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Synthesis and Application of Chiral Spiro Phospholane Ligand in Pd-Catalyzed Asymmetric Allylation of Aldehydes with Allylic Alcohols

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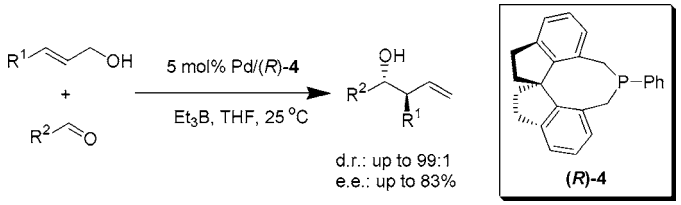
ABSTRACT



A novel chiral monodentate spiro phenylphospholane ligand 4 was prepared from a readily accessible, enantiomerically pure 1,1′-spirobiindane-7,7′-diol in high yield. This ligand has proven to be efficient for Pd-catalyzed enantioselective allylation of aldehydes with allylic alcohols. Aromatic, heteroaromatic, and aliphatic aldehydes gave homoallylic alcohols in good enantioselectivities (up to 83% ee) and excellent anti diastereoselectivities (up to 99:1 dr).

Catalytic enantioselective allylation of aldehydes represents one of the most efficient strategies for the synthesis of chiral homoallylic alcohols, which are versatile intermediates for variety of synthetically useful compounds.[1] Three types allylic reagents have been used so far in catalytic enantioselective allylation of aldehydes: allylmetal reagents in chiral Lewis acid- or Lewis base-catalyzed allylation; allylic halides in chromium-, zinc-, or indium-mediated allylation; and allyl esters in palladium-catalyzed allylation. The first two protocols have been extensively studied and well documented.[2] It was just quite recently that Zanoni and coworkers[3] first used allyl esters in their pioneering work in the catalytic enantioselective allylation of benzaldehyde by umpolung of π-allylpalladium complexes. However, although allylic alcohols have been used as allylic donators in Pd-catalyzed allylation of carbonyl compounds,[4] to our knowledge the asymmetric, catalytic, direct allylation of aldehydes with allylic alcohols has not been reported yet. In fact, the direct use of allylic alcohols in asymmetric allylation of aldehydes is advantageous in view of synthetic efficiency and green chemistry. Such use facilitates access to a broad range of chiral homoallylic alcohols without having to transform them to their derivatives bearing a wasteful leaving group. Herein we report our results on the investigation in Pd-catalyzed asymmetric allylation of aromatic, heteroaromatic, and aliphatic aldehydes with allylic alcohols in the presence of Et_3B, providing the corresponding homoallylic alcohols in good enantioselectivities and excellent diastereoselectivities.

The allylation of benzaldehyde with cinnamyl alcohol was chosen as a model reaction. In the initial investigation, the

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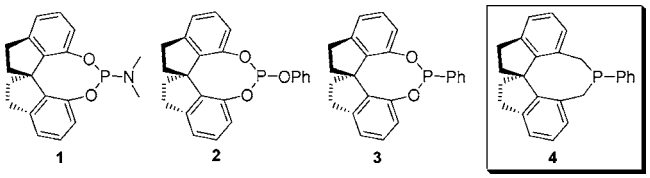
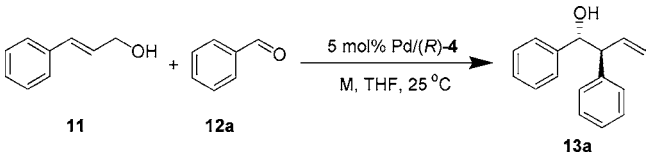


Figure 1. Chiral Spiro Monodentate Phosphorus Ligands

monodentate spiro ligands phosphoramidite **1**[5] (Figure 1) previously developed in our group was tested in this reaction. The palladium acetate (5 mol %) and ligand (10 mol %) were premixed in THF and stirred at 25 °C for 30 min, and then benzaldehyde **12**, cinnamyl alcohol **11**, and triethylboron were added sequentially. After the starting material was completely consumed, the reaction mixture was quenched with hydrochloric acid, and the product was purified by flash chromatography. It was disappointing that the allylation product 1,2-diphenylbut-3-en-1-ol (**13a**) was obtained in only 48% yield with 19% ee for the anti isomer (anti/syn = 94:6, Table 1, entry 1).

Table 1. Pd-Catalyzed Asymmetric Allylation of Benzaldehydes with Cinnamyl Alcohol: Ligands and Umpolung Reagents[a]



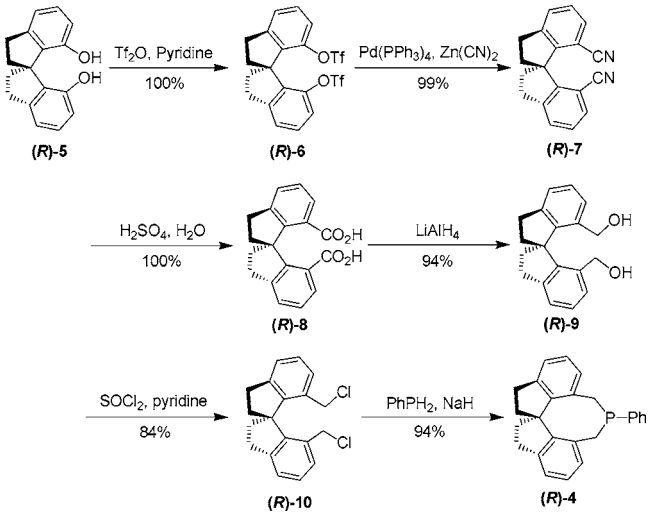
entry	ligand	M	time (h)	yield (%)[b]	anti/ syn[c]	% ee[d]
1	(*R*)-**1**	Et_3B	12	48	94/6	19
2	(*R*)-**2**	Et_3B	24	40	84/16	30
3	(*R*)-**3**	Et_3B	12	38	94/6	10
4	(*R*)-**4**	Et_3B	12	80	98/2	82
5	(*R*)-**4**	Et_2Zn	24	41	97/3	54
6	(*R*)-**4**	$SnCl_2$	48	0		

[a] Reaction conditions: $Pd(OAc)_2$, 0.05 equiv; ligands, 0.1 equiv; M, 5 equiv; PhCHO, 1.2 equiv; cinnamyl alcohol, 1.0 equiv (0.14 mmol); THF 0.8 mL at 25 °C. [b] Isolated yield. [c] Determined by GC or ^1H NMR. [d] Determined by chiral HPLC using a chiralpak AD-H column. The absolute configurations were (1*R*,2*S*)-.

We next tested another two monodentate spiro ligands, phosphite **2** and phosphonite **3**, which are highly efficient in the rhodium-catalyzed hydrogenation of functionalized olefins and other asymmetric reactions,[6] in this allylation reaction. However, the yields and the enantioselectivities of the allylation products were still unsatisfactory (entries 2 and 3). To achieve a full spectral comparison of spiro phosphorus ligands, the monodentate spiro phospholane ligand **4** was synthesized and found to be efficient for the Pd-catalyzed allylation of aldehydes with allylic alcohols in high yields, excellent diastereoselectivities, and good enantioselectivities.

The ligand (*R*)-**4** was synthesized from enantiomerically pure (*R*)-1,1′-spirobiindane-7,7′-diol (SPINOL, (*R*)-**5**) in high yield as shown in Scheme 1. The diol (*R*)-**5** was converted

Scheme 1. Synthesis of Phospholane Ligand **4**



into bistriflate **6** in quantitative yield[7] and cynated with $Zn(CN)_2$ catalyzed by $Pd(PPh_3)_4$ at 145 °C for 24 h to afford dicarbonitrile **7**. The use of $Zn(CN)_2$ as a cyanation reagent[8] is crucial for obtaining dinitrile **7** in high yield. When KCN or NaCN was applied, there was no target compound given even under harsh conditions. Hydrolysis of dinitrile **7** with diluted H_2SO_4 at reflux for 48 h produced diacid **8** smoothly. The reduction of **8** with $LiAlH_4$ in refluxing ether for 24 h yielded the benzyl diol **9** in 94% yield. Following the standard procedure, we converted the diol **9** to chloride **10** with $SOCl_2$, and condensation was performed with phenylphosphine to provide phenylphospholane ligand **4** in 94% yield.[9] Though this synthetic route takes six steps, its overall yield is quite high (74%).

When the ligand (*R*)-**4** was used in the allylation of benzaldehyde with cinnamyl alcohol, both the yield and the enantioselectivity of the reaction were remarkably improved (Table 1, entry 4). The enantioselectivity (82% ee) achieved with ligand **4** is not only higher than those obtained with the chiral spiro phosphorus ligands **1**−**3** but also higher than the highest ee value (70% ee) reported by Zanoni and coworkers[3] in the catalytic asymmetric aldehyde allylation by umpolung of π-allylpalladium complexes.

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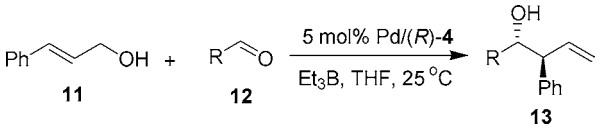
In addition to Et_3B, other well-known umpolung reagents such as Et_2Zn and $SnCl_2$ were also tested in the direct aldehyde allylation with allylic alcohols. Et_2Zn promoted the reaction with lower yield and enantioselectivity, while $SnCl_2$ gave no reaction (entries 5 and 6).

Under the optimal conditions, the allylation of various aldehydes with cinnamyl alcohol was examined, and the results are summarized in Table 2. For all substrates, the reactions demonstrate excellent diastereoselectivities. The electronic features of aromatic aldehydes apparently affect the yield and enantioselectivity of the reaction. The electron-rich aldehydes **12b** and **12c** showed higher yields but lower enantioselectivities (Table 2, entries 2 and 3), while electron-deficient aldehyde **12d** gave a lower yield and lower enantioselectivity (entry 4). Similar to benzaldehydes, α- and *β*-naphthaldehydes and furaldehyde also reacted with cinnamyl alcohol to produce the corresponding homoallylic alcohols in good yields and enantiomeric excesses (entries 5−7). It was delightful to find that the allylation of aliphatic aldehyde cyclohexanecarboxaldehyde was realized under the same conditions in 83% ee, albeit the yield was not very high (entry 8).

Table 2. Pd-Catalyzed Et_3B-Promoted Asymmetric Allylation of Aldehydes with Allylic Alcohols[a]



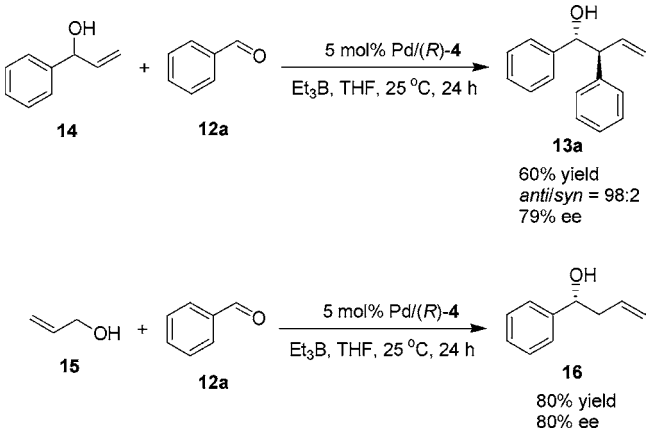
11 12 13

entry	R	time (h)	yield (%)	anti/syn	% ee
1	C_6H_5 (**12a**)	12	80 (**13a**)	98/2	82
2	4-$MeOC_6H_4$ (**12b**)	48	97 (**13b**)	99/1	74
3	2-$MeOC_6H_4$ (**12c**)	17	91 (**13c**)	95/5	69
4	4-$CF_3C_6H_4$ (**12d**)	12	71 (**13d**)	97/3	58
5	1-Np (**12e**)	12	99 (**13e**)	99/1	79
6	2-Np (**12f**)	12	95 (**13f**)	99/1	73
7	2-furyl (**12g**)	12	73 (**13g**)	99/1	78
8	*c*-C_6H_{11} (**12h**)	32	50 (**13h**)	99/1	83

[a] Conditions for the reactions and analyses are the same as those in Table 1.

When racemic 1-phenylprop-2-en-1-ol (**14**) was used as an allylic reagent, 79% ee was achieved (Scheme 2). Compound **14** is expected to form the same intermediate *π*-allyl palladium complex as 3-phenylprop-2-en-1-ol (**11**) in the allylation reaction. The same level of enantiocontrol obtained for these two compounds implied that the stereochemical memory effect does not exist in our system.[3,10] The simple allylic alcohol **15** also reacted with benzaldehyde under the standard conditions, giving 1-phenyl homoallylic alcohol **16** in good yield and enantioselectivity (Scheme 2).

Scheme 2



In summary, a new type of chiral spiro monodentate phospholane ligand **4** has been developed and successfully applied in palladium-catalyzed allylation of aldehydes. The enantioselectivities (up to 83% ee) achieved by ligand **4** represent the best results in the Pd-catalyzed asymmetric allylation of aldehydes by umpolung of *π*-allylpalladium complexes. In the reaction, the allylic alcohols were first used as allylic reagents. This makes the manipulation of the reaction simpler and the synthesis of optically active homoallylic alcohols more efficient.

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Supporting Information Available: Experiment details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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