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Enantioselective [2,3]Wittig Rearrangement Involving a Chiral Boron Enolate Terminus

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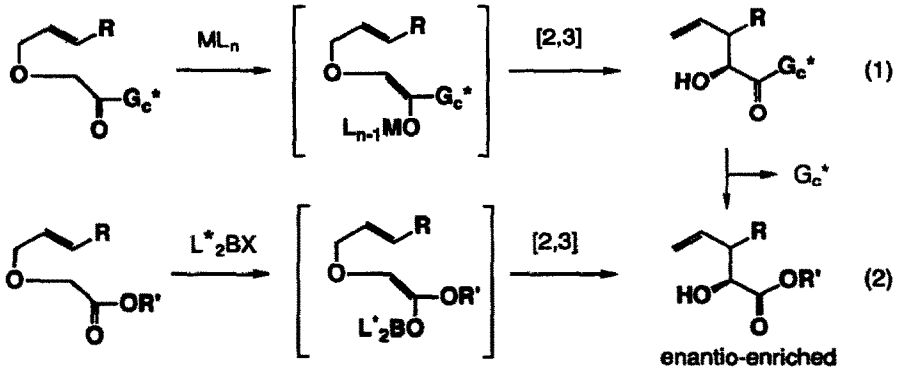
Abstract: *The first enantioselective version of the ester enolate [2,3]Wittig rearrangement is described which involves a chiral boron enolate with a chiral bis-sulfonamide ligand to provide a high enantioselectivity(>95%ee), along with a high threo diastereoselectivity.*

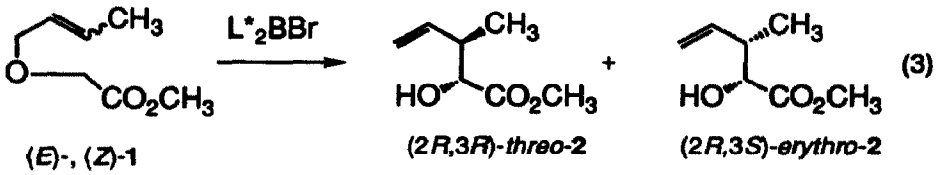
The [2,3]Wittig sigmatropic rearrangement enjoys wide application in organic synthesis.[2] Of special value among many variants is the "enolate [2,3]Wittig" rearrangement that involves an enolate as the migrating terminus to eventually provide α-hydroxy-β-alkyl carboxylic acid derivatives of biological and synthetic importance.[2] Recently several asymmetric versions of the enolate [2,3]Wittig process have been developed which involve a chiral enolate terminus generated from optically active substrates or auxiliaries (eq 1).[3] However, no example has been reported of the ***enantioselective*** version involving a chiral ligand-bound ester enolate.[4] Herein we wish to report the first example of the enantioselective version of the ester enolate [2,3]Wittig process (eq 2).[5] The key to this success is the use of a chiral boron enolate terminus containing a chiral bis-sulfonamide as the controller ligand (L*).

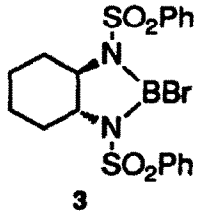


After several attempts,[6] we chose as a chiral ligand on boron chiral bis-sulfonamides, easily prepared from

commercially available (1*R*,2*R*)-1,2-diaminocyclohexane[7a] and (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane[7b], and prepared the chiral boron reagents **3** and **4** from BBr_3 and the chiral bis-sulfonamides according to the literature procedure.[7c]

First, we studied the rearrangement of (*E*)-**1** using the boron reagents **3** and **4** (eq 3). Thus, (*E*)-**1** was treated with a slight excess of **3** or **4** in the presence of Et_3N in CH_2Cl_2 at -50 °C to afford a diastereomeric mixture of the enantio-enriched α-hydroxy-β-methyl ester **2** in moderate yields.[8] The results are summarized in Table 1 (entries 1-4).





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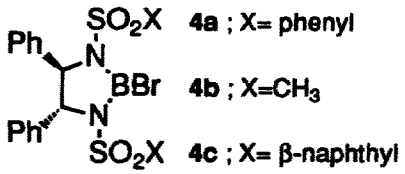


As seen in Table 1, the present rearrangements uniformly exhibit (*R*)-preference at C-2 of **2** and *threo* preference between the two new chiral centers. Interestingly, the yields and the levels of enantio- and diastereoselection vary critically with the structure of chiral ligands. While the use of **3** leads to the modest levels of enantioselectivity (62%ee) and *threo* selectivity (68%), the use of **4a** provides the highest degrees of enantioselectivity (96%ee) and *threo* selectivity (83%). Of particular interest is the relatively high *E*→*threo* selection observed here, which is in sharp contrast to the high *E*→*erythro* selections previously reported for the [2,3]Wittig rearrangements of (*E*)-**1** involving lithium,[9] zirconium,[10] tin,[11] titanium,[11] and dialkylboron [12] enolates.

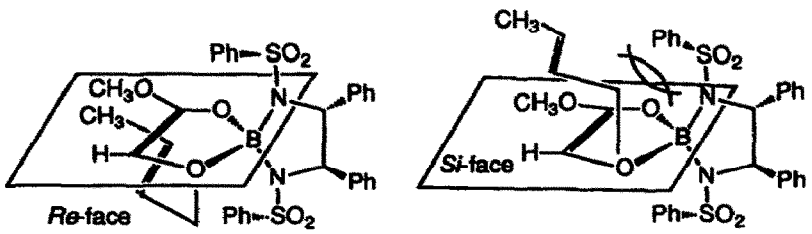
Next, we turned our attention to the rearrangement of (*Z*)-**1**. Under the same conditions as described above, (*Z*)-**1** was treated with **4a** to afford a stereoisomeric mixture of **2**, again, in a high enantioselectivity (94%ee) and *threo* selectivity (84%) (entry 5). These findings indicate that, surprisingly enough, the present rearrangements of (*E*)- and (*Z*)-**1** exhibit the identical senses of both enantio- and diastereoselection regardless of the crotyl geometry, suggesting that the stereo-directing power of the chiral ligand is much stronger than that of the substrate geometry.

Although we have no definitive explanation at present for the unusual *threo* selection owing to the great complexities of this process, the observed sense of enantioselection (2*R*) might be interpreted as follows. The enolization leads to the metal-chelated (*E*)-enolate which undergoes the [2,3]-shift preferentially from the bottom side (*re*-face) as depicted in formura **A**, where the steric repulsion between the crotyl and phenyl groups would be minimized.

Table 1. Eantioselective Rearrangements of (*E*)- or (*Z*)-1

Entry	Substrate	L^*_2BBr	%Yield	*threo*:*erythro* [a]	%ee [b]	Config.[c]
1	(*E*)-1	**3**	69	68:32	62 (*threo*)	2*R*,3*R*
					40 (*erythro*)	2*R*,3*S*
2	(*E*)-1	**4a**	66	83:17	96 (*threo*)	2*R*,3*R*
					71 (*erythro*)	2*R*,3*S*
3	(*E*)-1	**4b**	57	63:37	90 (*threo*)	2*R*,3*R*
					68 (*erythro*)	2*R*,3*S*
4	(*E*)-1	**4c**	27	66:34	90 (*threo*)	2*R*,3*R*
					55 (*erythro*)	2*R*,3*S*
5	(*Z*)-1	**4a**	56	84:16	94 (*threo*)	2*R*,3*R*
					38 (*erythro*)	2*R*,3*S*

(a) Determined by ^{1}HNMR analysis. (b) Determined by HPLC analysis of the MTPA esters (see ref 13). (c) Assigned by LIS-NMR analysis as described in our previous paper (ref 3a).



In summary, we have developed the first enantioselective version of the ester enolate [2,3]Wittig rearrangement which involves a chiral ligand-bound boron enolate to provide the α-hydroxy-β-methyl ester in a high enantio- and *threo*-selectivity. Futher efforts are in progress to prove this interesting process and to apply the present methodology to natural product synthesis.

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6. Initial attempts using $[(+)\text{-Ipc}]_2BX$ (X=Cl, Br, I, OTf) failed; no [2,3]Wittig product was obtained.
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8. **Typical Experimental Procedure**: To a solution of **4a** [prepared from (1*R*,2*R*)-1,2-*N*,*N*'-bis(benzenesulfonylamino)-1,2-diphenylethane (0.64g, 1.3 mmol)] in CH_2Cl_2 (3 mL) was added dropwise a solution of (*E*)-**1** (0.144g, 1 mmol) and Et_3N (0.21 mL, 1.5 mmol) in CH_2Cl_2 (2.5 mL) at -50 °C. The resulting mixture was stirred for 2 h at -50 °C and then quenched by addition of water at -50 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. Purification of the crude product by silica gel chromatography (hexane:ethyl acetate=13:1) gave **2** (0.095g, 66% yield).
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12. (a) Oh, T.; Wrobe, Z.; Rubenstein, S. M. *Tetrahedron Lett.* **1991**, *32*, 4647 [rearrangement with $(n\text{-Bu})_2BOTf$]. (b) Our unpublished result (ref 5). The rearrangement with 9-BBNOTf was found to exhibit 95% of *erythro* selection.
13. (*R*)-MTPA esters of **2** : HPLC [L-column ODS ; eluent , $CH_3CN : H_2O = 2 : 1$ (0.01*M* $AcONH_4$) ; flow rate 1.0 mL/min ; detection, 254 nm] : 2*S*,3*S* isomer, t_R=14.7 min ; 2*S*,3*R* isomer, t_R=15.2 min ; 2*R*,3*R* isomer, t_R=16.0 min ; 2*R*,3*S* isomer, t_R=16.6 min.

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