157. The First Asymmetric Intramolecular *Stetter* Reaction

Preliminary Communication

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The first asymmetric intramolecular *Stetter* reaction is reported, using the chiral triazolium salt **1** as catalyst. Starting from the easily accessible 4-(2-formylphenoxy)but-2-enoates **2**, this protocol opens up an enantioselective pathway to the benzo-annulated pyran-4-ones (chroman-4-ones) **3a–h** with good yields and enantiomeric excesses of up to 74%.

Introduction. – Since its discovery in 1973, the *Stetter* reaction evolved to one of the most important *Umpolung* procedures for the synthesis of 1,4-dicarbonyl compounds. It has since found widespread application in the synthesis of organic key intermediates and in natural-product synthesis [1]. Its central feature and great advantage is the catalytic *in situ* formation of the acyl-carbanion equivalent, which normally requires a further synthetic step. Recently, an interesting intramolecular variant of the *Stetter* reaction was developed by *Ciganek*, which leads to the formation of benzo-annulated furanones and pyranones [2]. These compounds are potential intermediates for the synthesis of heterocyclic analogs of steroids [3] and important building blocks for the preparation of certain isoflavonoids such as pterocarpans and isoflavanones, some of which display a strong fungicidal activity [4].

Recently, we published a novel asymmetric benzoin reaction using a chiral triazolium salt as catalyst [5]. Since our group has been working on an enantioselective variant of the *Stetter* reaction for several years[1]), we tried to extend the applicability of this new catalyst class to the enantioselective *Stetter* reaction.

Results and Discussion. – We now report the first enantioselective intramolecular catalytic *Stetter* reaction, which opens up a short and efficient pathway to enantiomerically enriched chroman-4-ones. Using the catalyst (4*S*,5*S*)-4-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-1-phenyl-4*H*-1,3,4-triazol-1-ium perchlorate (**1**) [5], which is readily available *via* a large-volume intermediate of the industrial chloroamphenicol synthesis [7], a variety of substituted (3,4-dihydro-4-oxo-2*H*-1-benzopyran-3-yl)acetates **3** was obtained in good yields with ee's up to 74%. The 4-(2-formylphenoxy)but-2-enoates **2** are easily

[1]) For other applications of (+)-(*S*,*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan and its *N*-Me derivative in asymmetric synthesis, see [6].

accessible *via* the corresponding salicylic aldehydes and 4-bromocrotonates [2]. As discussed earlier [5], the actual catalytic species, the nucleophilic carbene, is formed *in situ* by deprotonation of **1** with K_2CO_3 in the presence of the corresponding butenoate **2** (*Scheme*). The carbene first attacks the aldehyde function, leading to a species similar to that proposed by *Breslow* for the thiazolium-catalyzed benzoin reaction (*Breslow* intermediate) [5] [8]. The nucleophilic β-C-atom of this enamine then attacks the activated C=C bond of the *Michael* acceptor. After aqueous workup and column chromatography, the corresponding acetates **3** are obtained in 22–73% yield with ee's of 41–74% (*Table*).

Scheme

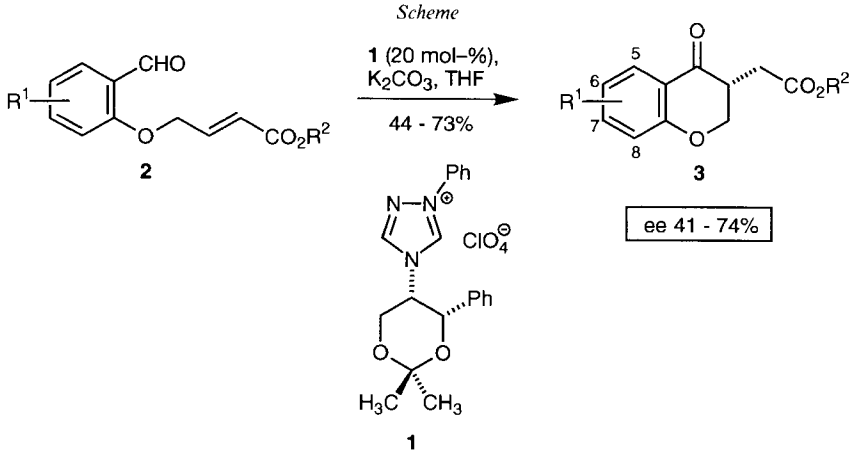

Table. *Chroman-4-ones* **3** *Prepared by Asymmetric* Stetter *Reaction Using the Chiral Catalyst* **1**

3	R[1a)]	R^2	Yield [%]	ee[b)] [%]	$[\alpha]_D^{r.t.}$ (c = 1, $CHCl_3$)	Config.[c)]
a	–	Me	73	60	−4.6	(*R*)
b	–	Et	69	56	−4.0	(*R*)
c	8-MeO	Me	44	68	−16.0	(*R*)
d	8-MeO	Et	69	62	−12.0	(*R*)
e	7-MeO	Me	22 (9)[d)]	71 (74)[d)]	−6.3	(*R*)
f	6-MeO	Me	56	61	−20.4	(*R*)
g	6-Cl	Me	50 (92)[e)]	41 (13)[e)]	−11.3	(*R*)
h	[5,6]-Ph[f)]	Me	51	65	+5.9	(*R*)

[a)] The position of the respective substituent is specified according to the numbering generally accepted for the chromanone system, as shown for the annulated benzo moiety of **3** in the *Scheme*.

[b)] The ee's were determined either by HPLC on chiral stationary phases, using a *Chiralcel OD* (*Daicel*) or a (*S,S*)-*Whelk-01* column, or by NMR shift experiments using (−)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as chiral cosolvent.

[c)] The absolute configuration of **3a** was determined by investigation of the chemical-shift nonequivalences of the *Mosher* derivatives[2]). The other absolute configurations were assigned assuming a uniform reaction mechanism.

[d)] This result was obtained with an extended reaction time (48 h) using 50 mol-% of catalyst **1**. The values given in parentheses originate from the reaction with the same substrate over 24 h using 20 mol-% of **1**.

[e)] This result was obtained over 14 h using 10 mol-% of catalyst **1**. The values given in parentheses originate from the reaction with the same substrate over 14 h using 20 mol-% of **1**.

[f)] A benzo ring is fused to the chromanone system along C(5) and C(6).

The ee's were determined by HPLC using chiral stationary phases. Racemic samples of the (3,4-dihydro-4-oxo-2*H*-1-benzopyran-3-yl)acetates were prepared using chiral thiazolium salts according to *Ciganek* [2]. The absolute configuration of **3a** was determined to be (*R*) by the well-established NMR shift nonequivalence technique using the *Mosher* derivatives[2]). The other absolute configurations were then assigned assuming a uniform reaction mechanism.

The observed absolute 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 intermediate formed by addition of the nucleophilic carbene to the aldehyde, therefore, directing the attack of the enoate *Michael* acceptor to occur with the less hindered face, *i.e.*, the *si*-face of the enamine (*Fig.*). The electrophilic part of the intermediate bearing the activated C=C bond is approached by the enamine β-C-atom (the part which is reminiscent of a *Breslow* intermediate) at its *si*-face, leading to an (*R*)-configuration at the newly formed stereogenic center.

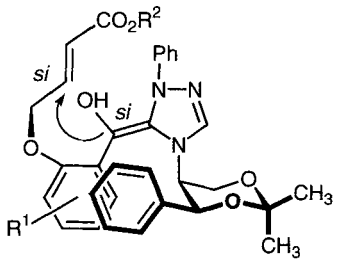

Figure. *Model explaining the facial selectivity in the asymmetric intramolecular* Stetter *reaction using catalyst* **1**

However, the strongly simplifying character of such a model should be kept in mind. As was outlined previously, the deactivation of the catalyst proceeds *via* the formation of the corresponding *N*-cyanobenzamidine [5]. Further investigations with regard to the extension of this new method to a wider range of substrates are currently in progress, as well as the search for tailored catalysts with higher activities and enantioselectivities.

Conclusion. – The method described here represents the first asymmetric intramolecular *Stetter* reaction protocol. It opens up a catalytic pathway to a range of enantiomerically enriched (3,4-dihydro-4-oxo-2*H*-1-benzopyran-3-yl)acetates **3** in good yields. Since both **1** and *ent*-**1** are readily available in large amounts, both enantiomers of **3** are accessible in excess.

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[2]) To elucidate the absolute configuration of **3a**, the pyranone moiety was reduced to the corresponding *cis*-configurated alcohol and subsequently converted to the *Mosher* ester with MTPA chloride. The absolute configuration of the stereogenic center formed in the course of the *Stetter* reaction was then assigned on the basis of the chemical-shift nonequivalences caused by the diatropic ring current of the Ph ring in the MTPA ester [9].

Experimental Part

To a stirred soln. of 1.25 mmol of 4-(2-formylphenoxy)but-2-enoate **2** and 0.118 g (0.25 mmol) of **1** in 40 ml of abs. THF, 17.5 mg of K_2CO_3 were rapidly added at r.t. After 24 h, the mixture was poured onto 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) to give the chroman-4-ones **3** as colorless or pale-yellow oils, or crystalline solids.

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