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Non-Racemic 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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Abstract

The simple and efficient asymmetric synthesis of 3°-carbamines **7** from *N*-TMS enamines (**3**) and either enantiomeric form of *B*-allyl-10-(phenyl)-9-borabicyclo[3.3.2]decane (**1**) is reported. The high reactivity (<1 h, -78 °C) and enantioselectivity (60–98% ee) of these substrates can be attributed to the fact that the complexation of **3** with **1** facilitates its isomerization to the corresponding *syn*-*N*-TMS ketimine complex from which allylation can occur. In addition to providing the homoallylic amines **7** with predictable stereochemistry, the procedure also permits the efficient recovery of the chiral boron moiety (50–65%) as air-stable crystalline pseudoephedrine complexes **8** which are directly converted back to **1** with allylmagnesium bromide in ether (98%).

The synthesis of non-racemic 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 non-racemic 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).

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 that similar behavior, namely that **1** would smoothly allylate the *N*-H ketimines derived from **2** in a predictable manner (*c.f.*, **9**, **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).

Treatment of **a-2a:3a** (90:10) with a 1:1 mixture of **1** and MeOH at $-78\text{ }^{\circ}\text{C}$ results in the clean formation of the desired *N*-boryl homoallylic amine (^{11}B NMR δ 51). An oxidative work-up 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** vs PhCOMe parallels a similar pattern observed in the allylboration of *N*-H aldimines vs aldehydes with *B*-allyl-10-TMS-9-BBD.^{4e} Our models for the key pre-transition states for these two processes are illustrated above (*c.f.*, **9** and **10**).

Seeking a more selective reaction protocol, we prepared ($\pm$)-*B*Et-10-Ph-9-BBD (**11**) as a non-reacting 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 $-78\text{ }^{\circ}\text{C}$ 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%.

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 $-78\text{ }^{\circ}\text{C}$ 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 forming 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 its being less substituted than *a*-**2a**, does not undergo allylboration with either **1** or its 10-TMS counterpart even after one 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 either to **5** or its rotomer **12**.

We view the larger TES vs 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 **3l** as an 83:17 *Z/E* mixture free of either ketimine tautomer. This mixture reacts rapidly with (+)-**1S** (1 h, -78 °C) to give **7lR** (67%) in 65% ee.⁹ Thus, with the larger Et vs 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 non-racemic 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 (CH₂Cl₂, -78 °C) affords **14b** (90%) and **15b** (57%) with oxidative (H₂O₂) and reductive (Me₂S) work-ups, 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 work-up, this new method has the advantage of producing the free 3°-carbamines **7** for subsequent conversions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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8. Performed using the Spartan '04 MM program.
9. With a 100% excess of *E/Z*-31, the less sterically encumbered *E*-31–1 complex is evidently formed and proceeds to product faster than with *Z*-31. Unreacted 31 is observed as exclusively the *Z* isomer.

Scheme 1.

Table 1*N*-TMS ketimines and enamines from nitriles

R	series	<i>a</i>-2:3^a	<i>s</i>-2:<i>a</i>-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

^aThe *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.

^bThe *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 SI).

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>)

^aYield of crystalline (+)-**8R** from (–)-**1R** or (–)-**8S** from (+)-**1S** reactions.

^bIsolated yield based upon **1**.

^cThe 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}