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Synthesis of Enantiomerically Pure Functionalised Amides (EPC-Synthesis) from Chiral β-Aminated Organolithium Intermediates

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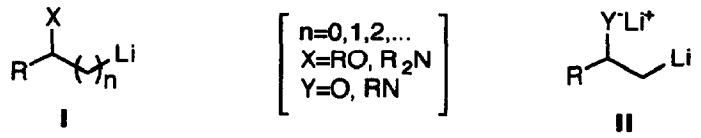
Abstract: The successive deprotonation-lithiation of chiral chloroamides **1** with *n*-butyllithium and lithium naphthalenide, respectively, at -78°C leads to the corresponding chiral β-aminated organolithium intermediates **2**, which by reaction with different electrophiles [H_2O, D_2O, Me_2S_2, $(CH_2)_5CO$, Bu^tCHO and PhCHO] yield, after hydrolysis, the corresponding enantiomerically pure compounds **3**. In the case of using aldehydes as electrophilic reagents, a mixture of diastereomers are obtained, which are easily separated by flash chromatography, so enantiomerically pure 1,3-aminoalcohol derivatives are accessible by this procedure.

Among the methodologies to obtain enantiomerically pure compounds[1] (EPC-synthesis[2]) one of choice for most contemporary chemists is based on the so called 'federal reserve note' (FRN[3]): this procedure consists in using easily available (commercially if it is possible) and cheap chiral starting materials for the preparation of the desirable chiral target molecules. On the other hand, we have investigated in the last decade the preparation and synthetic applications of functionalised organolithium compounds[4] of the type **I** in a racemic form[5], the corresponding oxygen- and nitrogen-containing systems (X=RO, R_2N) being the most widely studied. Among this type of intermediates, the corresponding ones with n=1 (d^2 reagents[6]) are specially interesting because of their instability/high reactivity due to their great tendency to undergo β-elimination , even at very low temperatures[7]. This problem has been overcome by placing a negative charge on the heteroatom (see **II**), so the β-elimination process can be inhibited at low temperatures. In the case of the corresponding aminated systems (**II**, Y=RN), they have been prepared at low temperature by (a) mercury/lithium transmetallation from the adequate aminomercurials[8]; (b) chlorine/lithium exchange in the case of *N*-(2-chloroethyl)amides[9]; and (c) arene-catalysed[10] reductive opening of aziridines[11]. In all cases racemic molecules are always prepared. The aim of this study is the general preparation of chiral β-aminated organolithium reagents of the type **II** (with Y=PhCON) following the above described route (b) and taking advantage of the FRN-method. To the best of our knowledge[5], only one example of a chiral intermediate of this type has been prepared following the route (c) starting from a chiral aziridine derived from (-)-ephedrine[11b].



The reaction of (*S*)-2-(benzoylamino)-1-chlorobutane [(*S*)-**1a**] with *n*-butyllithium at -78°C followed by lithiation with lithium naphthalenide[9,12] at the same temperature for 1 h[13] led to the corresponding chiral dianion (*R*)-**2a**, which by reaction with different electrophiles such as water, deuterium oxide, dimethyl disulphide and cyclohexanone, at temperatures ranging between -78 and 20°C, yielded, after hydrolysis with water, the correponding enantiomerically pure compounds **3aa-3ad** with the same configuration at the stereogenic centre as the starting material (Chart 1 and Table 1, entries 1-4). In the case of using pivalaldehyde or benzaldehyde as electrophilic reagents a 2:1 or 1:1 mixture of diastereomers **3ae** or **3af** was, respectively, obtained, so the asymmetric induction is poor[15] (Chart 1 and Table 1, entry 5 and 6). In spite of obtaining a diastereomers mixture for **3ae** and **3af**, the separation of the corresponding components in each case was easy by flash chromatography (silica gel, hexane/ethyl acetate), so we could isolate all diastereomers in enantiomerically pure form. The stereo-chemistry of diastereomers **3ae** and **3af** was tentatively assigned according to the 300 MHz ^{1}H NMR data previously reported[11b].

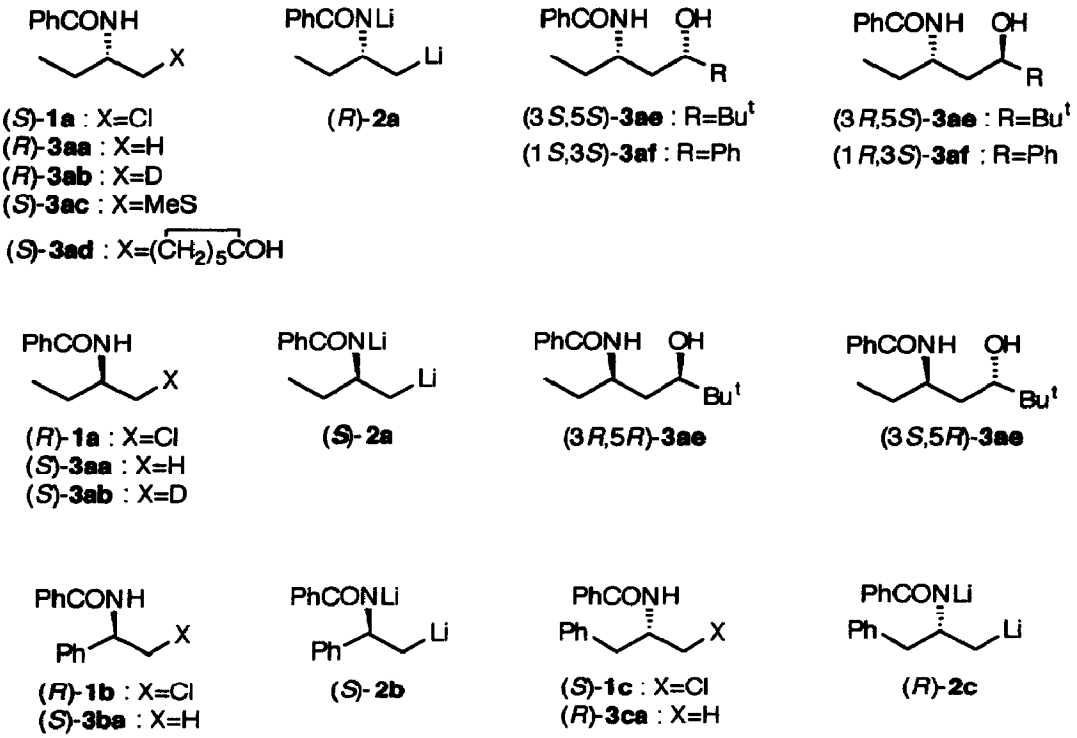


Chart 1.

Table 1. Preparation of Enantiomerically Pure Compounds **3**

Entry	Starting material	Intermediate	Electrophile	Product 3[a] No.	Config.	Yield (%)[b]	mp (°C)[c]	$[\alpha]_D^{25}$(°,c)[d]
1	(*S*)-**1a**	(*R*)-**2a**	H_2O	**3aa**	*R*	91	85-86	-21.5 (1.15)
2	(*S*)-**1a**	(*R*)-**2a**	D_2O	**3ab**	*R*	89	85-86	-22.9 (1.15)
3	(*S*)-**1a**	(*R*)-**2a**	Me_2S_2	**3ac**	*S*	88	96-97	+32.3 (1.15)
4	(*S*)-**1a**	(*R*)-**2a**	$(\overbrace{CH_2)_5CO}$	**3ad**	*S*	69	117-118	+7.5 (1.00)
5	(*S*)-**1a**	(*R*)-**2a**	Bu^tCHO	**3ae**	3*S*,5*S*	78[e]	103-104	+8.8 (0.95)
				3ae	3*R*, 5*S*		101-102	-19.2 (1.05)
6	(*S*)-**1a**	(*R*)-**2a**	PhCHO	**3af**	1*S*,3*S*	72[f]	117-118	+24.4 (0.73)
				3af	1*R*,3*S*		-[g,h]	-28.2 (1.34)
7	(*R*)-**1a**	(*S*)-**2a**	H_2O	**3aa**	*S*	85	85-86	+22.7 (1.05)
8	(*R*)-**1a**	(*S*)-**2a**	D_2O	**3ab**	*S*	85	85-86	+23.5 (0.81)
9	(*R*)-**1a**	(*S*)-**2a**	Bu^tCHO	**3ae**	3*R*,5*R*	69[e]	103-104	-8.5 (0.80)
				3ae	3*S*,5*R*		101-102	+18.4 (0.85)
10	(*R*)-**1b**	(*S*)-**2b**	H_2O	**3ba**	*S*	84	130-132	-5.1 (1.00)
11	(*S*)-**1c**	(*R*)-**2c**	H_2O	**3ca**	*R*	85	123-124	+2.2 (1.48)

[a] All isolated products **3** were >95% pure (from GLC and/or 300 MHz ^1H NMR) and were fully characterised spectroscopically (IR, ^1H and ^{13}C NMR and MS). [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroamide **1**. [c] From hexane/chloroform. [d] In dichloromethane; concentration is given in g/100 ml. [e] 2:1 Diastereomers ratio (GLC). [f] 1:1 Diastereomers ratio (300 MHz ^1H NMR). [g] Oil. [h] R_f 0.18 (hexane/ethyl acetate: 2/1).

The same process using the enantiomeric starting material (*R*)-**1a** gave the same results with the expected opposite absolute configurations. Thus, the reaction with water and deuterium oxide afforded compounds **3aa** and **3ab** with (*S*)-configuration (Chart 1 and Table 1, entries 7 and 8). The use of pivalaldehyde as electrophile led to the same 2:1 diastereomers mixture as above, but constituted by the corresponding enantiomers (Chart 1 and Table 1, entry 9). Flash chromatographic separation of both diastereomers was easily carried out as above.

Finally, we used two different starting chloroamides (*R*)-**1b** and (*S*)-**1c** under the same reaction conditions as above. Tne use of water as electrophile yielded the expected enantiomerically pure 'reduced' products **3ba** and **3ca**, respectively (Chart 1 and Table 1, entries 10 and 11).

Starting chiral materials **1a-c** were easily prepared in a tandem chlorination-benzoylation one-pot procedure from the corresponding commercially available aminoalcohols by successive treatment with thionyl

chloride ($CHCl_3$, 60°C, 5 h) and benzoyl chloride under basic conditions (2.5 M NaOH, 0°C, 2 h) in overal yields ranging between 51 and 76%[16].

From the results described in this paper we conclude that it is easy to prepare enantiomerically pure β-nitrogenated organolithium intermediates **2** (of the type **II**) from commercially available chiral starting aminoalcohols. The reaction of these dianions with electrophiles affords enantiomerically pure compounds **3**, which in the case of aldehyde derivatives yields a mixture of diastereomers easily separated by flash chromatography, so the corresponding enantiomeric 1,3-aminoalcohol derivatives **3ae** and **3af** are obtained in optically pure form. We think that this methodology is of general application for EPC-synthesis[2,17].

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12. The same lithiation using an arene-catalysed process[10] led to a decomposition of the starting material, so this methodology can not be applied in this process.
13. We found that it is not necessary to stirr the reaction mixture for 8 h in order to get the lithiation step. See references 9 and 14.
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15. Similar results were obtained using chiral β-oxygenated organolithium compounds; see, for instance, reference 5h. This behaviour should be attributed to the high reactivity of intermediates of the type **II**, even at very low temperatures.
16. Physical data for starting materials **1** follows (for conditions see Table 1, footnotes c and d): (*S*)-**1a**, mp 100-101°C, $[\alpha]_D^{25}$ -58.9° (1.35). (*R*)-**1a**, mp 100-101°C, $[\alpha]_D^{25}$ +60.3° (1.45). (*R*)-**1b**, mp. 121-122°C, $[\alpha]_D^{25}$ -38.9° (1.25). (*S*)-**1c**, mp 131-132°C, $[\alpha]_D^{25}$ +10.7° (1.20).
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