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# Synthesis and applications of $C_2$-symmetric guanidine bases

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**Abstract**—The preparation of the tetracyclic $C_2$-symmetric guanidinium salts **5** and **11**–**13** is reported together with their application to enantioselective transformations.

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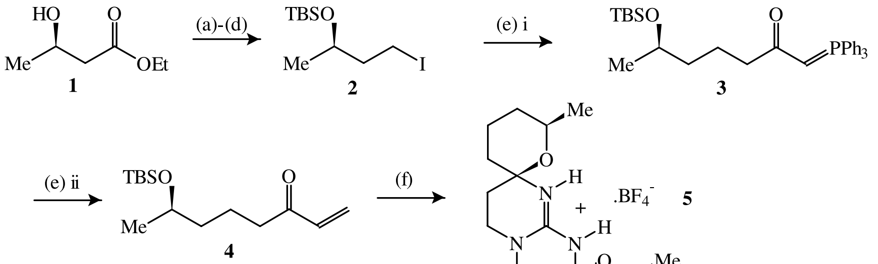
We have previously[1] reported the synthesis of the tetracyclic $C_2$-symmetric guanidine **5** in six steps from commercially available ethyl *R*-3-hydroxybutyrate **1**, the key step in this synthesis being the conjugate addition of guanidine to 2 equiv. of enone **4** (Scheme 1).

We wished to prepare a range of these compounds in order that we might investigate their applications as catalysts in asymmetric synthesis and envisaged that a similar strategy using *S*-(–)-malic acid **6** as our chiral-pool starting material would enable us to access a wide range of catalysts. Thus esterification of **6**, selective borane reduction of the C-1 ester[2] and acetonide formation was followed by $LiAlH_4$ reduction of the remaining ester function and iodination ($PPh_3/I_2$/imidazole) to give iodide **7** in good overall yield. This was then treated with lithiated acetylmethylene triphenylphosphorane **8** to give the intermediate phosphorane **9**, which on reaction with formaldehyde gave the required α,β-unsaturated ketone **10** in 72% yield. Treatment of this substrate with guanidine in DMF at rt for 24 h, followed by deprotection of the acetonide using methanolic HCl gave, after chromatography, the required guanidine base **11** in 45% yield. Purification of **11** proved somewhat difficult as it was an extremely polar material and very hygroscopic, factors which led us to believe that it might be impractical to use as a catalyst. We thus modified the final stage of the reaction, in that after guanidine addition and hydrolysis the crude reaction product was silylated with an excess of TBDMSCl or TBDPSCl and the chloride counterion exchanged with fluoroborate to give **12** and **13** in 29 and 36% yields, respectively (Scheme 2).



**Scheme 1.** *Reagents and conditions*: (a) TBDMSCl/imid (99%); (b) DIBAL-H (95%); (c) TosCl/Py (85%); (d) NaI/acetone (89%); (e) i. $CH_3COCHPPh_3$/*n*BuLi, ii. aq. $CH_2O$ (79%); (f) i. guanidine/DMF, ii. HCl/MeOH, iii. $NaBF_4$ (aq.) (44%).

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*Keywords*: phase transfer; catalysis; guanidine.

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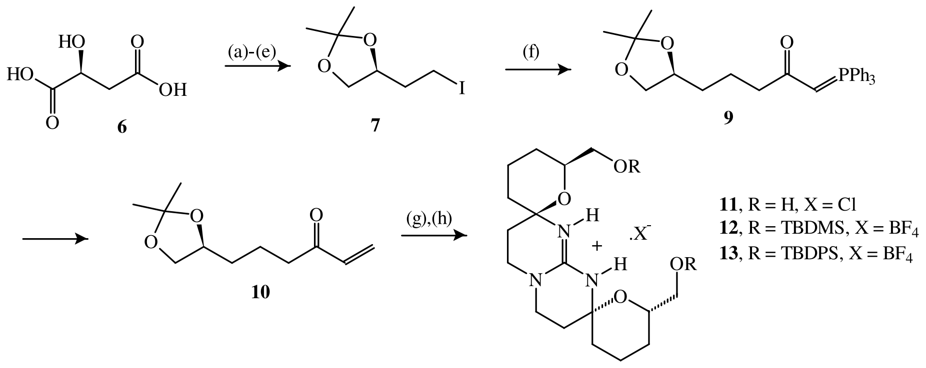


**Scheme 2.** *Reagents and conditions*: (a) MeOH/HCl (70%); (b) $BH_3$:$SMe_2$/$NaBH_4$ (92%); (c) $(MeO)_2CMe_2$, TosOH; (d) $LiAlH_4$ (60%, two steps); (e) $PPh_3I_2$/imid (91%); (f) i. $CH_3COCHPPh_3$ **8**/*n*BuLi, ii. aq. $CH_2O$ (72%); (g) i. guanidine/DMF, ii. HCl/MeOH (**11**; 45%); (h) as (g) then i. 3×$R_3SiCl$/imid, DMF, ii. ion exchange (**12**; 29%, **13**; 36%).

With these guanidinium salts in hand we investigated their application as catalysts in the conjugate addition of pyrrolidine **14** to the unsaturated lactone **15**, which is thought to involve an intermediate species such as **17**. (Fig. 1, Scheme 3).[3] We had previously shown that **5**·$HBF_4$ could increase the rate of the conjugate addition reaction by ca. 4-fold over the uncatalysed process and that exchanging the counterion to give **5**·$HBPh_4$ led to a 16-fold increase. We decided to investigate the catalysts **12**·$HBF_4$ and **13**·$HBF_4$ in this process and found that the TBDMS substituted base **12** gave an 11-fold rate increase, whereas the TBDPS substituted salt **13** gave only a 1.25 fold increase (Table 1, Scheme 3). In all of these reactions the product **16** was isolated in racemic form.

Nagasawa and co-workers have prepared a range of structurally similar bases to ours and have investigated this process. They found some correlation between 'cavity' size at the guanidine and relative rate of reaction based on crystallographic evidence.[4] Unfortunately we were unable to grow crystals of **12** or **13** suitable for X-ray analysis and can draw no direct conclusions of this nature. It is interesting to note that the salt **12**·$HBF_4$ which has the most lipophilic substituent has the highest catalytic activity, however the role the silyl substituents has on the cavity size might be a more telling factor.

We were keen to investigate other catalytic activities and were initially interested in the guanidine base catalysed nitro-aldol[5] (Henry reaction) and nitro-Michael[6] reactions. We found that all three of the free guanidine bases were catalysts for both these processes catalysing the reactions in good to high yields, however, disappointingly only low enantiomeric excesses were observed. For example, the best catalyst for the nitro-aldol reaction was the free base **5** which for the reaction of isovaleraldehyde **18** with nitromethane gave (*R*)-**19** in 52% yield and in 20% ee.[7] Similarly the base **5** catalysed the Michael addition of 2-nitropropane to chalcone **20** to yield (*S*)-**21** in 70% yield and 23% ee (Scheme 4).[8]

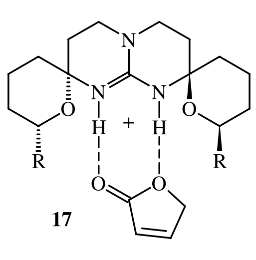
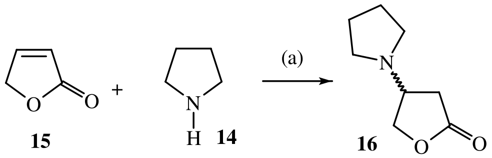


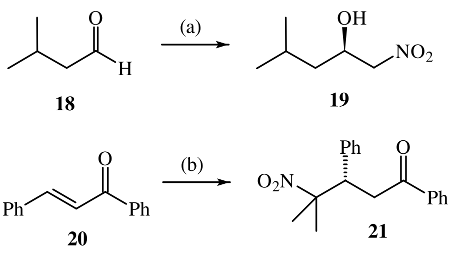
**Figure 1.**



**Scheme 3.** *Reagents and conditions*: (a) guanidinium salt, **5**, **12**, or **13** (0.1 equiv.), 0.3 M in $CDCl_3$, rt.

**Table 1.**

| Base | $t_{1/2}$ (min) | Relative rate increase |
|---|---|---|
| None | 135 | – |
| **5**·$HBF_4$ | 35 | 4.0 |
| **12**·$HBF_4$ | 12 | 11 |
| **13**·$HBF_4$ | 108 | 1.25 |



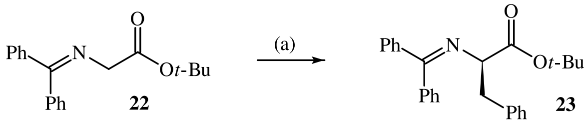
**Scheme 4.** *Reagents and conditions*: (a) i. **5**·$HBF_4$ (0.1 equiv.), NaOMe (0.09 equiv.), MeOH, 30 min then remove solvent; ii $CCl_4$ rt, **18**, $MeNO_2$, 16 h; (b) i. **5**·$HBF_4$ (0.1 equiv.), *t*-BuOK, (0.09 equiv.), THF, $(Me)_2CHNO_2$, **20**, rt, 24 h.

We next investigated the application of these catalysts in phase transfer catalysis (PTC)[9] and firstly investigated the benzylation of the glycinate Schiff's base **22**.[10] Thus, **22** and an excess of benzyl bromide, dissolved in cooled (0°C) $CH_2Cl_2$ were treated with the required catalyst (**5**·$HBF_4$, **11**·Cl, **12**·$HBF_4$ or **13**·$HBF_4$) in the presence of aqueous sodium hydroxide (2 M). A typical set of results for these reaction is shown in Table 2[11] (Scheme 5).

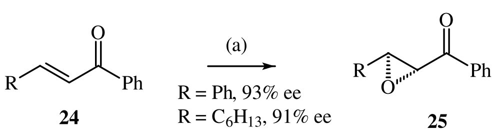
From these results is was apparent that the catalyst **5**·$HBF_4$ was the best catalyst for this transformation effecting nearly complete conversion of **22** to the desired product **23** which was obtained as the *R*-enantiomer with 86% ee. The catalyst **11**·Cl gave the worst results with very low conversion and low ee, which might be attributed to its poor solubility in the organic phase of the reaction. The silyl protected catalysts **12**·$HBF_4$ and **13**·$HBF_4$ also suffered from incomplete conversion; however, they still gave the alkylated products as the *R*-enantiomer in good ee's, 65 and 74%, respectively. The conversion rates for **12**·$HBF_4$ and **13**·$HBF_4$ could be raised to quantitative by increasing the concentration of the sodium hydroxide in the reaction or by allowing the reaction to progress for longer; however, this did not increase the levels of enantioselectivity. In all these reactions, the catalysts are very robust and remain unchanged and are removed from the reaction mixtures during isolation and purification of the product and can then be recycled by repeating the fluoroborate steps of their preparation (see Schemes 1 and 2). Our results and the selectivities are in agreement with the reactions reported by Nagasawa using structurally similar pentacyclic guanidine catalysts.[12]

**Table 2.**

| Entry | Catalyst | %Conv. (%) | ee (%) |
|---|---|---|---|
| 1 | **5**·$HBF_4$ | >97 | 86 (*R*) |
| 2 | **11**·Cl | 15 | 21 (*R*) |
| 3 | **12**·$HBF_4$ | 70 | 65 (*R*) |
| 4 | **13**·$HBF_4$ | 80 | 74 (*R*) |



**Scheme 5.** *Reagents and conditions*: (a) Base (0.1 equiv.), NaOH (2 M), BnBr (2 equiv.), $CH_2Cl_2$, 16 h 0°C–rt.



**Scheme 6.** *Reagents and conditions*: (a) **5**·$HBF_4$ (0.05 equiv.), NaOCl (aq.), Tol, 16 h 0°C–rt.

We have also investigated the application of the catalyst **5**·$HBF_4$ in the PTC epoxidation[13] of the chalcones **24** and have found it to be an excellent catalyst for this transformation. In the two examples shown the ee for product **25** where R = Ph was found to be 93% and in the case of **25** where R = $C_6H_{13}$ the ee was 91%.[14] These results compare very favourably with existing phase transfer catalysts for these processes and again the catalyst was isolated unchanged in an identical manner as described previously (Scheme 6).

In conclusion we have demonstrated that the tetracyclic catalysts **12**·$HBF_4$ and **13**·$HBF_4$ are easily prepared in high yield from (*S*)-malic acid and that these, and in particular, the previously reported catalyst **5**·$HBF_4$, are effective catalysts for phase transfer catalysed processes. We are currently investigating further applications of these and related catalysts and will report our findings in due course.

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11. Typical experimental procedure: The required guanidinium salt (0.04 mmol) and the glycinate Schiff's base **22** (120 mg, 0.407 mmol) were dissolved in dichloromethane (2 ml) and aqueous NaOH solution (2 ml, 2 M), was added. This mixture was cooled (0°C), vigorously stirred and BnBr (139 mg, 0.814 mmol, 120 μL) was then added in one portion. After stirring for 16 h the reaction had reached room temperature and further dichloromethane (10–15 ml) was added and the organic layer separated, dried ($MgSO_4$) and evaporated. Conversion rates were determined by $^1$H NMR and ees (±3%) were determined on a Bakerbond DNPG column (98.5:1.5 hexane: dioxane).
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14. **Typical experimental procedure**: The guanidinium salt **5**$\cdot HBF_4$ (0.04 mmol) and the chalcone **24** (R = Ph, 166 mg, 0.8 mmol) were dissolved in toluene (2 ml) and the mixture cooled (0°C) along with vigorous stirring. Sodium hypochlorite solution (2.4 ml, 8% aqueous solution) was then added and the reaction stirred to rt over 16 h. Dichloromethane (15 ml) was added and the organic layer separated, dried ($MgSO_4$) and evaporated. Purification by chromatography eluting with 3–5% diethyl ether in petrol gave **25** (R = Ph, 178 mg, 99% yield) as a solid, mp 74–76°C (lit. 76–77°C) $[\alpha]_D^{20}$ −250, (lit. $[\alpha]_D$ +195 for antipode of 86% ee).[13b] Enantiomeric excesses (±3%) were determined on a Chiralpak AD column (90: 10 hexane:EtOH for R = Ph and 99.5: 0.5 hexane:IPA for $R = C_6H_{13}$).