ORGANIC LETTERS

2006
Vol. 8, No. 15
3331−3334

N-Propargylamides via the Asymmetric Michael Addition of *B*-Alkynyl-10-TMS-9-borabicyclo[3.3.2]decanes to *N*-Acylimines

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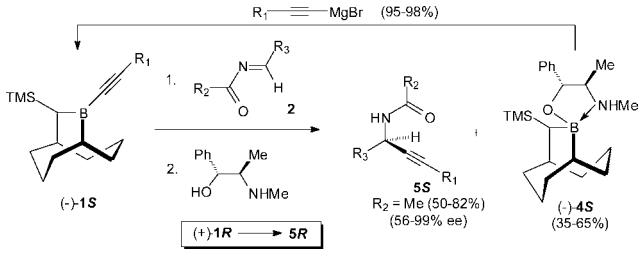
Received May 11, 2006

ABSTRACT



The asymmetric synthesis of *N*-propargylamides through Michael addition of the alkynylborane 1 to *N*-acylimines is reported. The *N*-acetylimines provide the best substrates for the process exhibiting high selectivity (56–95% ee) with predictable stereochemistry. In several cases, 5 crystallizes in essentially pure form (97–99% ee) and a single-crystal X-ray structure was also obtained for 5g (R_1 = R_2 = Me, R_3 = *o*-Cl–C_6C_4). The process regenerates 4 for its direct conversion back to 1 and facilitates the efficient recovery of the pseudoephedrine.

With more than 75% of drugs and drug candidates containing the nitrogen functionality, it is not surprising that the asymmetric synthesis of amines is the focus of continuing research. Versatile, multifunctional amines such as propargylic amines are of interest because they provide useful building blocks for the synthesis of more complex systems.[1,2o] Many organometallic routes to propargylic amines have been reported,[2] but until recently, the organoborane-based alkynylation of imines was an unknown process.[3] Recently, we reported several highly useful asymmetric organoborane conversions with the remarkably stable and versatile 10-substituted-9-borabicyclo[3.3.2]decanes (10-R-9-BBDs).[4] As an extension of those studies, we chose to evaluate the potential of *B*-alkynyl-10-trimethylsilyl-9-BBDs (**1**) to undergo 1,4-addition to *N*-acylaldimines as a convenient entry to nonracemic propargylic amides (**5**) (Scheme 1).

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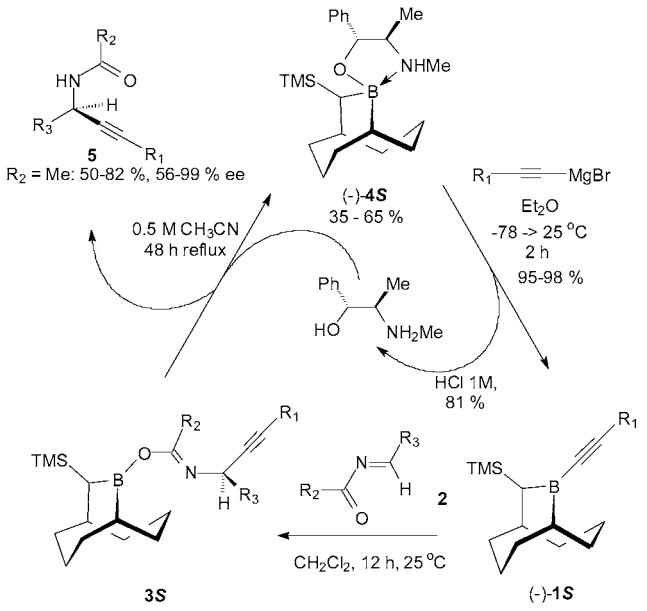
10.1021/ol0611595 CCC: $33.50
Published on Web 06/29/2006

Scheme 1



Alkynylboranes have been known to add to nonconjugated aldehydes and more slowly to ketones to give the corresponding propargyl alcohols.[5] With conjugated enones, 1,4-addition is observed resulting in β-alkynyl ketones.[6] More recently, this was developed into an effective asymmetric process employing chiral alkynylboronic esters.[5b] This preference for 1,4- vs 1,2-addition can be attributed to a favorable six-membered ring cyclic transition state for the alkynylation of the enone in its *cisoid* form. In a general sense, conjugate additions are highly useful processes,[7] with several of these methods involving organoboranes.[6,8]

Recently, we examined the allylation of *N*-TMS imines employing 10-R-9-BBD reagents.[4e,f] For the aldimines, the *N*-TMS derivatives were unreactive. However, with their in situ conversion to the corresponding *N*-H derivatives through a borane-mediated methanolysis, allylation was rapid even at −78 °C. In contrast to the rapid six-center allylation process, the four-center alkynylation of aldehydes, *N*-TMS, or *N*-H aldimines with **1** does not occur (1 week, 25 °C). By contrast, we felt that *N*-acylaldimines (**2**) could exhibit greater reactivity because these substrates can serve as Michael acceptors for **1**.[9] Among the available routes to these systems,[10] the Würthwein acylation of *N*-TMS aldimines with acid chlorides was particularly attractive and was employed for the synthesis of **2** for this study.[11,12]

We initially examined the role played by the acyl group with respect to both the efficiency of the addition and its enantioselectivity. Addition of 2 equiv of various *N*-acylaldimines **2** to **1a** (R_1 = Me) results in the complete formation of the borinic ester intermediate **3** (^{11}B NMR $\delta \sim 57$) in 12 h at 25 °C.[13] However, the alkynylation of the *N*-carbamoyl derivative (Table 1, entry 6) was very slow (1 week, 25 °C) and gave a low product yield and ee. From these results, we selected the *N*-acetylaldimines (R_2 = Me) for the present study because these were both easy to prepare and gave high product ee's (e.g., Table 1, **5e**).

Table 1. Michael Additions of **1*R*** to *N*-Acylaldimines (**2**)[a]

entry	R_2	R_3	**5**	yield (%)[b]	ee (%)[c]
1	Ph	2-C_4H_3O	**a**	89	83
2	Ph	Ph	**b**	73	70
3	Ph	2-C_4H_3S	**c**	85	83
4	*i*-Pr	Ph	**d**	86	94
5	**Me**	**Ph**	**e**	**72**	**95**
6	OEt	Ph	**f**	42	39

[a] For entries 2−6, the *B*-propynyl derivative **1a*R*** (R_1 = Me) was used. For the known **5a**, the *B*-heptynyl derivative **1e*R*** (R_1 = *n*-C_5H_{11}) was employed to verify the product stereochemistry. [b] Isolated yields after column chromatography. [c] Product ee determined by HPLC analysis with a Chiracel OD column.

Readily available through simple Grignard procedures, several alkynylboranes **1** were prepared (R_1 = Me (**a**),

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(12) All *N*-acyl (carbamoyl) imines were synthesized with the Würthwein method without further purification immediately prior to the addition to **1**.

(13) Use of 1.0 equiv of **2** in these processes provides **5** with similar selectivities and reaction yields but with significantly longer reaction times (ca. 1 week, 25 °C).

C(Me)=CH_2 (**b**), $(CH_2)_3Cl$ (**c**), *c*-C_3H_5 (**d**), $(CH_2)_4CH_3$ (**e**)) to introduce differing alkynyl substitution into the products **5**. Nonenolizable aldehydes were used to ultimately produce **2** through their *N*-TMS aldimines. Following the complete formation of **3**, the mixture was concentrated and the appropriate enantiomer of pseudoephedrine (PE) and acetonitrile were added. Transesterification occurs in 48 h at reflux temperature, ultimately providing **4** (35−65%) for the regeneration of **1**. The *N*-propargylamides **5** were isolated in good yields (61−82%) and high selectivity (56−95% ee). Interestingly, in several cases, the enantiomeric excess of **5** was significantly upgraded to 97−99% through recrystallization from hexane/ethyl acetate (see Table 2, entries 2, 4, and 5). The single-crystal X-ray structure of **5g** reveals intermolecular H-bonding between the amide hydrogen and the carbonyl oxygen of an adjacent molecule.[14] This secondary structure can account for the observed ee enhancement through the recrystallization of **5**.

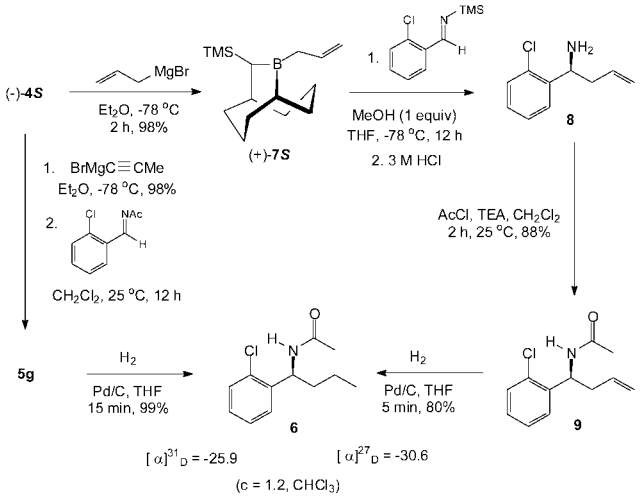
Table 2. Asymmetric Michael Addition of **1** to **2**

entry	R_1[a]	R_3	**5**	yield (%)[b]	ee (%)[c]
1	Me	Ph	**e**	72	95
2	Me	*o*-ClC_6H_4	**g**	54	70 (97)[d]
3	$(CH_2)_3Cl$	*p*-$MeOC_6H_4$	**h**	81	82
4	C(Me)=CH_2	*p*-$MeOC_6H_4$	**i**	61	84 (>99)[d]
5	*c*-C_3H_5	*o*-ClC_6H_4	**j**	61	74 (>99)[d]
6	*c*-C_3H_5	Ph	**k**	82	56
7	Me	*t*-Bu	**l**	50	68

[a] For entries 1 and 3−5, the (10*R*) enantiomers of **1** were used. For entries 2, 6, and 7, the (10*S*) enantiomers of **1** were used. [b] Isolated yields after column chromatography. [c] Product ee determined by HPLC analysis with a Chiracel OD column. [d] Enantiomeric excess after recrystallization of **5**.

The absolute stereochemistry of **5a** was assigned from the reported value for its rotation.[2a] Thus, (+)-(1*R*)-**5a** was obtained from (−)-**1e*R***. The BBD systems have been previously demonstrated to give both predictable and consistent selectivities in other asymmetric transformations.[4] However, to further confirm the stereochemical assignments of **5**, we carried out the catalytic hydrogenation of **5g** (from **1a*S***) which gave **6**, quantitatively (Scheme 2). This *N*-butylamide was also prepared by the asymmetric allylboration of *N*-H 2-chlorobenzaldimine (from its *N*-TMS precursor, MeOH, and (+)-**7*S***) which gave the known homoallylic amine **8**, with *S* stereochemistry.[4e] Following the acetylation of **8** to give **9**, its hydrogenation provides **6** (80%). With both procedures producing the same (−) enantiomeric form of **12**, it is clear that *N*-propargylamide **5g** also has the (1*S*) stereochemistry. This is also consistent with the above selectivity observed for **5a**.

Scheme 2



To provide a potential explanation for the observed product stereochemistry, we chose to examine eight possible diastereomeric pre-transition-state *cisoid syn-O*-acetylbenzaldimine complexes with **1** employing simple MM calculations. We constrained the α-alkynyl carbon−iminyl carbon distance to 3Å (Figure 1, dotted lines in red) which gave the lowest-energy complexes for the formation of *R* and *S* aminoboranes **3** from (−)-**1*R***, of which ***R*** is lower in energy (~2.5 kcal/mol) than ***S***. This semiquantitative model for the process is consistent with the general observation that the carbonyl oxygen coordinates the boron atom *cis* to the 10-TMS in the BBD system in a wide range of asymmetric processes. We view the reaction as occurring through a B−O coordinated six-membered transition state in which the close proximity of the now more electrophilic imine carbon facilitates the transfer of the nucleophilic alkynyl group.

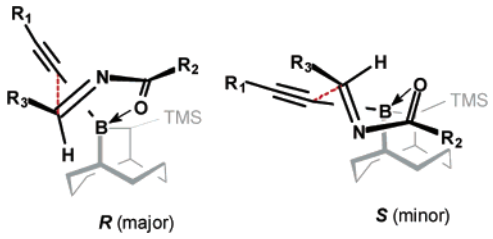


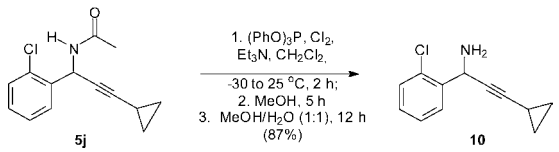
Figure 1. Proposed models for the observed stereochemistry of the alkynylation of **2** with (−)-**1*R***.

Finally, the deprotection of **5j** can be smoothly achieved with chlorine and triphenyl phosphite as reported by Prati.[15] This impressive procedure provides the free amine **10** in 87% yield (Scheme 3).

(14) These intermolecular interactions are apparent from the crystallographic data included in the Supporting Information.

(15) Spaggiari, A.; Blaszczak, L. C.; Prati, F. *Org. Lett.* **2004**, *6*, 3885.

Scheme 3



In summary, the reagents **1** are cleanly prepared from the enantiomerically pure air-stable crystalline complexes **4** through simple Grignard procedures which also permit the recovery of pseudoephedrine (81%). Reagents **1** cleanly add to *N*-acylimines (**2**) (12 h, 25 °C), efficiently producing *N*-propargylamides (**5**) following a nonoxidative pseudoephedrine workup which regenerates **4** (35−65%). Depending upon the enantiomeric form of **1** employed, either enantiomer of **5** can be prepared with predictable stereochemistry. The *N*-acetyl derivatives of **2** provide good to excellent selectivities (56−95% ee) in the formation of **5**, and these values were easily enhanced to >97% ee in several cases through a simple recrystallization. Moreover, deacetylation of **5** easily provides the corresponding amines (e.g., **10**). This borane-mediated Michael alkynylation of **2** provides a highly attractive method for the asymmetric synthesis of propargylamides and amines.

Acknowledgment. The support of the NSF (CHE-0517194), NIH SCORE (S06GM8102), and U.S. Department Ed. GAANN Program (P200A030197-04) is gratefully acknowledged. We wish to thank Dr. Gellert Mezei (University of Puerto Rico) for determining the X-ray structure of **5g**.

Supporting Information Available: Full experimental procedures, characterization data, selected spectra for **1**, **4**−**10**, and derivatives, and X-ray crystallographic data for **5g** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0611595