# Asymmetric Synthesis of Chromanones via N-Heterocyclic Carbene Catalyzed Intramolecular Crossed-Benzoin Reactions

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**Abstract:** The enantioselective synthesis of 3-hydroxy-4-chromanones bearing a quaternary stereocenter via an N-heterocyclic carbene catalyzed intramolecular crossed-benzoin reaction is described.

**Key words:** organocatalysis, N-heterocyclic carbenes, asymmetric synthesis, benzoin reaction, chromanones

Since the discovery of stable carbenes in the last decade of the 20th century,[1] N-heterocyclic carbenes have played an important role in the rapidly growing area of organocatalysis.[2] Beginning with the thiazolium unit of the coenzyme thiamine (vitamin $B_1$) the enormous catalytic potential of N-heterocyclic carbenes has enabled new organic reactions such as conjugate nucleophilic acylations,[3] transesterifications,[4] polymerizations,[5] β-alkylations,[6] hydroacylations,[7] trifluoromethylations,[8] and sila-Stetter reactions.[9] Asymmetric variants of carbene-catalyzed reactions such as the enantioselective benzoin condensation,[10] the asymmetric intramolecular Stetter reaction,[11] and the enantioselective intermolecular aldehyde-imine cross-coupling[12] exemplify their broad applicability in asymmetric organocatalysis.

Intermolecular benzoin reactions are usually limited to the synthesis of homobenzoins; recently, however, crossed versions have been developed via cyanide- or phosphite-catalyzed cross-silyl[13] and enzyme-catalyzed[14] reactions. Concerning the intramolecular crossed-benzoin cyclizations we[15b] and Suzuki et al.[15a,c] reported protocols utilizing commercial thiazolium salts as pre-catalysts to form different five- and six-membered α-hydroxy ketones. Enantioselective reactions of this type remained an unsolved problem until 2006, when we published a breakthrough with the first enantioselective intramolecular crossed-benzoin reaction employing new chiral tetracyclic and pyroglutamic acid based triazolium salts **1** and **2** as pre-catalysts.[16] α-Hydroxy tetralones were obtained bearing a quaternary stereocenter[17] with high yields and excellent enantiomeric excesses of up to 98%.

With the enantioselective intramolecular benzoin reaction established as a synthetic tool, and in combination with our efforts in the synthesis of bioactive natural products bearing a quaternary α-hydroxy ketone unit,[18] such as the 4-chromanone derivative (*S*)-eucomol[19] (**4**), we herein report our studies on the catalytic asymmetric synthesis of various 3-hydroxy-4-chromanones brought about by the chiral triazolium salts **1**–**3** as pre-catalysts (Figure 1).

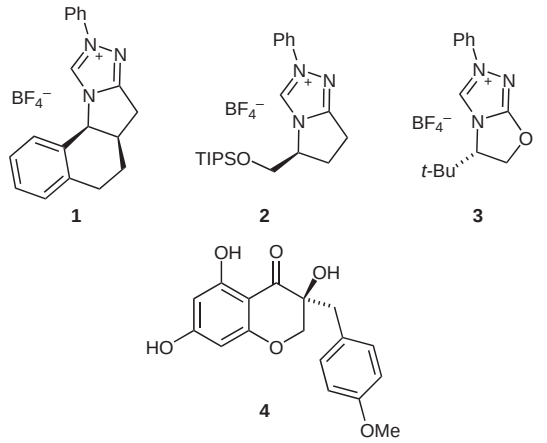


**Figure 1** Enantiopure pre-catalysts **1**–**3** and (*S*)-eucomol (**4**)

The sterically different pre-catalysts **1**–**3** were chosen in order to adjust the catalyst system to the steric and electronic properties of the substrates **5**. Therefore the aldehyde ketone **5a**[20] was investigated as a test substrate to determine appropriate conditions that favor the desired carbene-catalyzed cyclization to the chromanone **6a** in comparison to the base-catalyzed aldol condensation to the 3-hydroxy benzofuran **7** (Scheme 1).

Unfortunately, the conditions that successfully yielded α-hydroxy tetralones with tetracyclic pre-catalyst **1**[16a] [*t*-BuOK as base in THF (0.1 M) at r.t.] resulted in an almost 1:1 mixture of the desired chromanone **6a** and the benzofuran **7**, albeit accompanied by a high enantiomeric excess of 91% (Table 1). A screening of the reaction conditions indicated 10 mol% of the tetracyclic pre-catalyst **1** and substoichiometric amounts of KHMDS (9 mol%) as base at room temperature were suitable. A higher dilution (0.05 M) was also found to suppress the aldol reaction.

The ethyl-substituted chromanone **6a** was obtained with a high yield (90%) and an excellent asymmetric induction of 91% ee, that could be further increased to 94% ee by performing the reaction at 5 °C. Utilizing the TIPS-substituted triazolium salt **2** only the undesired aldol product was obtained and the more bulky pre-catalyst **3** showed a very low activity.

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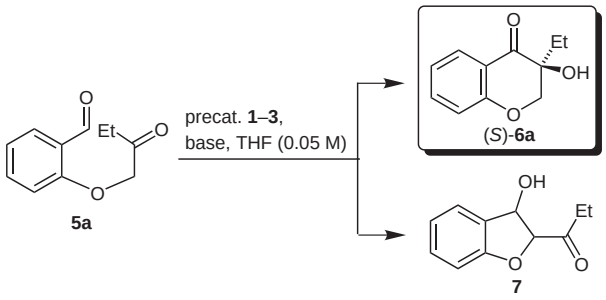
**Table 1** Optimization of the Asymmetric Intramolecular Benzoin Reaction[a]

| Entry | Pre-catalyst (mol%) | Base (mol%) | Temp | Time (h) | Yield of **6a** (%) | Yield of **7** (%) | ee (%)[b] (configuration)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1** (20) | *t*-BuOK (20) | r.t. | 24 | 42[d,e] | 54[e] | 91 (*S*) |
| 2 | **1** (10) | *t*-BuOK (9) | r.t. | 48 | 81[e] | 19[e] | 91 (*S*) |
| 3 | **1** (10) | DBU (9) | r.t. | 48 | 18 | 77 | – |
| 4 | **1** (20) | $Et_3N$ (20) | r.t. | 96 | – | 11[e] | – |
| 5 | **1** (10) | KHMDS (9) | r.t. | 48 | 90 | 2[e] | 91 (*S*) |
| 6 | **1** (20) | KHMDS (19) | 5 °C | 48 | 88 | 6[e] | 94 (*S*) |
| 7 | **2** (10) | KHMDS (9) | r.t. | 16 | – | 90[e] | – |
| 8 | **3** (20) | KHMDS (20) | r.t. | 72 | 18 | 8[e] | – |

[a] Conditions: THF (0.05 M) and **5a**.
[b] Determined by chiral stationary phase GC (Lipodex E).
[c] The absolute configuration was confirmed by X-ray analysis of the corresponding (*S*)-camphanyl ester of (*S*)-**6a**.[21]
[d] Reaction in THF (0.1 M).
[e] Conversion determined by GC.

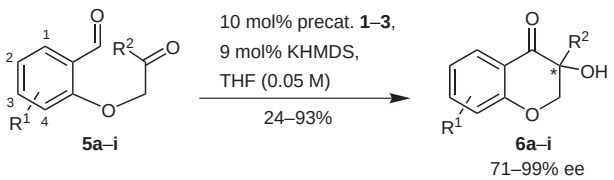



**Scheme 1** Optimization studies of the chromanone synthesis (Table 1)

After the adjustment of the reaction parameters several aldehyde ketones **5a**–**i** were transformed into the corresponding 3-hydroxy-4-chromanones **6a**–**i** (Scheme 2, Table 2).

Utilizing 10 mol% tetracyclic catalyst **1** and substoichiometric amounts of KHMDS (9 mol%) in THF at room temperature, the methyl-substituted chromanone **6b** could be obtained in a good yield (70%) and high enantiomeric excess (90%). The asymmetric induction could be further improved to 93% ee accompanied by a slightly decreased yield by running the reaction at 5 °C and employing 20 mol% catalyst **1**.

The increased steric demand at the ketone function of substrates **5** resulted in an increase in the enantiomeric excesses up to 95% accompanied by moderate to good yields. The isobutyl- and the cyclohexyl-substituted aldehyde ketones **5c** and **5d** could be cyclized revealing a broad tolerance of steric demand at the ketone function.




**Scheme 2** Scope of chromanones **6** (Table 2)

Activated substrates only required short reaction times and could also be converted with the bulkier catalyst **3**, resulting in most cases in better inductions. 2,4-Dibromo-substituted substrates **5e** and **5f** could be cyclized to the corresponding chromanones in high yields with the tetracyclic catalyst **1** at 0 °C, which were found to be the best conditions with the isobutyl-substituted substrate **5f** (92% ee). In contrast the ethyl-substituted aldehyde ketone **5e** showed the best results with catalyst **3** at room temperature (86% ee). Even complete asymmetric induction could be obtained utilizing the 2-nitro-substituted substrate **5g**. In this case the competing aldol reactions allowed only moderate yields of the chromanone **6g** (51%). These activated substrates enable the synthesis of both enantiomers, as the pre-catalysts **1** and **3** generate enantiomeric configurations at the newly formed stereocenter.

Sterically demanding functionalizations at the aromatic part of substrates **5** caused much lower conversions with pre-catalyst **1** even after long reaction times. The 2,4-di-*tert*-butyl-substituted aldehyde ketone **5h** showed a rather low activity and chromanone **6h** was obtained in only 30% yield accompanied by a reduced ee of 82%. By running the reaction at 45 °C the conversion could be improved to 50% with a minimal decrease of the enantiomeric excess (78%).

Furthermore the piperonyl-type aldehyde ketone **5i**, bearing a motif that can often be found in natural products, was also used as a substrate in the intramolecular benzoin reaction. Again higher temperatures were necessary to yield the desired chromanone **6i** with improved yields (43%) and a satisfactory ee of 88%. The TIPS-substituted catalyst **2** was tested with this highly functionalized substrate too. Chromanone **6i** could be synthesized at room temperature with an improved yield of 61% but a significant drop of the enantiomeric excess to 71%.

**Table 2** Scope of the Intramolecular Crossed-Benzoin Reaction of **5** to Yield Chromanones **6**[22]

| Product **6** | $R^1$ | $R^2$ | Precatalyst | Temp | Time (h) | Yield (%) | ee (%)[a] (configuration)[b] |
|---|---|---|---|---|---|---|---|
| **a** | H | Et | **1** | 5 °C | 48 | 88[c] | 94 (*S*) |
| **b** | H | Me | **1** | r.t. | 18 | 70 | 90 (*S*) |
| **b** | H | Me | **1** | 5 °C | 48 | 62[c] | 93 (*S*) |
| **c** | H | *i*-Bu | **1** | r.t. | 40 | 78[d] | 92 (*S*) |
| **c** | H | *i*-Bu | **1** | 5 °C | 24 | 46[c] | 95 (*S*) |
| **d** | H | *c*-Hex | **1** | r.t. | 72 | 53[c] | 94 (*S*) |
| **e** | 2,4-dibromo | Et | **1** | 0 °C | 18 | 92[c] | 76 (*S*) |
| **e** | 2,4-dibromo | Et | **3** | r.t. | 18 | 87[c] | 86 (*R*) |
| **f** | 2,4-dibromo | *i*-Bu | **1** | 0 °C | 24 | 93[c] | 92 (*S*) |
| **f** | 2,4-dibromo | *i*-Bu | **3** | 5 °C | 24 | 84[c] | 81 (*R*) |
| **g** | 2-nitro | *i*-Bu | **1** | 5 °C | 19 | 54 | 89 (*S*) |
| **g** | 2-nitro | *i*-Bu | **3** | 5 °C | 65 | 51 | 99 (*R*) |
| **h** | 2,4-di-*t*-Bu | Me | **1** | r.t. | 65 | 30[c] | 82 (*S*) |
| **h** | 2,4-di-*t*-Bu | Me | **1** | 45 °C | 24 | 50[c] | 78 (*S*) |
| **i** | 2,3-methylenedioxo | *n*-Pr | **1** | r.t. | 72 | 24 | 91 (*S*) |
| **i** | 2,3-methylenedioxo | *n*-Pr | **1** | 45 °C | 72 | 43[c] | 88 (*S*) |
| **i** | 2,3-methylenedioxo | *n*-Pr | **2** | r.t. | 48 | 61[c] | 71 (*S*) |

[a] Determined by chiral stationary phase GC (Lipodex E) or HPLC (Daicel Chiralpak AD).
[b] The absolute configuration was confirmed by X-ray analysis of the corresponding (*S*)-camphanyl esters of (*S*)-**6a** and (*S*)-**6f**.[21]
[c] Reaction with 20 mol% pre-catalyst and 19 mol% KHMDS.
[d] Reaction with 12 mol% pre-catalyst and 9 mol% KHMDS.

The absolute configuration of chromanone **6a** and **6f** was assigned by X-ray analysis of the corresponding (*S*)-camphanyl esters (Figure 2).[21] Thus, the absolute configuration of the quaternary stereocenter was determined to be *S* utilizing pre-catalyst **1**, which is in accordance with our postulated transition state.[16a]

In conclusion we have developed an efficient N-heterocyclic carbene catalyzed asymmetric intramolecular crossed-benzoin reaction yielding the title 3-hydroxy-4-chromanones. The application of three different triazolium salts as pre-catalysts enabled the adaptation of the catalyst system to the steric and electronic demands of the substrates. The application of our protocol in the organocatalytic asymmetric synthesis of natural products bearing this key structural motif, such as (*S*)-eucomol (**4**), is currently in progress.

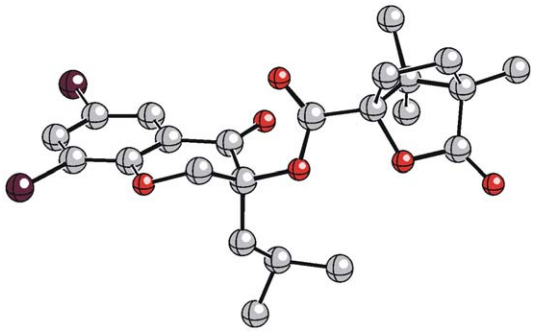


**Figure 2** X-ray structure of the (*S*)-camphanyl ester of (*S*)-**6f**

## Acknowledgment

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(20) Aldehyde ketones of type **5** can be synthezised by the reaction of the corresponding salicyl aldehydes, $K_2CO_3$ and α-bromo ketones in DMF at r.t.
(21) CCDC 607797 (**6a**) and CCDC 607796 (**6f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(22) All new compounds were fully characterized (IR, NMR, MS, elemental analysis, optical rotation, and melting point).
Enantioselective Intramolecular Crossed-Chromanone Cyclization to **6a**; Typical Procedure
In a Schlenk tube under argon at r.t. the pre-catalyst **1** (39.0 mg, 0.104 mmol, 20 mol%) was suspended in anhyd THF (9.5 mL). KHMDS (0.5 M in toluene; 198 μL, 0.099 mmol, 19 mol%) was added slowly, and the solution stirred for 15 min. The yellow solution was cooled to 5 °C and the aldehyde ketone **5a** (100 mg, 0.520 mmol) dissolved in anhyd THF (1.0 mL) was added to the carbene solution. The reaction mixture was stirred for 48 h, diluted with $CH_2Cl_2$, quenched with $H_2O$, extracted twice with $CH_2Cl_2$, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel ($Et_2O$–*n*-pentane, 1:8) to yield **6a** (88 mg, 88%) as a colorless solid; mp 48 °C; ee 94% [determined by chiral stationary phase GC (Lipodex E)]; $[\alpha]_D^{23}$ –10.3 (*c* 1.2, $CHCl_3$). IR (KBr): 3853, 3742, 3482, 2973, 2361, 2340, 1837, 1690, 1610, 1558, 1465, 1382, 1311, 1215, 1134, 1021, 942, 862, 758, 670, 533. $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ = 0.95 (t, 3 H, *J* = 7.4 Hz, $CH_3$), 1.81 (q, 2 H, *J* = 7.5 Hz, $CH_3CH_2$), 3.68 (s, 1 H, OH), 4.17 (d, 1 H, *J* = 11.4 Hz, CHH), 4.40 (d, 1 H, *J* = 11.4 Hz, CHH), 6.96–7.08 (m, 2 H, Ar), 7.48–7.54 (m, 1 H, Ar), 7.86–7.89 (m, 1 H, Ar). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 6.8 ($CH_3$), 27.6, 72.8 ($CH_2$), 73.0 (C), 117.9 (CH), 118.4 (C), 127.5, 136.5 (CH), 161.4 (C), 196.8 (CO). MS (EI): *m*/*z* (%) = 192 ($M^+$, 11), 122 (7), 121 [($M^+$ + 1) – 72, 100], 120 (11), 93 (7), 92 (18), 77 (5), 65 (6). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.29. Found: C, 68.69; H, 6.28.