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Nonracemic 3°-Carbamines from the Asymmetric Allylboration of *N*-Trimethylsilyl Ketimines with *B*-Allyl-10-phenyl-9-borabicyclo[3.3.2]decanes

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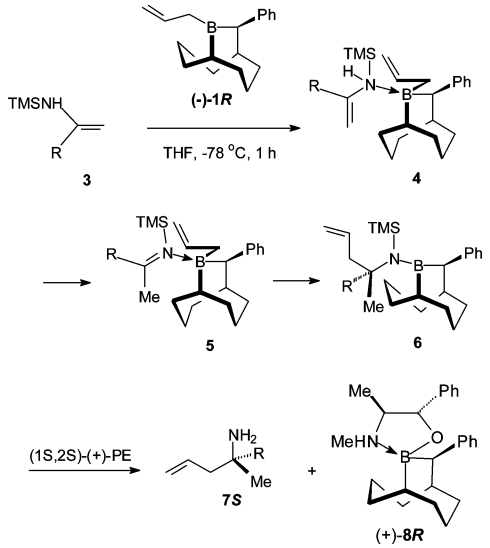
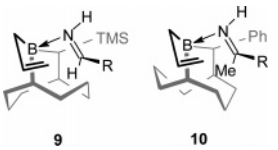
The synthesis of nonracemic 3°-carbamines from the asymmetric allylation of achiral ketimines represents an important synthetic challenge. These amines can be prepared through the asymmetric addition of Grignard and organolithium reagents to unsymmetrical chiral *N*-sulfinyl ketimines.[1] The asymmetric allylsilylation of ketone-derived *N*-benzoylhydrazones was also demonstrated to provide these nonracemic 3°-carbamines after the SmI_2-mediated reduction of the resulting homopropargylic hydrazines.[2] While no analogous asymmetric allylboration process is known for achiral ketimines or related compounds, new allylboranes and processes have been recently reported for the asymmetric allylboration of ketones.[3] Among these, the *B*-allyl-10-phenyl-9-borabicyclo[3.3.2]-decanes (9-BBDs) (**1**) contain a nearly ideal chiral pocket for the highly enantioselective allylation of methyl ketones.[3a] In the present study, we wish to report the asymmetric allylboration of *N*-TMS ketimines **2** generated in situ from the reaction of *N*-TMS enamines **3** with **1**. The new process can be viewed as occurring through an initial complex **4** followed by isomerization to **5**, allylation giving **6**, which provides the desired 3°-carbamines **7** after a pseudoephedrine (PE) workup (Scheme 1).

Scheme 1



Clearly, **3** is not an obvious choice as a substrate for the allylboration process. In fact, our plan was to follow an earlier protocol which was successful for the allylboration of *N*-H aldimines derived from the borane-mediated methanolysis of their *N*-TMS precursors.[4] Since the allylboration of the aldimines with the BBD systems does not occur until the *N*-TMS derivatives are converted to their *N*-H counterparts,[4e] we anticipated similar behavior, namely, that **1** would smoothly allylate the *N*-H ketimines derived from **2** in a predictable manner (cf. **9** and **10**).[5]



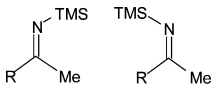
9 **10**

Mixtures of the *anti*-*N*-TMS ketimines (***a*-2**) and **3** were prepared through the Rochow protocol[6] from nitriles and LiMe followed by TMSCl (75−95%). These mixtures are thermally unstable, and heating usually increases the amount of **3** and also gives rise to minor amounts of the *syn*-ketimine ***s*-2** (Table 1).

Table 1. *N*-TMS Ketimines and Enamines from Nitriles

R	series	***a*-2:3**[a]	***s*-2:*a*-2:3**[b]
Ph	**a**	94:6	16:22:62
2-$MeOC_6H_4$	**b**	70:30	4:4:92
4-$MeOC_6H_4$	**c**	40:60	5:48:47
t-Bu	**d**	80:20	
c-Hx	**e**	60:40	
4-BrC_6H_4	**f**	45:55	15:35:50
4-MeC_6H_4	**g**	74:26	5:36:59
3-Py	**h**	60:40	4:9:87
4-$Me_2NC_6H_4$	**i**	81:19	
4-ClC_6H_4	**j**	60:40	10:26:64
2-thienyl	**k**	87:13	0:70:30

[a] The ***a*-2:3** ratios were estimated from the ^{13}C NMR analysis of the peak areas for the TMS signals. Other characteristic signals for these tautomers were also observed in each case. [b] The ***a*-2:3** mixtures were heated at reflux temperature (24−72 h), and the ratios of ***s*-2**, ***a*-2**, and **3** were estimated as above (see Supporting Information).



***a*-2** ***s*-2**

Treatment of ***a*-2a:3a** (90:10) with a 1:1 mixture of **1** and MeOH at −78 °C results in the clean formation of the desired *N*-boryl homoallylic amine (^{11}B NMR δ 51). An oxidative workup provided **7a*R*** in 80% yield and 52% ee. The *R* configuration of **7a*R*** is consistent with the allylboration of PhCOMe with **1** (i.e., *R*, 96% ee).[3a] The lesser ee for ***a*-2a:3a** versus PhCOMe parallels a similar pattern observed in the allylboration of *N*-H aldimines versus aldehydes with *B*-allyl-10-TMS-9-BBD.[4e] Our models for the key pretransition states for these two processes are illustrated above (cf. **9** and **10**).

Seeking a more selective reaction protocol, we prepared (±)-*B*-Et-10-Ph-9-BBD (**11**) as a nonreacting model for **1**. Its complexation with PhMeC═NH (4 equiv) was examined by ^{11}B NMR, revealing that **11** (δ 83) was completely converted to its imine complex (δ 1). Unexpectedly, we also noted that **11** is partially complexed (^{11}B NMR δ −1, ∼5%) with the excess 90:10 ***a*-2a:3a** mixture at −78 °C even before the addition of MeOH. Moreover, using 4 equiv of the 16:22:62 ***s*-2:*a*-2:3** mixture increases the complexation with **11** to ∼90%.

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Table 2. Asymmetric Allylboration of *N*-TMS Ketimines with **1**

3	1	8[a]	yield of 7[b](%)	% ee (abs. config.)[c]
a	*R*	63	75	92 (*S*)
b	*R*	52	58	94 (*S*)
c	*R*	48	55	92 (*S*)
d	*R*	58	50	98 (*S*)
e	*S*	64	66	70 (*R*)
f	*S*	61	65	70 (*R*)
g	*S*	65	67	84 (*R*)
h	*R*	50	71	60 (*S*)
i	*R*		82	94 (*S*)
j	*S*	60	74	64 (*R*)
k	*S*	65	80	60 (*R*)

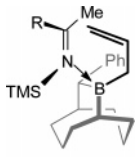
[a] Yield of crystalline **(+)-8*R*** from **(−)-1*R*** or **(−)-8*S*** from **(+)-1*S*** reactions. [b] Isolated yield based upon **1**. [c] The product ee's were determined by ^{31}P NMR analysis of their Alexakis thiophosphoric triamides.[7] The absolute configurations of **7** were based upon the known rotation of **7a**.[1a,2]

This suggested that ***a*-2:3** mixtures may undergo allylboration with **1** even without converting the *N*-TMS to the corresponding *N*-H ketimine. The allylboration process was examined with **(−)-1*R*** at −78 °C employing a 94:6 ***a*-2a:3a** mixture (2 equiv) with the finding that the addition was complete in 16 h. Significantly, the homoallylic amine **7a** was formed in 92% ee and with the opposite *S* absolute configuration from that obtained from PhMeC═NH! Moreover, under these same conditions, the 16:22:62 ***s*-2:*a*-2:3** mixture (2 equiv) also gave **7a*S***, again in 92% ee, with the reaction being complete in <1 h. This reactivity is consistent with the general process illustrated in Scheme 1, wherein **3** initially forms a complex with **1** which rapidly isomerizes to the reacting **5** complex which leads to **6** and ultimately to **7**. Clearly, **5** could also form directly from ***s*-2**, but even in cases where this isomer is not present, rapid allylboration occurs provided ample **3** is present to react with **1**, as illustrated in Scheme 1. Moreover, to gain additional support for our view of the process, the *anti* aldimine PhHC═NTMS (2 equiv) was found to partially complex **1** (~20% at −78 °C), but not its 10-TMS counterpart. However, this aldimine, despite being less substituted than ***a*-2a**, does not undergo allylboration with either **1** or its 10-TMS counterpart even after 1 week at 25 °C. These aldimines simply do not have access to their *syn* isomers because the enamine-based process is not an option for them.

We carried out the allylboration of the **2/3** mixtures (≥2 equiv of **2/3**) for 1 h at −78 °C with **1** to ultimately produce **8** (48−65%) and the desired 3°-carbamine **7** (50−82%) in high ee (60−98%) (Table 2). The complex **8** is easily recycled back to **1** (98%) with allylmagnesium bromide in ether.

As can be noted from these results, higher ee's for **7** are generally observed for aryl derivatives with electron-donating groups in the aromatic ring. Sterically biased examples (e.g., **3d**) also provide excellent substrates for this process. For the 4-BrC_6H_4 (**f**) series, we also prepared the mixture of *N*-triethylsilyl (TES) ketimine and its enamine (81:19). This also underwent allylboration with **(+)-1*S*** (1 h, −78 °C) to give **7f*R*** (60%) in somewhat lower ee (50%) than was observed with **3f** (70% ee).

Simple MM calculations[8] suggest that **3** strongly prefers (**a** series, ~5 kcal/mol) to complex **(−)-1*R*** *trans* to the 10-Ph group (i.e., **4**). Tautomerism leads to either **5** or its rotamer **12**.



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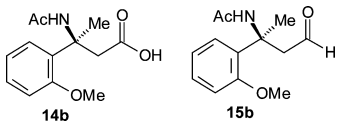
We view the larger TES versus TMS group as increasing the relative amount of the minor **7f*S*** enantiomer through this "upside-down" isomer which avoids TMS−Ph repulsions. Moreover, through the addition of EtMgBr to PhCN followed by TMSCl, we prepared the *N*-TMS propiophenone enamines **3l** as an 83:17 *Z/E* mixture free of either ketimine tautomer. This mixture reacts rapidly with **(+)-1*S*** (1 h, −78 °C) to give **7l*R*** (67%) in 65% ee.[9] Thus, with the larger Et versus Me inward group, repulsions between the BBD ring and this group apparently also increase the amount of **7** originating from this upside-down pathway, thereby lowering the product ee.

Clearly the carbamines **7** are rare with only **7a** being known in nonracemic form.[1a,2] With their ready availability through the present methodology, we chose to further demonstrate their utility through their conversion to the corresponding $\beta^{3,3}$-amino acids and β-amino aldehydes.[1a] Thus, acetylation of **7b** gives **13b** (80%) whose ozonolysis (CH_2Cl_2, −78 °C) affords **14b** (90%) and **15b** (57%) with oxidative (H_2O_2) and reductive (Me_2S) workups, respectively.



14b **15b**

The asymmetric allylboration of ketimines with the BBD reagent **1** has been accomplished in a unique manner utilizing their *N*-TMS enamines **3** to access the requisite *syn*-ketimine allylborane complexes **5**. The reagents **1** are readily prepared in either enantiomeric form and are easily recycled providing the 3°-carbamines **7** in high ee (60−98%). With the *N*-TMS substitution being readily hydrolyzed during workup, this new method has the advantage of producing the free 3°-carbamines **7** for subsequent conversions.

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Supporting Information Available: Experimental procedures, analytical data, and selected spectra for **1**−**3**, **7**, **8**, **13f**, **14f**, and **15g**, and derivatives and X-ray data for (+)-**8*R*** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Performed using the Spartan 04 MM program.
(9) With a 100% excess of *E*/*Z*-**3l**, the less sterically encumbered *E*-**3l**−**1** complex is evidently formed and proceeds to product faster than with *Z*-**3l**. Unreacted **3l** is observed exclusively as the *Z* isomer.

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