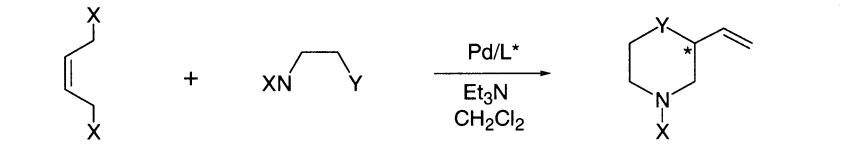
The Pd-catalyzed tandem allylic allylation of 1,4-diacetoxy-*cis*-2-butene **10a** with 2-(benzylamino)ethanol **11a** using chiral phosphinooxathiane ligand **1** or phosphinooxazinane ligands **2a**–**d** were examined in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ and triethylamine to give chiral 4-benzyl-2-vinylmorpholine **12a**; the results are summarized in Table 1. The reaction using chiral ligand **1** (5 mol%) in dichloromethane gave the product **12a** in 62% yield, but in very low enantiopurity (4% ee, entry 1). Reactions with chiral phosphinooxazinane ligands **2a**–**d** under the same conditions as ligand **1** gave higher enantiomeric excesses (entries 2–5). In particular, the bulkiest (*R*)-phenylethylated ligand **2d**[7] afforded the highest ee (87% ee) and in 47% chemical yield (entry 5). To optimize reaction conditions, we next examined the influences of temperature, the molar ratio of ligand **2d**, and the Pd(0) source (entries 6–9). Increasing temperature to 40°C brought about a decrease in enantioselectivity (83% ee, entry 6). Conversely, cooling to 0°C led to an increase in enantioselectivity (94% ee, entry 7) but in lower yields (60%).[8] Varying catalyst loading did not affect enantioselectivity (94% ee, entries 8 and 9), but did significantly influence chemical yield. Substituting $Pd_2(dba)_2{\cdot}CHCl_3$ for $[PdCl(\eta^3\text{-}C_3H_5)]_2$ resulted in a very sluggish but highly selective reaction (94% ee, entry 10). The chiral norbornane-based phosphinooxathiane and oxazolidine ligands (**13** and **14**),[6] used in a previous study were also tested under the same conditions as entry 7, but yielded disappointing results (entries 11 and 12). The reaction of 1,4-dicarbomethoxy-2-butene **10b** with **11a** was examined using chiral ligand **2d** in the presence of $[PdCl(\eta^3\text{-}C_3H_5)]_2$, or $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 13–15). The reaction using $[PdCl(\eta^3\text{-}C_3H_5)]_2$ at 0°C did not proceed at all (entry 13), even at room temperature gave **12a** in quite low yield (15%), but in high enantiomeric purity (92% ee, entry 14). On the other hand, the use of $Pd_2(dba)_3{\cdot}CHCl_3$ led to a slight increase in chemical yield (34%) and in enatioselectivity (94% ee, entry 15). The tandem allylic allylation of **10a** with 1,2-bis[benzylamino]ethane **11b** was also attemped using the chiral ligand **2d** and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ to give chiral 1,4-dibenzyl-2-vinylpiperazine **12b**. Increasing catalyst loading of **2d** from 5 to 10 mol% at room temperature gave only moderate enatioselectivities (52 and 53% ee, entries 16 and 17). Best results were obtained when the reaction was conducted at 0°C with 10 mol% of **2d** (50%, 70% ee, entry 18). From these results, the combination of chiral oxazinane ligand **2d** (10 mol%) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ was most effective to give **12a** in the tandem allylations of **10a** with **11a** or **11b**.

The obtained tandem product **12a** was converted easily to chiral morpholine alcohol **16** that is useful intermediate of NAS-181[4c] as follows (Scheme 4). The obtained product **12a** (94% ee) was converted to known carbamate **15**[5a] and subsequent ozonolysis and reduction gave the desired alcohol **16** in good yield and excellent enantioselectivity (91%, 94% ee).



Scheme 3.

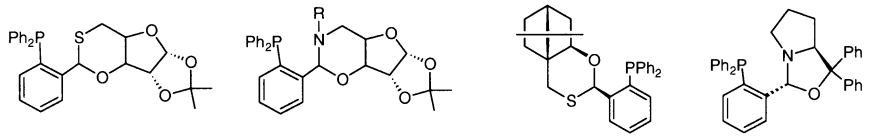
Table 1. Palladium-catalyzed tandem allylation using chiral ligands **1**, **2a–d**, **13**, and **14**



10
10a: X=OAc
10b: X=OCO_2Me

11
11a: X=CH_2Ph, Y=OH
11b: X=CH_2Ph, Y=NCH_2Ph

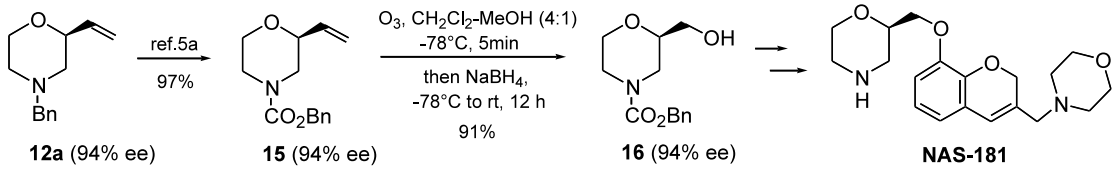
12
12a: X=CH_2Ph, Y=O
12b: X=CH_2Ph, Y=NCH_2Ph



1 **2a-d** **13** **14**

Entry[a]	Ligand (mol%)	Pd	Substrate	Nu	Temp (°C), Time (h)	Product, Yield(%)[b]	E.e.[c] (%)
1	**1** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 48	**12a**, 62	4 (S)[d]
2	**2a** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 48	**12a**, 95	69 (*S*)
3	**2b** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 48	**12a**, 90	58 (*S*)
4	**2c** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 48	**12a**, 58	43 (*S*)
5	**2d** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 48	**12a**, 47	87 (*S*)
6	**2d** (5)	$[PdCl(\eta^3C_3H_5)]_2$	**10a**	**11a**	40, 48	**12a**, 80	83 (*S*)
7	**2d** (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	0, 72	**12a**, 60	94 (*S*)
8	**2d** (10)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	0, 72	**12a**, 67	94 (*S*)
9	**2d** (2.5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	0, 72	**12a**, 35	94 (*S*)
10	**2d** (5)	$Pd_2(dba)_2CHCl_3$	**10a**	**11a**	0, 96	**12a**, 10	94 (*S*)
11	**13**, (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 24	**12a**, 81	10 (*S*)
12	**14**, (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11a**	r.t., 24	**12a**, 30	30 (*R*)
13	**2d**, (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10b**	**11a**	0, 96	**12a**, ---	---
14	**2d**, (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10b**	**11a**	r.t., 96	**12a**, 15	92 (*S*)
15	**2d**, (5)	$Pd_2(dba)_2CHCl_3$	**10b**	**11a**	r.t., 48	**12a**, 34	94 (*S*)
16	**2d**, (5)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11b**	r.t., 48	**12b**, 21	52 (*R*)
17	**2d**, (10)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11b**	r.t., 48	**12b**, 45	53 (*R*)
18	**2d**, (10)	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	**10a**	**11b**	0, 96	**12b**, 50	70 (*R*)

a) Molar ratio: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (entries 1-7, 11-14,16: 0.025 equiv., entry 9: 0.001 equiv., entries 17,18: 0.005 equiv.), $Pd_2(dba)_2 \cdot CHCl_3$ entries 10,15: 0.025 equiv.), **11a** (1 equiv.), **11b** (1 equiv.), Et_3N (2 equiv.), b) Isolated yields. c) Determined by HPLC analysis using a DAICEL Chiralcel OD-H. d) *S* or *R* configurations based on the specific rotation with literature data.[5a]



12a (94% ee) **15** (94% ee) **16** (94% ee) **NAS-181**

Scheme 4.

We have examined five new chiral xylofuranose-based phosphinooxathiane and phosphinooxazinane ligands **1** and **2a**–**d**. Particularly, **2d** has been found to be an efficient ligand for the asymmetric tandem allylic allylation of **11a**, providing the chiral 4-benzyl-2-vinylmorpholine **12a** or 1,4-dibenzyl-2-vinylpiperazine **12b** that are useful intermediates of biologically active compounds. Further applications and modifications of the ligands **1** and **2a**–**d** are in progress.

References

1. For recent reviews including palladium-catalyzed allylic substitution reactions; see: (a) Tsuji, J. *Palladium Reagents and Catalysis*; Innovations in Organic Synthesis; Wiley: New York, 1995; (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422; (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708; (d) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195–202; (e) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214.
2. (a) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025; (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687; (c) Pretot, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323–325; (d) Yonehara, K.; Hashizume, T.; Mori, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374–9380; (e) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285–286; (f) Fuji, K.; Ohnishi, H.; Moriyama, S.; Tanaka, K.; Kawabata, T.; Tsubaki, K. *Synlett* **2000**, *12*, 351–352; (g) Mino, T.; Hata, S.; Ohtaka, K.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2001**, *42*, 4837–4839; (h) Stranne, R.; Vasse, J.-L.; Moberg, C. *Org. Lett.* **2001**, *3*, 2525–2528; (i) Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y.; Williams, I. D. *Org. Lett.* **2002**, *4*, 1615–1618.
3. Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388–3390.
4. (a) Morie, T.; Kato, S.; Harada, H.; Yoshida, N.; Matsumoto, J. *Chem. Pharm. Bull.* **1994**, *42*, 877–882; (b) Sakurai, N.; Sano, M.; Hirayama, F.; Kuroda, T.; Uemori, S.; Moriguchi, A.; Yamamoto, K.; Ikeda, Y.; Kawakita, T. *Bioorg. Med. Lett.* **1998**, *8*, 2185–2190; (c) Berg, S.; Larsson, L.-G.; Renyi, L.; Ross, S. B.; Thorberg, S.-O.; Thorell-Svantesson, G. *J. Med. Chem.* **1998**, *41*, 1934–1942; (d) Dorsey, B. D.; McDonough, C.; McDaniel, S. L.; Levin, R. B. L.; Newton, C. L.; Hoffman, J. M.; Darke, P. L.; Zugay-Murphy, J. A.; Emilio, E. A.; Schleif, W. A.; Olsen, D. B.; Stahlhut, M. W.; Rutkowski, C. A.; Kuo, L. C.; Lin, J. H.; Chen, I.-W.; Michelson, S. R.; Holloway, M. K.; Huff, J. R.; Vacca, J. P. *J. Med. Chem.* **2000**, *43*, 3386–3399.
5. (a) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826–6832; (b) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asynmmetry* **1995**, *5*, 1021–1024.
6. For norbornane-based phosphinooxathiane ligand **13**, see: (a) Nakano, H.; Okuyama, Y.; Hongo, H. *Tetrahedron Lett.* **2000**, *41*, 4615–4618; (b) Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem.* **2001**, *66*, 620–625; (c) Nakano, H.; Suzuki, Y.; Kabuto, C.; Fujita, R.; Hongo, H. *J. Org. Chem.* **2002**, *67*, 5011–5014. For pyrrolidine-based phosphinooxazolidine ligand **14**, see: (d) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*. 1193–1198; (e) Nakano, H.; Okuyama, Y.; Suzuki, Y.; Fujita, Y.; Kabuto, C. *Chem. Commun.* **2002**, 1146–1147.
7. Ligand **2d**: mp 70–73°C; $[\alpha]_D^{22} = +46.92$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.21–1.27 (m, 6H), 1.43 (s, 3H), 2.81 (dd, $J = 13.6$, 2.5 Hz, 1H), 3.04 (dd, $J = 13.3$, 1.9 Hz, 1H), 3.74 (m, 1H), 3.87 (q, $J = 13.6$ Hz, 1H), 4.13 (m, 1H), 4.28 (d, $J = 3.6$ Hz, 1H), 5.84 (d, $J = 7.7$ Hz, 1H), 6.00 (d, $J = 3.6$ Hz, 1H), 6.90 (m, 1H), 7.14–7.48 (m, 17H), 7.90 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 26.21, 26.75, 43.55, 54.07, 73.67, 78.65, 83.53, 88.96(d), 105.68, 111.27, 126.10, 127.06, 127.61, 127.82, 128.10, 128.15, 128.19, 128.36, 128.46, 128.48, 128.63, 128.74, 129.49, 133.34, 133.63, 133.67, 133.78, 134.08, 136.20, 136.50, 136.64, 142.58, 142.92, 143.23. HRMS found: 565.241. Calcd for $C_{35}H_{36}NO_4P$ (M^+): 565.2382.
8. Typical procedure for tandem reaction (entry 3): A mixture of ligand **2d** (8.2 mg, 0.0145 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.7 mg, 0.004 mmol) in dry dichloromethane (3 ml) was strried at rt. After 1 h, triethylamine (0.080 ml, 0.58 mmol), **10a** (0.050 ml, 0.29 mmol), and **11a** (44 mg, 0.29 mmol) were added at 0°C and was stirred for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane/AcOEt = 5/1) to give a pure product **12a** (35.6 mg, 60%). The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 ml/min, hexane/2-propanol = 59/1, *S*-**12a**: 10.3 min, *R*-**12b**: 11.0 min).