# Memory Effects in Pd-Catalysed Allylic Alkylation: Stereochemical Labelling through Isotopic Desymmetrization

**Guy C. Lloyd-Jones* and Susanna C. Stephen**

**Abstract:** $^{2}$H-Labelled and $^{18}$O-labelled cyclopentenyl esters (±)-**4** and (±)-**5** are used as probes for memory effects in Pd-catalysed allylic alkylation. $^{2}$H-Labelled alkylation product **6** arising from stereospecific Pd-catalysed reaction of (±)-**4** was analysed by a novel $^{13}$C NMR method involving $^{2}$H-isotope shifts and paramagnetic diastereotopic shifts. When catalysts bearing the Trost modular ligand (*R,R*)-**3** were employed, variable memory effects were observed with the slower reacting chirality mismatched (*R*)-**4** substrate-catalyst pairing. The memory effect is dependent on nucleofuge steric bulk and not p$K_a$. Attack by [LiCH($CO_2CH_3$)$_2$] occurs with reversed site selectivity but (*R*)-**4** remains the mismatched substrate. Mismatched ionisation leading to a Pd-π-allyl in which (*R,R*)-**3** acts as a monophosphine ligand may explain the memory effect.

**Keywords:** allyl complexes · asymmetric catalysis · isotopic labeling · P ligands · palladium

## Introduction

In 1981 Fiaud and Malleron[1] reported that an *achiral* Pd catalyst gave an optically active allylic alkylation[2] product on reaction of enantiomerically enriched 2-cyclohexenyl acetate with [NaCH($CO_2CH_3$)$_2$]. Differential $S_N2$ and $S_N2'$*anti* rates in either formation or reaction of a σ-allyl-Pd intermediate (rather than *meso*-π-allyl-Pd) were suggested. These conclusions were later disputed by Trost and Schmuff[3] who reported that Pd($PPh_3$)$_4$-catalysed reaction of an enantiomerically enriched allylic lactone with [NaCH($CO_2CH_3$)$_2$] gave a racemic product via a fully *meso*-π-allyl-Pd intermediate. More recently, Trost and Bunt[4] reported on the Pd-catalysed addition of [NaCH($CO_2CH_3$)$_2$] to (±)-**1a** which gives (*S*)-**2** in 34% *ee* (Figure 1).

When enantiomerically enriched (*S*)-**1a** (55% *ee*) was used, ligand (*R,R*)-**3** gave about 47% *ee* (*S*)-**2** whereas ligand (*S,S*)-**3**) gave about 33% *ee* (*R*)-**2**.[5] This ran contrary to the assumed mechanism in which equal but opposite *ee* should be obtained from enantiomeric *meso*-π-allyl-Pd intermediates. This is not the case and the reaction therefore has some memory of the chirality of **1a**. It was suggested that reaction proceeds via an initial asymmetric intimate ion-pair {[(**3**)-Pd-($\eta^3$-*c*-$C_5H_7$)]$^+$[OAc]$^-$} in which the $AcO^-$ is closer to the α-allylic terminus (Figure 2). Coulombic attraction between the $Na^+$ ion of the malonate and the $[OAc]^-$ nucleofuge then guides the malonate to the α-carbon atom (see inset in Figure 2).

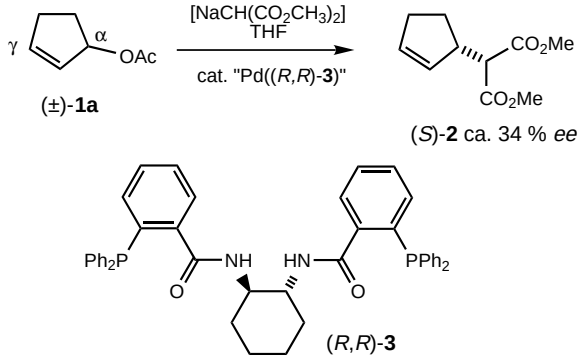


Figure 1. Pd-catalysed reaction of (±)-**1a** with [NaCH($CO_2CH_3$)$_2$] employing ligand (*R,R*)-**3**.[4]

Thus, with racemic (±)-**1a** and ligand (*R,R*)-**3**, a *matched* and *mismatched* manifold results in increased and decreased *ee* values relative to a solvent-separated *meso* ion-pair [(**3**)-Pd-($\eta^3$-*c*-$C_5H_7$)]$^+$ || $[OAc]^-$. The mechanism indicates a propensity for racemic substrates to give racemic products regardless of the ligand because of the nature of the initial ion-pair.[4] Herein we report a novel stereochemical labelling method and demonstrate its use in an investigation into whether the memory effect is caused by asymmetric ion-pairing.

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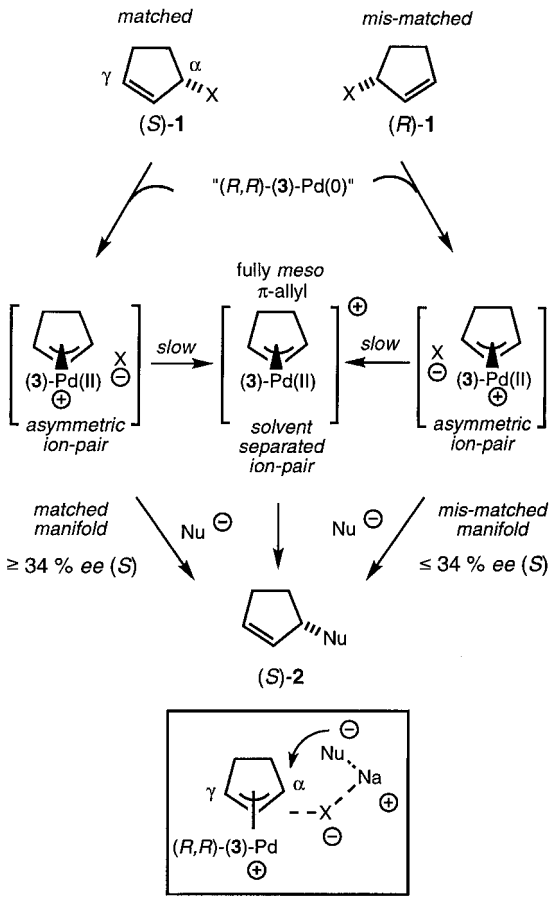
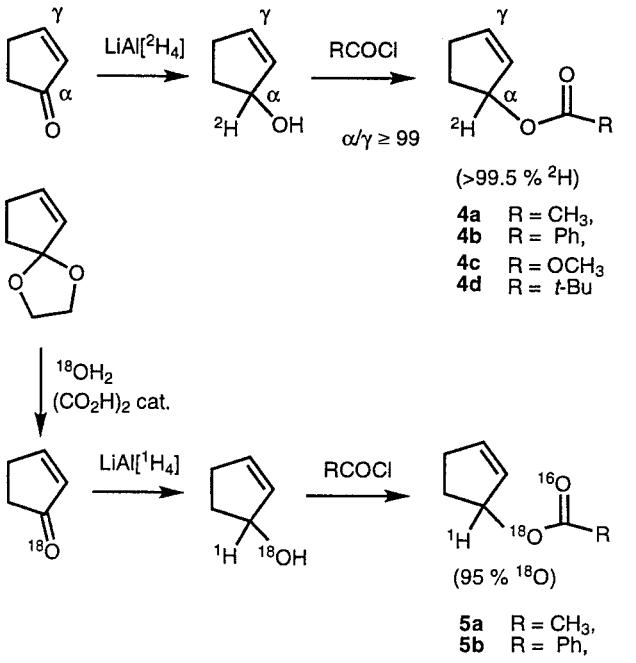



Figure 2. The asymmetric intimate ion-pairing proposed to account for the memory effect. Inset: schematic representation of mechanism for preferential $\alpha$-attack resulting in *increased* and *decreased ee* values in the *matched* and *mismatched* manifolds, respectively.[4]



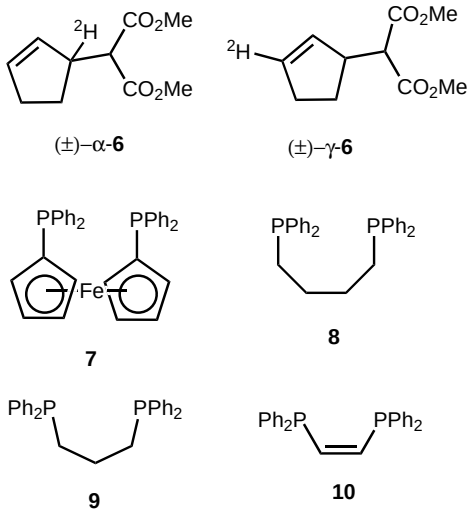

Scheme 1. Synthesis of $^2$H-labelled (±)-**4a–d** and $^{18}$O-labelled (±)-**5a** and (±)-**5b** substrates.

## Results and Discussion

**Substrate synthesis**: To study the memory effect in the reaction of **1** to give **2**, we prepared regiospecifically ($\alpha$) $^2$H-labelled cyclopentenyl substrates (±)-**4a–d** (>99.5% $^2$H, $\alpha/\gamma \geq 99/1$)[6, 7] and also alkyl-$^{18}$O-labelled cyclopentenyl substrates (±)-**5a** and (±)-**5b** (ca. 95% $^{18}$O ). Their synthesis is outlined in Scheme 1.

To test the general effect of the $^2$H-label, we treated (±)-**4a–d** with $[NaCH(CO_2CH_3)_2]$ to give **6** by using pro-catalysts $[Pd(L_2)(\eta^3\text{-}C_3H_5)]^+[O_3SCF_3]^-$ ($L_2 = \mathbf{7}-\mathbf{10}$). These rapid reactions afforded analytically pure (±)-**6** (91–99% yield) whose $\alpha/\gamma$ ratio was measured by $^2$H NMR spectroscopy.

There was no memory effect: irrespective of all reaction variables, the $\alpha/\gamma$ ratio of **6** was consistently 1.10 (±0.02). When a regiochemically scrambled sample ($\alpha/\gamma = 0.9$) of (±)-**4a** was employed[6] identical results were obtained. This secondary kinetic isotope effect (SKIE; $k_H/k_D = 0.91 \pm 0.01$), arises from an increase in p character[8] at the alkylated carbon atom and a decrease in p character at the alkenyl carbon on attack of Pd-π-allyl by malonate.[9] A much smaller $k_H/k_D =$ 0.98 (±0.01) was observed for W-catalysed alkylation[10, 11] of (±)-**4c** a reaction for which early, allyl cation-like, transition states have been postulated.[10c] This suggests a medium or late transition state for Pd-catalysed reaction, [12–14] however, ligand dependence is likely, for example, a more $S_N1$-like transition state is suggested for Pd catalysts bearing PN-phosphite ligands.[15]




### A: The matched manifold with racemic ligand (±)-3

***α/γ* Ratios:** We first studied the memory effect with pro-catalyst $[Pd(\eta^3\text{-}C_3H_5)((\pm)\text{-}\mathbf{3})][Cl]$ generated by addition of (±)-**3** to $[Pd(\eta^3\text{-}C_3H_5)]Cl_2$ ((±)-**3**/Pd = 1.5).[16] After complete consumption of substrate ((±)-**4a–d**), alkylation product (±)-**6** was isolated and the $\alpha/\gamma$ ratio measured by $^2$H-NMR spectroscopy (Table 1). With each nucleofuge (entries 1–4) we observed a different $\alpha/\gamma$ ratio in (±)-**6**. Acetate (±)-**4a** gave the largest $\alpha/\gamma$ ratio (3.8–4.0). In contrast to reactions with (*R,R*)-**3** in which (*S*)-**4** must proceed through the matched manifold and (*R*)-**4** through the mismatched mani-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fold, use of racemic (±)-**3** allows both enantiomers of (±)-**4** a 'choice' of manifold. The $\alpha/\gamma$ ratios of (±)-**6** in Table 1 are thus composite values from matched and mismatched manifolds. It will be shown later that selectivity for the matched over the mismatched manifold is >10:1 for acetate (±)-**4a** and thus, by using racemic ligand (±)-(**3**) and racemic acetate (±)-**4a** we were able to selectively study the matched manifold.

Table 1. Reactions of cyclopentenyl esters (±)-**4a**–**d** ($\alpha/\gamma \geq 99$, 0.12 M) with [$NaCH(CO_2CH_3)_2$] catalysed by 5 mol% Pd((±)-**3**) generated in situ in THF at 25 °C.

| Entry | Substrate | p$K_a$[a] | Pro-catalyst counter-ion | Equiv Nu | $\alpha/\gamma$ Ratio (±)-**6**[b] | Yield (±)-**6** [%][c] |
|---|---|---|---|---|---|---|
| 1 | (±)-**4a** | 4.75 | Cl[d] | 4.5 | 80/20 | 84 |
| 2 | (±)-**4b** | 4.19 | Cl | 4.5 | 68/32 | 98 |
| 3 | (±)-**4c** | –[e] | Cl | 4.5 | 68/32 | 99 |
| 4 | (±)-**4d** | 5.03 | Cl | 4.5 | 77/23 | 80 |
| 5 | (±)-**4a** | 4.75 | –[f] | 2.5 | 80/20 | 73 |

[a] p$K_a$ ($H_2O$) of nucleofuge conjugate acid. [b] $\alpha/\gamma$ Ratio by $^2H$ NMR ($CHCl_3$, 61 MHz). [c] Yield of analytically pure material after chromatography on silica gel. [d] Catalyst generated by addition of (±)-**3** to [Pd($\eta^3$-$C_3H_5$)]$Cl]_2$. [e] p$K_a$ in aqueous media unkown due to decarboxylation. [f] Catalyst generated from (±)-**3** and $Pd_2(dba)_3 \cdot dba$ (dba = dibenzylideneacetone).

**Intimate ion-pairing:** According to an asymmetric ion-pair model,[4] 1) the memory effect should be dependent upon *nucleophile concentration* (the rate of relaxation of the asymmetric Pd-allyl-nucleofuge ion-pair is unimolecular whilst nucleophilic attack is bimolecular); 2) there should be, to some degree, internal *return of nucleofuge* within the intimate ion-pair manifold; 3) palladophilic anions such a *chloride ion* may disrupt ion-pairing and 4) the increase in enantioselectivity relative to the solvent separated ion-pair would be nucleofuge dependent (the pKa and steric bulk of the nucleofuge would affect the degree of intimacy and localisation of the ion-pair). Using (±)-**4a** and (±)-**3** we tested the first three predictions.

1) Nucleophile concentration: $^2H$ NMR analysis of reactions of (±)-**4a** with one equivalent of [$NaCH(CO_2CH_3)_2$], in which [Pd($\eta^3$-$C_3H_5$)(±)-**3**)][Cl] was used as pro-catalyst and 4,4′-[$^2H_2$]-biphenyl as internal integration standard, demonstrated that the $\alpha/\gamma$ ratio of (±)-**6** is essentially constant throughout the reaction[17] (Figure 3).

As the reactions proceed, the concentration of nucleophile decreases linearly as the inverse of conversion of (±)-**4a**; four runs with 0.5 and 5 mol% catalyst loading gave the same linear relationship between [$\alpha$-**6**] and the total concentration of product [$\alpha$-**6** + $\gamma$-**6**] (gradient = 0.8; that is $\alpha/\gamma = 80/20$) (Figure 4). Thus the $\alpha/\gamma$ ratio and memory effect are independent of [$NaCH(CO_2CH_3)_2$] concentration in the matched manifold.

2) Return of nucleofuge: Internal return is characteristic of intimate ion-pairs.[18] The $^2H$ and $^{18}O$ labels were completely scrambled in (±)-**4a** and (±)-**5a, b** recovered from reactions with substoichiometric amount of [$NaCH(CO_2CH_3)_2$].[7] The $\alpha/\gamma$ ratio of (±)-**6** was (79 / 21) from (±)-**4a** and thus there

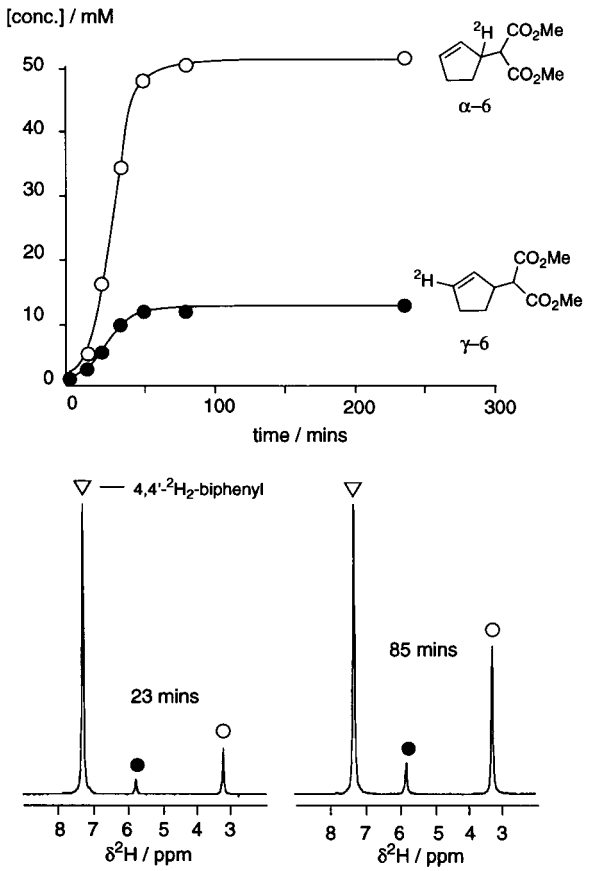


Figure 3. Graph: Time-course of reaction of equimolar (±)-**4a** with [$NaCH(CO_2CH_3)_2$] catalysed by 0.5 mol% [Pd($\eta^3$-$C_3H_5$)((±)-**3**)][Cl] pro-catalyst in THF at 25 °C with 4,4′-[$^2H_2$]-biphenyl as internal standard. Spectra: representative $^2H$ NMR spectra of worked-up reaction samples at 22 and 64% conversion.

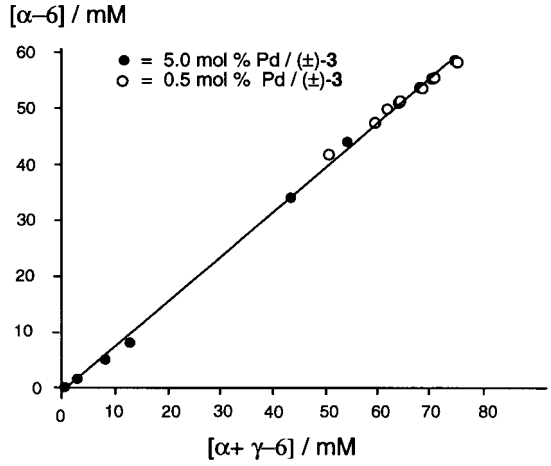


Figure 4. Relationship [$\alpha$-**6**] = 0.8 [$\alpha$ + $\gamma$-**6**] – 0.05 (mM); $R^2 = 0.99$ observed in four separate reactions of equimolar (±)-**4a** and [$NaCH(CO_2CH_3)_2$] with 5 and 0.5 mol% pro-catalyst [Pd($\eta^3$-$C_3H_5$)((±)-**3**)][Cl].

was no reversibility of the reaction. The $^{13}C$ NMR spectra[19] of the $\alpha$-allylic carbon atom of (±)-**5b** before (**I**) and after (**II**) reaction are shown in Figure 5.

Very different results were obtained when (±)-**4a** and (±)-**5a, b** were recovered, during catalyst turnover, from reactions with excess [$NaCH(CO_2CH_3)_2$]. There was ≤1% scrambling

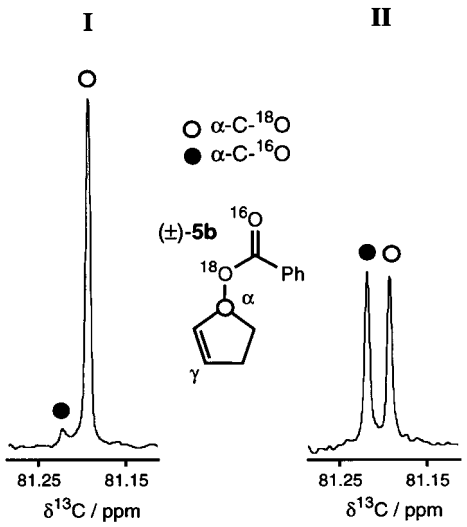


Figure 5. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) sub-spectrum of (C(1′)) of (±)-**5b** (95% $^{18}O$, before (**I**) and after (**II**) recovery from Pd(±)-(**3**) catalysed reaction with 0.85 equiv [$NaCH(CO_2CH_3)_2$].

of (±)-**4a** (58% conversion) and about 5% scrambling of (±)-**5a** and (±)-**5b** (42 and 61% conversion respectively). Thus there is some evidence for localised ($\alpha$) nucleofuge return.

3) Chloride ion: The effect of small, coordinating ions on Pd-catalysed allylic alkylations has been the subject of much recent attention. For example, iodide ion can improve regioselectivity[20] whilst fluoride can cause large increases in *ee* values in reactions catalysed by chiral Pd(′PN′) complexes.[21, 22] However, reaction of (±)-**4a** in the presence or absence of $Cl^-$ (Table 1, entries 1 and 5) gave **6** with identical $\alpha/\gamma$ ratio and therefore chloride ion is not responsible for the memory effect in the matched manifold.

### B: Matched and mismatched manifolds—memory effects with (*R,R*)-3

**Development of a $^{13}C$ analytical method:** With (±)-**3** the *regiochemical* outcome of the reaction was studied (Section A). To study the memory effect with (*R,R*)-**3**, the *stereochemical* outcome of both the matched and mismatched manifolds must be determined independently. Ideally one would use 100% *ee* substrates to study memory effects but often this is not practical. Trost and Bunt employed (*S*)-**1a** and (*S*)-**1b** (44, 55 and 64% *ee*) and normalised the data by a weighted average involving results obtained with (±)-**1a, b**.[4] This approach may be biased by kinetic resolution[27c] unless 100% substrate conversion is attained. We have developed an alternative and practical approach based on the double inversion of stereochemistry[23] in Pd-catalysed allylic alkylation with stabilised carbon nucleophiles[24] (Figure 6).

A combination of (+)-Eu(hfc)$_3$ (hfc = [3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]) and $^{13}C$-$^2H$ isotope shifts ($\beta$ or $\gamma$) gave base-line resolution of the regioisotopomeric enantiomers of **6** in the $^{13}C$ NMR sub-spectrum of C(4′)$H_2$[25] (Figure 7).

Once calibrated,[26] a conventional $^{13}C\{^1H\}$ NMR experiment on a 400 MHz ($^1H$) instrument allowed simultaneous

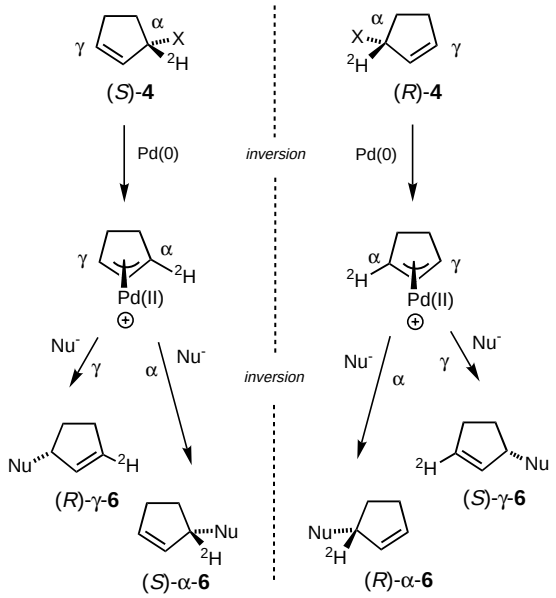


Figure 6. The stereochemical course of Pd-catalysed allylic alkylation of (*S*)-**4** and (*R*)-**4** leading to **6**.

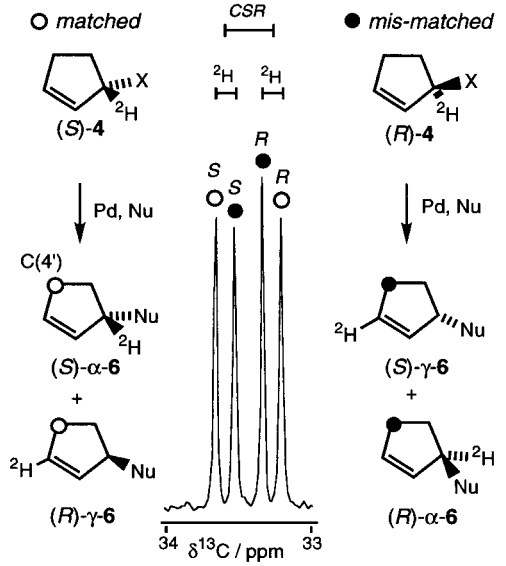


Figure 7. $^{13}C\{^1H\}$ NMR ($C_6D_6$) sub-spectrum of C(4′) in (±)-$\alpha/\gamma$-**6** (0.28 M) with [(+)-Eu(hfc)$_3$] (0.154 M).

but individual measurement of the *ee* value of **6** arising from (*S*)-**4** and (*R*)-**4** in *racemic* (±)-**4**.

**Nucleofuge dependence:** Despite a mechanism involving nucleofuge ion-pairing, it was earlier reported that the memory effect was the same with **1a** and **1c** (acetate and methyl carbonate nucleofuges).[4] With pro-catalyst [Pd($\eta^3$-$C_3H_5$)(*R,R*)-**3**][Cl] and (±)**4a–d** (Table 2, entries 1–4) this was indeed found to be the case—but only in the *matched manifold*: (*S*)-**4a–d** gave (*S*)-**6** of enantiomer ratio: 37 / 13 to 38 / 12 (*S*) / (*R*) (i. e. 50 ± 2% *ee*). The *mismatched manifold is* nucleofuge dependent: (*R*)-**4a** gave 28% *ee* (*S*)-**6**, (*R*)-**4b, c** both gave racemic (±)-**6** and enantioselectivity was reversed with (*R*)-**4d** which gave 8% *ee* (*R*)-**6** (Figure 8 **I**, **II**, **III**). The propensity of (*R*)-**4** to give (*R*)-**6** (i. e. $\alpha$ attack) increases with


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Table 2. Reactions of cyclopentenyl esters (±)-**4a–d** ($\alpha/\gamma \geq 99$, 0.12 M) with 4.5 equivalents of $[NaCH(CO_2CH_3)_2]$ with 5 mol% pro-catalyst '$[Pd(L)(\eta^3\text{-}C_3H_5)Cl]$'[a] in THF at 25 °C.

| Entry | (±)-**4** | Ligand (L) | $\alpha/\gamma$ Ratio **6**[b] | | *er*[c] (*S/R*)-**6** from: | | *ee*[d] **6** | Yield **6** | Rate ratio[f] |
|---|---|---|---|---|---|---|---|---|---|
| | | | L | ((±)-L)) | (*S*)-**4** ($\alpha/\gamma$) | (*R*)-**4**($\gamma/\alpha$) | [%] | [%][e] | (*S*)-**4**/(*R*)-**4** |
| 1 | **4a** | (*R,R*)-**3** | 55/45 | (80/20) | 38/12 | 32/18 | 40(*S*) | 88 | ≥ 10 |
| 2 | **4b** | (*R,R*)-**3** | 62/38 | (68/32) | 37/13 | 25/25 | 24(*S*) | 82 | 3 |
| 3 | **4c** | (*R,R*)-**3** | 62/38 | (68/32) | 38/12 | 25/25 | 29(*S*) | 79 | 2 |
| 4 | **4d** | (*R,R*)-**3** | 64/36 | (77/23) | 37/13 | 23/27 | 20(*S*) | 70 | ≥ 10 |
| 5 | **4a**[g] | (*R,R*)-**3** | 44/56 | (24/76) | 15/35 | 21/29 | 28(*R*) | 93 | ≥ 10 |
| 6 | **4d** | (*R,R*)-**3**[h] | 76/24 | (–)[i] | 37/13 | 5/17 | 17(*S*) | 50[j] | –[i] |
| 7 | **4a** | (*R,R*)-**11** | 52/48 | (–)[i] | – | – | – | 82 | –[i] |
| 8 | **4a** | (*R,R*)-**12** | 52/48 | (–)[i] | – | – | – | 82 | –[i] |
| 9 | **4a** | (*S*)-**13** | 52/48 | (52/48) | 28/22 | 26/24 | 7(*S*) | 88 | 1.0 |
| 10 | **4a** | (*R*)-**13** | 52/48 | (52/48) | 25/25 | 22/28 | 7(*R*) | 93 | 1.0 |
| 11 | **4a** | (*R*)-**14** | 52/48 | (55/45) | 35/15 | 33/17 | 32(*S*) | 81 | 1.4 |
| 12 | **4d** | (*R*)-**14** | 52/48 | (55/45) | 36/14 | 32/18 | 38(*S*) | 82 | 1.1 |
| 13 | **4a** | **16** | – | 54/46 | – | – | – | 18[k] | – |
| 14 | **4a** | **17** | – | 52/48 | – | – | – | 88 | – |

[a] Pro catalyst generated by addition of ligand to $[Pd(\eta^3\text{-}C_3H_5)]Cl]_2$. [b] $\alpha/\gamma$ Ratio by $^2H$ NMR spectroscopy ($CHCl_3$, 61 MHz). [c] Enantiomer ratios (*er* values) (*S/R*)-**6** by integration of $^{13}C\{^1H,^2H\}$ or $^{13}C\{^1H\}$ NMR spectra of C(4′), C(5′). [d] The *ee* of (*S/R*)-**6** by integration of $^{13}C\{^1H,^2H\}$ or $^{13}C\{^1H\}$ NMR spectra of both diastereotopic $CH_3$. [e] Yield of analytically pure material after chromatography on silica gel. [f] Calculated from result with racemic versus enantiomerically pure ligand. [g] With $[Li(CH(CO_2CH_3)_2]$ prepared in situ from BuLi and $CH_2(CO_2CH_3)_2$. [h] Catalyst generated by addition of (*R,R*)-**3** to $[Pd(\eta^3\text{-}C_3H_5)](MeCN)_2]^+ [O_3SCF_3]^-$. [i] Not determined. [j] Work-up after 5 days. [k] Extensive catalyst decomposition under reaction conditions.

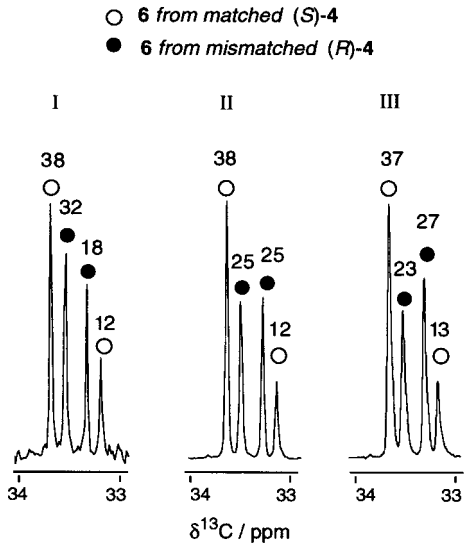



Figure 8. $^{13}C\{^1H\}$ NMR spectrum ($C_6D_6$, 0.154 M (+)-Eu(hfc)$_3$) of C(4′) of **6** (0.28 M) from ('Pd((*R,R*)-**3**)′) catalysed reaction of (±)-**4a** (**I**), (±)-**4c** (**II**) and (±)-**4d** (**III**) *matched manifold* products are the ouside pair.

increasing steric bulk of nucleofuge. This trend does not correlate with the p$K_a$ of the nucleofuge.

**Relative rates**: It is expected that substrates of type (±)-**1**, and thus (±)-**4**, might undergo kinetic resolution[27] with catalysts of type Pd((*R,R*)-**3**). Rather than measure the *ee* of **4** against conversion, we note that the $\alpha/\gamma$ ratios of **6** are a combination of a constant $\alpha/\gamma$ value (matched manifold) and a nucleofuge dependent ratio (mismatched manifold). Thus the $\alpha/\gamma$ ratios of **6** obtained with (±)-**3** allow an estimation of the selectivity the racemic catalyst has for one manifold over the other (Table 2, entries 1–4, far right-hand column). By this process, (±)-**4a–d** are all predicted to display matched manifold selectivity which translates to kinetic resolution when enantiomerically pure ligand is employed.[27c]

**Nucleophile counter-cation:** Trost et al. have reported that $[LiCH(CO_2CH_3)_2]$ gives the opposite enantioselectivity to $[NaCH(CO_2CH_3)_2]$ on Pd(*R,R*)-(**3**)-catalysed conversion of (±)-**1** to **2**[28]—but not on whether there is still a memory effect. Since the intimate asymmetric ion-pairing model[4] involves a coulombic attraction between the malonate counter-ion ($Na^+$) and the nucleofuge then (*S*)-**4a**, the *matched enantiomer* with $[NaCH(CO_2CH_3)_2]$ (external $\alpha$ attack) would become the *mismatched enantiomer* with $[LiCH(CO_2CH_3)_2]$ (external $\gamma$ attack) and vice versa. This is not observed (Table 2, entry 5). There is still a memory effect but (*S*)-**4a** remains the matched enantiomer—reacting faster and giving higher *ee* (Figure 9).

**Chloride ion:** By using $[Pd(R,R)\text{-}\mathbf{3})(\eta^3\text{-}C_3H_5)]^+[O_3SCF_3]^-$ generated in situ as pro-catalyst, pivaloate (±)-**4d** was treated with $[NaCH(CO_2CH_3)_2]$ under chloride-free conditions (Table 2, entry 6). As expected, reaction of matched (*S*)-**4d** was $Cl^-$ independent (see Table 2, entry 4). However, (*R*)-**4d** gave a larger memory effect (5/17 = 11/39, (*S*)-$\gamma$-**6**/(*R*)-$\alpha$-**6**)) and thus chloride ion $Cl^-$ (entry 4) reduces the memory effect in the mismatched manifold.[27c]

### C: Comparison with other ligands

In order to gain some insight into the possibility of unusual coordination modes of **3** being involved in the memory effect in the mismatched manifold, we studied a range of other ligands (Table 2, entries 7–14).

**Bidentate 'PP' and 'PN' ligands**: $\alpha/\gamma$ Ratios with chiral 'PP' ligands **11** and **12** (Table 2, entries 7 and 8) were no different to those with achiral 'PP' ligands **7** to **10**. With chiral 'PN' ligand **13** (Table 2, entries 9 and 10) the small and inconclusive differences may be the result of a SKIE. With 'PN' ligand **14**[29] (Table 2, entries 11 and 12) there was again a small difference in stereochemical outcome and the matched manifold is slightly faster with **4a** (ca. 1.4). With bulkier (±)-**4d** a very

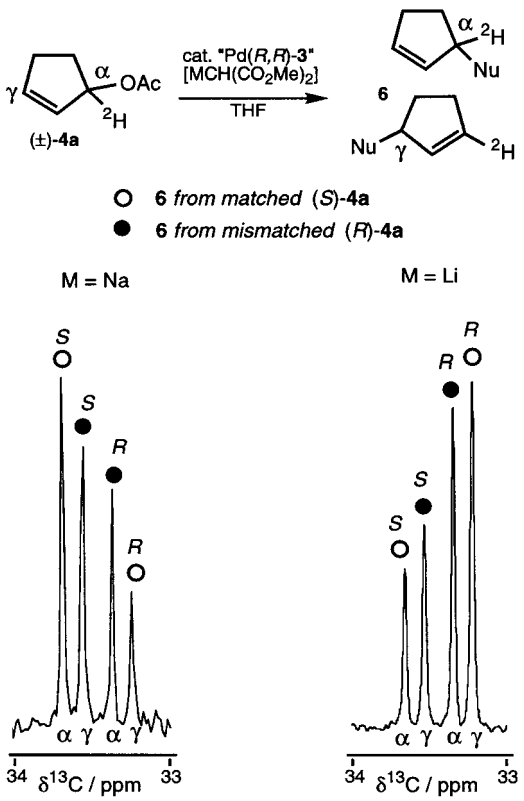
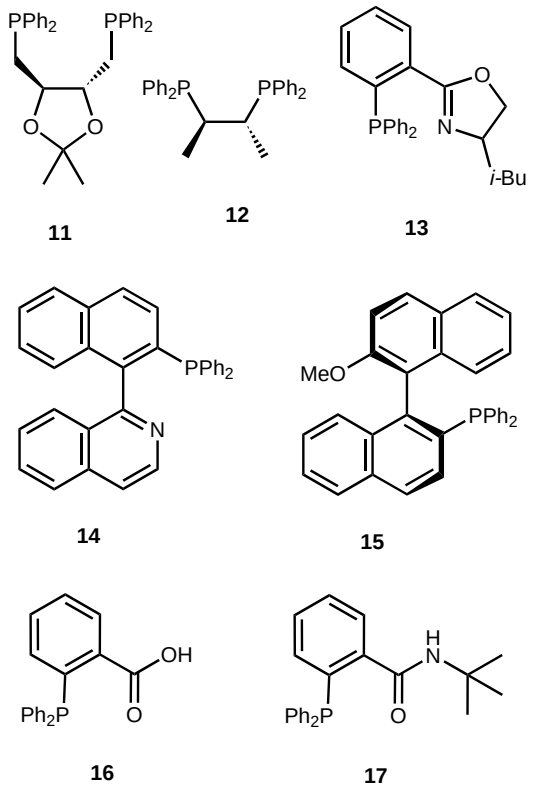



Figure 9. $^{13}C$ NMR analysis (as Figure 8) of C(4′)-**6** from reaction of (±)-**4a** with $[MCH(CO_2CH_3)_2]$, M = Na, Li.

slight increase in the memory effect was accompanied by a small decrease in kinetic selectivity for the matched manifold (1.1 versus 1.4).



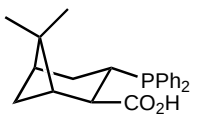

**Monodentate MeO-MOP ligand 15:** Very recently, Hayashi et al.[30] have reported near-perfect retention of regiochemistry in allylic alkylation catalysed by Pd complexes bearing the very bulky ligand **15** (′(*R*)-MeO-MOP′). Detailed NMR studies revealed monodentate coordination of a single ligand **15** to a Pd (π-cyclohexenyl) fragment, the fourth coordination site is occupied by a chloro ligand—even with excess **15** present. A chloro ligand is essential for memory effects with the ′P′ ligand **15** but not with ligand **3**.

**Monophosphane ligands 16 and 17**: With pro-anionic ligand **16** (Table 2, entry 13), slow turnover, accompanied by Pd black precipitation, gave (±)-**6** with $\alpha/\gamma$ ratio of 1.16 that may be the result of a small memory effect. With neutral ligand **17**, (Table 2, entry 14) there was no memory effect. Despite a ratio of **17**/Pd of 1/1, there was no trace of Pd black (unlike with $PPh_3$)[30a] and this suggests that **17** can function as a chelating ′PO′ ligand, when necessary in the catalytic cycle and therefore intimates that **3** may also do so if required.[31]

### D: Mechanistic aspects of the memory effect

**The matched manifold:** Selectivity for (*S*)-**2** from Pd-catalysed reaction of (±)-**1a** in the presence of (*R*, *R*)-**3**) increases in the order $Li^+$ (63 % *ee R*) , $Na^+$ (38 % *ee S*), $K^+$ (51 % *ee S*), $Cs^+$ (76 % *ee S*).[28] It has been suggested that this may reflect increasing relaxation of asymmetric intimate ion-pairs before nucleophilic attack.[4, 17a, 32] The results we have obtained suggest otherwise. It is thus instructive to compare the trend ($Li^+ \rightarrow Cs^+$) reported for (*R,R*)-**3** with trends observed with other asymmetric ligands. With 1,3-diarylpropenyl substrates, ′PN′ ligands of type **13** give the highest *ee* values[33] with low concentrations of $[KCH(CO_2CH_3)_2]$—lower *ee* values are obtained with $[NaCH(CO_2CH_3)_2]$.[34] Similarly, with the ′Quinap′ ligand **14**, the use of a crown ether to complex $Na^+$ gave best results.[12b] Late transition states have been suggested for these reactions[12] since stereocontrol is by developing ligand – alkene interactions.[35]

The *ee* values obtained with chiral PO ligand **18**[36, 37] follow the opposite order $Li^+ > Na^+ > K^+$. In contrast to the tight chiral pocket of **3**, ligand **18** was designed to create a relatively open chiral pocket so as to control the rotamer population of the slim cyclic *anti-anti* allyl system. Thus enantioselectivity is induced by **18**(Pd)-[$\eta^3$-allyl] interactions rather than developing **18**(Pd)-[$\eta^2$-alkene] interactions[35] and an earlier transition state will give greater kinetic differential ($\Delta\Delta G\ddagger$) and thus *ee*. The trends for **13**, **14** and **18** suggest that large, soft, less coordinating counter-ions, which cause greater charge delocalisation in the malonate anion, favour late transition states[12b]—perhaps through attenuated charge acceleration and increased frontier orbital control.[38]




**18**

Accordingly, with ligand (*R,R*)-(**3**) and (*S*)-**1** (and thus (*S*)-**4**) the smooth transition from $\gamma$-selective attack[39] (pro-*R*) to $\alpha$-selective attack (pro-*S*) as ($Li^+ \rightarrow Cs^+$) suggests an inversion of $\Delta\Delta G\ddagger$ from early ligand-allyl interactions to late ligand – alkene interactions. These early ($\gamma$) versus late ($\alpha$) selectiv-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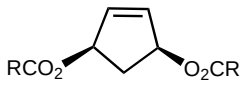
ities are consistent with the reverse reaction (substrate ionisation) in which ligand–alkene interactions, in a presumably early transition state, favour $\alpha$-ionisation ((*S*)-**4a**) over $\gamma$-ionisation ((*R*)-**4a**).

**Memory effects in the mismatched manifold:** It is in the *mismatched manifold* that the stereochemical dependence on nucleofuge occurs. Comparison of (*S*)- and (*R*)-**1** with bulkier *meso*-**19** is instructive.




**19**

Coordination of (*R,R*)-(**3**) through both P donor centres may cause perturbations in Pd-π-allyl electron distribution through distortion induced by steric interactions.[40] This distortion is a key feature in enantioselective nucleophilic attack on Pd-π-allyl systems with other ′PP′ and ′NN′ ligands,[41] and will also be important in the reverse reaction: ionisation.[12b] Despite the tight chiral pocket induced by the wide ligand bite-angle,[28] Pd(*R,R*)-(**3**) and related catalysts can both accommodate and enantioselectively ionise **19** which has a nucleofuge at *both* adjacent enantiotopic allylic positions[42]—one matched the other mismatched. This occurs formally by internal kinetic resolution[43] ––ionisation occurs selectively at the matched carbon. Ionisation at the *mismatched* carbon of **19** must therefore be highly disfavoured by steric clash arising in the rotational displacement of the Pd-π-[$\eta^2$-alkene] unit to form a Pd-π-[$\eta^3$-allyl] unit.[35]

In contrast to **19**, mismatched (*R*)-**1** does not bear a matched nucleofuge and can only ionise with disfavoured torquo-selectivity.[35] The resulting steric strain may be alleviated by breaking open the ′P,P′ chelate to give an ′open pocket′ before or during ionisation. This process would give rise to a (P,L)-Pd-(π-allyl) complex (L = unspecified non-phosphane ligand or vacant site) and it is therefore instructive to consider (P,N)-Pd-(π-allyl) complexes. Crystal structures[44] of these complexes indicate that the C–Pd bond to the allylic terminus *trans* to P is longer than that *trans* to N. Arguments have been put forward that the carbon *trans* to P should be attacked more rapidly by nucleophiles[12, 45] and, by reverse arguments, that ionisation should occur with the nucleofuge *trans* to P.[27a] Mismatched ionisation of (*R*)-**1** by a non-chelate complex of type ′Pd(*R,R*)-**3**′ should thus occur to give a (P,L)-Pd-[$\eta^3$-allyl] complex with $\alpha$-C *trans* to P and nucleophilic attack should also be $\alpha$-C and *trans* to P. A memory effect with $\alpha$-C selectivity would then be observed provided *endo-exo* rotamer equilibration or re-coordination of the second phosphine (13-membered chelate formation) is slow (Figure 10).

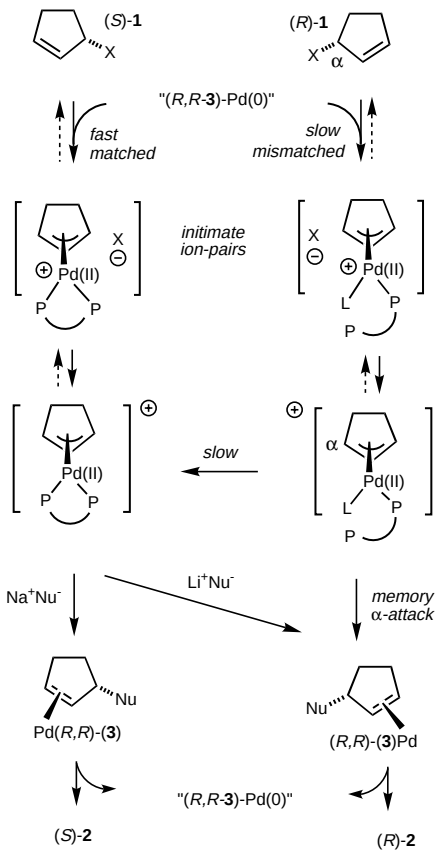
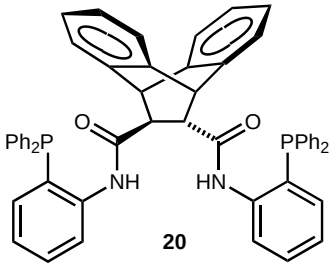


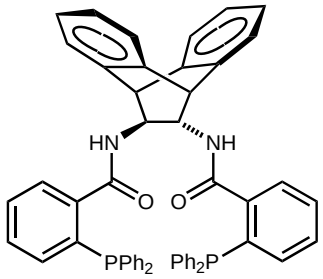

Figure 10. A mechanistic scheme for the memory effect. P is one of the two triaryl phosphane donors in (*R,R*)-**3**; L is a vacant site or an unspecified ligand for example amide C=O, chloride, nucleofuge etc.

**Ligand 3 as a ′PP′ versus ′P′, ′PO′ or ′PL′ ligand:** Monophosphane derivatives of (*R,R*)-**3** (one $Ph_2P$ replaced by $Ph_2C$ or H) generate Pd catalysts that induce lower and reversed enantioselectivity in the allylic alkylation of (±)-**1** and **19**.[46] However, memory effects may attenuate or reverse enantioselectivity and there is no direct evidence for the formation of [Pd(**3**)π-allyl] type complexes in which both P donors coordinate the Pd. Nonetheless, an NMR investigation[46] of the reaction of **3** with [$Pd_2dba_3 \cdot CHCl_3$] in which a $^3J_{P,P}$ coupling of 14.5 Hz, typical of *cis* phosphane ligand coordination is observed has been suggested as evidence that (*R,R*)-**3** acts as a ′PP′ bidentate ligand toward Pd. An X-ray crystal structure[47] of complex [Pd(**20**)π-allyl]$^+$[$ClO_4$]$^-$ in which both ligand P donor centres coordinate to a Pd allyl fragment has also been reported.

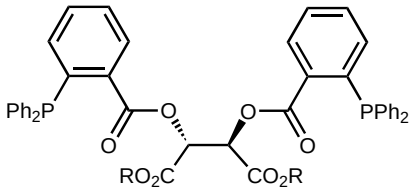
Ligand **20** affords the opposite sense of asymmetric induction to ligand **21** in Pd-catalysed reactions of **19** and diester based ligands, for example **22**, gave lower enantioselectivities than diamide based ligands (e. g. (*R,R*)-**3**). This suggests an important role of the carbonyl oxygens in these reactions.[31] By simple resonance arguments, esters are expected to be less metal-coordinating at carbonyl oxygen than amides. The quasi-meso ester–amide hybrid ligand **23** actually induces greater enantioselectivity than



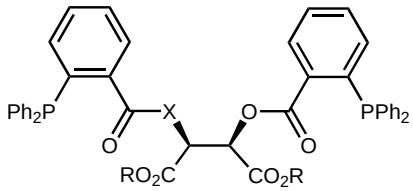

**20**




**21**



**22**



**23** X = NH
**24** X = O

**22** and thus does not behave like diester **24** which, being meso, would not induce enantioselectivity at all.[28]

## Conclusions

We have developed an effective and practical $^{13}C$ NMR method to study the stereochemical outcome from the Pd-catalysed addition of $[MCH(CO_2CH_3)_2]$ to racemic (±)-**4a–d**. Racemic $^2H$-labelled substrates are readily synthesised and this technique should be applicable to the study of other allylic alkylation reactions. Only one enantiomer of chiral ligand is required and use of substoichiometric nucleophile can give information on kinetic resolution. Using (±)-**4a–d**, (±)-**5a** and (±)-**5b**, we have studied the memory effects that occur when ligand (±)-**3** and (*R,R*)-**3** are employed in this reaction. Key results are: i) There is evidence for intimate ion-pairing in both the matched and mismatched manifolds, but this does not seem to be the cause of the memory effect. ii) In the *matched manifold*, the mechanism is likely to be normal that is involving a meso-π-allyl intermediate. iii) In the *mismatched manifold*, bulky nucleofuges give greater memory effects. iv) The *matched manifold* is kinetically favoured over the *mismatched*.[27c] v) With both $[NaCH(CO_2CH_3)_2]$ and $[LiCH(CO_2CH_3)_2]$, the same substrate–catalyst combination forms the matched pair—despite opposite regiochemical outcome on nucleophilic attack. vi) Chloride ion reduces the memory effect in the *mismatched manifold*.

Since no significant memory effects were observed with PO or PN ligands and, as discussed earlier, powerful memory effects have been reported for the very bulky monodentate ′P′ ligand **15**,[30] one interpretation of the results obtained with **3** is that due to unfavourable torquo-selectivity during the mismatched ionisation event, ligand **3** may act, at least in part of the catalytic cycle, as a very bulky ′P′ ligand which thus produces non-meso intermediates. Consistent with this is the observation that the presence of catalytic quantities of chloride ion substantially accelerate the reaction of the mismatched substrate.[27c] However, the true and possibly variable coordination nature of **3** to Pd throughout the various stages of the overall matched and mismatched catalytic cycles are as yet undetermined.

## Experimental Section

**General:** All manipulations were performed on a vacuum line (argon or nitrogen) using standard Schlenk techniques. THF, $Et_2O$, DMF and $CH_2Cl_2$ were anhydrous (Fluka) and, when appropriate, were degassed (freeze-thaw cycles) and then argon- or nitrogen-saturated prior to use. NMR: Bruker 600, Jeol GX400, Jeol Lambda 300, Jeol GX270. MS (EI): Micromass Autospec. Optical rotation: Perkin Elmer 141 polarimeter. Flash column chromatography: Merck silica gel 60 (0.04–0.063 mm). TLC: 0.25 mm, Merck silica gel 60 F254 visualising at 254 nm or with dilute acidic aqueous $KMnO_4$ solution. Elemental analyses were performed by the analytical service in the School of Chemistry, University of Bristol.

**Materials:** Ligand **13** was prepared according to a literature procedure.[48] Quinap ligand **14** was a gift from Dr. John M. Brown FRS, Oxford. Cyclopent-2-en-1-one, cyclopent-2-en-1-one diethylene ketal, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ligands **7–12** and ((+)-Eu(hfc)$_3$) were purchased from Aldrich and used as received. (±)- and (1*R,* 2*R*)-*trans*-1,2-diaminocyclohexane and 4-*N,N*-dimethylaminopyridine (DMAP) were purchased from Fluka and used as received. $H_2[^{18}O]$ (97% $^{18}O$, containing 25% $^2H_2{}^{18}O$), $[^2H_2]O$ (>99.5% $^2H$) and $LiAl[^2H_4]$ (>99.9% $^2H$) were purchased from Cambridge Isotope Laboratories. $[Pd(\eta^3\text{-}C_3H_5)]Cl]_2$ was purchased from Strem and recrystallised ($CH_2Cl_2$/hexane). $[NaCH(CO_2CH_3)_2]$[49] was recrystallised from MeOH and dried in vacuo. $[Pd(L_2)(\eta^3\text{-}C_3H_5)]^+[O_3SCF_3]^-$ were prepared in analytically pure form by addition of one equivalent of $L_2$ to $[Pd(MeCN)_2(\eta^3\text{-}C_3H_5)]^+[O_3SCF_3]^-$[50] in $CH_2Cl_2$, evaporation, then recrystallisation from $CH_2Cl_2$/$Et_2O$.

**Preparation of isotopically labelled compounds**

**(±)-1-[$^2H_1$]-cyclopent-2-en-1-ol and $^{18}O$-cyclopent-2-en-1-ol**: Cyclopentenone (12.89 mL, 154 mmol) in $Et_2O$ (125 mL) was added dropwise to a suspension of $LiAl[^2H_4]$ (2.21 g, 52.6 mmol) in $Et_2O$ (50 mL). After complete addition, water (12 mL) was added dropwise (CAUTION!) followed by $MgSO_4$ (ca. 10 g). The resulting suspension was stirred overnight and then filtered through Celite, the filtrate concentrated in vacuo (≥ 250 mmHg, 40 °C) to about 15 mL and distilled. (±)-1-[$^2H$]-cyclopent-2-en-1-ol was collected (ca. 20 mmHg, 59 °C) as a colourless liquid (10.5 g, 83%). $^1H$ NMR ($CDCl_3$, 400 MHz, 21 °C, TMS): $\delta = 6.0$ (ddd, $^3J$ (H,H) = 5.5, 2.4, 2.4 Hz, 1H; C(3)H), 5.8 (ddd, $^3J$(H,H) = 5.5, $^4J$(H,H) = 2.0, 2.0 Hz, 1H; C(2)H), 2.5 (m, 1H; C(4)H*syn*), 2.2 (m, 2H; C(4)H$_{anti}$, C(5)H$_{anti}$), 1.78 (m, 1H; C(5)H*syn*); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, 21 °C, TMS): $\delta = 135.1$ (C(3)), 133.3 (C(3)), 77.1 (t, $^1J(H,^2H) = 21$ Hz, C(1)), 33.2 (C(4)), 31.0 (C(5)); $^2H$ NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 4.78$ (br. s, C(1)$^2$H).[51][18]O-cyclopent-2-en-1-ol was prepared by identical procedure (with $LiAl[^1H_4]$) using $^{18}O$-cyclopentenone prepared by reaction of ice-cold cyclopentenone diethyleneketal (5.97 g, 47.3 mmol) with $H_2[^{18}O]$ (0.97 mL, 47.3 mmol) and oxalic acid (8 mg, 8.4 μmol). Analytical data: $^{18}O$-cyclopent-2-en-1-ol: $^{13}C\{^1H\}$ NMR ($C_6D_6$, 100 MHz, 21 °C): $\delta = 134.4$ (C(3)), 134.1 (C(2)), 77.3 (C(1)-$^{18}$OH), 33.5 (C(4)), 31.3 (C(5)); MS (EI): *m/z* (%): 85 (100) [$M - H^+$].

**Acetates (±)-4a and (±)-5a**: To a stirred solution of (±)-1-[$^2H_1$]-cyclopent-2-en-1-ol (2.5 g, 29.4 mmol) in $CH_2Cl_2$ (125 mL) was added $Et_3N$ (4.4 mL, 31.5 mmol), DMAP (6 mg, 0.05 mmol) and finally $Ac_2O$ (3.91 mL, 41.4 mmol). After 24 h, TLC (12/1 hexane/EtOAc) showed complete consumption of the cyclopent-2-en-1-ol ($R_f = 0.1$) and the reaction mixture was poured into water (100 mL), extracted with $CH_2Cl_2$ (150 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a colourless oil. Purification by silica-gel chromatography (4.5 × 21 cm) followed by fractional distillation afforded (±)-**4a** (2.1 g, 57%; b.p 48–55 °C, about 20 mmHg) as a colourless oil. $^1H$ NMR ($CDCl_3$, 270 MHz, 21 °C, TMS): $\delta = 6.11$ (m, 1H; C(3)H), 5.82 (m, 1H; C(2)H), 2.51 (m, 1H; C(4)H$_{syn}$), 2.30 (m, 2H; C(4)H$_{anti}$, C(5)H$_{anti}$), 2.03 (s, 3H; Me), 1.80 (m, 1H; C(5)H*syn*); $^2H$ NMR ($CHCl_3$, 46 MHz, 21 °C, $CDCl_3$): $\delta = 5.7$ (br. s, C(1)$^2$H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 21 °C, TMS): $\delta = 171.1$ (C=O), 137.7 (C(3)), 129.2 (C(2)), 80.2 (t, $^1J(H,^2H) = 24$ Hz, C(1)), 31.1 (C(4)), 29.7 (C(5)), 21.4 ($CH_3$). Compound (±)-**5a** was prepared by an identical procedure with $^{18}O$-cyclopent-2-en-1-ol. Analytical data for (±)-**5a**: $^{13}C\{^1H\}$ NMR ($C_6D_6$,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100 MHz, 21 °C): $\delta = 171$ (C=O), 37.1 (C(3)), 130.1 (C(2)), 80.40 (ca. 6 %, (C(1)-$^{16}$O), 80.37 (ca. 94 %, C(1)-$^{18}$O), 31.2 (C(4)), 30.1 (C(5)), 20.9 ($CH_3$).

**Benzoates (±)-4b and (±)-5b**: Compound (±)-**4b** was prepared in an identical manner to (±)-**4a** but with PhCOCl. Kugelrohr distillation (oven $T = 190$ °C, ca. 20 mmHg) gave (±)-**4b** (1.82g, 80 %) as a colourless oil, TLC, 19/1 hexane/EtOAc, $R_f = 0.3$. $^1$H NMR ($CDCl_3$, 300 MHz, 21 °C, TMS): $\delta = 8.03$ (dd, $^3J$(H,H) = 7, $^5J$(H,H) = 0.5 Hz, 2H; C(2′)H), 7.54 (ddd, $^3J$(H,H) = 9, 7, $^5J$(H,H) = 0.5 Hz, 2H; C(3′)H), 7.42 (tt, $^3J$(H,H) = 9 Hz, $^4J$(H,H) = 1 Hz, 1H; C(4′)H), 6.18 (m, 1H; C(3)H ), 5.94 (m, 1H; C(2)H), 2.54 (m, 1H; C(4)$H_{syn}$), 2.39 (m, 2H; C(4)$H_{anti}$, C(5)$H_{anti}$), 1.94 (m, 1H; C(5)$H_{syn}$); $^2$H NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 6.0$ (br. s, C(1)$^2$H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 21 °C, TMS): $\delta = 166.6$ (C=O), 137.8 (C(3)), 132.7 ($CH_{p\text{-arom}}$), 130.7 ($C_{i\text{-arom}}$), 129.6 ($CH_{o\text{-arom}}$), 129.3 (C(2)), 128.3 ($CH_{m\text{-arom}}$), 80.8 (t, $^1J$(H,$^2$H) = 24 Hz, C(1)), 31.2 (C(4)), 29.8 (C(5)). (±)-**5b**, from *$^{18}$O*-cyclopent-2-en-1-ol: $^{13}$C{$^1$H} NMR (75 MHz, $C_6D_6$, 21 °C): $\delta = 137.4$ (C(3)), 132.8 (C(2)), 130.0 ($CH_{o\text{-arom}}$, $CH_{p\text{-arom}}$), 129.9 ($C_{i\text{-arom}}$), 128.5 ($CH_{m\text{-arom}}$), 81.195 (ca. 95 %) (s; C(1)-$^{18}$O), 81.230 (ca. 5 %) (s; C(1)-$^{16}$O), 31.3 (C(4)), 30.2 (C(5)); MS (EI): *m/z* (%): 190 (4) [$M^+$] 149 (5), 105 (30), 88 (10), 86 (64), 84 (100), 77 (21).

**Methyl carbonate (±)-4c**: MeOCOCl (1.43 mL, 18.4 mmol) was added dropwise over 2 min. to a vigorously stirred solution of (±)-1-[$^2$H$_1$]-cyclopent-2-en-1-ol (1.0 g, 11.7 mmol) in pyridine (10 mL) and $CH_2Cl_2$ (30 mL) at 0 °C. After 1 h (TLC, 12/1 hexane/EtOAc) showed complete conversion and the reaction mixture was poured into aqueous $NH_4Cl$ (50 mL) and extracted with diethyl ether (150 mL). The organic extract was washed with portions of 2 M HCl (20 mL) until the washings were acidic, then washed with water (50 mL), brine (50 mL) and dried over $MgSO_4$. Concentration in vacuo followed by fractional distillation afforded (±)-**4c** (1.25 g, 75 %) as a colourless oil, b.p (76–80 °C, ca. 20 mmHg). $^1$H NMR ($CDCl_3$, 270 MHz, 21 °C, TMS): $\delta = 6.15$ (m, 1H; C(3)H), 5.88 (m, 1H; C(2)H), 3.77 (s, 3H; Me), 2.55 (m, 1H; C(4)$H_{syn}$), 2.32 (m, 2H; C(4)$H_{anti}$, C(5)$H_{anti}$), 1.92 (m, 1H; C(5)$H_{syn}$); $^2$H NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 5.58$ (br s, C(1)$^2$H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 21 °C, TMS): $\delta = 155.6$ (C=O), 138.6 (C(3)), 128.6 (C(2)), 83.9 (t, $^1J$ (H,$^2$H) = 24 Hz, C(1)), 54.5 ($CH_3$), 31.1 (C(4)), 29.6 (C(5)). Note: Chromatography on silica-gel causes scrambling of the $^2$H label (in our case: about 17 % (±)-γ-**4c**)—presumably by an ionic mechanism.

**Pivaloate (±)-4d**: Prepared in an identical manner to (±)-**4a** but with $Me_3COCl$. Kugelrohr distillation (oven $T = 150$ °C, ca. 20 mmHg) gave (±)-**4d** (1.82 g, 92 %) as a colourless oil, TLC, 12/1 hexane/EtOAc, $R_f = 0.5$. $^1$H NMR ($CDCl_3$, 270 MHz, 21 °C, TMS): $\delta = 6.1$ (m, 1H; C(3)H), 5.8 (m, 1H; C(2)H), 2.5 (m, 1H; C(4)$H_{syn}$), 2.3 (m, 2H; C(4)$H_{anti}$, C(5)$H_{anti}$), 1.75 (m, 1H; C(5)$H_{syn}$), 1.2 (s, 1H; C($CH_3$)$_3$); $^2$H NMR ($CHCl_3$,46 MHz, 21 °C, $CDCl_3$): $\delta = 5.6$ (br. s, C(1)$^2$H); $^{13}$C{$^1$H} NMR (75 MHz, $CDCl_3$, 21 °C, TMS): $\delta = 178.6$ (C=O), 137.2 (C(3)), 129.4 (C(2)), 89.9 (t, $^1J$ (H,$^2$H) = 24 Hz, C(1)), 38.6 (*C*($CH_3$)$_3$), 31.1 (C(4)), 29.7 (C(5)), 27.2 (C(*C*$H_3$)$_3$).

**4,4′-[$^2$H$_2$]-biphenyl**: This was prepared from 4-[$^2$H$_1$]-chlorobenzene (90.4 % $^2$H) by homocoupling[52] and purified by vacuum sublimation (65 °C, 0.1 mmHg), m. p. 69–72 °C, $^1$H NMR ($CDCl_3$, 400 MHz, 21 °C, TMS): $\delta =$ 7.67 (d, $^3J$(H,H) = 7.6 Hz, 4H; C(2,2′)H), 7.50 (d, $^3J$(H,H) = 7.7 Hz, 4H; C(3,3′)H); $^{13}$C NMR ($CDCl_3$, 100 MHz, 21 °C, TMS): $\delta = 141.0$ (C(1,1′)), 128.4 (C(3,3′)), 127.0 (C(2,2′) arom.), 126.8 (t, $^1J$ (H,$^2$H) = 24 Hz, C(4,4′)[$^2$H]); $^2$H NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 7.50$ (br. s, C(4,4′)$^2$H).

**Preparation of ligands**

**2-(Diphenylphosphino)benzoic acid 16:** This was prepared according to a procedure in *Inorganic Syntheses*.[53] In our hands this method gave **16** with one equivalent MeOH of crystallisation which must be removed [100 °C, 0.1 mmHg, 12 h] before preparation of **3**. Selected analytical data for **16**: $C_{19}H_{15}O_2P$ (306.30): calcd: C 74.51, H 4.94; found C 74.67, H 4.95. $^{31}$P NMR ($CDCl_3$, 122 MHz, 24 °C): $\delta = -4.1$ (s).

**Ligand 3 (R,R)-3 and (±)-3**: These were prepared by a modification of the literature procedure.[54] Thus, a solution of (1*R*, 2*R*)-*trans*-1,2-diaminocyclohexane (400 mg, 3.5 mmol) in $CH_2Cl_2$ (5 mL) was added to a solution of **16** (2.25 g, 7.35 mmol) and DMAP (4.9 mg, 0.04 mmol) in $CH_2Cl_2$ (40 mL). After addition of EDCI (1.57 g, 8.21 mmol) the slightly cloudy yellow solution was stirred at 25 °C for 2 h 45 min and then partitioned between $Et_2O$ (200 mL) and 1 M HCl (ca. 50 mL). The organic phase was separated, washed sequentially with a further two portions of 1 M HCl (ca. 50 mL), water (50 mL), three portions of 1 M $NaHCO_3$ (ca. 50 mL), water (50 mL) and saturated brine (50 mL). After the mixture had been dried ($MgSO_4$), the solvent was removed in vacuo and the residue crystallised from MeCN and dried in vacuo (50 °C, 0.1 mmHg). Ligand (*R,R*)-**3** (2.8 g, 55 %) was obtained as a white crystalline mass. $[\alpha]_D = 61$ ($c = 2.3$, $CH_2Cl_2$, 21 °C; ref. [54] $[\alpha]_D = 55$, $c = 2.85$, $CH_2Cl_2$); $C_{44}H_{40}N_2O_2P_2$ (690.76): calcd: C 76.51, H 5.84, N 4.06; found C 76.49, H 5.95, N 4.17. $^{31}$P NMR ($CDCl_3$, 122 MHz, 24 °C): $\delta = -9$ (s). MS (EI): *m/z* (%): 691 (12) [$M^+$] 612 (4), 535 (3), 387 (12), 304 (100), 288 (30), 226 (36), 183 (28), 84 (55). The minor (*S,S*)-enantiomer of **3** could not be detected by chiral HPLC. (±)-**3** was prepared in an identical manner.

**PO-ligand 17**: This was prepared from **16** (0.35 g, 1.14 mmol) in an identical manner to **3** but using *tert*-butylamine (0.110 mg, 1.5 mmol) and recrystallisation from hexane/$CH_2Cl_2$ to afford **17** as white needles (150 mg, 36 %). M.p. 157–159 °C. $C_{23}H_{24}NOP$ (361.42): calcd: C, 76.43, H, 6.69, N, 3.88 found C 76.46, H 6.37, N 3.75; $^{31}$P NMR ($CDCl_3$, 122 MHz, 21 °C): $\delta =$ −10.7 (s); $^1$H NMR ($CDCl_3$, 400 MHz, 21 °C, TMS): $\delta = 7.62$ (br. m, 1H), 7.41–7.31 (br. m, 7H), 7.34–7.24 (br. m, 5H), 6.87 (br. m, 1H), 5.72 (br. s, NH), 1.19 (s, 9H; $(CH_3)_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz, 21 °C, TMS) 168.3 (C=O), 142.9 (d, $^2J$(C,P) = 26 Hz, C(2)), 136.7 ($C_{ipso}$ $PPh_2$), 136.5 (C(1)), 133.9 (d, $^2J$(C,P) = 20 Hz; $C_{ortho}$ $PPh_2$), 133.8 (C(6)), 129.0 ($C_{para}$ $PPh_2$), 128.9 (C(4)), 128.6 (d, $^4J$(C,P) = 7 Hz; $C_{meta}$ $PPh_2$), 128.1 (C(3)), 51.9 (*C*($CH_3$)$_3$), 28.3 (C(*C*$H_3$)$_3$); MS (EI): *m/z* (%): 362 (0.5) [*M*H$^+$] 304 (100) [*M* − *t*BuH$^+$], 227 (35), 183 (20), 152 (6), 84 (10), 77 (14). IR (KBr) $\tilde{\nu} = 1635$, 1538 cm$^{-1}$ (C=O).

**Palladium-Catalysed allylic alkylations:** The following procedure for reaction of (±)-**4** with [NaCH($CO_2CH_3$)$_2$] catalysed by Pd(*R,R*)-(**3**) is typical: A mixture of [Pd($\eta^3$-$C_3H_5$)]Cl]$_2$ (7 mg, 0.019 mmol) and (*1R, 2R*)-**3** (40.4 mg, 0.058 mmol) were dissolved, under $N_2$, in THF (0.7 mL) and stirred at 25 °C for 20 min to afford a yellow solution. In a separate Schlenk tube, (±)-**4a** (100 μL, 0.78 mmol) was added by microsyringe to a solution of [NaCH($CO_2CH_3$)$_2$] (270.3 mg, 1.75 mmol) in THF (6 mL) followed immediately by the solution of [Pd($\eta^3$-$C_3H_5$)(*1R, 2R*)-**3** ]$^+$[Cl]$^-$ resulting in rapid formation of a slightly viscous yellow solution. TLC (12:1 hexane/EtOAc) after 5 min indicated the presence of **6** ($R_f = 0.34$) and absence of (±)-**4a** ($R_f = 0.50$). The reaction mixture was immediately quenched by addition of aqueous $NH_4Cl$ (10 mL, 2.65 M) and extracted with $CH_2Cl_2$ (4 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated to afford a pale brown oil and solid. This was applied to a pre-solvated silica gel column (2.5 × 25 cm) and eluted with 12:1 hexane/EtOAc, collecting 14 mL fractions (gravity column). Fractions 21 to 28 (containing material of $R_f = 0.34$) were evaporated to afford a mixture of (1′)[$^2$H$_1$]- and (3′)[$^2$H$_1$]-dimethyl (2′-cyclopentenyl)methanedicarboxylate α-**6** and γ-**6** as a colourless oil (136.0 mg, 88 %). $^1$H NMR ($CDCl_3$, 300 MHz, 21 °C, TMS) (**2**): $\delta =$ 5.84 (dddd, $^3J$(H,H) = 5.7, 2.2, 2.2 $^4J$(H,H) = 2.2 Hz, 1H; C(3′)H), 5.65 (dddd, $^3J$(H,H) = 5.7, 2.2, $^4J$(H,H) = 2.2, 2.2 Hz, 1H; C(2′)H), 3.37 (ddddd, $^3J$(H,H) = 8.1, 6.0, 5.7, 2.2 $^4J$(H,H) = 2.2 Hz, 1H; C(1′)H), 3.74 (s, 6H; 2 × $CH_3$), 3.28 (d, $^3J$(H,H) = 5.7 Hz, 1H; C(1)H), 2.35 (m, 2H; C(4′)$H_2$), 2.13 (dddd, $^2J$(H,H) = 12.7, $^3J$(H,H) = 8.1, 8.1, 5.7 Hz, 1H; C(5′)$H_{cis}$), 1.59 (dddd, $^2J$(H,H) = 12.7, $^3J$(H,H) = 8.6, 6.0, 6.0 Hz, 1H; C(5′)$H_{anti}$); $^{13}$C{$^1$H} NMR ($CDCl_3$, 75 MHz, 21 °C, TMS) (α-**6**): $\delta = 168.9$, 168.8 (2C=O), 132.8 (C(3′)), 131.05 (C(2′)), 56.3 (C(1)), 52.1, 52.0 (2$CH_3$), (44.8 (t, $^1J$(H,$^2$H) = 21 Hz, C(1′)), 31.5 (C(4′)), 27.5 (C(5′)); (γ-**6**): $\delta = 168.9$, 168.8 (2C=O); 132.5 (t, $^1J$(H,$^2$H) = 25 Hz, C(3′)), 131.0 (C(2′)), 56.4 (C(1)), 52.1, 52.0 (2$CH_3$), 44.2 (C(1′)), 31.4 (C(4′)), 27.4 (C(5′)); ((±)-**2**): $\delta = 168.9$, 168.8 (2C=O), 132.7 (C(3′)), 131.11 (C(2′)), 56.4 (C(1)), 52.1, 52.0 (2$CH_3$), (45.2 (C(1′)), 31.5 (C(4′)), 27.4 (C(5′)); $^2$H NMR ($CHCl_3$, 46 MHz, 21 °C, $CDCl_3$): $\delta = 5.85$ (br. s, C(3′)$^2$H; γ-**6**), 3.34 (br. s, C(1′)$^2$H; α-**6**) ratio α/γ = 0.55/0.45.

**Analysis of regioisotopomeric enantiomers of 6 by $^{13}$C NMR spectroscopy**: α/γ-**6** (40 mg, 0.20 mmol) was dissolved in $C_6D_6$ (0.70 mL) and then (+)Eu(hfc)$_3$ (132.0 mg, 0.11 mmol) added to give a clear bright yellow solution. The enantiomer ratios of the isotopomers were estimated by integration of the $^{13}$C{$^1$H, $^2$H} NMR (150 MHz, $C_6D_6$, 25 °C) spectrum acquired with a five second delay (d1) between [pulse-FID]. A 3.2 μs pulse was applied with a 0.999 second accumulation time and a total of 512 transients acquired. A shifted sine-bell squared weighting was applied before Fourier transform and integration was by cut and weigh. The {$^1$H, $^2$H} decoupling coils were switched off during d1 and on during accumulation time. A correction factor for each carbon signal was estimated by use of a 1.02/1.00 sample of racemic α-**6**/γ-**6** and then applied to the integral values of the reaction samples of interest. The following relative integrals (%) were obtained: (*S*)-α/γ-**6** (70 %) 54.06, 53.57

(($(CO_2CH_3)_2$); (*R*)-$\alpha/\gamma$-**6** (30%) 53.86, 53.72 (($(CO_2CH_3)_2$); (*S*)-$\alpha$-**6** (38%) 33.63 (C(4′)), 30.79 (C(5′)); (*R*)-$\alpha$-**6** (32%) 33.33 (C(4′)), 30.37 (C(5′)), (*S*)-$\gamma$-**6** (12%) 33.51 (C(4′)), 30.91 (C(5′)), (*R*)-$\gamma$-**6** (18%) 33.21 (C(4′)), 30.49 (C(5′)). Analysis by $^{13}C\{^1H\}$ NMR (100 MHz, $C_6D_6$, 21 °C) gave similar results (± 1%).

**Time-course studies**: The following procedure is typical: A mixture of $[Pd(\eta^3\text{-}C_3H_5)]Cl]_2$ (3.6 mg, 9.8 μmol) and (±)-**3** (20.4 mg, 29.5 μmol) were dissolved, under $N_2$, in THF (3 mL) and stirred at 25 °C for 20 min. In a 100 mL Schlenk tube, (±)-**4a** (500 μL, 3.94 mmol) was added by microsyringe to a solution of $[NaCH(CO_2CH_3)_2]$ (607 mg, 3.94 mmol) and 4,4′-$[^2H_2]$-biphenyl (353 mg, 2.26 mmol) in THF (36 mL). The solution of $[Pd(\eta^3\text{-}C_3H_5)(\pm)\text{-}\mathbf{3}\,]^+[Cl]^-$ was then rapidly transferred (with the aid of a further 1 mL THF) to the reaction mixture and then the first sample (5.6 mL) removed by syringe (within 5 s from addition of catalyst solution). The sample was immediately quenched into 10% aqueous $NH_4Cl$ (50 mL). After extraction with three portions of $CH_2Cl_2$ (10 mL), the combined extracts were dried ($MgSO_4$) and concentrated in vacuo (35 °C, 20 mmHg, 2 h to remove (±)-**4a** (checked by TLC), the residue (essentially a mixture of (±)-**6**, 4,4′-$[^2H_2]$-biphenyl and $CH_2(CO_2CH_3)_2$) was dissolved in $CHCl_3$ (containing 1% $CDCl_3$ and freshly filtered through alumina) and analysed by $^2H$ NMR (61 MHz). This indicated 2.8% conversion by integration of the $^2H$ signals arising from 4,4′-$[^2H_2]$-biphenyl, $\alpha$-**6** and $\gamma$-**6.** A further six samples were taken at 8, 23, 36, 52, 82 and 237 minutes, worked up and analysed in an identical manner.

**Recovery of (±)-4 and (±)-5 under turnover and non-turnover conditions:** Reactions performed as detailed above were monitored by TLC until about 50% conversion then rapidly worked up and substrate/product isolated by silica gel chromatography. Thus from (±)-**4a** was obtained: (±)-**4a** (67 mg, 42%) $^2H$ NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 6.11$ (< 2%, C(1)$^2$H), 5.7 (br. s, > 98% C(1)$^2$H) and (±)-**6** (136 mg, 55%), $^2H$ NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 5.85$ (br. s, 19%, C(3′)$^2$H; $\gamma$-**6**); $\delta = 3.34$ (br. s, 81%, C(1′)$^2$H; $\alpha$-**6**). From (±)-**5b** (16% recovery): $^{13}C\{^1H\}$ NMR (100 MHz, $C_6D_6$, 21 °C): $\delta = 81.230$ (10%) (s, C(1)-$^{16}$O) 81.195 (90%) (s, C(1)-$^{18}$O) and (±)-**2** (61% yield). From (±)-**5a** (20% recovery): $^{13}C\{^1H\}$ NMR (100 MHz, $C_6D_6$, 21 °C): $\delta = 80.40$ (11%), (s, C(1)-$^{16}$O), 80.37 (89%) (s, C(1)-$^{18}$O) and (±)-**2** (42% yield). For non-turnover conditions, reactions were performed with a 0.85/1.0 mole ratio of $[NaCH(CO_2CH_3)_2]$ to (±)-**4** or (±)-**5**. Thus from (±)-**4a**: (9% recovery) $^2H$ NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$) 6.11 (ca. 50%, C(3)$^2$H), 5.7 (br. s, ca. 50% C(1)$^2$H)) and (±)-**6** (20% yield) $^2H$ NMR ($CHCl_3$, 61 MHz, 21 °C, $CDCl_3$): $\delta = 5.85$ (br. s, 21%, C(3′)$^2$H; $\gamma$-**6**); 3.34 (br. s, 79%, C(1′)$^2$H; $\alpha$-**6**). With (±)-**5b**: (28% recovery) $^{13}C\{^1H\}$ NMR (100 MHz, $C_6D_6$, 21 °C): $\delta = 81.195$ (ca. 48%) (s, C(1)-$^{18}$O), 81.230 (ca. 52%) (s, C(1)-$^{16}$O) and (±)-**2** (58% yield).

**Acknowledgments:** S.C.S. thanks the University of Bristol for a postgraduate scholarship. G.C.L.-J thanks the Zeneca Strategic Research Fund for generous and ongoing support. We thank Dr. John M. Brown FRS (Oxford University) for detailed mechanistic discussion and for kindly providing samples of racemic and enantiomerically pure ′Quinap′ ligand **14**. We also thank Dr Pavel Kočovský (University of Leicester) for discussion regarding memory effects and for a pre-print of reference [24b]. We thank Dr. Ian H. Sadler, National Ultra High Field NMR Centre (University of Edinburgh) for 150 MHz NMR $^{13}C\{^1H,^2H\}$ spectra, Dr. Martin Murray (University of Bristol) for NMR spectral simulation and Dr. Torren M. Peakman (University of Bristol) for help with the acquisition of $^2H$ and $^{13}C$ NMR spectra. Katharine L. Bray (University of Bristol) prepared (*R*)-**13**, (*S*)-**13** and (±)-**13**, Dr. Jim Ramsden (Chirotech, UK) kindly assayed the *ee* of **3**, Dr. Brian E. Looker (GlaxoWellcome, UK) donated $^{18}OH_2$.

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[26] To avoid errors from differential $^{13}$C-relaxation, we calibrated by reference to (±)-**6** with $\alpha/\gamma$ ratio 1.02. Identical results (± 1%) were obtained by $^{13}$C{$^1$H, $^2$H} NMR at 600 MHz ($^1$H). For all reactions except Table 2, entry 6, the ratio of [$\alpha$-(*S*)-**6** + $\gamma$-(*R*)-**6**] to [$\alpha$-(*R*)-**6** + $\gamma$-(*S*)-**6**] was, within experimental error, 1:1 as predicted by a stereospecific mechanism.

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