Organosulfur Functionality as an Alternative Enantiocontrollable Coordinating Element in Chiral Phosphine Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylations

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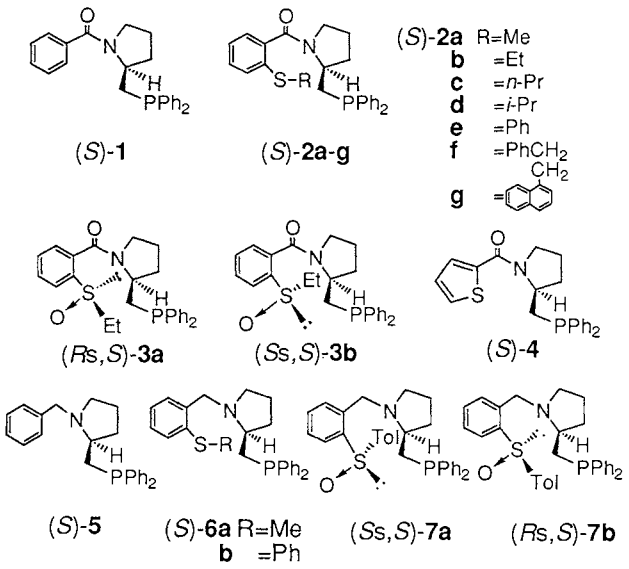
The synthesis of (*S*)-proline-derived phosphines bearing organosulfur groups and the use of them as chiral ligands in palladium-catalyzed asymmetric allylic alkylations were accomplished successfully. The mechanism is discussed on the basis of the stereochemical results, presumably by participation of organosulfur groups as alternative enantiocontrollable coordinating elements.

Increasing usefulness of a catalytic asymmetric synthesis[1] has been demonstrated for the synthesis of optically active compounds, particularly biologically active chiral compounds in the pharmaceutical fields, and resultingly, the development of new efficient chiral ligands has received much attention.[2] We wish to communicate herein new chiral phosphine ligands with organosulfur functionality as an alternative stereocontrollable coordinating element, and demonstrate their usefulness in palladlum-catalyzed asymmetric synthesis by the stereoelectronic assistance of organosulfur functionality.[3] We wish also to reveal the mechanism for the asymmetric induction, focused on the structure of the intermediary palladium complexes with the chelation by the phosphino and organosulfur groups.

Chiral amide ligands (*S*)-**2a-g** and (*Rs, S*)-**3a** and (*Ss, S*)-**3b** were prepared by acylation of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine[4] with 2-(sulfenyl or sulfinyl)benzoic acids using dicyclohexylcarbodiimide (DCC), which were obtainable by S-alkylation of 2-mercaptobenzoic acid using sodium hydride (followed by oxidation with *m*-chloroperbenzoic acid for **3a, b**). A thiophen ligand (*S*)-**4** was synthesized in a similar way by acylation with 2-thiophencarboxylic acid using DCC. The amino phosphines, (*S*)-**6a, b** and (*Ss,S*)-**7a** and (*Rs,S*)-**7b**, were prepared by lithiation of (*S*)-*N*-(2-bromobenzyl)-2-(diphenylphosphinomethyl)pyrrolidine with *n*-butyllithium followed by sulfenylation with dimethyl or diphenyl disulfide, or sulfinylation with (-)-menthyl (*S*)- or (*R*)-*p*-toluenesulfinate, respectively.

These chiral ligands obtained above were applied to palladium-catalyzed asymmetric alkylations of 1,3-diphenyl-2-propenyl acetate (**8**) with dimethyl malonate. The reactions of **8** with dimethyl malonate (3.0 equiv.) under the conditions with *N,O*-bis(trimethylsilyl)acetamide (BSA)[5] (3.0 equiv.) and a catalytic amount of NaOAc were carried out in dichloromethane in the presence of [PdCl(π-allyl)]2 (0.03 equiv.) and chiral sulfenyl ligands **2a-d,f,g** (0.06 equiv.) to give an alkylated product (*S*)-**9**.[6] The enantiomeric excess (e.e.) of the product **9** was determined by HPLC analysis with Chiralpak AD.[6] The results obtained are summarized in Table 1. The Table shows that the more bulky sulfenyl substituents in (*S*)-**2a-g** provided the higher degree of the asymmetric induction in proportion to the steric bulk, except for (*S*)-**2d,e**. Interestingly, the same reaction using (*S*)-**1**, (*S*)-**2e**, or (*S*)-**4** as a ligand gave (*R*)-**9**.

These results indicate that the phenylsulfenyl or thiophen sulfur groups could not participate for the formation of a chelate of a palladium catalyst with the phosphine, because of the rather low coordination ability of the aromatic sulfenyl groups compared with other alkyl sulfenyl functions.



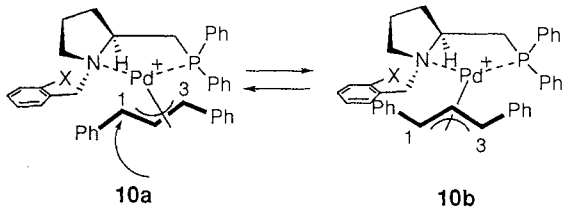
Scheme 1.

Scheme 2.

Introduction of a chiral sulfinyl functionality [(*Rs,S*)-**3a** and (*Ss, S*)-**3b**] in the system instead of the sulfenyl group presented a little lower enantioselectivity of (*S*)-**9** with different degree of the asymmetric induction depending on the diastereomers used, as listed in Table 1.

Comparatively, use of amino phosphines (*S*)-**5-7** as ligands in the above reaction provided (*R*)-**9**. These results indicate that the organosulfur functionality in (*S*)-**2a-d,f,g** and (*S*)-**3a,b** served as an alternative stereocontrollable coordinating element in the above palladium-catalyzed alkylation, whereas the same groups in (*S*)-**6,7** could not function as coordinating elements and instead, the amino nitrogen atoms would participate for the formation of five-membered chelates with the phosphine groups, as illustrated in Scheme 3.

The π-allylpalladium complex **10a** is preferred to **10b**, due to the steric interference between the pyrrolidine ring and the phenyl substituent at the C_1 allyl terminus in **10b**. The nucleophile attacks at the C_1 allyl terminus in **10a** *trans* to the better π-acceptor, which is the phosphine group in the current case, affording (*R*)-**9**.



Scheme 3.

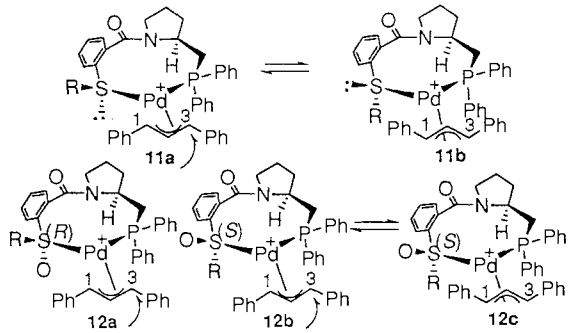
Table 1. The palladium-catalyzed asymmetric allylic alkylations of (±)-**8**[a]

Entry	Ligands	Reaction time/h	Yield/% of **9**	e.e/% of **9** [c]
1	(*S*)-**1**	14	69	42 (*R*)
2	(*S*)-**2a**	2	65	62 (*S*)
3	(*S*)-**2b**	3	72	72 (*S*)
4	(*S*)-**2c**	11	68	77 (*S*)
5	(*S*)-**2d**	16	54	31 (*S*)
6	(*S*)-**2e**	16	42	41 (*R*)
7	(*S*)-**2f**	8	76	84 (*S*)
8	(*S*)-**2g**	25	59	88 (*S*)
9	(*Rs*,*S*)-**3a**	24	72[b]	60 (*S*)
10	(*Ss*,*S*)-**3b**	50	51[b]	33 (*S*)
11	(*S*)-**4**	36	44	30 (*R*)
12	(*S*)-**5**	2	73	74 (*R*)
13	(*S*)-**6a**	40	76	82 (*R*)
14	(*S*)-**6b**	40	74	87 (*R*)
15	(*Ss*,*S*)-**7a**	18	69	59 (*R*)
16	(*Rs*,*S*)-**7b**	18	76	79 (*R*)

[a] The reactions of (±)-**8** with dimethyl malonate were carried out in dichloromethane at room temperature (except for entry 13-16 (at -20°C)) in the presence of BSA (3.0 equiv.), a catalytic amount of AcONa,[PdCl(π-allyl)]$_2$ (0.03 equiv.), and chiral ligands (0.06 equiv.). [b] Corrected yields based on the recovered starting materials. [c] The e.e. of the product **9** was determined by the HPLC analysis with Chiralpak AD.

With (*S*)-**2a-d,f,g** as ligands, presumably a nine-membered chelate would be formed by coordination of the organosulfur functionality and the phosphine group to the palladium catalyst. Inspection of a model of the nine-membered chelated intermediary palladium complex shows that an M-typed π-allylpalladium complex **11a** would be preferred to a W-typed complex **11b** in the conformational equilibrium of the rather flexible nine-membered chelated π-allylpalladium complex, due to the steric 1,3-diaxial-like interaction between the substituent on the sulfenyl group and the phenyl ring on the phosphine group in **11b**, as illustrated in Scheme 4. The nucleophile (malonate carbanion) would attack at the allyl terminus (C_3) in **11a** *trans* to the better π-acceptor, which is the sulfenyl group at the present case,[7] to furnish (*S*)-**9**. Increasing the size of the substituents on the sulfenyl groups resulted in enhanced enantiocontrol in the alkylation, presumably owing to the more selective alkylation at the C_3 site by the steric interference of the large substituent for the alkylation at the C_1. The rather low enantioselectivity obtained by (*S*)-**2d** is rationalized by the unaccessibility to the formation of the corresponding nine-membered chelate because of the steric effect by the secondary alkyl group on the sulfenyl sulfur atom.

Thus, the high level of the asymmetric induction presented by (*S*)-**2a-d,f,g** is rationalized by generation of another new chirality on the sulfenyl sulfur atoms in the formation of the intermediary nine-membered chelates. This rationalization is supported also by the results with diastereomeric chiral sulfoxides (*Rs*,*S*)-**3a** and (*Ss*,*S*)-**3b**. One of the diastereomers, presumably (*Rs*,*S*)-**3a**, presented the higher asymmetric induction than the other (*Ss*,*S*)-**3b**; namely (*Rs*,*S*)-**3a** would be a matched pair for the formation of the sterically favorable chelate (**12a**) in this palladium catalysis, whereas the other (*Ss*,*S*)-**3b** would be a mismatched one because of the sterical unaccessibility to the palladium catalyst for the formation of **12b,c**. In the confomational equilibrium of **12b,c**, the M-typed π-allylpalladium complex **12b** is slightly preferred to the W-typed one **12c** because of the steric interference between the two phenyl rings on the phosphine group and at the C_3 allyl terminus in **12c**. Therefore, the preferential alkylation occurs at the C_3 allyl terminus in **12a** or **12b**, *trans* to the better π-acceptor, which is presumably the sulfinyl group in this case,[3b] furnishing (*S*)-**9** with high or rather low enantioselectivity, respectively. The higher degree of the asymmetric induction with the sulfenyl ligands presumably arise also from the stronger coordination ability of the sulfenyl groups than the sulfinyl sulfur atoms.



Scheme 4.

Thus, conclusively, it is worth noting that the alkyl sulfenyl groups introduced in chiral phosphine ligands served as enantiocontrollable coordinating elements, providing extremely high enantioselectivity in the palladium-catalyzed asymmetric allylic alkylation.

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