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Synthesis of Highly Enantiomerically Enriched *N*-Boc-α-amino Ketones from Pseudoephedrine *N*-Boc-α-amino Acid Amides.

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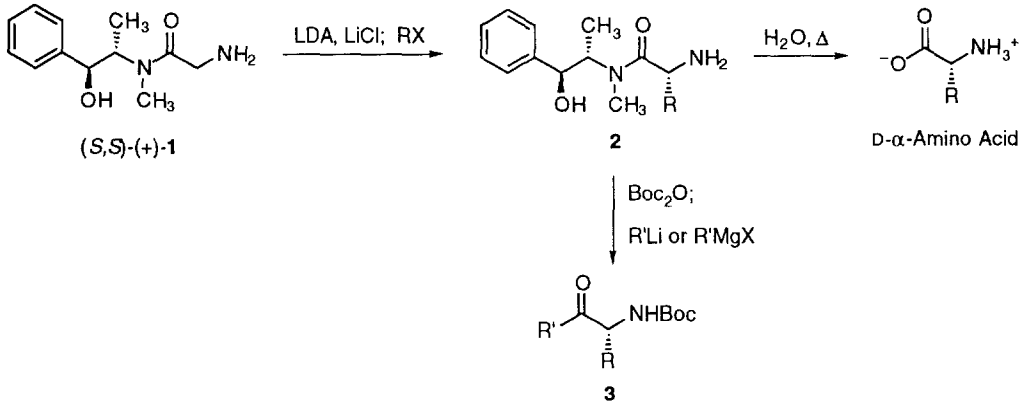
Abstract: *N*-Boc-α-amino ketones are synthesized efficiently and in high enantiomeric excess by the addition of organolithium and Grignard reagents to pseudoephedrine amides of *N*-Boc-α-amino acids, themselves available by the alkylation of pseudoephedrine glycinamide followed by *N*-protection.

We have recently shown that α-amino acids of either D- or L-configuration are readily prepared by the alkylation of (+)- or (–)-pseudoephedrine glycinamide (**1**)[1] followed by hydrolysis of the resulting alkylation products (**2**) under mild conditions (e.g., boiling water).[2] In this letter we describe the efficient synthesis of

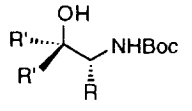


highly enantiomerically enriched *N*-Boc-α-amino ketones from the alkylation products **2** by *N*-protection followed by the addition of organolithium or Grignard reagents. The net transformation of pseudoephedrine glycinamide (**1**) into *N*-Boc-α-amino ketones **3** provides a practical and versatile method for the preparation of these valuable synthetic intermediates.

Prior preparations of enantiomerically enriched *N*-Boc-α-amino ketones have focused primarily on transformations of the natural α-amino acids.[3] For the synthesis of enantiomerically enriched α-amino ketones whose α-substituents are not among the side-chain residues of the naturally occurring amino acids, we felt that the sequence outlined above (**1**→**2**→**3**) would provide a particularly useful and concise preparative method. An

appealing feature of this methodology is the fact that the pseudoephedrine residue serves both to direct the sense of the alkylation reaction and, as shown in prior research,[4] as a group which promotes clean monoaddition of nucleophilic organometallic reagents, analogous to the widely used Weinreb amides.[5] Because both enantiomers of pseudoephedrine are inexpensive commodity chemicals, *N*-Boc-α-amino ketones derived from the rarer D-amino acids are also available by this methodology, as illustrated in the examples below.

Pseudoephedrine *N*-Boc-α-amino acid amides (***N*-Boc-2**) were prepared in ≥97% yield by the reaction of di-*tert*-butyl dicarbonate (Boc_2O, 1.2 equiv, 10% aqueous sodium carbonate solution, 0.75 equiv, dioxane, 0 °C) with the corresponding amines **2**, synthesized by the alkylation of (*S,S*)-(+)-**1** as previously described.[2] The addition of organolithium reagents to pseudoephedrine *N*-Boc-α-amino acid amides (***N*-Boc-2**) was generally a clean and efficient process, and produced the corresponding ketones **3** in 73-93% yield (Table 1). The reactions were conducted initially at –78 °C, where the addition was slow, with subsequent warming to 0 °C, where the addition was quite rapid. The product mixtures typically contained a few per cent of starting material and only traces of overaddition products (tertiary alcohols **4**). The ketones **3** were readily purified by column chromatography on silica gel. Additions of Grignard reagents to pseudoephedrine *N*-Boc-α-amino acid amides (***N*-Boc-2**) were generally less clean and slower than the corresponding organolithium additions, but nevertheless represent preparatively useful processes, with yields of ketones **3** typically in the range of 70-80% (Table 1). With simple unhindered Grignard reagents, the primary by-products of the reaction are the tertiary alcohols **4** and the aminals **5**, both produced in ~5% yield. With the more hindered isopropylmagnesium chloride (entry 8) the addition reaction was exceedingly slow, and proceeded with competitive attack at the carbamate to afford the by-product **6**, in 10% yield. The latter reaction (entry 8) is not a preparatively useful process. Both organolithium and Grignard additions afforded ketones of ≥95% ee when diastereomerically pure starting materials were employed. This was determined by reduction of the products **3** with methanolic sodium borohydride followed by Mosher esterification[6] of the resulting alcohols and ^1H NMR analysis. In most cases, products arising from the enantiomeric ketones **3** were not detectable within the limits of our instrumentation.



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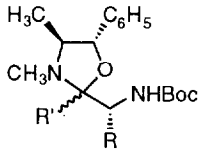

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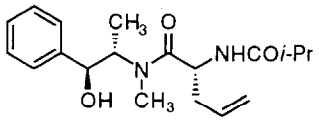

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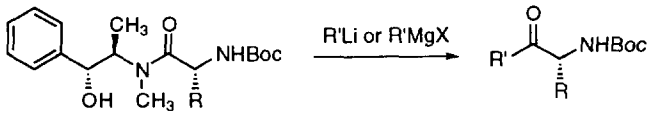
The methodology described herein provides ready access to a wide range of highly enantiomerically enriched *N*-Boc-α-amino ketones and serves to further expand the utility of pseudoephedrine as a chiral auxiliary in organic synthesis. The procedures that follow provide experimental detail to assist in designing protocols for specific applications.



N-Boc-2 **3**

Table 1. Addition of Organolithium and Grignard Reagents to *N*-Boc-Pseudoephedrine Amides 2

Entry	R	R′M (equiv)	Conditions†	Yield (%)	ee (%)
1	$PhCH_2$-	MeLi (3.5)	0 °C, 0.5 h	74	≥95
2	"	PhLi (3.5)	0 °C, 1 h	93	≥95
3	"	EtMgBr (5.0)	0 °C, 10 h	74	≥95
4	CH_2=$CHCH_2$-	MeLi (3.5)	0 °C, 1 h	86	≥95
5	"	MeMgBr (5.0)	23 °C, 20 h	83	≥95
6	"	EtMgBr (5.0)	23 °C, 20 h	72	≥95
7	"	n-OctylMgCl (5.0)	23 °C, 20 h	76	≥95
8	"	i-PrMgCl (6.0)	23 °C, 48 h	36	≥95
9	"	PhLi (3.5)	0 °C, 2.5 h	85	≥95
10	"	2-FurylLi (3.5)	0 °C, 3 h	85	≥95
11	CH_3CH_2-	EtMgBr (5.0)	23 °C, 20 h	71	≥95
12	"	n-OctylMgCl (5.0)	23 °C, 20 h	71	≥95
13	"	2-FurylLi (3.5)	0 °C, 4 h	80	≥95
14	c-$C_3H_5CH_2$-	MeLi (3.5)	0 °C, 1 h	74	≥95
15	"	PhLi (3.5)	0 °C, 4 h	73	≥95

† Initial additions were conducted at –78 °C for R′Li and at 0 °C for R′MgX.

(2*R*)-*N*-Boc-2-amino-1-(2-furyl)-4-penten-1-one (entry 10) A solution of 2-furyllithium in tetrahydrofuran (THF, ca. 0.78 M) was prepared by the addition of *n*-butyllithium (2.5 M in hexanes, 1.50 mL, 3.75 mmol, 3.5 equiv) to a solution of furan (0.28 mL, 3.85 mmol, 3.6 equiv) in THF (3.0 mL) at –78 °C followed by warming of the mixture to 0 °C. After stirring at 0 °C for 30 min, the resultant suspension of 2-furyllithium was cooled to –78 °C and treated with a solution of **(2*R*)-*N*-Boc-2** (R = 1-allyl, 0.387 g, 1.07 mmol, 1 equiv) in THF (1 mL plus two 0.5-mL washes). After 5 min, the reaction flask was transferred to an ice bath. The reaction mixture was stirred at 0 °C for 3 h then was cautiously poured into a stirred mixture of crushed ice and saturated aqueous ammonium chloride solution and the whole was extracted with ether (2 x 25 mL). The combined organic layers

were dried over sodium sulfate and concentrated, and the residue was purified by column chromatography on silica gel eluting with ethyl acetate-hexanes (grading from 1:7 to 1:3, respectively). (2*R*)-*N*-Boc-2-amino-1-(2-furyl)-4-penten-1-one was obtained as a clear oil (0.243 g, 85%). IR (neat) ν_{max} 3342, 2978, 1714, 1681, 1504, 1465, 1393, 1366, 1249, 1168 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1 H, H3'), 7.32 (d, *J* = 3.5 Hz, 1 H, H5'), 6.57 (dd, *J* = 3.5, 1.4 Hz, 1 H, H4'), 5.7 (m, 1 H, H4), 5.32 (br d, 1 H, NH), 5.1 (m, 3 H, H2 and H5), 2.7 (m, 1 H, H3), 2.4 (m, 1 H, H3), 1.43 (s, 9 H, Boc) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.9, 155.0, 150.7, 146.8, 132.0, 118.7, 118.5, 112.3, 79.6, 54.8, 37.0, 28.1 ; HRMS (FAB) for $C_{14}H_{20}NO_4$ (M+H), calcd, 266.1392; found, 266.1382.

(4*R*)-*N*-Boc-4-amino-3-hexanone (entry 11) A solution of ethylmagnesium chloride in ether (3.0 M, 1.70 mL, 5.1 mmol, 5.0 equiv) was added to an ice-cooled solution of **(2*R*)-*N*-Boc-2** (R = ethyl, 0.355 g, 1.01 mmol, 1 equiv) in THF (3.0 mL). After 10 min, the reaction mixture was allowed to warm to 23 °C and was held at that temperature for 20 h. The reaction solution was submitted to an aqueous work-up, as described above, and the crude product was purified by chromatography on silica gel eluting with ethyl acetate-hexanes (grading from 1:7 to 1:4, respectively). (4*R*)-*N*-Boc-4-amino-3-hexanone was isolated as a colorless oil (0.154 g, 71%). IR (neat) ν_{max} 3352, 2976, 1713, 1504, 1366, 1246, 1171 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (br d, *J* ~ 5 Hz, 1 H, NH), 4.32 (app q, *J* ~ 5 Hz, 1 H, H4), 2.52 (m, 2H, H2), 1.9 (m, 1 H, H5), 1.6 (m, 1 H, H5), 1.45 (s, 9 H, Boc), 1.09 (t, *J* = 7.2 Hz, 3 H, H1), 0.89 (t, *J* = 7.4 Hz, 3 H, H6) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 155.5, 79.7, 60.1, 33.1, 28.4, 25.0, 9.3, 7.6 ; HRMS (EI) for $C_{11}H_{22}NO_3$ (M+H), calcd, 216.1600; found, 216.1597. By-products isolated in separate fractions include the tertiary alcohol **4** (R, R′ = ethyl, 0.011 g, 4%) and the aminal **5** (R, R′ = ethyl, 0.010 g, 3%). In addition, 18 mg of starting material was recovered (5%).

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