Pyrrolidinopyridines in Palladium-Catalyzed Allylic Substitutions − Conformation of the Ligand

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Dedicated to Professor Jean Normant on the occasion of his 65th birthday

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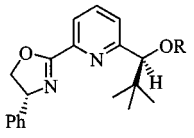
The (*R*,*R*)-2-[(2,5-dimethylpyrrolidin-1-yl)methyl]pyridines **4**, **5**, and **6** carrying a 2-hydroxyalkyl, 2-alkoxyalkyl or 2-siloxyalkyl substituent in the 6-position of the pyridine ring were prepared and assessed in palladium-catalyzed allylations of 1,3-diphenylpropenyl acetate with malonate. All ligands having 6-substituents with an *S* absolute configuration afforded the product with an *R* configuration in 80–84% *ee*, whereas those having substituents with an *R* absolute configuration gave the opposite product with a selectivity depending on the nature of the substituent (8–74% *ee*). It is believed that the enantioselectivity is dependent on the conformation of that substituent.

Introduction

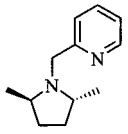
In the design of efficient chiral metal complexes for asymmetric catalysis, the electronic and steric properties of the ligand surrounding the metal have to be considered.[1] Rigid ligands with well-defined conformational spaces, commonly with the chirality residing in a chelate ring, are often employed in order to control the stereochemistry of the catalytically active metal complex.[2] Occasionally, in ligands containing freely rotating chiral substituents, favorable conformational preferences may also lead to high selectivity, at least when the ligand contains an additional stereocenter. In such cases, the different diastereomers may exhibit profoundly different properties in the catalytic process.[3]

Chiral 2-(1-hydroxyalkyl)- (**1**) and 2-(1-methoxyalkyl)-6-(4,5-dihydro-2-oxazolyl)pyridines (**2**) adopt different conformations in the palladium-catalyzed substitution of *rac*-1,3-diphenylpropenyl acetate with malonate.[4] Thus, the *R**,*R** isomer of the former and the *R**,*S** isomer of the latter were shown to result in high enantioselectivity (>99 and 98% *ee*, respectively), whereas the catalysts derived from the diastereomeric ligands exhibited lower selectivity and lower reactivity.[5] Furthermore, it was shown that the selective processes involved complexes with *pseudo*-C_2 symmetry and that complexes with the sterically bulky groups on the same side of the coordination plane were inferior.[4] Control of the stereochemistry could thus be achieved by selecting either the alcohol or the alkylated ligand.

In order to examine whether this control could be extended to other ligand systems, we have investigated the substitution of 1,3-diphenylpropenyl acetate with malonate employing 2-pyrrolidinopyridines carrying hydroxyalkyl, methoxyalkyl or siloxyalkyl substituents in the 6-position of the pyridine ring. The parent ligand **3** has previously been shown to give low enantioselectivity (18% *ee*) in the catalytic reaction.[6] With the new 2,6-disubstituted pyridine derivatives enantioselectivities up to 84% were observed. The results obtained indicate that the conformational preferences of the 6-substituents in the transition state of the process differ from those observed in the analogous pyridinooxazolines. The reasons for the different behavior of the two types of ligands are discussed below.



1: R = H
2: R = Me



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Results and Discussion

Preparation of the Ligands

As suitable derivatives of ligand **3**, we selected compounds **4**−**6**, containing a substituent with an alcohol, ether or siloxy substituent in the 6-position of the pyridine ring. In order to get insight into the preferred conformation of the ligands, each type of ligand was prepared in two diastereomeric forms. Two different routes were considered for the syntheses of the ligands.[7] The first involved the reaction of an electrophilic pyridine derivative with enantiopure *trans*-2,5-dimethylpyrrolidine,[8] the second treatment of a 1,4-dimesylate[9] or 1,4-diol cyclic sulfate[10] with a (2-aminomethyl)pyridine derivative. The latter methods often result in higher yields of *N*-substituted pyrrolidines and are therefore normally preferred. The former method was chosen for the preparation of the present ligands, however,

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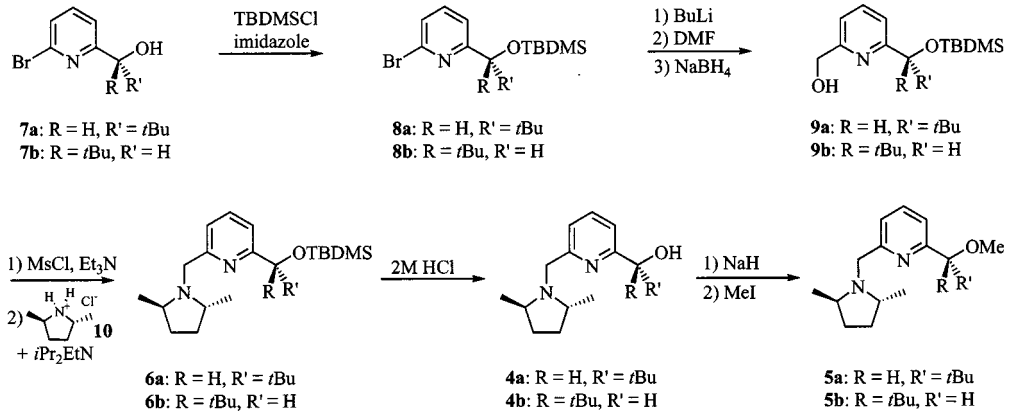


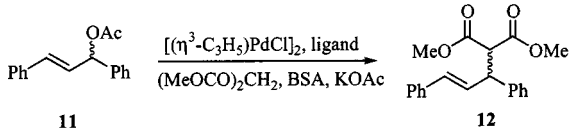
Scheme 1

as the pyridineamine was considered less readily accessible, particularly as an excess of the amine is commonly used. 6-Bromo-2-lithiopyridine was thus reacted with pivalonitrile and the ketone obtained reduced with (−)-*B*-bromodiisopinocampheylborane or (+)-*B*-chlorodiisopinocampheylborane to give **7a** and **7b**, respectively (Scheme 1). Protection of the alcohol group as a *tert*-butyldimethylsilyl ether (**8a** and **8b**), followed by lithiation and reaction with DMF and subsequent reduction[11] ($NaBH_4$) gave monoprotected dialcohols (**9a** and **9b**, respectively). The pyrrolidine required for the last step was obtained according to a published procedure by Baker's yeast reduction of 2,5-hexanedione,[12] reaction with benzylamine[9a] and cleavage of the benzylic amine using palladium on charcoal. Work up under acidic conditions prevented loss of the volatile chiral amine, and thus resulted in a high yield of the HCl salt of (*R*,*R*)-2,5-dimethylpyrrolidine (**10**), which was finally reacted with the mesylates of alcohols **9a** and **9b** to yield **6a** and **6b**, respectively. Alcohols **4a** and **4b** were obtained by treatment of **6a** and **6b** with HCl. Methylation of the alcohols with MeI in THF gave **5a** and **5b**.

The absolute configuration of the chiral alcohols obtained by asymmetric reduction was assigned according to the literature.[13] Alcohol **7a** was obtained in 99% *ee* after recrystallization according to GLC, whereas reduction with (+)-$(Ipc)_2BCl$ resulted in somewhat lower selectivity (91% as determined for **9b** by comparison of the optical rotation with that of **9a**, a value similar to that reported).[13] NMR spectroscopy of the final products as well as of the intermediates showed that all compounds were diastereomerically pure and thus that no epimerization at the benzylic position had occurred and that diastereomers originating from the minor isomer contaminating **7b** were removed.

Catalytic Reactions

Allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate (**11**) was performed in CH_2Cl_2 at room temperature in the presence of a (π-allyl)palladium-ligand complex generated in situ from 2 mol % of bis[(π-allyl)palladium chloride] and 6 mol % of the appropriate ligand. The nucleophile was generated from dimethyl malonate in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc (Scheme 2).[14] The reactions were run for four days to ensure complete conversion for the less reactive systems. The results are shown in Table 1.



Scheme 2

Table 1. Allylation of *rac*-**11** according to Scheme 2

Ligand[a]	Yield [%]	*ee* [%] (abs. conf.)
3		18 (*S*)
4a	13	27 (*S*)
4b	quant.	84 (*R*)
5a	quant.	74 (*S*)
5b	quant.	83 (*R*)
6a	4	8 (*S*)
6b	85	80 (*R*)

[a] 2 mol % of bis[(π-allyl)palladium chloride] and 6 mol % of the ligand were used.

The absolute configuration of the product turned out to depend on the absolute configuration at the benzylic center rather than on the configuration of the pyrrolidine ring, as ligands with *S* absolute configuration at that center resulted in *R*-**12** and vice versa. Of all the ligands **4**−**6**, those having *S* absolute configuration at the benzylic stereocenter proved to result in the highest enantioselectivity. The dichotomy previously observed with the analogous oxazoline ligands was thus absent.

Conformation of the Ligands

The enantioselectivity in asymmetric allylations is determined by the electronic and steric properties of the ligands.[15] In reactions proceeding via symmetrically substituted allyl systems, the enantioselectivity is determined by the regiochemistry of nucleophilic attack.[16] In metal complexes containing ligands with two different donor atoms,

nucleophilic attack usually takes place *trans* to the better π-acceptor. In ligands with donor atoms having similar properties, steric congestion directs attack of the nucleophile. Depending on whether the catalytic process has an early[17] or late transition state,[18] the outcome of the reaction is mainly determined by steric interactions distorting the allylic unit in the starting Pd^{II} complex or by the stability of the product olefin Pd^0 complex.[19] Any of these assumptions leads to the same conclusion.

Pyridine and oxazoline units exert similar *trans* influence and steric interactions are therefore expected to dominate in reactions with pyridinooxazoline ligands. Pyridine and pyrrolidine are also expected to differ little in *trans* influence,[20] although they have a difference in p*K*a value of about 5 units. As the present ligands lack rotational symmetry, two allyl palladium complexes may form. The site of nucleophilic attack is therefore determined by the steric properties of the more reactive π-allyl complex.

In the pyridinooxazoline series of ligands, the two types of ligands **1** and **2** have similar conformations, with an N−C−C−O dihedral angle of about 180°, in their π-allyl palladium complexes. During the catalytic reaction the alcohol ligands undergo a conformational change leading to a product olefin complex with a N−C−C−O dihedral angle of about 57°[4] and with a Pd−H distance of merely 2.41 Å. An alcohol ligand having sterically demanding groups on different sides of the coordination plane changes its conformation to have these groups on the same side of that plane, leading to decreased stereoselectivity and decreased reactivity. The reason for the conformational change is still unclear, but seems to originate from an interaction of Pd^0 with the hydrogen of the hydroxy group.[4]

Several features of the oxazoline and the pyrrolidine ligands differ. Within the present series of ligands, high stereoselectivity was observed with all ligands having *S* absolute configuration at the benzylic center, i e **4b**, **5b**, and **6b**. The absolute configuration of the product was shown to depend on the absolute configuration of that center and not on the configuration of the pyrrolidine unit. These ligands are assumed to adopt a conformation where the sterically demanding groups occupy the same side of the coordination plane. The differences in selectivity between the alcohol and ether ligands observed in the oxazoline series were thus absent. It is still unclear whether this is due to an earlier transition state, in which the type of conformational change that takes place in **1** and **2** has not yet occurred, or to the absence of Pd^0−H interactions. The mode of nucleophilic attack on the two π-allyl palladium complexes, in their assumed conformations, leading to the observed product is shown in Figure 1, A.

Conversely, profound differences were observed between the ligands **4a**, **5a**, and **6a**. Ligand **5a** exhibited only slightly lower enantioselectivity than the diastereomeric ligand **5b**, although affording a product with opposite absolute configuration. This ligand is expected to adopt a "*pseudo*-C_2" conformation with Pr chirality and is thus expected to yield the product with *S* absolute configuration,[21] in accordance with present observations (B, Figure 1). In order to ascertain whether the lower enantioselectivity of **4a** and **6a** is due to differences in conformation between the different types of ligands, in analogy to what was observed for **1** and **2**, further studies of the preferred conformations of the ligands in their metal complexes are required.

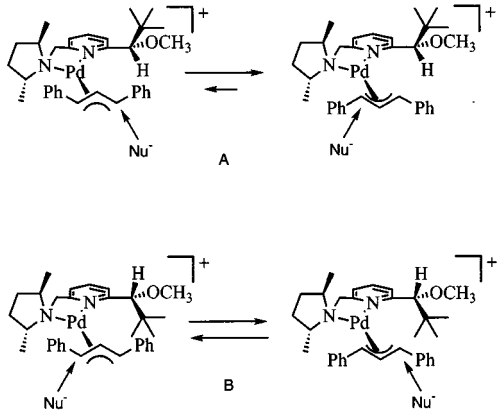


Figure 1. Assumed conformations of π-allyl palladium complexes with ligands **4b**, **5b**, and **6b** (A) and with ligand **5a** (B)

Conclusion

In the palladium-catalyzed substitution of 1,3-diphenylpropenyl acetate with malonate employing (*R*,*R*)-2-[(2,5-dimethylpyrrolidin-1-yl)methyl]pyridines with 2-alkoxyalkyl or 2-hydroxyalkyl substituents in the 6-position of the pyridine ring as ligands, those diastereomers of the ligand assumed to have the bulky groups on the same side of the coordination plane in the intermediate π-allyl palladium complex result in high enantioselectivity (80−84% *ee*), whereas for those assumed to adopt *pseudo*-C_2 conformation, the enantioselectivity is dependent on the nature of the substituent. The differences in selectivity between ligands containing methoxy and hydroxy substituents resemble those previously observed using analogously substituted pyridinooxazoline ligands, where a conformational change of the hydroxy ligand during the catalytic reaction was demonstrated.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker DMX 500 instrument. Chemical shifts are reported relative to $CHCl_3$. All reactions were performed under argon atmosphere. − Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Hexanes, dimethylformamide and methanol were dried over molecular sieves. − Flash chromatography was carried out using Merck silica gel 60H or SDS silica gel 60 A. − Optical rotations were measured on a Perkin−Elmer 343 Polarimeter. Melting points are uncorrected. − Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany.

(*R*)-1-(6-Bromopyridin-2-yl)-2,2-dimethylpropanol (7a) and (*S*)-1-(6-Bromopyridin-2-yl)-2,2-dimethylpropanol (7b): Compound **7b** was

prepared using the procedure of Bolm et al.[13] Compound **7a** was prepared analogously, using (−)-$(Ipc)_2BBr$ instead of (+)-$(Ipc)_2BCl$. Recrystallization from hexanes gave **7a** with 99% *ee* according to GLC (CP-Cyclodex B 236 M).

(2*R*,5*R*)-2,5-Dimethylpyrrolidine Hydrochloride (10): Compound **10** was prepared according to the procedure of Masamune at al.[9a] Instead of distilling the combined ether phases containing the pyrrolidine, they were extracted with small portions of conc. HCl. The pyrrolidine hydrochloride was isolated in 87% yield by removal of the water by Dean−Stark distillation using benzene. The material obtained was used directly for further transformations. A pure sample was obtained by recrystallization from MeOH and diethyl ether. Spectroscopic data were in agreement with those previously reported.[9a]

(1′*R*)-6-Bromo-2-[1′-(*tert*-butyldimethylsiloxy)-2′,2′-dimethylpropyl]pyridine (8a): Imidazole (1.16 g, 17.0 mmol) was added to a solution of **7a** (0.80 g, 3.28 mmol) and *tert*-butyldimethylsilyl chloride (1.19 g, 7.86 mmol) in DMF (4 mL). The solution was stirred at room temperature for 3 days. Saturated aqueous NH_4Cl (30 mL) was added and the stirring was continued for 1 h. The solution was extracted with diethyl ether (3 × 40 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (hexane/diethyl ether, 3:1) to give 950 mg of **8a** as a colorless solid (2.65 mmol, 81%). − M.p. 68−73 °C. − $[\alpha]_D^{20}$ = + 33.7 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = − 0.31 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 4.44 (s, 1 H), 7.33 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 1 H),. − ^{13}C NMR ($CDCl_3$): δ = −5.3, −4.6, 18.1, 25.86, 25.95, 36.4, 82.6, 121.2, 126.1, 137.8, 139.7, 164.9.

(1′*S*)-6-Bromo-2-[1′-(*tert*-butyldimethylsiloxy)-2′,2′-dimethylpropyl]pyridine (8b): Compound **8b** was prepared in the same way as **8a**. It was contaminated with (1′*S*)-6-chloro-2-[2′,2′-dimethyl-1′-(dimethyl-*tert*-butylsiloxy)propyl]pyridine, but could be used without further purification.

(1′*R*)-2-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′-dimethylpropyl]-6-hydroxymethylpyridine (9a): Butyllithium (0.7 mL, 1.75 mmol, 2.5 M) was added dropwise over a period of 20 min at −78 °C to a degassed solution of **8a** (500 mg, 1.40 mmol) in hexane, THF and diethyl ether (3.8 mL, 1:1:2). The solution was then stirred for 30 min. DMF (0.3 mL, 3.8 mmol) was added dropwise over a period of 3 min. After 50 min of stirring, methanol (1.60 mL) and $NaBH_4$ (60 mg, 1.59 mmol) were added at −78 °C. The reaction mixture was allowed to slowly reach room temperature and stirring was continued for 18 h. Saturated aqueous NH_4Cl (1 mL) was added and stirring was continued for another 1 h. The solvent was carefully evaporated. The residue was diluted with water (3 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/diethyl ether, 1:1) to give 360 mg of **9a** as a colorless solid (1.16 mmol, 84%). − M.p. 69−72 °C. − $[\alpha]_D^{20}$ = +59.9 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = −0.34 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 4.09 (t, *J* = 4.7 Hz, 1 H), 4.41 (s, 1 H), 4.71 (m, 2 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.63 (t, *J* = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −5.4, −4.8, 18.0, 25.75, 25.83, 36.2, 46.9, 82.8, 120.9, 121.8, 136.4, 153.9, 163.0.

(1′*S*)-2-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′-dimethylpropyl]-6-hydroxymethylpyridine (9b): Compound **9b** was prepared in the same way as **9a**. − M.p. 68−71 °C. − $[\alpha]_D^{20}$ = −54.8 (*c* = 1.0, $CHCl_3$). − $C_{17}H_{31}NO_2Si$: calcd. C 65.97, H 10.09, N 4.53; found C 66.09, H 10.15, N 4.49. Assuming an *ee* of 100% from **9a**, this corresponds to 91% *ee*. The NMR spectra were identical to those of **9a**.

(2′*R*,5′*R*,1′′*R*)-2-[1′′-(*tert*-Butyldimethylsiloxy)-2′′,2′′-dimethylpropyl]-6-[(2′,5′-dimethylpyrrolidin-1-yl)methyl]pyridine (6a): Methanesulfonyl chloride (0.138 mL, 1.78 mmol) was added dropwise over a period of 2 min at −23 °C to a solution of **9a** (500 mg, 1.62 mmol) and triethylamine (0.270 mL, 1.94 mmol) in dichloromethane (7.75 mL). The mixture was stirred for 1.5 h while the temperature was slowly increased to −15 °C and then at room temperature for 0.5 h. The reaction mixture was cooled to 0 °C and diluted with cold dichloromethane (10 mL) before it was washed with cold HCl (1 × 2 mL, 0.1 M) and cold saturated aqueous $NaHCO_3$ (1 × 2 mL). The organic phase was dried (Na_2SO_4) and carefully concentrated to a tan oil which was used directly without further purification. (2*R*,5*R*)-2,5-Dimethylpyrrolidine hydrochloride (438 mg, 3.23 mmol) and diisopropylethylamine (0.850 mL, 4.88 mmol) were added to a solution of the mesylate in acetonitrile (6 mL) at −78 °C. The mixture was degassed and the flask sealed before it was heated to 50 °C for 2 days. The solvent was removed in vacuo. The residue was treated with NaOH (5 mL, 2 M) and extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give a red brownish oil. The product was purified by flash chromatography (hexane/ethyl acetate, 4:1, triethylamine 1%) to give 481 mg of **6a** (1.23 mmol, 76%) as a yellow oil, purity 95% by NMR. This material could be further purified by additional flash chromatography (hexane/diethyl ether, 3:1, triethylamine 0.25%). − $[\alpha]_D^{20}$ = +2.7 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = −0.35 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 18 H), 0.94 (d, *J* = 6.3 Hz, 6 H), 1.35−1.40 (m, 2 H), 1.98−2.06 (m, 2 H), 3.07−3.11 (m, 2 H), 3.80 and 3.86 (AB, *J* = 14.8 Hz, 2 H), 4.45 (s, 1 H), 7.24 (d, *J* = 7.7 Hz, 1 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 7.57 (t, *J* = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −5.2, −4.8, 17.5, 18.1, 25.9, 26.0, 31.2, 36.2, 54.4, 55.8, 83.6, 120.2, 121.0, 135.4, 158.9, 161.7.

(2′*R*,5′*R*,1′′*S*)-2-[1′′-(*tert*-Butyldimethylsiloxy)-2′′,2′′-dimethylpropyl]-6-[(2′,5′-dimethylpyrrolidin-1-yl)methyl]pyridine (6b): Compound **6b** was prepared in the same way as **6a**, but purified by flash chromatography (hexane/ethyl acetate, 9:1, triethylamine 1%) to give 457 mg (1.17 mmol, 72%) of **6b** as a yellow oil, purity 95% by NMR. This material could be further purified by additional flash chromatography (hexane/ethyl acetate, 19:1, triethylamine 1%). − $[\alpha]_D^{20}$ = −86.0 (*c* = 0.70, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = −0.34 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 0.96 (d, *J* = 6.3 Hz, 6 H), 1.33−1.39 (m, 2 H), 1.97−2.02 (m. 2 H), 3.03−3.05 (m. 2 H), 3.71 and 3.91 (AB, *J* = 14.4 Hz, 2 H), 4.44 (s, 1 H), 7.26 (d, *J* = 7.6, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −5.2, −4.7, 17.3, 18.1, 25.9, 26.1, 31.1, 36.4, 54.0, 55.4, 83.4, 120.2, 121.2, 135.5, 158.8, 161.7. − $C_{23}H_{42}N_2OSi$: calcd. C 70.71, H 10.84, N 7.17; found C 70.63, H 10.76, N 7.03.

(2′*R*,5′*R*,1′′*R*)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)methyl]-6-(1′′-hydroxy-2′′,2′′-dimethylpropyl)pyridine (4a): **6a** (329 mg, 0.84 mmol) was dissolved in aqueous HCl (10 mL, 2 M) at 0 °C. The solution was stirred at room temperature for 30 h, then cooled to 0 °C and made alkaline by the addition of solid NaOH. The mixture was extracted with diethyl ether (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (hexane/ethyl acetate, 17:5, triethylamine 1%) to give 166 mg of **4a** (0.60 mmol, 71%) as a colorless solid. − M.p. 79.5−82 °C. − $[\alpha]_D^{20}$ = −62.9 (*c* = 0.54, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.90

(s, 9 H), 1.00 (d, J = 6.3 Hz, 6 H), 1.34−1.43 (m, 2 H), 1.97−2.05 (m, 2 H), 3.03−3.06 (m, 2 H), 3.75 and 3.90 (AB, J = 14.2 Hz, 2 H), 4.31 (d, J = 7.4 Hz, 1 H), 4.69 (d, J = 7.4 Hz, 1 H), 7.01 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.2, 25.9, 31.0, 36.4, 53.5, 55.3, 79.8, 120.7, 121.9, 135.8, 158.1, 159.3.

(2′*R*,5′*R*,1′′*S*)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)methyl]-6-(1′′-hydroxy-2′′,2′′-dimethylpropyl)pyridine (4b): Compound **4b** was prepared analogously to **4a**, but purified by flash chromatography (hexane/diethyl ether, 2:1, triethylamine 1%) to give **4b** as a colorless oil (70%). − $[\alpha]_D^{20}$ = −42.3 (c = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.97 (d, J = 6.2 Hz, 6 H), 1.36−1.43 (m, 2 H), 1.99−2.04 (m, 2 H), 3.08−3.09 (m, 2 H), 3.81 and 3.87 (AB, J = 14.8 Hz, 2 H), 4.32 (d, J = 7.2 Hz, 1 H), 4.59 (d, J = 7.2 Hz, 1 H), 7.01 (d, J = 7.6, 1 H), 7.40 (d, J = 7.6 Hz, 1 H), 7.57 (t, J = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.4, 25.9, 31.1, 36.3, 53.7, 55.6, 79.9, 120.6, 121.6, 135.8, 158.3, 159.6. − $C_{17}H_{28}N_2O$: calcd. C 73.87, H 10.21, N 10.13; found C 73.64, H 10.36, N 10.05.

(2′*R*,5′*R*,1′′*R*)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)methyl]-6-(1′′-methoxy-2′′,2′′-dimethylpropyl)pyridine (5a): Compound **5a** was prepared analogously to **5b**, but the reaction temperature was kept at 3 °C for 20 h and the product was purified by flash chromatography (hexane/ethyl acetate, 7:3, triethylamine 1%) to give **5a** as a colorless oil (40%). − $[\alpha]_D^{20}$ = −26.3 (c = 0.5, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 9 H), 0.94 (d, J = 6.3 Hz, 6 H), 1.34−1.44 (m, 2 H), 1.99−2.05 (m, 2 H), 3.12−3.16 (m, 2 H), 3.23 (s, 3 H), 3.86 (s, 2 H), 3.96 (s, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.63 (t, J = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.6, 26.2, 31.2, 35.5, 54.3, 55.9, 57.7, 92.7, 119.7, 121.1, 135.7, 159.1, 160.1,. − $C_{18}H_{30}N_2O$: calcd. C 74.44, H 10.41, N 9.64; found C 74.55, H 10.28, N 9.71.

(2′*R*,5′*R*,1′′*S*)-2-[(2′,5′-Dimethylpyrrolidin-1-yl)methyl]-6-(1′′-methoxy-2′′,2′′-dimethylpropyl)pyridine (5b): NaH (12 mg, 60%, 0.3 mmol) was added to a solution of **4b** (72 mg, 0.26 mmol) in THF (1.8 mL) at 0 °C. After stirring for 1 h, MeI (17 μL, 0.27 mmol) was added dropwise. The stirring was continued for 6 h at 0 °C. The reaction mixture was then allowed to slowly reach room temperature (5 h). Saturated aqueous NH_4Cl (0.6 mL) and water (5 mL) were added and the solution was extracted with diethyl ether (5 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (hexane/diethyl ether, 2:1, triethylamine 1%) to give 46 mg of **4b** (0.16 mmol, 61%) as a yellow oil. − $[\alpha]_D^{20}$ = −124.0 (c = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (s, 9 H), 0.98 (d, J = 6.3 Hz, 6 H), 1.35−1.43 (m, 2 H), 1.97−2.05 (m, 2 H), 3.03−3.06 (m, 2 H), 3.23 (s, 3 H), 3.74 and 3.93 (AB, J = 14.4 Hz, 2 H), 3.97 (s, 1 H), 7.20 (d, J = 7.7 Hz, 1 H), 7.41 (d, J = 7.7 Hz, 1 H), 7.62 (t, J = 7.7 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.2, 26.2, 31.1, 35.6, 53.9, 55.3, 57.7, 92.8, 119.6, 121.6, 135.9, 159.1, 159.6.

Catalytic Reaction: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.20 mg, 0.00603 mmol, 2 mol %) was added to the ligand (0.0181 mmol, 6 mol %) in degassed CH_2Cl_2 (0.66 mL) at −78 °C. The solution was degassed and sealed before it was heated to 50 °C while stirring for 2 h. Dimethyl malonate (89.62 mg, 0.678 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (184 mg, 0.904 mmol), *rac*-1,3-diphenyl-2-propenyl acetate (76.06 mg, 0.301 mmol) in CH_2Cl_2 (0.66 mL) and a few crystals of KOAc were added at −78 °C. The mixture was degassed at −78 °C, stirred at room temperature for 4 days and then filtered through a short pad of silica gel, using CH_2Cl_2 as eluent. The filtrate was concentrated in vacuo to give the product **10**. The enantiomeric excess for the product in the catalytic reaction was determined by HPLC using a chiral column (Chiralcel-OD).

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