²H-quadrupolar coupling-based analysis of stereochemical and regiochemical memory in the Pd-catalysed allylic alkylation of *iso*-cinnamyl type substrates employing the chiral monophosphine ligands 'MOP' and 'MAP'

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Abstract

The reaction of *iso*-cinnamyl acetate with $NaC(Me)(CO_2Me)_2$, catalysed by Pd–'MOP' (MOP = 2-methoxy-2′-diphenylphosphino-1,1′-binaphthalene) is known to proceed with a regiochemical memory effect that results in the predominant generation of the branched alkylation product. The analogous reaction employing 'MAP' as ligand (MAP = 2-*N*,*N*-dimethylamino-2′-diphenylphosphino-1,1′-binaphthalene) proceeds with 'normal' regioselectivity to generate predominantly the linear isomer of product. A ²H-NMR based analysis, employing quadrupolar coupling in a chiral liquid crystal matrix, has been developed to facilitate the simultaneous study of the regiochemical and stereochemical outcome of the reaction of both enantiomers of *iso*-cinnamyl ester substrates in ²H-labelled but racemic samples. The analysis allows the comparison of relative rates of two competing isomerisation processes occurring in the π-allyl intermediates in the Pd-catalysed reaction, one of which facilitates asymmetric induction, the other resulting in loss of regiochemical memory. It is demonstrated that the two processes are partially coupled and that this then limits the attainment of high global enantiomeric excess in the branched product to reactions that proceed with low regiochemical retention. A key factor for the observation of high regiochemical memory is found to be the nucleophilicity of the malonate anion and the electrophilicity of the Pd–π-allyl intermediate with reduction in the reactivity of either partner resulting in the onset of substantial loss of memory.
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Keywords: Palladium; Asymmetric catalysis; Memory effects; ²H-NMR; Liquid crystals

1. Introduction

In addition to applications in asymmetric target synthesis [1], the asymmetric Tsuji–Trost reaction (palladium-catalysed allylic alkylation) has become an extremely popular testing ground for chiral ligand design [2]. The best-explored substrates for such 'benchmarking' reactions are those that generate allylic intermediates in which there is identical 1,3-substitution, i.e. there is a π-allyl palladium intermediate containing a 'meso' allyl fragment that is desymmetrised by the chiral Pd-ligand assembly. The 'classic' examples of such substrates are the ubiquitous 1,3-diphenylpropenyl systems and the substantially more challenging cycloalkenyl esters which generate slim *anti,anti*-allyl fragments. With these substrates, both enantiomers of substrate can converge on the same set of equilibrating intermediates and the stereochemical outcome from each intermediate is then dependent on the regioselectivity of the attack of the nucleophile and the relative reactivity of the diastereoisomeric Pd–allyl intermediates. In principle, both enantiomers of substrate should therefore give the same enantiomeric excess of product and a racemic substrate can be converted in quantitative yield into a single enantiomer of product. In a number of cases,

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near-perfect ligands have indeed been developed and the combination of high selectivity for one diastereoisomeric Pd–allyl intermediate over the other together with efficient torquoselectivity [3] in the nucleophilic attack has been identified as the key components for their success. A 'memory effect' can be defined as the situation where isomeric substrates, e.g. enantiomers, give different products or product ratios, when the basic mechanism predicts that they should not. Since the first reports over two decades ago [4,5], there has recently been an increasing awareness that undetected stereochemical memory effects [6] in transition-metal catalysed asymmetric allylation reactions can compromise the benchmarking process, giving rise to misleadingly low enantioselectivities. We have an ongoing interest in determining the origins of such effects and have previously focused our efforts on the cycloalkenyl ester type substrates for which there are the most documented cases.
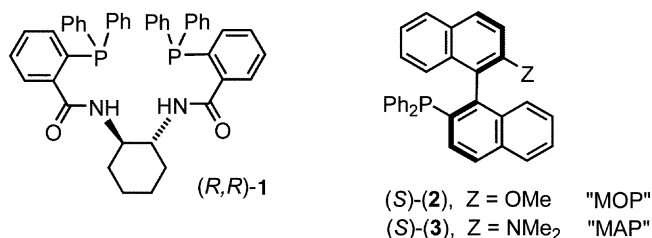
Powerful memory effects with such substrates (cyclopentenyl and cyclohexenyl esters) have been reported [6a–e,g] with the C_2-symmetric biphosphine 1 (the Trost Modular Ligand) [7] and with the monophosphine ligands 'MOP' (2) and 'MAP' (3) developed by Hayashi [8] and by us [9], respectively. With ligand 1, a number of factors have been identified as potential contributors to the net memory effect. These include intimate ion-pairing [6a], ionic strength [10], P,O-chelation [6e], Pd–allyl-oligomerisation [6i] and conformational loss of chelated ligand C_2-symmetry [10]. However, the origins of the memory effect with MOP and MAP are less complex [6g] and we have introduced a simple stereochemical convergence ('sc') term by which the effects are readily quantified through the deployment of a ^2H label at the stereogenic centre of the substrate [11].

Independent studies by Hayashi,[8] by us [6g,9] and more recently by Ding and coworkers [12] have identified that MOP/MAP ligands can display three [13] basic (P,X)-coordination modes towards Pd allyl fragments. In the presence of palladophilic anions such as chloride, the ligand operates as a monodentate monophosphine and a neutral complex is generated (see mode I in Fig. 1). In the absence of such ions, the ligand switches to a bidentate mode, in which 'X' can be the *ipso* carbon of the non-phosphine bearing ring (mode II) or the donor group Z (NMe₂ or OMe, mode III). However, mode II usually dominates over III [6g,9c,14]. In all three
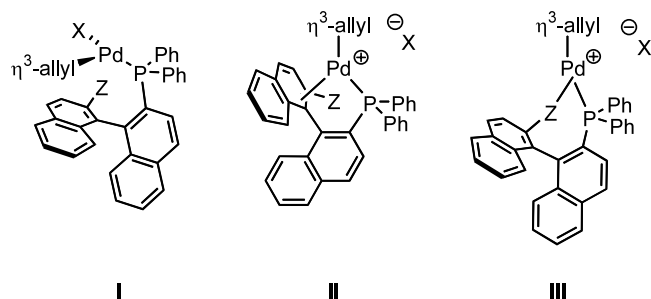

Fig. 1. The three basic coordination modes towards Pd–allyl fragments dispalyed by (S)-MOP (2; Z = OMe) and (S)-MAP (3; Z = NMe₂) ligands. Mode I results in a neutral complex, modes II and III result in cationic complexes.

binding modes, 1,3-symmetrical π-allyl systems result in the generation of two diastereoisomeric intermediates. In the case of cycloalkenyl π-allyl intermediates (π-C_5H_7 and π-C_6H_9), enantiodivergent generation of the diastereoisomeric intermediates coupled with very slow diastereoisomer interconversion results in powerful memory effects in reactions of cycloalkenyl esters (4) with the anion of dimethyl malonate, Scheme 1 [6c,d,g].

Analysis of the global enantioselectivity (ee$_g$) as a function of sc (facilitated by deployment of a ^2H label in racemic 1-^2H-4) allowed us to monitor our efforts to attenuate the memory effect in the reaction of cyclopent-2-enyl esters (4a) by systematic modification of reaction conditions [6g]. Ultimately we were able to reach the point where sc ≥ 98% and the 'latent selectivity' ('latent selectivity' is the global enantioselectivity that can be attained under full ligand control, i.e. under Curtin Hammett conditions) of the ligands were revealed. Under these conditions, 5a is generated in ca. 40% ee$_g$ in the presence of chloride and 60% ee$_g$ in its absence, suggesting that a bidentate ligand mode (II) is more effective at controlling the torquoselectivity [3] with small cyclic substrates [6g]. A key outcome from these studies was the observation that both the enantioselectivities and the memory effects observed in Pd-catalysed
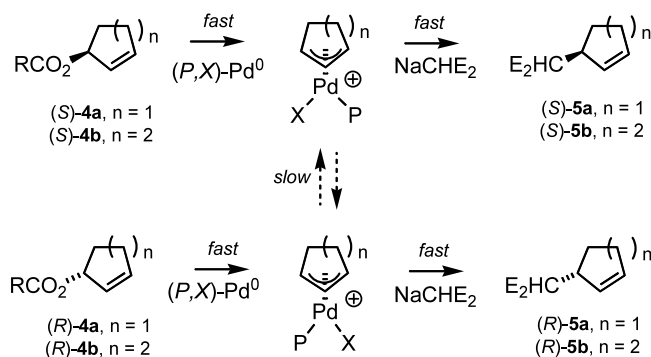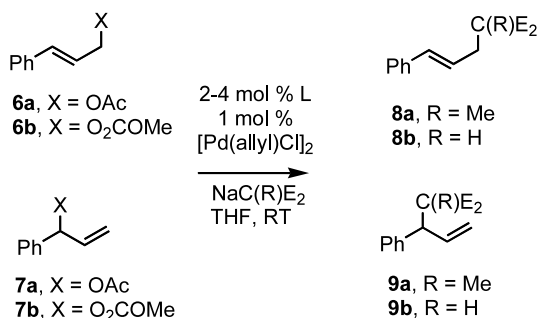

Scheme 1. Memory effects arising from slow diastereoisomer equilibrium in the Pd-catalysed allylic alkylation of cycloalkenyl esters employing MOP (2) and MAP (3) ligands. Ionisation and nucleophilic attack is proposed to occur selectively *trans* to the phosphine donor.

allylic alkylation of cycloalkenyl substrates using MOP and MAP ligands under the same conditions are essentially identical.

Although there is a general perception that memory effects are a negative factor in Pd-catalysed reactions, they can be used to good effect. For example regiochemical memory can be used to gain access to what are usually less-favoured regioisomeric products by suitable choice of allylic substrate. Hayashi has reported that cinnamyl (6a) and iso-cinnamyl (7a) acetates can be alkylated in the presence of 'Pd–MOP' with powerful regiochemical memory effects [6c]. Thus, on reaction in THF with NaC(Me)E$_2$, 6a gives ca. 80% 8a [6c,16] whilst 7a gives ca. 80% 9a, Scheme 2 [6c].

However, when we reacted 6a and 7a with NaC(Me)E$_2$, in the presence of Pd–MAP, in both cases we obtained 8a [9a,b] the linear and 'normal' [15] regioisomeric product from Pd-catalysed reactions involving cinnamyl intermediates, with 91% regioselectivity. Thus, in stark contrast to the reaction involving the ligand MOP, there is no regiochemical memory effect. Given the parity we had earlier found between MOP and MAP in terms of memory effects in the reaction of cyclopentenyl esters [6g,l] vide supra, we were rather intrigued by this result and set about studying the Pd–MOP/MAP catalysed reactions of iso-cinnamyl esters (7) with malonate nucleophiles in more detail. Herein we report in full on our investigation which has shed light on (a) the possible origin of the difference between MOP and MAP in these reactions and (b) the scope and limitations of employing Pd–MOP as a catalyst for the asymmetric generation of branched alkylation products such as 9.
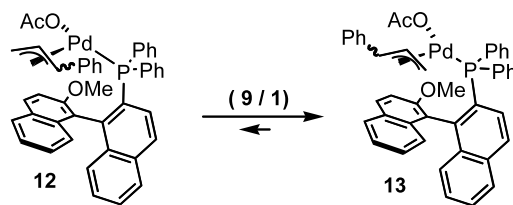
2. Results and discussion

2.1. Determination of the limiting conditions for regiochemical memory effects with Pd–MOP

As outlined above, the current mechanism [6c,g,l] for memory effects with (P,X)-ligands of the type MOP or MAP and cycloalkenyl esters (4) involves first the alkene complexing to a (P,X)-Pd(0) unit and then a selective oxidative ionisation such that the allylic carbon bearing the nucleofuge is trans-related to the P ligand. Enantiomeric substrates then produce diastereoisomeric π-allyl Pd intermediates and if the nucleophilic attack is faster than diastereoisomer equilibration, a stereochemical memory effect is apparent. An essentially identical model is also proposed by Hayashi for the regiochemical memory effect on Pd–MOP catalysed reaction of 6a or 7a with NaC(Me)E$_2$ to give 8a or 9a, respectively (Scheme 2) [6c]. Thus, regioisomeric intermediates 10 and 11 are generated selectively from 6a and 7a, respectively and, again, if capture by nucleophile is more efficient than equilibration, a memory effect is engendered, Scheme 3.

However, whilst it is clear that the 'normal' selectivity with Pd, when employing ligands such as PPh$_3$ or dppe, is heavily biased ($\geq 90\%$) towards 9 [6c,15,16], it is not clear what the latent selectivity is with the Pd–MOP system when equilibrium has been achieved. Indeed, two of the three coordination modes (I and III) might be expected to favour 11 where the bulkier aryl group is trans-related to the phosphine. Indeed, Hayashi has isolated the mode I type complex [Pd(OAc)(MOP)(Ph–π-C$_3$H$_4$)] and at -50 °C in CDCl$_3$, where the acetate coordinates Pd. NMR analysis indicates that this exists as a 10/90 ratio of regioisomers 12 and 13 (NB diastereoisomeric identies not established and minor isomer assumed to be regioisomer of major) corresponding to forms 10/11, in Scheme 3, where X = OAc and P = monodentate P-coordinated MOP [16].

Scheme 2. Regiochemical possibilities in the Pd-catalysed allylic alkylation of cinnamyl (6) and iso-cinnamyl (7) esters. In most cases, both 6 and 7 give 8. However, when MOP (2) is employed as ligand (L) and the anion of methyl dimethyl malonate (NaC(Me)E$_2$, where E = CO$_2$Me) is employed as nucleophile, there is a powerful regiochemical memory such that 6a gives 8a and 7a gives 9a with ca. 70–77% regioselectivity in both cases. In stark contrast when L = MAP (3), both 6a and 7a give 8a.

If this is the case under the catalytic reaction conditions and if 10 is equally or less reactive than 11, the latent selectivity of the system should be towards 9 (the unusual regioisomer) and the mis-matched substrate would therefore be the linear isomer 6a. In accordance with this analysis, the isolated acetate complex (existing as an equilibrium mixture of 12 and 13 in solution) reacts with NaC(Me)E$_2$ in THF at -20 °C to give 9a (12/88 ratio 8a/9a) [16]. However,
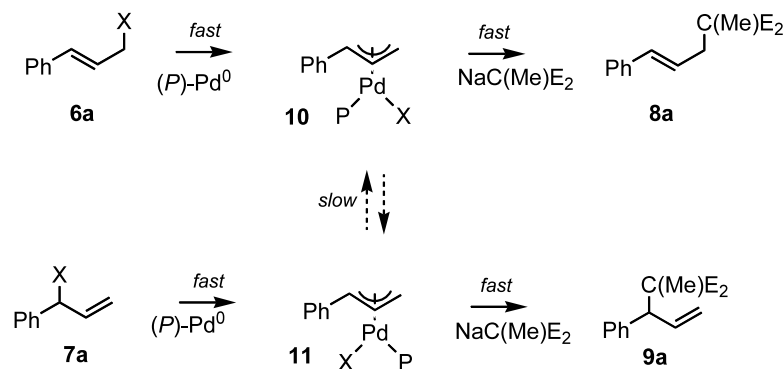
Scheme 3. Possible mechanism for regiochemical memory in the 'Pd–MOP' catalysed reaction of cinnamyl (**6**) and *iso*-cinnamyl (**7**) esters with the anion of methyl dimethyl malonate (NaC(Me)E$_2$) in which oxidative ionisation and nucleophilic attack occurs *trans* to the phosphine donor and regioisomeric intermediates **10** and **11** interconvert slowly.

this result then makes the reactions catalysed by MAP (Scheme 2) anomalous since mode **I**, expected in the presence of chloride, should also favour generation of **11** and thus give **9** as the major product, but this is not observed [9a]. A key issue in the stoichiometric reaction of the isolated acetate complex (**12/13**) is that although by analogy **11** may be favoured over **10**, if nucleophilic attack is faster than equilibration (i.e. non-Curtin Hammet conditions prevail), then this result (88% **9a**) does not necessarily reflect the latent regioselectivity of the catalytic system. In other words, a memory effect in the stoichiometric reaction may be as much of an issue as it is in the catalytic version.

Curiously, Hayashi et al. have never reported on the Pd–MOP catalysed reaction of **6a** and **7a** with the simpler nucleophile NaCHE$_2$, which is more commonly employed in Pd-catalysed allylic alkylation reactions. With 1-^{2}H-cyclohexenyl acetate (1-^{2}H-**4b**) as substrate, the regiochemical retention in the Pd–MOP catalysed reaction with NaC(Me)E$_2$ is essentially identical to that obtained with NaCHE$_2$ which generates **5b** ($n = 2$) [6c] and thus one might expect a similar outcome between NaCHE$_2$ and NaC(Me)E$_2$ in reactions involving **6a** and **7a**. However, we have found that the simple switch from NaC(Me)E$_2$ to NaCHE$_2$ has a dramatic effect, Scheme 4.

Thus, the regiochemical outcome with **7a** and NaCHE$_2$ is essentially reversed and the normal linear
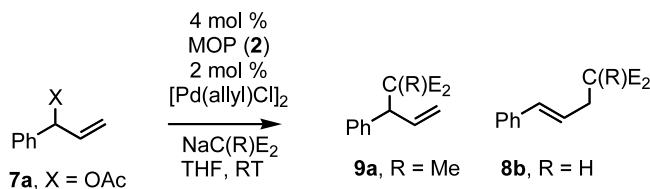
Scheme 4. The contrasting regioselectivity in the Pd–MOP catalysed reaction of *iso*-cinnamyl acetate with the anions of malonate esters: when NaC(Me)E$_2$ is employed, the branched product **9a** is obtained with 70% regioselectivity. In contrast, when the closely related nucleophile NaCHE$_2$ is employed, the 'normal' regioisomer **8b** is obtained with 70% regioselectivity.

regioisomer **8b** is obtained as the major product (70%), in line with the reaction of **7a** with either nucleophile but catalysed by Pd–MAP. These results strongly support the concept that the latent selectivity with MOP and MAP is in fact identical (favouring the generation of the linear product **8ab**) and that the regiochemical memory effect only occurs when NaC(Me)E$_2$ is employed as stoichiometric nucleophile in combination with MOP as ligand to generate **9a**. This may be understood in terms of attaining sufficient electrophilicity in the Pd–π-allyl complex and sufficient nucleophilicity in the malonate anion such that alkylation can occur in competition with equilibration of **10** and **11** under non-Curtin–Hammett conditions. Indeed, in our further studies into the stereochemistry of these reactions, vide infra, we have found that increasing asymmetric induction in **9a** correlates with decreasing regiochemical memory. Both processes arise from increased equilibration of isomeric Pd–π-allyl intermediates.

In monodentate mode (mode **I**) it is hard to rationalise the difference in reactivity between cinnamyl–π-allyl Pd complexes bearing MOP versus MAP. In bidentate mode **II** one would anticipate that the less electronegative Me$_2$N group in MAP (**3**) would facilitate greater stabilisation of the Pd–cinnamyl cation than the MeO group in MOP (**2**), in direct analogy to enamine versus enol ether type coordination. This proposed difference in reactivity is supported by ^{13}C-NMR and single crystal X-ray structures analysis of the cationic Pd–allyl MAP versus MOP complexes [6g,9b,c]. Furthermore, although MAP has a known preference for mode **II** coordination in cationic allyl complexes (π-C$_3$H$_5$ [6g,9b,c] and 1,3-Ph$_2$-π-C$_3$H$_3$ [12]), even if the cinnamyl complex populates mode **III**, then the same greater stabilisation by amine versus ether coordination is still expected to apply.

Nonetheless, even with the more reactive Pd–cinnamyl MOP complexes (**10** and **11**), NaC(Me)E$_2$ would have to be significantly more nucleophilic than simple NaCHE$_2$ if the origin of the memory effect has been

interpreted correctly. On simple grounds of σ-induction, the Me-group is expected to make NaC(Me)E$_2$ more reactive than NaCHE$_2$ [17]. However, in terms of steric hindrance, the opposite effect might be expected. Additionally, THF is very poor at solvating anions and thus a 'looser' solvation of the bulkier nucleophile is unlikely to be responsible. Furthermore, Na-chelation by the planar 1,3-dicarbonyl unit is not expected to be affected significantly by the *anti*-related H versus Me substituent at the central carbon. To test the relative reactivity of the two nucleophiles, we conducted a competition experiment in which we reacted *iso*-cinnamyl acetate **7a** with an excess of a mixture of the two nucleophiles in the presence of 2 mol% 'Pd–MOP', Scheme 5.

The outcome was dramatic with >90% of the alkylation product being **8a/9a**, the product derived from NaC(Me)E$_2$ and with the branched linear ratio 70/30, i.e. essentially the same as it is in the absence of added NaCHE$_2$. The same ratio was obtained when four equivalents NaC(Me)E$_2$ was employed.

2.2. Development of a method for analysis of stereochemical and regiochemical pathways in the Pd-catalysed reaction of iso-cinnamyl esters with dimethyl methyl malonate anion

Having determined that for the systems described herein, the powerful regiochemical memory effects that allow access to the less common branched product isomer **9**, are essentially restricted to the use of *iso*-cinnamyl esters of type **7**, with NaC(Me)E$_2$ as nucleophile and MOP as ligand, we became interested in exploring to what extent stereochemical memory effects may also accompany this process. In principle, the identical 3,3-substitution (H,H) of the π-cinnamyl unit should facilitate diastereofacial equilibration of the cinnamyl unit through π–σ–π equilibrium via the η^1-methylene isomer and thus interconversion of the two diastereoisomeric forms of the regioisomeric Pd-intermediates **10** and **11**. Indeed, Hayashi et al. have reported preparation of **9a** in up to 68% ee [16]. However, since
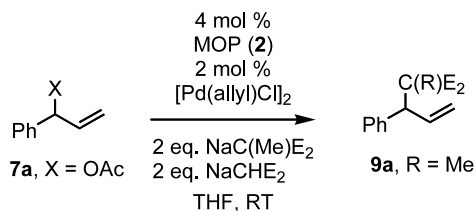
Scheme 5. Competition experiment between the nucleophiles NaC(Me)E$_2$ and NaCHE$_2$ for intermediates generated in the Pd–MOP catalysed allylic alkylation reaction of *iso*-cinnamyl acetate **7a**. The reaction generates the products derived from NaC(Me)E$_2$ in excess (>90%) over the products derived from NaCHE$_2$ (**8b/9b**), with moderate regioselectivity (ca. 70%) for **9a** over **8a**.

regioisomer interconversion has to be slow, relative to nucleophilic attack, for the regiochemical memory effect to operate, one might anticipate that the diastereofacial equilibration might be coupled to this process and thus 68% ee may not be the limiting selectivity for the system. Indeed, at −30 °C, the ee is found to increase to 86% [16]. The reactions of interest employ racemic *iso*-cinnamyl esters (**7**) and one might at first consider employing a ^{2}H-labelling technique in direct analogy to the method we developed for the study of memory effects with cycloalkenyl esters (Scheme 1) where the label was installed at the carbon bearing the nucleofuge. However, the process of interest, i.e., π–σ–π diastereofacial equilibration of π-cinnamyl intermediates, which cannot occur in cyclic allyl intermediates, will cause the reaction to lose its stereospecificity with regard to the ^{2}H label and this technique would not be informative. Realising that one requires two elements of stereochemical information in the labelling system to track both of the regio- and stereo-chemical processes, we chose to deploy a ^{2}H label at the terminus of the alkene unit in **7** and with a set (Z)-stereochemistry [18]. The consequence of this labelling strategy, is the possibility of the generation of six products, all of which must be resolved for simultaneous analysis of both the regioselectivity and stereoselectivity arising from both enantiomers of (±)-(1Z)-1-[^{2}H]-**7ab**, Scheme 6.

Seeking to develop a convenient spectroscopic technique for the analysis of the mixture of 3-[^{2}H]-**8a**/1-[^{2}H]-**9a** without recourse to physical separation [19], we tested the method pioneered by Courtieu et al. that involves ^{2}H{^{1}H}-NMR in a chiral liquid crystal matrix (CLCM) consisting of a solution of poly-benzyl-L-glutamate in CH$_2$Cl$_2$ [20]. The anisotropy, induced through partial ordering, causes quadrupolar coupling ($\Delta|\nu_Q|$) to be manifested in the ^{2}H{^{1}H}-NMR spectrum. By using a matrix of the appropriate concentration and viscosity [20a] we were able to resolve all six components, each appearing as a doublet in the ^{2}H{^{1}H}-NMR spectrum with different chemical shift (linear versus branched; the chemical shift anisotropy is negligible) or different quadrupolar coupling ($\Delta|\nu_Q|$). By synthesis of reference mixtures of the expected products (employing Pd, Mo- and W-catalysed reactions [18,21]) we were able to assign all six doublets, Fig. 2 (spectra **I**–**IV**).

The application of the ^{2}H-stereochemical labelling/CLCM analysis in combination with chiral HPLC analysis (OJ column), allows the study of the Pd–MOP catalysed reaction under memory effect conditions in reasonable detail. A typical spectrum (from Table 1, entry 1) is shown in Fig. 3.

As a starting point for comparison, we can define the 'benchmark' reaction as that involving *iso*-cinnamyl acetate ((±)-**7a**) with two equivalents NaC(Me)E$_2$ in THF at RT with (S)-MOP/[Pd(allyl)Cl]$_2$ as pro-catalyst (2 mol% Pd); the results are given in Table 1, entry 1.
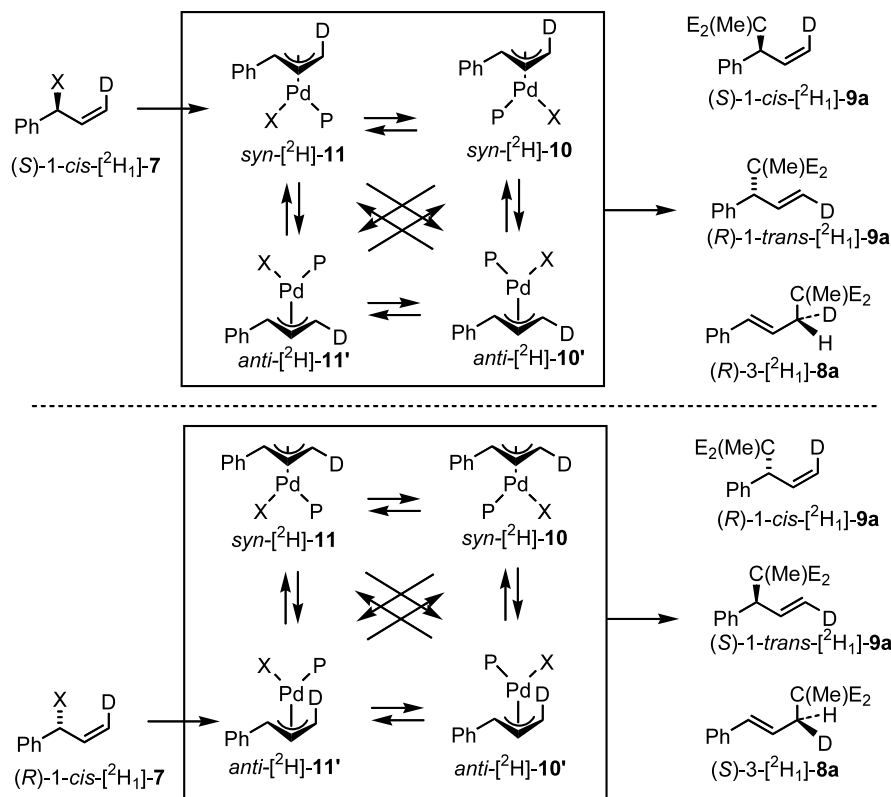
Scheme 6. A ^{2}H-labelling scheme to facilitate simultaneous analysis of the enantiomeric branched and linear products derived from stereospecific Pd-catalysed reaction (inv.−inv.) of both enantiomers of a racemic sample of *iso*-cinnamyl substrate (1-*cis*-[^{2}H$_1$]-7) with NaC(Me)E$_2$. Diastereoisomer interconversion is assumed to proceed exclusively via π−σ−π diastereofacial equilibration.

The reaction affords **8a/9a** in 85% yield, with 70% regioselectivity [22] for branched isomer **9a** in global ee$_g$ of 72% (*R*)-**9a**. ^{2}H NMR CLCM analysis clearly defines (*R*)-**7** as the matched enantiomer of substrate (giving (*R*)-**9a** in 93% ee) and (*S*)-**7** as mismatched (giving (*R*)-**9a** in 50% ee). The stereospecific nature of Pd-catalysed allylic alkylation in combination with the ^{2}H labelling method allows the enantiomer ratio of the linear product (chiral by virtue only of the ^{2}H/^{1}H configuration at C(3)) to be used to deduce the regiochemical memory effect obtained with enantiomers of substrate (see Scheme 6). Interestingly, the regioselectivity is essentially identical (thus, 3-[^{2}H$_1$]-**8a** is obtained in ca. 0% ee; see Fig. 3) and indeed this remains the case for all variations in reaction conditions, vide infra, suggesting that diastereoisomeric intermediates **11/11′** equilibrate with regioisomeric intermediates **10/10′** at similar rates.

2.3. Factors affecting stereochemical memory

By variation of the four basic parameters of: leaving group, temperature, solvent and presence or absence of chloride, we have briefly studied their individual and combined effects on the stereochemical and regiochemical [23] memory. The complete set of results is given in Table 1.

Comparison of entry 1 with entry 2, where a halide-free pro-catalyst is employed, reveals that the presence of chloride results in slightly higher regiochemical memory, but has little effect on the stereochemical memory and latent enantioselectivity. Acetate and chloride are both expected to coordinate to Pd to give neutral intermediates of the type [Pd(X)(*P*-MOP)(Ph−π-C$_3$H$_4$)], where X = OAc (**12/13**) or Cl [17,24], with the latter favoured by the palladophilicity of the halide. This result suggests that ionisation of the complex to generate cations of the type [Pd(*P,C*-MOP)(Ph−π-C$_3$H$_4$)], i.e. mode **II** or **III** complexation, may be involved in the interconversion of regioisomers. Maintaining the halide-free conditions (entry 2) but changing to a system where NaC(Me)E$_2$ is catalytically re-generated such that the concentration of nucleophile is low during the entire reaction (entry 3) results in a dramatic loss of regio-chemical memory and ca. 82% linear **8a** is generated. This is readily understood in terms of decreased efficacy of capture of the intermediates allowing efficient equilibration of regioisomeric complexes **10/10′** and **11/11′**. Accordingly, the stereochemical memory is further reduced such that a global ee$_g$ of 86% is attained. Returning to conditions of excess nucleophile (two equivalents) but conducting the reaction at −30 °C (entries 4 and 5) results in a decrease of the stereo-
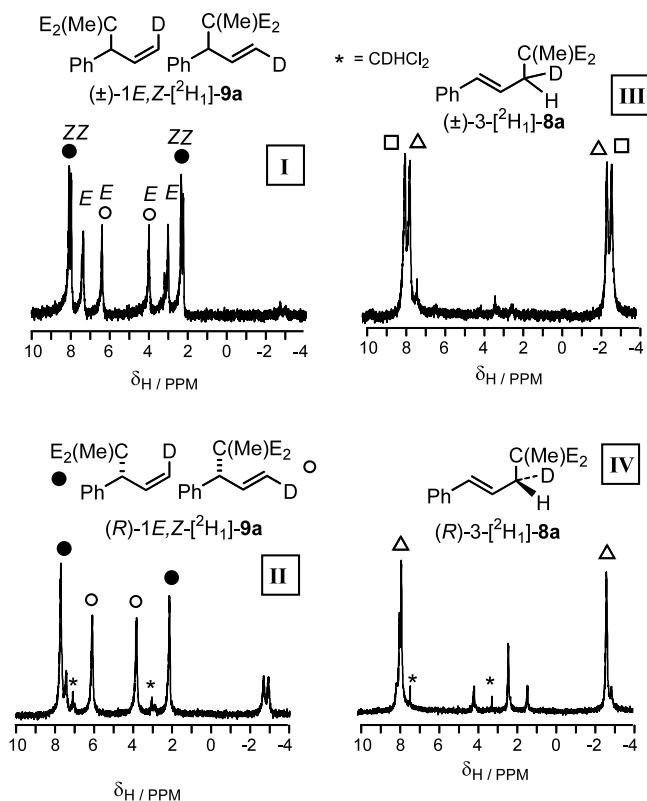
Fig. 2. Reference ^{2}H{^{1}H}-NMR spectra obtained in a chiral liquid crystal matrix generated from polybenzyl-L-glutamate in CH$_2$Cl$_2$ causing partial ordering and thus quadrupolar coupling. Spectrum **I**: reference racemic sample of branched product 1-[^{2}H$_1$]-**9a**. Spectrum **II** reference enantiomerically enriched sample of a cis/trans mixture of (R)-1-[^{2}H$_1$]-**9a**. Spectrum **III**: reference racemic sample of linear product 3-[^{2}H$_1$]-**8a**. Spectrum **IV**: reference enantiomerically enriched sample of (R)-3-[^{2}H$_1$]-**8a**. The following values act as a basis set for the quadrupolar couplings: (R)-3-[^{2}H$_1$]-**8a**, $\Delta|\nu_Q| = 597$ Hz; (S)-3-[^{2}H$_1$]-**8a**, $\Delta|\nu_Q| = 611$ Hz. (R)-cis-1-[^{2}H$_1$]-**9a**, $\Delta|\nu_Q| = 331$ Hz; (S)-cis-1-[^{2}H$_1$]-**9a**, $\Delta|\nu_Q| = 319$ Hz; (R)-trans-1-[^{2}H$_1$]-**9a**, $\Delta|\nu_Q| = 136$ Hz; (S)-trans-1-[^{2}H$_1$]-**9a**, $\Delta|\nu_Q| = 245$ Hz.

chemical memory with ee$_g$ values of 80–81% (compare 70–71% at RT) and an increase in regiochemical memory (80% **9a**). The opposite effects on relative equilibration rates (more diastereoisomer interconversion and less regioisomer interconversion) at decreased temperature suggests that entropic factors are more important for one process than the other.

Changing the 'escort' ion from Na to K in the nucleophile component is expected to make the nucleophile more charge delocalised [25] and this results in a decrease in stereochemical and regiochemical memory (compare entry 1 [Na] with entry 6 [K]) and thus a higher ee$_g$ (80%) and lower selectivity for **9a** (60%). It is interesting to note that in the absence of the ^{2}H labelling, the increased ee$_g$ might be interpreted as a significant increase in the latent selectivity, which is not the case. Changing from THF to CH$_2$Cl$_2$ as solvent, will reduce the concentration of the nucleophile (NaC(Me)E$_2$) due to its lower solubility in the latter.

This results in a decrease in stereochemical and regiochemical memory effect (compare entries 1 and 2 with entries 7 and 8) and there is the same trend for a decreased latent enantioselectivity in the absence of chloride (entry 7 vs. entry 8).

Using 1-cis-[^{2}H$_1$]-**7b** as substrate, thus employing methyl carbonate as nucleofuge instead of acetate, the regiochemical memory effect is reduced (compare entries 1 and 2 with entries 9 and 10). An analogous, but more extreme effect has been observed with cyclopentenyl substrates [6l]. Interestingly, in the current case the methylcarbonate (or methoxide) counter-ion results in a decreased latent enantioselectivity. On conducting the same reaction in the presence of chloride but with catalytically re-generated nucleophile, the high latent enantioselectivity is restored (entry 11). The low nucleophile concentration may possibly facilitate ion-exchange with Cl prior to nucleophilic attack. However, as observed with the acetate substrate, the low nucleophile concentration results in loss of regiochemical memory. Finally, it was of interest to compare the stereochemical memory effect and also the latent enantioselectivity with NaCHE$_2$ as nucleophile (entry 12) or MAP (**3**) as a ligand (entry 13) since these modifications result in loss of regiochemical memory under the 'benchmark' conditions. In the case of NaCHE$_2$ as nucleophile, the global ee$_g$ obtained under standard conditions (compare entry 1 with entry 12) is essentially identical. However the latent enantioselectivity with NaC(Me)E$_2$ is higher. In the case of MAP (**3**) the latent enantioselectivity is substantially lower (entry 13).

3. Conclusions

As earlier reported by Hayashi et al. [6(c),16] the reaction of iso-cinnamyl esters (**7**) with excess NaC(Me)E$_2$, catalysed by Pd–MOP complexes generated in situ, can proceed with significant regiochemical memory that favours generation of the branched isomer of product (**9a**). The electrophilicity of the [Pd(P,X-MOP)(Ph–π-C$_3$H$_4$)] intermediate (where MOP (**2**) functions as a mono- or bi-dentate ligand, with P trans related to the benzylic carbon) together with the nucleophilicity of the NaC(Me)E$_2$ are both essential components in maintaining regiochemical memory. Intermediates bearing the closely related ligand MAP (**3**) are not sufficiently electrophilic for nucleophilic attack to occur prior to extensive isomer equilibration resulting in generation of linear isomer **8a** in excess [9a]. This may be attributed to the availability of stabilising interactions with the Me$_2$N group, either directly or via an enamine-like coordination [6g,l,9]. Similarly, the closely related nucleophile NaCHE$_2$ is not sufficiently reactive to capture nascent π-cinnamyl Pd–MOP intermediates prior to equilibration. Furthermore, low con-

Table 1
The effect of leaving group, temperature, solvent and presence or absence of chloride on the 'Pd–(S)-MOP' catalysed reaction of *iso*-cinnamyl esters **7a** and **7b** with NaC(Me)E$_2$ (E = CO$_2$Me)

Entry	Substrate	Solvent	T (°C)	Mol% Cl [a]	Ratio 9a/8a [b]	Ee 9a from (R)-7 [c]	Ee 9a from (S)-7 [c]	Ee$_{global}$ 9a [d]	Yield (%) [e]
1	(±)-**7a**	THF	21	2	70/30	50 (R)	93 (R)	72 (R)	85
2	(±)-**7a**	THF	21	0	60/40	49 (R)	91 (R)	70 (R)	80
3 [f]	(±)-**7a**	THF	21	0	18/82	75 (R)	>95 (R)	86 (R)	85
4	(±)-**7a**	THF	−30	2	80/20	ND	ND	80 (R)	82
5	(±)-**7a**	THF	−30	0	80/20	69 (R)	89 (R)	81 (R)	80
6 [g]	(±)-**7a**	THF	21	2	40/60	65 (R)	95 (R)	80 (R)	82
7	(±)-**7a**	CH$_2$Cl$_2$	21	2	60/40	44 (R)	94 (R)	70 (R)	91
8	(±)-**7a**	CH$_2$Cl$_2$	21	0	43/57	33 (R)	87 (R)	63 (R)	90
9	(±)-**7b**	THF	21	2	63/37	0	79 (R)	31 (R)	78
10	(±)-**7b**	THF	21	0	61/39	42 (R)	87 (R)	59 (R)	91
11 [f]	(±)-**7b**	THF	21	0	14/86	67 (R)	>95 (R)	82 (R)	62
12 [h]	(±)-**7a**	THF	21	2	30/70	60 (S) [i]	80 (S) [i]	71 (S) [i]	84 [i]
13 [j]	(±)-**7a**	THF	21	2	16/84	0	38 (R)	18 (R)	75

[a] Depending on whether 2 mol% [Pd(allyl)Cl]$_2$ or 4 mol% [Pd(allyl)(MeCN)$_2$]OTf is used as pro-catalyst pre-cursor. The pro-catalyst was generated in situ by reaction of MOP (**2**) with Pd–allyl source (2 mol% Pd; the Pd/L ratio is 1/1) prior to addition of (±)-**7ab** and two equivalents NaC(Me)E$_2$ (freshly prepared from NaH and HC(Me)E$_2$). Substrate concentration at time zero = 0.16–0.18 mM. For full details see Section 4

[b] Determined by ^{1}H- and by ^{2}H-NMR.

[c] Calculated from ee$_{global}$ and ^{2}H{^{1}H}-NMR in CLCM analysis.

[d] Determined by chiral HPLC (OJ column).

[e] Yield of pure product mixture obtained after column chromatography on silica-gel.

[f] Nucleophile generated in situ from 2 mol% NaOAc; two equivalents *N,O*-bis(trimethylsilyl)acetamide and two equivalents HC(Me)E$_2$.

[g] Nucleophile is generated from KH thus giving KC(Me)E$_2$.

[h] CH$_2$E$_2$ employed as pro-nucleophile giving NaCHE$_2$.

[i] Product is a mixture of **8b** and **9b**. The pseudo-inversion of configuration arises from change in substituent priorities between –C(Me)E$_2$ and –CHE$_2$.

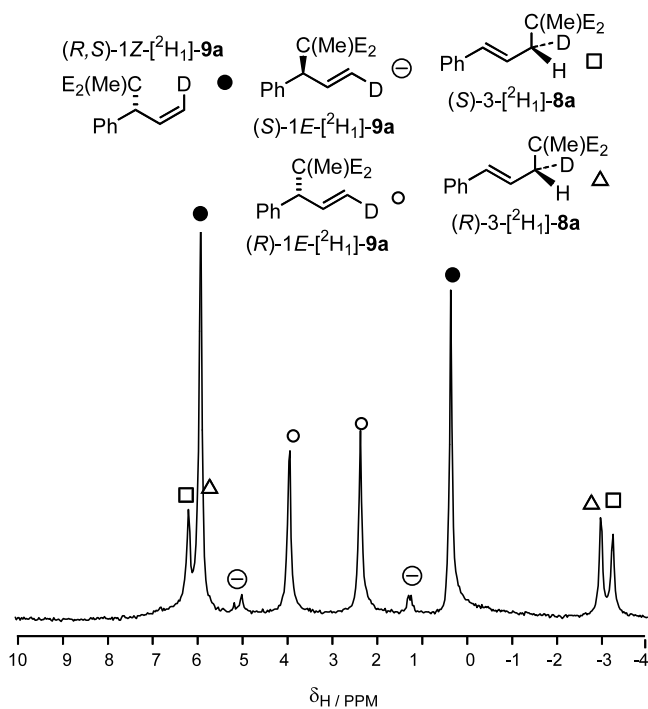[j] (S)-MAP (**3**) employed as ligand instead of (S)-MOP (**2**).

Fig. 3. A typical ^{2}H{^{1}H}-NMR spectra obtained in a chiral liquid crystal matrix generated from polybenzyl-L-glutamate in CH$_2$Cl$_2$ used in combination with chiral HPLC (OJ column) to analyse regiochemical and stereochemical memory effects in the Pd–MOP catalysed allylic alkylation of *iso*-cinnamyl esters (**7**). For assignments see Fig. 2.

centrations of NaC(Me)E$_2$ (e.g. when this is re-generated in situ catalytically) also result in loss of regiochemical memory. These results suggest that earlier studies [16] on the regioselectivity and enantioselectivity in stoichiometric alkylation of isolated samples of [Pd(OAc)(MOP)(Ph–π-C$_3$H$_4$)] (**12**) by NaC(Me)E$_2$ at −30 °C are under kinetic and not thermodynamic control.

The stereospecific nature of the Pd-catalysed process allows deployment of ^{2}H-labelled *iso*-cinnamyl esters, where the label is located at the (Z)-position of the alkene, to facilitate simultaneous analysis of the stereochemical and regiochemical memory arising in the reaction of either enantiomer of the racemic substrate (Scheme 6). Quantification is readily achieved by analysis of the product mixture (^{2}H labelled **8a** and **9a**) using the method of Courtieu and coworkers [20] which involves ^{2}H{^{1}H}-NMR in a chiral liquid crystal matrix (Figs. 2 and 3). Using this technique to track diastereofacial equilibration of the cinnamyl unit through π−σ−π equilibrium it is demonstrated that the matched enantiomer of substrate generates the branched product in high ee (90 to ≥ 95%) whilst the mismatched substrate gives the same enantiomer of the branched isomer but in a lower ee. Thus, the stereochemical memory effect attenuates the asymmetric induction that is potentially achievable through the latent selectivity of

the ligand. The degree of attenuation of the limiting global ee$_g$ (ca. 95%) is inversely correlated to the extent of equilibration. Competing with π–σ–π equilibration is equilibration of regioisomeric Pd–allyl intermediates (**10/10′** and **11/11′**, Schemes 3 and 6). This equilibration attenuates the degree of regiochemical memory and thus reduces the branched/linear ratio of products (**9a/8a**) when an *iso*-cinnamyl ester (**7ab**) is employed as substrate. The latent regioselectivity of the system is for the linear product **8a**. Two major mechanisms for the equilibration of regioisomeric neutral Pd–π-cinnamyl intermediates (interconversion of **10** and **11**) can be envisaged. The first is through π–σ–π equilibrium and the second is through ligand rotation (Pd–P rotation in a tri-coordinate intermediate or Berry pseudorotation in a penta-coordinate intermediate), Scheme 7.

At a given temperature, the processes facilitating loss of stereochemical and regiochemical memory appear to be partly coupled. In other words, changes in reaction conditions that increase one process tend to increase the other. However, temperature facilitates partial uncoupling and higher global enantioselectivity (up to 81% ee$_g$) with higher regiochemical retention (up to 80%) can be achieved at −30 °C (Table 1, entries 4 and 5). It is noted that the higher ee$_g$ attained at this temperature, as compared to at RT, is not due to a significant increase in latent selectivity but due to greater diastereoisomeric equilibrium. Indeed, at RT, even greater equilibrium can be achieved by using catalytically regenerated nucleophile (up to 86% ee$_g$). However, the cost of such

equilibrium is loss of regiochemical memory and thus **8a** is obtained as the major product instead of the desired **9a** (Table 1, entry 3). Overall, these results suggest that one process has a greater entropic change associated with some of its individual steps than the other. For example, loss of stereochemical memory could proceed via steps involving a greater decrease in entropy, or equally, loss of regiochemical memory could proceed via steps involving a greater increase in entropy. At present it, although it is clear that stereochemical equilibration (**11** with **11′**) proceeds via π–σ–π equilibrium [26], is not possible to exactly define which of the three mechanisms for regiochemical equilibration (**10** with **11**) are operative (Scheme 7). Nonetheless, based on the temperature/entropy effects one may speculate that (a) Berry pseudorotation (Scheme 7) would become more competitive at lower temperature; (b) π–σ–π equilibrium then Pd–C rotation (B, Scheme 7) in competition [27] with C–C rotation (A, Scheme 7) would be unlikely to show a large entropic differential and (c) ionisation of a neutral mode **I** type complex to generate a cationic (*P*,*C*)-MOP complex (mode **II**) would be entropically favoured. In earlier studies on the rate of diastereoisomer interconversion of π-cycloalkenyl Pd complexes of MOP (as Scheme 1, *n* = 1 and 2), which would correspond to regioisomer interconversion in the present system, it was found that the process is faster in ionic mode **II** type complexes than in neutral mode **I** type complexes [6c,g] Thus, if stereochemical equilibration (**11** with **11′**) proceeds via π–σ–π
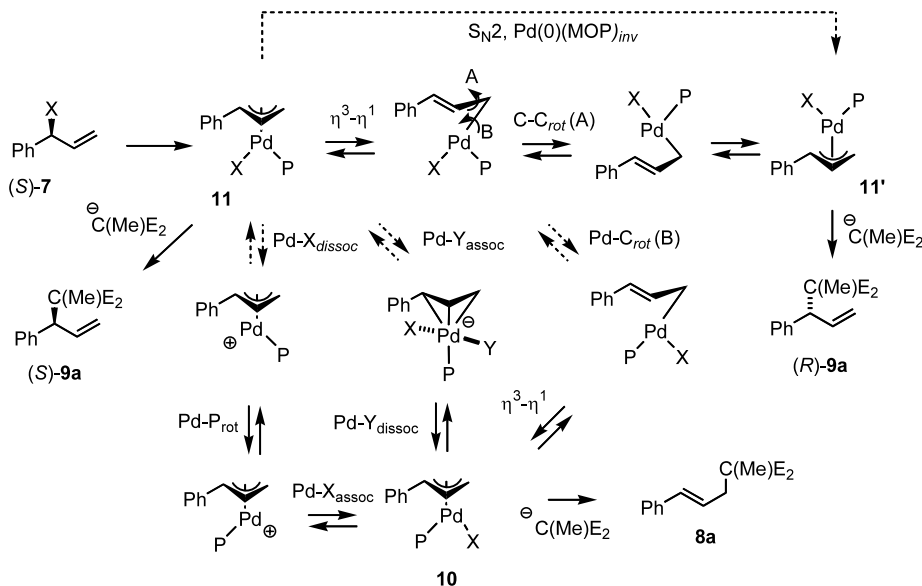
Scheme 7. Mechanisms for loss of regiochemical and stereochemical memory in Pd–(*S*)-MOP catalysed alkylation of the mismatched enantiomer (*S*)- of isocinnamyl ester **7** by the anion of methyl dimethyl malonate. Two modes for loss of stereochemical memory (interconversion of **11** and **11′**) are outlined at the top of the scheme: (i) S$_N$2-type displacement by Pd(0); and (ii) conversion to an η^1-complex and then C–C rotation (process 'A'). The former is not competitive since there is no loss of stereospecificity when D-labelled samples are employed. Three modes for loss of regiochemical memory (interconversion of **10** and **11**) are outlined in the lower half of the scheme: (i) Pd–P rotation in a tri-coordinate intermediate; (ii) Berry pseudorotation in a penta-coordinate intermediate; and (iii) conversion to an η^1-complex and then Pd–C rotation (process 'B'). Note that analogous pathways for interconversion of **10′** and **11′** are not shown.

equilibrium in a mode **I** complex and regioisomer interconversion proceeds via Pd–P rotation in a cationic tridentate complex generated via a mode **II** type complexation, decreased temperature would make loss of regiochemical memory less competitive.

In summary, the powerful regiochemical memory effect [3c,16] reported for the reaction of *iso*-cinnamyl acetate (**7a**) with $NaC(Me)E_2$ catalysed by the bulky monophosphine ligand MOP (**2**) to generate **9a** rather than the 'normal' isomer **8a** is highly sensitive to conditions. Change in the ligand from MOP (**2**) to the closely related ligand MAP (**3**) [9] or the nucleophile from $NaC(Me)E_2$ to the closely related $NaC(H)E_2$, or a major decrease in nucleophile concentration all result in the loss of regiochemical memory thereby favouring the generation of the linear product **8** rather than branched isomer **9**. Accompanying the regiochemical memory is a stereochemical memory effect. The two processes are closely related, but greater attenuation of the latter versus the former can be engendered by conducting the reaction at lower temperatures ($-30\,^\circ C$), suggesting an exploitable difference in entropy accompanying the two processes. Attenuating the stereochemical memory allows the latent enantioselectivity of the catalyst system for the generation of **9a** to be approached. With MOP (**2**) as ligand, this limiting selectivity is high ($> 90\%$ ee). On the basis of the geometry of the MOP, Cl and π-allyl ligands in the crystal structure of the complex $[ClPd(Me_2-\eta^3-C_3H_3)(P\text{-MOP})]$ in which mode **I** type coordination is apparent [13a] one may rationalise the stereochemical memory effect (in terms of matched and mismatched substrates of type **7**) and the sense of asymmetric induction by consideration of forms **11** and **11′** [28]. On the basis of a simple argument involving steric strain between the Ph and methoxy–naphthyl ring in **11**, one might predict that the diastereoisomer that is attacked preferentially (**11′**) is also the thermodynamically favoured form, Fig. 4 [29].

In contrast, with MAP (**3**) the limiting selectivity is substantially lower (≤ 38 ee), suggesting that a different

coordination mode (e.g. mode **II** or **III**, rather than mode **I**, see Fig. 1) is operative during the reaction. The stabilising effect of such complexation (**II** or **III**) is then consistent with the essentially complete loss of regiochemical memory with this ligand system as compared to MOP.

4. Experimental

4.1. General

Anhydrous solvents (THF, CH_2Cl_2) were obtained by passage through an activated-alumina drying train (Anhydrous Technologies) and reactions were carried out under nitrogen using standard Schlenk techniques. Ligands (MOP (**2**) and MAP (**3**) [9a], labeled substrates (($\pm$)-3-[$^2H_1$]-**6ab** and ($\pm$)-1-[$^2H_1$]-**7ab**) [18] and pro-catalysts ([(π-C_3H_5)Pd(MeCN)$_2$)][O_3SCF_3] [30] were prepared by standard routes. PBLG (polybenzyl-L-glutamate) (DP = 564) was purchased from Sigma. NMR experiments were performed on JEOL GX or Eclipse instruments, operating at 400 MHz (^{1}H). Flash column chromatography: Merck silica gel 60 eluting with a constant gravity head of ca. 15 cm solvent. TLC: 0.25 mm, Merck silica gel 60 F254 visualising at 254 nm and with acidic (H_2SO_4) aq. $KMnO_4$ solution (ca. 2%). Yields refer to analytically pure samples obtained after chromatography on silica gel.

4.2. Allylic alkylation: typical procedure for data in Table 1

4.2.1. Excess nucleophile in the presence of chloride ion at room temperature (r.t.) (entry 1)

A solution of $NaC(Me)E_2$ freshly prepared from $HC(Me)E_2$ (94 µl, 0.71 mmol) and sodium hydride (60% in mineral oil, 28 mg, 0.71 mmol) in anhydrous THF (1.5 ml) was added to a solution of [PdCl(π-C_3H_5)]$_2$ (2.8 mg, 7.8 µmol) and MOP (**2**) (7.3 mg, 15.6
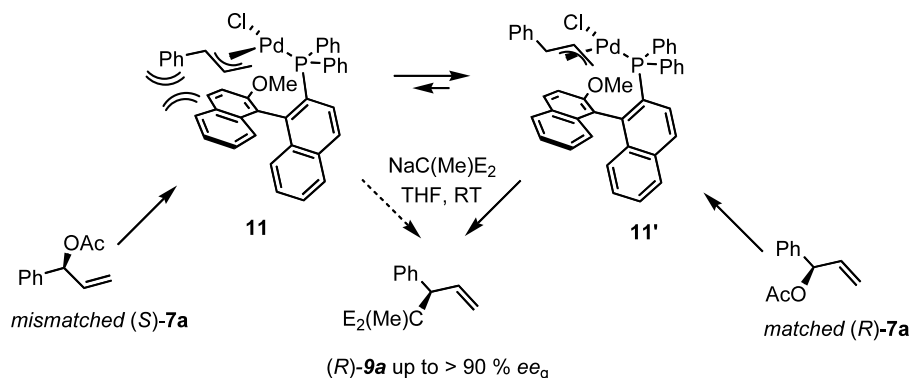

Fig. 4. Possible origin of asymmetric induction in the formation of branched regioisomer **9a** on the basis of a mode **I** type coordination of the (*S*)-enantiomer of MOP (**2**) to a Cl-bearing Pd–π-cinnamyl unit and preferential attack of diastereoisomer **11′**, formed from matched substrate (*R*)-**7a**.

μmol) in anhydrous THF (0.7 ml). The allylic substrate cis-1-^{2}H-7a (68 mg, 0.39 mmol) was added and the mixture stirred at r.t. until completion of the reaction (as indicated by TLC). The mixture was diluted with diethyl ether and the catalyst was removed by filtration through a short silica gel pad. The filtrate was evaporated and the residue was chromatographed using silica gel (1.5 × 15 cm, hexane–ethyl acetate, 4:1 v/v) to afford a mixture of 3-^{2}H-6a/1-^{2}H-7a (87 mg, 85%) as a colourless oil.

4.2.2. Catalytic nucleophile in the absence of chloride at r.t. (entry 3)

A solution of HC(Me)E$_2$ (94 μl, 0.56 mmol), the allylic substrate cis-3-[^{2}H]-7a (49 mg, 0.28 mmol) and BSA (138 μl, 0.56 mmol) in anhydrous THF (2 ml) was added to a solution of [Pd(η^3-C$_3$H$_5$)(MeCN)$_2$][OTf] (4.3 mg, 11.3 μmol) and MOP (2) (5.3 mg, 11.3 μmol) in anhydrous THF (0.4 ml). The reaction was then initiated with 1.1 mg (5 mol%) of sodium acetate and the mixture was stirred at r.t. until complete. Work-up as above.

4.3. Sample preparation for chiral liquid crystal matrix (CLCM) $^2H\{^1H\}$-NMR

The preparation of the sample is very important as it can affect the quality and reproducibility of the NMR spectra. The samples were prepared by the following procedure: PBLG (85–88 mg) was weighed directly into a 5 mm o.d. NMR tube and a solution of the product (16–25 mg) in dichloromethane (400–500 mg) was added. All samples were of the same length (3.3 cm) and were centrifuged in both directions (× 3000 rpm). The extent of centrifugation is also an important factor in obtaining good quality NMR spectra. The NMR tube was centrifuged for 1 h in each direction and then 30 min in each direction and then analyzed within 1 h. All NMR spectra were obtained on an Eclipse 400 NMR spectrometer at 23 ± 1 °C. The NMR tube was not spun in the magnet. Although the absolute values of the quadrupolar couplings were found to vary from experiment to experiment (by up to ca. 4%), control experiments varying: (i) concentration of PBLG, (ii) degree of polymerization of the PBLG, (iii) analyte concentration, and (iv) temperature, demonstrated that the $\Delta|v_Q|$ values varied in a directly proportional manner. Consequently, $\Delta|v_Q|$ values could be normalized to allow confident assignment from real analyte mixtures, an example of which is shown in Fig. 3. The following values act as a basis set: (R)-3-[^{2}H$_1$]-8a, $\Delta|v_Q|$ = 597 Hz; (S)-3-[^{2}H$_1$]-8a, $\Delta|v_Q|$ = 611 Hz; (R)-cis-1-[^{2}H$_1$]-9a, $\Delta|v_Q|$ = 331 Hz; (S)-cis-1-[^{2}H$_1$]-9a, $\Delta|v_Q|$ = 319 Hz; (R)-trans-1-[^{2}H$_1$]-9a, $\Delta|v_Q|$ = 136 Hz; (S)-trans-1-[^{2}H$_1$]-9a, $\Delta|v_Q|$ = 245 Hz.

4.4. Preparation of reference mixtures for $^2H\{^1H\}$-NMR in CLCM

Sample 1 (Fig. 2, spectrum I): an orange–red solution of [W(CO)$_3$(η^6-C$_7$H$_8$)] (16.8 mg 0.047 mmol) and 2,2-bipyridine (7.38 mg, 0.047 mmol) in degassed nitrogen-saturated anhydrous tetrahydrofuran (0.5 ml) under nitrogen was heated to 60 °C for 15 min, resulting in a homogeneous brown–black solution. After cooling to 25 °C, sodium dimethyl methyl malonate prepared from dimethyl methyl malonate (107 μl, 0.81 mmol) and (60%) sodium hydride (32.3 mg, 0.81 mmol) in anhydrous THF (3 ml) was added. The suspension was stirred vigorously at 60 °C for 10 min. The resulting grey–black solution was cooled to 25 °C and combined with (±)-(3E)-1-[^{2}H]-6b (60 mg, 0.31 mmol). After heating to 60 °C for 18 h, the deep red homogeneous solution was quenched with 50% saturated aqueous solution of NH$_4$Cl (1 ml) and the mixture extracted with CH$_2$Cl$_2$ (3 × 20 ml). The combined extracts were dried (MgSO$_4$) and then filtered through a short plug of silica gel. The solvent was removed under reduced pressure and the crude red-coloured oil purified by column chromatography on silica gel (2.5 × 20 cm, elution with hexane–ethyl acetate, 9:1 v/v) to afford (±)-(E/Z)-1-[^{2}H]-9a (66 mg, 88% yield, 4/96 ratio 8a/9a). The same reaction conducted using (±)-1-cis-[^{2}H]-7b gave a pure sample of (±)-(Z)-1-[^{2}H]-9a (spectrum not shown) allowing assignment of cis and trans isomers, with both cis isomers displaying the larger quadrupolar coupling.

Sample 2 (Fig. 2, spectrum II): a mixture of [(CO)$_3$Mo(η^6-C$_7$H$_8$)] (14.1 mg, 0.052 μmol) and (2R)-(−)-N,N′-3-phenyl-1,2-diaminobutylbis(2-pyridine-carboxamide) [18], (27 mg, 0.078 μmol) was dissolved in anhydrous degassed tetrahydrofuran (0.5 ml). Sodium dimethyl malonate in anhydrous degassed tetrahydrofuran (1 ml), generated from dimethyl methyl malonate (139 μl, 1.03 mmol) and NaH (60%, 41 mg, 1.03 mmol) were successively added to the deep red solution. The mixture was stirred at 60 °C overnight (20 h), then diluted with diethyl ether (20 ml), quenched with 5% saturated aqueous solution of NaHCO$_3$ (1 × 5 ml) and washed with water (1 × 1 ml). The mixture was extracted with dichloromethane (3 × 20 ml) and dried (MgSO$_4$). The combined extracts were evaporated and the crude product purified by flash column chromatography on silica gel (2.5 × 20 cm, elution with hexane–ethyl acetate, 6:1 v/v) to give a 3/1 mixture of (R)-(E/Z)-1-[^{2}H]-9a (78% ee by HPLC on OJ chiral column; and (±)-[^{2}H]-8a as a colourless oil (67 mg, 49% 95 ^{2}H/H, B:L = 3:1, 78% ee).

Sample 3 (Fig. 2, spectrum III): a mixture of [Pd(η^3-C$_3$H$_5$)(MeCN)$_2$][OTf] (2.2 mg, 0.0058 μmol) and dppf ((3.2 mg, 0.0058 μmol) was dissolved in THF (0.5 ml). The solution was stirred under nitrogen at 25 °C for 15 min to afford a brown solution. Sodium dimethyl

methyl malonate in THF (6 ml), generated from dimethyl methyl malonate (238 μl, 1.79 mmol) and (60%) sodium hydride 71 mg, 1.42 mmol) and a solution of ($\pm$)-(3E)-1-[^{2}H]-**6a** (63 mg, 0.36 mol) in THF (0.5 ml) were successively added. The mixture was stirred overnight at 25 °C then diluted with diethyl ether and washed successively with 5% aqueous saturated solution of NaHCO$_3$ and water. The organic phase was dried (MgSO$_4$) and the crude product was purified by column chromatography on silica gel (1.5 × 15 cm, elution with hexane–ethyl acetate, 4:1, v/v), to afford ($\pm$)-1-[^{2}H]-**8a** as a colourless oil (45 mg, 60%, > 95% regioselectivity).

Sample 4 (Fig. 2, spectrum **IV**): this was prepared by an identical procedure to sample 3, but employing (R, 3E)-1-[^{2}H]-**6a** (92% ee) [18] to afford (S)-1-[^{2}H]-**8a** as a colourless oil (> 95% regioselectivity, > 90% ee).

Analytical data for ^{2}H-labelled products from allylic alkylation reactions: (1E)-3-[^{2}H]-**8a**: ^{1}H-NMR (400 MHz, CDCl$_3$, 22 °C, TMS): δ = 7.41–7.19 (m, 5H; arom. H), 6.45 (dd, ^3J(H,H) = 15.6, ^4J(H,H) = 1.2 Hz, 1H; C(1)H), 6.07 (dd, ^3J = 15.6, 7.3 Hz, 1H; C(2)), 3.73 (s, 6H; 2 × OCH$_3$), 2.79–2.73 (m, 1H; C(3)), 1.46 (s, 3H; CH$_3$); ^{13}C{^{1}H}-NMR (100 MHz, 23 °C, TMS): δ = 172.32 (2 × C=O), 137.05 (C$_{ipso}$), 134.12 (C(1)), 128.46, 127.38, 126.19 (arom. CH), 124.05 (C(2)), 60.35 (C(4)), 52.52 (2 × OCH$_3$), 39.10 (t, ^1J(C,^{2}H) = 20.0 Hz; C(3)), 19.98 (CH$_3$); ^{2}H{^{1}H}-NMR (61 MHz, CH$_2$Cl$_2$, 23 °C, CDCl$_3$): δ = 2.82 (br. s; C(1)^{2}H); MS (EI): m/z (%): 263 (2.3). ^{1}H-NMR (400 MHz, CDCl$_3$, 21 °C, TMS): 1-[^{2}H]-**9a**: δ = 7.35–7.19 (m, 5H; arom. H), 6.37–6.26 (m, 1H; C(2)H), 5.11 (*trans*-^{2}H-isomer: d; ^3J = 17.1; 1-*cis*-^{2}H-isomer: ^3J = 10.0 Hz; 1H; C(3)), 4.15 (d, ^3J = 8.8 Hz, 1H; C(3)H), 3.71 (s, 3H; OCH$_3$), 3.61 (s, 3H; OCH$_3$), 1.43 (s, 3H; CH$_3$); ^{13}C-NMR (100 MHz, 22 °C, TMS): δ = 171.49 (C=O), 171.29, 139.04 (C$_{ipso}$), 136.64 (C(2)), 129.47, 128.15, 127.12 (arom. CH), 117.47 (t, ^1J(C,^{2}H) = 23.0 Hz; C(1)), 58.84 (C(3)), 54.47 (C(4)), 52.32, 52.38 (OCH$_3$), 18.37 (CH$_3$); ^{2}H-NMR (61 MHz, CH$_2$Cl$_2$, 22 °C, CDCl$_3$): δ = 5.12 (br. s; C(1)^{2}H); MS (EI) (mixture of 3-[^{2}H]-**8a** and 1-[^{2}H]-**9a**): m/z (%): 263 (2) [M$^+$], 204 (15), 171 (7), 144 (20), 129 (9), 118 (100), 92 (13), 84 (70), 59 (7).

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(c) B.M. Trost, D.L. Van Vranken, Chem. Rev. 96 (1996) 395 (see also Ref. [1]).

[3] (a) Torquoselectivity refers to the rotational selectivity in the displacement of the η^3-Pd–p-[C(1)–C(2)–C(3)] allyl unit about the Pd–allyl axis as the nucleophile attacks C(1) or C(3) to generate an η^2-Pd–p-[C(3)=C(2)]–C(1) or η^2-Pd–p-[C(1)=C(2)]–C(3) alkene complex respectively. For discussions see: A. Pfaltz, Acta Chem. Scand. 50 (1996) 189;
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[13] (a) Within the limitation to Pd π-allyl complexes, where the two other ligands in the square plane are restricted to occupy mutually *cis*-related sites, MOP (and most likely MAP) does not form bis monodentate P-coordinated complexes of the type $L_2Pd(allyl)$, even in the presence of a large excess of ligand: see Refs. [6c,8]. However, with $PdCl_2$ and two equivalents of ligand, complexes of the form L_2PdCl_2 are formed since the two bulky phosphine ligands can then occupy *trans*-related sites see: T. Hayashi, H. Iwamura, M. Naito, Y. Matsumoto, Y. Uozumi, M. Miki, K. Yanaga, J. Am. Chem. Soc. 116 (1994) 775;
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[15] (a) For a designed exception see: R. Prétôt, A. Pfaltz, Angew. Chem. Int. Ed. Engl. 37 (1998) 323;
(b) R. Prétôt, G.C. Lloyd-Jones, A. Pfaltz, Pure Appl. Chem. 70 (1998) 1035. Note that the linear product is the thermodynamic product: DFT calculations suggest that linear **9a** is 14.9 kcal mol^{-1} more stable than **8a** and **9b** is ca. 10.5 kcal mol^{-1} more stable than **8b** (DFT calculations were performed using the B3LYP basis set and executed through the SPARTAN interface).

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[18] We have recently employed this technique for the analysis of Mo-catalysed reactions of **7b** with $NaCHE_2$: A.V. Malkov, I. Starý, L. Gouriou, G.C. Lloyd-Jones, V. Langer, P. Spoor, V. Vinader, P. Kočovský, J. Am. Chem. Soc., submitted for publication.

[19] In our earlier studies with the analogous CHE_2-derived product mixtures we tested the use of a combined paramagnetic chiral shift reagent/^{2}H-isotope shift method (^{13}C-NMR) in analogy to our analysis of the ^{2}H-labelled dimethyl cyclopentenyl malonates, Scheme 1, see Refs. [6d,g,i]. However, differentiating *cis*- and *trans*-isomers of branched ^{2}H-labelled products was not possible since the differential isotope shifts were negligible. Moreover, the spectral window between ca. 3.5 and 7 ppm in the ^{1}H-NMR became crowded by non-alkene signals on attempting a conventional paramagnetic chiral shift reagent analysis.

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[22] Despite following the same procedure, we have been unable to attain the 77% regioselectivity for **9a** reported by Hayashi et al. [6c]. Instead we consistently obatain **8a/9a** in 30/70 ratio. However, the ee$_g$ we observe in **9a** (72% ee) is slightly higher than the value of 68% reported by Hayashi et al. [16]. This self consistent deviation suggests that under our conditions we experience slightly more equilibration.

[23] Regiochemical selectivity is essentially independent of substrate chirality and thus the global ee$_g$ values can be used directly calculate matched and mismatched enantioselectivities without need for regioisomeric weighting.

[24] Unlike MAP (**3**), it seems that with MOP (**2**), a bidentate *P,C*-coordination may be especially favoured with small allyl units such as π-allyl or π-cycloalkenyl.

[25] This change is reflected in a significantly decreased association constants in DMSO: $KC(Me)E_2$ $K_{assoc.}$ = 2.05±0.03; $NaC(Me)E_2$ $K_{assoc.}$ = 3.22±0.09: E.M. Arnett, S.G. Maroldo, S.L. Schilling, J.A. Harrelson, J. Am. Chem. Soc. 106 (1984) 6759.

[26] The possibility of Pd(0) effecting an S_N2-type displacement of the allyl unit, thereby facilitating diastereofacial exchange, is ruled out by the stereospecificity observed in the reactions.

[27] In a neutral mode **I** type coordination, the complementary *trans* influences of Cl (or X) and Ar_3P would be expected to facilitate C=C dissociation and thus C–C rotation (A, Scheme 7) without significant competitive Pd–C rotation (B, Scheme 7) since the latter would result in the π- and σ-systems (C=C/Ar_3P and X/sp^3-C) losing their favourable *trans* relationships.

[28] The memory effect and stereospecific nature of the Pd-catalysed reaction allow one to deduce which of the two intermediates is attacked preferentially since nucleophilic attack *trans* to the phosphine in **11′** gives rise to the observed major enantiomer of product ((*R*)-**9a**). Crucial to this analysis is that the analogous complexes where the Ph ring is in the *anti* position (as opposed to the *syn* position in **11** and **11′**) are not involved. Acyclic allyl complexes with solely *anti*-located substituent are rare. Support for this comes from the geometry of the isolated acetate complex (**12/13**) where Ph is in the *syn* position in the major regioisomer—see Ref. [16] and the lack of *cis* isomers of **8a** evident in the product mixtures.

[29] It is noted that the opposite argument that the more strained and less favoured regioisomer (**10/10′**) would be attacked preferentially under equilibrium conditions has to be invoked when the regiochemical outcome is considered. Of course, the two allyl termini are not equivalent and thus further factors must also be considered, including: (i) a greater steric interaction between nucleophile and allyl group is expected on attack of **11/11′** adjacent to the Ph ring; and (ii) the products are not degenerate and **8a** is thermodynamically more favoured since the alkene unit is disubstituted and conjugated with the Ph ring.

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