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The Fate of the Stereogenic Centre Linked to Palladium Upon Reaction with an Alkyne

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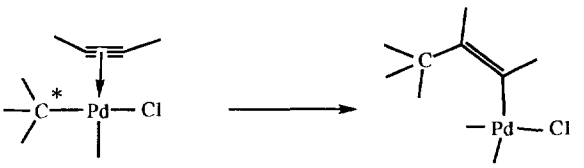
Abstract: *An enantiomerically enriched cyclopalladated 8-ethylquinoline derivative reacted with dimethyl acetylenedicarboxylate to yield a [2.3.3] cyclazine with virtually the same enantiomeric enrichment. This study provides evidence for a concerted alkyne insertion in the Pd-C bond.*

Introduction

The mechanistic elucidation of reactions involving organometallic reagents is often aided by a study of the stereochemical course of such processes. An excellent illustration of this concept is provided by the study of the migratory insertion reactions of carbon monoxide with palladium (0) or iron cyclopentadienyl complexes which were shown to proceed with retention of configuration of the migrating alkyl moeity.[1]

Substantial evidence has already been provided for the first step of the insertion of an alkyne in the Pd-C bond of cyclopalladated complexes. Following η^2-coordination of the alkyne[2] (as in **I**, Scheme 1), *cis* insertion into the Pd-C bond can occur to give a vinyl palladated complex **II**. We anticipated that a study of the fate of a stereogenic centre linked to palladium during such an insertion in the metal-carbon bond might be interesting for mechanistic purposes.

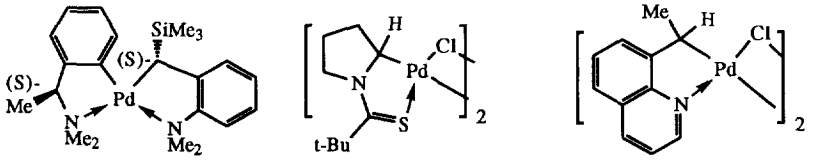


Scheme 1 **I** **II**

Results and Discussion

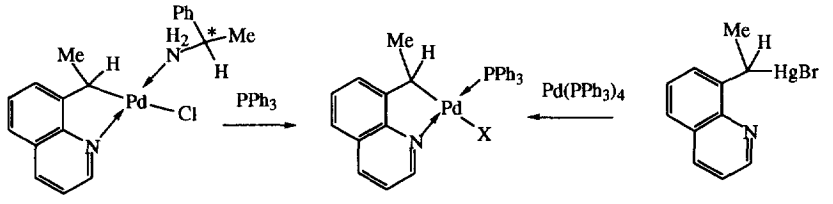
(i) Resolution of a Cyclopalladated Complex Containing an Asymmetric Metallated Carbon Atom

In line with the above criterion we sought methods for the preparation of an enantiomerically enriched cyclopalladated derivative containing a stereogenic centre linked to the metal. Only a few examples of these complexes are described in the literature and they would appear to be difficult to obtain in enantiomerically enriched form. **III**, for example, (see Scheme 2) was made from treating the corresponding chloro-bridged cyclopalladated complex with the lithium salt of a silylated dimethyl aminotoluene derivative and obtained in diastereomerically enriched form by a rather tricky resolution technique involving fractional crystallisation.[3] Recently, a method for obtaining enantiomerically enriched **IV** was disclosed which described its synthesis in racemic form by a C-H activation reaction followed by a resolution technique effected with (*S*)-proline.[4] Recovery of enantiomerically enriched **IV** was possible by removal of the amino acid with HCl.



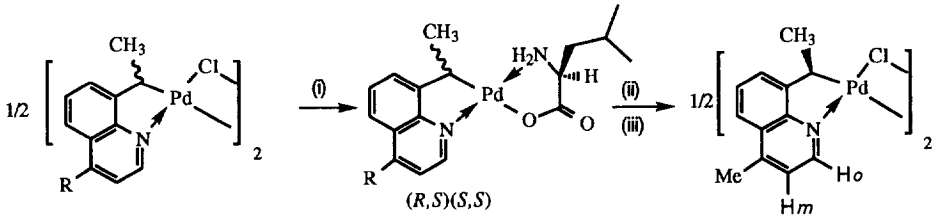
Scheme 2 III IV 1a

Complexes **1**, obtained by the C-H activation of 8-ethylquinoline derivatives, were chosen for our study. Methods have already been reported for the synthesis of the enantiomerically enriched phosphine bound monomer **V**. The bridge splitting reaction of racemic **1a** with optically active (1-phenylethyl)amine followed by crystallisation led to the diastereomerically enriched amine bound monomeric complex **VI**, which afforded **V** upon reaction with triphenylphosphine.[5] This method would, however, appear to suffer from reproducibility problems. A second procedure necessitated the prior resolution of an 8-bromoethylquinoline derivative and the handling of a toxic mercury complex **VII** obtained by the oxidative addition of this ligand on metallic mercury. A transmetallation reaction with a Pd(0) salt afforded **V**.[6]



Scheme 3 VI V VII

In a preliminary communication, we reported a method for the resolution of **1** employing (S)-leucine as a chiral auxiliary.[7] The initial reaction of **1** with the amino acid affords a 1:1 mixture of diastereomers, **2**. A series of fractional precipitations leads to diastereomerically enriched **2**, which upon treatment with HOAc, followed by LiCl addition, regenerates **1** with e.e.'s of up to 45%. One of the diastereomers of **2b** was established as having a (*S, S*)- configuration by an X-ray diffraction study. Other derivatives, such as **2c** (see Experimental) could be formed with other amino acids although their attempted resolution was unsuccessful. ^{1}H COSY NMR was employed for the proton attribution of **2b**. The chirality of the molecule was manifested by the diastereotopicity of the NH_2 protons of the leucine fragment which for (*S,S*)-**2b** were found separately at $\delta = 2.5$ and 4.6 ppm. The isopropyl CH proton and neighbouring CH_2 and CHN protons of the leucine part were all found to be difficult to interprete multiplets, and the aromatic region presented diagnostic doublets for the H*m* and H*o* protons. For (*R,S*)-**2b** the NH_2 protons could be found at $\delta = 2.1$ and 4.3 ppm and the multiplet for the CHN proton was superimposed on the quartet due to the CH linked to palladium. Quite curiously, one of the separated diastereomers of **2a** displayed a similar phenomenom in that the CHN and $CHCH_3$ signals were superimposed at $\delta = 3.75$ ppm and the respective NH protons could be found at $\delta = 2.1$ and 4.4 ppm. By analogy we attributed this diastereomer as having the (*R, S*) configuration.



1a; R = H.
1b; R = Me.

(*R*,*S*)(*S*,*S*)

2a; R = H.
2b; R = Me.

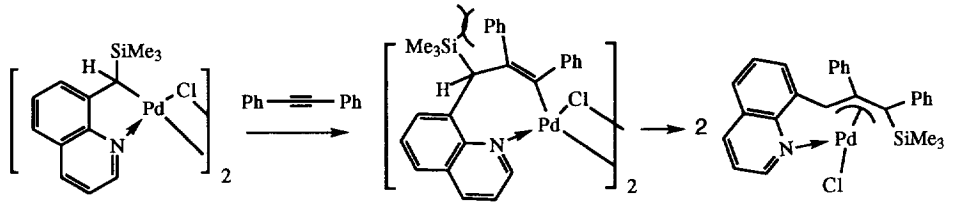
(*R*)-**1b**; e.e. = 45%

(i) (*S*)-leucine
(ii) resolution by fractional precipitation
(iii) HOAc, MeOH; LiCl.

Equation 1

(ii) Reactivity of Racemic 1 towards Disubstituted Alkynes

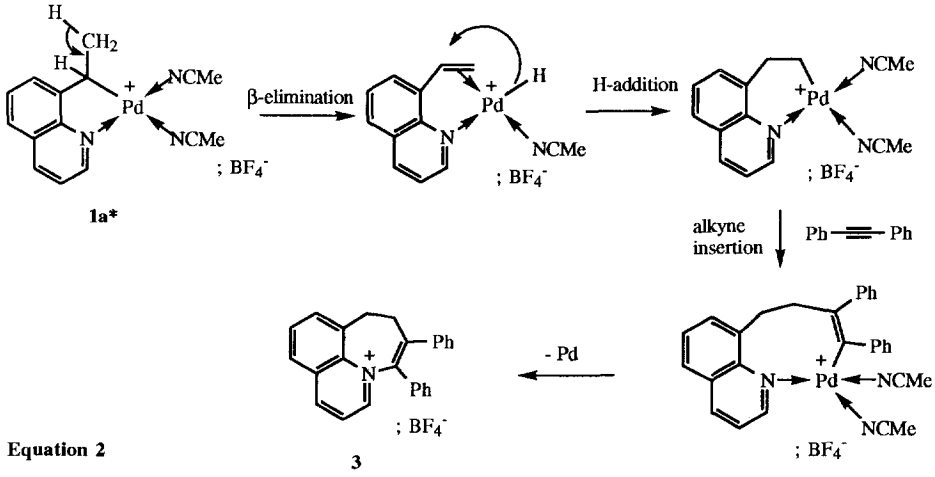
Given the ready availability of **1** in enantiomerically enriched form, we were interested in probing its reactivity towards disubstituted alkynes. One obvious prerequisite for our study was the need for a reaction where we could actually find the stereogenic centre of the starting material in the final product. For example, the reaction of the related (racemic) derivative **1c** with diphenylacetylene would be unhelpful for our study as it was shown to proceed with a skeletal rearrangement and loss of the initial stereogenic centre. The final π-allyl palladium containing complex **VIII** was the result of a 1,3 sigmatropic shift of the labile trimethylsilyl group due to steric hindrance in the inserted alkyne intermediate.[8]



Scheme 4 **1c** **VIII**

When we reacted the racemic cationic derivative **1a*** with the same alkyne, a cationic heterocyclic product, **3**, was obtained. The latter is thought to be the result of an initial β-hydride elimination of the metallated ethyl group. Intramolecular Markownikoff addition of the resulting palladium hydride species to the olefin bound palladium cationic complex is followed by insertion of the alkyne in the Pd-C bond. Palladium loss furnishes **3** (see equation 2).

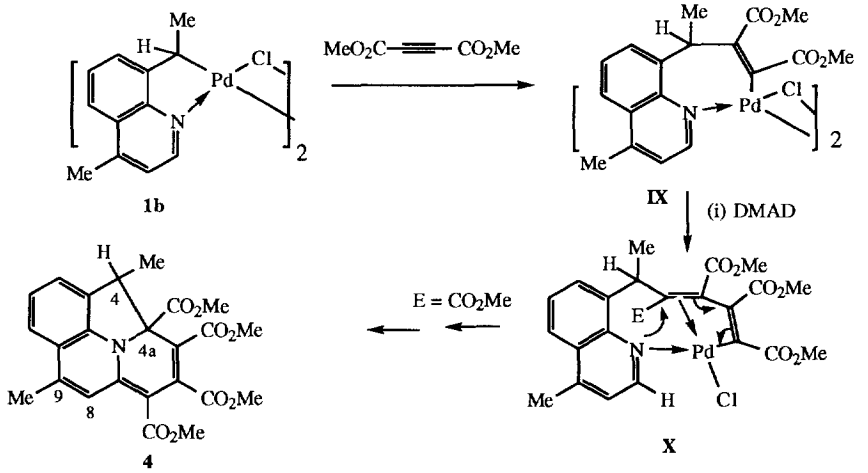
When a racemic sample of **1b** was reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing chlorobenzene (PhCl) a palladium free compound was obtained. This product, **4**, was formed in ca. 40% yield and gave spectroscopic data that were typical of a [2.3.3] cyclazine derivative.[9] A peak was observed in its mass spectrum at m/z= 453 and its ^{1}H NMR spectrum displayed a simple aromatic region, and four resonances for the methoxy groups around δ = 3.5 ppm. A doublet (at δ = 1.69 ppm) and a quartet (at δ = 4.4 ppm) for the methyl group and proton at C-4 respectively, and a doublet for the remaining C-9 Me group at δ = 2.6 ppm could also be found (for partial atom labelling see Equation 3).



1a* 3

Equation 2

Given the relative simplicity of its ^1H NMR spectrum, we concluded that **4** was formed as a single diastereomer and quite fortuitously the original stereochemical information contained in **1b** can now be found in **4**. We assumed an *anti* arrangement, based mainly on steric grounds, for the relative stereochemistry of **4** obtained.



1b IX X 4

Equation 3

By analogy with related work on cyclazine formation[9] this reaction must involve an initial carbon-carbon bond formation by the insertion of the alkyne in the Pd-C bond of **1b**, although the inserted intermediate **IX** for this reaction could never be isolated. Even when using a default of the alkyne, **4** was recovered along with unreacted **1b**. **IX** can then further react with DMAD, giving the equally ephemeral doubly-inserted complex **X**. The C-N bond is formed by an intramolecular nucleophilic attack of the quinoline unit on the η^3 butadienyl unit in **X**.

(iii) The Reaction of Enantiomerically Enriched 1 with an Acetylene

The reaction shown above was now carried out using enantiomerically enriched **1b.** Given that the specific rotation of enantiopure **4** is unknown, we sought methods complementary to polarimetry for the e.e. determination of the heterocyclic product. *R*(-)-1-(9-anthryl)-2,2,2-trifluoroethanol, **5**, has already been shown to be an effective ^{1}H NMR chiral shift reagent[10] for the e.e. determination of oxaziridines in which the nitrogen atom is a non-inverting stereogenic centre. It is thought that **5** forms diastereomeric solvates with the basic sites of the heterocyclic substrate (N and O atoms), giving rise to a spectral non-equivalence for each of the two separate enantiomers of the original heterocycle. A comparison of the integration of specific signals common to both enantiomers enables the e.e determination.

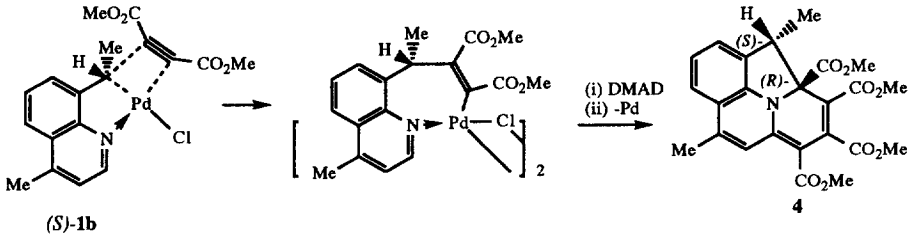
The addition of **5** to the racemic cyclazine **4** was chosen as a test reaction for ^{1}H NMR studies at 200 MHz. Different molar ratios of **5** to **4** were chosen and best results were obtained using a two to threefold excess of **5** and this could be acheived using as little as 5-10 mg of combined material.[11] With a 2.5:1 molar ratio of **5**:**4**, the two enantiomers for the C-4 methyl signal at δ= 1.72 ppm now appeared as poorly separated doublets (3.2 Hz separation of the signals) and the C-9 methyl at δ=2.61 ppm appeared as two well separated doublets (13.2 Hz separation at 200 MHz) of equal intensity. Other signals were separated but these were either difficult to interpret (eg, the CH quartet at C-4 or the CO_2Me signals) or hidden in the aromatic region under the excess of **5** employed. Higher molar ratios of **5**:**4** engendered resolution problems due to the greater viscocity of the solution and lower molar ratios gave insufficient separation of the signals. The efficacy of **5** as a chiral shift reagent with **4** can no doubt be attributed to the availability of basic sites (ester groups) in the latter.

Complex *(R)*-**1b** (e.e. = 33%) was reacted with DMAD according to the given conditions to yield **4**. A polarimetric measurement revealed that the latter was indeed optically active ($[\alpha]_D^{298K}$ = -3.6)[12] and a ^{1}H NMR study in the presence of **5** showed the heterocyclic product to have a e.e. = 28% by integration of the well separated C-9 methyl signals which were no longer of equal intensity. *(R)*-**1b** (e.e. = 45 %) equally afforded **4** with an e.e. = 40%. Starting with the other antipode, *(S)*-**1b** (e.e. = 28%) furnished **4** with an $[\alpha]_D^{298K}$ = +6.0 [12] and, hence, the other enantiomer was obtained. Using **5** and the usual ^{1}H NMR technique an e.e. = 21% was calculated for **4** by integration of the C-9 methyl groups.

Proposed mechanism

Enantiomerically enriched **1b** can afford **4** with at least 75 % incorporation of the e.e. of the starting material. These observations provide evidence for a concerted type alkyne insertion of DMAD in the Pd-C bond of **1b**, as the first step in this reaction, whereby the stereogenic centre linked to Pd in **1b** is found at C-4 in **4**.

The mechanism that we propose for the C-C bond formation during the first step of this reaction is outlined in Scheme 5. Starting with *(S)*-**1b**, of known configuration, η^2-coordination of DMAD is followed by a concerted *cis* insertion in the Pd-C bond (a monomeric Pd complex is shown for simplicity [2(ii)]). This is most likely to occur with a retention of configuration and, hence, the newly formed stereogenic centre will have a (*S*)-configuration. Nevertheless, since the absolute configuration of **4** is unknown, we have no definite argument as to rule out the possibility of an inversion of configuration on the palladated carbon atom of **1b**. The rest of this reaction follows on from Equation 3. Following this reasoning, *(R)*-**1b** should afford *(R)*-, *(S)*-**4**.



Scheme 5

However, the term 'concerted' is used here, with a certain degree of circumspection. One might also suggest a mechanism invoking the intermediacy of a carbanion or a radical which might also be rationalised if the initial rupture of the C-Pd bond were to be followed by an insertion of the alkyne, so rapid that racemisation of the intermediate would not be possible. However, these proposed alternative carbanion or radical pathways can be considered as being very similar to a concerted type pathway and an important point is that the C-C bond formation occurs aided by the proximity of the metal centre.

Conclusion

It is indeed possible to prepare enantiomerically enriched cyclopalladated complexes **1** and **2** containing an asymmetric metallated carbon atom by the use of a resolution technique employing *(S)*-leucine as chiral auxiliary. **1b**, in only partially enantiomerically enriched form, was shown to be particularly useful in the study of the palladium mediated formation of a C-C bond between a disubstituted alkyne and a metallated carbon atom, which provides further support for a concerted type process.[1(ii)] These results may hold promise for the use of our palladium mediated synthesis of heterocycles in stereoselective heterocycle synthesis.[13]

Experimental

All solvents were distilled prior to use and reactions were carried out using conditions described elsewhere.[14] DMAD, the amino acids employed in this study, and **5** were used as obtained from commercial sources. ^{1}H NMR (300 MHz) data have already been reported for **2a** and **2b**.[7]

Synthesis of 4-Methyl-8-Ethylquinoline: An ethanolic solution (200 mL) of 3-buten-2-one (21 mL, 0.35 mol) was added dropwise, at 70°C, over two hours, to an ethanol suspension (200 mL) of 2-ethylaniline hydrochloride (48g, 0.31 mol from 2-ethylaniline and conc. HCl), $FeCl_3$ (130 g) and anhydrous $ZnCl_2$ (6 g). After heating to reflux for 2 h, the residue was left to stand overnight. Most of the ethanol was removed *in vacuo*, then KOH (ca. 30g) was cautiously added. Steam distillation of the black tar, using superheated steam, gave a first fraction (ca. 400 mL of H_2O) that after usual ether extraction, drying etc, contained mainly 2-ethylaniline. The next two litres of the distillate contained virtually pure 4-methyl-8-ethylquinoline (17 g, 32%, after usual ether extraction, and further distillation under reduced pressure). ^{1}H NMR (δ in ppm, $CDCl_3$, 293 K, 300 MHz); 1.39 (t, 3H, $^3J_{HH}$ = 7.4 Hz, Me); 2.69 (s, 3H, Me); 3.32 (q, 2H, CH_2); 7.20 (d, 1H, $^3J_{HH}$ = 3.9 Hz, H^{ar}); 7.48 (t, 1H, H^{ar}); 7.56 (d, 1H, $^3J_{HH}$ = 6.8 Hz, H^{ar}); 7.85 (d, 1H, $^3J_{HH}$ = 8.2 Hz, H_m); 8.79 (d, 1H, H_o).

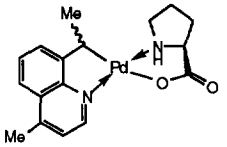
Synthesis of 1b: A suspension of 4-methyl-8-ethylquinoline (1.76, 1.03 mmol) and $Pd(OAc)_2$ (2.24 g, 1.0 mmol) in CH_2Cl_2 (50 mL) was stirred overnight at rt. After Celite filtration to remove traces of palladium metal formed during the reaction, the filtrate was evaporated to dryness and the resulting red mass (acetate

dimer) thoroughly washed with pentane to remove the acetic acid formed, then dried. LiCl (700 mg) was added to a suspension of the red solid in acetone (50 mL) and after 20 mn stirring, water was added (200 mL) to yield a brown solid which was collected by filtration and dried. The latter was washed with further water, CH_2Cl_2 (3x 25 mL), MeOH (20 mL), hexane (30 mL), then dried. The pale brown solid was obtained typically in 70-85% yield (ca. 2.5 g). Anal. Calc.; C, 44.14; H, 3.78; N, 4.20 for $C_{12}H_{12}NClPd$. 0.25 CH_2Cl_2. Found, C, 44.22; H, 3.74 N, 4.04. ^1H NMR (300 MHz, $CDCl_3$/ pyridine d-5); 0.98 (d, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3); 2.69 (s, 3H, CH_3); 3.93 (q, 1H, CH); 7.22 (m, 1H, H^{ar}); 7.52 (m, 2H, H^{ar}); 7.74 (d, 1H, $^3J_{HH}$ = 5.2 Hz, H_m); 9.47 (d, 1H, H_o).

Synthesis and Resolution of 2a: For **2a** an identical procedure for both the synthesis (orange solid, 88% yield) and resolution of **2b** was employed. Anal. Calc.; C, 50.04; H, 5.48; N, 6.77 for $C_{17}H_{22}N_2O_2Pd$. 0.25 CH_2Cl_2. Found, C, 49.97; H, 5.63; N, 6.57.

Synthesis of 2b: **1b** (620 mg, 2 mmol), *(S)*-leucine (300 mg, 1.31 mmol) and Na_2CO_3 (230 mg, 2.17 mmol) were stirred in methanol (40 mL) at rt until dissolution (ca. 1 h). The resulting dark solution was evaporated to dryness and dried *in vacuo*. After usual CH_2Cl_2 extraction, Celite filtration, then concentration of the organic extracts to ca. 20 mL, hexane was added (50 mL) and the resulting beige precipitate (1:1 ratio of diastereomers, 635 mg, 78%) was collected by filtration and dried. Anal. Calc.; C, 51.21; H, 5.77; N, 6.54 for $C_{18}H_{24}N_2O_2Pd$. 0.25 CH_2Cl_2. Found, C, 51.38; H, 5.88; N, 6.63.

Resolution of 2a: To a warm CH_2Cl_2 solution (30 mL) of **2** (510 mg) was added hexane (10 mL). After 10 mn refrigeration at -20°C, the yellow precipitate was collected by filtration and dried (ca. 300 mg, d.e. = 26%, *(S,S)*-) and the filtrate evaporated to dryness (d.e.= 16%, *(R,S)*-). Several repetitions of this procedure enabled the two diastereomers to be separated in ca. 50 mg quantities with d.e.'s around 90%.



2c

2c was obtained by an identical procedure to that employed for the synthesis of **2a** using **1b** (310 mg, 1 mmol), *(S)*-proline (150 mg, 1.30 mmol) and Na_2CO_3 (150 mg, 1.41 mmol). (Yield: 315 mg, 81% beige solid, 1:1 mixture of diastereomers).Anal. Calc.; C, 50.29; H, 5.01; N, 6.80 for $C_{17}H_{20}N_2O_2Pd$. 0.25 CH_2Cl_2. Found, C, 50.35; H, 5.16; N, 6.74. ^1H NMR (300 MHz); 0.84 (m, 2H, a.a. proton); 1.30 & 1.35 (d, 3H, $^3J_{HH}$ = 7.3 Hz, $C\underline{H}_3CHPd$); 1.8 - 2.35 (m, 3H, a.a. protons); 2.62 (2s, 3H, *p*-Me); 3.3 & 3.7 (m, 2H, a.a; protons); 4.0 & 4.13 (q, 1H, $^3J_{HH}$ = 7.3 Hz, $PdC\underline{H}Me$); 7.13 (d, 2H, $^3J_{HH}$ = 4.7 Hz, superimposed H*m*); 7.43-7.66 (m, 3Harom); 8.73 & 8.83 (d, 1H, $^3J_{HH}$ = 4.7 Hz, H*m*).

Hydrolysis of 2b (for d.e. = 33 %): A sample of **2b** (130 mg, 0.32 mmol, *((S,S)*, d.e. = ca. 33% by NMR) was stirred overnight at rt in MeOH: acetic acid (20 mL: 0.3 mL, pH = 1). The solvent was removed *in vacuo*. After thorough pentane washing and drying, the residue was precipitated from CH_2Cl_2/ pentane. Treatment of this residue in acetone (3 mL) and LiCl (ca. 50 mg, 1.2 mmol) for 0.5 h, followed by the addition of water afforded a yellow precipitate (90 mg, 90%) which was collected by filtration and dried. ^1H NMR of the product showed it to be **1b** and analysis of its leucinate derivative **2b** showed it to have a d.e. of 28% *((S,S))*.

Synthesis of 3: **1*** (350 mg, 0.81 mmol), made by the usual method[14] from **1** and $AgBF_4$, and diphenylacetylene (350 mg, 1.96 mmol) were heated to reflux in chlorobenzene (50 mL) for 1.25 h. After Celite filtration, to remove the metallic palladium formed, the yellow solution was evaporated to dryness. The orange residue was stirred with pentane (2 x 10 mL) and filtered. **3** was obtained as white needles from CH_2Cl_2/pentane at -20 °C (64 mg, 19 %). Anal. Calc.; C, 71.29; H, 4.75; N, 3.33 for $C_{25}H_{20}NBF_4$. Found, C, 71.15; H, 4.90; N, 3.20. ^1H NMR (200 MHz, CD_3CN); 3.77 & 4.05 (2d, 2H, CH_2, $^2J_{HH}$ = 18.1 Hz); 3.75 & 4.10 (2d, 2H, CH_2, $^2J_{HH}$ = 18.2 Hz); 6.41-8.31 (m, 14 Harom); 8.99 (dd, 1H, $^3J_{HH}$ = 8.1 Hz, H*p*); 9.30 (dd, 1H, $^3J_{HH}$ = 5.6 Hz, H*o*). m/z: 333 (M^+, 100%).

Synthesis of 4H-4a, 5, 6, 7, tetracarbomethoxy-9-methyl-indolo[2, 7, 1-*cde*] quinolizine 4: Racemic **1b** (310 mg, 1 mmol) and DMAD (300 mg, 2.11 mmol) were heated to reflux in PhCl for 0.5 h. After solvent evaporation, the black residue was extracted with CH_2Cl_2 (80 mL) and filtered over an alumina column. Elution with CH_2Cl_2 (50 mL) afforded a colourless fraction which was discarded. With CH_2Cl_2/acetone (50 mL:20 mL), then acetone, (60 mL) an orange fraction was obtained. Solvent evaporation yielded an orange oil (165 mg, 36%) which afforded a red solid (101 mg) from CH_2Cl_2/hexane at -20°C. Other inseparable products were obtained which prevented us from obtaining pure **4**, and unsatisfactory combustion analyses and ^{13}C spectra were a consequence. ^1H NMR (300 MHz); 1.72 (d, 3H, $^3J_{HH}$ = 7.0 Hz, Me); 2.57 (d, 3H, $^4J_{HH}$ = 0.8 Hz, Me at C-9); 3.63- 3.88 (4s, CO_2Me); 4.40 (q, 1H, CH); 7.34 & 7.53 (2m, 3H, aromatics); 8.25 (d, 1H, $^4J_{HH}$ = 0.8 Hz, H arom).m/z: 453 (M^+, 7%), 395 (M^+ -CO_2Me + H, 100%).

The reactions involving DMAD and **1b** with e.e.'s > 0% were carried out using this technique.

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(11) A typical procedure involved **5** (5.1 mg, 18.5 µmol) and **4** (3.4 mg, 7.5 µmol) in 0.5 mL of $CDCl_3$.
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