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REGIOCONTROL IN Pd-CATALYZED ALLYLIC SUBSTITUTION WITH P,N-LIGAND

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Dedicated to Professor Yuichi Kanaoka in recognition of his outstanding contributions to the area of heterocyclic chemistry.

Abstract – A racemic ligand, (±)-*N*-[2-(diphenylphosphino)naphthyl]-2-(pyrrolidinylmethyl)piperidine, has been found to exhibit better regioselectivity than the racemic Pfaltz ligand, BINAP and dppp in the palladium-catalyzed regioselective allylic substitution with the use of (*E*)-1-phenyl-4-alkoxy-2-butenyl acetate as the substrate.

In the course of our studies in relation to synthetic organic chemistry based on the N-Ar axis,[1,2] we have developed a novel chiral ligand (**1**) mimicking N-Ar axial chirality on the following concept:[3] our chiral ligand (**1**) may have the two diasteromers due to the N-Ar axis and the chiral carbon in solution (Figure 1). But, if the N-Ar axis in (**1**) is configurationally flexible, and the complexation of (**1**) and a metal is largely reflected by the asymmetric center of pyrrolidinyl group **A** in (**1**), one of the two diastereomer complexes due to the N-Ar axis, is expected to be selectively formed (**2** in Figure 1), leading to the creation of favorable asymmetric environment.

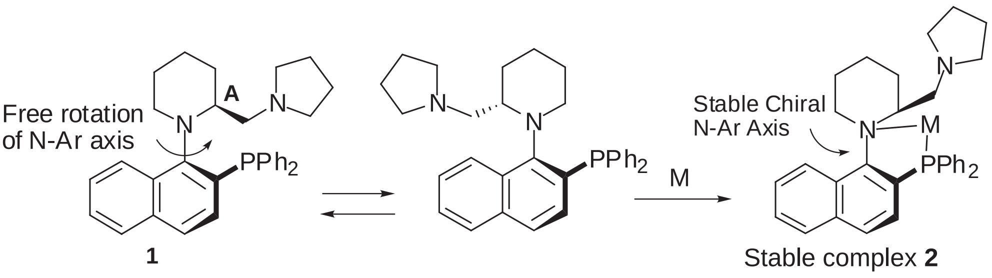
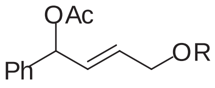


Figure 1

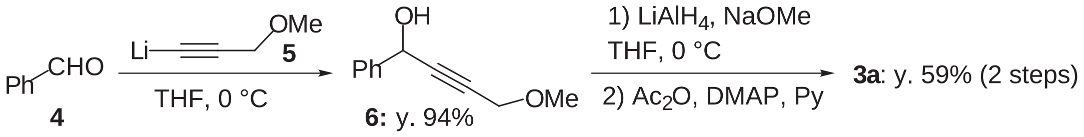
This designed ligand (**1**) has been found to exhibit 99% ee with the use of (*E*)-1,3-diphenyl-2-propenyl acetate as the standard substrate, and has achieved slightly better results than the representative Pfaltz[4] and Trost[5] ligands with the use of (*E*)-1-phenyl-3-trimethylsilyl-2-propenyl acetate as the substrate, in the palladium-catalyzed asymmetric allylic substitution with dimethyl malonate as the pronucleophile.[3] In order to explore further application of the ligand (**1**), we planned to search for a suitable achiral reaction with the racemic ligand ((±)-**1**) as the initial goal with the aim of application to asymmetric reaction. We concentrated on a palladium-catalyzed regioselective allylic substitution, because the lack of regioselectivity is often a problem[6]. In this paper, we would like to report our investigation of this reaction with the racemic ligand ((±)-**1**).

(*E*)-1-Phenyl-4-methoxy-2-butenyl acetate (**3a**) and (*E*)-1-phenyl-4-silyloxy-2-butenyl acetates (**3b-d**) were chosen as substrates. The substrate (**3a**) was prepared as shown in Scheme 1. Alkynylation of benzaldehyde (**4**) with the lithium acetylide (**5**) in THF at 0 ℃ afforded the coupling product (**6**). The reduction[7] of the triple bond in (**6**) with $LiAlH_4$ and NaOMe in THF at 0 ℃ and subsequent acetylation of the OH group afforded the substrate (**3a**) in 59% yield (2 steps). Likewise, other substrates (**3b-d**) were prepared. The representative preparation of (**3d**) is shown in Scheme 2. Alkynylation of aldehyde (**4**) with the lithium acetylide (**7**) and subsequent deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group afforded the coupling product (**8**) in 75% yield. After reduction of the triple bond in (8), chemoselective silylation and subsequent acetylation afforded the substrate (**3d**) in 66% yield (3 steps).

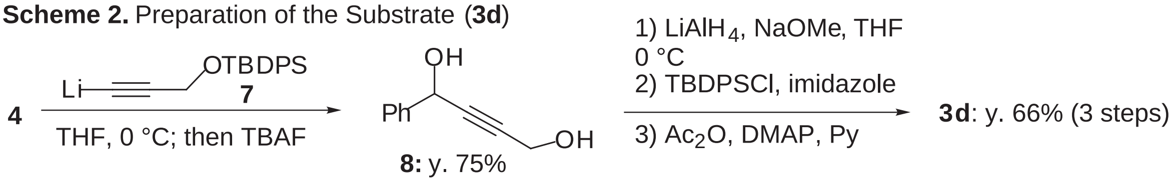


3a: R=Me
3b: R=TMS
3c: R=TBDMS
3d: R=TBDPS

Scheme 1. Preparation of the Substrate (**3a**)

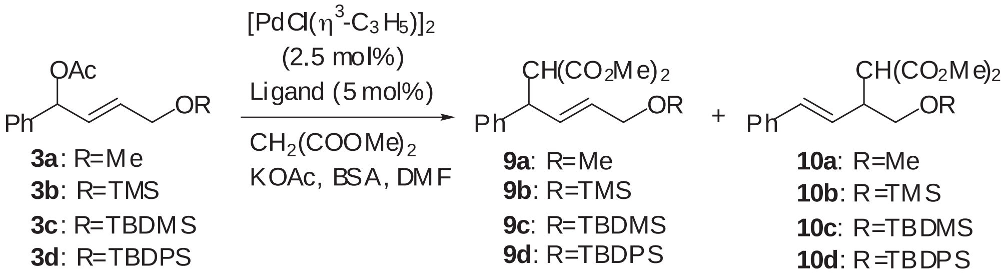


Scheme 2. Preparation of the Substrate (**3d**)

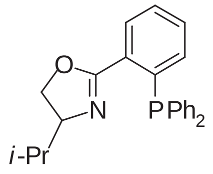


With the four substrates available, the regioselective allylic substitution was examined. The results are shown in Table 1. As can be seen in entry 1, treatment of the substrate (**3a**) with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5 mol%), the racemic ligand ((±)-**1**) (5 mol%), dimethyl malonate (3 equiv), *N*,*O*-bis(trimethylsilyl)acetamide[8] (BSA) (3 equiv) and KOAc (5 mol%) in DMF at rt afforded (**9a**) in 60% yield together with (**10a**) (39%).[9,10] Nucleophilic attack took place preferentially at the phenyl-substituted side. Reducing the reaction temperature from room temperature to 0 ℃ increased slightly the regioselectivity (**9a**: 65%, **10a**: 24%, entry 2). Contrary to this result, in the case of the racemic Pfaltz ligand (**11**), BINAP[11] (**12**) and dppp (**13**), no regioselectivity was observed (entries 3-5). This better regioselectivity with our ligand ((±)-**1**) might be due to low reactivity[12] of the π-allyl intermediate, compared with the ligands (**11-13**), although further investigation is needed to understand the effects of these ligands. Furthermore, reaction of the substrates (**3b-d**) bearing a sterically bulky silyl group, afforded better regioselectivity than that of the substrate (**3a**) (enrties 6-8). Among them, the substrate (**3d**) bearing a TBDPS group, gave the best selectivity (entry 8).

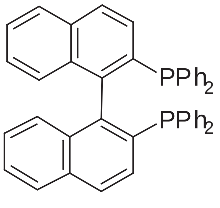
Table 1. Regioselective Allylic Substitution



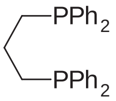
Entry	Substrate (R=)	Ligand	Temp	Time (h)	Yield (%)	
					9	**10**
1	**3a** (R=Me)	**1**	rt	1	60	39
2	**3a** (R=Me)	**1**	0 °C	3	65	24
3	**3a** (R=Me)	**11**	rt	1	48	47
4	**3a** (R=Me)	**12**	rt	2	44	48
5	**3a** (R=Me)	**13**	rt	48	43	41
6	**3b** (R=TMS)	**1**	rt	2	60	20
7	**3c** (R=TBDMS)	**1**	rt	2	66	22
8	**3d** (R=TBDPS)	**1**	rt	48	72	15



racemic Pfaltz ligand **11**



racemic BINAP **12**



dppp **13**

In conclusion, we have found that our racemic ligand ((±)-**1**) exhibits better regioselectivity than the racemic Pfaltz ligand (**11**), BINAP (**12**) and dppp (**13**). Asymmetric regioselective allylic substitution with (**6a-d**) catalyzed by the Pd/chiral ligand[13] (**1**) complex is now in progress in our laboratory.

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