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Modified Chiral Triazolium Salts for Enantioselective Benzoin Cyclization of Enolizable Keto-Aldehydes: Synthesis of (+)-Sappanone B

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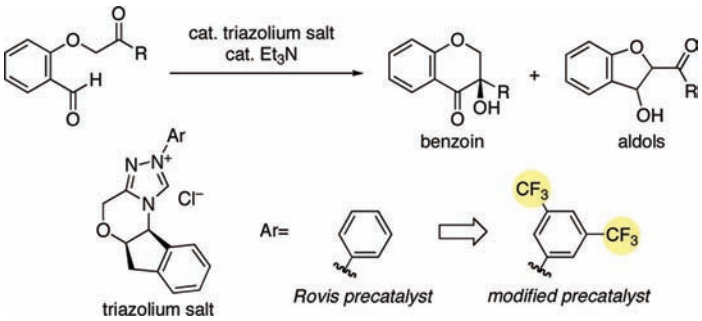
ABSTRACT



Asymmetric synthesis of (+)-sappanone B (1), a natural product with a 3-hydroxy chromanone structure, was achieved via enantioselective benzoin cyclization by using a modified Rovis catalyst and triethylamine. This catalyst enabled the successful benzoin cyclization of readily enolizable keto-aldehydes.

We recently reported the catalytic asymmetric benzoin cyclization of keto-aldehydes[1] by using Rovis triazolium salt,[2] opening an enantioselective route to chiral, nonracemic cyclic ketols. To explore the scope, we became interested in applying this reaction to the synthesis of various natural products. (+)-Sappanone B[3] (**1**, Figure 1) is one of the targets selected along these lines. It is a homoisoflavonoid[4] with significant, recently discoverd xanthine oxidase inhibitory activity, which was isolated from the heartwood of *Caesalpinia sappan* Leguminosae.[5]

We initially centered our attention on the *absolute stereocontrol*.[6] However, preliminary model studies immediately suggested that the real issue was the low cyclization yield for the enolizable keto-aldehydes.

In this Letter, we report modifications of the Rovis triazolium salts by introducing electron-withdrawing substituent(s) to facilitate the generation of the key carbene spiecies under mild basic conditions, enabling the stereocontrolled synthesis of **1**.[7]

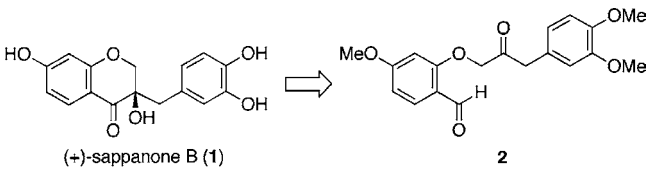


Figure 1. Structure and retrosynthesis of (+)-sappanone B (**1**).

(1) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492−3494.

(2) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299.

(3) (a) Saitoh, T.; Sakashita, S.; Nakata, H.; Shimokawa, T.; Kinjo, J.-E.; Yamahara, J.; Yamasaki, M.; Nohara, T. *Chem. Pharm. Bull.* **1986**, *34*, 2506−2511. (b) Namikoshi, M.; Nakata, H.; Yamada, H.; Nagai, M.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, *35*, 2761−2773. (c) Namikoshi, M.; Nakata, H.; Nuno, M.; Ozawa, T.; Saitoh, T. *Chem. Pharm. Bull.* **1987**, *35*, 3568−3575.

(4) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1981**, *40*, 105−152.

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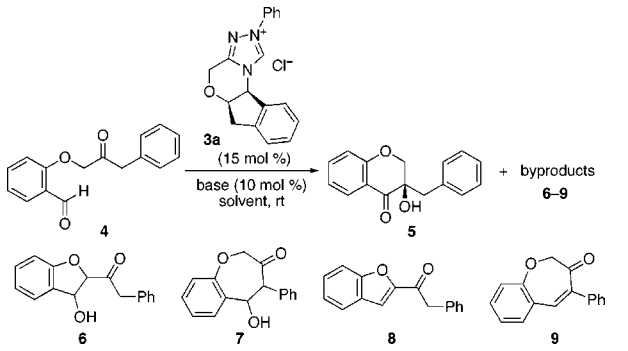
Table 1. Asymmetric Benzoin Cyclization of Keto-Aldehyde **4** by Using Triazolium Salt **3a**[a]



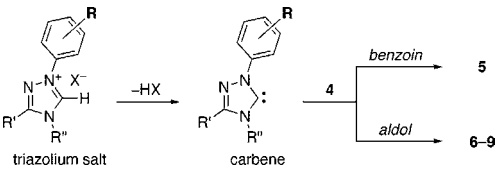
				α-ketol **5**		byproducts **6**–**9**
entry	base	solvent	time/h	yield/%	ee/%	yield/%[b]
1	DBU	THF	3.5	10	93	78
2	Et_3N	THF	26	56	88	31
3	Et_3N	toluene	24	39	92	57
4[c]	KHMDS	toluene	7	31	94	53

[a] All reactions were performed on 1.0 mmol of **4** with a combination of precatalyst **3a** (15 mol %) and base (10 mol %) at room temperature. Enantiomeric excess was assessed by HPLC analysis on CHIRALPAK AD-H. [b] Containing a small amount of unidentified byproduct(s). [c] Reaction was performed with prior generated carbene [by mixing **3a** (15 mol %) with KHMDS (10 mol %) for 10 min (toluene, rt)].

Table 1 represents the initial experiments that revealed the issue. When model keto-aldehyde **4** was treated with triazolium salt **3a** and DBU (THF, room temperature, 3.5 h), the corresponding α-ketol (*R*)-**5**[8] was obtained in only 10% yield (entry 1). The low yield was due to the competing intramolecular aldol reactions to give byproducts, 5- and 7-membered aldols **6** and **7** (R_f 0.2, silica gel TLC, EtOAc/hexane = 1:3) and their dehydration products **8** and **9** (R_f 0.6) in 78% combined yield. Such prevalence of aldol reactions was not surprising in view of the high acidities of the protons adjacent to the carbonyl group in **4**. We examined a weaker base, triethylamine, which led to a better yield of **5** (56%) with a slight decrease in the ee (entry 2).[9] While the ee of **5** was recovered by use of toluene as a solvent, the side reactions again became serious (entry 3). Moreover, prior generation of the carbene was also ineffective (entry 4), implying that the carbene also served as a base to promote the aldol cyclization (Scheme 1).[10]

Faced with this dilemma, we decided to change the catalyst precursor (Scheme 1). The idea was that if electron-withdrawing group(s) were installed in the *N*-phenyl group,

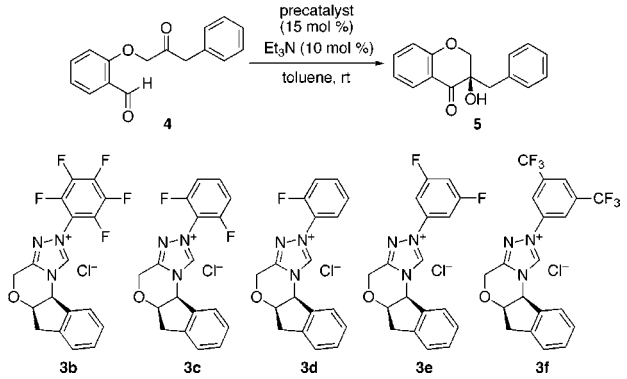
Scheme 1. Two Possible Actions of Carbene Catalyst Generated from Triazolium Salt



the triazolium salt would become more acidic, making the generation of the key carbene species possible with a weaker base, that is, less capable of enolizing **4**. Since the generated carbene would also be less basic, the problematic aldol reactions would be minimized.

To test this idea, we used a known precatalyst **3b**[11] with a C_6F_5 group (Table 2, entry 1). Indeed, aldol reactions were

Table 2. Reactions with Modified Triazolium Salts[a]



			α-ketol **5**		byproducts **6**–**9**
entry	precatalyst	time/h	yield/%	ee/%	yield/%
1	**3b**	2	93	68	0
2	**3c**	2	94	81	0
3	**3d**	5	67	88	32
4	**3e**	8	85	92	12
5	**3f**	5	87	94	11

[a] All reactions were performed with 1.0 mmol of **4** with a combination of precatalyst **3b**–**f** (15 mol %) and Et_3N (10 mol %) at 0.3 M in toluene at room temperature. Enantiomeric excess was assessed by HPLC analysis on CHIRALPAK AD-H.

completely suppressed, although the enantioselectivity was unfortunately diminished.

Encouraged by these data, we prepared several new triazolium salts **3c**–**f** possessing fluorine or trifluoromethyl group(s) on the *N*-phenyl group with hopes of finding a catalyst that could be capable of suppressing the aldol

(5) Nguyen, M. T. T.; Awale, S.; Tezuka, Y.; Tran, Q. L.; Kadota, S. *Chem. Pharm. Bull.* **2005**, *53*, 984–988.

(6) (a) Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1993**, *58*, 1751–1753. (b) Arnoldi, A.; Bassoli, A.; Borgonovo, G.; Merlini, L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2447–2453. (c) Jew, S.-S.; Kim, H.-A.; Kim, J.-H.; Park, H.-G. *Heterocycles* **1997**, *46*, 65–70.

(7) For a related study, see: Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431–2434.

(8) The (*R*) configuration of α-ketol **5** was confirmed by X-ray analysis of the corresponding (*S*)-camphanyl derivative. See ref 1.

(9) Use of various bases of different strength (KHMDS, KO*t*-Bu, quinuclidine) was unfruitful, invariably producing **6**–**9** in 50–70% yield.

(10) For the basicity of imidazol-2-ylidene in THF, see: Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757–5761 and references cited therein.

(11) (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728. (c) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553.

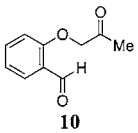
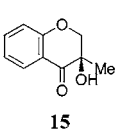
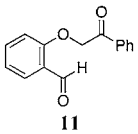
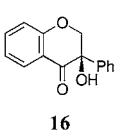
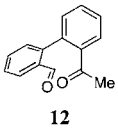
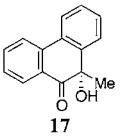
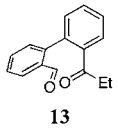
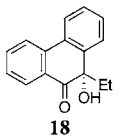
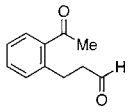
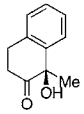
reaction without sacrificing the enantioselectivity. The reactivity profiles of **3c**−**f** were compared by the cyclization of keto-aldehyde **4** (Table 2, entries 2−5).

Several trends became obvious: (1) Introduction of the ortho-substituents led to a decreased ee:[12] Although *o*,*o*′-difluoro precatalyst **3c** could suppress the side reaction completely, the ee was slightly lower (entry 2). In the case of the *o*-fluoro precatalyst **3d**, a sizable amount of the aldol byproducts was produced (entry 3). (2) Meta-disubstituted precatalysts gave favorable results in suppressing the aldol reaction without loss of the ee: *m*,*m*′-Difluoro precatalyst **3e** gave the product in high yield as well as high ee (entry 4). The *m*,*m*′-bis(trifluoromethyl) precatalyst **3f** gave the best result, providing optimal yield and ee (entry 5).

Having found a promising triazolium salt **3f**, the scope and limitation were compared with that of **3a** with attention to the reactivity, enantioselectivity, and the extent of competing aldol reaction (Table 3). In every case listed, the cyclization yields were higher with modified precatalyst **3f** in comparison to the original Rovis precatalyst **3a**. The enantioselectivities were generally better with **3f**, except in one case. Entry 1 shows the reaction of keto-aldehyde **10** having a methyl group: Cyclization occurred smoothly with **3f** in an excellent selectivity, while aldol-type side reactions were serious when **3a** was used. Entry 2 shows the reaction of highly enolizable keto-aldehyde **11** to give 3-hydroxyisoflavanone **16**.[13] The yield was extremely low in the case of **3a** (13%), whereas **3f** gave a much better yield with an excellent selectivity (61% yield, 90% ee), although side products were also observed (27%). Biaryl keto-aldehydes[1] **12** and **13** showed the same trend (entries 3 and 4). The optimized conditions by using **3f** led to the high-yield formation of (*S*)-α-ketols with excellent selectivities.[14] Furthermore, cyclization of aryl keto-aliphatic aldehyde **14** was possible only with **3f** to give α-ketol **19** in high yield, albeit with moderate selectivity (entry 5).

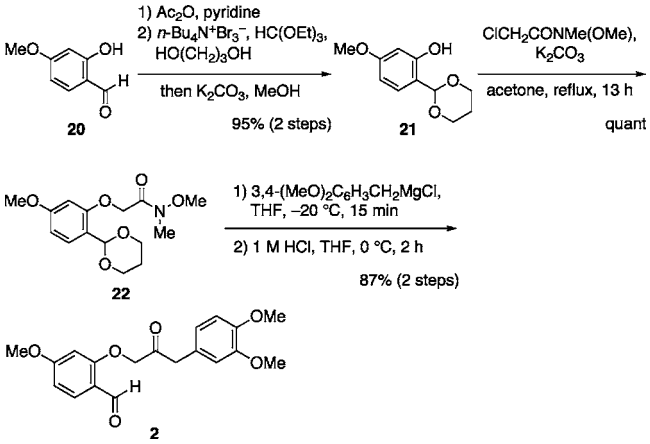
At this stage, we embarked on the synthesis of (+)-sappanone B (**1**). As the cyclization substrate, keto-aldehyde **2** was prepared from the commercially available aldehyde **20** in five steps (Scheme 2). After acetylation of the phenol in **20**, the aldehyde was protected as a 1,3-dioxane acetal, and deacetylation gave phenol **21** in 95% yield.[15] Although a detour, this temporary acetylation was essential, since the direct acetalization of **20** failed under a variety of conditions. Alkylation of phenol **21** with *N*-methoxy-*N*-methylchloroacetamide[16] proceeded in quantitative yield of Weinreb amide **22**. Treatment of amide **22** with a benzyl Grignard reagent,[17] followed by hydrolysis of the acetal gave keto-aldehyde **2** in 87% yield (2 steps).

Table 3. Enantioselective Benzoin Cyclizations of Keto-Aldehydes **10**−**14**[a]

entry	keto-aldehyde	α-ketol[b]	precatalyst	time/h	yield/%	ee/%
1	 **10**	 **15**	**3f**	1	90	94
			3a	24	53[c]	91
2	 **11**	 **16**	**3f**	17	61[d]	90
			3a	25	13[c]	79
3	 **12**	 **17**	**3f**	3	95	78
			3a[e]	15	73[c]	39
4	 **13**	 **18**	**3f**	12	92	96
			3a[f]	18	47[c]	90
5	 **14**	 **19**	**3f**[g]	24	90	60
			3a[f]	64	5	67

[a] Unless otherwise indicated, all reactions were performed with **3f** or **3a** (15 mol %) and Et_3N (10 mol %) in toluene at room temperature. Enantiomeric excesses were assessed by HPLC analysis on CHIRALPAK AD-H or CHIRALCEL OD-H. [b] The absolute configurations were confirmed by X-ray analysis of the corresponding (*S*)-camphanyl derivatives. [c] The corresponding byproducts were also obtained (entry 1: 43%; entry 2: 82%; entry 3: 18%; entry 4: 37%). [d] The corresponding benzofuran and aldol were also obtained in 27% combined yield. [e] Performed with **3a** (10 mol %) and DBU (20 mol %) in THF. [f] Performed with **3a** (20 mol %) and DBU (20 mol %) in THF. [g] Performed with **3f** (20 mol %) and Et_3N (20 mol %) in toluene.

Scheme 2. Preparation of Keto-Aldehyde **2**

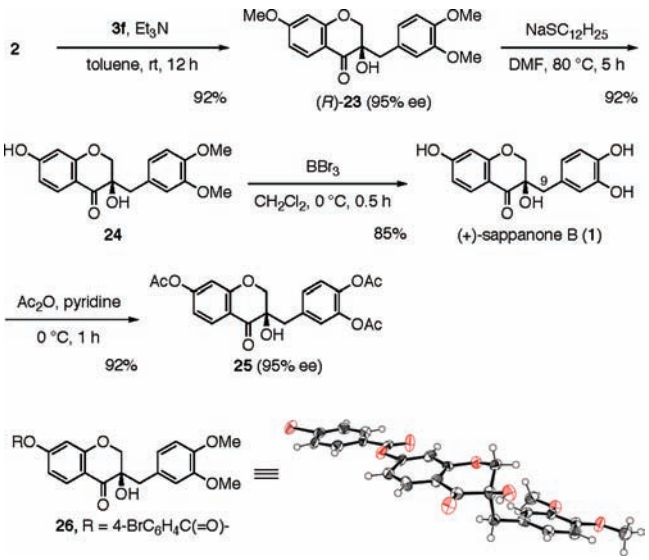


(12) The corresponding reaction by using the triazolium salt with the *ortho*-mono-methylated *N*-phenyl group [15 mol %, Et_3N (10 mol %), toluene, room temperature] provided α-ketol **5** in poorer selectivity (44%, 62% ee).

(13) (a) Minhaj, N.; Tasneem, K.; Khan, Z.; Zaman, A. *Tetrahedron Lett.* **1977**, *18*, 1145−1148. (b) Kim, C.-M.; Ebizuka, Y.; Sankawa, U. *Chem. Pharm. Bull.* **1989**, *37*, 2879−2881. (c) Vila, J.; Balderrama, L.; Bravo, J. L.; Almanza, G.; Codina, C.; Bastida, J.; Connolly, J. *Phytochemistry* **1998**, *49*, 2525−2528. (d) Gutierrez-Lugo, M.-T.; Woldemichael, G. M.; Singh, M. P.; Suarez, P. A.; Maiese, W. M.; Montenegro, G.; Timmermann, B. N. *Nat. Prod. Res.* **2005**, *19*, 173−179.

(14) The origin of the reversal of stereoinduction between biaryl keto-aldehyde and others is under investigation.

Scheme 3. Synthesis of (+)-Sappanone B (**1**) and X-ray Crystallographic Structure of 4-Bromobenzoyl Derivative **26**



Keto-aldehyde **2** was subjected to the crucial benzoin cyclization step (Scheme 3). Pleasingly, the above-mentioned conditions worked well, even with a reduced amount of catalyst [**3f** (7.5 mol %), Et_3N (7.5 mol %), room temperature, 12 h],[18] and tri-*O*-methyl sappanone B[6a] (**23**) was obtained in excellent yield and enantioselectivity (92%, 95% ee) with the (*R*) configuration (vide infra).

Among three methyl protecting groups for the phenols, the one para to the carbonyl group was cleanly detached by using an odorless thiolate[19] to give phenol **24** in 92% yield [$NaSC_{12}H_{25}$ (5 equiv), DMF, 80 °C, 5 h]. The (*R*) stereochemistry was confirmed by the X-ray analysis of 4-bromobenzoyl derivative **26** [4-bromobenzoyl chloride (3 equiv), pyridine, room temperature, 5 h].[20] Finally, the remaining two methyl groups were removed by BBr_3 (3 equiv, CH_2Cl_2, 0 °C) to give **1** as white amorphous solid in 85% yield after purification by column chromatography on *oxalated silica gel*.[21] No loss of the ee was observed during these demethylation processes, as evidenced by chiral HPLC analysis of the tri-*O*-acetyl derivative **25** [Ac_2O, pyridine (v/v 1/2), 0 °C]. The specific rotation of synthetic **1** ($[\alpha]_D$ +51 for 95% ee, *c* 1.0, MeOH) agreed with the reported value[3] ($[\alpha]_D$ +51.6, *c* 1.00, MeOH). Other physical data[3] for the synthetic sample (^1H NMR, ^{13}C NMR, IR) were identical with those of the natural product.[22]

Acknowledgment. We are grateful to Banyu Pharmaceutical Co., Ltd. for the gift of (1*S*,2*R*)-1-amino-2-indanol and Central Glass Co., Ltd. for the gift of 3,5-bis(trifluoromethyl)aniline. We express our gratitude to Prof. Dr. Hiyoshizo Kotsuki, Kochi University, for helpful suggestion on the preparation of oxalated silica gel. We also thank Dr. Hidehiro Uekusa and Ms. Sachiyo Kubo, Tokyo Institute of Technology, for X-ray analyses. This work was partially supported by the 21st Century COE program (Tokyo Institute of Technology) and a Grant-in-Aid for Scientific Research (JSPS). A JSPS Research Fellowship for Young Scientists to H.T. is also gratefully acknowledged.

Supporting Information Available: Spectroscopic and analytical data of the compounds in Tables 2 and 3, Schemes 2 and 3, and the synthetic sample of (+)-sappanone B (**1**), as well as crystal data for compound **26** and (*S*)-camphanyl derivatives of **15**, **16**, and **19** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070929P

(15) Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842−5845.

(16) Dolling, U. H.; Frey L. F.; Tillyer, R. D.; Tschaen, D. M. PCT Int. Appl. WO 97/10195, 1997.

(17) Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, *39*, 1126−1131.

(18) It should be noted that the cyclization by using **3a** [15 mol %, Et_3N (10 mol %), toluene] gave α-ketol (*R*)-**23** in substantially lower yield (24%, 92% ee).

(19) Sodium dodecanethiolate was prepared by mixing dodecanethiol with sodium methoxide (28 wt % in MeOH) followed by evaporation (see the Supporting Information). For odorless thiols and sulfides, see: Nishide, K.; Ohsugi, S.; Miyamoto, T.; Kumar, K.; Node, M. *Monatsh. Chem.* **2004**, *135*, 189−200.

(20) For the X-ray analysis of 4-bromobenzoyl derivative **26**, see the Supporting Information.

(21) Application of **1** onto a commercial silica gel caused a serious tailing of a spot or a band, rendering the assay and purification of **1** extremely difficult. The situation was cleared by the use of oxalated silica gel. For oxalated silica gel, see the Supporting information and; Cameron, D. W.; Riches, A. G. *Aust. J. Chem.* **1997**, *50*, 409−424.

(22) The spectroscopic analysis of synthetic **1** revealed that all the signals coincided with those of the natural product, except for the signal of C-9 (δ 38.9, conceiled by d_6-DMSO). Although the reported value for C-9 in ref 3a was δ 30.6, no peak was observed at this position. The signal of C-9 appeared at δ 40.7 in d_6-acetone. See the Supporting information.