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A stereoselective aldol reaction via diisopinocampheyl boron-enolate in preparation of chromane carboxylate with quaternary carbon

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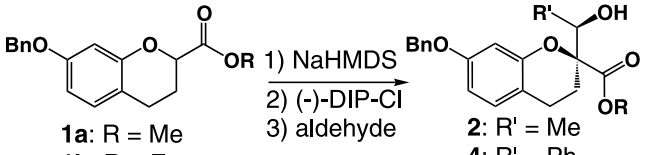
Abstract—A highly stereoselective aldol reaction was observed on chromane carboxylate ester **1** via the corresponding diisopinocampheyl boron-enolate using commercially available (–)-DIP-Cl reagent. The aldol product **2c** was obtained in 89% yield with 48 dr and 92% ee. Further studies indicate that stereoselective formation of the enolate and proper chiral ligand on boron are responsible for the exceptional diastereo- and enantioselectivity in the aldol reaction. © 2003 Published by Elsevier Science Ltd.

The enantioselective aldol reaction is among the most useful transformations in organic chemistry and has been intensely studied. In recent years, enantioselective aldol approaches have been applied to the synthesis of a variety of complex chiral molecules.[1–6] In the aldol reaction, up to two new chiral centers are established in a single step. A current limitation of the approach stems from the fact that selectivity is often poor when one of the newly formed stereocenters is a quaternary carbon.

Boron-mediated aldol reactions have been very useful in achieving stereochemical control, often resulting in aldol product with predictable and high stereoselectivity. Because of the smaller size of boron compared with other metals, it is believed that boron-mediated aldol reactions proceed through a tighter six-membered chair-like transition state.[3] Thus the *E*-/*Z*-geometry of the boron-enolates will be converted selectively into the *anti*-/*syn*-configuration in the aldol products. When an achiral boron reagent is used, a predictably high diastereoselectivity usually results. Absolute stereocontrol can be achieved by this method using a chiral enolate or a chiral aldehyde.[7] By the use of chiral boron reagents, Patterson and others[3,5] have shown that the aldol reactions can occur with excellent diastereoselectivity and good enantioselectivity. The method has found general success on ketones, thioesters and imides, etc. However, the protocol generally does not work on simple ester substrates, since the boron-enolate cannot be generated under the enolization conditions by the use of a boron triflate and a tertiary amine base. Generation of boron-enolate from the corresponding alkaline metal enolate (Li, Na, or K) is a simple and viable alternative, but examples are rare[8] in the literature, and its use in stereoselective aldol reactions has not been previously explored. Chromane carboxylates, especially the ones with quaternary carbons, were pursued heavily by the pharmaceutical industry with multiple applications. They were seen as leukotriene D_4 (LTD_4) inhibitors[9a] for treatment of allergic reactions and inflammatory conditions; as peroxisome proliferator activated receptor (PPAR) agonists[9b] for treatment of type **2** diabetes; and for their antioxidants/antiarrythmic[9c] activity. Numerous publications[9] described the preparation and usage of this important class of compounds. However, it remains a great challenge in establishing the stereogenic quaternary carbon on the chromane-ring system, so far to the best of our knowledge, no effective methods reported in the literature. Recently, we were interested in the preparation of chiral chromane intermediates with general structure **2**–**4** through aldol reactions. We have found that the chiral boron enolate derived from the corresponding Na-enolate of ester **1**[10] and commercially available (–)-DIP-Cl,[11,12] reacted with acetaldehyde or benzaldehyde to give **2** or **4** in excellent stereoselectivity in the aldol reaction (Eq. (1)).



1a: R = Me
1b: R = Et
1c: R = *i*Pr

2: R' = Me
4: R' = Ph

(1)

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The unusually high diastereoselectivity (expressed as diastereomer ratio or dr) and enantioselectivity (expressed as ee%) of the aldol reaction warranted a detailed study. Herein we report our findings in this and related reactions.

Treatment of ester **1** with NaHMDS in THF at low temperature followed by addition of acetaldehyde gave a mixture of four stereoisomers with dr (**2**+**2′**:**3**+**3′**) of 1:3 (Scheme 1). When the Na-enolate was trapped with triethylsilyl chloride, **7** (structure determined by NOE experiments) was obtained exclusively as the *Z*-stereoisomer. The Na-enolate **5** could be observed by NMR with a clean spectrum, but NOE experiments were not indicative of its configuration, possibly owing to aggregation. The clean NMR of the Na-enolate suggests exclusive formation of one isomer, presumably the *Z*-configured enolate as shown in structure **5**.

In the chiral aldol reaction, (–)-DIP-Cl was added to the Na-enolate followed by reaction with acetaldehyde. One of the four stereoisomers (**2**) was formed in excellent diastereo- and enantioselectivity.[13]

A significant steric effect of the ester in **1** on the stereoselectivity of the aldol reaction was discovered. The results are summarized in Table 1. While the methyl and ethyl ester gave similar selectivity, the isopropyl ester (**1c**) gave much improved stereoselectivity. Up to 48 dr and 92% ee was obtained with the isopropyl ester in the aldol reaction. The relative and absolute stereochemistry of the major product **2** was determined to be *R* (tertiary alcohol center) and *S* (quaternary center).[14] The stereochemical outcome of this reaction is consistent with a *Z*-boron-enolate (**6**) and a six-membered chair like transition state in the aldol reaction.[3]

To probe the origin of the high diastereoselectivity, the effect of ligand on boron was also investigated. Reaction of the Na-enolate of **1c** with dicyclohexyliodoborane and subsequent aldol reaction with acetaldehyde produced the aldol products in similar diastereomer ratio (39:1), as racemate. This result suggests that the diastereoselectivity was not influenced significantly by the ligands on boron but was primarily determined by enolate geometry configuration (the same *Z*-enolate was assumed in the reaction).

(1)

Another set of results also illustrate the influence of enolate geometry on the diastereoselectivity of the aldol reaction. When the same set of reaction conditions were applied to an analogous substrate **11**, the aldol reaction with acetaldehyde gave product with poor dr (ca. 2) and good ee (89% ee and 83% ee, respectively, for the major and minor diastereomers). When the Na-enolate intermediate was trapped with triethylsilyl chloride, a pair of silyl ketene acetals with *E*- and *Z*-configuration in ca. 2:1 ratio were formed. Apparently, the poor dr in this aldol reaction is a result of poor control of enolate geometry. Two different boron-enolates react individually, each gives good enantioselectivity in the aldol reaction. The oxygen in the chromane system plays an important role in controlling the enolate geometry, which is a necessary requirement for a stereoselective aldol reaction.

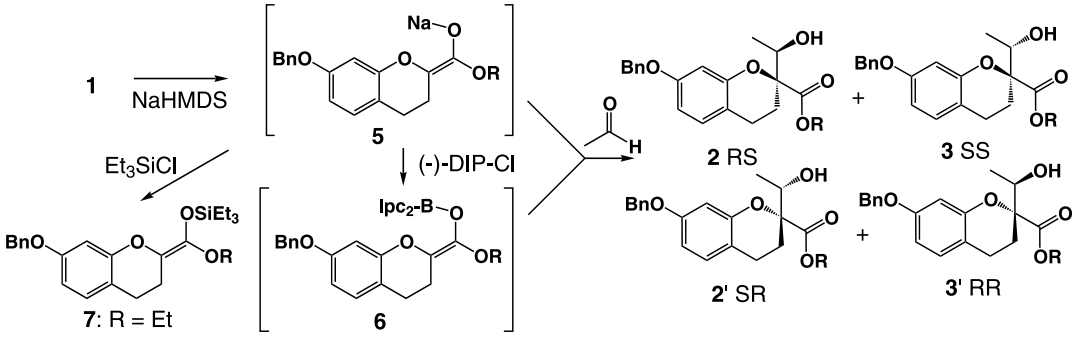
The high enantioselectivity of these aldol reactions was clearly a result of the powerful auxiliary effect from the chiral diisopinocampheyl groups on the boron-enolates. Use of lower ee DIP-Cl in these aldol reactions gave lower ee products.

From a practical perspective, solid (–)-DIP-Cl is very sensitive to moisture and requires careful handling under an inert atmosphere in order to obtain good conversion and yield. We have found it is best to prepare the (–)-DIP-Cl[11,12] fresh and use it as a solution in THF for the aldol reaction. With this protocol, the aldol reaction can be achieved consistently in good yield. It was observed that ca. 2 equivalents of (–)-DIP-Cl are needed for the desired stereoselectivity. With less than 1.5 equivalents (–)-DIP-Cl, the selectivity eroded

Table 1. Influence of R group in ester **1** on the stereoselectivity in aldol reaction*

Substrates	dr (**2**+**2′**:**3**+**3′**)	Major **2** ee%	Yield (isolated) (%)
1a (R = Me)	28.9	87	88
1b (R = Et)	35.1	86	85
1c (R = *i*Pr)	48.0	92	89

* The dr and ee% of the aldol product was determined by chiral SFC analysis.



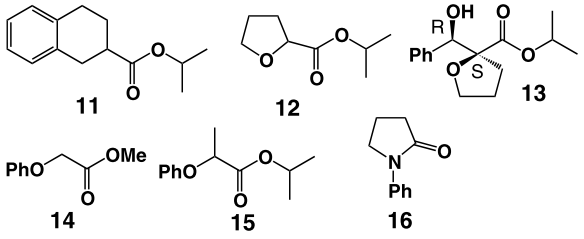
Scheme 1. Studies on the stereoselective aldol reaction.

significantly. While it is not clear why 2 equivalents are needed, an NMR study of the conversion from Na-enolate into boron-enolate did correlate well with the observed result. When 1.0 equivalent of boron reagent (dicyclohexyliodoborane was used for simplicity) was added to the Na-enolate of **1a**, the NMR of the reaction mixture became complicated indicating multiple species. As the amount of boron reagent increased to ca. 2.0 equivalents, the NMR spectrum of the reaction mixture became much cleaner and simpler, indicating complete consumption of the Na-enolate and clean formation of the boron-enolate.

A typical experimental procedure is as follows

Preparation of (−)-DIP-Cl solution: Into a 25 mL round bottom flask under a nitrogen atmosphere was added 4.4 mL anhydrous THF and cooled to −10°C. Then (+)-(α)-pinene (>97 ee%, 2.47 mL, 15.5 mmol) was added followed by addition of monochloroborane dimethyl sulfide complex (0.77 mL, 7.4 mmol). The reaction mixture was aged at −10°C for 30 min and gradually warmed to room temperature overnight, affording ca. 1 M solution of (−)-DIP-Cl that was used in the chiral aldol reaction without further purification.

Chiral aldol reaction: Into a solution of 1 M NaHMDS (5.0 mL, 5.0 mmol, in THF) at −30°C was added a solution of *i*Pr ester **1c** (1.14 g, 3.5 mmol) in 7 mL THF via syringe over 20 min. The resulting solution was cooled to −65°C and aged for 30 min. Then the preformed (−)-DIP-Cl solution (total amount as indicated above) was added to the reaction mixture over 30 min. After aging at −65°C for 45 min, acetalaldehyde (1.0 mL, 17.8 mmol) was added and the reaction mixture was aged at −65°C for 30 min. Then 20 mL 0.5N HCl was added. The two-layer mixture was extracted with 30 mL EtOAc and the organic extract was further washed with 10 mL brine. Analysis of the crude product indicated a dr of 48:1 and 92% ee. Quantitative assay showed ca. 92% yield of the aldol product. Purification of the crude product by silica gel chromatography with 6:1 hexanes/EtOAc solvent afforded (*RS*)-isomer **2c** in 89% isolated yield.[15]



In attempts to expand the scope of the chiral aldol reaction, only limited success was achieved. Good stereoselectivity was obtained for the aldol reaction of the tetrahydrofuran carboxylate **12**, giving aldol product **13** in 72% isolated yield with dr = 54 and 93% ee. (Stereochemistry of product **13** was assigned to be *RS* based on analogy to the chromane system.) However, we observed poor selectivity with several acyclic ester and lactone/lactam substrates such as **14**, **15**, and **16** etc.[16] Based on these studies, it seems that two conditions are necessary for the stereoselective aldol reaction. The first is high E/Z stereocontrol in the formation of the boron-enolate, which usually translates into high diastereoselectivity. The second is matching substrate with proper chiral ligand on the boron, which translates into high enantioselectivity. The easy accessibility of alkaline metal enolates and the availability of DIP-Cl in both enantiomerically pure forms make this protocol practical and attractive.

In summary, highly stereoselective aldol reactions between chromane ester **1** and acetaldehyde or benzaldehyde were observed. Detailed investigations revealed that the exceptional stereoselectivity is a combined result of excellent control of enolate geometry and a good match between substrate and chiral ligand on the boron reagent.

Acknowledgements

The authors thank Dr. C. Welch and Ms. J. Chilenski for separation and analysis of the chiral aldol products, and Dr. D. Mathre for X-ray analysis.

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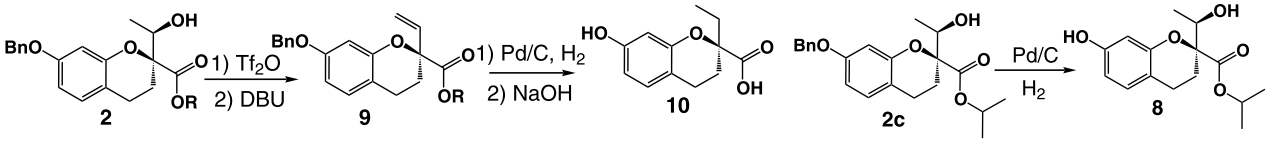
13. Various methods were explored for the chiral aldol reaction with limited success before we discovered the boron-mediated aldol reaction, which gave far superior results. The methods investigated included chiral Lewis acid-catalyzed Mukaiyama type aldol through silyl ketene acetal **7** and chiral aldol reaction of Zn-enolate with chiral diamine or aminoalcohol ligands etc.
14. The absolute stereochemistry at the quaternary center of the product **2** was determined by conversion of **2** into chiral acid **10** and comparison with a standard sample of **10** with known stereochemistry. The relative stereochemistry of **2c** was determined by X-ray crystallography of derivative **8**.[14]



15. Characterization data for aldol products. **2c**, oil, ^{1}H NMR ($CDCl_3$) δ 7.3–7.5 (5H, m), 6.91 (1H, d, $J=8.3$ Hz), 6.61 (1H, d, $J=2.5$ Hz), 6.54 (1H, dd, $J=2.5$, 8.3 Hz), 4.95–5.15 (3H, m), 4.09 (1H, q, $J=6.5$ Hz), 2.70 (1H, ddd, $J=2.6$, 5.9, 16.6 Hz), 2.60 (1H, ddd, $J=5.3$, 12.4, 16.6 Hz), 2.35 (1H, ddd, $J=2.6$, 5.3, 10.8 Hz), 1.92 (1H, ddd, 5.9, 10.8, 12.4 Hz), 1.32 (3H, d, $J=6.5$ Hz), 1.24 (3H, d, $J=6.3$ Hz), 1.16 (3H, d, $J=6.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 171.5, 158.5, 154.4, 137.2, 129.7, 128.6, 127.9, 127.5, 113.6, 108.7, 102.6, 83.6, 71.5, 70.1, 69.4, 25.2, 21.8, 21.7, 21.6, 17.4. HRMS: calcd for $C_{22}H_{27}O_5$ (M+H): 371.1853. Found 371.1857.

The chiral aldol product **2c** (0.8 g) was dissolved in 100 mL EtOH and 0.2 g 10% Pd/C was added. The mixture was hydrogenated at 40 psi and room temperature for 12 h to give the free phenol **8** cleanly. Purification of the phenol by silica gel chromatography (hexanes:EtOAc = 1:1) afforded 0.7 g **8** as a white solid. ^{1}H NMR ($CDCl_3$) δ 6.86 (d, 1H, $J=8.2$ Hz), 6.47 (d, 1H, $J=2.5$ Hz), 6.38 (dd, 1H, $J=8.2$, 2.5 Hz), 5.07 (sep, 1H, $J=6.3$ Hz), 4.10 (q, 1H, $J=6.4$ Hz), 2.68 (ddd, 1H, $J=16.4$, 5.6, 2.6 Hz), 2.58 (ddd, 1H, $J=16.4$, 12.8, 5.6 Hz), 2.34 (ddd, 1H, $J=13.2$, 5.6, 2.6 Hz), 1.91 (ddd, 1H, $J=13.2$, 12.8, 5.6 Hz), 1.32 (d, 3H, $J=6.4$ Hz), 1.25 (d, 3H, $J=6.3$ Hz), 1.17 (d, 3H, $J=6.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 171.5, 155.1, 154.2, 129.7, 113.1, 108.4, 103.5, 83.5, 71.4, 69.4, 25.1, 21.6, 21.5, 21.4, 17.1. Mp 160.9°C. Further crystallization in 1:1.5 $CHCl_3$/toluene provided X-ray quality crystals. X-Ray analysis showed it to be the (*RS*) isomer. Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.24. HRMS: calcd for $C_{15}H_{20}O_5Na$ (M+Na): 303.1203. Found 303.1209.

Reaction with benzaldehyde: Product **4c**, 86% isolated yield, dr = 33, and 97% ee. **4c**: oil, ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (m, 10H), 6.86 (d, 1H, $J=8.4$ Hz), 6.69 (d, 1H, $J=2.5$ Hz), 6.52 (dd, 1H, $J=2.5$, 8.4 Hz), 5.05 (s, 2H), 5.0–5.2 (m, 2H), 2.58 (m, 2H), 2.30 (m, 1H), 1.61 (m, 1H), 1.24 (d, 3H, $J=6.3$ Hz), 1.14 (d, 3H, $J=6.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 171.4, 158.5, 154.2, 138.6, 137.2, 129.6, 128.6, 128.4, 128.2, 128.0, 127.9, 127.6, 113.5, 108.6, 102.7, 83.7, 78.0, 70.1, 69.7, 26.1, 21.8, 21.6, 21.5. HRMS: calcd for $C_{27}H_{29}O_5$ (M+H): 433.2010. Found 433.2011.

Furan isopropyl ester **12** with benzaldehyde: Product **13** was obtained in 72% isolated yield with dr = 54 and 93% ee. **13**: oil, ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5H), 5.05 (m, 1H), 4.97 (s, 1H), 3.93 (m, 1H), 3.83 (m, 1H), 2.03 (m, 2H), 1.72 (m, 1H), 1.49 (m, 1H), 1.22 (d, 6H, $J=6.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 173.5, 139.0, 127.9, 127.8, 127.6, 89.0, 76.6, 69.7, 68.9, 31.6, 25.0, 21.6, 21.5. HRMS: calcd for $C_{15}H_{20}O_4Na$ (M+Na): 287.1254. Found 287.1264.
16. The aldol reaction was neither diastereo- nor enantioselective for **14** and **15**, aldol reaction of **16** gave ca. 50% yield with modest selectivity: dr = 7 and 45% ee.