Organic LETTERS

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Stereocontrol in Asymmetric S_E' Reactions of γ-Substituted α,β-Unsaturated Aldehydes

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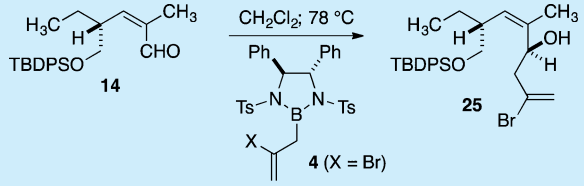
Supporting Information

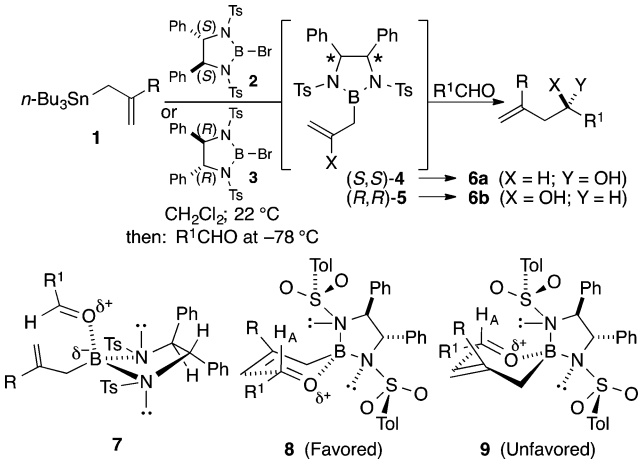
ABSTRACT: Asymmetric S_E' reactions of (*E*)- and (*Z*)-γ-substituted-α,β-unsaturated aldehydes have been studied for the stereocontrolled preparation of nonracemic alcohols. Mild exchange reactions of allylic stannanes provide access to chiral 1,3-bis-(tolylsulfonyl)-4,5-diphenyl-1,3-diaza-2-borolidines. These reagents display reactivity with the γ-substituted α,β-unsaturated aldehydes, which is characterized by matched and mismatched elements of stereocontrol. Computational analysis (using density functional theory) provides valuable insights to guide reaction development.



Asymmetric S_E' processes are widely recognized as important reactions for stereocontrolled synthesis.[1,2] Prior studies demonstrate impressive levels of stereoselectivity for reactions of allyl and crotyl nucleophiles with aliphatic aldehydes.[2] Corey first described (*R*,*R*)- and (*S*,*S*)-1,2-diamino-1,2-diphenylethane *N*,*N*-sulfonamides as chiral auxiliaries leading to B-allyl-1,3,2-diazaborolidines for asymmetric allylation.[3] Our subsequent studies have utilized the quantitative exchange of allylic stannanes with chiral bromoboranes to incorporate a wide variety of functionality into the reactive components.[4] In this manner, these asymmetric S_E' reactions have offered favorable chemoselectivity for key convergent operations, and this aspect has proven to be particularly beneficial for total syntheses of hennoxazole A,[5] amphidinolide K,[6] and leucascandrolide macrolactone.[7] An iterative strategy employing this asymmetric S_E' methodology provided a key contribution leading to the total synthesis of phorboxazole A,[8] and we have described the role of reinforcing diastereoselectivity resulting from the presence of vicinal chirality located within the allyl nucleophile for these S_E' reactions.[4b] In this paper, we describe diastereoselection for reactions of chiral, nonracemic *B*-allyl-1,3,2-diazaborolidines with (*E*)- and (*Z*)-γ-substituted-α,β-unsaturated aldehydes (Scheme 1). These processes proceed via matched and mismatched transition states (TS), achieving impressive stereocontrol in optimal cases. Computational analysis has provided useful insights for planning successful syntheses of functionalized, chiral allylic alcohols.

Studies have demonstrated a mild and quantitative exchange reaction of allylic stannanes **1** with the enantiomeric *B*-bromo-1,3,2-diazaborolidines (*S*,*S*)-**2** (or (*R*,*R*)-**3**) to produce nonracemic reagents such as (*S*,*S*)-**4** and (*R*,*R*)-**5**. Diastereofacial selectivity in the subsequent S_E' reaction of **4** to yield **6a** is induced upon coordination and activation of the aldehyde. Thus, the conformation of the heterocyclic auxiliary shown in **7**

Scheme 1. Asymmetric S_E' Reactions of *B*-Allyl-1,3,2-diazaborolidines 4 and 5



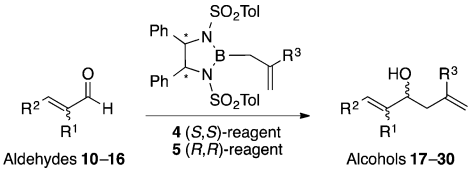
is dictated by the phenyl substituents as each toluenesulfonyl group is disposed *trans* to the adjacent aryl ring. Favored Zimmerman–Traxler TS **8** leads to the *S*-homoallylic alcohol **6a**. The unfavored arrangement in **9** projects nonbonded interactions of the tolyl substituent and the allylic methylene. The influence of hydrogen bonding of aldehydic hydrogen H_A with nitrogen or oxygen lone pairs in **8** may provide additional stability (vide infra).[9]

A wide variety of vinyl (C-2) substituents are tolerated (R = H, Br, Cl, $SiMe_3$, $SnBu_3$, CH_3). This site may also incorporate a complex carbon chain featuring additional elements of asymmetry and functionality. In these examples, the stereo-

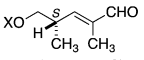
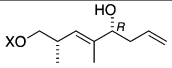
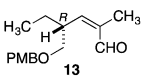
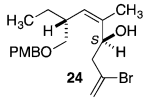
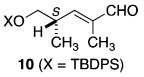
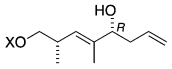
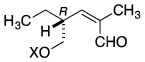
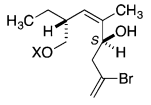
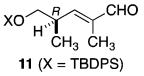
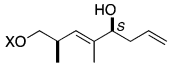
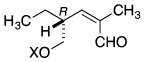
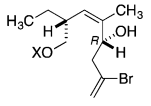
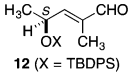
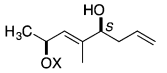
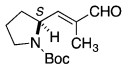
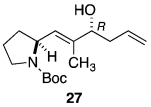
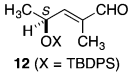
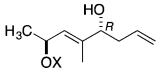
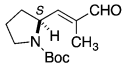
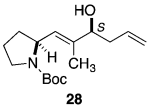
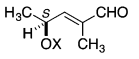
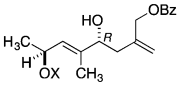
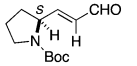
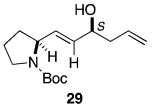
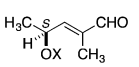
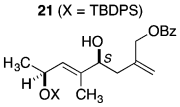
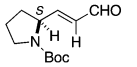
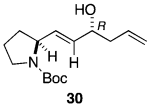
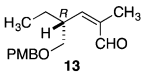
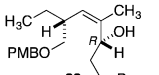
Received: November 19, 2013
Published: December 31, 2013

   dx.doi.org/10.1021/ol403351x | *Org. Lett.* 2014, 16, 468–471

Table 1. Reactions of α,β-Unsaturated Aldehydes with 4 and 5

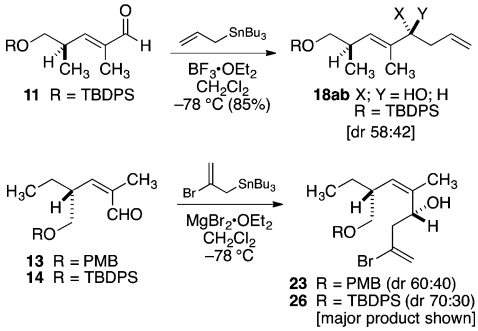


Aldehydes **10**–**16** Alcohols **17**–**30**

entry	aldehyde	allylborane[a]	major product	yield (dr *R*:*S*)	entry	aldehyde	allylborane[a]	major product	yield (dr *R*:*S*)
1	 **10** (X = TBDPS)	**5** (R^3 = H)	 **17** (X = TBDPS)	73% (99:1)[b]	9	 **13**	**4** (R^3 = Br)	 **24**	82% (45:55)[c]
2	 **10** (X = TBDPS)	**4** (R^3 = H)	 **17** (X = TBDPS)	72% (64:36)[b]	10	 **14** (X = TBDPS)	**4** (R^3 = Br)	 **25** (X = TBDPS)	82% (5:95)[c]
3	 **11** (X = TBDPS)	**4** (R^3 = H)	 **18** (X = TBDPS)	73% (6:94)[b]	11	 **14** (X = TBDPS)	**5** (R^3 = Br)	 **26** (X = TBDPS)	85% (99:1)[b]
4	 **12** (X = TBDPS)	**4** (R^3 = H)	 **19** (X = TBDPS)	75% (1:99)[b]	12	 **15**	**5** (R^3 = H)	 **27**	85% (99:1)[b]
5	 **12** (X = TBDPS)	**5** (R^3 = H)	 **20** (X = TBDPS)	76% (86:14)[b]	13	 **15**	**4** (R^3 = H)	 **28**	84% (36:64)[b]
6	 **12** (X = TBDPS)	**5** (R^3 = CH_2OBz)	 **21** (X = TBDPS)	75% (95:5)[b]	14	 **16**	**4** (R^3 = H)	 **29**	86% (6:94)[b]
7	 **12** (X = TBDPS)	**4** (R^3 = CH_2OBz)	 **22** (X = TBDPS)	74% (16:84)[b]	15	 **16**	**5** (R^3 = H)	 **30**	85% (97:3)[b]
8	 **13**	**5** (R^3 = Br)	 **23**	84% (94:6)[c]					

[a]Nonracemic boranes **4** and **5** (1.3 equiv) were generated by transmetalation of starting allylic stannanes in CH_2Cl_2 at 22 °C under argon. Aldehydes **10**–**16** (1.0 equiv) were added at −78 °C in CH_2Cl_2 with continued stirring over 2 h. For entries 12–15, excess **4** or **5** (2.6 equiv) was utilized. Products were isolated following flash silica gel chromatography. [b]Ratio (dr) was determined by analytical HPLC on a silica (2) column (250 × 4.6 mm; 5 μm) and elution with ethyl acetate in hexanes. [c]Ratio (dr) was determined by integration of selected signals in the ^{1}H NMR spectrum.

Scheme 2. Lewis Acid Catalyzed S_E' Reactions



genicity of the newly formed alcohol is imposed by the chiral auxiliary. Our recent studies of this methodology for natural product synthesis have provided surprising results for nonracemic γ-substituted-α,β-unsaturated aldehydes in which the chirality of the γ-carbon of the aldehyde affects the expected outcome. Detailed studies of α,β-unsaturated aldehydes in this asymmetric allylation have not been previously described, as the prior art includes only one example using (*E*)-cinnamyl aldehyde.[3] Thus, we have examined the scope of the reaction with a compilation of results in Table 1.

The (*S*,*S*)-allylborane **4** and the (*R*,*R*)-antipode **5** were conveniently generated by exchange using allyl-tri-*n*-butylstannane. In a similar fashion, nonracemic, C-2 substituted *B*-allylborolidines **4** and **5** (X = Br, and X = CH_2OBz; Bz = benzoate) were also prepared. A series of chiral, nonracemic aldehydes were available via standard techniques as outlined in the Supporting Information. The element of stereochemistry at the γ-position was readily incorporated from chiral pool precursors. Relevant cases of interest for our target initiated studies required α-methyl substitution in these (*E*)- and (*Z*)-α,β-unsaturated systems. Using a standard protocol, the reactions of Table 1 provided yields ranging from 72% to 86%. Our data indicate that stereochemistry of the γ-carbon in these aldehydes creates matched and mismatched processes with the appropriate boron auxiliary.

In most cases, our analyses of product mixtures were undertaken by HPLC using a silica (2) column (250 × 4.6 mm; 5 μm) and elution with ethyl acetate in hexanes. In some examples, the integration of selected proton signals in the NMR

dx.doi.org/10.1021/ol403351x | *Org. Lett.* 2014, 16, 468–471

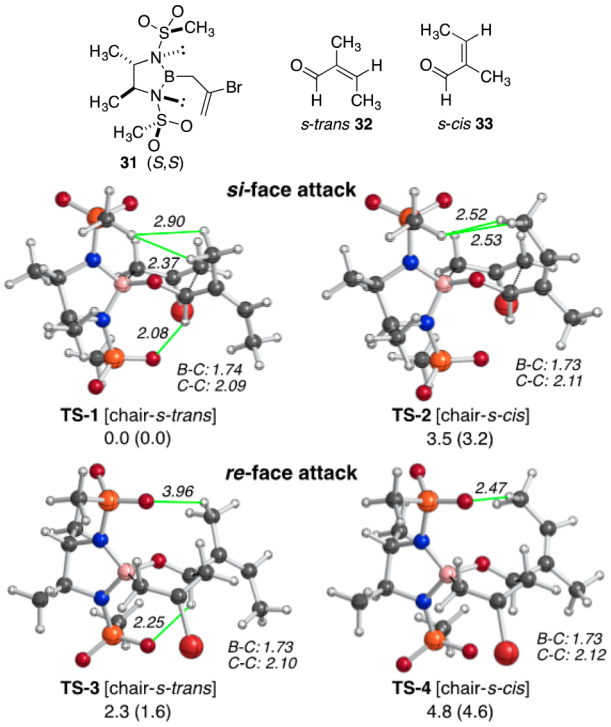


Figure 1. Relative energies of chairlike TS structures optimized with B3LYP/6-31G(d) in the gas phase (single point calculations with M06-2X/6-31G(d,p) in DCM (CPCM) in parentheses). All energies include ZPE from gas phase geometries. Selected distances are shown in angstroms.

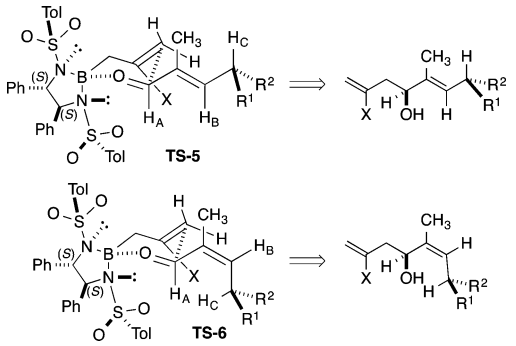
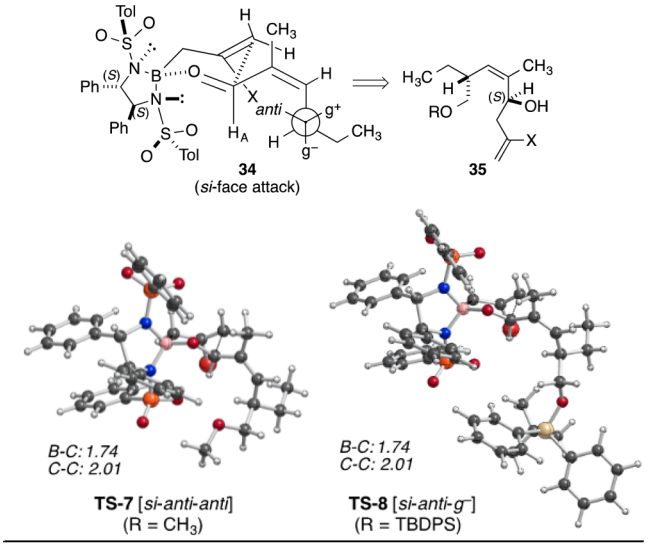


Figure 2. Matched TS arrangements of the (*S*,*S*)-borane.

spectra of crude products was used to estimate the ratio (dr) of diastereomers. Matched reactions (entries 1, 3, 4, 6, 8, 11, 12, and 15) often proceed with excellent diastereoselectivity. To examine the inherent bias of facial selectivity due to the presence of γ-chirality, aldehydes **11**, **13**, and **14** were utilized for Lewis acid catalyzed reactions with allyl-tri-*n*-butylstannane and 3-tri-*n*-butylstannyl-2-bromo-1-propene, respectively (Scheme 2). Allylation of (*E*)-**11** at −78 °C using boron trifluoride etherate gave alcohols **18ab** (dr 58:42 for *S*,*R*) in 85% yield. Likewise, the (*Z*)-aldehyde **13** (R = $CH_2C_6H_4OMe$) smoothly reacted with $MgBr_2$ etherate in CH_2Cl_2 to give a 60:40 ratio favoring the *R*-alcohol **23** (X = OH; Y = H). The presence of the larger diphenyl-*tert*-butylsilyl ether (TBDPS) in **14** led to a small improvement in the production of the *R*-isomer in the product mixture **26** (dr 70:30). A conformational bias of these *E*- and *Z*-aldehydes favors the formation of the *R*-allylic alcohol, and this preference is greatly accentuated in matched reactions involving the (*R*,*R*)-1,3,2-diazaborolidines **5**.



entry	TS	rotamer	$\Delta E^{\ddagger}$ ($\Delta H^{\ddagger}$)
1	**TS-7** *si*-face	anti	0.2 (0.0)
		g^-	2.2 (2.2)
		g^+	1.7 (1.6)
2	**TS-7** *re*-face	anti	0.0 (0.0)
		g^-	1.9 (2.0)
		g^+	1.4 (1.5)
3	**TS-8** *si*-face	anti	4.0 (4.1)
		g^-	0.0 (0.0)
		g^+	5.7 (6.0)
4	**TS-8** *re*-face	anti	4.3 (4.7)
		g^-	4.0 (4.4)
		g^+	5.1 (5.5)

Figure 3. TS analysis for reactions of (*S*,*S*)-borane with aldehydes **13** and **14** using ONIOM calculations: B3LYP/6-31G(d):HF/3-21G(d) (only phenyl groups were treated with HF). The 18 lowest TS structures were examined for each system, but only the lowest six for each are shown.

Interestingly, our experimental studies achieve equally impressive stereocontrol with *E*- and *Z*-aldehydes.

A computational study was undertaken to provide further insights.[10] Model system **31** was used to examine the effect of (a) chairlike versus boatlike TS arrangements; (b) reactivity of the *s-trans* conformer **32** versus *s-cis*-conformer **33** for a model aldehyde; and (c) *re*-face versus *si*-face attack. We find that, in general, (a) boatlike TS arrangements are 4−6 kcal/mol higher in energy than corresponding chairlike TS (see the Supporting Information), (b) the *s-trans* aldehyde conformer **32** leads to a lower energy TS, and (c) a clear preference for **TS-1** (Figure 1) derived from *si*-face attack using the chiral (*S*,*S*)-borane is predicted.[11]

Calculations have demonstrated the importance of minimizing $A^{1,3}$-strain. Thus, matched cases of γ-substituted *E*- and *Z*-aldehydes **10**−**15** (Table 1) involve **TS-5** and **TS-6** as displayed for the (*S*,*S*)-auxiliary in Figure 2. Hydrogens H_A, H_B, and H_C define a vertical plane in **TS-5** and **TS-6** in which the less sterically demanding substituent (R_1) projects into a region that is also occupied by conformers of the tolylsulfonyl group. This added feature generally accounts for high diastereoselectivity in the matched cases of Table 1.

A comparison of entries 9 and 10 (Table 1) shows that a change in the ether protecting group of homochiral aldehydes **13** (PMB) and **14** (TBDPS) can substantially restore high stereoselectivity in this mismatched reaction. In agreement with

dx.doi.org/10.1021/ol403351x | *Org. Lett.* 2014, 16, 468−471

experiment, calculations (Figure 3) predict low facial selectivity for formation of methyl ether **35** (R = CH_3), since this group avoids unfavorable steric interactions in both *si*- and *re*-face additions (not shown). Rotamers of the methylene bearing the ether substituent (OCH_3) favor an *anti*-relationship with respect to the vicinal ethyl group in **34** as shown in **TS-7** (Figure 3, entries 1 and 2).[12] However, the TBDPS ether of aldehyde **14** undergoes selective *si*-face attack by rotation to avoid nonbonded interactions with the sulfonyl substituent (g^- position in **34**) as shown in **TS-8** (entry 3) while the corresponding *re*-face TS (entry 4) is substantially destabilized by additional steric interactions, thereby predicting the observed diastereoselectivity.[13]

In summary, we have shown that asymmetric S_E' reactions of nonracemic γ-substituted *E*- and *Z*-α,β-unsaturated aldehydes feature matched and mismatched TS structures resulting from nonbonded steric interactions with chiral 1,3-bis(tolylsulfonyl)-4,5-diphenyl-1,3-diaza-2-borolidine auxiliaries. The minimization of 1,3-allylic strain in the aldehyde is a contributing factor. Generally, matched cases of nonracemic γ-substituted aldehydes and boranes led to excellent diastereoselection in the production of complex homoallylic alcohols. The choice of large protecting groups in proximite locations can result in unanticipated levels of diastereoselectivity in mismatched cases.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation (Grant No. CHE1055441). We acknowledge the UC Davis R. B. Miller Graduate Fellowship (O.G.).

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(10) All computations were carried out using *GAUSSIAN09, Rev. B.01*, Gaussian, Inc., Wallingford, CT, 2009. See the Supporting Information for details.

(11) Computations showed a 1.4−3.2 kcal/mol preference for arrangement **8** for various model α,β-unsaturated aldehydes. In these arrangements, the nitrogens are slightly distorted from trigonal planar, and the nitrogen lone pair is positioned to bisect the O−S−O bond angle of the sulfonyl group. For our TS arrangements, the nitrogen lone pair does not appear to provide a stabilizing interaction with the formyl hydrogen (>3Å). However, favorable interactions between the sulfonyl oxygens and the aldehydic hydrogen H_A may offer incremental stabilization in TS-1 and TS-3. See the Supporting Information for further discussions.

(12) Full optimizations in solvent (dichloromethane; CPCM;UFF) showed similar results.

(13) Full optimizations on the two lowest energy TS structures at the B3LYP/6-31G(d) level predict a lesser, but still substantial, energetic difference (~3 kcal/mol).