

TETRAHEDRON LETTERS

## CATALYSIS OF BENZOIN CONDENSATION BY CONFORMATIONALLY-RESTRICTED CHIRAL BICYCLIC THIAZOLIUM SALTS

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Abstract: Two new conformationally-restricted chiral bicyclic thiazolium salts have been synthesized by a concise, high-yielding route. These salts are effective catalysts for the benzoin condensation, affording benzoin in 20-30% yield, with a similar range of enantiomeric excesses. © 1998 Elsevier Science Ltd. All rights reserved.

First reported by Ukai et al.,<sup>2</sup> the thiazolium salt catalyzed benzoin condensation has been the subject of considerable investigation.<sup>3</sup> A mechanism for this reaction, which has withstood the test of time, was first proposed in a landmark paper by Breslow.<sup>4</sup> Aside from serving as a good model for the mode of action of the coenzyme thiamine pyrophosphate,<sup>5</sup> thiazolium salts are of interest because they promote the formation of a carbon-carbon bond, with the attendant chiral center, under mild conditions. Several research groups have synthesized thiazolium salts bearing a chiral unit on the nitrogen in an effort to induce asymmetry during the *C*-*C* bond-forming step.<sup>6</sup> Among the first and best are the  $\alpha$ -aryl-*N*-ethyl thiazolium salts (1) reported by Sheehan and Hara,<sup>6e</sup> which yielded benzoin with low to modest ee's. We reasoned that the low ee's obtained by these and other groups resulted from the free rotation available to the chiral side-chain, which provided inadequate discrimination between the two prochiral faces of the presumed nucleophilic intermediate (2). We postulated that restricting the rotation of the chiral side-chain, by locking it in a ring (e.g., 3), would more effectively block just one face of the thiazole and, hence, improve enantioselectivity of the nucleophilic addition step. We describe here the synthesis and catalytic activity of two such conformationally restricted thiazolium salts.<sup>7,8</sup>



So as to allow a direct assessment of the effect of conformational restriction on asymmetric induction, the phenyl- and 1-naphthyl-substituted catalysts were synthesized. The synthesis of these closely-related thiazolium salts is described in Scheme 1. The chiral units were prepared from styrene and 1-vinylnaphthalene, which were dihydroxylated under the Sharpless protocol, using DHQD<sub>2</sub>PHAL as the

chiral ligand, to give the corresponding glycols (5a,b) in quantitative yield and 89% and 86% ee's, respectively.<sup>9</sup> Recrystallization increased the ee's to >96%, with very good recovery of material. On treatment with trimethyl orthoacetate and TMSCl followed by  $K_2CO_3$  in methanol the diols were transformed into the respective epoxides (6a,b),<sup>10</sup> with >96% ee, as shown by chiral HPLC analysis. The thiazole portion (7) was readily prepared by alkylation of *p*-toluenesulphonamide with 4-chloromethylthiazole<sup>11</sup> in aqueous NaOH. The two epoxides were then condensed with sulphonamide 7<sup>12</sup> using triton B as the base catalyst to give the cyclization precursors 8a,b in good yield. The alcohok were converted into the corresponding mesylates, which upon warming in CH<sub>3</sub>CN underwent cyclization to the desired chiral bicyclic thiazolium salts, 9a and 9b.<sup>13</sup>



The two catalysts were then examined in the benzoin condensation and some of the results are shown in Table 1. The reactions were carried out under an inert atmosphere in either MeOH or a mixture of MeOH and water, generally using triethylamine as the base. The heterogeneous reaction mixtures were stirred vigorously at room temperature for the times indicated, and the benzoin formed was isolated, purified by flash chromatography, and analyzed by HPLC on a chiral stationary phase (Welko-S,S column, Regis). From the several dozen conditions examined, most using the phenyl-substituted catalyst 9a, it is clear that the yield and ee's of the benzoin is significantly affected by subtle changes in the reaction conditions. Entries 1-4 show that while the yield of benzoin increases with longer reaction times the asymmetric induction diminishes. Several different bases were examined for the reaction using catalyst 9a (e.g., K<sub>2</sub>CO<sub>3</sub>, pyridine, Borax), but none were as effective as Et<sub>3</sub>N. The one exception was aqueous Na<sub>2</sub>HPO<sub>4</sub>, which afforded benzoin in a measurable yield and 26% ee (entry 5). When the reaction was carried out at 30 °C (entry 6), conditions employed by Sheehan for his phenyl-substituted catalyst (entry 7), benzoin was obtained in 65% yield with 15% ee. These results are consistent with the initial hypothesis, that restricting the conformation of the phenyl group enhances, albeit modestly, the asymmetric induction in the benzoin condensation.

Based on Sheehan's work, the naphthyl-substituted thiazolium salt (9b) was expected to give benzoin in a lower yield but with significantly higher ee than the phenyl-substituted salt (9a). In fact, the two catalyst were found to exhibit similar reactivity, as might have been expected *a priori*. Comparison of entries 2 and 8, and entries 4 and 9, shows that the yield of benzoin is slightly higher and the ee slightly lower with catalyst 9a than 9b. As with catalyst 9a, the reaction with 9b at 30 °C gave benzoin in higher yield but with lower ee (entry 10). Thus, whereas restricting the rotation of the phenyl-substituted salt resulted in improved asymmetric induction, such restriction of the naphthyl system did not lead to commensurate improvement in the catalyst's effectiveness. The small differences in asymmetric induction observed here for the conformationally-restricted phenyl and naphthyl catalysts would not have been surprising, but for Sheehan's report of large differences in the reactivity of analogous unrestricted salts 1a and 1b. It is particularly noteworthy that under our optimized reaction conditions, Sheehan's catalyst 1b afforded benzoin in 48% ee and with remarkably improved yield (*cf.* entries 11 and 12). To our knowledge this represents the best ee/yield result for a chiral thiazolium salt catalyzed benzoin condensation.

Entry <sup>a</sup>	PhCHO (mmol)	Solvent (ratio, amount)	Catalyst ( <b>9a</b> or <b>9b</b> , mmol)	Base (mmol)	Time (h)	% Yield (isolated)	% ее
1	1.17	MeOH, 0.5 mL	<b>9a</b> , 0.12	Et <sub>3</sub> N, 0.13	0.6	< 2%	28
2	1.17	MeOH : H <sub>2</sub> O 1 : 2.5, 0.5 mL	<b>9a</b> , 0.12	Et <sub>3</sub> N, 0.12	8	20	24
3	1.17		<b>9a</b> , 0.12	Et <sub>3</sub> N, 0.14	12	30	23
4	2.15	MeOH : H <sub>2</sub> O 1 : 2.5, 1.0 mL	<b>9a</b> , 0.22	Et <sub>3</sub> N, 0.24	24	27	20
5	1.17	0.5M Na <sub>2</sub> HPO <sub>4</sub> 0.5 mL	<b>9a</b> , 0.14		8	13	26
6 <sup>b</sup>	1.36	MeOH, 0.68 mL	<b>9a</b> , 0.136	Et <sub>3</sub> N, 0.129	24	65	15
7 <sup>b,c</sup>	1 eq.	MeOH	<b>1a</b> , 0.1 eq.	Et <sub>3</sub> N, 0.095 eq.	24	78	7.8
8	2.54	MeOH : H <sub>2</sub> O 1 : 2.5, 1.0 mL	<b>9b</b> , 0.25	Et <sub>3</sub> N, 0.28	8	18	30
9	2.54	H H	<b>9b</b> , 0.22	Et <sub>3</sub> N, 0.24	24	26	27
10 <sup>b</sup>	0.74	MeOH, 0.2 mL	<b>9b</b> , 0.075	Et <sub>3</sub> N, 0.078	6	45	16
11 <sup>b,c</sup>	1 eq.	MeOH	<b>1b</b> , 0.1 eq.	Et <sub>3</sub> N, 0.095 eq.	6	6.1	51.5
12	2.16	MeOH : H <sub>2</sub> O 1 : 2.5, 1.0 mL	1b, 0.22	Et <sub>3</sub> N, 0.24	6	52	48

Table 1. Benzoin Condensation Using Chiral Thiazolium Salts

<sup>a</sup>Unless indicated, the reactions were carried out at ambient temperature (20-23 °C). <sup>b</sup>Reaction carried out at 30 °C, bath temperature. <sup>c</sup>Data taken from Sheehan and Hara's work, reference 6e.

The benzoin obtained in all of these condensations was enriched in the R enantiomer, determined through comparison of its optical rotation with authentic samples. The observed asymmetric induction can be rationalized by invoking a steric model. The enamine formed by the reaction of the thiazolium ylide with benzaldehyde is expected to possess the E geometry, which minimizes allylic strain. If it is assumed that one face of the enamine is effectively blocked by the aryl group, then the reaction with the second benzaldehyde should occur from the other, open face. A final requirement to explain the observed preponderance of the R

enantiomer is that the enamine reacts preferentially with the *Si* face of benzaldehyde, possibly via a hydrogen-bonded transition state in which the phenyl group of benzaldehyde is oriented so as to minimize steric interactions (A or C vs. B or D). The low asymmetric induction observed in the reaction suggests that this last point, the orientation of the phenyl group, has not been properly addressed in our catalyst design.



In conclusion, we have developed an efficient, high-yielding route to conformationally-restricted chiral thiazolium salts. These salts catalyze the benzoin condensation, affording benzoin in 20-30% yield, and with a similar range of ee's.

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