Enantiopure Guanidine Bases for Enantioselective Enone Epoxidations: 2, Cyclic Guanidines

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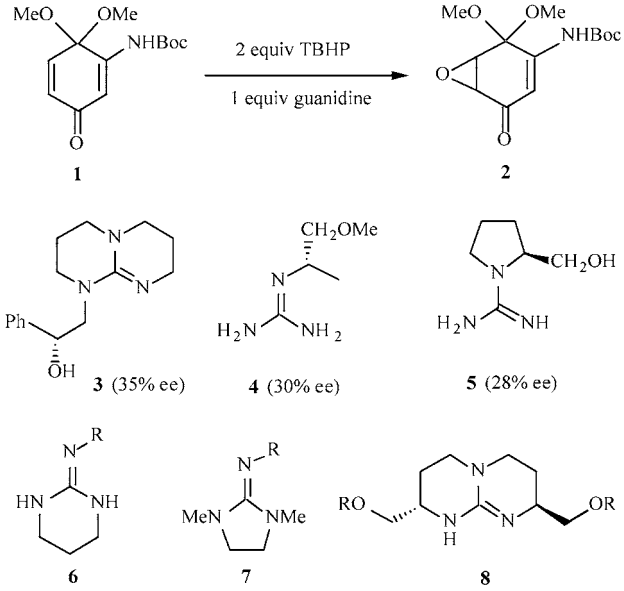
Abstract: A range of structurally and functionally varied enantiopure cyclic and bicyclic guanidines has been prepared and evaluated in the enantioselective epoxidation of 3-*tert*-butoxycarbonylamino-4,4-dimethoxycyclohexa-2,5-dien-1-one **1** using *tert*-butylhydroperoxide. Encouraging enantiomeric excesses were observed (up to 60%). Low enantiomeric excesses were also observed with 2-methylnaphthoquinone and *trans*-chalcone.

Key words: enantioselective, epoxidation, enones, guanidines, stereoselectivity

There have been a number of recent advances concerning the enantioselective epoxidation of electron-deficient alkenes but the epoxidation of cyclic enones has presented particular problems.[1] As discussed in more detail in the accompanying paper,[2] we have investigated the use of asymmetric phase-transfer epoxidation,[3] and asymmetric epoxidations using sugar-derived hydroperoxides.[4] We have also reported *t*-butylhydroperoxide (TBHP)-mediated epoxidation reactions effected by enantiopure guanidines (Scheme 1).[2,5] We employed 3-*tert*-butoxycarbonylamino-4,4-dimethoxycyclohexa-2,5-dien-1-one **1** with *tert*-butylhydroperoxide as the test system as the product epoxide **2** is a versatile synthetic intermediate for the preparation of manumycin and related natural products.[6]

Of the enantiopure guanidine-catalysts prepared in these earlier studies, the best enantiomeric excesses (ee) observed were using compounds **3**,[5] **4**[2] and **5**[2] (Scheme 1), but despite optimisation studies the reactions were slow and the maximum ee was 35%. Given that the best ee was obtained using the bicyclic guanidine **3**, we decided to incorporate greater conformational rigidity into the guanidines and investigate the monocyclic and bicyclic systems **6**–**8** (Scheme 1).

We first studied the preparation of monocyclic guanidines **6** as shown in Scheme 2. The novel guanylating agent **10** was prepared from commercially available **9**[7] using the Mitsunobu protocol shown in Scheme 2.[8] Reaction of **10** with chiral primary amines gave Boc-protected guanidines **11**. Deprotection was then carried out by treatment with 3 M anhydrous methanolic HCl followed by ion-exchange chromatography on Amberlite® resin. Using this procedure, a range of functionally varied, enantiopure monocyclic guanidines **6a**–**g** were prepared as free bases.[9]



Scheme 1

We also attempted the *N*-methylation of these monocyclic bases but only produced complex mixtures. In addition, the reduction of the Boc-derivatives **11** to the corresponding *N*-methyl analogues proved unsuccessful. We therefore explored an alternative route to *N*-methylated systems based on chloroamidine chemistry (Scheme 3). Chloroamidine **12** has been developed as an amidine transfer agent.[10] Generation of **12** followed by treatment with (*R*)-α-methylbenzylamine successfully gave guanidine **7a** (Scheme 3). Unfortunately, the attempted extension of this methodology to prepare the corresponding 6-membered ring systems **13** and **14** proved problematic.[11]

The final series of enantiopure guanidines investigated in this study were **8a**–**c**. The synthesis of the C_2-symmetric guanidine **8a** has been reported in the literature where it has been used as an anion receptor.[12] The route described by Schmidtchen's group,[12b] commencing from L-asparagine and L-methionine, was successfully employed to prepare diol **8a**, and by minor modification, the silylated guanidines **8b** and **8c** (Figure 1).

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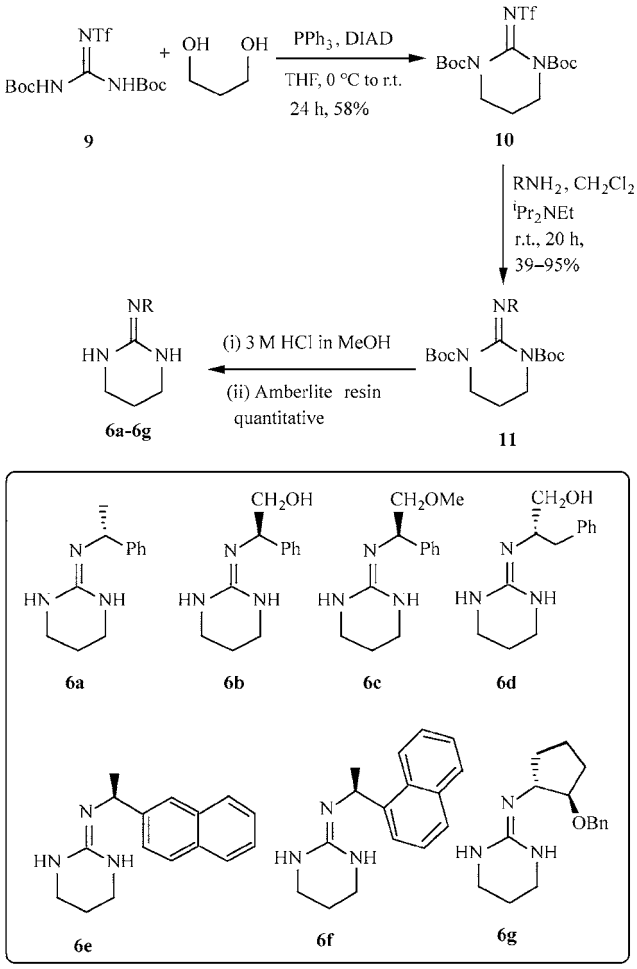
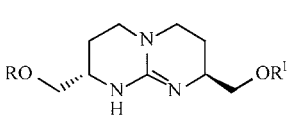


Scheme 2



R = R^I = H **8a**
R = R^I = TBS **8b**
R = H, R^I = TBDPS **8c**

Figure 1

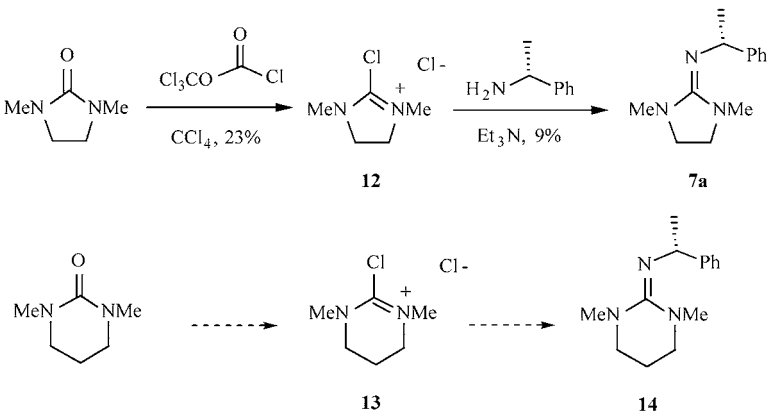
Table 1 Asymmetric Epoxidation of Enone **1** Using Chiral Guanidine Bases[a]

	Guanidine	Yield (%)	RSM[b] (%)	ee 2[c] (%)
i	**6a**	49	0	39 (–)
ii	**6b**	34	41	60 (+)
iii	**6c**	56	0	40 (+)
iv	**6d**	45	37	38 (–)
v	**6e**	50	0	50 (+)
vi	**6e**	67[d]	0	44 (+)
vii	**6f**	37	0	41 (+)
viii	**6g**	52	0	26 (+)
ix	**7a**	0	–	–
x	**8a**	74[e]	0	48 (–)
xi	**8b**	45	0	0
xii	**8c**	10	0	0

[a] 2 Equiv TBHP, 1 equiv base, 5% IPA in toluene, r.t., 7 d.
[b] RSM = recovered starting material 1.
[c] The sign in brackets indicates which enantiomer of **2** was formed; ee was determined by chiral HPLC.[13]
[d] Reaction stopped after 24 h.
[e] Reaction was complete after 48 h.

All of the enantiopure guanidines described were evaluated in the epoxidation of enone **1**; the results are summarised in Table 1.

It is immediately noticeable that these cyclic and bicyclic guanidines give much higher ee than previously observed.[2,5] The 50% ee achieved with monocyclic guanidine **6e** (entry v) and the 48% ee with bicycle **8a** (entry x) are particularly interesting, showing that both monocyclic and bicyclic structural types are viable. However, it is the 60% ee achieved with the phenylglycinol-derived guanidine **6b** (entry ii) that is of greatest note. In addition, the ineffectiveness of guanidine **7a** as an epoxidation mediator (entry ix) is rather surprising.

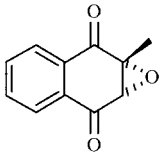


Scheme 3

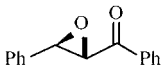
Within the series of monocyclic guanidines **6**, there is a good correlation between the absolute stereochemistry of the original amine and the predominant enantiomer of epoxide **2**: thus, **6a** and **6d** give a predominance of (–)-**2**, in contrast to the other members of the series which favour formation of (+)-**2**. By comparison of the results obtained with **6b** and **6c** (entries ii and iii, respectively), it can be noted that the free alcohol functionality improves the enantioselectivity but decreases the yield of the reaction (as observed before).[2] In contrast to the earlier study,[2] however, the enantioselectivity of this series of guanidines appears to be improved by introduction of a larger aryl group adjacent to the chiral centre (compare entries i and v). Guanidines **6e** and **8a** were notable in that the epoxidation reaction was complete in 24–48 hours (entries vi and x).

The C_2-symmetric guanidine **8a** was also extremely effective in the enantioselective epoxidation reaction giving epoxide **2** in 74% yield and 48% ee in a relatively fast transformation (entry x). Unfortunately, attempts to modify structure **8a** in order to optimise its activity were unsuccessful (entries xi, xii).

Finally, we explored the use of guanidine **6b** for the epoxidation of 2-methylnaphthoquinone and *trans*-chalcone (Figure 2). Although these epoxidations were not optimised, it was extremely encouraging to observe that guanidine **6b** gives enantioselectivity with both cyclic enones (**1** and 2-methylnaphthoquinone) as well as with the acyclic enone, *trans*-chalcone.



68% yield
31% ee



71% yield
15% ee

Figure 2 Epoxidation of 2-methylnaphthoquinone and *trans*-chalcone using **6b**/TBHP

In summary, we have prepared a range of novel guanidines and demonstrated that these give encouraging ee (up to 60%) and yields (up to 74%) in the epoxidation of substituted cyclohexenone **1** with *tert*-butylhydroperoxide, and that either enantiomer can be obtained. We have also established that guanidine **6b** can mediate the epoxidation of 2-methylnaphthoquinone and *trans*-chalcone. Given the ease of preparation of guanidines **6**, we are currently preparing additional analogues to optimise ee and yield and extend the range of substrates. We are also investigating their use in natural product synthesis and in other guanidine-mediated asymmetric processes.

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(8) All new compounds were fully characterised by ^{1}H NMR, ^{13}C NMR and IR, plus HRMS or elemental analysis.
(9) **Preparation of 6b.** HCl salt: (a) (*R*)-(–)-2-Phenylglycinol (189 mg, 1.38 mmol) was added to a solution of di-*tert*-butyl-2-[(trifluoromethanesulfonyl)imino]dihydro-1,3(2*H*,4*H*)-pyrimidinecarboxylate **10** (300 mg, 0.69 mmol) and diisopropyl(ethyl)amine (0.24 cm^3, 1.38 mmol) in CH_2Cl_2 (4 cm^3), under a nitrogen atmosphere. The solution was stirred at r.t. for 18 h before the solvent was removed under reduced pressure and the residue purified by flash silica chromatography (CH_2Cl_2:MeOH, 50:1) to afford di-*tert*-butyl-2-[(1*R*)-2-hydroxy-1-phenylethylimino]dihydro-1,3(2*H*,4*H*)-pyrimidinecarboxylate **11** (208 mg, 71%) as a clear gum, $[\alpha]_D^{20}$ +18.7 (*c* 1.25, $CHCl_3$) which was fully characterised. (b) The Boc-protected guanidine **11** (200 mg, 0.48 mmol) was dissolved in approx. 3 M anhyd. methanolic HCl (20 cm^3) and was stirred at r.t., under nitrogen, for 18 h. The solvent was then removed under reduced pressure to afford *N*-[(1*S*)-1-phenyl-2-hydroxyethyl]-*N*-tetrahydro-2(1*H*)-pyrimidinylideneaminehydrochloride **6b**. HCl quantitatively (124 mg) as a gum, $[\alpha]_D^{20}$ –40.9 (*c* 1.0, MeOH). IR(neat): ν_{max} = 3365 (OH), 3029 and 2096 (CH), 1695 (CN_3) cm^{-1}. MS (CI): *m/z* = 220 (100) [MH$^+$], 202 (21), 138 (27), 100 (25), 75 (31). HRMS (CI): Calcd for $C_{12}H_{18}N_3O$: 220.1450. Found: [MH$^+$]: 220.1456 (–2.7 ppm error), which gave consistent ^{1}H and ^{13}C NMR spectra.
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(13) Chiral HPLC was carried out using a Chiralcel OJ column (25 cm × 4.6 mm) with hexane–isopropanol (98:2) as eluent at a flow rate of 1 mL/min and detection at 276 nm.
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