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Stereoselective Synthesis of Functionalized *trans*-2,5-Disubstituted Tetrahydrofurans

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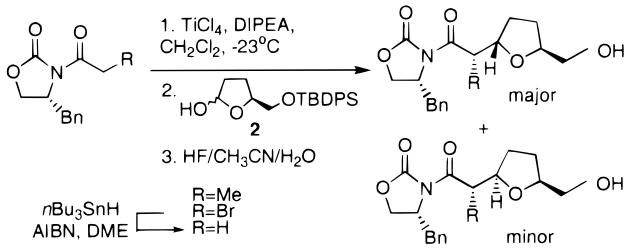
ABSTRACT

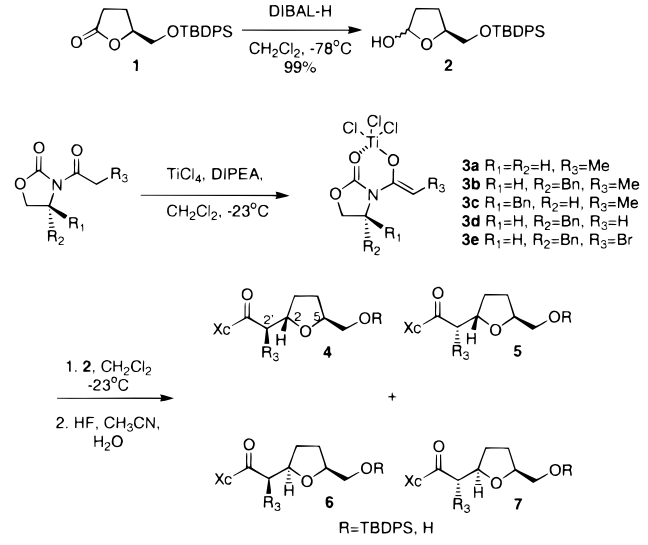


The addition of the titanium enolates of *N*-acetyl, *N*-propionyl, and *N*-bromoacetyl (*R*)-oxazolidin-2-ones to γ-lactol 2, derived from (*S*)-glutamic acid, afforded *trans*- and *cis*-2,5-disubstituted tetrahydrofurans (*trans*/*cis* ratio: R = H, 2:1; R = Me, 8:1; R = Br, 10:1) after desilylation with aqueous HF/CH_3CN. Chromatographic separation and $LiBH_4$ reduction allowed the efficient preparation of the corresponding *trans*-2,5-disubstituted tetrahydrofuran diols and the recovery of the chiral auxiliary.

The stereoselective synthesis of 2,5-disubstituted tetrahydrofuran rings has received much attention since they occur as building blocks in many interesting natural products such as cytotoxic polyethers[1] and acetogenins.[2] The Lewis acid-promoted substitution at the anomeric center of 5-substituted-γ-lactols via an intermediate oxocarbenium ion is one of the strategies explored;[3] however, studies involving the stereoselective addition of chiral and prochiral nucleophiles to cyclic oxocarbenium ions are scarce. The usefulness of the stereochemically defined titanium enolate of chiral oxazolidinones in aldol[4] and in the addition to cyclic *N*-acyliminium ions[5] reactions led us to explore their reactions with chiral oxocarbenium ion derived from lactol **2**, a useful building block for the asymmetric synthesis of tetrahydrofuran-containing natural products. In this paper we report the utility of chiral oxazolidin-2-ones in the stereoselective synthesis of 2,5-disubstituted tetrahydrofuran rings with the simultaneous formation of two new stereogenic centers.

Initially, we examined the addition of achiral titanium(IV) enolate **3a**[6] to lactol **2**, derived from (*S*)-glutamic acid[7] (Scheme 1). The chlorotitanium enolate was generated by the sequential addition of 1.1 equiv of $TiCl_4$ and 1.1 equiv

Scheme 1



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of diisopropylethylamine to a cold solution (−23 °C) of the corresponding N-substituted oxazolidin-2-one in CH_2Cl_2 followed by the dropwise addition of a CH_2Cl_2 solution of lactol **2**. A 4:4:1:1 mixture of the four possible adducts (*trans*-**4a**:*trans*-**5a**:*cis*-**6a**:*cis*-**7a**) was isolated in 61% yield (Table 1). The major isomers *trans*-**4a** and *trans*-**5a** were

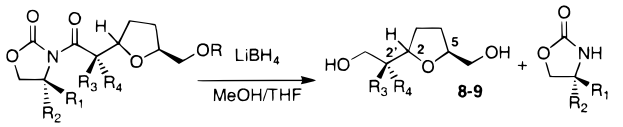
Table 1. Diastereoselective Reactions of Chlorotitanium Enolates **3a**−**e** with Lactol **2**

enolate	R	R_1	R_2	R_3	adducts (ratio)	yield (%) ($^3J_{2',2}$ (Hz))
3a	TBDPS	H	H	Me	**4a**:**5a**:**6a**:**7a** (4:4:1:1)[b]	61 (**4a**, 6.8; **5a**, 9.3)
3b	H	H	Bn	Me	**5b**:**7b** (8:1)[a]	58[c,d] (**5b**, 9.3)
3c	H	Bn	H	Me	**4c**:**6c** (3.5:1)[a]	55[c,d] (**4c**, 6.8; **6c**, 9.3)
3d	H	H	Bn	H	**4/5d**:**6/7d** (2:1)[b]	57[c,d]
3e	H	H	Bn	Br	**5e**:**7e** (10:1)[b]	57[c,d] (**5e**,9.5; **7e**, 6.0)

[a] Determined by GC analysis. [b] Determined in the crude mixture by ^{1}H NMR spectroscopy (500 MHz) in $CDCl_3$. [c] Yields (two steps) after purification of the crude mixture by filtration through a pad of silica gel. [d] TBDPS group deprotection with HF/CH_3CN, except for **5e**/**7e** where HF/pyridine was used.

separated by column chromatography on silica gel, and their configurations were determined after conversion to the corresponding diols (TBDPS deprotection and reduction with $LiBH_4$, Table 2) and were compared with those of the diols

Table 2. Reduction of *N*-Acyloxazolidin-2-ones



adduct	R	R_1	R_2	R_3	R_4	diol	yield (%)[a]
4a[b]	TBDPS	H	H	Me	H	(2′*S*,2*S*)-**8**	90
4c	H	Bn	H	Me	H	(2′*S*,2*S*)-**8**	87
5a[b]	TBDPS	H	H	H	Me	(2′*R*,2*S*)-**8**	89
5b	H	H	Bn	H	Me	(2′*R*,2*S*)-**8**	88
6c	H	Bn	H	Me	H	(2′*S*,2*R*)-**8**	88
4/5d	H	H	Bn	H	H	(2*S*)-**9**	89

[a] Chiral oxazolidin-2-ones recovered in good yields (85−95%). [b] Adducts **4a** and **5a** were desilylated (HF, CH_3CN, H_2O) prior to reduction with $LiBH_4$.

derived from *trans*-**4c** and *trans*-**5b** (structure established by X-ray diffraction analyses, Figure 1).

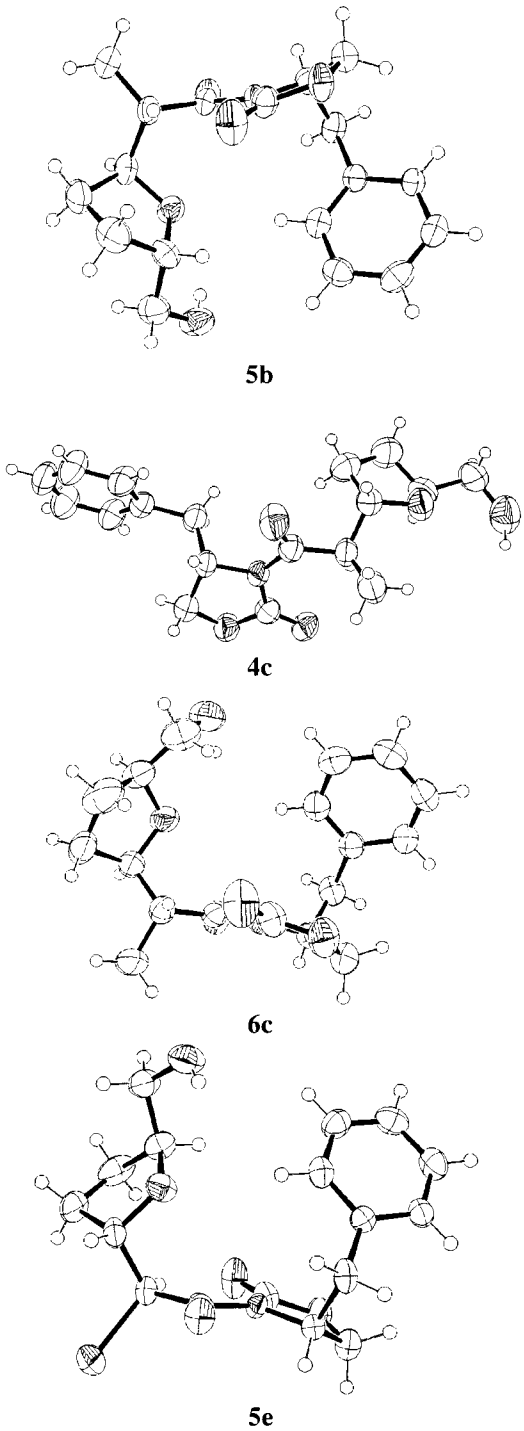


Figure 1. ORTEP drawing of **5b**, **4c**, **6c**, and **5e**.

The lack of facial discrimination observed for achiral titanium enolate **3a** led us to examine the impact of chiral

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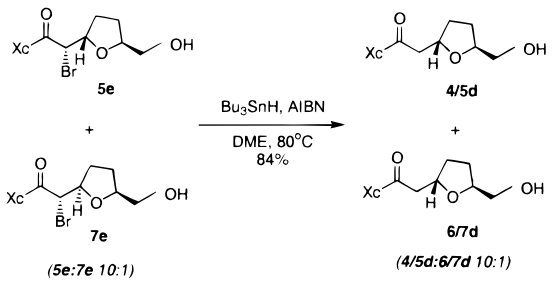
(2) (a) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423. (b) Hoppe, R.; Scharf, H. D. *Synthesis* **1995**, 1447.
(3) Schmitt, A. S.; Reissig, H. U. *Chem. Ber.* **1995**, *128*, 871 and references therein.
(4) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(5) Pilli, R. A.; Alves, C. F.; Böckelmann, M. A.; Mascarenhas, Y. P.; Nery, J. G.; Vencato, I. *Tetrahedron Lett.* **1999**, *40*, 2891.
(6) Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283.

titanium(IV) enolates **3b** and **3c**[6] in the process. The addition of a CH_2Cl_2 solution of lactol **2** to titanium(IV) enolates **3b** and **3c** afforded only two diastereoisomers in 8:1 and 3.5:1 ratios, respectively (Table 1), revealing complete facial control by the chiral titanium enolate (only products arising from the addition to the *re* face of enolate **3b** and to the *si* face of enolate **3c** were observed). After TBDPS group deprotection with HF/CH_3CN, the diastereoisomers *trans*-**5b**, *trans*-**4c**, and *cis*-**6c** were separated by column chromatography and fully characterized. The stereochemistry of the minor isomer *cis*-**6c** was established by X-ray diffraction analysis (Figure 1). The diastereoisomeric 2,5-disubstituted tetrahydrofurans were readily distinguishable by ^{1}H NMR spectroscopy as the vicinal coupling constants ($^3J_{2',2}$) for the protons in the newly created stereogenic centers were diagnostic of their relative stereochemistry: $J = 9.3$ Hz for *trans*-**5b** and *cis*-**6c** and $J = 6.8$ Hz for *trans*-**4c** (Table 1).

Unfortunately, low diastereoselection (2:1) was observed in the addition of chiral titanium(IV) enolate derived from *N*-acetyl oxazolidin-2-one **3d**, revealing the importance of the substitution pattern of the enolate in the stereochemical course of the reaction.[8] Preparatively useful access to *trans*-**4/5d** was eventually secured in 84% yield through the *n*-Bu_3SnH reduction of bromo derivative *trans*-**5e** (structure established by X-ray difraction analysis, Figure 1) formed in 57% yield (10:1 diastereoisomeric mixture) from the corresponding titanium enolate **3e** (Scheme 2).

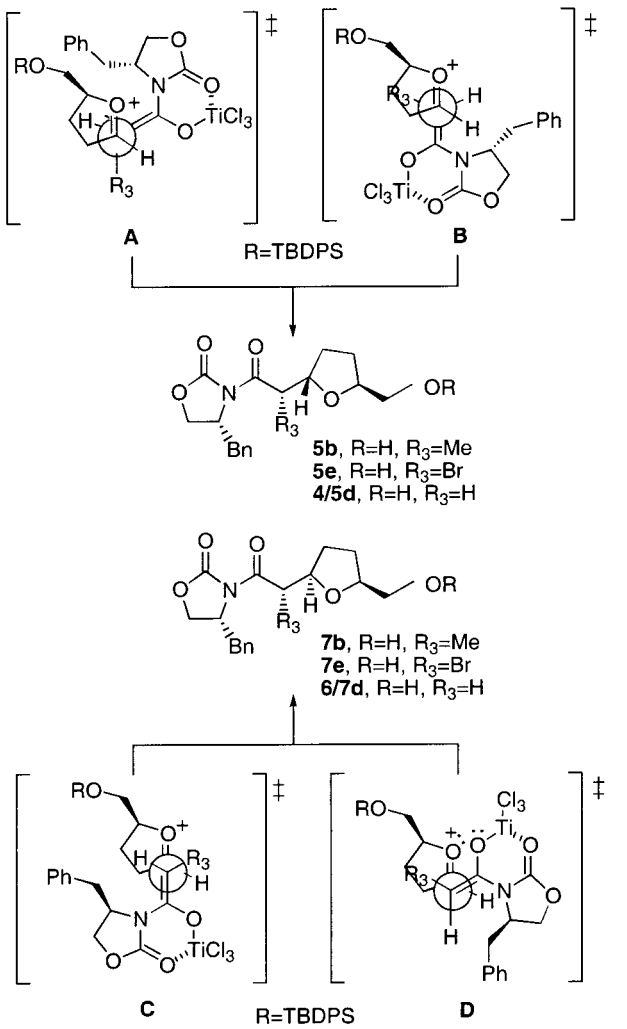
Scheme 2



The reaction of enolates **3a**−**e** with the oxocarbenium ion derived from **2** can produce up to four diastereoisomeric 2,5-disubstituted tetrahydrofurans. The stereochemical outcome of the reactions investigated seems to be ruled by an open transition state with the favored approach of the less hindered face of a *Z*-configured internally coordinated titanium enolate to the more sterically available *re* face of the intermediate oxocarbenium ion (Scheme 3).

The preferential formation of *trans*-**5b** can be rationalized either through a synclinal (**A**, Scheme 3) or an antiperiplanar

Scheme 3



(**B**) approach of the titanium enolate *re* face to the *re* face of the oxocarbenium ion derived from **2**. While the former arrangement minimizes the steric interaction between the methyl group of the enolate and the methylene groups of the oxocarbenium ion, the latter one alleviates steric interaction between the oxazolidinone ring and the oxocarbenium ion.

The formation of the minor isomer *cis*-**7b** requires the antiperiplanar approach of the titanium enolate *re* face to the sterically hindered oxocarbenium ion *si* face (**C**). In this case, the synclinal approach (**D**) seems to be less favored due not only to steric interactions involving the methyl group in the enolate and the -CH_2OTBDPS group of the oxocarbenium ion but also to the electronically disfavored interaction involving nonbonded electron pairs in closely spaced oxygen atoms (Scheme 3).

The improved diastereoselection in the addition of bromoenolate **3e** (*trans*-**5e**:*cis*-**7e** = 10:1) results from severe steric interaction between the bromine atom and the -CH_2OTBDPS group in the synclinal approach leading to *cis*-**7e** as well as to the repulsive electronic interactions in the antiperiplanar approach involving nonbonded electron pairs of the bromine

(7) (a) Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 3887. (b) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049.

(8) Low levels of asymmetric induction were also observed in the aldol reaction of boron and titanium enolates of *N*-acetyloxazolidin-2-ones: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

atom and the oxygen atom of the oxocarbenium ion. Accordingly, the decrease in the diastereoselection observed for **3d** is accounted for on the basis of the lack of a discriminating group at the nucleophilic center of **3d** (R = H) and denotes the poor facial selectivity of the oxocarbenium ion.

In summary, 2,5-disubstituted tetrahydrofuran rings were prepared through the addition of titanium(IV) enolate **3a**−**e** to the oxocarbenium ion derived from lactol **2**. We have shown that the levels of the diastereoselection in the reactions are modulated by the nature of the R_3 group in the enolate and by the intrinsic chirality of the oxazolidin-2-one. Compounds *trans*-**5b**, *trans*-**4**/**5d**, and *trans*-**5e** were prepared in good yields and diastereoisomeric ratio, and their utilization in the asymmetric synthesis of natural 2,5-*trans*-disubstituted tetrahydrofurans is under investigation.

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Supporting Information Available: General procedures and characterization data for compounds **4a**, **5a**, **5b**, **4c**, **6c**, **4**/**5d**, **5e**, **(2′*R*,2*S*,5*S*)-8**, **(2′*S*,2*S*,5*S*)-8**, **(2′*S*,2*R*,5*S*)-8**, and **(2*S*,5*S*)-9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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