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Asymmetric routes in the reaction of cyclic ketene ortho ester with aldehydes involving the use of chiral Lewis acid

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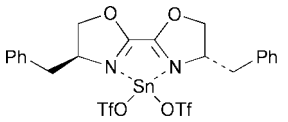
Enantio- and diastereoselective synthesis of *threo* 2 and *erythro* 3 was accomplished by the conversion of 1 with aldehydes promoted by chiral borane 10; enantioselctivities range from 45–95% ee, while diastereoselectivities vary from 4.3–49 : 1 with 8 different aldehydes.

The availability of efficient synthetic methods for achieving absolute stereocontrol *via* a catalytic process in the construction of acyclic systems is of considerable current interest in synthetic chemistry.[1] During the past decades, substantial progress has been made, and as a result, many enantioselective synthetic routes have been extensively explored.[2] Nonetheless, only a few methods exist to establish all stereoisomers selectively, despite their plentiful synthetic potential.[3] Recently we have disclosed novel synthetic methods for the synthesis of both diastereomers **2** and **3** in high levels of stereoselectivity from the ketene ortho ester **1** with an aldehyde mediated by a Lewis acid catalyst (Scheme 1). This highly stereocontrolled transformation for the synthesis of **2** involves the diastereoselective generation of a carbon–carbon bond to form **4** and introduction of ester functionality from hydrolysis of the ortho ester intermediate **4**.[4] A reversal of diastereoselectivity to obtain **3** was realized by an epimerization of intermediate **4** under basic conditions.[5]

The general feature of this transformation is the synthesis of highly functionalized compounds from simple starting materials in high diastereoselectivity. The characteristic feature of this chemical transformation process has encouraged us to carry out further investigation concerning absolute stereoselection to establish all four stereoisomers. This research led to the discovery of efficient enantioselective routes in forming *threo* **2** and *erythro* **3** with high levels of diastereoselectivity and moderate to excellent enantioselectivity. In the course of this study, the absolute configuration of the major component was unambiguously established by comparison with a synthetic sample.

From the mechanistic perspective, major functions for the stereoselectivity are immediately discernable in the catalytic process. Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, the following pathway could be a probable stereochemical route on the basis of product population. We reasoned that if **5** could be a stereochemical model, then it might be possible to control facial selectivity by a chiral catalyst in a predictable fashion. Preliminary investigations for the stereochemical transformation of **1** with aldehyde indicated that the conversion to the corresponding **2** could not be satisfied with a variety of chiral Lewis acids including BINOL–Ti(IV), and bisoxazoline complexes with Cu, Sc, Zn mainly due to a lack of reactivity.[6] However, bisoxazoline–$Sn(OTf)_2$ complex **6**[7] and chiral borane **7**[8] could be a chiral promoter for the enantioselective conversion. Initial attempts to convert **1** to **2** with benzaldehyde in the presence of **6** (20 mol%) at −20 °C in CH_2Cl_2 were met with limited success, providing moderate enantioselectivity with poor diastereoselectivity (47% yield, 76% ee, 2 : 1 dr). A survey of modifications of ligands provided no significant advantages in terms of reactivity and stereoselectivity. On the other hand, reaction of **1** with benzaldehyde in the presence of **7** occurred readily at −78 °C; this chiral Lewis acid was generally superior and chosen for systematic studies.



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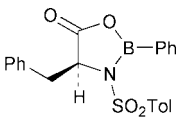

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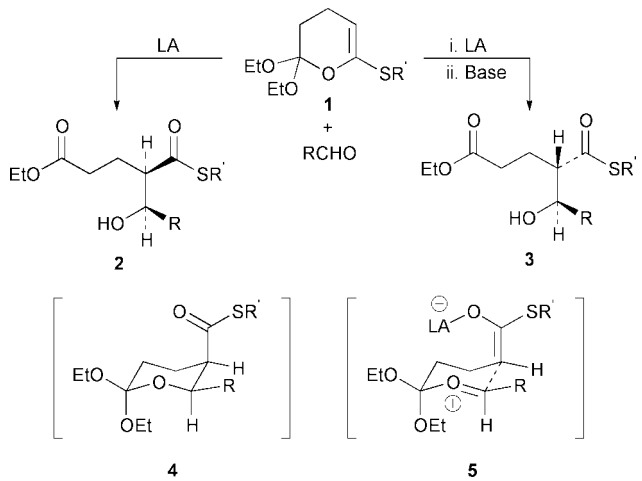
Reaction of **1** (R′ = Et) with benzaldehyde in the presence of 20 mol% of **7** for 24 h afforded **2** and **3** in 57% isolated yield in a ratio of 72 : 28 with 77% ee. The lack of diastereoselectivity was attributed to acidic media in the reaction mixture causing epimerization of reaction intermediate **4** for long reaction times. Thus, diastereoselectivity was enhanced by the use of 1 eq. of **7** within 2 h, providing 78% yield in 91 : 9 dr with 83% ee (−78 °C for 2 h in CH_2Cl_2). After surveying numerous modifications of *N*-sulfonylamino acids, the remarkable observation has been made that the use of **10** as a chiral promoter led to the best results in terms of chemical yields and stereoselectivities (PhCHO, 95% yield, **2**:**3** = 97 : 3, 93% ee): (a) chiral Lewis acid **10** was prepared from the reaction of **8** with **9**[9] at 23 °C for 2 h;[10] (Scheme 2) (b) reaction at −78 °C for 30 min in CH_2Cl_2 were the optimal conditions, while with longer reaction times, especially more than 2 h, diminished diastereoselectivity was observed; (c) R^1 = Et in **1** was generally superior to others such as Me and Pr^i in terms of chemical availability and efficacy. It is worthy of note that efficient recovery of the chiral ligand **8** was made after work up procedure.

Under optimal conditions, the reaction was performed by the addition of **1** (R^1 = Et) to a solution of benzaldehyde and **10** in CH_2Cl_2 at −78 °C. After stirring for 30 min, the reaction mixture was quenched with 2 N aqueous HCl followed by work up and silica gel chromatography to afford *threo* **2a** with *erythro* **3a** in a ratio of 97 : 3 as judged by 500 MHz ^{1}H NMR of crude products. With the notion that this protocol might lead to a general and efficient method for the synthesis of multifunctional



Scheme 1

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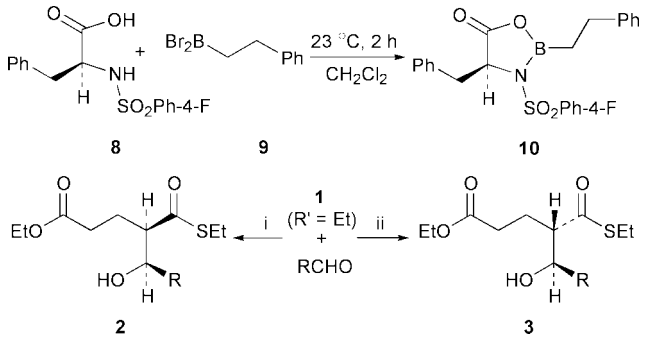

Scheme 2 *Reagents and conditions*: i, **10**, −78 °C, 30 min, CH_2Cl_2; ii, **10**, −78 °C , 2 h, CH_2Cl_2, then DBU, pyridine, −78 °C–23 °C, 24 h.

substances, we set out to determine the scope of reaction with various aldehydes. Indeed, the method is successful with a variety of aldehydes and affords products of high diastereomeric purity with moderate to good enantioselectivies as summarized in Table 1. The ee values were determined by 500 MHz ^{1}H NMR of the corresponding (+)-MTPA ester and/or HPLC or GC analysis using a chiral column as indicated in Table 1.

Table 1 Diastereo- and enantioselective synthesis of **2**[a]

Entry	RCHO	Product	dr (**2**:**3**)[b]	Ee (%)[c]	Yield (%)[d]
1	Ph	**a**	97:3	93	95
2	4-Br-Ph	**b**	95:5	95	88
3	CH_3	**c**	92:8	91	78
4	$PhCH_2$	**d**	95:5	88	77
5	$PhCH_2CH_2$	**e**	94:4	90	83
6	C_6H_{13}	**f**	92:8	84	77
7	PhCH=CH	**g**	81:19	74	79
8	Me_2CH	**h**	88:12	45	61

[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 30 min.[b] Diastereomeric ratio was determined by the analysis of 500 MHz ^{1}H NMR spectra of crude products (all entries) and by GC analysis using HP^{-1} (Hewlett-Packard, cross linked methyl siloxane, 25 m × 0.32 mm × 0.52 μm, entries 3, 4, 6, 8).[c] Ees were determined by preparation of (+)-MTPA ester derivatives, analysis by 500 MHz ^{1}H NMR spectra (entries 1,2,3,4,8) and by HPLC analysis using chiral column (Chiracel OD-H, 3–5% Pr^{i}OH in hexanes, entries 1,2,5,7) and by GC (FID, Chiral Dex-30, G-TA, gamma-cyclodextrin Trifluoroacetyl, 30 m × 0.32 mm, entries 3,6,8).[d] Yields refer to isolated and purified products.

With our research scope of the asymmetric synthesis of *threo* **2**, we turned our attention next to examine possibility of this approach for a reversal of diastereoselectivity.[5] Under optimal conditions, the reaction was performed by addition of **1** to **10** and benzaldehyde in CH_2Cl_2 at −78 °C. After 2 h at −78 °C, freshly distilled pyridine (20 eq.) and DBU (10 eq.) was added during which time a white precipitate was formed. After stirring for 30 min at −78 °C, the cooling bath was removed and the temperature was allowed to rise to 23 °C for 24 h.† After cooling to 0 °C, the reaction mixture was quenched with 2 N aqueous HCl in EtOH followed by work up and silica gel chromatography to afford *erythro* **3a** along with *threo* **2a** in a ratio of 95:5 as judged by 500 MHz NMR of crude products with virtually identical enantiomeric purity compared to that of **2a** in Table 1. In addition, parallel experiments were performed with a variety of aldehydes and the results are summarized in Table 2.

Absolute configuration of **3a** was unambiguously established by a comparison of synthetic samples as illustrated in Fig. 1.‡

In summary, this paper describes methodologies for the enantioselective and diastereoselective synthesis of **2** and **3** in a general and efficient way as a result of the present investigation because of the simplicity of the reaction and the ready availability and efficient recovery of the chiral ligand, and also, absolute configurations of products were unambiguously confirmed by the experiments.

Table 2 Diastereo- and enantioselective synthesis of **3**[a]

Entry	RCHO	Product	dr (**3**:**2**)	Ee (%)	Yield (%)
1	Ph	**a**	95:5	92	88
2	4-Br-Ph	**b**	96:4	95	73
3	CH_3	**c**	91:9	90	75
4	$PhCH_2$	**d**	94:6	86	81
5	$PhCH_2CH_2$	**e**	98:2	91	88
6	C_6H_{13}	**f**	95:5	81	74
7	PhCH=CH	**g**	91:9	71	68
8	Me_2CH	**h**	93:7	48	53

[a] Conditions for analysis of diastereo- and enatioselectivities were identical with Table 1.

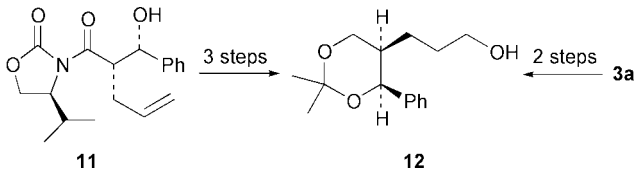

Fig. 1 Determination of absolute configuration.

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Notes and references

† It is important to report that the higher temperature especially over 50 °C for the epimerization of intermediate **4** resulted in seriously diminished chemical yields.

‡ Evans aldol product **11** (9:1 dr)[11] was converted to **12** by 3 steps [i, $LiAlH_4$, −78 °C–0 °C, THF; ii, $MeC(OMe)_2Me$, *p*TsOH (5 mol%), CH_2Cl_2; iii, 9-BBN, 0–23 °C THF, then NaOH, H_2O, 40% overall]. Compound **3a** was also transformed to **12** [i, $LiAlH_4$, −78 °C–0 °C, THF; iii, $MeC(OMe)_2Me$, *p*TsOH (5 mol%), CH_2Cl_2, 67% overall]. Both synthetic **12** from **11** and **3a** has not only the same specific rotation sign but also the identical NMR spectra of (+)-MTPA ester derivatives.

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