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A triazine core for a new class of Sharpless asymmetric dihydroxylation ligands

Catherine Anne McNamara,[a] Frank King[b] and Mark Bradley[a,*]

[a]Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK
[b]Johnson Matthey Research and Technology, PO Box 1, Belasis Avenue, Billingham, Cleveland TS23 1LB, UK

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Abstract—Sharpless asymmetric dihydroxylation ligands were synthesized using a triazine spacer group in two, high yielding steps from cheap, readily available starting materials. The ligands, gave good enantioselectivities in the asymmetric dihydroxylation of alkenes and may provide a very economic alternative to current systems.

The catalytic asymmetric dihydroxylation of alkenes with osmium tetroxide in the presence of bis-cinchona alkaloid derivatives (**1**–**3**, Fig. 1) has provided a remarkable tool by which a range of optically pure diols can be easily obtained in high yields and with excellent enantioselectivities.[1,2] The synthesis of a range of analogues, using a number of heterocyclic spacer groups between the two chiral moieties (four different possible alkaloid moieties are used: quinine **4** and its pseudoenantiomer quinidine **6** and their dihydro analogues hydroquinine **5** and hydroquinidine **7**), has afforded a set of ligands capable of performing the transformation across a broad range of alkene substrates (Fig. 1).[2–4]

Herein, the synthesis of a new ligand with a triazine spacer group between the two chiral moieties (**9**, Scheme 1) is reported. Compound **9** was synthesized in two, high yielding steps from inexpensive, readily available starting materials; 4-bromoaniline, cyanuric chloride and quinine as shown in Scheme 1.[5] Such construction allows for broad diversification of the ligand, with the availability of many aniline and amine derivatives for the first reaction. Thus 4-bromoaniline was dissolved in acetone/water (1:1) and added to a suspension of cyanuric chloride in a crushed ice/acetone mixture (1:1) to give **8**. Following drying under vacuum, the mono-substituted triazine was dissolved in dry THF and added to the anion of quinine, generated in situ with NaH to afford **9** in 98% isolated overall yield.

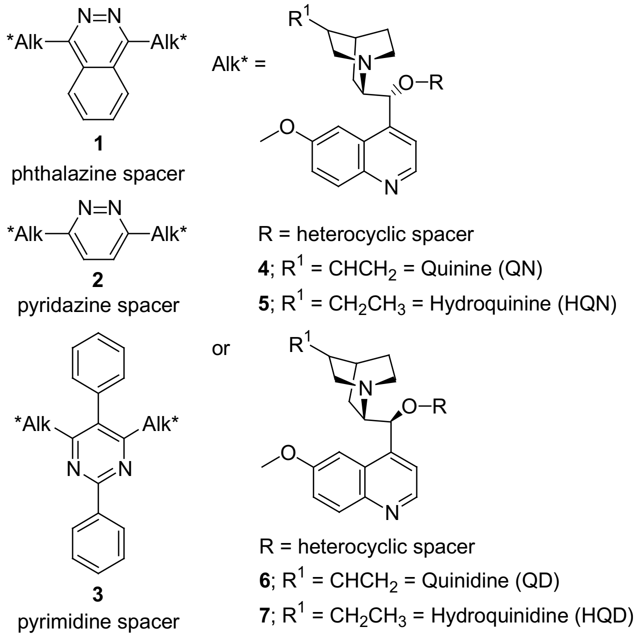

Figure 1. Range of ligands with different heterocyclic spacer groups used in the asymmetric dihydroxylation of alkenes.

Results for the asymmetric dihydroxylation of several alkenes, using $K_3Fe(CN)_6$ as a secondary oxidant are shown in Table 1 with the results obtained for Sharpless'

Keywords: Triazine; Sharpless; Dihydroxylation.

* Corresponding author. Tel.: +44 23 80593598; fax: +44 23 80596766; e-mail: mb14@soton.ac.uk

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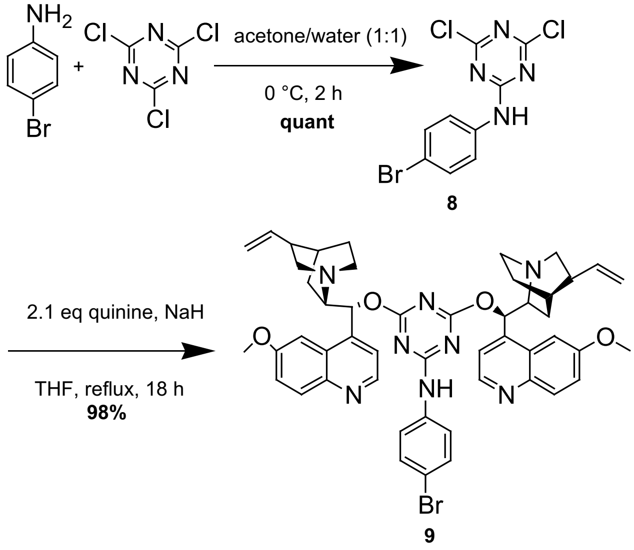
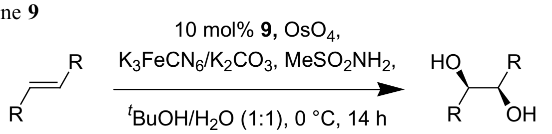
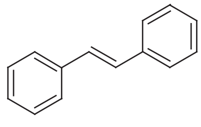
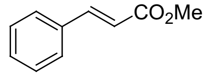
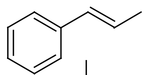
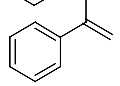
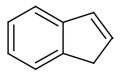


Scheme 1. Synthesizes of tri-substituted triazine **9**.

Table 1. Enantioselective dihydroxylation of alkenes mediated with triazine **9**



	Alkene	Yield (%)	ee (%)[a]	Sharpless[b]
1		75	>99	>99
2		Quant	>99	97[c]
3		78	93	97
4		85	64	94
5		90	26	42

Experimental conditions: 0.6 mmol alkene, 9 μmol OsO$_4$, 1.8 mmol K$_3$FeCN$_6$, 1.8 mmol K$_2$CO$_3$, 0.6 mmol MeSO$_2$NH$_2$ and 0.06 mmol chiral triazine catalyst.

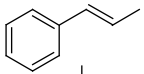
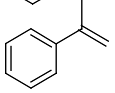
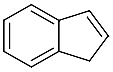
[a] ee was determined by RP-HPLC on a Chiralpak AD-RH column, using 20% MeCN/H$_2$O as solvent with a flow rate of 0.5 mL/min.

[b] See Ref. 1b.

[c] Value reported for the ethyl ester.

phthalazine ligand (**1**, Fig. 1), added for comparison. It was immediately evident that the catalyst was most selective for *trans*-substituted alkenes, which all gave greater than 90% ee (unoptimized). For two alkenes the catalyst was found to be comparable to those reported for the Sharpless derivative (Table 1, entries 1 and 2), while for other alkene geometries, lower ee's were observed, similar to the pyrimidine ligand (**3**, Fig. 1)[4] where the ee achieved for α-methyl styrene and indene were only 69% and 35% (Table 1, entries 4 and 5), respectively, suggesting that the 1,3 and 1,4 relationship between the chiral moieties is important (Fig. 1).

Table 2. Enantioselective dihydroxylation of alkenes catalyzed by the triazine catalysts with different alkaloid moieties attached

Alkene	2-(4-Bromophenyl(amino))-1,3,5-triazine core ee (%)			
	QN	HQN	HQD	QD
	93	94	86	92
	64	64	64	74
	26	24	29	22

In order to ascertain if any differences in ee would occur as a result of the incorporation of the different chiral ligands (HQN, QD, HQD), the synthesis of the three analogues of **9** was undertaken in a manner similar to that shown in Scheme 1.

Table 2 shows the ee's achieved by catalysis with the different alkaloid moieties with conditions similar to those described in Table 1. Overall no significant differences in ee for the different ligands were observed, suggesting that diols of both configurations are achievable.

Since the triazine moiety contains three sites, which can be substituted it was considered interesting to investigate the catalytic activity of the *C*-3 symmetric ligand, which was synthesized in a manner similar to that for **9**, in 66% yield from cyanuric chloride and 3.1 equiv of quinine. This had a disastrous result on the catalytic activity; ee's dropped from 94% to 76%, 64% to 42% and 24% to 2% for β-methyl styrene, α-methyl styrene and indene, respectively. This supports previous observations[6] that the presence of a binding pocket for the alkene is crucial for high enantioselectivities. It appears that the aniline moiety is necessary for the construction of such a pocket, hence the function of the third component is not merely as a steric block.

In summary a novel Sharpless-type asymmetric dihydroxylation ligand with a triazine core was synthesized in two, easy, high yielding steps from readily available starting materials, and may offer an economic alternative to current systems. The catalyst was found to be active in the asymmetric dihydroxylation of alkenes, especially those of *trans*-geometry. As cyanuric chloride can be easily and selectively reacted with a variety of nucleophiles including thiols, phenols and Grignard reagents,[7] it could therefore serve as an extremely useful spacer group to further extend the scope of the asymmetric dihydroxylation reaction.

Acknowledgements

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References and notes

1. (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968; (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
2. 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. Q.; Zhang, X. L. *J. Org. Chem.* **1992**, *58*, 2768.
3. (a) Lohray, B. B.; Bhusan, V. *Tetrahedron Lett.* **1992**, *33*, 5113; (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828.
4. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
5. Synthesis of **8**: A solution of cyanuric chloride (10.0 g, 54 mmol) in acetone (100 mL) was heated to 50 °C and added to stirred crushed ice/water (200 mL). To the resulting fine white slurry 4-bromoaniline (18.7 g, 10.8 mmol), dissolved in an acetone/water mixture (1:1, 100 mL) was added dropwise with vigorous stirring. After stirring for 2 h at 0 °C the resulting yellow suspension was filtered, washed with cold water (20 mL) and dried under vacuum to yield the title compound as a pale yellow solid (17.1 g, 3.9 mmol).
   Synthesis of **9**: Compound **8** (17.1 g, 53.9 mmol) was dissolved in dry THF (50 mL) and added to a stirred suspension of quinine (36.4 g, 54 mmol) and NaH (60% dispersion in mineral oil) (6.5 g, 0.17 mol) in THF (200 mL). The reaction mixture was refluxed overnight, then quenched by transfer into saturated NH_4Cl (100 mL). The phases were separated, the product extracted into ethyl acetate (3 × 200 mL) and the solvent removed in vacuo to afford a yellow solid, which was chromatographed in ethyl acetate on base activated alumina to give the title product as a white slurry, 4-bromoanaline (47.3 g, 53 mmol, 98%).
6. (a) Becker, H.; Ho, P. T.; Kolb, H. C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 7315; (b) Kolb, H. C.; Anderson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278; (c) Lohray, B. B.; Bhusan, B.; Nandanan, E. *Indian J. Chem. Sec. B: Org. Chem. Inc. Med. Chem.* **1996**, *35B*, 1119; (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319.
7. (a) Delia, T. J.; Nagarajan, A. *J. Heterocycl. Chem.* **1998**, *35*, 269; (b) Menicagli, R.; Samaritani, S.; Zucchelli, V. *Tetrahedron* **2000**, *56*, 9705.