Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 9287–9290

TETRAHEDRON
LETTERS

# High *trans* selectivity in the copper bis(oxazoline)-catalyzed asymmetric cyclopropanation of olefins by (trimethylsilyl)diazomethane

Marcia B. France,* Allyn K. Milojevich, Tracy A. Stitt and Angela J. Kim

*Department of Chemistry, Washington and Lee University, Lexington, VA 24450, USA*

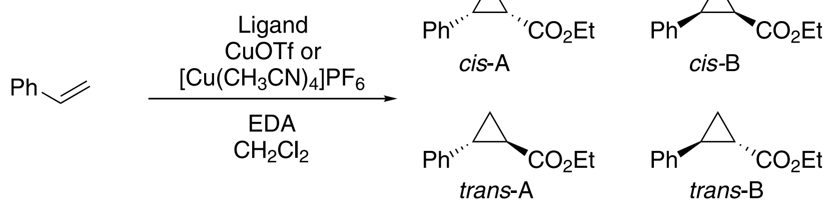
Received 12 August 2003; revised 21 September 2003; accepted 13 October 2003

**Abstract**—Copper(I) bis(oxazoline) species are among the most enantioselective cyclopropanation catalysts that have been reported, although these catalysts generally give low diastereoselectivities. We have observed greatly improved diastereoselectivities using (trimethylsilyl)diazomethane as the carbon source. We have also identified several bis(oxazoline) species that also give comparable or higher enantioselectivities with (trimethylsilyl)diazomethane compared to the more readily available ethyl diazoacetate. The application of this methodology to several olefins has been explored.

Cyclopropyl groups are found in a wide variety of synthetic and naturally occurring compounds of interest.[1–6] A number of catalyst systems have been developed for the asymmetric cyclopropanation of olefins.[7–11] Many of these are based on the decomposition of diazo compounds and are believed to proceed through a metal carbenoid intermediate. These systems include copper complexes of chiral Schiff base, bipyridine, semicorrin, and bis(oxazoline) ligands as well as rhodium carboxamides and porphyrins, ruthenium pybox, and cobalt and ruthenium salen complexes.

The most widely studied class of diazo reagents for the intermolecular cyclopropanation reaction is the α-diazoesters. The cyclopropanation of styrene, a common test substrate, results in the formation of four stereoisomers (Eq. (1)). The use of commercially available ethyl diazoacetate (EDA) in this reaction generally gives diastereoselectivities less than 2:1 in favor of the *trans* stereoisomer.[10] Diastereoselectivities can be improved by increasing the bulk of the ester functionality.[7,12–19] Improved diastereoselectivities have also been observed in the rhodium(II)-catalyzed decomposition of vinyldiazomethanes.[20] However, such diazo compounds are not commercially available and therefore must be prepared prior to use. Nishiyama has also reported high *trans* selectivities in the asymmetric cyclopropanation of styrene with ruthenium(II) pybox complexes. While the diastereoselectivities again increase with increasing bulk of the diazo group, even with EDA high *trans*/*cis* ratios on the order of 10.1:1 have been observed.[21] However, these ruthenium catalysts are less active than copper catalysts.[7,21,22]

In the course of our investigations of the asymmetric cyclopropanation of styrene with diazo compounds catalyzed by copper salen and diimine complexes, we observed that the use of commercially available (trimethylsilyl)diazomethane (TMSDM) leads to extremely high diastereoselectivities. In some cases,



(1)

---

*Keywords*: cyclopropanation; diazo compounds; enantioselection; diastereoselection.

* Corresponding author.

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.068

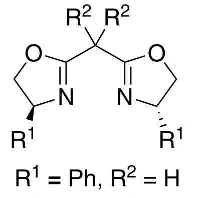
only trace amounts of the *cis* isomer could be detected by GC. To our knowledge, relatively few examples of cyclopropanations with TMSDM have been reported. One of the earliest reports involved an achiral copper system, in which a *trans*/*cis* ratio of 9.3:1 was observed for the cyclopropanation of cyclohexene.[23] The few systems that have been reported reveal that *trans* isomers are strongly favored in the copper-catalyzed cases,[24–26] but no one has thoroughly explored this phenomenon. While our salen and diimine systems gave only low to moderate enantioselectivities, the observation of high diastereoselectivities led us to investigate whether such a strong preference for the *trans* isomer would also be observed in reactions using other catalyst systems previously known to give high enantioselectivities.

A variety of commercially available compounds was tested in the cyclopropanation of styrene with EDA and TMSDM in $CH_2Cl_2$ at room temperature.[27] These included copper complexes of bis(oxazoline) ligands **1**–**9** and semicorrin ligand **10** as well as Doyle's dirhodium catalyst $Rh_2(4S\text{-MEOX})_4$ (MEOX = methyl 2-oxooxazolidine-4-carboxylate), and Davies' dirhodium complex $Rh_2(S\text{-TBSP})_4$ (TBSP = *N*-*p*-*tert*-butylbenzenesulfonyl prolinate). While the rhodium complexes showed a slightly increased preference for the *trans* isomer with TMSDM over EDA, diastereoselectivities were only on the order of 2.5. Under our conditions, reaction of ligand **8** with $[(p\text{-cymene})RuCl_2]_2$ (Nishiyama's system)[22] gave improved yield with TMSDM, but lower diastereo- and enantioselectivities than EDA did. However, all copper complexes showed improved *trans* diastereoselectivities with the use of TMSDM over EDA, and several gave such a strong preference for the *trans* product that only trace amounts of the *cis* isomer could be detected by GC on a chiral column.

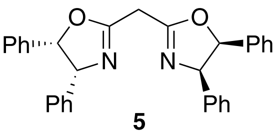
Of the copper compounds studied, the best results were obtained for ligands **1**, **2** and **9** using $[Cu(CH_3CN)_4]PF_6$ as the catalyst precursor. In fact, these ligands not only gave improved diastereoselectivities with TMSDM but they also gave comparable or higher enantioselectivities to those obtained with EDA. In addition, despite the widespread use of CuOTf as a catalyst precursor in such reactions,[28] it was found to be less effective than $[Cu(CH_3CN)_4]PF_6$, giving lower enantio- and diastereoselectivities with ligands **1**, **2** and **9**. The results for ligands **1**, **2** and **9** are shown in Table 1. Interestingly, while ligand **4** is known to give the best results for the asymmetric cyclopropanation of styrene with EDA as the diazo compound, it did not give the best results when TMSDM was used as the diazo species. For comparison purposes, the results for reactions with ligand **4** are also included in Table 1. Many important variables affect enantio- and diastereoselectivities, such as the time allowed for metal ligand complexation, addition time differences, substrate catalyst loading, and solvent, making direct comparison of results from different laboratories difficult.[9] In our hands, the enantioselectivities observed with ligand **4** were slightly lower than those reported previously,[16] but diastereoselectivities were comparable. The data in Table 1 thus provide a reference for the enantio- and diastereoselectivities obtained under the reaction conditions employed in this study.

The absolute configurations for the products derived from EDA and ligands **1**, (*S*,*S*)-**2**, **3**, **4**, **7**, and **9** correlate with those reported in the literature.[16,17] The enantiomeric preference is not affected by the choice of copper catalyst precursor. The absolute configurations for the products derived from TMSDM have not been determined. However, in each case, these ligands all favored the enantiomer that came out in the opposite elution order as the EDA analogue did. This might be due to a preference for the opposite enantiomer or it might be due to a difference in the elution order of the (trimethylsilyl)cyclopropane stereoisomers relative to the ester-functionalized cyclopropanes. As would be expected, ligands (*R*,*R*)-**2**, **5**, and **6** showed a preference for the opposite enantiomer in all cases. Due to low enantioselectivities in some or all cases, trends with ligands **8** and **10** could not be determined.

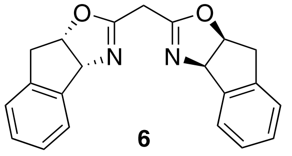
In order to study the effect of substrate in these reactions, a variety of substituted styrenes was tested in the reaction with ligands **2** and **9** using $[Cu(CH_3CN)_4]PF_6$. The results are presented in Table 2. In general, these again showed high diastereoselectivities and good to



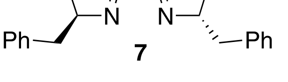
**1** $R^1$ = Ph, $R^2$ = H
**2** $R^1$ = Ph, $R^2$ = Me
**3** $R^1$ = *t*-Bu, $R^2$ =H
**4** $R^1$ = *t*-Bu, $R^2$ = Me



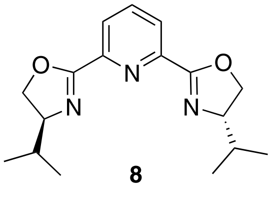
**5**



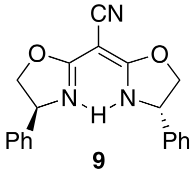
**6**



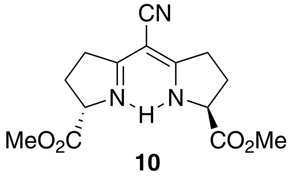
**7**



**8**



**9**



**10**

**Table 1.** Cyclopropanation of styrene with TMSDM and CuOTf or $[Cu(CH_3CN)_4]PF_6$ in the presence of various ligands

| Ligand | Metal | Diazo | Yield[a] | *trans*/*cis* | %ee *cis*[b] | %ee *trans*[b] | Major *cis*[c] | Major *trans*[c] |
|---|---|---|---|---|---|---|---|---|
| **1** | CuOTf | EDA | 51 | 1.3 | 11 | 17 | B | A |
| **1** | CuOTf | TMSDM | 87 | 3.3 | 6 | 0 | B | |
| **1** | $[Cu(CH_3CN)_4]PF_6$ | EDA | 78 | 1.9 | 54 | 61 | B | A |
| **1** | $[Cu(CH_3CN)_4]PF_6$ | TMSDM | 50 | *trans*[d] | | 65 | | B |
| (*R*,*R*)-**2** | CuOTf | EDA | 57 | 2.5 | 57 | 67 | A | B |
| (*R*,*R*)-**2** | CuOTf | TMSDM | 45 | 3.3 | 9 | 2 | A | A |
| (*R*,*R*)-**2** | $[Cu(CH_3CN)_4]PF_6$ | EDA | 68 | 2.4 | 56 | 69 | A | B |
| (*R*,*R*)-**2** | $[Cu(CH_3CN)_4]PF_6$ | TMSDM | 67 | 29.7 | 47 | 62 | B | A |
| (*S*,*S*)-**2** | CuOTf | EDA | 84 | 2.4 | 54 | 67 | B | A |
| (*S*,*S*)-**2** | CuOTf | TMSDM | 50 | 6.3 | 5 | 2 | A | B |
| (*S*,*S*)-**2** | $[Cu(CH_3CN)_4]PF_6$ | EDA | 58 | 2.4 | 54 | 67 | B | A |
| (*S*,*S*)-**2** | $[Cu(CH_3CN)_4]PF_6$ | TMSDM | 60 | 30.8 | 43 | 63 | A | B |
| **4** | CuOTf | EDA | 55 | 2.6 | 91 | 96 | B | A |
| **4** | CuOTf | TMSDM | 45 | 23.2 | 50 | 69 | A | B |
| **4** | $[Cu(CH_3CN)_4]PF_6$ | EDA | 53 | 2.3 | 86 | 92 | B | A |
| **4** | $[Cu(CH_3CN)_4]PF_6$ | TMSDM | 26 | 9.2 | 15 | 43 | A | B |
| **9** | CuOTf | EDA | 99 | 1.9 | 40 | 30 | B | A |
| **9** | CuOTf | TMSDM | 34 | 5.0 | 1 | 11 | A | B |
| **9** | $[Cu(CH_3CN)_4]PF_6$ | EDA | 56 | 1.4 | 31 | 27 | B | A |
| **9** | $[Cu(CH_3CN)_4]PF_6$ | TMSDM | 35 | *trans*[d] | | 88 | | B |

[a] Yields were determined relative to dodecane as an internal standard and are corrected by calibration with samples of known ratio.

[b] Product mixtures were analyzed by GC equipped with a J&W Scientific Cyclodex B column.

[c] Absolute configurations for the products derived from EDA correspond to that shown in Eq. (1). The absolute configurations for the products derived from TMSDM were not determined, and the designation A or B refers to the elution order.

[d] Only the *trans* isomer was detected.

**Table 2.** Cyclopropanation of styrene derivatives with TMSDM and $[Cu(CH_3CN)_4]PF_6$ in the presence of ligands **2** and **9**

| Substrate | Ligand | Yield[a] | *trans*/*cis* | %ee *cis*[b,c] | %ee *trans*[b] | Major *cis*[d] | Major *trans*[d] |
|---|---|---|---|---|---|---|---|
| Styrene | (*R*,*R*)-**2** | 47 | 29.7 | 47 | 61 | B | A |
| Styrene | (*S*,*S*)-**2** | 49 | 30.8 | 43 | 63 | A | B |
| Styrene | **9** | 17 | 24.6 | >99 | 84 | A | B |
| 4-Bromostyrene | (*R*,*R*)-**2** | 72 | *trans*[e] | | 68 | | A |
| 4-Bromostyrene | (*S*,*S*)-**2** | 86 | *trans*[e] | | 66 | | B |
| 4-Bromostyrene | **9** | 21 | *trans*[e] | | 81 | | B |
| 4-Chlorostyrene | (*R*,*R*)-**2** | 31 | 30.6 | 61 | 67 | B | A |
| 4-Chlorostyrene | (*S*,*S*)-**2** | 80 | 39.4 | 48 | 67 | A | B |
| 4-Chlorostyrene | **9** | 26 | 14.4 | 25 | 80 | A | B |
| 4-Methylstyrene | (*R*,*R*)-**2** | 74 | 19.8 | 90 | 55 | B | A |
| 4-Methylstyrene | (*S*,*S*)-**2** | 54 | 22.6 | 38 | 58 | A | B |
| 4-Methylstyrene | **9** | 9 | 8.2 | >99 | 75 | A | B |
| 4-Vinylanisole | (*R*,*R*)-**2** | 66 | 14.7 | 47 | 46 | B | A |
| 4-Vinylanisole | (*S*,*S*)-**2** | 80 | 20.2 | 61 | 49 | A | B |
| 4-Vinylanisole | **9** | 35 | *trans*[e] | | 98 | | B |

[a] Yields were determined relative to dodecane as an internal standard and are corrected by calibration with samples of known ratio.

[b] Product mixtures were analyzed by GC equipped with a J&W Scientific Cyclodex B column.

[c] It is very difficult to obtain accurate GC integration for the *cis* isomers of the products formed with TMSDM since they are formed in such low yield (all less than 5%) and the resulting GC peaks are very small.

[d] The absolute configurations for the products were not determined, and the designation A or B refers to the elution order.

[e] Only the *trans* isomer was detected.

high enantioselectivities. The enantiomeric preferences paralleled the trends seen with styrene.

In conclusion, the effect of TMSDM on diastereoselectivities seems to be a general phenomenon with $[Cu(CH_3CN)_4]PF_6$ as catalyst precursor. This may be due to the steric bulk of the TMS group in analogy to the effects seen with diazoacetates upon increasing the steric requirements of the ester group.[7,12–19]

## Acknowledgements

Financial Support from the American Chemical Society-Petroleum Research Fund, Research Corporation, and the Jeffress Memorial trust is gratefully acknowledged. A.K.M., T.A.S. and A.J.K. thank Washington and Lee University for R. E. Lee Undergraduate Research Fellowships, and M.B.F. thanks WLU for

Glenn Grants. We thank Philip C. Trimmer, W. Chadwick Ellis, Geoffrey C. Cooper, James A. Browne, and J. Turner Vosseller for technical assistance.

## References

1. Wong, N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-U.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
2. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.
3. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.
4. Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537.
5. Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251–2253.
6. Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627.
7. Doyle, M. P. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; Wiley-VCH: New York, 2000; pp. 191–228.
8. Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
9. Rovis, T.; Evans, D. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; Wiley: New York, 2001; Vol. 50; pp. 1–150.
10. Davies, H. M. L.; Antoulinakis, E. G. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2001; Vol. 57, pp. 1–326.
11. Noels, A. F.; Demonceau, A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrman, W. A., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 2, pp. 793–808.
12. Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, *18*, 2599.
13. Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
14. Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
15. Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
16. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
17. Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430.
18. Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.
19. Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919–7946.
20. Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243–7246.
21. Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223.
22. Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247–1262.
23. Haszeldine, R. N.; Scott, D. L.; Tipping, A. E. *J. Chem. Soc., Perkin 1* **1974**, 1440–1443.
24. Maas, G.; Seitz, J. *Tetrahedron Lett.* **2001**, *42*, 6137–6140.
25. Aoyama, T.; Iwamoto, Y.; Nishigaki, S.; Shiori, T. *Chem. Pharm. Bull.* **1989**, *37*, 253–256.
26. Seyferth, D.; Menzel, H.; Dow, A. W.; Flood, T. C. *J. Organomet. Chem.* **1972**, *44*, 279–290.
27. Typical cyclopropanation procedure: a solution of ligand (0.03 mmol) and metal precursor (0.015 mmol) in methylene chloride (1.5 mL) was stirred for 25 min under nitrogen. Styrene (8.7 mmol) was added and the solution was stirred an additional 30 min. A solution of diazo compound (0.86 mmol) in methylene chloride (1.5 mL) was added over 16 h using a syringe pump.
28. Doyle, M. P.; Peterson, C. S.; Zhou, Q.-L.; Nishiyama, H. *Chem. Commun.* **1997**, 211.