Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 1049–1051

Synthesis and catalytic activity of TentaGel-supported asymmetric dihydroxylation $(DHQ)_2PHAL$ ligand

Jihane Achkar,[a] Joseph R. Hunt,[b] Rachel L. Beingessner[c] and Hicham Fenniri[c,*]

[a]*DSM Nutritional Products Ltd, Nutrition Research and Development, Wurmisweg 576, CH-4303 Kaiseraugst, Switzerland*
[b]*Department of Chemistry and Biochemistry, University of California-Los Angeles, 607 Charles E. Young Drive East, Los Angeles, CA 90095-1569, USA*
[c]*National Institute for Nanotechnology and Department of Chemistry, University of Alberta, 11421 Saskatchewan Drive, Edmonton, Alberta, Canada T6G 2M9*

Received 31 December 2007; accepted 3 April 2008
Available online 12 May 2008

Abstract—An efficient scheme for the synthesis and catalytic activity of TentaGel-supported Sharpless's $(DHQ)_2PHAL$ dihydroxylation ligand is described.

1. Introduction

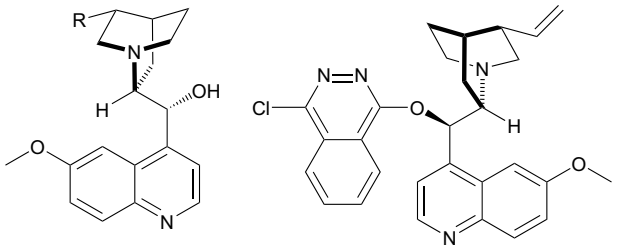
Since its discovery by Sharpless et al.,[1] the ligand-accelerated catalytic (LAC) asymmetric dihydroxylation (AD) of olefins with cinchona alkaloid-based ligands such as $(DHQ)_2PHAL$ has seen tremendous developments and applications in organic synthesis.[2] In particular, owing to its cost, several solid phase-supported versions of the AD ligand were reported[3] in order to take advantage of the recyclability of the catalyst, straightforward separation of the reaction product and the amenability of this format to automated and high throughput parallel synthesis. Both insoluble[3a–h] and soluble[3h–j] polymeric supports were optimized to produce high yields and enantioselectivities in the LAC-AD of a variety of olefins. While each of these supports has its advantages, the insoluble polymeric ones present the added convenience of being easier to isolate through simple filtration. Building on this unique feature, we report here the use of an alternative scaffold that combines the advantages of insoluble polymeric matrices with solution-like reactivity and solvent compatibility of polyethylene glycol (PEG), thus providing more flexibility in terms of substrate and solvent compatibility, yet preserving all the advantages of an insoluble matrix. TentaGel, a graft copolymer of polystyrene (PS) and PEG, was chosen to highlight the feasibility and advantages of this approach.

2. Results and discussion

The symmetrical $(DHQ)_2PHAL$ ligand **4** was prepared in one step from 1,4-dichlorophthalazine and dihydroquinine **1** in 72% yield (Fig. 1).[4] Quinine **2** was reacted with 1 equiv of 1,4-dichlorophthalazine under basic conditions in anhydrous toluene with concurrent azeotropic distillation of water to give the monosubstituted chlorophthalazine **3** in 62% yield after crystallization. Similarly, treatment of **3** under the same conditions with 1 equiv of dihydroquinine **1** yielded the disubstituted phthalazine **5** in 64% yield after crystallization.[3i] Reacting 1,4-dichlorophthalazine with quinine **2** first rather than with dihydroquinine **1** dramatically simplified the purification of **3** and produced **5** in a very pure and crystalline form. Chiral ligand **5** was then reacted with 3-mercaptopropionic acid or methyl-3-mercaptopropionate under radical conditions to yield the substituted $(DHQ)_2PHAL$ ligands **6** and **7** in 75% and 84%, respectively.[5] The structure of **7** was confirmed by NMR and mass spectrometry data. Compound **6** was then attached to the resin under standard peptide coupling conditions, while the methyl ester **7** was loaded by simply heating a 0.1 M solution of **7** in anhydrous *N*,*N*-dimethylformamide at 100 °C with 0.2 equiv of TentaGel-S-NH_2 until the Kaiser test[6] turned negative (indicating completion of the reaction, ~48 h). After drying the beads under vacuum, the unreacted free amines (inaccessible sites, <1%) were capped with acetic anhydride.[7–9]

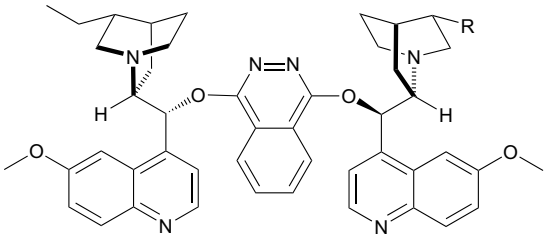
* Corresponding author. Tel.: +1 780 641 1750; fax: +1 780 641 1601; e-mail: hicham.fenniri@nrc-cnrc.gc.ca

0957-4166/$ - see front matter Crown Copyright © 2008 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.04.007



1, Dihydroquinine, R: CH_2-CH_3
2. Quinine, R: $CH{=}CH_2$

3



4, R: CH_2-CH_3
5, R: $CH{=}CH_2$
6, R: $CH_2CH_2SCH_2CH_2COOH$
7, R: $CH_2CH_2SCH_2CH_2COOCH_3$
8, R: $CH_2CH_2SCH_2CH_2CONH$-**TentaGel**

Figure 1. Synthesis of TentaGel-$(DHQ)_2PHAL$ catalyst.

A comparison of the catalytic activity of ligands **4** and **8** using styrene for the LAC-AD reaction is summarized in Table 1. As noted previously by Sharpless et al.,[10] the 'second cycle' problem is presumably responsible for the lower enantiomeric excess (ee) observed with the 4-methylmorpholine-*N*-oxide (NMO) co-oxidant (entries 3 and 5). This effect is even more pronounced with the resin-supported catalyst (entry 5). Interestingly, the yields and ee's were remarkably higher with the $K_3Fe(CN)_6$ co-oxidant and were comparable to those obtained with the free ligand. Even though no attempts were made to improve the yield and ee (e.g., lower temperature, slow addition of olefin, higher ligand/olefin ratio), the 91% ee obtained under the latter conditions is one of the highest reported for an insoluble resin-supported AD catalyst.[3a–h] In addition, with the $K_3Fe(CN)_6$ co-oxidant, attempts to recycle the resin-bound catalyst 3 times (isolated each time by filtration and washed with EtOAc and H_2O and dried under high vacuum) resulted in no apparent loss of activity or enantioselectivity.

Table 1. Asymmetric dihydroxylation of styrene (0.2 M) to 1-phenyl-1,2 ethanediol

Entry	Ligand (1 mol %)	Conditions[a]	Isolated yield	% ee[b]
1	None	A	74	Racemic
2		B	48	Racemic
3	**4**	A	85	63
4		B	80	99
5	**8**	A	61	25
6		B	85	91

[a] Sharpless's dihydroxylation reaction conditions.[1,2] Conditions A: OsO_4 (0.2 mol %), NMO (3 mol equiv/styrene), acetone/H_2O (10/1), 20 °C. Reaction stopped after 12 h. Conditions B: OsO_4 (0.2 mol %), $K_3Fe(CN)_6/K_2CO_3$ (3 mol equiv/styrene), *t*-BuOH/H_2O (1/1), 20 °C. Reaction stopped after 12 h.

[b] Determined by chiral HPLC (CHIRALCEL OD-H, 0.46 cm i.d. × 25 cm length, chiral phase: cellulose bis-3,5-dimethyl-phenylcarbamate on 5 μm silica substrate, solvent: 2-propanol/hexane (95/5), flow rate 1 mL/min, $\lambda = 254$ nm).

To further illustrate the catalytic activity of TentaGel-supported $(DHQ)_2PHAL$, four styrene derivatives were dihydroxylated in the presence of $K_3Fe(CN)_6/K_2CO_3$ (3 mol equiv/styrene) and *t*-BuOH/H_2O (1/1) at 20 °C for 48 h (Table 2). With the exception of entry 7, the ee's obtained using the resin-supported ligand **8** were comparable to those with the free ligand **4**. These results again represent the un-optimized reaction conditions, thereby illustrating the potential of TentaGel-supported $(DHQ)_2PHAL$ for such transformations.

Table 2. Asymmetric dihydroxylation of styrene derivatives (0.2 M)

Entry	Styrene derivative	Ligand[a]	% ee of dihydroxylated product[b]
1	2-Chlorostyrene	**8**	96
2		**4**	98
3	2,6-Dichlorostyrene	**8**	86
4		**4**	93
5	4-(Trifluoromethyl)styrene	**8**	82
6		**4**	74
7	3-Fluorostyrene	**8**	63
8		**4**	82

[a] Sharpless's dihydroxylation general reaction conditions.[1,2] Styrene derivative (0.2 M), OsO_4 (0.2 mol %), ligand **4** or ligand **8** (1 mol %), $K_3Fe(CN)_6/K_2CO_3$ (3 mol equiv/styrene), *t*-BuOH/H_2O (1/1), 20 °C. Reaction stopped after 48 h.

[b] Determined by chiral HPLC (CHIRALCEL OD-H, 0.46 cm i.d. × 25 cm length, chiral phase: cellulose bis-3,5-dimethyl-phenylcarbamate on 5 μm silica substrate, solvent: 2-propanol/hexane (95/5), flow rate 1 mL/min, $\lambda = 254$ nm). Results are based on a single experiment.

3. Conclusion

In conclusion, ee's obtained with the TentaGel-$(DHQ)_2PHAL/K_3Fe(CN)_6$ system are for the most part analogous to those obtained with the free ligand and are among the highest ever achieved for an insoluble polymer-supported AD ligand under the reaction conditions described in Tables 1 and 2.

Acknowledgements

This work was supported by Research Corporation (Cottrell award to H.F.), the Trask Trust Fund, the National Institute for Nanotechnology and the University of Alberta.

References

1. Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
2. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

3. (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003–3006; (b) Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321–11328; (c) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929–6930; (d) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S. G. *Tetrahedron: Asymmetry* **1996**, *7*, 645–648; (e) Nandanan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1997**, *38*, 2577–2580; (f) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559–6562; (g) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385–3466; (h) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21–27; (i) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527–1530; (j) Kuang, Y. Q.; Zhang, S. Y.; Wei, L. L. *Synth. Commun.* **2003**, *33*, 3545–3550.
4. Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844–849.
5. Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121–4126.
6. Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147–157.
7. Spectral data of compounds **4**,[4] **5**[3i] and **6**[3i] are in agreement with the literature.
8. *Preparation of* **7** *from* **5**: Compound **5** (0.23 g, 0.29 mmol), methyl-3-mercaptopropionate (0.35 g, 2.93 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 0.024 g, 0.15 mmol) were dried under high vacuum and then refluxed in benzene (30 mL) for 24 h. Additional AIBN (0.021 g, 0.13 mmol) was then added and refluxing was maintained for 12 more hours. Note that the starting material and product have the same R_f by TLC (10% MeOH/CH_2Cl_2), so the reaction must be pushed to completion. The solvent and excess methyl-3-mercaptopropionate were removed under high vacuum and the solid was purified by flash chromatography (SiO_2, 0–5% MeOH/CH_2Cl_2) to provide **7** as a white solid in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 8.68–8.58 (m, 2H), 8.36–8.25 (m, 2H), 8.02–7.88 (m, 4H), 7.58 (br s, 2H), 7.42 (m, 2H), 7.39–7.31 (m, 2H), 7.12–6.98 (m, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.67 (s, 3H), 3.54–2.93 (m, 6H), 2.79–1.20 (m, 26H), 0.82 (t, $J = 7.9$ Hz, 3H). PDMS: calcd [M] = 896.5; obsd [M+1] = 897.7.
9. *Preparation of* **8** *from* **6**: TentaGel-S-NH_2 (300 μmol/g, 0.47 g, 142 μmol), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU, 0.16 g, 425 μmol), 1-hydroxybenzotriazole hydrate (HOBt·H_2O, 0.02 g, 100 μmol), diisopropylethylamine (0.11 g, 850 μmol) and **6** (0.25 g, 283 μmol, 0.1 M final concentration) were shaken at 20 °C for 30 h in anhydrous CH_2Cl_2 and *N*,*N*-dimethylformamide (1/1 v/v, 3 mL). The progress of the reaction was followed using the Kaiser test.[6] The resin beads were then filtered and washed sequentially with DMF, CH_2Cl_2, DMF, CH_2Cl_2 and diethylether (3 × 15 mL each). After drying the beads under vacuum, the unreacted free amines (inaccessible sites, <1%) were capped as follows: 3 min room temperature treatment with 0.75 vol of 6.5% (w/v) 4-dimethylaminopyridine in THF and 0.25 vol of 40% (v/v) acetic anhydride in 2,6-lutidine, followed by extensive washes of the resin with THF, DMF, CH_2Cl_2 and MeOH. *Preparation of* **8** *from* **7**: TentaGel-S-NH_2 (300 μmol/g, 11 mg, 3.3 μmol) and **7** (13 mg, 14.5 μmol) were shaken at 100 °C for 48 h in anhydrous DMF (enough to cover the resin with solvent). The progress of the reaction was monitored using the Kaiser test.[6] The resin beads were then filtered and washed sequentially with DMF, CH_2Cl_2, DMF, CH_2Cl_2 and diethylether (3 × 3 mL each). After drying the beads under vacuum, the unreacted free amines were capped as described previously.
10. Ogino, Y.; Chen, H.; Kwong, H. L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965–3968.