

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, (\pm)-*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 diastereomers 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.

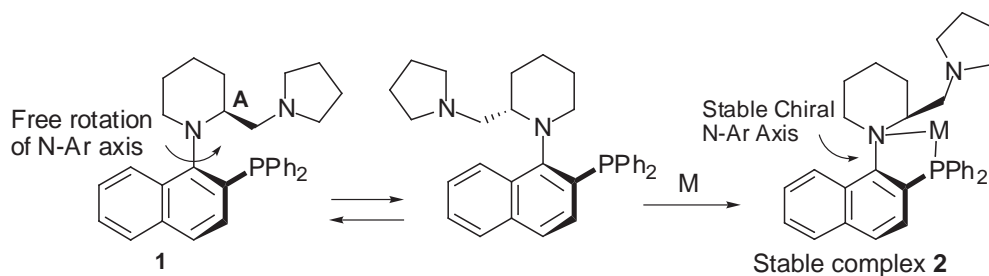
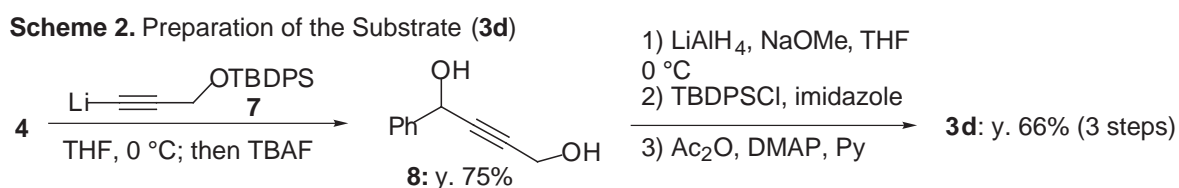
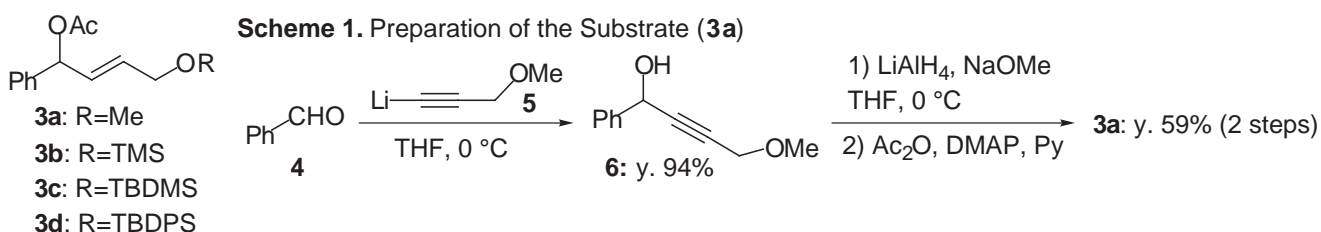


Figure 1

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 Pfaltz⁴ and Trost⁵ 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 problem⁶. In this paper, we would like to report our investigation of this reaction with the racemic ligand ((±)-**1**).

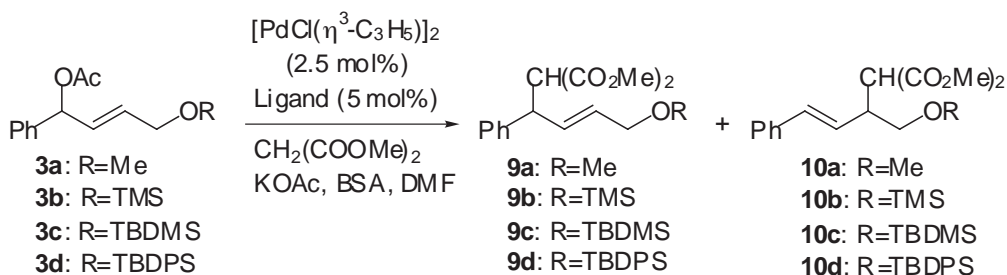
(*E*)-1-Phenyl-4-methoxy-2-butenyl acetate (**3a**) and (*E*)-1-phenyl-4-silyloxy-2-butenyl acetates (**3b-d**) were chosen as substrates. The substrate (**3a**) was prepared as shown in Scheme 1. Alkynylation of benzaldehyde (**4**) with the lithium acetylide (**5**) in THF at 0 °C afforded the coupling product (**6**). The reduction⁷ of the triple bond in (**6**) with LiAlH₄ and NaOMe in THF at 0 °C 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).



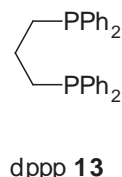
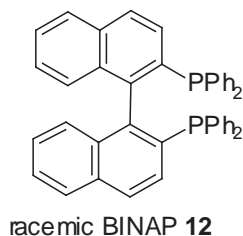
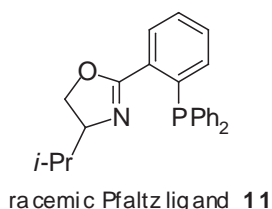
With the four substrates available, the regioselective allylic substitution was examined. The results are shown in Table 1. As can be seen in entry 1, treatment of the substrate (**3a**) with [PdCl(η³-C₃H₅)]₂ (2.5 mol%), the racemic ligand ((±)-**1**) (5 mol%), dimethyl malonate (3 equiv), *N,O*-bis(trimethylsilyl)acetamide⁸ (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 °C increased slightly the regioselectivity (**9a**: 65%, **10a**: 24%, entry 2). Contrary to this result, in the case of the racemic Pfaltz ligand (**11**), BINAP¹¹ (**12**) and dppp (**13**), no regioselectivity was observed (entries 3-5). This better regioselectivity with our ligand ((±)-**1**) might be due to low reactivity¹² 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**) (entries 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



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 ligand¹³ (**1**) complex is now in progress in our laboratory.

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