

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

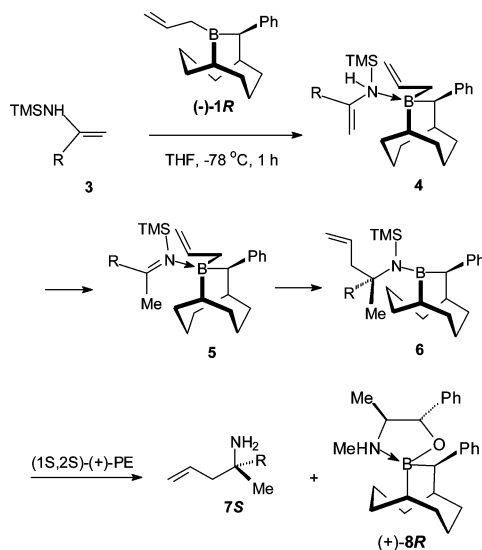
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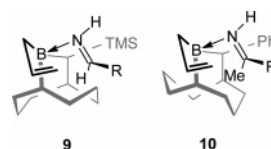
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The synthesis of nonracemic 3°-carbamines from the asymmetric allylation of achiral ketimines represents an important synthetic challenge. These amines can be prepared through the asymmetric addition of Grignard and organolithium reagents to unsymmetrical chiral *N*-sulfinyl ketimines.¹ The asymmetric allylsilylation of ketone-derived *N*-benzoylhydrazones was also demonstrated to provide these nonracemic 3°-carbamines after the SmI₂-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,^{4c} 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

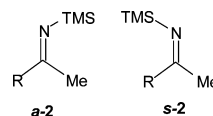


Mixtures of the *anti*-*N*-TMS ketimines (**a-2**) and **3** were prepared through the Rochow protocol⁶ from nitriles and LiMe followed by TMSCl (75–95%). These mixtures are thermally unstable, and heating usually increases the amount of **3** and also gives rise to minor amounts of the *syn*-ketimine *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 ₆ H ₄	b	70:30	4:4:92
4-MeOC ₆ H ₄	c	40:60	5:48:47
<i>t</i> -Bu	d	80:20	
<i>c</i> -Hx	e	60:40	
4-BrC ₆ H ₄	f	45:55	15:35:50
4-MeC ₆ H ₄	g	74:26	5:36:59
3-Py	h	60:40	4:9:87
4-Me ₂ NC ₆ H ₄	i	81:19	
4-ClC ₆ H 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 ¹³C 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).



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 (¹¹B NMR δ 51). An oxidative workup provided **7aR** in 80% yield and 52% ee. The *R* configuration of **7aR** 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.^{4c} 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 ¹¹B NMR, revealing that **11** (δ 83) was completely converted to its imine complex (δ 1). Unexpectedly, we also noted that **11** is partially complexed (¹¹B 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%.

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

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

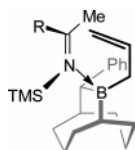
^a Yield of crystalline (+)-**8R** from (–)-**1R** or (–)-**8S** from (+)-**1S** reactions. ^b Isolated yield based upon **1**. ^c The product ee's were determined by ³¹P NMR analysis of their Alexakis thiophosphoric triamides.⁷ The absolute configurations of **7** were based upon the known rotation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

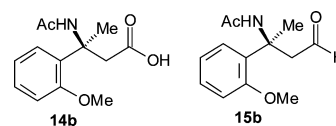
As can be noted from these results, higher ee's for **7** are generally observed for aryl derivatives with electron-donating groups in the aromatic ring. Sterically biased examples (e.g., **3d**) also provide excellent substrates for this process. For the 4-BrC₆H₄ (**f**) series, we also prepared the mixture of *N*-triethylsilyl (TES) ketimine and its enamine (81:19). This also underwent allylboration with (+)-**1S** (1 h, –78 °C) to give **7fR** (60%) in somewhat lower ee (50%) than was observed with **3f** (70% ee).

Simple MM calculations⁸ suggest that **3** strongly prefers (**a** series, ~5 kcal/mol) to complex (–)-**1R** *trans* to the 10-Ph group (i.e., **4**). Tautomerism leads to either **5** or its rotamer **12**.

**12**

We view the larger TES versus TMS group as increasing the relative amount of the minor **7fS** 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 **3i** as an 83:17 *Z/E* mixture free of either ketimine tautomer. This mixture reacts rapidly with (+)-**1S** (1 h, –78 °C) to give **7iR** (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 β^{3,3}-amino acids and β-amino aldehydes.^{1a} Thus, acetylation of **7b** gives **13b** (80%) whose ozonolysis (CH₂Cl₂, –78 °C) affords **14b** (90%) and **15b** (57%) with oxidative (H₂O₂) and reductive (Me₂S) workups, respectively.



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 (+)-**8R** (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*-**3i**, the less sterically encumbered *E*-**3i**–**1** complex is evidently formed and proceeds to product faster than with *Z*-**3i**. Unreacted **3i** is observed exclusively as the *Z* isomer.

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