On the Question of the Symmetry of Formally Symmetrical π-(Allyl)palladium Cationic Intermediates in Allylic Alkylations

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Symmetry plays a major role in many asymmetric allylic alkylation reactions.[1] The underlying assumption for many such processes is that palladium catalyzes ionization of allylic leaving groups to form *meso* intermediates. This proposal permits racemic substrates to be entirely converted into products of high ee under the influence of chiral ligands around palladium (see Figure 1) without resorting to a kinetic resolution. The selectivity of the alkylation step for one of two diastereomeric transition states presumably determines the ee of the reaction. The formation of *meso* intermediates is the *sine qua non* of this mechanistic motif. However, this fundamental assumption may not be entirely correct!

Some of the experimental factors which increase the ee of these reactions led us to question this assumption and to believe that some process which occurs *before* the alkylation step could be adversely affecting the ee of the reaction.[1b] Given the mechanism outlined in Figure 1, it is hard to imagine what process detrimental to the ee could be occurring before the alkylation step. We thus began to consider that perhaps a rigorously *meso* intermediate is not formed, at least initially. Previously, Fiaud[2] proposed involvement of a (σ-allyl)palladium intermediate in such reactions to explain results that appeared to be at odds with this fundamental assumption. However, subsequent studies from these laboratories put such a conclusion in doubt.[3] The extensive studies in carbonium ion chemistry including that of allyl cations where ion pair effects are known to influence the regio- and stereochemistry[4] suggest consideration of ion pairs in palladium-catalyzed reactions, especially because the solvents normally employed are rather nonpolar. If the leaving group (typically an acetate or similar derivative) were to form an intimate or tight ion pair with the cationic (π-allyl)palladium intermediate, then it might retain some memory of the starting material stereochemistry due to the asymmetric configuration of the ion pair as depicted in Figure 2.

This mechanism makes the following prediction. With a given enantiomer of the starting material, one enantiomer of the chiral ligand should give a product having a higher ee than that obtained with the other enantiomer of the ligand (i.e., matched/mismatched pair). The reverse situation involving the different enantiomers of the starting material and one enantiomer of the chiral ligand would also form a matched/mismatched pair.

As some of the samples of the asymmetric starting materials (*S*)-**1** and (*S*)-**2**[5−7] were of different ee, the resulting product ee

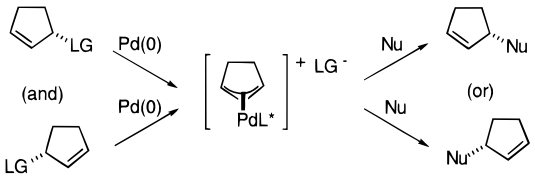


Figure 1. Assumed mechanism for asymmetric alkylation.

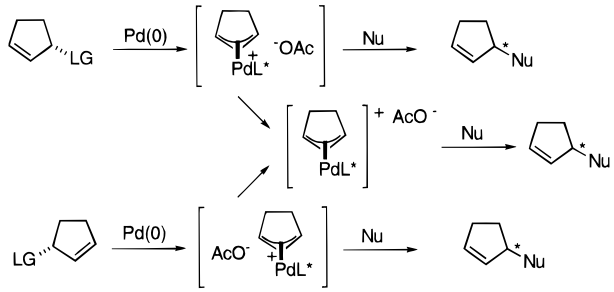


Figure 2. Substrate ion pair mechanism for asymmetric alkylation.

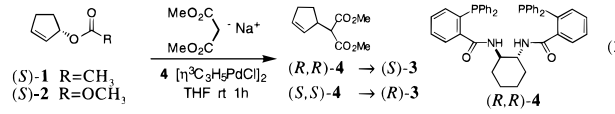
data needed to be normalized so that valid comparisons could be made. In doing so, it is convenient to refer to the enantiomeric ratio (er) of a reaction or a compound (defined here in matrix notation as [(*S*),(*R*)]. A reaction with an enantiomerically enriched starting material can be considered to proceed in two parts: the pure enantiomer and the racemate. The observed er of a reaction (er_{obs}) is then the average of the enantiomeric ratios for the pure enantiomer (er_{100}) and that of the racemate ($er_{\pm}$) weighted by the percentage of each present as stated mathematically in eq 1, which upon rearrangement of terms gives eq 2.

$$er_{obs} = (ee_{SM})(er_{100}) + (1 - ee_{SM})(er_{\pm}) \quad (1)$$

$$er_{100} = [er_{obs} - er_{\pm}(1 - ee_{SM})]/ee_{SM} \quad (2)$$

The terms on the right side of eq 2 can all be determined experimentally. Thus, eq 2 allows the er_{obs} for a reaction to be extrapolated to the er (er_{100}) that would have been obtained if the starting material had been enantiomerically pure (see supporting information for a sample calculation). Alkylations of racemates (±)-**1** and (±)-**2** with (*R*,*R*)-**4** under the same conditions as shown in eq 3 were performed to obtain a value for $er_{\pm}$ for each substrate: [67,33] for (±)-**1** and [69,31] for (±)-**2**. The values used for $er_{\pm}$ for each substrate with (*S*,*S*)-**4** were assumed to be the opposite of those obtained with (*R*,*R*)-**4** since they proceed through enantiomeric transition states (even in a postulated ion pair mechanism).

Using samples of (*S*)-**1** of 44% and 55% ee, asymmetric alkylations were performed with both (*R*,*R*)-**4** and (*S*,*S*)-**4** in THF as outlined in eq 3.[1b]



The ee's were determined by the combination of optical rotation data and ^{1}H NMR chiral shift studies. The value for $[\alpha]_D$ max of −85.2° was obtained from an extensive series of ^{1}H NMR chiral shift studies with Eu((+)-hfc)$_3$ (see supporting information for data and sample spectra). Both the original enantioselectivity data and the data extrapolated to 100% ee starting material via eq 2 are shown in Table 1 ((*R*,*R*)-**4**) and Table 2 ((*S*,*S*)-**4**). Comparing both the raw and normalized data, it is apparent that (*S*)-**1** forms a *matched* pair with (*R*,*R*)-**4** and a *mismatched* pair with (*S*,*S*)-**4** of fairly modest, but measurable magnitude.

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(4) (a) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46. (b) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley & Sons: New York, 1974; Vol. 1, Chapter 3. (c) Kantner, S. S.; Humski, K.; Goering, H. L. *J. Am. Chem. Soc.* **1982**, *104*, 1693. (d) Gallina, C. *Tetrahedron Lett.* **1985**, *26*, 519. (e) Gassman, P. G.; Singleton, D. A.; Kagechika, H. *J. Am. Chem. Soc.* **1991**, *113*, 6271.

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(6) The ee of this reaction with the simple five-membered-ring substrate in contrast to this reaction with other ring sizes is known to be extremely sensitive to temperature. On a larger scale, the internal reaction temperature may not have been rigorously maintained at −78 °C as required for this substrate.

(7) Optical rotation data for the acetate (*S*)-**1** was in agreement with the ee determined from the mandelate ester. See: Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721.

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Table 1. Alkylations of (*S*)-**1** with (*R,R*)-**4**

ee_{SM} (‰)	yield (%)	ee_{obs} (%)	er_{obs}	ee_{100} (%)	er_{100}
44	63	44	72:28	56	78:22
55	69	45	73:27	54	77:23
55	61	52	76:24	66	83:17
55	71	45	73:27	54	77:23

Table 2. Alkylations of (*S*)-**1** with (*S,S*)-**4**

ee_{SM} (%)	yield (%)	ee_{obs} (%)	er_{obs}	ee_{100} (%)	er_{100}
44	35	27	37:63	16	42:58
55	77	31	34:66	28	36:64
55	67	34	33:67	34	33:67
55	79	34	33:67	34	33:67

Table 3. Alkylations of (*S*)-**2**[a]

ligand	yield (%)	ee_{obs} (%)	er_{obs}	ee_{100} (%)	er_{100}
(*R,R*)-**5**	86	45	73:27	50	75:25
	75	50	75:25	56	78:22
(*S,S*)-**5**	88	29	35:65	24	38:62
	91	33	33:67	32	34:66

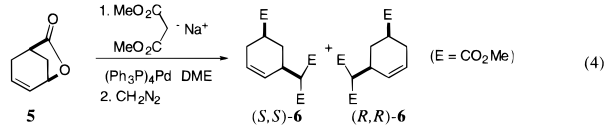
[a] The starting material was of 64% ee (ee_{SM}).

Since ion pairs are proposed to be involved in this phenomenon, changing the leaving group from acetate to carbonate might be expected to have an effect. However, when (*S*)-**2** of 64% ee was employed as the starting material under otherwise identical conditions as before, a similar matched/mismatched pair was observed with the two enantiomers of the chiral ligand (see Table 3). This finding stands in contrast (though not contradiction) to results for the palladium-catalyzed addition of sodium benzenesulfinate to certain allylic substrates in which the acetate and carbonate leaving groups gave rise to products with different ee's.[8] Hence, a fine balance must exist between the rates of asymmetric ion pair relaxation to a *meso* intermediate and nucleophilic addition, both of which can be functions of the leaving group and the nucleophile.

In all these cases, the matched product ((*S*)-**3** from (*S*)-**1** or (*S*)-**2** with (*R,R*)-**4**) has an absolute configuration which appears to be a direct replacement of the starting material stereochemistry.[9] This retention of absolute stereochemistry could be explained by a Coulombic attraction between the negatively charged leaving group (acetate or carbonate) and the positively charged counterion of the nucleophile. If the initially formed π-allyl/leaving group ion pair were asymmetric due to the configuration of the starting material, then nucleophilic addition would show a preference for attack at the position formerly occupied by the leaving group (α substitution in the nomenclature typically employed with allylic substitutions).

Although (σ-allyl)palladium species are known to account for the racemization of some chiral π-allyl complexes and *syn*−*anti* interconversion of substituents,[10] considerable evidence suggests that they cannot be alkylated before isomerizing to the π-allyl intermediate. ^{1}H NMR and product distribution evidence indicates that the π-allyl species is the predominant and reactive intermediate present in solution.[11] The rate of alkylation of chiral aryl substituted (π-allyl)palladium intermediates has been determined to be 10^1-10^2 times slower than the rate of racemization,[12] which in turn must be slower than the rate of $\sigma-\pi$ isomerization. For alkyl-substituted π-allyl intermediates, alkylations with optically active substrates capable of racemizing through a $\pi-\sigma-\pi$ mechanism were found to retain optical activity in the product only when alkylated with a preformed, intramolecular nucleophile.[13] Thus, alkylation of an incipient chiral, (σ-allyl)palladium species before loss of stereochemical memory occurred via isomerization to a π-allyl intermediate is not a likely explanation for the apparent memory effect in asymmetric alkylation reactions.

The invoking of a nonsymmetrical intimate ion pair nicely accounts for the apparent dichotomy of the earlier results of Fiaud[2] and ourselves.[3] Fiaud's reactions all dealt with alkylations involving a dissociated leaving group (acetate), whereas, in our case, the leaving group was tethered to the substrate as in eq 4. The tethering of the leaving group geometrically



5 (*S,S*)-**6** (*R,R*)-**6** (4)

constrains it to lie in the plane of symmetry of the resulting (π-allyl)palladium cationic intermediate thereby making it truly *meso*. Thus, a memory effect was precluded in this case. A mechanism involving the formation of and partial nucleophilic addition to an initial asymmetric ion pair (see Figure 2) is consistent with the results of Fiaud, the alkylation reaction of **5**, the present results, and the findings from other studies of asymmetric (π-allyl)palladium catalysis.[1b,14]

These results have important ramifications in seeking asymmetric induction in metal-catalyzed allylic alkylations. While the effect is modest, the results indicate a propensity for racemic substrates to give racemic products regardless of the ligand because of the nature of the initial ion pair. To optimize asymmetric induction, reaction parameters that favor symmetrization of the ion pair will be needed. It does not mean that the intervention of such intermediates will always have an observable effect on the observed enantioselectivity since it depends upon the rate of equilibration of intimate ion pairs or of symmetrization to solvent-separated ion pairs relative to nucleophilic attack. An observable effect will depend upon the specific reaction being investigated. Thus, in any case where enantioselectivity is independent of the configuration of the starting allylic ester, this simply may mean that nucleophilic attack is slow relative to these equilibrations. Further investigations of this surprising and interesting phenomenon are certainly warranted and are underway.

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Supporting Information Available: Experimental alkylation procedure, chiral shift and optical rotation data, sample spectra, and a sample calculation (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(9) Note that a change in the Cahn−Ingold−Prelog priority rules may in some cases cause the (*R*) or (*S*) nomenclature to change irrespective of this retention of configuration.

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(14) For products where rotation data can now be compared to the Fiaud results, the retained or differential ee's are in the range 5−20%. See: Helmchen, G.; Gabler, B.; Sennhenn, P. *Tetrahedron Lett.* **1994**, *35*, 8595.

(15) For an example, see: von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuberger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.