STEREOSPECIFICITY IN THE CARBOPALLADATIONS OF CHIRAL ALLENES FOLLOWED BY INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION REACTIONS

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Abstract —2-Halophenyl derivatives bearing nucleophilic centers at the appropriate sites reacted with chiral allenes under palladium-catalyzed reaction conditions, *via* carbopalladation followed by intramolecular nucleophilic substitution, to give heterocycles or carbocycles by selecting nitrogen anions or carbanions as nucleophiles, respectively. The stereospecificity in these conversions of chiral allenes into cyclic compounds was determined by HPLC analysis with chiral column, and the mechanistic pathway in this transformation is rationalized on the basis of the stereochemistry of the similar intermolecular reaction process which was already established by us.

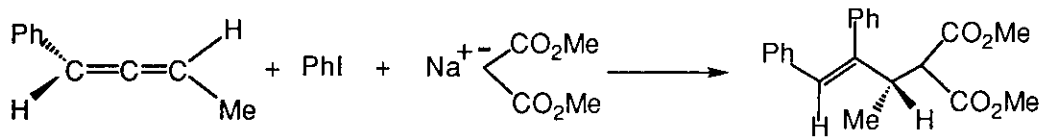
Axial chirality has received much attention for the stereochemically characteristic behavior in various types of the reactions, and currently many methodologies of asymmetric synthesis using the chirality as the starting chiral source are reported.[1] In particular, chirality of allene compounds has aroused much interest for the preparation of optically active compounds in organic synthesis, and the increasing usefulness of them as three-carbon units in organic synthesis has been demonstrated especially in the field of palladium chemistry.[2]

We wish to communicate herein enantiospecificity in the formation of heterocycles and carbocycles by palladium-catalyzed reactions of chiral allenes *via* carbopalladations followed by intramolecular nucleophilic substitutions.

In general, allenes provide π-allylpalladium complexes by the β-functionalization of allenes with aromatic or olefinic halides under palladium-catalyzed reaction conditions, the reactions of which with nucleophiles lead to the facile direct conversion into α,β-difunctionalized products.[3] Namely, α-aryl olefins or 1,3-dienes are prepared directly from allenes by this simple one-pot reaction process.

Likewise, palladium-catalyzed reactions of allenes with iodobenzenes or vinyl halides bearing nucleophilic parts in appropriate sites afford heterocycles or carbocycles by selecting nitrogen anions or carbanions as nucleophiles.[4]

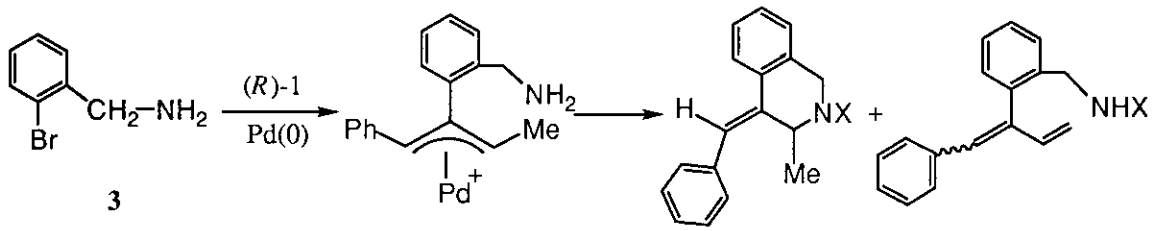
The palladium-catalyzed reaction of a chiral allene ((*R*)-**1**) with iodobenzene and sodium malonate as a nucleophile provided (*S*)-**2** with complete stereospecificity, and the stereochemistry of the reaction was already established by us.[5] Successively, we have taken much interest in the enantiospecificity of the palladium-catalyzed intramolecular reactions of chiral allenes in the silimar reaction proceeding.



(*R*)-**1** (*S*)-**2**

Scheme 1

The palladium-catalyzed reaction of allene ((*R*)-**1**) with 2-bromobenzylamine (**3**) was carried out in refluxing THF in the presence of $Pd(dba)_2$ (0.05 equiv.) and triphenylphosphine (PPh_3) (0.10 equiv.) using NaH or Et_3N (1.5 equiv.) as base to give products (**4a**) and (**5a**), which were identified as the corressponding acetamides (**4b**) (6 % yield from (*R*)-**1**) and (**5b**) (21 % yield from (*R*)-**1**).



3

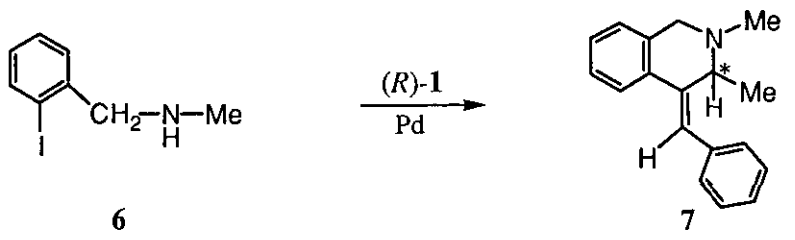
4a X= H
b = Ac

5a X= H
b = Ac

Scheme 2

The palladium-catalyzed reaction of an optically pure allene ((*R*)-**1**) with *N*-methyl-2-iodobenzylamine (**6**) was carried out under the same reaction conditions as described above to afford optically active cyclized product, tetrahydroisoquinoline derivative (**7**) with slightly low enantiomeric excess (e.e.), along with the recovered starting materials (about 30%). The e.e of the product (**7**) was determined by HPLC analysis with SUMICHIRAL OA-4800. The stereospecificity in the transformation of (*R*)-**1** into **7** was obtained on the basis of the e.e. of the product (**7**), and is summarized in Table 1.

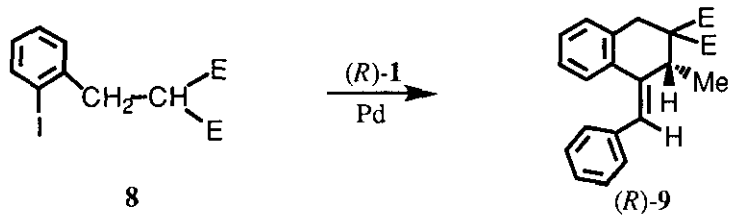
The reactions of (*R*)-**1** under heating in toluene or DMF provided (±)-**7**: the chirality of the allene was almost completely lost under the reaction conditions.



6 7

Scheme 3

Similarly, the intramolecular reactions of (*R*)-**1** with carbonucleophile were successfully achieved. The palladium-catalyzed reaction of an optically pure allene ((*R*)-**1**) with dimethyl (2-iodobenzyl)-propanedioate (**8**) sodium enolate (generated by treating with NaH) was carried out in refluxing THF in the presence of $Pd(dba)_2$ (0.05 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (0.10 equiv.) to give cyclized product, tetralin derivative ((*R*)-**9**) with 50 % e.e. The e.e. of the product was determined by HPLC analysis with SUMICHIRAL OA-3100. The absolute configuration of the product (**9**) was deduced by the mechanism proposed on the basis of the intermolecular results. The results obtained under other reaction conditions are summarized in Table 1.



8 (*R*)-9

Scheme 4

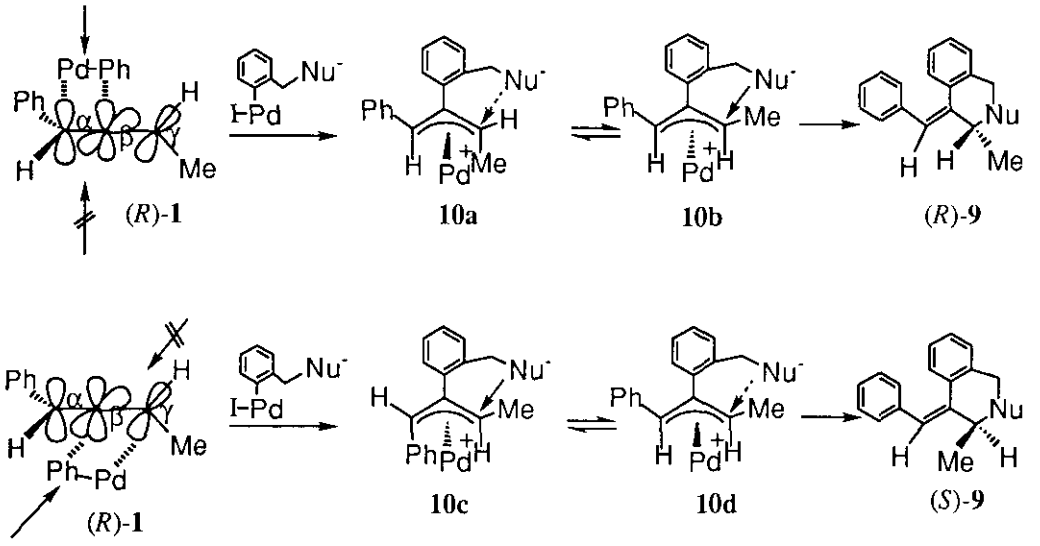
Table 1. Stereospecificity in the Synthesis of Heterocycle (**7**) and Carbocycle (**9**) by the Palladium-catalyzed Reactions of (*R*)-**1**[a)]

Reactant	Solvent	Reaction temp.(°C)	Reaction time (h)	Product	Yield (%) of product	e.e. (%) of product[d)]
6	THF[b)]	66	12	**7**	9	56
	THF	66	12	**7**	18	46
	DME[b)]	85	12	**7**	8	31
	DME	85	12	**7**	30	28
	MeCN	81	12	**7**	24	13
8	THF	66	18	**9**	61	50
	THF[c)]	66	18	**9**	68	35
	DME	85	18	**9**	63	34

a) The reactions of (*R*)-**1** with **6** or **8** (sodium enolate was generated by treating with NaH (1.2 equiv.)) were carried out in the presence of $Pd(dba)_2$ (0.05 equiv.), PPh_3 (0.10 equiv.) [or dppf (0.05 equiv.) for **8**] and Et_3N (1.5 equiv.) for **6**.
b) Reacted without Et_3N.
c) Reacted in the presence of Ag_2CO_3 (1.2 equiv.).
d) The e. e. of the product was determined by HPLC analysis with SUMICHIRAL OA-4800 for **7**, or with OA-3100 for **9**.

The geometry of the olefinic parts in the products (**7**) and (**9**) was established as *E* and *Z*, respectively, by the NOE observation in the NMR spectral analysis; the NOE was observed between both the hydrogen and the methyl groups at the C_3 chiral center, and the phenyl group in **7**, or the olefin hydrogen in **9**.

The mechanism of the carbopalladation of a chiral allene and the subsequent intramolecular nucleophilic substitutions is rationalized on the basis of the stereochemistry of the similar reaction proceeding with the intermolecular nucleophilic substitution, which was already established by us.[5] The initially-formed aromatic palladium iodide would attack to the phenyl-substituted carbon-carbon double bond (Ph-C=C) preferentially from the upward hydrogen (Cγ) side due to the steric interference by the methyl group at Cγ, as designated in Scheme 5, to give a rather stable π-allylpalladium complex (**10a**) which would be converted at equilibrium into the more stable π-allyl isomer (**10b**). The intramolecular nucleophilic substitution in **10a** and, or **10b** from the back side of the palladium catalyst would occur at the sterically less-crowded part (Cγ) to produce (*R*)-**9**. Similarly, in the reaction with the methyl-substituted carbon-carbon double bond (Me-C=C) in (*R*)-**1**, the aromatic palladium iodide would access to the double bond preferentially from the front hydrogen (Cα) side, due to the steric interruption by the phenyl group at the back side, to yield a π-allylpalladium complex (**10c**), which has rather severe steric hindrance between the phenyl (Cα) and the hydrogen (Cγ) groups in the allyl system and accordingly would be equilibrated into the more stable π-allylpalladium complex (**10d**). The intramolecular nucleophile would react at the sterically favored Cγ position from the back side of the palladium catalyst in **10d** to give (*S*)-**9**.



Scheme 5

The rather low stereospecificity in these intramolecular palladium-catalyzed reactions indicates that presumably both of the two pathways described above might proceed rather competitively in contrast with the intermolecular reactions, providing preferablly (*R*)-**9** owing to the steric reasons, the favorable formation of **10a** in preference to **10c**, as mentioned above.

The great difference in the geometry of the olefins between products (**7**) and (**9**) is rationalized as follows. The carbonucleophile would react at the allylic site (Cγ) in the π-allylpalladium complex, rather immediately before the complete equilibration is attained in allylic system, at the initial stage of the formation of the stable π-allyl isomer (**10a**) because of the considerably high reactivity of the nucleophilic center.

However, since the nitrogen anion is a slightly less reactive species, the reactions with it would occur after the complete equilibration in π-allyl systems would be established, and thereby (*E*)-isomer was prepared preferentially.

Thus, the palladium-catalyzed synthetic methods with chiral allenes *via* carbopalladation followed by intramolecular nucleophilic substitutions provided a facile entry to chiral heterocycles and carbocycles with slightly low enantiospecificity.

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