Sterically Congested, "Roofed" β-Iminodisulfides as New Chiral Ligands for Palladium-Catalyzed, Asymmetric Allylic Alkylation

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The preparation of a new class of "roofed" β-iminodisulfides from sterically congested, conformationally rigid chiral 2-thiazolidinones is described. A functional survey of palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate proved that symmetrical "roofed" β-iminodisulfides are efficient chiral ligands, showing enantioselectivity opposite that associated with chiral "roofed" β-iminothioether ligands.

Key words β-iminodisulfide; asymmetric allylic alkylation; β-iminothioether; palladium-catalyzed; opposite stereoselectivity

Palladium-catalyzed asymmetric allylic alkylation is a well-studied organic chemistry protocol, because it is a powerful tool for enantioselective formation of carbon–carbon and carbon–heteroatom bonds.[1—7] Similar to other chiral catalyst systems, the enantioselectivity of this reaction mostly depends on the character of the chiral ligand that is coordinated to palladium. Therefore, various chiral ligands have been developed and discovery of novel chiral ligands for this reaction remains an important research goal.

Chiral β-aminosulfides and their derivatives,[8,9] which are principally prepared from the corresponding 2-amino alcohols and/or α-amino acids, are used less frequently in this reaction system. However, Anderson *et al.*,[10,11] Page and colleagues,[12] Braga *et al.*,[13,14] and Tokuda *et al.*[15] have reported good to excellent chemical yields and enantioselectivities using these compounds, indicating that chiral β-aminosulfides have potential as effective chiral ligands.

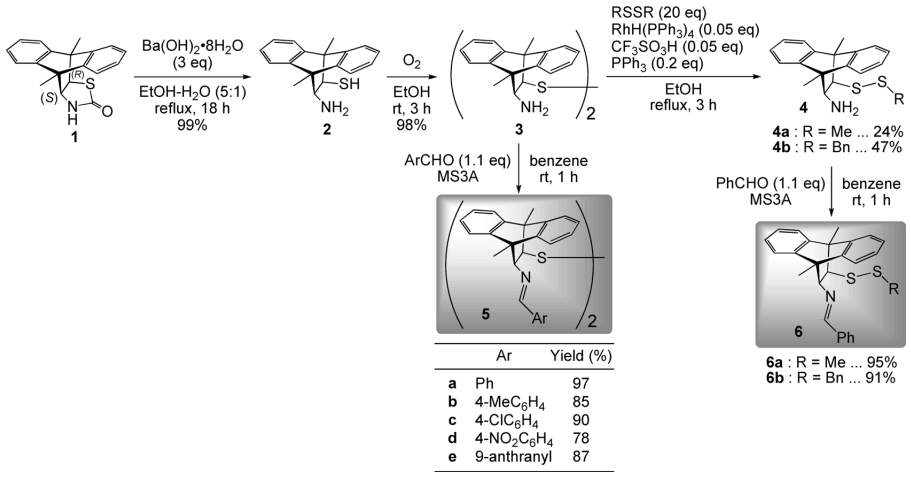
By contrast, one study suggested that β-aminodisulfides, the dimeric form of β-aminothiols, showed poor reactivity and enantioselectivity when used as chiral ligands for the palladium-catalyzed asymmetric allylic alkylation reaction.[13] Generally, chiral β-aminodisulfide ligands have received little attention in the field of catalytic asymmetric synthesis. Therefore, additional investigation of β-aminodisulfides as chiral ligands is intriguing.[16]

We previously reported that conformationally rigid and sterically bulky chiral "roofed" 2-iminothioethers, which were prepared by thermal [4+2] cycloaddition of a simple 5-membered heterocycle, 2-thiazolone, to cyclic dienes, followed by optical resolution and ring-cleavage, showed excellent yields and enantioselectivities for the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.[15] Based on this result, we envisaged that the dimer of this unique skeleton would show similar results.

In this paper, we wish to describe the preparation and application of sterically congested "roofed" β-iminodisulfides as efficient chiral ligands for palladium-catalyzed asymmetric allylic alkylation.

Starting from the "roofed" *cis*-2-aminothiol (**2**), which was readily obtained from the chiral 2-thiazolidinone (**1**)[17] by hydrolytic ring cleavage with $Ba(OH)_2$ in ethanol under reflux, aerial oxidation of **2** in ethanol afforded the chiral and symmetrical "roofed" β-aminodisulfide (**3**). Disulfide exchange between the symmetrical β-aminodisulfide (**3**) and a dialkyl disulfide in the presence of $RhH(Ph_3P)_4$ as a catalyst[18,19] afforded a unsymmetrical disulfide (**4**). Both β-aminodisulfides (**3**, **4**) were subsequently treated with aryl aldehyde in the presence of molecular sieves to yield the corresponding symmetrical and unsymmetrical β-iminodisulfide (**5**, **6**), respectively (Chart 1).[20]

We initially tested the catalytic activity of the symmetrical "roofed" β-iminodisulfide **5a**–Pd(II) complex, prepared *in situ*. The Pd(II)-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**7**) with dimethyl malonate under standard conditions, in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a base and a catalytic amount of KOAc in CH_2Cl_2, did not proceed well, and gave the corresponding product (**8**) in only 6% yield and 12% ee (Table 1, entry 1).



	Ar	Yield (%)
a	Ph	97
b	4-MeC_6H_4	85
c	4-ClC_6H_4	90
d	4-$NO_2C_6H_4$	78
e	9-anthranyl	87

Chart 1

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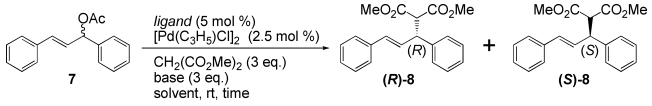
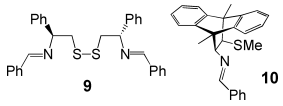
Table 1. Palladium-Catalyzed Asymmetric Allylic Alkylation with β-Iminodisulfide Type Ligand



Entry	Ligand	Base	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**5a**	BSA/KOAc[c]	CH_2Cl_2	24	6	12 (*S*)
2	**5a**	BSA/KOAc[c]	Toluene	24	9	48 (*R*)
3	**5a**	BSA/KOAc[c]	THF	24	Trace	—
4	**5a**	BSA/KOAc[c]	MeCN	24	18	36 (*R*)
5	**5a**	BSA/KOAc[c]	DMSO	24	NR	—
6	**5a**	NaH	CH_2Cl_2	24	5	15 (*S*)
7	**5a**	NaH	Toluene	24	17	38 (*S*)
8	**5a**	NaH	THF	24	14	50 (*S*)
9	**5a**	NaH	MeCN	24	46	26 (*S*)
10	**5a**	NaH	DMSO	12	98	50 (*S*)
11	**5a**	Cs_2CO_3	CH_2Cl_2	24	Trace	—
12	**5a**	Cs_2CO_3	Toluene	24	Trace	—
13	**5a**	Cs_2CO_3	THF	24	Trace	—
14	**5a**	Cs_2CO_3	MeCN	24	Trace	—
15	**5a**	Cs_2CO_3	DMSO	1	97	24 (*S*)
16	**6a**	BSA/KOAc[c]	CH_2Cl_2	24	NR	—
17	**6a**	NaH	DMSO	24	Trace	—
18	**6a**	Cs_2CO_3	DMSO	24	Trace	—
19	**6b**	BSA/KOAc[c]	CH_2Cl_2	24	NR	—
20	**6b**	NaH	DMSO	24	Trace	—
21	**6b**	Cs_2CO_3	DMSO	24	6	52 (*S*)
22	**9**	BSA/KOAc[c]	CH_2Cl_2	24	NR	—
23	**9**	Cs_2CO_3	DMSO	24	NR	—
24	**10**	Cs_2CO_3	MeCN	0.25	93	83 (*R*)

a) Isolated yields. *b*) Determined by HPLC (Daicel CHIRALPAK AD-H, hexane : *i*-PrOH = 19 : 1, flow 1.0 ml/min). *c*) KOAc 5 mol%.



Based on our previous success with a "roofed" β-iminothioether–Pd(II) complex, we investigated the effects of various solvents (*i.e.*, toluene, tetrahydrofuran (THF), MeCN and dimethyl sulfoxide (DMSO)). Unfortunately, none of them gave yields greater than 20% (entries 2—5).

We next examined the effects of a base on this reaction. Using NaH as a base, the reaction proceeded sluggishly in CH_2Cl_2, toluene or THF (less than 17%, entries 6—8), and moderate product yield (46%) was observed using MeCN (entry 9). To our surprise, excellent yield and 50% ee were obtained in DMSO (entry 10). The effect of DMSO on the reaction rate was dramatically enhanced in the presence of Cs_2CO_3 as a base. Although 97% yield was achieved after only 1 h, the selectivity was not as good (24% ee, entry 15).

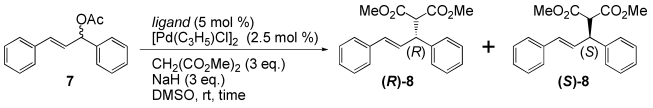
Catalytic activity of the unsymmetrical "roofed" β-iminodisulfides (**6a**, **6b**)–Pd(II) complexes were also tested, but, unfortunately, negative results were observed (entries 16—21). It is intriguing that the symmetrical "non-roofed" β-iminodisulfide **9**, prepared from (*S*)-phenylglycine, did not work as a chiral ligand in this reaction system (entry 23).[21]

It should be noted that almost all of the alkylated products **8** resulting from use of the symmetrical "roofed" β-iminodisulfide **5a** showed the (*S*)-configuration, while use of the "roofed" β-iminothioether **10** produced the (*R*)-configuration (entry 24).

Table 2 summarizes the optimization of the imino moiety of the symmetrical β-iminodisulfide ligand (**5a**—**e**) in the presence of NaH in DMSO. Although *p*-substituted benzylidene ligands showed lower activities than the *N*-benzylidene compound (**5a**), they showed higher enantioselectivities (entries 2—4). The results obtained using electron-withdrawing substituents (*p*-Cl, *p*-NO_2) were superior to those obtained using an electron-donating substituent (*p*-Me), and *p*-chlorobenzylidene ligand gave the best selectivity (72% ee). The 9-anthranylmethylidene moiety, which showed the highest ee value for the β-iminothioether-Pd(II) system,[15] showed lower selectivity (16% ee).

While the precise mechanism of "roofed" β-iminodisulfide **5**-Pd(II)-catalyzed asymmetric allylic alkylation is not clear, considering both early work using "roofed" β-iminothioether **10** and the results of the present study, the most plausible hypothesis for this reaction is depicted in Fig. 1.[22]

Table 2. Palladium-Catalyzed Asymmetric Allylic Alkylation with Symmetrical β-Iminodisulfide Ligands Using NaH as Base in DMSO



Entry	Ligand	Time (h)	Yield[a] (%)	ee[b]
1	**5a**	12	98	50 (*S*)
2	**5b**	24	47	55 (*S*)
3	**5c**	24	61	72 (*S*)
4	**5d**	24	57	67 (*S*)
5	**5e**	24	85	16 (*S*)

a) Isolated yields. *b*) Determined by HPLC (Daicel CHIRALPAK AD-H, hexane : *i*-PrOH = 19 : 1, flow 1.0 ml/min).

Thus, there are two possible diastereomeric π-allylic palladium complexes—**11** (M-type) and **12** (W-type). Steric repulsion between the disulfide moiety of the 2-iminothioether ligand and the phenyl ring of the π-allyl substrate appears greater than that from the "roof" moiety of the ligand, rendering the intermediate (**12**) more feasible than **11**. Nucleophilic attack at the π-allyl complex would occur at a *trans*-position relative to the sulfur atom, which is a better electron acceptor, to preferentially give the (*S*)-alkylated product (**8**).

In conclusion, a new "roofed" β-iminodisulfide appeared to work as a chiral ligand for the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with good enantioselectivity, but in the opposite configuration resulting from use of the β-iminothioether ligand. This is the first report that β-iminodisulfide itself has the potential to provide a unique chiral environment. Additional studies are currently in progress.

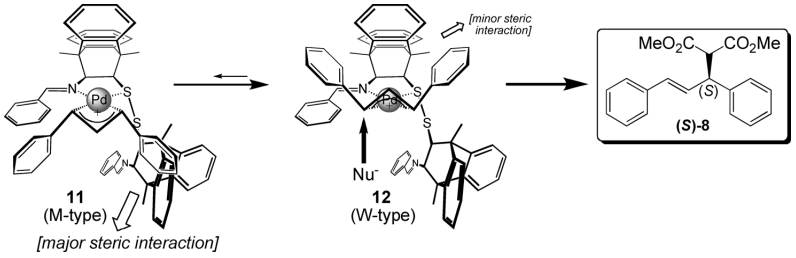


Fig. 1. Plausible Asymmetric Induction Process of Palladium-Catalyzed Asymmetric Allylic Alkylation *via* π-Allylpalladium Complex Intermediate

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16) β-Aminodisulfides have proven to be effective catalysts for the enantioselective addition of of diethylzinc to aldehyde, providing chiral secondary alcohols in high ees. In this case, the catalytically active species have been shown to be thiazazincolidines, derived from the cleavage of the disulfide bond by diethylzinc. See: Braga A. L., Galetto F. Z., Rodrigues O. E. D., Silveira C. C., Paixão M. W., *Chirality*, **20**, 839—845 (2008).
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20) Spectroscopic data of the typical 2-iminodisulfide ligands (**5a**, **5c**, **6b**) are as follows. Compound (**5a**): colorless amorphous solid; $[\alpha]_D$ +821.0° (c=1.00, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.60 (6H, s), 1.77 (6H, s), 3.04 (1H, d, J=8.5 Hz), 3.44 (1H, d, J=8.5 Hz), 6.88—6.90 (2H, m), 7.03—7.44 (20H, m), 7.53—7.55 (4H, m), 7.99 (2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 15.5, 16.9, 46.4, 47.1, 69.8, 78.2, 121.1, 121.4, 122.5, 122.9, 125.3, 125.7, 125.7, 126.0, 128.4, 128.5, 130.7, 135.9, 141.7, 143.0, 144.3, 145.8, 160.5. MS (FAB) m/z: 737 $(MH)^+$; HR-MS Calcd for $C_{50}H_{45}N_2S_2$ $(MH)^+$ 737.0969, Found 737.3024. Compound (**5c**): colorless amorphous solid; $[\alpha]_D$ +467.6° (c=0.42, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.59 (6H, s), 1.79 (6H, s), 2.99 (2H, d, J=8.7 Hz), 3.40 (2H, d, J=8.7 Hz), 6.91—7.46 (24H, m), 7.93 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.7, 17.0, 46.4, 47.1, 69.9, 78.2, 121.3, 121.4, 122.5, 123.0, 125.5, 125.9, 125.9, 126.1, 128.9, 129.7, 134.2, 136.8, 141.6, 142.9, 144.2, 145.7, 158.8. MS (FAB) m/z: 827 $(MNa)^+$; HR-MS Calcd for $C_{50}H_{42}Cl_2N_2S_2Na$ $(MNa)^+$ 827.2064, Found 827.2060. Compound (**6b**): colorless amorphous solid; $[\alpha]_D$ +394.8° (c=1.00, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.64 (3H, s), 2.14 (3H, s), 3.07 (1H, d, J=8.7 Hz), 3.39 (1H, d, J=8.7 Hz), 3.65 (2H, s), 7.06—7.38 (16H, m), 7.57—7.61 (2H, m), 8.05 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 15.6, 17.3, 43.6, 46.5, 47.1, 68.1, 78.0, 121.3, 121.4, 122.5, 123.0, 125.3, 125.8, 125.95, 126.02, 126.9, 128.2, 128.49, 128.54, 129.2, 130.7, 135.9, 137.6, 141.4, 143.2, 144.2, 145.8, 160.6. MS (FAB) m/z: 492 $(MH)^+$; HR-MS Calcd for $C_{32}H_{30}NS_2$ $(MH)^+$ 491.9940, Found 492.1820.
21) We speculate that "roofed" β-iminodisulfides **5** have *cis*-fused imino and disulfide moiety with fixed conformation and therefore bidentate site would coordinate to Pd easily and tightly to show the higher catalytic activity than other β-iminosulfides. To the contrary, the direction of the binding site of "non-roofed" β-iminodisulfide **9** is not conformationally fixed and also has diverse chelation patterns with Pd, thus, possibly showing less reactivity.
22) It has been known that the oxidative addition of disulfides into Pd(0) gives the thiopalladium species and dialkyl disulfides show lower reactivity or instability than diaryl disulfides.[23,24] To check the state of the disulfide ligand **5a** in the presence of Pd(0) species, DTNB (5,5′-dithiobis(2-nitrobenzoic acid)), commonly used to quantify the concentration of thiol groups in a sample, was added to the mixture of ligand **5a**, $[Pd(C_3H_5)Cl]_2$ (0.5 eq) and allylacetate **7** (2 eq) in THF, followed by the addition of 3 eq of $NaCH(CO_2Me)_2$ in THF at 20 °C. The solution acquired the same color as it did when dibenzyl disulfide was used in place of **5a**. However, different color was acquired when benzylmercaptane was added in place of **5a**. This difference was qualitative by visual check and did not show the exact state of the catalyst and/or ligand. However, this results seemed to be the indirect evidence for non-participation of thiolate from disulfide **5a** and Pd(0) in the reaction. In addition, the stability of disulfide **5a** was also supported by the fact that the treatment of diaminodisulfide **3** with $NaBH_4$ in EtOH gave none of the corresponding aminothiol **2**.
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