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Pd-catalyzed asymmetric allylation with a novel C_2-symmetric bisphosphinite ligand: 3*R*,3′*R*-bis(diphenylphosphinoxy)-6,6,6′,6′-tetramethyl-2*S*,2′*S*-di-4*H*-pyran

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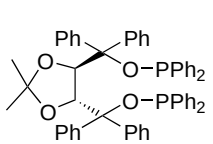
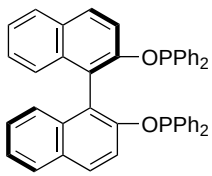
Abstract—A novel C_2-symmetric chiral bisphosphinite ligand, 3*R*,3′*R*-bis(diphenylphosphinoxy)-6,6,6′,6′-tetramethyl-2*S*,2′*S*-di-4*H*-pyran, was synthesized from D-mannitol and examined for palladium-catalyzed asymmetric allylic substitution. Under the optimized conditions, the allylation product can be obtained in up to 91.2% ee.

Asymmetric synthesis based on transition metal-catalyzed processes has attracted a great deal of interest because of its high efficiency for construction of enantiomerically enriched molecules.[1] How to design and develop efficient chiral ligands for transition metal-catalyzed reactions has become one of the most intense areas of investigation. Chiral phosphines represent one type of the most useful and versatile ligands for metal-catalyzed asymmetric reactions. In contrast to chiral phosphine ligands, phosphinites have not been well developed due to their lower stability in protic solvents and air. However, some, such as TADDOP, BINAPO and others, have demonstrated sufficient stability, particularly in the pure form.[2] The advantages of such kinds of ligands are their convenient preparation and high availability. Recently, several types of superior C_2-symmetric bisphosphinite ligands with various scaffolds such as BDPAB, SpiroP and BICPO, have been prepared and successfully utilized in asymmetric catalysis.[3] In the present work, we report preliminary results on the synthesis of a novel C_2-symmetric bisphosphinite ligand, 3*R*,3′*R*-bis-(diphenylphosphinoxy)-6,6,6′,6′-tetramethyl-2*S*,2′*S*-di-4*H*-pyran **1**, and its application in asymmetric allylic substitution.

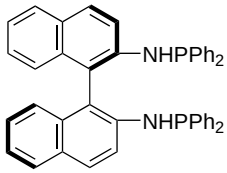
A synthesis of the precursor of **1**, the C_2-symmetrical scaffolded diol **6**, was first reported by Wang in 1997.[4] Starting from D-mannitol, 2,2-dimethyl-4,5-bis-oxi-



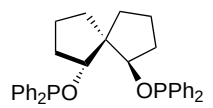
TADDOP



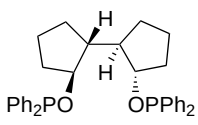
BINAPO



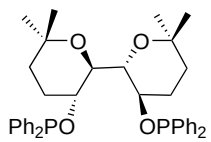
BDPAB



SpiroP



BICPO



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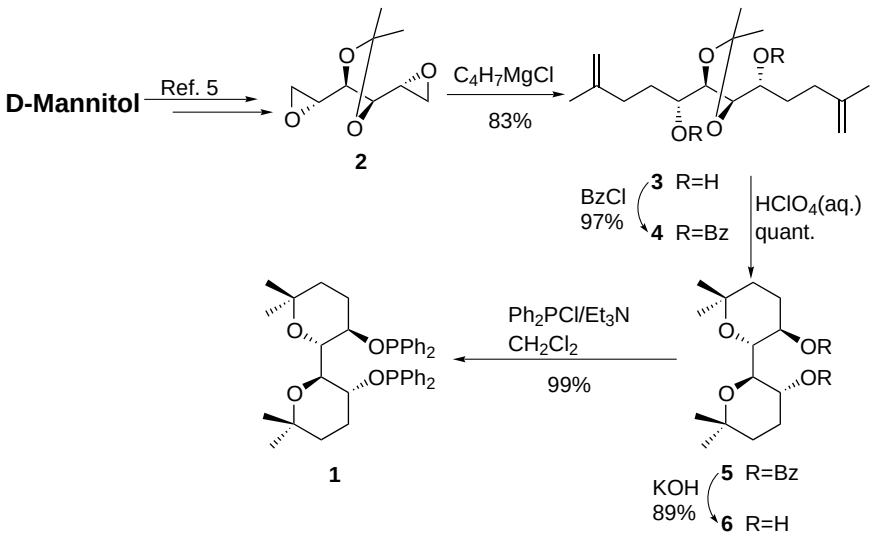
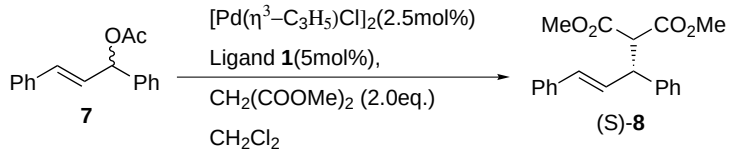
ranyl-[1,3]dioxolane **2** can be easily prepared according to the literature procedure.[5] Grignard addition of 2-methyl propenyl mangnesium chloride to **2** afforded **3** in 83% yield. Treatment of **3** with benzoyl chloride in the presence Et_3N gave the corresponding benzoate ester **4** in 97% yield. Quantitative $HClO_4$-catalyzed cyclization of **4** yielded **5**, which can be transformed to **6** upon alkaline hydrolysis in 89% yield (Scheme 1). Compound **6** has four stereogenic centers with a C_2-symmetric backbone containing two tetrahydropyran rings and should be an interesting chiral ligand scaffold for asymmetric catalysis. With this interesting precursor in hand, we tried to transform **6** into its phosphinite by reacting with Ph_2PCl. The reaction of **6** with Ph_2PCl in the presence of Et_3N at room temperature was found to be highly efficient and gave the bisphosphinite **1** in 99% yield.

In order to evaluate the asymmetric induction efficiency of **1**, palladium-catalyzed allylic substitution of 1,3-diphenyl-2-propen-1-yl acetate **7** with dimethyl malonate was taken as the model reaction. Reactions of racemic **7** with dimethyl malonate were carried out in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand **1** (5 mol%) and base (2.0 equiv.). Table 1 shows the details of our results. It was found that the choice of



Scheme 1. Preparation of C_2-symmetric bisphosphinite ligand **1**.

Table 1. Asymmetric allylation of **7** with dimethyl malonate promoted by Pd-**1** complex[a]



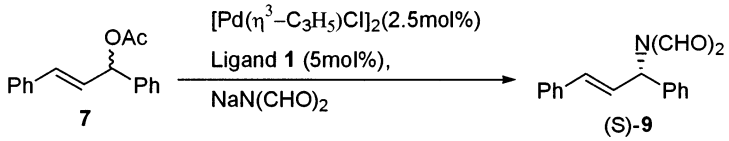
Entry	Base	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	BSA	KOAc	THF	0	1	92	69.7
2	BSA	KOAc	Toluene	0	1.5	97	69.5
3	BSA	KOAc	CH_3CN	0	0.5	97	68.7
4	BSA	KOAc	$ClCH_2CH_2Cl$	0	2	98	65.9
5	BSA	KOAc	CH_2Cl_2	0	0.5	91	77.4
6	BSA	LiOAc	CH_2Cl_2	0	3	76	64.2
7	$CsCO_3$	KOAc	CH_2Cl_2	0	3	77	78.7
8	NaH	KOAc	CH_2Cl_2	0	0.7	95	73.2
9	Et_2Zn	KOAc	CH_2Cl_2	0	0.3	95	81.0
10	Et_2Zn	LiOAc	CH_2Cl_2	0	1.5	96	81.9
11	Et_2Zn	KOAc	CH_2Cl_2	−20	10	95	88.1
12	Et_2Zn	LiOAc	CH_2Cl_2	−20	15	97	88.3
13	Et_2Zn	KOAc	CH_2Cl_2	−40	24	49	91.2

[a] Reactions were carried out using standard Schlenk techniques; the catalysts were generated in situ from the Pd precursor and bisphosphinite ligand: $[Pd(C_3H_7)Cl]_2$/**1**/base/malonate/**7** = 0.025:0.05:2:2:1.

[b] Isolated yield based on 1,3-diphenyl-2-propenyl acetate.

[c] Determined by HPLC on Chiralpak AD column (hexane:^{i}propanol = 90:10; 1.0 mL/min; t_S = 9.5 min, t_R = 13.0 min); the absolute configuration of the product was assigned to be *S* by comparison of chiroptical values with those of the literature.[8]

Table 2. Asymmetric allylic amination of **7** with sodium diformylamide promoted by Pd-**1** complex[a]



Entry	Solvent	SDFA (equiv.)	Et_3N (equiv.)	Temp. (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	$ClCH_2CH_2Cl$	3		24	20	42	59.6
2	$ClCH_2CH_2Cl$	3	2	24	18	60	69.7
3	CH_3CN	3	2	24	5	75	67.0
4	THF	3	2	24	5	38	70.3
5	Toluene	3	2	24	22	35	68.7
6	CH_2Cl_2	3	2	24	22	60	70.5
7	DMF	3	2	24	22	15	67.8
8	$ClCH_2CH_2Cl$	3	1	0	20	56	74.2
9	$ClCH_2CH_2Cl$	5	2	0	19	80	76.7

[a] Reactions were carried out using standard Schlenk techniques; the catalysts were generated in situ from the Pd precursor and the bisphosphinite ligand **1**: Pd/ligand/**7** = 0.025:0.05:1.

[b] Isolated yield based on 1,3-diphenyl-2-propenyl acetate.

[c] Determined by HPLC on Chiralpak AD column (hexane:^{i}propanol = 95:5; 0.8 mL/min; $t_S = 28.7$ min, $t_R = 31.8$ min). The absolute configuration of the product was assigned to be *S* by comparison of chiroptical values with those of the literature.[9]

the solvent for the reaction is very important both in terms of yield and enantioselectivity. When *N*,*O*-bis(trimethylsilyl)acetamide (BSA) combined with catalytic amount of KOAc[6] was taken as base, dichloromethane was disclosed to be superior to other solvents including THF, toluene, acetonitrile and 1,2-dichloroethane (entry 5 versus entries 1–4). Further screening of bases included in the reaction (entries 6–10) showed that diethylzinc combined with small amount of KOAc or LiOAc as the base was better than BSA, $CsCO_3$ or NaH. This result was consistent with that reported by Fuji.[7] By decreasing the reaction temperature to −20°C (entries 11–12) with Et_2Zn as a base in the presence of KOAc or LiOAc, the enantioselectivities of the reaction can be further improved to 88.1 and 88.3%, respectively. A remarkable increase in enantiomeric excess (up to 91.2% ee) with moderate yield was observed at −40°C (entry 13).

Sodium diformylamide (SDFA) has been found to be an advantageous amination reagent for Pd-catalyzed allylic amination in our laboratory.[9] We then examined the asymmetric induction efficiency of our bisphosphinite ligand **1** in the palladium-catalyzed asymmetric allylic amination of (±)-**7** with SDFA. Table 2 summarizes the details of our results. After optimization of the reaction by altering the reaction solvents, the amount of additive and reaction temperature, the aminated product (*S*)-**9** can be obtained in up to 80 yield and 76.4% ee. This is the first example of a bisphosphinite–Pd-catalyzed asymmetric allylic amination with SDFA as nucleophile.

In conclusion, a novel bisphosphinite ligand with C_2-symmetry has been prepared from the easily available natural product D-mannitol. Its application in palladium-catalyzed asymmetric allylation and amination was examined and products with up to 91.2 and 76.7% ee were obtained, respectively. Further studies on the synthesis of other C_2-symmetric ligands derived from **6** and their applications in asymmetric catalysis are undergoing in our laboratory.

Acknowledgements

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