Organic LETTERS

Letter

pubs.acs.org/OrgLett

Completely Stereocontrolled Aldol Reaction of Chiral β-Amino Acids

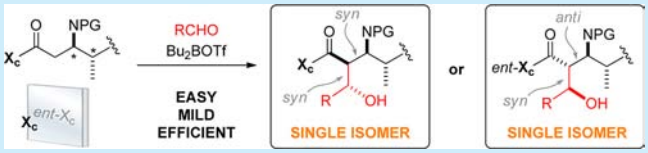
Martin Gazvoda,[†] Kathrin Höferl-Prantz,[‡] Roland Barth,[‡] Wolfgang Felzmann,[‡] Andrej Pevec,[†] and Janez Košmrlj*,[†]

[†]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, SI-1000 Ljubljana, Slovenia

[‡]Sandoz Development Centre Austria, Chemical Development, Sandoz Austria GmbH, Biochemiestraße 10, A-6250 Kundl, Tirol, Austria

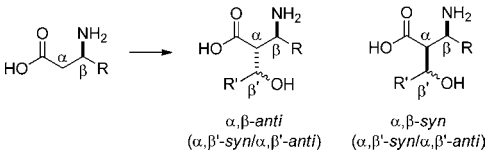
Supporting Information

ABSTRACT: A general protocol to independently access stereoisomerically pure β′-hydroxy-β-amino acid derivatives that is based on dibutylboron triflate-mediated aldol reaction of suitably protected β-amino acids bearing chiral oxazolidinone auxiliary is reported. The method smoothly afforded *syn*-aldol (α,β′-*syn*) products in pure form and excellent isolated yield. Both α,β-*syn* and α,β-*anti* isomers are readily accessible solely through the choice of the oxazolidinone chirality. This method allows for the preparation of stereoisomeric β′-hydroxy-β-amino acid derivatives that were previously unreported.



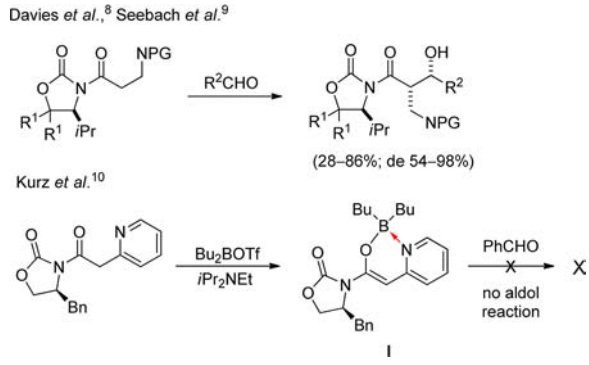
The requirement of the pharmaceutical industry for chiral chemical entities has been one of the major driving forces in the development of asymmetric synthetic methods. The aldol reaction is a powerful means of carbon−carbon bond construction, allowing the formation of up to two stereocenters in a single step with remarkable stereoselectivity.[1,2] Because of work of Evans and others, it allows access to all stereoisomers, even with β-hydroxy carboxylic acid substrates. In stark contrast, aldol reactions of chiral β-amino acid nucleophiles with good diastereo- and enantioselectivity remain largely unexplored (Scheme 1).

Scheme 1. Anticipated Stereoisomeric Aldol Products of β-Amino Acid Nucleophiles



A substrate-controlled version has been realized using *N*-alkyl-*N*-α-alkylbenzyl-functionalized β-amino esters[3,4] and lactones[5−7] by employing lithium diisopropylamide (LDA) for enolate formation. It results in α,β-*anti* isomers with rather unpredictable although in some cases acceptable diastereoselectivity. Surprisingly, only a few reports of boron-mediated reactions are precedented. Davies et al. reported the reaction of *N*-benzyl-*N*-α-methylbenzyl β-amino acid derivatives with SuperQuat auxiliary and 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate (9-BBNOTf) to produce α,β′-*syn* aldols (Scheme 2).[8] Despite the relative simplicity of the substrates lacking the chirality at the β-carbon atom, a decrease in both the stereoselectivity and the yield was noted and was attributed to the choice of the nitrogen protecting groups. Similar observations were made by Seebach et al. using *N*-Boc protection and dibutylboron triflate for enolate formation.[9] The interference of the β-nitrogen atom on the course of the reaction is greatly illustrated by a report of Kurz et al. In this case, dibutylboron triflate-mediated addition of a 2-(2-pyridyl)acetyloxazolidinone derivative to benzaldehyde failed completely, yielding stable boryl enolate intermediate **I**, instead (Scheme 2).[10]

Scheme 2. Previous Results on Boron-Mediated Aldol Reaction of Achiral β-Amino Acids[a]



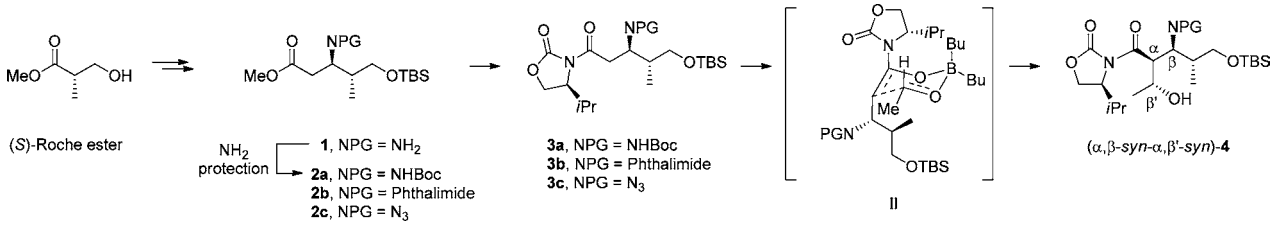
[a]For details, see text.

Until now, no general method has existed that allows the intrinsic diastereocontrol exhibited by the substrate to be overridden and provides access to α,β-*anti* or α,β-*syn* aldol products with comparable selectivity. This is surprising as these scaffolds are of prime importance in the chemistry of β-amino acids,[11] the corresponding peptides,[12] β-aminolactones,[5] and β-lactams,[13] to name just a few. Noteworthy, in the context of β-lactams, is that a unified access to β′-hydroxy-β-amino acid derivatives would be beneficial for SAR studies in a search for

Received: December 6, 2014
Published: January 23, 2015

DOI: 10.1021/ol503523h
Org. Lett. 2015, 17, 512−515

Scheme 3. Model *β*-Amino Acid Substrates 3 Selected to Probe the Dibutylboron Triflate Mediated Aldol Reaction into 4



new lead antibiotics, superior to thienamycin and other potent carbapenams, carbapenems, and carbacephems.

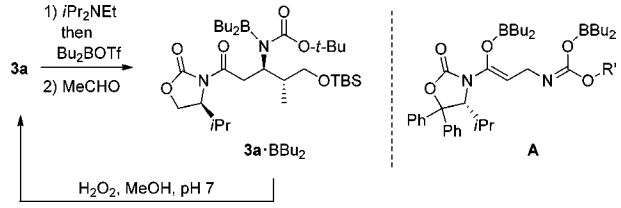
We selected compound **1** (Scheme 3) as a model *β*-amino acid on the basis of the following considerations: (a) it holds functionalization that should challenge the chemistry through the intrinsic conformational restriction and functional group tolerance, (b) an additional stereochemical challenge may be posed by the *γ*-stereocenter, which impacts LDA-mediated aldol reactions,[3] (c) in numerous postaldol manipulations the selected functionalization gives easy access to compounds of biological interest through well-established chemistry, and (d) enantiopure **1** can be easily prepared from (*S*)-Roche ester.[14]

It was expected that after the appropriate nitrogen atom protection (**1** → **2**), followed by ester group saponification and amidation with (*S*)-4-isopropyloxazolidin-2-one yielding **3**, the dibutylboron triflate mediated aldol reaction with acetaldehyde would afford the desired aldol product **4** (Scheme 3). The oxazolidinone auxiliary was selected vs others on the basis of its simplicity, availability, and price. By selecting the appropriate reaction conditions, the formation of **4** should proceed through the (*Z*)-boryl enolate intermediate and the six-membered chairlike Zimmerman−Traxler transition state **II**.[15] We hypothesized that in the latter the side chain of the *β*-amino acid should have little or no influence on the stereochemical outcome affording preferentially the *α,β-syn-α,β′-syn* isomer **4**. If successful, this would provide an entry to *β′*-hydroxy-*β*-amino acid derivatives that were previously inaccessible.

To avoid the potential boron−nitrogen interactions with the *β*-amino nitrogen atom as discussed above, it was important to identify a suitable protecting group NPG. The report of Seebach et al.[9] prompted us to initially examine Boc protection.[16] In our case, an attempted aldol reaction under the standard[2] reaction conditions by premixing **3a** with Bu_2BOTf at −78 °C, subsequent enolate formation by addition of *i*-Pr_2NEt, and sequential addition of acetaldehyde returned a complex mixture of products, but no desired *β′*-hydroxy-*β*-amino acid derivative could be detected by ^1H NMR and HRMS analyses. The spectra indicated that neither Boc nor TBS ether groups were tolerated by the reaction conditions, presumably due to trace amounts of triflic acid that accompanied Bu_2BOTf. Accordingly, the decomposition of **3a** was completely suppressed by changing the order of Bu_2BOTf and *i*-Pr_2NEt addition, with the latter being introduced first to ensure basic reaction conditions throughout the reaction. Unfortunately, in this case, no traces of the aldol product could be detected by HRMS analysis of the reaction mixture, whereas NMR spectroscopy revealed the presence of unreacted **3a** and a new species, **3a**·BBu_2 (vide infra, Scheme 4).

To shed light on this, the reaction mixture of **3a** with *i*-Pr_2NEt/Bu_2BOTf was analyzed by multinuclear NMR spectroscopy in CD_2Cl_2.[14] On the basis of $^1H-^{15}N$ *gs*-HMBC spectral analysis, the nitrogen atom of the newly formed species was shielded significantly (δ_N = 38 ppm vs 90 ppm in **3a**), clearly indicating

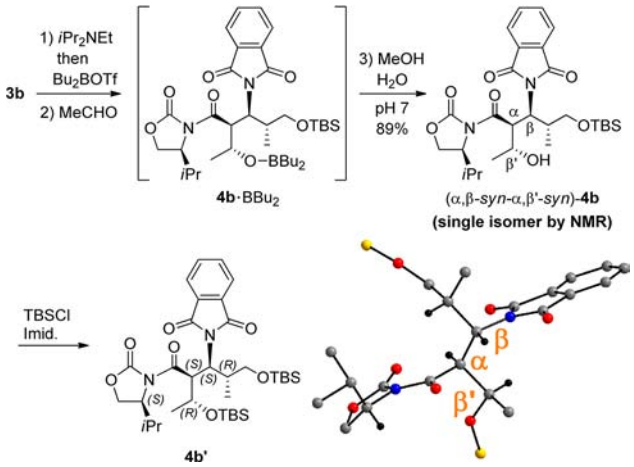
Scheme 4. Reaction of 3a with *i*-Pr_2NEt/Bu_2BOTf To Form 3a·BBu_2 and Intermediate A Proposed by Seebach et al.



close B−N interaction.[17] This species was tentatively assigned the structure of **3a**·BBu_2 by NMR spectroscopy (Scheme 4).[18] Alkaline hydrogen peroxide released **3a** from **3a**·BBu_2 (Scheme 4).[14] The result is in sharp contrast to the suggestion of Seebach et al.[9] that boron interacts with the carbamate carbonyl oxygen atom (structure **A**, Scheme 4).[19]

Phthalimide **3b** was expected to provide an effective *β*-nitrogen atom protection, disabling B−N interactions as observed for **3a**·BBu_2.[20] Thus, compound **3b** was combined with *i*-Pr_2NEt, Bu_2BOTf, and acetaldehyde (Scheme 5), leading

Scheme 5. Synthesis of 4b and 4b′ and a Part of the X-ray Structure of 4b′



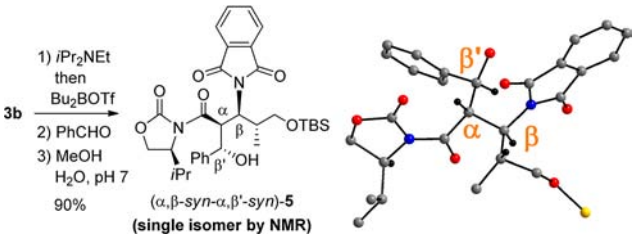
to a single product. On the basis of ^1H NMR spectral analysis, the crude reaction mixture consisted of the desired aldol product **4b** and unreacted starting material **3b** in a 92:8 ratio by integration with no other diastereomeric aldol products detectable. It is noteworthy that in contrast to the standard alkaline hydrogen peroxide conditions,[1d,2b,e] the hydroxyl group of **4b** could be liberated from the dibutylboron **4b**·BBu_2 adduct solely by the addition of water. Such mild workup conditions provide a wide compatibility with various functional groups. Product **4b** and unreacted starting material **3b** were isolated after flash chromatography in 89% and 4% yield, respectively. The absolute stereochemistry of **4b** was established unambiguously by X-ray

DOI: 10.1021/ol503523h
Org. Lett. 2015, 17, 512−515

crystallography via TBS protection of the β'-hydroxyl group to provide the crystalline **4b′** (Scheme 5).[21]

Excellent results with the smallest possible aldehyde prompted us to test the bulkier aromatic aldehyde, benzaldehyde. The reaction of **3b** also afforded *syn*-aldol product **5** (Scheme 6). The

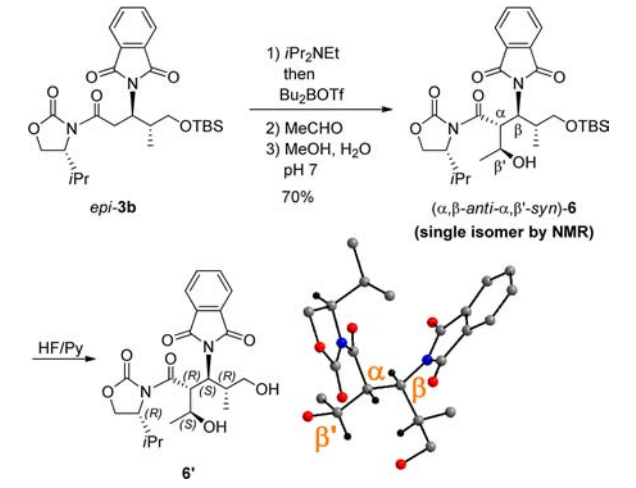
Scheme 6. Synthesis of 5 and a Part of its X-ray Structure



conversion was quantitative as judged by ^{1}H NMR analysis, with no other isomers or byproducts being detected. The product was isolated in 90% yield. The stereochemistry of **5** was confirmed by single-crystal X-ray analysis.[21]

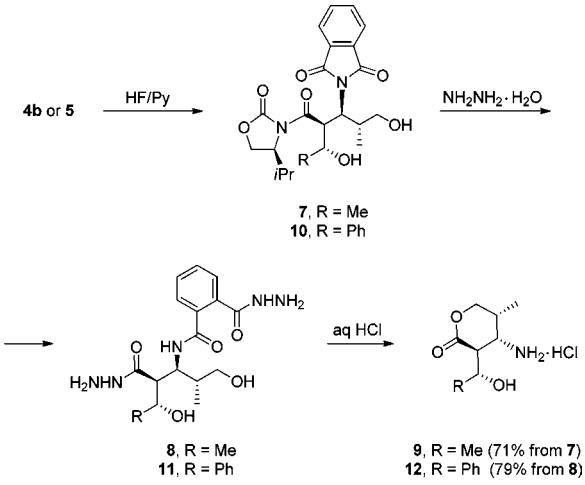
The fact that the dibutylboron triflate-mediated aldol reaction of **3b** resulted in the formation of **4b** and **5** with complete stereocontrol indicates formation through the transition state **II** shown in Scheme 3 and that the configurations at the β- and γ-stereocenters have indeed no impact. This was additionally proven by the aldol reaction of acetaldehyde with the epimeric (*R*)-4-isopropyloxazolidin-2-one derivative *epi*-**3b**, which resulted in α,β-*anti*-α,β'-*syn*-**6** as the sole isomer (Scheme 7). Its absolute stereochemistry was determined by X-ray crystallography via TBS deprotection of the primary hydroxyl group to provide crystalline **6′**.

Scheme 7. Synthesis of 6 and 6′ To Confirm the Stereochemistry through the X-ray Structure



Finally, to prove the applicability of this method, we were prompted to transform **4b** and **5** into the corresponding β-amino-δ-lactones **9** and **12** (Scheme 8). Briefly, deprotection of the β-amino nitrogen atom in **4b** by a variety of the reaction conditions[22] including hydrazinolysis, aminolysis with butylamine or methylamine, and $NaBH_4/CH_3CO_2H$ failed. The removal of the phthalimide group through hydrazinolysis requires strongly acidic reaction conditions, which turned out to be incompatible with the OTBS ether in **4b**. Hence, **4b** was first TBS deprotected to afford **7**[14] and then subjected to

Scheme 8. Conversion of 4b and 5 into Lactones 9 and 12, Respectively



$NH_2NH_2{\cdot}H_2O$. Surprisingly, this resulted in the removal of (*S*)-4-isopropyloxazolidin-2-one in nearly quantitative yield and the formation of dihydrazide **8** (Scheme 8). The auxiliary could be recovered in high purity and reused without loss of stereoselectivity in the aldol reaction. Even though numerous methods are available for the oxazolidinone auxiliary cleavage affording esters, primary alcohols, Weinreb amides, and carboxylic acids,[2d,e,23] to our knowledge, this is the first report on hydrazinolysis. In a one-pot procedure from **7**, acid-promoted hydrolysis of **8** resulted in spontaneous formation of δ-lactone **9** in enantiomerically pure form and 71% yield. Lactone **12** was prepared analogously from **10** through dihydrazide **11** in 79% isolated yield.

In conclusion, we have reported the first transformation of chiral β-amino acids into the corresponding β'-hydroxy-β-amino acid derivatives by an Evans aldol reaction. These densely functionalized products are formed in complete stereoselectivity and in excellent yields. The methodology is mild and robust, readily affording both the α,β-*syn* and the α,β-*anti* isomers independently and in stereochemically pure form, which were previously inaccessible without the need of tedious chromatographic separations from complex mixtures of isomers. This is of the utmost importance for bulk synthesis of advanced non-crystallizable compounds. Our protocol employs one of the simplest Evans oxazolidinone auxiliaries, which can be recovered in pure form and reused. The choice of the nitrogen protecting group was found to be crucial and was described in detail. Work is in progress toward the application of this chemistry to access α,β'-*anti*-aldols as well as to further explore the substrate and aldehyde scope.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and spectroscopic and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: janez.kosmrlj@fkkt.uni-lj.si.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/ol503523h
Org. Lett. 2015, 17, 512−515

■ ACKNOWLEDGMENTS

This work was financed by Sandoz Austria GmbH and the Ministry of Education, Science and Sport, Republic of Slovenia, the Slovenian Research Agency (Grant Nos. P1-0230 and P1-0175).

■ REFERENCES

(1) Selected reviews: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. *2*, pp 133−238. (d) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. *2*, pp 239−275. (e) Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. *2*, pp 301−319. (f) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200. (g) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947. (h) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (i) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75. (j) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004. (k) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2006. (l) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506−7525. (m) Kan, S. B. J.; Ng, K. K.-H.; Paterson, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 9097−9108. (n) *Modern Methods in Stereoselective Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2013.

(2) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. (c) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−32. (d) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526. (e) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83−91. Gage, J. R.; Evans, D. A. *Organic Synthesis*; Wiley: New York, 1993; Collect. Vol. *VIII*, pp 339−343.

(3) Tsukada, N.; Shimada, T.; Gyoung, Y. S.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **1995**, *60*, 143−148.

(4) (a) Davies, S. G.; Fenwick, D. R. *Chem. Commun.* **1997**, 565−566. (b) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067−9068. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162. (d) Ma, D.; Sun, H. *Tetrahedron Lett.* **2000**, *41*, 1947−1950. (e) Davies, S. G.; Smethurst, C. A. P.; Smith, A. D.; Smyth, G. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2437−2441. (f) Baldwin, I. C.; Briner, P.; Eastgate, M. D.; Fox, D. J.; Warren, S. *Org. Lett.* **2002**, *4*, 4381−4384. (g) Chernega, A.; Davies, S. G.; Elend, D. L.; Smethurst, C. A. P.; Roberts, P. M.; Smith, A. D.; Darren Smyth, G. *Tetrahedron* **2007**, *63*, 7036−7046.

(5) (a) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659−1660. (b) Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020−3024. (c) Collis, M. P.; Perlmutter, P. *Tetrahedron Asymmetry* **1996**, *7*, 2117−2134.

(6) An example of a stereoselective aldol reaction of chiral tin enolates is also reported, see: Iwasawa, N.; Mukayama, T. *Chem. Lett.* **1986**, 637−640.

(7) For recent examples of related chemistry on α-amino acids, see: Seiple, I. B.; Mercer, J. A. M.; Sussman, R. J.; Zhang, Z.; Myers, A. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 4642−4647.

(8) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812−2825.

(9) Gessier, F.; Schaeffer, L.; Kimmerlin, T.; Flögel, O.; Seebach, D. *Helv. Chim. Acta* **2005**, *88*, 2235−2249.

(10) Baringhaus, K.-H.; Matter, H.; Kurz, M. *J. Org. Chem.* **2000**, *65*, 5031−5033.

(11) (a) *Enantioselective Synthesis of β-Amino Acids*; Juraisti, E., Soloshonok, V. A., Eds.; John Wiley & Sons: Hoboken, 2005. (b) Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 3351−3354. (c) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056−1073.

(12) (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1836−1837. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (d) Porter, E. A.; Wang, X.; Lee, H.-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565. (e) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (f) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111−1239. (g) Johnson, L. M.; Gellman, S. H. *Meth. Enzymol.* **2013**, *523*, 408−429.

(13) (a) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437−4492. (c) Xu, J. *Tetrahedron* **2012**, *68*, 10696−10747. (d) Wright, P. M.; Seiple, I. B.; Myers, A. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 8840−8869.

(14) For details, see the Supporting Information.

(15) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

(16) Attempts to prepare *N*,*N*-di-Boc protected derivative **3d** (NPG = $N(Boc)_2$ by using literature proceduresemploying either excess $(Boc)_2O$/DMAP/ACN or LDA/$(Boc)_2O$ failed.

(17) Wrackmeyer, B.; Kupče, E.; Köster, R.; Seidel, G. *Magn. Reson. Chem.* **1992**, *30*, 393−397.

(18) The results were corroborated by an independent experiment wherein model compound *i*-PrNHBoc was allowed to react with *i*-Pr_2NEt/Bu_2BOTf.[14]

(19) Significant deshielding of the sp^2-nitrogen atom would be expected in an **A**-type intermediate, similar to that of dimethyl *N*-cyclohexylimidocarbonate (δ_N = 181 ppm).[14]

(20) Azide functionality in **3c** was initially considered as an alternative to Boc and phthalimide, however, treating compound **2c** with either LiOH, *i*-Pr_2NEt/Bu_2BOTf/MeCHO, or LDA/MeCHO resulted in elimination of HN_3 and the formation of (*R*,*E*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-4-methylpent-2-enoate as the sole product.[14]

(21) Although the X-ray data for **4b′** and **5** were poorly refined due to very weakly diffracting crystals,[14] the results can serve as an unambiguous proof of the absolute configuration at the newly formed stereocenters in the aldolization steps.

(22) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: Hoboken, 2007; pp 790−793.

(23) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093−2126.

DOI: 10.1021/ol503523h
Org. Lett. 2015, 17, 512−515