with *m*-chloroperbenzoic acid in $CHCl_3$: bp 68–71 °C (15 mmHg), 45%.

(b) Attempted Trimethylsilylation. A 10-mmol sample of **12** and 14 mmol of Me_3SiCl in 50 mL of the Trapp mixture were treated at −116 °C with 11 mmol of *tert*-butyllithium in pentane. After the usual reaction time and workup an 85% yield of 1-(trimethylsiloxy)-1,3,5,7-cyclooctatetraene was isolated: ^1H NMR δ 0.3 (s, 9 H), 5.2–5.85 (s, 7 H). By treatment with semicarbazide hydrochloride it was converted into the known semicarbazone of 2,4,6-cyclooctatrienone, mp 192–193 °C (lit.[19] mp 193 °C).

3,4-Epoxy-1-phenyl-1-butyne (13). (a) Preparation. Oxidation of 205 mmol of 1-phenyl-3-buten-1-yne with 350 mmol of benzonitrile and 450 mmol of 30% hydrogen peroxide in 5 g of $KHCO_3$ and 250 mL of methanol at 60 °C gave 63% of **13**: bp 55–60 °C (0.1 mmHg); ^1H NMR δ 2.76 (m, 2 H), 3.35 (t, 1 H), 7.0–7.35 (m, 5 H).

(b) Trimethylsilylation. The epoxide (50 mmol) and Me_3SiCl (100 mmol) dissolved in 180 mL of the Trapp mixture were treated at −110 °C with 75 mmol of *tert*-butyllithium. Usual reaction time and workup gave a crude product containing no **13**. Distillation and subsequent column chromatography gave 65% of 3,4-epoxy-1-phenyl-3-(trimethylsilyl)-1-butyne: ^1H NMR δ 0.32 (s, 9 H), 2.89 (d, 1 H, J = 6.5 Hz), 3.20 (d, 1 H), 7.2–7.4 (m, 5 H). Anal. Calcd for $C_{13}H_{16}OSi$: C, 67.20; H, 6.94. Found: C, 67.45; H, 6.69.

1-Cyano-1,2-epoxy-2-methylpropane (14). A solution of 10 mmol of **14** and 11 mmol of Me_3SiCl in 20 mL of the Trapp mixture was treated at −110 °C with 10 mmol of lithium diisopropylamide in hexane over 10 min. The mixture was allowed to warm to −80 °C over 45 min and then rapidly to 0 °C and hydrolyzed. Usual workup gave essentially pure 1-cyano-1,2-epoxy-2-methyl-1-(trimethylsilyl)propane (**41**) in 95% yield: ^1H NMR δ 0.3 (s, 9 H), 1.35 (s, 3 H), 1.60 (s, 3 H). Anal. Calcd for $C_8H_{15}NOSi$: C, 59.60; H, 8.34. Found: C, 59.85; H, 8.10.

Diethyl *cis*-2,3-Epoxysuccinate (15). A solution of 150 mmol of **15** and 180 mmol of Me_3SiCl in 250 mL of the Trapp mixture was treated at −110 °C with 180 mmol of lithium diisopropylamide in a dropwise manner over 60 min. The mixture was then warmed to −40 °C and hydrolyzed. By ^1H NMR analysis the crude product contained 10% of **15**, 4% of the disilylated (**42**), product, and 86% of the monosilylated (**43**) product. By fractional distillation the diethyl 2,3-epoxy-2-(trimethylsilyl)succinate (**43**) was isolated (70%): bp 83–85 °C (0.05 mmHg); ^1H NMR δ 0.19 (s, 9 H), 1.3 (t, 6 H, J = 7 Hz), 3.33 (s, 1 H), 4.17 (q, 4 H). Anal. Calcd for $C_{11}H_{20}O_5Si$: C, 50.75; H, 7.74. Found: C, 50.70; H, 7.65.

Unsuccessful Lithiations. Ethylene oxide with Me_3SiCl and *tert*-butyllithium gave the straightforward ring-opened product, t-$BuCH_2CH_2OSiMe_3$; 1,2-epoxycyclooctane with Me_3SiCl and *tert*-butyllithium gave a small amount of silylation (10%); *trans*-2,3-epoxy-1,3-diphenyl-1-propanone with LDA gave the reduced product, 2,3-epoxy-1,3-diphenyl-1-propanol and with *n*-butyllithium and Me_3SiCl gave 1,2-epoxy-1,3-diphenyl-3-(trimethylsiloxy)heptane; 1-phenyl-2-(trimethylsilyl)aziridine with the *tert*-butyllithium–TMEDA complex gave some 2-(trimethylsilyl)-3,3-dimethyl-2-butene; 2-phenylthiirane with *tert*-butyllithium gave some styrene.

Acknowledgment. We are grateful for the support of this research through Grants CA-14540 and CA-28335 from the Public Health Service.

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Substrate Leaving Group Control of the Enantioselectivity in the Palladium-Catalyzed Asymmetric Allylic Substitution of 4-Alkyl-1-vinylcyclohexyl Derivatives

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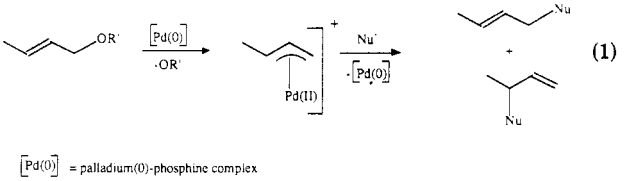
Received January 3, 1990

The strong influence of the nature of the leaving group in allylic derivatives in their enantioselective Pd-catalyzed substitution by nucleophile is reported. Analysis of the stereochemical course of the Pd-catalyzed substitution of achiral *trans*-4-*tert*-butyl-1-vinylcyclohexyl derivatives with nucleophiles indicates the enantioselective step to be oxidative addition of the allylic substrate onto the chiral Pd complex. The asymmetric induction may be understood as the result of the selection by the chiral Pd catalyst between two reactive enantiomeric conformations of the allylic substrate and, hence, was shown to be strongly dependent upon reaction conditions and especially upon the nature of the substrate leaving group. Indeed, dimethyl 2-[(4-*tert*-butylcyclohexylidene)methyl]malonate (**4**) was synthesized with 27, 48, and 78% ee through Pd-catalyzed reaction of sodium dimethyl malonate in THF with *trans*-4-*tert*-butyl-1-vinylcyclohexyl carbonate (**1c**), acetate (**1a**) and 4-methoxybenzoate (**1h**), respectively, in the presence of BINAP as the chiral ligand. In dioxane, **4** was produced from 4-methoxybenzoate **1h** with 90% ee.

Introduction

The palladium-catalyzed allylic substitution reaction has been thoroughly studied and has received wide study for asymmetric synthesis.[1] This reaction is considered to proceed in two steps (eq 1). The initial oxidative addition of the allylic substrate to a Pd^0 complex produces an η^3-allyl complex, which is then attacked by a nucleophile.



(1)

[Pd(0)] = palladium(0)-phosphine complex

In preceding papers,[2,3] we described the asymmetric synthesis of chiral 4-substituted cyclohexylidene com-

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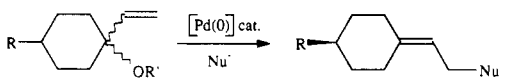
Table I. Solvent Effect on the Reaction of Sodium Dimethyl Malonate with *cis*- or *trans*-3 (Equation 3)

substrate 3	solvent	yield of 7,[a] %	ee, %
cis	THF	78	17 ± 5
trans	THF	75	23 ± 6
cis	DMF	71	11 ± 4
trans	DMF	85	18 ± 5
cis	CH_2Cl_2	67	16 ± 4
trans	CH_2Cl_2	87	16 ± 4
cis	toluene	36	0
trans	toluene	20	16 ± 4
cis	CH_3CN	82	19 ± 5
trans	CH_3CN	87	16 ± 4
cis	dioxane	74	28 ± 6
trans	dioxane	80	26 ± 6
cis	DME	77	24 ± 6
trans	DME	82	29 ± 7
cis	DME[b]	47	29 ± 7
trans	DME[b]	48	23 ± 6
cis	diglyme	61	28 ± 7
trans	diglyme	80	20 ± 5

[a] Isolated yield. [b] In the presence of 200 mol % 18-crown-6.

pounds **4–6** by the palladium-catalyzed reaction of allylic acetates **1a** and **2** with sodium dimethyl malonate or morpholine (eq 2). The enantiomeric excess of the



(2)

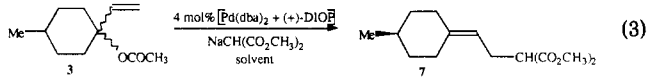
1a, R = *t*-Bu, R' = $COCH_3$
2, R = Ph, R' = $COCH_3$
3, R = Me, R' = $COCH_3$
4, R = *t*-Bu, Nu = $CH(CO_2CH_3)_2$
5, R = *t*-Bu, Nu =
6, R = Ph, Nu = $CH(CO_2CH_3)_2$
7, R = Me, Nu = $CH(CO_2CH_3)_2$

product depended on the geometry (cis or trans) of the substrate and the nature of the phosphine employed as ligand of the palladium. Product **4** was obtained with 40% ee in the reaction of *trans*-**1a** with sodium dimethyl malonate through catalysis by a chiral Pd–BINAP[4] complex. This reaction represented the first asymmetric synthesis of such axially dissymmetric molecules through the use of chiral transition-metal catalysts.

We report here our results of different aspects of this reaction: the influence of the solvent and temperature in the Pd–DIOP-catalyzed reaction of *cis*- and *trans*-**3** with sodium dimethyl malonate, as well as the important leaving group effect observed in the reaction of *trans*-4-*tert*-butyl-1-vinylcyclohexyl derivatives **1a–l** with sodium dimethyl malonate catalyzed by a Pd–BINAP complex. Finally, we will discuss on the origin of the enantioselectivity of the allylic alkylation in this particular system.

Results

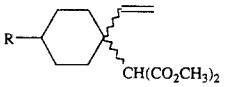
Influence of the Solvent. Data for the reaction of both *cis*-**3** and *trans*-**3** in various solvents with (+)-DIOP[5] as chiral diphosphine and sodium dimethyl malonate as nucleophile (eq 3) are collected in Table I. Enantiomeric



(3)

excesses were calculated from optical rotation, assigning an $[\alpha]_D$ value of 7.7 ± 1.2° for optical rotation of enantiomerically pure **7**. This value has been established by extrapolation of $[\alpha]_D$ values for four samples of different enantiomeric purity, the corresponding ee's of which have been measured by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.

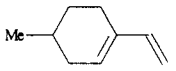
In all solvents, the reaction took place regiospecifically to give the chiral product **7**; no trace of the achiral branched isomers *cis*- or *trans*-**8a** (R = Me) was detected.



8
a, R = Me
b, R = tBu

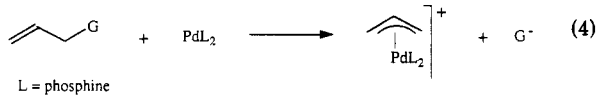
Yields were generally good, except in toluene or in the presence of crown ether. Ethereal solvents, such as THF, dioxane, or DME, gave the best optical rotations. The enantioselectivity was lower in highly coordinating solvents (diglyme or in the presence of crown ether).

Influence of the Reaction Temperature. The enantioselectivities for the reaction of both *cis*-**3** and *trans*-**3** with (+)-DIOP as chiral diphosphine and sodium dimethyl malonate as nucleophile (eq 3) were roughly unaffected (21–30% ee) by temperatures ranging from 0 to 40 °C. The chemical yields were optimal at room temperature. At higher temperature (40 °C), the yields decreased due to a competitive elimination reaction that gave diene **9**.



9

Influence of the Leaving Group. Allylic activation by Pd(0)–phosphine complexes allows the use of allylic substrates with functionalities that usually fail to serve as leaving groups in the noncatalyzed nucleophilic displacements (eq 4).



L = phosphine
(4)

The relative rates for the η^3-allylpalladium complex forming step have been evaluated[6] for a series of allylic substrates, including acetates and phosphates. Although allylic acetates are by far the most commonly used allylic substrates in Pd-catalyzed substitutions, other allylic compounds have been reacted with some particular benefit. As an example, allylic pivalates, being more hindered than acetates, are less susceptible to competitive attack of the carbonyl function by the nucleophile.[7] The preparation of stereochemically pure allylic benzoates from the corresponding alcohols is often easier than the acetates as they are usually crystalline.[8]

The ionized group G^- (or its fragment) may be basic enough to deprotonate an organic acid (e.g., dimethyl malonate) and produce a carbonucleophile. Allylic amidates[9] or isoureas[10] liberate the basic amide and ureide anions through Pd-induced ionization, whereas allylic carbamates[11] and carbonates[12] yield after decarboxylation

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Table II. Leaving Group Effect in Reaction of Sodium Dimethyl Malonate with *trans*-1a–l (Equation 5)

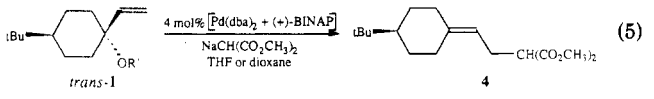
substrate		reaction in THF			reaction in dioxane		
no.	R′	yield,[a] %	regioselectivity[b]	ee,[c] %	yield,[a] %	regioselectivity[b]	ee,[c] %
1a	$COCH_3$	89	88 ± 1	48 ± 4	74	86 ± 1	49 ± 5
1b	COC_6H_5	79	90 ± 1	64 ± 5	77	95 ± 1	76 ± 5
1c	$COOCH_3$	74	87 ± 1	27 ± 3			
1d	$COC(CH_3)_3$	52	88 ± 1	30 ± 3			
1e	$CON(CH_3)_2$	86	85 ± 1	63 ± 5	73	93 ± 1	87 ± 6
1f	$CON[CH(CH_3)_2]_2$	65	79 ± 1	47 ± 4			
1g	COC_6H_4-2-CH_3O	68	96 ± 1	72 ± 5	77	91 ± 1	80 ± 5
1h	COC_6H_4-4-CH_3O	79	96 ± 1	78 ± 6	63	96 ± 1	90 ± 6
1i	COC_6H_4-2-Br	65	91 ± 1	38 ± 4			
1j	COC_6H_4-4-Br	57	93 ± 1	56 ± 5			
1k	CO-1-$C_{10}H_7$	72	94 ± 1	66 ± 5	54	97 ± 1	72 ± 5
1l	CO-2-$C_{10}H_7$	55	96 ± 1	63 ± 5	73	92 ± 1	81 ± 6

[a] Isolated yield of substitution products (4 + 8b). [b] Percent of chiral product 4 in the mixture of 4 + 8b, determined by GLC analysis. [c] Calculated assuming $[\alpha]_D^{20}$ −15.7 ± 0.3° for enantiomerically pure 4 and confirmed by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.

of the ionized moieties amides and alcoholates, respectively.

In some cases, the ionized group may behave as a nucleophile, the overall process resulting in a rearrangement of the allylic substrate. In the Pd-catalyzed sulfinate–sulfone rearrangement,[13] a C–O bond is broken and a C–S bond is formed. Other allylic substrates have been occasionally investigated, such as allylic phosphates,[14] sulfones,[15] phenoxides,[16] ethers,[17] silyl ethers,[17] sulfides,[17] and allylic nitro compounds.[18] However, implications of the nature of the leaving group of the allylic substrate in Pd-catalyzed enantioselective syntheses have not yet been investigated.[1]

Some derivatives of *trans*-4-*tert*-butyl 1-vinylcyclohexanol, the carboxylates, acetate **1a**, benzoate **1b**, pivalate **1d**, methoxybenzoates **1g** and **1h**, bromobenzoates **1i** and **1j**, and naphthoates **1k** and **1l**, carbonate **1c**, and the carbamates *N,N*-dimethyl **1e** and *N,N*-diisopropyl **1f**, were prepared and used as substrates for palladium-catalyzed allylic substitution. Results for alkylation of *trans*-**1a–l** by sodium dimethyl malonate are listed in Table II. BINAP was used as chiral ligand, and reactions were carried out in THF (eq 5).



trans-1 4 (5)

a, R′ = $COCH_3$
b, R′ = COC_6H_5
c, R′ = $COOCH_3$
d, R′ = $COC(CH_3)_3$
e, R′ = $CON(CH_3)_2$
f, R′ = $CON[CH(CH_3)_2]_2$
g, R′ = COC_6H_4-2OCH_3
h, R′ = COC_6H_4-4OCH_3
i, R′ = COC_6H_4-2Br
j, R′ = COC_6H_4-4Br
k, R′ = CO-1-$C_{10}H_7$
l, R′ = CO-2-$C_{10}H_7$

Under these conditions, the substitution did not take place regiospecifically (achiral isomers *cis*- and *trans*-**8b** (R = *t*-Bu) of **4** were detected), but the regioselectivity was very good (79–96%). The enantioselectivity was improved, compared to the result reported earlier (<40% ee in the alkylation of acetate **1a** with BINAP):[2,3] a great modification of reaction selectivities was observed through reversal of the sequence of addition of the reactants (catalytic solution + allylic substrate on the nucleophile solution, see the Experimental Section).

The nature of the leaving group OR′ is also very important for the enantiomeric excess of the product: methyl carbonate **1c** gave the lowest ee (27%) while 4-methoxybenzoate **1h** gave the highest enantioselectivity (78% ee) (and the best regioselectivity, 96%) under otherwise identical conditions. This result suggests the oxidative addition to be the enantioselective step of the overall substitution (see discussion below).

The electronic properties of the leaving group appear to be important in the control of the enantioselectivity; *o*- and *p*-bromobenzoates showed lower selectivities (38 and 56% ee, respectively) than benzoate (64% ee), while, with *o*- and *p*-methoxybenzoates, **4** was obtained with higher ee's (72 and 78% ee, respectively) compared to benzoate. The steric hindrance brought by an ortho substituent is not beneficial: 2-bromobenzoate (38% ee) and 2-methoxybenzoate (72% ee) are less efficient than their 4-substituted counterparts (56 and 78% ee, respectively). Moreover, the ee of product **4** from 4-methoxybenzoate **1h** could be increased to 90% by carrying out the reaction in dioxane (eq 5, Table II).

A BINAP-containing Pd material could be isolated from the reaction mixture by chromatography, the structure of which has not yet been elucidated. However this compound proved to be an active catalyst in the reaction of 4-methoxybenzoate **1h** with sodium dimethyl malonate to give **4** (75% yield, 78% ee).

Discussion

In the following, the stereochemical course of the reaction will be discussed in an attempt to analyze the origin of the enantioselectivity and to give a rationale for the dependence of the asymmetric induction upon the nature of the substrate leaving group.

1. Oxidative Addition. The η^3-allyl forming step has been shown to be under strong stereoelectronic control of the allylic substrate:[19] the C–O bond to be broken and the metal–carbon bond (after metal coordination to the C–C double bond) should have an antiperiplanar arrangement. For each acetate *cis*- and *trans*-**1a**, only two chiral conformations (enantiomeric **A** and **B**, probably in rapid equilibrium) possess a C–O bond orthogonal to the plane of the C–C double bond (Figure 1) and are reactive to a low-valent palladium complex to give an η^3-allylpalladium complex. Through anti attack of a Pd^0 complex, each conformer (**1A**, **1B**) leads respectively to a palladium complex (**10A** or **10B**) in which the η^3-allyl ligand is chiral. The configuration of the η^3-allyl ligand is related to the

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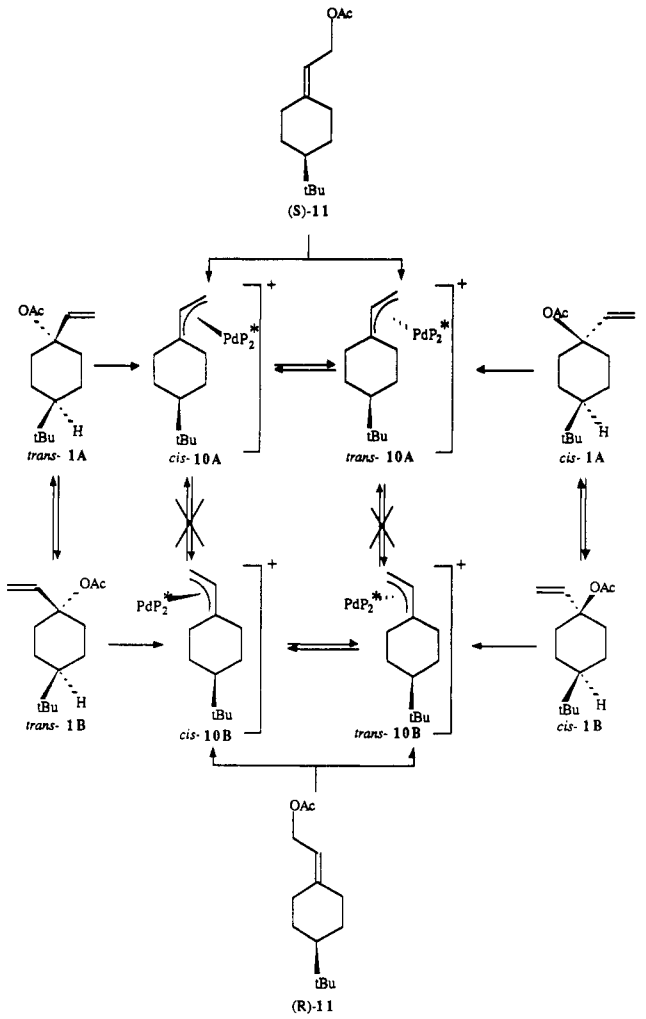

Figure 1. Oxidative addition on *cis*- and *trans*-**1a** and (*R*)- and (*S*)-**11** allylic acetates.

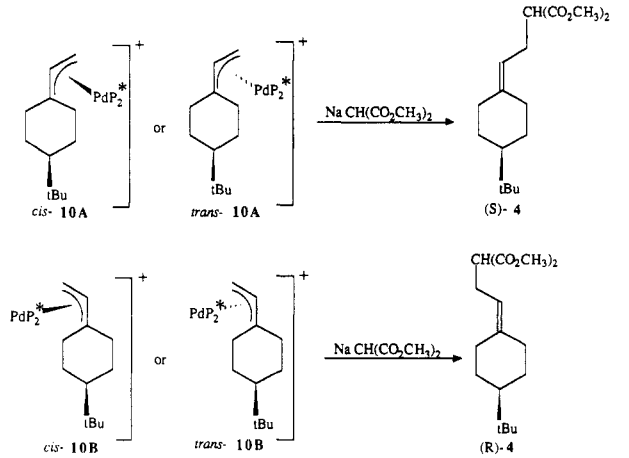

Figure 2. Nucleophilic attack on complexes **10**.

configuration of the starting allylic acetate conformer.

2. Nucleophilic Attack. Figure 2 illustrates the second step of the reaction. The configuration of product **4** is related to the configuration of the η^3-allyl ligand in complex **10** that undergoes the nucleophilic attack. Each type (**A** or **B**) of complex **10** leads respectively to enantiomeric (*S*)-**4** and (*R*)-**4**, regardless of its cis or trans geometry.

3. Stereochemical Stability of η^3-Allylpalladium Intermediates. Two processes can account for the isomerization of η^3-allyl complexes: a bimolecular S_N2 displacement by a Pd^0 complex[20] (Figure 3) consisting of a

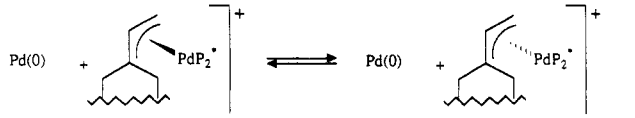

Figure 3. S_N2 displacement of an η^3-allylpalladium complex by a Pd^0 complex.

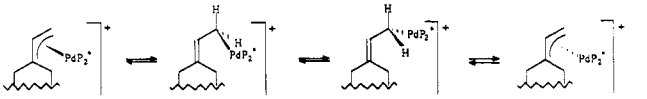

Figure 4. η^3–η^1–η^3 process involving a palladium–primary carbon bond.

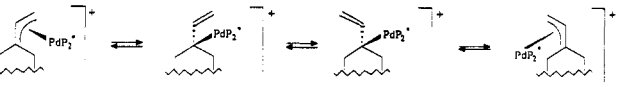

Figure 5. η^3–η^1–η^3 process involving a palladium–tertiary carbon bond.

cis–trans isomerization of complex **10**, that cannot convert a type **A** to a type **B** complex; a monomolecular η^3–η^1–η^3 process[21] consisting of a cis–trans isomerization of **10** (Figure 4) or an **A**–**B** isomerization of **10** (Figure 5), only the latter leading to the enantiomerization of the allylic ligand. Since this process involves the formation of a palladium–tertiary carbon bond, it should be disfavored relative to the others[22] and isomerization of **10A** (cis or trans) to **10B** (cis or trans) is unlikely.

4. Consequences. After coordination and oxidative addition on the allylic substrate, *enantiomerization of the η^3-allyl ligand is likely a slow process.* Each complex (**10A** or **10B**, not in equilibrium) gives an enantiomer of **4** (*S* and *R*, respectively). Consequently, the asymmetric induction arises from the production at different rates of η^3-allyl complexes with enantiomeric η^3-allyl ligands such as **10A** and **10B**. This would be the result of a discrimination by the chiral Pd(0) complex in the coordination of the olefinic bond of the allylic substrate: between either two enantiotopic faces of the symmetric, nonchiral conformation or the two most reactive enantiomeric conformations **1A** and **1B**. *The oxidative addition step is the enantioselective step for the overall substitution.*

The following results and interpretations are presented as support for the preceding conclusion. The large influence of the leaving group proves the importance of oxidative addition step on the enantioselectivity of the reaction: This is the only step where the leaving group can affect the asymmetric induction. The diastereomeric substrates *cis*- and *trans*-**1a** gave different asymmetric inductions with the same phosphine ligand:[2,3] This fact indicates that the isomerization of η^3-allyl complexes is not fast relative to the nucleophilic attack. The following transfer reactions (eq 6) were carried out on linear acetate **11**, partially resolved by lipase-catalyzed acetylation.[23]

Starting from (*S*)-**11** (*R*, respectively), oxidative addition gave *cis*- or *trans*-**10A** (**10B**); nucleophilic attack on **10A** (**10B**) led to (*S*)-**4** ((*R*)-**4**) (see Figure 1). Since no rapid equilibration between **10A** and **10B** is possible, each en-

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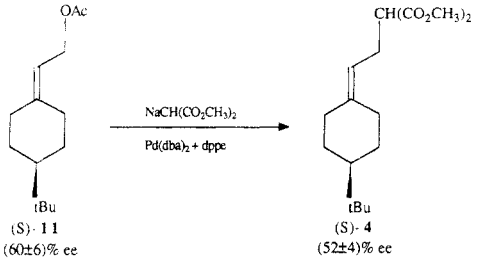

(6)

antiomer of **11** should give the corresponding enantiomer of **4**, without any loss of optical purity, even with an achiral catalyst: the transfer reactions in eq 6 were carried out with dppe (bis(diphenylphosphino)ethane) as the catalyst phosphine ligand.

These two reactions allow us to assign the absolute configurations to the enantiomers of **4**: *S* for dextrorotatory and *R* for the levorotatory (optical rotations measured in toluene) and also, combined with asymmetric induction experiments of Table II, to calculate optical rotation for enantiomerically pure **4**: $[\alpha]^{20}_D$ 15.7 ± 0.3°. This value is in good agreement with ^{1}H NMR measurement, in the presence of Eu(hfc)$_3$.

Conclusion

The palladium-catalyzed substitution of 4-alkyl-1-vinylcyclohexyl derivatives constitutes the first enantioselective synthesis of cyclohexylidene compounds through transition-metal complex catalysis. No temperature effect and a moderate solvent dependence were noted. The enantioselectivity of the reaction is strongly influenced by the nature of the leaving group. Up to 90% ee could be reached in the asymmetric synthesis of dimethyl 2-[(4-*tert*-butylcyclohexylidene)methyl]malonate (**4**) by a proper choice of the nature of the starting allylic derivative and of the reaction solvent.

Analysis of the stereochemical course of the reaction suggests that, unlike the enantioselective palladium-catalyzed substitutions previously described,[1] the enantioselective step is the oxidative addition of the allylic substrate onto the Pd^0 complex. Therefore, the enantioselectivity would not depend upon the nature of the nucleophile involved in the reaction. This point will be soon examined, and enantioselective syntheses of other chiral cycloalkylidene compounds from 4-alkyl-1-vinylcyclohexyl derivatives will be investigated.

Experimental Section

General Procedures. All reactions involving palladium catalysis were carried out under argon by Schlenk techniques. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl immediately before use. Other solvents were dried from CaH_2 and distilled prior to use.

^{1}H NMR spectra were recorded at 250 MHz, with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 883 spectrometer, and are reported in reciprocal centimeters. Mass spectra were obtained by GC/MS at 70 eV. GLC analyses were carried out with a 25-m CPSil 19CB capillary column.

The following materials were obtained from commercial sources: Pd(dba)$_2$ (were dba denotes dibenzylideneacetone); Eu(hfc)$_3$ (were hfc denotes 3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato); (*R*)-(+)-BINAP;[4] (+)-DIOP.[5]

The synthesis of acetate *trans*-**1a** is described in ref 3.

***cis*- and *trans*-1-Ethenyl-4-methylcyclohexanol Acetates 3.** 4-Methylcyclohexanone (61 mL, 0.498 mol) in 200 mL of THF was slowly added to a THF solution of vinylmagnesium bromide (from magnesium (12 g) and vinyl bromide (35.25 mL, 0.500 mol)). The reaction mixture was refluxed for 1 h, stirred overnight at room temperature, and then poured into ice. After extraction with ether, the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude product was distilled (85 °C (12 mmHg)) to give a cis/trans mixture of 4-methyl-1-vinylcyclohexanols (in a 46:54 ratio) with 60% yield.

The two isomers were separated by two successive spinning-band distillations. Anal. Calcd for *cis*-4-methyl-1-vinylcyclohexanol ($C_9H_{16}O$) (88% isomerically pure): C, 77.09; H, 11.50. Found: C, 77.12; H, 11.40. Anal. Calcd for *trans*-4-methyl-1-vinylcyclohexanol (92% isomerically pure) ($C_9H_{16}O$): C, 77.09; H, 11.50. Found: C, 77.31; H, 11.38.

Acetic anhydride (3.6 mL, 38 mmol) was added to a solution of *cis*- or *trans*-4-methyl-1-vinylcyclohexanol (4.47 g, 32 mmol) and 4-(dimethylamino)pyridine (DMAP) (400 mg, 3.28 mmol) in pyridine (6 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) and then by bulb-to-bulb distillation.

cis-**3**: 4.15 g, 71% yield; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 6 Hz), 1.10–1.45 (3 H, m), 1.45–1.65 (4 H, m), 2.05 (3 H, s), 2.25–2.40 (2 H, m), 5.07 (1 H, dd, J = 11 and 1 Hz), 5.10 (1 H, dd, J = 18 and 1 Hz), 6.10 (1 H, dd, J = 18 and 11 Hz); IR (liquid film) 2927, 2858, 1737, 1448, 1369, 1230, 1018; MS, *m/e* (relative intensity) 122 (62), 107 (33), 95 (26), 94 (29), 93 (82), 83 (40), 81 (39), 80 (22), 79 (52), 67 (25), 55 (45), 43 (100), 41 (36), 39 (20). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.47; H, 9.81.

trans-**3**: 3.8 g, 65% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6 Hz), 1.0–1.25 (2 H, m), 1.40–1.80 (5 H, m), 1.95 (3 H, s), 2.15–2.30 (2 H, m), 5.25 (1 H, dd, J = 11 and 1 Hz), 5.27 (1 H, dd, J = 18 and 1 Hz), 6.15 (1 H, dd, J = 18 and 11 Hz); IR (liquid film) 2927, 2869, 1737, 1450, 1369, 1242, 1017; MS, *m/e* (relative intensity) 122 (57), 107 (32), 95 (24), 94 (27), 93 (81), 83 (50), 81 (43), 80 (20), 79 (54), 67 (28), 55 (53), 43 (100), 41 (36), 39 (22). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.37; H, 9.77.

Propanedioic Acid, Dimethyl Ester Sodium Salt. Sodium hydride (3 g of a 80% dispersion in mineral oil, 100 mmol of NaH) was washed with pentane (4 × 10 mL) and then dried under vacuum. A 100-mL portion of THF was added, followed by 11.5 mL (100 mmol) of dimethyl malonate in a 2-h period. The turbid mixture was filtered and the solvent evaporated. The white-gray solid was stored under argon.

General Procedure for Palladium-Catalyzed Reactions of *cis*- or *trans*-3. A typical reaction procedure is as follows: a mixture of Pd(dba)$_2$ (23 mg, 0.04 mmol) and (+)-DIOP (20 mg, 0.04 mmol) was stirred for 0.25 h in 1 mL of THF. *cis*-**3** (193 mg, 1.06 mmol) in THF (1 mL) was then added by syringe. After further 0.25 h of stirring, the solution was added to a stirred suspension of sodium dimethyl malonate (230 mg, 1.49 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature overnight and then diluted with ether (10 mL) and the organic phase washed with 2 × 10 mL of 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 (silica, cyclohexane/ethyl acetate, 9:1) and then by bulb-to-bulb distillation to give **7**: 78% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 5 Hz), 0.85–1.05 (2 H, m), 1.45–1.60 (1 H, m), 1.65–1.80 (3 H, m), 1.90–2.20 (2 H, m), 2.50–2.65 (3 H, m), 3.35 (1 H, t, J = 7.5 Hz), 3.73 (6 H, s), 5.0 (1 H, t, J = 7.5 Hz); IR (liquid film) 2952, 2847, 1754, 1437, 1341, 1231, 1153, 1030, 961, 947, 858, 698; MS, *m/e* (relative intensity) 254 (M^+) (2), 145 (100), 133 (49), 132 (21), 123 (21), 122 (57), 107 (36), 93 (88), 91 (28), 81 (58), 79 (54), 77 (30), 67 (39), 59 (22), 55 (41), 41 (31). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.17; H, 8.56.

1-Ethenyl-4-(1,1-dimethylethyl)cyclohexanol Derivatives 1b–l. The reported procedure for the synthesis of *N,N*-dimethylcarbamates[24] was used and is illustrated as follow for the synthesis of **1f**: 500 mg of a 35% dispersion of potassium hydride in mineral oil was washed with pentane (4 × 10 mL) and dried under vacuum to give 55.5 mg (1.38 mmol) of dry KH, which was

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dissolved in THF (5 mL). Then *trans*-4-*tert*-butyl-1-vinylcyclohexanol[25] (207 mg, 1.14 mmol) in THF (5 mL) was added dropwise at −10 °C. The mixture was allowed to warm to room temperature, maintained there for 0.5 h, and recooled at −10 °C. *N,N*-Diisopropylcarbamoyl chloride (207 mg, 1.22 mmol) was added dropwise. After being stirred overnight at room temperature, the reaction mixture was diluted with ether (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). 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 (silica, cyclohexane/ethyl acetate, 9:1) and then by bulb-to-bulb distillation.

trans-**1b** (benzoate, from benzoyl chloride): 153 mg, 47% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.10–1.30 (3 H, m), 1.70–1.85 (4 H, m), 2.55–2.65 (2 H, m), 5.35 (1 H, dd, *J* = 11 and 1 Hz), 5.40 (1 H, dd, *J* = 18 and 1 Hz), 6.38 (1 H, dd, *J* = 18 and 11 Hz), 7.35–7.60 (3 H, m), 7.95–8.00 (2 H, m); IR (liquid film) 2947, 2868, 1717, 1314, 1283, 1263, 1112, 1024, 710; MS, *m/e* (relative intensity) 121 (21), 108 (21), 107 (27), 105 (76), 93 (58), 91 (31), 80 (34), 79 (100), 77 (61), 57 (90), 55 (23), 41 (52). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.80; H, 8.90.

trans-**1c** (methyl carbonate, from methyl chloroformate): 153 mg, 56% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.05–1.15 (3 H, m), 1.55–1.80 (4 H, m), 2.40–2.50 (2 H, m), 3.70 (3 H, s), 5.40 (1 H, dd, *J* = 11 and 1 Hz), 5.45 (1 H, dd, *J* = 18 and 1 Hz), 6.10 (1 H, dd, *J* = 18 and 11 Hz); IR (liquid film) 2945, 2867, 1746, 1414, 1365, 1288, 944, 908, 794; MS, *m/e* (relative intensity) 121 (23), 108 (23), 107 (24), 93 (67), 91 (22), 80 (34), 79 (91), 57 (100), 44 (22), 41 (31). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.66; H, 10.16.

trans-**1d** (pivalate, from pivaloyl chloride): 227 mg, 75% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.00–1.20 (3 H, m), 1.15 (9 H, s), 1.45–1.75 (4 H, m), 2.35–2.50 (2 H, m), 5.28 (1 H, dd, *J* = 11 and 1 Hz), 5.31 (1 H, dd, *J* = 18 and 1 Hz), 6.18 (1 H, dd, *J* = 18 and 11 Hz); IR (liquid film) 2955, 2870, 1732, 1481, 1367, 1286, 1163, 1129, 1029; MS, *m/e* (relative intensity) 110 (21), 109 (41), 108 (25), 107 (20), 95 (38), 93 (28), 79 (28), 58 (30), 57 (100), 41 (35). Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.75; H, 11.13.

trans-**1e** (dimethylcarbamate, from dimethylcarbamoyl chloride): 150 mg, 52% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.00–1.30 (3 H, m), 1.55–1.80 (4 H, m), 2.35–2.50 (2 H, m), 2.85 (6 H, s), 5.30 (1 H, dd, *J* = 11 and 1 Hz), 5.33 (1 H, dd, *J* = 18 and 1 Hz), 6.17 (1 H, dd, *J* = 18 and 11 Hz); IR (liquid film) 2943, 2869, 1703, 1449, 1386, 1367, 1193; MS, *m/e* (relative intensity) 109 (31), 95 (44), 93 (26), 81 (26), 79 (39), 72 (57), 67 (27), 57 (100), 41 (21). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.99; H, 10.68; N, 5.44.

trans-**1f** (diisopropylcarbamate, from diisopropylcarbamoyl chloride): 162 mg, 46% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.00–1.30 (12 H, m), 1.55–1.80 (4 H, m), 2.45–2.55 (2 H, m), 3.70–3.80 (2 H, m), 5.28 (1 H, dd, *J* = 11 and 1 Hz), 5.31 (1 H, dd, *J* = 18 and 1 Hz), 6.19 (1 H, dd, *J* = 18 and 11 Hz); IR (liquid film) 2966, 2870, 1691, 1436, 1367, 1317, 1299, 1133, 1051; MS, *m/e* (relative intensity) 309 (M^+) (2), 146 (23), 109 (26), 95 (33), 86 (47), 79 (26), 57 (100), 44 (21), 43 (23), 41 (28). Anal. Calcd for $C_{19}H_{35}NO_2$: C, 73.73; H, 11.40; N, 4.52. Found: C, 73.62; H, 11.19; N, 4.39.

trans-**1g** (2-methoxybenzoate, from 2-methoxybenzoyl chloride): 306 mg, 85% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.05–1.30 (3 H, m), 1.65–1.85 (4 H, m), 2.60 (2 H, m), 3.90 (3 H, s), 5.35 (1 H, dd, *J* = 11 and 1 Hz), 5.42 (1 H, dd, *J* = 18 and 1 Hz), 6.28 (1 H, dd, *J* = 18 and 11 Hz), 6.90–7.00 (2 H, m), 7.40–7.50 (1 H, m), 7.70–7.80 (1 H, m); IR (liquid film) 2947, 1727, 1491, 1466, 1310, 1254, 1128, 1076, 1025, 755. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.73; H, 9.06.

trans-**1h** (4-methoxybenzoate, from 4-methoxybenzoyl chloride): 292 mg, 81% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.05–1.30 (3 H, m), 1.60–1.85 (4 H, m), 2.60 (2 H, m), 3.85 (3 H, s), 5.34 (1 H, dd, *J* = 11 and 1 Hz), 5.40 (1 H, dd, *J* = 18 and 1 Hz), 6.27 (1 H, dd, *J* = 18 and 11 Hz), 6.90 (2 H, d, *J* = 9 Hz), 7.95 (2 H, d, *J* = 9 Hz); IR (KBr disk) 2951, 2866, 1709, 1607, 1314, 1280, 1255, 1165, 1112, 1027, 772. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.11; H, 8.99.

trans-**1i** (2-bromobenzoate, from 2-bromobenzoyl chloride): 329 mg, 79% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.00–1.30 (3 H, m), 1.70–1.90 (4 H, m), 2.60 (2 H, m), 5.38 (1 H, dd, *J* = 11 and 1 Hz), 5.45 (1 H, dd, *J* = 18 and 1 Hz), 6.28 (1 H, dd, *J* = 18 and 11 Hz), 7.20–7.40 (2 H, m), 7.60–7.75 (2 H, m); IR (liquid film) 2948, 2868, 1730, 1299, 1250, 1125, 1026, 746.

trans-**1j** (4-bromobenzoate, from 4-bromobenzoyl chloride): 229 mg, 55% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.05–1.35 (3 H, m), 1.60–1.85 (4 H, m), 2.60 (2 H, m), 5.35 (1 H, dd, *J* = 11 and 1 Hz), 5.40 (1 H, dd, *J* = 18 and 1 Hz), 6.25 (1 H, dd, *J* = 18 and 11 Hz), 7.55 (2 H, d, *J* = 8 Hz), 7.85 (2 H, d, *J* = 8 Hz); IR (KBr disk) 2945, 1713, 1589, 1285, 1263, 1105, 1011, 757.

trans-**1k** (1-naphthoate, from 1-naphthoyl chloride): 260 mg, 68% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.10–1.35 (3 H, m), 1.65–1.95 (4 H, m), 2.65 (2 H, m), 5.40 (1 H, dd, *J* = 11 and 1 Hz), 5.49 (1 H, dd, *J* = 18 and 1 Hz), 6.37 (1 H, dd, *J* = 18 and 11 Hz), 7.40–7.60 (3 H, m), 7.80–7.90 (1 H, m), 8.00 (1 H, d, *J* = 8 Hz), 8.10 (1 H, d, *J* = 7 Hz), 8.85 (1 H, d, *J* = 8 Hz); IR (liquid film) 2951, 2868, 1714, 1282, 1246, 1197, 1128, 1025, 1004, 781. Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.32; H, 8.34.

trans-**1l** (2-naphthoate, from 2-naphthoyl chloride): 149 mg, 39% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (9 H, s), 1.10–1.35 (3 H, m), 1.70–1.95 (4 H, m), 2.65 (2 H, m), 5.37 (1 H, dd, *J* = 11 and 1 Hz), 5.45 (1 H, dd, *J* = 18 and 1 Hz), 6.32 (1 H, dd, *J* = 18 and 11 Hz), 7.45–7.60 (2 H, m), 7.80–8.05 (4 H, m), 8.55 (1 H, s); IR (KBr disk) 2955, 2865, 1714, 1280, 1226, 1199, 1131, 1098, 956, 782. Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.23; H, 8.53.

General Procedure for Palladium-Catalyzed Reactions of *trans*-1a-l. A typical reaction procedure is as follows: a mixture of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and (+)-BINAP (12.5 mg, 0.02 mmol) was stirred for 0.25 h in 0.5 mL of THF. *trans*-**1a** (113 mg, 0.50 mmol) in THF (1 mL) was then added by syringe. After being stirred for 0.25 h, the solution was added to a stirred suspension of sodium dimethyl malonate (160 mg, 1.04 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature overnight and then diluted with ether (10 mL) and the organic phase washed with 2 × 10 mL of 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 (silica, cyclohexane/ethyl acetate, 9:1) and then by bulb-to-bulb distillation to give a mixture of **4** and *cis*- + *trans*-**8b** in an 88.0:6.2:5.8 ratio: 133 mg, 89% yield; $[\alpha]^{20}_D$ −6.61 ± 0.27° (*c* 2.89, toluene), corresponding to $[\alpha]^{20}_D$ −7.51 ± 0.40° (*c* 2.89, toluene) for pure **4**; ee 48 ± 4%. Characteristics of **4** are given in ref 3.

Further elution (eluent ethyl acetate) gave 40 mg of an optically active yellow material, $[\alpha]^{20}_D$ +393 ± 4° (*c* 2, AcOEt). Of this compound 20 mg was dissolved in 1 mL of dioxane; 121 mg (0.38 mmol) of 4-methoxybenzoate **1h** in 0.5 mL of dioxane was added. After 0.25 h of stirring, this solution was added to a stirred suspension of sodium dimethyl malonate (192 mg, 0.60 mmol) in dioxane (0.5 mL). The reaction was then conducted as described earlier to give 84.5 mg (0.29 mmol) of **4**: yield 75%; regioselectivity 96%; $[\alpha]^{20}_D$ −11.72 ± 0.39° (*c* 2.52, toluene), corresponding to $[\alpha]^{20}_D$ −12.22 ± 0.54° (*c* 2.52, toluene) for pure **4**; ee 78 ± 5%.

Palladium-Catalyzed Reaction of 1l with the Sodium Salt of Propanedioic Acid, Dimethyl Ester. A mixture of $Pd(dba)_2$ (23 mg, 0.04 mmol) and dppe (1,2-bis(diphenylphosphino)ethane) (16 mg, 0.04 mmol) was stirred for 0.25 h in 1 mL of THF. A 220-mg (0.98-mmol) portion of (*S*)-**11** ($[\alpha]^{20}_D$ +9.23 ± 0.31° (*c* 1.95, EtOH), 60 ± 6% ee) in THF (1 mL) were added by syringe. After a further 0.25 h of stirring, the solution was added to a stirred suspension of sodium dimethyl malonate (240 mg, 1.56 mmol) in THF (1 mL). The reaction mixture was stirred at room temperature overnight and then diluted with ether (10 mL) and the organic phase washed with 2 × 10 mL of 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 (silica, cyclohexane/ethyl acetate, 9:1) and then by bulb-to-bulb distillation to give **4**: 179 mg, 89% yield; $[\alpha]^{20}_D$ +8.15 ± 0.37° (*c* 1.95, toluene). Examination of the ^{1}H NMR spectrum in the

(25) Ouellette, R. J.; Litpak, K.; Booth, G. E. *J. Org. Chem.* **1965**, *31*, 546.

presence of $Eu(hfc)_3$ gave ee 56 ± 5%. Calculation with $[\alpha]^{20}_{D\,max}$ +15.7 ± 0.3° gave ee 52 ± 4%.

The same reaction was conducted on (*R*)-11 (228 mg, 1.02 mmol) ($[\alpha]^{20}_D$ −4.97 ± 0.34° (*c* 1.65, EtOH), 33 ± 5% ee) and gave 211 mg (70% yield) of 4: $[\alpha]^{20}_D$ −4.37 ± 0.28° (*c* 2.15, toluene). Examination of the ^1H NMR spectrum in the presence of $Eu(hfc)_3$ gave ee 30 ± 5%. Calculation with $[\alpha]^{20}_{D\,max}$ −15.7 ± 0.3° gave ee 28 ± 3%.

Stereoselective Cyclization of (2-Bromophenyl)- and (2-Iodophenyl)alkynes Catalyzed by Palladium(0) Complexes

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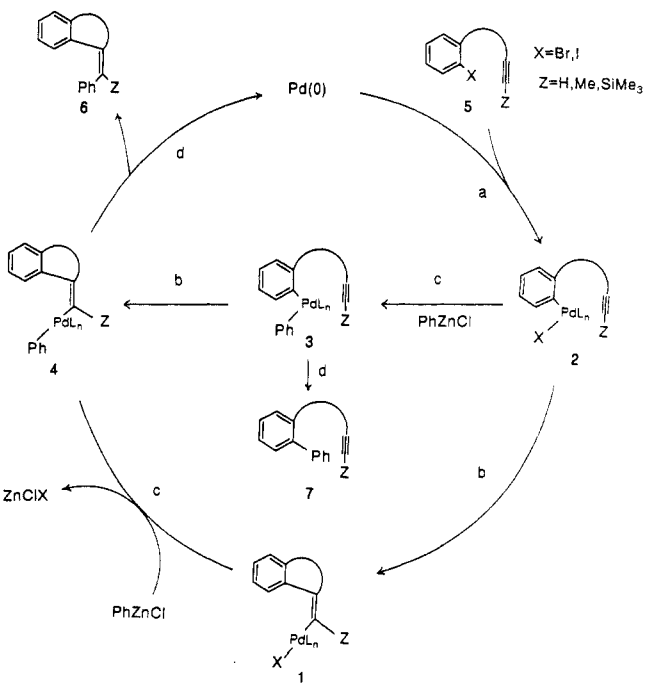
The Pd(II)-intermediate generated by intramolecular arylation of alkynes can be further cross-coupled with phenylzinc chloride to recycle the Pd(0) catalyst and give stereodefined exocyclic indans and tetralins. For example, (*Z*)-1-benzylideneindan can be obtained in 60% yield from 4-(2-iodophenyl)-1-butyne and phenylzinc chloride in the presence of 5 mol % of $Pd(PPh_3)_4$ in THF at room temperature. The alkynyl group can be terminal or internal. Several features and the mechanism of the process are discussed.

The usefulness of the highly regio- and stereoselective coupling involving the Pd-catalyzed arylation or alkenylation of olefins (Heck reaction) has been widely recognized by synthetic chemists.[1] Although particular attention has been paid to the Pd-catalyzed intramolecular arylation of alkenes to form cyclic or heterocyclic compounds,[2] the number of papers reporting the potential utility of the Pd-catalyzed intramolecular arylation of alkynes is still very small.[3] One obvious reason is that the Pd-catalyzed intramolecular arylation of alkynes was limited by the lack of a β-hydride elimination pathway for the Pd(II) intermediate to recycle Pd(0) complexes. It is also well documented that the coupling of organic electrophiles with organometallic reagents catalyzed by a Pd(0) complex (for example, vinyl halide and phenylzinc chloride in the presence of Pd(0) catalyst)[4] involves a Pd(II) intermediate after the oxidative addition step. Thus, we intended to use the alkenylpalladium(II) intermediate 1 generated by the arylation of alkynes for further cross-coupling reactions. The objectives of this investigation were (1) to explore the applications of Pd-catalyzed arylation of alkynes, (2) to demonstrate the generality of the cross-coupling reaction by using palladium as the catalyst, and (3) to synthesize stereodefined exocyclic indanes and tetralins (Scheme I).

Scheme I. Proposed Mechanism for the Cyclization and Coupling Reaction of Aryl Halides 5 with Phenylzinc Chloride in the Presence of Pd(0) Catalyst[a]



[a] (a) Oxidative addition; (b) cis-carbopalladation; (c) transmetalation; (d) reductive elimination.

Results and Discussion

Two requirements must be met for the successful execution of this catalytic process. (1) Either the intramolecular cis-carbopalladation of **2** must be faster than the

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