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Synthesis of new enantiomerically pure C_1- and C_2-symmetric *N*-alkyl-benzimidazolium and thiazolium salts

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Abstract—Starting from the commercially available enantiopure (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol novel enantiomerically pure benzimidazoles were prepared; *N*-alkylation gave chiral benzimidazolium salts, which were tested in asymmetric benzoin condensations. The synthesis of conceptually new, enantiomerically pure, C_2 symmetric bis-thiazolium and bis-benzimidazolium salts was also developed. These new chiral heterocycles were employed as catalysts in the asymmetric dimerisation of benzaldehyde to give benzoin with moderate enantioselectivity.

Thiazolium-catalyzed additions of acyl anions to aldehydes or imines are reactions of great synthetic relevance. The benzoin condensation[1,2] (between two aldehydes) and the Stetter reaction[3] (between an aldehyde and a Michael acceptor) are two examples of this type of transformation, which leads to highly functionalized products, with the formation of a new stereocenter. The generally accepted mechanism of the benzoin condensation is shown in Figure 1. Since 1966, when Sheehan et al. reported for the first time the use of an enantiopure alkyl thiazolium salt in the self-condensation of benzaldehyde,[4,5] several differently substituted chiral thiazolium salts have been prepared and tested, always showing moderate enantioselectivity (up to 57% ee).[6–11] A common feature of all these catalysts is the presence of a chiral group attached to the nitrogen atom of the thiazole; the conformational freedom of such a group makes it difficult to predict which face of intermediate C would be shielded, and is responsible for the low stereoselection (Fig. 1).

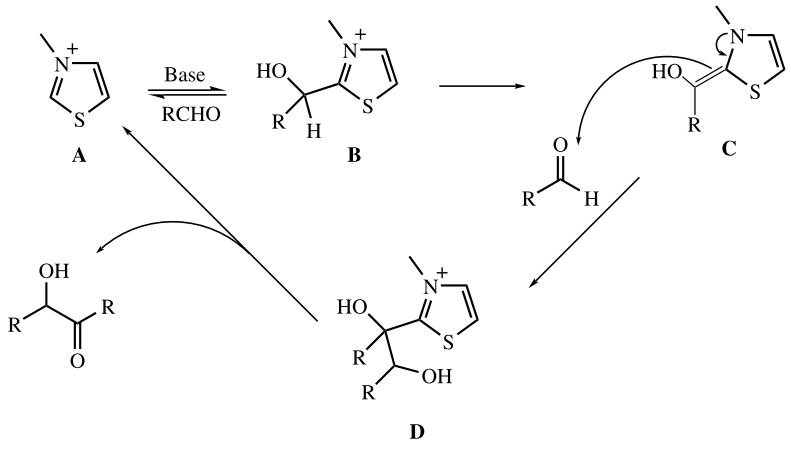

Figure 1. Mechanism of thiazolium salt catalyzed benzoin condensation.

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A breakthrough in the field was obtained by Enders in 1995, via the use of the chiral 1,2,4-triazolium salt **1** as a catalyst for the dimerisation of benzaldehyde, to afford the corresponding benzoin in 66% yield and 75% ee (Fig. 2).[12,13] Comparable enantioselectivities were later obtained by Knight and Leeper, by employing the bicyclic triazolium salt **2**.[14] The comparison between the enantiomeric excess obtained with **2** (80% ee) and a similar, bicyclic thiazolium salt **3** (20.5% ee) seems a clear indication of the importance of the *N*-aryl ring in determining the stereochemical outcome of the reaction. In **2** it is possible that the benzyl group at the stereocenter preferably shields one side of the intermediate C in Figure 1, with the *N*-phenyl playing a decisive role, in pre-orienting the approach and the attack of the second molecule of aldehyde.

However catalyst **1** was unstable because of degradation due to competing deprotonation at the 3-position, to irreversibly give an *N*-cyanobenzamidine, via triazole ring opening.[13] In order to solve the problem, we decided to investigate the catalytic activity of chiral *N*-alkyl benzimidazolium salts, structurally inspired by catalyst **1** and in which degradation is not possible. Recently Enders has developed the new chiral triazolium salts **4**[15] which are able to promote asymmetric benzoin condensation with enantiomeric excesses up to 93%. A similar bicyclic triazolium salt **5**[16] has also been described as very efficient catalyst for intramolecular Stetter reactions (ee up to 97%) (Fig. 2). Prompted by these works, we report herein the synthesis of C_1 and C_2 symmetric, conceptually new, chiral benzimidazolium and thiazolium salts and preliminary studies on their catalytic activity.

The synthesis of a chiral benzimidazolium salt is described in Scheme 1. The commercially available enantiomerically pure (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol **6** was reacted with *ortho*-fluoro nitrobenzene, in the presence of potassium carbonate in aqueous ethanol for 60 h to give **7** in 57% non optimized yield; reduction of the nitro group followed by the reaction with formic acid gave the benzimidazole **8** in 65% overall yield.[17] Protection of the diol with 2,2-dimethoxypropane afforded **9**. Alkylation with iodomethane in acetonitrile gave the enantiomerically pure *N*-methyl-benzimidazolium salt **10** in 95% yield.[18]

The ability of these chiral salts to act as a catalyst in asymmetric benzoin reaction of benzaldehyde was then investigated. Optimal reaction conditions were established by preliminary experiments carried out with the achiral salt **11** (Scheme 1). Selected data are shown in Table 1. The *N*-methyl salt **11** promoted the reaction as well in THF with DBU (entry 1), or NaH (entry 2), as in methanol with DBU (entry 3) or NaOH 50% (entry 4). Having established that *N*-methyl benzimidazolium salts were efficient catalysts, the activity of the chiral salt **10** was investigated.[19] Unfortunately **10** proved to be less reactive than **11**, as it did not catalyze the reaction in the previously explored conditions (see for example entry 5 versus 1). The best result obtained was by using 5 mol% of the catalyst, in the presence of NaH as base in THF; in these conditions the benzoin was obtained in 31% yield after 2 h reaction at 60°C, as a racemic mixture.

Disappointed by the modest reactivity and enantioselectivity shown by these catalysts, we decided to explore the behavior of completely new chiral salts. Thus, the synthesis of C_2-symmetric enantiomerically pure salts containing a stereogenic axis as stereochemical element able to control the outcome of the reaction was attempted (Scheme 2).

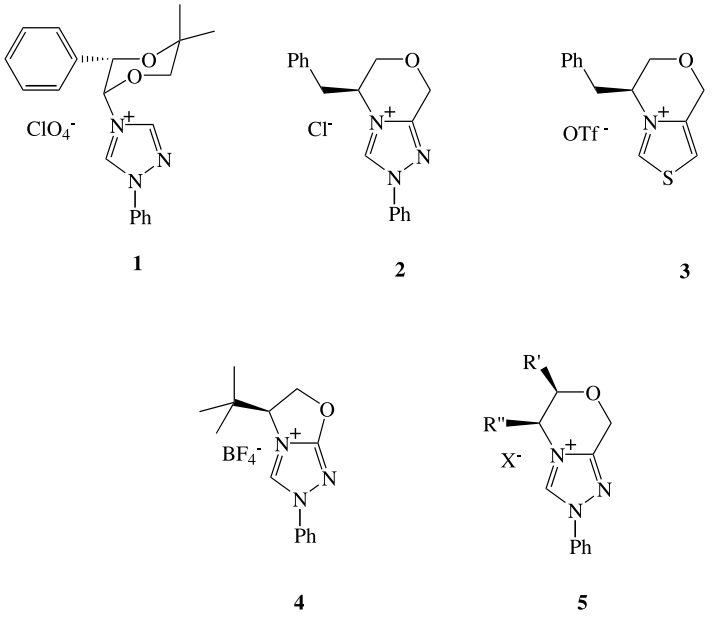
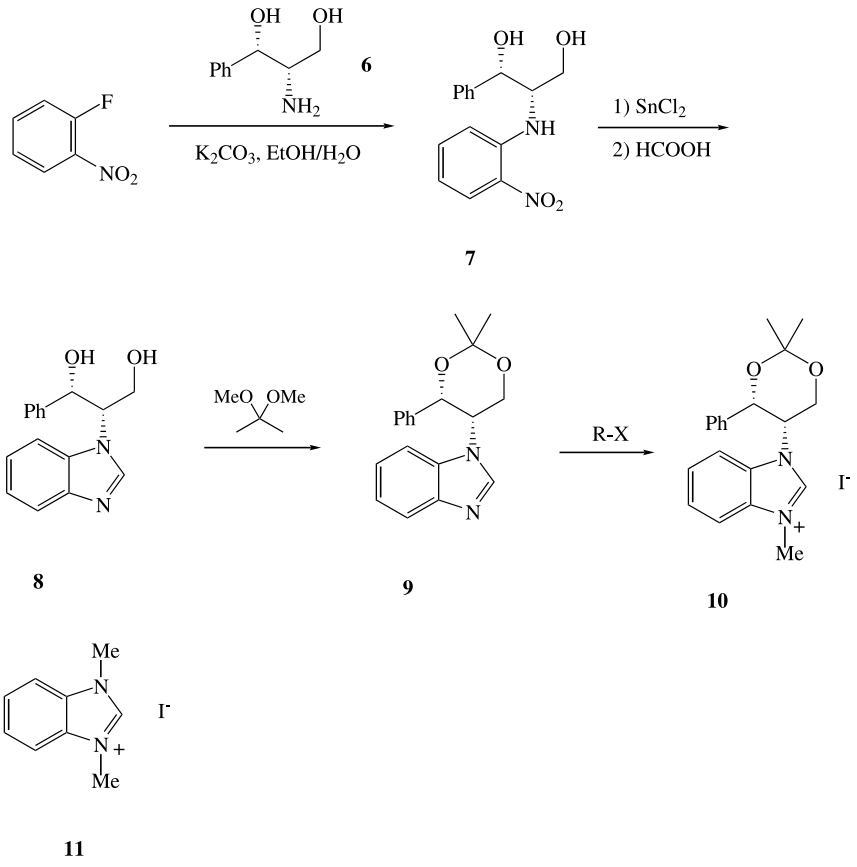


Figure 2. Chiral thiazolium and triazolium salts.



Scheme 1. Synthesis of new chiral salt **10**.

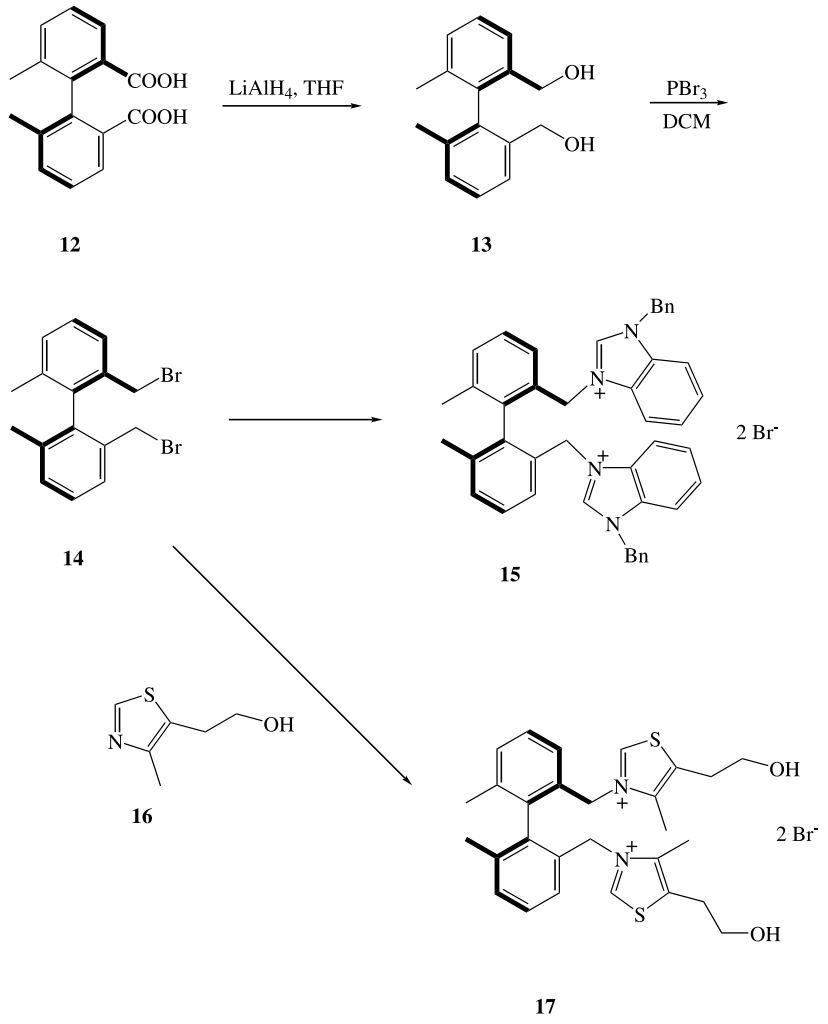
Table 1. Benzoin reaction catalyzed by 5% mol of new *N*-alkyl benzimidazolium salts

Entry	Catalyst	Solvent	Base	*T* (°C)	Time (h)	Yield (%)
1	**11**	THF	DBU	65	2	41
2	**11**	THF	NaH	65	2	93
3	**11**	MeOH	DBU	65	2	42
4	**11**	MeOH	NaOH 50%	25	20	48
5	**10**	THF	DBU	65	20	–
6	**10**	DCM	BEMP	65	20	5
7	**10**	THF	NaH	65	2	31

(*R*)-6,6′-Dimethylphenyl-2,2′-dicarboxylic acid **12**[20] was reduced with $LiAlH_4$ to give the corresponding diol **13** in 83% yield; the reaction with phosphorus tribromide afforded dibromide **14** in 81% yield. Treatment of **14** with *N*-benzyl-benzimidazole in acetonitrile at 60°C for 40 h afforded the enantiopure bis-(*N*-benzylbenzimidazolium) salt **15**. Analogously, treatment of **14** with (4-methyl-5-thiazolyl)-2-ethanol **16** in acetonitrile gave the corresponding chiral bis-(*N*-benzyl-thiazolium) salt **17** in its enantiomerically pure form.[18]

Preliminary experiments have demonstrated that while **15** is not an efficient catalyst for benzoin condensation, the bis thiazolium salt is able to promote the dimerisation of benzaldeyhde. For instance, 5% mol of **17** catalyzed the reaction in methanol, in the presence of triethylamine as base, to give after 4 h reaction at 60°C the product in 40% yield, with modest enantioselectivity (15% ee).[21]

In conclusion new enantiomerically pure catalysts for the benzoin condensation have been prepared, including, for the first time, C_2-symmetric bis-(*N*-alkyl benzimidazolium) and bis-(*N*-benzyl-thiazolium) salts. These conceptually new chiral heterocycles were tested as catalysts in the asymmetric dimerisation of benzaldehyde to give benzoin in moderate yield and enantioselectivity. Further experiments are currently in progress to modify the structure of the chiral salt in order to improve the chemical and the stereochemical efficiency of the catalyst.



Scheme 2. Synthesis of new C_2-symmetric salts **15** and **17**.

Acknowledgements

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References

1. Ugai, T.; Tanaka, S.; Dokawa, J. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269–300.
2. Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
3. Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley-Interscience: New York, 1991; Vol. 40, p. 407.
4. Sheenan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666–3667.
5. Sheenan, J.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196–1199.
6. Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478.
7. Zhao, C.; Chen, S.; Wu, P.; Wen, Z. *Acta Chimica Sinica* **1988**, *46*, 784–787.
8. Marti, J.; Castells, J.; Lopez-Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521–524.
9. Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611–3614.
10. Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3615–3618.
11. Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925–2928.
12. Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021–1024.
13. Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217–1221.
14. Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1893.
15. Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1743–1745.
16. Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299.
17. Ralph, J. T. *Synth. Commun.* **1989**, *19*, 1381–1387.
18. All new compounds have been fully characterized and showed spectral data in agreement with the proposed structure.
19. The corresponding *N*-benzyl chiral salt did not catalyse benzoin condensation in any of the numerous experimented reaction conditions.
20. For the use of acid **12** as chiral template in the stereoselective synthesis of supramolecular structures, see: Woods, C. R.; Benaglia, M.; Siegel, J. S.; Cozzi, F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1831–1833.
21. Determined by HPLC on a chiral stationary phase.