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CHIRALITY TRANSFER FROM C-O TO C-C IN THE PALLADIUM CATALYZED ScN' REACTION OF (E)- AND (Z)-ALLYLIC CARBONATES WITH CARBONUCLEOPHILE

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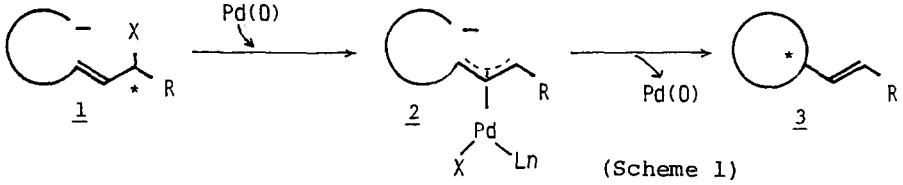
Summary: Very efficient intramolecular chirality transfer has been achieved in reactions of the (E)- and (Z)-allyl carbonates **10** and **14** by using Pd(0) and the bicyclic phosphite **11** and phosphine **13** as the catalyst. Reactions of **10** and **14** in the presence of **11** and a base gave the (3R)-lactones **12** and (3S)-**12**, respectively, with 96% and 94% chirality transfer. While the reactions using **13** in the absence of a base gave (3R)-**12** and (3S)-**12** with 90% and 65% chirality transfer.

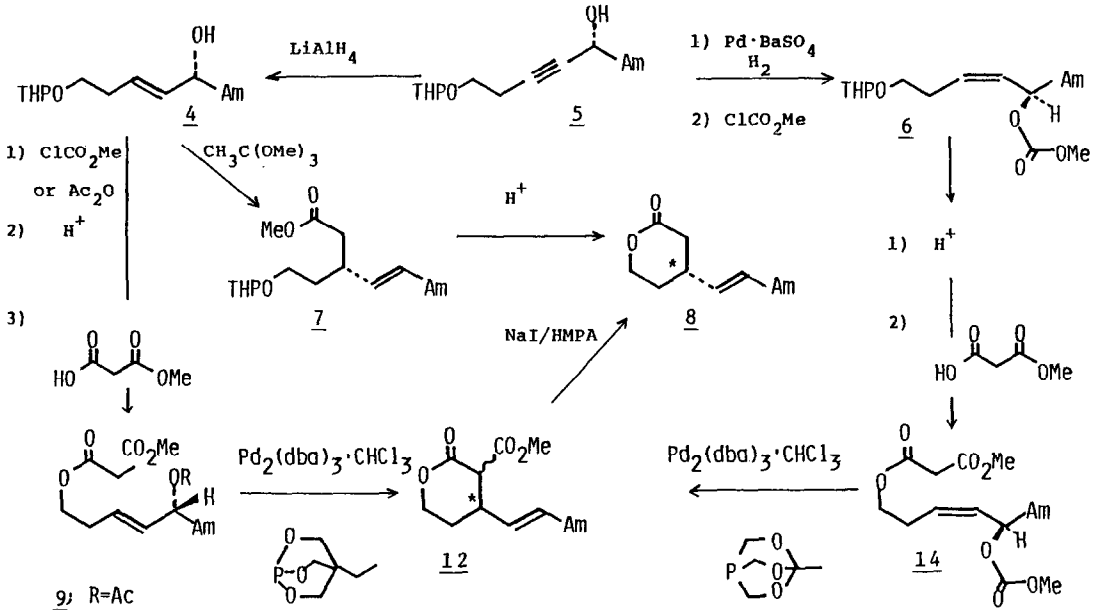
Palladium-catalyzed inter- and intramolecular alkylations involving various allylic compounds are useful for synthesis of highly functionalized compounds, particularly when chirality transfer is possible.[1] Earlier studies on the palladium-catalyzed allylation indicate that both the oxidative addition of Pd(0) to the allylic compound (1→ 2) and the alkylation of nucleophile with π-allylpalladium (2→ 3) (Scheme 1), proceed with inversion of the stereochemistry. It is also known by NMR study of π-allylpalladium that the isolated 1,3-unsymmetrically substituted π-allyl systems such as **2** never racemize and only undergo epimerization via π-σ-π mechanism.[2] However no report dealing with mechanism of the racemization of π-allylpalladium **2** during the alkylation has appeared.



(Scheme 1)

We report here efficient chiral cyclizations of methyl (5R)-methoxycarbonyloxy-(3E)-decenyl malonate (**10**) and its (Z)-isomer **14** by using $Pd_2(dba)_3.CHCl_3$ and the bicyclic phosphite **11** and phosphine **13** as the catalyst. We observed crucial effects of a base and concentration of the palladium catalyst on the optical yield in these reactions. Success of the complete chirality transfer requires (1) stereoselective oxidative addition, (2) no racemization of π-allylpalladium, (3) regioselective, and (4) stereoselective alkylation. So far items (1) and (4) have been cleared, and the regioselection can

be solved by an intramolecular alkylation, since the formation of 5- and 6-membered rings is much faster than the formation of 7- and 8-membered rings.[3] Thus the racemization process depends upon the stability of π-allylpalladium **2**. The loss of enantiomeric (or diastereomeric) purity of π-allylpalladium has been observed when the leaving group was acetate.[4] This was explained by the cis attack of acetate anion, formed at oxidative addition step, perhaps by prior coordination with metal. Palladium catalyzed allylations with allylic carbonates[5] and 1,3-diene monoepoxides[6] are different from allylation with allylic acetates, and this type of racemization is impossible since the alkoxide anion formed by the oxidative addition and decarboxylation does not act as a nucleophile, but acts as a base to remove an acidic proton from nucleophiles.



(Scheme 2)

(Table 1)

No	Substrate	Ligand, Base	Time	Pd(0) mol %	Yield of 12	$[\alpha]_D^{25}$ of 8	Chirality Transfer
1	9	11, NaH	3 hr	10	72 %	+10.0 (R)	75 %
2	10	11, –	20 min	20	71	+ 5.4 (R)	41
3	10	11, –	30 min	10	62	+ 7.7 (R)	58
4	10	11, –	70 min	3	88	+10.4 (R)	78
5	10	11, NaH	10 min	10	53	+12.8 (R)	96
6	10	13, –	3 hr	10	65	+12.0 (R)	90
7	10	13, NaH	90 min	10	65	+13.3 (R)	100
8	14	11, –	30 min	10	67	- 7.3 (S)	55
9	14	11, NaH	10 min	10	63	-12.5 (S)	94
10	14	13, –	3 hr	10	73	- 8.6 (S)	65
11	14	13, NaH	90 min	10	68	-13.2 (S)	99

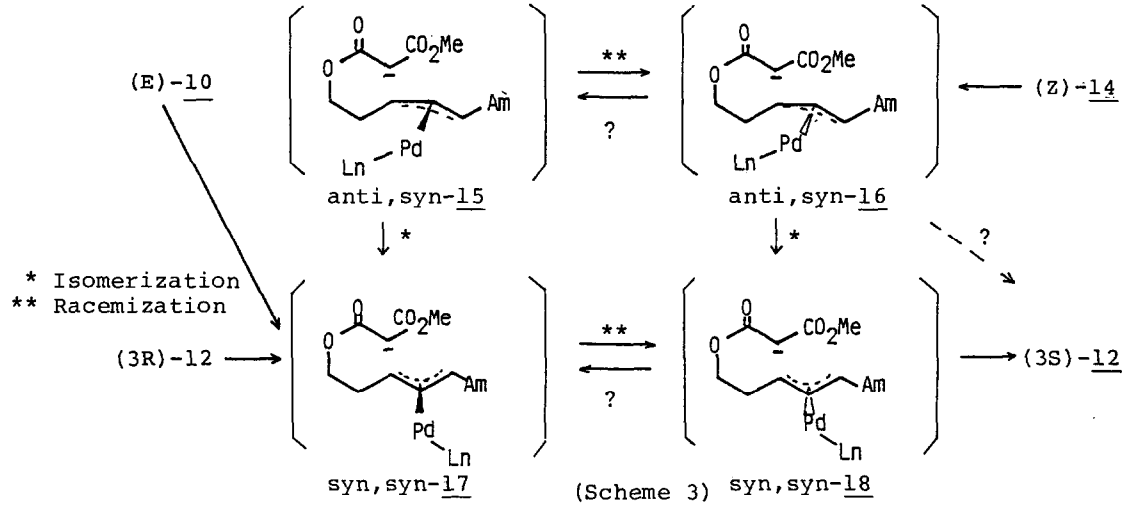
Starting materials **9**, **10**, and **14** were prepared from (5R)-alcohol **5** (61% ee), which was obtained by the asymmetric reduction of the corresponding ketone (Scheme 2). The authentic (3R)-lactone **8** (61% ee $[\alpha]_D$ +13.3, c=1.3, $CHCl_3$) was synthesized by the known stereoselective Claisen rearrangement of **4**, followed by lactonization of **7**. Claisen rearrangement of **4** should proceed with higher than 96% stereoselectivity based on the Chain's result.[7] The degrees of chirality transfer in the palladium catalyzed cyclization were determined by comparison of $[\alpha]_D$ values with that of the authentic (3R)-**8**.

A typical procedure for the cyclization is as follows. A catalyst solution was prepared by mixing $Pd_2(dba)_3.CHCl_3$ and three equivalents of phosphite **11** or phosphine **13** in DMSO for 30 min at 40 °C. To the catalyst solution, a DMSO solution of the ester without base (procedure A), or a THF solution of the ester and NaH (procedure B), was added dropwise at 40 °C. The absolute stereochemistry and the optical purity of the cyclized product **12** were determined by conversion to the lactone **8**.

Results are summarized in Table 1. The following characteristics are derived from these cyclizations. (1) The allylic carbonate moiety of **10** is the better leaving group than the corresponding allylic acetate in the procedure B for the oxidative addition and also the chirality transfer (No 1, 5). (2) In the presence of a base (procedure B), cyclizations of (E)-allylic carbonate **10** and (Z)-isomer **14** proceed with higher than 94% chirality transfer, regardless of ligand (No 5, 7, 9, 11). (3) In the absence of a base (procedure A), cyclizations of (E)-allylic carbonate **10** and (Z)-isomer **14** give generally lower degree of chirality transfer than that in the procedure B (No 3 vs 5, 6 vs 7, 8 vs 9, 10 vs 11). (4) The degree of chirality transfer depends on the concentration of palladium; the higher concentration gives the lower optical yield (No 2, 3, 4).

Results of these reactions can be rationalized by the following mechanism (Scheme 3). The stable syn,syn complex **17** having the phosphine as the ligand, formed from (E)-**10** with inversion by oxidative addition, is quite stable and the following alkylation proceeds from the opposite side of palladium to give (3R)-**12** (No 6). The same complex **17** having the phosphite instead of the phosphine, however, partially racemizes to the syn,syn **18** to give a mixture of (3R)- and (3S)-**12** in the procedure A (No 3). Similarly in the procedure A, the less stable anti,syn-**16** having phosphine or phsophite as ligand, generated from (Z)-**14**, partially racemizes to the stable syn,syn-**17** via complex **15** or **18** (No 8, 10). On the other hand, in the procedure B the syn,syn-**17** and anti,syn-**16** were alkylated, regardless of ligand, with less racemization to give (3R)-**12** and (3S)-**12**, respectively (No 5, 7, 9, 11). Thus prior formation (procedure B) or posterior formation (procedure A) of the anion of nucleophile to the generation of π-allylpalladium complex has influenced on the optical yields, i.e. racemization process. One rational explanation for the racemization of **17** to **18** or **16** to **15** is that π-allylpalladium is displaced from the opposite side of complex by Pd(0) present in the reaction medium, as a strong nucleophile, with

inversion of stereochemistry. Faller[2a] and Bosnich[2b] have discussed the rapid epimerization of the less stable anti,syn π-allylpalladium complexes such as **15** and **16** to the corresponding stable syn,syn complexes **17** and **18** via π-σ-π interconversion. But this may not always be so. The difference of the optical yield in cyclizations of (E)-**10** and (Z)-**14** in the presence of phosphite (No 6, 10) indicated that the π-σ-π isomerization was not always faster than the nucleophilic attack of π-allylpalladium complex by Pd(0) or carbonucleophile.



(Scheme 3)

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