Pergamon

Tetrahedron Letters 39 (1998) 4099–4102

TETRAHEDRON LETTERS

Asymmetric Aminohydroxylation of Substituted Styrenes Using *t*-Butyl Carbamate

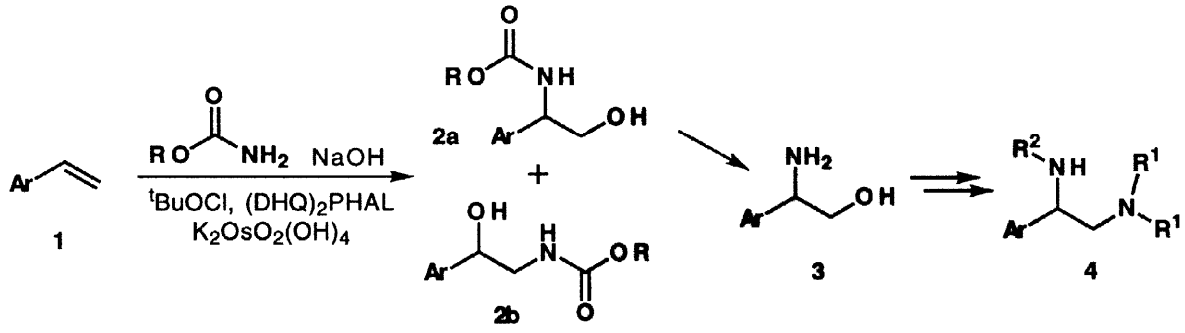
Peter O'Brien,[a]* Simon A. Osborne[b] and Daniel D. Parker[a]

[a] Department of Chemistry, University of York, Heslington, York YO1 5DD, UK
[b] Parke-Davis Neuroscience Research Centre, Forvie Site, Robinson Way, Cambridge CB2 2QB, UK

Received 11 December 1997; revised 20 March 1998; accepted 27 March 1998

Abstract: A variety of substituted styrenes have been aminohydroxylated using *t*-butyl carbamate to give either enantiomer of highly enantiomerically enriched *N*-Boc protected amino alcohols in good yields. Better levels of regioselectivity were observed with $(DHQ)_2PHAL$ than with $(DHQD)_2PHAL$ even though the enantioselectivities observed were comparable. One of the amino alcohol products was converted into a novel chiral diamine.

We have an on-going interest[1-3] in the preparation of chiral diamines like **4** as we have been using their lithium amides as chiral bases in enantioselective epoxide rearrangement reactions.[4] One[2] of our approaches to diamine synthesis involves *N,N*-dialkylation of (*R*)-phenylglycinol (**3**; Ar = Ph) followed by aziridinium ion formation and reaction with an amine. During our diamine synthetic studies, we had shown that it was relatively simple to prepare both enantiomers of diamines **4** with a range of R^1 and R^2 groups.[1-3] However, we had never prepared diamines with aromatic substituents other than a phenyl ring since the starting materials are not commercially available.[5-7] As it would be useful to prepare diamines **4** with Ar ≠ Ph, we decided to explore the preparation of arylglycinols *via* Sharpless asymmetric aminohydroxylation[8-13] of substituted styrenes **1**. A study into the asymmetric aminohydroxylation of several styrenes **1** and the use of one of the products in the preparation of a new chiral diamine are the subject of this paper.

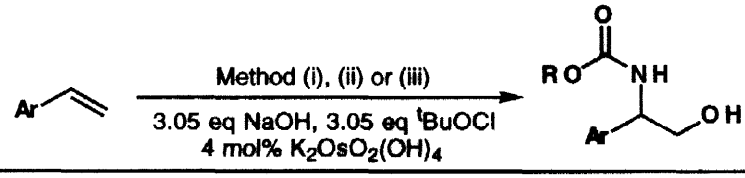


The only suitable method that Sharpless has reported for the asymmetric aminohydroxylation of styrene derivatives involves the use of osmium tetroxide [produced from $K_2OsO_2(OH)_4$], a chiral alkaloid ligand [*eg* $(DHQ)_2PHAL$] and a sodium *N*-chlorocarbamate salt (generated *in situ* from an alkyl carbamate, sodium hydroxide and *t*-butyl hypochlorite). Under these conditions, aminohydroxylation of styrenes **1** can produce two regioisomers **2a** and **2b** but, in the known[9,10] examples, amino alcohols **2a** of high (≥90%) enantiomeric excess were isolated as the major products.

0040-4039/98/$19.00
PII: S0040-4039(98)00665-0

As a starting point, we decided to investigate the aminohydroxylation of styrene **5**, 2-chlorostyrene **6** and 2-vinylnaphthalene **7** using benzyl carbamate [method (i)].[9,10] Our plan was to isolate the major regioisomeric amino alcohol **2a** in each case. As can be seen from Table 1 (Entries 1, 4 and 7), the initial results were not very promising. However, on changing to ethyl carbamate [method (ii)] or *t*-butyl carbamate[10,14] [solvent: 2:1 *n*-propanol-water; method (iii)], reasonable quantities of amino alcohols were produced. Although purification of the crude products (by chromatography) was complicated by the presence of excess alkyl carbamate, moderate to good yields of the expected[15] major products[16] (≥84% ee as judged by chiral HPLC[17,18]) were obtained (Table 1). The conditions for the *t*-butyl carbamate reactions (6 mol% ligand, 0 °C, 2:1 *n*-propanol-water[10,14]) are superior to those with benzyl or ethyl carbamates since higher enantioselectivities and isolated yields of amino alcohols are obtained as a rule (compare entries 2 and 3 or entries 8 and 9 in Table 1); a related bonus is that subsequent *N*-deprotection is straightforward.

Table 1: *Asymmetric Aminohydroxylation of Styrenes using Benzyl, Ethyl and t-Butyl Carbamate*



Method (i): 3.1 eq BnO_2CNH_2, 5 mol% ligand, 1:1 ^{n}PrOH-water, 0 °C, 1.5-4.5 h
Method (ii): 3.1 eq EtO_2CNH_2, 5 mol% ligand, 1:1 ^{n}PrOH-water, rt, 0.5-3.5 h
Method (iii): 3.1 eq ^{t}BuO_2CNH_2, 6 mol% ligand, 2:1 ^{n}PrOH-water, 0 °C, 1 h

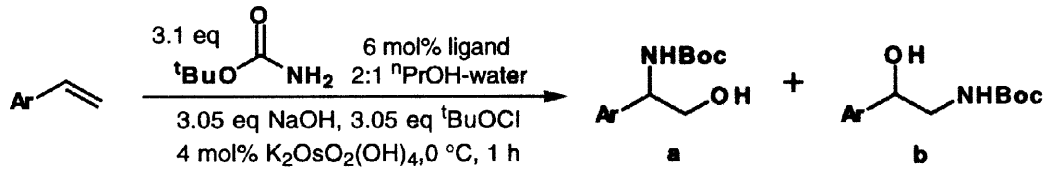
Entry	Ar	Alkene	Method	Ligand	R	Product	Yield (%)	ee (%)
1	Ph	**5**	(i)	$(DHQ)_2PHAL$	Bn	(*S*)-**8a**	8	–
2	Ph	**5**	(ii)	$(DHQD)_2PHAL$	Et	(*R*)-**9a**	44	88
3	Ph	**5**	(iii)	$(DHQ)_2PHAL$	^{t}Bu	(*S*)-**10a**	58	94
4	2-ClC_6H_4	**6**	(i)	$(DHQD)_2PHAL$	Bn	(*R*)-**11a**	0	–
5	2-ClC_6H_4	**6**	(ii)	$(DHQD)_2PHAL$	Et	(*R*)-**12a**	44	84
6	2-ClC_6H_4	**6**	(iii)	$(DHQ)_2PHAL$	^{t}Bu	(*S*)-**13a**	41	92
7	2-naphthyl	**7**	(i)	$(DHQD)_2PHAL$	Bn	(*R*)-**14a**	0	–
8	2-naphthyl	**7**	(ii)	$(DHQD)_2PHAL$	Et	(*R*)-**15a**	35	96
9	2-naphthyl	**7**	(iii)	$(DHQ)_2PHAL$	^{t}Bu	(*S*)-**16a**	48	98

The success of the *t*-butyl carbamate conditions prompted us to use them to carry out a detailed study of the aminohydroxylation of substituted styrenes. The results are summarised in Table 2.[19] From the ^{1}H NMR spectra of the crude product mixtures, we were able to determine the ratio of regioisomeric amino alcohols (**a** : **b**) and regioisomers **a** were isolated by chromatography. In almost all cases, it was impossible to obtain pure samples of regioisomers **b** as they co-eluted with the excess *t*-butyl carbamate.

Whilst we cannot draw firm conclusions from the results obtained for the aminohydroxylation of styrenes using *t*-butyl carbamate, it is useful to highlight the following points: (i) useful *N*-Boc protected amino alcohols of high enantiomeric excess are generated from a range of alkenes; (ii) ***regioselectivity is ligand dependent*** with better regioselectivity (and therefore higher yields) obtained with $(DHQ)_2PHAL$; (iii)

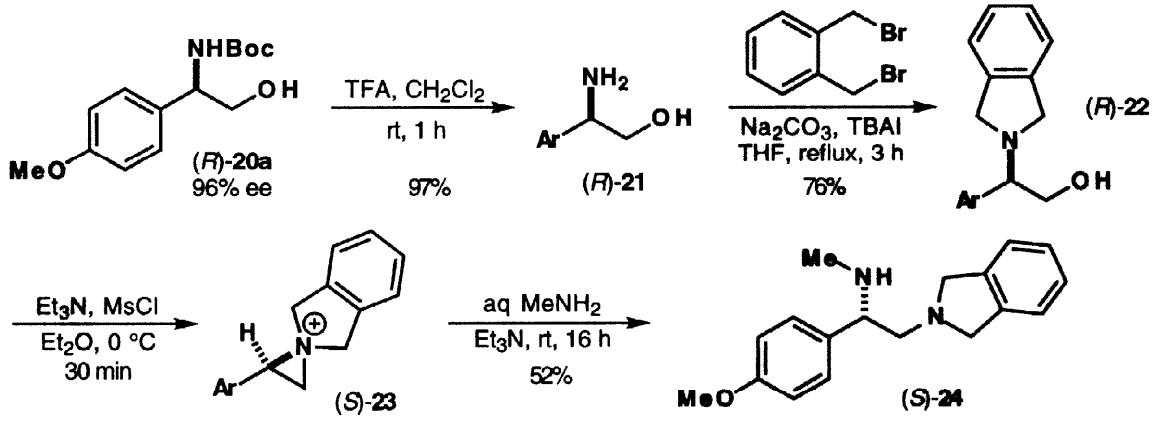
enantioselectivity of formation of regioisomers **a** *is not ligand dependent* (compare entries 5 and 6 or 7 and 8 in Table 2); (iv) very high enantioselectivities are observed with Ar = 2-naphthyl or 4-$MeOC_4H_6$ (entries 8 and 9 in Table 1; entries 7 and 8 in Table 2); (v) regioisomers **b** are produced with low enantiomeric excess.[20]

Table 2: *Asymmetric Aminohydroxylation of Styrenes using t-Butyl Carbamate*



Entry	Ar	Alkene	Ligand	a : b	Product	Yield (%)	ee (%)
1	Ph	**5**	$(DHQ)_2PHAL$	80 : 20	(*S*)-**10a**	58	94
2	Ph	**5**	$(DHQD)_2PHAL$	64 : 36	–	–	–
3	2-ClC_6H_4	**6**	$(DHQ)_2PHAL$	70 : 30	(*S*)-**13a**	41	92
4	2-ClC_6H_4	**6**	$(DHQD)_2PHAL$	64 : 36	–	–	–
5	2-$MeOC_6H_4$	**17**	$(DHQ)_2PHAL$	55 : 45	(*S*)-**19a**	43	87
6	2-$MeOC_6H_4$	**17**	$(DHQD)_2PHAL$	45 : 55	(*R*)-**19a**	34	88
7	4-$MeOC_6H_4$	**18**	$(DHQ)_2PHAL$	85 : 15	(*S*)-**20a**	74	98
8	4-$MeOC_6H_4$	**18**	$(DHQD)_2PHAL$	68 : 32	(*R*)-**20a**	65	96

As it was possible to prepare highly enantiomerically enriched *N*-Boc protected arylglycinols using asymmetric aminohydroxylation, we were keen to show that these compounds could be used for diamine synthesis. Thus, amino alcohol (*R*)-**20a** of 96% ee [obtained from **18** using $(DHQD)_2PHAL$] was deprotected using TFA to afford arylglycinol (*R*)-**21**.[21] *N,N*-Dialkylation using α,α'-dibromo-*ortho*-xylene (according to our procedure[3]) generated (*R*)-**22** which was treated sequentially with mesyl chloride and methylamine in the usual manner to give the novel diamine (*S*)-**24** in 40% overall yield from (*R*)-**21**.



In summary, we have described several new asymmetric aminohydroxylation reactions using *t*-butyl carbamate as the nitrogen source. The reaction can be used to prepare a range of *N*-Boc protected amino alcohols and our observation that regioselectivity is ligand-dependent is worthy of note. Enantiomerically enriched *N*-Boc protected amino alcohols are useful compounds in synthesis: we have converted them into arylglycinols and diamines; they are also suitable for elaboration into amino acids (arylglycines[9,10]).

General procedure for asymmetric aminohydroxylations using t-butyl carbamate

A solution of *t*-butyl carbamate (545 mg, 4.65 mmol) in *n*-propanol (6 cm^3) was sequentially treated with a freshly prepared solution of sodium hydroxide (183 mg, 4.6 mmol) in water (12.2 cm^3) and *t*-butylhypochlorite (0.53 cm^3, 4.6 mmol). After stirring for 5 min, the solution was cooled to 0 °C and a solution of the ligand $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ (71 mg, 0.09 mmol) in *n*-propanol (6 cm^3) was added. Then, a solution of the alkene (1.5 mmol) in *n*-propanol (12.2 cm^3) was added followed by addition of $K_2OsO_2(OH)_4$ (22.5 mg, 0.06 mmol). After 1 h at 0 °C, the green solution became pale yellow and there was no starting material present by TLC analysis. Saturated aqueous sodium sulfite solution (10 cm^3) was added and the solution was stirred for 15 min. Then, the two layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which was analysed by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 3:1, 2:1 or 1:1 light petroleum (40-60 °C)-EtOAc as eluent gave the amino alcohols.

Acknowledgements: We thank Parke-Davis Neuroscience Research Centre for funding this project and we are extremely grateful to Mr Tim Underwood and Mr Simon Bryant of GlaxoWellcome Physical Sciences Department for carrying out the chiral HPLC work. In addition, we gratefully acknowledge Professor K. B. Sharpless for providing us with unpublished results on the use of *t*-butyl carbamate and Dr Y. Landais for useful discussions.

References and Notes

1. O'Brien, P.; Poumellec, P. *Tetrahedron Lett.*, **1996**, *37*, 5619-5622.
2. de Sousa, S. E.; O'Brien, P. *Tetrahedron Lett.*, **1997**, *38*, 4885-4888.
3. de Sousa, S. E.; O'Brien, P.; Poumellec, P. *Tetrahedron: Asymmetry*, **1997**, *8*, 2613-2618.
4. O'Brien, P.; Poumellec, P. *Tetrahedron Lett.*, **1996**, *37*, 8057-8058.
5. Styrene oxide (Aldrich Chemical Company) and phenylglycinol (Lancaster Synthesis) are available.
6. Koga has described the use of diamines **4** with aromatic groups other than phenyl in the asymmetric deprotonation of 4-substituted cyclohexanones but he did not comment on how they were prepared: Toriyama, M.; Sugasawa, K.; Shindo, M.; Tokutake, N.; Koga, K. *Tetrahedron Lett.*, **1997**, *38*, 567-570.
7. Rossiter has reported an asymmetric dihydroxylation route to diamines **4** with non-phenyl aromatic groups: Miao, G.; Rossiter, B. E. *J. Org. Chem.*, **1995**, *60*, 8424-8427.
8. Li, G.; Chang, H-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 451-454; Li, G.; Sharpless, K. B. *Acta Chem. Scand.*, **1996**, *50*, 649-651.
9. Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 2813-2817.
10. Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1998**, *120*, 1207-1217.
11. Rudolph, J.; Sennhenn, P.C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 2810-2813.
12. For useful applications of asymmetric aminohydroxylation in synthesis, see: Angelaud, R.; Landais, Y.; Schenk, K. *Tetrahedron Lett.*, **1997**, *38*, 1407-1410; Upadhya, T. T.; Sudalai, A. *Tetrahedron: Asymmetry*, **1997**, *8*, 3685-3689.
13. For overview articles on asymmetric aminohydroxylation, see: Reiser, O. *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 1308-1309; Casiraghi, G.; Rassu, G.; Zanardi, F. *Chemtracts-organic*, **1997**, *10*, 318-321.
14. Sharpless, K. B. personal communication: 2:1 *n*-propanol-water solvent system was recommended to us by Sharpless as he had observed significant levels of *dihydroxylation* with a greater proportion of water.
15. By preparing authentic samples of (*S*)-**9a** and (*S*)-**10a** from (*S*)-phenylglycinol, we were able to establish the sense of induction in the reactions with styrene **5** and the stereochemistries indicated in the remainder of this paper are assigned by analogy. They are consistent with those obtained by Sharpless (references 10 and 14).
16. All new compounds were characterised by ^1H and ^{13}C NMR spectroscopy, microanalysis and high resolution mass spectrometry.
17. Chiral HPLC (observed at 215 nm) was carried out on either Chiralpak AD, Chiralcel OD-H, Chiralcel OJ or Regis (*S,S*) Whelk-O 1 columns using solutions of 5-20% *i*-propanol or ethanol in heptane as the mobile phase at a flow rate of 1.0 mL min^{-1}.
18. Chiral HPLC (Table 1): **9a**, Chiralcel OJ; **10a** and **16a**, Regis (*S,S*) Whelk-O 1; **12a**, Chiralcel OD-H; **13a** and **15a**, Chiralpak AD.
19. Chiral HPLC (Table 2): **19a**, Chiralcel OJ; **20a**, Chiralcel OD-H.
20. For example, a 25% yield of amino alcohol **19b** (36% ee; Chiralcel OD-H) was isolated from the reaction of alkene **17** using $(DHQ)_2PHAL$ and a 23% yield of amino alcohol **9b** (74% ee; Chiralcel OD-H) was isolated from the reaction of alkene **5** using $(DHQD)_2PHAL$.
21. All of the amino alcohols in Table 2 have been converted into the corresponding arylglycinols.