ORGANIC LETTERS

2007
Vol. 9, No. 20
3881−3884

A New Method for the Synthesis of Chiral β-Branched α-Amino Acids

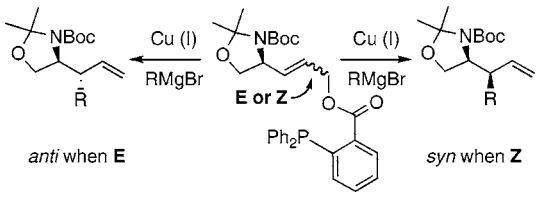
Thomas Spangenberg,[†,‡] Angèle Schoenfelder,[†] Bernhard Breit,*[,‡] and André Mann*[,†]

Département de Pharmacochimie de la Communication Cellulaire UMR 7175-LC-1 ULP/CNRS, Faculté de Pharmacie 74 route du Rhin BP 60024, F-67401 Illkirch, France, and Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, D-79104 Freiburg, Germany

andre.mann@pharma.u-strasbg.fr; bernhard.breit@organik.chemie-freiburg.de

Received June 1, 2007

ABSTRACT



A new method for the synthesis of chiral β-branched α-amino acids based on a copper-mediated directed allylic substitution reaction with Grignard reagents is reported. This is the first case in which a δ-stereogenic center is controlling the diastereoselectivity of an *o*-DPPB-directed allylic substitution. Depending on the alkene geometry of the starting material either diastereomer, anti or syn, is accessible with good levels of acyclic stereocontrol.

Synthesis of β-branched α-amino acids requires the control over adjacent stereocenters. To achieve this goal three major synthetic strategies have appeared in the literature: (i) the azaenolate-Claisen rearrangement for the synthesis of syn adducts;[1,2] (ii) the Meerwein−Eschenmoser−Claisen rearrangement, an alternative to reach the anti diastereomers;[3] and (iii) the Overman imidate rearrangement, requiring the oxidation of an allylamine.[4,5] In previous work we[6] and others[7−9] have shown that the oxazolidine moiety in Garner's aldehyde is a useful control element to achieve high levels of π-diastereofacial discrimination in the course of 1,4 conjugate addition. We also explored the use of Garner's aldehyde as a precursor for seco-kainic acid, isoleucine, or ADDA.[6,10] In this context, we were wondering whether it would be possible to construct the two epimeric alkenyloxazolidines **1** and **2** from the corresponding *E* and *Z* allylalcohols **3** and **4**, via a S_N2' displacement reaction (Scheme 1). Indeed, deprotection of the aminoalcohol function in **1** and **2** followed by oxidation could regenerate the α-amino acid function and would represent a new synthesis of β-branched α-amino acids equipped with an additonal terminal alkene function, amenable for further chemical elaborations.

[†] Département de Pharmacochimie de la Communication Cellulaire UMR 7175-LC-1 ULP/CNRS.

[‡] Albert-Ludwigs-Universität Freiburg.

(1) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

(2) (a) Kazmaier, U. *Angew. Chem., Int. Ed.* **1994**, *33*, 998. (b) Kazmaier, U.; Maier, S. *J. Org. Chem.* **1999**, *64*, 4574. (c) Kazmaier, U.; Deska, J.; Watzler, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4855.

(3) (a) Qu, H.; Gu, X.; Min, B. J.; Llu, Z.; Hruby, V. J. *Org. Lett.* **2006**, *8*, 4215. (b) Coats, B.; Montgomery, D.; Sterenson, P. J. *Tetrahedron Lett.* **1994**, *50*, 4025.

(4) Jamieson, A. G.; Sutherland, A.; Willis, C. L. *Org. Biomol. Chem.* **2004**, *2*, 808.

(5) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579.

(6) (a) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C. G.; Boulanger, Th.; Norberg, B.; Evrard, C.; Durant, F. *J. Org. Chem.* **1991**, *56*, 5729. (b) D'Aniello, F.; Mann, A.; Taddei, M.; Wermuth, C. G. *Tetrahedron Lett.* **1994**, *35*, 7775. (c) D'Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447.

(7) Hannessian, S.; Sumi, K. *Synthesis* **1991**, 1083.

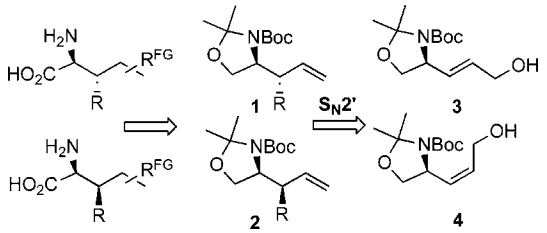
(8) Flamant-Robin, C.; Wang, Q.; Sasaki, N. A. *Tetrahedron Lett.* **2001**, *42*, 8483.

(9) Rastogi, S. K.; Kornienko, A. *Tetrahedron: Asymmetry* **2006**, *17*, 3170.

(10) Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C. G. *Tetrahedron Lett.* **1990**, *31*, 1011.

10.1021/ol071305m CCC: $37.00
Published on Web 09/06/2007

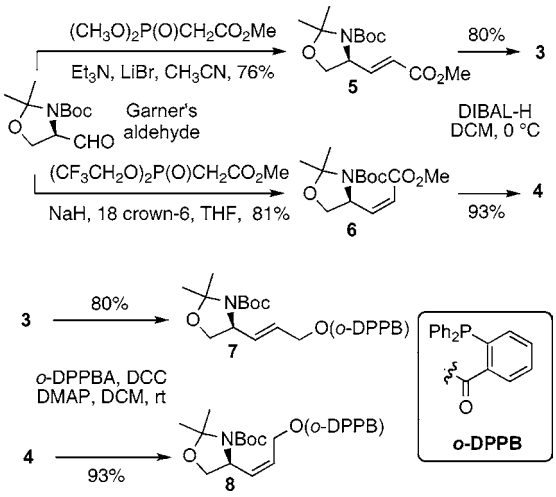
Scheme 1. Approach toward β-Branched α-Amino Acids



The allylic substitution with organocopper reagents is an attractive operation since in contrast to many other transition-metal catalyzed allylic substitutions it allows the introduction of hard nucleophiles such as alkyl, alkenyl, and aryl substituents.[11] However, the simultaneous control of regio- and stereochemistry is still a difficult problem, and only a few successful examples are known.[12,13] One solution to this problem makes use of reagent-directing leaving groups which control the trajectory of the incoming copper nucleophile to occur as an exclusive γ-attack.[14,15] Additionally, a directing leaving group reverses the stereochemical course of the allylic substitution to occur as a syn process as opposed to the natural anti attack relative to the leaving group.[16] In this regard the *o*-diphenylphosphanyl benzoate (*o*-DPPB) has proved to be an efficient controller of regio- and stereochemistry in the course of the allylic substitution reaction with secondary and primary allylic substrates.[17] Excellent S_N2' selectivity and perfect levels of 1,3-*syn* chirality transfer have been observed in many cases for cyclic and acyclic derivatives.[18,19] However, it was unknown whether a stereogenic center in δ-position of a primary allylic substrate would exert any influence on the stereochemical course of the intramolecular delivery of the organometallic nucleophile from either face of the π-system in allylic *o*-DPPB esters such as **7** or **8**.[20]

Preparation of allylic substrates **7** and **8** commenced from (*R*)-Garner's aldehyde.[21,22] Conversion to enoates **5** and **6** was achieved employing either a modified Horner−Wadsworth−Emmons reaction for the *E* isomer (**6**)[6,23] or the Stille−Gennari procedure for the *Z* isomer (**5**).[7,24] Chemoselective ester reduction occurred upon treatment with DIBAL. Finally esters **7** and **8** were obtained using Steglich's esterification conditions with *o*-DPPB acid (Scheme 2).[25]

Scheme 2



In a first series of experiments allylic *o*-DPPB esters **7** and **8,** respectively, were subjected to the reaction conditions of the directed allylic substitution with methyl magnesium bromide in the presence of 0.5 equiv of $CuBr{\cdot}SMe_2$ in diethylether (Table 1). In accordance with previous investigations, optimal results were obtained upon slow syringe pump addition of the Grignard reagent to a solution of the allylic *o*-DPPB ester precomplexed with copper(I). Thus, for *E*-substrate **7** under optimized conditions excellent S_N2' selectivity and a remarkable diastereoselectivity in favor of the *anti*-S_N2' product **1a** (dr 85:15) was obtained (Table 1, entry 3). Even better, and most interestingly, opposite diastereoselectivity was observed for *Z*-substrate **8** (dr 95:5) in favor of *syn*-S_N2' product **2a**. Hence, depending on alkene geometry both diastereomeric allylic substitution products **1a** and **2a** are accessible with good levels of acyclic stereocontrol exerted by a stereogenic center in δ-position.

(11) (a) Yamamoto, Y. *Methods of Organic Chemistry* (*Houben-Weyl*); Thieme: Stuttgart, Germany, 1995; Vol. E21, pp 2011−2040. (b) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 188−223.

(12) (a) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1987**, 1596. (b) Ibuka, T.; Akimoto, N.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 4055. (c) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111. (d) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627. (e) For a review on the progress in enantioselective catalysis with chiral copper catalysts see: Yorimitsu, H.; Oshima, K. *Angew. Chem.* **2005**, *117*, 4509; *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439.

(13) Orientating experiments with other leaving groups such as OAc, Cl, or $PO(OEt)_2$ have shown that in these cases the S_N2 product is formed preferentially.

(14) (a) Gallina, C. *Tetrahedron Lett.* **1982**, *23*, 3094. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715. (c) Smitrovich, J. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 12998. (d) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601.

(15) (a) Barsanti, P.; Calò, V.; Lopez, L.; Marchese, G.; Naso, F.; Pesce, G. *J. Chem. Soc., Chem. Commun.* **1978**, 1085. (b) Calò, V.; Lopez, L.; Carlucci, W. F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2953. (c) Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A. M. *J. Org. Chem.* **1990**, *55*, 2294.

(16) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(17) (a) Breit, B.; Demel, P. *Adv. Synth. Catal.* **2001**, *343*, 429. (b) Demel, P.; Keller, M.; Breit, B. *Chem. Eur. J.* **2006**, *12*, 6669.

(18) (a) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786. (b) Breit, B.; Demel, P.; Grauer, D.; Studte, C. *Chem. Asian J.* **2006**, *1*, 586.

(19) (a) Breit, B.; Herber, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3790. (b) Herber, C.; Breit, B. Chem. Eur. J. **2006**, *12*, 6684. (c) Herber, C.; Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5267.

(20) So far only two reports have addressed stereoinduction from a stereocenter located in δ-position relative to the leaving group of an allylic substrate. (a) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121. (b) Belelie, J.; Chong, M. J. *J. Org. Chem.* **2002**, *67*, 3000.

(21) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772.

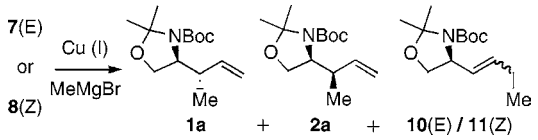
(22) For a review on the use of Garner's aldehyde see: Liang, X.; Andersch, J.; Bobs, M. *J. Chem. Soc., Perkin Trans 1*, **2001**, 2137.

(23) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

(24) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Shimamoto, K.; Ohfune, Y. *J. Med. Chem.* **1996**, *39*, 407. (c) Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.***1992**, *114*, 998.

(25) Höfle, G.; Steglich, W.; Vorgrüggen, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569.

Table 1. Results of Copper-Mediated Directed Allylic Substitution of Allylic *o*-DPPB Esters **7** and **8** with Methyl Magnesium Bromide: Influence of Reaction Conditions

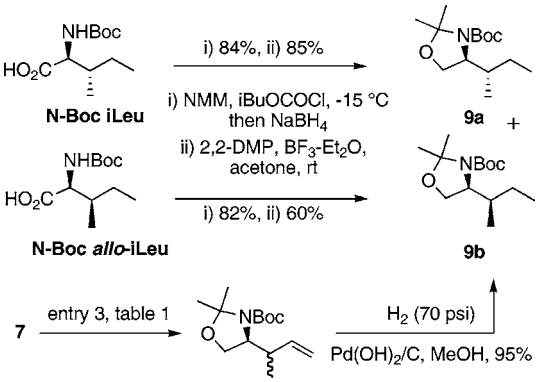


entry[a]	cpd	equiv [MR]	S_N2'/S_N2 **1a** + **2a**/ **10** + **11**[b]	syn/anti **2a**/**1a**[c]
1	**7**(*E*)	0.5 CuBr.SMe_2/1.6 MeMgBr	95/5	25/75
2	**7**(*E*)	0.5 CuBr.SMe_2/1.6 MeMgBr	69/31	33/67
3	**7**(*E*)	0.5 CuBr.SMe_2/1.6 MeMgBr	98/2	15/85
4	**7**(*E*)	0.5 CuBr.SMe_2/2 MeMgBr	96/4	21/79
5	**7**(E)	0.5 CuBr.SMe_2/2 MeMgBr	92/8	18/82
6	**7**(*E*)	1 CuBr.SMe_2/2 MeMgBr	93/7	24/76
7	**7**(*E*)	0.5 CuI/2 MeMgBr	84/16	22/78
8	**7**(*E*)	0.5 CuCN/2 MeMgBr	89/11	28/72
9	**8**(*Z*)	0.5 CuBr.SMe_2/1.6 MeMgBr	98/2	95/5
10	**8**(*Z*)	0.5 CuBr.SMe_2/2 MeMgBr	97/3	95/5

[a] All reactions were performed in Et_2O, except for entry 1 which was run in DCM. The reactions were performed at 20 °C, except for entries 2 and 4, run at 0 and 35 °C, respectively. In all cases the concentration of the reaction was 0.02 M, MeMgBr 1.0 M in Et_2O was added by syringe pump (300 μL/h). [b] The S_N2'/S_N2 ratio was determinated by GC, the observed S_N2 adducts **10** and **11** were prepared from Garner's aldehyde via a Wittig olefination (*E*/*Z*: 7/93 with $Ph_3P{=}CHMe$) and were employed for identification purposes in the crude reaction mixture by GC/MS. [c] Complete conversion of **7** or **8** was observed.

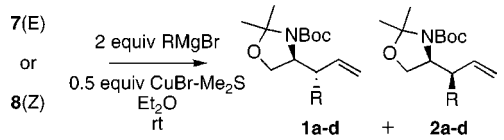
Assignment of the absolute configuration of **1a** and **2a** was achieved upon transformation to known *N*-Boc isoleucine and *N*-Boc allo-isoleucine (Scheme 3).

Scheme 3. Assignment of the Absolute Stereochemistry



With the optimized reaction conditions in hand, we decided to probe the influence of more spatially demanding nucleophiles on the regio- and diastereoselectivity of the directed allylic substitution. Thus, the reaction of substrates **7** and **8** with a series of alkyl Grignard reagents was studied. Results are summarized in Table 2. In all cases (R = Et, *n*Bu, and *i*Pr) complete conversion and almost quantitative yields of allylic substitution product were obtained **1a**−**d** and **2a**−**d** (Table 2, entries 1−8).

Table 2. Results of Copper-Mediated Directed Allylic Substitution of Allylic *o*-DPPB Esters **7** and **8** with Grignard Reagents



entry[a]	cpd	RMgBr R	S_N2'/S_N2	syn/anti[b] (products)	yield (%)[c]
1	**7**(*E*)	Me	98/2	15/85 (**2a/1a**)	78
2	**7**(*E*)	Et	96/4	15/85 (**2b**:**1b**)	91
3	**7**(*E*)	*n*Bu	98/2	17/83 (**2c/1c**)	97
4	**7**(*E*)	*i*Pr	98/2	7/93 (**2d/1d**)	97
5	**8**(*Z*)	Me	96/4	97/3 (**2a/1a**)	86
6	**8**(*Z*)	Et	99/1	97/3 (**2b/1b**)	98
7	**8**(*Z*)	nBu	98/2	98/2 (**2c/1c**)	96
8	**8**(*Z*)	*i*Pr	95/5	95/5 (**2d/1d**)	98

[a] RMgBr (2 equiv) at 0.1 M was added at a rate of 3 mL/h to a solution of **7** or **8** precomplexed with of CuBr−Me_2S (0.5 equiv) in Et_2O at rt (0.01 M). [b] Configuration of **1b**−**d** and **2b**−**d** assigned on analogy with **1a** and **2a** by GC/MS. [c] Isolated products after column chromatography.

Regioselectivity toward the S_N2' product was high in all cases. Furthermore, it proved generally that from *E*-substrate **7** *anti*-diastereomers **1a**−**d** were formed preferentially, whereas the corresponding *Z*-substrate **8** furnished the syn diastereomers **2a**−**d** diastereoselectively. Interestingly, diastereoselectivity was more or less independent from the nature of the Grignard reagent employed.

As a rationale for the stereochemical outcome of these reactions, we assume that the reaction follows the pathway of a directed allylic substitution based on previous extensive control experiments[17] (Figure 1). Thus, for *E*-substrate **7** it

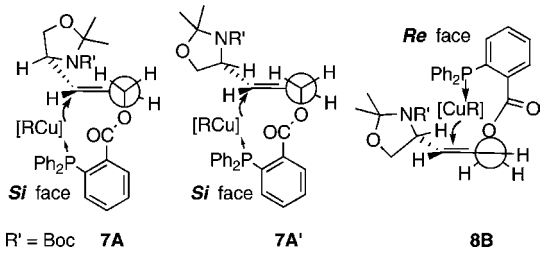


Figure 1. Rationale for the regio- and stereocontrol.

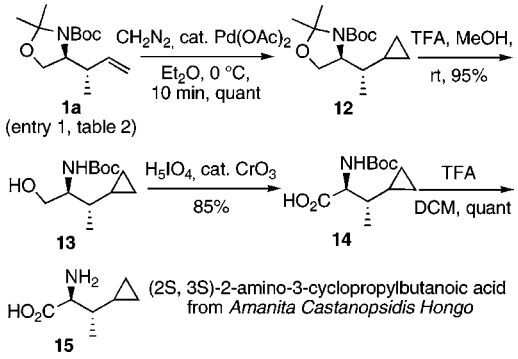
is plausible that reactive conformations (**7A**) or (**7A′**) are accounting for the observed stereochemical outcome. Both conformations are in agreement with stereoelectronic re-

quirements for the S_N2' reaction[16] and minimize allylic $A^{1,3}$ strain.[26] Directed attack from the least hindered *Si* alkene face provides the anti diastereomer preferentially.

In the case of *Z*-substrate **8**, conformation (**8B**) with delivery of the alkyl nucleophile to the sterically less-hindered *Re* face could explain the preferred formation of the syn diastereomer. The pronounced $A^{1,3}$ strain expected for a cis disubstituted alkene could be responsible for the higher diastereoselectivities observed for the *Z*-*o*-DPPB ester **8**.

Our methodology has been applied toward the synthesis of (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid (**15**), isolated from the mushroom *Amanita castanopsidis Hongo*, a naturally occurring amino acid.[27] As its absolute configuration is related to iLeu, we started from substitution product **1a** (dr 85:15) (Scheme 4). Cyclopropanation of **1a** occurred upon treatment with diazomethane in the presence of a catalytic amount of palladium acetate to furnish fully protected amino acid precursor **12**.[28] Cleavage of the acetonide with TFA in methanol and subsequent oxidation of the primary alcohol toward the carboxylic acid with HIO_4 and CrO_3 furnished the Boc-protected amino acid **14** in good overall yield. Cleavage of the Boc group under standard conditions yielded the desired β-branched amino acid **15** quantitatively (dr 9:1).

Scheme 4



Employing the *o*-DPPB group as a reagent-directing leaving group, chemo-, regio-, and diastereoselective allylic substitution of allylic alcohols **3** and **4** derived from Garner's aldehyde is possible. This is the first case in which a δ-stereogenic center is controlling the diastereoselectivity of a *o*-DPPB-directed allylic substitution. Depending on the alkene geometry of the starting material either diastereomer, syn or anti, is accessible with good levels of acyclic stereocontrol. A rational has been proposed including reactive conformations minimizing $A^{1,3}$ strain. The allylic substitution products **1a**−**d** or **2a**−**d** constitute valuable building blocks for the construction of natural and unnatural β-branched α-amino acids as demonstrated with the synthesis of natural (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid.

Acknowledgment. This work was supported by the Ministère délégué à l'Enseignement Supérieur et à la Recherche (T.S.), by the Fonds der Chemischen Industrie (B.B.) and the Krupp-Award for Young University Teachers (B.B.).

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071305M

(26) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1844.
(27) Morimoto, Y.; Takaishi, M.; Kinoshita, T.; Sakaguchi, K.; Shibata, K. *Chem. Commun.* **2002**, 42.
(28) Suda, M. *Synthesis* **1981**, 714.