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-diyi Bis-alanine*

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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 ABAAAs 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.1,2 Another area where ABAAPs have been used is in the studies of the bipheromycins or related compounds3-11 and other structures.12-19 It has also been found that the aromatic rings of the side chains of aromatic amino acids tend to assemble in domains in the inner parts of proteins.20-24 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.5,25-28 In the first step, a double Heck coupling was performed between an aromatic dihalide and a suitably protected amidoacrylate under modified Heck reaction conditions29,30 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-diyi bis-alanine and its derivatives (I) from 2,6-dibromopyridine, we found in the literature that

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Fig. 1. Generalized formulas of the compounds discussed.
2-bromopyridine does not couple with methyl acetamidoacrylate under Heck reaction conditions.\textsuperscript{31} 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\textsuperscript{32,33} and, interestingly, although 2,6-dichloropyridine forms such a dimeric complex [2 (X = Y = Cl)], Scheme 1], the equilibrium lies mostly towards the monomer.\textsuperscript{34} 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 amidocarboxylic acids, 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 dihydroxy amino acid derivatives. Also reported is the successful enatioselective synthesis of Cbz, Me-protected pyridine-2,6-diy-l-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 Pd(OAc)\textsubscript{2} or Pd(db), 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-diodopyridine (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(db)\textsubscript{2} has been reported\textsuperscript{31} to be a better catalyst than Pd(OAc)\textsubscript{2} 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 monocoupling 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.\textsuperscript{27} 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(1) iodide as a co-catalyst have been reported.\textsuperscript{35,36} However, these reac-

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* List of abbreviations: CODE = 1,5-cyclooctadiene, NBD = norbornadiene, DIPAMP = 1,2-bis[2-methoxyphenyl]phenylphosphino]ethane, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, PROPHOS = 1,2-bis(diphenylphosphino)propane, DPPE = 1,2-bis(diphenylphosphino)ethane, db = dibenzylidene acetone, Cbz = benzoyloxycarbonyl, Boc = tert-butyloxycarbonyl, Tcoc = trimethylsilylhexyloxycarbonyl, DNBPG = N-(3,5-dinitrobenzoyl)phenylglycine.
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 = Pd⁰ or Pd³). The dihydroamino 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-bromoisodobenzene 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. On increasing the reaction temperature a modest yield of the N-Boc-2-indolecarboxylate 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. Now the bis-dihydroamino acid derivative 7 was obtained from 2,6-diformylpyridine in excellent yield (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 acid 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) using the [Rh(COD)[(R,R)-DIPAMP]]BF₄ catalyst on N-AcAlaValGluNHMe as did Ojima on the pentapeptide NAcΔTrpAlaGlyΔPheleOmMe. Our own results on the bis-dihydroferrocene derivative 11 using [Rh(NBD)[((R)-PROPHOS)]ClO₄·0.5CH₂Cl₂ as hydrogenation catalyst gave only a low stereoselection (d.r. 62:38; e.e. 8%)(28) while the biphenylmocin-related biphenyl derivative 12 gave essentially one enantiomer only using Rh-DIPAMP as a catalyst.⁴¹

In this work catalytic hydrogenation of 7 using the [Rh(COD)(DPPE)]BF₄ 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 [Rh(COD)[(R)-BINAP]]ClO₄·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
was diasteromerically 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.

Such 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 CuCl₂ (15) and the RhCl₃ (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 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.⁴²–⁴⁴ 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 pyridinediyal-alanines to other reactions, where asymmetric catalysis can be expected.

In conclusion, we have demonstrated that pyridine-2,6-diyal bis-alanines may be easily prepared in optically pure form via the phosphonoglucose condensation route followed by asymmetric hydrogenation using Rh(COD)2[(R,R)-DIPAMP]BF₄ as a catalyst. Metal complexes of pyridinediyal bis-alanines may be useful in asymmetric catalysis although this area has yet to be developed further. Also, mono-Heck coupling of 2,6-dibromocyclohexane, 2,6-diiodo-2,2-dibromo-2,2-dimethyl 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 F₂₅₄), and for column chromatography Matrix™ (35–70 mm) silica gel was used. HPLC analyses were performed using Nuclear SiO₂ columns and for stereoisomer determinations a Baker DNBP chiral (covalent) column was used. Melting points are uncorrected.¹H and ¹³C 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 (3e). Methylithium (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 diethylether (65 ml) at −25°C and the resulting mixture was stirred for 2 h. During the next 2 h the temperature was gradually raised to 0°C and then water was added. The ether layer was washed with water (3 × 15 ml), dried and evaporated to afford a dark brown oil, which was chromatographed [SiO₂; heptane–CH₂Cl₂ (8:2)] to give 3e (0.51 g, 59%); b.p. 100–104°C/20 mmHg (lit. 45 45 b.p. 102–103°C/20 mmHg).

2-Bromo-6-[2-(tert-butoxycarbonylamo)-2-(benzylloxycarbonyl) ethenyl]pyridine (5a). A mixture of 2,6-dibromopyridine (237 mg, 1.00 mmol), benzyl (2-tert-butoxycarbonylamo)acrylate 42 (821 mg, 2.96 mmol), Pd(OAc)₂ (14 mg, 0.062 mmol), Bu₃NCl (278 mg, 1.00 mmol), NaHCO₃ (210 mg, 2.50 mmol) in DMF (12 ml) was heated with stirring under nitrogen at 80°C for 18 h. The reaction mixture was cooled, diluted with water (25 ml) and extracted with CH₂Cl₂ (3 × 25 ml). The combined organic phases were washed with water (2 × 10 ml), brine (1 × 10 ml), and dried over Na₂SO₄. Evaporation of the solvent left a dark brown residue, which was chromatographed [SiO₂; heptane–EtOAc (9:1)] to give 5a (120 mg, 28%) as a colourless viscous oil. TLC Rf = 0.17 (heptane–EtOAc 9:1). IR (film): 3240, 1734, 1720, 1635. ¹H NMR (CDCl₃): δ 1.49 (s, 9 H, t-Bu), 5.28 (s, 2 H, PhCH₂), 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). ¹³C NMR (CDCl₃): δ 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 (EI⁺): m/z 432. HRMS (FAB⁺): obs. 433.0797, M + H calc. 433.0764.

2-Isodo-6-[2-(tert-butoxycarbonylamino)-2-(benzoxlyoxycarbonyl) ethenyl]pyridine (5b). The reaction was performed according to the procedure described for 5a. The crude product obtained from 2,6-diodopyridine 46 (331 mg, 1.00 mmol) was chromatographed [SiO₂; heptane–EtOAc (8:2)] to give pure 5b (80 mg, 17%) as a viscous oil. TLC Rf = 0.13 (heptane–EtOAc 9:1). IR (film): 3235, 2985, 1735, 1720, 1630. ¹H NMR (CDCl₃): δ 1.50 (s, 9 H, t-Bu), 5.29 (s, 2 H, PhCH₂), 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). ¹³C NMR (CDCl₃): δ 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 (FAB⁺): obs. 481.0618, M + H calc. 481.0624.

2-Methoxy-6-[2-(tert-butoxycarbonylamino)-2-(benzoxlyoxycarbonyl) ethenyl]pyridine (5e). 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 [SiO₂; heptane–EtOAc (9:1)] to give 5e (37 mg, 20%). TLC Rf = 0.31 (heptane–EtOAc 8:2). IR (film): 3300, 1735, 1722, 1635. ¹H NMR (CDCl₃): δ 1.48 (s, 9 H, t-Bu), 2.55 (s, 3 H, Py-Ch₂), 5.29 (s, 2 H, PhCH₂), 6.21 (s, 1 H, olefinic-H), 7.00 (dd, 2 H, J 7.8 Hz, J 2.4 Hz, Py-3 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). ¹³C NMR (CDCl₃): δ 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 (FAB⁺): obs. 369.1815, M + H calc. 369.1814.

2-Methoxy-6-[2-(tert-butoxycarbonylamino)-2-(benzoxlyoxycarbonyl) ethenyl]pyridine (7). A solution of 2,6-pyrindinedicarbaldehyde (1.0 g, 7.4 mmol) in THF (10 ml) was added dropwise to a stirred solution of phosphonate ester 10³⁷ (5.70 g, 17.2 mmol) and tetramethylguanidine (1.98 g, 17.2 mmol) in THF (40 ml) at 0°C. The mixture was stirred at 0°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 × 25 ml). The organic extract was washed with brine (1 × 25 ml) and dried (Na₂SO₄). 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 [SiO₂; heptane–EtOAc (3:1)]. TLC Rf = 0.29 (heptane–EtOAc 3:2). M.p. 130–131°C (from acetone–hexane). IR (KBr): 3310, 2948, 1740, 1720, 1638. ¹H NMR (CDCl₃): δ 3.81 (s, 6 H, COOCH₃), 5.01 (s, 4 H, PhCH₂), 6.70 (s, 2 H, olefinic-H), 7.14 (d, 2 H, J 7.8 Hz, Py-3 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). ¹³C NMR (CDCl₃): δ 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-(benzoxycarbonylamino)-2-(methoxycarbonyl)ethyl] pyridine [(+)-8]. Compound 7 (1.80 g, 3.30 mmol) and Rh(B(n-COD)(R,R)(DIPAMP))-BF₄⁻ (65 mg, 0.085 mmol, 2.5 mol%) were combined in degassed MeOH (75 ml) and pressurized to 65 psi with H₂. 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 [SiO₂; heptane-EtOAc (1:1)] to give (+)-8 (1.7 g, 94%) as colourless crystalline solid. [α]D²⁰ +27.9° (c 2.60, CHCl₃). M.p. 89 °C (hexane-ether). Chiral phase HPLC analysis (DNBP covalent) displayed one peak (solvent: hexane-2-ProOH (9:1); flow rate: 0.75 ml min⁻¹; tR = 31.53 min). IR (KBr): 3282, 1743, 1710, 1677. ¹H NMR (CDCl₃): δ 3.20-3.34 (m, 4 H, Py-CH₃), 3.68 (s, 6 H, COOCH₃), 4.82-4.86 (m, 2 H, N-CH₂-COO), 4.98 (q, 4 H, J 12.14 Hz, PhCH₂), 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). ¹³C NMR (CDCl₃): δ 39.59, 52.34, 52.97, 66.66, 121.91, 127.85, 128.30, 136.40, 136.99, 156.00, 156.29, 172.27. Anal. C, H, N.

The same procedure was applied using [Rh(COD)(R)-[BINAP]]ClO₄ 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-(benzoxycarbonylamino)-2-(methoxycarbonyl)ethyl] pyridine [(+)-8]. Hydrogenation of 7 (55 mg, 0.10 mmol) was performed as above using [Rh(COD)(DPEP)]BF₄⁻ (4 mg, 0.005 mmol, 5 mol%). which, after chromatography, afforded (+)-8 (55 mg, 98%) as a viscous liquid. Chiral phase HPLC analysis (DNBP covalent: solvent: n-hexane-2-ProOH (9:1); flow rate: 0.75 ml min⁻¹) displayed three peaks (tR = 31.06, 32.296 and 34.496 min). Co-injection with (+)-8 enhanced the middle peak. The ¹H NMR data for the (+)-form were identical with those of (+)-8. ¹H NMR data for meso-8 (CDCl₃): δ 4.74-5.07 (m, 6 H, CH₃- and benzyl CH₃), 6.02 (d, 1 H, J 8.2 Hz, NH). ¹³C NMR (CDCl₃): 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, 158.82. 172.21.

Hydrogenation experiments using the Rh-DPEP 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 H₂ was completed after 24 h. The catalyst was then filtered off, the solvent was evaporated and the residue was purified by column chromatography [SiO₂; toluene-methanol (8:2) and 0.2% of NEt₃] to afford 9 (310 mg, 90%) as a pale yellow viscous oil, which solidified on standing. M.p. 75-76 °C, [α]D²⁰ +4.2° (c 1.1, CHCl₃). IR (KBr): 3368, 1730, 1594. ¹H NMR (CDCl₃): δ 1.73 (brs, 4 H, NH₂), 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, COOCH₃), 3.99 (dd, 2 H, J 7.8 Hz, J 4.8 Hz, N-CH₂-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). ¹³C NMR (CDCl₃): δ 42.26, 51.97, 53.96, 121.79, 136.77, 157.35, 175.69. MS (FAB⁺): m/z 282. HRMS (EI⁺): obs. 281.1370, calc. 281.1375.

Preparation of the CuCl₃ complex 16-0.5 THF-0.5 H₂O. A solution of CuCl₃·2H₂O (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 N₂. 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 CH₂Cl₂-Et₂O 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⁺): obs. 379.0360, M-Cl+H (C₁₇H₁₅ClCuCN₃O₂), calc. 379.0360.

Preparation of RhCl₃ complex 16-MeOH. A solution of (-)-9 (50.1 mg, 0.178 mmol) and RhCl₃·3H₂O (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 [SiO₂; EtOAc-MeOH (19:1)] to furnish 16-MeOH (60 mg, 67%) as an orange solid. M.p. >280 °C (decomp.) (recrystallized from CH₂Cl₂-Et₂O as orange needles). [α]D²⁰ +206° (c 0.550, CH₂Cl₂). IR (KBr): 3300, 3210, 1725, 1603, 1576, 1465, 1430, 1312, 1300, 1218, 1092, 910, 810. ¹H NMR (CDCl₃): δ 5.31 (dd, 2 H, J 15.3 Hz, J 1.2 Hz, Py-CH), 3.69 (dt, 2 H, J 12.0 Hz, J 4.5 Hz, PyCH), 3.90 (s, 6 H, COOCH₃), 3.98 (dd, 2 H, J 15.3 Hz, J 11.4 Hz, N-CH₂-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). ¹³C NMR (CDCl₃): δ 40.89, 52.44, 53.57, 126.41, 139.39, 161.45, 169.50. Anal. C, H, N. HRMS (FAB⁺): obs. 488.9496, M+H (C₁₇H₁₅ClCuCN₃O₂HCl), calc. 488.9496.

Cyclopropanation of styrene with ethyl diazoacetate in the presence of 15-0.5 THF-0.5 H₂O. 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-0.5H₂O (10 mg, 0.024 mmol, 1 mol%) at 55 °C under N₂. When the addition was complete, the reaction mixture was stirred for another 2 h at 55 °C. After cooling, the material was chromatographed [SiO₂; first heptane then heptane–EtOAc (19:1)], which gave a mixture of cis- and trans-cyclopropanes 17 (225 mg, 65%). From ¹H NMR (CDCl₃), the ratio of cis:trans was found to be 1:2.2. This mixture was separated by HPLC [SiO₂ 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 $t_f$ 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.  

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$_4$.

References


Received September 25, 1995.