ORGANIC LETTERS

2007
Vol. 9, No. 6
1081−1084

β-Silylated Homopropargylic Amines via the Asymmetric Allenylboration of Aldimines

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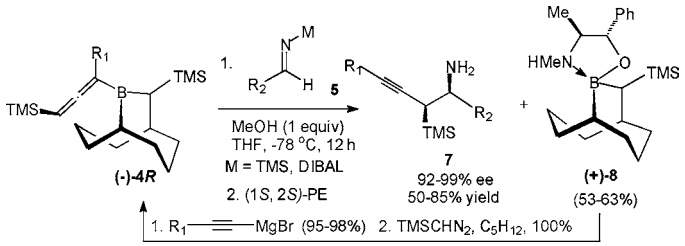
Received January 10, 2007

ABSTRACT

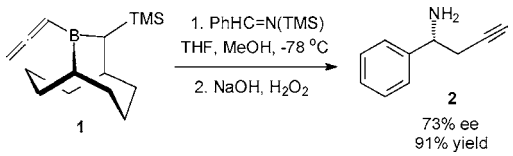


The asymmetric synthesis of α-trimethylsilylpropargylic carbamines (7) through the addition of allenylboranes 4 to *N*-H aldimines is reported. The insertion of $TMSCHN_2$ into enantiomerically pure *B*-alkynyl-10-TMS-9-borabicyclo[3.3.2]decanes 3 followed by a sterically driven 1,3-suprafacial borotropic shift proceeds with complete stereospecificity to produce 4 in diastereomerically and enantiomerically pure form. These reagents give 7 (51–85%, syn/anti >99%, 92–9% ee) permitting the recovery of 8 (53–63%). Allenylboranes 4 also provide a convenient route to optically pure allenylsilanes 13 (55–94%) through their protonolysis.

Homopropargylic amines constitute an important class of nitrogen-containing building blocks whose asymmetric synthesis represents a challenging task. Their racemic synthesis through the allenylation of *N*-substituted imines is accomplished employing a variety of allenylmetallics, including *B*-allenyl-9-BBN.[1,2] However, until now, the asymmetric allenylboration of imines has not been reported.

Recently, we have developed a number of new organoborane reagents for asymmetric conversions which contain the remarkably versatile 10-trimethylsilyl-9-borabicyclo[3.3.2]-decane (10-TMS-9-BBD) ring system. For example, either aldehydes or *N*-H aldimines provide effective substrates for asymmetric allylation with these reagents.[3] This suggested that the corresponding *B*-allenyl reagent **1**[4] might provide a highly selective route to **2** through the allenylboration of *N*-H aldimines, generated from either their *N*-TMS or *N*-DIBAL precursors. As a representative example, we chose to add *N*-TMS benzaldimine to **1** in the presence of 1 equiv of MeOH. This affords **2** efficiently (91%) in good optical purity (73% ee) (Scheme 1). This observed selectivity of **1** with benzaldimine compared to benzaldehyde (93% ee) is consistent with a general trend wherein aldehydes provide

Scheme 1



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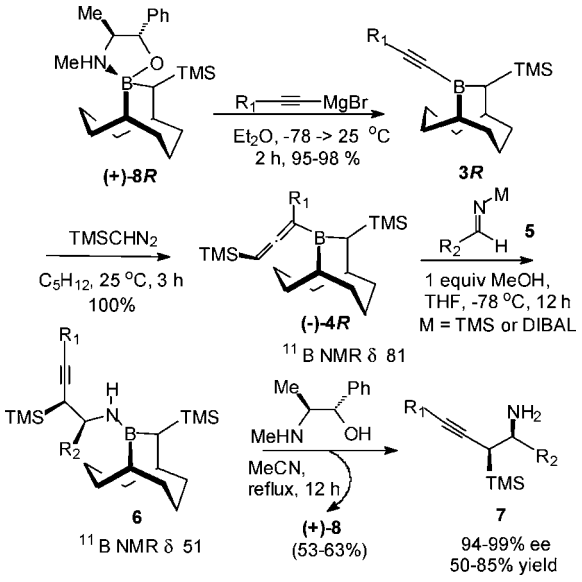
10.1021/ol070074g CCC: $37.00
Published on Web 02/13/2007

higher selectivities than do their imine counterparts. This diminution in selectivity can be attributed to the lesser size difference between the atoms which are coordinated to the boron atom, that is, the allenyl sp^2 carbon vs either the iminyl NH or the smaller aldehydic O. This suggested that by increasing the effective size of the allenyl group, the selectivity of the allenylboration could be enhanced. Fortunately, we had recently discovered a novel entry to more substituted *B*-allenyl-10-TMS-9-BBDs (**4**) in optically pure form.[5] These result from a stereospecific CH(TMS) insertion into *B*-alkynyl-10-TMS-9-BBDs (**3**) followed by a sterically driven suprafacial 1,3-borotropic shift of the resulting propargylborane to give **4** as a single diastereomer (Scheme 2). For aldehydes, **4** (94−99% ee) is more enantioselective than is **1** (93−95% ee).

Scheme 2



Readily available through simple Grignard procedures, several alkynylboranes (**3**) were prepared (R_1 = Me (**a**), $(CH_2)_3Cl$ (**b**), *c*-C_3H_5 (**c**), $(CH_2)_4CH_3$ (**d**)) from the enantiomerically pure crystalline complexes **8** (Scheme 2). In this process, pseudoephedrine (PE) can be recovered (81%) through the addition of HCl to the insoluble Mg^{+2} salts formed as byproducts from this metathesis. Addition of $TMSCHN_2$ to **3** results in an antiperiplanar 1,2-B→C alkynyl group migration to give an α-silylated propargylborane, which undergoes a sterically driven 1,3-suprafacial borotropic rearrangement to ultimately give **4**.[5]

Allenylation with **4** was conducted with the *N*-H imines derived from either *N*-TMS or *N*-DIBAL aldimines **5**.[6] Addition of 1 equiv of methanol to a mixture of **4** and **5** in THF triggers the smooth allenylboration process (12 h, −78 °C). Following the complete formation of **6**, the mixture was concentrated and the appropriate enantiomer of PE and acetonitrile were added. Transesterification occurs in 12 h at reflux temperature ultimately providing **8** (53−63%), which can be recycled for the regeneration of **4**. The α-TMS propargylic carbamines **7** were isolated in high yields (51−85%) and excellent selectivity (>99% syn, 92−99% ee). While **4b** ($R_1 = (CH_2)_3Cl$) is particularly selective (99% ee), even **4a** (R_1 = Me) adds to acetaldimine to provide **7h** in 92% ee (Table 1, entry 8).

Table 1. Allenylboration of *N*-H Aldimines with **4**[a]

entry	**4**	R_2 in **5**	**7**	yield (%)[a]	ee (%)[b]
1	**b**	2-C_4H_3S	**a**	51	99
2	**b**	$CH(CH_3)_2$	**b**	66	99
3	**b**	4-$MeOC_6H_4$	**c**	72	99
4	**b**	Ph	**d**	85	99
5	**d**	Ph	**e**	84	99
6	**c**	Ph	**f**	78	99
7	**a**	Ph	**g**	77	94
8	**a**	CH_3	**h**	83	92

[a] Isolated yields after column chromatography. [b] Product ee determined utilizing ^{31}P NMR after the conversion of **7** to their phosphoramide derivatives through the alexakis procedure.[7]

The remarkable enantioselectivity observed for this process can be attributed to the difference in size between the α-substituted allenic carbon and the incoming aldimine (Figure 1). We examined pre-transition state complexes **A**

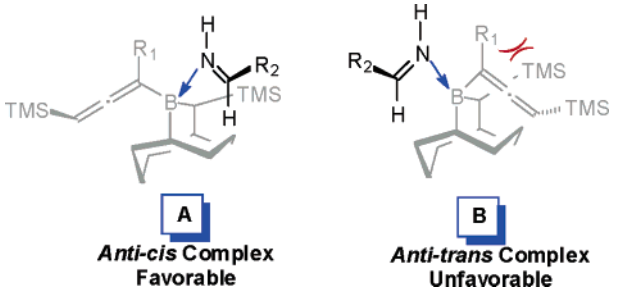


Figure 1. Proposed models for the observed stereochemistry in the allenylboration of *N*-H aldimines with (−)-**4*R***.

(anti/cis) and **B** (anti/trans) computationally, which reveals that **A** is favored over **B**. This is because the unfavorable steric interactions of the allenyl CHR_1 moiety with the 10-TMS substitution are absent in **A**. This model is consistent with the diminution in enantioselectivity observed with a reduction in the size of R_1 to methyl (94%, Table 1, entry 7).[8]

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The syn relative stereochemistry of the α-TMS-propargylic carbamines **7** was confirmed from the single-crystal X-ray structure of **7d** (Figure 2). This is also consistent with our

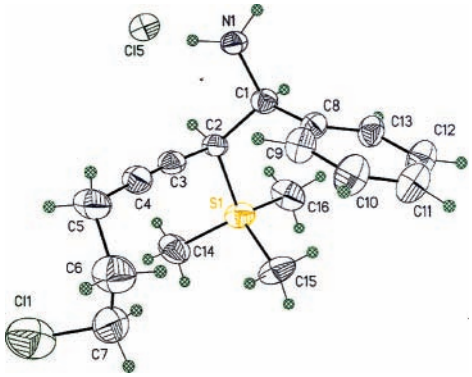
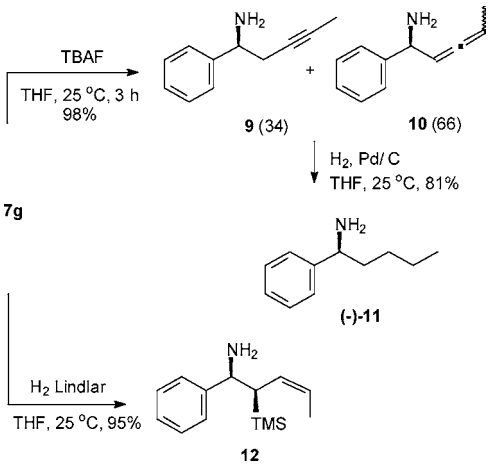


Figure 2. Single-crystal X-ray structure of **7d** hydrochloride

findings in the allenylboration of aldehydes with **4**.[5] The absolute stereochemistry of these amines **7** was obtained through the conversion of (1*R*, 2*R*)-**7g** (from ***4Sa***) to 1-amino-1-phenylpentane **11**. In contrast to their carbinol counterparts which easily undergo elimination, *β*-TMS carbamines react with TBAF (1 equiv) to produce a 34:66 mixture of propargylic (**9**) and allenic (**10**) carbamines.[9] Catalytic hydrogenation of this mixture with exactly 2 equiv of H_2 provides (1*S*)-**11**. The assignment of the absolute configuration of **11** was based upon its specific rotation compared to the literature value (see Scheme 3).[10] The *S*

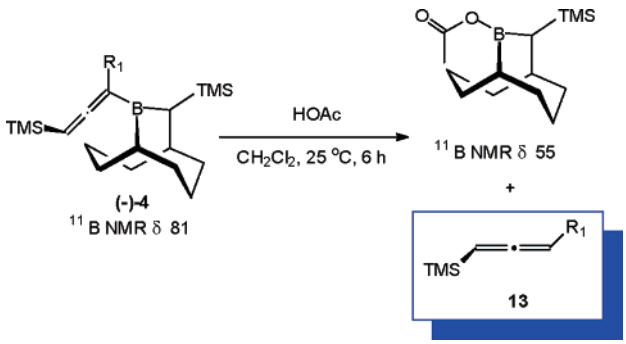
Scheme 3



configuration for **11** is consistent with the stereochemistry expected from the favored pre-transition state complex **A**.

As a useful application of **7**, we carried out the semireduction of **7g** to provide a particularly convenient entry to the nonracemic homoallylic amine **12**. This process retains the two contiguous stereogenic centers with the introduction of the *Z*-allylsilane functionality (Scheme 3).

Scheme 4



Allenylboranes smoothly undergo protonolysis with acetic acid to provide the corresponding allenes.[11] Taking advantage of the high optical purity of our allenylboranes **4**, we chose to explore their conversion to optically pure allenylsilanes **13**. These are useful for several transformations such as their

Table 2. Asymmetric Synthesis of Allenylsilanes **13**

entry	R_1	**4**	**13**	yield (%)[a]	$[\alpha]_D$[b]
1	Me	***Sa***	**a**	55	+94.0
2	$(CH_2)_3Cl$	***Rb***	**b**	86	−107.4
3	*c*-C_3H_5	***Sc***	**c**	87	+40.6
4	C_5H_{11}	***Rd***	**d**	94	−39.6

[a] Isolated yields after column chromatography. [b] Specific rotations were determined in either $CDCl_3$ or CH_2Cl_2 solution. See Si for the conditions employed for each example.

addition to aldehydes and for cycloadditions.[12] Allenylsilanes are usually prepared through the organocuprate addition to propargyl carbamates or mesylates.[13] Other methods for the synthesis of allenylsilanes include the palladium-catalyzed bis-silylation of optically active propargylic alcohols[14] and

(8) The equilibrium distance between the *γ*-allenyl carbon atom and the iminyl carbon is ∼3.4 Δ. Constricting this distance to 3.0 Δ, increases this energy difference (**A** vs **B**, R_1 = Me, R_2 = Ph) to >1 kcal/mol.

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the palladium-catalyzed hydrosilylation of enynes.[15] Axially chiral allenylboranes are known and their protonolysis does produce optically active allenes.[16] Addition of 1 equiv of glacial acetic acid to **4** affords **13** in good yields (55−97%) after 6 h at 25 °C. Since this reaction proceeds with retention of configuration either enantiomer of the allenylsilane can be synthesized depending on the enantiomer of **4** employed.

In summary, the allenylborane reagents **4** are simply prepared from the enantiomerically pure air-stable crystalline complexes **8** through a two-step operation involving a Grignard procedure to give the alkynylborane **3** followed by treatment with $TMSCHN_2$ to result in an insertion/rearrangement that gives **4** in both diasteromerically and enantiomerically pure form. This method also permits the recovery of pseudoephedrine (81%). Reagents **4** cleanly add to *N*-H imines (**5**) (12 h, −78 °C), efficiently producing α-TMS-propargylic carbamines (**7**) following a non-oxidative pseudoephedrine workup that regenerates **8** (53−63%) for recycling. Depending upon the enantiomeric form of **4** employed, either enantiomer of **7** can be prepared with predictable stereochemistry. The addition of **4** to *N*-H imines proved to be a highly selective process (92−99% ee) for the synthesis of the homopropargylic amines **7**, even for the more challenging substrates such as acetaldimine. Reagents **1** can also be transformed into the corresponding optically pure allenylsilanes **13** through simple protonolysis in good to excellent yields (55−94%).

Acknowledgment. The support of the NSF (CHE-0517194), NIH SCORE (S06GM8102), and U.S. Department of Education GAANN Program (P200A030197-04) is gratefully acknowledged. We wish to thank Dr. Hong Zhao (University of Puerto Rico) for determining the X-ray structure of **7d** hydrochloride.

Supporting Information Available: Full experimental procedures, characterization data, selected spectra for **2**−**4**, **7**−**13**, and derivatives and X-ray crystallographic data for **7d** hydrochloride. This material is available free of charge via the Internet at http://pubs.acs.org.

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