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STERICALLY CONGESTED "ROOFED" 2-IMINOTHIOETHERS AS NEW CHIRAL LIGANDS FOR PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

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Abstract – The preparation of a new class of "roofed" aminothiol derivatives, from sterically congested, conformationally rigid chiral 2-thiazolidinones is described. The compounds function as efficient chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in the presence of cesium carbonate as a base.

Development of methodologies for efficient asymmetric carbon-carbon bond formation is one of the most important areas in the field of organic synthesis.[1] Among such methods, chiral transition metal-catalyzed reactions have proven to be both useful and versatile. Generally, high enantioselectivities in such reactions depend on the use of well-designed chiral ligands. Various types of homo- and hetero-donor chiral ligands have been designed and prepared, including bisoxazoline (N-N),[2] bisphosphine (P-P)[3] and oxazoline-phosphine (N-P)[2e,4] ligands.

Focusing on the N-S type ligands, several types of thioether-oxazolines[5] and thioether-pyridines (quinoline)[6] have been prepared and provide good to excellent enantioselectivities. To the contrary, only a few reports of the use of thioether-amine (imine) ligands,[7] which are easily prepared from the corresponding 2-aminothiols derived from α-amino acids, have appeared.

We recently developed some chiral "roofed" 2-thiazolidinones, which are conformationally rigid and sterically bulky, by the thermal [4+2] cycloaddition of a simple 5-membered heterocycle, 2-thiazolone, to

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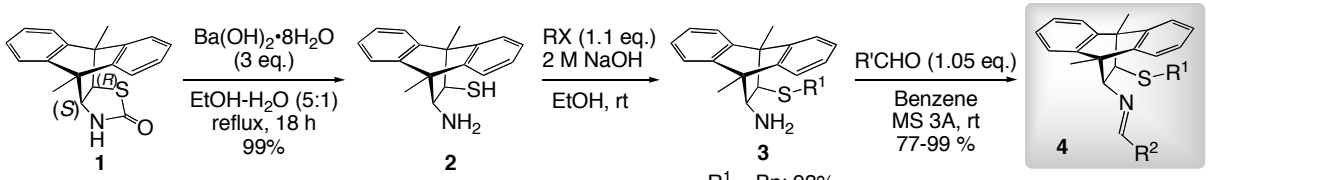
This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

cyclic dienes followed by optical resolution.[8] These compounds have proven to be excellent chiral auxiliaries for use in asymmetric C-C bond formation reactions, including the α-alkylation of carbonyl compounds[8] and β-conjugate addition reactions. The excellent stereoselectivities obtained in these reactions prompted us to apply this unique skeleton to new types of chiral "roofed" 2-aminothiol ligands and to test them as chiral ligands in catalytic asymmetric reactions.

In this paper, we report on some sterically congested "roofed" 2-iminothioethers as new chiral ligands for palladium-catalyzed asymmetric allylic alkylation, leading to excellent enantioselectivity.

Starting from the "roofed" *cis*-2-aminothiol (**2**), which is readily obtained from the chiral 2-thiazolidinone (**1**)[8] by hydrolytic ring cleavage with $Ba(OH)_2$ in ethanol under reflux, nine types of new "roofed" 2-iminothioether ligands (**4**)[9] were prepared by the *S*-alkylation of **2** followed by the formation of the imines (Scheme 1).



	R^1	R^2
a	Bn	Ph
b	Bn	*p*-MeC_6H_4
c	Bn	*p*-$MeOC_6H_4$
d	Bn	*p*-ClC_6H_4
e	Bn	*p*-$NO_2C_6H_4$
f	Bn	1-Naphthyl
g	Bn	9-Anthranyl
h	Me	Ph
i	Me	9-Anthranyl

Scheme 1

Enantioselective palladium-catalyzed allylic alkylation has been extensively studied because it is a powerful tool for the enantioselective formation of carbon-carbon and carbon-heteroatom bonds.[3e,10] Although various types of chiral ligands have been used in this reaction, 2-iminothioethers, established by Anderson *et al*., represent the only case of a 2-iminothioether-Pd catalyzed allylic alkylation.[7a] Therefore, we chose enantioselective palladium-catalyzed allylic alkylation as a model reaction for the evaluation of the chiral 2-iminothioether ligands.

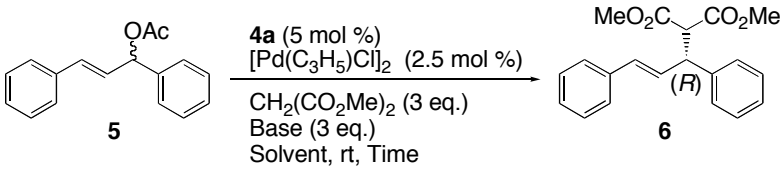
We initially tested the activity of the "roofed" 2-iminothioether (**4a**)-Pd(II) complex, prepared *in situ*, as a catalyst. Thus, the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a base in CH_2Cl_2 proceeded to give the corresponding product (**6**) in 80% ee, but only in 31% yield (Table 1, Entry 1).

However, the yields were greatly dependent on the nature of the solvent: good results (85% yield, 84% ee and 72% yield, 84% ee) were obtained in toluene and acetonitrile, respectively (Entries 2, 4).

We also investigated the effects of the base in this reaction. Using NaH as a base, the reactions proceeded well in toluene and acetonitrile to give yields of 96% and 89%, respectively, but a slight decline of enatioselectivity was observed (Entries 6, 8). It is interesting to note that Cs_2CO_3 dramatically accelerated the reactions in various solvents to give good to excellent yields and also 80-83% ee (Entries 9-12).[11] The

combination of Cs_2CO_3 and acetonitrile showed the best performance giving a 93% yield in only 15 minutes (Entry 12).

Table 1. Palladium-catalyzed asymmetric allylic alkylation with an iminothioether type ligand



Entry	Base	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)	Entry	Base	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	BSA / KOAc[c]	CH_2Cl_2	24	31	80	7	NaH	THF	24	73	63
2	BSA / KOAc[c]	Toluene	24	85	84	8	NaH	MeCN	2	89	79
3	BSA / KOAc[c]	THF	24	13	83	9	Cs_2CO_3	CH_2Cl_2	3	93	81
4	BSA / KOAc[c]	MeCN	3	72	84	10	Cs_2CO_3	Toluene	3	90	81
5	NaH	CH_2Cl_2	24	49	71	11	Cs_2CO_3	THF	3	78	80
6	NaH	Toluene	3	96	61	12	Cs_2CO_3	MeCN	0.25	93	83

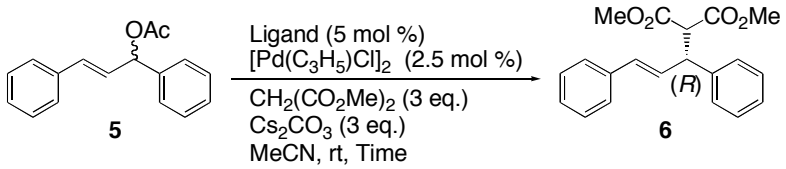
[a]Isolated yields.
[b]Determined by HPLC (Daicel CHIRALPAK AD-H, Hexane:*i*-PrOH = 19:1, flow 1.0 mL/min).
[c]KOAc 5 mol %.

Table 2 summarizes the optimization of the 2-iminothioether ligand (**4**) for the Pd(II)-catalyzed asymmetric allylic alkylation of **5** with dimethyl malonate in the presence of Cs_2CO_3 in acetonitrile. Almost all the reactions proceeded very rapidly, being complete in one hour. We initially investigated the substituent effect of the *N*-benzylidene moiety (Entries 2-5). Regardless of whether electron-withdrawing or electron-donating substituents were present at the *para*-position, no significant improvement in the enantioselectivities was observed. The 1-naphthylmethylidene ligand gave a slightly higher enantioselectivity (86% ee, Entry 6) and the sterically bulky 9-anthranylmethylidene moiety showed a 90% enantioselectivity (Entry 7). These results suggest that steric factors are more important than the electronic features for the *N*-benzylidene moiety. Enantioselectivities were also improved by replacing the *S*-benzyl with an *S*-methyl group (Entries 1 vs. 8, and 7 vs. 9) and 95% ee was observed at 0 °C (Entry 10).

Generally, in the case of nitrogen-sulfur chiral chelate ligands used in Pd(II)-catalyzed asymmetric allylic alkylation reactions, it is assumed that the sulfur atom is a better electron acceptor[12] and nucleophilic attack at the π-allyl complex occurs at a *trans*-position to the sulfur atom because of the longer palladium-allyl terminus bond length than other ligands. To the contrary, Anderson *et al.*[7a] reported that 2-iminothioether-Pd catalyzed allylic alkylation occurs at a *trans*-position to the imine and the enantioselectivity is controlled by the steric environment of the chiral 2-iminothioether chelate ligand.

While the precise mechanism for "roofed" 2-iminothioether (**4a**)-Pd(II)-catalyzed asymmetric allylic alkylation reaction is not clear, the most plausible hypothesis for this reaction is depicted in Figure 1.

Table 2. Palladium-catalyzed asymmetric allylic alkylation with an iminothioether type ligand using Cs_2CO_3 as base in MeCN



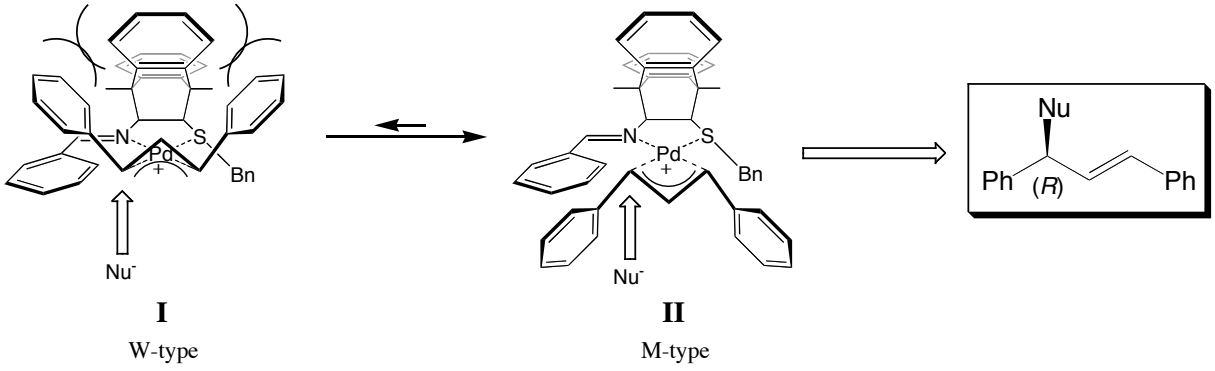
5 **6**

Entry	Ligand	R^1	R^2	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4a**	Bn	Ph	0.25	93	83
2	**4b**	Bn	*p*-MeC_6H_4	0.5	99	81
3	**4c**	Bn	*p*-$MeOC_6H_4$	0.25	99	78
4	**4d**	Bn	*p*-ClC_6H_4	0.25	77	78
5	**4e**	Bn	*p*-$NO_2C_6H_4$	1	96	69
6	**4f**	Bn	1-Naphthyl	0.5	93	86
7	**4g**	Bn	9-Anthranyl	0.5	98	90
8	**4h**	Me	Ph	0.5	90	87
9	**4i**	Me	9-Anthranyl	0.5	93	93
10[c]	**4i**	Me	9-Anthranyl	5	90	95

[a]Isolated yields.
[b]Determined by HPLC (Daicel CHIRALPAK AD-H, Hexane:*i*-PrOH = 19:1, flow 1.0 mL/min).
[c]The reaction was carried out at 0 °C.

Thus, there are two possible diastereomeric π-allylic palladium complexes, **II** (M-type) and **I** (W-type). A steric interaction between the "roof" moiety of the 2-iminothioether ligand and the phenyl ring of the π-allyl substrate would render intermediate (**II**) more feasible than **I**, and a nucleophilic attack at the π-allyl complex would occur at a *trans*-position to the sulfur atom, a better electron acceptor,[12] to preferentially give the (*R*)-alkylated product (**6**).

Focusing on intermediate (**II**), the phenyl ring of the π-allyl substrate and the *N*-benzylidene moiety would be in close proximity and we therefore speculate that the sterical bulkiness of the *N*-benzylidene moiety would activate the reactivity of the π-allyl terminus *trans* to the sulfur atom, thus giving the higher enantioselectivities. To the contrary, diminishing the sterical interaction between the phenyl ring of the π-allyl substrate and the thioether moiety would lead to an increased enantioselectivity. Therefore, the "roofed" 2-iminothioether ligand (**4**) has two characteristics for providing good to excellent enantioselectivity; a sulfur atom as a better electron acceptor (electronic factor) and an *N*-benzylidene moiety and a thioether moiety (steric factor).



I **II**
W-type M-type

Figure 1. Plausible asymmetric induction process of palladium-catalyzed asymmetric allylic alkylation *via* π-allylpalladium complex intermediate.

In summary, a new "roofed" iminothioether type ligand showed exellent enantioselectivity for the palladium-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with dimethy malonate. These results indicate that ligands are promising in asymmetric catalysis in which transition metals are used. Further studies are currently in progress.

ACKNOWLEDGEMENTS

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9. Spectroscopic data of the typical 2-iminothioether ligands (**4a**, **4g** and **4i**) are as follows. Compound (**4a**): colorless amorphous; $[\alpha]_D$ +394.5 ° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.11 (3H, s), 3.03 (1H, d, *J* = 8.6 Hz), 3.19 (1H, d, *J* = 8.6 Hz), 3.70 (1H, d, *J* = 13.4 Hz), 3.74 (1H, d, *J* = 13.4 Hz), 7.13-7.53 (18H, m), 8.06 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 17.2, 38.2, 46.6, 46.9, 57.7, 78.1, 121.0, 121.45, 121.46, 122.8, 125.4, 125.8, 125.9, 126.6, 128.2, 128.4, 128.5, 128.9, 129.0, 130.5, 136.2, 138.6, 142.5, 143.8, 144.8, 146.6, 160.4. MS (FAB): *m*/*z* 460 $(MH)^+$; HRMS calcd for $C_{32}H_{30}NS$ 460.2099, found 460.2166. Compound (**4g**): yellow amorphous; $[\alpha]_D$ +166.0 ° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (3H, s), 2.26 (3H, s), 3.18 (1H, d, *J* = 8.4 Hz), 3.55 (2H, s), 3.72 (1H, d, *J* = 8.4 Hz), 7.00-7.50 (17H, m), 7.97-8.00 (2H, m), 8.48 (1H, s), 8.79-8.82 (2H, m), 9.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 17.2, 38.7, 46.9, 47.2, 57.6, 81.3, 120.9, 121.8, 122.75, 122.83, 125.2, 125.58, 125.64, 125.7, 126.0, 126.1, 126.6, 126.8, 128.2, 128.9, 129.0, 130.4, 130.9, 131.2, 131.4, 138.7, 142.4, 144.0, 144.3, 147.0, 159.6. MS (FAB): *m*/*z* 560 $(MH)^+$; HRMS calcd for $C_{40}H_{34}NS$ 560.2412, found 560.2490. Compound (**4i**): yellow amorphous; $[\alpha]_D$ +121.2 ° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (3H, s), 1.92 (3H, s), 2.24 (3H, s), 3.19 (1H, d, *J* = 8.4 Hz), 3.89 (1H, d, *J* = 8.4 Hz), 7.22-7.50 (12H, m), 7.95-7.99 (2H, m), 8.47 (1H, s), 8.77-8.81 (2H, m), 9.43 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 17.4, 18.3, 46.9, 60.1, 81.3, 120.7, 121.9, 122.7, 123.0, 125.1, 125.59, 125.64, 125.7, 126.0, 126.1, 126.8, 128.9, 130.5, 131.2, 131.4, 132.2, 142.3, 144.0, 144.2, 147.4, 159.8. MS (FAB): *m*/*z* 484 (MH^+); HRMS calcd for $C_{34}H_{30}NS$ 484.2099, found 484.2188.
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