Pergamon

*Tetrahedron Letters*, Vol. 38, No. 7, pp. 1145-1148, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00010-5

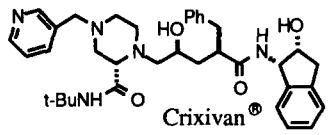
# A Conformational Toolbox of Oxazoline Ligands.

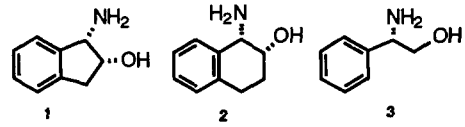
**Ian W. Davies,*‡ Linda Gerena, Dongwei Cai, Robert D. Larsen, Thomas R. Verhoeven, and Paul J. Reider**

Department of Process Research, Merck & Co., Inc., R801-205, P.O. Box 2000, Rahway, NJ 07065.

*Summary: A toolbox of bis(oxazoline) and pyridinebis(oxazoline) ligands 6, 7, 8 has been used to probe conformational effects in Cu(II)-catalyzed Diels-Alder and Ru(II)-catalyzed cyclopropanation reactions.*

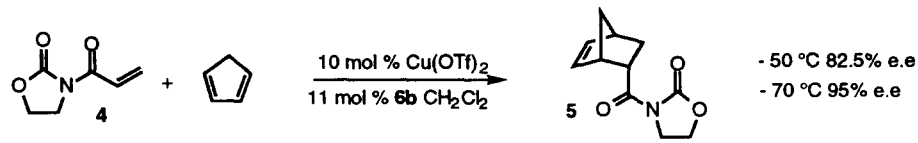

The HIV protease inhibitor Crixivan® is one of a family of compounds that has received FDA approval for the treatment of AIDS.[1] In the synthesis of Crixivan®,[2] an expedient way of producing large quantities of 1*S*,2*R*-*cis* aminoindanol **1** was established — which is also applicable to tetrahydronaphthalene **2** — using a Jacobsen epoxidation and a unique Ritter-type reaction.[3] As a result of these studies commercial quantities of aminoindanol **1** have become available. The oxazolidinone derived from aminoindanol **1** is a very efficient Evans-type auxiliary for Diels-Alder reactions.[4] The indane (in), tetrahydronaphthalene (thn), and phenyl (ph) toolbox of oxazolidinones were used as probes to determine the role of conformation in these reactions. In this paper the ligands **6**, **7**, and **8** are used to probe conformational effects systematically in two representative asymmetric reactions, the Diels-Alder and cyclopropanation.




1 2 3

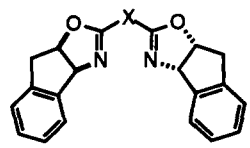
The indane ligand **6b** provides excellent levels of stereocontrol in the two-point binding copper (II)-catalyzed Diels-Alder reaction of acrylimide **4** and cyclopentadiene to give norbornene **5** (Scheme 1).[5] Since our initial disclosure, similar observations have been reported by Ghosh.[6] Although the indane ligand **6b** provided high levels of induction, we did not have a systematic way of probing the role of conformation. In order to achieve this we examined the in-**6b**, thn-**7b**, and ph-**8b** derived ligands together with spiro-ligands **6** - **8c**. The ligands were prepared in 56 - 72% yield by alkylation of the parent **6** - **8a** (X = $CH_2$).[7]



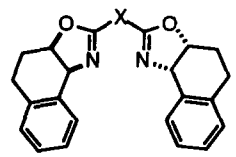

4 5

**Scheme 1**

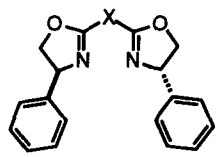
To compare the selectivity of the six ligands we performed the Diels-Alder reaction at - 50 °C in dichloromethane using 10 mol% Cu(OTf)2 and 11 mol% ligand. The results are shown in Table 1 and Chart 1.



in **6 a, b, c, d**



thn **7 a, b, c, d**



ph **8 a, b, c, d**

**a** X = $CH_2$ **b** X = $CMe_2$

**c** X =

**d** X =

| entry | ligand | % e.e. endo **5**[a] | % d.e. **5**[a] |
|---|---|---|---|
| 1 | **6b** | 82.5 (S) | 96 |
| 2 | **7b** | 38 (S)[b] | 95 |
| 3 | **8b** | 30 (S)[c] | 84 |
| 4 | **6c** | 89.5 (S) 96[d] | 95 97[d] |
| 5 | **7c** | 49 (S)[b] | 91.5 |
| 6 | **8c** | 46 (S) | 85 |

**Table 1:** Reaction of acrylimide **4** and cyclopentadiene at - 50 °C. a) Chiracel OD-H on a Berger Instruments SFC at 210 nm, 1 $mLmin^{-1}$, 200 Bar using 1% MeOH as modifier. b) Ent-**7** was used in these cases and gave *R*-**5**. c) - 70 °C 1hr, - 50 °C 3hr. d) at - 65°C

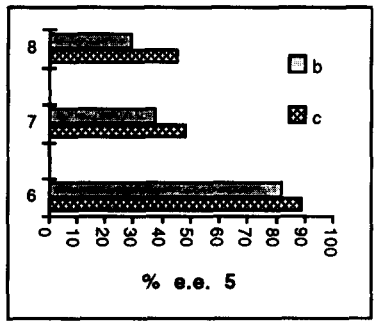
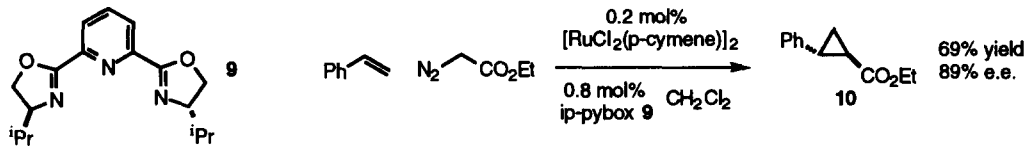



**Chart 1**

Two clear trends emerge from this study. Firstly, in all cases the spiroligands **6** - **8c** provide better levels of stereocontrol than the dimethyl ligands **6** - **8b.** Secondly, the indane ligands provide much higher levels of stereocontrol than either the tetrahydronaphthalene or the phenyl ligands. *For indane* ***6c*** *the reaction proceeded with 96 % e.e. at - 65 °C.* By systematically changing the phenyl group to the indane and introducing a spirocenter we have increased the selectivity from 30 to 96% e.e. Inspection of molecular models revealed that the thn-**7c** ligand can attain a conformation approaching that of the ph-**8c** whereas the indane **6c** is essentially rigid. Additionally, the orientation of the aromatic plane, defined by the location of C4-H in the chiral pocket,[8] is crucial to obtaining high enantioselectivity. Discussion of the actual coordination structure of the complexes —the sense of induction is fully consistent with a square planar (or slightly distorted) copper(II)-complex[9] — will have to be postponed until further computational studies have been completed.[10]

Nishiyama introduced pyridine-bis(oxazoline) ligands — pybox ligands— for hydrosilylation reactions and they have also been used effectively in cyclopropanation reactions (scheme 2).[11] More recently pybox ligands have been successfully used in Cu(II)-catalyzed Mukiayama aldol reactions.[12] We have also investigated the cyclopropanation reaction which takes place within the coordination sphere of the metal using the analogous pybox series **6** - **8d.** In contrast to the ip-pybox **9** which gave high enantiomeric excesses in this reaction the ph-pybox **8d** "gave poorer results in yields and % e.e.'s".[11] This observation presented us an ideal opportunity to explore the role of ligand conformation in the cylopropanation reaction. The results of the study using pybox ligands **6** - **8d** are shown in Table 2 and Chart 2.[13]




**Scheme 2**

| entry | ligand | % e.e. *trans* **10**[a,b] | % d.e.[c] | % yield |
|---|---|---|---|---|
| 1 | ip-pybox, **9** | 89 (1*R*, 2*R*)[11] | 84 | 66 - 69 |
| 2 | in-pybox, **6d** | 59.5 (1*S*, 2*S*) | 81 | 51 |
| 3 | thn-pybox, **7d** | 41 (1*R*, 2*R*)[d] | 78 | 47 |
| 4 | ph-pybox, **8d** | 76 (1*R*, 2*R*) | 72 | 30 |

**Table 2:** Ru-catalyzed cyclopropanation at 21 °C using syringe pump addition of diazoacetate over 10 hours. a) Using a Chiracel OD-H on a Berger Instruments SFC at 210 nm, 1 mLmin$^{-1}$, 200 Bar using 2% MeOH as modifier. b) Confirmed by α in $CDCl_3$. c) By nmr on the crude mixture. d) Ent-**7d** was used in this case and gave the (1*S*,2*S*) cyclopropane.

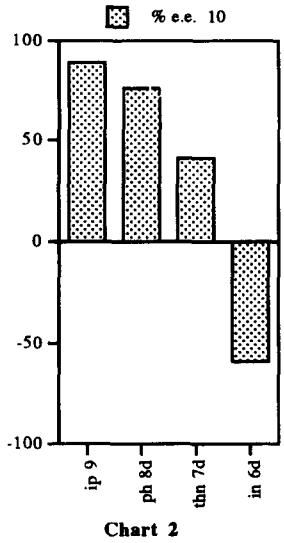



**Chart 2**

The ph-pybox **8d** and thn-pybox **7d** gave the same (1*R*,2*R*) cyclopropane **10** as ip-pybox **9**. In contrast, the in-pybox **6d** gave (1*S*,2*S* ) *ent*-**10**.[14] The stereochemical outcome of the reaction with ip-pybox **9** is explained by *re*-face attack of styrene on the *re*-face of the *trans*- carbene (Fig. 1).

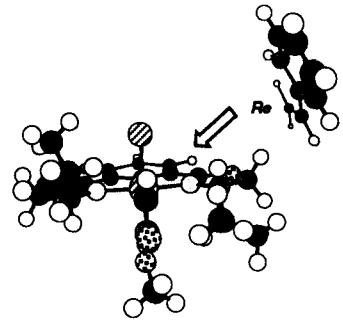



**Figure 1:** Ru(ip-pybox)($CHCO_2Me$)$Cl_2$

Since in-pybox **6d** gave the (1*S*,2*S* ) cyclopropane, the *si*-face of styrene must approach the *si*-face of the carbene. Inspection of molecular models revealed an unfavorable steric interaction between styrene and the *trans*-carbene complex (Fig. 2).

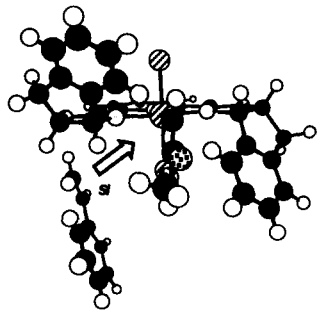



**Figure 2:** Ru(in-pybox)(*trans*-$CHCO_2Me$)$Cl_2$

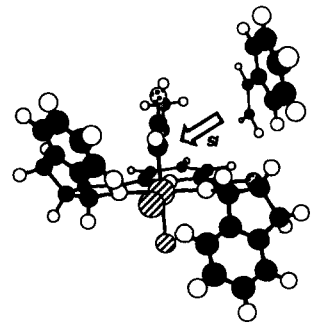



**Figure 3:** Ru(in-pybox)(*cis*-$CHCO_2Me$)$Cl_2$

However, *si*-face attack of the *cis*-carbene with the *si*-face of styrene is relatively unhindered (Fig. 3).[15,16] If this is correct, then the rigid indane ligand induces a change in the coordination stereochemistry at the metal, whilst the more flexible thn-**7d** and ph- **8d** allow reaction through a *trans*-carbene. Using this model, increasing the size of the indane $C_4$-substituent may favor the formation of the *cis*-carbene. The synthesis of these indanes is currently under investigation.

In summary, the in-, thn-, ph-oxazolines **6**, **7**, **8** can be used as a toolbox to probe ligand conformations in transition metal-catalyzed reactions. In the first case, this series has provided ligands that give rise to higher levels of asymmetric induction (from 30 to 96% e.e). In the second case, this toolbox has offered leads for ligand design. The desirable attribute of these ligands is their ability to probe conformation systematically which aids opimization of enantioselectivity. The orientation of aromatic planes has very recently been identified by Jacobsen as an important secondary catalyst-substrate interaction, and thus useful as a design principle in asymmetric catalysis.[17] This toolbox should prove useful in exploring this arena, in high through-put screens[18] and will be informative in other reactions involving oxazolines *e.g.* Pd-catalyzed allylic alkylation[19] and conjugate radical addition.[20]

Acknowledgment: We would like to thank Professor Nishiyama for helpful discussions.

## References

‡ email: ian_davies1@merck.com

1. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *PNAS USA*, **1994**, *91*, 4096.
2. Maligres, P. E.; Upadhyay, V.; Rossen, K.; Ciancosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 2195.
3. Davies, I. W.; Reider, P. J. *Chemistry & Industry* **1996**, 412.
4. Davies, I. W.; Senanayake, C. H; Castonguay, L.; Larsen, R. D.; Verhoeven T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619.
5. Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 1725.
6. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.
7. Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753.
8. The ligand is a bis[3a,8a-dihydro-8*H*-indeno[1,2-d]oxazole.
9. Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.
10. See: Burton, V. J.; Deeth, R. J.; Kemp, C. M.; Gilbert, P. J. *J. Am. Chem. Soc.*, **1995**, *117*, 8407.
11. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500. Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223. Nishiyama, H.; Itoh, Y.; Sugawara, Y; Matsumoto, H.; Aoki, K; Itoh, K. *Bull. Chem. Soc., Jpn.* **1995**, *68*, 1247.
12. Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.
13. Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem. in press.*
14. For a very recent example of ligand effects in cyclopropanation and aziridination that may be clarified using this toolbox see: Harm, A. M.; Knight, J. G.; Stemp, G. *Tetrahedron Lett.* **1996**, *37*, 6189; Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677.
15. For reaction of a *cis*-carbene see: Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336. Although in the X-ray structures of ip-pyboxRu$(OCOCH_3)_2$CO and (pybox)Ru$Cl_2(\eta^2$–$C_2H_4)$ the CO and ethylene are *trans*, the sterically demanding in-pybox may override this electronic preference.
16. For an isolable Ru-carbene complex: Park, S-B.; Sakata, N.; Nishiyama, H. *Chem. Eur. J.* **1996**, *2*, 303. The ruthenium carbene complex of the methyl estercould not be detected by NMR.
17. Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156.
18. Burgess, K.; Lim, H-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Intl. Ed. Eng.* **1996**, *35*, 220
19. von Matt, P.; Lloyd-Jones, G.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, MN.; Ruegger, H.; Pregosin, P. *Helv. Chim. Acta* **1995**, *78*, 265. Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, *15*, 2065. von Matt, P.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
20. Sibi, M.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

(*Received in USA* 4 *October* 1996; *accepted* 30 *December* 1996)