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Synthesis, applications and mechanistic investigations of C_2 symmetric guanidinium salts

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ABSTRACT

A range of guanidinium catalysts was prepared in six or seven synthetic steps and applied to the phase transfer alkylation of a glycinate Schiff's base in 21–86% ee as well as the phase transfer epoxidation of some chalcones in 85–94% ee. Using a spectrophotometric method, pK_a values in the range 13.2–13.9 in DMSO have been determined for some of the catalysts highlighting an increase in basicity relative to achiral tetramethylguanidine (pK_a=13.0) and a mechanism involving the protonated guanidinium ion as a phase transfer catalyst is proposed. The use of two of the catalysts for the addition of nucleophiles in Michael addition reactions was investigated and both were found to be effective catalysts. A counterion effect was apparent in these reactions, but no enantioselectivity was observed.

1. Introduction

The guanidine motif is ubiquitous in nature and the protonated guanidinium side chain of the amino acid, arginine, leads to key highly selective hydrogen-bonding and electrostatic interactions with carboxylate and phosphate anionic groups.[1] Many applications of guanidines in synthesis[2] are known and their use as Brønsted base catalysts have been reported.[3] More recently applications of guanidines and protonated guanidines as either bases or hydrogen bond donors in bifunctional organic catalysis have also been reported.[4] We have previously reported the application of C_2 symmetric guanidinium salts in phase transfer catalysis, and in Michael additions, and report our findings in more detail.

2. Preparation of guanidine catalysts 7a–d

Previously[5] we reported the synthesis of the tetracyclic C_2-symmetric guanidines **7a**–**d** by the conjugate addition of guanidine to the enones **3** and **6**. These enones were prepared from either ethyl *R*-3-hydroxybutyrate **1** or (*S*)-malic acid **4** in five and six steps, respectively. (Scheme 1).

The key reaction in both of these syntheses is the conjugate addition of guanidine to 2 equiv of the enones **3** or **6**, which proceeds in good yield and gives the products **7a** and **7b**, respectively. In the case of the parent catalyst **7a**, the conjugate addition product was easily purified by column chromatography and crystallization from ether/petrol. The hydroxyl substituted catalyst **7b** was found to be very hygroscopic and was thus converted to the silyl-protected catalysts **7c** and **7d** in reasonable overall yield. Catalyst **7e** was prepared by ion exchange of **7a** with $NaBPh_4$.

3. Phase transfer alkylation and epoxidation reactions

With the catalysts **7a**–**d** in hand, we were interested in the applications of these catalysts to phase transfer catalysis (PTC)[6] and firstly investigated the benzylation of the glycinate Schiff's base **8**[7] leading to the alkylated product **9**. (Scheme 2, Table 1).

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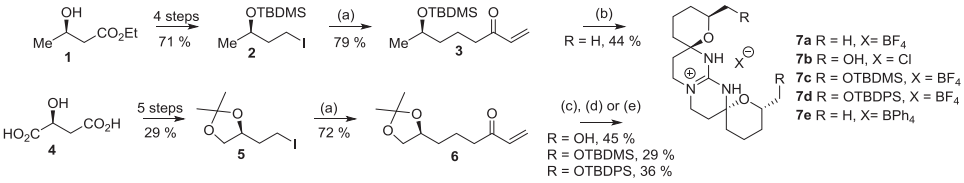
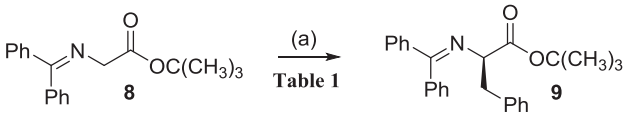


Scheme 1. (a) i) $CH_3COCHPPh_3$, *n*BuLi, ii) CH_2O. (b) i) guanidine/DMF, ii) HCl/MeOH, iii) $NaBF_4$ (aq). (c) i) guanidine/DMF, ii) HCl/MeOH. (d) As (c) then i) TBDMSCl, imidazole, DMF, ii) $NaBF_4$ (aq). (e) As in (c) then i) TBDPSCl, imidazole, DMF ii) $NaBF_4$ (aq).



Scheme 2. (a) Catalyst 7, (0.1 equiv), NaOH (2 M), BnBr (2 equiv), CH_2Cl_2, 16 h 0 °C-rt.

Table 1
Phase transfer benzylation of **8**

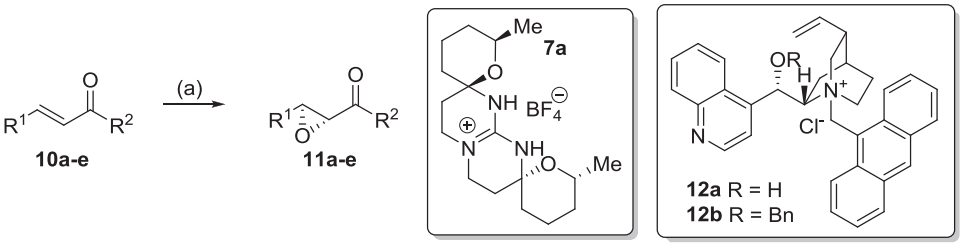
Entry	Catalyst 7	% Conv.	ee[a]
1	**7a**	>97%	86% (*R*)
2	**7b**	15%	21% (*R*)
3	**7c**	70%	65% (*R*)
4	**7d**	80%	74% (*R*)

[a] ±3%.

From these results it was apparent that the guanidine **7a** is the best catalyst for this transformation effecting nearly complete conversion of **8** to the desired product **9**, which was obtained as the *R*-enantiomer in 86% ee. The catalyst **7b** gave the worst results with very low conversion and low ee, which can be attributed to its poor solubility in the organic phase of the reaction. The silyl protected catalysts **7c** and **7d** gave a lower percentage conversion but, still gave the alkylated products as the *R*-enantiomer in good ee, 65% and 74%, respectively. The conversion rates for **7c** and **7d** could be raised to quantitative by increasing the concentration of sodium hydroxide in the reaction, or by allowing the reaction to progress for longer. However, this did not increase the ee of the product. The catalysts **7a**, **7c** and **7d** are tolerant to these reaction conditions, may be removed from the reaction mixtures during isolation and purification of the product and can then be recycled by repeating the fluoroborate ion exchange steps of their preparation (Scheme 1). Our results and the selectivities observed are in agreement with the reactions reported by Nagasawa using structurally similar pentacyclic guanidine catalysts.[8]

We next focused on the application of **7a** to the PTC epoxidation of chalcones **10a**–**e**[9] (Scheme 3) and found it to be an excellent catalyst for this transformation. We initially investigated the epoxidation of chalcone **10a** (R^1=R^2=Ph) with NaOCl and found that the catalyst was effective over a range of 0.1 to 0.025 equiv and gave the chalcone epoxide **11a** in consistent ee and in high yields (Table 2, entries 1–3). We wished to see if changes in the counter-ion of the hypochlorite had any effect on the ee or effectiveness of the process and thus investigated the use of LiOCl and KOCl in the reaction (both generated by the addition of the corresponding alkali metal hydroxide to trichloroisocyanuric acid (TCCA)[10]). In both cases the reaction was slower and generally needed 0.1 equiv of **7a** to effect complete conversion, however, the ees of the products were in accordance with those observed with NaOCl (entries 4 and 5). A reaction was performed using NaOCl generated in situ from NaOH and TCCA (entry 3), which was again correspondingly slower and required a higher catalyst loading but gave a comparable ee. The reason for the slower rate of reaction was unclear, and the method for the generation of the hypochlorite might be the cause. Following this, a series of chalcones **10b**–**e** (entries 6–9) were investigated and in general the ees were very good (85–94%). In the case of the chalcone **10e** (entry 9), this substrate proved to be unreactive to these conditions and no epoxide formation was observed. Epoxidation of **10e** under the conditions reported by Lygo[9] using catalysts **12a** (entry 10) and **12b** (entry 11) did give the desired epoxide but both the percentage yield and ees were poor in contrast to other examples of this reaction. This result would suggest that the presence of electron donating groups on the aromatic ketone, are detrimental to the reaction when catalysed with **7a** (see Scheme 4).

In order to probe the role of guanidinium salts **7a**–**e** in this reaction, we were keen to investigate the pK_as of these species. We thus determined the pK_a values for the catalysts **7a**–**d**, the previously prepared guanidinium salt **13**[11] and the conjugate acid of simple tetrasubstituted guanidine **14** in DMSO using a spectrophotometric method employing colorimetric indicators.[12] The pK_a values for **7a**–**d**, **13** and **14** (Table 3) were all relatively similar in value in the range 13.0–13.9. The pK_a of commercially available tetramethylguanidine **14** was calculated as 13.04, which is in good agreement with the literature values of 13.0 and 13.2 determined in DMSO, albeit using different methods.[13] As an internal calibration, the pK_a of acetic acid was also calculated as 12.48 using the spectrophotometric method, which is in accordance with the literature value of 12.31.[14] The small increases in pK_as between catalysts **13** and **7a**–**d** relative to tetramethylguanidine **14** would be expected due to the electron-donating nature of the pyran scaffold, which will stabilise the cationic guanidinium ion relative to the neutral



Scheme 3. (a) **7a**, **12a** or **12b** (0.1–0.025 equiv), MOCl (aq), toluene, 16–72 h 0 °C–rt. M=Li, Na, K; R^1, R^2: See Table 2.