105. A Novel Asymmetric Benzoin Reaction Catalyzed by a Chiral Triazolium Salt

Preliminary Communication

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Using the chiral triazolium salt **1** as catalyst, a novel asymmetric variant of the benzoin reaction is reported. For the first time, the scope of the method is extended to a broader range of aromatic aldehydes **2**, affording the acyloins **3a–h** in yields of 22–72% and enantiomeric excesses up to 86%.

Introduction. – The benzoin reaction is one of the oldest reactions in organic chemistry, found serendipitously by *Liebig* and *Wöhler* in 1832 [1]. Onium salts have been known to catalyze the benzoin reaction since the early work of *Ukai et al.*, who discovered the catalytic activity of 3-ethylthiazolium bromide again by serendipity [2]. The efforts of several groups to design an asymmetric variant of this classic organic reaction led to the development of some chiral thiazolium-based catalysts [3–6]. Yet, the enantioselectivities achieved in the preparation of benzoin were low-to-moderate with the yields being very low. The best results obtained so far were published by *Sheehan et al.*[1]) (6% yield, ee 52%, 10 mol-% catalyst), *Tagaki et al.* [4] (20% yield, ee 35%, 5 mol-% catalyst), *López-Calahorra* and coworkers [5] (20% yield, ee 26%, 10 mol-% catalyst) and *Zhao et al.* [6][1]) (20–30% yield, ee 47–57%). The application of any of these chiral catalysts in the condensation of other aromatic aldehydes than benzaldehyde has not been reported yet.

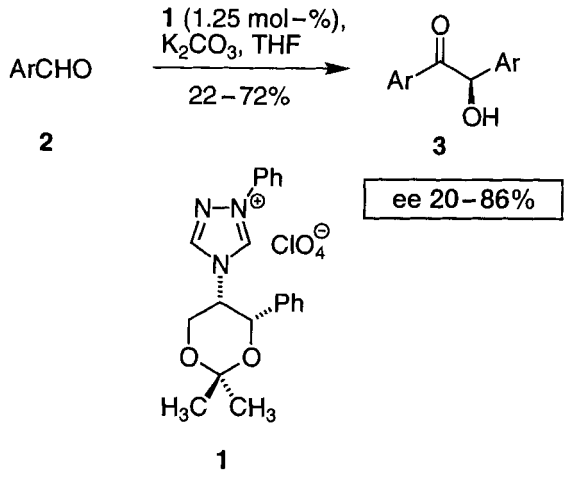
Recently, the use of triazolium salts or stable triazol-5-ylidenes in the benzoin-type condensation of formaldehyde was described by us, leading to a strongly enhanced activity compared with conventional catalysts, *i.e.*, thiazolium salts [8].

Results and Discussion. – We now wish to report the first chiral triazolium-based catalyst, (4*S*,5*S*)-4-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1-phenyl-4*H*-1,2,4-triazol-1-ium perchlorate (**1**), which is readily available *via* a large-volume intermediate of the industrial chloroamphenicol synthesis[2]). Triazolium salt **1** turned out to catalyze the benzoin reaction affording benzoin in significantly improved yields and enantioselectivi-

[1]) For other works related to this subject, see also [7].

[2]) For other applications of (*S*,*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan and its *N*-methyl derivative, see [9].

Scheme 1



ties with a considerably decreased amount of catalyst (1.25 mol-% catalyst)[3]) (*Scheme 1*). In the course of our study, the applicability of the catalyst **1** was extended to the condensation of a variety of aromatic aldehydes, leading to the corresponding aromatic acyloins with moderate-to-good yields and enantioselectivities up to 86%.

The actual catalytic species, the corresponding nucleophilic carbene, is formed *in situ* by deprotonation of triazolium salt **1** with K_2CO_3 in the presence of the corresponding aldehyde **2** (*Scheme 1*). This carbene then engages into a catalytic cycle corresponding to the well-known catalytic cycle first proposed by *Breslow* for the thiazolium-catalyzed acyloin condensation [8] [10]. After aqueous workup and column chromatography or precipitation the corresponding acyloins **3** are obtained in 22–72% yield with ee values of 20–86% (*Table*).

The ee values were determined by HPLC using chiral stationary phases. Racemic samples of the acyloins were prepared using achiral triazolium catalysts. The absolute configuration of the obtained benzoin was found to be (*R*) by correlation of the optical rotation of **3a** with literature data [11]. The other absolute configurations were then assigned assuming a uniform reaction mechanism.

The observed configuration of the products is in compliance with a simple transition-state model where the Ph group of the dioxane moiety shields the *re*-face of the *Breslow*

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[3]) Higher catalyst concentrations generally lead to higher yields but to lower enantioselectivities. The catalyst amount used throughout this work represents the optimum with regard to the total turnover number and the enantioselectivity. In most cases, the enantioselectivity also decreases with an increase of the reaction time. 60 h is again a compromise with regard to ee and yield. The time dependence of the asymmetric induction is probably due to partial racemization possibly caused by the base present in the reaction mixture. However, nucleophilic carbenes themselves are rather strong bases, and, therefore, a certain degree of racemization might be inevitable.

Table. *Acyloins* **3** *Prepared by Asymmetric Benzoin Reaction Using the Chiral Catalyst* **1**

3	Ar	Yield [%]	ee[a]) [%]	$[\alpha]_D^{r.t.}$ (c = 1, MeOH)	Config.[b])
a	Ph	66	75	−108.4	(*R*)
b	3-$MeOC_6H_4$	41	66	−105.9	(*R*)
c	4-$MeOC_6H_4$	22 (5)[c])	86 (87)[c])	−76.2	(*R*)
d	3-MeC_6H_4	54	76	−86.8	(*R*)
e	4-MeC_6H_4	46 (28)[c])	82 (84)[c])	−130.8	(*R*)
f	4-FC_6H_4	48	44	−41.2	(*R*)
g	4-ClC_6H_4	51	29	−12.3	(*R*)
h	4-BrC_6H_4	72	20	−2.3	(*R*)

[a]) The ee values were determined by HPLC on chiral stationary phases, using either a *Chiracel OD* (*Daicel*) or a (*S,S*)-*Whelk-01* column.

[b]) The absolute configuration of **3a** was determined by correlation of the optical rotation with literature data [11]. The other absolute configurations were assigned assuming a uniform reaction mechanism.

[c]) These results were obtained using 5 mol-% of catalyst **1**. The values given in parentheses originate from the reaction with the same aldehyde using 1.25 mol-% of **1**.

intermediate [10] (corresponding to the intermediate formed by addition of the first aldehyde molecule to the nucleophilic carbene in the thiazolium-catalyzed acyloin condensation); therefore, directing the attack of the incoming second aldehyde molecule to occur from the less hindered side, *i.e.*, the *si*-face (*Fig.*). The aldehyde molecule itself approaches the *Breslow* intermediate with its *si*-face, leading to an (*R*)-configuration at the newly formed stereogenic center. However, caution is advisable given the simplifications inherent to such a model, since nonlinear temperature dependence of the enantiose-

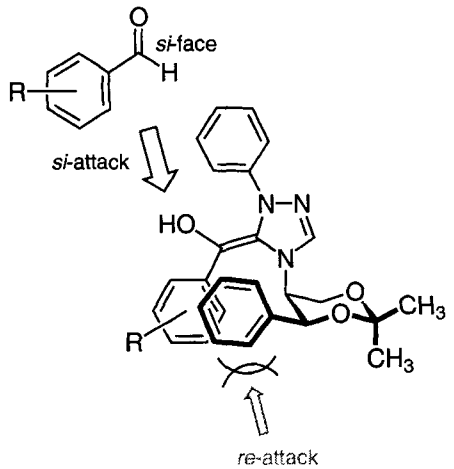
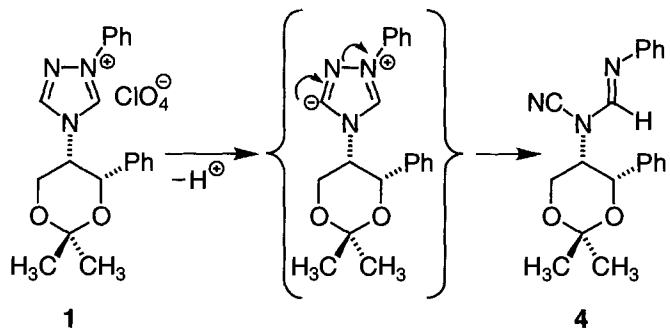


Figure. *Model explaining the facial selectivity in the asymmetric benzoin reaction using catalyst* **1**

lectivities has been observed. Further investigations in this regard are to be carried out and will be reported in due course.

The deactivation of catalyst **1** in the course of the catalysis proceeds *via* the competing deprotonation in position 3, irreversibly leading to the formation of *N*-cyanobenzamidine **4** *via* ring opening of the triazole moiety[4]) (*Scheme 2*).

Scheme 2



Conclusion. – The method described here presents a novel asymmetric benzoin reaction protocol. For the first time, it opens a catalytic pathway to, in some cases, highly enantiomerically enriched acyloins in satisfactory yields. Since both **1** and *ent*-**1** are readily available in large amounts, both enantiomers of the acyloins are accessible. In the case of benzoin itself, preliminary studies have shown the possibility of further enantiomeric enrichment by recrystallization.

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Experimental Part

To a stirred soln. of 44 mmol of ArCHO and 0.240 g of **1** (0.55 mmol) in 40 ml of abs. THF, 0.035 g K_2CO_3 (0.25 mmol) was rapidly added at r.t. After 60 h, the reaction mixture was poured into H_2O, extracted with CH_2Cl_2, and dried (Na_2SO_4). The solvent was evaporated and the residue purified by flash column chromatography (silica gel; Et_2O/pentane 1:1) or by precipitation/crystallization to give the aromatic acyloins as colorless or pale-yellow crystalline solids.

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[4]) Compound **4** was unambiguously characterized by IR, NMR, mass spectrometry, and elemental analysis.

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