COMMUNICATION

# Comparison of chiral thiazolium and triazolium salts as asymmetric catalysts for the benzoin condensation

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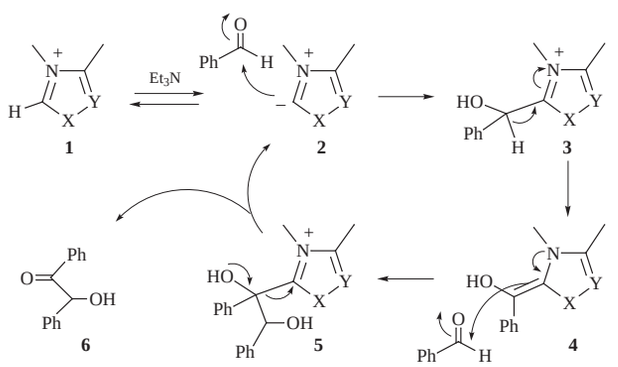
**Chiral bicyclic 1,2,4-triazolium salts having a defined face of the heterocyclic ring hindered have been synthesised and they catalyse the benzoin condensation in good yield; the enantiomeric excesses obtained (up to 80%) are much better than with closely related thiazolium salts and the opposite enantiomer of benzoin predominates.**

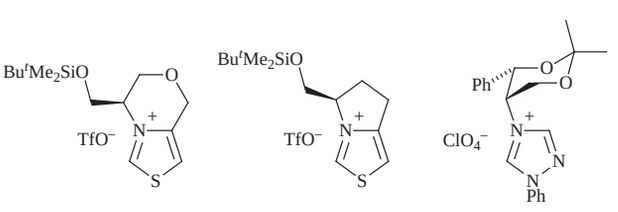
Thiamin and other thiazolium salts, *e.g.* **1** (X = S, Y = CH), have long been known[1] to catalyse the formation of acyloins from aldehydes (the benzoin condensation) under mildly basic conditions. The mechanism (Scheme 1) involves initial



**Scheme 1** Mechanism for the benzoin condensation catalysed by a thiazolium (X = S, Y = CH) or triazolium (X = NPh, Y = N) salt and a base (*e.g.* $Et_3N$)

deprotonation at C-2 to give an ylid **2** followed by nucleophilic addition to an aldehyde. The electron-withdrawing thiazolium ring then allows deprotonation at C-2α of the adduct **3** and the resulting enamine **4** attacks the second aldehyde molecule. Release of acyloin **6** from the adduct **5** regenerates the ylid and completes the catalytic cycle.

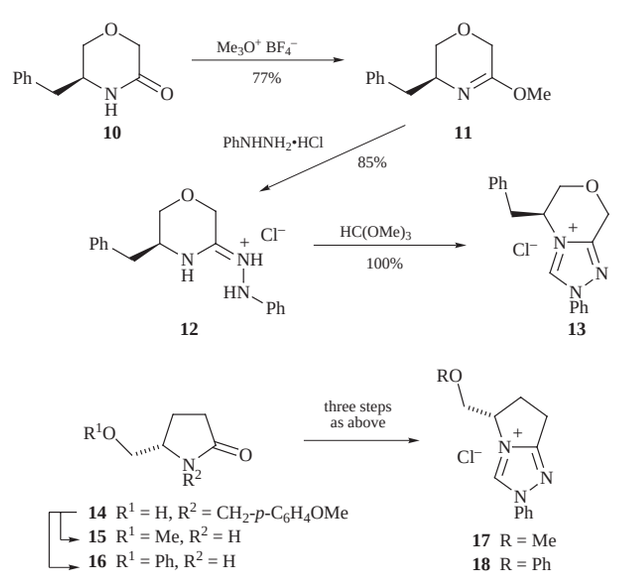
A number of chiral thiazolium salts have been made and tested for asymmetric catalysis of the benzoin condensation.[2–5] The enantiomeric excesses (ees) observed varied from negligible to moderate (*ca.* 50%) at best. All these chiral catalysts consisted of a chiral group attached solely to the nitrogen atom of a thiazole. As a result, free rotation of the chiral group is possible and so it is difficult to predict which face of the enamine intermediate **4** would be more hindered. We recently reported[6,7] the first examples of chiral thiazolium salts, such as **7** and **8**, where



the chiral group is part of a further ring, which results in one face of the heterocyclic ring being clearly more hindered than the other. Unfortunately this did not result in any great improvement in the enantiomeric excess of the benzoin formed (*ca.* 20%).

While this work was in progress, two papers appeared[8,9] which showed that 1,2,4-triazolium salts, *e.g.* **1** (X = NPh, Y = N), are effective catalysts for the benzoin-type condensation, particularly for the dimerisation of formaldehyde to give glycolaldehyde. The mechanism for the triazolium salts is thought to be the same as for thiazolium salts, as shown in Scheme 1. Furthermore, Enders *et al.* reported[10] that chiral triazolium salt **9** catalyses formation of benzoin with 75% ee. The explanation offered was that one side of the heterocyclic ring of **9** is hindered by the phenyl ring of the chiral substituent.

If this hypothesis is correct, then it remains to be explained why much larger enantiomeric excesses can be obtained with triazolium salts in which one face is hindered than with thiazolium salts. With triazolium salt **9** rotation of the chiral group is possible, however, and it is not absolutely certain which face will be more hindered during the key step of the mechanism. We therefore decided to make triazolium salts **13**, **17** and **18** (Scheme 2), analogous to thiazolium salts **7**



**Scheme 2**

and **8**, in which the chiral group is fixed by being part of a second ring.

Simple triazolium salts have previously been made from amides[11] and our syntheses of the bicyclic triazolium salts followed a similar approach starting with lactams. The synthesis of **13** started with lactam **10**, derived from L-phenylalaninol by literature procedures.[12] Methylation with Meerwein's reagent gave imino ether **11** and then reaction with phenylhydrazine hydrochloride gave amidrazone hydrochloride **12**.[13] Formylation and cyclisation of **12** was affected cleanly by heating with trimethyl orthoformate, giving triazolium salt **13** in quantitative yield (65% overall yield from **10**).

The syntheses of **17** and **18** started from the known

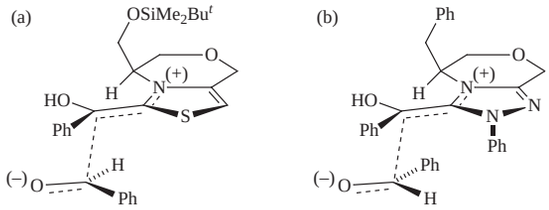



**Fig. 1** Preferred transition states proposed for the step **4**→**5** using (a) thiazolium catalyst **7**, (b) triazolium catalyst **13**

*p*-methoxybenzyl protected lactam **14**, derived from L-pyroglutamic acid.[14] The hydroxy group of **14** was either methylated using NaH and MeI or converted to the phenyl ether under Mitsunobu conditions. Deprotection using ceric ammonium nitrate[14] then gave lactams **15** and **16**. The same three steps as used for **10**→**13** gave triazolium salt **17** in 49% overall yield from **15** and triazolium salt **18** in 48% overall yield from **16**.

The three enantiomerically pure triazolium salts **13**, **17** and **18** were then tested as catalysts for the benzoin condensation of benzaldehyde, *p*-tolualdehyde and *p*-chlorobenzaldehyde (Table 1). The conditions used for catalysts **13** and **17** ($Et_3N$ in MeOH at room temperature for 18 h) were the same as employed previously[6] with the thiazolium salts **7** and **8** and have not been optimised. Improved yields could easily be obtained by extending the reaction time but the ees tended to decrease, especially when using the more reactive *p*-chlorobenzaldehyde. For catalyst **18** the standard reaction conditions gave high yields (*ca.* 80%) but low ees. This catalyst is considerably faster than the other two and it appears that this allows the benzoin to racemise by reversal of the reaction. For this reason the reactions using this catalyst shown in the Table were performed using less catalyst and less base.

The Table shows that much better ees were obtained with the triazolium than the thiazolium salts. The ee of 80% using catalyst **13**, is the best ever reported for the formation of benzoin. The ee obtained for formation of toluoin from tolualdehyde using catalyst **13** was slightly higher still. Catalysts **17** and **18** gave ees which, although not quite as good as those obtained using **13**, were much better than obtained with the corresponding thiazolium salt **8**.

The absolute configuration of the benzoin formed is consistent between the three triazolium salts tested here: catalyst **13** is hindered on the top face (as drawn) and produces predominantly (*S*)-benzoin, whereas **17** and **18** are hindered on the bottom face and produce (*R*)-benzoin. Catalyst **9** also fits this pattern in that the conformation that was proposed (shown in structure **9**) is hindered on the bottom face and this catalyst also produces mainly (*R*)-benzoin.[10] The most striking observation, however, is that the triazolium salts produce benzoin of the *opposite* absolute configuration to that produced by thiazolium salts of the same configuration. Thus thiazolium catalysts **7** and **8** are both hindered on the top face but produce predominantly (*R*)-benzoin.

We believe that the significant difference between triazolium and thiazolium catalysts is that the *N*-phenyl group of the former is much bulkier than the sulfur atom of the latter. Molecular mechanics calculations indicate that the *N*-phenyl group is almost perpendicular to the plane of the heterocyclic ring in the intermediate **4** (X = NPh) and so can have significant steric interactions with the incoming benzaldehyde molecule. On the basis of molecular mechanics studies on the intermediate **5** we suggest that the preferred transition states for the key reaction **4**→**5**, in which the chiral centre of the product is generated, are as shown in Fig. 1. In both these transition states the carbonyl group of the incoming aldehyde molecule is *anti* to the carbon–carbon double bond of the enamine **4**; for the thiazolium salts (*e.g.* **7**, Fig. 1a) the phenyl ring of the benzaldehyde molecule has a slight preference for lying under the sulfur atom of the heterocyclic ring but for the triazolium salts (*e.g.* **13**, Fig. 1b) the phenyl ring of the aldehyde would have an unfavourable steric interaction with the *N*-phenyl group of the catalyst in the equivalent orientation and therefore the hydrogen atom of the aldehyde occupies this position instead.

This model appears to explain all the existing information but clearly further results are needed to prove that the transition states shown in Fig. 1 are indeed the preferred ones. It is hoped that a better understanding of the stereochemical constraints of this reaction will lead not only to the design of more effective asymmetric catalysts but also to a better insight into the architecture of thiamin diphosphate dependent enzymes.

**Table 1** Enantiomeric excesses of the acyloins produced using catalysts **13**, **17** and **18** compared to catalysts **7** and **8**

| | | Acyloin[a] | | | |
|---|---|---|---|---|---|
| Catalyst | Aldehyde | Yield (%) | $a_D$ | *R*/*S* | ee (%) |
| **7**[6] | $C_6H_5CHO$ | 34 | −32 | *R* | 19.5 |
| **8**[6] | $C_6H_5CHO$ | 50 | −34 | *R* | 20.5 |
| **13** | $C_6H_5CHO$ | 45 | +130 | *S* | 80[b,c] |
| **13** | *p*-$MeC_6H_4CHO$ | 38 | +107 | *S* | 82.5[b] |
| **13** | *p*-$ClC_6H_4CHO$ | 11 | +32 | *S* | 76[d] |
| **17** | $C_6H_5CHO$ | 47 | −78 | *R* | 48[c] |
| **17** | *p*$MeC_6H_4CHO$ | 28 | −75 | *R* | 61[b] |
| **17** | *p*-$ClC_6H_4CHO$ | 27 | −17 | *R* | 40[c] |
| **18** | $C_6H_5CHO$ | 22 | −103 | *R* | 63[b,c] |
| **18** | *p*-$MeC_6H_4CHO$ | 11 | −56 | *R* | 68[b] |
| **18** | *p*-$ClC_6H_4CHO$ | 12 | −26 | *R* | 65[d] |

[a] Reaction conditions: aldehyde (*ca.* 1 mol $dm^{-3}$); for **13** and **17**, catalyst (30 mol%), $Et_3N$ (33 mol%) in MeOH at room temperature for 18 h [except **13** with *p*-$ClC_6H_4CHO$, catalyst (10 mol%) and $Et_3N$ (5 mol%)]; for **18**, catalyst (5 mol%), $Et_3N$ (5 mol%) in MeOH at room temperature for 48 h. [b] Ee determined by NMR analysis of the Mosher's ester. [c] Ee determined by optical rotation;[16] [d] Ee determined by NMR analysis in the presence of (*S*)-1,1,1-trifluoro-2-(9-anthryl)ethanol.

## Experimental

### General procedure for the synthesis of triazolium salts

A solution of the lactam (**10**, **15** or **16**) in dichloromethane was added dropwise to a suspension of a slight excess of trimethyloxonium tetrafluoroborate in dichloromethane. The mixture was stirred for 12 h at room temperature, then diluted with dichloromethane, washed with ice-cold saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb vacuum distillation to give the imino ether (58–77%) as an oil.

A solution of the imino ether (1 equiv.) in methanol was heated with phenylhydrazine hydrochloride (1 equiv.) at 50 °C for 2 h and then evaporated under reduced pressure. The residue was recrystallized from methanol or ethanol to give the amidrazone hydrochloride (*ca.* 85%).

The amidrazone hydrochloride was heated with an excess of trimethyl orthoformate–methanol (2:1) in a sealed tube at 80 °C for 12 h. The solution was then evaporated under reduced pressure and dried under high vacuum to give the triazolium salt (quantitative yield).

Data for triazolium salt **13**: $[a]_D^{20}$ −26.4 (*c* 8 mg $cm^{-3}$ in methanol) (Found: C, 64.25; H, 5.68; N, 12.83. $C_{18}H_{18}ClN_3O + 0.4\ H_2O$ requires C, 64.53; H, 5.66; N, 12.54%); $\nu_{max}$(neat)/$cm^{-1}$ 3028, 2928, 1582, 1532, 1496, 1111, 1093, 762, 721, 704 and 687; $\delta_H$(250 MHz, $CDCl_3$) 3.17 (1 H, dd, *J* 13 and 11) and 3.87 (1 H, dd, *J* 13 and 4.5, PhC$H_2$), 3.97 and 4.03 (each 1 H, dd, *J* 12.5 and 3, CHC$H_2$), 4.99 and 5.12 (each 1 H, d, *J* 16, $OCH_2$), 5.24–5.35 (1 H, m, CHN), 7.14–7.25 (3 H, m), 7.32–7.44 (5 H, m) and 7.92–8.02 (2 H, m, 2 × Ph) and 12.91 (1 H, s, 3-H); $\delta_C$(250 MHz, $CDCl_3$) 39.0 (*C*$H_2$Ph), 57.2 (CHN), 62.1 and 65.0 (2 × $CH_2$), 120.2 (2 C), 127.5, 128.9 (2 C), 129.9 (2 C),

130.1 (2 C) and 130.5 (10 × phenyl-CH), 134.6 and 134.9 (2 × phenyl-C), 141.6 (C-8a) and 149.2 (C-3); *m*/*z* (EI) 292 ($M^+$ for cation, 1%), 291 (9), 290 (47), 159 (7), 117 (15) and 91 (100).

**Benzoin condensation**

A solution of benzaldehyde (200 $mm^3$, 1.97 mmol) in methanol (1.8 $cm^3$) was degassed by two cycles of freeze–pump–thawing. An aliquot of this solution (0.5 $cm^3$, 0.492 mmol) was added to the catalyst, followed by degassed triethylamine, and the mixture stirred at room temperature (see footnote to table for quantities and times). The solution was then diluted with dichloromethane (20 $cm^3$), washed with water (10 $cm^3$), dried ($Na_2SO_4$) and evaporated under reduced pressure. Purification by flash chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:4), gave benzoin as needles. The optical rotation of the benzoin was measured in methanol as solvent, and was converted into its (*R*)-Mosher's ester by a standard procedure.[15]

## Acknowledgements

We thank the LINK Initiative in Asymmetric Synthesis for a studentship (to R. L. K.), Dr Jonathan Fray, Pfizer and Dr Rob Ward, SmithKline Beecham, for helpful discussions and the EPSRC Mass Spectrometry Service at Swansea for mass spectra.

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*Paper* 8/01896K
*Received* 9*th March* 1998
*Accepted* 8*th May* 1998