Enantioselective Allylic Substitutions Catalyzed by [(Hydroxyalkyl)pyridinooxazoline]- and [(Alkoxyalkyl)pyridinooxazoline]palladium Complexes

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Highly enantioselective (up to >99% ee) palladium-catalyzed substitution of *rac*-3-diphenyl-2-propenyl acetate with dimethyl malonate as nucleophile was achieved using 2-(1-hydroxyalkyl)-6-(4,5-dihydro-2-oxazolyl)pyridines and 2-(1-alkoxyalkyl)-6-(4,5-dihydro-2-oxazolyl)pyridines as ligands for palladium. The selectivity was found to be highly dependent on the nature of the substituents on the ligand and on the relative configuration of the two stereogenic centers present in the ligand. The results are discussed in terms of the conformation of the ligands in the intermediate π-allylpalladium complexes.

Introduction

Methods for carbon−carbon bond formation are one of the key issues in organic synthesis. One versatile method to achieve this is the palladium-catalyzed allylation of carbon nucleophiles,[1] and this reaction has therefore been extensively studies over the last years.[2] A variety of chiral ligands have been presented that efficiently induce asymmetry in the product. Traditionally, ligands with phosphorus as donor atoms have been employed, but in recent years, a variety of nitrogen ligands have proven to be highly useful as well.[2f]

Among the successful nitrogen-containing ligands that have been employed for the substitution of *rac*-1,3-diphenyl-2-propenyl acetate, which serves as a model substrate to compare the outcome of different ligands, are those having C_2 symmetry[3] as well as C_1 symmetry.[4] The origin of selectivity, however, may be different with the two types of ligands. With a C_2-symmetric ligand, the enantioselectivity is determined solely by the regioselectivity of attack on the π-allyl group. In the presence of a C_1-symmetric ligand, two different π-allylpalladium complexes may be obtained, each one having the possibility to be attacked by the nucleophile at two different sites, leading to a larger number of possible transition states in this case. The approach of the nucleophile occurs far from the stereogenic center in the ligand, and therefore, preference for attack probably originates principally in the difference in bonding to palladium. This is in turn affected by the steric influence excerted by the ligand, which commonly results in different carbon−palladium distances, and, in particular, by the different *trans* influence of the ligand donor atoms.[5] This latter factor is more easily controlled when truly asymmetric ligands are employed, in which donor atoms with different properties may be chosen. Provided the two complexes obtained using C_1-symmetric ligands differ in stability/reactivity, high enantiocontrol may therefore be expected also with this type of ligand. That this really is the case has recently been demonstrated using phosphinooxazolines,[4b−d] thiophenooxazolines,[4f] and phosphinoamines[6] as ligands for palladium.

Inspired by this analysis and by the recent reports of successful results obtained from the use of ligands lacking twofold rotational axes,[4] we decided to investigate the usefulness of our previously prepared 2-(1-hydroxyalkyl)-6-(4,5-dihydro-2-oxazolyl)pyridines[7] in the palladium-catalyzed allylation of *rac*-1,3-diphenyl-2-propenyl acetate. This type of ligand has the advantage that large structural variations are possible in that the substituents in the oxazoline ring and in the alcohol part of the molecule as well as the relative configuration of the two stereogenic centers can be varied; in addition, the alcohol group can be alkylated using different electrophiles. This allows optimization of reaction conditions and also provides some information about the stereochemistry of the reaction.

Results and Discussion

Ligand Preparation. Oxazolinylpyridines containing a secondary (**1**−**4**) or a tertiary (**5**) alcohol function as well as methyl ether derivatives (**1c,d**, **3c**,[7] and **3d**[7]) of some of the alcohols were prepared for use in the catalytic reaction under study. Oxazolinylpyridine **6**[8] was prepared in order to serve as a reference ligand.

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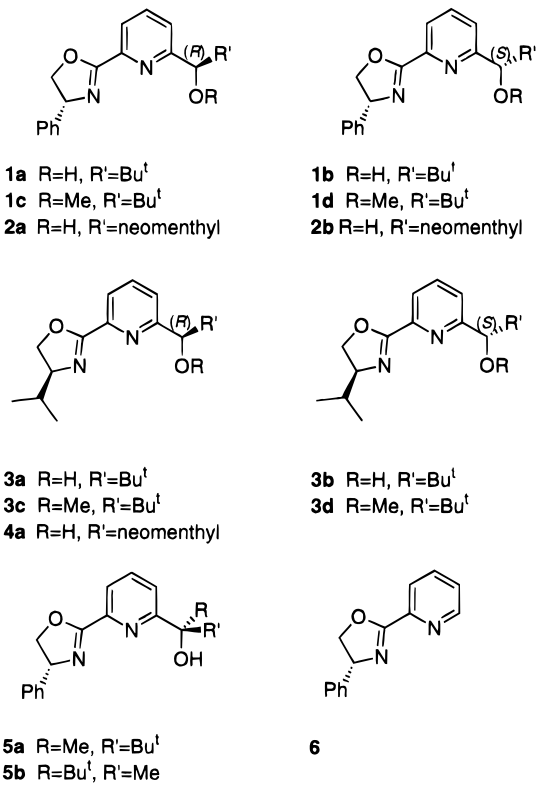


Ligands **1**, **3**, and **5** were obtained from racemic 2-(1-hydroxyalkyl)pyridines according to a previously described procedure affording the stereochemically pure products via final chromatographic separation of diastereoisomers.[7] Ligands **2a** and **4a**, on the other hand, were prepared from enantiomerically pure (*R*)-[(1*S*,2*S*,5*R*)-1-(2-isopropyl-5-methyl)cyclohexyl](2-pyridyl)methanol (**7**, which in turn is readily obtained starting from (−)-menthol[9]) using the same procedure, as described in Scheme 1 for **2a**. In this procedure, **7** was transformed in two steps via *N*-oxide **8** to a mixture of nitriles **9a** and **9b**.[10] Reaction of this mixture with sodium methoxide followed by the appropriate amino alcohol yielded the desired ligand. Upon prolonged reaction time in the last step of the reaction sequence, epimerization at the benzylic position occurred, thus giving access also to **2b**.

Ligands **5a** and **5b** were prepared by an analogous procedure starting from ketone **10**, obtained by reaction of 2-lithiopyridine with pivalonitrile; the required tertiary pyridyl alcohol **11** was prepared by reaction of **10** with methylmagnesium iodide (Scheme 2). Final chromatographic separation yielded pure **5a** and **5b**. Since the ligands proved not to be useful in the catalytic allylation reaction (see below), their absolute configuration was not assigned.

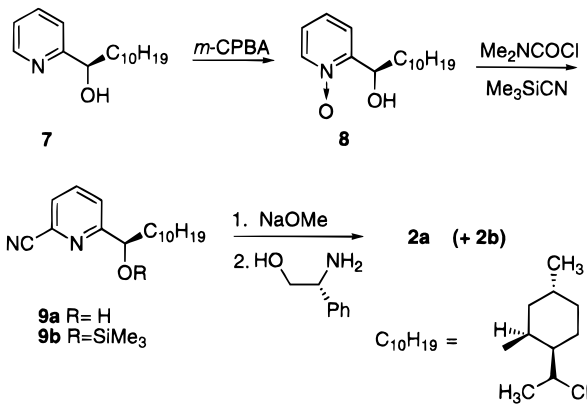
Allylic Alkylations. Allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate (**12**) was performed in CH_2Cl_2 at room temperature in the presence of a (π-allyl)palladium−ligand complex generated *in situ* from 2.5 mol % of bis[(π-allyl)palladium chloride] and 5 mol % of the appropriate ligand. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc (Scheme 3).[3b,11] The results of the catalytic reaction are summarized in Table 1.

Table 1. Enantioselective Allylation of 12 with Dimethyl Malonate According to Scheme 3

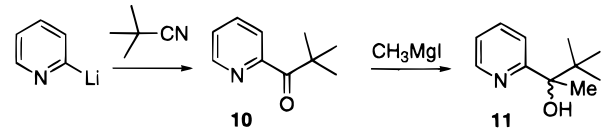
entry	ligand	yield[a] (%)	ee[b] (%)
1	**1a**	81	95 (*R*)
2	**1b**	96	90 (*R*)
3	**1c**	67	15 (*R*)
4	**1d**	97	>99 (*R*)
5	**2a**	83	>99 (*R*)
6	**2b**	*c*	39 (*R*)
7	**3a**	79	78 (*S*)
8	**3b**	96	91 (*S*)
9	**3c**	91	99 (*S*)
10	**3d**	85	33 (*S*)
11	**4a**	91	45 (*S*)
12	**5a**	0	
13	**5b**	0	
14	**6**	97	50 (*R*)

[a] Isolated yield after chromatography. [b] Determined by HPLC analysis of **13** using a chiral column (Chiralcel-OD). Results determined from duplicate experiments. [c] Not determined.

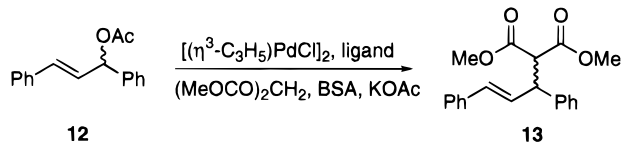
Scheme 1



Scheme 2



Scheme 3



The reactions proceeded smoothly with most of the ligands to give high yields (67−97%) of products **13**, although a reaction time of 4 days was needed. The absolute configuration of the product (assigned from optical rotation measurements and comparison with literature data[12]) was controlled by the absolute configuration at the stereogenic center in the oxazoline ring, such that ligands with (*S*) configuration at that center resulted in preferred formation of (*S*)-**13** while those with (*R*) configuration resulted in (*R*)-**13**. The effect of the hydroxyalkyl or alkoxyalkyl substituent was, depending on the configuration at the center, to enhance or reduce the stereoselectivity, the amount of this effect being dependent on the nature of the substituent. For alcohols carrying a *tert*-butyl group, only a moderate difference

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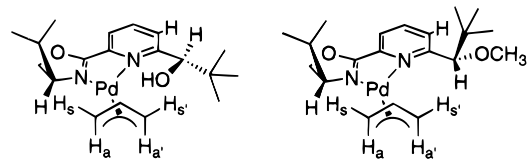
between the diastereomers was observed. Thus, **1a** and **1b** gave (*R*)-**13** with 95 and 90% ee, respectively (Table 1, entries 1 and 2) and **3a** and **3b** gave (*S*)-**13** with 78 and 91% ee, respectively (Table 1, entries 7 and 8). Exchanging the *tert*-butyl substituent for the more sterically demanding neomenthyl group resulted in considerably larger differences in the stereocontrolling efficiency between the diastereomeric ligands. Ligand **2a** gave (*R*)-**13** with an ee of over 99%, while **2b** gave the same compound with only 39% ee (Table 1, entries 5 and 6, respectively). These results show that ligands with the same absolute configuration at the two stereogenic centers become even more efficient when changing the *tert*-butyl group to a neomenthyl group, while those with the opposite configuration at the two centers become less efficient. This trend was confirmed by a comparison between **3a** and **4a** (Table 1, entries 7 and 11).

With the *O*-methylated ligands, an even more dramatic difference in the stereochemical outcome of the reactions was observed when diastereomeric ligands were employed (Table 1, entries 3 and 4, 9 and 10). Reaction using ligand **1d** resulted in (*R*)-**13** of >99% ee while **1c** gave only 15% ee. What is worth noting here is that with the ligands containing an ether function, the highest induction was observed for those having opposite absolute configuration at the two stereogenic centers, in contrast to what was observed with the alcohols (compare entries 1 and 3 and entries 2 and 4).

The two diastereomeric tertiary alcohols **5a** and **5b** were also utilized as ligands in the allylic substitution reaction. This did not result in any product under the conditions employed for **1**−**4** (the starting material was recovered quantitatively), possibly due to the fact that these ligands are too sterically crowded to enable coordination to palladium.

Reaction employing oxazolinylpyridine **6** proceeded faster than those with the other ligands and was complete in less than 24 h (compared to 4 days for ligands **1**−**4**). However, an ee of merely 50% was observed (Table 1, entry 14).

Conformation of the Ligands. The explanation for the contrasting behavior of the alcohol derivatives and the corresponding methyl ethers is likely to be found in the conformation of the catalytically active metal complexes. We have recently demonstrated, both theoretically and experimentally, that in their most stable conformation the carbon−oxygen bond in 2-(1-alkoxyalkyl)pyridines is parallel to the pyridine ring with the heteroatoms *anti* to each other.[13] 2-(1-Hydroxyalkyl)pyridines adopt a planar *syn* or *anti* conformation depending on whether the alcoholic proton is hydrogen bonded to the pyridine nitrogen or not. Upon coordination to palladium, the hydroxy group no longer can take part in hydrogen bonding to the nitrogen atom, but it may well interact with the metal ion. Since the isomers with (*R*,*R*)* configuration afforded the highest stereoselectivities for ligands containing an alcohol group, whereas the (*R*,*S*)* diastereomers yielded better results when the *O*-methylated ligands were employed, it seems likely that the ligands also adopt different conformation after coordination to palladium.



14 **15**

Figure 1. Conformation of complexes **14** and **15**, as deduced from NOE experiments.

In order to obtain some information about the conformation of the ligands in complexes of the type believed to be intermediates in the catalytic reaction, (η^3-allyl)-[(4′*S*,1″*S*)-2-(3′,4′-dihydro-4′-isopropyl-2′-oxazolyl)-6-(1″-hydroxy-2″,2″-dimethylpropyl)pyridine-*N*,*N*]palladium(II) hexafluorophosphate (**14**) and (η^3-allyl)[(4′*S*,1″*S*)-2-(3′,4′-dihydro-4′-isopropyl-2′-oxazolyl)-6-(1″-methoxy-2″,2″-dimethylpropyl)pyridine-*N*,*N*]palladium(II) hexafluorophosphate (**15**) were prepared from **3b** and **3d**, respectively, and their NMR spectra studied. Assignments were made using two-dimensional ^{13}C,^{3}H heteronuclear correlation and ^{1}H-NOESY experiments. The spectra of **15** showed signals indicating the presence of two complexes, believed to be isomers. What was interesting to note was that the alcohol was not deprotonated, the hydroxy proton appearing as a doublet at δ 3.59.

In addition to the expected NOE's between protons in the ligand and between protons in the allyl group, some interesting effects were noted. In both complexes, NOE's were observed from the *tert*-butyl group to $H_{a'}$, $H_{s'}$, and the proton in the 3-position in the pyridine ring (H_3, Figure 1). The hydroxy proton in **14** showed an interaction with $H_{s'}$, while no interaction was observed between the methoxy protons and $H_{s'}$ or $H_{a'}$ in **15**. Instead, a NOE between the methoxy proton and H_3 was observed. On the other hand, there was no contact between the hydroxy proton in **14** and H_3. Finally, a NOE between the benzylic proton and a proton in the allyl group ($H_{a'}$) was observed only in **15**. These observations are consistent with conformations at least close to those shown in Figure 1.

Stereochemistry of the Catalytic Reaction. What is probably important for the stereoselectivity of the present reaction is that the pyridylcarbinol part of the ligand is planar, leading to a rigid arrangement with the sterically demanding substituent residing on one side of the complex. Accepting the model derived from the NMR spectroscopic investigation, one can conclude that for the most efficient ligands, the two bulky groups—one on the oxazoline ring and the other on the pyridyl alcohol part of the molecule—are situated at the opposite sides of the plane defined by the heterocyclic rings in complexes derived from ligands containing alcohol as well as ether functions.

This assumption implies that π-allylpalladium complexes A and B (Figure 2) are those expected from alcohol **1a** (with *R*,*R* configuration), whereas C and D are those expected from ether ligand **1d** (with *R*,*S* configuration), each of them affording higher stereoselectivity than the diastereomers **1b** (alcohol with *R*,*S* configuration) and **1c** (ether with *R*,*R* configuration), respectively. This model also explains the larger difference in enantioselection exerted by the diastereomeric ethers than by the isomer alcohols, since in the assume conformations, the sterically demanding group is in closer proximity to the allyl group in the *O*-alkylated ligands. Since the absolute

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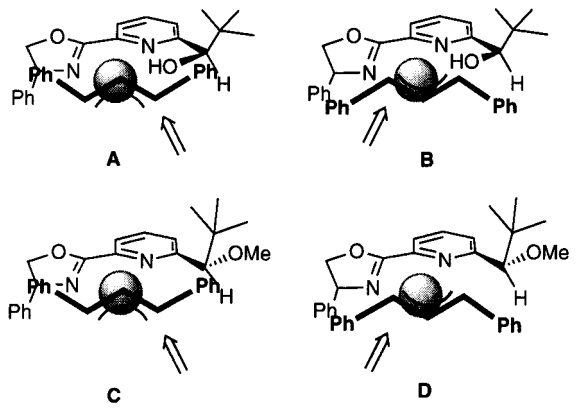

Figure 2. Regiochemistry of nucleophilic attach on π-allylpalladium complexes derived from **1a** (A or B) and **1d** (C or D).

configuration of the products formed in the catalytic reaction has been determined, once the structure of the reacting complex is known, the site of preferred nucleophilic attack can be elucidated (the arrows shown in Figure 2). A comparison with complexes derived from phosphinooxazolines[14] would favor the assumption that B and D are the preferred complexes. However, preliminary NOE experiments indicate that instead A and C are the preferred complexes, suggesting that nucleophilic attack occurs trans to the oxazoline ring.[15]

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, in $CDCl_3$, unless otherwise stated. Enantiomeric excesses were determined using a chiral HPLC-column (Chiralcel-OD). The assignment of the absolute configuration of compound **13** was done by optical rotation measurements and comparison with literature data. THF and diethyl ether were distilled from benzophenone ketyl. For column chromatography, Merck Kieselgel 60H was used. Ligands **1a,b**, **3a**−**d**,[7] and **6**[8] were prepared according literature procedures. Elemental analyses were performed by Analytische Laboratorien, Lindlar.

(4′*R*,1″*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(1″-methoxy-2″,2″-dimethylpropyl)pyridine (1c). Compound **1a**[7] (100 mg, 0.32 mmol) was dissolved in dry THF (5 mL). NaH (18 mg 60%, 0.45 mmol) was added, and the reaction mixture was stirred for 1 h, whereafter MeI (50 mg, 0.35 mmol) was added dropwise. The mixture was stirred for an additional 4 h, and the solvent was evaporated. The crude product was purified by MPLC on silica gel (hexane to EtOAc, continuous gradient) to give 61 mg (59%) of **1c** as a white solid: $[\alpha]_D^{20}$ +119° (*c* 0.43, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 8.12 (1H, dd, J = 8, 1 Hz), 7.81 (1H, t, J = 8 Hz), 7.56 (1H, dd, J = 8, 1 Hz), 7.25−7.41 (5H, m), 5.46 (1H, dd, J = 10, 9 Hz), 4.92 (1H, dd, J = 9, 10 Hz), 4.01 (1H, t, J = 9 Hz), 4.21 (1H, s), 3.28 (3H, s), 0.95 (9H, s); ^{13}C NMR (125.8 MHz) δ 164.62, 161.51, 145.81, 142.45, 136.70, 129.19, 128.11, 127.23, 124.28, 123.47, 92.69, 75.94, 70.60, 58.26, 36.01, 26.50. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; O, 9.86. Found: C, 73.82, H, 7.37; O, 10.04.

(4′*R*,1″*S*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(1″-methoxy-2″,2″-dimethylpropyl)pyridine (1d). The ligand **1d** was prepared starting from **1b**[7] (170 mg, 0.55 mmol) according to the method used for **1c**, resulting in 52 mg (29%) of **1d** and, due to epimerization, 63 mg (35%) of **1c**. **1d**: $[\alpha]_D^{20}$ −5.4° (*c* 2.1, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 8.09 (1H, dd, J = 8, 1 Hz), 7.78 (1H, t, J = 8 Hz), 7.54 (1H, dd, J = 8, 1 Hz), 7.25−7.41 (5H, m), 5.44 (1H, dd, J = 10, 9 Hz), 4.90 (1H, dd, J = 9, 10 Hz), 4.38 (1H, t, J = 9 Hz), 4.18 (1H, s), 3.25 (3H, s), 0.93 (9H, s).

(*R*)-[(1*S*,2*S*,5*R*)-1-(2-Isopropyl-5-methyl)cyclohexyl](2′-pyridyl)methanol *N*-Oxide (8). To a solution of **7**[9] (0.9 g, 3.63 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C was added *m*-CPBA (1.02 g, 80%, 4.73 mmol) in portions. After the reaction mixture was stirred for 3 days at room temperature, an additional amount of CH_2Cl_2 (35 mL) was added, and the reaction was terminated by bubbling NH_3(g) through the reaction mixture. The white ammonium salt formed was filtered off and the filtrate dried over $MgSO_4$. Evaporation of the solvent and thorough drying gave 0.94 g (98%) of the desired *N*-oxide as a white solid: mp 144.5 °C; $[\alpha]_D^{20}$ −20.6° (*c* 0.53, CH_2Cl_2); ^{1}H NMR δ 8.21 (1H, d, J = 6.7 Hz), 7.18−7.35 (3H, m), 6.15 (1H, d, J = 11.3 Hz), 4.94 (1H, app t, J = 10.4 Hz), 3.02−3.09 (1H, m), 2.05−2.16 (1H, m), 1.75−1.9 (2H, m), 1.3−1.45 (2H, m), 1.1 (3H, d, J = 6.4 Hz), 0.98−1.04 (2H, m), 0.84−0.97 (2H, m), 0.91 (3H, d, J = 6.4 Hz), 0.65 (3H, d, J = 6.4 Hz).

(*R*)-[(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-cyclohexyl]-(6′-cyano-2′-pyridyl)methanol (9a) and (*R*)-[(1*S*,2*S*,5*R*)-2-Isopropyl-5-methyl-1-cyclohexyl](6′-cyano-2′-pyridyl)-[(trimethylsilyl)oxy]methane (9b). To a solution of **8** (0.89 g, 3.36 mmol) in CH_2Cl_2 (25 mL) were added dropwise *N*,*N*-dimethylcarbamoyl chloride (0.36 mL, 3.36 mmol) and, after 2.5 h, trimethylsilyl cyanide (0.54 mL, 4.03 mmol). The mixture was stirred overnight at room temperature followed by 8 h at reflux and then allowed to cool to room temperature, whereafter 1 equiv each of *N*,*N*-dimethylcarbamoyl chloride and trimethylsilyl cyanide were added again. After an additional night of stirring at reflux, the reaction was terminated by addition of saturated aqueous Na_2CO_3 (25 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phases were dried over $MgSO_4$. Evaporation *in vacuo* gave a yellow oil that was purified by flash chromatography on silica gel (6 × 2.5 cm column, hexane:EtOAc 4:1) to give **9a** (0.12 g, 13%) together with the corresponding silylated alcohol **9b** (0.6 g, 52%), both as white solids. **9a**: mp 97 °C; $[\alpha]_D^{20}$ +3.5° (*c* 0.58, CH_2Cl_2); ^{1}H NMR δ 7.80 (1H, t, J = 7.64 Hz), 7.62 (1H, dd, J = 7.6, 1.2 Hz), 7.52 (1H, dd, J = 7.6, 1.2 Hz), 5.02 (1H, app t, J = 8.2 Hz), 2.67 (1H, d, J = 7.9 Hz), 2.32−2.40 (1H, m), 1.88−2.1 (1H, m), 1.77−1.90 (2H, m), 1.38−1.52 (2H, m), 1.10−1.2 (1H, m), 1.04 (3H, d, J = 6.4 Hz), 0.93−0.99 (1H, m), 0.92 (3H, d, J = 6.4 Hz), 0.84−0.91 (2H, m), 0.67 (3H, d, J = 6.4 Hz). **9b**: mp 126 °C; $[\alpha]_D^{20}$ +2.6° (*c* 0.58, CH_2Cl_2); ^{1}H NMR δ 7.81 (1H, t, J = 7.47 Hz), 7.71 (1H, dd, J = 7.4, 1.2 Hz), 7.57 (1H, dd, J = 7.4, 1.2 Hz), 5.08 (1H, d, J = 9.5 Hz), 2.32−2.41 (1H, m), 1.76−1.90 (2H, m), 1.61−1.75 (1H, m), 1.3−1.44 (2H, m), 1.03−1.11 (1H, m), 1.06 (3H, d, J = 6.4 Hz), 0.87−0.94 (1H, m), 0.90 (3H, d, J = 6.4 Hz), 0.75−0.87 (2H, m), 0.62 (3H, d, J = 6.4 Hz), −0.12 (9H, s). Anal. Calcd for $C_{20}H_{32}N_2OSi$: C, 69.72; H, 9.36; N, 8.13. Found C, 69.71; H, 9.23; N, 8.13.

(4′*R*,1″*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-[1″-hydroxy-1″-((1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-cyclohexyl)-methyl]pyridine (2a) and (4′*R*,1″*S*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-[1″-hydroxy-1″-((1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-cyclohexyl)methyl]pyridine (2b). Imidate. To a solution of **9a** (0.47 g, 1.72 mmol) or **9b** (0.6 g, 1.72 mmol) in methanol (10 mL) was added sodium methoxide (18.6 mg, 0.34 mmol). The mixture was stirred for 3 days at room temperature and the solvent removed under reduced pressure to give the expected product as a white oil, which was used without further purification: ^{1}H NMR δ 9.12 (1H, br s), 7.76 (2H, m), 7.37 (1H, dd, J = 7, 1.83 Hz), 5.03 (1H, app t, J = 8.2 Hz), 4.02 (3H, s), 2.75 (1H, d, J = 7.6 Hz), 2.34−2.42 (1H, m), 2.02−2.14 (1H, m), 1.77−1.88 (2H, m), 1.4−1.63 (2H, m), 1.07−1.18 (2H, m), 1.06 (3H, d, 6.4 Hz), 0.93 (3H, d, J = 6.4 Hz), 0.82−0.91 (2H, m), 0.66 (3H, d, J = 6.4 Hz).

To the above imidate (0.69 g, 2.27 mmol) in CH_2Cl_2 (20 mL) was added a solution of (*R*)-2-phenylglycinol (0.31 g, 2.27 mmol) in CH_2Cl_2 (5 mL). After a few drops of concd H_2SO_4 were added, the mixture was stirred at reflux for 4 days, and then saturated aqueous Na_2CO_3 (30 mL) was added. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phases were

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dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave a yellow oil that consisted of a mixture of **2a** and **2b**. The relative ratio of the two diastereoisomers depended on the reaction time; that is, the longer the time, the more epimerization. Separation of the two diastereoisomers was performed by flash chromatography on silica gel (8 × 3 cm column, hexane:EtOAc 1.5:1 (300 mL)) to yield 0.1 g of compound **2b** as a colorless oil (40%) and 0.154 g of compound **2a** as a white solid (60%) in a total yield of 30%. **2a**: mp 152 °C; $[\alpha]_D^{20}$ +42° (*c*, 0.3, CH_2Cl_2); ^{1}H NMR δ 8.08 (1H, dd, J = 7.6, 0.9 Hz), 7.76 (1H, t, J = 7.6 Hz), 7.45 (1H, dd, J = 7.6, 0.9 Hz), 7.27−7.4 (5H, m), 5.44 (1H, dd, J = 10.4, 8.5 Hz), 5.07 (1H, dd, J = 9.2, 7.3 Hz), 4.89 (1H, dd, J = 10.4, 8.5 Hz), 4.37 (1H, app t, J = 8.5 Hz), 2.91 (1H, d, J = 7.3 Hz), 2.36−2.43 (1H, m), 2.01−2.12 (1H, m), 1.76−1.87 (m, 2H), 1.42−1.67 (2H, m), 1.06−1.19 (2H, m), 1.05 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.83−0.97 (2H, m), 0.66 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 163.84, 136.90, 128.87, 127.82, 126.69, 123.79, 123.21, 75.45, 74.93, 70.33, 49.85, 42.33, 39.10, 35.96, 30.12, 27.03, 24.93, 22.73, 22.66, 22.28. Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.50; H, 8.22; O, 8.15. Found: C, 76.34; H, 8.06; O, 8.42. **2b**: $[\alpha]_D^{20}$ +51.5° (*c* 0.47, CH_2Cl_2); ^{1}H NMR δ 8.05 (1H, dd, J = 7.6, 0.9 Hz), 7.77 (1H, t, J = 7.6 Hz), 7.46 (1H, dd, J = 7.6, 0.9 Hz), 7.27−7.4 (5H, m), 5.45 (1H, dd, J = 10.3, 8.5 Hz), 5.08 (1H, dd, J = 9.2, 7 Hz), 4.88 (1H, dd, J = 10.3, 8.5 Hz), 4.37 (1H, app t, J = 8.5 Hz), 2.85 (1H, d, J = 7.3 Hz), 2.36−2.43 (1H, m), 2.01−2.11 (1H, m), 1.75−1.86 (2H, m), 1.42−1.69 (2H, m), 1.06−1.2 (2H, m), 1.06 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.82−0.97 (2H, m), 0.65 (3H, d, J = 6.4 Hz); ^{13}C NMR 164.05, 136.9, 128.83, 127.77, 126.84, 123.75, 123.13, 75.4, 74.98, 70.27, 49.9, 42.35, 39.12, 35.98, 30.13, 26.98, 24.9, 22.71, 22.67, 22.26; TLC (silica gel) hexane:EtOAC 1:1, (**2a**) R_f 0.3, (**2b**) R_f 0.43.

(4′*S*,1″*R*)-2-(3′,4′-Dihydro-4′-isopropyl-2′-oxazolyl)-6-(1″-hydroxy-1″-((1*S*,2*S*,5*R*)-2-isopropyl-5-methyl-1-cyclohexyl)methyl]pyridine (4a). Compound **4a** was prepared in 30% yield (0.11 g, colorless oil) according to the procedure described for **2a** and **2b** starting from the same imidate (0.32 g, 1.05 mmol) and (*S*)-valinol (0.108 g, 1.05 mmol). No epimerization was observed: $[\alpha]_D^{20}$ −50° (*c* 0.67, CH_2Cl_2); ^{1}H NMR δ 7.95 (1H, dd, J = 7.6, 0.9 Hz), 7.75 (1H, t, J = 7.6 Hz), 7.41 (1H, dd, J = 7.6, 0.9 Hz), 5.06 (1H, d, J = 9.1 Hz), 4.48 (1H, dd, J = 9.5, 7.9 Hz), 4.11−4.26 (2H, m), 2.91 (1H, br s), 2.34−2.42 (1H, m), 1.99−2.13 (1H, m), 1.85−1.95 (1H, m), 1.75−1.86 (1H, m), 1.55−1.68 (2H, m), 1.42−1.55 (1H, m), 1.07−1.19 (1H, m), 1.05 (3H, d, J = 5.5 Hz), 1.04 (3H, d, J = 5.5 Hz), 0.98−1.04 (1H, m), 0.93 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.4 Hz), 0.79−0.91 (2H, m), 0.62 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 163.8, 146.12, 136.8, 123.37, 122.87, 75.02, 72.8, 70.72, 49.86, 42.33, 39.1, 35.97, 32.82, 30.17, 26.96, 24.92, 22.7, 22.64, 22.25, 19.00, 18.17.

2,2-Dimethyl-1-(2-pyridyl)propanone (10). To a solution of 2-bromopyridine (4 g, 25 mmol) in diethyl ether (100 mL) at −78 °C under nitrogen atmosphere was added BuLi (11 mL, 2.5 M in hexane, 27.5 mmol) over a period of 30 min. The mixture became brown with time, and after the mixture was stirred for 1 h, pivalonitrile (2.5 g, 30 mmol) was added dropwise to the mixture (becoming dark), which was stirred for an additional 2 h at −78 °C followed by 0.5 h at room temperature. The reaction was then quenched with 1 M H_2SO_4 (100 mL) and stirred for 2 h. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, dichloromethane was removed under reduced pressure, and the resulting brown oil was purified by Kugelrohr distillation (90 °C, 0.07 mmHg) to yield a colorless liquid (20 g, 49%): ^{1}H NMR δ 8.6−8.62 (1H, m), 7.86−7.9 (1H, m), 7.78 (1H, td, J = 7.6, 1.8 Hz), 7.36 (1H, ddd, J = 7.6, 4.7, 1.2 Hz), 1.45 (9H, s).

(±)-3,3-Dimethyl-2-(2-pyridyl)-2-butanol (11). A solution of **10** (1.0 g, 6.1 mmol) in diethyl ether (10 mL) was added dropwise to a solution of methylmagnesium iodide in diethyl ether (15 mL), prepared from dry Mg (0.150 g, 6.1 mmol) and methyl iodide (0.86 g, 6.1 mmol). The mixture became yellow, and precipitate of the same color was formed. The reaction mixture was then stirred at reflux overnight, and saturated aqueous NH_4Cl (15 mL) was added. The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated *in vacuo*, giving a yellow liquid that was purified by flash chromatography on silica gel (6 × 3.5 cm column, hexane:EtOAc 9:1 (250 mL) and 1:1 (50 mL)) to yield 0.85 g of compound **12** (78%) as a colorless liquid: ^{1}H NMR δ 8.5−8.53 (1H, m), 7.66 (1H, td, J = 7.3, 1.8 Hz), 7.32−7.34 (1H, m), 7.18 (1H, ddd, J = 7.3, 4.8, 0.9 Hz), 5.54 (1H, s), 1.54 (3H, s) 0.90 (9H, s).

(±)-3,3-Dimethyl-2-(2-pyridyl)-2-butanol *N*-Oxide. This compound (brown oil) was prepared according to the procedure described in **8** in a yield of 99% (0.92 g) starting from **11** (0.85 g, 4.73 mmol) and *m*-CPBA (1.32 g 80%, 6.15 mmol): ^{1}H NMR δ 9.6 (1H, s), 8.15−8.17 (1H, m), 7.32−7.34 (2H, m), 7.21−7.23 (1H, m), 1.58 (3H, s), 1.01 (9H, s).

(±)-3,3-Dimethyl-2-(6-cyano-2-pyridyl)-2-[(trimethylsilyl)oxy]butane. This compound (yellow oil) was prepared according to the procedure described for **9a** and **9b**, without any trace of the corresponding alcohol, in a yield of 60% starting from the above *N*-oxide (0.92 g, 4.7 mmol), *N*,*N*-dimethylcarbamoyl chloride (0.86 mL, 9.4 mmol), and trimethylsilyl cyanide (1.5 mL, 11.28 mmol), added in two portions: ^{1}H NMR δ 7.83 (1H, dd, J = 8.2 and 0.9 Hz), 7.73 (1H, t, J = 8.2 Hz), 7.52 (1H, dd, J = 8.2, 0.9 Hz), 1.68 (3H, s), 0.84 (9H, s), 0.06 (9H, s). Anal. Calcd for $C_{15}H_{24}N_2OSi$: C. 65.17; H, 8.75. Found C, 65.33; H, 8.89.

(4′*R*,2″*R*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(2″-hydroxy-3″,3″-dimethyl-2″-butyl)pyridine (5a) and (4′*R*,-2″*S*)-2-(3′,4′-Dihydro-4′-phenyl-2′-oxazolyl)-6-(2″-hydroxy-3″,3″-dimethyl-2″-butyl)pyridine (5b). Imidate. The same procedure as **2a** and **2b** was followed. Starting from 0.78 g (2.82 mmol) of (±)-3,3-dimethyl-2-(6-cyano-2-pyridyl)-2-[(trimethylsilyl)oxy]butane and 0.030 g (0.56 mmol) of sodium methoxide 0.83 g (95%) of imidate was obtained as a colorless oil: ^{1}H NMR δ 9.16 (1H, br s), 7.67−7.79 (3H, m), 4.00 (3H, s), 1.73 (3H, s), 0.87 (9H, s), 0.06 (9H, s).

The imidate (0.83 g, 2.68 mmol) was then treated with (*R*)-2-phenylglycinol (0.37 g, 2.68 mmol) in CH_2Cl (30 mL), affording a mixture of both trimethylsilyl ethers of **5a** and **5b**. Deprotection by tetrabutylammonium fluoride (0.758 g, 2.40 mmol) in THF (10 mL) afforded a mixture of **5a** and **5b**, which were separated by flash chromatography on silica gel (11 × 2.5 cm column, hexane:EtOAc 1.5:1 (150 mL), 1:1 (100 mL), 1:1.5 (100 mL), 1.5:3.5 (100 mL)). The two compounds were used directly for the allylic alkylation test without determining their absolute configuration. First diastereoisomer (**5a** or **5b**): ^{1}H NMR δ 8.06 (1H, dd, J = 7.6, 0.9 Hz), 7.77 (1H, t, J = 7.6 Hz), 7.47 (1H, dd, J = 7.6, 0.9 Hz), 7.27−7.40 (5H, m), 5.4−5.5 (2H, m), 4.87 (1H, dd, J = 10.4, 8.6 Hz), 4.37 (1H, t, J = 8.6 Hz), 1.57 (3H, s), 0.93 (9H, s). ^{13}C NMR δ 163.86, 144.13, 142.01, 136.43, 128.83, 127.77, 126.84, 123.55, 122.45, 75.28, 70.35, 38.73, 25.84, 22.94. Second diastereoisomer (**5a** or **5b**): ^{1}H NMR δ 8.08 (1H, dd, J = 7.9, 0.9 Hz), 7.77 (1H, t, J = 7.9 Hz), 7.48 (1H, dd, J = 7.9, 0.9 Hz), 7.27−7.40 (5H, m), 5.41−5.49 (2H, m), 4.89 (1H, dd, J = 10.4, 8.6 Hz), 4.34 (1H, t, J = 8.6 Hz), 1.58 (3H, s), 0.93 (9H, s); ^{13}C NMR δ 163.82, 144.04, 141.98, 136.44, 128.86, 127.80, 126.84, 123.57, 122.48, 75.39, 70.34, 38.75, 25.81, 22.88.

General Procedure for Palladium-Catalyzed Allylic Alkylation of 12. The ligand (6 mol %) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2 mol %) were dissolved in dry CH_2Cl_2 (2 mL). The solution was degassed at −78 °C and put under argon atmosphere before the reaction vessel was sealed. The reaction mixture was heated to 50 °C for 2 h and then cooled to −78 °C. *rac*-1,3-Diphenyl-2-propenyl acetate (1 equiv) in dry CH_2Cl_2 (2 mL) was added followed by dimethyl malonate (2.25 equiv), BSA (3 equiv), and a few crystals of KOAc. The reaction was degassed and put under argon atmosphere before the vessel was sealed. The reaction mixture was stirred at room temperature for 4 days and then diluted with diethyl ether and washed with three portions of ice-cooled saturated aqueous NH_4Cl. After drying ($MgSO_4$) and evaporation of the solvent the residual dimethyl malonate and BSA were removed under vacuum at 130 °C. Chromatographic workup of the residue resulted in pure **13** (67−92% yield). The enantiomeric excess

was determined by chiral HPLC and in some cases confirmed by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent. The absolute configuration was determined by polarometric measurements.

(η^3-Allyl)-[(4′*S*,1″*S*)-2-(3′,4′-dihydro-4′-isopropyl-2′-oxoazolyl)-6-(1″-hydroxy-2″,2″-dimethylpropyl)pyridine-*N*,*N*]-palladium(II) Hexafluorophosphate (14). A solution of bis[(π-allyl)palladium chloride] (44 mg, 0.12 mmol) and **3b**[7] (66 mg, 0.24 mmol) in dry CH_2Cl_2 (6 mL) was heated to 50 °C for 2 h in a sealed vessel under an argon atmosphere. The reaction mixture was allowed to reach room temperature, and $AgPF_6$ (90 mg, 0.35 mmol) in THF (6 mL) was added. After 30 min, the mixture was filtered through a pad of Celite. The filtrate was washed with brine and dried ($MgSO_4$) and the solvent evaporated to give 109 mg of **14** (100%) as white crystals: ^{1}H NMR δ 8.13 (1H, t, J = 8 Hz), 8.08 (1H, dd, J = 7, 1 Hz), 7.87 (1H, d, J = 7 Hz), 5.72−5.83 (1H, m, allylic center), 4.85 (1H, app t, J = 9 Hz, OCH_2), 4.80−4.84 (1H, br, H-*syn*), 4.81 (1H, d, J = 3.5 Hz, C*H*OH), 4.71 (1H, dd, J = 9, 6 Hz, OCH_2), 4.3−4.5 (2H, br, H-*syn* and CHN), 3.59 (1H, d, J = 3.5 Hz), 3.05−3.30 (2H, H-*anti*), 2.21 (1H, br, C*H*(CH$_3$)$_2$), 1.03 (3H, d, J = 6 Hz), 0.85−1.0 (3H, m), 0.97 (9H, s).

(η^3-Allyl)-[(4′*S*,1″*S*)-2-(3′,4′dihydro-4′-isopropyl-2′-oxazolyl)-6-(1″-methoxy-2″,2″-dimethylpropyl)pyridine-*N*,*N*]-palladium(II) Hexafluorophosphate (15). Bis[(π-allyl)-palladium chloride] (36 mg, 0.098 mmol) and **3d**[7] (57 mg, 0.196 mmol) in dry CH_2Cl_2 (6 mL) were reacted according to the procedure used for the preparation of **14**. After treatment with $AgPF_6$ (120 mg, 47 mmol) in THF (6 mL), 90 mg (97%) of **15** was isolated as a light yellow solid. Major complex: ^{1}H NMR δ 8.18 (1H, t, J = 8 Hz), 7.97 (1H, br), 7.91 (1H, d, J = 8 Hz), 5.87 (1H, br, allylic center), 4.92−5.03 (1H, m, OCH_2), 4.69 (1H, dd, J = 9, 6 Hz, OCH_2), 4.54 (1H, br, CHN), 4.45 (2H, br, H-*syn*, major complex), 4.30 (1H, s, C*H*OCH$_3$), 3.33 (3H, s), 3.24−3.31 (1H, m, H-anti directed toward the oxazoline), 3.20 (1H, bd, J = 5.5 Hz, H-*anti* directed toward the ether part), 2.01−2.28 (1H, m, C*H*(CH$_3$)$_2$), 0.8−1.1 (6H, m), 0.97 (9H, s). Minor complex: ^{1}H NMR δ 8.18 (1H, t, J = 8 Hz), 7.97 (1H, br), 7.91 (1H, d, J = 8 Hz), 5.78 (1H, br, allylic center), 4.92−5.03 (1H, m, OCH_2), 4.69 (1H, dd, J = 9 and 6 Hz, OCH_2), 4.62 (2H, br, H-*syn*), 4.54 (1H, br, CHN), 4.30 (1H, s, C*H*OCH$_3$), 3.63−3.73 (1H, m, H-*anti* directed toward the ether part), 3.59−3.66 (1H, m, H-*anti* directed toward the oxazoline), 3.33 (3H, s), 2.01−2.28 (1H, m, C*H*(CH$_3$)$_2$), 0.8−1.1 (6H, m), 0.97 (9H, s).

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Supporting Information Available: ^{1}H NMR spectra of compounds **1c,d**, **2a,b**, **4a**, **14**, and **15** and ^{13}C NMR spectra of compounds **1c**, **2a,b**, and **4a** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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