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Asymmetric γ-Methoxyallylation with the Robust 10-TMS-9-Borabicyclo[3.3.2]decanes‡

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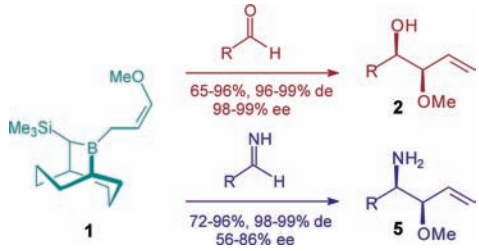
ABSTRACT



The asymmetric γ-methoxyallylboration of aldehydes with the configurationally very stable 1 gives nonracemic *threo*-β-methoxyhomoallylic alcohols 7 (65−93%) with excellent selectivity (96−99% de, 98−99% ee). The corresponding homoallylic amines 10 are obtained from *N*-H aldimines with similar efficiency (72−96%) and with excellent diastereoselectivity (98% de) but with lower enantioselectivity (56−86% ee). These new reagents provide ready access to a Taxol side chain derivative.

Recent studies in our laboratories have revealed that the robust 10-trimethylsilyl-9-borabicyclo[3.3.2]decane (10-TMS-9-BBD) ring system provides a highly effective stereocontrol element for many asymmetric organoborane conversions.[1,2] Embedded in this fascinating new chemistry are many examples where sterically driven 1,3-borotropic rearrangements can play a profound role in determining the actual reagents produced and the products that result from their reactions. These phenomena were particularly evident in our new synthesis of 1,3-diols derived from 1,3-diborylpropenes, wherein the BBD substitution produces distinctly different chemistry than has been observed from related compounds with other boryl groups.[2] Since these arrangements can have stereochemical consequences upon the reactions of interest, we chose to examine another important organoborane conversion, namely, the Hoffmann γ-methoxyallylboration of aldehydes, which leads to syn-1,2-diols.[3] We felt that this process would benefit from the greater selectivity of the 10-TMS-9-BBD systems versus the corresponding diisopinocampheylborane (Ipc_2B) reagents, provided the derived reagents were configurationally stable under their reaction conditions.

First reported by Hoffmann in 1981, the diastereoselective addition of γ-methoxyallylboranes to aldehydes gave *threo*-β-methoxyhomoallyl alcohols with good diastereoselectivity (≥96% de).[3] An asymmetric variant to this process was later reported by Brown[4] using isomerically pure (*Z*)-(γ-methoxyallyl)diisopinocampheylboranes. While it was observed

‡ This work is dedicated to Professor Dr. M. Frederick Hawthorne for his revolutionary concepts and extraordinary contributions to boron chemistry.

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that these reagents are configurationally unstable above −78 °C, they add smoothly to aldehydes at this temperature to provide the desired alcohols in ≥98% de and 88−92% ee. Numerous synthetic applications for γ-methoxyallylboration have been found for the synthesis of highly oxygenated natural products.[6] To assess the potential of BBD reagents to enhance the value of this important process, it was decided to prepare the (*Z*)-(γ-methoxyallyl)-10-TMS-9-BBD reagents (**1**) and evaluate their behavior in the methoxyallylboration of aldehydes and aldimines.

Allyl methyl ether is metalated with *sec*-butyllithium in THF at −78 °C (Scheme 1).[7] The resulting *cis*-organolithium reagent **3** is treated with either enantiomeric form of *B*-methoxy-10-trimethylsilyl-9-BBD (**4**) at −78 °C, giving the organoborate complex **5** that reacts with TMSCl to generate **1** in 85% yield. Representative aldehydes were added to **1** in THF at −78 °C to produce **6** (see Supporting Information), which was treated with the appropriate pseudoephedrine to provide **8** and the *threo*-β-methoxyhomoallyl alcohols **7** in 65−96% yield with excellent diastereoselectivity (96−99%) and optical purity (98−99% ee). These results are summarized in Table 1.

Scheme 1

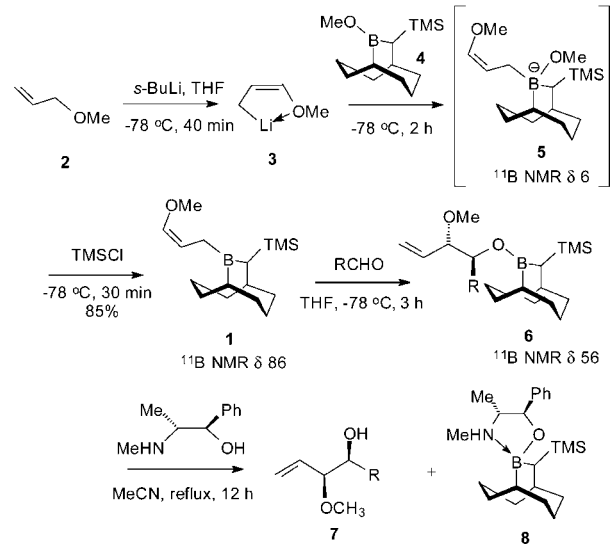

Table 1. Asymmetric γ-Methoxyallylboration of Representative Aldehydes with **1**

1	R	**7**[a]	**8**	ee[b]	de	abs config[c]
R	**a**, Me	65	61	98	98	*S*,*S*
R	**b**, Pr[d]	93	53	98	98	*S*,*S*
S	**c**, *i*-Pr	65	71	98	98	*R*,*R*
R	**d**, Ph	90	76	99	99	*S*,*S*
S	**e**, *t*-Bu	89	50	98	98	*R*,*R*
S	**f**, CH=CHMe	80	50	98	96	*R*,*R*

[a] Yield was based on the amount of the aldehyde used. [b] Calculated from the ^{31}P NMR peak areas using the Alexakis method (see Figure 2).[5] [c] The absolute configuration was determined by comparison of optical rotation with literature values.[3] [d] (3*R*,4*R*)-**7b** was prepared in 88% yield (98% de and ee) from **1***S*.

For analysis purposes, the racemic reagent ((±)-**1**) was prepared to evaluate its thermal stability with respect to *cis*/*trans* isomerization. In marked contrast to the instability of the Ipc_2B reagents, the pure *cis* geometry of **1** was retained upon warming to room temperature. After either 4 d at 36 °C or 14 h at 80 °C, a ∼70:30 *cis*/*trans* mixture is formed. Further heating at 80 °C or attempted vacuum distillation of this mixture at 0.1 mmHg leads to decomposition without significantly changing the *cis*/*trans* ratio.

Because of the unusual stability of these trialkylboranes, we were able to obtain clear NMR spectral data for **1** as is illustrated for the vinylic hydrogens in this mixture (Figure 1).

The clean resolution of the ^{31}P NMR signals derived from the isomeric Alexakis *P*-alkoxy-1,3,2-diazaphosphor-olane derivatives of **7a** can be seen in Figure 2. Thus, these esters from **7a** with another thermally isomerized *cis*/*trans* mixture of (±)-**1** shows that this borane reagent gives rise to all four of the possible isomeric products. However, the *erythro* isomers are essentially absent (<1%) from the unisomerized (±)-**1**. Prepared from (10*R*)-**1**, (2*S*,3*S*)-**7d** is produced with no detectable amount of the *erythro* (*anti*) diasteromers and

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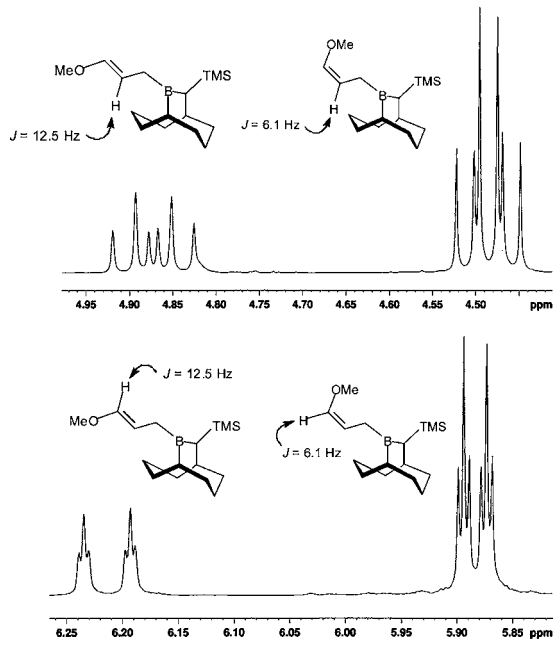


Figure 1. Vinylic region of **1** after *cis*/*trans* isomerization.

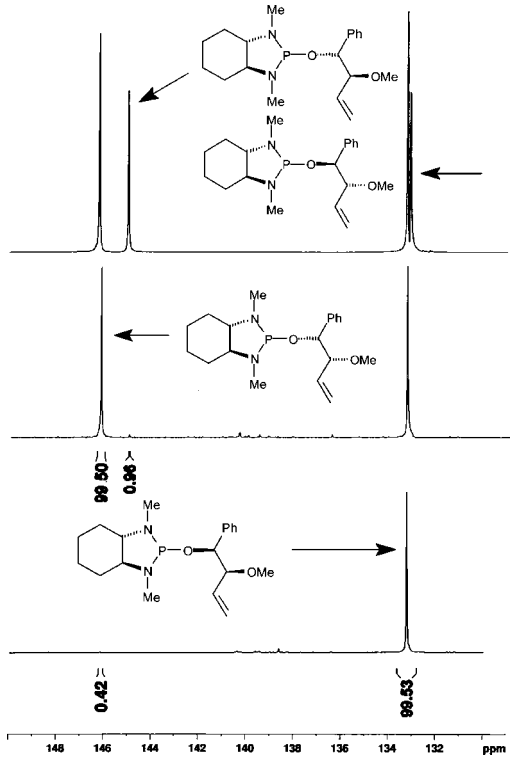


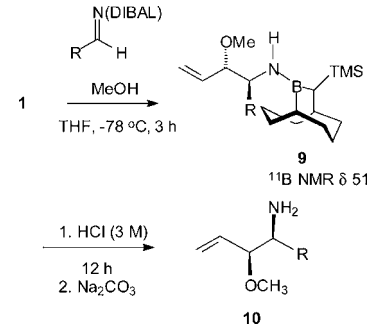
Figure 2. ^{31}P NMR spectra of the unpurified Alexakis esters of **7d** derived from *cis*/*trans*-(±)-**1** (top), *cis*-(±)-**1** (middle, peak area δ 146.2 vs 145.0 is >99:1), and *cis*-(10*R*)-**1** (bottom, peak area δ 133.3 vs 146.2 is >99.5:0.5. Also see Supporting Information.

<0.5% of (2*R*,3*R*)-**7d**. These results reveal that **1** exhibits higher enantioselectivity in its addition to aldehydes than the corresponding $(Ipc)_2B$ reagents (~90% ee).[3]

It was of interest to determine the selectivity of **1** in its additions to *N*-H aldimines. These substrates are generated in situ from the methanolysis of the corresponding *N*-DIBAL derivatives, which in turn are produced from the Isuno hydroalumination of nitriles.[8] Previous studies with the BBD systems led us to expect lower selectivities for this process than we had observed for aldehydes.[9]

The addition of *N*-DIBAL aldimines to **1** in THF solution at −78 °C followed by MeOH (1 equiv) results in the clean formation of **9** (^{11}B NMR δ ~51) (Scheme 2). An acidic

Scheme 2



workup provides the corresponding *threo*-β-methoxy homoallylic amines **10** in 72−96% yield (98−99% de, 56−86% ee) (Table 2). These selectivities are somewhat lower than with γ-OMOM-allylB$(Ipc)_2$ (cf. R = Ph, 75%, 98% de, 86% ee vs 65%, 98% de, 95% ee[10] (86% ee)).[12a]

The synthesis of the side chain of Taxol (Figure 3) and derivatives continues to be of interest due to the availability

Table 2. Asymmetric γ-Methoxyallylboration of Representative Aldimines with **1**

1	R	**10** (%)[a]	ee[b]	de[c]	abs config[d]
R	**a**, Ph	75	86	98	*S*,*S*
S	**b**, 2-thienyl	96	56	98	*S*,*R*
S	**c**, *c*-Hx	78	72	98	*R*,*R*
R	**d**, *p*-$MeOC_6H_4$	72	84	98	*S*,*S*
R	**e**, Bn	77	80	98	*S*,*S*

[a] Isolated yield from acidic workup. [b] Calculated from the ^{31}P NMR peak areas using the Alexakis method (see Figure 2).[5] [c] Determined by ^{1}H NMR analysis. [d] The absolute stereochemistry of **10d** was assigned on the basis of its conversion to the known methyl carbamate derivative.[11] Others were assigned on the basis of this and the known stereochemistry of **7**.

of the baccatin III or 10-deacetylbaccatin III core unit (see Figure 3, red portion) from the renewable leaves of *Taxus baccata*.[12]

The simple synthesis of the Taxol side chain derivative **11** was accomplished from **10a** (1*S*,2*S*) through benzoylation followed by Sharpless oxidation[13] in 70% overall yield (Figure 3).

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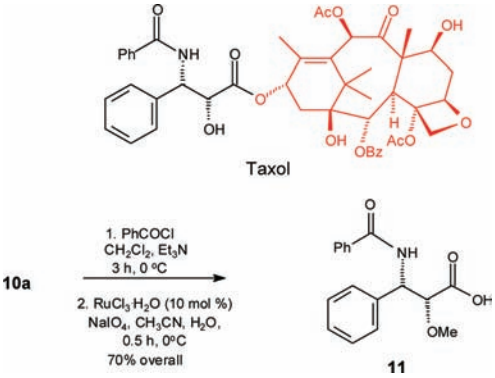

Figure 3. Synthesis of a side chain derivative of Taxol.

The absolute configuration of the amines was determined by comparison of the sign of the optical rotation to that of a precursor to (−)-4-*epi*-cytoxazone.[14] This carbamate derivative was prepared from **10d** and MeOCOCl/TEA in CH_2Cl_2 in 82% yield. The optical rotation confirmed the (1*S*,2*S*) configuration of **10d**.[15]

In our previous studies,[1] we developed working models for the origin of the enantioselectivities observed with the BBD reagents that were based upon the relative energies of the eight diastereomeric pretransition state complexes. As shown in Figure 4 (**12a**), the most stable *B*-chiral complex positions the carbonyl oxygen atom *cis* to the TMS group in an *anti* aldehyde-**1** adduct that is down with respect to the BBD ring. Sarotti and Pellegrinet[16] recently performed B3LYP/6-31G*-level calculations on the transition state energies for the allylboration of aldehydes and ketones with the BBD reagents. The 10-R substitution was found to provide a sterically based preference for the chairlike transition state with *cis*, *anti* down geometry that was consistent with our simple models (cf. **12a**). The *N*-H aldimines are less selective than are aldehydes because the NH is larger than O and thus closer in size to the α-sp^3 allylic carbon atom. This narrows the energetic difference between the *cis* versus *trans* adducts relative to the 10-TMS group, resulting in lower selectivity.

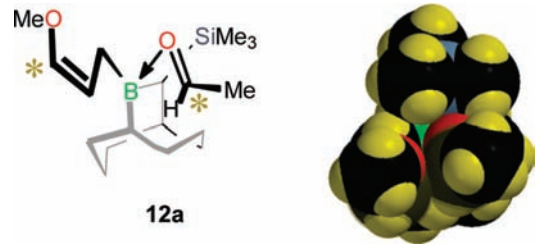

Figure 4. MM-generated preferred pretransition state model (**12a**) for the γ-methoxyallylboration of MeCHO with **1** (d(C*−C*) = 3.5 Å.

In summary, the new *B*-(*Z*-γ-methoxyallyl)-10-TMS-9-BBD reagents **1** add smoothly to aldehydes and *N*-H aldimines to provide the corresponding *syn*-β-methoxy homoallylic alcohols (65−93%) and amines (72−96%), respectively. Because the reagents **1** are configurationally stable, the process is highly diastereoselective (99% *syn*). The enantioselectivity of **1** is higher for aldehydes (96−99% ee) than for aldimines (56−86% ee). The amino alcohol **10a** was readily converted to the Taxol side chain derivative **11**.

Acknowledgment. The support of the NSF (CHE-0848192) is gratefully acknowledged.

Supporting Information Available: Full experimental procedures, characterization data, selected spectra for **1**, **4**, **6**−**8**, **10**−**11** and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In ref 14 the structures are correct, but there are errors in the compound naming that can be confusing.

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