

# Catalytic Asymmetric Synthesis of Bis-armed Aromatic Amino Acid Derivatives. Problems Related to the Synthesis of Enantiomerically Pure Bis-methyl Ester of the (*S,S*)-Pyridine-2,6-diyl Bis-alanine\*

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Basu, B. and Frejd, T., 1996. Catalytic Asymmetric Synthesis of Bis-armed Aromatic Amino Acid Derivatives. Problems Related to the Synthesis of Enantiomerically Pure Bis-methyl Ester of the (*S,S*)-Pyridine-2,6-diyl Bis-alanine. – Acta Chem. Scand. 50: 316–322. © Acta Chemica Scandinavica 1996.

(*S,S*)-Pyridine-2,6-diyl bis-alanines **8** and **9** carrying protecting groups suitable for peptide synthesis have been synthesised from 2,6-pyridinedicarbaldehyde by the phosphonoglycine condensation route followed by catalytic hydrogenation with Rh{(COD)[(*R,R*)-DIPAMP]}BF<sub>4</sub>. The alternative route via double Heck coupling of 2,6-dibromopyridine and benzyl Boc-amidoacrylate was unsuccessful although mono-coupling could be achieved. The reasons for this failure are discussed as well as the failure of two mono-armed didehydroamino acid derivatives to undergo hydrogenation with Rh-bisphosphine catalysts. The CuCl<sub>2</sub> and RhCl<sub>3</sub> complexes of the bis-amino derivative **9** were prepared; a 20% e.e. was achieved in the cyclopropanation of styrene with ethyl diazoacetate using the Cu(II)-complex as a catalyst.

Aromatic bis-armed amino acids (ABAA) are found as subunits in several very interesting biologically active molecules. In particular, structures based on dimers of tyrosine and related amino acids (the acronym of ABAA of the phenyl alanine type is ABAAPs, see Fig. 1) have attracted great interest since they are present in a variety of peptide antibiotics such as vancomycin, teicoplanin, bouvardin, K-13 and others, and much synthetic effort has been directed toward the synthesis of these molecules.<sup>1,2</sup> Another area where ABAAPs have been used is in the studies of the biphenomycins or related compounds<sup>3–11</sup> and other structures.<sup>12–19</sup> It has also been found that the aromatic rings of the side chains of aromatic amino acids tend to assemble in domains in the

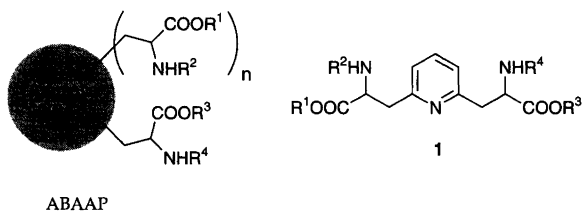


Fig. 1. Generalized formulas of the compounds discussed.

\* Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

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inner parts of proteins.<sup>20–24</sup> Thus, ABAAPs may mimic the structures created by non-covalent Ar–Ar interactions by cross-linking the peptide loops.

In addition to the applications of ABAAPs in these biologically related areas, they may be used as ligands for chelation with appropriate metals. The resulting complexes may be further used as chiral catalysts in asymmetric synthesis. Motivated by all of these possibilities we developed, several years ago, a two-step method for the synthesis of protected phenylene bis-alanines and related compounds.<sup>5,25–28</sup> In the first step, a double Heck coupling was performed between an aromatic dihalide and a suitably protected amidoacrylate under modified Heck reaction conditions<sup>29,30</sup> leading to bis-didehydroamino acid derivatives, largely of *Z,Z*-configuration. In the second step these bis-didehydroamino acid derivatives were hydrogenated in the presence of chiral homogeneous catalysts. This route is attractive since both steps are catalytic and the amidoacrylates may be obtained carrying many different protecting groups. In contrast with many other methods for amino acid synthesis this route is mild enough to allow delicate and useful protecting groups to be present during the entire operation.

While employing this strategy to synthesise pyridine-2,6-diyl bis-alanine and its derivatives (**1**) from 2,6-dibromopyridine, we found in the literature that

Table 1. Result of the Heck coupling experiments of **3** and **4**.

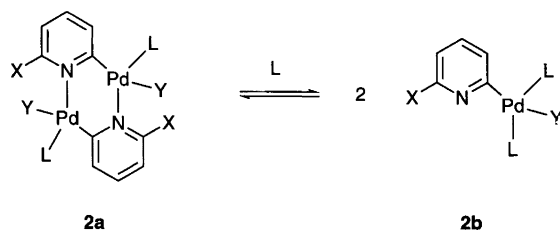
Entry	Starting material	<b>4</b> /equiv.	Pd-cat. (mol%)	PPh <sub>3</sub> /equiv.	Yield of <b>5</b> (%)
1	<b>3a</b>	<b>3</b>	Pd(OAc) <sub>2</sub> (6)	0	28
2	<b>3a</b>	1.5	Pd(OAc) <sub>2</sub> (100)	0	30
3	<b>3a</b>	1.5	Pd(OAc) <sub>2</sub> (6)	0.4	0
4	<b>3a</b>	1.5	Pd(OAc) <sub>2</sub> (6)	0.1	0
5	<b>3a</b>	1.5	Pd(OAc) <sub>2</sub> (6)	0.01	20
6	<b>3a</b>	1.5	Pd <sub>2</sub> (dba) <sub>3</sub> (3)	0	20
7	<b>3b</b>	2.9	Pd(OAc) <sub>2</sub> (6)	0	20
8	<b>3b</b>	1.5	Pd <sub>2</sub> (dba) <sub>3</sub> (3)	0	17
9	<b>3c</b>	1.5	Pd(OAc) <sub>2</sub> (6)	0	20
10	<b>3d</b>	1.5	Pd(OAc) <sub>2</sub> (3)	0	0
11	<b>3e</b>	1.5	Pd(OAc) <sub>2</sub> (6)	0	27
12	2,5-Dibromopyridine	2.9	Pd(OAc) <sub>2</sub> (6)	0	0

2-bromopyridine does not couple with methyl acetoacrylate under Heck reaction conditions.<sup>31</sup> This was explained by the formation of a stable dimeric Pd-complex **2** (X=H, Y=Br), after initial oxidative addition of palladium to the carbon-halogen bond, thus blocking further catalytic activity.

Such complexes have been studied<sup>32,33</sup> and, interestingly, although 2,6-dichloropyridine forms such a dimeric complex [**2** (X=Y=Cl), Scheme 1], the equilibrium lies mostly towards the monomer.<sup>34</sup> Moreover, it was found that the dimeric complex of 2,6-dichloropyridine is a much more efficient catalyst than that of 2-chloropyridine in the Pd-catalysed coupling of methylmagnesium bromide and 2-chloropyridine. When triphenylphosphine was added to the less reactive complex **2** (X=H, Y=Cl) it did work as a catalyst giving the same yield as with the dichloro complex **2** (X=Y=Cl). We therefore reasoned that the Pd-complex resulting from 2,6-dibromopyridine would not block the coupling with amidoacrylates, in contrast with that from 2-bromopyridine.

We present here our results on the Heck coupling of some substituted halopyridines together with attempts at catalytic hydrogenation of the resulting didehydroamino acid derivatives. Also reported is the successful enantioselective synthesis of Cbz, Me-protected pyridine-2,6-diyl-bis-alanine along with some preliminary experiments using the corresponding bis-amine **9** as a chiral ligand in the Cu-catalysed cyclopropanation of styrene with ethyl diazoacetate.

The Heck coupling of several halopyridines with benzyl Boc-amidoacrylate was attempted in the presence of



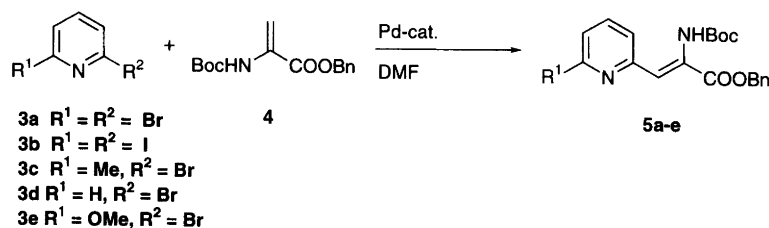
Scheme 1. Dimeric pyridine-Pd complexes formed from the oxidative addition products. L = ligand.

Pd(OAc)<sub>2</sub> or Pd<sub>2</sub>(dba)<sub>3</sub> as catalysts and the results are summarized in Scheme 2 and Table 1.\*

Unfortunately, the Heck reaction with 2,6-dibromopyridine (**1a**) or 2,6-diiodopyridine (**1b**) did not give rise to any bis-coupled product but did result in the mono-coupling products **5a** and **5b**, respectively, although in modest yields (entries 1, 5–8). Several variations of the reaction conditions did not improve the situation. As seen in the table the presence of a stoichiometric amount of the palladium catalyst did not significantly increase the yield (entry 2) and the presence of triphenylphosphine in more than catalytic amounts stopped the reaction (entries 3–5). Pd<sub>2</sub>(dba)<sub>3</sub> has been reported<sup>31</sup> to be a better catalyst than Pd(OAc)<sub>2</sub> but in our experiments no significant difference was found (entries 6 and 8). We could verify that 2-bromopyridine (**3d**) did not couple, nor did 2,5-dibromopyridine (entries 10 and 12). However, 2-bromo-6-methylpyridine (**3c**) and 2-bromo-6-methoxypyridine (**3e**) gave the mono-coupling product in about the same yield as 2,6-dibromopyridine (**3a**) (entries 9, 11).

The reluctance of **3a** and **3b** to undergo bis-coupling is in contrast with several examples in the benzene series where bis-coupling occurred even when the olefin was present in amounts of less than 2 equiv.<sup>27</sup> This and the negative Heck coupling results of **3d** and 2,5-dibromopyridine indicate that metal complexes such as **2** are formed, which involve the pyridine nitrogen. These data seem to be consistent with the idea that the increased bulk at the 6-position may prevent the metal from being trapped as a stable complex. Bis-coupling of 2,6-dibromopyridine with acetylenic groups in the presence of an amine base and copper(I) iodide as a co-catalyst have been reported.<sup>35,36</sup> However, these reac-

\* List of abbreviations: COD = 1,5-cyclooctadiene, NBD = norbornadiene, DIPAMP = 1,2-bis[(*o*-methoxyphenyl)phenylphosphino]ethane, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, PROPHOS = 1,2-bis(diphenylphosphino)propane, DPPE = 1,2-bis(diphenylphosphino)ethane, dba = dibenzylidene acetone, Cbz = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, Teoc = trimethylsilyloxyethyl, DNBPG = *N*-(3,5-dinitrobenzoyl)phenylglycine.



Scheme 2. Attempted Heck reactions with halopyridines.

tion conditions did not give any coupling products when applied to our reactions.

If additional coordinating atoms are introduced into the product it is possible that new complexes may be assembled, which trap the catalyst metal. Some of our products may do just this as indicated in Fig. 2 ( $M = \text{Pd}^{\text{II}}$  or  $\text{Pd}^0$ ). The didehydroamino acid side arm should have the capacity to act as a donor ligand and thus create a chelating system in combination with the pyridine nitrogen. In cases where stable complexes with the metal are formed the reaction is stopped or slowed down, which would explain why bis-coupling did not occur with **3a** and **3b**.

We earlier used similar reasoning to explain why *o*-bromiodobenzene gave only the mono-coupling product despite excess of the olefin, although in that case we invoked trapping of the palladium after the second oxidative addition step.<sup>27,28</sup> On increasing the reaction temperature a modest yield of the *N*-Boc-2-indolecarbonylate was obtained.

Even if the mono-coupling products had formed, other methods are obviously necessary for the preparation of bis-armed derivatives. Thus, the palladium-catalysed bis-coupling attempts on the pyridine system were abandoned and we turned instead to the phosphonoglycine condensation method as described by Schmidt *et al.*<sup>37,38</sup> Now the bis-didehydroamino acid derivative **7** was obtained from 2,6-diformylpyridine in excellent yield

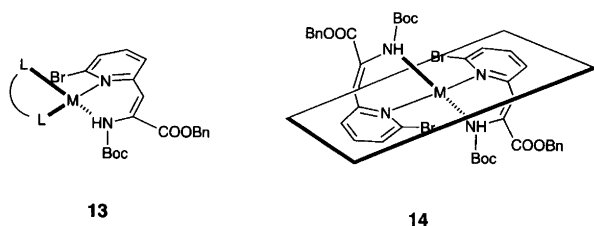
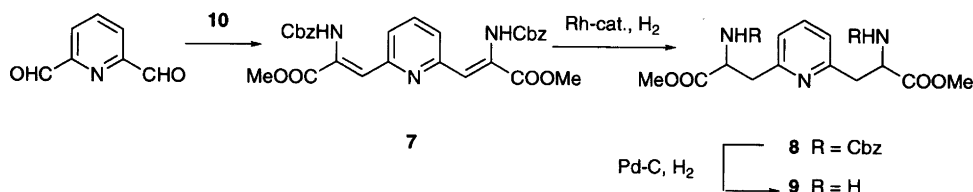


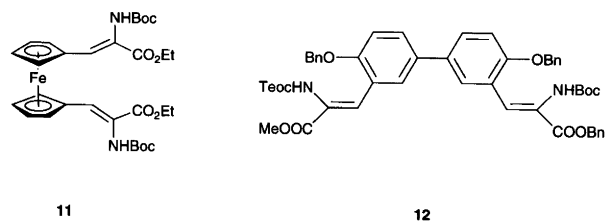
Fig. 2. For  $M = \text{Rh}$  (I), L-L is DPPE or DIPAMP; for  $M = \text{Pd}$  (II), L-L may be Br, Br; for  $M = \text{Pd}$  (0), L-L may be solvent or other neutral ligands.



Scheme 3.  $(\text{MeO})_2\text{OPCH}(\text{NHCBz})\text{COOMe}$  (**10**).

(Scheme 3) and in high stereoisomeric purity ( $>98\%$  *Z,Z*) as determined by chiral-phase HPLC (a DNBPG covalent column was used throughout).

In the peptide and amino acid area there are only a few examples reported of double asymmetric catalytic hydrogenation in the literature. Kagan and Poulin obtained a very high stereoselection (d.r. 98:2; e.e.  $>95\%$ ) using the  $\{\text{Rh}(\text{COD})[(R,R)\text{-DIPAMP}]\}\text{BF}_4$  catalyst on *N*-Ac $\Delta$ Phe $\Delta$ PheOMe<sup>39</sup> as did Ojima on the pentapeptide NAc $\Delta$ TyrAlaGly $\Delta$ PhelleOMe.<sup>40</sup> Our own results on the bis-didehydroferrocene derivative **11** using  $\{\text{Rh}(\text{NBD})[(R)\text{-PROPHOS}]\}\text{ClO}_4 \cdot 0.5\text{CH}_2\text{Cl}_2$  as hydrogenation catalyst gave only a low stereoselection (d.r. 62:38; e.e. 84%)<sup>26</sup> while the biphenomycin-related biphenyl derivative **12** gave essentially one enantiomer only using Rh-DIPAMP as a catalyst.<sup>41</sup>



In this work catalytic hydrogenation of **7** using the  $[\text{Rh}(\text{COD})(\text{DPPE})]\text{BF}_4$  catalyst gave a very pure product in high yield. The stereoisomeric distribution was determined by chiral-phase HPLC and is shown in Fig. 3. Obviously there are some interactions from one arm on the reduction of the other, since the amount of the *meso* compound is only 24% (diastereomeric ratio 76:24) while statistically it should be 50%. However, we do not know yet whether it is the unsaturated arm or the saturated arm that interacts in this case. Asymmetric hydrogenation of **7** using the  $\{\text{Rh}(\text{COD})[(R)\text{-BINAP}]\}\text{ClO}_4 \cdot \text{THF}$  catalyst (the commercial-grade catalyst was used directly) gave only a low yield of the hydrogenated product (46%). Chiral-phase HPLC analysis revealed that this product

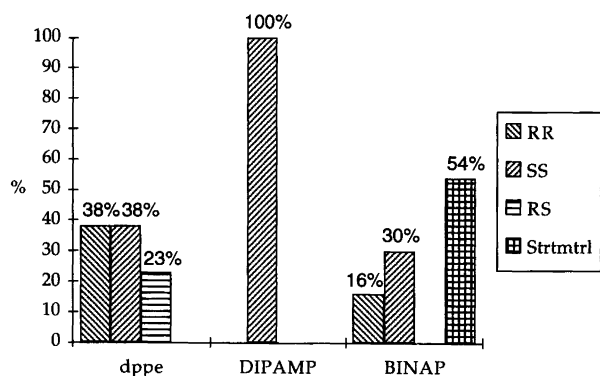


Fig. 3. Stereoisomeric distribution in the Rh-catalytic hydrogenation of **7** using different bis-phosphine ligands.

was diastereomerically pure but the e.e. was only *ca.* 30%. Finally, a high chemical yield of **8** with >99% e.e. was achieved with the use of the Rh-DIPAMP catalyst.

Attempts to hydrogenate the mono-armed amino acid derivatives **5a** and **5c** using the Rh-DPPE catalyst were unsuccessful. After our experiences with the Heck couplings of **3a** and **3b** this was not surprising and one may suspect that compounds **5a** and **5c** may trap the catalyst in the form of stable complexes **13** or **14** (M=Rh), essentially as mentioned above for the Pd-trapping. By building a model it is easy to construct complexes in which the metal atom is part of a six-membered ring if the carbamate nitrogen acts as a donor atom, perhaps by some degree of pyramidalisation.

Such complexes would be unable both to coordinate the olefin and undergo oxidative addition of hydrogen. However, there is a problem to explain why the bis-armed analogue gives excellent hydrogenation with high e.e., using the Rh-DIPAMP catalyst. This and other details of organometallic reactions of the above pyridines await further examination and we are now trying to isolate and determine the structures of complexes that may be formed in these reactions.

These speculations are somewhat supported since metal complexes of **9**, obtained by removal of the Cbz-groups of **8**, are easy to prepare, such as the CuCl<sub>2</sub> (**15**) and the RhCl<sub>3</sub> (**16**) complexes shown schematically in Fig. 4. Suitable crystals for X-ray crystallographic structure determination have not yet been obtained, but HRMS-data and elemental analyses as well as NMR spectral data for **16** support the suggested structures.

As mentioned, we were interested to find out whether

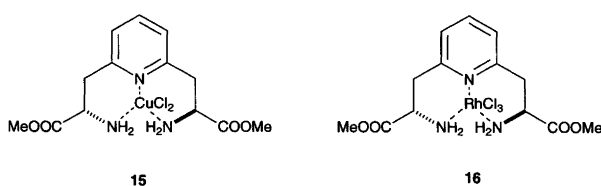
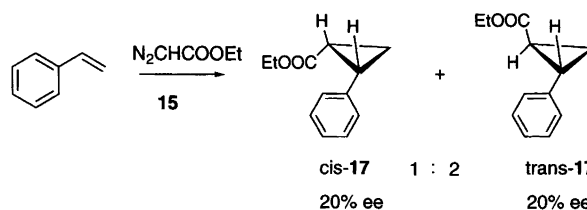


Fig. 4. The complexes are shown without solvents of crystallisation.



Scheme 4. Catalytic asymmetric cyclopropanation using the complex **15** as catalyst.

complexes based on the bis-armed pyridine structure might be useful in asymmetric catalysis. We therefore chose, as a suitable test reaction, the cyclopropanation of styrene with ethyl diazoacetate, since complexes reminiscent of **15** and **16** work very well in this reaction according to the literature.<sup>42-44</sup> (Scheme 4). To date our results are not particularly impressive: the copper complex **15** gave 20% e.e. in both the *trans*- and the *cis*-cyclopropanes **17** as determined by chiral-phase GLC. Nevertheless, these modest results are still an indication that it may be worthwhile to investigate further the application of complexes based on the bis-armed pyridinediyl-alanines to other reactions, where asymmetric catalysis can be expected.

In conclusion, we have demonstrated that pyridine-2,6-diyl bis-alanines may be easily prepared in optically pure form via the phosphonoglycine condensation route followed by asymmetric hydrogenation using Rh{(COD)}[(*R,R*)DIPAMP]}BF<sub>4</sub> as a catalyst. Metal complexes of pyridinediyl bis-alanines may be useful in asymmetric catalysis although this area has yet to be developed further. Also, mono-Heck coupling of 2,6-dibromo-, 2,6-diiodo-, 2-bromo-6-methyl and 2-bromo-6-methoxypyridine with benzyl Boc-amidoacrylate is possible. Didehydroamino acid derivatives **5a** and **5c** resisted catalytic hydrogenation under our standard conditions. Further investigations in this area are being actively pursued.

## Experimental

TLC analyses were performed on silica gel plates (Merck, Kieselgel 60 F<sub>254</sub>), and for column chromatography Matrex<sup>TM</sup> (35–70 mm) silica gel was used. HPLC analyses were performed using Nucleosil SiO<sub>2</sub> columns and for stereoisomer determinations a Baker DNBPG chiral (covalent) column was used. Melting points are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian XL 300 spectrometer, operating at 300 and 75.43 MHz, respectively, and the chemical shifts are measured with reference to tetramethylsilane (TMS). Mass spectra were recorded on a JEOL JMX-DX 303 mass spectrometer. Optical rotations were measured with a Perkin Elmer 141 polarimeter at the sodium D-line and at ambient temperature. IR spectra were recorded with a Perkin Elmer 298 infrared spectrophotometer. Elemental analyses were done at Mikro Kemi AB, Uppsala,

Sweden. 2-Bromo-, 2,6-dibromo-, 2,5-dibromo-, and 2,6-diformylpyridine were commercial products and used as received.

**2-Bromo-6-methylpyridine (3c).** Methyl lithium (3.5 ml, 1.6 M in ether) was added dropwise to a solution of 2,6-dibromopyridine (1.20 g, 5.06 mmol) in dry diethyl ether (65 ml) at  $-25^{\circ}\text{C}$  and the resulting mixture was stirred for 2 h. During the next 2 h the temperature was gradually raised to  $0^{\circ}\text{C}$  and then water was added. The ether layer was washed with water ( $3 \times 15$  ml), dried and evaporated to afford a dark brown oil, which was chromatographed [ $\text{SiO}_2$ ; heptane- $\text{CH}_2\text{Cl}_2$  (8:2)] to give **3c** (0.51 g, 59%); b.p.  $100\text{--}104^{\circ}\text{C}/20$  mmHg (lit.<sup>45</sup> b.p.  $102\text{--}103^{\circ}\text{C}/20$  mmHg).

**2-Bromo-6-[2-(tert-butoxycarbonylamino)-2-(benzyloxycarbonyl)ethenyl]pyridine (5a).** A mixture of 2,6-dibromopyridine (237 mg, 1.00 mmol), benzyl (2-tert-butoxycarbonylamino)acrylate **4**<sup>25</sup> (821 mg, 2.96 mmol),  $\text{Pd}(\text{OAc})_2$  (14 mg, 0.062 mmol),  $\text{Bu}_4\text{NCl}$  (278 mg, 1.00 mmol),  $\text{NaHCO}_3$  (210 mg, 2.50 mmol) in DMF (12 ml) was heated with stirring under nitrogen at  $80^{\circ}\text{C}$  for 18 h. The reaction mixture was cooled, diluted with water (25 ml) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 25$  ml). The combined organic phases were washed with water ( $2 \times 10$  ml), brine ( $1 \times 10$  ml), and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent left a dark brown residue, which was chromatographed [ $\text{SiO}_2$ ; heptane-EtOAc (9:1)] to give **5a** (120 mg, 28%) as a colourless viscous oil. TLC  $R_f=0.17$  (heptane-EtOAc 9:1). IR (film): 3240, 1734, 1720, 1635.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.49 (s, 9 H, *t*-Bu), 5.28 (s, 2 H, Ph- $\text{CH}_2$ ), 6.12 (s, 1 H, olefinic-H), 7.10 (d, 1 H,  $J$  7.5 Hz, Ar-H), 7.27-7.50 (m, 7 H, Ar-H), 10.32 (s, 1 H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.02, 67.54, 81.13, 110.26, 123.25, 125.72, 126.81, 128.21, 128.39, 135.16, 135.29, 138.83, 140.15, 152.25, 155.73, 164.99. MS ( $\text{EI}^+$ ):  $m/z$  432. HRMS ( $\text{FAB}^+$ ): obs. 433.0797,  $M+H$  calc. 433.0764.

**2-Iodo-6-[2-(tert-butoxycarbonylamino)-2-(benzyloxycarbonyl)ethenyl]pyridine (5b).** The reaction was performed according to the procedure described for **5a**. The crude product obtained from 2,6-diiodopyridine<sup>46</sup> (331 mg, 1.00 mmol) was chromatographed [ $\text{SiO}_2$ ; heptane-EtOAc (8:2)] to give pure **5b** (80 mg, 17%) as a viscous oil. TLC  $R_f=0.13$  (heptane-EtOAc 9:1). IR (film): 3235, 2985, 1735, 1720, 1630.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.50 (s, 9 H, *t*-Bu), 5.29 (s, 2 H, Ph- $\text{CH}_2$ ), 6.08 (s, 1 H, olefinic-H), 7.14 (d, 1 H,  $J$  7.8 Hz, Py-H), 7.28-7.42 (m, 6 H, Py-H and Ar-H), 7.53 (d, 1 H,  $J$  7.8 Hz, Py-H), 10.43 (1 H, s, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.09, 67.62, 81.13, 110.23, 115.61, 123.67, 128.26, 128.44, 128.47, 132.39, 135.24, 135.37, 137.92, 152.34, 156.36, 165.05. HRMS ( $\text{FAB}^+$ ): obs. 481.0618,  $M+H$  calc. 481.0624.

**2-Methyl-6-[2-(tert-butoxycarbonylamino)-2-(benzyloxycarbonyl)ethenyl]pyridine (5c).** The crude product obtained from the reaction of **3c** (86 mg, 0.50 mmol) with **4** (205 mg, 0.740 mmol) performed as above, was chromatographed [ $\text{SiO}_2$ ; heptane-EtOAc (9:1)] to give **5c** (37 mg, 20%). TLC  $R_f=0.31$  (heptane-EtOAc 8:2). IR (film): 3300, 1735, 1722, 1635.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.48 (s, 9 H, *t*-Bu), 2.55 (s, 3 H, Py- $\text{CH}_3$ ), 5.29 (s, 2 H, Ph- $\text{CH}_2$ ), 6.21 (s, 1 H, olefinic-H), 7.00 (dd, 2 H,  $J$  7.8 Hz,  $J$  2.4 Hz, Py-3-H and Py-5-H), 7.27-7.45 (m, 5 H, Ar-H), 7.55 (t, 1 H,  $J$  7.8 Hz, Py-4-H), 11.35 (s, 1 H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  24.35, 28.17, 67.40, 80.73, 112.30, 121.36, 122.17, 128.19, 128.45, 134.27, 135.62, 136.95, 152.80, 154.46, 157.03, 165.45. HRMS ( $\text{FAB}^+$ ): obs. 369.1815,  $M+H$  calc. 369.1814.

**2-Methoxy-6-[2-(tert-butoxycarbonylamino)-2-(benzyloxycarbonyl)ethenyl]pyridine (5e).** The crude product obtained from the reaction of **3e**<sup>46</sup> (76 mg, 0.40 mmol) with **4** (170 mg, 0.614 mmol) performed as above, was chromatographed [ $\text{SiO}_2$ ; heptane-EtOAc 9:1] to give **5e** (41 mg, 27%). TLC  $R_f=0.21$  (heptane-EtOAc 8:2). IR (film): 3205, 2970, 1722, 1636.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.47 (s, 9 H, *t*-Bu), 3.98 (s, 3 H, Py- $\text{OCH}_3$ ), 5.30 (s, 2 H, Ph- $\text{CH}_2$ ), 6.25 (s, 1 H, olefinic-H), 6.65 (d, 1 H,  $J$  7.8 Hz, Py-H), 6.82 (d, 1 H,  $J$  7.8 Hz, Py-H), 7.33-7.46 (m, 5 H, Ar-H), 7.56 (t, 1 H,  $J$  7.8 Hz, Py-4-H), 10.91 (s, 1 H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.10, 53.49, 67.49, 80.76, 110.04, 113.19, 118.27, 128.22, 128.44, 128.49, 133.44, 135.50, 139.24, 152.07, 152.45, 162.65, 165.18. HRMS ( $\text{FAB}^+$ ): obs. 385.1772,  $M+H$  calc. 385.1763.

**2,6-Bis-[2-(benzyloxycarbonylamino)-2-(methoxycarbonyl)ethenyl]pyridine (7).** A solution of 2,6-pyridinedicarbaldehyde (1.0 g, 7.4 mmol) in THF (10 ml) was added dropwise to a stirred solution of phosphonate ester **10**<sup>37</sup> (5.70 g, 17.2 mmol) and tetramethylguanidine (1.98 g, 17.2 mmol) in THF (40 ml) at  $0^{\circ}\text{C}$ . The mixture was stirred at  $0^{\circ}\text{C}$  for 4 h and then at room temperature overnight. The solvent and volatiles were evaporated off *in vacuo* and the residue was partitioned between EtOAc (100 ml) and water ( $2 \times 25$  ml). The organic extract was washed with brine ( $1 \times 25$  ml) and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of the solvent left a semi-solid residue which was crystallized twice from methanol-benzene to yield **7** (2.5 g, 62%). Further batch of pure **7** (1.25 g, 31%) was obtained by chromatography of the residue from the mother liquor [ $\text{SiO}_2$ ; heptane-EtOAc (3:1)]. TLC  $R_f=0.29$  (heptane-EtOAc 3:2). M.p.  $130\text{--}131^{\circ}\text{C}$  (from acetone-hexane). IR (KBr): 3310, 2948, 1740, 1720, 1638.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.81 (s, 6 H,  $\text{COOCH}_3$ ), 5.01 (s, 4 H, Ph- $\text{CH}_2$ ), 6.70 (s, 2 H, olefinic-H), 7.14 (d, 2 H,  $J$  7.8 Hz, Py-3-H and Py-5-H), 7.28-7.33 (m, 8 H, Ar-H), 7.66 (t, 1 H,  $J$  7.8 Hz, Py-4-H), 9.07 (s, 2 H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  52.68, 67.64, 118.44, 123.98, 128.2, 128.37, 128.47, 130.69, 135.51, 137.32, 152.9, 153.28, 165.13. Anal. C, H, N.

(+)-(S,S)-2,6-Bis-[2-(benzyloxycarbonylamino)-2-(methoxycarbonyl)ethyl]pyridine [(+)-**8**]. Compound **7** (1.80 g, 3.30 mmol) and Rh{(COD)}[(R,R)DIPAMP]}-BF<sub>4</sub> (65 mg, 0.085 mmol, 2.5 mol%) were combined in degassed MeOH (75 ml) and pressurized to 65 psi with H<sub>2</sub>. The reduction was carried out at 45 °C for 60 h. The solvent was then evaporated off and the residue was purified by column chromatography [SiO<sub>2</sub>; heptane-EtOAc (1:1)] to give (+)-**8** (1.7 g, 94%) as colourless crystalline solid. [ $\alpha$ ]<sub>D</sub><sup>25</sup> +27.9° (c 2.60, CHCl<sub>3</sub>). M.p. 89 °C (hexane-ether). Chiral phase HPLC analysis (DNBPG covalent) displayed one peak (solvent: hexane-2-PrOH (9:1); flow rate: 0.75 ml min<sup>-1</sup>; t<sub>R</sub>=31.53 min). IR (KBr): 3282, 1743, 1710, 1677. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.20–3.34 (m, 4 H, PyCH<sub>2</sub>), 3.68 (s, 6 H, COOCH<sub>3</sub>), 4.82–4.86 (m, 2 H, N-CH-COO), 4.98 (q, 4 H, J 12.45 Hz, PhCH<sub>2</sub>), 6.18 (d, 2 H, J 8.4 Hz, NH), 6.93 (d, 2 H, J 7.5 Hz, Py-3-H and Py-5-H), 7.25 (m, 10 H, Ar-H), 7.45 (t, 1 H, J 7.5 Hz, Py-4-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 39.59, 52.34, 52.97, 66.66, 121.91, 127.85, 128.30, 136.40, 136.99, 156.00, 156.29, 172.37. Anal. C, H, N.

The same procedure was applied using {Rh(COD)}[(R)-[BINAP]}ClO<sub>4</sub>·THF as catalyst, which gave a mixture of the enantiomers (R,R):(S,S) 16%:30% together with 54% of unchanged starting material (Fig. 2).

(±)-2,6-Bis-[2-(benzyloxycarbonylamino)-2-(methoxycarbonyl)ethyl]pyridine [(±)-**8**]. Hydrogenation of **7** (55 mg, 0.10 mmol) was performed as above using [Rh(COD)(DPPE)]BF<sub>4</sub> (4 mg, 0.005 mmol, 5 mol%), which, after chromatography, afforded (±)-**8** (55 mg, 98%) as a viscous liquid. Chiral phase HPLC analysis [DNBPG covalent; solvent: n-hexane-2-PrOH (9:1); flow rate: 0.75 ml min<sup>-1</sup>] displayed three peaks (t<sub>R</sub>=31.016, 32.296 and 34.496 min). Co-injection with (+)-**8** enhanced the middle peak. The <sup>1</sup>H NMR data for the (±)-form were identical with those of (+)-**8**. <sup>1</sup>H NMR data for meso-**8** (CDCl<sub>3</sub>): δ 4.74–5.07 (m, 6 H, -CH- and benzylic CH<sub>2</sub>), 6.02 (d, 1 H, J 8.2 Hz, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ (only the peaks that came separately from its diastereomer are noted) 39.08, 53.23, 53.32, 121.95, 127.90, 128.34, 136.34, 137.15, 155.82, 172.21.

Hydrogenation experiments using the Rh-DPPE catalyst as above with the mono-armed derivatives **5a** and **5c** were unsuccessful.

(-)-(S,S)-2,6-Bis-[2-amino-2-(methoxycarbonyl)ethyl]pyridine [(-)-**9**]. A solution of (+)-**8** (670 mg, 1.22 mmol) in MeOH (20 ml) was hydrogenated in the presence of Pd-C (10%, 100 mg) at 1 atm pressure and room temperature. Uptake of the calculated amount of H<sub>2</sub> was completed after 24 h. The catalyst was then filtered off, the solvent was evaporated and the residue was purified by column chromatography [SiO<sub>2</sub>; toluene-methanol (8:2) and 0.2% of NEt<sub>3</sub>] to afford **9** (310 mg, 90%) as a pale yellow viscous oil, which solidified on standing. M.p. 75–76 °C, [ $\alpha$ ]<sub>D</sub><sup>25</sup> -4.2° (c 1.1, CHCl<sub>3</sub>) IR (KBr): 3368, 1730, 1594. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.73 (brs,

4 H, NH<sub>2</sub>), 3.05 (dd, 2 H, J 14.1 Hz, J 7.8 Hz, PyCH), 3.22 (dd, 2 H, J 14.1 Hz, J 4.8 Hz, PyCH), 3.72 (s, 6 H, COOCH<sub>3</sub>), 3.99 (dd, 2 H, J 7.8 Hz, J 4.8 Hz, N-CH-COO), 7.00 (d, 2 H, J 7.8 Hz, Py-3-H and Py-5-H), 7.52 (t, 1 H, J 7.8 Hz, Py-4-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 42.26, 51.97, 53.96, 121.79, 136.77, 157.35, 175.69. MS (FAB<sup>+</sup>): m/z 282. HRMS (EI<sup>+</sup>): obs. 281.1370, calc. 281.1375.

*Preparation of the CuCl<sub>2</sub> complex 15·0.5 THF·0.5 H<sub>2</sub>O.* A solution of CuCl<sub>2</sub>·2H<sub>2</sub>O (31.0 mg, 0.182 mmol) in THF (1 ml) and one drop of water was added to a stirred solution of (-)-**9** (51.2 mg, 0.182 mmol) in THF (1.5 ml) under N<sub>2</sub>. The mixture was stirred at room temperature for 2 h, after which the precipitated solid was filtered off, washed with THF and dried. Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O afforded the title complex (72 mg, 87%). M.p. 181–182 °C. IR (KBr) 3300, 3260, 3180, 1725, 1600, 1570, 1465, 1260, 1210, 1068, 808. Anal. C, H, N. HRMS (FAB<sup>+</sup>): obs. 379.0360, M-Cl+H (C<sub>13</sub>H<sub>19</sub>ClCuN<sub>3</sub>O<sub>3</sub>), calc. 379.0360.

*Preparation of RhCl<sub>3</sub> complex 16·MeOH.* A solution of (-)-**9** (50.1 mg, 0.178 mmol) and RhCl<sub>3</sub>·3H<sub>2</sub>O (47.9 mg, 0.178 mmol) in MeOH (3.5 ml) was stirred under argon for 2 h at room temperature and then heated under gentle reflux for 1 h. The volatiles were removed *in vacuo* and the residue was purified by chromatography [SiO<sub>2</sub>; EtOAc-MeOH (19:1)] to furnish **16**·MeOH (60 mg, 67%) as an orange solid. M.p. >280 °C (decomp.) (recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O as orange needles). [ $\alpha$ ]<sub>D</sub><sup>25</sup> +206° (c 0.550, CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr): 3300, 3210, 1725, 1603, 1576, 1465, 1430, 1312, 1300, 1218, 1092, 910, 810. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.51 (dd, 2 H, J 15.3 Hz, J 1.2 Hz, PyCH), 3.69 (dt, 2 H, J 12.0 Hz, J 4.5 Hz, PyCH), 3.90 (s, 6 H, COOCH<sub>3</sub>), 3.98 (dd, 2 H, J 15.3 Hz, J 11.4 Hz, N-CH-COO), 4.75 (m, 2 H, NH), 5.07 (m, 2 H, NH), 7.37 (d, 2 H, J 7.8 Hz, Py-3-H and Py-5-H), 7.81 (t, 1 H, J 7.8 Hz, Py-4-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 40.89, 52.44, 53.57, 126.41, 139.39, 161.45, 169.50. Anal. C, H, N. HRMS (FAB<sup>+</sup>): obs. 488.9496, M+H (C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>RhCl<sub>3</sub>), calc. 488.9496.

*Cyclopropanation of styrene with ethyl diazoacetate in the presence of 15·0.5 THF·0.5 H<sub>2</sub>O.* Ethyl diazoacetate (250 mg, 2.19 mmol) in styrene (250 mg) was added dropwise over a period of 1 h to a stirred mixture of styrene (260 mg, 2.49 mmol) and the copper complex **15**·0.5THF·0.5H<sub>2</sub>O (10 mg, 0.024 mmol, 1 mol%) at 55 °C under N<sub>2</sub>. When the addition was complete, the reaction mixture was stirred for another 2 h at 55 °C. After cooling, the material was chromatographed [SiO<sub>2</sub>; first heptane then heptane-EtOAc (19:1)], which gave a mixture of *cis*- and *trans*-cyclopropanes **17** (225 mg, 65%). From <sup>1</sup>H NMR (CDCl<sub>3</sub>), the ratio of *cis*:*trans* was found to be 1:2.2. This mixture was separated by HPLC [SiO<sub>2</sub> Nucleosil; heptane-EtOAc (97:3)]. Both *cis* and *trans* derivatives were then analysed by chiral-phase GC (Alpha-Dex 120, from Supelco) and found to

have ca. 20% e.e. in both isomers. The  $t_R$  values at 100 °C for the *cis* isomers were 119.12 and 120.22 min, and for the *trans* isomers 171.73 and 173.69 min. The isolated *cis*- and *trans*-cyclopropane derivatives had NMR data in accordance with literature values except for the chemical shift of 1-H of *trans*-17, which we recorded at 1.59 ppm in contrast with the reported 2.52 ppm.<sup>47</sup>

**Acknowledgements.** We thank The Swedish Natural Science Research Council for economic support and for a post-doctoral fellowship to B. B. We are also grateful to G. D. Searle & Co. for generous gifts of Rh{(COD)}[(*R,R*)-DIPAMP]}BF<sub>4</sub>.

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Received September 25, 1995.