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Palladium-catalyzed asymmetric synthesis of axially chiral molecules

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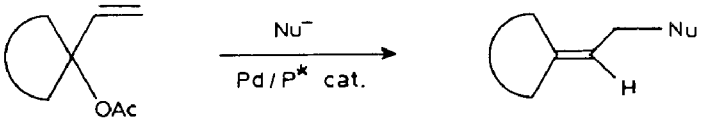
Abstract

The asymmetric synthesis of chiral 3-alkylidene bicyclo[3.3.0]octane and 4-substituted 1-alkylidene cyclohexane systems has been carried out (in up to 40% ee) by the palladium-catalyzed reaction of allylic acetates with sodium dimethyl malonate or morpholine.

Introduction

Chiral cycloalkylidenes of type I and II have been synthesized in optically active form by various procedures: (a) resolution of racemic material (either by separation of diastereomeric salts [1–5] or by kinetic resolution) [6]; (b) asymmetric synthesis involving asymmetric Wittig-type olefination [7–10], asymmetric elimination from chiral sulfoxides [11] or sulfoximides [12], or asymmetric dehydrohalogenation of haloacids [13].

We reported in a preliminary note [14] the first asymmetric synthesis of an axially dissymmetric molecule through the use of chiral transition metal catalysts. We now present our results in detail for the palladium-catalyzed asymmetric synthesis of some representative molecules of type I and II, viz. **1–4**, from the achiral allylic acetates *cis*- and *trans*-**6** and *cis*- and *trans*-**8** and **10**, according to the general scheme:



achiral chiral

P* = optically active phosphine

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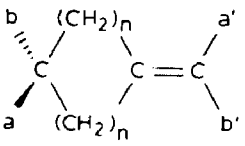
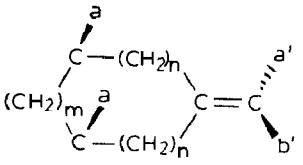
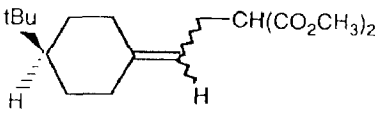


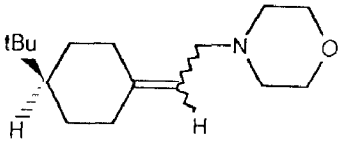
$a \neq b$; $a' \neq b'$ (I)



$a' \neq b'$ (II)



(1)



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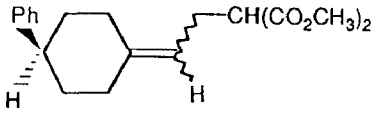

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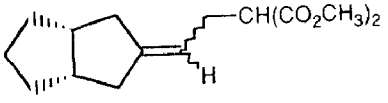

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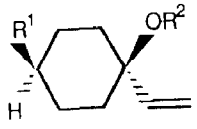
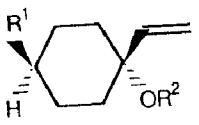
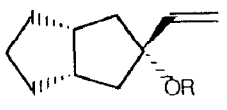


cis-(5): R^1=*t*Bu, R^2=H
cis-(6): R^1=*t*Bu, R^2=Ac
cis-(7): R^1= Ph, R^2=H
cis-(8): R^1= Ph, R^2=Ac



trans-(5): R^1=*t*Bu, R^2=H
trans-(6): R^1=*t*Bu, R^2=Ac
trans-(7): R^1= Ph, R^2=H
trans-(8): R^1= Ph, R^2=Ac



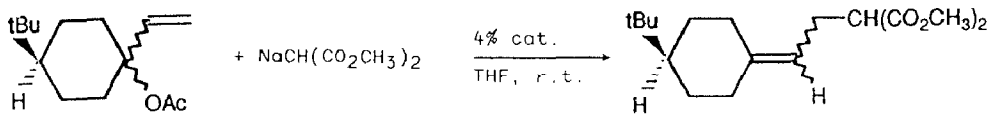
(9), R=H
(10), R=Ac

Results and discussions

Palladium-catalyzed alkylation of cis- and trans-4-t-butyl-1-vinylcyclohexyl acetates **6** *with sodium dimethyl malonate*

The diastereomeric alcohols *cis*-**5** and *trans*-**5** were readily prepared in 46/54 ratio by reaction of 4-t-butyl cyclohexanone with an excess of vinylmagnesium bromide in THF. They were separated by flash chromatography on silica.

The corresponding acetates reacted with sodium dimethyl malonate in THF at room temperature in the presence of a ($Pd(dba)_2$ + dppe) catalyst to give the single product **1** (70% isolated yield):



(6) (1)

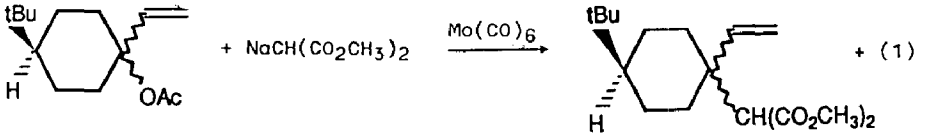
Table 1

Palladium-catalyzed asymmetric alkylation of *cis*-**6** and *trans*-**6** with sodium dimethyl malonate [a]

Substrate	Phosphine [b]	**1** Yield (%, isolated)	$[\alpha]_D^{20}$ (conc.) [c] (°)	ee (%)
cis-**6**	(+)-DIOP	60	−2.8±0.6 (1.19)	20±5 [d]
cis-**6**	(*S*,*S*)-CHIRAPHOS	73	<1 (1.12)	<10 [e]
cis-**6**	(*R*)-(+)-PROPHOS	70	<1 (1.36)	<10 [e]
cis-**6**	(*R*)-(+)-BINAP	82	−3.2±0.4 (1.72)	25±5 [d]
cis-**6**	(*R*)-(−)-PHENPHOS	57	<1 (2.35)	<10 [e]
trans-**6**	(+)-DIOP	82	−1.2±0.5 (1.37)	10±6 [e]
trans-**6**	(*S*,*S*)-CHIRAPHOS	68	−5.2±0.5 (1.77)	33±5 [d]
trans-**6**	(*R*)-(+)-PROPHOS	62	+1.9±0.4 (1.71)	15±3 [e]
trans-**6**	(*R*)-(+)-BINAP	74	−5.1±0.5 (1.47)	40±5 [d]
trans-**6**	NMDPP	42	<1 (1.29)	<5 [d]
trans-**6**	(*S*,*S*-BDPP	58	−1.1±0.5 (3)	9±5 [e]
trans-**6**	(*R*)-(−)-PHENPHOS	59	+1.0±0.5 (2.5)	8±5 [e]

[a] 1 mmol substrate, 0.04 mmol $Pd(dba)_2$, 0.4 mmol diphosphine or 0.08 mmol monophosphine in 2 ml THF, then 3 ml of a 0.5 *M* THF solution of $NaCH(CO_2CH_3)_2$. [b] See Experimental section for meaning of acronyms. [c] In toluene. [d] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$. [e] Calculated from the optical rotation, assuming a value of $[\alpha]_D$ of 12.5° for enantiomerically pure **1**.

The excellent regioselectivity contrasts with that observed by Trost [15,16] for the molybdenum-catalyzed alkylation of *cis*-**6** or *trans*-**6**, which gave isomeric achiral **11** as the major product.



(6) (11)

The Pd-catalyzed reaction carried out on a mixture of diastereomeric acetates *cis*-**6** and *trans*-**6** showed that the *cis*-isomer was ca. 10 times more reactive than the *trans*. This result can be rationalized by assuming that the *anti*-periplanar approach [17] of the palladium to the C–O bond to be broken is *trans* to the t-butyl group for *cis*-**6**, and therefore favored over the *cis* approach to the t-butyl group for the *trans*-isomer.

Results for the asymmetric catalysis carried out on both *cis*-**6** and *trans*-**6** with various optically active mono- and diphosphines are shown in Table 1. For each phosphine the reaction took place regiospecifically, to give the product resulting from attack by the nucleophilic centre to the less-substituted end of the intermediate allylic palladium complex. The ee of the product was determined by ^1H NMR spectroscopy in presence of $Eu(hfc)_3$ (mole Eu/mole substrate ≃ 0.7) by examination of the external diastereotopy of the methoxy groups in **1** *.

The asymmetric induction can be interpreted as the result of the selection by the palladium complex of two reactive enantiomeric conformations **6A** and **6B** of the

* δ (ppm) 4.41 and 4.48, minor enantiomer; 4.46, major enantiomer, for which the internal diastereotopy is not revealed.

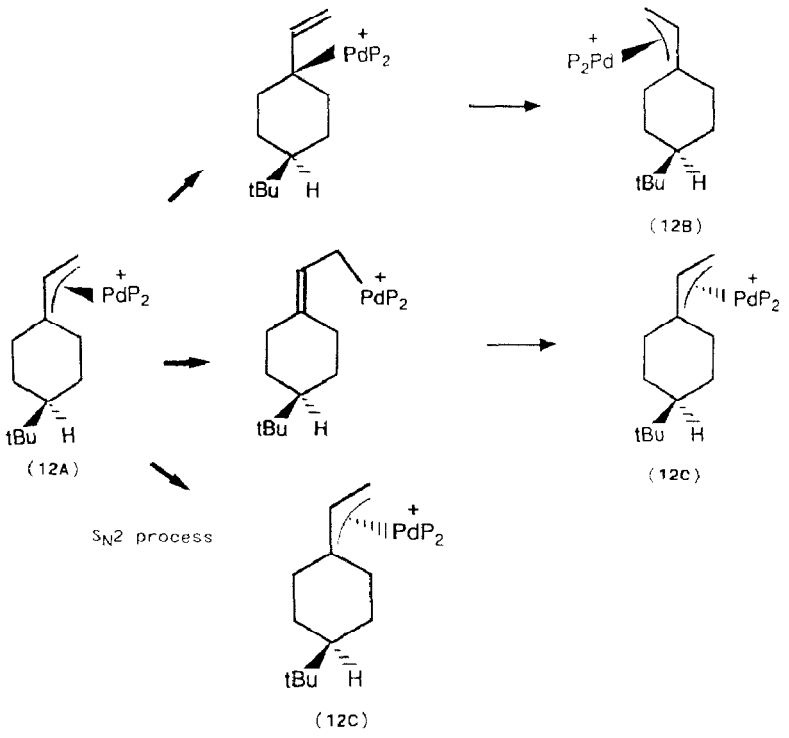
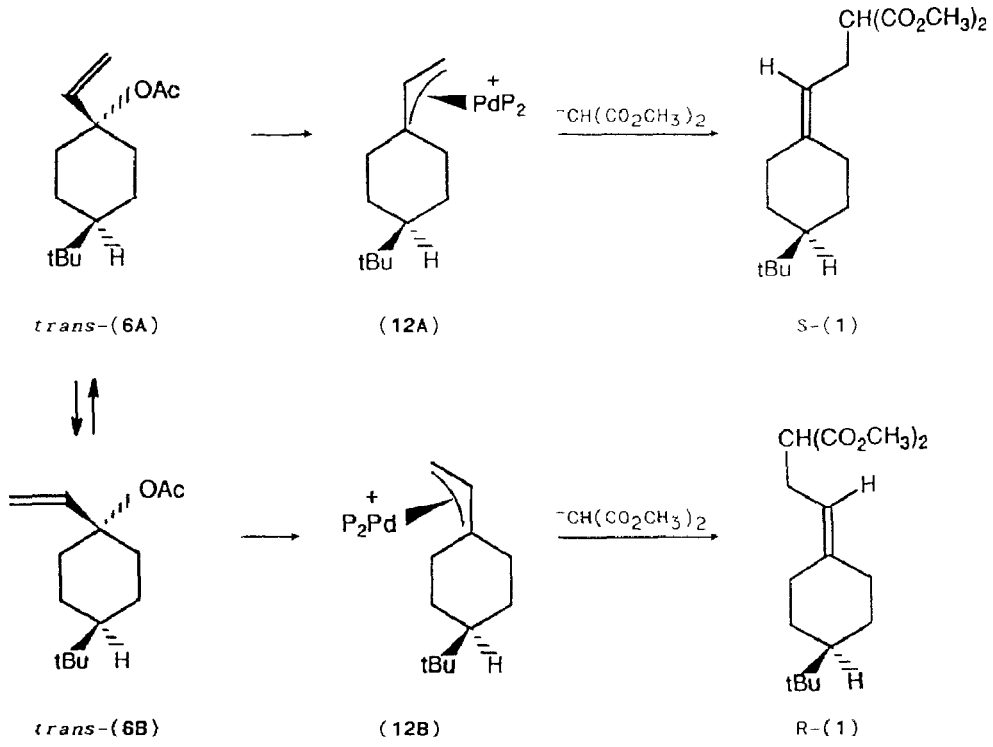


Fig. 1. Suggested process for the epimerization of the π-allylpalladium complex **12A**.



substrate, to give initially diastereomeric cationic complexes **12A** and **12B**. These complexes then lead to (*S*)-1 and (*R*)-1, respectively.

Two processes can be suggested to account for the isomerization of allyl complexes (Fig. 1), namely a monomolecular $\pi \rightarrow \sigma \rightarrow \pi$ process [18] and a bimolecular S_N2 displacement of the π-allylic ligand by a Pd^0 complex [19]. Depending on the mode of formation of the intermediate σ-complex from **6A** (Pd–C(1) or Pd–C(3) σ bond), the $\pi \rightarrow \sigma \rightarrow \pi$ process would lead to complex **12B** or **12C**, whereas the S_N2 process would lead to **12C**. Since the $\pi \rightarrow \sigma \rightarrow \pi$ process involving the formation of a palladium–tertiary carbon bond should be disfavored relative to a process involving a Pd–primary carbon bond [20], isomerization **12A** → **12B** is unlikely.

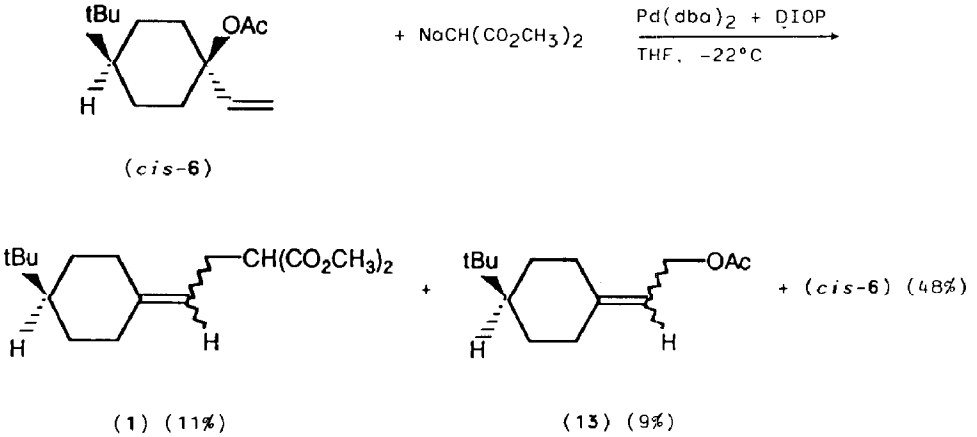
Moreover, the fact that the diastereomeric substrates generally give different asymmetric inductions with the same phosphine indicates that the isomerization of the π-allylpalladium complexes is not fast compared with their reaction with the nucleophile. Thus the most probable isomerization process for **12A** gives **12C**. Reaction of the nucleophile with **12A** or **12C** yields (*S*)-**1**. Thus overall (*S*)-**1** originates from the initial ionization of **6A** while (*R*)-**1** comes that of **6B**.

Consequently, the most likely origin of the asymmetric induction for the Pd-catalyzed reaction of sodium dimethyl malonate with *cis*- or *trans*-**6** lies in the selection by the chiral Pd^0 complex between the enantiomeric conformers of the allylic substrate.

Influence of the amount of optically active ligand and the reaction temperature

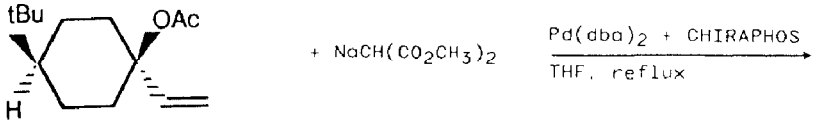
When the reaction in the case of *cis*-**6** was carried out with two molar equivalents of phosphine ((+)-DIOP) relative to $Pd(dba)_2$ there was no significant modification of the asymmetric induction ($[\alpha]_D^{20} - 2.1°$ (*c* 1.05, toluene), compared $[\alpha]_D^{20} - 2.8°$ (*c* 1.2, toluene) for 1 equivalent of DIOP).

Reaction of *cis*-**6** with sodium dimethyl malonate was carried out at low (−22°C) temperature with 4 mol-% ($Pd(dba)_2$ + DIOP) catalyst for 24 h. Along with the expected product **1** (11%), the isomerized allylic acetate **13** was isolated (9%), and 48% of *cis*-**6** was recovered:

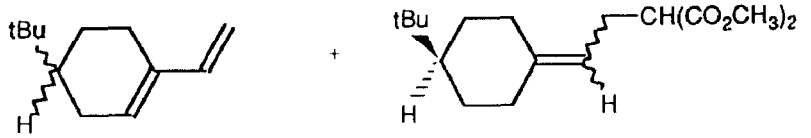


The isomerized linear allylic acetate **13** was never isolated in the experiments at room temperature. Moreover, the product **1** showed a lower specific optical rotation ($[\alpha]_D^{20} - 1.2°$ (*c* 1.2, toluene)) than that obtained at room temperature ($[\alpha]_D^{20} - 2.8°$ (*c* 1.2, toluene)).

The yield of product **1** from the reaction at reflux temperature (with CHIRAPHOS as a ligand) was lower (44%) owing to formation of the diene **14** as elimination product:



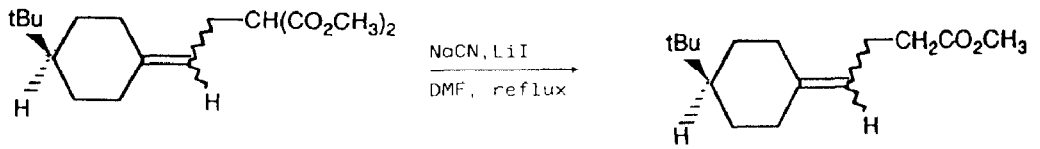
(*cis*-**6**)



(**14**) (35%) (**1**) (44%)

Furthermore the ee of the isolated product **1** was lower ($[\alpha]_D^{20}$ −4.1° (*c* 1.6, toluene)) than for the reaction at room temperature (see Table 1).

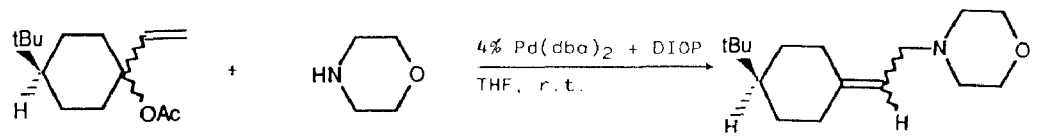
Decarbomethoxylation of **1** by Krapcho's procedure [21] gave the optically active product **15**.



(**1**) $[\alpha]_D^{20}$ −0.9° (**15**) $[\alpha]_D^{20}$ −1.0°

Palladium-catalyzed amination of cis-6 and trans-6 with morpholine

Substitution of the acetate group in *cis*-**6** and *trans*-**6** by morpholine (with (+)-DIOP as the optically active ligand) gave the optically active amine **16**, with respectively $[\alpha]_D^{20}$ −0.9° (*c* 1.1, toluene) and $[\alpha]_D^{20}$ −0.4 (*c* 1.2, toluene). The corresponding ee could not be determined *.



(*cis*-**6**) or (*trans*-**6**) (**16**) (69%)

* The use of $Eu(hfc)_3$ did not induce sufficient ^1H chemical shift differences between enantiomers to allow a proper determination of the ee.

Table 2

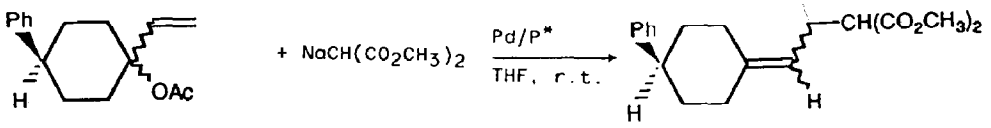
Palladium-catalyzed asymmetric alkylation of **8** with sodium dimethyl malonate [a]

Substrate	Phosphine	3 yield (%) [b]	$[\alpha]_D^{20}$ (conc.) [c] (°)
cis-**8**	DIOP	82	−2.3 (1.77)
trans-**8**	DIOP	84	−5.4 (1.7)
cis-**8**	NMDPP	52	+1.3 (1.67)
trans-**8**	NMDPP	58	+0.6 (1.62)

[a] 1 mmol substrate, 0.04 mmol $Pd(dba)_2$, 0.04 mmol DIOP or 0.08 mmol NMDPP in 2 ml THF, then 3 ml of a 0.5 *M* THF solution of $NaCH(CO_2CH_3)_2$. [b] Isolated yield. [c] In toluene.

Palladium-catalyzed alkylation of cis- and trans-4-phenyl-1-vinylcyclohexyl acetates (8) with sodium dimethyl malonate

Results for alkylation of *cis*-**8** and *trans*-**8** are listed in Table 2.



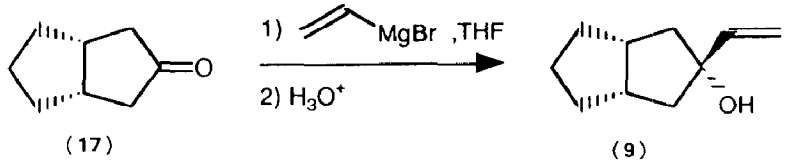
(*cis*-8) or
(*trans*-8)

(3)

The asymmetric induction depends both on the stereochemistry of the starting acetate and on the nature of the inducing optically active phosphine. The asymmetric induction appears to be better with the diphosphine DIOP than with the monophosphine NMDPP. The corresponding ee could not be evaluated *.

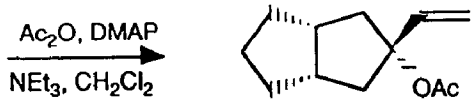
Palladium-catalyzed alkylation of endo-3-vinylbicyclo[3.3.0]octane-3-yl acetate (10) with sodium dimethyl malonate

The bicyclic allylic acetate **10** was obtained by acetylation of the corresponding alcohol **9** prepared as a single stereoisomer by reaction of bicyclo[3.3.0]octane-3 one (**17**) with vinylmagnesium bromide:



(17)

(9)



(10)

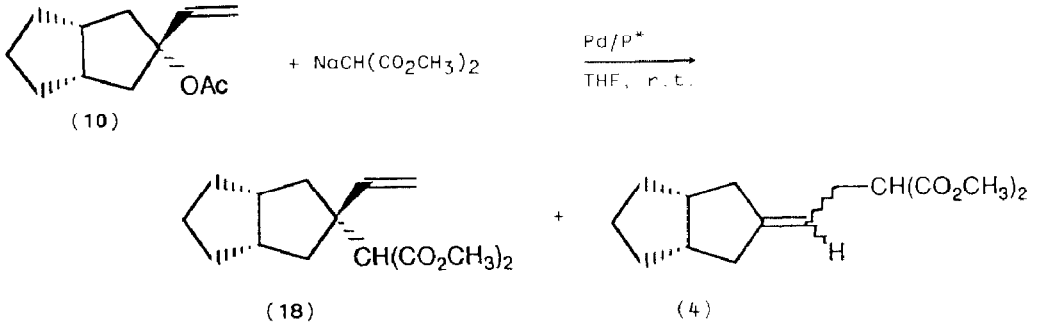
The palladium-catalyzed alkylation of **11** with sodium dimethyl malonate was not regioselective, leading to two regioisomers, **18** (achiral) and **4** (chiral):

Table 3

Palladium-catalyzed alkylation of **10** by sodium dimethyl malonate [a]

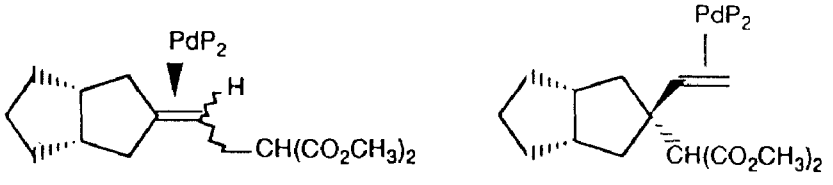
Phosphine	Yield (%) [b]	**4**/**18** [c]	$[\alpha]_D^{20}$ [d] (conc.) (°)	$[\alpha]_D^{20}$ [e]	ee [f] (%)
DPPE	35	87/13			
PPh_3	41	19/81			
(+)-DIOP	61	71/29	−0.4 (1.9)	−0.5	
CHIRAPHOS	79	95/5	−1.1 (2.7)	−1.2	16 ± 5
BINAP	81	69/31	−0.2 (2.6)	−0.2	

[a] Substrate (1 mmol); catalyst: $Pd(dba)_2$ (0.04 mmol) + 0.04 mmol (diphosphine) or 0.08 ml monophosphine in 2 ml THF, then 3 ml of a 0.5 *M* THF solution of $NaCH(CO_2CH_3)_2$. [b] Isolated. [c] Determined by GLC and confirmed by ^1H NMR spectroscopy. [d] In toluene for the product mixture **4**/**18**. [e] Calculated value for **4**. [f] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.



(10) (18) (4)

The relative amounts of **18** and **4** were very dependent upon the nature of the phosphine used (Table 3). The regioselectivity can be tentatively interpreted in terms of the steric hindrance in the π-olefinic palladium complexes **19** and **20** produced at the end of the catalytic cycle [22].



(19) (20)

Formation of the less-hindered π-olefinic complex **20** would be favoured for bulky phosphines, such as PPh_3. By chance, chiraphos gave both the best regio- and enantioselectivity: $[\alpha]_D^{20}$ −1.2° (*c* 2.7, toluene) (≃ 16 ± 5% ee).

The asymmetric induction probably arises from a selection between two enantiomeric reactive conformations **10A** and **10B** of **10** by the optically active palladium complex (Fig. 2). It is also likely that only the two *exo* complexes would be present, the *endo* complexes being too much sterically congested.

Conclusion

Asymmetric synthesis of chiral 3-alkylidene bicyclo[3.3.0]octane and 4-substituted 1-alkylidenecyclohexane systems has been carried out (in up to 40% ee) through palladium-catalyzed substitution of allylic acetates. The asymmetric induction may be interpreted as the result of the selection by the chiral palladium(0)

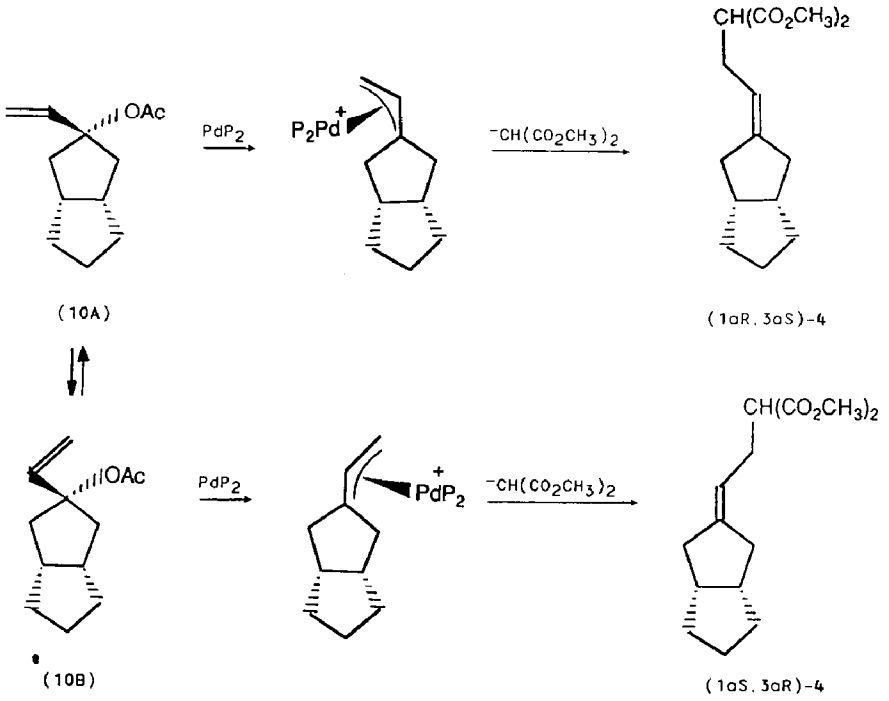


Fig. 2. Asymmetric induction scheme for the Pd-catalyzed reaction of sodium dimethyl malonate with **10**.

complex of two enantiomeric conformers of the substrate in fast equilibrium (Curtin–Hammett conditions) [23].

Specific ligands have been previously constructed to give high asymmetric induction in palladium-catalyzed allylations, depending on the nature of the enantioselective catalytic step: enantioface selection in an enolate by a chiral palladium complex [24], and preferential attack by an achiral nucleophile of one end of a *meso*-π-allyl fragment bound to a chiral template [25]. We are currently seeking to establish the structural requirements for the design of ligands which will provide efficient selection between the enantiomeric conformations of allylic acetates **6**, **8** and **10**.

The asymmetric synthesis of new cycloalkylidene systems, involving both further achiral allylic substrates and additional nucleophiles is at present under investigation, in order to permit evaluation of their chiroptical properties.

Experimental

General

All reactions were carried out under argon by Schlenk techniques. THF was distilled under argon from sodium benzophenone ketyl immediately before use.

^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer at 250 MHz and 62.898 MHz, respectively, in $CDCl_3$ solution containing tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin–Elmer 883 spectrometer, and are reported in cm^{-1}. Mass spectra (MS) (at 70 eV) were

obtained with a R-10 gas chromatograph/mass spectrometer. GLC analyses were carried out with a 25 m CPSil 19CB capillary column on a Carlo Erba 4130 instrument. Optical rotations were measured with a Perkin–Elmer 241 polarimeter.

The following materials were obtained from commercial sources: $Pd(dba)_2$ (were dba denotes dibenzylideneacetone): (+)-DIOP: (4*S*,5*S*)-2,3-*O*-isopropylidene-2,3-hydroxy-1,4-bis-diphenylphosphinobutane [26], $[\alpha]_D^{20}$ 12.5° (*c* 8, $CHCl_3$); (*S*,*S*)-CHIRAPHOS: (2*S*,3*S*)-bis(diphenylphosphino)butane [27], $[\alpha]_D^{20}$ −211° (*c* 1.5, $CHCl_3$); (*R*)-(+)-PROPHOS: (*R*)-(+)-1,2-bis(diphenylphosphino)propane [28], $[\alpha]_D^{20}$ 186° (*c* 1, acetone); (*R*)-(+)-BINAP: (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [29], $[\alpha]_D^{20}$ 233° (*c* 0.3, toluene); NMDPP: neomentyldiphenylphosphine [30], $[\alpha]_D^{20}$ 87° (*c* 1.6, CH_2Cl_2); (*R*)-(−)-PHENPHOS: 1,2-bis(diphenylphosphino)-1-phenylethane [31], $[\alpha]_D^{20}$ −9.6° (*c* 0.71, toluene): (*S*,*S*)-(−)-BDPP: (−)-(2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane [32], $[\alpha]_D^{20}$ −124° (*c* 3.0, $CHCl_3$).

The following materials were prepared by reported procedures: *cis*- and *trans*-4-t-butyl 1-vinylcyclohexanols **5** [33], *cis*- and *trans*-4-phenyl 1-vinylcyclohexanols [34] **7** and the bicyclic ketone **17** [35].

Synthesis of cis-6 and trans-6

Acetic anhydride (0.25 ml, 2.65 mmol) was added to a solution of *cis*- or *trans*-**5** (437 mg, 2.4 mmol), Et_3N (0.4 ml, 2.87 mmol), and DMAP (30 mg, 0.25 mmol) in anhydrous ether (2 ml). The mixture was stirred overnight, then diluted with ether (50 ml) and washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and water, then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica, cyclohexane/ethyl acetate: 9/1), then by bulb-to-bulb distillation.

cis-6: R_F 0.55, b.p. 100 °C (0.4 mmHg) (84% yield). ^1H NMR ($CDCl_3$) δ 0.87 (s, 9H), 1.0–1.1 (m, 1H), 1.2–1.5 (m, 4H), 1.55–1.7 (d, 2H), 2.03 (s, 3H), 2.3–2.5 (d, 2H), 5.08 (d, 1H, *J* 11 Hz), 5.12 (d, 1H, *J* 17.5 Hz), 6.1 (dd, 1H, *J* 17.5 and 11 Hz). ^{13}C NMR ($CDCl_3$) δ 22.0, 22.3, 27.5, 32.3, 35.0, 47.0, 81.3, 112.8, 142.3, 169.9. IR (liquid film) 2947, 1740, 1448, 1366, 1263, 1231, 1184, 1016, 956. MS (chemical ionization, NH_3), *m/e* (relative intensity) 242 ($M^+ + 18$)(3), 182(49), 166(21), 165(100), 164(54), 121(32), 109(23), 108(70), 107(39). Found: C, 75.00; H, 10.77. $C_{14}H_{24}O_2$ calc: C, 74.95; H, 10.78%.

trans-6: R_F 0.6; b.p. 100 °C (0.4 mmHg) (79% yield). ^1H NMR ($CDCl_3$) δ 0.83 (s, 9H), 1.0–1.2 (m, 3H), 1.5–1.8 (m, 4H), 1.95 (s, 3H), 2.4–2.5 (d, 2H), 5.3 (d, 1H, *J* 11 Hz), 5.32 (d, 1H, *J* 17.5 Hz), 6.16 (dd, 1H, *J* 17.5 and 11 Hz). ^{13}C NMR ($CDCl_3$) δ 22.3, 24.1, 27.5, 32.2, 36.0, 47.4, 82.1, 116.5, 139.3, 169.7. IR (liquid film) 2946, 2868, 1738, 1367, 1243, 1017, 928. MS (chemical ionization, NH_3) *m/e* (relative intensity) 242 ($M^+ + 18$)(0.3), 182(42), 166(25), 165(100), 164(41), 121(32), 108(63), 107(39). Found: C, 74.63; H, 10.82. $C_{14}H_{24}O_2$ calc: C, 74.95; H, 10.78%.

Reaction of cis-6 and trans-6 with sodium dimethyl malonate in presence of the [Pd(dba)$_2$ + phosphine] catalyst system

A mixture of $Pd(dba)_2$ (23 mg, 0.04 mmol), diphosphine (0.04 mmol) or monophosphine (0.08 mmol) was stirred for 0.25 h in 1 ml THF. *Cis*-**6** or *trans*-**6** (224 mg, 1 mmol) in THF (1 ml) was then added by syringe followed, after further 0.25 h stirring, by 3 ml (syringe) of a 0.5 *M* solution of sodium dimethyl malonate (prepared by reaction of dimethyl malonate with NaH in THF). The homogeneous

reaction mixture was stirred at room temperature for 16 h, the products being monitored by GLC analysis. The reaction mixture was diluted with ether (10 ml) and the organic phase washed with 2×10 ml saturated aqueous NH_4Cl. The aqueous phases were extracted with ether (3×10 ml) and the combined ethereal phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography to give **1** with 70% yield. ^1H NMR ($CDCl_3$) δ 0.85 (s, 9H), 0.85–1.2 (m, 3H), 1.55–1.75 (m, 1H), 1.75–1.95 (m, 2H), 2.0 (d, 1H), 2.2 (d, 1H), 2.45–2.75 (m, 3H), 3.4 (t, 1H, *J* 8 Hz), 3.72 (s, 6H), 5.0 (t, 1H, *J* 8 Hz). MS (70 eV): *m/e* (relative intensity) 296 (M^+)(3), 164(21), 145(92), 133(37), 121(36), 108(40), 107(40), 106(21), 95(21), 94(28), 93(65), 92(22), 91(33), 81(24), 80(33), 79(70), 77(23), 69(20), 57(100), 55(28), 41(45). IR (liquid film) 2951, 2867, 1755, 1741, 1437, 1365, 1338, 1233, 1149. Found: C, 69.08; H, 9.52. $C_{17}H_{28}O_4$ calc: C, 68.88; H, 9.52%.

*Reaction of trans-**6** with sodium dimethyl malonate, catalyzed by Pd(dba)$_2$ + chiraphos, in THF at reflux temperature*

The procedure described above was used, but with reaction in refluxing THF. Purification by flash chromatography on silica (cyclohexane/ethyl acetate: 9/1) gave 57 mg (35% yield) of the diene **15** (R_F 0.65): MS *m/e* (relative intensity) 164 (M^+)(27), 121(31), 93(58), 91(28), 80(48), 79(100), 57(48), and 134 mg (44% yield) of **1** (R_F 0.2) ($[\alpha]_D^{20}$ −4.10 (*c* 1.5, toluene)).

*Decarbomethoxylation of **1** to **16***

A mixture of **1** (972 mg, 3.28 mmol) $[\alpha]_D^{20}$ −0.9° (*c* 1.45, toluene), sodium cyanide (160 mg, 3.26 mmol), and lithium iodide (2.8 g, 21 mmol) in DMF (20 ml) was stirred at 120 °C for 16 h. The mixture was allowed to cool then into water (50 ml). After extraction with ether (3×20 ml), the combined ethereal extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (silica, cyclohexane/ethyl acetate: 9/1) to give 502 mg (64% yield) of **16** ($[\alpha]_D^{20}$ −1° (*c* 0.88, toluene)). ^1H NMR ($CDCl_3$) δ 0.8 (s, 9H), 0.85–1.2 (m, 3H), 1.65 (t, 1H), 1.85 (s, 2H), 2.0 (d, 1H), 2.15 (dq, 1H), 2.3 (d, 4H), 2.6 (dq, 1H), 3.65 (s, 3H), 5.0 (s, 1H). MS: *m/e* (relative intensity) 238 (M^+)(7), 182(28), 150(85), 108(27), 107(32), 93(21), 81(21), 79(40), 67(21), 57(100), 55(20), 41(42).

*Palladium-catalyzed amination of cis-**6** and trans-**6** with morpholine*

The reaction was carried out as above starting from **6** (226 mg, 0.1 mmol), $Pd(dba)_2$ (23 mg, 0.04 mmol), (+)-DIOP (20 mg, 0.04 mmol) and morpholine (110 µl, 1.26 mmol), to give after flash chromatography **16**. ^1H NMR ($CDCl_3$) δ 0.85 (s, 9H), 0.9–1.3 (m, 3H), 1.6–2.1 (m, 4H), 2.3 (d, 1H), 2.5 (s, 4H), 2.7 (d, 1H), 2.95 (d, 2H, *J* 8 Hz), 3.7 (t, 4H, *J* 5 Hz), 5.18 (t, 1H, *J* 8 Hz). IR (liquid film) 2955, 2858, 1480, 1454, 1394, 1366, 1330, 1313, 1289, 1269, 1241, 1119, 1005, 906, 870, 856. MS (70 eV) *m/e* (relative intensity) 251 (M^+)(7), 93(32), 88(90), 87(100), 86(68), 79(24), 57(79), 41(23).

*Synthesis of cis-**8** and trans-**8***

Acetic anhydride (1.2 ml, 12.69 mmol) was added to a solution of *cis*- or *trans*-4-phenyl 1-vinylcyclohexanol (2.2 g, 10.9 mmol), Et_3N (1.9 ml, 13.6 mmol) and DMAP (110 mg, 0.9 mmol) in anhydrous ether (15 ml). After work-up the crude

product was purified by flash chromatography (silica, cyclohexane/ethyl acetate: 9/1), then bulb-to-bulb distillation.

cis-**8**: R_F 0.5; b.p. 180 °C (0.5 mmHg) (77% yield). ^{1}H NMR ($CDCl_3$) δ 1.5–1.75 (m, 3H), 1.75–1.9 (m, 3H), 2.1 (s, 3H), 2.4–2.65 (m, 3H), 5.17 (dd, 1H, *J* 11 and 0.7 Hz), 5.21 (dd, 1H, *J* 17.5 and 0.7 Hz), 6.18 (dd, 1H, *J* 17.5 and 11 Hz), 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.1, 29.0, 34.8, 43.2, 80.8, 113.2, 126.1, 126.7, 128.4, 142.1, 146.7, 169.9. IR (liquid film): 2931, 1742, 1448, 1368, 1257, 1220, 1197, 1115, 1016, 957, 923, 758, 700. MS, *m/e* (relative intensity) 184(10), 105(10), 104(100), 93(11), 91(14), 43(18).Found: C, 78.82; H, 8.07. $C_{16}H_{20}O_2$ calc: C, 78.65; H, 8.25%.

trans-**8**: R_F 0.45; b.p. 190 °C (0.8 mmHg) (75% yield, m.p. 47–49 °C (lit.: 49–50 °C [36]). ^{1}H NMR ($CDCl_3$) δ 1.5–1.75 (m, 2H), 1.75–1.95 (m, 4H), 2.0 (s, 3H), 2.45–2.7 (m, 3H), 5.35 (dd, 1H, *J* 11 and 1 Hz), 5.40 (dd, 1H, *J* 18 and 1 Hz), 6.25 (dd, 1H, *J* 18 and 11 Hz), 7.1–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.3, 30.5, 35.6, 43.2, 81.5, 116.9, 126.1, 126.7, 128.3, 139.2, 146.0, 169.7. IR (KBr disc): 2936, 1738, 1494, 1452, 1369, 1267, 1235, 1021, 929, 762, 702. MS, *m/e* (relative intensity) 184(19), 156(12), 105(10), 104(100), 103(10), 93(11), 91(13), 43(15). Found: C, 78.72; H, 8.30. $C_{16}H_{20}O_2$ calc: C, 78.65; H, 8.25%.

Synthesis of ***3***

3 was obtained from *cis*- or *trans*-**8** by the procedure described above for the synthesis of **1**: m.p. 60–62 °C. ^{1}H NMR ($CDCl_3$) δ 1.35–1.6 (m, 2H), 1.8–2.1 (m, 3H), 2.1–2.35 (m, 2H), 2.6–2.85 (m, 4H), 3.4 (t, 1H, *J* 8 Hz), 3.8 (d, 6H), 5.1 (t, 1H, *J* 8 Hz), 7.15–7.35 (m, 5H). IR (KBr disc): 2933, 1752, 1731, 1451, 1436, 1351, 1336, 1279, 1235, 1197, 1153, 705. MS *m/e* (relative intensity) 316 (M^+)(3), 145(72), 133(33), 104(100), 93(22), 91(35). Found: C, 72.17; H, 7.90; $C_{19}H_{24}O_4$ calc: C, 72.13; H, 7.65%.

Synthesis of ***9***

To 0.1 mole of vinylmagnesium bromide in THF (150 ml) was added a solution of 6 g (48 mmol) of bicyclo[3.3.0]octane-3-one (**17**) in 10 ml of THF. When the reaction was complete the mixture was carefully hydrolyzed with 50 ml of saturated aqueous NH_4Cl. The organic layer was dried ($MgSO_4$) and evaporated. Distillation of the crude product gave 6.5 g (88%) of **9**. m.p. 37–39 °C. ^{1}H NMR ($CDCl_3$) δ 1.3–1.8 (m, 9H), 1.9–2.05 (dd, 2H), 2.45 (m, 2H), 5.05 (dd, 1H, *J* 11 and 1 Hz), 5.23 (dd, 1H, *J* 17.5 and 1 Hz), 6.02 (dd, 1H, *J* 17.5 and 11 Hz). IR (KBr disc): 3285, 2947, 2861, 1470, 1446, 1413, 1328, 1302, 1153, 1124, 1002, 915. MS (70 eV) *m/e* (relative intensity) 152 (M^+)(3), 123(21), 95(24), 85(22), 84(61), 83(25), 82(33), 81(50), 79(36), 70(44), 69(26), 67(74), 55(100), 53(23), 41(44), 39(32). Found: C, 78.45; H, 10.54. $C_{10}H_{16}O$ calc: C, 78.90; H, 10.59%.

Synthesis of ***10*** *by acetylation of* ***9***

Acetic anhydride (0.63 ml, 6.7 mmol) was added to a solution of **9** (918 mg, 6 mmol), Et_3N (1.1 ml, 7.2 mmol), and DMAP (75 mg, 0.6 mmol) in anhydrous ether (10 ml). After usual work-up, bulb to bulb distillation (80 °C, 0.5 mmHg) afforded 993 mg (85%) of **10**. ^{1}H NMR ($CDCl_3$) δ 1.3–1.7 (m, 8H), 2.0 (s, 3H), 2.3–2.5 (m, 4H), 5.16 (dd, 1H, *J* 11 and 1 Hz), 5.21 (dd, 1H, *J* 17.5 and 1 Hz), 6.08 (dd, 1H, *J* 17.5 and 11 Hz). ^{13}C NMR ($CDCl_3$) δ 22.1, 25.2, 33.5, 40.2, 43.9, 89.1, 114.3, 139.6, 170.1. IR (liquid film): 2947, 2864, 1741, 1642, 1448, 1414, 1367, 1255, 1237, 1122,

1083, 1043, 1018, 924, 737. Found: C, 74.65; H, 9.27. $C_{14}H_{18}O_2$ calc: C, 74.19; H, 9.34%.

Reaction of ***10*** *with sodium dimethyl malonate, using (Pd(dba)$_2$ + phosphine) as a catalytic system*

The reaction was carried out as described above for the alkylation of **6** but starting from 194 mg (1 mmol) of **10**. The product was obtained after flash chromatography as a mixture of regioisomers **4** and **18**, the relative amounts were determined GC/MS and ^{1}H NMR spectroscopy.

^{1}H NMR (of a 95/5 mixture of **4**/**18**) δ 1.15–1.35 (m, 2H), 1.35–1.85 (m, 4H), 2.3–2.55 (m, 4H), 2.6 (t, 2H, *J* 7.5 Hz), 3.4 (t, 1H, *J* 7.5 Hz), 3.75 (s, 6H), 5.1 (t, 1H, *J* 7.5 Hz). IR (liquid film) (of a 95/5 mixture of **4**/**18**): 2949, 2863, 1757, 1741, 1436, 1340, 1238, 1198, 1155.

4 MS (70 eV): *m/e* (relative intensity) 266 (M^+)(2), 145(50), 135(22), 134(100), 133(30), 119(21), 106(24), 105(53), 92(23), 91(33), 79(42), 77(22).

18 MS (70 eV): *m/e* (relative intensity) 266 (M^+)(4), 206(46), 135(41), 134(87), 133(32), 132(26), 119(34), 106(36), 105(82), 95(39), 93(36), 92(34), 91(74), 81(64), 80(20), 79(55), 77(25), 67(100), 65(24), 59(30), 41(27).

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