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1,3-Diastereocontrol with Bromoallenes. Synthesis of Enantiomerically Pure β-Branched α-Amino Acids

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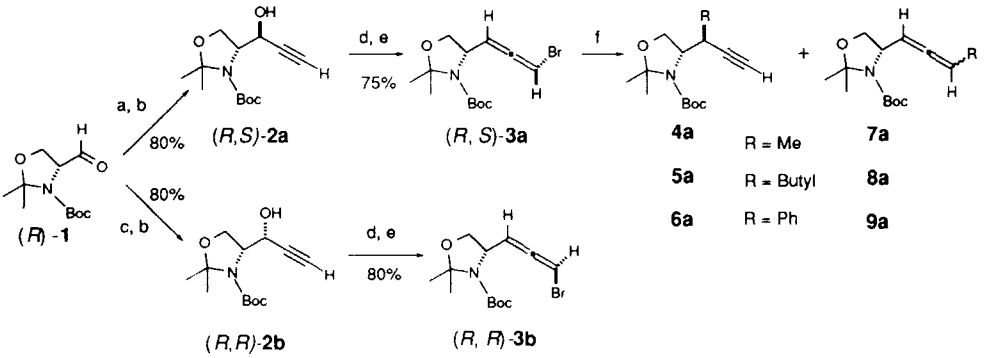
Abstract: Bromoallenes **3a** and **3b** derived from (D)-Serine undergo S_N2' alkylation with organo copper reagents to give alkynyl amino alcohol derivatives. These compounds can be further transformed into branched enantiomerically enriched α-amino acids as, for example (L)-Isoleucine and (L)-Alloisoleucine.

During the last decade the S_N2' substitution in allylic systems with organometallic reagents was extensively studied.[1-3] This kind of reaction, performed on allenic substrates remained relatively unexplored, excepted for the pioneering work of Corey on alkylation of simple bromoallenes.[4-6] As we were embarked in the preparation of ß-substituted amino acids,[7] we decided to investigate the regio- and diastereoselectivity of the S_N2' substitution in homochiral bromoallenes **3a** and **3b**, derived from (D)-Serine, where the 1, 3 oxazolidine ring behaves as a synthetic equivalent of an α amino acid.[8] It was anticipated that if appropriate S_N2' conditions were found and the displacement followed the *anti*-rule in respect to the allenic leaving group,[4] a predictable 1,3-transfer of chirality would occur. Therefore, to make such a reaction of practical use, we needed to control the regiochemistry of the reaction and the degree of the 1,3-diastereocontrol. In this letter, we present our result relative to these questions, together with immediate application to the synthesis of homochiral β-branched α-amino acids. The preparation of bromoallenes **3a** and **3b** starting from the configurationally stable aldehyde **1**[9,10] is depicted in scheme 1.



Reagents: a. $LiC{\equiv}CSiMe_3$, HMPA; b. NH_4F, THF; c. $MgBrC{\equiv}CSiMe_3$, CuI; d. MsCl, TEA, CH_2Cl_2; e. CuBr, LiBr; f. see Table.

Scheme 1

The addition of lithiated trimethylsilylacetylene in the presence of HMPA gave the anti adduct **2a**, whereas the reaction of **1** with the magnesium anion of trimethylsilylacetylene in THF, in the presence of CuI, gave the syn adduct **2b**.[11] The alkynols **2a** and **2b** were converted, through the corresponding mesylates, into bromoallenes **3a** and **3b** using Li_2CuBr_2.[12]According to earlier reports,[13-16] Li_2CuBr_2 displaces the mesylate in an *anti* S_N2' fashion to produce enantiomerically pure bromoallenes **3a** and **3b**. Thus in an exploratory step a number of organocuprates were reacted with allenes **3a** and **3b,** in order to find out the best conditions which gave the major amount of the S_N2' over the S_N2 substitution (Table 1). We discovered that inverse addition of organocuprates to the bromoallenes **3a** gave far better results in terms of yields and regioselectivity. Surprisingly, this experimental procedure has not been considered before. The Gilman cuprates (entries 1, 2, 5, 6, 9 and 10) and the higher order cuprates (entries 4, 8, and 12) gave the alkynes compounds **4a**, **5a** and **6a** as main products together with minor amounts of the substituted allenes **7a**, **8a** and **9a**, whereas the lower order cyanocopper reagents gave no reaction, in contrast to previous reports (entries 3, 6, and 9).[4,5] With regard to

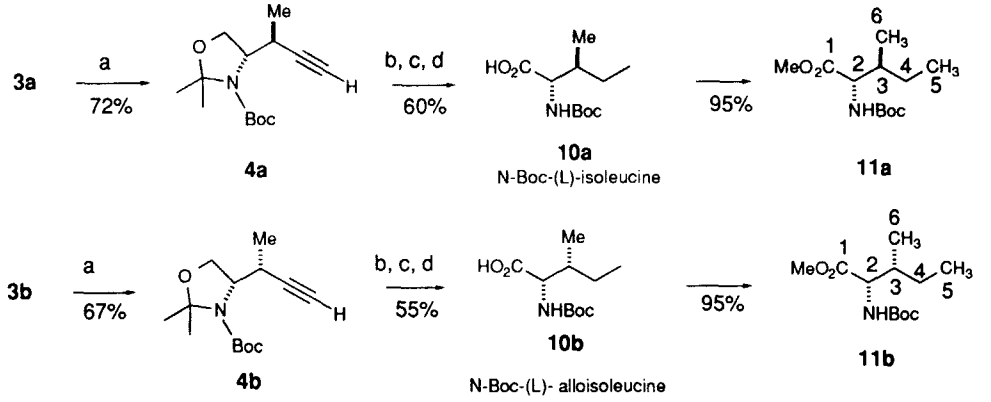
Table: Results of the reaction of various organocopper reagents with bromoallene **3a.**

Entry	Reagents	Ratio Alkyne/Allene[a]	Overall yield%[b]	Yield of alkyne%[c]
1	$MeCuMgBr_2$. LiBr	90 : 10[d]	90	72
2	Me_2CuILi_2	60 : 40[d]	70	37
3	MeCuCNLi	no reaction	-	-
4	$Me_2CuCNLi_2$	90 : 10[d]	74	55
5	$BuCuMgBr_2$. LiBr	85 : 15[e]	85	65
6	Bu_2CuILi_2	95 : 5[e]	70	60
7	BuCuCNLi	no reaction	-	-
8	$Bu_2CuCNLi_2$	95 : 5[e]	76	57
9	$PhCuMgBr_2$.LiBr	80 : 20[f]	65	45
10	Ph_2CuILi_2	95 : 5[f]	72	62
11	PhCuCNLi	no reaction	-	-
12	$Ph_2CuCNLi_2$	95 : 5[f]	60	47

a.Determined by ^1H NMR (200 MHz, $CDCl_3$) on the crude at 50° to avoid the signals du to rotamers; b. Yield of the mixture alkynes and allenes; c. isolated yield of the alkynes; d. ratio **4a / 7a**; e. ratio **5a / 8a**; f. ratio **6a / 9a**.

the regioselectivity of the reaction, it may be assumed that the heteroatoms in the oxazolidine ring contributed to anchor the organometallic reagent, allowing a regioselective delivery of the nucleophilic group. From a preparative point of view, the allenic by-products can be easily separated by column chromatography. The obtained alkynes are single products as it appears in ^1H and ^{13}C NMR spectroscopy, confirming an *anti* selectivity in the approach of the cuprate to the allenic double bond. [17] The complete diastereocontrol in this case allows the preparation of the possible isomers of these compounds. The divergence of chirality realized during the addition of the acetylenic derivative to the aldehyde is propagated during the formation of the bromoallenes and during the alkylation reaction. This sequence of two contiguous anti S_N2' reactions gives a result which is analogous to a *syn* ipso S_N reaction on the propargylic mesylates of the **2a** and **2b**.

The enantiomeric oxazolidines **4a** and **4b** can be easily transformed into β-branched α-amino acids. An example of the elaboration of this structure was realised converting **4a** and **4b** into (L)-isoleucine and (L)-alloisoleucine respectively, in order to carry out a reliable chemical correlation.[18] Hydrogenation of the triple bonds of compounds **4a** and **4b**, with subsequent ring opening of the oxazolidine in mild acidic conditions followed by oxidation of the primary alcohol with PDC in DMF gave rise to N-Boc isoleucine **10a** and allo-isoleucine **10b** in good overall yields (Scheme 2). Products **10a** and **10b** match the optical rotations of the authentic samples[19,20] and the corresponding esters **11a-11b** were up to 95 % pure as shown by ^{13}C NMR spectroscopy, inspecting the signals for C(2), C(4) and C(6).[21] It must be emphasized that starting from (L)-serine and following the same procedure the corresponding unnatural isoleucines can be prepared.



Reagents: a. $Me_2CuCNLi_2$, THF, -78°C; b. PtO_2, H_2, MeOH; c. PPTS, EtOH, reflux; d. PDC, DMF; e. Me_3SiCHN_2.

Scheme 2.

In summary we have shown that diastereomeric bromoallenes may be used as relay between propargyl alcohols and propargyl alkyls with retention of configuration. Accordingly with the reported examples the further elaboration of the triple bond can constitute a general protocol for the synthesis of substituted α-amino acids.[22]

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17. *Typical experimental procedure (entry 4) for the preparation of* **4a**: To a mixture of CuCN (145 mg, 1.6 mmol, 5 eq.) in anhydrous THF (5 ml) was added at -78°C a solution of MeLi (1.6 M in Et_2O solution, 2 mL, 3.2 mmol, 10 eq). After 30 min stirring, the formed organocuprate is slowly transferred via a cannula to a solution of bromoallene **3a** (100 mg, 0.31 mmol) in THF (4 mL).After completion of the addition, the reaction mixture was maintained at -78°C for 5 min and allowed to warm to room temperature. After 1 h, the reaction is quenched with saturated NH_4Cl and extracted with ether (3x20 mL).The organic layer was dried, concentrated and purified by column chromatography on silica gel eluting with hexane/ether: 9/1, to afford pure alkyne **4a** as an oil (56 mg, 72%).^1H NMR (200 MHz, $CDCl_3$ 50°C) δ 1.16 (d, 3H, J 7.1 Hz, 1.50 (s, 9H), 1.61 (s, 6H), 2.02 (d, 1H, J 2.5Hz), 3.21 (bs, 1H), 4.03 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$ 50°C) δ 3.3; 14.6; 26.2; 27.9; 28.5; 59.9; 64.7; 69.6; 79.9; 81.2; 94.1.
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21. Selected analytical data for compound **11a**: ^{13}C NMR (50 MHz, $CDCl_3$ 50°C) δ 11.3; 15.4 (C_6); 25.2 (C_4); 28.3; 38.1; 51.5; 58.2 (C_2); 79.7; 155.4; 172.6.
12b: ^{13}C NMR (50 MHz, $CDCl_3$ 50°C) δ 11.5; 14.5 (C_6); 26.2 (C_4); 28.3; 37.8; 51.7; 57.3 (C_2); 79.7; 155.6; 173.0.
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