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

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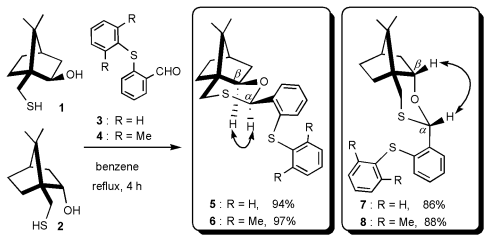
Easily prepared, chiral sulfideoxathiane ligands are described which give excellent enantioselectivity (up to 99% ee) in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with a range of alkyl malonate nucleophiles.

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.* bisoxazolines[2]), P–P (*e.g.* Trost's P–P ligands[3]), N–P (phosphinooxazoline[4]), and S–P (Evans S–P ligands and our phosphinooxathianes[5]) 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 C_2-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 mercaptoisoborneol or mercaptoborneol with phenylthiobenzaldehydes and because the lack of C_2-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.

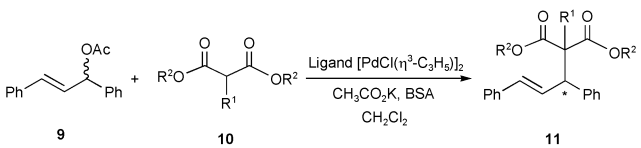
The requisite chiral ligands **5**–**8** were easily prepared by the condensation of commercially available (1*S*)-(−)-10-mercaptoisoborneol **1** or (1*S*)-(−)-10-mercaptoborneol **2** with 2-(phenylthio)- or 2-(2,6-dimethylphenylthio)benzaldehydes (**3** and **4**)[7] in good yields (86–97%) (Scheme 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 $[PdCl(\eta^3\text{-}C_3H_5)]_2$ 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 Asymmetic 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 (*R*)
2	**6** (2)	H	Me	rt (15)	100	94 (*R*)
3	**7** (2)	H	Me	rt (9)	100	49 (*S*)
4	**8** (2)	H	Me	rt (13)	100	75 (*S*)
5	**6** (2)	H	Me	0 (48)	92	98 (*R*)
6[b]	**6** (5)	H	Me	0 (48)	100	93 (*R*)
7[b]	**6** (1)	H	Me	0 (120)	40	94 (*R*)
8[b]	**6** (0.5)	H	Me	0 (144)	38	92 (*R*)
9	**6** (2)	Me	Me	0 (48)	96	96[e] (*S*)
10	**6** (2)	Me	Et	0 (48)	100	99[e] (*S*)

[a] Molar ratio for entries 1–5 and 9, 10: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (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: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (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/

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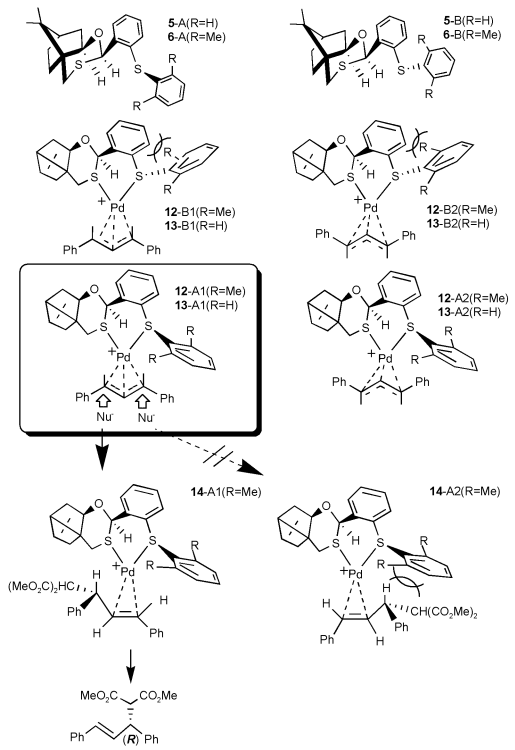
To optimize reaction conditions, we next examined the effect of the molar ratio of ligand **6** at 0 °C. The use of 5 mol% of **6** brought about a slight decrease in enantioselectivity (93% ee) (entry 6). At low catalytic loadings (1 mol% and 0.5 mol%) the reactions gave good levels of enantioselectivity (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 calculations[9] 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

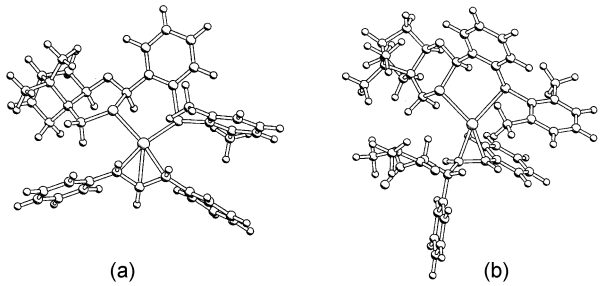


Fig. 1 Optimized structures of (a) **12**-A1 and (b) **14**-A1.

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