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Short Communication

Application of (2′*R*,5′*R*)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)-methyl]pyridine and (2′*R*,5′*R*)-2-[(2′,5′-Diphenylpyrrolidin-1-yl)methyl]pyridine to the Palladium-Catalyzed Allylic Alkylation

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Extensive efforts are currently devoted to the design and synthesis of chiral ligands for use in asymmetric metal catalysis.[1,2] Among the ligands that have proved capable of chirality transfer to the reacting substrates are those containing nitrogen atoms as donors.[3]

We have recently shown that (4′*R*)-2-(4′-phenyl-4′,5′-dihydro-2-oxazolyl)pyridine (**1**) can be used as a ligand in the palladium-catalyzed allylic substitution[4] of *rac*-1,3-diphenyl-2-propenyl acetate using dimethyl malonate as the source of the nucleophile, to afford the product with *R* configuration with moderate enantioselectivity (50% ee).[5] When a 2-hydroxyalkyl or 2-alkoxyalkyl substituent was introduced into the 6-position of the pyridine ring, dramatic changes in the selectivity occurred. The 2,6-disubstituted pyridine derivatives coordinate to palladium in the same manner as **1**, via the two nitrogen atoms, while the substituent in 6-position serves as a steric scaffold capable of increasing or decreasing the enantioselectivity. With ligands **2** and **3** (with *R* and *S* absolute configuration, respectively, at the stereogenic center in the 6-position of the ring, shown in Fig. 1 in their most stable conformations[6]), 95 and >99% ee, respectively, were observed, whereas with the corresponding diastereomers, **4** and **5**, merely 90 and 15% ee, respectively, were attained.[5]

In order to study the effect of exchanging the oxazoline ring for other chiral groups, we were interested in the preparation of pyridine compounds possessing chiral nitrogen-containing substituents in the 2-position of the heterocyclic ring. 2-(Pyrrolidin-1-ylmethyl)pyridines were considered as suitable candidates for this purpose, and such compounds were therefore prepared. During our study, a paper describing the synthesis of the same compounds appeared.[7] This prompted us to publish our preliminary results regarding their use as ligands in palladium-catalyzed allylic substitutions.

Results and discussion

Ligands **6a** and **6b** were prepared via a procedure (Scheme 1) involving reduction of ketones **7a** and **7b** using baker's yeast (for **7a**) or (−)-diisopinocampheylchloroborane [(−)Ipc_2BCl] (for **7b**), to give alcohols **8a** and **8b**. Reaction of the corresponding dimes-

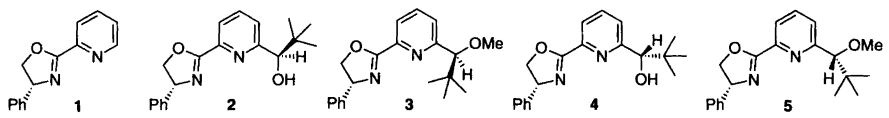

Fig. 1. Structures of ligands **1–5**.

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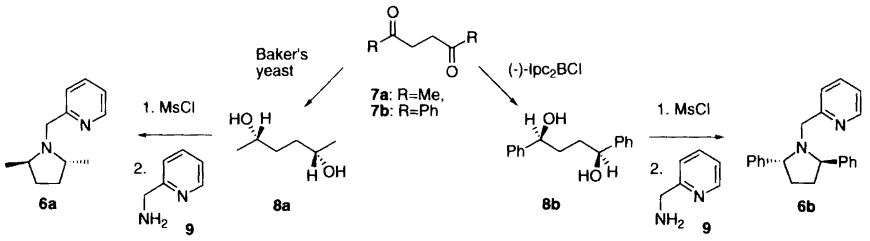
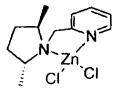


Scheme 1.

ylates with excess 2-(aminomethyl)pyridine (**9**, 8 and 15 equiv., respectively) afforded the desired bidentate ligands (2′*R*,5′*R*)-2-[(2′,5′-dimethylpyrrolidin-1-yl)methyl]pyridine (**6a**, 60% yield after Kugelrohr distillation) and (2′*R*,5′*R*)-2-[(2′,5′-diphenylpyrrolidin-1-yl)methyl]-pyridine (**6b**, 34% yield after chromatography).

In order to study the coordination behavior of ligand **6a**, a complex with zinc(II) chloride was prepared. The ^{1}H NMR spectrum of the complex (**10**) indicates that



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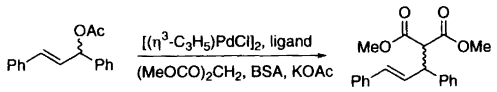
bidentate coordination takes place, since protons in the pyrrolidine ring which are symmetry-related in the free ligands become diastereotopic in the complex.

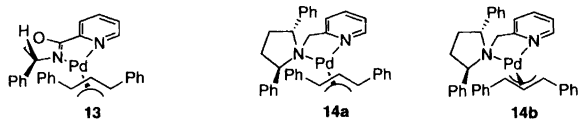
Compounds **6a** and **6b** were employed as ligands in the palladium-catalyzed allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate (**11**) using dimethyl malonate as nucleophile [eqn. (1)].[8] With **6a** as ligand, *S*-**12**



11 **12** (1)

was obtained in 18% ee, whereas *R*-**12** was obtained with higher selectivity, 64% ee, when **6b** was employed as the ligand. The latter is also higher than that observed using **1** as the ligand, suggesting that the pyrrolidine ring has a more efficent steric influence on the allyl group than the oxazoline ring.

π-Allylpalladium complexes are known to be intermediates in palladium-catalyzed allylic alkylation.[4] Two diastereomeric palladium complexes may form as intermediates when C_1-symmetric ligands **1**–**5** are used in the allylation reaction. This is also the case with ligands **6a** and **6b** (with a C_1-symmetric pyrrolidine substituent four different complexes would be possible). The major product usually originates from the most abundant isomer.[9] We have previously found that complex **13** is preferred



13 **14a** **14b**

over its diastereomer, and that attack of the nucleophile occurs *trans* to the oxazoline ring to give the isomer with *R* configuration as the major product. It seems reasonable to assume that **14a** is favored over **14b**, since in **14b** there is a severe steric interaction between the two phenyl rings. As the absolute configuration of the product is known, it can be concluded that nucleophilic attack on the π-allyl ligand probably occurs *trans* to the pyrrolidine ring.

Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded for samples in $CDCl_3$ at 400 and 100.6 MHz, respectively, with $SiMe_4$ as an internal standard. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

(2′R,5′R)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)methyl]pyridine (**6a**). 2-(Aminomethyl)pyridine (15 equiv.) and the dimesylate of **8a** were reacted (neat) at room temperature under nitrogen for 6 days. The product (60% yield) was isolated after addition of NaOH, extraction with hexane, and distillation. $[\alpha]_D^{20}$ −69 (*c* 0.8, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were in accordance with those published.[7]

(2′R,5′R)-2-[(2′,5′-Diphenylpyrrolidin-1-yl)methyl]pyridine (**6b**). 2-(Aminomethyl)pyridine (15 equiv.) and the dimesylate of **8b** were reacted (neat) at room temperature under nitrogen for 3.5 days. The product (34%) was isolated by extraction with hexane followed by chromatography (silica gel; gradient elution with hexane–ethyl acetate). White crystals, which decomposed on standing, were obtained from ethyl acetate. $[\alpha]_D^{20}$ +70 (*c* 0.7, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were in accordance with those published.[7] MS *m/z* 315 [$(M+H)^+$], 222 ($M^+ - CH_2py$), 95 [$(CH_2py+H)^+$].

Catalytic reaction. The reactions of *rac*-1,3-diphenyl-2-propenyl acetate (**11**) with dimethyl malonate were run in CH_2Cl_2 at ambient temperature for ca. 4 days, using a previously described procedure, employing bis[(π-allyl)palladium chloride] as the catalyst precursor and *N,O*-bis(trimethylsilyl)acetamide (BSA) and KOAc for the regeneration af the nucleophile.[10] Enantioselectivities were determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$.

***6a*–*ZnCl*$_2$ (10).**[11] $ZnCl_2$ (48.8 mg, 0.3 mmol) was melted and cooled under vacuum in a nitrogen atmosphere in order to remove water. THF (3 ml) was added, followed by a solution of **6a** (57.45 mg, 0.3 mmol) in THF (1.5 ml). The reaction was stirred at ambient temperature for 24 h, after which the solvent was removed and the resulting complex was recrystallized from ethanol to yield white crystals (21.8 mg, 0.067 mmol). ^{1}H NMR: δ 8.64 (td, *J* 1.2 and 5.2 Hz, 1 H), 7.99 (dt, *J* 1.7 and 7.8 Hz, 1 H), 7.54 (ddd, *J* 1.1, 5.8 and 7.7 Hz, 1 H), 7.44 (app d, *J* 7.9 Hz, 1 H), 4.30 (d, *J* 15.7 Hz, 1 H), 3.93 (d, *J* 15.7 Hz, 1 H), 4.18 (dquintet, *J* 6.8 and 3.1 Hz, 1 H), 3.28 (app. sextet, *J* 7 Hz, 1 H), 2.46–2.34 (m, 1 H), 2.20–2.08 (m, 1 H), 2.01–1.89 (m, 1 H), 1.68–1.58 (m, 1 H), 1.17 (d, *J* 6.5, 3 H), 1.09 (d, *J* 6.8, 3 H). ^{13}C NMR: δ 155.7, 147.8, 140.9, 124.9, 122.8, 61.9, 60.3, 55.0, 30.1, 29.0, 18.6, 15.3.

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