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## Communications

### Chiral Pyridinyloxazolidine Ligands for the Pd-Catalyzed Asymmetric Allylic Alkylation


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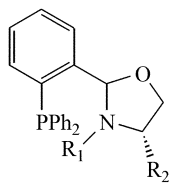
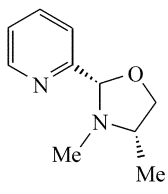
Asymmetric carbon-carbon bond-forming reaction is one of the most valuable processes for construction of enantiomerically enriched molecules. Considerable research has been done on Pd-catalyzed asymmetric allylic alkylation.[1,2] In particular, the search of new chiral ligands is an important chapter in the area and remains an area of intense research. We have previously found that phosphinooxazolidines **1** bearing $sp^3$ nitrogen donor are useful ligands in the asymmetric allylic alkylation.[3] The oxazolidines obtainable by simple synthetic route seem to be potential ligands for the asymmetric catalysis. As part of our continuing interest in oxazolidines, we herein disclose the preparation of new chiral pyridinyloxazolidines and their application in asymmetric allylic alkylation.




**1**

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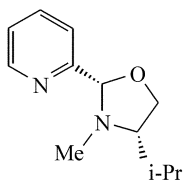


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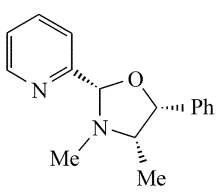
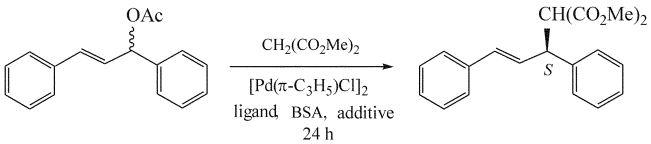



**4**

The oxazolidines **2-4** were obtained through condensation of commercially available 2-pyridinecarboxaldehyde and optically pure (*S*)-*N*-methylalaninol, (*S*)-*N*-methylvalinol and (1*R*,2*S*)-ephedrine in good yields of 80%, 84%, and 90% respectively. The reaction leads to the formation of new

**Table 1**. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate[a]

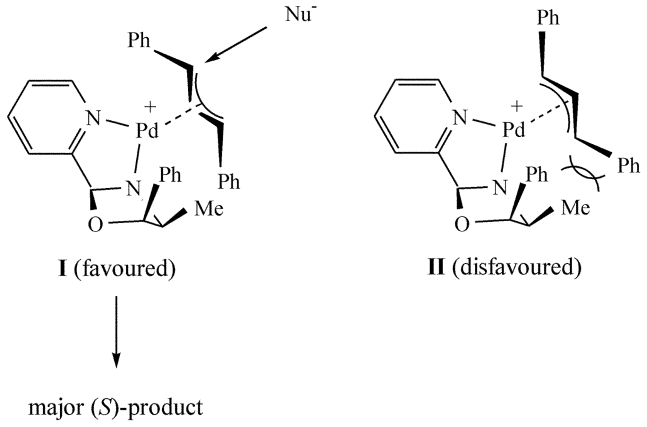



| Ligand | Solvent | Additive (MOAc) | Temp. (°C) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| **2** | $CH_2Cl_2$ | KOAc | 10 | 92 | 37 |
| **3** | $CH_2Cl_2$ | KOAc | 10 | 62 | 8 |
| **3** | THF | KOAc | 10 | 34 | 5 |
| **4** | $CH_2Cl_2$ | LiOAc | 10 | 81 | 61 |
| **4** | $CH_2Cl_2$ | NaOAc | 10 | 71 | 73 |
| **4** | $CH_2Cl_2$ | KOAc | 0 | 84 | 75 |
| **4** | $CH_2Cl_2$ | KOAc | 10 | 97 | 80 |
| **4** | $CH_2Cl_2$ | KOAc | 10 | 80 | 76 |
| **4** | $CH_2Cl_2$ | KOAc | 20 | 96 | 75 |
| **4** | THF | KOAc | 10 | 80 | 68 |

[a]Reactions were carried out with $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (2.5 mol%), the ligand (10 mol%), BSA (3 equiv.), MOAc (4 mol%) and dimethyl malonate (3 equiv.). [b]Measured as %-conversion into the product by GC. [c]Determined by HPLC with a chiralcel OD-H column. Absolute configuration was assigned by the sign of the optical rotation and the elution order from a chiral column.

stereocenter C2 on the oxazolidine ring. Interestingly, each oxazolidine was diastereomerically pure within NMR detection limits. The *cis*-relative configuration at C2 was assigned on the basis of the $^1$H NMR spectral data[4] and the previous studies.[5] Reaction of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate/*N,O*-bis(trimethylsilyl)acetamide (BSA) combined with a small amount of metal acetate (MOAc) was carried out in the presence of a palladium catalyst generated in situ from $\pi$-allylpalladium chloride dimer and the ligand. The reaction conditions and results are summarized in Table 1. Ligand **3** having a bulky isopropyl group at C4 gave poor results in terms of enantioselectivity as well as reactivity. The palladium catalyst derived from ligand **3** may be too congested to exert good catalytic activity. Ligand **2** having methyl group provided somewhat higher % ee than **3**. The effect of substituent at C5 was again examined with ligand **4** bearing phenyl group at C5. Interestingly, the ee was dramatically improved to 80% ee. Introduction of an additional phenyl group at C5 resulted in a significant increase of enantioselectivity. The substituent seems to assist the stereochemical control of the reaction. When three kinds of acetate salts (Li, Na, K) were employed as an additive, potassium acetate gave the best results in terms of enantioselectivity and reactivity. Reaction temperature had a little influence on the enantioselectivity at temperature between 0 °C and 20 °C. In addition, $CH_2Cl_2$ as solvent gave better reactivity and enantioselectivity than THF.

This reaction using ligand **4** gave the (*S*)-product predominantly. The stereochemical outcome obtained here indicates that the nucleophilic attack to the carbon atom of the $\pi$-allyl moiety takes place preferentially at trans position to the oxazolidine nitrogen in the less sterically-hindered *endo*-$\pi$-allylpalladium complex (**I**). In the case of *exo*-$\pi$-allyl complex (**II**), severe steric repulsion is generated between the phenyl as well as the methyl group on the oxazolidine ring and the phenyl group in the substrate.




**I** (favoured) **II** (disfavoured)

major (*S*)-product

In conclusion, a new kinds of pyridine-based oxazolidines could be used as chiral ligands in the asymmeric Pd-catalyzed allylic alkylation. It is noteworthy that the phenyl group in ligand **4** exerts considerable influence on the enantioselectivity. Further synthesis of chiral oxazolidines and their application are underway in our laboratory.

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4. Selected data for **4**: yield 90%; MS: *m*/z 254 ($M^+$); $^1$H-NMR: ($CDCl_3$, 250 MHz) 8.62 (d, *J* 4.8 Hz 1H), 7.81-7.19 (m, 8H), 5.18 (d, *J* 8.1 Hz 1H), 4.82 (s, 1H), 3.02 (m, 1H), 2.29 (s, 3H) 0.74 (d, *J* 6.3 Hz, 3H); Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.51; H, 7.18; N, 11.09.
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