Tetrahedron Letters, Vol. 34, No. 46, pp. 7375-7378, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Modified Cinchona Alkaloid Ligands: Improved Selectivities in the Osmium Tetroxide Catalyzed Asymmetric Dihydroxylation (AD) of Terminal Olefins

Mark P. Arrington, Youssef L. Bennani, Thomas Göbel, Patrick Walsh, Shu-Hai Zhao and K. Barry Sharpless*

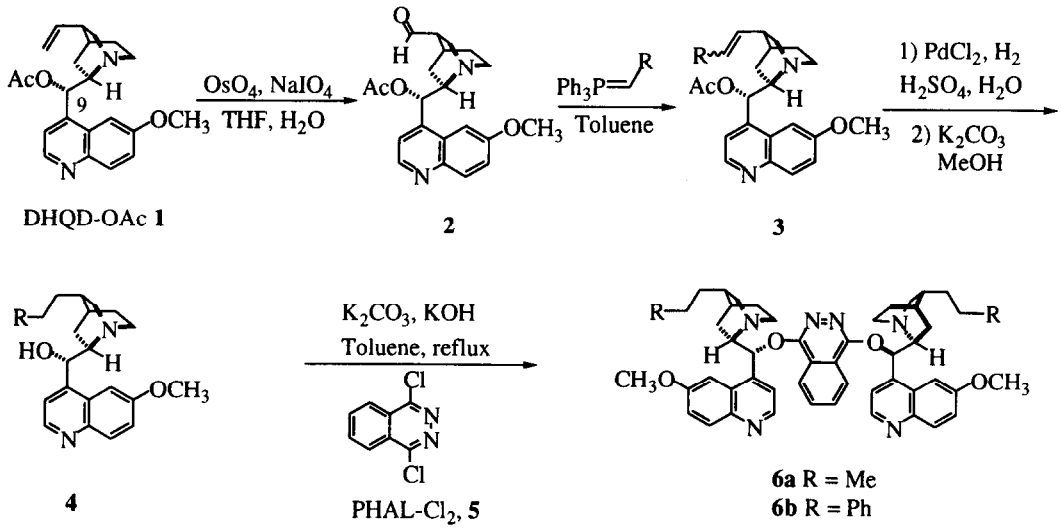
Department of Chemistry, The Scripps Research Institute
10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Abstract: *Modification on the quinuclidine and the quinoline moieties of the bis cinchona-alkaloid phthalazine ligands resulted in improved enantioselectivities in the osmium tetroxide catalyzed dihydroxylation of olefins. For the first time 1-decene, a common model for terminal aliphatic olefins, afforded enantioselectivities of over ninety percent.*

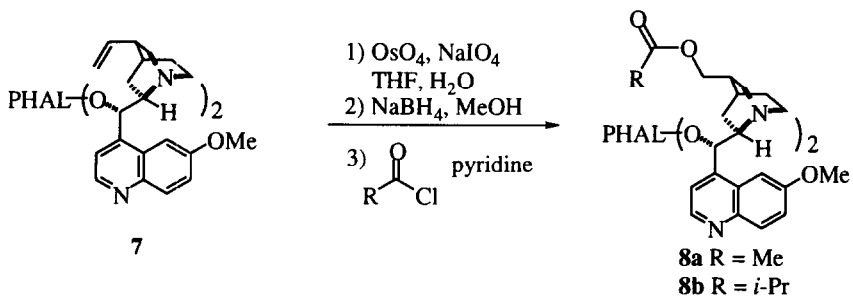
Extensive structure-enantioselectivity relationship studies (*SER*) have resulted in the rapid development of the osmium-catalyzed asymmetric dihydroxylation of olefins.[1] The asymmetric dihydroxylation of *trans*-disubstituted and trisubstituted olefins is now achieved with greater than 90% enantioselectivity employing the dihydroquinidine and dihydroquinine phthalazine-based ligand systems [$(DHQD)_2PHAL$ and $(DHQ)_2PHAL$]. Recently, we have found a new class of ligands, the bis-cinchona alkaloid substituted pyrimidine ligands,[2] that give exceptional ee's for branched terminal olefins. However, even with the success of the pyrimidine ligands there is still room for improvement in the enantioselectivity for the AD of aliphatic terminal olefins.

To date, all of the reported ligands for the *catalytic* asymmetric dihydroxylation of olefins are dihydroquinidine or dihydroquinine derivatives functionalized at the C-9 hydroxyl group of the alkaloid backbone. In nearly all of these ligands, the dihydroquinidine derivatives show superior enantioselectivities (typically between 0 - 7% ee) relative to the pseudoenantiomeric dihydroquinine analogs. These two alkaloids differ only in the relative position of the ethyl substituent on the quinuclidine core, and we therefore decided to examine the influence of this group on the enantioselectivity of the AD.

Starting from quinidine ester **1,** dihydroxylation/oxidative cleavage employing $OsO_4/NaIO_4$ yielded aldehyde **2** which was converted to the quinidine analogs **3** by a Wittig reaction. Subsequent hydrogenation and hydrolysis of the acetate afforded alcohol **4**. Base mediated condensation with 1,4-dichlorophthalazine ($PHAL\text{-}Cl_2$), **5**, gave the desired phthalazine derivatives **6a** and **6b** with the extended sidechains.

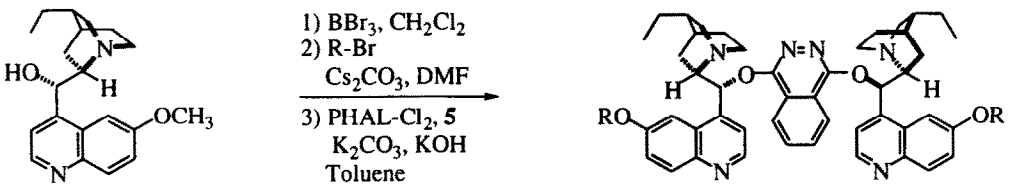


A second more direct approach started from the phthalazine bis-quinidine ligand **7**. In a three step procedure, the double bond was cleaved oxidatively and the resulting aldehyde reduced to the corresponding alcohol. Esterification with acyl chlorides yielded derivatives **8a** and **8b**.



These new ligands were tested in the catalytic AD using 1-decene as a model substrate for the aliphatic terminal olefin class. The results are listed in Table 1. Ligands **6a** and **8a** resulted in higher ee's relative to their unmodified counterpart $(DHQD)_2PHAL$ (**10a**). However, further increase in the size of the R group as with **6b** and **8b** led to a slight decrease in enantioselectivity for the AD of 1-decene.

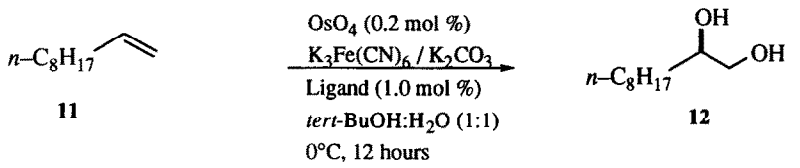
Another interesting starting point for ligand modification is the methoxy substituent in the quinoline moiety. Molecular modeling[3] and X-ray crystallographic analyses[4] of the free and osmium tetroxide bound ligands reveal that the methoxy group is always directed toward the quinuclidine nitrogen. Furthermore, earlier investigations indicated that the absence of this group resulted in a decrease in enantioselectivities.[5] We therefore investigated the effect of the size of the alkoxy substituent on the enantioselectivity. Demethylation of dihydroquinidine **9** with BBr_3 followed by selective alkylation of the phenolic hydroxy group yielded modified alkaloids. Subsequent coupling with 1,4-dichlorophthalazine **5** afforded the desired compounds **10a - f**.



9 **10a - f**

Ligands **10b - f,** modified in the alkoxy substituent on the quinoline moiety, were evaluated for the AD of 1-decene (Table 1). Most of the altered quinoline ligands showed superior enantioselectivities

Table 1[a]



11 **12**

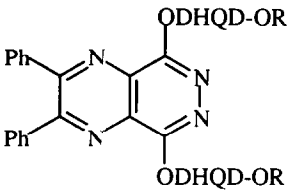
Ligand **6**			Ligand **10**		
	R	ee [%][b]		R	ee [%][b]
6a	Methyl	88	**10a**	Methyl	84[b]
6b	Phenyl	86	**10b**	Ethyl	88
			10c	*n*-Pentyl	91
Ligand **8**					
	R	ee [%][b]	**10d**	*i*-Propyl	82
8a	Methyl	88	**10e**	*i*-Butyl	90
8b	*i*-Propyl	86	**10f**	*i*-Pentyl	92

(a) All ligands gave satisfactory spectroscopic data (^{1}H NMR, IR and HRMS). (b) Enantiomeric excess (ee) of the diol **12** was determined by HPLC (Pirkle 1A; 0.5 % *i*-PrOH-hexane, 1.5 ml / min.) of the corresponding bis-MTPA esters[1]

relative to $(DHQD)_2PHAL$, **10a**. Introduction of sterically more demanding substituents, such as the *i*-propyl group in **10d**, however, led to a decrease in enantioselectivity. This result, as well as similar

observations with **6a - b** and **8a - b**, may be due to small changes in ligand conformation upon introduction of larger groups.

Further studies reveal that improved selectivities through elaboration of the quinoline group are not restricted to the parent phthalazine spacer. Alteration of the bridge spanning the 9-hydroxy groups[6] in combination with the modified quinoline core (**13a - b**) resulted in increased enantioselectivity for the dihydroxylation of 1-decene from 89 to 92 %.



		ee [%]
13a	R = Me	89
13b	R = *n*-Prop	92

In summary, minor modifications of the methoxy and the ethyl substituents of the cinchona alkaloid ligands have led to improved enantiomeric excesses for the AD of 1-decene, and for the first time ee's exceeding ninety percent were realized for this substrate.

Acknowledgments

This work was supported by a grant from The National Institutes of Health (GM 28384). T.G. thanks the Deutsche Forschungsgemeinschaft (DFG) for providing a fellowship. P.J.W. thanks the National Science Foundation for a postdoctoral fellowship (CHE-9002184).

References and Notes

1. a) Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K., Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. b) Sharpless, K.B.; Amberg W.; Beller, M.; Hou, C.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.
2. Crispino, G.A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z-. M. Xu, D.; Sharpless, K.B. *J. Org. Chem.* in press.
3. Kolb, H.C.; Svendsen, J.S.; Sharpless, K.B. unpublished results.
4. a) Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Chadha, R. K.; Davis, W.; Hartung, J.; Jeong, K.-S.; Ogino; Y.; Shibata, T.; Sharpless, K.B. *J. Org. Chem.* **1993**, *58*, 844. b) Svendson, J.S.; Markó, I.; Jacobsen, E.N.; Pulla Rao, C.; Bott, S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, *54*, 2263.
5. Hentges, S.G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
6. Bennani, Y. L.; Sharpless , K. B. unpublished results.

(Received in USA 10 May 1993; accepted 16 September 1993)