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# Development of a novel chiral spiro ligand bearing oxazoline

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**Abstract**—The synthesis of bis(oxazoline) ligand **1** bearing a spiro skeleton is achieved via double ring-closing metathesis (RCM) of tetraene **2** and subsequent oxazoline ring formation using *N*-bromosuccinimide (NBS). The Cu-spiro bis(oxazoline) complexes prepared from **1** and $Cu(OTf)_2$ or $Cu(OAc)_2$ act efficiently as chiral catalysts for promoting carbonyl-ene reactions or Henry reactions with good enantiocontrol.


## 1. Introduction

The design of enantiomerically pure chiral ligands is one of the most important challenges in the development of asymmetric catalysts.[1] Recently, our group reported the first design and synthesis of chiral spiro ligands bearing isoxazolines [spiro bis(isoxazoline) ligands; SPRIXs],[2a–e] pyrazoles,[2f] and isoxazoles,[2g] as shown in Figure 1. The rigidity of the spirocyclic framework of these ligands, and of SPRIXs in particular, appears to reduce the conformational obscurity in the transition state and consequently promote Pd(II)-mediated enantioselective reactions such as the Wacker-type cyclization of alkenyl alcohols[2b] and the carbonylation of alkenylamines in the presence of carbon monoxide.[2c]

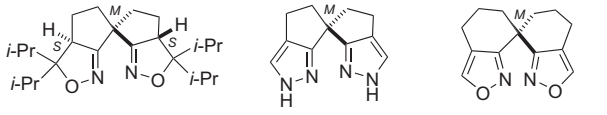


**Figure 1.** Chiral spiro ligands bearing isoxazolines, pyrazoles, and isoxazoles.

To investigate further the unique chirality of spiro ligands in enantioselective reactions, we herein report the first design and synthesis of spiro bis(oxazolines) **1** and compare the ligand-acceleration effect of **1** with SPRIXs.

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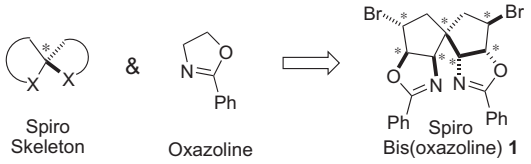
Over the past decade, a large number of chiral oxazoline ligands have been prepared and successfully applied in a variety of asymmetric reactions.[3] The incorporation of oxazoline heterocyclic units into a rigid spiro skeleton would provide a new class of chiral ligands.[4]

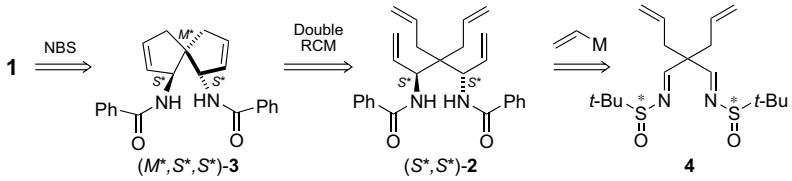
## 2. Results and discussion

The first step was to design a spiro bis(oxazoline) compound with seven stereogenic centers (Scheme 1). Among all the possible diastereomers of the spiro compounds, only **1,** which can be constructed by the reaction of (*M**,*S**,*S**)-**3** with *N*-bromosuccinimide (NBS),[5] was expected to function as a bidentate ligand. In fact, the result of molecular modeling for all diastereomers on MOPAC (AM1) suggested that **1** has the shortest *N*–*N* atomic distance (2.74 Å) and the smallest out-of-plane angle between the two C–N bonds (51.5°).




**Scheme 1.** Design of spiro bis(oxazoline) **1**.

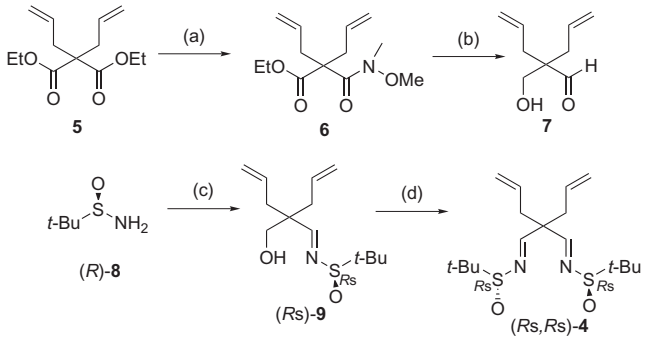
Our retrosynthetic strategy for spiro bis(oxazoline) **1** is outlined in Scheme 2. In this strategy, the key compound (*M**,*S**,*S**)-**3** is synthesized by ring-closing metathesis (RCM)[6] of tetraene (*S**,*S**)-**2** prepared by




**Scheme 2.** Retro synthetic strategy for spiro bis(oxazoline) **1**.

the stereoselective addition of vinyl metal reagents to chiral *t*-butanesulfinyl imines **4**.[7]

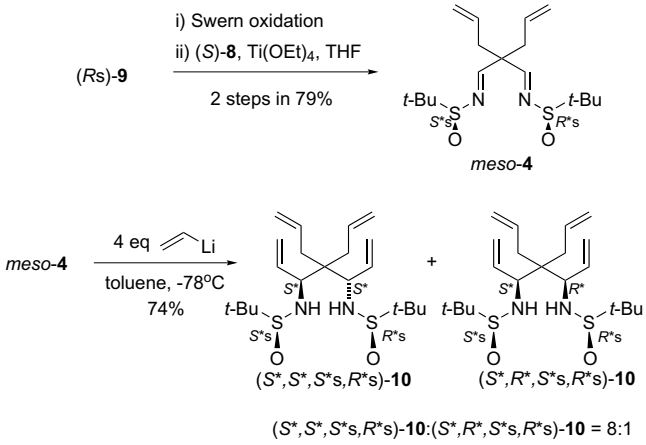
In order to construct the cyclization precursor **3** with the (*M**,*S**,*S**) configuration, (*R*s,*R*s)-**4** was prepared as follows (Scheme 3): diethyl 2,2-diallyl malonate **5** was converted to the Weinreb amide **6** in 85% yield by the reaction of MeONHMe with *i*-PrMgBr.[8] After the reduction of **6** by $LiAlH_4$, the obtained mono-aldehyde **7** was used directly in the next imine formation. In the presence of $Ti(OEt)_4$, condensation of **7** with (*R*)-*t*-butyl sulfinamine (*R*)-**8** afforded (*R*s)-**9** in 55% yield. After the oxidation of (*R*s)-**9**, the resulting aldehyde was reacted with (*R*)-**8** to afford (*R*s,*R*s)-**4** in 78% yield.[9]




**Scheme 3.** Synthesis of *t*-butanesulfinyl imine (*R*s,*R*s)-**4**. Reagents and conditions: (a) MeONHMe–HCl, *i*-PrMgBr, THF, −20 °C, 85%; (b) $LiAlH_4$, THF; (c) **7**, $Ti(OEt)_4$, THF, 55% (two steps from **6**); (d) (i) Swern oxidation, (ii) (*R*)-**8**, $Ti(OEt)_4$, THF, 78% (two steps from (*R*s)-**9**).

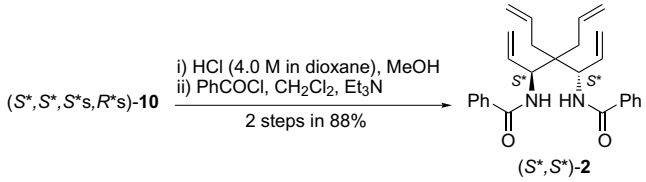
Diastereoselective 1,2-addition of vinyl metal reagents to (*R*s,*R*s)-**4** was then examined. However, the diastereoselective 1,2-addition of vinyl metal reagents, such as vinyl magnesium bromide or vinyl lithium, with or without a Lewis acid to (*R*s,*R*s)-**4** predominantly afforded undesired adduct (*S*,*R*,*R*s,*R*s)-**10** in low yields (~20%).

Thus, *meso*-**4** with an (*S**s,*R**s)-configuration was also prepared using (*R*s)-**9** with (*S*)-**8** in 79% yield according to the method described for (*R*s,*R*s)-**4**. The obtained *meso*-**4** was then reacted with vinyl metal reagents. Among the various conditions attempted, the use of vinyl lithium (toluene solution) for *meso*-**4** gave the desired product (*S**,*S**,*S**s,*R**s)-**10** together with (*S**,*R**,*S**s,*R**s)-**10** as an undesirable diastereomer in a ratio of 8:1, as shown in Scheme 4. Diastereomer (*S**,*S**,*S**s,*R**s)-**10** and (*S**,*R**,*S**s,*R**s)-**10** were separable by silica gel column chromatography (acetone/hexane = 1:6). A solution of (*S**,*S**,*S**s,*R**s)-**10** in MeOH




**Scheme 4.** Diastereoselective 1,2-addition of vinyl lithium reagent to *meso*-**4**.

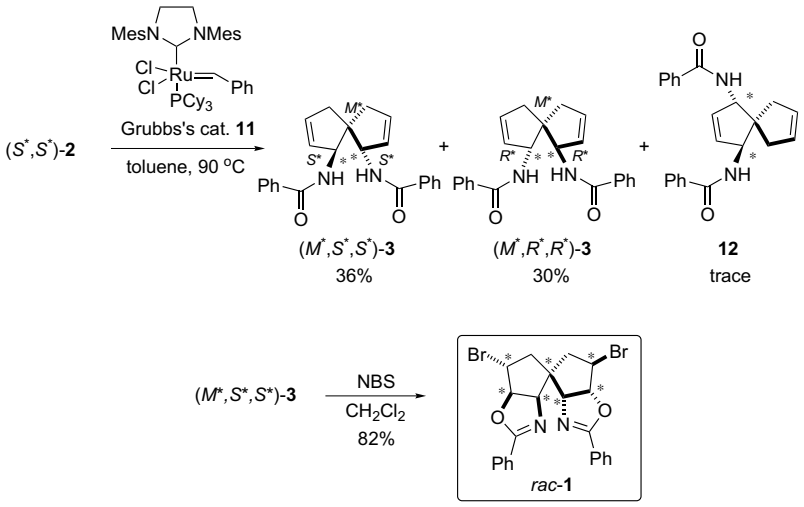
was treated with HCl (4.0 M in dioxane) to cleave the *t*-butyl sulfinimine moiety, with the resulting product reacted with benzoic acid chloride to afford the cyclization precursor (*S**,*S**)-**2** in 88% yield (Scheme 5).




**Scheme 5.** Synthesis of cyclization precursor (*R**,*R**)-**2**.

RCM of (*S**,*S**)-**2** with Grubbs's catalyst **11**[6b] proceeded to afford the desired spiro amide (*M**,*S**,*S**)-**3** (36%) and (*M**,*R**,*R**)-**3** (30%), together with a trace amount of **12** (Scheme 6). Finally, the desired spiro bis(oxazoline) ligand **1** was synthesized in 82% yield via oxazoline ring formation promoted by NBS, as shown in Scheme 6. This reaction proceeded with high diastereoselectivity, with no other diastereomer being observed.

The coordinative ability of spiro bis(oxazoline) ligand **1** to transition metals was briefly examined by mixing **1** with metal salts such as $CuCl_2$, $Pd(OCOCF_3)_2$, and $Pd(CH_3CN)_2Cl_2$ in $CH_2Cl_2$. In all cases, the mixture of **1** and metal salts produced characteristic color changes. In particular, all peaks in the nuclear magnetic resonance (NMR) spectrum of the complex (**1**-$Pd(CH_3CN)_2Cl_2$; 1/1) were significantly shifted downfield compared to the original spectrum. These results




**Scheme 6.** Synthesis of spiro bis(oxazoline) **1**.

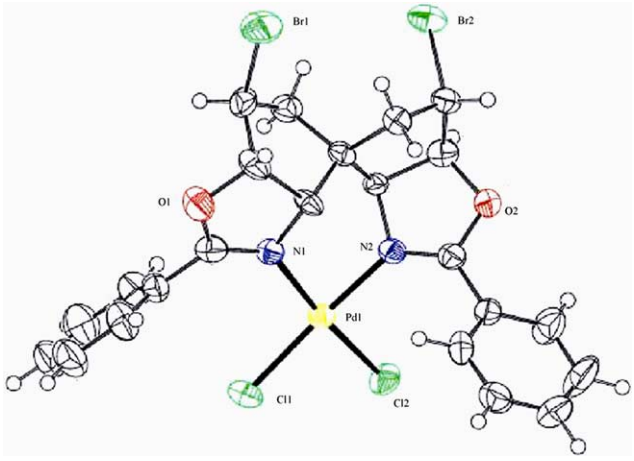


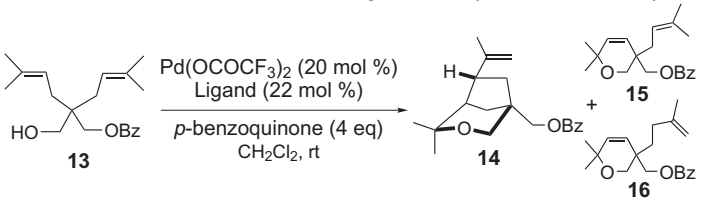

**Figure 2.** ORTEP drawing of $PdCl_2$–(±)-**1** complex.

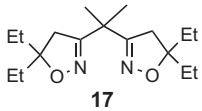
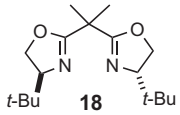
indicate the spontaneous formation of metal complexes with ligand **1**. X-ray analysis of a single crystal obtained by recrystallization from a 1:1 mixture of ligand **1** with $PdCl_2$ in acetone–hexane revealed a $PdCl_2$–**1** complex structure in which **1** acts as a bidentate ligand (Fig. 2).[10]

Enantiomerically pure **1** was readily obtained by separation using a chiral stationary phase column.[11] Initially, enantiomerically pure **1** was applied in the Pd(II)-mediated enantioselective Wacker-type cyclization of the alkenyl alcohol (Table 1).[2b]

In contrast to using Pd(II)–SPRIX and Pd(II)–**17** (entries 2 and 3),[2e] no cyclization product was detected when the Pd–bis(oxazoline) complex was utilized (entries 1 and 4). This clearly shows that the isoxazoline moieties in the ligand play an important role in promoting the

**Table 1.** Comparison of acceleration effects of isoxazoline and oxazoline ligands on asymmetric tandem cyclization

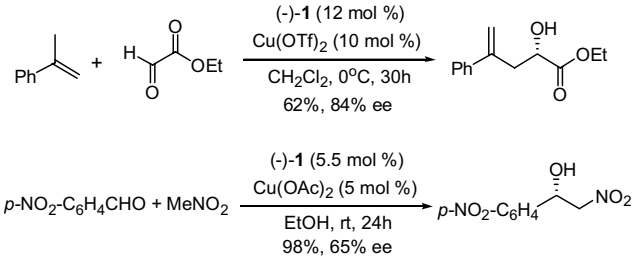



| Entry | Ligand | Time (h) | Yield (%)[a] | Product ratio [ee (%)] | | |
|---|---|---|---|---|---|---|
| | | | | **14** | **15** | **16** |
| 1 | (−)-**1** | 50 | Trace | — | — | — |
| 2[b] | (*M*,*S*,*S*)-*i*-Pr–SPRIX | 8 | 73 | 57(93) | 20(31) | 23(48) |
| 3 |  **17** | 23 | 91 | 41 | 41 | 18 |
| 4 |  **18** | 45 | Trace | — | — | — |
| 5 | None | 67 | 34 | 26 | 66 | 8 |

[a] Total yield.
[b] The reaction at 0 °C for 85 h gave **14** (65%, 95% ee), **15** (5%, 45% ee), and **16** (26%, 60% ee).

cyclization. The lack of catalytic activity when **1** and **18**[12] were applied in the above reaction may be attributable to the strong Lewis basicity of the metal-coordinating oxazolines in comparison with that for isoxazolines.[2e]

Although the Pd(II)–**1** complex did not promote the tandem reaction from **13** to **14**, the Cu(II)–**1** complex catalyzed both the carbonyl-ene reaction[13] of α-methyl styrene with ethyl glyoxylate, and the Henry reaction[14] of nitromethane with *p*-nitrobenzaldehyde to afford the corresponding products with moderate enantioselectivity (Scheme 7). These results indicate that spiro bis(oxazoline) functions effectively as an asymmetric ligand. This ligand-acceleration ability is a promising feature that has proven to be useful in studies of other catalytic asymmetric reactions.




**Scheme 7.** Asymmetric reactions promoted by Cu(II)-spiro bis(oxazoline) ligand **1**.

## 3. Conclusion

In conclusion, novel spiro bis(oxazoline) **1** was synthesized as a new class of bidentate ligand, and the coordinative ability of **1** for metal salts was confirmed by NMR and X-ray crystallographic analysis.

## Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan and the Uehara Memorial Foundation. We thank the technical staff of the Materials Analysis Center of the Institute of Scientific and Industrial Research (ISIR), Osaka University, for technical assistance.

## References

1. (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Synthesis I–III*; Springer: Berlin, 1999; (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000; (c) Kobayashi, Y., Ed. *Latest Frontiers of Organic Synthesis*; Research Signpost, 2002.
2. (a) Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795; (b) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907; (c) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711; (d) Muthiah, C.; Arai, M. A.; Shinohara, T.; Arai, T.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 5201; (e) Shinohara, T.; Wakita, K.; Arai, M. A.; Arai, T.; Sasai, H. *Heterocycles* **2003**, *59*, 587; (f) Takizawa, S.; Honda, Y.; Arai, M. A.; Kato, T.; Sasai, H. *Heterocycles* **2003**, *60*, 2551; (g) Wakita, K.; Arai, M. A.; Kato, T.; Shinohara, T.; Sasai, H. *Heterocycles* **2004**, *62*, 831.
3. Review of bis(oxazoline) ligands for asymmetric catalysis: (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339; (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1; (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325; (d) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.
4. Several chiral ligands with spiro skeletons have been reported (a) Chan, A. S. C.; Hu, W.-H.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.-Z.; Mi, A.-Q.; Yan, M.; Sun, J.; Lou, R.-L.; Deng, J.-G. *J. Am. Chem. Soc.* **1997**, *119*, 9570; (b) Tamura, N.; Takahashi, T.; Nakajima, M.; Hashimoto S. *Abstracts*, 26th Symposium on Progress in Organic Reactions and Syntheses, Osaka, Japan, November 20–21, 2000; p 58; (c) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404; (d) Kandula, S. V.; Puranik, V. G.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 5015; (e) Lait, S. M.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2004**, *15*, 155.
5. (a) Goodman, L.; Winstein, S. *J. Am. Chem. Soc.* **1957**, *79*, 4788; (b) Baldwin, J. E.; Kelly, D. R.; Ziegler, C. B. *J. Chem. Soc., Chem. Commun.* **1984**, 133.
6. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953; (c) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247; (d) Martin, R.; Alcon, M.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896.
7. (a) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011; (b) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883; (c) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772; (d) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303; (e) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3.
8. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
9. The direct conversion of **5** to **4** via the corresponding dialdehyde resulted in a low yield of **4**.
10. Crystal data for $PdCl_2$–(±)-**1** complex: monoclinic, space group *C*2/*c*, $a = 12.05(1)$ Å, $b = 14.87(1)$ Å, $c = 14.54(1)$ Å, $\beta = 112.43(6)°$, $V = 2408(3)$ Å$^3$, $Z = 4$, $R = 0.037$, $Rw = 0.021$.
11. HPLC conditions: Daicel Chiralpak AD ($\phi$ 2 cm × 25 cm), *i*-PrOH/hexane = 1:29, 5.0 mL/min, 31 min [(*M*,*R*,*R*,*R*,*R*,*R*,*R*)-**1**, $[\alpha]_D^{26} = -112.7$ (*c* 0.69, $CHCl_3$)], 41 min [(*P*,*S*,*S*,*S*,*S*,*S*,*S*)-**1**, $[\alpha]_D^{26} = +113.4$ (*c* 0.67, $CHCl_3$)]. The absolute configuration of **1** was determined by exciton CD Cotton effects in $CHCl_3$.
12. (a) Rush, S.; Reinmuth, A.; Risse, W. *Macromolecules* **1997**, *30*, 7375; (b) Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Commun.* **1998**, 2377; (c) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3417.
13. Procedure for carbonyl-ene reaction: A mixture of ligand (−)-**1** (0.012 mmol) and $Cu(OTf)_2$ (0.006 mmol) in $CH_2Cl_2$ (0.8 mL) was stirred at 0 °C for 2 h. To this solution was added α-methyl styrene (0.20 mmol) and ethyl glyoxylate (1.2 mmol). After stirring for a further 30 h at 0 °C, the reaction was quenched by the addition of water, and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by

silica gel column chromatography (ethyl acetate/hexane = 1:8) to afford the product in 62% yield with 84% ee. The enantiomeric excess of the products was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS, hexane/*i*-PrOH = 9:1, flow rate = 0.5 mL/min).

14. Procedure for Henry reaction: A mixture of ligand (−)-**1** (0.055 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol) in EtOH (1.5 mL) was stirred at rt for 1 h. To the resulting clear blue solution was added nitromethane (10 mmol) and *p*-nitrobenzaldehyde (1.0 mmol). After stirring for a further 24 h at rt, the volatile components were removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:8) to afford the product in 98% yield with 65% ee. The enantiomeric excess of the products was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9:1, flow rate = 1.0 mL/min). The product was identical in all respects to the spectra reported by Evans et al., Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.