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# Stereoselective Aldol Reaction of Glutarimides Using Pseudo $C_2$ Symmetry

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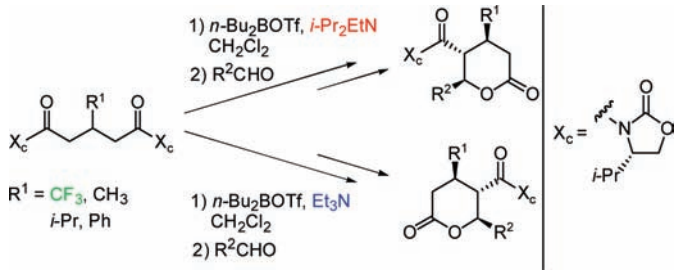
## ABSTRACT




**The boron aldol reaction of $\beta$-substituted glutaric imides bearing an oxazolidinone-based auxiliary proceeds with excellent diastereoselectivity; switching the tertiary amine employed between *i*-$Pr_2$EtN or $Et_3$N affords enantiomeric lactone product.**

In recent years, trifluoromethyl-containing compounds have been growing in importance and value because of their strategic applications in the medicinal and functional materials fields.[1] We have pursued the development of the syntheses of chiral $CF_3$-containing compounds by use of desymmetrization of $\beta$-$CF_3$-substituted glutaric acid derivatives; their pseudo $C_2$ symmetry enables concomitant stereocontrol of two or three chiral centers by a single nucleophilic reaction of the corresponding enolates toward aldehydes.[2−4] However, very limited numbers of investigations of this methodology have appeared, even for nonfluorinated substrates.[5] We report herein that the boron enolate derived from the $\beta$-substituted glutarimides with the oxazolidinone-based auxiliary reacted with aldehydes in excellent diastereoselectivity and led to facile access to enantiomeric lactones **2** and **3**, just by switching the tertiary amine employed between *i*-$Pr_2$EtN and $Et_3$N. Another important point is that this efficient route was also successfully applied to the corresponding nonfluorinated substrates **5a**−**5c** with similarly high levels of stereocontrol and chemical yield.

We first examined conditions for formation of the boron enolate from the imide **1** and its reactivity toward benzaldehyde as the representative electrophile (Table 1). To a solution of **1** in $CH_2Cl_2$ were added 1.1 equiv of *n*-$Bu_2$BOTf and 1.2 equiv of *i*-$Pr_2$EtN in this order at 0 °C, and the reaction mixture was stirred for 0.5 h at the same temperature. Upon addition of 1.3 equiv of benzaldehyde at −80 °C to this enolate, four diastereomers of **4** were formed in 34% combined yield (entry 1, Table 1 and Figure 1). When

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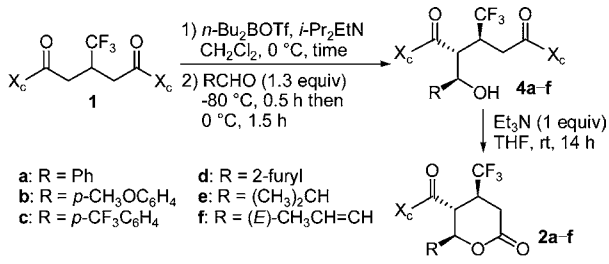
**Table 1.** Lewis Acid Catalyzed Aldol Reactions and Lactonizations




| entry | *n*-$Bu_2$BOTf (equiv) | *i*-$Pr_2$EtN (equiv) | time (h) | R | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 1.1 | 1.2 | 0.5 | Ph | 34[b] |
| 2 | 2.2 | 2.3 | 0.5 | Ph | 77[b] |
| 3 | 3.0 | 3.3 | 0.5 | Ph | 77[b] |
| 4 | 4.0 | 4.4 | 0.5 | Ph | 87[b] |
| 5[c] | 4.0 | 4.1 | 0.5 | Ph | 80 |
| 6[c] | 4.0 | 4.1 | 0.5 | *p*-$CH_3OC_6H_4$ | 86 |
| 7[c] | 4.0 | 4.1 | 0.5 | *p*-$CF_3C_6H_4$ | 79 |
| 8[c] | 4.0 | 4.1 | 0.5 | 2-furyl | 84 |
| 9[c] | 4.0 | 4.1 | 1.0 | *i*-Pr | 0 |
| 10[c,d] | 2.2 | 2.3 | 1.0 | *i*-Pr | 69 |
| 11[c] | 2.2 | 2.3 | 1.0 | (*E*)-$CH_3CH$=CH | 60 |

[a] Isolated yield of the sole stereoisomer **2** unless otherwise noted. [b] A combined $^{19}$F NMR yield of diastereomer mixtures of alcohols **4a** and lactones **2a**. [c] Lactonization condition: the reactant **4** and $Et_3N$ (0.4 mmol, 1 equiv) were stirred in THF at rt for 14 h. [d] $TiCl_4$ (0.52 mmol) was used.

**1** was treated with more than 2 equiv of *n*-$Bu_2$BOTf and *i*-$Pr_2$EtN, **4a** was obtained with good to excellent selectivity in good yields by way of bisenolate (entries 2−4), and the best yield was attained by use of 4.0 equiv of *n*-$Bu_2$BOTf and 4.4 equiv of *i*-$Pr_2$EtN with contamination of the corresponding lactone **2a** (entry 4, Table 1 and Figure 1).[6] Because the amount of the latter compound was increased by cyclization during the workup, we attempted lactonization *in situ*. After several experiments, we found that stirring of the crude reaction mixture overnight in the presence of an equimolar amount of $Et_3N$ in THF at room temperature led to complete conversion of the initial aldol product **4a** to the desired lactone **2a** as a single 3,4-*anti*-4,5-*anti* stereoisomer. Fortuitously, the low solubility of **2a** facilitated its isolation.

Next, we examined the scope and limitation of this reaction (Tables 1 and 2). Electron-rich, electron-deficient, and heteroatom-containing aromatic aldehydes were reacted with **1** in a similar manner to form lactones **2** in 79−86% yields (Table 1, entries 5−8). No reaction was observed for aliphatic aldehydes such as isobutyraldehyde and crotonaldehyde with recovery of **1** unchanged (Table 1, entry 9). We reasoned that an excess amount of *n*-$Bu_2$BOTf and *i*-$Pr_2$EtN caused enolization of these aldehydes, which would result in their complete deactivation and no reaction. This was supported by the fact that when 2.2 equiv of *n*-$Bu_2$BOTf and small excess amounts (2.3 equiv) of *i*-$Pr_2$EtN were used, the desired

(6) In all cases yields and stereoselectivity were determined for the crude mixtures by integration of the $^{19}$F NMR signals.

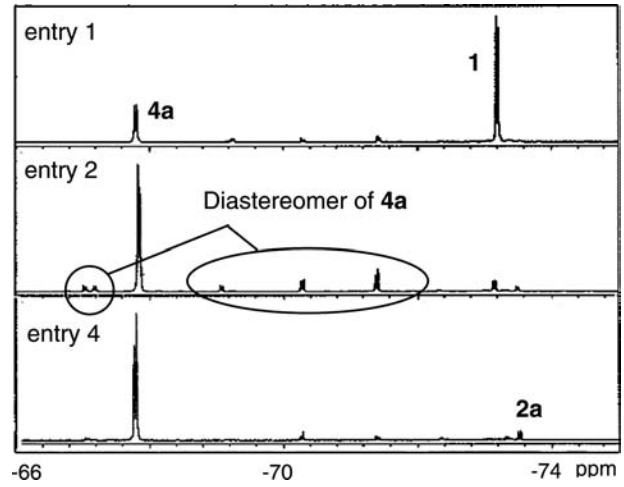


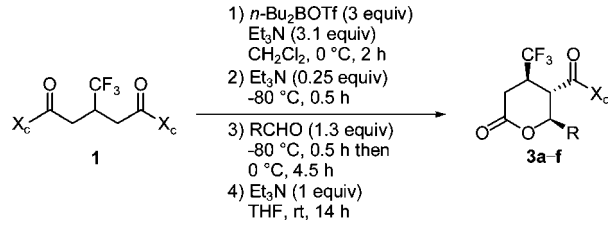

**Figure 1.** Part of the 282.65 MHz $^{19}$F NMR spectra (in $CDCl_3$ at 25 °C) of crude products before lactonization.

products were obtained in good yields (Table 1, entries 10 and 11). While addition of $TiCl_4$ demonstrated the effective improvement of the reactivity for isobutyraldehyde (Table 1, entry 10), this was not the case for crotonaldehyde, which yielded only a complex mixture.

During the course of optimization of this reaction, we discovered that switching the tertiary amine from *i*-$Pr_2$EtN to $Et_3N$ conveniently afforded stereoisomeric aldol products again with high selectivity.

Although this phenomenon was irreproducible at first, a detailed exploration of the reaction conditions highlighted the importance of quantity of the amine employed. The addition of small amounts of the amine before condensation

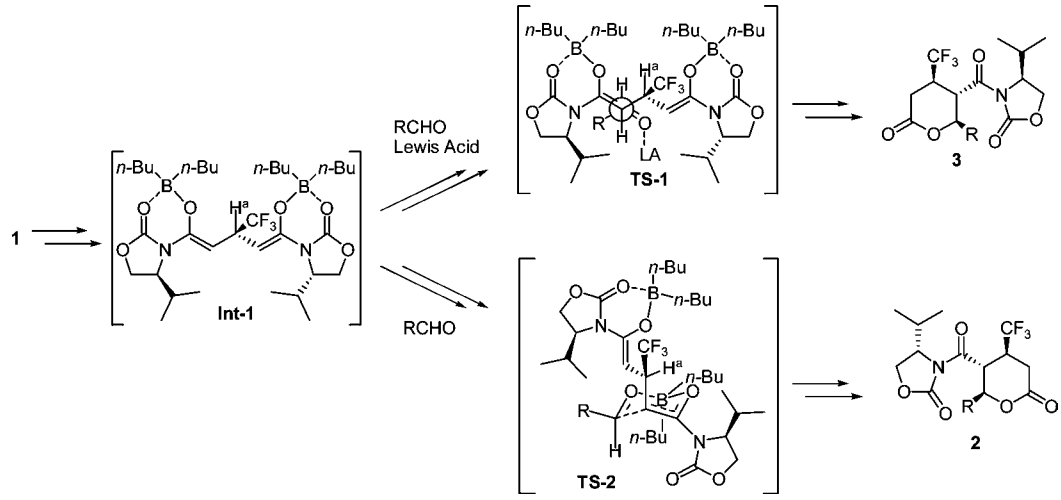
**Table 2.** Evans Aldol Reactions and Lactonizations[a,b]




| entry | R | product | yield (%)[c] |
|---|---|---|---|
| 1 | Ph | **3a** | 77 |
| 2 | *p*-$CH_3OC_6H_4$ | **3b** | 77 |
| 3 | *p*-$CF_3C_6H_4$ | **3c** | 75 |
| 4 | 2-furyl | **3d** | 60 |
| 5 | *i*-Pr | **3e** | trace |
| 6 | (*E*)-$CH_3CH$=CH | **3f** | trace |

[a] Enolization condition: a mixture of imide **1** (0.4 mmol), *n*-$Bu_2$BOTf (0.88 m), and $Et_3N$ (1.24 mmol) was stirred in $CH_2Cl_2$ at 0 °C for 2 h, and the solution was stirred for further 0.5 h at −80 °C after addition of $Et_3N$ (0.1 mmol). [b] Lactonization condition: $Et_3N$ (0.4 mmol) was added, and the mixture was stirred at rt for 14 h. [c] Isolated yield of the sole stereoisomer **3**

**Scheme 1.** Proposed Reaction Mechanism of Lewis Acid Catalyzed Aldol and Evans Aldol Reaction

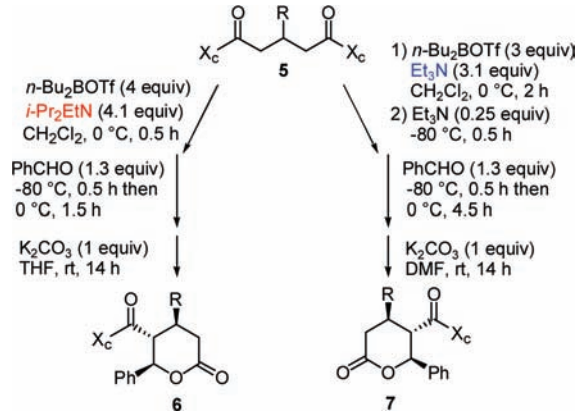



with aldehydes, which removerd excess *n*-$Bu_2$BOTf, was essential for a successful outcome. This protocol prevented *n*-$Bu_2$BOTf acting as a Lewis acid and ensured that the reaction proceeded *via* the well-known rigid six-membered cyclic transition state. This process afforded lactones **3**, or their enantiomers, in good isolated yield and as single stereoisomers highly reproducibily (Table 2). Absolute configurations of these compounds were unambiguously determined by X-ray crystallographic analysis.[7] Although aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde, *p*-(trifluoromethyl)benzaldehyde, and 2-furaldehyde gave the corresponding lactones **3** in good to high yields (Table 2, entries 1−4), the reaction with aliphatic aldehydes such as isobutyraldehyde and crotonaldehyde did not proceed at all (Table 2, entries 5 and 6).

Finally, the imides **5** including nonfluorinated groups at the 3 position instead of a $CF_3$ group were treated with benzaldehyde under the same conditions. Like the trifluoromethylated glutarimide **1**, these gave the corresponding lactones **6** or **7** in a tertiary amine-dependent manner in high yields and with slightly lower but still excellent diastereoselectivities, except for the case of **5d** (Table 3).[8] This result clearly demonstrated the versatility of the present pathway, which worked excellently for nonfluorinated and fluorinated substrates alike.

The reaction mechanism proposed is illustrated in Scheme 1. Bis-*Z*-enolate **Int-1** could be exclusively generated from the imide **1** when exposed to *n*-$Bu_2$BOTf and tertiary amine.[9] As a result of the well-accepted 1,3-allylic strain concept, the $H^a$ atom should occupy the same plane of both enolate double bonds. If the activation of aldehydes is performed by Lewis acids such as *n*-$Bu_2$BOTf or $TiCl_4$, the acyclic transition state **TS-1** would be the pathway of choice and aldehydes would approach to the boron enolate from the least

**Table 3.** Two Different Aldol Pathways for Nonfluorinated Substrates[a]




| entry | R in **5** | amine | lactone | yield (%)[b] | dr[c] |
|---|---|---|---|---|---|
| 1 | $CH_3$ (**a**) | *i*-$Pr_2$EtN | **6a** | 77 | 93:7 |
| | | $Et_3N$ | **7a** | 83 | 90:10 |
| 2 | *i*-Pr (**b**) | *i*-$Pr_2$EtN | **6b** | 91 | 96:4 |
| | | $Et_3N$ | **7b** | 89 | 91:9 |
| 3 | Ph (**c**) | *i*-$Pr_2$EtN | **6c** | 75 | 93:7 |
| | | $Et_3N$ | **7c** | 83 | 95:5 |
| 4 | OTBS (**d**) | *i*-$Pr_2$EtN | **6d** | *d* | |
| | | $Et_3N$ | **7d** | *d* | |

[a] The reactions were carried out in 0.4 mmol scale. [b] Combined isolated yield of two diastereomers after chromatography, and stereochemistry of the minor diastereomer was not determined. [c] Ratios were determined by integration of the $^1$H NMR peaks spectrum of the two diastereomer mixture after column chromatography. [d] Complex mixture.

(7) Crystal data for **2a**, **3c**, and **6a**: CCDC 681300−681302 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(8) The *n*-$Bu_2$BOTf-mediated *syn*-aldol reaction of *N*-acyl-2-oxazolidinone containing a *β*-methoxy group could only proceed with difficulty, and the oxazolidinone substrate produced *anti*-aldol product in high diastereoselectivity and moderate yield; see: Hajra, S.; Giri, A. K.; Karmakar, A.; Khatua, S. *Chem. Commun.* **2007**, 2408–2410.

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hindered *si* face of the *pro-S* enolate, avoiding the unfavorable steric interaction between the oxazolidinone isopropyl and $CF_3$ groups.[10,11] However, when no extra Lewis acids are present in the mixture (*vide supra*), this reaction is believed to proceed *via* the six-membered chairlike transition state **TS-2** where nonactivated aldehydes would occupy the least hindered *re* face of the *pro-R* enolate. The observed difference in stereoselectivity with the two amines may be a consequence of formation of an excess *i*-$Pr_2EtN$•*n*-$Bu_2BOTf$ complex, which was completely formed at 25 °C within 30 min. This would act as a more potent Lewis acid than $Et_3N$•*n*-$Bu_2BOTf$ because the bulkier amine *i*-$Pr_2EtN$ would form a much weaker B···N interaction with *n*-$Bu_2BOTf$ compared to the one made with $Et_3N$.[12] The higher Lewis acidity of the former complex would allow *i*-$Pr_2EtN$ to follow the acyclic TS **TS-1**, while **TS-2** would be more favorable when $Et_3N$ was employed, leading to predominant formation of **2** and **3**, respectively.

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(12) For a recent example of *anti* diastereoselective aldol reaction using $Et_2BOTf$ and *i*-$Pr_2EtN$, see: Fraser, B. H.; Gelman, D. M.; Perlmutter, P.; Vounastos, F. *Tetrahedron: Asymmetry* **2006**, *17*, 1152–1155.

Under the reaction conditions, the "double" aldol reaction at both sites was not observed at all, which could be understood as a result of inherently lower reactivity of the resultant monoenolate and increased steric compression around the reaction site after the first aldol reaction, working cooperatively.

In conclusion, it has been demonstrated that aldol-based desymmetrization of $\beta$-substituted glutarimides **1** and **5** with the chiral oxazolidinone auxiliary is an extremely efficient method for constructing $\delta$-lactones containing three consecutive chiral centers with a high level of stereocontrol. The significant advantage of this desymmetrization approach is that either enantiomeric lactone can be easily synthesized by selection of the appropriate amine, *i*-$Pr_2EtN$ or $Et_3N$, without recourse to time-consuming procedures such as changing the chiral auxiliaries to their enantiomers. Studies on the scope and limitation of the desymmetrization of these glutaric imides with other electrophiles are currently being investigated in our laboratory.

**Supporting Information Available:** Experimental procedures and characterization data for all new prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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