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Asymmetric Propargylboration of Aldimines and Ketimines with the Borabicyclo[3.3.2]decanes: Novel Entries to Allenyl Carbinamines, Amino Acids, and Their α-Methyl Counterparts

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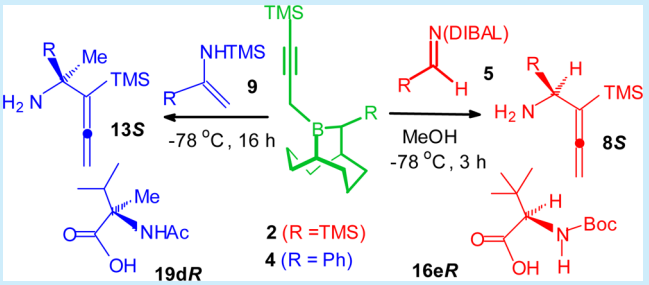
Supporting Information

ABSTRACT: Available in either enantiomerically pure form through quantitative Grignard procedures from air-stable crystalline complexes (**1**, **3**), the *B*-γ-TMS propargylic derivatives of the 10-TMS- (**2**) and 10-phenyl-9-borabicyclo[3.3.2]decanes (**4**) provide highly selective entries to 2°-allenyl carbinamines (**8**, 60−85%, 78−99% ee) and their 3° counterparts (**13**, 62−82%, 95−99% ee) through their additions to aldimines and ketimines, respectively. The absolute configurations of these amines were obtained from the known amino acid derivatives **16e*R*** and **19d*R*** through the ozonolysis of **8e*R*** and **13d*R*** and from the single-crystal X-ray structure of **14f*R***.

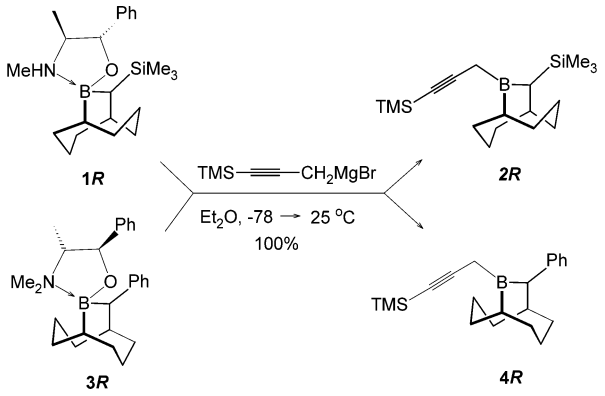


For over a decade, we have employed the robust 10-R-9-borabicyclo[3.3.2]decanes (BBDs) in highly effective chiral ligation for a wide variety of asymmetric organoborane conversions. In this regard, we have demonstrated that the 10-trimethylsilyl (TMS) derivatives are extremely effective in their additions to aldehydes and aldimines,[1] while their 10-phenyl counterparts are particularly selective in the corresponding additions to ketones and ketimines.[2] One application that has been relatively unexplored is in the potential of the propargylboration of aldimines to provide a very useful entry to nonracemic allenyl carbinamines, products which can undergo a variety of further useful conversions.[3,4] The selectivities of these reported processes can vary as can the regiochemistry of the additions. Moreover, the asymmetric propargylation of ketimines has not been reported.

Previous studies in our laboratories have revealed that the enantiomerically pure air-stable crystalline complexes **1** and **3** can provide, through simple Grignard procedures, either enantiomer of the reagents **2** and **4** both quantitatively and in optically pure form (Scheme 1).[1c,2c] The use of the TMS group to provide the propargylic rather than the allenylic form of the boranes was first demonstrated by Wang et al.,[5a] a process which was adapted and developed by Brown et al.[5b] for the asymmetric synthesis of homoallenic alcohols. Wang also applied this methodology to the racemic synthesis of homoallenyl amines.[6] Our use of the Grignard vs the corresponding lithium reagent previously employed was based upon the insolubility of the magnesium byproduct which, greatly facilitates the procedure.

The 10-TMS BBD reagent **2** was found to add smoothly to aldehydes at −78 °C to provide allenyl carbinols (60−87%, 94−98% ee), whereas the less hindered 10-Ph reagent **4** adds

Scheme 1. Preparation of Propargylboranes 2 and 4



to methyl ketones to give the corresponding 3°-carbinols (62−82%, 78−98% ee). Moreover, we had also found that *N*-H aldimines and *Z*-TMS ketimines (from their enamine precursors) were excellent substrates for allylboration and related processes with the appropriate BBD reagents.[1d,2b] This led us to examine the novel asymmetric propargylboration of imines with **2** and **4** with the goal of providing allenyl carbinamines in a highly selective manner.

The generation of *N*-DIBAL aldimines (**5**) was easily accomplished through Itsuno's partial reduction of representative nitriles with DIBAL-H.[7,8] In each case, the imine was added to **2** at −78 °C followed by the addition of 1 molar equiv of MeOH[8a] to provide the corresponding *syn* *N*-H

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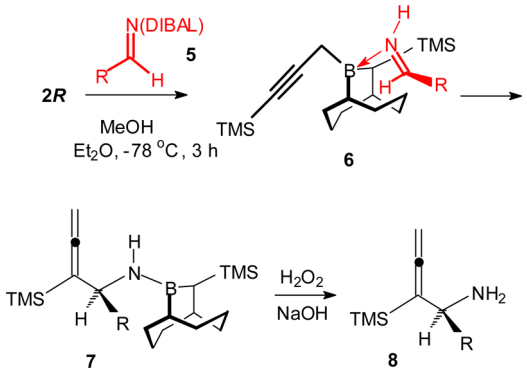
aldimines.[1d,9] After 3 h, the aminoborane intermediate **7** was observed by ^{11}B NMR δ 50. An oxidative workup (3 equiv of H_2O_2 and 3 M NaOH, reflux 3 h) was employed to provide the allenyl carbinamines **8** (60−85%) in 78−99% ee (Table 1). As can be seen from these data, the observed selectivities

Table 1. Propargylboration of N-H Aldimines with 2



series	R	2	yield of 8[a] (%)	ee[b] (%)	config[c]
a	4-MeOC$_6$H$_4$	*R*	85	78	*S*
b	Ph	*R*	70	90	*S*
b	Ph	*S*	70	90	*R*
c	2-Th[d]	*R*	60	92	*R*
d	*i*-Pr	*S*	69	95	*R*
e	*t*-Bu	*S*	70	99	*R*
f	*c*-Pr	*S*	80	90	*R*

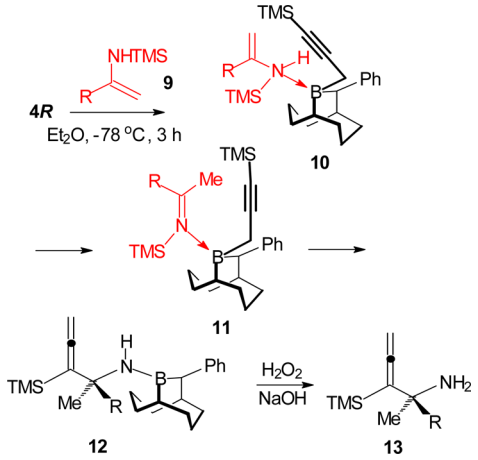
[a]Isolated yield employing a 1:1:1 ratio of **2**/**5**/MeOH. [b]Enantiomeric excess determined by the NMR of the Mosher amide derivatives. [c]Absolute configuration was determined by comparison of the literature published optical rotations of the desilylated allene **8b′** and of the known amino acid **16e**.[7,8] [d]2-Thienyl.

generally exceed 90% ee. Simple molecular mechanics calculations (Spartan 08) suggest that the somewhat lower selectivity (i.e., 78% ee) observed for the 4-methoxyphenyl example (**8a**) may be due to adverse steric interactions between the γ-TMS and 4-methoxy groups in the transition state (see pretransition state **6**).

We were very pleased that compounds such as **8** could be constructed with ease in such a highly selective manner. Built into these products are the very useful chiral amine and allenylsilane functional groups. It is no wonder that this process has been identified as an important new conversion in organoborane chemistry.[3,4]

The success of the above process led us to address the greater challenge of the construction of the *tert*-alkylamines (**13**) in optically pure form. Previous studies in our laboratories had revealed that the 10-Ph-9-BBDs were extremely well-suited to the allylation, allenylation, and propargylation of methyl ketones.[2,7] We had also discovered that the allylation of *N*-TMS ketimines could also be accomplished to achieve higher selectivities than with the corresponding *N*-H ketimines.[2b] Whereas no allylboration was observed with **5** and **2**, the corresponding process between **9** and **4** is an excellent pairing that exhibits nearly perfect selectivity. The stereochemical aspects of the imine proved to be critical to the success of this process. This issue was resolved when we found that their enamine isomers provide a simple entry through tautomerization to the *Z*-ketimine geometries which are required for the addition to take place. Since these *Z*-ketimines are minor components of even the equilibrated mixtures, their generation through the borane-mediated process greatly facilitates the addition process.[2b] Thus, methyllithium was added to representative nitriles, the intermediates were silylated, and the mixtures were allowed to equilibrate to provide greater amounts of the *N*-silylenamines (**9**).[2b,10] The addition of 2 equiv of **9** to **4** was conducted at −78 °C, and after 16 h, the aminoborane intermediate **12** was observed by ^{11}B NMR δ 55. We view the borane-mediated enamine to *Z*-ketimine tautomerism (i.e., **10** → **11**) to be facilitated by **9**.[11] The mixture was allowed to reach room temperature, after which an oxidative workup (3 equiv of H_2O_2 and 3 M NaOH, reflux 3 h) gave the desired amines **13** with remarkable selectivity (95−99% ee) (Table 2).

Table 2. Propargylboration of *Z*-TMS Ketimines with 4



series	R	4	yield of 13[a] (%)	ee[b] (%)	config[c]
a	*c*-Hx	*S*	62	97	*R*
b	4-MeOC$_6$H$_4$	*S*	75	95	*R*
c	Ph	*S*	62	99	*R*
d	*i*-Pr	*S*	82	99	*R*
e	*c*-Pr	*R*	80	99	*S*
f	4-BrC$_6$H$_4$	*S*	78	99	*R*

[a]Isolated yield based upon **4** (1:2 ratio of **4**/**9**). [b]Enantiomeric excess determined by NMR analysis of the Mosher amide derivatives. [c]Absolute configuration was determined by single-crystal X-ray structure analysis of *N*-Boc-protected amine **14f*R*** and through the ozonolysis of **17d*R*** to provide the known **19d*R***.

To establish the absolute stereochemistry of **13**, the single-crystal X-ray structure of **14f*R*** (*N*-Boc derivative of **13f*R***) was obtained from the **4*S*** BBD reagent (Figure 1). This is consistent with the stepwise process depicted above in Table 2. The "upside down" orientation of the ketimine (i.e., **11**) is in complete accord with the observed selectivity of γ-alkoxyallylboration[2d] but is opposite to the product stereochemistry obtained from the simple allylboration of ketimines with the BBD reagents.[2b] While the attack of **4** by **9** from the 10-Ph side of the molecule is possible, MM calculations suggest that this is energetically unfavorable (ca. 20 kJ/mol) compared to **10**. However, the preference for **11** over other orientations for the addition is less clear and may even be due to steric factors present during its formation through protonation.[11]

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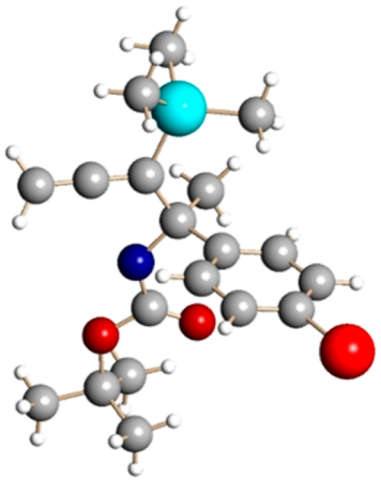
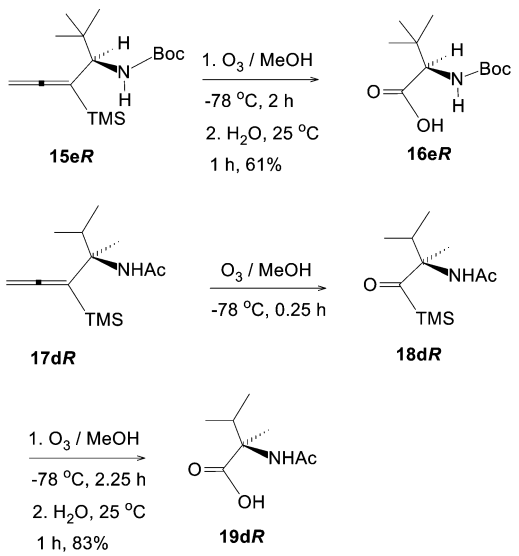


Figure 1. Single-crystal X-ray structure of **14f*R***.

As potential applications for the present new chemistry, we chose to demonstrate the role of these new allenyl carbinamines, **8** and **13**, as useful precursors to amino acids through simple ozonolysis procedures. For these purposes, we chose to prepare the known *N*-Boc amino acid **16e*R*** and the *N*-Ac α-methyl amino acid **19d*R***. After the installation of the appropriate *N*-protection, the allenes in MeOH were treated with excess ozone to obtain the desired acids. For **16e*R***, treatment of **15e*R*** with ozone for 2 h at −78 °C followed by warming to room temperature and addition of water gave the desired amino acid in 61% yield as a known mixture of carbamate rotamers (Scheme 2).[12] Their negative rotation agreed with the reported *R* configuration of **8d*R*** that was obtained from **2*S***, consistent with our interpretation of the process as presented in Table 1.

The ozonolysis of **17d*R*** was carried out in a manner similar to that used for **15e*R*** except that the process was interrupted after 15 min and examined by ^{13}C NMR. This revealed the intermediacy of the acylsilane **18d*R*** whose downfield carbonyl carbon (δ 242) was clearly evident.[1c] After the oxidation and hydrolysis processes were completed, pure **19d*R*** was isolated in 83% yield as the *R* enantiomer consistent with the process depicted in Table 2 ($[\alpha]^{20}_D$ +4.5 (*c* 1.0 MeOH), lit.[13] (for *S* enantiomer); $[\alpha]^{20}_D$ −1.4 (*c* 1.0 EtOH).

Scheme 2. Amino Acids from the Ozonolysis of 15e*R* and 17d*R*



In summary, the γ-TMS propargylboranes **2** and **4**, which are easily prepared in either enantiomeric forms, provide a very selective entry to allenyl carbinamines **8** and **13** through their additions to *N*-H aldimines and *N*-TMS enamines, respectively. High selectivity (≥90% ee) is generally observed for the aldimines in all but a *para*-substituted phenyl example (**8a**, 78% ee). The generation of *Z*-TMS ketimines though a borane-mediated tautomerism of the corresponding enamines results in the smooth formation of the 3°-alkyl carbinamines being formed from **4** as essentially single enantiomers (95−99% ee). The ozonolysis of these allenyl carbinamines provides a simple and novel entry to amino acids (**16**) and their α-methyl counterparts (**19**) in high optical purity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03506.

X-ray data for compound **14f*R*** (CIF)

Full experimental procedures and spectroscopic data for **8**, **13**, **14f*R***, **16e*R***, **17d*R***, and **19d*R*** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799. (b) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (c) Hernández, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397. (d) Hernandez, E.; Canales, E.; Gonzalez, E.; Soderquist, J. A. *Pure Appl. Chem.* **2006**, *78*, 1389. (e) Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331. (f) Canales, E.; Gonzalez, A. Z.; Soderquist, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 397. (g) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081. (h) González, A. Z.; Román, J. G.; Alicea, E.; Canales, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 1269. (i) Román, J. G.; Soderquist, J. A. *J. Org. Chem.* **2007**, *72*, 9772. (j) Soto-Cairoli, B.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 401. (k) Muñoz-Hernández, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571. (l) González, J. R.; González, A. Z.; Soderquist, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 9924. (m) Kister, J.; DeBaillie, A. C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174. (n) Soderquist, J. A. In *Comprehensive Chirality*; Yamamoto, H., Carreira, E., Eds.; Elsevier: Amsterdam, 2012; pp 691−739 and references cited therein. (o) González, J. A.; Soderquist, J. A. *Org. Lett.* **2014**, *16*, 3840. (p) González, E.; Muñoz-Hernández, L.; Alicea,

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Org. Lett. XXXX, XXX, XXX−XXX

E.; Singaram, B.; Kabalka, G. W.; Soderquist, J. A. *Org. Lett.* **2015**, *17*, 4368.

(2) (a) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572. (b) Canales, E.; Hernández, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712. (c) Hernández, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089. (d) Muñoz-Hernández, L.; Seda, L. A.; Wang, B.; Soderquist, J. A. *Org. Lett.* **2014**, *16*, 4052.

(3) (a) Ramadhar, T. R.; Batey, R. A. *Synthesis* **2011**, *2011*, 1321. For recent developments in the propargylaton of imines, see: (b) Mszar, N. W.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3362. (c) Wu, H.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3780. (d) Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci.* **2011**, *2*, 807. (e) Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. *Org. Lett.* **2015**, *17*, 5340. (f) Fandrick, D. R.; Hart, C. R.; Okafor, I. S.; Mercadante, M. A.; Sanyal, S.; Masters, J. T.; Sarvestani, M.; Fandrick, K. R.; Stockdill, J. L.; Grinberg, N.; Gonnella, N.; Lee, H.; Senanayake, C. H. *Org. Lett.* **2016**, *18*, 6192.

(4) (a) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595. (b) Lachance, H.; Hall, D. G. *Org. React.* **2009**, *73*, 1. Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217.

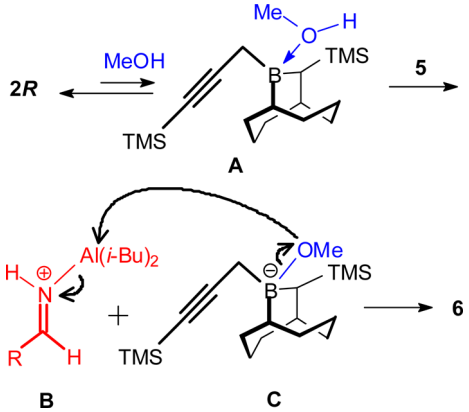
(5) (a) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (b) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130.

(6) Nikam, S. S.; Wang, K. K. *J. Org. Chem.* **1985**, *50*, 2193.

(7) Watanabe, K.; Kuroda, S.; Yokoi, A.; Ito, K.; Itsuno, S. *J. Organomet. Chem.* **1999**, *581*, 103.

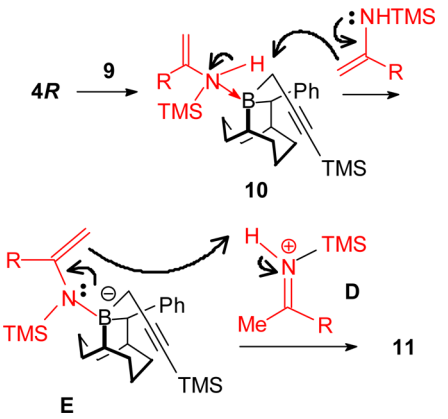
(8) For alternative methods for the asymmetric allylation of imines, see: (a) Chen, G.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 825. (b) Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5* (12), 2145. (c) Chen, J. L.-Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 10992 and references cited therein. (d) Van der Mei, F. W.; Miyamoto, H.; Silverio, D. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4701. (e) Huang, Y.-Y.; Chakrabarti, A.; Morita, N.; Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11121.

(9) We view this methanolysis process as occurring in a stepwise manner analogous to our conclusions based upon studies on the related allylboration process:[1d] This differs from the originally proposed termolecular process.[14] Thus, the **2*R***/MeOH adduct **A** is deprotonated by **5**, which gives **B**, which is attacked at aluminum by **C** to give DIBAL-OMe and the *syn N*-H aldimine, which adds to **2*R*** to give **6**.



(10) Ahlbrecht, H.; Duber, E.-O. *Synthesis* **1982**, *1982*, 273.

(11) We view the tautomerism of **10** to provide **11** as occurring through the stepwise process as illustrated below. Deprotonation of **10** by **5** gives **D** and **E**. The protonation of **E** by **D** followed by complexation provides **11**.



(12) ^{1}H NMR and ^{13}C NMR spectroscopic data for these carbamate rotomers were previously reported: Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

(13) Cilibrizzi, A.; Schepetkin, I. A.; Bartolucci, G.; Crocetti, L.; Dal Piaz, V.; Giovannoni, M. P.; Graziano, A.; Kirpotina, L. N.; Quinn, M. T.; Vergelli, C. *Bioorg. Med. Chem.* **2012**, *20*, 3781.

(14) Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217.

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Org. Lett. XXXX, XXX, XXX−XXX