Epoxidation of Electron Deficient Alkenes Using *tert*-Butyl Hydroperoxide and 1,5,7-Triazabicyclo[4.4.0]dec-5-ene and its Derivatives

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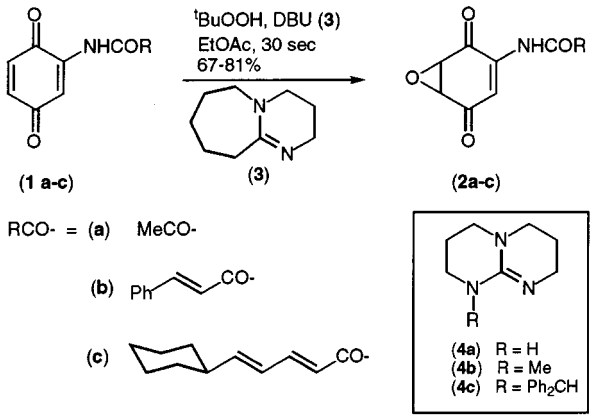
Abstract: The title cyclic guanidine (**4a**) is an efficient promoter of enone epoxidation by *tert*-butyl hydroperoxide. Optimisation studies are reported and the procedure applied to cyclic and acyclic ketones, quinones and naphthoquinones. *N*-Substituted guanidine (**4c**) proved best for the epoxidation of 2-amidobenzoquinones. Preliminary asymmetric epoxidation studies are also discussed.

Key words: epoxidation, alkenes, guanidine

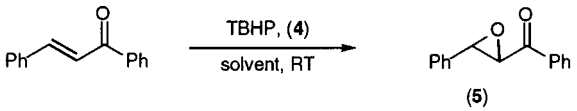
The epoxidation of electron deficient alkenes, a process of great synthetic importance, can be achieved in a number of ways.[1] Many of these procedures utilise aqueous hydrogen peroxide and inorganic bases but in examples where these conditions cause problems, the use of anhydrous *tert*-butyl hydroperoxide (TBHP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **3**) in dichloromethane has been recommended.[2,3] We have made use of this procedure during our studies on the total synthesis of manumycin and related epoxyquinone antibiotics (Scheme 1).[4] All of the quinones **2** are very sensitive to alkali and undergo rapid transformation to an unidentified black dyestuff under standard alkaline peroxide conditions but the DBU procedure was extremely fast and efficient.



Scheme 1

In seeking to optimise this epoxidation procedure, we decided to investigate the use of the corresponding 1,5,7-triazabicyclo[4.4.0]dec-5-enes (**4**),[5] a group of strong bases with pKa (ca. 13)[6] similar to or slightly greater than DBU. The parent compound (**4a**) and its *N*-methyl derivative **4b** have both been used to catalyse Michael additions,[7] as have enantiopure *C*-substituted analogues.[8] We were attracted to bicyclic guanidine bases **4** for several reasons. Compounds **4a** and **4b** are commercially available and the conversion of **4a** into other *N*-substituted analogues is well described.[9] We felt that this gave the potential for tuning the reactivity of the bases and for preparing enantiomerically pure analogues. In addition, the preparation of solid-supported base is possible: this application was reported during the course of our study.[10]

We commenced this study by examining the epoxidation of *trans*-chalcone using anhydrous TBHP (5.5 *M* in decane) (Scheme 2 and Tables 1-3). We were delighted to see that the oxidation proceeded smoothly in a range of solvents using guanidine **4a** as shown in Table 1. We also established (Tables 1 and 2), that epoxidation proceeded efficiently using sub-stoichiometric quantities of **4a** but that the reaction slows dramatically when less than 0.3 equivalents are employed. It should be noted that the reaction proceeded to completion at a much faster rate when one equivalent or more of **4a** was employed but a lower yield of product was obtained, presumably due to base-promoted side reactions. Further studies showed that the reaction still proceeded efficiently with just a slight excess of oxidant (5.5 equiv. TBHP, 90% **5**; 1.1 equiv. TBHP, 78% **5**), and that guanidine **4a** also catalysed epoxidation with hydrogen peroxide and other peroxides, even in the presence of water (Table 3).



Scheme 2

Table 1 Chalcone epoxidation with 0.3 eq. (**4a**) in several solvents

TBHP equivalents	solvent	*trans*-chalcone epoxide (**5**) yield	reaction time
5.5	dichloromethane	93%	240 min
5.5	chloroform	90%	280 min
5.5	toluene	85%	120 min
5.5	tetrahydrofuran	84%	120 min
5.5	acetonitrile	82%	55 min
5.5	*iso*-propanol	72%	70 min

Table 2 Variation of the equivalents of guanidine (**4a**) in $CHCl_3$

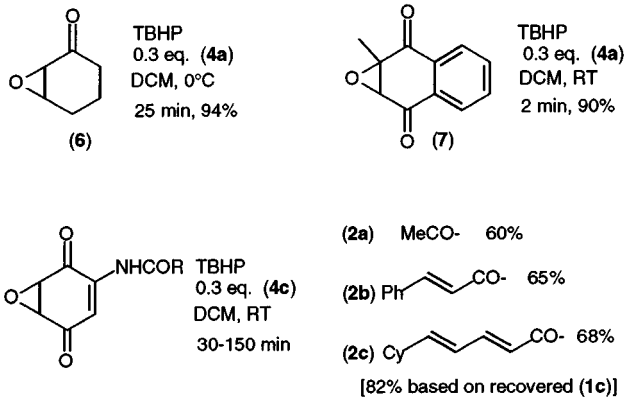
guanidine (**4a**) equivalents	TBHP equivalents	*trans*-chalcone epoxide (**5**) yield	reaction time
2.0	5.5	63%	40 min
1.0	5.5	71%	100 min
0.5	5.5	84%	210 min
0.3	5.5	90%	280 min
0.1	5.5	95%	51 h

Table 3 Variation of the oxidant

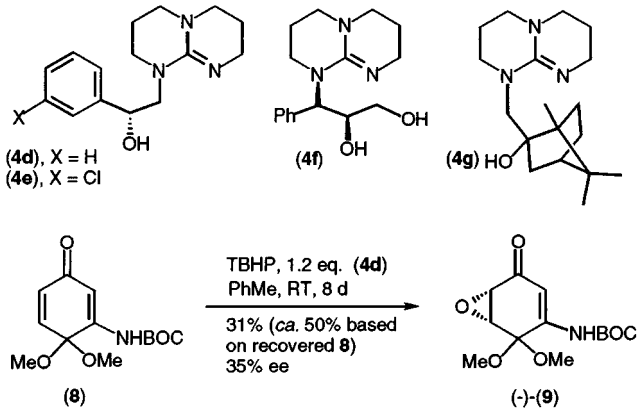
guanidine (**4a**) equivalents	oxidant (5.5 equivalents)	*trans*-chalcone epoxide (**5**) yield	reaction time
0.3	33.5% H_2O_2	96%	10 min
0.3	cumene hydroperoxide (80% in cumene)	81%	400 min
0.3	TBHP (70% in water)	92%	290 min
0.3	TBHP (5.5 *M* in decane)	93%	240 min

We also examined the epoxidation of other substrates (Table 4). Cyclohexenone oxide (**6**) and naphthoquinone oxide (**7**) were both produced in high yields using catalytic amounts of guanidine **4a**. In addition, this procedure was employed in the synthesis of deoxypreussomerin A.[11] However, epoxidation of quinones **1a-c** proceeded rather violently under these conditions with the reaction mixture turning black within seconds and only low yields (33-45%) of epoxides **2a-c** being isolated. Use of the *N*-methyl guanidine **4b** gave slightly better yields but the reaction was still very fast. We therefore prepared the *N*-benzhydryl guanidine **4c**[12] and found that with this catalyst the epoxidation of these sensitive quinones proceeded more slowly and in much higher yields (60% - 68%).

Table 4 Variation of the substrates



We have also prepared a range of enantiomerically pure guanidines (e.g. **4d-g**, Scheme 3).[13,14] Preliminary studies illustrate the potential of these reagents, although considerable optimisation is clearly required. Thus, for example, epoxidation of enone **8** with TBHP in the presence of **4d** gave a predominance of epoxide (-)-(**9**) {$[\alpha]_D$ - 65 (c 0.98, $CHCl_3$); 35% ee}, a valuable building block in antibiotic synthesis.[4,15] The enantiomer of **4d** was also prepared and this was used to produce (+)-**9** with a similar enantiomeric purity.



Scheme 3

In summary, we have shown that a number of cyclic guanidines **4** promote the TBHP-mediated epoxidation of electron deficient alkenes,[16] and that enantiomerically pure guanidines show promise in asymmetric epoxidations.

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(12) Kosasayama, A.; Konno, T.; Higashi, K.; Ishikawa, F. *Chem. Pharm. Bull.* **1979**, *27*, 841; we prepared **4c** directly by alkylation of **4a** with benzhydryl bromide.
(13) All new compounds were fully characterised by high field ^1H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectrometry.

(14) **4d-f** were prepared from **4a** by reaction with the corresponding epoxide; **4g** was prepared by deprotonation of **4b** and trapping with camphor.
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(16) **Representative procedure:** 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (**4a**) (81 mg, 0.58 mmol) was added to a stirred solution of 2-methyl-1,4-naphthoquinone (100 mg, 0.58 mmol) and anhydrous *tert*-butyl hydroperoxide in decane (5.5 *M*, 0.55 mL, 3.03 mmol) in dichloromethane (4 mL) at RT. After 2 min the reaction had gone to completion (tlc) whereupon the mixture was diluted with dichloromethane (15 mL) and extracted with saturated aqueous iron(II) sulfate solution (2 x 15 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography on silica gel using petrol ether-ethyl acetate (5:1) as the eluent gave 2,3-epoxy-2-methyl-1,4-naphthoquinone (**7**) (98.4 mg, 90%) as colourless needles, m.p. 96 °C (lit.[17] 95-98 °C) with consistent spectroscopic data.
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