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B-Allyl-10-Ph-9-borabicyclo[3.3.2]decanes: Strategically Designed for the Asymmetric Allylboration of Ketones

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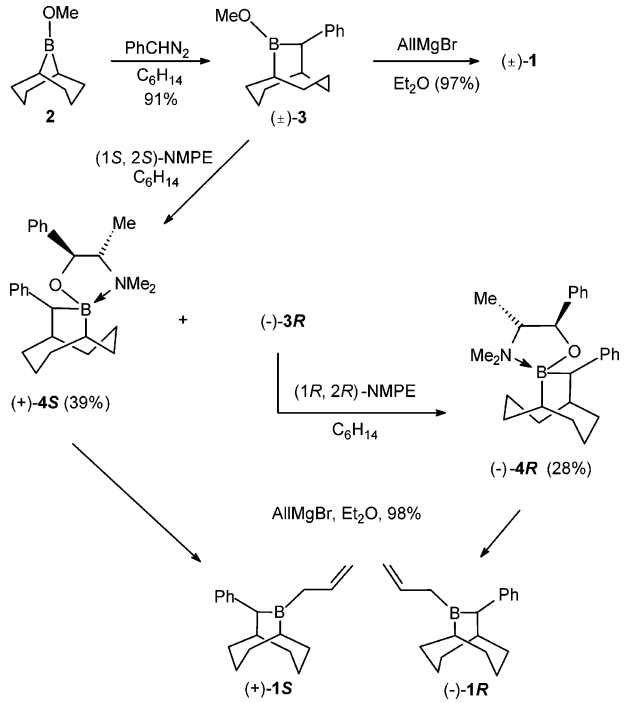
The asymmetric allylation of aldehydes provides a highly effective method for the preparation of nonracemic homoallylic alcohols.[1] However, a general procedure for preparation of 3°-homoallylic alcohols through the asymmetric allylation of ketones has remained conspicuously wanting. These substrates can be selectively allylated with allylsilanes through their chiral ketals, but obtaining the free alcohols is nontrivial and inconvenient.[2] Recently, significant progress has been made with stereoelectronically biased ketones (e.g., PhCOMe) through the use of asymmetric catalysts and either allyltins or achiral allylboronic ester reagents or, alternatively, through the stoichiometric reactions of chiral allylboronic esters derived from 3,3′-disubstituted-1,1′-bi-2-naphthol.[3] Unfortunately, these methods are significantly less selective for dialkyl ketones containing pendent groups, which are more similar in size (e.g., $PhCH_2CH_2COMe$). Careful examination of these and other systems employed for asymmetric allylation suggested that a fully elaborated "chiral pocket" may better address the challenges posed by these ketones. We envisioned a process in which the smaller of the two groups could better fit into this pocket. A key feature in this new design paradigm was the inclusion of a "chiral floor", which we felt could be achieved through the incorporation of the reactive site into a bicyclic system.

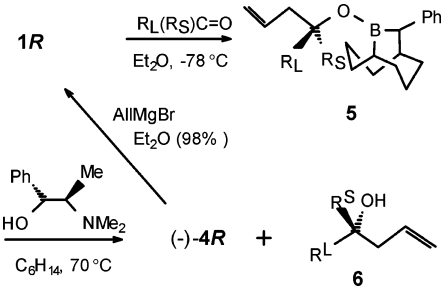
Recently, we reported the synthesis of the *B*-allyl- and *B*-crotyl-10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (BBDs) and their additions (3 h, −78 °C) to aldehydes achieving excellent selectivities (94 → 99% ee, >98:2 dr) with a wide range of substrates.[4] Unfortunately, with these reagents, the asymmetric allylboration of acetophenone is both very slow (2 days, 25 °C) and far less selective (62% ee). This disappointing result led us to view the 10-TMS-9-BBD system as providing a chiral pocket which is receptive to aldehydic hydrogens, but is too small to easily accommodate even a methyl group. With model studies suggesting that this pocket may be incrementally enlarged with a 10-Ph rather than 10-TMS BBD system, we chose to prepare the reagents **1** for the asymmetric allylboration of methyl ketones.

The preparation of the thermally stable (±)-**3** from **2** was accomplished through the simple reaction of the stable $PhCHN_2$, which cleanly inserts the CHPh group into a ring B−C bond (hexanes, 10 h, 0 °C, 90%) (Scheme 1). In contrast to its essentially air-stable 10-TMS counterpart, **3** is readily oxidized in the open atmosphere, but is indefinitely stable when handled and stored under nitrogen. Employing a modified version of the Masamune resolution protocol,[5] (±)-**3** was added to 0.5 equiv of (1*S*,2*S*)-*N*-methylpseudoephedrine (NMPE) in hexanes which provides (+)-**4*S*** as a pure crystalline compound (39%). After concentration of the supernatant to remove the liberated MeOH, 0.5 equiv of (1*R*,2*R*)-NMPE was added to a fresh solution of the residue in hexanes, ultimately giving a 28% yield of the pure crystalline (−)-**4*R***. Reversing this order gives first, (−)-**4*R*** and second, (+)-**4*S***, also in a 67% combined total yield of enantiomerically pure forms of **4** from (±)-**3**! These complexes are air-stable and can be stored indefinitely. The complex (+)-**4*R*** is wholly chelated in the solid state, while in solution, **4** exists in both the open and closed forms (^{11}B NMR (C_6D_6) δ 55.5, 10.0). The preparation of the *B*-allyl reagents (+)-**1*S*** or (−)-**1*R***

Scheme 1



Scheme 2



through the reaction of either complex **4** with allylmagnesium bromide in Et_2O is both simple and efficient (98%). The byproduct NMPE Mg^{2+} salt is easily converted back to NMPE for reuse (86%).

The reagents **1** were examined in the asymmetric allylboration of representative ketones (Scheme 2). In contrast to the slow and moderately selective reactions of its 10-TMS counterpart, **1** reacts rapidly with methyl ketones (≤3 h, −78 °C). The resulting 3°-homoallylic alcohols (**6**) are obtained efficiently (70−92%) in high enantiomeric excess (81−99%) (Table 1). These selectivities equal or exceed the selectivities of any known process for sterically biased methyl ketones (**6a**,**c**−**e**,**h**,**i**). With the more demanding cases, where the groups on the ketone are similar in size, the levels of enantioselectivity observed with **1** are particularly noteworthy (i.e., **f** (MEK, 87% ee), **g** (MVK, 81% ee). With the ethyl ketone,

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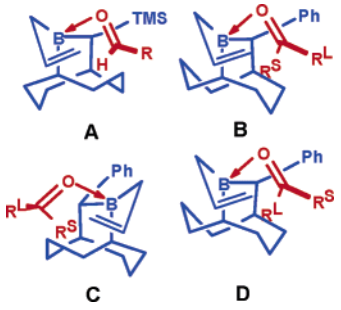
Table 1. Allylboration of R_LR_SCO with **1**

R_L	R_S	**1**	series	**6** (%)[a]	%ee[b] (abs config)
Ph	Me	*R*	**a**	92	96 (*R*)
Ph	Et	*S*	**b**	70	94 (*S*)
4-BrC_6H_4	Me	*S*	**c**	96	98 (*S*)
4-$MeOC_6H_4$	Me	*S*	**d**	89	94 (*S*)
4-$O_2NC_6H_4$	Me	*R*	**e**	90	>98 (*R*)
Et	Me	*S*	**f**	80	87 (*R*)
CH_2=CH	Me	*S*	**g**	77	81 (*S*)
i-Pr	Me	*S*	**h**	74	92 (*S*)
t-Bu	Me	*R*	**i**	70	99 (*R*)
Ph	H	*R*	**j**	82	90 (*R*)

[a] All runs were made in duplicate (at least), and the **a** and **e** series were performed with both (−)-**1*R*** and (+)-**1*S***. The intermediate **5** was isolated and converted to **6,** and **4** was recovered (67−82%) via the NMPE workup procedure. [b] Product enantiomeric excesses were determined by conversion to the Alexakis esters and analysis by ^{31}P NMR. For **6a**,**d**, this enantiomeric excess value was confirmed by HPLC (DAICEL CHIRACEL OD, hexane/2-propanol 99:1).

propiophenone, the allylation is significantly slower (~8 h, −78 °C) than that with methyl ketones, but **1** still exhibits high selectivity (**6b** (94% ee)). In a competitive experiment employing a 1:1.33:1.33 mixture of **1**, PhCOMe, and PhCOEt, the acetophenone is selectively allylated, leaving the propiophenone completely unreacted. With PhCHO, **1** is less selective (90% ee) than with its 10-TMS counterpart (≥98% ee).[4] Additionally, when the allylation of PhCOMe is conducted at 0 °C, the homoallylic alcohol **6a** is obtained in 90% ee. This modest diminution in enantioselectivity at significantly higher allylation temperatures is a signature feature of the rigid bicyclic BBD reagents.

The predictability and consistently high levels of enantioselectivity in the allylation of ketones with **1** warrant further discussion. As previously discovered,[4] the 10-TMS system is ideally suited for the asymmetric allylation of aldehydes, but is too hindered to effectively allylate ketones. The greater reactivity and selectivity of **1** are a direct result of the changes engendered in the chiral pocket with the 10-Ph versus 10-TMS substitution. A comparison of the single-crystal X-ray structure of (+)-**4*S*** versus the analogous pseudoephedrine complex of the 10-TMS-9-BBD system[4] suggests that this reactivity can be attributed both to (1) the lesser steric bulk of the Ph versus TMS groups, and (2) the shorter C−Ph (1.53 Å) versus C−TMS (1.87 Å) bond, which forces the more open chair component of the favored boat/chair conformation of the ring to be cis to the Ph group. This is reversed for the 10-TMS system, where the boat component is favored on this side (cf., **B** vs **A**).



The 10-substituted-9-BBD ring clearly defines a chiral pocket, as is illustrated in the energetically favored pretransition state complexes **A** and **B** for aldehydes and ketones, respectively.[6] These complexes are anti with respect to the borane/carbonyl compound, cis with respect to position of carbonyl relative to the 10-R group, and "down" with respect to the orientation of the aldehyde or ketone with respect to the ring system. Eight diastereomeric complexes can result by varying these three parameters. All four of the "up" complexes are prevented from reaching energetically competitive transition states by adverse interactions with the 10-R groups. For substrates with groups which differ greatly in size (e.g., RCHO, ArCOMe), anti-complexation is clearly dominant (cf., **B** vs **D**). This leads to **B** being preferred over its "trans" counterpart **C** on steric grounds with the smaller oxygen atom versus the methylene of the allyl group being best positioned "cis" to the 10-R substituent. This is a major effect, and allylation occurs nearly exclusively with (−)-**1*R*** on the *re* face of the stereoelectronically biased ketones (see Table 1, (+)-**1*S*** 6 *si* face) as it does in the analogous aldehyde process with the 10-TMS reagent (96 → 99% ee).[4,7] However, for even methyl groups, this pocket is too small with the 10-TMS system, and slow allylation at 25 °C is less selective with respect to the cis versus trans reaction pathways. Fortunately, with **1**, the combination of smaller flat Ph group and chair form of the ring on the cis side works in concert to provide an ideal pocket for methyl groups, and the allylation is both rapid and highly selective at low temperatures (**B**). With a leading Et versus Me group, computational analysis reveals that the Et group must rotate away from the ring to form a viable pretransition state complex resulting in a slower reaction for propio- versus acetophenone. However, both do react at low temperature with high enantioselectivity. As a consequence, for ketones such as MEK and MVK (Table 1, series **f**, **g**), in addition to **C**, the isomeric syn complex, **D**, must also be considered as a potential source of diminished enantioselectivity.

The reagents **1** are easily prepared in either enantiomerically pure form from air-stable precursors and are highly reactive, environmentally friendly, and fully recyclable. In combination with their high selectivities for a wide range of unsymmetrical ketones, these features of the new BBD reagents make them highly attractive alternatives to existing methods for the asymmetric allylation of ketones.

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Note Added after ASAP Publication. In the Supporting Information published on the Internet July 30, 2005, there was an error in Figure 2 on page 2. The SI published August 4, 2005, is correct.

Supporting Information Available: Experimental procedures, analytical data and selected spectra for **1**, **4**, **6**, and derivatives, and X-ray data for (+)-**4*S***. This material is available free of charge via the Internet at http://pubs.acs.org.

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