Asymmetric Induction in the Palladium-catalyzed Nucleophilic Substitution Reactions of Chiral β-Sulfinylallylic Systems

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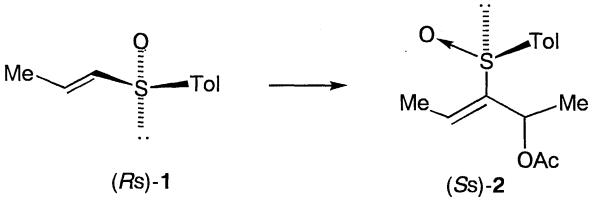
The first example of the palladium-catalyzed asymmetric nucleophilic substitutions of chiral β-sulfinylallylic systems is described. The degree of the asymmetric induction was dependent on the reaction conditions, especially a phosphine ligand used. The plausible mechanism of the asymmetric induction is proposed on the basis of the stereochemical results obtained.

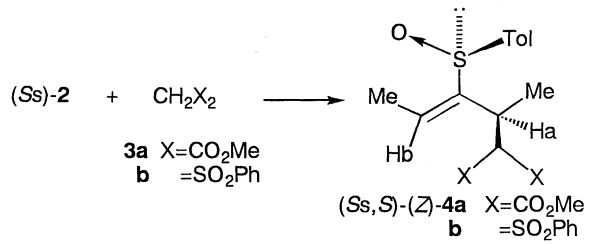
Recently the stereochemistry of palladium-catalyzed reactions of chiral allylic systems has been revealed by many investigators.[1] We have developed novel methodologies for asymmetric carbon-carbon bond formation with transition metal catalysts employing chiral allyl esters,[2] chiral enamines,[3] imines, or hydrazones bearing phosphine groups,[4] and intramolecular metallo-ene reactions of chiral allylic sulfones.[5] Furthermore, we have reported quite recently the stereochemistry of the transition metal-catalyzed transformations of chiral α-sulfinyl α-olefinic cyclopropane derivatives into cyclopentene compounds.[6] The reactions proceed via chiral π-allyl transition metal complexes bearing chiral sulfinyl groups at the α sites of π-allyl systems. We have taken much interest in the chemical reactivity of these complexes, the stereochemistry, and the asymmetric induction in the transition metal-catalyzed reactions of chiral α-sulfinyl-π-allylic systems. The results stimulate us to make further investigation on the reactions of chiral π-allyl transition metal complexes bearing chiral sulfinyl groups at the β sites of the allylic systems. Previously, few report has been published on reactions of π–allyl transition metal complexes bearing electron-withdrawing groups at the β sites. We wish to communicate the first example of the asymmetric nucleophilic substitution reactions of chiral β-sulfinyl-π-allylpalladium complexes, and disclose the stereochemistry of the reactions and the plausible mechanism of the asymmetric induction on the basis of the stereochemical outcome.

The model compound of a chiral β-sulfinyl allylic system, (*Ss*)-**2**, was readily obtainable from chiral vinylic sulfoxide (*Rs*)-**1** by treating of (*Rs*)-**1** with LDA followed by reaction with acetaldehyde and the subsequent acetylation. This compound (*Ss*)-**2** obtained above was confirmed to be a 1:1 diastereomeric mixture by the HPLC analysis.

The palladium-catalyzed reactions of (*Ss*)-**2** with dimethyl



Scheme 1.



Scheme 2.

malonate (**3a**) were carried out in THF at room temperature in the presence of $Pd(OAc)_2$ (0.1 equiv.) and a phosphine ligand (0.2 equiv.) using NaH (1.1 equiv.) as a base, giving (*Ss*,*S*)-(*Z*)-**4a**. The results using various phosphine ligands are summarized in Table 1. The diastereomeric excess (d.e.) of the product (*Ss*,*S*)-(*Z*)-**4a** was determined by the HPLC analysis. The structure of the phosphine ligand used was extremely effective on the asymmetric induction and the reactivity. The use of PPh_3 or dppm as a ligand produced (*Ss*,*S*)-(*Z*)-**4a** in a very poor yield with low d.e.. However, the use of other phosphine ligands such as dppe, dpppropane, dppb, dpppentane, dpph, and dppf improved the chemical and optical yields remarkably. The highest optical yield (79%) of (*Ss*,*S*)-(*Z*)-**4a** was obtained on the use of dpph as a ligands, as indicated in Table 1. The (*Z*)-configuration between the *p*-toluenesulfinyl group and the methyl substituent at the olefinic site was determined by the NMR analysis: a NOE was observed between the olefinic hydrogen (Hb) and the hydrogen (Ha) at the chiral center, whereas no NOE was observed between the methyl group at the olefinic site and the hydrogen (Ha). The absolute configuration of the newly created asymmetric carbon in the product **4a** was determined as (*S*)-configuration by the chemical correlation of the product **4a** to

Table 1. The palladium-catalyzed asymmetric substitution reactions of (*Ss*)-**2** with **3a**[a]

Ligand	Reacion time/h	Yield of (*Ss*,*S*)-**4a**/%	d.e. of (*Ss*,*S*)-**4a**/%[b]
PPh_3	12	11	4
dppm	3	9	39
dppe	3	77	29
dppe	12	32	29
dpppropane	3	84	45
dppb	3	63	57
dpppentane	3	63	67
dpph	3	79	79
dppf	3	47	51

[a] The reactions of (*Ss*)-**2** with **3a** were carried out in THF at room temperature in the presence of $Pd(OAc)_2$ (0.1 equiv.) and a ligand (0.2 quiv.) using NaH (1.1 equiv.) as a base.

[b] The d.e. of the product (*Ss*,*S*)-**4a** was determined by HPLC analysis.

Table 2. The palladium-catalyzed asymmetric nucleophilic substitution reactions of (*Ss*)-**2** with **3b**[a]

Catalyst	Ligand	Yield of (*Ss*)-**4b**/%	d.e. of (*Ss*)-**4b**/%[b]
$Pd(OAc)_2$	PPh_3	51	40
$Pd_2(dba)_3\ CHCl_3$	PPh_3	10	26
$Pd(OAc)_2$	dppm	67	56
$Pd(OAc)_2$	dppe	41	43
$Pd(OAc)_2$	dpppropane	41	48
$Pd(OAc)_2$	dppb	53	62
$Pd(OAc)_2$	dpppentane	28	57
$Pd(OAc)_2$	dpph	33	56

[a] The reactions of (*Ss*)-**2** with **3b** were carried out under refluxing in THF for 2 h in the presence of a catalyst (0.1 equiv.) and a ligand (0.2 equiv.) using NaH (1.1 equiv.) as a base.

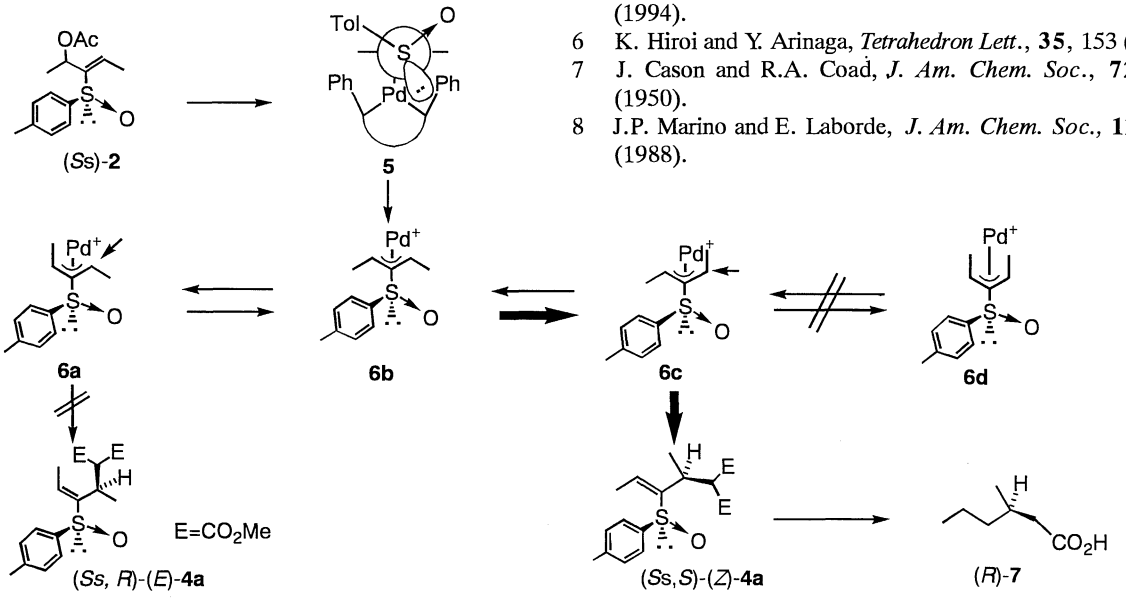
[b] The d.e. of the product (*Ss*)-**4b** was determined by HPLC analysis.

(*R*)-3-methylhexanoic acid (**7**)[7] by reductive desulfenylation with Raney Ni and hydrolytic decarboxylation with 10% aqueous HCl.

Similarly, asymmetric induction in this system was observed on the use of bis(phenylsulfonyl)methane (**3b**) as a nucleophile, even though a little higher reaction temperature was required in this case. The reactions of (*Ss*)-**2** with **3b** were carried out under refluxing in THF using $Pd(OAc)_2$, $Pd(dba)_2$, $Pd(dba)_3 \cdot CHCl_3$ or $Pd(PPh_3)_4$ as a catalysts, to give (*Ss*)-**4b**. The results are summarized in Table 2. The reaction of (*Ss*)-**2** with **3b** did not occur by the catalysis with $Pd(PPh_3)_4$ or $Pd(dba)_2-PPh_3$ (at room temperature or under refluxing in THF), and the starting (*Ss*)-**2** was recovered. The highest d.e. (62%) of (*Ss*)-**4b** was obtained by using $Pd(OAc)_2$ and dppb. The chemical yield of (*Ss*)-**4b** was a little lower, compared to that of (*Ss,S*)-**4a**, because of the steric bulk of the nucleophile.

The mechanism of the asymmetric induction in the palladium-catalyzed reaction of (*Ss*)-**2** with sodium enolate of **3a** was rationalized on the basis of the stereochemical results observed. It was confirmed by the HPLC analysis of the starting (*Ss*)-**2** recovered before completion of the reaction that the asymmetric carbon center at the allylic site in (*Ss*)-**2** used was still remained racemic during the course of the reaction. This means that this asymmetric substitution reaction was not resulted by kinetic resolution. Therefore, the initial attack of the palladium catalyst to the allylic system **2** would be underwent by the steric effect of the chiral sulfinyl group in (*Ss*)-**2**, without any steric control of the asymmetric carbon center at the allylic site. The palladium catalyst would be reacted from the sterically less crowded downward direction of the lone pair side of the chiral sulfinyl group in the conformationally most stable form of (*Ss*)-**2** (shown in Scheme 3) having *syn*-coplanarity between the sulfur-oxygen bond and the carbon-carbon double bond of the chiral vinylic sulfoxide,[8] to form a π-allylpalladium complex **5**. Among the geometrical isomers **6a-d** of the π-allylpalladium complex, the isomers **6b,d** might be almost nonexistent, because of the steric interference between the tolyl and sulfinyl oxygen groups and the two dimethyl groups. Based on the stereochemistry of the product, it might be most reasonable that the reaction would proceed by the alkylation of **6c** from the back side direction to the palladium catalyst, to give (*Ss,S*)-(*Z*)-**4a**. Presumably, the reaction of the nucleophile at **6c** would be sterically more preferred to that at **6a**.

Thus, chiral sulfinyl groups at the β sites in allylic systems represented asymmetric induction in the palladium-catalyzed nucleophile substitution reactions. This is the first example for asymmetric induction reactions *via* π-allyl transition metal complexes bearing chiral sources at the β sites.



Scheme 3.

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