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(*E*)-2-Boryl 1,3-Dienes from the 10-TMS-9-BBDs: Highly Selective Reagents for the Asymmetric Synthesis of *anti*-α,β-Disubstituted β-Allenylamines from the Allylboration of Aldimines

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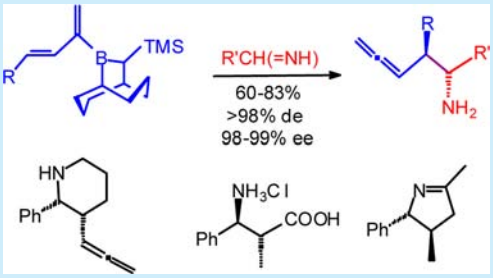
Supporting Information

ABSTRACT: The asymmetric allylboration of *N*-H aldimines with optically pure *trans*-4-substituted-2-boryl-1,3-dienes **6** is described. These organoboranes **6** serve as near-perfect asymmetric allylborating agents for *N*-H aldimines for the preparation of *anti*-1,2-disubstituted-3,4-pentadien-1-amines **11** as essentially single diastereomers in enantiomerically pure form (>98% de, ≥98% ee). Enantiomerically pure *cis*-2,3-disubstitued piperidines **12** and α,β-disubstituted-β-amino acids **17** are readily prepared through the standard protocols. A novel Ru-catalyzed hydroamination provides *trans*-4,5-disubstituted-1-pyrrolines **21** from **11**.

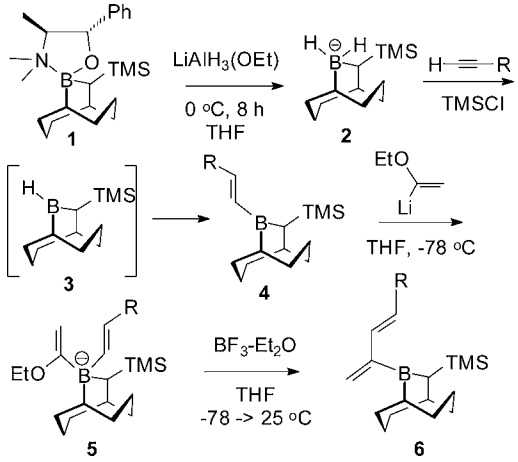


The omnipresence of amines in natural products and pharmaceuticals provides the impetus for the development of new asymmetric methods for their synthesis. A breakthrough in the construction of nonracemic homoallylic amines occurred with the discovery that borane-mediated generation of *N*-H imines from their *N*-metalloimine precursors, which resulted in the development of very useful new substrates for allylboration.[1,2] A number of variants can be made on these additions including their γ-alkoxyallyl- and allenylborations.[3] Recent interest in the related asymmetric addition to aldimines has included the discovery of both stoichiometric and catalytic processes.[4] The *N*-substitution can play a critical role in directing the addition,[4g,h] or it can merely act as a spectator group as is the case for the allylboration of *N*-H aldimines.[3] Unfortunately, the allylborations of these aldimines are normally somewhat less selective than for the additions to the corresponding aldehydes.[2,3] Employing the 9-borabicyclo[3.3.2]decanes (BBDs), we had observed that α-substitution in the allenylboranes could markedly increase their selectivity (i.e., 73 → 99% ee) in the allenylboration of these *N*-H aldimines.[3c,5] This phenomenon has been observed in related processes.[6,7] Recently, we discovered a novel entry to 2-boryl-1,3-dienes (**6**) through a hydroboration/carbenoid insertion pathway (Scheme 1).[8] We viewed these as "elaborated allylborating" agents, and indeed, their additions to aldehydes proceeds with near-perfect diastereo- and enantioselectivity through borinic esters **7** to form *anti*-1,2-disubstituted-3,4-pentadien-1-ols **8** (>99% de, 98−99% ee).[8]

With its α-methylene substitution, these reagents **6** were excellent candidates for the more demanding *N*-H aldimine substrates. The allylboration process was performed by employing the *N*-H aldimines derived from their *N*-DIBAL precursors.[2b]

The addition of 1 equiv of MeOH to a mixture of **6** and the *N*-DIBAL imine in THF at −78 °C triggers the allylboration process with the formation of the *N*-H aldimines. However, it was observed that, after 12 h, the addition of **6** to the aldimine in THF at −78 °C was incomplete as judged by the ^{11}B NMR analysis of a mixture of **6** (δ 81) and the borinic amide **7** (δ 47). To improve this conversion, we opted to use 2 equiv of *N*-DIBAL aldimines and MeOH relative to **6**, allowing the admixture to reach room temperature slowly and remain at that temperature for 6 h, which results in complete addition. Once the borinic amide **9** was formed, a standard oxidative workup with alkaline H_2O_2 was used. Surprisingly, this process permitted us to isolate the corresponding *N*-(β-allenylalkyl)-aldimines **10** through column chromatography, employing amine-treated silica gel (99:1 hexane:Et_3N). The conversion of

Scheme 1. Hydroboration/Vinylidene Insertion to 6



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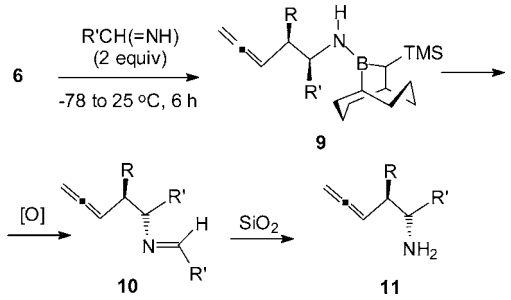
9 to the condensed imine products **10** greatly facilitated their isolation by chromatography due to their low polarity compared to the diol byproduct derived from the oxidation of the BBD moiety. These imines were easily hydrolyzed through standard silica gel column chromatography. After the aldehydes had eluted with hexane-ether (98:2), the free amine **11** was obtained by elution with EtOAc.

The β-allenylamines **11** were isolated in high yields (60−83%) and with remarkably high stereoselectivities (≥99% de and ≥98% ee). Differing functional groups in the aldimine, including both electron-donating and electron-withdrawing groups as well as aromatic and aliphatic aldimines, did not play a role in the selectivities observed for **6**.

Interestingly, entry **e** in Table 1 did not give **10e** nor **11e** after the oxidative workup but, rather, the cyclized product

Table 1. Asymmetric 2-Dienylboration of Representative N−H Aldimines with 6

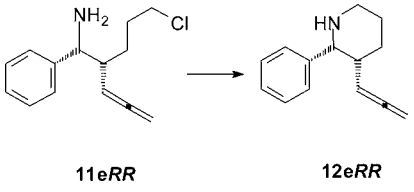


6	11, R, R′	yield[a] (%)	de[b] (%)	ee[c] (%)	config[d]
R	**a**, Me, Ph	83	>98	99	*R,R*
S	**a**, Me, Ph	83	>98	99	*S,S*
R	**b**, Pn,[e] *p*-MeOC$_6$H$_4$	71	>98	99	*R,R*
S	**c**, Pn, *p*-ClC$_6$H$_4$	80	>98	99	*S,S*
S	**d**, Pn, Ph	74	>98	98	*S,S*
R	**e**, Cl(CH$_2$)$_3$, Ph	78	>98	99	*R,R*
R	**f**, c-Pr, Ph	76	>98	99	*R,S*
R	**g**, Pn, *i*-Pr	60	>98	98	*S,R*

[a]Isolated yields of analytically pure **11** except for **e**, which is for piperidine (+)-**12e*RR***. [b]Only one diastereoisomer observed by NMR. [c]Product ee determined by ^{13}C and ^{1}H NMR after conversion of **11** to the corresponding Mosher amide derivatives. [d]The absolute configuration was determined by oxidation of **15a*RR*** to the corresponding ((2*R*,3*S*)-2-methyl-3-phenyl-3-aminopropanoic acid hydrochloride) ((+)-**17a*RS***). The *R/S* notations in the compound numbering follow the standard order for IUPAC naming. [e]Pn = *n*-pentyl.

(2*R*,3*R*)-2-phenyl-3-(propa-1,2-dienyl)piperidine ((+)-**12e*RR***). This product is presumably formed by an intramolecular 6-*exo-tet* Baldwin cyclization[9] of the amine with the terminal ε-CH$_2$Cl rather than condensing with the PhCHO present in the concentrated reaction mixture (Scheme 2).

Scheme 2. Cyclization of 11e to Piperidine 12e



The high enantioselectivity observed for this process can be attributed to the differences in size between the C═CH$_2$ substitution on the α-carbon with respect to boron and the incoming *N*-H imine (Figure 1, ΔE_{13-14} = 3.3 kcal/mol). These

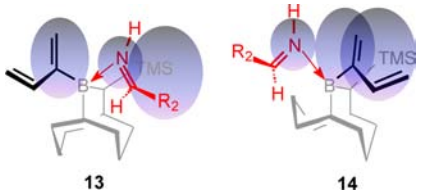
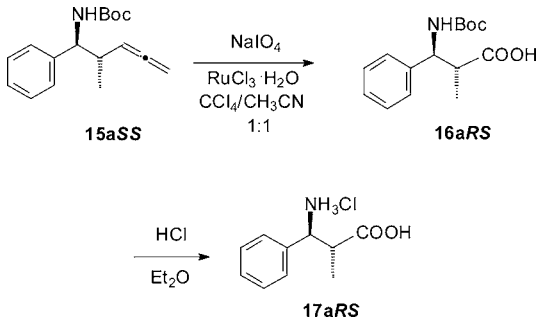


Figure 1. Pretransition-state models depicting the relative steric interactions in the 2-dienylboration of aldimines with **6**.

differences increase dramatically, the repulsions between this carbon and the 10-TMS group. Therefore, the imine's approach to **6** is dominated by **13** over **14** and the other possible diastereomeric complexes which could ultimately lead to **9**.

The absolute configuration of **11** was confirmed through the conversion of the corresponding *N*-Boc-protected amine from **11a*SS*** (i.e.,**15a*SS***) and its oxidation to the known α-substituted-β-amino acid ((2*R*,3*S*)-2-methyl-3-phenyl-3-amino-propanoic acid hydrochloride, (+)-**17a*RS*** (Scheme 3). The

Scheme 3. Synthesis of (+)-17a*RS* for the Determination of the Absolute Stereochemistry of 11a



Sharpless oxidative procedure[10] with catalytic RuCl$_3$ and NaIO$_4$ gave **16a*RS***, which was not purified, but rather, converted to **17a*RS*** (56%), an important intermediate for the synthesis of natural products and molecules with pharmacological properties (Scheme 3). It should be noted that our observed rotation for **17a*RS*** is more than *double* the previously reported value (cf. $[\alpha]^{25}_{D}$ = +22.0 (*c* 1.3 in MeOH) vs lit.[11] $[\alpha]^{25}_{D}$ = +10.2 (*c* 1.9 in MeOH).

The Takahashi Ru-catalyzed cyclocarbonylation of **11** appeared to be a very interesting application for β-allenyl carbinamines.[12−14] While this process is successful for alcohols such as **8**,[8] seemingly contradictory results had been reported for β-allenyl carbinamines similar to **11**. Whereas Kang reported that α-substituted *N*-sulfonyl and benzyl derivatives of β-allenylamines provide the corresponding 6-substituted α,β-unsaturated-δ-lactams (42−85%),[13] Takahashi observed that β-substituted β-allenylamines give ∼1:1 mixtures of *endo* and *exo* isomeric 5-substituted α,β-unsaturated-δ-lactams (ca. 80%).[12b] Since **11** contains substitution at both these positions, we were curious as to what its behavior would be in this process. We duplicated Kang's conditions employing the *N*-Ts derivative of **11a*RR*** (**18**), observing a 56:44 *endo/exo* mixture of inseparable lactams.[13] Takahashi's protocol with **11a*RR***, also gave a low

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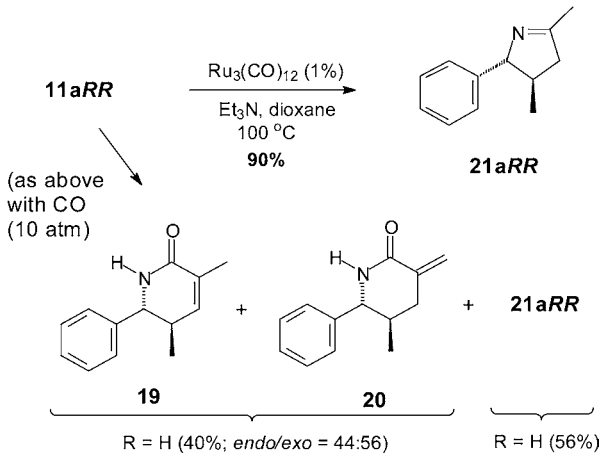
yield (40%) of a 44:56 *endo*:*exo* mixture of lactams (**19**/**20**)[12b] together with the novel pyrroline, **21a*RR*** (56%) (Scheme 4).

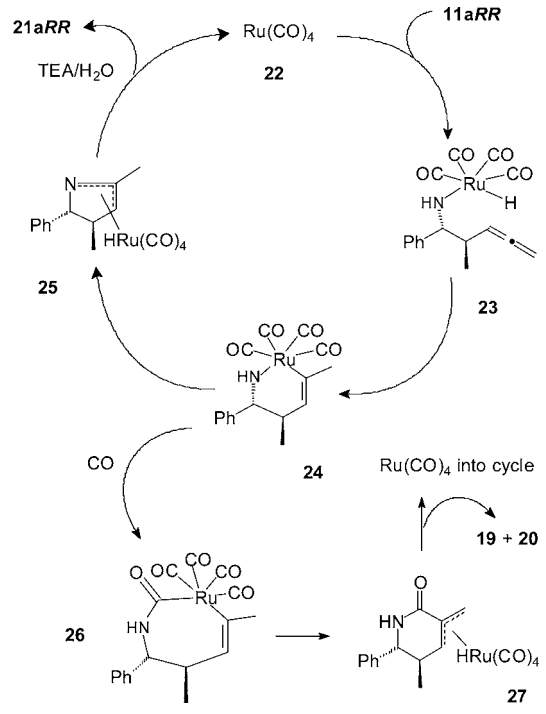
Scheme 4. Ru-Catalyzed Synthesis of Pyrroline 21a*RR* from *β*-Allenylamine 11a*RR*



While chromatographic separation of the **19**/**20** mixture was successful in providing the *endo*-lactam (+)-**19a*RR*** in pure form, the yield was very low (15%). However, the real value of this process appeared to us to be the development of a novel enantio- and stereoselective synthesis of *trans*-5,6-disubstituted-1-pyrrolines (**21**). Thus, by conducting this process under a N_2 rather than CO atmosphere, the isolated yield of **21a*RR*** *was increased to 90%*, a truly noteworthy result.[14]

Our explanation for this process is outlined in Scheme 5. Selecting the mononuclear $Ru(CO)_4$ as a reasonable catalyst for this cyclization,[13−15] its oxidative addition into NH bonds is consistent with a known *γ*-alkynylamine to 1-pyrroline conversion.[14] With the addition of RuH to the allene, the adduct **24** has two choices, either to permit CO insertion to form **26**, which collapses to **27**, or alternatively, it can reductively give the RuH **25**. With **24**, the elimination to form **25** is evidently faster than with the analogous oxaruthenacycle derived from **8**, and the pathway leading to **21**, rather than **19**/**20**, dominates the observed chemistry. The 5-substitution in **27** may influence the hydride transfer, favoring **20** over **19** to lessen the (5-Me---$Ru(CO)_4$) interactions. This would appear to be a very convenient entry to these substituted 1-pyrrolines from **11**.

Scheme 5. Possible Mechanistic Pathways to 19 and 20 and Pyrroline 21



In summary, the versatile 2-boryl-1,3-diene **6** has been employed in the asymmetric allylboration of *N*-H aldimines, which are generated in situ from their *N*-DIBAL precursors. The product amines **11** were obtained in good yields (60−83%) with excellent isomeric (>98% *anti*) and optical purities (98−99% ee). Their utility was demonstrated in their conversion to the *cis*-2,3-disubstituted piperidine **12**, to *anti*-*α*,*β*-disubstituted-*β*-amino acids **17** through a Sharpless oxidation and to enantio- and diastereomerically pure *trans*-4,5-disubstituted-1-pyrrolines **21** via a Ru-catalyzed hydroamination.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and spectroscopic data for **4**, **6**, **10**−**12**, **15**, **17**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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