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Chiral 2,2′-bipyridines, 5,6-dihydro-1,10-phenanthrolines and 1,10-phenanthrolines as ligands for enantioselective palladium catalyzed allylic substitution

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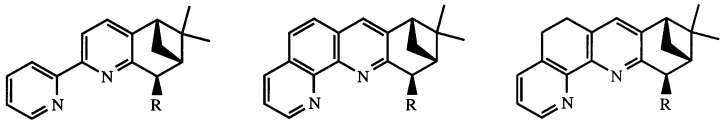
Abstract

A number of chiral 5,6-dihydro-1,10-phenanthrolines, 5,6-dihydrobenzo[*b*]-1,10-phenanthrolines and 5,6,7,8-tetrahydro-2-quinolinylquinolines derived from (−)-pinocarvone were prepared and assessed in the enantioselective palladium catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. The introduction of a benzo-fused substituent on the pyridine ring not containing the chiral backbone resulted in the drastic reduction of the stereoselectivity of the reaction. Enantioselectivities up to 81% were obtained. © 2000 Published by Elsevier Science Ltd.

1. Introduction

We recently reported the successful application of chiral 2,2′-bipyridines **1**[1] and 1,10-phenanthrolines **2**[2] (Scheme 1) as chiral controllers for the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylallyl acetate with dimethyl malonate. These preliminary investigations indicated that the palladium catalysts derived from analogue series of ligands **1** and **2** provide a similar enantioselecivity but a very different catalytic activity. This different behaviour has been ascribed to the different conformational mobility induced in the catalyst by the



1a-d **2a-e** **3a-e**

a : R= H; **b** : R= Me; **c** : R= *n*-Bu; **d** : R= Bn; **e** : R= *i*-Bu

Scheme 1.

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heterocyclic template. The five-membered chelate ring resulting from the coordination of these ligands to the metal is most probably locked in a single conformation in the case of 1,10-phenanthroline derivatives, whereas a certain degree of conformational mobility is allowed in the case of 2,2′-bipyridine ligands, due to the inherently higher flexibility of this backbone. An intermediate situation could be possible in the 5,6-dihydro-1,10-phenanthrolines **3** in which the 3,3′-bridge can control the relative orientation of the two rings and thus influence the shape of the chelating bite-angle.

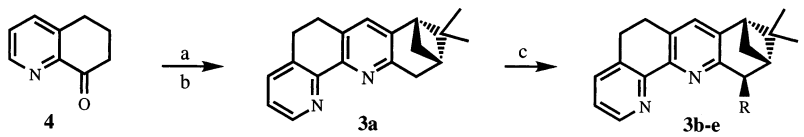
On this basis, pursuing our interest in this field, we have prepared a number of the new dihydrophenanthrolines of type **3**. Moreover, in order to study the effect of a substituent bonded to the pyridine ring not containing the chiral backbone on the catalytic activity and stereoselectivity, we have synthesized the 5,6-dihydrobenzo[*b*]-1,10-phenanthrolines **7a–c** and the 5,6,7,8-tetrahydro-2-quinolinylquinolines **9a–c** which differ from the related ligands **3a**,**c**,**d** and **1a**,**c**,**d** by the presence of a benzo-fused ring on the unsubstituted pyridine cycle. Moreover, in order to compare a homogeneous series of ligands we have prepared the bipyridine **1c**.

In this paper we report the synthesis of compounds **1c**, **3**, **7** and **9** and the results obtained with these ligands in the palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate which are the model substrate and nucleophile for comparing the activity and selectivity of different catalytic systems.[3]

2. Results and discussion

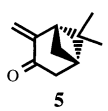
2.1. Synthesis of ligands

Dihydrophenanthroline **3a** was obtained by conjugate addition of the lithium enolate of the tetrahydroquinolone **4** with (–)-pinocarvone **5** followed by azaanellation of the unisolated 1,5-dicarbonyl intermediate with the ammonium acetate–acetic acid system[2] (63% overall yield) (Scheme 2). Then the red solution of lithiated **3a** (obtained by treatment with LDA at –40°C for 2 h) was quenched with the appropriate alkyl iodide to give ligands **3b–e** in 35–67% yield. The use of alkyl iodide was necessary on account of the unexpectedly low reactivity of the lithium salt of **3a**.



R= **a**: H, **b**: CH_3, **c**: $CH_2(CH_2)_2CH_3$, **d**: CH_2-C_6H_5, **e**: $CH_2CH(CH_3)_2$

a: LDA, THF, -78 °C, 2h; then **5** from -78 °C to slowly r.t.; b: AcOH, AcO NH_4, THF, reflux, 2h; c: LDA, THF, -40 °C, 2h; then CH_3I or $CH_3(CH_2)_2CH_2I$ or $C_6H_5CH_2I$ or $(CH_3)_2CHCH_2I$ at -78 °C



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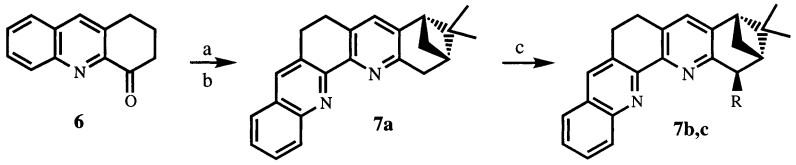
Scheme 2.

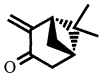
Dihydrobenzophenanthroline **7a** and 2-quinolinylquinoline **9a** were obtained in 56 and 36% yields, respectively, following the protocol used to obtain **3a** from 4-oxo-1,2,3,4-tetrahydroacrydine **6** (Scheme 3) and 2-acetylquinoline **8** (Scheme 4). Compounds **7a** and **9a** were deprotonated with LDA at –40°C for 2 h and then treated with butyl or benzyl iodide to give

the corresponding alkylated compounds. Whereas ligands **7b**,**c** were obtained in moderate yields (67 and 53%, respectively), the introduction of an alkyl group into the 8-position of **9a** was very difficult, giving the alkylated compounds **9b**,**c** in low yield (36 and 26%, respectively) even if hexamethylphosphoric triamide (HMPA) or tetramethylethylenediamine were used as co-solvents.



R= **a**: H, **b**: $CH_2(CH_2)_2CH_3$, **c**: CH_2-C_6H_5,

a: LDA, THF, -78 °C, 2h; then **5** from -78 °C to slowly r.t.; b: AcOH, AcO NH_4, THF, reflux, 2h; c: LDA, THF, -40 °C, 2h; then $CH_3(CH_2)_2CH_2I$ or $C_6H_5CH_2I$ at -78 °C.



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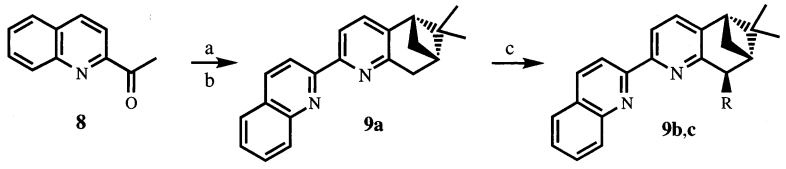
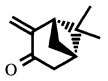
Scheme 3.



R= **a**: H, **b**: $CH_2(CH_2)_2CH_3$, **c**: CH_2-C_6H_5,

a: LDA, THF, -78 °C, 2h; then **5** from -78 °C to slowly r.t.;
b: AcOH, AcO NH_4, THF, reflux, 2h;
c: LDA, THF, -40 °C, 2h; then $CH_3(CH_2)_2CH_2I$ or $C_6H_5CH_2I$ at -78 °C



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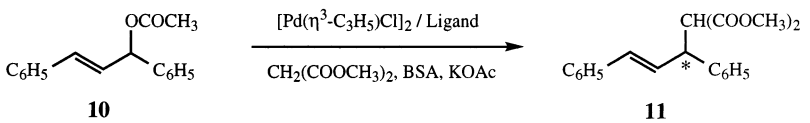
Scheme 4.

Finally, we prepared the bipyridine **1c** by alkylation with butyl iodide of **1a** which was available in our laboratory.[1]

2.2. Palladium-catalyzed allylic alkylation

The conditions of the catalytic allylic alkylation (Scheme 5) entail the use of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and the generation of the nucleophile by the in situ treatment of dimethyl malonate with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in a methylene chloride solution.[4]



10 **11**

Scheme 5.

Dihydrophenanthrolines **3a–e** were able to provide effective palladium catalysts (Table 1, entries 3, 6, 9, 12 and 14). Total conversion of the starting material was achieved with these ligands in less than 140 minutes to give high yields of dimethyl 1,3-diphenylprop-2-enylmalonate **11**. The introduction of alkyl groups on the 11-position of dihydrophenanthroline **3a** was crucial for the stereoselectivity of the process. Thus, dihydrophenanthroline **3a** gave much lower enantiomeric excess than the 11-substituted dihydrophenanthrolines **3b–e**. Among these ones the best stereoselectivity (81% ee) was obtained with the 11-*iso*-butyl substituted ligand **3e**. In all cases the absolute configuration of the substitution product **11** was controlled by the absolute configuration at the stereogenic centre at the 11-position of the heterocyclic ring, resulting in preferred formation of (*R*)-**11**. Moreover, since the 11-unsubstituted dihydrophenanthroline **3a**

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]

Entry	Ligand	R	React. time (min)[b]	Yield[c]	% ee[d]	Conf.
1	**1a**	H	180	93	11	*R*[e]
2	**2a**	H	30	93	4	*R*[f]
3	**3a**	H	15	87	3	*R*
4	**1b**	Me	720	95	74	*R*[e]
5	**2b**	Me	35	95	78	*R*[f]
6	**3b**	Me	35	92	70	*R*
7	**1c**	*n*-Bu	780	88	85	*R*
8	**2c**	*n*-Bu	25	93	84	*R*[f]
9	**3c**	*n*-Bu	90	96	72	*R*
10	**1d**	Bn	2880	94	89	*R*[e]
11	**2d**	Bn	25	88	34	*R*[f]
12	**3d**	Bn	8	95	40	*R*
13	**2e**	*i*-Bu	45	91	70	*R*[f]
14	**3e**	*i*-Bu	140	98	81	*R*
15	**7a**	H	75	93	2	*R*
16	**7b**	*n*-Bu	55	87	6	*R*
17	**7c**	Bn	75	89	23	*R*
18	**9a**	H	120	83	4	*R*
19	**9b**	*n*-Bu	3600	77	14	S
20	**9c**	Bn	5040	86	6	*R*

[a] Reaction of the ligand (10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5% mol) in CH_2Cl_2 (2 ml) at rt.

[b] Isolated yields.

[c] Determined by ^1H NMR using $Eu(hfc)_3$ as the chiral shift reagent.

[d] The assignment is based on the sign of the optical rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P. V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143.

[e] Data taken from Ref. 1.

[f] Data taken from Ref. 2.

gave the same sense of enantioselection as the 11-substituted ones, it is reasonable to think that in dihydrophenanthrolines **3** the stereocentre at the 11-position and those at the 8- and 10-positions are in a matching relationship. It should be noted that, since the maximum enantiomeric excess of ligands **3** is 91% (that of (1*R*)-(+)-α-pinene used as starting material), a higher asymmetric induction can be foreseen, excluding asymmetric amplification process, if the same ligands could be used in enantiomerically pure form. Thus, for the enantiomerically pure ligand **3e**, an enantiomeric excess of 89% can be expected.

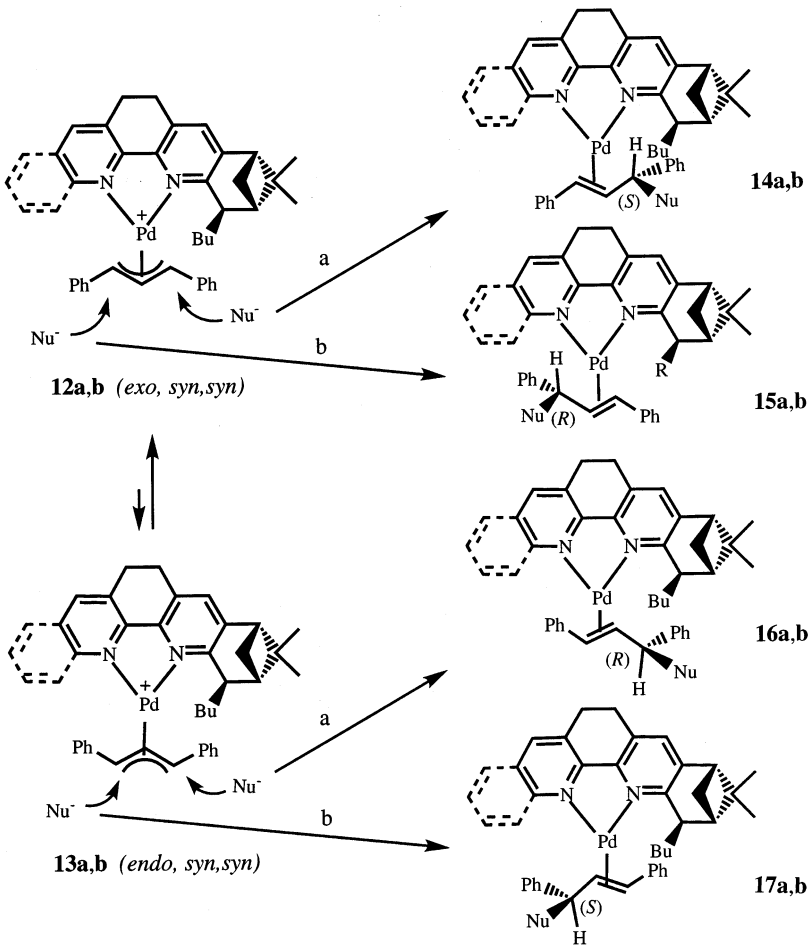
Comparison within the analogue series of these heterocycles shows that bipyridines **1** provided less effective palladium catalysts than the related phenanthrolines **2** and dihydrophenanthrolines **3** which, in turn, possess very similar catalytic activity (Table 1). Thus, whereas bipyridines required several hours to convert the starting material **10** completely, ligands **2** and **3** needed only a few minutes. This trend is independent of the substituent. The greatest differences were found with the palladium catalysts derived from ligands bearing the substituent. In fact **2d** and **3d** were more reactive than **1d**, affording the alkylation product in 25 and 8 minutes, respectively, whereas with the latter reaction required 48 hours to be complete.

Concerning the stereoselectivity of the reaction, there are no significant differences between the three kinds of ligands, except in the case of the benzyl substituent in which the stereodifferentiating ability of the bipyridine **1d** was much better (89% ee) than of the related phenanthroline **2d** and dihydrophenanthroline **3d** (ca 40% ee).

Our expectations were particularly disappointed by the results obtained with both dihydrobenzophenanthrolines **7b**,**c** and 2-quinolinylquinolines **9b**,**c**, where an enantioselectivity higher than the one observed with the unsubstituted counterparts **3c**,**d** and **1c**,**d** was confidently expected. In fact it has been shown that in C_1-symmetric heterobidentate ligands containing the pyridine ring such as oxazolinylpyridines[5] and pyridinethioethers[6] the presence of a substituent on the 6-position of the pyridine had the effect of increasing the enantioselectivity of the reaction. However, the introduction of a benzo-fused substituent on the pyridine ring not containing the chiral backbone resulted in a drastic reduction of the stereoselectivity of the reaction for ligands **7b**,**c** and of both stereoselectivity and reaction rate for ligands **9b**,**c**. Moreover, in the case of the *n*-butyl derivative **9b**, the reaction product **11** showed the (*S*) prevailing configuration, which is opposite to the expected one.

Rationalization of the steric course of the nucleophilic substitution is difficult because the accepted mechanism for palladium catalyzed allylic substitutions, which proceeds through a 1,3-diphenyl-η^3-allyl intermediate, foresees that the nucleophile attacks the allylic termini of two alternative diastereomeric π-allyl palladium complexes (both with *syn*, *syn* geometry): these may interconvert through various mechanisms and are present at the equilibrium in a different ratio (other isomers with different geometries could be present but they are much less stable and so their presence can be disregarded).[7] Scheme 6 depicts the two diastereomeric Pd(η^3-1,3-diphenylallyl) complexes **12a**,**b** (*exo*, *syn*, *syn*) and **13a**,**b** (*endo*, *syn*, *syn*) (*exo* configuration refers to the relative orientation of the central allylic C–H vector pointing away from the *n*-butyl substituent) derived from ligands **3c** or **7b**. The products can be formed via four pathways and the preferred one, according to the stereochemical outcome, arises by reaction at the allylic carbon *trans* or *cis* to the pyridine nitrogen connected to the stereocentre of the *exo* or *endo* isomers, respectively (path b in **12** or a in **13**). For a decision between these possibilities, the assumption of an early transition state in which the more abundant isomer is the more reactive one, is helpful.[8] From this, in conjunction with the known configuration of the products of allylic substitution, it is deduced that for ligands **3** (same arguments can be made with ligands **1** and **2**) the nucleophile attacks the carbon *trans* preferentially to the tetrahydroquinoline ring of the *exo* isomer (path

b in **12**). With ligands **3**, introduction of alkyl groups on the 11-position of the tetrahydroquinoline ring increases the enantioselectivty proportionally to the improvement of the ratio between **12** and **13**. Therefore, the capacity of the ligand to stabilize one of the two diasteromeric complexes is a crucial point in determining its stereodifferentiating ability. This could be increased by controlling the steric requirement, not only of a substituent on the 11-position of the tetrahydroquinoline ring, but also by introducing a substituent on the other pyridine ring which assists the chirogenic element to increase the stabilization of the sterically favoured diastereomer. On these grounds, ligands **7b**,**c** and **9b**,**c** should display a better effectiveness in the enantioselection than the corresponding unsubstituted counterparts. Instead, they appear to be worse enantioselective catalysts.



Scheme 6.

A possible explanation of the observed selectivity for both ligands **7b**,**c** and **9b**,**c** can be obtained by taking into account a late transition state which relates to severe steric interactions during the formation of the Pd(0) olefin complexes which are postulated as the primary products upon nucleophilic attack.[9]

According to this model, the evolving pyramidalization of the carbon being attacked by the nucleophile would 'push back' the allylic phenyl group either toward the chirogenic element present on the tetrahydroquinoline ring (for instance from 12 to 14, Scheme 6) or the substituent on the other pyridine ring (for instance from 12 to 15, Scheme 6). Thus that position of the allylic termini would be favoured in which there is sufficient space to avoid the unfavourable steric interaction between the proximal phenyl group of the diphenylallyl moiety and the substituent bonded to tetrahydroquinoline or pyridine rings. Therefore, with ligands such as **3c**, the nucleophilic attack will occur preferentially on the carbon *trans* to the tetrahydroquinoline ring of the *exo* isomer (from **12a** to **15a**, Scheme 6).

A strikingly different situation is found with ligands **7b**, where the nucleophilic attack on the carbon *trans* to the tetrahydroquinoline ring of the *exo* isomer (from **12b** to **15b**) engenders severe steric interactions between the benzo-fused substituent on the pyridine and the phenyl group bonded at the forming stereocentre. This fact, leading to a decrease in the rate of nucleophilic attack at this position, which is now only slightly favoured with respect to the *cis* one (from **12b** to **14b**), causes a drastic reduction of the enantioselectivity. An extreme situation is found with ligand **9b**, for which the observed switch of chiral induction can be explained in terms of preferential nucleophilic attack on the carbon *cis* to the tetrahydroquinoline ring of the *exo* isomer.

In summary, both early and late transition states lead to the conclusion that the preferred product arises from the more abundant *exo* isomer but only arguments based on a late transition state explain the stereochemical outcome obtained with all ligands of **7** and **9**.

3. Experimental

3.1. General methods

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^{1}H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyser. 5,7-Methano-6,6-dimethyl-2-(2-pyridinyl)-5,6,7,8-tetrahydroquinoline **1a**,[1] 5,6,7,8-tetrahydro-8-quinolone **4**,[10] 4-oxo-1,2,3,4-tetrahydroacridine **6**,[11] 2-acetylquinoline **8**[12] were prepared according to reported procedures. (−)-Pinocarvone **5** was prepared from (1*R*)-(+)-α-pinene (91% ee/GLC, Aldrich).[13]

3.2. (8S,10S)-8,10-Methano-9,9-dimethyl-5,6,8,9,10,11-hexahydrobenzo[b][1,10]phenanthroline **3a**

A solution of 5,6,7,8-tetrahydro-8-quinolone **4** (1.47 g, 10 mmol) in anhydrous THF (5 ml) was added dropwise at −78°C to a solution of lithium diisopropylamine (10 mmol) in anhydrous THF (50 ml). The resulting solution was stirred at −40°C for 2 h and then a solution of (−)-pinocarvone (1.5 g, 10 mmol) in THF (5 ml) was added dropwise at −40°C. After 15 min at −40°C, the solution was allowed to slowly reach rt and then poured into a mixture of ammonium acetate (3.85 g, 50 mmol) and acetic acid (50 ml). The flask was connected with a distillation head and the THF was distilled off over a 3 h period. Most of the acetic acid was

removed under reduced pressure and the residue taken up with H_2O and extraced with ethyl ether. The organic phase was separated, washed with a 5% NaOH solution and then dried on anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 1/1) to give pure **3a**: 1.19 g (43%); mp 200–201°C; $[\alpha]_D^{25}$ +68.9 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.68 (d, 1H, J = 4.5 Hz), 7.48 (d, 1H, J = 7.5 Hz), 7.14 (dd, 1H, J = 4.5 Hz, J = 7.5 Hz), 7.06 (s, 1H), 3.30 (d, 2H, J = 2.4 Hz), 2.89 (m, 4H), 2.76 (t, 1H, J = 5.4 Hz), 2.68 (m, 1H), 2.39 (m, 1H), 1.40 (s, 3H), 1.26 (d, 1H, J = 9.9 Hz), 0.69 (s, 3H). Anal. calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.71; H, 7.41; N, 10.24.

*3.3. (8*S,*10*S,*11*R*)-8,10-Methano-9,9,11-trimethyl-5,6,8,9,10,11-hexahydrobenzo[*b*][1,10]-phenanthroline* ***3b***

A solution of the pyridine **3a** (1.38 g, 5 mmol) in anhydrous THF (4 ml) was added at −78°C to a solution of lithium diisopropylamine (5 mmol) in anhydrous THF (25 ml). The resulting solution was stirred at −40°C for 2 h. Then a solution of methyl iodide (0.71 g, 5 mmol) in THF (4 ml) was added dropwise at −78°C. After 15 min at −78°C, the solution was allowed to slowly reach rt and then treated with H_2O. The organic phase was separated and the aqueous phase extracted twice with ethyl ether. The combined organic phases were dried on anhydrous Na_2SO_4, the solvent evaporated and the residue purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 1/1) to give pure **3b**: 0.87 g (60%); 49–50°C; $[\alpha]_D^{25}$ −30.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.67 (dd, 1H, J = 1.5, 4.8 Hz), 7.48 (dd, 1H, J = 1.5, 7.5 Hz), 7.14 (dd, 1H, J = 4.8, 7.5 Hz), 7.03 (s, 1H), 3.18 (m, 1H), 2.88 (m, 4H), 2.75 (t, 1H, J = 5.7 Hz), 2.55 (m, 1H), 2.18 (m, 1H), 1.43 (d, 3H), 1.41 (s, 3H), 1.34 (d, 1H, J = 9.9 Hz), 0.66 (s, 3H). Anal. calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.66; H, 7.69; N, 9.55.

*3.4. (8*S,*10*S,*11*R*)-11-Butyl-8,10-methano-9,9-dimethyl-5,6,8,9,10,11-hexahydrobenzo[*b*][1,10]-phenanthroline* ***3c***

The procedure described for the preparation of **3b** was followed using butyl iodide: 0.70 g (42%); oil; $[\alpha]_D^{25}$ −57.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.67 (dd, 1H, J = 1.5, 4.8 Hz), 7.48 (dd, 1H, J = 1.5, 7.5 Hz), 7.14 (dd, 1H, J = 4.8, 7.5 Hz), 7.03 (s, 1H), 3.19 (m, 1H), 2.89 (m, 4H), 2.75 (t, 1H, J = 5.7 Hz), 2.50 (m, 2H), 2.37 (m, 1H), 1.50–1.30 (m, 5H), 1.42 (s, 3H), 1.34 (d, 1H, J = 9.9 Hz), 0.92 (t, 3H, J = 7.2 Hz), 0.66 (s, 3H). Anal. calcd for $C_{23}H_{28}N_2$: C, 83.09; H, 8.49; N, 8.43. Found: C, 83.19; H, 8.48; N, 8.55.

*3.5. (8*S,*10*S,*11*R*)-8,10-Methano-9,9-dimethyl-11-phenylmethyl-5,6,8,9,10,11-hexahydrobenzo-[b][1,10]phenanthroline* ***3d***

The procedure described for the preparation of **3b** was followed using benzyl iodide: 1.28 g (52%); 86–88°C; $[\alpha]_D^{25}$ +46.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.71 (d, 1H, J = 4.2 Hz), 7.53 (d, 1H, J = 7.2 Hz), 7.30 (m, 4H), 7.20 (m, 2H), 7.10 (s, 1H), 4.01 (dd, 1H, J = 13.5, 4.2 Hz), 3.56 (m, 1H), 2.94 (m, 4H), 2.76 (dd, 1H, J = 5.7, 11.1 Hz), 2.67 (d, 1H, J = 12.3 Hz), 2.53 (m, 1H), 2.05 (m, 1H), 1.47 (d, 1H, J = 9.9 Hz), 1.32 (s, 3H), 0.63 (s, 3H). Anal. calcd for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.33; H, 7.22; N, 7.75.

3.6. (8S,10S,11R)-8,10-Methano-11-(2-methylpropyl)-9,9,-dimethyl-5,6,8,9,10,11-hexahydrobenzo[b][1,10]phenanthroline **3e**

The procedure described for the preparation of **3b** was followed using 2-methylpropyl iodide: 0.73 g (44%); 57–59°C; $[\alpha]_D^{25}$ −56.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.70 (d, 1H, $J=4.8$ Hz), 7.51 (d, 1H, $J=7.5$ Hz), 7.16 (dd, 1H, $J=4.8$, 7.5 Hz), 7.04 (s, 1H), 3.33 (m, 1H), 2.89 (m, 4H), 2.76 (t, 1H, $J=5.7$ Hz), 2.51 (m, 1H), 2.38–2.18 (m, 2H), 1.73 (m, 1H), 1.54 (m, 1H), 1.43 (s, 3H), 1.35 (d, 1H, $J=9.9$ Hz), 1.02 (d, 3H, $J=6.6$ Hz), 0.96 (d, 3H, $J=6.6$ Hz), 0.67 (s, 3H). Anal. calcd for $C_{23}H_{28}N_2$: C, 83.09; H, 8.49; N, 8.43. Found: C, 83.23; H, 8.32; N, 8.35.

3.7. (8S,10S)-8,10-Methano-9,9-dimethyl-5,6,8,9,10,11-hexahydrodibenzo[b,l][1,10]phenanthroline **7a**

A solution of 4-oxo-1,2,3,4-tetrahydroacridine **6** (1.97 g, 10 mmol) in anhydrous THF (5 ml) was added dropwise at −78°C to a solution of lithium diisopropylamine (10 mmol) in anhydrous THF (50 ml). The resulting solution was stirred at −40°C for 1 h and then a solution of (−)-pinocarvone (1.5 g, 10 mmol) in THF (5 ml) was added dropwise at −40°C. After 15 min at −40°C, the solution was allowed to slowly reach rt and was then poured into a mixture of ammonium acetate (15.4 g, 0.2 mol) and acetic acid (50 ml). The flask was connected with a distillation head and the THF was distilled off over a 3 h period. Most of the acetic acid was removed under reduced pressure and the residue taken up with H_2O and extracted with CH_2Cl_2. The organic phase was separated, washed with a 5% NaOH solution and then dried on anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 7/3) to give pure **7a**: 1.83 g (56%); mp 197°C; $[\alpha]_D^{25}$ +112.2 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.37 (d, 1H, $J=8.1$ Hz), 7.97 (s, 1H), 7.75 (dd, 1H, $J=1.2$, 9.0 Hz), 7.65 (ddd, 1H, $J=1.2$, 6.9, 8.4 Hz), 7.50 (ddd, 1H, $J=1.2$, 6.9, 8.4 Hz), 7.15 (s, 1H), 3.40 (s, 2H), 3.14 (m, 2H), 2.98 (t, 2H, $J=6.9$ Hz), 2.82 (t, 1H, $J=5.4$ Hz), 2.71 (m, 1H), 2.42 (m, 1H), 1.43 (s, 3H), 1.32 (d, 1H, $J=9.6$ Hz), 0.72 (s, 3H). Anal. calcd for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.75; H, 6.64; N, 8.76.

3.8. (8S,10S,11R)-11-Butyl-8,10-methano-9,9-dimethyl-5,6,8,9,10,11-hexahydrodibenzo[b,l]-[1,10]phenanthroline **7b**

A solution of the pyridine **7a** (1.63 g, 5 mmol) in anhydrous THF (3 ml) was added at −78°C to a solution of lithium diisopropylamine (5 mmol) in anhydrous THF (25 ml). The resulting solution was stirred at −40°C for 2 h. Then a solution of butyl iodide (0.92 g, 5 mmol) in THF (3 ml) was added dropwise at −40°C. After 15 min at −78°C, the solution was allowed to slowly reach rt and then treated with H_2O. The organic phase was separated and the aqueous phase extracted twice with ethyl ether. The combined organic phases were dried on anhydrous Na_2SO_4, the solvent evaporated and the residue purified by chromatography on neutral aluminium oxide (benzene/petroleum ether = 9/1); 1.28 g (67%); oil; $[\alpha]_D^{25}$ +22.5 (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.32 (d, 1H, $J=8.1$ Hz), 7.91 (s, 1H), 7.71 (d, 1H, $J=8.1$ Hz), 7.64 (dt, 1H, $J=1.2$, 6.9 Hz), 7.46 (dt, 1H, $J=1.2$, 8.1 Hz), 7.08 (s, 1H), 3.24 (m, 1H), 3.10 (m, 2H), 2.93 (dd, 2H, $J=6.6$, 7.5 Hz), 2.78 (t, 2H, $J=5.4$ Hz), 2.55 (m, 2H), 2.39 (m, 1H), 1.60–1.25 (m, 4H), 1.43 (s, 3H), 1.36 (d, 1H, $J=8.4$ Hz), 0.95 (t, 3H, $J=6.9$ Hz), 0.68 (s, 3H). Anal. calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.75; H, 6.74; N, 7.44.

3.9. (8S,10S,11R)-8,10-Methano-9,9-dimethyl-11-phenylmethyl-5,6,8,9,10,11-hexahydrodibenzo[b,l][1,10]phenanthroline **7c**

The procedure described for the preparation of **7a** was followed using benzyl iodide. Chromatographic eluent: benzene/petroleum ether = 9/1; 1.10 g (53%); mp 108–110°C; $[\alpha]_D^{25}$ +65.8 (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.32 (d, 1H, J = 8.4 Hz), 7.95 (s, 1H), 7.73 (d, 1H, J = 7.8 Hz), 7.65 (t, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.2 Hz), 7.39–7.28 (m, 4H), 7.26–7.18 (m, 1H), 7.15 (s, 1H), 4.11 (dd, 2H, J = 4.2, 9.6 Hz), 3.64 (m, 1H), 3.15 (m, 1H), 2.99 (t, 2H, J = 7.2 Hz), 2.78 (t, 2H, J = 6.0 Hz), 2.73 (d, 1H, J = 13.2 Hz), 2.56 (m, 1H), 2.37 (m, 1H), 2.09 (m, 1H), 1.47 (d, 1H, J = 9.6 Hz), 1.33 (s, 3H), 0.65 (s, 3H). Anal. calcd for $C_{30}H_{28}N_2$: C, 86.49; H, 6.78; N, 6.73. Found: C, 86.33; H, 6.77; N, 6.88.

3.10. (5S,7S)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-quinolinyl-5,7-methanoquinoline **9a**

A solution of 2-acetylquinoline **8** (0.85 g, 5 mmol) in anhydrous THF (3 ml) was added dropwise at −78°C to a solution of lithium diisopropylamine (5 mmol) in anhydrous THF (25 ml). The resulting solution was stirred at −40°C for 2 h and then a solution of (−)-pinocarvone (0.75 g, 5 mmol) in THF (5 ml) was added dropwise at −40°C. After 15 min at −40°C, the solution was allowed to slowly reach rt and then poured into a mixture of ammonium acetate (3.85 g, 50 mmol) and acetic acid (25 ml). The flask was connected with a distillation head and the THF was distilled off over a 3 h period. Most of the acetic acid was removed under reduced pressure and the residue taken up with H_2O and extracted with ethyl ether. The organic phase was separated, washed with a 5% NaOH solution and then dried on anhydrous Na_2SO_4. The solvent was evaporated and the residue purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 1/1) to give pure **9a**: 0.54 g (36%); mp 134–135°C; $[\alpha]_D^{25}$ +69.8 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.54 (d, 1H, J = 8.7 Hz), 8.31 (d, 1H, J = 7.5 Hz), 8.24 (d, 1H, J = 8.7 Hz), 8.16 (d, 1H, J = 8.7 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.71 (t, 1H, J = 6.9 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.38 (d, 1H, J = 7.5 Hz), 3.23 (d, 2H, J = 2.4 Hz), 2.84 (t, 1H, J = 5.7 Hz), 2.72 (m, 1H), 2.42 (m, 1H), 1.43 (s, 3H), 1.34 (d, 1H, J = 9.9 Hz), 0.69 (s, 3H). Anal. calcd for $C_{21}H_{20}N_2$: C, 83.95; H, 6.72; N, 9.33. Found: C, 83.78; H, 6.88; N, 9.44.

3.11. (5S,7S,8R)-8-Butyl-5,6,7,8-tetrahydro-6,6-dimethyl-2-quinolinyl-5,7-methanoquinoline **9b**

A solution of **9a** (0.86 g, 5 mmol) in anhydrous THF (3 ml) was added at −78°C to a solution of lithium diisopropylamine (5 mmol) in anhydrous THF (25 ml). The resulting solution was stirred at −40°C for 2 h. Then a solution of butyl iodide (0.92 g, 5 mmol) in THF (3 ml) was added dropwise at −40°C. After 15 min at −78°C, the solution was allowed to slowly reach rt and then treated with H_2O. The organic phase was separated and the aqueous phase extracted twice with ethyl ether. The combined organic phases were dried on anhydrous Na_2SO_4, the solvent evaporated and the residue purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 40/1) to give pure **9b**: 0.46 g (26%); oil; $[\alpha]_D^{25}$ −13.5 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.62 (d, 1H, J = 8.4 Hz), 8.35 (d, 1H, J = 7.5 Hz), 8.25 (d, 1H, J = 8.7 Hz), 8.18 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.72 (t, 1H, J = 8.4 Hz), 7.51 (t, 1H, J = 8.1 Hz), 7.38 (d, 1H, J = 7.5 Hz), 3.10 (m, 1H), 2.82 (t, 1H, J = 5.7 Hz), 2.57 (m, 1H), 2.43 (m, 2H), 1.61–1.19 (m, 5H), 1.44 (s, 3H), 1.36 (d, 1H, J = 9.9 Hz), 0.99 (t, 3H, J = 7.2 Hz), 0.66 (s, 3H). Anal. calcd for $C_{25}H_{28}N_2$: C, 84.22; H, 6.92; N, 7.86. Found: C, 86.21; H, 6.88; N, 7.69.

3.12. (5S,7S,8R)-5,6,7,8-Tetrahydro-6,6-dimethyl-8-phenylmethyl-2-quinolinyl-5,7-methanoquinoline **9c**

The procedure described for the preparation of **9a** was followed using benzyl iodide. Chromatographic eluent: benzene/petroleum ether = 40/1; 0.68 g (35%); oil; $[\alpha]_D^{25}$ +62.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.64 (d, 1H, J = 8.4 Hz), 8.39 (d, 1H, J = 7.8 Hz), 8.25 (d, 1H, J = 8.4 Hz), 8.16 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.1 Hz), 7.21 (t, 1H, J = 8.1 Hz), 7.51 (t, 1H, J = 6.9 Hz), 7.40 (d, 1H, J = 7.8 Hz), 7.33 (m, 5H), 3.90 (dd, 1H, J = 13.6, 3.6 Hz), 3.43 (d, 1H, J = 10.5 Hz), 2.83 (t, 1H, J = 5.7 Hz), 2.75 (d, 1H, J = 11.7 Hz), 2.58 (m, 1H), 2.15 (m, 1H), 1.45 (d, 1H, J = 9.9 Hz), 1.35 (s, 3H), 0.63 (s, 3H). Anal. calcd for $C_{28}H_{26}N_2$: C, 86.11; H, 6.72; N, 7.18. Found: C, 86.22; H, 6.66; N, 7.29.

3.13. (5S,7S,8R)-8-Butyl-6,6-dimethyl-5,7-methano-2-(2-pyridinyl)-5,6,7,8-tetrahydroquinoline **1c**

The procedure described for the preparation of **9b** was followed starting from **1a**. Compound **1c** was purified by chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 95/5; 0.98 g (64%); oil; $[\alpha]_D^{25}$ +5.42 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.65 (d, 1H, J = 4.8 Hz), 8.45 (d, 1H, J = 7.8 Hz), 8.07 (d, 1H, J = 7.8 Hz), 7.80 (dt, 1H, J = 7.8, 1.8 Hz), 7.31 (d, 1H, J = 7.8 Hz), 7.26 (m, 1H), 3.04 (m, 1H), 2.79 (t, 1H, J = 5.7 Hz), 2.55 (m, 1H), 2.35 (m, 2H), 1.50 (m, 5H), 1.45 (s, 3H), 1.33 (d, 1H, J = 9.9 Hz), 0.97 (t, 3H, J = 7.2 Hz), 0.65 (s, 3H). Anal. calcd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.44; H, 8.33; N, 9.19.

3.14. Allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate: general procedure

A solution of ligand (0.04 mmol, 10 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4 mg, 2.5 mol%) in dry CH_2Cl_2 (2 ml) was stirred at rt for 15 min. This solution was treated successively with a solution of *rac*-(E)-1,3-diphenyl-2-propenyl acetate (0.4 mmol) in CH_2Cl_2 (1 ml), dimethyl malonate (1.2 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (1.2 mmol) and anhydrous potassium acetate (3.5 mol%). The reaction mixture was stirred for the appropriate time (see Table 1) until conversion was complete as shown by TLC analysis (light petroleum/ether = 3/1). The reaction mixture was diluted with ether (25 ml), washed with ice-cold saturated aqueous ammonium chloride. The organic phase was dried on Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum/ether = 3/1) to afford dimethyl 1,3-diphenyl-prop-2-enylmalonate. The enantiomeric excess was determined by the ^1H NMR spectrum in the presence of enantiomerically pure shift reagent Eu(hfc)$_3$; splitting of the signals for one of the two methoxy groups was observed.

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