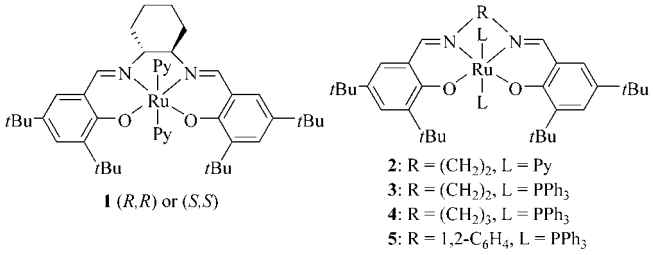
Asymmetric Catalysis

# Axial Ligand Effects: Utilization of Chiral Sulfoxide Additives for the Induction of Asymmetry in (Salen)ruthenium(II) Olefin Cyclopropanation Catalysts**

*Jason A. Miller, Bradley A. Gross, Michael A. Zhuravel, Wiechang Jin, and SonBinh T. Nguyen**

The enantioselective synthesis of compounds containing the cyclopropyl fragment has recently received considerable attention, largely because of the frequent occurrence of cyclopropanes in natural products and their importance as valuable synthetic intermediates.[1–3] Although many methods have been developed, transition-metal-catalyzed asymmetric cyclopropanation has emerged as one of the most efficient routes for the formation of optically pure cyclopropanes.[1,4] However, the syntheses of the necessary chiral catalysts for this important transformation are often rather laborious. A general and facile method for the asymmetric synthesis of a cyclopropanation catalyst has yet to be developed.

Recently, we have focused on cultivating efficient methods for the development of asymmetric catalysts. We began by improving on our previously reported (salen)ruthenium(II) asymmetric cyclopropanation system. This catalyst system has been shown to be highly effective for the cyclopropanation of olefins with the carbene precursor ethyl diazoacetate (EDA).[5] However, although the use of chiral catalyst **1** (Scheme 1) has led to exceptional selectivity and high yields for the cyclopropanation of olefins with EDA, these results




***Scheme 1.*** Asymmetric **1** and achiral (salen)ruthenium(II) cyclopropanation catalysts **2**–**5**. Py = pyridine.

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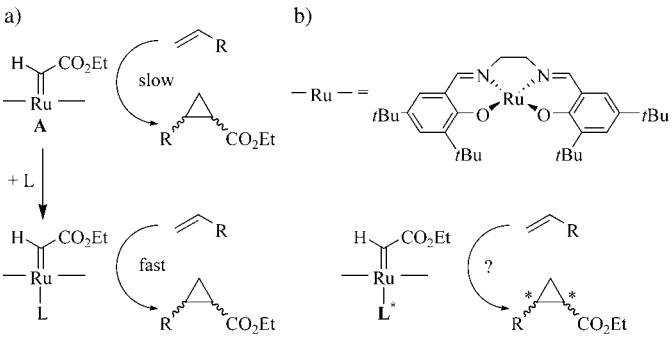
[**] This work was supported by the National Institute of Health and the DuPont Company. J.A.M. is an ACS Division of Organic Chemistry Nelson J. Leonard Fellow sponsored by Organic Synthesis, Inc., and S.T.N. is an Alfred P. Sloan Research Fellow. We also thank the Packard Foundation for partial financial support and Prof. M. J. Hynes for his help with the WinEQNMR program. Salen = N,N′-bis(salicylidene)ethylenediamine.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

can not necessarily be extended to all olefin substrates. For some olefins, multiple catalysts containing different chiral diamine backbones must be examined before optimal results can be achieved. The synthesis of a series of chiral salen-based catalysts with differing backbones is both expensive and time consuming so an alternative approach is needed to expedite the screening of new olefins and diazo compounds for the cyclopropanation reaction.

Previous work in our group has demonstrated a significant ligand-accelerated catalysis effect for certain substrates through what is presumed to be axial ligand binding and further activation of the ruthenium carbene cyclopropanation intermediate (Scheme 2a).[6] We hypothesized that this could be used to our advantage and an optically pure Lewis base

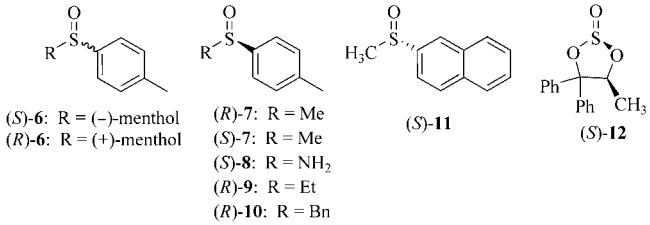



***Scheme 2.*** a) Ligand-accelerated catalysis in olefin cyclopropanation catalyzed by a (salen)ruthenium(II) complex. b) A chiral Lewis base **L*** ligated axially to an achiral (salen)ruthenium–carbene cyclopropanation intermediate could induce asymmetry.

could be used to bind axially to an achiral catalyst as an alternative to using the preformed chiral (salen)ruthenium(II) catalyst **1**. The Lewis base, if paired correctly with the catalyst (both electronically and sterically), should force an achiral salen ligand into an asymmetric conformation, thus transferring enantioselectivity to the cyclopropanation reaction occurring on the opposite axial face of the catalyst. This approach would allow the use of the inexpensive and readily synthesized achiral catalysts **2**–**5** and the facile screening of a nearly endless library of chiral Lewis bases **L*** that can function as ligands to the metal carbene intermediate (Scheme 2b). Related strategies were previously employed by Katsuki and co-workers with varying degrees of success for the (salen)manganese(III)-catalyzed asymmetric epoxidation of olefins through the application of chiral amines[7,8] and chiral pyridine *N*-oxides.[9] Walsh and co-workers also reported considerable enhancement in selectivity when chiral additives were used to convey asymmetry into an achiral titanium precatalyst for the addition of an ethyl nucleophile to aldehydes.[10–12] A recent review by Walsh et al. touched on the potential application of this novel and exciting approach to catalyst screening.[13]

Herein, we describe the first example of an asymmetric cyclopropanation mediated by a combination of achiral (salen)ruthenium(II) catalysts **2**–**5** and a catalytic amount of chiral sulfoxide additives (**6**–**12**; Scheme 3). Sulfoxides were chosen as a test class of chiral Lewis bases because they have

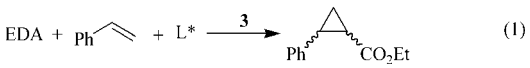
 DOI: 10.1002/ange.200460887  




***Scheme 3.*** Sulfoxide Lewis bases used as chiral additives for the cyclopropanation of olefins with achiral (salen)ruthenium(II) complexes.

been recently used as ligands in asymmetric catalysis.[14,15] Sulfoxide ruthenium(II) complexes are well known[12,16] and chiral sulfoxides have centers of asymmetry that are very close to the ruthenium center during coordination and should have a high probability of transmitting chirality to a flexible salen ligand.

We screened several chiral sulfoxides (**6**–**12**) individually as catalytic additives for the cyclopropanation of styrene with EDA catalyzed by the achiral catalyst **3** [Eq. (1); Table 1]. In




(1)

***Table 1:*** The cyclopropanation of styrene and EDA with **3** and chiral sulfoxides **6**–**9**.[a]

| L* | Yield [%][b] | *cis*/*trans* | *cis ee* [%][c] | *trans ee* [%][c] |
|---|---|---|---|---|
| none | 92 | 1:7.5 | – | – |
| (*S*)-**6** | 86 | 1:7.3 | 23 (*S*,*R*) | 5 (*S*,*S*) |
| (*R*)-**6** | 87 | 1:7.2 | 23 (*R*,*S*) | 5 (*R*,*R*) |
| (*S*)-**7** | 84 | 1:7.5 | 50 (*S*,*R*) | 42 (*S*,*S*) |
| (*R*)-**7** | 86 | 1:7.6 | 57 (*R*,*S*) | 46 (*R*,*R*) |
| (*S*)-**8** | 85 | 1:7.2 | 40 (*R*,*S*) | 10 (*R*,*R*) |
| (*R*)-**9** | 96 | 1:7.4 | 51 (*R*,*S*) | 29 (*R*,*R*) |
| (*R*)-**10** | 90 | 1:7.3 | 56 (*R*,*S*) | 45 (*R*,*R*) |
| (*S*)-**11** | 90 | 1:7.3 | 41 (*S*,*R*) | 45 (*S*,*S*) |
| (*S*)-**12** | 87 | 1:7.4 | 33 (*R*,*S*) | 16 (*R*,*R*) |

[a] Reaction conditions: EDA (0.5 mmol), styrene (2.5 mmol), **3** (1 mol%), **L*** (10 mol%), $CH_2Cl_2$ (5 mL), RT, 12 h. [b] Yield determined by GC analysis based on EDA with undecane as an internal standard. [c] Absolute configuration determined from chiral GC analysis versus known standards.

general, the addition of these chiral additives does not affect either the yield or diastereoselectivity of the reaction. Furthermore, reversing the chirality of the sulfoxide (that is, (*S*)-**6** versus (*R*)-**6** and (*S*)-**7** versus (*R*)-**7**) leads to opposite enantioselectivities, thus lending support to the supposition that the chirality of the product is a direct result of the Lewis base additive.

These preliminary results were quite promising. Even with a very low concentration of additive in solution (10 mol% relative to EDA), *ee* values of up to 57% were noted. These results suggested to us that (*R*)-(+)-methyl *p*-tolyl sulfoxide (*R*)-**7** was the best chiral additive for the cyclopropanation of styrene. This was somewhat surprising in light of the small size of the methyl substituent on (*R*)-**7** relative to the larger menthol substituents on additive **6**. The use of additives with amino ((*S*)-**8**), ethyl ((*R*)-**9**), and benzyl ((*R*)-**10**) substituents on the *p*-tolyl sulfoxide was also investigated to probe for the optimal steric environment; however, none of these compounds proved as successful as (*R*)-**7**. (*S*)-Methyl 2-naphthyl sulfoxide ((*S*)-**11**) was used to determine the effect of adding steric bulk to the other side of the sulfoxide. Surprisingly, this also yielded lower enantioselectivities than (*R*)-**7**. Additive (*R*)-**7** was, however, expected to produce higher enantioselectivities than the cyclic compound (*S*)-**12**, in which the cone angle of the chiral center is considerably smaller.

As we previously reported, the olefin cyclopropanation product can be readily separated from a reaction mixture containing solvent, catalyst, and excess olefin.[17] This same isolation strategy can also be applied in the current case when a chiral Lewis base is also present in solution. As a representative example, the optically enriched styrene cyclopropanation product produced in the presence of additive (*R*)-**7** could be isolated in excellent yield (94%). Further details on the isolation procedure can be found in the Experimental Section.

Additive (*R*)-**7** was then subjected to a range of reaction conditions and catalysts to optimize the enantioselectivity for the cyclopropanation of styrene (Table 2). The enantioselectivity of the reaction increased to nearly 70% with respect to the *cis* isomer when 50 mol% of (*R*)-**7** was used with **3** (Table 2, entry 5). The same increase was noted when the solvent amount was decreased and the amount of sulfoxide added was maintained at 10 mol% (Table 2, entries 6 and 7). Decreasing the temperature of the reaction also positively affected the *ee* value of the products; when the reaction temperature was lowered to −78 °C and the additive concentration increased, the *cis* and *trans* products were obtained in 93 and 87% *ee*, respectively (Table 2, entry 9). These promising results are amongst the highest *ee* values reported for asymmetric induction resulting from the action of a chiral additive on an achiral catalyst.

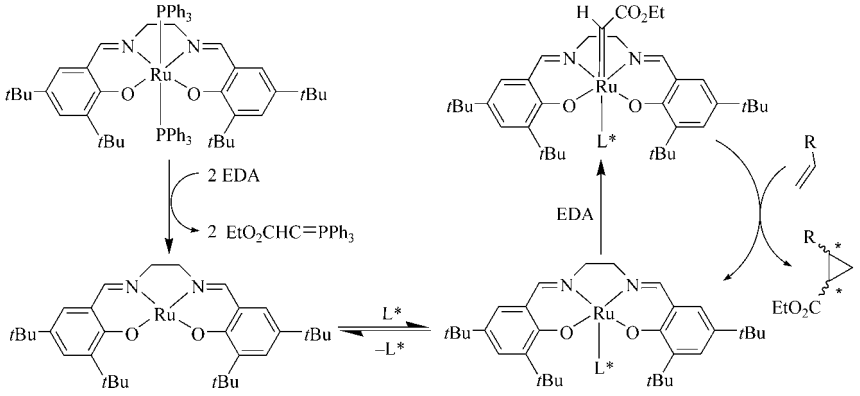
***Table 2:*** Optimization of reaction conditions for the cyclopropanation of styrene and EDA with sulfoxide (*R*)-**7**.[a]

| Entry | Cat. | (*R*)-**7** [mol%] | $CH_2Cl_2$ [mL] | *T* [°C] | Yield [%][b] | *cis*/*trans* | *cis ee* [%][c] | *trans ee* [%][d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **2** | 10 | 5.0 | 25 | 87 | 1:7.6 | 41 | 19 |
| 2 | **3** | 10 | 5.0 | 25 | 86 | 1:7.6 | 57 | 46 |
| 3 | **4** | 10 | 5.0 | 25 | 90 | 1:5.7 | 27 | 13 |
| 4 | **5** | 10 | 5.0 | 25 | 89 | 1:7.8 | 0 | 0 |
| 5 | **3** | 50 | 5.0 | 25 | 88 | 1:7.3 | 67 | 57 |
| 6 | **3** | 10 | 3.5 | 25 | 88 | 1:7.0 | 65 | 57 |
| 7 | **3** | 10 | 2.5 | 25 | 85 | 1:6.9 | 72 | 64 |
| 8 | **3** | 10 | 2.5 | 0 | 90 | 1:7.4 | 85 | 81 |
| 9 | **3** | 10 | 0.0[e] | −78[f] | 92 | 1:6.7 | 93 | 87 |

[a] Reaction conditions: EDA (0.5 mmol), styrene (2.5 mmol), cat. (1 mol%), 12 h. [b] Yield determined by GC analysis based on EDA with undecane as an internal standard. [c] *R*,*S* configuration in all cases. [d] *R*,*R* configuration in all cases. [e] Reaction was carried out in neat styrene. [f] Original temperature followed by slow warming to RT over 6 h.

We propose that the mechanism of asymmetric induction for Equation (1) involves the axial coordination of the chiral sulfoxide to the ruthenium center as a key induction step in the reaction stereoselectivity (Scheme 4). Initial reaction of




***Scheme 4.*** Proposed mechanism of asymmetric induction through a chiral additive.

EDA with the axial triphenylphosphane ligands of **3**–**5** causes the rapid formation of phosphorus ylides, which do not bind significantly to the metal center.[18] This leaves the axial positions of the catalyst open to coordination by the chiral sulfoxide. The chiral additive can then bind preferentially to one of the two chiral conformers of the achiral (salen)ruthenium complex,[7–9] thus effectively forcing the larger achiral salen ligand to adopt a preferred chiral conformation. Therefore, the asymmetry of the additive is transmitted/amplified to the opposite axial position where a ruthenium carbene can interact stereoselectively with an olefin to complete the cyclopropanation cycle. Balsells and Walsh termed this phenomenon *chiral environment amplification*.[12] The catalytic formation of cyclopropanes through this induced chiral environment, especially when coupled with ligand-accelerated catalysis (Scheme 2a), would afford an excess of one enantiomer, as expected from our work with preformed chiral (salen)ruthenium(II) complexes.[5] Catalyst **5**, with the rigid phenylene diamine backbone, yielded no enantioselectivity when chiral sulfoxide (*R*)-**7** was used as an additive (entry 4), which is consistent with our proposed mechanism.

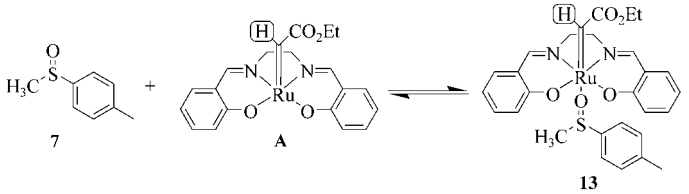
Catalyst **4**, which contains the propylenediamine backbone, yields the same sense of chiral induction as the ethylenediamine analogue **3** in the presence of (*R*)-**7** (Table 2, entries 3 and 2), as could be predicted from the proposed mechanism in Scheme 4. It is also reassuring that the *cis*/*trans* ratio is very close to that when the reaction is carried out in the absence of a chiral additive (1:6.2).

The addition of either (*R*)-**7** or (*S*)-**7** to the cyclopropanation reaction of styrene with EDA using the chiral preformed catalyst **1** (*R*,*R* or *S*,*S*) results in no increase or decrease in the enantiomeric excess of the cyclopropane product compared to use of the chiral catalyst alone. These match/mismatch experiments suggest that the backbone of a chiral catalyst overrides the chirality of an additive and, therefore, plays a larger role in asymmetric induction.

The use of (*R*)-**7** and catalyst **2**, which contains pyridine axial ligands, together with led to lower optical enrichment of the product cyclopropanes compared to when **3**, which loses both $PPh_3$ moieties at the beginning of the catalytic cycle, was employed (see entries 1 and 2). This effect is most likely because of competition between the pyridine and the additive for the axial position of the catalyst. Pyridine binds strongly to the ruthenium(II) center,[5] so coordination of the chiral additive is hindered. Titration data suggest that this is indeed the case, as addition of increasing amounts of pyridine to a mixture of (*R*)-**7** and **3** leads to linearly decreasing enantiomeric excess.

Control experiments with either a chiral sulfoxide/EDA system or preformed sulfoxide ylides,[19] both with and without the (salen)ruthenium(II) catalyst **3**, confirm that the metal center is necessary for catalytic activity and that the reaction does not occur through a pathway that requires the formation of a sulfoxide ylide. These results are consistent with our proposed mechanism and fully support the idea of chiral induction by an axial ligand.

Further support for our proposed mechanism was obtained by examining the binding mode of the sulfoxide to **A** by NMR spectroscopy.[20] The changes in the chemical shift of the resonances for the α-methyl protons in **7** when it was alone in solution and when it was in solution with the carbene complex **A** were compared ($\delta = 2.07$ versus $\delta = 2.14$ ppm, respectively), thus indicating that **7** binds through the sulfoxide oxygen atom. This small change in chemical shift ($< 0.1$ ppm) is diagnostic of the oxygen-atom binding mode; binding through the sulfur atom produces a much larger change ($> 1$ ppm).[15] Furthermore, analysis of the carbene proton of the (salen)ruthenium carbene cyclopropanation intermediate allowed us to calculate the binding constant for the formation of the bound complex **13** [Eq. (2); salen *t*Bu




(2)

groups omitted for clarity]. Figure 1 shows that increasing concentrations of sulfoxide in solution leads to a downfield shift of the carbene proton. These data were used to calculate a binding constant of $K_{eq} = 129 \pm 6\ \text{M}^{-1}$ using WinEQNMR software.[21]

Although binding at the ruthenium center to the oxygen atom of the sulfoxide group is inferred by our spectroscopic observations (see above), it is possible that a Curtin–Hammett situation may occur in which the oxygen-bound complex is not necessarily the active species responsible for the excellent cyclopropanation enantioselectivities. That is,

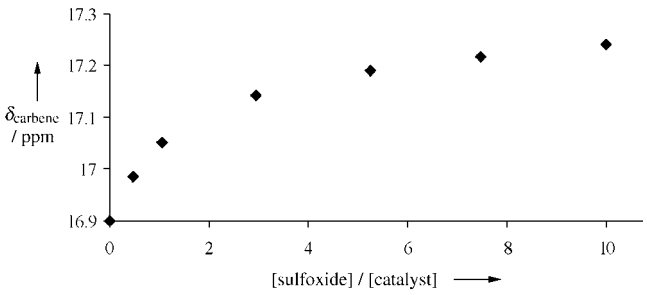


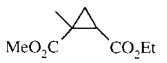
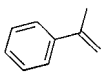
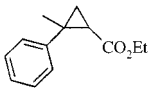
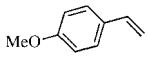
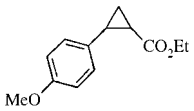
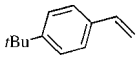
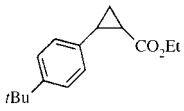
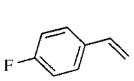
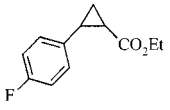
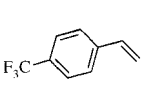
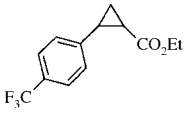

***Figure 1.*** Changes in the chemical shift of the ruthenium carbene proton on addition of sulfoxide **7**.

the sulfur-bound carbene complex could be present in a minute quantity that cannot be observed by NMR spectroscopy but is primarily responsible for the asymmetric induction. Further mechanistic experiments are in progress to help elucidate this possibility and the results will be published at a later date.

We have also extended this sulfoxide-induced chiral amplification strategy to the cyclopropanation of other olefins (Table 3). Quite promising enantioselectivities were observed for these substrates despite having a limited library of chiral sulfoxides, such as **6**–**12**. As observed with styrene, diastereoselectivities remained similar both with and without the chiral additives. These exciting results prove that styrene is not a unique case and that this method is, in fact, applicable to other olefins. Interestingly, although additive (*R*)-**7** induces the greatest enantioselectivities for styrene and its *para*-substituted derivatives, it is not the best chiral Lewis base for all other substrates: methyl methacrylate gave the best results when (*R*)-benzyl *p*-tolyl sulfoxide (*R*)-**10** was utilized, whereas (α-methyl)styrene required the use of (*R*)-**6**. Table 3 shows representative results for these two substrates with some of the optimally performing sulfoxides. These results show that a combinatorial approach can be used to simultaneously screen the substrate and chiral additives for optimum selectivity and reaction conditions. As with styrene, the cyclopropanation products of the substrates listed in Table 3 can be readily isolated in yields closely matching those calculated by GC-calibration techniques.

In conclusion, we have found an efficient and facile method for the development of new (salen)ruthenium(II) catalysts for the asymmetric cyclopropanation of olefins. This exciting modular approach is amenable to parallel-screening optimization and has great potential advantages over traditional catalyst development and synthetic methods. We feel that this approach may also be extended to other types of catalysis where one metal coordination site is free during a reaction. The initial selectivities with this achiral catalyst/chiral Lewis base system are very promising and provide a solid proof-of-concept that chirality can be introduced into a complex cyclopropanation system through the addition of a simple optically active additive. Screening experiments with other classes of chiral additives is underway and optimization data will be reported in due course.

***Table 3:*** Optimized results for the cyclopropanation of various olefins with EDA by using chiral sulfoxides to induce asymmetry into achiral catalyst **3**.[a]

| Substrate | Product | Additive | Yield [%][b] | *cis*/*trans* | *cis ee* | *trans ee* |
|---|---|---|---|---|---|---|
|  |  | (*R*)-**6** | 86 | 1:45.7 | – | 47 |
| | | (*R*)-**7** | 98 | 1:40.2 | – | 68 |
| | | (*R*)-**10** | 98 (84[c]) | 1:45.8 | – | 80 |
|  |  | (*R*)-**6** | 97 (89[c]) | 1:1.1 | 43 | 53 |
| | | (*R*)-**7** | 97 | 1:1.4 | 10 | 3 |
| | | (*R*)-**10** | 97 | 1:1.3 | 0 | 0 |
|  |  | (*R*)-**7** | 97 (97[c]) | 1:5.9 | 89 | 87 |
|  |  | (*R*)-**7** | 95 (88[c]) | 1:4.8 | 93 | 87 |
|  |  | (*R*)-**7** | 86 (92[c]) | 1:5.8 | 80 | 83 |
|  |  | (*R*)-**7** | 98 (98[c]) | 1:7.8 | 79 | 86 |

[a] Reaction conditions: EDA (0.5 mmol), olefin (2.5 mmol), **3** (1 mol%), additive (10 mol%), 12 h. [b] Yield determined by GC analsis relative to styrene cyclopropane based on EDA with undecane as an internal standard. [c] Yield of isolated cyclopropane (see the Supporting Information for details).

## *Experimental Section*

General procedure for the asymmetric cyclopropanation of olefins with EDA using (salen)ruthenium(II) complexes **1**–**5** and chiral sulfoxide additives **6**–**12**:[22] A mixture of achiral ruthenium catalyst (0.005 mmol), olefin (2.5 mmol), and sulfoxide (0.05 mmol for 10 mol% and 0.25 mmol for 50 mol%) in $CH_2Cl_2$ (2.5 mL) was placed in a 25-mL round-bottom flask under $N_2$ in a drybox. A three-times degassed $CH_2Cl_2$ (2.5 mL) solution of EDA (0.50 mmol) and undecane internal standard (0.50 mmol) was slowly added by a gas-tight syringe over a period of 20 min under $N_2$. After the addition was complete, the reaction mixture was allowed to stir for 12 h at room temperature. A sample of the solution was then passed through a short plug of silica gel (0.3 × 3 cm) to remove the catalyst and the plug was washed with $CH_2Cl_2$ (15 mL). The combined organic solutions were analyzed by using standard-phase GC for diasteroselectivity and either chiral-phase GC or HPLC for enantioselectivity.

Received: June 7, 2004
Revised: February 9, 2005
Published online: May 18, 2005

**Keywords:** cyclopropanation · ligand-accelerated catalysis · ruthenium · salen · sulfoxides

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