

Novel and efficient chiral sulfideoxathiane ligands for palladium-catalyzed asymmetric allylic alkylation†

Yuko Okuyama,^a Hiroto Nakano,^{*a} Kouichi Takahashi,^a Hiroshi Hongo^a and Chizuko Kabuto^{*b}

^a Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan.

E-mail: hnakano@tohoku-pharm.ac.jp; Fax: 81 22 275 2013; Tel: 81 22 234 4181

^b Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan. E-mail: kabuto@kiki.chem.tohoku.ac.jp

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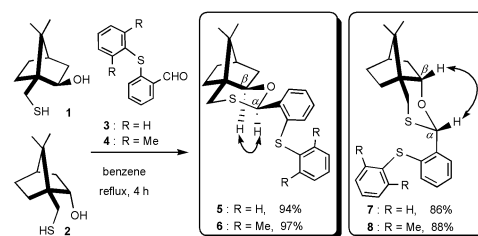
Easily prepared, chiral sulfideoxathiane ligands are described which give excellent enantioselectivity (up to 99% ee) in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with a range of alkyl malonate nucleophiles.

Carbon-carbon bond formation is one of the most important reactions in synthetic organic chemistry. One useful and popular method is palladium-catalyzed allylation,¹ and asymmetric versions of this reaction have also been extensively studied over the last decade.¹ Strategies for controlling enantioselectivity in Pd-catalyzed asymmetric reactions have depended on the design and application of chiral ligands. Although many of the efficient homo- and hetero-donor chiral ligands such as N-N (e.g. bisoxazolines²), P-P (e.g. Trost's P-P ligands³), N-P (phosphinooxazoline⁴), and S-P (Evans S-P ligands and our phosphinoxathianes⁵) types have been exploited and utilized, the S-S type ligand has not, in spite of having advantages such as lower cost, toxicity and oxidation potential. To the best of our knowledge, only one example employing C₂-symmetric S-S type ligands in the allylic alkylation has been reported,⁶ by Gómez and co-workers, but this only afforded modest asymmetric induction (up to 81% ee) owing to the donor sites being insufficiently different for discrimination between both terminal allylic carbons in the intermediate.⁶ We planned to synthesize the asymmetric S-S type ligands **5–8** having a borneol backbone because the ligand can be prepared easily from the reactions of mercaptoisborneol or mercaptoborneol with phenylthiobenzaldehydes and because the lack of C₂-symmetry in the ligand may give rise to more than one intermediate complex whose reactivities determine the enantioselection. Herein, we wish to report that the easily prepared S-S type sulfideoxathiane ligand **6** showed dramatic reactivity and enantioselectivity (up to 99% ee) in all cases of the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **9** with dimethyl and dialkyl methylmalonate nucleophiles **10a–c**. This is the first time that the allylic alkylation has been catalyzed with excellent enantioselectivity by a chiral homo-donor S-S type ligand.

The requisite chiral ligands **5–8** were easily prepared by the condensation of commercially available (1*S*)-(–)-10-mercaptoisborneol **1** or (1*S*)-(–)-10-mercaptoborneol **2** with 2-(phenylthio)- or 2-(2,6-dimethylphenylthio)benzaldehydes (**3** and **4**)⁷ in good yields (86–97%) (Scheme 1). In all four cases (**5–8**), the assigned stereochemistry at the α-position of the 1,3-oxathiane ring was determined by NOE difference spectra (NOEDS). NOE enhancement was observed between the hydrogen at the α-position and the hydrogen at the β-position when the α- and β-positions were irradiated, respectively (Scheme 1).^{5b–d}

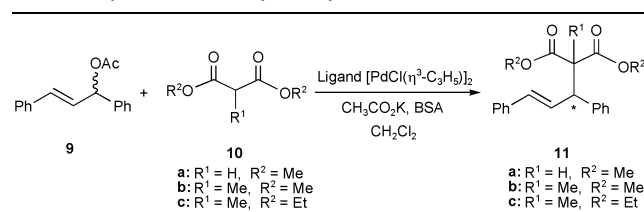
The Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate **9** with dimethyl malonate **10a** using chiral ligands **5–8** was examined in the presence of [PdCl(η³-C₃H₅)₂] and *N,O*-bis(trimethylsilyl)acetamide (BSA)⁸ to give the allylation

product **11a**; the results are summarized in Table 1. Initially, chiral ligands **5–8** (2 mol%) were tested at room temperature. The ligands showed excellent reactivity, but the enantioselectivity greatly depended on the individual ligand structure. Thus, ligands **5** and **7** containing a linking phenylthio moiety gave the corresponding product **11a** in low enantiopurity (**5**: 57% ee, **7**: 49% ee), whereas ligands **6** and **8**, incorporating a bulkier linked 2,6-dimethylphenylthio moiety, brought about high asymmetric induction (**6**: 94% ee, **8**: 75% ee) (entries 1–4). In particular, chiral ligand **6** afforded **11a** in high levels of enantiomeric excess (94% ee) at room temperature, while reaction at 0 °C improved enantioselectivity to 98% ee (entry 5).



Scheme 1

Table 1 Asymmetric Pd-catalyzed allylation of acetate **9**



Entry ^a	Ligand (mol%)	R ¹	R ²	Temp./°C (Time/h)	Yield ^c (%)	Ee ^d (%) (Config ^f)
1	5 (2)	H	Me	rt (12)	100	57 (<i>R</i>)
2	6 (2)	H	Me	rt (15)	100	94 (<i>R</i>)
3	7 (2)	H	Me	rt (9)	100	49 (<i>S</i>)
4	8 (2)	H	Me	rt (13)	100	75 (<i>S</i>)
5	6 (2)	H	Me	0 (48)	92	98 (<i>R</i>)
6 ^b	6 (5)	H	Me	0 (48)	100	93 (<i>R</i>)
7 ^b	6 (1)	H	Me	0 (120)	40	94 (<i>R</i>)
8 ^b	6 (0.5)	H	Me	0 (144)	38	92 (<i>R</i>)
9	6 (2)	Me	Me	0 (48)	96	96 ^e (<i>S</i>)
10	6 (2)	Me	Et	0 (48)	100	99 ^e (<i>S</i>)

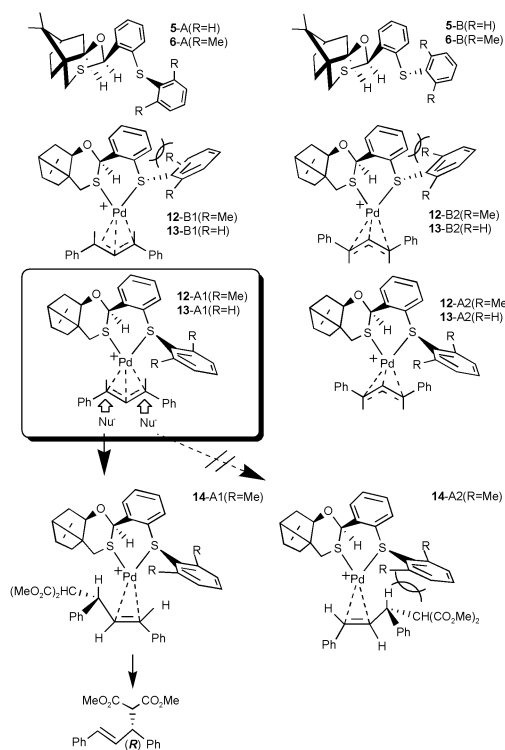
^a Molar ratio for entries 1–5 and 9, 10: [PdCl(η³-C₃H₅)₂] (0.01 equiv.), malonates (3 equiv.), *N,O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv.), potassium acetate (0.02 equiv.), **9** (1 equiv.), ligands **5–8** (0.02 equiv.). ^b Molar ratio for entries 6–8: [PdCl(η³-C₃H₅)₂] (5 mol%: 0.025 equiv., 0.1 mol%: 0.005 equiv., 0.5 mol%: 0.0025 equiv.), dimethyl malonate (3 equiv.), BSA (3 equiv.), potassium acetate (0.02 equiv.), **9** (1 equiv.), ligand **6** (5 mol%: 0.05 equiv., 1 mol%: 0.0105 equiv., 0.5 mol%: 0.005 equiv.). ^c Isolated yields. ^d Determined by chiral HPLC using a Daicel OD-H column. ^e Determined by chiral HPLC using a Daicel (OD-H + OD-H) column. ^f *R* or *S* configuration based on the specific rotation with literature data.^{1e,f}

† Electronic supplementary information (ESI) available: experimental details. See <http://www.rsc.org/suppdata/cc/b2/b211031h/>

To optimize reaction conditions, we next examined the effect of the molar ratio of ligand **6** at 0 °C. The use of 5 mol% of **6** brought about a slight decrease in enantioselectivity (93% ee) (entry 6). At low catalytic loadings (1 mol% and 0.5 mol%) the reactions gave good levels of enantioselectivity (1 mol%: 94% ee and 0.5 mol%: 92% ee), albeit in low chemical yields (entries 7 and 8). From these results, the most effective set of reaction conditions was given by 2 mol% of ligand **6** at 0 °C.

We also examined the reactions of acetate **9** with bulkier dimethyl- and diethyl methylmalonates **10b** and **10c** as nucleophiles under the optimized reaction conditions. The reaction with **10b** gave the corresponding product **11b** in satisfactory enantiomeric excess (96% ee) and the chemical yield (96%) (entry 9). Further, the bulkiest malonate **10c** achieved near complete stereocontrol (99% ee) with quantitative yield to give the product **11c**, which has been difficult to secure in high optical purity.^{4a,b}

Finally we examined semi-empirical MO calculations⁹ in order to explain the remarkable difference of the enantioselectivity between ligands **5** (R = H) and **6** (R = Me). A reaction mechanism for the Pd-catalyzed allylic alkylation was proposed similar to the case of Evans *et al.*^{5a} Scheme 2 shows the possible models for ligands, palladium π -allyl complexes, and palladium-olefin complexes. For ligands **5** and **6**, two isomers of each (**5-A**, **5-B**, **6-A** and **6-B**) are considered due to the orientation of the phenyl substituent. For the next palladium π -allyl complexes in **6**, a total of four isomers, **12-A1** and **12-A2** from **6-A**, and **12-B1** and **12-B2** from **6-B** are considered due to the orientation of the π -allyl moiety. Geometry optimizations show that **6-A** is preferred over **6-B** by about 2 kcal mol⁻¹ in energy, and in palladium π -allyl complexes **12-A1** is preferred by about 2 kcal mol⁻¹ over the others. In contrast, the two conformers **5-A** and **5-B** of ligand **5** show the same in energy and also no essential difference is shown between two palladium π -allyl complexes **13-B1** and **13-B2** with the lowest energy. These results give support that the reaction of ligand **6**



Scheme 2

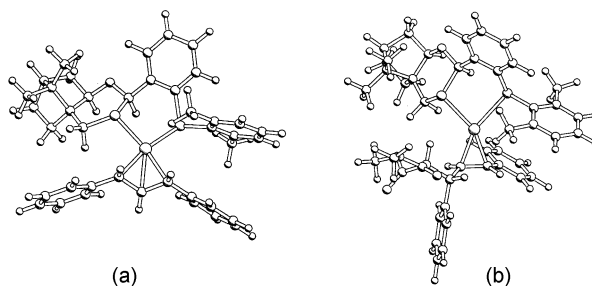


Fig. 1 Optimized structures of (a) **12-A1** and (b) **14-A1**.

proceeds *via* selective conformers. Furthermore, the calculations for the final palladium-olefin complexes of ligand **6** show that **14-A1** is preferred by more than 4 kcal mol⁻¹ over **14-A2**. Thus, MO calculations give a rationale for high ee for **6** and low ee for **5** and the optimized structures (Fig. 1) indicate that the steric hindrance of dimethyl groups attached to the phenyl ring of **6** controls the conformation.

In conclusion, the developed sulfideoxathiane ligand **6** was prepared easily in one step and showed dramatic reactivity and enantioselectivity for the allylic alkylation of acetate **9** with three kinds of malonates (96–100%, 96–99% ee), comparable to the results of the Evans group.^{5a} As another advantage, the ligand **6** is considerably stable in air and may be superior for practical use to ligands containing the phosphorus atom.

Notes and references

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- AM1 optimization was carried out using WINMOPAC 3.5 version (Fujitsu inc.) and PM 3 optimization was done using Mac Spartan 02 (Wave function inc.). ΔH_f energies obtained from MO calculations and stereo views of optimized structures are presented in Supporting Information†.