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Structurally Simple Pyridine *N*-Oxides as Efficient Organocatalysts for the Enantioselective Allylation of Aromatic Aldehydes

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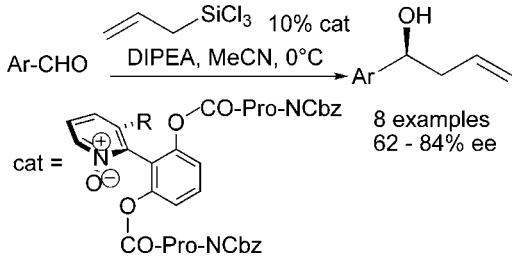

A series of structurally simple pyridine *N*-oxides have readily been assembled from inexpensive amino acids and tested as organocatalysts in the allylation of aldehydes with allyl(trichloro)silane to afford homoallylic alcohols. (*S*)-Proline-based catalysts afforded the products derived from aromatic aldehydes in fair to good yields and in up to 84% enantiomeric excess (ee). The allylation of heteroaromatic, unsaturated, and aliphatic aldehydes was less satisfactory. By running the reaction in the presence of achiral and chiral additives and structurally different catalysts, we collected some insights into the relationship between the stereochemical outcome and the catalyst's structural features. Even if the ee's obtained are inferior to the best values observed with other catalysts, this work concurs to show that structurally simple pyridine *N*-oxides can also promote the allylation reaction with satisfactory stereocontrol.

Introduction

In recent years, appropriately defined "the golden age of organocatalysis",[1] the possibility of effectively replacing metal-based enantioselective catalysts with wholly organic molecules while maintaining high levels of chemical efficiency and stereocontrol has been demonstrated. A key issue for the success of this approach resides in the structural simplicity of the organocatalyst[2] that should be much more readily available than its organometallic counterparts.

An ideal organocatalyst should be a molecule present in the chiral pool: proline and quinine are suitable examples. If a nonnatural catalyst is required, it must be obtained by modification of an inexpensive, commercially available, enantiopure material whose manipulation must be kept to minimum. As a part of a project devoted to the identification of new organocatalysts that fulfill the above-mentioned requirements, we became interested in developing structurally simple *N*-oxides as chiral Lewis base catalysts.[1,3,4] Inspection of literature data[5,6] led us to consider mono-*N*-oxides as promising candidates.[5e−h,7] Mono-*N*-oxides are more easily obtained than bis-[5a−d] and tris-*N*-oxides,[5j] the synthesis of which requires relatively long procedures often involving a resolution process or a stereoselective synthesis as the key step.

On the basis of some encouraging literature precedents[5g,5k,7] and considering synthetic simplicity as a major goal of our effort, it was also decided to avoid the presence of a stereogenic axis but to maintain a biaryl bond in the proximity of the catalyst's active site. Indeed, embedding a stereogenic axis in the catalyst

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(3) For leading references to the use of Lewis basic organocatalysts, see: (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, 167 and references therein. (b) Rowlands, G. J.; Kentish Barnes, W. *Chem. Commun.* **2003**, 2712. (c) Kobayashi, S.; Suigira, M.; Ogawa, C. *Adv. Synth. Catal.* **2004**, *346*, 1023.

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has often proved to be a winning strategy in achieving high levels of stereocontrol,[5a−d,5f] but it also made the synthesis of the catalyst quite complex, calling for the stereoselective formation of a difficult-to-control stereogenic element. Here, we describe the facile synthesis of some structurally simple amino-acid-derived pyridine *N*-oxides that catalyze the enantioselective allylation of aromatic aldehydes with allyl(trichloro)-silane[8] in up to 84% enantiomeric excess (ee).

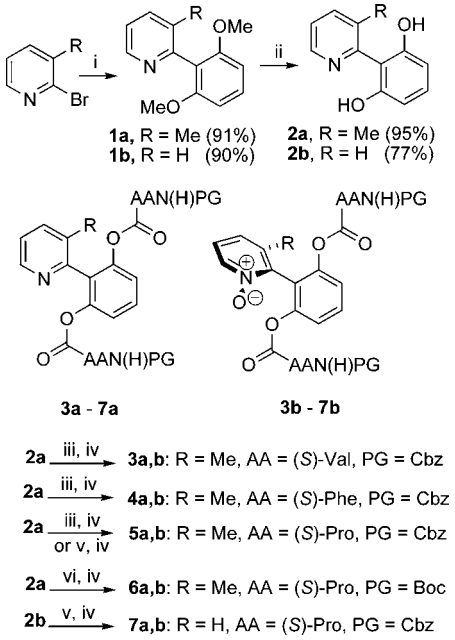
Results and Discussion

The catalysts were readily assembled as described in Scheme 1. A two-step procedure involving Suzuki coupling of 2,6-dimethoxyphenyl boronic acid with the corresponding 2-bromopyridines to afford **1a** and **1b** followed by demethylation with pyridine hydrochloride allowed 2-(2,6-dihydroxyphenyl)-pyridines **2a** and **2b** in 86 and 70% overall yields, respectively.

Condensation of **2a** with *N*-Cbz-protected (*S*)-valine, (*S*)-phenylalanine, and (*S*)-proline under standard conditions (HOBt, EDC) afforded the corresponding bisesters **3a**−**5a** in 50−60% unoptimized yield. Proline-derived compound **5a** (that eventually led to the most stereoselective catalyst, see below) was better obtained by esterification of **2a** with *N*-Cbz prolinoyl chloride[9] (97% average yield of several runs), a reaction that also allowed the synthesis of adduct **7a** from bisphenol **2b**. *N*-Boc proline derivative **6a** was prepared in 76% yield by a condensation carried out in the presence of DCC and catalytic DMAP. Conversion of **3a**−**7a** to the corresponding *N*-oxides **3b**−**7b** occurred uneventfully by reaction with *m*-CPBA in 75−85% yield.

The catalytic activity of the *N*-oxides was established using the allylation of benzaldehyde to afford homoallylic alcohol **8a** as the model reaction (Scheme 2). A typical experiment involved the use of 0.1 mol equiv of catalyst, 1.2 mol equiv of allyl-(trichloro)silane, and 3 mol equiv of DIPEA in acetonitrile[10] for 48 h at different temperatures. Isolated yields and ee's, as determined by HPLC, are collected in Table 1; the (*S*) absolute configuration was assigned to the predominant isomer of **8a** by comparison of optical rotation.

SCHEME 1. Synthesis of Catalysts 3b−7b[a]



[a] Reagents and conditions: (i) 2,6-dimethoxyphenyl boronic acid, 0.1 mol equiv of $Pd(OAc)_2$, 0.4 mol equiv of PPh_3, 2 M aqueous Na_2CO_3, DME, reflux, 70 h; (ii) excess Py·HCl, neat, 200 °C, 3 h; (iii) 2 mol equiv of *N*-Cbz-protected amino acid, 2.4 mol equiv each of HOBt and EDC, CH_2Cl_2/DMF 1:1, room temperature, 15 h; (iv) 1.5 mol equiv of 70% *m*-CPBA, CH_2Cl_2, room temperature, 15 h; (v) 2 mol equiv of *N*-Cbz prolinoyl chloride, THF, reflux, 15 h; (vi) 2 mol equiv of *N*-Boc proline, 2.1 mol equiv of DCC, 0.2 mol equiv of DMAP, THF, room temperature, 15 h.

As can be seen from the reported data, catalyst **5b**, derived from *N*-Cbz proline, was more stereoselective than those obtained from valine (**3b**) or phenylalanine (**4b**) (entry 3 vs 1 and 2). By lowering the reaction temperature to 0 °C, a satisfactory 68% ee was obtained with catalyst **5b** (entry 4), although the reaction proceeded in moderate yield (45%). The addition of tetrabutylammonium iodide did not improve the yield and slightly depressed the ee (entry 5). The yield was increased to 75% and the ee was slightly decreased to 63% by doubling the amount of catalyst (entry 6). The use of 0.1 mol equiv of catalyst **6b** derived from *N*-Boc proline (entry 7) allowed us to increase the yield to 87% while maintaining a good level of stereocontrol (62% ee). The latter was increased to 67% by further lowering the reaction temperature to −20 °C (entry 8). The removal of the methyl substituent on the pyridine ring as in catalyst **7b** affected very slightly the outcome of the reaction (entry 9 vs 4).

Having thus identified the proline-derived catalysts **5b**−**7b** as the more efficient ones, we extended their use to the allylation of other aromatic aldehydes to afford alcohols **8b**−**8h** (Scheme 2 and Table 2). The reported data show that ee's equal to or greater than 60% could be obtained, with a maximum value of 84% ee observed in the case of the 3-nitrophenyl-substituted alcohol **8f** (entry 5).

The dependence of the chemical yield on the electronic nature of the aryl substituents in the aldehydes was not easily rationalized. However, independently of the catalyst employed, higher ee's were observed starting from electron-poor aldehydes (alcohols **8e**, **8f**, and **8h**; entries 4, 5, 7, 10, and 11). As in the

(5) For the use of *N*-oxides as organocatalysts in the allylation reaction, see: (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (c) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329. (d) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, *346*, 1169. (e) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1049. (f) Malkov, A. V.; Dufkovà; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674. (g) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kocovsky, P. *J. Mol. Catal. A: Chemical* **2003**, *196*, 179. (h) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, *68*, 9659. (i) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kocovsky, P. *Org. Lett.* **2005**, *7*, 3219. (j) Wong, W.-L.; Lee, C.-S.; Leung, H.-K.; Kwong, H.-L. *Org. Biomol. Chem.* **2004**, *2*, 1967. (k) Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005**, *17*, 396. (l) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151.

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(7) Reports appeared while this work was being completed that confirmed the validity of this approach: see ref 5i and 5l.

(8) For a review on the allylation of aldehydes with ally(trichloro)silane, see: Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 2090.

(9) Huang, J.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3455.

(10) The use of other solvents (toluene, dichloromethane, dichloroethane, THF, DME) led to lower yields and ee. The best result (25% yield, 42% ee) was observed in dichloromethane.

SCHEME 2. Synthesis of Alcohols 8 and 9 and Catalysts 10−12

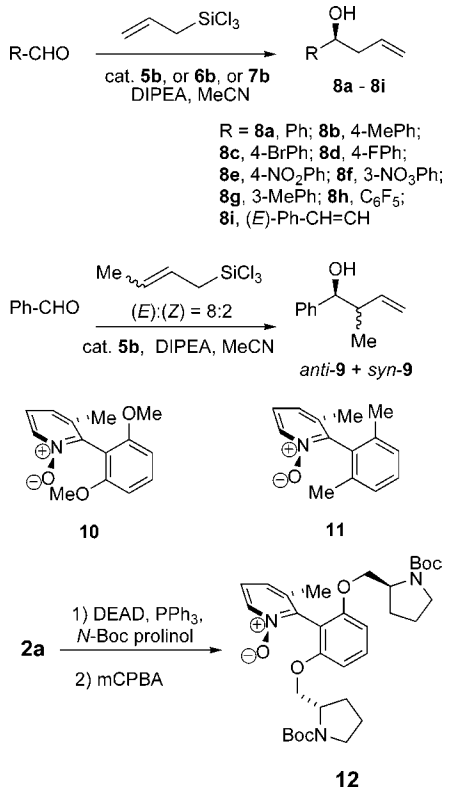

TABLE 1. Stereoselective Synthesis of Homoallylic Alcohol 8a

entry	catalyst	amino acid	temp	yield %	ee %	abs conf.
1	**3b**	Val	room temp	85	0	
2	**4b**	Phe	room temp	53	6	
3	**5b**	Pro	room temp	51	25	(*S*)
4	**5b**	Pro	0 °C	45	68	(*S*)
5	**5b**	Pro	0 °C	45[a]	61	(*S*)
6	**5b**	Pro	0 °C	75[b]	63	(*S*)
7	**6b**	Pro	0 °C	87	62	(*S*)
8	**6b**	Pro	−20 °C	40	67	(*S*)
9	**7b**	Pro	0 °C	50	60	(*S*)

[a] In the presence of 1.2 mol equiv of tetrabutylammonium iodide. [b] In the presence of 0.2 mol equiv of catalyst.

TABLE 2. Stereoselective Synthesis of Homoallylic Alcohols 8b−8h

entry	catalyst	Ar	product	yield %	ee %	abs conf.
1	**5b**	4-MePh	**8b**	65	71	(*S*)
2	**5b**	4-BrPh	**8c**	46	71	(*S*)
3	**5b**	4-FPh	**8d**	50	62[a]	(*S*)
4	**5b**	4-NO_2Ph	**8e**	38	76	(*S*)
5	**5b**	3-NO_2Ph	**8f**	60	84	(*S*)
6	**5b**	3-MePh	**8g**	45	73	(*S*)
7	**5b**	C_6F_5	**8h**	40	73[a]	(*S*)
8	**6b**	4-BrPh	**8c**	56	66	(*S*)
9	**6b**	4-FPh	**8d**	68	60[a]	(*S*)
10	**6b**	4-NO_2Ph	**8e**	60	76	(*S*)
11	**7b**	4-NO_2Ph	**8e**	51	73	(S)

[a] Determined by HPLC on the corresponding acetates obtained by quantitative reaction with Ac_2O in pyridine at room temperature.

case of the reaction involving benzaldehyde, those involving other aldehydes catalysts **6b** and **7b** led to somewhat higher yields and slightly lower ee's than catalyst **5b** (entries 2−4 vs 8−11).

Extension of the reaction promoted by catalyst **5b** to electron-poor heteroaromatic aldehydes under the conditions of entry 4, Table 1, afforded the corresponding alcohols in good yield (2-pyridylcarbaldehyde, 88%; 2-thiazolylcarbaldehyde, 70%) but in virtually racemic form (ee < 10%). The presence of the coordinating heterocyclic nitrogen on these substrates can account for this poor stereocontrol. Electron-rich heteroaromatic aldehydes reacted sluggishly, if at all. The **5b**-catalyzed allylation of cinnamaldehyde and 3-phenylpropanal was also attempted. Although the latter proved to be poorly reactive (20% yield), the former gave adduct **8i** in fair yield (61%) and low ee (31%). Thus, the reactivity trend observed with catalyst **5b** (aromatic aldehydes > α,β-unsaturated aldehydes ≫ aliphatic aldehydes) does not differ from that of the other *N*-oxides described in the literature.[5] Finally, the use of catalyst **5b** was extended to the reaction of benzaldehyde with an 8:2 mixture of (*E*)- and (*Z*)-crotyl(trichloro)silane (conditions of entry 4, Table 1; Scheme 2). An 8:2 mixture of diastereoisomeric alcohols *anti*-**9** and *syn*-**9** was obtained in 40% yield, with the anti isomer having a 69% ee. The fact that the *anti:syn* diastereoisomeric ratio reflected the (*E*):(*Z*) ratio of the starting silane is generally considered[5] a strong indication that a six-membered cyclic chairlike transition structure is involved in the allylation (see below).

With the aim of understanding how the various structural components of the catalysts affected the stereochemical outcome of the reaction, the allylation of benzaldehyde was carried out in the presence of different catalysts and additives under the conditions of entry 4, Table 1.

First of all, it was demonstrated that the presence of the *N*-oxide function was essential for the reaction to take place: no reaction was observed with pyridine **5a** as the catalyst. It is generally assumed that the *N*-oxide oxygen coordinates the silicon atom to form the catalytically active species.[5] However, our catalysts present other sites potentially capable of silicon coordination, namely the oxygens of the ester and carbamate groups present in the catalyst's sidearms. To check whether coordination by these sites affects the course of the reaction, two syntheses of **8a** were performed in the presence of 0.1 mol equiv of **5b** and 0.4 mol equiv of *N*-Cbz pyrrolidine or (*S*)-methyl *N*-Cbz prolinate as additives, respectively. Even with this large additive/catalyst ratio, only a slight decrease in the ee was observed in both cases (from 68 to 63%), thus suggesting that either the ester's or the carbamate's oxygens do not interact with the silicon atom or, if coordination does indeed occur, that this should not be a decisive factor to achieve stereoselectivity.

To try to understand if the phenolic oxygen can participate in silicon coordination (a possibility recently examined by Kocovsky et al.[5g,5i]), two other allylations of benzaldehyde were carried out. One was performed in the presence of 0.1 mol equiv each of *N*-oxide **5b** and the achiral, methoxy-bearing *N*-oxide **10** (Scheme 2); from this reaction compound, **8a** was obtained in a virtually racemic form (2% ee, 70% yield). The other experiment was similarly performed in the presence of 0.1 mol equiv each of *N*-oxide **5b** and the achiral, methyl-bearing *N*-oxide **11** (Scheme 2) that has roughly the same steric hindrance as that of **10** but lacks the phenolic oxygens; from this reaction compound, **8a** was obtained in 75% yield and 30% ee. On the basis of these experiments, it seems possible that the *N*-oxide oxygen and one of the phenolic oxygens of **5b** are

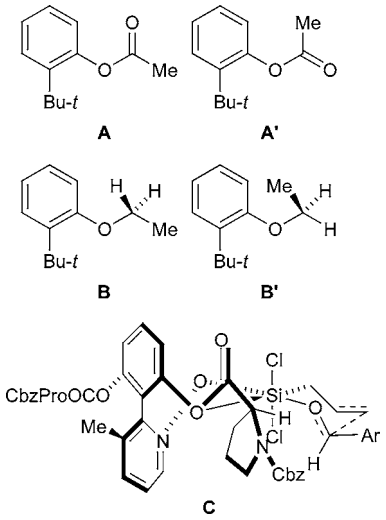

FIGURE 1. Conformational analysis and proposed transition structure.

involved in silicon coordination and that this coordination helps to stereocontrol the reaction. Indeed, the achiral *N*-oxide **10**, which provides the same pattern of chelating sites as that of **5b**, effectively competes with the chiral catalyst in promoting the reaction, and in its presence, a virtually racemic product is obtained; the achiral but not doubly coordinating *N*-oxide **11** is less effective in competing with **5b**, and the ee of product **8a** is decreased but not erased.[11]

To further substantiate this hypothesis, *N*-oxide **12** (Scheme 2) lacking the ester carbonyl oxygen but still featuring the phenolic oxygen was prepared by a Mitsunobu reaction of phenol **2a** with commercially available *N*-Boc prolinol followed by pyridine *N*-oxidation (45% unoptimized overall yield, Scheme 2). When the allylation of benzaldehyde was carried out using this catalyst under the conditions of entry 6, Table 1, alcohol (*S*)-**8a** was obtained in 90% yield and 45% ee. Thus, the yield was very similar to that observed with the related catalyst **6b** (90 vs 87%), but the ee was lower (45 vs 62%). Extension of the use of **12** to the synthesis of (*S*)-**8b** (73% yield, 45% ee; cfr. entry 1, Table 2) and (*S*)-**8e** (92% yield, 56% ee; cfr. entry 4, Table 2) confirmed this trend. By considering these results together with those obtained by running the reaction in the presence of different catalysts and additives (see above), it seems possible that the higher stereoselectivity observed with catalysts **5b** and **6b** with respect to **12** can in part be due to the reduced conformational mobility of the sidearms of **5b** and **6b** that contain an ester rather than an ether bond.

Molecular mechanics (MM2) calculations on model compounds confirmed this hypothesis. Indeed, 2-*tert*-butyl-1-acetoxybenzene (Figure 1), a model for the ester-bearing catalysts such as **5b**, was shown to exist almost exclusively as in conformation **A**, featuring the C═O bond virtually eclipsed with the aromatic ring and an *s-cis* arrangement of the ester moiety; the *s-trans* conformation **A′** is about 8 kcal/mol less stable than **A**. On the other hand, in 2-*tert*-butyl-1-ethoxybenzene (a model for **12**), conformation **B** is only 0.9 kcal/mol more stable than **B′**, which is therefore largely accessible at the reaction temperature.

(11) It must be noted that both **10** and **11** are less sterically hindered and, hence, are likely to be better catalysts than **5b** because they can have a stronger *N*-oxide/silicon interaction.

By implementing the results of this conformational analysis with those of the above-mentioned experiments, transition structure **C** (Figure 1) can be proposed to tentatively explain the stereochemical result of the allylation reaction promoted by catalyst **5b**. In this model, the hypervalent silicon atom (commonly believed to be involved in this type of reaction)[5,6] is coordinated by the pyridine *N*-oxide oxygen and the phenolic oxygen of one sidearm. The bulky proline residue effectively blocks one side of the adduct and accommodates the aldehyde better than the sterically more requiring allyl residue as its *cis* substituent. The proposed model of stereoselection is in agreement with (i) the observed formation of (*S*) homoallylic alcohols, (ii) the scarce influence exerted on the stereoselectivity by the presence of the methyl substituent of the pyridine ring of **7b** and by the steric hindrance of the proline N-protective group, and (iii) the higher stereoselection observed in the reactions catalyzed by **5b** relative to those catalyzed by **12**; this observation seems to be due to the fact that the stereodirecting proline group is forced to be closer to the core of the transition structure in the former than in the latter because of the presence of the ester bond.

Conclusions

In conclusion, a series of pyridine mono-*N*-oxides, readily assembled from inexpensive amino acids, have been prepared and tested as organocatalysts in the allylation of aldehydes with allyl(trichloro)silane to afford homoallylic alcohols. The use of (*S*)-proline-based catalysts allowed us to obtain the products from aromatic aldehydes in fair to good yields and ee's. The allylation of heteroaromatic, unsaturated, and aliphatic aldehydes was less satisfactory. By running the reaction in the presence of achiral and chiral additives and structurally different catalysts, some insights into the dependence of the stereochemical outcome on the catalyst's structure were obtained. Even if the ee's obtained are lower than the best values observed so far with other catalysts, this work has demonstrated the possibility that structurally simple pyridine *N*-oxides can also promote the allylation reaction with satisfactory stereocontrol. Work is in progress to test the catalysts in other enantioselective reactions and to identify other readily obtained pyridine *N*-oxides as chiral organocatalysts.

Experimental Section

Synthesis of 1a and 2a. A. Suzuki Coupling of 2-Bromo-3-methylpyridine with 2,6-Dimethoxyphenyl Boronic Acid. To a stirred solution of 2-bromo-3-methylpyridine (1.00 g, 5.52 mmol) in DME (110 mL) were added $Pd(OAc)_2$ (124 mg, 0.552 mmol) and PPh_3 (0.58 g, 2.21 mmol) in this order. After 20 min of stirring at room temperature, 2,6-dimethoxyphenyl boronic acid (1.005 g, 5.52 mmol) and Na_2CO_3 (23 mL of a 2 M aqueous solution) were added to the yellow solution. The resulting mixture was refluxed under vigorous stirring for 70 h. Most of the solvent was evaporated, and the residue was extracted with AcOEt (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product. This was purified by flash chromatography with an 8:2 dichloromethane (DCM)/AcOEt mixture as eluant to afford 2-(2,6-dimethoxyphenyl)-3-methylpyridine **1a** in 91% yield as a white solid (mp 93−94 °C). IR (DCM): 1610, 1450, 1298, 1131 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, J = 4.8 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.14 (dd, J = 7.6, 4.8 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 3.69 (s, 6H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 154.3, 146.6, 137.0, 133.2, 129.4, 121.9, 104.0,

55.8, 18.6. Elemental anal. calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.08; H, 6.48; N, 6.33.

B. Demethylation.[12] Pyridine hydrochloride was prepared by adding HCl (417.7 mL of a 37% w/w aqueous solution, 213 mmol) to pyridine (15.8 mL, 195 mmol). Water was removed under vacuum, and the resulting melted residue was added to a flask containing 2-(2,6-dimethoxyphenyl)-3-methylpyridine (1.15 g, 5.01 mmol). The mixture was stirred at 200 °C for 3 h. After the flask was cooled at about 80 °C, hot water (8 mL) was added, and the mixture was poured into warm water (18 mL). The pH was adjusted to neutrality by addition of 10% w/w NaOH, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product. This was purified by flash chromatography with a 6:4 DCM/EtOAc mixture as eluant to afford 2-(2,6-hydroxyphenyl)-3-methylpyridine **2a** in 95% yield as a white solid (mp 184 °C). IR (DCM): 3350, 1654, 1465, 1028 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 9.05 (bs, 2H), 8.38 (d, J = 4.2 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.18 (dd, J = 7.5, 4.2 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.39 (d, J = 9.0 Hz, 2H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, DMSO): δ 155.6, 155.0, 146.0, 136.7, 132.8, 128.6, 121.7, 115.3, 106.4, 18.4. Elemental anal. calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.41; N, 7.03.

Synthesis of 3a and 3b. A. Esterification. To a stirred solution of *N*-Cbz valine (200 mg, 0.79 mmol) in a DMF/DCM mixture (2 + 2 mL) at 0 °C were added EDC (183 mg, 095 mmol) and HOBT (146 mg, 0.95 mmol). After 20 min, 2-(2,6-hydroxyphenyl)-3-methylpyridine **2a** (80 mg, 0.397 mmol) was added and the reaction mixture was stirred for 24 h under nitrogen at room temperature. EtOAc was added, and the organic phase was washed with water and a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by flash chromatography with a 60:40 hexanes/EtOAC mixture as eluant. (*S*,*S*)-3-Methyl-2-[2′,6′-bis(*N*-Cbz-valinoxy)-phenyl]pyridine **3a** (0.24 mmol, 60%) was obtained as a white solid (mp 65 °C). $[\alpha]^{23}$ −82.0 (*c* 0.4 in DCM). IR: 1765, 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.44 (d, J = 4.8 Hz, 1H), 7.50 (d, J = 5.8 Hz, 1H), 7.48 (m, 1H), 7.30−7.40 (m, 10H), 7.15−7.20 (m, 2H), 7.12 (m, 1H), 5.20−5.10 (m, 2H), 5.12 (m, 2H), 4.25 (m, 1H), 2.08 (s, 3H), 1.9 (m, 1H), 1.8 (m, 1H), 0.9 (d, J = 5.8 Hz, 3H), 0.85 (d, J = 5.8 Hz, 3H), 0.5 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 156.1, 150.0, 148.4, 148.3, 146.5, 138.3, 136.0, 134.3, 129.5, 128.4, 128.3, 128.1, 126.2, 123.2, 120.4, 120.5, 67.5, 59.0, 30.6, 18.8, 18.7, 16.6. Elemental anal. calcd. for $C_{38}H_{41}N_3O_8$: C, 68.35; H, 6.19; N, 6.29. Found: C, 68.45; H, 6.18; N, 6.28.

B. N-Oxidation. To a stirred solution of the diester (160 mg, 0.24 mmol) in DCM (5 mL) cooled at 0 °C was added 70% *m*-CPBA (90 mg, 0.36 mmol). After 15 min of stirring at 0 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for 15 h. A saturated aqueous solution of $NaHCO_3$ was then added, and the aqueous phase was extracted twice with DCM. The combined organic phases were repeatedly washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product. This was purified by flash chromatography with a 98:2 DCM/MeOH mixture as eluant to afford (*S*,*S*)-3-methyl-2-[2′,6′-bis(*N*-Cbz-valinoxy)-phenyl]pyridine *N*-oxide **3b** in 77% yield as a white solid (mp 73 °C). $[\alpha]^{23}$ −9.3 (*c* 0.31 in DCM). IR(DCM): ν 1766, 1721, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 3.5 Hz, 1H), 7.50 (t, J = 6.3 Hz, 1H), 7.30−7.40 (m, 10H), 7.20 (m, 2H), 6.95 (m, 2H), 5.17 (m, 2H), 5.05 (m, 2H), 4.30 (m, 1H), 4.20 (m, 1H), 2.01 (s, 3H), 1.90−2.00 (m, 2H), 0.85 (d, J = 5.5 Hz, 3H), 0.80 (d, J = 5.5 Hz, 3H), 0.70 (d, J = 5.2 Hz, 3H), 0.65 (d, J = 5.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 156.9, 150.1, 148.8, 148.1, 147.5, 138.7, 136.9, 134.1, 130.5, 129.4, 129.3, 127.1, 126.1, 123.2, 120.9, 119.5, 67.7, 59.6, 30.7, 18.8, 18.5, 17.6, 17.0. Elemental anal. calcd for $C_{38}H_{41}N_3O_9$: C, 66.75; H, 6.04; N, 6.15. Found: C, 66.88; H, 6.02; N, 6.09.

Synthesis of 5a and 5b. A. Esterification. To a stirred solution of 2-(2,6-hydroxyphenyl)-3-methylpyridine (100 mg, 0.497 mmol), TEA (0.554 mL, 3.476 mmol), and a catalytic amount of DMAP in dry THF (6 mL) was added a solution of crude *N*-Cbz prolinoyl chloride (prepared from 263 mg, 1.04 mmol, of *N*-Cbz proline)[9] in dry THF (5 mL). The mixture was refluxed for 15 h under nitrogen, and the solvent was evaporated. The residue was purified by flash chromatography with a 98:2 DCM/MeOH mixture as eluant. (*S*,*S*)-3-Methyl-2-[2′,6′-bis(*N*-Cbz-prolinoxy)phenyl]pyridine **5a** (0.481 mmol, 97%) was obtained as a white solid (mp 64 °C). $[\alpha]^{23}$ −140.0 (*c* 0.3 in DCM). IR: 1772, 1703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.50 (bd, J = 4.2 Hz, 1H), 7.40−7.60 (m, 1H), 7.30−7.40 (m, 10H), 7.15−7.30 (m, 2H), 6.70 (q, J = 5.9 Hz, 1H), 5.04−5.20 (m, 4H), 4.25−4.40 (m, 2H), 3.30−3.58 (m, 4H), 2.18, 2.14, 2.12, and 2.07 (4s, 3H overall), 1.70−1.95 (m, 2H), 1.60−1.75 (m, 2H), 1.20−1.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.0, 154.5, 151.5, 148.5, 146.6, 137.6, 134.5, 129.3, 128.4, 128.0, 127.9, 127.0, 122.9, 120.5, 120.0, 67.0, 66.9, 59.0, 58.5, 46.7, 46.1, 30.2, 29.2, 23.9, 22.9, 19.4, 18.3. Elemental anal. calcd for $C_{38}H_{37}N_3O_8$: C, 68.76; H, 5.62; N, 6.33. Found: C, 68.95; H, 5.58; N, 6.78.

B. N-Oxidation. Following the procedure described for **3b**, (*S*,*S*)-3-methyl-2-[2′,6′-bis(*N*-Cbz-prolinoxy)phenyl]pyridine *N*-oxide **5b** was obtained in 85% yield as a white solid after flash chromatography with a 96:4 DCM/MeOH mixture as eluant (mp 60 °C). $[\alpha]^{23}$ −10.3 (*c* 0.36 in DCM). IR(DCM): ν 2923, 2854, 1769, 1701, 1459, 1376, 1125 cm^{-1}. ^1H NMR (300 MHz, DMSO, 77 °C): δ 8.17 (d, J = 6.5 Hz, 1H), 7.51 (t, J = 8.3 Hz, 1H), 7.30−7.40 (m, 10H), 7.28 (t, J = 6.5 Hz, 1H), 7.16 (d, J = 6.5 Hz, 1H), 7.07 (bd, J = 8.1 Hz, 2H), 5.00−5.17 (m, 4H), 4.30−4.40 (m, 2H), 3.27−3.43 (m, 4H), 3.15−3.25 (m, 1H), 2.97 (bs, 1H), 2.00−2.18 (m, 2H), 1.91 (s, 3H), 1.40−1.80 (m, 4H). ^{13}C NMR (75 MHz, DMSO, 77 °C): δ 170.0, 169.5, 155.0, 154.5, 149.5, 142.5, 138.5, 137.2, 136.9, 136.5, 136.54, 130.6, 130.4, 128.4, 127.9, 127.8, 126.7, 126.3, 120.4, 120.1, 120.0, 67.0, 66.9, 59.2, 58.5, 46.8, 46.7, 30.5, 29.2, 24.0, 23.2, 18.5, 18.3. Elemental anal. calcd for $C_{38}H_{37}N_3O_9$: C, 67.15; H, 5.49; N, 6.18. Found: C, 67.48; H, 5.62; N, 6.09.

Synthesis of (*S*,*S*)-2-[2′,6′-Bis(2-methyloxy-*N*-Boc-pyrrolidine)phenyl]-3-methylpyridine *N*-oxide 12. A. Mitsunobu Reaction. To a stirred solution of 2-(2,6-hydroxyphenyl)-3-methylpyridine **2a** (0.201 g, 1.0 mmol), *N*-Boc prolinol (0.402 g, 2.0 mmol), and triphenylphosphine (0.629 g, 2.4 mmol) in dry THF (43 mL) cooled at 10 °C was added dropwise DEAD (1.1 mL of a 40% solution in toluene, 2.4 mmol). The cooling bath was removed, and the progress of the reaction was monitored by TLC. After 24 h of stirring at room temperature, volatile materials were removed under vacuum and the residue was filtered through a short column of silica gel for flash chromatography using EtOAc as eluant. The resulting crude product was used as such for the N-oxidation.

B. N-Oxidation. Following the procedure described for **3b**, product **12** was obtained (45% overall yield from **2a**) as a white solid after flash chromatography with a 9:1 DCM/MeOH mixture as eluant (mp 68−70 °C). $[\alpha]^{23}$ −38.4 (*c* 0.1 in DCM). IR: 1685, 1400, 1265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 47 °C): δ 8.25 (bm, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.21 (bm, 2H), 6.72 (d, J = 7.7 Hz, 1H), 6.71 (bd, J = 7.7 Hz, 1H), 4.20 (B part of AB system, J = 9.1 and 3.3 Hz, 1H), 4.03 (A part of AB system, J = 9.1 and 1.9 Hz, 1H), 4.00 (m, 2H), 3.95 (m, 1H), 3.80 (m, 1H), 3.25 (bm, 4H), 2.03 (s, 3H), 1.84 (B part of AB system, 2H), 1.82 (A part of AB system, 2H), 1.69 (m, 4H), 1.45 (bs, 18H). ^{13}C NMR (75 MHz, $CDCl_3$, 47 °C): δ 157.0, 154.3, 145.5, 138.0, 137.0, 131.1, 126.3, 123.6, 110.0, 105.8, 105.2, 79.4, 69.5, 69.0, 68.4, 55.8, 47.0, 46.7, 46.4, 28.9, 28.5, 28.0, 27.5, 23.8, 23.4, 23.0, 22.5, 18.8. Elemental

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anal. calcd for $C_{32}H_{45}N_3O_7$: C, 65.84; H, 7.77; N, 7.20. Found: C, 66.01; H, 7.83; N, 7.05.

Allylation reaction. General procedure. To a stirred solution of catalyst (0.03 mmol) in acetonitrile (2 mL) kept under nitrogen were added an aldehyde (0.3 mmol) and diisopropylethylamine (DIPEA, 0.154 mL, 0.9 mmol), in this order. The mixture was then cooled to 0 °C, and allyl(trichloro)silane (0.054 mL, 0.36 mmol) was added dropwise by means of a syringe. After 48 h of stirring at 0 °C, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was allowed to warm to room temperature, and water (2 mL) and EtOAc (5 mL) were added. The organic phase was separated, and the aqueous phase was extracted 3 times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature to afford the crude products. These were purified by flash chromatography with different hexane/EtOAc mixtures as eluants. The yield and ee for each reaction are indicated in the Tables. The assignment of the (*S*) absolute configuration to the predominant isomer formed in each reaction rests on comparison of signs of optical rotation with those reported in the literature.

1-Phenyl-3-buten-1-ol 8a. This product was purified with a hexane/EtOAc 90:10 mixture as eluant. It had ^{1}H NMR data in agreement with those reported in the literature.[5c] The enantiomeric excess was determined by HPLC on a Chiracel OD column (hexane/2-propanol 95:5; flow rate 0.8 mL/min; λ 220 nm): $t_R = 10.4$ min, $t_S = 11.3$ min.

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Supporting Information Available: Synthesis and characterization of catalysts **1b**, **2b**, **4a**, **4b**, **6a**, **6b**, **7a**, and **7b**, synthesis of *N*-oxides **10** and **11**,[13] and HPLC analysis details for products **8a**−**i**[14−17] and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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