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Highly Functionalized *tertiary*-Carbinols and Carbinamines from the Asymmetric γ-Alkoxyallylboration of Ketones and Ketimines with the Borabicyclodecanes

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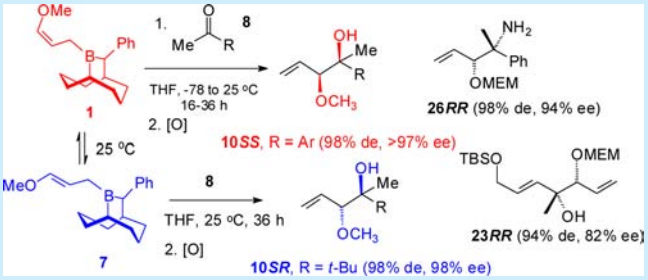
Supporting Information

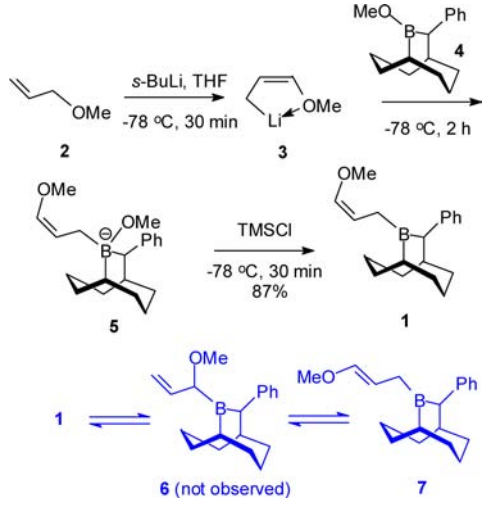
ABSTRACT: The first asymmetric γ-alkoxyallylboration of representative ketones provides β-alkoxy *tert*-homoallylic alcohols **10** whose diastereoselectivities range from 99% *syn* (acetophenone) to 99% *anti* (pinacolone) both with high ee (>95%). This distribution is attributable to the *c*/*t* isomerization of the BBD reagents and the greater reactivity of **7** vs **1** and of aromatic vs alkyl ketones. A ketone-based direct synthesis of a fostriecin intermediate and the *tert*-amine **26** are reported, each with high selectivities.



In the hierarchy of chemical conversions, allylboration meets all of the criteria for a "top-10" reaction, because it is enantio-, diastereo-, and regioselective in its construction of new C−C bonds and incorporates useful functional groups for further structural elaboration.[1] The utility of γ-alkoxyallylboranes in this regard, first demonstrated to be both diastereo- and regioselective by Hoffmann in 1981,[2] was upgraded to a highly asymmetric conversion by Brown in 1988 with his diisopinocampheylborane [$B(Ipc)_2$] reagents.[3] Many notable applications of this method have been forthcoming, including the cytotoxic agents, peloruside A by De Brabander[4] and palmerolide A by Nicolaou[5] to mention only two.[6] Aldimines are also useful substrates for these reagents.[7] Early on, it was recognized that the $B(Ipc)_2$-based reagents were ineffective for the allylboration of ketones or ketimines.[8] This has led to the use of aldehydes in the allyboration process followed by an oxidation/nucleophilic alkylation sequence which can give undesired diastereomeric products.[9a] While our 10-TMS-9-BBD reagents have proven to be highly competitive with the $B(Ipc)_2$ systems for both aldehydes and aldimines, we knew that they were ineffective for more hindered substrates.[10] Fortunately, the corresponding 10-Ph-9-BBD ligation has been found to be ideally suited to more hindered substrates such as ketones and ketimines.[11] As a new approach to highly functionalized *tertiary*-carbinols and carbinamines, we chose to examine the γ-alkoxyallylboration of these substrates with **1**.

The preparation of **1** was accomplished by the initial metalation of allyl methyl ether with *s*-BuLi in THF at −78 °C. The resulting *cis*-lithium reagent **3** is treated with *B*-methoxy-10-phenyl-9-BBD (**4**) at −78 °C, producing the organoborate complex **5**, which is demethoxylated with TMSCl to generate **1** in 87% yield (Scheme 1).

Scheme 1. Hoffmann Approach to 1



The *Z*-10-TMS counterpart of **1** (i.e., **11**) has remarkable configurational stability.[10b,i,k] The stereochemical integrity of the *B*-crotyl-9-BBD system is also remarkable, the behavior of which has been studied computationally.[12] However, this is not the case for **1**, which isomerizes much more rapidly [i.e., **1**/**7** (*Z*/*E*) = 84:16 (1 h); 74/26 (2 h); 54/46 (24 h)] at 25 °C. While this process was not allowed to reach equilibrium, MM calculations (Spartan 06) suggest that **7** is *ca.* 1 kcal/mol more stable than **1**. However, since **1** is generated at −78 °C, and it adds to **8a** at this temperature without significant *Z* → *E*

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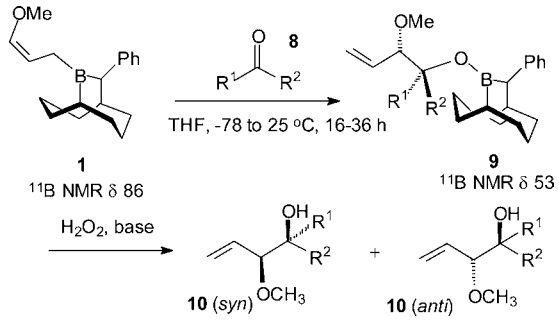
isomerization, we carried out the allylborations at −78 °C for 8 h. This was followed by a slow warm-up to 25 °C to result ultimately in the formation of **10**, employing overall reaction times of 16−36 h (Table 1).

Table 1. Asymmetric γ-Methoxyallylboration of Representative Ketones with 1[a]



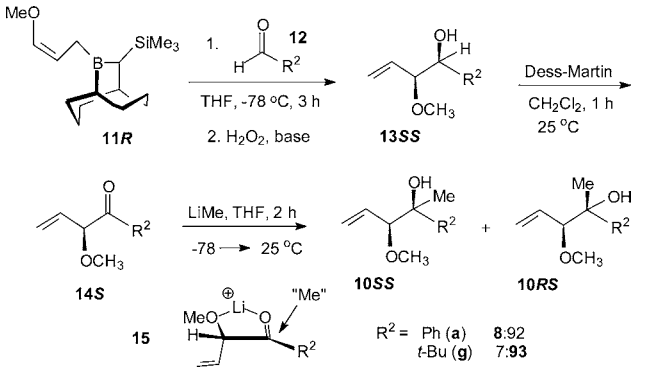
1	8, R^1, R^2	10[b]	dr[c]	ee[d]	config[e]
S	**a**, Me, Ph	78	99:1	97	*R,R*
S	**b**, Me, *p*-BrC_6H_4	88	99:1	98	*R,R*
S	**c**, Me, CH=CHPh	65	97:3	84	*R,R*
S	**d**, Et, Ph	68	85:15	84	*R,R*
R	**e**, Me, Et	60	73:26	70	*S,S*
R	**f**, Me, *i*-Pr	54	56:44	68	*S,S*
S	**g**, Me, *t*-Bu	45	1:99	98	*R,S*

[a]Reactions were maintained at −78 °C for 8 h and then, with the indicated reaction times, were allowed to slowly warm to 25 °C and stirred at rt **a,b,c** (8 h); **d** (12 h); **e,f,g** (28 h). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of the reaction mixture prior to purification. Analysis of the purified **10a−g** revealed dr values (*syn*/*anti*) of 99:1, 99:1, 98:2, 93:7, 78:22, 61:39, and 1:99, respectively. [d]Calculated from the ^{31}P NMR peak areas using the Alexakis method.[13] [e]The absolute stereochemistry of **10a** was assigned on the basis of the oxidation/nucleophilic addition protocol to the known secondary *threo*-β-methoxyhomoallylic alcohol (**13SS**).[10i] Others were assigned based on this determination for the stereochemistry of **10a**.

Knowing the susceptibility of **1** to *Z*/*E* isomerization to **7**, we were pleased with the high *syn* selectivity exhibited for the additions to aromatic and vinylic ketones **8a−c** which was understandably lower (i.e., 70% de) for the slower reacting ethyl ketone **8d**. This suggested that allylboration is faster than isomerization for the aromatic and unsaturated methyl ketones. This contrasts with the slower addition to aliphatic ketones, which shows a regular increase in the amount of *anti*-alcohol **10** with increasing R^2 bulk [i.e., 26, 44, 99 for **10e−g** (R^2 = Et, *i*-Pr, *t*-Bu), respectively]. The pinacolone example (**8g**) was particularly interesting because even after 36 h, the addition had reached only ca. 50% completion (monitored by ^{11}B NMR). It was the 98% product de which alerted us to the fact that **10g** may have had the *anti*, rather than *syn*, stereochemistry. Clearly, the formation of **10e,f** as diastereomeric mixtures would be otherwise enigmatic.

We chose to conduct several experiments to be certain of the absolute and relative stereochemical features of **10** since these systems were unknown. First, a competitive experiment employing **8a**, **8g**, and (±)-**1** in a 1:1:1 ratio revealed that *only* **8a** reacts, showing that pinacolone is particularly unreactive toward the *Z*-allylborane. Second, a trend was identified in the ^{13}C NMR of **10** for the signal of the methoxy carbon at ca. 56 ppm. The signals for the *syn* isomers are consistently upfield relative to their *anti*-counterparts. Third, because Hoffmann had found that his *E*-γ-methoxyallylboronates were more reactive than their *Z*-counterparts,[14] we allowed (±)-**1** to isomerize to an ∼50:50 *E*/*Z* mixture (**7**/**1**) in THF (24 h at 25 °C), followed by the addition of 0.5 equiv of either **8e** or **8f**, which gives the product **10e** or **10f**, respectively, as ca. 9:1 *anti*/*syn* mixtures consistent with the greater reactivity of **7** vs **1**. However, the addition of 1 equiv of **8b** to a 54:46 **1**/**7** mixture faithfully produces **10b** as a 55:45 *syn*/*anti* product mixture. Fourth, we conducted independent syntheses of the carbinols **10a** and **10g** to establish their *syn*- and *anti*-configurations, respectively, from the allylation process (Scheme 2).

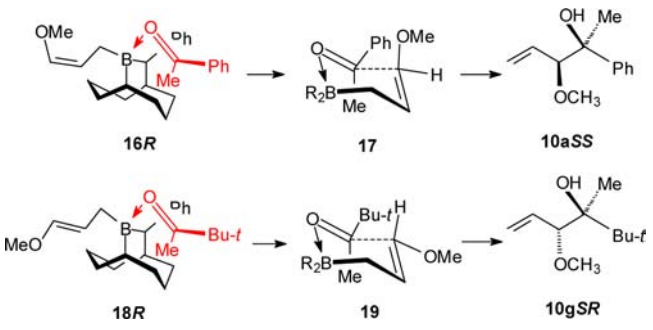
Scheme 2. Independent Syntheses of 10



To this end, the allylboration of PhCHO was carried out with the 10-TMS reagent **11*R***[10i] to provide the known **13a*SS***, which was oxidized with the Dess-Martin periodane to afford the nonracemic ketone **14a*S***. Addition of LiMe to the chelate **15** produces only a minor amount (8%) of the *syn*-isomeric alcohol **10a*SS***, the major product (92%) being the *anti*-isomer, **10a*RS***.[9,15] Conversion of these alcohols to their Alexakis esters[13] and ^{31}P NMR analysis of this mixture, compared to that from the allylboration of acetophenone, establishes the (*R,R*) absolute configuration of **10a*RR*** from the **1*S*** reagent. Repeating the sequence for **12g** (R^2 = *t*-Bu) employing (±)-**11** provides the *anti*-alcohol **10g*R**S*** as the major isomeric product (93%), which matched the diastereomer obtained from the γ-methoxyallylboration of **8g**. We were now confident that **7**, but not **1**, is reacting with pinacolone.

To explain the crossover from *syn* → *anti* stereochemistry in **10** with the lowering of ketone reactivity, it is helpful to examine the pretransition state model **16** vs **18** (Scheme 3). With increased *O*-basicity, flat aromatic (and vinylic) ketones

Scheme 3. Models to Explain the *syn vs anti* Diastereoselectivities



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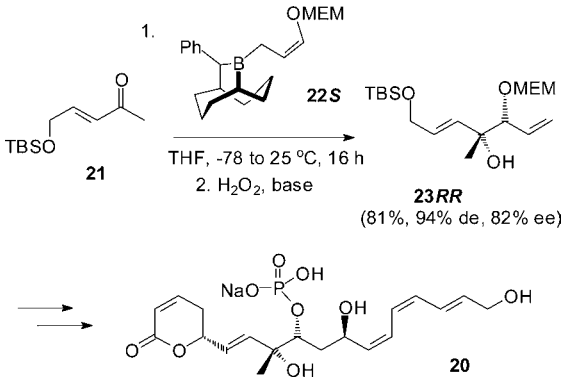
reach **17** and, with a lack of severe (Ph—OMe_{ax}) repulsions, proceed smoothly through **9**, ultimately producing the *syn*-alcohol **10a*SS*** from **1*R***. However, with pinacolone, more significant (*t*-Bu—OMe_{ax}) repulsions would exist in a transition state analogous to **17** (see Supporting Information). Thus, this ketone reacts exclusively with **7** after it forms from **1**, proceeding through **18**/**19**, ultimately giving the *anti*-product, **10g*SR*** from **7*R***. The stereochemistry of only C-3 changes with this phenomenon. The approach of **8** to the boranes is *anti B*-complexation, down with respect to the BBD ring and *cis* to the 10-Ph group in each case with 10*R*-boranes producing (2*S*)-alcohols.

An interesting application for this new method was suggested by the work of Boger who prepared the cytoxic compound, fostriecin, a natural product containing the *syn*-3° homoallylic 1,2-diol moiety (**20**, Scheme 4). It is isolated from *Streptomyces*

Scheme 4. Synthesis of the C_5–C_{11} Fragment of Fostriecin (20)

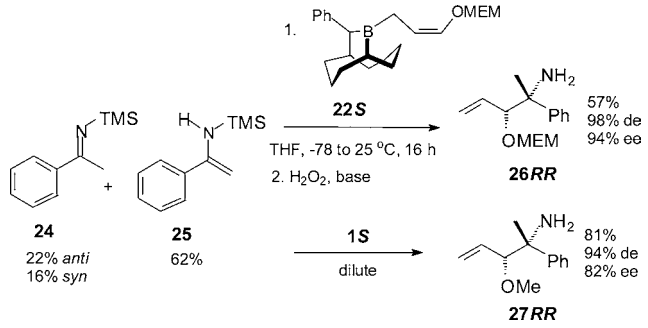


pulveraceus and selectively inhibits protein phosphatase 2A (PP2A).[16] As can be seen from Scheme 2, the typical *Z*-alkoxyallylboration of aldehydes followed by an oxidation/reductive methylation gives the *anti*-carbinol, not the desired *syn*-stereochemistry which is found in **20**. This is precisely what Ramachandran found in his reported synthesis of a precursor to the unnatural 8-epi-fostriecin employing $B(Ipc)_2$ reagents for the allylation.[9a] With the added versatility of the BBDs, we were able to γ-alkoxyallylborate the known ketone **21**[9b] with **22*S*** to obtain directly the desired *syn*-3°-carbinol precursor to fostriecin **23*RR*** in 81% yield, 94% de, and 82% ee! Careful comparison of our NMR data to those reported for the *anti*-isomer confirmed our *syn*-stereochemistry, and the (*R*,*R*) absolute configuration follows from **10a** and the related **10c** (Scheme 4).

We identified another important application for the BBDs to distinguish them from more limited $B(Ipc)_2$ systems. The allylation of ketimines through their borane-facilitated enamine → *Z*-ketimine isomerization is a process which we discovered some time ago (Scheme 5).[11b]

Employing **22*S***, which was available from a modified Ramachandran protocol,[7] we carried out the *Z*-γ-alkoxyallylboration of an enamine–ketimine mixture (i.e., **24**/**25**) to obtain the desired *syn*-β-OMEM 3°-carbinamine **26*RR*** (57%, 98% de, 94% ee)! This result was particularly gratifying especially when one compares this to the only reported example employing $B(Ipc)_2$ systems in related processes, namely Jäger's *Z*-γ-methoxyallylboration of a methanolized mixture of **24**/**25**. This was reported to give the MeO analogue

Scheme 5. γ-Alkoxyallylboration of 24/25 with 22*S* and 1*S*



of **22** (46%, 90% de, 20% ee).[8b,17] We conducted the *Z*-γ-methoxyallylboration of **24**/**25** with a diluted **1*S*** in an attempt to slow the allylboration to produce more of the *anti*-**27**, which would permit a comparison of the NMR signals for both diastereomers of the carbinamine. We lacked confidence that the low ee and rotation of **27** would permit its reliable absolute stereochemical assignment based upon the $B(Ipc)_2$ data alone (*cf.*, 20% ee, $[\alpha]^{20}_D$ −2.7 (*c* 1.0 $CHCl_3$) vs 80% ee, $[\alpha]^{20}_D$ −18.4 (*c* 1.1 $CHCl_3$)). However, we were confident in the reported *syn*-stereochemistry of this amine.[8b]

A solution to this issue was found through the use of VCD (vibrational circular dichroism, see Supporting Information) for the determination of the absolute configuration of **26*RR***. VCD couples optical activity to infrared vibrational spectroscopy wherein a differential response of a chiral molecule to left and right circularly polarized light is observed. The analysis was performed by a numerical comparison describing the similarity in the range 1000–1600 cm^{-1} between the calculated IR and the VCD spectra for the enantiomer at the B3LYP/6-31G(d) level and the observed IR and VCD spectra for the sample. These data are wholly consistent with the *R*,*R* (*syn*) configuration of **26** and, by analogy, **27**.

However, the (*R*,*R*) stereochemistry from the *S*–borane reagents was entirely unexpected. Bulky enamines such as **25** would be expected to attack **1** or **22** *trans* to the 10–Ph group rather than the *cis*–positioning of the carbonyl oxygen in **8** as is illustrated for **16** and **18** in Scheme 3. Therefore, we had expected the opposite (*S*,*S*) stereochemistry. Our observations together with the *syn* product stereochemistry also indicated that this was a relatively rapid addition process occurring with little *Z* → *E* isomerization of the boranes. Our previous studies had suggested that added congestion could lead to increasing amounts of an "upside down" orientation for 10–Ph-9-BBD reacting with *N*-silyl ketimines.[11b] We illustrate this geometry (**29**) together with the "down" orientation (**28**), which we view as the dominant process for the simple, unsubstituted allyl analogue of **1** (Figure 1). This orientation removes the repulsive interactions between the TMS group and the OMEM and Ph groups in the chair-like TS that would be

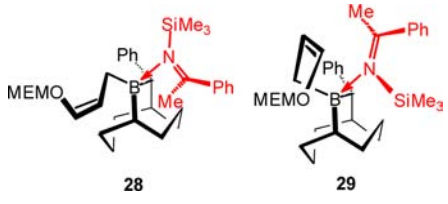


Figure 1. γ-Alkoxyallylation of *N*-TMS Ketimines with **1**.

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expected from **28**. *Therefore, **29** would appear to be a better alternative*, and it predicts the correct stereochemistry for **26*RR***.

In summary, the 10-Ph-9-BBDs have proven to be effective reagents for the γ-alkoxyallylboration of ketones and ketimines. We observed a wide range of diasteroselectivities which reflect the stereochemistry of the actual reacting borane. The initial *Z*−stereochemistry of **1** is reflected in the high product *syn*−diasteroselectivity of aromatic and vinylic ketones. Aliphatic ketones are slower to undergo allylboration and $Z \rightarrow E$ (**1** → **7**) isomerization permits the greater reactivity of the latter to dominate the allylboration process for these ketones, especially for pinacolone (**8g**), but even with less bulky ketones when they are used in substoichiometric quantitites (i.e., 9:1 dr). The use of the 10-Ph-9-BBD reagents permits the direct synthesis of 3°-carbinols such as was demonstrated for a fostriecin precursor **23** and carbinamines **26** and **27** with excellent diastereo− and enantioselectivities in contrast to the low selectivities exhibited by $B(Ipc)_2$ for these applications.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and spectroscopic data for **1**−**7**, **10**, **11**, **13**−**14**, **26**, **27**, and VCD analysis data. 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.

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(17) While we observed both a diminution of the product ee and also, a reversal of the absolute stereochemistry with the simple allylboration of ketimines with added MeOH,[11b] no differences were observed for **1S**, which gave the same efficiency and stereochemical outcome for the addition to **24**/**25** with or without the MeOH. This strongly suggests that no *N*-H ketimine is forming with the present system. This hydrolysis process[18] has been examined in greater detail, and the failure of **1** to catalyze the methanolysis of **24**/**25** is consistent with this picture.[10c,11b]

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