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# A New, Chiral Bis-Benzothiazine Ligand

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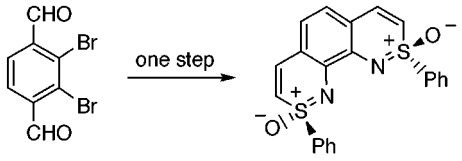
## ABSTRACT

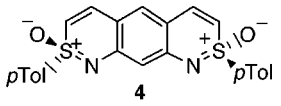



**The synthesis and application of a new, chiral bis-benzothiazine ligand are described.**

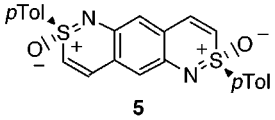
The development of new chiral ligands for transition metal-catalyzed organic reactions is at the forefront of research in synthetic organic chemistry.[1] Such studies have not only potentially very important practical ramifications but also provide for new insights into the chemistry of metals and their interactions with organic substrates.

Among the various classes of donor ligands that have been introduced are those bearing two N atoms,[2] some of which have had a major impact on catalytic asymmetric synthesis.[3] A subset of this class of ligands are the bis-sulfoximines, and they are the subject of this paper. The utility of sulfoximine-based ligands is only currently being realized.[4]

We recently reported that the reaction of sulfoximine **1** with 2-bromobenzaldehyde **2** under conditions reported by Bolm for C−N bond formation (Buchwald−Hartwig reaction) afforded the benzothiazine **3** in good yield (Scheme 1).[5,6] In this reaction, both carbon−nitrogen and carbon−carbon bond formation occurred in a single operation. We anticipated that more complex structures could be prepared by this method and demonstrated that bis-benzothiazines **4** and **5** could be synthesized from the corresponding dibromodialdehydes. We thus set out to synthesize a bis-benzothiazine that could serve as a ligand.



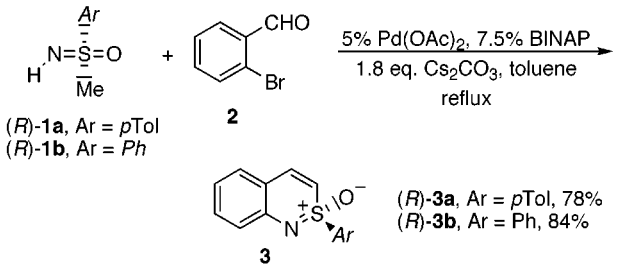

**4**




**5**

At the time we began our work, the synthesis of bis-sulfoximines using the Buchwald−Hartwig approach was not known. Recently, however, Bolm and co-workers reported that 1,2-dibromobenzene afforded the bis-sulfoximine **8** in good yield using the Buchwald−Hartwig reaction (Scheme 2) and that **8** was an exceptional ligand in the copper-catalyzed Diels−Alder reaction of ethyl glyoxalate and 1,3-cyclohexadiene.[7]

**Scheme 1**




(1) Handy, S. T. *Curr. Org. Chem.* **2000**, *4*, 363−395.
(2) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497−526.
(3) For example, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1−45.
(4) For leading references, see: Reggelin, M.; Zur, C. *Synthesis* **2000**, 1−64.
(5) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2419−21.
(6) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *37*, 5731−34.

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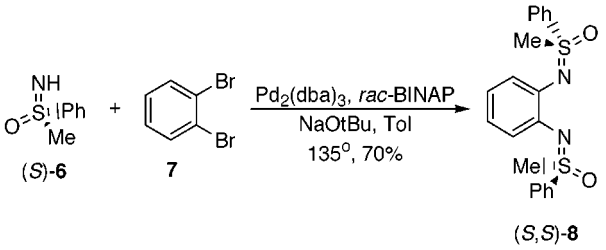
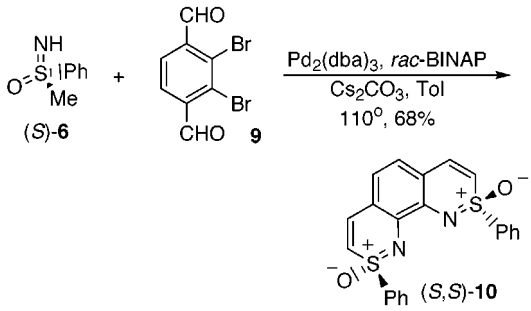
**Scheme 2**




We prepared both enantiomers of bis-benzothiazine **10** using the procedure we reported earlier starting with the dialdehyde **9** (Scheme 3).[8,9] The choice of sulfoximine **6** was

**Scheme 3**



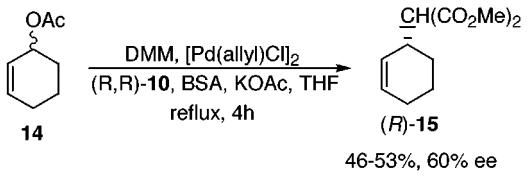

based on its ready availability in enantiomerically pure form.[10]

With both enantiomers of **10** in hand, we decided to examine its utility as a ligand and chose to examine the palladium-catalyzed asymmetric allylic alkylation reaction, a standard in the evaluation of many new ligands.[11,12] Treatment of racemic 1,3-diphenylallyl acetate with dimethyl malonate in the presence of bistrimethylsilyl acetamide (BSA) afforded alkylation product in good yield and with reasonable enantiomeric excess. The results are summarized in Table 1. The reactions were conducted at reflux temperatures using 2.5 mol % of the palladium source, 10 mol % ligand, 3 equiv of BSA, and catalytic potassium acetate. The first eight entries of Table 1 show that solvent effects are important in the reaction. Relatively nonpolar solvents afforded good yields and enantiomeric excesses while reaction in dichloromethane and acetonitrile afforded only racemic material in moderate yield. For the most part, it appeared that the source of palladium was not significant, except when a phosphine ligand was present that could compete with the chiral ligand and thereby produce nearly racemic product.

With these results in hand, we prepared the ligand **8** and evaluated its ability to serve as a ligand in these reactions. Interestingly, only low yields and low enantiomeric excesses were observed (Table 1, entries 15 and 16).[13] A monodentate ligand (**3b**) gave low yields of product with low ee (Table 1, entry 17).

Helmchen has suggested that the evaluation of ligands for asymmetric allylation extend beyond the model system **11**.[14] We thus tested our ligand in the reaction of racemic cyclohexenyl acetate with dimethyl malonate as shown in Scheme 4.[15] Using either enantiomer of **10**, the product was

**Scheme 4**




obtained in only moderate yields with a moderate degree (60% ee) of enantioselectivity (Scheme 4).

In summary, we have shown that the bis-benzothiazine **10** is an effective ligand in asymmetric allylic alkylation reactions. The modular approach used in the synthesis of

(7) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830−31.

(8) The dialdehyde **9** was prepared by oxidation of the corresponding *p*-xylene, a known compound. See: Gronowitz, S.; Hansen, G. *Ark. Kemi* **1967**, *27*, 145−151.

(9) **Preparation of (*R,R*)-10 and (*S,S*)-10.** A dry 100 mL flask equipped with a magnetic stirring bar and a reflux condenser was charged with $Pd_2$-$dba_3$ (75 mg, 0.08 mmol, 10 mol %), *rac*-BINAP (76 mg, 0.12 mmol, 15 mol %), and toluene (40 mL). Dialdehyde **9** (240 mg, 0.82 mmol) was added, followed by the (*R*)-**6** (635 mg, 4.10 mmol, 5 equiv) and cesium carbonate (800 mg, 2.46 mmol, 3 equiv). The mixture was then heated in an oil bath at 110 °C for 48 h. After being cooled to ambient temperature, the solution was diluted with dichloromethane, filtered through a pad of Celite, and concentrated in vacuo to give a brown oil. Purification of the product by flash chromatography afforded (*R,R*)-**10** as an orange solid (230 mg, 68%). Mp: 277−286 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.92−7.89 (m, 4 H), 7.66 (d, $J$ = 9.7 Hz, 2 H), 7.60−7.47 (m, 6H), 7.02 (s, 2H), 6.41 (d, $J$ = 9.7 Hz, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ 141.7, 139.8, 138.0, 133.1, 129.4, 128.7, 120.7, 117.3, 110.4. Anal. Calcd for $C_{22}H_{16}N_2O_2S_2$: C, 65.32; H, 3.99; N, 6.92. Found: C, 65.57; H, 4.22; N, 6.82. $[\alpha]_{589}$: −1316.1 ($c$ = 1.13, $CHCl_3$). Data for (*S,S,*)-**10**. Same procedure as above. Anal. Calcd for $C_{22}H_{16}N_2O_2S_2$: C, 65.32; H, 3.99; N, 6.92. Found: C, 65.45; H, 4.04; N, 6.74. $[\alpha]_{589}$: +1316.6 ($c$ = 1.05, $CHCl_3$).

(10) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 909−912.

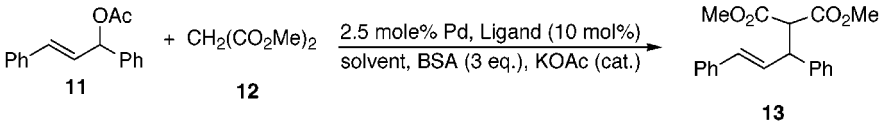
(11) For leading references, see: Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8E.

(12) **General Procedure for the Palladium-Catalyzed Allylic Substitution of *rac*-1,3-Diphenyl-2-propenyl Acetate with Dimethyl Malonate.** A solution of ligand (0.02 mmol, 10 mol %) and Pd compound (2.5 mol %) in dry solvent (2 mL) was stirred at room temperature for 1 h. This solution was treated successively with a solution of *rac*-1,3-diphenyl-2-propenyl acetate (0.2 mmol), dimethyl malonate (0.6 mmol), *N,O*-bis-(trimethylsilyl)acetamide (0.6 mmol), and a catalytic amount of anhydrous potassium acetate. The reaction mixture was refluxed for a given time (see Table 1). The reaction mixture was cooled to room temperature, diluted with diethyl ether (10 mL), and washed with saturated aqueous ammonium chloride. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ether = 4/1) to give the product. The enantiomeric excess was determined by $^1$H NMR spectroscopy in the presence of the enantiomerically pure shift reagent Eu(hfc)$_3$. Splitting of the signals for one of the two methoxy groups was observed.

(13) At room temperature, neither **8** nor **10** was an effective ligand for the allylic alkylation reaction. Little progress was noted in the conversion of **11** to **13** even after 13 days (TLC). The reaction using **8** was also not productive at elevated temperatures in toluene, benzene and dichloromethane.

(14) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203-214.

**Table 1.** Reaction of Racemic 1,3-Diphenylallyl Acetate with Dimethyl Malonate in the Presence of Chiral Ligands under Various Conditions




| entry | ligand | Pd source | solvent | time[a] (h) | yield[b] (%) | ee[c] (%) | config[d] |
|---|---|---|---|---|---|---|---|
| 1 | (*R*,*R*)-**10** | $[Pd(allyl)Cl]_2$ | THF | 5 | 80 | 80 | *S* |
| 2 | (*S*,*S*)-**10** | $[Pd(allyl)Cl]_2$ | THF | 3.5 | 90 | 80 | *R* |
| 3 | (*R*,*R*)-**10** | $[Pd(allyl)Cl]_2$ | benzene | 3 | 90 | 82 | *S* |
| 4 | (*S*,*S*)-**10** | $[Pd(allyl)Cl]_2$ | benzene | 3 | 85 | 82 | *R* |
| 5 | (*R*,*R*)-**10** | $[Pd(allyl)Cl]_2$ | toluene | 3.5 | 85 | 78 | *S* |
| 6 | (*S*,*S*)-**10** | $[Pd(allyl)Cl]_2$ | toluene | 3.5 | 70 | 78 | *R* |
| 7 | (*R*,*R*)-**10** | $[Pd(allyl)Cl]_2$ | $CH_2Cl_2$ | 4 | 30 | 0 | *e* |
| 8 | (*R*,*R*)-**10** | $[Pd(allyl)Cl]_2$ | $CH_3CN$ | 5 | 45 | 0 | *e* |
| 9 | (*R*,*R*)-**10** | $Pd_2dba_3$ | THF | 3.5 | 75 | 86 | *S* |
| 10 | (*S*,*S*)-**10** | $Pd_2dba_3$ | THF | 3.5 | 69 | 86 | *R* |
| 11 | (*S*,*S*)-**10** | $Pd(OAc)_2$ | THF | 7.5 | 67 | 73 | *R* |
| 12 | (*R*,*R*)-**10** | $Pd(OAc)_2$ | THF | 7.5 | 68 | 73 | *S* |
| 13 | (*S*,*S*)-**10** | $Pd(PPh_3)_4$ | THF | 5 | 90 | 16 | *R* |
| 14 | (*R*,*R*)-**10** | $Pd(PPh_3)_4$ | THF | 5 | 79 | 6 | *S* |
| 15 | (*S*,*S*)-**8** | $[Pd(allyl)Cl]_2$ | THF | 5 | 31 | 0 | *e* |
| 16 | (*S*,*S*)-**8** | $Pd_2dba_3$ | THF | 4 | 30 | 0 | *e* |
| 17 | (*R*)-**3b** | $[Pd(allyl)Cl]_2$ | THF | 6 | 15 | 28 | *R* |

[a] All reactions were performed at reflux. [b] Isolated yield. [c] Determined by $^1H$ NMR using $Eu(hfc)_3$ as shift reagent. [d] The absolute configuration was determined by comparing the specific rotation with the literature value. [e] Product was racemic.

our and Bolm's ligand should make possible the high throughput synthesis for the evaluation and optimization of steric and electronic effects in ligands of this type. Future studies on the application of **10** and related ligands in asymmetric synthesis is in progress. Results will be reported in due course.

(15) **Procedure for the Palladium-Catalyzed Allylic Substitution of *rac*-Cyclohexenyl Acetate with Dimethyl Malonate.** A solution of **10** (14.4 mg, 0.035 mmol, 10 mol %) and $[Pd(allyl)Cl]_2$ (3.26 mg, 0.008, 2.5 mol %) in dry THF (2 mL) was stirred at room temperature for 1 h. This solution was treated successively with a solution of *rac*-cyclohexenyl acetate (50 mg, 0.35 mmol), dimethyl malonate (125 $\mu$L, 1.07 mmol), *N*,*O*-bis-(trimethylsilyl)acetamide (267 $\mu$L, 1.07 mmol), and a catalytic amount of anhydrous potassium acetate. The reaction mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (10 mL), and washed with saturated aqueous ammonium chloride. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ether = 4/1) to give the product. The enantiomeric excess was determined by $^1H$ NMR spectroscopy in the presence of enantiomerically pure shift reagent $Eu(hfc)_3$ by integration of the signals of the methine proton signal of the malonate moiety.

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**Supporting Information Available:** Procedure for the synthesis of (*R*)-**3b**. Spectral data for **3b**, **10**, **13**, and **15** as well as examples of spectral and specific rotation data for selected examples from Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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