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Cyclohexenylboration of Aldehydes and Ketones with the Borabicyclo[3.3.2]decanes (BBDs)

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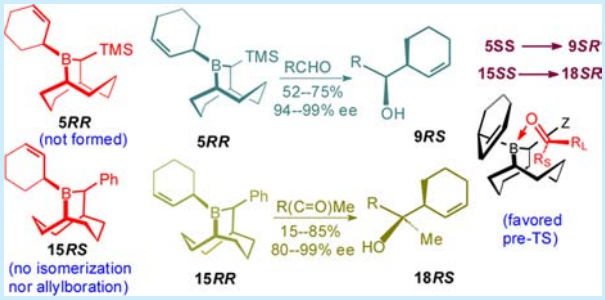
Supporting Information

ABSTRACT: Asymmetric hydroboration of 1,3-cyclohexadiene with **4*R*** produces the allylborane **5*RR*** as essentially a single diastereomer (i.e., no observable **5*RS***), and its addition to representative aldehydes provides **9*RS*** (52−75%) with excellent selectivity (94−99% ee). By contrast, a similar sequence with the 10-Ph-BBD reagent, **14*R***, results in a ca. 45:55 mixture of **15*RR*** and **15*RS***. However, their addition to methyl ketones provides the corresponding 3°-homoallylic alcohols (**18*RS***) with excellent selectivity (80−99% ee) but in low yields (15−52%) because **15*RS*** is unreactive toward either allylboration or isomerization to **15*RR***. Thus, with 2 equiv of **15**, the yield of **18** (R = Ph) is increased from 52% to 85%. Boranes **5*SS*** and **15*SS*** provide enantiomeric alcohols.



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 10-substituted borabicyclo-[3.3.2]decanes (BBDs) have demonstrated truly remarkable versatility and selectivity in a wide variety of asymmetric allylation and related organoborane conversions. The 10-trimethylsilyl (TMS) derivatives are extremely effective in their additions to aldehydes and aldimines,[2] while their 10-Ph counterparts are particularly selective in the corresponding additions to ketones and ketimines.[3] BBD reagents have proven to be effective for the asymmetric hydroboration of simple alkenes including 2-methyl-1-alkenes and allenylboranes.[4a,5] This suggested that by combining asymmetric hydroboration with allylboration, the versatility of the BBDs could be extended to novel applications for this sequence. For these purposes, we felt that the selectivity of the BBD systems could be compared to these processes with Brown's diisopinocampheylborane (Ipc_2B) reagents and then extended to ketones, an unworkable substrate for this bulky system. We selected 1,3-cyclohexadiene as our substrate because this system had been well-studied by Brown et al.[6] It takes full advantage of the effectiveness of the $(Ipc)_2B$ chiral ligation in both the hydroboration of 1,3-cyclohexadiene and in its cyclohexenylboration of aldehydes. Alternative procedures have also been developed to access nonracemic cycloalk-2-enylboranes for this purpose.[7] The present system would produce 2°-carbinols containing the 2-cyclohexenyl moiety, which can be found in potent 20S proteasome inhibitors such as salisporamide A and cinnabar-amide A.[8] With the 10-Ph BBDs, we hoped to extend this method to include ketones.

The addition of $TMSCHN_2$ to *B*-MeO-9-BBN provides racemic *B*-MeO-10-TMS-9-BBD (±)-**1**, quantitatively.[2] The air-stable crystalline 10-TMS complexes **2*R*** and **2*S*** are both available in enantiomerically pure forms from (±)-**1** through asequential resolution (67% total yield, see Supporting Information) and are now commercially available. Reduction of these complexes with $LiAlH_3(OEt)$ provides clear, stable solutions of the borohydrides **3** which are easily separated from the insoluble dialkoxyalane byproducts.[4a,d] The borane reagents **4** are generated *in situ* through the addition of TMSCl to an equimolar solution of **3** and 1,3-cyclohexadiene in ether, the hydroboration being completed over 2 h (0 → 25 °C). We also prepared (±)-**5** through (±)-**4** from (±)-**1** (Scheme 1, illustrated for **5*RR***). These trialkylboranes exhibit a broadened ^{11}B NMR signal (δ 82). Purification provides **5*RR*** and its regioisomer **6*RS***, in a 93:7 ratio, as determined through the ^{13}C NMR analysis of the vinylic carbon region for this mixture as well as directly by the ^{11}B NMR of their borohydrides generated with activated KH.[4b] The alkaline hydrogen peroxide oxidation of these boranes confirmed this distribution, affording 2-cyclohexen-1-ol (**7**) and its 3-isomer (**8**) in the same 93:7 ratio. Moreover, the analysis of the Alexakis esters[9] revealed

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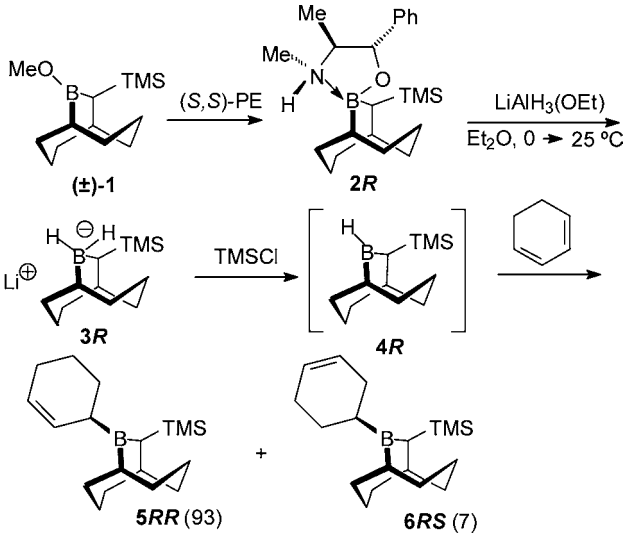
Scheme 1. Hydroboration Route to 5



that **7** had been formed in 99% ee! This indicated that the hydroboration had provided the "allylborane" **5** as *essentially a single diastereomer*.

The hydroboration of *cis*-2-butene with **4** is quite selective (i.e., 84% ee).[4a] This follows from the alkene's approach to **4** being favored on the side opposite to the 10-TMS group with the *cis*-substituents positioned away from this bulky group (*cf.*, Figure 1, **A** vs **E**). It is gratifying that, with the cyclohexadiene

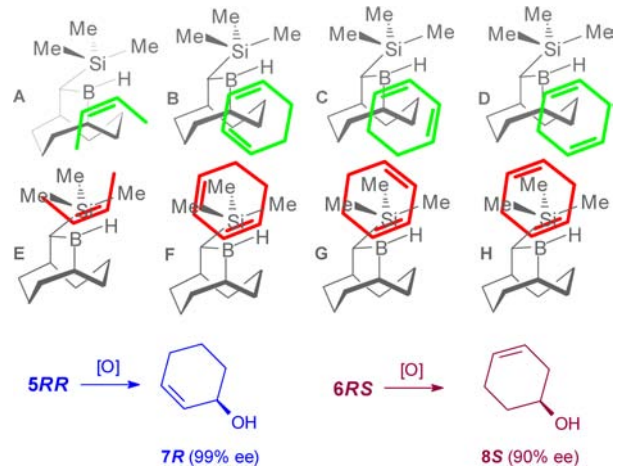
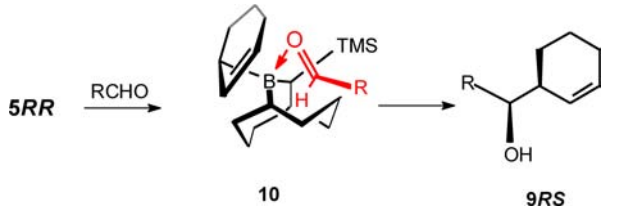


Figure 1. Models for **4***R* and *cis*-alkenes (favored, disfavored).

system, the process is even more selective. We view this as attributable to enhanced unfavorable steric interactions in **F** vs **B** compared to **E** vs **A**. Oxidation of **5***RR* gives **7***R* in 99% ee. The homoallylic borane **6** was independently prepared through the hydroboration of 1,4-cyclohexadiene with **4***R* and its oxidation to **8***S* (90% ee) (*cf.*, **C** or **D** vs **G** or **H**, respectively). The enantiomeric borane **4***S*, prepared from **2***S*, gives **5***SS* and **6***SR* in the same 93:7 ratio.

With a clear understanding of the hydroboration of 1,3-cyclohexadiene with **4**, we carried out the asymmetric allylboration of representative aldehydes with **5** (containing 7% of unreactive **6**). The addition proceeds smoothly at −78 °C, producing the corresponding homoallylic alcohols **9** (Table 1). The exclusive formation of the *syn*-homoallylic alcohols **9**

Table 1. Asymmetric Cyclohexenylboration of Representative Aldehydes with 5



5	R	9[b]	yield[c]	ee[a]	config[b]
RR	Ph	a*RS*	71	96	1*R*,1′*S*
SS	Ph	a*SR*	75	94	1*S*,1′*R*
RR	*i*-Bu	b*SS*	56	96	1*S*,1′*S*[c]
RR	*t*-Bu	c*RS*	63	99	1*R*,1′*S*
RR	CH=CHPh	d*RS*	52	96	1*S*,1′*S*[c]

[a]Calculated from the ^{31}P NMR peak areas using the Alexakis method.[9] [b]Absolute configuration was determined by comparison to the optical rotations of reported known compounds.[6,11] [c](*S*,*S*) Absolute configuration due to relative group priority changes.

follows directly from a closed Zimmerman−Traxler chairlike transition state.[10] In our pretransition state carbonyl−borane complex model **10**, the smaller carbonyl oxygen is *cis* to the 10-TMS group, with the aldehydic R group *anti* to the borane and down relative to the TMS group. The model correctly predicts the relative and absolute stereochemistry of **9** and other related processes for the BBD systems.[2,3] The absolute configuration of **9** was assigned based upon reported optical rotation values.[6,11] The 10-TMS-9-BBD is extremely well suited for this combination of asymmetric organoborane conversions because both the hydroboration and allylboration are highly selective and also are properly paired. Thus, the alkene approaches **4** from the face opposite to the TMS group (i.e., **B**) whereas the aldehyde approaches **5** from the same side (i.e., **10**). This permits the allylboration to occur through a cyclic transition state as would be expected from the optimal geometry as is illustrated in **10**.[12]

Previous studies have revealed that the 10-Ph-9-BBD reagents are ideally suited to the allylation of ketones.[3] To prepare these reagents, we took advantage of our synthesis of **14**.[4a] This follows a similar reaction sequence as the one used for **4**. Beginning with (±)-**11**, this borane is sequentially resolved with the enantiomers of *N*-methylpseudoephedrine (NMPE) giving both enantiomers of **12** as pure air-stable crystalline compounds. Reduction of **12** with $LiAlH_3(OEt)$ provides solutions of the borohydrides **13**, which are used for the generation of **14** and the hydroboration of 1,3-cyclohexadiene. We expected little selectivity, in this process, because the hydroboration of *cis*-2-butene with **14***R* had given 2*R*-butanol with only 32% ee compared to 84% ee with **4***S*. Moreover, we faced challenging stereochemical assignment issues because the absolute stereochemistries of the product 3°-alcohols were unknown. We prepared both **14***R* and **14***S*, through the reaction sequence outlined in Scheme 2 and (±)-**14** from (±)-**11**.

Unfortunately, the hydroboration of 1,3-cyclohexadiene with **14***R* provided 2-cyclohexenol in essentially racemic form, i.e., 10% ee (Scheme 2). The regiochemistry of the addition was very similar to that found for **4**, namely **15**/**16** = ca. 90:10, which led to this ratio of 2- and 3-cyclohexenols after the oxidation of the hydroboration mixture. The adduct **16** was formed as a 1:1 diastereomeric mixture (see Supporting

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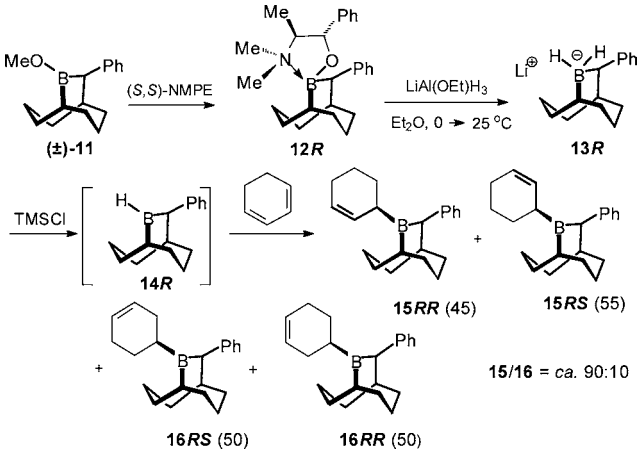
Scheme 2. Hydroboration Route to 15

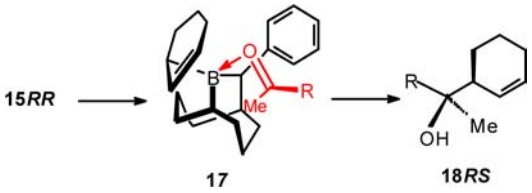


Information).[4b] We view this lack of enantiofacial selectivity as being due to the combination of the lesser reach of the 10-Ph vs 10-TMS and in changes in the ring conformations for **4** vs **14**.[4a,c]

Despite the low observed selectivity in the formation of **15**, we examined the cyclohexenylboration of methyl ketones. Surprisingly, we obtained **18** with excellent enantioselectivities (80−99% ee). Normally, with non-*B*-chiral cycloalk-2-enylborane−carbonyl transition states, the allylation is controlled exclusively by the chirality of the α-center, not by the achiral *B*-center (*e.g.*, $(Ipc)_2B$ and reported boronic ester derivatives).[2l,6,7] This is not the case with **15**. Consistent with only **15*RR*** (or **15*SS***), but not **15*RS*** (nor **15*SR***), undergoing addition to methyl ketones, the isolated yields of **18**, obtained as exclusively *syn* diastereomers, were low (15−52%, see Table 2). Moreover, the high levels of enantioselectivities closely mirror those observed in the simple allylboration of ketones with the 10-Ph-9-BBD reagents.[3a]

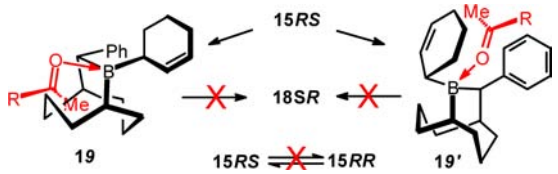
To add support to our hypothesis that only the *RR* (or *SS*) isomers of **15** can undergo allylboration, we first conducted simple MM (Spartan 08) calculations on **17** vs **19**, concluding that the large repulsive Me--Ph interactions between the ketones and the 10-Ph-9-BBD group are probably responsible for the failure of **19′** to lead to competitive allylboration. For **19**, Ph-cyclohexenyl repulsions and others are issues. Second, we monitored the hydroboration mixture of **15** over several days, confirming that it was configurationally stable.[2b,i,13] After the addition of 1 equiv of methyl isopropyl ketone (MIK) at −78 °C, ^{13}C NMR data were collected at 1, 20, and 90 h at rt, which indicated that $t_{1/2}$ = ∼20 h (45% reaction) and only 57% had reacted after 90 h at this temperature. In a separate experiment, in refluxing ether, ^{11}B NMR revealed that the reaction had only proceeded to ca. 50% completion in 19 h. These data suggest that (1) the diastereomeric **15*RR*** (or **15*SS***) and **15*RS*** (or **15*SR***) are not in rapid equilibrium and (2) only **15*RR*** (or **15*SS***) is reacting with the ketones, which accounts for the observed low yields. To gain further support for the latter assertion, we conducted the allylboration employing a 2:1 **15**/ketone ratio. **18a** was obtained in 85% yield from acetophenone, up from 52% with the 1:1 stoichiometry. With *p*-$ClC_6H_4C(=O)Me$, it was 60%, up from 17% with the 1:1 stoichiometry. Further, we repeated the 2:1 stoichiometric reaction of **15*RR*** with acetophenone, isolating, first, the **18a*RS*** (73%) followed by, second, a 4:1 mixture of **7** and **8** in 78% yield. As expected, this mixture gave a smaller, negative specific rotation than does pure **7*S*** (i.e., $[\alpha]_D^{20}$ − 9.3 (*c* 1.5, $CHCl_3$)). This allylboration was also examined by ^{11}B NMR through their KH*-derived borohydrides[4b] which give resolved signals for these diastereomeric species. After 2 h at 25 °C, **15*R**R**** (δ − 9.0) was >80% consumed in its reaction with PhC(=O)Me, while the **15*R**S**** (δ − 8.0) remained unreacted (Figure 2).

Table 2. Asymmetric Cyclohexenylboration of Representative Ketones with 15



15	R	18	yield[a]	ee[b]	config[c]
RR	Ph	a*RS*	48	98	1*R*,1′*S*
SS	Ph	a*SR*	52(85)	99	1*S*,1′*R*
SS	*i*-Pr	b*RR*	48	99	1*R*,1′*R*
SS	$CH{=}CH_2$	c*RR*	15	84	1*R*,1′*R*
RR	$CH{=}CH_2$	c*SS*[d]	17	80	1*S*,1′*S*
RR	4-ClC_6H_4	d*RS*	17	99	1*R*,1′*S*
SS	4-ClC_6H_4	d*SR*	(60)	92	1*S*,1′*R*
RR	4-$MeOC_6H_4$	e*RS*	32	96	1*R*,1′*S*

[a]Yield with 2:1 of **15**/ketone. [b]Calculated from the ^{31}P NMR peak areas using the Alexakis method.[9] [c]Absolute configuration was assigned by independent synthesis of **18a*SR***. [d]A minor amount (11%) of *anti*-isomer was removed during workup.



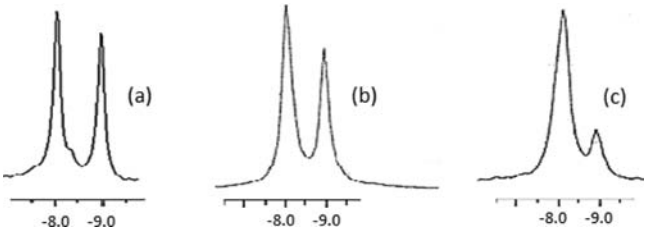


Figure 2. Borohydrides from (a) initial **15*R**S**/15*R**R**** mixture, (b) 15 min 1:1 PhC(=O)Me/**15**, and (c) after 2 h (25 °C).

The specific rotation for a *syn*-diastereomer of **18a** was reported by Yamamoto,[14] but its absolute configuration could not be determined. Our value, $[\alpha]_D^{25}$ = −56 (*c* 1.1, CH_2Cl_2), agrees well with his −50 value, but we also lacked definitive data to assign the absolute stereochemistry to this alcohol. To address this issue, we oxidized the known **9a*SR*** with PDC to produce **20a*R***,[15] which was treated with MeMgBr at −30 °C to produce an 80:20 mixture of **18a*SR*** and **18a*RR*** (Scheme 3). This mixture was derivatized to form their Alexakis esters for analysis by ^{31}P NMR.[9] The signal from the 80% diastereomer (Cram product) matched that from our *syn* **18a*SR*** product. The **15a*SS*** gives the (1*S*,1′*R*) isomer of **18a** which is also the absolute configuration of Yamamoto's carbinol. The absolute stereochemistries of the other alcohols were assigned by analogy to **18a*SR***.

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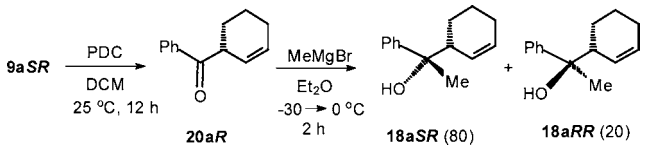
Scheme 3. Independent Syntheses of 18a*RR* and 18a*RS*



In summary, the hydroboration of 1.3-cyclohexadiene with the 10-TMS-9-BBD reagent **4** produces the allylborane **5** as an essentially pure diastereomer. Its addition to representative aldehydes provides **9** as single diastereomeric products in 94−99% ee in 52−75% isolated yields, equaling or exceeding those obtained with the $B(Ipc)_2$ reagents. While **14** produces the analogous BBD adducts **15** in low de (10%), only the *SS* (or *RR*) 10-Ph-9-isomers undergo the cyclohexenylboration of methyl ketones. The novel *syn* 3°-alcohols **18** were isolated in low yields (15−52%), but with excellent enantiomeric purities (80−99% ee). It was further discovered that the *RS* and *SR* diastereomers of **15** fail to undergo either the cyclohexenylboration of ketones or allylic rearrangement to their reactive ***RR*** and ***SS*** counterparts at significant rates. By employing a 2:1 **15**/ketone ratio, the yields of **18** were raised to 85% from 52% for **18a** and from 17% to 60% for **18d**. Thus, for the first time, ketones were successfully employed in the asymmetric cyclohexenylboration process, and the significance of *B*-chirality in allylboration was revealed. The versatility and chemical diversity exhibited by the BBD systems, especially for organoborane conversions employing ketone substrates, places them in a privileged position among asymmetric organoborane reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02194.

Full experimental procedures and spectroscopic data for **1**−**9**, **11**−**16**, **18**, and **20** (PDF)

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Notes

The authors declare no competing financial interest.

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