ORGANIC LETTERS

2004
Vol. 6, No. 1
19−22

Highly Functionalized Organolithium Reagents for Enantiomerically Pure α-Amino Acid Synthesis

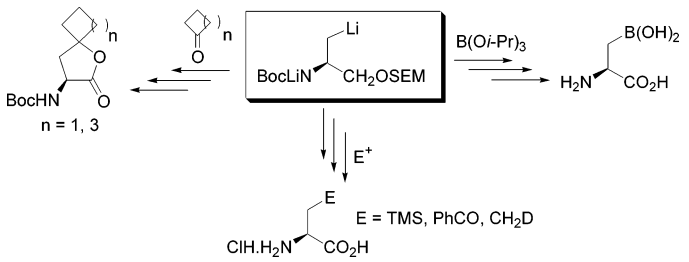
Martin N. Kenworthy, John Paul Kilburn, and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

rjkt1@york.ac.uk

Received October 14, 2003

ABSTRACT



Highly functionalized L-serine-derived organolithium reagents have been generated and reacted with a variety of electrophiles, delivering novel enantiomerically pure adducts. These adducts were then converted into homochiral amino alcohols and novel nonproteinogenic α-amino acids, including an aspartic acid mimic that has been synthesized in an enantiomerically pure form for the first time.

Nucleophilic alanine equivalents are much sought-after in organic synthesis.[2−6] Such reagents are particularly valuable for the preparation of enantiopure, nonproteinogenic α-amino acids,[1] enantiopure α-amino alcohols, and other related "chiral building blocks" for use in natural product synthesis. Examples of these systems include aspartate-derived anion **1**,[2] related sulfonyl reagent **2**,[3] Wittig reagent **3**,[4] and the nickel-based reagent **4**.[5] Although innovative and potentially useful, these reagents have not been widely accepted, possibly due to the difficulty of preparation, the additional steps needed to remove the anion-stabilizing activating group or to readjust the oxidation level, and in the case of reagent **4**, the low reactivity.

More recently, the organozinc reagent **5** introduced by Jackson et al.[6] has proved to be particularly versatile and

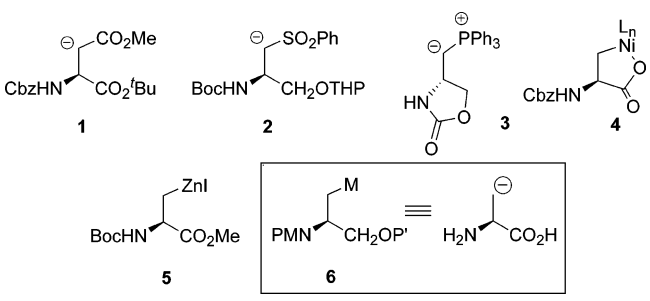


Figure 1. Alanine Anion Equivalents.

(1) For general reviews of amino acid synthesis, see: Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989; Organic Chemistry Series, Vol. 7. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197−4212.

(2) Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6309−6318. See also: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed.* **1981**, *20*, 971−971. Wolf, J.-P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3164−3173.

(3) Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069−6072. Sasaki, N. A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1989**, *30*, 1943−1946.

(4) Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509−7516 and references therein. See also: Itaya, T.; Mizutani, A.; Iida, T. *Chem. Pharm. Bull.* **1991**, *39*, 1407−1414.

(5) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1990**, *31*, 4783−4786.

(6) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397−3404. Rodriguez, A.; Miller, D. D.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 973−977 and references therein.

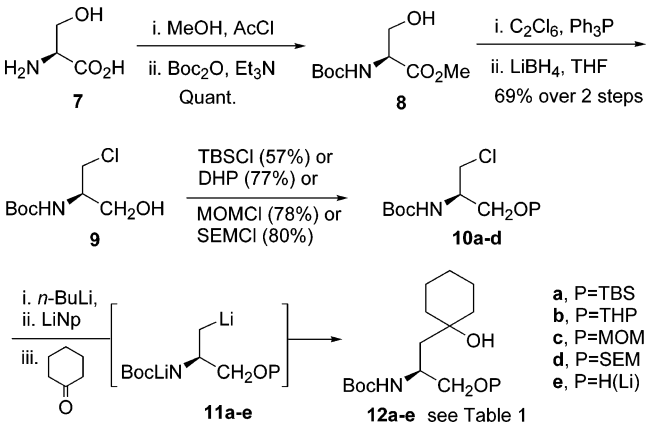
10.1021/ol0360039 CCC: $27.50
Published on Web 12/05/2003

has been successfully adopted by other groups for the preparation of a number of natural products and medicinally active compounds. However, this reagent is also limited in terms of the range of compatible electrophilic trapping agents, often requiring transmetalation to copper or the addition of palladium-catalysts to enhance reactivity. This low reactivity means reaction with simple aldehydes/ketones is not possible.

In natural product syntheses under current investigation in our laboratory,[7] we required a highly reactive organometallic reagent **6** capable of addition to hindered ketones. Herein we describe the successful development and application of reagents **6** (M = Li).

Following on from our earlier studies, we decided to explore the preparation of reagents **6** commencing from a proteinogenic α-amino acid (Scheme 1).[8] Thus, standard

Scheme 1. Initial Studies



conditions[9] were employed to convert L-serine **7** via alcohol **8** into chloroalkane **9**. Protection of alcohol **9** was undertaken using a number of different groups giving the key lithiation precursors **10a**−**d**.

We were now in a position to investigate the generation of organolithium reagents **11** (Scheme 1). It was obviously crucial to generate a dianionic species to minimize the possibility of β-elimination. We therefore employed the butyllithium−lithium naphthalenide (LiNp) combination developed by Yus et al. for chloroamide lithiation.[10] This protocol was employed with the unprotected alcohol **9** and with the protected derivatives **10a**−**d**, and the reaction mixture was then quenched with cyclohexanone with the aim of evaluating the procedure in terms of the yield of adducts **12a**−**e** (Table 1).

Table 1. Metalation−Trapping of **10a**−**d** and **9**[a]

entry	precursor	product[b]
i	**10a**, P = TBS	**12a**, P = TBS, 0%
ii	**10b**, P = THP	**12b**, P = THP, 57%
iii	**10c**, P = MOM	**12c**, P = MOM, 82%
iv	**10d**, P = SEM	**12d**, P = SEM, 82%
v[c]	**9**	**12e**, P = H, 0%

[a] THF, −78 °C; (i) *n*-BuLi (1.1 equiv), (ii) LiNp (2.5−3.0 equiv), (iii) E^+ (1.5−2.5 equiv). [b] Isolated yields. [c] Performed with 2.1 equiv of *n*-BuLi.

We were delighted to observe promising results with THP, MOM, and SEM protection (entries ii−iv), indicating the possibility that an additional coordinating site in the protecting group might be advantageous. The unprotected alcohol **9** gave no product, and nor did the silyl ether **10a**. No further work was carried out with **10b** in view of the diastereomeric nature of the adducts. Deprotection studies showed that the SEM ether **12d** could be deprotected cleanly using 0.1 M HCl in MeOH (3 h, rt) delivering **12e** (P = H) in 79% yield.

The SEM system was therefore chosen for further study, and a range of electrophiles were employed to trap the organolithium reagent **11d** (Table 2). Thus, in addition to cyclohexanone (entry i), cyclobutanone, benzaldehyde, Weinreb amides, carbon dioxide, trimethylsilyl chloride, and CD_3OD were all successfully employed as electrophilic trapping agents, giving adducts **12d**, **14**, **17**, **20**, **22**, **24**, **26**, and **29**, respectively, in yields ranging from 75 to 98% (entries ii−vii).

In most cases, removal of the SEM-protecting group proceeded smoothly, giving alcohols **12e**, **15**, **18**, **27**, and **30** in unoptimized but reasonable yields (entries i−iii, vi and vii). The main exceptions (entry iv) involved hydrolysis of ketone adducts **20** and **22** where the only observed products were the furans **21** and **23**, respectively, resulting from a cyclization−aromatization sequence. In addition (entry v), the alcohol resulting from deprotection of ester **24** underwent partial lactonization, and a second treatment of the crude material with CSA in benzene completed lactonization, giving γ-lactone **25**.[11]

The alaninol derivatives obtained by deprotection were then oxidized to the corresponding Boc-protected amino acids, which were converted into their methyl esters using trimethylsilyl diazomethane to aid isolation. In this manner, fully protected amino acids **19**,[12] **28**, and **31** were obtained in reasonable yields (entries iii, vi, and vii). Oxidation of 1°/3° diols **12e** and **15** under these conditions gave the spirocyclic lactones **13** and **16**, respectively, by in situ lactonization (entries i and ii). It should be noted that the problems with hydrolyzing the ketone adducts such as **20** and **22** were overcome by double oxidation of the deprotected benzaldehyde adduct **18**, thus allowing the synthesis of γ-keto-α-amino acid **19** (entry iii).[12]

(7) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237−3239. McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385−1393.

(8) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802−1815. Collier, P. N.; Campbell, A. D.; Patel, I.; Taylor, R. J. K. *Tetrahedron* **2002**, *58*, 6117−6125 and references therein.

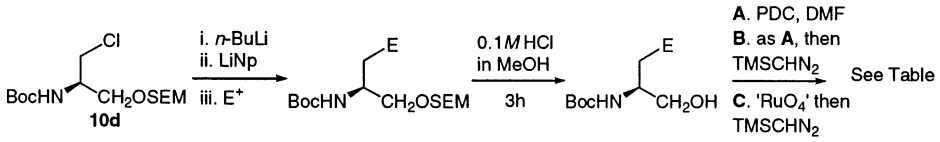
(9) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31−33.

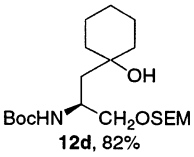
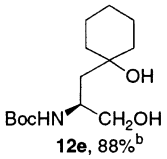
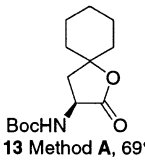
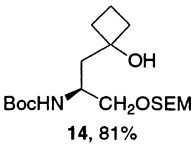
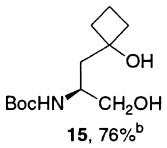
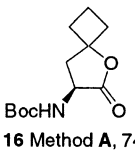
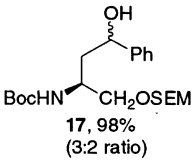
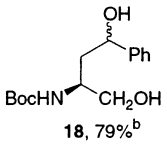
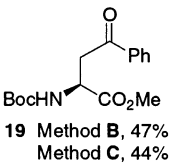
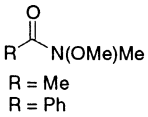
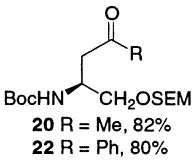
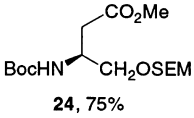
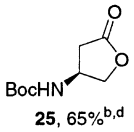
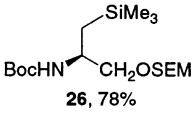
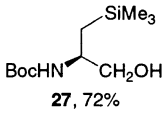
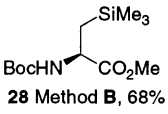
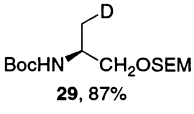
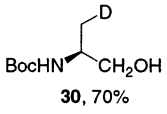
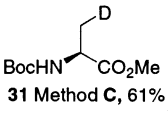
(10) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2911−2922. Review of functionalized organolithium reagents: Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867−926.

(11) Yoda, H.; Nakagami, Y.; Takabe, K. *Tetrahedron Lett.* **1994**, *35*, 169−172.

(12) Jackson, R. F. W.; Turner, D.; Block, M. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 865−870.

Table 2. Metalation−Trapping−Methanolysis−Oxidation of **10e**[a]



	electrophile	adduct	methanolysis product	oxidation product
i		 **12d**, 82%	 **12e**, 88%[b]	 **13** Method **A**, 69%
ii		 **14**, 81%	 **15**, 76%[b]	 **16** Method **A**, 74%
iii	PhCHO	 **17**, 98% (3:2 ratio)	 **18**, 79%[b]	 **19** Method **B**, 47% Method **C**, 44%
iv	 R = Me R = Ph	 **20** R = Me, 82% **22** R = Ph, 80%	 **21**, R = Me[c] **23**, R = Ph[c]	-
v	CO_2, then $TMSCHN_2$	 **24**, 75%	 **25**, 65%[b,d]	-
vi	Me_3SiCl	 **26**, 78%	 **27**, 72%	 **28** Method **B**, 68%
vii	CD_3OD	 **29**, 87%	 **30**, 70%	 **31** Method **C**, 61%

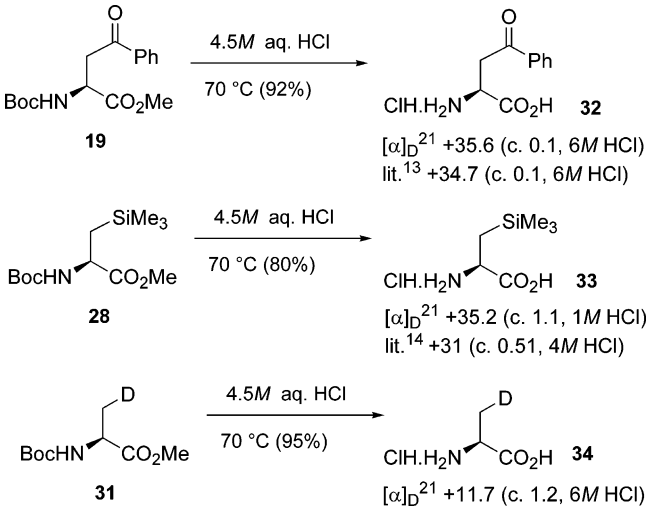
[a] All new compounds were fully characterized by NMR spectroscopy, IR, and HRMS. Trapping of **11d** was performed using the electrophile indicated. Deprotection was performed using 0.1 M HCl in MeOH for 3 h. Oxidation/esterification was performed using method **A** (PDC, DMF), method **B** ((i) PDC, DMF; (ii) $TMSCHN_2$), or method **C** ((i) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/H_2O/CH_3CN$; (ii) $TMSCHN_2$). Isolated yields are shown. [b] Based on recovered starting material (isolated yields were **12e**, 79%; **15**, 65%; **18**, 64%; **25**, 50%). [c] Desired deprotected product was not observed. Due to the volatility of **21** and **23**, isolated yields were not obtained; these were the only products observed by TLC and ^1H NMR spectroscopy (see text). [d] Lactonization of **25** was completed by treatment with CSA in PhH.[11]

The protected amino acids shown in Table 2 were easily hydrolyzed (Scheme 2). Thus, treatment of the *N*-Boc amino ester **19** with 4.5 M HCl at 70 °C for 3 h gave the hydrochloride salt **32** in 92% yield. The optical rotation was in good agreement with the published value {$[\alpha]^{21}_D$ +35.6 (*c* 0.1, 6 M HCl); lit.[13] +34.7 (*c* 0.1, 6 M HCl)}. Similarly, trimethylsilylalanine was obtained as its hydrochloride salt **33** from **28** in 80% yield {$[\alpha]^{21}_D$ +35.2 (*c* 1.1, 1 M HCl); lit.[14] +31 (*c* 0.51, 4 M HCl)}. The deutero-alanine HCl salt **34** was obtained in 95% yield from **31** in the same manner {$[\alpha]^{21}_D$ +11.7 (*c* 1.2, 6 M HCl)}. This "labeled" amino acid has been observed from the reaction of alanine with hydroxyl

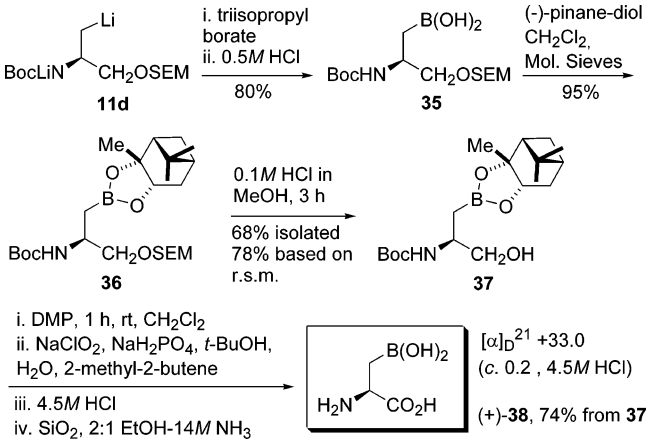
(13) Lin, W.; He, Z.; Zhang, H.; Zhang, X.; Mi, A.; Jiang, Y. *Synthesis* **2001**, 1007−1009.

(14) Walkup, R. D.; Cole, D. C.; Whittlesey, B. R. *J. Org. Chem.* **1995**, *60*, 2630−2634.

Scheme 2. Preparation of (+)-α-Amino Acids



Scheme 3. Preparation of Aspartic Acid Mimic (+)-**38**



radicals[15] but has never been isolated and characterized. Future employment of this deuterated amino acid (+)-**34** could be envisaged in biological studies.

Finally, we used this new methodology to complete the first asymmetric synthesis of the aspartic acid mimic (+)-**38**, in which the β-carboxylic acid has been substituted by a boronic acid (Scheme 3). This has been synthesized as a racemate,[16,17] and in one case resolution was performed by separation of a dipeptide derivative.[17]

Reaction of the functionalized organolithium reagent **11d** with triisopropylborate delivered the boronic acid **35** in 80% yield (Scheme 3). To manipulate the boronic acid adduct **35**, protection as the (−)-pinane-diol boronate ester was undertaken. This was followed by methanolysis of the SEM ether **36**, giving the alcohol **37** in reasonable yield. The oxidation of alcohol **37** was found to be sensitive to the reagent used. Fortunately, sequential Dess−Martin/chlorite oxidations gave the crude carboxylic acid,[18] which was directly deprotected using 4.5 M HCl. The crude hydrogen chloride salt of the amino acid could then be purified on silica gel eluting with 2:1 EtOH−14 M NH_3[19] to deliver the aspartate mimic (+)-**38**, {$[\alpha]^{21}_D$ +33.0 (*c* 0.2, 4.5 M HCl)}.[20] This constitutes the first asymmetric synthesis of the aspartic acid mimic (+)-**38**, increasing its usefulness in future biological tests.

In summary, we have prepared a number of highly functionalized organolithium reagents from L-serine using the Yus procedure in the key lithiation step and established that they can be employed as alaninol/alanine anion equivalents. The optimum SEM-protected reagent **11d** has been used to prepare a range of novel adducts that were hydrolyzed to give alaninol derivatives and then oxidized to give known and novel nonproteinogenic amino acids as their protected derivatives. A selection of these compounds were converted into the amino acid hydrochloride salts. We were also able to undertake the first asymmetric synthesis of the aspartic acid mimic (+)-**38**.

We are currently optimizing the use of these new organolithium alaninol/alanine anion equivalents and also exploring the potential of transmetalated analogues. We are also utilizing this new methodology in complex natural product synthesis.

Acknowledgment. We thank Elsevier Science for postdoctoral support (M.N.K.) and Novo Nordisk for research leave funding (J.P.K.).

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

OL0360039

(15) Nukuna, B. N.; Goshe, M. B.; Anderson, V. E. *J. Am. Chem. Soc.* **2001**, *123*, 1208−1214.
(16) Kinder, D. H.; Ames, M. M. *J. Org. Chem.* **1987**, *52*, 2452−2454.
(17) Hsiao, G. K.; Hangauer, D. G. *Synthesis* **1998**, 1043−1046.
(18) Both purification (silica gel) and esterification ($TMSCHN_2$) led to complex mixtures.
(19) (a) Collet, S. C.; Bauchat, P.; Danion-Bougot, R.; Danion, D. *Tetrahedron: Asymmetry* **1998**, *9*, 2121−2131. (b) Collet, S.; Carreaux, F.; Boucher, J.-L.; Pethe, S.; Lepoivre, M.; Danion-Bougot, R.; Danion, D. *J. Chem. Soc., Perkin 1* **2000**, 177−182.
(20) $[\alpha]_D$ was obtained as the HCl salt, obtained by treatment with 10% HCl followed by evaporation.